11th Annual Virtual Comprehensive Hematology & Oncology Review

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

11th Annual Virtual Comprehensive Hematology & Oncology Review Course

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Review Questions for ALL Talks/Education Modules

Acute Lymphoblastic Leukemia in Adults

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11th Annual SCCA Comprehensive Heme/Onc Review Course

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Outline & Objectives

- Epidemiology and Classification
- Risk Stratification
- Front-line Treatment and Role of HCT
- Relapsed/Refractory Disease

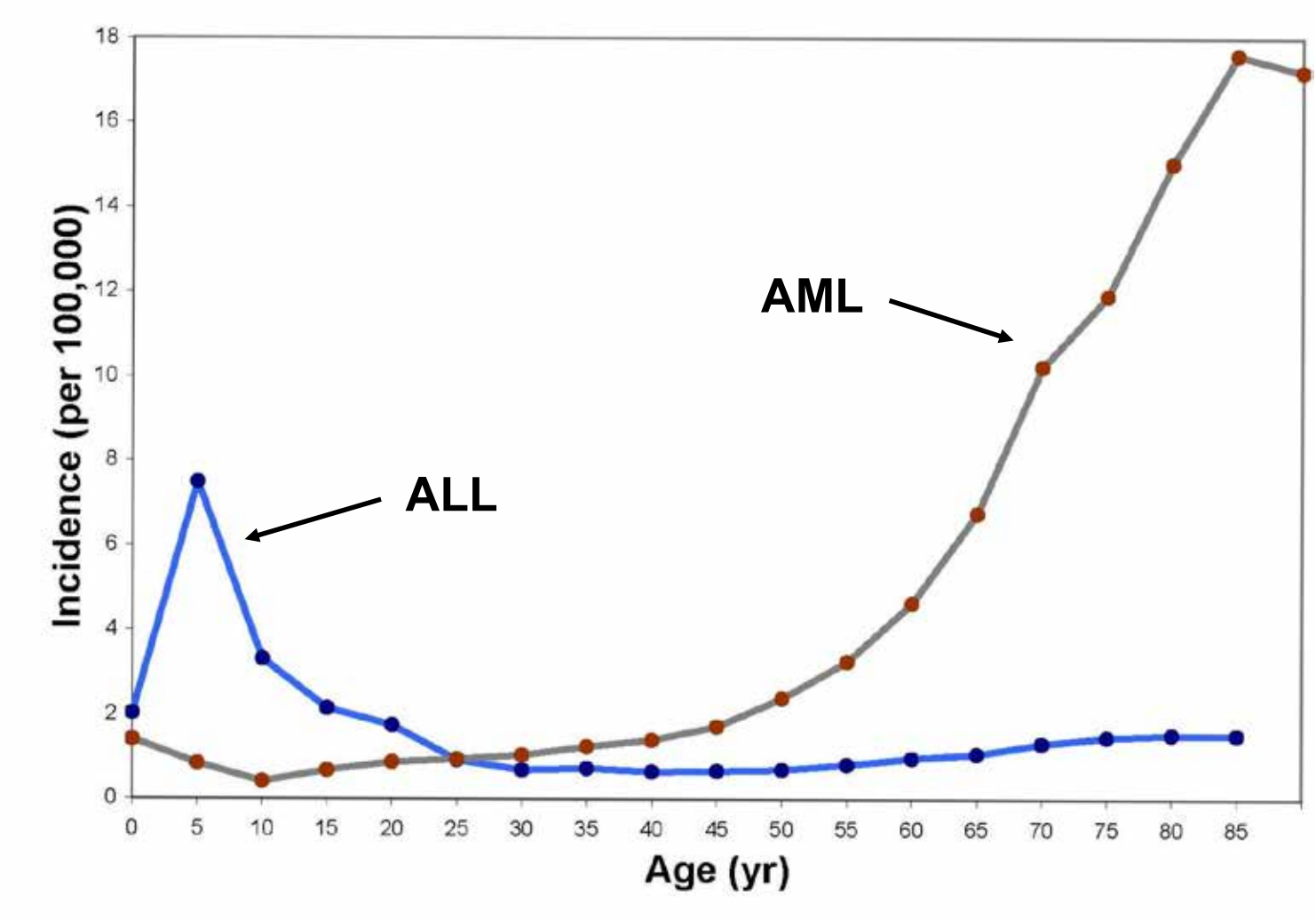
Epidemiology and Classification

Leukemia in the U.S., 2020

	New Cases	Deaths
ALL	**6,150**	**1,520**
CLL	21,040	4,060
AML	19,940	11,180
CML	8,450	1,130
Other	4,950	5,210
Total	60,530	23,100

Siegel, *et al*. *CA Cancer J Clin* 2020;70:7-30.

Acute Leukemia Incidence by Age



Adult ALL: Lineage Assignment

- B-lineage:
  - ***Strong*** CD19 with ≥ ***1*** of the following also strong: CD79a, cytoplasmic CD22, or CD10

  OR

  - ***Weak*** CD19 with ≥ ***2*** of the following also strong: CD79a, cytoplasmic CD22, or CD10
- T-lineage:
  - Strong cytoplasmic CD3 (with antibodies to CD3 ε chain)

  OR

  - Strong surface CD3

Arber, et al. *Blood*. 2016;127:2391-2405.

Risk Stratification

Classical Risk Factors at Presentation

- Age > 35

- High WBC
  - B-lineage: >30,000
  - T-lineage: >100,000

Major Cytogenetic Categories in Adult ALL

t(9;22) (Ph+)	19%
Ph-	81%
Favorable	
High hyperdiploidy	10%
Unfavorable	
t(4;11)	7%
-7	6%
+8	10%
Low hypodiploidy/near triploidy	4%
Complex	5%
iAMP21	Rare

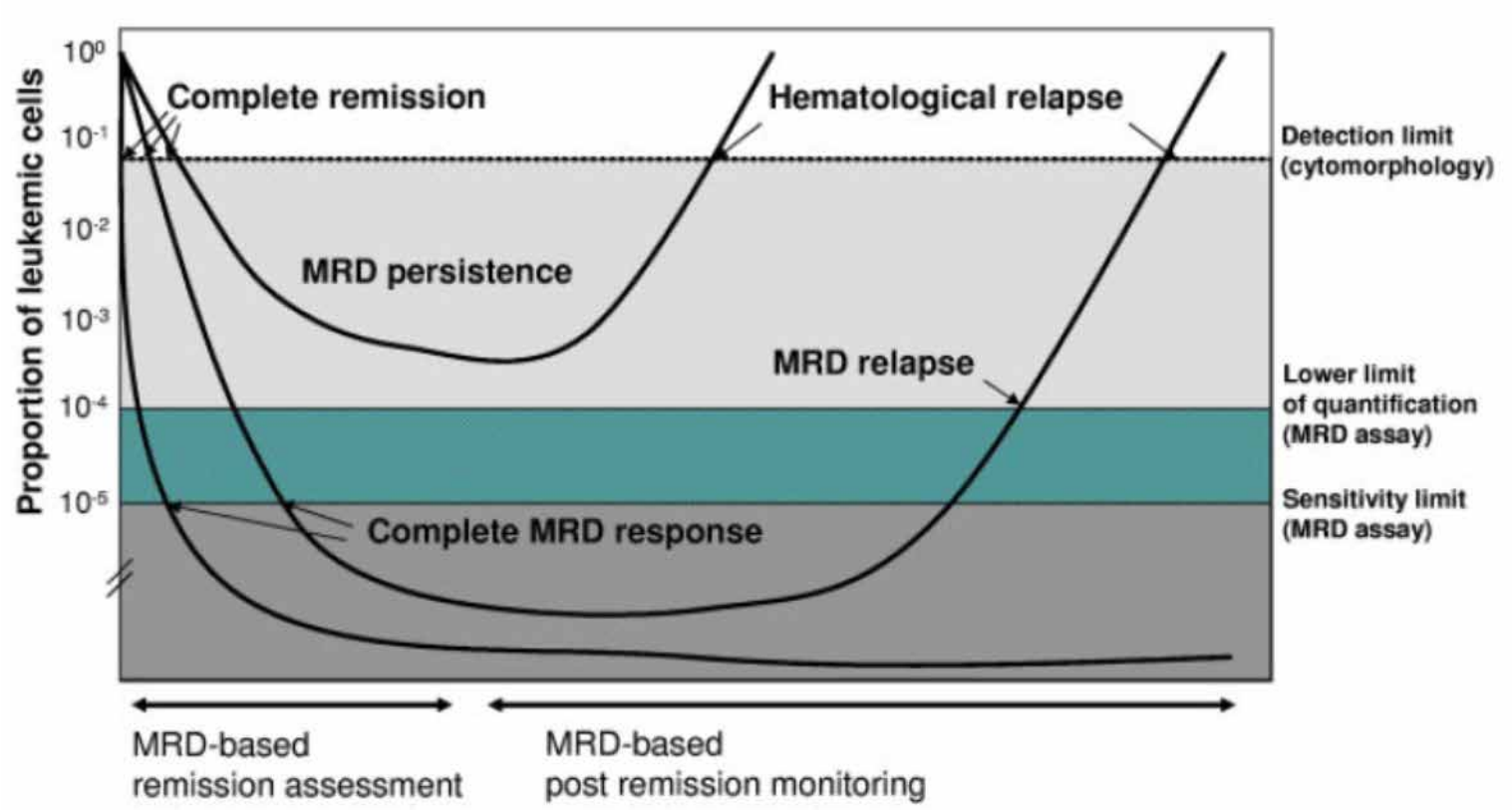
Wetzler, *et al*. *Blood*. 1999;11:3983-39
Moorman, *et al*. *Blood*. 2007;109:3189-97

Early T-Cell Precursor (ETP)-ALL

- Distinct immunophenotype
  - Cytoplasmic CD3
  - Lack CD1a and CD8
  - Weak or absent CD5
  - Often co-express stem cell or myeloid markers → "subset" of biphenotypic leukemia
- Felt to have a relatively poor prognosis

Mullighan. *ASH Educational Program*. 2012:389-96.

Conceptualization of MRD



Bruggemann, *et al. Blood*. 2012;107:4470-81.

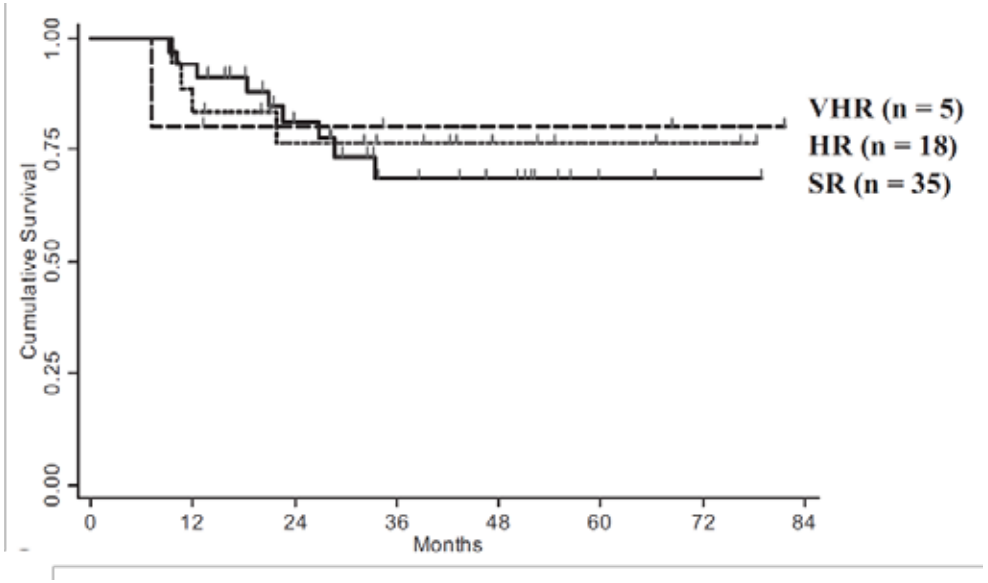
Measurement of MRD in ALL

Target	Method	% Pts.	Sensitivity	Pros	Cons
IG and TCR gene rearrangements	RQ-PCR	~90%	0.01-0.001	Sensitive	Laborious
Fusion transcripts (e.g., BCR-ABL1)	RQ-PCR	~40%	0.01-0.001	Sensitive	Applicability
Leukemia immunophenotype	MFC	~95%	0.01	Rapidly Applicable	User expertise
IG and TCR gene rearrangements	NGS/HTS	Unk	0.00001	Most Sensitive	Role still unclear

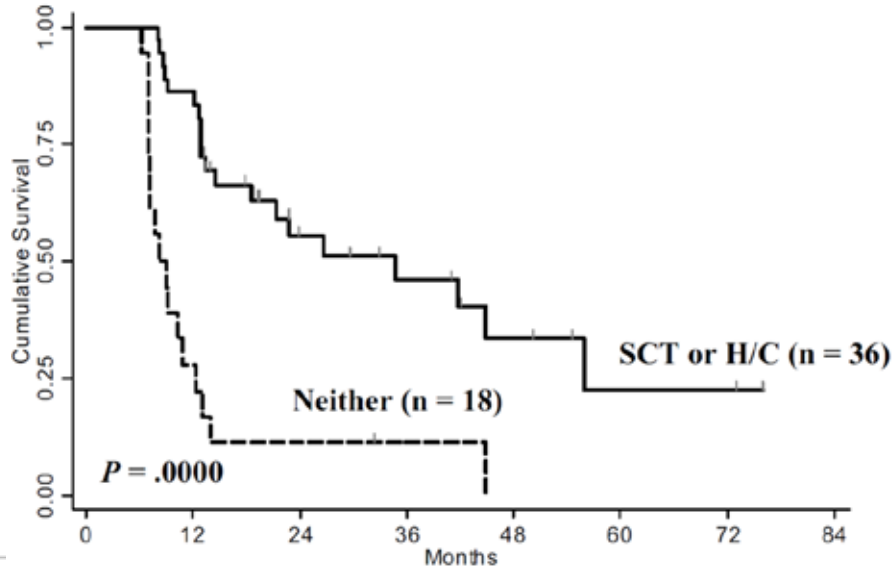
Modified from Bruggemann, *et al. Blood*. 2012;107:4470-81.

NILG-ALL 09/00: Importance of MRD Status

DFS Among MRD^{neg} Patients



DFS Among MRD^{pos} Patients



In a multivariate analysis of patients with complete data (n = 93), only two factors were predictive of relapse:

- MRD^{pos}
- High WBC

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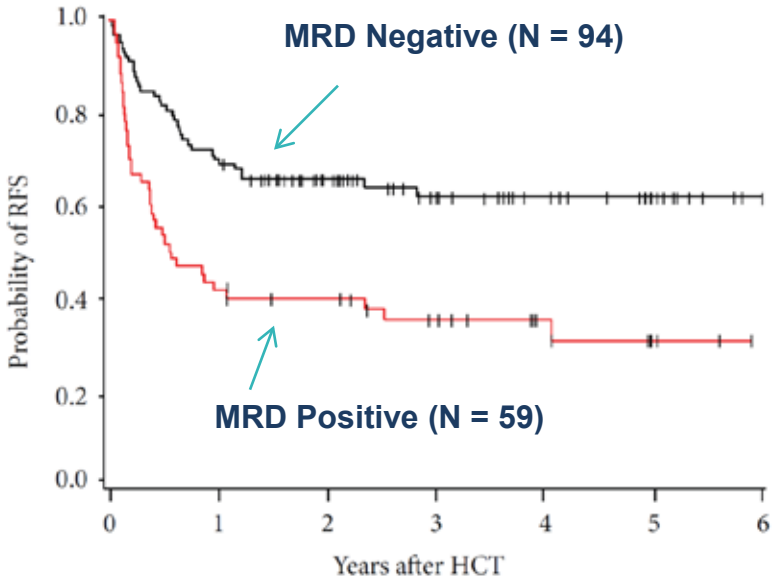
Bassan, *et al*. *Blood*. 2009;113:4153-62.

MRD Predicts Outcome after Allo HCT: The Fred Hutch Experience

Myeloablative HCT



Bar, *et al. Leuk Res Treatment*. Epub 2014 Mar 23.

Non-Myeloablative HCT

Outcomes are anecdotally abysmal if MRD ≥ 0.01%

Ram, et al. Haematologica. 2011;96:1113-20.

Risk Stratification in ALL: Summary

Past

- Age
- WBC at Diagnosis
- Cytogenetics

Present

- MRD
- WBC at Diagnosis
- Cytogenetics
- (Molecular sub-classification)

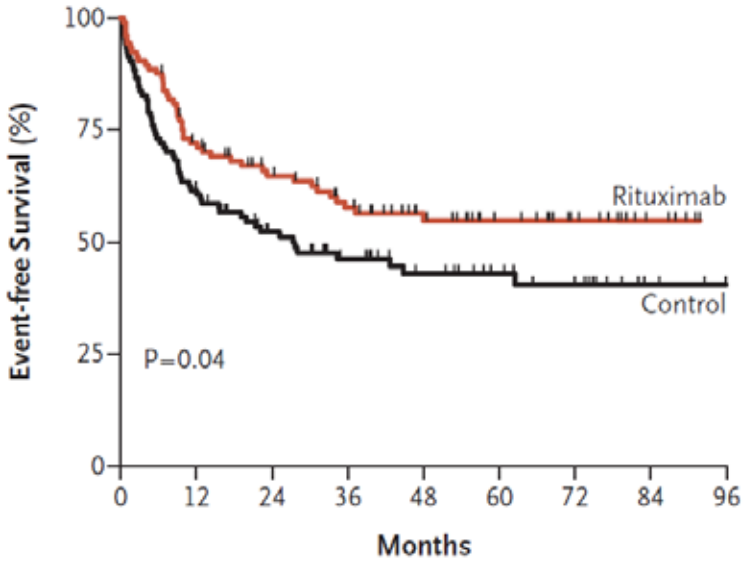
Front-Line Therapy

Contemporary Treatment

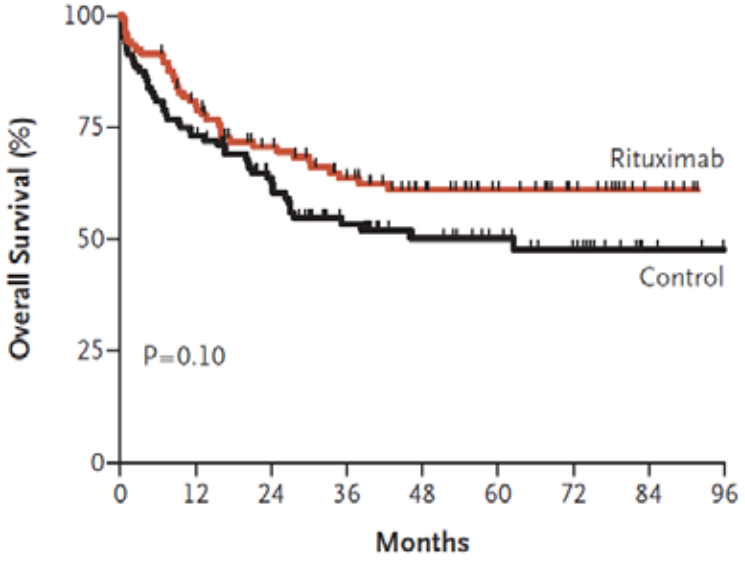
Group	N	Median age (range)	Ph+ (%)	T-cell (%)	CR	DFS at 3-9 yrs (%)
UKALL XII/ ECOG2993	1826	31 (15-65)	19	20	91	38
CALGB 19802	163	41 (16–82)	18	–	78	35
GIMEMA ALL 0288	778	27.5 (12–60)	22	22	82	29
GMALL 05/03	1163	35 (15–65)	24	24	83	35
GOELAMS 02	198	33 (15–59)	22	21	86	41
Hyper-CVAD	288	40 (15–92)	17	13	92	38
JALSG-ALL93	263	31 (15–59)	22	21	78	30
LALA-94	922	33 (15–55)	23	26	84	36

Pui & Evans. *New Engl J Med*. 2006;354:166-78.

Rituximab Improves Outcomes in CD20+ B-ALL: GRAALL-2005/R



No. at Risk									
Control	104	63	45	34	25	19	14	6	3
Rituximab	105	73	58	47	35	26	18	10	5



No. at Risk									
Control	104	75	57	38	28	22	16	6	3
Rituximab	105	82	64	51	39	28	19	10	5

- CD20 positivity = expression on ≥ 20% of blasts
- More patients in R group received HCT (34% vs 20%)
- Adjust for HCT in CR1 → R group had significantly better EFS *and* OS

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Maury, *et al. New Engl J Med.* 2016;375:1044-53.

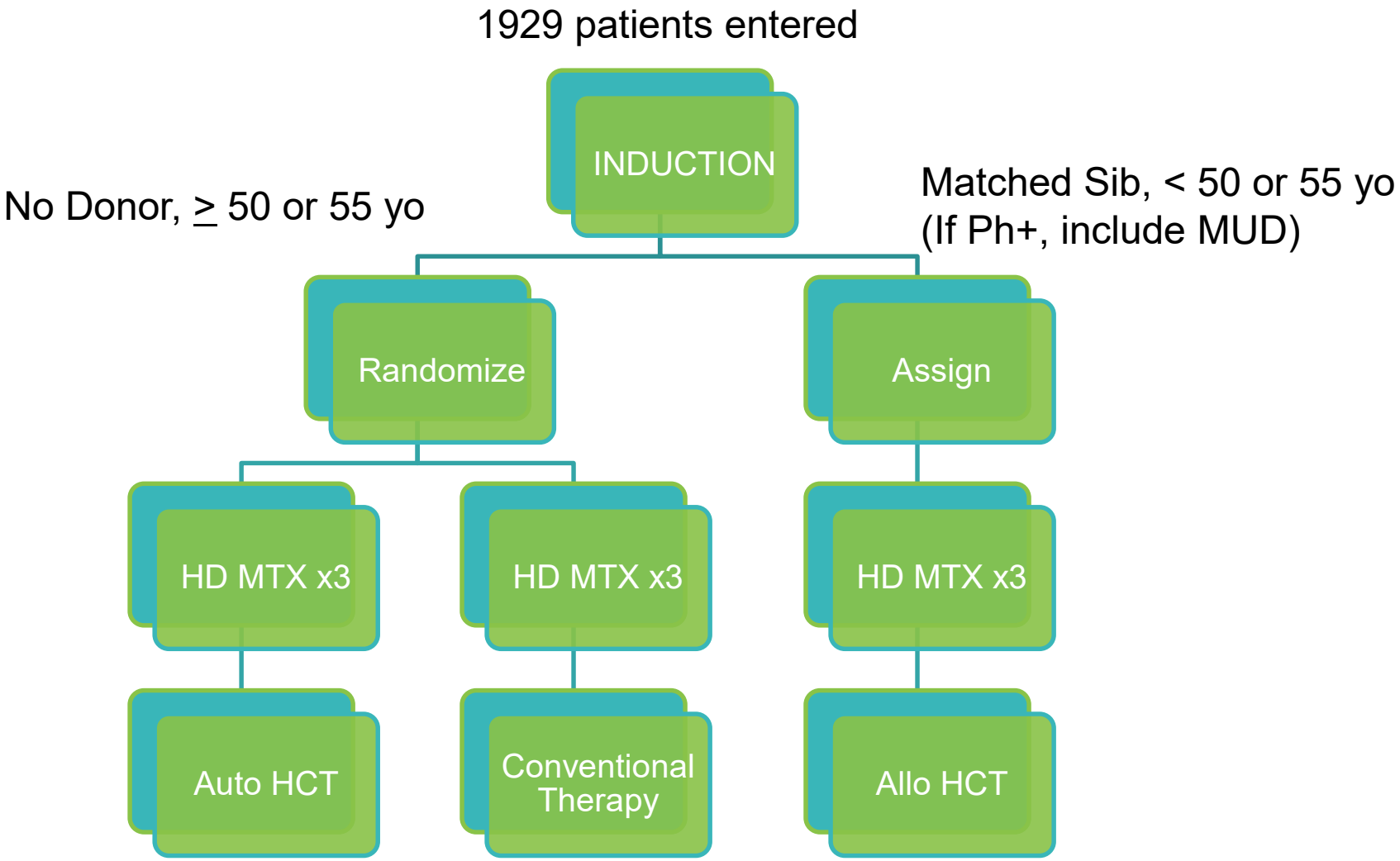
Adult ALL: CNS Prophylaxis

- Without prophylaxis – risk of CNS relapse is 35%
- With prophylaxis – risk is 10%
- Risk factors include
  - ↑ WBC
  - ↑ LDH
  - T-cell or mature B-cell phenotype (i.e., Burkitt)
- ? Need for cranial XRT if IT MTX is used

Post-Remission Therapy of Adult ALL

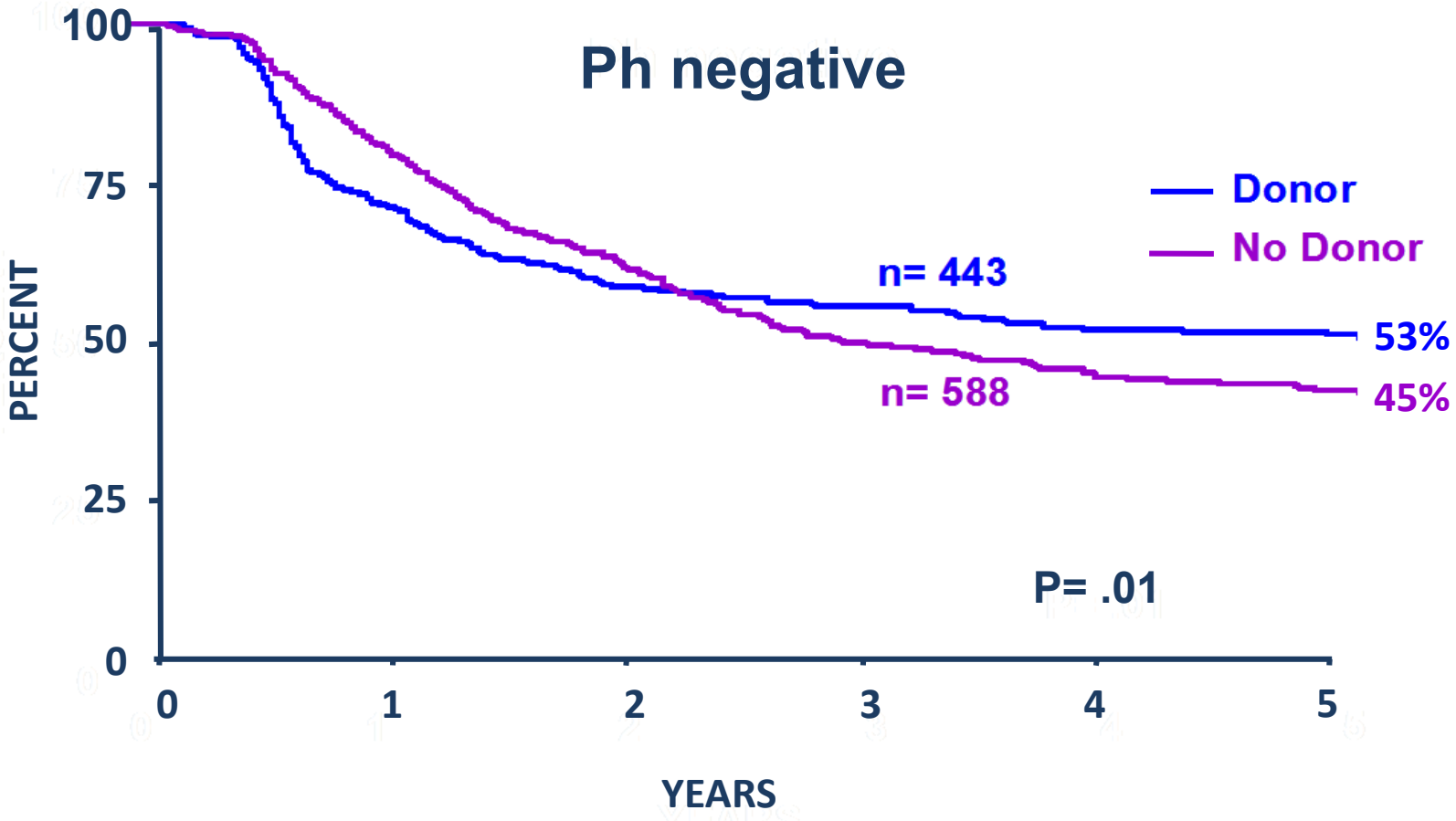
- Intensive multi-drug consolidation followed by maintenance chemotherapy
- Allogeneic transplantation

MRC UKALL XII/ECOG2993



Rowe, *et al. Blood*. 2005;106:3760-7.
Goldstone, *et al. Blood*. 2008;111:1827-33.

UKALL XII / ECOG2993: Overall Survival



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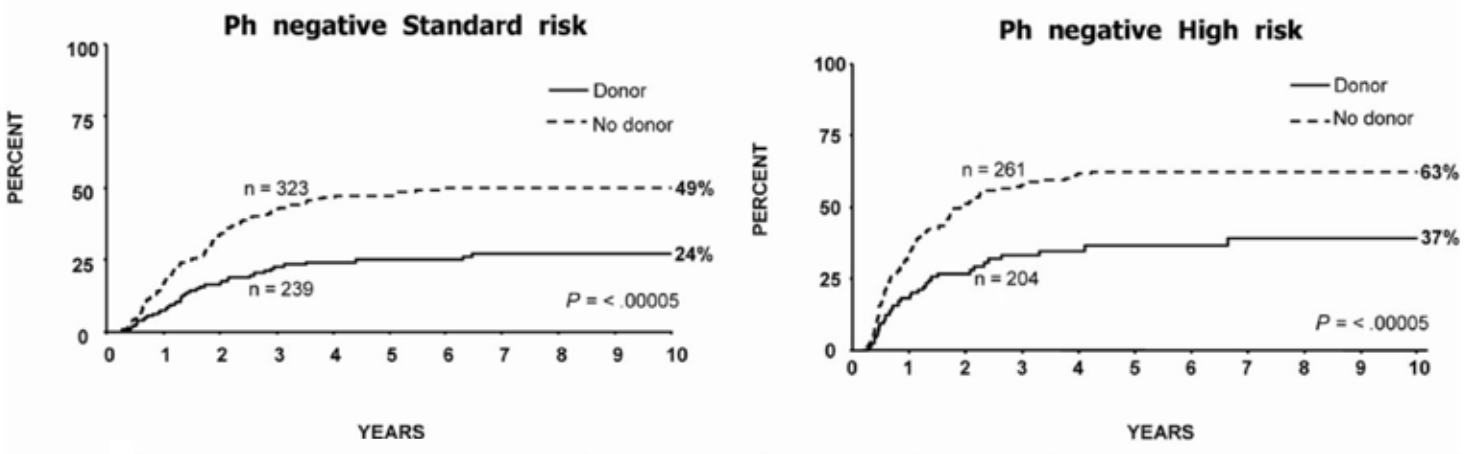
Goldstone, *et al*. *Blood*. 2008;111:1827-33.

UKALL XII/ECOG2993: Less Relapse but More NRM with Allo

Less Relapse



More NRM

	3 months	6 months	1 year	2 years
High Risk				
Donor	1.5	7.3	26.0	35.8
No Donor	1.2	2.0	10.3	13.6
Standard Risk				
Donor	0.4	3.4	17.6	19.5
No Donor	0.3	1.2	5.3	6.9

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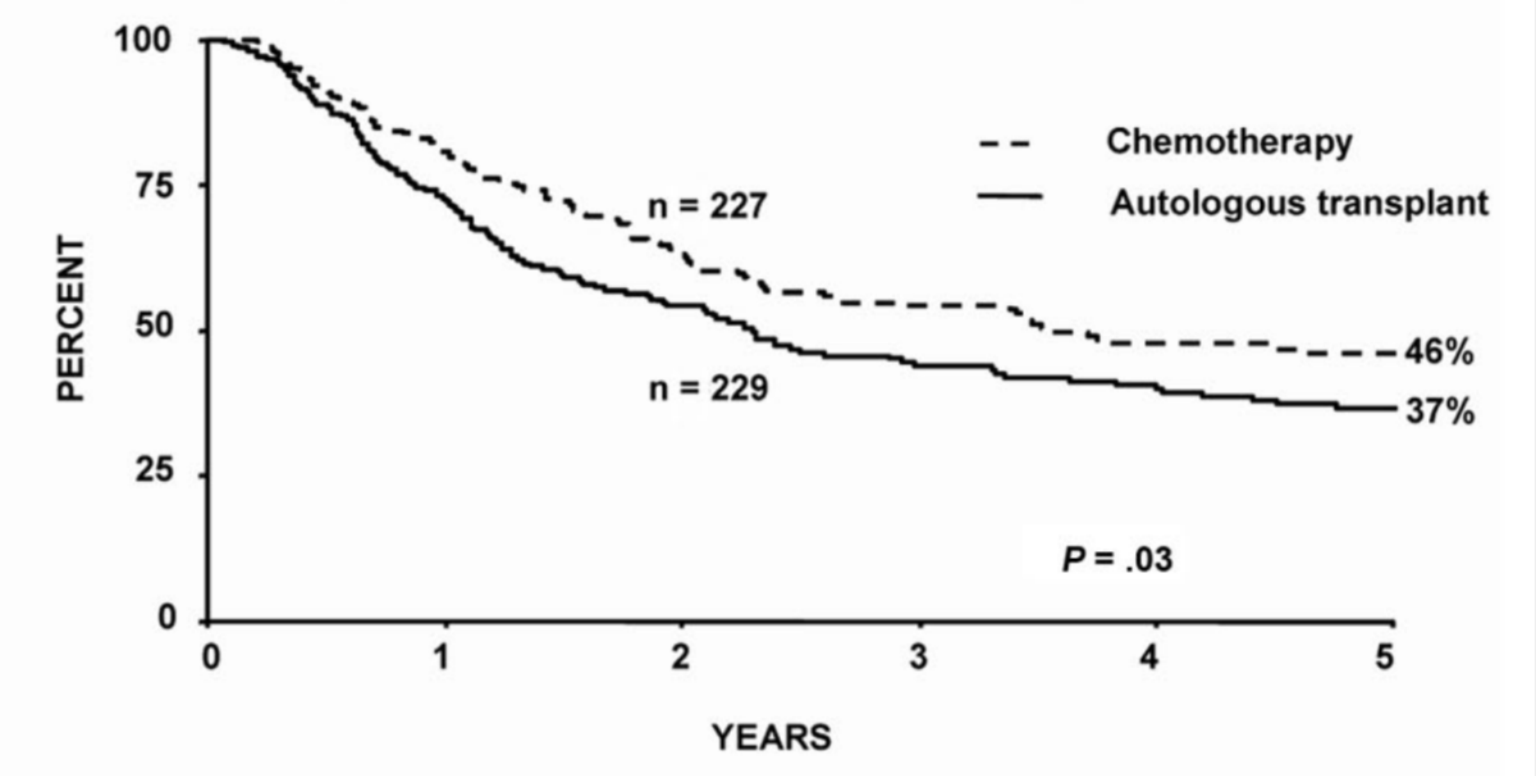
Goldstone, *et al*. *Blood*. 2008;111:1827-33.

UKALL XII/ECOG2993: Auto x 1 vs POMP x 2 years



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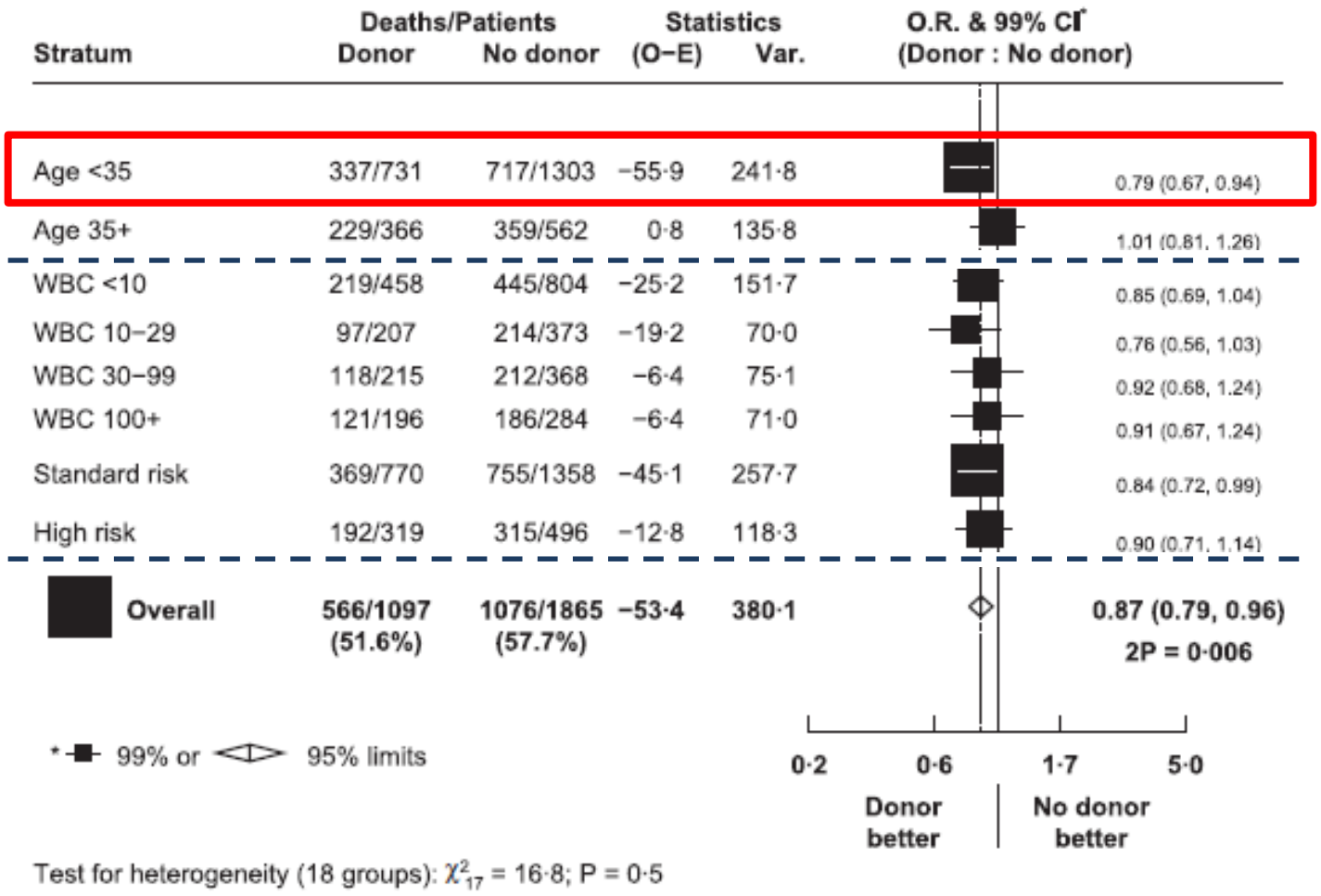
Goldstone, *et al*. *Blood*. 2008;111:1827-33.

Donor vs No-Donor Meta-Analysis: Ph- ALL in CR1



Only sub-group with improved mortality with allogeneic HCT = Age < 35

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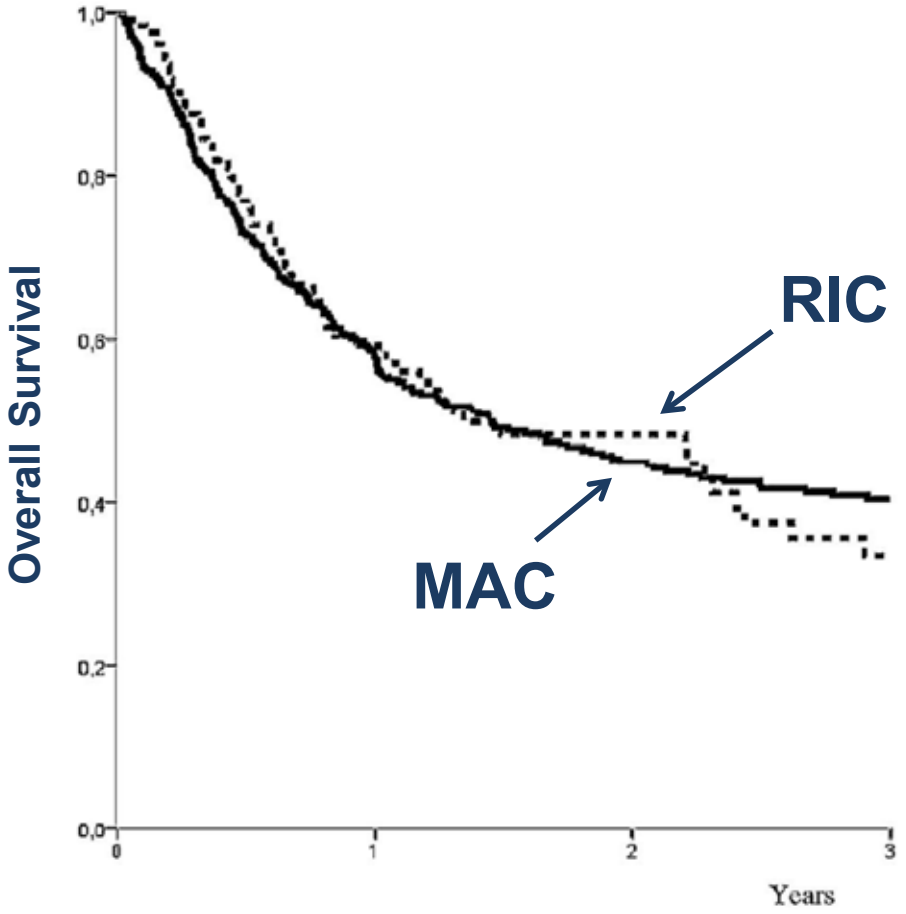
Modified from Gupta, *et al. Blood.* 2013;121:339-50.

Comparison of RIC vs MAC: EBMT

Characteristics:

- Any ALL in CR1 or CR2
- 45 years or older
- MSD PBSCT or BMT from 1997-2007

127 RIC's vs 449 MAC's

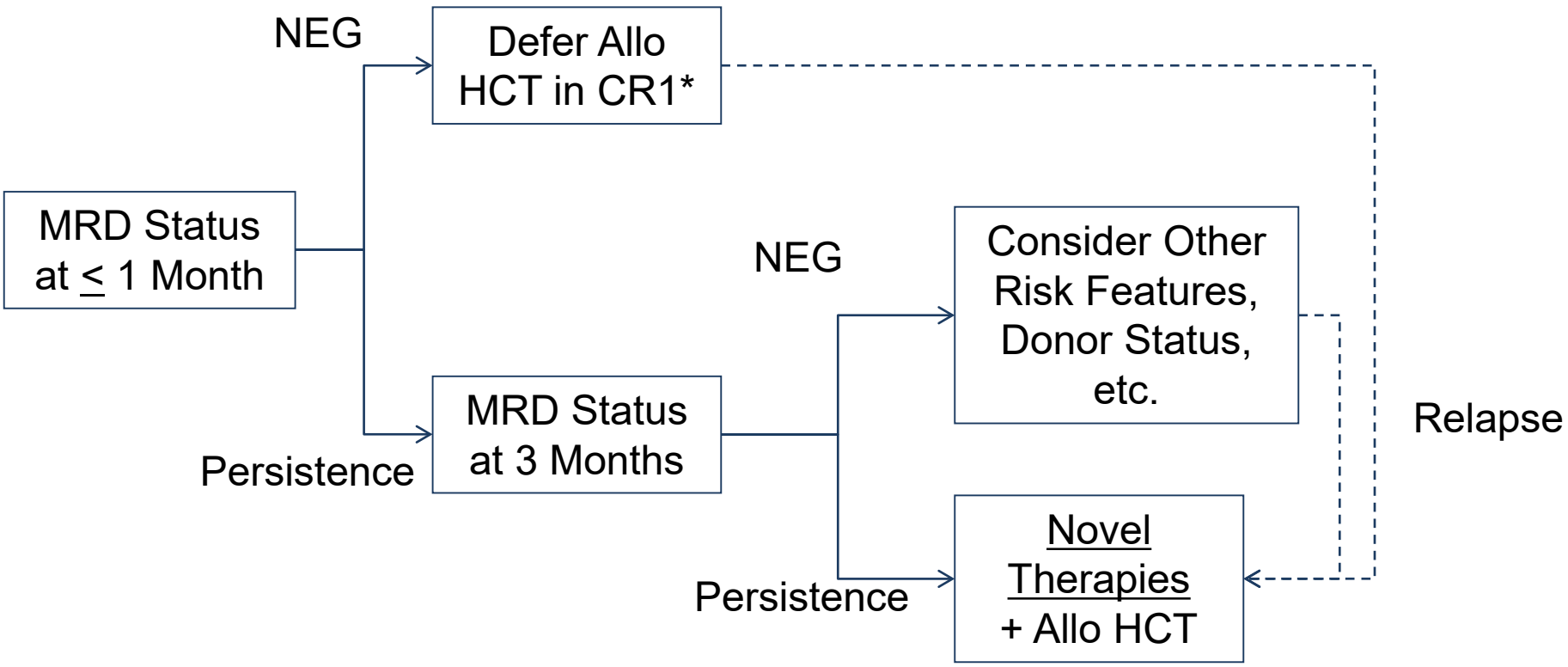


Mohty, *et al*. *Blood*. 2010;116:4439-43.

Summary: Role of HCT in CR1 for ALL

- Level I evidence supporting matched related-donor myeloablative allogeneic HCT in CR1 for adults with ALL, though overall benefit is modest
- Autologous HCT is not superior (and is likely inferior) to prolonged maintenance therapy
- Reduced-intensity/non-myeloablative allogeneic HCT may be reasonable in pts ineligible for high-intensity conditioning, based on retrospective/registry data
- Improved risk-stratification methods can help determine which patients are most likely to benefit from allogeneic HCT in CR1 (particularly MRD)

MRD and Transplant for Ph-, *KMT2A*- ALL: The Cassaday Approach

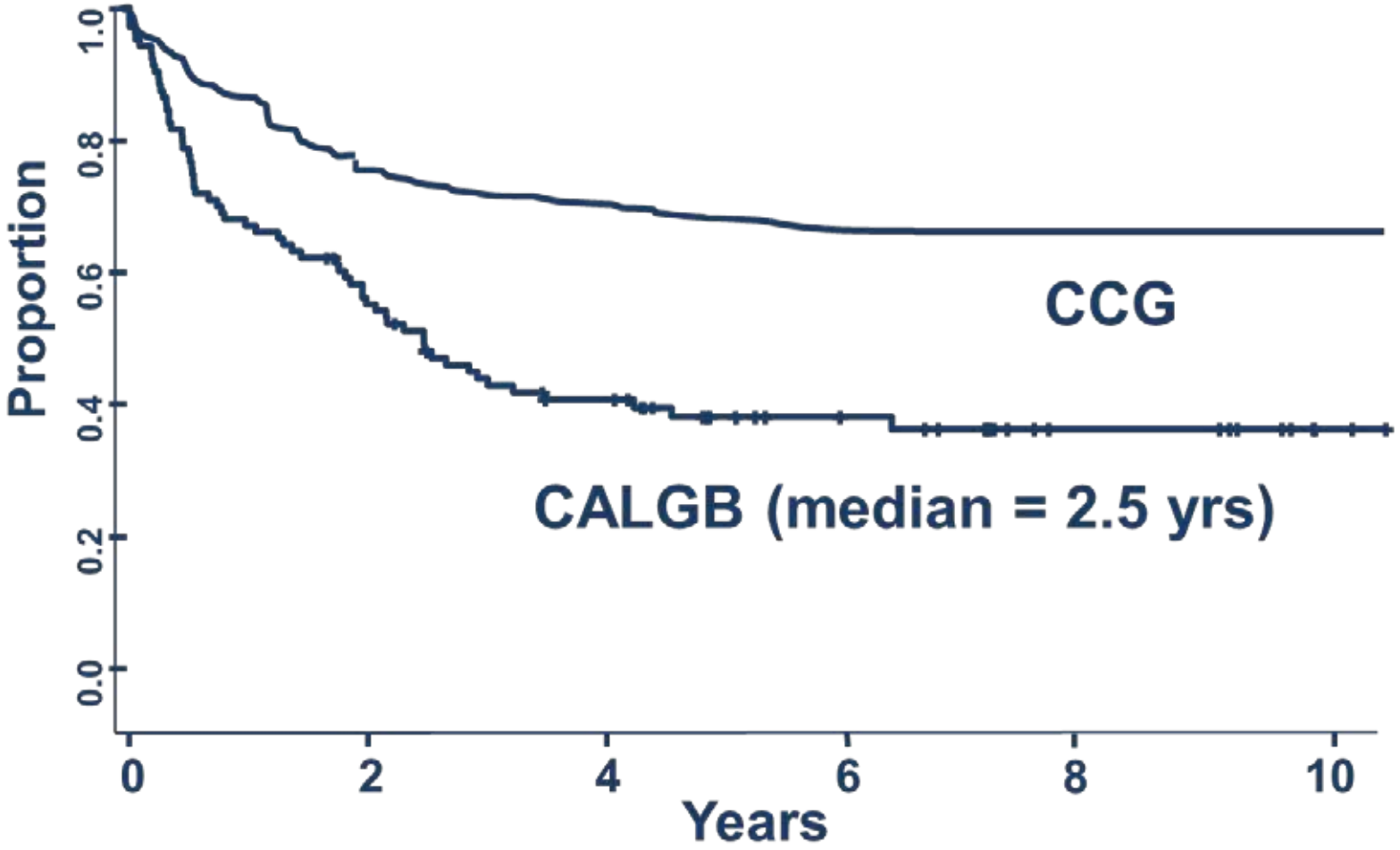


* Assuming patients can complete a full course of treatment and remain MRD negative

Specific Scenarios:

Adolescents and Young Adults (AYA)

EFS of Young Adults (16-21 yo) on CCG and CALGB Trials for ALL (1988-1995)



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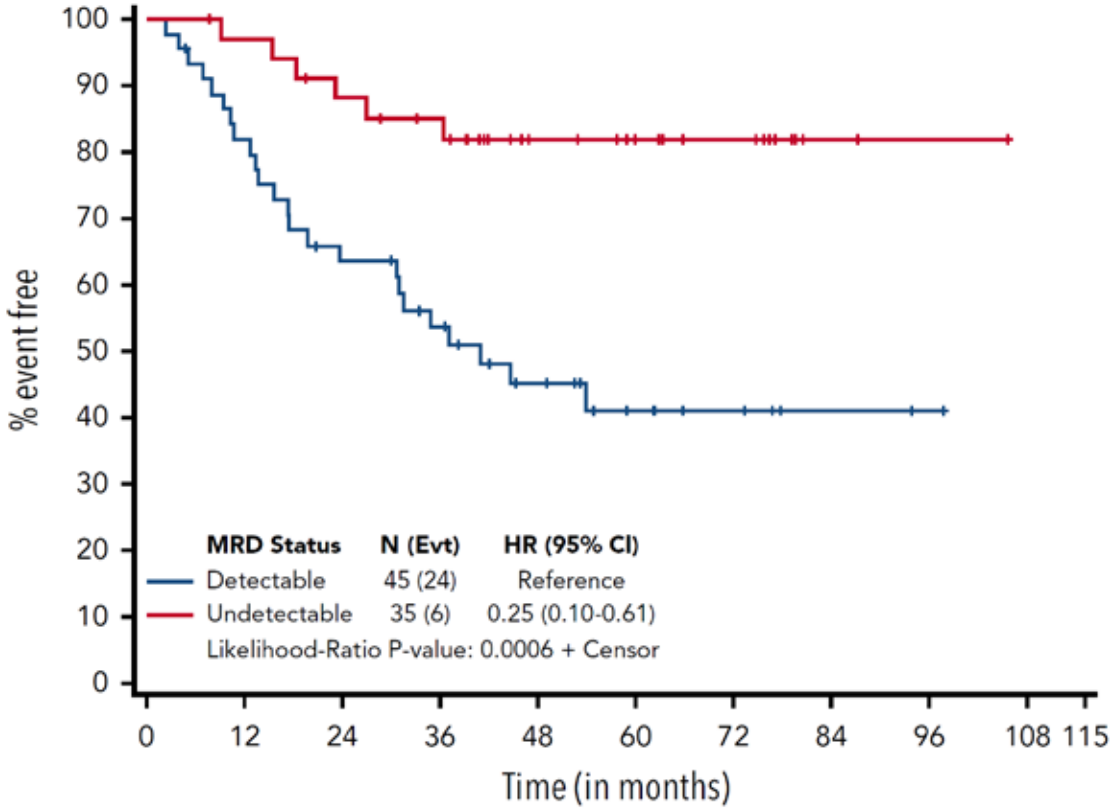
Stock, *et al*. *Blood*. 2008;112:1646-54.

Pediatric vs. Adult Therapy for ALL: Reasons for Different Outcomes

- Therapies are different
- Doctors are different
- Patients are different

EFS by MRD Status: C10403



- **Of 263 patient who achieved remission, only 20 (8%) underwent HCT in CR1 → reserve HCT for MRD+?**
- **Increased BMI associated with worse outcome**

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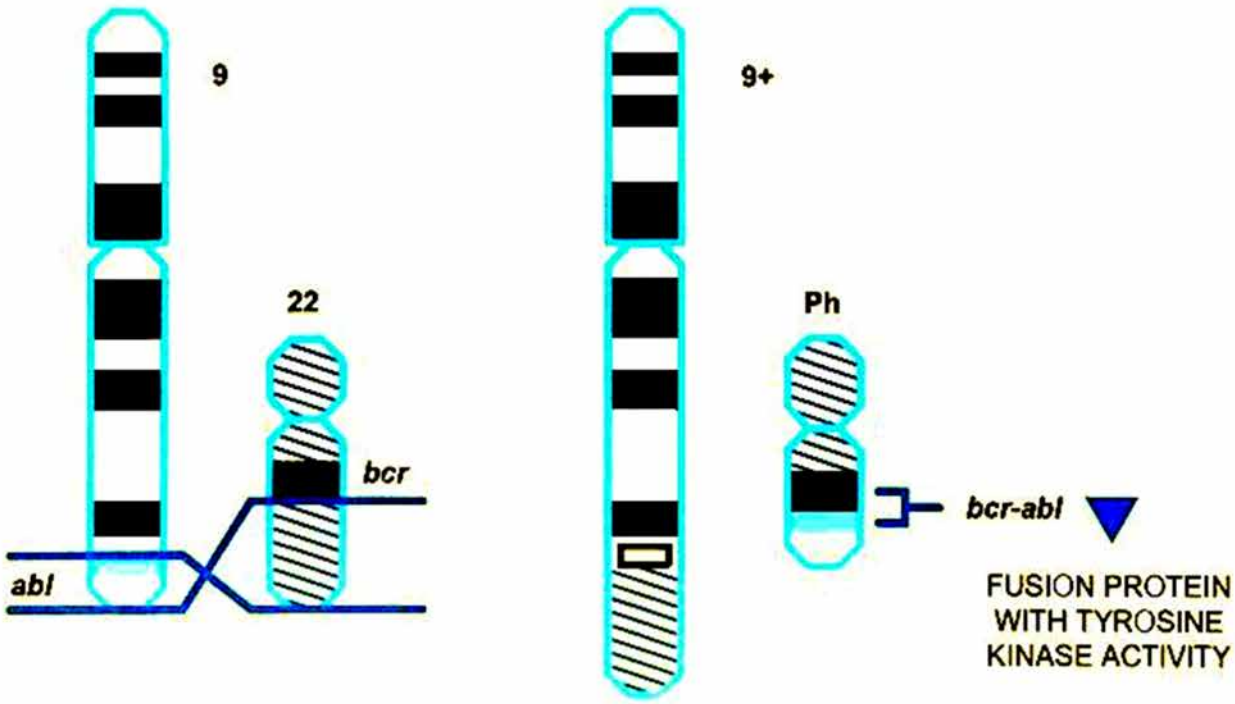
Stock, *et al. Blood.* 2019;133:1548-59.

Specific Scenarios:

Ph+ ALL

The Philadelphia Chromosome: t(9;22) Translocation



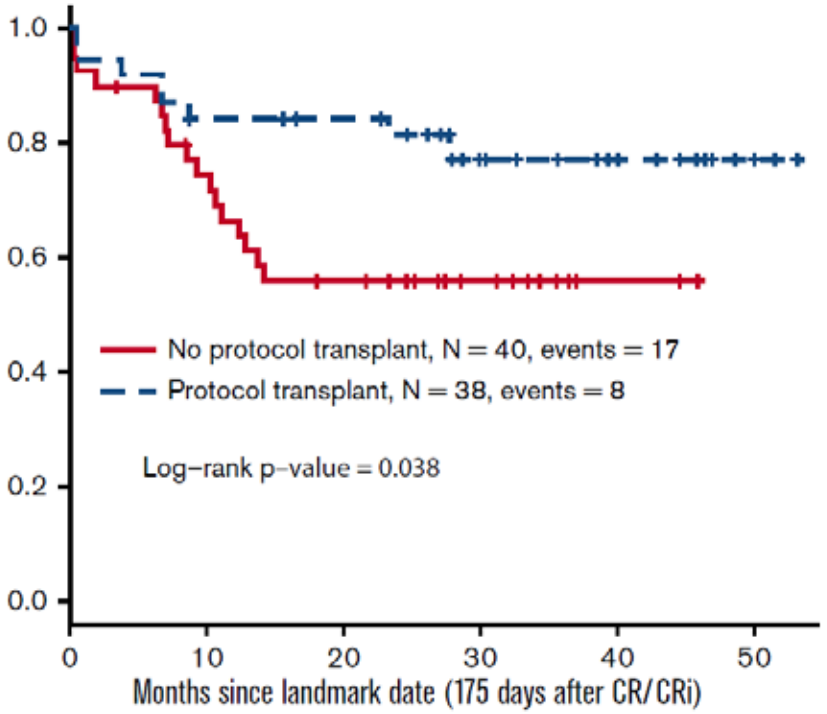
Management of Ph+ ALL: Summary

- The basics:
  - Include TKI with chemotherapy

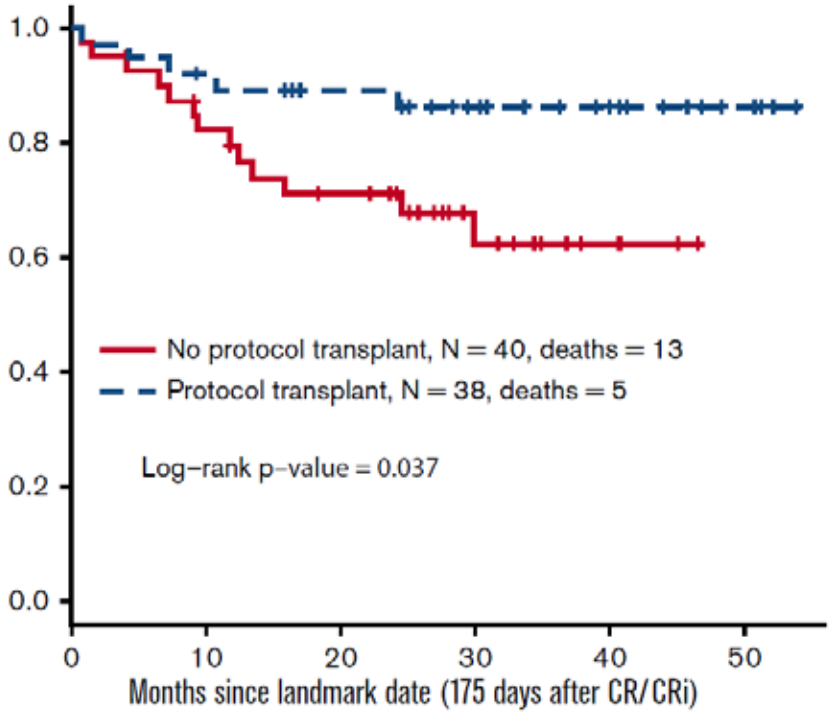
- Controversial topics:
  - Is one particular TKI superior?
  - How much chemo is necessary?
  - HCT in CR1 for all patients?

SWOG 0805: HyperCVAD + Dasatinib

Relapse-Free Survival



Overall Survival



- All patients with matched donor were “encouraged” to undergo allogeneic HCT followed by dasatinib maintenance
- If no HCT, dasatinib-based maintenance therapy

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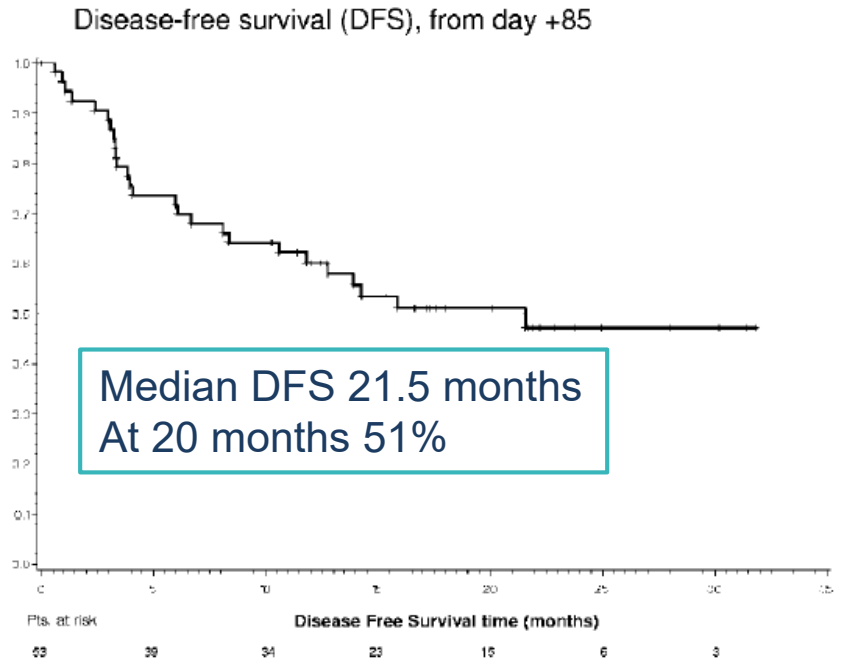
Ravandi, *et al*. *Blood Advances*. 2016;1:250-9.

Lower-Intensity Options: Likely Safer, but Less Effective?

GIMEMA LAL1205:

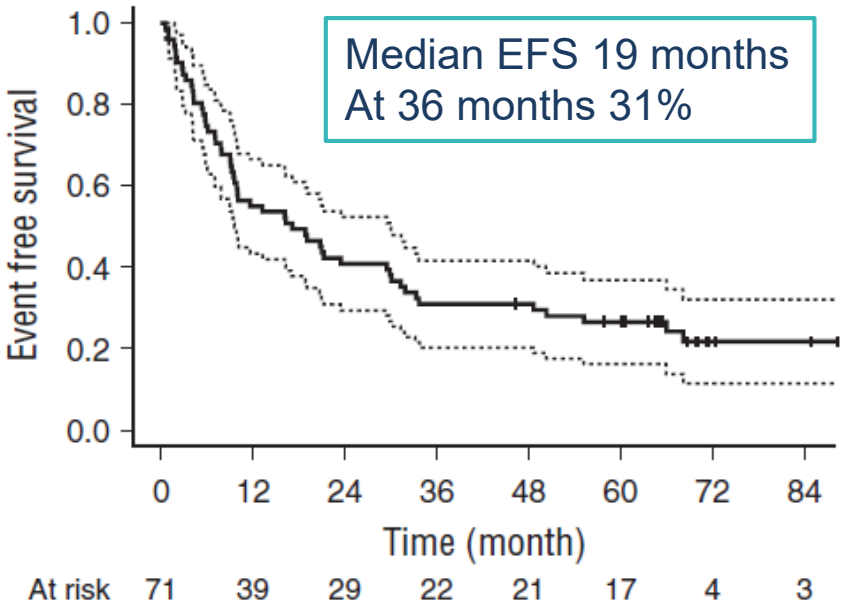
Dasatinib + Prednisone



Foa, *et al*. *Blood*. 2011;118:6521-8.

EWALL-PH-01:

Dasatinib + Low-Intensity Chemo



Rousselot, *et al*. *Blood*. 2016;128:774-82.

T315I mutations at relapse are COMMON

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Specific Scenarios:

ALL In The Elderly

Outcomes with Different Approaches for Older Patients with ALL

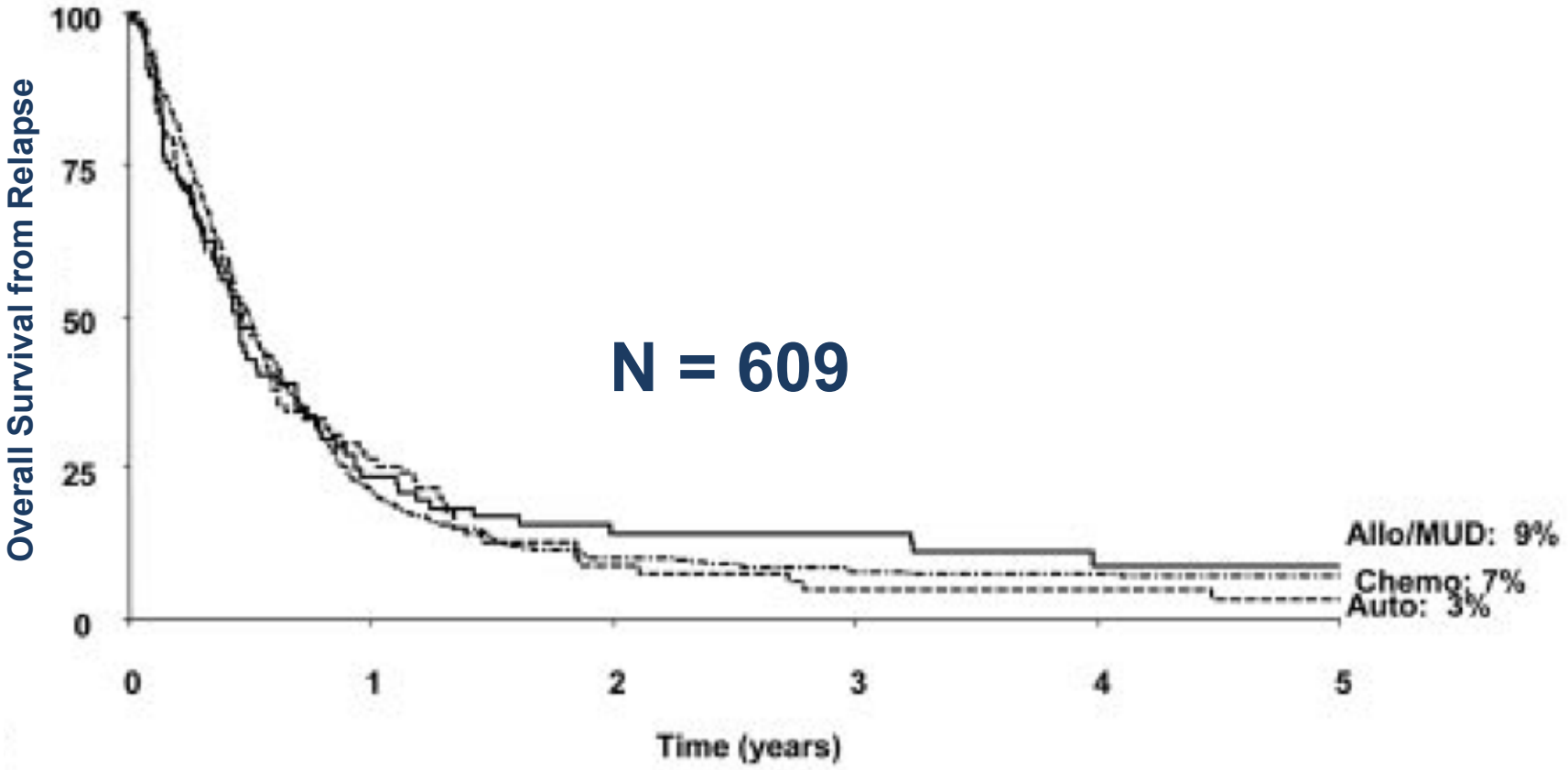
Approach	N	CR Rate	Early Death Rate	Survival (Median/2-yr)
Population-Based Studies	N/R	40%	N/R	6-30%
Palliative Treatment	94	43%	24%	7 mo
Intense chemotherapy designed for younger adults	519	56%	23%	14%
Prospective studies specifically for older adults	447	71%	15%	33%

Author's Conclusion: "Palliative, supportive treatment in acute leukemia does not, in general, reduce the risk of early death and does not improve quality of life compared to moderate intensive chemotherapy."

Reviewed by Gokbuget. *Blood*. 2013;122:1366-75.

Relapsed/Refractory ALL

Outcome of Relapsed ALL: UKALL XII/ECOG2993



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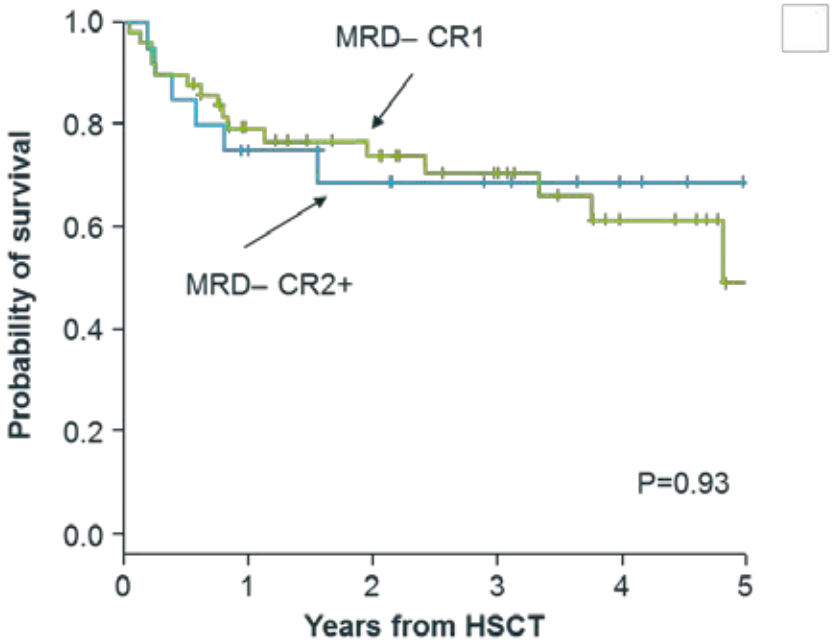
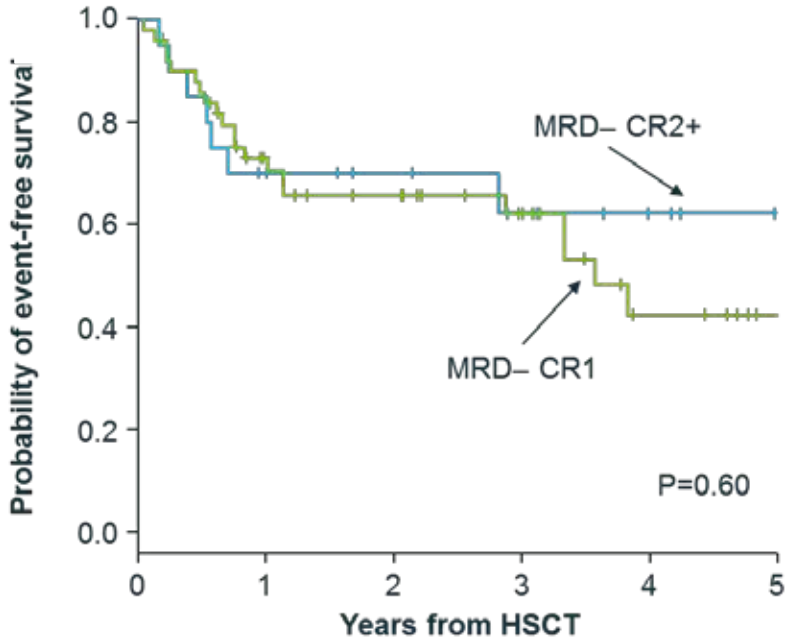
Fielding, *et al*. *Blood*. 2007;109:944-50.

HCT in MRD^{Neg} CR2+ Comparable to MRD^{Neg} CR1





Patients who achieve MRD^{Neg} CR1 are significantly more likely to achieve MRD^{Neg} CR2+ if they relapse.

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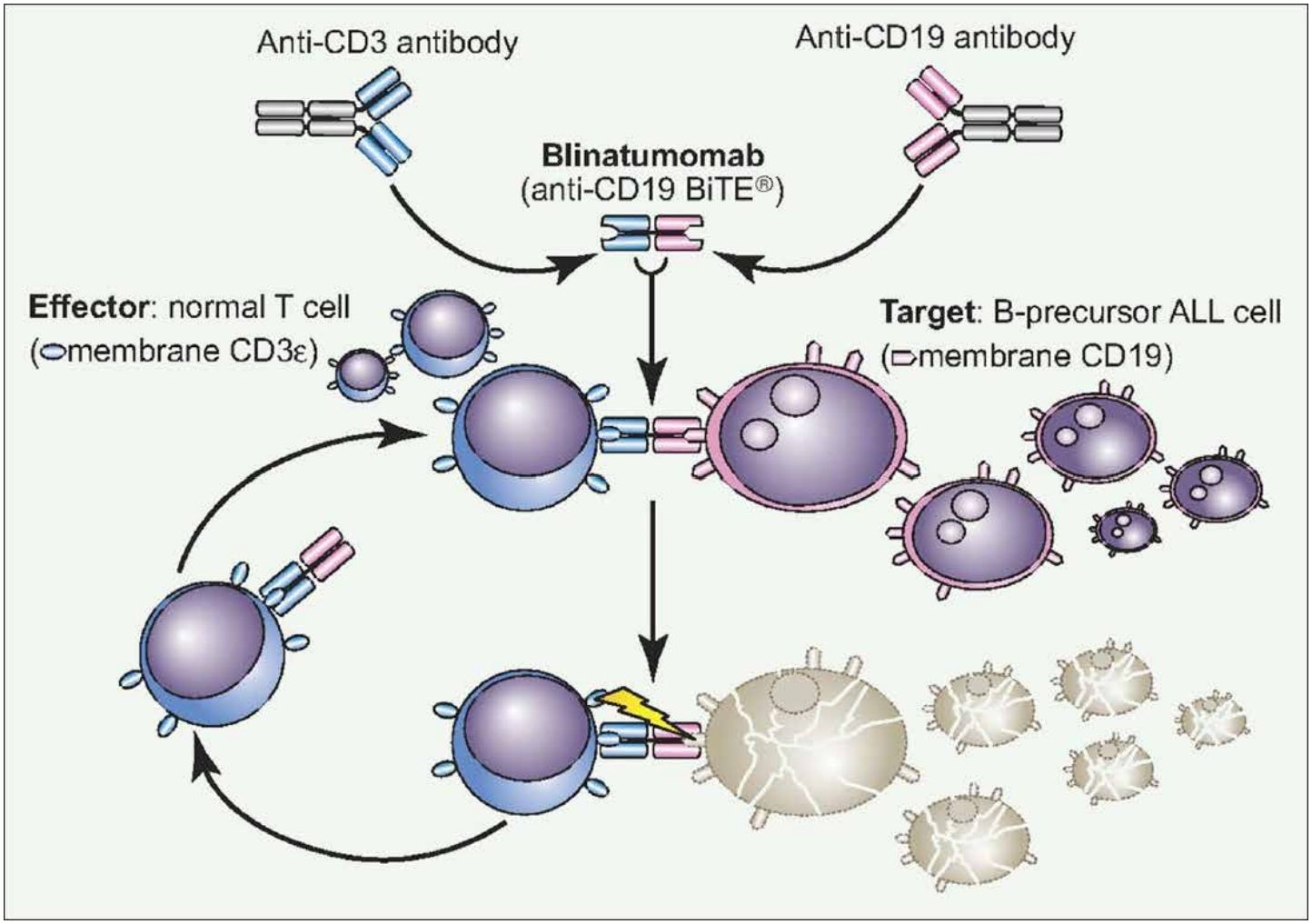
Revised from Cassaday, *et al*. *Leuk Lymphoma*. 2016;57:2109-118.

Options for Relapsed/Refractory ALL

- Purine analogues
  - Nelarabine (T-ALL)
  - Clofarabine (age ≤ 21; ≥ 2 prior therapies)
- Liposomal vincristine (≥ 2 prior therapies; Ph- only)
- *ABL* kinase inhibitors: ponatinib (Ph+ with T315I or no other option)
- CD3-CD19 BiTE: blinatumomab
- CD22 antibody-drug conjugate: inotuzumab ozogamicin
- CD19 CAR-T cells: tisagenlecleucel (age ≤ 25; refractory or ≥ 2nd relapse)

Blinatumomab = Bispecific T-Cell Engager



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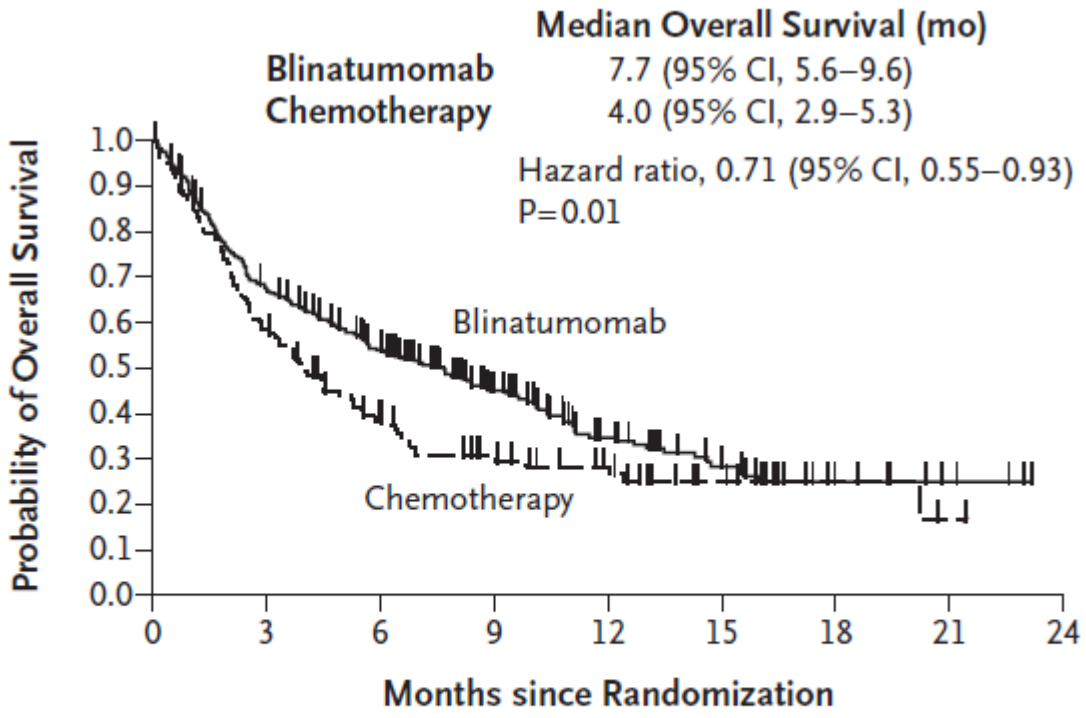
Kapoor, *et al. Clin Cancer Invest J.* 2014;3(6):577-8.

Blinatumomab for Rel/Ref B-ALL



- Given as 24-hr continuous infusion: 4 weeks on, 2 weeks off
- Side-Effects: neurologic toxicity, cytokine release syndrome

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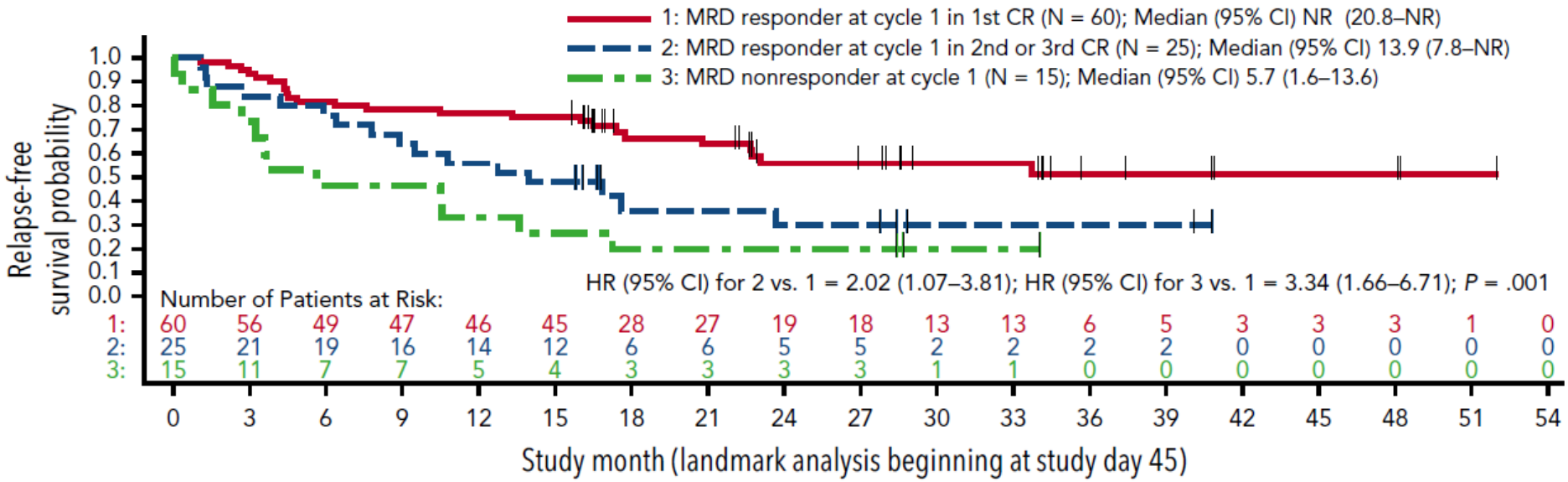
Kantarjian, *et al*. *New Engl J Med*. 2017;376:836-47.

Blinatumomab for MRD



- 78% achieve complete MRD response
- CRS and severe neurotoxicity are uncommon (~10%)
- If no HCT or chemo after response to blin, 25% in continuous CR (median f/u = 24 mo)

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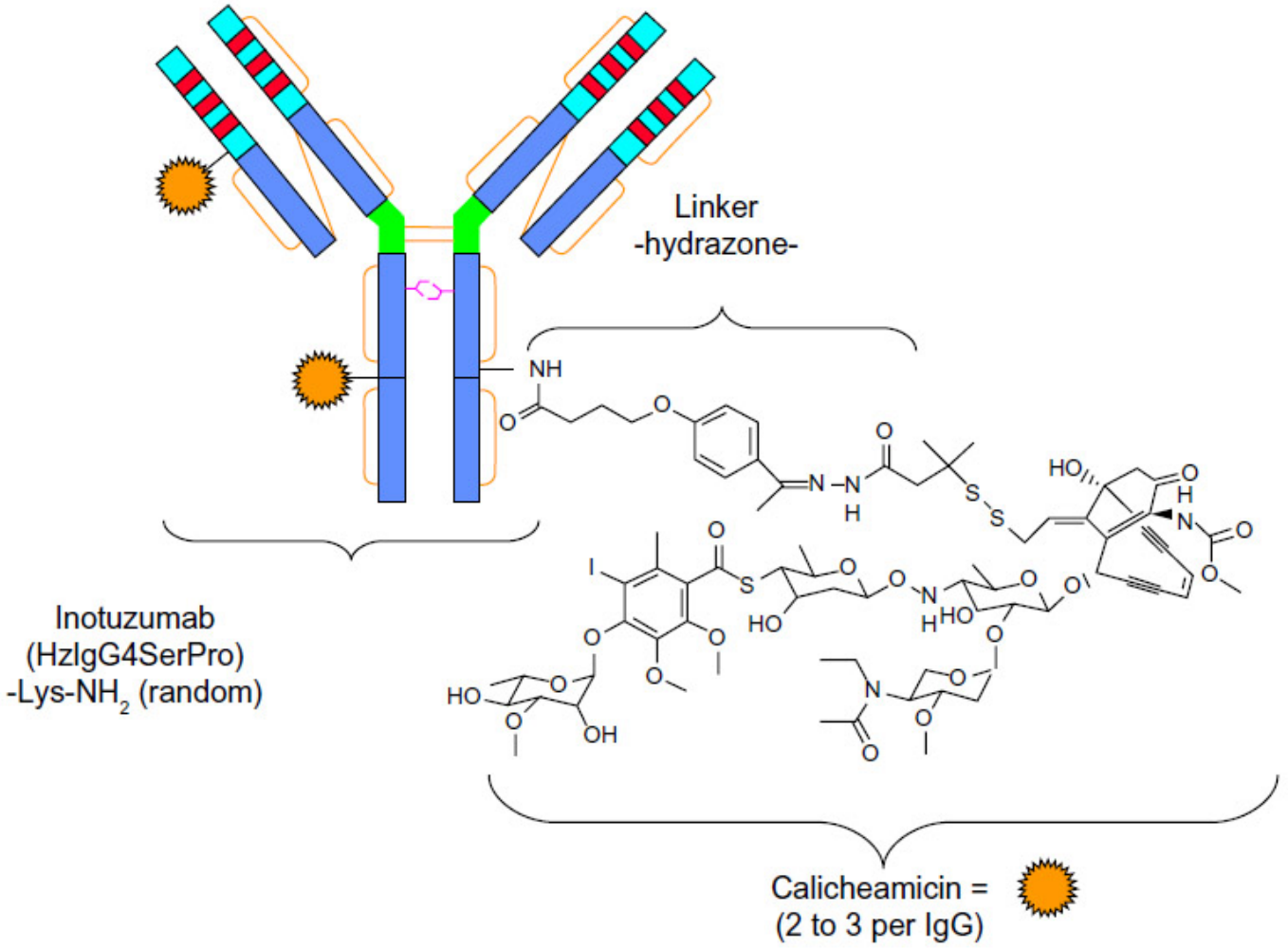
Gokbuget, *et al. Blood*. 2018;131:1522-31.

Inotuzumab Ozogamicin = Anti-CD22 ADC



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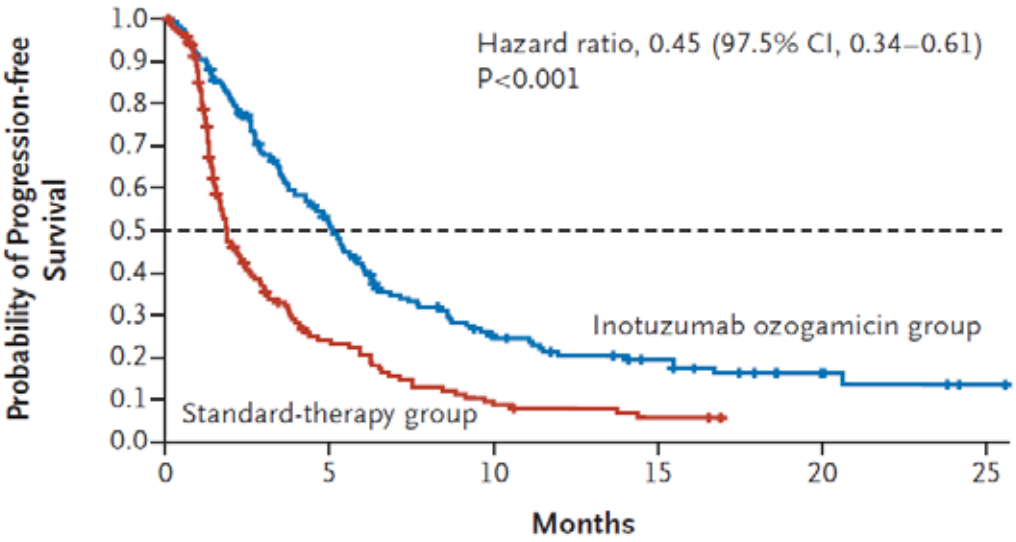
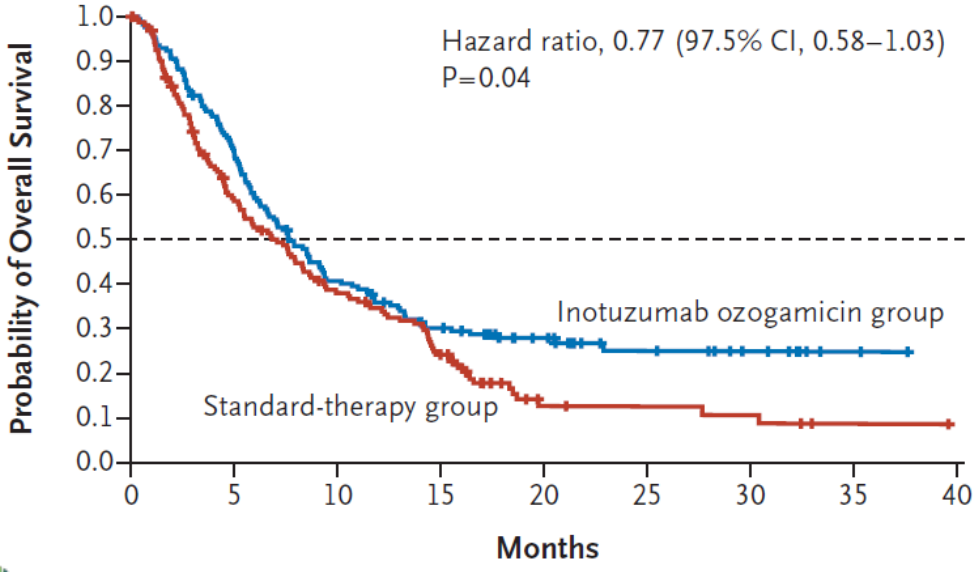
Thomas. *Blood Lymph Cancer: Targets and Therapy*. 2014;4:1-8.

Inotuzumab Ozogamicin for Rel/Ref B-ALL





- Dosing:
  - 1-hr IV infusion
  - Days 1, 8, &15
  - Every 21 (C1) to 28 (C2+) days
- Side effects:
  - SOS/VOD
  - Elevated ALT/AST
  - Cytopenias

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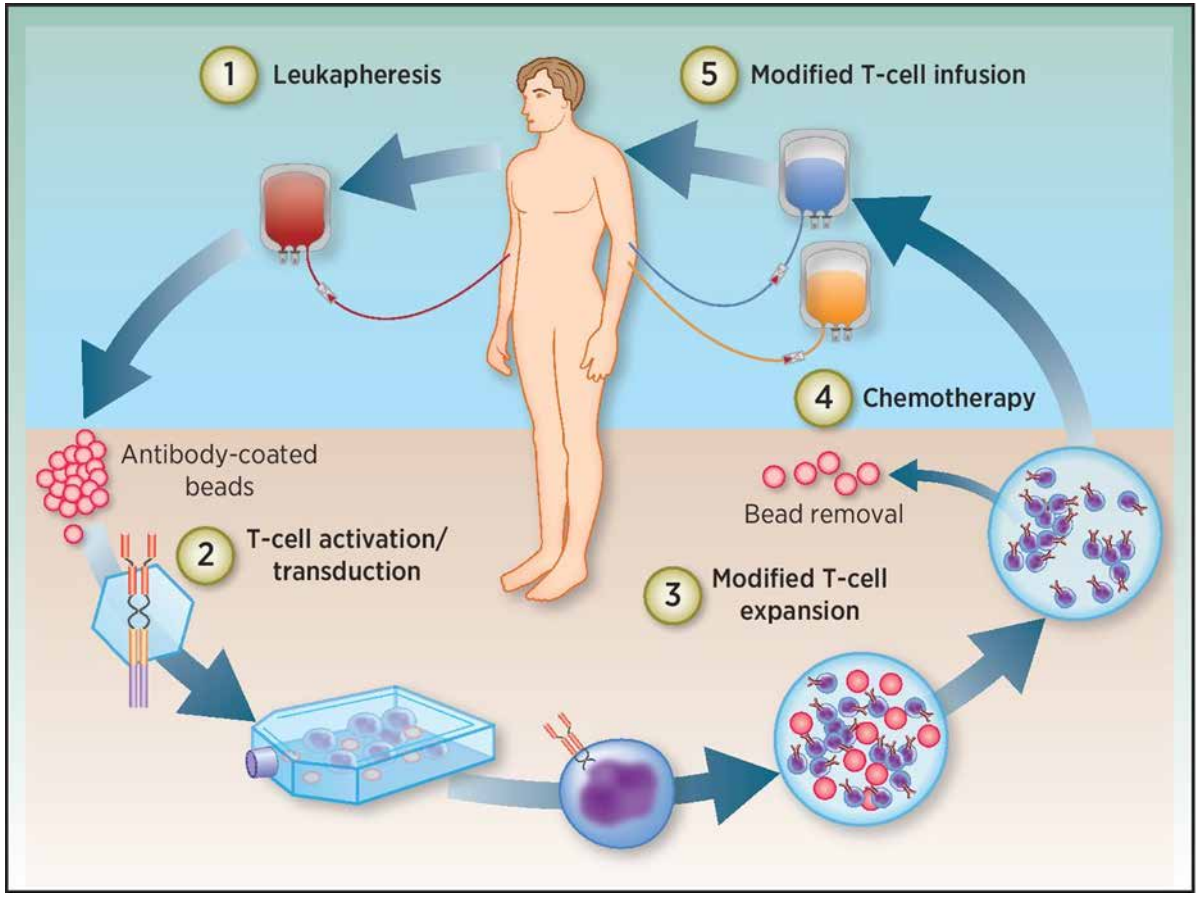
Kantarjian, *et al. New Engl J Med.* 2016;375:740-53.

Tisagenlecleucel = CD19 CAR-T Cells



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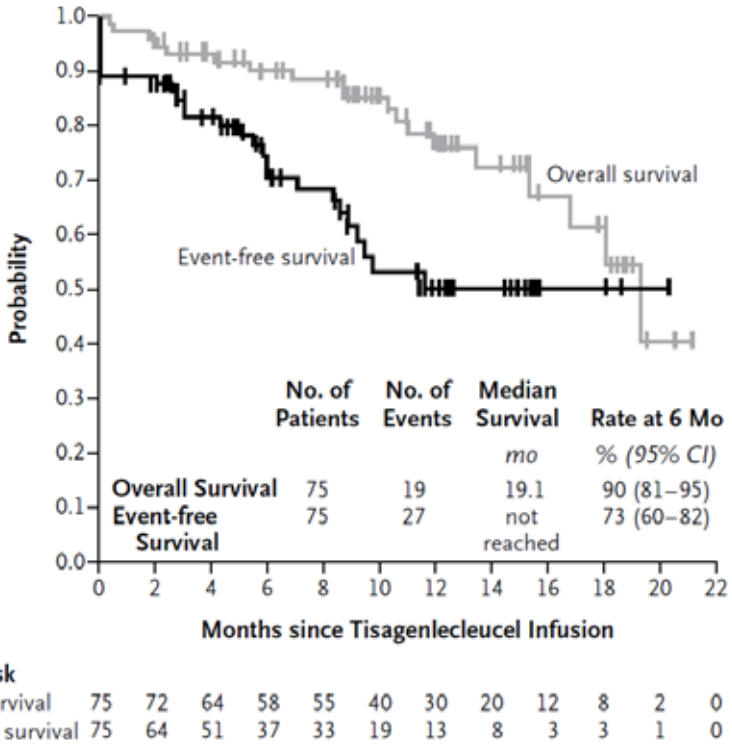
Maus & June. *Clin Cancer Res*. 2016;22(8):1875-84.

Tisagenlecleucel in Children and Young Adults with Rel/Ref B-ALL

- Multicenter, single-arm phase II trial (ELIANA)
- 107 pts screened → 92 enrolled → 75 treated
  - Median age = 11 yr
  - Median prior therapies = 3 (range: 1-8)
- CR/CRi rate within 3 mo:
  - Treated: 81% (all MRD^{Neg})
  - ITT: 66% (all MRD^{Neg})
- Toxicity:
  - 77% developed CRS
  - 47% admitted to ICU
  - 13% had Grade 3 neuro events
  - 19 deaths, 4 not due to relapse



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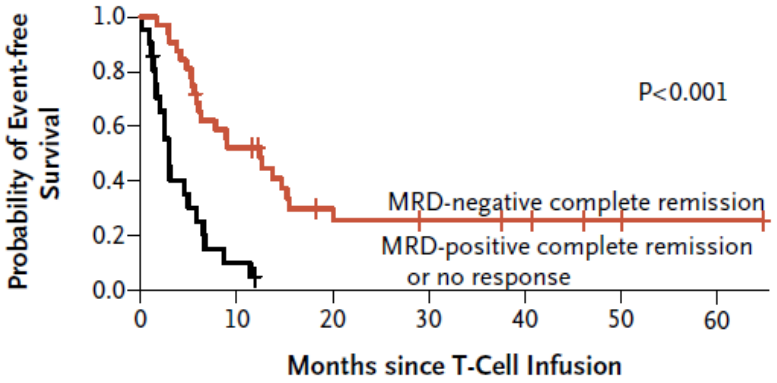
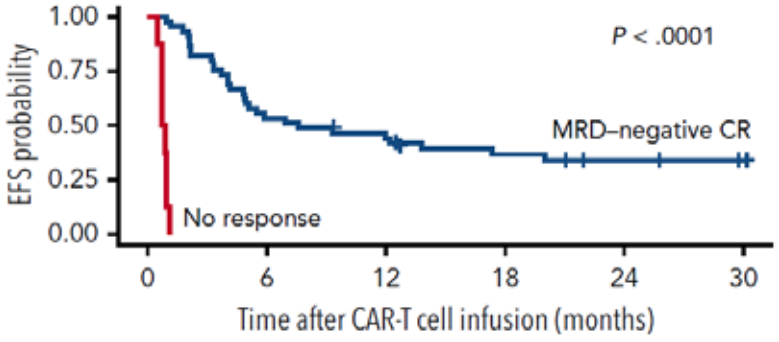
Maude, *et al. New Engl J Med.* 2018;378:439-48.

Long-Term Outcomes with CAR-T Cells in Adults with Rel/Ref B-ALL



Park, *et al. New Engl J Med.* 2018;378:449-59.



Hay, *et al. Blood.* 2019;133:1652-63

- Factors associated with better EFS:
  - Lower disease burden
  - Lower LDH
  - Higher platelet count
  - Use of fludarabine
- Role of HCT after CAR-T is controversial

ALL in Adults: Summary

- Disease risk primarily defined by WBC, cytogenetics, and response to therapy (MRD)
- Several standard options for front-line therapy
- Allogeneic HCT in CR1 reserved for high-risk patients—MRD may be best tool to determine this
- Single-agent options for relapsed/refractory disease:
  - B-ALL: inotuzumab ozogamicin, blinatumomab (including MRD), tisagenlecleucel
  - T-ALL: nelarabine
  - Ph+: ponatinib
  - Ph-: liposomal vincristine

THANK YOU

FRED HUTCH
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fredhutch.org

UNIVERSITY of WASHINGTON

Metastatic breast cancer

Natasha Hunter, MD

Aug 18, 2020

Disclosures

I have nothing to disclose.

Learning objectives

- To review the appropriate diagnostic workup for metastatic breast cancer (MBC)
- To review current guidelines for the treatment and monitoring of metastatic breast cancer
- To understand recent key developments in drugs to treat MBC

Lecture structure

- Case based
- NCCN-guideline focused
- Emphasis on standard therapies

Locally recurrent disease: Case 1

60 yo patient with a history of stage IIIA ER/PR positive, HER2 negative L breast cancer treated 6 years prior with neoadjuvant anthracycline-based chemotherapy, lumpectomy with sentinel lymph node biopsy (SLNB), radiation and 5 years of an aromatase inhibitor, presents with an expanding mass near her lumpectomy scar. Biopsy demonstrates invasive ductal carcinoma with similar histology to her prior tumor. Your next step is:

A) Mastectomy with (SLNB)
B) Mastectomy with axillary lymph node dissection (ALND)
C) Chemotherapy
D) A and C
E) B and C

Locally recurrent disease: Case 1

- Answer: B Mastectomy with ALND
  (Of note, actual real first step: Probably restaging)
- Patients with prior mastectomy should undergo surgical resection (if possible) and radiation to the chest wall and supraclavicular area (if the chest wall was not previously irradiated). Benefit of repeat SLN biopsy after mastectomy is unknown, not encouraged.
- Patients with prior breast-conserving surgery and radiation therapy with prior SLNB: NCCN panel consensus recommendation is mastectomy and level I/II axillary dissection.

Locally recurrent disease: Chemotherapy?

- CALOR trial: Studied effect of chemotherapy after complete resection in patients with isolated locoregional recurrence
- Adjuvant chemotherapy improved DFS and OS. Five-year OS 88% vs. 76%, *P* .024 in chemo vs non-chemo group.
- Benefit of adjuvant chemotherapy greater in hormone-receptor negative disease: DFS = 67% versus 35% versus in ER-positive disease, DFS 70% versus 69% (HR, 0.94; 95% CI, 0.47–1.89).

Aebi S, Gelber S, Anderson SJ, et al. Chemotherapy for isolated locoregional recurrence of breast cancer (CALOR): a randomised trial. Lancet Oncol 2014;15:156-163

Diagnosis and workup: Case 2

A 52 yo woman presents with a self-detected R breast lump. Diagnostic mammogram demonstrates a 4 cm R breast mass at 3:00, N+8. MRI shows 5.1 cm unifocal mass, and 3 suspicious-appearing axillary lymph node. Biopsy reveals grade 2 invasive lobular carcinoma, ER+ (95%), PR+ (75%), HER2 1+. She inquires about next steps. You advise:

A.) Neoadjuvant chemotherapy with ddAC/T

B.) Surgical resection with SLNB

C.) PET scan

D.) Biopsy to evaluate extent of disease

E.) CT C/A/P and bone scan

Diagnosis and workup: Staging scans

- Answer: E.
  NCCN guidelines: “For patients presenting with disease confined to the breast (stage I to II) the NCCN Panel does not recommend routine systemic imaging in the absence of signs or symptoms suspicious for metastatic disease. According to the panel, additional tests may be considered in patients who present with locally advanced (T3 N1-3 M0) disease and in those with signs or symptoms suspicious for metastatic disease.”

Diagnosis and workup: PET vs. CT/bone scan

- Why not a PET?
- The non-diagnostic CT scans used for PET under-evaluate the lungs and the liver compared with contrast-enhanced diagnostic CT scans.
- FDG PET/CT is optional, may be most helpful when other imaging is equivocal

Diagnosis and workup: Case 2, con't

The patient undergoes CT C/A/P and bone scan, which reveal multiple lesions in liver, the largest measuring 2 cm, and diffuse metastases to the spine and axial skeleton. The patient endorses lower back pain x 2 months which you suspect corresponds to an L3 lesion. She inquires about next steps. You advise:

A) Initiate treatment with a CDK 4/6 inhibitor and endocrine therapy
B) MRI spine w/ referral to radiation oncology for RT to L3
C) Liver biopsy
D) L3 biopsy

Diagnosis and workup: Biopsy

- Answer: C, Liver biopsy
- Metastatic disease should be biopsied at first presentation or at first recurrence in order to confirm the diagnosis and determine tumor histology and molecular profile.
- Soft tissue tumor biopsy preferred over bone sites as demineralization procedures degrade proteins and DNA needed for IHC, FISH and molecular assays.
- Retest ER, PR and HER2 status: Primary and metastatic sites can be discordant.

Diagnosis and workup: Markers

- Molecular/IHC markers for MBC (i.e., not standard for early stage) w/ clinical significance: PIK3CA, MSI (rare), NTRK, TMB, PDL1, possibly ERBB2, others (FGFR2, AKT)
- Genetic testing: Germline BRCA1/2 mutations should be assessed in all patients with recurrent or metastatic breast cancer as positive results have implications for therapy

Treatment: Case 2, con't

This patient's biopsy of her largest liver mass returns with the same histology as index tumor (ER/PR+, HER2-). Molecular analysis reveals a PIK3CA mutation. You advise:

A) Tamoxifen

B) CDK 4/6 inhibition plus endocrine therapy

C) Alpelisib plus fulvestrant

D) Capecitabine

Treatment: First line therapy for HR+ disease

- Answer: B, CDK4/6 inhibition plus endocrine therapy.
- Aromatase inhibitor in combination with CDK4/6 inhibition is a preferred first-line treatment.
- Trials of all three medications in this class have demonstrated improved PFS over AI alone: MONALEESA-2 and -7 (ribociclib), PALOMA-2 (palbociclib), MONARCH-3 (abemaciclib).
- Ribociclib has also shown an OS benefit
- Only MONALEESA 7 looked at premenopausal patients, but all these agents are given to young patients along with ovarian suppression or BSO.

Treatment for HR+ MBC: Similarities and differences within the CDK4/6 class

- All CDK 4/6 inhibitors exhibit hematologic toxicities (neutropenia, leukopenia), GI toxicities, elevated LFTs, increased risk of pulmonary embolism, prolonged QTc
- Ribociclib: Higher rate of QTc prolongation, administration requires cardiac monitoring
- Abemaciclib: higher incidence of both all-grade and Grade 3/4 gastrointestinal toxicities, may (?) have some blood/brain barrier penetration, and can be given as monotherapy.

Sammons SL et al, Curr Cancer Drug Targets. 2017 Sep; 17(7): 637–649.

Treatment for HR+ MBC: Other first-line therapies

- Fulvestrant monotherapy. (Improved time to progression was seen with fulvestrant compared to anastrazole, FIRST study)
- Fulvestrant + AI (mixed trial results, FACT and SoFEA)
- Fulvestrant + CDK4/6 inhibitor
- Monotherapy with endocrine agents

Ellis MJ, Llombart-Cussac A, Feltl D, et al. J Clin Oncol 2015;33:3781-3787.
Bergh J, Jonsson PE, Lidbrink EK, et al. J Clin Oncol. 2012;30:1919-1925
Johnston SR, Kilburn LS, Ellis P, et al. Lancet Oncol 2013;14:989-998.

Treatment: Case 2, con't

Nine months later, scans reveal that the patient's tumor has progressed, demonstrating enlarging mediastinal nodes and new bone metastases. As a next line of therapy you choose:

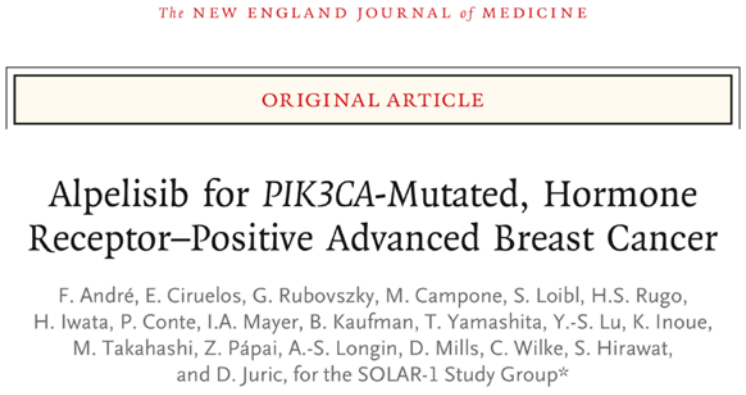
- Fulvestrant monotherapy
- Exemestane + everolimus
- Targeted therapy
- Any of the above

Treatment: Case 2, con't

- Answer: D, any of the above. Acceptable second line regimens for HR+ MBC include:
  - Fulvestrant monotherapy
  - Fulvestrant + CDK 4/6 inhibitor
  - Exemestane + everolimus (only approved FDA second line)
  - Targeted therapy when appropriate. In this patient, many would choose a targeted therapy given her PIK3CA mutation.

Second line therapy for HR+ MBC: Targeted agents

- *PIK3CA* mutations: ~40% of patients with hormone-receptor positive, HER2-negative breast cancer
- PFS=11.0 months in the alpelisib–fulvestrant group, vs 5.7 months in the placebo–fulvestrant group
- FDA approval: May 24, 2019, along with approval for companion diagnostic
- For ER/PR+ patients with advanced breast cancer following progression on or after endocrine-based treatment



Treatment: Case 3

45 year old woman with a history of stage IIIB ER/PR negative, HER2+ breast cancer presents with metastatic recurrence to liver and bone three years out from curative therapy. Liver biopsy reveals histology similar to her original tumor. Her performance status is ECOG 0-1. You recommend:

A) HER2 directed monotherapy
B) Taxane + trastuzumab
C) Taxane + trastuzumab and pertuzumab

Treatment: Case 3

- Answer: C, Taxane + trastuzumab and pertuzumab.
- CLEOPATRA: Compared efficacy and safety of docetaxel + trastuzumab and pertuzumab versus docetaxel versus docetaxel + trastuzumab as first-line treatment women with HER2-positive metastatic breast cancer. The addition of pertuzumab resulted in improvement in PFS (median, 18.5 versus 12.4 months. At 30 months: Statistically significant improvement in OS for pertuzumab-containing regimen.

Baselga J, Cortes J, Kim SB, et al. N Engl J Med 2012;366:109- 119.

Treatment for HER2+ MBC: Which taxane?

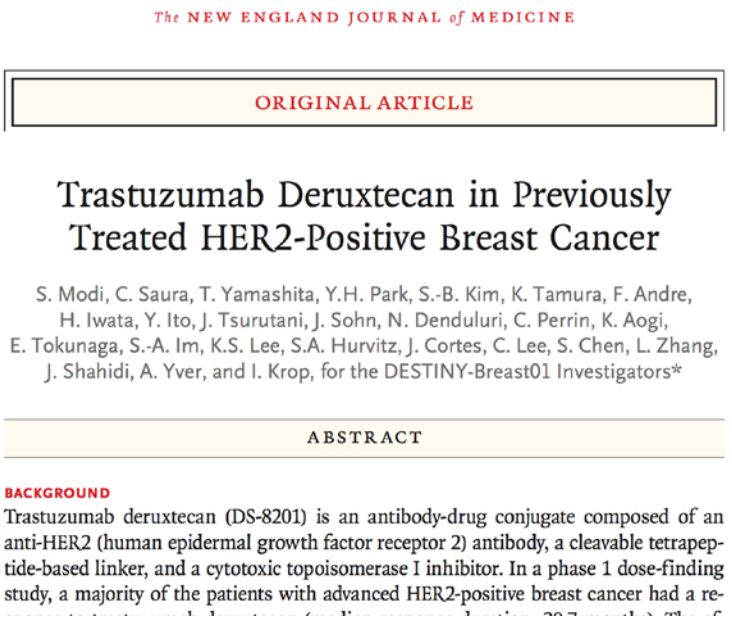
- PERUSE study: Patients with advanced HER2-positive breast cancer received docetaxel, paclitaxel or nab-paclitaxel with trastuzumab + pertuzumab: Median PFS comparable among agents. Paclitaxel demonstrated more neuropathy (31% vs. 16%) than docetaxel, but less febrile neutropenia (1% vs. 11%) and mucositis (14% vs. 25%).
- NCCN recommends a taxane plus pertuzumab and trastuzumab in first line: Docetaxel + HP is a category 1, paclitaxel + HP is a category 2A recommendation.

Treatment for HER2+ MBC: Other regimens

- TDM-1, a drug antibody conjugate, trastuzumab to the microtubule-inhibitory agent DM1 (first line, MARIANNE study, has activity in second line as well, EMILIA)
- Trastuzumab + paclitaxel +/- carboplatin, docetaxel, vinorelbine, capecitabine
- Lapatinib + capecitabine or trastuzumab
- HER2 directed agents + anthracycline and cyclophosphamide CONTRAINDICATED (27% rate of cardiac dysfunction)

Treatment for HER2+ MBC: New agents

- Patients with HER2 positive disease previously treated with trastuzumab, untreated or symptomatic brain metastases excluded
- Primary endpoint was overall response rate: 60.9% (95% CI, 53.4 to 68.0), of which 6.0% had a complete response. Disease control rate was 97.3% (95% CI, 93.8 to 99.1),



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Trastuzumab Deruxtecan in Previously Treated HER2-Positive Breast Cancer

S. Modi, C. Saura, T. Yamashita, Y.H. Park, S.-B. Kim, K. Tamura, F. Andre, H. Iwata, Y. Ito, J. Tsurutani, J. Sohn, N. Denduluri, C. Perrin, K. Aogi, E. Tokunaga, S.-A. Im, K.S. Lee, S.A. Hurvitz, J. Cortes, C. Lee, S. Chen, L. Zhang, J. Shahidi, A. Yver, and I. Krop, for the DESTINY-Breast01 Investigators*

ABSTRACT

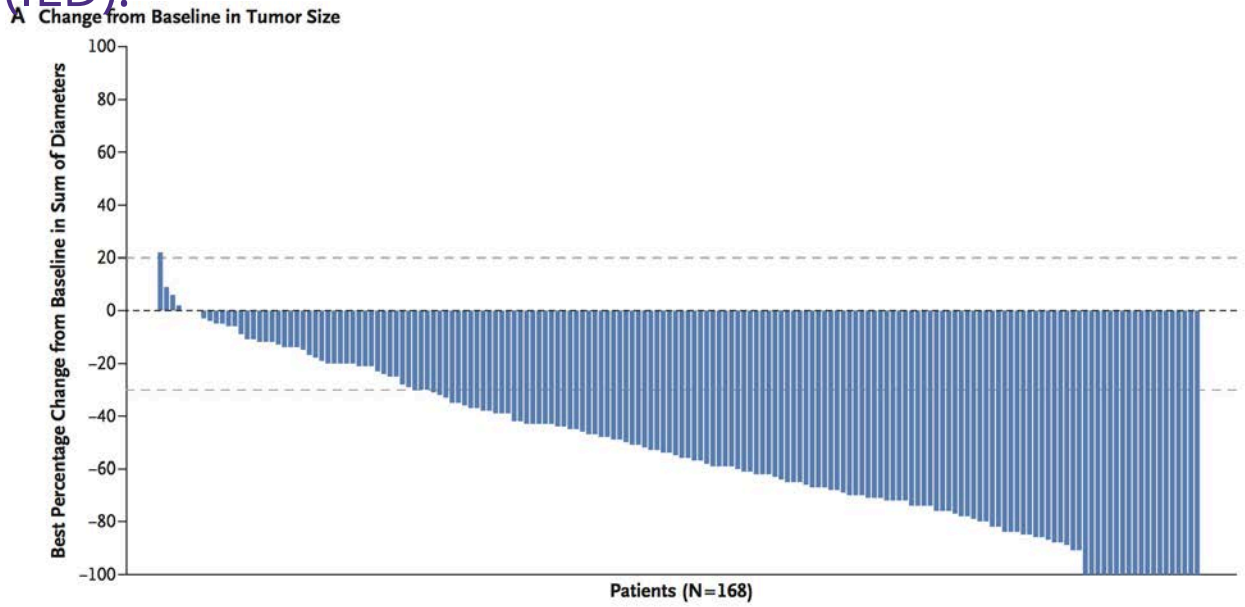
BACKGROUND

Trastuzumab deruxtecan (DS-8201) is an antibody-drug conjugate composed of an anti-HER2 (human epidermal growth factor receptor 2) antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor. In a phase 1 dose-finding study, a majority of the patients with advanced HER2-positive breast cancer had a re-

Modi S et al. N Engl J Med 2020;382:610-21.

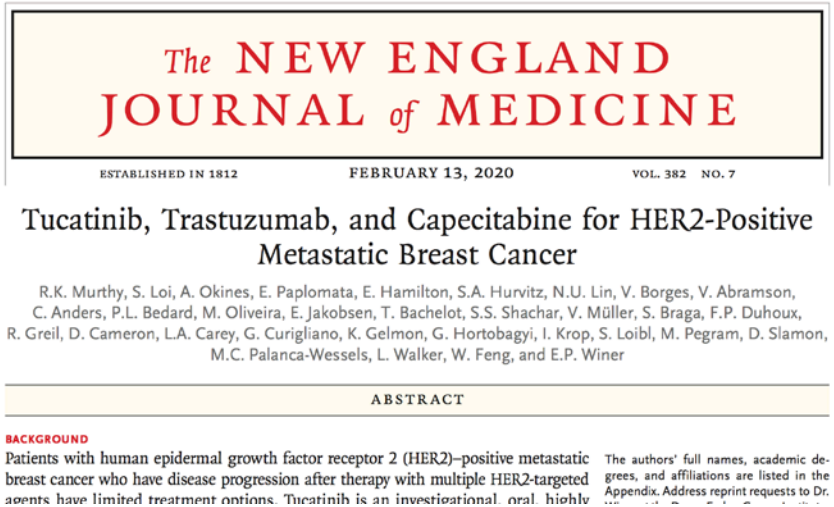
Treatment for HER2+ MBC: New agents

- FDA grants accelerated approval in Dec. 2019 for patients with HER2+ disease after two prior lines of therapy
- 13.6% of patients developed interstitial lung disease, leading to at least four deaths. Agent is contraindicated for patients with pneumonitis or interstitial lung disease (ILD).



Treatment for HER2+ MBC: New agents

- HER2CLIMB: Tucatinib + trastuzumab + capecitabine
- Patients with HER2+ disease with progression on two prior lines of therapy
- PFS for Tucatinib combo vs. placebo combo 7.8 vs. 5.6 months ($p<0.001$)
- FDA approval in April 2020 for use after ONE prior line of therapy



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 13, 2020 VOL. 382 NO. 7

Tucatinib, Trastuzumab, and Capecitabine for HER2-Positive Metastatic Breast Cancer

R.K. Murthy, S. Loi, A. Okines, E. Paplomata, E. Hamilton, S.A. Hurvitz, N.U. Lin, V. Borges, V. Abramson, C. Anders, P.L. Bedard, M. Oliveira, E. Jakobsen, T. Bachelot, S.S. Shachar, V. Müller, S. Braga, F.P. Duhoux, R. Greil, D. Cameron, L.A. Carey, G. Curigliano, K. Gelmon, G. Hortobagyi, I. Krop, S. Loibl, M. Pegram, D. Slamon, M.C. Palanca-Wessels, L. Walker, W. Feng, and E.P. Winer

ABSTRACT

BACKGROUND

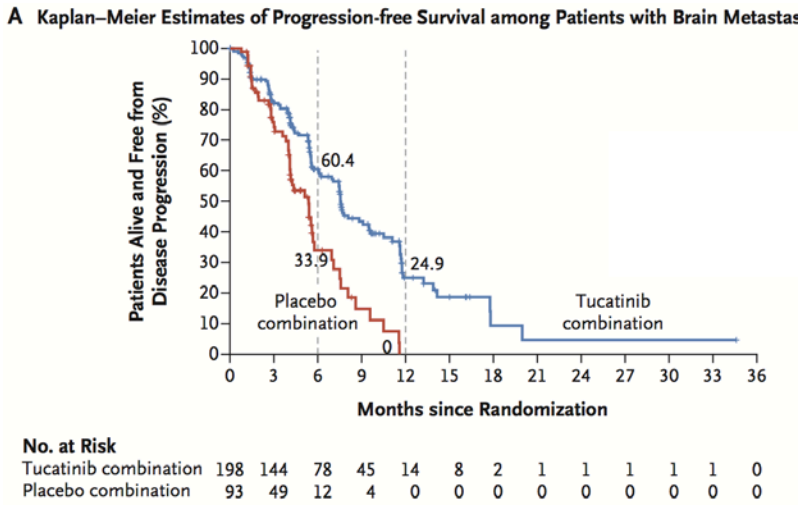
Patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer who have disease progression after therapy with multiple HER2-targeted agents have limited treatment options. Tucatinib is an investigational, oral, highly

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr.

Murthy et al. N Engl J Med 2020; 382:597-609

Treatment of HER2+ MBC: New agents

- Patients with brain metastases included unless in need of immediate treatment. Patients with untreated brain mets >2 cm enrolled with approval from the medical monitor. Patients with leptomeningeal disease were excluded.
- Risk of CNS progression reduced by 68% in patients with brain metastases, with a median CNS-PFS of 9.9 vs 4.2 months.



Murthy et al. N Engl J Med 2020; 382:597-609

Treatment for HER2+ MBC: What about HR+ disease?

- PERTAIN trial: Postmenopausal women assigned to first-line pertuzumab plus trastuzumab and an AI or trastuzumab plus an AI, with a ~3 month improvement in PFS for triplet combo
- If patient is treated initially with chemotherapy and trastuzumab plus pertuzumab, and the chemotherapy is stopped, endocrine therapy may be added.
- NCCN includes other trastuzumab combinations (e.g., fulvestrant or tamoxifen), but should be considered only after chemotherapy plus HER2-directed therapy or in some patients with indolent disease

Rimawi M et al. J Clin Oncol 2018;36:2826-2835.

Treatment: Case 4

A 58 year old woman with a large, clinically node positive breast tumor; biopsy demonstrates a high-grade invasive ductal carcinoma, ER/PR/HER2 negative. Aside from moderate axillary pain, she is asymptomatic. What will be the most important factor in choosing her first therapy?

A) Mutations on molecular testing
B) Additional immumohistochemistry testing
C) Presence of visceral disease
D) Brain MRI results

Treatment for mTNBC: Immunotherapy

- Answer: B, Additional immumohistochemistry testing (i.e., PDL1)
- IMpassion 130: Patients with treatment-naïve TNBC randomized to atezolizumab plus nab-paclitaxel vs. placebo plus nab-paclitaxel.
- At a median follow-up of 12.9 months, PFS was 7.2 vs. 5.5 months for treatment arm vs. placebo, also a trend towards better OS (not significant).

Schmid P et al. N Engl J Med 2018; 379:2108-2121

Treatment for mTNBC: Immunotherapy

- In patients with PD-L1-expressing tumors, PFS was 7.5 vs. 5 months and and OS (25 vs. 15.5 months; HR 0.62, 95% CI 0.45-0.86).
- In March 2019 FDA grants accelerated approval for atezolizumab + nab-paclitaxel in the first line for patients with PD-L1 expressing tumors; also approves the VENTANA PD-L1 Assay as the companion diagnostic for identifying PD-L1 expression.

Schmid P et al. N Engl J Med 2018; 379:2108-2121

Treatment for mTNBC: Chemotherapeutic agents

- Taxanes (paclitaxel), anthracyclines (doxorubicin and liposomal doxorubicin), anti-metabolites (capecitabine and gemcitabine), microtubule inhibitors (eribulin and vinorelbine), platinum agents
- Single agent chemotherapy → Lower response rates and time to progression, but multi-agent chemo → more toxicity and no overall survival benefit.

Treatment for mTNBC: Case 5

A 46 yo woman with a BRCA1 mutation transfers care to you. She has breast cancer metastatic to her lungs, pleura, liver, and mediastinum, ER/PR/HER2 neg. Her disease has progressed on paclitaxel. PDL1 is negative. She feels well, has few symptoms, is still working. What do you recommend next?

A) Capecitabine

B) Olaparib

C) Ixabepilone

D) Atezolizumab + nab paclitaxel

Treatment for mTNBC: BRCA mutations

- OlympiAD trial (NEJM 2017): Among patients with HER2-negative metastatic breast cancer and a germline *BRCA* mutation, olaparib monotherapy provided a significant benefit over standard therapy; median progression-free survival was 2.8 months longer and the risk of disease progression or death was 42% lower with olaparib monotherapy than with standard therapy.
- FDA has approved olaparib in advanced breast, ovarian, fallopian tube, peritoneal, and pancreatic cancer for patients with germline BRCA mutations.
- Other PARPi w/ FDA approval: rucaparib, talazoparib, niraparib (not yet approved for brea

Robson M et al. N Engl J Med 2017; 377:523-533

Treatment: Bone metastases

- In metastatic bone disease, bisphosphonate treatment is associated with fewer skeletal-related events (SREs), fewer pathologic fractures, and lower need for radiation and surgery to treat pain.
- No impact on OS
- Dosing can be Q4 vs Q12 weeks w/ no significant difference in SREs in multiple trials. Reminder: Q6 months is nonmetastatic dosing for osteoporosis.

Treatment: Role for surgery and radiation

- Multiple studies demonstrating no survival advantage for resection of breast tumor in setting of metastatic disease (exception: Turkish Federation MF07-01 trial, but groups were arguably not well balanced)
- Palliative role for surgery in case of painful breast tumors, impending fractures.
- Palliative role for radiation in pain control, stabilization of bone tumors, treatment of CNS disease

Surveillance: Principles of monitoring MBC

- Monitoring includes periodic assessment of symptoms, physical exam, lab tests, imaging, and blood biomarkers
- Same imaging modality should be used consistently to allow “apples to apples” monitoring
- Optimal frequency of testing is uncertain
- Frequency of monitoring can be reduced in patients who have long-term stable disease.

Thanks!

Management of Multiple Myeloma: Board Review

Andrew Cowan, MD
Assistant Prof. of Medicine
Div. Of Medical Oncology
University of Washington, SCCA, and FHCRC

Disclosures

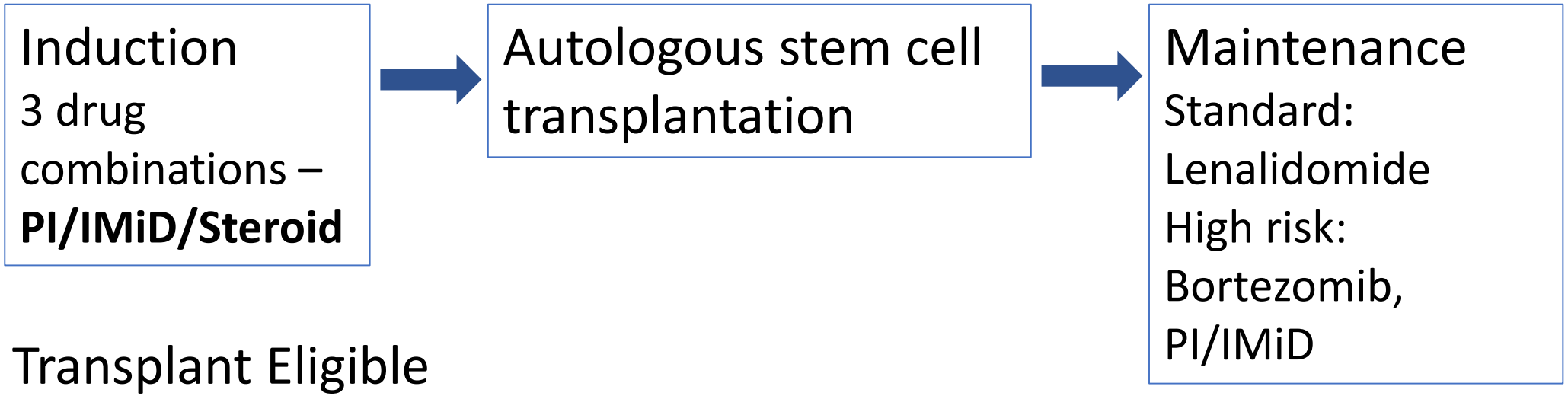
- Research Funding: Janssen, AbbVie, Bristol Myers Squibb
- Consultancy: Janssen, Celgene, Cellectar, Sanofi

Goals

- Review risk stratification for multiple myeloma
- Review treatment strategies for transplant eligible multiple myeloma
- Review treatment strategies for transplant-ineligible multiple myeloma
- Discuss treatment of relapsed/refractory multiple myeloma

What is the current best practice for treatment?

Transplant Eligible



Not Transplant Eligible

Supportive Care

Risk stratification in multiple myeloma

- Disease burden – beta 2 microglobulin, LDH
- Tumor-specific factors – circulating plasma cells (extreme example is plasma cell leukemia)
- Genetic factors - chromosomal abnormalities

Revised-International Staging System for Myeloma

ISS or R-ISS Stage	ISS Criteria	R-ISS Criteria
I	Serum beta-2 microglobulin < 3.5 mg/L, serum albumin ≥ 3.5 g/dL	ISS Stage I AND standard risk CA by iFISH and normal LDH
II	Not ISS stage I or III	Not R-ISS stage I or III
III	Serum beta-2 microglobulin ≥ 5.5 mg/L	ISS Stage III AND either high-risk CA by iFISH or high LDH

Palumbo et al, JCO 2015

Incidence of chromosomal abnormalities in multiple myeloma

Genomic aberration	Incidence, % (no. of patients analyzed for the aberration)
del(13)	48 (936)
t(11;14)(q13;q32)	21 (746)
t(4;14)(p16;q32)	14 (716)
Hyperdiploidy	39 (657)
MYC translocations	13 (571)
del(17p)	11 (532)

Avet-Loiseau et al, Blood 2007

What does “high-risk” myeloma mean?

- Outcomes for many patients with myeloma are improving
- However, a subset of patients (20-25%) with certain biologic, genetic, and excess disease burden have poorer outcomes, even with novel agents and new therapies
- New strategies to identify and offer more effective treatments for these patients are needed

Current conception of high risk myeloma by the IWMG and others

- IMWG: Revised ISS definition of high-risk
  - ISS Stage III (Elevated Beta-2 Microglobulin (> 5.5 mg/L))
  - **AND**
    - 1. High risk Chromosomal abnormalities:
      - Deletion 17p
      - t(4;14), t(14;16)
  - **OR**
    - 2. Serum LDH > upper limit of normal
- Circulating tumor cells (plasma cells – extreme case is plasma cell leukemia)
- Gene expression profiling
- Complex karyotypes
- Other chromosomal changes: 1p deletion or 1q amplification on FISH; t(14;20) translocation on FISH
- Extramedullary disease
- Plasmablastic morphology

WJ Chang et al Leukemia 2014

High Risk Chromosomal Changes

- IgH translocations – 40% of cases (chr 14)
  - t(4;14): 4p16 – *FGFR3* – deregulation of fibroblast growth factor
  - t(14;16): 16q23 – *MAF* – deregulation of *c-MAF* proto-oncogene
  - t(14;20): 20q11 – *MAFB* – deregulation of *MAFB* oncogene

- Del(17p) – *p53* – clonal immortalization, resistance to apoptosis

- 1q amplification – *CKS1B* – activation of cyclin dependent kinase → deregulation of cell cycle control

Sonneveld et al Blood 2016

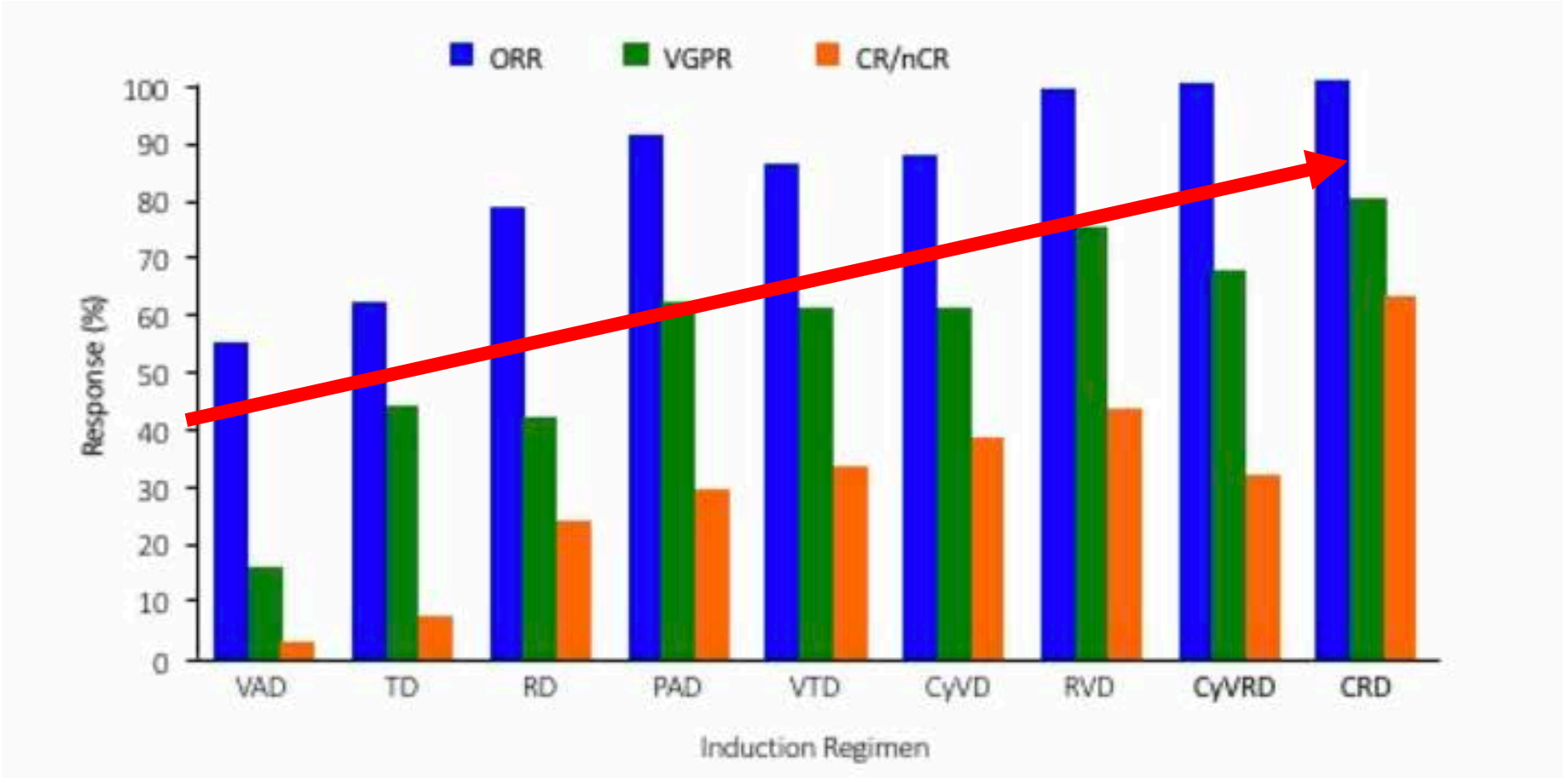
What is the preferred upfront treatment approach?

- Induction with IMID/PI 3 drug combination, followed by autologous stem cell transplantation (Attal, NEJM 2017)
- On the horizon: 4 drug induction including a monoclonal antibody – CASSIOPEIA – Dara-VTD, and GRIFFIN - DaraRVD
- Maintenance therapy with IMID post transplant, for standard risk (McCarthy JCO 2017)
- Maintenance therapy with PI post transplant for high-risk cytogenetics (Del(17p) and t(4;14) (HOVON-65)
- Intravenous bisphosphonates (MRC IX trial)

Multiple Myeloma Approved Drugs

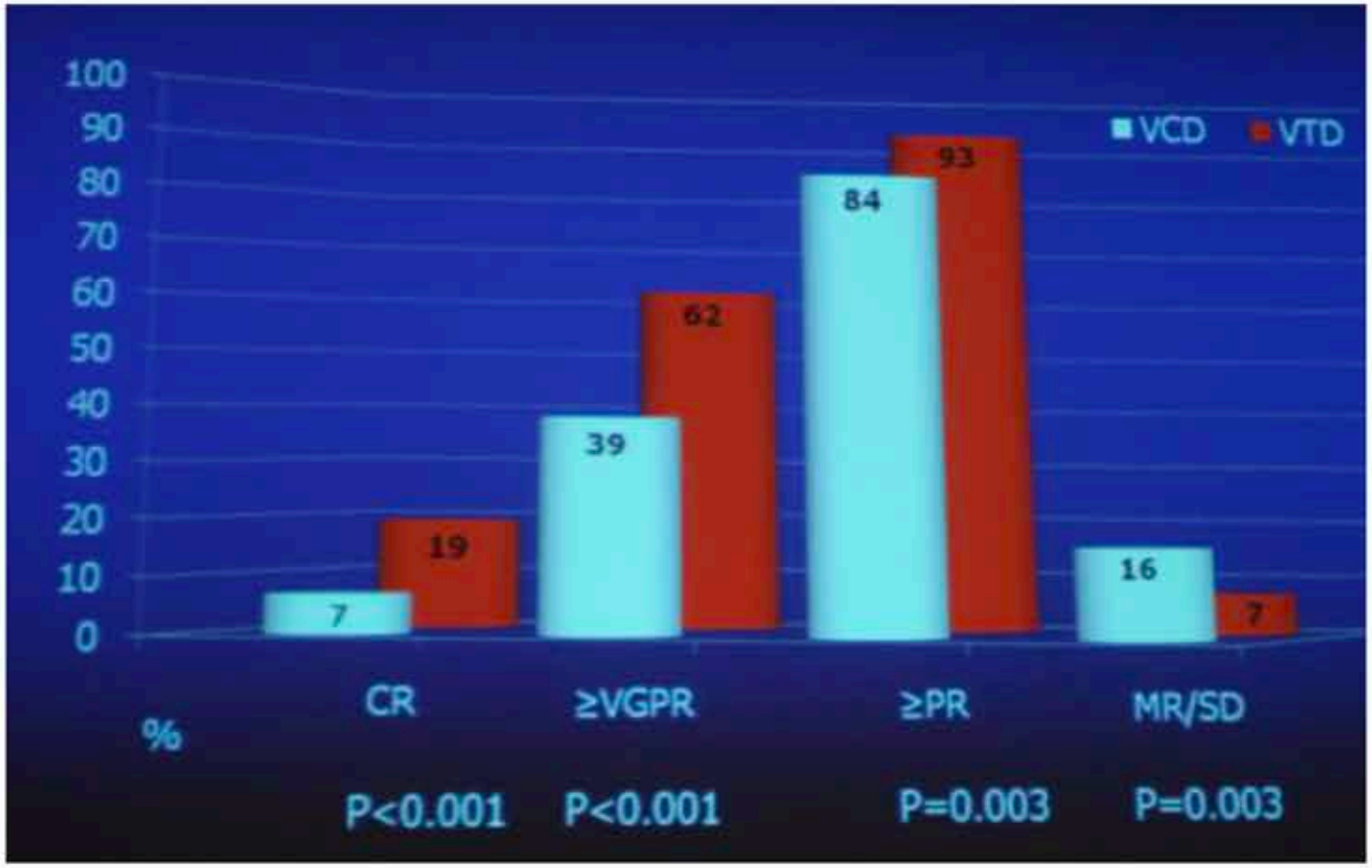
- Proteasome inhibitors
  - Bortezomib
  - Carfilzomib
  - Ixazomib
- Immunomodulatory agents
  - Lenalidomide
  - Pomalidomide
  - Thalidomide
- Selective Inhibitors of Nuclear Export (SINE)
  - Selinexor
- Monoclonal antibodies
  - Daratumumab (CD38)
  - Isatuximab (CD38)
  - Elotuzumab (SLAMF7)
- Alkylating agents
  - Melphalan
  - Cyclophosphamide
  - Bendamustine
- HDAC Inhibitors
  - Panobinostat

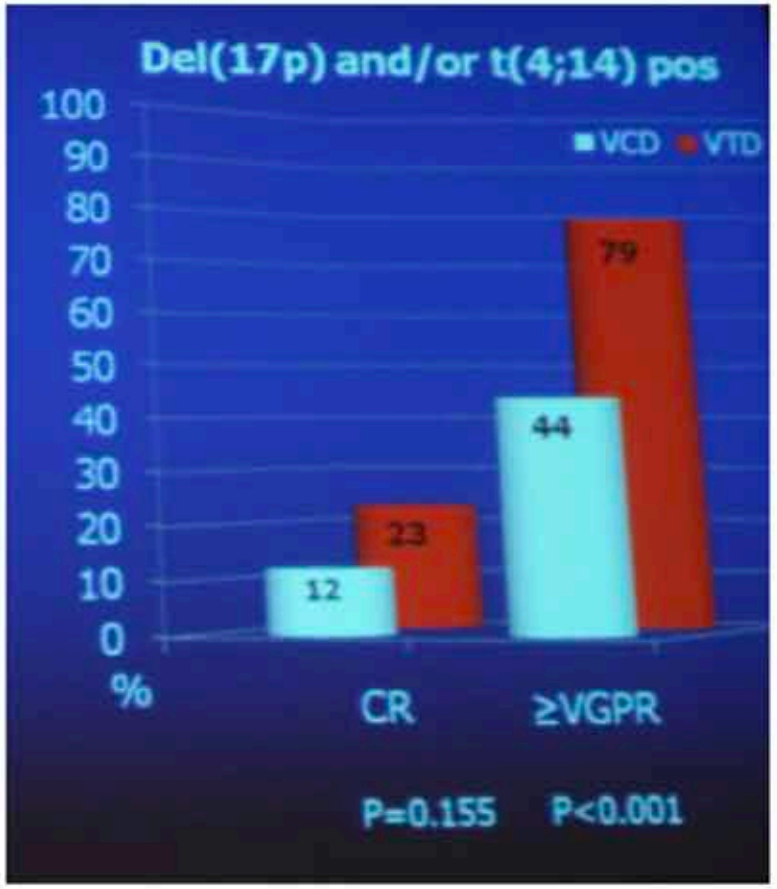
The overall, more than VGPR and nCR/CR rates for a selection of phase 2 and phase 3 trials incorporating novel agents.



A. Keith Stewart et al. Blood 2009;114:5436-5443;
Jakubowiak et al, Blood 2012

Does it matter which 3 drugs are used?





Cavo M et al, ASH 2014

IMID/PI Combination most effective

Table 1. Response to VTD and VCD induction therapy

All patients	*VTD (n = 236)*	*VCD (n = 236)*	P
Complete response	44 (19%; 14–24)	13 (6%; 3–8)	< 0.001
Very good partial response or better	151 (64%; 58–70)	87 (37%; 31–43)	< 0.001
Partial response or better	220 (93%; 90–96)	192 (81%; 76–86)	< 0.001
Stable disease	16 (7%; 4–10)	38 (16%; 11–21)	0.001
Progressive disease	0 (0%)	6 (3%; 1–5)	0.015
Patients with ISS 2-3	*VTD (n = 129)*	*VCD (n = 129)*	
Complete response	26 (20%; 13–27)	5 (4%; 1–7)	< 0.001
Very good partial response or better	86 (67%; 59–75)	45 (35%; 27–43)	< 0.001
Patients with t(4;14) and/or del(17p)	*VTD (n = 53)*	*VCD (n = 53)*	
Complete response	12 (23%; 11–34)	4 (8%; 0–15)	0.030
Very good partial response or better	44 (83%; 73–93)	25 (47%; 34–61)	< 0.001

Abbreviations: ISS, international staging system; VCD, bortezomib with cyclophosphamide plus dexamethasone; VTD, bortezomib with thalidomide plus dexamethasone. Data are number of patients (%; 95% CI). Comparisons were performed by χ^2 test or Fisher's test, as appropriate.

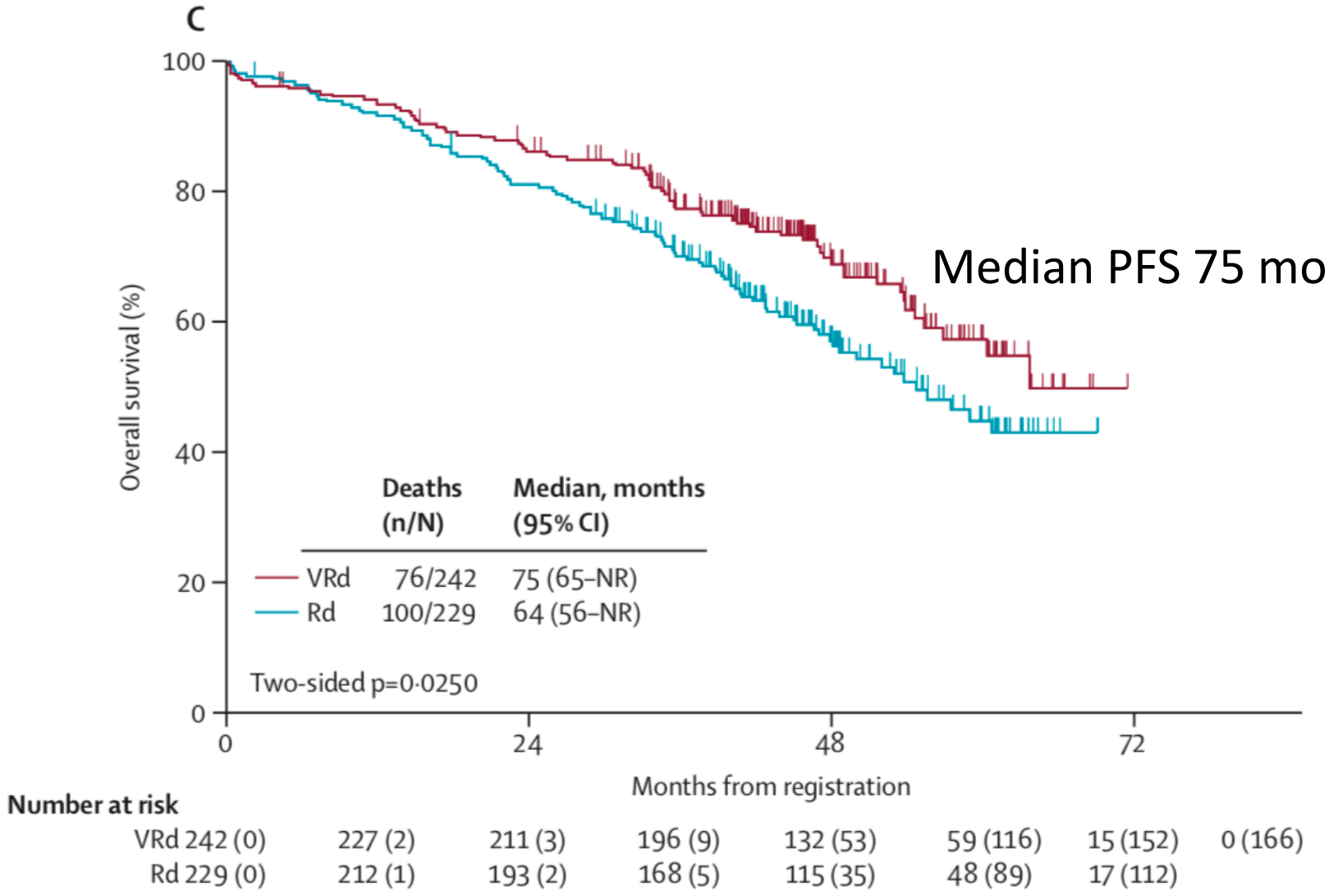
Cavo et al, Leukemia 2016

Triple drug induction is superior to doublet

	Patients given bortezomib with lenalidomide and dexamethasone (VRd group; n=216)*	**Patients given lenalidomide and dexamethasone (Rd group; n=214)***
Confirmed response	34 (15·7%)	18 (8·4%)
Very good partial response	60 (27·8%)	50 (23·4%)
Partial response	82 (38%)	85 (39·7%)
Overall response rate (partial response or better)	**176 (81·5%)**	**153 (71·5%)**
Stable disease	34 (15·7%)	52 (24·3%)
Stable disease or better	210 (97·2%)	205 (95·8%)
Progressive disease or death	6 (2·8%)	9 (4·2%)

Durie B et al Lancet 2017

Superiority of RVD over Rd: SWOG S0777

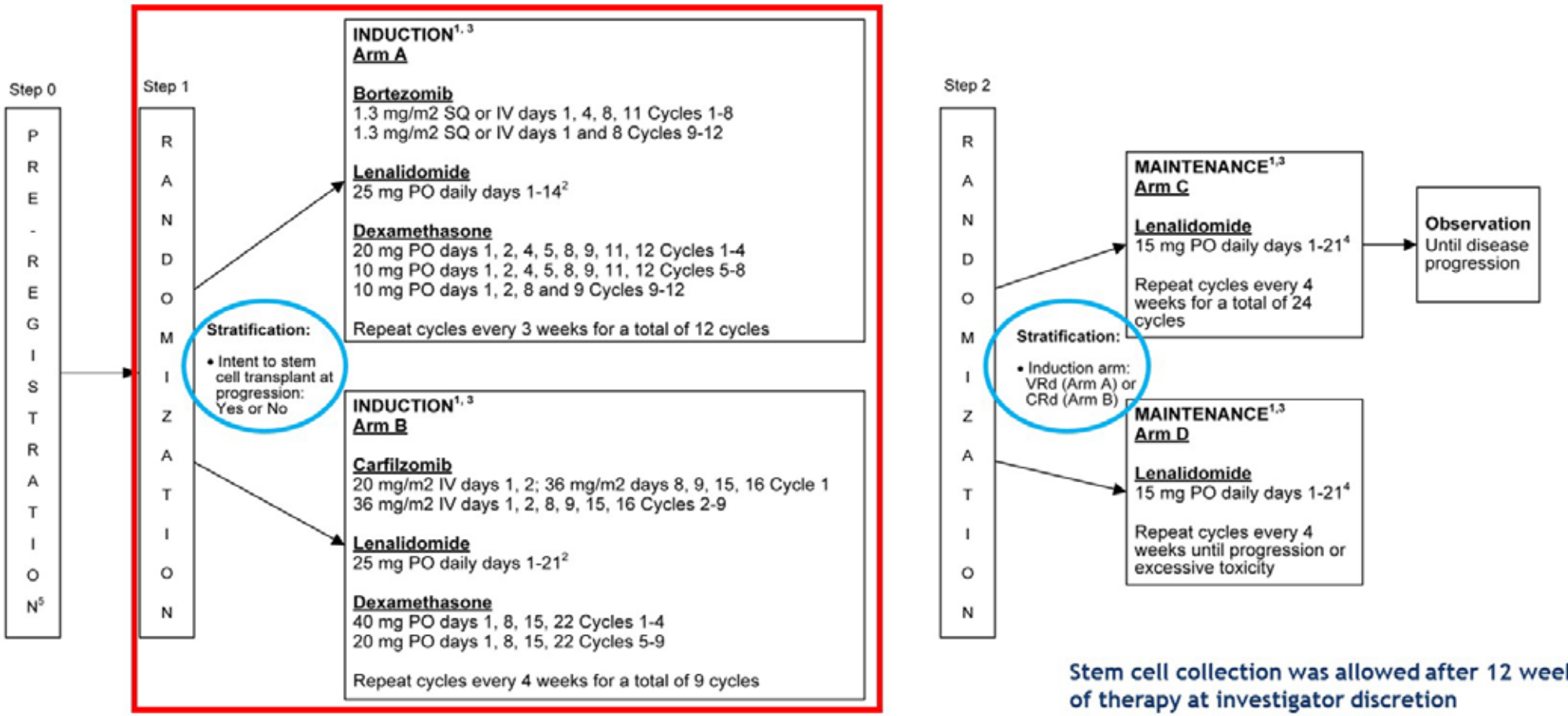


Median PFS 75 months

Durie B et al Lancet 2017

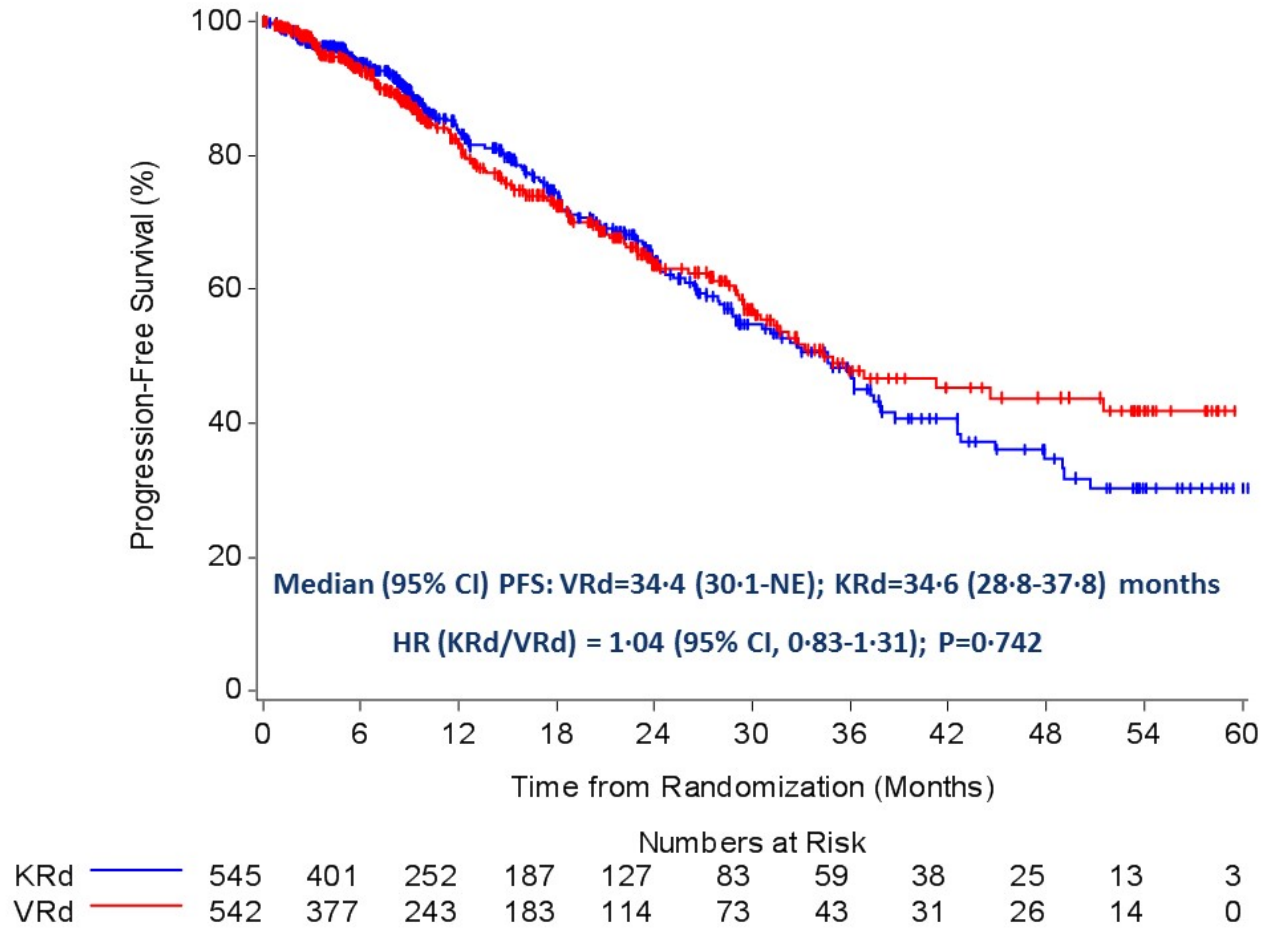
ENDURANCE: RVd vs KRd, ASCO 2020

Patient Randomization and Treatment Schedule



Stem cell collection was allowed after 12 weeks of therapy at investigator discretion

Progression Free Survival from Induction Randomization



- 2nd interim analysis of PFS (Jan 2020): 298 PFS events (75% of 399 planned)
- Median (95% CI) estimated follow up of 15 (13-18) months
- For patients >/= 70 years, median PFS(95% CI) for VRd = 37 (29-NE) and KRd = 28 (24-36) months
- With censoring at SCT or alternative therapy: Median PFS (95% CI) for VRd = 31·7 (28·5-44·6) and KRd = 32·8 (27·2-37·5) months

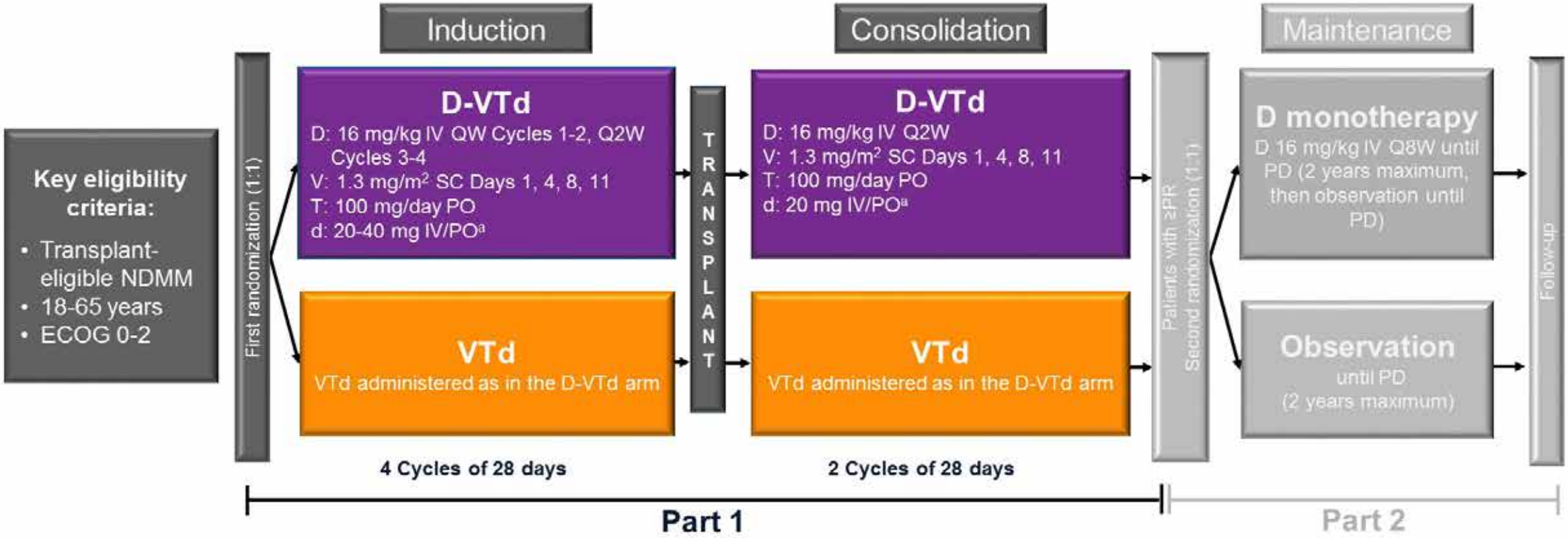
4 drug combinations

- RVd is the standard of care for newly diagnosed MM… but does adding a CD38 antibody improve outcomes?

- 2 key studies in transplant eligible MM:
  - CASSIOPEIA: Daratumumab + VTd vs VTd
  - GRIFFIN: Daratumumab + RVd vs RVd

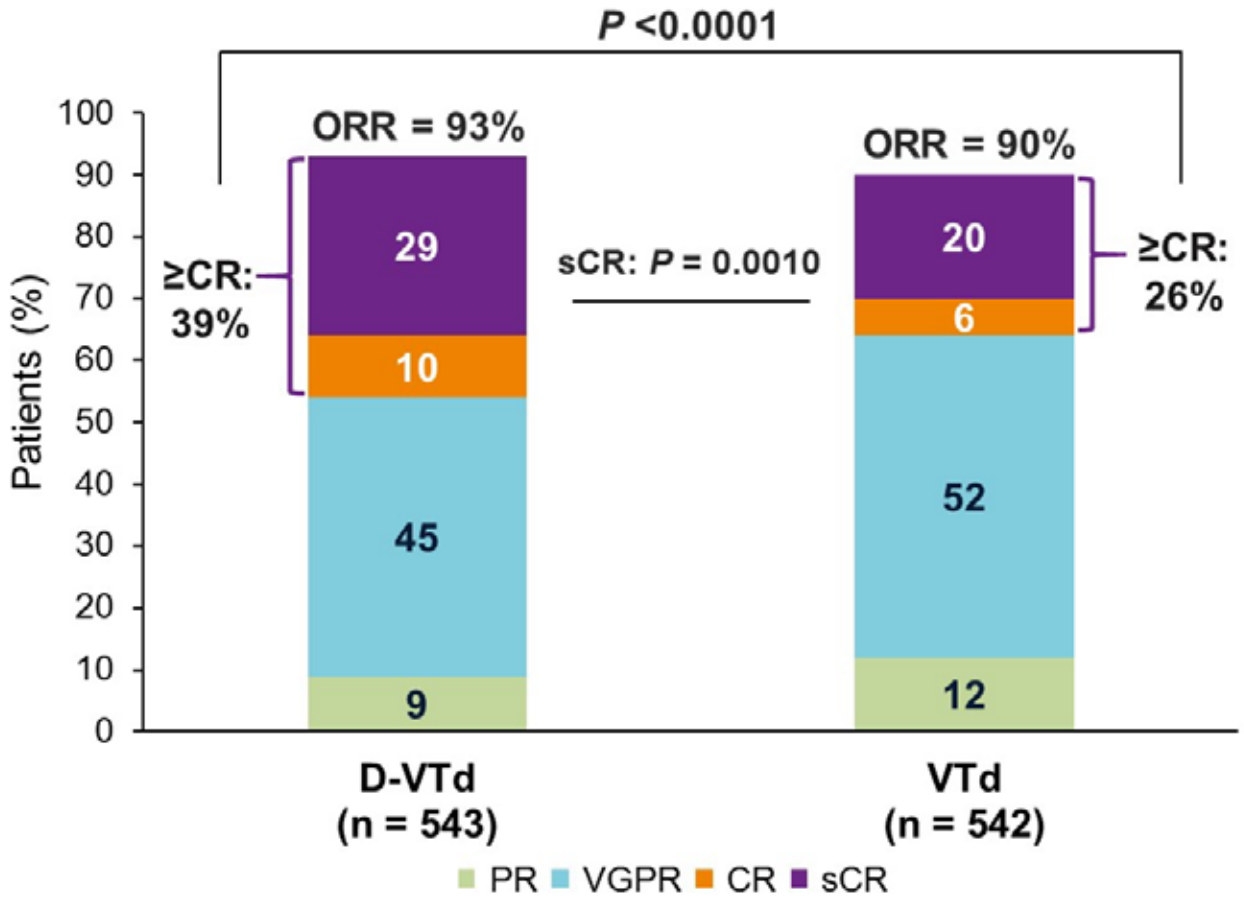
CASSIOPEIA Study Design

- Phase 3 study of D-VTd versus VTd in transplant-eligible NDMM (N = 1,085), 111 sites from 9/2015 to 8/2017



D-VTd, daratumumab/bortezomib/thalidomide/dexamethasone; VTd, bortezomib/thalidomide/dexamethasone; ECOG, Eastern Cooperative Oncology Group; IV, intravenous; QW, weekly; Q2W, every 2 weeks; SC, subcutaneous; PO, oral; PR, partial response; Q8W, every 8 weeks; PD, progressive disease.
[a]Dexamethasone 40 mg on Days 1, 2, 8, 9, 15, 16, 22, 23 of Cycles 1-2 and Days 1 & 2 of Cycles 3-4; 20 mg on Days 8, 9, 15, 16 of Cycles 3-4; 20 mg on Days 1, 2, 8, 9, 15, 16 of Cycles 5-6.

Efficacy: Post-consolidation Depth of Response



- Primary endpoint
  - Post-consolidation sCR
    - 29% D-VTd vs 20% VTd
    - Odds ratio, 1.60; 95% CI, 1.21-2.12; *P* = 0.0010

- sCR definition
  - All required:
    - SIFE negative
    - UIFE negative
    - <5% plasma cells in the BM
    - Four-color flow negativity
    - Normal FLC ratio
    - Disappearance of all plasmacytomas

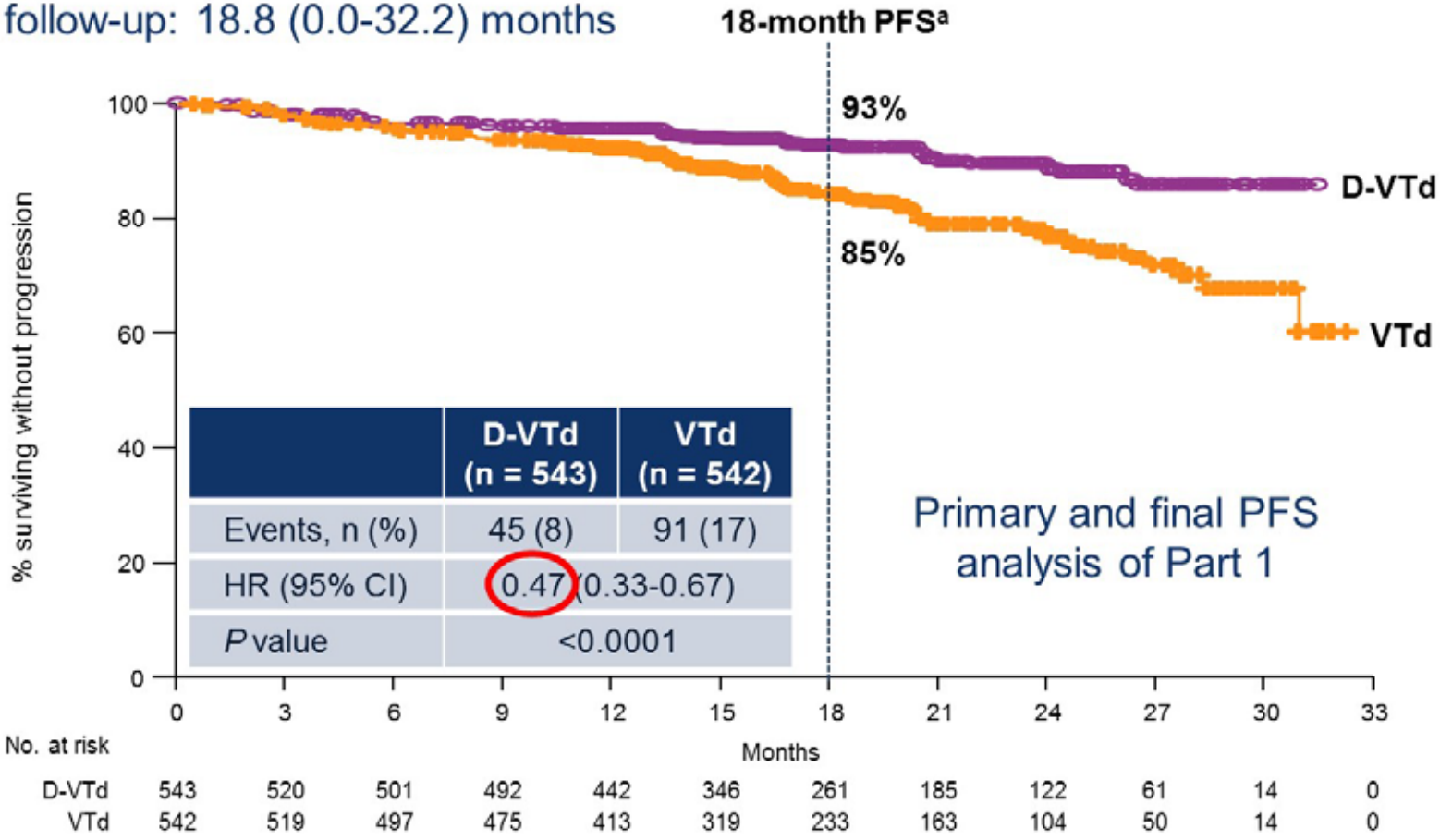
The addition of daratumumab to VTd improved depth of response

ORR, overall response rate; VGPR, very good partial response; CI, confidence interval; SIFE, serum immunofixation; UIFE, urine immunofixation; BM, bone marrow; FLC, free light chain.

Presented By Philippe Moreau at 2019 ASCO Annual Meeting

Efficacy: PFS From First Randomization

- Median (range) follow-up: 18.8 (0.0-32.2) months



	D-VTd (n = 543)	VTd (n = 542)
Events, n (%)	45 (8)	91 (17)
HR (95% CI)	0.47 (0.33-0.67)	
P value	<0.0001	

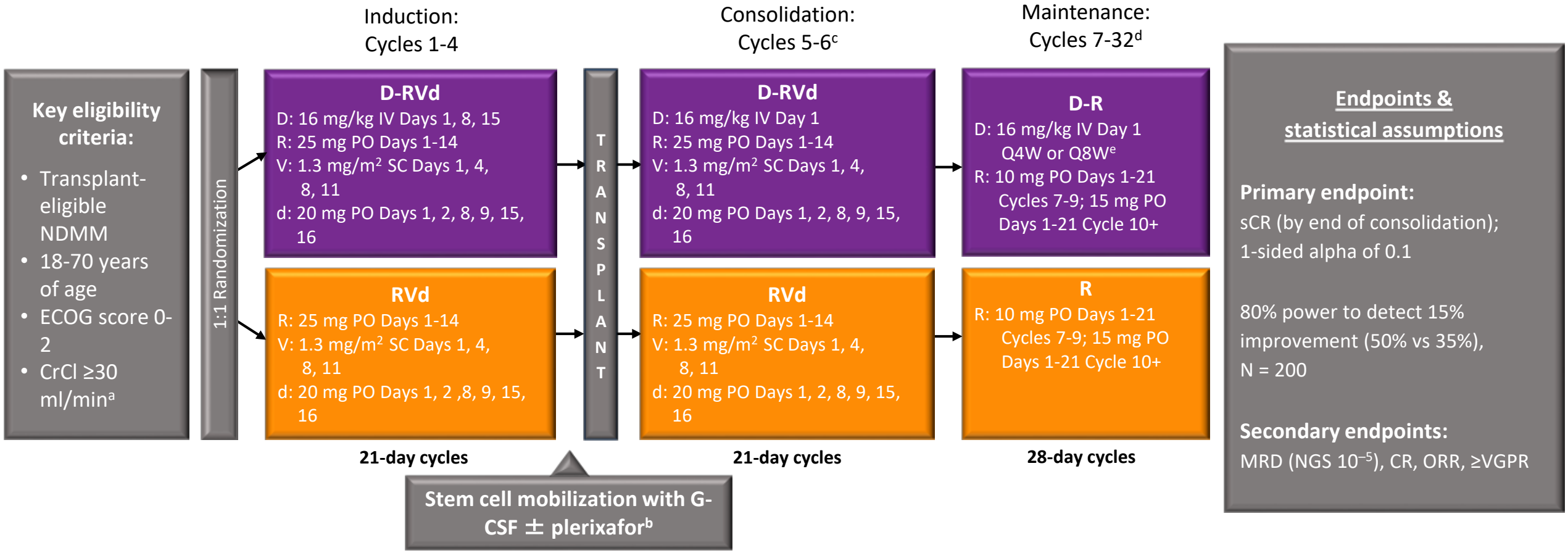
Primary and final PFS analysis of Part 1

53% reduction in the risk of progression or death in the D-VTd arm

HR, hazard ratio.
[a]Kaplan-Meier estimate.

GRIFFIN (NCT02874742): Randomized Phase

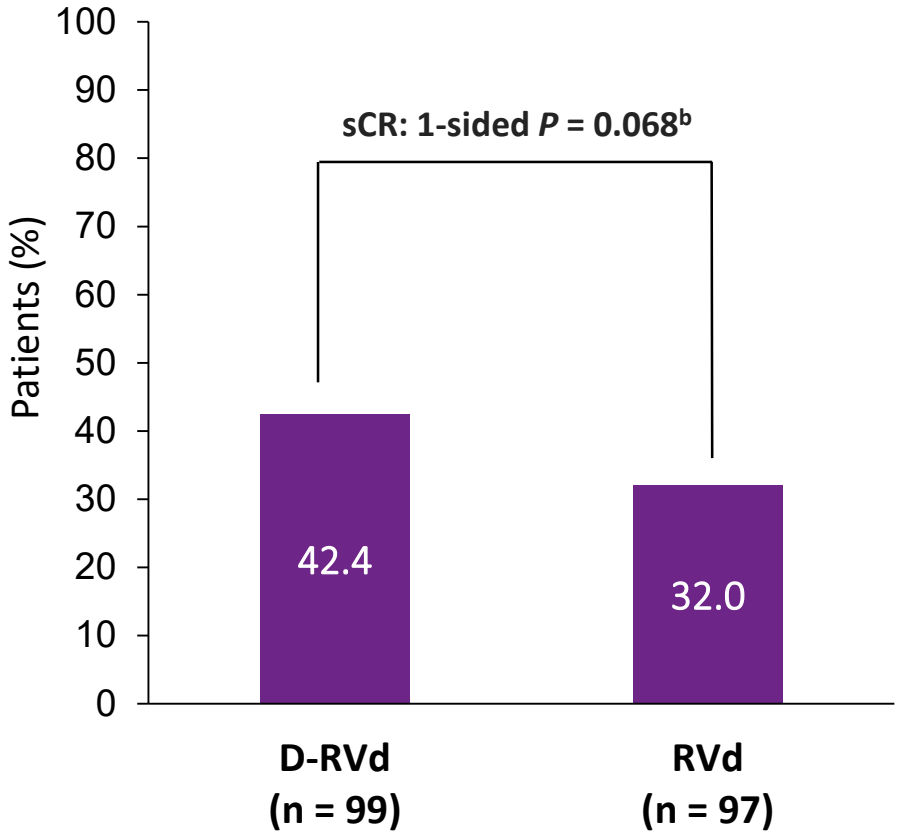
- Phase 2 study of D-RVd vs RVd in transplant-eligible NDMM, 35 sites in US with enrollment from 12/2016 and 4/2018



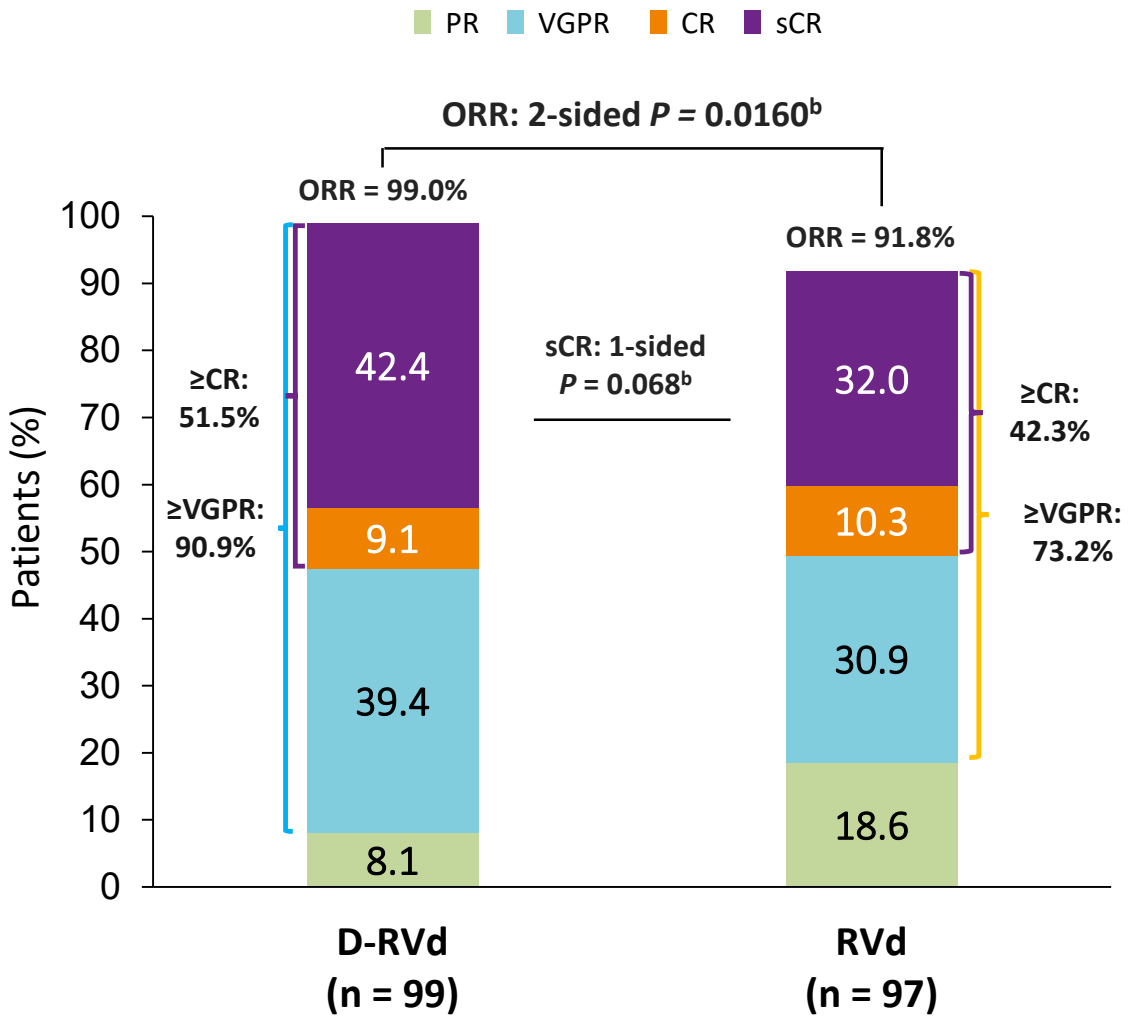
Voorhees P et al. ASH Annual Meeting, Orlando, 2019

Primary Endpoint: sCR by the End of Consolidation[a]

- **Primary endpoint met at pre-set 1-sided alpha of 0.1**
  - sCR by end of consolidation
    - 42.4% D-RVd vs 32.0% RVd
    - Odds ratio, 1.57; 95% CI, 0.87-2.82; 1-sided *P* = 0.068[b]



Post-consolidation depth of response[a]



Voorhees P et al. ASH Annual Meeting, Orlando, 2019

Treatment considerations for high-risk chromosomal abnormalities

- IFM 2005 01 – bortezomib showed better EFS and OS for patients with t(4;14)
- HOVON65/GMMG-HD4 – bortezomib based induction and maintenance showed improved outcomes for Del(17p)
- GIMEMA trial of VTD vs TD – in t(4;14) pts, OS was improved with VTD
- Conclusion: bortezomib *partly* overcomes the adverse effect of t(4;14) on PFS and SO, and del(17p) on PFS

Sonneveld et al, Blood 2016

Summary

- Modern PI/IMID combinations can overcome high-risk changes and improve outcomes for standard risk patients
- 4 drug combinations including a CD38 antibody are likely the future of induction therapy
- Can consider alkylator/PI combo for acute renal insufficiency, change to IMID/PI after renal function improves
- Goal of induction: deep response!
  - Usually like to see at least PR, ideally VGPR or better before autologous transplant

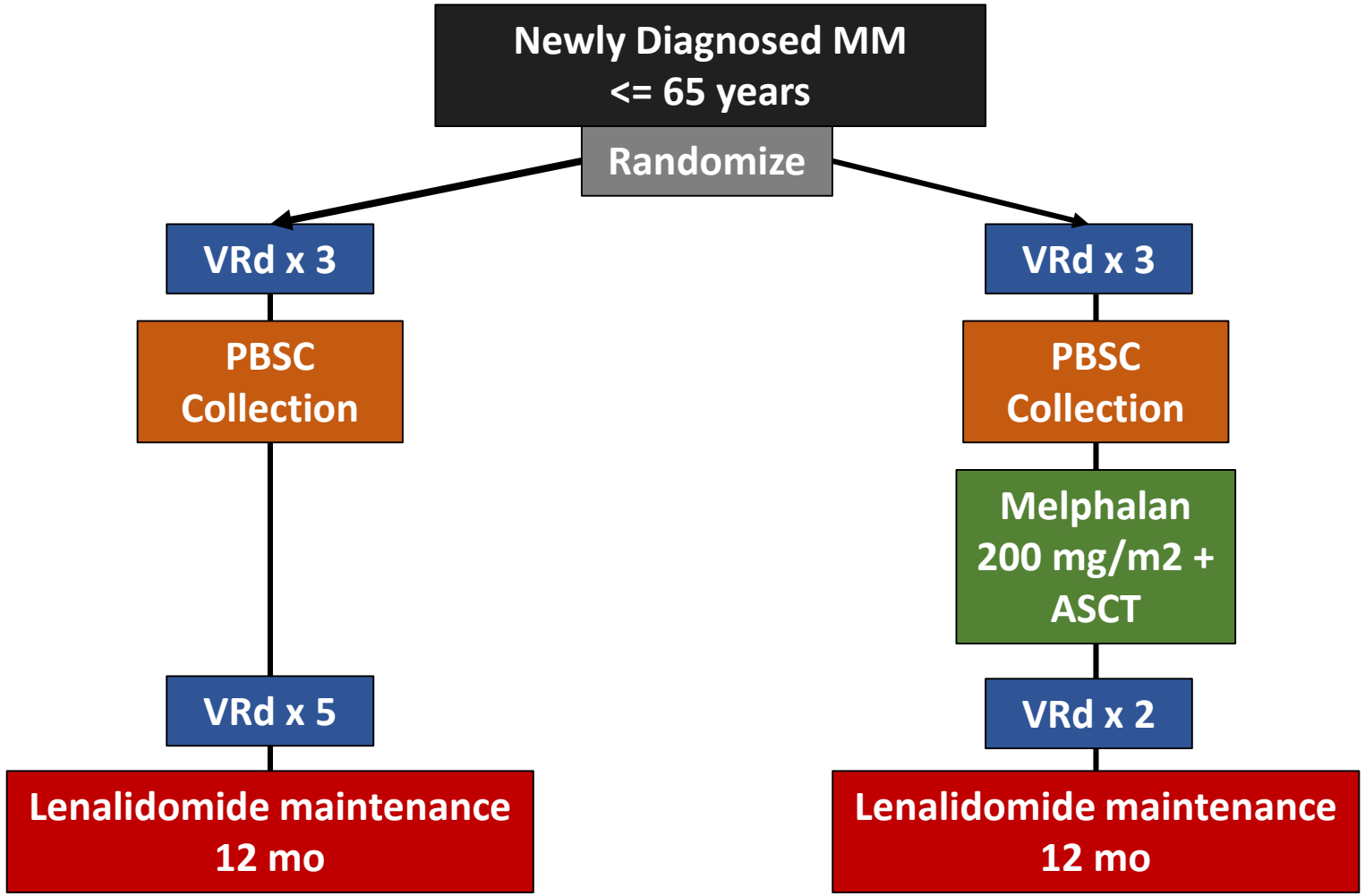
Autologous stem cell transplantation for multiple myeloma

- Remains a cornerstone of management for eligible newly diagnosed patients – randomized trials show benefit for PFS
- Most recommend early or delayed transplant, rather than no transplant after induction therapy
- Very low treatment related mortality in modern era (1-2%)
- Acute regimen toxicities (mucositis, infections, diarrhea) are manageable

Transplant eligible vs ineligible

- What factors are important?
- Age – not an absolute contraindication
- Comorbidities, general level of health (“eyeball test”)
- Patient preference

IFM 2009: Study Design

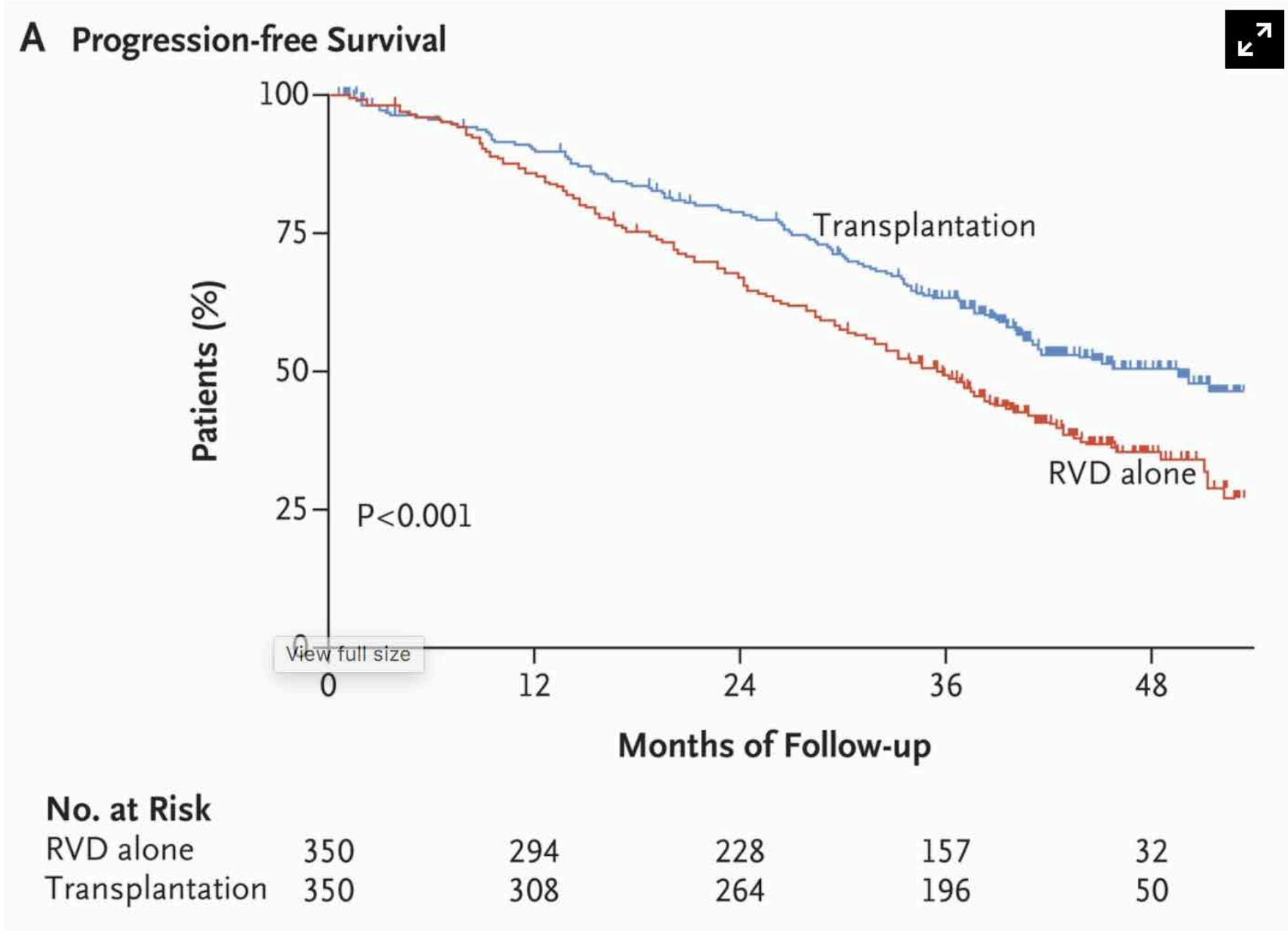


ASCT at relapse

Attal NEJM 2017

IFM 2009 Results

- Median PFS significantly longer in the ASCT arm, 50 mos vs 36 months ($p<0.001$) – primary endpoint
- Benefit observed across all subgroups (high risk vs standard)
- Higher percentage of CR in the transplant arm
- No overall survival benefit observed


A Progression-free Survival
100
75
50
25
0
Patients (%)
Transplantation
RVD alone
P<0.001
View full size
0
12
24
36
48
Months of Follow-up
No. at Risk
RVD alone 350 294 228 157 32
Transplantation 350 308 264 196 50

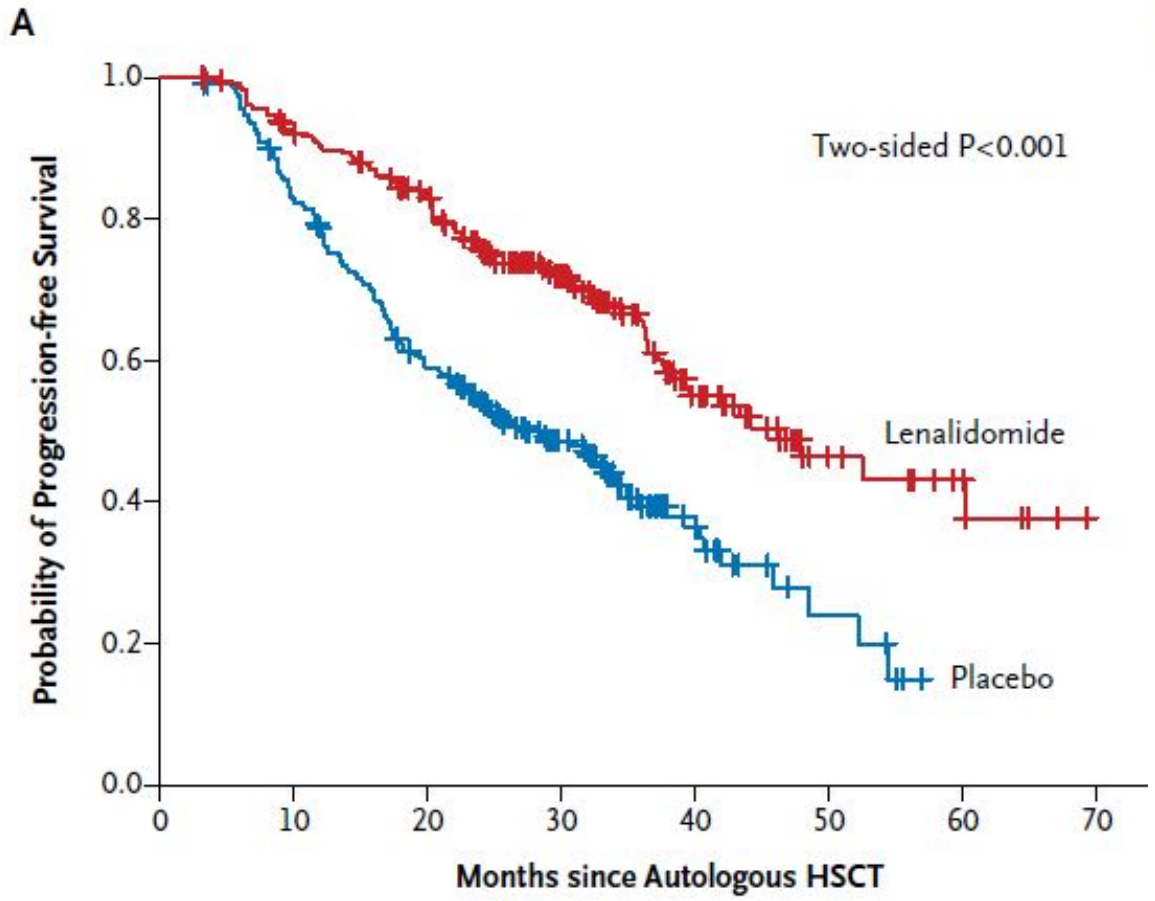
Lenalidomide Maintenance Post ASCT Improves PFS

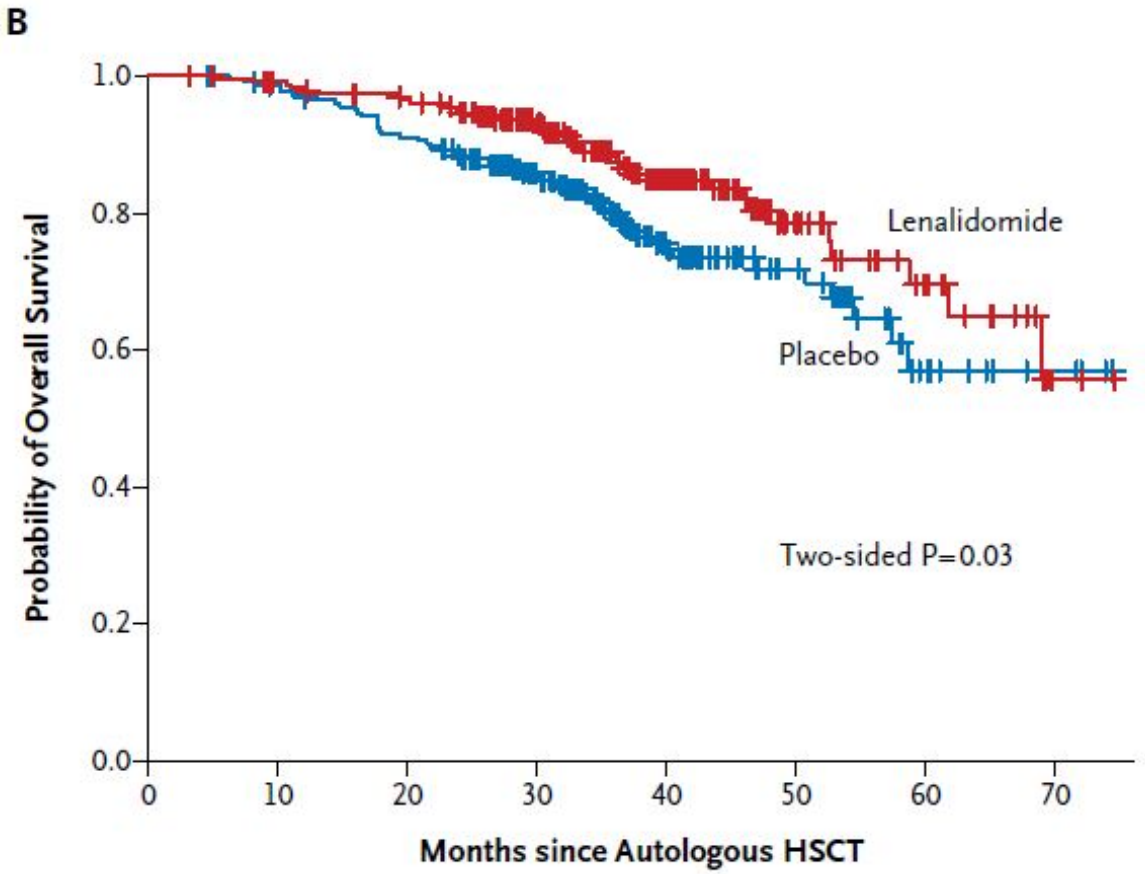
- Lenalidomide maintenance improves PFS post ASCT
  - Attal et al NEJM 2012:
    - 614 patients; Len maintenance 10 mg daily, increased to 15 mg if tolerated, vs Placebo
    - Primary end point: PFS
    - PFS 41 mos vs 23 mos, $p<0.001$.
  - Attal ASH 2013, update:
    - 5 year PFS: 42 vs 18 mo. No difference in 5 year OS!
  - Lenalidomide stopped at median of 2 years due to secondary primary malignancy (SPM) concern

Lenalidomide Maintenance Post ASCT Improved PFS and OS in 1 study

- McCarthy et al, NEJM 2012
  - 460 patients, randomized to lenalidomide at starting dose of 10 mg, or placebo, post ASCT, daily, until progression
  - Median time to progression, 46 mo vs 27 mo ($p<0.001$)
  - 3 year OS rate 88% vs 80%

Lenalidomide Maintenance Improves PFS and OS, McCarthy NEJM 2012





Meta-Analysis of Lenalidomide Maintenance after ASCT

- McCarthy et al, JCO, July 2017
- Used documentation from 3 RCTS (CALGB 100104, GIMEMA , IFM 2005)
- 1208 patients in meta analysis
- Median OS:
  - Not reached for lenalidomide maintenance group
  - 86 months for the placebo/obs group
  - P = 0.001

Summary – Lenalidomide Maintenance Post-ASCT

- Lenalidomide maintenance post ASCT improved PFS in several large studies
- Lenalidomide maintenance post-ASCT improved OS in one study (McCarthy et al)
- Meta analysis of 3 RCTs showed OS benefit with lenalidomide maintenance

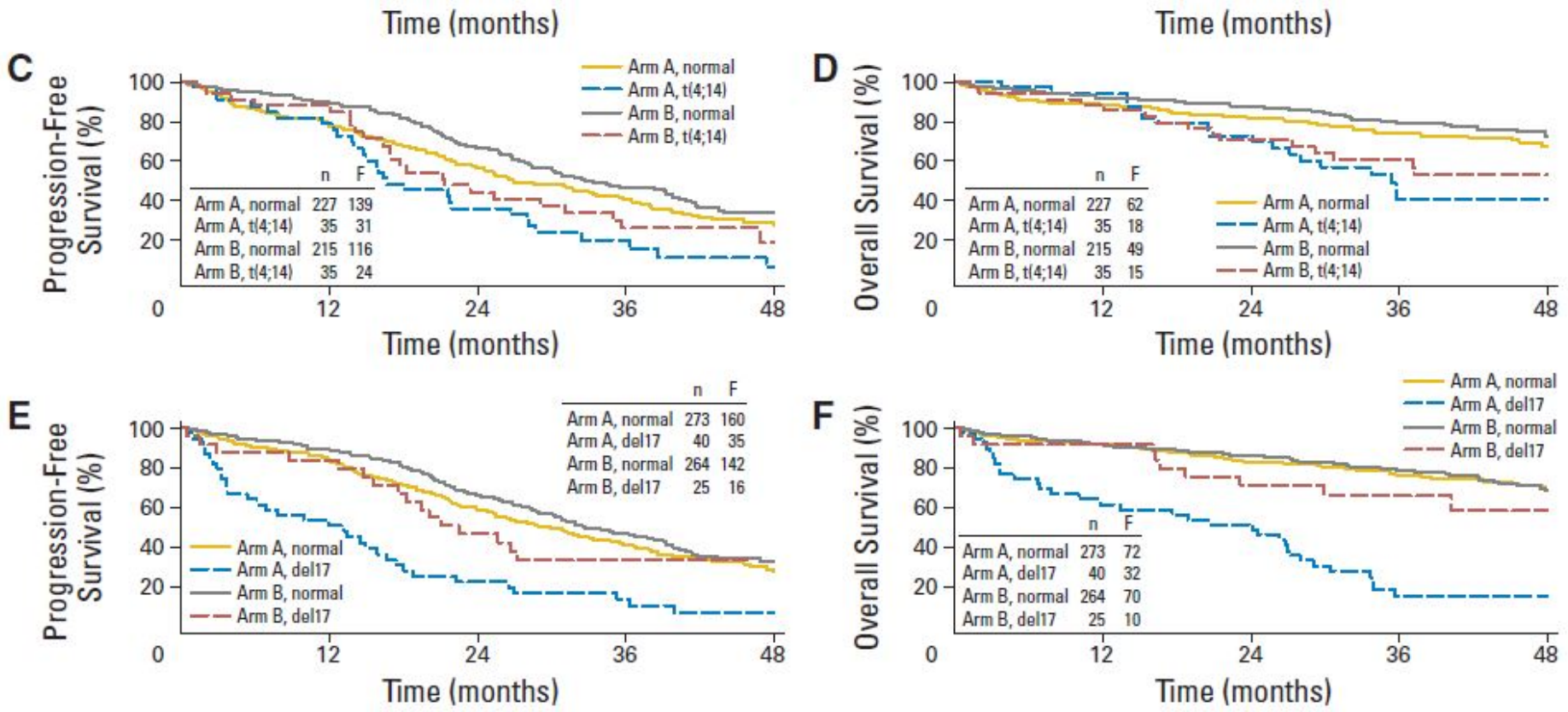
Bortezomib Maintenance: HOVON-65/GMMG-HD4 Trial

- Study design:
  - Randomized study, PAD (bortezomib) vs VAD induction, followed by transplant, followed by maintenance with either
    - Thalidomide 50 mg daily x 2 years
    - Bortezomib 1.3 mg/m2 Q2week x 2 years
- CR rate superior:
  - After PAD induction, 15 vs 31%
  - After bortezomib maintenance, 34 vs 49%

Sonneveld et al JCO 2012

t(4;14) - PFS

t(4;14) - OS



Del(17p)- PFS

Del(17p)- OS

Sonneveld et al JCO 2012

Bortezomib Maintenance Post ASCT Improves Outcome for Del(17p)

- Analysis of the HOVON-65 trial data
- Looked at the prognostic value of 12 chromosomal abnormalities
- Patients with t(4;14) receiving bortezomib based treatment had a prolonged median PFS (25.3 vs 21.7 mo), and improved 3 year OS rate (66 vs 44%)
- Patients with del(17p13) receiving bortezomib had a prolonged median PFS (26 vs 12 mos), improved 3 year OS (17 vs 69%)

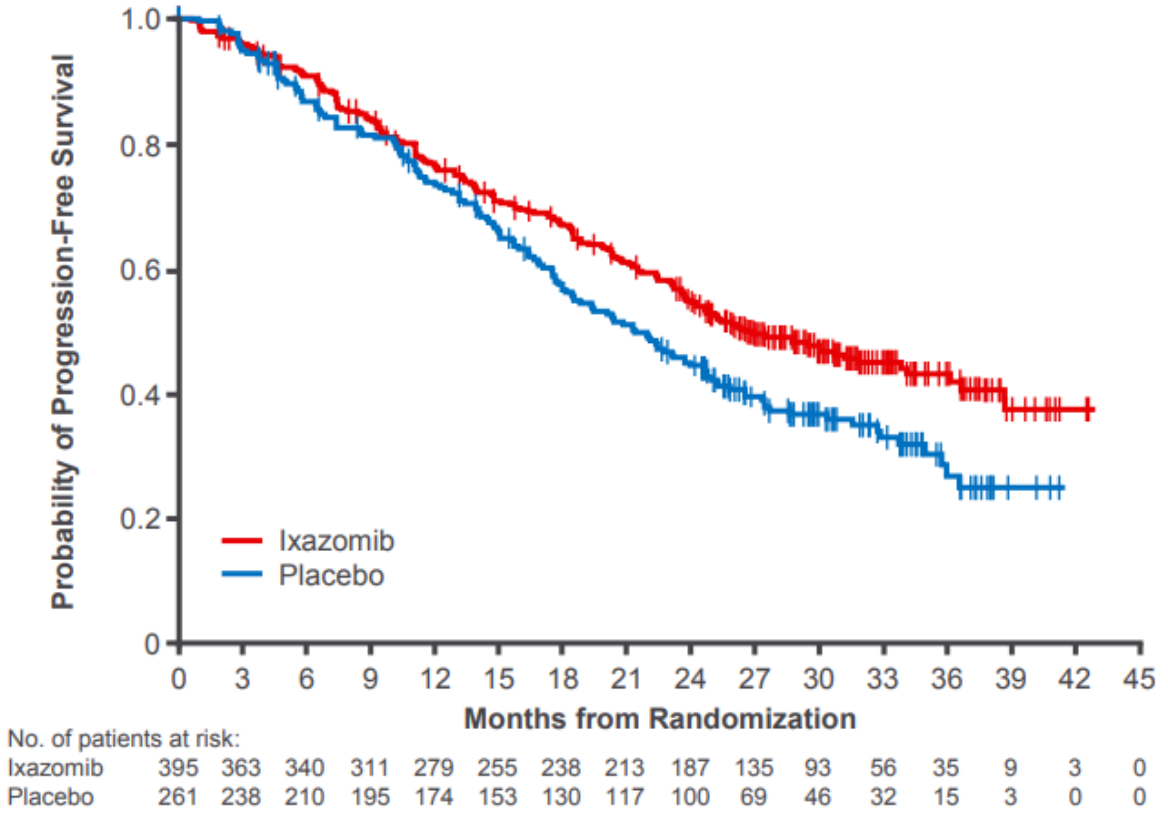
Neben et al. Blood 2012

Summary – Bortezomib maintenance for high-risk myeloma

- Aggregate data from analysis of the HOVON-65/GMMG HD4 trial indicates a benefit for bortezomib maintenance post ASCT, given every 2 weeks for 2 years, particularly for those patients with the following chromosomal abnormalities:
  - **Del(17p)**
  - **t(4;14)**

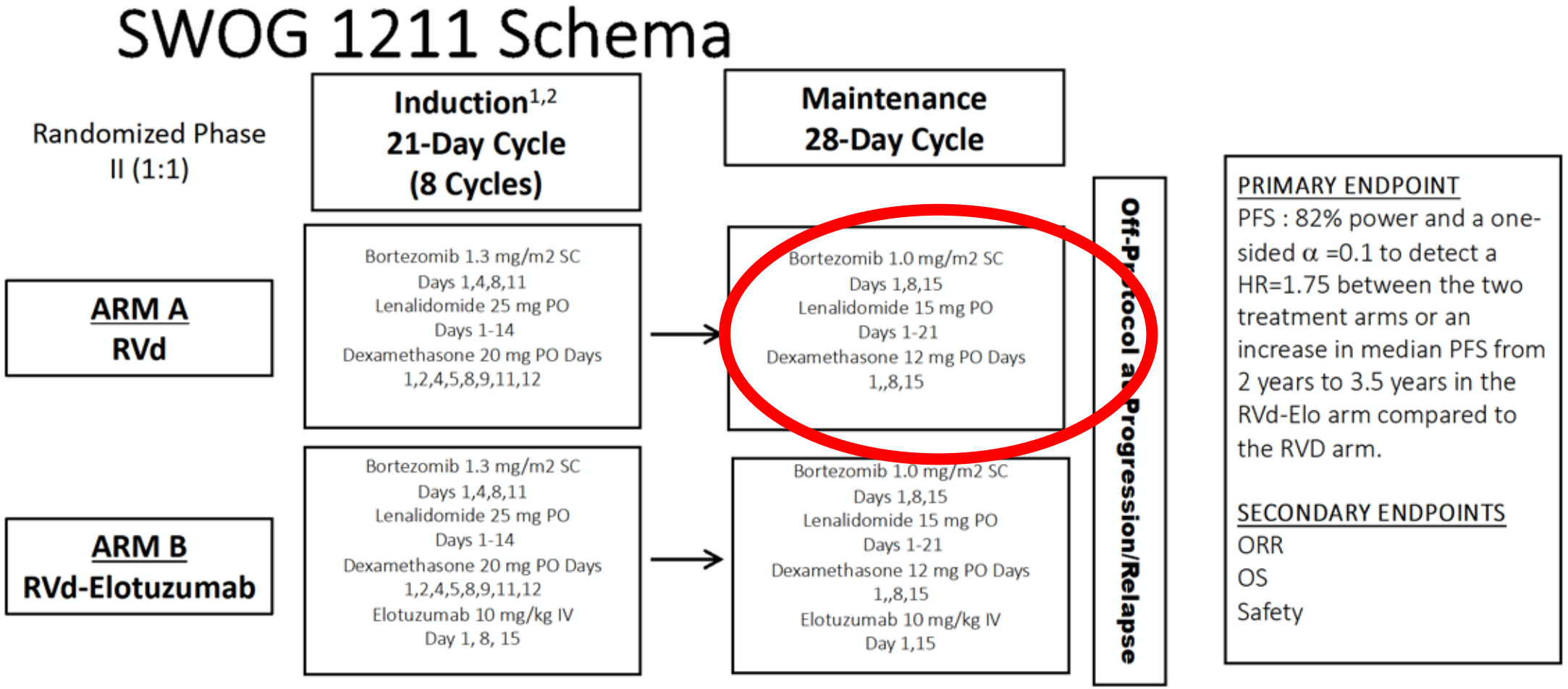
Ixazomib maintenance improves PFS post ASCT

- 39% improvement in overall PFS from time of randomization for patients receiving ixazomib vs placebo maintenance:
  - HR: 0.72; 95% CI: 0.582-0.890
  - P=0.002
  - Median 26.5 months vs 21.3 months
- At a median follow-up of 31 months, median OS not reached in either treatment arm



Dimopoulos M et al, ASH Annual Conference 2018

RVd Maintenance for high-risk MM



SWOG CANCER RESEARCH NETWORK

Opened to all National Clinical Trials Network members

NCI National Clinical Trials Network | NCI Community Oncology Research Program

Usmani S et al. EHA Annual Meeting 2020

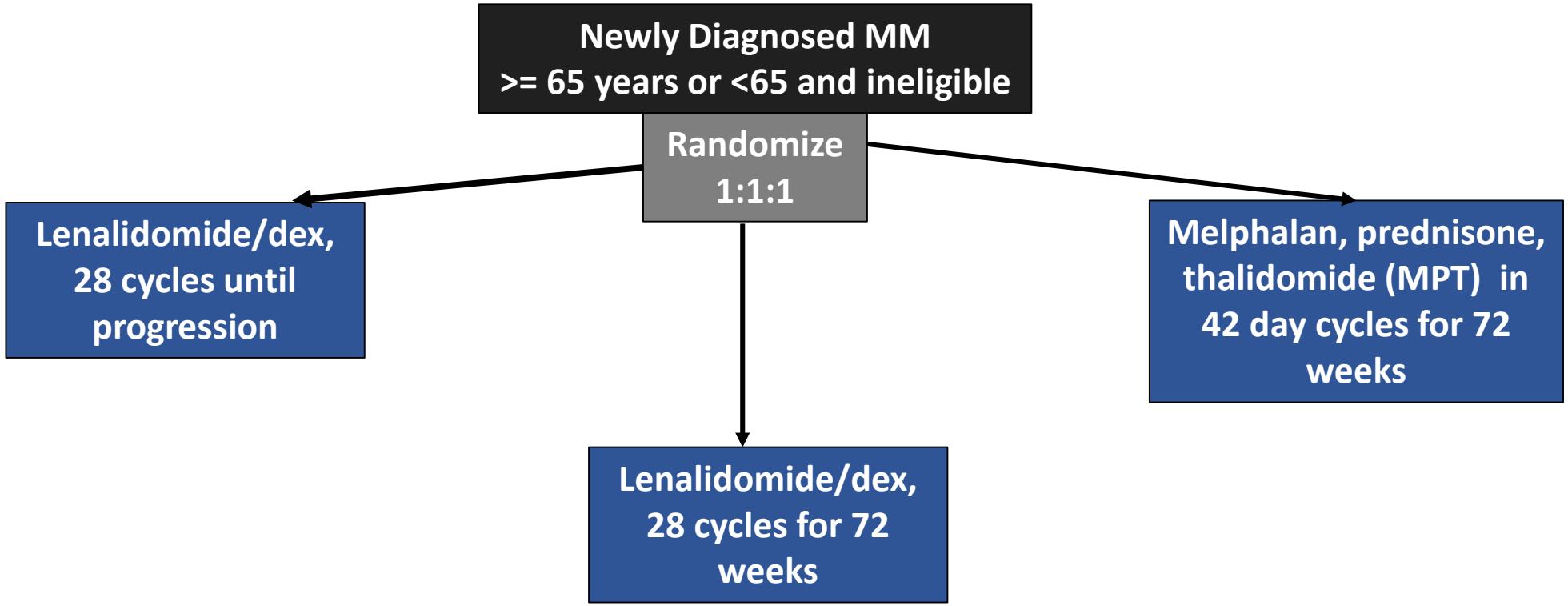
Treatment of non-transplant eligible myeloma, newly diagnosed

- Consider triplet combination, or
  - IMID/PI Triplet combination – RVD lite
  - Daratumumab, lenalidomide, dexamethasone – MAIA trial

- Consider doublet for frail/elderly
  - Lenalidomide/low dose dexamethasone
  - Bortezomib/low dose dexamethasone

- Other options
  - Alkylator/PI combination (CyBorD)
  - Daratumumab+VMP (ALCYONE Trial, NEJM 2018) **

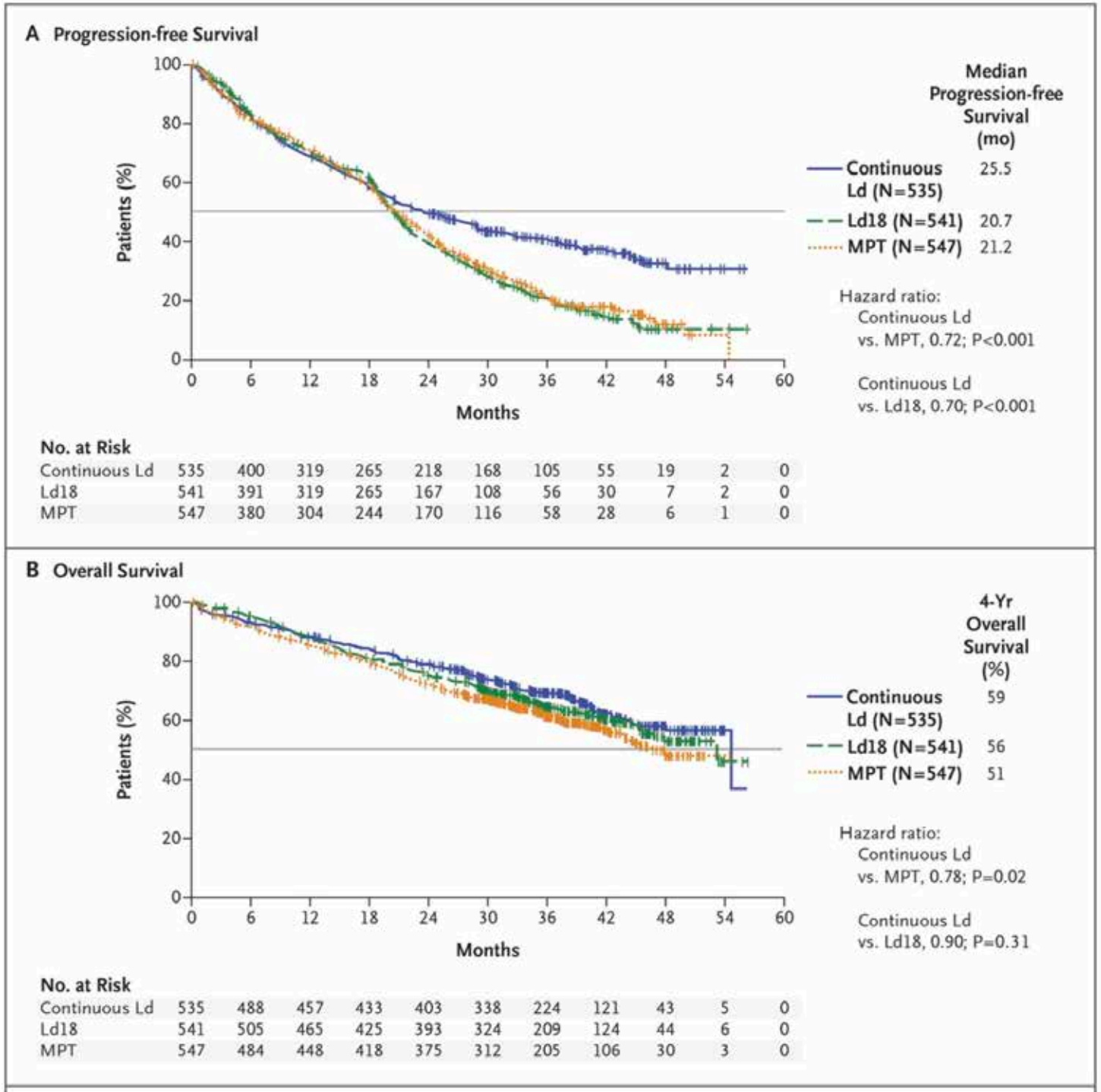
FIRST Trial – Randomized study of Rd, MPT



Benboubker et al NEJM 2014

All patients received:

- Antithrombotic prophylaxis
  - Low dose aspirin, 70-100 mg/day
  - DVT/PET within 5 years: LMWH, Heparin, Warfarin



Benboubker et al NEJM 2014

Table 2. Response Rates and Time to Response.

Variable	Continuous Lenalidomide–Dexamethasone (N=535)	Lenalidomide–Dexamethasone for 18 Cycles (N=541)	MPT (N=547)
Overall response — no. (%)	402 (75)*	397 (73)*	341 (62)
Complete response	81 (15)	77 (14)	51 (9)
Very good partial response	152 (28)	154 (28)	103 (19)
Partial response	169 (32)	166 (31)	187 (34)
Stable disease — no. (%)	101 (19)	111 (21)	145 (27)
Progressive disease — no. (%)	7 (1)	12 (2)	19 (3)
Response could not be evaluated — no. (%)	25 (5)	21 (4)	42 (8)
Median time to response — mo†	1.8‡	1.8‡	2.8

Benboubker et al NEJM 2014

Modified RVD ("RVD-Lite") for elderly/frail

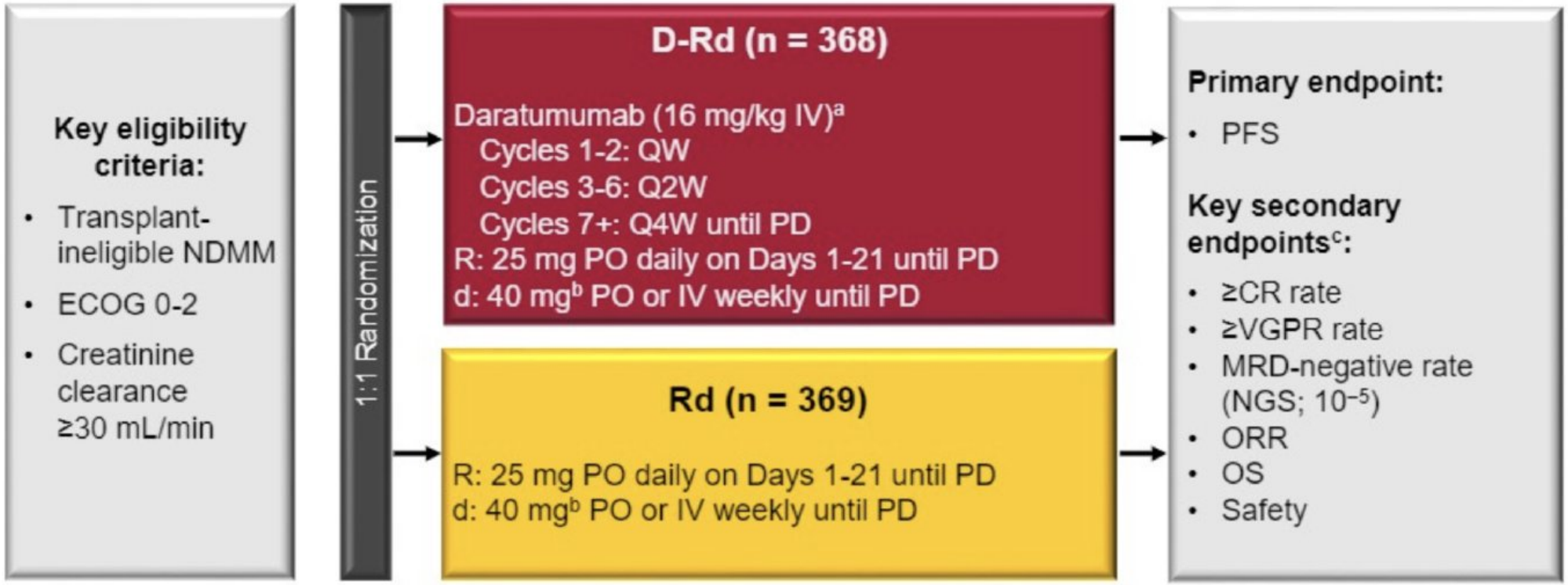
- Dosing
  - Lenalidomide 15 mg days 1-21 of a 35 day cycle
  - Bortezomib 1.3 mg/m2 weekly days 1, 8, 15, 22
  - Dexamethasone 20 mg twice weekly for pts ≤75 yrs and days 1, 8, 15, 22 for pts older than 75
- 53 patients treated
- Median age of patients: 72 years
- iORR - 90% (10 CR, 14 VGPR, 12 PR, 4 SD)
- Toxicities manageable:
  - Grade 3 or greater toxicities included hypophosphatemia in 15 (31%) and rash in 5 (10%) pts.
  - Fatigue most common, in 31/49 (63%) patients, mostly grade 1-2
  - Peripheral neuropathy of any grade was reported in 21/49 (43%) pts including grade 1 (11, 22%), 2 (9, 18%), and 3 (1, 2%).

O'Donnell et al ASH 2015

Dara-Rd vs Rd: MAIA Trial – Study Design

MAIA Study Design

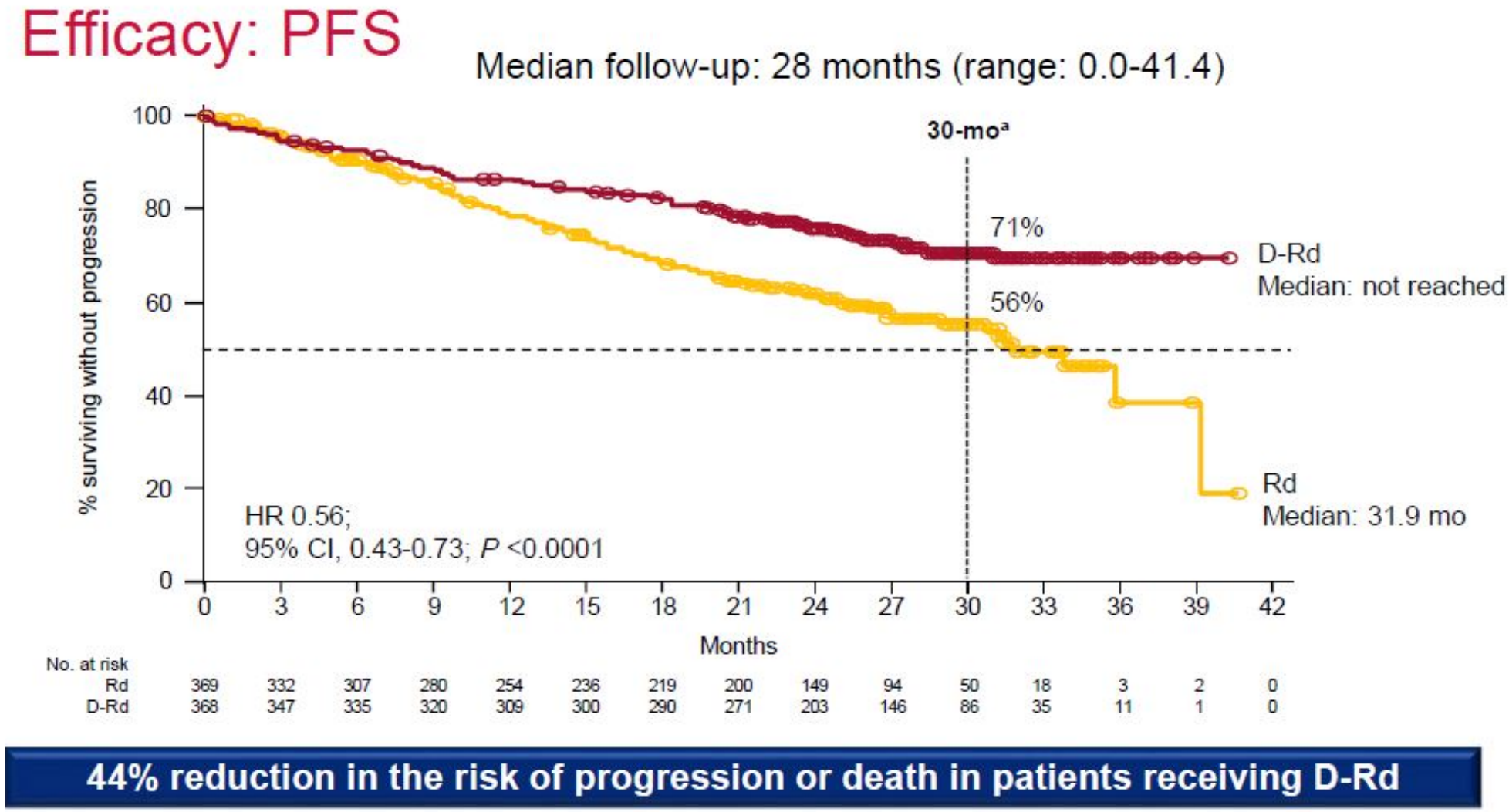
- Phase 3 study of D-Rd vs Rd in transplant-ineligible NDMM (N = 737)



[a]On days when daratumumab was administered, dexamethasone was administered to patients in the D-Rd arm and served as the treatment dose of steroid for that day, as well as the required pre-infusion medication.
[b]For patients older than 75 years of age or with BMI <18.5, dexamethasone was administered at a dose of 20 mg weekly.
[c]Efficacy endpoints were sequentially tested in the order shown.

Facon T, Kumar SK, Plesner T, et al. Phase 3 randomized study of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (MAIA). Abstract #LBA-2. Presented at the 2018 ASH Annual Meeting, December 4, 2018; San Diego, CA.

MAIA Trial: Dara-Rd vs Rd Upfront Treatment for ASCT-ineligible NDMM Patients



44% reduction in the risk of progression or death in patients receiving D-Rd

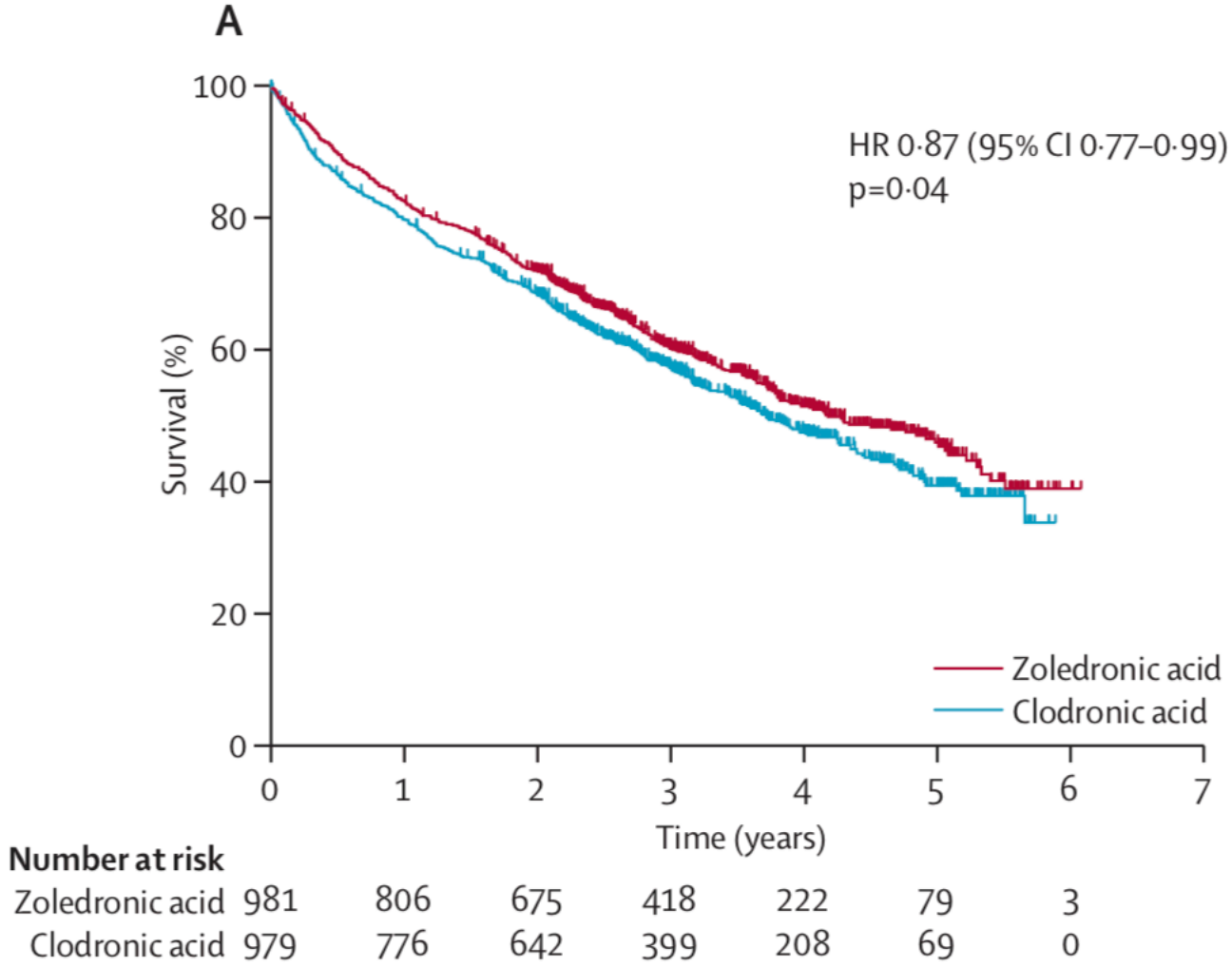
Facon T, Kumar SK, Plesner T, et al. Phase 3 randomized study of daratumumab plus lenalidomide and dexamethasone (D-Rd) versus lenalidomide and dexamethasone (Rd) in patients with newly diagnosed multiple myeloma (NDMM) ineligible for transplant (MAIA). Abstract #LBA-2. Presented at the 2018 ASH Annual Meeting, December 4, 2018; San Diego, CA.

Myeloma therapy - dosing in frail patients

Frontline treatment	Second-line treatment	Following lines of treatment
Lenalidomide-steroid R*: 10-15 mg/d, d 1-21 d: 10 mg/d once weekly or P: 25 mg/d every other d	**Bortezomib-steroid** V: 1.3 mg/m^2 once weekly d: 10 mg/d once weekly or P: 25 mg/d every other d	**Melphalan-prednisone** M: 2 mg every other d P: 25 mg/d every other d
Bortezomib-steroid V: 1.3 mg/m^2 once weekly d: 10 mg/d once weekly or P: 25 mg/d every other d	**Lenalidomide-steroid** R*: 10-15 mg/d, d 1-21 d: 10 mg/d once weekly or P: 25 mg/d every other d	**Cyclophosphamide-prednisone** C: 50 mg every other d P: 25 mg/d every other d
	Re-treatment	**Thalidomide-prednisone** T: 50 mg every other d P: 25 mg/d every other d

Bisphosphonates for bone health in multiple myeloma: MRC IX trial

- Randomized study comparing first-line treatment with zoledronic acid as compared with clodronate in newly diagnosed MM: MRC IX
- Only reported bisphosphonate to show survival benefit (5.5 mos)
- 3-4% risk of ONJ seen in this study



Supportive care – hypercalcemia, HSV/VZV and VTE

- Hypercalcemia:
  - Hydration, bisphosphonates (Zoledronic acid), steroids, +/- calcitonin

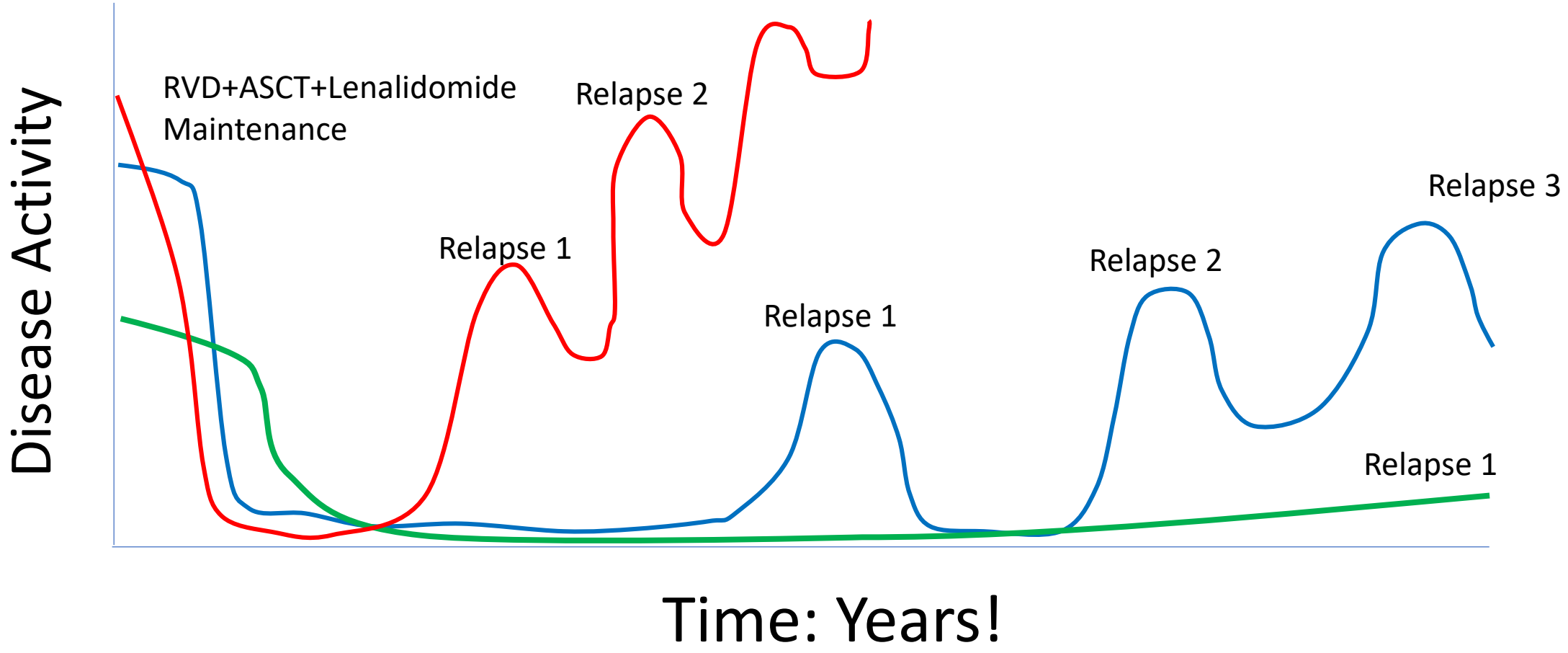
- Herpes zoster prophylaxis
  - Acyclovir or valacyclovir
  - For ALL patients receiving proteasome inhibitors or daratumumab

- VTE
  - Aspirin 81-325 mg PO daily for all patients receiving IMiDs
  - Therapeutic anticoagulation for patients at high risk for VTE

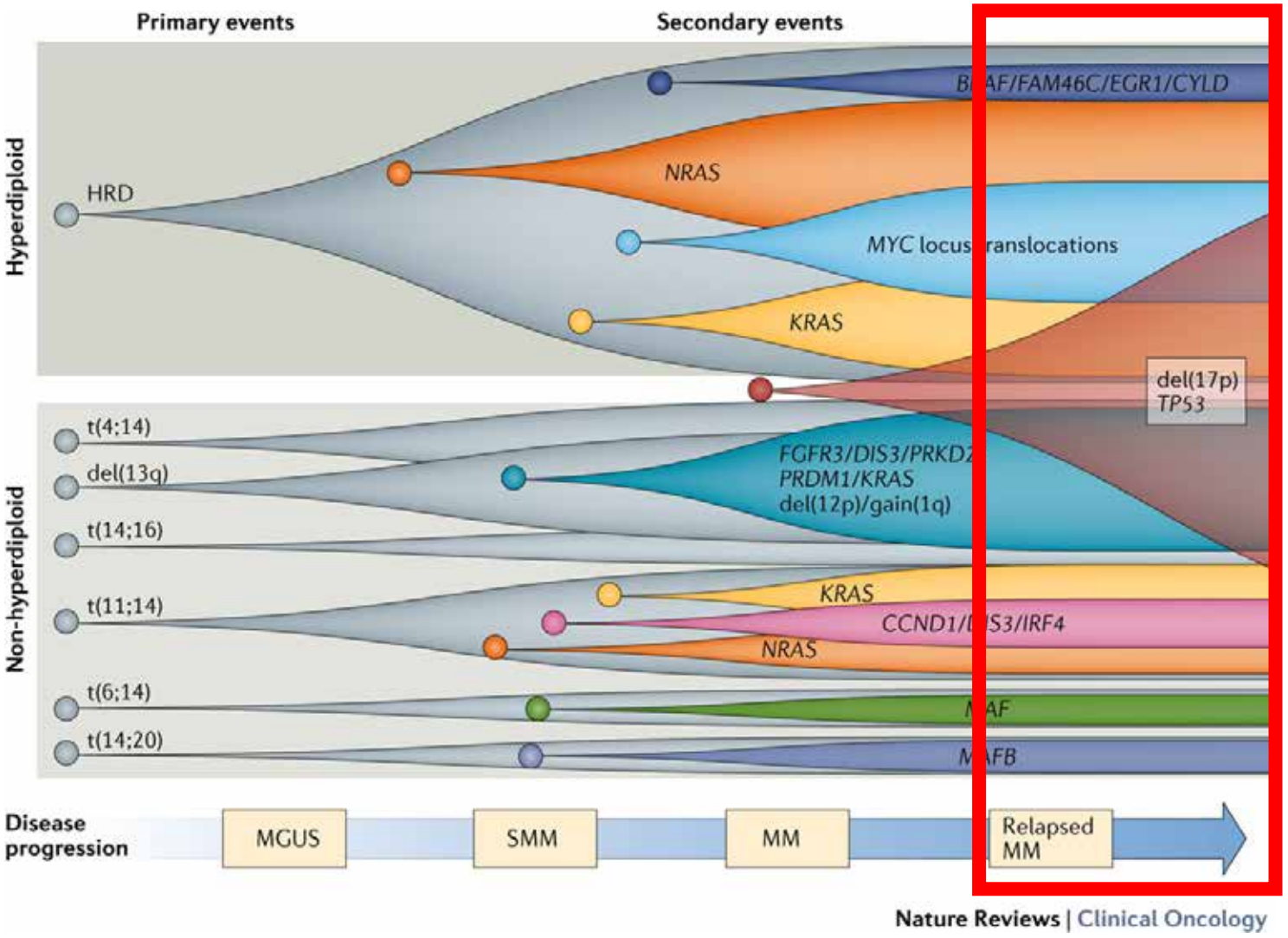
Why does treating relapsed MM seem so challenging?

Dingli D et al, Mayo clin Proc 2017 Apr;92(4):578-598; R Core Team (2013). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/.

Relapsed Multiple Myeloma is Not One Disease!



Relapsed MM is a Biologically and Genetically Heterogeneous Disease



Manier, S. *et al.* (2016) Genomic complexity of multiple myeloma and its clinical implications
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2016.122

Key Questions to Ask for R/R MM

- 1. Sensitivity to PI/IMID/CD38?
- 2. Toxicity from prior therapy, and baseline comorbidities?
- 3. Urgent need to treat / how aggressive?
- 4. Prior autologous stem cell transplant?

Key Phase 3 Trials for Relapsed MM

Trial	Regimen and Comparator	Prior Therapies	N	Median PFS, Mo	Population
POLLUX[a]	DRd vs Rd	≥1	569	NR vs 18.4	IMiD sensitive
ELOQUENT-2[b]	ERd vs Rd	1 – 3	646	19.4 vs 14.9	IMiD sensitive
ASPIRE[c]	KRd vs Rd	1 – 3	792	26.3 vs 17.6	PI/IMiD sensitive
CANDOR[d]	KDd vs Kd	1 – 3	466	NR vs 15.8	PR to ≥ 1 prior line
CASTOR[e]	DVd vs Vd	≥1	498	NR vs 7.2	PI sensitive
ENDEAVOR[f]	Kd vs Vd	1 – 3	929	18.7 vs 9.4	PI sensitive
PANORAMA[g]	PanoVd vs Vd	1 – 3	768	12 vs 8.7	PI sensitive
ARROW[h]	Kd weekly vs Kd twice wk	≥2	478	11.2 vs 7.6	Carfilzomib naive

[a] Dimopoulos et al, NEJM 2016 Oct 6:275(14):1319-1331; [b] Lonial S et al, NEJM 2015 Aug 13;373(7):621-31; [c] Stewart AK et al, NEJM 2015 Jan 8;372(2):142-52; [d] Dimopoulos et al, Lancet 2020; [e] Palumbo et al, NEJM 2016 Aug 25;375(8):754-66; [f] Dimopoulos et al Lancet Oncol 2016 Jan;17(1):27-38 [g] San-Miguel JF et al, Lancet Haematol 2016 Nov;3(11):e506-e515; Moreau P et al, Lancet Oncol 2018 Jul;19(7):953-964

In General, 3 Drugs >> 2 Drugs

- Many studies have shown that 3 drug treatment is superior to 2 drug therapy for relapsed multiple myeloma
- In general, 3 drug regimens should be the standard for treatment of relapsed MM
- However, cannot always use a one size fits all approach – personalization is key

Toxicities from Prior Therapy & Other Comorbidities to Consider

- Bortezomib – peripheral neuropathy (with or without pain)
- COPD/Asthma – can use daratumumab, but cautiously
- Congestive heart failure – careful with carfilzomib
- General frailty – 2 drug vs 3 drug

Carfilzomib for Relapsed Multiple Myeloma

- Options for use:
  - Carfilzomib + Dexathasone (ENDEAVOR)[a]
  - Carfilzomib + IMID (ASPIRE)[b]
  - Carfilzomib + Alkylator[c]
  - Carfilzomib + Monoclonal Antibody (MMY1001)[d]
- Is retreatment with bortezomib an option?
- Choice of PI should be driven by safety issues, patient preference (e.g., peripheral neuropathy history, or cardiac/renal issues)
- Consider for 'aggressive relapse' – proteasome inhibitors tend to work quickly

a. Dimopoulos et al Lancet Oncol 2016 Jan;17(1):27-38; b. Stewart AK et al, NEJM 2015 Jan 8;372(2):142-52 c. Bringhen et al, Blood 2014 Jul 3;124(1):63-9; d. Chari A et al, ASCO Annual Conference 2018

Weekly Carfilzomib – ARROW Trial

Arm A: Once-weekly carfilzomib + dex

(30 min infusion of K)

Carfilzomib 20 mg/m^2 IV D1 (Cycle 1)
Carfilzomib 70 mg/m^2 IV D8, 15 (Cycle 1), D1, 8, 15 (Cycle 2+)
Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

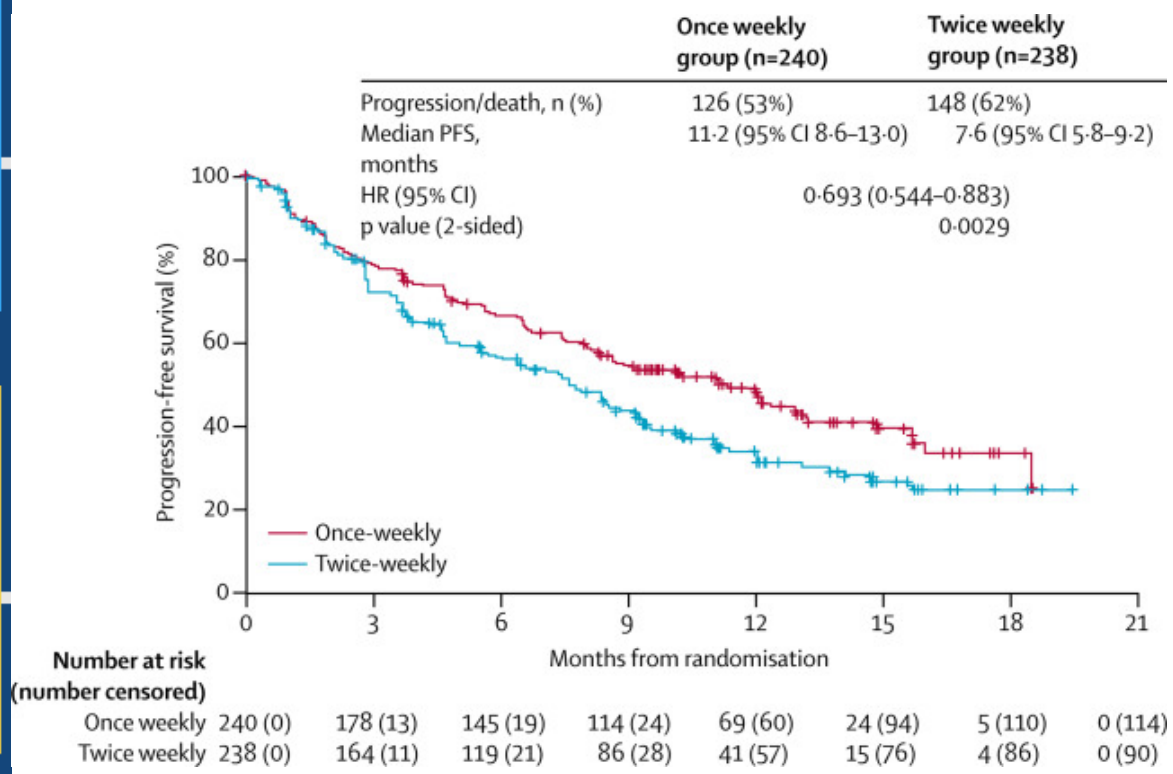
28-day cycles

Arm B: Twice-weekly carfilzomib + dex

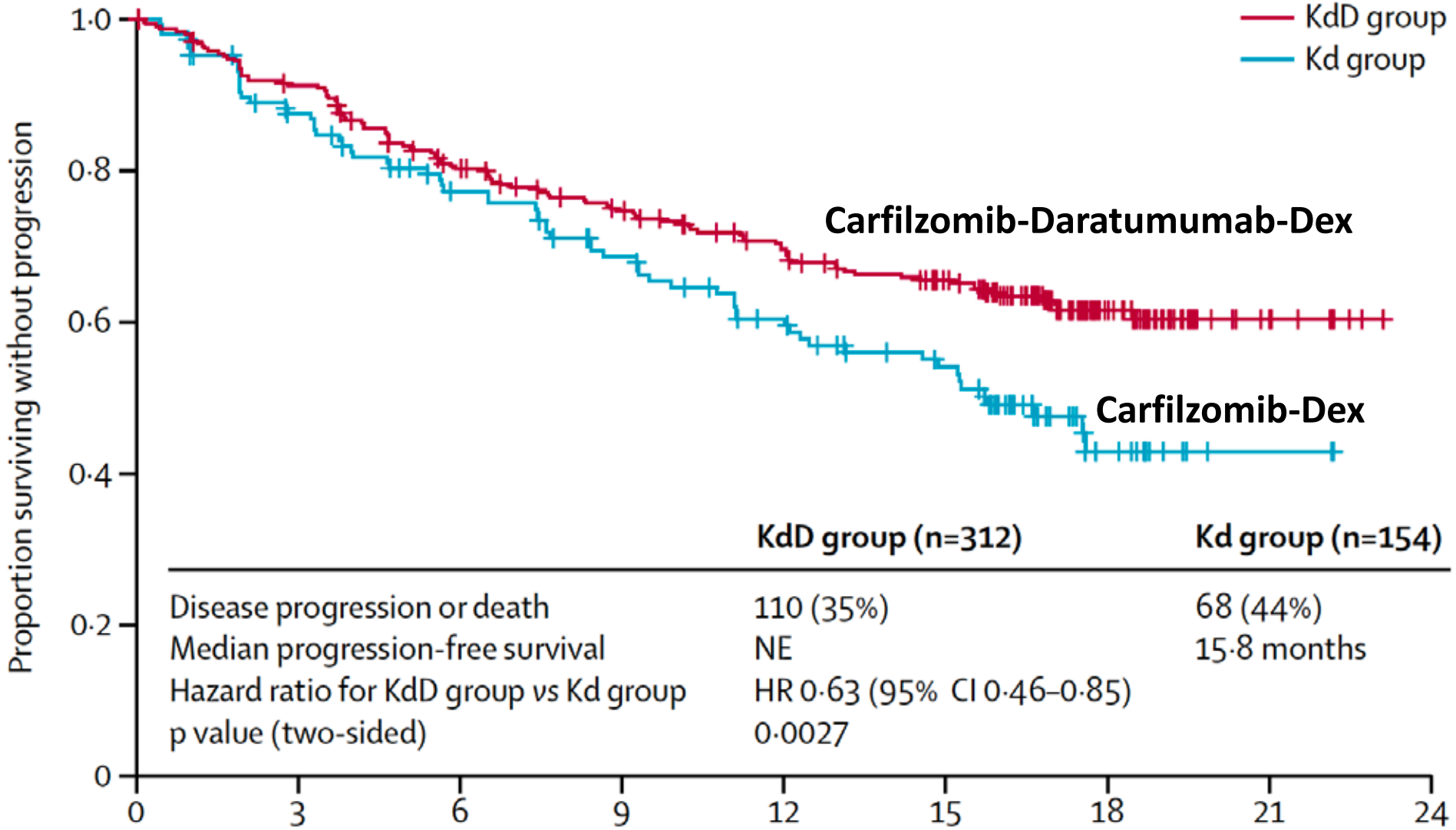
(10 min infusion of K)

Carfilzomib 20 mg/m^2 IV D1, 2 (Cycle 1)
Carfilzomib 27 mg/m^2 IV D8, 9, 15, 16 (Cycle 1), D1, 2, 8, 9, 15, 16 (Cycle 2+)
Dexamethasone 40 mg IV/PO D1, 8, 15 (All cycles)
Dexamethasone 40 mg IV/PO D22 (Cycles 1-9 only)

Primary end point: PFS



Moreau P et al, Lancet Oncology 2018 Jul;19(7):953-964



	KdD group (n=312)	Kd group (n=154)
Disease progression or death	110 (35%)	68 (44%)
Median progression-free survival	NE	15·8 months
Hazard ratio for KdD group *vs* Kd group	HR 0·63 (95% CI 0·46–0·85)	
p value (two-sided)	0·0027	

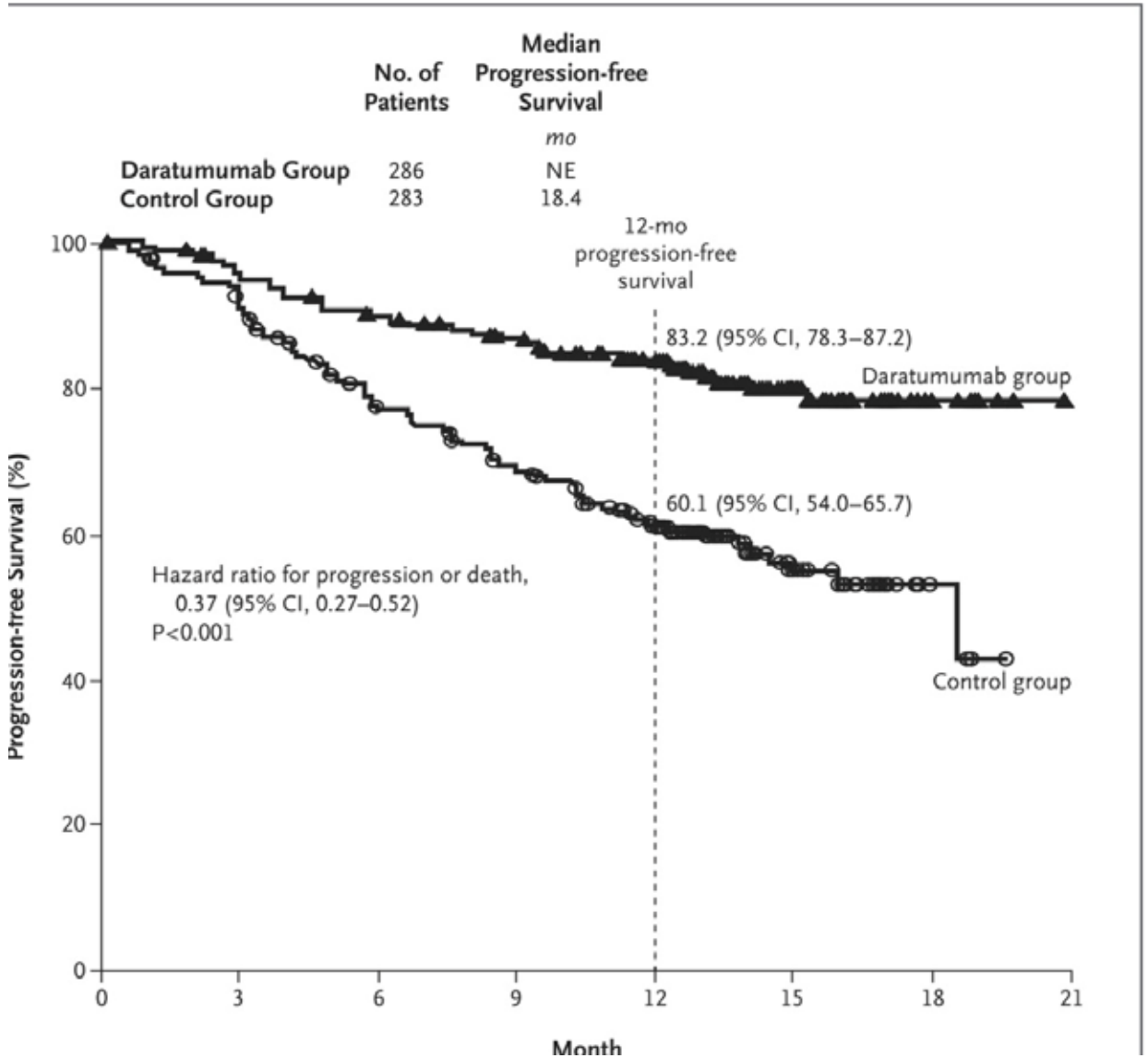
Number at risk

KdD group	312	279	236	211	189	165	57	14	0
Kd group	154	122	100	85	70	55	13	2	0

Dimopoulos et al. Lancet 2020

Daratumumab for Relapsed MM

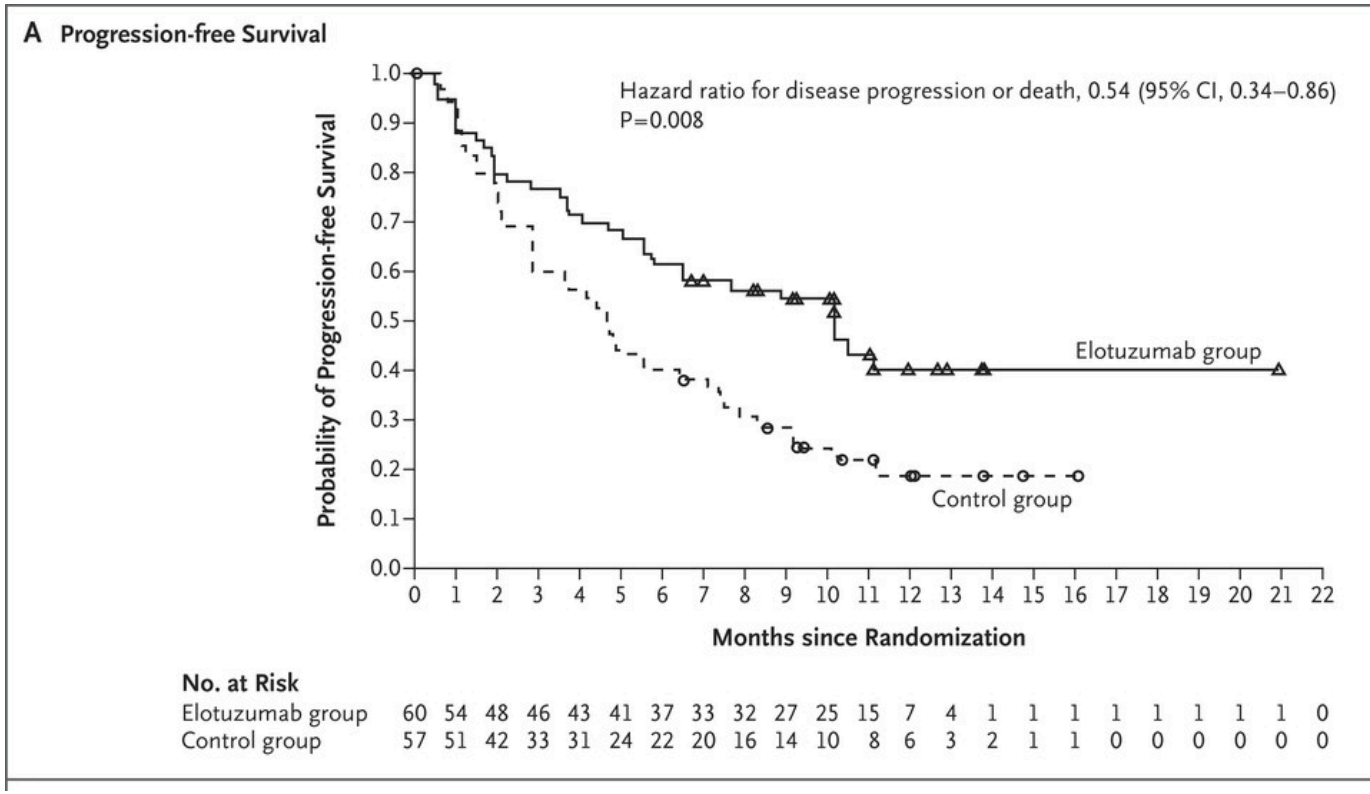
- Daratumumab, lenalidomide, and dexamethasone
  - POLLUX Trial, NEJM 2016[a]
- Daratumumab, bortezomib, dexamethasone
  - CASTOR Trial, NEJM 2016[b]
- Daratumumab, pomalidomide, dexamethasone
  - EQUULEUS, Blood 2017[c]
- Daratumumab and dexamethasone
  - SIRIUS Trial, Blood 2016[d]



a.Dimopoulos et al, NEJM 2016 Oct 6:275(14):1319-1331
b. Palumbo et al, NEJM 2016 Aug 25;375(8):754-66
c. Chari A et al, Blood 2017 Aug 24;130(8):974-981
d. Lonial S et al, Lancet 2016 Apr 9;387(10027):1551-60

Elotozumab / IMiD for Relapsed MM

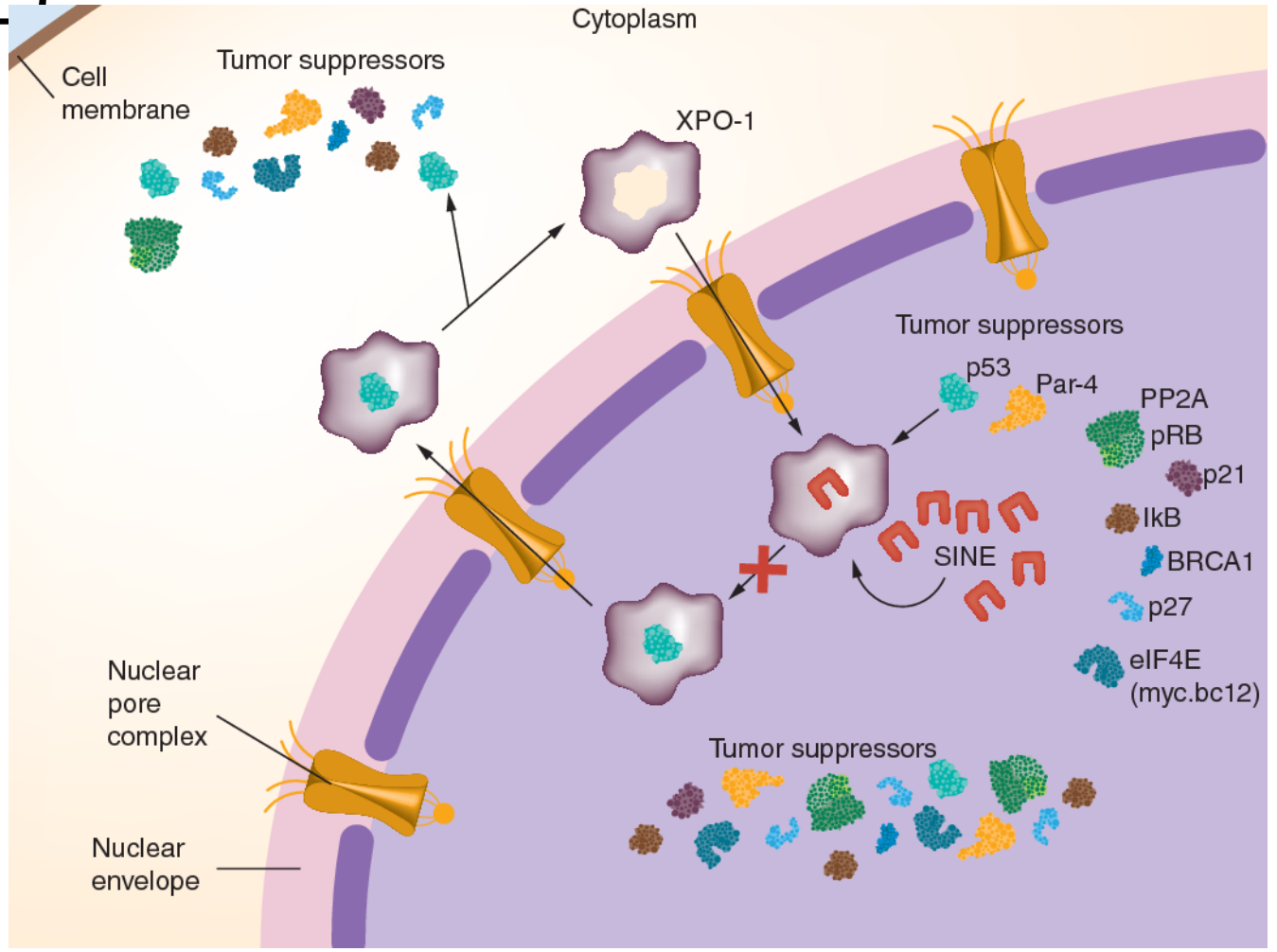
- Important – Elotuzumab has no single agent activity
- SLAMF7 Monoclonal Antibody
- ELOQUENT-2 Trial: Elotuzumab, lenalidomide, dexamethasone[a]
- ELOQUENT-3 Trial: Elotuzumab, pomalidomide, dexamethasone[b]



a. Lonial S et al, NEJM 2015 Aug 13;373(7):621-31
b. Dimopoulos et al NEJM 2018 Nov 8;379(19):1811-1822

Selinexor: First in class, oral Selective Inhibitor of Nuclear Export (SINE)[1-3]

- Exportin 1 (XPO1): major nuclear export protein for:
  - Tumor suppressor proteins, Glucocorticoid receptor, oncoprotein mRNAs
- XPO1 – highly overexpressed in MM; correlate with poor prognosis, drug resistance

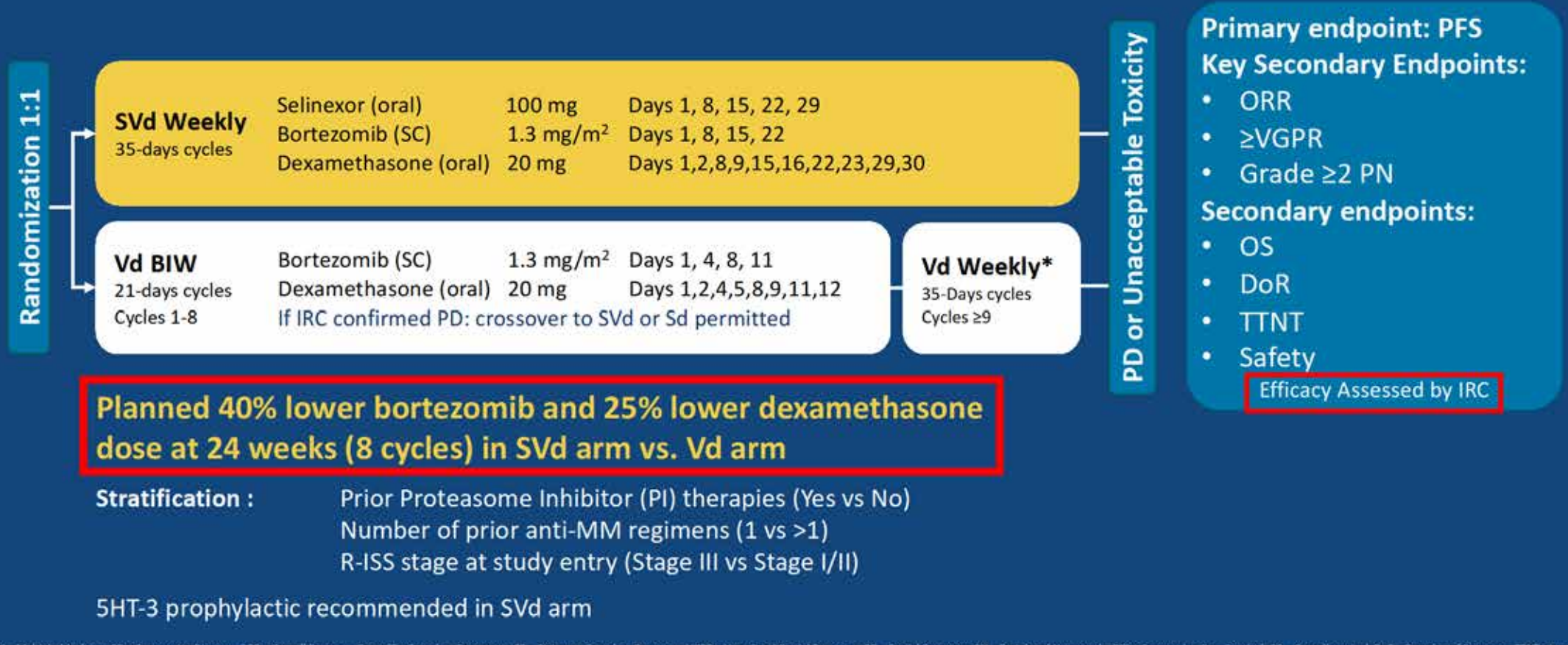


1. Schmidt et al, Leukemia, 2013; 2. Tai et al, Leukemia 2013; 3. Argueta et al, Oncotarget 2018, 4. Talati et al, Int J Hematologic Onc 2018

Selinexor: Phase 2B STORM Trial

- STORM Trial: Selinexor 80 mg and Dexamethasone 20 mg twice weekly
- Population: PI/IMiD, Daratumumab resistant
- Overall response rate: 26.2%
  - sCR (2), VGPR (6), PR (24)
- Median PFS 3.7 mos (5.3 mos if ≥ PR), median OS of 8.6 months
- FDA Approval 7/2019 for relapsed multiple myeloma

BOSTON Trial: Phase 3, Global, Randomized, Open Label, Controlled Study in Patients with Multiple Myeloma who Had Received 1-3 Prior Therapies



Planned 40% lower bortezomib and 25% lower dexamethasone dose at 24 weeks (8 cycles) in SVd arm vs. Vd arm

Stratification : Prior Proteasome Inhibitor (PI) therapies (Yes vs No)
Number of prior anti-MM regimens (1 vs >1)
R-ISS stage at study entry (Stage III vs Stage I/II)

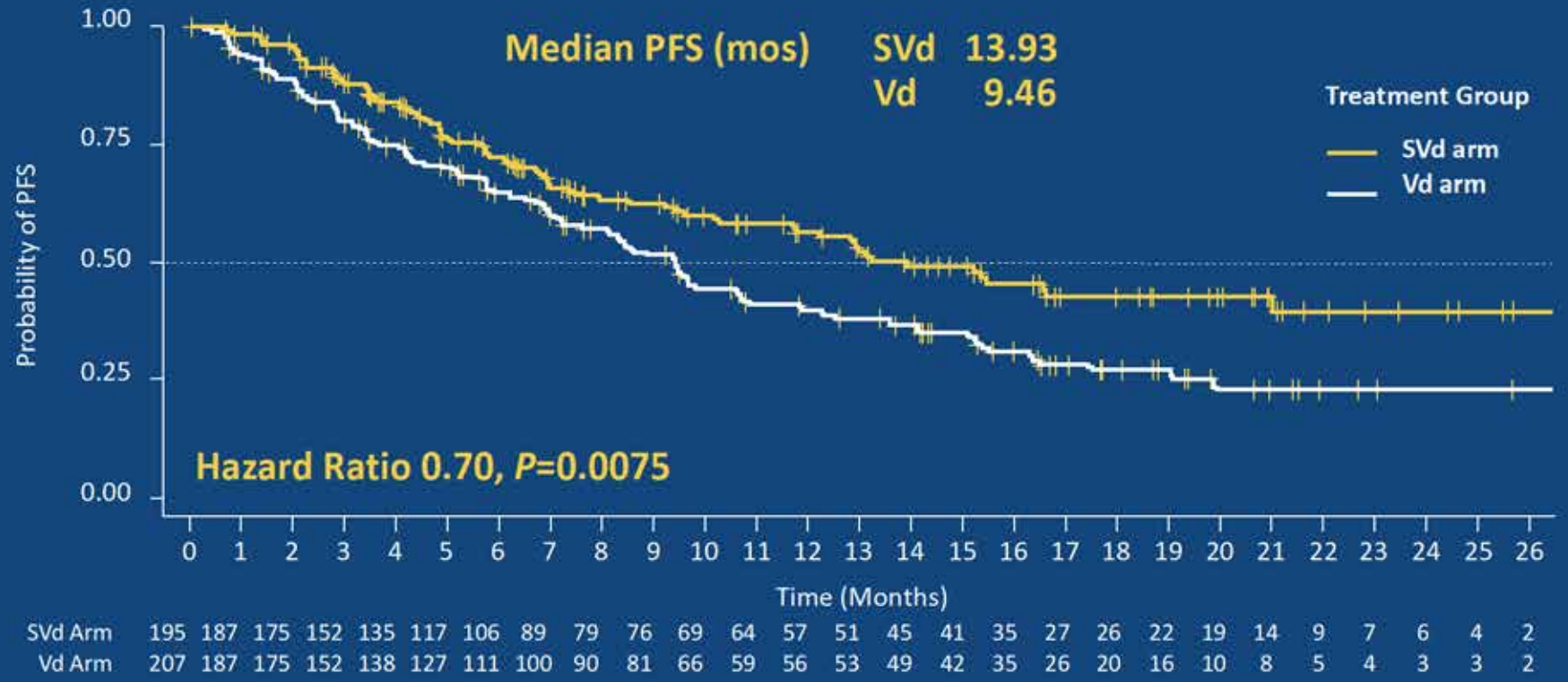
5HT-3 prophylactic recommended in SVd arm

MM = Multiple Myeloma, PD = Progressive Disease, ORR = Overall Response Rate, CR= Complete Response, sCR = Stringent Complete Response, VGPR = Very Good Partial Response, PR = Partial Response, PN = Peripheral Neuropathy PFS = Progression Free Survival, OS = Overall survival, DoR = Duration of Response, TTNT: time to Next Therapy, IRC = Independent Review Committee, IMWG = International Myeloma Working Group. PFS defined as: Time from date of randomization until the first date of progressive disease, per IMWG response criteria, or death due to any cause, whichever occurred first, as assessed by IRC. ORR: Any response ≥PR (ie, PR, VGPR, CR, or sCR) based on the IRC's response outcome assessments, according to IMWG response criteria (Kumar et al. Lancet oncology 2016). All changes in MM disease assessments were based on baseline MM disease assessments. * Vd weekly dosing and schedule for cycles≥ 9 as per SVd arm description

Dimopoulos MA et al, ASCO Annual Meeting 2020

BOSTON Trial: PFS significantly longer with SVd compared to Vd

Early and Sustained PFS benefit (assessed by IRC)



Intention-to-treat (ITT) population N=402, Data cut-off February 18, 2020
*HR=Hazard Ratio 95% CI=0.53–0.93 one-sided *P* value

Median follow-up 13.2 and 16.5 months in SVd and Vd arms respectively

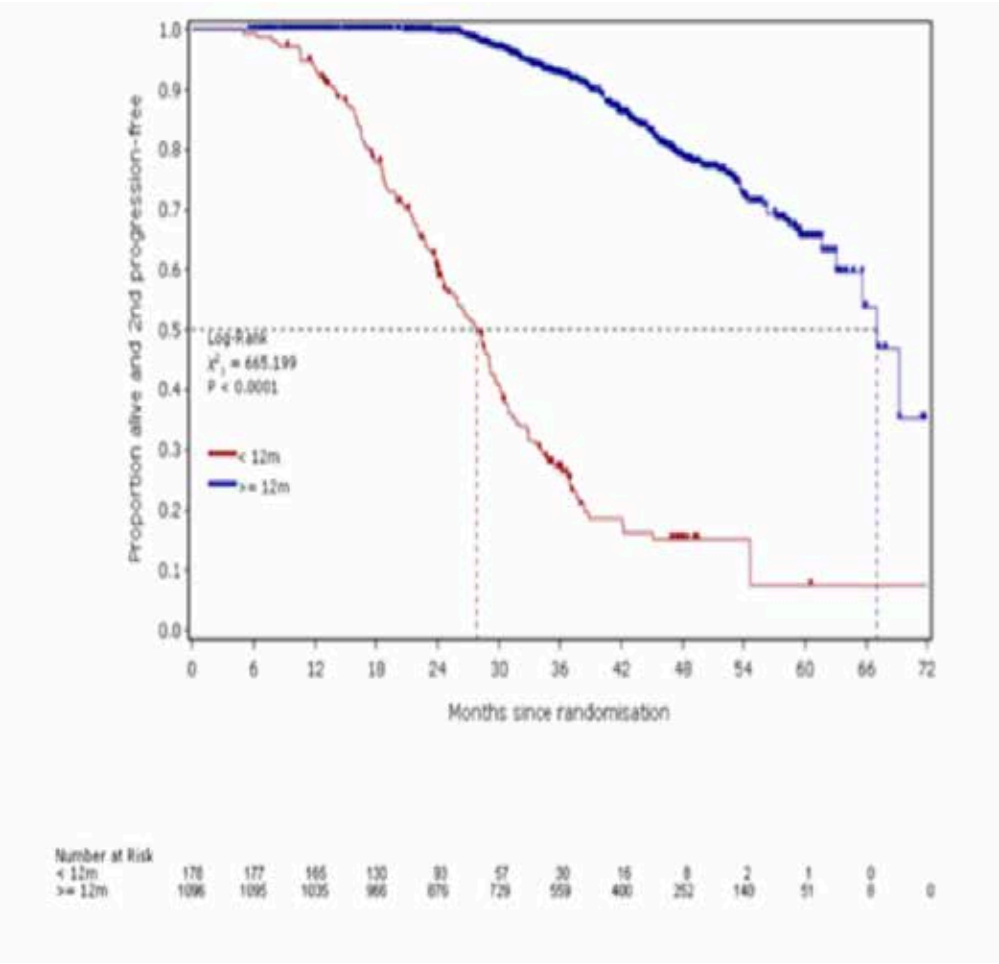
Dimopoulos MA et al, ASCO Annual Meeting 2020

The Type, Timing of MM Relapse is Important

- Biochemical (i.e., rise in M protein or serum free light chains), vs clinical (i.e., new onset **CRAB** symptoms or extramedullary disease)

- Timing of relapse - example: relapse post autologous

  - In MRC IX Trial: Relapse at < 12 months post autologous stem cell transplant associated with worse PFS[a]



Bygrave CA et al, ASH Annual Conference 2018, San Diego

Using Genetic Changes to Guide Treatment Choice

- High risk Myeloma: e.g., Del(17p), t(4;14), t(14;16), t(14;20), 1q+/1p-, continuous therapy, 3 drug regimens.

- t(11;14) – sensitivity to venetoclax, a BCL2 inhibitor – investigational at this time, not FDA approved

- Plasma cell leukemia – unique disease biology. Anthracycline based regimens (e.g., VTD PACE, Hyper CVAD)

What About Late Relapse after Transplant?

- Current state of underlying organ function / frailty index?
- Stem cells still stored? (viability has been good at our center up to 10 years and beyond)
- Relapse on maintenance or not on maintenance?
- Age, willingness to undergo second transplant?

When to consider 2nd transplant as a treatment for relapsed multiple myeloma

- A patient who previously underwent autologous transplantation may be eligible for a second transplant if the duration of remission from the first transplant was > 18-24 months (probably 3-4 years if on maintenance therapy).
- If no maintenance was received post transplant #1, then it should be considered strongly after transplant #2
- If initial therapy only included RVD and maintenance (no transplant), then autologous transplant should be STRONGLY considered as the next best therapy once in remission

Laubach et al, Leukemia 2016 May;30(5):1005-17; Attal et al, Blood 2017 Apr 6;376(14):1311-1320

Outcomes for Salvage Transplant in Relapsed MM

	Months from auto-SCT2, median (range)	
Time to progression after auto-SCT1 (N)	PFS	OS
<12 months (9)	5.6 (3–8)	12.6 (4–23)
<18 months (25)	7.1 (6–8)	19.4 (10–42)
<24 months (47)	7.3 (6–10)	22.7 (13–62)
<36 months (68)	7.6 (7–12)	30.5 (19–62)

Gonsalves WI et al BMT 2013 Apr;48(4):568-73

Summary

- Upfront myeloma treatment: transplant ineligible vs eligible; 3 drugs are superior (and 4, coming soon)!
- There are many options for treating relapsed multiple myeloma, and…

  Personalization is key!
- Choose therapies based on prior sensitivity, disease status, toxicities, and general state of the patient (frail vs robust)
- Autologous transplantation should be considered in appropriate patients

Thank you – PATIENTS AND FAMILIES

- UW/FHCRC/SCCA Heme Malig/MM
  - Damian Green
  - Edward Libby
  - Pamela Becker
  - David Coffey
  - Leona Holmberg
  - Sherilyn Tuazon
  - Teresa Hyun
  - Ajay Gopal

Seattle Cancer Care Alliance
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Adjuvant Breast Cancer

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Disclosures

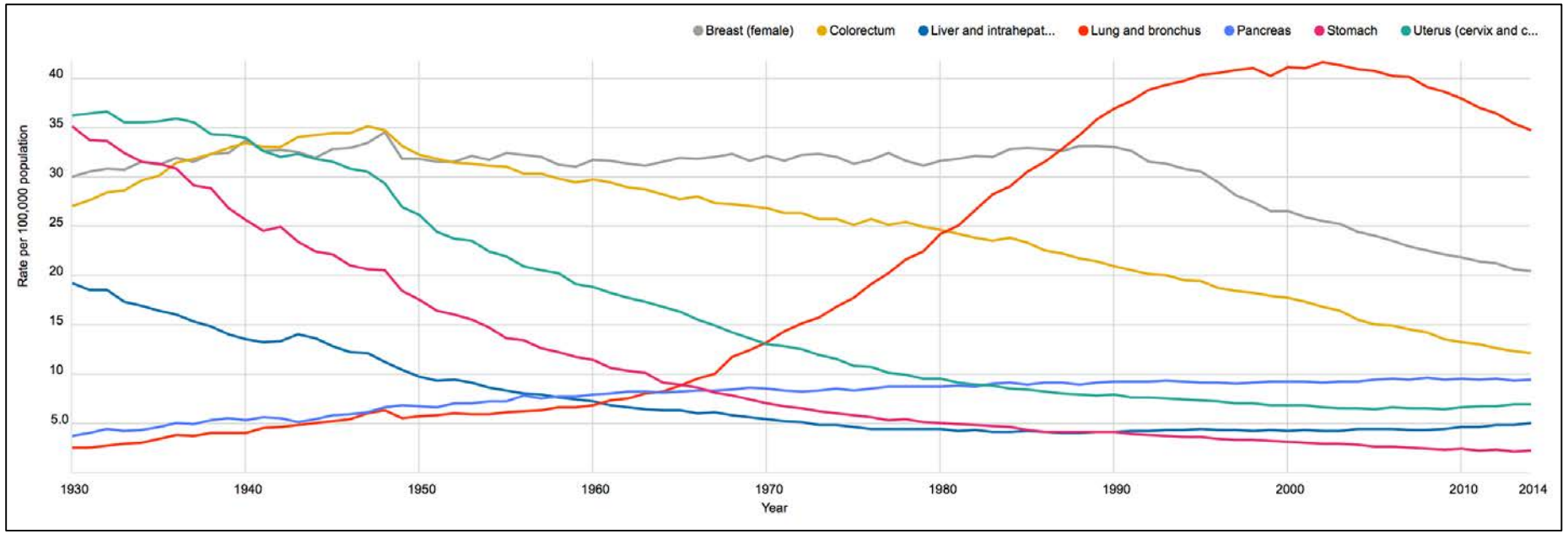
- Financial Interests:
  - None

Overview

- Breast Cancer epidemiology
- Breast Cancer local therapy
- ER/PR+ Breast Cancer
  - Adjuvant Anti-Estrogen Therapy
  - Indications for Chemotherapy
- HER2+ Breast Cancer
  - Adjuvant Trastuzumab
  - Neoadjuvant Pertuzumab
- Adjuvant Chemotherapy

Breast Cancer - Epidemiology

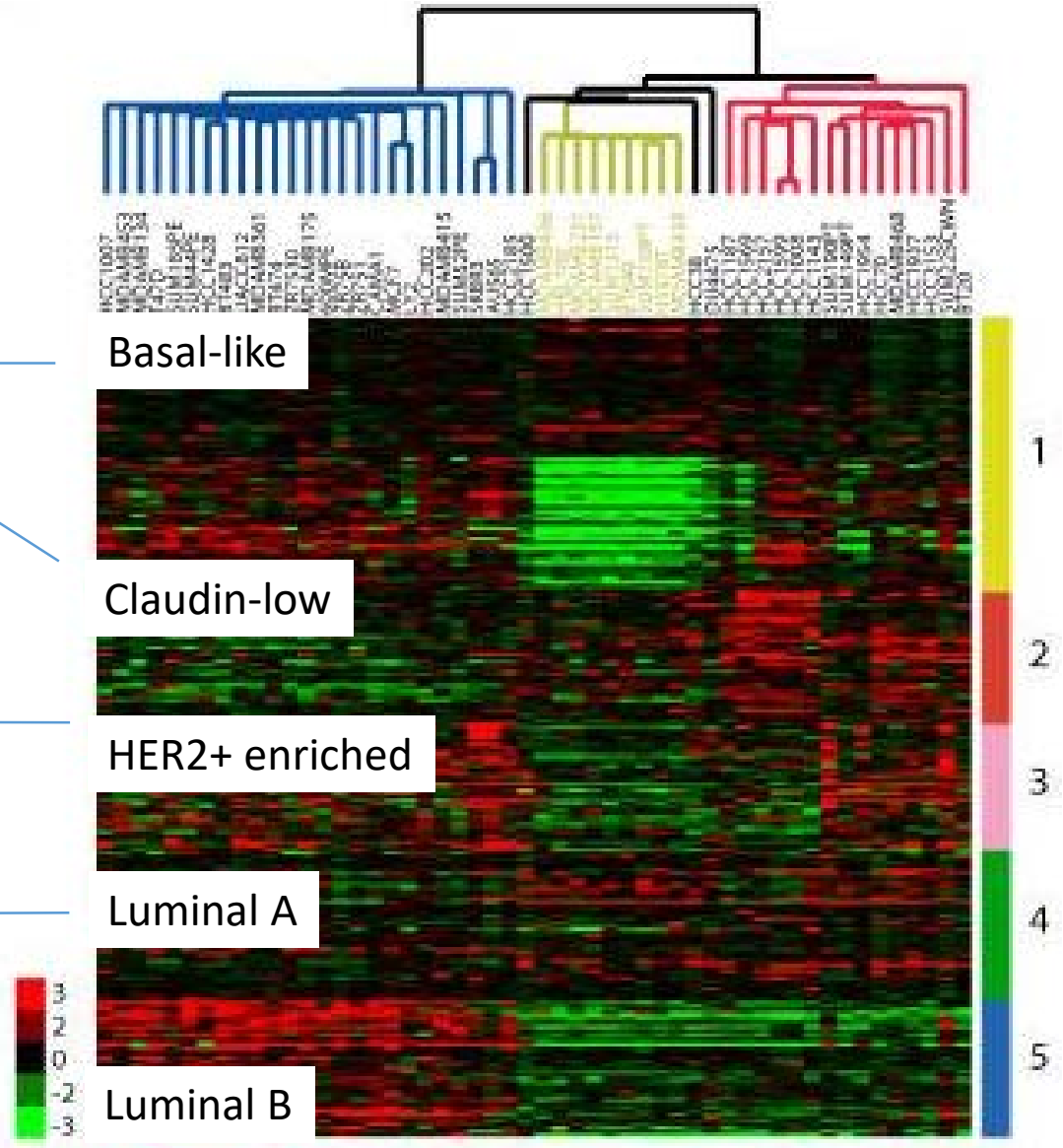
- Most common cancer in women and 2nd leading cause of cancer death in the US
- It is estimated that 268,600 individuals were diagnosed and 41,760 died of breast cancer in 2019
- 5 year Overall Survival 91%



American Cancer Society. Breast Cancer Facts & Figures 2019 – 2020 at www.cancer.org.

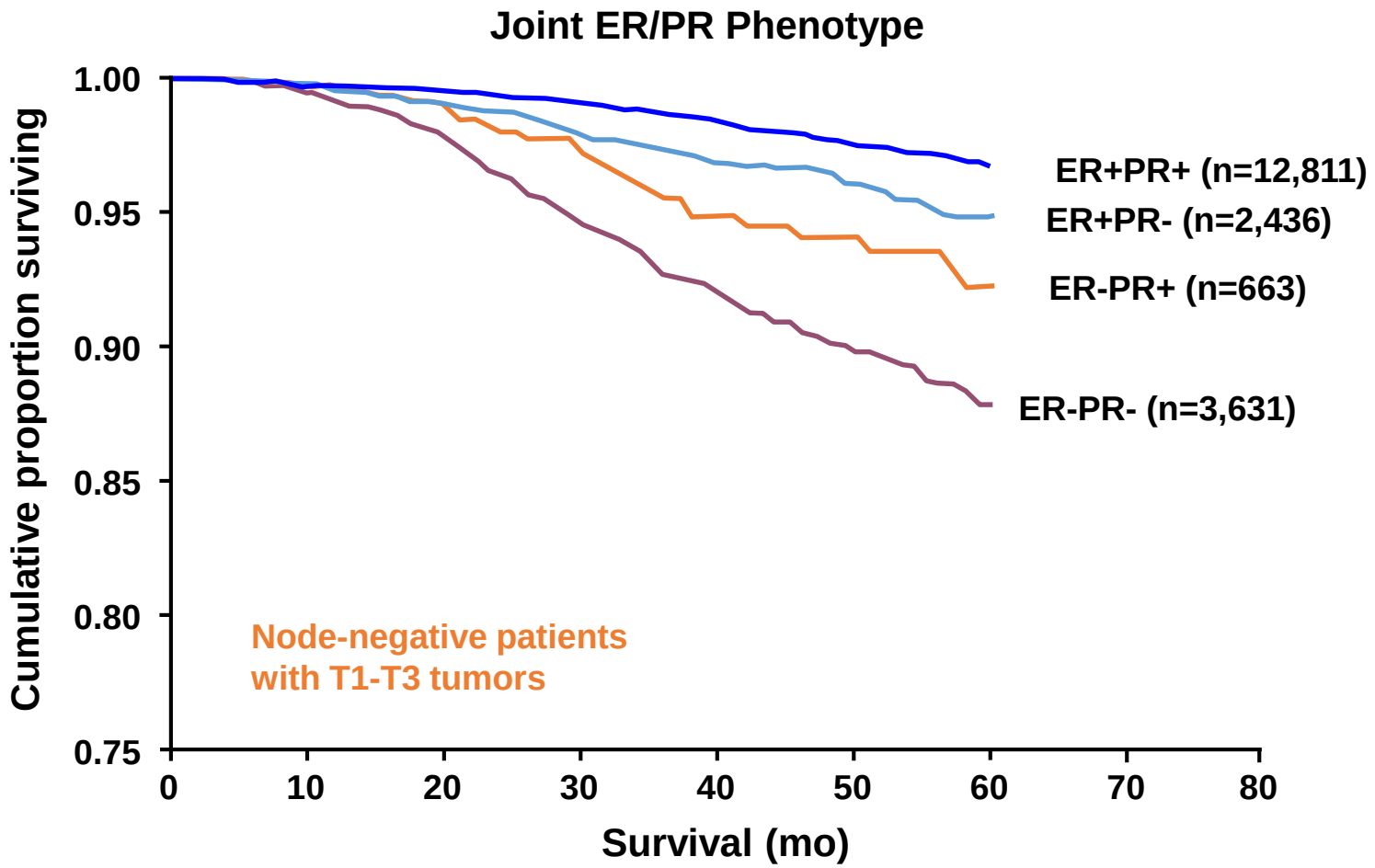
Breast Cancer Subtypes

- Triple Negative Breast Cancer (TNBC)
  - Estrogen Receptor (ER),Progesterone receptor (PR), and HER2 negative
  - Tx: Chemotherapy alone
- HER2 Positive Breast Cancer
  - HER2 overexpressing or amplified
  - Tx: Chemotherapy + HER2 therapy
- Hormone Receptor Positive BCa
  - Estrogen Receptor (ER) and / or Progesterone receptor (PR) positive
  - Tx: Anti-estrogen, Chemotherapy



Prat A, et al. Breast Cancer Res. 2010

Breast Cancer–Specific Survival by Joint Hormone Receptor Expression (SEER Data)

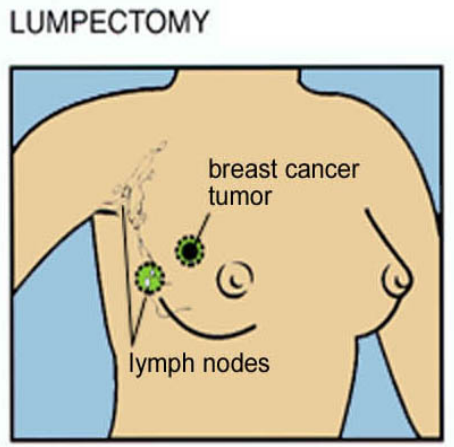


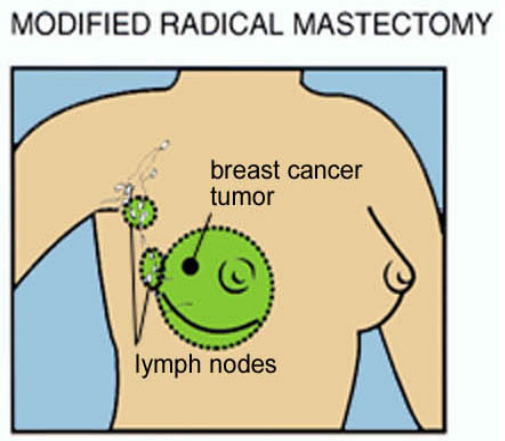
Anderson et al. *J Clin Oncol.* 2001;19:18.

Breast Cancer – Local Therapy

- Lumpectomy + Radiation (BCT) vs Mod Rad Mastectomy
  - 6 randomized trials
  - No survival difference

- Contraindications to breast conservation therapy (BCT)
  - Prior radiation
  - Multifocal disease
  - Ongoing pregnancy
  - Poor cosmetic outcome
  - Connective tissue disease involving the skin





Breast Cancer – Local Therapy

- Sentinel lymph node localization or Axillary LN dissection (AXLND)
  - Randomized trials confirmed utility of sentinel LN localization
- Is completion axillary LN dissection required for +SLN?
- ACOSOG Z0011 (Z11) Trial
  - Enrolled pts with clinically node negative w T1/T2 primary but <3+ LNs on SLN localization
  - Randomized to: Completion AXLND + XRT vs XRT alone
  - Results: No difference in DFS or OS at 10 yrs. follow-up

Giuliano AE, et al. JAMA. 2017

Biomarker testing

- ER and PR testing
  - Up to 20% inaccuracy
  - Determine on all invasive and recurrent cancers
  - Positive >1% positive tumor nuclei
- HER2
  - Up to 20% inaccuracy
  - Determine on all invasive cancers
  - Positive if IHC 3+ or FISH amplified
  - ASCO/CAP 2018 guidelines

Adjuvant Anti-Estrogen Therapy ER/PR+ Breast Cancer

Adjuvant Therapy – ER/PR+ disease

- Foundation of adjuvant therapy – anti-estrogen therapy
- Chemotherapy is not need in all cases
- Chemotherapy is always needed for:
  - Large primary tumor >5cm (T3 or T4)
  - >3+ axillary LNs
  - High Oncotype RS (>25)
  - High Risk Mammaprint (Clinically High Risk)
  - Inflammatory breast cancer

How Effective is Adjuvant Tamoxifen?

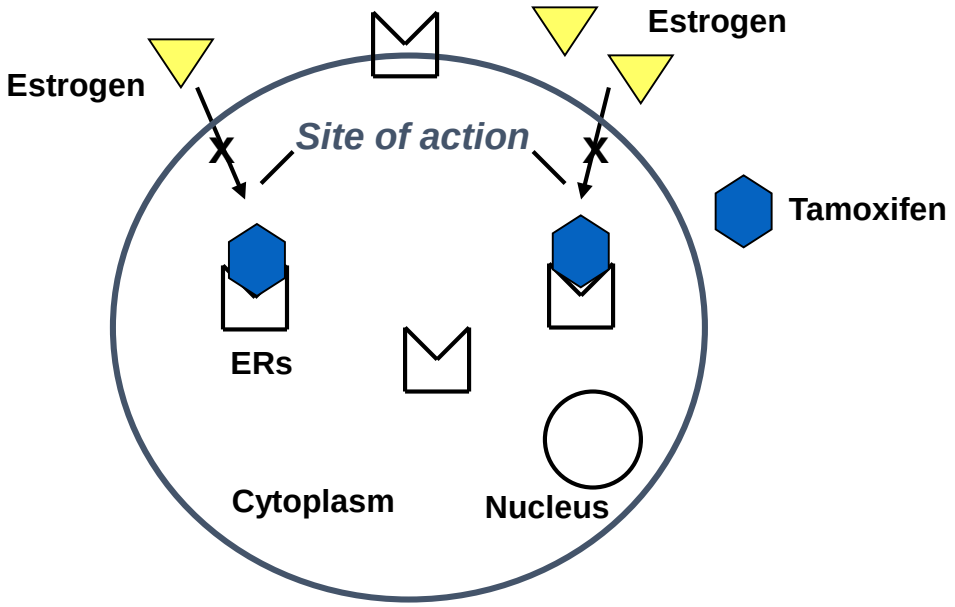
ER/PR+ Breast Cancer

Tamoxifen

- Selective estrogen receptor modulator (SERM)
  - Agonist: bone, liver, uterus
  - Antagonist: breast, CNS
- Effective in pre- and post-menopausal states
- Side effects:
  - Hot flashes
  - Mood alterations
  - Hair Thinning
  - Endometrial carcinoma (rare)
  - DVT/PE (rare)

Estrogen Receptor Antagonists

- Compete with estrogen binding to receptor[1]

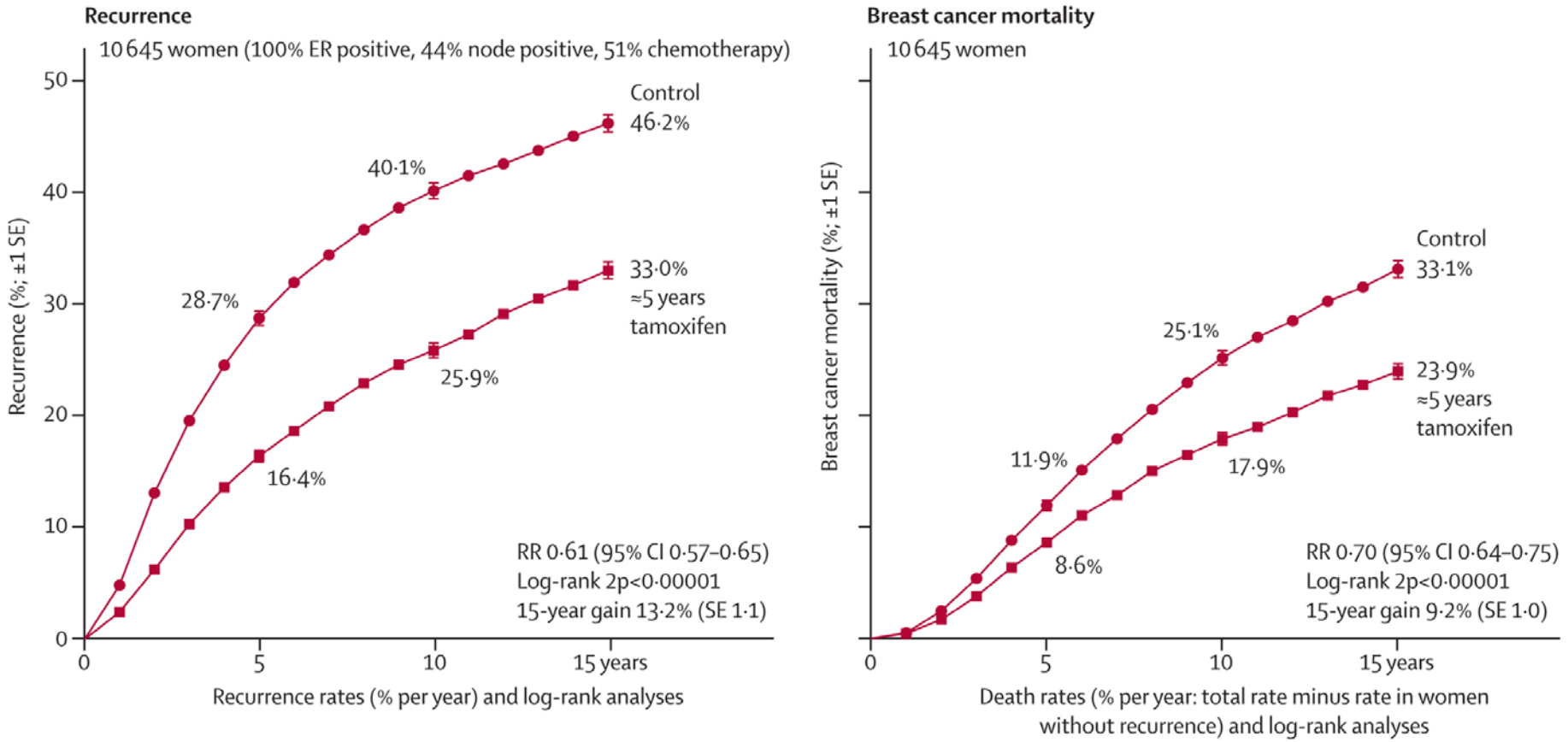


1. Gradishar WJ, Jordan VC. *Hematol Oncol Clin North Am*. 1999

EBCTCG Overview, 2000
% Alive with and without Tamoxifen in ER+

	5 years	*10 years*	*15 years*
Tamoxifen	91.4	80.9	73.0
Control	87.8	73.2	64.0
Reduction in Risk (SE)	3.6 (0.7)	7.8 (1.0)	9.0 (1.4)

Benefits of Adjuvant Tamoxifen (5 yrs., ER+)



Davies et al. EBCTCG, Lancet. Sept 2011

Post-menopausal women: Are Aromatase Inhibitors (AIs) Better Than Tamoxifen?

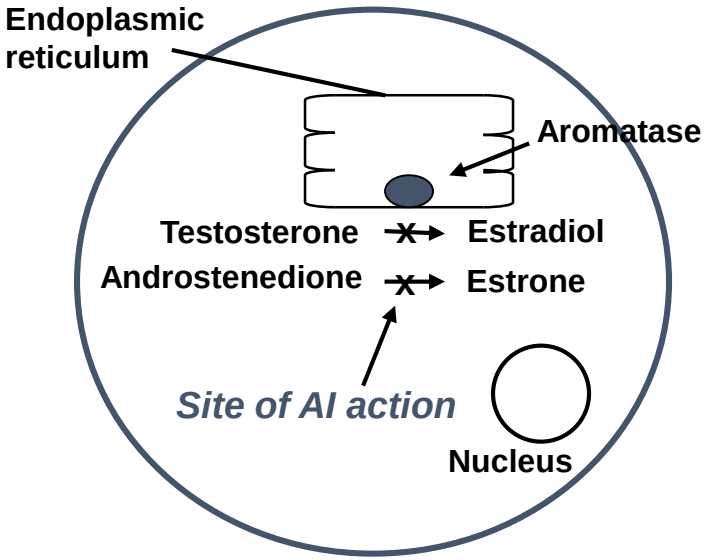
ER/PR+ Breast Cancer

Aromatase inhibitor (AI)

- Blocks aromatase, that converts androgens to estrogens
  - Aromatase is the main source of estrogen in post-menopausal women
- Side effects that of estrogen loss:
  - Hot flashes
  - Mood disturbances
  - Hair thinning
  - Accelerated loss of bone mineral density
  - Musculoskeletal pain and stiffness

Aromatase Inhibitors

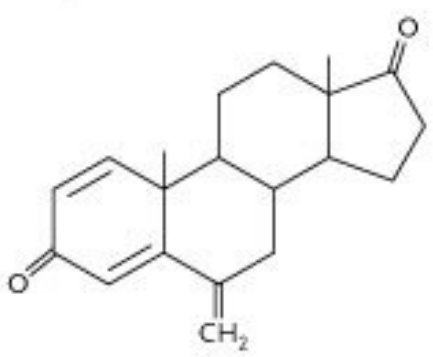
- Inhibit synthesis of estrogens[1,2]



1. Gradishar WJ, Jordan VC. *Hematol Oncol Clin North Am*. 1999; 2. Goldhirsch A, Gelber RD. *Semin Oncol*. 1996.

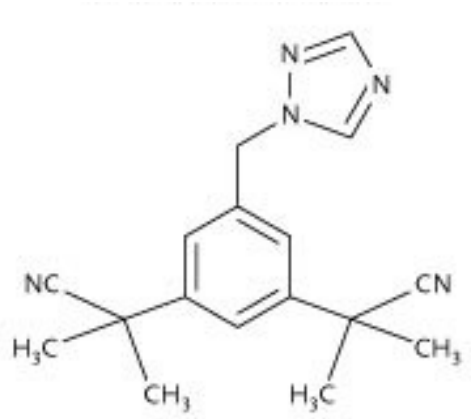
Aromatase Inhibitors

Steroidal Inactivator:

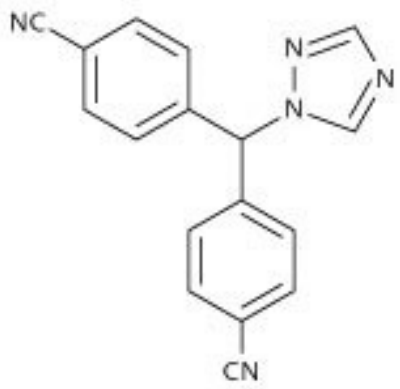


Exemestane
(third generation)

Nonsteroidal Inhibitors:



Anastrazole
(third generation)

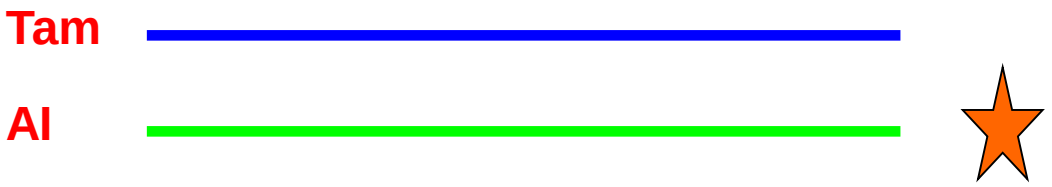


Letrozole
(third generation)

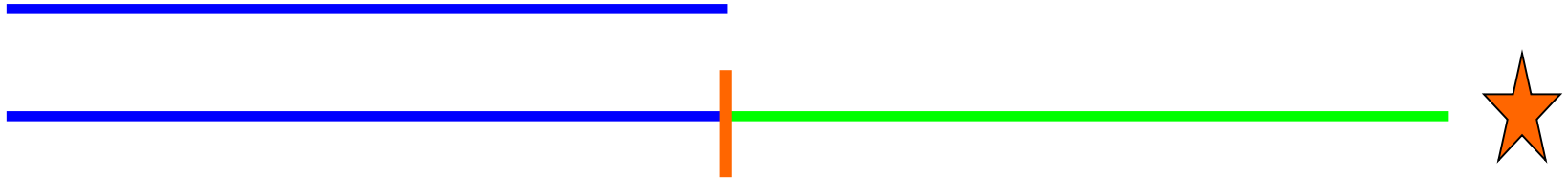
Smith et al. NEJM. 2003

Adjuvant Hormonal Therapy in ER+ Postmenopausal Breast Cancer

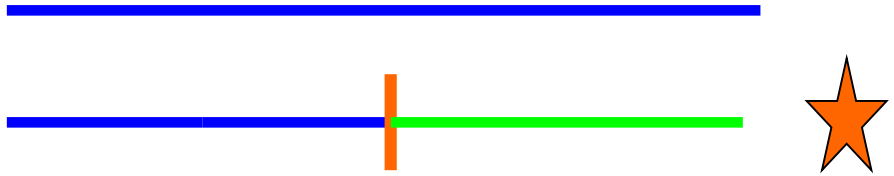
ATAC 2001: Tamoxifen *vs.* Anastrazole



MA-17 2003: Tamoxifen +/- Letrozole



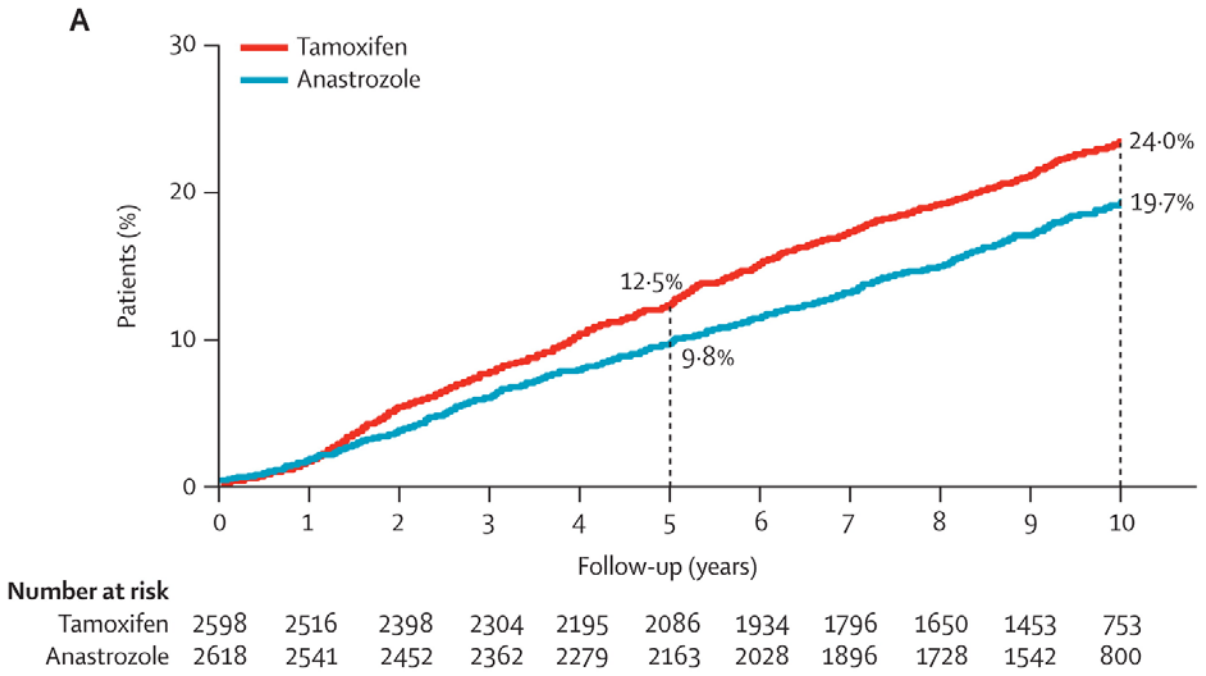
IES 2004: Tamoxifen *vs.* Switch to Exemestane



ATAC: Adjuvant Anastrazole vs Tamoxifen

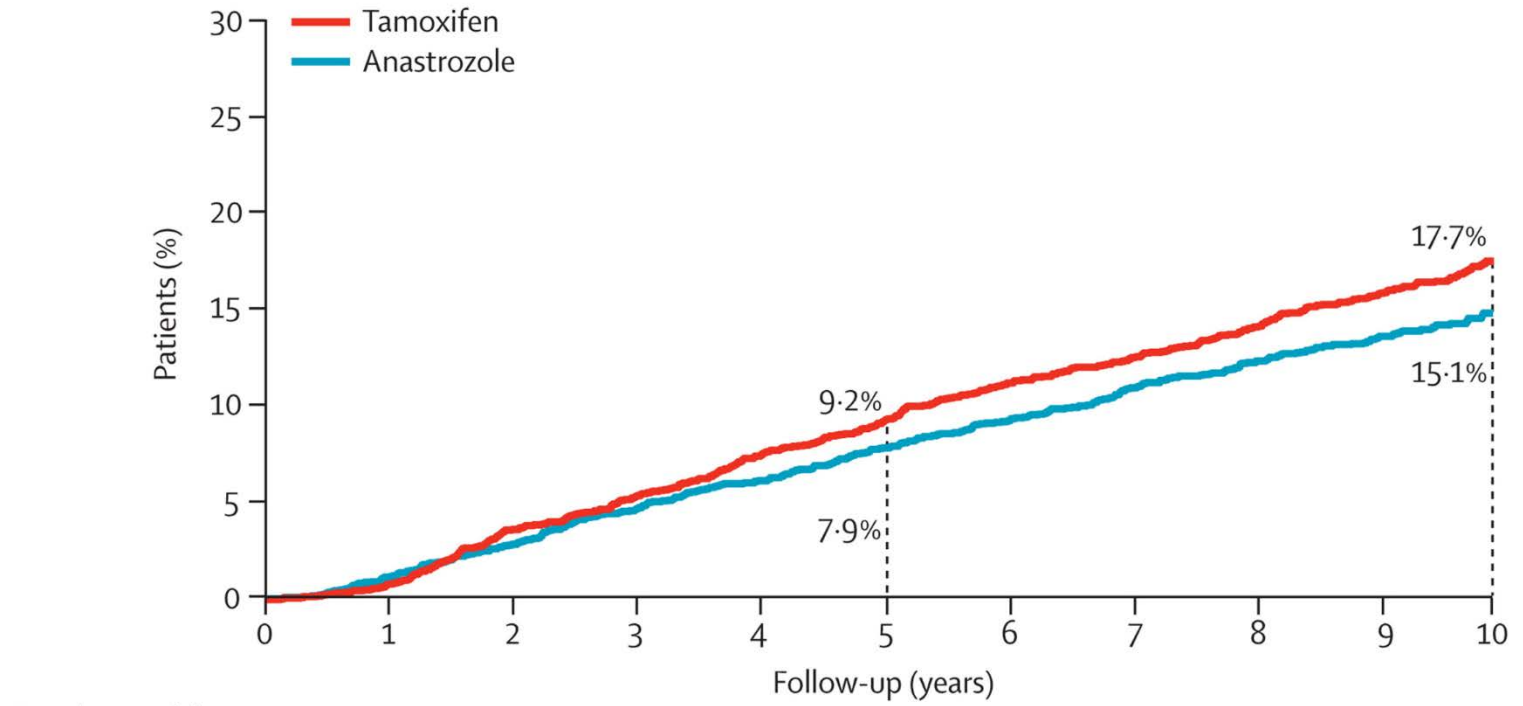
- 10 year follow-up of Anastrazole vs Tamoxifen in post-menopausal women

- Anastrazole significantly improved:
  - Time to recurrence
  - Disease-free survival
  - Time to distant recurrence



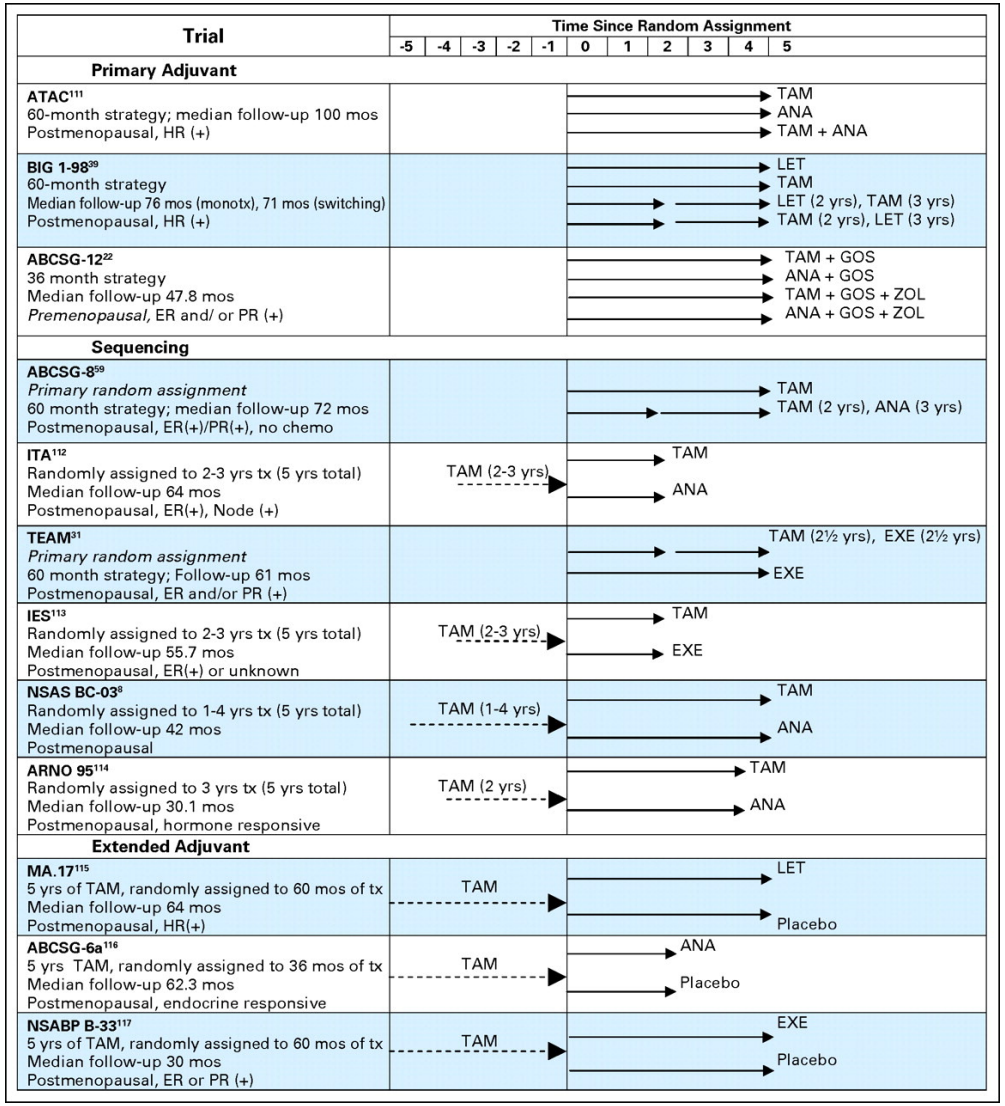
Cuzick et a. Lancet Oncol. 2010 Dec;11(12):1135-41.

ATAC: Time to distant recurrence



Cuzick et a. Lancet Oncol. 2010 Dec;11(12):1135-41.

Adjuvant Aromatase Inhibitor Trials



Absolute Gain in DFS of AI vs Tam at 3-6 yrs.

AI vs Tamoxifen Primary	2-4%
Tam -> AI Sequential	3-5%
Tam x 5 yrs. -> AI Extended	6%

Burstein et al. JCO 2010

Extended Adjuvant Anti-Estrogen Therapy

ER/PR+ Breast Cancer

Benefit of Tamoxifen by Period of Follow-up

	Events/woman-years		
	Tamoxifen	Control	Ratio of annual event rates (SE)
Years 0-1	3.2%	6.5%	0.47 (0.05)
Years 2-4	3.6%	5.9%	0.58 (0.05)
Years 5-9	2.6%	3.5%	0.69 (0.06)
Years 10+	2.6%	2.5%	1.01 (0.11)

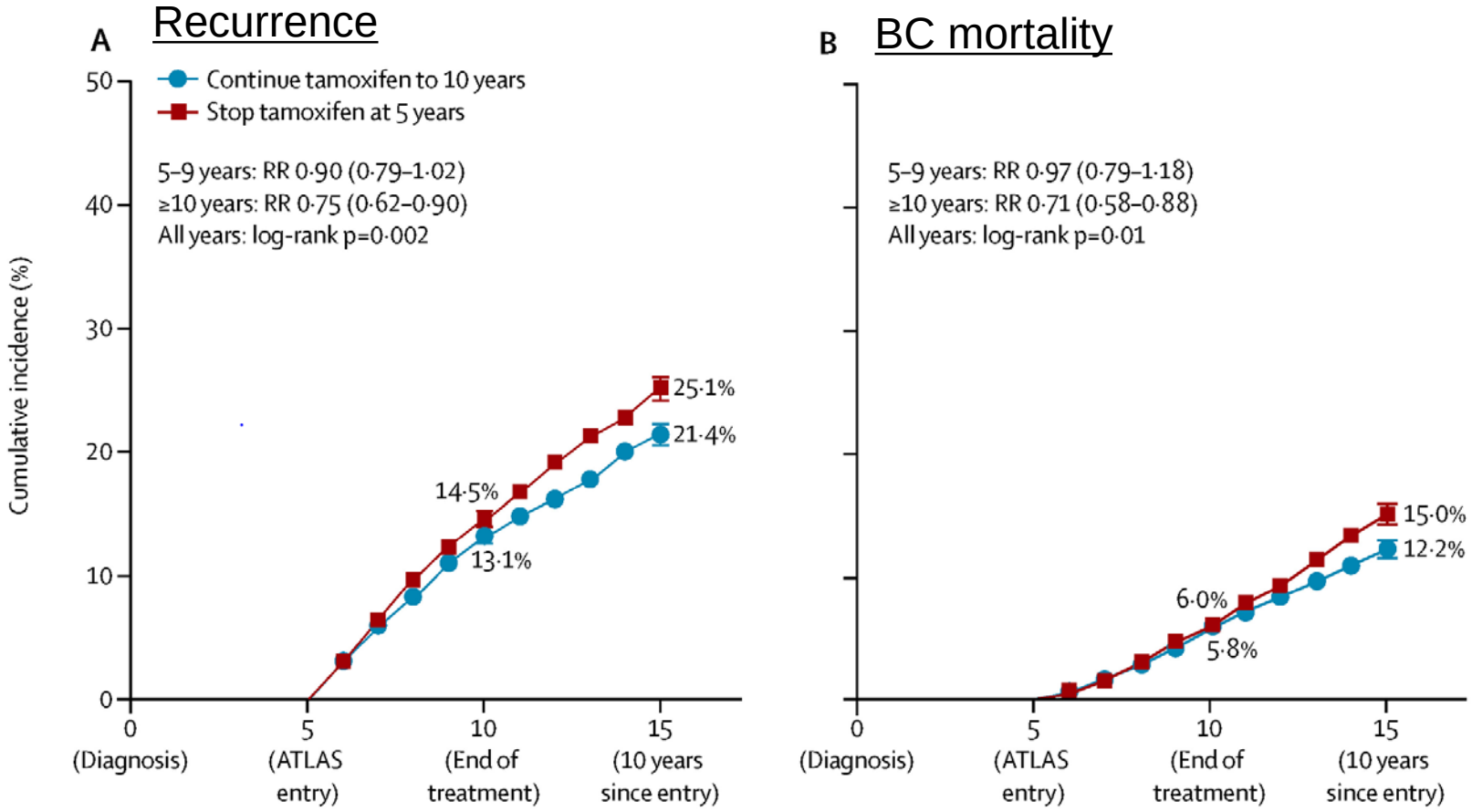
The benefit of 5 years of tamoxifen extends to 10 years, after which recurrence rates are similar.

EBCTCG, Lancet 365:1687-1717, 2005

ATLAS: 5 vs 10 yrs. of Tamoxifen

- N=6,846 who had received 5 yrs. of Tamoxifen

- Randomized to:
  - Additional Tam x 5 yrs.
  - Stopping Tam



- reduced BC mortality (331 *vs* 397 deaths, p=0·01)

- reduced overall mortality (639 *vs* 722 deaths, p=0·01)

Davies et al. Lancet. 2012 Dec 4.

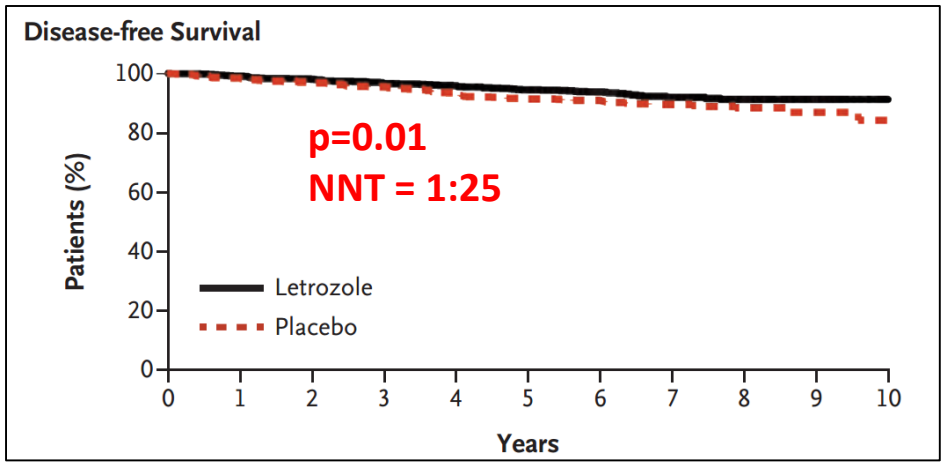
ATLAS: Adverse Events

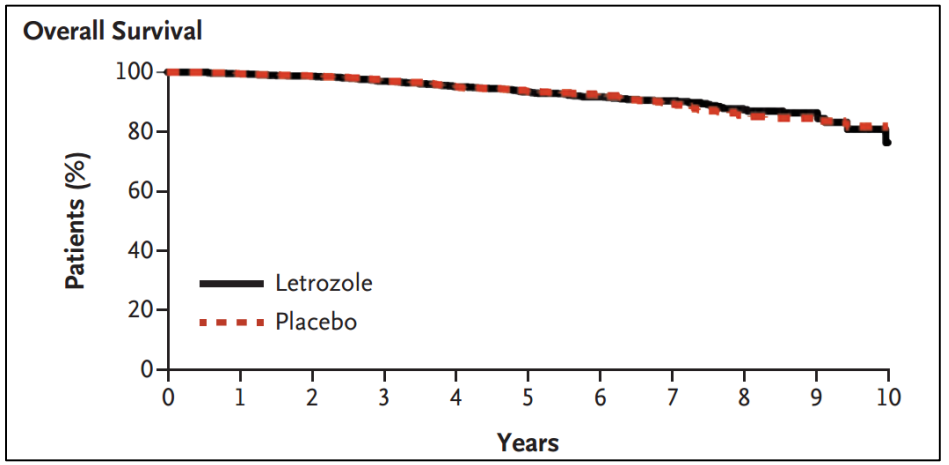
Death without recurrence			
Vascular death			
Stroke	1·03 (0·72–1·46)	0·89	
Pulmonary embolus	1·21 (0·48–3·04)	0·69	
Heart disease§	0·85 (0·69–1·03)	0·10	
Neoplastic death			
Endometrial cancer¶	1·49 (0·71–3·13)	0·29	
Other neoplastic disease	1·01 (0·74–1·39)	0·94	
Other death			
Specified cause	1·03 (0·83–1·28)	0·80	
Unspecified cause	1·06 (0·86–1·32)	0·58	
Second cancer incidence			
Contralateral breast cancer	0·88 (0·77–1·00)	0·05	
Endometrial cancer¶	1·74 (1·30–2·34)	0·0002	**+53 cases**
Primary liver cancer	0·99 (0·20–4·90)	0·99	
Colorectal cancer	0·86 (0·58–1·27)	0·44	
Unspecified site	0·99 (0·83–1·18)	0·91	
Non-neoplastic disease (ever hospitalised or died)			
Stroke	1·06 (0·83–1·36)	0·63	
Pulmonary embolus	1·87 (1·13–3·07)	0·01	**+20 cases**
Ischaemic heart disease	0·76 (0·60–0·95)	0·02	
Gallstones	1·11 (0·80–1·54)	0·54	
Cataract	1·11 (0·79–1·56)	0·54	
Bone fracture	0·86 (0·61–1·21)	0·39	

Davies et al. Lancet. 2012 Dec 4.

MA.17R: Extended Adjuvant with AI

- Breast cancer pts who had completed 5 yrs. of adjuvant anti-estrogen therapy
- 5-year disease-free survival rate:
  - Letrozole - 95%
  - Placebo - 91%
- No significant difference in overall survival





Goss et al, NEJM 2016

MA.17R: +10 years AI?

Variable	Letrozole (N=959)	Placebo (N=959)
	number (percent)	
Patients with a recurrence of the primary cancer or with contralateral breast cancer	67 (7.0)	98 (10.2)
Recurrence*†	55 (5.7)	68 (7.1)
Local breast	8 (0.8)	10 (1.0)
Local chest wall	6 (0.6)	7 (0.7)
Regional	5 (0.5)	13 (1.4)
Distant	42 (4.4)	53 (5.5)
Contralateral breast cancer†	13 (1.4)	31 (3.2)

NNT = Distant Mets1:100

NNH =

1. Fracture, 1:20 (14% v 9%, p=0.001)
2. New osteoporosis, 1:20 (11% v 6%, p<0.001)

Goss et al, NEJM 2016

Pre-menopausal women and adjuvant anti-estrogen therapy

ER/PR+ Breast Cancer

Adjuvant ovarian suppression

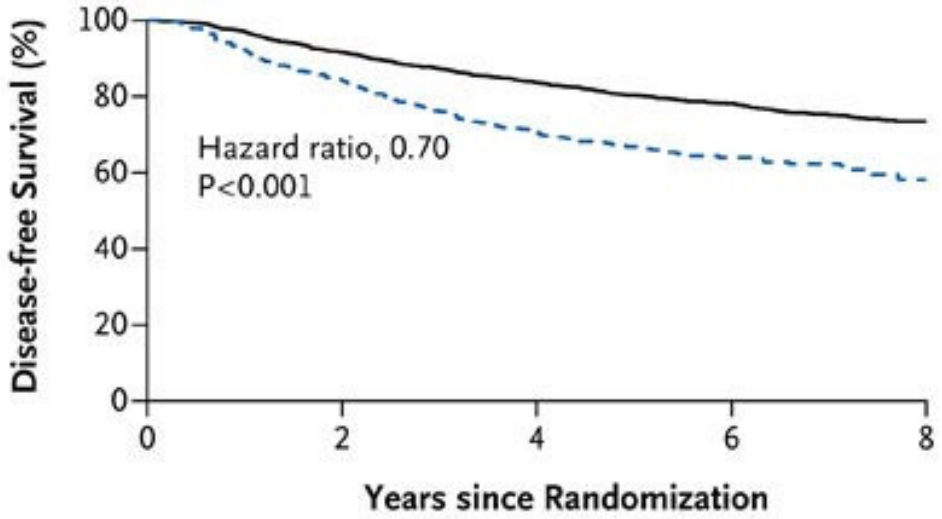
- In pre-menopausal women ovarian supression:
  - Further decreases risk of recurrence
  - Enable use of Aromatase Inhibitors

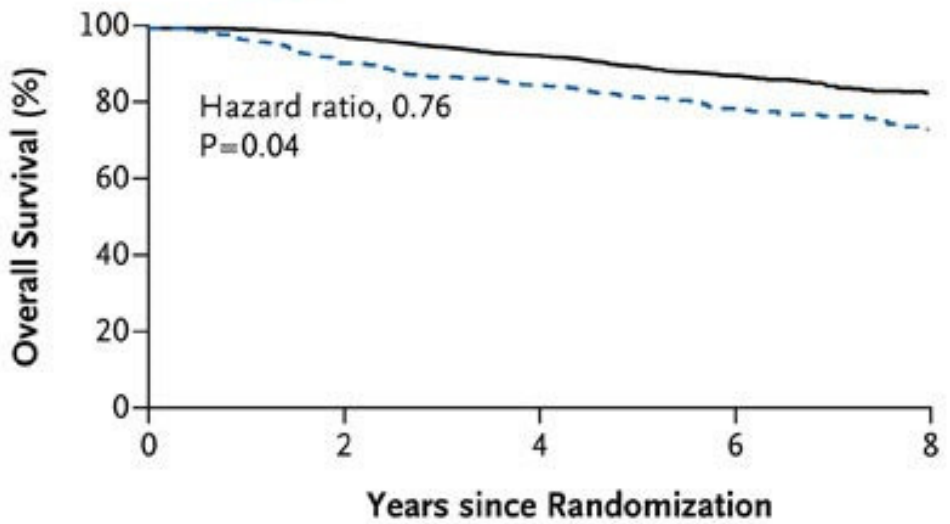
- Direct
  - Medical: GnRH analogues
    - Goserelin, Leuprolide
  - Surgical: oophorectomy
  - Radiation

- Indirect:
  - Chemotherapy-induced

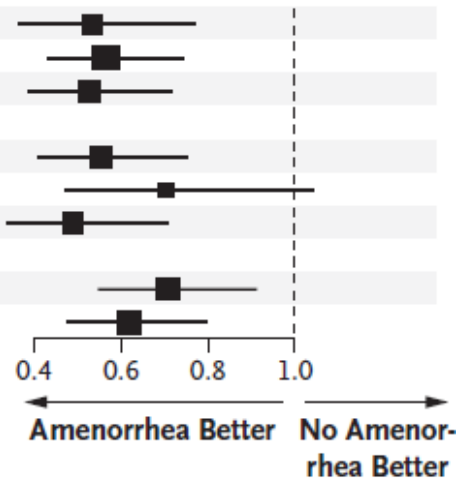
The NEW ENGLAND JOURNAL of MEDICINE

Longer Therapy, Iatrogenic Amenorrhea, and Survival in Early Breast Cancer





Subgroup	No. of Patients	No. of Events		Hazard Ratio
		No Amenorrhea	Amenorrhea	
Sequential ACT	752	34	143	0.53
Doxorubicin–docetaxel	788	83	127	0.56
Concurrent ACT	771	55	150	0.53
Age				
<40 yr	528	98	71	0.55
40–44 yr	477	34	91	0.70
>44 yr	1203	32	227	0.49
ER status				
Negative	592	96	147	0.71
Positive	1719	76	273	0.62

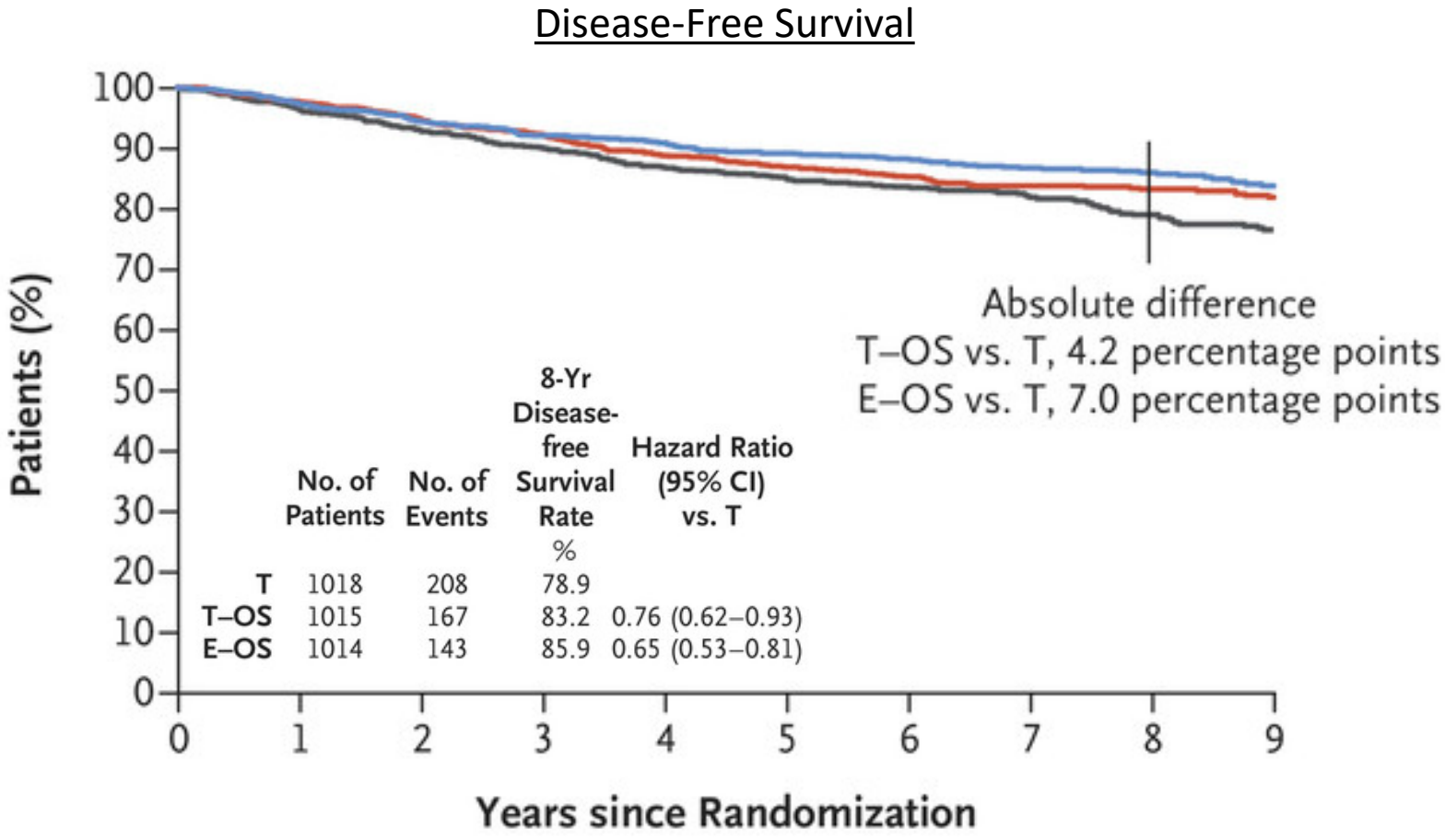


Swain NEJM 2010

SOFT and TEXT Trial – Pre-menopausal

- Pre-menopausal women Combined analysis of:
  - Tamoxifen
  - OS + Tamoxifen
  - OS + AI
- OS + AI significantly reduced recurrence

- Clinical application:
  - Most pre-menopausal women only need Tam
  - Consider OS + AI with high risk features
    - <35yo
    - Received chemotherapy



PA Francis et al. N Engl J Med 2018;379:122-137.

Which ER/PR+ Patients Need Chemotherapy

ER/PR+ Breast Cancer

Clinically Available Genomic Profiling Assays in Breast Cancer

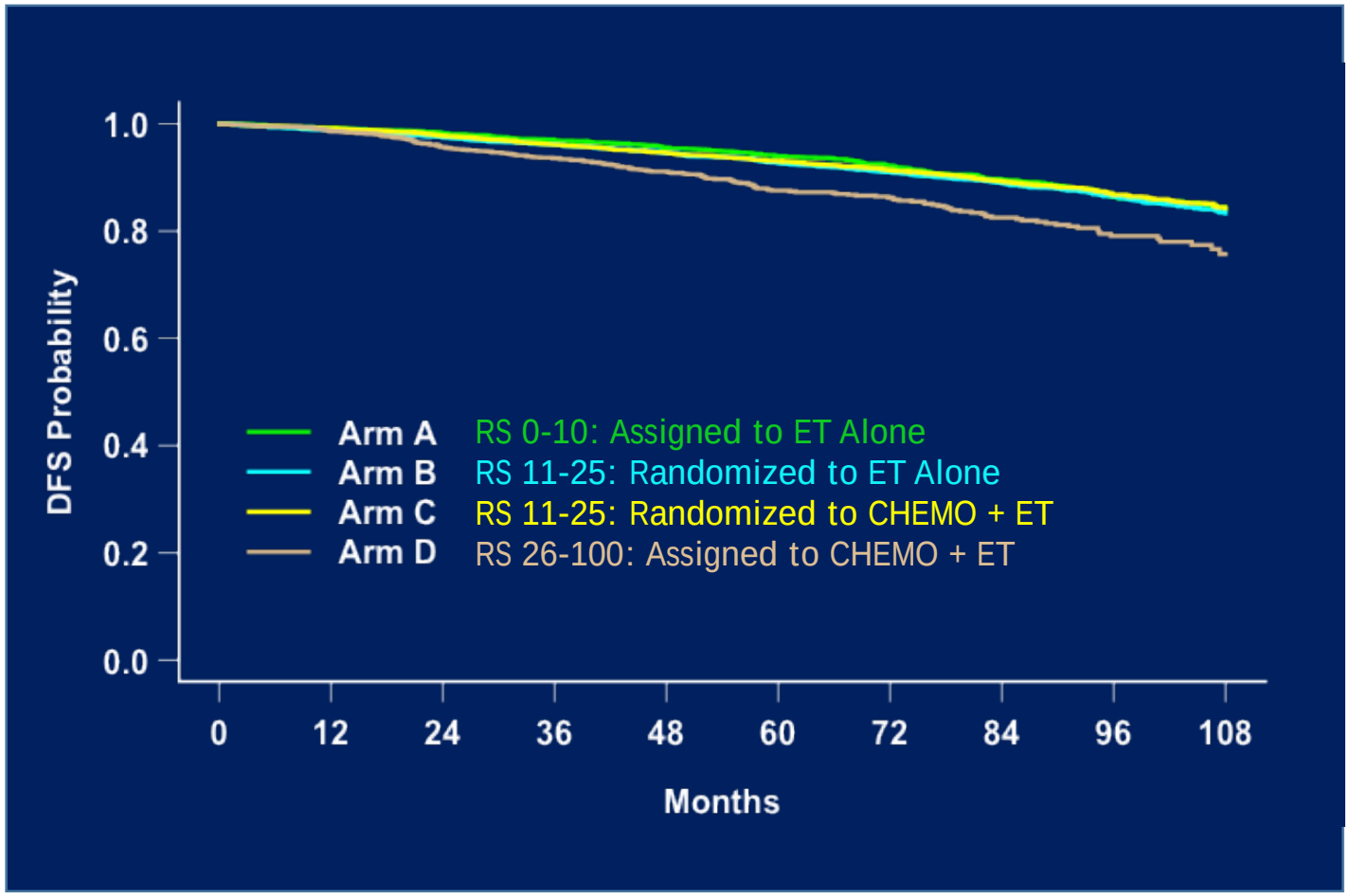
- Oncotype Dx
- Mammaprint
- Prosigna
- Breast Cancer Index

Oncotype Dx: Indications for assay

Criteria:

- Invasive breast cancer
- Hormone receptor positive (ER+ and/or PR+)
- HER2 negative (IHC 0-1+ or FISH/ISH non-amplified)
- pT1b (>0.5cm to 1.0cm) AND histologic grade 2 or 3, LVI
- pT1c or pT2

TAILORx: Prospective Validation for Oncotype Dx, 9-yr event rates



Arm A: ET alone (RS 0-10)
3% Distant recurrence rate

Arms B & C: Randomized (RS 11-25)
5% Distant recurrence rate overall

Arm D: Chemo + endocrine (RS 26-100)
13% Distant recurrence rate despite chemotherapy + endocrine therapy

Sparano J et al, N Engl J Med 2018

TAILORx: Benefit of Chemotherapy in Women ≤50yo

- Interaction between Age – Recurrence Score – Chemotherapy
  - Some chemotherapy benefit in women ≤ 50yo with a RS of 16-25
  - Greatest impact on distant recurrence with RS 21-25

Subgroup Age ≤50 years				
RS 0-10	RS 11-15	RS 16-20	RS 21-25	RS 26-100
No CT Benefit	No CT Benefit	~1.5% CT Benefit	~7% CT Benefit	Large CT Benefit

Sparano J et al, N Engl J Med 2018

TAILORx: Integrating Clinical Risk and Recurrence Score

- Low Clinical Risk tumors:
  - ≤ 1cm and high grade
  - ≤ 2cm and int. grade
  - ≤ 3cm and low grade
- High Clinical Risk tumors:
  - Everything else

	Estimated Absolute Chemo Benefit Not Stratified by Clinical Risk	Clinical Risk	No.	Estimated Absolute Chemo Benefit Stratified by Clinical Risk
RS 16-20 (N=886)	Δ +1.6% (±SE 1.9%)	Low	671 (76%)	Δ -0.2% (±SE 2.1%)
		High	215 (24%)	Δ +6.5% (±SE 4.9%)
RS 21-25 (N=476)	Δ +6.5% (+SE 3.7%)	Low	319 (67%)	Δ +6.4% (±SE 4.9%)
		High	157 (33%)	Δ +8.7% (±SE 6.2%)

Absolute difference in distant recurrence rates by chemo use in women ≤ 50 stratified by Recurrence Score and clinic risk

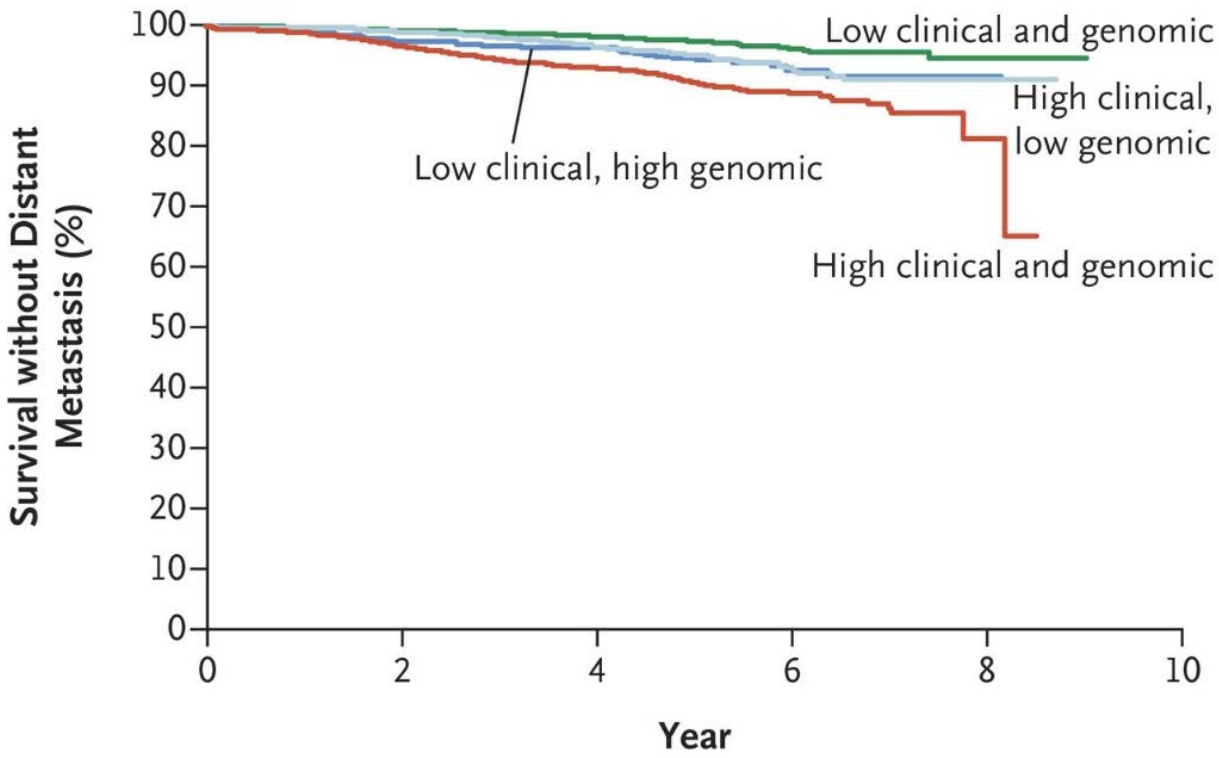
Sparano J et al, ASCO 2019, abstract #503

MINDACT Trial: Mammaprint

- Phase III Trial
- Mammaprint - 70-gene assay

- Clinical High + Low genomic risk
  -> No benefit from chemotherapy

- Clinical High + High genomic risk
  -> Benefit from chemotherapy



Cardoso et al. NEJM. 2016

Mammaprint: Indications for assay

- Consider with patients who are <u>Clinical High Risk</u> (per Adjuvant! Online)
  - Grade 1 and >3cm or >2cm with 1-3+ LNs
  - Grade 2 and >2cm +/- 1-3+ LNs
  - Grade 3 and >1cm +/- 1-3+ LNs

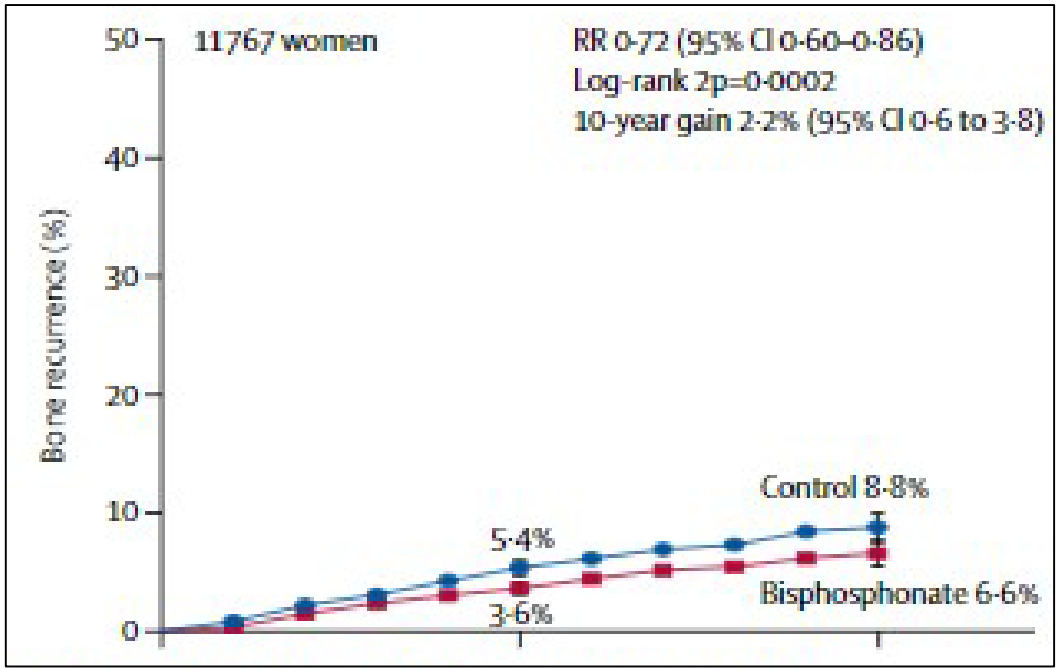
HER2 status	Grade	Nodal status	Tumor Size	Clinical Risk in Mindact
HER2 negative	well differentiated	N-	≤ 3 cm	C-low
			3.1-5 cm	C-high
		1-3 positive nodes	≤ 2 cm	C-low
			2.1-5 cm	C-high
	moderately differentiated	N-	≤ 2 cm	C-low
			2.1-5 cm	C-high
		1-3 positive nodes	Any size	C-high
	poorly differentiated or undifferentiated	N-	≤ 1 cm	C-low
			1.1-5 cm	C-high
		1-3 positive nodes	Any size	C-high

Cardoso et al, NEJM. 2016

Adjuvant Bisphosphonates

- Meta-analysis of adjuvant bisphosphonates
- Post-menopausal women:
  - Significant reduction in bone recurrence (RR 0·83, 0·73–0·94; 2p=0·004)
- SEs:
  - Osteonecrosis of the jaw
  - Renal impairment

Bone recurrence rate/year (%) events/woman-years



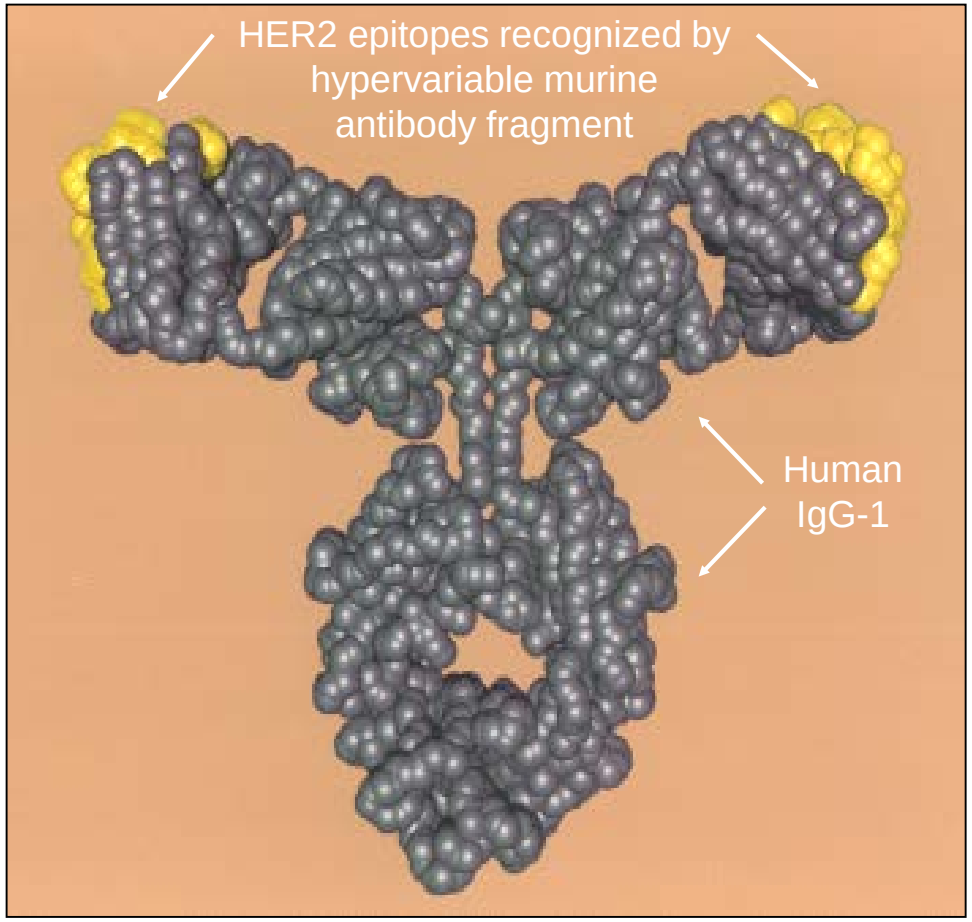
EBCTCG, Lancet 2015

HER2+ Breast Cancer

HER2 Positive Breast Cancer

- 25–30% of breast cancers
- Human epidermal growth factor receptor 2 (HER2) important in cell signaling and proliferation
- Overexpression of HER2 correlates with a more aggressive breast cancer
- HER2+ disease diagnosed by immunohistochemistry (IHC) or gene amplification by fluorescence *in-situ* hybridization (FISH)
  - ASCO/CAP updated guidelines - 2018

Trastuzumab (Herceptin): humanized anti-HER2 antibody



- Targets HER2 protein's ECD
- High affinity and specificity
- 95% human, 5% murine
  - Increases potential for recruiting immune effector mechanisms
- Fc portion recruits and interacts with immune effector cells
- Extensively investigated mechanisms of action

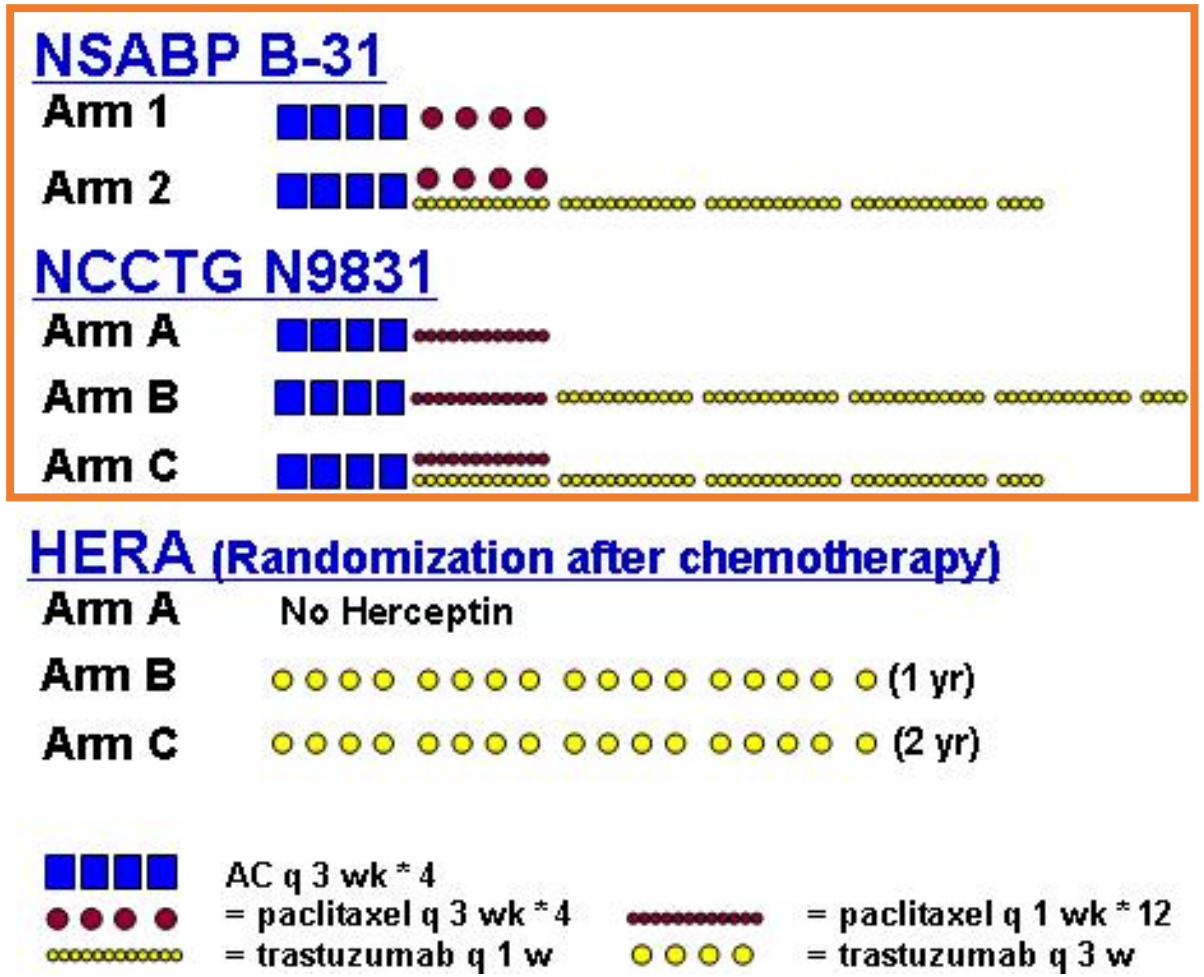
Pivotal adjuvant trastuzumab trials: patient characteristics

- HER2 positive (IHC 3+ or FISH amplified) invasive breast cancer, post lumpectomy/mastectomy

- Nodal status
  - Node positive (NSABP B-31)
  - Node positive or high-risk node negative (NCCTG N9831, HERA, BCIRG 006)

- No previous or current cardiac disease

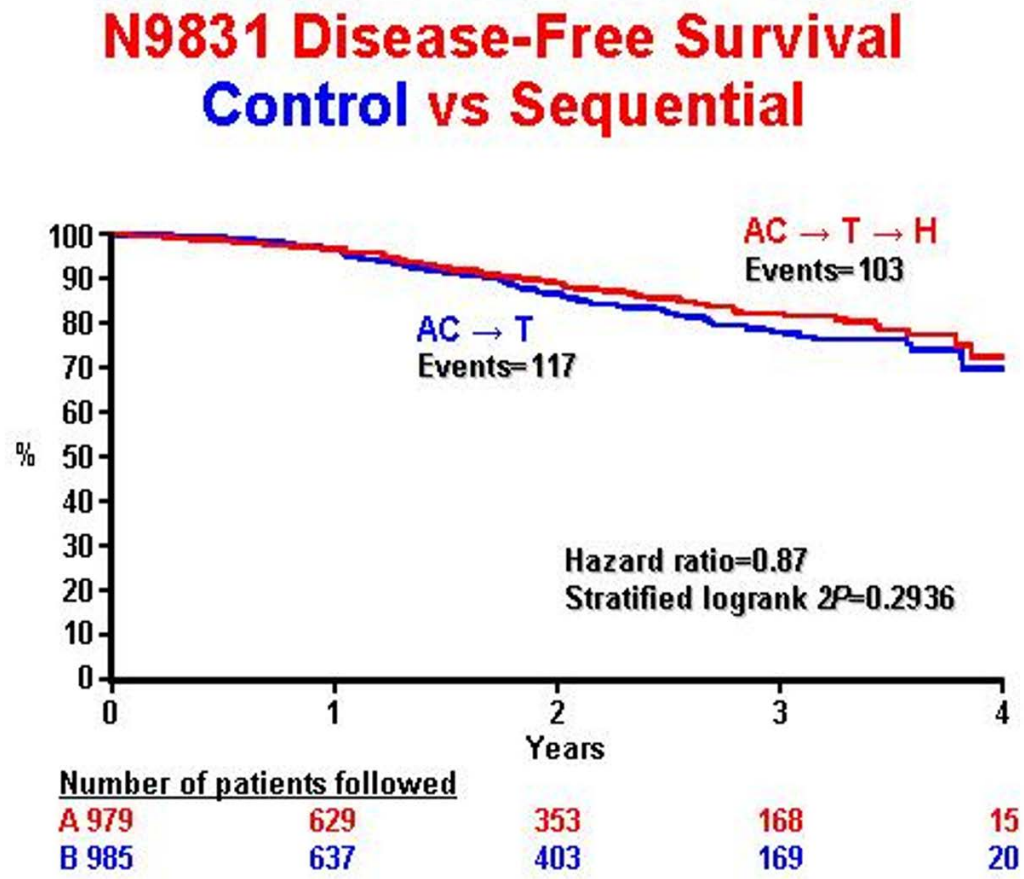
HER2+ Randomized Phase III Trials



No vs. sequential vs. concurrent

NCCTG N9831: Sequential Trastuzumab

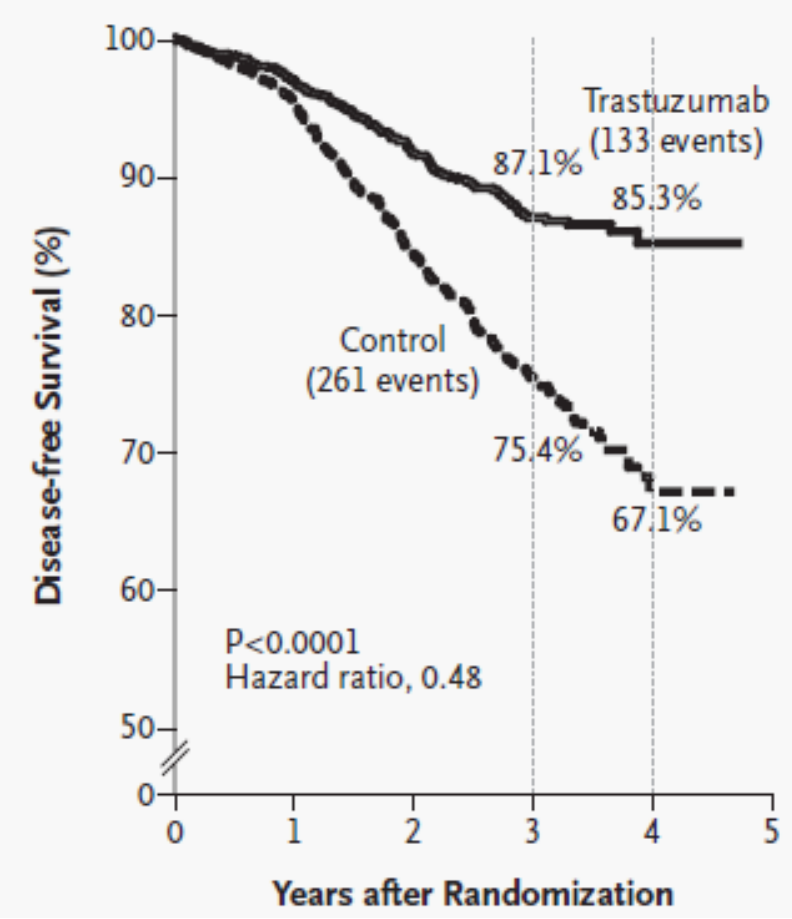
- Sequential vs Chemo alone
  - No benefit from sequential Trastuzumab



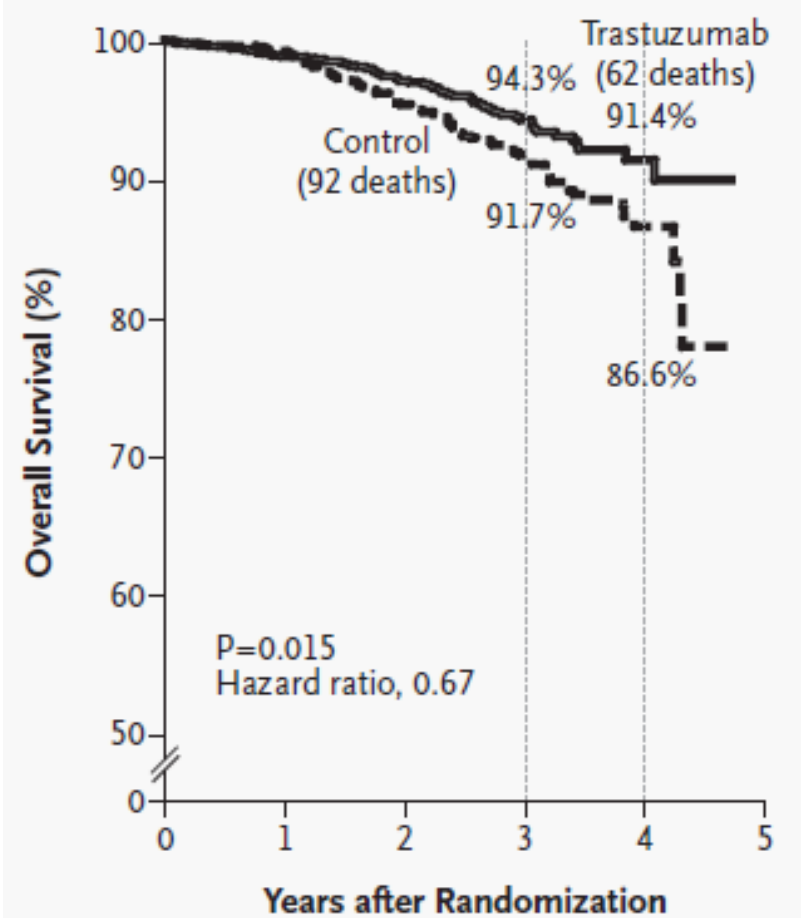
Romond et al; NEJM 2005

Combined Analysis of B-31 and N9831

- Trastuzumab improved DFS



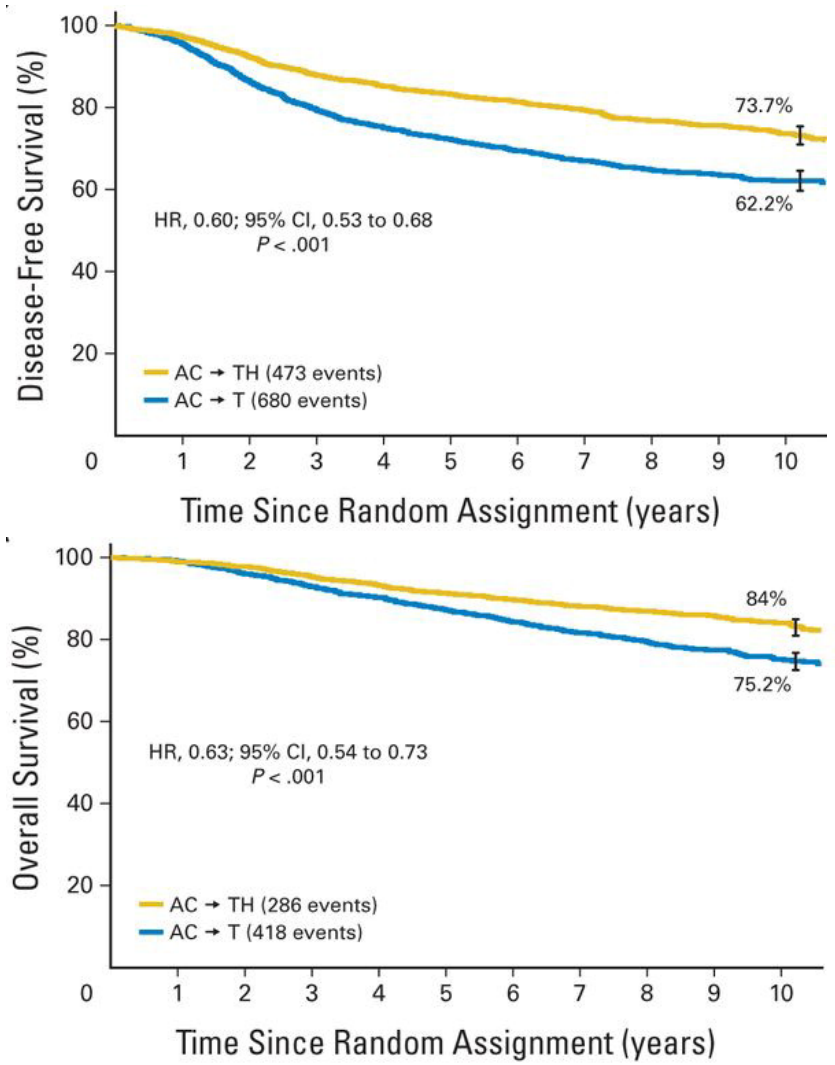
- Trastuzumab improved OS



Romond et al; NEJM 2005

Combined analysis of B31 and N9831 – 10 yr.

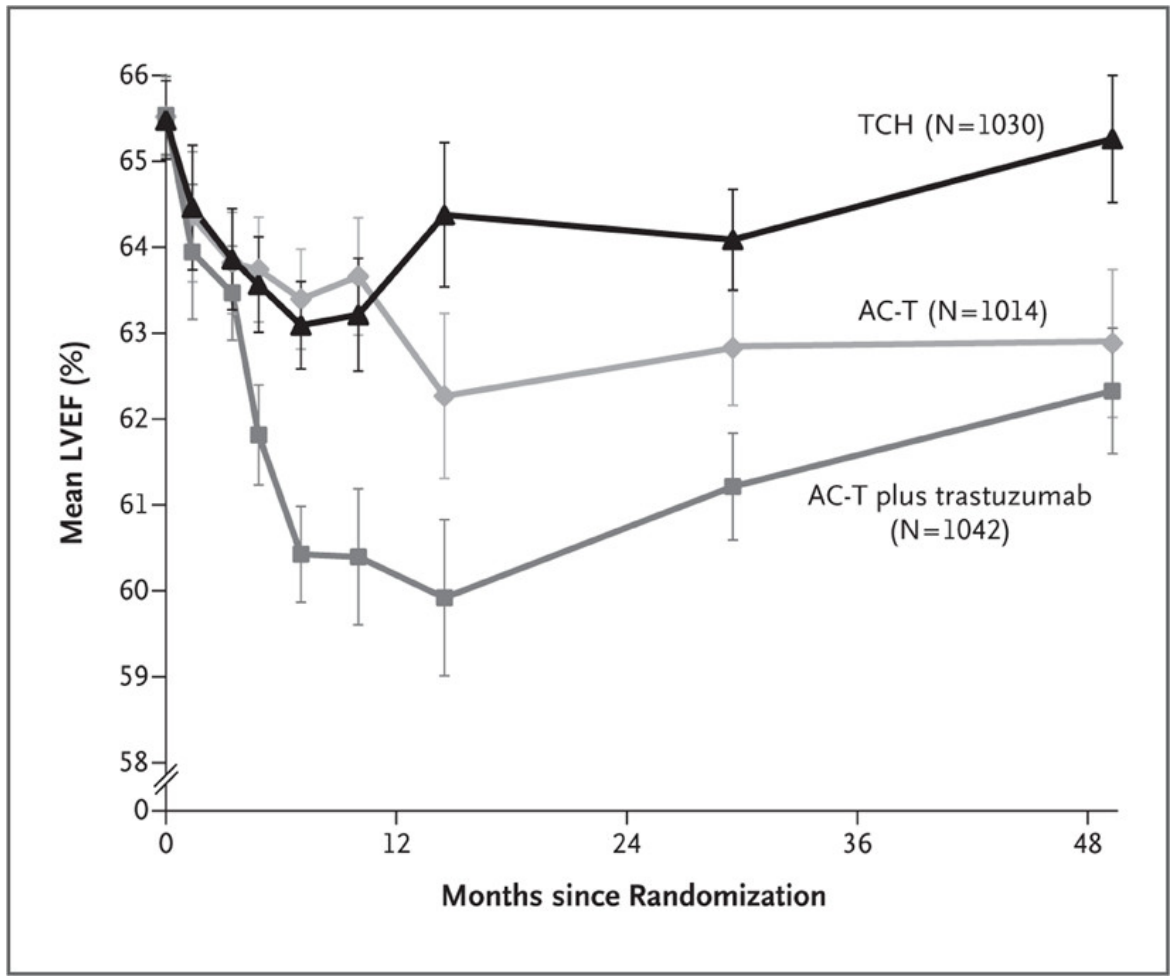
- Adding Trastuzumab to chemotherapy resulted in:
  - Improved DFS – 40%
  - Improved OS – 37%
- Acceptable toxicity
  - Cardiac events – 3%



Perez et al. JCO. 2014

CV Risk: Trastuzumab and Anthracyclines

Clinical Event	AC-T	AC-T plus Trastuzumab	TCH
		number of events	
Total events	201	146	149
Distant breast-cancer recurrence	188	124	144
Grade 3 or 4 congestive heart failure	7	21	4
Acute leukemia	6	1	1†



CV side effects w/ Anthracycline and Trastuzumab:

- 15% will have clinically significant decrease in EF
- 1-3% w/ symptomatic CHF

Slamon et al. NEJM, 2011

Duration of Trastuzumab (HER2 therapy)

- HERA Trial: 1 year vs 2 years of Trastuzumab
  - No difference between 2-year vs 1-year for DFS (HR, 0.99, 95% CI, 0.85-1.14; *P*=0.86)
  - OS was also similar between both groups (HR, 1.05, 95% CI, 0.86-1.28; *P*=0.63)
  - Asymptomatic cardiac dysfunction was higher after 2 years of trastuzumab (7.2% vs. 4.1%)

- PHARE Trial: 6 months vs 1 year of Trastuzumab
  - HR for DFS in the study was 1.28 (95% CI: 1.05-1.56; p=0.29).
  - The non-inferiority of 6 months of trastuzumab compared to 12 months could not be demonstrated
  - Could not prove noninferiority of 6 months

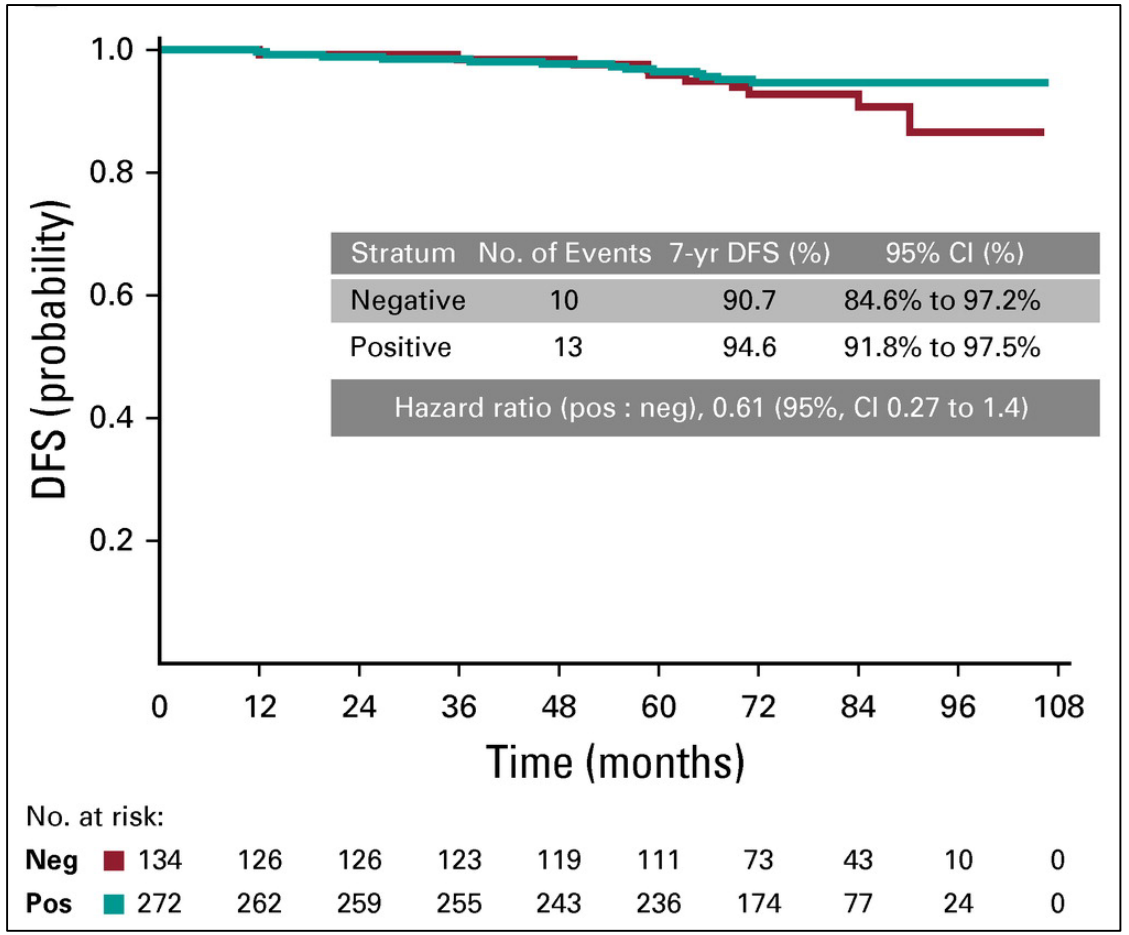
Gelber RD et al. 2012 ESMO 2012, Abstract LBA6.
Pivot X et al. ESMO 2012, Abstract

Stage I HER2+ breast cancers: APT Trial

- APT Trial
  - Multicenter, Single-Arm Trial
  - Paclitaxel + Trastuzumab
- Eligibility:
  - HER2+ (3+ or FISH>2.0)
  - Primary tumor ≤ 3cm

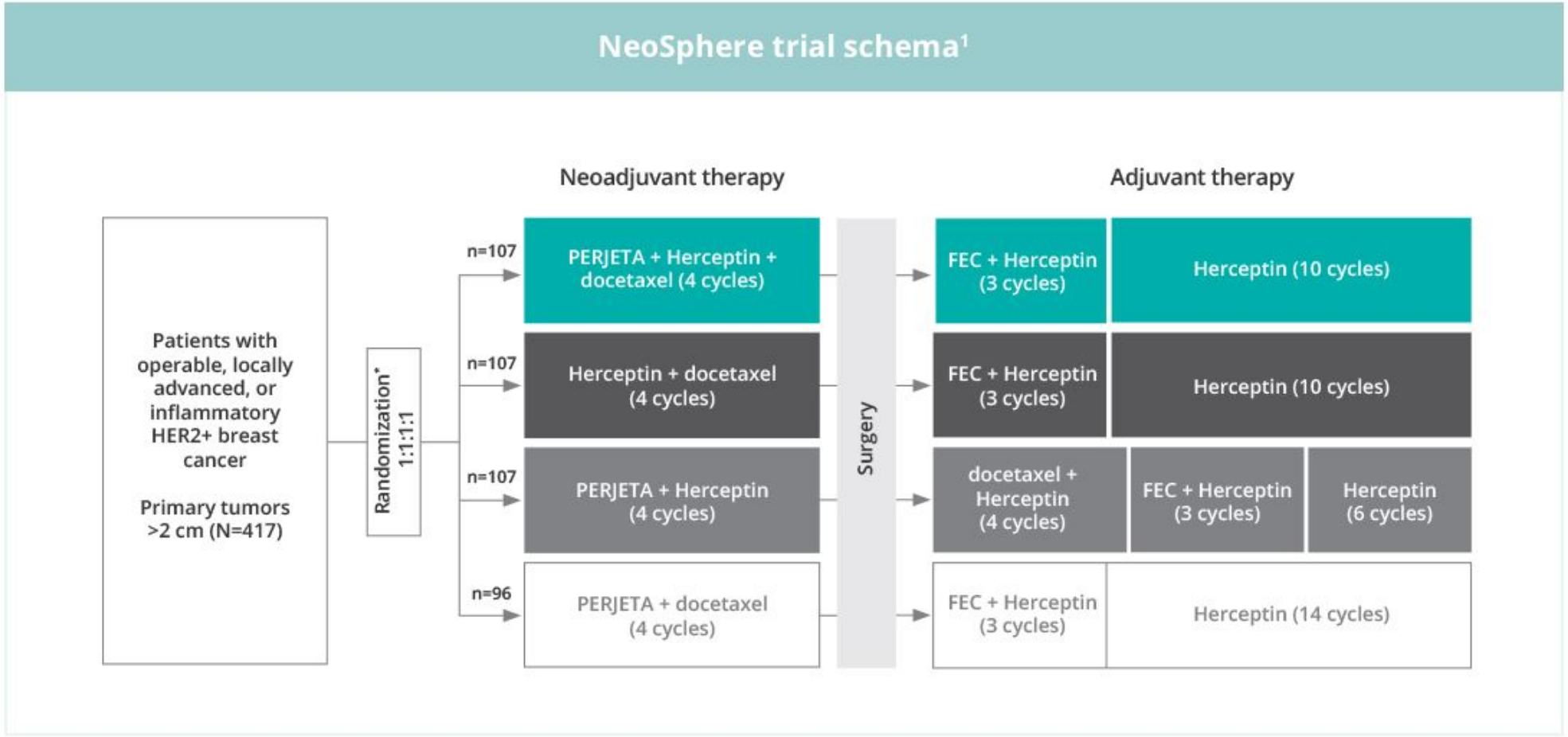
- Results:
  - 7 yr. Relapse Free Interval:
    - 97.5% at 7 yrs.

  - DFS by HR status:
    - HR positive: 94.6%
    - HR negative: 90.7%



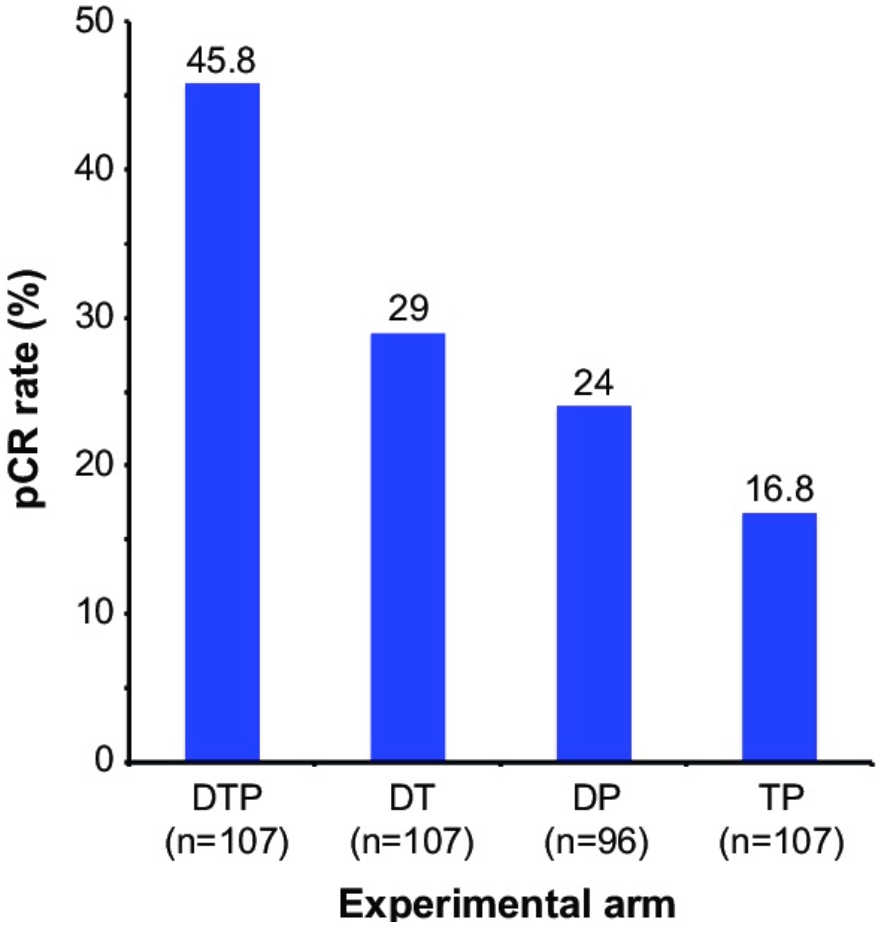
Tolaney EM, et al. JCO 2019

Neosphere Trial: Neoadjuvant Pertuzumab



Neosphere Trial: Path complete response

- Highest pathologic CR rate in the Pertuzumab + Trastuzumab + Docetaxel arm
  - 45.8% (95% CI 36.1-55.7)
- Most common grade ≥3 AEs:
  - Neutropenia
  - Febrile neutropenia
  - Leukopenia

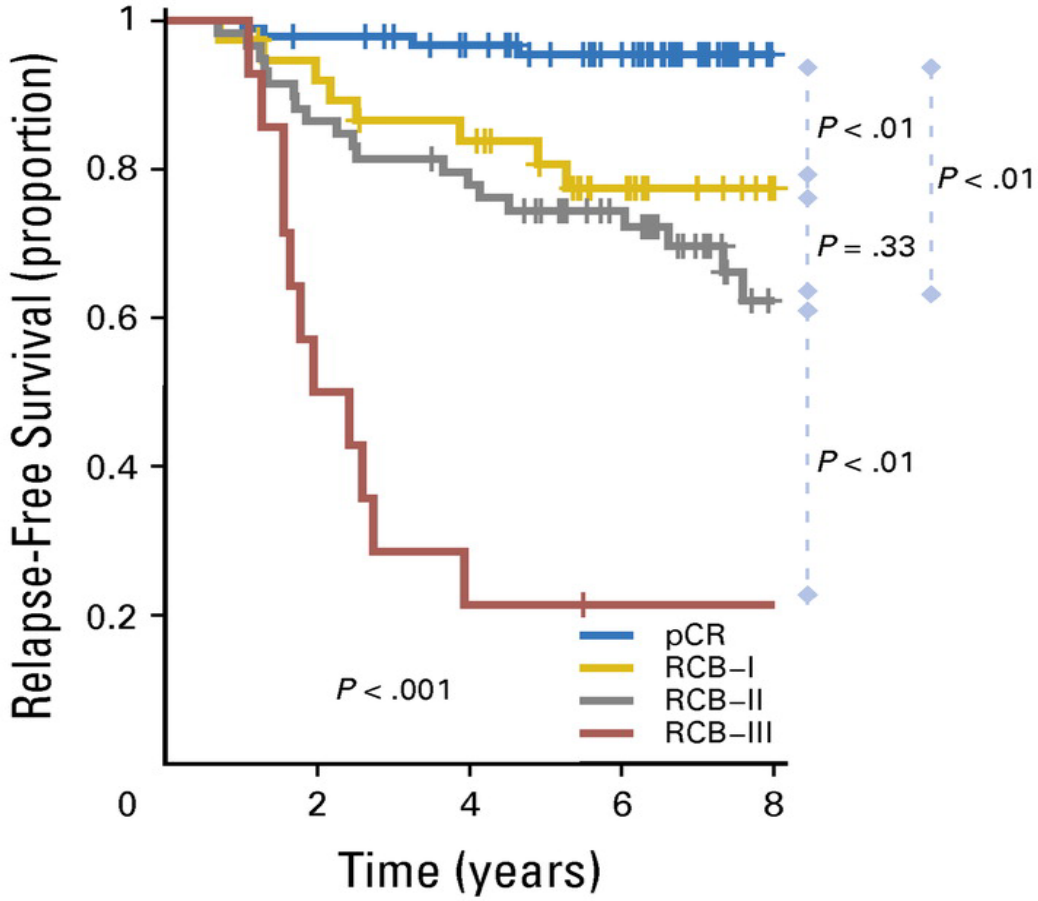


Schiemann et al. Cancer Management and research. 2016

Residual disease after neoadjuvant therapy

Residual Cancer Burden (RCB) - Prognostic

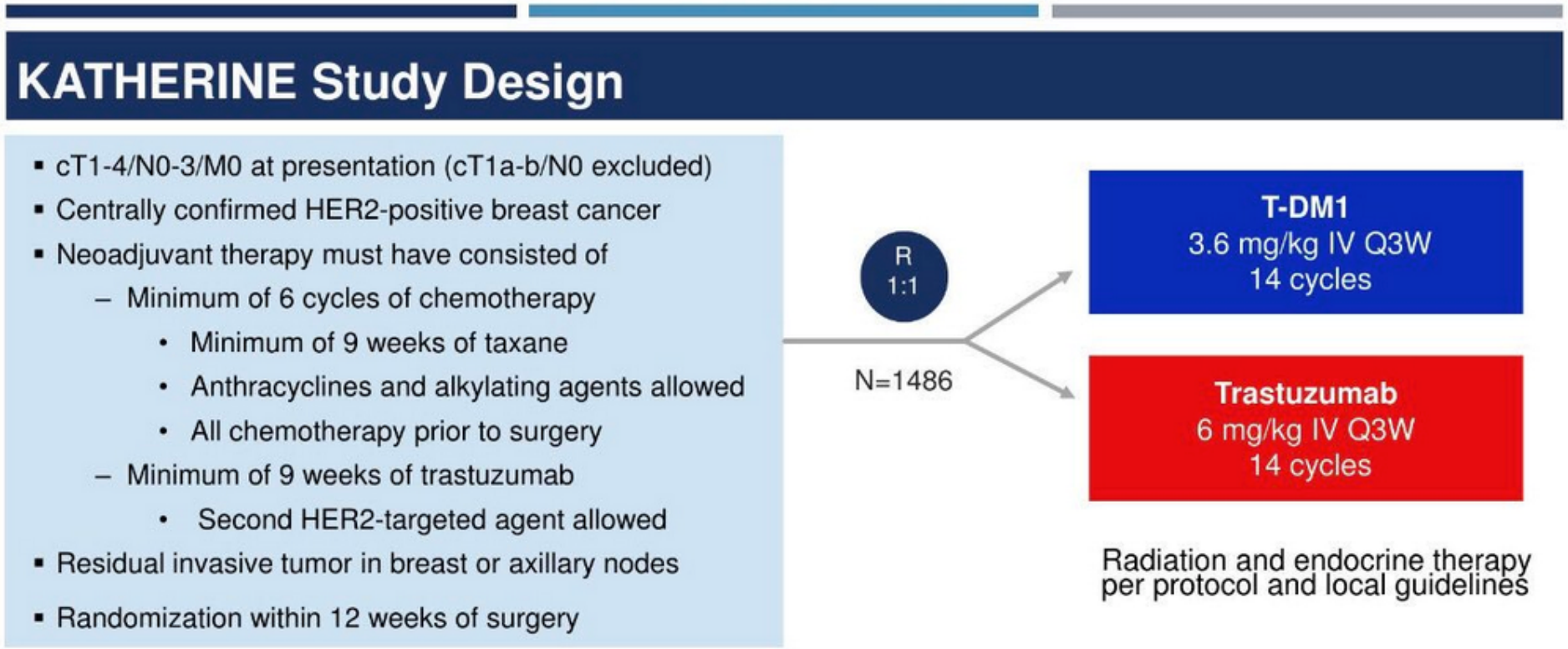
- pCR had RFS of 95% - 5 yrs. and 10 yrs.)
- RCB-I (RFS of 81% - 5 yrs., 77% - 10 yrs.)
- RCB-II (RFS of 74% - 5 yrs., 47% - 10 yrs.)
- RCB-III (RFS of 21% - 5 yrs. and 10 yrs.)



* Additional Therapies Needed

Symmans et al JCO 2017

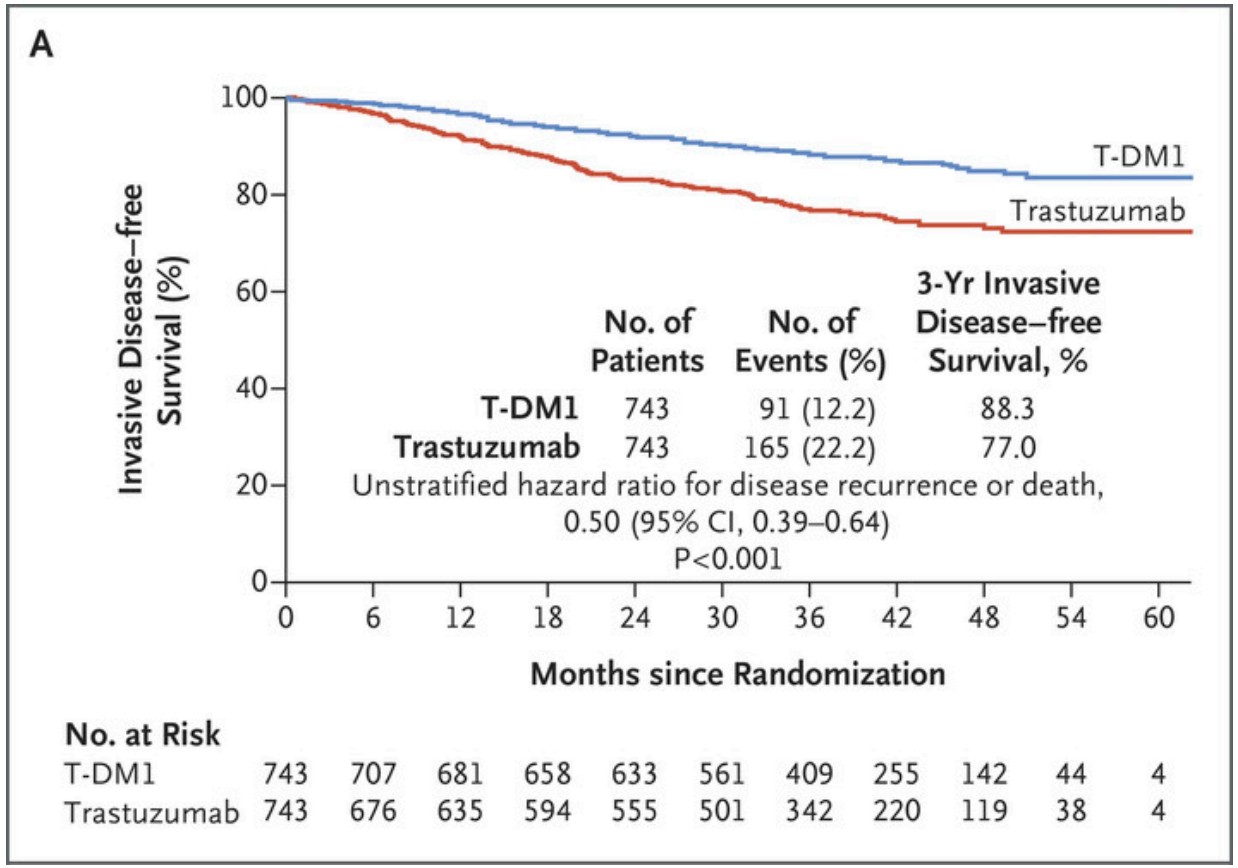
KATHERINE Study – Adjuvant TDM-1



Stratification factors:

- Clinical presentation: Inoperable (stage cT4 or cN2–3) vs operable (stages cT1-3N0-1)
- Hormone receptor: ER or PR positive vs ER negative and PR negative/unknown
- Preoperative therapy: Trastuzumab vs trastuzumab plus other HER2-targeted therapy
- Pathological nodal status after neoadjuvant therapy: Positive vs negative/not done

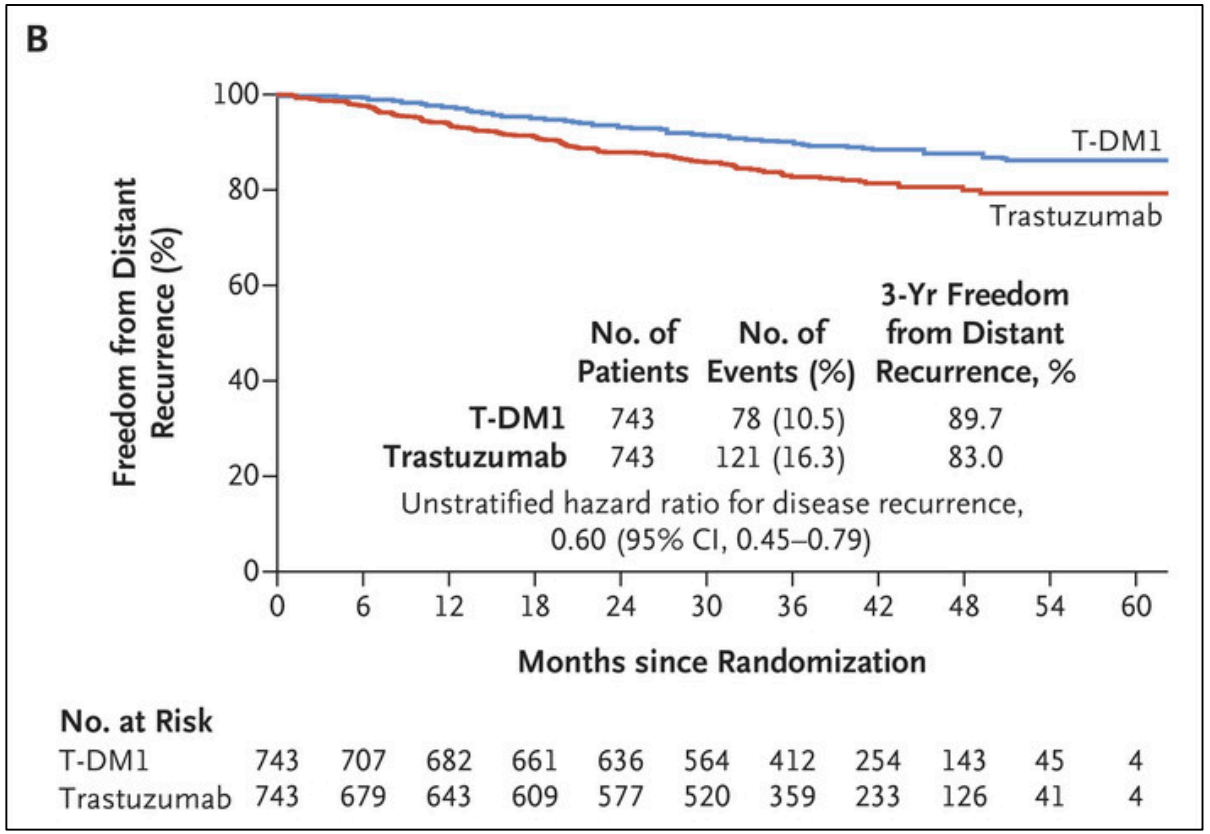
KATHERINE – Invasive disease-free survival



- Invasive disease occurred in:
  - TDM-1: 91 (12.2%) patients
  - Trastuzumab: 165 (22.2%) patients
- Estimated invasive disease-free survival at 3 years:
  - TDM-1: 88.3%
  - Trastuzumab: 77.0%

Von Minckwitz et al. NEJM. Feb 14, 2019

KATHERINE – Distant recurrence



- Distant recurrences:
  - TDM-1: 78 (10.5%) patients
  - Trastuzumab: 121 (16.3%) patients
- To date no significant difference in overall survival
- Adverse events leading to discontinuation occurred in:
  - TDM-1: 133 (18.0%)
  - Trastuzumab: 15 (2.1%)

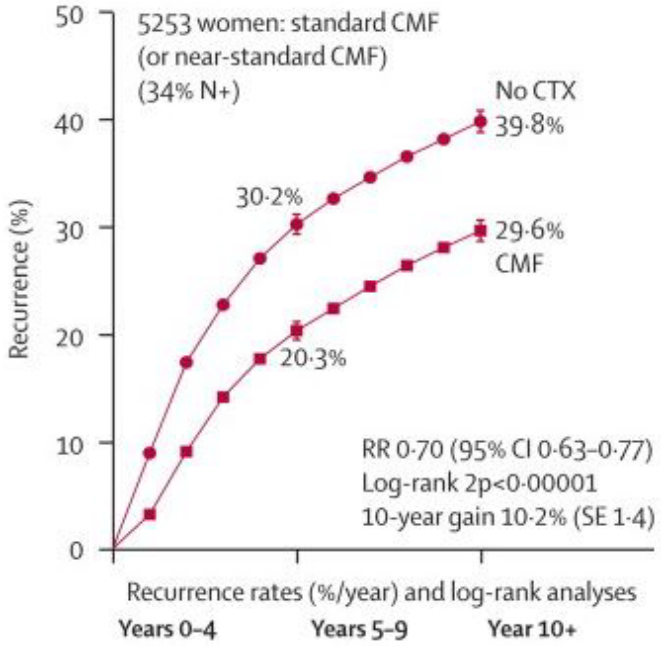
Von Minckwitz et al. NEJM. Feb 14, 2019

Chemotherapy regimens

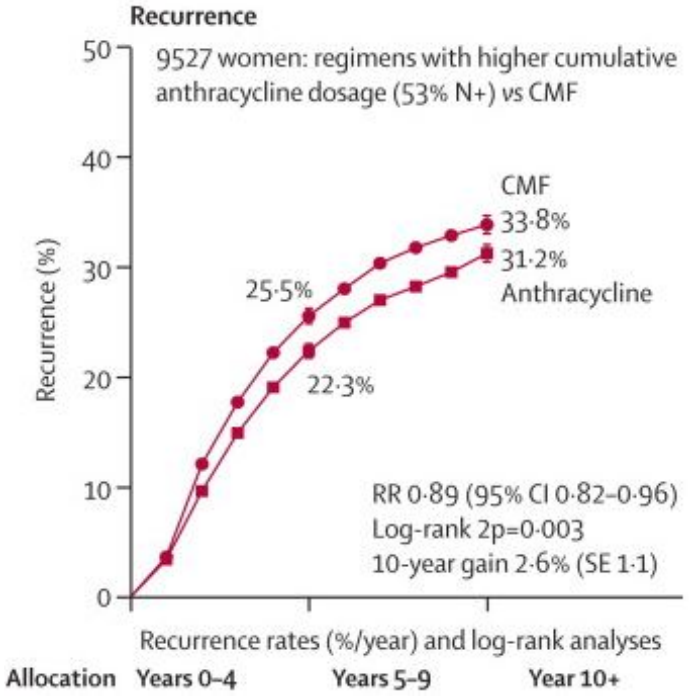
Localized or locally advanced breast cancer

Benefits of Adjuvant Chemotherapy

- Polychemo. vs No Chemo, results in:
  - Decreased risk of recurrence
  - Decreased breast cancer mortality
  - Improved OS



- CMF vs Anthracycline Based chemotherapy

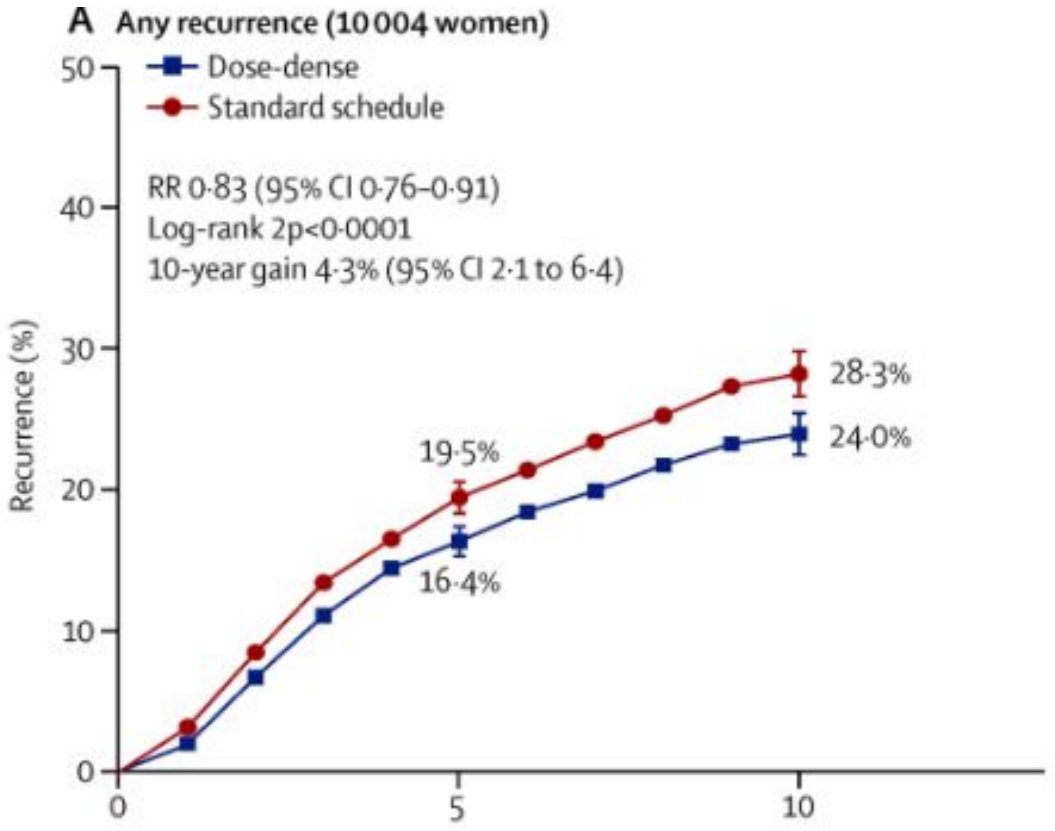


EBCTCG, Lancet. 2012

Dose Density – Q2 vs 3 weekly Anthracycline

- Meta-analysis of 26 studies adjuvant chemo trials

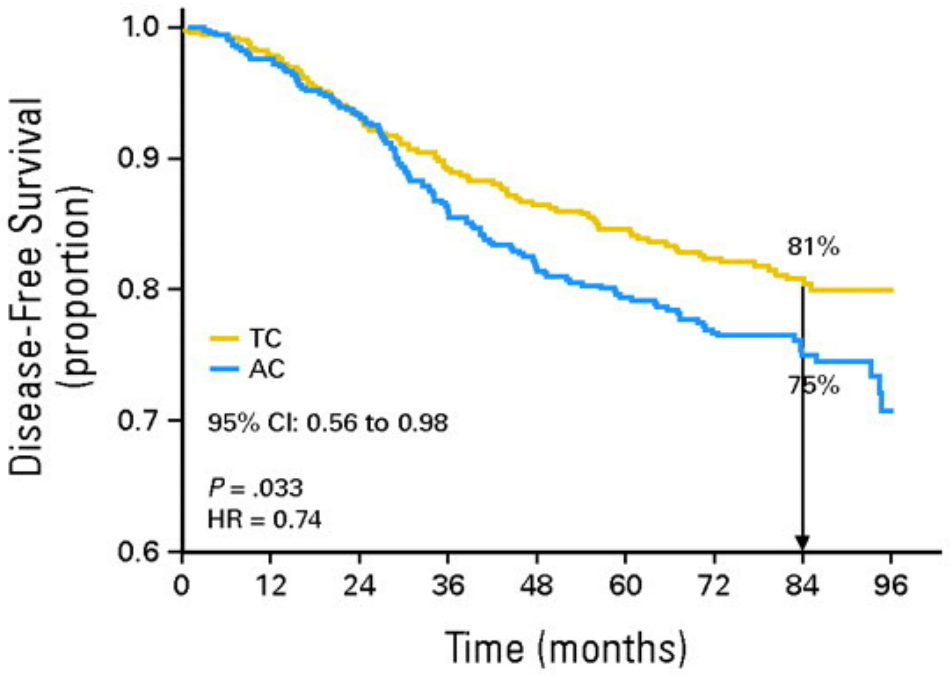
- Dose Dense Q2 weekly chemo is superior to Q3 weekly chemo in reducing:
  - Risk of recurrence
  - Breast cancer mortality



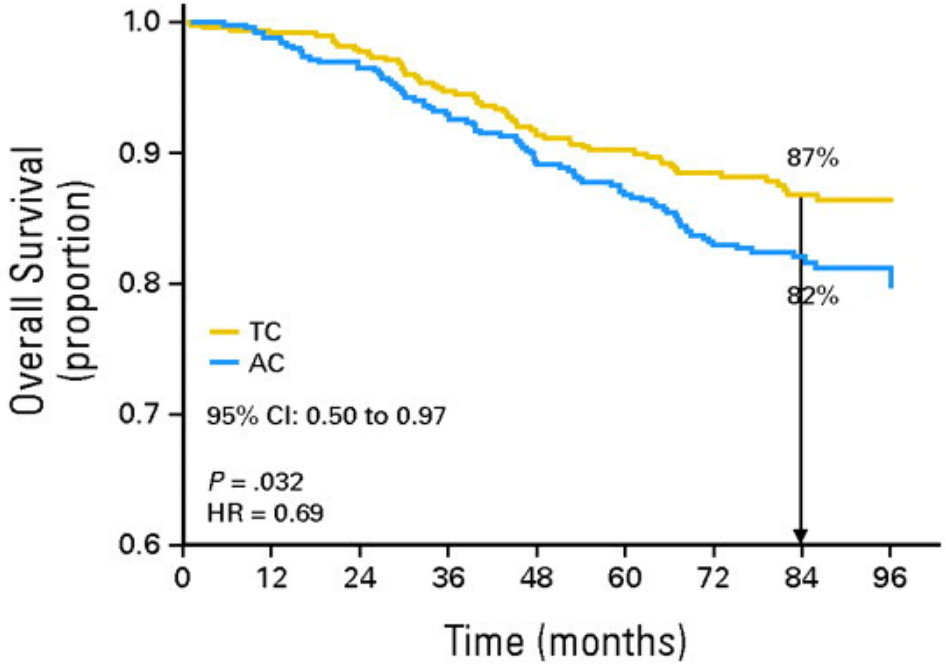
EBCTCG, Lancet 2019

Adjuvant Taxane vs Anthracycline Chemo

- TC associated with improved DFS compared to Q3 wk. AC



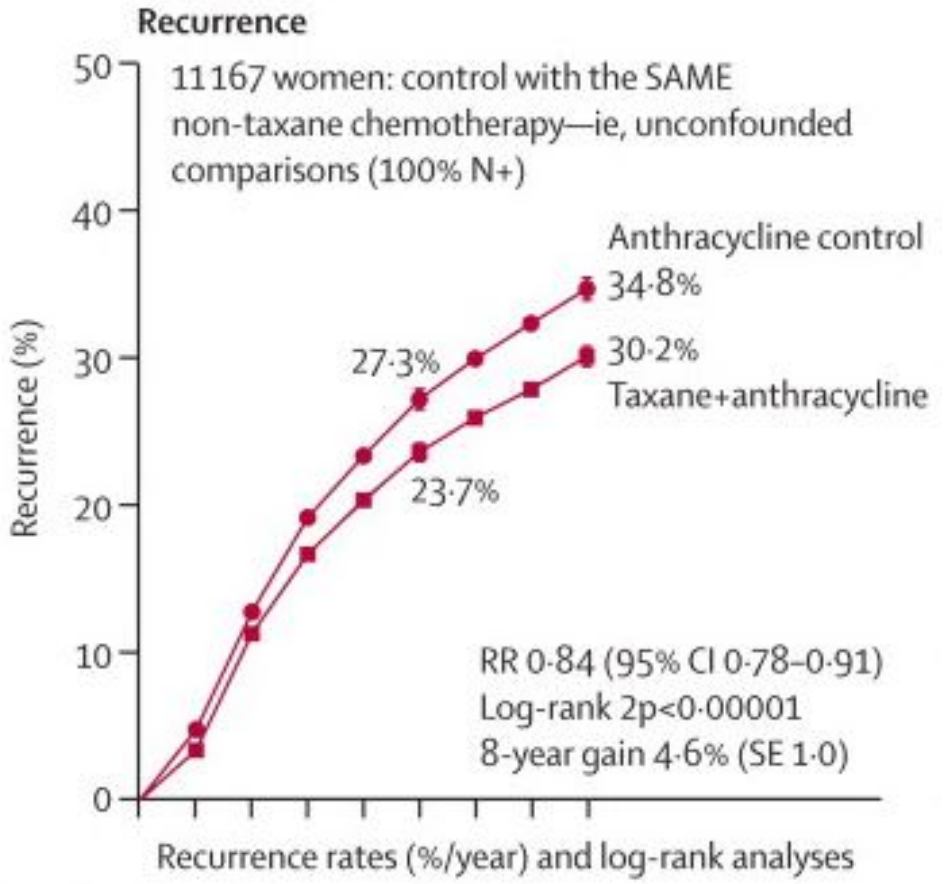
- TC associated with improved OS compared to Q3 wk. AC



Jones JCO 2009

Adjuvant chemotherapy: Taxane + Anthracycline

- Addition of Taxane chemotherapy to Anthracycline resulted in:
  - Decreased risk of recurrence
  - Decreased breast cancer mortality
  - Improved overall survival



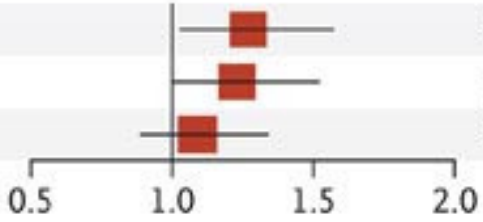
EBCTCG, Lancet. 2012

The NEW ENGLAND JOURNAL of MEDICINE

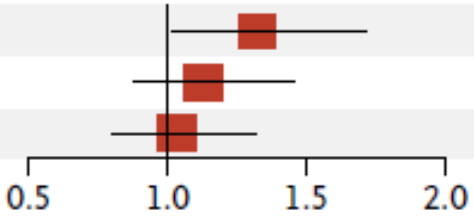
Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer

What is the optimal Taxane and schedule?

Treatment Group	No. of Patients	Hazard Ratio for Disease-free Survival (98.3% CI)	P Value
Weekly paclitaxel	2484	1.27 (1.03–1.57)	0.006
Docetaxel every 3 wk	2489	1.23 (1.00–1.52)	0.02
Weekly docetaxel	2483	1.09 (0.89–1.34)	0.29



Treatment Group	No. of Patients	Hazard Ratio for Overall Survival (98.3% CI)	P Value
Weekly paclitaxel	2484	1.32 (1.02–1.72)	0.01
Docetaxel every 3 wk	2489	1.13 (0.88–1.46)	0.25
Weekly docetaxel	2483	1.02 (0.80–1.32)	0.80



Sparano et al, NEJM. 2008

Cochrane Database of Systematic Reviews

Preoperative chemotherapy for women with operable breast cancer

- Meta-analysis of 14 trials
- Neoadjuvant vs Adjuvant Chemotherapy
  - Equivalent OS rates (HR 0.98, 95% CI, 0.87 to 1.09)
  - Equivalent DFS rates (HR 0.97, 95% CI 0.89-1.07)
- Neoadjuvant associated with improved breast conservation rates
- Pathologic complete response associated w/ significant improvements in:
  - OS (HR 0.48, 95% CI 0.33-0.69)
  - DFS (HR 0.48, 95% CI 0.37-0.63)

Mieog et al. Cochrane Database Syst Rev.2007

Adjuvant chemotherapy regimens

- Preferred Regimens (NCCN)
  - Dose-Dense AC followed by Paclitaxel wkly
  - Dose-Dense AC followed by Paclitaxel Q2 wkly
  - TC (Docetaxel/Cyclophos) Q3 wkly

- Additional Regimens (NCCN)
  - Dose dense AC (Doxorubicin/Cyclophos)
  - AC Q3 wkly
  - CMF
  - AC Q3 wkly followed by Paclitaxel wkly

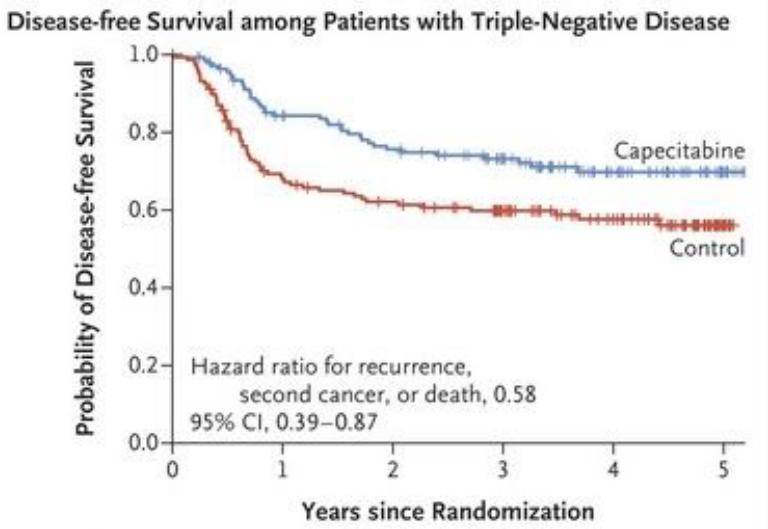
Triple Negative Breast Cancer

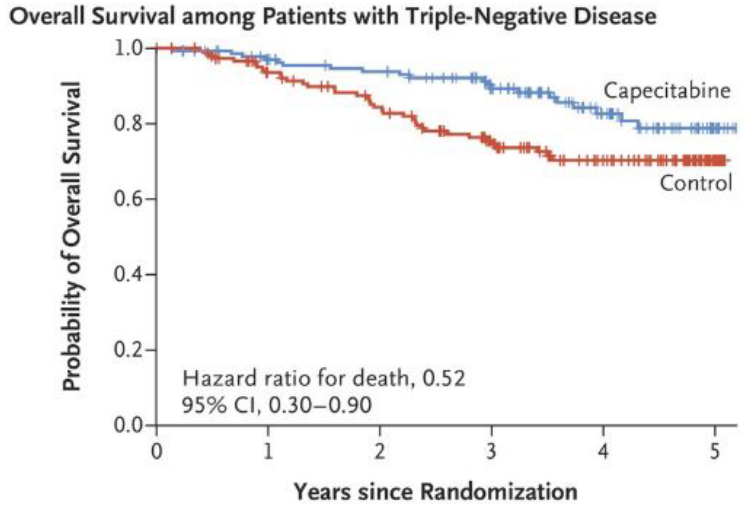
The NEW ENGLAND JOURNAL of MEDICINE

Adjuvant Capecitabine for Breast Cancer after Preoperative Chemotherapy

- HR+ and TNBC patients with residual disease after neoadjuvant chemo

- In TNBC patients adjuvant Capecitabine improved:
  - Disease-free survival
  - Overall Survival



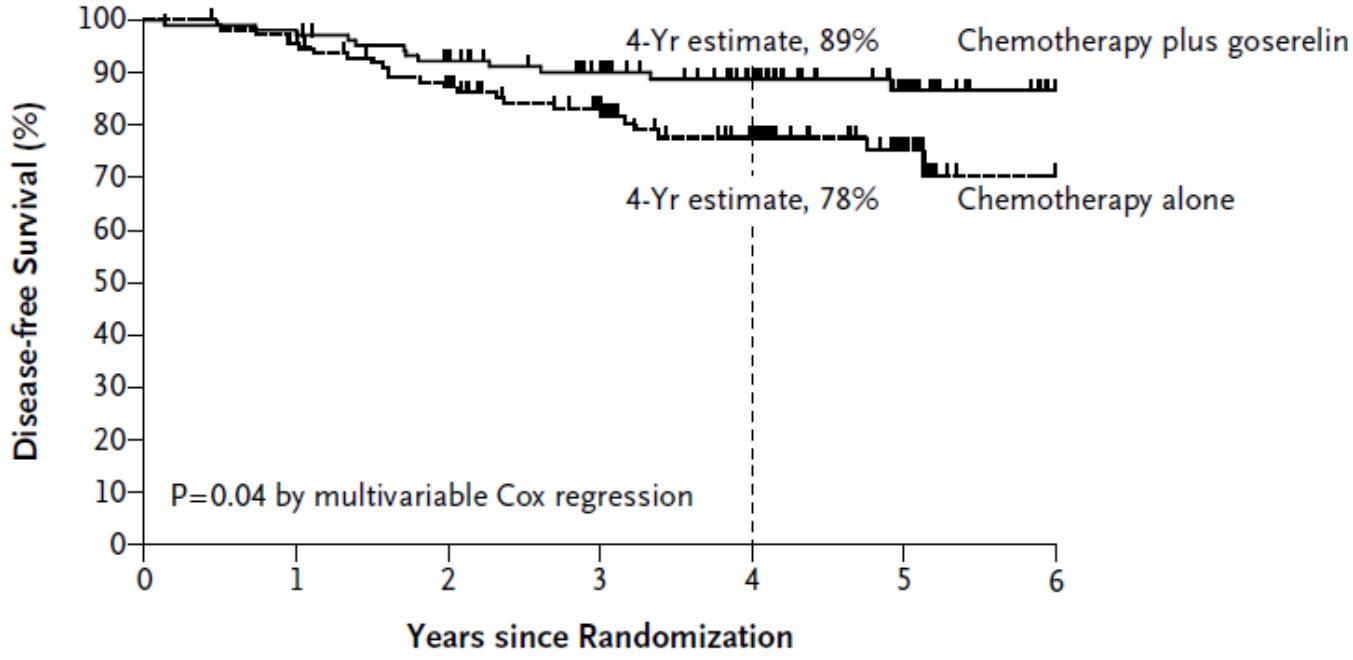


Masuda N, et al. NEJM. 2017

The NEW ENGLAND JOURNAL of MEDICINE

Goserelin for Ovarian Protection during Breast-Cancer Adjuvant Chemotherapy

- Pre-menopausal undergoing adjuvant chemo assigned to:
  - Goserelin + chemotherapy
  - Chemotherapy alone
- Goserelin associated with:
  - Less ovarian failure
  - More pregnancies (21% vs 11%)
  - Improved DFS and OS



Moore, NEJM 2015

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Indolent Non-Hodgkin Lymphoma: 2020

Solomon A Graf

VA/UW/FHCRC

Disclosures

Research Support

* TG Therapeutics
* BeiGene
* AstraZeneca / Acerta Pharma

Consulting / Advisory

* MorphoSys

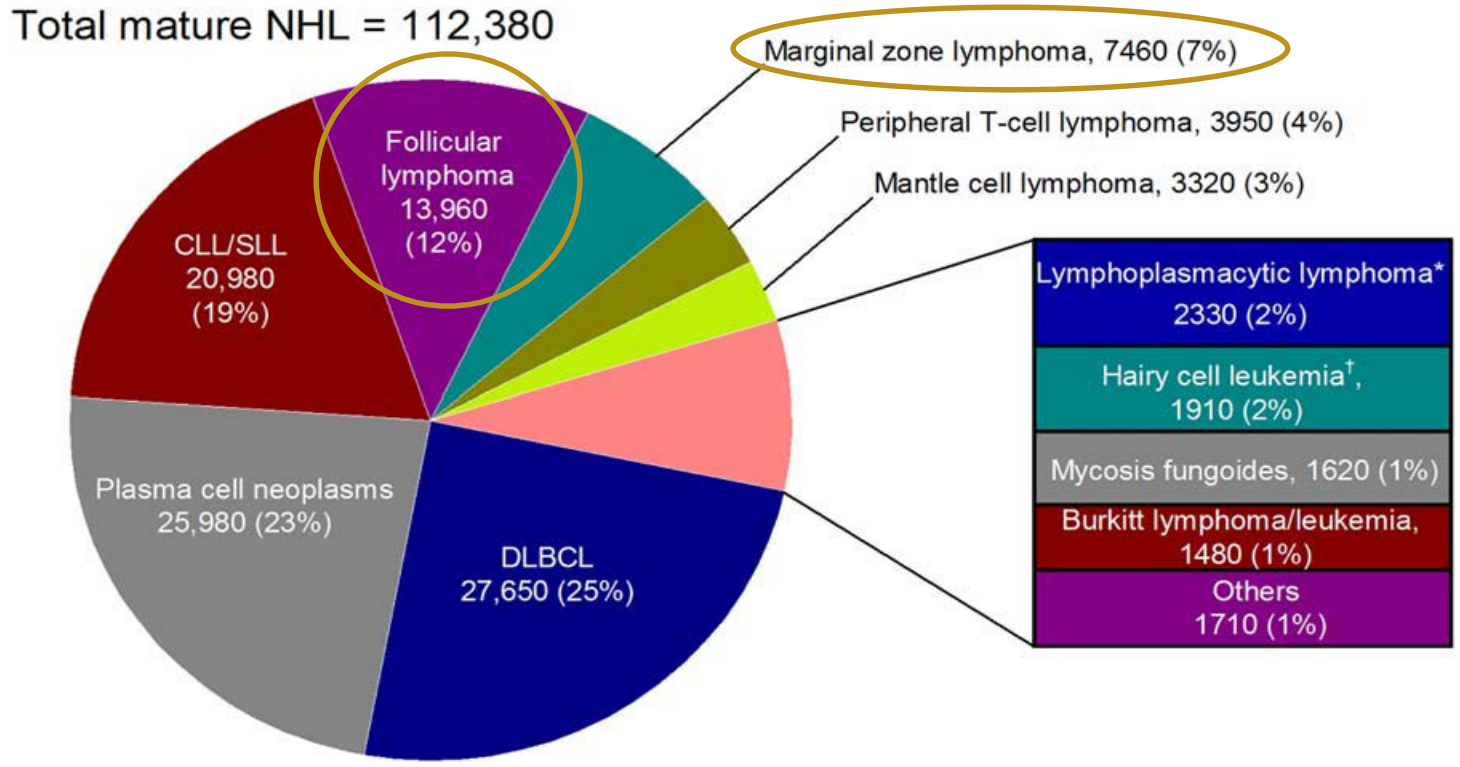
Objectives

- Epidemiology and pathology
- Management
  - Indication for treatment, options for frontline and relapsed/refractory
- Areas of unmet need and anticipated next steps

Natural History

- Presents with advanced disease, progresses slowly
- Iterative treatment responses and relapses
- Not thought curable with conventional therapies
  - Exceptions include certain examples of limited stage disease treated with local therapies
- Most patients die from causes unrelated to lymphoma

Epidemiology



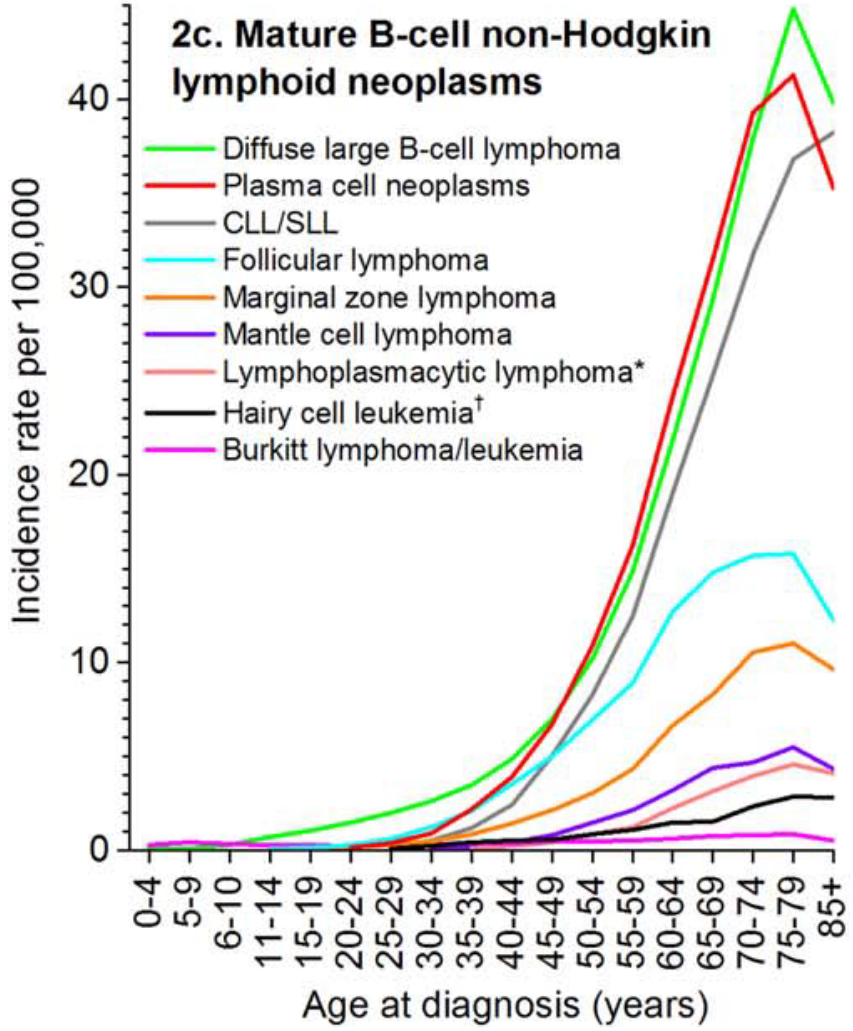
Estimated Cases and Distribution of Mature Non-Hodgkin Lymphoid Neoplasm Subtypes: US, 2016

Teras et al. CA Cancer J Clin 2016;66:443–459

Risk Factors

- Follicular lymphoma
  - Autoimmune conditions
  - Cigarette smoking (women)
  - Benzene, other solvents
  - Agent Orange, other herbicides

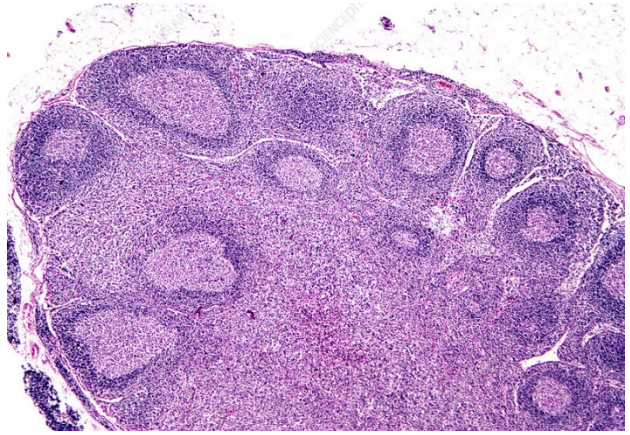
- Marginal zone lymphoma
  - As above, also specific infections (e.g. H pylori)



Teras et al. CA Cancer J Clin 2016;66:443–459
https://www.publichealth.va.gov/exposures/agentorange/conditions/nonhodgkinslymphoma.asp

Work-up

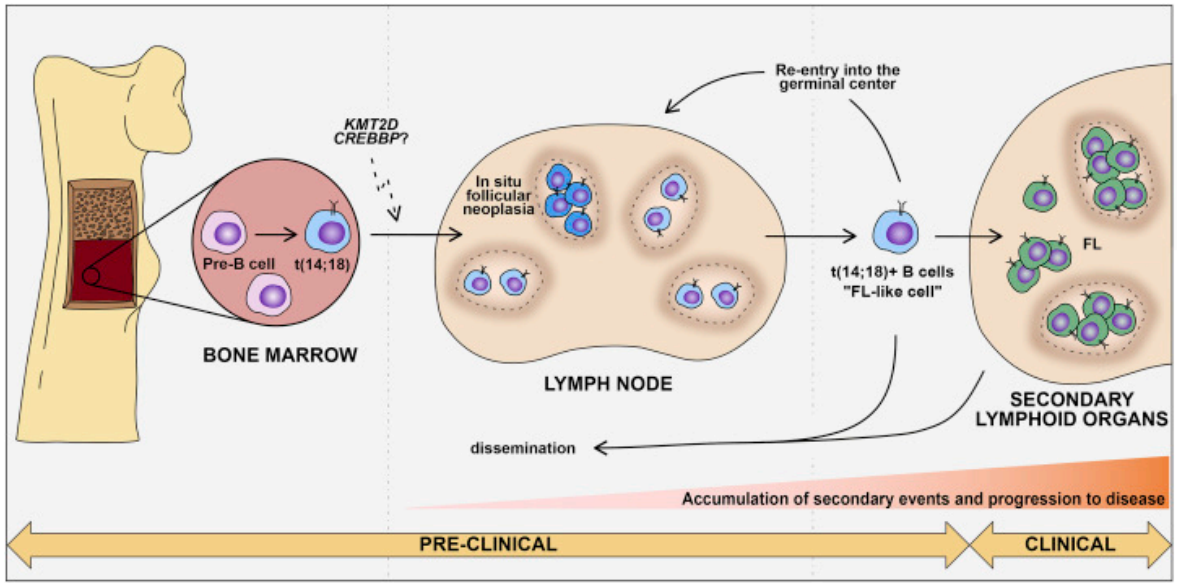
- Excisional or incisional biopsy preferred to core (FNA inadequate)
- Labs including LDH, hepatitis B
- Diagnostic CT, whole-body PET
- Marrow exam (clinical stage I-II disease)



Choi et al. Arch Pathol Lab Med. 2018;142:1330-1340
https://www.sciencephoto.com/media/115304/view/normal-human-lymph-node

Typical Follicular Lymphomagenesis

- B cells differentiate in lymph node germinal centers
- Maturation occurs by random genetic modification followed by antigen driven selection
- FL arises from developmentally-blocked germinal center B cells



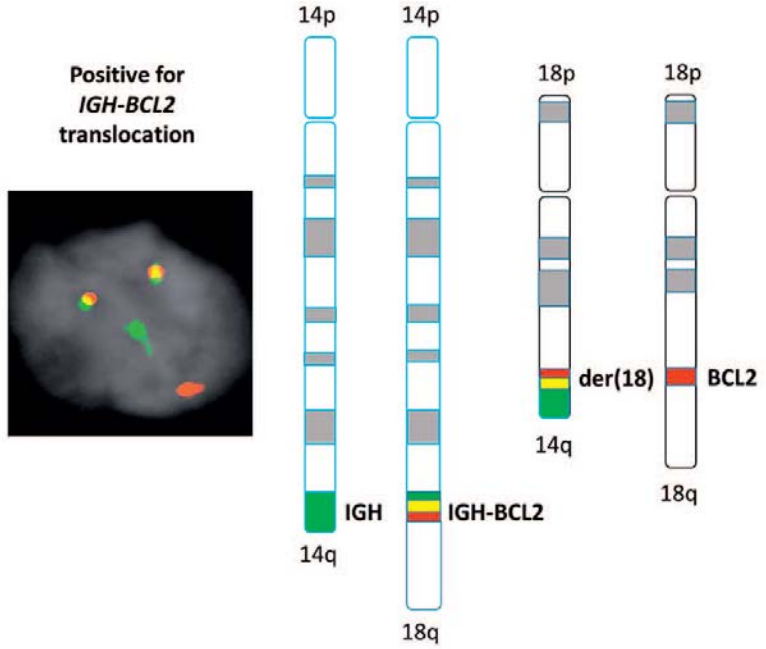
- 1st step: acquisition of t(14;18) that occurs in the bone marrow (pre-B cell stage)
  - Leads to constitutive expression of anti-apoptotic protein BCL-2
- B cells with t(14;18) that enter the germinal center (highly mutagenic environment) are at risk for developmental arrest leading to clonal expansion, new mutations, and ultimately FL

Lackraj et al Best Pract Res Clin Haematol. 2018 Mar;31(1):2-14.

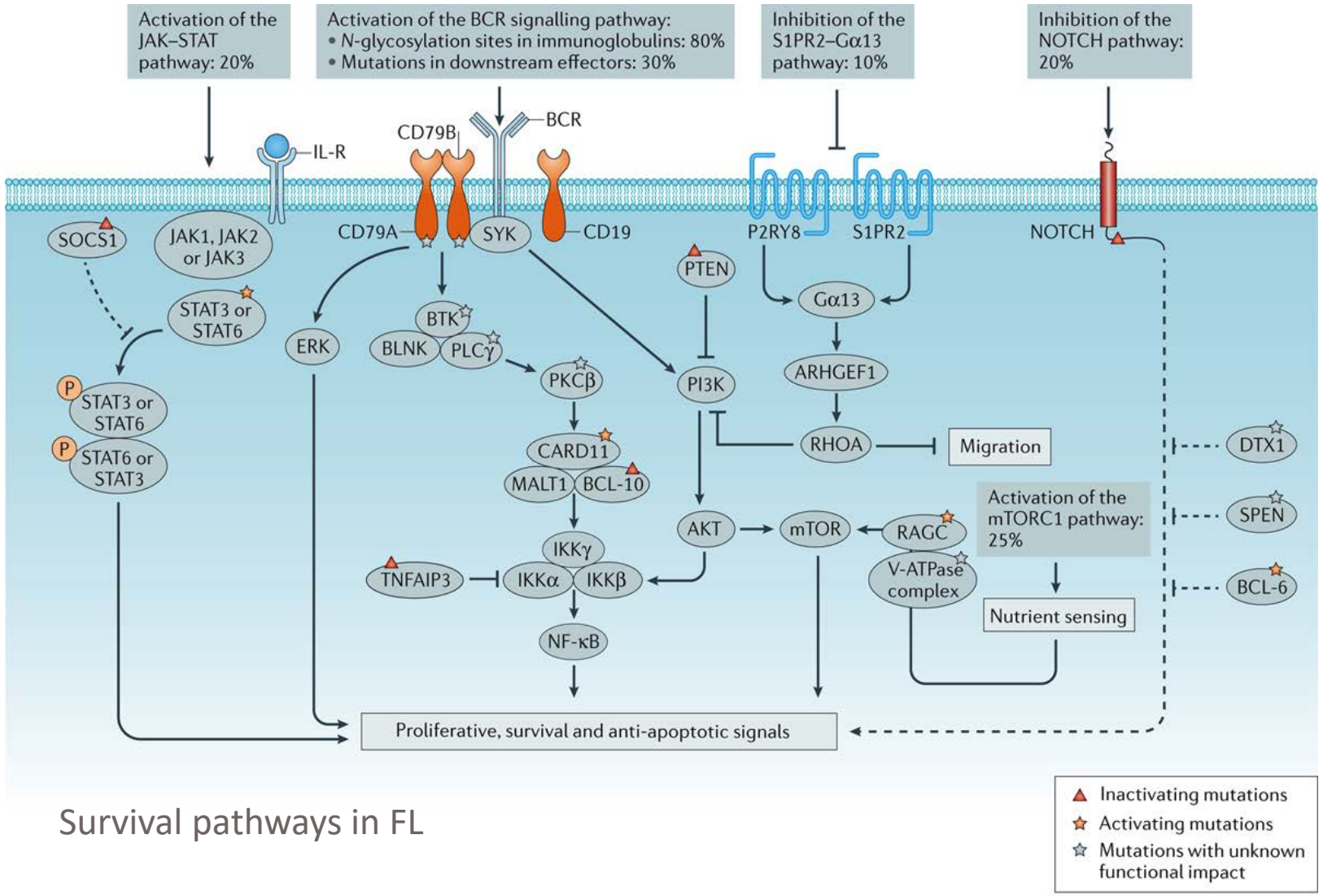
Molecular Characteristics: Typical FL

- Light chain restricted
- Pan B-cell markers (CD20+, CD19+)
- Arise from germinal center B-cells, thus CD10+ and BCL6+
- Also typically BCL2+ and CD5-

- [t(14;18)(q32;q21)] ~85% of cases
  - Juxtaposes Ig heavy chain promoter with *BCL-2*
  - Constitutive BCL-2 expression (anti-apoptosis)
  - Variants [t(2;18)] and [t18;22)]
    - Alternative *BCL-2* juxtapositions (kappa LC / lambda LC)



Pathways in Follicular Lymphomagenesis



Survival pathways in FL

→ **Also, mutations in epigenetic modifiers occur in nearly 90% of cases of FL**

Huet et al. Nat Rev Cancer. 2018 Apr;18(4):224-239

Pediatric-type FL

- Definitive entry in 2016 WHO Lymphoma Classification

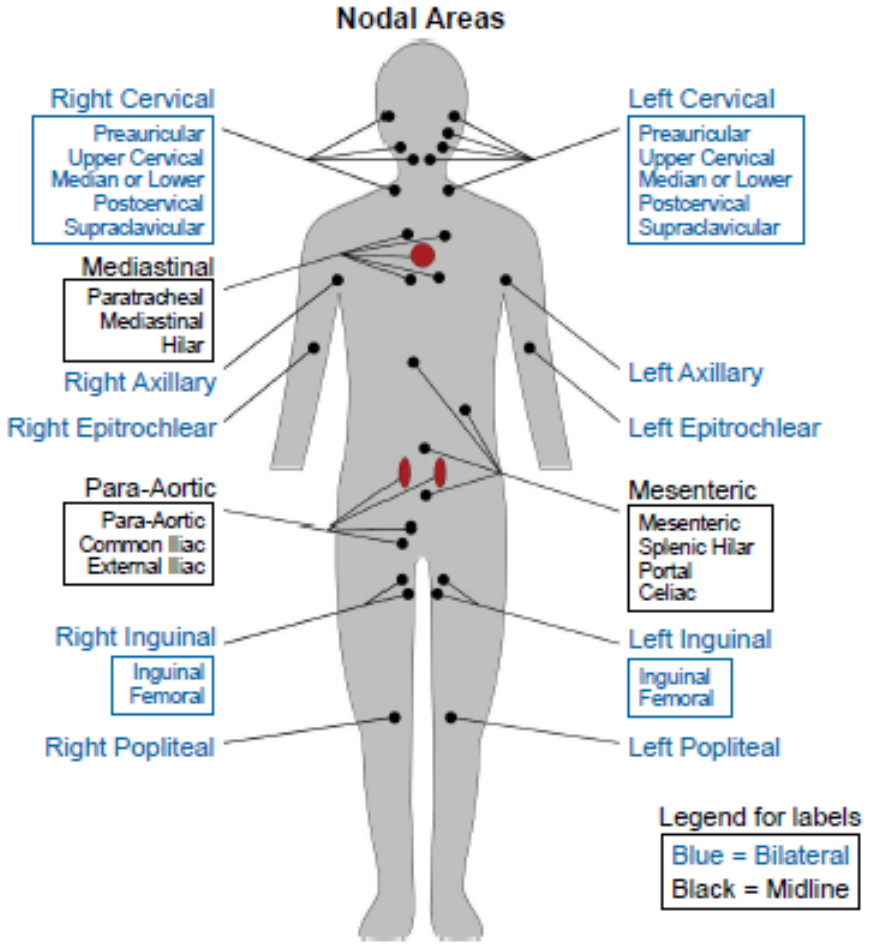
- Clinical presentation
  - Localized disease
  - Males > Females
  - Not necessarily young patients!

- Key pathologic/molecular features
  - High Ki67 (> 30%)
  - No t(14;18)
  - (Not commonly mutated in epigenetic modifiers)
  - (Low genetic complexity)

- Local therapy preferred

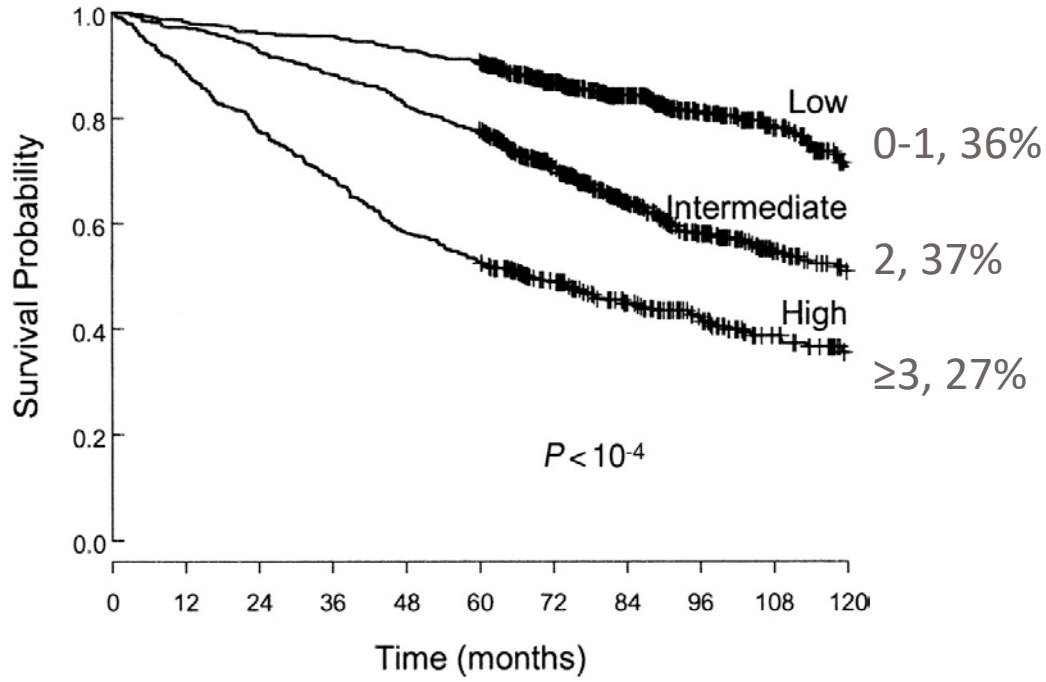
Clinical Characteristics of Follicular Lymphoma

- Median age at diagnosis approximately 65 years
- Multiple sites of waxing and waning adenopathy
- Approximately 25% present with B symptoms
- 65-70% stage III/IV



Follicular Lymphoma International Prognostic Index

- N = 4,167 diagnosed 1985 - 1992
- Adverse factors
  - Nodal areas (> 4) — No
  - LDH (elevated) — L
  - Age (> 60) — A
  - Stage (III/IV) — S
  - Hemoglobin (< 12 g/dL) — H



Celigny et al Blood. 2004 Sep 1;104(5):1258-65

Next Generation FLIPIs

	FLIPI	FLIPI-2	PRIMA-PI	M7-FLIPI
Age	✔	✔		✔
Stage	✔			✔
Hemoglobin	✔	✔		✔
LDH	✔			✔
Nodal sites	✔			✔
B2M ≥ 3 gm/L		✔	✔	
Marrow inv		✔	✔	
Mass ≥ 6 cm		✔		
ECOG				✔
7-gene mutations				✔

Federico et al. J Clin Oncol 27: 4555-4562, 2009; Jurinovic et al. Blood 128: 1112-20; Huet et al, ICML 2017; Salles et al. Blood. 2018 Jul 5;132(1):49-58.

Advanced Stage FL: Treatment Initiation

Table 2. Spontaneous Regressions in Initially Untreated Patients.*

	No. of Patients (%)	Months to Regression		Months of Regression	
		median	*range*	*median*	*range*
Total	19/83	8	2–120	>13	>4–>72
FSC/NLPD	13/44 (30)	7	2–120	15	>4–>72
FM/NM	3/18 (17)		2–23		>4–12
SL/DLWD	3/21 (14)		26–93		6–>72

FSC = Follicular small cleaved; FM = follicular mixed; SL = small lymphocytic; DLWD = diffuse well differentiated lymphocytic

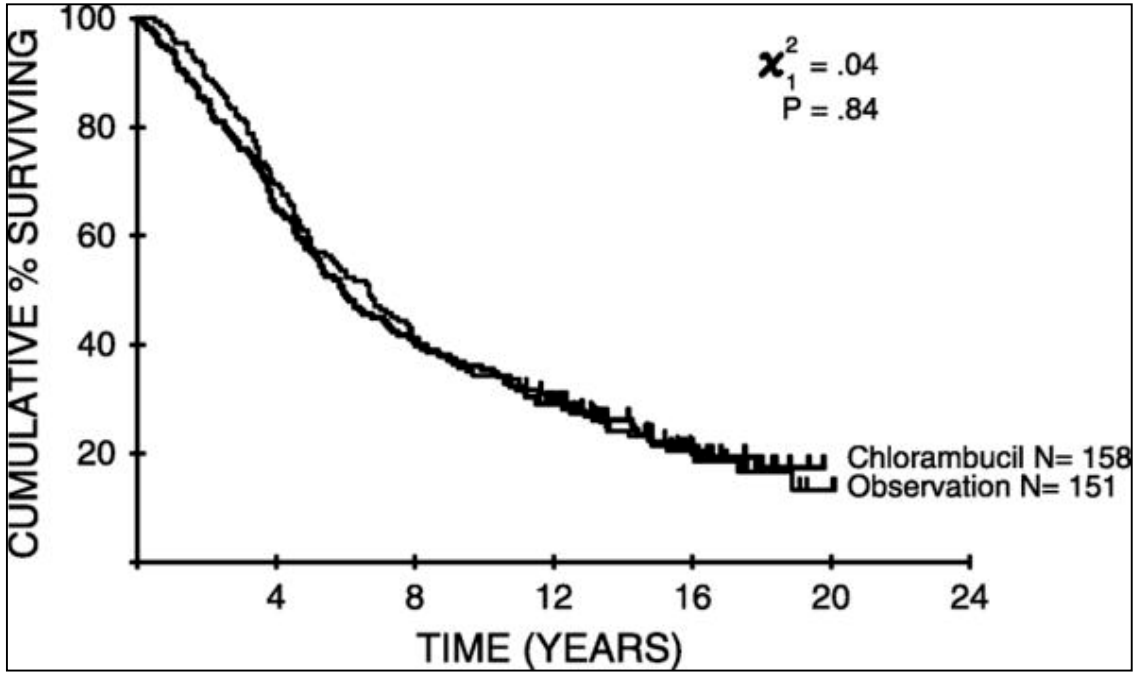
Hornig, NEJM 1984.

Advanced Stage Early Treatment (Chlorambucil)

Asymptomatic stage III/IV FL N = 309

RANDOMIZE

- Observation
- Chlorambucil

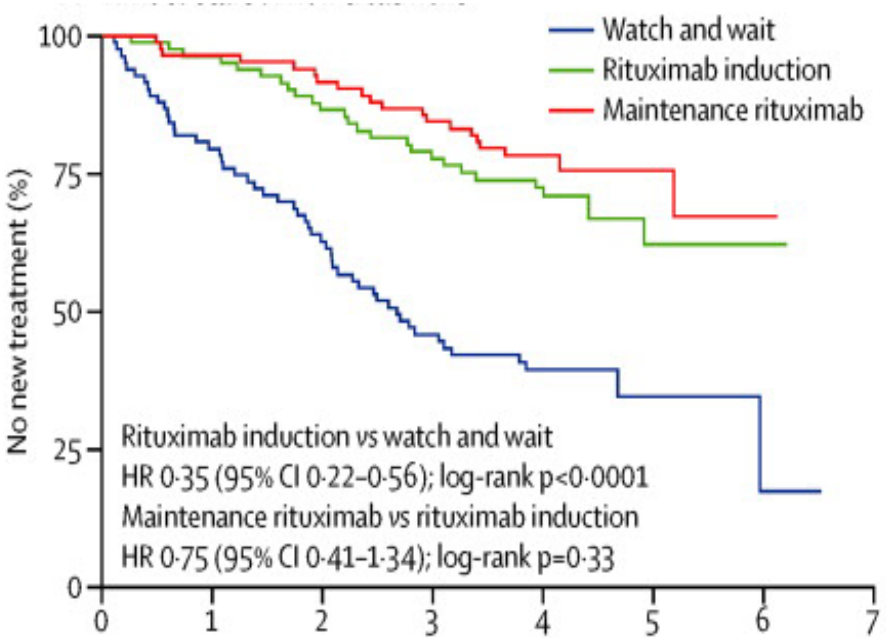


19% did not require treatment at 10 years

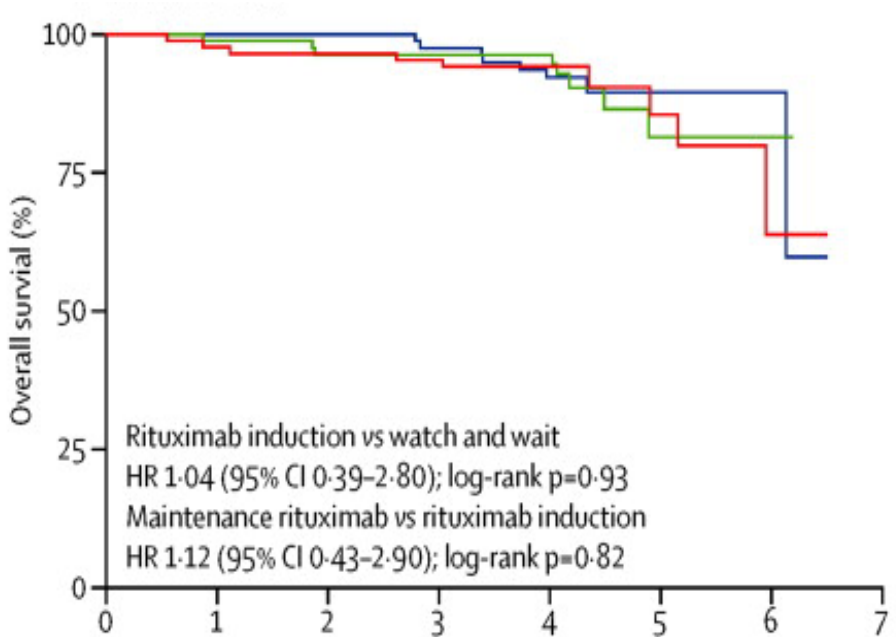
Ardeshna et al, Lancet. 2003 Aug 16;362(9383):516-22

Advanced Stage Early Treatment (Rituximab)

Time to Next Treatment



Overall Survival



- Those that received induction plus maintenance rituximab had some benefit related to anxiety
- Conversation on toxicities, costs, and potential for never requiring therapy

Ardeshna et al, Lancet Oncol. 2014 Apr;15(4):424-35

Groupe d'Etude des Lymphomes Folliculaires Criteria

- Involvement of ≥ 3 nodal sites, each > 3 cm
- Any lesion > 7 cm

} "Bulky"

- B symptoms
- Splenomegaly
- Threatened organ function
- Pleural/peritoneal effusion
- Cytopenias (leukocytes < 1k or platelets < 100k) or leukemia

- NCCN: also, steady or rapid progression, candidate for trial

- Median time between diagnosis and start of treatment = 2 to 3 years

Solal-Celigny et al. J Clin Oncol 1998; 16:2332-2338
Nastoupil et al. Br J Haematol. 2016 Mar;172(5):724-34

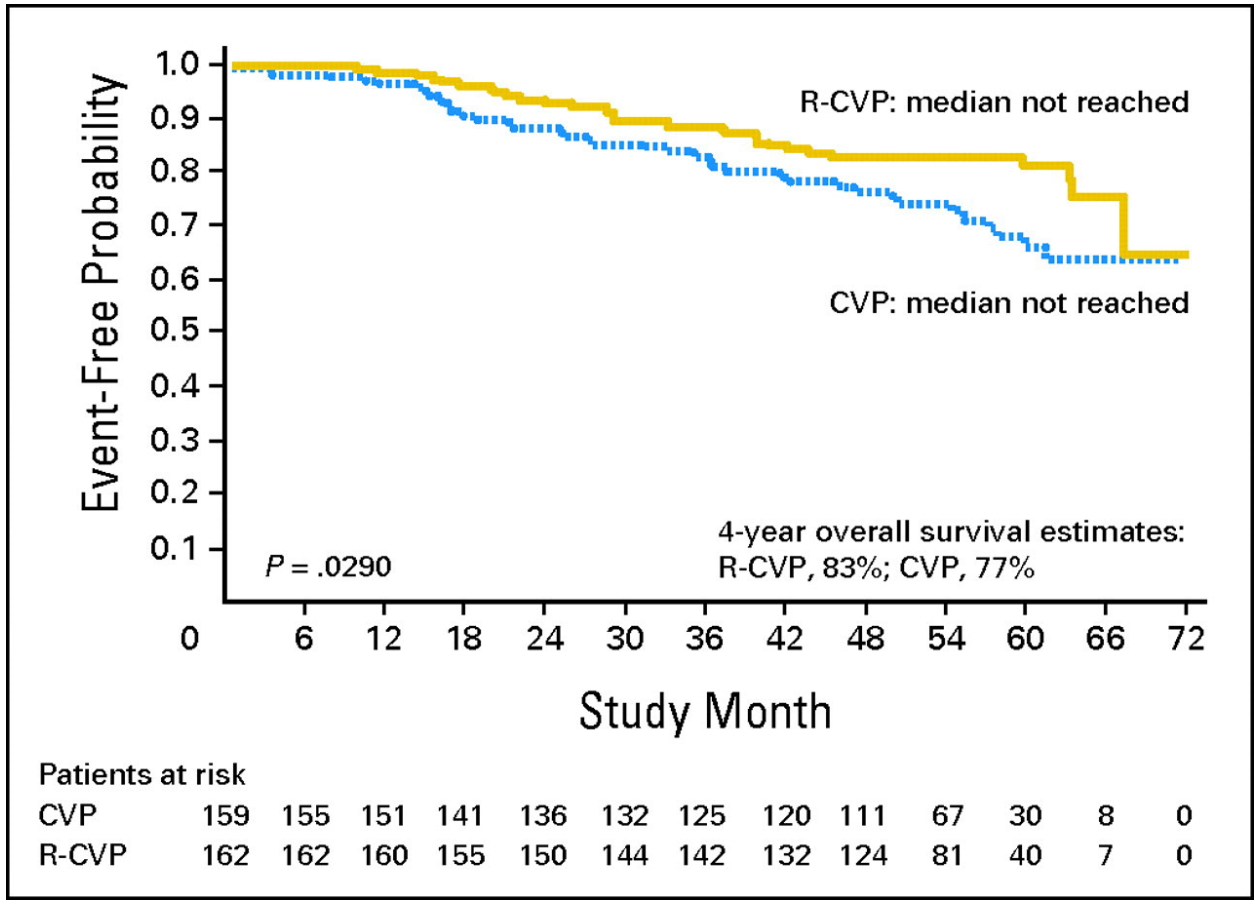
Frontline Treatment: Addition of Rituximab

FL stage III/IV + Treatment Indication

RANDOMIZE

R-CVP x8

CVP x8



Marcus et al. J Clin Oncol. 2008 Oct 1;26(28):4579-86

Primary Rituximab and (Maintenance v Observation) PRIMA

Untreated FL, stage III/IV; grade 1-3a
High tumor burden

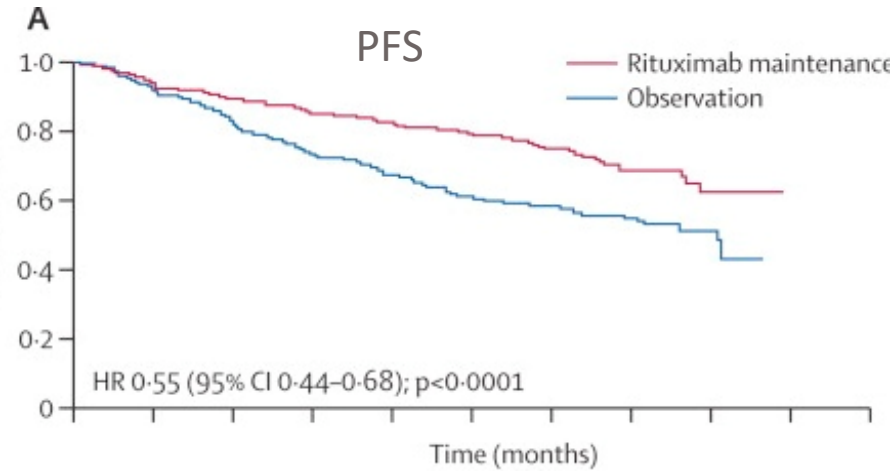
→ R-chemo

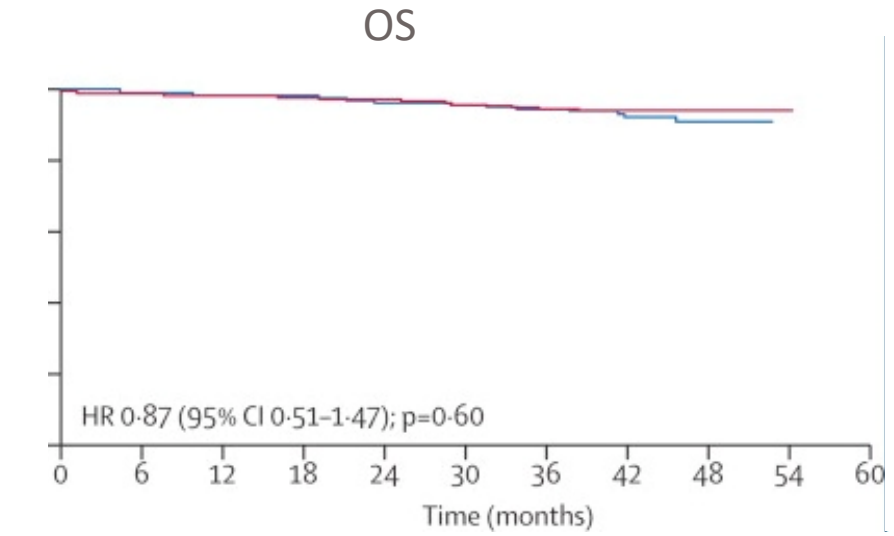
- R-FCM (4%)
- R-CVP (23%)
- R-CHOP (74%)

→ CR/PR
N = 1,018

→ RANDOMIZE

- → Observation
- → R q2mo x2 yrs





Salles et al. Lancet. 2011 Jan 1;377(9759):42-51.
Updated 2019 ASCO (9 years follow-up)

PRIMA: Toxicity

	Observation (n=508)		Rituximab maintenance (n=501)	
	Grade 3/4	Leading to treatment discontinuation	Grade 3/4	Leading to treatment discontinuation
All adverse events	84 (17%)	8 (2%)	121 (24%)	19 (4%)†
Neoplasia	17 (3%)	6 (1%)	20 (4%)	5 (1%)
Neutropenia	5 (1%)	0	18 (4%)	0
Febrile neutropenia	2 (<1%)	0	1 (<1%)	1 (<1%)
Infections	5 (1%)	0	22 (4%)	4 (1%)
CNS disorders	13 (3%)	0	10 (2%)	0
Cardiac disorders	5 (1%)	0	11 (2%)	1 (<1%)
Pregnancy	NA	2 (<1%)	NA	3 (1%)

- Logistics, financial

Salles et al. Lancet. 2011 Jan 1;377(9759):42-51.

Rituximab Extended Schedule or Re-treatement (RESORT)

Untreated FL: advanced stage, grade 1-2, **Low tumor burden**

→ R qweek x4

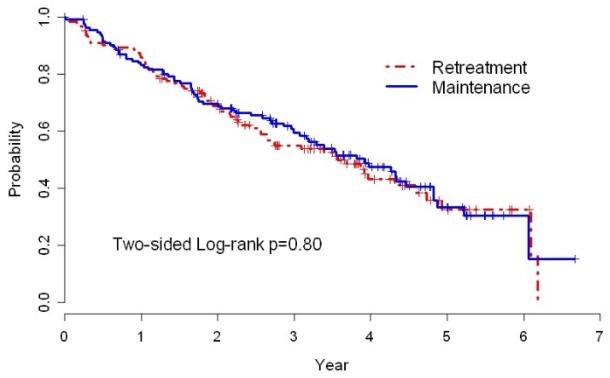
→ CR or PR

→ RANDOMIZE

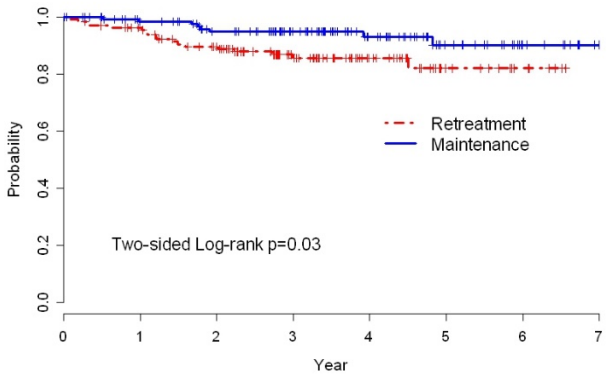
→ Observation → Repeat rituximab weekly x4 at progression (if TTP > 6 mo)

→ Rituximab q3 mo until progression

Time to treatment failure



Time to first cytotoxic chemo



Doses of Rituximab

	Min	Max	Median	Mean
Re-treat	4	16	4	4.5
Maint	5	31	15.5	15.8

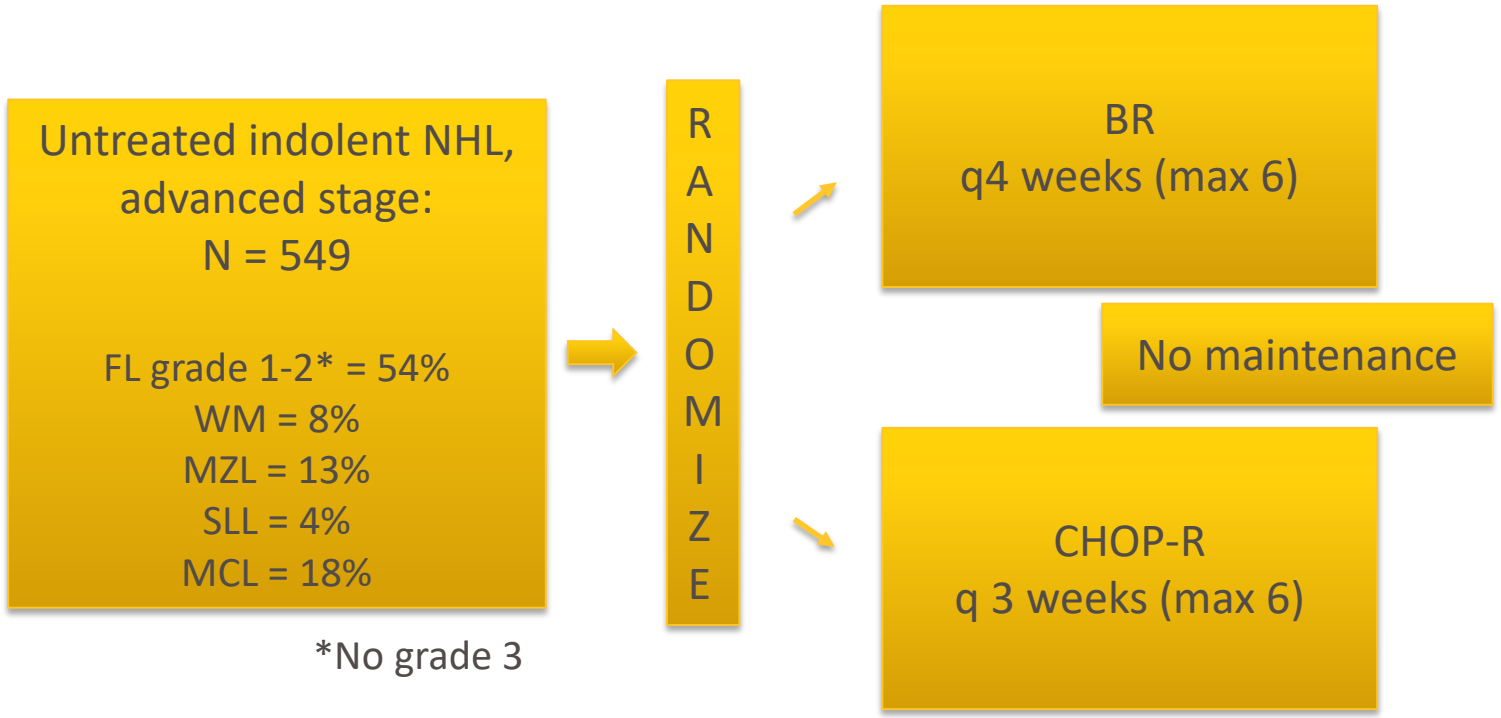
Kahl et al. J Clin Oncol. 2014 Oct 1;32(28):3096-102.

Rituximab Hyaluronidase

- Subcutaneous injection over ~ 5 minutes
- Efficacy and safety are similar to IV
- May be substituted after patients have received 1st full dose of IV rituximab
- Time-saving (for patients and infusion clinic) → monitor for 15 min post injection
- Injection-site erythema in 11%

eMPR.com accessed June 2020.

BR vs CHOP-R (StiL NHL1)

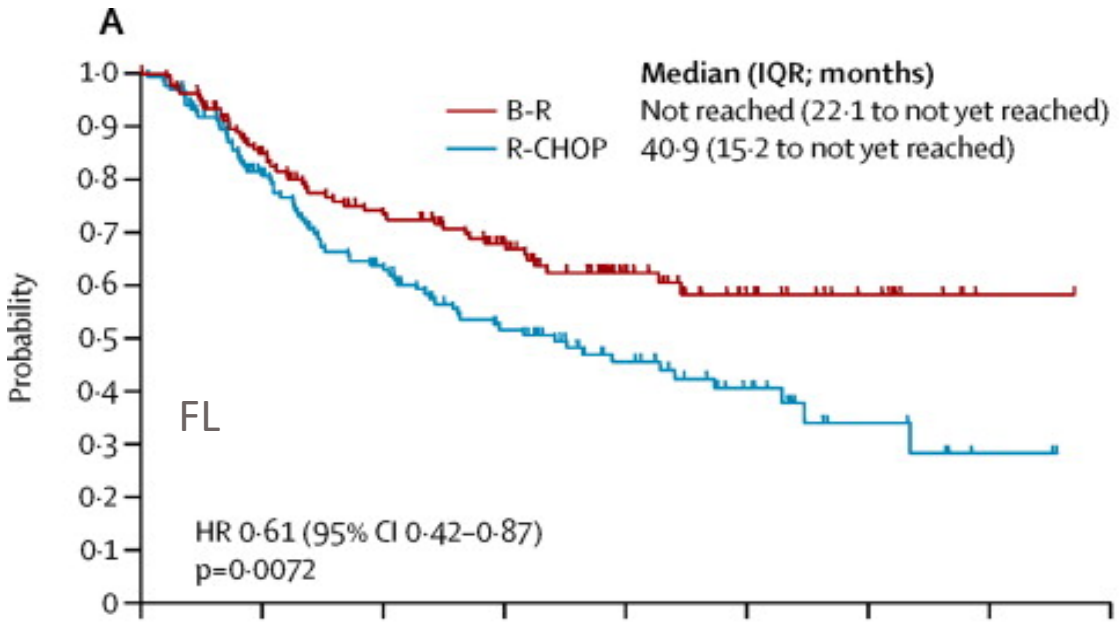


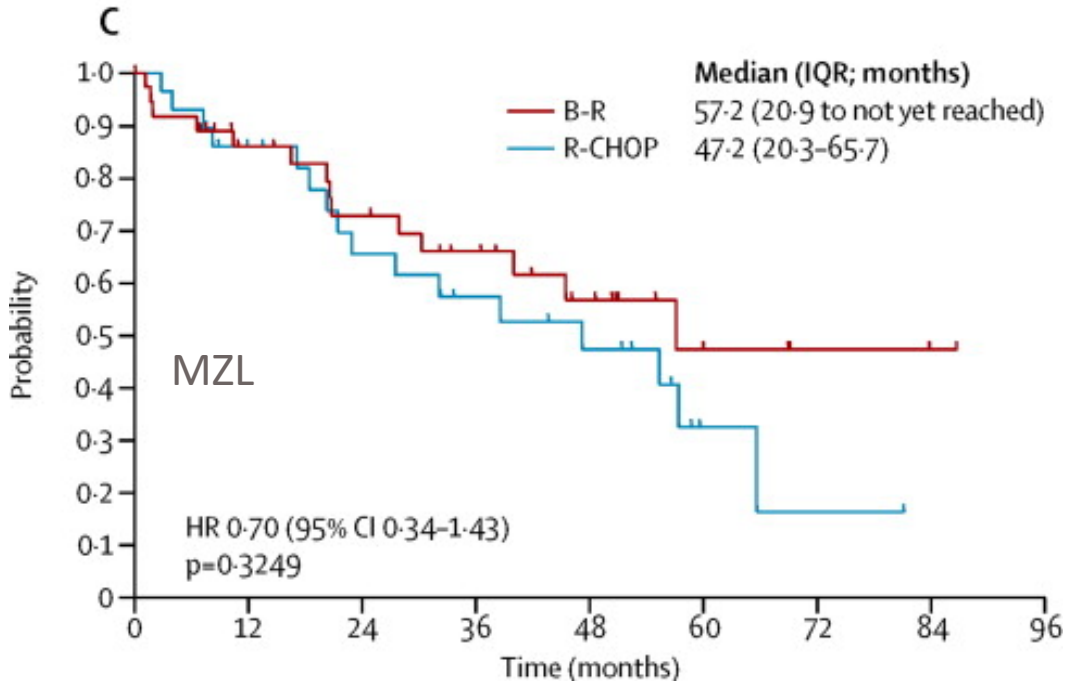
	B-R N = 260	CHOP-R N = 253	P
Alopecia	0	245	< 0.0001
Paresthesias	18	73	< 0.0001
Stomatitis	16	47	< 0.0001
Allergic reaction	40	15	0.0003
Infections	96	127	0.0025
Sepsis	1	8	0.0190
Neutropenia G3/4	11%	47%	

Rummel et al. Lancet. 2013 Apr 6;381(9873):1203-10.

StiL NHL1

	BR	CHOP-R
ORR	93%	91%
CR	40%	30%

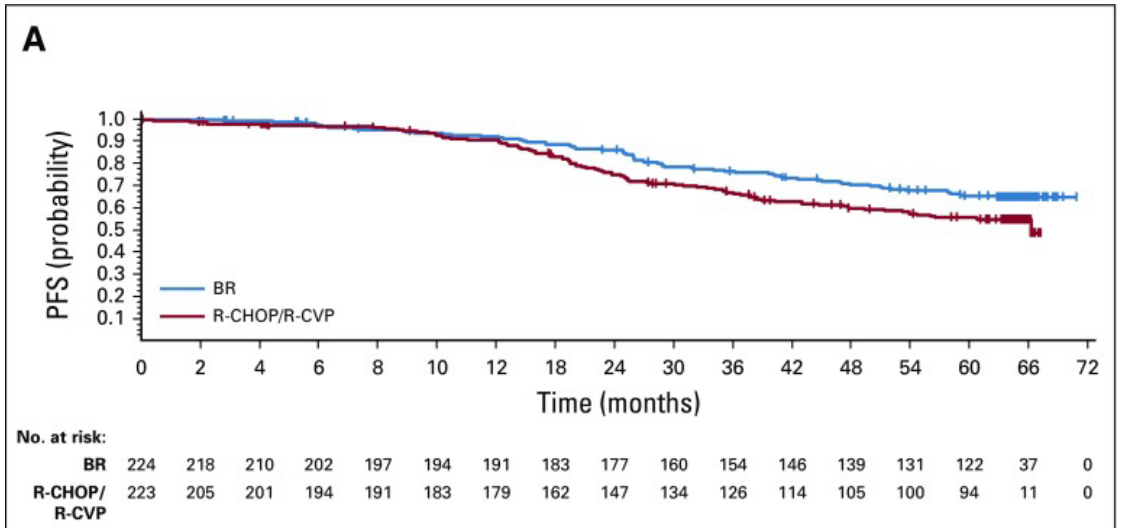


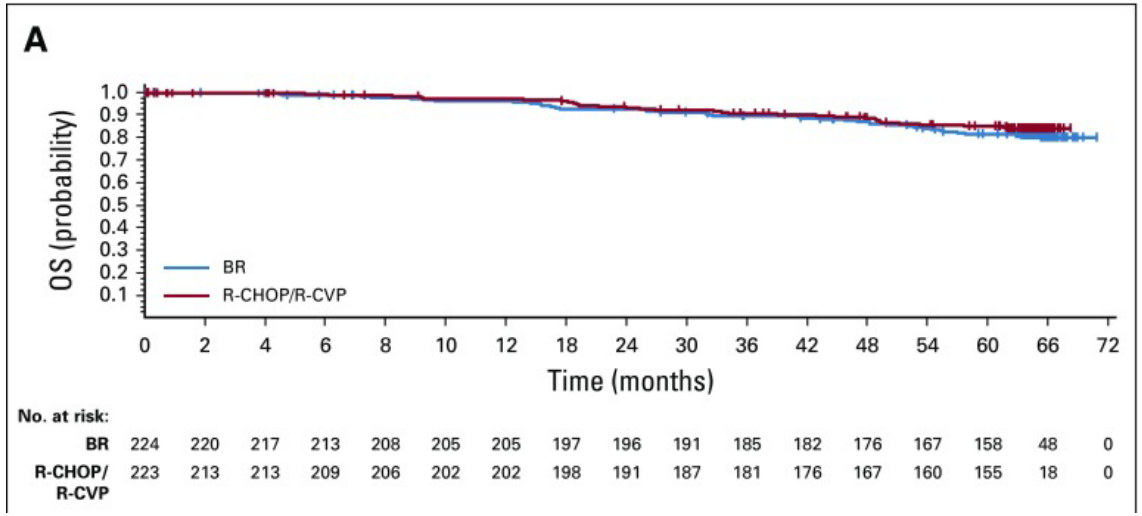


- No difference in OS

Rummel et al. Lancet. 2013 Apr 6;381(9873):1203-10.

BRIGHT: BR vs R-CVP or R-CHOP (5-year follow-up)





- Primary endpoint: noninferior CR rate (31% vs 25%; P for NI = .0225)
- 5 year PFS 65.5% vs 55.8% (HR 0.61, 95% CI 0.45 – 0.85; P = .0025)
- No difference in OS
- Comparable safety data to StiL
- Use of maintenance rituximab at discretion of clinician; similar across arms

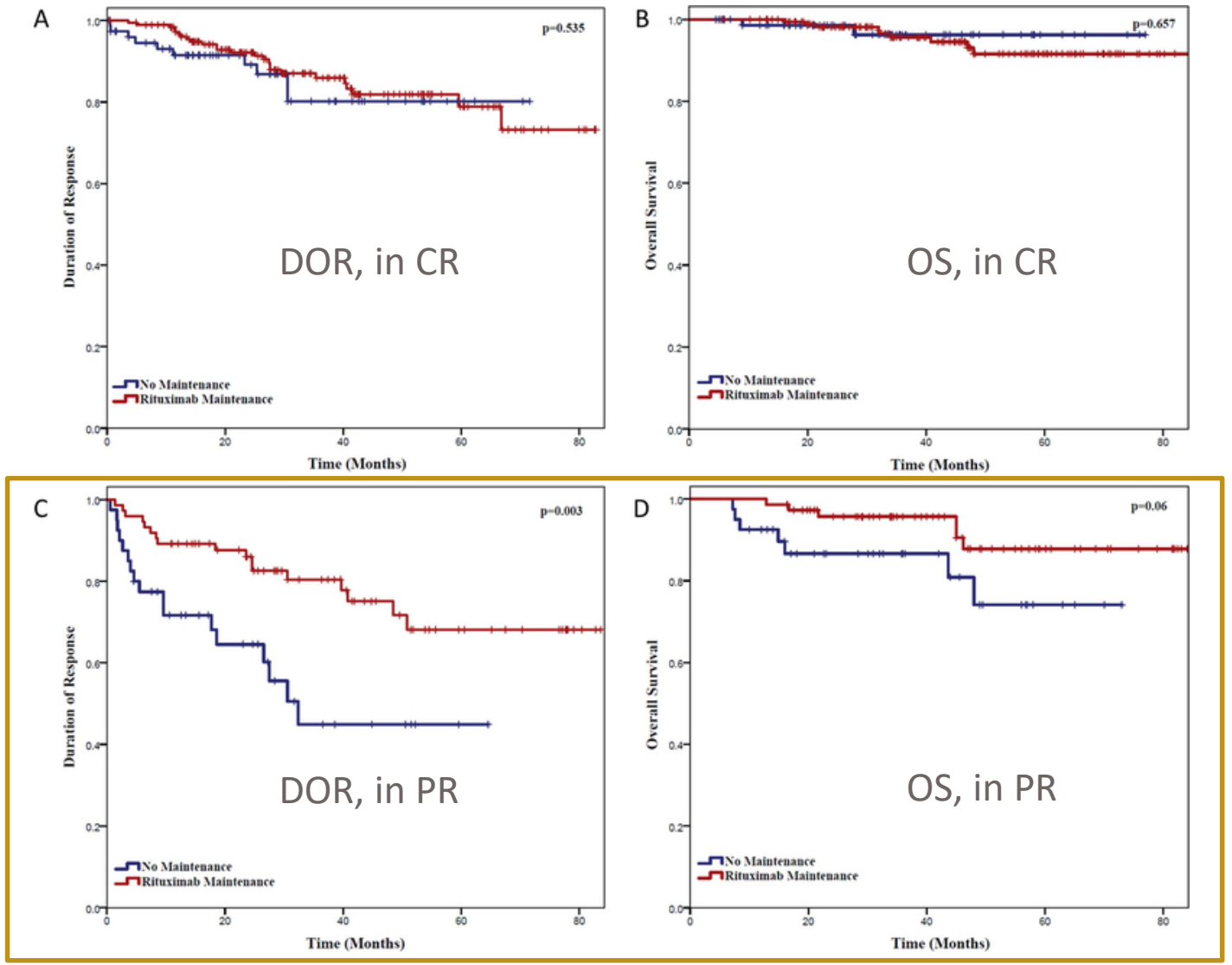
Flinn et al. J Clin Oncol . 2019 Apr 20;37(12):984-991.

Maintenance Rituximab after BR

- Retrospective, limited to patients in CR or PR after induction BR (at least 4 cycles)
- Findings comparable to other, cross-trial analyses

Maintenance Rituximab after R-chemo

For	Neutral/Against
PR	CR
Concern for toxicity from 2nd line	
	Cost, time
	Some toxicity

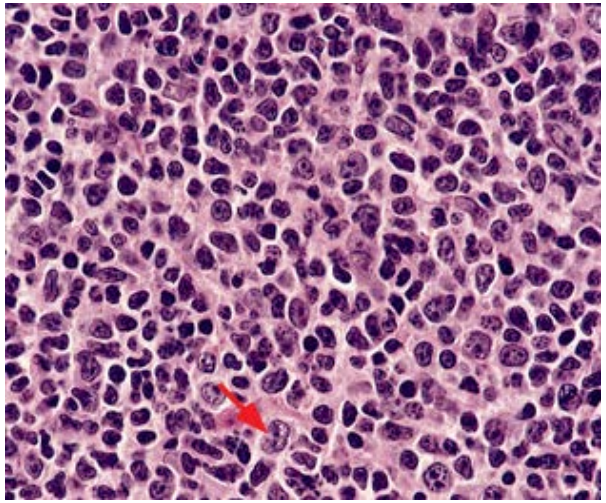


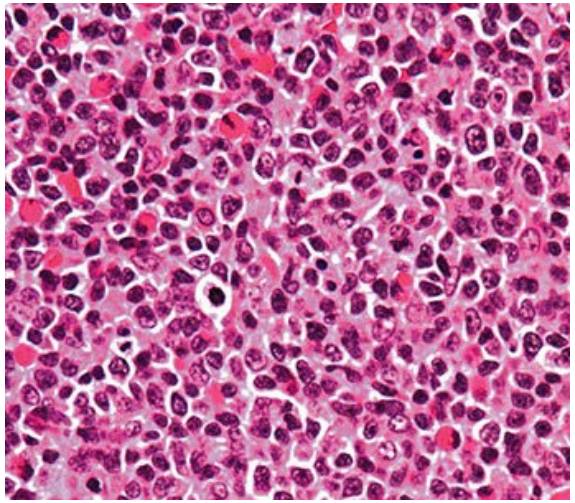
Hill et al. Br J Haematol. 2019 Feb;184(4):524-535.

BR for Frontline Treatment of FL

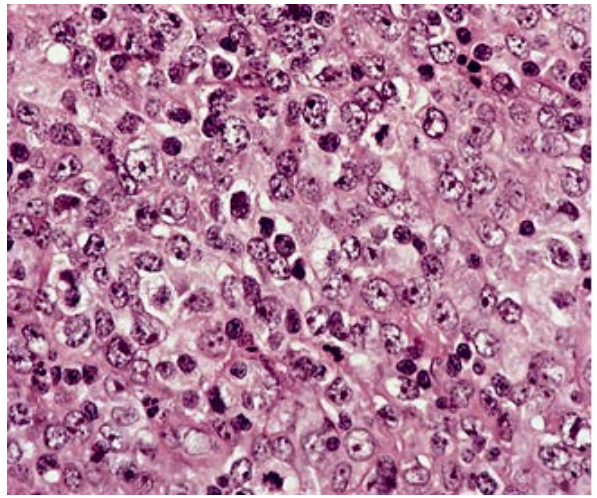
https://substance.etsmtl.ca accessed July 2020

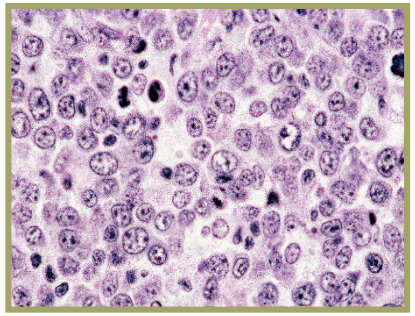
FL Histologic Grade





25-30% of FL

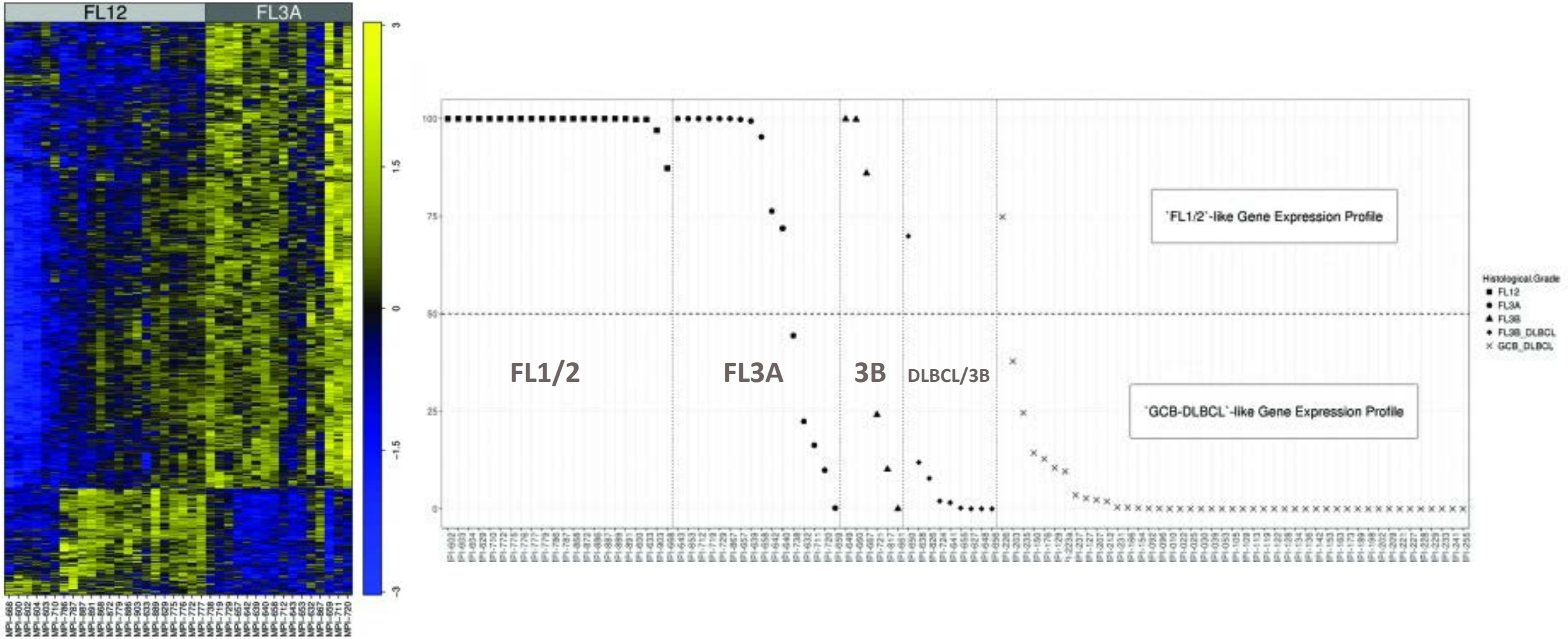




	1/2	3A	3B
Diffuse areas	Absent	Absent	Present
Centrocytes	Present	Present	Absent
Marrow invasion	Frequent	Frequent	Uncommon
CD10+	100%	83%	43%
***BCL2* break**	88%	58%	9%

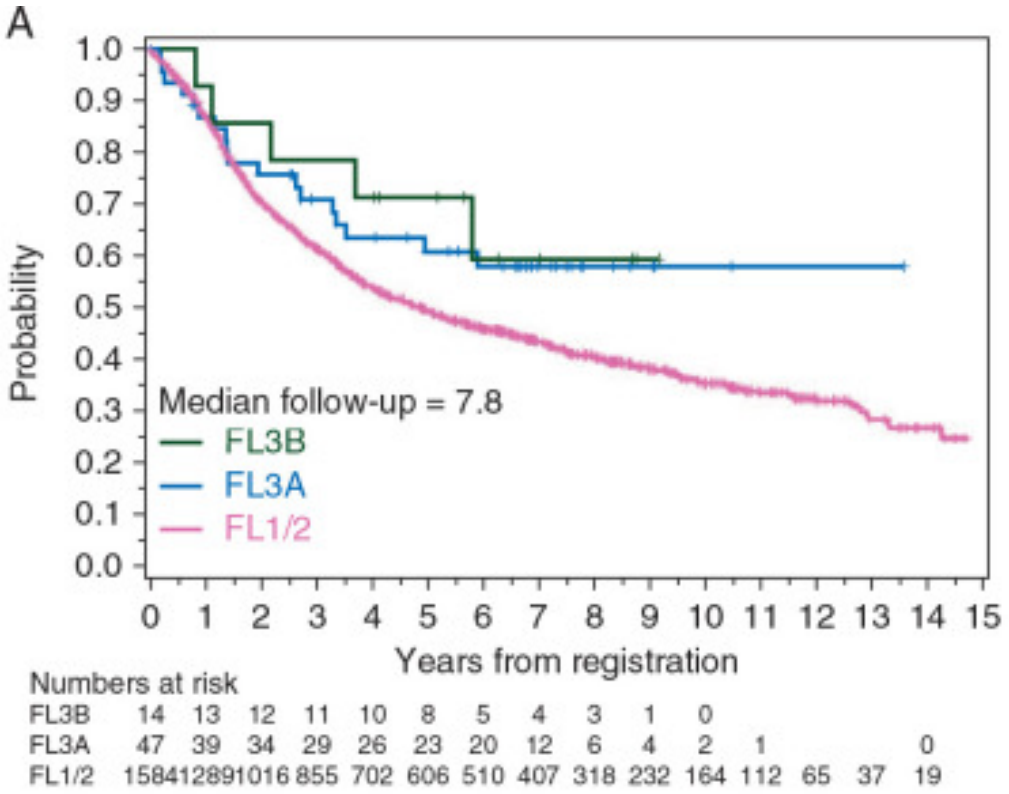
Horn et al. Haematologica. 2011 Sep;96(9):1327-34

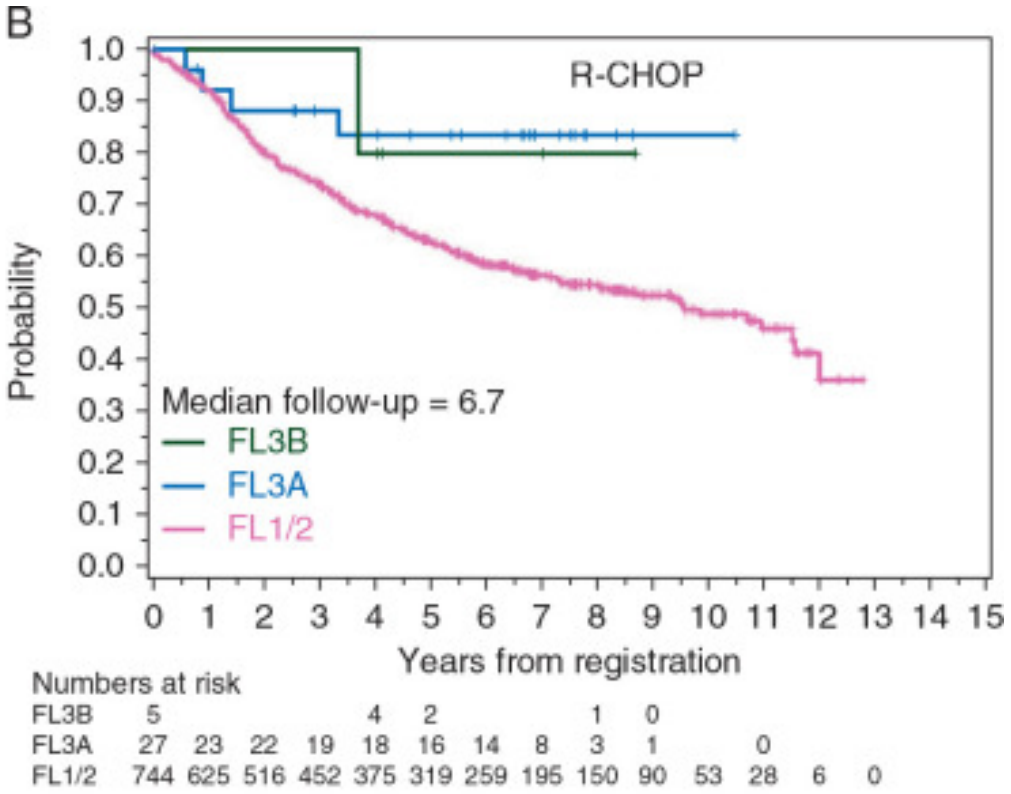
FL Histologic Grade



Horn et al. Haematologica. 2018 Jul;103(7):1182-1190

FL PFS by Grade





Koch et al. Ann Oncol. 2016 Jul;27(7):1323-9

R-Chemo Frontline for Advanced FL: Conclusions

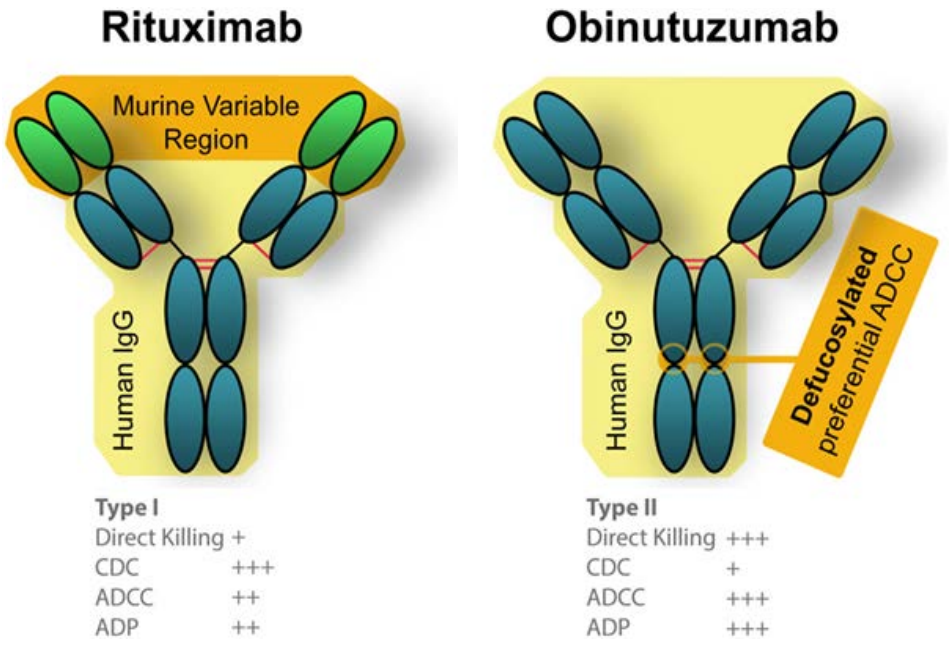
- BR preferred standard for bulky disease, treatment indication
- R-CHOP perfectly acceptable alternative considering no difference in OS
  - Deserves particular consideration in case of 3A grade

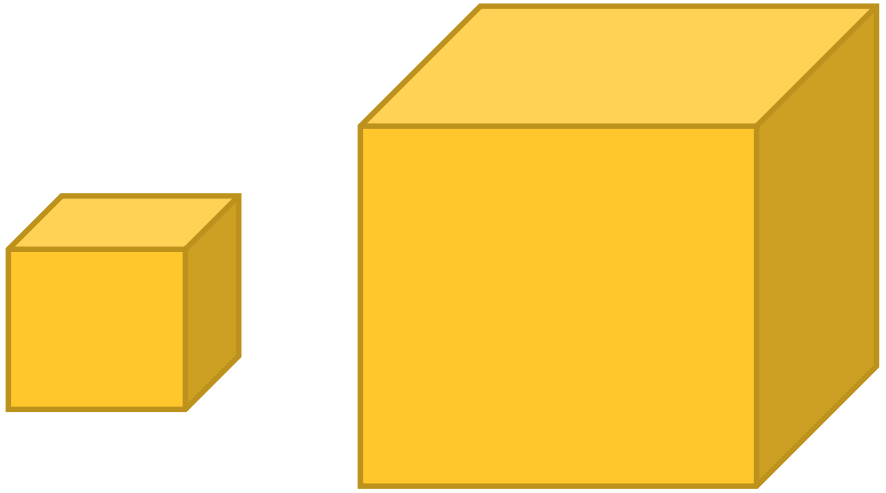
- Maintenance rituximab can be offered
  - Benefit and limitations in shared-decision making

Alternatives to R-Chemo: #1, O-Chemo

- Obinutuzumab binds overlapping epitope of CD20 (as rituximab) but in different orientation: results in different CD20 arrangement in cell membrane and increased apoptosis (type II)

- By manipulating glycosylation of cells that produce obinutuzumab, improvement in direct cell death and higher antibody dependent cell-mediated cyto-toxicity (via NK cell recruitment) is achieved

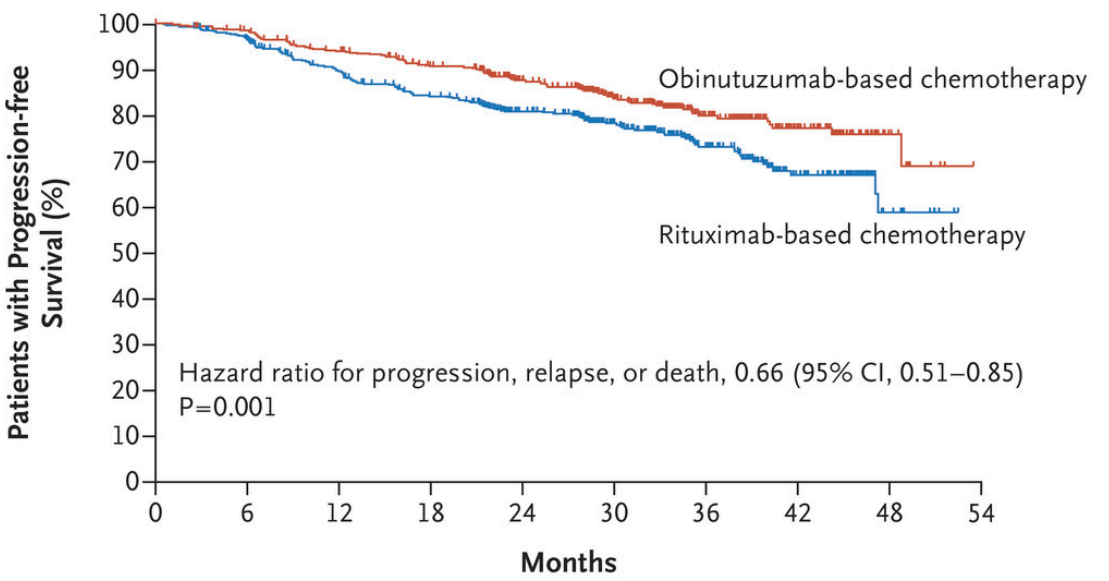


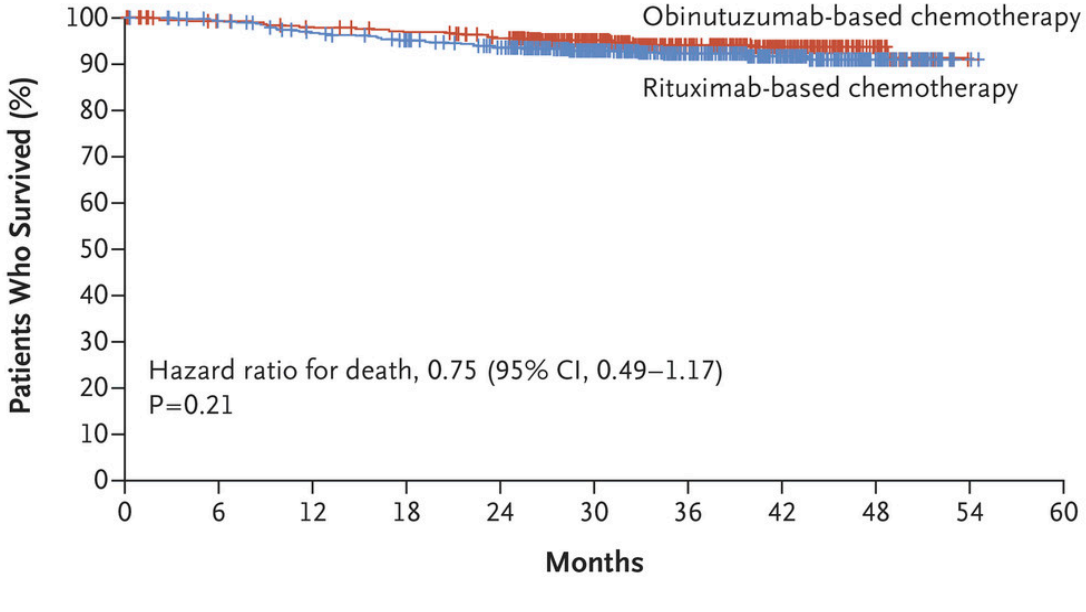


Pierpont et al. Front. Oncol., 04 June 2018

GALLIUM: R-Chemo vs O-Chemo, Frontline FL

- FL only, grades 1 – 3A
- Maintenance antibody given q2 mo x2 years
- Dosing: obinutuzumab: 1000 mg days 1, 8, 15 of C1 then 1000 mg D1 subsequent cycles





Marcus et al. N Engl J Med. 2017 Oct 5;377(14):1331-1344

GALLIUM: Higher Toxicity with O-Chemo, Bendamustine

Table 3. Adverse Events and Serious Adverse Events, According to Treatment Phase, and Selected Grade 3 to 5 Adverse Events during Treatment, According to Chemotherapy Agent and Treatment Phase in the Safety Population.*

Event	Overall Trial†		Induction Phase		Maintenance and Observation Phases		Follow-up	
	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=595)	Rituximab Group (N=597)	Obinutuzumab Group (N=548)	Rituximab Group (N=535)	Obinutuzumab Group (N=427)	Rituximab Group (N=428)
No. of events	10,311	9343	7012	6533	3002	2578	295	230
Patients with ≥1 adverse event — no. (%)								
Any event	592 (99.5)	587 (98.3)	580 (97.5)	577 (96.6)	501 (91.4)	458 (85.6)	130 (30.4)	106 (24.8)
Event of grade 3 to 5	444 (74.6)	405 (67.8)	357 (60.0)	336 (56.3)	205 (37.4)	169 (31.6)	56 (13.1)	33 (7.7)
Event of grade 5‡	24 (4.0)	20 (3.4)§	4 (0.7)	3 (0.5)	10 (1.8)	10 (1.9)	10 (2.3)	7 (1.6)
Infection¶	—	—						
Bendamustine	—	—	27/338 (8.0)	26/338 (7.7)	52/312 (16.7)	39/305 (12.8)	25/270 (9.3)	6/263 (2.3)
CHOP	—	—	14/193 (7.3)	13/203 (6.4)	7/179 (3.9)	11/187 (5.9)	2/128 (1.6)	2/143 (1.4)
CVP	—	—	3/61 (4.9)	4/56 (7.1)	5/57 (8.8)	1/43 (2.3)	1/44 (2.3)	2/45 (4.4)

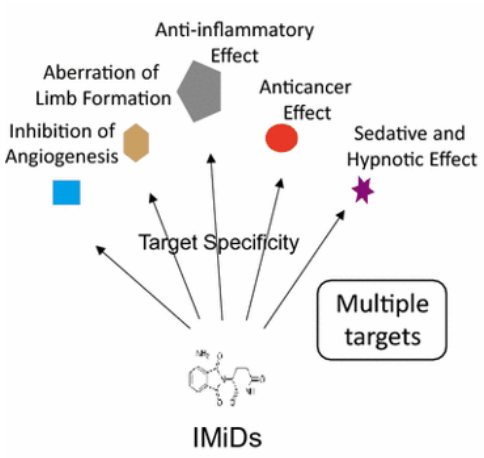
- Bendamustine associated OIs: PJP and VZV prophylaxis, especially with B-O

Marcus et al. N Engl J Med. 2017 Oct 5;377(14):1331-1344

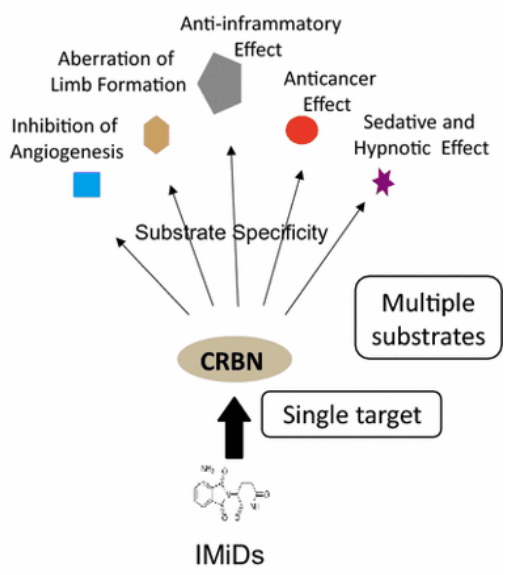
Alternatives to R-Chemo: #2, R-Lenalidomide

- Lenalidomide: immune-mediated inflammatory disease immunomodulatory agent
- Combined with rituximab: enhanced antibody-dependent cellular cytotoxicity and direct cytotoxicity

Older model



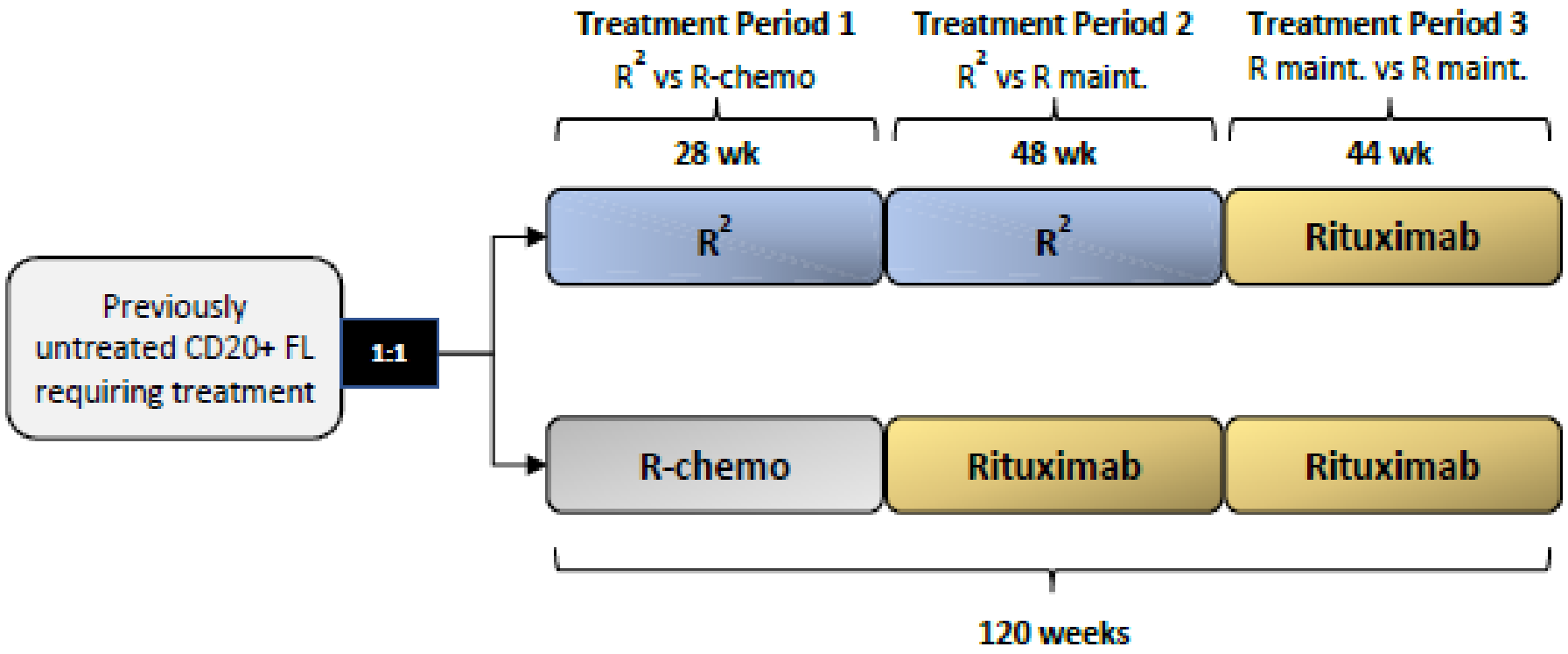
Newer model



- Cereblon is a substate receptor of a ubiquitin ligase; executes pleiotropic effects of lenalidomide

Ito et al. Int J Hem. 2016 Sep;104(3):293-299

RELEVANCE: Lenalidomide + Rituximab vs R-Chemo



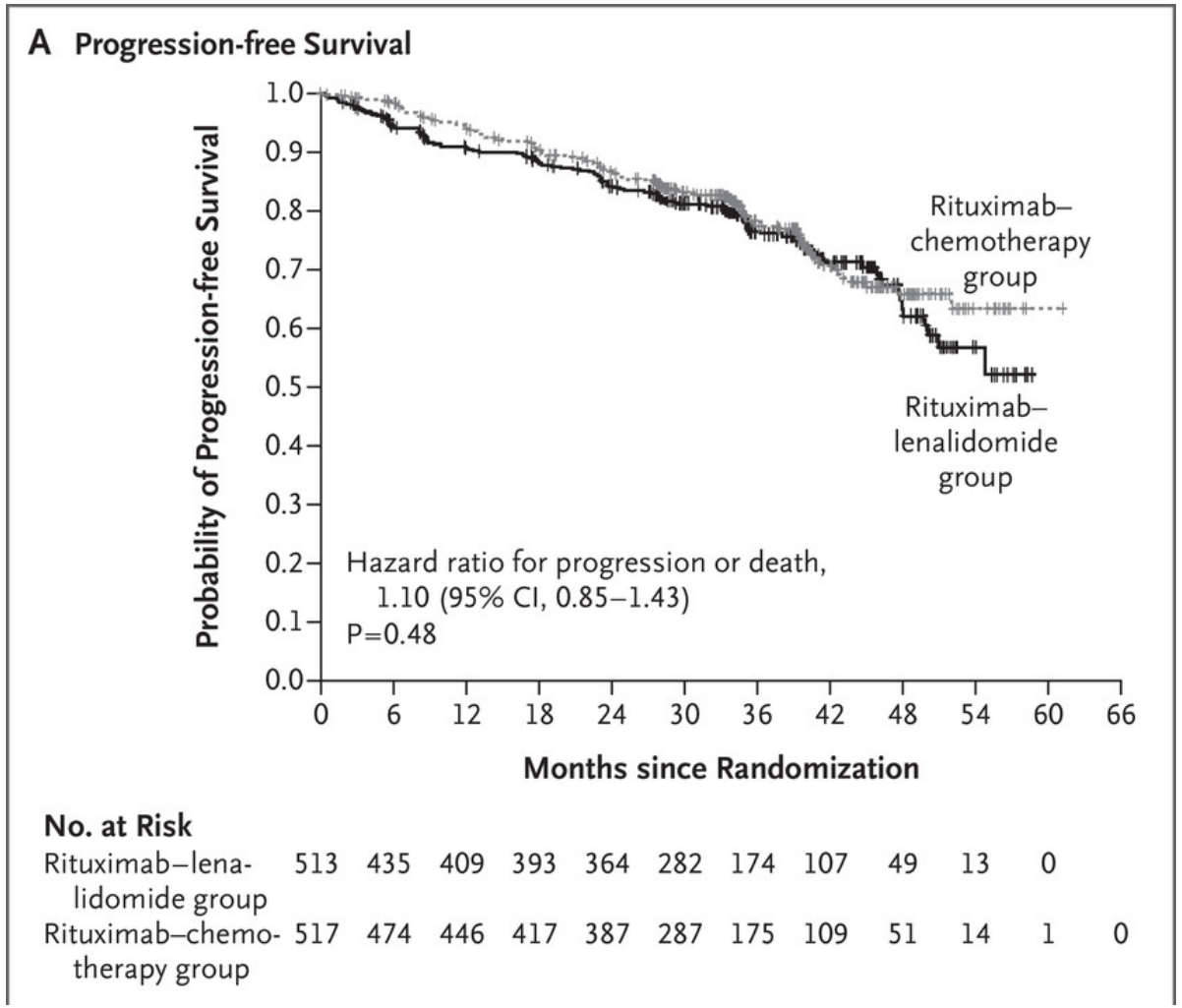
Morschhauser et al. NEJM. 2018 Sep 6;379(10):934-947

RELEVANCE: “Inferior” Primary End-Point?

- N = 1,030
- CR / CRu at 24 months
  - R2 = 48%
  - R-chemo = 53% (P = 0.13)

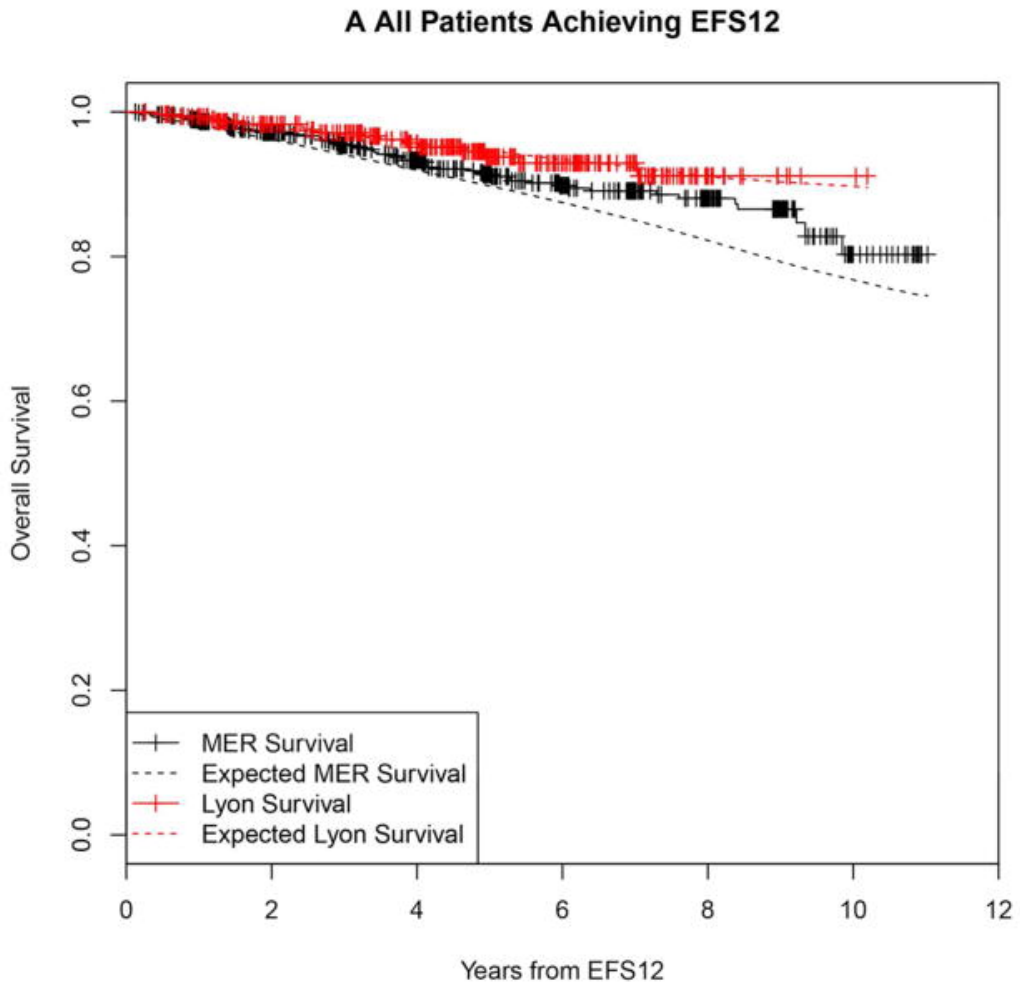
- Toxicity
  - Overall, comparable frequencies
  - R2 = less nausea, vomiting
  - R2 = more rash, diarrhea
  - R2 = toxicities drawn out

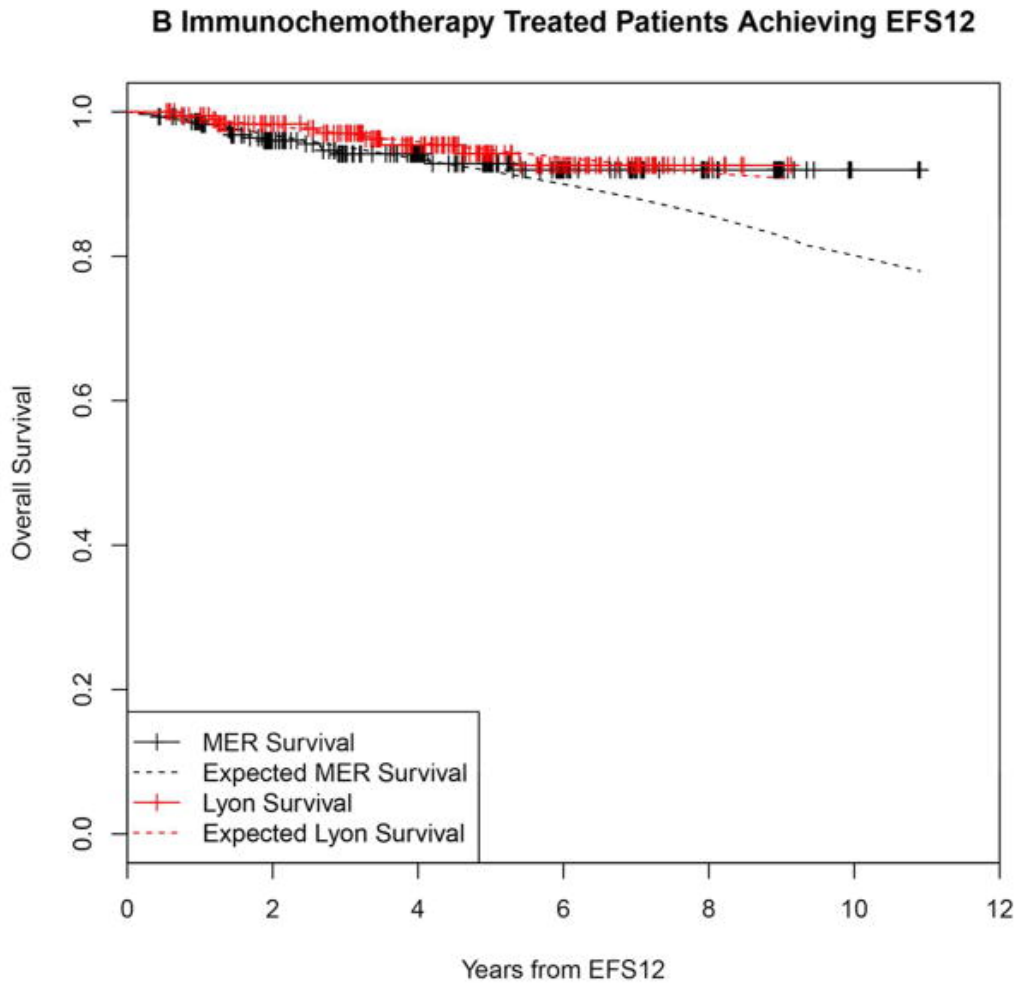
- No FDA approval (though NCCN inclusion)



Morschhauser et al. NEJM. 2018 Sep 6;379(10):934-947

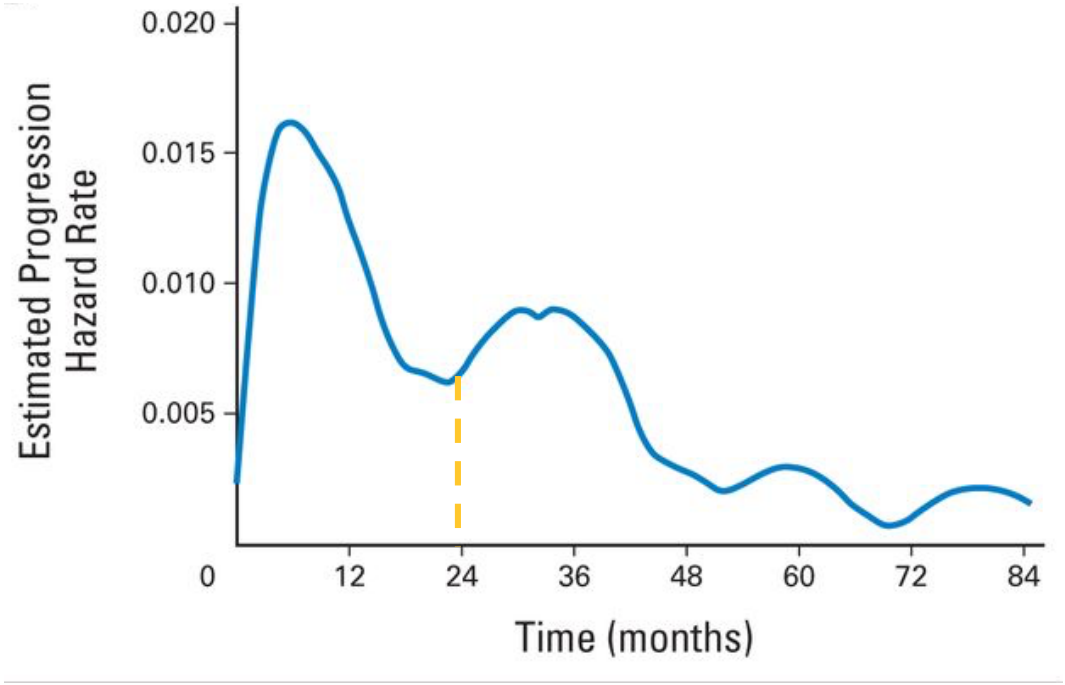
Outcomes of Patient with FL and “EFS12”

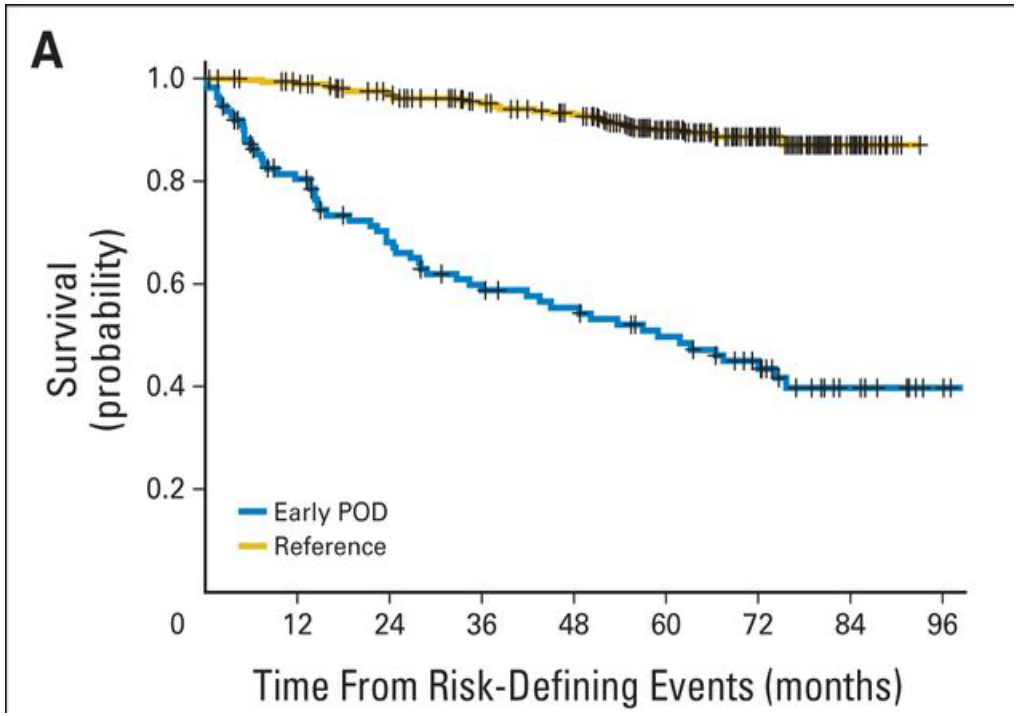




Maurer et al. Am J Hematol. 91: 1096-1101, 2016

Follicular Lymphoma: Relapse



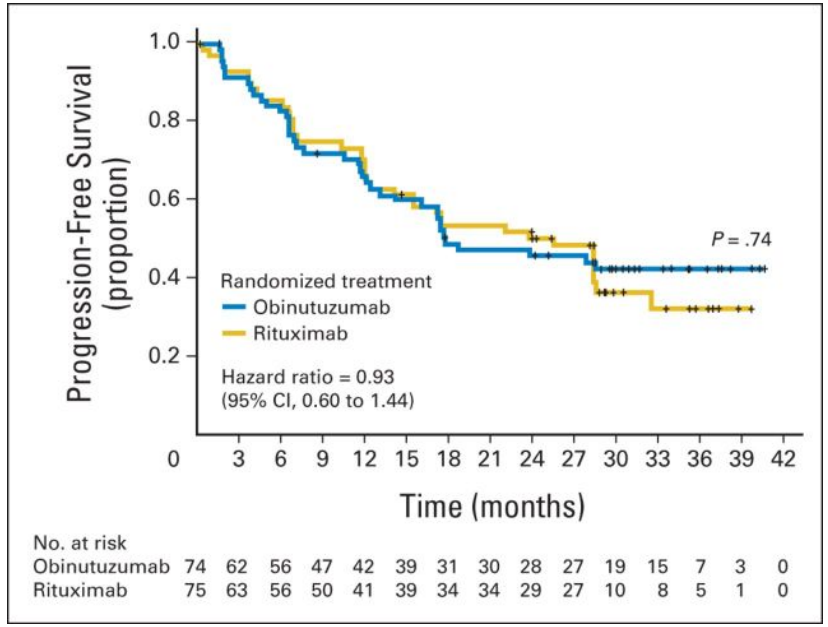


- Risk of progression highest in 24 months after R-CHOP
- In the 20% with "early" (< 24 mo) progression, survival markedly worse (independent of FLIPI)
- To date, no reliable marker for early POD or preferred treatment

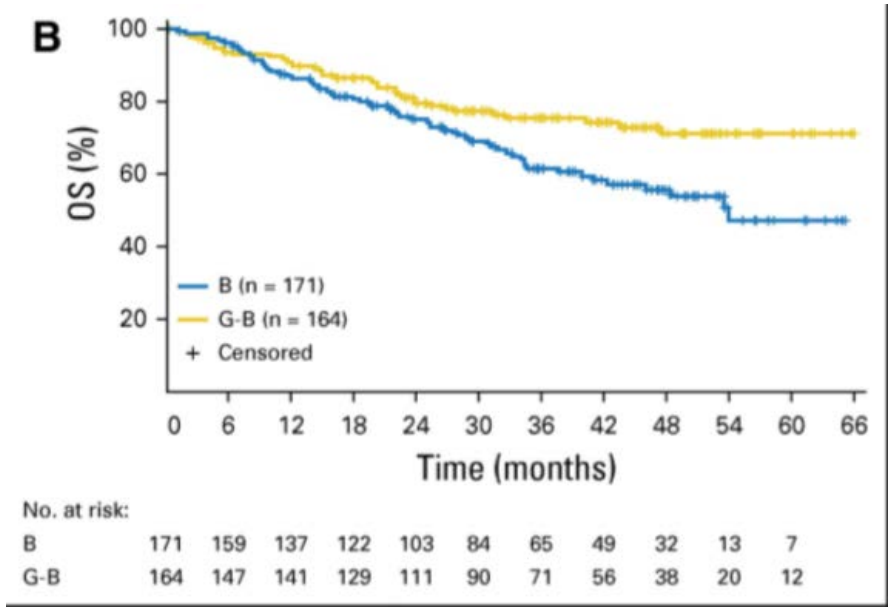
Casulo et al. J Clin Oncol. 2015 Aug 10;33(23):2516-22

Relapsed FL: Treatment

- Treatment indication?
- Switch out chemotherapy backbone and/or antiCD20
  - Obinutuzumab vs rituximab in R/R FL
  - GAUSS (R-sensitive): equivalent outcomes; GADOLIN (R-resistant): superior survival (albeit, to nothing)



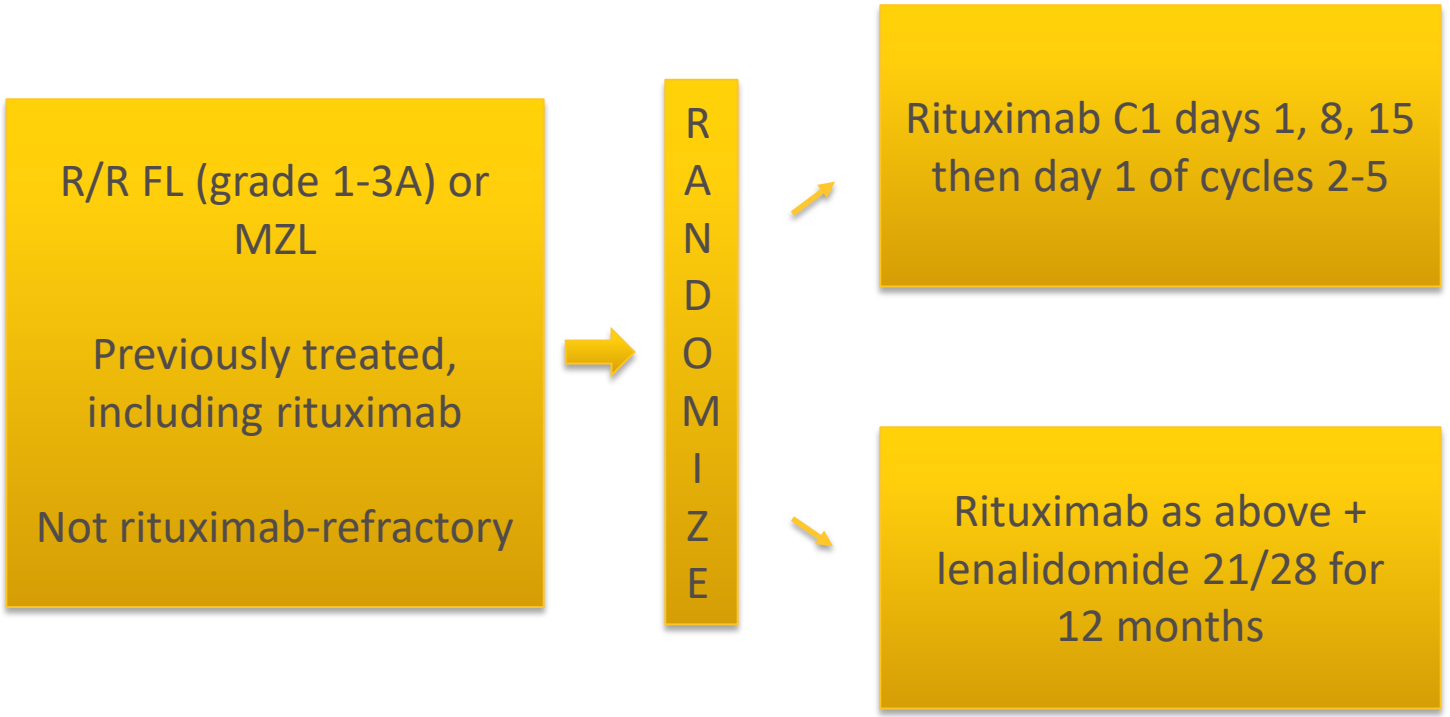
Sehn et al. J Clin Oncol. 2015 Oct 20;33(30):3467-74.



Cheson et al. J Clin Oncol. 2018 Aug 1;36(22):2259-2266.

R2 in the R/R Setting: AUGMENT

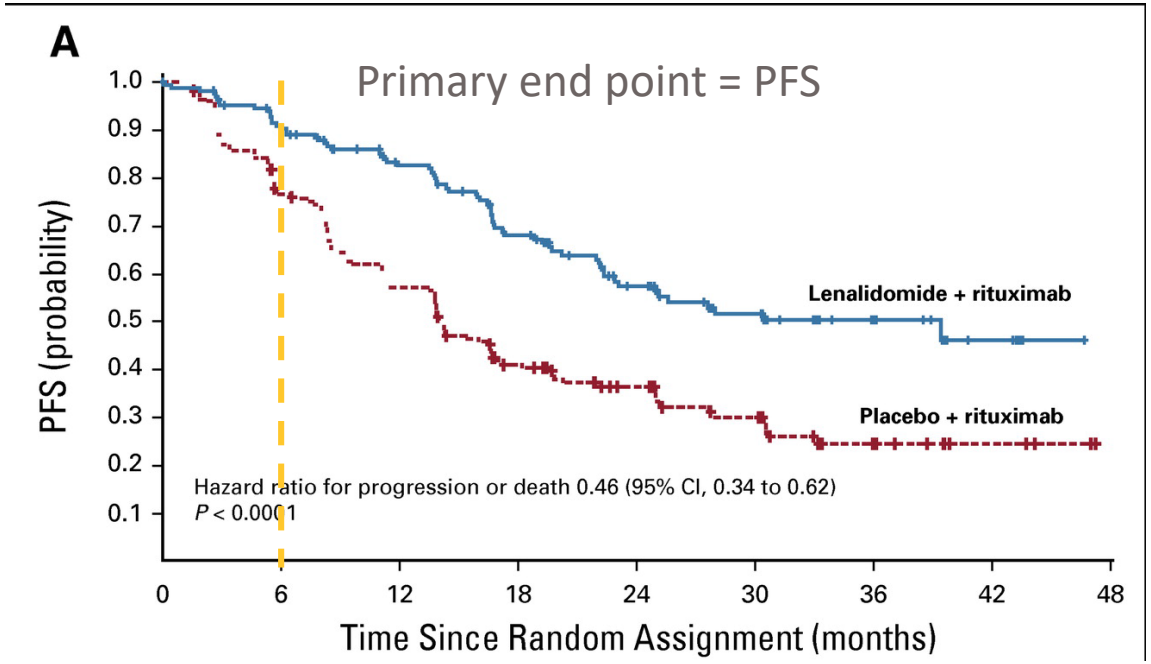
- FL grade 1 – 3A or MZL, previously treated, and in need of treatment for relapse. Prior treatment necessarily included rituximab, though cannot be considered rituximab-refractory

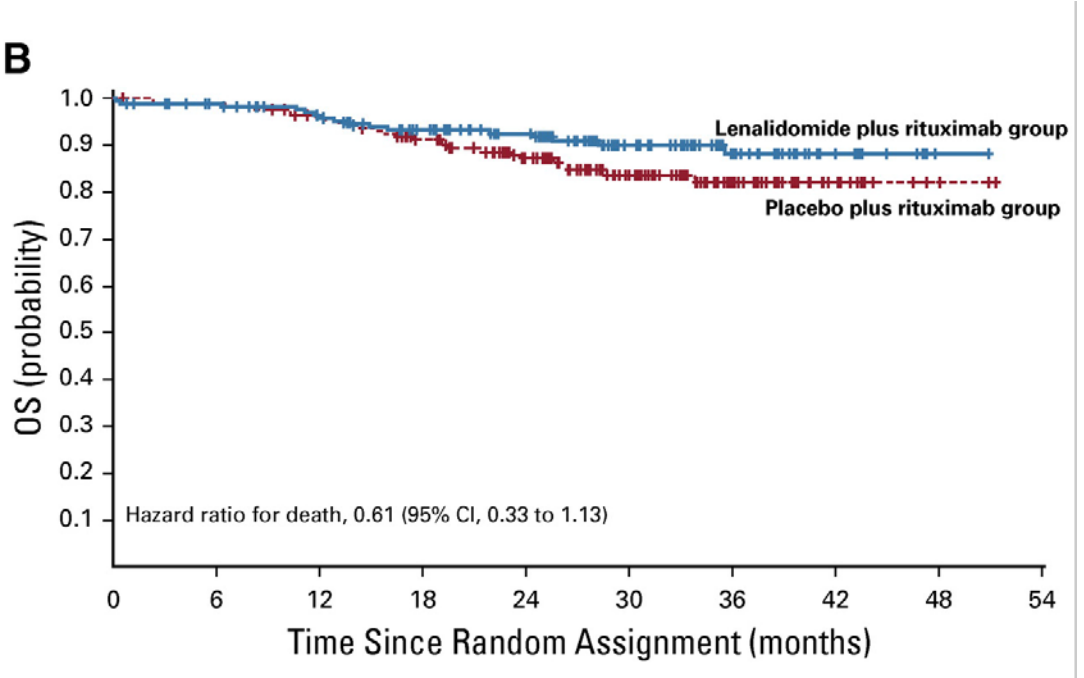


- ORR 78 vs 53% (P < 0.001)
- CR 34 vs 18% (P = .001)

Leonard et al. J Clin Oncol. 2019 May 10;37(14):1188-1199.

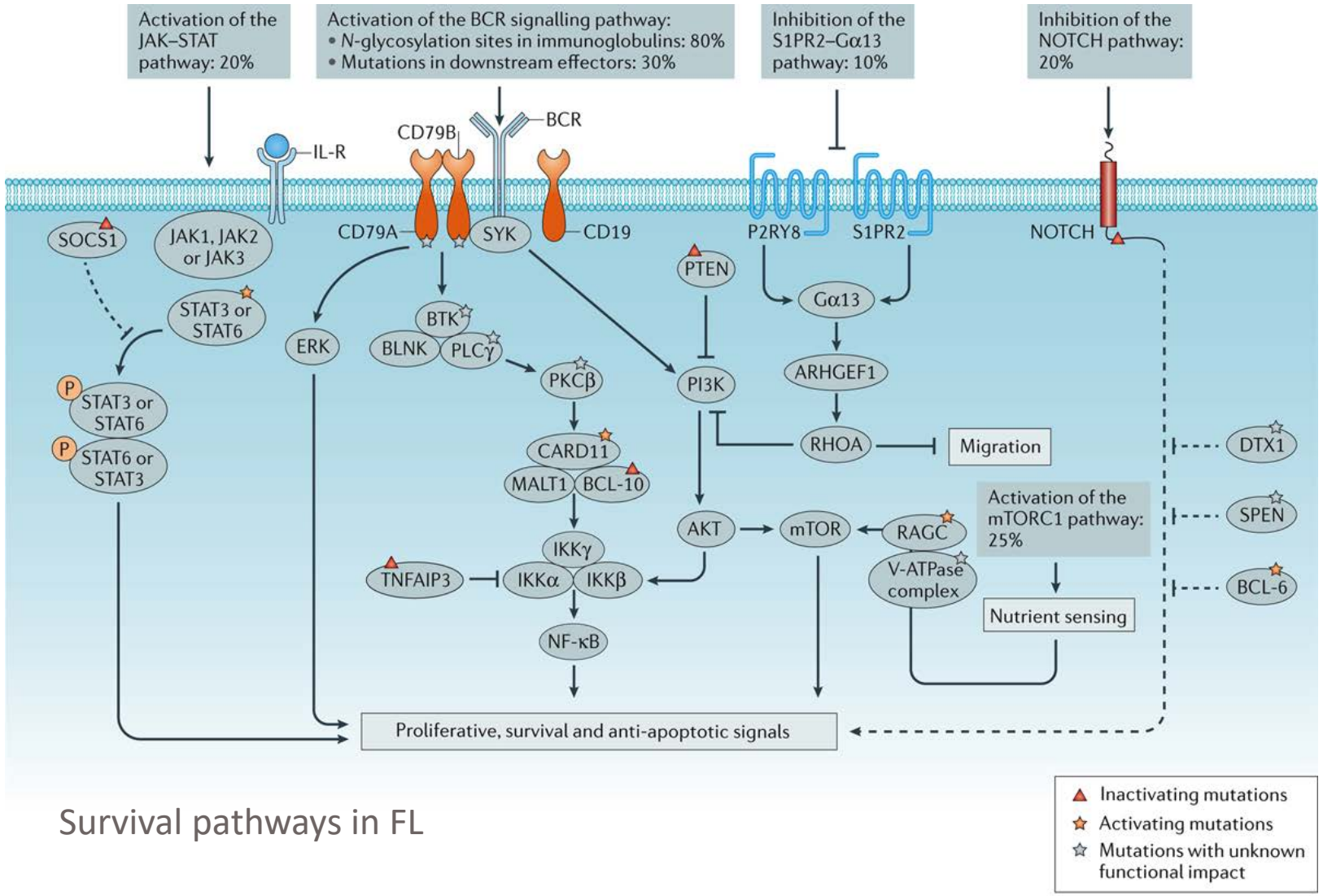
AUGMENT: Results





Leonard et al. J Clin Oncol. 2019 May 10;37(14):1188-1199.

Molecular Targets in Follicular Lymphoma



Survival pathways in FL

→ Also, mutations in epigenetic modifiers occur in nearly 90% of cases of FL

Huet et al. Nat Rev Cancer. 2018 Apr;18(4):224-239

Other Oral Oncolytics for R/R iB-NHL

	FL	MZL
BTK inhibitors		Ibrutinib
PI3K inhibitors	Idelalisib Copanlisib Duvelisib	

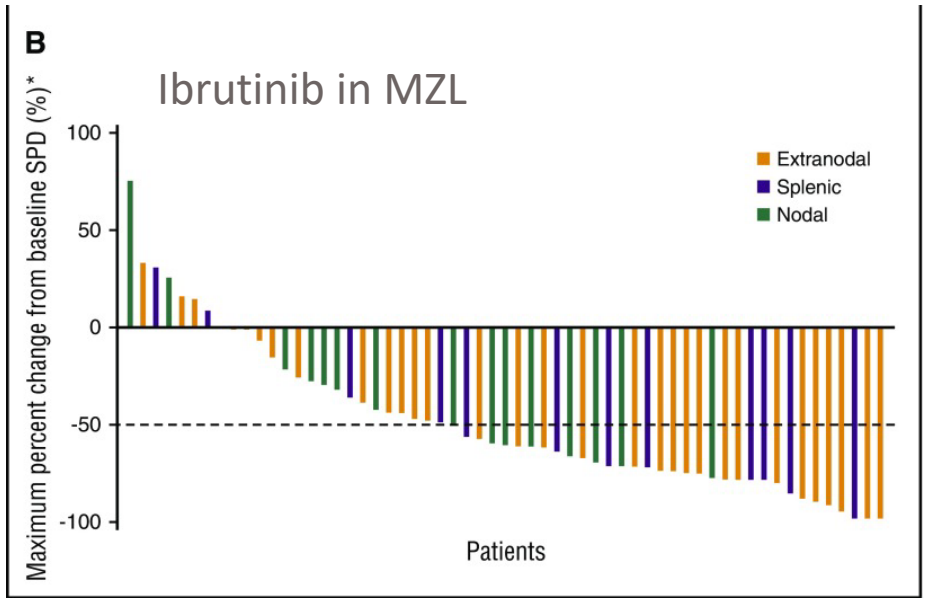
	Setting	ORR	CR	mPFS
Idelalisib (δ)	Double refractory (R, alkylator) FL	56%	6%	11.0 mo
Duvelisib (γ,δ)	Double refractory (R, alkylator) FL	47%	2%	9.5 mo
Copanlisib* (α,δ)	≥2 prior lines of therapy for FL	59%	12%	11.0 mo
Ibrutinib	≥1 prior anti-CD20 therapy in MZL	48%	3%	14.2 mo

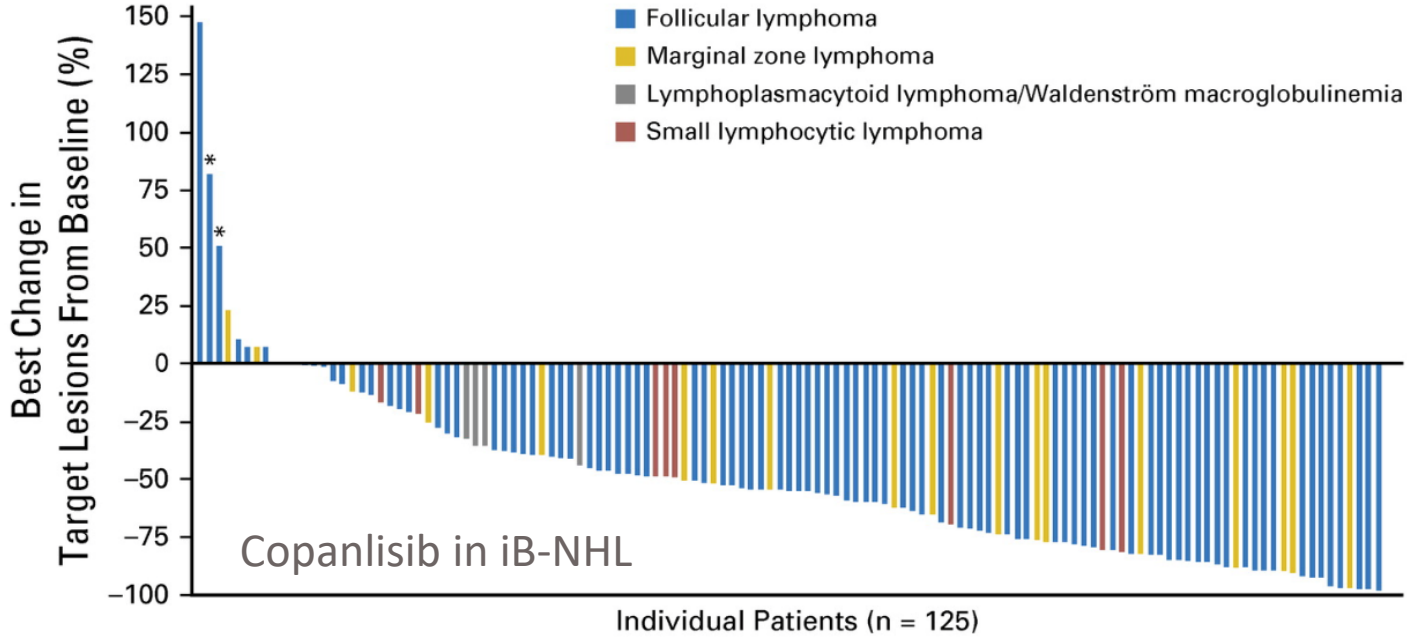
*IV on days 1, 8, 15 q28

Gopal et al. N Eng J Med. 2014 Mar 13;370(11):1008-18
Dreyling et al. J Clin Oncol. 2017 Dec 10;35(35):3898-3905
Flinn et al. J Clin Oncol. 2019 Apr 10;37(11):912-922
Noy et al. Blood. 2017 Apr 20;129(16):2224-2232

Single Arm Phase 2 Studies of Oral Oncolytics for R/R iBNHL

- Primary endpoint = ORR

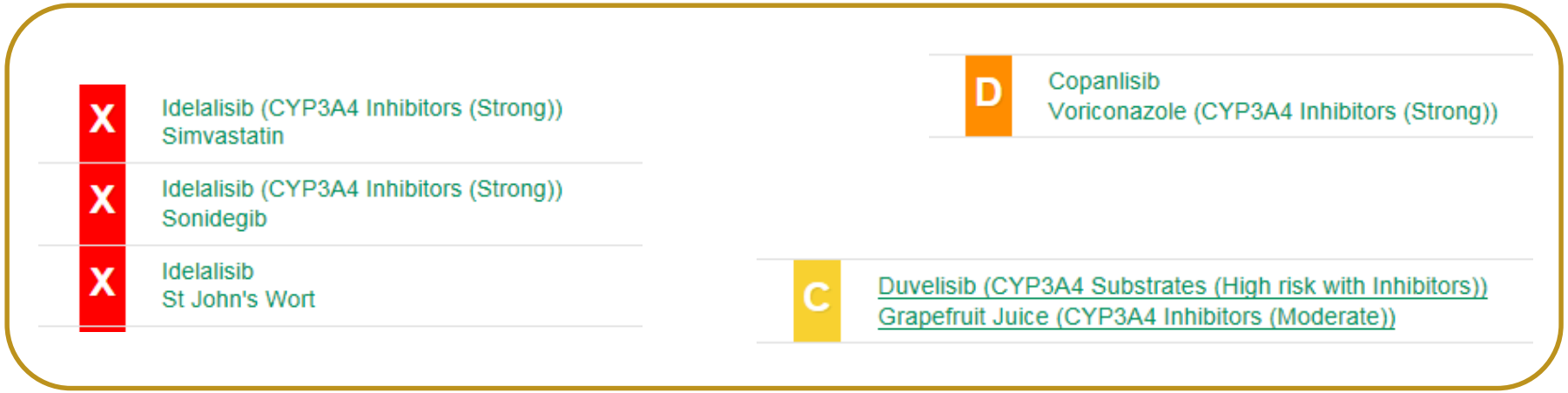




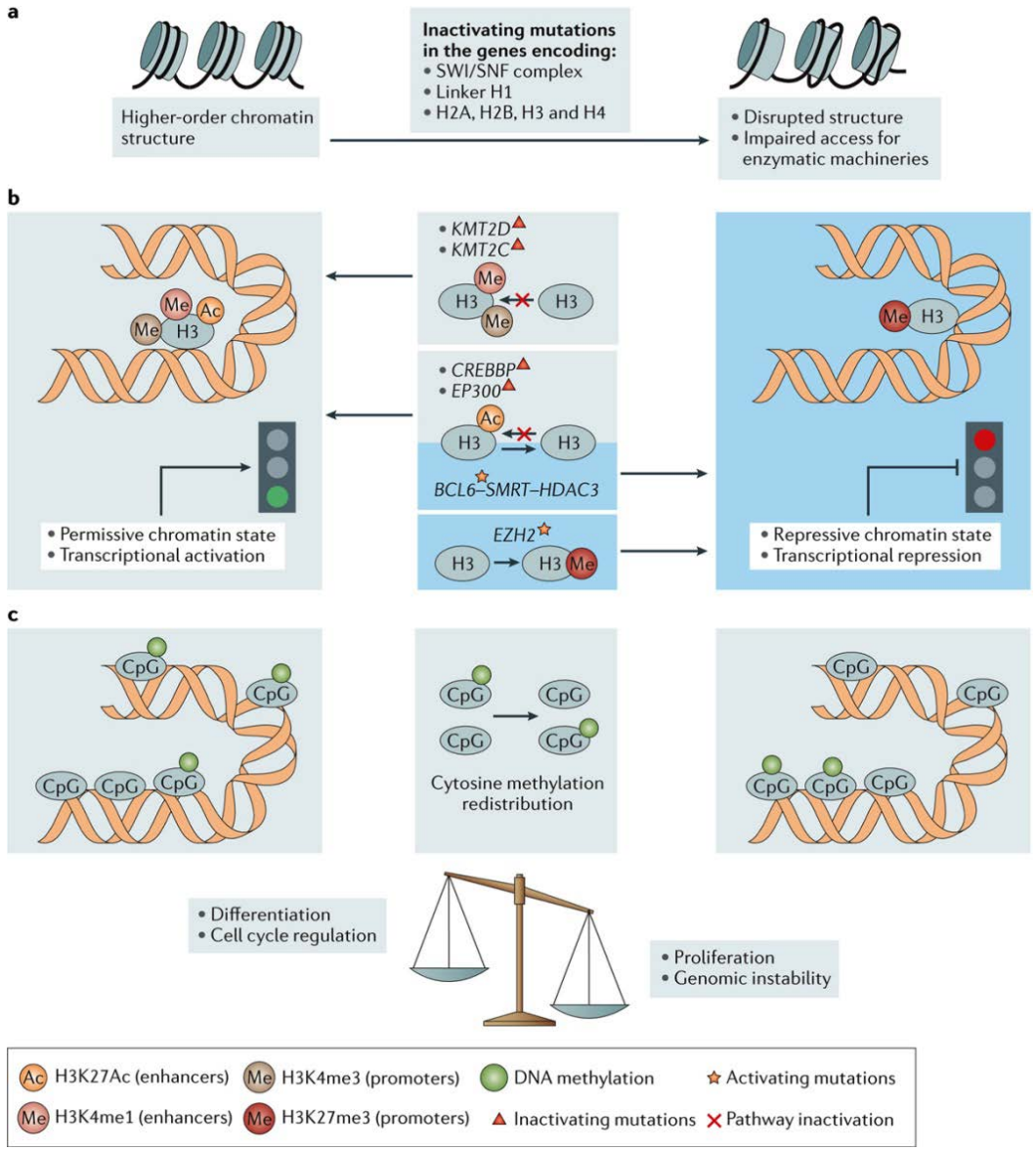
Dreyling et al. J Clin Oncol. 2017 Dec 10;35(35):3898-3905
Noy et al. Blood. 2017 Apr 20;129(16):2224-2232

Toxicities of Targeted Oral Oncolytics

	Key Toxicities	Recommended prophylaxis
Idelalisib Duvelisib	Opportunistic infections, transaminitis, diarrhea/colitis, pneumonitis, intestinal perforation, dermatologic events	PJP; CMV monitoring
Copanlisib	OI's, Hyperglycemia (short-lived), hypertension	PJP
Ibrutinib	Atrial fibrillation, hemorrhage	



Zeste Homolog 2 (EZH2)

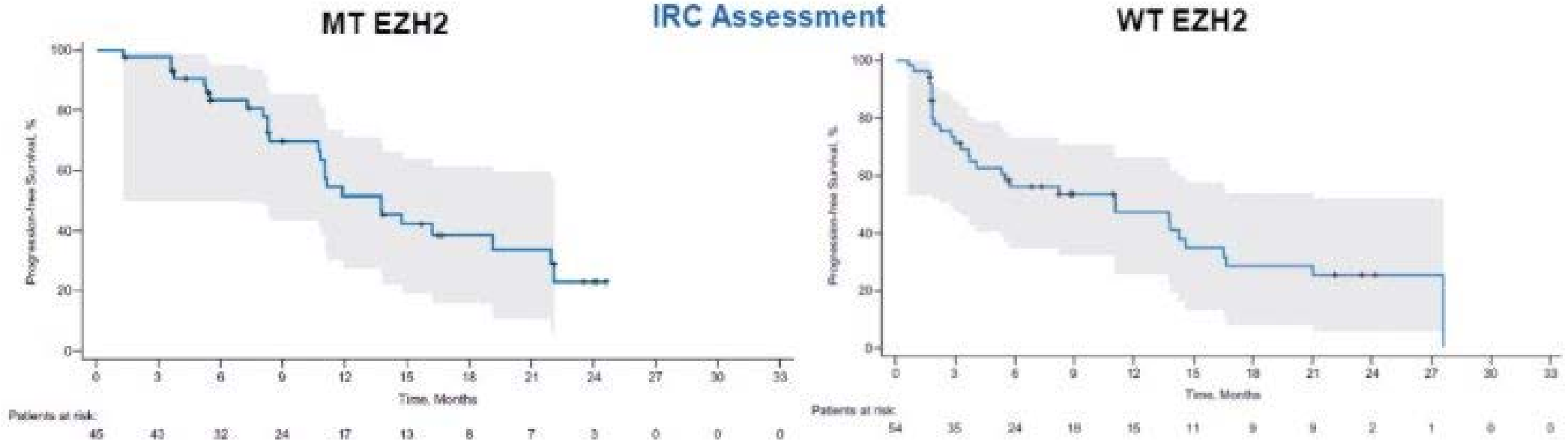


- Genetic lesions that disrupt histone-modifying enzymes occur in nearly all cases of FL
- Gain of function mutation to *EZH2* found in ~20% of FL
- Reduction in histone methyltransferase EZH2 activity → B cell differentiation

Huet et al. Nat Rev Cancer. 2018 Apr;18(4):224-239
Morschhauser et al. ASH Congress 2019.

Zeste Homolog 2 (EZH2) Inhibitor: Tazemetostat

- **Median PFS of 13.8 and 11.1 months was Observed in MT and WT EZH2 Cohorts**



- ORR in N = 45 *EZH2* mutant FL = 69% (13% CR); mDOR = 11 mo
- ORR in N = 54 *EZH2* WT FL = 34% (4% CR); mDOR = 13 mo
- AEs = fatigue, URI, MSK pain, nausea, abdominal pain

- Accelerated approval in June 2020: *EZH2* mutant FL: 2 prior therapies; *EZH2* WT FL: no satisfactory alternatives
- Companion diagnostic for *EZH2* mutation also approved

Morschhauser et al. ASH Congress 2019.

Topics of Special Interest in iB-NHL: 2020

- Early relapse
  - Prediction

	High risk FLIPI*, %	High risk m7-FLIPI, %	High risk POD24-PI, %
Sensitivity	70-78	43-61	61-78
Specificity	56-58	79-86	67-73

*High-risk pre-treatment FLIPI found in 75% of patients with POD24 and 40% of patients without POD24

  - Bottom line: ongoing research into clinical, molecular, radiographic factors
  - Management
    - Biopsy if possible: HT identified in 20% - 75% of cases of early relapse

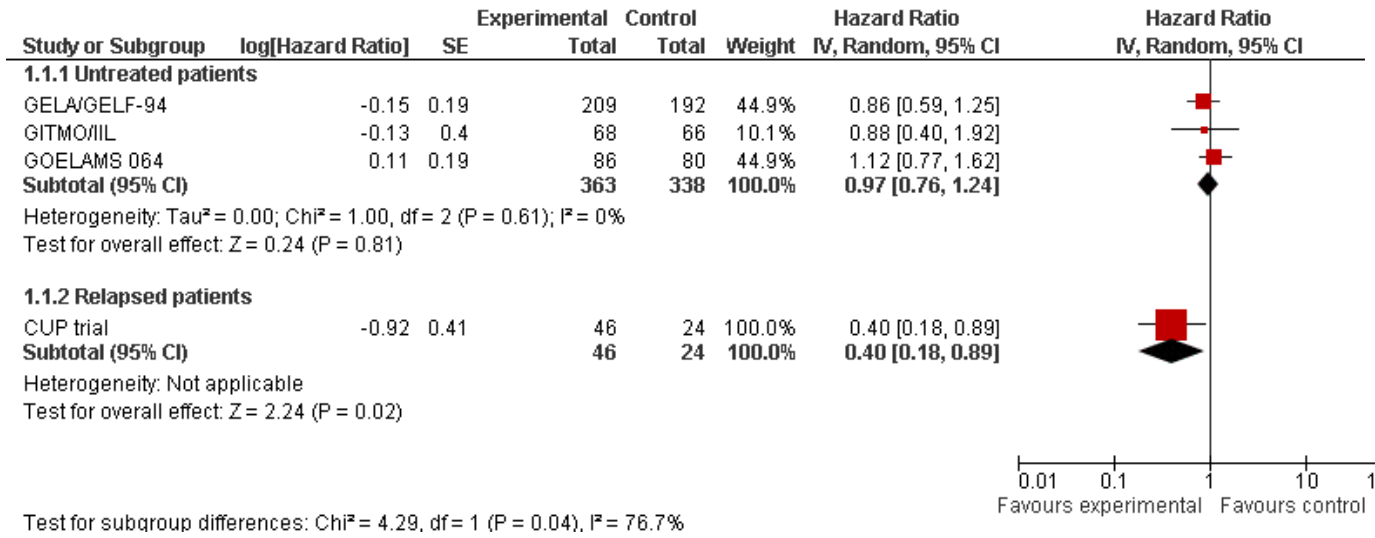
- Cellular therapy
  - Autologous SCT
  - CAR-T
  - Bi-specifics

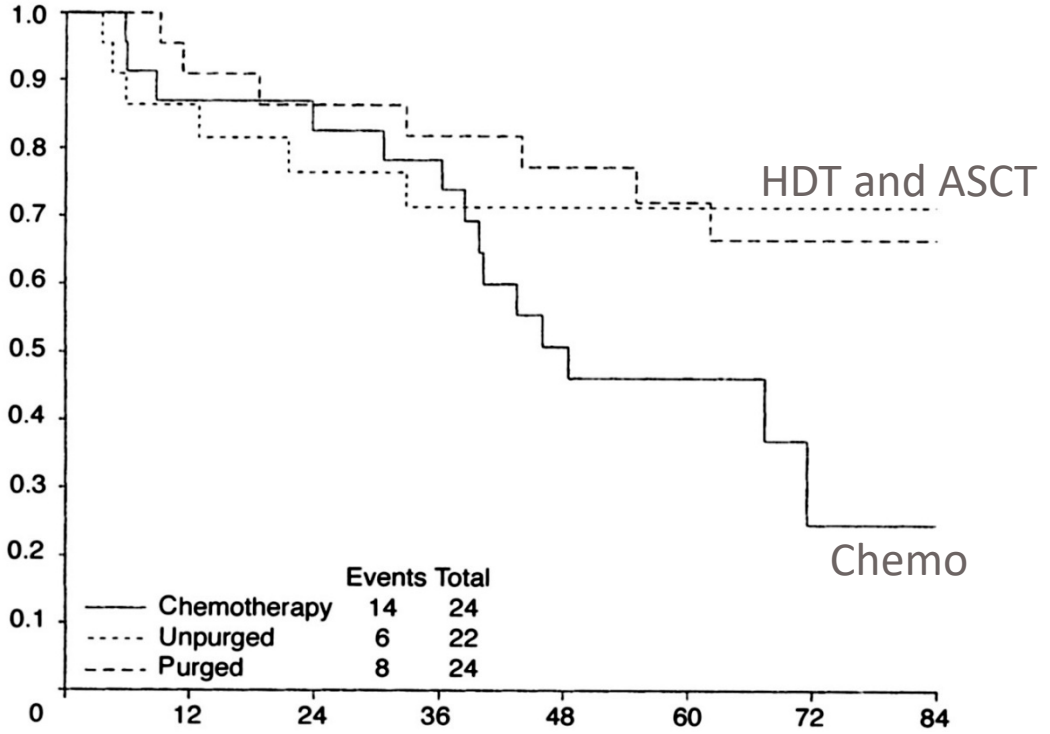
No current FDA approval

Casulo et al. Blood . 2019 Apr 4;133(14):1540-1547

High Dose Therapy and Autologous SCT in FL

- CUP trial (2003, pre-rituximab)
- Randomized 70 patients with at least PR to 3 cycles of R-CHOP(like) for relapsed FL to HDT and autoSCT or 3 more cycles

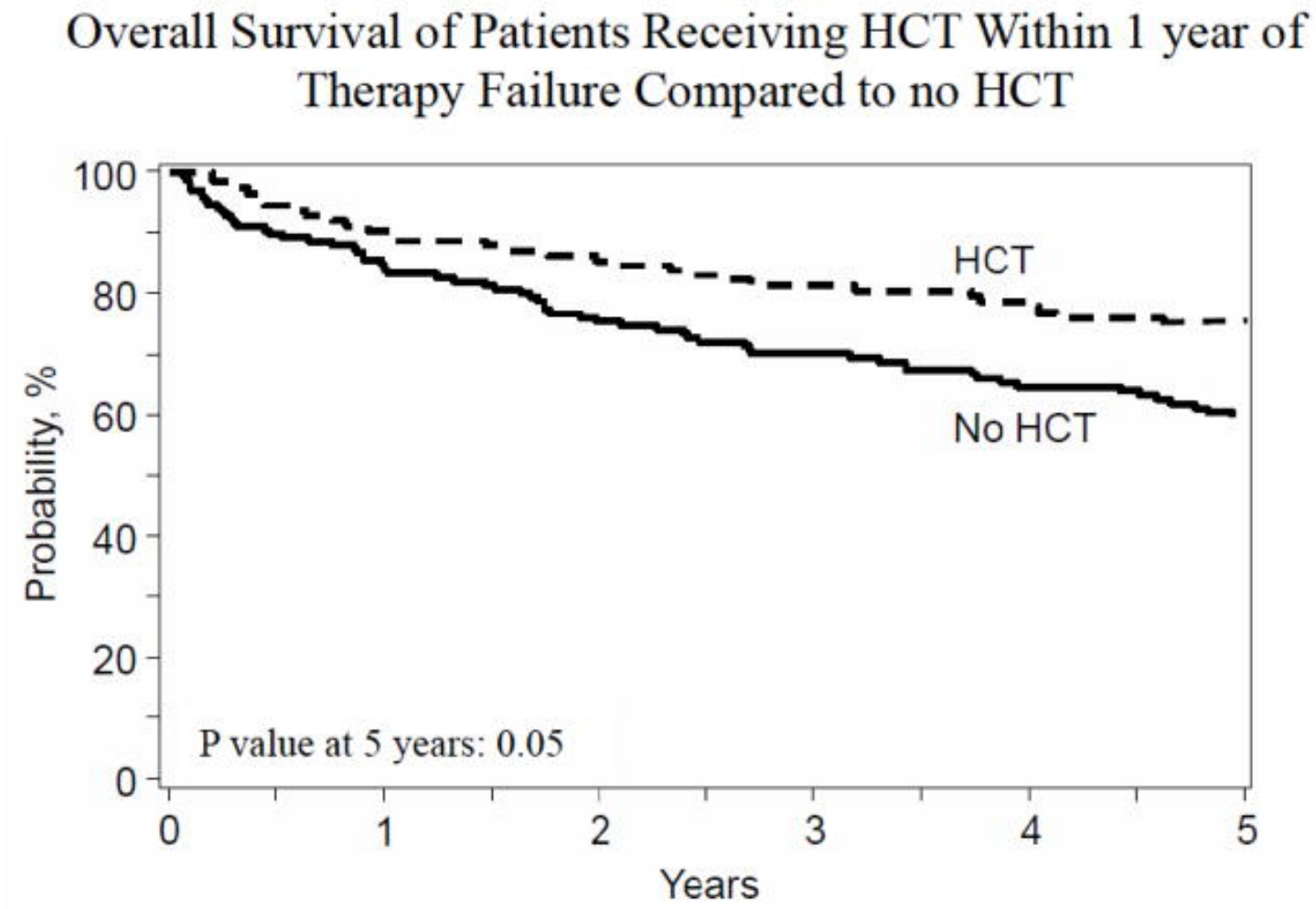




Schouten et al. JCO 21: 3918, 2003
Schaaf et al. Cochrane Database of Systematic Reviews 2012

HDT and ASCT for Early Relapse FL

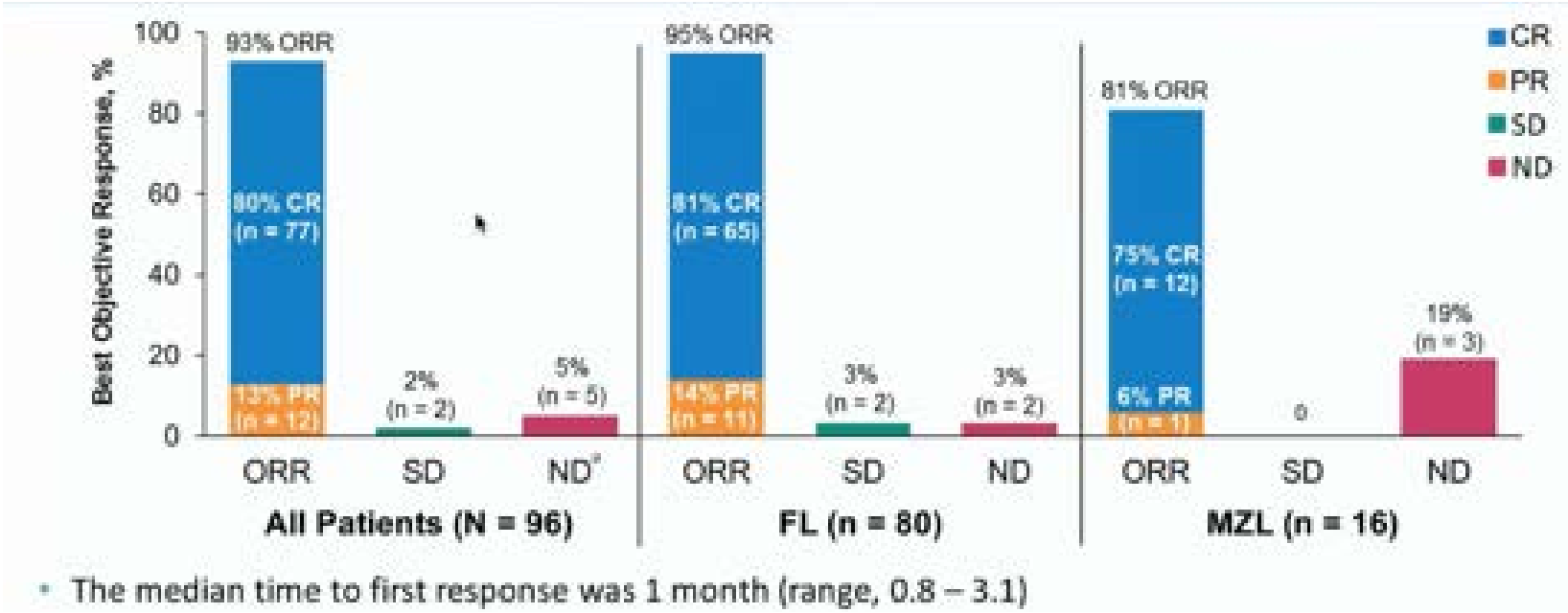
- Retrospective analysis of CIBMTR and NLCS (N = 174 + 175)
- Overall, no significant improvement in OS with ASCT
- Planned subgroup: OS benefit if early ASCT (within 1 year of ETF), 73 vs 60% at 5 years



Casulo et al., Biol Blood Marrow Transplant. 2018 Jun;24(6):1163-1171

CAR-T for iB-NHL

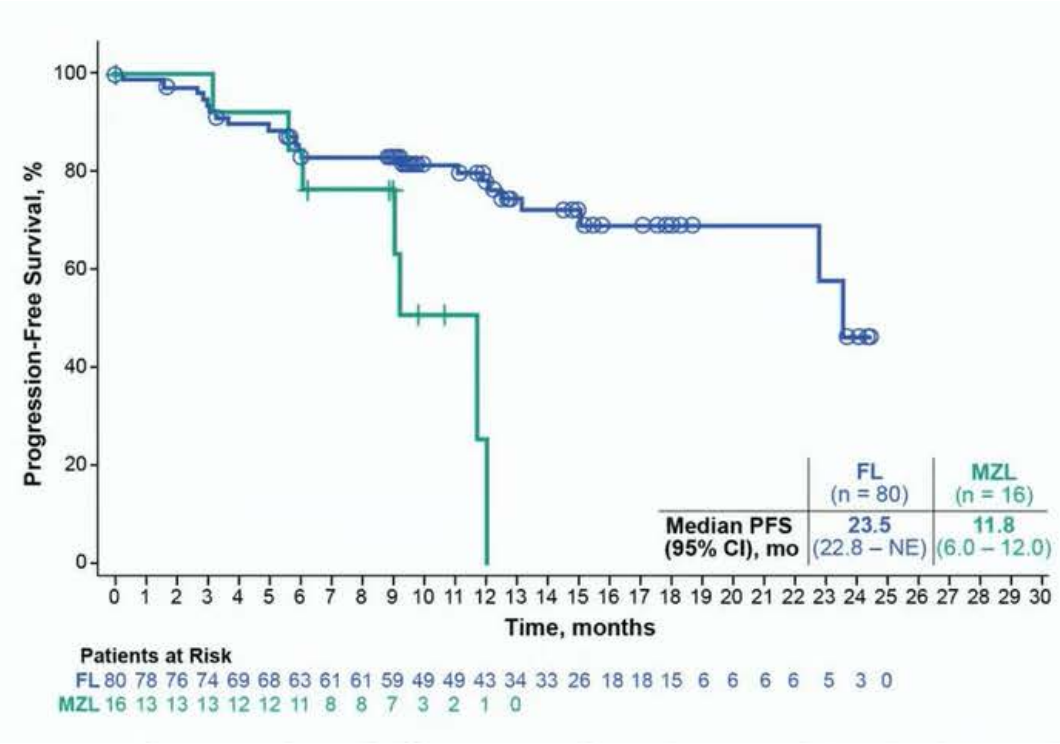
- ZUMA-5: R/R iB-NHL
  - N = 96 (80 FL, 14 MZL)
  - 66% with POD24
  - ORR 94% in 87 evaluable patients
    - ORR 95% in cases of FL with 80% CR rate

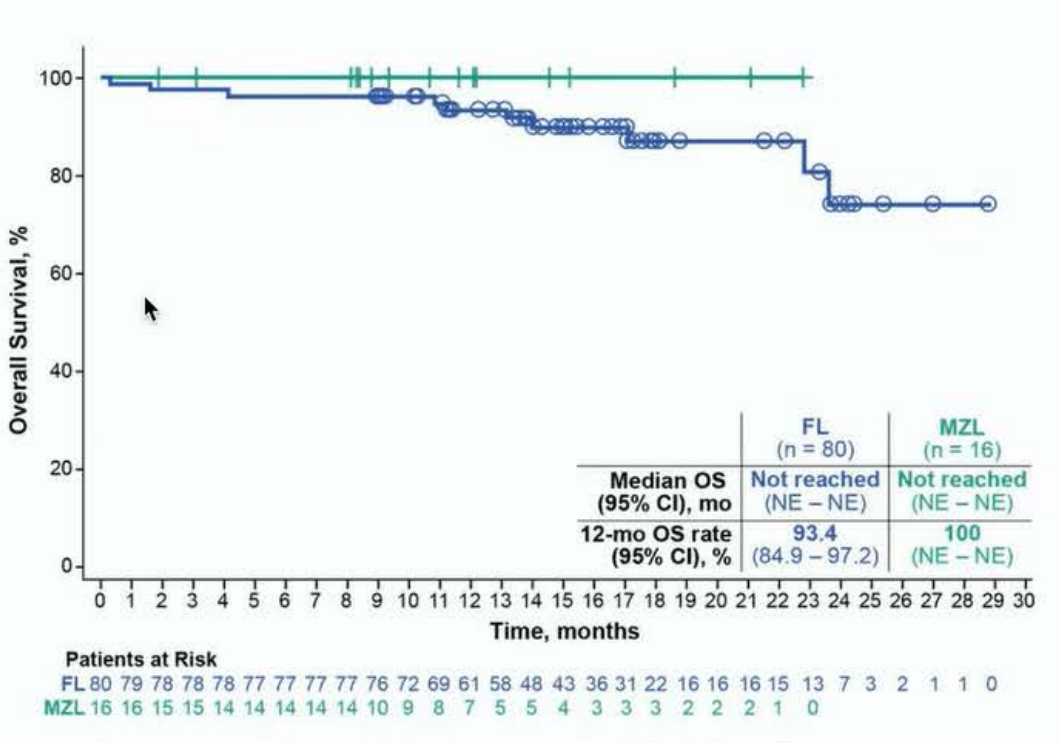


- The median time to first response was 1 month (range, 0.8 – 3.1)

Jacobson et al. ASCO Congress 2020

CAR-T for iB-NHL

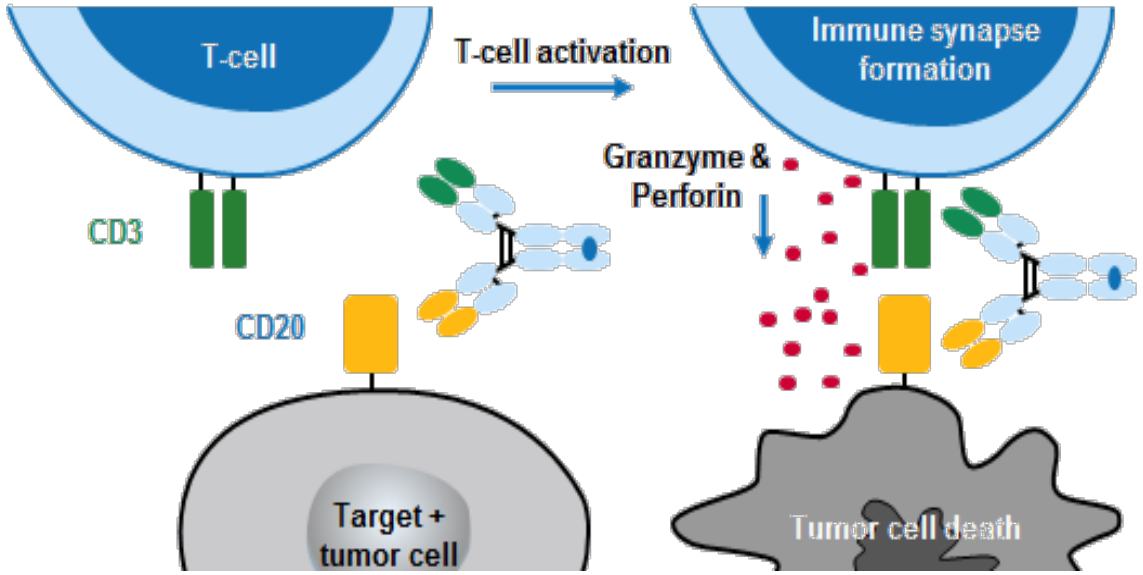




Jacobson et al. ASCO Congress 2020

Bi-Specific Antibodies

- Mosunetuzumab: redirects T cells to engage and eliminate B cells



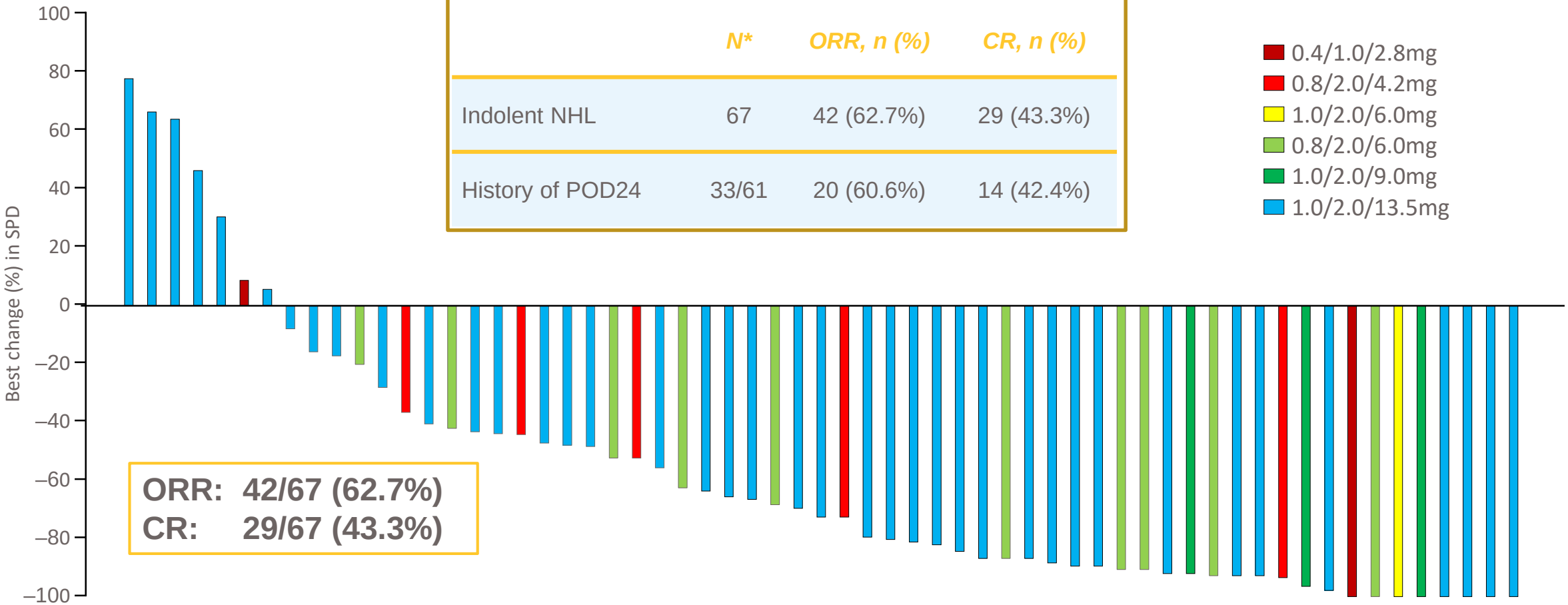
All Gr AEs in >15% pts	*N=270*
Cytokine release syndrome	78 (28.9%)
Neutropenia‡	65 (24.1%)
Fatigue	55 (20.4%)
Hypophosphatemia	52 (19.3%)
Diarrhea	45 (16.7%)
Pyrexia	44 (16.3%)
Headache	42 (15.6%)
Nausea	41 (15.2%)

	Grade 3 or Higher	Tocilizumab
CRS	1.1%	3%
NAEs	3.7%	

Schuster et al. ASH Congress 2019

Mosunetuzumab in R/R iB-NHL

	N*	ORR, n (%)	CR, n (%)
Indolent NHL	67	42 (62.7%)	29 (43.3%)
History of POD24	33/61	20 (60.6%)	14 (42.4%)



Indolent NHL: FL (Grade 1–3A), marginal zone lymphoma and small lymphocytic lymphoma

Schuster et al. ASH Congress 2019

Summary

- iB-NHL often not a life-limiting diagnosis
- Clinical variables
  - remain standard for prognostic stratification
  - inform treatment initiation and follow-up
- New options in frontline and relapsed settings allow better precision fitting of treatment to patient
- Oral targeted oncolytics associated with important limitations and toxicities
- Cellular therapies likely to have a growing role in certain iB-NHL, e.g. early relapse

Marginal Zone Lymphoma

- Extranodal MZL, nodal MZL, splenic MZL
- Immunophenotype: typically negative for CD10, CD5, and BCL2
- Advanced stage: generally apply FL principles and management

Site	Putative pathogen	Treatment	ORR
Gastric EMZL	Heliobacter pylori	PPI + triple antibiotics	~75%
Ocular adnexal MZL	Chlamydia psittaci	Doxycycline	~50%
MZL, splenic lymphoma, MALT	Hepatitis C	IFN, DAA's	~75%
Small intestinal variant EMZL	Campylobacter jejuni		
Pulmonary EMZL	Achromobacter xylosoxidans		
Cutaneous MALT	Borrelia burgdoferi (Lyme)		

Zucca et al. Clin Cancer Res 2014;20:5207-5216

Questions

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Endometrial and Cervical Cancers

11th Annual Comprehensive Hematology/Oncology Review

Kathryn Pennington, MD
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Division of Gynecologic Oncology
University of Washington Medical Center
September 2020

Disclosures

None

Endometrial Cancer

Uterine Cancer

Histologic Types

Adenocarcinoma:

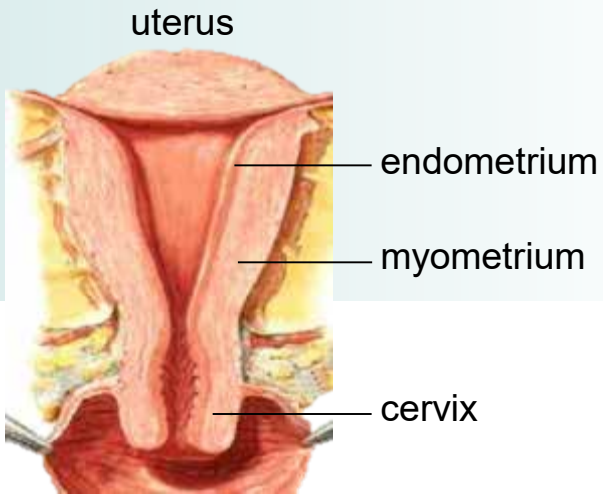
- Endometrioid
- Mucinous
- Clear cell
- Serous
- Carcinosarcoma

Sarcoma:

- Leiomyosarcoma
- Endometrial stromal sarcoma
- Adenosarcoma

Epidemiology

- 4th most commonly diagnosed cancer in US females
- **65,620 new cases** estimated in 2020 **(12,590 deaths)**



Endometrial Adenocarcinoma

Clinicopathologic Subtypes

Type I

Endometrioid Histology grade1-2 *(estrogen-related)*

- Risk factors include those leading to ↑ exposure to unopposed estrogen
- Often associated with PTEN mutations
- May demonstrate microsatellite instability

Type II

(non-estrogen related)

- Grade 3 endometrioid
- Non-endometrioid histologies:
  - Serous
  - Clear cell
- Associated with p53 mutations, chromosomal instability

Endometrial Cancer
Factors Increasing Risk

- Unopposed estrogen stimulation

	Risk
• **Obesity**	**3-10X**
• **Estrogen-only HRT**	**4-8X**
• **PCOS**	**2-6X**
• **Tamoxifen**	**2-3X**
• **Granulosa cell tumors**	**5X**
• **Nulliparity**	**2X**

- Increasing Age
- Diabetes
- Genetics (Lynch syndrome)

Endometrial Cancer

Tamoxifen

Tamoxifen = **SERM** (behaves as estrogen agonist at the endometrium)

- Associated with small but significantly ↑ risk of endometrioid adenocarcinoma and carcinosarcoma
- Causes cystic hypertrophy of endometrium
- **ALL** patients on tamoxifen should have annual pelvic exam and be asked about postmenopausal or irregular vaginal bleeding or discharge
- No benefit to use of U/S and endometrial biopsy for endometrial cancer screening

Curtis RE et al. *J Nat'l Cancer Inst* 2004.
ACOG Committee Opinion 336. ACOG June 2006.

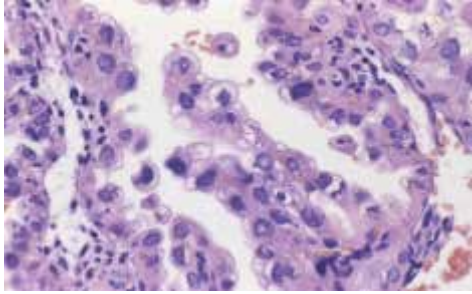
Lynch syndrome

- ~3–5% of endometrial cancers
- Due to autosomal dominant mutation in mismatch repair genes – *MLH1, MSH2, MSH6, PMS2*
- 40–60% lifetime risk of endometrial cancer
  - Mean age at presentation: 40s
  - Ovarian cancer ~12% lifetime risk*
  - Screening with endometrial biopsy, possibly with U/S and CA 125, can be considered
  - Consider prophylactic hysterectomy and removal of tubes/ovaries

Lindor NM et al. *JAMA* 2006.

Endometrial Cancer

Poor Prognosis Histologies



- **Clear cell and serous carcinomas**
  - Nearly 70% will have extrauterine disease at presentation
  - In recent SEER review, serous and clear cell carcinomas accounted for 10% and 3% of all endometrial carcinomas, but responsible for 39% and 8% of deaths, respectively

Hamilton CA et al. *Br J Cancer* 2006.

- **Carcinosarcoma**
  - Considered a high-grade carcinoma, with sarcomatous dedifferentiation
  - <5% of uterine cancers but poor prognosis
- **Squamous**
  - Rare but aggressive

Endometrial Cancer

Survival by Stage (FIGO 2009)

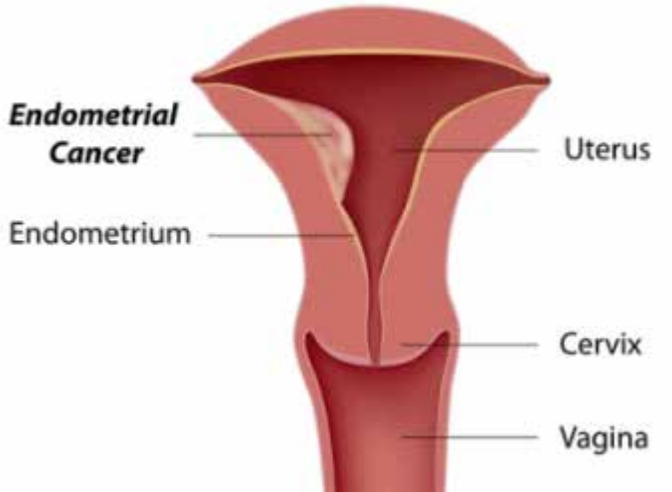
Stage	Survival	
IA	90%	<50% myometrial invasion
IB	81%	>50% myometrial invasion
II	81%	Cervical stroma involvement
IIIA	69%	Uterine serosa or adnexal involvement
IIIB	53%	Vaginal and/or parametrial involvement
IIIC1-2	51-58%	Pelvic, paraaortic lymph node involvement
IVA	22%	Bowel or bladder mucosa
IVB	21%	Distant metastasis (includes intra-abdominal disease, inguinal nodes)

Endometrial Cancer
Treatment

- Surgical staging
  - Total hysterectomy/removal of tubes and ovaries ± pelvic/periaortic lymphadenectomy or sentinel lymph node biopsy
  - Minimally invasive approach as effective as open surgery

Walker JL et al. *J Clin Oncol* 2012.

- Adjuvant radiation
  - If risk factors for recurrence present
- Chemotherapy
  - Advanced stages, high-risk histology



Endometrial Cancer
Fertility-Sparing

CANDIDATES:

- Grade 1 endometrioid histology on D&C
- Disease confined to endometrium on MRI (no myometrial invasion)
- No evidence of metastatic disease on imaging
- No contraindications to medical therapy or pregnancy

Endometrial Cancer
Fertility-Sparing

Management:

- Continuous progestin-based therapy
  - Megestrol, Medroxyprogesterone, or Levonorgestrel IUD
- Endometrial sampling every 3-6 months
  - If complete response: encourage conception. Hysterectomy after childbearing complete
  - 50-70% complete response. 20-35% relapse after initial CR

Gunderson CC et al. *Gynecol Oncol* 2012
Baker J et al. *Gynecol Oncol* 2012

Endometrial Cancer
Lymph node dissection

- Two large RCTs failed to show survival benefit
- Can identify those at high risk of recurrence and guide adjuvant therapy
- Who benefits most, and extent of LND highly debated
  - "Mayo criteria": Risk of LN involvement <2% if grade 1-2, <50% myometrial invasion, and tumor <2 cm
  - Sentinel lymph node dissection another standard of care

Panici PB et al. JNCI 2008
ASTEC study group. Lancet 2009
Mariani Aet al. Gyn Onc 2008.
Milam MR et al. *Obstet Gynecol* 2012.
Rossi EC et al Lancet Oncol 2017.

Endometrial Cancer
Postoperative Treatment

- Low Risk: Grade 1-2, confined to endometrium
  - Observation
- Intermediate Risk: Stage IA (with myoinvasion), stage IB, stage II
  - Low-intermediate risk: observation
  - High-intermediate risk: brachytherapy or RT
- High Risk: Stage III-IV; high-risk histology (serous, clear cell, carcinosarcoma) any stage
  - Chemotherapy ± radiation

Endometrial Cancer
Case Studies

- 55 yo s/p laparoscopic hyst, BSO. No lymphadenectomy done
  - Grade 2
  - 1 cm tumor, no myometrial invasion
  - Peritoneal wash positive
- Management?

A. Observation, she is low-risk

B. Pelvic RT, because she did not receive lymph node dissection

C. Chemotherapy, because the peritoneal wash was positive

Endometrial Cancer
Case Studies

- 65 yo s/p laparoscopic hyst, BSO, sentinel node biopsy.
  - Grade 1
  - 70% myometrial invasion
  - Lymphovascular space invasion (LVSI) present
  - Sentinel nodes negative
- Management?

A. Observation; she is low-risk

B. Vaginal brachytherapy; she is high-intermediate risk

C. Pelvic RT; she is high-intermediate risk

Postoperative Treatment
High-intermediate Risk

- GOG99
  - Risk factors: Outer third myometrial invasion, grade 2-3, LVSI
  - HIR group: age≥70 + 1 risk factor, age 50-69 + 2 risk factors, age<50 + 3 risk factors
- PORTEC 1*
  - Risk factors: Age>60, ≥50% myometrial invasion, grade 3
  - HIR group: 2 risk factors

➢ Pelvic RT in HIR: reduced risk of locoregional recurrence (13-18%->5%), no overall survival benefit

Postoperative Treatment
High-intermediate Risk

- PORTEC 2: Non-inferiority trial of vaginal brachytherapy vs. pelvic RT in stage I with HIR, stage IIA*
  - Vaginal recurrence rate the same (1.6-1.8%), 5-yr locoregional relapse rate 5% vs 2% (not significant), less toxicity with brachytherapy

Nout RA et al. PORTEC-2 *Lancet* 2010.

- Conclusion: Vaginal brachytherapy is as effective as pelvic RT for preventing locoregional recurrence for:
  - Grade 1-2 ≥50%
  - Grade 3 <50%

Endometrial Cancer
Case Studies

- 65 yo s/p laparoscopic hyst, BSO, sentinel node biopsy.
  - Grade 1
  - 70% myometrial invasion
  - Lymphovascular space invasion (LVSI) present
  - Sentinel nodes negative
- Management?

A. Observation; she is low-risk

B. Vaginal brachytherapy; she is high-intermediate risk

C. Pelvic RT; she is high-intermediate risk

Endometrial Cancer

Case Studies

WARNING: CONTROVERSIAL CASE!

- 68 yo s/p laparoscopic hyst, BSO, sentinel node biopsy.
  - Grade 3, 85% myometrial invasion
  - Lymphovascular space invasion (LVSI) present
  - Sentinel nodes negative
- Management?

A. Vaginal brachytherapy

B. Pelvic RT

C. Chemotherapy + vaginal brachytherapy

D. B or C are reasonable

E. Chemotherapy + Pelvic RT

Postoperative Treatment

High-intermediate Risk – Chemotherapy?

- GOG 249: Pelvic RT vs. vaginal brachytherapy + carbo/taxol x3 in stage I with HIR*, stage II, stage I-II clear cell/serous
  - No difference in RFS or OS, no diff in subgroups

Randall ME et al. JCO 2019.

- PORTEC 3: Pelvic RT vs. cisRT + carbo/taxol x4 in stage I gr3 with deep myometrial invasion and/or LVSI, Stage II or III, serous or clear cell
  - Subgroup analysis: No difference in FFS or OS for stages I-II

deBoer SM et al. *Lancet Oncol* 2018.

Endometrial Cancer

Case Studies

WARNING: CONTROVERSIAL CASE!

- 68 yo s/p laparoscopic hyst, BSO, sentinel node biopsy.
  - Grade 3, 85% myometrial invasion
  - Lymphovascular space invasion (LVSI) present
  - Sentinel nodes negative
- Management?

A. Vaginal brachytherapy

B. Pelvic RT

C. Chemotherapy + vaginal brachytherapy

D. B or C are reasonable

(E. Chemotherapy + Pelvic RT)

NCCN Guidelines

Surgically Staged – Stage I

FIGO Stage	Histologic Grade	Adjuvant Treatment
IA	G1, G2	Observation preferred or Vaginal brachytherapy if any risk factors[o,p]
	G3	Vaginal brachytherapy preferred or Consider observation if no myoinvasion and no lymphovascular space invasion[o]
IB[l]	G1, G2	Vaginal brachytherapy preferred or Consider observation if no risk factors[o]
	G3	RT (vaginal brachytherapy and/or EBRT) ± systemic therapy[q]

[q] risk factors that would lead to EBRT ± systemic therapy are: age, LVSI, and depth of myoinvasion. Risk factors are continuous variables. Risk of recurrence is higher with older age (especially >60 yrs), extensive LVSI, and deeper myoinvasion (>50%). Also, when there are more risk factors present, the risk of recurrence is higher.

Endometrial Cancer
Case Studies

- 63 yo s/p laparoscopic hyst, BSO, sentinel node biopsy.
  - Grade 2
  - 30% myometrial invasion
  - Left pelvic sentinel node positive
- Management?

  A. Pelvic RT

  B. Chemotherapy ± vaginal brachytherapy

  C. Chemotherapy + pelvic RT, because adding pelvic RT improves survival

Postoperative Treatment
Advanced Stage Disease

- Historical gold standard? Radiation
- **GOG 122**
  PFS and OS advantage with doxorubicin + cisplatin vs whole abdominal radiation
- **GOG 177** Randall ME et al. *J Clin Oncol* 2006.

  Addition of paclitaxel to AP improved survival
- **GOG 209** Fleming GF et al. *J Clin Oncol* 2004.

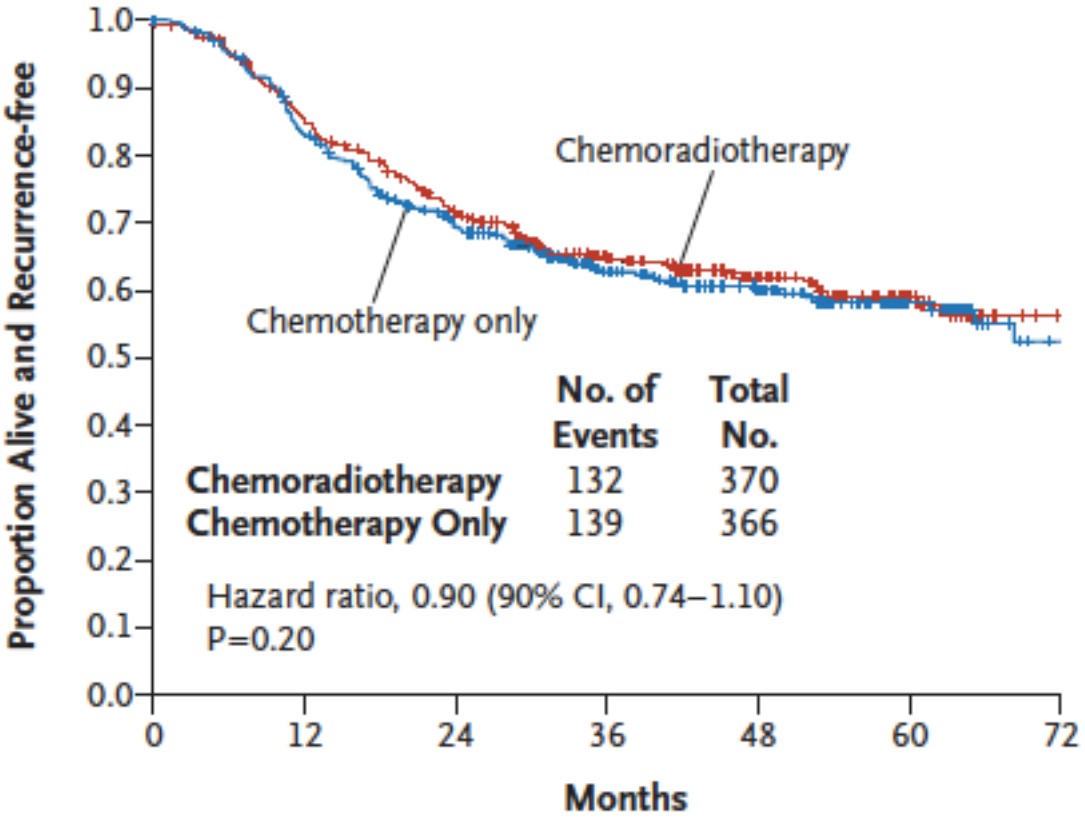
  Non-inferiority of carboplatin/paclitaxel to TAP
- **RTOG 9708** Miller D et al. *Gynecol Oncol* 2012.
  RT followed by chemotherapy associated with excellent survival rates in high-risk patients

  Greven K et al. Gynecol Oncol 2006.
- **New standard of care: chemo ± radiation**

Endometrial Cancer
Advanced Stage Disease

- **GOG 258:** Stage III, IV <2cm residual
  - Chemotherapy (Carbo/taxol x6)

  vs. ChemoRT (cisRT, then carbo/taxol x4)



Addition of RT to chemotherapy did not improve RFS

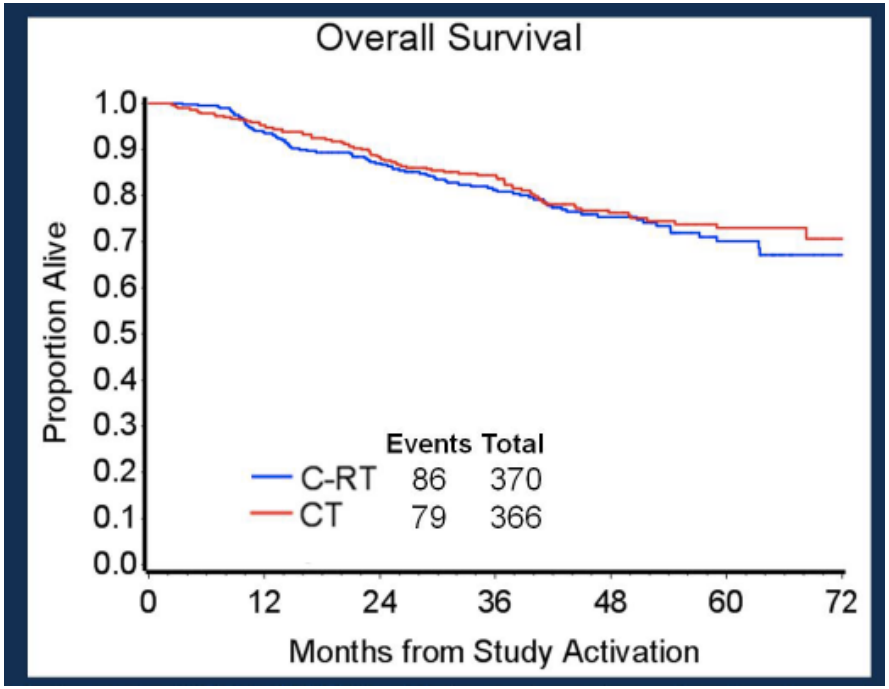
<u>5-yr RFS:</u>
Chemo - 58%
ChemoRT - 59%

Matei D et al. NEJM 2019.

Endometrial Cancer
Advanced Stage Disease

- **GOG 258:** Stage III, IV <2cm residual
  - Chemotherapy (Carbo/taxol x6)

  vs. ChemoRT (cisRT, then carbo/taxol x4)



<u>5-yr OS estimates:</u>
Chemo - 73%
ChemoRT - 70%

(Data not mature for final analysis)

Matei D et al. ASCO 2017.

Endometrial Cancer
Advanced Stage Disease

- **GOG 258:**

ChemoRT arm vs. chemotherapy:

- ↓ vaginal recurrence (2% vs 7%)
- ↓ pelvic and PA node recurrence (11% vs 20%)
- ↑ distant recurrence (27% vs 21%)

Matei D et al. NEJM 2019.

Endometrial Cancer
Advanced Stage Disease

- PORTEC 3: Pelvic RT vs. cisRT + carbo/taxol x4
  - Addition of chemo to RT improved 5-yr FFS 76% vs. 67%

<u>Subgroup analysis:</u>

Stage I-II – no diff in FFS

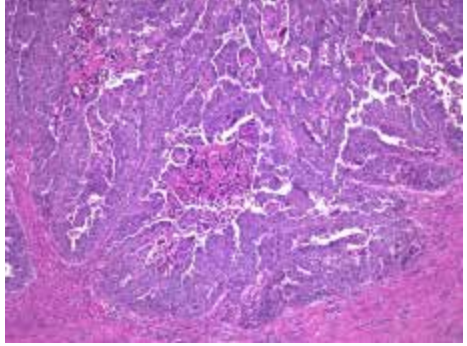
Stage III – chemoRT with improved FFS (69% vs 58%, p=0.031), no diff in OS (79% vs 70%, adjusted p=0.07)

-reinforces importance of chemo in stage IIII

deBoer SM et al. *Lancet Oncol* 2018.

Postoperative Treatment

Poor Prognosis Histology



Serous Carcinoma and Clear Cell Carcinoma

- Comprehensive surgical staging, including upper abdominal evaluation
- CA125 levels often reflect disease response to treatment
- Associated with high frequency of distant recurrence, even in early stage disease
- Retrospective data suggests benefit chemotherapy (platinum-taxane) in all stages
  - Exception: If disease limited to endometrial polyp, possibly if limited to endometrium

Boruta DM et al. *Gynecol Oncol* 2009.
Kelly MG et al. *Gynecol Oncol* 2005.

Endometrial Cancer
Case Studies

- 63 yo s/p laparoscopic hyst, BSO, sentinel node biopsy.
  - Grade 2
  - 30% myometrial invasion
  - Left pelvic sentinel node positive
- Management?

A. Pelvic RT

B. Chemotherapy ± vaginal brachytherapy

C. Chemotherapy + pelvic RT, because adding pelvic RT improves survival

Postoperative Treatment

Poor Prognosis Histology

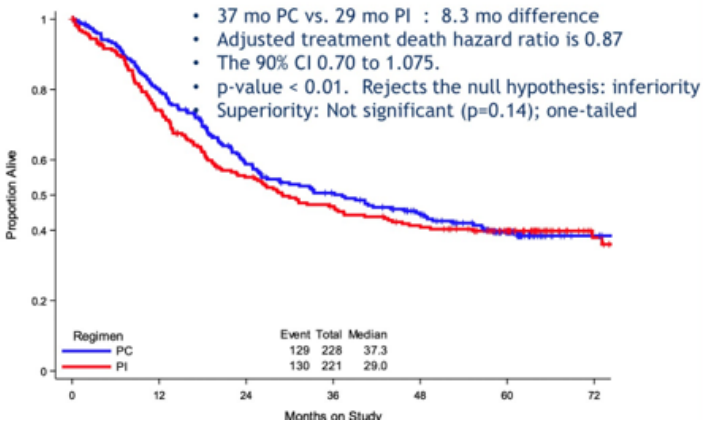
Carcinosarcoma

- Ifosfamide and paclitaxel previously associated with greatest survival benefit

Bansal N et al. *Obstet Gynecol* 2008.
Tanner EJ et al. *Gynecol Oncol* 2011.
Homesley HD et al. *J Clin Oncol* 2007.

- **GOG 261:** RCT comparing ifosfamide/paclitaxel to carboplatin and paclitaxel (OS primary endpoint)

Carbo/taxol non-inferior!



Powell et al. ASCO 2019.

Uterine Adenocarcinoma
Surveillance & Recurrence

- **Surveillance**
  - Physical exam, including pelvic, every 3-6 months for 2 years, then every 6-12 months
  - Pap test no longer recommended
  - Consider CA125, if elevated preoperatively
  - Counseling on lifestyle changes

- **Recurrence**
  - ↑ Recurrence risk with high-risk histology
  - Sites: Type 1—Local (pelvis/vagina) most common
    Type 2—Distant (outside pelvis)

Recurrent Uterine Adenocarcinoma
Treatment

- Consider radiation for local vaginal recurrence or isolated recurrence in nodal beds
- Surgical resection can be an option for *isolated* recurrences
- Hormonal therapy
  - Most effective in **low-grade** endometrioid cancers
  - Medroxyprogesterone/tamoxifen – RR 27%
  - Progestins – RR 15-20%
- Chemotherapy
  - For many, carboplatin/paclitaxel is 1st line
  - RR 50-60%

Carey MS et al. *Gynecol Oncol* 2006.

Recurrent Uterine Adenocarcinoma
Treatment

- Second-line chemotherapy (RR 10-25%): doxorubicin, taxanes (weekly), ifosfamide
- Biologics:
  - Bevacizumab
  - Pembrolizumab in MSI-high
- Two prospective studies (GOG 86P, ENDO-7) demonstrated PFS benefit of adding bevacizumab to chemotherapy
- Phase 2 study of everolimus and letrozole demonstrated clinical benefit rate of 40%
  - Notable lack of response in patients with serous tumors
- Pembrolizumab and Lenvatinib:

  Response rate 40-50%

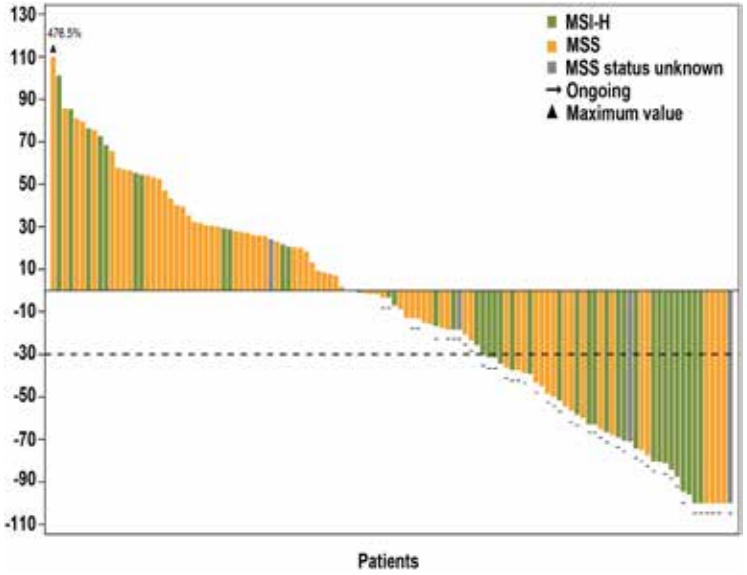
Carey MS et al. *Gynecol Oncol* 2006.
Oza AM et al. *J Clin Oncol* 2011.
Aghajanian C et al. *J Clin Oncol* 2011.
Slomovitz BM et al. *J Clin Oncol* 2015.
Makker et. Lancet Oncol 2019.

Recurrent Uterine Adenocarcinoma

Immune checkpoint inhibitors - ORR

	Avelumab[1]	Durvalumab[2]	Dostarlimab[3]	Durvalumab*[4]	Durvalumab + Tremelimumab*[4]	Pembrolizumab + lenvatinib*[5]
MMRd	26.7% (7.8-55.1)	43%	49%	NA	NA	50% (6.8-93.2)
MMRp	6.25% (0.16-30.2)	3%	20%	15%	11%	39.6% (21.9 – 51.2)

1. Konstantinopoulos et al. ASCO 2019 Abs 5502 2. Antill et al. ASCO 2019 Abs 5501 3. Oaknin et al. SGO 2019 4. Rubinstein et al. ASCO 2019 Abs 5582 5. Makker et al. Lancet Oncol. 2019 20(5): 711-718



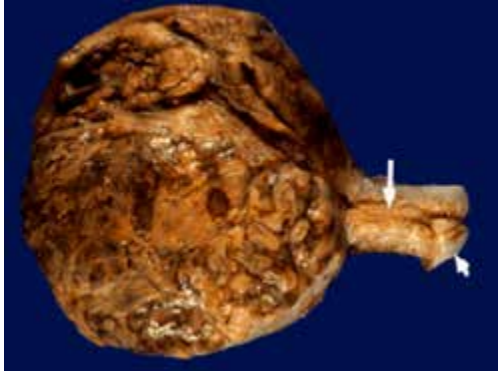
Dostarlimab: clinically meaningful responses regardless of MSI status

- >50% reduction in total tumor burden in 85% of MSI-H and 69% of MSS responders
- ~50% of responders remained on therapy >1 yr

Avelumab predictors of response:

- responses seen regardless of PD-L1 status
- tumor mutational burden and TILs did not predict response

Uterine Sarcomas
Background & Evaluation



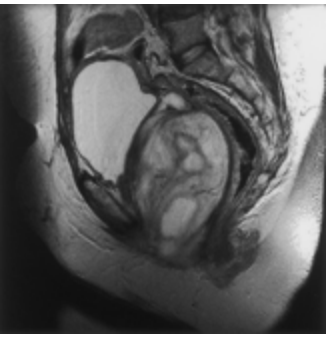
- Epidemiology
  - *Rare*—only 3% of all uterine malignancies
- Risk Factors
  - Prior pelvic radiation
  - ↑ Rate leiomyosarcomas in African Americans
- Surgery

• Hysterectomy, ± removal of ovaries, ± lymphadenectomy
• Surgery one of few interventions with impact on uterine sarcomas

FIGO Staging
Leiomyosarcoma

- Stage I: Limited to uterus
  - IA: <5 cm
  - IB: >5 cm
- Stage II: Extends beyond uterus, within pelvis
  - IIA: Involves adnexa
  - IIB: Involves other pelvic tissues
- Stage III: Infiltrates abdominal tissues
  - IIIA: One site
  - IIIB: > 1 site
  - IIIC: Regional LN mets
- Stage IV: Bowel/bladder invasion or DM
  - IVA: Involvement of bladder/bowel mucosa
  - IVB: Distant mets

Uterine Sarcomas
Treatment



- **Leiomyosarcoma**
  - Gemcitabine/docetaxel active in advanced stages of disease, superior to historical treatments

    Hensley ML et al. *Gynecol Oncol* 2008.
  - No survival benefit of adjuvant RT in early stage

    Reed et al. Eur *J Ca* 2008.
  - No survival benefit of adjuvant chemotherapy in early stage disease

    GOG20: Doxorubicin vs obs Omura et al. *J Clin Oncol* 1985

    GOG277:

GOG 277	Gemcitabine/docetaxel x 4 Doxorubicin x 4	Observation

.Hensley ML et al. *J Clin Oncol* 2018.

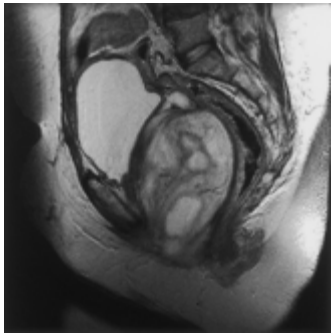
Uterine Sarcomas
Treatment

- **Leiomyosarcoma**
  - GeDDis: Gemcitabine/Docetaxel vs. Doxorubicin as first-line in advanced/metastatic – similar PFS/OS

    Seddon et al. *Lancet Oncol* 2017.

  - Doxorubicin + olaratumab: no better than doxorubicin alone

    Tap WD et al. *ASCO 2019*.



  - GOG 250 (phase III trial): no benefit to adding bevacizumab to gemcitabine/docetaxel

    Hensley ML et al. *J Clin Oncol* 2015.

  - Recurrent disease: pazopanib, trabectedin, ifosfamide, dacarbazine, eribulin. Consider hormonal blockade if ER/PR+, slow pace.

Uterine Sarcomas
Treatment

- **Low-grade Endometrial Stromal Sarcoma**
  - Hormonal therapy 1st line: Aromatase inhibitors, progestins, GnRH analogs, fulvestrant
- **High-grade Endometrial Stromal Sarcoma/ Undifferentiated Uterine Sarcoma**
  - Chemo often offered due to high risk of recurrence. Doxorubicin-based therapy first-line.
  - Consider radiation to reduce local recurrence

Cervical Cancer

Histologic Types

- Squamous cell ~70%
- Adenocarcinoma ~25%
- Adenosquamous
- Glassy cell
- Small cell

Epidemiology

- Peak age incidence 40–60 yo
- 2020:

US

13,800 new cases
4,290 deaths

Significantly ↓ incidence due to implementation of screening with Pap

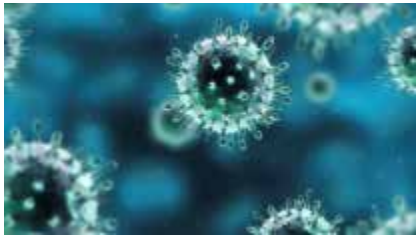
Worldwide

>85% of all cases of cervical cancer occur in low-resource countries

Global Cancer Facts & Figures, 4th ed. American Cancer Society.

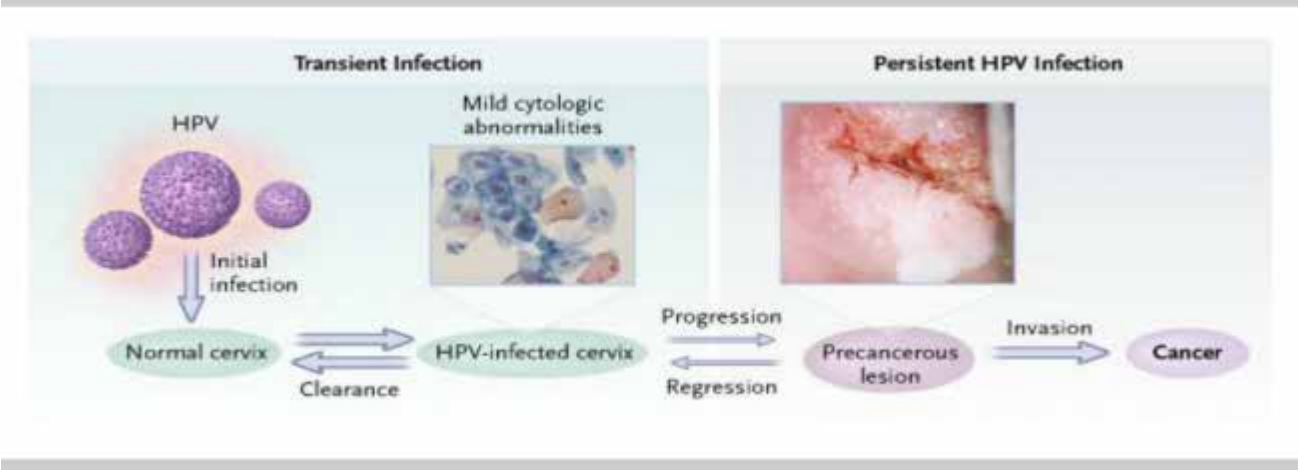
Cervical Cancer
Risk Factors

- Smoking
- Multiple sexual partners
- Sexually transmitted infection
- Immunosuppression
  - HIV/AIDS
  - Prior organ transplant recipient
- HPV infection



Cervical Cancer
Role of HPV

- Human papilloma virus incorporated into cellular genome; persistent infection can ➔ dysplasia
- HPV oncoproteins E6 and E7 lead to inactivation of p53 and Rb
- >20 high-risk types associated with anogenital cancers
  - Types 16 & 18: >70% of cervical cancers



Wright & Schiffman. *N Engl J Med* 2003.

Cervical Cancer
HPV Vaccine

Available

Gardasil: Quadrivalent *(types 6,11,16,18)*
Cervarix: Bivalent *(types 16,18)*
Gardasil 9: Nanovalent *(types 6, 11, 16, 18, 31, 33, 45, 52, 58)*

- Significantly ↓ incidence squamous and glandular dysplasia and carcinoma *in situ*

  FUTURE II Study Group. *N Engl J Med* 2007; Joura EA et al. *Lancet* 2007. Joura EA et al. N Engl J Med 2015.

- ACIP, ACS, ACOG, AAP: **ALL** girls and boys should be vaccinated against HPV at age 9–12 yrs

- Approved for all genders, ages 9-26, now expanded to include ages 27-45

Cervical Cancer
Screening

- Start at age 21
- Ages 21-29: Pap every 3 years
- Ages 30-65: Co-testing with Pap and HPV every 5 years (new: HPV testing alone every 5 years also acceptable by USPSTF)
- Age >65: No screening if normal prior screening
- Screen even if vaccinated
- No screening after hysterectomy with removal of cervix, unless prior CIN3/cancer

Cervical Cancer

Diagnosis and staging

- Diagnosis via biopsy
- Previously clinically staged – NEW staging FIGO 2018 allows imaging and pathology
  - Pelvic exam (speculum, bimanual, rectovaginal)
  - Biopsies, cervical cone/LEEP
  - Cystoscopy
  - Proctosigmoidoscopy
  - Intravenous pyelogram (IVP)
  - Chest x-ray
  - US, CT, MRI, PET scan now allowed
  - Pathology from lymph nodes, other surgical or biopsy specimens now allowed

Cervical Cancer

Staging - OLD

Stage	Spread
Stage I	**Confined to cervix (disregard corpus extension)**
IA	Diagnosed only by microscopy
IA1	≤3 mm depth and ≤7mm horizontal spread
IA2	>3 and ≤5 mm depth, and ≤7mm horizontal spread
IB	Clinically visible, or microscopic lesion greater than IA
IB1	≤4 cm tumor
IB2	>4 cm tumor
Stage II	**Beyond uterus, but no to pelvic sidewall or lower third of vagina**
IIA	Vaginal involvement (less than upper two-thirds)
IIA1	≤4 cm tumor
IIA2	>4 cm tumor
IIB	Parametrial invasion

Cervical Cancer

Staging - OLD

Stage	Spread
Stage III	**Extends to pelvic sidewall* and/or involves lower third of vagina**
IIIA	Involves lower third of vagina (no pelvic sidewall)
IIIB	Extends to pelvic sidewall, and/or causes hydronephrosis or non-functioning kidney
Stage IV	**Involves bowel or bladder mucosa, or extends beyond true pelvis**
IVA	Bowel or bladder mucosa (bullous edema not sufficient)
IVB	Distant metastases (extends beyond true pelvis)

Cervical Cancer

New Staging - 2018

Stage	Spread
Stage I	**Confined to cervix (disregard corpus extension)**
IA	Diagnosed only by microscopy, with maximum depth <5mm
IA1	<3 mm depth
IA2	≥3 mm and <5 mm depth
IB	Depth invasion ≥5 mm, confined to cervix
IB1	<2 cm in greatest dimension
IB2	≤2 cm and <4 cm
IB3	≥4 cm
Stage II	**Beyond uterus, but not to pelvic sidewall or lower third of vagina**
IIA	Vaginal involvement (less than upper two-thirds)
IIA1	<4 cm in greatest dimension
IIA2	≥4 cm
IIB	Parametrial invasion

Cervical Cancer

New Staging - 2018

Stage	Spread
Stage III	**Involves lower third of vagina and/or extends to pelvic sidewall* and/or involves pelvic or paraaortic lymph nodes**
IIIA	Involves lower third of vagina (no pelvic sidewall extension)
IIIB	Extends to pelvic sidewall*
IIIC	Involvement of pelvic and/or paraaortic lymph nodes, irrespective of tumor size and extent
IIIC1	Pelvic lymph node metastasis only
IIIC2	Paraaortic lymph node metastasis
Stage IV	**Involves bowel or bladder mucosa, or extends beyond true pelvis**
IVA	Bowel or bladder mucosa (bullous edema not sufficient)
IVB	Distant metastases (extends beyond true pelvis)

* or causes hydronephrosis or nonfunctioning kidney

Cervical Cancer

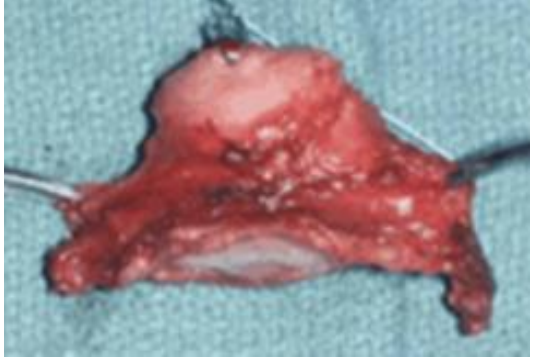
Management

Spread	Stage	Recommended therapy
Confined to cervix, microinvasive	IA1	Simple hysterectomy or cone
Confined to cervix, ≤4 cm	IA2-IB2	Surgery or Chemoradiation
Bulky cervix and/or locally advanced disease	IB3-IVA	Chemoradiation
Distant spread	IVB	Chemotherapy ± radiation

Cervical Cancer
Early Stage Disease

- **Surgical**
  - Ex-lap, radical hysterectomy with pelvic lymphadenectomy
  - Favored approach for preservation of sexual function
- ~~(Minimally invasive approach feasible with excellent short-term outcomes)~~ Ramirez PT et al. NEJM 2018.
- **Non-Surgical**
  - External beam radiation with chemosensitization, followed by brachytherapy

Cervical Cancer
Fertility-Sparing



- Radical trachelectomy with lymphadenectomy
- Criteria:
  - Reproductive age / Desires to preserve fertility
  - Squamous cell or adenocarcinoma (no high-risk histologies)
  - Stage IA1 with LVSI, IA2, or IB1
  - Tumor size ≤2 cm* with limited endocervical extension (assessed by colpo, MRI)
  - No evidence of lymph node metastasis
  - LVSI is a risk factor for nodal recurrence, but not a strict contraindication

Kim CH et al. *Gynecol Oncol* 2012.
Diaz JP et al. *Gynecol Oncol* 2008.

Cervical Cancer
Case Studies

- 52 yo with stage IB2 cervical SCC (3 cm tumor) s/p ex-lap, radical hyst, BSO, sentinel lymph node biopsy
  - Depth of cervical stromal invasion: 50%
  - LVSI present
  - Sentinel nodes negative
- Management?

A. Observation, she is low-risk

B. Pelvic RT, she is intermediate-risk

C. ChemoRT, she is high-risk

Cervical Cancer

Indications for Post-op Treatment

Intermediate-Risk

LVSI	Depth of cervical stromal invasion	Tumor size (clinical)
+	Deep third	Any
+	Middle third	≥2 cm
+	Superficial third	≥5 cm
-	Middle or deep	≥4 cm

With combination of risk factors, **pelvic radiation** ↓ risk of recurrence (28% ->15%)

Sedlis A. *Gynecol Oncol* 1999.

Cervical Cancer
Case Studies

- 52 yo with stage IB2 cervical SCC (3 cm tumor) s/p ex-lap, radical hyst, BSO, sentinel lymph node biopsy
  - Depth of cervical stromal invasion: 50%
  - LVSI present
  - Sentinel nodes negative
- Management?

A. Observation, she is low-risk

B. Pelvic RT, she is intermediate-risk

C. ChemoRT, she is high-risk

Cervical Cancer
Case Studies

- 65 yo with stage IB2 cervical adenocarcinoma (3.5 cm tumor) s/p ex-lap, radical hyst, BSO, bilateral pelvic and common iliac LND
  - Depth of cervical stromal invasion: 85%
  - LVSI present
  - One of 16 pelvic lymph nodes positive
- Management?

  A. Pelvic RT

  B. RT with cisplatin-based chemosensitization

  C. Chemotherapy

Cervical Cancer
Indications for Post-op Treatment

- **High-Risk**
  - Positive lymph nodes
  - Parametrial disease
  - Positive/close margins

Postop adjuvant treatment with **chemoradiation** to ↓ recurrence and improve overall survival

Peters WA. *JCO* 2000.

Cervical Cancer
Case Studies

- 65 yo with stage IB2 cervical adenocarcinoma (3.5 cm tumor) s/p ex-lap, radical hyst, BSO, bilateral pelvic and common iliac LND
  - Depth of cervical stromal invasion: 85%
  - LVSI present
  - One of 16 pelvic lymph nodes positive

➢ Management?

A. Pelvic RT

B. RT with cisplatin-based chemosensitization

C. Chemotherapy

Cervical Cancer

Locally Advanced Disease - Optimizing Chemoradiation

- Radiation historical treatment for cervical cancer
- 5 RCTs in 1990s showed significant survival benefit with chemotherapy and radiation for stage IB2-IVB diseases

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Strong consideration should be given to chemoradiation instead of RT alone

- Chemo regimens not consistent across studies
  - Weekly cisplatin (40 mg/m^2) most feasible, least toxicity
  - Cisplatin and 5-fluorouracil
  - Mitomycin

Recommendations

NCCN National Comprehensive Cancer Network

"concurrent cisplatin-containing chemotherapy"

Eifel PJ et al. *Semin Radiat Oncol* 2006.

Cervical Cancer

Locally Advanced Disease - Optimizing Chemoradiation

- Radiation with concurrent chemotherapy, followed by brachytherapy
  - Radiation dose goal: 80–85 Gy
- International Phase III trial in advanced disease:

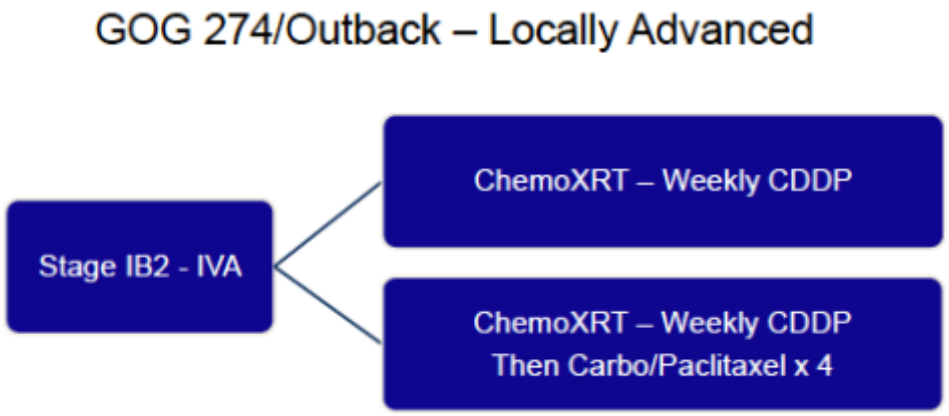
Weekly Cisplatin & Gemcitabine Concurrent EBRT/Brachytherapy Adjuvant Cis/Gem q 21d x 2 cycles	Weekly Cisplatin Concurrent EBRT/Brachytherapy

- Gemcitabine + cisplatin arm associated with significant improvement in PFS/OS
- ↑ Toxicity in cis/gem arm, concern regarding the monitoring for side effects
- Unclear if benefit due to concurrent or post-radiation chemotherapy

Duenas Gonzalez A et al. *J Clin Oncol* 2011.

Cervical Cancer
Ongoing Controversies

- Assessing the specific benefit of chemotherapy after primary chemoradiation



Cervical Cancer

Locally Advanced Disease – Alternatives to Chemoradiation?

- Neoadjuvant chemotherapy followed by radical surgery instead?

  Inferior to chemoRT

  - Phase III RCT in stage IB2-IIB cervical cancer:

    -ChemoRT vs. Neoadj Carbo/taxol x3 followed by radical hysterectomy (+- post-op RT or chemoRT if indicated)

    -ChemoRT with superior 5-yr DFS 77% vs. 69%

    Gupta S et al. *J Clin Oncol* 2018.

  - EORTC GCG 55994:

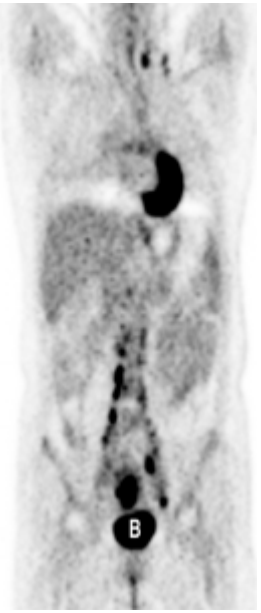
    -Similar finding, ChemoRT superior to neoadj chemotherapy followed by surgery (5-yr PFS 66% vs 57%)

    ASCO 2019.

Cervical Cancer
Nodal Status

- Lymph node involvement important prognostic indicator
  - 5-yr DSS 50–60% with pelvic lymph node involvement, 20–40% with paraaortic lymph nodes
- **Diagnostic Techniques**
  PET/CT:
  - Best sensitivity/specificity for nodal involvement

  MRI:
  - Less sensitivity for nodes
  - ↑ accuracy for determining local invasion/spread
- Consider lymph node dissection in setting of PET/CT showing bulky nodes, or (+) pelvic LN but negative PALN



Gien & Covens. *J Surg Oncol* 2009.
Uzan C et al Oncologist 2011
Ramirez PT et al. Cancer 2011

Cervical Cancer
Surveillance

- NCCN Recommendations:

  Pelvic exam every 3-6 months for complete responders

  - Consider imaging, as clinically indicated
  - Although Pap tests routinely used, may not be accurate in detecting recurrence

- Future use PET/CT scan: Assessment of metabolic response
  - A post-treatment PET/CT performed at 3-6 months after chemoradiation can be used to identify early persistence/recurrence

NCCN Clinical Practice Guidelines. Cervical Cancer. Version I. 2012.
Kidd EA et al. *Int J Radiat Oncol Biol Phys* 2012.

Recurrent Cervical Cancer
Rate & Patterns

- Majority occur within 2 years of primary treatment
- Recurrence sites:
  Local: Vaginal cuff, cervix, ovaries
  Distant: Lungs, paraaortic/supraclavicular lymph nodes, abdominal cavity most common
- Poor prognosis with recurrence
  - Review of 3 prospective clinical trials showed OS of 6-13 months
  - Importance of focusing on QOL and incorporating palliative care

Elit L et al. *Gynecol Oncol* 2009.
Chase DM et al. *Gynecol Oncol* 2012.

Metastatic/Recurrent Cervical Cancer
Treatment Options—Chemotherapy

- **GOG 204**: Comparison of 4 cisplatin-based doublets for recurrent cervical cancer favored cis/taxol

Monk BJ et al. *J Clin Oncol* 2009.

- **GOG 240:**
  Comparison of chemotherapy ± bevacizumab
  - No difference between chemo arms
  - Arms containing bev with significant improvement in PFS, OS, ORR

Tewari K et al. *NEJM*. 2014.

- **JCOG 0505**
  - Randomized phase III trial of cis/T vs carbo/T
  - Similar OS – carbo/taxol not inferior
  - However, if no prior cis, OS shorter with carbo/T

Kitagawa R et al. *J Clin Oncol* 2015.

Recurrent Cervical Cancer
Treatment Options

- **Chemotherapy – Second-line options:**
  - Abraxane, Paclitaxel, Ifosfamide, Topotecan, Carboplatin, Pemetrexed, Vinorelbine, Irinotecan
  - Response rates 15-29%
- **Radiation**
  - Consider if no prior RT or have recurrence outside irradiated field
- **Surgery**
  - Patients with central (i.e., pelvic/vaginal) recurrence: potential candidates for pelvic exenteration

Benn T et al. *Gynecol Oncol* 2011.

Recurrent Cervical Cancer
Immunotherapy

- Strong rationale for immunotherapy in HPV-related cancers

  Liao JB. *Gynecol Oncol* 2016

- Adoptive T-cell therapy?
  - NCI trial of 9 patients receiving T-cells harvested & expanded from tumor showed 3/9 had objective tumor responses

    Stevanovic S et al. *J Clin Oncol* 2015.

- Immune checkpoint inhibitors
  - Pembrolizumab – now FDA-approved (if PD-L1+)

    - Keynote-158 (cohort E): Overall response rate 14.3%

    - Keynote-028: ORR 12.5%

  - Nivolumab

    -Checkmate-358 (cervix cancer cohort n=19, PDL1+ not required): ORR 26%

QUESTIONS

katypenn@uw.edu

Transfusion Medicine

Jill Johnsen, MD
Associate Member, Bloodworks
Associate Professor, University of Washington

Bloodworks Northwest

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

Transfusion

Transfusion is one of the most common inpatient procedures[1]

Transfused *daily* in the U.S.[2] :

- 36,000 U red blood cells (RBCs)
- 7000 U platelets
- 10,000 U plasma

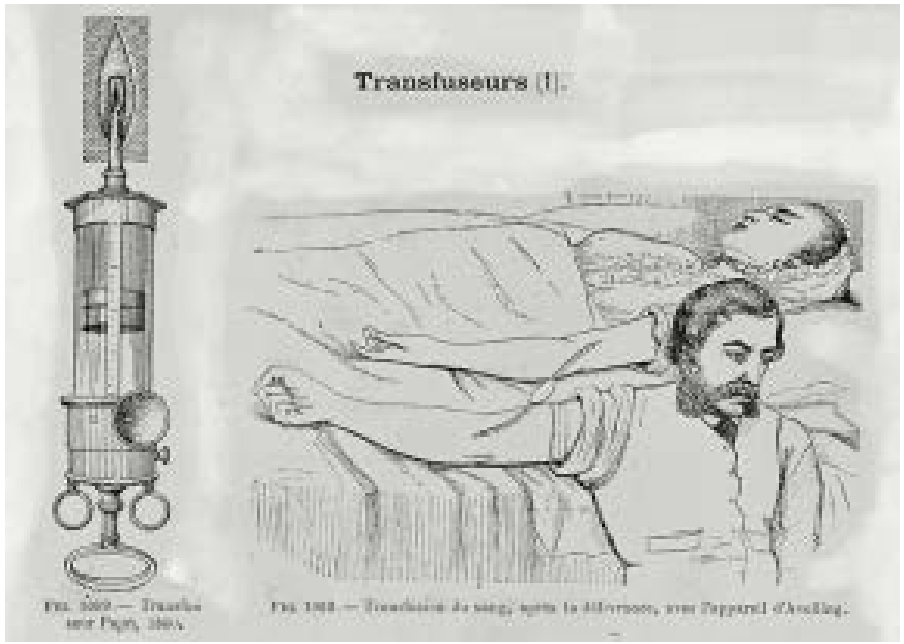
Source: ASH Image Bank.

1. Delaney M, Wendel S, Bercovitz RS, et al; Biomedical Excellence for Safer Transfusion (BEST) Collaborative. Transfusion reactions: prevention, diagnosis, and treatment. *Lancet.* 2016;388(10061):2825-2836.

2. American Red Cross. Blood needs & blood supply. Available at: https://www.redcrossblood.org/donate-blood/how-to-donate/how-blood-donationshelp/blood-needs-blood-supply.

Transfusion: Progress from a potentially lethal procedure to a now largely safe and common treatment

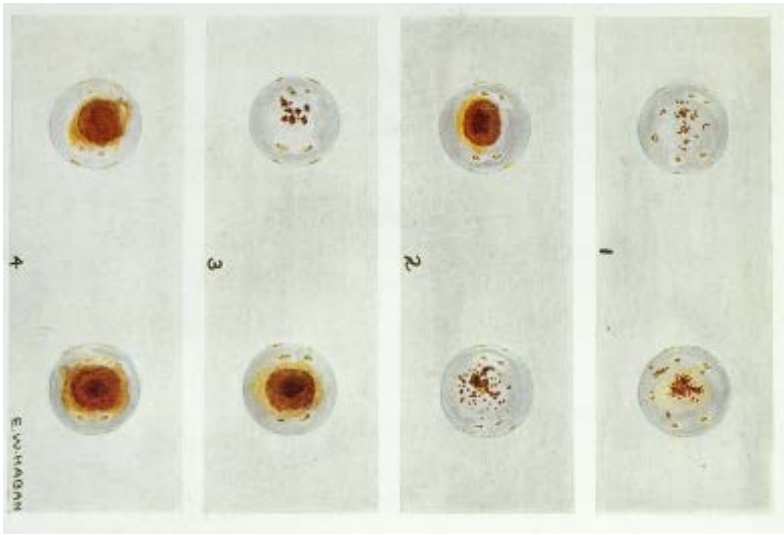
A patient having blood let from his right arm, while the blood of a dog is transfused into his left arm. Engraving, ca.1692.
Wellcome Library, London



Blood transfusion used during childbirth, including instruments. From Gustave-Joseph Alphonse Witkowski's Histoire des accouchements, ca. 1887. *Wellcome Library, London*

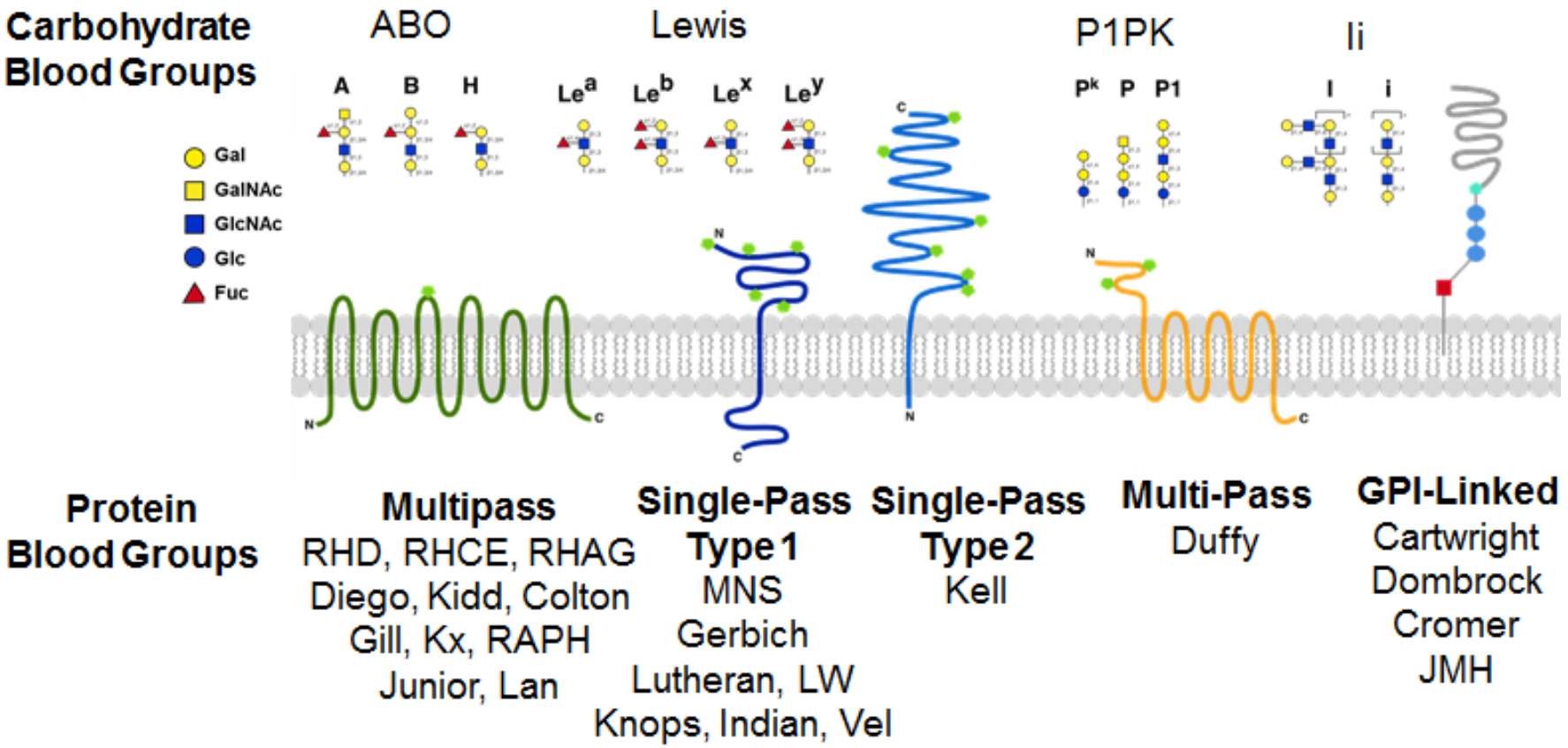
Discovery of ABO made safe transfusion possible

	ABO Blood Group			
RBC Antigens	O 	A 	B 	AB 
Alleles	OO	AO or AA	BO or BB	AB
Anti-A	✳		✳	
Anti-B	✳	✳		



The four blood groups. From Laurence H Snyder's Blood Grouping in Relation to Clinical and Legal Medicine, 1929. *Wellcome Library, London*

Now over 300 known red cell blood group antigens[1]



1. Johnsen J. Hematology (ASH Education Program). Dec 5;2015(1):168-76

Patient may need a transfusion? - order a “type and screen”

“**TYPE**” is a test to determine blood type

ABO and RhD (D) are considered in all transfusions

Extended typing tests for other blood groups (next most common: C,E,K)

Forward type: detects antigens on the patient’s RBCs using reagent antibody

Reverse type: detects antibodies in plasma/serum using reagent RBCs

“**SCREEN**” is a test to identify presence of anti-RBC antibodies

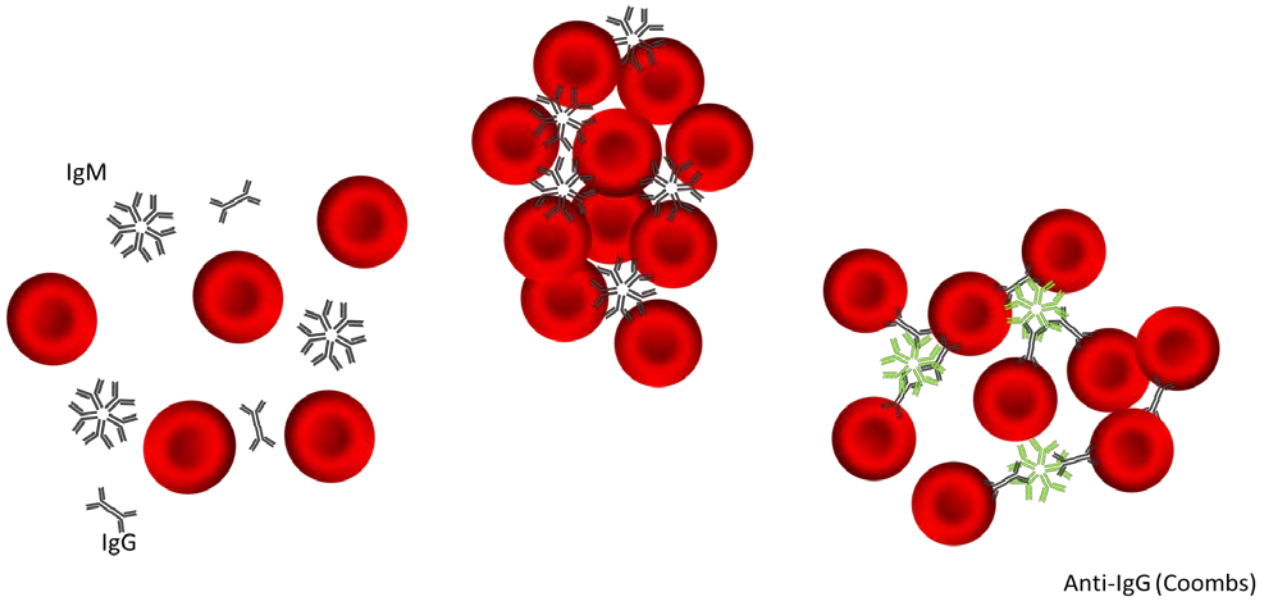
(Ordering a type and screen is a good time to consider IV access)

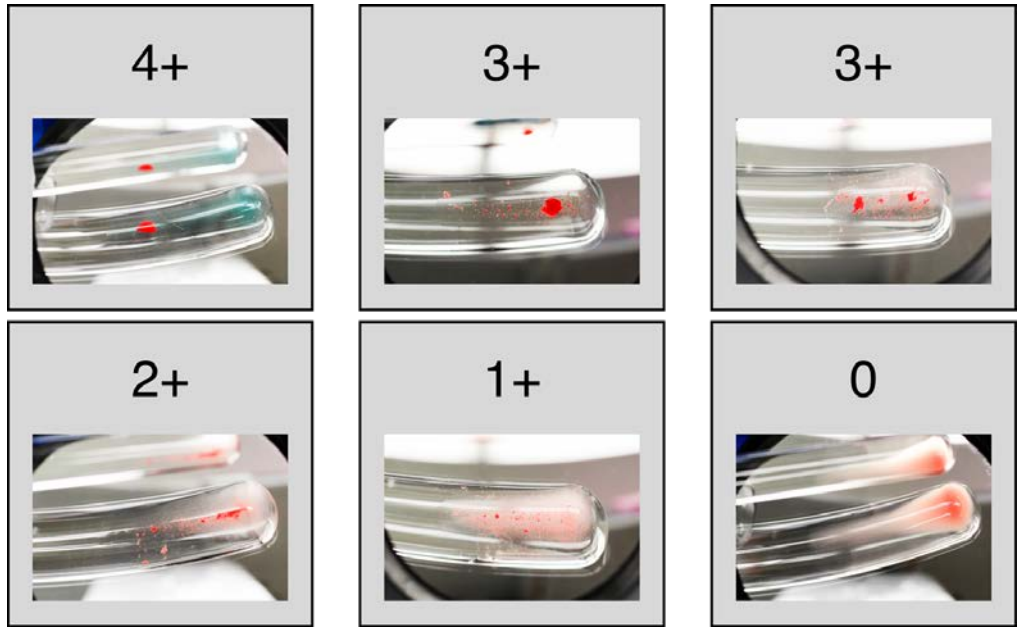
TYPE: Routine blood group testing is based on interaction of RBCs with anti-RBC antibodies

All transfusions: ABO, D.

Higher risk transfusions: C, E, K, potentially others

Genotyping can also be done, can test more blood groups at once





Tube testing image courtesy of Kerry Lannert

SCREEN: test for anti-RBC antibodies

Incubation of patient plasma/serum with red cells from 2-3 very well characterized “reagent” blood cell donors

- Collectively, these donors present the non-ABO blood group antigens likely to provoke allosensitization and transfusion reactions

PANOSCREEN
Master List

IMMUCOR, INC. Norcross, GA 30071 USA
US LICENSE NO: 886
LOT NO: 23502
EXPIRES: 2014/08/15

412-10

PANOSCREEN

VIAL	Donor	Rh - Hr							Kell						Duffy		Kidd		Lewis		P	MN				Luth-eran		X_g
		D	C	c	E	e	V	C^w	K	k	Kp^a	Kp^b	Js^a*	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	P_1	M	N	S	s	Lu^a	Lu^b	Xg^{*a}
I	R1R1 B8691	+	+	0	0	+	0	0	0	+	0	+	0	+	+	+	+	+	+	0	+	+	0	+	+	0	+	+
II	R2R2 C4281	+	0	+	+	0	0	0	0	+	0	+	0	+	0	+	+	0	0	+	+	0	+	+	0	0	+	0
III	rr G1239	0	0	+	0	+	0	0	+	+	0	+	0	+	+	0	0	+	+	0	+	0	+	0	+	+	+	+	+

* Indicates those antigens whose presence or absence may have been determined using only a single example of a specific antibody.

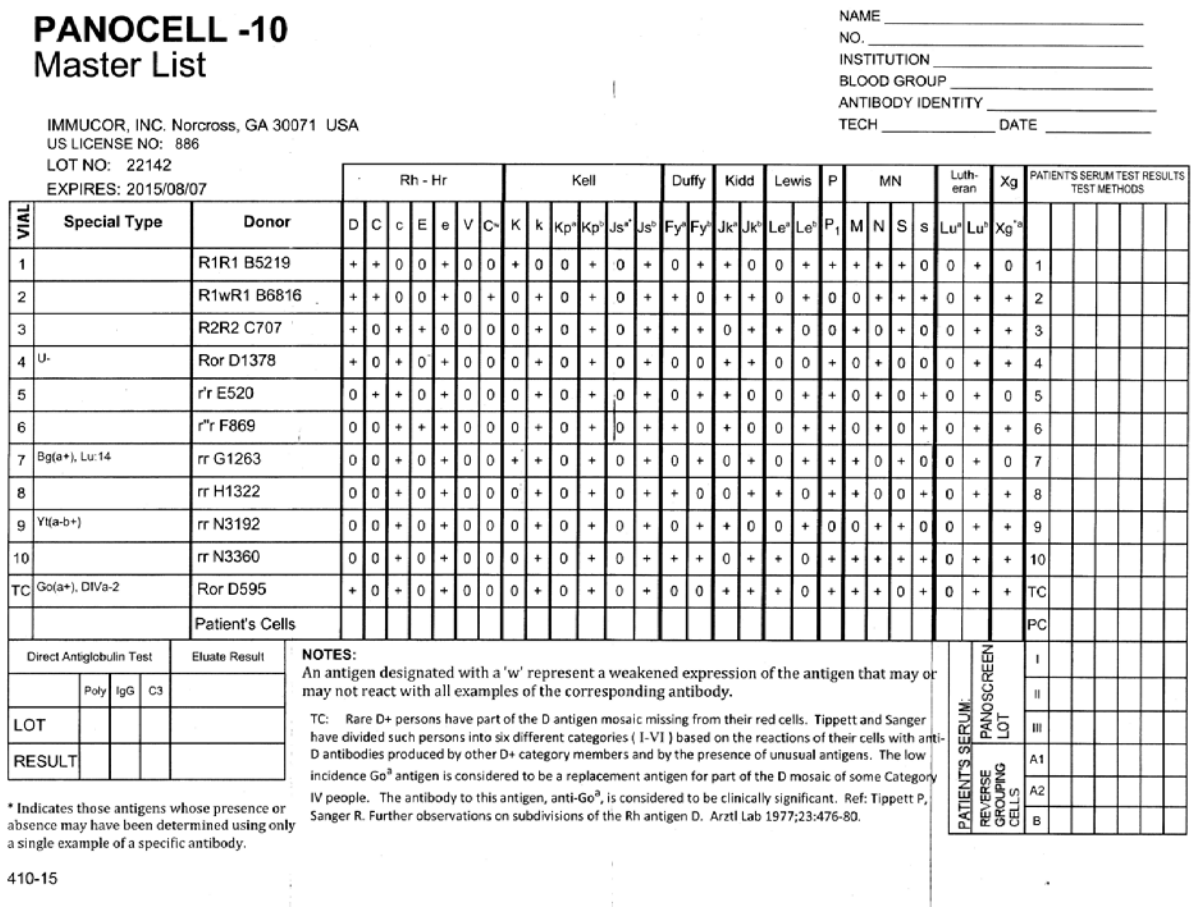
Antibody screen positive? Next step: Antibody identification

Antibody identification

A logic puzzle

Tests agglutination against a panel of 10-16 human red cells that express blood group antigens in different combinations

- Can take hours to days to solve
- Can be confounded by interfering agents (e.g. warm antibodies, some drugs)



PANOCELL -10
Master List

NAME _____
NO. _____
INSTITUTION _____
BLOOD GROUP _____
ANTIBODY IDENTITY _____
TECH _____ DATE _____

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EXPIRES: 2015/08/07

VIAL	Special Type	Donor	Rh - Hr						Kell						Duffy		Kidd		Lewis		P	MN				Luth-eran		Xg	PATIENT'S SERUM TEST RESULTS TEST METHODS
			D	C	c	E	e	V	C^w	K	k	Kp^a	Kp^b	Js^a	Js^b	Fy^a	Fy^b	Jk^a	Jk^b	Le^a	Le^b	P_1	M	N	S	s	Lu^a	Lu^b	Xg^{a*}	
1		R1R1 B5219	+	+	0	0	+	0	0	+	0	0	+	0	+	0	+	+	0	0	+	+	+	+	0	0	+	0	1	
2		R1wR1 B6816	+	+	0	0	+	0	+	0	+	0	+	0	+	+	0	+	+	0	+	0	0	+	+	+	0	+	+	2	
3		R2R2 C707	+	0	+	+	0	0	0	0	+	0	+	0	+	+	+	0	+	+	0	0	+	0	+	0	0	+	+	3	
4	U-	Ror D1378	+	0	+	0	+	0	0	0	+	0	+	0	+	0	0	+	+	0	0	+	0	+	0	0	0	+	+	4	
5		r'r E520	0	+	+	0	+	0	0	0	+	0	+	0	+	0	+	+	0	0	+	+	0	+	0	+	0	+	0	5	
6		r''r F869	0	0	+	+	+	0	0	0	+	0	+	0	+	+	0	+	0	0	+	+	0	+	0	+	0	+	+	6	
7	Bg(a+), Lu:14	rr G1263	0	0	+	0	+	0	0	+	+	0	+	0	+	0	+	0	+	0	+	+	+	0	+	0	0	+	0	7	
8		rr H1322	0	0	+	0	+	0	0	0	+	0	+	0	+	+	0	0	+	0	+	+	+	0	0	+	0	+	+	8	
9	Yt(a-b+)	rr N3192	0	0	+	0	+	0	0	0	+	0	+	0	+	0	+	+	0	0	+	0	0	+	+	+	0	0	+	+	9	
10		rr N3360	0	0	+	0	+	0	0	0	+	0	+	0	+	+	+	0	+	+	0	+	+	+	+	+	0	+	+	10	
TC	Go(a+), DIVa-2	Ror D595	+	0	+	0	+	0	0	0	+	0	+	0	+	0	0	+	+	+	0	+	+	+	0	+	0	+	+	TC	
		Patient's Cells																											PC	

Direct Antiglobulin Test				Eluate Result
	Poly	IgG	C3	
LOT				
RESULT				

* Indicates those antigens whose presence or absence may have been determined using only a single example of a specific antibody.

NOTES:
An antigen designated with a 'w' represent a weakened expression of the antigen that may or may not react with all examples of the corresponding antibody.

TC: Rare D+ persons have part of the D antigen mosaic missing from their red cells. Tippett and Sanger have divided such persons into six different categories (I-VI) based on the reactions of their cells with anti-D antibodies produced by other D+ category members and by the presence of unusual antigens. The low incidence Go^a antigen is considered to be a replacement antigen for part of the D mosaic of some Category IV people. The antibody to this antigen, anti-Go^a, is considered to be clinically significant. Ref: Tippett P, Sanger R. Further observations on subdivisions of the Rh antigen D. Arztl Lab 1977;23:476-80.

PATIENT'S SERUM:		
REVERSE GROUPING CELLS	PANOSCREEN LOT	I
		II
		III
		A1
		A2
		B

410-15

Patient needs a transfusion: order a "Type and Cross"
TYPE, SCREEN, and Crossmatch

CROSSMATCH: identifies blood components for transfusion in *this* patient

If negative antibody screen:

- **Electronic Crossmatch** (most common!)
- Immediate Spin Crossmatch
  - Rapid mixing of patient serum with donor RBCs for ABO compatibility

If positive antibody screen:

- **Full Crossmatch**
  - Requires incubations and Coombs reagent to test that the patient's serum does not react with donor RBCs
  - Takes ≥45 minutes
  - Takes *a lot* longer if there is an antibody to a high incidence (very common) antigen

Blood components are from blood donors

- **Volunteer blood donors**
- Complete a health assessment and questionnaire
- Meet minimum physiologic criteria
- Blood is sampled for testing
  - **Blood groups:** minimum **ABO and D** (including testing for weak D)
    - Other blood groups in recurring donors and/or for special situations
  - **Blood borne pathogen testing:**
    - Serology: HIV-1/2, HCV, HTLV-I/II, HBc, HBsAg, syphilis
    - Nucleic acid testing: HCV RNA, HIV-1 RNA, WNV RNA, HBV DNA
    - At least once: serology negative for *Trypanosoma cruzi*
    - More recent additions: Zika, *Babesia microti*

Blood components for transfusion

- **Red cells** (packed red blood cells, or PRBCs): increase Hgb ~1 g/dL*
  - Hct 65-80% in 225-350mL, stored at 4C, *shelf life 42 days*
- **Platelets** (160-400 mL in plasma): increase platelets ~40-50 K/uL*
  - single donor (pharesis) or pooled (4-6 donors from whole blood centrifugation)
  - stored at RT, *shelf life 5 days*
- **Plasma** (albumin, coag factors, fibrinolytic proteins, Igs, others): 200-250mL
  - fresh plasma or fresh frozen plasma (FFP)
  - stored frozen, shelf life one year; *thawed shelf life 24 hours*

<u>Further manufacturing:</u>

- **Cryoprecipitate** (insoluble cold precipitate of plasma):
  - fibrinogen, VWF, factor VIII, factor XIII
- Prothrombin complex concentrates (thrombin, FIX, FX, FVII), IVIg, Albumin, etc.

*in average-sized adults

Infectious risks of transfusion

Transfusion-Transmitted Infection	Residual Risk Per Transfused Component
HIV	1 in 1,467,000
Hepatitis C	1 in 1,149,000
Hepatitis B	1 in 282,000
West Nile Virus	Uncommon
Cytomegalovirus	50-85% of donors are carriers. Leukocyte reduction is protective.
Bacterial Infection	1 in 2-3,000 (mostly platelets)
Parasitic Diseases Babesiosis, Chagas, Malaria	Relatively uncommon

Weinstein R. Red Blood Cell Transfusion: A Pocket Guide for the Clinician. American Society of Hematology. November, 2016.

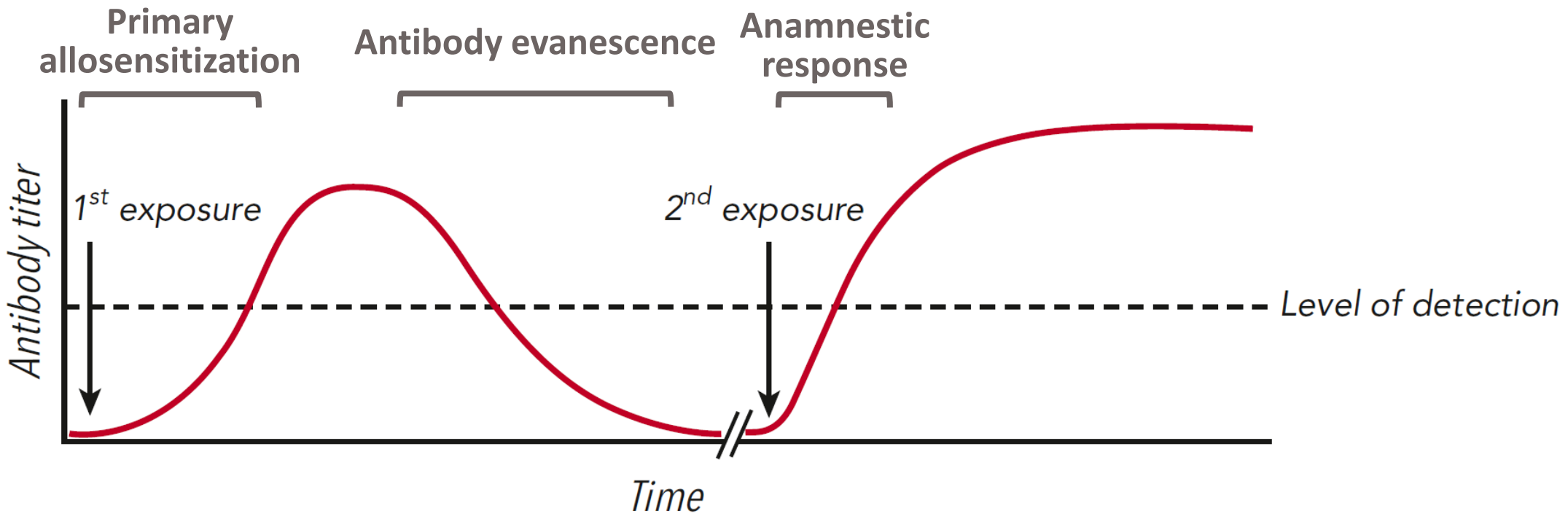
Immediate immunologic complications of transfusion

- **Hemolytic transfusion reaction (HTR)**
  - Destruction of RBCs by anti-blood group antibodies, life-threatening
- **Immune-mediated platelet destruction** (alloantibodies: HLA or platelet)
- **Febrile non-hemolytic reaction** (anti-WBC antibodies, cytokines)
  - Anti-pyretics can offer symptom relief; if recurrent consider leukocyte reduction
    - Incidence <1% leukocyte reduced RBCs, 5% leukocyte reduced platelets
- **Transfusion-related lung injury (TRALI)**
  - Acute hypoxemia, non-cardiogenic pulmonary edema within 6 hours
  - Due to donor anti-WBC antibodies, pro-inflammatory molecules in stored components
- **Allergic reactions** (1-3% of plasma-containing components)
  - Common, mild, self-limited urticarial reaction, usually responsive to antihistamines
- **Anaphylactoid/anaphylactic reactions** (rare, IgA-deficient patients high risk)
  - If refractory to meds, consider washed cellular components to reduce plasma exposure

Delayed immunologic complications of transfusion

- **Delayed hemolytic transfusion reaction** (destruction of RBCs)
  - Similar to HTR: hemolysis due to either anamnestic or new alloimmune response
- **Alloimmunization** to (donor) antigens (any blood cell antigens or plasma proteins)
  - Blood components contain things not on the label (*e.g. in platelets*: some RBCs, WBCs)
- **Post-transfusion purpura (PTP)**
  - Rare, dramatic, self-limited purpura 7-10 days later
  - Platelet specific antibody destroys autologous and allogeneic platelets, IVIg can treat
- **Transfusion-associated graft-vs-host disease (TA-GVHD)** (rare)
  - Transfused allogeneic T-cells (from any component with viable T-cells)
  - Risks for TA-GVHD: severe cellular immunodeficiency, purine analagues (e.g. fludarabine), haploidentical HLA to a homozygous donor
  - Irradiated components are indicated for patients at risk for TA-GVHD

Model of events leading to delayed hemolytic transfusion reaction (DHTR)[1]



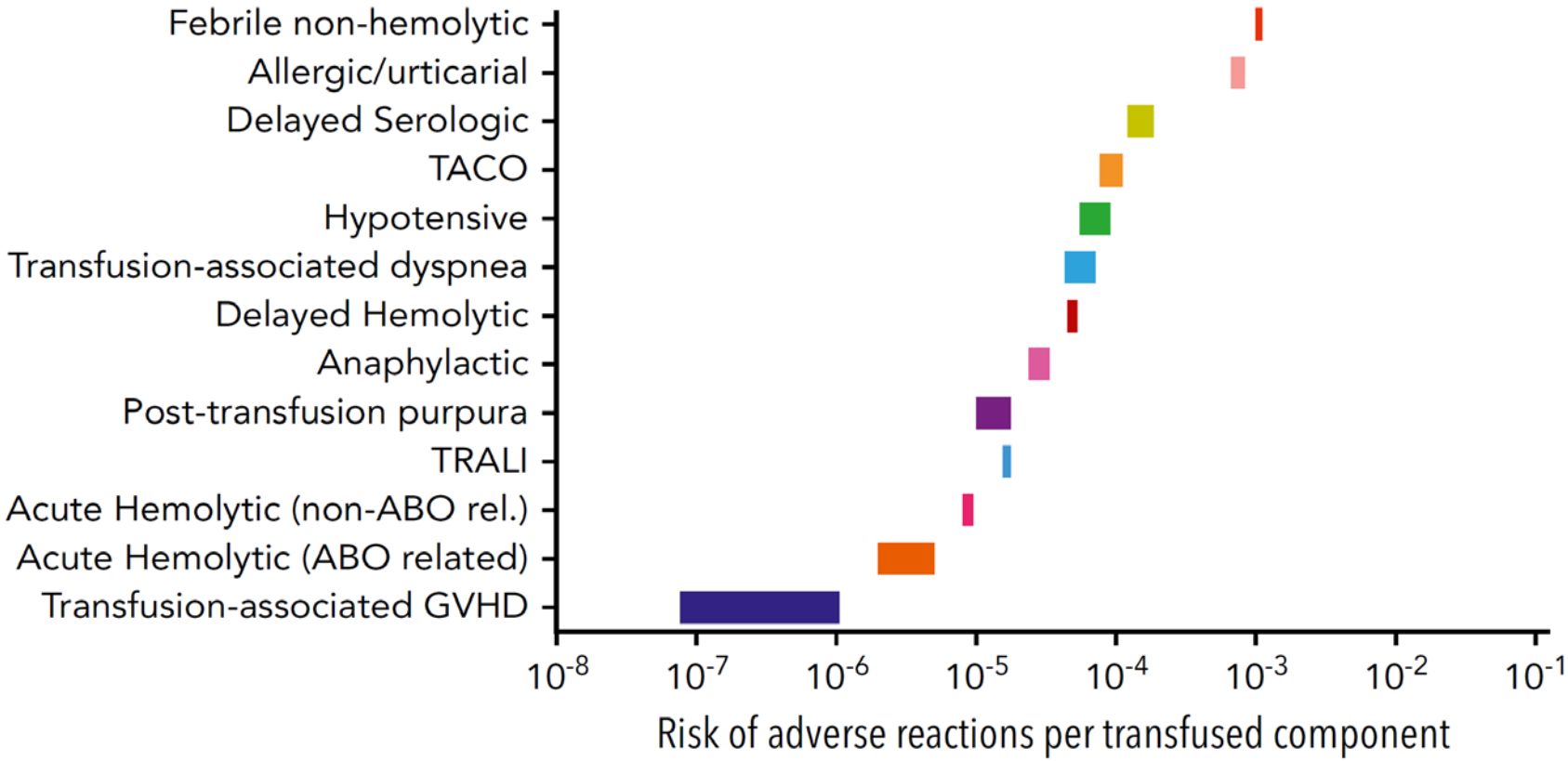
1. Tormey C. and Hendrickson J. Transfusion-related red blood cell alloantibodies: induction and consequences. *Blood* 2019;133(17);1821-1830. (2019)

Other (non-immune) complications of transfusion

- **Transfusion-associated circulatory overload (TACO)**
  - From excessive volumes or excessively rapid rates: treat pulmonary edema, reduce fluids
- **Hypothermia: from infusing large volumes of cold components**
  - Risks arrhythmia/arrest and coagulopathy: mitigated by blood warmers
- **Metabolic complications: usually with large volume / rapid transfusions**
  - Citrate "toxicity" : chelation of ionized calcium by the citrate anticoagulant in blood components
- **Iron overload**
- **Donor-transmitted infectious agents**: Viruses, bacteria, parasites, variant Creutzfeldt-Jakob
- **Bacterial sepsis or endotoxin rxns from contamination (infrequent, life-threatening):**
  - Most common culprit component is platelets
  - Treat aggressively with antibiotics and supportive care
- **Cytomegalovirus (CMV): can reside in donor WBCs**
  - Risks for immunocompromised patients and premature infants of seronegative mothers
  - Risks reduced by transfusing CMV-seronegative or leukocyte-reduced components

Noninfectious adverse outcomes per unit transfused[1]

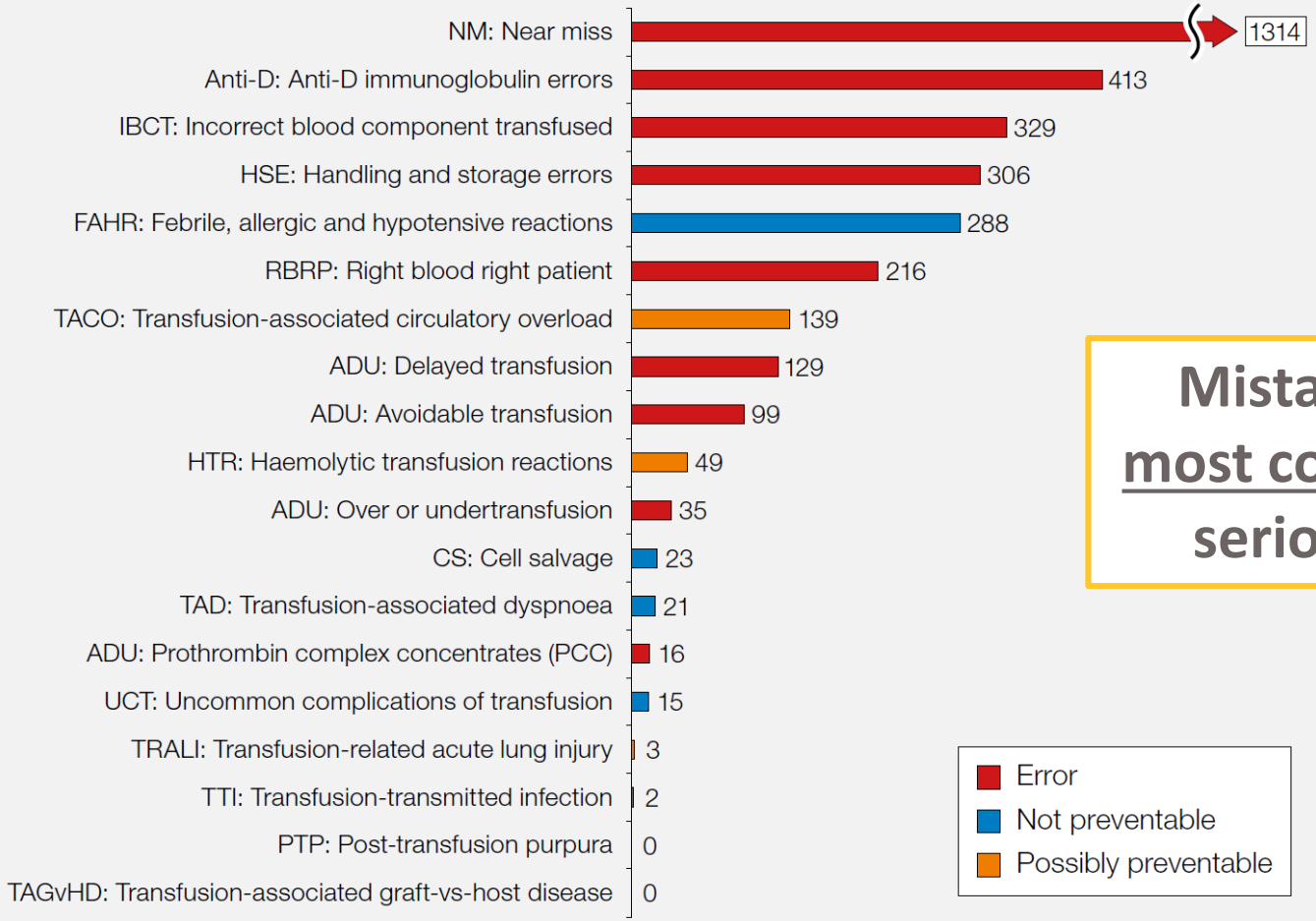
From National Blood Collection and Utilization Surveys 2011-2015



1. *In:* Goel R., *et al.* Noninfectious transfusion-associated adverse events and their mitigation strategies. *Blood* 2019 133: 1831-1839

Serious Hazards Of Transfusion (SHOT) 2019[1]

Summary data for 2019 (n=3397)



Mistakes are the most common of the serious hazards

1. *www.shotuk.org*

When to transfuse PRBCs?

Choosing Wisely®
An initiative of the ABIM Foundation

AABB Choosing Wisely (#1): Don't transfuse more units of blood than absolutely necessary.

ASH Choosing Wisely (#1): Don't transfuse more than the minimum number of red blood cell (RBC) units necessary to relieve symptoms of anemia or to return a patient to a safe hemoglobin range (7 to 8 g/dL in stable, non-cardiac in-patients).

- Transfuse for symptoms and/or hemoglobin
  - **Threshold 7.0-8.0g/dL** for most hospitalized, stable patients
  - **Threshold 8.0g/dL** for pre-existing cardiovascular disease
- Order one PRBC unit unless actively bleeding (use weight-based dosing in children)
  - Order more units only after re-assessment
  - Remember that *each unit of blood* carries risks
- **Liberal transfusion strategies do not improve outcomes compared to restrictive strategies**
- **Unnecessary transfusion generates costs and exposes patients to risks without likely benefit**

Adapted from *www.choosingwisely.org*

When not to transfuse: Asymptomatic iron deficiency anemia

Choosing Wisely®
An initiative of the ABIM Foundation

AABB Choosing Wisely (#2):

Don't transfuse red blood cells for iron deficiency without hemodynamic instability.

- Cheaper and safer alternatives to treat iron deficiency (*e.g.* iron treatment)
- Unless otherwise meet criteria for transfusion, *don't transfuse*

Adapted from *www.choosingwisely.org*

High risk for transfusion AEs: Sickle cell disease patients

Choosing Wisely®
An initiative of the ABIM Foundation

ASH Choosing Wisely (#7):

Don't routinely transfuse patients with sickle cell disease (SCD) for chronic anemia or uncomplicated pain crisis without an appropriate clinical indication.

- SCD patients are at higher risk for harm from unnecessary PRBC transfusion
  - alloimmunization to minor blood group antigens
  - iron overload
- Even most severe types of SCD (baseline hemoglobin 7-10 g/dl) usually tolerate further temporary hemoglobin reductions without symptoms.
  - IV fluids may contribute to a decrease in hemoglobin by 1-2 g/dL
  - routine transfusion in this setting should be avoided
- No evidence transfusion reduces SCD vaso-occlusive crisis pain!
- Guidance for transfusion in SCD is in the NHLBI 2014 guidelines

Adapted from *www.choosingwisely.org*

“Universal” blood and emergencies

Choosing Wisely®
An initiative of the ABIM Foundation

“Universal units”: O-negative RBCs, AB-positive (male) plasma

- Mitigate risks of ABO incompatibility
- Reduce risks of allosensitization to D

AABB Choosing Wisely (#5): Don’t transfuse O negative blood EXCEPT:

- **to O negative patients**
- **in emergencies for women of child bearing potential with unknown blood group.**

- O-negative PRBC units are in chronic short supply
  - Shortages are exacerbated by overutilization for patients who are not O-negative
  - Common practice during shortages to transfuse O-positive in males, use low titer anti-A plasma

Adapted from *www.choosingwisely.org*

Blood testing for transfusion: Monitoring recommendations

Choosing Wisely®
An initiative of the ABIM Foundation

AABB Choosing Wisely (#4):

Don't perform serial blood counts on clinically stable patients.

- Unless bleeding or otherwise unstable, transfusion (PRBCs or platelets) should use the results from the first labs of the day
- Multiple blood draws to recheck the transfusion threshold can lead to:
  - excessive phlebotomy
  - iatrogenic anemia
  - unnecessary transfusions

Limit blood draws!!

Adapted from *www.choosingwisely.org*

When not to use plasma and PCCs: Warfarin reversal

Choosing Wisely®
An initiative of the ABIM Foundation

AABB Choosing Wisely (#3):

Don't routinely use blood products to reverse warfarin.

ASH Choosing Wisely (#4):

Don't administer plasma or prothrombin complex concentrates for non-emergent reversal of vitamin K antagonists
(i.e. outside of the setting of major bleeding, ICH, or emergency surgery)

- Rationale: blood products have risks, are costly, and are rarely indicated
- Most patients can be reversed with holding warfarin and/or vitamin K
- For serious bleeding or emergency surgery / invasive procedures only:
  - prothrombin complex concentrates (PCCs)
  - (plasma)

Adapted from *www.choosingwisely.org*

When to transfuse plasma

- Preoperative or bleeding patients who require replacement of multiple coagulation factors *(e.g.,* liver disease, DIC)
- Patients undergoing massive transfusion
- Patients on warfarin who are actively bleeding or in need of an immediate invasive procedure
- Patients with coagulation factor or plasma protein deficiencies, congenital or acquired, for which no specific products are available (e.g. FXI, C1 inhibitor)
- Thrombotic thrombocytopenic purpura (TTP)

See lectures on coagulation for underlying disorders and management

When to transfuse platelets?

- Thresholds for platelet transfusion are evolving: the general trend is towards more conservative use of platelet transfusion
  - PLADO trial
  - Pragmatic use of a scarce resource
- Thrombocytopenia: correction of quantitative defects
  - Prophylactic transfusion: historically PLT <10k, but PLADO trial used threshold < 5K
  - For invasive procedures, trauma, and active bleeding in patients with moderate to severe thrombocytopenia
  - Rapidly falling platelet count with active bleeding or significant consumption
- Platelet dysfunction: correction of qualitative defects
  - Consider functional platelet count to be the predicted post-transfusion platelet count

See lectures on thrombocytopenia for causes and management

THANK YOU!

Head and Neck Cancer

11th Annual Comprehensive Hematology and Oncology Review Course

Cristina P. Rodriguez, MD
Associate Professor
University of Washington

Disclosures

	Cristina Rodriguez(Presenter)	**Stephen Smith (spouse)**
Institutional Research Funding	AstraZeneca Ayala Bristol Myers Squibb Cue Biopharma Kura Merck	AcertaPharma AstraZeneca Genentech Incyte Merck Pharmacyclics Portola Seattle Genetics
AdvisoryBoard/ Consultancy	Cue Biopharma	Astra Zeneca Merck

I. Mucosal Squamous Cell Carcinomas

- epidemiology and pathogenesis
- staging
- treatment
  - locally advanced disease
    - unresectable/organ preservation
    - postoperative therapy
  - metastatic disease

II. Thyroid Cancer

III. Salivary Gland Cancer

Part I

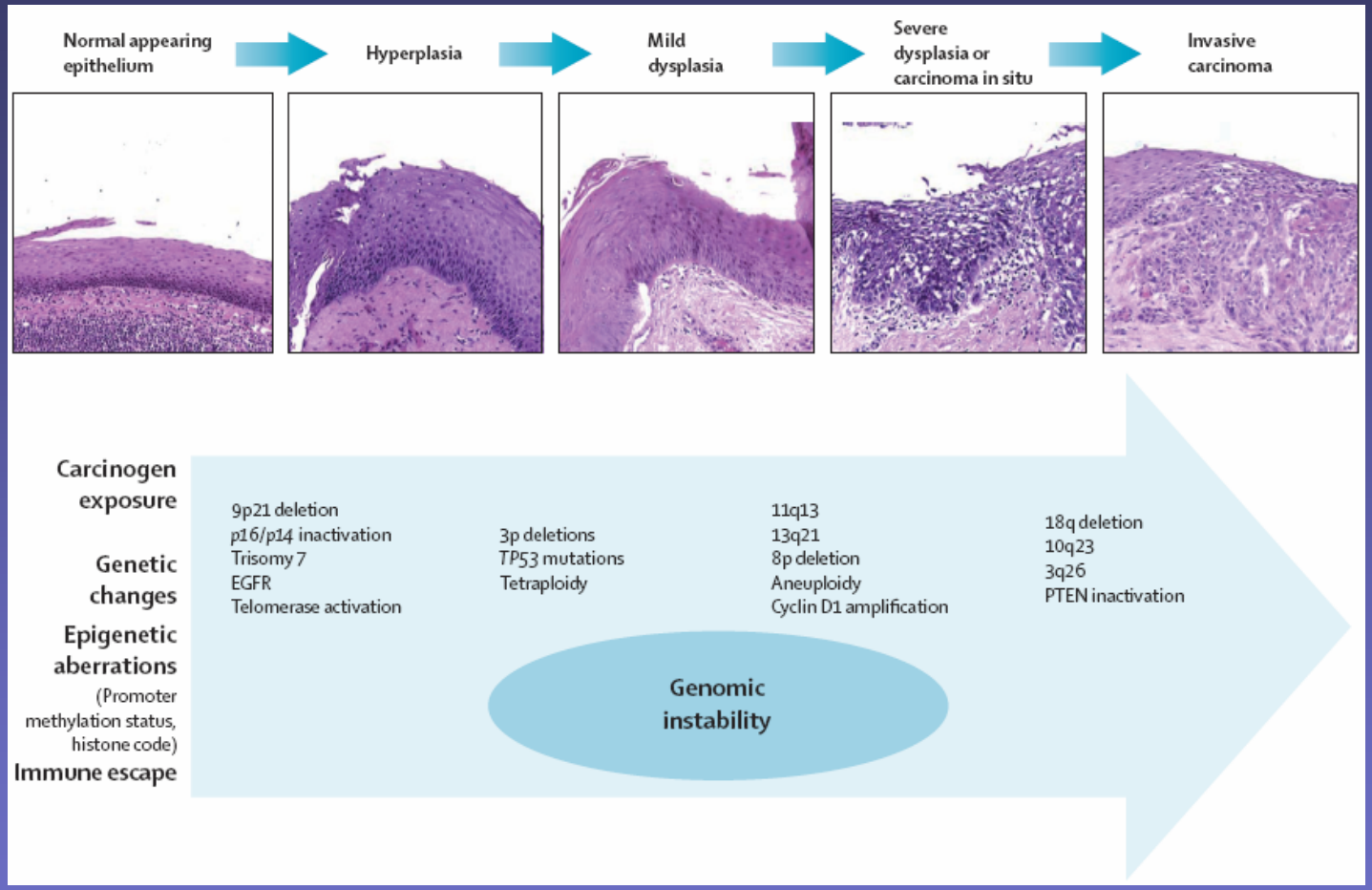
Mucosal squamous cell carcinomas of the head and neck

Pathogenesis

Causally linked to exposure to

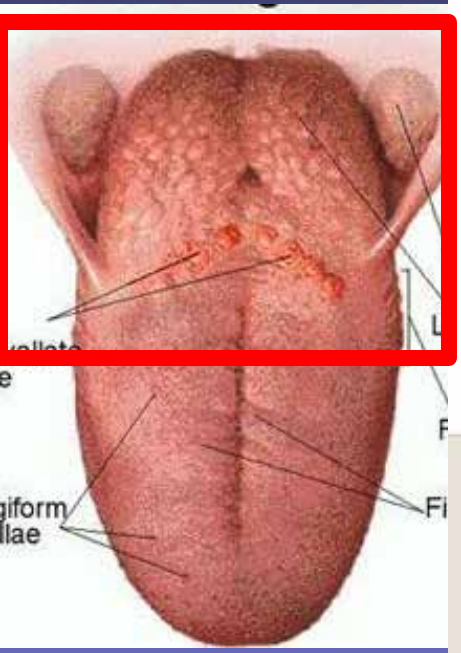
1. Tobacco and alcohol
   - oral cavity, larynx, hypopharynx
   - declining in incidence
   - economic and racial disparity
2. Viral infection
   - HPV in oropharynx, increasing incidence
   - EBV in nasopharynx

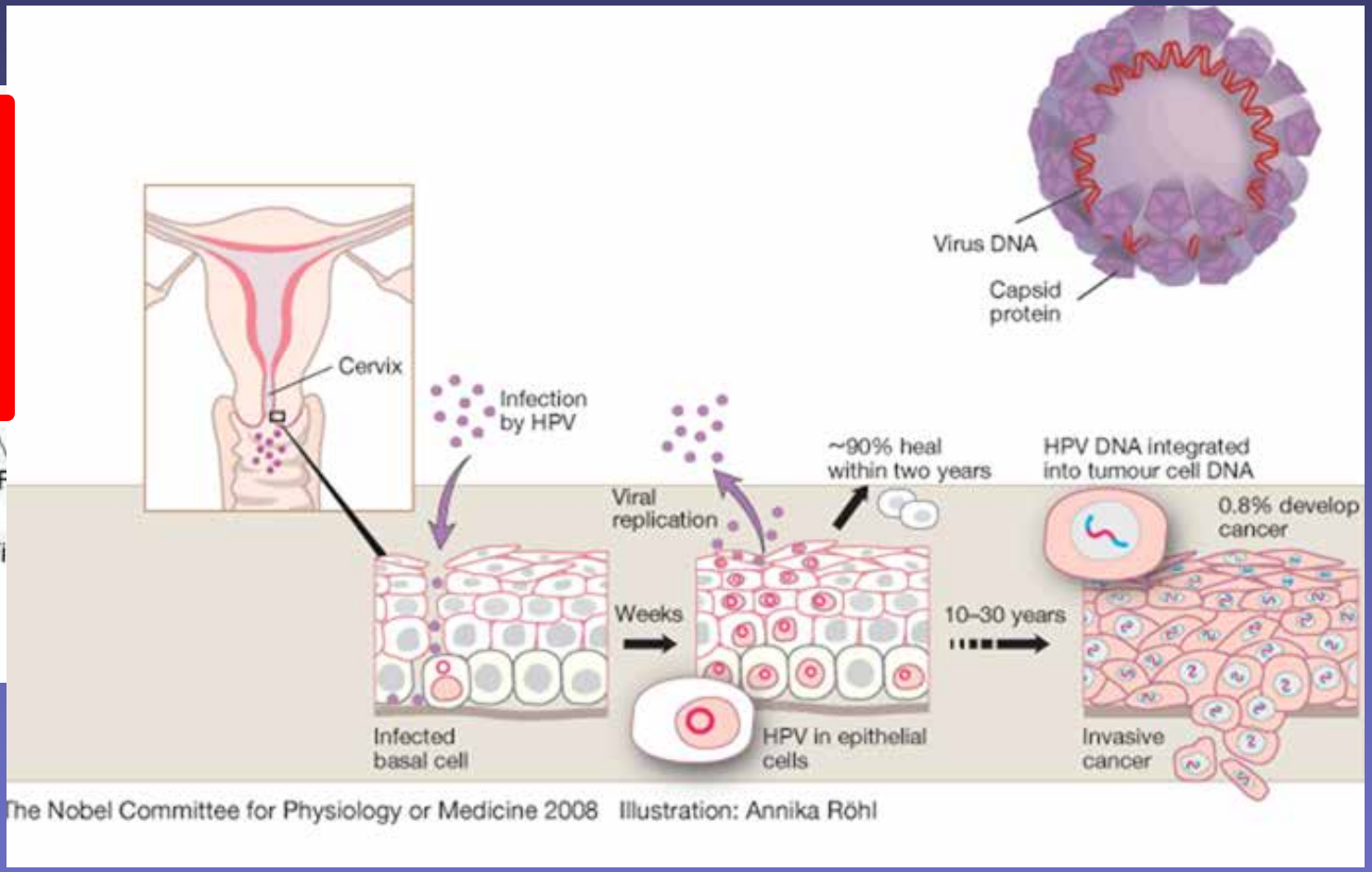
Tobacco and Alcohol



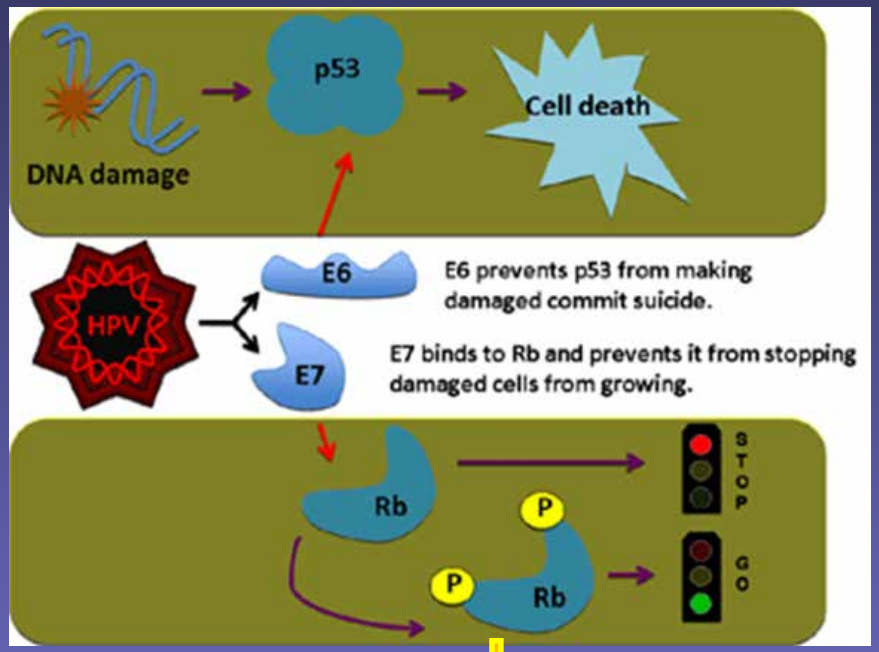
Argiris et al. Lancet. 2008 May 17;371(9625):1695-709.

The oropharynx and HPV16

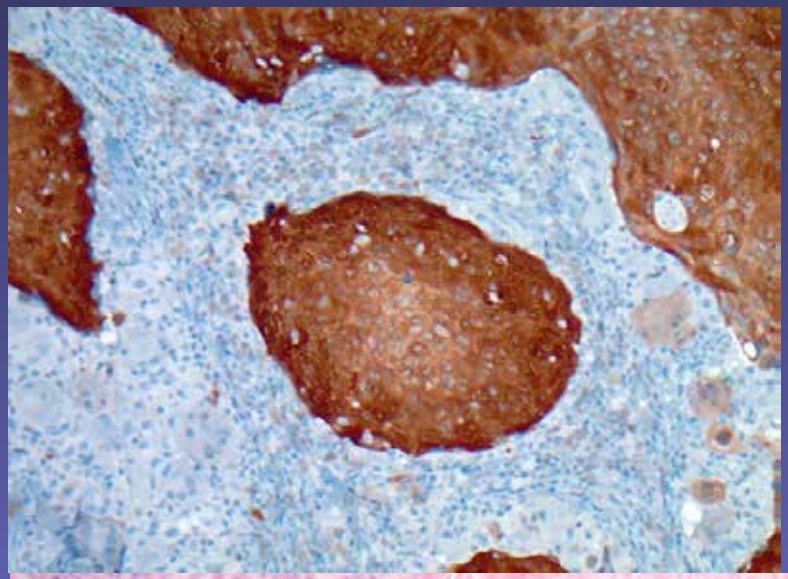


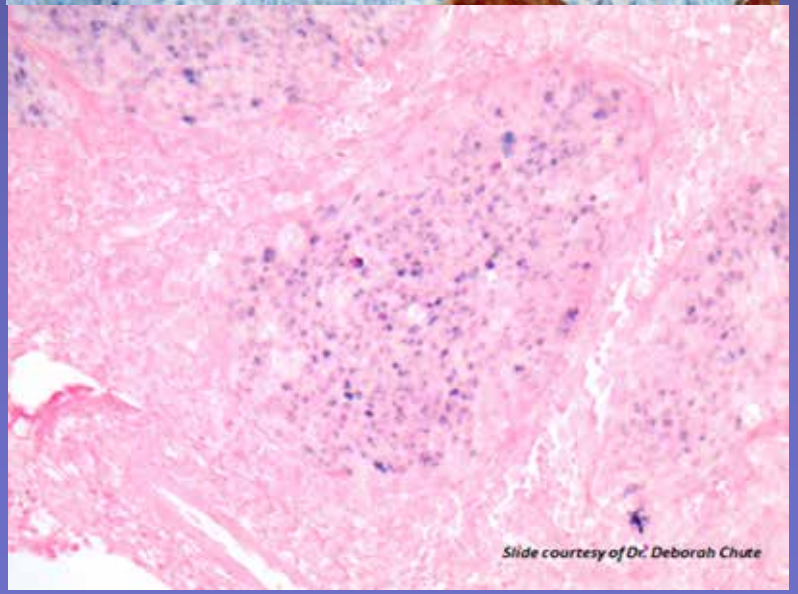


HPV and p16



p16 upregulation





http://genetics.thetech.org/ask/ask359

Patient Characteristics

	HPV related	Non HPV related
Median age	58	68
Race	Caucasian	Higher proportion of African Americans and minorities
Sex	Male	Male
Risk Factors	Sexual activity	Tobacco Alcohol
Performance Status	Minimal comorbidity	Frequent vascular, cardiac, pulmonary comorbidity

Tumor Characteristics

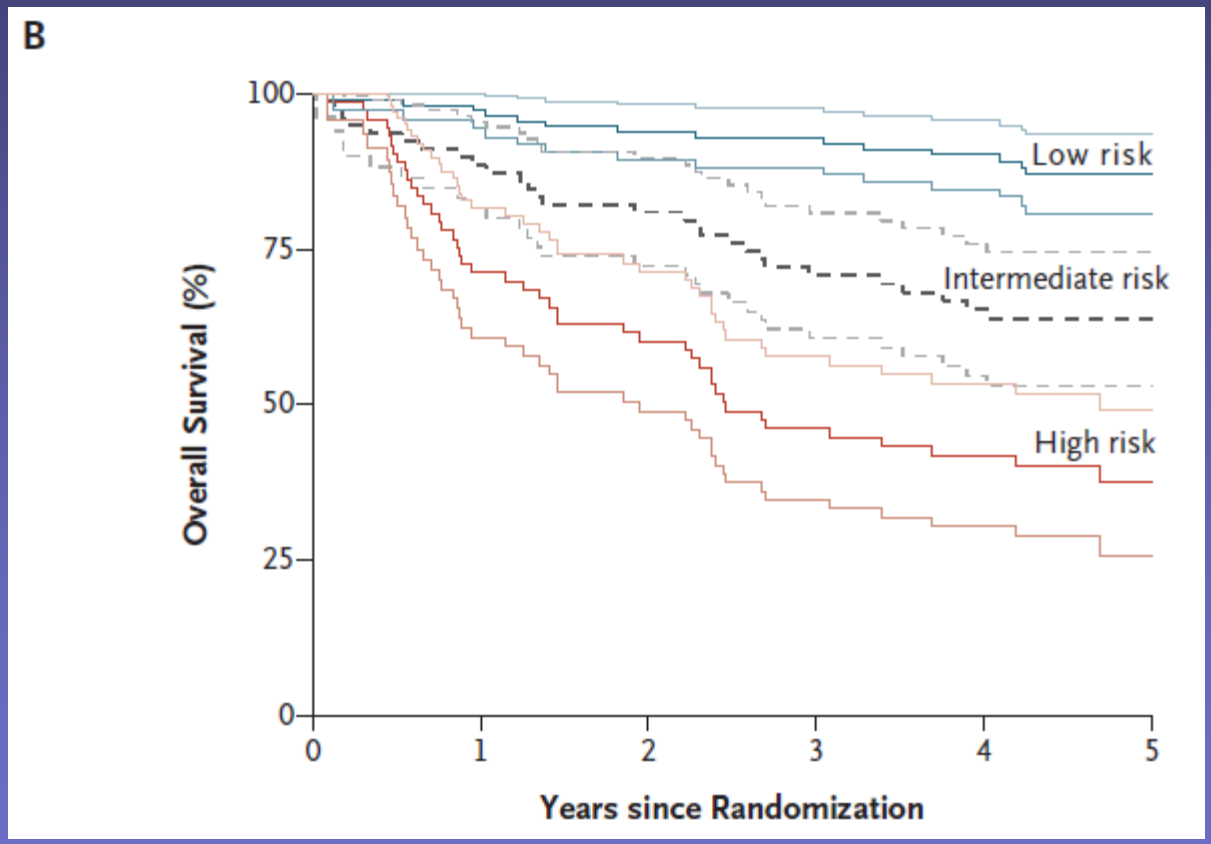
	HPV related	Non HPV related
Subsite	Tonsil Base of tongue	Oral tongue Larynx/Hypopharynx
T/N at presentation	Small T, large N Cystic lymph node appearance	Bulkier primary tumors
Tumor differentiation	Poorly differentiated, nonkeratinizing, basaloid	Well to poorly differentiated
P53, Rb status	Wild type	Mutant

Clinical Behavior

	HPV related	Non HPV related
Chemotherapy responsiveness	High	Lower
Prognosis in curative setting	Excellent 5 year survival	Low rate of long term survivors
Survival expectation in R/M setting	~24 mos	~9mos
Failure patterns	Late recurrences Non pulmonary metastases	Distant, mostly lung Second primary tumors due to condemned mucosa

HPV+ OPC is heterogeneous

RTOG 0129



Ang KK et al. N Engl J Med. 2010 Jul 1;363(1):24-35.

Key points on HPV+OPC

- IHC for p16 is highly correlated with HPV-positivity ***in the oropharynx***
- Completion of HPV+ clinical trials have established standards of care
- Treatment deescalation remains a research question in active investigation

Staging

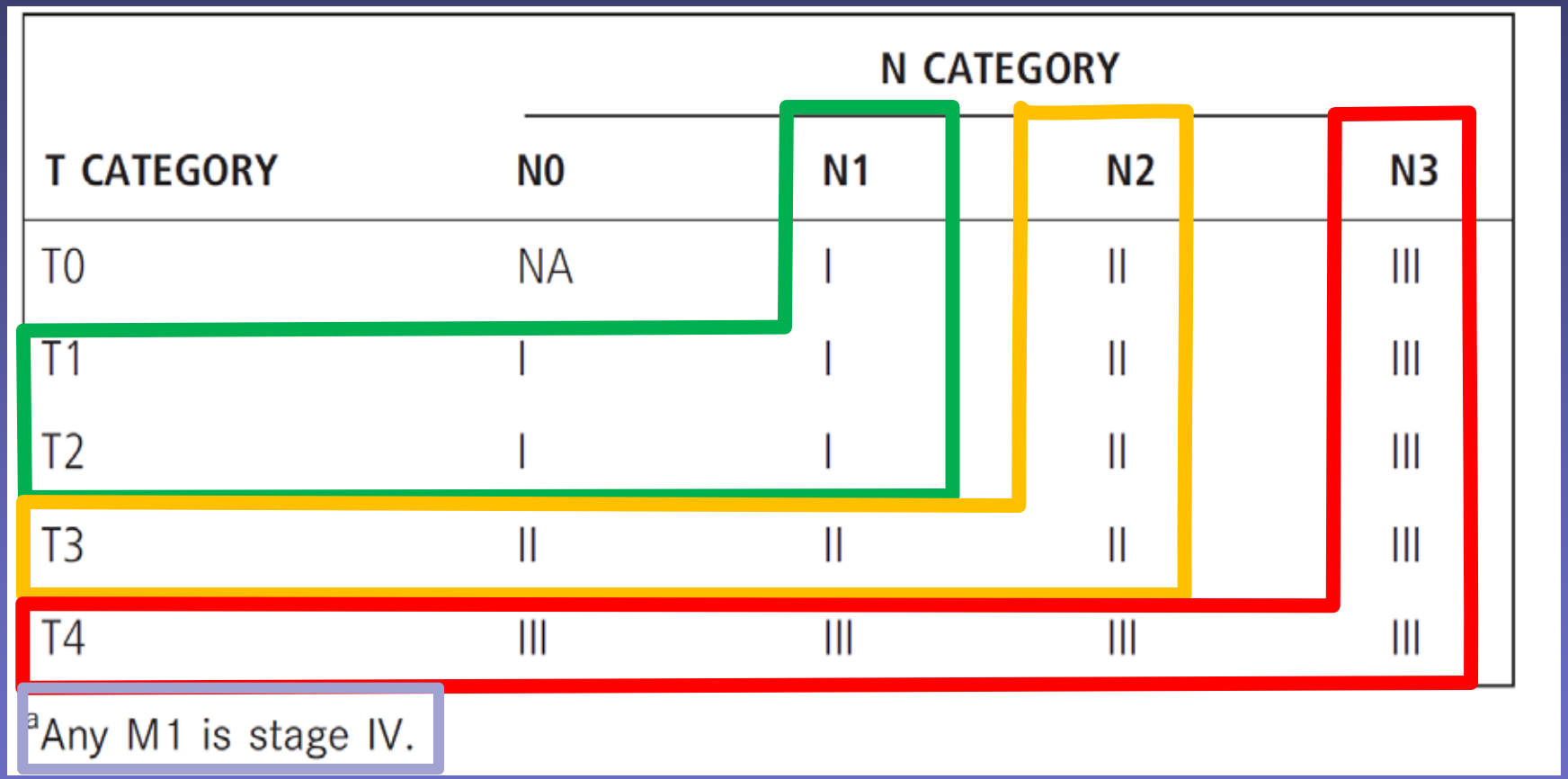
- General Principles:
  - T1-2 lesions small
  - T4 lesions invade into surrounding structures
  - N3 >6cm nodes
- Unknown primaries (Tx)
  - Occur in 10-13% of cases
  - Curable
- **HPV related OPC is now staged separately**

STAGING: AJCC v. 8
NonHPV related

Stage I	T1	N0	M0	15% new diagnoses Surgery or XRT with curative intent 70% or greater 5 year Overall Survival
Stage II	T2	N0	M0	
Stage III	T3 T1-3	N0 N1	M0 M0	75% of new diagnoses Curable with multimodality therapy Usually chemotherapy + XRT 30-50% 5 year over all survival
Stage IVA	T4a T1-4a	N0-1 N2	M0 M0	
Stage IVB	T4b Any T	Any N N3	M0 M0	
Stage IVC	Any T	Any N	M1	10% new diagnoses Incurable, median survival <1 yr

AJCC Cancer Staging Manual, Seventh Edition (2002)

STAGING: AJCC v. 8
HPV related OP Cancer



T CATEGORY	N CATEGORY N0	N1	N2	N3
T0	NA	I	II	III
T1	I	I	II	III
T2	I	I	II	III
T3	II	II	II	III
T4	III	III	III	III

[a]Any M1 is stage IV.

AJCC Cancer Staging Manual, Seventh Edition (2002)

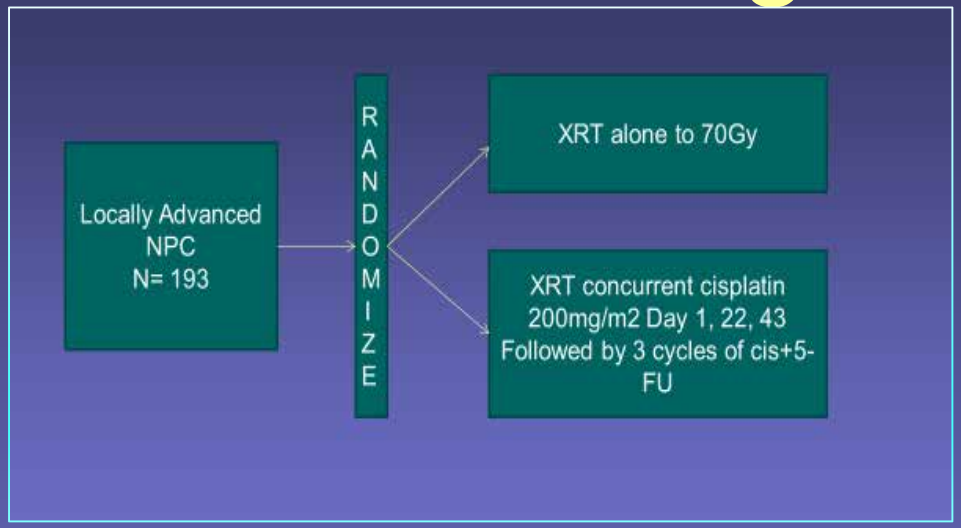
Locally Advanced Disease

- Curative intent approach is possible
  - Surgery (preferred for oral cavity)
  - Radiation
  - Chemotherapy as a single modality: NOT curative
- Multidisciplinary assessment is critical
- Functional outcome/ long term QOL

Organ Preservation: Nasopharyngeal Carcinoma

- Epidemiologically distinct
- EBV associated
- Unresectable at diagnosis
- Classic presentation:
  - Middle ear effusions in adults
  - Level V (post triangle) LAD
- Intuitive subset to explore nonsurgical, curative intent therapy

Nasopharyngeal carcinoma: Intergroup 0099



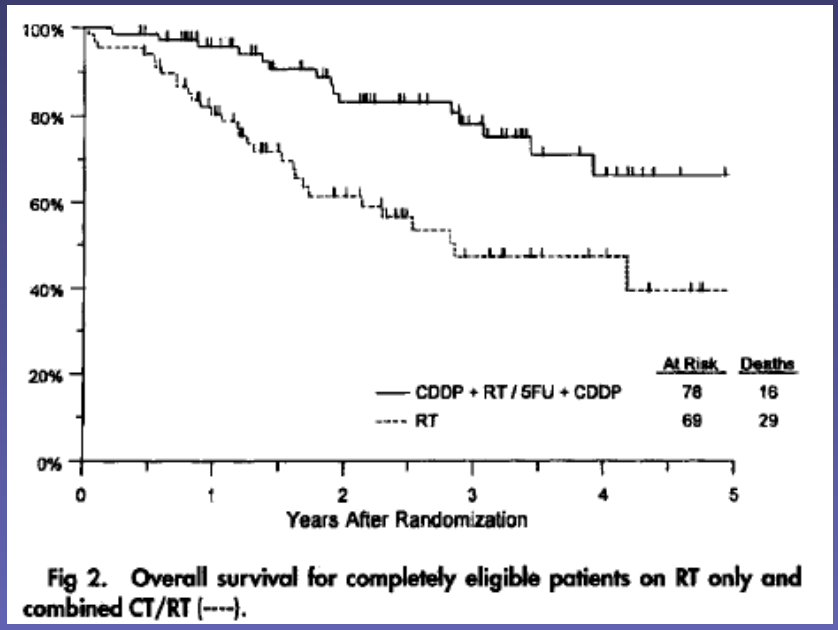
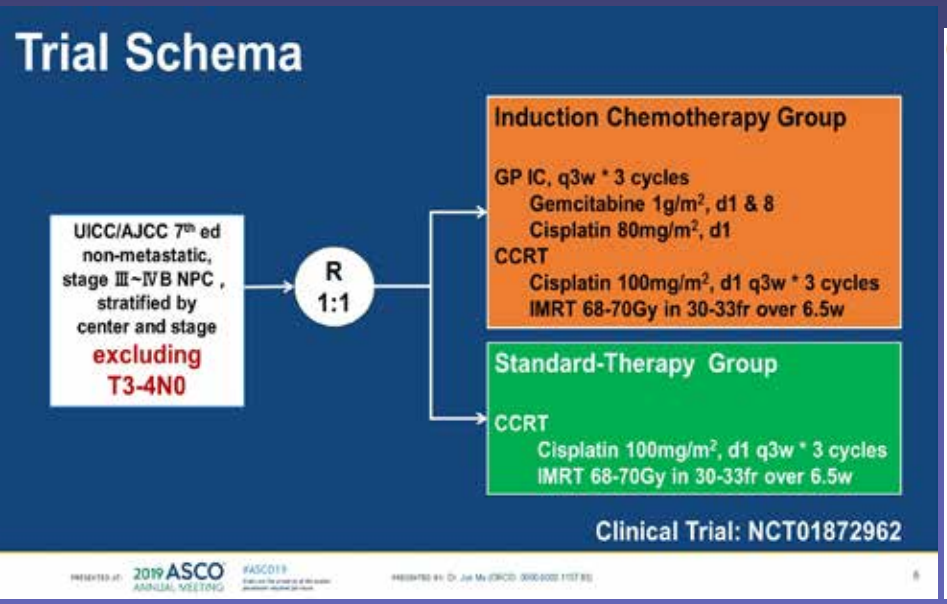


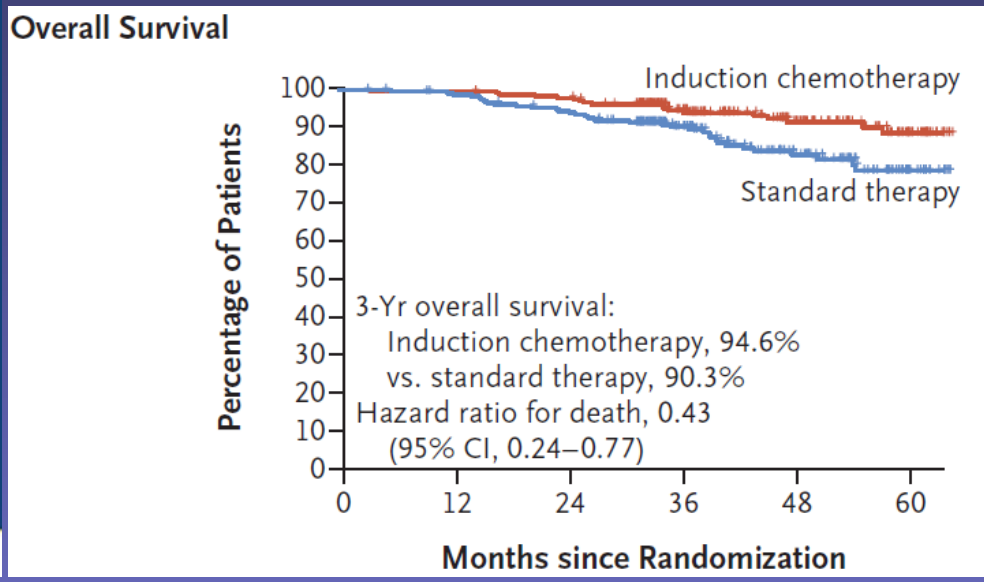
Fig 2. Overall survival for completely eligible patients on RT only and combined CT/RT (----).

- PFS and OS advantage to experimental arm
- Subsequent RCTs in SE Asia have shown no advantage to adjuvant chemo

Al- Sarraf. J Clin Oncol 16:1310-1217 1998

Induction chemotherapy: Nasopharyngeal Carcinoma





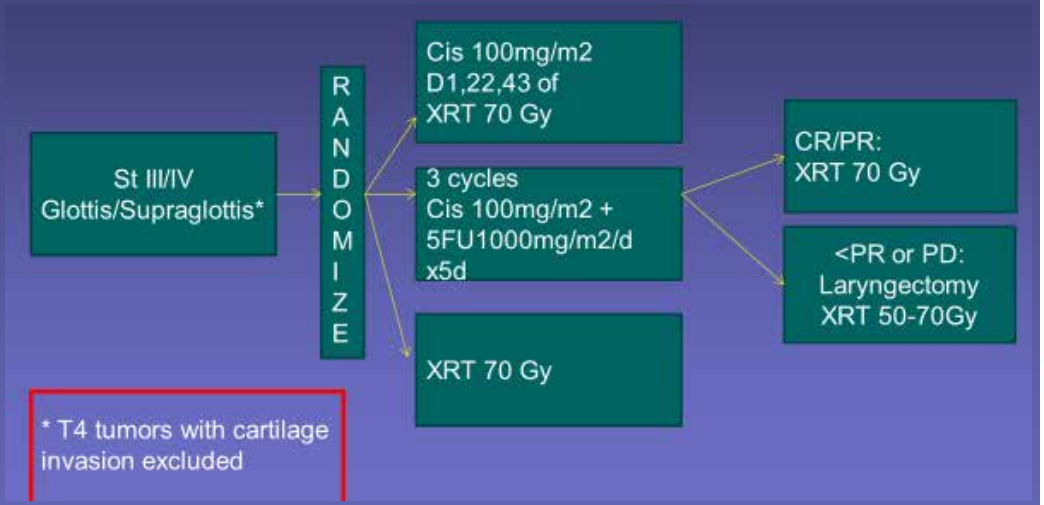
- RFS and distant FFS superior in Exp arm.

Zhang et al. N Engl J Med. 2019 May 31

Organ Preservation: Laryngeal Carcinoma

- Laryngectomy was historical standard of care
- VA Larynx Trial (NEJM 1991)
  - Randomized phase III larynx study
  - surgery vs. chemo followed by XRT for responders
  - 64% in experimental arm had successful organ preservation
  - OS similar, attributed to successful surgical salvage

Landmark Studies in Organ Preservation: Larynx Ca RTOG 91-11



Forastiere AA et al. NEJM. 2003; 22(349) 2091-98.

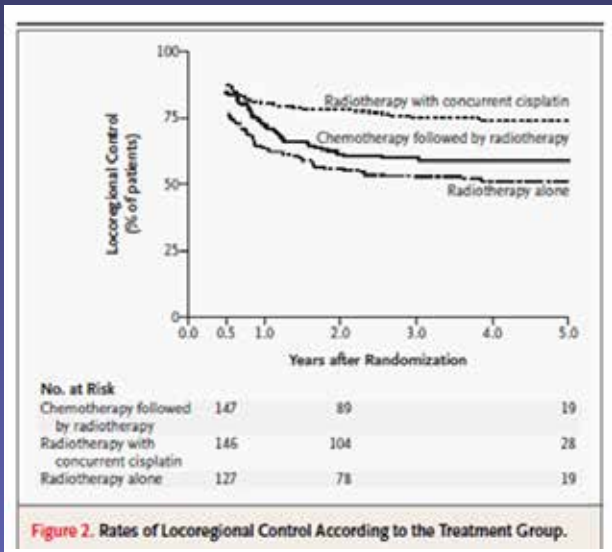


Figure 2. Rates of Locoregional Control According to the Treatment Group.

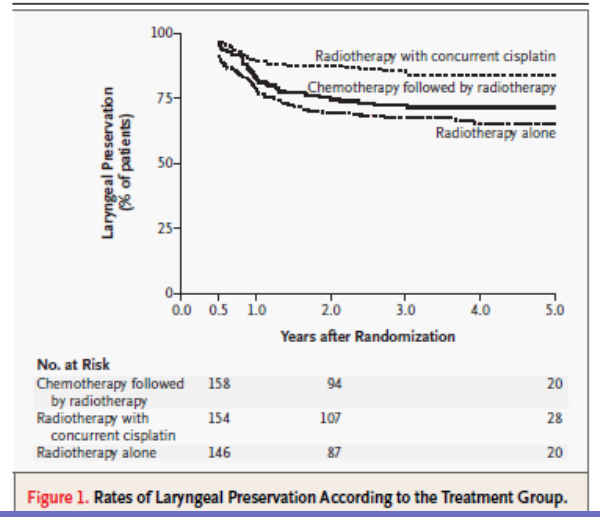


Figure 1. Rates of Laryngeal Preservation According to the Treatment Group.

Organ Preservation: Larynx Cancer RTOG 91-11

Table 2. Grade 3 or 4 Acute Toxic Effects, According to the Treatment Group.*

Toxic Effect	Cisplatin plus Fluorouracil Followed by Radiotherapy						Radiotherapy with Concurrent Cisplatin (N=171)			Radiotherapy Alone (N=171)		
	Chemotherapy Period (N=168)			Radiotherapy Period (N=156)								
	grade 3	grade 4	total	grade 3	grade 4	total	grade 3	grade 4	total	grade 3	grade 4	total
	number of patients (percent)											
Hematologic	43	44	87 (52)	13	10	23 (15)	64	17	81 (47)	3	2	5 (3)
Infection	4	5	9 (5)	2	0	2 (1)	7	0	7 (4)	2	0	2 (1)
Mucosal (stomatitis)	27	7	34 (20)	36	2	38 (24)	64	9	73 (43)	40	1	41 (24)
Pharyngeal or esophageal	—	—	—	30	0	30 (19)	60	0	60 (35)	32	0	32 (19)
Laryngeal	—	—	—	20	1	21 (13)	29	2	31 (18)	23	5	28 (16)
Dermatologic (in radiation field)	—	—	—	16	0	16 (10)	10	2	12 (7)	15	0	15 (9)
Nausea or vomiting	20	3	23 (14)	0	0	0	28	7	35 (20)	0	0	0
Renal or genitourinary	3	0	3 (2)	2	0	2 (1)	6	1	7 (4)	0	0	0
Neurologic	5	1	6 (4)	0	0	0	8	1	9 (5)	0	0	0
Other	20	7	27 (16)	16	2	18 (12)	58	11	69 (40)	9	1	10 (6)
Overall maximal severity	62	49	111 (66)	66	13	79 (51)	99	32	131 (77)	71	9	80 (47)

Forastiere AA et al. NEJM. 2003; 22(349) 2091-98.

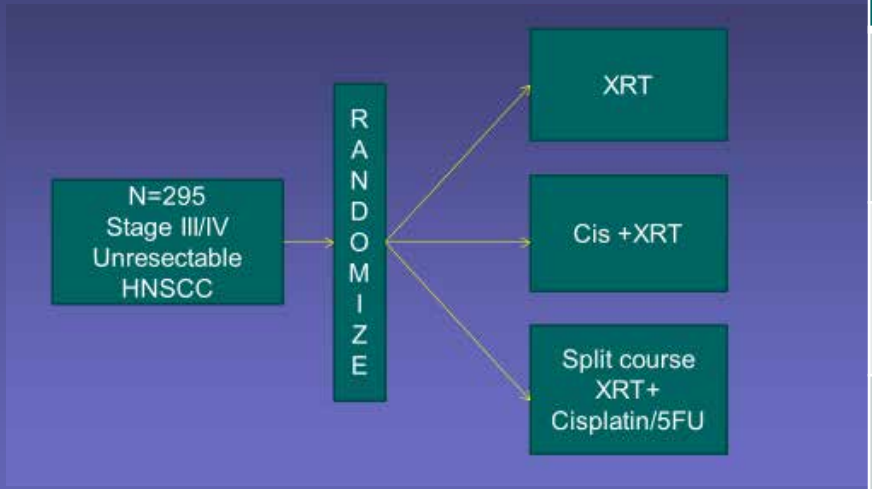
Landmark Studies in Organ Preservation: RTOG 91-11

- Distant metastasis decreased in groups receiving chemotherapy
- Overall survival not significantly different among treatment groups
  - Success of salvage surgery
- Long term results reported in 2013
  - Results hold up with 6.9 years median F/U

Forastiere AA et al. NEJM. 2003; 22(349) 2091-98.

Forastiere A et al. J Clin Oncol. 2013 Mar 1;31(7):845-52.

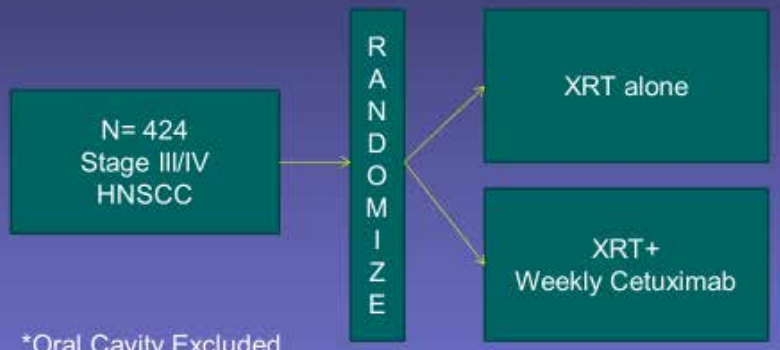
Organ Preservation: Intergroup Study



	Arm A XRT	Arm B cisXRT	Arm C splitXRT
OS (3yr)	23%	**37% A vs B p=0.14**	27%
DSSurvival (3yr)	33%	**51% A vs B p=0.01**	41%
Distant Failure	17.9%	21.8%	19.1%
Toxicity	51%	**85% A vs B p<.0001**	**72% A vs C P<.0001**

Adelstein et al. J Clin Oncol, 2003; 21(1):92-8.

Organ Preservation with cetuximab: Bonner Study



	XRT alone	XRT+ Cetux	p Value
LRCl(3yr)	34%	**47%**	p<.01
PFS(3yr)	31%	**37%**	p=.04
OS(3yr)	45%	**55%**	p=.05
Gr ≥3 toxicity	52%	56%	ND

Bonner JA. NEJM 2006:354:567-78.

Landmark Studies in Organ Preservation: Bonner Study

- 60% had oropharynx primaries
  –Subsequent HPV testing shows lower (but present) magnitude of benefit in HPV negative OP pts
- No impact on distant metastatic failure rate
- No identifiable biomarker for response
- Control arm not regarded as standard of care
  – RTOG 1016 with published showing inferiority compared to cis+XRT in HPV+ population

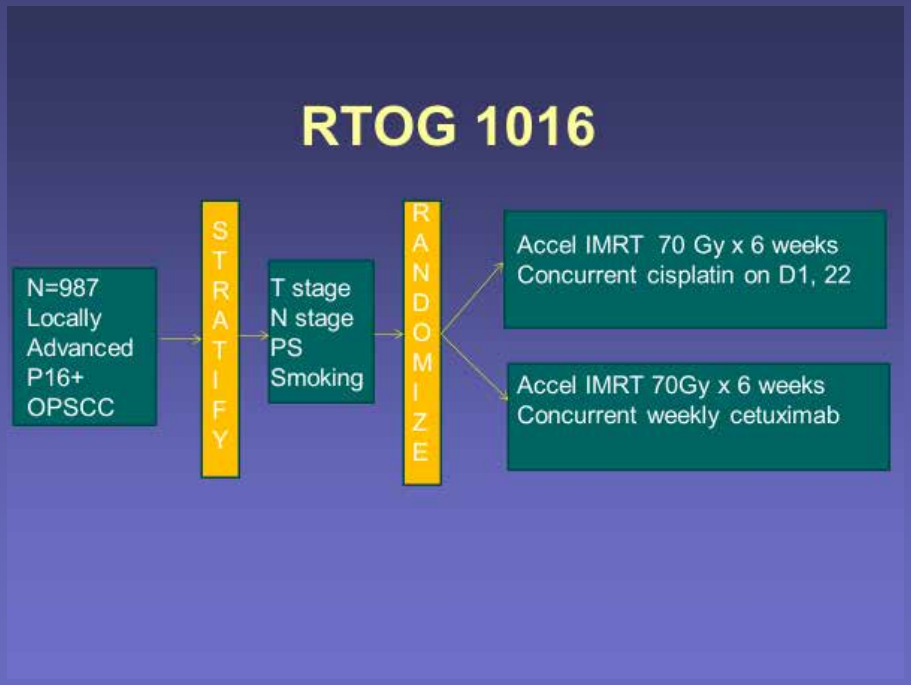
Bonner JA. NEJM 2006:354:567-78.

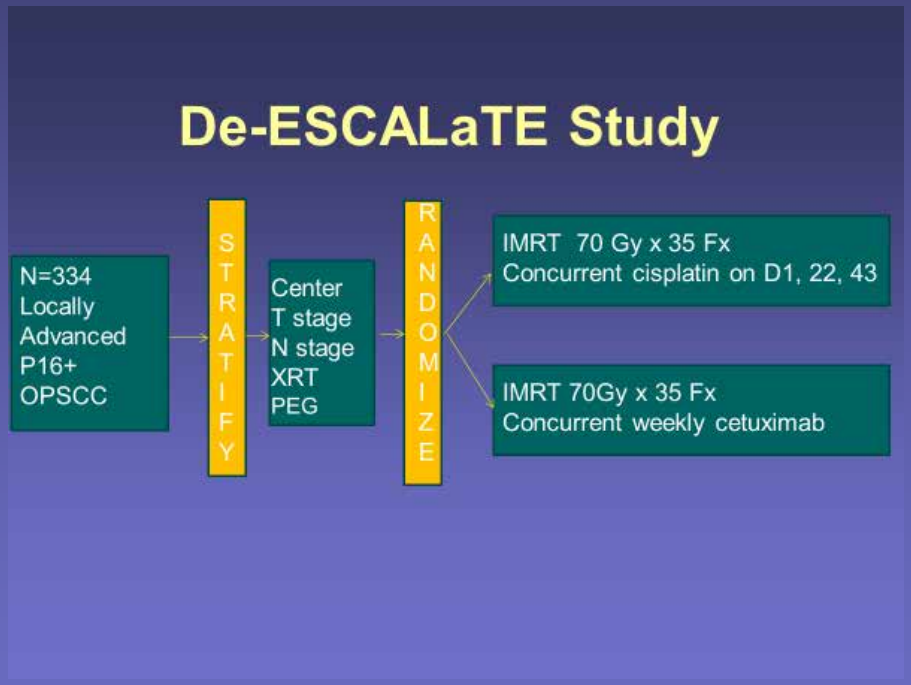
Rosenthal et al. J Clin Oncol. 2016 Apr 20;34(12):1300-8

Organ Preservation: Oropharyngeal Carcinoma

- Recognition of superior prognosis
- Therapeutic standards developed in preHPV era
  - Toxicities of concern, overtreatment
- Treatment deescalation an intuitive direction

Organ Preservation: Oropharyngeal Carcinoma

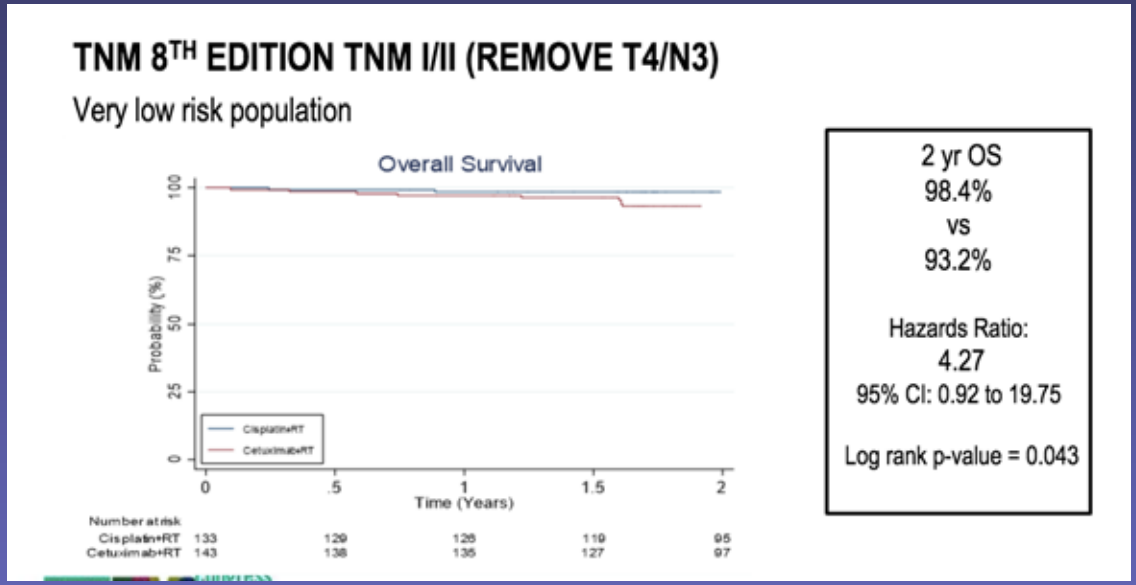




Gillison et al. Lancet.2019 Jan 5;393(10166):40-50
Mehanna et al. Lancet. 2019 Jan 5;393(10166):51-60

Phase III clinical trials in HPV + OPC

- RTOG 1016 and De-ESCALaTE
  - Superiority of cisplatinXRT vs. CetuxXRT in OS, LRC
  - No difference in acute/late tox
  - T score higher in cisXRT in 1016



De-escalation remains a research question in HPV+ OPC

Gillison et al. 2019 Jan 5;393(10166):40-50
Mehanna et al. Lancet. 2019 Jan 5;393(10166):51-60

Functional Imaging after definitive chemoradiation

- Planned neck dissections (ND) post chemoXRT was standard of care for N3 or bulky N2b disease
- PET-NECK randomized 564 pts to ND vs. surveillance with PET-CT at 12 weeks post CRT
- Necks with nonPETavid LNs <1cm observed in exp arm
- Less NDs done in exp arm, no difference in OS

Mehanna et al. N Engl J Med. 2016 Apr 14;374(15):1444-54

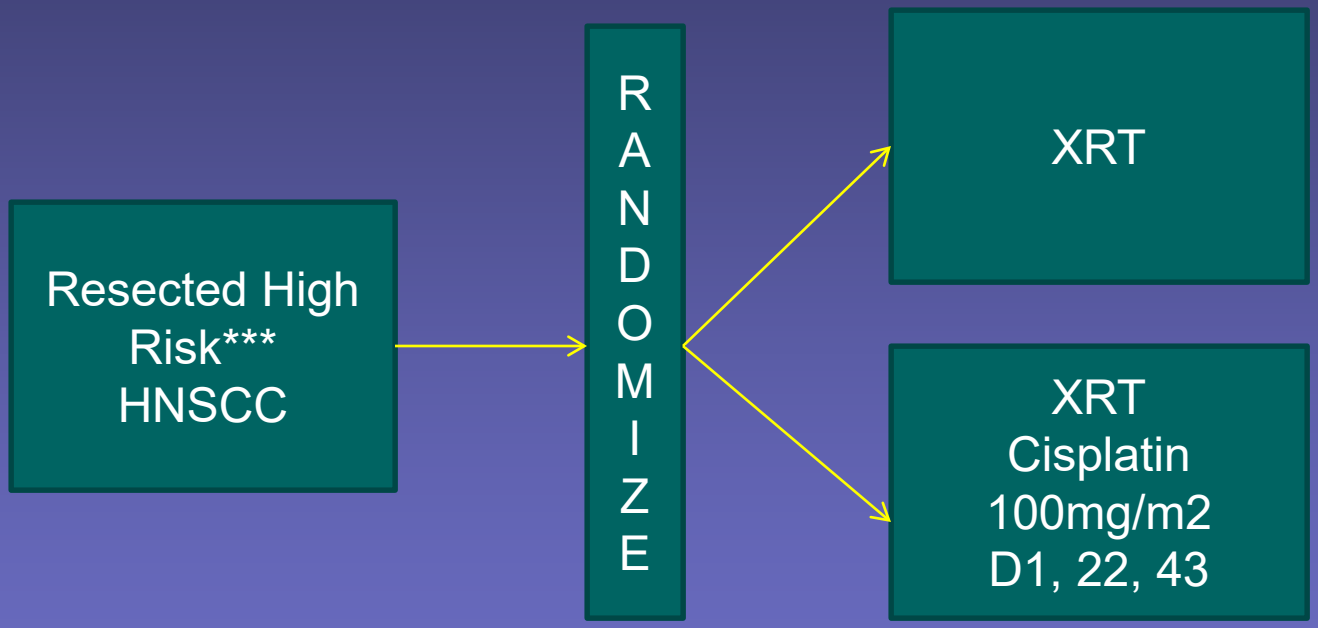
KEY POINTS: Locally advanced disease

- Organ preservation/unresectable disease
  - Concurrent bolus cisplatin based chemoradiation supported by RTOG 91-11, Intergroup, RTOG 1016, DE-ESCALaTE, Intergroup 099
  - CetuximabXRT is inferior to cisXRT in the HPV+OPC
  - Neoadjuvant gem/cis for locally advanced NPC with nodal burden
- PET-CT can be used after chemoXRT to guide need for neck dissection

KEY POINTS: Locally advanced disease

- A multidisciplinary approach is essential
- Patient selection is critical
  - Not everyone is meant for nonsurgical treatment approach
  - Remember exclusion criteria in organ preservation studies
- Deescalation in HPV+ remains a research question

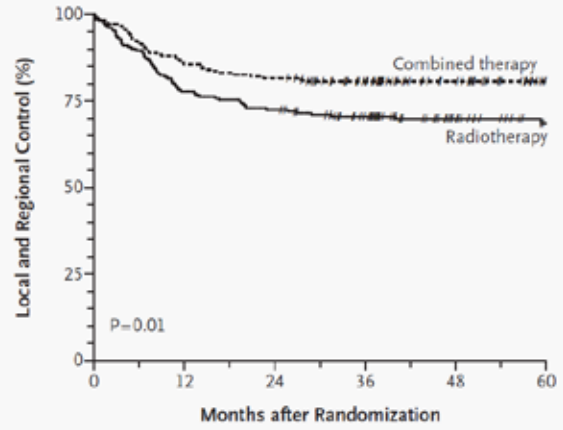
Postoperative therapy RTOG and EORTC studies



*** Eligibility criteria varied in 2 studies

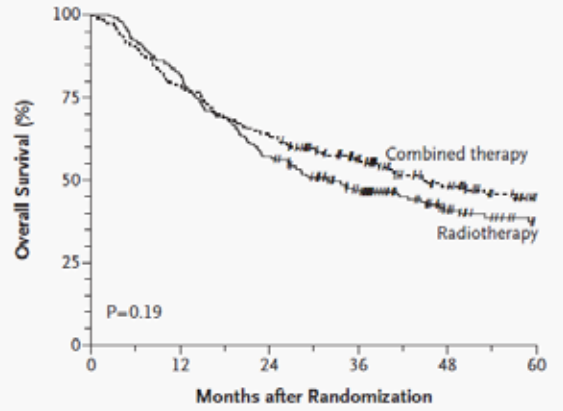
Bernier et al. N Engl J Med. 2004;350(19):1945
Cooper et al. N Engl J Med. 2004;350(19):1937

RTOG 9501



No. at Risk			
Combined therapy	206	123	26
Radiotherapy	210	108	24

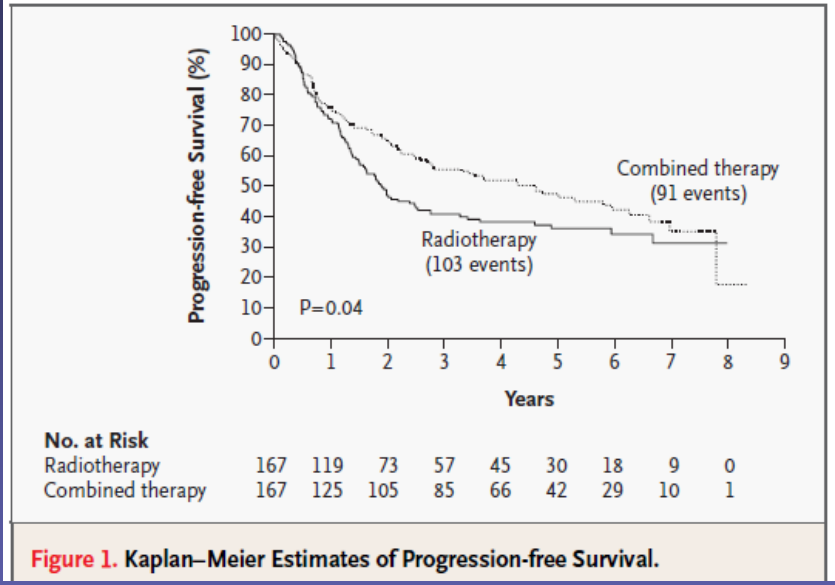
Figure 1. Rates of Local and Regional Control.



No. at Risk			
Combined therapy	206	132	27
Radiotherapy	210	120	26

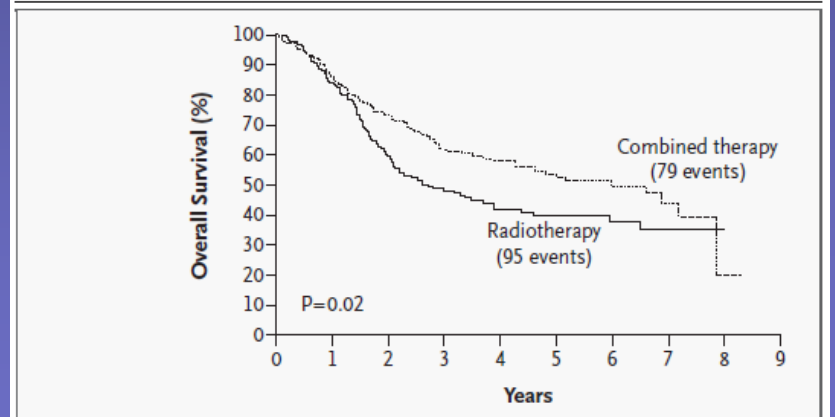
Figure 3. Kaplan–Meier Estimates of Overall Survival.
Overall survival did not differ significantly between groups (P=0.19 by the log-

EORTC 22931



No. at Risk									
Radiotherapy	167	119	73	57	45	30	18	9	0
Combined therapy	167	125	105	85	66	42	29	10	1

Figure 1. Kaplan–Meier Estimates of Progression-free Survival.



No. at Risk									
Radiotherapy	167	139	93	68	49	31	19	9	0
Combined therapy	167	141	118	93	72	47	33	11	1

Figure 2. Kaplan–Meier Estimates of Overall Survival.

Pooled Analysis

Overall survival advantage to Cisplatin + XRT for

- Positive surgical margin
- Extracapsular extension

LRC, PFS benefit confirmed

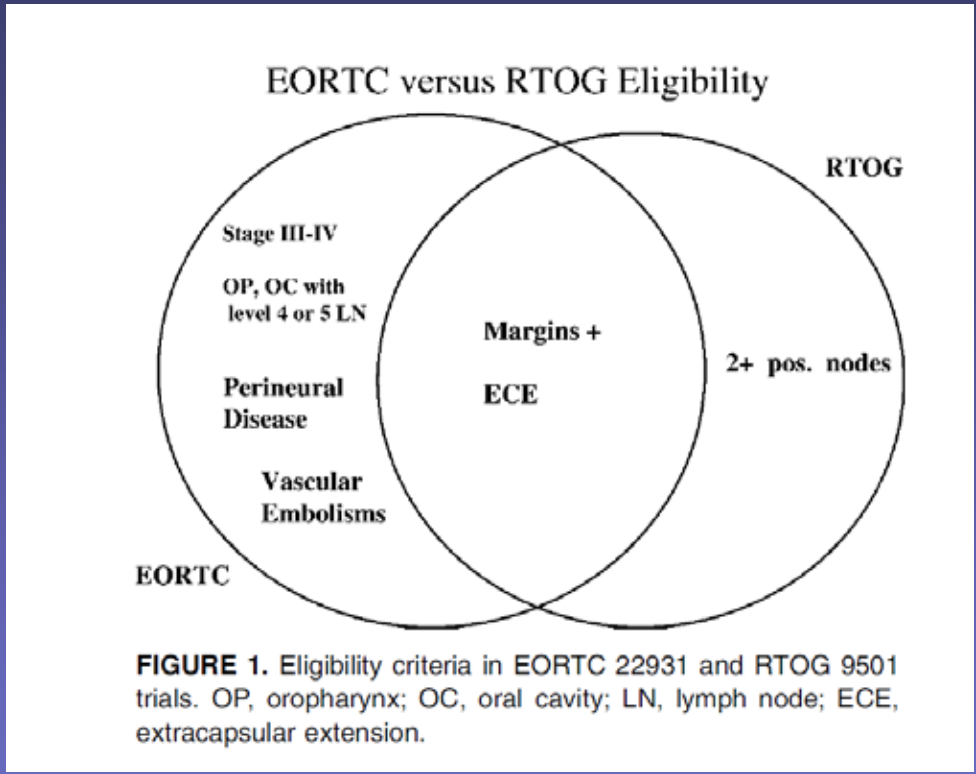


FIGURE 1. Eligibility criteria in EORTC 22931 and RTOG 9501 trials. OP, oropharynx; OC, oral cavity; LN, lymph node; ECE, extracapsular extension.

Bernier et al. Head Neck. 2005 Oct;27(10):843-50.

Alternative cisplatin dosing + XRT in postoperative setting

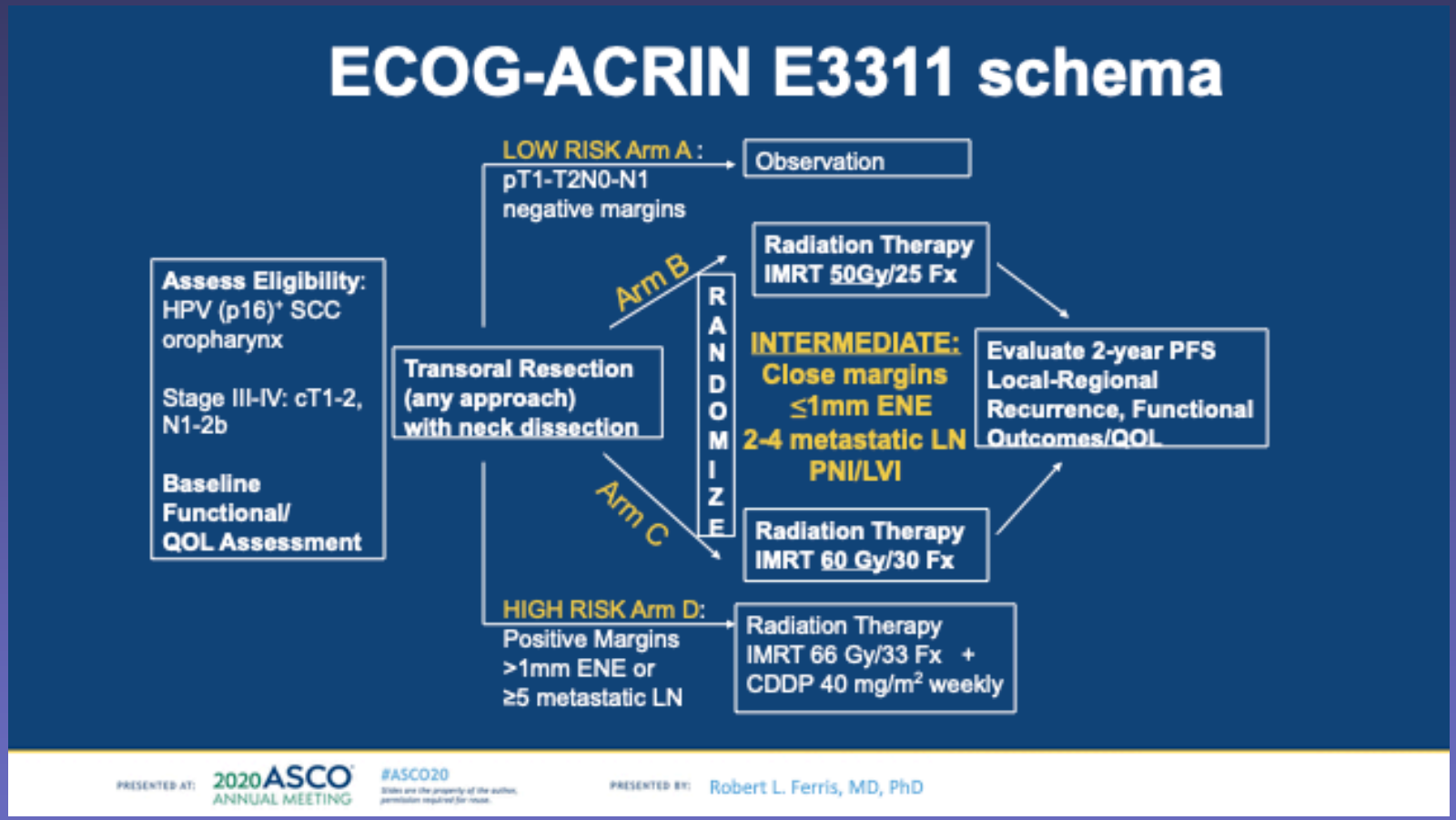
- Randomized phase III study of 30mg/m2 vs 100mg/m2
  - Indian population, mostly adjuvant post resection
  - Inferior LRC with weekly

***Noronha, et al JCO 2018*.**

- Randomized phase III study of 40mg/m2 vs 100mg/m2
  - Japanese study in adjuvant setting for high risk disease
  - Weekly dosing non-inferior

Kiyota et al. ASCO 2020 Abs 6502

Postop treatment in HPV+ OPC



- Arm B met 2 yr PFS threshold, will be compared to nonsurgical therapy

KEY POINTS: postoperative therapy

- High Risk pathologic features that benefit from concurrent cis+XRT:
  - Positive margins
  - Extracapsular nodal extension
- Most data is with 100mg/m2 on days 1,22, 43 of therapy
  - If weekly cisplatin given, use 40mg/m2

The Cisplatin Ineligible Patient

- No randomized data specific to population
  - This is changing

Trial	Treatment Population	N	Intervention
REACH **NCT02999087**	Stage III/IVb HNSCC	688	Avel + cis + RT vs cis + RT Avel + cetux + RT vs cis + RT
NRG-HN004 **NCT03258554**	Cisplatin-unfit locally advanced HNSCC	523	Durva + RT vs cetux + RT

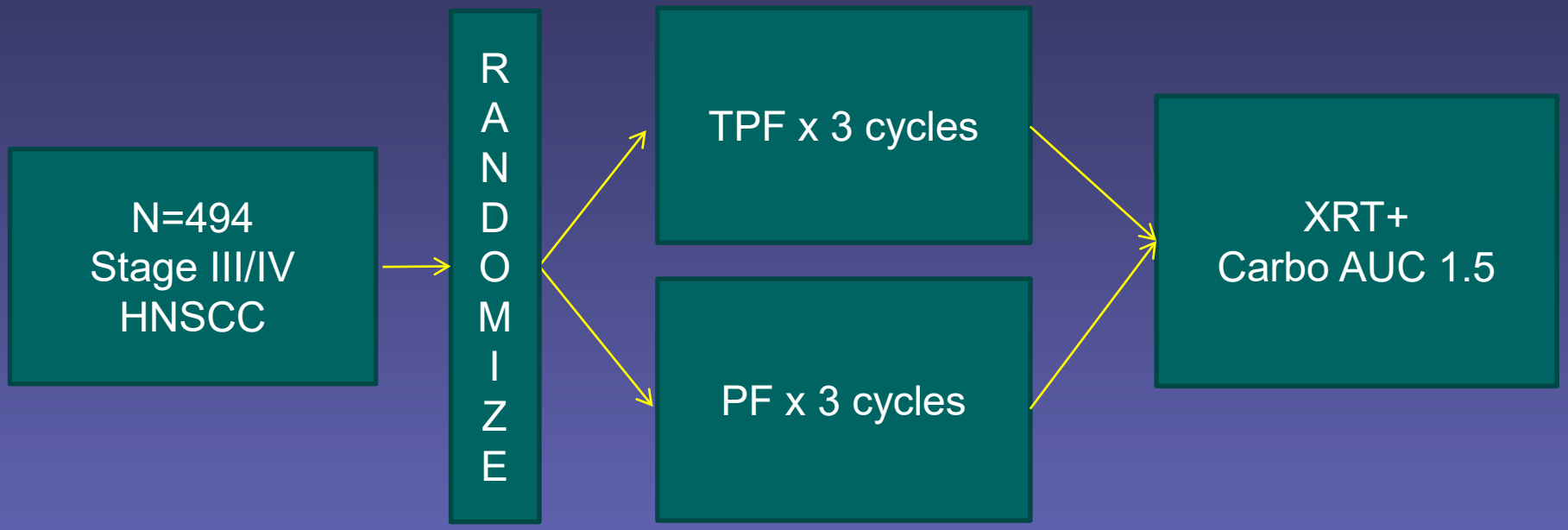
- No data in the postoperative setting

Non bolus cisplatin XRT regimens in Phase III trials

Trial	N	N(%) p16+ OPSCC	Arms	Results
GORTEC 9401[1]	226	Unknown	XRT vs Carbo+5FU XRT	OS DFS superior in carbo+F5u XRT
GORTEC 2007-01[2]	406	41(21%) of 236 OPC	CetuxXRT vs Carbo5FUCetuxXRT	PFS and LRC superior in Carbo5FUCetuxXRT
Bonner IMCL9815[3,4]	253	75(41%) of evaluable pts	XRT vs Cetux XRT	OS and LRC superior in CetuxXRT
TROG 12.01 NCT01855451	189	189 (100%)	Weekly cisplatin +70Gy Cetuximab +70Gy	Pending

[1]Denis et al. J Clin Oncol 2004
[2]Tao et al. J Clin Oncol 2018
[3]Rosenthal et al. J Clin Oncol 2015
[4]Bonner et al. N Eng J Med 2006

Induction Chemotherapy: TAX 324



RESULTS:

- OS, CR rates statistically better in TPF Arm
- Higher rates of hematologic toxicities in TPF arm, with some pts unable to proceed with XRT
- Controversial design due to control arm

Posner M et al. N Engl J Med. 2007 Oct 25;357(17):1705-15.

Induction vs. ChemoXRT trials

Trial	Design	Accrual	OS/PFS	Other findings
PARADIGM[1]	R Phase III TPF chXRT vs Cis XRT	Planned: 330 Actual: 145	No difference in 3 yr PFS and OS	Higher rate of Neutropenic Fever in Induction Arm
DECIDE[2]	R Phase III UofC ChXRT Vs TPF chXRT	Actual: 285	No difference in ORR, OS, PFS	No difference in distant failure

In both studies: control arm performed better than historical controls

[1] ***Haddad R et al. Lancet Oncol. 2013 Mar;14(3):257-64***

[2] ***Cohen et al. J Clin Oncol. 2014 Sep 1;32(25):2735-43.***

Ongoing Clinical Investigation: Themes

- Therapeutic intensification
  - Incorporation of IO agents into standard of care chemoXRT, including neoadjuvant and maintenance PD1
- Therapeutic deintensifcation for HPV+
  - Upfront surgical approaches
  - IO + XRT in NRG HN005
- Cisplatin ineligible pts
  - NRG HN004, Reach study

Ongoing Clinical Investigation: definitive therapy

Trial	Treatment Population	N	Intervention
KEYNOTE-412[1]	LAHNSCC (HPV+ for select stages/primary sites)	780	Pembro + cis + RT vs. placebo + cis + RT
JAVELIN HN100[2]	LAHNSCC HPV- HNSCC (HPV+ for select stages/primary sites)	640	Avel + chemoRT vs chemoRT alone
IMSTAR-HN[3]	Stage III/IV p16- OPC, L, HP, OC	276	Neoadjuvant nivo, surgery, and adj chemoRT + adj nivo ± ipi vs SOC surgery + chemoRT
KEYNOTE-689[4]	Resectable stage III/IVa L, HP, OC, p16-OPC Stage III p16+ OPC	600	Pembro prior to surgery/with adj chemoRT vs surgery
IMvoke010[5]	LAHNSCC treated with curative-intent therapy	400	Atezo vs placebo after chemoRT
KEYCHAIN[6]	LAHNSCC p16+ OPC, L, OC	114	Cis + RT vs pembro + RT
HN005[7]	Locally advanced good risk p16+ OPC	711	Cis 70GyRT vs Cis 60GyRT vs Nivo 60GyRT

1. NCT03040999. 2. NCT02952586. 3. NCT03700905. 4. NCT03765918. 5. NCT03452137
6. NCT03383094 7. *NCT03952585*

Ongoing clinical investigation: postoperative therapy

Trial (NCT Identifier)	Phase	N	Endpt	Intervention
PATHOS (NCT02215265)	III	242	QOL/OS	TORS followed by risk stratification. Low: observation Intermediate: randomized to 50 vs 60 Gy High: randomized between 60Gy +/- cisplatin
ORATOR2 (NCT03210103)	IIR	140	OS	Randomize XRT +/- chemotherapy vs TORS
SIRS (NCT02072148)	II	200	DFS LRC	TORS followed by risk stratification Low: observation Intermediate: 50 Gy XRT High: 60 Gy XRT + cisplatin
DELPHII (NCT03396718)	I	384	LRC	TORS followed by risk stratification. Low: observation; Intermediate: 50 Gy XRT High: 60 Gy XRT + cisplatin

Metastatic Disease

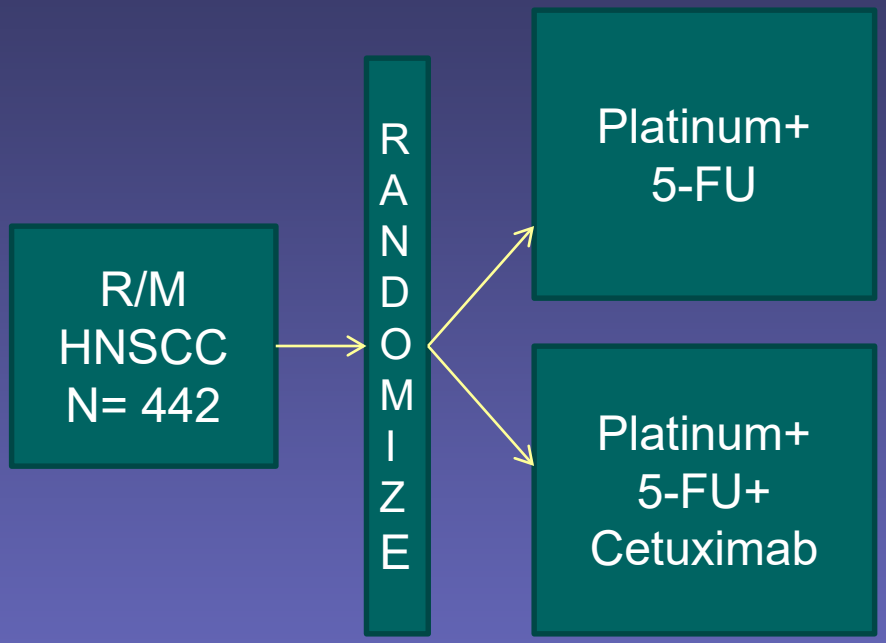
- Poor prognosis, survival measured in months (longer for HPV+ patients)

- Multiple active single agents

- Combination vs. single agent chemotherapy trials reproducibly:

1. Improve response rates
2. Increase toxicity
3. Do not improve in survival

Until 2008: EXTREME trial



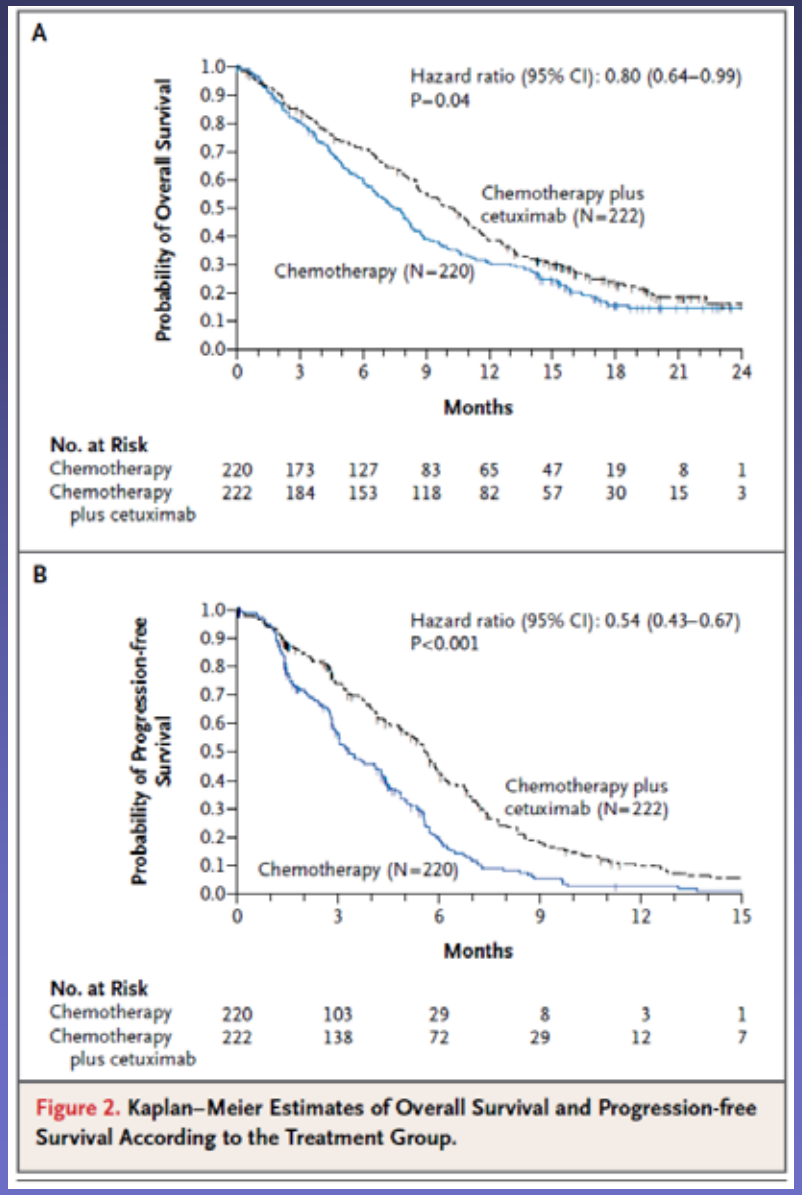
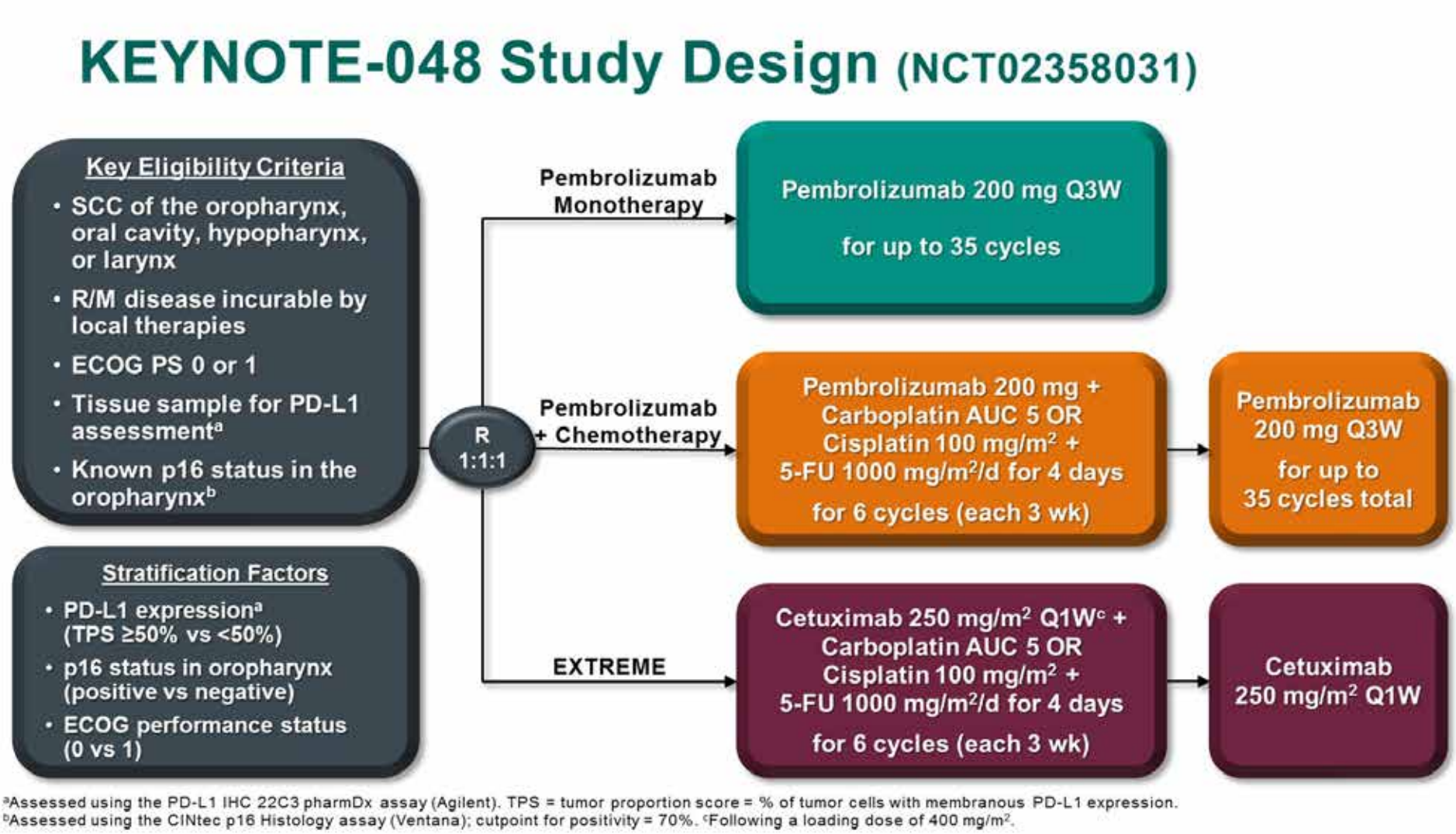


Figure 2. Kaplan–Meier Estimates of Overall Survival and Progression-free Survival According to the Treatment Group.

Vermorken J et al. N Engl J Med 2008;359:1116-1127

First Line Approval for Immune checkpoint inhibitor: Keynote 48



[a]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.
[b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%. [c]Following a loading dose of 400 mg/m².

Note:
Results for CPS <1 not reported
Pembro + chemo high rates of Gr 3 AE

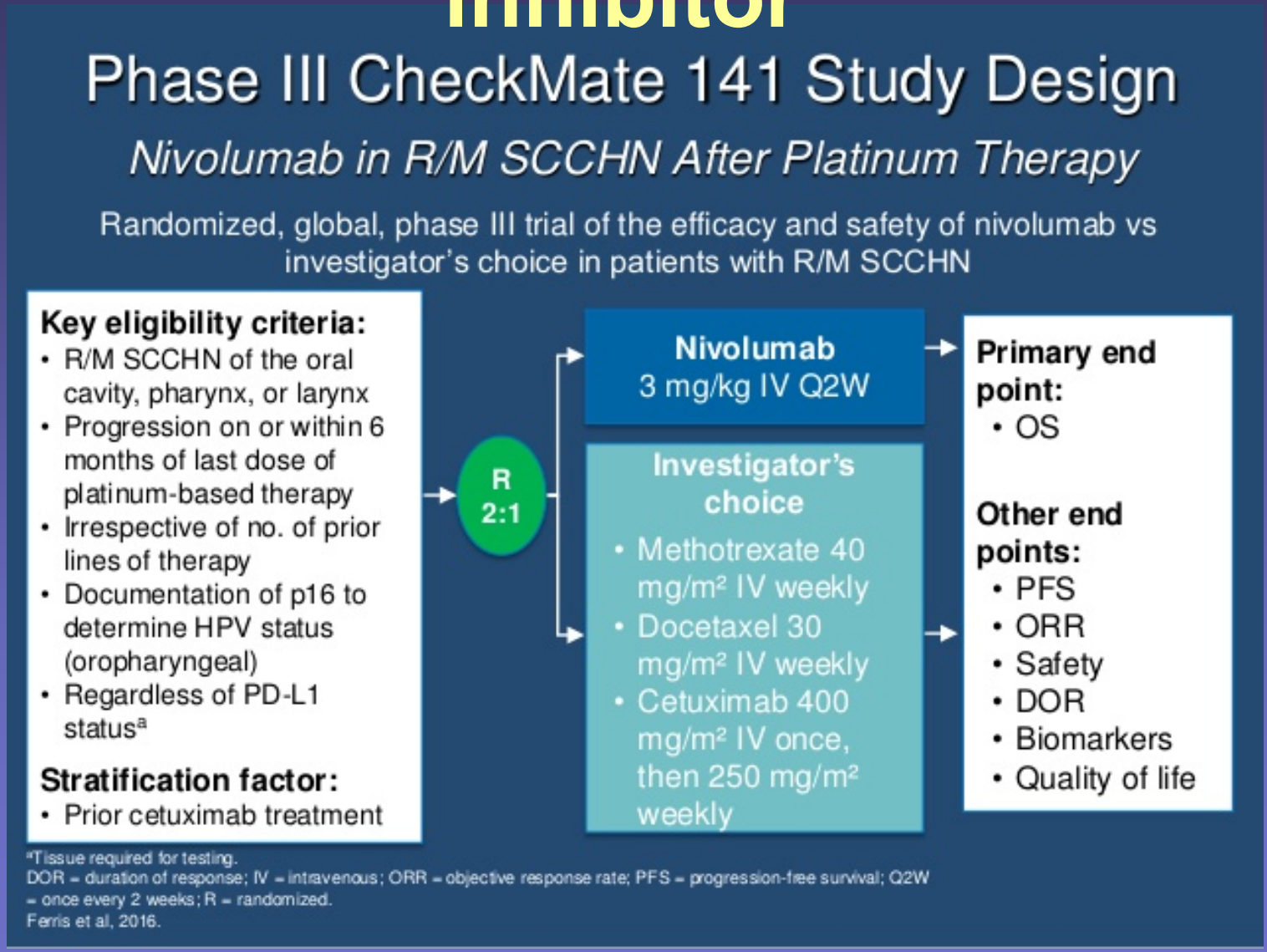
Summary of Overall Su

Population	IA2[1] HR (95% CI)	FA HR (95% CI)
Pembrolizumab monotherapy vs EXTREME		
PD-L1 CPS ≥20	0.61 (0.45–0.83); *P* = 0.0007[a]	0.58 (0.44–0.78)[c]
PD-L1 CPS ≥1	0.78 (0.64–0.96); *P* = 0.0086[a]	0.74 (0.61–0.90)[c]
Total	0.85 (0.71–1.03)[b]	0.83 (0.70–0.99); *P* = 0.0199[d]
Pembrolizumab + chemotherapy vs EXTREME		
PD-L1 CPS ≥20	—	0.60 (0.45–0.82); *P* = 0.0004[a]
PD-L1 CPS ≥1	—	0.65 (0.53–0.80); *P* < 0.0001[a]
Total	0.77 (0.63–0.93); *P* = 0.0034[a,b]	0.72 (0.60–0.87)[c]

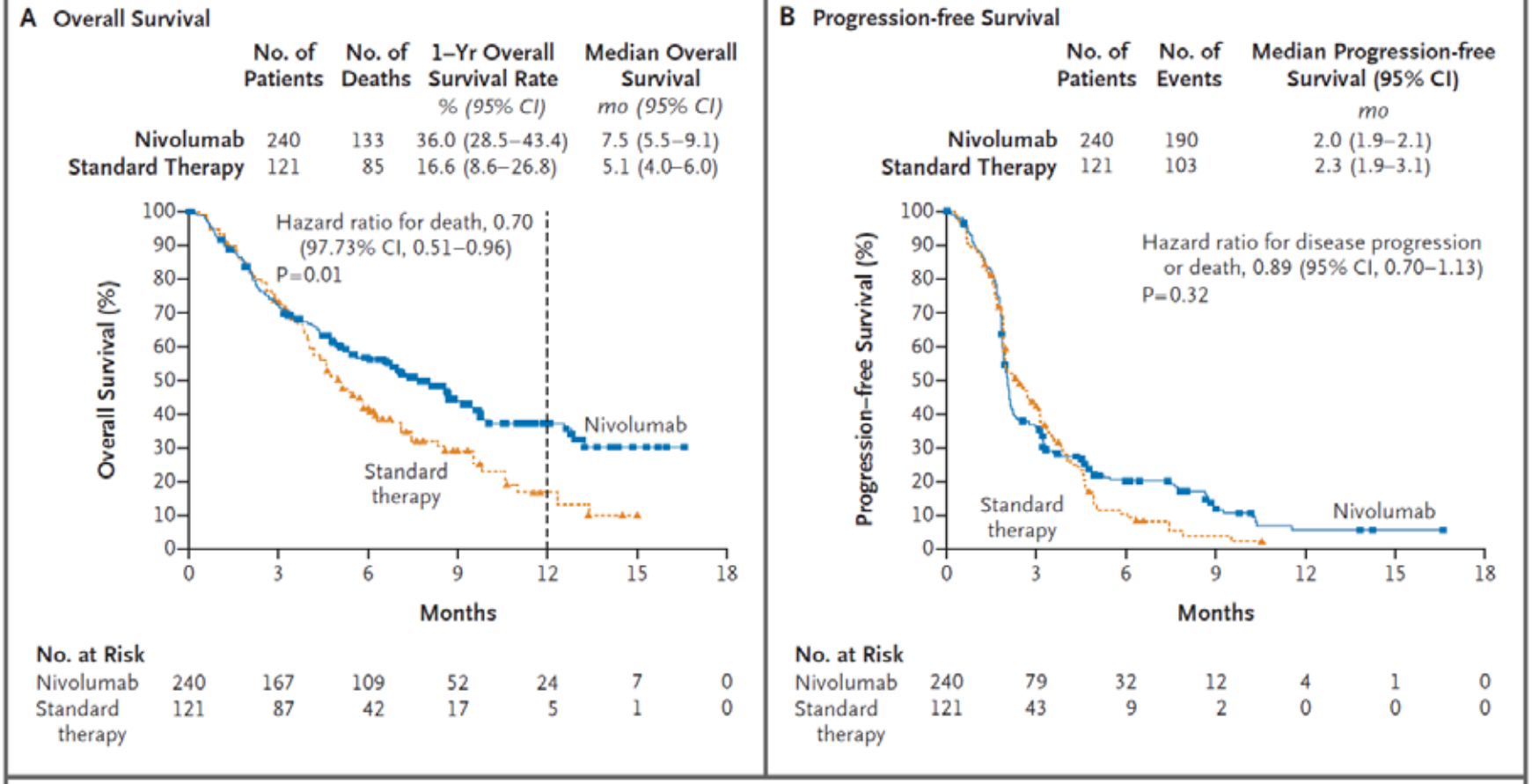
[a]Superiority demonstrated. [b]Noninferiority demonstrated (boundary of 1.2). [c]No statistical testing performed. [d]Superiority not demonstrated.

1. Burtness B et al. *Ann Oncol* 2018;29(suppl 8):LBA8_PR.

Second line Immune checkpoint inhibitor



Checkmate 141 results



Exploratory biomarker data: OS benefit independent of p16 status
Higher magnitude of OS benefit in >1% PDL1 tumors

Ferris, et al. NEJM 2016 Nov 10;375(19):1856-1867

Pembrolizumab

E Cohen_ESMO 2017

Phase 3 KEYNOTE-040 Study (NCT02252042)

Key Eligibility Criteria

- SCC of the oral cavity, oropharynx, hypopharynx, or larynx
- PD after platinum-containing regimen for R/M HNSCC or recurrence or PD within 3-6 mo of multimodal therapy using platinum[a]
- ECOG PS 0 or 1
- Known p16 status (oropharynx)[b]
- Tissue sample[c] for PD-L1 assessment[d]

Stratification Factors

- ECOG PS (0 vs 1)
- p16 status[b] (positive vs negative)
- PD-L1 TPS[d] (≥50% vs <50%)

R 1:1

Pembrolizumab
200 mg IV Q3W
for 2 y

Methotrexate 40 mg/m² QW[e]
OR
Docetaxel 75 mg/m² Q3W
OR
Cetuximab 250 mg/m² QW[f]

- Clinically stable patients with radiologic PD could continue treatment until imaging performed ≥4 wk later confirmed PD
- Crossover not permitted

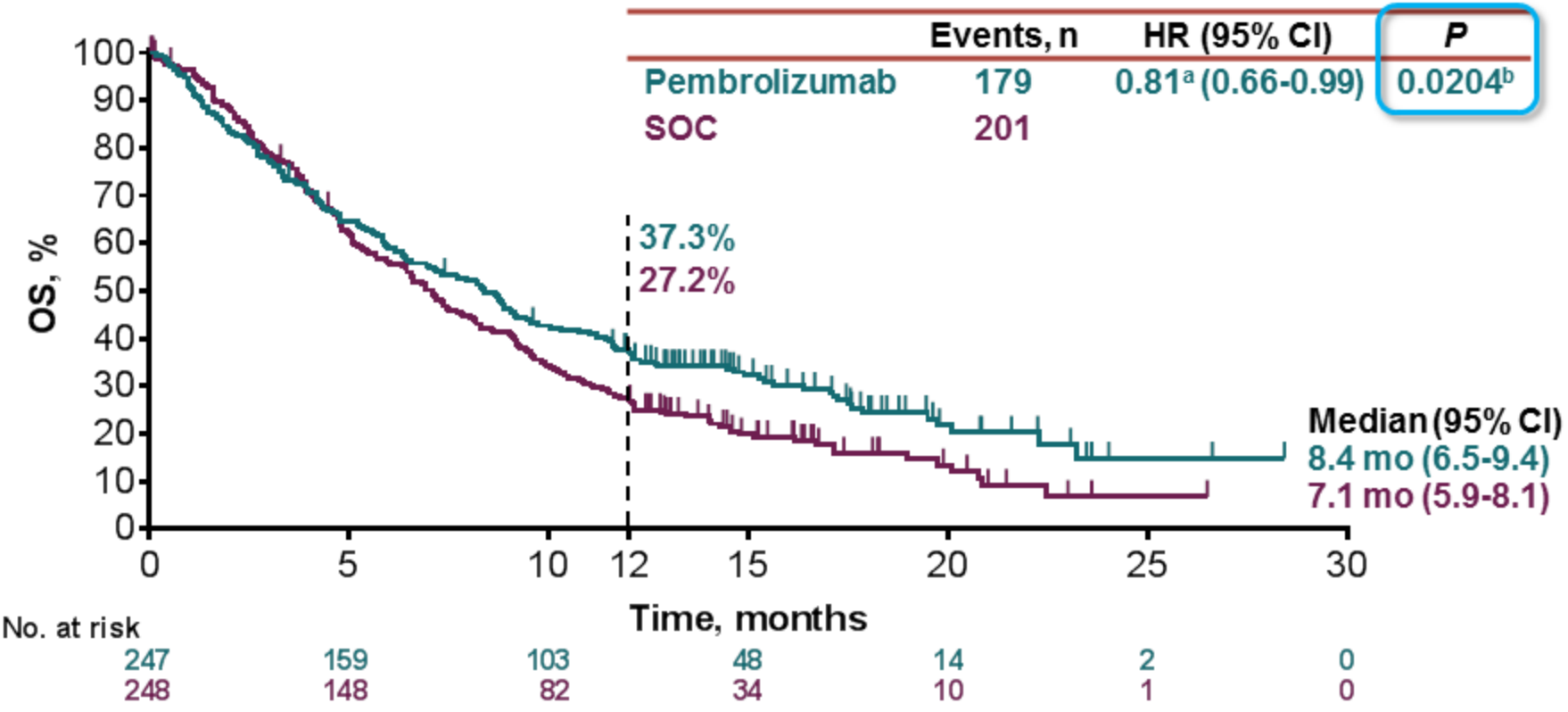
[a]Limit of 2 prior therapies for R/M HNSCC. [b]Assessed using the CINtec p16 Histology assay (Ventana); cutpoint for positivity = 70%.
[c]Newly collected preferred. [d]Assessed using the PD-L1 IHC 22C3 pharmDx assay (Agilent Technologies). TPS = tumor proportion score = % of tumor cells with membranous PD-L1 expression.
[e]Could be increased to 60 mg/m² QW in the absence of toxicity. [f]Following a loading dose of 400 mg/m².

Cohen et al. ESMO 2017 Abstract LBA45_PR

Keynote-40

E Cohen_ESMO 2017

Overall Survival in ITT Population



[a]Cox proportional hazards model with treatment as a covariate stratified by the randomization stratification factors. Initially reported data: HR 0.82 (95% CI, 0.67-1.01), $P = 0.0316$. After the initial report, updated survival data were obtained for 4 patients. [b]One-sided P value based on the log-rank test stratified by the randomization stratification factors. Data cutoff date: May 15, 2017.

ESMO congress

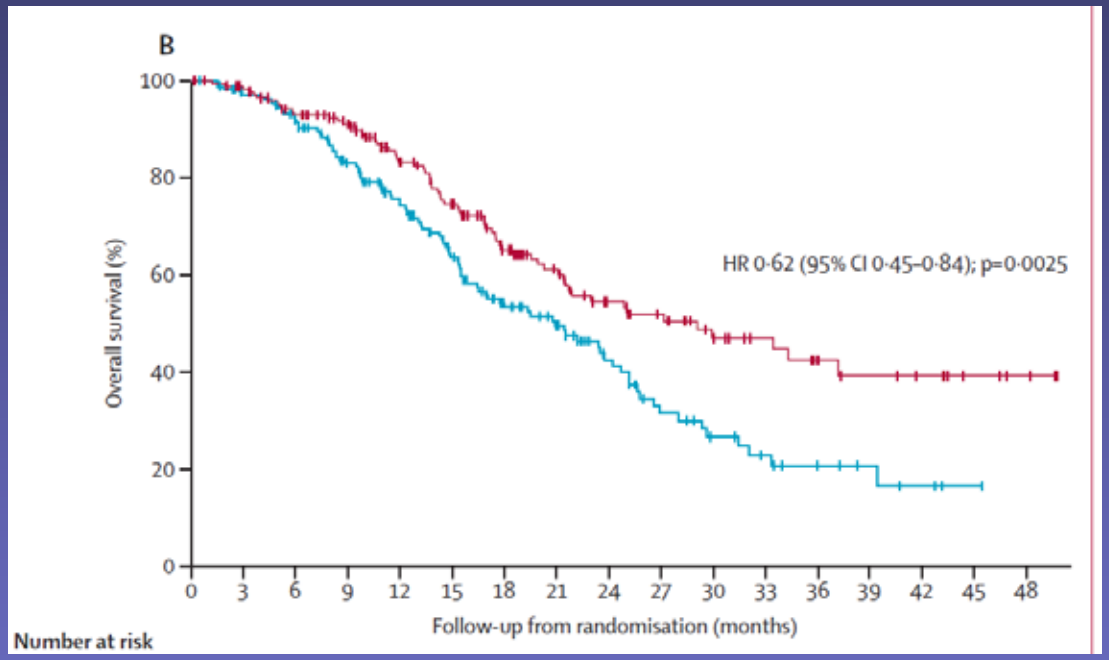
Metastatic NPC

- Randomized Phase III
- N=362, first line R/M

- Gemcitabine + Cisplatin vs. 5-FU+ Cisplatin

- PFS advantage to GC

- Hematologic toxicities with GC compared to mucosal for FC



Zhang et a. Lancet. 2016 Oct 15;388(10054):1883-1892.

KEY POINTS: Metastatic Disease

- Non NPC
  - Pembro/Plat/5-FU prolongs OS compared EXTREME in R/M setting
  - Pembro monotherapy with OS benefit in CPS≥1
  - Nivolumab and Pembrolizumab prolong OS in plat treated R/M disease compared to 2nd line systemic tx (independent of PDL1 or HPV status)
- NPC
  - Gem+Cis improves PFS compared to 5-FU Cis

Future landscape of head and neck cancer therapy

- Deescalation studies in good risk HPV
  - Upfront surgery(robotic) vs lower dose XRT
- Immune checkpoint combinations in R/M
- Cellular therapeutics in R/M
- Integration of immune checkpoint inhibitors into curative intent therapy
- Epidemiologic changes with prophylactic vaccines

Part II
Thyroid Cancer

Thyroid Cancer Review

- **Differentiated Thyroid Cancer**
  - Papillary (85%) and Follicular (5%)
  - Familial in 3-9% (AFP,Cowden's, Werner's)

- **Medullary thyroid Cancer (5%)**
  - Parafollicullar C cells, produce calcitonin
  - Familial (less common, MEN2) or Sporadic (majority)
  - RET

- **Anaplastic thyroid Cancer**
  - Elderly patients, rapid growth, airway compromise
  - Evolved from prior differentiated cancers

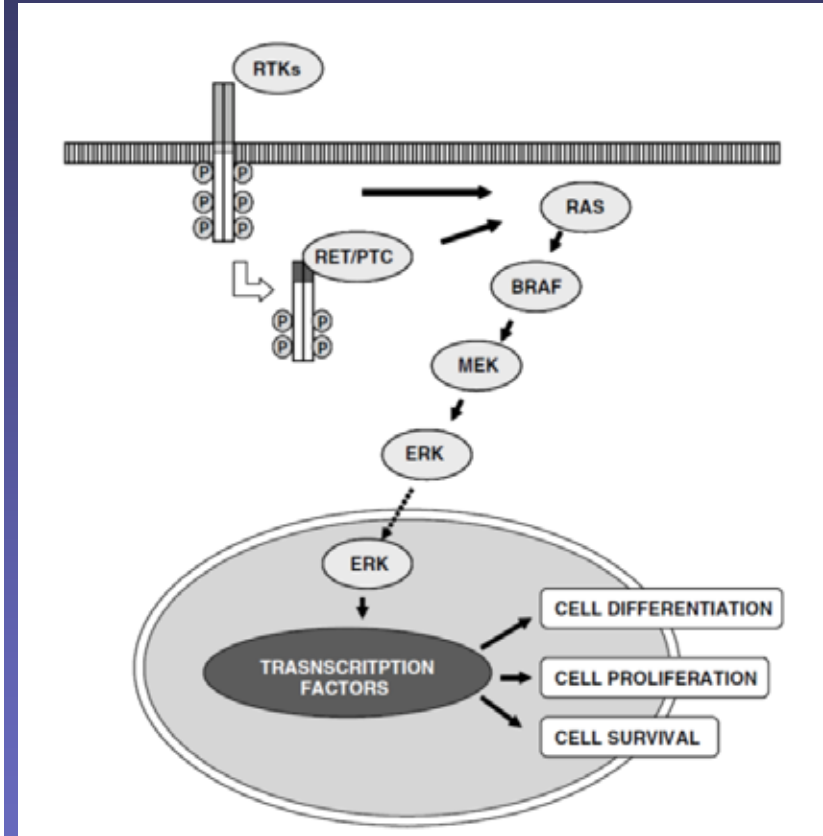
The historical role of the medical oncologist

	Agent	N	Histology	Objective Response Rate	Overall Survival
Gottleib, 1974	doxorubicin	30	All	11 (37%)	Responding patients: 11 months
Shimaoka, 1985	Doxorubicin vs cisplatin & doxorubicin	92	All	7 (17%) vs. 11 (26%)	< 24 months
Williams, 1986	Doxorubicin and cisplatin	22	All	2 (9%)	NR
Ain, 2000	Paclitaxel	20	ATC	10 (53%)	Median OS: 25 weeks

Kondo T et al. Nat Rev Cancer. 2006 Apr;6(4):292-306.

Molecular targets in Thyroid Cancers

Tumor type	*Prevalence (%)*
Papillary carcinoma	
BRAF	45
RET/PTC	20
RAS	10
TRK	<5
Follicular carcinoma	
RAS	45
PAX8-PPARγ	35
PIK3CA	<10
PTEN	<10
Medulllary carcinoma	
Familial forms of *RET*	>95
Sporadic *RET*	50
Poorly differentiated carcinoma	
RAS	35
β-Catenin (*CTNNB1*)	20
TP53	20
BRAF	15
Anaplastic carcinoma	
TP53	70
β-Catenin (*CTNNB1*)	65
RAS	55
BRAF	20



MAPK signaling pathway

Nikiforov YE. Mod Pathol. 2008 May;21 Suppl 2:S37-43

FDA approved TKIs in RAI refractory DTC

Agent	Target	Evidence	ORR	PFS	OS	AEs
Lenvatinib[1]	VEGF, BRAF, FGFR, RET, KIT	R Ph III vs. Placebo SELECT (N=392)	**64.8%** vs 1.5% (p<0.001)	18.3 vs 3m (p<0.001)	NS	75.9% vs 9.9%
Sorafenib[2]	VEGF, BRAF, RET RAF, PDGFR	R Ph III vs. Placebo DECISION (N=417)	**12.2%** vs 0.5%	10.8 vs. 5.8m (p<0.0001)	NS	37.2 vs 26.3%
Selpercatinib[3]	RET	Ph1/2 N=27	**62%**	NR	NR	Mostly Gr1/2

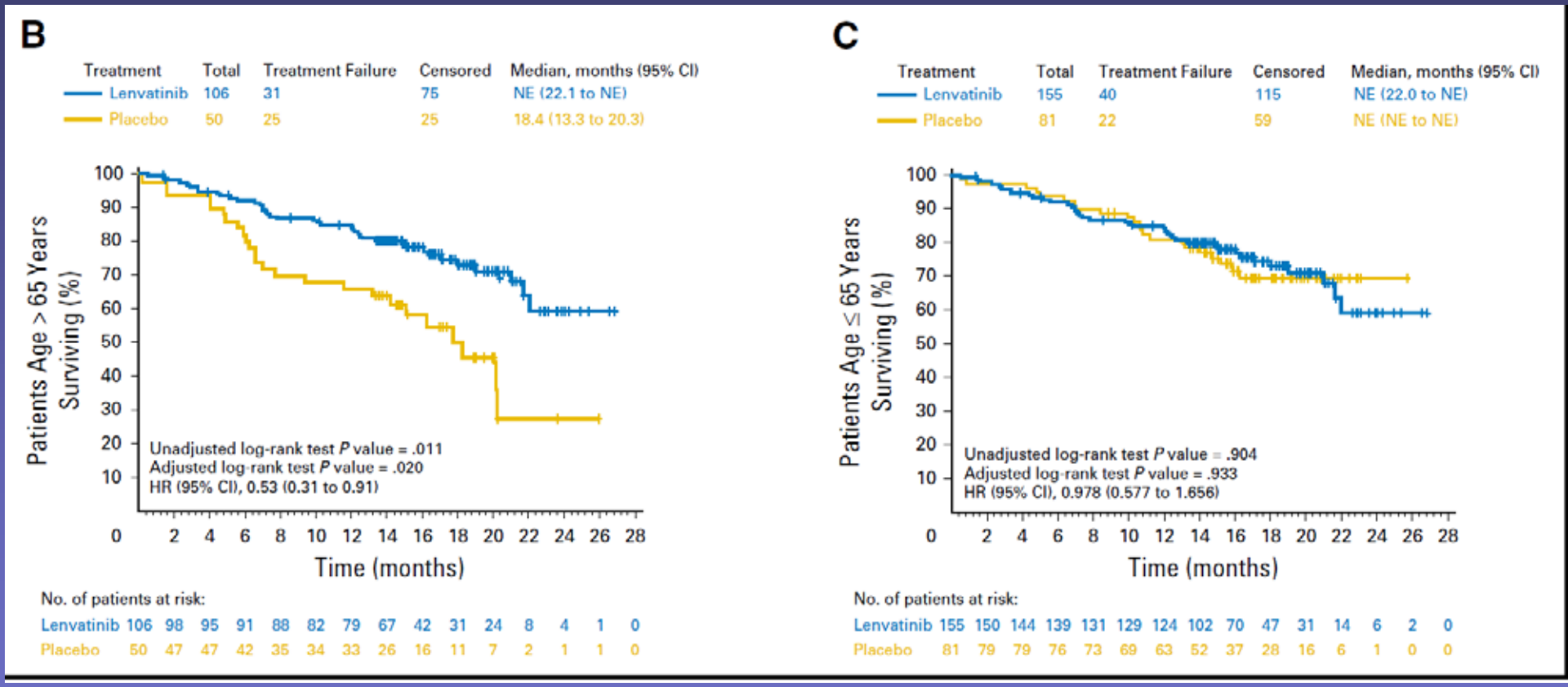
** Other multikinase inhibitors have activity in DTC, studied in nonrandomized phase II trials: axitinib, cabozantinib, pazopanib, sunitinib.

[1]Schlumberger et al. N Engl J Med. 2015 Feb 12;372(7):621-30.

[2]Brose et al. Lancet. 2014 Jul 26;384(9940):319-28.

[3]Wirth et al. ESMO 2019

SELECT Trial Update



Brose et al. J Clin Oncol 2017 Aug 10; 35(23):2692-2699

FDA approved TKIs in MTC

Agent	Target	Evidence	Obj. Response Rate	PFS	OS	Adverse Events
Vandetanib[1]	RET VEGF EGFr	R Ph III vs.Plac ZETA (N=331)	45% vs 13% (p<0.01)	NR vs 19.3 m (p<0.01)	NR	GI: 56 vs 26%
Cabozantinib[2]	RET MET VEGF	R Ph III vs. Plac EXAM (N=330) noXover	28% vs 0%	11.2 vs. 4m (p<0.0001)	NS	Gr3 69% vs 33%
Selpercatinib[3]	RET	Phase I/2 Libretto N=226	56%	NR	NR	Most Gr1/2

[1]Wells, et al. J Clin Oncol. 2012 Jan 10;30(2):134-41.
[2]Elisei et al. J Clin Oncol. 2013 Oct 10;31(29):3639-46.
[3]Wirth et al. ESMO 2019

Anaplastic Thyroid Cancer

- Often unresectable and metastatic at diagnosis, very poor prognosis
- Controlling local disease and improving QOL are priorities of therapy
- Radiation often concurrent with chemotherapy often used to achieve treatment goals
- Paclitaxel has a response rate of ~50%
- Dual BRAF/MEK inh. For BRAF V600E+

BRAF and MEK inhibition

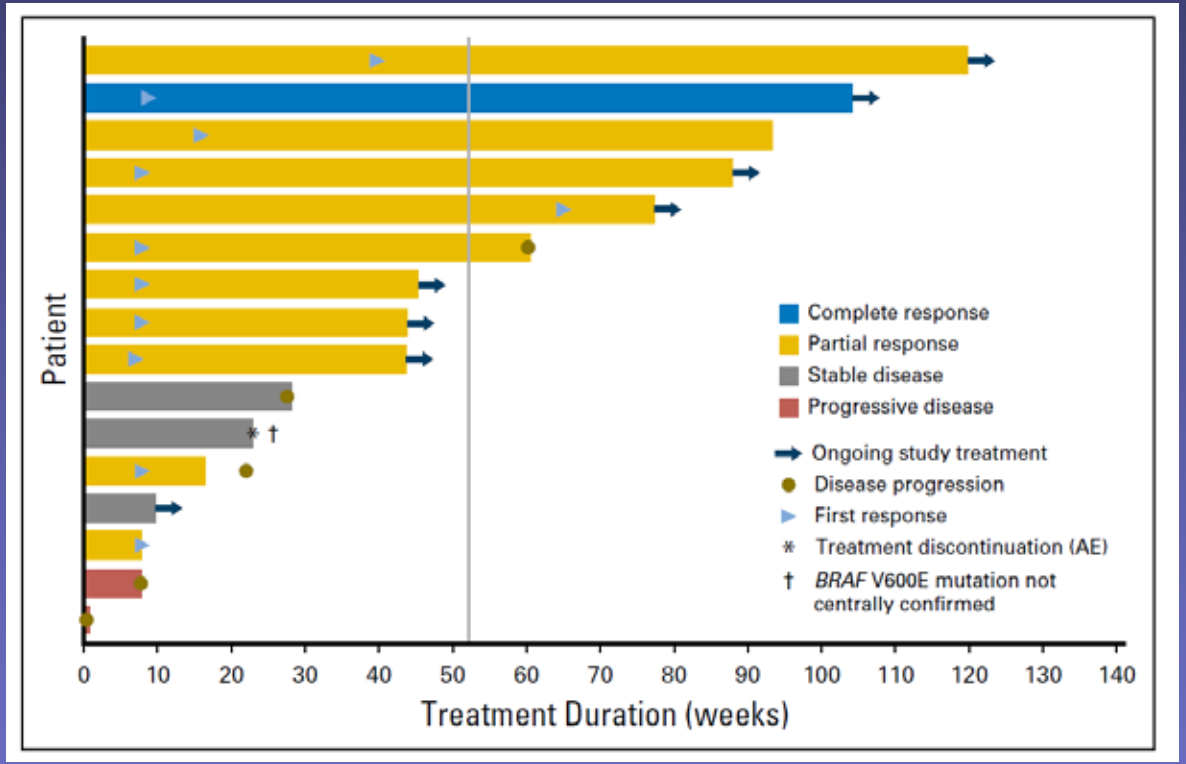
Phase I clinical experience with dabrafenib and trametinib

N= 16 pts with BRAF v600e mutations

Responses in 11 (69%)

80% previously treated with XRT

FDA approved



Subbiah et al. J Clin Oncol. 2018 Jan 1;36(1):7-13

Key Points: Thyroid Cancer

- Multikinase inhibitors are for thyroid cancer independent of mutational status
  - RAI refractory differentiated thyroid cancer
    - Lenvatinib and sorafenib
  - Medullary Thyroid Cancer
    - Vandetanib and cabozantinib
- Anaplastic thyroid cancer
  - Recognize and attempt local control
  - Test for BRAF V600E

Part III
Salivary Gland Cancer

Salivary Gland Cancers

- Uncommon (5% of head and neck CA)
- Diverse histology (2017 WHO)
  - Most common: adenoid cystic (ACC), mucoepidermoid carcinoma, adenocarcinoma
- Variable clinical behavior
  - Indolent subtypes such as ACC
- Molecular profiling
  - Secretory Carcinoma (*ETV6-NTRK3* fusion)

Salivary Gland Cancer: Local or Locally advanced

- Surgical resection of localized disease
- Postoperative radiation therapy in high risk disease
  - Data to support Neutron Radiation
  - Photon radiation also extensively studied and reported in postoperative setting
  - Concurrent chemoradiation being studied in RTOG 1008

Salivary Gland Cancer: Metastatic

- No current standard of care
  - Small trials with heterogeneous population
    - Low response rates, stable disease
    - Contemporary experience with single agent paclitaxel and gemcitabine-cisplatin
  - Recent reports/publications
    - Lenvatinib in adenoid cystic (15%ORR)
    - Entrectinib in NTRK mutant sal gland cancer
    - Trastuzumab+chemo and TDM1 in Her2+
    - Androgen deprivation in AR+ sal gland cancer
    - Pembro in PDL1>1% (10% ORR)
- Clinical trials preferred


Thank you!
rodrigcr@uw.edu

SUMMARY TABLE 1
Definitive XRT in Locally Advanced HNSCC

Disease	Standard/s of Care	Evidence
Locally advanced p16+ oropharynx cancer	cisplatin 100mg/m2 bolus + XRT	**RTOG 1016** **DE-ESCALaTE** OS, LRC benefit vs. cetuxXRT
Unresectable HNSCC of OC, OP, L, HP	cisplatin 100mg/m2 day 1, 22, 43 of XRT	**Intergroup Study** OS, DSS and LRC advantage vs XRT or splitXRT
Unresectable HNSCC of OC, OP, L, HP	cetuximab weekly concurrent with XRT	**Bonner Study** OS, LRC and PFS advantage vs XRT
St III-IVB Larynx CA (supraglottis or subglottis)	cisplatin 100mg/m2 day 1, 22, 43 of XRT	**RTOG 91-11** Larynx Preservation and LRC benefit vs XRT or ind.+ XRT

SUMMARY TABLE 2 Noncisplatin regimens Locally Advanced HNSCC

Disease	Standard/s of Care	Evidence
Unresectable HNSCC of OC, OP, L, HP	cetuximab weekly concurrent with XRT	**Bonner Study** OS, LRC and PFS advantage vs XRT
Locally advanced Oropharynx cancer	Carbo + inf 5FU days 1, 22 and 43 of XRT	**GORTEC 94-01** OS and LRC advantage vs. XRT alone

SUMMARY TABLE 3 Checkpoint inhibitors in Metastatic HNSCC

Line of therapy (biomarker)	Drug or Regimen	Evidence
1st line (CPS 1 or higher)	Pembrolizumab monotherapy	[1]Keynote-48 Phase III trial
1st line (any CPS)	Pembrolizumab + carboplatin + 5FU	[1]Keynote-48 Phase III trial
2nd line post cisplatin	Nivolumab	[2]Checkmate 141 Phase III trial
2nd line post cisplatin	Pembrolizumab	[3]Keynote-40 Phase III trial

[1]Rischin et al. ASCO 2019 abstract 6000
[2]Ferris, et al. NEJM 2016 Nov 10;375(19):1856-1867
[3]Cohen et al. Lancet 2019 Jan 12;393(10167):156-167

SUMMARY TABLE 4
Nasopharyngeal Cancer

Disease	Standard/s of Care	Evidence	Emerging Evidence
Locally Advanced NPC	Cisplatin + XRT (consider adjuvant cis+5FU)	Intergroup 0099 OS and PFS vs XRT alone	No adjuvant therapy after CRT noninferior in endemic studies
Node+ Locally advanced NPC	Gemcitabine cisplatin followed by cisXRT	Zhang et al NEJM Phase III study OS advantage vs. cisXRT	
1st line R/M NPC	Cisplatin + gemcitabine x 6 cycles	**Zhang R Ph III** PFS adv. vs cis + 5-FU	PD1 inhibitors have activity (Keynote-28)

SUMMARY TABLE 5
Thyroid Cancer

Disease	Standard/s of Care	Evidence
RAI refractory differentiated thyroid cancer	Sorafenib	Ph III DECISION trial PFS adv. vs placebo
	Lenvatinib	Ph III SELECT trial ORR, PFS adv. vs placebo ORR 64%, allowed prior TKI
Medullary Thyroid Cancer	Vandetanib	Ph III ZETA study PFS adv. vs. placebo
	Cabozantinib	Ph III EXAM study PFS adv. vs. placebo
RET mutated thyroid ca	Selpercatinib	Ph1/2 LIBRETTO study
Anaplastic Thyroid	Paclitaxel	Ph II data, 53% ORR
	Dabrafenib + Trametinib	Ph I data in BRAF V600E mutated pts

SUMMARY TABLE 6
Salivary Gland Cancer

Disease	Standard/s of Care	Evidence/Emerging Data
Local or locally advanced sal. gland cancer	Resection followed by postop XRT for high risk disease	Historical improvement with postop Adjuvant Concurrent chemoXRT under study
Metastatic sal. gland cancer	No treatment standard Clinical trial preferred	Consider molecular profiling: NTRK, Her2/AR inhibitors have activity Trials for specific molecular abberrations available

Hodgkin Lymphoma

Ryan Lynch MD
Assistant Professor, University of Washington, Division of Medical Oncology
Assistant Member, Fred Hutchinson Cancer Research Center, Clinical Research Division
Seattle, Washington

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

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Goals

- Provide an overview of the evidence supporting current clinical practice
- Since this also serves as a board review, I will refrain from addressing “early” data, unless it may immediately affect clinical practice
- I will try to summarize the points that are most likely to be addressed or not addressed on the exam

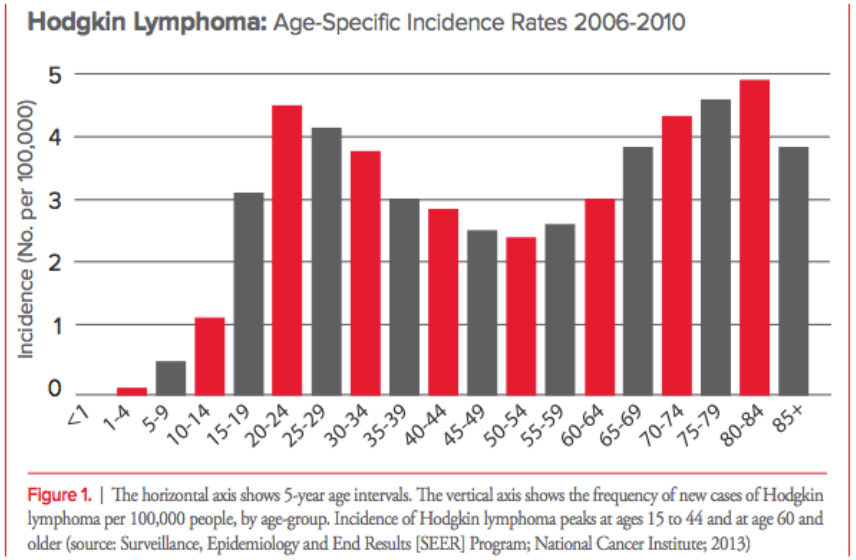
Outline

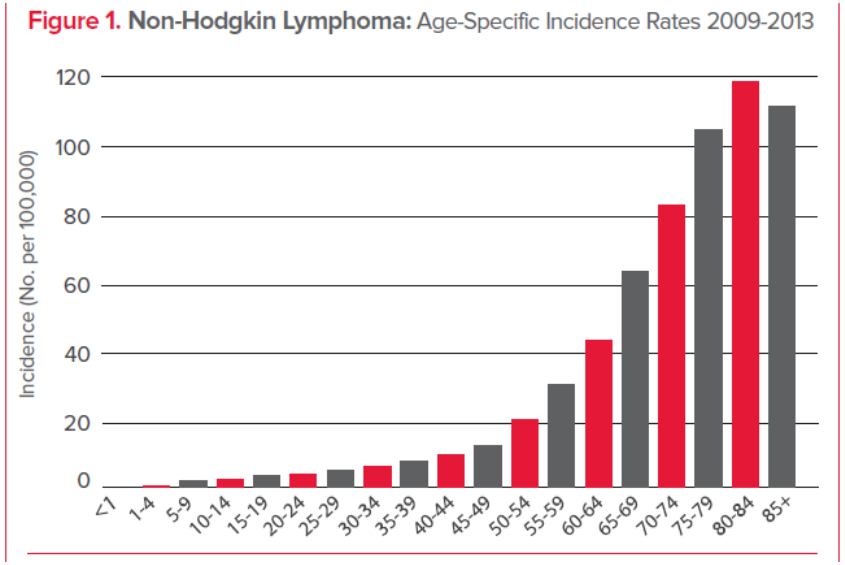
- Background
- Early Stage (Stage I-II)
- Advanced Stage (Stage III-IV)
- Relapsed/refractory patients
- Survivorship
- Nodular lymphocyte predominant HL

Background

- Classical Hodgkin lymphoma (CHL) represents ~ 10% of all lymphomas
- 8000 new cases annually in the United States
- Highly curable with frontline therapy (chemotherapy +/- RT)
  - Early stage > 90%
  - Advanced stage ~ 75%

Hodgkin vs. non-Hodgkin lymphoma incidence by age





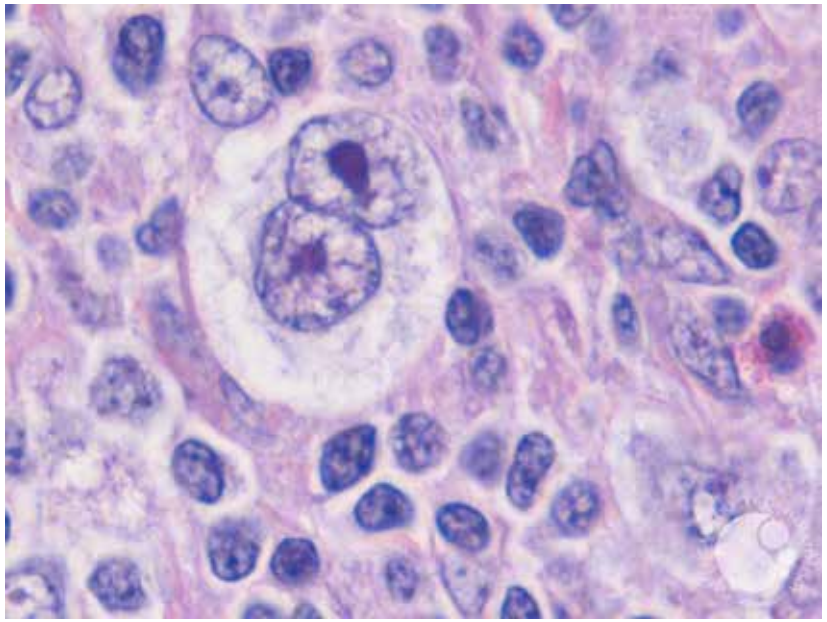
SEER Data, chart from Leukemia & Lymphoma Society

Hodgkin lymphoma can be challenging to diagnose

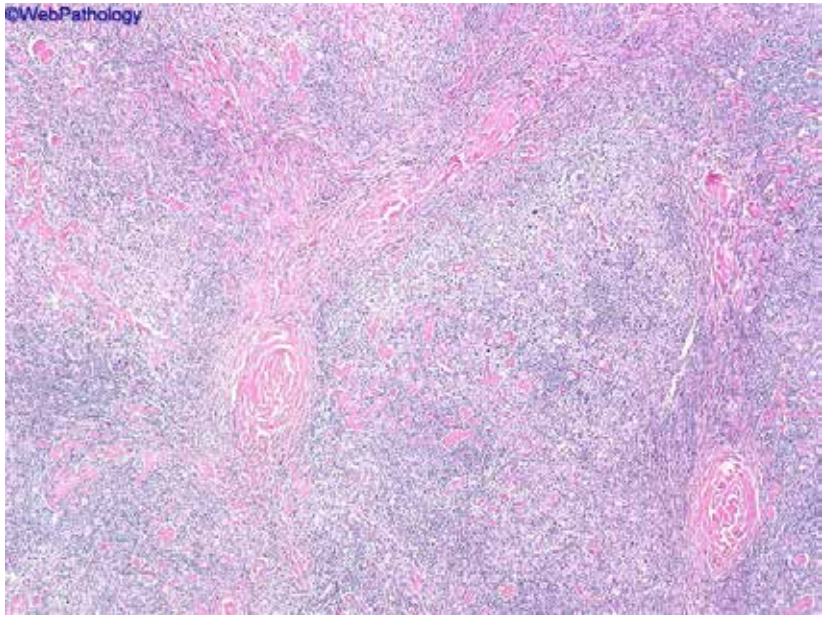
- Mostly comprised of an inflammatory infiltrate with bands of sclerosis
- FNA and flow cytometry often negative
- CORE biopsies are often sufficient, but if there are insufficient RS cells in the specimen, it may be non-diagnostic
- Excisional biopsies when possible offer the highest chance of diagnosis and excluding similar entities
  - Diffuse large B-cell lymphoma
  - Primary mediastinal B-cell lymphoma
  - Nodular lymphocyte predominant Hodgkin lymphoma
  - Anaplastic large cell lymphoma (peripheral T-cell lymphoma)
- **It is common to see patients with symptoms for 6-12 months before diagnosis!**

Hodgkin Reed-Sternberg cell

The malignant cell is rare



Hematology.org



WebPathology.com

Hodgkin lymphoma staging

Stage	Definition
I	single lymph node or extranodal site
II	two or more involved lymph node regions on the same side of the diaphragm
III	lymph node involvement on both sides of the diaphragm
IV	presence of diffuse or disseminated involvement of one or more extralymphatic organs

- A – absence of B symptoms
- B – Presence of B symptoms

- Stage I-II – Early stage
  - Favorable
  - Unfavorable
- Stage III-IV - Advanced stage
  - Risk stratified by International Prognostic Score (IPS)

Unfavorable Criteria – early stage

Risk Factor	GHSG	EORTC	NCCN
Age		≥50	
Histology			
ESR and B symptoms	>50 if A; >30 if B	>50 if A; >30 if B	>50 or any B symptoms
Mediastinal mass	MMR > .33	MTR > .35	MMR > .33
# Nodal sites	>2*	>3*	>3
E lesion	any		
Bulky			>10 cm

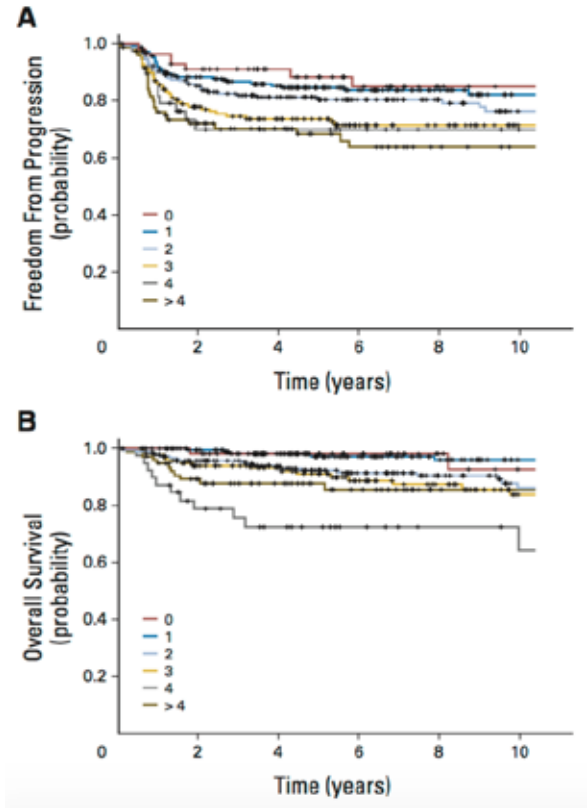
GHSG = German Hodgkin Study Group
EORTC = European Organization for the Research and Treatment of Cancer

MMR = Mediastinal mass ratio, maximum width of mass/maximum intrathoracic diameter
MTR = Mediastinal thoracic ratio, maximum width of mediastinal mass/intrathoracic diameter at T5-6

NCCN Guidelines, Hodgkin Lymphoma, Version 3.2016

IPS – risk stratification for advanced HL

- Serum albumin < 4 g/dL
- Hemoglobin < 10.5 g/dL
- Male
- Age >45 y
- Stage IV
- WBC: ≥15,000/microL
- Absolute lymphocyte count <600/uL and/or <8 % of the total WBC



Moccia et al. J Clin Oncol 30:3383-8, 2012

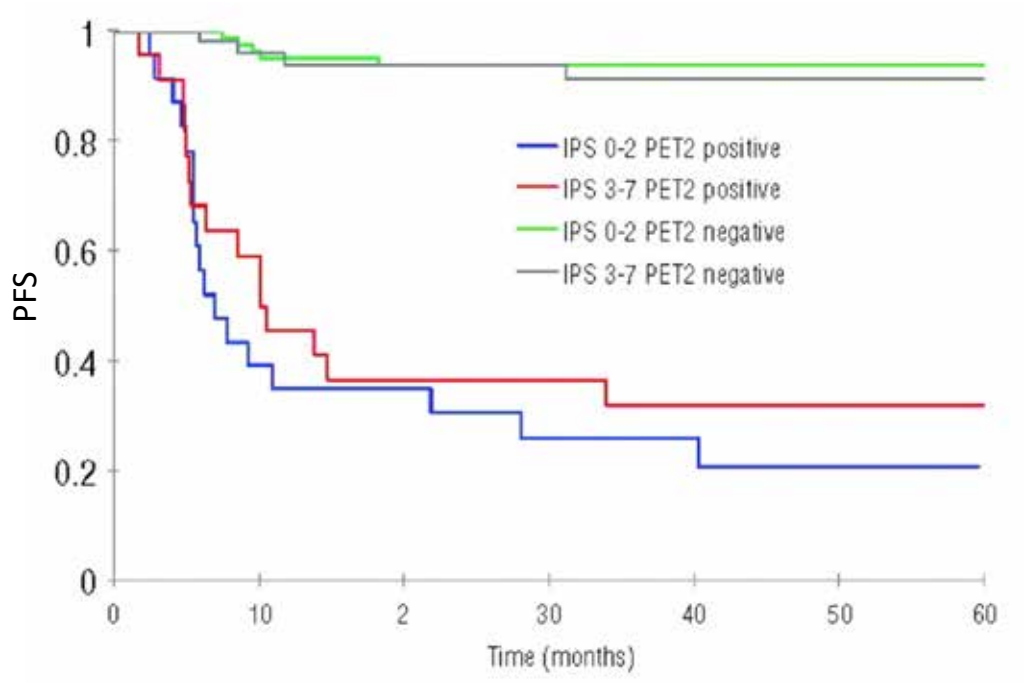
Deauville 5-point score

- Standardizes PET/CT response assessment
- Based on mediastinal and liver max SUV
- Reduces inter-user variability

Score	PET/CT scan result
1	No uptake
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately higher than liver
5	Uptake markedly higher than liver and/or new lesions
X	New areas of uptake unlikely to be related to lymphoma

Barrington SF, et al. J Clin Oncol 32:3048-58, 2014

Prognostic value of interim-PET using Deauville 5-point criteria



Gallamini A et al. Haematologica 99:1107-13, 2014

Hodgkin Lymphoma

Expected outcomes and goals of therapy in 2020

Stage	% Cured with primary therapy	Therapeutic Priority
Early stage favorable (Stage I-II)	90	Reduce Toxicity
Early stage unfavorable (stage I, II with risk factors*)	80-85	Increase Efficacy
Advanced stage (bulky IIB, III, IV)	75-80	Increase Efficacy

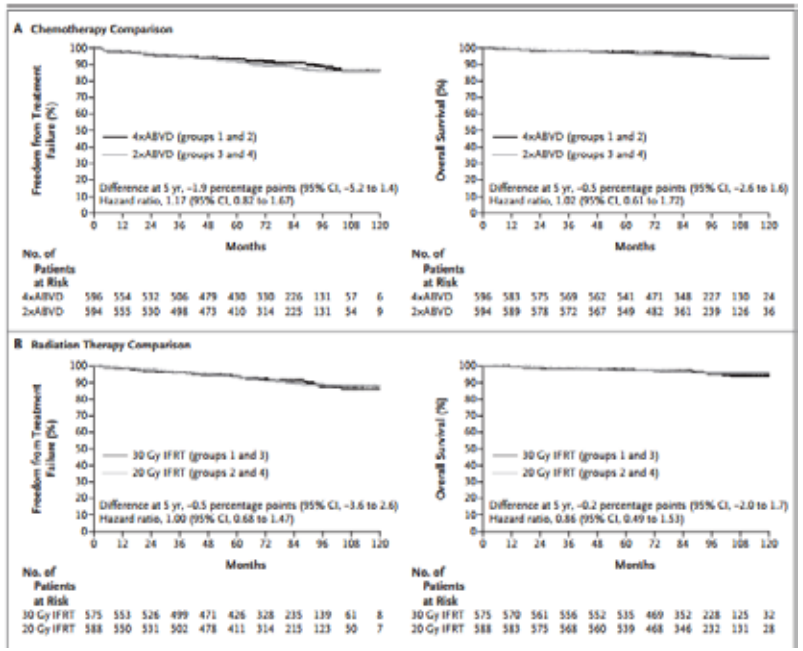
* Large mediastinal mass, extranodal extension, ≥ 3 nodal sites, elevated ESR; age ≥ 50, MC histology

Take home - background

- Fair game
  - Ann arbor staging
  - Deauville score (would be in the context of a clinical question, but should know what it means if a question says “PET scan was Deauville 2”
- Should understand, but likely don’t need to memorize
  - Components of IPS score
  - Favorable/unfavorable criteria
    - EXCEPT for GHSG > 2 sites = unfavorable

Early Stage

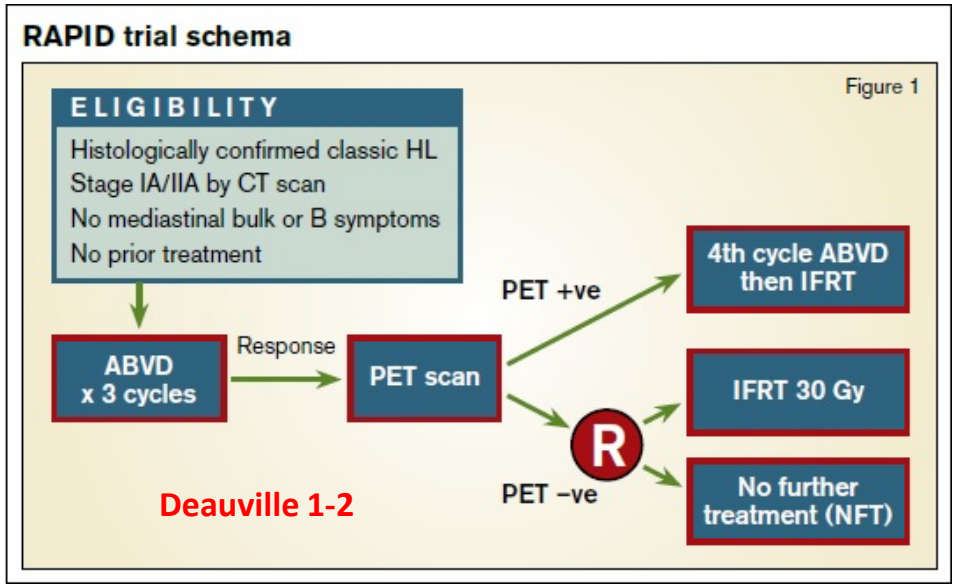
Early stage favorable HL- abbreviated chemo plus radiation

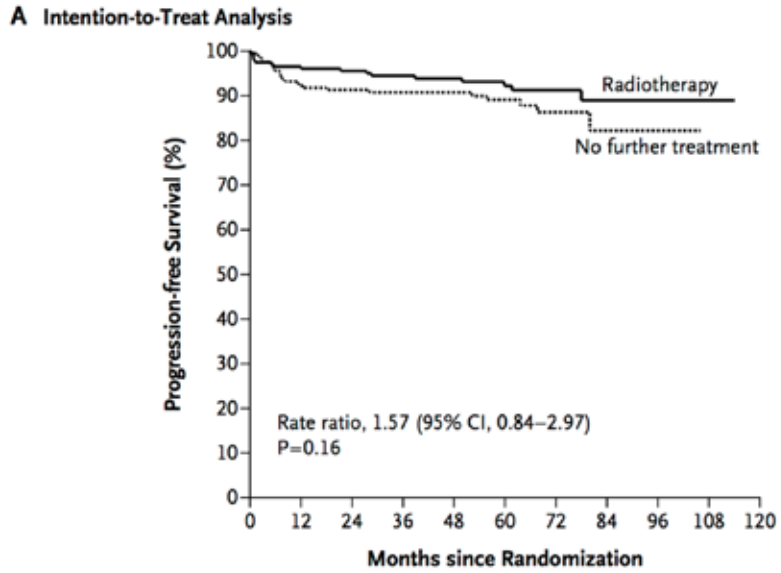


Engert A, et al: N Engl J Med 363:640-52, 2010

- GHSG HD10 trial
- 4 Arm study
  - Chemo ABVD x2 vs. x4
  - RT 30 Gy vs. 20 Gy
- ABVD X 2 + 20 Gy IFRT = ABVD X 4 + 30 Gy IFRT
- GHSG unfavorable criteria
  - ESR > 50, > 30 if B symptoms
  - MMR > 0.33
  - More than 2 nodal sites
  - Any E lesion

RAPID trial – PET adapted elimination of XRT in early stage HL

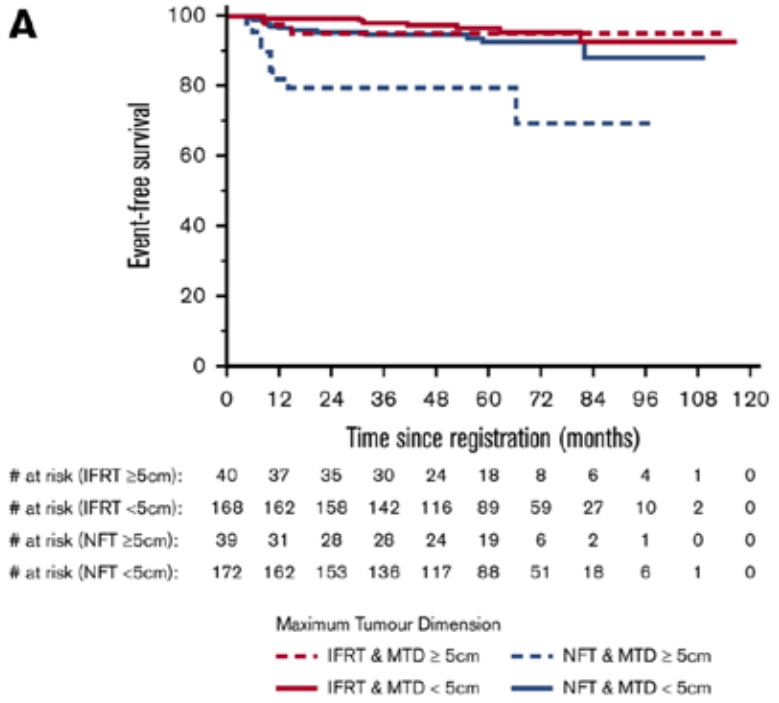




* No difference in OS

Radford J et al: N Engl J Med 372:1598-607, 2015

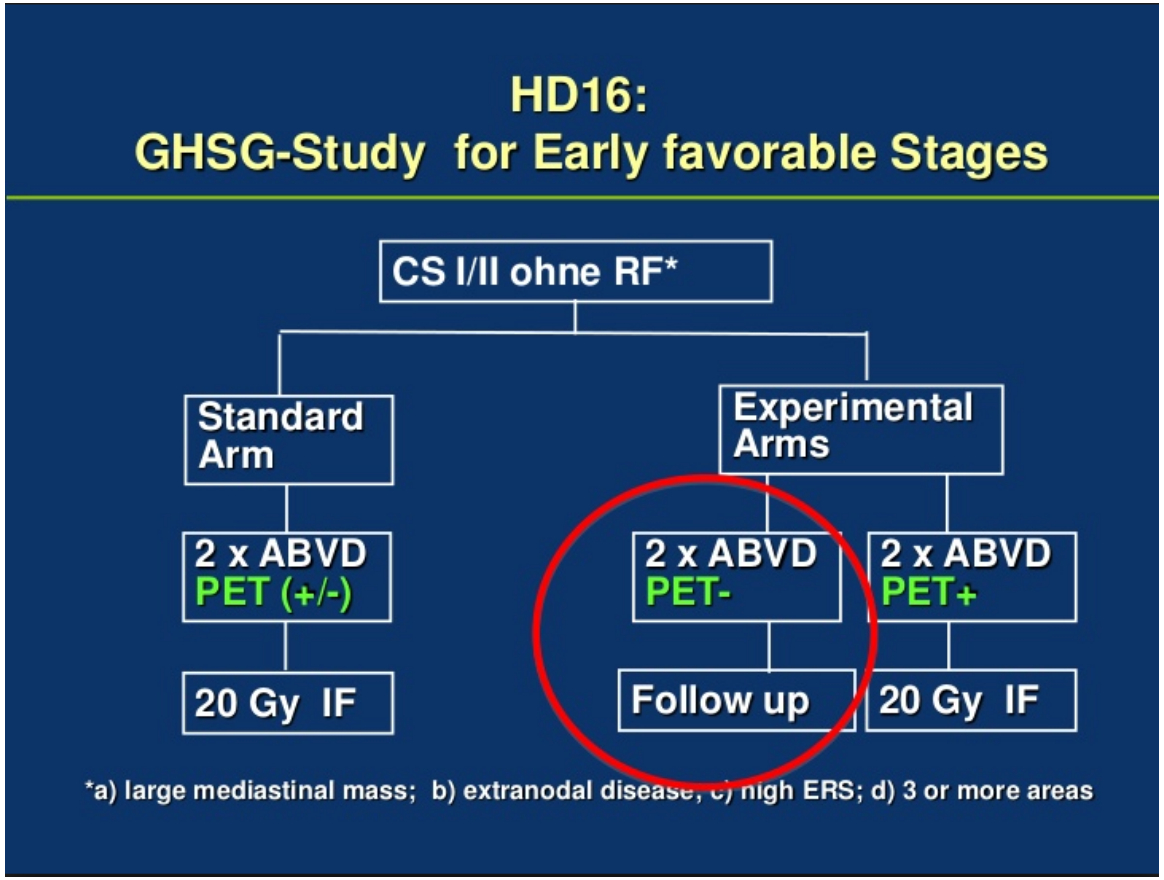
Maximum tumor dimension impacts outcomes when RT omitted



- MTD ≥ 5 cm correlates with worse outcomes when RT omitted

Adapted from Ilidge et al. ISHL 2018

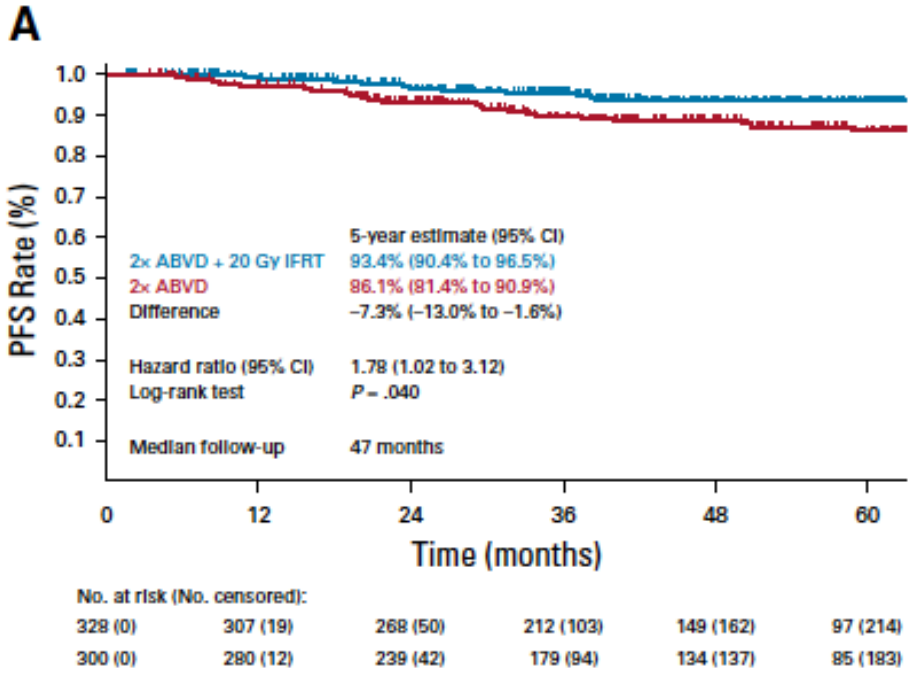
HD16 study



Deauville 1-2

Adapted from slide from Volker Diehl 2011

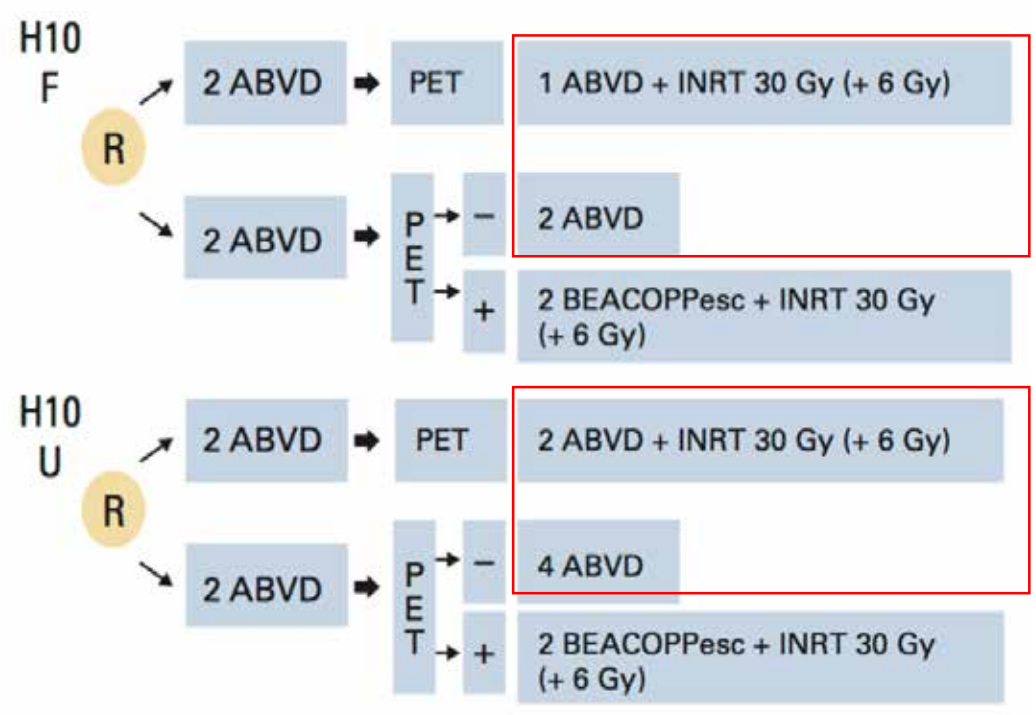
Inferior outcomes seen in early stage PET2neg patients with omission of RT



- **Radiation CANNOT be safely omitted in PET negative early stage favorable patients after 2 cycles ABVD**

Fuchs et al. JCO 2018

EORTC H10 - PET-adapted therapy in early stage HL



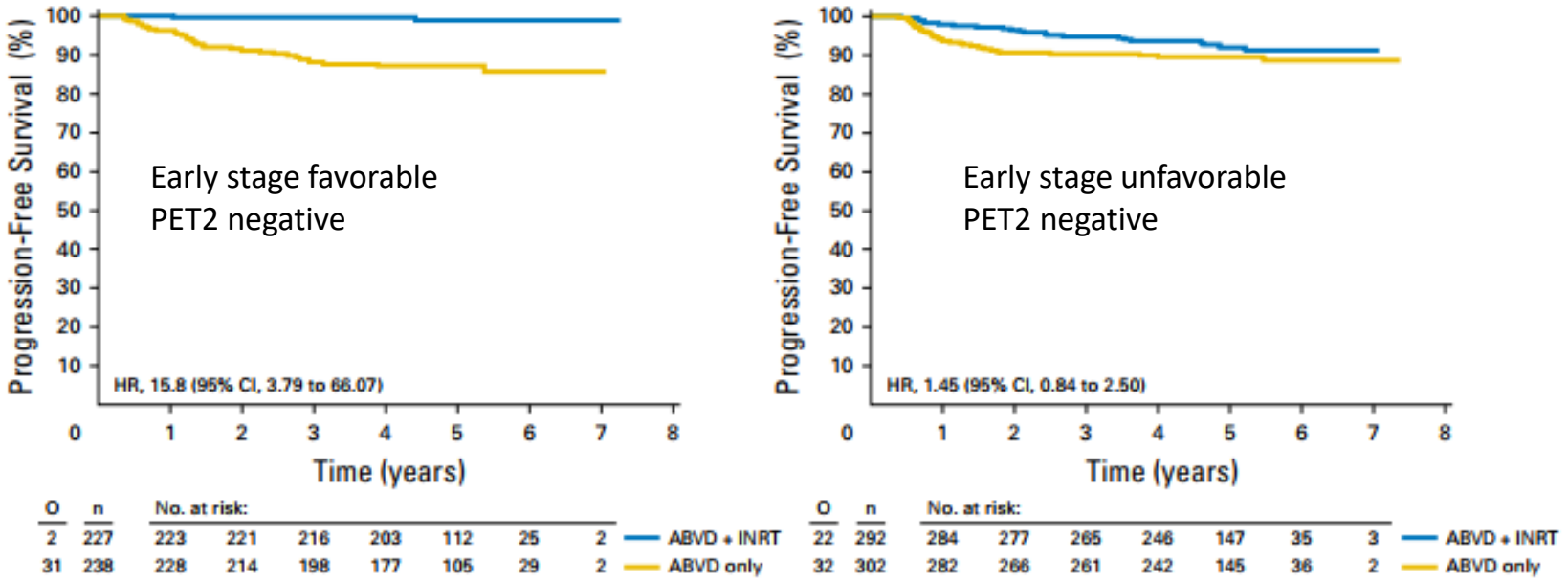
Deauville criteria not used (IHP criteria)

1950 patients enrolled

- **PET-negative experimental arm closed by independent data monitoring committee due to excess events**

Higher risk of progression in ES-favorable patients without RT

ES-unfavorable received ABVD x 6 without RT instead of ABVD x 4



Andre MPE, et al. J Clin Oncol 35:1786-1794, 2017

Early Stage Boards Take Home Points

- **GHSG early stage favorable patients can be treated with ABVD x 2 + 20 Gy**
- ABVD x 4-6 + RT is reasonable in other cases of early stage HL
  - If not meeting RAPID criteria and considering omitting RT, then ABVD x 6 should be given
- **Patients who are interim PET positive represent higher risk group and should receive consolidative RT**
- Radiotherapy offers small PFS benefit even in interim PET negative patients
  - RAPID – PET3 neg represents low risk group that can have RT eliminated in select patients
- **Unlikely to have a question that asks you if should or should not give RT in interim PET neg patients**

Advanced Stage

How do we treat advanced stage HL?

- ABVD
  - **Doxorubicin, bleomycin**, vinblastine, dacarbazine
- Escalated BEACOPP
  - **Bleomycin**, etoposide, **doxorubicin**, cyclophosphamide, vincristine, procarbazine, prednisone
- Stanford V (for IPS 0-2, never seen it used for advanced stage HL, even at Stanford)

- Brentuximab vedotin + AVD (FDA approval March 2018)

How do we treat advanced stage HL?

- **ABVD**
- **Escalated BEACOPP**

- Brentuximab vedotin + AVD

ABVD vs. escBEACOPP

- 75% success rate (FFS)
- Extremely low infertility
- Low rates of
  - heme toxicity
  - febrile neutropenia
  - treatment-related mortality
- 1% secondary malignancies at 10 years

- 90% success rate (FFTF)
- High rates of infertility that increases with age (~60% at age 30)
- Higher rates of
  - heme toxicity
  - febrile neutropenia
  - treatment-related mortality
- 10% secondary malignancies at 10 years

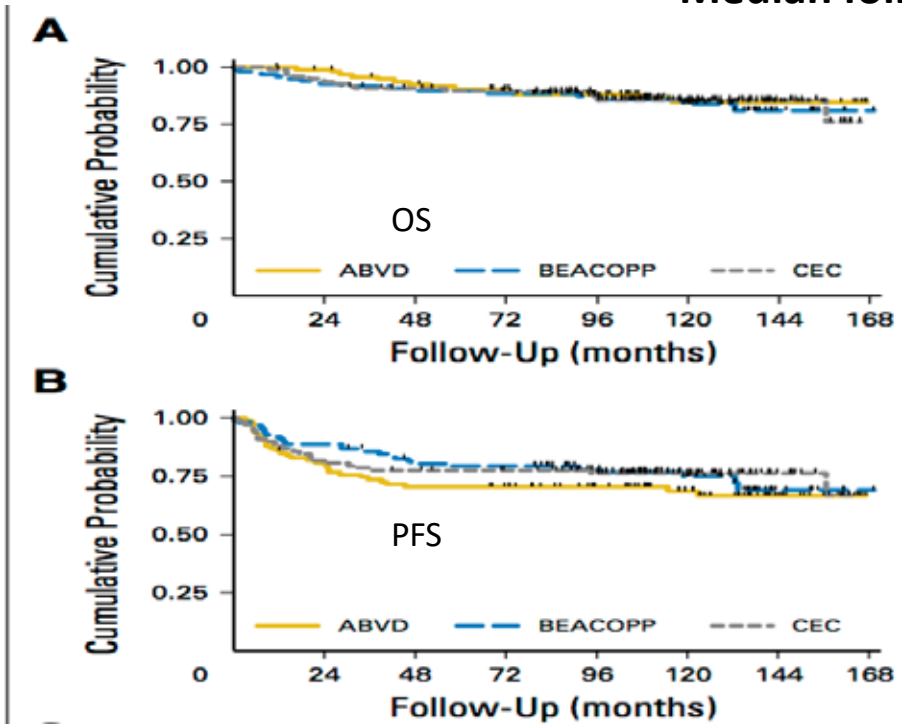
With long term follow-up (10 years), no statistical difference in overall survival

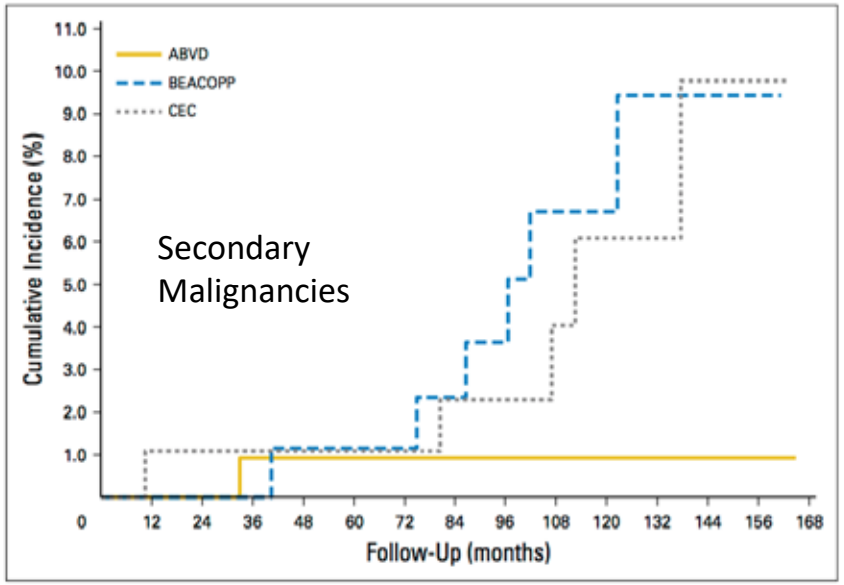
Why is escBEACOPP x 6 not standard of care in North America?

Importance of long term follow-up: HD2000

ABVD x 6 vs escBEACOPP x 4 + $BEACOPP_{baseline}$ x 2

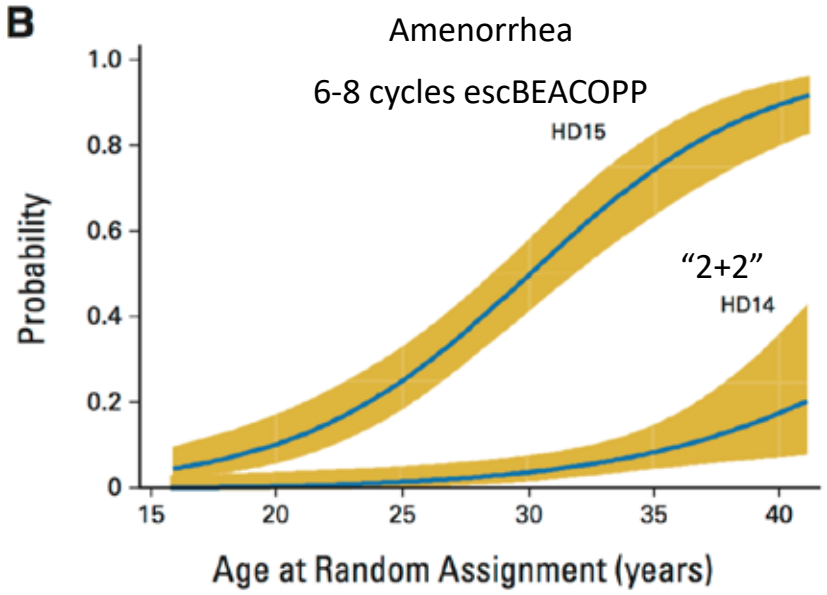
Median follow up 10 years

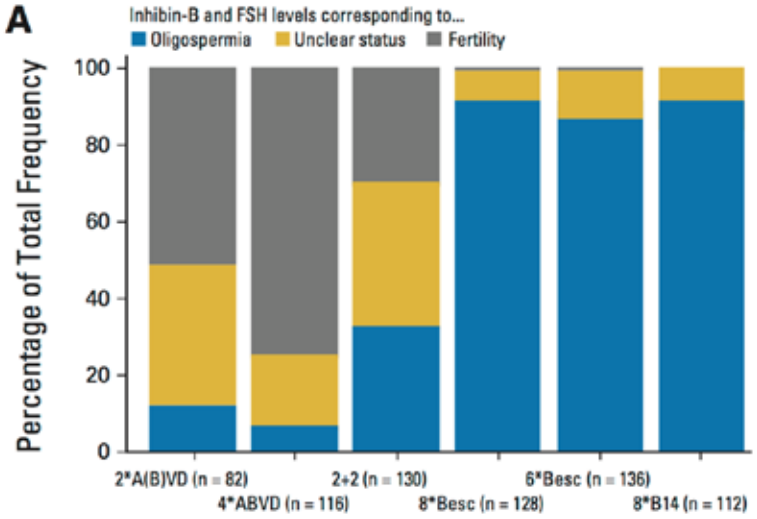




Merli F, Luminari S, Gobbi PG, et al:. J Clin Oncol, 2015

Sterility with BEACOPP

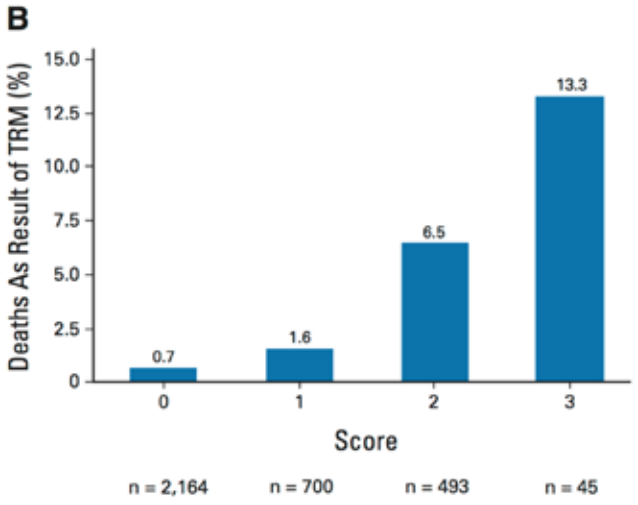


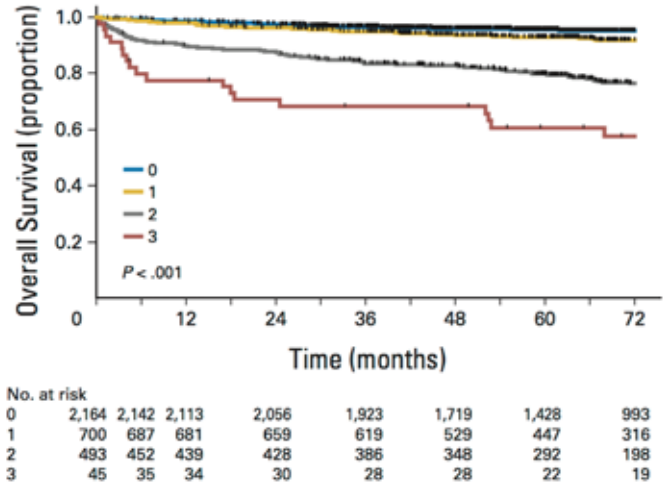


Behringer K, et al. J Clin Oncol 31:231-9, 2013

escBEACOPP is not for everyone

Treatment-related mortality risk score (add factors)



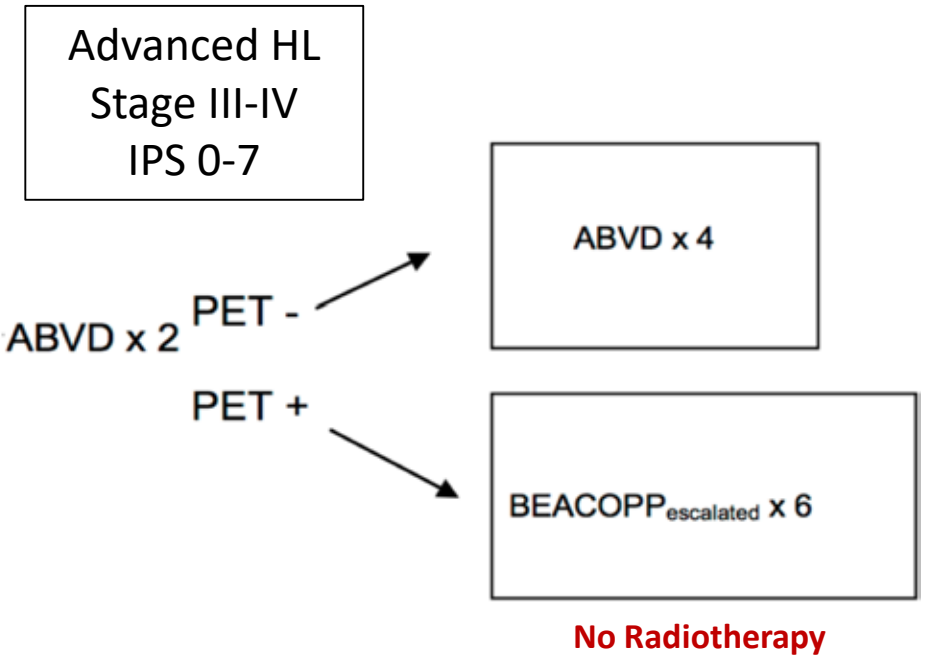


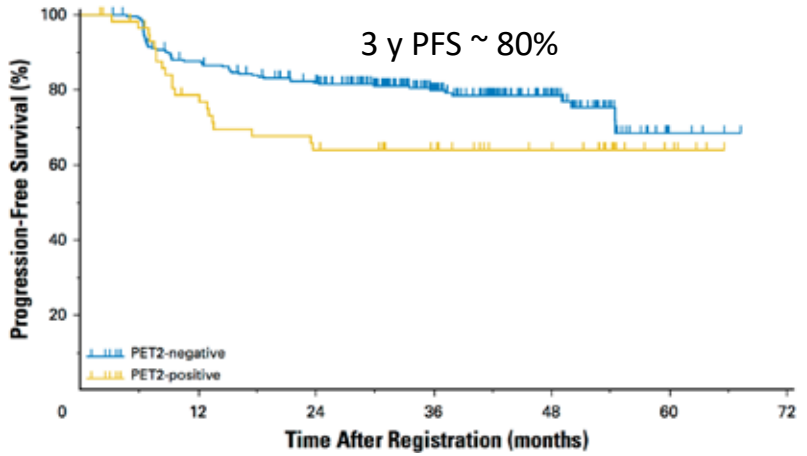
Points	Age	PS
0	< 40	0-1
1	40 - 49	2
2	≥ 50	

Wongso D, et al. J Clin Oncol 31:2819-24, 2013

Can we determine which subset of patients may benefit from intensification of treatment to escBEACOPP?

US Intergroup S0816 trial: Study design



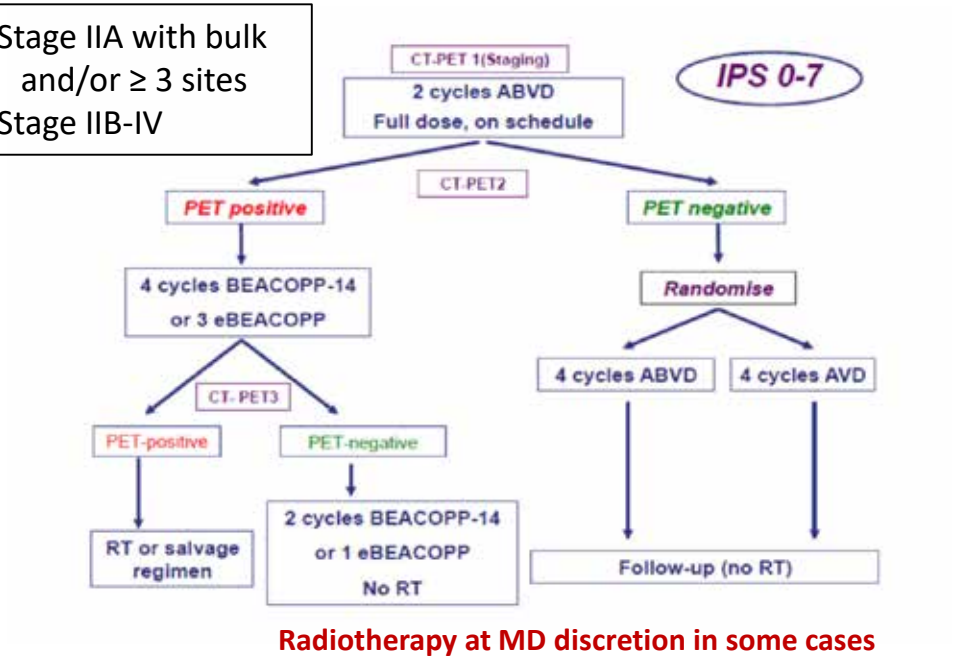


- **Median follow up 39.7 months**
- **escBEACOPP x6 after positive PET-2 improves PFS compared to historical controls**

Press OW, et al: J Clin Oncol, 2016

RATHL Trial: Study design

Stage IIA with bulk and/or ≥ 3 sites
Stage IIB-IV



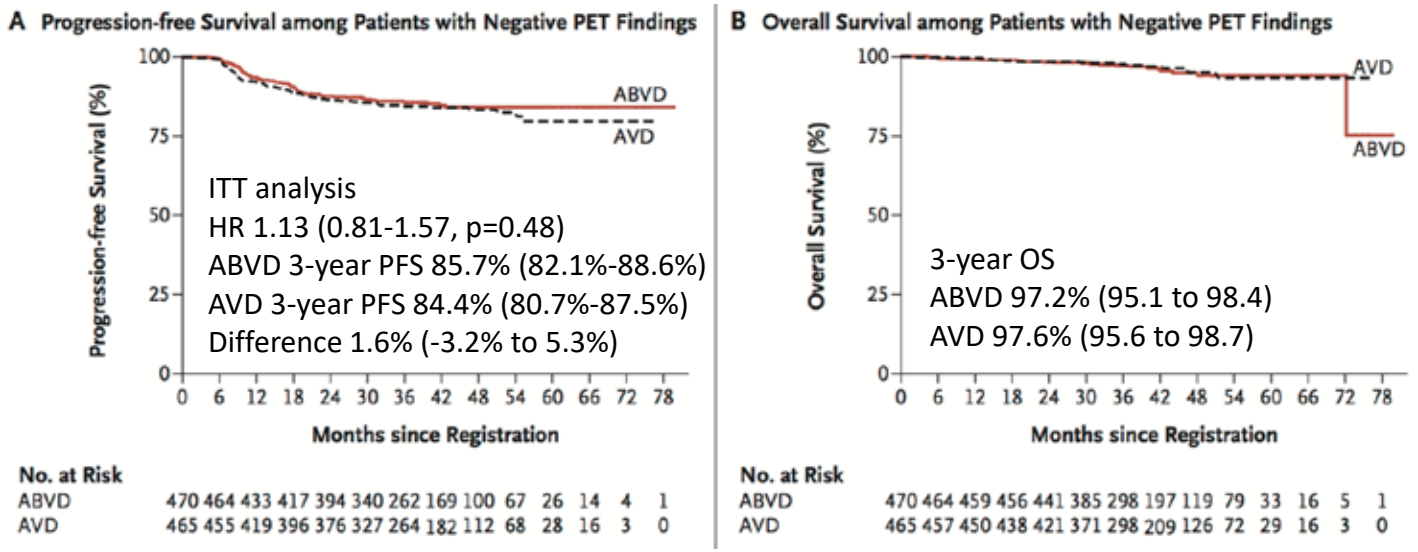
Radiotherapy at MD discretion in some cases

Characteristic	Number or %
Median age	33 (18-79)
Male	55%
Stage II III IV	41% 31% 28%
B symptoms	61%
Bulky disease	31%
PS 0-1	96%
IPS 0-1 2-3 ≥ 4	34% 49% 18%

Johnson P, et al. N Engl J Med 374:2419-29, 2016

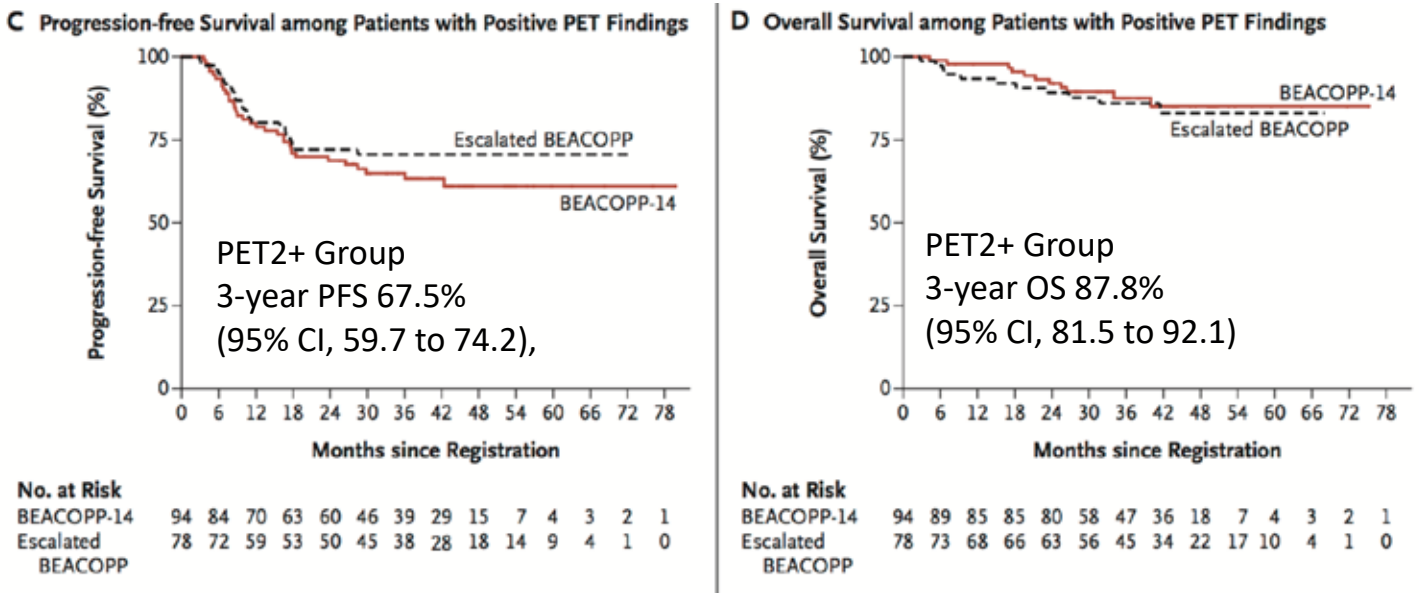
RATHL Trial: Results in PET2 negative patients

Median follow up 41 months



- No statistical difference in 3-year PFS and OS
- Just outside pre-determined non-inferiority margin of 5%

RATHL trial: Results in PET2 positive patients



- **Improved PFS in PET2 positive patients compared to historical controls**

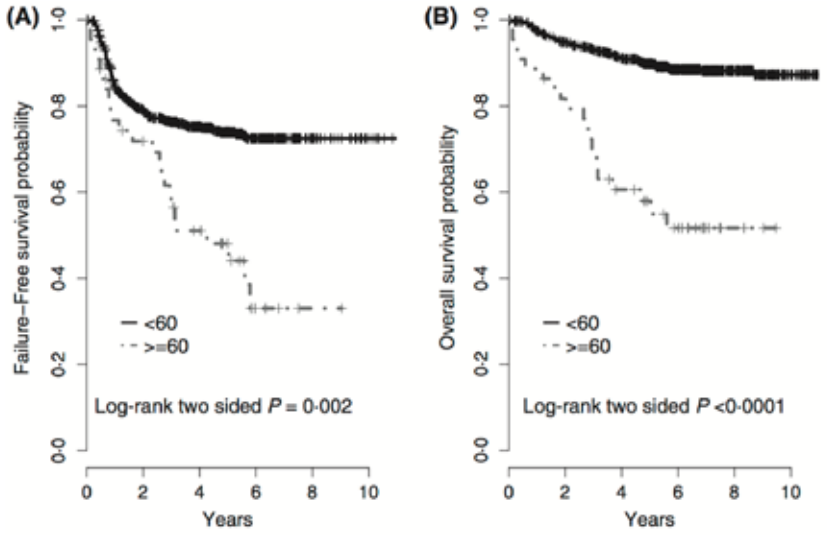
Johnson P, et al. N Engl J Med 374:2419-29, 2016

ABVD in patients age ≥ 60

- GHSG analysis of 117 patients receiving ABVD on HD10 and HD11 studies
  - Lower proportion of patients with RDI ≥ 80% (59% vs. 85%)
  - Higher TRM (5% vs. <1%)

Böll B, et al. J Clin Oncol 31:1522-9, 2013

Inferior outcomes in advanced HL patients age ≥ 60



- 45 patients treated with ABVD or Stanford V in E2496 trial

Evens AM, et al. Br J Haematol 161:76-86, 2013

Increased toxicity and TRM in patients age ≥ 60

	Age ≥ 60 years (n = 45)			Age < 60 years (n = 789)		
	Grade†			Grade†		
	3	4	5	3	4	5
Toxicity type	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Haematological	11 (24)	31 (69)	–	372 (47)	308 (39)	–
Non-haematological	14 (31)	6 (13)	4 (9)	322 (41)	53 (7)	2 (<1)

- 11/45 (24%) patients developed bleomycin lung toxicity
  - 2/11 (18%) died

Evens AM, et al. Br J Haematol 161:76-86, 2013

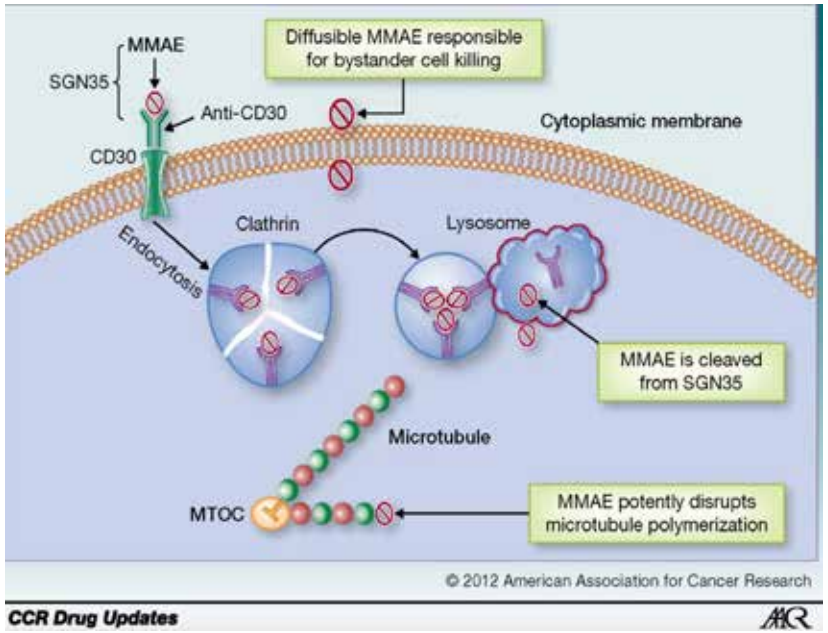
- De-escalation based on negative interim PET has been widely adopted and integrated into NCCN guidelines
- Escalation to escBEACOPP remains controversial due to lack of control arm, though is an option for select patients

- Do novel agents have the opportunity to improve efficacy while minimizing long term side effects?

Brentuximab vedotin

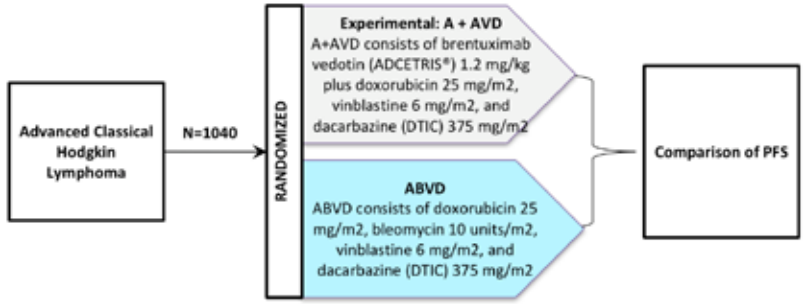
- Anti-CD30 antibody-drug conjugate
- FDA approved
  - Relapsed HL after auto HSCT
  - Failure of 2 regimens in patients not eligible for transplant
  - Consolidation for high risk HL patients after auto HSCT
  - CD30+ mycosis fungoides/cutaneous ALCL
  - Relapsed ALCL

  - *Untreated Advanced HL with chemotherapy*



Deng C, et al. Clin Cancer Res 19:22-7, 2013

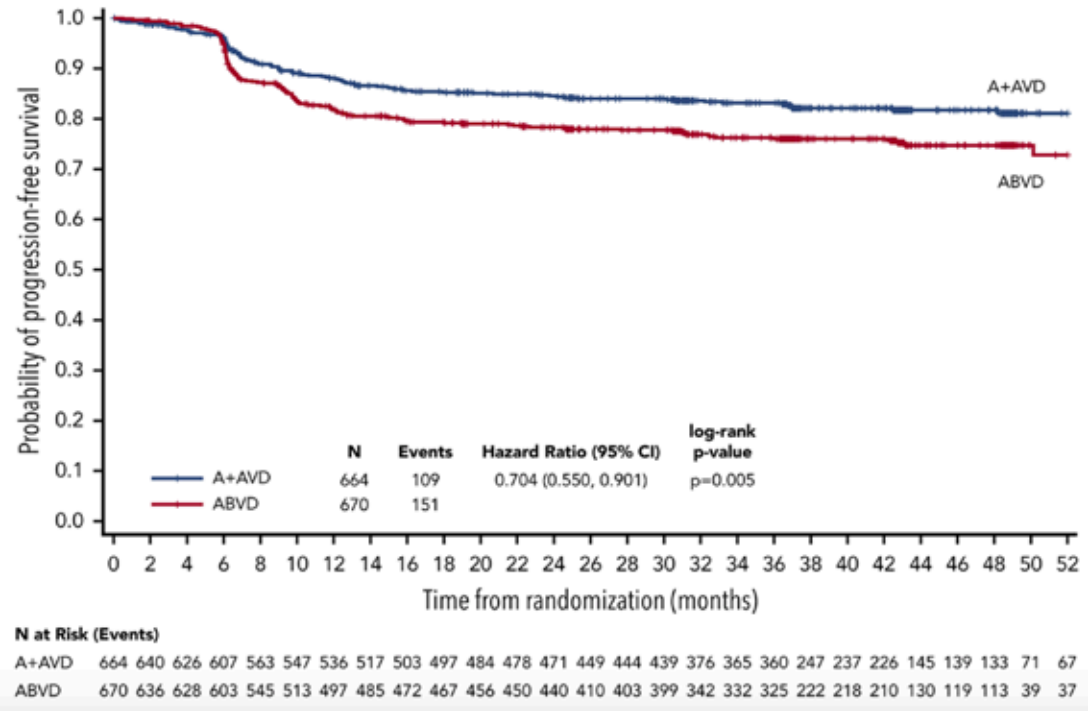
Can brentuximab improve outcomes in patients with advanced stage HL?



- International phase III randomized clinical trial
  - Brentuximab + AVD (A-AVD)
  - ABVD

Characteristic	Number or %
Median age Age ≥ 45 Age ≥ 60	36 (18-83) 34% 14%
Male	58%
Stage III IV	36% 64%

A-AVD associate with modest mPFS improvement over ABVD



- Median follow up 37.1 months
- Primary endpoint - 3 year modified PFS
  - A-AVD: 83.1% (95% CI 79.9-85.9)
  - ABVD: 76.0% (95% CI 72.4–79.2)

Benefit not as strong as predicted but was statistically significant

Connors et al. NEJM 2018
Straus et al. Blood 2020

A-AVD associated with higher rates of toxicity

- A-AVD: 7/9 on study deaths due to neutropenia (no primary GCSF)in the A+AVD arm were associated with neutropenia
- ABVD: 11/13 on study deaths due to pulmonary toxicity
- Protocol later amended to give A-AVD patients primary GCSF (n=83)
  - Febrile neutropenia reduced from 19% to 11%
  - Grade ≥3 infections reduced from 18% to 11%.

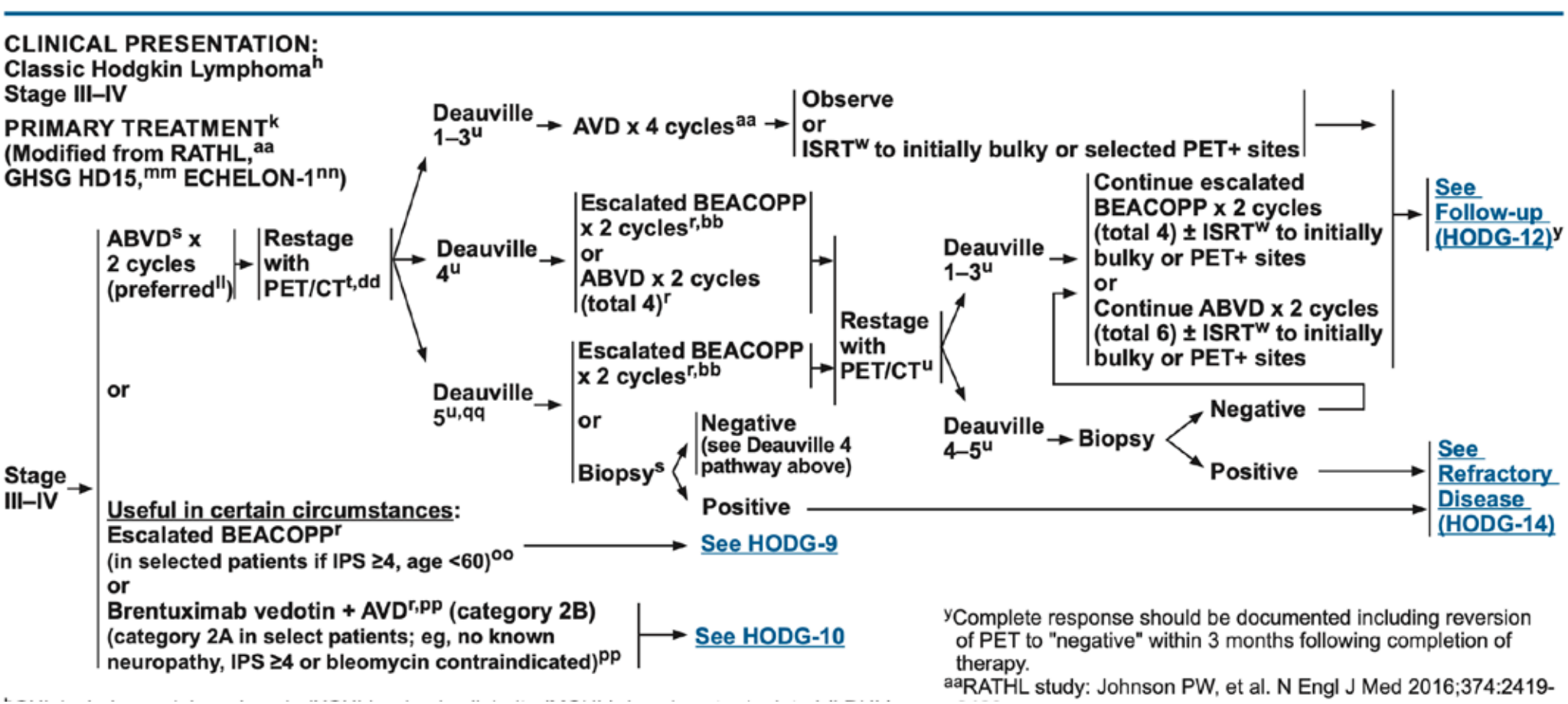
Toxicity	A-AVD	ABVD
Neutropenia	58%	45%
Febrile neutropenia	19%	8%
Grade ≥ 3 infection	18%	10%
Peripheral neuropathy	67%	43%
Peripheral neuropathy grade ≥ 3	11%	2%
Pulmonary toxicity grade ≥ 3	≤ 1%	3%

Should A-AVD be the new standard of care for advanced stage HL?

- **FOR**
- Improved 2 year mPFS
  - Statistically significant and met pre-specified end point
  - Predicted 8% vs. 4.9% difference
- Fewer relapses mean fewer patients subjected to cost/toxicity/infertility due to auto transplant
- Febrile neutropenia/infection likely overstated since only 83 patients had later mandated GCSF
- Not up to individual providers to decide a regimen based on cost if patients insurance will cover a more efficacious treatment

- **AGAINST**
- **NNT: 14 patients to prevent one treatment failure (based on 3 year data)**
- **Most patients who fail can likely be salvaged with brentuximab-based salvage regimen**
- A-AVD is more toxic
- A-AVD + GCSF costs $$$
  - > $100,000 for Brentuximab alone

NCCN Hodgkin Guidelines



Take home points for boards– Advanced stage

- **It is reasonable to omit bleomycin after cycle 2 if interim PET negative (Deauville 1-3)**
- escBEACOPP should NOT be given to patients age 60+
- For younger patients, you will not have to decide between AAVD, ABVD, escBEACOPP, but should get at least 6 cycles
  - AAVD has not been widely adopted by experts outside of high risk patients (stage IV, IPS 4+) due to toxicity concerns (cat 2B except for IPS 4-7)
- Unlikely to have questions on escalation after positive interim PET due to lack of control arm (not in NCCN guidelines, but can be done for select patients

Relapsed/refractory HL

- Clinical trials strongly recommended in this setting!

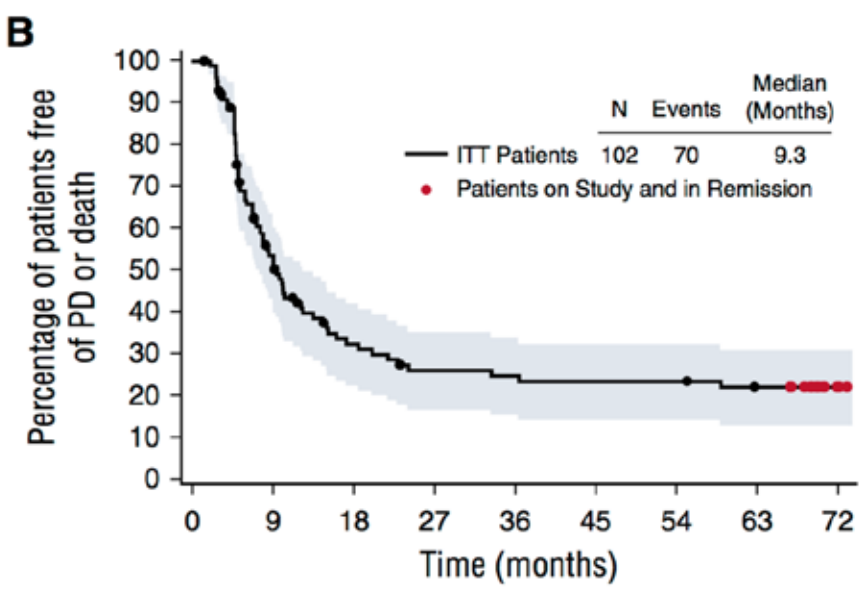
- 1st relapse in autologous transplant eligible patient
  - Salvage chemotherapy followed by autologous transplant
    - ICE, DHAP, GND, Brentuximab + bendamustine
      - Increasing evidence that brentuximab-based salvage may have higher CR rates
    - Brentuximab maintenance x 1 year for those with relapse within 1 year or extranodal sites at relapse (unclear impact in those with prior brentuximab)
  - Patients who do not achieve complete metabolic response are unlikely to be cured with transplant and should be considered for alternate salvage or treatment with novel agents

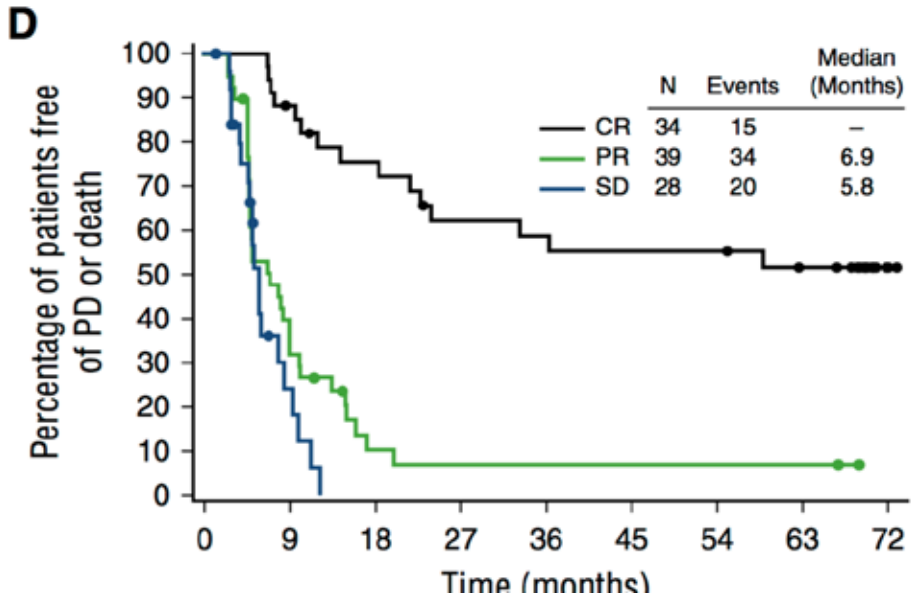
Novel drugs in treatment of relapsed HL

- Anti-CD30 antibody/drug conjugate
  - Brentuximab vedotin

- PD1 inhibitors
  - Nivolumab
  - Pembrolizumab

Brentuximab in patients who relapsed after autologous transplant



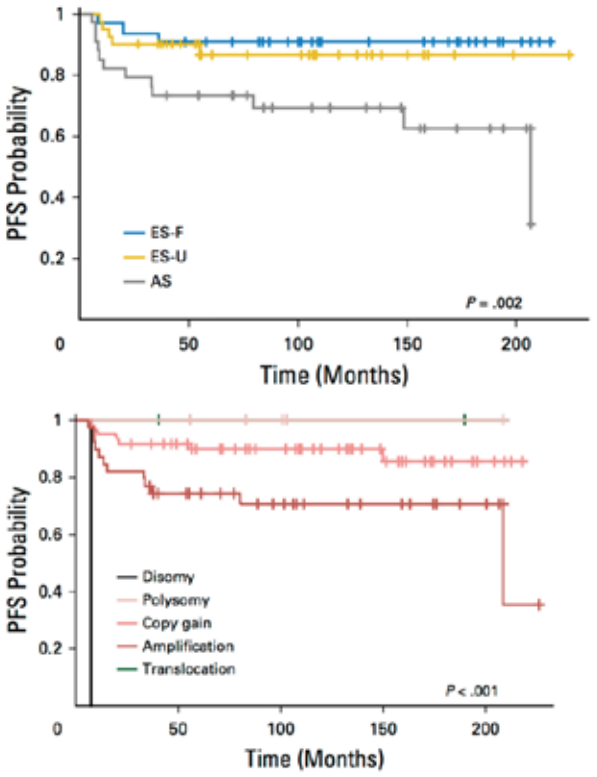


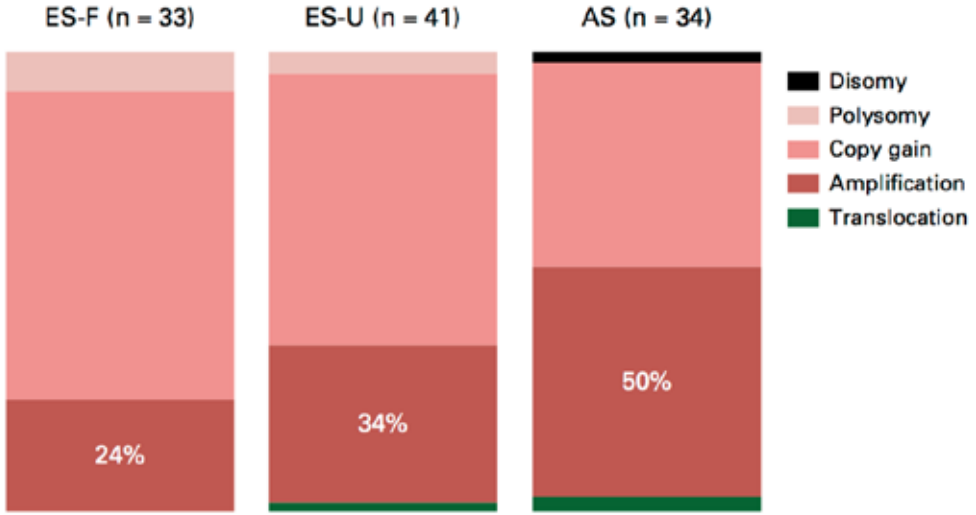
- **5 year end of study analysis**
- **9% (9/100) of patients achieved sustained CR without additional therapy**

Chen R, et al: Blood 128:1562-6, 2016

Hiding in plain sight: better understanding of HL biology

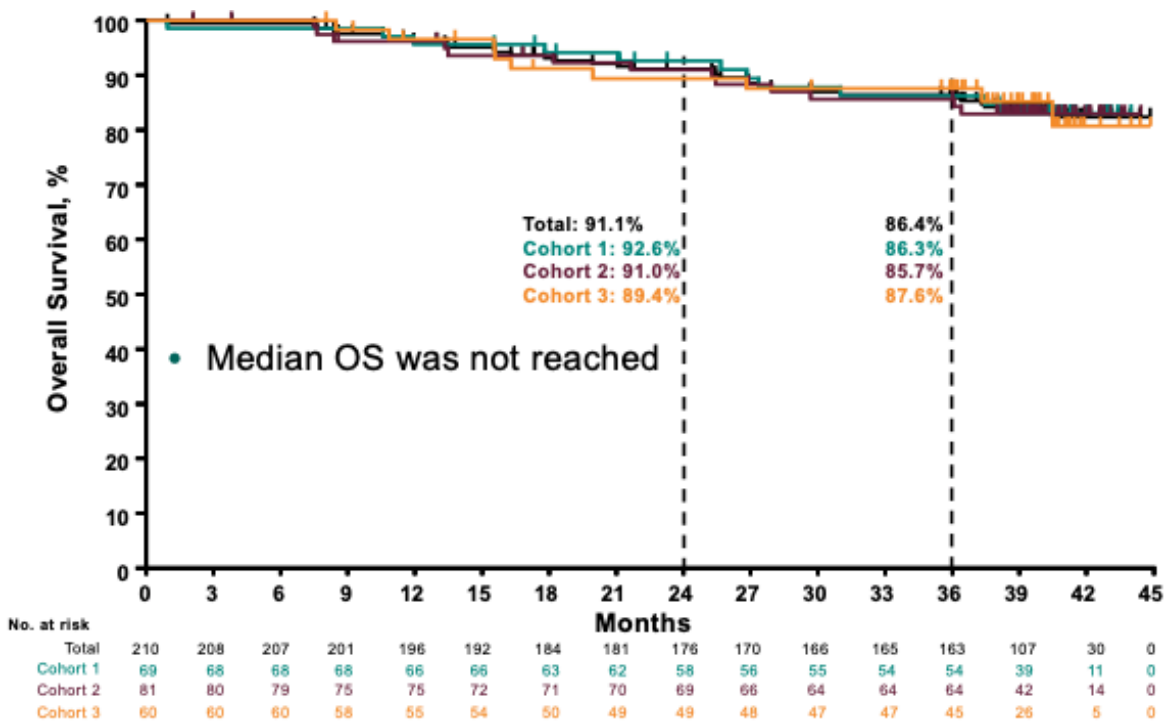
9p24.1 locus include PDL1, PDL2, JAK2

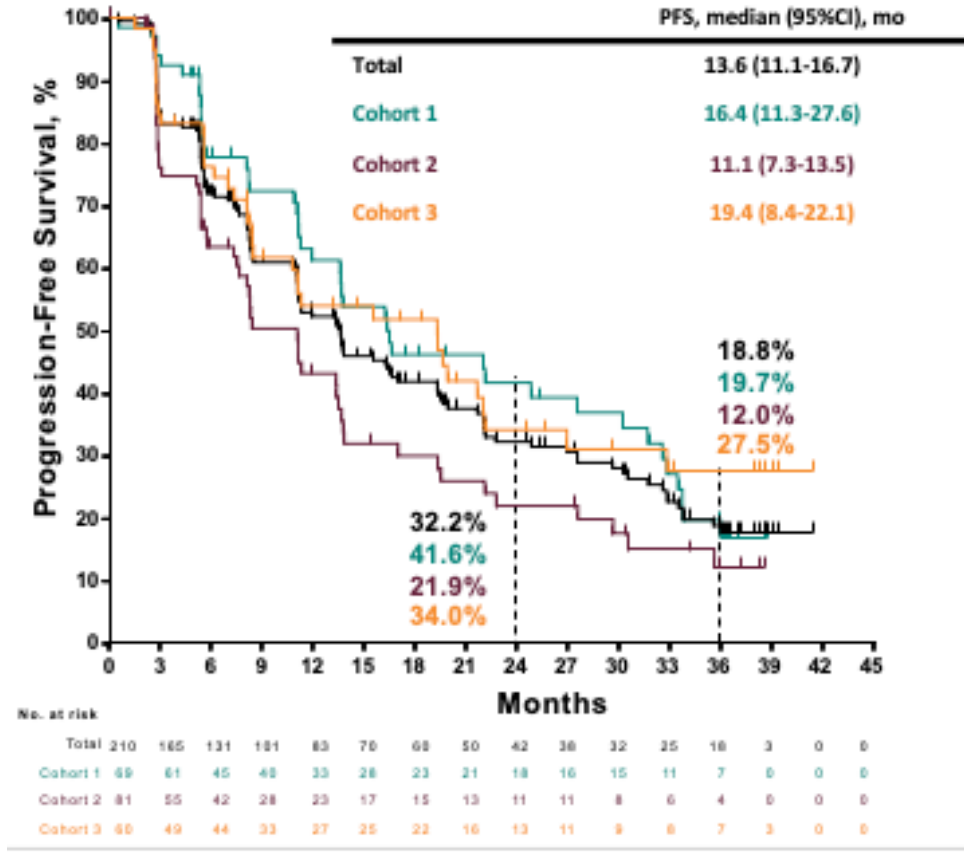




Roemer MG, et al. J Clin Oncol 34:2690-7, 2016

Long term follow up - pembrolizumab





- Visually, PFS and OS appear better with pembro (3 year OS 86%!)

Zinzani et al. ASH 2019

Boards take home points – relapsed HL

- **Salvage chemo then auto HCT if in CR for 1st relapse/primary refractory disease and transplant eligible**
- **Brentuximab maintenance x 1 year for those with relapse within 1 year/extranodal sites at relapse**
- Know mechanisms of novel agents and toxicities
  - Brentuximab – NEUROPATHY and cytopenias (esp if with chemo) and
  - PD1 inhibitors – autoimmune effects
- Transplant ineligible/transplant failure
  - For boards – would give brentuximab then PD1 agents (may be changing due to recent keynote-204 data)
  - In clinical practice – these patients should be STRONGLY considered for trials (combinations of novel agents)

Survivorship

- THERE IS ALMOST ALWAYS A SURVIVORSHIP QUESTIONS – THEY LOVE THIS TOPIC!!!

NCCN Surveillance Guidelines

Relapse detection

- Clinic visits
  - Every 3 months for first 2 years
  - Every 6 months years 3-5
  - Every 12 months beyond year 5
- Imaging
  - **NO PET SCANS IN ABSENCE OF SUSPECTED RELAPSE/SYMPTOMS**
  - **CT at clinician discretion in first 2 years**
- **Lab studies**
  - CBC, ESR (if elevated at diagnosis), chemistry panel

Late effect detection

- Clinic visits
  - Every 3 months for first 2 years
  - Every 6 months years 3-5
  - Every 12 months beyond year 5
- **Imaging**
  - **Breast imaging 7 years post RT**
  - Cardiac echo at 10 years
  - Carotid US at 10 years if neck RT
- Lab studies
  - CBC, ESR (if elevated at diagnosis), chemistry panel
  - **TSH if neck RT yearly** , Lipid panel every other year (can be done with PCP)

Nodular lymphocyte predominant Hodgkin lymphoma

- VERY rare subtype (about 400 new cases in US each year)
- Typically acts like an indolent lymphoma, so wide variety of treatment options (observation, chemotherapy, radiation) are accepted depending on clinical scenario

- So what can they test you on?

CHL vs. NLPHL pathology

	Classical HL	Nodular lymphocyte predominant HL
Tumor cells	Diagnostic RS cells. Mononuclear or lacunar cells	"L&H" or "popcorn" cells
Background	Lymphocytes, histiocytes, eosinophils, plasma cells	Lymphocytes, histiocytes
Fibrosis	Common	Rare
CD15	+ (15% can be negative)	-
CD30	+	-
CD20	-	+
PAX5	Dim +	+
EBV	+/-	-

Other take home points - NLPHL

- Consider chemotherapy (rituximab containing regimen, R-CHOP, R-ABVD) for advanced stage, symptomatic patients
- Observation reasonable in asymptomatic advanced stage patients
- Limited stage patients have high rates of disease control with radiotherapy
- Late relapse common, often > 10 years after initial treatment
- Patients can **transform to T-cell/histiocyte rich DLBCL**
  - Spleen involvement highly predictive of eventual transformation
  - Re-biopsy if suspicion of transformation
  - **DOES NOT TRANSFORM TO CLASSICAL HODGKIN LYMPHOMA!**

Other special issues!!!

- No bone marrow biopsy needed at diagnosis if PET used for staging and no marrow involvement
  - Consider biopsy for unexplained cytopenias
    - Anemia common, but other cytopenias are not
- Avoid routine growth factors with ABVD due to ? increased risk of pulmonary toxicity (no primary prophylaxis)
- NO dose delays with ABVD due to neutropenia – treat on time with standard doses. Inferior outcomes with decreased dose intensity. Consider prophylactic antibiotics
- Repeat biopsy with refractory disease or relapse prior to starting subsequent therapy.

Questions?

Gastroenteropancreatic Neuroendocrine Tumors

Kit Wong, MD
Assistant Professor, Medical Oncology
University of Washington School of Medicine
Seattle Cancer Care Alliance

2020 Annual Comprehensive Hematology & Oncology Review Course

UNIVERSITY of WASHINGTON

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

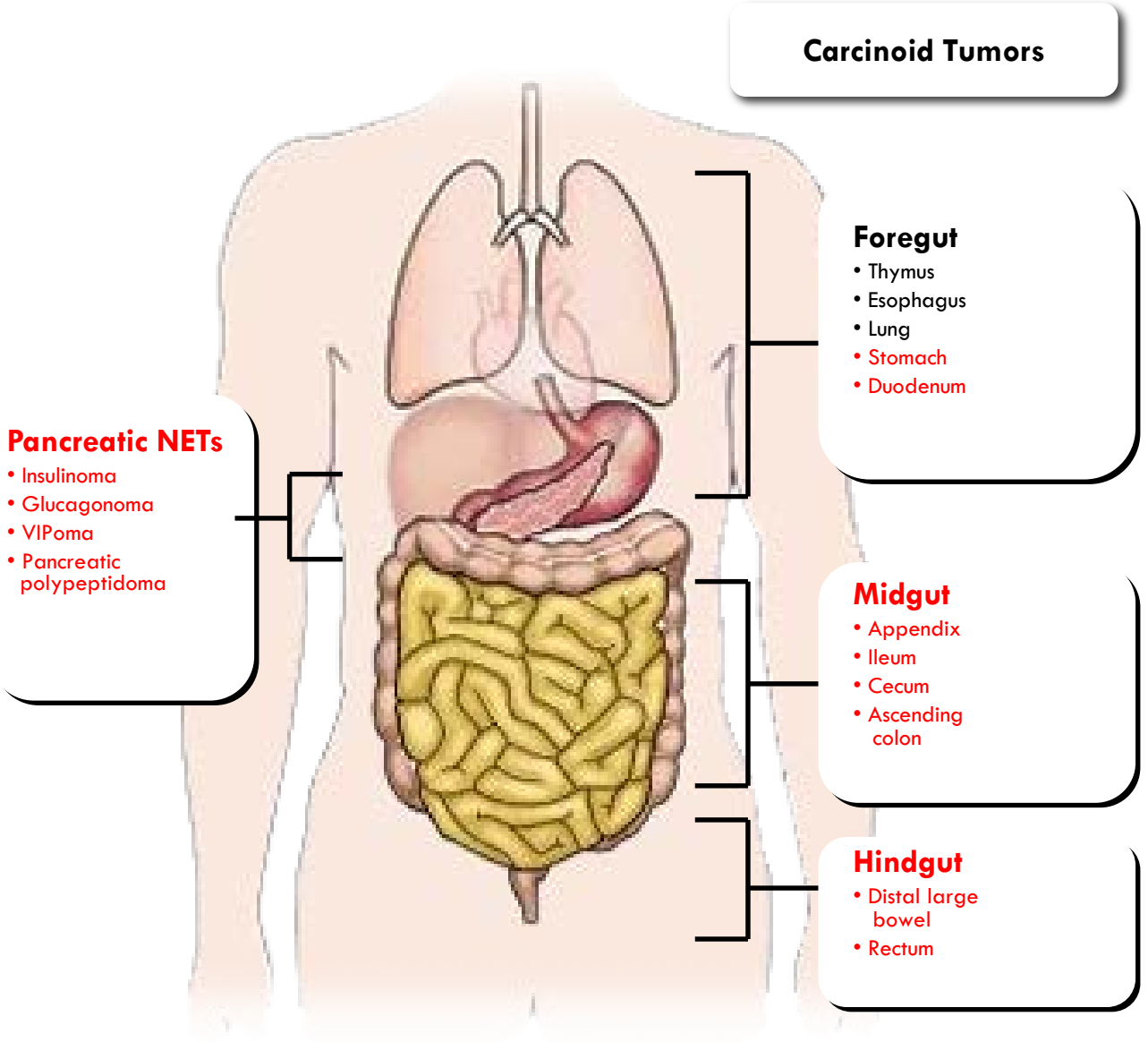
Disclosures

- Research funding through institution: Pfizer, Tanabe, Shanghai DeNovo, Genentech, Adaptimmune, Replimmune
- Advisory board: HalioDx

Abbreviations

- NET = neuroendocrine tumor
- PNET = pancreatic neuroendocrine tumor
- GEP NET = gastroenteropancreatic neuroendocrine tumor = neuroendocrine tumor of GI tract and pancreas

Sites of NETs



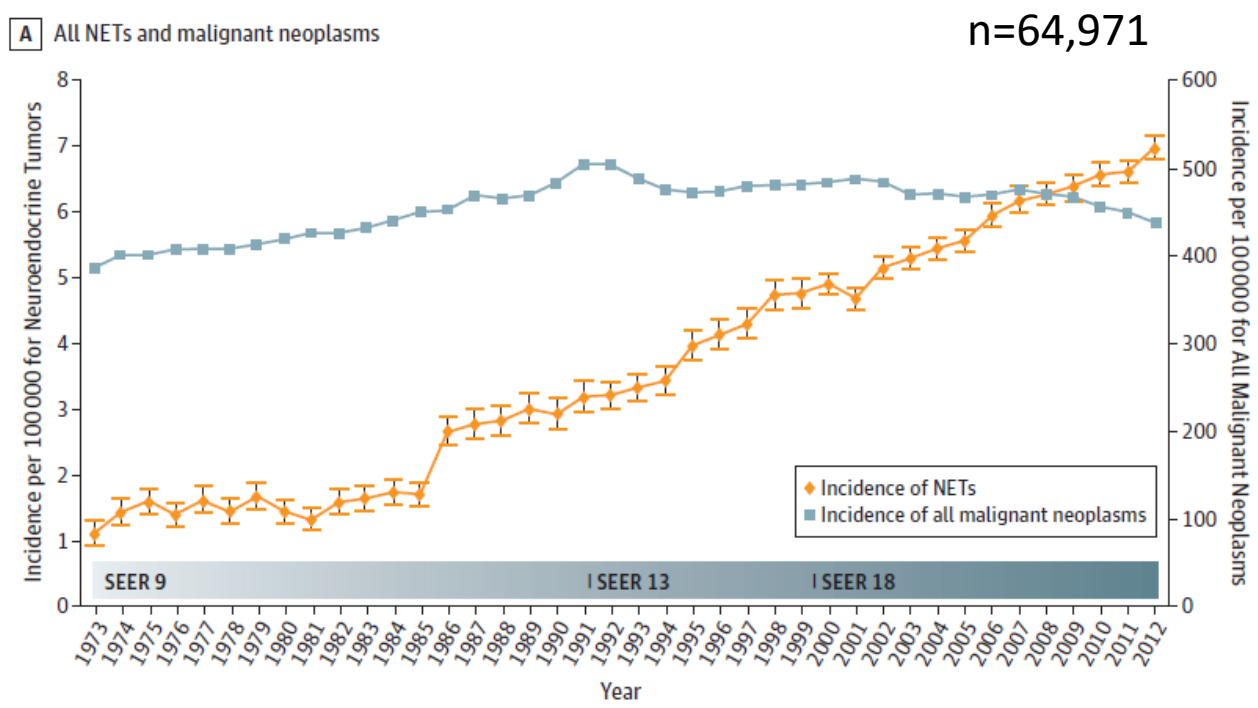
- Neuroendocrine cells found at various body sites
- Produce hormones and peptides with biological activity
- NETs can arise in different organs
- GI tract and pancreas are common sites of origin for NETs
- Some cases of unknown primary

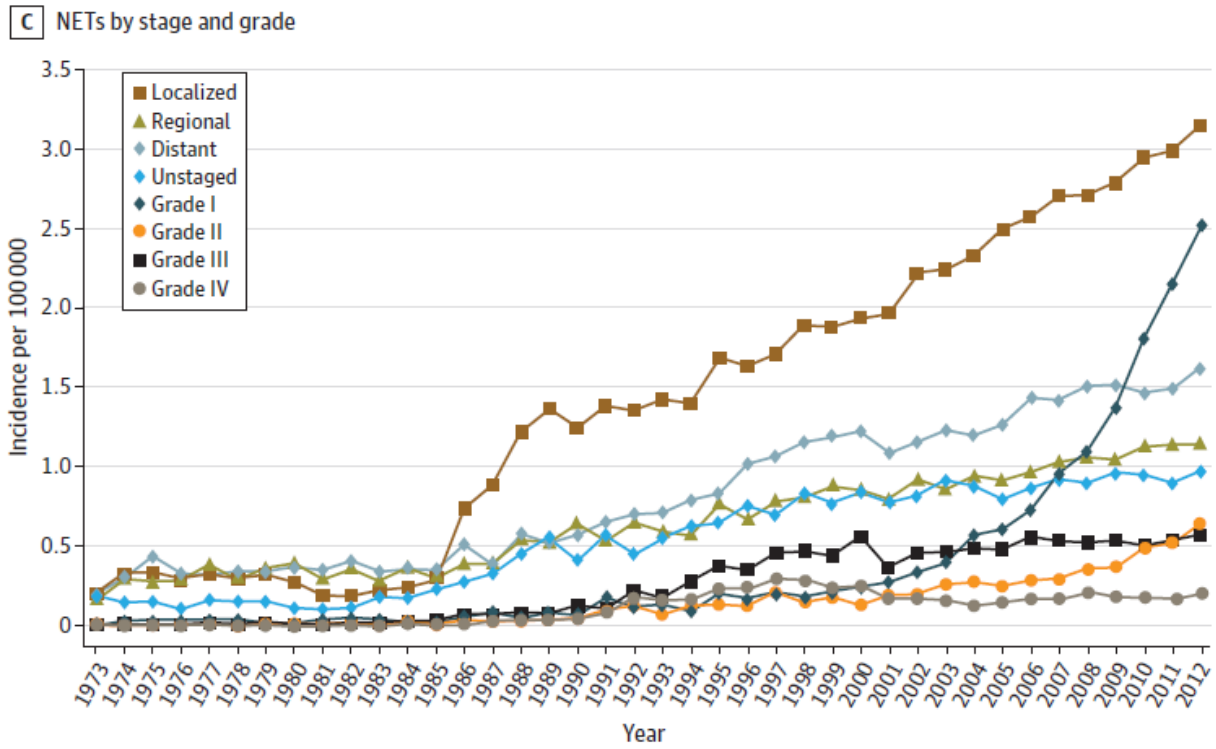
Epidemiology – SEER data

6.4-fold increase in incidence of all NETs from 1973 to 2012

Increased incidence of earlier stage disease

Figure 1. Incidence Trends of Neuroendocrine Tumors (NETs) From 1973 to 2012

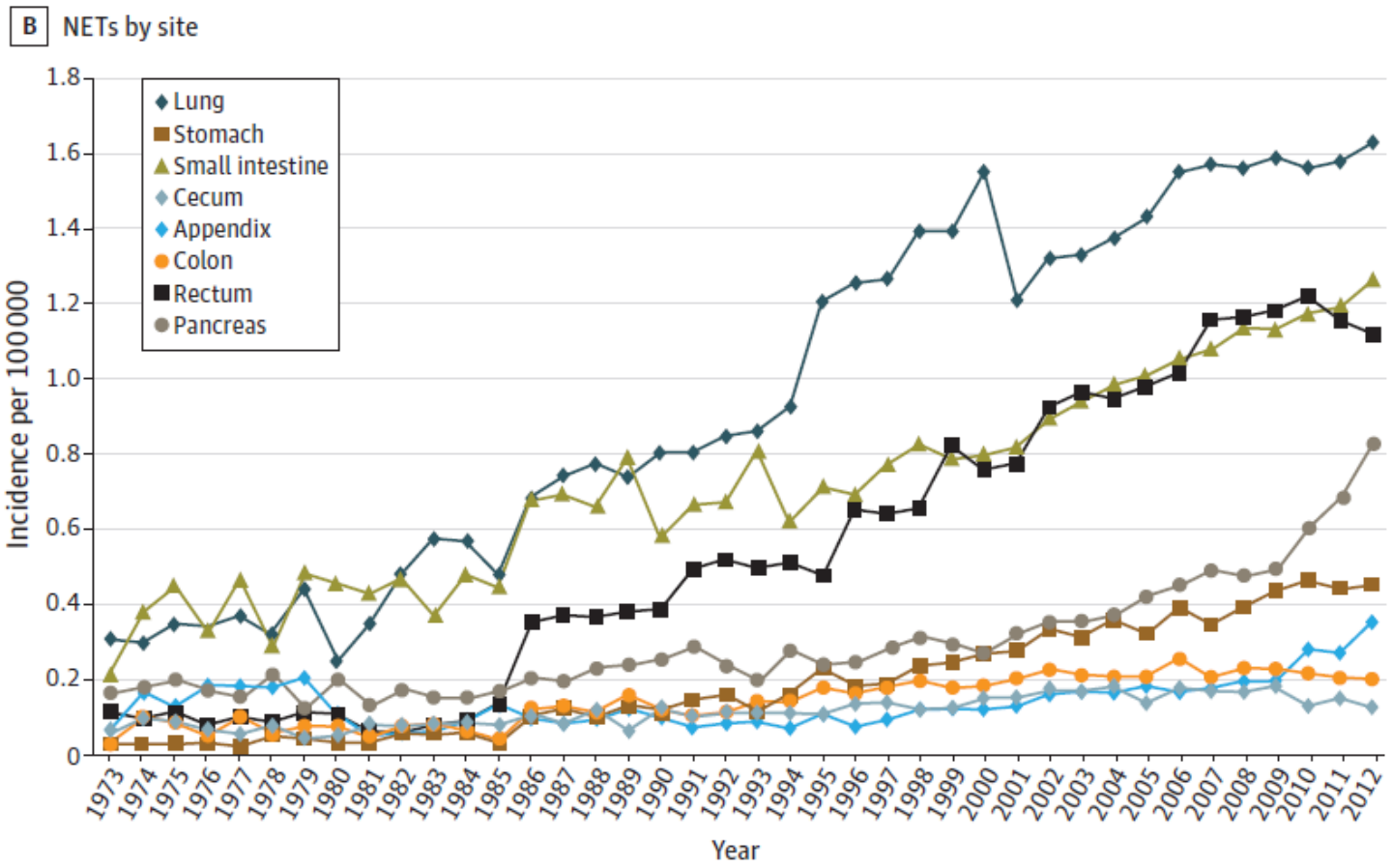




Trends may be related to improved diagnostic tests and more awareness of disease

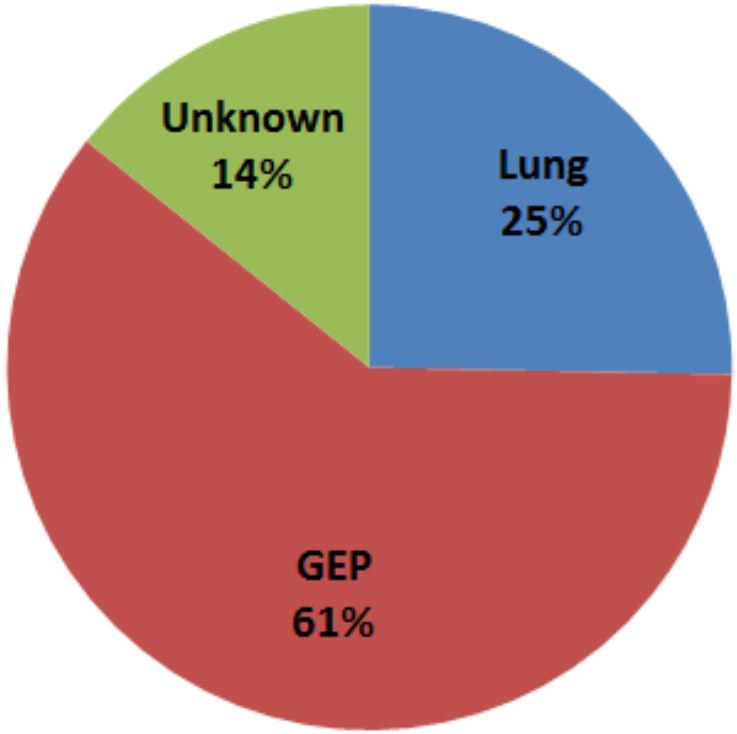
Dasari et al. JAMA Oncol. 2017;3:1335.

Incidence of NETs by anatomic site



Incidence per 100,000 persons (SEER 18, 2000-2012 data):

- Lung: 1.49
- GEP NETs: 3.56
- Unknown primary: 0.48



Among GEP NETs:
Small intestine: 29%
Rectum: 29%
Pancreas: 13%

Dasari et al. JAMA Oncol. 2017;3:1335.

Pathologic classification

- GEP NETs are characterized by strong immunohistochemical staining of synaptophysin and chromogranin
- Very heterogeneous group of tumors with different biology and behavior
- WHO classification – based on degree of proliferation (Ki67 index, mitotic count)

2010 WHO classification for gastrointestinal tract NETs (carcinoid tumors)

		GEP NETs[7]		
Differentiation	Grade	NET	Proliferative Rate	
Well-differentiated	G1 (low grade)	NET	< 2 mitoses/10 hpf AND < 3% Ki-67 index	**Neuroendocrine tumor**
	G2 (intermediate grade)	NET	2-20 mitoses/10 hpf OR 3%-20% Ki-67 index	
Poorly differentiated	G3 (high grade)	Neuroendocrine carcinoma small-cell type; neuroendocrine carcinoma large-cell type	> 20 mitoses/10 hpf OR > 20% Ki-67 index	**Neuroendocrine carcinoma**

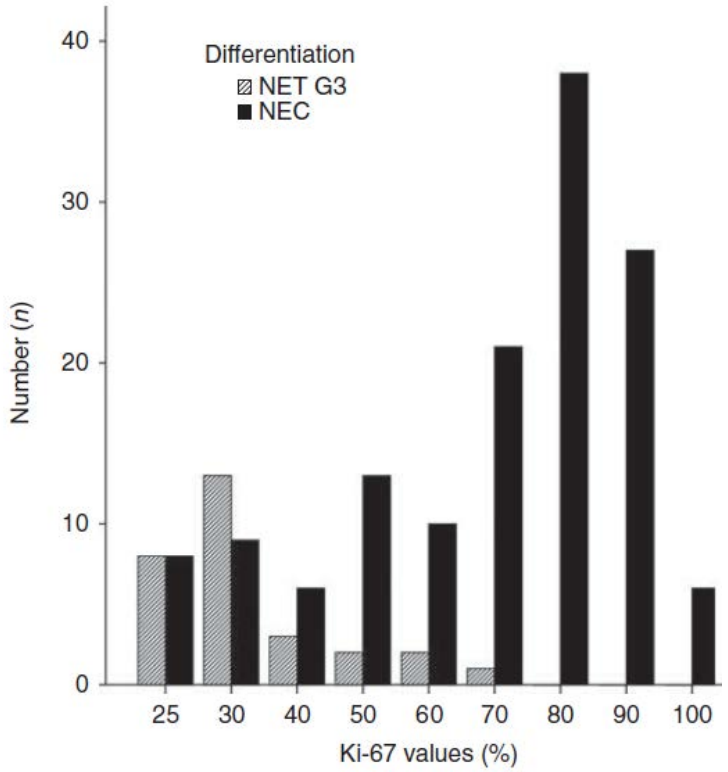
Abbreviations: GEP, gastroenteropancreatic; hpf, high-powered field; NET, neuroendocrine tumor.

1. Modlin et al. Lancet Oncol 2008;9:61. 2. Bosman et al. WHO Classification of Tumours of the Digestive System (ed 4), 2010.

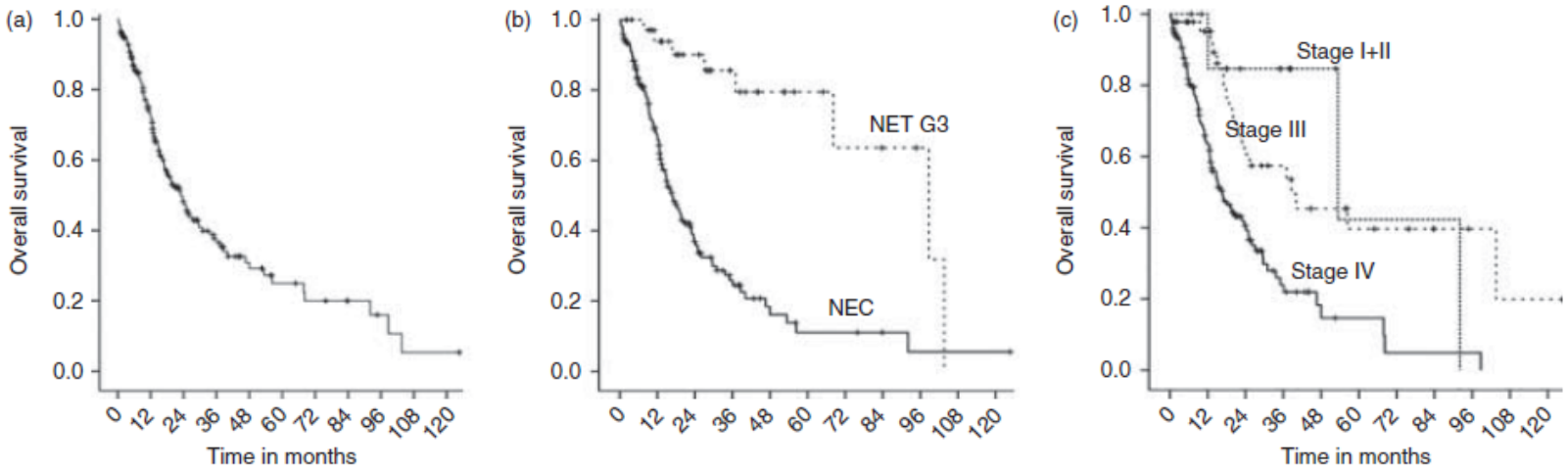
Grade 3 well-differentiated NETs (WD NETs)

- Distinct group of tumors from grade 3 poorly differentiated neuroendocrine carcinomas (PD NECs)
- Compared to PD NECs, the grade 3 WD NETs are more likely to:
  - Be diagnosed at earlier age and be functional
  - Have lower Ki67 (typically 21-55%)
  - Have +ve somatostatin receptor imaging
  - Carry mutations associated with low/intermediate grade NETs (i.e. mutations in DAXX, ATRX, MEN1)
  - Have longer overall survival (i.e. median OS 98.7 months for WD NETs vs. 17.0 months for PD NECs, $p<0.001$)

Heefeld et al. Endocr Relat Cancer 2015;22:657.



WD G3 NETs have lower Ki67



Cell differentiation and TNM stage are independent prognostic factors for grade 3 neuroendocrine neoplasms

Heefeld et al. Endocr Relat Cancer 2015;22:657.

2017 WHO classification for PNET

Neoplasm				Proliferation	
Type	Differentiation Status	Definition	Grade	Ki67 (% of ≥500 cells)	Mitotic Count (2 mm^2)
NEN	Well differentiated	NET	G1	<3	<2
			G2	3–20	2–20
			G3	>20	>20
	Poorly differentiated	NEC	(default G3)	>20	>20
		Small cell type			
		Large cell type			
MiNEN[a]	Well/poorly differentiated	*NET or NEC*	*G1-G3*	See above	See above
		ADC[b] or SCC	*G1-G3*	See Ref.[11]	See Ref.[11]

- Takes into account the heterogeneity of PNETs
- Grade 3 includes both well-differentiated PNET (PanNET G3) and poorly differentiated pancreatic NEC (PanNECs G3)
- Cell differentiation distinguishes between NET and NEC, not Ki67 value
- Therapy for the well-differentiated G3 tumors needs to be further studied

Inzani et al. Endocrinol Metab Clin N Am 2018;47:463.

Prognosis

- Wide range of prognosis based on:
  - Stage at diagnosis (localized > regional > distant)
    - By AJCC TNM staging system (stages 1-4)
  - Grade (well diff > poor diff)
  - Age at diagnosis (younger > older)
  - Primary site
  - Time of diagnosis (2000-2004 < 2005-2008 < 2008-2012)
    - Greater improvement in survival for advanced GEP NETs (especially carcinoids) due to better therapies

Dasari et al. JAMA Oncol. 2017;3:1335.

Functionality

- GEP NETs may produce and secrete bioactive amines and peptides (hormones, neuromodulators) causing clinical symptoms
- Classified as functional vs. non-functional
- Symptoms do not correlate with tumor burden
- Treatment of clinical syndromes of hormone excess: somatostatin analogue (SSA), except insulinoma

Carcinoids (8-35% functional)	PNETs (10-40% functional)
- Carcinoid syndrome → flushing, diarrhea, right sided valvular fibrosis, bronchoconstriction - Typically associated with serotonin and midgut NETs in the setting of liver metastases	Secretion of: - *Insulin (insulinoma) → hypoglycemia - *Gastrin (gastrinoma) → PUD - Vasoactive intestinal peptide (VIPoma) → diarrhea, hypoK - Glucagon (glucagonoma) → flushing, diarrhea, hyperglycemia

1. Choti et al. J Clin Oncol 2012;30:suppl abstr 4126. 2. Soga et al. J Exp Clin Cancer Res 1999;18:133. 3. Oberg K. Semin Oncol 2010;37:594. 4. Halfdanarson et al. Ann Oncol 2008;19:1727.

Characteristics of carcinoid tumors by location

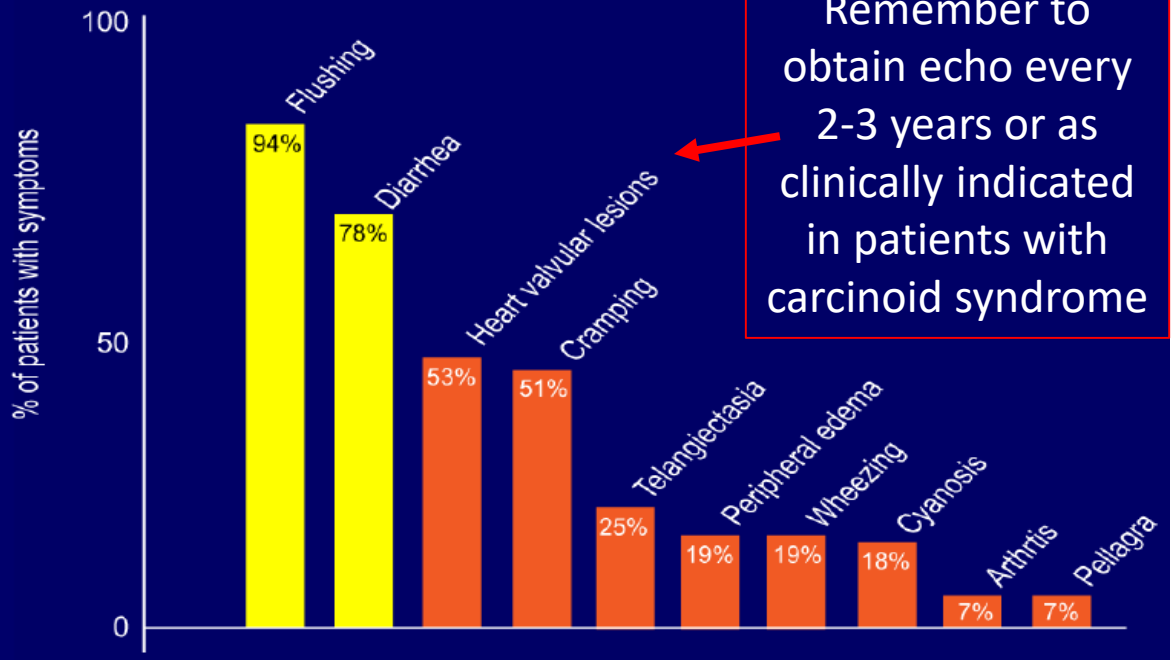
	Foregut	Midgut	Hindgut
Localization	Stomach, duodenum, bronchus, thymus	Jejunum, ileum, appendix, ascending colon	Transverse, descending, and sigmoid colon, rectum, genitourinary
Secretory products	5-hydroxytryptophan, histamine, multiple polypeptides	Serotonin prostaglandins, polypeptides	Variable
Carcinoid syndrome	Rare, and atypical when it happens (angioedema, hive-like pink flushing, rash)	**Classic** (flushing, diarrhea, wheezing due to bronchoconstriction, R valvular involvement)	Rare (usually found on lower GI endoscopy, patients may present with obstructive symptoms)

1. Loughrey et al. Endocrinol Metab Clin N Am 2018;47:557. 2. UptoDate.

Carcinoid syndrome

- Occurs in approximately 8% to 35% of patients with NETs and occurs mostly in cases of patients with hepatic metastases[1]
- Consequence of vasoactive peptides such as serotonin, histamine, or tachykinins released into the circulation[2,3]
- Manifested by episodic flushing, wheezing, diarrhea, and, potentially, the eventual development of carcinoid heart disease[2,3]

Percentage of patients with symptoms of carcinoid syndrome[4]



Remember to obtain echo every 2-3 years or as clinically indicated in patients with carcinoid syndrome

1. Rorstad O. *J Surg Oncol*. 2005; 89:151-60.
2. Modlin IM, Kidd M, Latich I, Zikusoka MN, Shapiro MD. *Gastroenterology*. 2005;128:1717-1751.
3. Vinik A, Moattari AR. *Dig Dis Sci*. 1989;34(3 Suppl):14S-27S.
4. Creutzfeldt W. *World J Surg*. 1996;20:126-131.

Workup

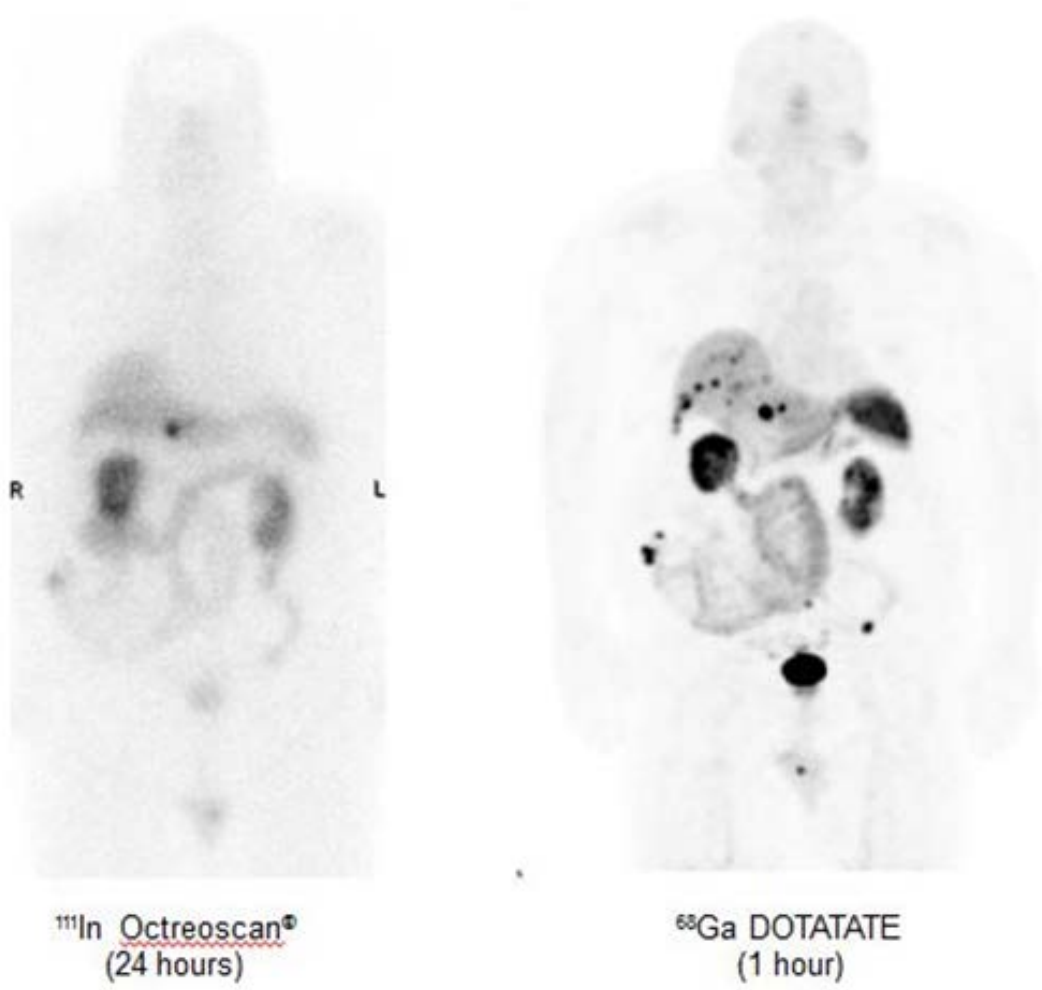
- Goals of workup
  - Assess primary site and stage
  - Characterize aggressiveness (grade, differentiation) – need tissue
  - Establish functionality
- NCCN guidelines (v2.2020)
  - Recommend: multiphasic CT or MRI abdomen/pelvis
  - As appropriate:
    - CT chest with or without contrast
    - Somatostatin receptor-based imaging (Ga68 dotatate PET/CT preferred, or Octreoscan)
    - Endoscopy
    - Biochemical evaluation as clinically indicated (if suspicious symptoms present)

NCCN Practice Guidelines (Neuroendocrine Tumors). https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

Somatostatin receptor-based imaging

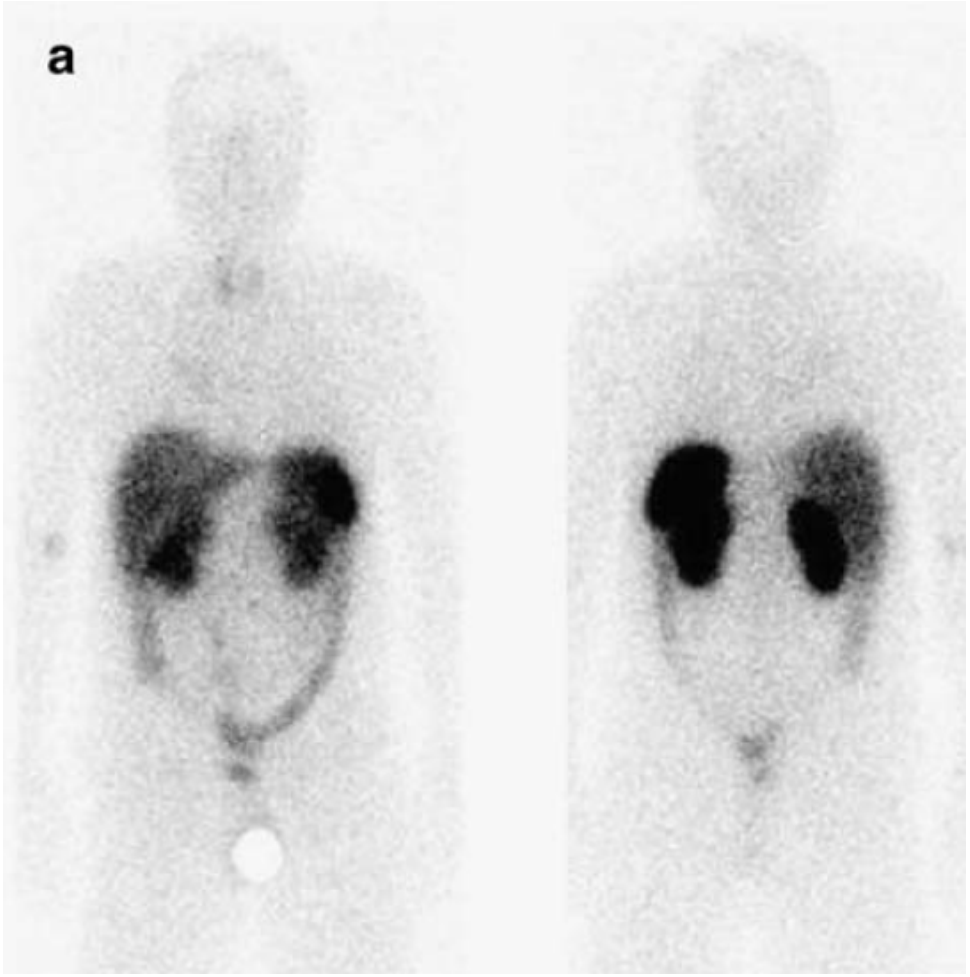
- >90% well-differentiated GEP NETs express variable levels of SSTR
- Imaging using radiolabelled SSAs
  - Bind to SSTR2 and 5 on NET cells
  - OctreoScan (Indium-111 pentetreotide)
  - Functional PET imaging (68Ga DOTATATE PET/CT) – more sensitive for detecting small lesions, shorter time (30-60 min)

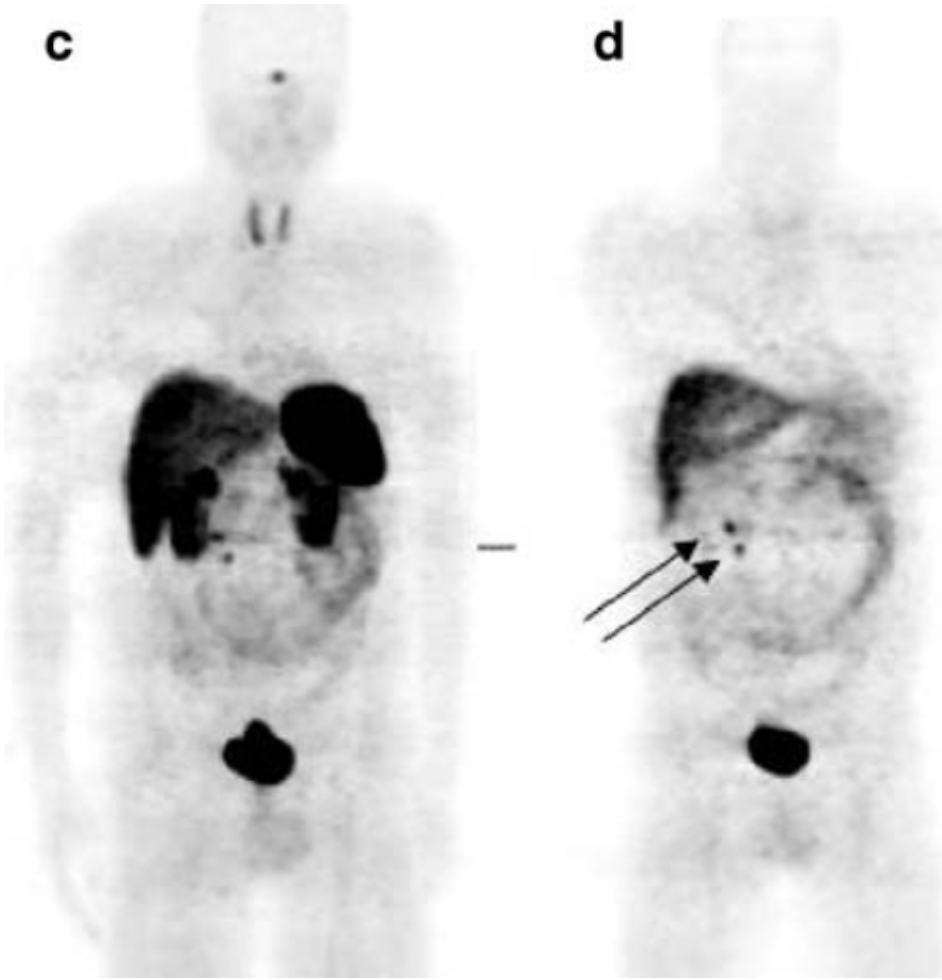
- **Should stop short-acting SSA 24 hours and long-acting SSA 5-6 weeks before imaging**
- **NOT recommended for routine surveillance**



http://www.carcinoid.org/2014/06/30/carcinoid-cancer-foundation-awards-grant-to-stanford-university/.

Kidd et al. Nat Rev Clin Oncol 2016;13:691.





111-In-DTPAOC SPECT

68-Ga-DOTATOC PET

Buchmann et al. Eur J Nucl Med Mol Imaging 2007;34:1617.

Biochemical testing (NCCN v2.2020)

	Location	Clinical Symptoms	Testing
NETs of Gastrointestinal Tract, Lung, and Thymus	Primary tumors in GI tract (ileum, appendix, rectum), lung, or thymus	• Primary tumors in the GI tract usually are not associated with symptoms of hormone secretion unless extensive metastasis. • Symptoms of hormone secretion may include flushing, diarrhea, cardiac valvular fibrosis, and bronchoconstriction. • Bronchial/thymic tumors may be associated with classic carcinoid syndrome as well as Cushing's syndrome.	• Chromogranin A (category 3) • 24-hour urine or plasma 5-HIAA ▸ Foods to avoid for 48 hours prior to and during testing: avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts/pecans, plantains, kiwi, dates, grapefruit, honeydew, or walnuts. • Test for Cushing's syndrome (NE-C, 2 of 3)
PanNET (see subtypes below)	Pancreas	Depends on hormone secreted, can be clinically silent	• Serum pancreatic polypeptide (category 3) • Chromogranin A (category 3)
Insulinoma	Pancreas	Hypoglycemia	• While hypoglycemic: ▸ Serum insulin ▸ Pro-insulin ▸ C-peptide • See Workup for insulinoma (PanNET-3)
VIPoma	Most common in pancreas, can be extra pancreatic	Diarrhea, hypokalemia	Serum VIP
Glucagonoma	Pancreas	Flushing, diarrhea, hyperglycemia, dermatitis, hypercoaguable state	Serum glucagon
Gastrinoma	Pancreas or duodenum	Gastric ulcers, duodenal ulcers, diarrhea	Serum gastrin[a]

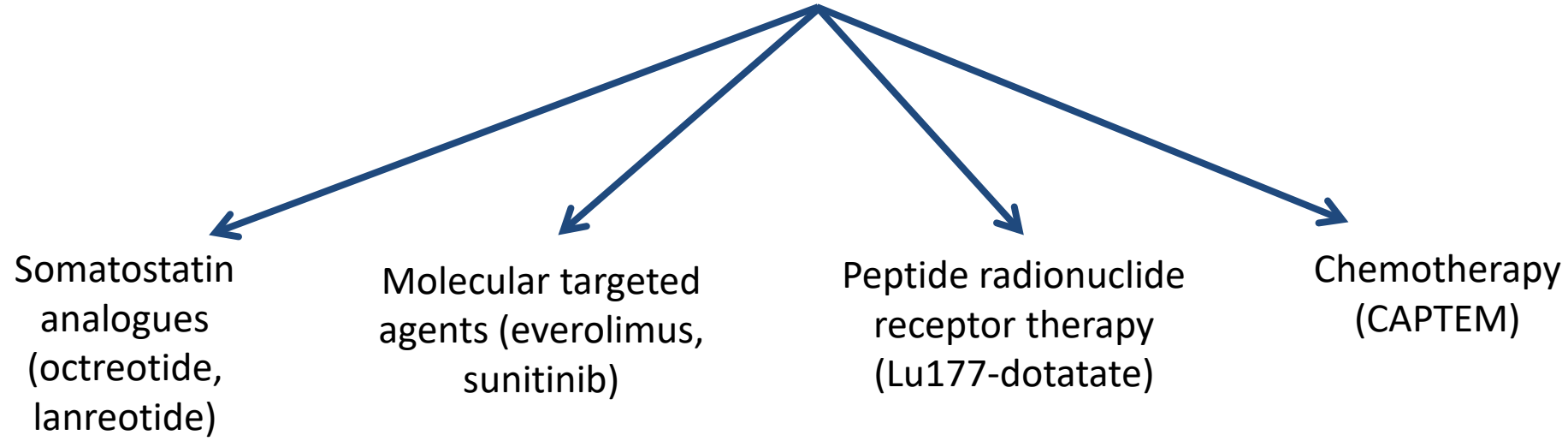
- Chromogranin A
  - Ubiquitous distribution in neuroendocrine tissues, stored in secretory granules and secreted with modified amines
  - Sensitive, but non-specific
  - Trend is more important

NCCN Practice Guidelines (Neuroendocrine Tumors). https://www.nccn.org/professionals/physician_gls/pdf/neuroendocrine.pdf

False elevations

- Chromogranin A
  - Proton pump inhibitors (should be discontinued at least 2 weeks before)
  - Other disorders: endocrine, GI, cardiac, inflammatory diseases, renal impairment, other non-GI cancers
- 24h urinary 5-HIAA (5-hydroxyindoleacetic acid)
  - Ingestion of tryptophan/serotonin-rich foods
  - Avoid for 48h before measurement: avocado, banana, cantaloupe, eggplant, pineapple, plum, tomato, hickory nut/pecan, plantain, kiwi, date, grapefruit, honeydew, walnut
  - Malabsorption syndromes

Systemic therapy for metastatic GEP NETs



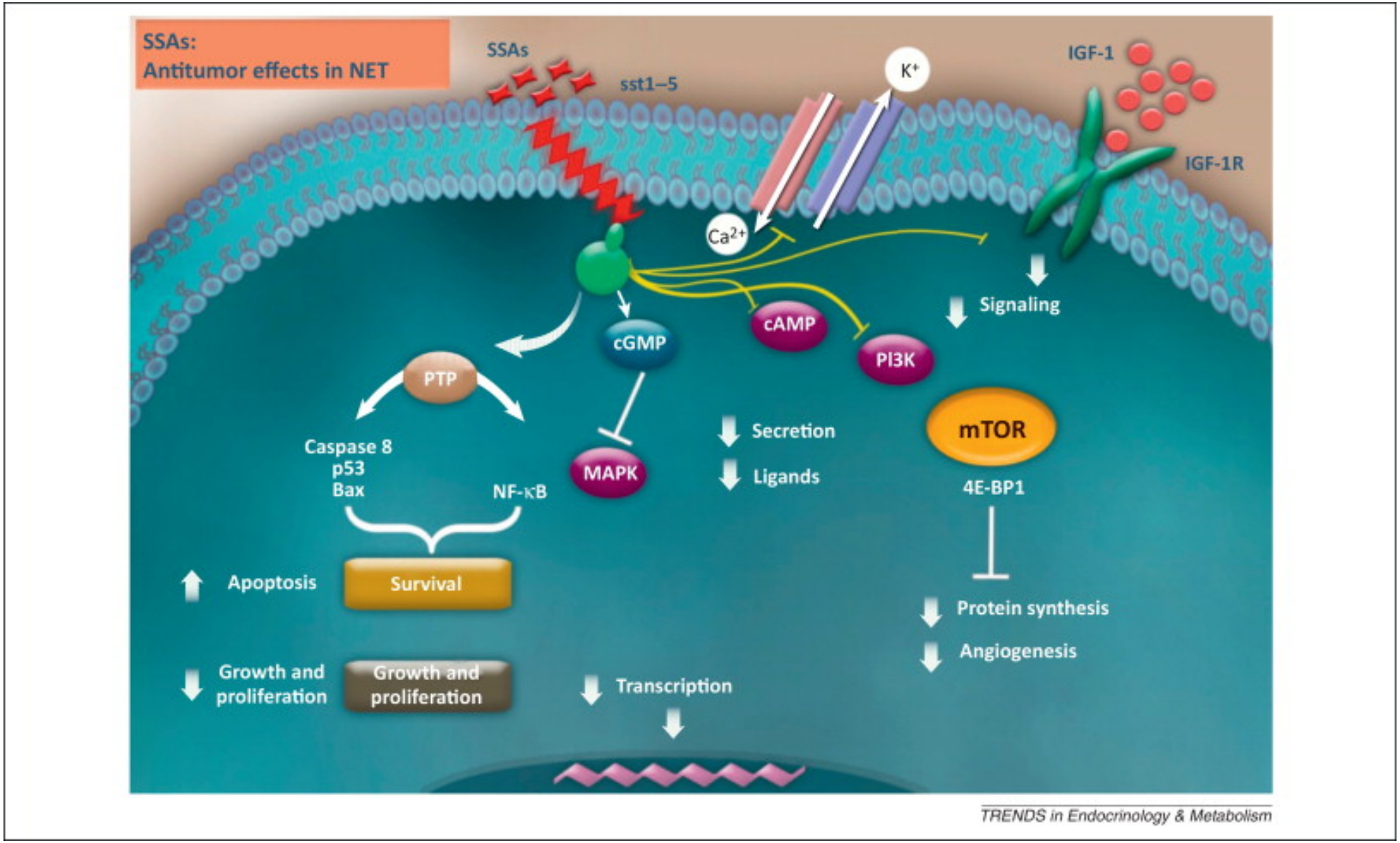
- For symptom (if present) and tumor control
- Multidisciplinary approach if appropriate
- Therapy selection depends on:
  - Carcinoid vs. PNET, grade and cell differentiation, SSTR expression, symptoms, tumor burden, rate of growth

Systemic therapy for symptoms

- Clinical symptoms associated with hormone secretion
- SSA is mainstay of treatment
  - Octreotide
    - Highest affinity for SSTR2
    - Short-acting and long-acting formulations
    - Recommend short-acting for 2-3 weeks until steady levels of octreotide LAR are reached
  - Lanreotide (SSTR2) and pasireotide (SSTR1,2,3,5)
    - Equally effective as octreotide in controlling carcinoid syndrome
- Telotristat – for refractory carcinoid syndrome-related diarrhea
  - Tryptophan hydroxylase inhibitor in serotonin synthesis pathway
- Consider octreotide during surgery to avoid carcinoid crisis

1. Strosberg et al. J Clin Oncol 2014;19:930. 2. O'Toole et al. Cancer 2000;88:770. 3. Wolin et al. J Clin Oncol 2013;31:suppl 15s;abst 4031.

SSAs have anti-tumor activity against GEP NETs and inhibit growth factors



Chalabi et al. Trends in Endocrinology & Metabolism 2014;25:115.

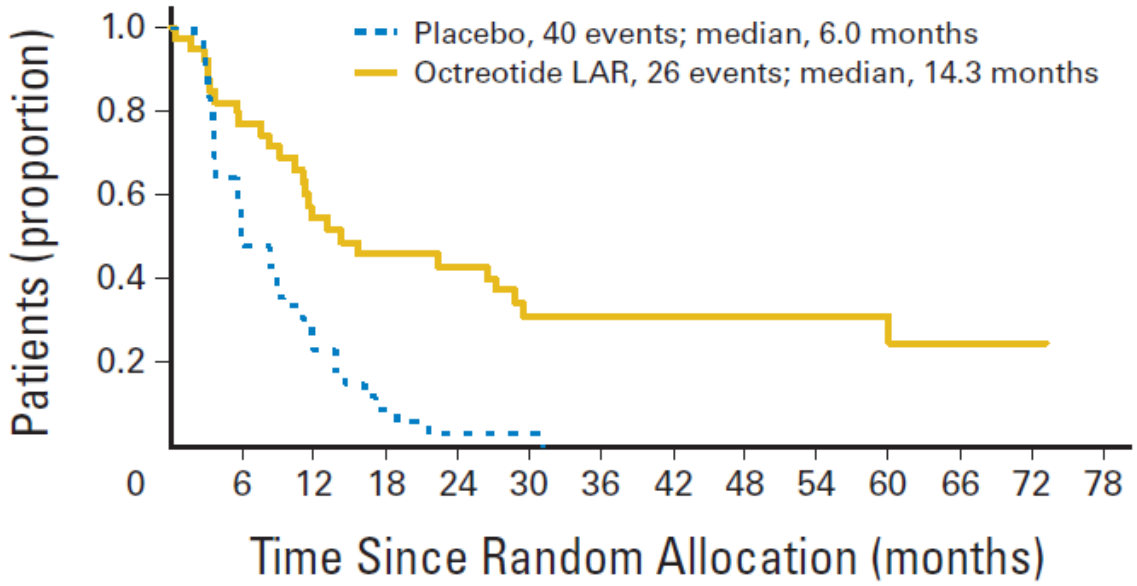
Octreotide

PROMID trial

Patients with metastatic well-differentiated midgut NETs, treatment naïve

- Octreotide LAR 30 mg IM every month (n=42)
- Placebo (n=43)

A



No. of patients at risk

Placebo	43	21	9	3	1	1	0	0	0	0	0	0	0	0
Octreotide LAR	42	30	19	16	15	10	10	9	9	6	5	3	1	0

Log-rank test stratified by functional activity: $P = .000072$, HR = 0.34 (95% CI, 0.20 to 0.59)

- Improvement in median time to progression (HR 0.34, 95% CI 0.2-0.59, p=0.000072)
- Stable disease: 67% vs. 37% (at 6m)
- No improvement in overall survival
- Both functional and non-functional tumors responded
- Most common adverse events related to GI tract (diarrhea, flatulence)

Rinke et al. J Clin Oncol 2009;27:4656.

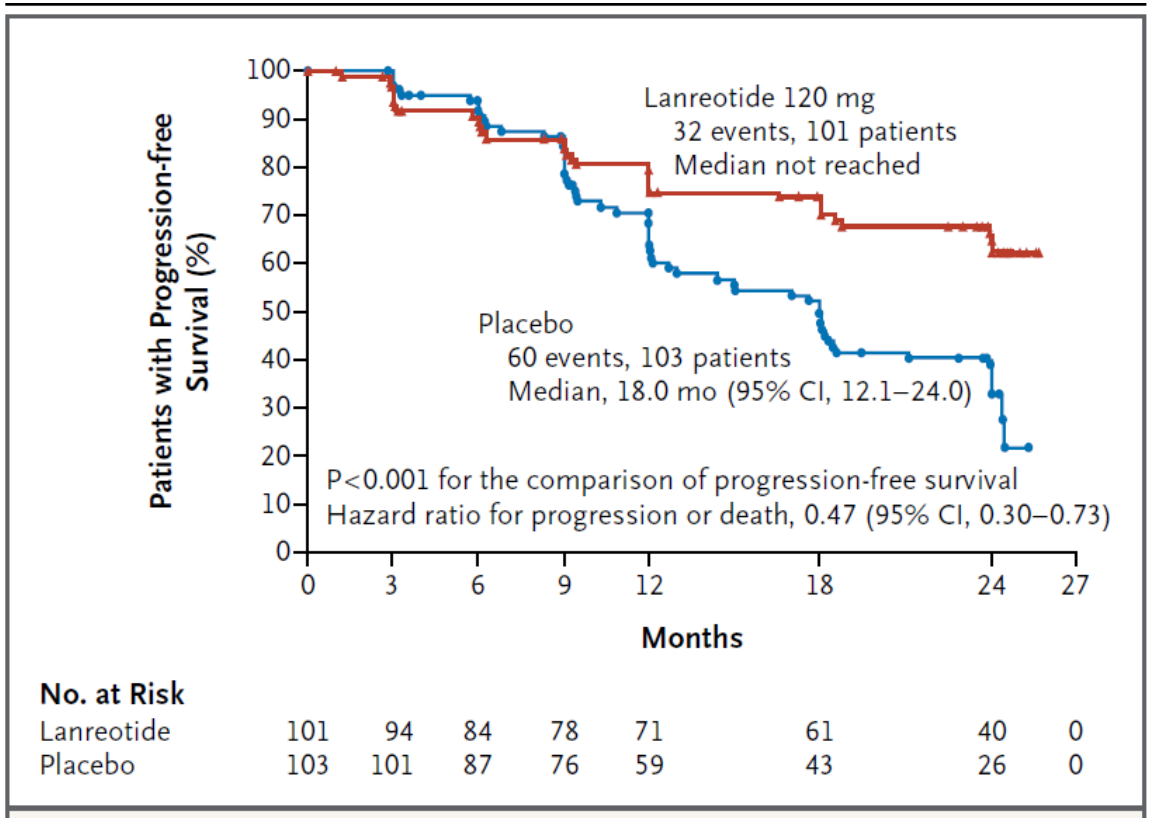
Lanreotide

CLARINET trial

- Patients with metastatic well differentiated NETs
  - PNET, mid/hindgut, unknown origin
    - SSTR positive, non-functioning

→ Lanreotide 120 mg deep SC every 28 days (n=101)

→ Placebo (n=103)



- Improvement in median progression-free survival
- PFS (at 24m): 65% vs. 33%
- Greater rate of reduction in chromogranin A by >50%
- No improvement in overall survival or quality of life
- Most common side effect: diarrhea (26% vs. 9%)

Caplin et al. N Engl J Med 2014;371:224.

Side effects of SSAs

- Injection site pain (8-10%)
- Nausea (9-30%)
- Abdominal cramps (4-44%), diarrhea (7-58%), steatorrhea (0-4%), flatulence (0.5-13%)
- Hyperglycemia (15%)
- Cholelithiasis/biliary sludge (52-62%)
  - Consider prophylactic cholecystectomy if anticipate long-term use
  - Assess with ultrasound of gallbladder and bile ducts every 6-12 months
  - Gallstones may be treated with ursodiol

1. Narayanan and Kunz. J Natl Compr Canc Netw 2015;13:109. 2. BC Cancer Agency Drug Manual.

Everolimus

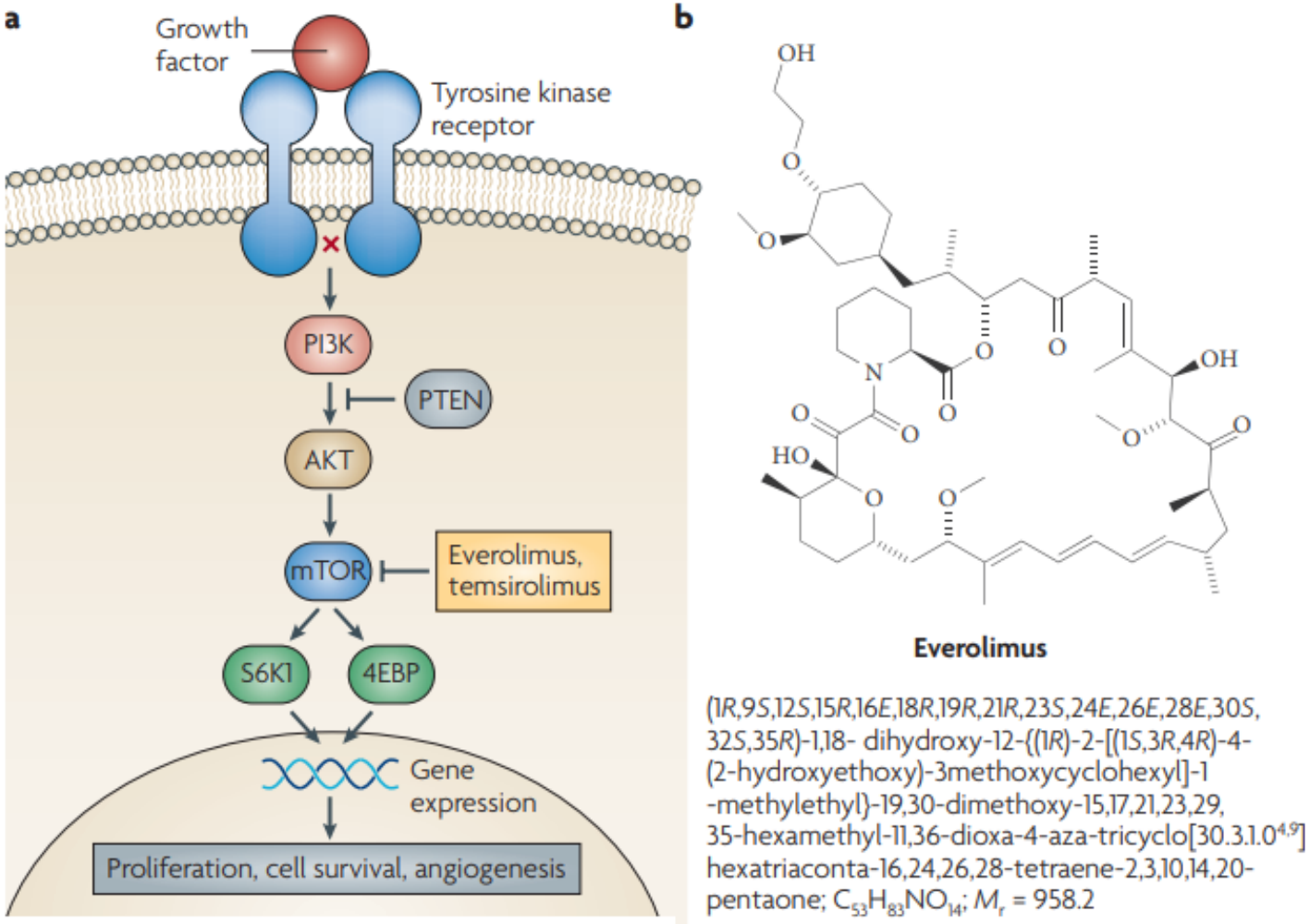


Figure 1 | **Selected signalling pathways and drugs for RCC. a** | A simplified overview of the PI3K–AKT–mTOR pathway, together with points of action of drugs for RCC. **b** | Everolimus.

Atkins et al. Nat Rev Drug Discov 2009;8:535.

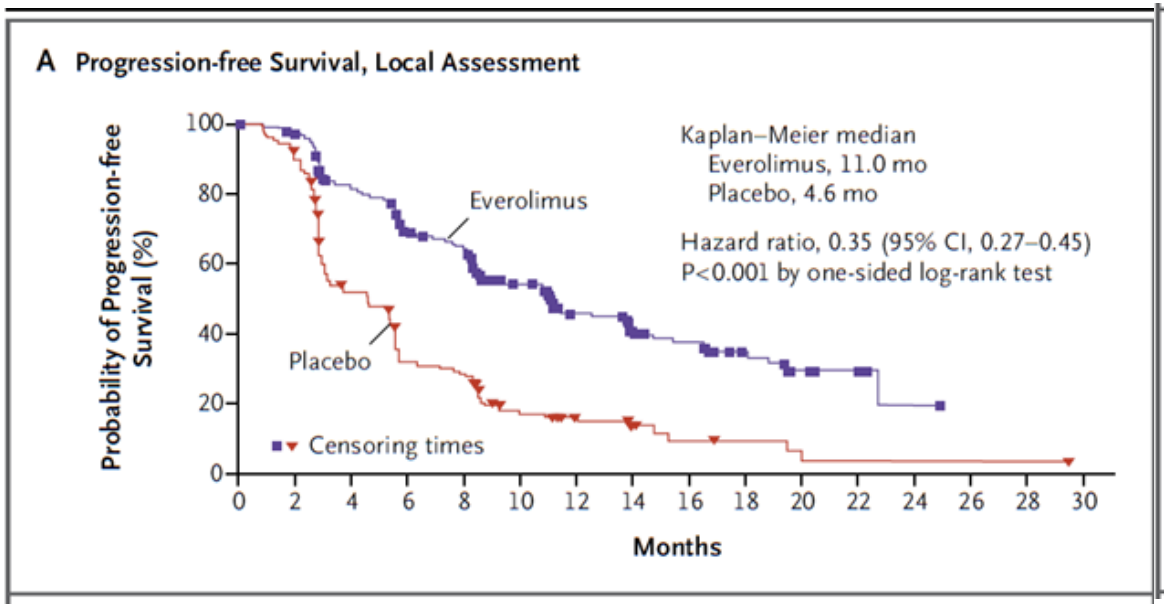
Everolimus – RADIANT3

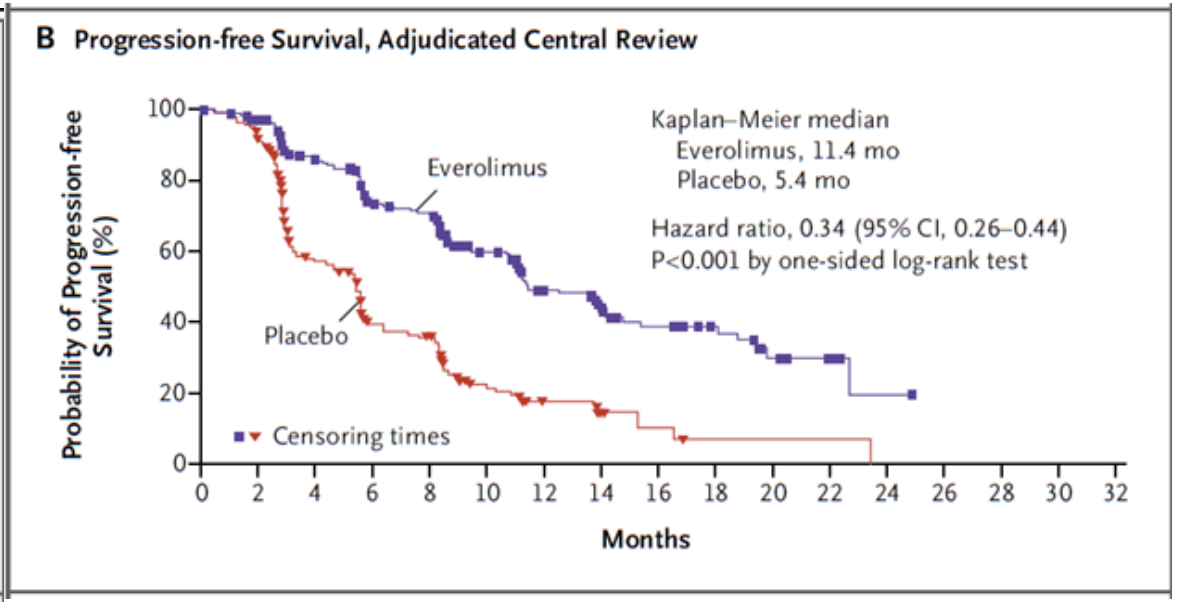
- Patients with metastatic well-differentiated PNETs
- Disease progression in last 12 months
  - Any # and type of prior therapy

→ Everolimus 10 mg daily (n=207)

→ Placebo (n=203)

ORR: 5% vs. 2%
SD: 73% vs. 51%





Yao et al. N Engl J Med 2011;364:514.

Everolimus – RADIANT4

- Patients with metastatic well-differentiated NETs of GI or lung
- Non-functioning

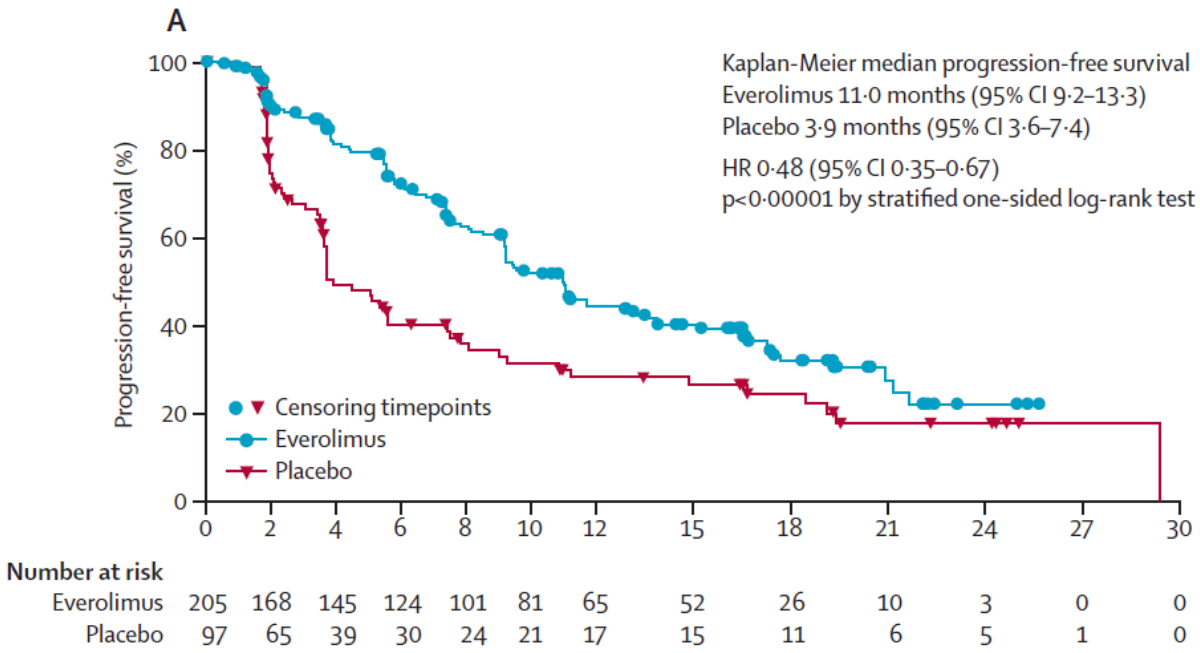
2:1

Everolimus 10 mg daily (n=205)

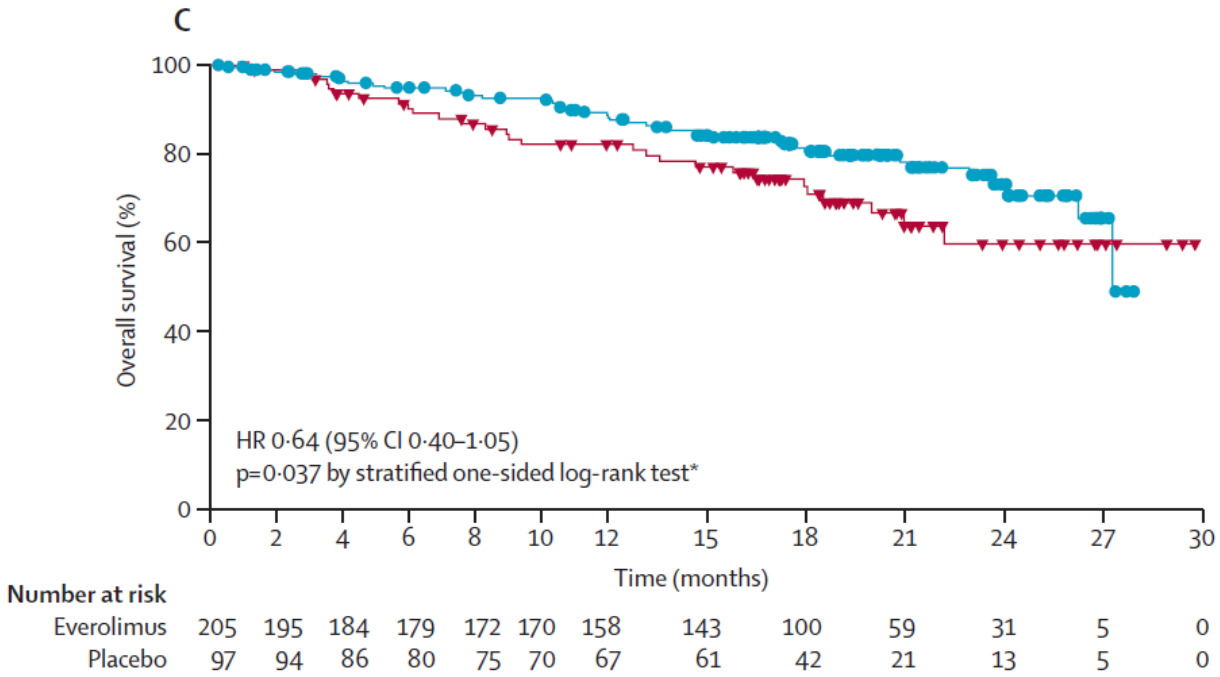
Crossover NOT allowed

Placebo (n=97)

ORR: 2% vs. 1%
SD: 81% vs. 64%



PFS by central review



OS

Yao et al. Lancet 2016;387:968.

	Everolimus (n=202)					Placebo (n=98)				
	All grades	Grade 1	Grade 2	Grade 3	Grade 4	All grades	Grade 1	Grade 2	Grade 3	Grade 4
Stomatitis*	127 (63%)	72 (36%)	37 (18%)	18 (9%)	0	19 (19%)	17 (17%)	2 (2%)	0	0
Diarrhoea	63 (31%)	30 (15%)	18 (9%)	13 (6%)	2 (1%)	16 (16%)	10 (10%)	4 (4%)	2 (2%)	0
Fatigue	62 (31%)	35 (17%)	20 (10%)	5 (2%)	2 (1%)	24 (24%)	17 (17%)	6 (6%)	1 (1%)	0
Infections†	59 (29%)	12 (6%)	33 (16%)	10 (5%)	4 (2%)	4 (4%)	1 (1%)	3 (3%)	0	0
Rash	55 (27%)	42 (21%)	12 (6%)	1 (<1%)	0	8 (8%)	6 (6%)	2 (2%)	0	0
Peripheral oedema	52 (26%)	30 (15%)	18 (9%)	4 (2%)	0	4 (4%)	2 (2%)	1 (1%)	1 (1%)	0
Nausea	35 (17%)	26 (13%)	6 (3%)	2 (1%)	1 (<1%)	10 (10%)	7 (7%)	3 (3%)	0	0
Asthenia	33 (16%)	8 (4%)	22 (11%)	2 (1%)	1 (<1%)	5 (5%)	4 (4%)	1 (1%)	0	0
Anaemia	33 (16%)	5 (2%)	20 (10%)	8 (4%)	0	2 (2%)	0	1 (1%)	1 (1%)	0
Decreased appetite	32 (16%)	22 (11%)	9 (4%)	1 (<1%)	0	6 (6%)	2 (2%)	4 (4%)	0	0
Non-infectious pneumonitis‡	32 (16%)	5 (2%)	24 (12%)	3 (1%)	0	1 (1%)	0	1 (1%)	0	0
Dysgeusia	30 (15%)	26 (13%)	3 (1%)	1 (<1%)	0	4 (4%)	4 (4%)	0	0	0
Pruritus	26 (13%)	19 (9%)	6 (3%)	1 (<1%)	0	4 (4%)	4 (4%)	0	0	0
Cough	26 (13%)	18 (9%)	8 (4%)	0	0	3 (3%)	3 (3%)	0	0	0
Pyrexia	22 (11%)	14 (7%)	4 (2%)	2 (1%)	2 (1%)	5 (5%)	4 (4%)	1 (1)	0	0
Hyperglycaemia	21 (10%)	5 (2%)	9 (4%)	7 (3%)	0	2 (2%)	2 (2%)	0	0	0
Dyspnoea	21 (10%)	4 (2%)	15 (7%)	2 (1%)	0	4 (4%)	2 (2%)	1 (1)	0	1 (1)

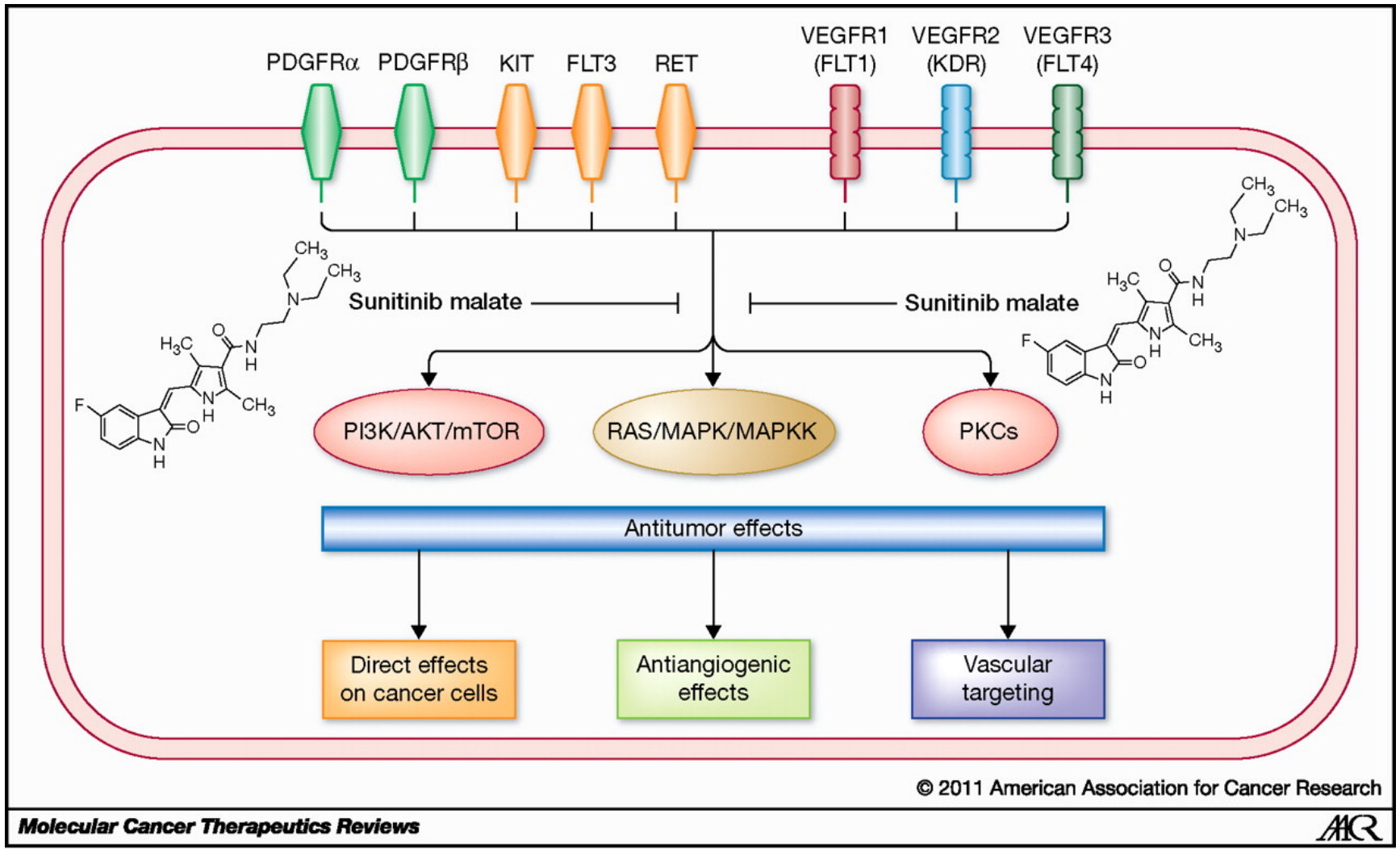
*Included in this category are stomatitis, aphthous stomatitis, mouth ulceration, and tongue ulceration. †All types of infections are included. ‡Included in this category are pneumonitis, interstitial lung disease, lung infiltration, and pulmonary fibrosis.

Table 3: Treatment-related adverse events reported in at least 10% of patients (safety population)

Most significant toxicities: stomatitis, diarrhea, fatigue, infections, rash
Possible hyperglycemia and pneumonitis

Yao et al. Lancet 2016;387:968.

Sunitinib



Aparicio-Gallego et al. Mol Cancer Ther 2011;10:2215.

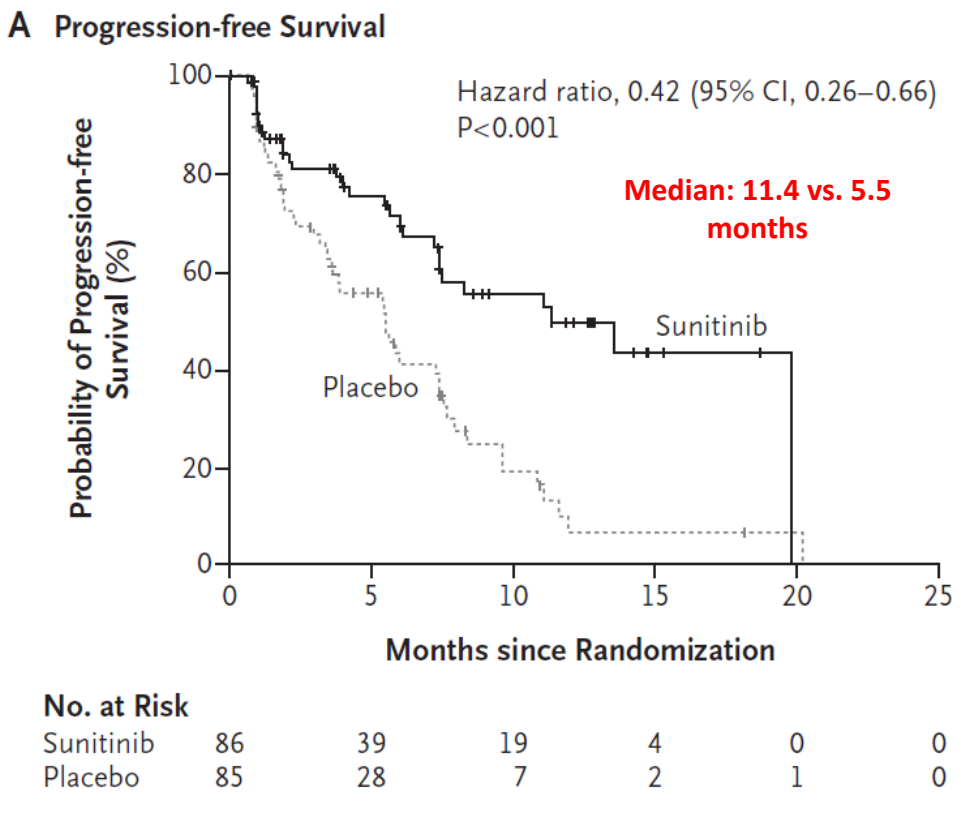
Sunitinib

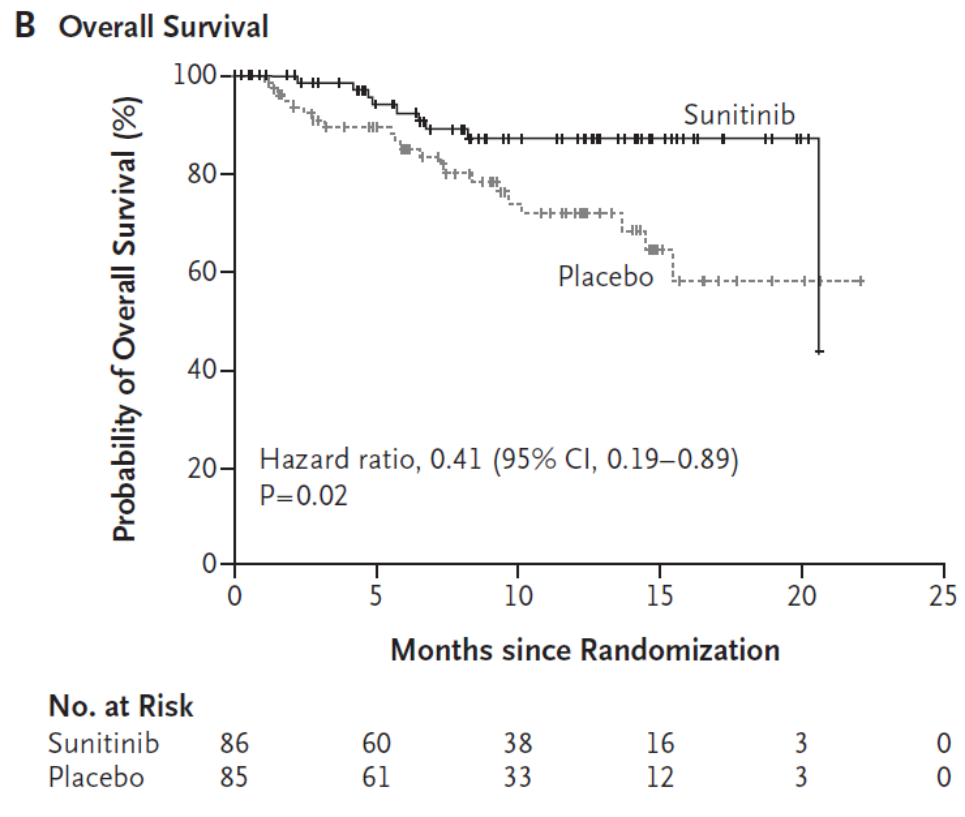
- Patients with metastatic well-differentiated PNET
- Progressed in last 12 months

→ Sunitinib 37.5 mg daily (n=86)

→ Placebo (n=85)

ORR: 9.3% vs. 0%





Benefit observed across subgroups

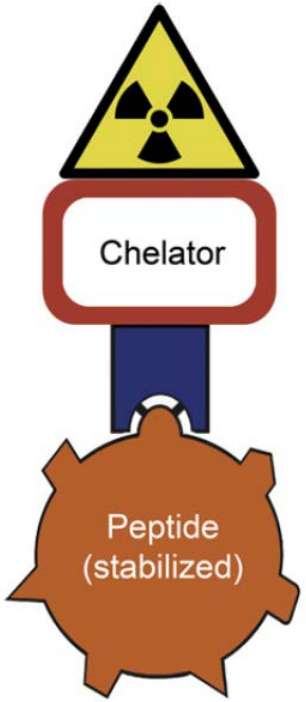
Raymond et al. N Engl J Med 2011;304:501.

Table 3. Common Adverse Events in the Safety Population.*

Event	Sunitinib (N=83)			Placebo (N=82)		
	All Grades	Grade 1 or 2	Grade 3 or 4	All Grades	Grade 1 or 2	Grade 3 or 4
	number of patients (percent)					
Diarrhea	49 (59)	45 (54)	4 (5)	32 (39)	30 (37)	2 (2)
Nausea	37 (45)	36 (43)	1 (1)	24 (29)	23 (28)	1 (1)
Asthenia	28 (34)	24 (29)	4 (5)	22 (27)	19 (23)	3 (4)
Vomiting	28 (34)	28 (34)	0	25 (30)	23 (28)	2 (2)
Fatigue	27 (32)	23 (28)	4 (5)	22 (27)	15 (18)	7 (8)
Hair-color changes	24 (29)	23 (28)	1 (1)	1 (1)	1 (1)	0
Neutropenia	24 (29)	14 (17)	10 (12)	3 (4)	3 (4)	0
Abdominal pain	23 (28)	19 (23)	4 (5)	26 (32)	18 (22)	8 (10)
Hypertension	22 (26)	14 (17)	8 (10)	4 (5)	3 (4)	1 (1)
Palmar–plantar erythrodysesthesia	19 (23)	14 (17)	5 (6)	2 (2)	2 (2)	0
Anorexia	18 (22)	16 (19)	2 (2)	17 (21)	16 (20)	1 (1)
Stomatitis	18 (22)	15 (18)	3 (4)	2 (2)	2 (2)	0
Dysgeusia	17 (20)	17 (20)	0	4 (5)	4 (5)	0
Epistaxis	17 (20)	16 (19)	1 (1)	4 (5)	4 (5)	0
Headache	15 (18)	15 (18)	0	11 (13)	10 (12)	1 (1)
Insomnia	15 (18)	15 (18)	0	10 (12)	10 (12)	0
Rash	15 (18)	15 (18)	0	4 (5)	4 (5)	0
Thrombocytopenia	14 (17)	11 (13)	3 (4)	4 (5)	4 (5)	0
Mucosal inflammation	13 (16)	12 (14)	1 (1)	6 (7)	6 (7)	0
Weight loss	13 (16)	12 (14)	1 (1)	9 (11)	9 (11)	0
Constipation	12 (14)	12 (14)	0	16 (20)	15 (18)	1 (1)
Back pain	10 (12)	10 (12)	0	14 (17)	10 (12)	4 (5)

Raymond et al. N Engl J Med 2011;304:501.

Peptide receptor radionuclide therapy (PRRT)



Radionuclide — $[^{111}In\text{-}DTPA^{0}]Octreotide$

Chelator — $[^{90}Y\text{-}DOTA^{0},Tyr^{3}]Octreotide$

$[^{177}Lu\text{-}DOTA0,Tyr^{3}]Octreotide$

Cyclic Octapeptide — $[^{177}Lu\text{-}DOTA0,Tyr^{3}]Octreotate$

^{177}Lu-dotatate

- Delivers radionuclides directly to tumor cells via SSTR
- Used for SSTR-positive metastatic well-differentiated NETs in Europe since 1990s
- Lutetium-177 is a beta and gamma emitting radionuclide

Kunz PL. J Clin Oncol 2015;33:1855.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Phase 3 Trial of ^{177}Lu-Dotatate for Midgut Neuroendocrine Tumors

J. Strosberg, G. El-Haddad, E. Wolin, A. Hendifar, J. Yao, B. Chasen, E. Mittra, P.L. Kunz, M.H. Kulke, H. Jacene, D. Bushnell, T.M. O'Dorisio, R.P. Baum, H.R. Kulkarni, M. Caplin, R. Lebtahi, T. Hobday, E. Delpassand, E. Van Cutsem, A. Benson, R. Srirajaskanthan, M. Pavel, J. Mora, J. Berlin, E. Grande, N. Reed, E. Seregni, K. Öberg, M. Lopera Sierra, P. Santoro, T. Thevenet, J.L. Erion, P. Ruszniewski, D. Kwekkeboom, and E. Krenning, for the NETTER-1 Trial Investigators*

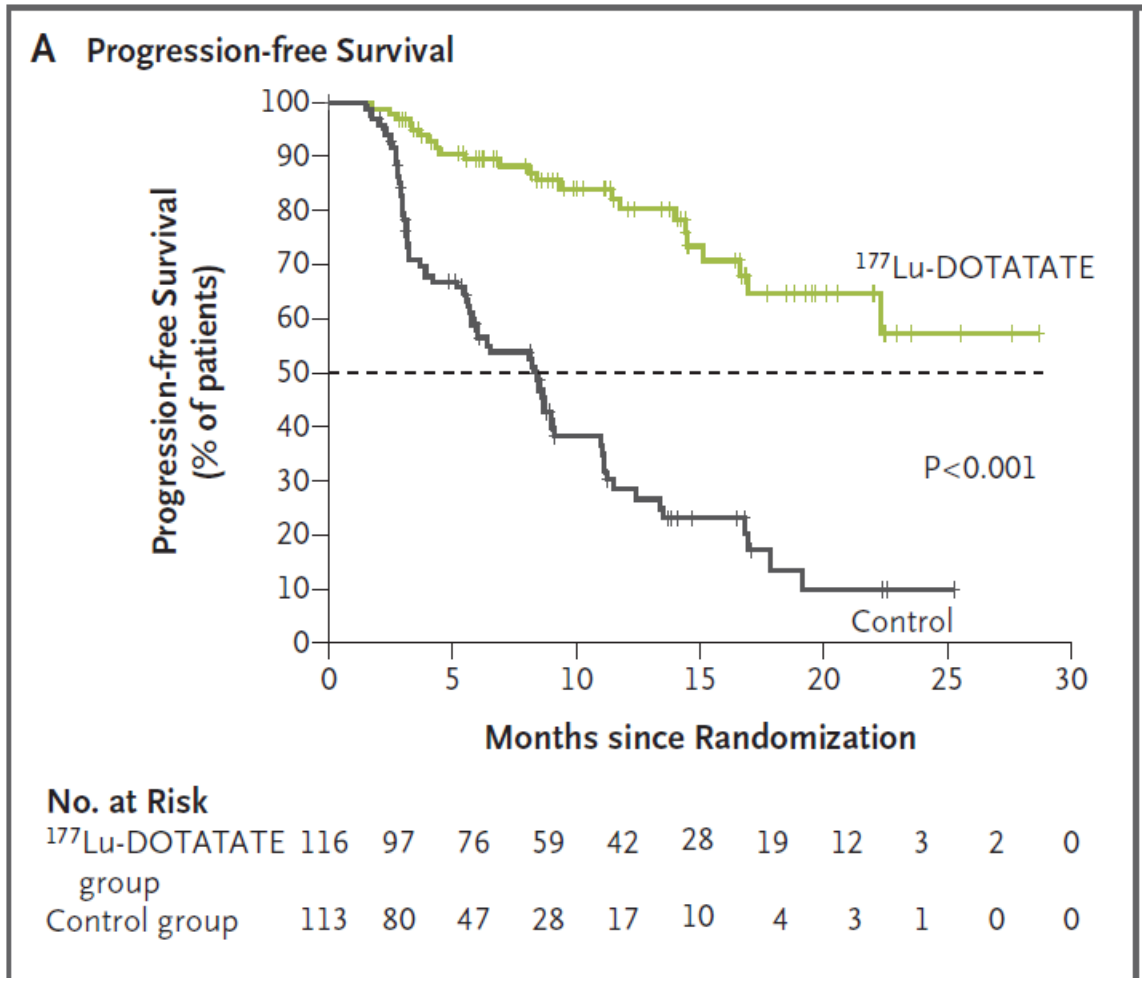
- Patients with metastatic well-differentiated midgut NETs
  - SSTR-positive
- Progressed during treatment with octreotide LAR for at least 12 wks prior to study

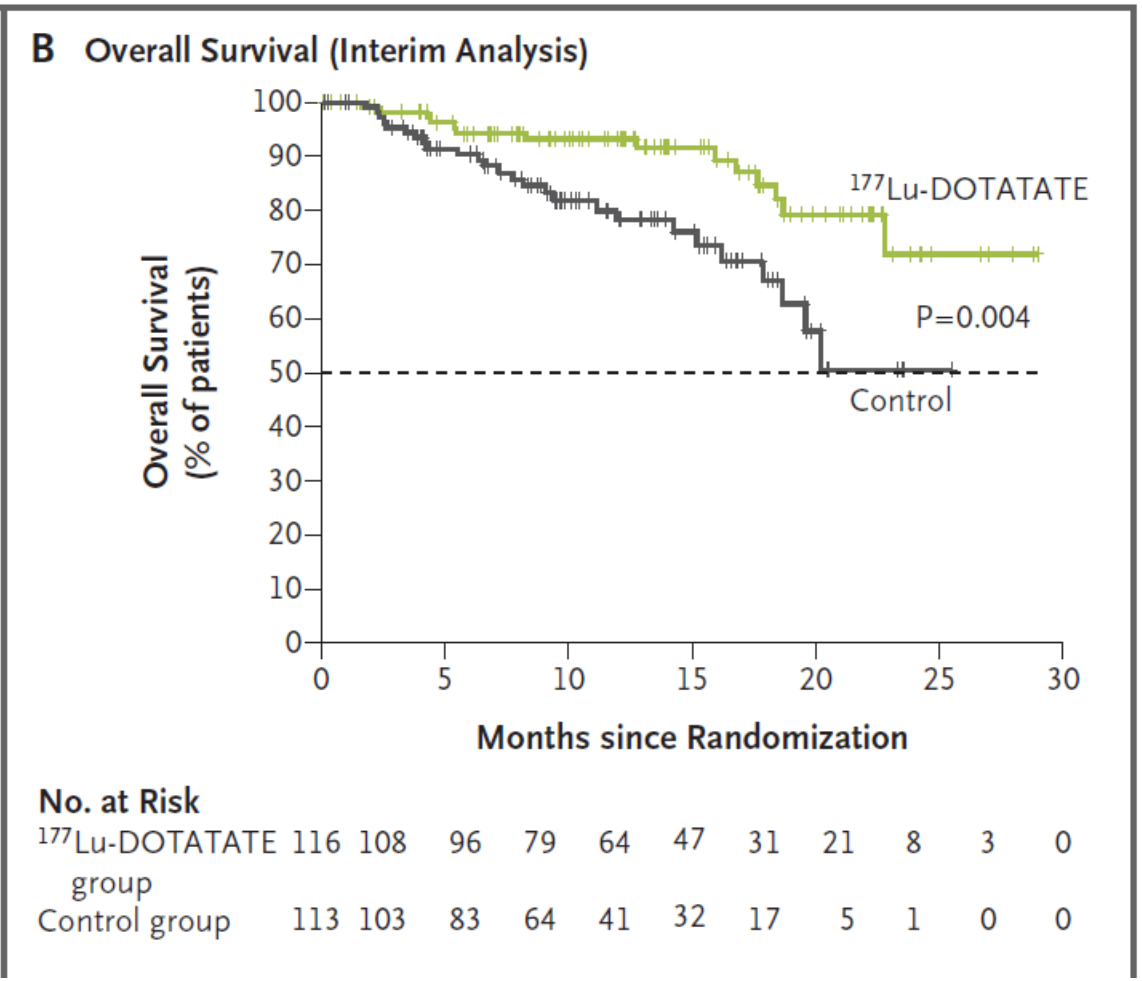
→ 177Lu-Dotatate 7.4 GBq/200mCi every 8 weeks x 4 + octreotide LAR 30 mg IM (n=116)

→ Octreotide LAR 60 mg IM every 4 weeks (n=113)

- For renal protection, IV amino acid solution (lysine, arginine) given concomitantly for at least 4 hours starting 30 min before infusion of 177Lu-Dotatate
- Octreotide LAR given 24 hours after each infusion of 177Lu-Dotatate, then monthly

Strosberg et al. N Engl J Med 2017;376:125.





Rate of progression-free survival at 20 months: 65% vs. 11%

Median PFS: not reached vs. 8.4 months (HR 0.21, 95% CI 0.13-0.33, p<0.001)

Interim analysis for overall survival: 14 vs. 26 deaths (p=0.004)

Strosberg et al. N Engl J Med 2017;376:125.

Table 2. Objective Tumor Response.*

Response Category	^{177}Lu-Dotatate Group (N = 101)	Control Group (N = 100)	P Value†
Complete response — no. (%)	1 (1)	0	
Partial response — no. (%)	17 (17)	3 (3)	
Objective response			
No. with response	18	3	
Rate — % (95% CI)	18 (10–25)	3 (0–6)	<0.001

Table 3. Overview of Adverse Events (Safety Population).*

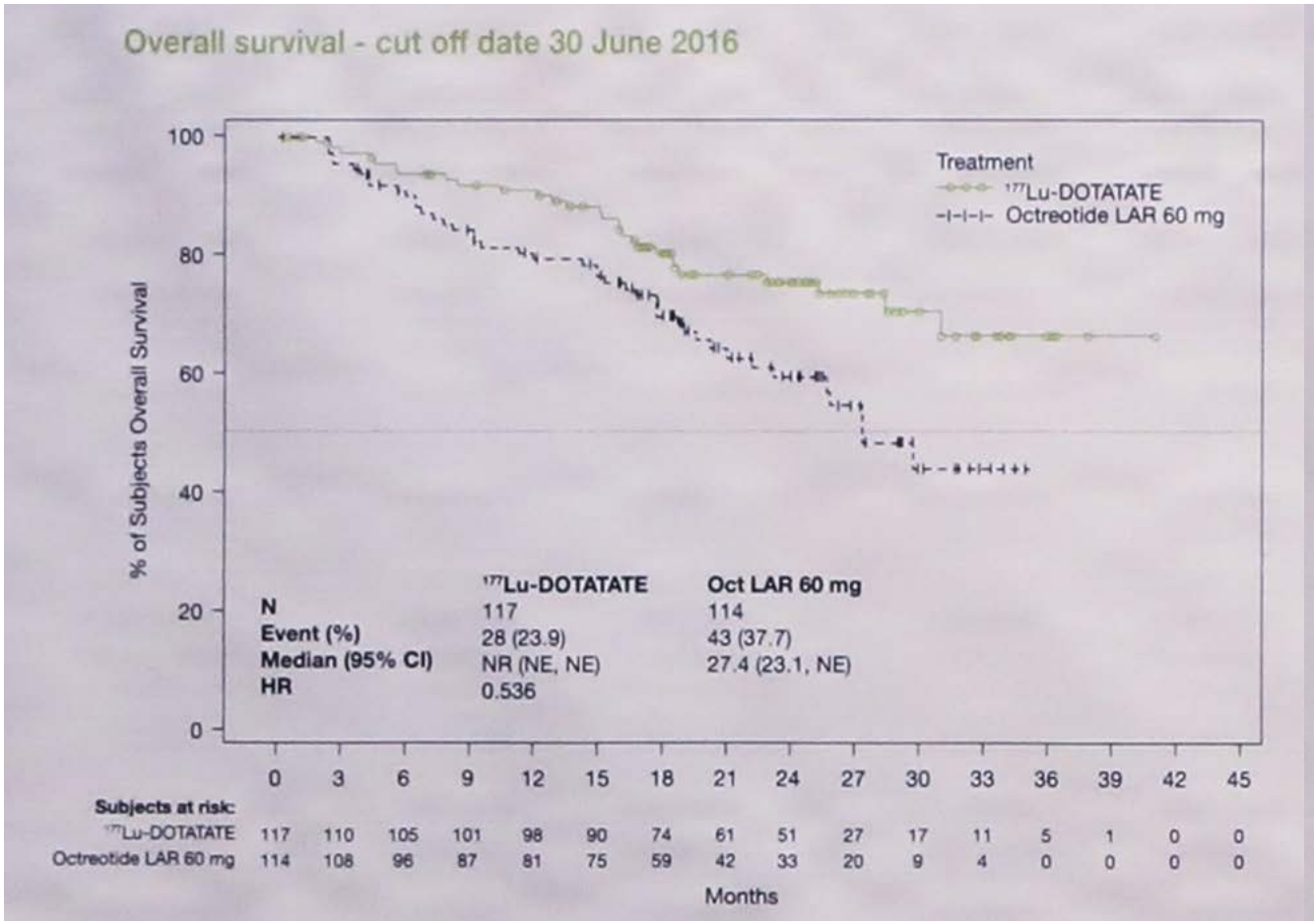
Event	^{177}Lu-Dotatate Group (N = 111)	Control Group (N = 110)	P Value†
	number of patients (percent)		
Adverse event			
Any	106 (95)	95 (86)	0.02
Related to treatment	95 (86)	34 (31)	<0.001
Serious adverse event			
Any	29 (26)	26 (24)	0.76
Related to treatment	10 (9)	1 (1)	0.01
Withdrawal from trial because of adverse event			
Because of any adverse event	7 (6)	10 (9)	0.46
Because of adverse event related to treatment	5 (5)	0	0.06

* The safety population included all patients who underwent randomization and received at least one dose of trial treatment.
† P values were calculated with the use of Fisher's exact text.

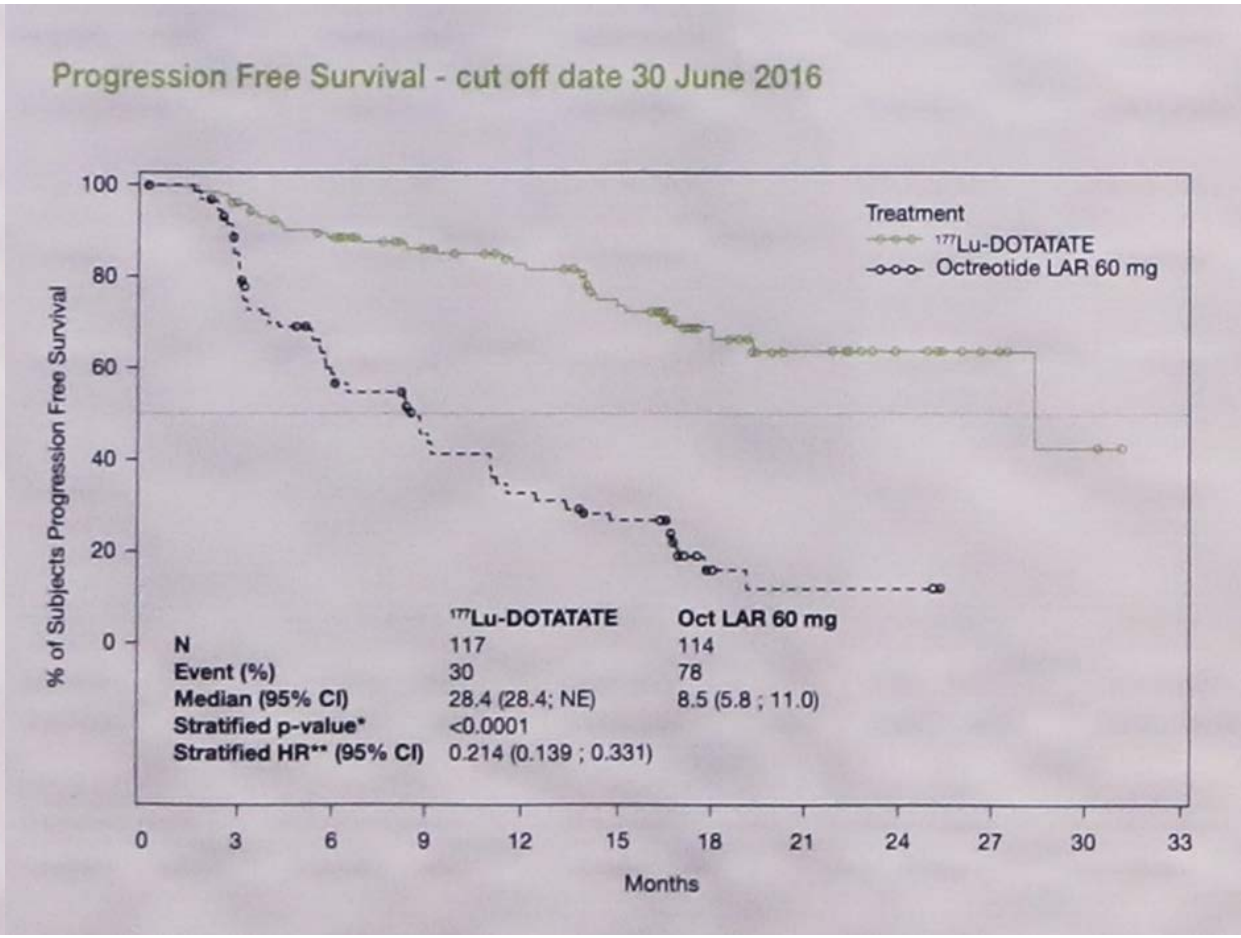
- **177Lu-Dotatate group:**
  - Nausea 59%, vomiting 47% (due to amino acid), fatigue/asthenia 40%
  - Grade 3 or 4: neutropenia 1%, thrombocytopenia 2%, lymphopenia 9% (none in control group)
- No renal toxicity observed at median follow-up duration of 14 months
- 1 patient developed myelodysplastic syndrome possibly related to PRRT

Strosberg et al. N Engl J Med 2017;376:125.

Update of NETTER-1



Median OS: not reached vs. 27.4 months



Median PFS: 28.4 vs. 8.5 months
(HR 0.214, 95% CI 0.139-0.331, p<0.0001)

Strosberg et al. J Clin Oncol 2018;36:suppl abstr 4099.


U.S. Department of Health and Human Services

FDA U.S. FOOD & DRUG ADMINISTRATION

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FDA News Release

FDA approves new treatment for certain digestive tract cancers

SHARE TWEET LINKEDIN PIN IT EMAIL PRINT

For Immediate Release January 26, 2018

Release

The U.S. Food and Drug Administration today approved Lutathera (lutetium Lu 177 dotatate) for the treatment of a type of cancer that affects the pancreas or gastrointestinal tract called gastroenteropancreatic neuroendocrine tumors (GEP-NETs). This is the first time a radioactive drug, or radiopharmaceutical, has been approved for the treatment of GEP-NETs. Lutathera is indicated for adult patients with somatostatin receptor-positive GEP-NETs.

"GEP-NETs are a rare group of cancers with limited treatment options after initial therapy fails to keep the cancer from growing," said Richard Pazdur, M.D., director of the FDA's Oncology Center of Excellence and acting director of the Office of Hematology and Oncology Products in the FDA's Center for Drug Evaluation and Research. "This approval provides another treatment choice for patients with these rare cancers. It also demonstrates how the FDA may consider data from therapies that are used in an expanded access program to support approval for a new treatment."

PRRT approved for refractory SSTR-expressing well-differentiated GEP NETs

Pharmacokinetics:

- Half-life 6.71 days
- Poorly metabolized and mainly excreted renally as intact compound
  - 60% eliminated in urine within 24h; 65% within 48h

Use in patients with CKD:

- CrCl <30 mL/min: contraindicated
- CrCl <50 mL/min: not recommended
- Mild to moderate CKD with CrCl ≥50 mL/min: use with caution, consider dose reduction

1. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm594043.htm 2. Lutathera® monograph

Practical considerations for ^{177}Lu-Dotatate

- Interval between each infusion is 8 (+/-1) weeks, can be extended up to 16 weeks for toxicity
- May use half-dose (3.7 GBq) due to toxicity
- *No long-acting SSA within 4 weeks of treatment
- *No short-acting SSA within 24 hours of treatment
- Concomitant infusion of amino acid solution is required for renal protection (over 4 hours)
  - Composition: lysine 25g, arginine 25g in 1L NS

Lutathera® monograph

Chemotherapy

- Carcinoids
  - Generally do not respond well to chemotherapy
  - May be considered for progressive disease with no other standard or trial options
- PNETs
  - Activity has been shown with alkylating agents
  - May be initially considered for bulky, rapidly progressing, and/or symptomatic well-differentiated PNETs
    - Greater response rate
  - Synergistic activity of temozolomide and capecitabine in PNET in preclinical and early studies

A randomized phase II study of temozolomide or temozolomide and capecitabine in patients with advanced pancreatic neuroendocrine tumors: A trial of the ECOG-ACRIN Cancer Research Group (E2211)

Pamela L. Kunz[1], Paul J. Catalano[2,3], Halla S. Nimeiri[4], George A. Fisher Jr[1], Teri A. Longacre[1], Carlos J. Suarez[1], James C. Yao[5], Matthew H. Kulke[6], Andrew E. Hendifar[7], James C. Shanks[8], Manisha H. Shah[9], Mark M. Zalupski[10], Edmond Schmulbach[11], Diane L. Reidy-Lagunes[12], Jonathan R. Strosberg[13], Peter J. O'Dwyer[14], and Al B. Benson III[4] on behalf of the E2211 Study Team

[1]Stanford University, [2]Dana Farber Cancer Institute, [3]ECOG-ACRIN Biostatistics Center, [4]Northwestern University, [5]MD Anderson Cancer Center, [6]Boston University, [7]Cedars Sinai Medical Center, [8]Saint John's Hospital Healtheast, [9]Ohio State Comprehensive Cancer Center, [10]University of Michigan Comprehensive Cancer Center, [11]Kaiser Permanente South San Francisco, [12]Memorial Sloan Kettering Cancer Center, [13]Moffitt Cancer Center, [14]University of Pennsylvania

ECOG-ACRIN cancer research group
Reshaping the future of patient care

Presented By Pamela Kunz at 2018 ASCO Annual Meeting

E2211 Study Design

Progressive, G1/G2, metastatic pancreatic NETs

R 1:1

n=72

ARM A:
Temozolomide 200 mg/m^2 po QD days 1-5

n=72

ARM B:
Capecitabine 750 mg/m^2 po BID days 1-14
Temozolomide 200 mg/m^2 QD days 10-14

Cycle length = 28 days; max 13 cycles.
Imaging performed every 12 weeks (RECIST 1.1)

Stratified by:
- Prior everolimus
- Prior sunitinib
- Concurrent octreotide

Primary Endpoint:
- PFS (local review)

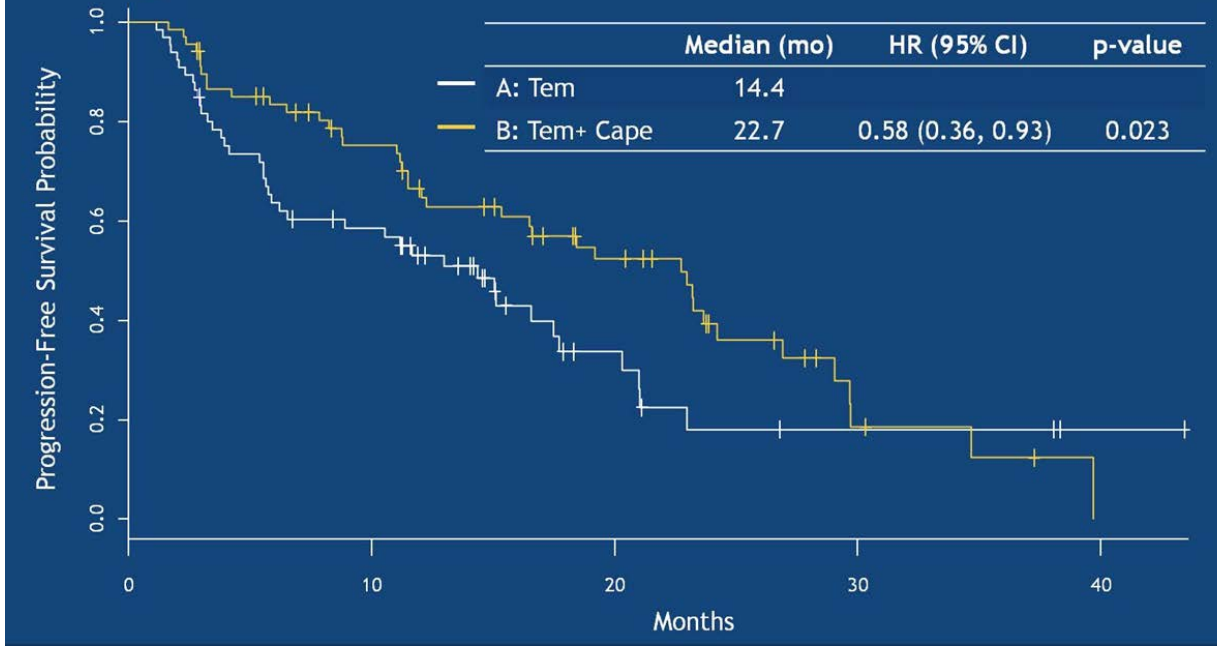
Secondary Endpoints:
- RR
- OS
- Toxicity

Correlative Endpoints:
- MGMT by IHC
- MGMT by promoter methylation

Concurrent SSAs allowed

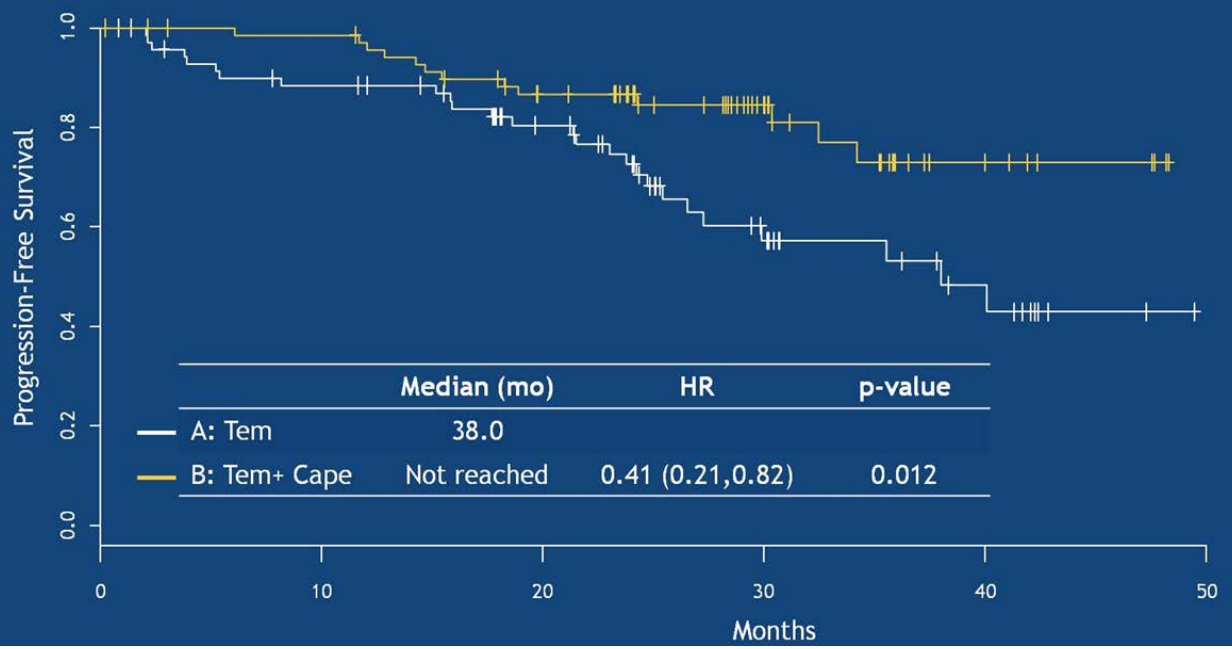
NCT01824875

Progression Free Survival



	Median (mo)	HR (95% CI)	p-value
A: Tem	14.4		
B: Tem+ Cape	22.7	0.58 (0.36, 0.93)	0.023

Overall Survival



	Median (mo)	HR	p-value
A: Tem	38.0		
B: Tem+ Cape	Not reached	0.41 (0.21,0.82)	0.012

	Temozolomide (N=72)	Temozolomide + Capecitabine (N=72)
Time from Diagnosis (months)	24.4 mo	34.0 mo
*WHO Grade		
Low (Grade 1)	45.1%	68.1%
Intermediate (Grade 2)	54.9%	31.9%

Survival by Grade

- Grade was not associated with PFS/OS
- PFS/OS benefits were observed after adjusting for grade

Kunz et al. J Clin Oncol 2018;36:suppl; abstr 4004.

Response Rates

	Temozolomide (N=72)	Temozolomide + Capecitabine (N=72)	p-value
Complete response	2.8%	0	
Partial response	25.0%	33.3%	
Stable disease	40.3%	48.6%	
Progressive disease	19.4%	13.9%	
Unevaluable	12.5%	4.2%	
Objective Response Rate (CR+PR)	27.8%	33.3%	0.47
Disease Control Rate (CR+PR+SD)	68.1%	81.9%	
Response Duration (median)	9.7 mo	12.1 mo	

- Safety
  - Grade 3/4 treatment-related AEs: 44% vs. 22% (p=0.007)
  - Most common grade 3/4 AEs with CAPTEM – neutropenia (13%), thrombocytopenia (8%), nausea/vomiting (8%), diarrhea (8%), lymphopenia (5%), fatigue (5%)

Kunz et al. J Clin Oncol 2018;36:suppl; abstr 4004.

Summary of systemic therapy for unresectable or metastatic well-differentiated GEP NETs

Carcinoid tumor

- SSA (octreotide, lanreotide)
- PRRT
- Everolimus

PNET

- SSA (octreotide, lanreotide)
- PRRT
- Everolimus
- Sunitinib
- CAPTEM

Other cytotoxic chemotherapy regimens may be considered (less preferred) (for instance, FOLFOX or CAPOX)

No data to support a specific sequence of systemic therapy options
Consider clinical trials

Thank you for your attention!

Chronic Lymphocytic Leukemia
and
Hairy Cell Leukemia

Mazyar Shadman, MD , MPH

Associate Professor, Fred Hutch and University of Washington

Member, NCCN guidelines committee for CLL/HCL

Comprehensive Hematology & Oncology Review Course
2020

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Disclosures

Research Funding:

- Beigene, Mustang Biopharma, Celgene, BMS, Genentech, Pharmacyclics, Acerta Pharma, Astra Zeneca, AbbVie, Gilead Sciences, Sunesis, TG Therapeutics, Merck

Advisory Board/Consultancy:

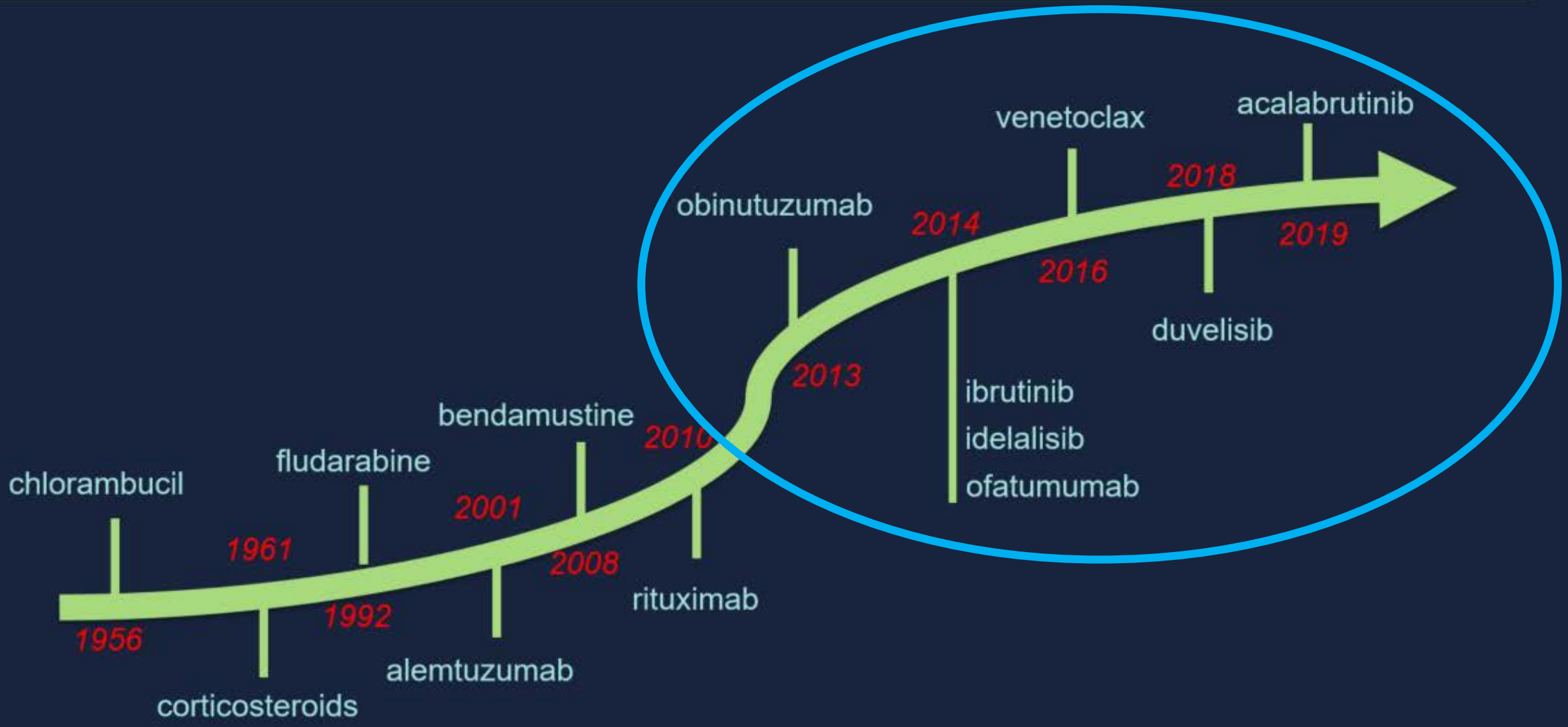
- AbbVie, AstraZeneca, Genentech, Beigene, Morphosys, Merck, Verastem, Pharmacyclics, ADC therapeutics, Atara Biotherapeutics, Sound Biologics, Gilead Sciences

Disclosures

- Main purpose of this presentation is **“Board Review”**

- Will not discuss **experimental** treatments:
  - New biomarkers (prognostic and predictive)
  - New and unapproved BTKis or PI3Kis
  - Topic of MRD with venetoclax
  - Combination studies (ibrutinib + venetoclax, etc)
  - Details on CAR-T cell therapy (will have one slide)

Approved drugs for CLL



FRED HUTCH

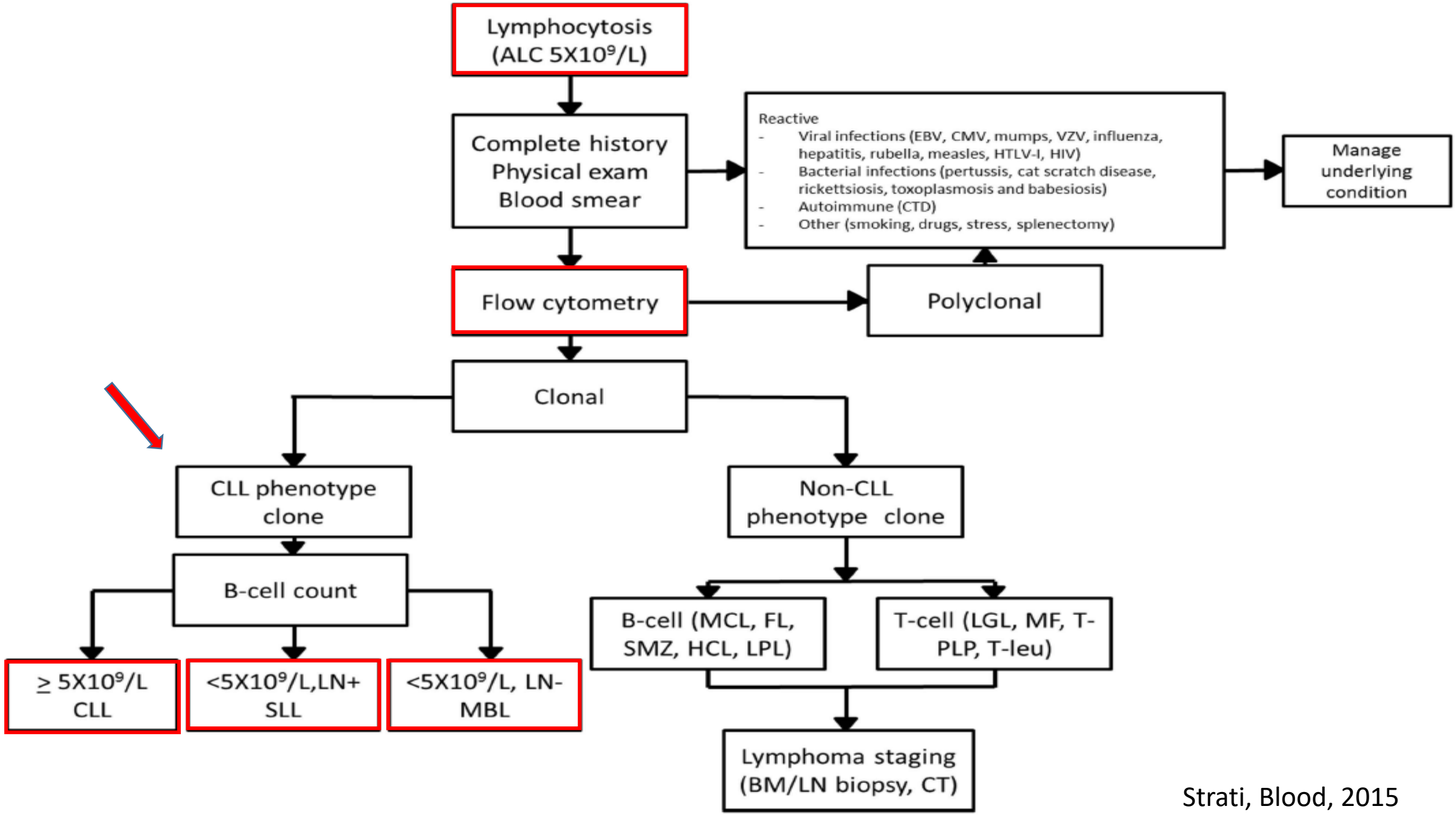
Epidemiology

- CLL/SLL is the most common leukemia in adults in western countries
  - 4.5 cases per 100,000
- Median age ~ 70 years
- Slight male predominance (1.7:1)
- Familial risk (7-8 fold)
- Caucasians > African Americans > Asian Pacific Islanders
- Genetic > Environmental

Top 10 topics in CLL

1. Initial diagnosis and appropriate work-up
2. Prognostic and predictive markers
3. Important therapeutic agents for CLL
4. Who should be treated?
5. Is there a role for early intervention in “high-risk” patients?
6. Treatment options for treatment-naïve patients (without del17p/P53 mutation)
7. Treatment options for previously treated patients (without del17p/P53 mutation)
8. Treatment options for patients with del17p/P53 mutation
9. Cellular therapies (CAR-T cell and Allogeneic Transplant)
10. Practical points about novel drugs

1. Initial diagnosis and appropriate work-up



Strati, Blood, 2015

Immunophenotypic Features

	CD5	CD10	CD23	CD103	BCL6	CD20	Cyclin D1
CLL/SLL	+	-	+	-	-	+ (weak)	-

Immunophenotypic Features

	CD5	CD10	CD23	CD103	BCL6	CD20	Cyclin D1
CLL/SLL	+	-	+	-	-	+ (weak)	-
MCL	+	-	-	-	-	+	+
LPL	-	-	-	-	-	+	-
sMZL	-	-	-	-	-	+	-
FL	-	+/-	-/+	-	+	+	-
HCL	-	-	-	+	-	+	+/-

	CD23	Cyclin D1	t(11,14)
CLL/SLL	+	-	-
MCL	-	+	+

MBL (monoclonal B cell lymphocytosis)

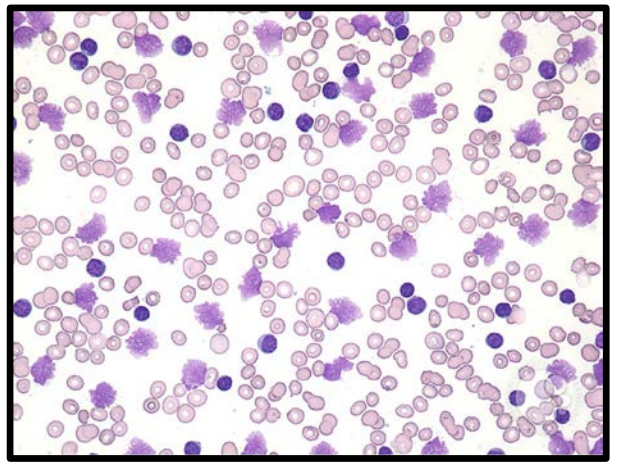
- < 5x 10^9/L monoclonal B- cells in the PB AND no lymphadenopathy
- Almost all cases of CLL are preceded by MBL but only a small percentage of persons with MBL will ultimately develop CLL
- **Low-count MBL (< 0.5x 10^9/L) ➔ rarely progresses to CLL**
- **High-count MBL (≥0.5x 10^9/L) ➔ progresses to CLL at a rate of 1-2% /year**
- Up to 17 percent of first-degree family members of patients with CLL were found by flow cytometry to have MBL
- **Screening of family members is NOT recommended**

Strati, Blood, 2015

Diagnosis

- **Flow cytometry** of **blood** is **essential and adequate** to make the diagnosis
- Biopsy may be needed if PB flow cytometry is not conclusive
- Cytogenetic and molecular studies are informative for prognostic and/or therapy determination .
- Baseline CT scan (or PET) is **NOT** required for asymptomatic patients

  (The ASH "Choosing Wisely" List)



American Society of Hematology
Helping hematologists conquer blood diseases worldwide

American Board of Internal Medicine®

2.Prognostic and predictive markers

Staging for CLL

Rai Staging System for Chronic Lymphocytic Leukemia			
Stage	Risk	Clinical Features	Overall Survival, y
Rai			
0	Low	Lymphocytosis in peripheral blood and bone marrow only	>10
I/II	Intermediate	Lymphadenopathy ± hepatosplenomegaly	7
III/IV	High	Anemia ± thrombocytopenia	<4

Some use Ann Arbor staging for SLL

Molecular Biomarkers for CLL

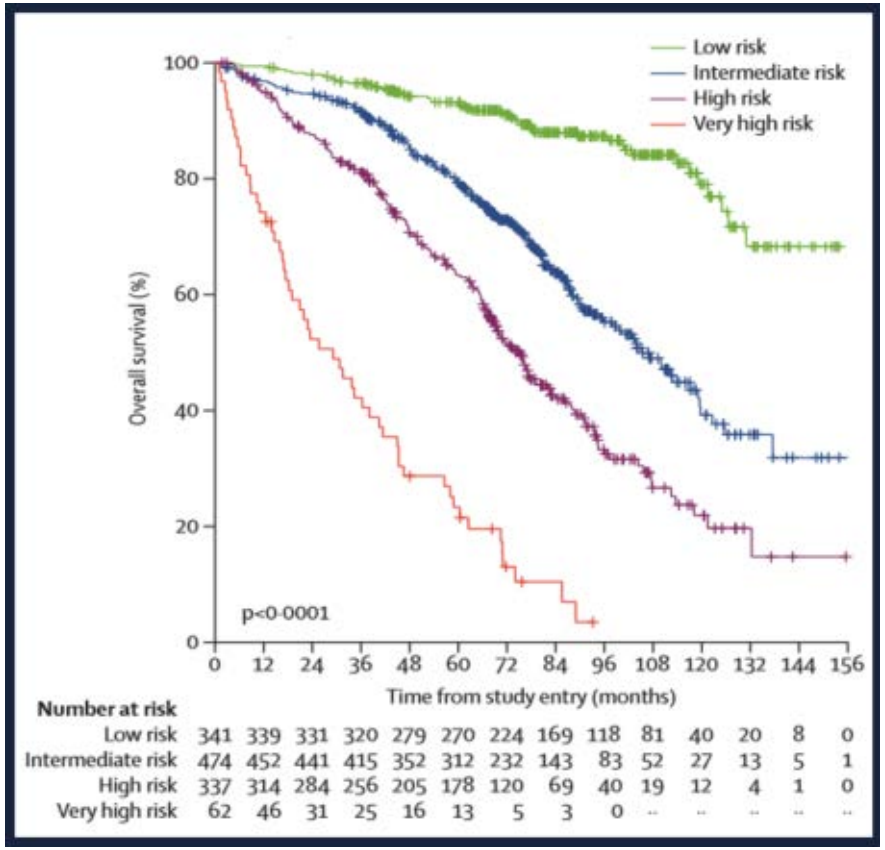
	FISH	Karyotype	Mutations
Unfavorable	del (17p) del (11q)	Complex (>3 abnormalities) (> 5?)	TP53 unmutated IGHV (≤ 2%) * NOTCH-1 SF3B1 BIRC3 ATM
Neutral	Normal +12		
Favorable	del (13q) (sole abnormality)		mutated IGVH (>2%)

* If chemotherapy is used

Prognostic Models: CLL-IPI

Characteristic	Points
Del(17p) or TP53 mutation	4
Serum beta-2-macroglobulin ≥ 3.5mg/L	2
Un-mutated IgVH	2
Rai Stage I-IV	1
Age > 65 years	1

Points	Risk Group	5-y OS (%)	10-yr OS (%)
0-1	Low	93	79
2-3	Int	79	39
4-6	High	63	22
7-10	Very High	23	4



- ✓ Developed for chemoimmunotherapy
- ✓ Not validated for novel agents

CLL-IPI Group, Lancet Oncol 2016

3. Important therapeutic agents for CLL

Treatment options for CLL

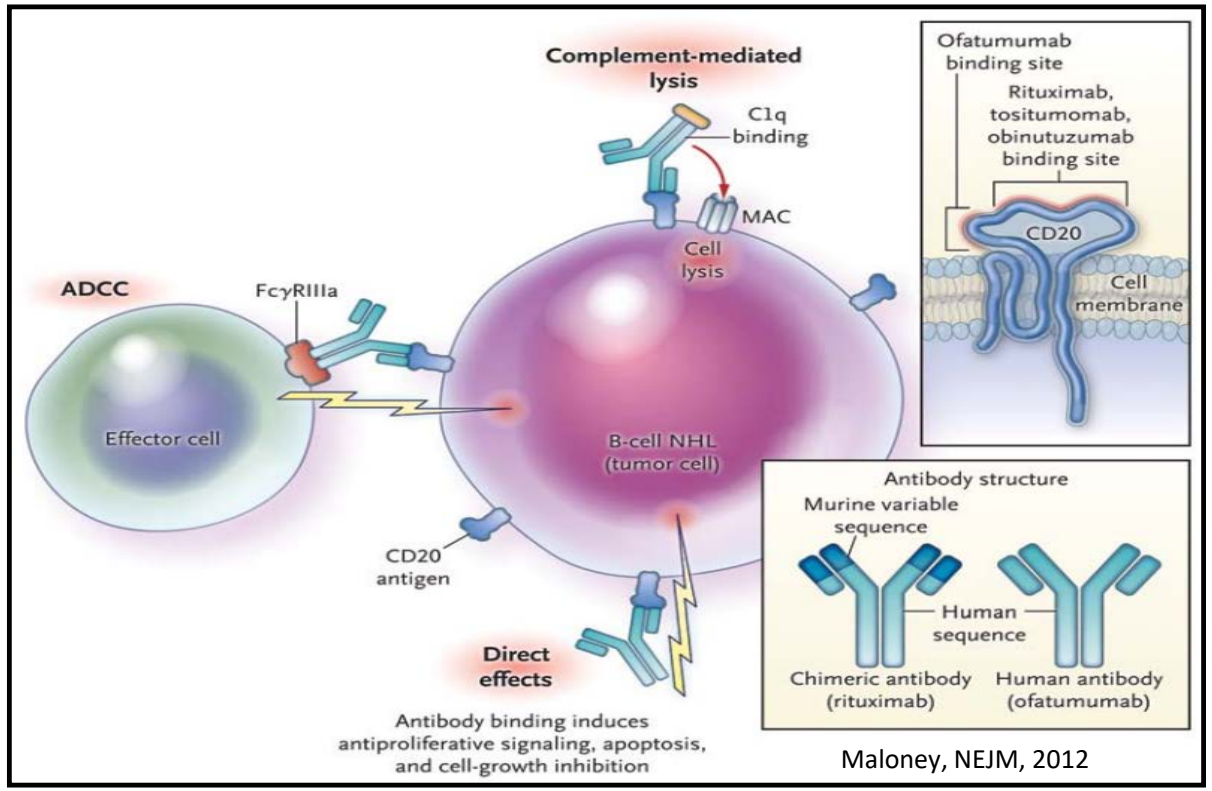
Chemotherapy	anti-CD20 Abs	BCR inhibitors	BCL-2 inhibitor

• fludarabine
• cyclophosphamide
• bendamustine
• chlorambucil
	• rituximab
	• ofatumumab
	• obinutuzumab
	• ublituximab *
		• **BTK inhibitors**
		  • ibrutinib
		  • acalabrutinib
		  • zanubrutinib*†
		• **PI3K inhibitors**
		  • idelalisib
		  • duvelisib
		  • umbralisib *
			• **venetoclax**

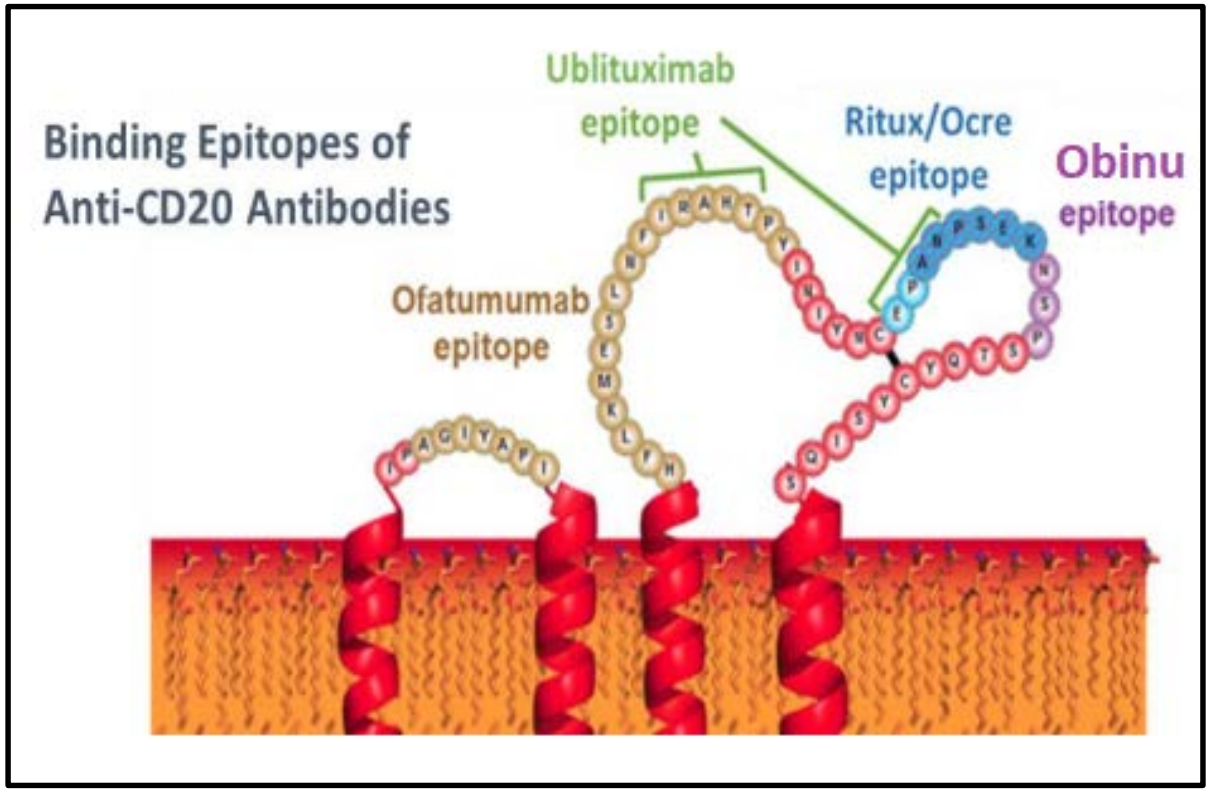
* Not FDA approved for CLL as of August 2020

† Approved for MCL

Anti-CD20 antibodies

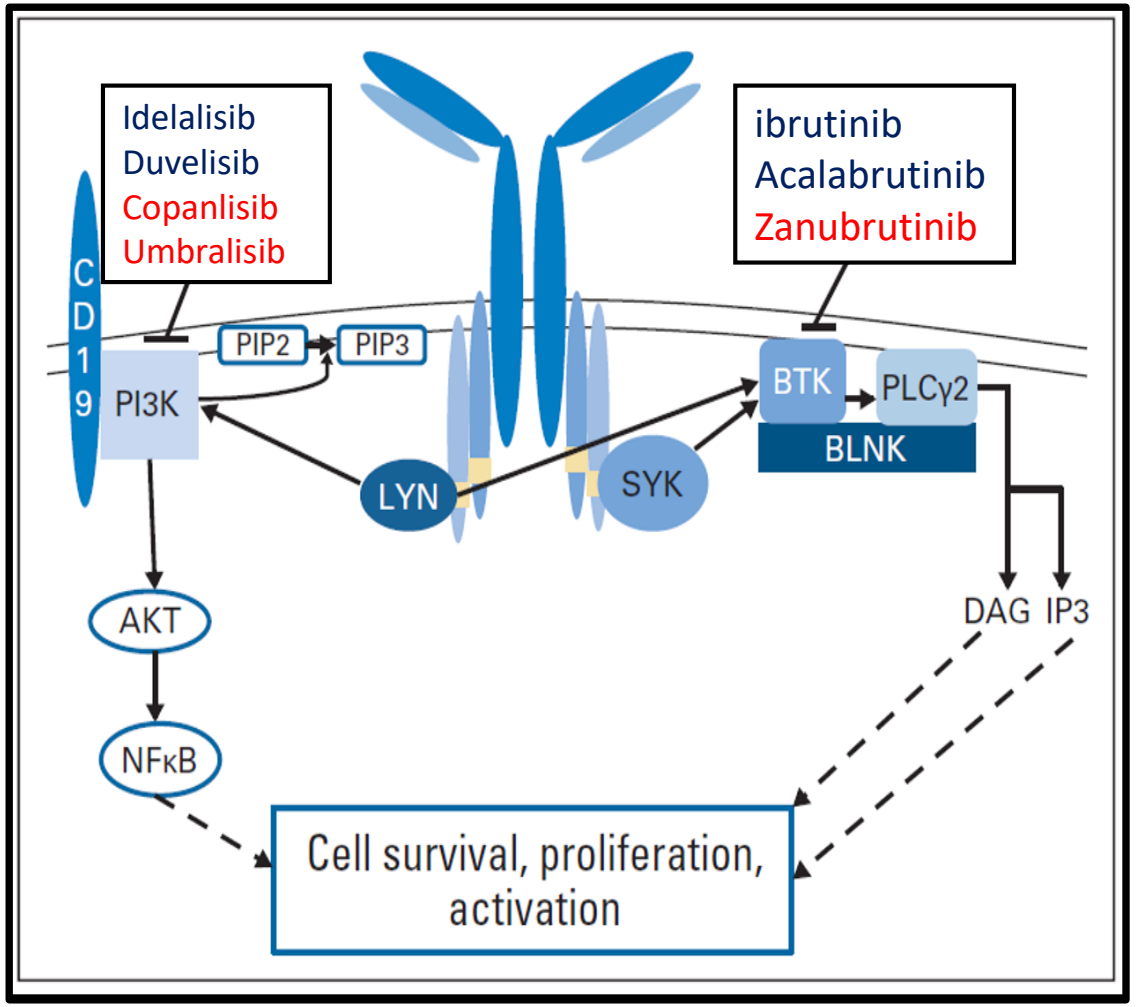


Maloney, NEJM, 2012

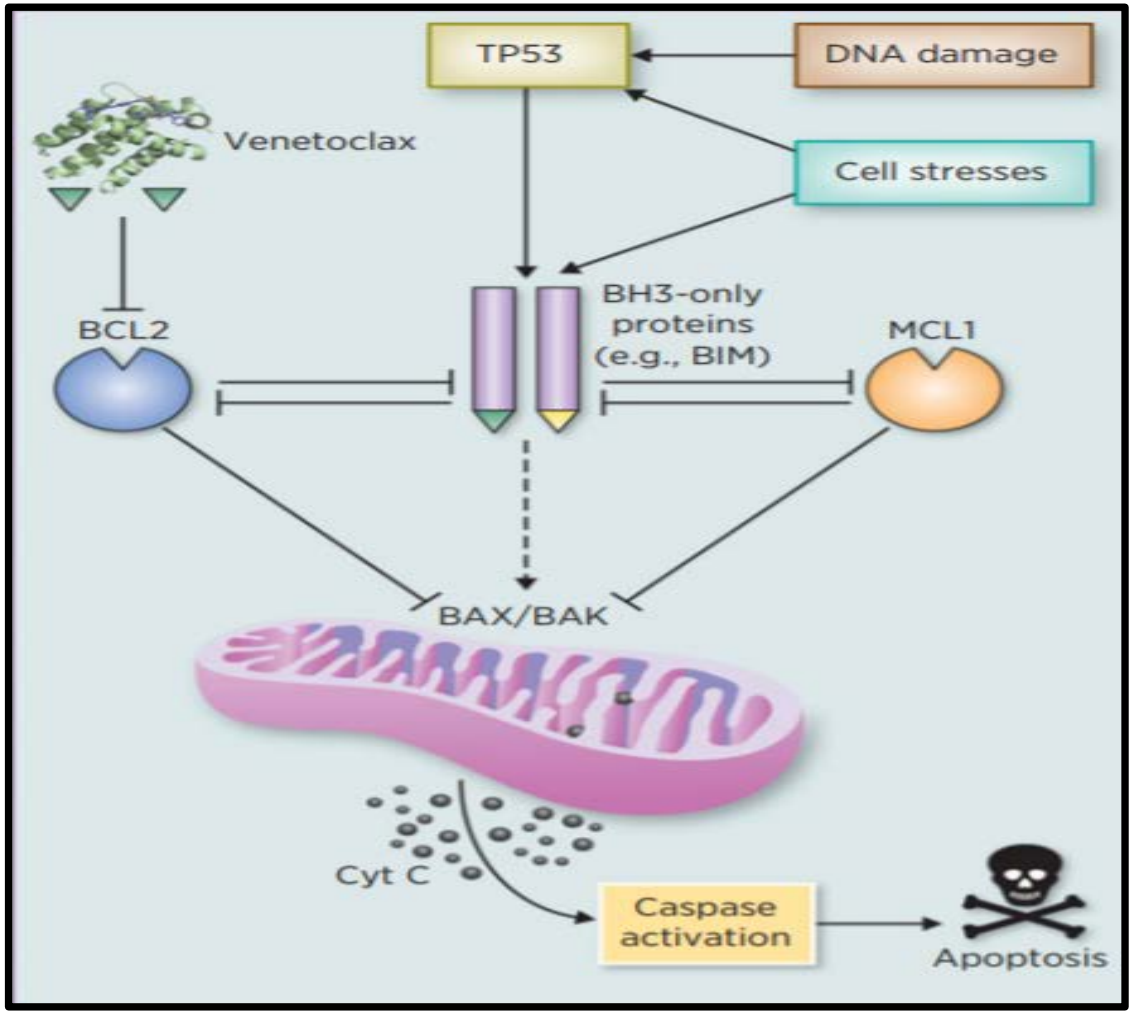


		Glycoengineered	Type	Direct effect	CDCC	ADCC
Rituximab	chimeric	No	I	↑	↑↑↑↑	↑↑
ofatumumab	humanized	No	I	↑	↑↑↑↑	↑↑
obinutuzumab	humanized	Yes	II	↑↑↑↑	↑	↑↑↑
ublituximab	chimeric	Yes	I	↑	↑↑↑↑	↑↑↑↑

BCR Pathway inhibitors vs. BCL2 antagonist



Byrd, JCO,2014



Roberts, CCR Drug Updates,2017

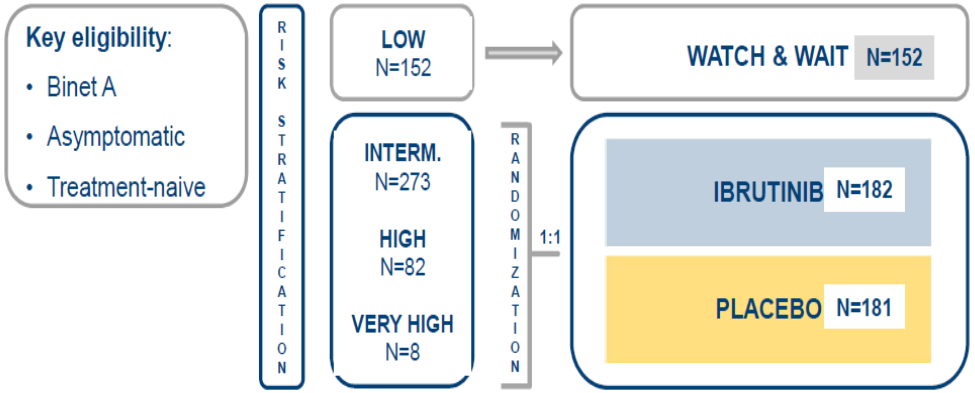
4. Who needs to be treated?

Indications for treatment

- Progressive marrow failure
- Massive , progressive or symptomatic lymphadenopathy or organomegaly
- Constitutional symptoms
- Autoimmune anemia and/or thrombocytopenia that is poorly responsive to corticosteroids or other standard therapy
- ~~Lymphocyte doubling time~~

5. Is there a role for early intervention in “high-risk” patients?

CLL-12 Study – Early intervention with Ibrutinib

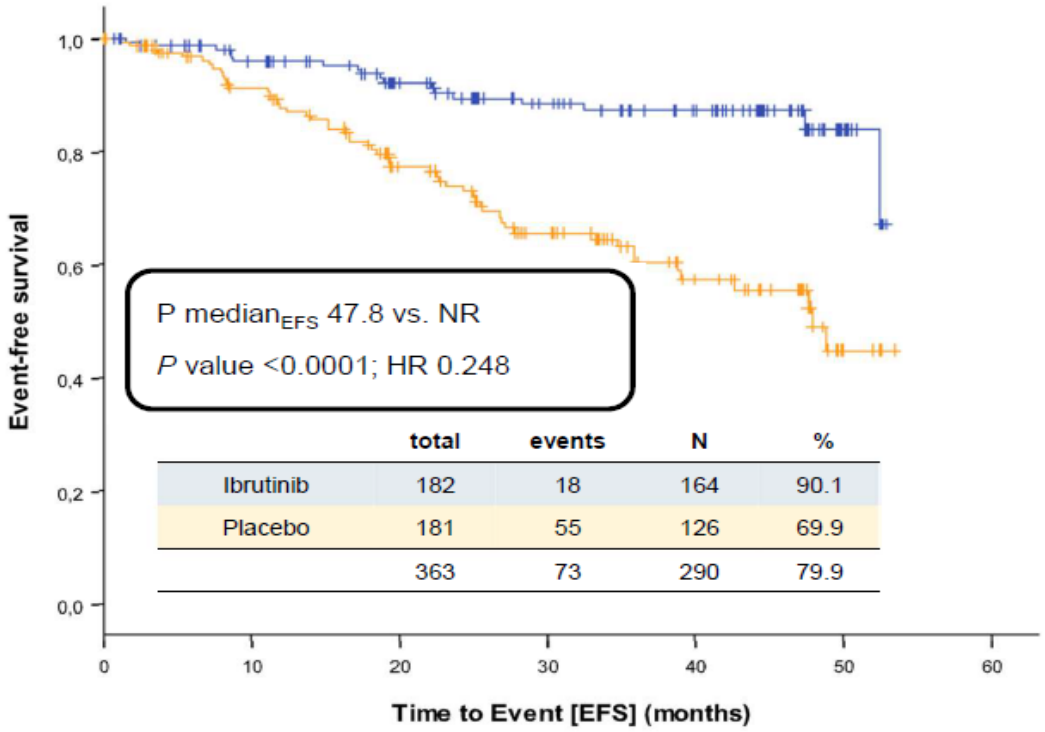


Phase 3, placebo-controlled, double-blind, multicenter trial

Primary endpoint EFS: time from randomization until symptomtatic PD, new treatment, death

Secondary endpoints: survival, PFS, TFS, TTNT, ORR, safety

π_2 : median EFS from 24 to 48 months with ibrutinib (superiority test)



	total	events	N	%
Ibrutinib	182	18	164	90.1
Placebo	181	55	126	69.9
	363	73	290	79.9

- No OS benefit
- Study is powered for OS so longer follow-up would be interesting
- **Early intervention with ibrutinib is NOT recommended at this time**

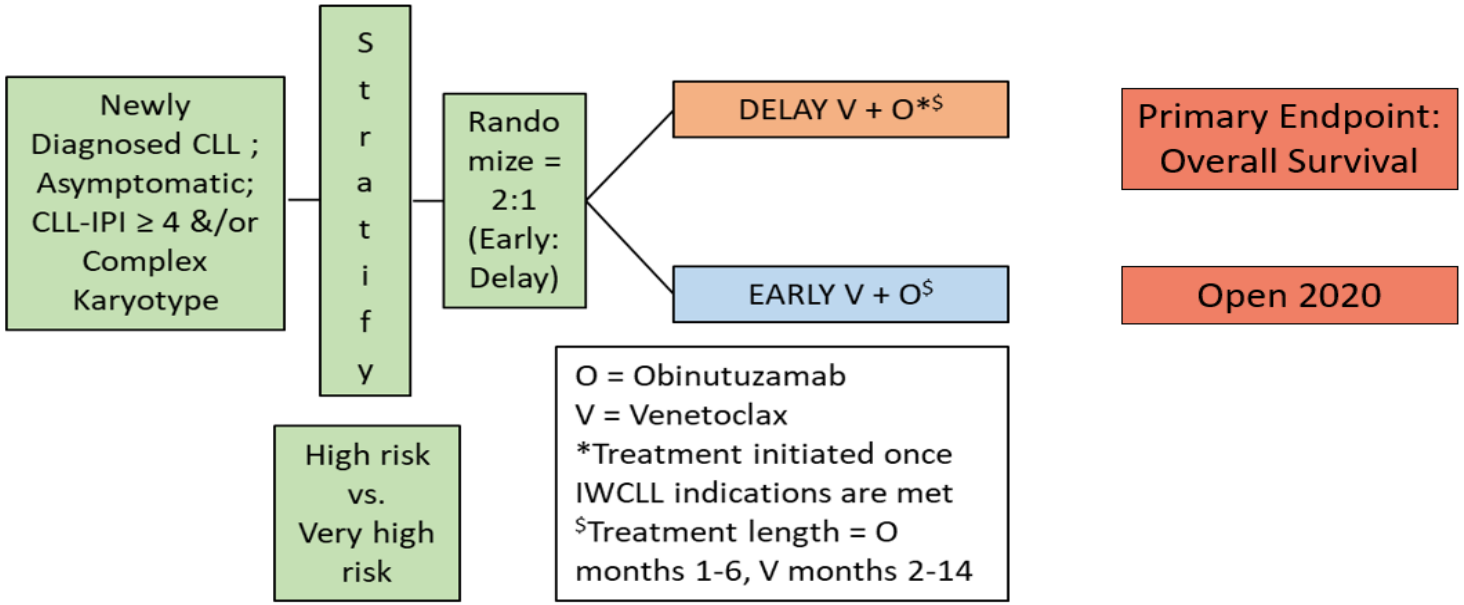
Langerbeins, Lugano (15-ICML) meeting , 2019

Upcoming US Intergroups Early Intervention Trial with Venetoclax

CLL-IPI

Characteristic	Points
Del(17p) or TP53 mutation	4
Serum beta-2-macroglobulin ≥ 3.5mg/L	2
Un-mutated IgVH	2
Rai Stage I-IV	1
Age > 65 years	1

Points	Risk Group
0-1	Low
2-3	Int
4-6	High
7-10	Very High



Courtesy: Dr. Deborah Stephens (study PI)

SWOG
Leading cancer research. Together.

6. Treatment options for treatment-naïve patients (without del17p/P53 mutation)

First line treatment
for patients with normal TP53

For all pts:

Acalabrutinib ± G

OR

Ibrutinib

OR

Venetoclax + G

FCR is <u>not preferred</u> but can be a <u>reasonable option</u> for selected patients if:

- younger than 65 and fit
- mutated IGHV
- no evidence of del17p or TP53 mutation
- (no evidence of del 11q)

G = Gazyva = obinutuzumab

Frontline (normalTP53)

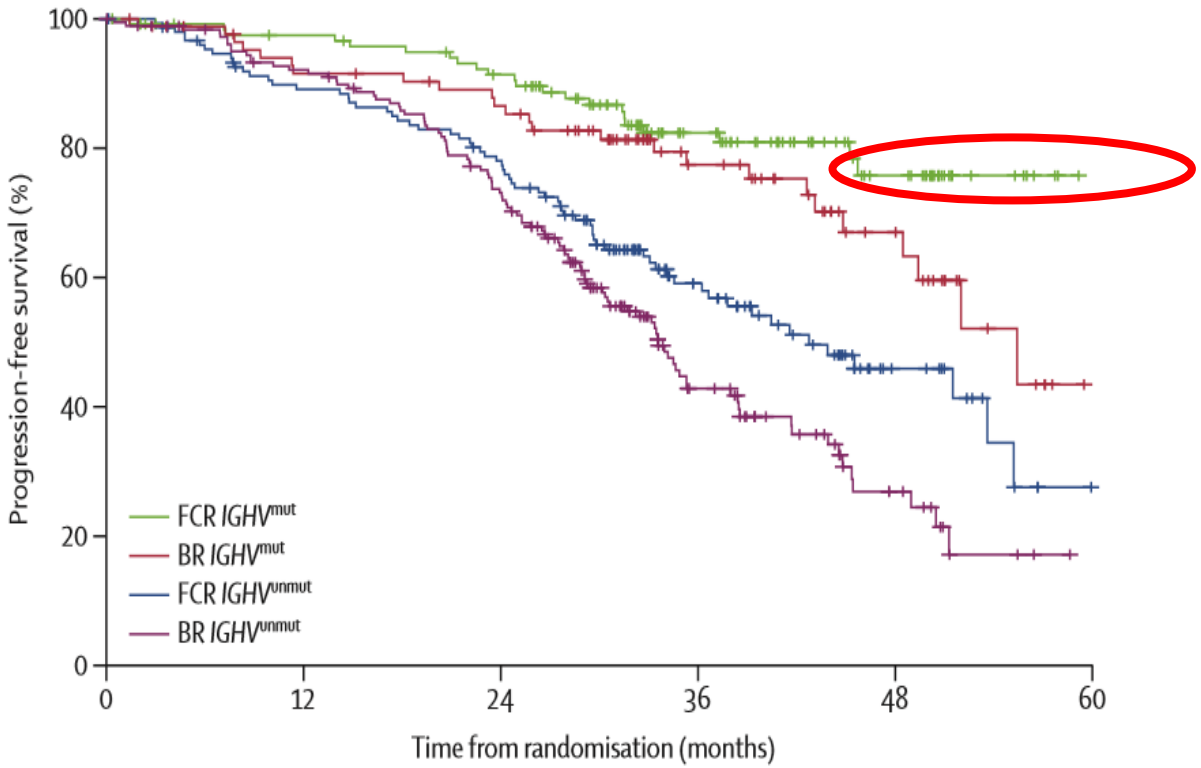
Historical studies from the “chemo era”

Study	Treatments	N	Result	Outcome	Notes
German CLL10	FCR vs. BR	564	FCR > BR	PFS but not OS	No benefit if > 65 AML/MDS: 5% with FCR
German CLL11	CHL-obino vs. CHL-ritux vs. CHL	780	CHL-obino > CHL-ritux > CHL	PFS and OS	
RESONATE-2	Ibrutinib vs. CHL	269	Ibrutinib > CHL	PFS and OS	

Eichhorst, Lancet Oncology, 2016 ; Eichhorst, ASH, 2016; Geode, NEJM, 2014; Geode, Leukemia, 2015; Burger, NEJM,2015

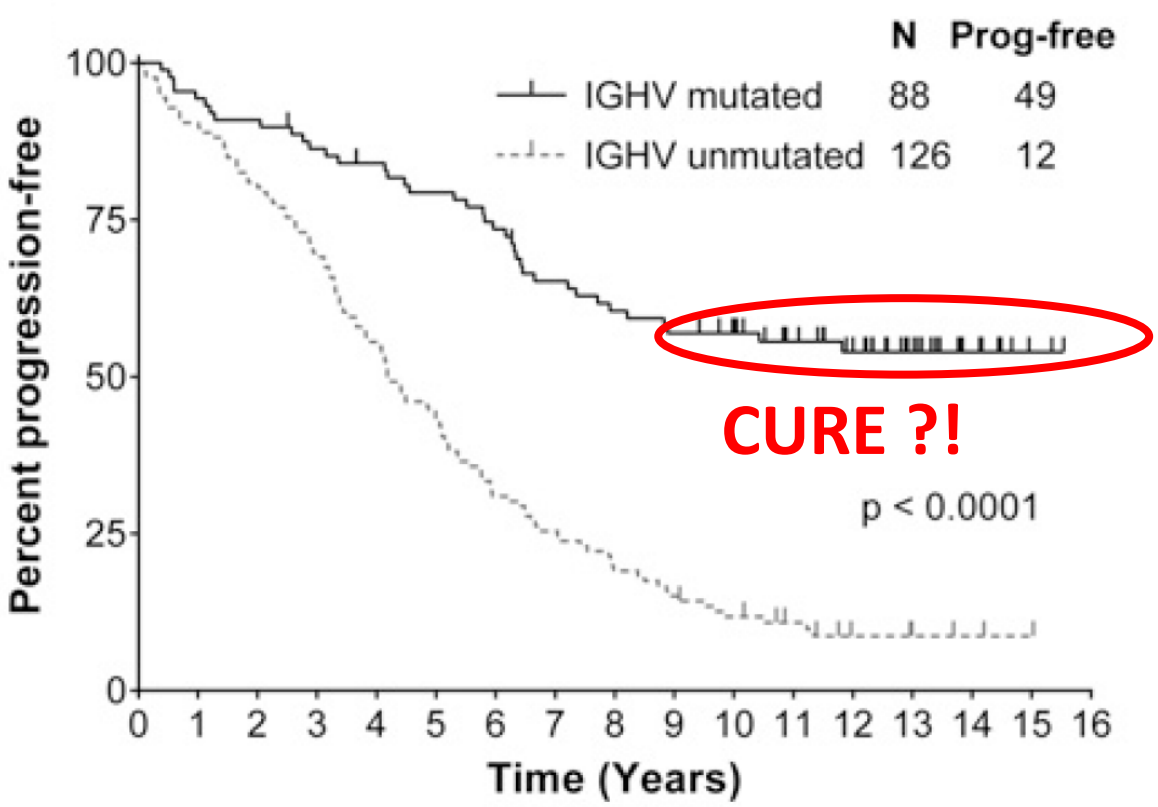
IGHV mutation as a predictive marker for FCR

CLL10 Study



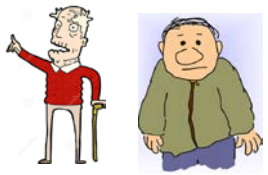
Eichhorst, Lancet Oncology, 2016

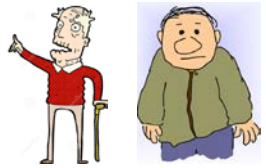
MD Anderson



Thompson, Blood, 2106

First line – Summary of novel vs. chemo studies



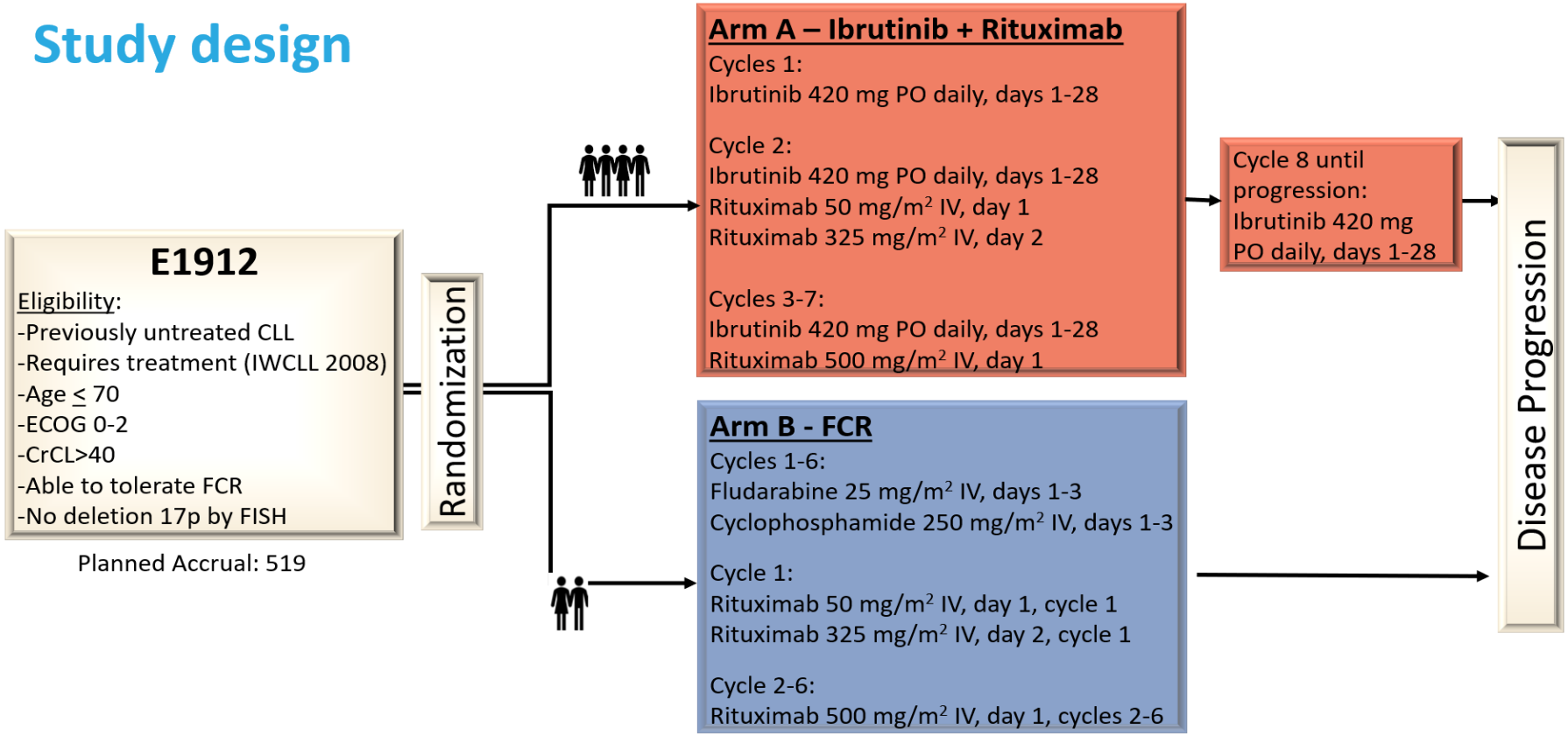


Fit and young	**FCR**	? (E1912)	**Ibrutinib +R**
Older	**BR**	? (A041202)	**Ibrutinib ± R**
Older or with comorbid conditions	**CHL+G**	? (iLLUMINATE)	**Ibrutinib +G**
Older or with comorbid conditions	**CHL+G**	? (ELEVATE)	**acalabrutinib ± G**
with comorbid conditions	**CHL+G**	? (CLL14)	**Venetoclax+ G**

G = obinutuzumab
R = rituximab

FCR vs. IB+R (E1912 Study)

Study design



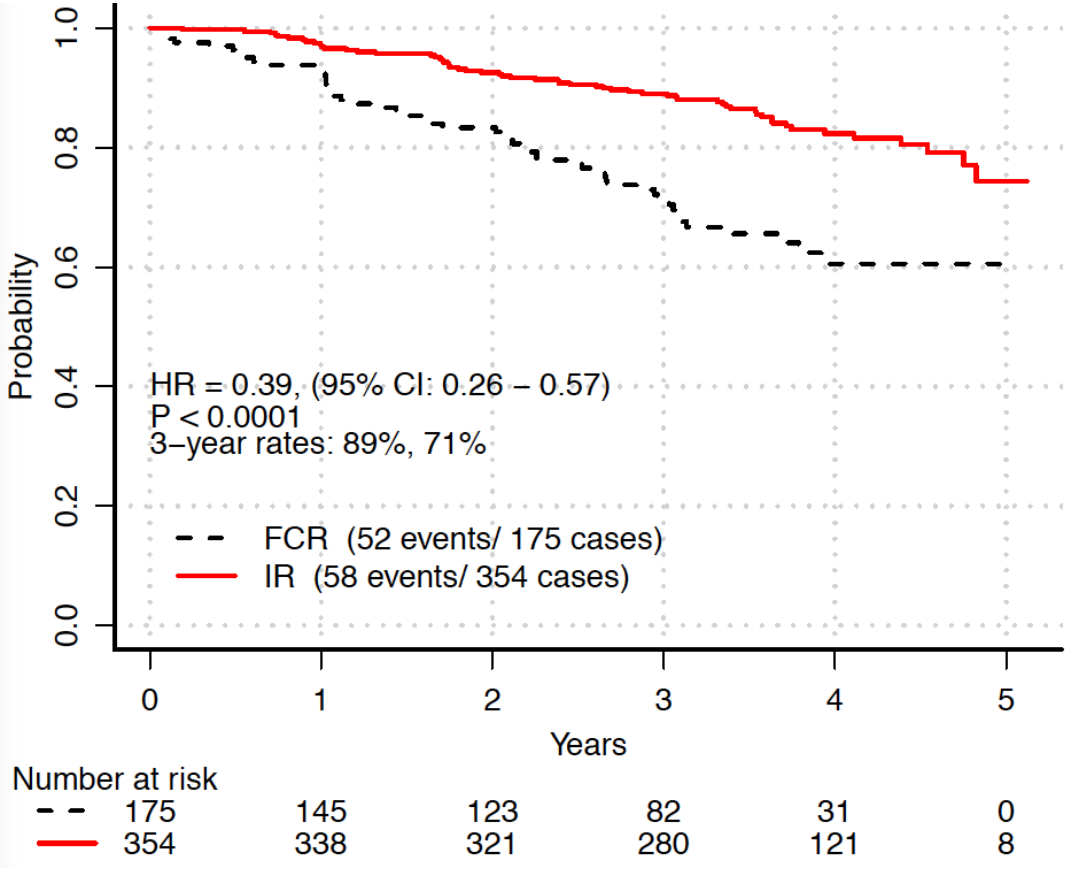
ECOG-ACRIN cancer research group | Reshaping the future of patient care

Shanafelt. NEJM,2019

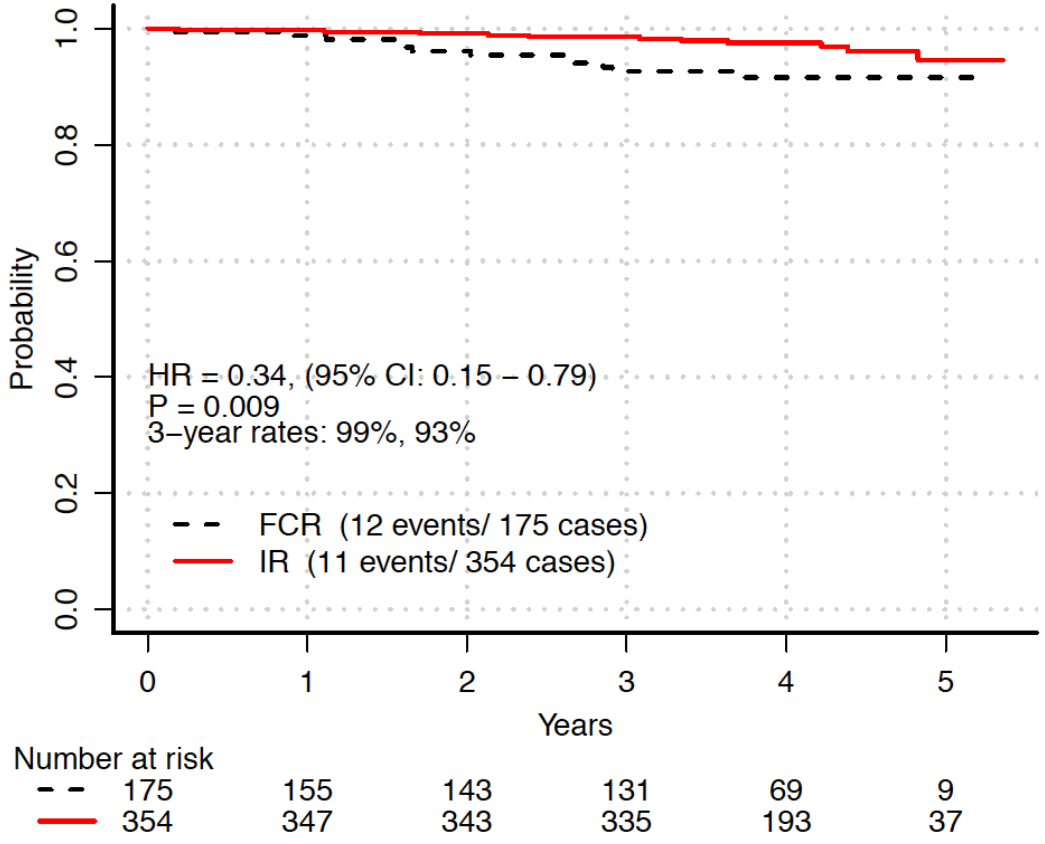
FCR vs. IB+R (E1912 Study)

(48 months follow-up)

Progression-free Survival



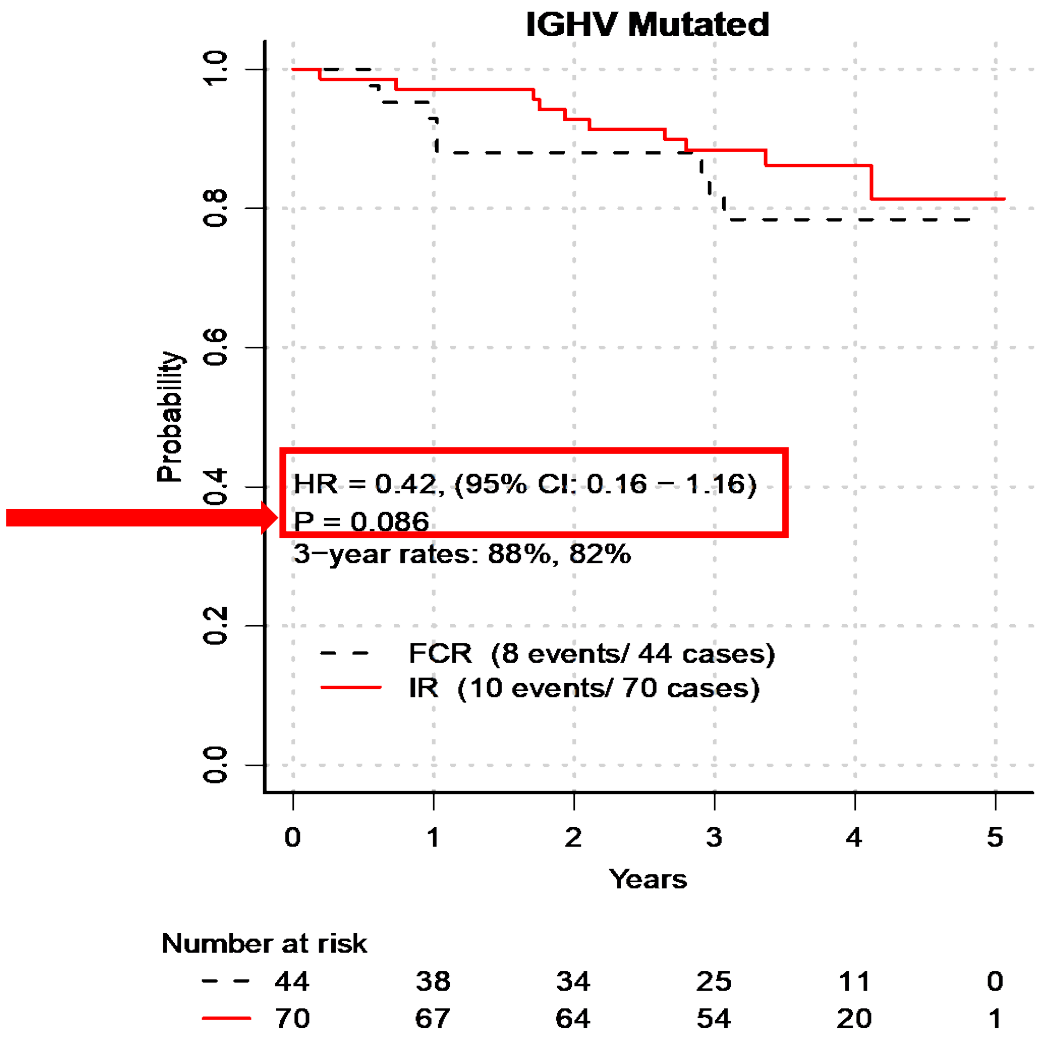
Overall Survival

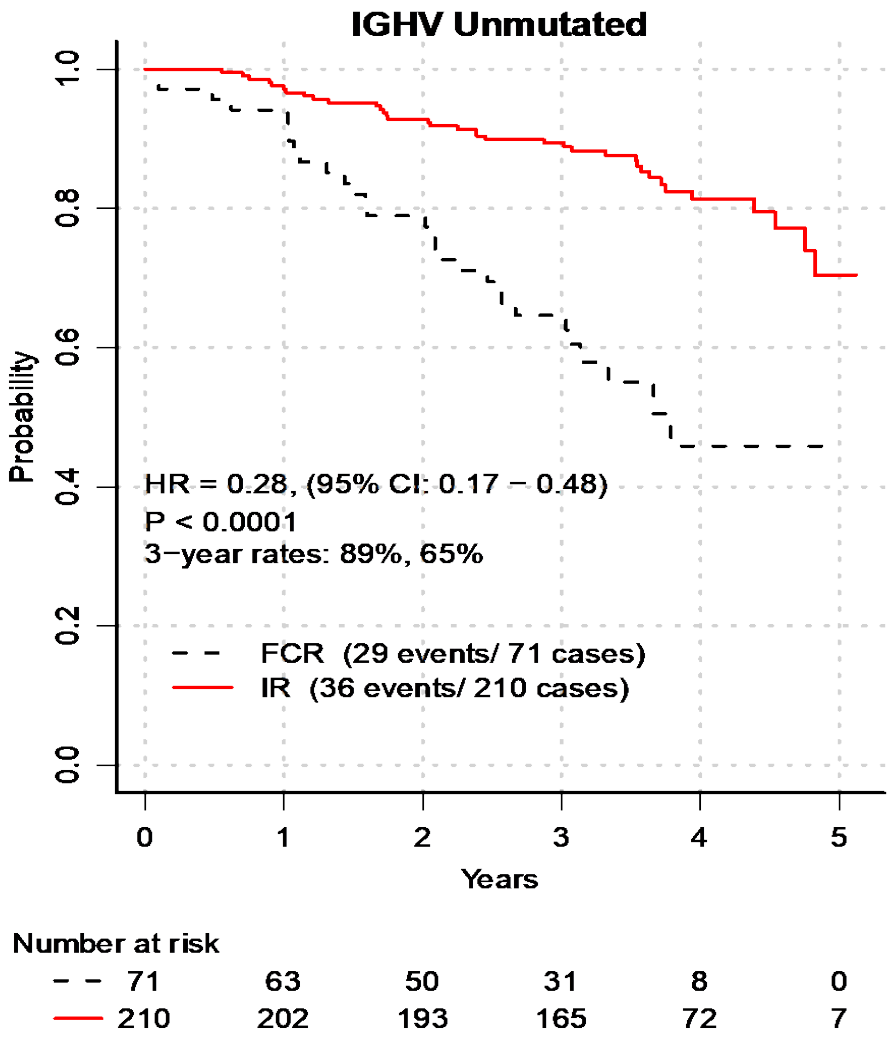


Shanafelt, ASH,2019

FCR vs. IB+R (E1912 Study)

(48 months follow-up)



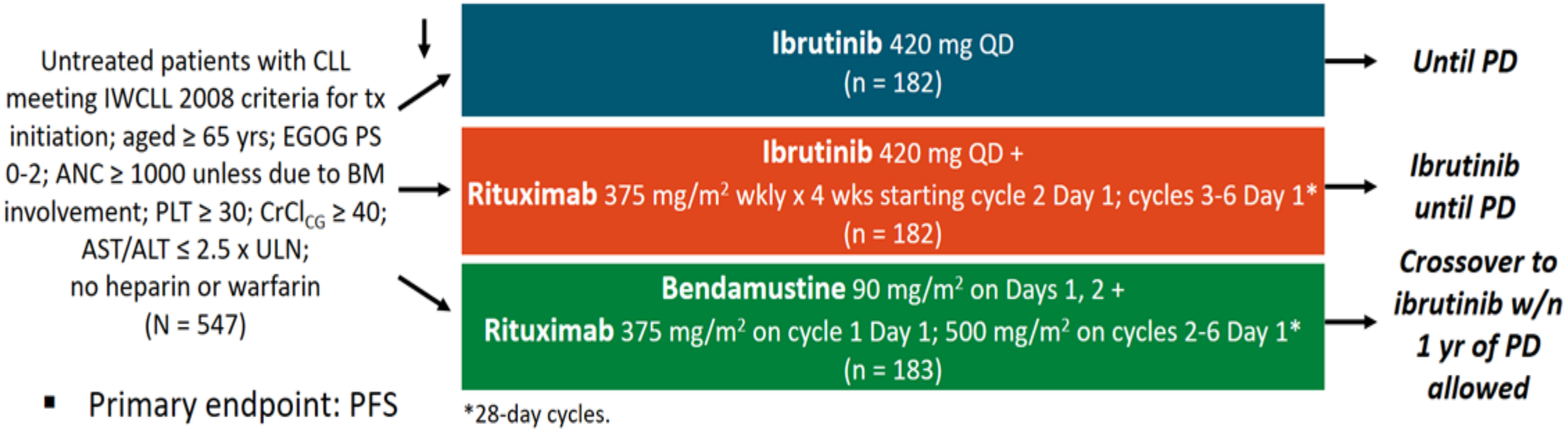


Shanafelt, ASH,2019

BR vs. IB+R vs. IB (A041202 Study)

- Multicenter, randomized, double-blind phase III study (data cutoff: October 4, 2018)

Stratified by Rai stage (high vs intermediate risk), del(11q22.3) or del(17p13.1) (presence vs absence), ZAP-70 methylation (< vs ≥ 20%)



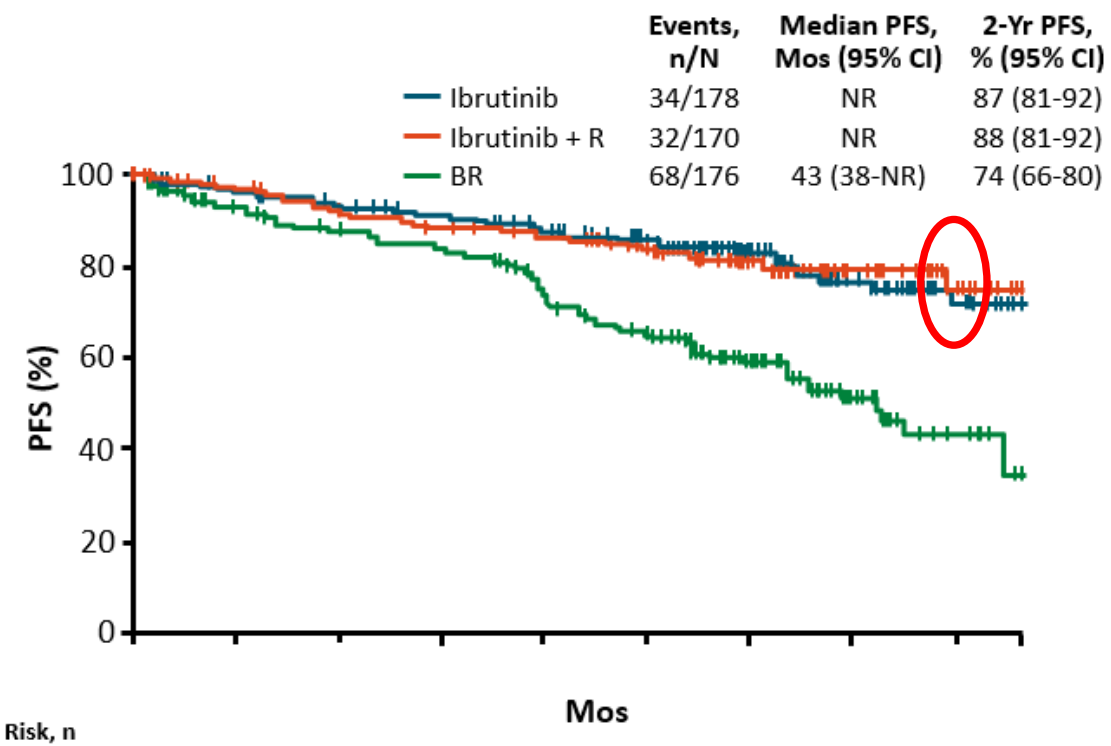
*28-day cycles.

- Primary endpoint: PFS

Woyach,NEJM,2018

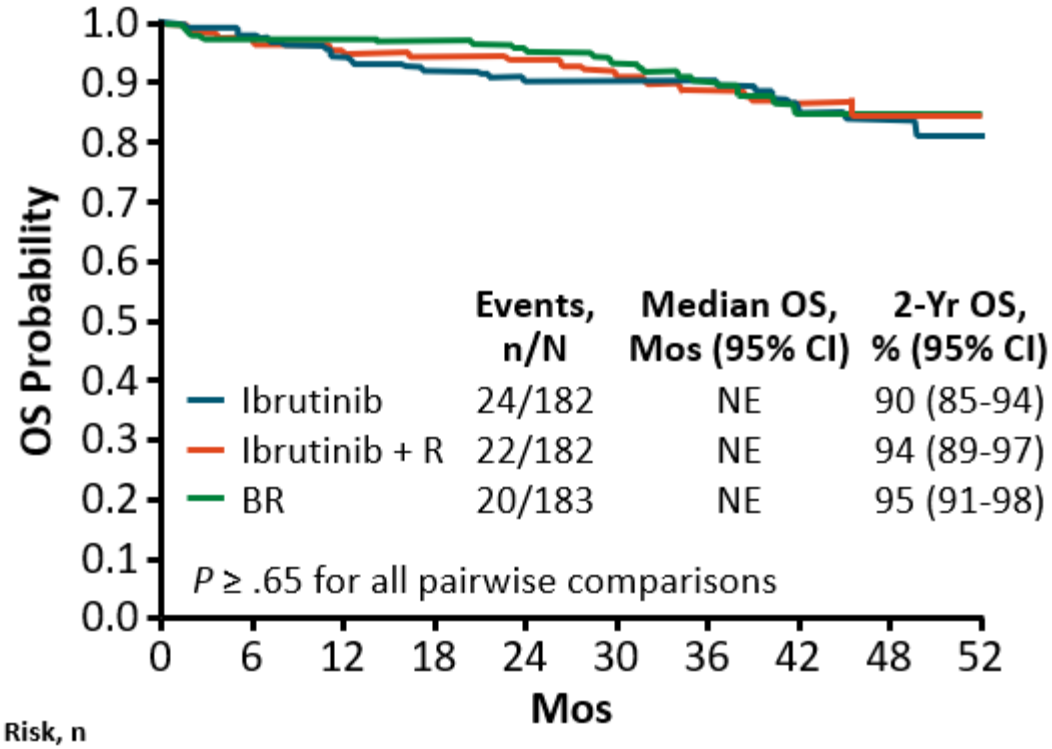
A041202: Results

Progression-Free Survival



Patients at Risk, n										
Ibrutinib	178	165	154	147	136	120	78	45	22	0
Ibrutinib + R	170	159	145	138	132	115	74	40	20	0
BR	176	140	129	122	103	88	57	26	11	0

Overall Survival



Patients at Risk, n										
Ibrutinib	182	175	166	161	156	146	100	62	26	1
Ibrutinib + R	182	172	169	165	161	147	100	55	24	1
BR	183	166	163	160	153	143	98	53	23	1

Woyach,NEJM,2018

IB+G vs. CHL+G (iLLUMINATE)

- Randomized, open-label, multicenter phase III trial

Stratified by ECOG PS (0-1 vs 2), del(17p)/del(11q) (+/+ vs +/- vs -/+ vs -/-)

Untreated patients with CLL/SLL needing treatment by iwCLL criteria, ≥ 65 yrs or < 65 yrs with comorbidities* (N = 229)

Ibrutinib 420 mg PO QD continuously + **Obinutuzumab** IV for 6 cycles† (n = 113) → ***Ibrutinib continued until PD or unacceptable toxicity***

Chlorambucil 0.5 mg/kg PO D1,15 for 6 cycles + **Obinutuzumab** IV for 6 cycles† (n = 116) → ***If IRC-confirmed progression, crossover to next-line single-agent ibrutinib permitted***

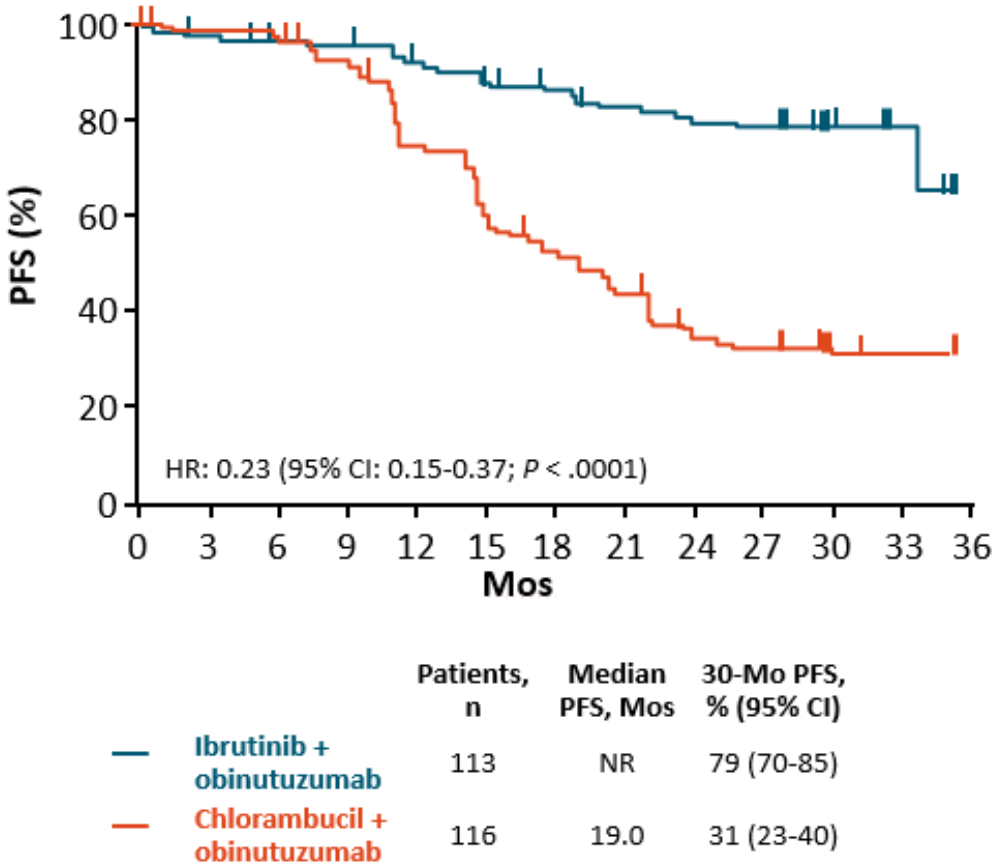
*Cumulative Illness Rating Score > 6, creatinine clearance < 70 mL/min, and/or del(17p)/*TP53* mutation.
†Cycle 1: 100 mg, Days 1; 900 mg, Day 2; 1000 mg, Days 8, 15. Cycle 2-6: 1000 mg, Day 1.

- Primary endpoint: PFS

Moreno, Lancet Oncology, 2018

IB+G vs. CHL+G (iLLUMINATE) Results

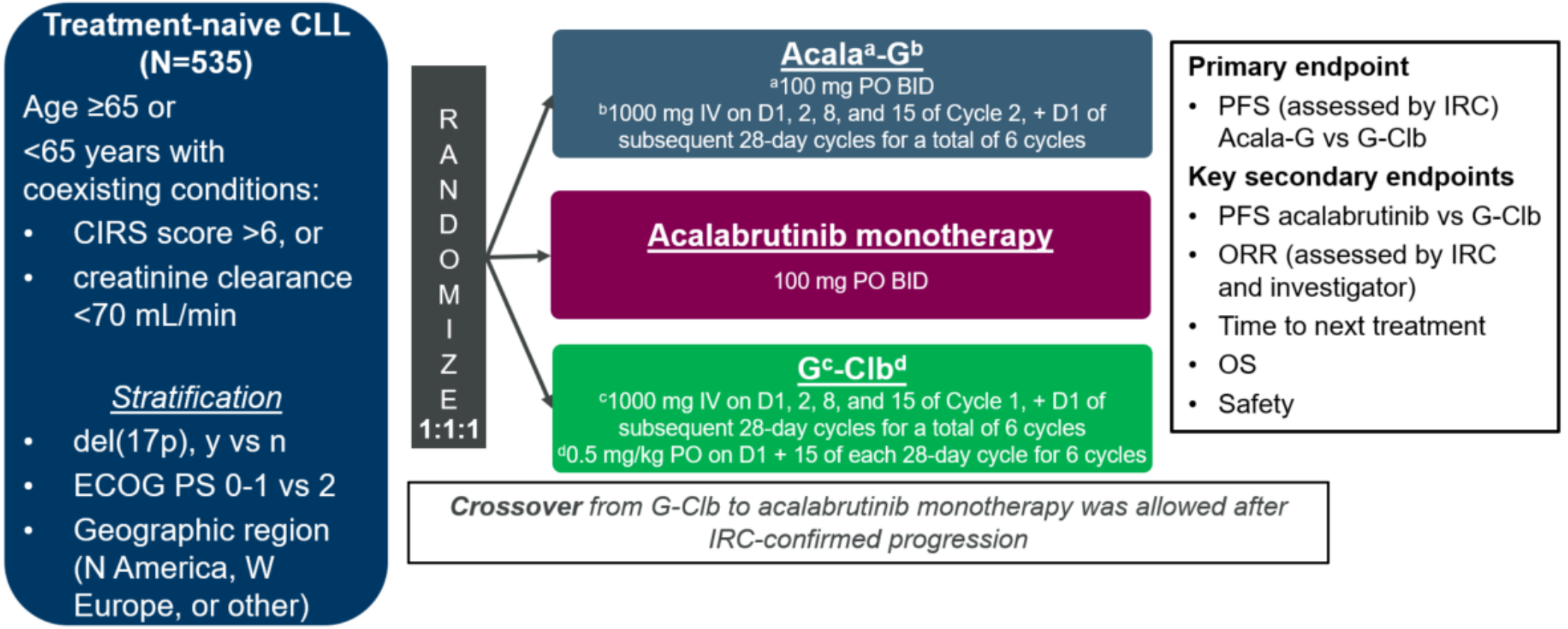
Progression-free Survival



No Overall Survival Benefit

Moreno, Lancet Oncology, 2018

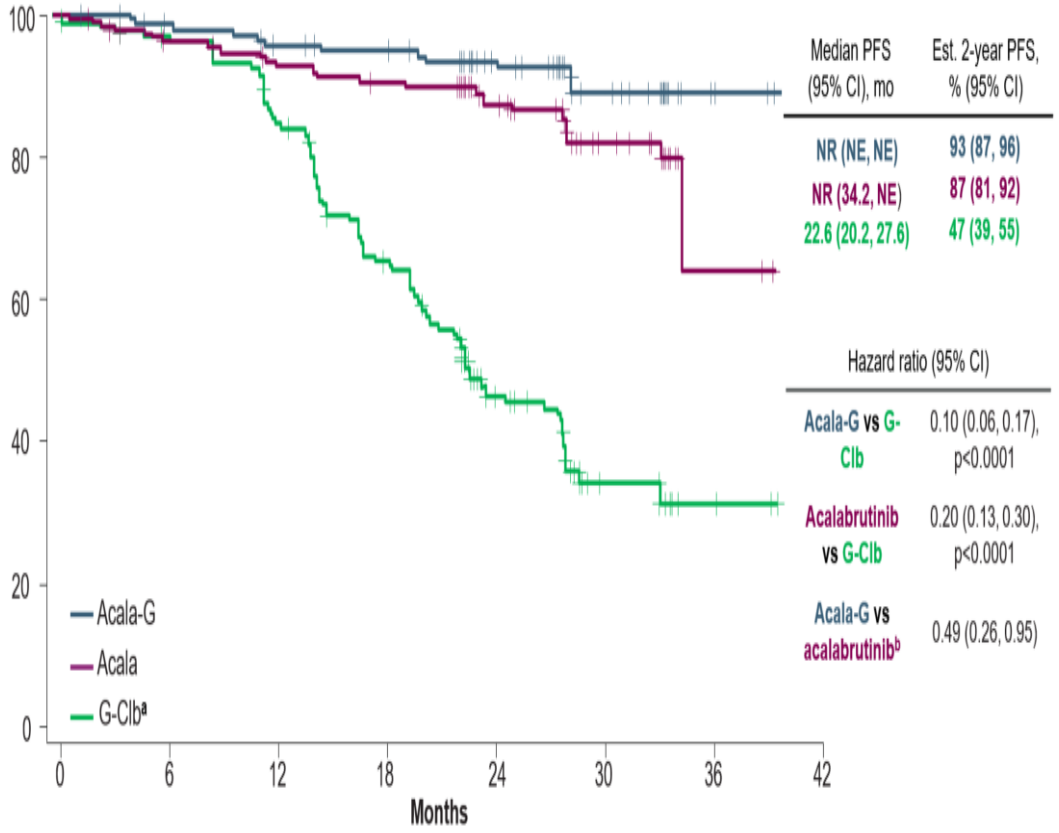
Acalabrutinib ± G vs. CHL+G (ELEVATE)



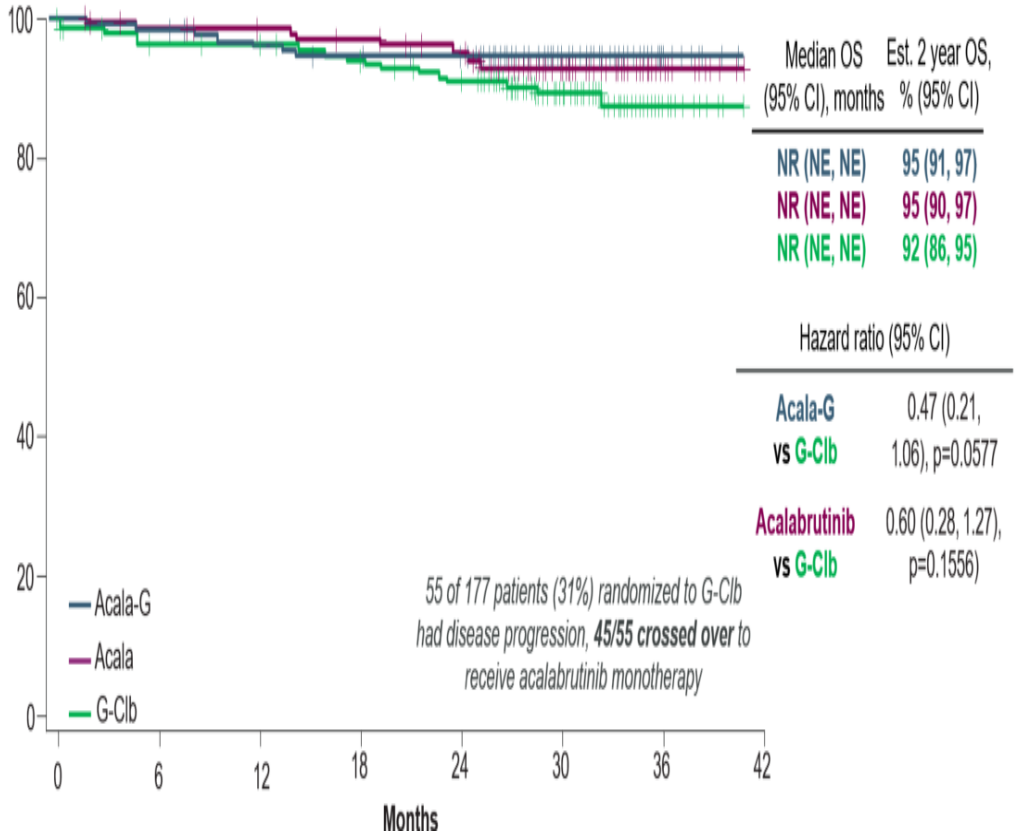
Sharman, Lancet, 2020

Acalabrutinib ± G vs. CHL+G (ELEVATE)

Progression-free Survival

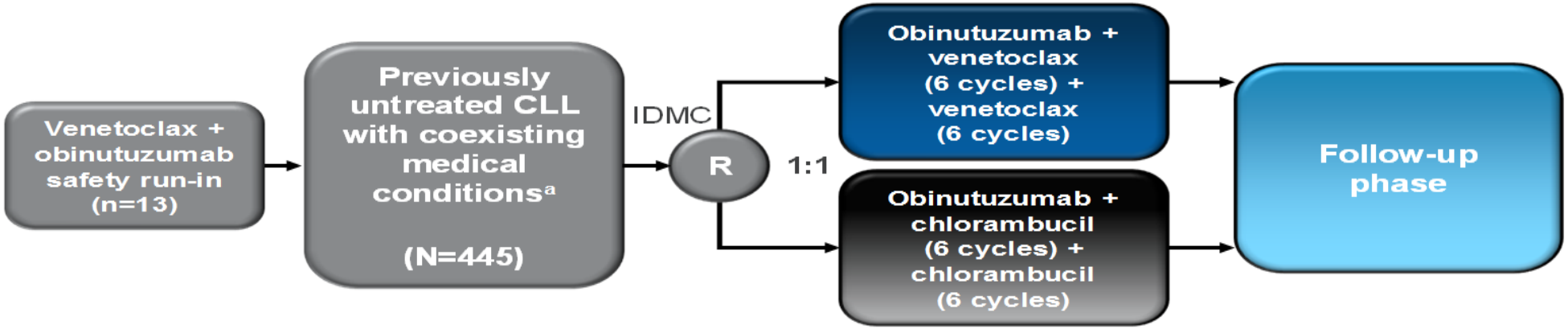


Overall Survival



Sharman, Lancet, 2020

Venetoclax + G vs CHL + G (CLL-14)



Primary endpoint:

- PFS as assessed by investigator[3]

Secondary endpoints[3]:

- PFS as assessed by IRC
- MRD
- ORR
- CR rate
- DOR
- EFS
- OS
- TTNT
- Safety

[a]CIRS >6 and/or CrCl <70 mL/min

Fischer, NEJM,2019

Venetoclax and TLS

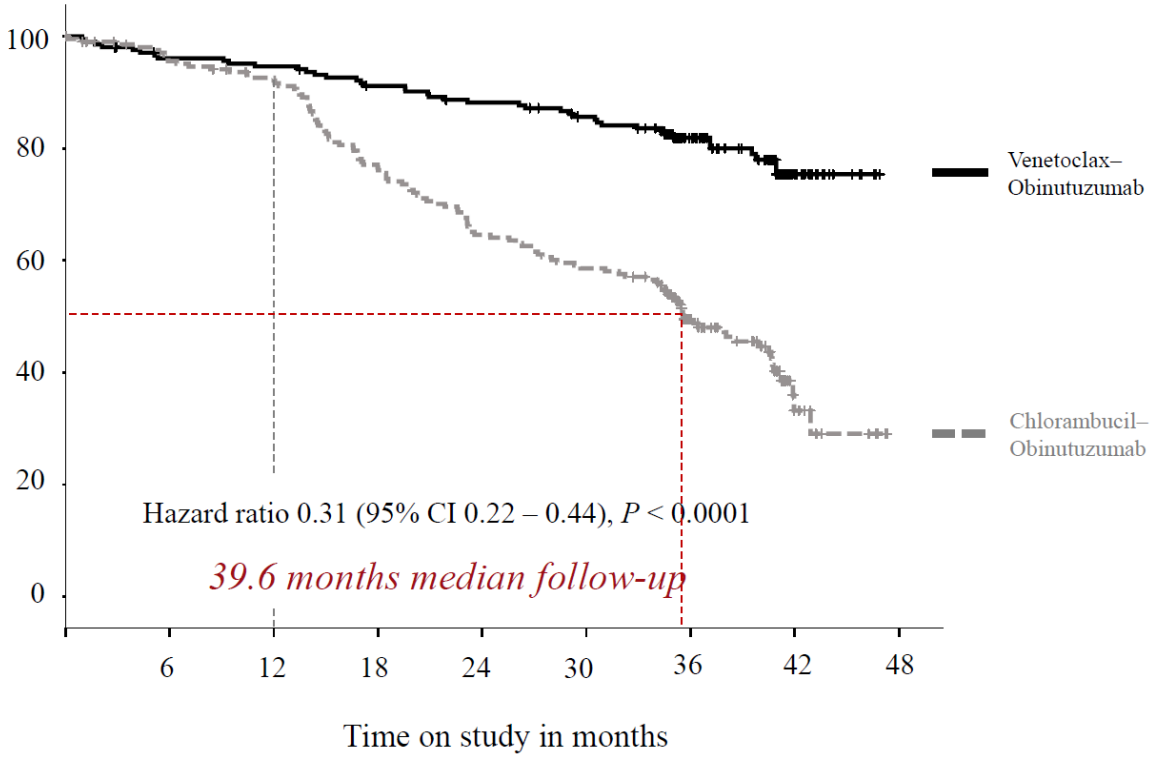
Figure 1: Dosing Schedule for Ramp-up Dose

Tumor Burden		Prophylaxis		Blood Chemistry Monitoring[c]
		Hydration[a]	Anti-hyperuricemics	Setting and Frequency of Assessments
Low	All LN <5 cm AND ALC <25 × 10^9/L	Oral (1.5-2 L)	Allopurinol[b]	**Outpatient** • Pre-dose, 6-8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp up doses
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 × 10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	**Outpatient** • Pre-dose, 6-8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp up doses • Consider hospitalization for patients with CrCl <80 mL/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 × 10^9/L AND any LN ≥5 cm	Oral (1.5-2 L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol;consider rasburicase ifbaseline uric acid is elevated	**In hospital at first dose of 20 mg and 50 mg** • Pre-dose, 4, 8,12 and 24 hours **Outpatient at subsequent ramp-up doses** • Pre-dose, 6-8 hours, 24 hours

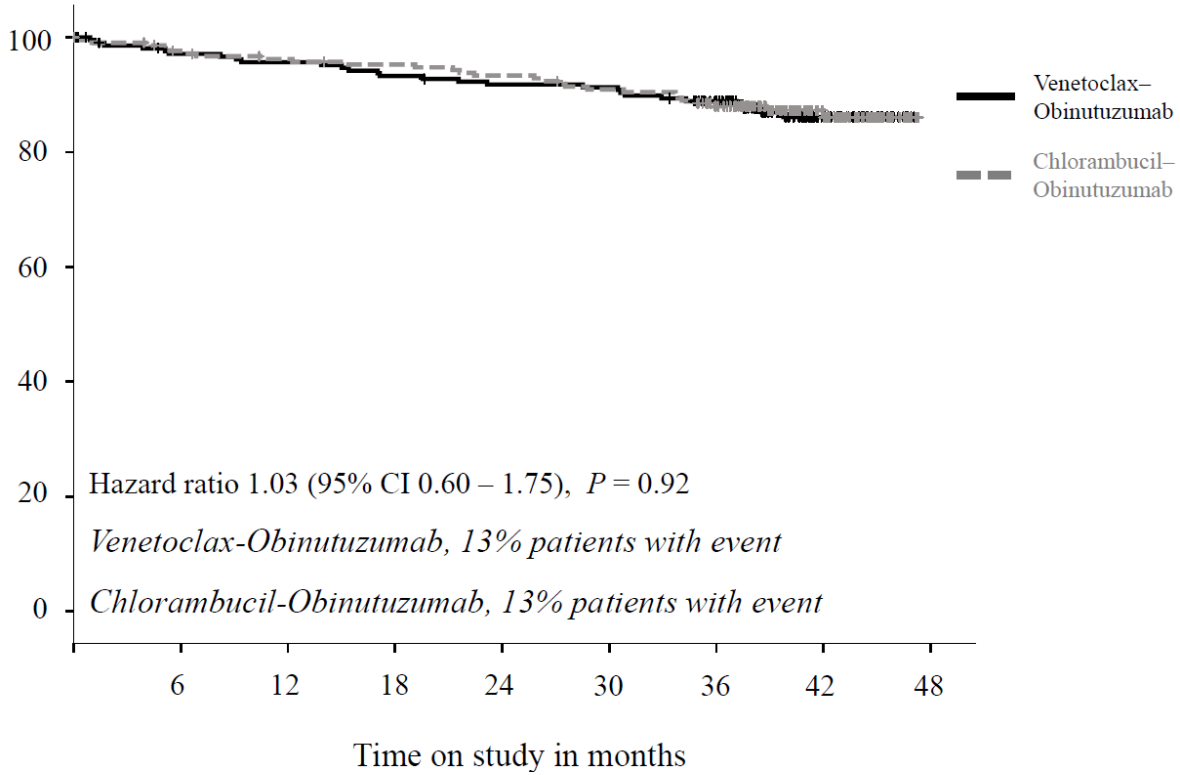
- For patients at risk of TLS, monitor blood chemistries at 6-8 hours and at 24 hours after each subsequent ramp-up dose

Venetoclax + G vs CHL + G (CLL-14)

Progression-free Survival



Overall Survival

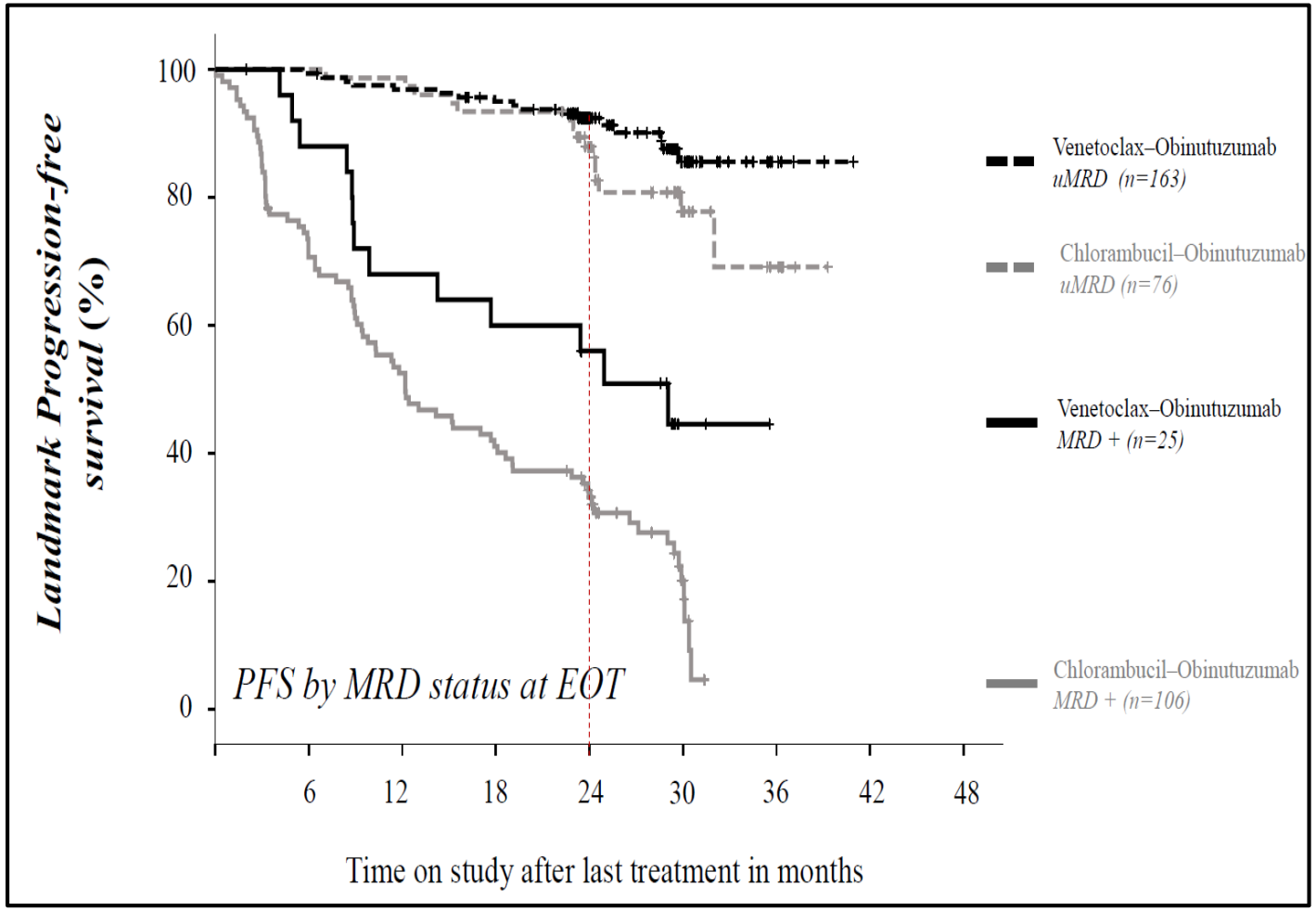


Fischer, ASH,2019

uMRD4 at the end of treatment (12 months) and PFS

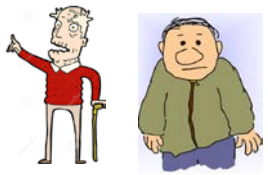
	Venetoclax-Obinutuzumab	Chlorambucil-Obinutuzumab	*P* value
Number of patients, N	216	216	
Peripheral blood			
Negative ($<10^{-4}$)	76 %	35 %	< 0.001
Negative ($<10^{-4}$) in complete response	42 %	14 %	< 0.001
Bone marrow			
Negative ($<10^{-4}$)	57 %	17 %	< 0.001
Negative ($<10^{-4}$) in complete response	34 %	11 %	< 0.001

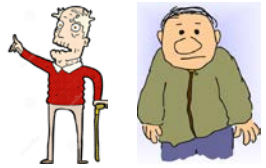
By ASO-PCR 3 months after completion of treatment



Fischer, ASH,2019

First line – Summary of novel vs. chemo studies





Fit and young	**FCR**	< (E1912)	**Ibrutinib +R**
Older	**BR**	< (A041202)	**Ibrutinib ± R**
Older or with comorbid conditions	**CHL+G**	< (iLLUMINATE)	**Ibrutinib +G**
Older or with comorbid conditions	**CHL+G**	< (ELEVATE)	**acalabrutinib ± G**
with comorbid conditions	**CHL+G**	< (CLL14)	**Venetoclax+ G**

G = obinutuzumab
R = rituximab

First line treatment
for patients normal TP53

For all pts:

Acalabrutinib ± G

OR

Ibrutinib

OR

Venetoclax + G

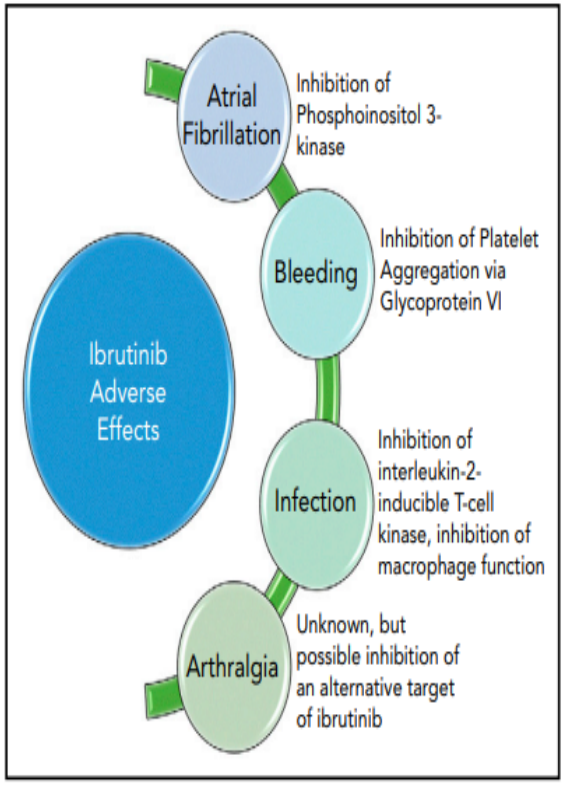
FCR is <u>not preferred</u> but can be a <u>reasonable option</u> for selected patients if:

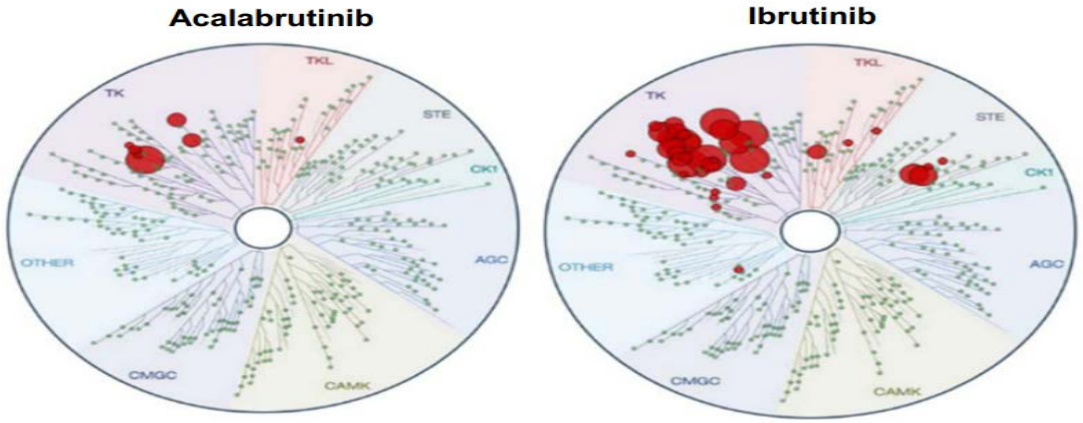
- younger than 65 and fit
- mutated IGHV
- no evidence of del17p or TP53 mutation
- (no evidence of del 11q)

G = Gazyva = obinutuzumab

Acalabrutinib or Ibrutinib

- Head-to-head trial is done in the relapsed setting and will be reported “soon”



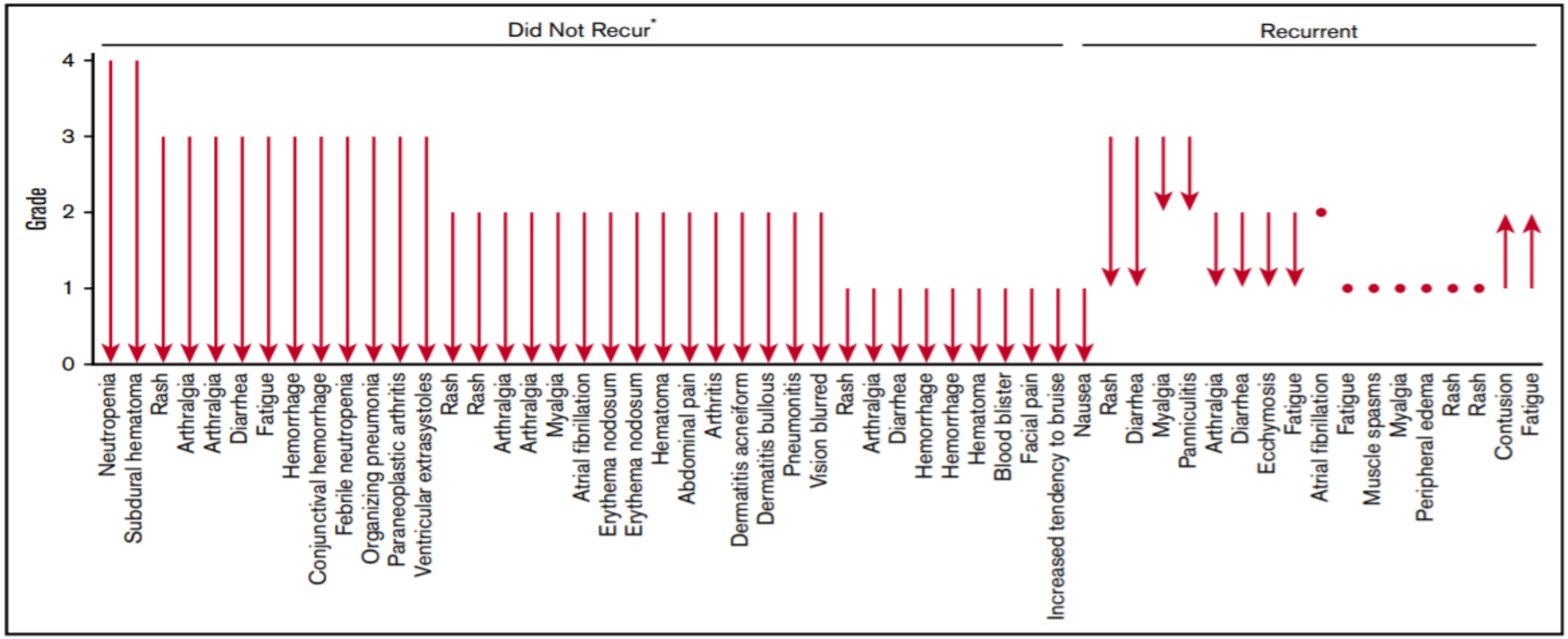


Treatment discontinuation rates due to toxicity

Ibrutinib	Frontline: 15% Relapsed: 22%
Acalabrutinib	Frontline: no data Relapsed: 12%

Mato, Haematologica, 2018 ; Yazdi,ASH,2019; Roeker, Clin Cancer Research, 2019 ;Shadman, ASH,2019; Stephens, Blood, 2019

Acalabrutinib in Ibrutinib intolerant patients



of 61 ibrutinib-related AEs associated with intolerance, 72% did not recur and 13% recurred at a lower grade with acalabrutinib

Awan, Blood Adv, 2019

BTKis vs. Ven-G

BTKi (Acalabrutinib/Ibrutinib)	Ven-G
Indefinite treatment (responses mostly PR)	Fixed-duration ; High CR and uMRD rate
Long-term efficacy data available	Time-limited treatment
Easier to start	Better tolerated and easier to continue
Preferred in patients who: • Can't follow the ramp-up schedule for venetoclax • Significant/unstable renal issues	Preferred in patients with: • Cardiac (arrythmia, HTN) • Bleeding issues
IB is studied against stronger regimens: (FCR and BR)	Deep remissions (@ MRD level) – would expect the same in younger pts
Can use after Ven and is effective	Can use after BTKi and is effective

- **No head-to-head comparison**
- **Both are reasonable options**
- **Consider patient and disease factors**
- **Look at pros and cons for each**

7. Treatment options for previously treated patients (without del17p/P53 mutation)

Previously Treated CLL Summary

For all pts:

Acalabrutinib OR **Ibrutinib** OR **Venetoclax + R**

Duvelisib OR **Idelalisib**

R = rituximab

Previously Treated CLL Summary

1. **First**
   - **Venetoclax + Rituximab**
     or
   - **BTKi : Ibrutinib or acalabrutinib**

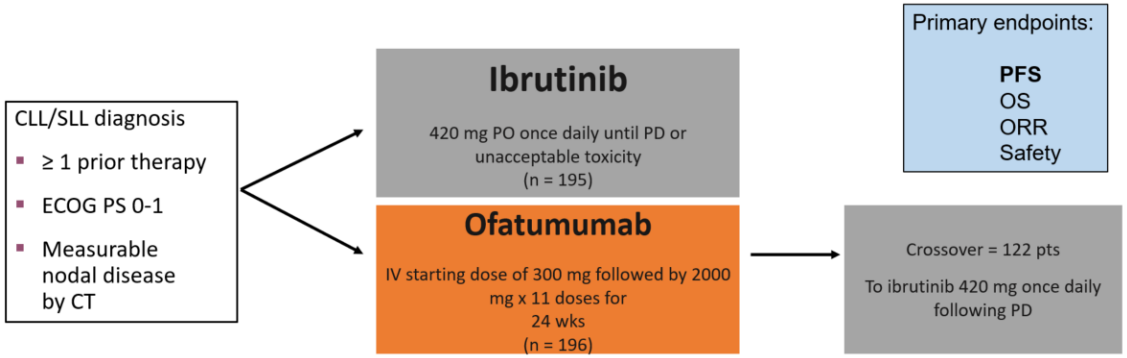
2. **Second**
   - **Ibrutinib/acalabrutinib if previously treatment with Ven**
   - **Ven-R if previously treated with BTKi (ibrutinib or acalabrutinib)**

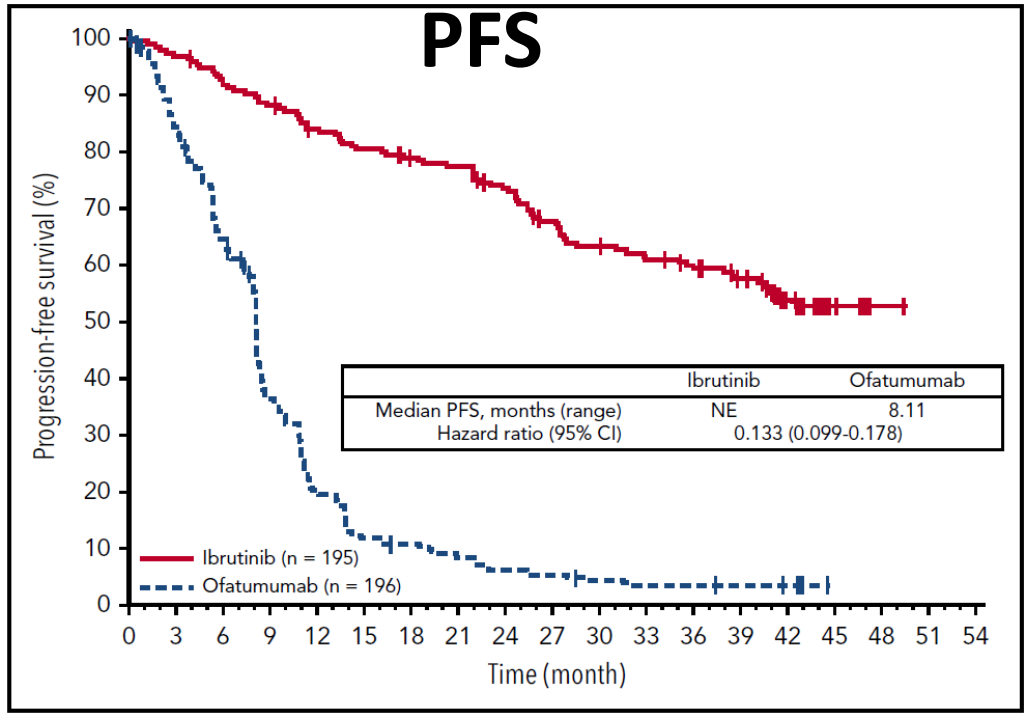
3. **Third**
   - **Idelalisib+ rituximab OR duvelisib**

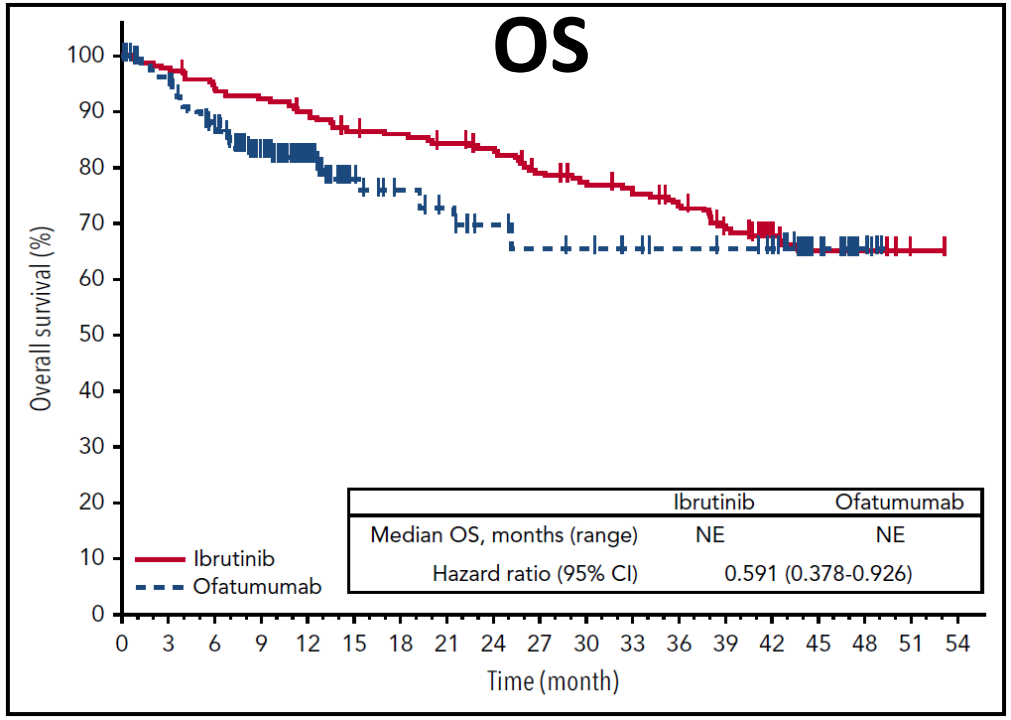
Previously treated CLL : Principles

1. **Repeat FISH panel - look for del (17p) or TP53 mutation**
2. Bone marrow needs to be repeated to assess for MDS if prior FCR
3. Very limited role for chemoimmuntherapy (almost never)

Ibrutinib vs Ofatumumab in R/R CLL (RESONATE: Phase III)

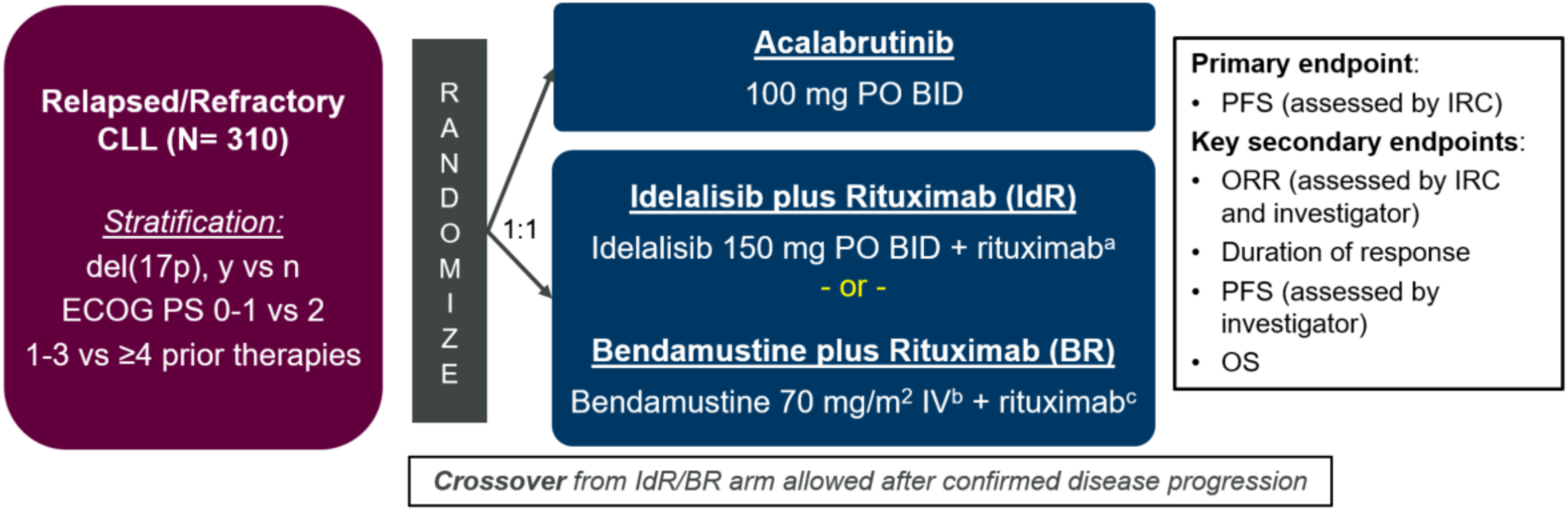






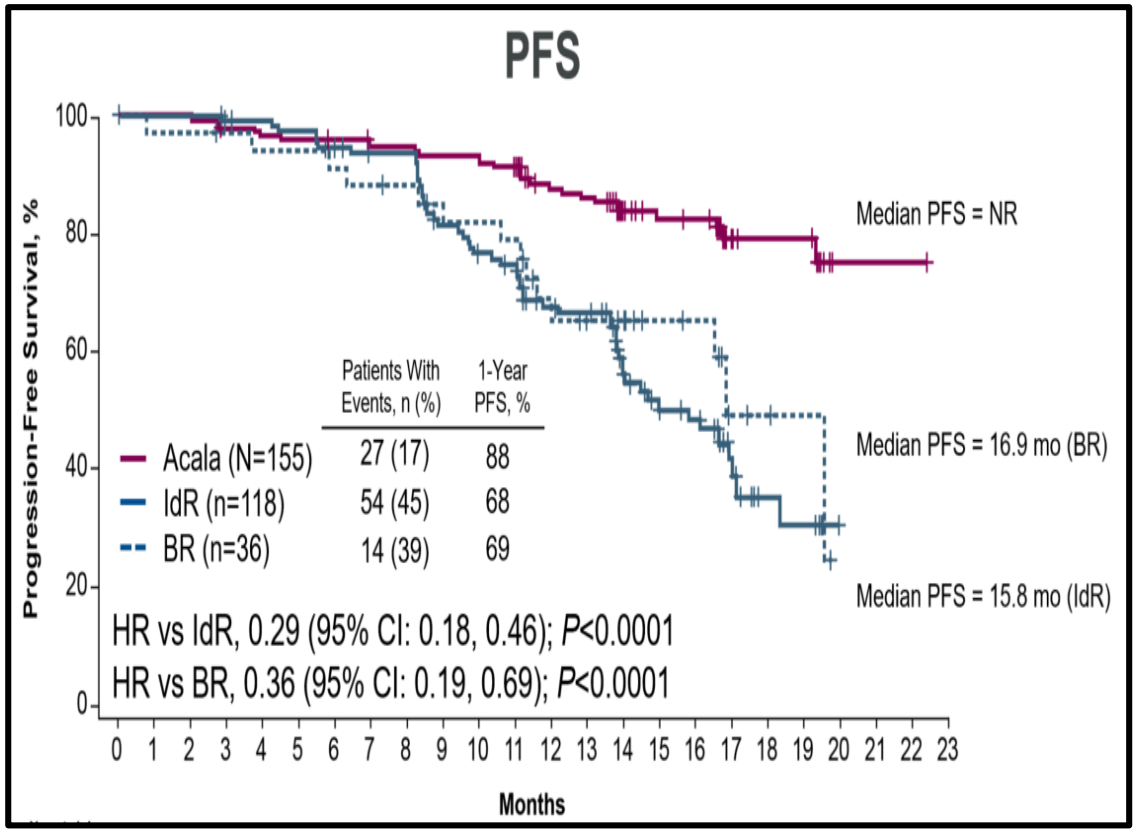
Byrd, NEJM, 2014 ; Byrd, Blood, 2019

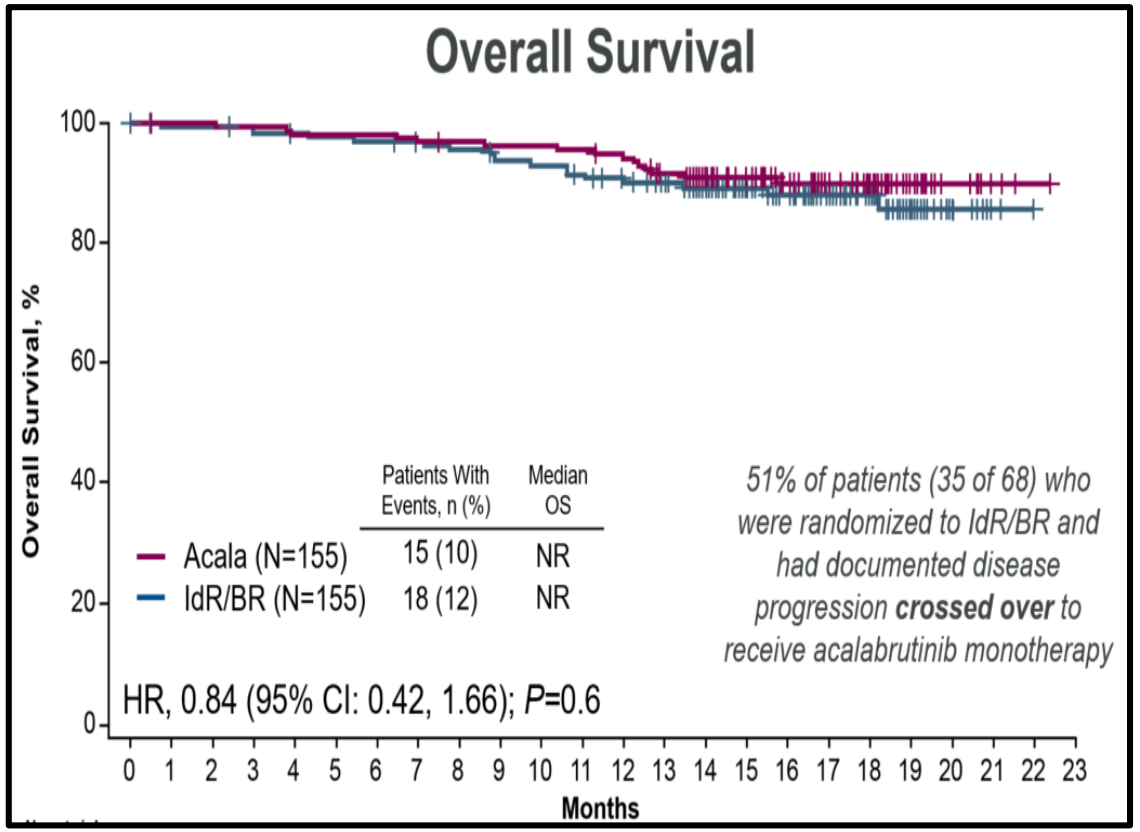
Acalabrutinib vs. Investigator choice for relapsed CLL (ASCEND Study)



Ghia,JCO,2020[54]

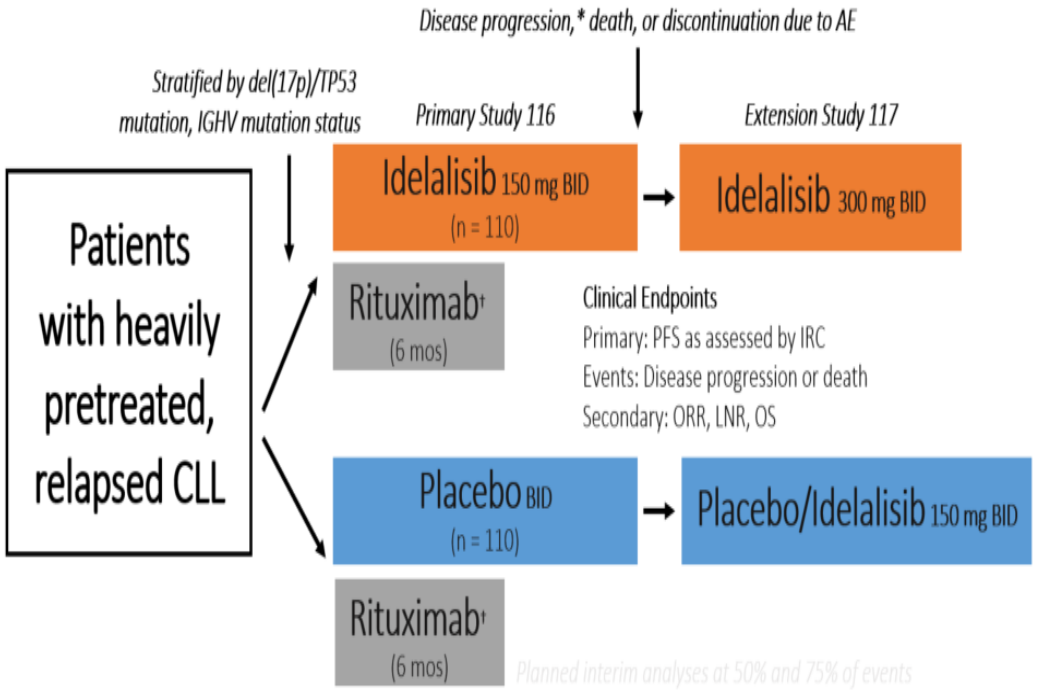
Acalabrutinib vs. Investigator choice for relapsed CLL (ASCEND Study)

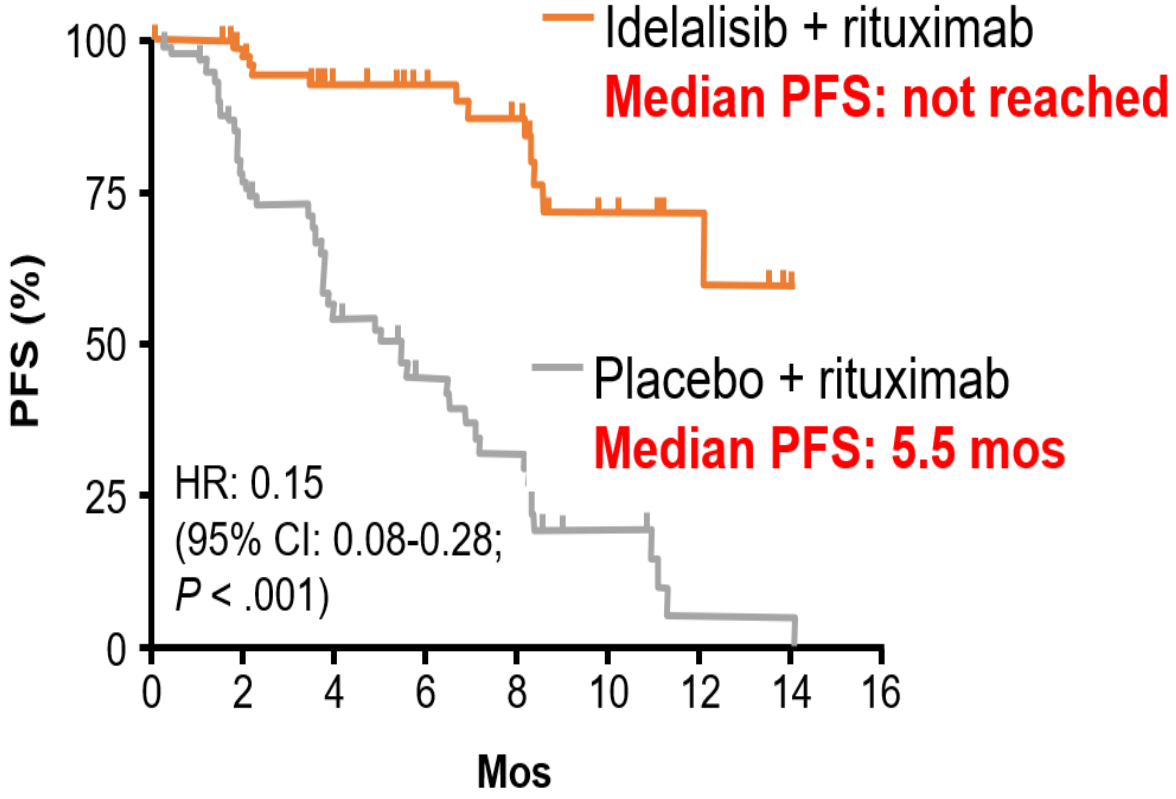




Ghia, JCO, 2020

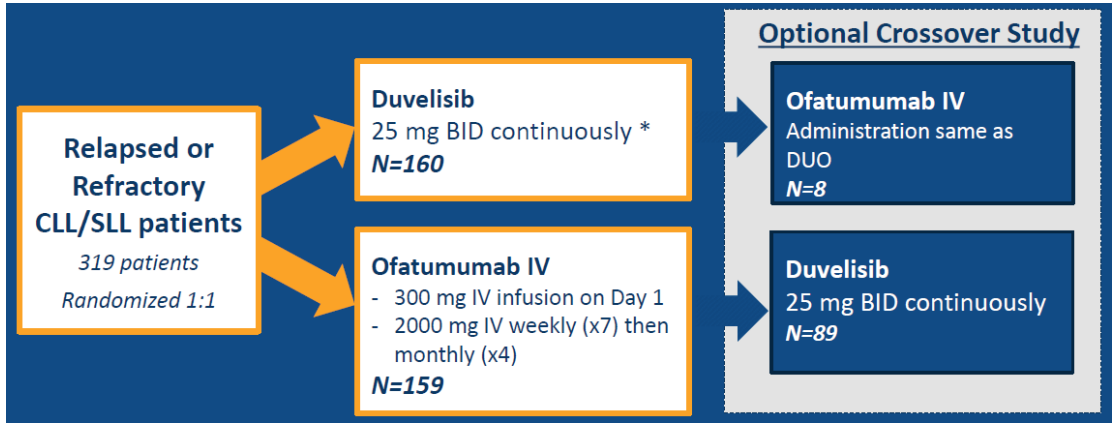
Idelalisib and Rituximab for Previously Treated Patients

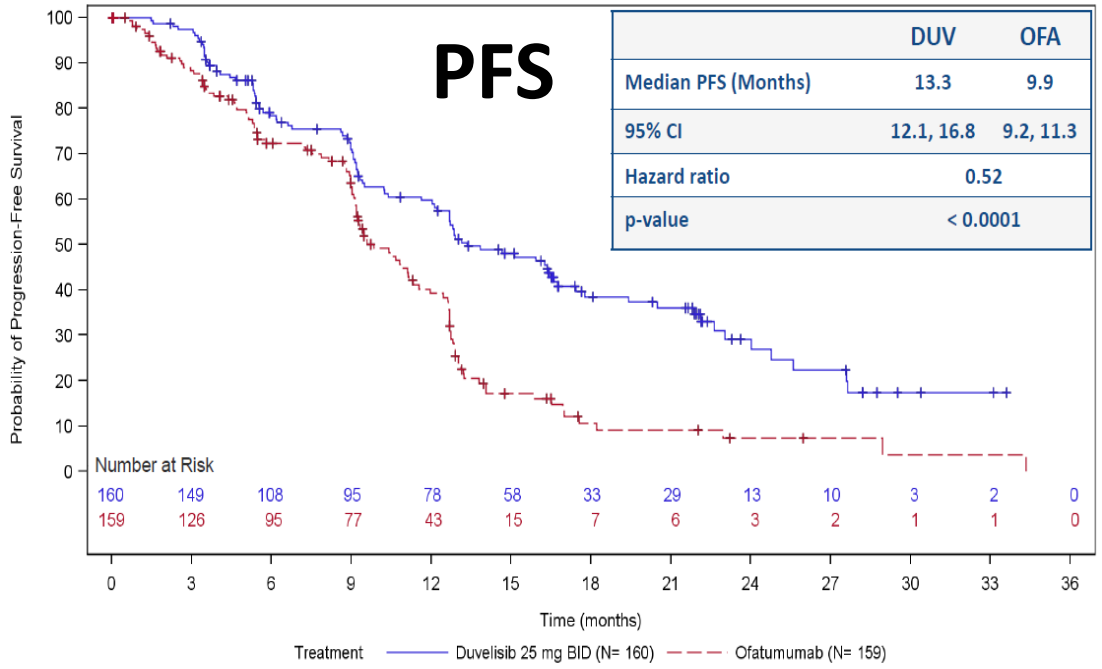


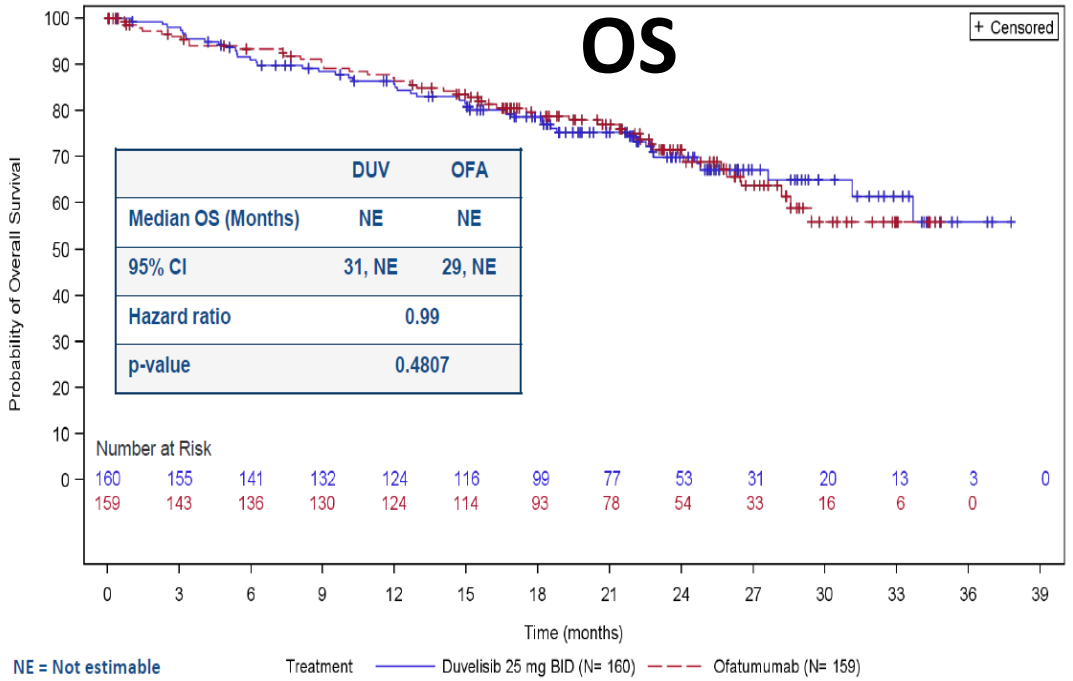


Furman, NEJM,2014

Duvelisib vs Ofatumumab (DUO trial) - Relapsed/Refractory

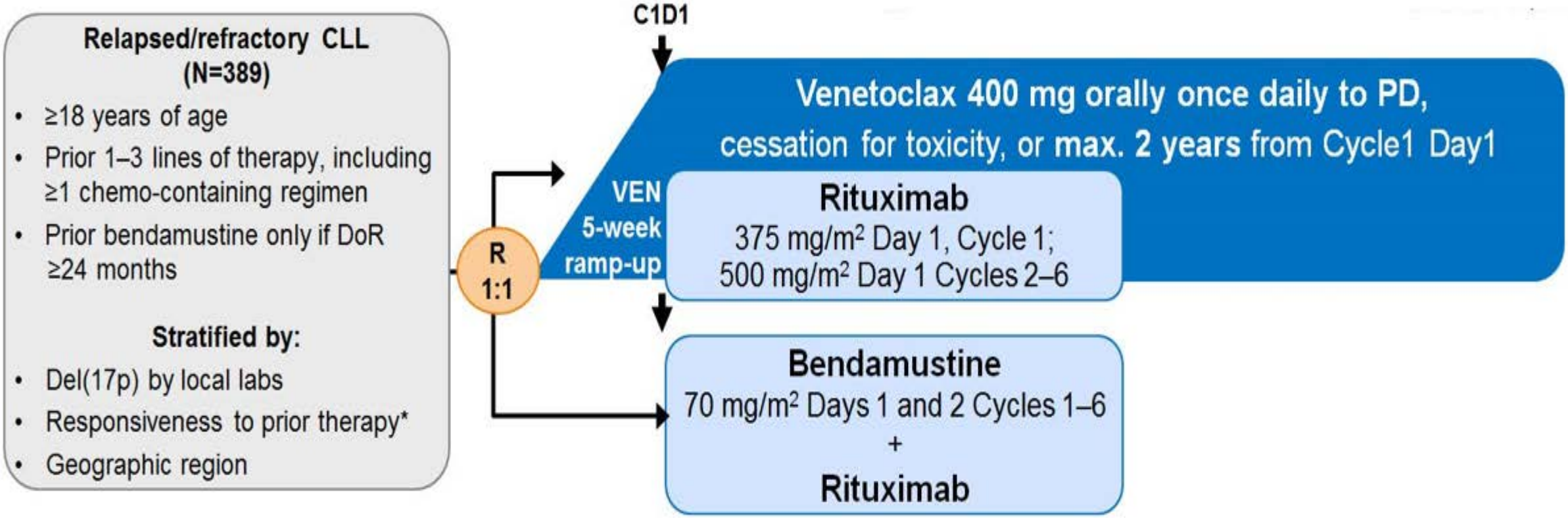






Flinn, Blood, 2018

Ven-R vs. BR in R/R CLL (MURANO Study)

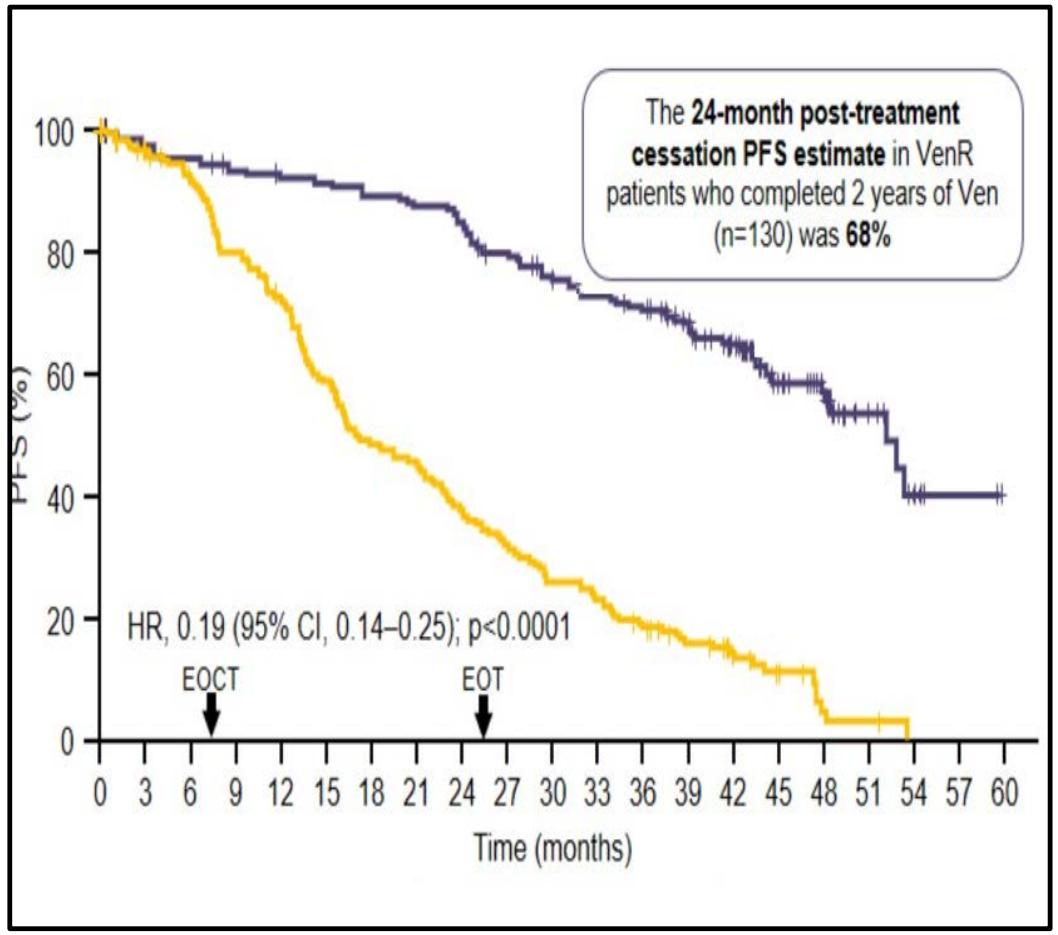


Primary Endpoint	INV-assessed PFS

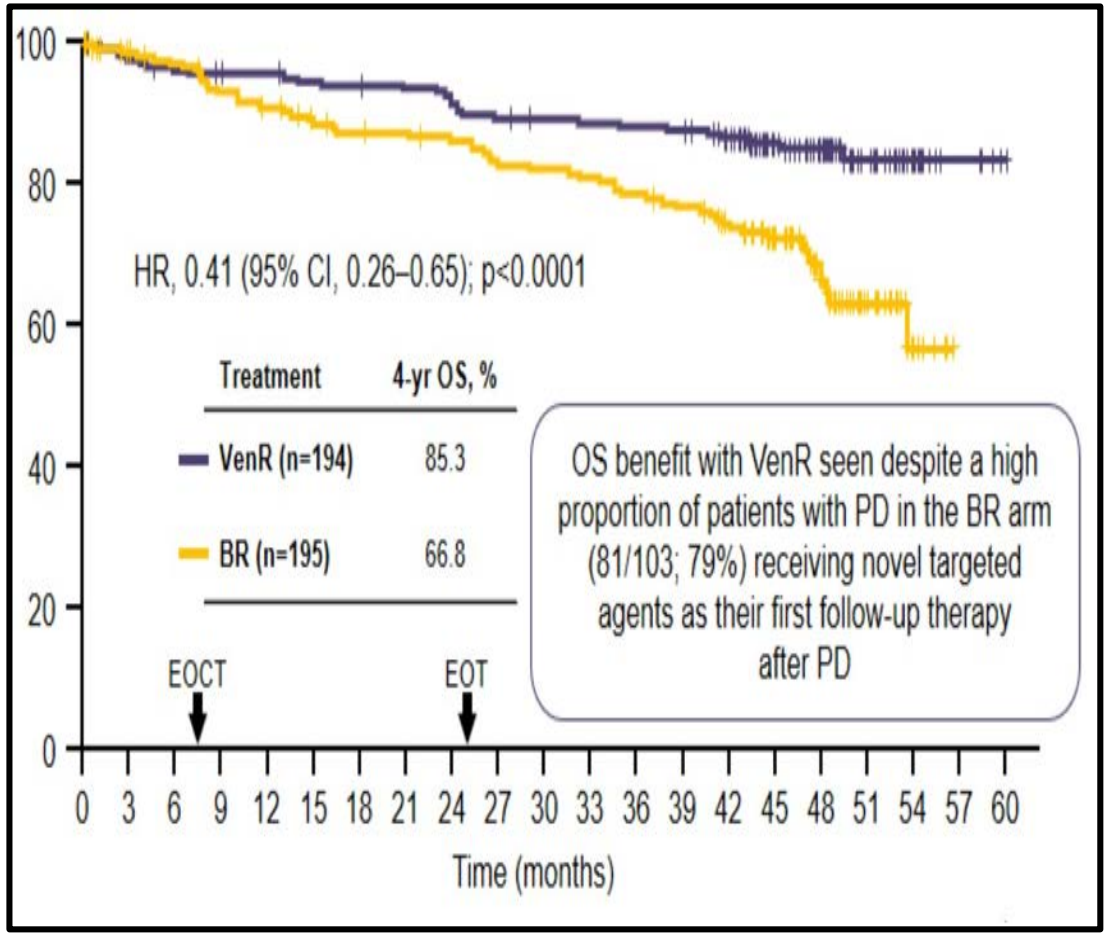
Seymour, NEJM,2018

Ven-R vs. BR in R/R CLL (MURANO Study)

PFS



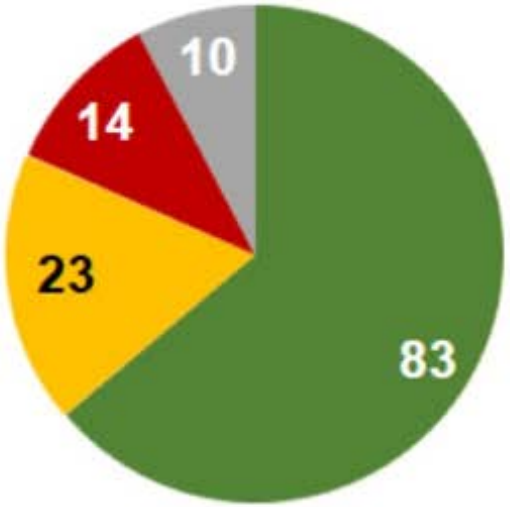
OS

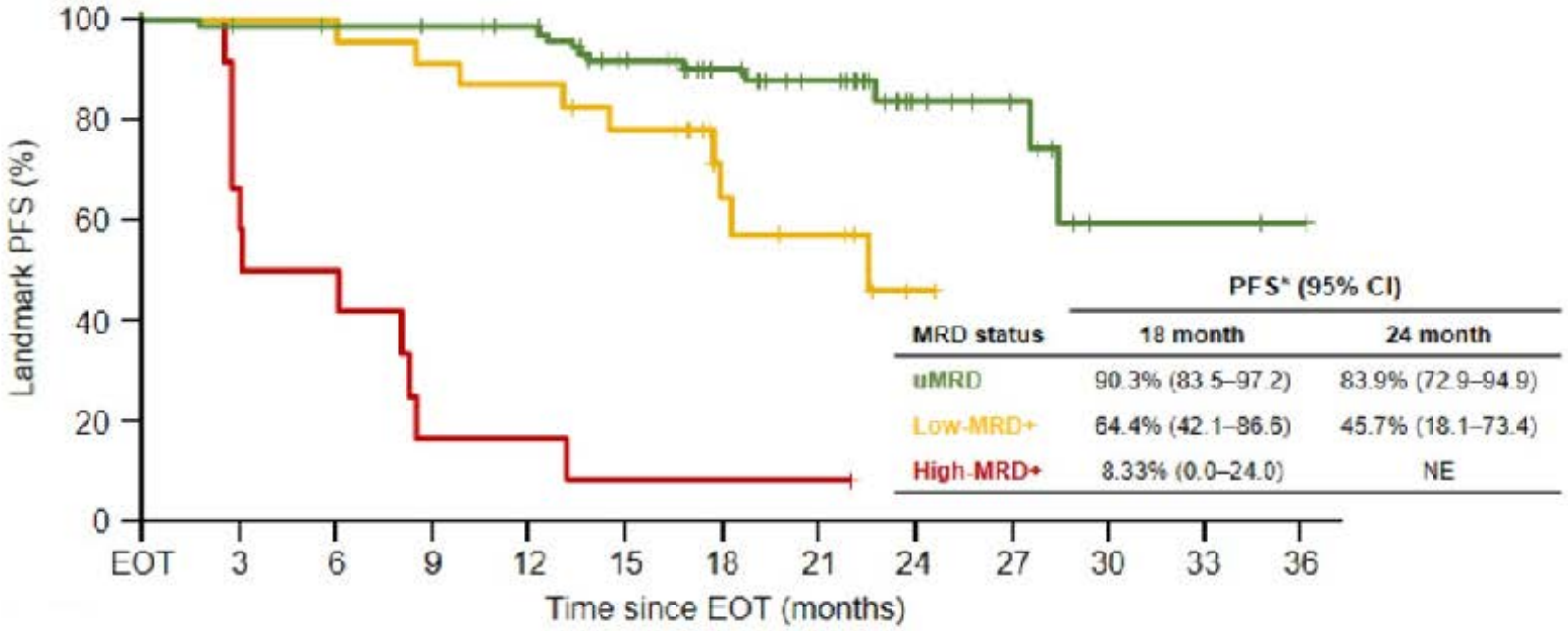


Seymour, ASH,2019

Ven-R outcomes (MRD and PFS)

MRD status at EOT (month 24; n=130)





MRD status	PFS* (95% CI) 18 month	24 month
uMRD	90.3% (83.5–97.2)	83.9% (72.9–94.9)
Low-MRD+	64.4% (42.1–86.6)	45.7% (18.1–73.4)
High-MRD+	8.33% (0.0–24.0)	NE

Status off-therapy, n (%)	uMRD ($<10^{-4}$) n=83	Low-MRD+ (10^{-4}–10^{-2}) n=23	High-MRD+ ($>10^{-2}$) n=14	Unknown n=10
Progression-free	72 (86.7)	14 (60.9)	1 (7.1)	8 (80.0)
PD	11 (13.3)	9 (39.1)	13 (92.9)	2 (20.0)

Seymour, ASH, 2019

Novel Agents for R/R setting

	Acalabrutinib/ Ibrutinib	Venetoclax	Duvelisib/ Idelalisib
Target	BTK	BCL-2	PI3K delta+gamma / delta
Duration	Indefinite	2-years	Indefinite
Addition of Anti CD20 Ab	No major benefit Faster "response"	Recommended	Idelalisib + R Duvelisib monotherapy
Major side effect (concern)	Bleeding (anticoagulation)	TLS (initially)	Colitis (diarrhea) Infections (FDA alert)
Other side effects	• Body pain • Fatigue • Hypertension • A fib	• Neutropenia	• Pneumonitis • Transaminitis (mainly idela) • PJP • CMV
FDA label for CLL	All settings	All settings	Relapsed

Previously Treated CLL Summary

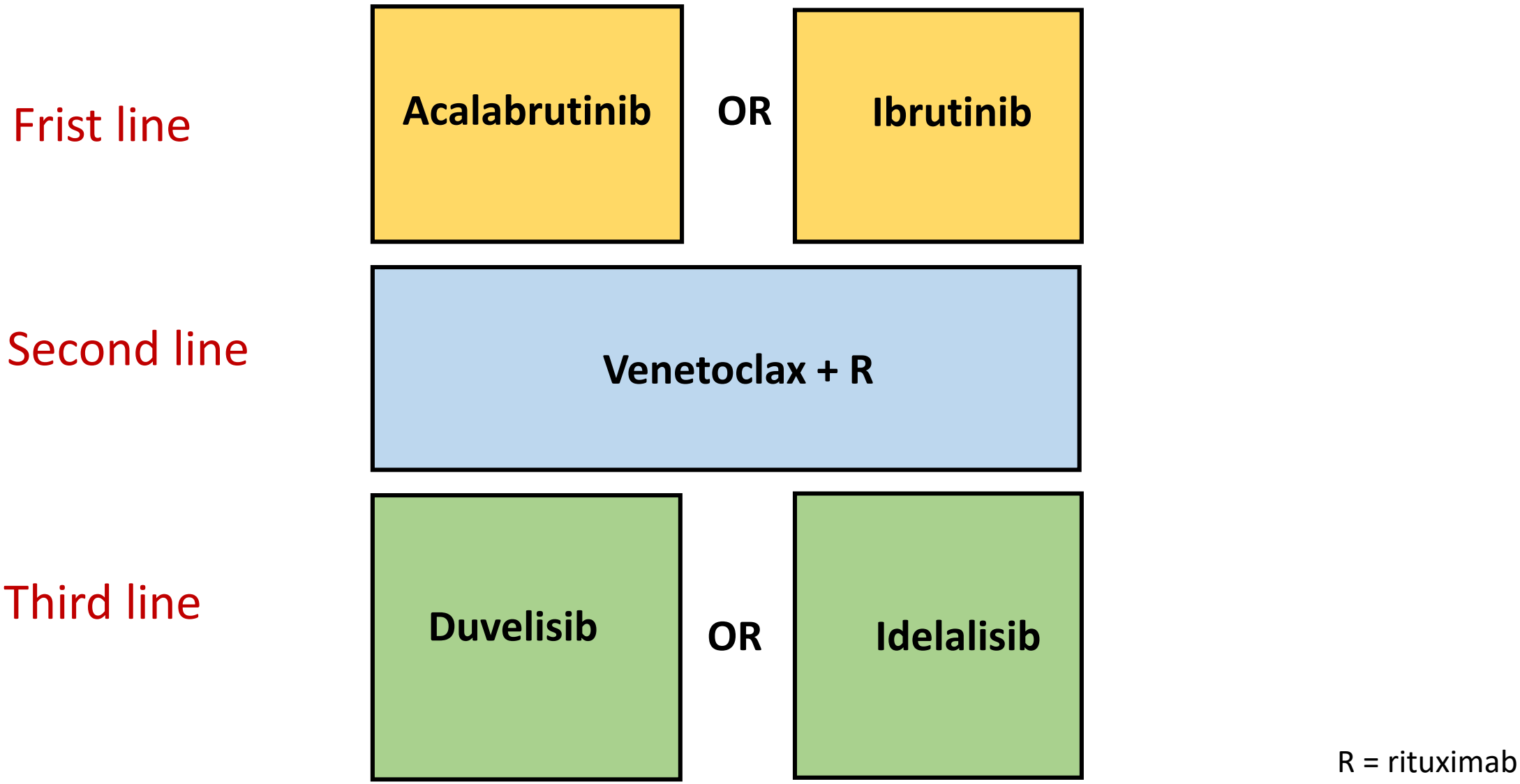
1. **First**
   - **Venetoclax + Rituximab**
     or
   - **Ibrutinib or acalabrutinib**

2. **Second**
   - **Ibrutinib/acalabrutinib if previously treatment with Ven**
   - **Ven-R if previously treated with BTKi (ibrutinib or acalabrutinib)**

3. **Third**
   - **Idelalisib+ rituximab OR duvelisib**

8. Treatment options for patients with del17p/P53 mutation

CLL with del17p or TP53



R = rituximab

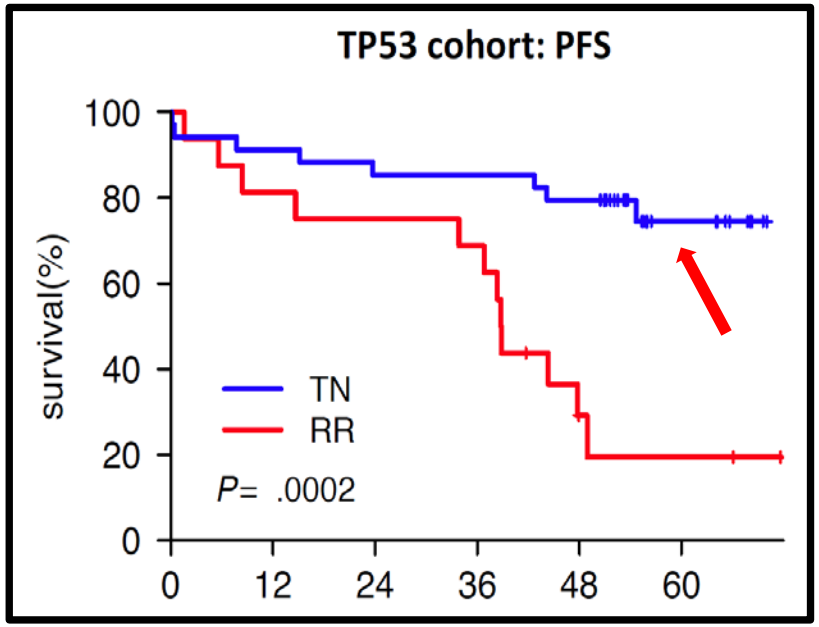
There is no role for chemotherapy in abnormal TP53 (deletion or mutation)

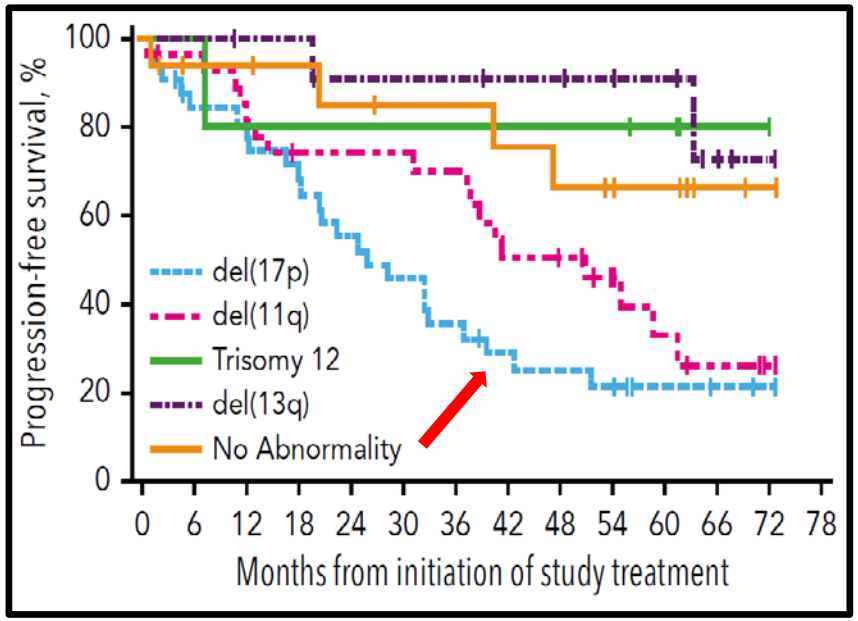
Regimen	PFS
FCR (frontline)	11.3 m
Alemtuzumab (frontline)	11 m
BR (frontline)	7.9 m
HDMP + R	7.5m
BR (relapsed)	7 m
FC (frontline)	6.5 m
FCR (relapsed)	5 m

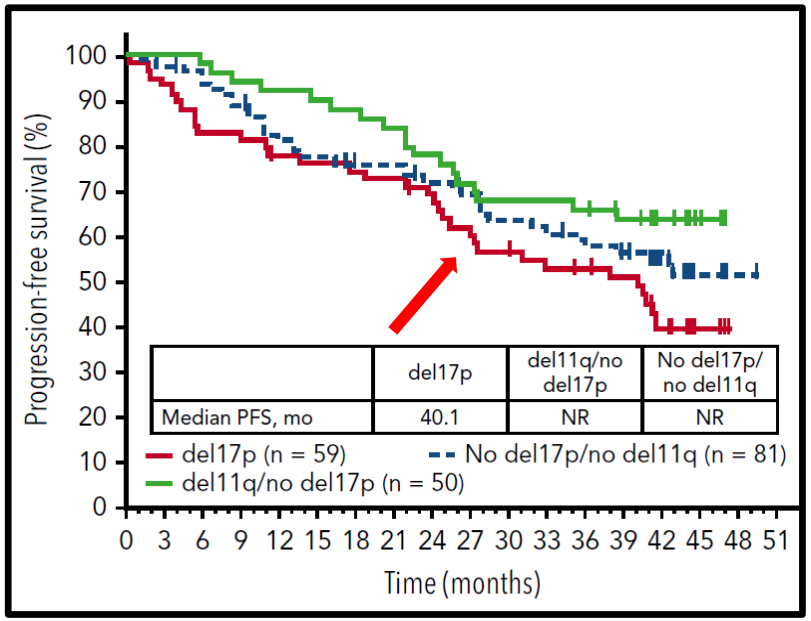
5 – 11 months

Ibrutinib for abnormal TP53

Study	Setting	Outcome
NIH study	TN R/R	5-year PFS 74% 5-year PFS 19%
PCYC-1102/1103 5-year f/u	R/R	median PFS 26 m
RESONATE f/u	R/R	Median PFS 40 m



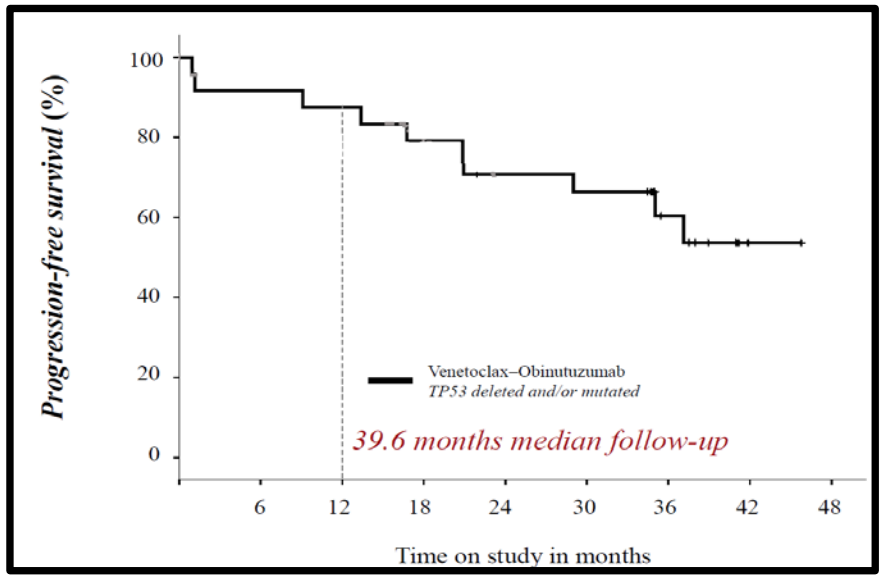


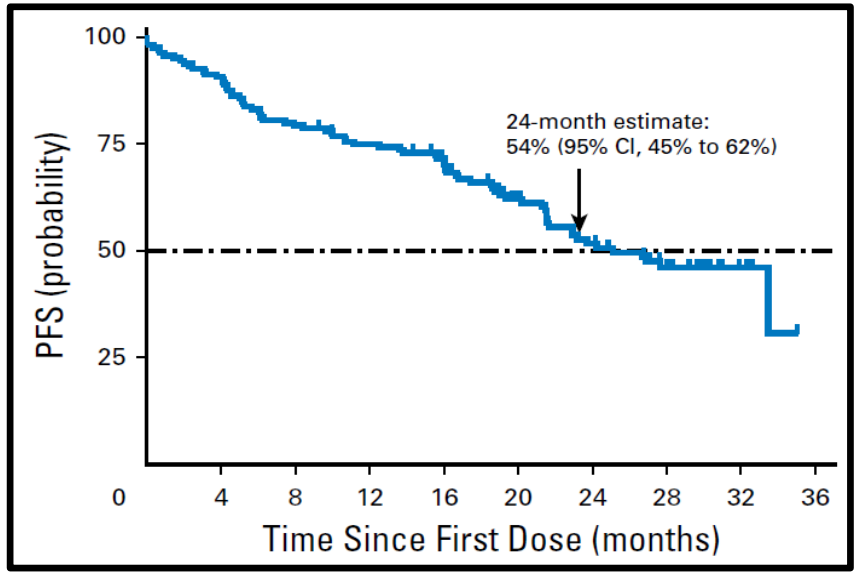


Ahn,Blood,2018 ; O'Brien, Blood, 2018; Byrd, Blood, 2019

Venetoclax for abnormal TP53

Study	Setting	Outcome
CLL14	TN	24 m PFS 74%
M13-982 study	R/R	24 m PFS 54% m PFS 27 m
MURANO	R/R	m PFS 48 m

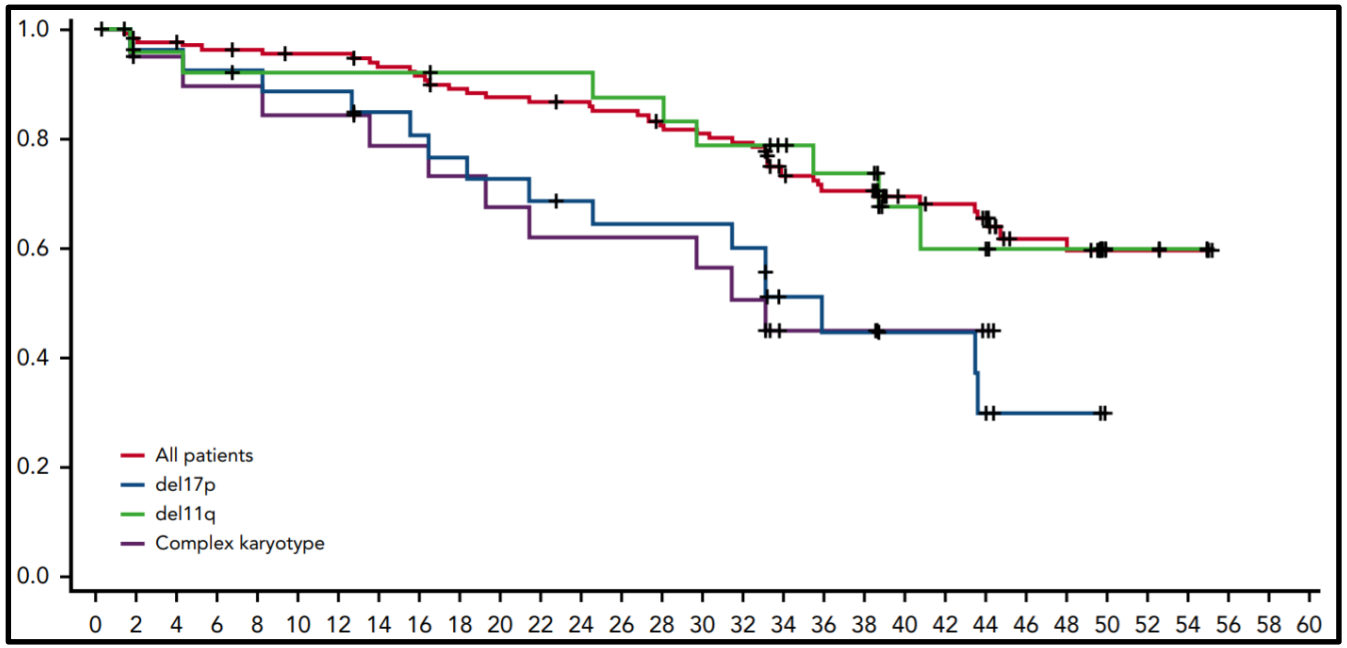




Fischer, ASH, 2019; Stilgenbauer, JCO,2018; Seymour, ASH, 2019

Acalabrutinib for abnormal TP53

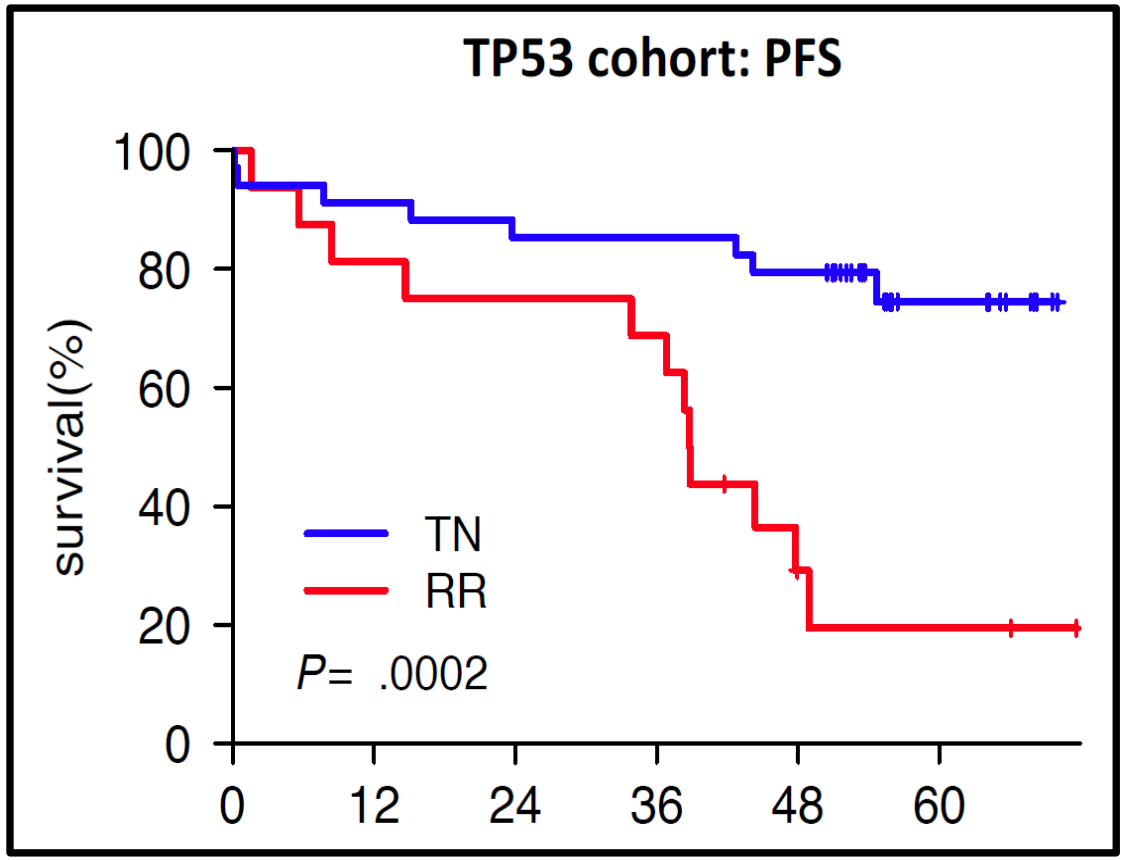
Study	Setting	Outcome
ELEVATE TN	TN	Not reported
ACE-CL-001	R/R	PFS 36m (21 – NR)
ASCEND	R/R	Not reported



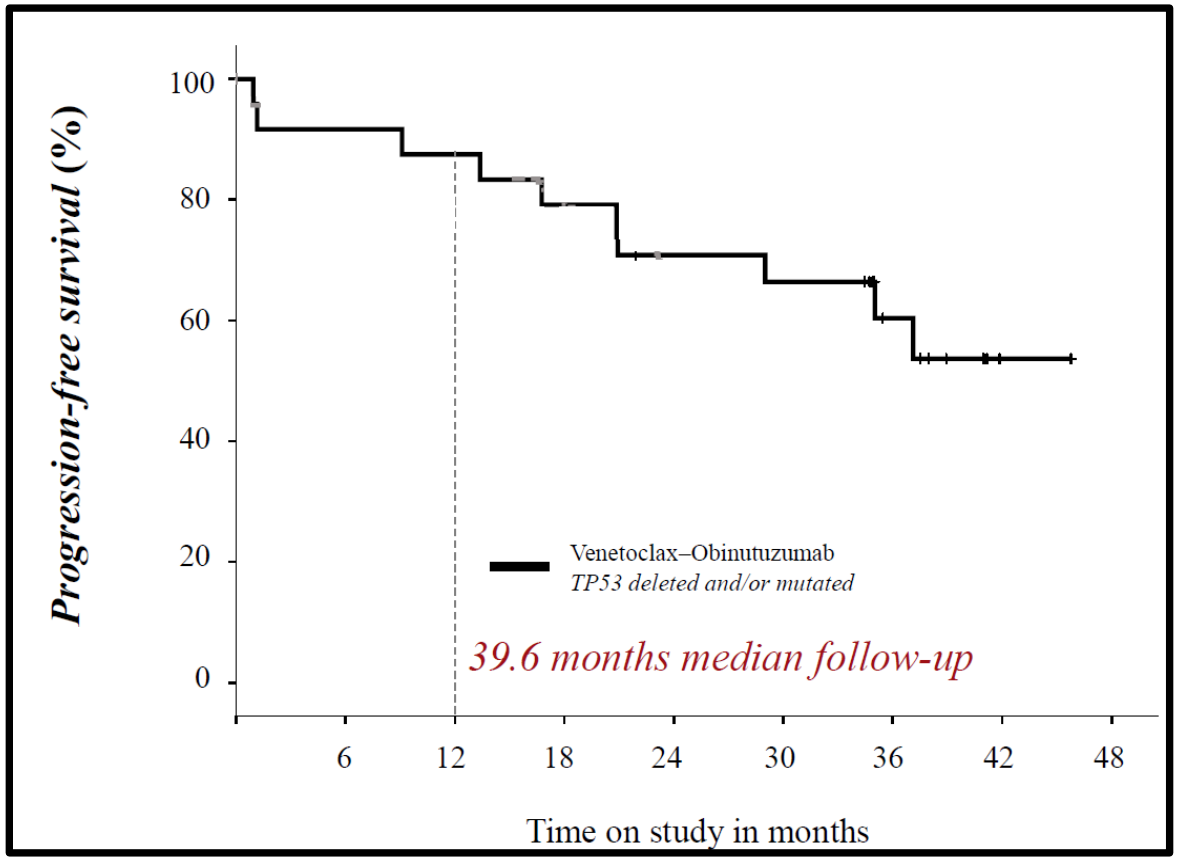
Sharman,ASH, 2019; Byrd, Blood, 2020; Ghia,15-ICML,2019

Ibrutinib vs. Ven-G for first-line treatment in CLL patients with abnormal TP53

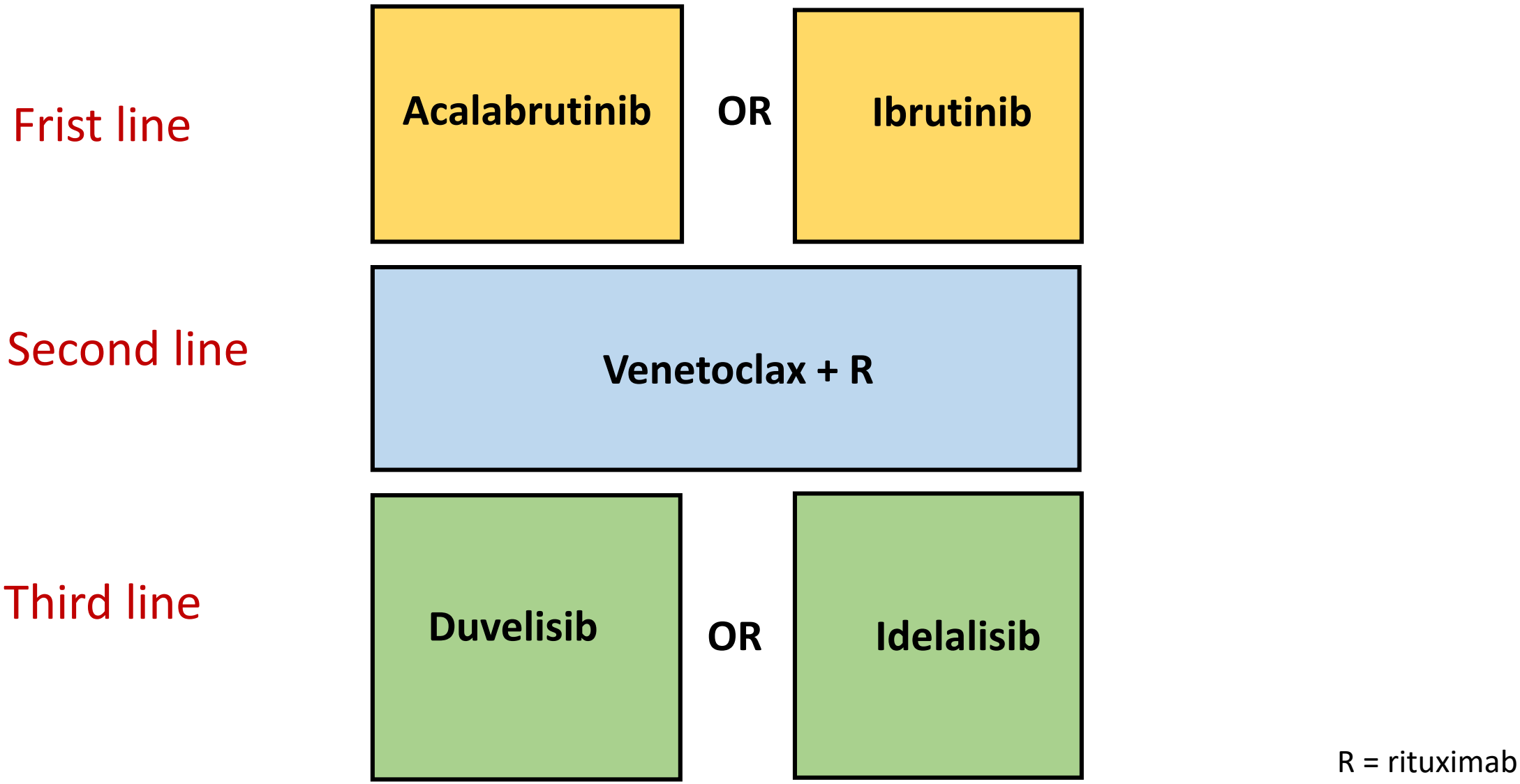
Ibrutinib



Venetoclax



CLL with del17p or TP53

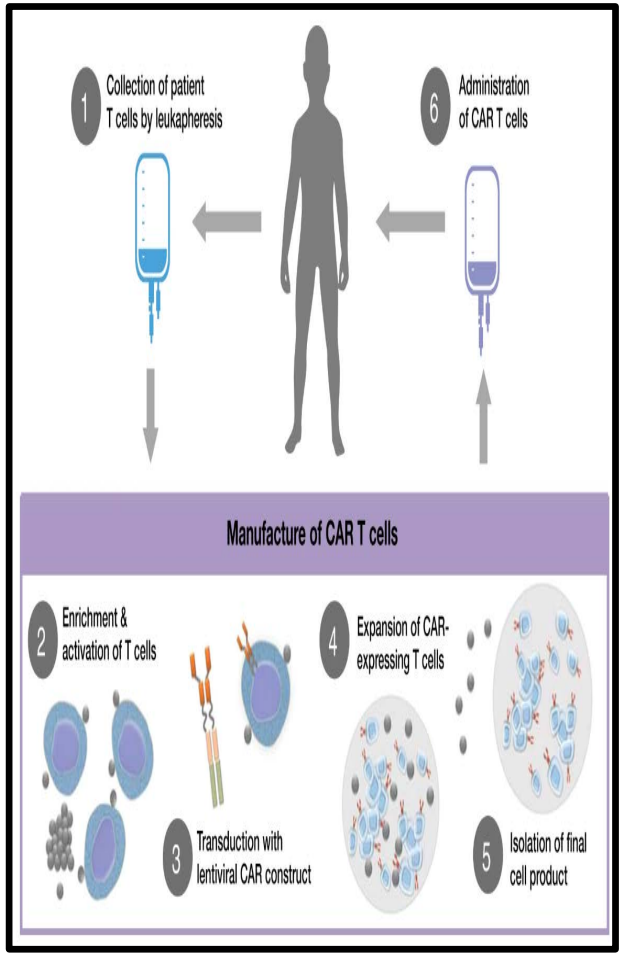


R = rituximab

9. Cellular therapies for CLL

CAR-T for CLL

- Experimental, not FDA approved
- Registration studies are currently ongoing
- Long-term remissions ~ 30-35%
- Best predictor od response: MRD neg after treatment
- Recommend before alloSCT, if available



Allogeneic SCT for High Risk CLL

- Reduced intensity/ Nonmyeloablative allogeneic transplant

Author	Shadman	Kramer	Sorror	Dreger	Brown	Khouri	Khouri	Michallet
Year	**2019**	**2017**	**2008**	**2013**	**2013**	**2011**	**2017**	**2013**
N	55	90	82	90	76	86	26	40
Conditioning	Flu-TBI-R	variable	Flu-TBI	FC± ATG	Flu-Bu	FCR	BFR	FCR
Follow-up (yr)	3	10	5	6	5	5	3	3
OS	**54**	**51**	**50**	**58**	**63**	**51**	**82**	**55**
PFS	**45**	**34**	**39**	**38**	**43**	**36**	**63**	**46**
NRM	**38 (<12)***	**20**	**23**	**23**	**16**	**17**	**8**	**27**
aGVHD	20	?	16-23	14	17	7	4	23
Extensive cGVHD	66	?	49-53	55	48	56	45	29

50
40
20-25

*** in pts without comorbidities**

10. Practical points about novel drugs

New Agents: Practical Considerations

- BTKi: ibrutinib and acalabrutinib
- PI3Ki: idelalisib and duvelisib
- Venetoclax

BTKis (ibrutinib/acalabrutinib)

- **Common side effects:**
  - Muscle/bone pain
  - Cytopenia
  - Hypertension
  - Diarrhea (early , reversible)

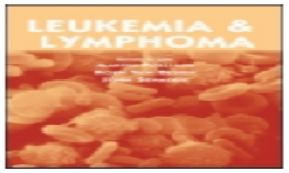
- **Serious side effect:**
  - Bleeding: (peri-procedural management)
  - Atrial fibrillation
  - Opportunistic infections: PJP, aspergillosis (?) (case reports)

- **Second generation BTKi, acalabrutinib has a better toxicity profile**
  - **Acalabrutinib**

PI3Kis (idelalisib/duvelisib)

- Important side effects
  - LFT abnormalities (idelalisib)
  - Pneumonitis
  - CMV reactivation and PJP (FDA alert 2016)

- Colitis/Diarrhea
  - Median time to grade III/IV : 7 months
  - Not responsive to anti-motility agents
  - Corticosteroids ; treat as aGVHD



Management of adverse events associated with idelalisib treatment: expert panel opinion

Steven E. Coutré, Jacqueline C. Barrientos, Jennifer R. Brown, Sven de Vos, Richard R. Furman, Michael J. Keating, Daniel Li, Susan M. O'Brien, John M. Pagel, Martin H. Poleski, Jeff P. Sharman, Nai-Shun Yao & Andrew D. Zelenetz

Don’t use Idelalisib in treatment naïve patients!

Toxicity Frequency

	Phase I	Overall relapsed	Upfront Pts ≥ 65 yo	Upfront younger Pts
Number of patients	54	760	64	24
Median prior treatments	5 (2-14)	≥ 1	0	0
Median age	63 (37-82)	66 (21-91)	71 (65-90)	67 (58-85)
Median time to therapy (months)	15 (0.2-49)	-	22 (0.8 – 46)	8 (0.7-16)
Grade≥ 3 transaminitis	1.9%	14%	23%	52%
Grade ≥3 Colitis/diarrhea	5.6%	14%	42%	13%
Any grade pneumonitis	5.6%	3%	3%	13%
Reference	Brown Blood 2014	Coutre EHA 2015	O’Brein Blood 2015	Lampson ASH 2015

Venetoclax

Figure 1: Dosing Schedule for Ramp-up Dose

Tumor Burden		Prophylaxis		Blood Chemistry Monitoring[c]
		Hydration[a]	Anti-hyperuricemics	Setting and Frequency of Assessments
Low	All LN <5 cm AND ALC <25 × 10^9/L	Oral (1.5-2 L)	Allopurinol[b]	**Outpatient** • Pre-dose, 6-8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp up doses
Medium	Any LN 5 cm to <10 cm OR ALC ≥25 × 10^9/L	Oral (1.5-2 L) and consider additional intravenous	Allopurinol	**Outpatient** • Pre-dose, 6-8 hours, 24 hours at first dose of 20 mg and 50 mg • Pre-dose at subsequent ramp up doses • Consider hospitalization for patients with CrCl <80 mL/min at first dose of 20 mg and 50 mg; see below for monitoring in hospital
High	Any LN ≥10 cm OR ALC ≥25 × 10^9/L AND any LN ≥5 cm	Oral (1.5-2 L) and intravenous (150-200 mL/hr as tolerated)	Allopurinol;consider rasburicase ifbaseline uric acid is elevated	**In hospital at first dose of 20 mg and 50 mg** • Pre-dose, 4, 8,12 and 24 hours **Outpatient at subsequent ramp-up doses** • Pre-dose, 6-8 hours, 24 hours

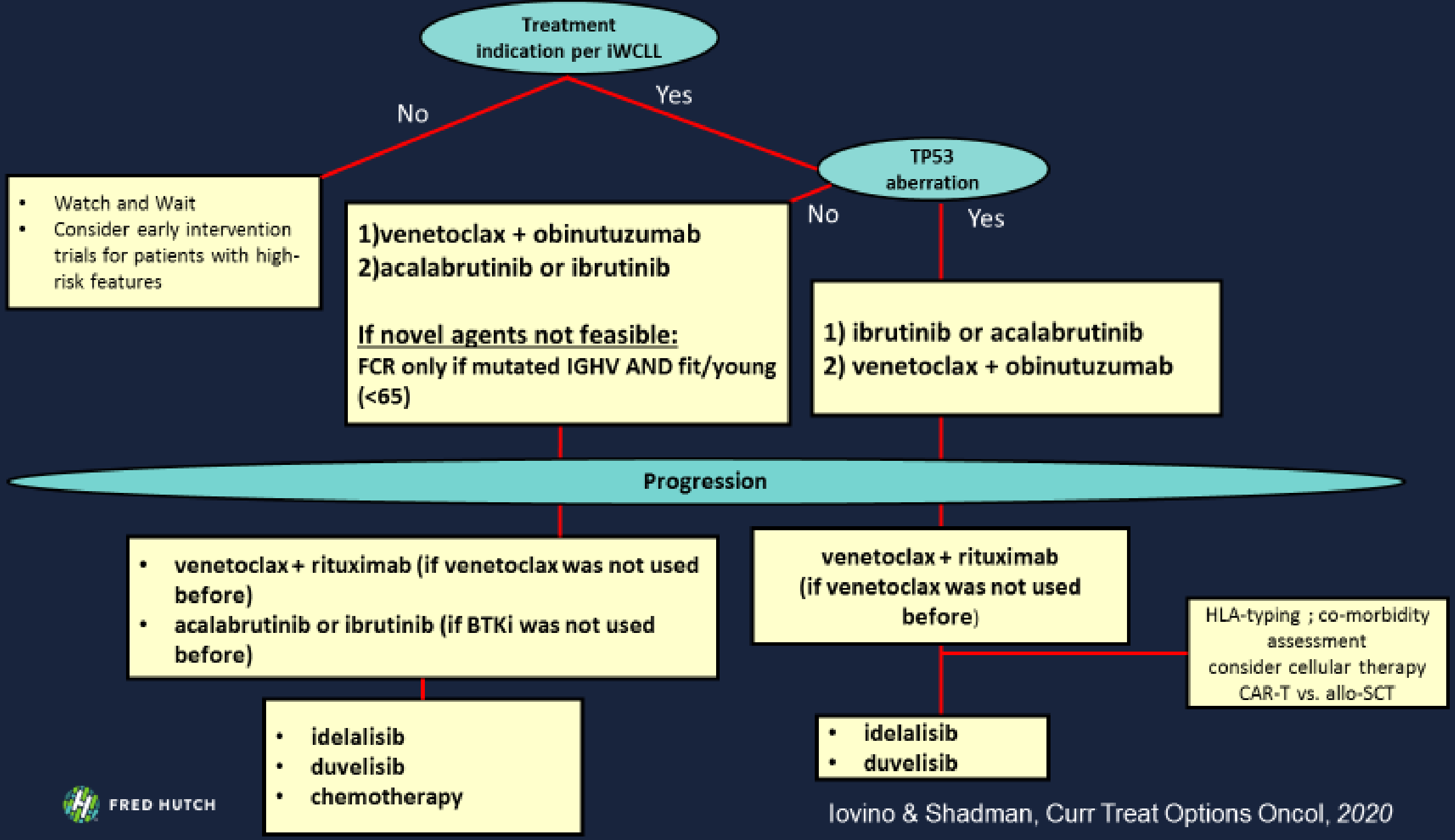
- For patients at risk of TLS, monitor blood chemistries at 6-8 hours and at 24 hours after each subsequent ramp-up dose

Venetoclax

- Consider debulking strategies
- Follow the standard ramp-up schedule
- Coordinate with the inpatient team
- Selected patients can be treated using the “escalated inpatient ramp-up” *
- Follow ALL TLS labs (not just uric acid!)

- Will take some effort to start

* Jones. Lancel Onc, 2017


Treatment indication per iWCLL
No
Yes
Watch and Wait
Consider early intervention trials for patients with high-risk features
TP53 aberration
No
Yes
1)venetoclax + obinutuzumab
2)acalabrutinib or ibrutinib
If novel agents not feasible:
FCR only if mutated IGHV AND fit/young (<65)
1) ibrutinib or acalabrutinib
2) venetoclax + obinutuzumab
Progression
venetoclax + rituximab (if venetoclax was not used before)
acalabrutinib or ibrutinib (if BTKi was not used before)
idelalisib
duvelisib
chemotherapy
venetoclax + rituximab (if venetoclax was not used before)
HLA-typing ; co-morbidity assessment
consider cellular therapy
CAR-T vs. allo-SCT
idelalisib
duvelisib
FRED HUTCH
Iovino & Shadman, Curr Treat Options Oncol, 2020

CLL (Night before the test)

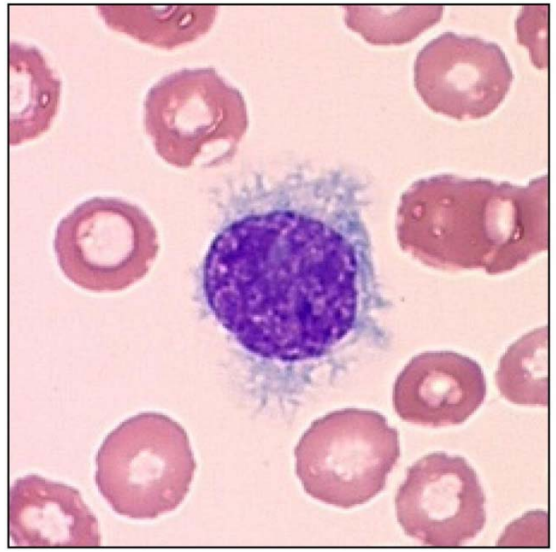
1. Flow cytometry is critical (and adequate) to make the diagnosis
2. Remember CLL immunophenotype (and differences with MCL and other lymphomas)
3. Review Indications for treatment. This hasn't change even with new agents.
4. Check FISH before each line of treatment (r/o del 17p/P53 mutation)
5. Frontline (no del17p or P53mutation): Ven-G or BTKi (acalabrutinib is better tolerated). FCR reasonable for: fit,<65 and mutated IGHV.
6. Relapsed setting: Ven-R or BTKi (acalabrutinib better tolerated), idelalisib/duvelisib.
7. For del 17p patients: BTKi (more data with ibrutinib), Ven-R, cellular therapy, idelalisib/duvelisib.
8. BTKi: initial lymphocytosis (is OK), bleeding, Afib, HTN, body pain (acalabrutinib is better tolerated)
9. Idelalisib/duvelisib: lymphocytosis (is OK), colitis, pneumonitis, hepatitis (more with idela), PJP, CMV – Don't use in frontline setting
10. Venetoclax: watch for TLS at the beginning. Ramp-up HAS to be done!

Hairy Cell Leukemia

- Uncommon chronic B cell lymphoid neoplasm

- Small mature B cell lymphoid cells with abundant cytoplasm and "hairy" projections within the peripheral blood, bone marrow, and splenic red pulp

- Splenomegaly and cytopenias



Hairy cell Leukemia
(Diagnosis)

	CD11c	CD25	CD103	CD123	CD10	CD21	CD23	CD5	CD20	CD19	CD22	Annexin A1
HCL	+	+	+	+	-	-	-	-	+	+	+	+

BRAF V600E mutation is a disease-defining event

HCL variant:

CD25 (-) , CD123 (-), annexin A1 (-) and BRAF V600E (-)

Hairy cell Leukemia

- **Clinical presentation**
  - Splenomegaly
  - Cytopenias (infections, bleeding)
  - Constitutional symptoms

- **Treatment Indications:**
  - Systemic symptoms
  - Splenic discomfort
  - Recurrent infections
  - Cytopenias (Hb <11, ANC < 1000, bleeding due to plt <100,000)

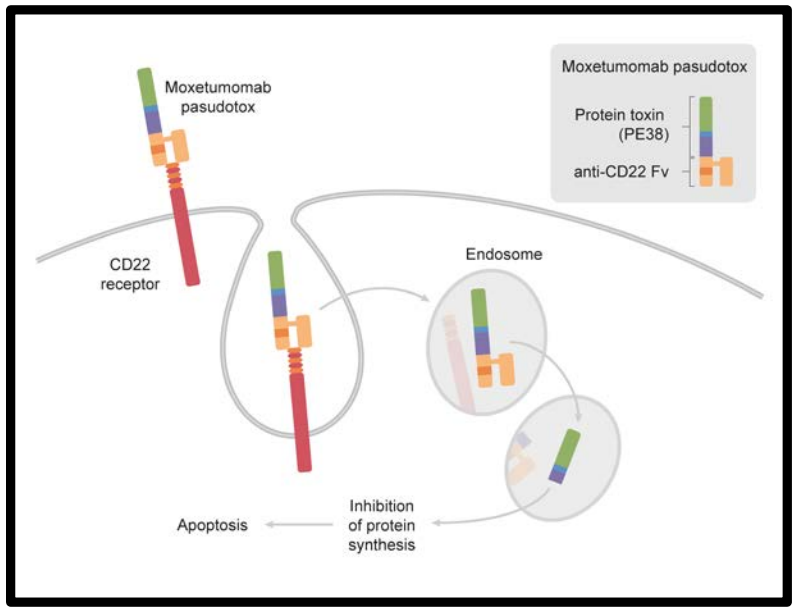
Hairy Cell Leukemia

Treatment

- **First Line**
  - Purine analogs
    - **Cladrabine (2-CdA)** – Up to 80% CR with a CR duration of 57 months (7 – 246) after a single cycle
    - **Pentostatin**
- **Refractory (failure in less than a year) or Relapsed disease**
  - Purine analogs ± Rituximab
  - INF-alfa
  - Rituximab
  - **BRAF targeting agents (Vemurafenib)**
  - **Moxetumomab Pasudotox** (anti CD22 immunotoxin conjugate)

Moxetumomab Pasudotox for R/R HCL

- Anti CD22 immunotoxin conjugate
- IV ; D1,3,5 of 28D cycle (up to 6 cycles)
- At least 2 prior systemic therapies, including a purine analog
- **Efficacy:**
  - ORR: 75%
  - durable CR: 30%
  - MRD eradication 34% of all CRs
- **Unique side effects**
  1. Hemolytic-uremic syndrome
  2. Capillary leak syndrome
  - supportive care and discontinuation were effective
  - could occur at any cycle



Please Consider Clinical Trials!

mshadman@fredhutch.org

FRED HUTCH

Medicine
UNIVERSITY of WASHINGTON

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

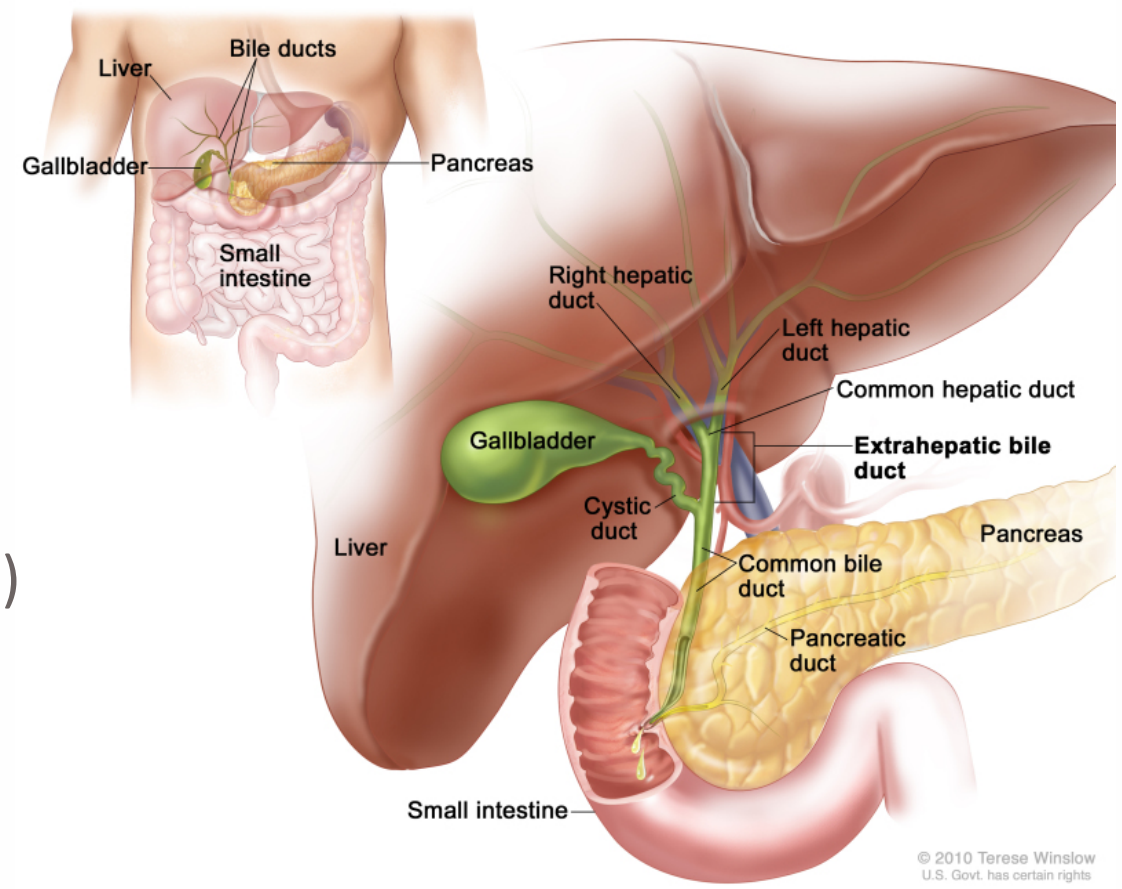
2020 Comprehensive Oncology Review
Biliary Tract Cancers

David B. Zhen, MD
Assistant Professor, Medical Oncology
University of Washington
Fred Hutchinson Cancer Research Center
Seattle Cancer Care Alliance

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

Biliary Tract Cancer: Classification

- **Cholangiocarcinoma**
  - Intrahepatic
  - Extrahepatic
    - Perihilar (Klatskin Tumor)
    - Distal
    - (Some include ampullary cancers)
- **Gallbladder cancer**



Biliary Tract Cancer: Statistics

- Relatively rare in United States (1-2 cases/100,000 population)
- Precise incidence/prevalence confounded by varying classifications in databases
- ~10,000-12,000 incident cases/year
  - ~9,000 extrahepatic/gallbladder
  - ~3,000 intrahepatic cholangiocarcinoma
- Changing Incidence Trends:
  - **Increase** of intrahepatic cholangiocarcinoma
  - **Decrease** of incidence of extrahepatic/gallbladder cancer
- Incidence increases with age (average 50-70 years)

Siegel RL, et al. *CA Cancer J Clin*. 2020.
Jepsen P, et al. *J Natl Cancer Inst*. 2007.
West J, et al. *Br J Cancer*. 2006.
Welzel TM, et al. *J Natl Cancer Inst*. 2006.
Shaib YH, *et al. Hepatol*. 2004.

Biliary Tract Cancer: Risk Factors

Frequently Sporadic; Often no identifiable strong risk factor

Intrahepatic	Extrahepatic	Gallbladder
Male > Female	Male > Female	Female > Male
Cirrhosis	Primary Sclerosing Cholangitis (10-15% lifetime risk)	Gallstones
Hepatitis B	Choledochal cyst (10-15% lifetime risk)	Obesity
Hepatitis C	Liver fluke infection	Hispanic/ Native American
Diabetes Mellitus	Diabetes Mellitus	Diabetes Mellitus
Obesity	Thorotrast exposure	
Alcohol Use		

Biliary Tract Cancers: Clinical Presentation

- **Intrahepatic Cholangiocarcinoma**
  - Often incidentally found on imaging
  - RUQ pain
  - Anorexia
  - Weight loss

- **Extrahepatic/Perihilar/Gallbladder**
  - Biliary obstruction/Cholangitis
  - Abdominal pain
  - Weight loss
  - **1-2% rate incidental gallbladder adenocarcinoma at time of cholecystectomy**

Biliary Tract Cancer: Diagnosis

- **Often misdiagnosed as cancer of unknown primary**
- **Biliary tract cancer is a CLINICAL diagnosis in setting of following:**
  - Dominant liver mass(es) (i.e. intrahepatic) or
  - Perihepatic/peripancreatic/gallbladder mass (i.e. extrahepatic) or
  - CBD biliary obstruction with suspicious/confirmed ERCP brushings (e.g. hilar/Klatzkin's tumor)

    +
  - Pathology suggesting upper GI or pancreaticobiliary primary source

    +
  - Ruled out for other primary GI cancer (i.e. rule out gastroesophageal mass or pancreatic mass)
- **Correct diagnosis is critical to guide treatment options, including new approved targeted agents and eligibility for clinical trials**

Biliary Tract Cancer: Staging

- Different staging systems for intrahepatic vs perihilar vs distal vs gallbladder

- TNM Staging (AJCC 8th edition, 2017)
  - Size and # tumors important for intrahepatic
  - Depth of invasion (in mm) important for extrahepatic
  - # lymph nodes important for all EXCEPT for intrahepatic

Biliary Tract Cancer: Staging Summary (AJCC 8th Ed)

	Intrahepatic	Perihilar	Extrahepatic	Gallbladder
T1	1 tumor w/o vascular invasion and is T1a = ≤5 cm T1b = ≥5 cm	Confined to bile duct	Bile duct wall invasion <5 mm	T1a: Invade lamina propia T1b: Invade muscle layer
T2	One tumor w/ vascular invasion OR Multiple tumors +/- vascular invasion	T2a/b: Invades adipose or liver tissue	Bile duct wall invasion 5-12 mm	T2a/b: Invades perimuscular connective tissue
T3	Any tumor perforating visceral peritoneum	Invades unilateral branches portal v or hepatic aa	Bile duct wall invasion >12 mm	Involvement of serosa or invasion of liver or adjacent organs
T4	Any tumor with direct invasion of local extrahepatic structures	Invades main PV or bilateral branches or CHA	Involves celiac axis, SMA, and/or CHA	Invades portal v, hepatic aa, or two or more extrahepatic organs
N1	Any + regional nodes	1-3	1-3	1-3
N2	N/A	≥4	≥4	≥4

Biliary Tract Cancers: Goals of Therapy

- Curative intent for resectable tumors
- Palliative for unresectable/metastatic disease
- General criteria for unresectable tumors
  - Distant metastatic disease
  - Nodal involvement beyond porta-hepatis
  - Extrahepatic adjacent organ invasion
  - Invasion of main portal vein and main hepatic artery

Surgical Management of Resectable Biliary Tract Cancer

Surgical Management

- Intrahepatic: Hepatic resection +/- portal LN dissection
- Perihilar/Distal: Bile duct resection + cholecystectomy + Whipple
- Gallbladder: Cholecystectomy + hepatic segmental resection (IVB/V), lymphadenectomy, possible bile duct excision

Resectable Perihilar Cholangiocarcinoma: Specific Points

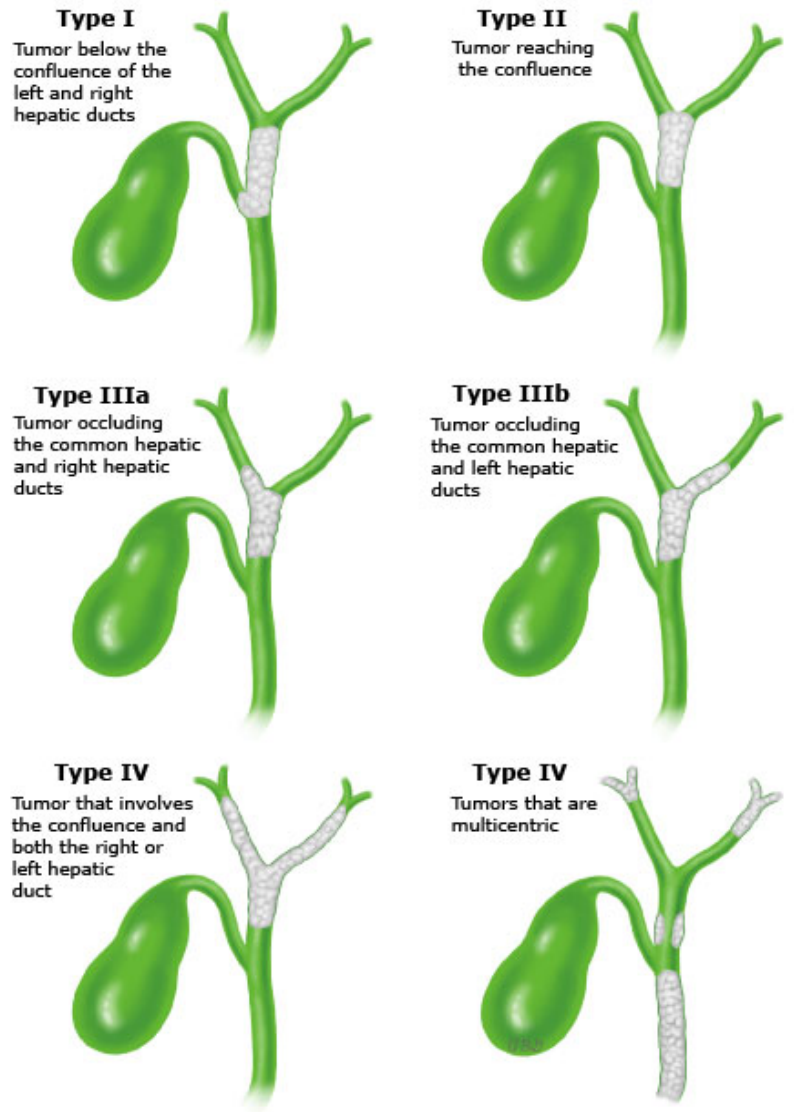
- High recurrence rates due to early involvement of confluence of hepatic ducts

- Neoadjuvant chemoradiation + liver transplantation for select patients:
  - Primary sclerosing cholangitis
  - Solitary tumor with radial diameter < 3 cm
  - No evidence of non-regional/distant disease

- Referral to specialized center/multidisciplinary evaluation important

- AVOID percutaneous biopsy in localized, perihilar disease given risk of seeding

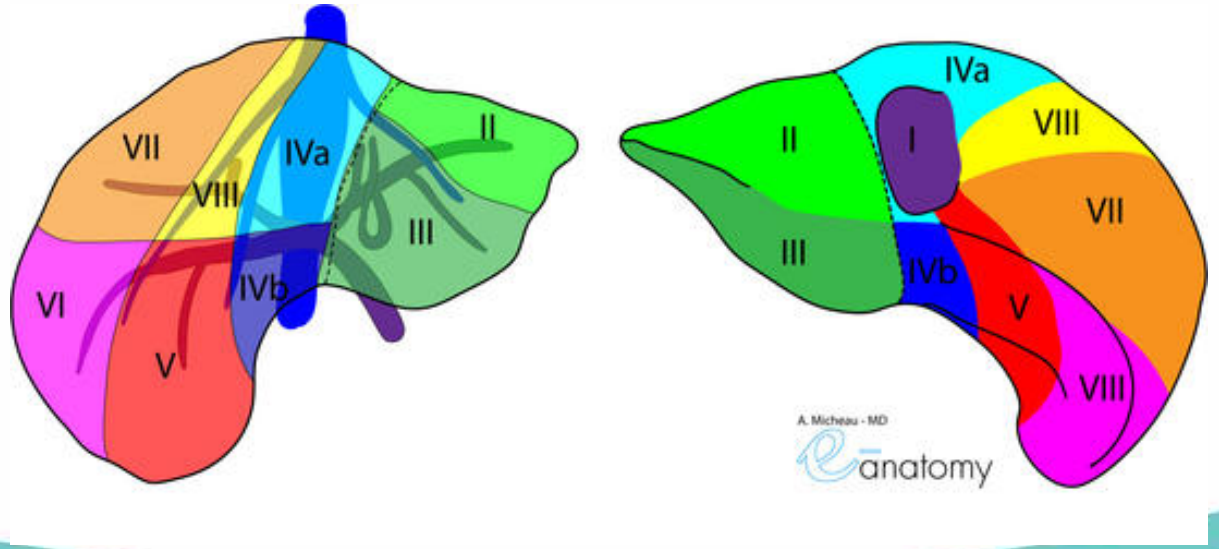
Bismuth-Corlette Classification



UpToDate, 2020

Resectable Gallbladder Cancer: Specific Points

- **Know ≥T1b = muscle invasive disease**
- **Simple cholecystectomy is sufficient for T1a disease** (75-100% long term survival)
- **For ≥T1b, extended resection is needed** (Cholecystectomy + hepatic segmental resection (segments IVB/V), lymphadenectomy, possible bile duct excision (7%-60% long term survival)



Adjuvant Therapy for Biliary Tract Cancer

Outcomes for Resectable Disease: Retrospective Series

Study	n	Tumor location	5-year survival
Nakeeb et al. *Ann Surg*. 1996	294	Intrahepatic, Hilar, and Distal	44% intrahepatic 11% hilar 28% distal
Jang et al. *Ann Surg*. 2005	151	Extrahepatic/Distal	32.5%
Fong et al. *Br J Surg*. 1996	104	Distal	54%
Choi et al. *Ann Surg Onc*. 2009	64	Intrahepatic	39.5%
DeOliveira et al. *Ann Surg*. 2007	564	Intrahepatic, Hilar, and Distal	63% intrahepatic 30% hilar 27% distal
Paik et al. *J Gastroenterol Hepatol*. 2008	97	Intrahepatic	31.1%
Lang et al. *J Am Coll Surg*. 2009	83	Intrahepatic	30% (if R0 resection)
Kosuge et al. *Ann Surg*. 1999	65	Hilar	51.6% (if R0 resection)
Tsao et al. *Ann Surg*. 2000	255 (US and Japan)	Hilar	43% (US) and 25% (Japan)

Adjuvant Therapy: Current NCCN Guidelines

	Gallbladder	Intrahepatic	Perihilar Extrahepatic
R0 N-	- Observe - Chemo (5FU or Gem) - CRT	- Observe - Chemo	- Observe - Chemo - CRT
R1/R2 N+	- CRT - Chemo - CRT/Chemo	- Chemo/CRT - CRT	- Chemo - CRT - CRT/Chemo

Important Points:

- **Adjuvant capecitabine is standard of care per BILCAP study** (Primrose JN et al, Lancet Oncol, 2019)
- **The role of radiation is still unclear**
- **Some small retrospective series suggest survival benefit with chemoradiation, typically in extrahepatic, margin+, or nodal+ disease**

Adjuvant Therapy: Historical Data

Large SEER analysis suggests benefit of adjuvant chemoradiation vs. chemotherapy alone for resected gallbladder cancer

- Recommend incorporating adjuvant chemoradiation in patients with at least T2 or N1 disease.

Meta-analysis conclusions-- based upon limited retrospective data from ~20 trials of biliary tract cancers:

- In patients with + nodes, suggestion of benefit from adjuvant therapy

  Chemotherapy OR chemoradiation: OR .49, p=.004

- In patients with + margins, suggestion of benefit from adjuvant therapy

  Mostly radiation or chemoradiation: OR 0.36, p=.002

- Unclear role of adjuvant radiation alone in node +, margin – patients

Wang SJ et al. JCO 29(35) Dec 2011
Horgan et al. JCO 30(16) April 2012

SWOG S0809: Adjuvant Chemotherapy + Chemoradiation in Extrahepatic Biliary Tract Cancer

- **Phase II trial, single arm trial attempted to establish a standard practice for adjuvant therapy of extrahepatic Cholangiocarcinoma/Gallbladder**
  - 79 evaluable patients
  - **pT2-4 AND either N+ or R1 resection**
  - 4 cycles Gemcitabine/Capecitabine → capecitabine-based chemoradiation 54-59 Gy

	All pts (%, 95% CI)	Extrahepatic	Gallbladder
2-yr OS	65 (53-74)	**68 (54-79)**	**56 (35-73)**
2-yr DFS	54 (40-66)	**54 (39-66)**	**48 (28-66)**
2-yr LR	11 (4-18)	13 (4-22)	8 (0-19)

*Differences in extrahepatic and gallbladder were not statically significant

- **Key results**:
  - Treatment well tolerated
  - 86% completed planned therapy
  - Promising median OS 34 months
  - Applicability of results limited by a Phase II, single arm study and to extrahepatic disease only

Ben-Josef E et al. J Clin Oncol, 2014;33:261-2622

BILCAP STUDY: ADJUVANT CAPECITABINE

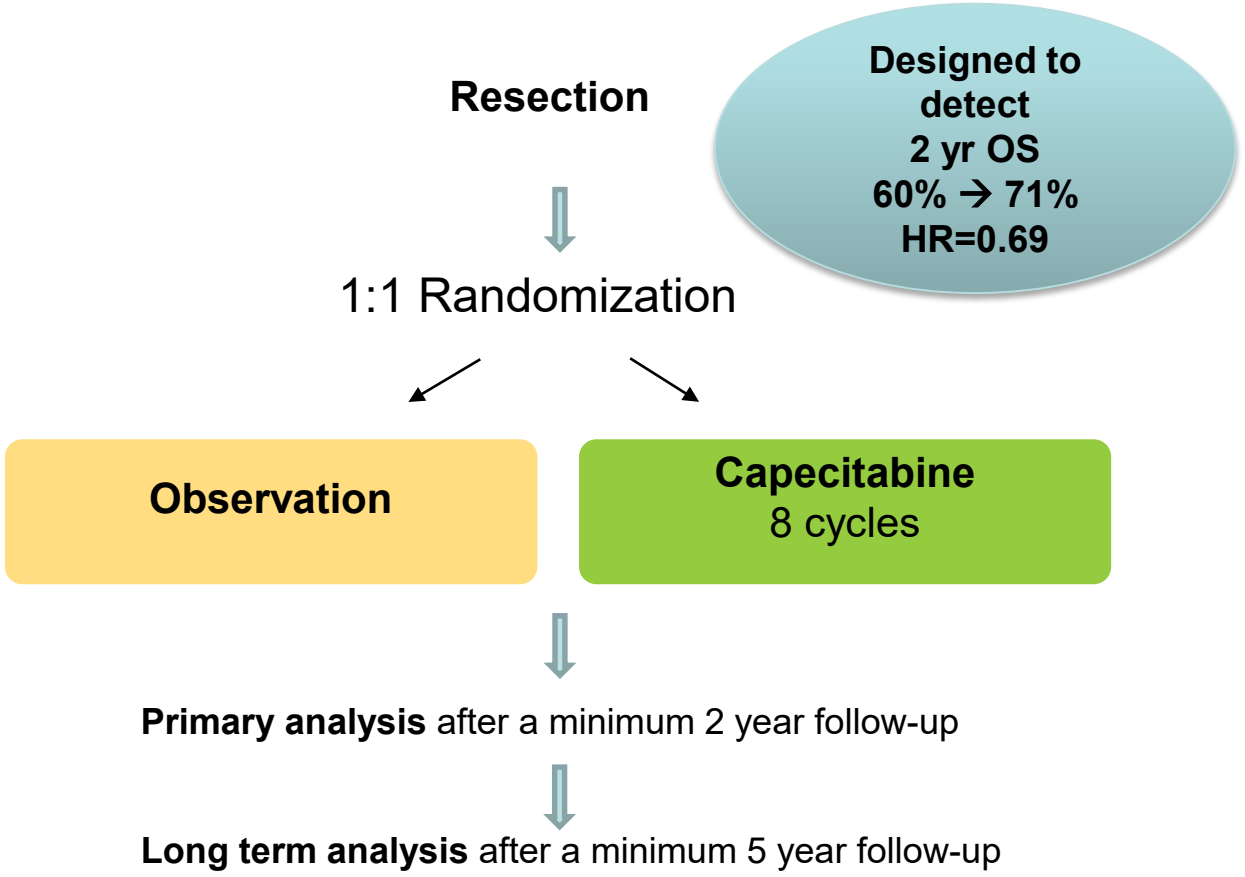
- Phase III randomized, open-label study

Interventions

- Observation vs
- Capecitabine (1250mg/m^2) twice a day on day 1 to 14 of a 3 weekly cycle for 24 weeks (8 cycles)
- Treatment initiated within 16 wks of surgery

Outcome measures

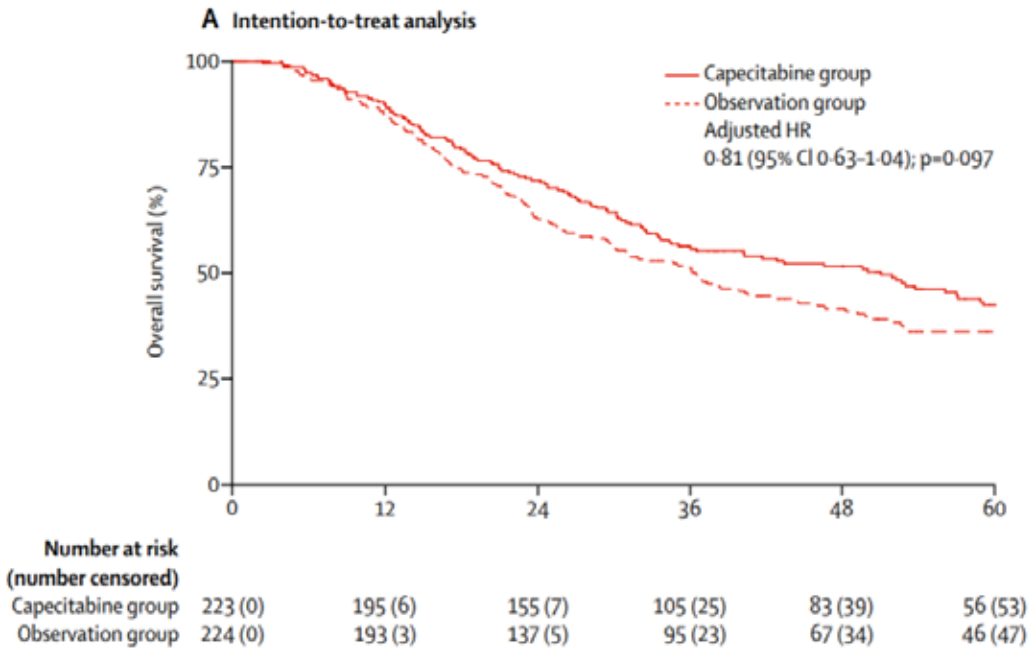
- Primary: Overall survival (OS) by intention-to-treat
- Secondary:
  - Outcome by per-protocol analysis
  - Relapse free survival (RFS)
  - Toxicity, Quality of life, Health economics



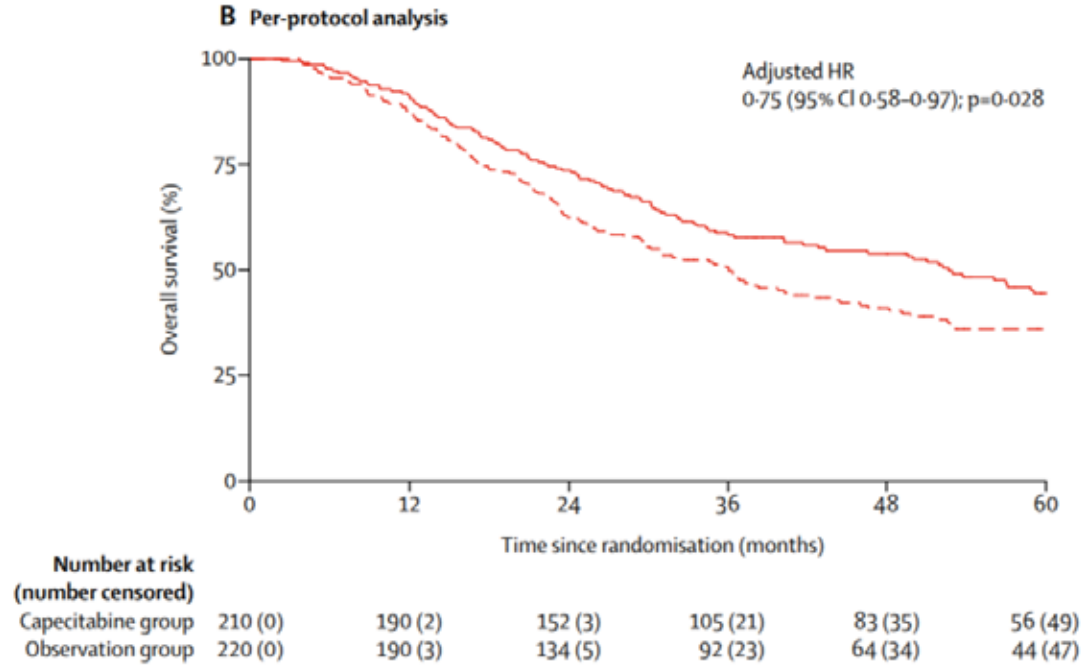
Primrose JN et al. Lancet Oncol 2019; 20: 663-73

BILCAP: Main Results

Intention-to-treat analysis



Per-protocol analysis

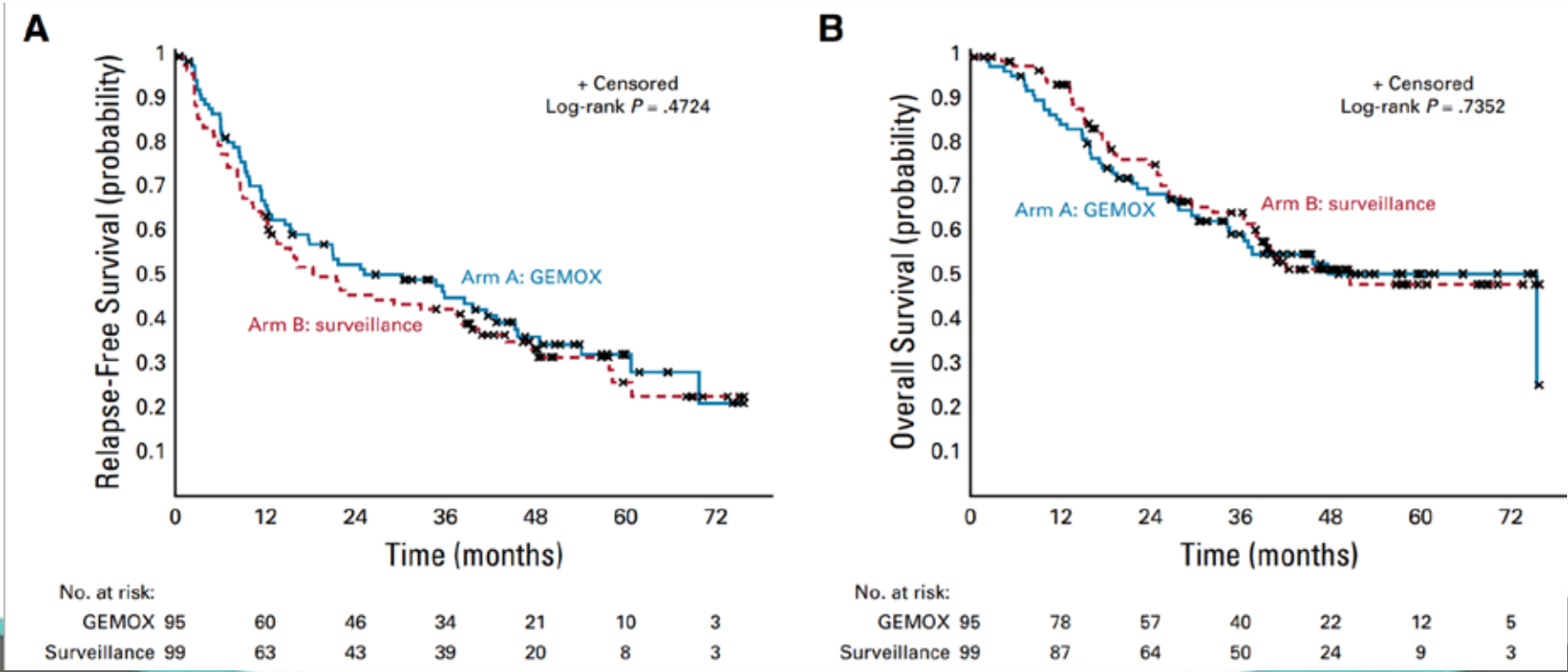


- No OS benefit in ITT analysis, but **OS benefit seen in Per-protocol Analysis**
- Difference of 17 patients ineligible/withdrawal of consent prior to starting treatment
- **Median OS: 53 mo vs 36 months**
- **Median RFS: 25.9 mo vs 17.5 mo (similar for both ITT and per-protocol analysis)**
- **Main Point: Adjuvant capecitabine is standard of care**

Primrose JN et al. Lancet Oncol 2019; 20: 663-73

? Benefit of Combination Adjuvant Chemo w/ GEMOX: Prodige 12/Accord 18/Unicancer GI STUDY

- Ph3 Adjuvant GEMOX x 6 mo vs surveillance
- Primary Endpoint: RFS / Secondary Endpoint: OS
- **Conclusion: No benefit of adjuvant GEMOX**



Edeline J et al. J Clin Oncol 2019; 37: 658-667.

BILCAP vs PRODIGE 12

	BILCAP (ITT Analysis)				PRODIGE 12			
	Cape N=223	Obs N=224	HR (95% CI)	p	GEMOX N=95	Obs N=99	HR (95% CI)	p
Median RFS	24.4 mo	17.5 mo	0.75 (0.58 – 0.98)	0.033	30.4 mo	18.5 mo	0.88 (0.62-1.25)	0.48
Median OS	51.1 mo	36.4 mo	0.81 (0.63-1.04)	0.097	75.8 mo	50.8 mo	1.08 (0.70-1.66)	0.74

- Possible reasons for conflicting outcomes
  - Different primary endpoint (OS in BILCAP vs RFS in PRODIGE 12)
  - Greater statistical power in BILCAP vs PRODIGE
  - Effects on OS benefit with therapy received at time of recurrence
- ACTICCCA-1 Trial Ongoing: Adjuvant Gemcitabine/Cisplatin vs Capecitabine

Primrose JN et al. Lancet Oncol 2019; 20: 663-73.
Edeline J et al. J Clin Oncol 2019; 37: 658-667.

Adjuvant Therapy Conclusions

- Adjuvant capecitabine prolongs survival in all grossly resected biliary tract cancers and is standard of care

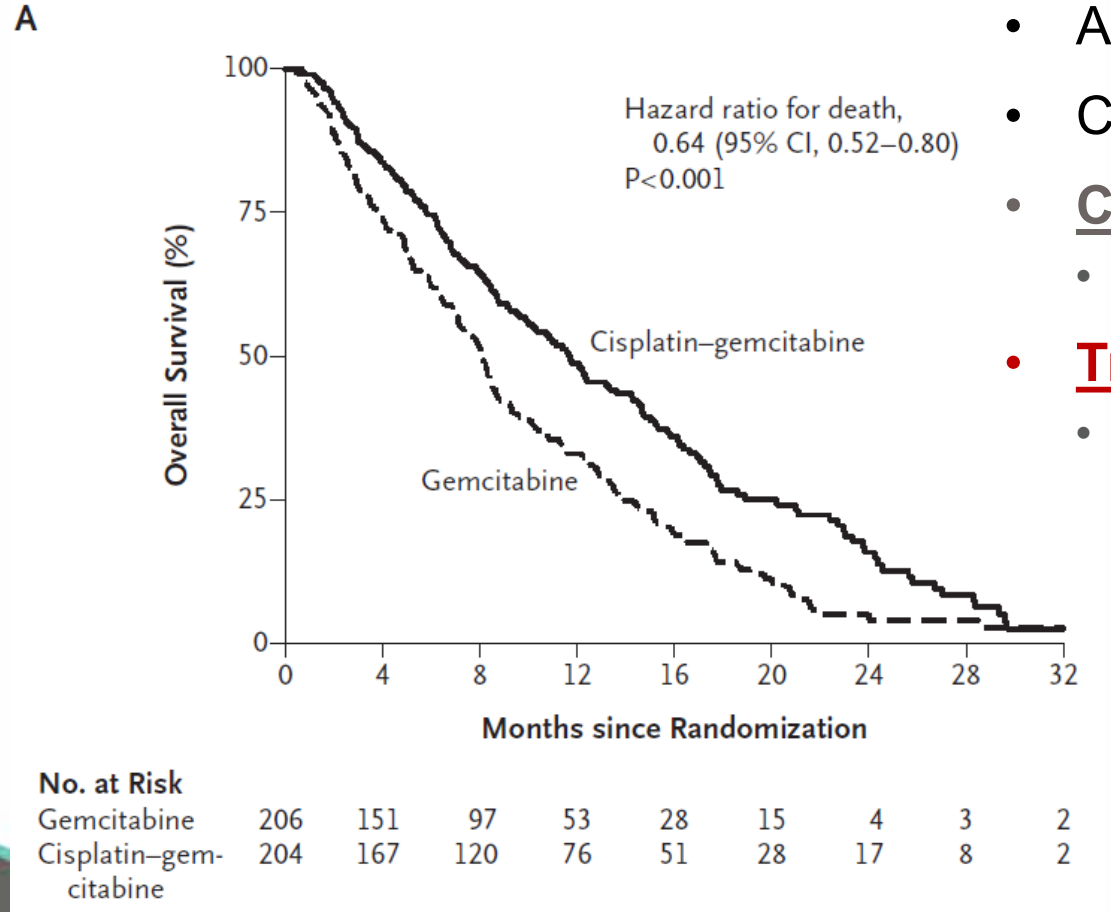
- Role of radiation for node/margin+ disease remains unclear although retrospective data supports its use
  - T2 or greater, M0 gallbladder
  - Extrahepatic disease (especially node+ or margin + based on SWOG S0809)

- Role of adjuvant combo chemo remains unclear (await ACTICCA-1 results)

2019 ASCO Practice Guideline for Resectable Biliary Tract Cancers:
Schroff RT et al. J Clin Oncol 2019; 37 (12): 1015-1027

Advanced/Metastatic Disease

Advanced/Metastatic Disease:
Gemcitabine/Cisplatin is Standard of Care in 1L



- ABC-02 Trial: Randomized, phase III study
- Conducted at 37 centers in UK
- **Control arm:**
  - Gemcitabine 1000 mg/m2 Days 1, 8, 15 q28 days
- **Treatment arm:**
  - Gemcitabine 1000 mg/m2 + Cisplatin 25mg/m2 Days 1,8 q21 days

- Improved DCR: 81.4% vs. 71.8% (p=0.049)
- **Median survival 11.7 vs. 8.1 months** (p<0.001)
- Treatment compliance better in the Gem + Cis arm

Valle J. et al. N Engl J Med 2010;362:1273-81.

ABC-06: FOLFOX is Standard 2L for Metastatic Disease

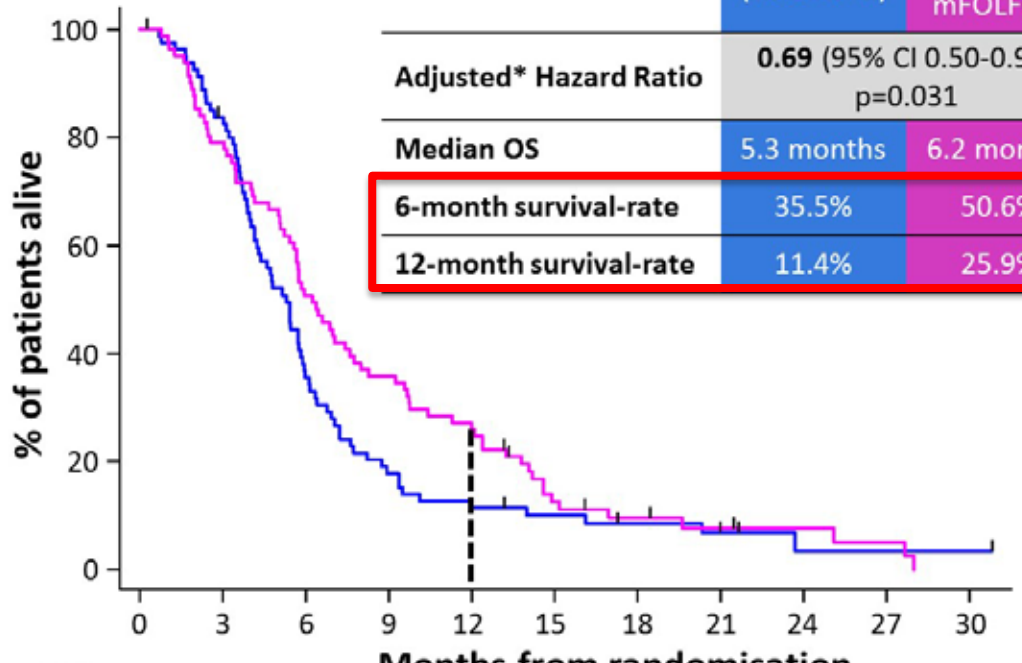
Primary end-point: Overall Survival (ITT)

- The **primary end-point was met**: adjusted* HR was 0.69 (95% CI 0.50-0.97; p=0.031) for OS in favour of ASC + mFOLFOX arm (vs ASC)

- No marked evidence was identified against the key proportional hazards assumption**; which confirmed the validity of using the Cox Regression analysis

*adjusted for platinum sensitivity, albumin and stage
**proportional hazards assumption test p-value 0.6521
ITT: intention-to-treat analysis; ASC: active symptom control

Overall survival by trial arm



	Arm A (ASC alone)	Arm B (ASC + mFOLFOX)
Adjusted* Hazard Ratio	**0.69** (95% CI 0.50-0.97) p=0.031	
Median OS	5.3 months	6.2 months
6-month survival-rate	35.5%	50.6%
12-month survival-rate	11.4%	25.9%

Lamarca A, et al. Abstract 4003. 2019 ASCO Annual Meeting

Targeted Therapy for Biliary Tract Cancers

	Intrahepatic	Extrahepatic	Gallbladder	Comments
% *FGFR2* fusions/ *FGFR1-3* alterations	**10-15**	0	3	• **Pemigatinib FDA Approved Apr 2020**[1] • ORR 35.5%; DCR ~80%
% *IDH 1/2* substitution	**15-20**	0	0	• In NCCN Guidelines; pending FDA Approval • ORR 2%, DCR 53%[2]
% MSI-H/dMMR	**1-3**	**1-3**	**1-3**	• In NCCN Guidelines • PD1 inhibitors: ORR 30-50%[3]
% *NTRK* fusions	**1-2**	**1-2**	**1-2**	• In NCCN Guidelines • Larotrectinib/Entrectinib: ORR ~40-70%[4-5]
% *BRAF V600E*	**5**	3	1	• ORR 36%, DCR 75% with BRAK/MEK inhibition[6]
% *ERBB2* (Her-2) amplification	3-4	**11**	**16**	• ORR ~40% with trastuzumab/pertuzumab[7] • Multiple ongoing basket trials with novel agents
% *ARIDA1A* Alterations	18	12	13	• Rationale for checkpoint inhibition and BET, EZH2, PARP inhibitors

KEY POINT:
Perform broad molecular profiling early in treatment course for advanced biliary tract cancer

*Table modified from 2019 ASCO Discussion by Dr. William P. Harris and data derived from Javle MM et al, Cancer 2016; 122(24) 3828-3847.

[1] Abou-Alfa GK et al. Lancet Oncol 2020; 21(5):671-684. [2]Abou-Alf GK et al. Lancet Oncol 2020; 21(6):796-807. [3]Le DT et al. N Engl J Med 2015. [4]Drilon A et al. N Engl J Med 2018;378:731-9. [5]Doebele RC et al. Lancet Oncol 2020; 21: 271–82. [6]Wainberg Z et al. ASCO GI 2019. Abstract 187. [7]Javle MM et al. ASCO GI 2017. Abstract 402.

FIGHT-202 Study: Pemigatinib in ≥2L for *FGFR* Altered Metastatic Biliary Tract Cancer

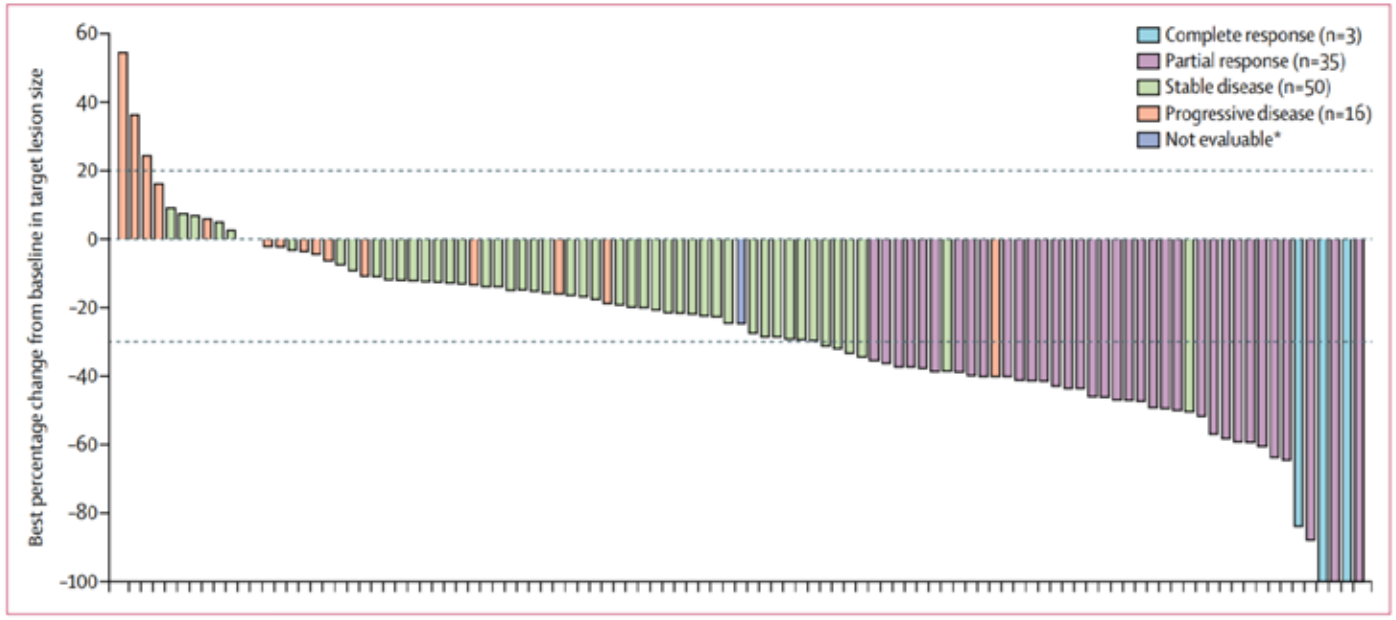
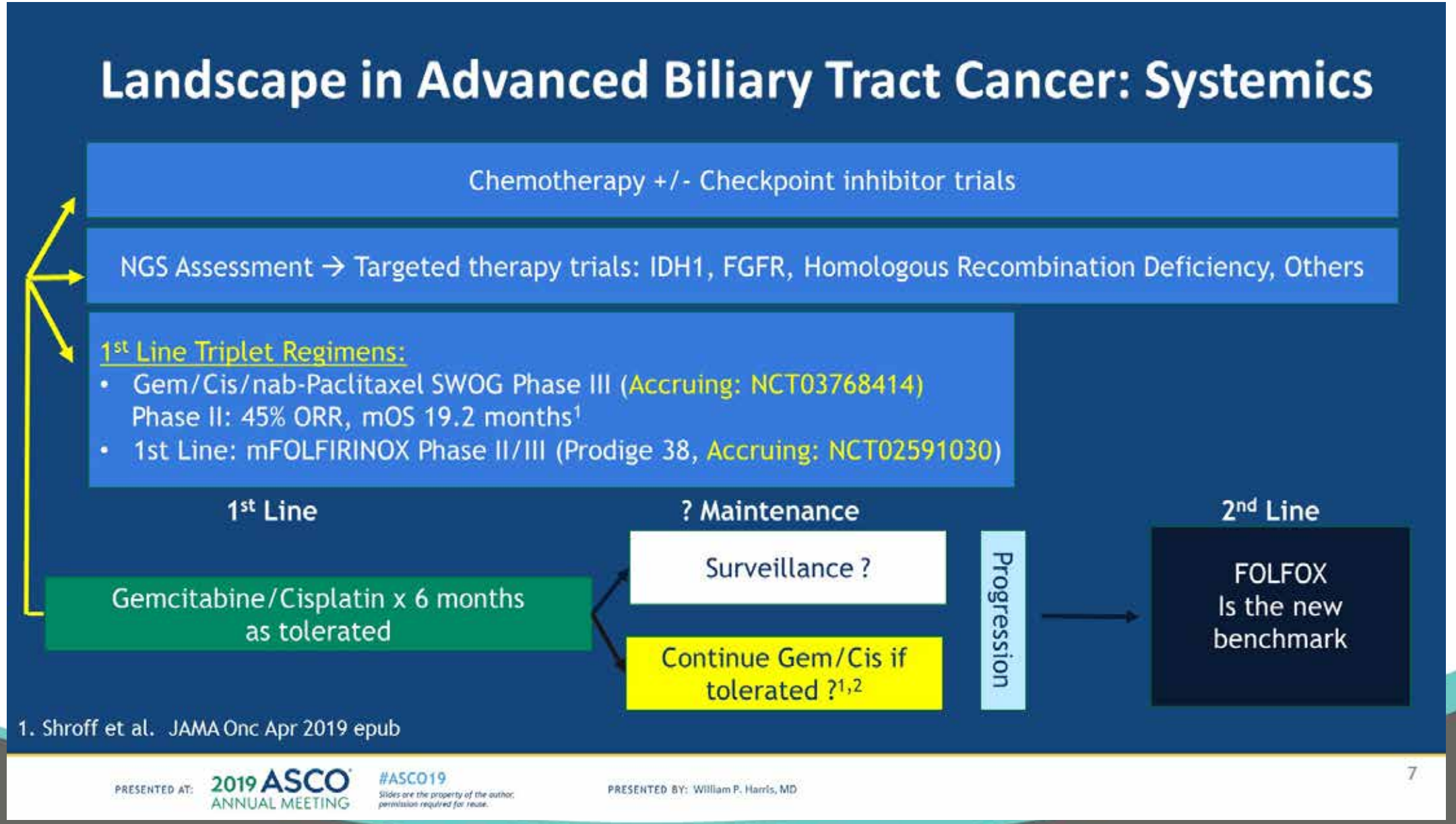


Figure 2: **Best percentage change from baseline in target lesion size for individual patients with *FGFR2* fusions or rearrangements**
Coloured bars indicate confirmed responses assessed by RECIST 1·1. FGFR=fibroblast growth factor receptor. RECIST 1.1=Response Evaluation Criteria in Solid Tumors version 1.1. *Patient had a decrease in target lesion size but was not evaluable for response using RECIST.

Abou-Alfa GK et al. Lancet Oncol 2020; 21(5):671-684.

- Phase 2, single arm global study
- Pts progressed 1 prior line tx, ECOG 0-2
- 3 cohorts: 1) *FGFR2* fusion/rearrangements 2) Other *FGF/FGFR* alterations 3) No *FGF/FGFR* alterations
- Tx: Pemigatinib (oral *FGFR1-3* inhibitor) 13.5 mg po daily D1-14 q21 days
- Primary endpoint: ORR
- Activity seen in *FGFR2* fusion pts w/ ORR 35.5%, DCR 82.2%
- Median PFS 6.9 mo, OS 21.1 mo
- Conclusion: Pemigatinib should be a standard of care option for advanced biliary cancers with *FGFR2* fusions

Evolving Landscape of Biliary Tract Cancer



Presented By William Harris at 2019 ASCO Annual Meeting

Conclusions for Biliary Tract Cancer

- Biliary tract cancer should be diagnosed in the correct clinical context
- Adjuvant capecitabine x 6 months prolongs survival for resected biliary tract cancer
- Possible benefit of adjuvant chemoradiation in retrospective series
  - Extrahepatic cholangiocarcinoma (especially node+ or margin +)
  - T2 or greater, M0 gallbladder
- ≥T1b (muscle invasive) gallbladder ca require extended hepatectomy + LN staging
- Gemcitabine + Cisplatin is the standard of care 1L treatment for advanced disease
- FOLFOX is now the established 2nd line treatment for advanced/metastatic disease
- Molecular profiling should be performed → High frequency of actionable mutations
- Pemigatinib is FDA approved for advanced biliary tract cancers with *FGFR2* fusions
- Consider clinical trial enrollment when available

Comprehensive Hematology & Oncology Review: MPNs

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10/6/2020

Slide and picture contributions from Dan Martin, Bart Scott, Joachim Deeg

Disclosures

Research funding: Bayer, Pfizer, Jazz, Novartis,Tolero, Imago

Advisory board: Agios

ABIM & MPNs

Hematology

- MPN- 4.5%:
  - CML
  - PV and secondary erythrocytosis
  - Myelofibrosis
  - ET
  - Mastocytosis
  - CNL

Oncology

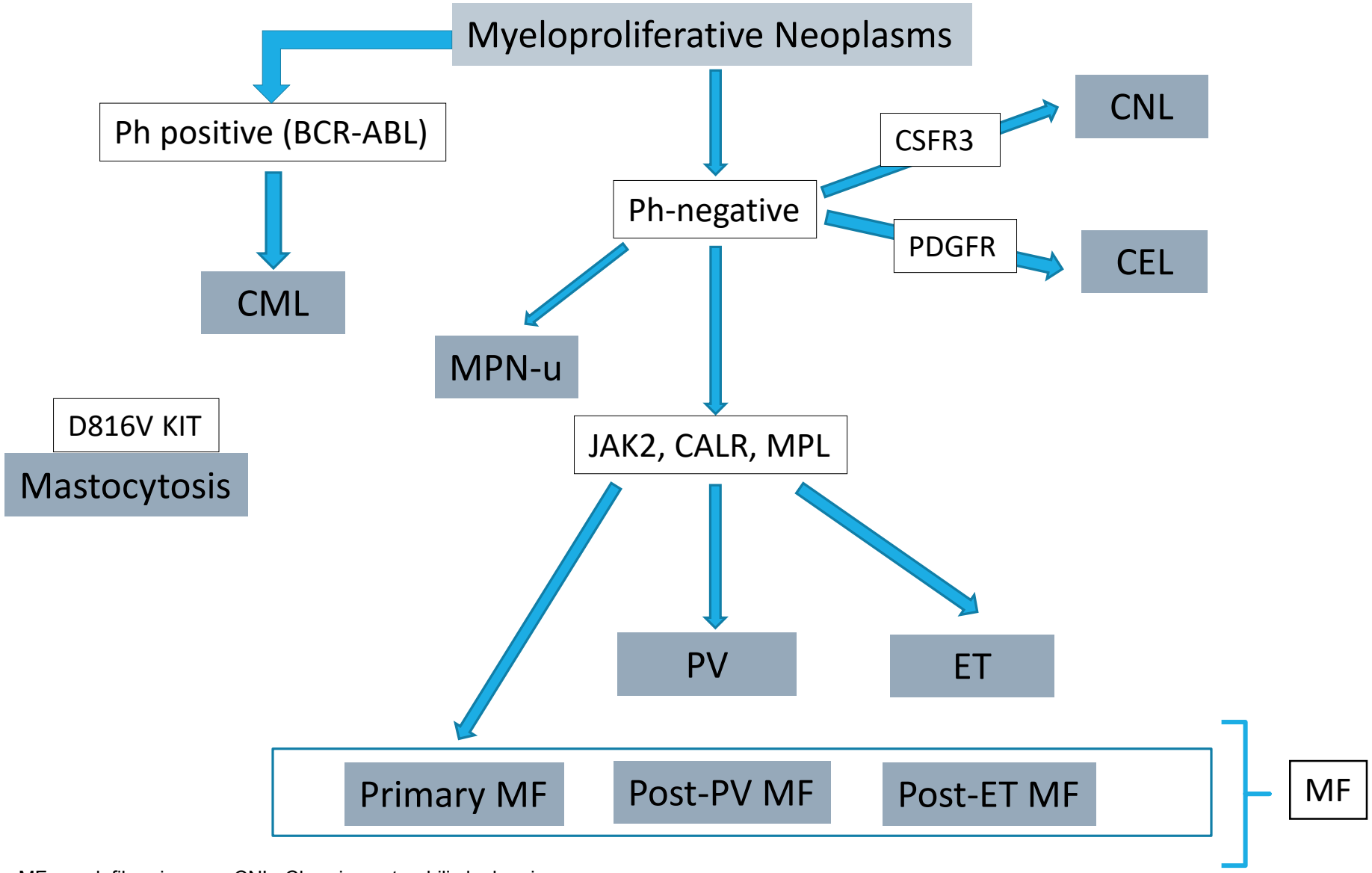
- CML and MPNs: 2%, focus on diagnosis, testing, treatment/care decisions

Overview

1) Overview MPNs

2) Presentation, Diagnosis, Risk Stratification, Treatment
   - Polycythemia vera
   - Essential thrombocythemia
   - Myelofibrosis

3) “Pearls” for mastocytosis, chronic neutrophilic leukemia (CNL), CMML

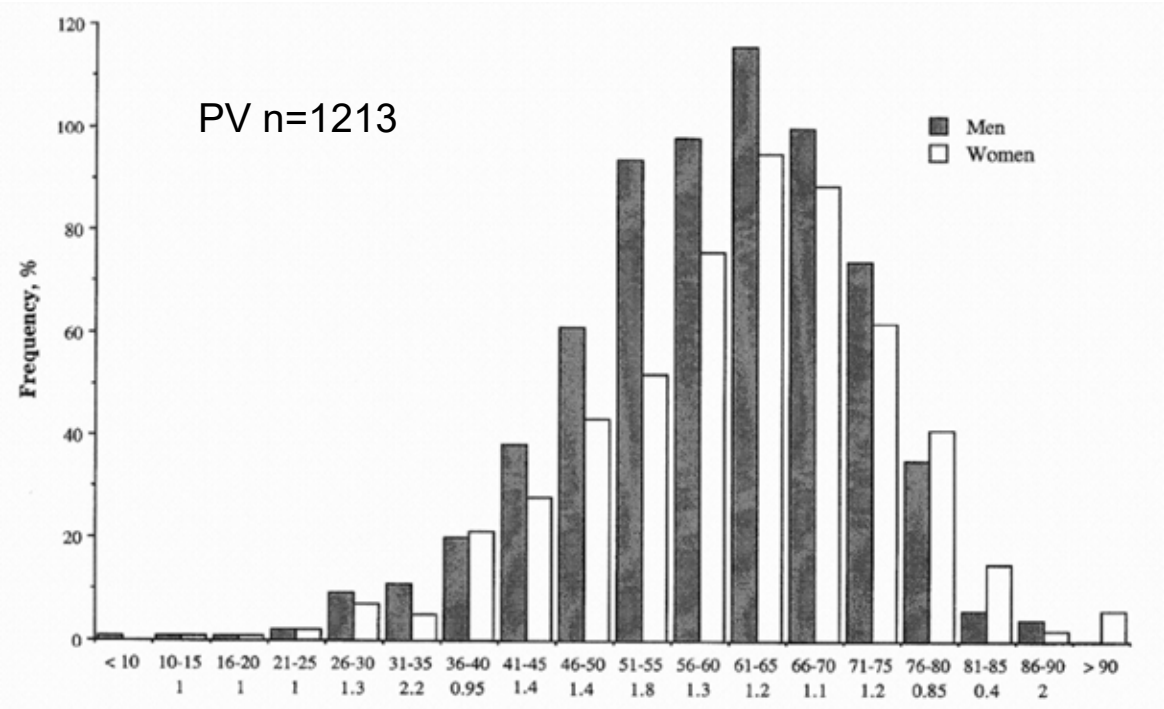


MF=myelofibrosis CNL=Chronic neutrophilic luekemia
PV=polycythemia vera CEL=Chronic Eosinophilic Leukemia
ET=essential thrombocythemia CML=chronic myeloid leukemia

Arber et al. *Blood*. 2016;127(20):2391-2405.

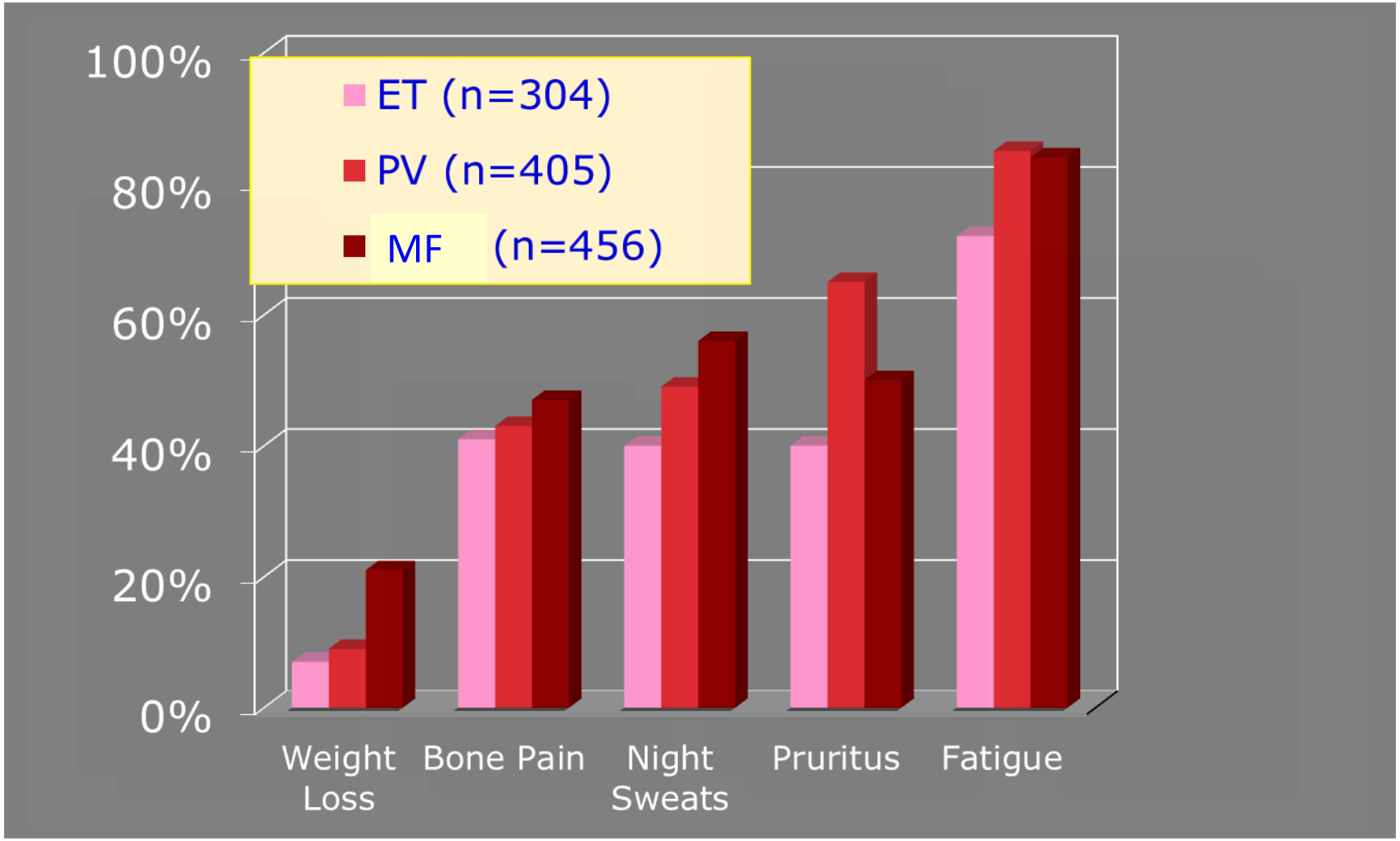
Epidemiology of MPN

- ET: 1.55-2.53/100,000 Median age 72
- PV: 1.9/100,000 Median age 62
- MF: 0.3-1.46/100,000 Median age 67



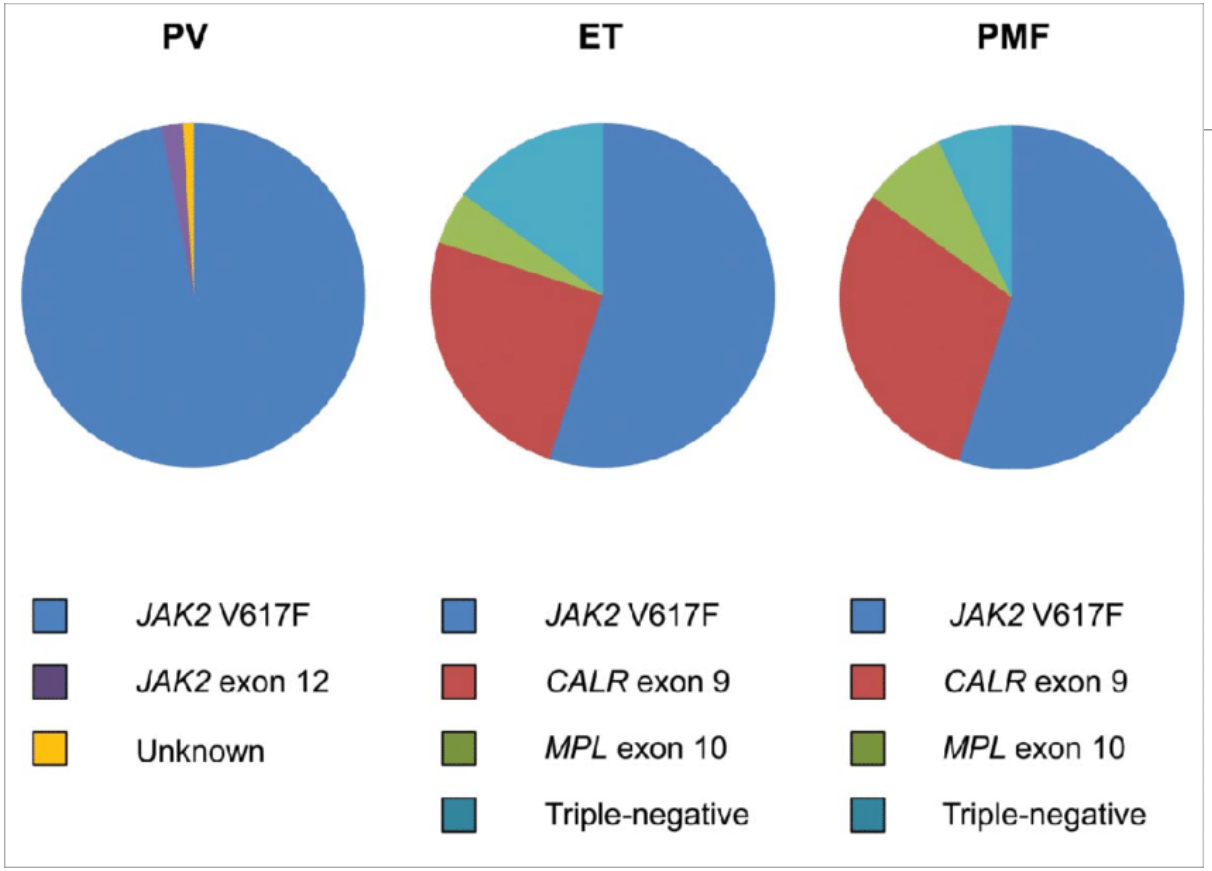
GISP *Ann Intern Med.* 1995;123:656-664

Symptoms in 1179 MPN Patients



Mesa R et. al. *Cancer* 2007;109:68-76

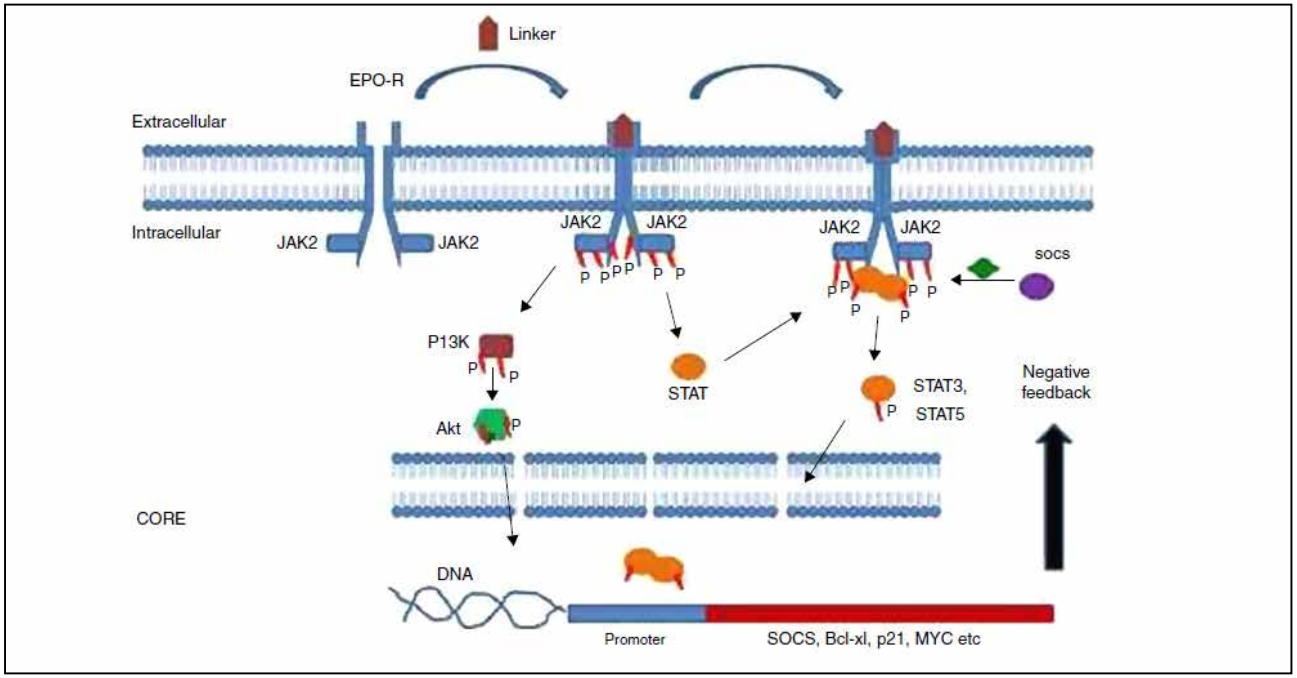
Mutations in MPNs



Disease	Mutation	%Patients
PV	JAK2 V16F JAK2 Exon 12	95-97% 2-4%
ET	JAK2 V16F CALR MPL “triple-neg”	60-65% 20-25% 5% 10-15%
PMF	JAK2 V16F CALR MPL “triple-neg”	60-65% 20-25% 5% 10-15%

Langabeer. JAKSTAT 2016; 5 (2-4): e1248011.

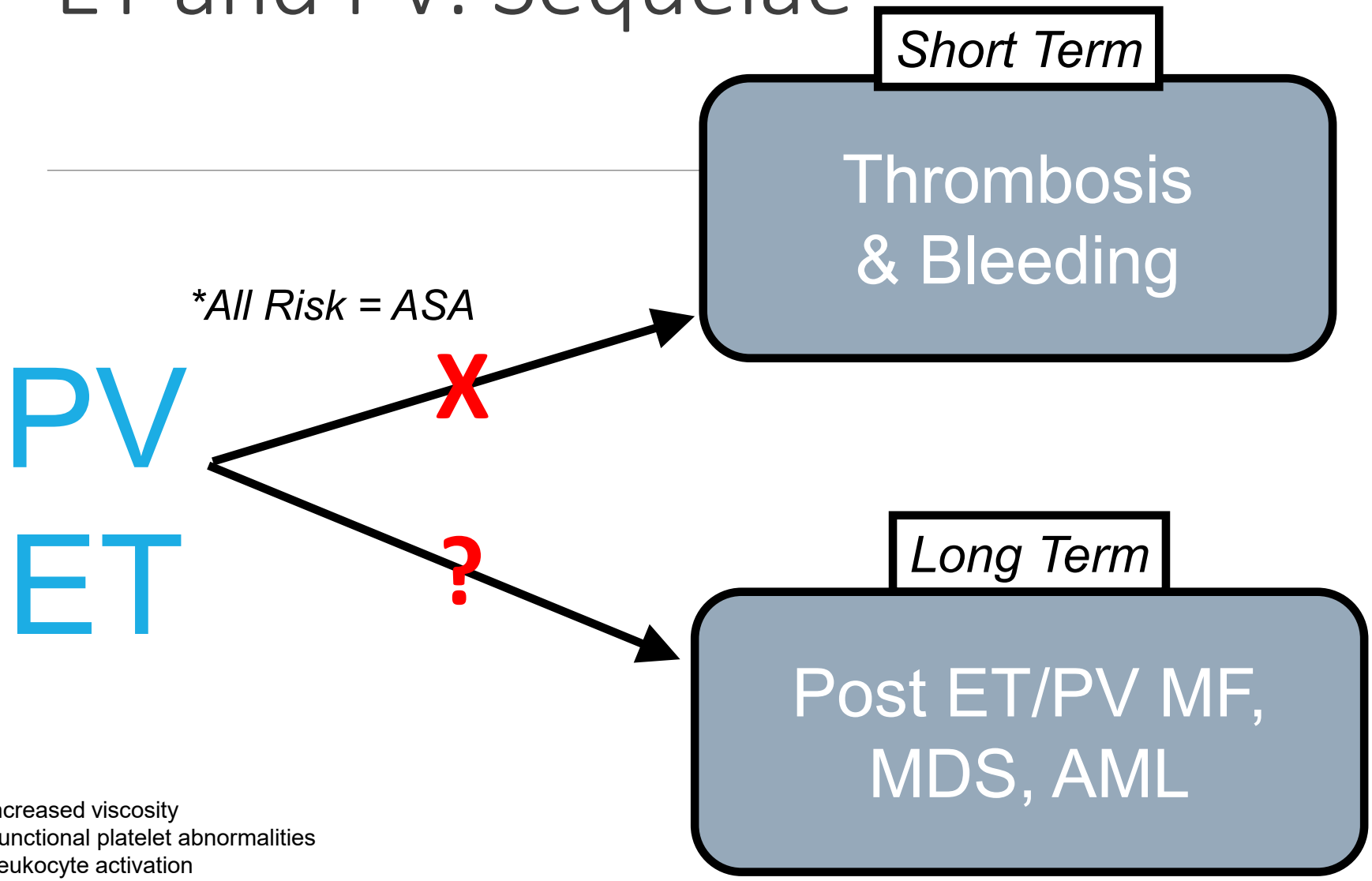
MPN Etiology: Role of *JAK2* Mutation



V617F single point mutation in *JAK2* gene → an altered protein that constitutively activates the JAK/STAT signal transducers and activators of transcription pathways

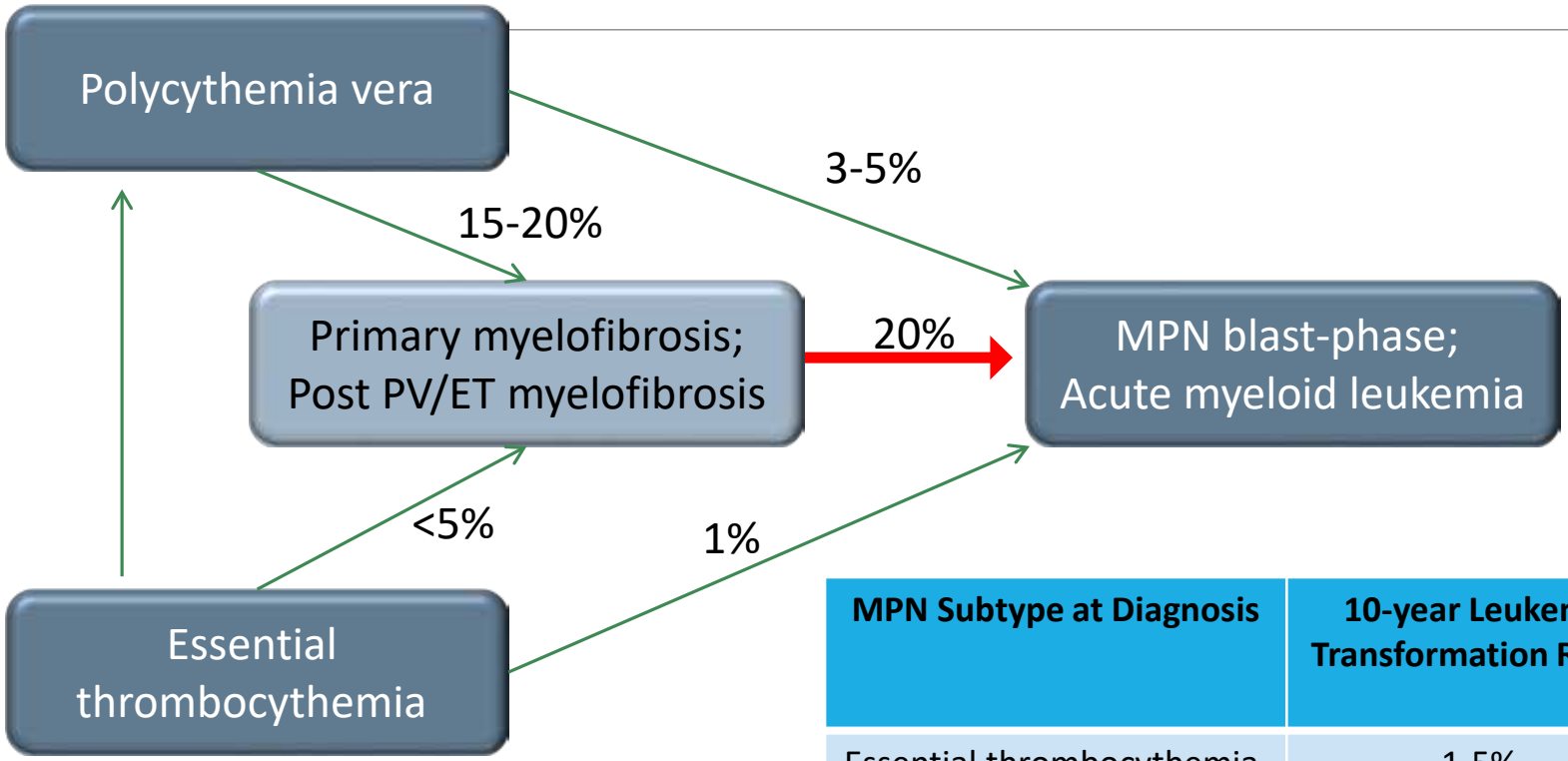
Affects the expression of genes involved in regulation of apoptosis and regulatory proteins and modifies the proliferation rate of hematopoietic stem cells

ET and PV: Sequelae



Increased viscosity
Functional platelet abnormalities
Leukocyte activation
Increased platelets lead to acquired VWD

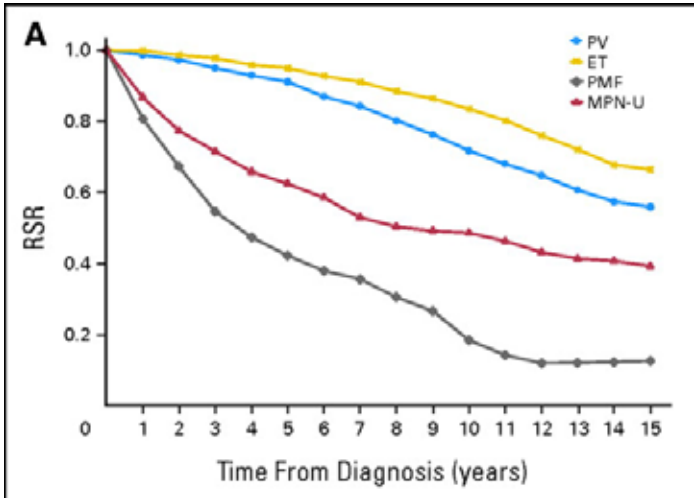
Transformation to MF and AML



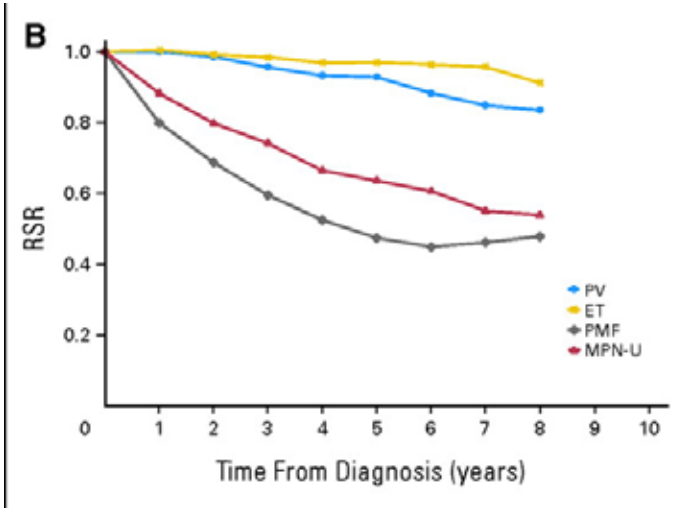
MPN Subtype at Diagnosis	10-year Leukemic Transformation Rate [2]
Essential thrombocythemia	1-5%
Polycythemia vera	3-5%
Primary myelofibrosis	20%

1.Tefferi A. *Am J Hematol*. 2008;83:491-497; 2. Rampal, Mascarenhas. *Curr Opin Hematol.* 2014;21:65-71.

MPN survival improving over time



1993-2008



2001-2008

Malin Hultcrantz et al. JCO 2012;30:2995-3001

Case 1

33 yo M with no PMH, presented with painful/red toes, later developed joint pain and pruritis

Physical: plethoric, no joint abnormalities

CBC: WBC21, Hgb 18.8, HCT 48, plts 490

- Epo level <1

JAK2 VI6F mutation found positive on peripheral blood, BCR-ABL neg

Bone marrow: hypercellular >95%, trilineage hematopoiesis and proliferation, no fibrosis or increased blasts

Diagnosis of PV was made:

- Start Aspirin 81 mg daily
- Started phlebotomy target HCT <45%
- Did not tolerate phlebotomy → hydrea→ did not control symptoms → ruxolitinib

Erythromelalgia

Polycythemia Vera: Presentation

MPN IWG Study presenting signs/symptoms

- Laboratory evaluation:
  - Hemoglobin – median 18.4 g/dL (range 15.1 to 26.5)
  - Hematocrit – median 55% (range 36 to 78%)
  - Leukocyte count – median 10,400/mL (range 3000 to 172,000)
  - Platelet count – median 466,000/mL (range 70 to 2,370,000)
  - Elevated lactate dehydrogenase – 50%
- Hypertension – 46%
- Palpable spleen – 36%
- Pruritus (aquagenic) – 36%
- Vasomotor symptoms (eg, erythromelalgia) – 29%
- Arterial thrombosis – 16%
- Venous thrombosis – 7%
- Major hemorrhage – 4%

Tefferi et al, Leukemia 2013; 27 (9): 1874

Diagnostic Criteria

Start with CBC, Epo level and JAK2 V16F/BCR-ABL mutation; exclude secondary causes

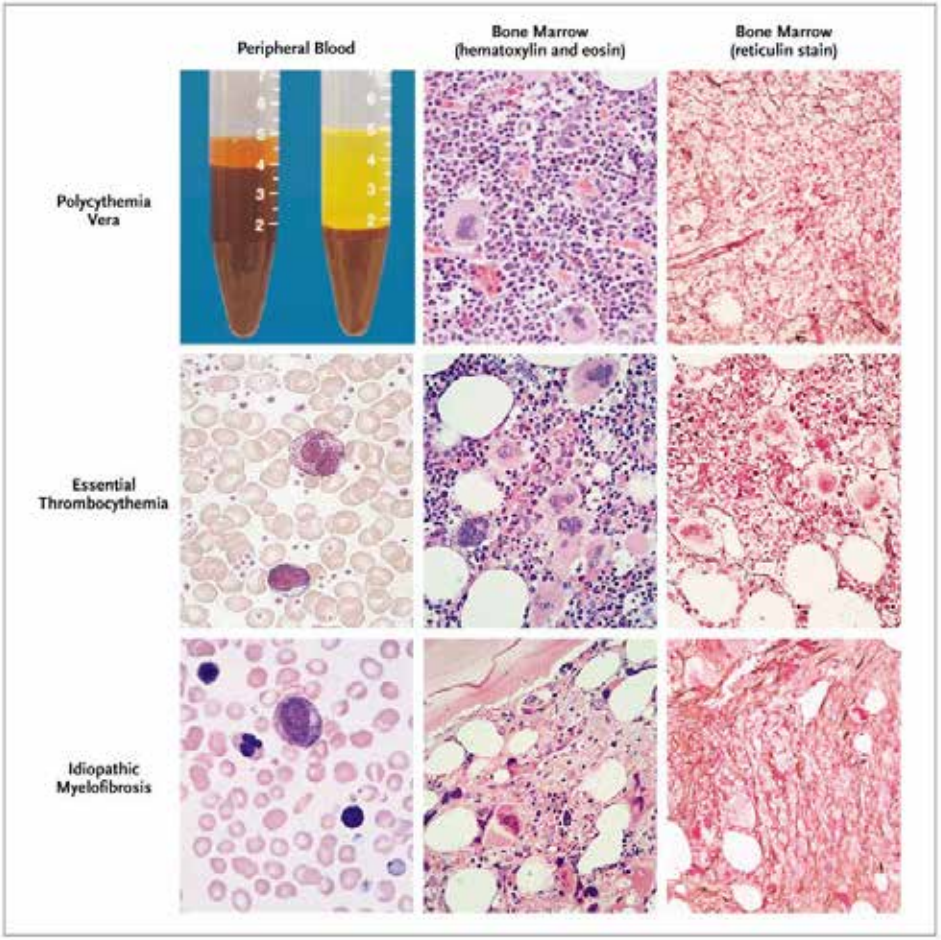
WHO Criteria: PV

Major Criteria (all 3 major or first 2 with minor)

- Hgb > 16.5 g/dL (HCT 49) in men, 16 g/dL HCT (48) in women or increased RCM*
- †BM Trilineage Proliferation (panmyelosis)
- *JAK2V617F* or *JAK2* exon 12 mutation

Minor Criteria

- Low Epo level (<3mU/mL)



†Criterion number 2 (BM biopsy) may not be required in cases with sustained absolute erythrocytosis: Hgb>18.5 g/dL in men (HCT55.5%) or >16.5 g/dL in women (HCT49.5%) if major criterion 3 and the minor criterion are present.

**Initial myelofibrosis (up to 20% of patients) can only be detected by performing a BM biopsy; may predict a more rapid progression to overt myelofibrosis (post-PV MF).

*elevated RCM > 25% above predicted

Arber et al. *Blood*. 2016;127(20):2391-2405.
Campbell P et al. *N Engl J Med.* 2006;355:2452-2466

PV Risk Stratification

LOW RISK:

- Age <60
- No history of thrombosis

HIGH RISK

- Age> 60 OR
- History of thrombosis

[1]Finazzi et al. *Blood.* 2007;109:5104-5111

PV: Treatment

Phlebotomy to maintain HCT <45%

Aspirin

Cardiovascular risk-factor modification

Hydroxyurea

Interferon

Ruxolitinib

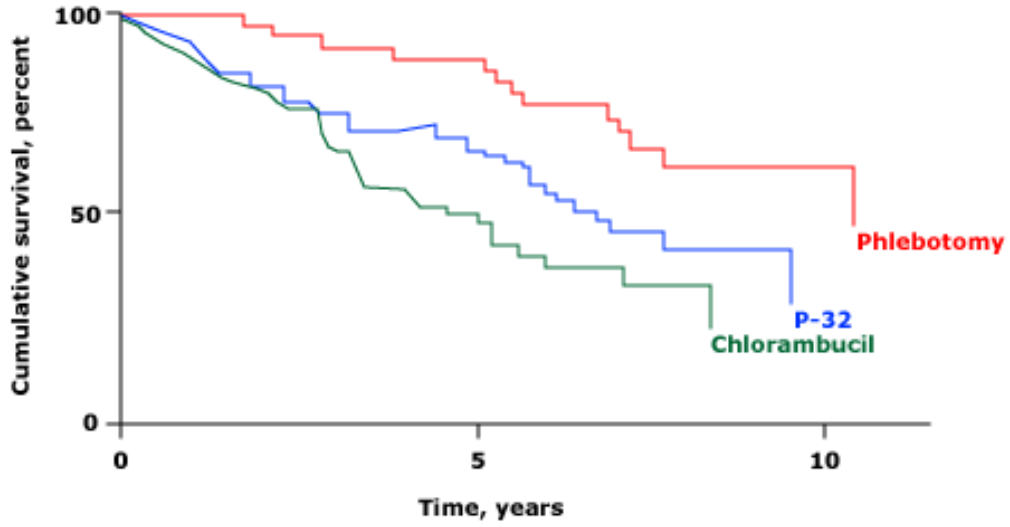
Chemo X

ALL

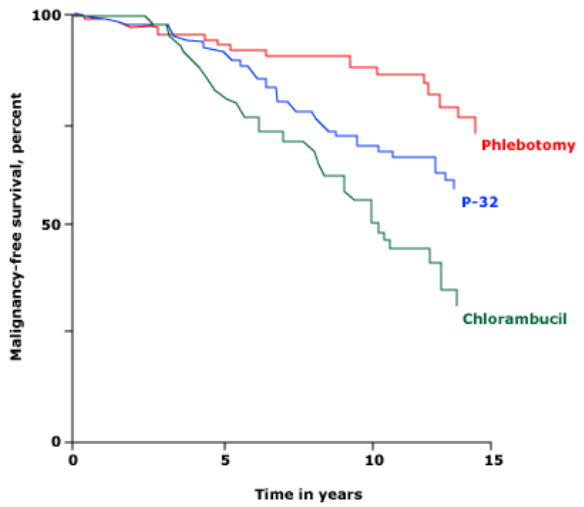
High-risk OR uncontrolled PV symptoms

Initial trials in PV: no more chemo

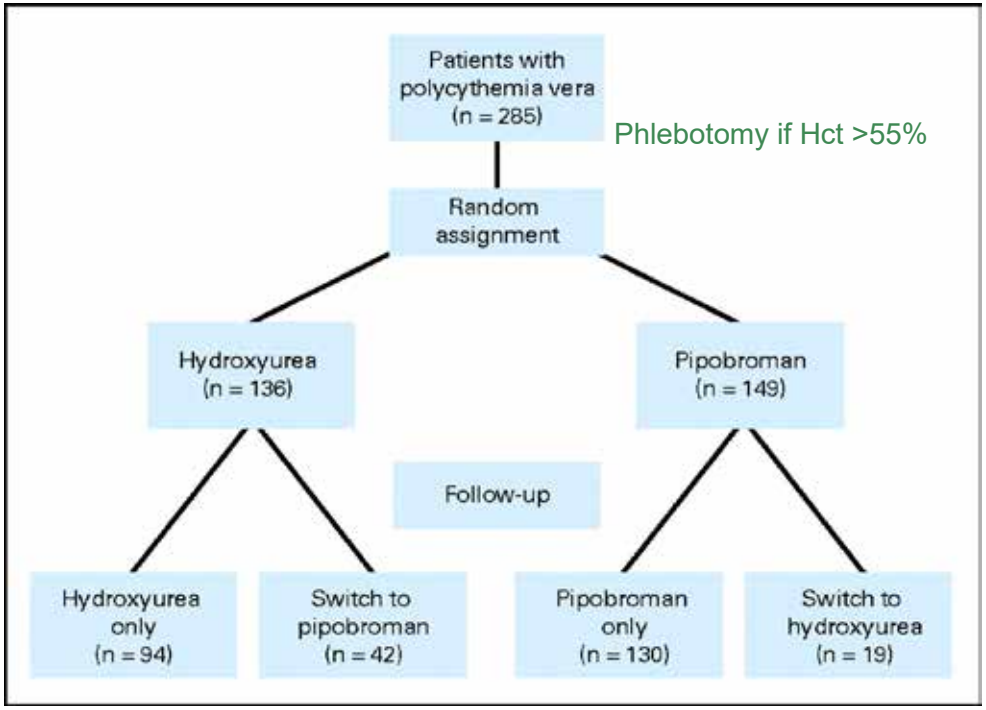
Lower cumulative survival with chemotherapy in polycythemia vera



Lower malignancy-free survival with chemotherapy in polycythemia vera



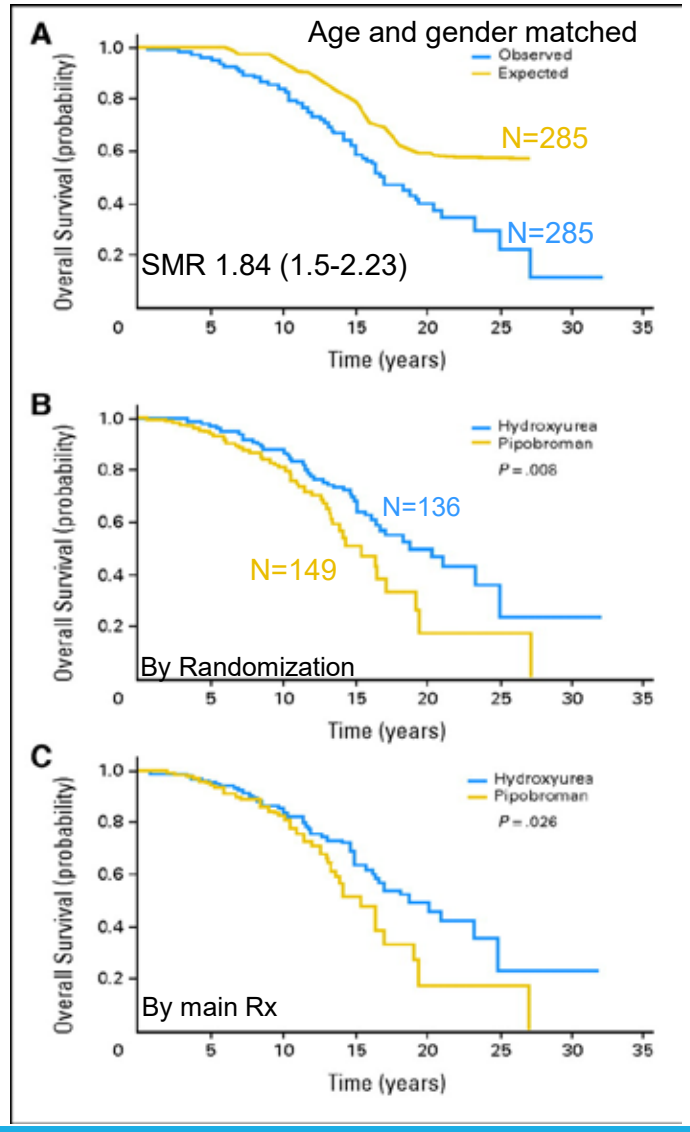
Hydroxyurea vs. Pipobroman (alkylating agent) in PV



Switch to Pi HR 2.06 (95% CI 1.09-3.87, *p*=0.026)

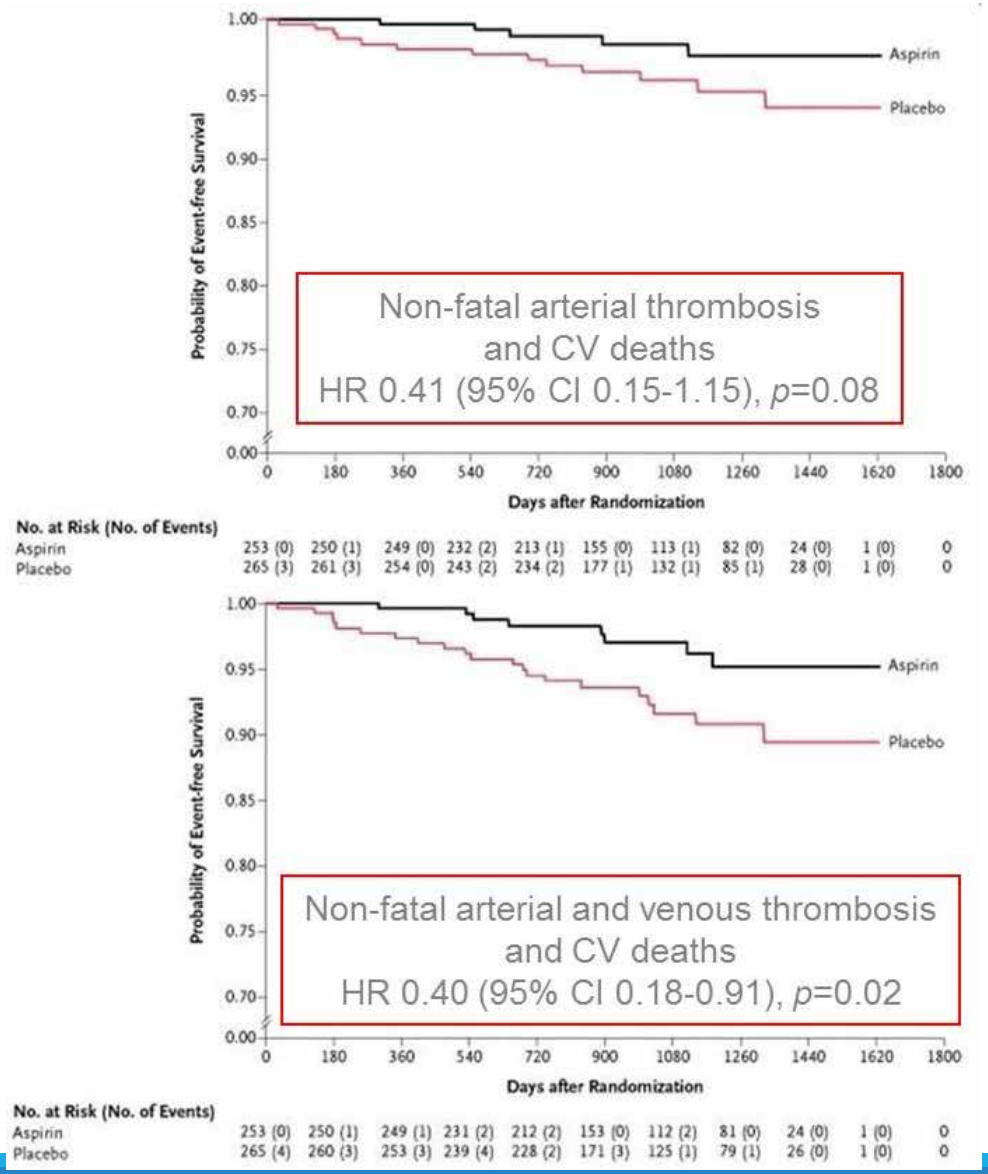
Switch to HU HR 1.37 (95% CI 0.61to 3.08), *p*=0.45

<u>Cause of death</u>
MDS/AML 54%
Thrombosis 15%



Kiladjian J et al. *J Clin Oncol.* 2011;29:3907-3913
Najean Y et al. *Blood.* 1997;90:3370-3377

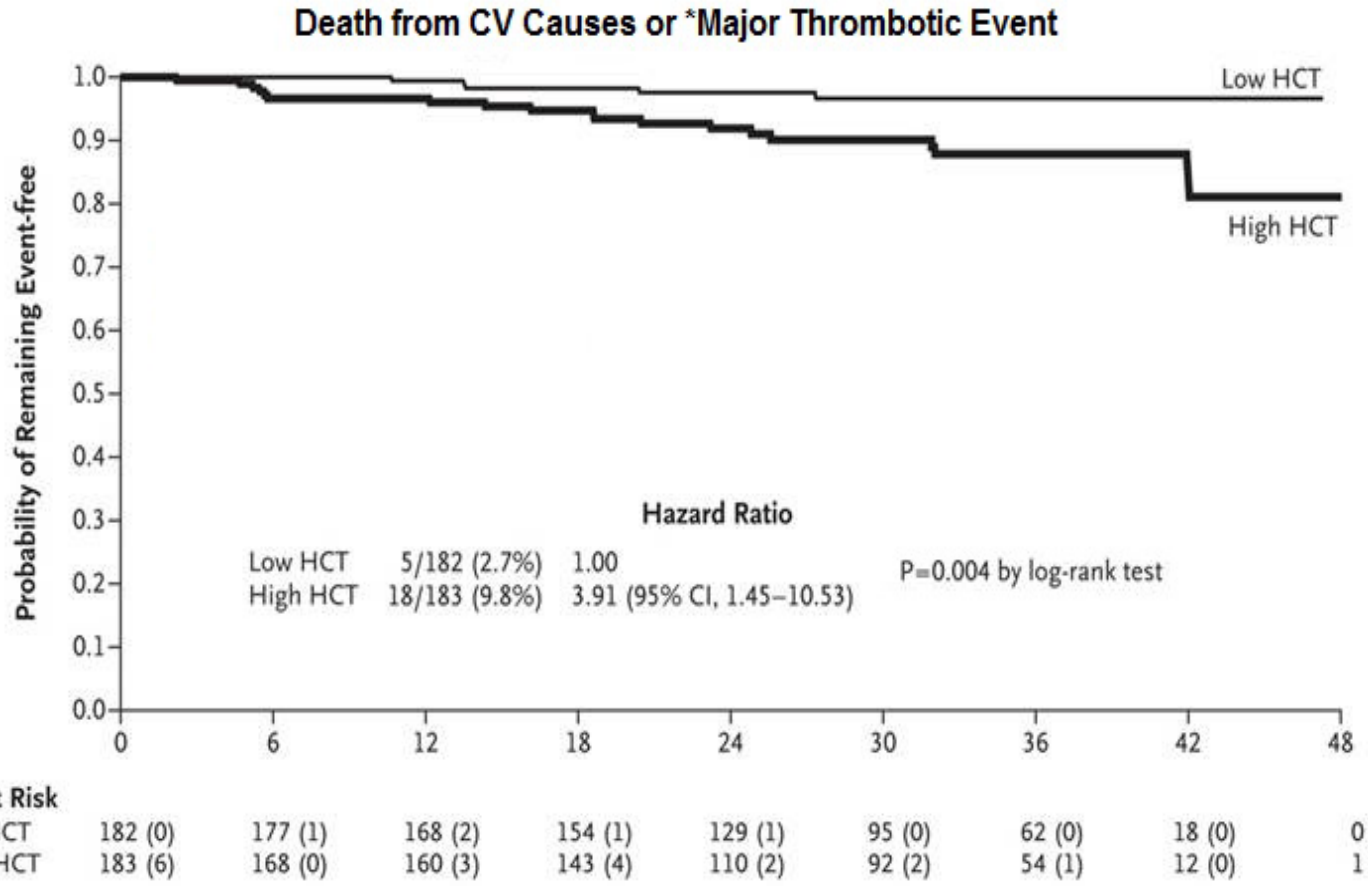
ECLAP TRIAL: RCT ASA vs. Placebo in PV



- 500 PV patients randomized to Aspirin 100 mg daily vs placebo
- Reduced risk combined endpoint non-fatal arterial+venous thrombosis +CV deaths
- No reduction in overall mortality
- No increase incidence bleeding

Landolfi R et al. *N Engl J Med.* 2004;350:114-124.

Target HCT in PV: CYTO-PV Trial

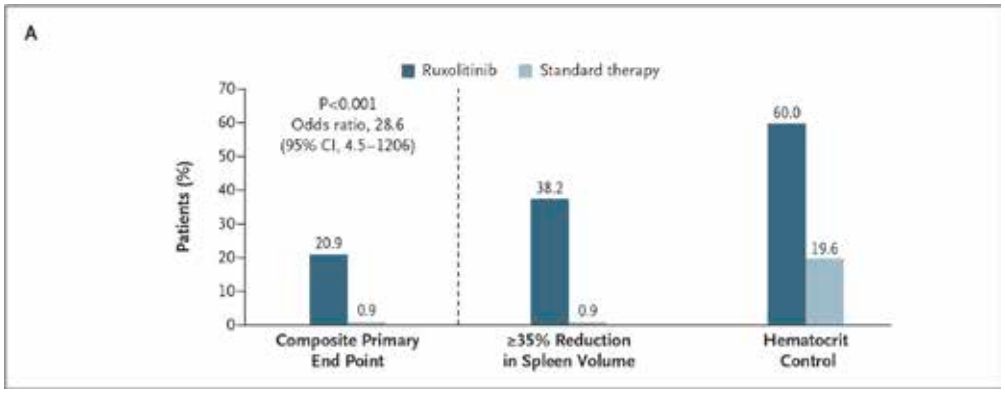


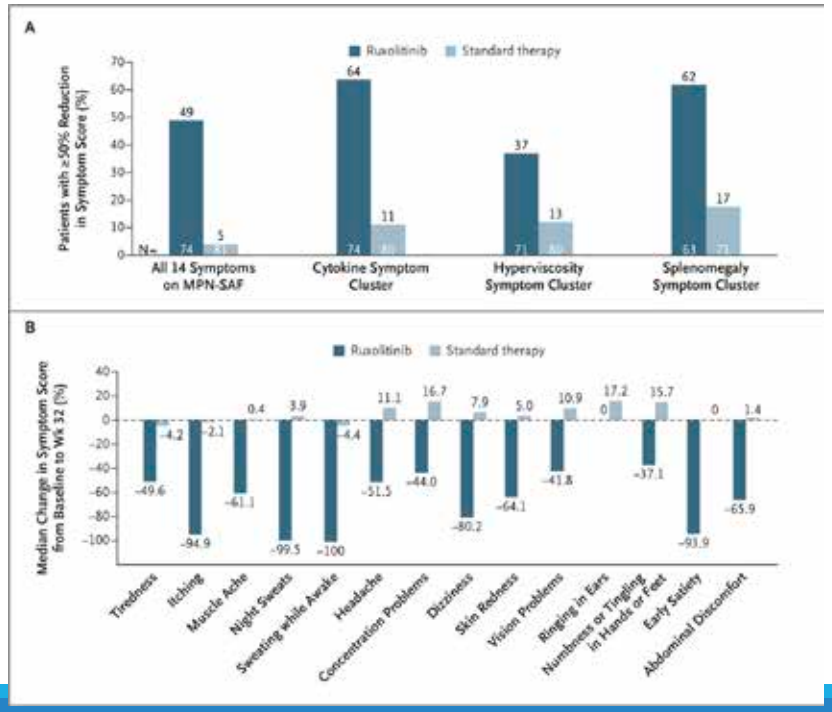
<45%

45-50%

Marchioli R., et al. *Thrombosis* 2011;2011:794240
Marchioli R., et al. *N Engl J Med* 2013;368:22-33

RESPONSE: Ruxolitinib vs BAT in PV





Open label, 222 patients with PV
Resistant (46%) or intolerant to HU (54%)

Randomly assigned to:

Ruxolitinib (110)

BAT (112): 59% HU, INF 12%, pipobroman 2%, no med 15%

Primary endpoint HCT control (wk 32) and >35% reduction spleen volume

Symptoms evaluated by MPN-SAF TSS

Vannucchi et al. NEJM 2015; 372 (5): 426-35.
Verstovsek et al. Haematologica 2016; 101 (7): 821.

Thrombosis Risk-Adapted Management of PV

Category	Characteristics	Treatment
Low-risk	Age <60 AND No thrombosis	Phlebotomy : goal HCT <45 Aspirin 81 mg daily Address CV risk factors
High-risk	Age ≥ 60 OR Thrombosis history	All of the above AND Cytoreductive Therapy: 1) 1st Line: Hydrea PegIFN 1) 2nd Line: Ruxolitinib PegIFN Busulfan (age >70)

Indications for cytoreduction in low-risk pts may include:

- Poor tolerance of phlebotomy
- Progressive leukocytosis
  - Platelets > 1500 x 10^9/L (risk of bleeding)
  - Severe disease-related symptoms

**Pts with plts >1 million should be tested for acquired VWD prior to initiation of Aspirin

Barbui T, et al. J Clin Oncol. 2011;29:761-770. Tefferi A, et al. Am J Hematol. 2015;90:162-173.

Case #1.5

40 yo M with presenting with fatigue, pruritus and burning after showers and sexual activity

On exam: ruddy, plethoric, obese

CBC: white count of 8, hemoglobin of 18.5, plts 455

History:

- Non-smoker
- Lives in Seattle area
- No history of lung disease
- Not on diuretics
- Girlfriend says he snores and “stops breathing” all night long
- Self-injects testosterone x 4 years
- Epo level is 18

Primary vs secondary polcythemia

Polycythemia vera: EPO independent

Secondary polycythemia: EPO dependent

- Appropriate Epo production:
  - High altitude
  - COPD
  - OSA/obesity
  - Smoking
  - Diuretics
  - Carbon monoxide poisoning (chronic)
  - ***Anabolic steroids, testosterone, blood doping***
- Inappropriate Epo production:
  - Tumors: RCC, HCC, uterine leiomyoma
  - Renal ischemia
  - Hereditary defects in Epo/associated proteins/high-affinity oxygen Hgb (familial polycythemia)

Distinguish these by history and Epo level

Case 2

31 yo F found to have thrombocytosis to 550k on routine lab check 2010

JAK2, MPL negative; +CALR

Bone marrow: normocellular, trilineage hematopoeisis, atypical megakaryocytic proliferation, no increased blasts, no fibrosis, normal cytogenetics

Monitored for 10 years, plts decreased in 2 pregnancies

2018 – plts rose to 1.85 million, developed headaches, fatigue, chest tightness, heavy menstrual bleeding

VWF testing negative

Initiated on Aspirin and PegIFN → plts now 500K, symptoms improved

Essential Thrombocythemia (ET)

- Asymptomatic ~50%
- Vasomotor symptoms – 13-40%
  - Headache
  - Lightheadedness
  - Syncope
  - Atypical chest pain
  - Acral paresthesia
  - Livedo reticularis
  - Erythromelalgia (burning pain of the hands or feet with erythema and warmth)
  - Transient visual disturbances (eg, amaurosis fugax, scintillating scotomata, ophthalmic migraine)
- Splenomegaly – 35%
- Thrombosis – 9-20% (fetal loss 11%)
- Hemorrhage – 3-37%

Wolanskyu AP et al. Br J Haematology 2005; 131 (2): 208.

Diagnostic Criteria

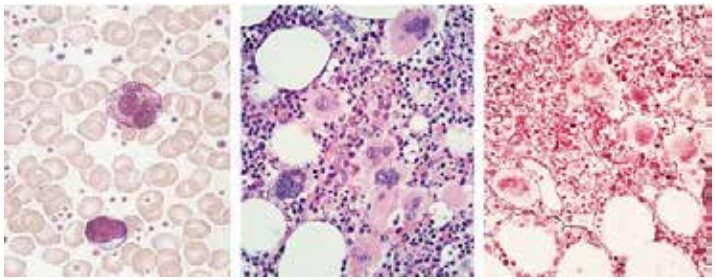
WHO Criteria: ET

Major Criteria (all 4 major or first 3 with minor)

- Plt Count ≥ 450 x 10^9/L sustained
- BM bx: megakaryocyte proliferation with increased # of enlarged mature megakaryocytes. No significant increase in granulo/erythropoiesis
- Not meeting WHO criteria for : PV¥, MF†, CML‡, MDS∫
- *JAK2V617F, CALR, or MPL mutation*

Minor Criteria (all 3 major or first 2 with minor)

- Presence of a clonal maker or no evidence of reactive thrombosis§



¥ failure of Fe to increase Hgb in setting of a low ferritin
† absence of relevant reticulin or collagen fibrosis, leukoerythroblastosis, or abnml meg morphology (n/c ratio, hyperchromatic, bulbous, irregularly folded nuclei, and clustering)
‡ absence of BCR-ABL1.
∫ absence of erythroid and granulocytic dysplasia
§ the presence of a condition associated with reactive thrombocytosis (Fe def, infection, inflammation, met cancer, connective tissue disease, lymphoproliferative d/o) does not exclude possibility of ET

Arber et al. *Blood*. 2016;127(20):2391-2405.
Campbell P et al. *N Engl J Med*. 2006;355:2452-2466

ET Prognostic Models

IPSET

	Scores		
Risk factors	**0**	**1**	**2**
Age, y	< 60		≥ 60
WBC count, × 10^9/L	< 11	≥ 11	
History of thrombosis	No	Yes	

Low risk implies a sum of scores equal to 0; intermediate risk, a sum of scores equal to 1-2; and high risk, a sum of scores equal to 3-4.

ET indicates essential thrombocythemia; and WBC, white blood cell count.

Risk	% Pts	Median OS
Low (0)	48%	NR
Intermediate (1-2)	47%	24.5 years
High-risk (3-4)	5%	13.8 years

IPSET-Thrombosis

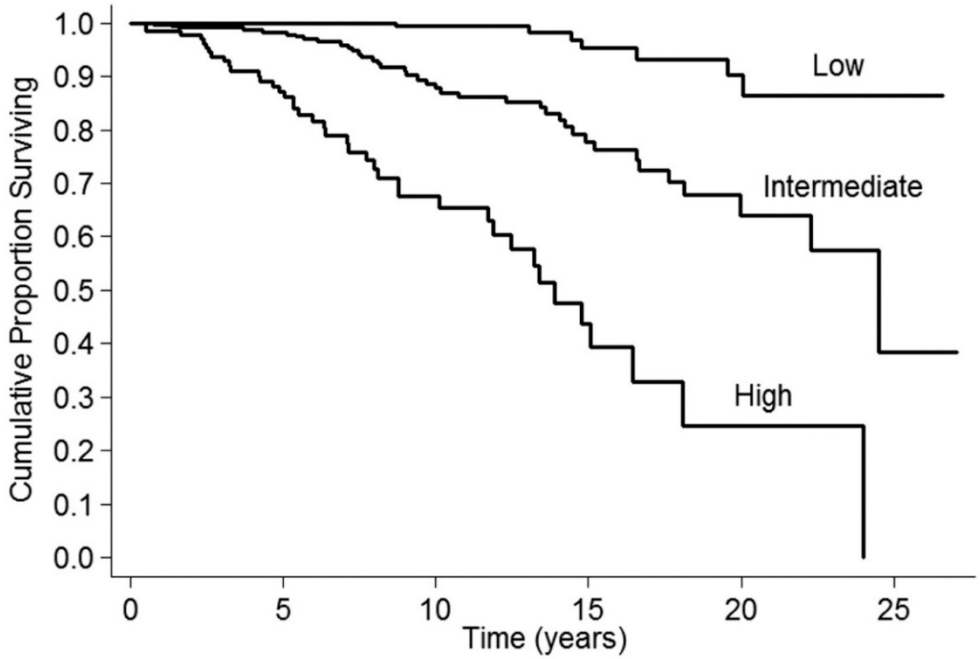
Risk factor	HR	Score
Age > 60 y	1.50	1
Cardiovascular risk factors	1.56	1
Previous thrombosis	1.93	2
*JAK2*V617F	2.04	2

Low risk implies a score = 0-1; intermediate risk, score = 2; and high risk, score ≥ 3.

Risk	%/year thrombosis
Low (0-1)	1%
Intermediate (2)	2.4%
High-risk (>2)	3.6%

Passamonti F et al. Blood 2012; 120 (6): 1197-1201; Barbui T et al, Blood 2012; 120 (26): 5128-33.

IPSET Risk Stratification



Number at risk

Low	342	211	123	63	25	3
Intermediate	374	223	109	51	15	2
High	151	84	32	10	2	0

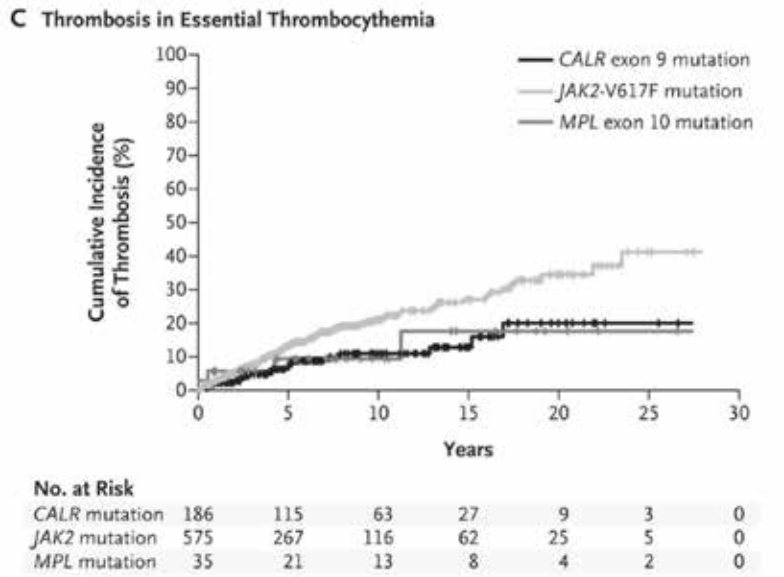
867 patients total

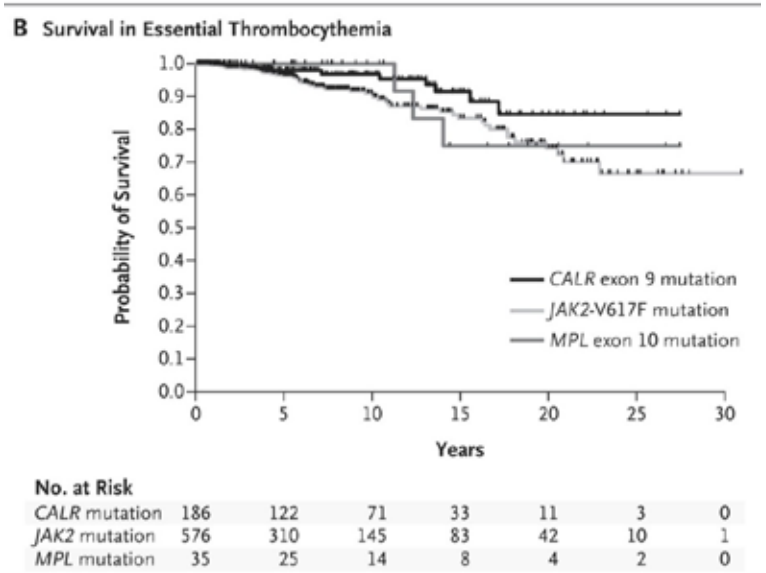
<u>87 patients died</u>
51% thrombosis
10% hemorrhage
17% AML/MDS
22% other cancer

Passamonti et al. *Blood* 2012;120:1197-1201
Barbui et al. Blood 2012;120:5128-5133

Impact of Mutations on prognosis

JAK2 associated with higher thrombotic risk than CALR



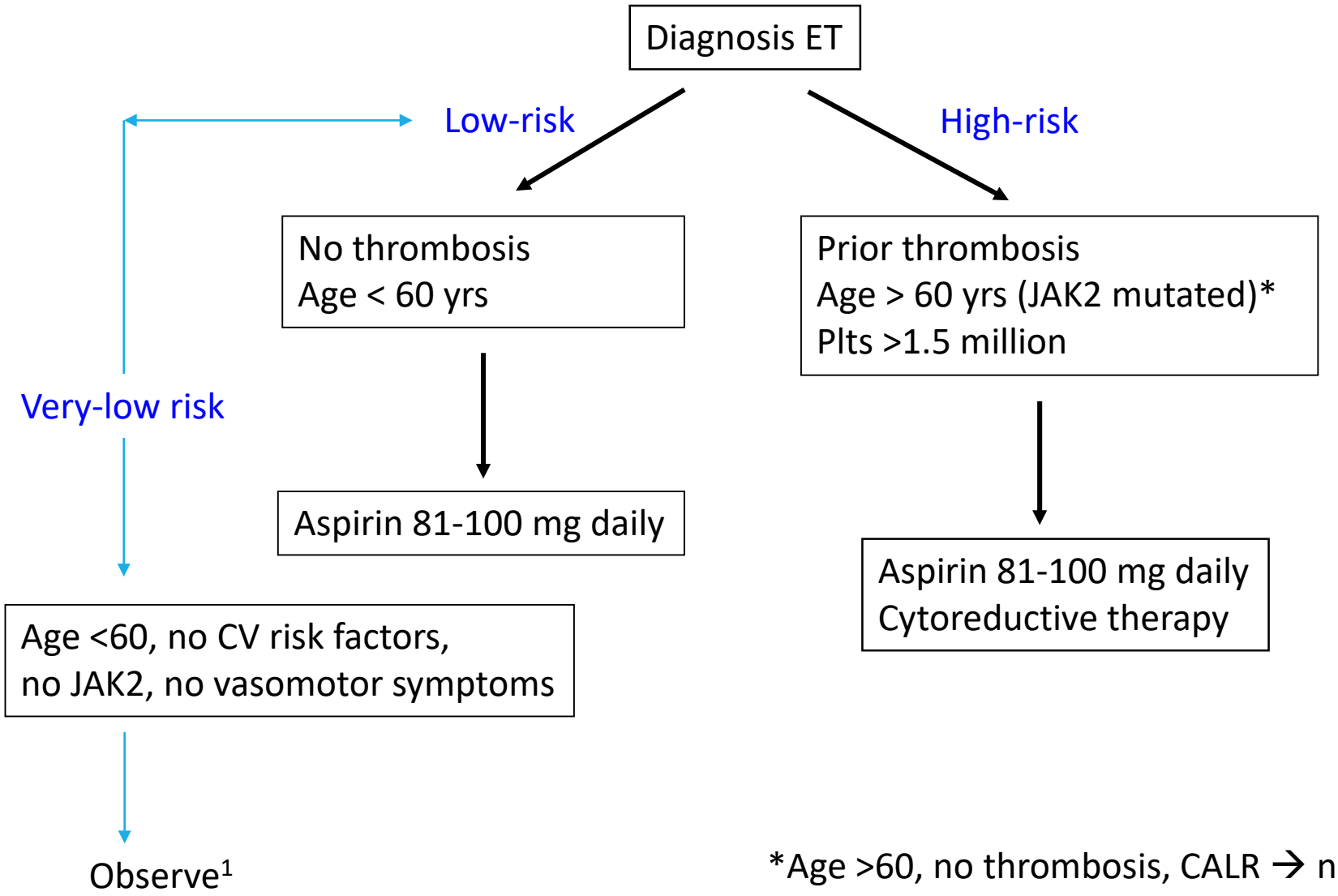


Klampfl T et al. *N Engl J Med* 2013;369:2379-2390

ET: Treatment Options

- Observation
- Aspirin
- Hydroxyurea
- Interferon
- Anagrelide
- ~~Ruxolitinib~~

Treatment Recs for ET

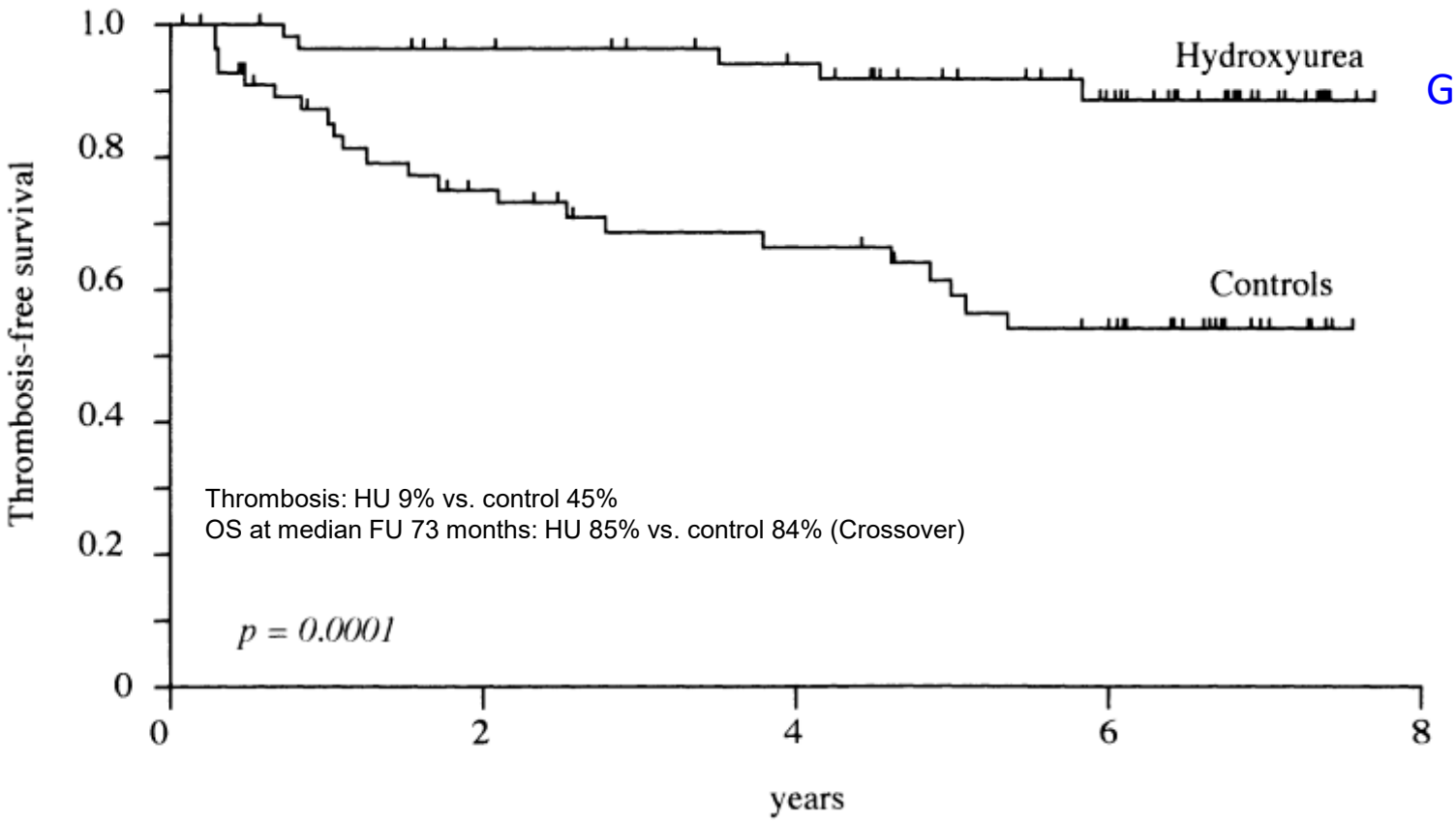


*Age >60, no thrombosis, CALR → no HU?

1 Ruggeri M et al. Br J Haematology. 1998l 103 (3): 772.

Beer et al. *Blood*. 2011;117:1472-1482
Alvaraz-Larrán et al. *Blood*. 2010;116:1205-1210

Hydrea in High-Risk ET: RCT

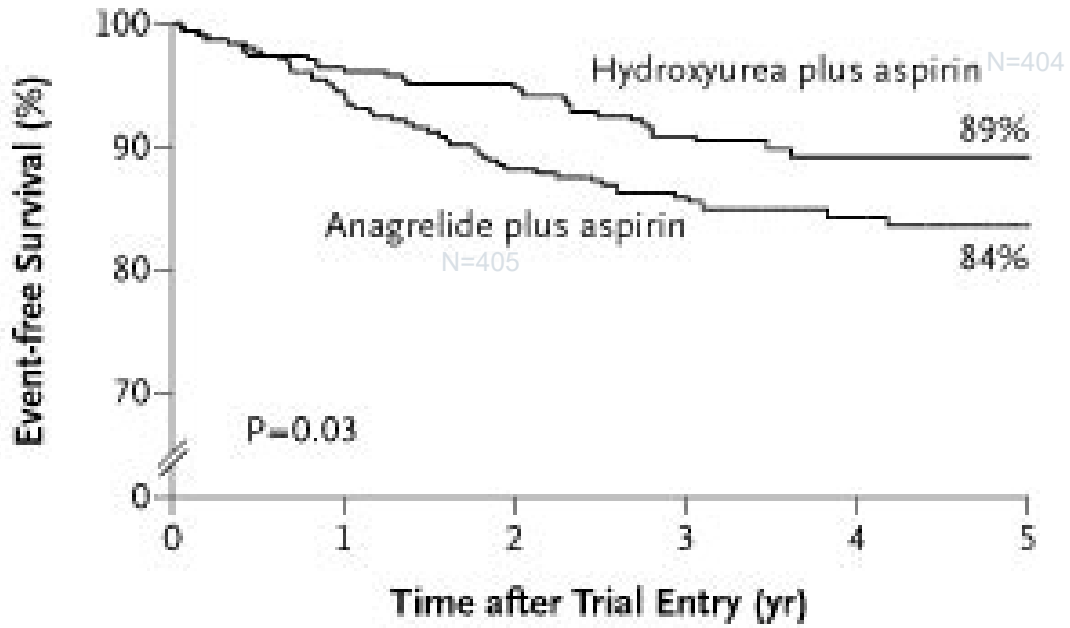


Goal plt <600K

Age > 60 or previous thrombosis and plt ≤ 1.5 million

Cortelazzo et al. *N Engl J Med.* 1995;332:1132
Finazzi et al. *Br J Haematol.* 2000;110:577-583

Hydrea vs. Anagrelide (+ASA)



No. at Risk

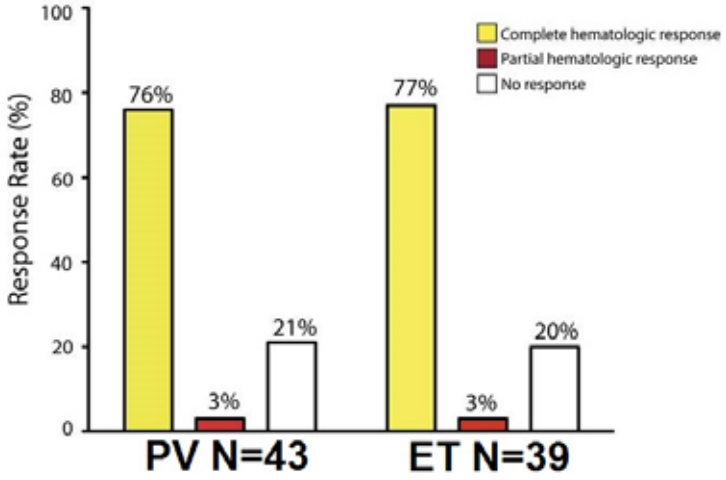
Hydroxyurea plus aspirin	404	388	298	204	129	57
Anagrelide plus aspirin	405	379	272	190	119	52

Composite endpoint: arterial and venous thrombosis, hemorrhage, death from vascular causes

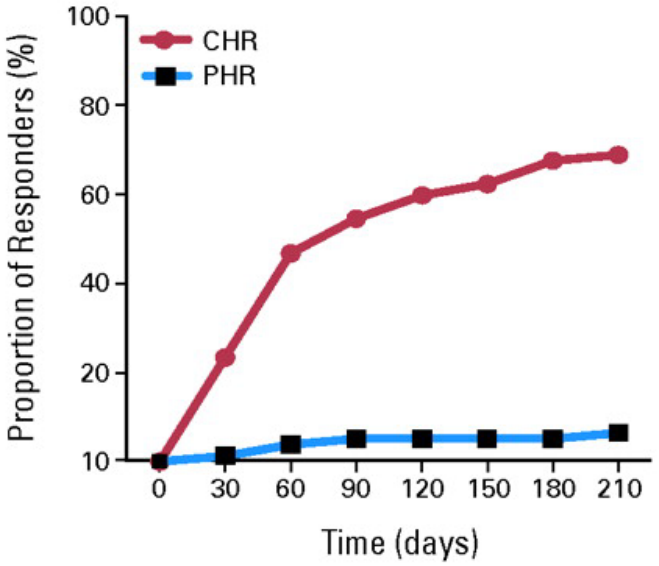
Anagrelide-treated patients had a significantly greater increase in bone marrow reticulin and a higher rate of transformation into myelofibrosis at five years (7 versus 2 percent, odds ratio 2.9, 95% CI 1.2-6.9)

Harrison et al. *N Engl J Med.* 2005;353:33-45
Gisslinger et al. Blood. 2013;121:1720-1728

PEG-IFN-α-2a



Hematologic Response



Molecular Response

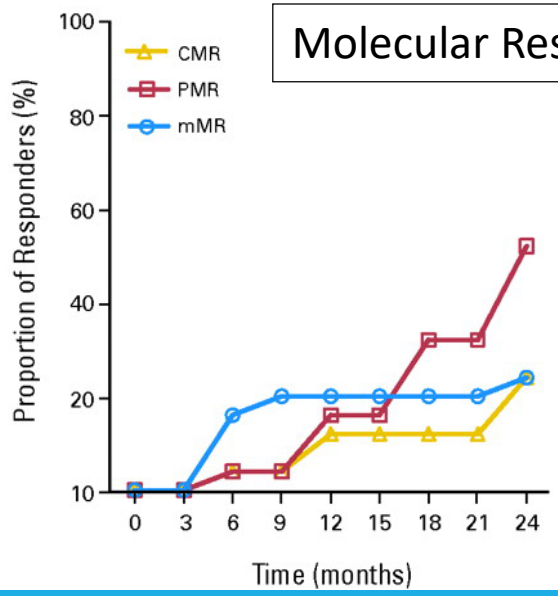


Table 2. Molecular response rates to PEG-IFN-α-2a therapy

*JAK2*V617F allele burden	PV (n = 40) number (%)	ET (n = 18) number (%)
CMR (undetectable)	7 (18)	3 (17)
PMR (>50% decrease)	14 (35)	6 (33)
mMR (20%-49% decrease)	3 (8)	3 (17)
No response	16 (40)	6 (33)

*Gowin et al. *Haematologica* 2012;97:1570-1573

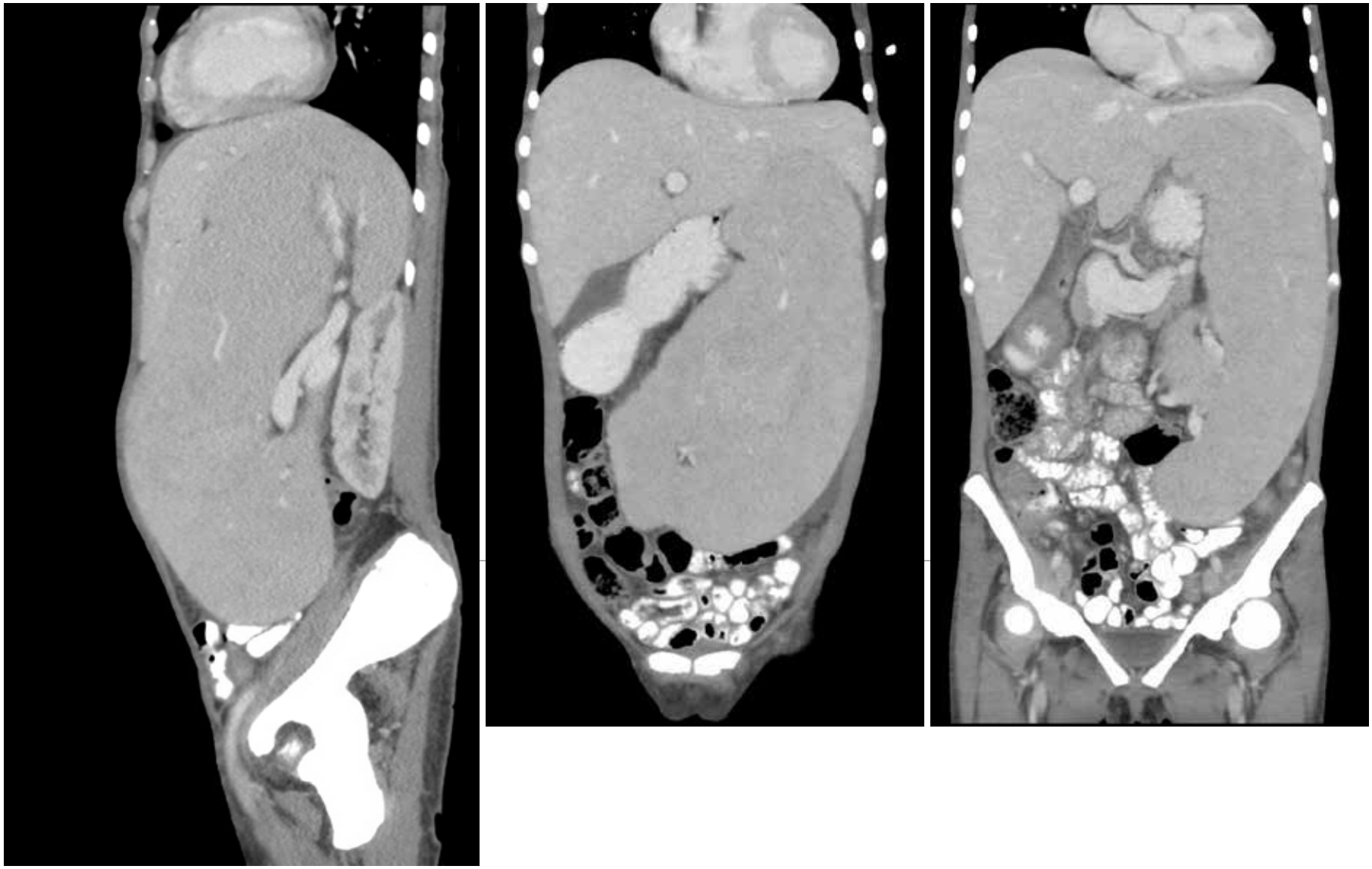
Quintás-Cardama et al. *J Clin Oncol*. 2009;27:5418-5424
Quintás-Cardama et al. *Blood*. 2013;122:893-901

Case 3

55 yo F with no PMH p/w bilateral leg swelling and DOE. Did not respond to herbal tea/supplements/CBD oil

- ROS: 20 lb wt loss/2 months, night sweats
- PE: tachycardia, holosystolic murmur, JVD, LE edema, splenomegaly
- Labs: Hgb 3.4, WBC 5.9, plts 79, normal BMP, ferritin 487, iron sat 38%, B12 548, folate >24, LDH 584, INR 1, Hapto 64, normal BR, smear: tear drop cells
  - → 13 units of PRBCS
  - CT Abdomen
  - Bone marrow biopsy

CT Abdomen



Bone marrow biopsy

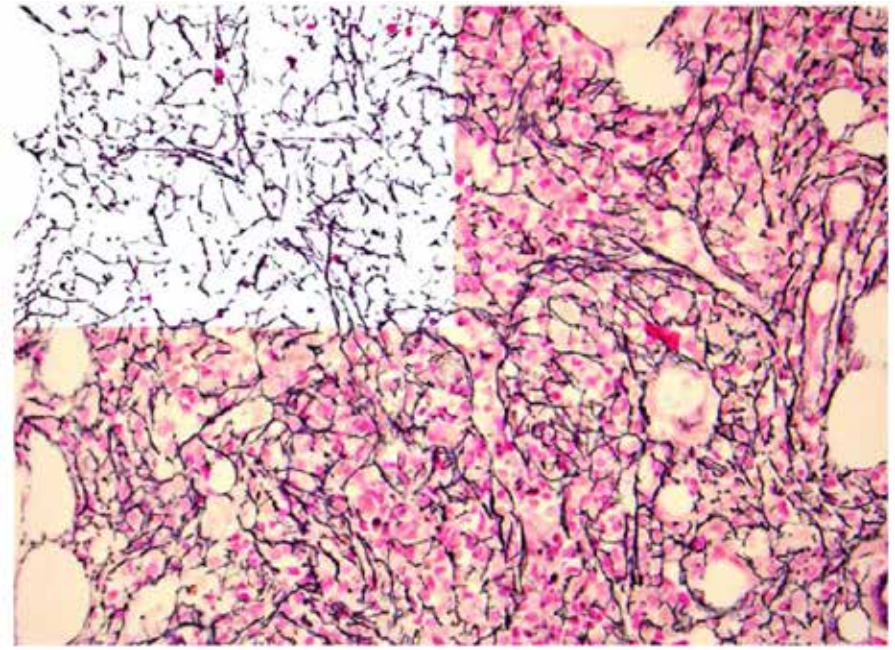
Hypercellular 90%; Megakaryocytic atypia

WHO Grade 3/3 fibrosis

No increased blasts on morphology or flow

Cytogenetics: 46, XX, del(7)(q11.2q22)[4]/46, XX[2]

+ JAK2 V617F and ASXL1 mutation



MF Diagnostic Criteria

WHO Criteria: Primary MF

Major criteria *(all 3 major + 1 minor)*

- Megakaryocyte proliferation and atypia with reticulin or collagen fibrosis grade 2 or 3
- Does not meet WHO criteria for other myeloid disorders (ET, PV, CML, MDS)
- Clonal marker (*JAK2*, *MPL*, *CALR*), presence of another clonal marker, or absence of reactive fibrosis §

Minor criteria *(2 consecutive determinations)*

- Increase in serum LDH >ULN
- Palpable splenomegaly
- Leukocytosis (≥11x10^9/L)
- Anemia
- Leukoerythroblastosis

§ infection, autoimmune, chronic inflammatory, hairy cell leukemia or other lymphoid neoplasm, met malignancy, or toxic chronic myelopathies

IWG Criteria[2]: Post-ET MF & Post-PV MF

Major criteria *(all required)*

- Previous diagnosis of ET or PV
- Grade 2-3 bone marrow fibrosis (on 0-3 scale) or Grade 3-4 bone marrow fibrosis (on 0-4 scale)

Minor criteria *(must meet 2)*

- ≥5 cm increase in palpable splenomegaly or new splenomegaly
- Leukoerythroblastosis
- One or more constitutional symptoms
- Increase in serum LDH **(Post-ET MF only)**
- Anemia with a Hgb ≥2 mg/mL decrease from baseline **(Post-ET MF only)**
- Anemia or sustained loss of requirement for either cytoreductive treatment or phlebotomy **(Post-PV MF only)**

[1] Arber, et al. *Blood*. 2016;127(20):2391-2405
[2]Barosi G, et al. *Leukemia*. 2008;22(2):437-438.

MF Disease Features

85% or more of MF patients present with palpable splenomegaly at the time of diagnosis[1]

60% to 80% of MF patients report spleen-related symptoms[2]

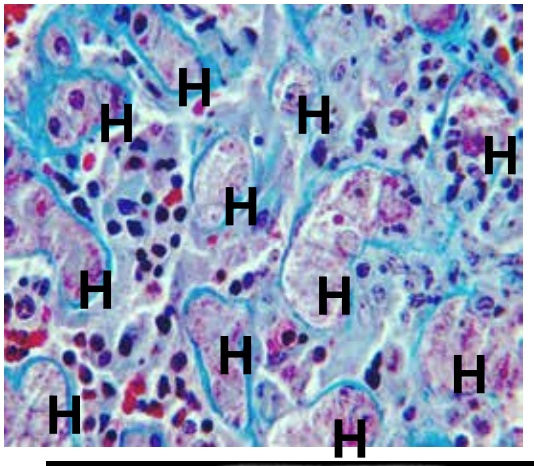
- Abdominal pain/discomfort, early satiety

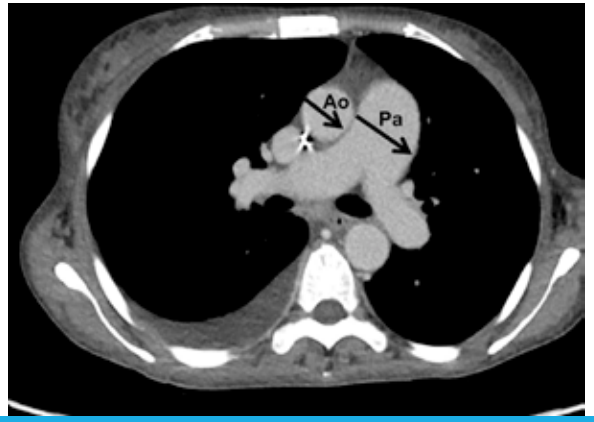
Other MF symptoms that can be present include[3]

- Pruritus- 50%
- Night sweats – 56%
- Bone pain – 47%

Extramedullary features:

- Sinusoidal hepatic fibrosis
- Extramedullary hematopoiesis (collage deposition blue)
- Pulmonary and portal HTN





Pictures courtesy of G.McDonald and R Salit

[1]Barosi G. *J Clin Oncol*. 1999;17:2954-2970.
[2]Scherber RM, et al. *Blood*. 2011;118(2):401-408.
[3]Mesa RA, et al. *Leuk Res*. 2009;33:1199-1203.

PMF - Risk Classification

Age > 65 years (1)

Constitutional symptoms (1)

Hgb < 10 /L (2)

WBC > 25,000 (1)

PB blasts ≥ 1% (1)

Abnormal chromosomes*

Plts <100,000

Transfusion dependence

Absence of CALR

High-risk mutations^

Marrow fibrosis ≥ grade 2

HMR genes: ASXL1, EZH2, SRSF2, IDH 1/2, U2AF1

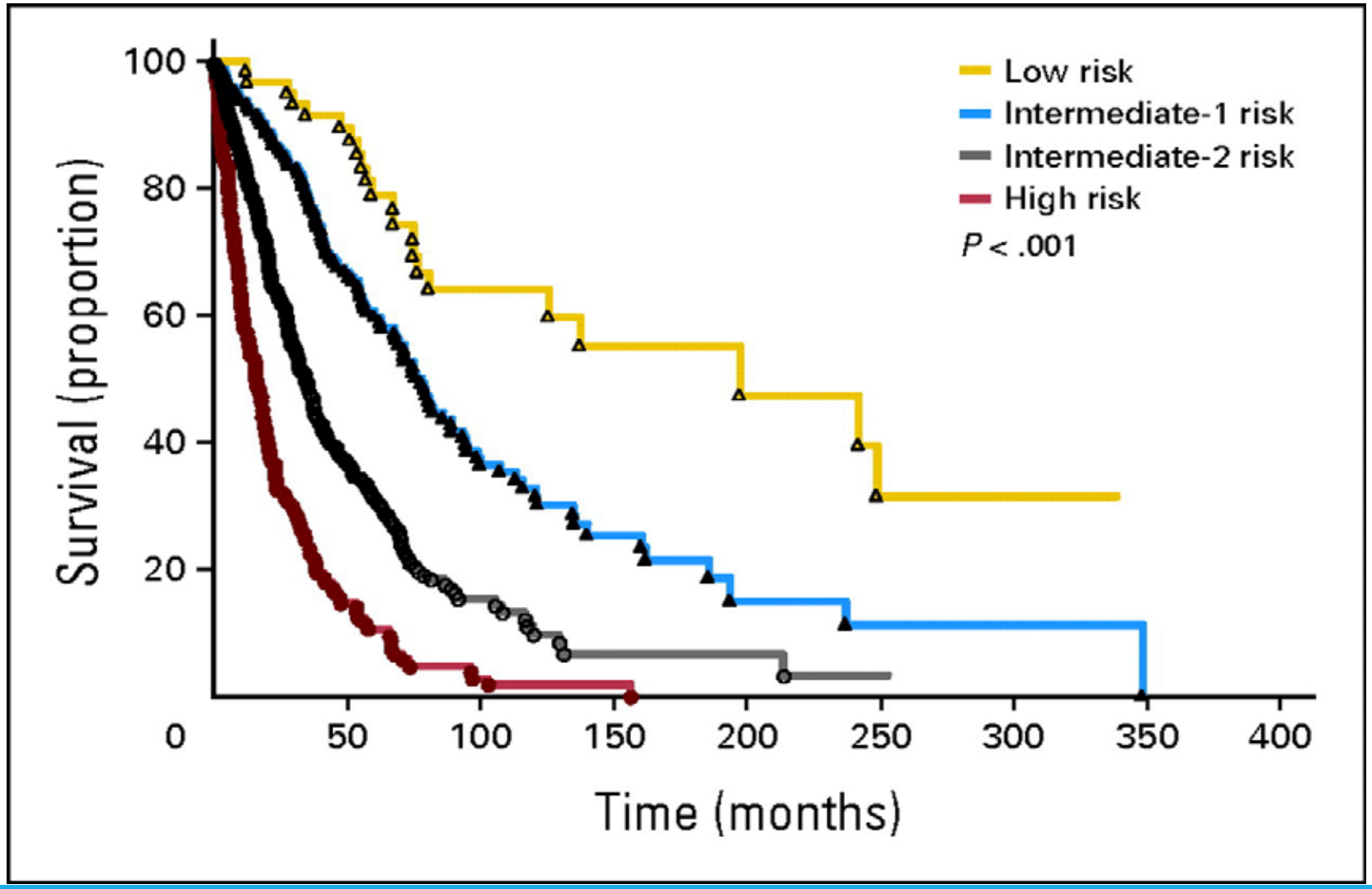
DIPSS

DIPSS-plus

MIPSS70-plus

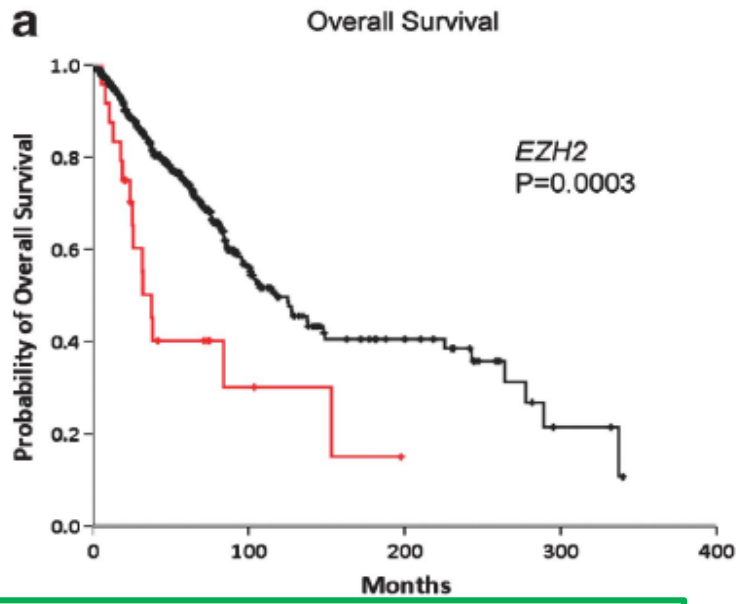
*+8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3) or 11q23 rearrangement ^ any abnormal karyotype other than normal or sole abnormalities in 20q-, 13q-, +9, chromosome 1 translocation/duplication, -Y or sex chromosome abnormality other than –Y

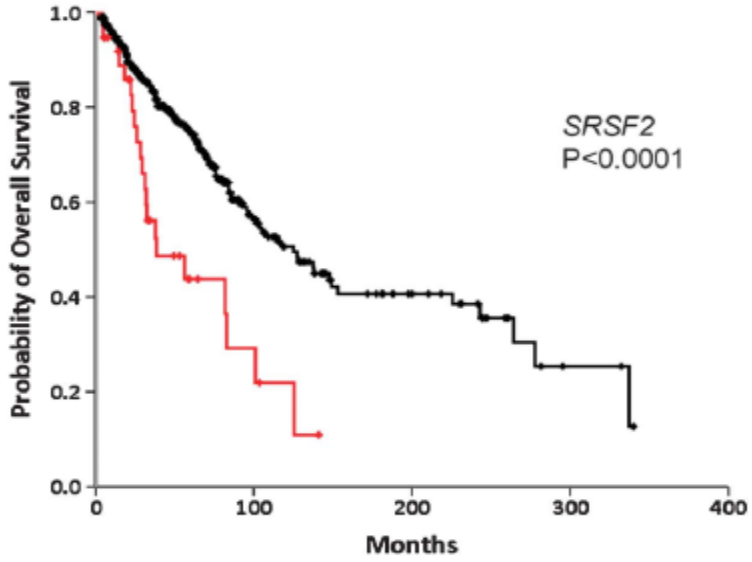
DIPSS-plus and Survival

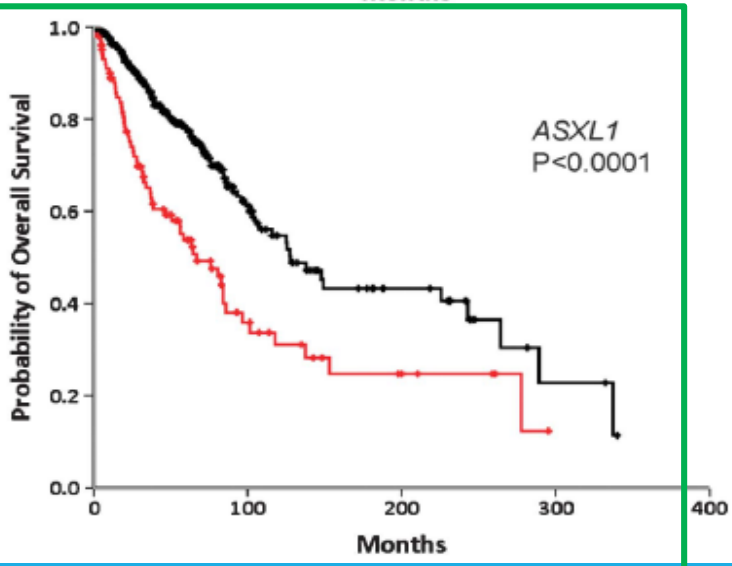


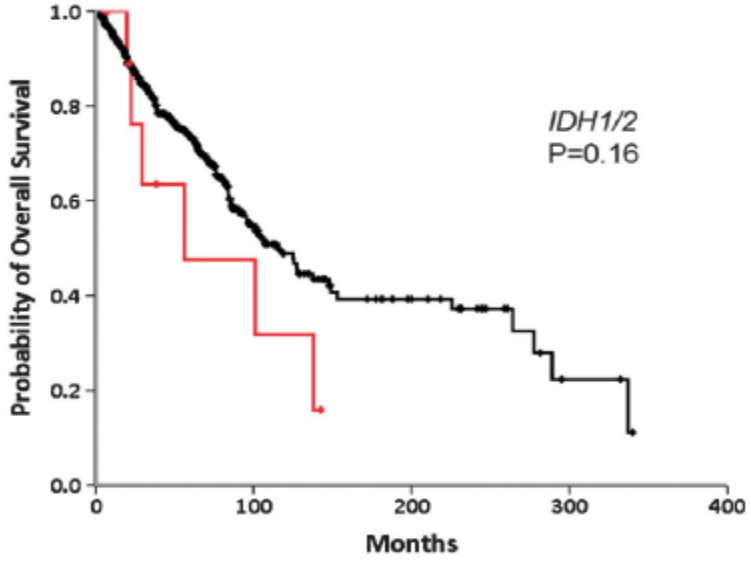
N. Gangat et al, JCO 29: 392, 2010

Overall Survival by Mutation









WT

Mut

Vannucchi et al. 2013. Leukemia. 27: 1861

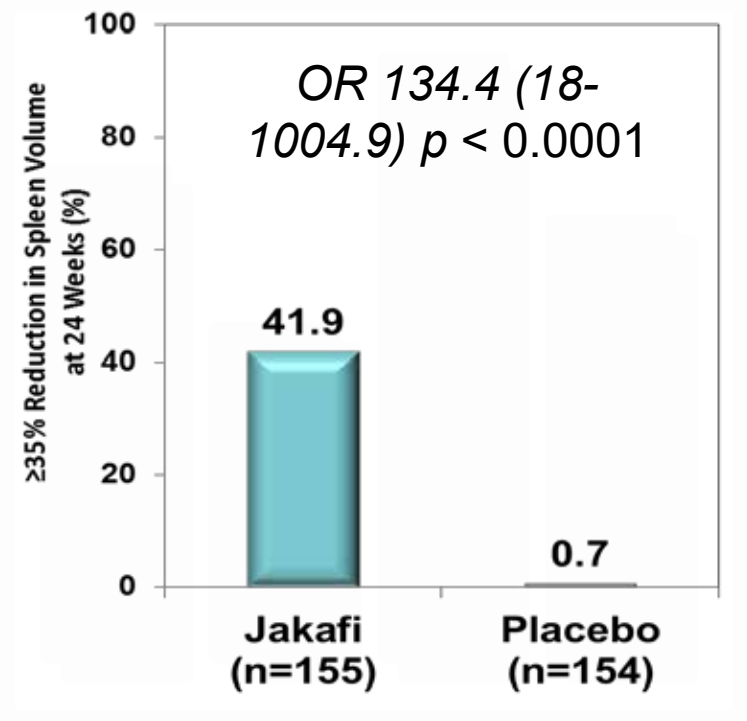
Treatment Options

- Active surveillance in low-risk disease
- Hydrea for proliferative disease, splenomegaly
- Anemia: Lenalidomide/prednisone, danazol
- Newest options:
  - Ruxolitinib (Jakafi) – JAK1/2 inhibitor: best for splenomegaly, constitutional symptoms, pruritis
  - Fedratinib (Inrebic) – JAK2 inhibitor; just approved
- Allogeneic stem cell transplant for higher risk disease (generally DIPSS int-2 and high-risk)

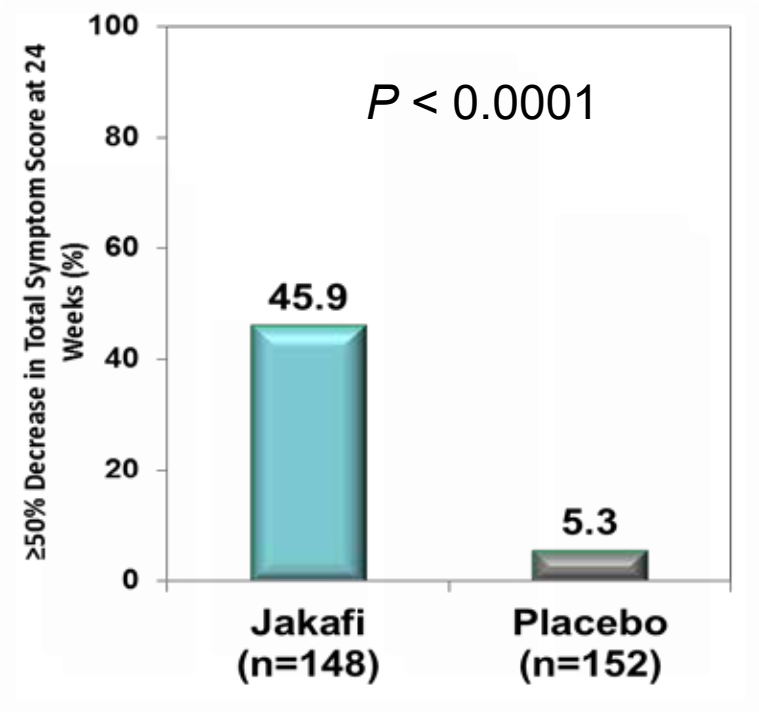
Kroger et al. Blood 2015; 125 (21): 3347-3350

COMFORT-1 : MF patients randomized to Ruxolitinib or placebo

DECREASE SPLEEN VOLUME



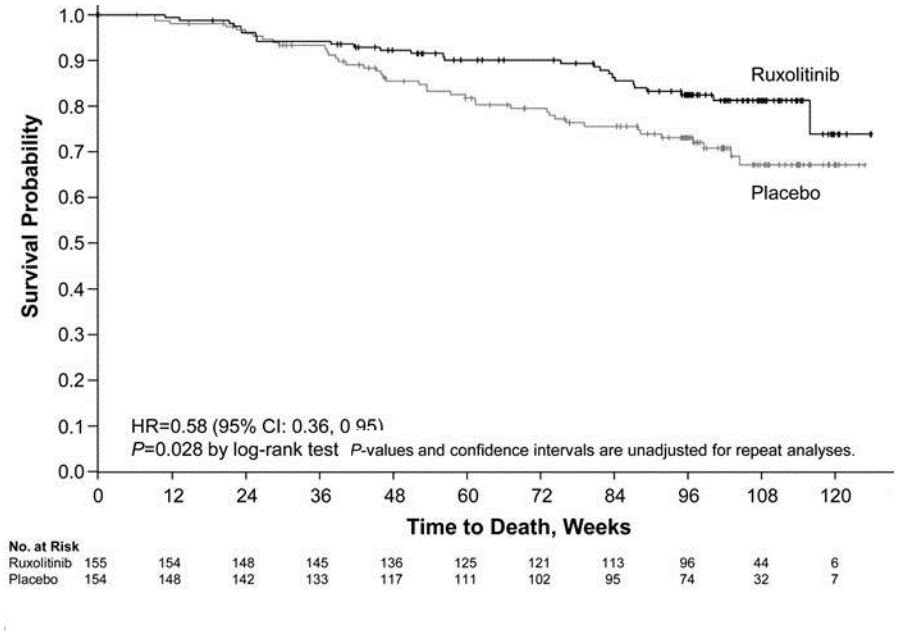
IMPROVEMENT MF SYMPTOMS



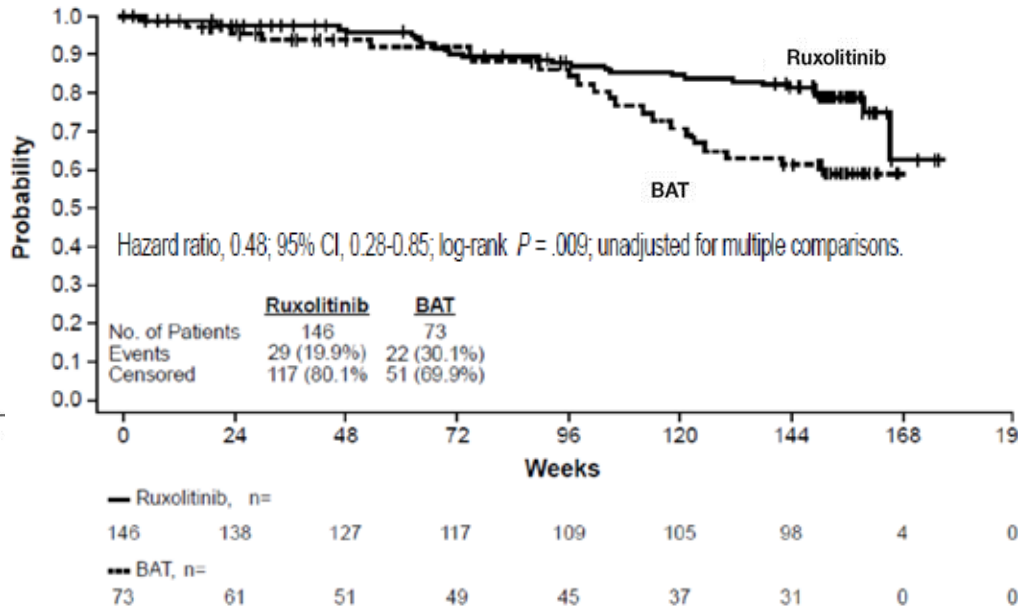
Verstovsek et al. *N Engl J Med.* 2012;366:799-807
Scherber et al. *Blood.* 2011;118:401-408

Comfort 2: MF patients randomized to Ruxolitinib vs. BAT

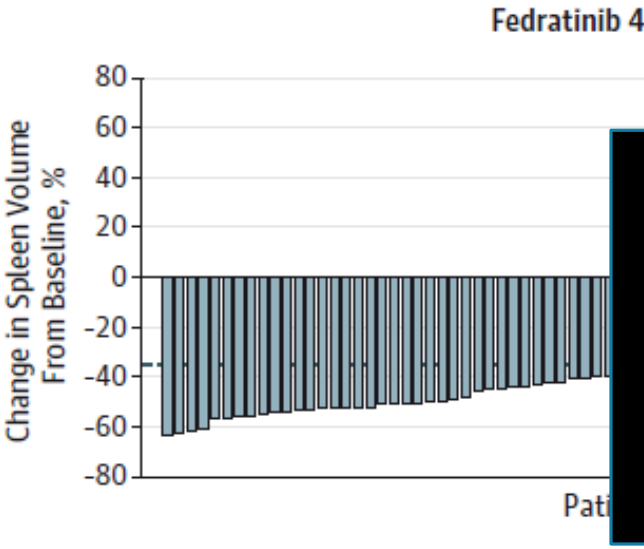
COMFORT 1



COMFORT 2



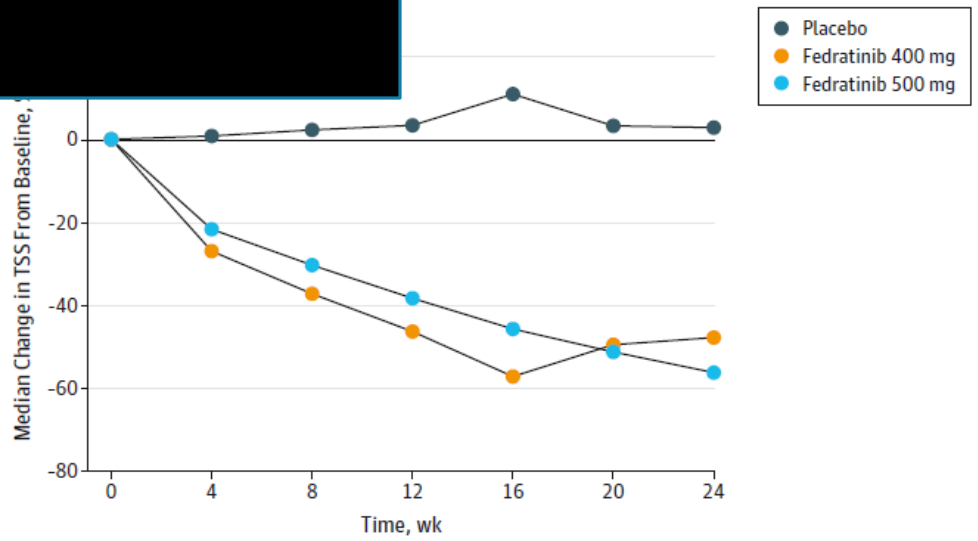
Fedratinib: JAKARTA Trials



37% >35% spleen volume reduction vs. 1% placebo; med duration 18 mo

BLACK BOX WARNING:
WERNICKE ENCEPHALOPATHY:
CHECK THIAMINE level (B1)
PRIOR TO STARTING THERAPY

40%: > 50% reduction in MF-TSS vs. 9% placebo

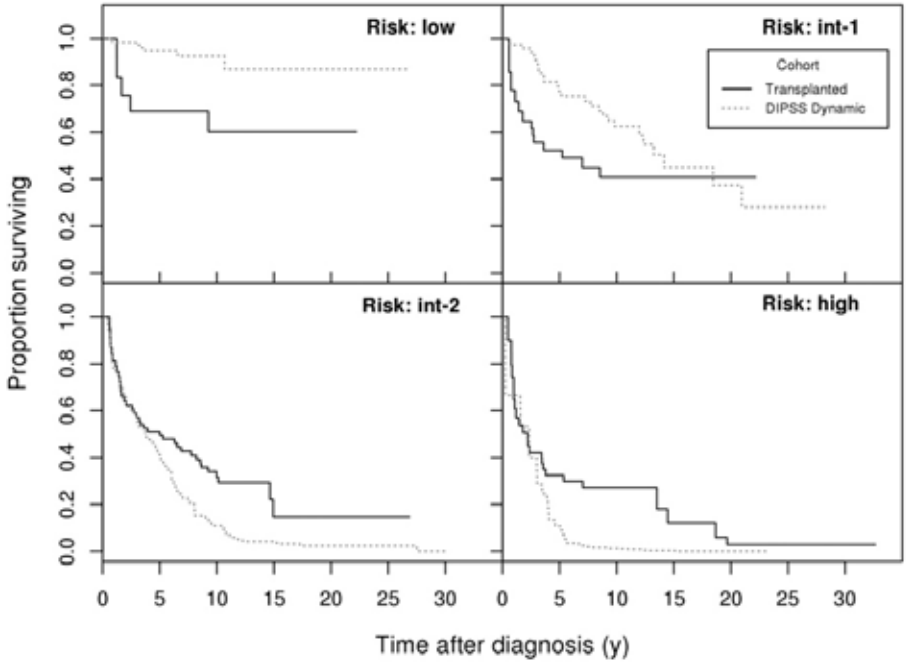


Pardanani A. et al. JAMA Oncology 2015; 1 (5): 643-651.
Harrison C et al. Lancet Haematology 2017; 4: e317-24

So, Whom and When to Transplant?

Disease characteristics:

- DIPSS int 1 – some patients (adverse risk mutations, 2+ mutations?, triple negative disease?) will benefit
- DIPSS int 2/high –indication for HCT
- Disease progression – HCT only real option
- Loss of response to JAK inhibitor



Kroger et al, Blood 2015; 125 (21): 3347-3350

Risk Factors for transplant

Comorbidities

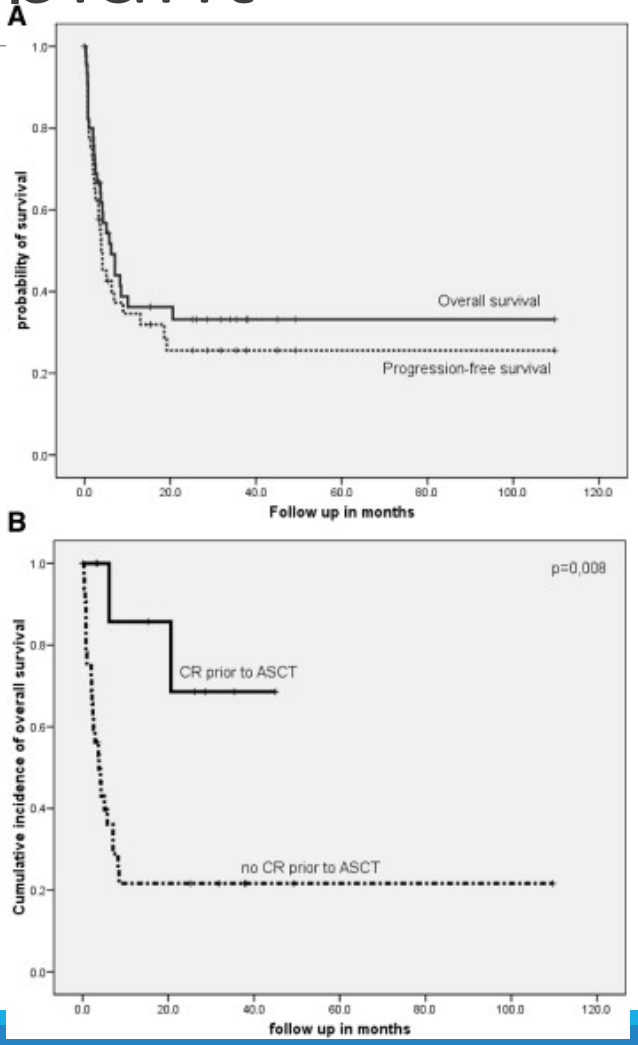
Pulmonary or portal HTN

Extramedullary hematopoiesis/disease

Massive splenomegaly (>22 cm)

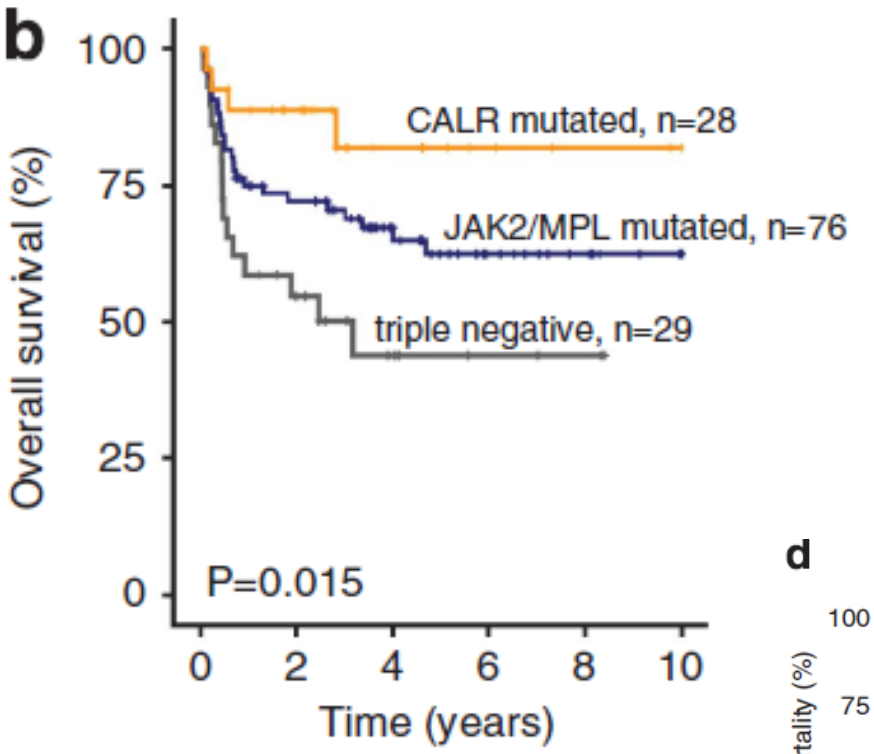
Adverse mutations

Leukemic transformation



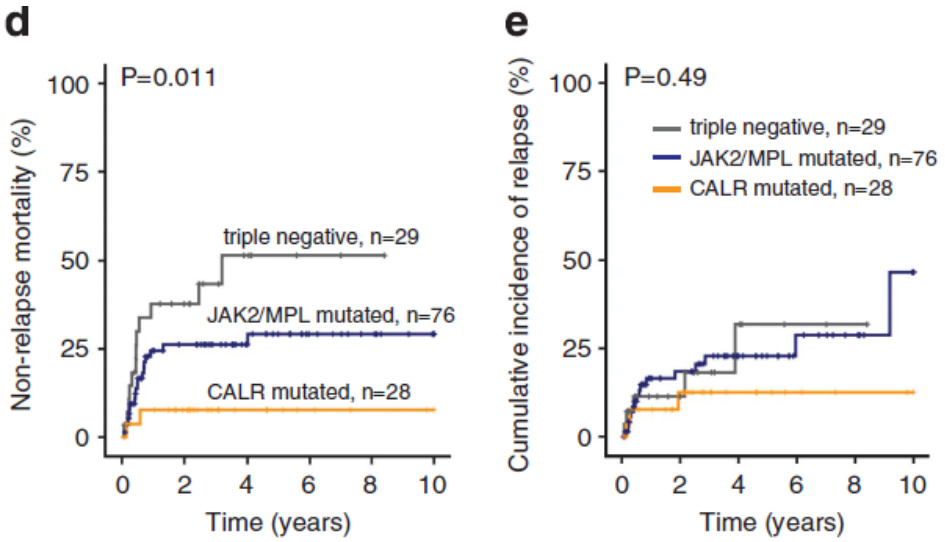
Alchalby H et al. Biology of Blood and Marrow Transplant 2014; 20 (2): 279-81.

Mutations and transplant outcome



CALR mutated patients have prolonged OS after HCT, both due to decreased relapse and non-relapse mortality

Triple-negative patients do worst



Case 3

High-risk DIPSS plus score

No response to Ruxolitinib (low dose due to baseline plts)

Referred to transplant, still with massive splenomegaly up to 27 cm, cachexia at 38 kg (BMI 15)

Patient had splenectomy given size and severe malnutrition, tolerated it well

Now >1 year s/p matched, unrelated donor stem cell transplant, doing well

MPN-accelerated/blast phase

MPN-AP (10-19% blasts) and MPN-BP (≥20% blasts) difficult to treat

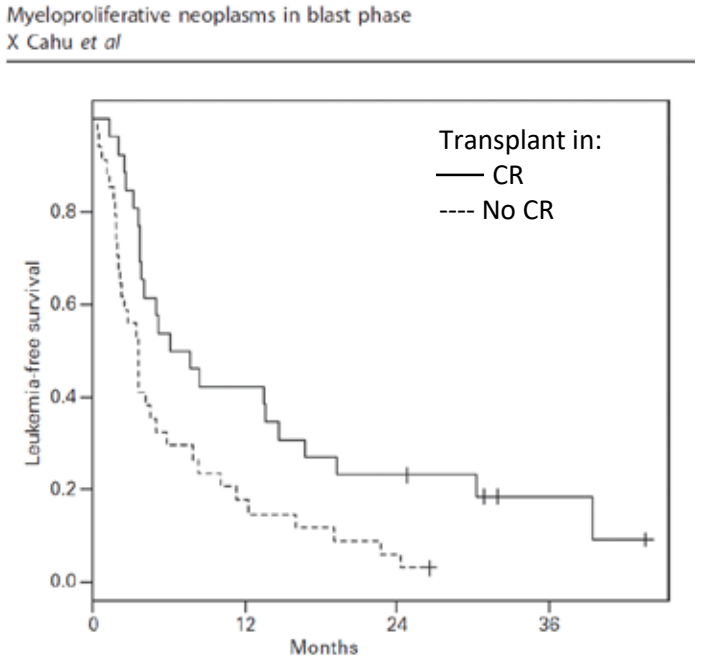
- ~15% PV, 3-5% ET, 20% MF will progress to AML

Sequelae of their chronic underlying MPN (eg splenomegaly, fibrosis) often complicate their treatment

Prognosis in absence HCT 3-6 months

Treatment options:

- Hypomethylating therapy (HMA)
- AML-induction type therapy
- Early clinic experience with HMA+ruxolitinib



Tefferi et al. Leukemia 2018; 32(5): 1200-1210; Tam et al., Blood 2008; 112 (5): 1628-1637; Alchalby et al, Biol Blood Marrow Transplant 201420(2): 279-281; Cahu Bone Marrow Transplant 2014;49 (6): Bose et al. Leukemia 2020; epub; Assi et al. AJH 2017; 93: 277-285; Rampal et al. Blood Advances 2018; 2(24): 3572-3580.

Mastocytosis

No longer consider an MPN in WHO 2016

Cutaneous mastocytosis- limited to skin

Systemic mastocytosis involve extracutaneous organs

- >70% adults have D816V KIT mutations
- Systemic mastocytosis with an associated hematologic neoplasm (SM-AHN)

Skin, GI, neuropsychiatric, anaphylaxis, episodic mediator release:

- episodes of vasodilation, hypotension, flushing, pruritus, syncope, abdominal pain, nausea, vomiting, diarrhea, fatigue, and headache

Midostaurin is a new treatment option

Chronic Neutrophilic Leukemia (CNL)

WHO Criteria: CNL

1) PB WBC >25 x10^9/L
2) Hypercellular BM
3) Not meeting WHO criteria for CML, PV, ET, PMF
4) No PDGFRA, PDGFRB, FGFR1, or PCM1-JAK2
5) Presence of CSF3R T6181 or other activating CSF3R mutation
   OR if no CSF3R mutation: persistent neutrophilia >3 months, no cause of reactive neutrophilia, splenomegaly, or clonality of myeloid cells by cytogenetic or molecular studies

Mature granulocytic proliferative in blood and marrow, hepatosplenomegaly
Short survival (<2 years)
Treatment (?): Ruxolitinib, interferon, dasatanib

Arber et al. *Blood*. 2016;127(20):2391-2405.

CMML

WHO Criteria: CMML[1]

1) Persistent (>3 months) PB monocytosis ≥ $1x10^9$/L, with monocytes accounting for ≥ 10% of the WBC count
2) Not meeting WHO criteria CML, PMF, PV, ET*
3) No evidence of PDGFRA, PDGFRB, FGFR1, PCM1-JAK2
4) <20% blasts/blast equivalents in blood and marrow
5) Dysplasia in ≥1 myeloid lineages, unless:
    1) There is a clonal cytogenetic/molecular abnormality §
    2) Monocytosis persisted >3 months
    3) Reactive causes excluded

*Monocytosis can develop with MPNs, so prior documented MPN excludes CMML

§ Commonly: *TET2*, *SRSF2*, *ASXL1*, *SETBP1*

Presentation: leukocytosis, cytopenias, splenomegaly (25%), hepatomegaly, lymphadenopathy, effusions, constitutional symptoms

Stratification:

CMML-0/1/2 (blast percentage <5/5-9, 10-19% in the marrow)
Myelodysplastic CMML vs myeloproliferative CMML (WBC < 13 vs >13 x 10^9/L)
Risk models: CPSS-Mol[2]: wbc, cytogenetics, PRBC dependence, mutational analysis

Treatment for symptoms or cytopenias: hydrea, hypomethylating agents, induction chemo, HCT

Arber et al. *Blood*. 2016;127(20):2391-2405; Elena C et al, Blood 2016; 128 (10): 1408-17).

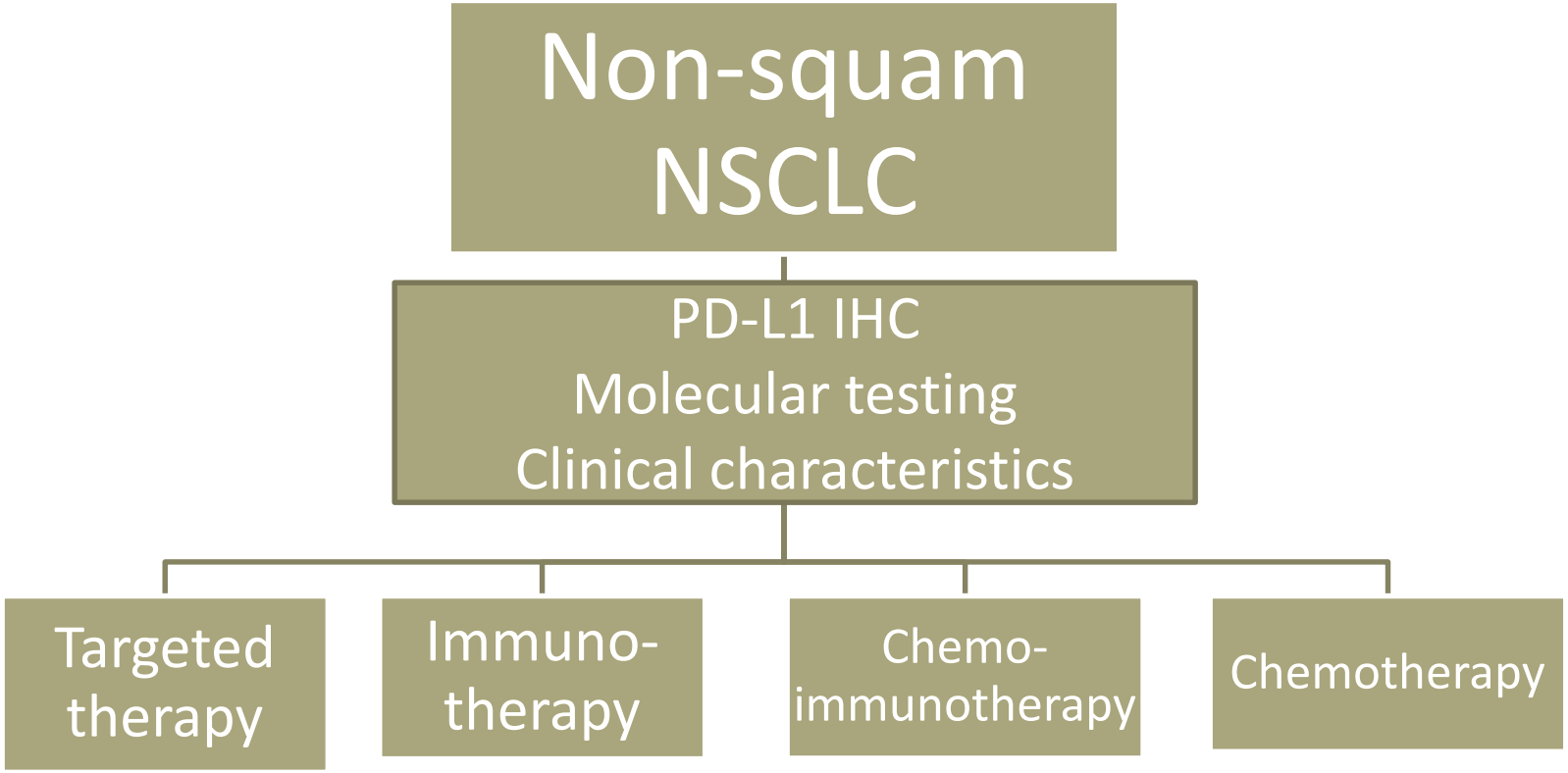
Comprehensive Hematology & Oncology Review : Metastatic NSCLC

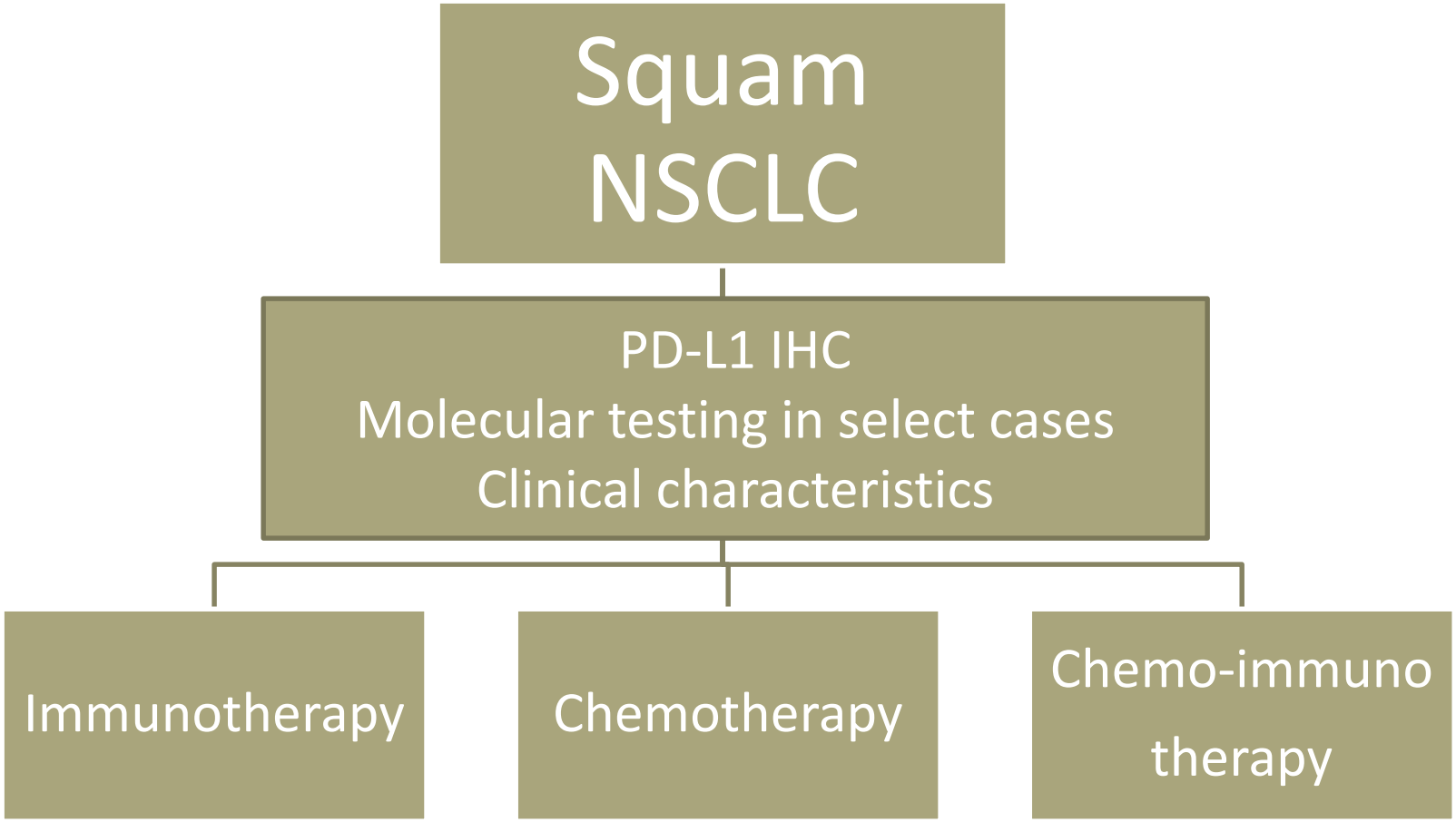
Christina Baik MD, MPH
University of Washington
Seattle Cancer Care Alliance
Fred Hutchinson Cancer Research Center

August 2020

Outline

- Targeted therapy
- Immune checkpoint inhibitor therapy
  - Monotherapy
  - Chemo-immunotherapy
- Chemotherapy


Non-squam NSCLC
PD-L1 IHC
Molecular testing
Clinical characteristics
Targeted therapy
Immuno-therapy
Chemo-immunotherapy
Chemotherapy


Squam NSCLC
PD-L1 IHC
Molecular testing in select cases
Clinical characteristics
Immunotherapy
Chemotherapy
Chemo-immuno therapy

TARGETED THERAPY

Actionable molecular subtypes in lung adenocarcinoma (i.e. available FDA approved drugs in Aug 2020)

Alteration	Prevalence (estimates)
EGFR mutations (non-exon 20 insertion)	15-20%
ALK rearrangement	3-5%
ROS1 rearrangement	1-2%
BRAF V600E mutation	1-2%
NTRK rearrangement	<1%
MET exon 14 skipping mutation	3-4%
RET rearrangement	1-2%

MET exon14 skipping mutation

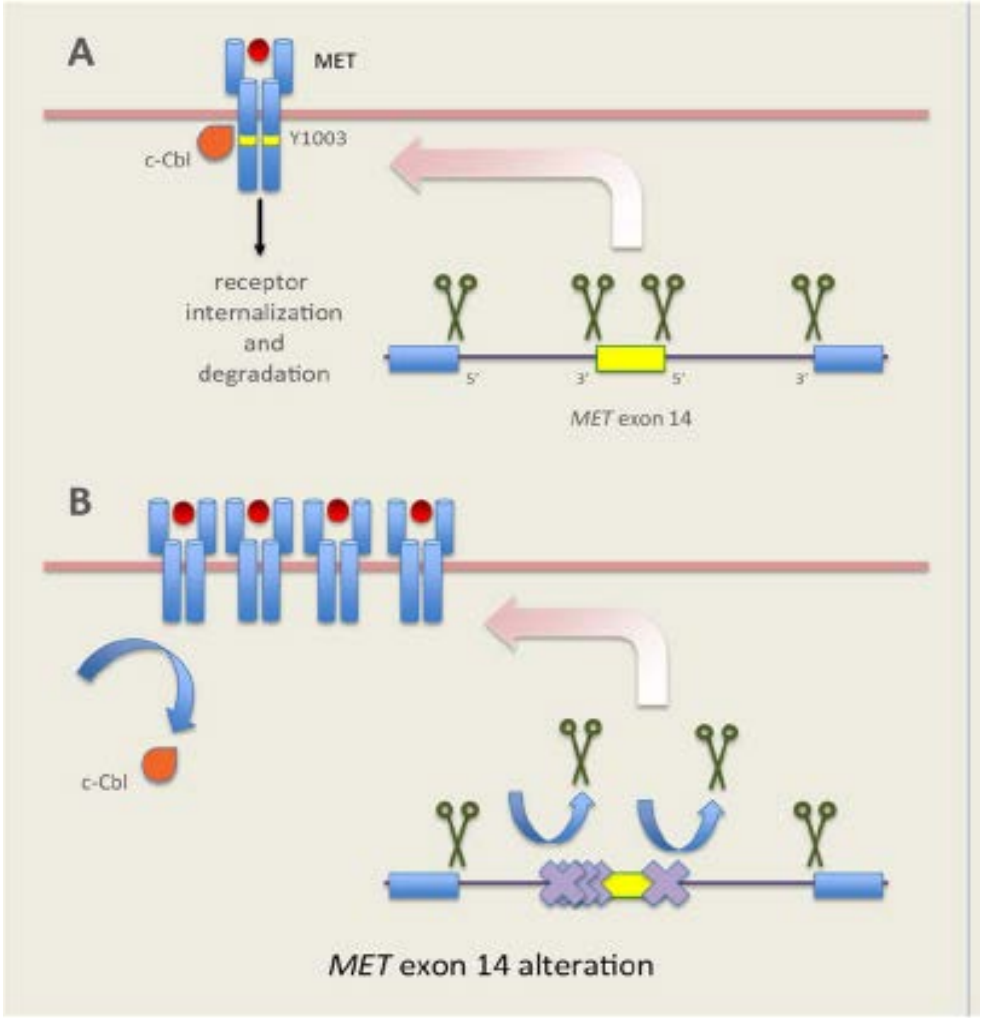
Clinical characteristics

- 3-4% of NSCLC
- Older patients
- Often observed in patients with smoking history
- Present in 20-30% of sarcomatoid histology

Characteristic	*MET* Exon 14 (n = 28)
Median age (range), years	72.5 (59-84)
Sex	
Male	9 (32)
Female	19 (68)
Smoking history, pack-years*	
Never-smoker	10 (36)
≤ 10	3 (11)
> 10	15 (53)
Race	
White, non-Hispanic	28 (100)
Asian	0 (0)
Black	0 (0)
White, Hispanic	0 (0)
Unknown	0 (0)
Histology	
Adenocarcinoma	18 (64)
Pleomorphic with adenocarcinoma component	4 (14)
NSCLC, poorly differentiated	5 (18)
Squamous	0 (0)
Adenosquamous	1 (4)

Drilon et al. JTO 2017; 12(1):15-26
Awad et al. JCO 2016; 34:721-730

MET exon14 skipping mutation

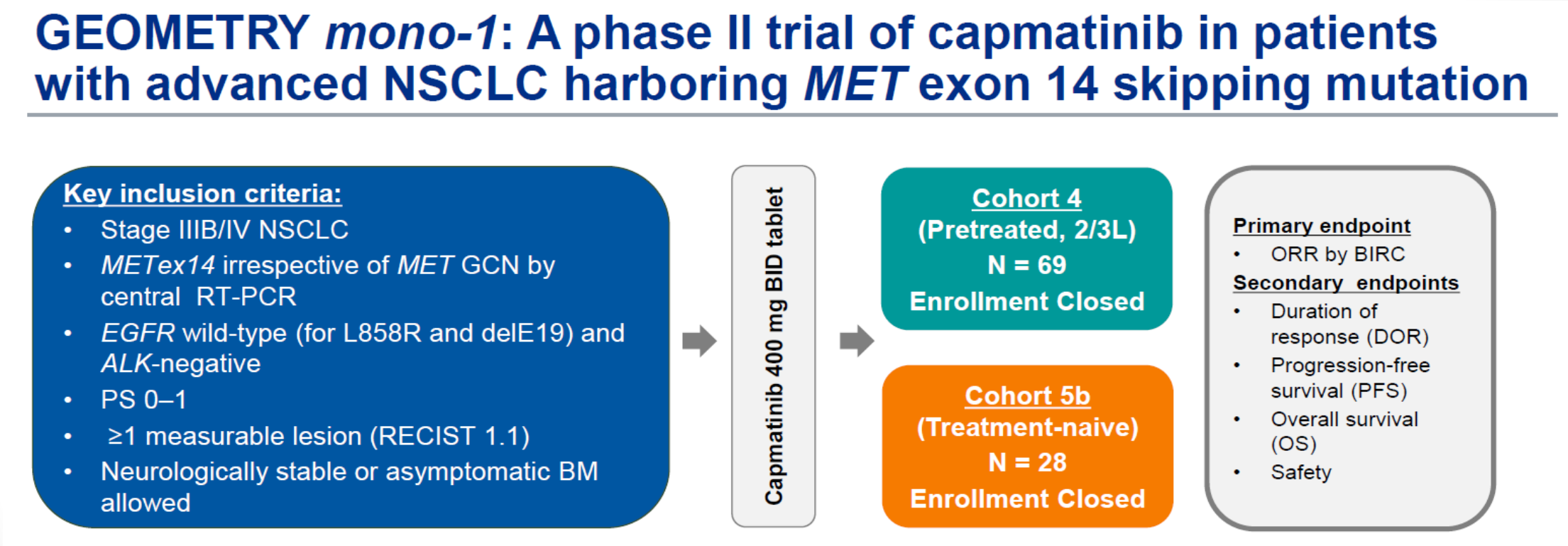


Drilon et al. JTO 2017;12(1): 15-26

- cMET: Transmembrane receptor tyrosine kinase
- Binding to ligand results in receptor activation and cell survival and proliferation
- cMET is degraded when c-Cbl binds to exon 14 region and results in ubiquitination
- In MET exon14 skipping (splice) mutation, there is abnormal splicing resulting in skipping of exon 14 which is the site of c-Cbl binding → less degradation and sustained cMET activation

MET exon14 skipping mutation

Capmatinib: First FDA approved MET inhibitor for MET exon14 mutation



Garon et al. Abs CT082 AACR 2020

MET exon14 skipping mutation - capmatinib

	Previously treated (n=69)	Treatment naïve (n=28)
ORR % (95% CI)	40.6 (28.9-53.1)	67.9 (47.6-84.1)
DCR % (95% CI)	78.3 (66.7-87.3)	96.4 (81.7-99.9)
DOR months (95% CI)	9.72 (5.55-12.98)	11.14 (5.55-NE)

ORR, overall response rate;
DCR, disease control rate; DOR, duration of response

Several other MET inhibitors under investigation: e.g. tepotinib, savolitinib, etc

Most common treatment related AEs (≥10%, all grades), n (%)	All Patients N = 334	
	All Grades	Grade 3/4
Any	282 (84.4)	119 (35.6)
Peripheral edema	139 (41.6)	25 (7.5)
Nausea*	111 (33.2)	6 (1.8)
Increased blood creatinine†	65 (19.5)	0
Vomiting*	63 (18.9)	6 (1.8)
Fatigue	46 (13.8)	10 (3.0)
Decreased appetite*	42 (12.6)	3 (0.9)
Diarrhea	38 (11.4)	1 (0.3)

Garon et al. CT082 AACR 2020

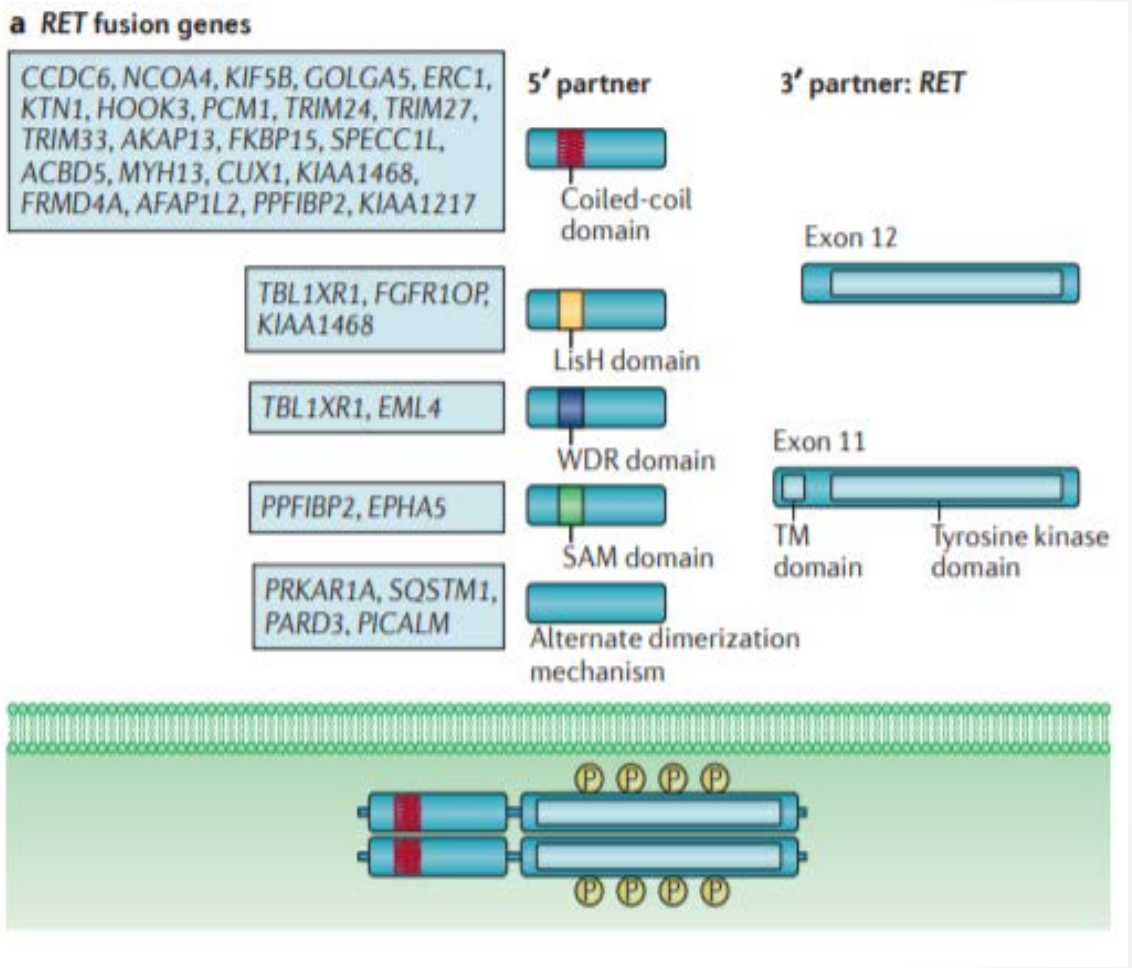
RET rearrangement

Clinical characteristics

- 1-2% of all NSCLC
- Mostly seen in never / minimal smokers

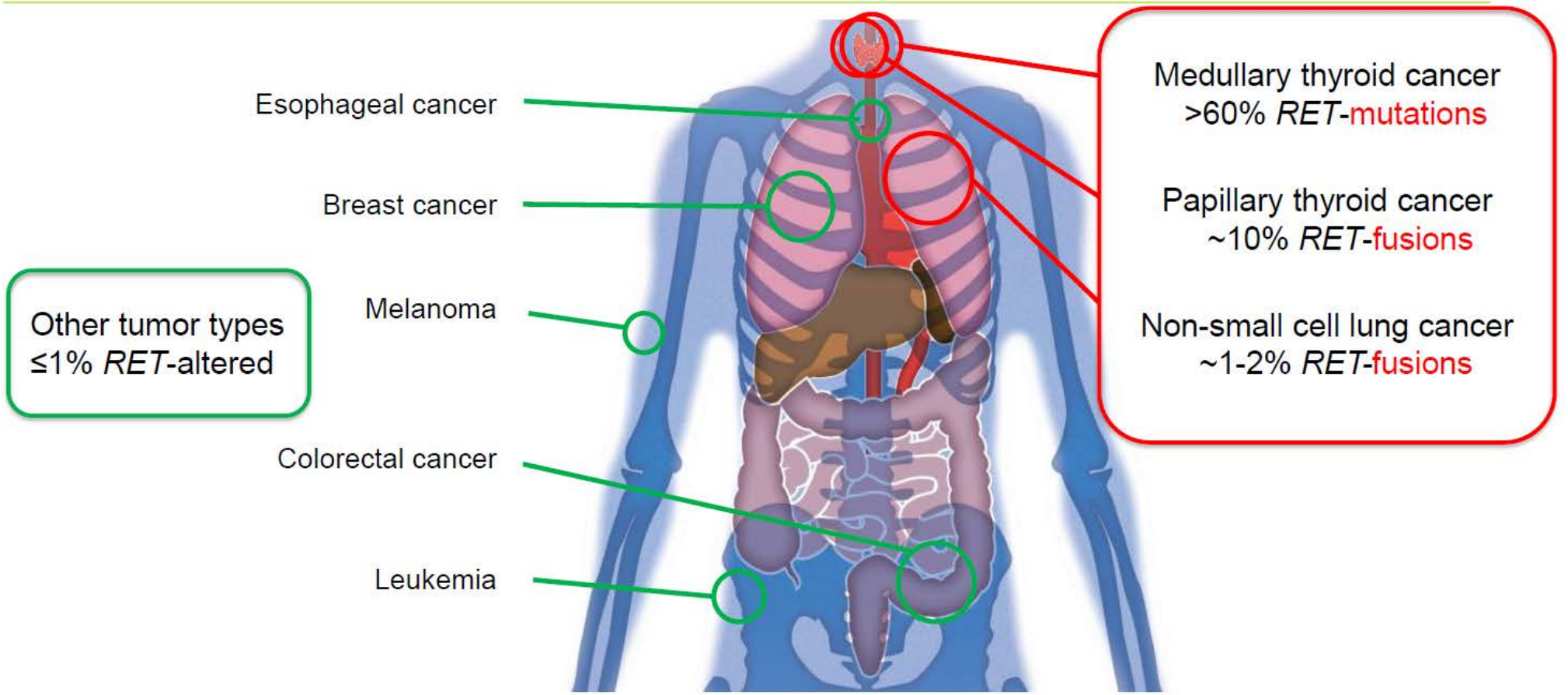
Mechanism of action

Receptor protein fuses with partner protein, inducing dimerization and activation



Drilon et al. Nat Rev Clin Onc 2018; 15:151

RET is a rare driver of multiple, diverse tumor types[1,2]



1. Drilon A et al. *Nat Rev Clin Oncol*. 2018;15:151-67 2.Kato S, et al. *Clin Cancer Res* 2017;23:1988-1997.

Subbiah et al. AACR 2018

RET rearrangement: Selpercatinib

Selpercatinib:

FDA approved in May 2020 for RET rearranged NSCLC / iodine refractory thyroid cancer and RET mutant medullary thyroid cancer

<u>LIBRETTO-001, phase 2 trial</u>
(n=253 NSCLC)

- ORR 68% (58-76)
- DOR 20.3 mos (13.8-24)
- PFS 18.4 mos (12.9-24.9)

Treatment emergent adverse events (mostly gr1-2)	
Dry mouth	32%
Diarrhea	31%
Hypertension	29%
Transaminitis	26-28%
Fatigue	24%
Constipation	22%
Headaches	20%
Nausea	19%
Peripheral edema	19%
Increased creatinine	18%

Drilon et al. WCLC 2019

Selective RET inhibitors

	selpercatinib[1]	pralsetinib[2]
ORR in naïve	85% (69-95)	71% (NA)
ORR in chemo-pretreated	68% (58-76)	60% (42-76)
PFS	18.4	NR
DoR	20.3	NR
Intracranial activity	91 (59-100)%	78 (NA)%
Safety (G3%)*		
HTN	14%	13%
Transaminitis	6-7%	3%
Anemia, Neutropenia	NA	7%, 13%
Drug discontinuation rate	1.7%	7%
Activity against MTC RET mutations	Yes	Yes
Tumor agnostic RET fusion activity	Yes	Yes

Doebele. WCLC 2019; Gainor et al. ASCO 2019

EGFR mutation+ NSCLC

- 10-15% NSCLC
- More common in never smoker, Asians, women
- Most common mutations: Exon 19 deletion and exon 21 L858R

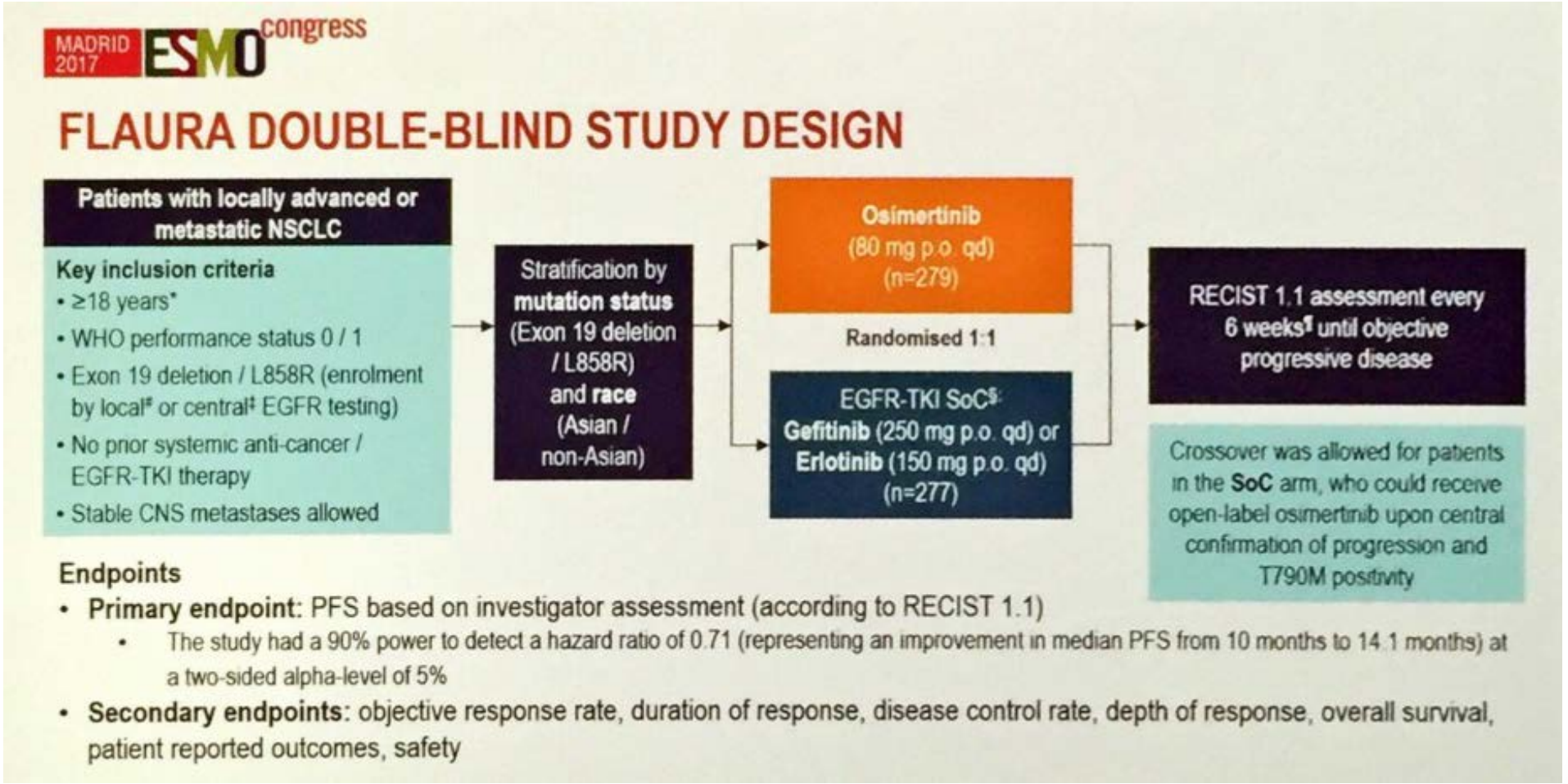
FDA approved EGFR TKIs		
1st generation	2nd generation	3rd generation
Erlotinib (+/- ramucirumab)	Afatinib	Osimertinib
Gefitinib	Dacomitinib	

General principles

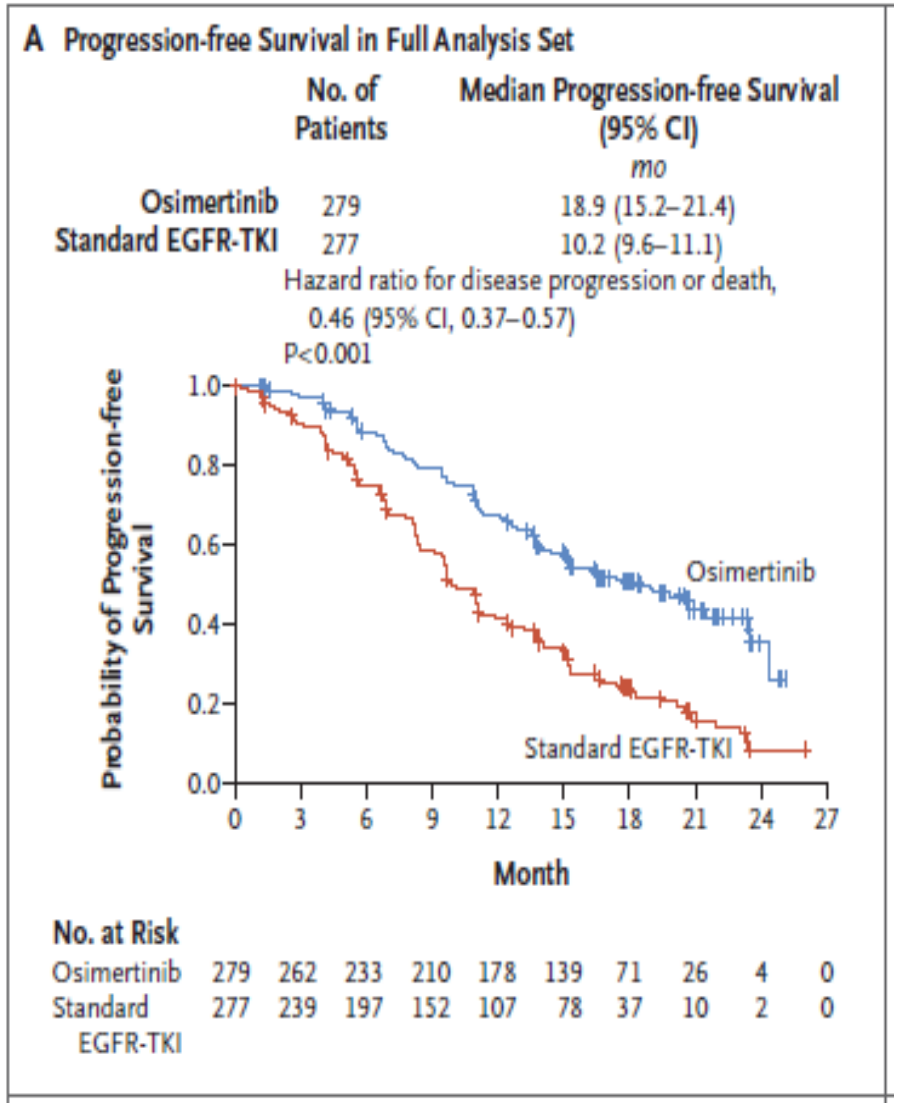
- TKI treatment is superior to platinum doublet in the first line setting
- Efficacy of 1st and 2nd gen TKIs are similar, although PFS with dacomitinib higher
- Using a 2nd gen TKI after a 1st gen TKI is not effective
- 50-60% of patients develop T790M resistance mutation after 1st and 2nd gen TKIs

→ Only active FDA approved drug that is active against T790M is osimertinib

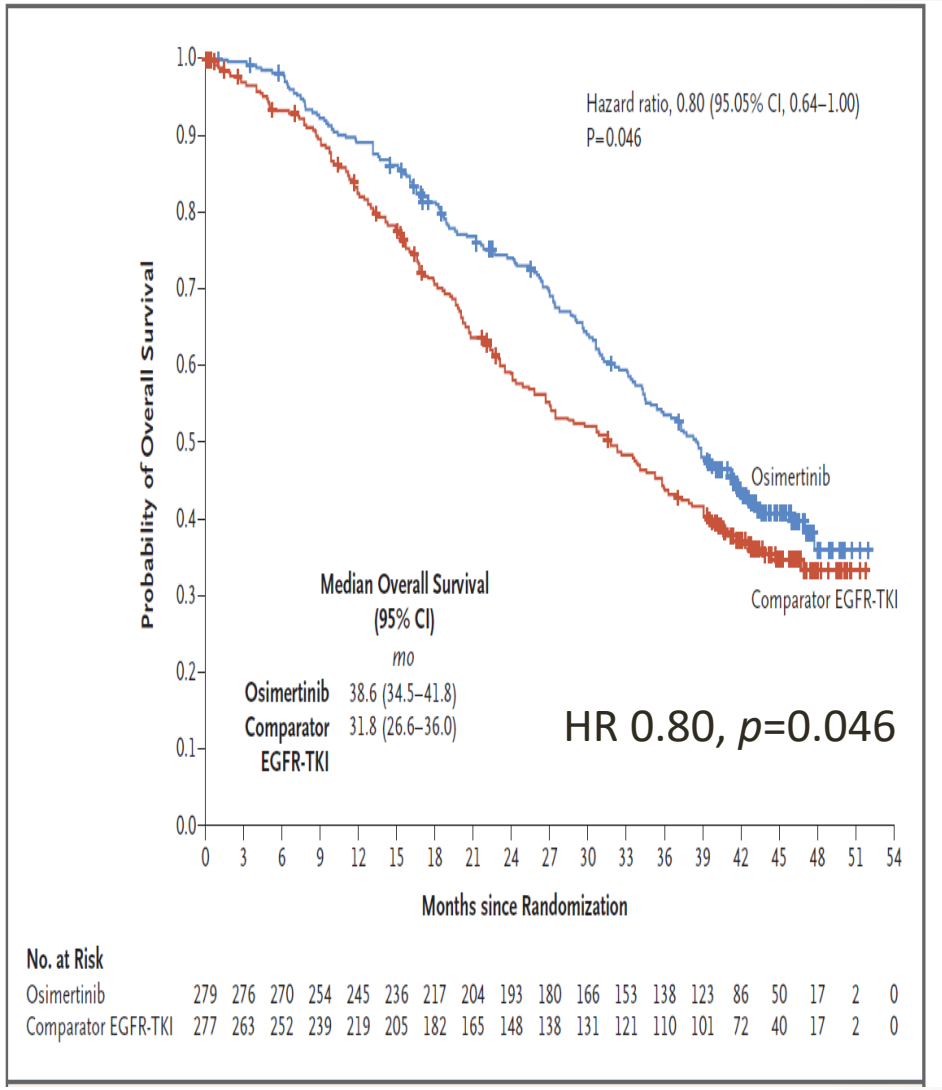
First line osimertinib



Ramalingam ESMO 2017



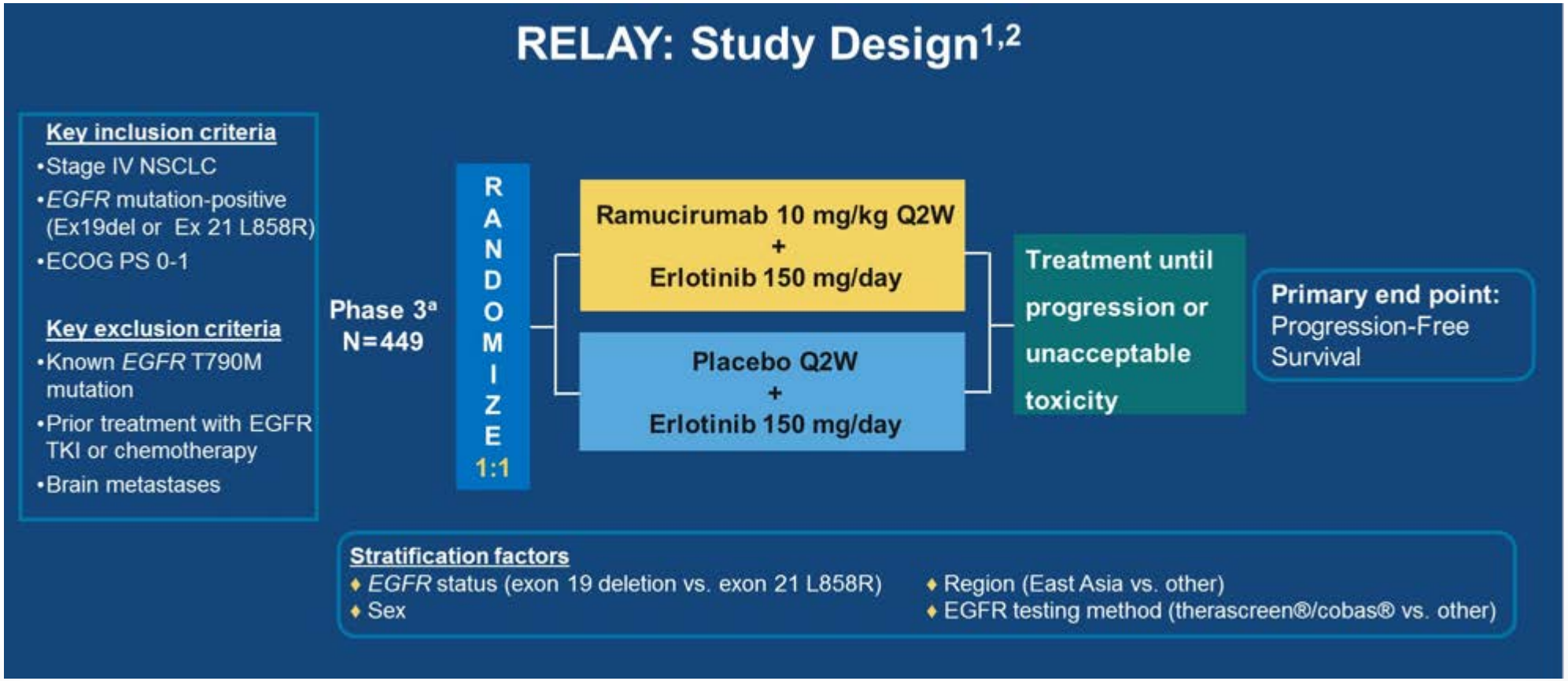
Soria *et al*. NEJM 2018; 378(2): 113-125



Ramalingam *et al*. NEJM 2020; 382(1);41-50

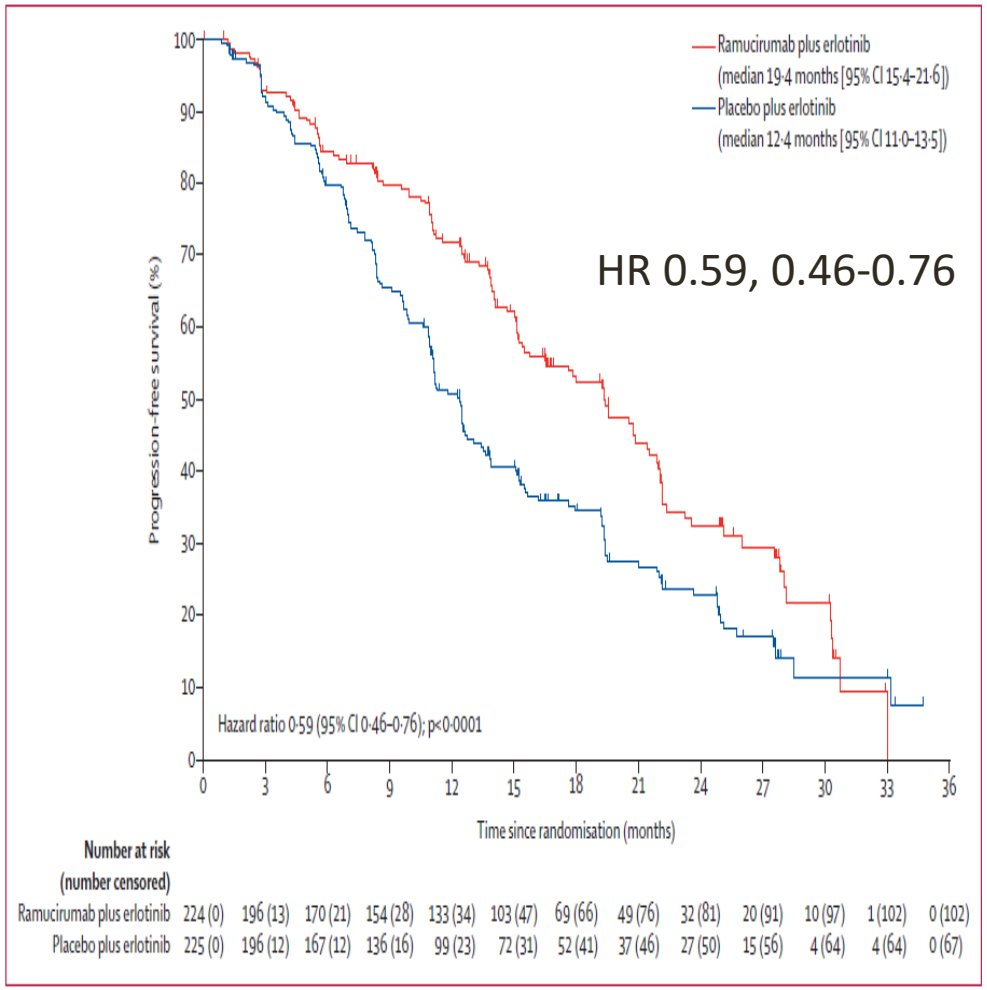
Erlotinib + ramucirumab

Erlotinib and ramucirumab FDA approved in May 2020



Nakagawa *et al.* RELAY. Lancet Oncol 2019;20:1655-1669

Erlotinib + ramucirumab



	Ram + E	Placebo + E
PFS (mos)	19.4 (15.4-21.6)	12.4 (11-13.5)
ORR %	76 (71-82)	75 (69-80)
DCR %	95 (92-98)	96 (93-98)
DOR (mos)	18 (13.9-19.8)	11.1 (9.7-12.3)

- Overall survival data immature
- There is a similar trial with bevacizumab which showed similar PFS benefit but no OS benefit (NEJ026, Maemondo et al. Abs 9506. ASCO 2020)

Nakagawa *et al.* RELAY. Lancet Oncol 2019;20:1655-1669

EGFR summary

- First line options:
  - Osimertinib upfront (has become the preferred approach in US)
  - Erlotinib +/- ramucirumab (no CNS met), afatinib, dacomitinib, gefitinib → osimertinib if T790M+ (about 50%)
- EGFR exon 20 insertion is NOT sensitive to the above TKIs (trials ongoing with exon 20 targeting TKIs)
- Post-osimertinib:
  - Most of these patients will need chemo
  - Consider trial participation (Emerging resistance mechanisms: MET amplification, HER2 amplification, C797X mutation, etc)

ALK rearrangement

- 3-5% NSCLC
- Associated with young age, no smoking
- FDA approved tests:
  - FISH (fluorescence *in situ* hybridization)
  - Immunohistochemistry (D5F3 antibody)

ALK rearranged NSCLC

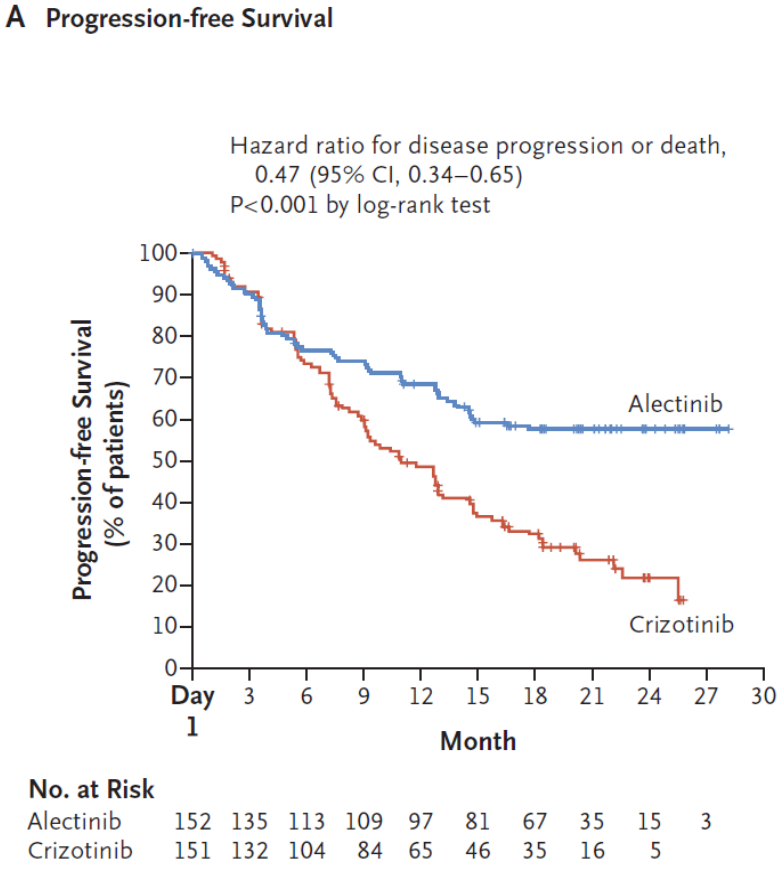
FDA approved ALK inhibitors		
1st generation	2nd generation	3rd generation
Crizotinib	Alectinib	Lorlatinib
	Ceritinib	
	Brigatinib	

General principles

- All of the above TKIs except lorlatinib are approved as first line therapy
- Second generation TKIs have become standard first line therapy, even though crizotinib is an option
- Second generation TKIs are active after crizotinib but unclear if active after another 2nd gen TKI (although there is some data for brigatinib after alectinib)
- Lorlatinib active after crizotinib and modestly active after second generation TKIs

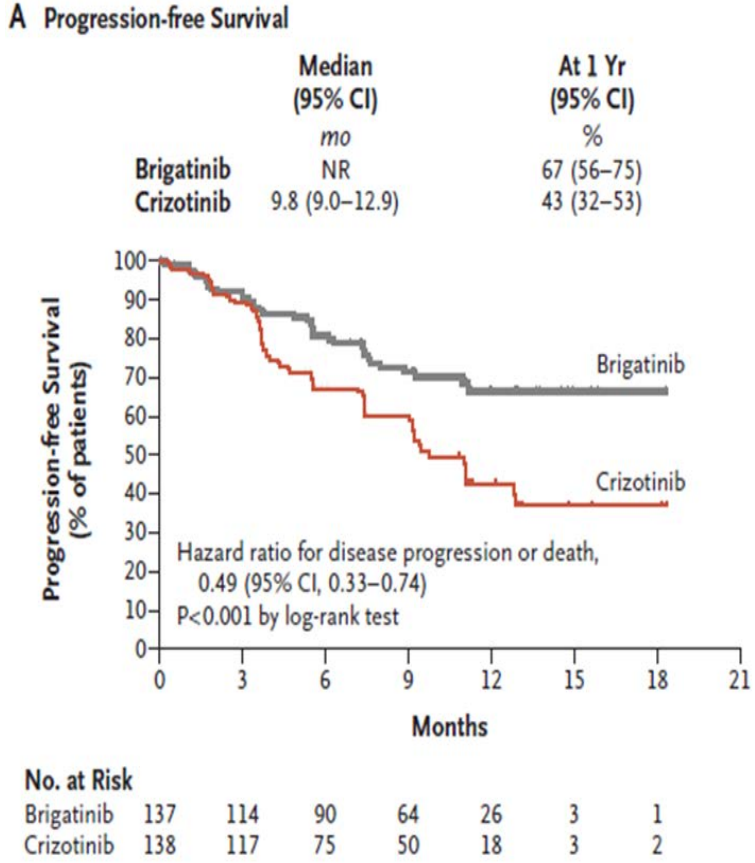
First line therapy:

Alectinib



Peters *et al*. NEJM 2017. DOI: 10.1056/NEJMoa1704795

Brigatinib



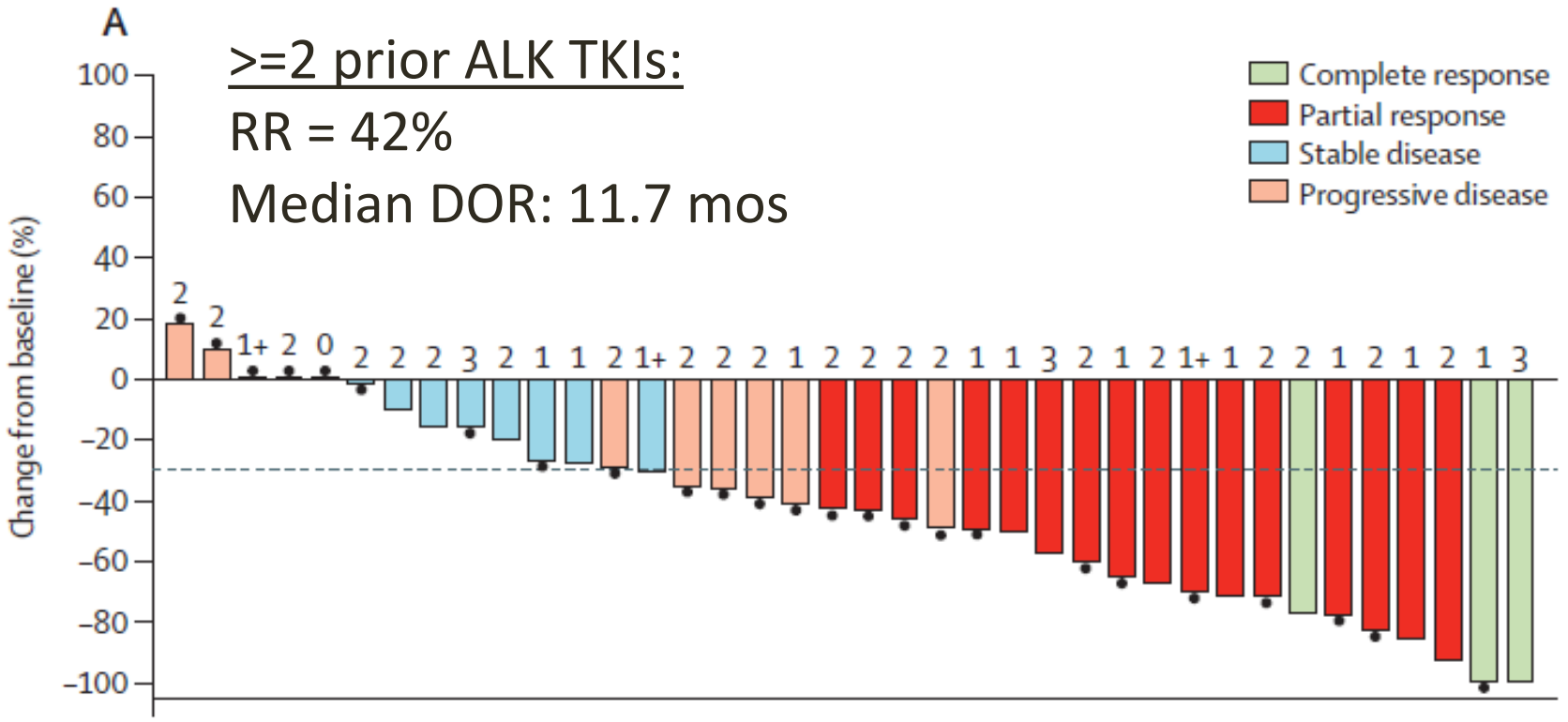
Camidge et al. DOI: 10.1056/NEJMoa191071

ALK first line therapy

Drug	Progression free survival (median, mos)
Crizotinib (1)	10.9
Ceritinib (2)	16.6
Alectinib (3,4)	~ 35
Brigatinib (5,6)	~24-29

(1) Solomon *et al*. NEJM 2014; 371: 2167-2177
(2) Soria *et al*. Lancet 2017;389:917-29
(3) Peters *et al*. NEJM 2017. DOI: 10.1056/NEJMoa1704795
(4) Camidge *et al*. JTO 2019; 14(7): 1233-1243
(5) Camidge *et al*. DOI: 10.1056/NEJMoa191071
(6) Camidge et al. Doi.org/10.1200/JCO.20.00505

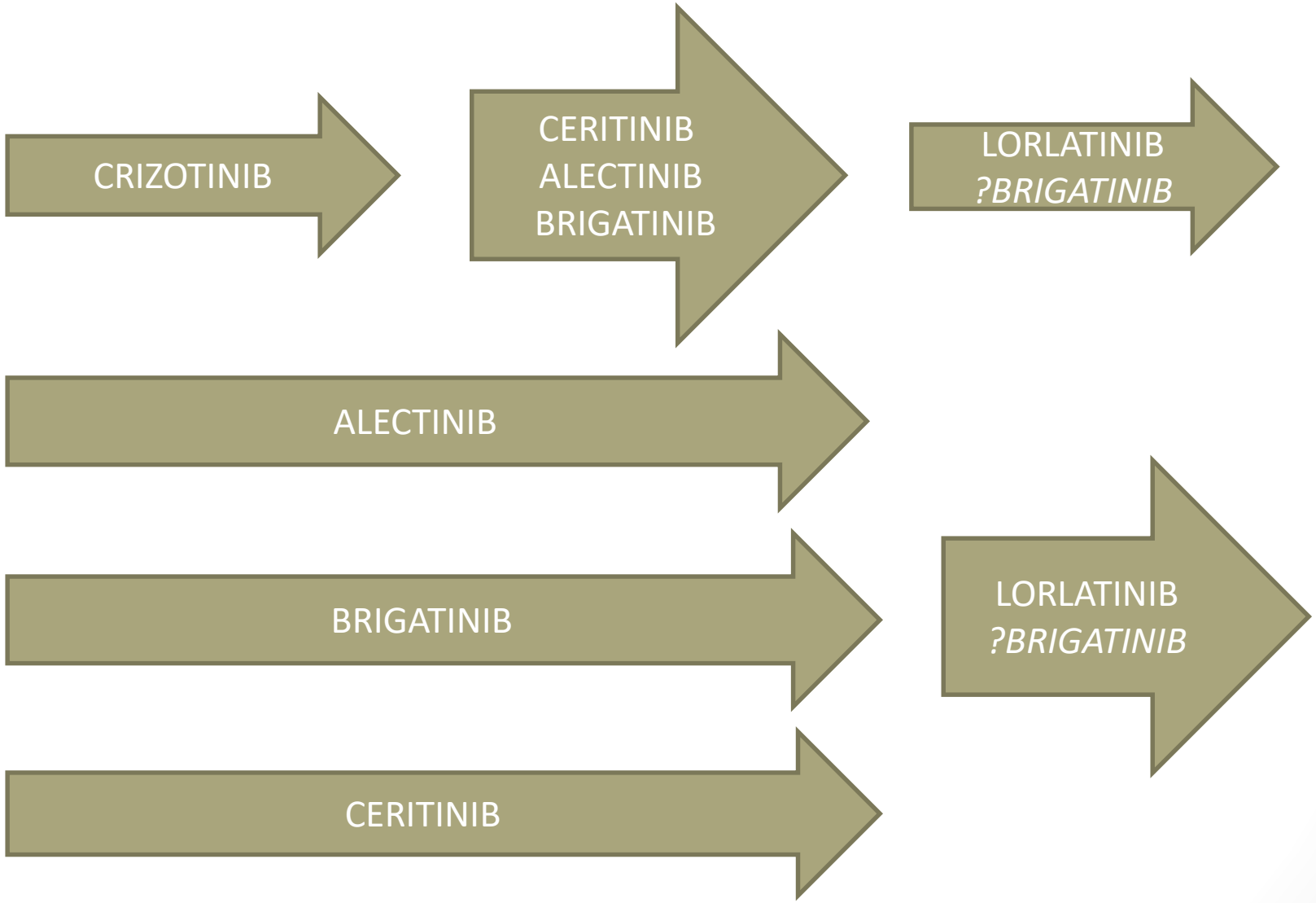
3rd generation ALK inhibitor: Lorlatinib



Shaw *et al*. Lancet Oncol 2017; 18(12): 1590-1599

Currently approved after a second generation TKI

ALK therapy: Optimal sequence?

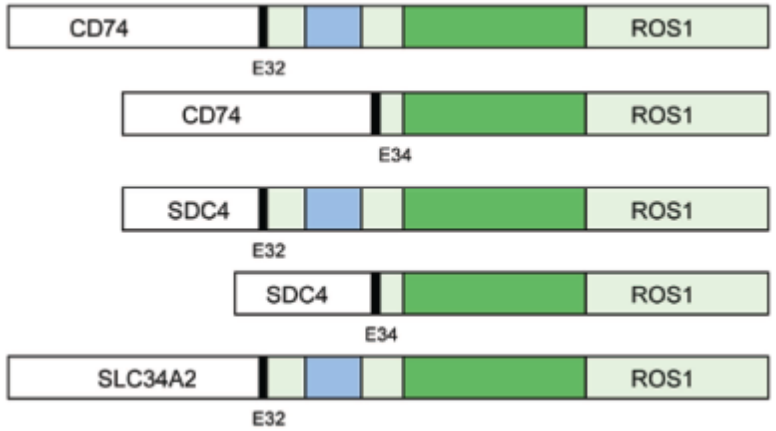


Toxicities

CRIZOTINIB	CERITINIB	ALECTINIB	BRIGATINIB	LORLATINIB
Diarrhea	Diarrhea	Myalgia	Diarrhea	Increased cholesterol / triglyceride
Nausea	Nausea	Constipation	HTN	Peripheral edema / neuropathy
Visual changes	Abdominal cramps	Peripheral edema / Weight gain	Early pulmonary toxicity (uncommon)	Cognitive changes (mild)

ROS1 rearranged NSCLC

- Fusion of ROS1 tyrosine kinase domain with 1 of 12 different partner proteins
- Younger patients with no/light smoking history
- Occur in 1-2% of NSCLC



Gainor *et al*. Oncologist 2013;18:865

ROS1 rearranged NSCLC

- First line options: Crizotinib, Entrectinib, (Ceritinib – off label)
  - Entrectinib and ceritinib not active in crizotinib pre-treated (different from ALK in which ceritinib is active after crizotinib)
- Lorlatinib active after crizotinib but not yet FDA approved (ORR 26.5, 12.9-44.4; median PFS 8.5mos)

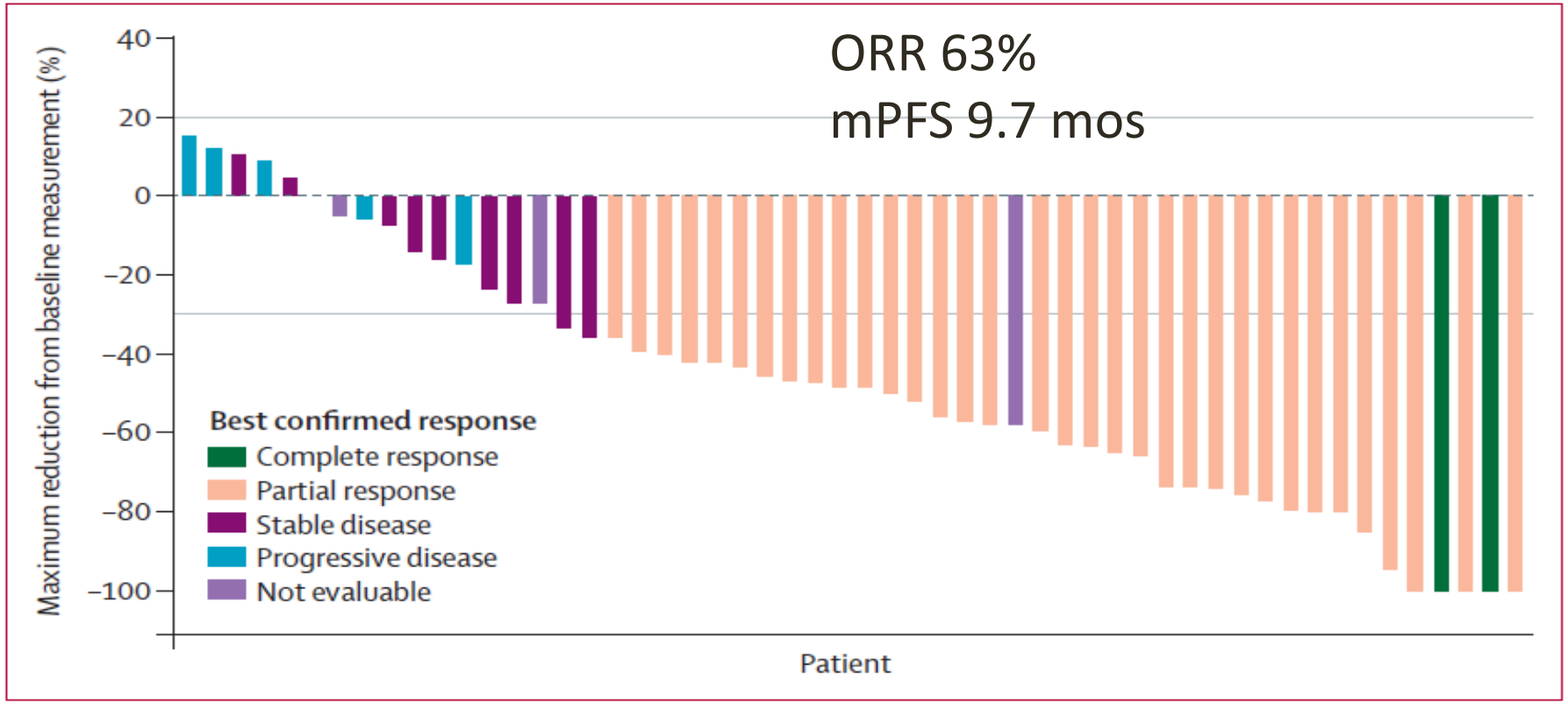
	RR, %	PFS, mos	CNS RR
Crizotinib (n=50)	72 (58-84)	19.2 (14.4-NR)	N/A
Entrectinib (n=53)	77.4 (64-88)	19.0 (12.2-36.6)	55% (n=20)

Shaw et al. NEJM 2014; 371: 1963
Doebele et al. OA02.01 WCLC 2018
Ou et al. WCLC 2018

BRAF V600E

- Occur in 1-4% of NSCLC
- Present regardless of smoking history
- Dabrafenib (BRAFi) + trametinib (MEKi) – only approved regimen

  (Planchard *et al*. Lancet Oncol 2016; 17: 984-993)



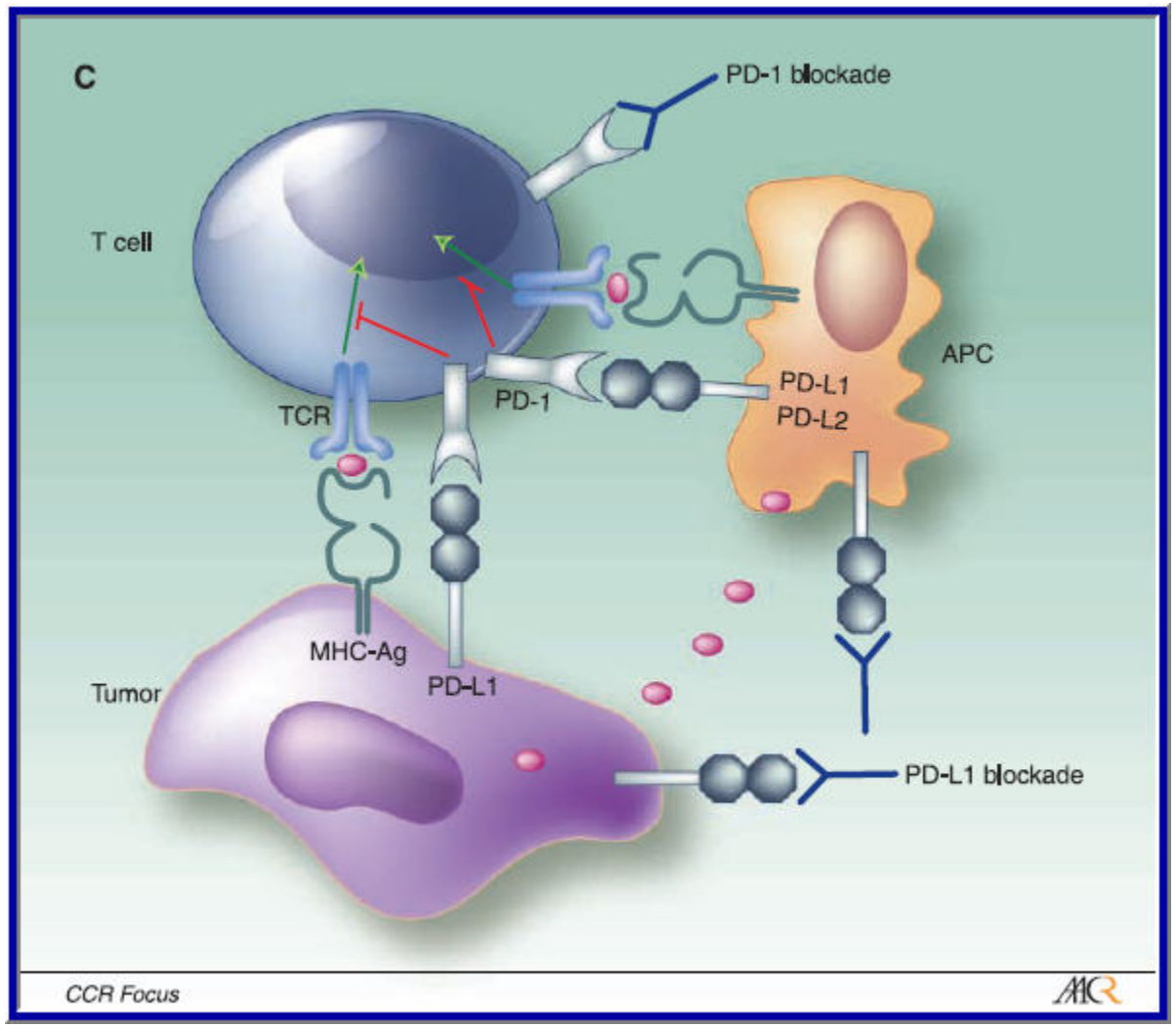
NTRK rearrangement

- NTRK+ NSCLC is rare (<1%), although not clearly characterized
  - DNA based next-generation sequencing is often used but likely limited sensitivity
  - Limited data on clinical characteristics but seen more commonly in light smokers but also observed in patients with smoking history
- Two FDA approved drugs (for all solid tumor with NTRK fusion without resistance mutations):
  - **Larotrectinib** (ORR 80%, 95% CI 61-85; PFS not reached. Drilon *et al*. NEJM 2018)
  - **Entrectinib** (ORR 57%, 95% CI 43-71; PFS 11.2 mos, 95% CI 8.0-14.9. Demetri *et al* ESMO 2018)

FDA approved (as of July 2020)						
EGFR (non-exon20 ins)	**ALK**	**ROS1**	**BRAF V600E**	**NTRK**	**MET exon14**	**RET**
Erlotinib Gefinitb Afatinib Dacomitinib Osimertinib	Crizotinib Alectinib Ceritinib Brigatinib Lorlatinib	Crizotinib Entrectinib (Lorlatinib)	Dabrafenib + trametinib	Larotrectinib Entrectinib	Capmatinib	Selpercatinib

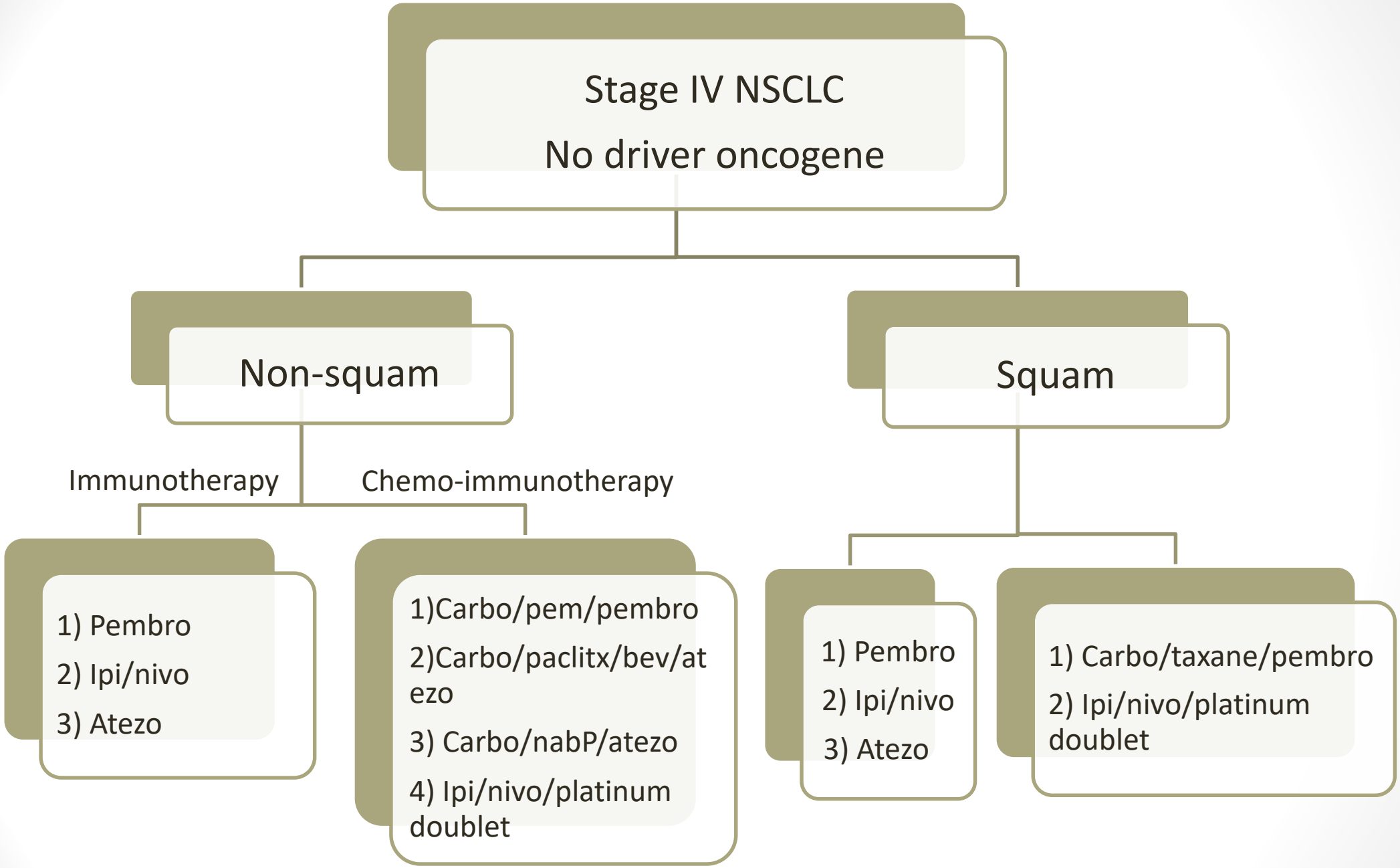
Investigational (active drugs in trials)			
EGFR (exon20 ins)	**HER2**	**KRAS**	**MET amplification**
Poziotinib TAK788 (mobocertinib) Tarloxotinib	Trastuzumab deruxtecan Trastuzumab emtansine Poziotinib TAK788 Tarloxotinib	AMG510 (G12C) MRTX849	Tepotinib Capmatinib Sym015 Savolitinib

Immune checkpoint inhibitors (ICIs)



FDA approved ICIs in metastatic NSCLC

	Type of drug	First-line	Later line (post chemo)
Pembrolizumab	Anti-PD1	Monotx: ≥1% PD-L1 (IHC 22C3) With chemo: No PD-L1 requirement	≥1% PD-L1
Nivolumab	Anti-PD1	In combination with ipilimumab in ≥1% PD-L1 (IHC 28-8) With ipi and chemo: No PD-L1 requirement	No PD-L1 requirement
Atezolizumab	Anti-PD-L1	Monotx: Tumor PDL1 ≥50%, immune PD-L1 ≥10% (IHC SP142) With chemo: no PD-L1 requirement	No PD-L1 requirement


Stage IV NSCLC
No driver oncogene
Non-squam
Squam
Immunotherapy
Chemo-immunotherapy
1) Pembro
2) Ipi/nivo
3) Atezo
1)Carbo/pem/pembro
2)Carbo/paclitx/bev/atezo
3) Carbo/nabP/atezo
4) Ipi/nivo/platinum doublet
1) Pembro
2) Ipi/nivo
3) Atezo
1) Carbo/taxane/pembro
2) Ipi/nivo/platinum doublet

First-line: Pembrolizumab

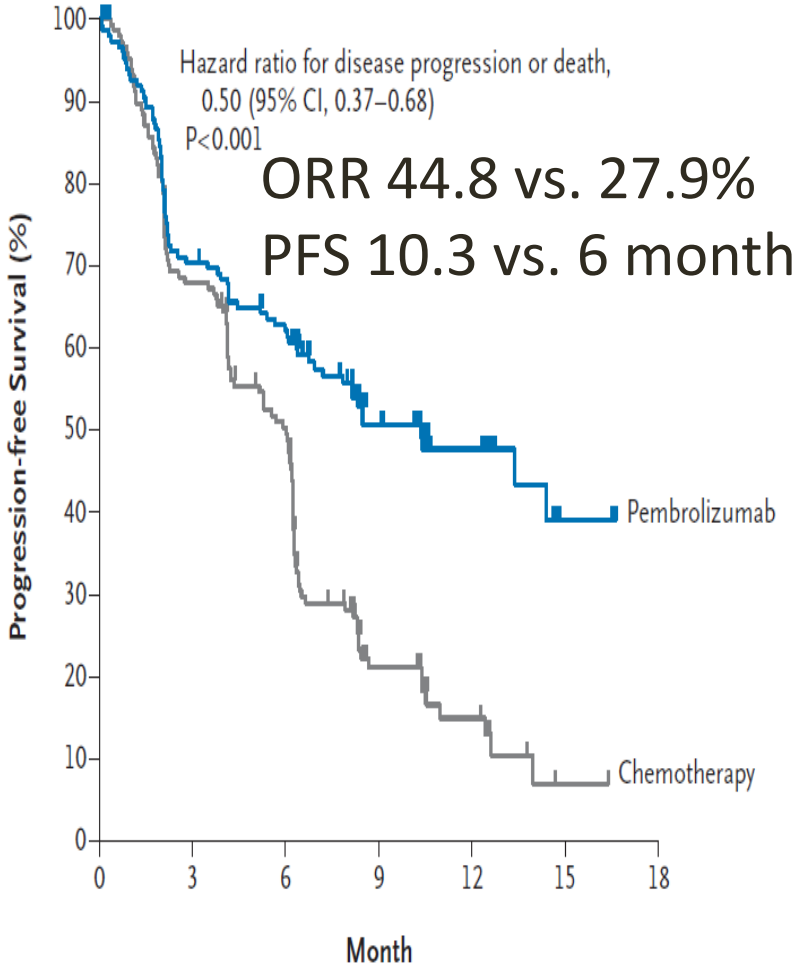
- Metastatic NSCLC
- No EGFR / ALK
- ECOG 0-1
- No untreated CNS met
- No history of pneumonitis
- PDL1 >=50% (KN-24)
- PDL1 >=1% (KN-42)

→ Pembrolizumab 200mg q3wk x 2 years

→ Platinum doublet chemo

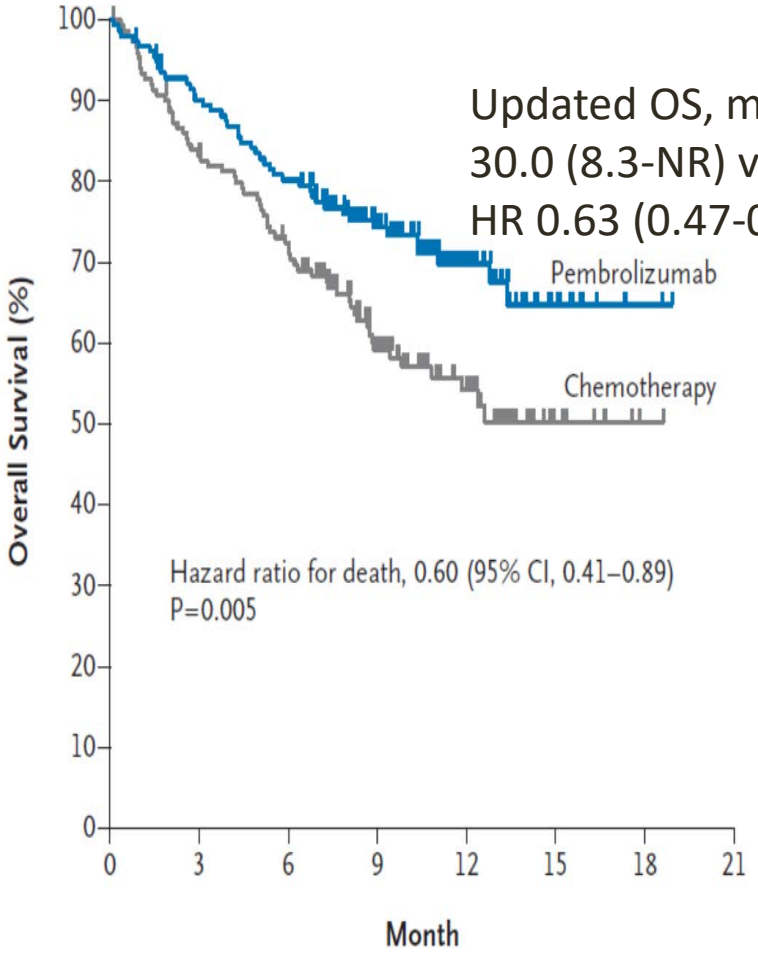
Brahmer *et al*. ASCO 2017 abs #9000
Lopes et al. ASCO 2018 abs LBA4

Pembrolizumab: ≥ 50% PD-L1



ORR 44.8 vs. 27.9%

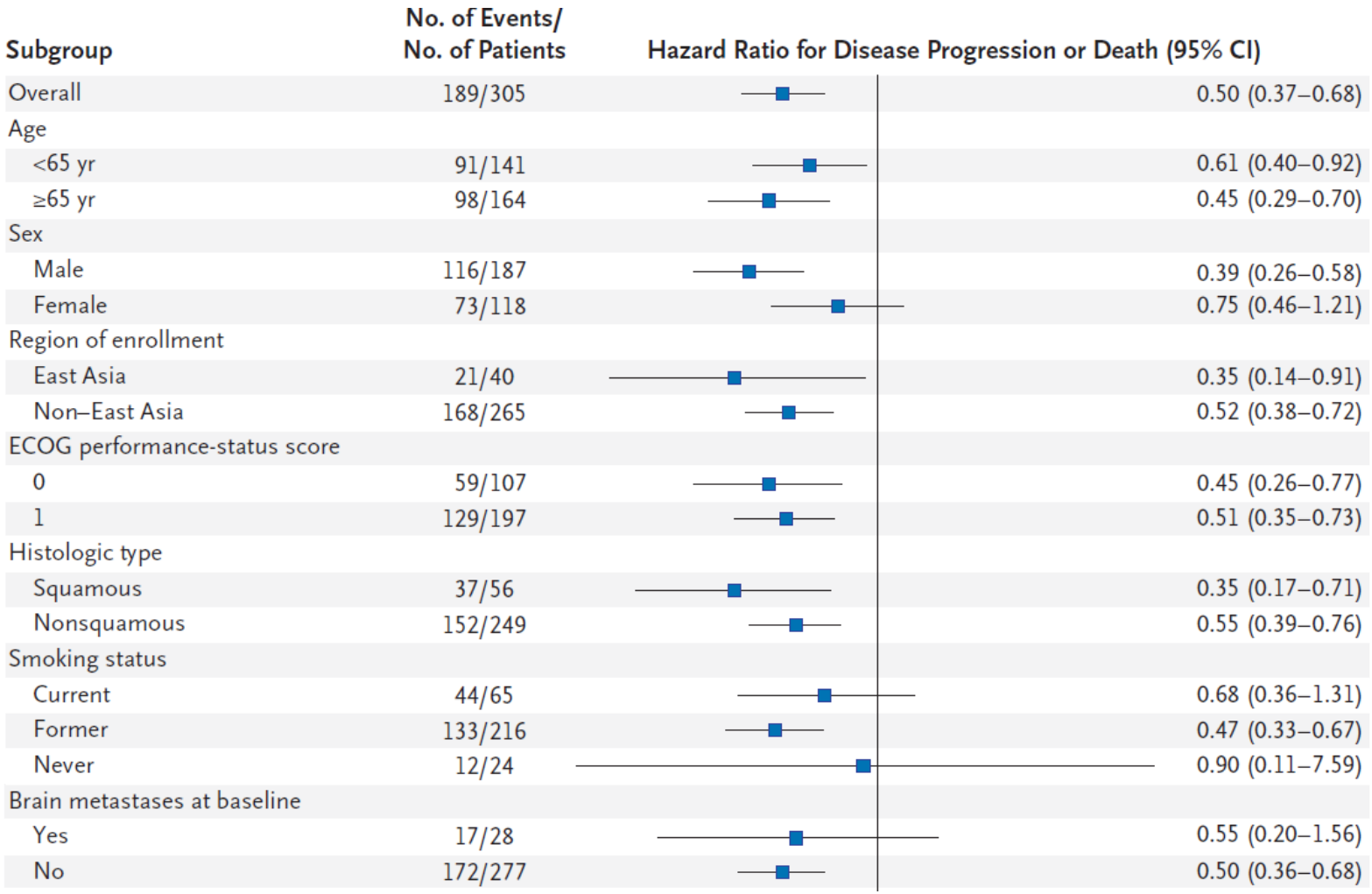
PFS 10.3 vs. 6 months



Updated OS, mos:
30.0 (8.3-NR) vs 14.2 (9.8-19)
HR 0.63 (0.47-0.86)

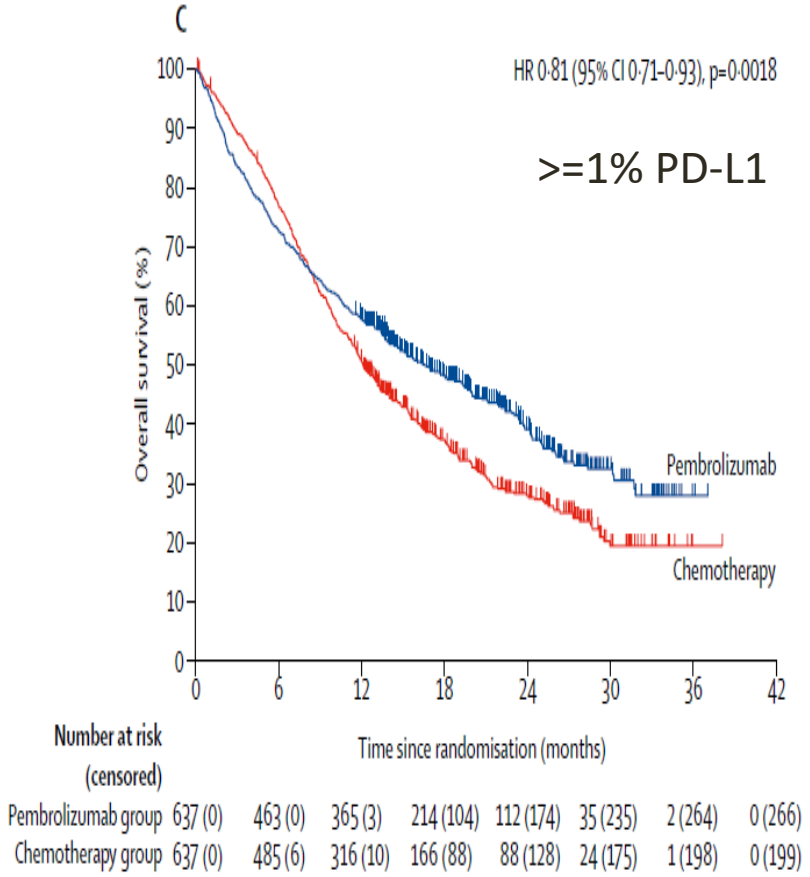
Reck *et al*. NEJM 2016; 375 (19):1923-1833
Reck et al. JCO 2019; 37:537-546

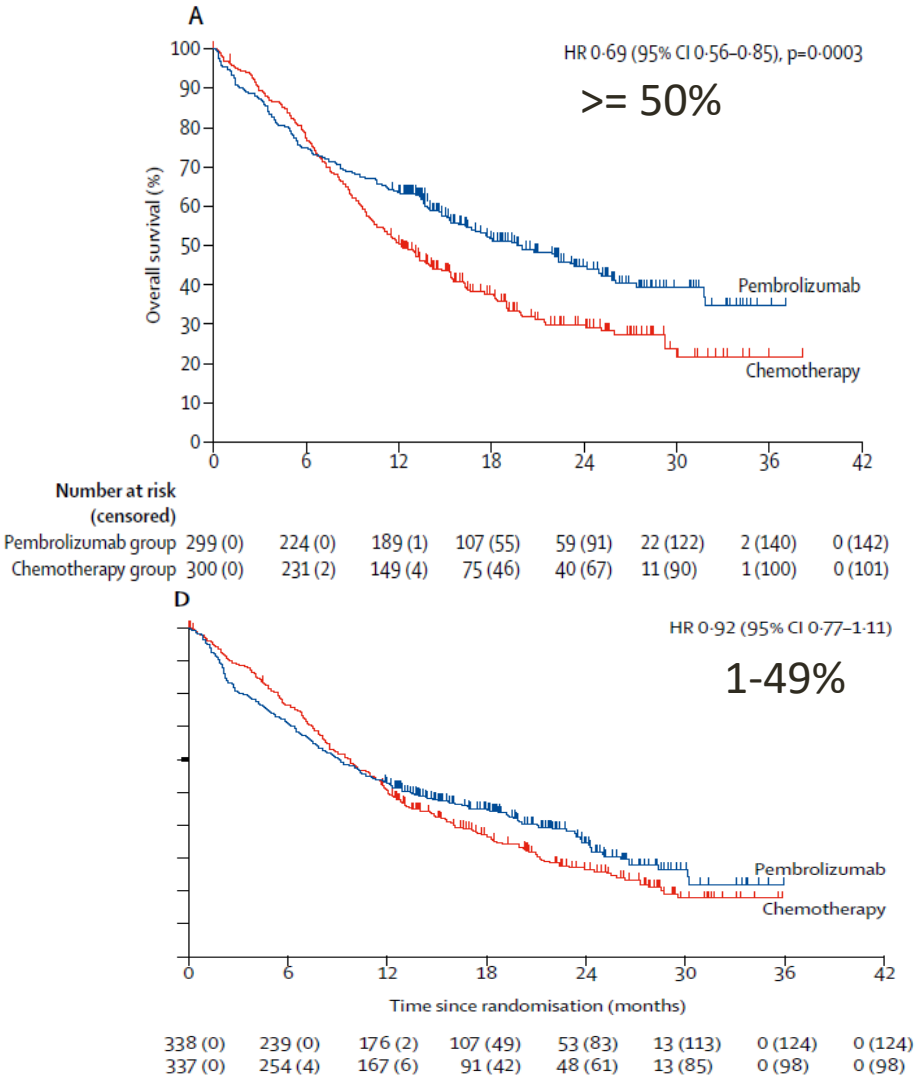
First-line pembrolizumab



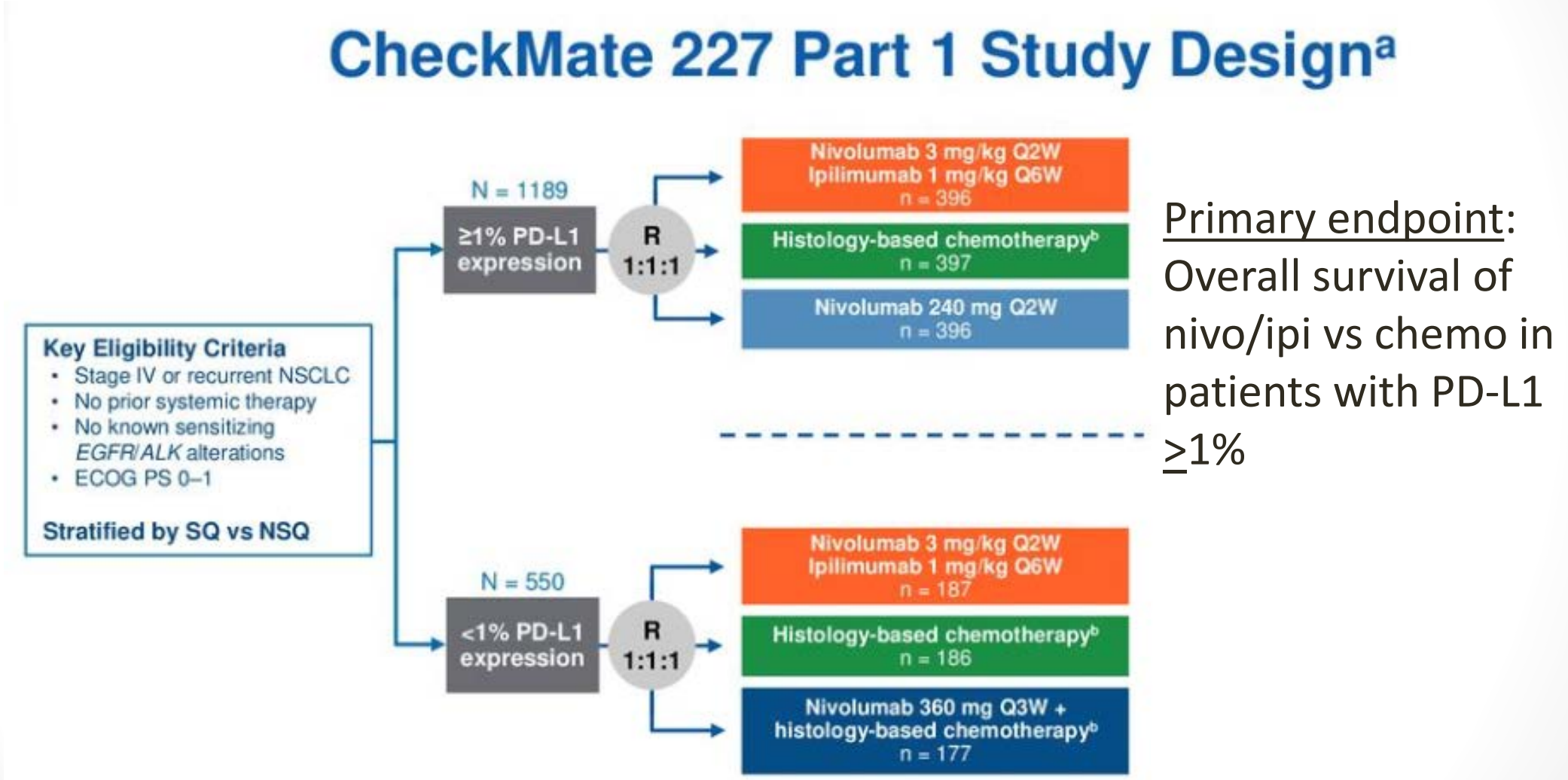
Reck *et al*. NEJM 2016; 375 (19):1923-1833

Pembrolizumab: ≥1%



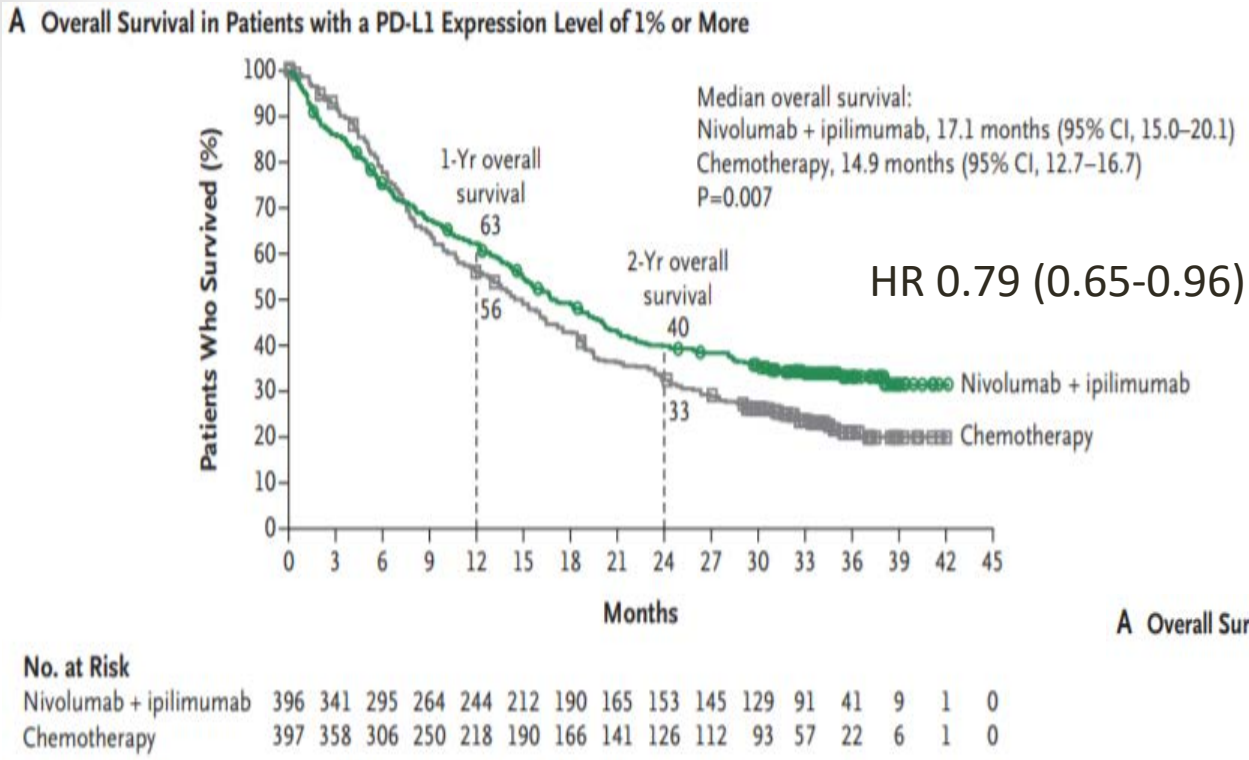


First line ipilimumab and nivolumab



Primary endpoint: Overall survival of nivo/ipi vs chemo in patients with PD-L1 ≥1%

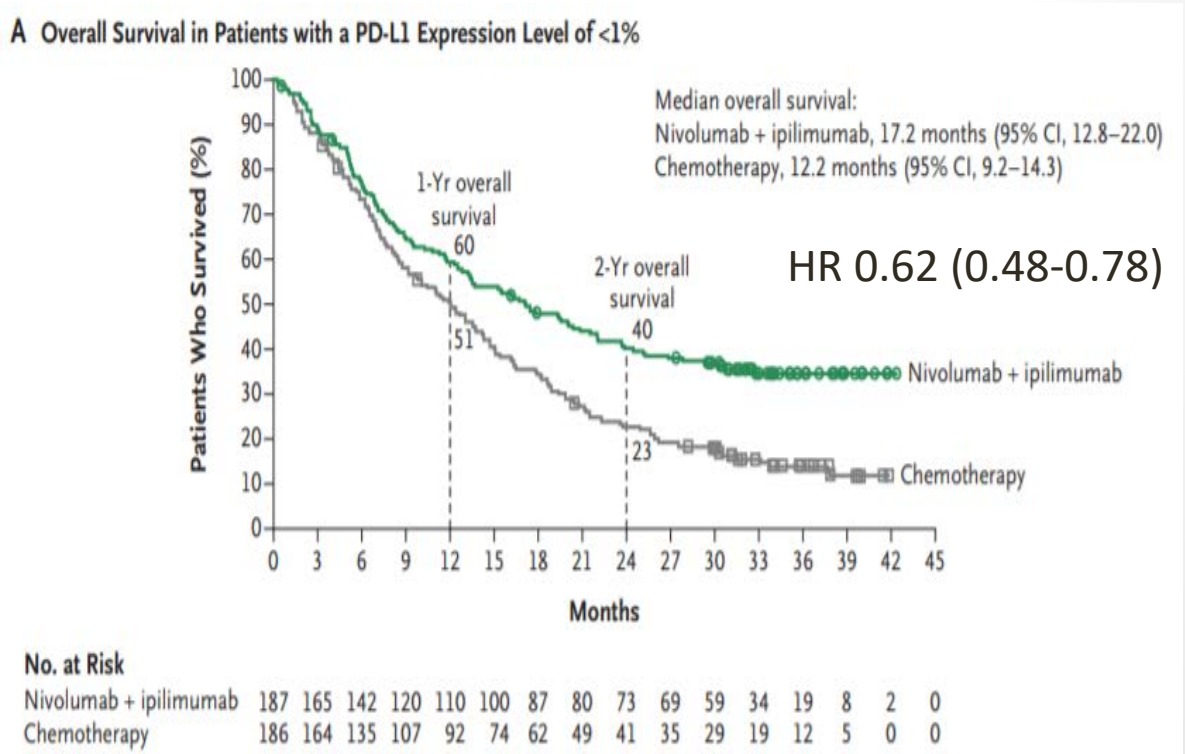
Hellmann et al. NEJM 2019; 381:21



HR 0.79 (0.65-0.96)

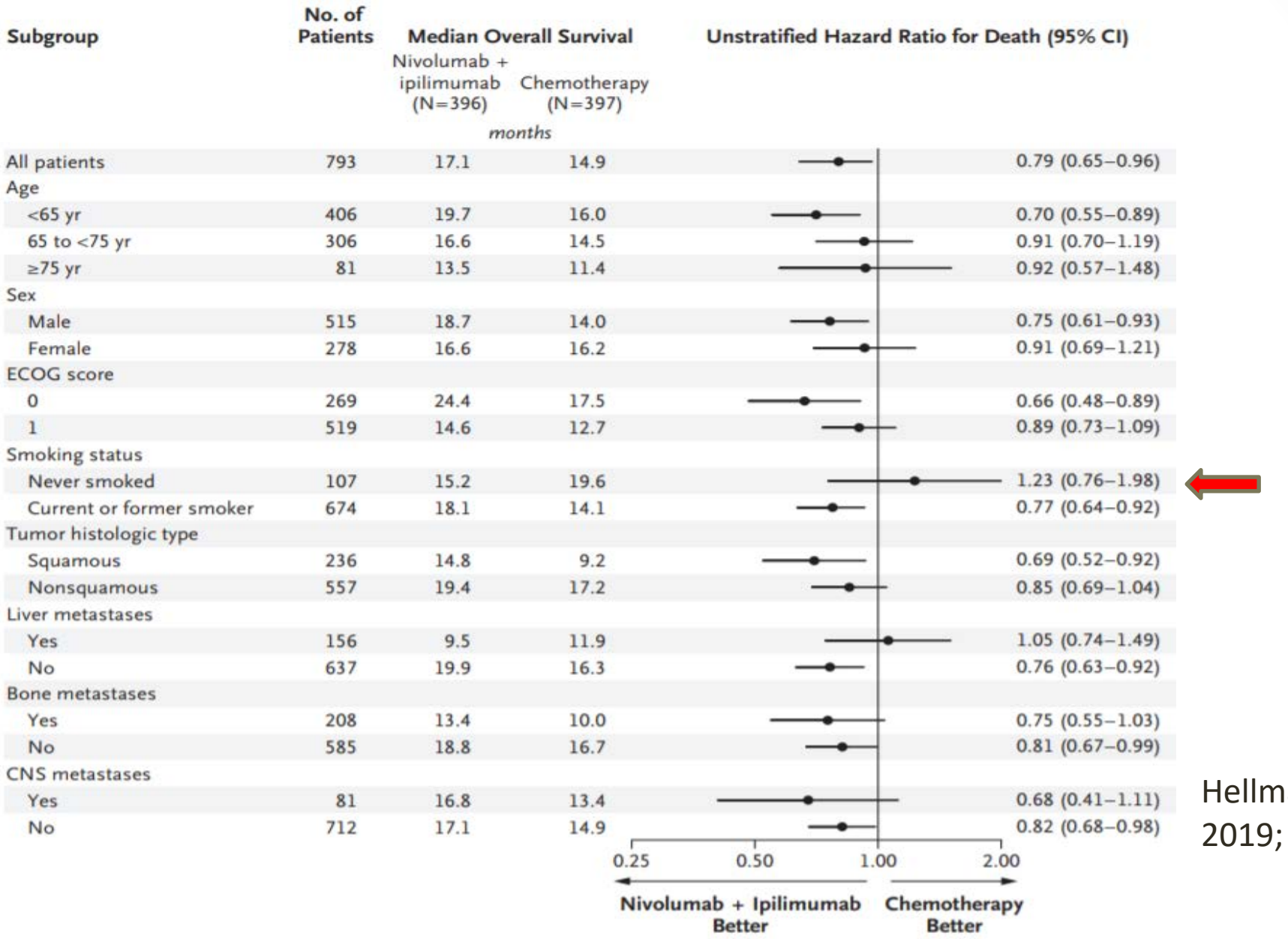
PD-L1 negative

PD-L1 positive



HR 0.62 (0.48-0.78)

Hellmann et al. NEJM 2019; 381:21



Hellmann et al. NEJM 2019; 381:21

FDA approved ipilimumab / nivolumab for NSCLC with PD-L1 >=1% (IHC 28-8) in May 2020

Chemo-immunotherapy

Regimen (ref)	n	ORR (%)	PFS (mos)	OS (mos)
Non-squamous NSCLC				
Carboplatin / pemetrexed +/- pembrolizumab(1,6)	616	47.6 v 18.9	8.8 v 4.9 (HR 0.52,0.43-0.64)	22 vs 10.7 (HR 0.49, 0.38-0.64)
Carbo/paclitax/bevacizumab +/- atezolizumab(2)	692	63.5 v 48	8.3 v 6.8 (HR 0.62, 0.52-0.74)	19.2 v 14.7 (HR 0.78, 0.64-0.96)
Carbo/nabP +/- atezo (3)	724	49.2 v 31.9	7.0 v 5.5 (HR 0.64, 0.54-0.77)	18.6 v 13.9 (HR 0.79, 0.64-0.98)
Both histology				
Platinum chemo +/- ipi/nivo(4)	719	38 v 25	6.7 v 5.0 (HR 0.68, 0.57-0.82)	15.6 v 10.9 (HR 0.66, 0.55-0.80)
Squamous NSCLC				
Carbo/paclitx or nabP +/- pembro(5)	559	57.9 v 38.4	6.4 v 4.8 (HR 0.56, 0.45-0.70)	15.9 v 11.3 (HR 0.64, 0.49-0.85)

nabP, *nab*-paclitaxel

(1)Gandhi NEJM 2018;378:2078 (2)Socinski NEJM 2018;378:2288 (3) West et al LancetOnc 2019; 20:924
(4)Reck ASCO 2020;Abs9501 (5)Paz-Ares NEJM 2018; 379:2040 (6) Gadgeel et al. JCO 2020

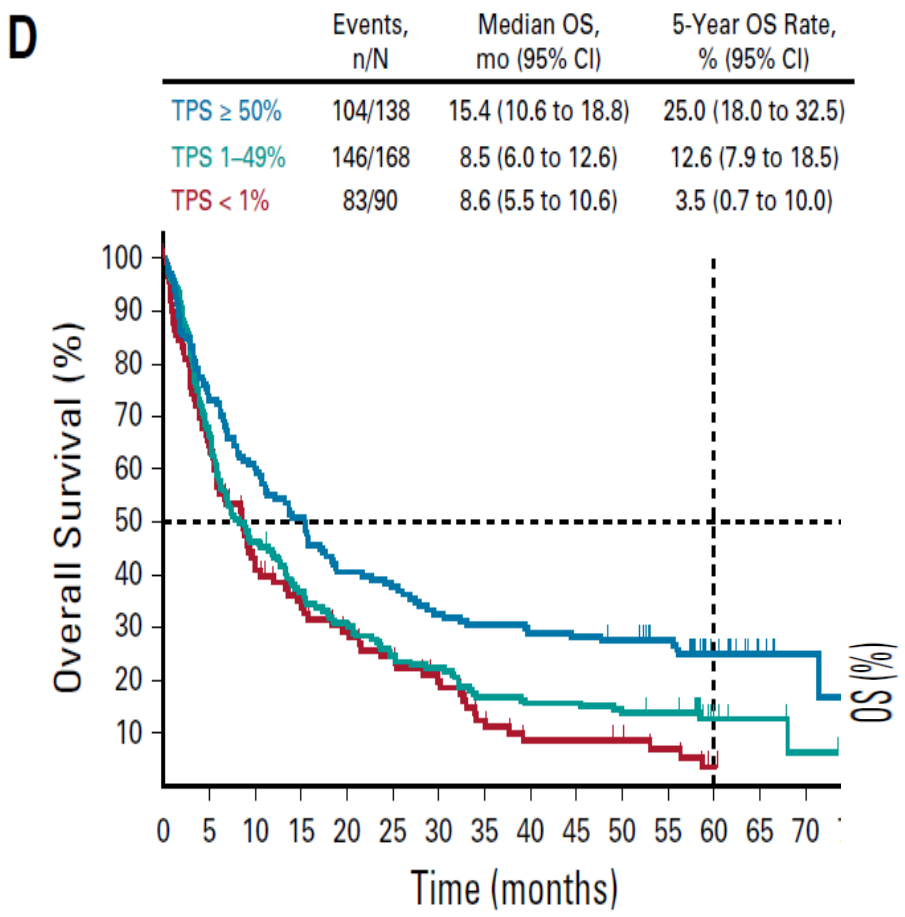
Second line ICI therapy (compared to docetaxel)

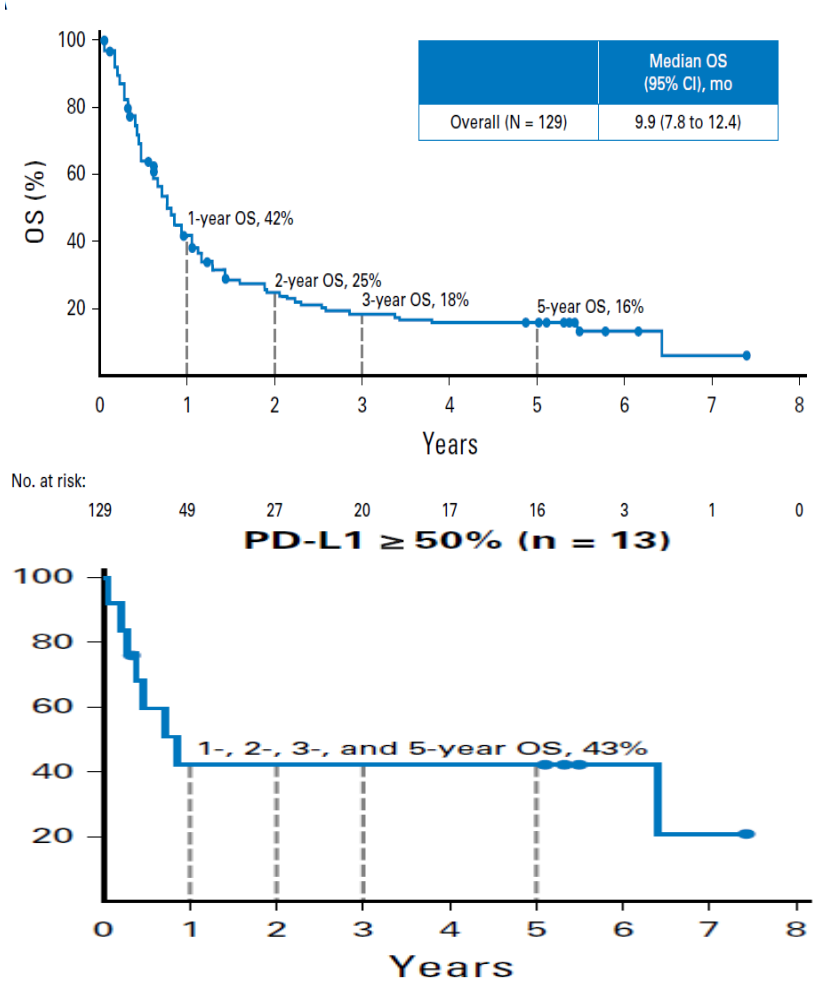
Drug	PD-L1 IHC	ORR (%)	PFS (mos)	OS (mos)
Nivolumab* (1)	Not required	19 vs 12	2.3 vs 4.2	12 vs 9.4
Pembrolizumab**(2)	>=1% (22C3)	18 vs 9	3.9 vs 4.0	10.4 vs 8.5
Atezolizumab (3)	Not required	14 vs 13	2.8 vs 4.0	13.8 vs 9.6

(1) Borghaei *et al*. CheckMate-057. NEJM 2015; 373 (17): 1627-39
(2) Herbst *et al*. KEYNOTE-010. Lancet 2016; 387: 1540-50
(3) Rittmeyer *et al*. OAK. Lancet 2017; 389: 255-265

* Non-squamous histology
**2mg/kg

We are starting to see long term survivors





Pembrolizumab: Garon et al. JCO 2019
doi:10.1200/JCO.19.01207

Nivolumab: Gettinger et al. JCO 2018
Doi:10.1200/JCO.2017.77.0412

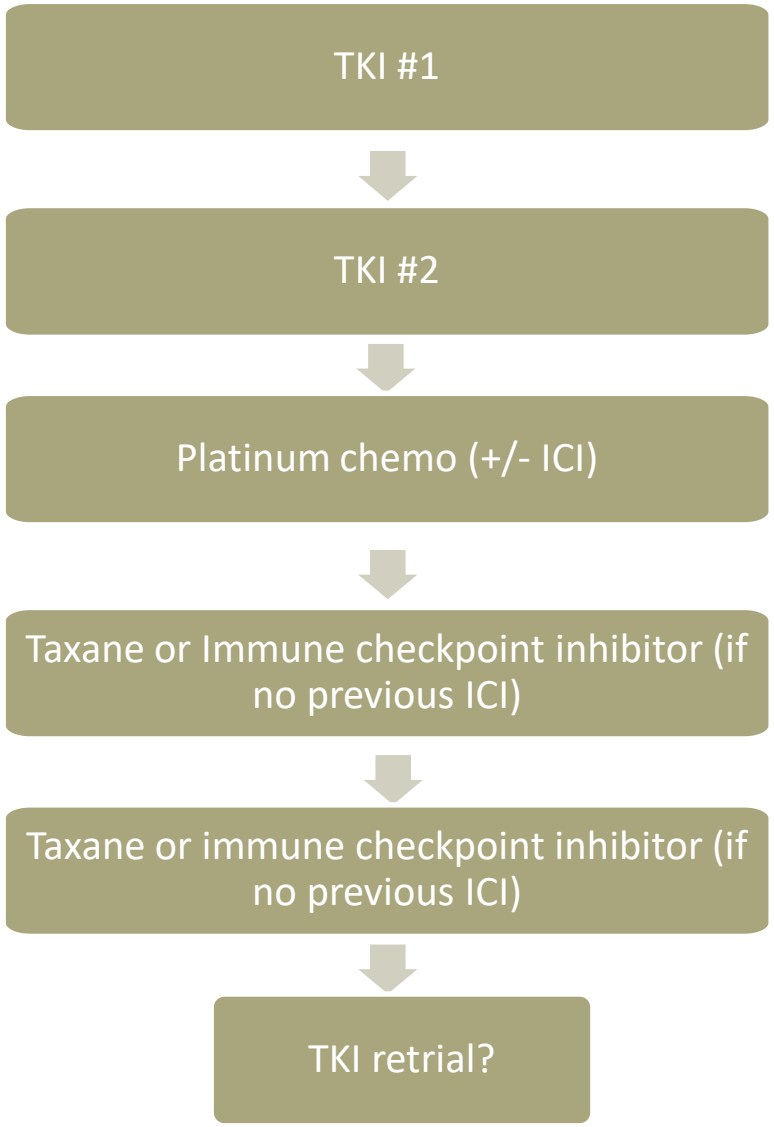
Summary - Immune checkpoint inhibitor

- Pembrolizumab or atezolizumab monotherapy is a reasonable option for PD-L1 high tumors (e.g. >50% using 22C3 IHC) as first-line therapy (but no head-to-head data vs chemo-immunotherapy)
- In PD-L1 1-49% patients, I prefer chemo-immunotherapy since the benefit of pembro alone does not appear to be significantly better compared to chemo alone (my personal opinion)
- I also prefer chemo-immunotherapy in high PD-L1 patients if high response rate is desired (e.g. symptomatic disease burden)
- When to use ipi/nivo? Perhaps in patients intermediate / low or negative PD-L1 expression who want to avoid chemo (but FDA approved only in PD-L1 expressed patients)

Brief overview of chemotherapy (for patients not eligible for immunotherapy first line e.g. active autoimmune disease)

- A few pearls on chemo / anti-angiogenetic therapy
  - Platinum doublet is standard of care in immunotherapy ineligible patients
  - Pemetrexed only approved for non-squamous histology
  - Bevacizumab contraindicated in squamous histology (fatal hemoptysis)
  - Ramucirumab with docetaxel can be used in select patients
- Squamous cell carcinoma:
  - Platinum + gemcitabine
  - Platinum + taxane **(no bevacizumb)**
  - Cisplatin + gemcitabine + **necitumumab**
- Non-squamous cell carcinoma:
  - Platinum + **pemetrexed** → maintenance pemetrexed
  - Platinum + paclitaxel + bevacizumab → maintenance bevacizumab
- Later line chemo (post-immunotherapy):
  - Docetaxel +/- ramucirumab in **both** histologies (no history of hemoptysis)

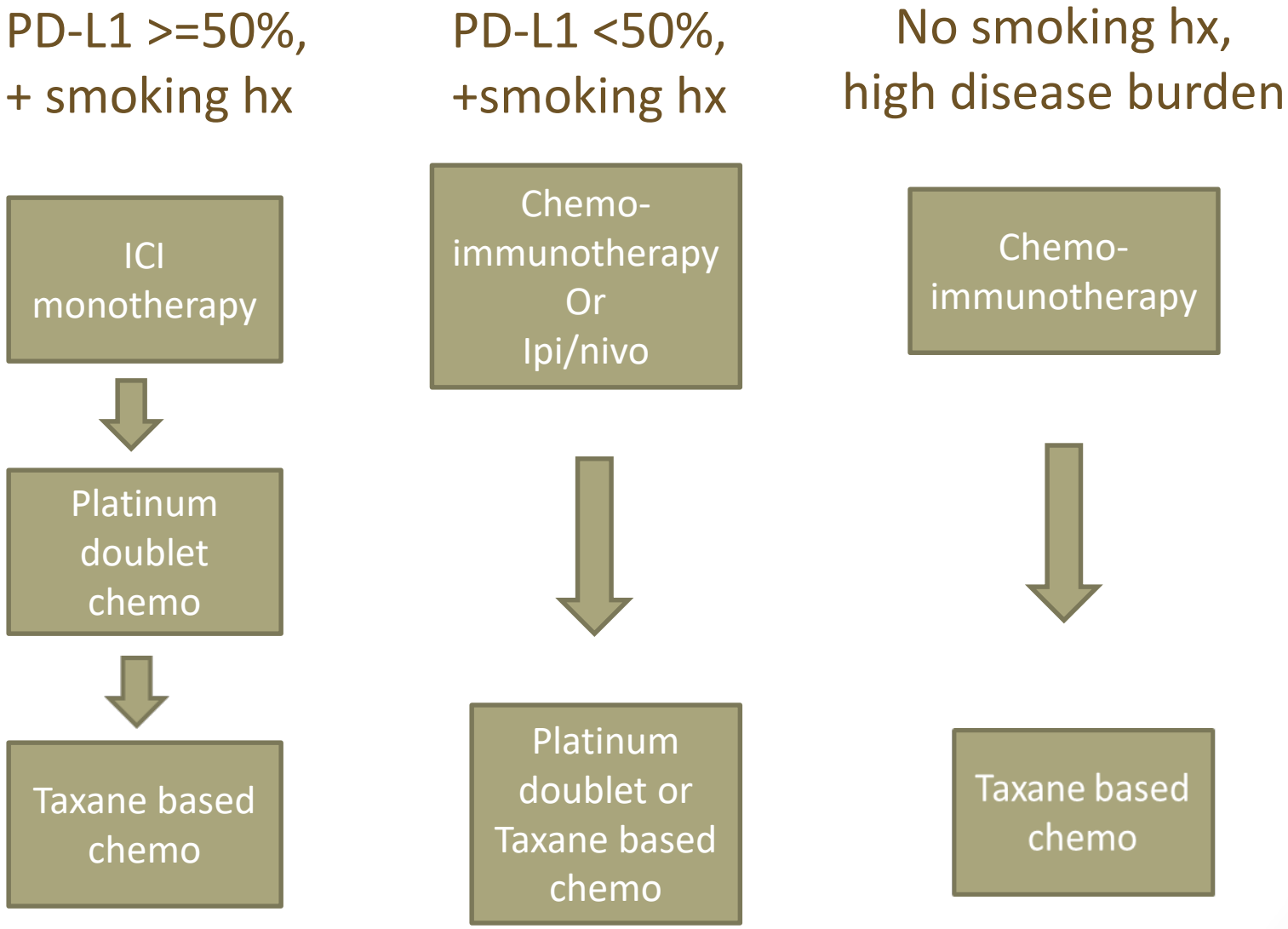
+ Molecular target



Data for frontline TKI:

- Strongest for: EGFR, ALK
- No randomized data but very compelling: ROS1, RET, NTRK
- Data not entirely clear but reasonable: BRAF V600E, MET exon14

No targetable genetic alteration, good PS (my personal practice)



Stage IV NSCLC – final thoughts

- Complete molecular testing as much as possible
  - All non-squamous histology
  - Squamous histology if light smoking history, small specimen

- Blood based molecular testing is helpful but recognize that has limited sensitivity, especially in patients with low disease burden / intrathoracic only disease → complete tissue testing as much as possible if blood based test is negative

- Oncogene driven NSCLC (especially EGFR, ALK, ROS1, RET): Immune checkpoint inhibitor monotherapy has low activity, even in PDL1 high patients. Exhaust TKI options first before considering immunotherapy based treatments

- Emerging data indicate that the combination of TKI + immunotherapy is associated with high rates of toxicities

- Use of immunotherapy continues to evolve – stay tuned

Monoclonal gammopathies and multiple myeloma

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Associate Professor of Medicine
Medical Oncology

UNIVERSITY *of* WASHINGTON

MGUS: definition

- **All three criteria must be met:**
  - **Serum monoclonal protein < 3 gm/dl**
  - **Clonal bone marrow plasma cells < 10%**
  - **Absence of end-organ damage (CRAB)**

MGUS: background

- MGUS is present in 3% of the general population≥50 years old, 5.3% ≥ 70 but only 0.3% among those <50 years old
- These premalignant conditions can progress to lymphoproliferative diseases(NHL,CLL,WM), amyloidosis, multiple myeloma or monoclonal immunoglobulin deposition disease(MIDD)
- Rate of progression of IgG & IgA MGUS to multiple myeloma is 1% per year
- Rate of progression of IgM MGUS is 1.5%/yr

Outcome of MGUS

- Cohort of 241 patients with MGUS was followed up to 39 years (median, 13.7 years)
- Twenty-seven percent (n = 64) developed multiple myeloma (44), Waldenstrom's macroglobulinemia (7), primary AL amyloidosis (8), or a lymphoproliferative disorder (5)
- Interval from recognition of MGUS to diagnosis of multiple myeloma or a related disorder ranged from 1 to 32 years (median 10.4 years)

Rajkumar. Lancet Oncol .2014;15(12): e538-48.

MGUS: risk stratification

Risk group	*No. of patients*	*Relative risk*	*Absolute risk of progression at 20 years (%)*	*Absolute risk of progression at 20 years accounting for death as a competing risk (%)*
Low-risk (serum M protein <1.5 gm/dl, IgG subtype, normal FLC ratio (0.26–1.65)	449	1	5	2
Low-intermediate-risk (any 1 factor abnormal)	420	5.4	21	10
High-intermediate-risk (any two factors abnormal)	226	10.1	37	18
High-risk (all three factors abnormal)	53	20.8	58	27

Rajkumar. Lancet Oncol .2014;15(12): e538-48.

Management of low-risk MGUS

SPEP ≤ 1.5 g/dL, IgG isotype, and normal FLC ratio

- **Majority of patients are low risk (50%)**
- **Risk of progression to MM or related malignancy low**
- **Baseline marrow or skeletal survey not routinely indicated if labs are normal**
- **BM required if pt has unexplained anemia, renal insufficiency, hypercalcemia or bone lesions**
- **f/u SPEP in 6 months, if stable follow every 2–3 yrs or when symptoms suggestive of a PC malignancy arise**

Go. Blood. 2018;131(2):163-173.

Rajkumar. Lancet Oncol .2014;15(12): e538-48.

Management of low-risk MGUS

SPEP ≤ 1.5 g/dL, IgG isotype, and normal FLC ratio

- **Lifetime risk of progression in low risk MGUS is 2% !**
- **Probability of finding ≥ 10% plasma cells in these patients is 4.7%**
- **Probability of finding bone lesions is 2.5%**
- **Routine skeletal imaging and bone marrow biopsy in low-risk MGUS has a low yield**

Go. Blood. 2018;131(2):163-173.

Rajkumar. Lancet Oncol .2014;15(12): e538-48.

Management of all other MGUS patients (intermediate and high risk)

- BM aspirate and biopsy at baseline to rule out underlying PC malignancy are recommended
- Conventional cytogenetics and FISH needed
- **Skeletal survey (out of date)** or **low-dose whole body CT, CT/PET or bone marrow MRI**
- CT of chest abdomen and pelvis in IgM MGUS for asymptomatic retroperitoneal lymph nodes
- If testing is normal follow with SPEP and CBC in 6 months and then annually for life

Go. Blood. 2018;131(2):163-173.

Light chain MGUS

- Roughly 80% of patients with multiple myeloma have IgH expression (ie, IgG, IgA, IgM, IgD, and IgE); no IgH is expressed in the remaining 20%
- One estimate is that 0.8% of the population ≥ 50 has light-chain MGUS
- Defined as an abnormal free light-chain ratio with no IgH expression, plus increased concentration of the involved light chain

Dispenzieri. Lancet 2010; 375: 1721–28.

Light chain MGUS

- Risk of progression to MM in light-chain MGUS is 0·3% per 100 person-years as compared to 0.5 % in patients with IGH expression
- 23% of this group have or will develop renal disease
- Periodic monitoring of renal function is prudent
- Can progress to light chain myeloma and/or AL(light chain) amyloidosis

Dispenzieri. Lancet 2010; 375: 1721–28.

Amyloidosis

blood
2006 108: 2520-2530
Prepublished online Jun 22, 2006;
doi:10.1182/blood-2006-03-001164

Dangerous small B-cell clones

Giampaolo Merlini and Marvin J. Stone

- **Protein misfolding disorder**
- **Soluble proteins aggregate as extracellular insoluble amyloid fibrils, causing functional and structural organ damage**
- **Plasma cell clone generally modest in size (median percentage of plasma cells in marrow = 7%)**
- **Lambda light chains >> kappa (lambda/kappa 4:1)**
- **Molecular basis for tissue localization to heart, kidney, liver, or other organs is not understood**

Diagnosis depends on an alert hematologist

- Non-diabetic nephrotic syndrome
- Heart failure (HF) with *preserved ejection fraction* (HFpEF)
- Peripheral neuropathy
- Unexplained hepatomegaly and/or increased alkaline phosphatase
- Autonomic neuropathy with weight loss
- Unexplained fatigue
- Edema
- Unintentional weight loss

YOU GOTTA TYPE THE AMYLOID !

- There is a differential diagnosis that must be considered when diagnosing amyloidosis (Congo red deposits found in tissue)
- Light chain (AL) amyloidosis
- Inherited (ATTR)
- Reactive systemic [AA] amyloidosis
- Wild-type transthyretin amyloidosis ATTRwt; or senile systemic amyloidosis
- β2-microglobulin [β2M] dialysis-related amyloidosis
- Others

Definition of smoldering:
To burn slowly but with no flame

Smoldering multiple myeloma (SMM)

- Multiple myeloma is defined as smoldering (asymptomatic) or active (symptomatic)
- Criteria for smoldering multiple myeloma are as follows:
- M-protein in serum: IgG ≥3 g/dL, IgA >1 g/dL *or*
- Bence-Jones protein >1 g/24h *and/or*
- Bone marrow clonal plasma cells ≥10%.
- **Absence of CRAB criteria** including myeloma defining events

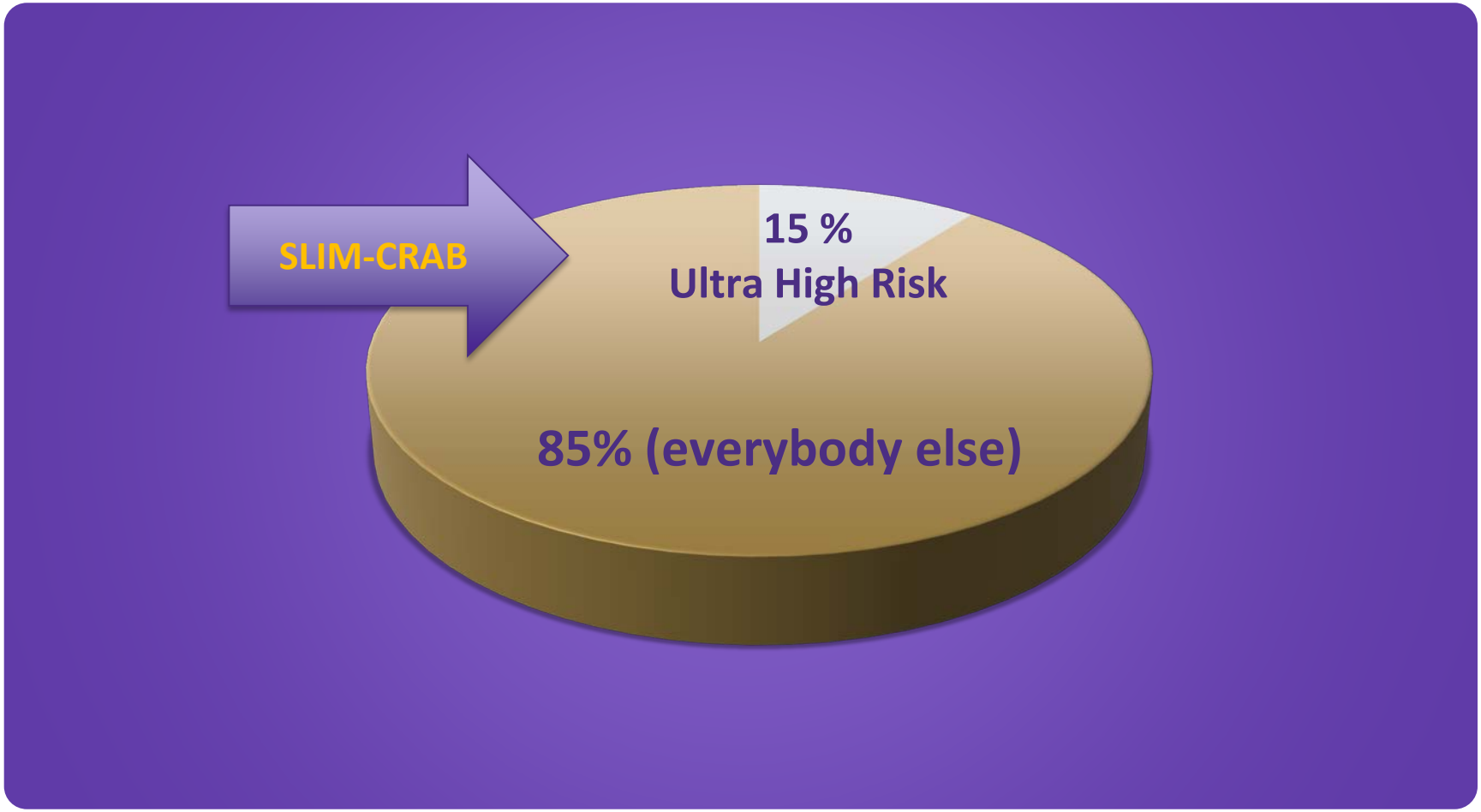
Rajkumar. Lancet Oncol.2014;15(12): e538-48.

Smoldering Multiple Myeloma

- By definition, SMM is an asymptomatic condition
- Clinical course of SMM reported by Kyle in retrospective study of 276 patients between 1970 and 1995
- Risk of progression to symptomatic myeloma (CRAB) was 10% per year for the first 5 years
- After 5 years, the risk of progression decreased to 3% per year for the next 5 years and 1% per year thereafter

Kyle. N Engl J Med 2007;356:2582-90.

SMM: 2014



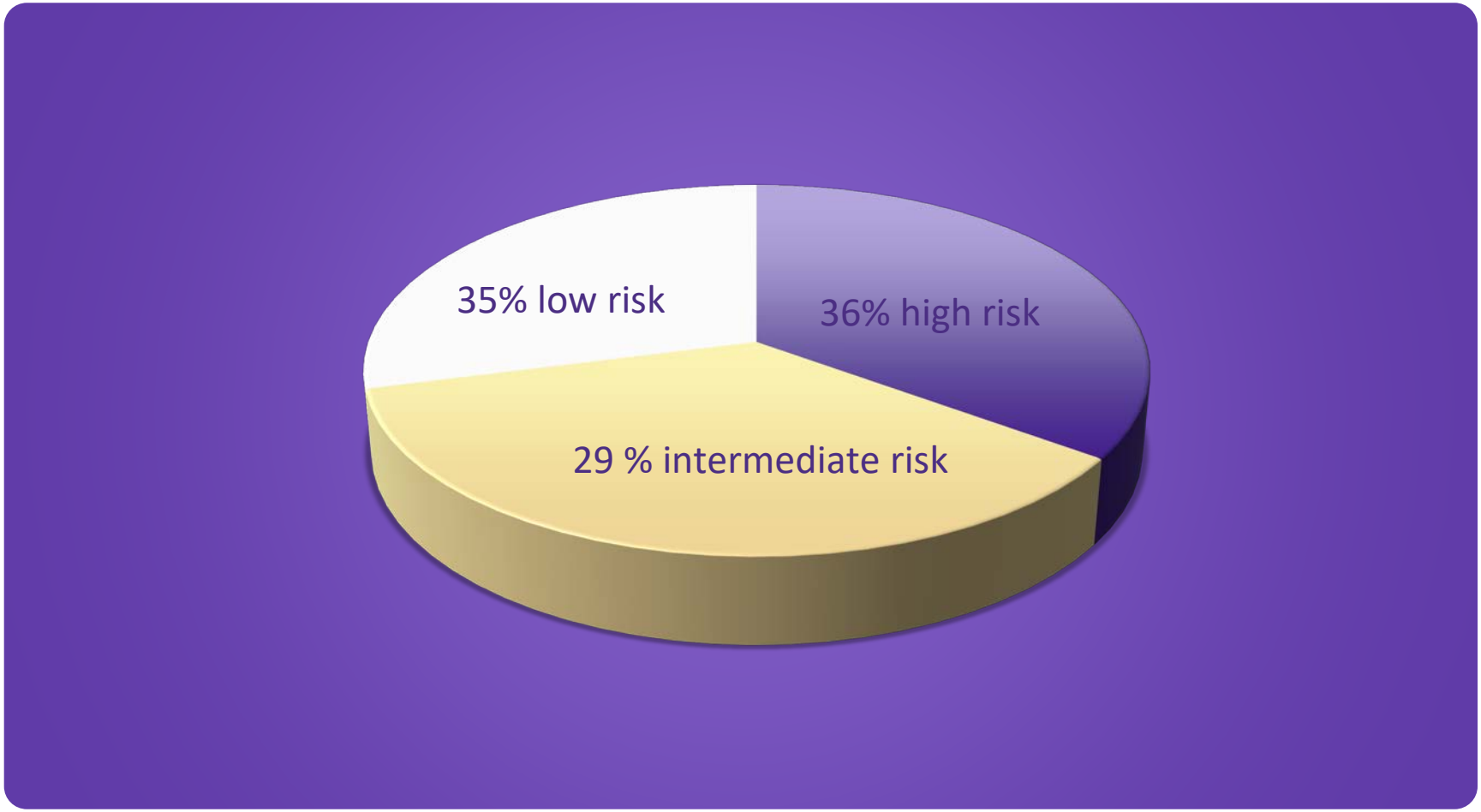
Rajkumar, Lancet Oncol. 15, e538–e548 (2014).

Current state of the art in classification of risk for progression in SMM [20/2/20 criteria]

- Stratified 421 pts into three groups: low risk (no risk factors; *n* = 143(35%); intermediate risk (one of three risk factors; *n* = 121 (29%); and high risk (≥2 of the three risk factors; *n* = 153(36%)
- Median TTP for low-, intermediate-, and high-risk groups were 110, 68, and 29 months,($p < 0.0001$)
- **CONCLUSION: BMPC% > 20%, M-protein > 2 g/dL, and FLCr > 20 at diagnosis can be used to risk stratify patients with SMM**

Lakshman. Blood Cancer J. 2018 Jun; 8(6): 59

New classification of SMM 2020



Lakshman. Blood Cancer J. 2018 Jun; 8(6): 59

Other proposed risk factors for progression in SMM

Clonal BMPCs ≥10% and any one or more of the following:
Serum M protein ≥30g/L
IgA SMM
Immunoparesis with reduction of 2 uninvolved immunoglobulin isotypes
Serum involved/uninvolved FLC ratio ≥8 (but <100)
Progressive increase in M protein level (evolving type of SMM; increase in serum M protein by ≥25% on 2 successive evaluations within a 6-month period)
Clonal BMPCs 50%-60%
Abnormal PC immunophenotype (≥95% of BMPCs are clonal) and reduction of ≥1 uninvolved immunoglobulin isotypes
t(4;14) or del(17p) or 1q gain
Increased circulating PCs
MRI with diffuse abnormalities or 1 focal lesion
PET-CT with focal lesion with increased uptake without underlying osteolytic bone destruction

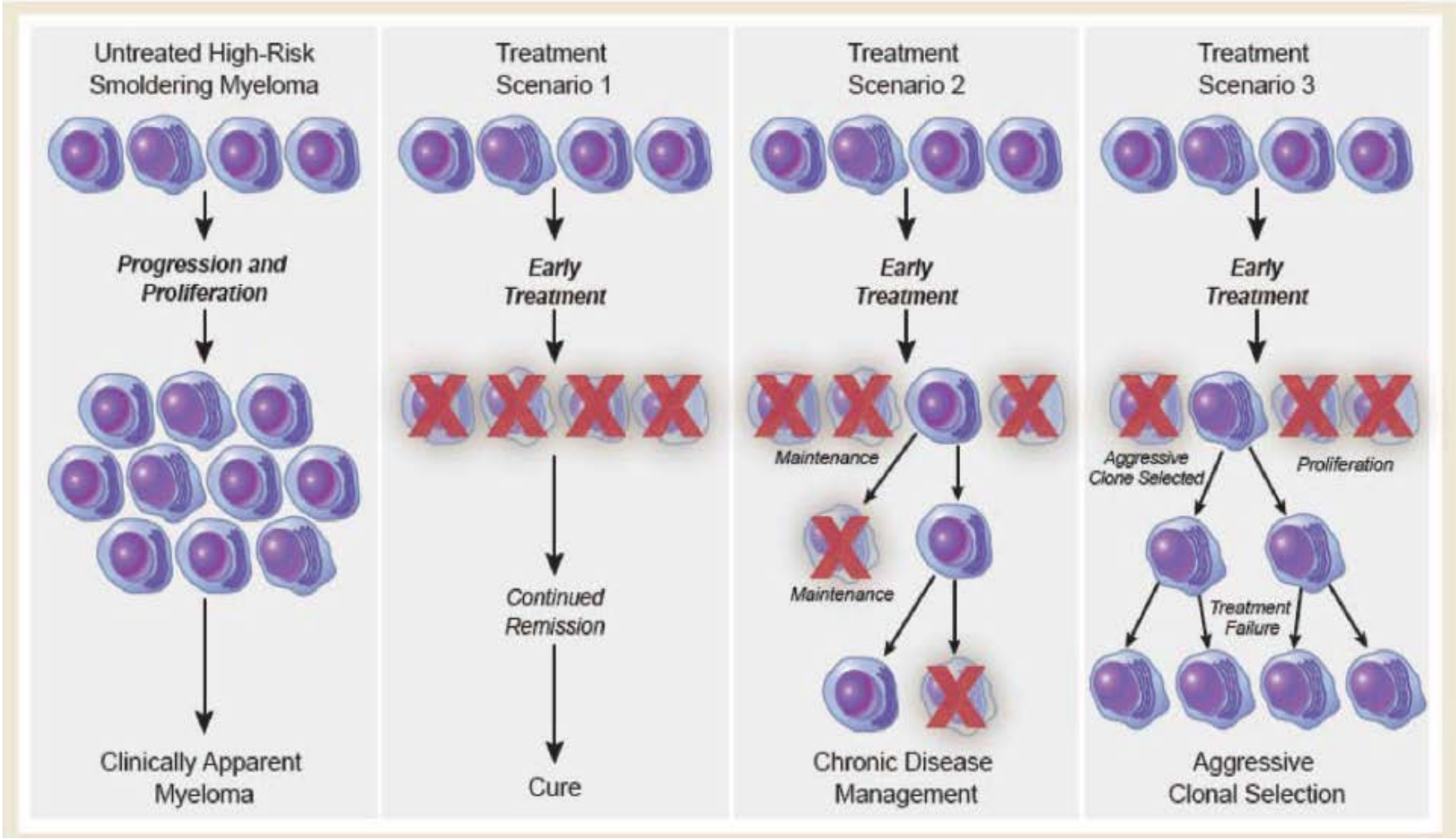
Rajkumar. Lancet Oncol .2014;15(12): e538-48.

High risk SMM 2020

- The Lakshman criteria have gained a high level of acceptance
- Still no pathological or molecular feature that distinguishes SMM patients who have only clonal premalignant PCs from those who have clonal malignant myeloma cells
- Outside of a trial ….**treatment is still not indicated**
- Watch and worry
- For higher risk patients regular reassessment and annual imaging

Rajkumar. Lancet Oncol .2014;15(12): e538-48.

Possible scenarios resulting from early treatment of smoldering myeloma



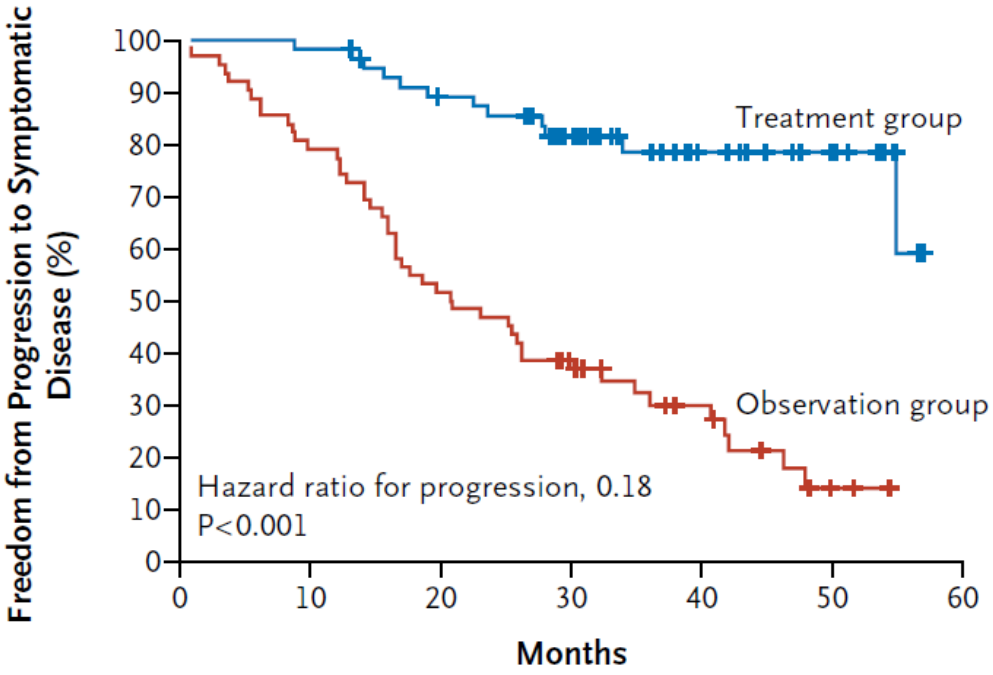
Landgren ASH 2017

1st Positive Treatment Study of SMM

- **QuiRedex**
- Randomized, open-label, phase 3 trial,119 pts
- Len/dex for 9 cycles followed by maintenance len(10mg) X 2years versus observation
- At median follow-up 40 months, median time to progression not reached vs. 21 months; HR 0.18
- 3-year OS (94% vs. 80%);HR for death, [0.31]
- Long term f/u published in 2016

Mateos N Engl J Med 2013;369:438-47 .

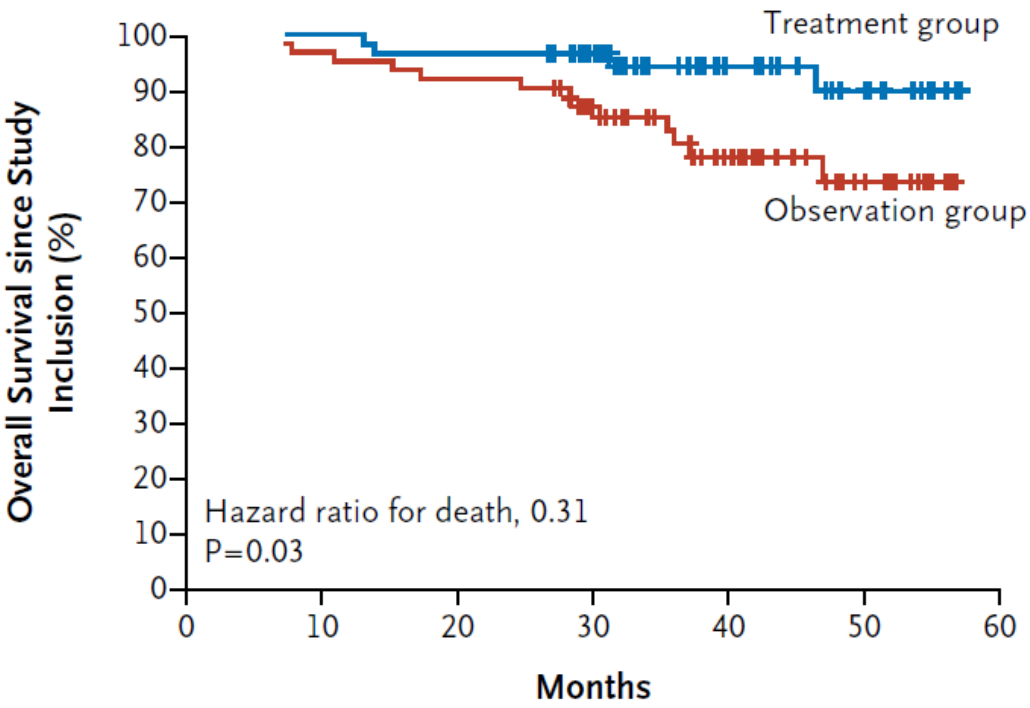
Modern Treatment Studies in High Risk SMM: (QuiRedex)



No. at Risk							
Treatment group	57	57	48	38	20	14	0
Observation group	62	49	32	21	11	3	0

Mateos N Engl J Med 2013;369:438-47 .

Modern Treatment Studies in High Risk SMM: (QuiRedex)



No. at Risk							
Treatment group	57	57	55	48	26	17	0
Observation group	62	60	57	46	27	17	0

But the QuiRedex study was not accepted as the standard of care

- A combination regimen (len + dex) used and therefore the added value of lenalidomide could not be clearly isolated
- Modern imaging not used at randomization (no CT/PET or MRI) leading to concerns regarding possible enrollment of patients with symptomatic MM
- Multiparametric flow cytometry criteria used to define high-risk SMM not readily available outside of the centers that conducted the trial, which limited the generalizability of results.
- Only 11% of patients in the observation arm who experienced disease progression were treated with lenalidomide (reflecting its limited availability at the time) which likely accounted for differences in OS

Mateos N Engl J Med 2013;369:438-47 .

ECOG E3A06: A Randomized Trial of Lenalidomide Versus Observation in Smoldering Multiple Myeloma

- Single-agent lenalidomide vs observation in intermediate- or high-risk SMM
- Lenalidomide 25 mg on days 1 to 21 of a 28-day cycle
- 182 pts randomly assigned. Median follow-up is 35 months.
- Definition intermediate or high risk- dx within 60 months and abnormal serum free light chain (FLC) ratio (<0.26 or >1.65) by serum FLC assay

Lonial, J Clin Oncol 38:1126-1137.

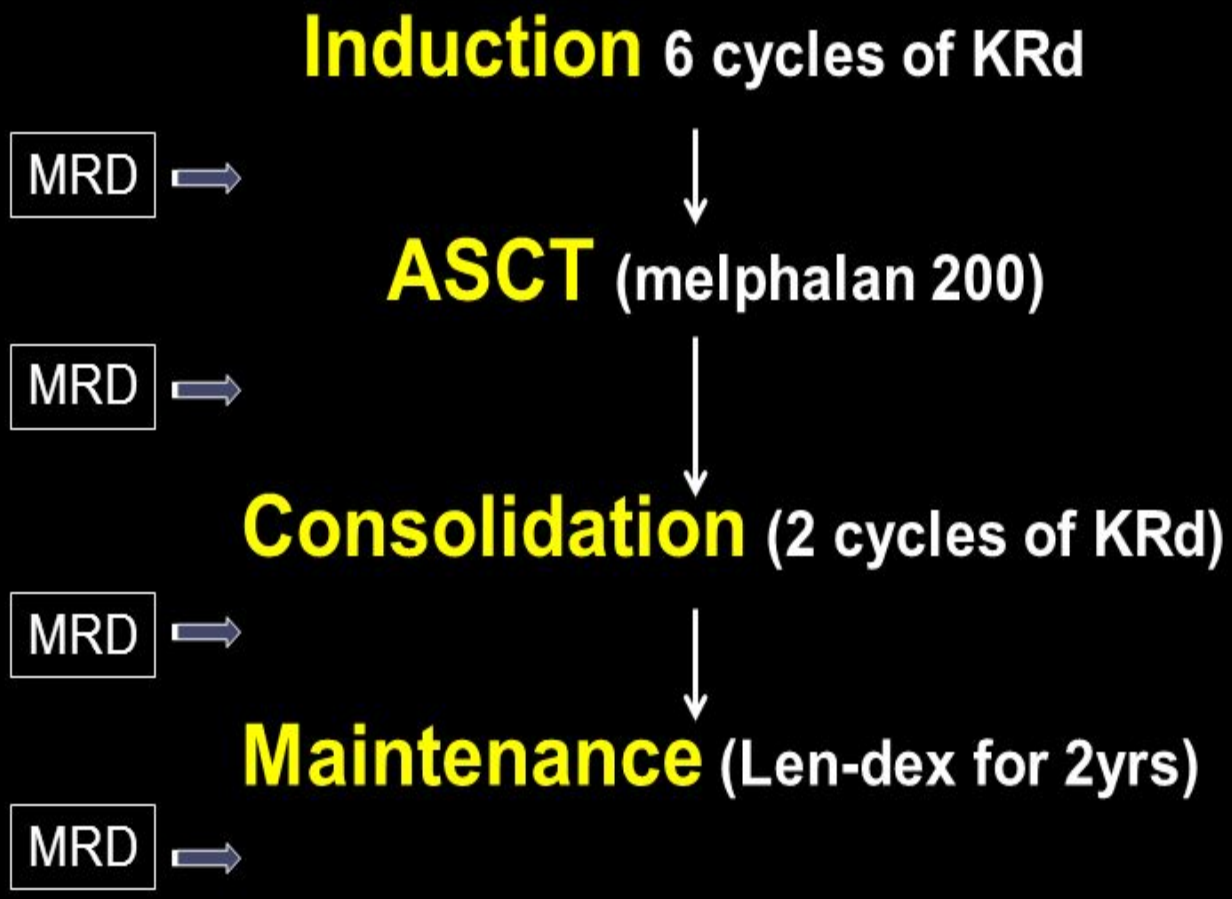
ECOG E3A06

- Overall response rate 50% (95% CI, 39% to 61%) treated pts, no responses in the observation arm.
- PFS significantly longer with lenalidomide compared with observation (hazard ratio, 0.28; 95% CI, 0.12 to 0.62; P = .002)
- One, 2, and 3 year PFS was 98%, 93%, and 91% for the lenalidomide arm versus 89%, 76%, and 66% for the observation arm

E3A06 conclusions

- Early intervention with lenalidomide in smoldering multiple myeloma significantly delays progression to symptomatic multiple myeloma and the development of end-organ damage
- But …treatment of smoldering multiple myeloma is still not SOC

Curative Estrategia Smoldering Alto Riesgo (CESAR trial) (n:90)



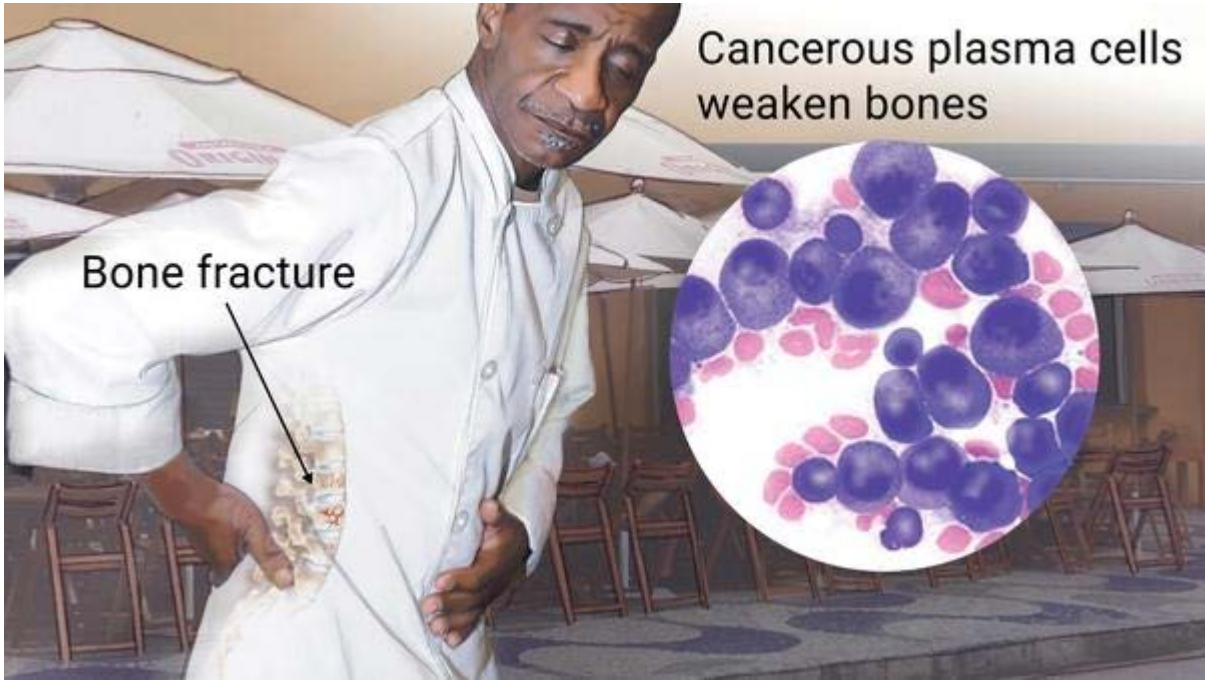
Primary objective: To evaluate the proportion of patients in sustained immunophenotypic response at 5 years

Hypothesis: At least 50% of patients will achieve the objective

20 centers

Many studies ongoing in SMM

- Phase 3 DETER-SMM: DaraRd vs Rd
- Phase 2 KRd vs Rd
- Phase 2 ASCENT: DaraKRd vs Rd
- Phase 3 AQUILA: Dara SQ vs observation
- Phase 2: Isatuximab
- Phase 1b: PVX 410 vaccine
- Others


Cancerous plasma cells
weaken bones
Bone fracture

Diagnosis of MM

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

CRAB

Hypercalcemia: >1 mg/dL higher than the upper limit of normal or >11 mg/dL

Renal insufficiency: CrCl <40 mL/min or serum creatinine > 2 mg/dL

Anemia: Hgb >2.0 g/L below the lower limit of normal, or <10 g/L

Bone lesions: one or more **osteolytic lesions** on skeletal radiography, CT, or PET-CT

Any one or more of the following biomarkers of malignancy:

Clonal bone marrow plasma cell percentage ≥60%

Involved:uninvolved serum free light chain ratio ≥100

>1 focal lesion on MRI studies

(each focal lesion must be 5 mm or more in size)

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Hereditary Cancer Syndromes

Cynthia Handford, MSc, LCGC
chandford@seattlecca.org

Better together.

Objectives

- Review indications for genetic testing and genetic counseling in the oncology setting
- Review of specific hereditary cancer syndromes
- Discuss details of genetic testing and the possible implications for patient care

Genetic Counseling in Hereditary Cancer

- Genetic counselors can help determine which patients would benefit from genetic testing, as well as how genetic testing may help their oncology team when determining treatment recommendations
- Determine appropriate genetic testing based on personal and family history
- Discuss implications for family members based on testing results
- Referrals/recommendations for screening and prevention of future cancers based on most recent guidelines
- Address any insurance concerns regarding genetic testing
- Work with oncology with tumor/germline genetic testing for treatment recommendations
- Referrals for research studies or support groups

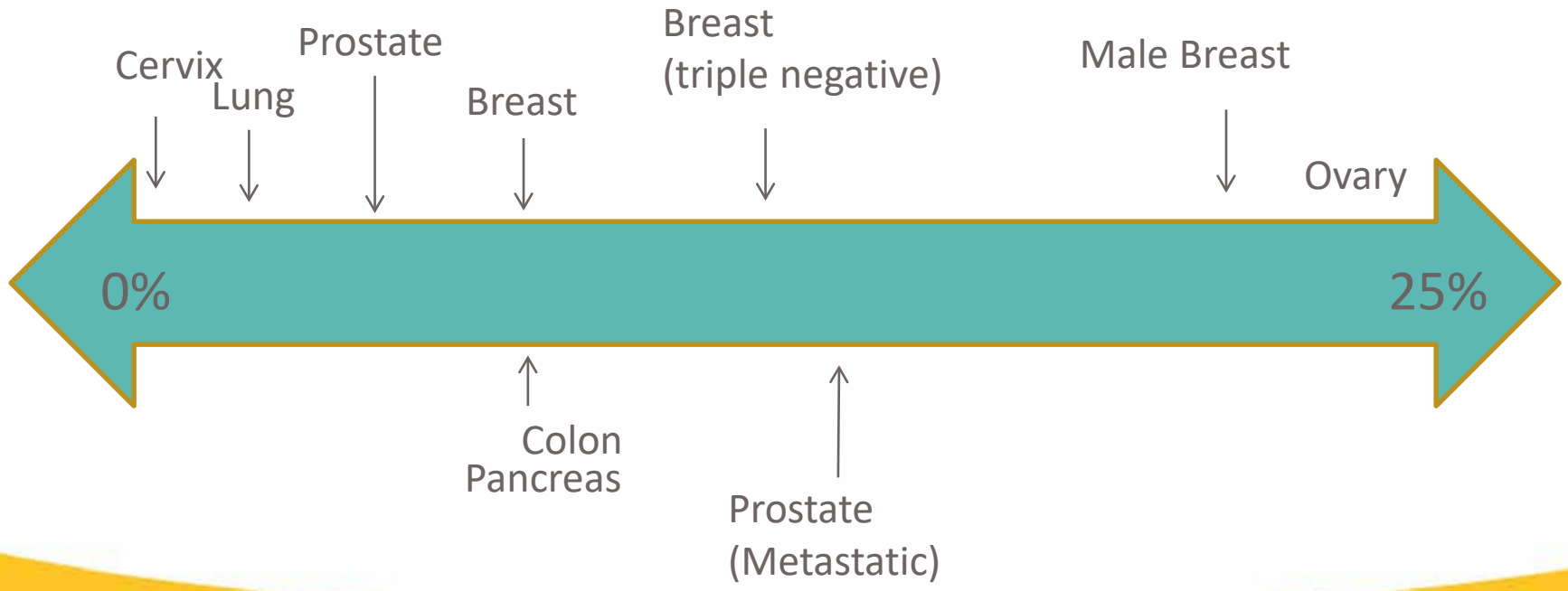
Which patients need genetics?

Approximately 5-10% of cancers are due to a pathogenic mutation in a known hereditary cancer gene.

Criteria for genetic testing:

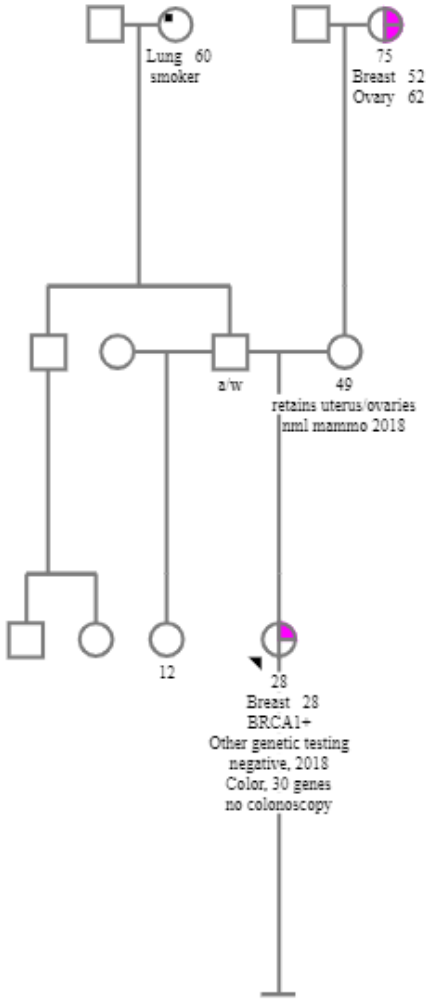
- Unusually early age of cancer onset (e.g., premenopausal breast cancer).
- Multiple primary cancers in a single individual (e.g., colorectal and endometrial cancer).
- Bilateral cancer in paired organs or multifocal disease (e.g., bilateral breast cancer or multifocal renal cancer).
- Clustering of the same type of cancer in close relatives.
- Cancers occurring in multiple generations of a family.
- Occurrence of rare tumors (e.g., male breast cancer, adrenocortical carcinoma, granulosa cell tumor of the ovary, ocular melanoma, or duodenal cancer).
- Occurrence of epithelial ovarian, fallopian tube, or primary peritoneal cancer.
- Concern for germline mutations following tumor testing results (e.g. BRCA mutation in breast tumor tissue)
- Occurrence of metastatic prostate cancer, regardless of age
- Occurrence of pancreatic cancer, regardless of age
- All breast cancers??

Which cancers are more likely to be hereditary?



Hereditary breast and ovarian cancer syndrome (HBOC)

- Mutations in BRCA1 or BRCA2
- Autosomal dominant inheritance
- Associated with increased risk of breast, ovarian, prostate, and pancreatic cancer
- Approximately 1/500 individuals carry mutations in BRCA1 or BRCA2
  - 1/40-1/50 frequency in Ashkenazi Jewish individuals



Risk of malignancy in HBOC

Cancer Type	General Population Risk	Risk for Malignancy [1]	
		BRCA1	BRCA2
Breast	12%	46%-87%	38%-84%
Second primary breast	~10-15%	40% within 20 years	26% within 20 years
Ovarian	1%-2%	39%-55%	16.5%-27%
Male breast	0.1%	1.2%	Up to 8.9%
Prostate	10-15%	Slightly elevated	Elevated (high grade, metastatic)
Pancreatic	0.50%	1%-3%	2%-7%
Melanoma (cutaneous & ocular)	1.6%		Elevated Risk

Source: Petrucelli N, Daly MB, Pal T. BRCA1- and BRCA2-Associated Hereditary Breast and Ovarian Cancer. 1998 Sep 4 [Updated 2016 Dec 15]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews®. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1247/

Management for HBOC

Surveillance

- Clinical breast exam every 6-12 months, starting at age 25
- Annual breast MRI starting at age 25
- Annual mammogram starting at age 30
- For men – clinical breast exam and prostate cancer screening
- Pancreatic cancer screening considered if Fhx

Surgical

- Discuss option of bilateral mastectomy
- Risk reducing salpingo-oophorectomy (RRSO)
    - Age 35-40 for BRCA1
    - Age 40-45 for BRCA2

Management for HBOC

- Men:
  - Breast self-exam training and education starting at age 35y
  - Clinical breast exam every year, starting at age 35y
  - Recommend prostate cancer screening at age 45

- Treatment implications of HBOC
  - Surgical planning
  - Radiation treatment
  - Possible use of PARP inhibitors


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Maintenance Olaparib in Patients with Newly Diagnosed Advanced Ovarian Cancer

K. Moore, N. Colombo, G. Scambia, B.-G. Kim, A. Oaknin, M. Friedlander,

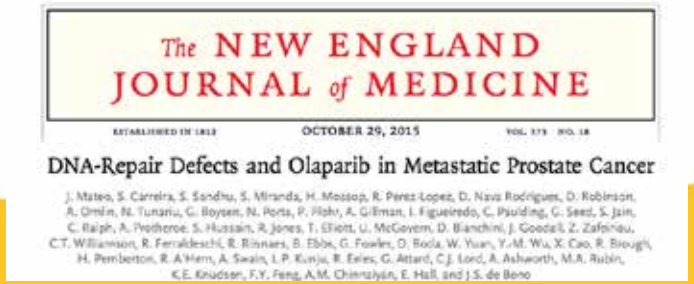

The NEW ENGLAND JOURNAL of MEDICINE


Talazoparib in Patients with Advanced Breast Cancer and a Germline BRCA Mutation


ORIGINAL ARTICLE

Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D.,


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 OCTOBER 29, 2015 VOL. 373 NO. 18

DNA-Repair Defects and Olaparib in Metastatic Prostate Cancer

J. Mateo, S. Carreira, S. Sandhu, S. Miranda, H. Mossop, R. Perez-Lopez, D. Nava Rodrigues, D. Robinson, A. Omlin, N. Tunariu, G. Boysen, N. Porta, P. Flohr, A. Gillman, I. Figueiredo, C. Paulding, G. Seed, S. Jain, C. Ralph, A. Protheroe, S. Hussain, R. Jones, T. Elliott, U. McGovern, D. Bianchini, J. Goodall, Z. Zafeiriou, C.T. Williamson, R. Ferraldeschi, R. Riisnaes, B. Ebbs, G. Fowler, D. Roda, W. Yuan, Y.-M. Wu, X. Cao, R. Brough, H. Pemberton, R. A'Hern, A. Swain, L.P. Kunju, R. Eeles, G. Attard, C.J. Lord, A. Ashworth, M.A. Rubin, K.E. Knudsen, F.Y. Feng, A.M. Chinnaiyan, E. Hall, and J.S. de Bono

Cowden Syndrome

- Mutations in PTEN gene
- Autosomal dominant inheritance
- Increased risk of:
  - Breast
  - Uterine
  - Thyroid
  - Colon (polyps and/or cancer)
- Other Findings:
  - Macrocephaly
  - Intellectual disability
  - Hamartomas
  - Lipomas

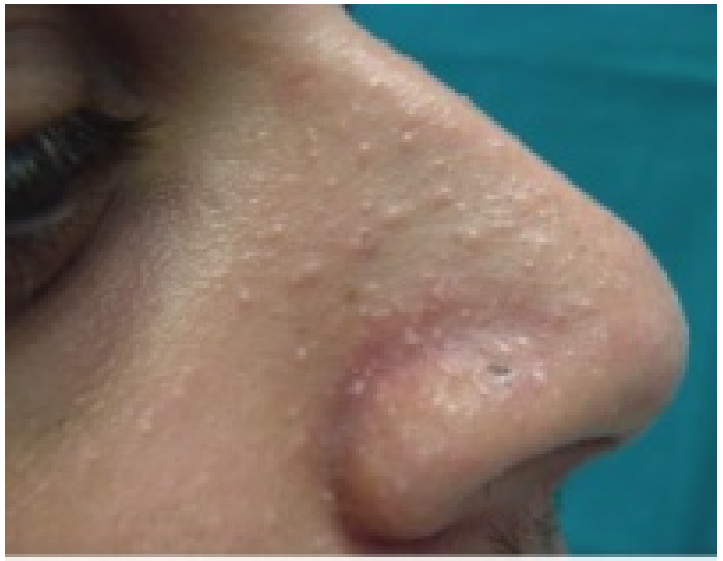


Figure. Hamartomas characteristic of Cowden syndrome.

Source: Marcio A Oliveira et al.

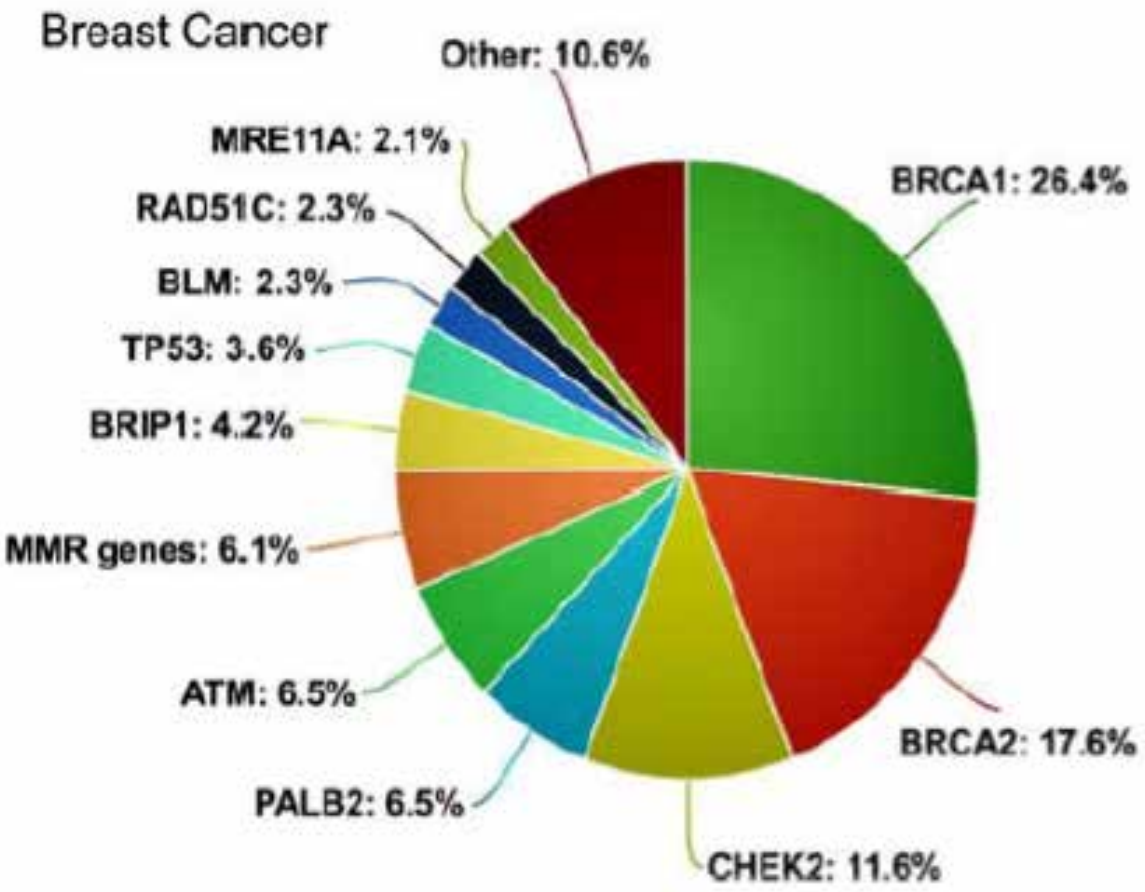
Li Fraumeni Syndrome (LFS)

- Mutations in TP53 gene
- Autosomal dominant inheritance
- Increased risk of:
  - Breast
  - Brain
  - Sarcoma
  - Adrenocortical Carcinoma
- Childhood cancers can be seen in LFS
- Highly penetrant cancer syndrome
  - 50% risk of cancer by age 40
  - 90% risk of cancer by age 60

Other hereditary breast cancer genes

- PALB2
  - Breast, ovary, pancreas, prostate
- ATM
  - Breast, pancreas
- CHEK2
  - Breast, colon
- CDH1
  - Diffuse gastric cancer and lobular breast cancer
- BARD1, BRIP1, RAD51C, RAD51D
  - Breast and/or ovary

Hereditary breast cancer



Hereditary Breast and Ovarian Cancer Syndrome: Moving Beyond BRCA1 and BRCA2 Lien N. Hoang, MD and Blake C. Gilks, MD, FRCPC

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a-e]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
ATM	**Increased risk of female breast cancer[f]** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[g,h] • RRM: Evidence insufficient, manage based on family history	**Potential increase in ovarian cancer risk** • RRSO: Evidence insufficient; manage based on family history	• **Pancreatic** ▸ See PANC-A • **Unknown or insufficient evidence for prostate cancer**
	Comments: Counsel for risk of autosomal recessive condition in offspring. ATM mutation should not lead to a recommendation to avoid radiation therapy at this time. See Discussion for information regarding the c.7271T>G variant.		
BARD1	**Potential increase in female breast cancer (including triple negative) risk with insufficient evidence for risk management**	**Unknown or insufficient evidence for ovarian cancer risk**	**Unknown or insufficient evidence for other cancers**
BRCA1	**Increased risk of breast cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Increased risk of ovarian cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Pancreatic, Prostate** • See *BRCA* Pathogenic Variant-Positive Management
BRCA2	**Increased risk of breast cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Increased risk of ovarian cancer** • See *BRCA* Pathogenic Variant-Positive Management	**Pancreatic, Prostate, Melanoma** • See *BRCA* Pathogenic Variant-Positive Management
	Comment: Counsel for risk of autosomal recessive condition in offspring.		
BRIP1	**Potential increase in female breast cancer (including triple negative) risk with insufficient evidence for risk management**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	**Unknown or insufficient evidence for other cancers**
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *BRIP1* appears to be sufficient to justify consideration of risk-reducing salpingo-oophorectomy. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset of ovarian cancer.		

RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

Continued
Footnotes on GENE-A 5 of 5

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a-e]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
CDH1	**Increased risk of female lobular breast cancer[f]** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 30 y[g,h] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	**Diffuse gastric cancer** • See NCCN Guidelines for Gastric Cancer: Principles of Genetic Risk Assessment for Gastric Cancer
	Comments: There is controversy over how to manage gastric cancer risk in individuals with pathogenic/likely pathogenic variants in *CDH1* in the absence of a family history of gastric cancer. However, one small study found that >50% of such individuals had gastric cancer identified at the time of risk-reducing total gastrectomy (Jacobs MF, et al. Gastroenterology 2019;157:87-96). Cleft lip with or without cleft palate has been associated with *CDH1* pathogenic/likely pathogenic variants (Frebourg T, et al. J Med Genet 2006;43:138-142).		
CDKN2A	**No increased risk of breast cancer**	**No increased risk of ovarian cancer**	**Increased risk of pancreatic cancer** • See PANC-A
CHEK2	**Increased risk of female breast cancer[f]** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[g,h] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	**Colon** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
	Comments: Risk data are based only on frameshift pathogenic/likely pathogenic variants. The risks for most missense variants are unclear but for some pathogenic/likely pathogenic variants, such as Ile157Thr, the risk for breast cancer appears to be lower. Management should be based on best estimates of cancer risk for the specific pathogenic/likely pathogenic variant.		
MSH2, MLH1, MSH6, PMS2, EPCAM[i]	**Unknown or insufficient evidence for breast cancer risk[g]** • Manage based on family history	**Increased risk of ovarian cancer** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	**Colon, Uterine, Others** • See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal **Pancreatic (insufficient evidence for PMS2)** • See PANC-A
	Comment: Counsel for risk of autosomal recessive condition in offspring.		

RRM: Risk-reducing mastectomy

Continued
Footnotes on GENE-A 5 of 5

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a-e]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
NBN	**Increased risk of female breast cancer for individuals with 657del5 variant[f]** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[g,h] • RRM: Evidence insufficient, manage based on family history	**Potential increase in ovarian cancer risk,** • RRSO: Evidence insufficient; manage based on family history	**Unknown or insufficient evidence for other cancers**
	Comments: Current data suggest that breast cancer risks are not increased for pathogenic/likely pathogenic variants other than 657del5. Counsel for risk of autosomal recessive condition in children.		
NF1	**Increased risk of female breast cancer[f]** • Screening: Annual mammogram with consideration of tomosynthesis starting at age 30 y and consider breast MRI with contrast from ages 30–50 y[g,h] • RRM: Evidence insufficient, manage based on family history	**No increased risk of ovarian cancer**	• **Malignant peripheral nerve sheath tumors, GIST, others** • Recommend referral to *NF1* specialist for evaluation and management
	Comments: At this time, there are no data to suggest an increased breast cancer risk after age 50 y. Screening recommendations only apply to individuals with a clinical diagnosis of NF. Consider possibility of false-positive MRI results due to presence of breast neurofibromas.		
PALB2	**Increased risk of female breast cancer[f]** • Screening: Annual mammogram with consideration of tomosynthesis and breast MRI with contrast at 30 y[g,h] • RRM: Discuss option of risk-reducing mastectomy	**Potential increase in ovarian cancer risk** • RRSO: Evidence insufficient; manage based on family history	• **Pancreatic** ▸ See PANC-A • **Unknown or insufficient evidence for other cancers**
	Comments: Counsel for risk of autosomal recessive condition in offspring.		
PTEN	**Increased risk of female breast cancer** • See Cowden Syndrome Management	**No increased risk of ovarian cancer**	See Cowden Syndrome Management

RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

Continued
Footnotes on GENE-A 5 of 5

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

CANCER RISK MANAGEMENT BASED ON GENETIC TEST RESULTS[a-e]

The inclusion of a gene in this table below does not imply the endorsement either for or against multi-gene testing for moderate-penetrance genes.

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
RAD51C	**Potential increase in triple-negative female breast cancer risk with insufficient evidence for risk management**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	N/A
	Comments: Counsel for risk of autosomal recessive condition in offspring. Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *RAD51C* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
RAD51D	**Potential increase in triple-negative female breast cancer risk with insufficient evidence for risk management**	**Increased risk of ovarian cancer** • Consider RRSO at 45–50 y	N/A
	Comments: Based on estimates from available studies, the lifetime risk of ovarian cancer in carriers of pathogenic/likely pathogenic variants in *RAD51D* appears to be sufficient to justify consideration of RRSO. The current evidence is insufficient to make a firm recommendation as to the optimal age for this procedure. Based on the current, limited evidence base, a discussion about surgery should be held around age 45–50 y or earlier based on a specific family history of an earlier onset ovarian cancer.		
STK11	**Increased risk of female breast cancer** • Screening: See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome • RRM: Evidence insufficient, manage based on family history	**Increased risk of non-epithelial ovarian tumors** • See NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome	• See NCCN Guidelines for Genetic/ Familial High-Risk Assessment: Colorectal - Peutz-Jeghers syndrome • **Pancreatic**, see PANC-A
TP53	**Increased risk of female breast cancer** • See Li-Fraumeni Syndrome Management	**No increased risk of ovarian cancer**	• See Li-Fraumeni Syndrome Management • **Pancreatic,** see PANC-A

RRM: Risk-reducing mastectomy
RRSO: Risk-reducing salpingo-oophorectomy

Footnotes on GENE-A 5 of 5

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Lynch Syndrome (formerly known as HNPCC)

- Mutations in mismatch repair genes (MLH1, MSH2 (EPCAM), MSH6, and PMS2)
- Associated with an increased risk of colon, uterine, stomach, ovarian, and other cancers.
- Autosomal dominant inheritance
- Many patients have MSI or IHC testing to screen for Lynch Syndrome
  - Validated for colon and endometrial cancers, can be used on other tissue types
  - Based on results, further somatic testing may be indicated
    - MLH1 hypermethylation, BRAF testing
  - Germline testing may be indicated with or without MSI or IHC
  - Abnormal MSI/IHC is NOT diagnostic of Lynch Syndrome

Cancer Risks in Lynch Syndrome by Gene Compared to the General Population

	General Population Risk[1]	*MLH1*		*MSH2* (For EPCAM, see footnote 10)		*MSH6*		*PMS2*	
		Risk	Average age of diagnosis	Risk	Average age of diagnosis	Risk	Average age of diagnosis	Risk	Average age of diagnosis
Colorectal[1-6]	4.5%	46%–49%	43–45 years	43%–52%	44 years	15%–44%	51–63 years	12%–20%	47–66 years
Endometrial[1-6]	2.7%	43%–57%	49 years	21%–57%	47–48 years	17%–46%	53–55 years	0%–15%	49–56 years
Breast[2,3,7]	13%	12%–17%	53 years	12%	52 years	0%–13%	52 years	NE	
Ovarian[1,2,7]	1.3%	5%–20%	44–47 years	10%–38%	43–44 years	1%–11%	44–48 years	NE	
Gastric[1,2,7,8]	<1%	5%–7%	49–52 years	0.2%–16%	49–52 years	0%–5%	49–63 years	NE	
Pancreas[2]	1.5%	6%	52–57 years	NE		NE		NE	
Bladder[2,7,9]	2.5%	2%–4%	53–59 years	4%–17%	53–59 years	2%	53–71 years	NE	
Biliary tract[1,2]	<1%	2%–4%	50 years	0.02%	57 years	NE		NE	
Urothelial[1,2,7,9]	<1%	0.2%–5%	52-60 years	2%–18%	52–61 years	0.7%–7%	52–69 years	NE	
Small bowel[1,7]	<1%	0.4%–11%	46-47 years	1%–10%	46–48 years	0%–3%	46–54 years	NE	
Prostate[2,3,7,11]	11.6%	0%–17%	59 years	30%–32%	59 years	0%–5%	59 years	NE	
Brain/CNS[2]	<1%	NE		NE		Not reported	Not reported	NE	

Management for Lynch Syndrome

Surveillance

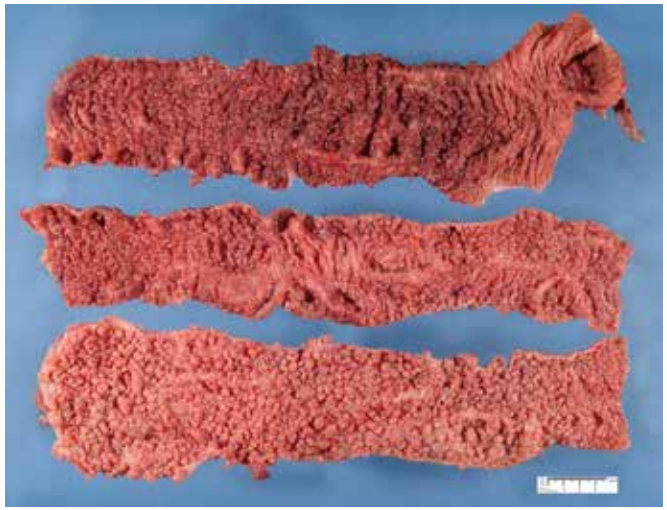
- Colonoscopy every 1-2 years, starting at age
  - 20-25 (MLH1, MSH2)
  - 30-35 (MSH6, PMS2)
- Consider upper endoscopy at age 40 and repeat every 3-5 years
- Consider annual urinalysis starting at age 30-35
- Consider endometrial biopsy starting at age 30-35
- Consider annual physical/neurologic exam starting at age 25-30
- Pancreatic cancer screening considered if Fhx

Surgical

- Discuss option of TAH+/-BSO (depending on gene) after family is complete
- Discuss surgical options with physician regarding future colon cancer risk

Familial Adenomatous Polyposis

- Caused by mutations in the APC gene
- Autosomal dominant
- Classic form:
  - 100-1000's of colon/rectal/gastric polyps
  - Risk of extracolonic findings
    - Desmoids
    - Osteomas
    - Supernumerary teeth
    - CHRPE
    - Thyroid cancer
  - Recommend colonoscopy annually starting at age 10-15y
    - Colectomy common in 20's
  - Attenuated form:
    - 10-100 polyps over a lifetime



Other polyposis conditions

- MYH-associated Polyposis (MUTYH)
  - Adenomas, can be throughout GI tract
  - Autosomal recessive
- Peutz-Jeghers Syndrome (STK11)
  - Hamartomatous polyps, increased cancer risk (breast colon cancer, pancreas), oral freckling (childhood)
- Juvenile Polyposis (BMPR1A and SMAD4)
  - Juvenile type polyps, colon & stomach cancer
  - SMAD4 also causes hereditary hemorrhagic telangiectasia (HHT)
- Serrated Polyposis Syndrome

Table 4: Recommended Management for Patients with Pathogenic Variants in Genes That May Confer a Risk for Colorectal Cancer

GENE	RECOMMENDATION
APC	See NCCN Guidelines for Familial Adenomatous Polyposis (FAP-1)
BMPR1A	See NCCN Guidelines for Juvenile Polyposis Syndrome (JPS-1)
LS genes *(MLH1, MSH2, MSH6, PMS2, EPCAM)*	See NCCN Guidelines for Lynch Syndrome (LS-1)
MUTYH biallelic pathogenic variants	See NCCN Guidelines for *MUTYH*-Associated Polyposis (MAP-1)
PTEN	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
STK11	See NCCN Guidelines for Peutz-Jeghers Syndrome (PJS-1)
SMAD4	See NCCN Guidelines for Juvenile Polyposis Syndrome (JPS-1)
TP53	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
GREM1[g]	• Begin colonoscopy at age 25–30 y and every 2–3 y if negative. If polyps are found, colonoscopy every 1–2 y with consideration of surgery if the polyp burden becomes unmanageable by colonoscopy. • Surgical evaluation if appropriate.
POLD1[g]	
POLE[g]	
AXIN2[g]	
NTHL1 biallelic pathogenic variants[g]	
MSH3 biallelic pathogenic variants[g]	
APC I1307K pathogenic variant[g] *CHEK2*[g,h]	• For probands with CRC and one of these pathogenic variants: ▸ See surveillance recommendations for post-CRC resection: ◊ NCCN Guidelines for Colon Cancer and NCCN Guidelines for Rectal Cancer • For probands unaffected by CRC with a first-degree relative with CRC: ▸ Colonoscopy screening every 5 y, beginning at age 40 or 10 y prior to age of first-degree relative's age at CRC diagnosis. • For probands unaffected by CRC and no first-degree relative with CRC: ▸ Colonoscopy screening every 5 y, beginning at age 40. • For CHEK2, also see See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic
iMUTYH heterozygotes[g]	• For probands unaffected by CRC with a first-degree relative with CRC: ▸ Colonoscopy screening every 5 y, beginning at age 40 y or 10 y prior to age of first-degree relative's age at CRC diagnosis. See screening recommendations in NCCN Guidelines for Colorectal Cancer Screening. • There are no specific data available to determine screening recommendations for a patient with an *MUTYH* heterozygous pathogenic variant and a second-degree relative affected with CRC. See NCCN Guidelines for Colorectal Cancer Screening. • For probands unaffected by CRC with NO family history of CRC: ▸ Data are unclear as to whether specialized screening is warranted for *MUTYH* heterozygous carriers unaffected by CRC with no family history of CRC.[i]
ATM, BLM, GALNT12, RNF43, RPS20	• Available data are insufficient to provide specialized colorectal cancer screening recommendations at this time. See NCCN Guidelines for Colorectal Cancer Screening.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

See footnotes on GENE-7.

Other hereditary cancer genes

- GREM1, POLD1, POLE, MSH3
  - Colon
- SDHA, SDHB, SDHC, SDHD
  - Pheochromocytoma, paraganglioma
- MEN1, RET
  - Endocrine neoplasias
- BAP1
  - Mesothelioma, ocular melanoma, cutaneous melanoma
- CDKN2A
  - Pancreatic cancer, melanoma
- Familial MDS/AML
  - Eg GATA2, DDX41, CEBPA, RUNX1

Genetic testing for hereditary cancers

- Past testing was targeted to specific genes
  - BRCA1, BRCA2, TP53
- Now NextGen panels are most widely used
  - Breast cancer panels (8-25 genes)
  - Breast and GYN panels (15-40 genes)
  - Colon panels (10-25 genes)
  - Comprehensive cancer panels (50-100+ genes)
- Allows for higher detection rate in shorter turn around time for patients
- Increased possibility of incidental findings and uncertain information

Genetic testing for hereditary cancers

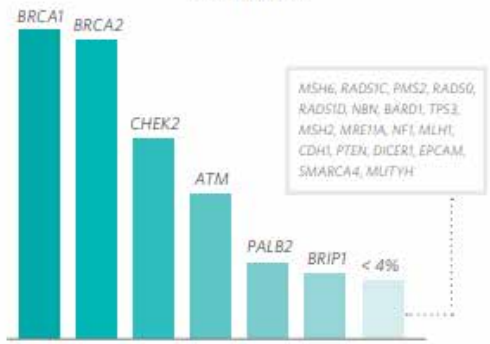
- Possible results from genetic testing
  - Positive
    - Confirmed diagnosis of hereditary cancer syndrome
    - Discuss gene specific screening/surveillance recommendations
    - Discuss familial implications
  - Negative
    - May need further testing in the future
    - Make recommendations based on personal and family history
  - Variant of uncertain significance
    - Clinically treated like a negative test result
    - Can be very confusing for the patient
    - Recommendations should be made based on family history, not the specific variant
    - Reclassification is the goal
      - Family/segregation studies
      - RNA studies

Mutation Distributions

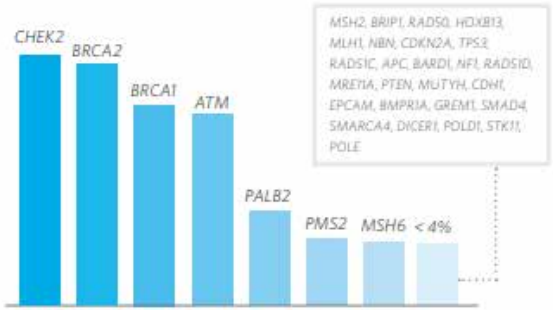
ORDERING THE RIGHT TEST CAN PROVIDE THE MOST ACCURATE AND COMPREHENSIVE ANSWERS

BreastNext®

OvaNext®

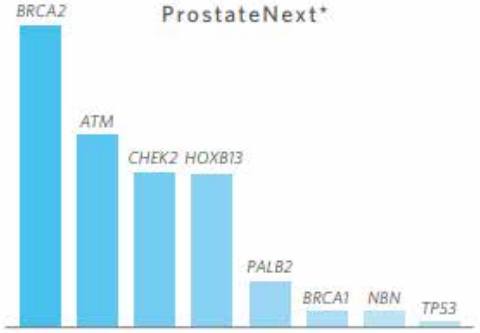


CancerNext®



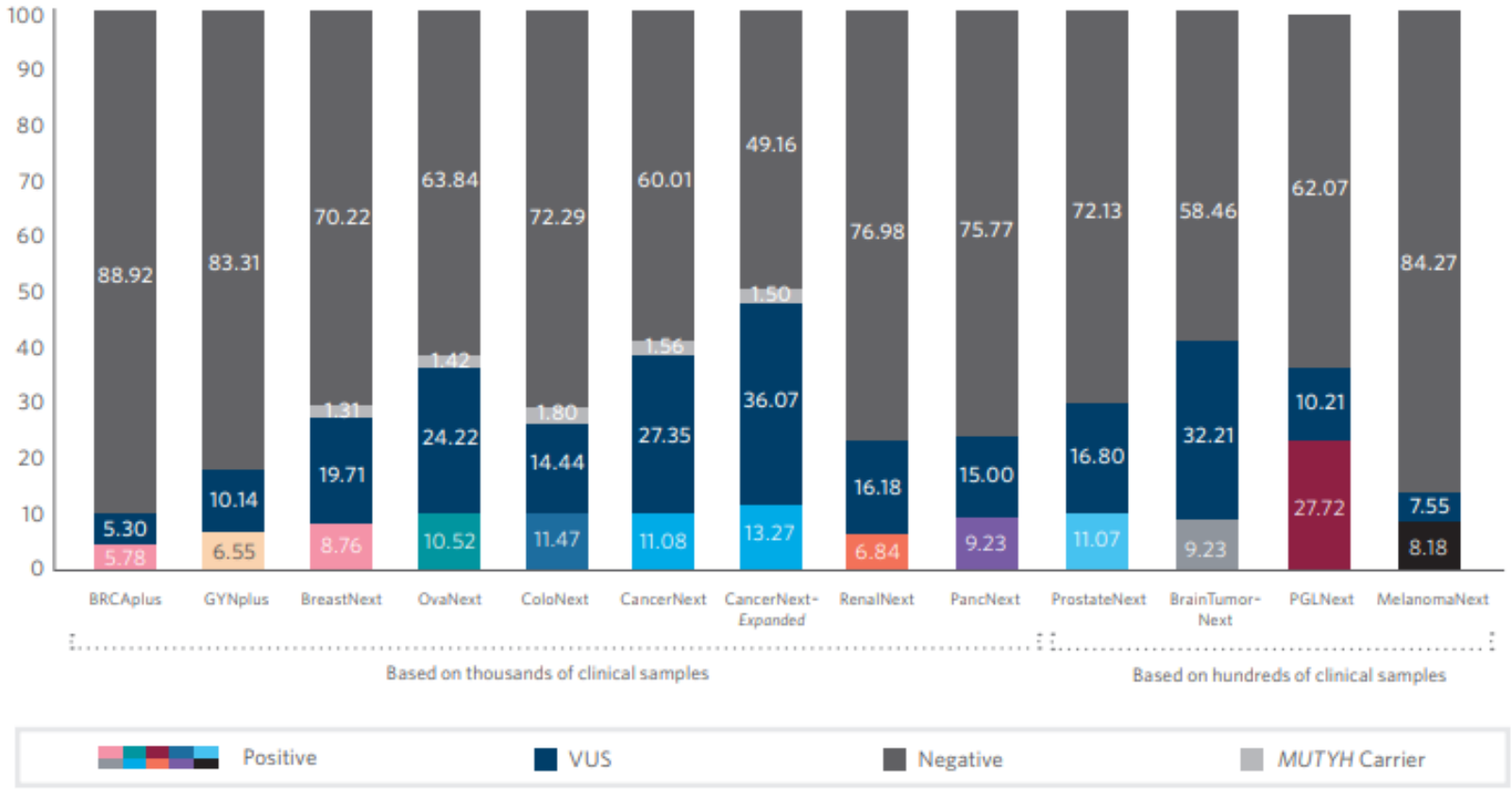
ColoNext®

ProstateNext®



Hereditary Cancer Panel Experience

UNDERSTANDING DISEASE BETTER THROUGH DATA SHARING AND TRANSPARENCY

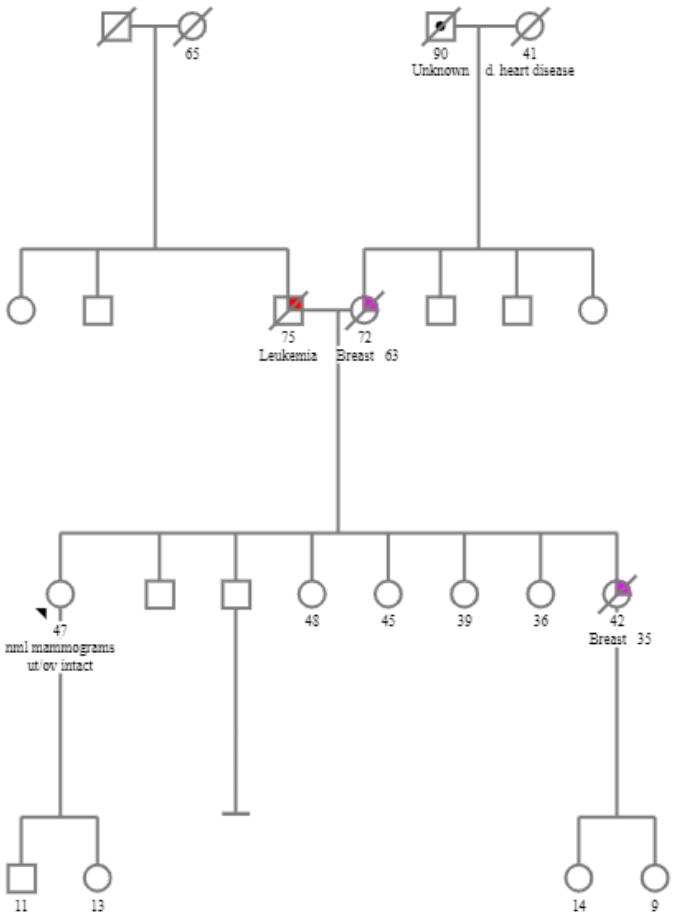


BRCA1 and *BRCA2* VUS Rate: 3.33%

Case Examples

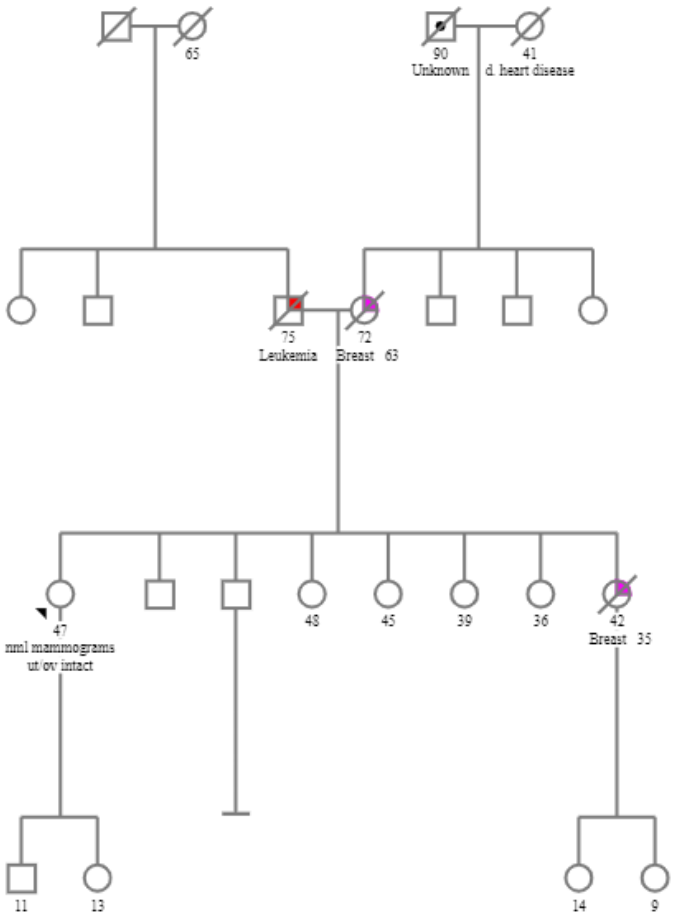
Case #1

- 47 year old woman presents to genetic counseling regarding family history of breast cancer and leukemia



Case #1

- 47 year old woman presents to genetic counseling regarding family history of breast cancer and leukemia
- Decides to proceed with genetic testing
  - BRCA1 and BRCA2 sequencing and rearrangement analysis



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- 47 year old woman presents to genetic counseling regarding family history of breast cancer and leukemia
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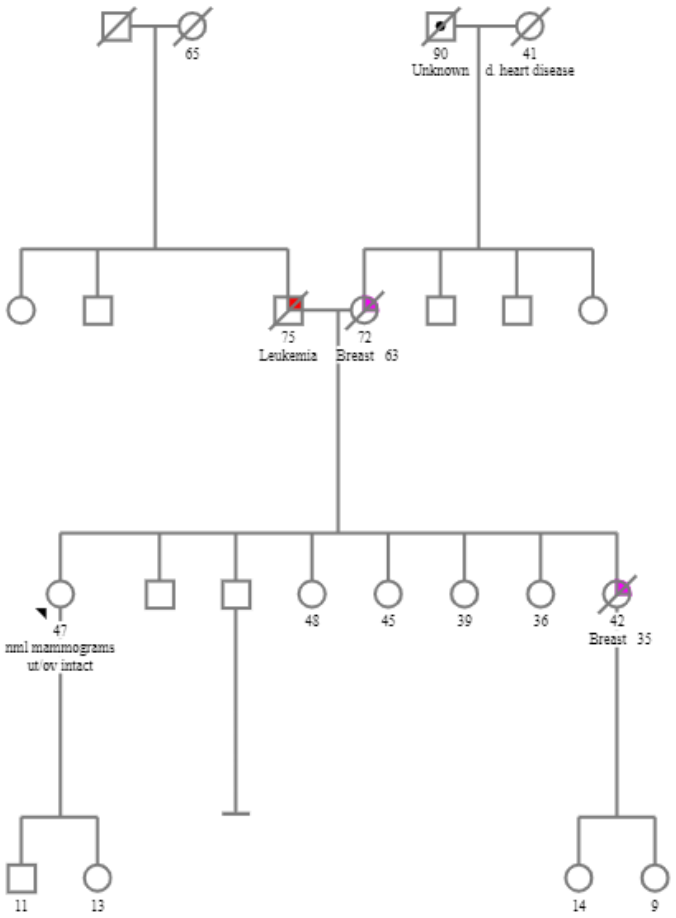
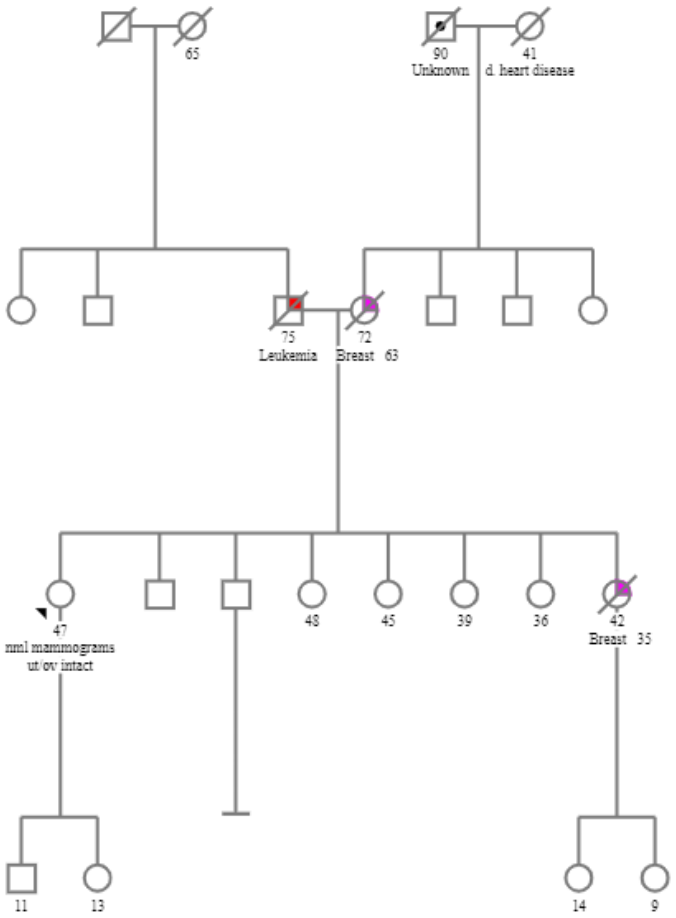
    - Testing was done in 2011, prior to NextGen panels, and prior to Supreme Court ruling regarding gene patenting

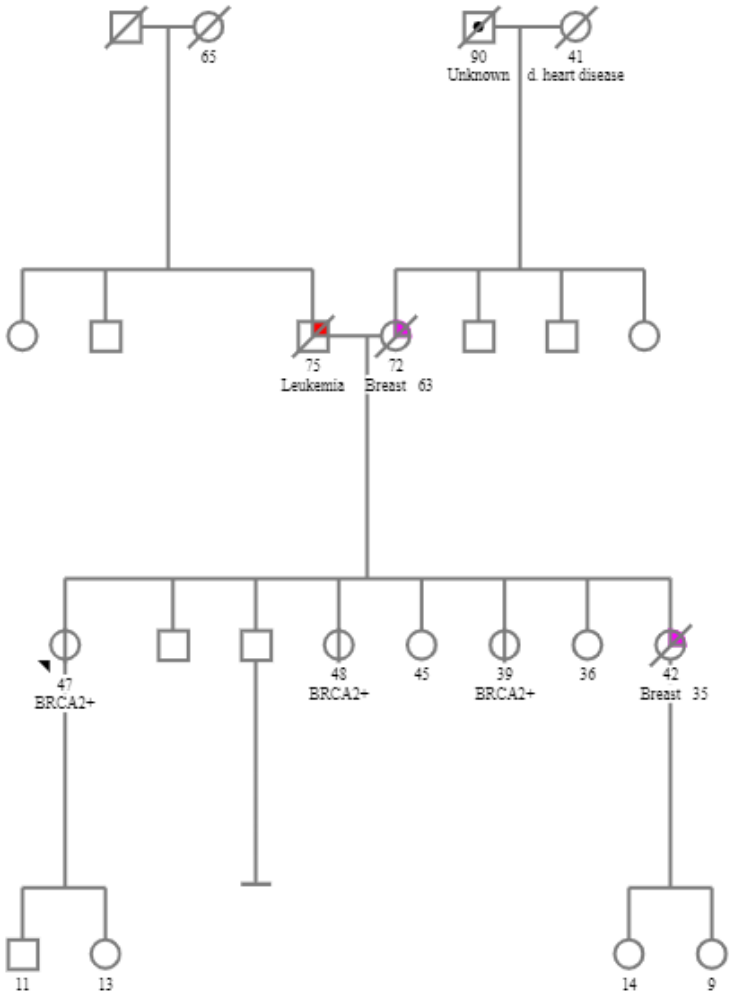


Case #1

- 47 year old woman presents to genetic counseling regarding family history of breast cancer and leukemia
- Decides to proceed with genetic testing
  - BRCA1 and BRCA2 sequencing and rearrangement analysis
    - Testing was done in 2011, prior to NextGen panels, and prior to Supreme Court ruling regarding gene patenting
  - Tests positive for a BRCA2 pathogenic mutation
  - Passes along information to family members
  - Sisters all pursue genetic testing
    - Individuals with positive testing proceed with increased breast cancer screening and surgical removal of ovaries and fallopian tubes



Case #1


65
90
Unknown
41
d. heart disease
75
Leukemia
72
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BRCA2+
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BRCA2+
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Breast 35
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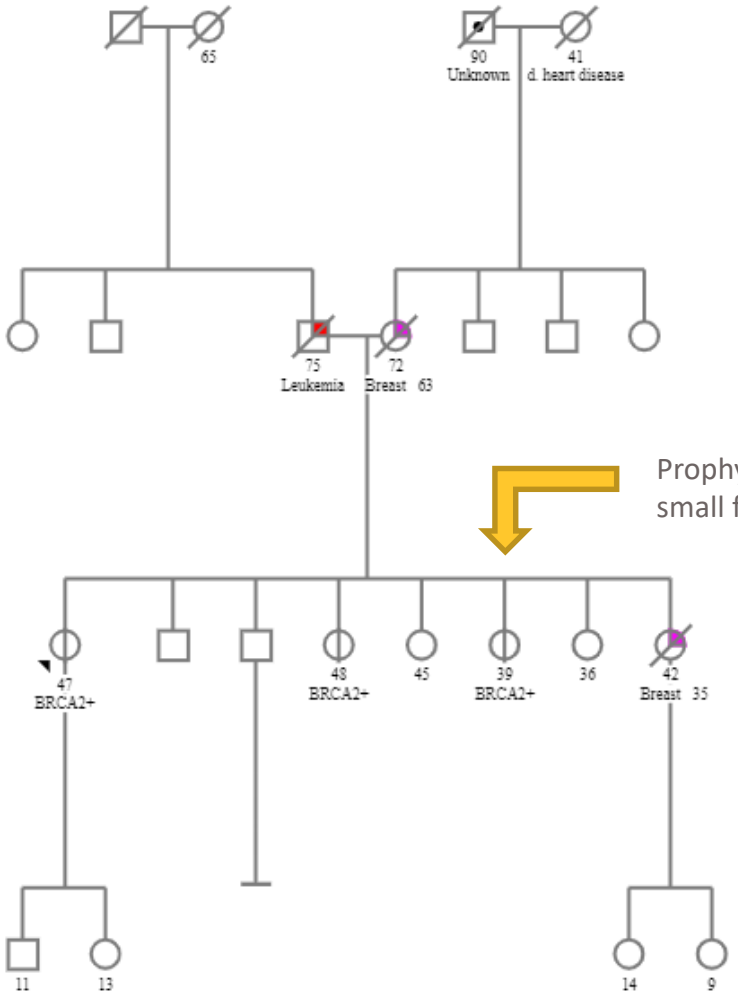
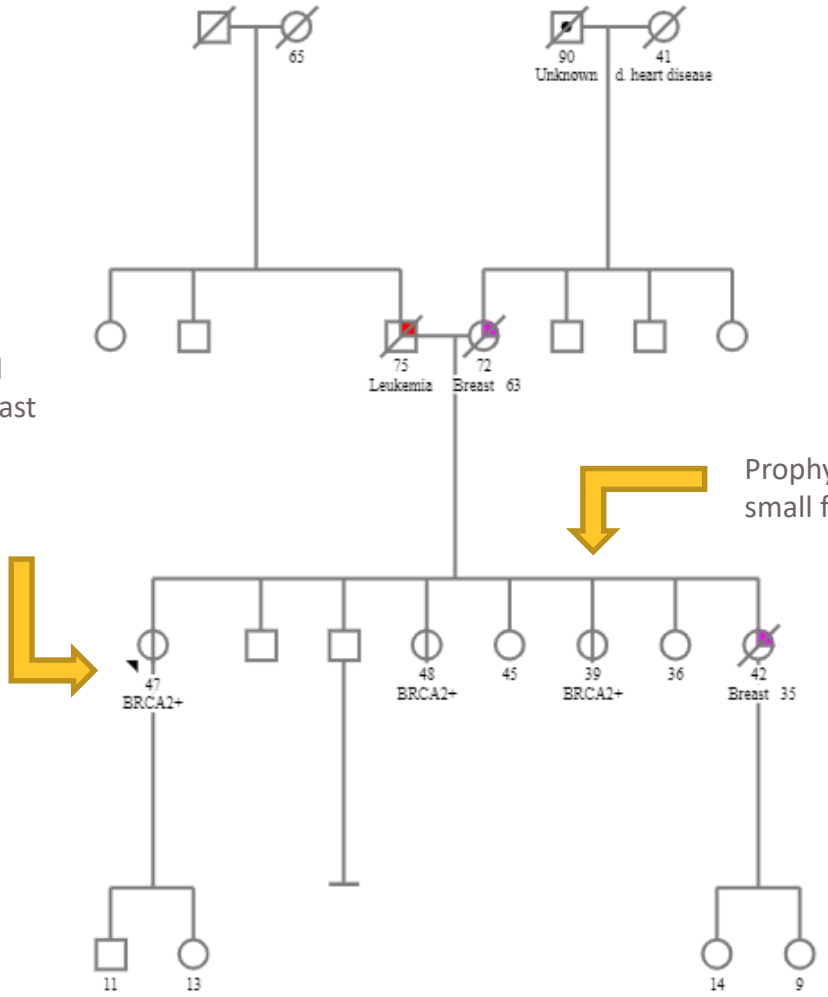
Case #1



Prophylactic mastectomy: pathology showed small focus of invasive breast cancer

Case #1

Follow up from proband:
GC received email 2 years after testing, stating that patient's employer bought her 23andMe for Christmas. Her results showed a "lower than average risk for breast cancer". Patient was confused as to why results were discordant.



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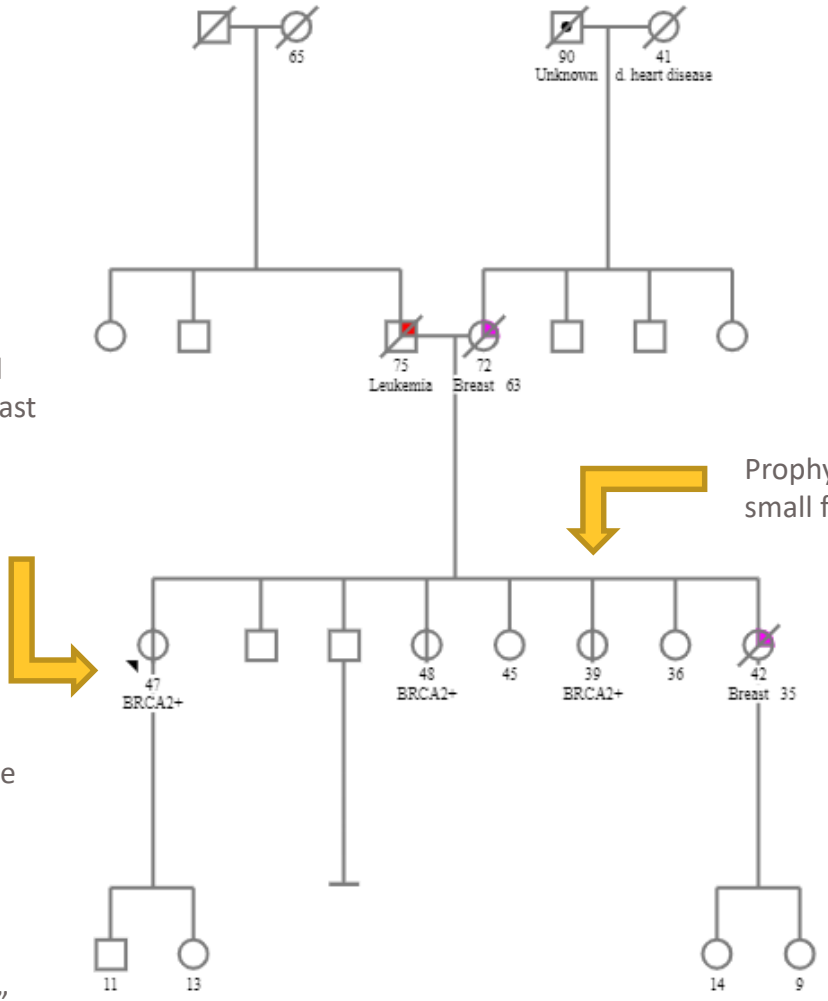


Prophylactic mastectomy: pathology showed small focus of invasive breast cancer

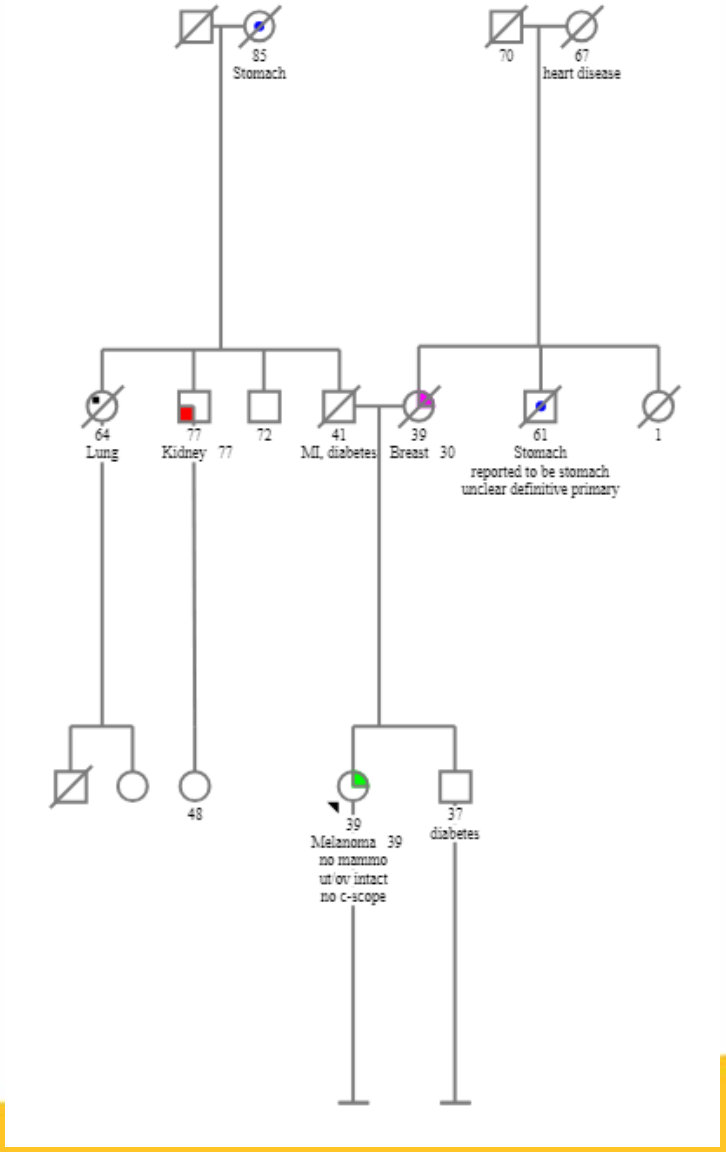
She stated "If I had done 23andMe before I had genetic testing with you, I never would have made that appointment. I would have assumed I was clear, and didn't need to worry about an increased risk of cancer."

Moral of the story…

- All genetic testing is not created equally!
- Choice of laboratory and specific test matters
  - Make sure appropriate genes are analyzed
  - Confirm appropriate gene coverage (PMS2 pseudogene region)
  - Insurance coverage/cost
  - Some labs contribute to research/databases, some do not
- Ideal to do it right the first time
  - Delay of treatment
  - Lack of insurance coverage for multiple genetic tests

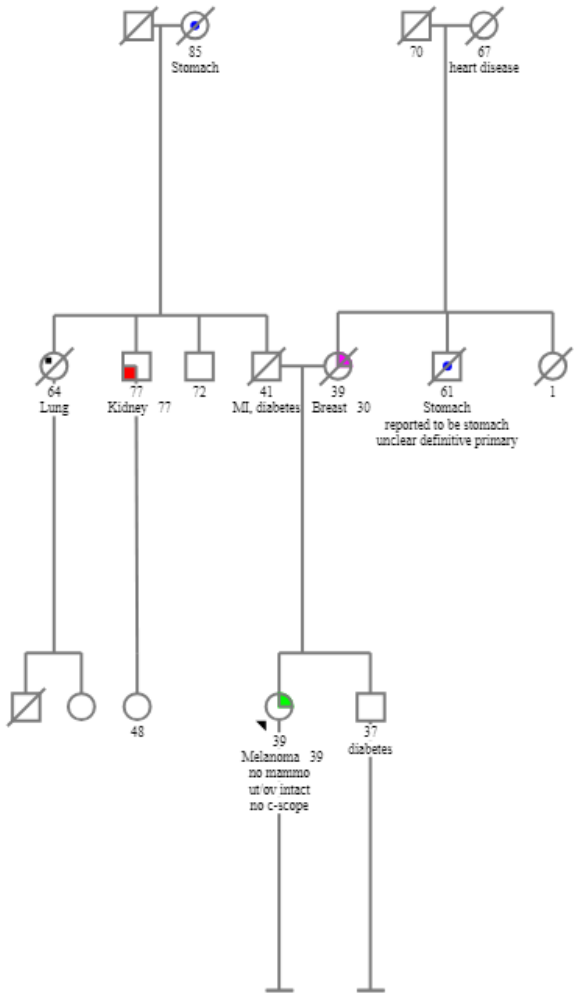
Case #2

- 39 year old woman recently diagnosed with melanoma presents for genetic counseling
- Family history includes breast, kidney, and gastric cancer



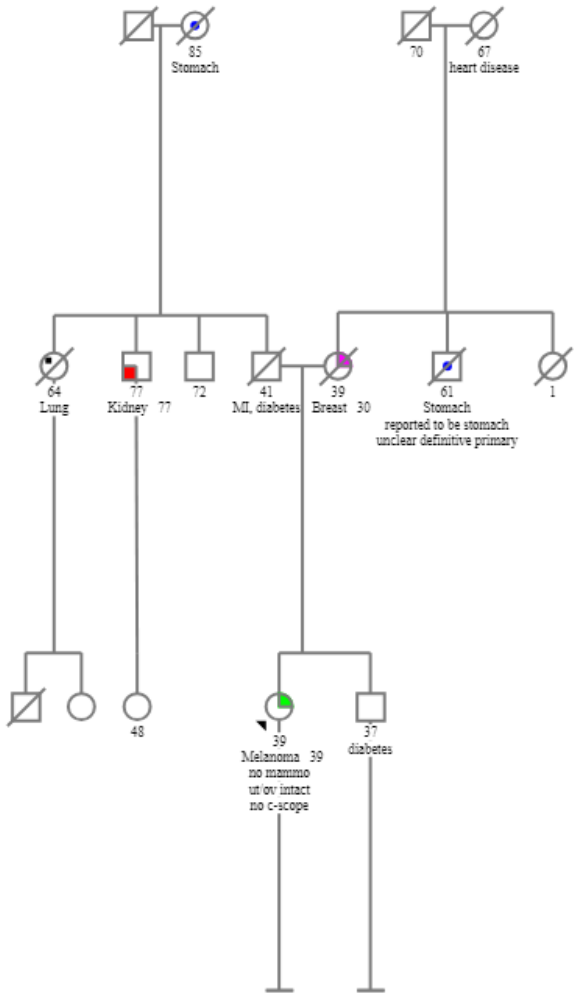
Case #2

- 39 year old woman recently diagnosed with melanoma presents for genetic counseling
- Family history includes breast, kidney, and gastric cancer
- Patient decides to proceed with comprehensive genetic testing
  - 46 genes



Case #2

- 39 year old woman recently diagnosed with melanoma presents for genetic counseling
- Family history includes breast, kidney, and gastric cancer
- Patient decides to proceed with comprehensive genetic testing
  - 46 genes
- Results show:
  - Pathogenic variant in ATM
  - 2 variants of uncertain significance
    - BRCA2
    - SMARCA4



Case #2

Gene	Breast Cancer Risk and Management	Ovarian Cancer Risk and Management	Other Cancer Risks and Management
ATM	**Increased risk of breast cancer** • Screening: Annual mammogram with consideration of tomosynthesis and consider breast MRI with contrast starting at age 40 y[f,g] • RRM: Evidence insufficient, manage based on family history	**Potential increase in ovarian cancer risk, with insufficient evidence for recommendation of RRSO**	Unknown or insufficient evidence for pancreas or prostate cancer
	Comments: Insufficient evidence to recommend against radiation therapy. Counsel for risk of autosomal recessive condition in offspring.		

- Patient referred to breast and ovarian cancer prevention clinic to discuss breast cancer screening
- Also referred to GI cancer prevention clinic to review data associated with ATM mutations and pancreatic cancer risk
- Considering enrollment in research study, with goal of reclassifying her BRCA2 and SMARCA4 mutations

Responses to genetic testing

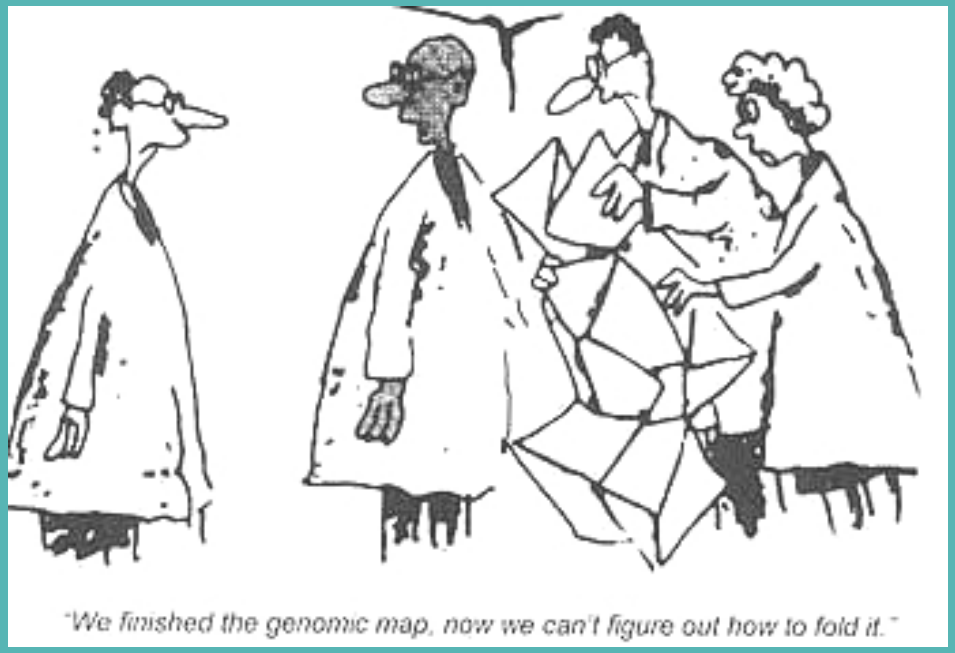
- Deciding to proceed with genetic testing can be a difficult decision
  - Many more patients pursue genetic testing than in the past
- Concern about privacy and genetic discrimination
  - Genetic Information Non-Discrimination Act of 2008 (GINA)
- Concern about family members
  - Parental guilt, survivor guilt, family dynamics
- Emotional responses vary
  - Range from devastation to complete relief
  - Most patients need time to cope with positive results
  - Support groups (FORCE, Lynch Syndrome international, etc.)
  - Anxiety, uncertainty, concern about future cancer risk

Conclusions

- Many patients may benefit from genetic counseling/testing at the time of diagnosis, in order to help determine best treatment plan
- The scope of hereditary cancer syndromes is complex and constantly changing
- Single gene testing is usually not the most appropriate for patients
  - Way more than just BRCA1, BRCA2 and/or Lynch Syndrome
  - Panel testing leads to higher VUS rate as well as incidental findings

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine



"We finished the genomic map, now we can't figure out how to fold it."

Thank you!

Questions | chandford@seattlecca.org
Phone | 206-606-1629

Better together.

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Benign White Cell Disorders

Comprehensive Hematology & Oncology Review

October 10, 2020

Michael Linenberger, MD

Professor, Hematology, UW

Robert & Phyllis Henigson Endowed Chair in Hematology

Disclosures

I have no disclosures or conflicts of interest

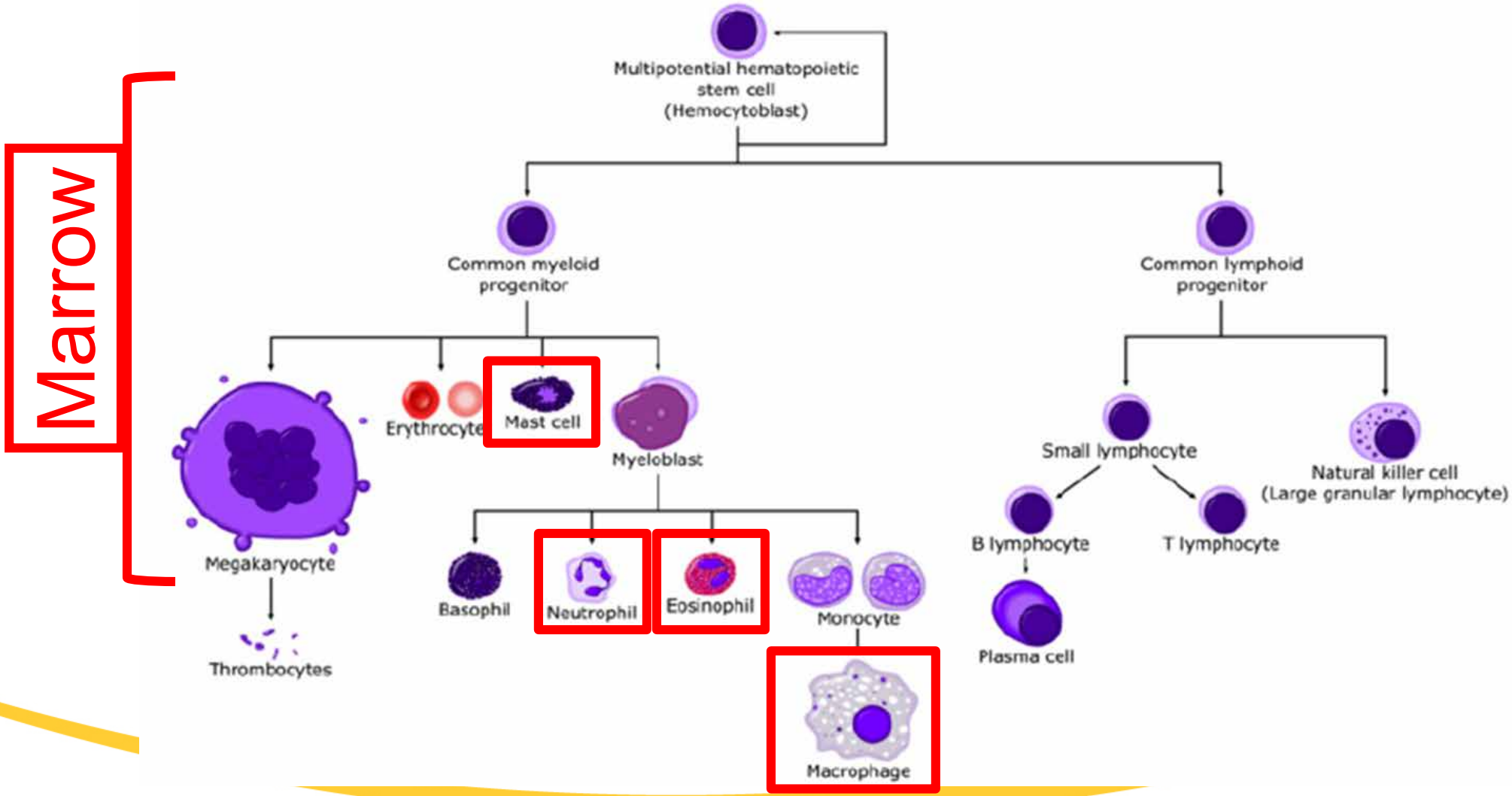
Objectives

- Diagnose and manage congenital and acquired neutropenias and non-clonal neutrophilia
- Recognize the causes, evaluation and treatment of disorders involving eosinophils and mast cells
- Understand the pathobiology and management of HLH and macrophage activation syndromes

Peripheral Blood Leukocyte Counts

	Range (#/mcL)	Differential (%)
Total WBC	**4,300 - 10,000**	
Neutrophils	1,800 - 7,000	42 - 70
Neutrophilic Bands	0 - 200	< 2
Monocytes	0 - 800	0 - 8
Lymphs (T, B, NK)	1,000 - 4,800	10 - 40
Eosinophils	0 - 500	0 - 5
Basophils	0 - 200	0 - 2

Hematopoiesis: Normal Blood & Immune Cells



Clinical Case 1: Neutropenia

- 40 yo woman presents with fever, leg sores & flank pain; she was seen 8 days ago for an uncomplicated UTI
- **PMH:** Bipolar affective disorder; illicit substance and alcohol abuse; possible rheumatoid arthritis
- **Medications:** Ciprofloxacin (day 8), lithium, aspirin, risperidone (day 20) for recent acute manic event
- **Exam:** Temp 40.5° C, BP 88/44, Pulse 110. Oriented but lethargic. Nonsuppurative leg ulcers & inguinal adenopathy; left flank & general abdominal pain

Clinical Case 1: Diagnostic Studies

- **Lab Data**

Hemoglobin 12.8 gm/dL	MCV 92 fl
WBC 4,910 /mcL	Plt ct 395,000/mcL
Neutrophils 10 /mcL	Lymphs 3,700 /mcL
Monocytes 900 /mcL	Eosinophils 300 /mcL

- **Urinalysis:** Esterase (+); no WBC; 3+ RBC
  Gram stain: gram negative rods
- **Chest X-ray:** Clear
- **KUB:** No obstruction

Acquired Neutropenia

Disorders of Granulopoiesis

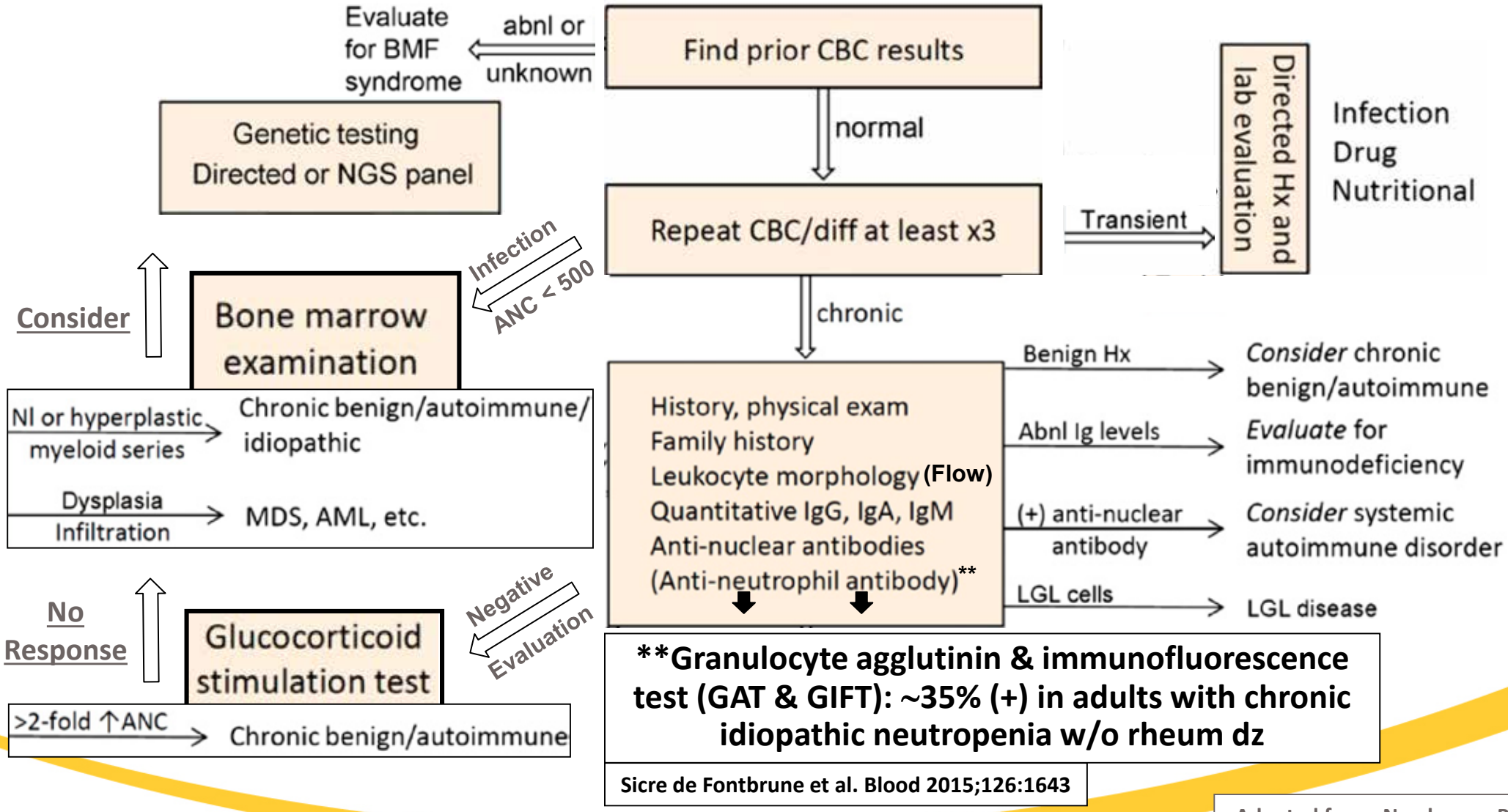
- Drugs (dose-dependent and idiosyncratic)
- Chronic idiopathic neutropenia
- Nutritional deficiency (B12, folate)
- Infections (HIV, CMV, EBV, parvovirus, others)
- 1º hematopoietic disorder (MDS, aplastic anemia)

Peripheral Destruction

- Immune / autoimmune (RA, SLE)
- Large granular lymphocytic (LGL) leukemia
- Infection (EBV, HIV, *H pylori*)
- Drugs (idiosyncratic immune-mediated)

Splenic Sequestration

Diagnostic Approach to Neutropenia

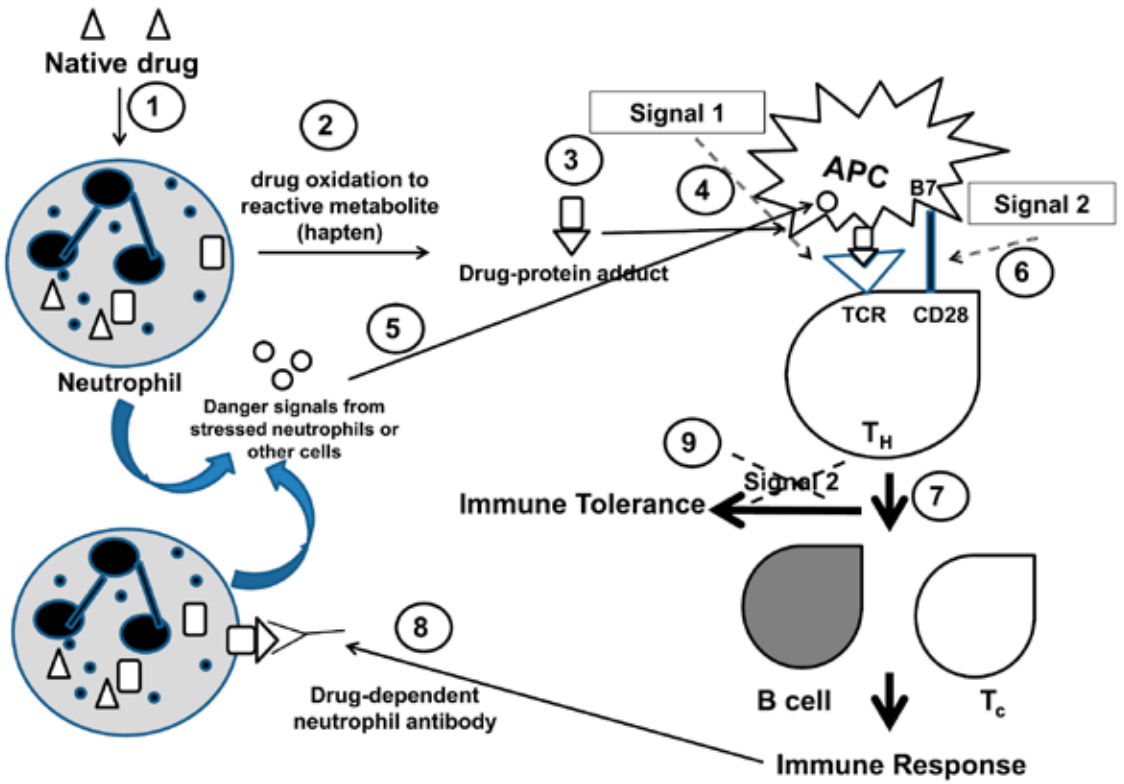


****Granulocyte agglutinin & immunofluorescence test (GAT & GIFT): ~35% (+) in adults with chronic idiopathic neutropenia w/o rheum dz**

Sicre de Fontbrune et al. Blood 2015;126:1643

Adapted from: Newburger P. Hematology Am Soc Hematol Educ Program **2016;38**

Idiosyncratic Drug-Induced Neutropenia



Curtis BR Hematology Am Soc Hematol Educ Program 2017(1):187

Table 2. Drugs most frequently reported to cause IDIN

Huber et al[7]	Medrano-Casique et al[5]
Carbamazepine†	Benzylpenicillin†
Clozapine†	Cefipime†
Metamizole (dipyrone)†	Linezolid
Sulfasalazine†	Meropenem†
Thiamazole†	Metronidazole
	Piperacillin-tazobactam†
	Teicoplanin
	Tobramycin
	Torsemide
	Vancomycin†

Andrés et al[9]	Curtis*
Amoxicillin†	Cefipime
Carbimazole†	Ceftriaxone‡
Clozapine†	Ciprofloxacin‡
Cotrimoxazole†	Clindamycin
Cefotaxime	Ibuprofen
Noramidopyrine	Levetiracetam
Piperacillin-tazobactam	Piperacillin-tazobactam‡
Salazopyrine	Quetiapine
Ticlopidine†	Sulfamethoxazole/trimethoprim‡
Valganciclovir	Tacrolimus
	Vancomycin‡
	Venlafaxine

†Five most frequently associated drugs. ‡Five most suspected drugs.

Management of Drug-Induced Neutropenia

- Withdraw all nonessential drugs, herbals, OTC meds
- **Expect ANC recovery within 1-2 wk of drug removal;** slower for ANC <100/mcL, sepsis, severe infection
- Broad-spectrum antibiotics as indicated for fever and infection or prophylaxis (case-by-case basis)
- **Marrow Biopsy: If abnormal RBC/plts or delayed recovery**
- **G-CSF:** Beneficial for ANC < 100/mcL (even w/o infection); consider with ANC < 500/mcL in elderly ± infection, severe comorbidity, sepsis

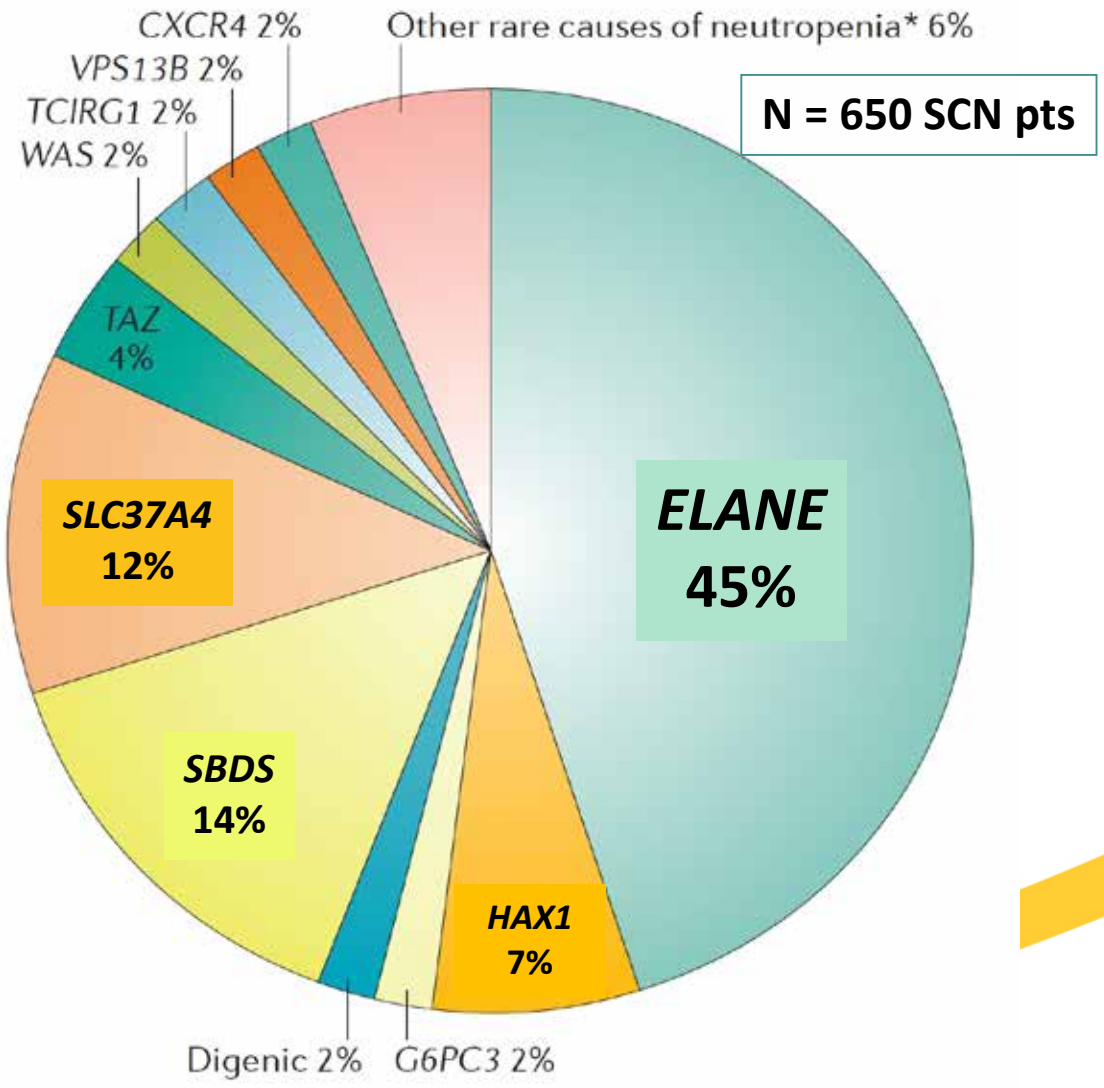
Autoimmune Neutropenia

- RA, SLE, Sjögren's; some drugs (PTU, rituximab)
- **Felty syndrome:** RA (usually severe), splenomegaly (90%) & neutropenia
  - Anti-G-CSF Ab (70%); ± ↑ oligoclonal CTLs (LGLs)
- **SLE-associated neutropenia (25-50% incidence)**
  - Anti-SSA/Ro; anti-SSB/La; TNF-related apoptosis
- **Therapy:** Glucocorticoids, methotrexate, cyclosporine, G-CSF* (low dose)

  ***Beware** → Sx flare, leukocytoclastic vasculitis, ↑spleen

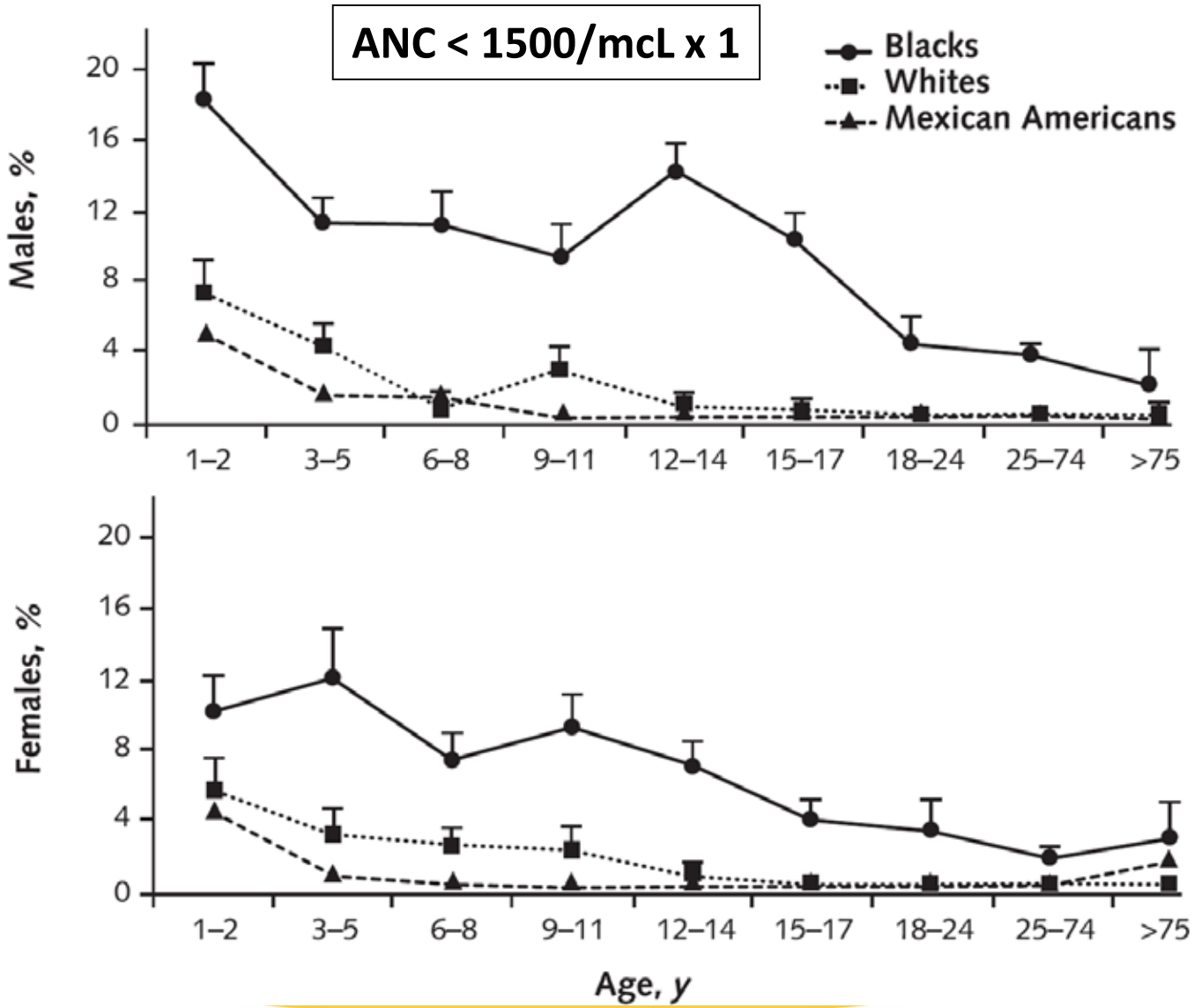
Congenital Neutropenia

- Severe congenital neutropenia (SCN)
- Cyclic neutropenia
- Multilineage disorders
  - Chediak-Higashi
  - Wiskott-Aldrich syndrome
  - Griscelli syndrome
- “Ethnic neutropenia”



Skokowa J et al. Nat Rev Dis Primers 2017;3:17032

Incidence of “Ethnic Neutropenia”



Hsieh MM et al.
Ann Intern Med
2007;146:486

Chronic Idiopathic Neutropenia

- **Dx of exclusion:** Chronic ANC < 500/mcL; **w/o 1° disorder/drug/infection**
- **Med age:** 25 yo (adult > child)
- **Prevalence:** 1.7%
- **Etiology:** Marrow suppressive T-cells/cytokines[1]
- **Treatment / Course: SCNIR Registry data[2,3]**
  - 54% w/o tx pre-entry to registry → most maintained on G-CSF
  - Med. G-CSF dose 1 mcg/kg/day
  - Infrequent ↓ plts, ↑ spleen, osteopenia (no MDS/AML)

- **Caucasian = 95%**
- **F:M = 2 : 1**
- **– "Remissions" = Rare**

[1] Exp Hematol 2008;36:293 [2]Am J Hematol 2003;72:82 [3]Dale D & Bolyard A. Curr Opin Hematol 2017;24:46

Clinical Case 2: Referral for Leukemia

- 28 yo Palestinian, 9 mo episodic abd pain (q4 wk); ED visits **w/ ↑ WBC**
- **Pain:** No triggers; acute; resolves in 12-36 hrs
- **ROS:** ± Fever; + sweats; 10 lb wt loss
- **PMH:** Orchitis
- **Meds:** Codeine, testosterone
- **FH:** Noncontributory (left Middle East 10 yrs ago)
- **PE:** Afebrile; nl BS, general tender, no organomegaly
- **Labs:** Hct 40%, **WBC 13,000/mcL**, **ANC 9,600/mcL;** plt ct 250,000/mcL; ESR 45; nl amylase / Cr; **U/A 3+ protein**
- **CT:** ± **Mesenteric LAD;** nl liver/spleen/kidneys

Non-Clonal Neutrophilia – Differential Dx

(Negative *BCR-ABL, JAK2 V617F, CALR, MPL, CSFR3*)

- **Secondary / Reactive / ↓ Sequestration**
  - Infection, inflammation (obesity, smoking)
  - Asplenia
  - Drugs (lithium, corticosteroids, G-CSF)
  - Tumor (G-CSF-secreting)
- **Constitutional:** Down syndrome w/leukemoid rxn's, transient MPD
- **Primary neutrophil disorders with 2^{o} neutrophilia**
  - Familial Mediterranean Fever: PMNs are auto-activated
  - Leukocyte adhesion deficiency: PMNs can't adhere/migrate
  - Chronic Granulomatous Disease: PMNs can't kill

Clinical Case 3: Eosinophilia

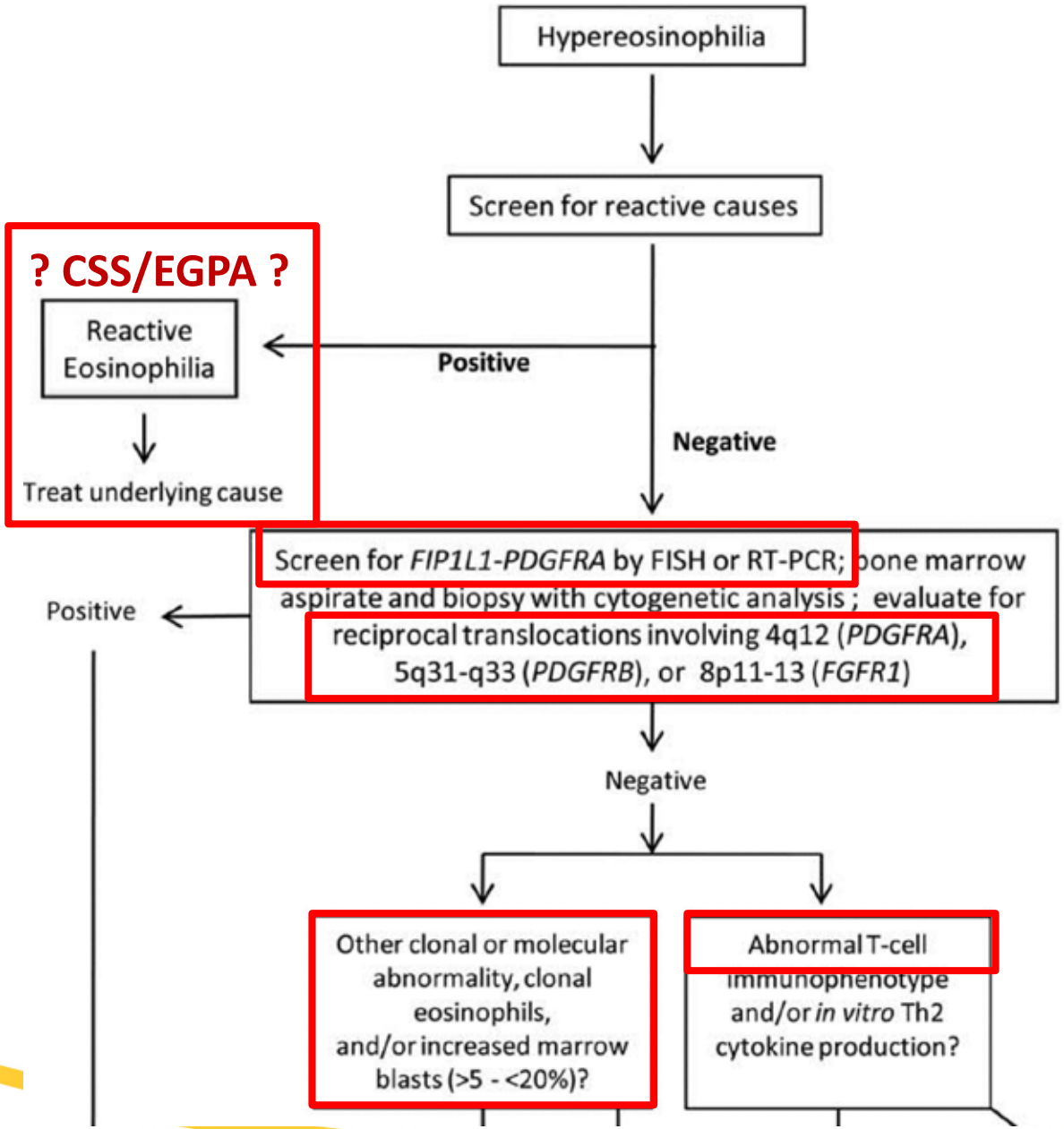
- 19 yo M admitted to outside hospital after cardiac arrest
- **PMH:** Aspergers / ADHD & asthma
- Admission Data from outside hospital
  - **Troponin 8.41**
  - **BNP 12,087**
  - Utox (+) for amphetamines (lisdexamfetamine)
  - **TTE – LVEF 15-20%,** severe concentric LVH & hypokineses, ballooning apex
  - IABP placed → transfer to UWMC

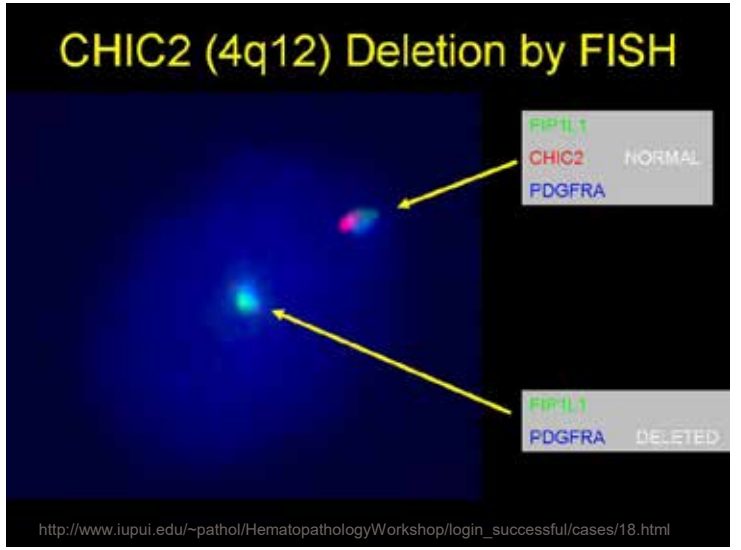
Clinical Case 3: Laboratory Data

	Day 1	Day 2	Day 3	1 Mo PTA
WBC	14.70	17.65	18.74	25
Hg	11.3	15.8	16.4	
HCT	31	43	46	
PLT	116	171	236	
% Neutrophils	36	43	42	
% Lymph	14	8	8	
% Monocytes	6	10	8	
% Eosinophils	44	38	40	69
%Basophils	0	1	1	
Abs. Eos	6.4	6.65	7.53	17.3

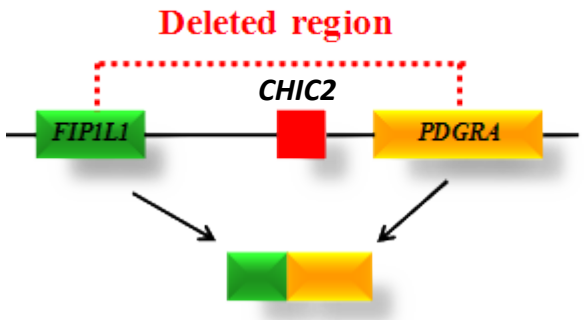
Hypereosinophilia

- **Eosinophil ct > 1,500/mcL for > 1 month, on ≥ 2 occasions**
  - **Or** > 1,500/mcL & life-threatening organ dysfunction
  - **Or** > 20% BM eos; extensive tissue eos + degranulation
- **Idiopathic Hypereosinophilic Syndrome (HES)**
  - Hypereosinophilia & evidence of end-organ involvement
  - Lack of evidence for other causes of hypereosinophilia
    - Neoplasm (MPN; LPD; carcinoma)
    - Parasite (strongyloides, hookworm, scabies, filaria)
    - Addisons
    - Collagen vascular disease (CSS/EGPA, IBD, sarcoidosis)
    - Other (chronic TB, HIV, cocciodiomycosis)
    - Drugs
    - Allergy (asthma, atopic dermatitis)

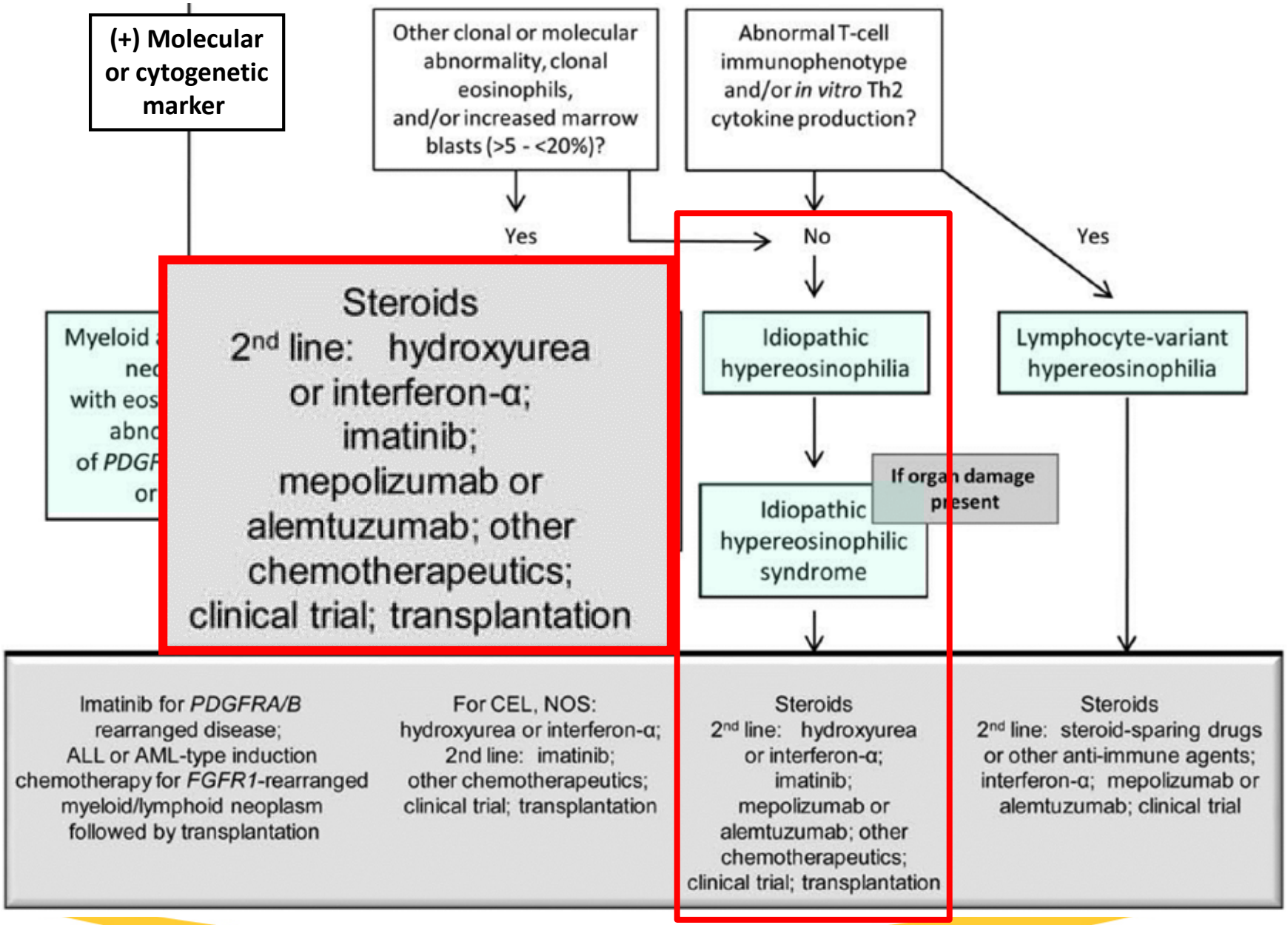




***FIP1L1-PDGRA* fusion gene**



Gotlib J. Am J Hematol 2014;89:326



Gotlib J. Am J Hematol 2014;89:326

Clinical Case 4: Mast Cell Disease

- 57 yo man, 6 mos episodic abd pain, nausea, diarrhea
- **Provocative features:** ? Stress & spicy food ?
- **Pain:** Gradual onset, cramping → nausea, diarrhea; resolves w/in 5d
- **Additional:** Occasional episodes flushing, presyncope, hives/pruritis
- **PMH:** Gastric ulcer 1 yr ago; urticaria x 3yr
- **Meds:** Omeprazole
- **PE**: Pigmented macules, (+) dermatographism
- **Labs:** Hct 45%, WBC 5600/mcL, plt ct 195,000/mcL; normal LFTs; normal amylase & VIP; **Tryptase 30 ng/mL (nl < 11.5 ng/mL)**

24º urine Histamine/Creatinine: 2100 nmol/g (nl < 386 nm/g)

Clinical Case 4: Skin Manifestations

Urticaria pigmentosa

Darier's Sign

https://healthjade.com/urticaria-pigmentosa/ https://www.healthline.com/health/urticaria-pigmentosa

Cutaneous Mast Cell Disease

- **Urticaria pigmentosa**
  - Maculopapular rash, Darier's sign, ± histamine-type sx's
  - **Skin Biopsy:** Nl mast cells, Kit+ (CD117), (-) *c-kit* mutations
  - **In Childhood:** Usually resolves spontaneously after puberty
  - **In Adults:** R/O systemic mastocytosis and associated clonal non-mast cell disease (marrow/blood studies)
  - Indolent course, good prognosis if no progression
- **Mediators:** Histamine; tryptase; TGF-b; IL's; proteases

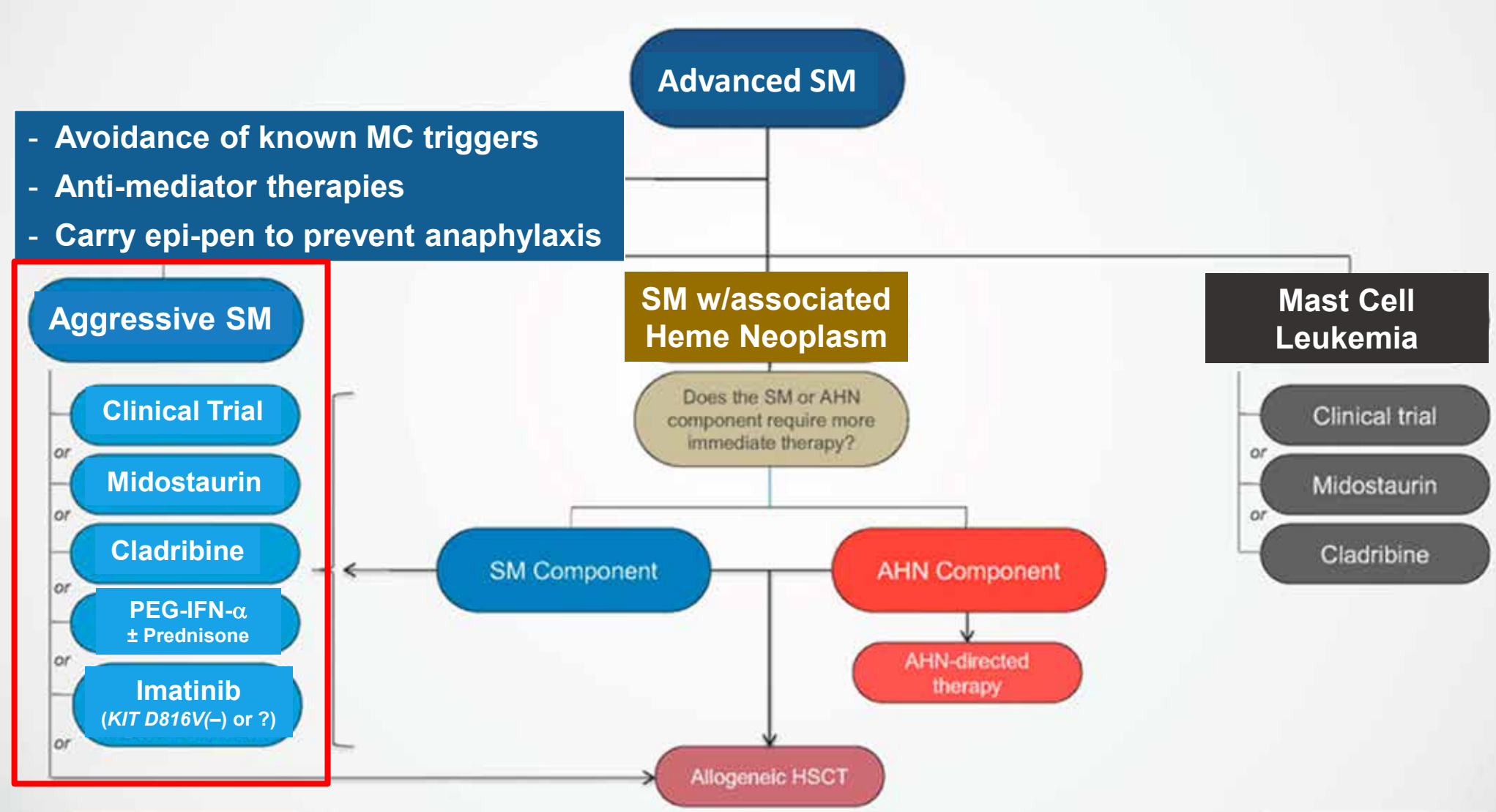
Systemic Mastocytosis (SM): WHO 2016

- **Major Criteria**
  - Multifocal, dense mast cell infiltrates (> 15 aggregating, atypical spindle cells) in marrow or extracutaneous tissue
- **Minor Criteria**
  - BM/organ infiltrates with > 25% atypical/spindle mast cells
  - *c-kit* point mutation (D816V >> others) in marrow/tissue
  - Kit+ (CD117) mast cells that co-express CD2 and/or CD25
  - Serum tryptase > 20 ng/mL

"Indolent SM": Low-level MC; no marrow/tissue dz

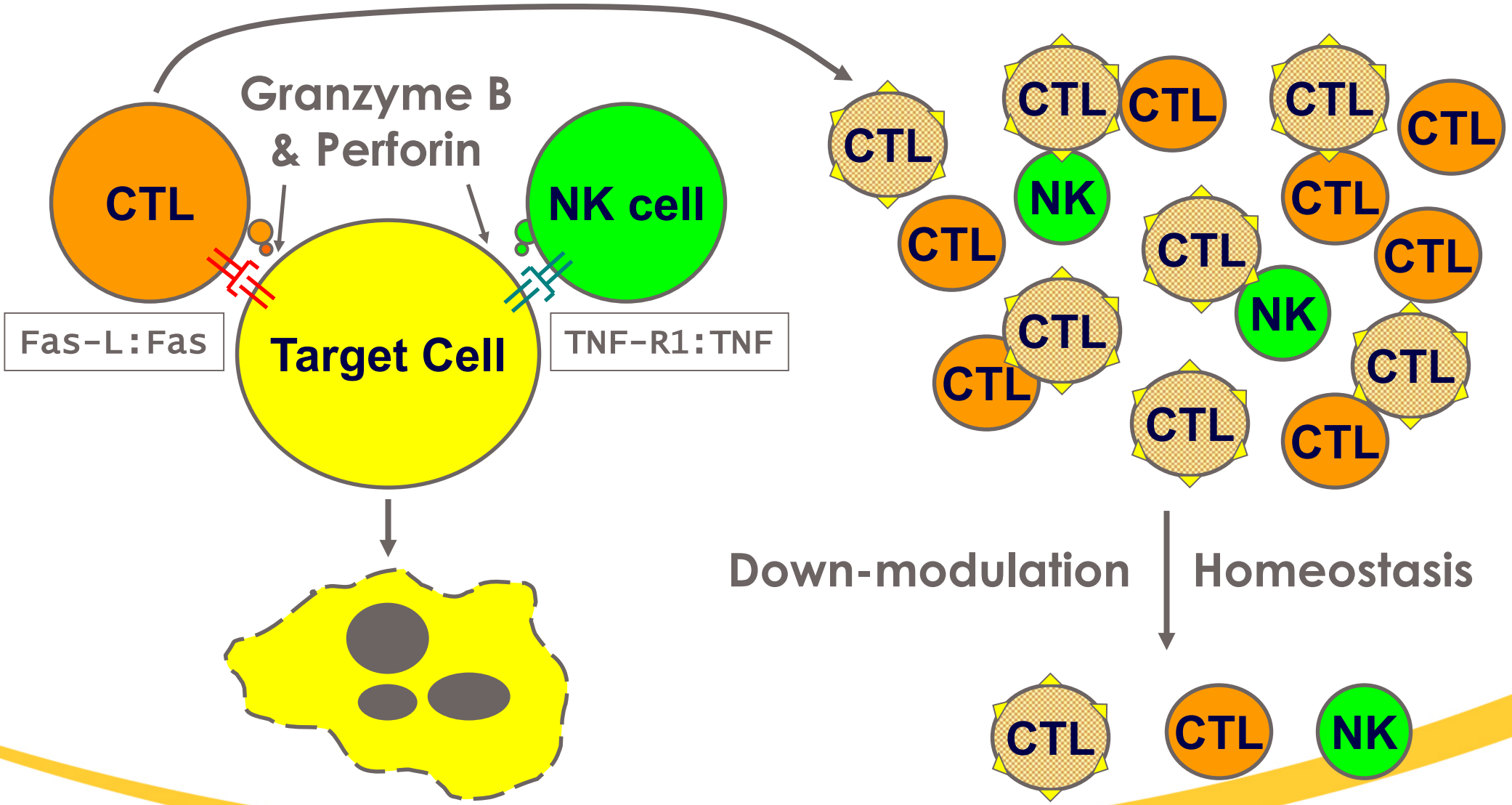
*Diagnosis requires: 1 major & 1 minor or 3 minor criteria

Advanced SM: Subtypes & Treatment

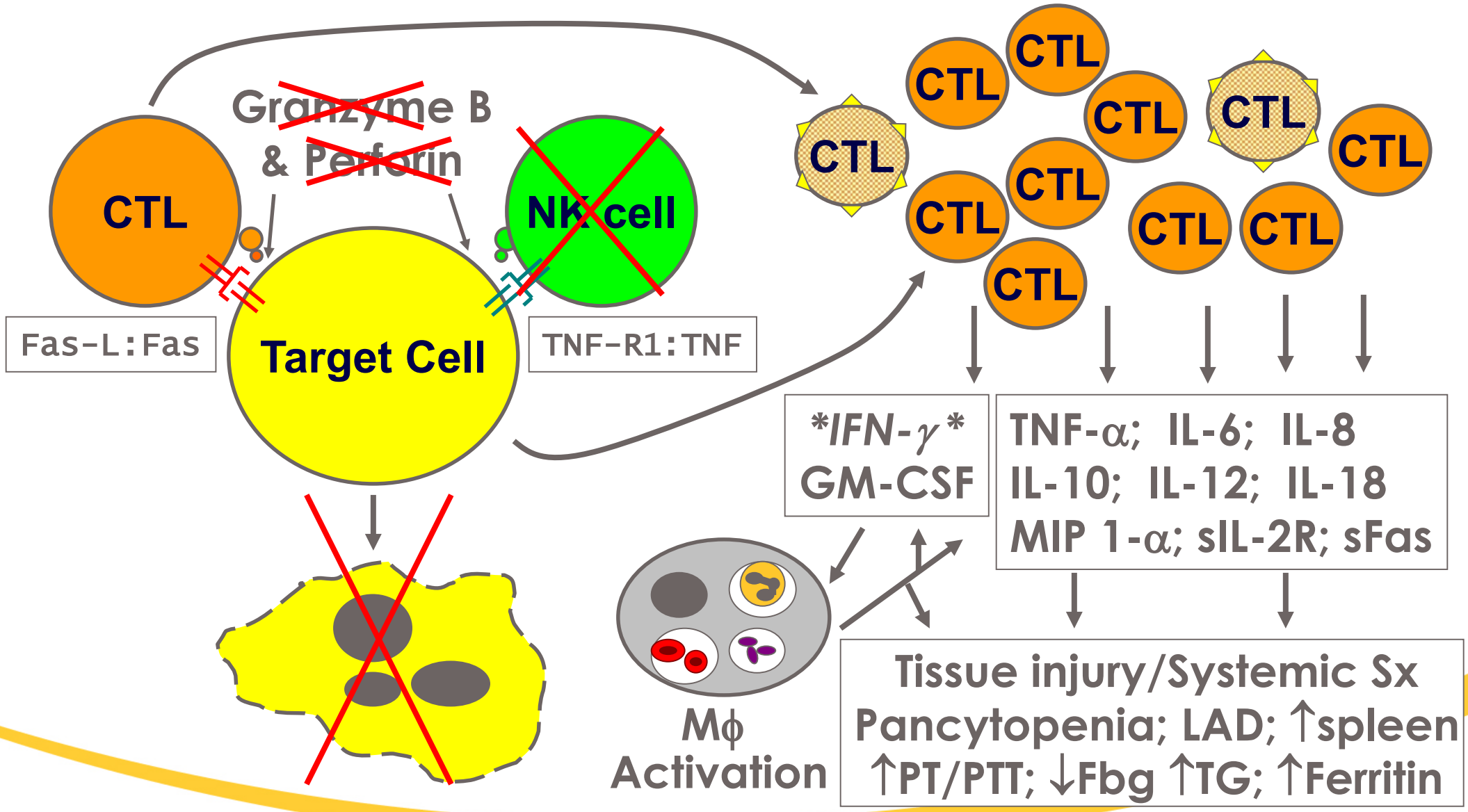


Adapted from: Gotib J. Hematology Am Soc Hematol Educ Program. 2018 Nov 30;2018(1):**132:1769**

CTL & NK Cytotoxicity: “Kiss of Death”



Hemophagocytic Lymphohistiocytosis (HLH)



Familial HLH: Inherited NK Cell Defects

- **Primary HLH associated with lymphocyte cytotoxic defects**
  - **FHL2 - *PRF1*** (perforin; pore-forming) (50% cases)
  - **FHL3 - *UNC 13D*** (cytolytic granule secretion) (30%)
  - **FHL4 - *STX11*** (intracellular vesicle transport)
  - **FHL5 – *STXBP2*** (syntaxin binding protein; membrane fusion)
  - – X-linked lymphoproliferative synd. 1 (***SHD21A***)
  - – FHL1 9q21.3 locus 6
  - – Griscelli syndrome 2 (***RAB27A***)
  - – Chediak-Higashi syndrome (***LYST***)

- **Abnormal Inflammasome/Inflammation**
  - ***– BIRC4***
  - ***– NLRC4***
  - ***– HMOX1***
  - ***– SLC7A7***

- **Immune Deficiencies with <u>sporadic</u> HLH**
  - – Lymphoproliferative syndrome I ***(ITK)***
  - – CD27 deficiency (***CD27***)
  - – Hermansky-Pudlak syndrome ***(AP3BI)***
  - – X-SCID ***(IL2RG)***
  - – XMEN syndrome (**MAGT1**)
  - – Others

*Emile JF et al. Blood 2016;127:2672-81 (Classification of Histiocytoses)

Acquired/2º HLH: Impaired NK/CTL Activity

Consider with pancytopenia, "sepsis syndrome" &/or MODS*

- **Infection-associated:** Virus (EBV, CMV, HIV), bacteria, parasite, fungal
- **Malignancy-associated:** B- or T-cell NHL, HL, NK, myeloid, solid tumor
- **Immune Deficiencies:** Post-transplant, post-chemoimmunotherapy
- **Iatrogenic immune activation:** Cytokine release syndrome
- **Sporadic:** 15% associated with hypomorphic allele for fHLH

****Mortality = 40 – 60%****

Macrophage Activation Syndrome (MAS-HLH) – Rheumatic disorders

- SLE, vasculitis, ***systemic-onset juvenile idiopathic arthritis, *adult onset Still disease** (*consider screen for hypomorphic alleles for fHLH); others

Emile JF et al. Blood 2016;127:2672-81 (Classification of Histiocytoses)

*Ravelli A et al. Ann Rheum Dis 2016;75:481

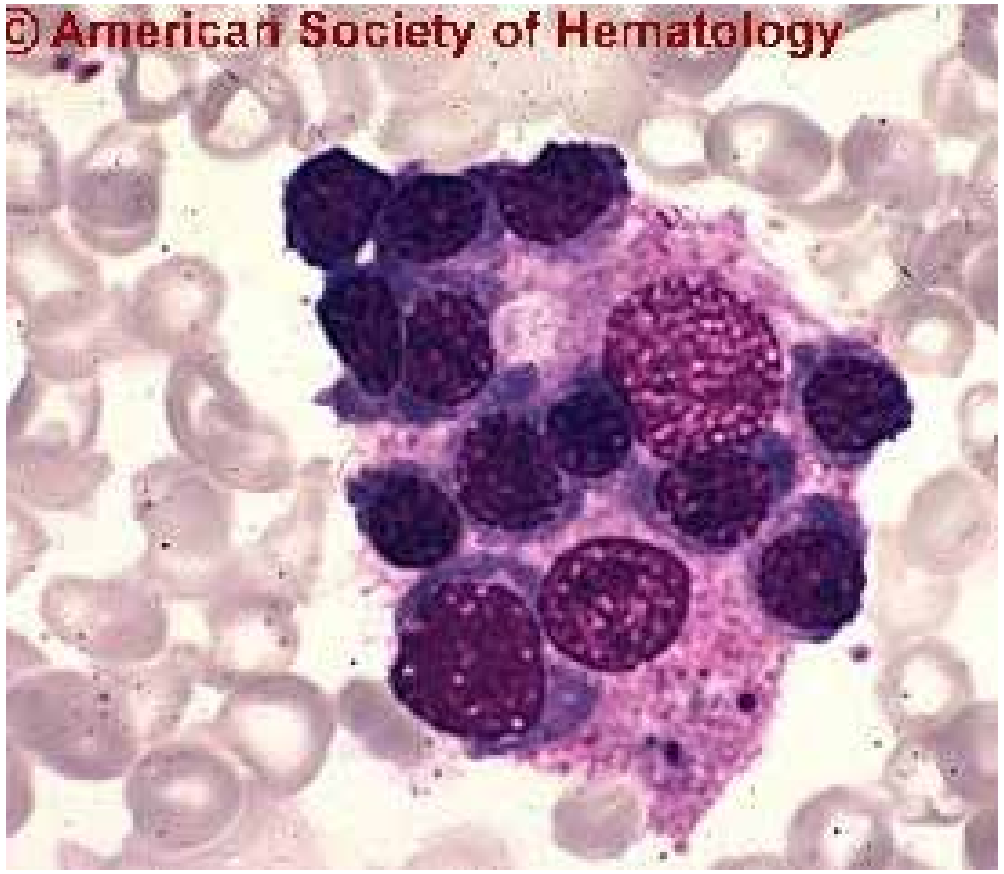
HLH: Clinical Dx Criteria (need ≥5)
[Macrophage Activation Syndrome (MAS)]

1. **Fever ≥7 days** (92-100% in adults w/HLH)
2. **Splenomegaly** (26-100%)
3. **Cytopenias ≥2 cell lines**
   – Hgb <9 gm/dL (59-94%) – Plt <100,000/mcL (86-96%) – PMN <1,000/mcL (25-100%)
4. **Ferritin ≥ 500 mg/L** (85-100%; low specificity in adults except > 10,000[1])
5. **Triglycerides >265 mg/dL** (30-89%) **or Fbg <150 mg/dL** (38-62%)
6. **Hemophagocytosis** in BM; LN; CSF (52-100%) (***poor sensitivity/specificity***)
7. **Low/absent NK activity** (36%; ↑ Sens/Spec w/perforin & CD107a flow assay[2])
8. **Soluble CD25 (sIL-2Rα) >2400 U/mL** (77-100%)

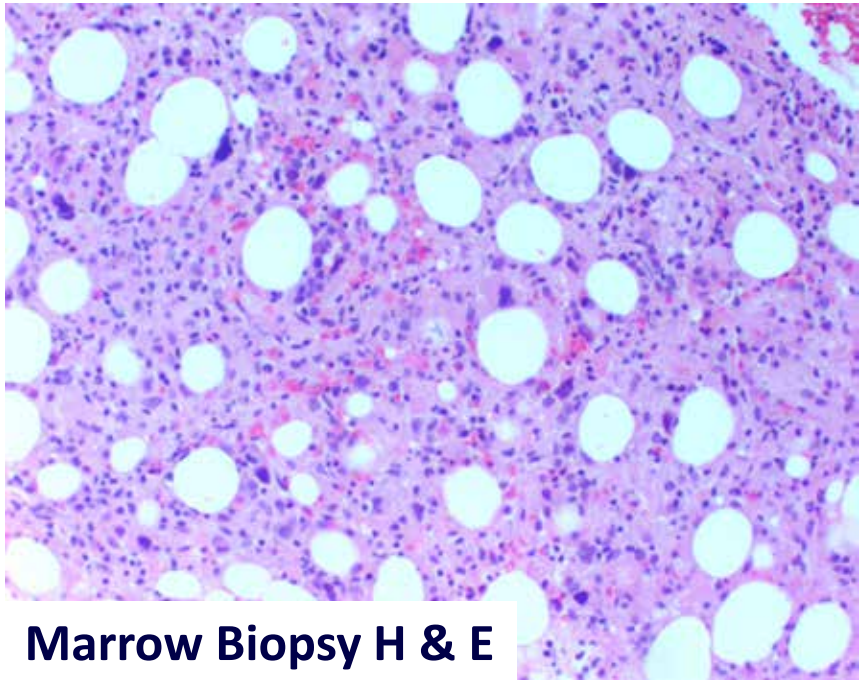
HScore for reactive HLH*
http://saintantoine.aphp.fr/score/
*Fardet L et al. Arthritis Rheumatol 2014;66:2613

[1] Rubin TS et al. Blood 2017;129:2993 [2]Nikiforow S & Berliner N et al. Hematology Am Soc Hematol Educ Program 2015;183-89

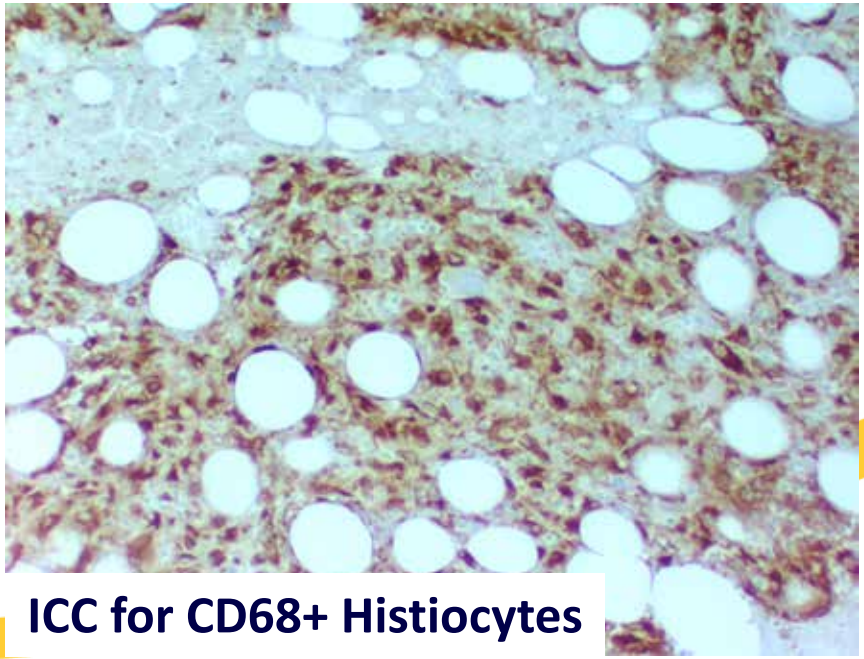
HLH: Marrow Findings



Cytophagic Histiocyte (aspirate)

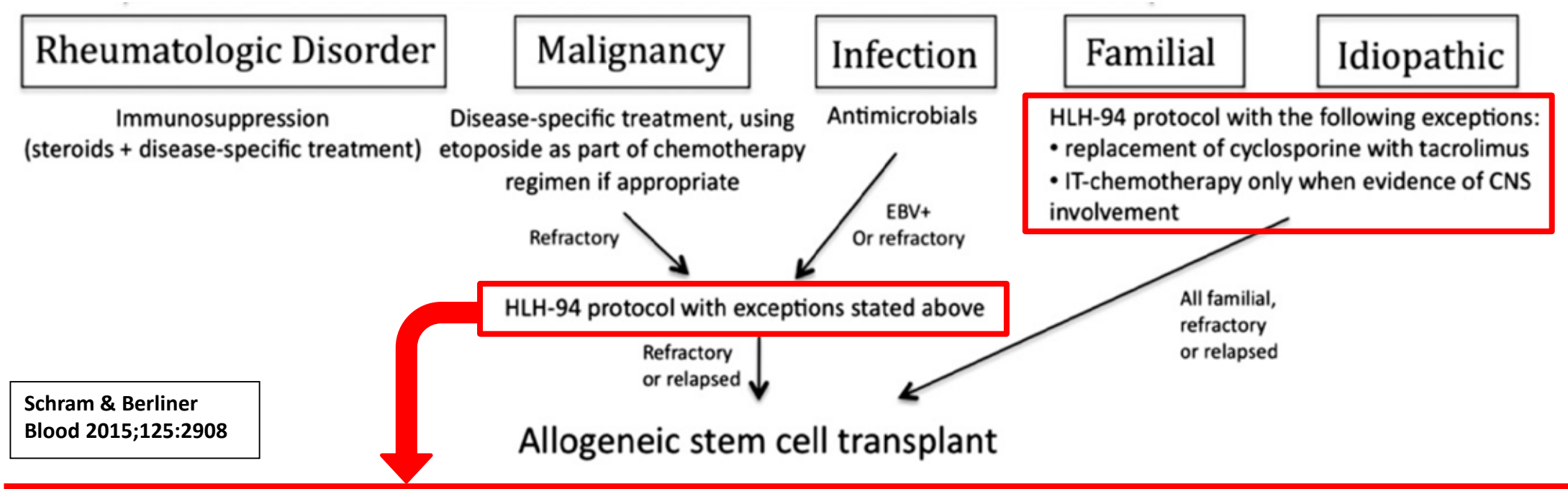


Marrow Biopsy H & E



ICC for CD68+ Histiocytes

HLH: Treatment Algorithm



Schram & Berliner
Blood 2015;125:2908

HLH-94 protocol

Dexamethasone + VP-16 + CSA [or tacrolimus] + IT chemo

Secondary

± Dexa/VP-16, IVIg, ATG, CSA, Alemtuzumab

MAS/Adult-Onset Still's

Hi-dose steroids, ± CSA [tacrolimus], Anakinra, Cytoxan, IVIg, plasma exchange

Primary/Familial HLH Therapy: Anti-IFNγ

- **Emapalumab-Izsg (Gamifant®)**
  - IFNγ blocking antibody (given with dexamethasone)
  - FDA approved for primary HLH
  - Refractory, recurrent or progressive or with intolerance to conventional HLH therapy
- **Clinical trial of 34 pediatric patients (median age 1 yo)***
  - Suspected or confirmed primary HLH - refractory, recurrent or progressive or intolerant of conventional therapy
  - **65% response; 70% able to proceed to BMT**
  - Common side effects: Infections, hypertension, infusion-related reactions, low potassium & fever

*Locatelli F, et al. NEJM 2020;382:1811-22

Summary

- Important to recognize the causes & management of acquired neutropenias & possible 1º congenital disorders
- Reactive hypereosinophilia & mastocytosis may be pathological; targeted treatment is available for clonal disorders
- HLH & MAS represent 1º & acquired disorders driven by CTL/NK dysregulation & cytokine storm → multisystem complications; early Dx is critical; Tx: Underlying trigger & aggressive immunosuppression (HLH-94) as needed

Questions

Thank You

Sarcoma Board Review 2020

Seth M. Pollack

Seattle Cancer Care Alliance

Fred Hutchinson Cancer Research Center

University of Washington

Disclosures

Honoraria/advisory: Daiichi Sankyo, Apexigen

Grants/research: Immune Design, Merck, EMD Serono, Incyte, Omeros, Presage, Janssen, Juno

Outline

1) Overview (etiology/risk factors/diagnosis)

Soft Tissue Sarcomas:

2) Non-GIST soft tissue sarcoma

    - Includes treatment of select “benign,” aggressive tumors

3) GIST

4) Bone Sarcomas

- Osteosarcoma
- Ewing sarcoma

Sarcoma (1% of all cancer - percentages include children and adults; 20,000 patients all combined)

Bone Sarcomas (10%):

- Osteosarcoma
- Ewings Sarcoma
- Chondrosarcoma
- Giant Cell Tumor
- Other

Soft Tissue Sarcoma (STS)

GIST (18%)

RMS (3%)

Other "special" STS:
Kaposi's (3%)
DFSP (5%) etc.

Non-GIST
Non-RMS
Not special
STS:

Or, in other words, what I usually call: STS

Ducimetriere et al 2011

Risk Factors

- Lymphedema
  - Stewart-Treves (cutaneous angiosarcoma)
- Immunodeficiency
  - Human herpes virus 8 (Kaposi's Sarcoma)
- Chemical exposures?
- Role of Trauma?
- Radiation:
  - <1% of treated patients
  - Median latency 10 years following RT
  - Rarely seen with doses <40 Gy
  - Increased risk with anthracyclines + alkylating agents
  - Undifferentiated pleomorphic sarcoma (UPS) most common subtype
  - Angiosarcomas in breast cancer patients
- Genetics…

Genetic Predisposition For Sarcoma

- Neurofibromatosis (type 1) – Malignant Peripheral Nerve Sheath Tumors (MPNST) and others
- Retinoblastoma – Osteosarcoma, leiomyosarcoma and others
- Li-Fraumeni syndrome – Many Sarcoma types
- Gardener's syndrome (familial adenomatous polyposis) – Desmoid Tumors [1]

- Other Syndromes: Tuberous sclerosis (rhabdomyosarcoma) , Rothmond-Thomas Syndrome (Osteosarcoma) , Costello Syndrome (Rhabdomyosarcoma), Beckwith-Wiedmann Synodrome (Rhabdomyosarcoma), Multiple Enchondromas (Chondrosarcoma) [2]

[1]Thomas et al J. Surg Onc 2015
[2]Pakaksama et al., Ped Clin N. Amer. 2002

Biopsy

For Extremity Tumors:

- Usually core biopsy or incisional biopsy preferred.
  - Extremity masses should be biopsied through a small *longitudinal* incision so that entire biopsy tract can be excised at the time of resection
- Tru-cut core biopsies may be adequate.
- FNA has no role in initial diagnosis of extremity STS. May document a recurrence.
- Excisional biopsy for small <3 cm superficial tumors.

For abdominal tumors, biopsy is not helpful unless:

- Suspect lymphoma or germ-cell tumor
- Plan to give preoperative chemotherapy and/ or radiation
- Tumor is unresectable

Lewis J, Brennan MF. Current Probl Surg 33: 817: 1996
Mankin HJ et al. J Bone Joint Surg 78A:656-63: 1996

Histological Subtype: Expert Review is Key

- Presant and colleagues reviewed 216 sarcoma cases to see if experienced academic pathologist would agree with pathologists who see few sarcomas.
- Experienced pathologist have a high degree of concordance
- However, in experienced pathologists misclassify sarcomas 27% of time
- 6% of tumors initially called “sarcomas” were not actually sarcoma

Summary: any pathology thought to be sarcoma should be reviewed by an experienced bone and soft tissue pathologist.

Presant et al. JCO 1986

Histological Grade

- Histological grade predicts risk of metastasis and survival
- FNLCC (most common): based on differentiation, mitosis, necrosis. Slightly improvement in predictive power over histology based NCI system.
- Grade is of no prognostic value in certain subtypes:
  - MPNST
  - Extraskeletal myxoid chondrosarcoma
- Others are always considered high grade
  - Angiosarcoma
  - PNET

Guillon, JCO 1997
Coindre, Arch Pathol Lab Med. 2006

Translocation-related Sarcomas

Disease	Chromosomal Change	Fusion Gene	Frequency
Ewing's/PNET	t(11;22) or t(21;22)	*EWS-FLI1* *EWS-ERG*	85% 5-10%
Synovial sarcoma	t(x;18)	*SYT-SSX*	> 90%
Myxoid liposarcoma	t(12;16)	*CHOP-TLS*	> 75%
Alveolar rhabdomyosarcoma	t(2;13) or t(1;13)	*PAX3-FKHR* *PAX7-FKHR*	70% 15%
Clear cell sarcoma	t(12;22)	*EWS-ATF1*	> 75%
Desmoplastic small round cell tumor	t(11;22)	*EWS-WT1*	> 90%

Standard Imaging/Staging Approach

MRI:
• important for extremities (e.g. muscle versus tumor/fat), head and neck, chest wall
•Accurate at defining tumor relationship to muscle, fascial planes, bones and neurovascular bundles

CT:
•Initial chest CT recommended to evaluate for metastatic disease in all sarcoma patients
•Used as main evaluation for primary sarcomas in the abdomen and pelvis.

Other imaging including PET may play a role in select circumstances

Soft Tissue Sarcoma Staging

Stage IA	G1,2	T1a,b	N0	M0
Stage IB	G2	T2a,b	N0	M0
Stage IIA	G3,4	T1a,b	N0	M0
Stage IIB	G3,4	T2a	N0	M0
Stage III	G3,4	T2b	N0	M0
Stage IV	Any G	Any T	N1	M1

5 year Survival by AJCC Stage	
Stage I	**90%**
Stage II	**70%**
Stage III	**50%**
Stage IV	**10-20%**

Stojadinovic A, Leung DH et al. J Clin Oncol 20; 4344-52: 2002

Staging of Bone Sarcomas

		Enneking Stage	AJCC Stage
IA	Low grade	Intracompartmental	< 8 cm
IB	Low grade	Extracompartmental	> 8 cm
IIA	High grade	Intracompartmental	< 8 cm
IIB	High grade	Extracompartmental	> 8 cm
III	Any grade	N1 or M1	Skip metastasis
IVA	Any grade	Has no stage IV	Lung only mets
IVB	Any grade		Lymph node or other sites

Key “pearls” for Overview (etiology/risk factors/diagnosis)

- Translocations and heritable syndromes are easy to test. Memorize these.
- Transverse incisions and FNA are “no-no’s” for evaluation of soft tissue masses
- Review pathology with an experienced bone and soft tissue pathologist
- Grade and tumor size are both important predictors of local recurrence, distant metastasis and survival.

Outline

1) Overview (etiology/risk factors/diagnosis)

Soft Tissue Sarcomas:

2) Non-GIST soft tissue sarcoma

    - Includes treatment of select “benign,” aggressive tumors

3) GIST

4) Bone Sarcomas

- Osteosarcoma
- Ewing sarcoma

Prognostic Factors in STS

- **Histologic grade – includes:** Differentiation (histology specific), mitotic rate, extent of necrosis
- **Tumor size (Stage includes size and grade)**
  Other tumor-related factors
- Depth (superficial/deep to fascia)
- Site (extremity vs trunk/retroperitoneum; distal vs proximal) **Treatment setting**
- Better outcomes at high-volume sarcoma centers: Improved R0 margin rate, local recurrence rate, 30-day mortality, overall survival and functional outcomes
- **Adherence to guidelines — associated with improved survival**

Adapted from *Research to Practice Soft Tissue Sarcoma Grand Rounds*
Abarca T et al. *J Surg Oncol* 2018;117:1479; Bagaria SP et al. *Sarcoma* 2018a, b; Gutierrez JC et al. *Ann Surg* 2007;245:952; Clasby R et al. *Br J Surg* 1997;84(12):1692; Gustafson. *Acta Orthop Scand* 1994;65(1):47; Voss RK et al. *Ann Surg Oncol* 2017;24(11):3271.

Treatment of Localized STS

- Surgery + RT (most common)
- Surgery + chemo + RT – may make sense for large high grade tumors where surgery is difficult
- Neoadjuvant Chemo – may play a role for larger, higher grade tumors
- Adjuvant Chemo – controversial and not definitively proven but likely plays a role for some patients

Extremity Soft Tissue Sarcoma Surgery

- Whenever possible, function- and limb- sparing procedures should be performed
- As long as the entire tumor is removed, less radical procedures do not adversely affect local recurrence or outcome
- Goal is complete removal of the tumor with negative (2-3 cm) margins and maximal preservation of function

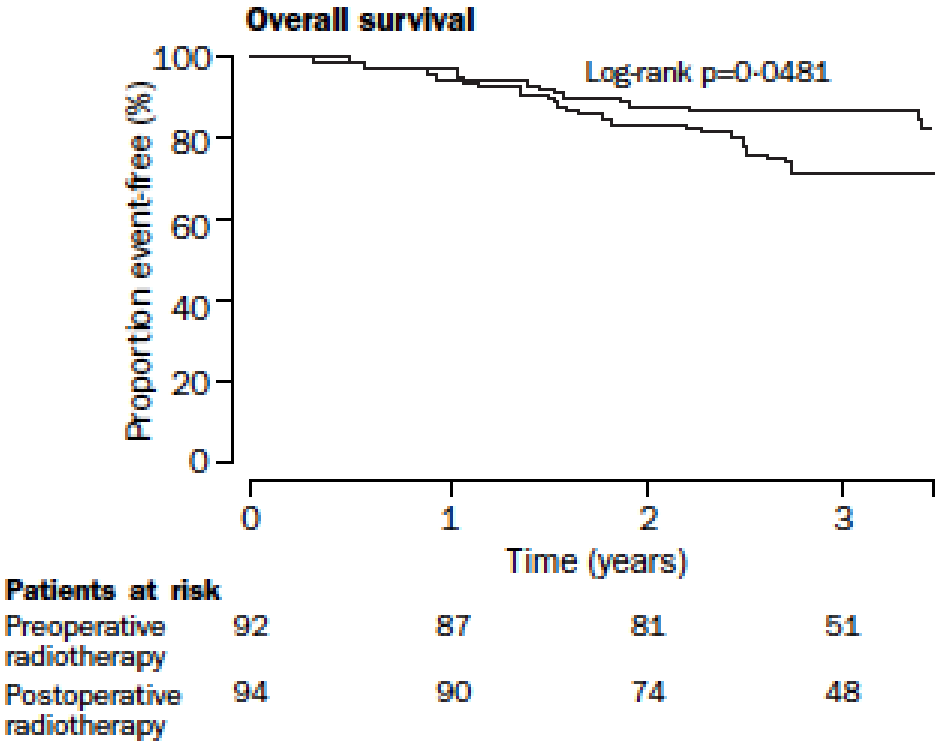
Rosenberg SA, Tepper J et al. Ann Surg 196; 305-15: 1982

Extremity Soft Tissue Sarcoma: Adjuvant Radiation

- Wide surgical excision alone is adequate for small lesions <5 cm
- Consider adjuvant RT with high grade lesions greater than 5 cm or with resection margin <1 cm
- RT choices include IORT and Brachytherapy

Yang J, Chang A, et al. J Clin Oncol 16;197-203: 1998

Adjuvant versus Neoadjuvant Radiation



Neoadjuvant Radiation:
Higher rates of wound complications
Higher rates of returning to the operating room.

Adjuvant Radiation:
Higher rates of edema and fibrosis
Higher rates of radiation associated fractures.

Although the O'sullivan series showed better survival with neoadjuvant rads compared with post-op rads, others have criticized it as it was not an intention-to–treat analysis

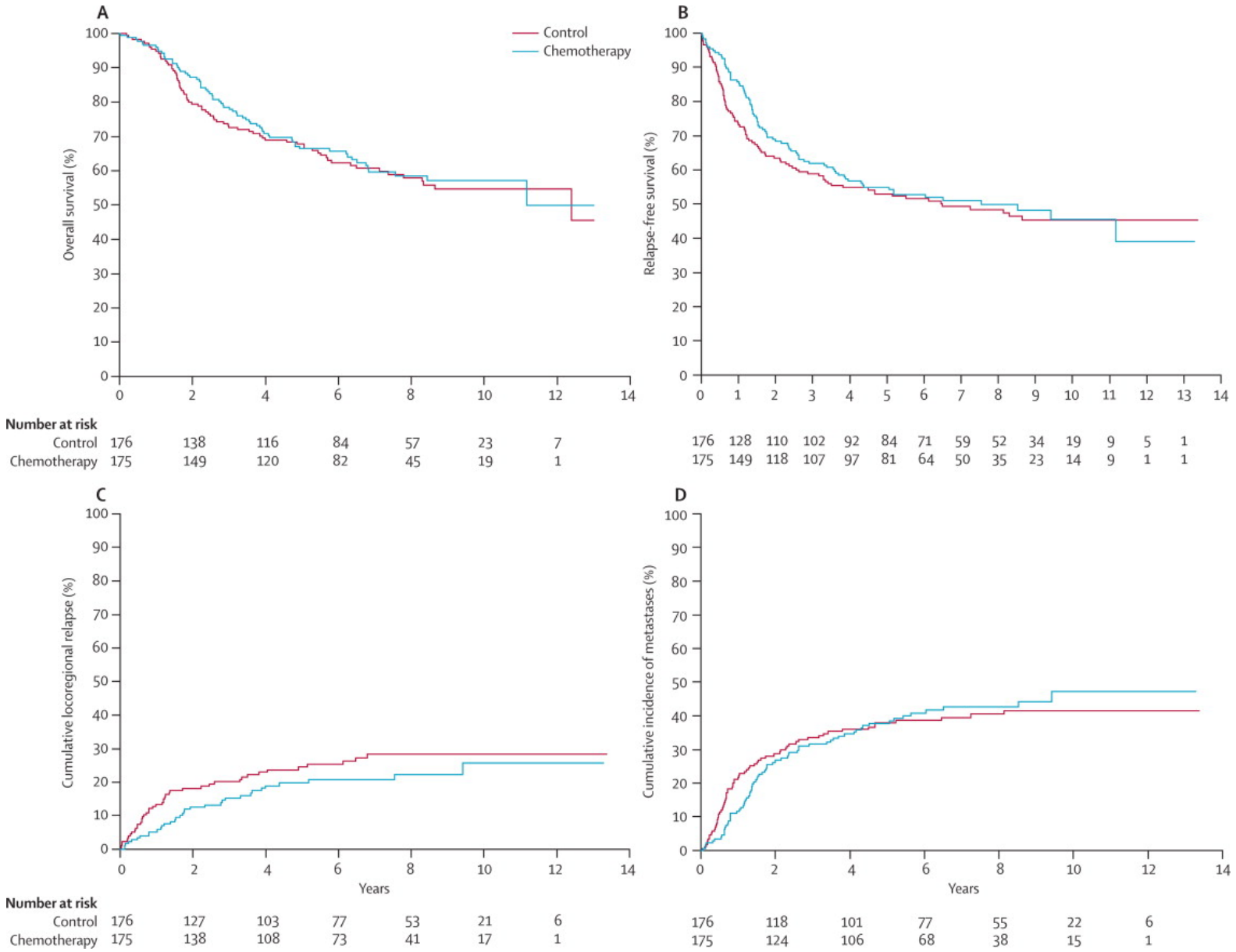
O´Sullivan et al, Lancet, 2002

Adjuvant Chemotherapy

- The role of chemotherapy is established in some special cases:
  - Ewing's/ PNET
  - "Pediatric type" rhabdomyosarcoma (Embryonal or Alveolar)
- Local therapy alone only cures 10-20%.
- Addition of combination chemotherapy affords cure rate of
  - 60-70% in Ewing's/ PNET
  - 60-90% in embryonal rhabdomyosarcoma

These are relatively rare tumor types in the adult population …

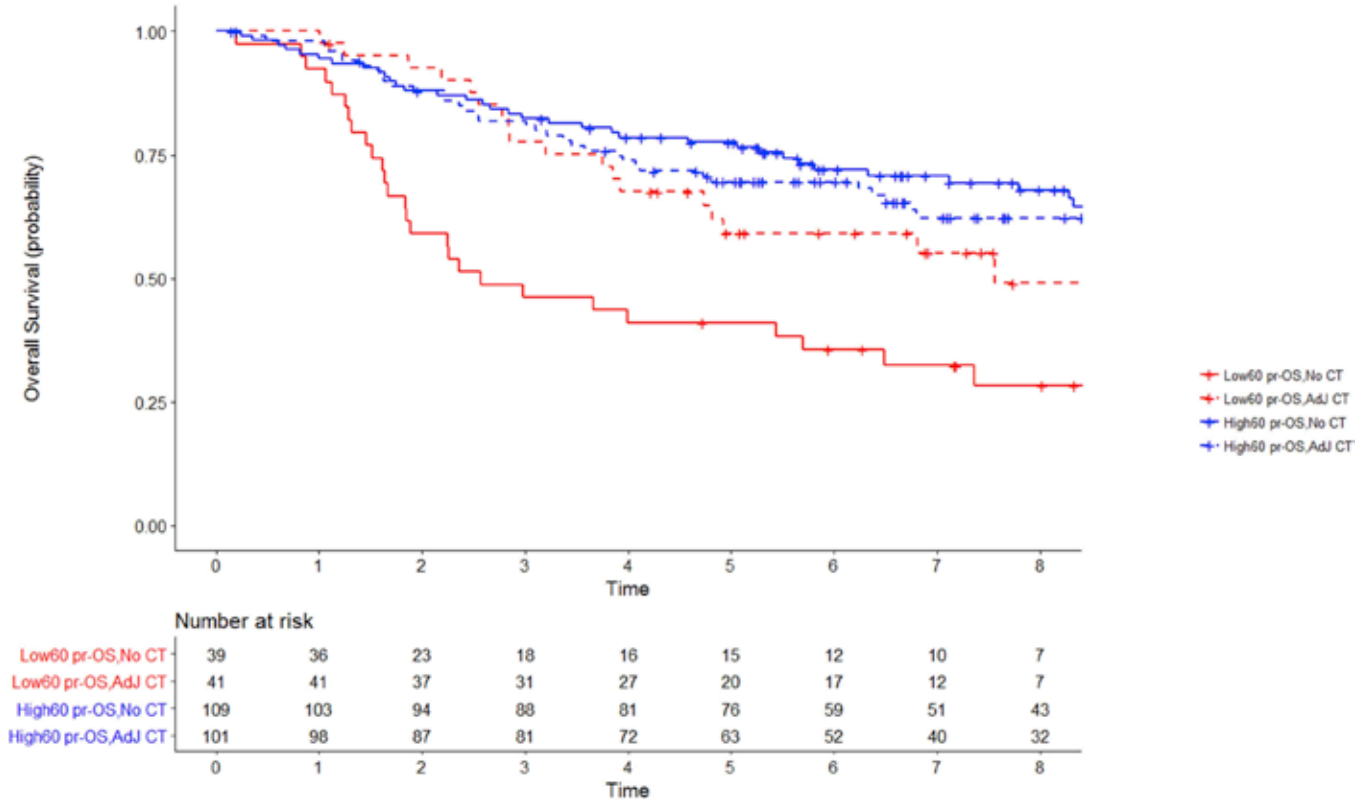
EORTC Adjuvant trial



Randomised trial ± doxorubicin 75mg/m^2 + ifosfamide 5g/m^2 + lenograstim q 3wk x 5 Woll P et al, Lancet 2012

Navigating Adjuvant Chemo:

- High-risk patients identified using the “sarculator” nomogram.
- For these patients, in the EORTC adjuvant trial, chemo improved survival
- Most sarcoma physicians in the US are giving adjuvant chemotherapy to their most high-risk patients.



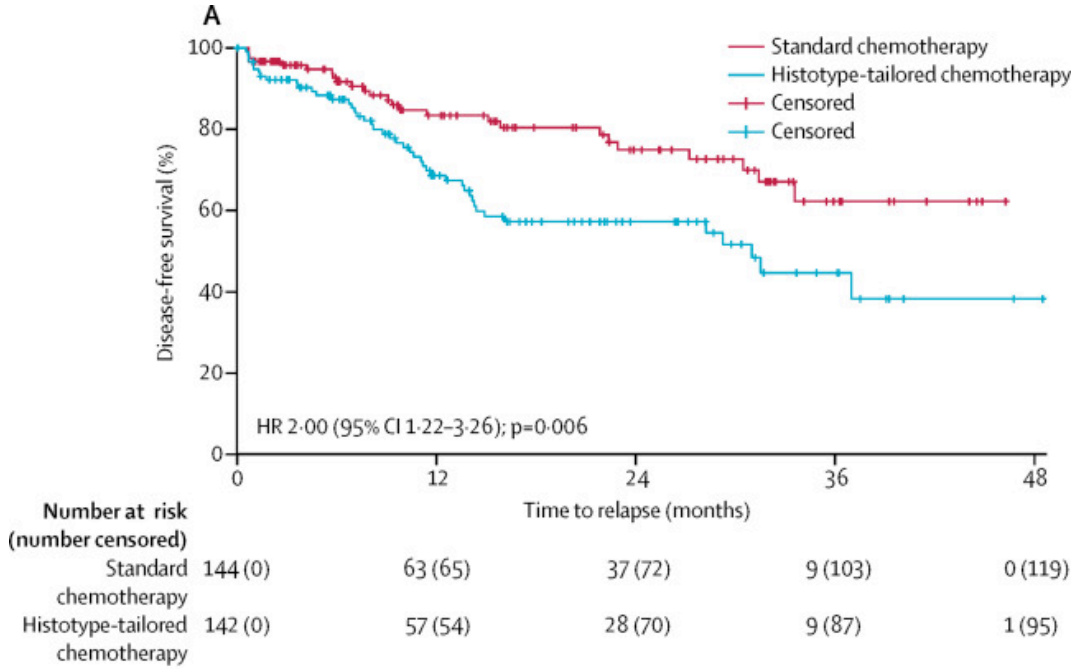
Pasquali et al., *Eur J. Cancer* 2019

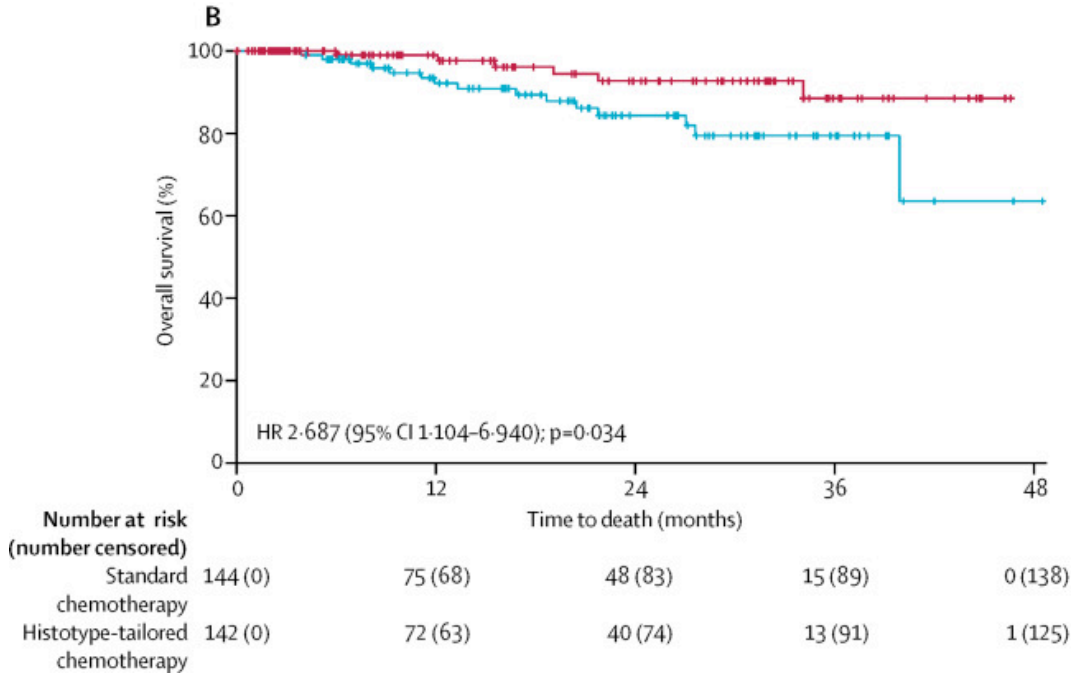
Neoadjuvant Chemo:

For many patients, it makes more sense to give chemotherapy in the neoadjuvant setting.

Neoadjuvant AIM leads to superior outcomes compared with histology-tailored regimens in high risk patients.

Some have interpreted this as a survival benefit for AIM generally.



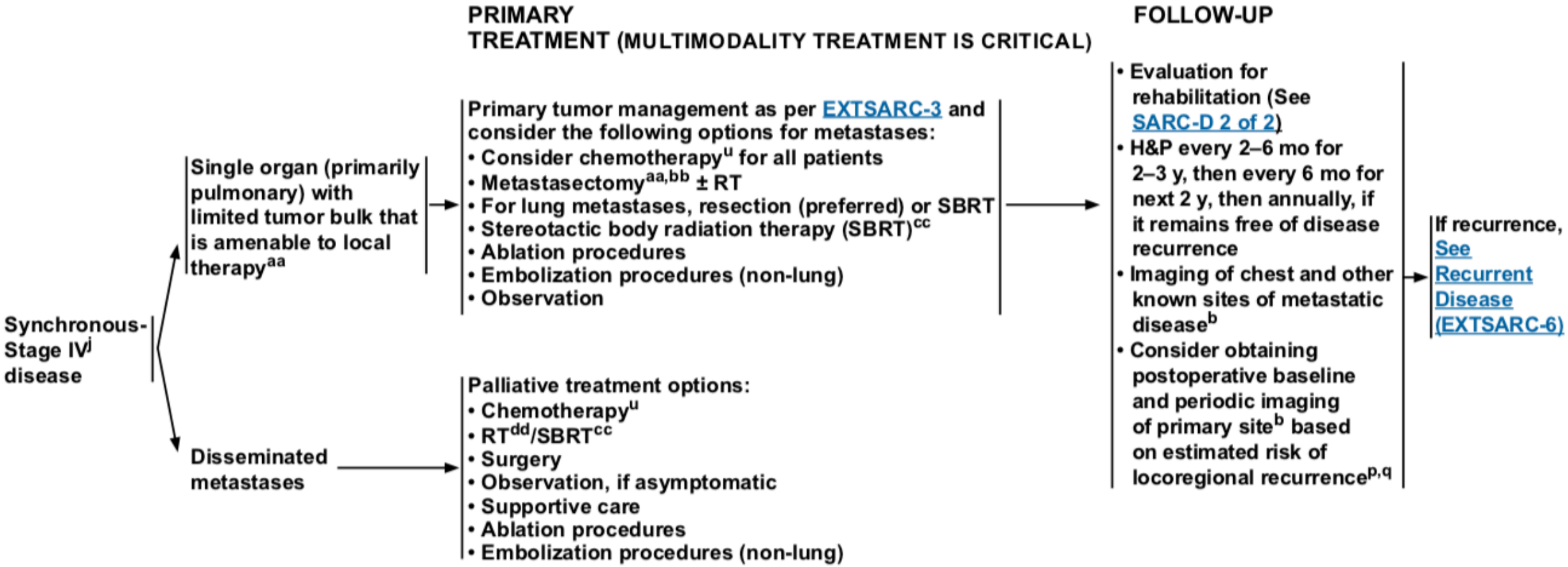


Surveillance

- Chest Imaging Q3-6 months 2-3 years, the every 6 months until 5 years, then annually
- Consider period imaging of primary site.

Options for Metastatic Soft Tissue Sarcoma (according to NCCN):

Note: both surgery and SBRT may be good options for patients with isolated/metastatic disease



NCCN Practice Guidelines 2020

Principals Systemic therapy in soft tissue sarcoma

- Chemotherapy: mainstay of treatment for unresectable/ metastatic disease

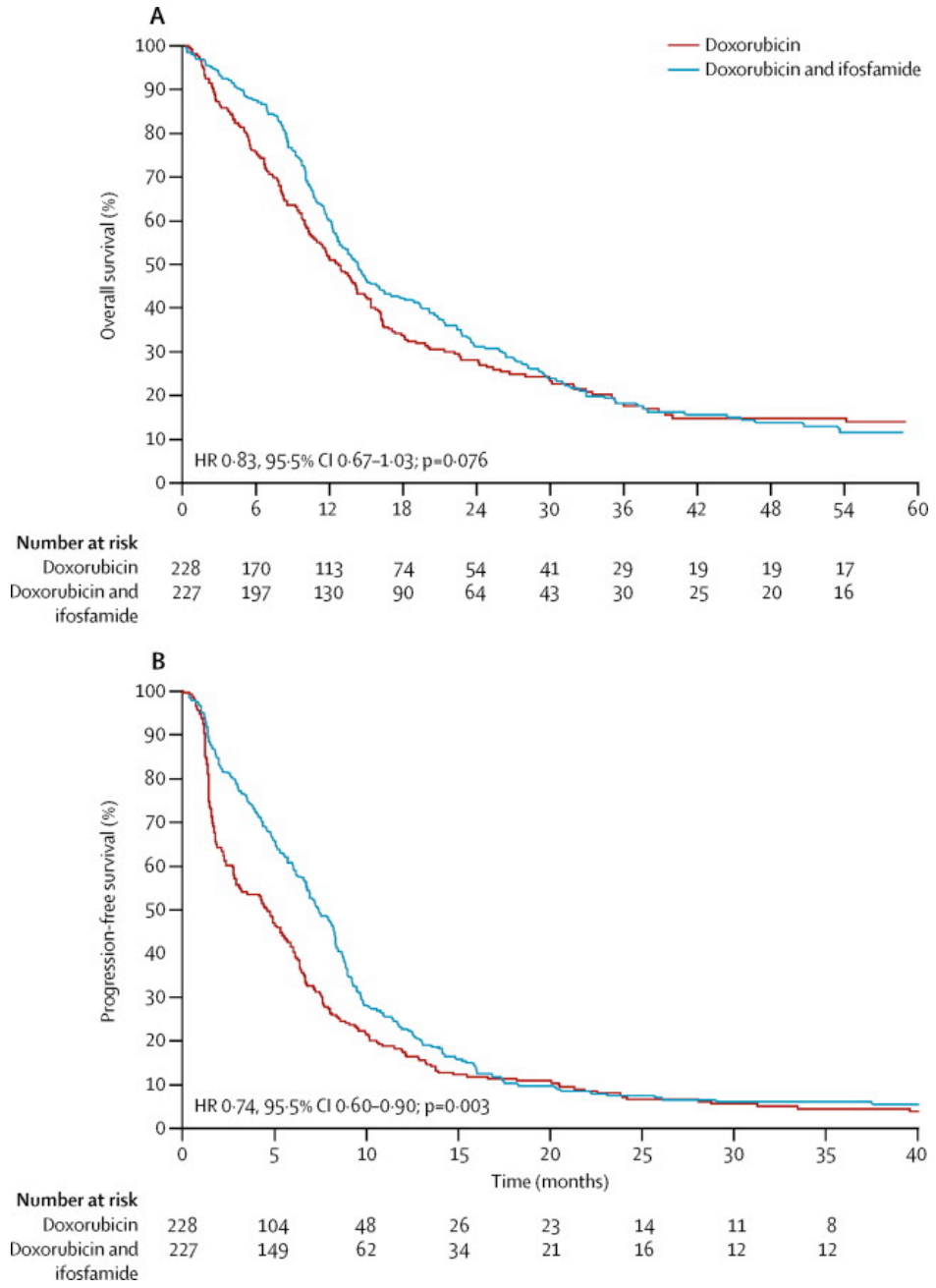
- Previously “one size fits all” approach to therapy:
  - Anthracycline +/- ifosfamide

- Other agents:
  - Gemcitabine/ docetaxel
  - Eribulin
  - Trabectedin
  - Pazopanib
  - Older agents (e.g. decarbazine etc)

Constantinidou A, et al. Expert Rev Anticancer Ther 13(2); 211-23: 2013

Although chemotherapy should be tailored to an individual, anthracycline-based therapy (dox alone or in AIM) is generally the gold standard front line.

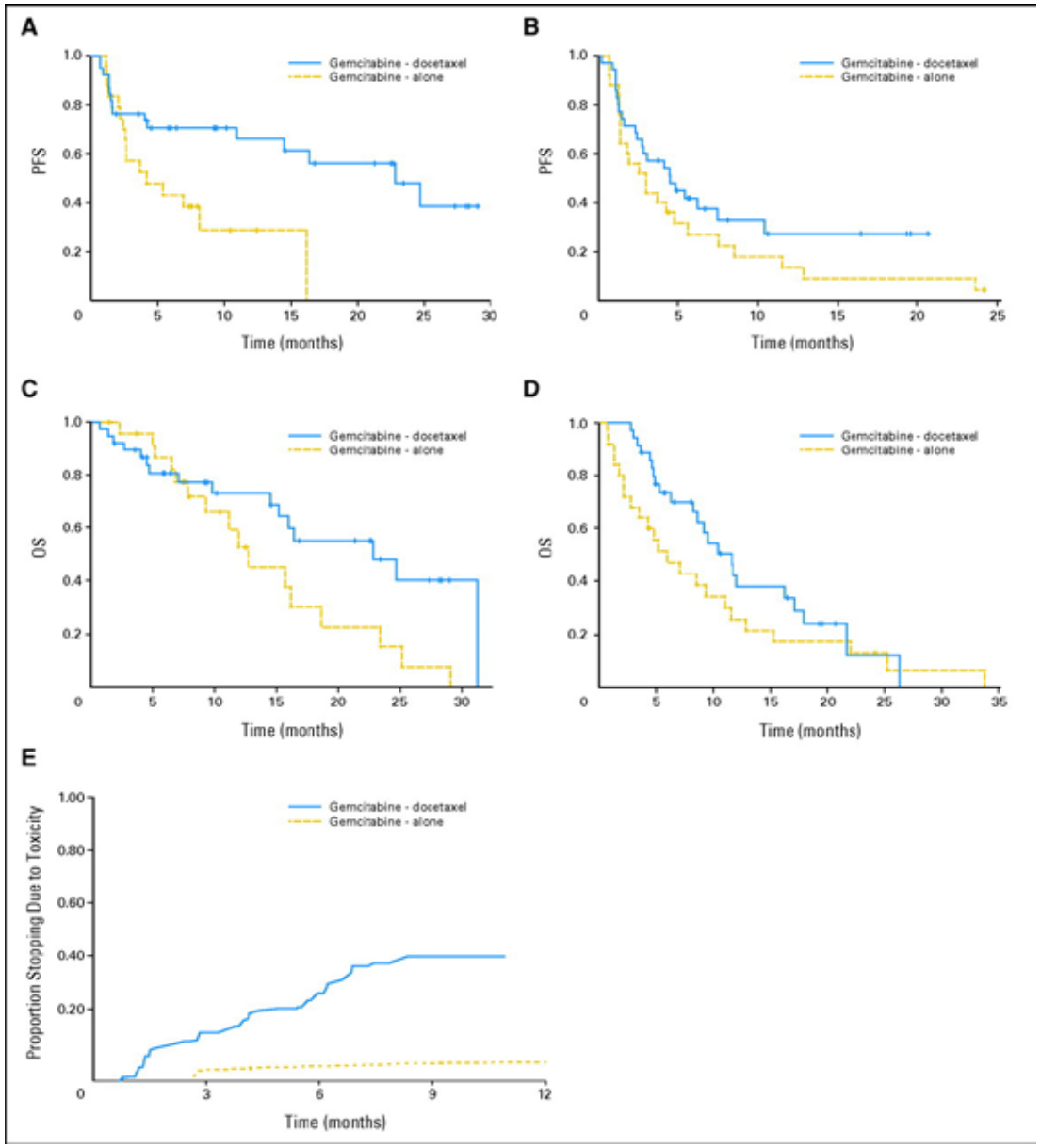
- EORTC randomized Phase III trial:
  - Doxorubicin + ifosfamide versus doxorubicin alone (N=455)
- Median PFS:
  - 7.4 (95%CI, 6.6-8.3) v 4.6 (95%CI, 2.9-5.6) months
  - (HR 0.72, 95%CI; 0.59-0.88, p=0.002)
- Median OS: No significant difference
- Dox+ifos more toxic



Judson I et al, Lancet 2014

Gemcitabine and docetaxel

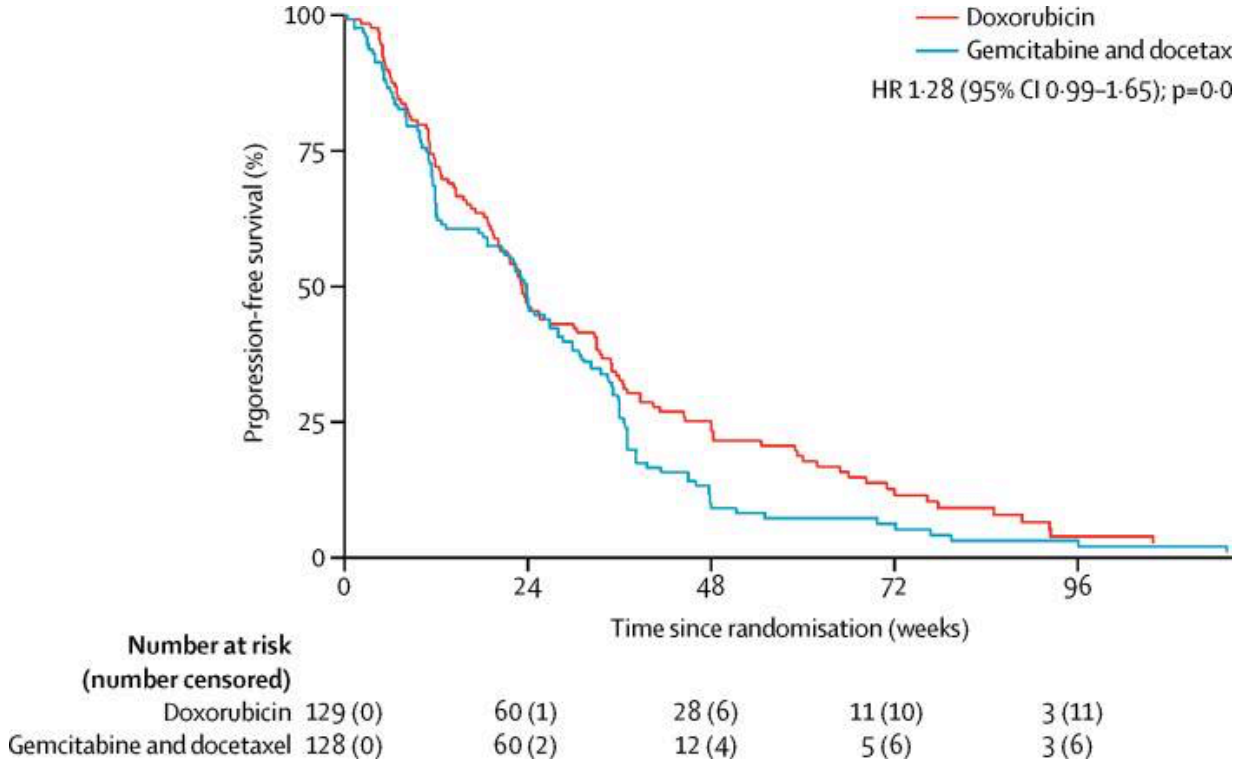
- Randomized Phase II trial, N=122
- Gemcitabine
  - Response rate: 8%
  - Median PFS: 3.0
  - Median OS: 11.5 months
- Gemcitabine/ docetaxel
  - Response rate: 16%
  - Median PFS: 6.2 months
  - Median OS: 17.9 months
- Other Gemcitabine Based Combinations:
  - Navelbine
  - Decarbazine

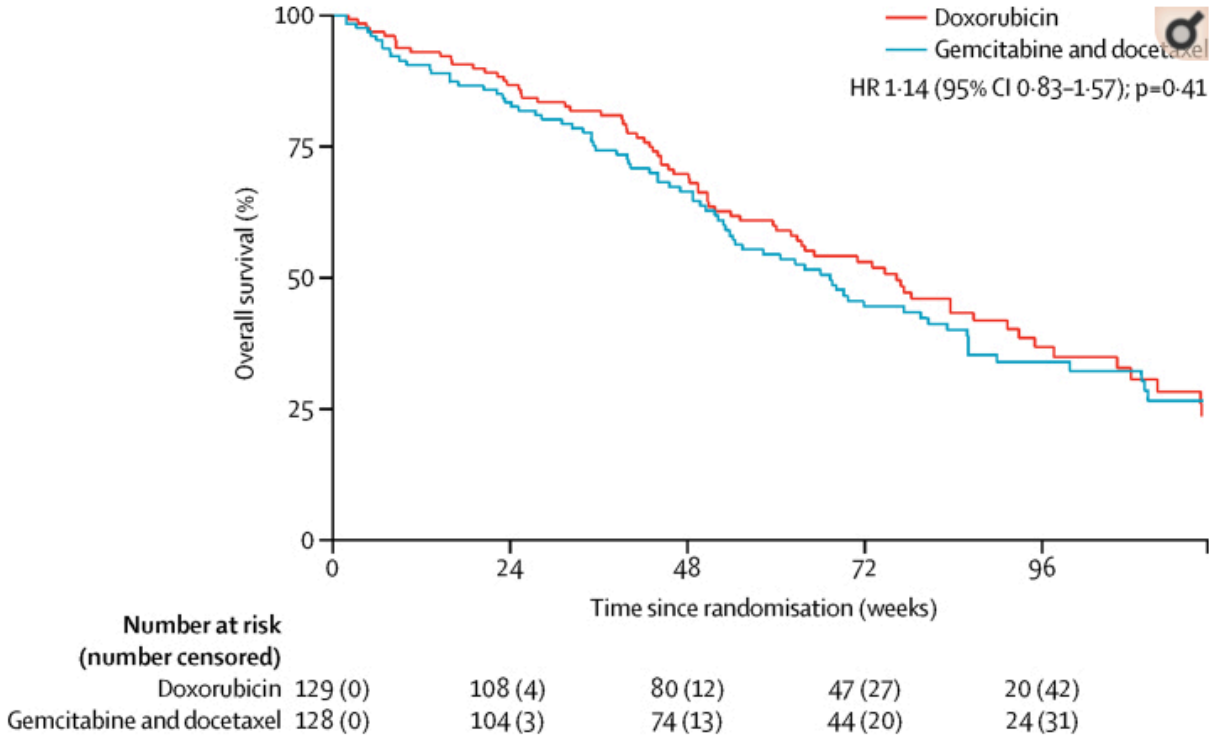


Maki R et al JCO 25; 2755-2763: 2007

Geddis trial: gem/tax vs. dox

No benefit to up front gem/tax instead of dox for STS (including the subset of LMS patients)





Seddon et al., *Lancet* 2017

PFS: Pazopanib Phase III trial

	Placebo	Pazopanib
Median (months)	1.5	4.6
Hazard ratio (95%CI)	1	0.31 (0.24-0.4)
P value	<0.0001	

	N (%)	HR	CI	p-value
Overall	369	0.31	0.24-0.4	<0.0001
LMS	158 (43%)	0.31	0.2-0.47	<0.0001
Synovial	38 (10%)	0.19	0.23-0.6	0.0002
Other	173 (47%)	0.36	0.25-0.52	<0.0001

Van der Graaf WT et al. *Lancet* 6736; 60651-60655: 2012

Eribulin versus dacarbazine in previously treated patients with advanced liposarcoma or leiomyosarcoma: a randomised, open-label, multicentre, phase 3 trial

OS

PFS

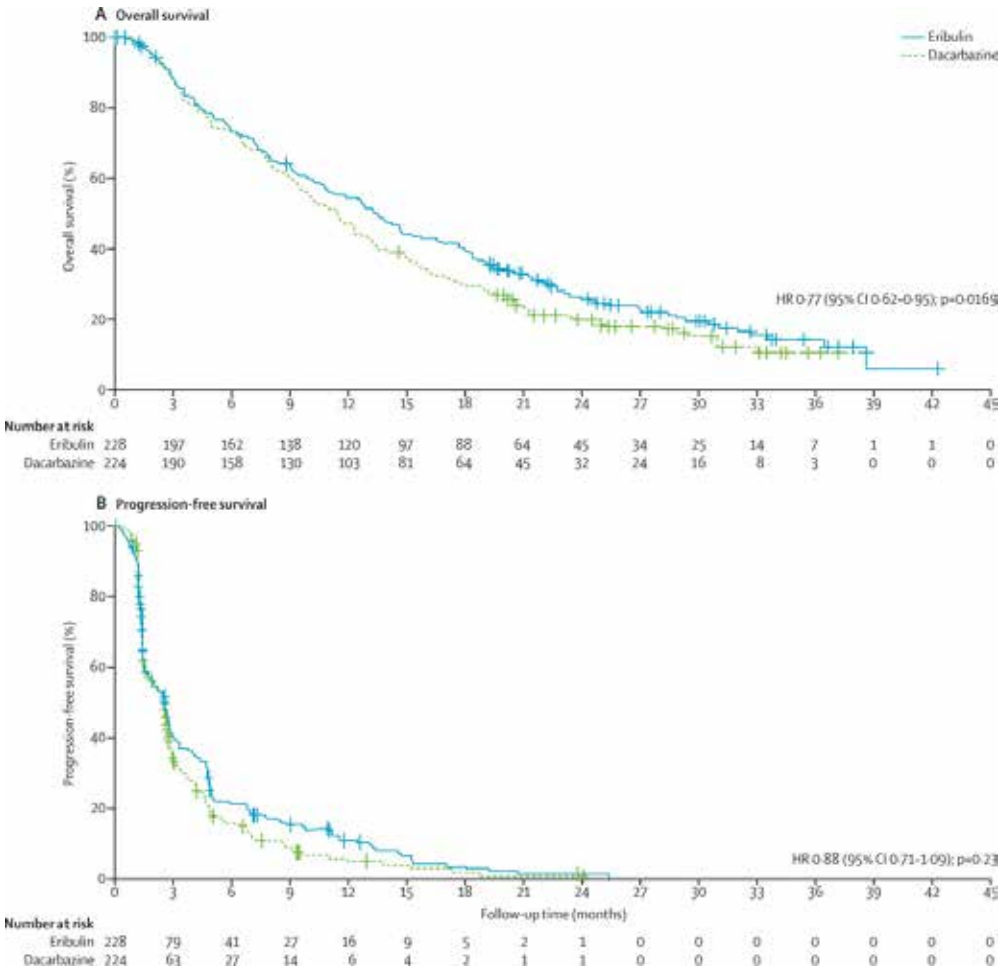
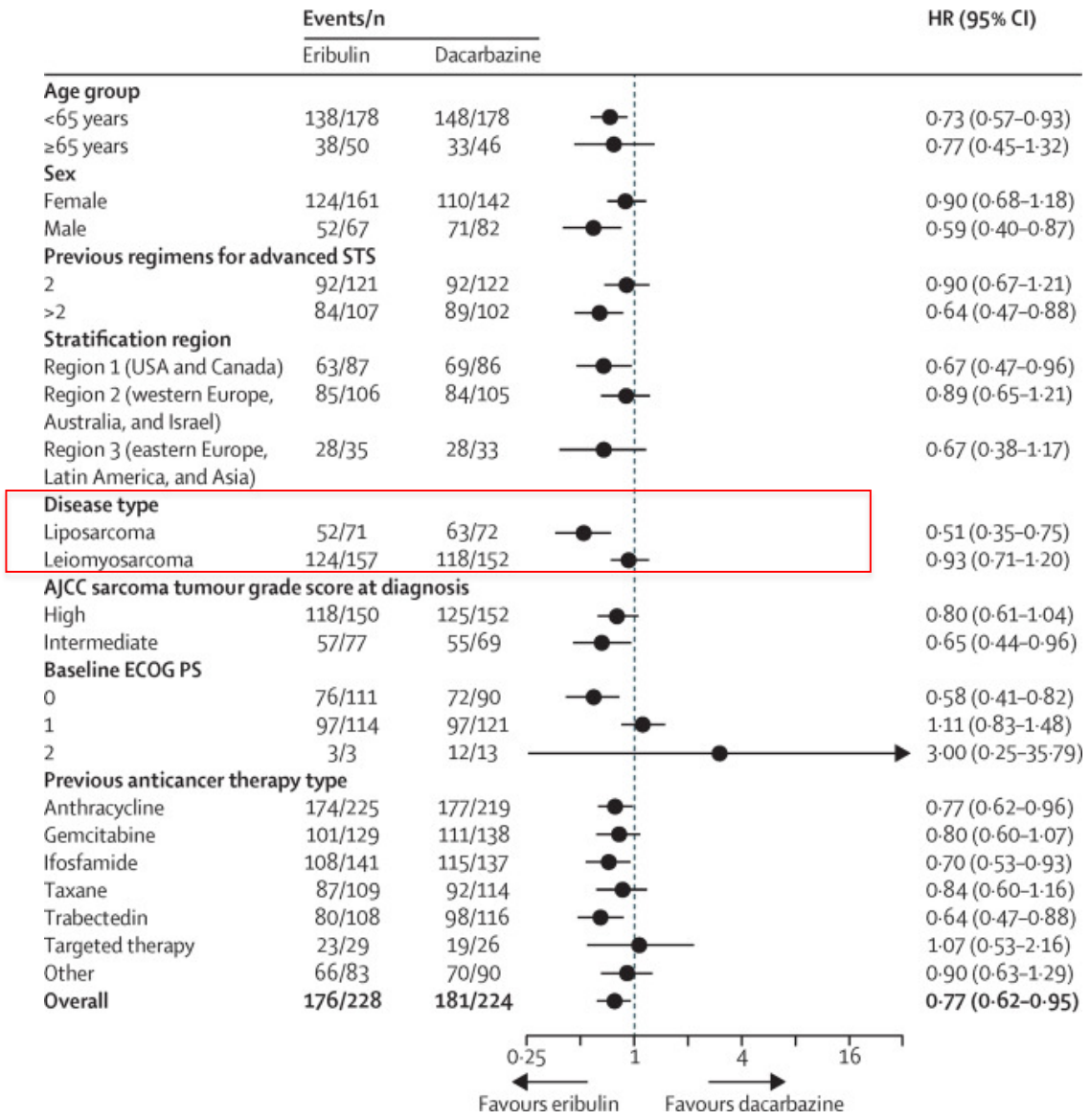


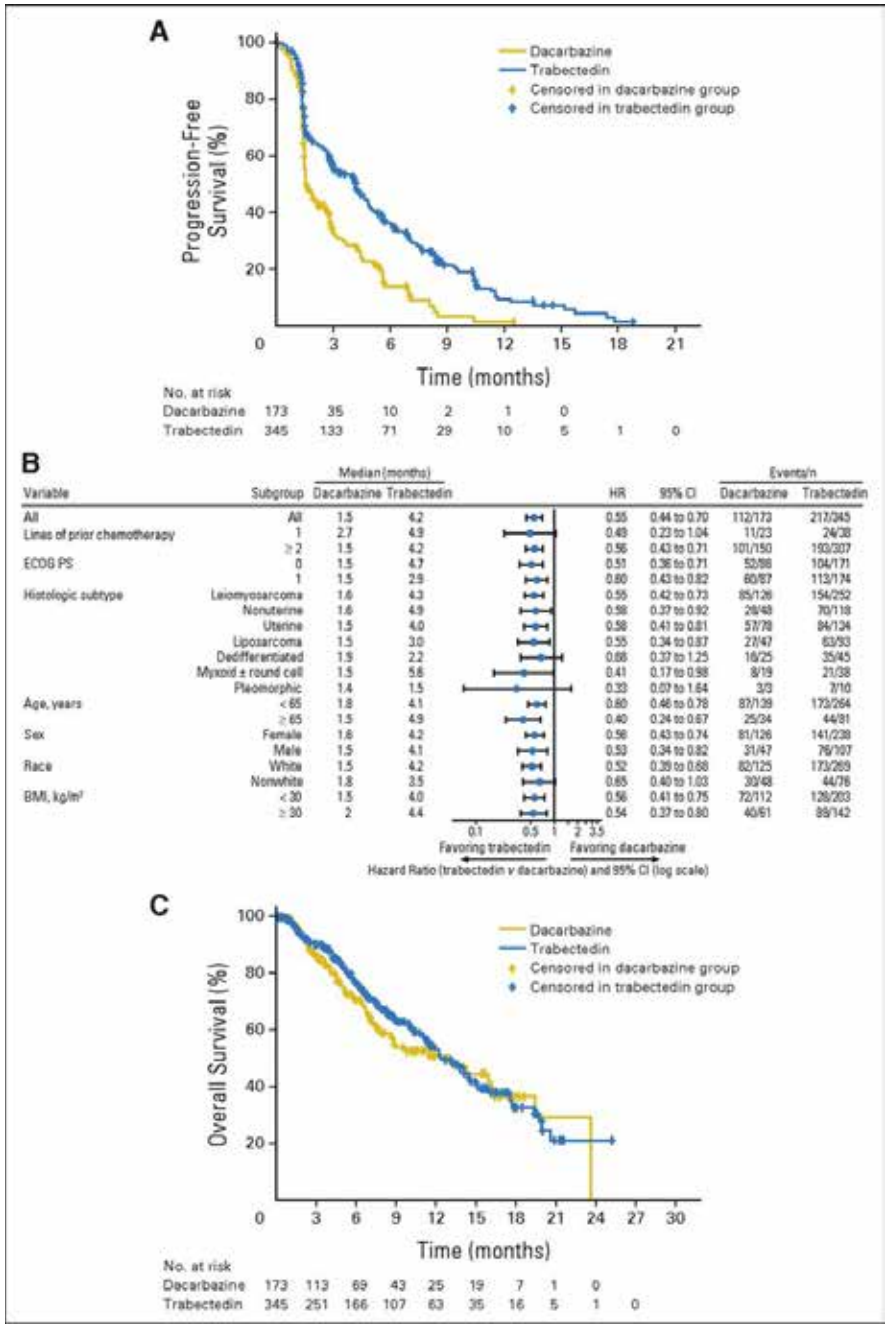
Figure 2. Overall survival (A) and progression-free survival (B)HR=hazard ratio.



Schöffskii et al., Lancet 2016

Trabectedin is FDA approved for liposarcoma and leiomyosarcoma

Kaplan-Meier estimates of progression-free survival, subgroup analyses, and overall survival at the interim analysis.



George D. Demetri et al. JCO 2016;34:786-793

JOURNAL OF CLINICAL ONCOLOGY ASCO

Trabectedin monotherapy after standard chemotherapy versus best supportive care in patients with advanced, translocation-related sarcoma: a randomised, open-label, phase 2 study

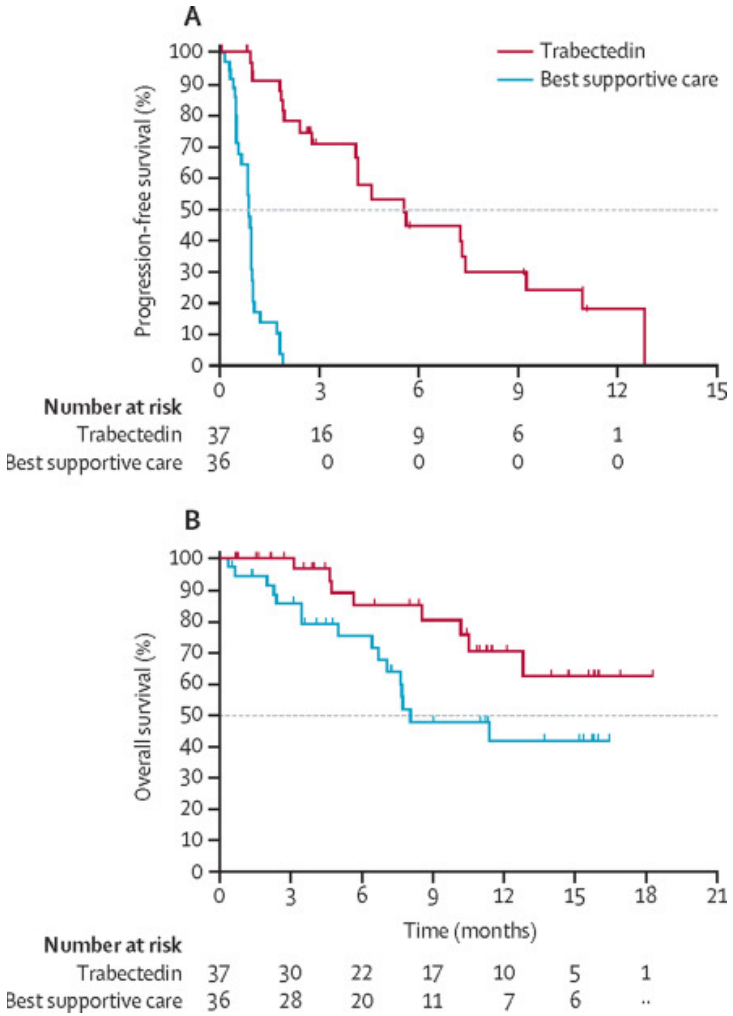


Figure 2. Kaplan-Meier plot of progression-free survival by central radiology imaging review (A) and overall survival (B) in the full analysis set

Akira Kawai et al., Lancet 2016
null, Volume 16, Issue 4, 2015, 406–416
http://dx.doi.org/10.1016/S1470-2045(15)70098-7

Kaposi's Pearls

- HHV8 associated cancer, AIDS defining in setting of HIV
- KS most commonly involves skin. Extracutaneous spread: oral cavity, GI tract, lungs + lymph nodes
- For HIV associated disease, most important is to get HIV under control
- For local disease, surgery. Sytstemic therapy generally not required. Radiation, imiquimod also options.
- For systemic disease, paclitaxel and liposomal doxorubicin are very effective options.

Aversa SM Crit Rev Oncol Hem 53; 253-265: 2005

Histological subtype specific approaches

- **Angiosarcoma:**
  - Paclitaxel
    - Penel et al, JCO 26; 5269-5274: 2008
    - Shlemmer et al, EJC 44; 2433-2436: 2008
- **Perivascular epithelioid cell tumours (PEComa):**
  - mTOR inhibition (sirolimus)
    - Wagner et al, JCO 28; 2010
- **Chordoma:**
  - Imatinib
    - Stacchiotti S et al, JCO 2012
  - Imatinib + sirolimus
    - Stacchiotti S et al, Annals Oncology 20; 1886-1894: 2009

Outline

1) Overview (etiology/risk factors/diagnosis)

Soft Tissue Sarcomas:

2) Non-GIST soft tissue sarcoma

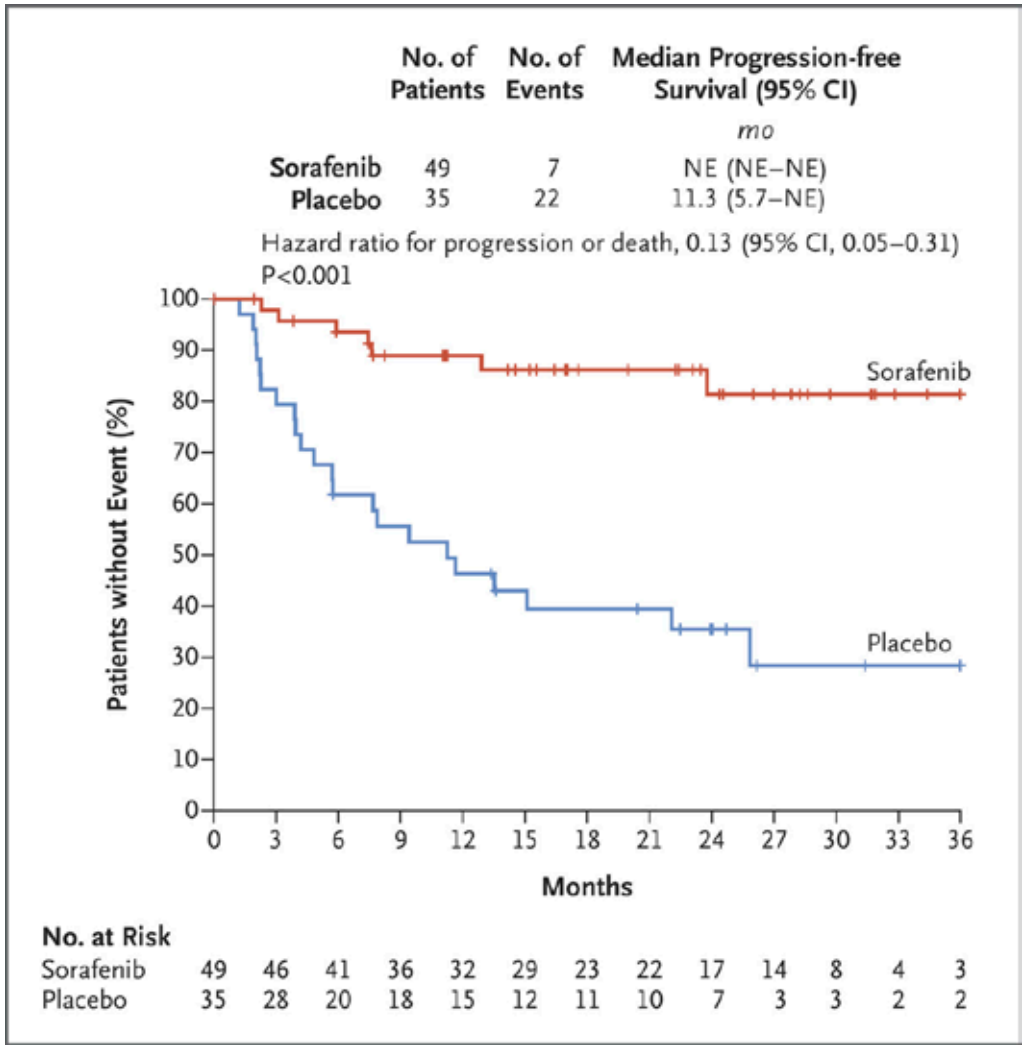
    - Includes treatment of select “benign,” aggressive tumors

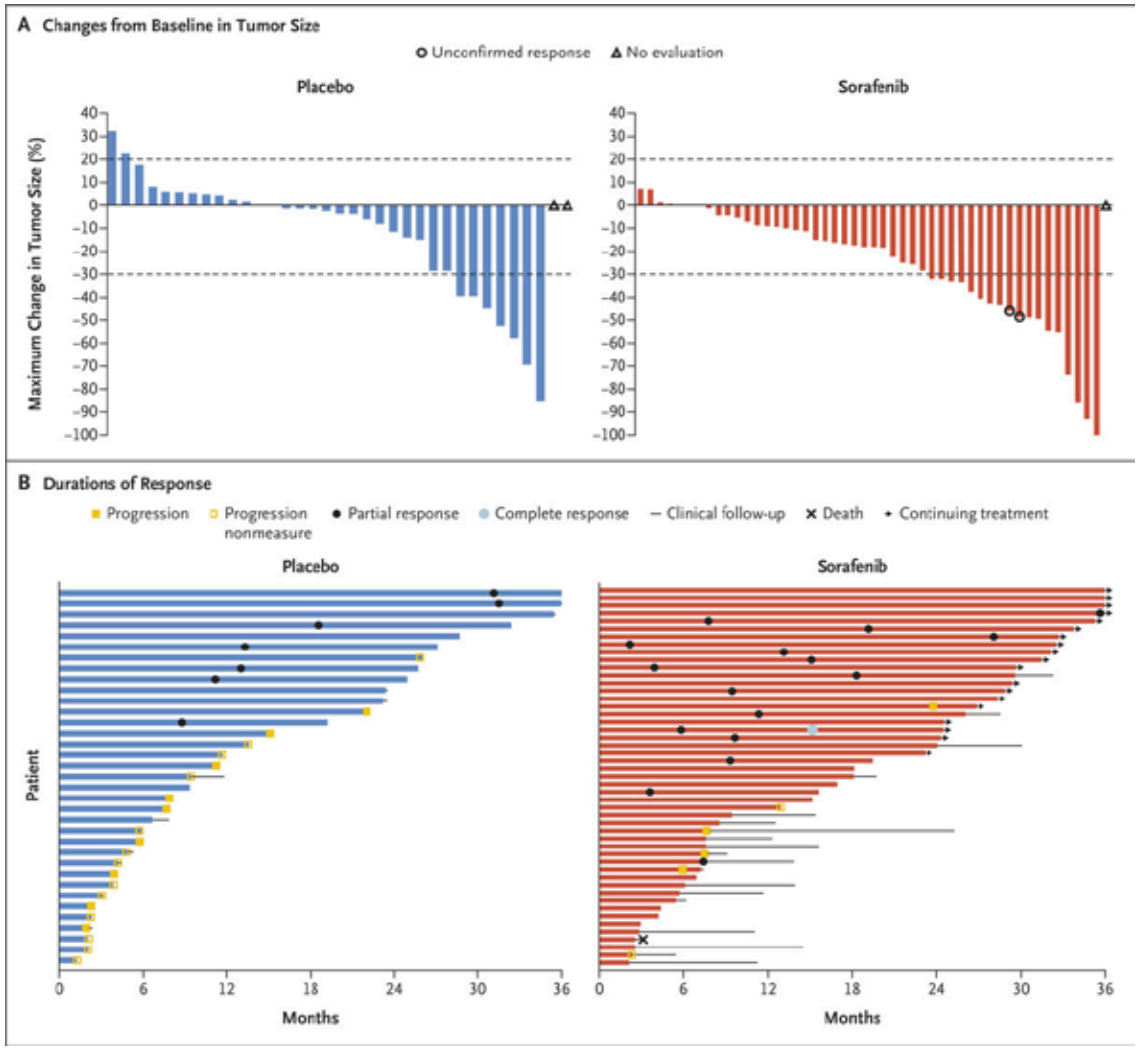
3) GIST

4) Bone Sarcomas

- Osteosarcoma
- Ewing sarcoma

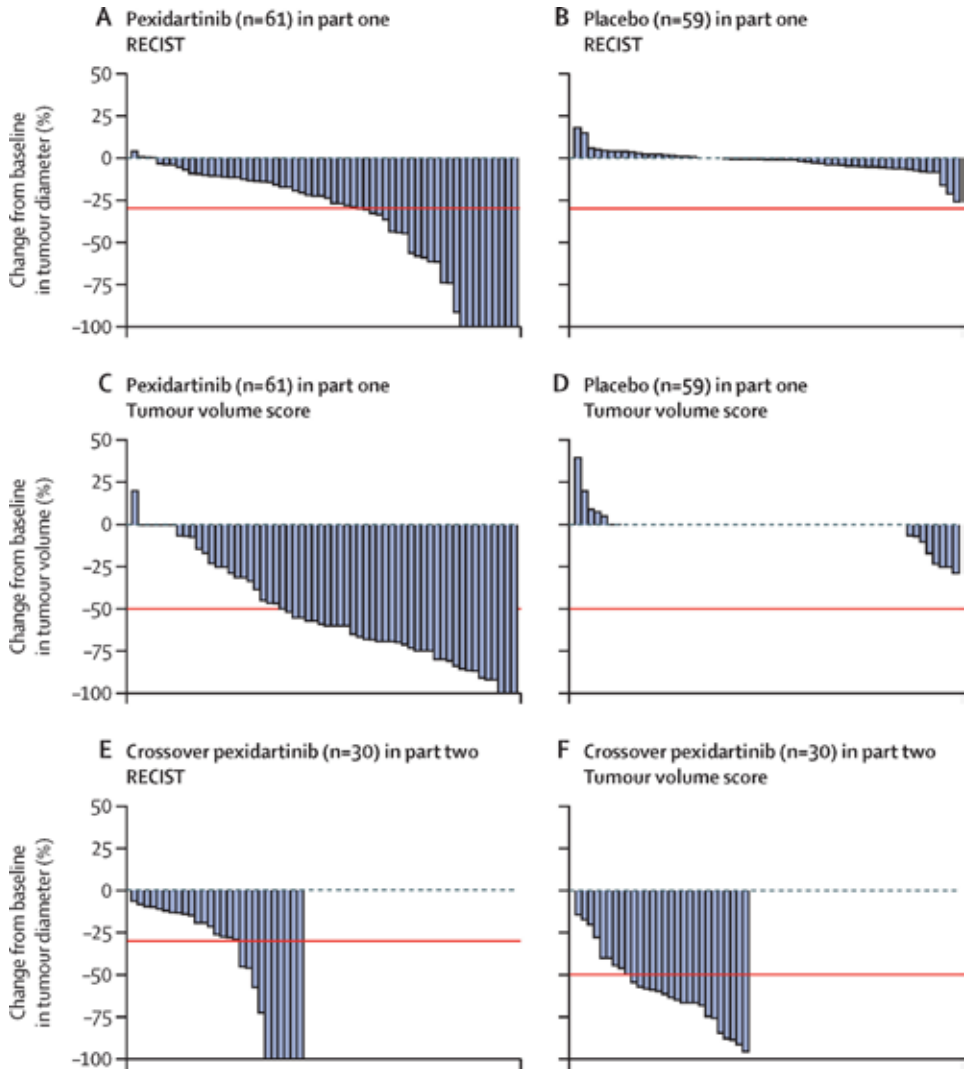
Desmoid Tumors Respond To Sorafenib





MM Gounder et al. N Engl J Med 2018;379:2417-2428.

Tenosynovial Giant Cell Tumor



Histological subtype

- **Giant cell tumor of bone:**
  - **Rank-L driven tumors**
  - **Denusomab**
    - Thomas D et al, Lancet Onc 11; 275-280; 2010
- **Inflammatory myofibroblastic tumours:**
  - ALK mutations (approx. 50%)
  - Crizotinib can be effective
    - Butrynski et al, NEJM 363; 2010

- **Dermatofibrosarcoma:**
  - PDGFB-COL1A1 fusion
  - Imatinib Sensitive
    - Stacchiotti et al., CCR 2016; 22(4)

Key “pearls” for non-GIST Soft Tissue Sarcomas

- Surgery is the mainstay of therapy of treatment for localized disease
- Radiation plays an important role for large/high grade tumors or when wide excision is not feasible.
- The role of chemotherapy for localized disease is a “work in progress”
- AIM has no proven survival benefit over single agent doxorubicin
- Pazopanib, trabectedin and eribulin are important options
- Individual histologic subtypes have unique biologies that can be important therapeutically

Outline

Overview (etiology/risk factors/diagnosis)

Soft Tissue Sarcomas

- Non-GIST soft tissue sarcoma
  - (includes Kaposi's and rare subtypes)
- GIST

Bone Sarcomas

- Osteosarcoma
- Ewing sarcoma

Outline

1) Overview (etiology/risk factors/diagnosis)

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    - Includes treatment of select “benign,” aggressive tumors

3) GIST

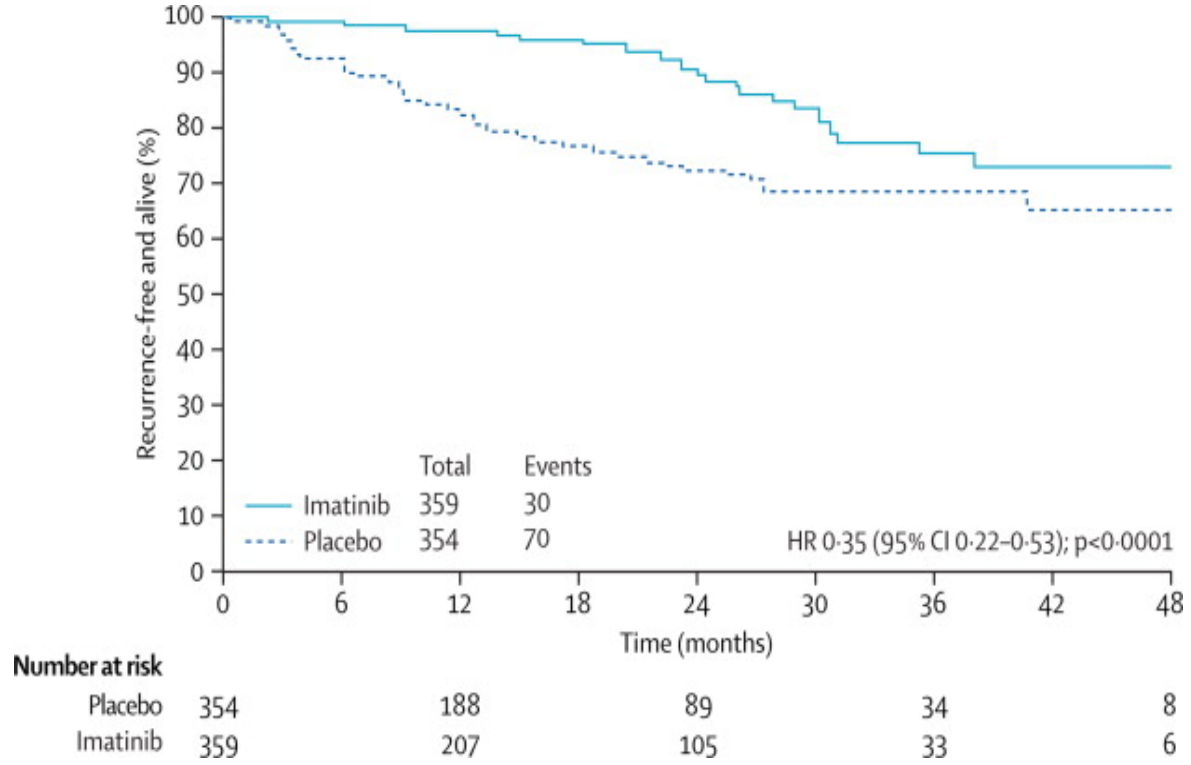
4) Bone Sarcomas

- Osteosarcoma
- Ewing sarcoma

GIST

5000 new cases/year

85%-95% have activating KIT or PDGF mutation



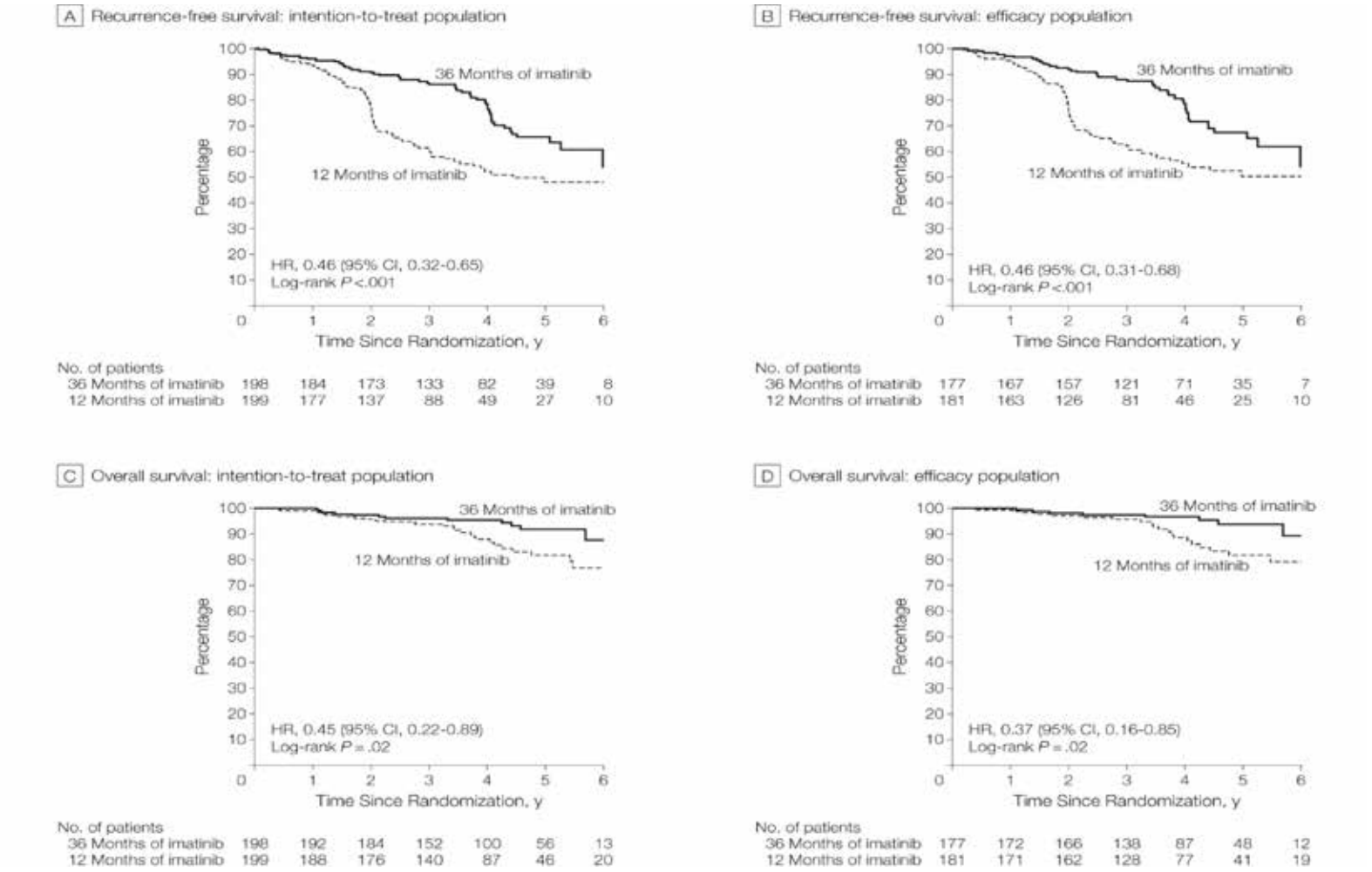
Major Risk Factors

- Size > 5 cm
- Mitosis > 5/ 50 hpf
- Small bowel location

The Original Adjuvant Studies for Imatinib in GIST showed RFS benefits for 1 year of treatment in high risk patient populations.

De Matteo R et al, Annals Surg 231(1): 51-8: 2000

OS Benefit for 3 vs 1 Year of Adjuvant Imatinib: Should you ever stop imatinib?



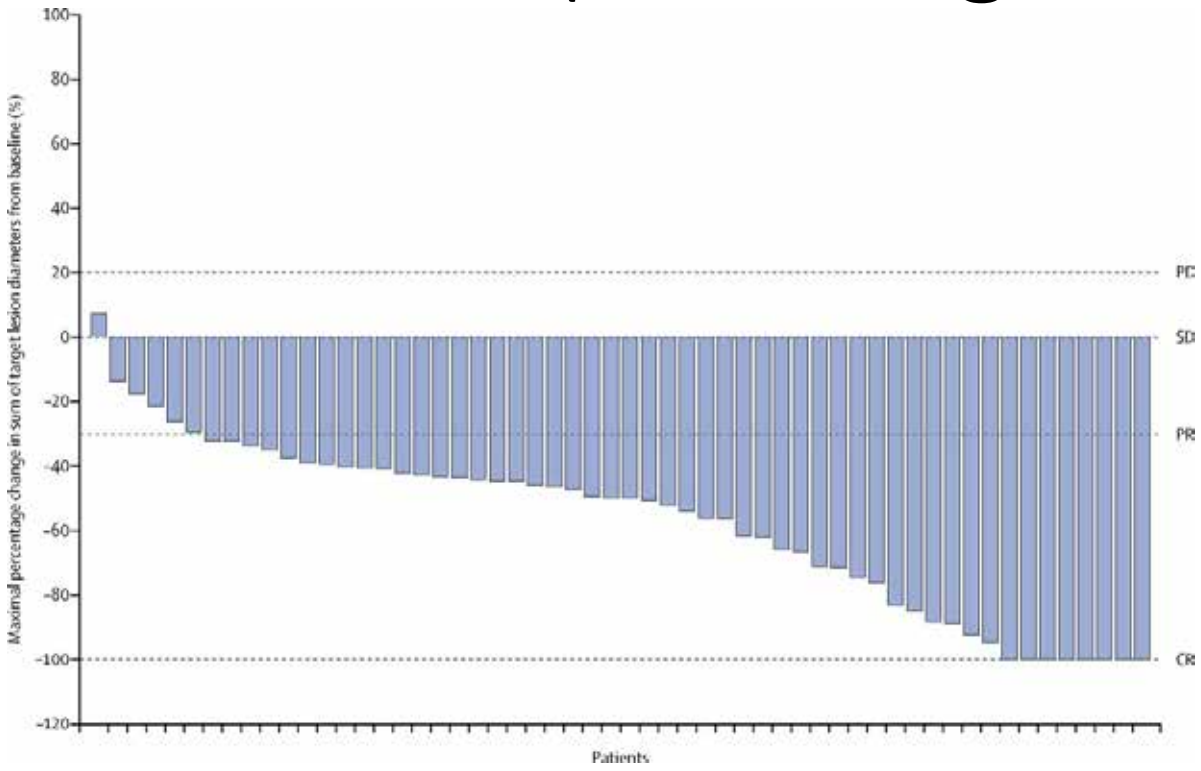
Joensuu H et al, JAMA 307; 1265-1272: 2012

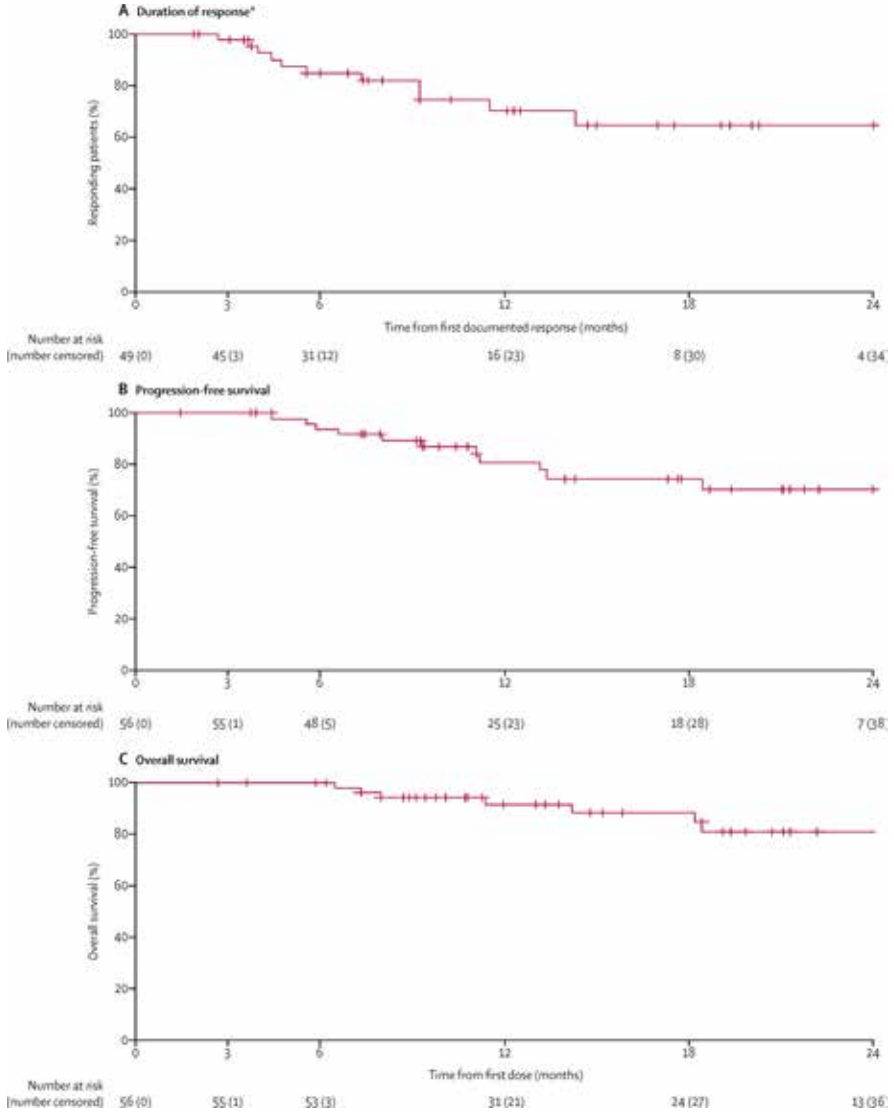
Surveillance

CT abd/pelvis every 3-6 months for 3-5 years then annually

For Metastatic disease: Should Front Line Treatment Always be Imatinib 400mg?

Avapritinib is FDA Approved for Exon 18 mutations of PDGFRA (including D842V)

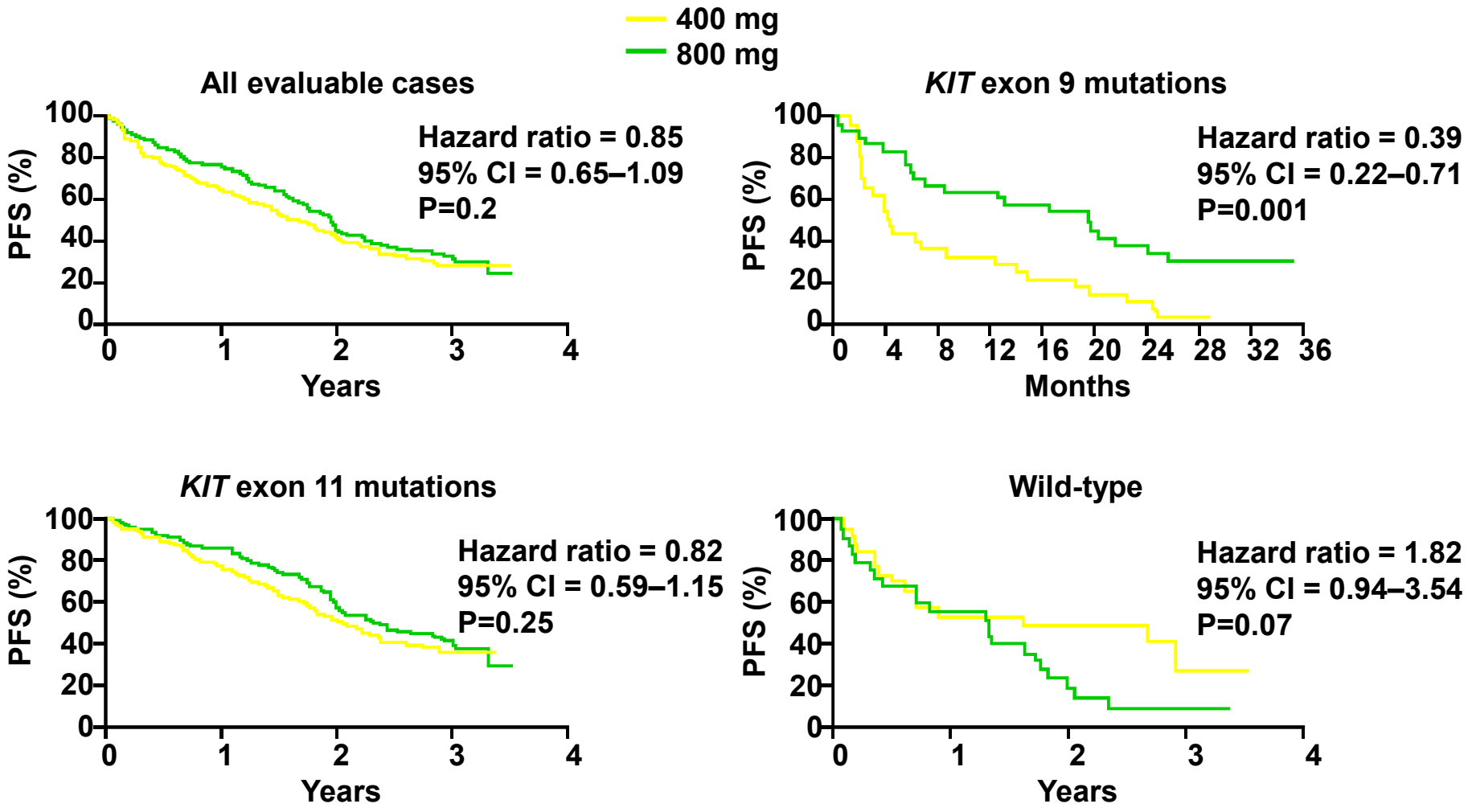




Hinrich et al., Lancet Onc 2020

Imatinib Dose dependency and mutational status

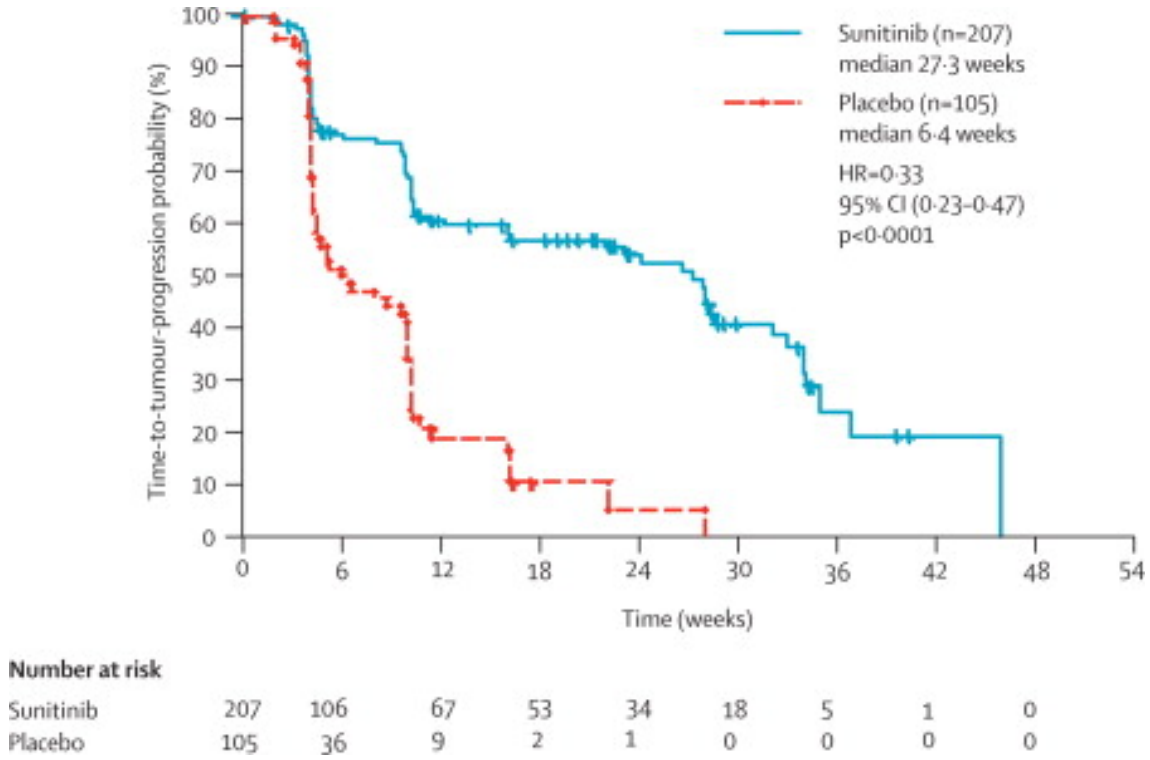
Benefit of using higher dose of imatinib for patients with Exon 9 mutation is probably preserved whether it is started initially or increased at time of progression.



Debiec-Rychter M et al, *Eur J Cancer* 42; 1093–1103: 2006

Sunitinib

- TKI: KIT, PDGFRs, VEGFR 1-3, FLT3
- Phase III: 312 patients randomised to
  - Sunitinib
  - Placebo
- Sunitinib median PFS 24.1 weeks
- Placebo median PFS 6.0 weeks
  - P<0.0001
- OS significantly longer sunitinib arm
  - p=0.007



Demetri G et al, Lancet 368; 1329-1338; 2006

Efficacy and safety of regorafenib for advanced gastrointestinal stromal tumours after failure of imatinib and sunitinib (GRID): an international, multicentre, randomised, placebo-controlled, phase 3 trial

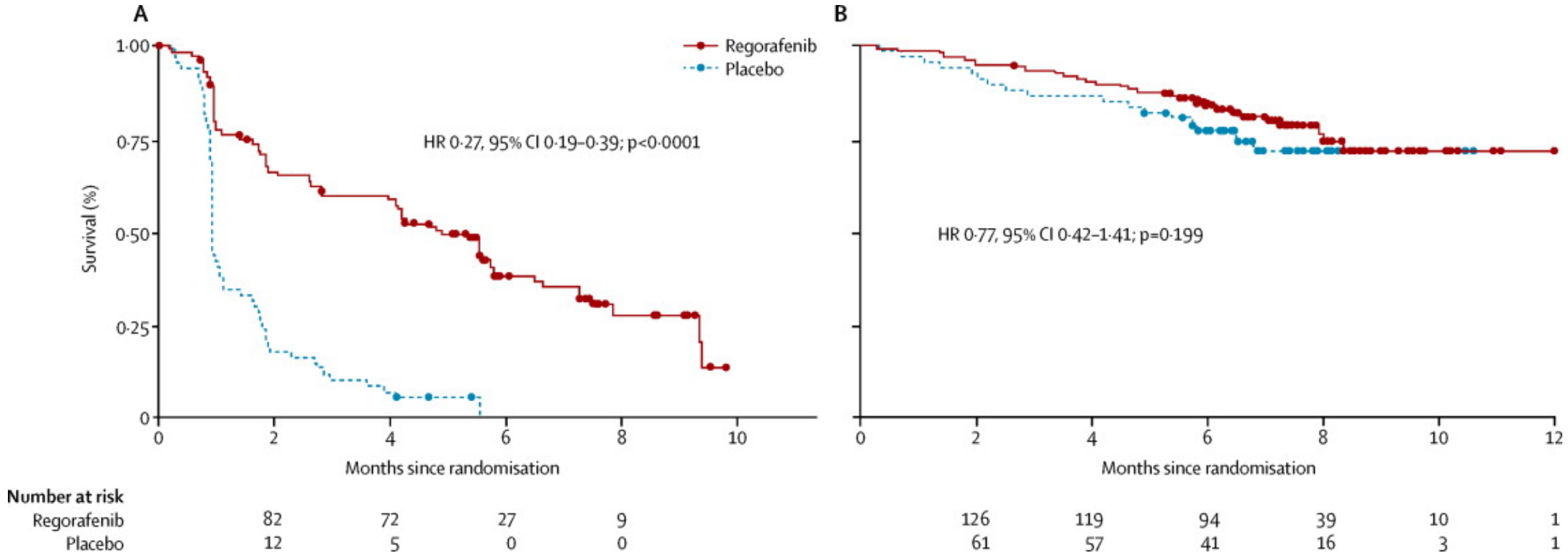
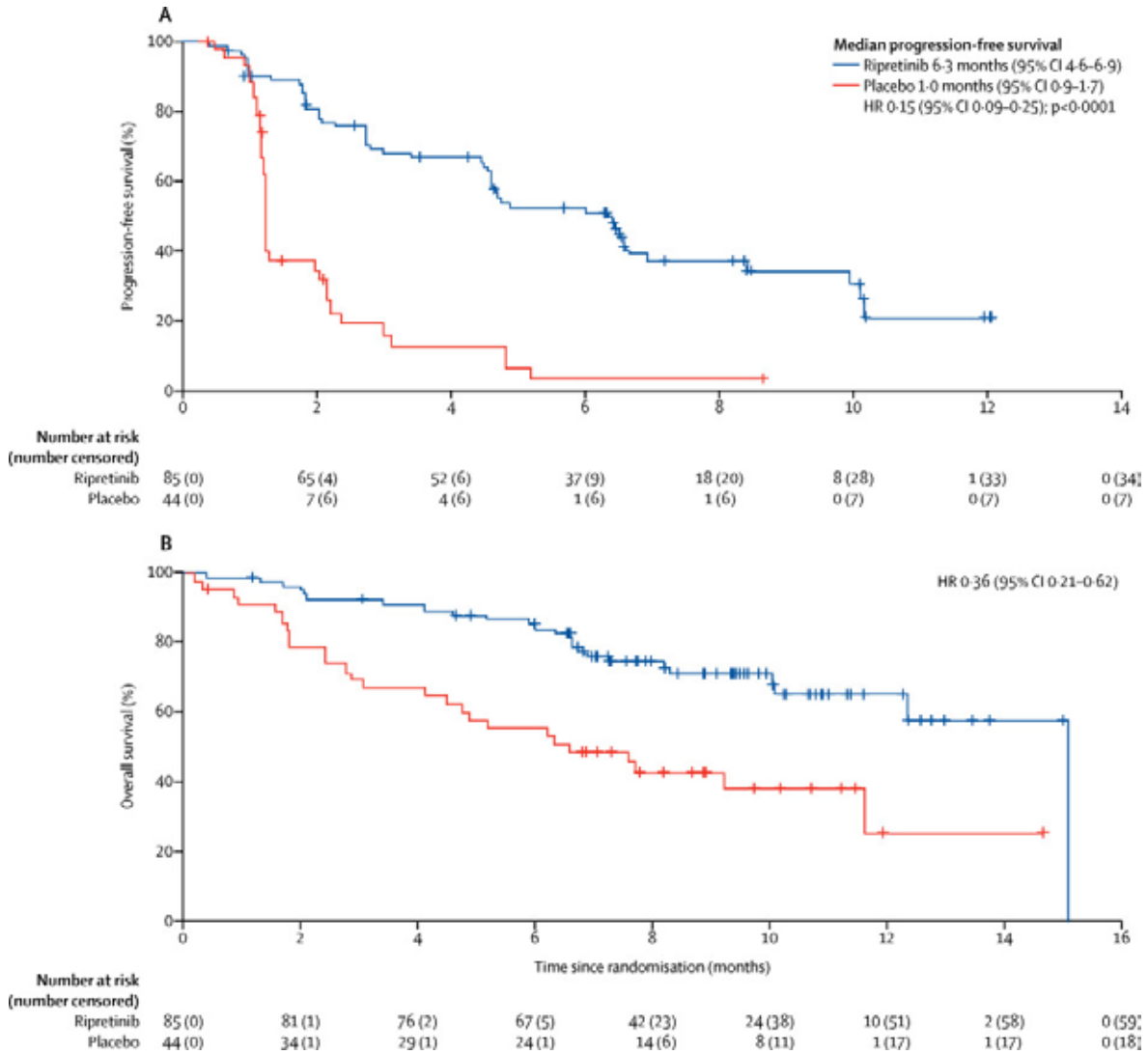


Figure 2. Kaplan-Meier survival analysis after treatment with regorafenib or placebo(A) Progression-free survival, per central review (primary endpoint, final analysis). (B) Overall survival (interim analysis). HR=hazard ratio.

George D Demetri, et al. Lancet Oncology, Issue 9863, 2013, 295–302

http://dx.doi.org/10.1016/S0140-6736(12)61857-1

Repritinib Now Approved for 4th Line GIST



Blay et al., Lancet Oncology 2020

Key “pearls” for GIST

- Size, mitosis, location are important risk factors for localized GIST
- 3 years of adjuvant imatinib improves survival for localized disease
- 800 mg of imatinib is no better than 400 mg except for patients with exon 9 mutation
- Avapritinib should be considered for D842V mutation
- Sunitinib then regorafenib for patients with imatinib refractory metastatic GIST.
- Repritinib is now approved for 4th line

Outline

1) Overview (etiology/risk factors/diagnosis)

Soft Tissue Sarcomas:

2) Non-GIST soft tissue sarcoma

    - Includes treatment of select “benign,” aggressive tumors

3) GIST

4) Bone Sarcomas

- Osteosarcoma
- Ewing sarcoma

Bone Sarcomas

- Osteosarcoma
- Chondrosarcoma
- Ewings Sarcoma

Others: rare bone tumors, Giant Cell tumor of bone

“Classic” Osteosarcoma vs. Ewings Sarcoma Characteristics

Osteosarcoma

- Rarely associated with “B symptoms”
- Predilection for *metaphyseal* region of long bones
- Most common sites: distal femur, proximal tibia, proximal humerus (80-90% occur in long bones)

Ewings Sarcoma

- Frequently associated with “B symptoms.” Patients can sometimes appear quite ill.
- Predilection for *diaphyseal* region of long bones
- Pelvis and ribs also common sites of disease

Both frequnently present with painful bone mass.

Osteosarcoma Epidemiology

- 400 cases/ year USA
- Most common primary bone tumor in children and young adults
- Median age 20 years
  - 30% of cases occur in patients over 40

Treatment Approach in Osteosarcoma

- Intramedullary (>90% of cases – “classical osteosarcoma): almost always high grade. Chemotherapy essential.
- Low grade = excellent prognosis, no need for chemotherapy (regardless of location)
- Parosteal osteosarcoma –generally low grade, much better prognosis: wide excision only. After resection, only if high grade component is found, consider chemotherapy.
- Periosteal osteosarcoma (considered “intermediate” risk): wide excision. If high grade component is seen, use chemo

High Grade Localized Osteosarcoma: Chemotherapy is absolutely critical

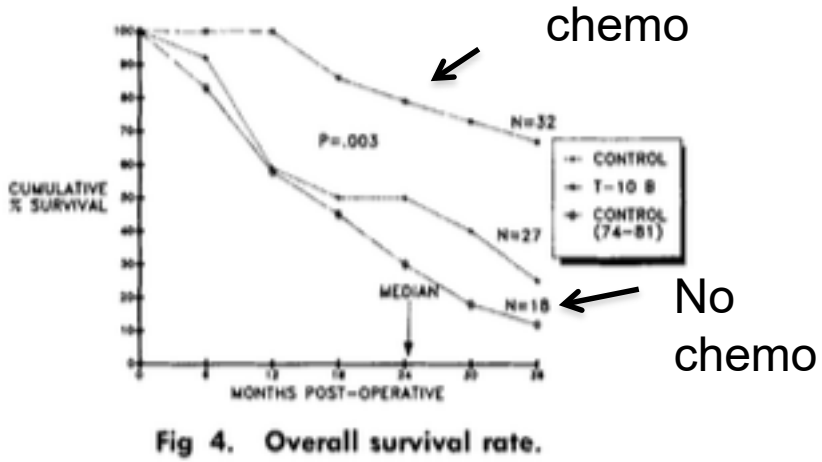


Fig 4. Overall survival rate.

Eilber F et al. J Clin Oncol 5; 21-26: 1987

- Doxorubicin based chemotherapy (generally with cisplatin) is critical for all osteosarcoma patients
- High Dose Methotrexate is often given to younger patients (with less evidence)

Link MP et al. N Engl J Med 314; 1600-1606: 1986

Histological Response to Neoadjuvant Chemotherapy: Predictor of Outcome

- 5-year survival:
  - 75-80% for good responders (>90% tumor necrosis) compared
  - 45-55% for poor responders.

- Patients with little or no necrosis at surgery still benefit from chemotherapy compared to surgery alone.

Bielack SS et al. JCO 3; 776-90: 2002
Souhami RL et al. Lancet 350; 911-17: 1997
Bramwell V et al. JCO 10; 1579-91; 1992

Surveillance in bone tumors

- Chest Imaging Q3-6 months 2-3 years, the every 6 months until 5 years, then annually
- Consider period imaging of primary site.

Recurrent Osteosarcoma

- Five-year survival: 23-29%
  - Complete surgical resection required to achieve cure
- No standard chemotherapy schedule
  - Clinical trial participation
- Other treatment options:
  - Radiation to metastatic sites
  - Samarium-153
  - Bisphosphonates
  - Radiofrequency ablation

Ferrari S et al. J Clin Oncol 21; 710-715: 2003
Kempf-Bielack B et al. J Clin Oncol 20; 559-568: 2005

Ewing Sarcoma: Epidemiology

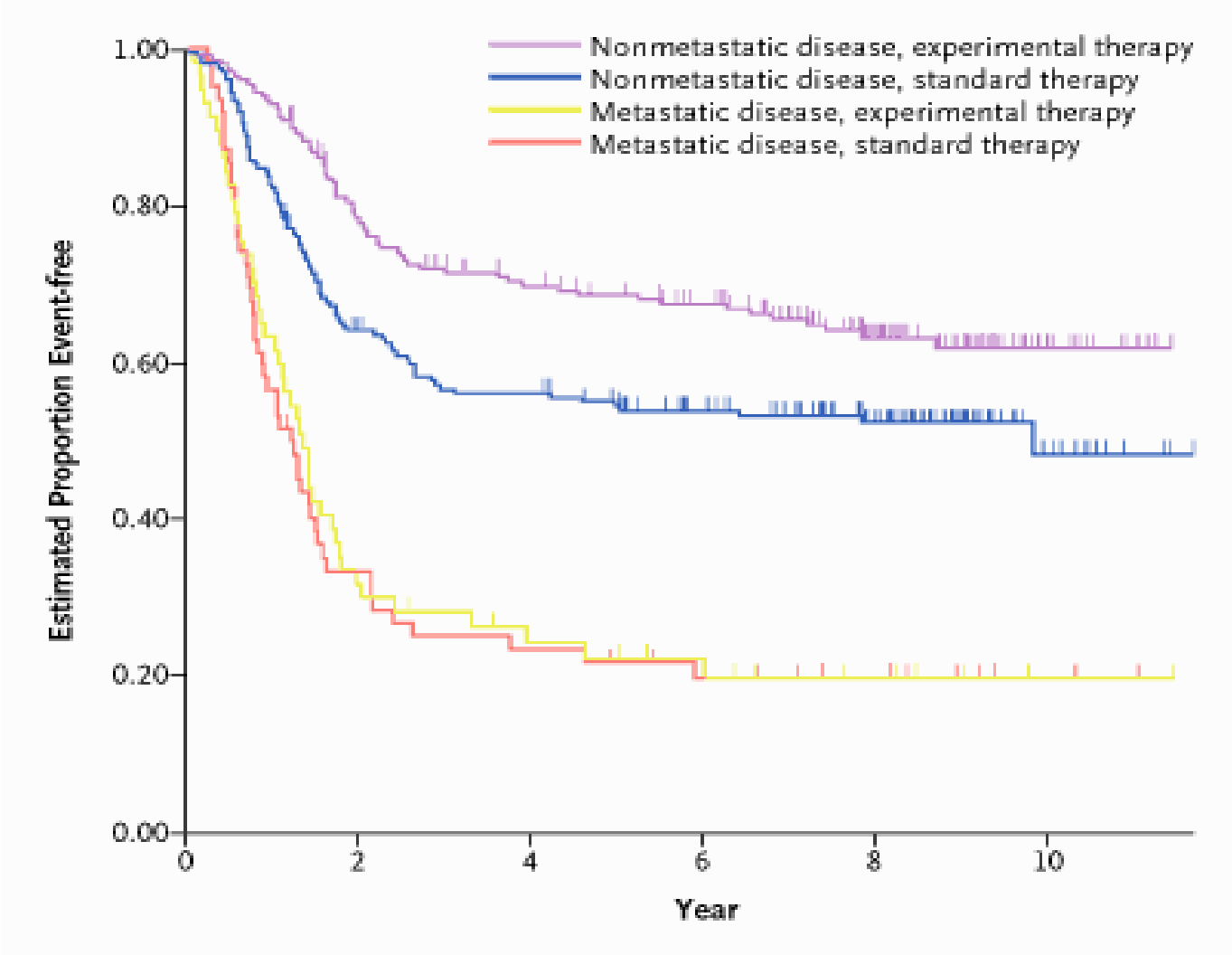
- 200 cases/ year
- Second most common bone malignancy in children and adolescents
- Peak incidence between ages 10 and 20 years
  - 20% of cases in older patients
  - Slight male predominance (1.4:1)
  - Mainly occurs in Caucasians
- No hereditary or congenital syndromes
- No known risk factors

Ewing Sarcoma: Management

- Chemotherapy and radiotherapy sensitive
  - Surgery/ radiation only: <10% 4 year EFS
  - Multimodal therapy including chemotherapy: >70% year EFS

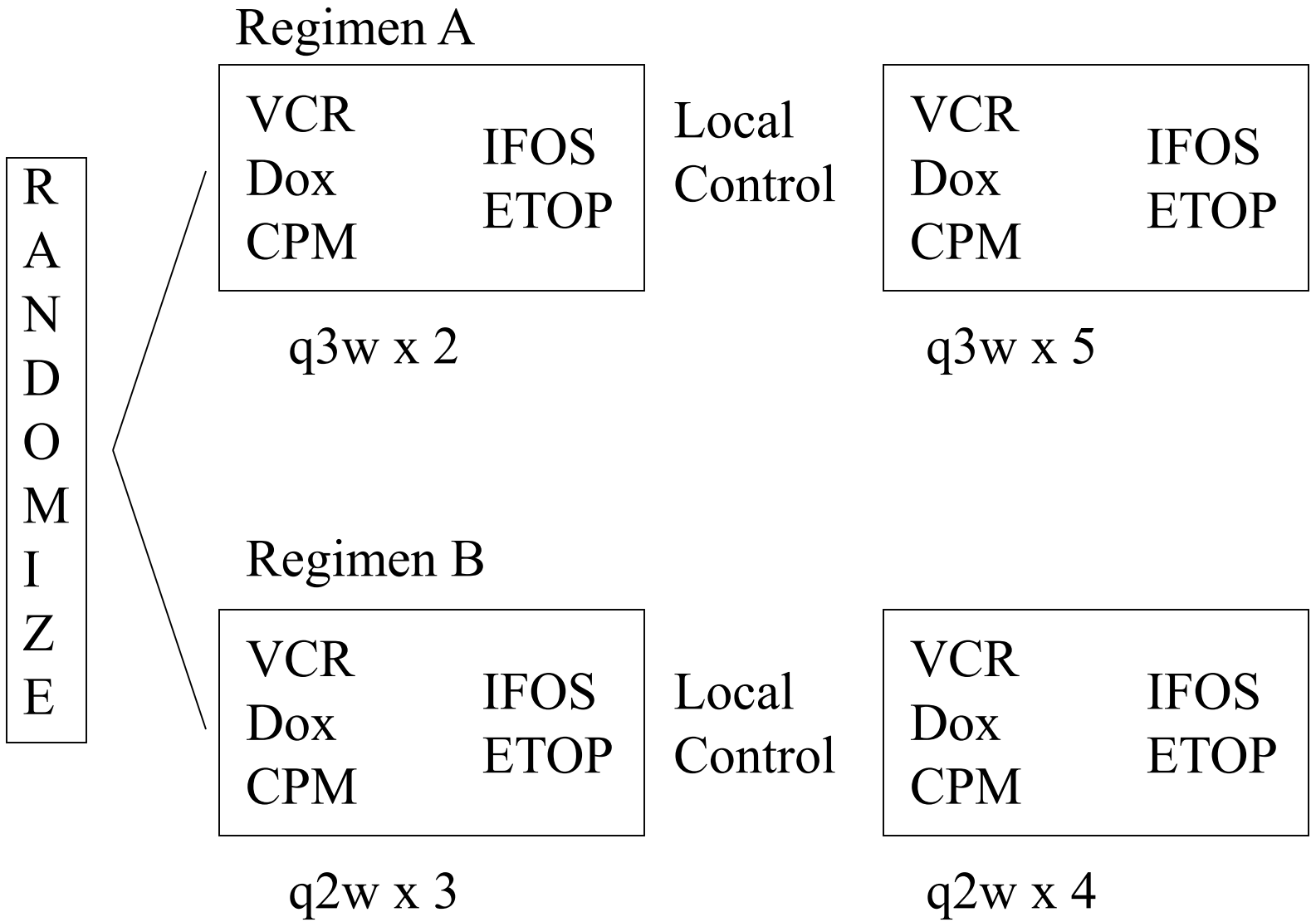
- Poor prognostic factors:
  - Age
  - Metastasis at diagnosis
  - Poor histological response to therapy
  - Tumor size
  - Large pelvic tumors

Addition of ifosfamide/VP-16

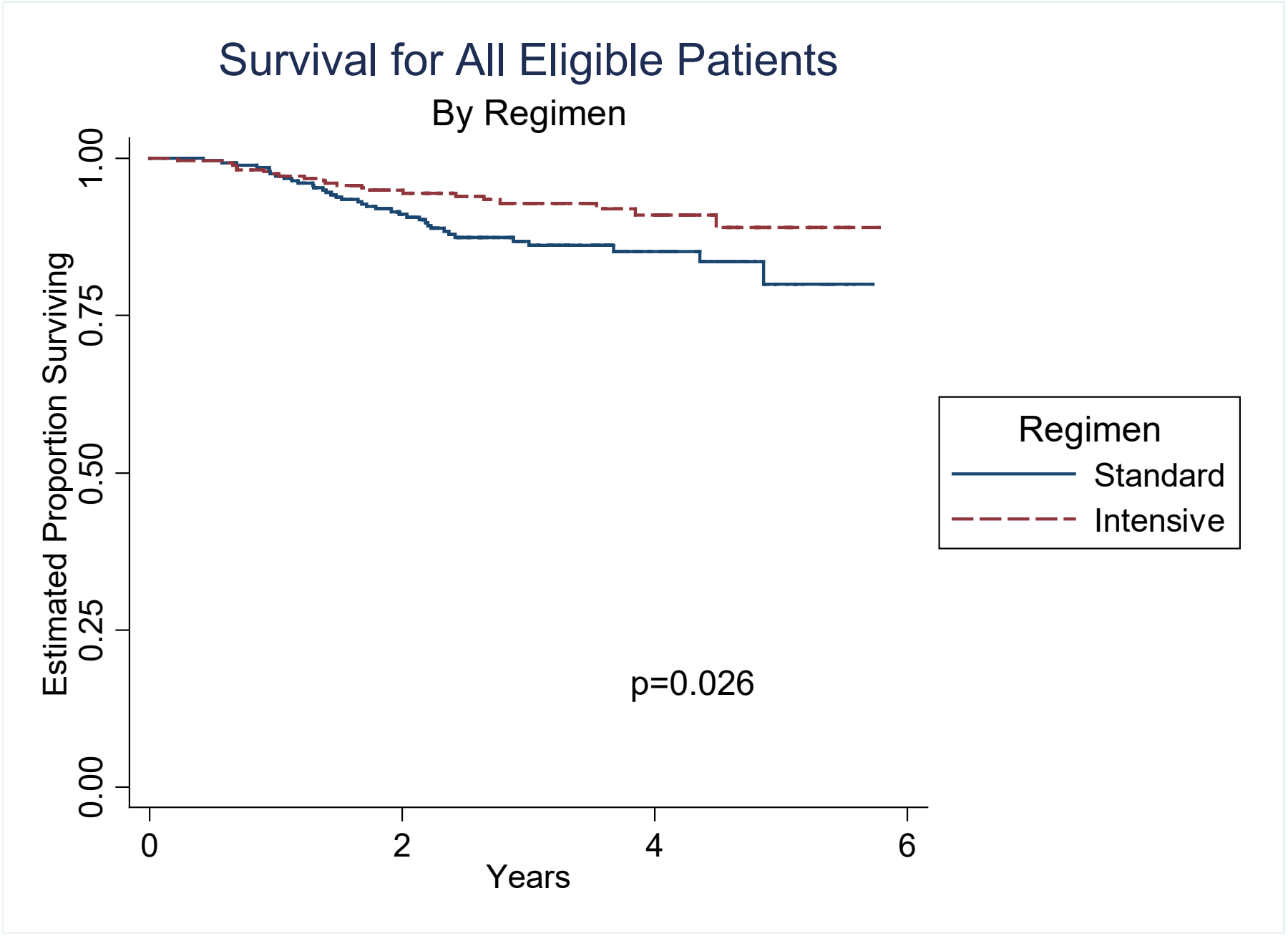


Grier et al. NEJM 348; 694-701: 2003

COG AEWS0031: dose-dense therapy in Ewing family tumors



Womer RB et al, J Clin Oncol 30(33); 4148-4154: 2012



Womer RB et al, J Clin Oncol 30(33); 4148-4154: 2012

Recurrent/ Metastatic Ewing

- 5-year relapse-free survival in metastatic patients:[1]
  - 29% lung only
  - 19% bone only
  - 8% combined lung and bone

- Relapsed: Long-term survival $\leq$ 20%

- Salvage chemotherapy schedules:
  - Irinotecan + temozolamide[2]
  - Cyclophosphamide + topotecan[3]
  - Gemcitabine + docetaxel[4]

- High dose chemotherapy: Benefit uncertain[5]

[1]Cotterill et al JCO 18; 3108-3114: 2000
[2]Wagner LM et al. Ped Blood Cancer 48; 132-139: 2007
[3]Saylors RL et al. J Clin Oncol 19; 3463-3469: 2001
[4]Navid F et al. Cancer 113: 419-425: 2008
[5]Balamuth NJ, Womer RB. Lancet Onc 11; 184-192: 2010

Key “pearls” for Bone Tumors

- Doxorubicin based chemotherapy makes a **huge** impact on survival for Ewings and high grade osteosarcoma. Don’t ever miss this one.
- Necrosis following chemotherapy is a predictor of survival in osteosarcoma but doesn’t change your treatment
- Ifosfamide improves survival for patients with Ewings Sarcoma
- An interval compressed schedule improves survival in young patients with Ewings sarcoma.

Sarcoma: Conclusion

- Each subtype is different
- Surgical resection: mainstay for localized disease
- Chemotherapy is controversial for most localized soft tissue sarcomas, critical for Ewings sarcoma and Osteosarcomas
- GIST – 3 years adjuvant imatinib for high risk disease. Imatinib, sutinib, regorafenib, repritinib in metastatic disease
- Lack of options in the advanced setting, more research is needed.

Chronic Myeloid Leukemia in 2020

Vivian G. Oehler, MD
Associate Member, Fred Hutch
Associate Professor, Division of Hematology, University of Washington

ASH, ASCO and beyond

1. Identifying higher risk chronic phase CML at diagnosis

2. Selecting first-line therapy: first vs. second generation tyrosine kinase inhibitors

3. Stopping TKI therapy: who is eligible, who succeeds, and how to qualify

4. Updates on TKI toxicities

5. New therapeutic strategies

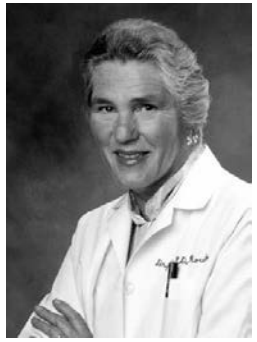
CML epidemiology

- Clonal disorder arising in a hematopoietic stem cell driven by the fusion protein Bcr-Abl
- It is estimated 8,450 people in the US will be diagnosed with CML in 2020, accounting for ~15% of new cases of leukemia
- In the US, CML is most frequently diagnosed in people ages 65 to 74 years.

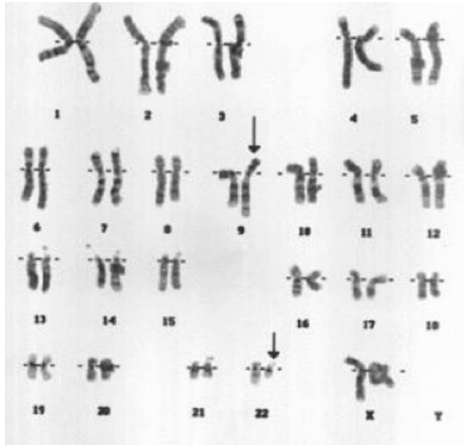
Huang X, et al. *Cancer*. 2012; 118:3123-3127.
Bower H, et al. *J Clin Oncol*. 2016;34:2851-2857
O'Hare T, et al. *Nat Rev Cancer.* 2012;12:513-526.
NCI. SEER Stat Fact Sheets: Chronic Myeloid Leukemia (CML). https://seer.cancer.gov/statfacts/html/cmyl.html. Accessed July 1, 2020.

The Philadelphia story: Bcr-Abl, the hallmark and driver of CML

David Hungerford and Peter Nowell

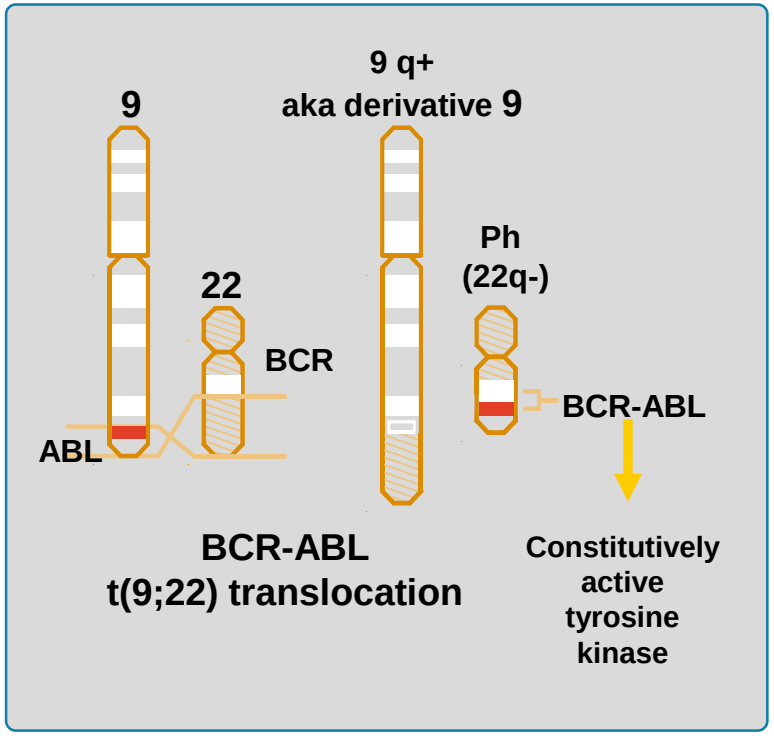


Janet Rowley

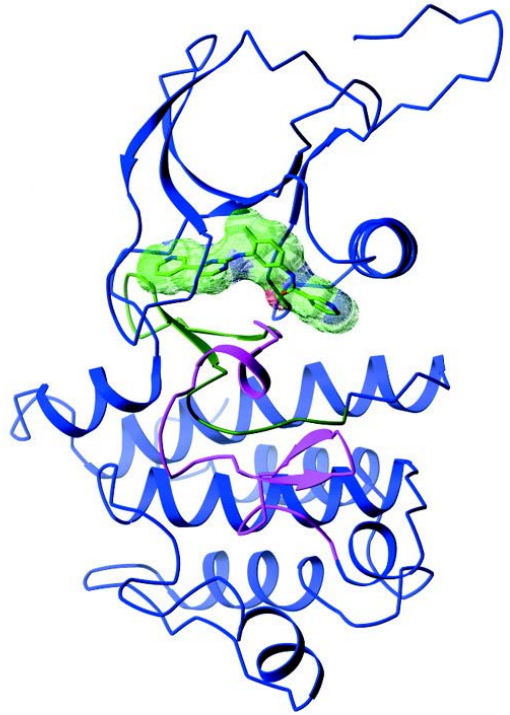


- The first chromosomal abnormality
- The first cytogenetic rearrangement

- The first targeted therapy



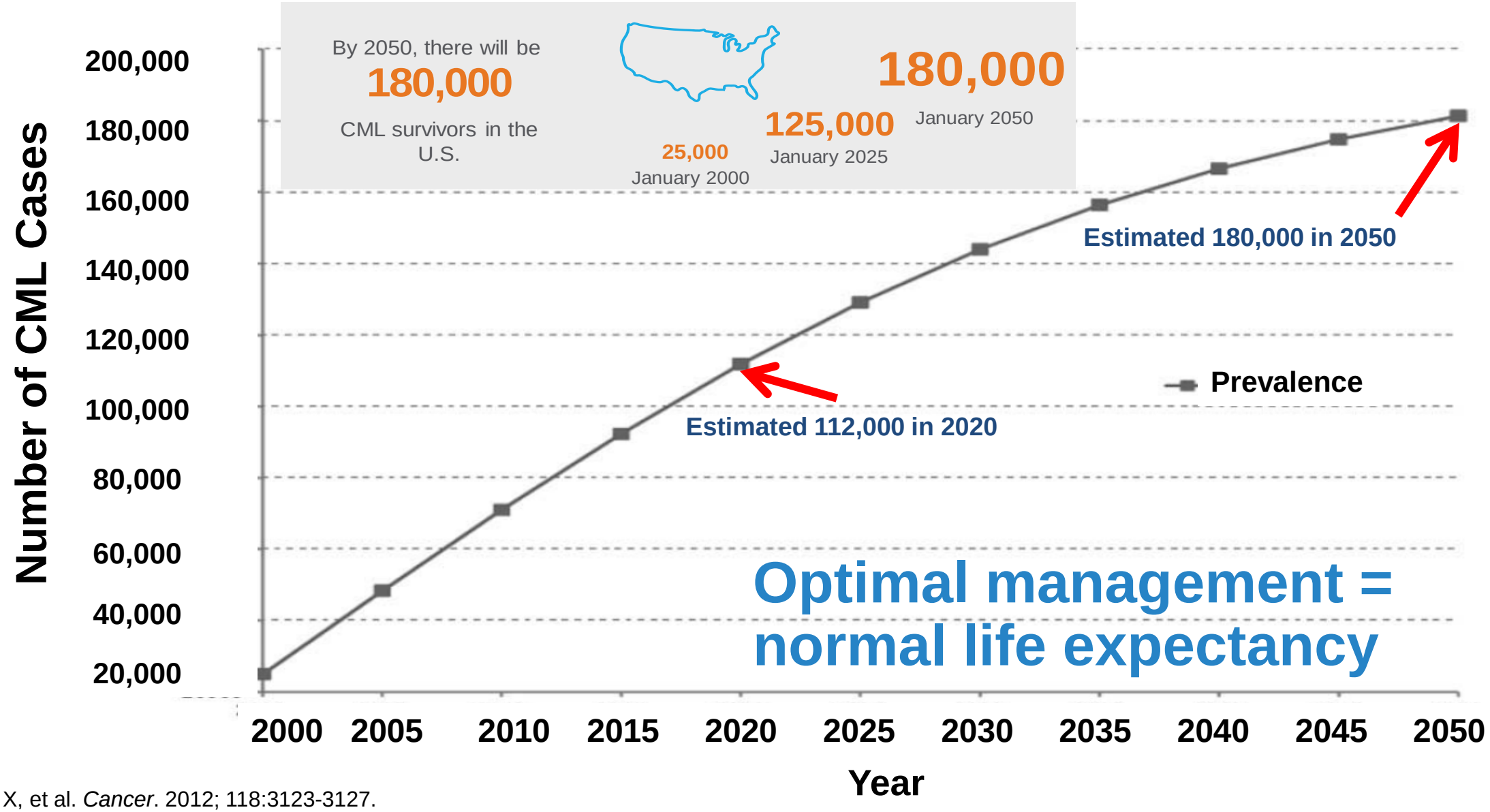
Crystal structure of the catalytic domain of Abl complexed to imatinib



Schindler et al. *Science*. 2000;289:1938-1942.

https://www.oncolink.org/cancers/leukemia/chronic-myelogenous-leukemia-cml/the-philadelphia-chromosome.
http://www.ohsu.edu/xd/health/services/cancer/about-us/druker/

The Uncommon Becomes Common



Huang X, et al. *Cancer*. 2012; 118:3123-3127.
Bower H, et al. *J Clin Oncol*. 2016;34:2851-2857

CML treatment choices in 2020

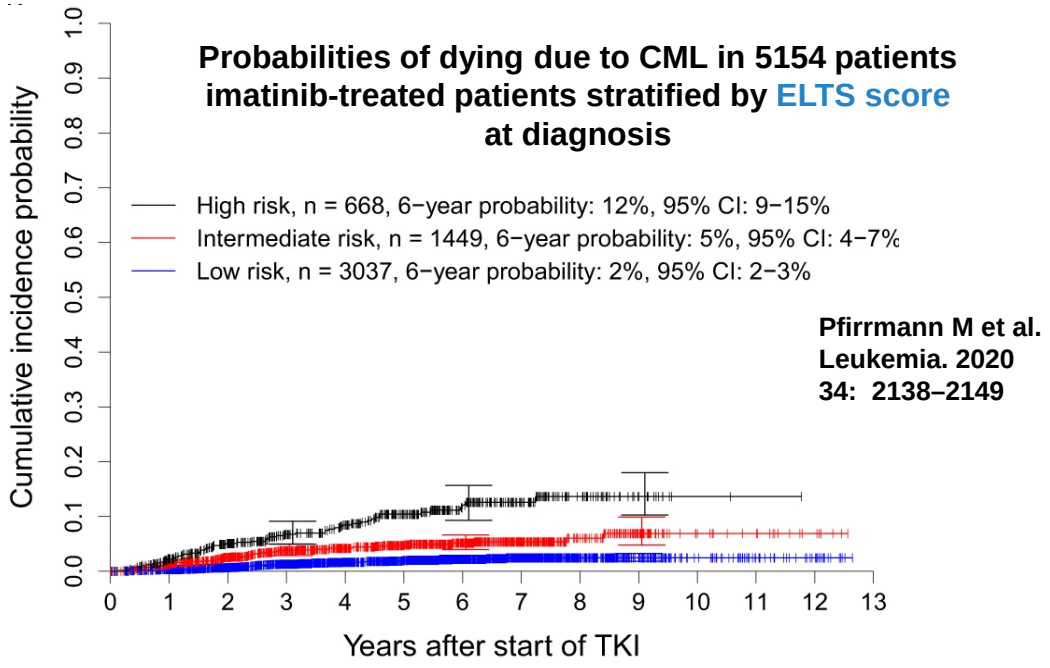
Compound	TKI Generation	First Line	Second Line	Third Line
Imatinib	First	●		
Dasatinib	Second	●	●	●
Nilotinib	Second	●	●	●
Bosutinib	Second	●	●	●
Ponatinib	Third		● (T315I)	● (T315I or “for whom no other tyrosine kinase inhibitor therapy is indicated”)
Omacetaxine	NA			●

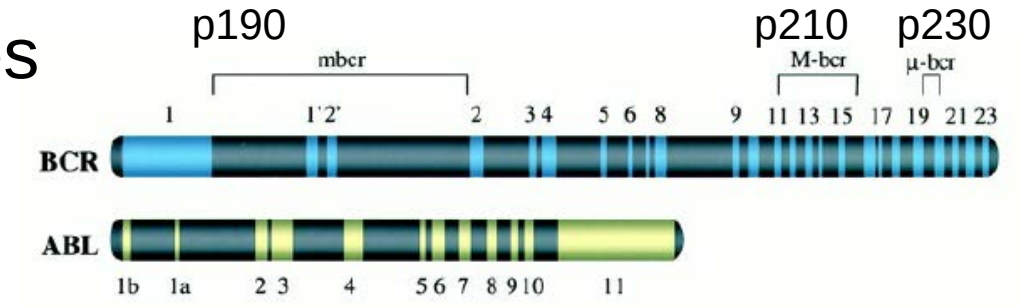
Identifying higher-risk patients at diagnosis:

Risk scores, cytogenetic and molecular abnormalities

Identifying risky CP CML patients at diagnosis

- Sokal, Hasford (*EURO)*
- **NEW: EUTOS Long-term survival Score (ELTS)**
  1. Same clinical and lab parameters as Sokal, but weighting is different
  2. Classifies fewer patients as high-risk and is better at identifying patients at risk for dying of CML
- Additional chromosomal abnormalities
- p190 transcript has been associated with poorer outcomes



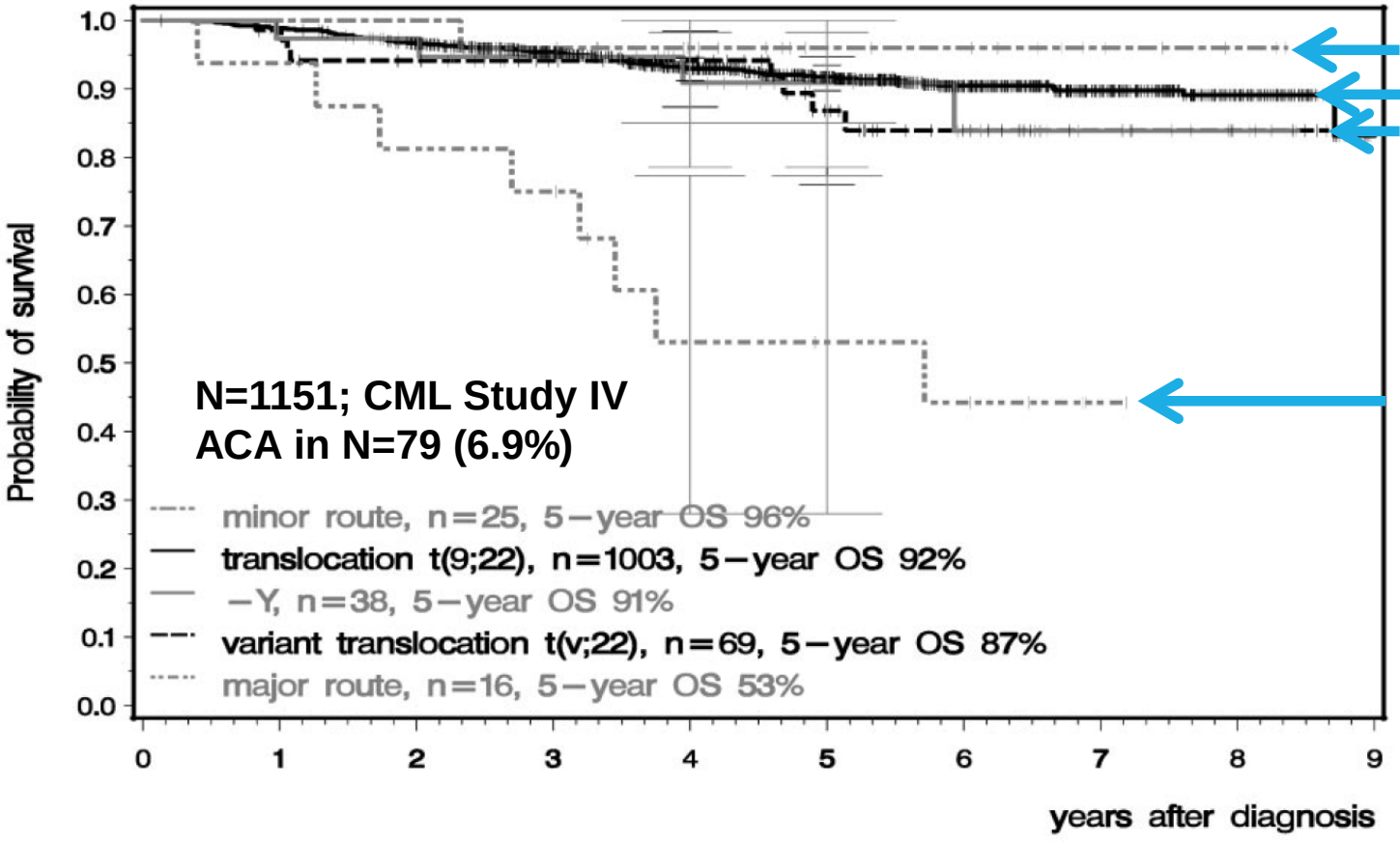


Castagnetti et al. J Clin Oncol. 2010; 28(16): 2748
Quintas-Cardama et al. Cancer. 2011; 117: 5085
Jain P et al. Blood, 2016 127:1269-1275
Geelen IGP et al. Leukemia. 2018;32(10):2299-2303.

Testoni et al. Blood. 2011; 117: 6793
Verma et al. Blood. 2009; 114: 2232
Eunice Laurent et al. Cancer Res 2001; 61:2343-2355

Additional cytogenetic abnormalities (ACA) at diagnosis or acquired during therapy impact TKI response

Major Route (more common)	Minor Route (rarer)
trisomy 8, second Ph chromosome, isochromosome (17)(q10)], and complex karyotype	t(3;12), t(4;6), t(2;16), and t(1;21)



Minor route ACA - 5-year OS 96%
t(9;22) alone – 5-year OS 92%
Variant translocation 5-year OS 87%

Major route ACA 5-year OS 53%

Consider patients with the following higher-risk

1. isochrome(17q), -7/del7q, 11q23, 3q26.2 aberrations, or complex aberrant karyotypes
2. *trisomy 8, 2nd Ph-chromosome, trisomy 19* may be less worrisome

Fabarius et al. Blood. 2011 Dec 22;118(26):6760-8.
Fabarius et al. Ann Hematol. 2015;94(12):2015-2024.
Wang W et al. Blood. 2016;127(22):2742-2750.

Identifying risky CP CML patients at diagnosis

NOT PROGNOSTIC

- Most variant translocations- (e.g. 3-way rearrangements of the Philadelphia chromosome)
- Other transcripts besides p210 or p190
  - *But much harder to monitor*

Castagnetti et al. J Clin Oncol. 2010; 28(16): 2748
Quintas-Cardama et al. Cancer. 2011; 117: 5085
Jain P et a. Blood 2016 127:1269-1275
Testoni et al. Blood. 2011; 117: 6793
Verma et al. Blood. 2009; 114: 2232
Eunice Laurent et al. Cancer Res 2001;61:2343-2355

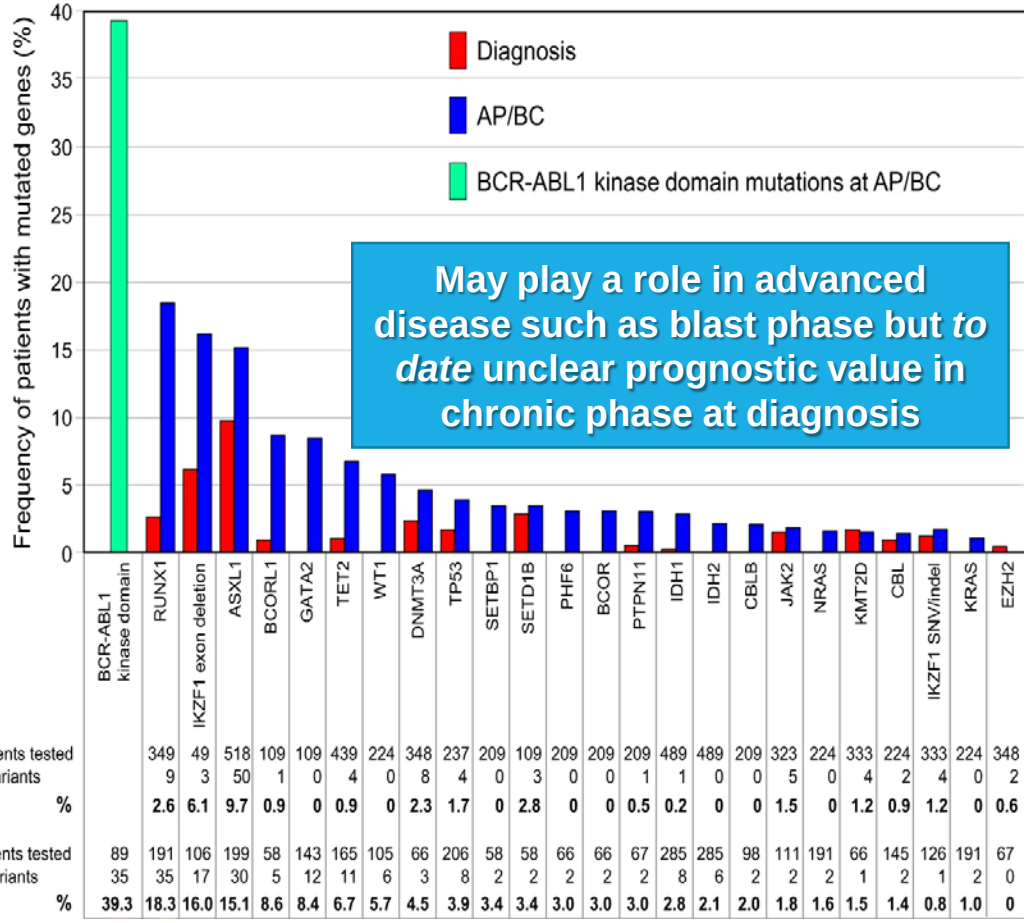
The mutational landscape in CML at diagnosis and at disease progression

Chronic phase	Accelerated phase	Blast crisis
Driven by Bcr-Abl	Additional cytogenetic changes	Development of acute leukemia
Cell differentiation is intact	Increasing blasts %	Block in differentiation
Median duration 3-5 years	Median duration 6-9 months	Median survival 3-6 months

Median survival is ~7-12 months with TKI therapy

ASXL1 (CDS), CBL (CDS), CSF3R (Exons 14, 15, 17), DNMT3A (CDS), EZH2 (Exons 15-20), FBXW7 (CDS), FGFR1 (Exons 4, 11-17, partial 18), FLT3 (p.D835H), GATA1 (Exons 2-3), GATA2 (Exons 3-5), HRAS (Exon 1-2), Hotspot, IDH1(p.R132), IDH2 (Exon 4), JAK2 (Exon 12, 14, 16), KIT (8-18), KMT2A (CDS), KRAS (CDS), MAP2K1 (Exons 2, 3, 6), MPL (Exon 10), MYD88 (Exon 3-5), NGS, NOTCH1 (Exons 20, 26, 27), NPM1 (Exon 12), NRAS (CDS), PDGFRA (Exons 12-18), PHF6 (CDS), PTEN (CDS), RB1 (CDS), RUNX1 (Exon 4-8), SF3B1 (Exon 14-16), SRSF2 (Exon 1), STAG2 (CDS), STAT3 (Exons 20-21), TET2 (CDS), TP53 (CDS), U2AF1 (Exons 2, 6), WT1 (CDS), ZRSR2 (CDS)

- Increased frequency of these mutations as CML progresses from chronic phase to accelerated or blast phase
- Most common mutations detected are RUNX1, IKZF1, and ASXL1



	BCR-ABL1 kinase domain	RUNX1	IKZF1 exon deletion	ASXL1	BCORL1	GATA2	TET2	WT1	DNMT3A	TP53	SETBP1	SETD1B	PHF6	BCOR	PTPN11	IDH1	IDH2	CBLB	JAK2	NRAS	KMT2D	CBL	IKZF1 SNV/indel	KRAS	EZH2
Diagnosis																									
No. of patients tested		349	49	518	109	109	439	224	348	237	209	109	209	209	209	489	489	209	323	224	333	224	333	224	348
No. with variants		9	3	50	1	0	4	0	8	4	0	3	0	0	1	1	0	0	5	0	4	2	4	0	2
%		2.6	6.1	9.7	0.9	0	0.9	0	2.3	1.7	0	2.8	0	0	0.5	0.2	0	0	1.5	0	1.2	0.9	1.2	0	0.6
AP/BC																									
No. of patients tested	89	191	106	199	58	143	165	105	66	206	58	58	66	66	67	285	285	98	111	191	66	145	126	191	67
No. with variants	35	35	17	30	5	12	11	6	3	8	2	2	2	2	2	8	6	2	2	2	1	2	1	2	0
%	39.3	18.3	16.0	15.1	8.6	8.4	6.7	5.7	4.5	3.9	3.4	3.4	3.0	3.0	3.0	2.8	2.1	2.0	1.8	1.6	1.5	1.4	0.8	1.0	0

Branford et al. Leukemia (2019) 33:1835–1850.

Selecting 1st line therapy

Selecting first-line therapy: NCCN 1.2021

Risk stratify: Sokal, Hasford, and EUTOS long-term survival scores

Chronic phase CML

Low-risk score →

- **Imatinib or generic imatinib 400 mg QD or**
- **Bosutinib 400 mg QD or**
- **Dasatinib 100 mg QD or**
- **Nilotinib 300 mg BID**

Intermediate- or high-risk score →

Preferred regimens*:
- Bosutinib 400 mg QD or
- Dasatinib 100 mg QD or
- Nilotinib 300 mg BID

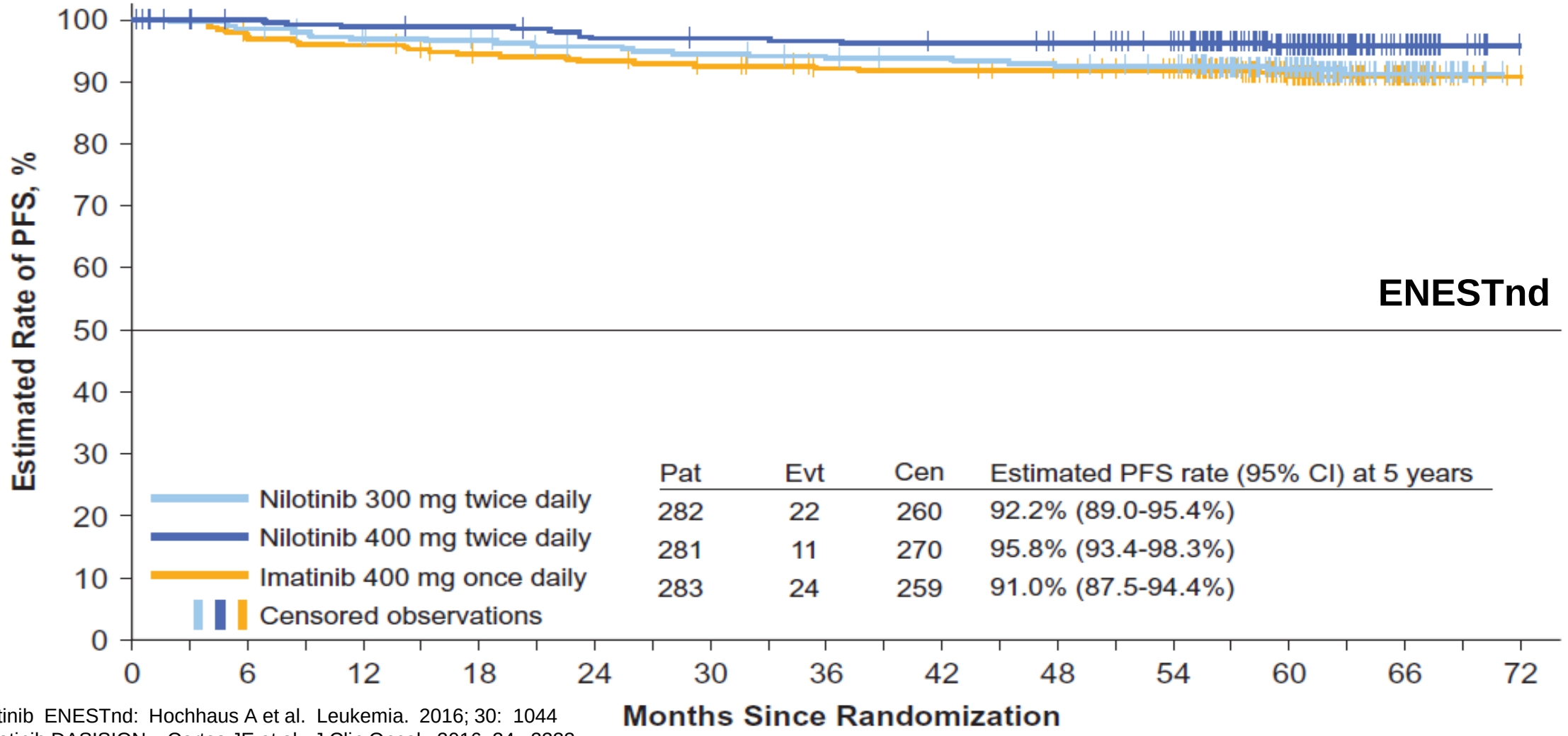
Other recommended regimen:**
- Imatinib or generic imatinib 400 mg QD

* Based on preliminary data from the BFORE trial and long-term follow-up data from the DASISION and ENESTnd trials, **second-generation TKIs are preferred for patients with an intermediate- or high-risk score**, especially for young women whose goal is to achieve a deep and rapid molecular response and eventual drug discontinuation of TKI therapy for family planning purposes

** **Imatinib may be preferred** for older patients with **comorbidities** such as cardiovascular disease

Clinical trial, if available can be considered for all patients

No difference in PFS or OS for 1st vs. 2nd generation TKIs



Nilotinib ENESTnd: Hochhaus A et al. Leukemia. 2016; 30: 1044
Dasatinib DASISION : Cortes JE et al. J Clin Oncol. 2016; 34: 2333
Bosutinib BFORE: Cortes JE et al. J Clin Oncol. 2018 2018; 36: 231

Benefits of first-line 2nd generation TKI use: fewer mutations

ENESTnd

	Nilotinib 300 mg twice daily (n = 282), n	Nilotinib 400 mg twice daily (n = 281), n	Imatinib 400 mg once daily (n = 283), n
Patients with mutations	12	11	22
New mutations by Sokal score			
Low	1	2	1
Intermediate	5	3	8
High	6	6	13

Hochhaus A et al. Leukemia. 2016 May;30(5):1044-54

Benefits of first-line 2nd generation TKI use: fewer cases of progression to AP or BC on nilotinib

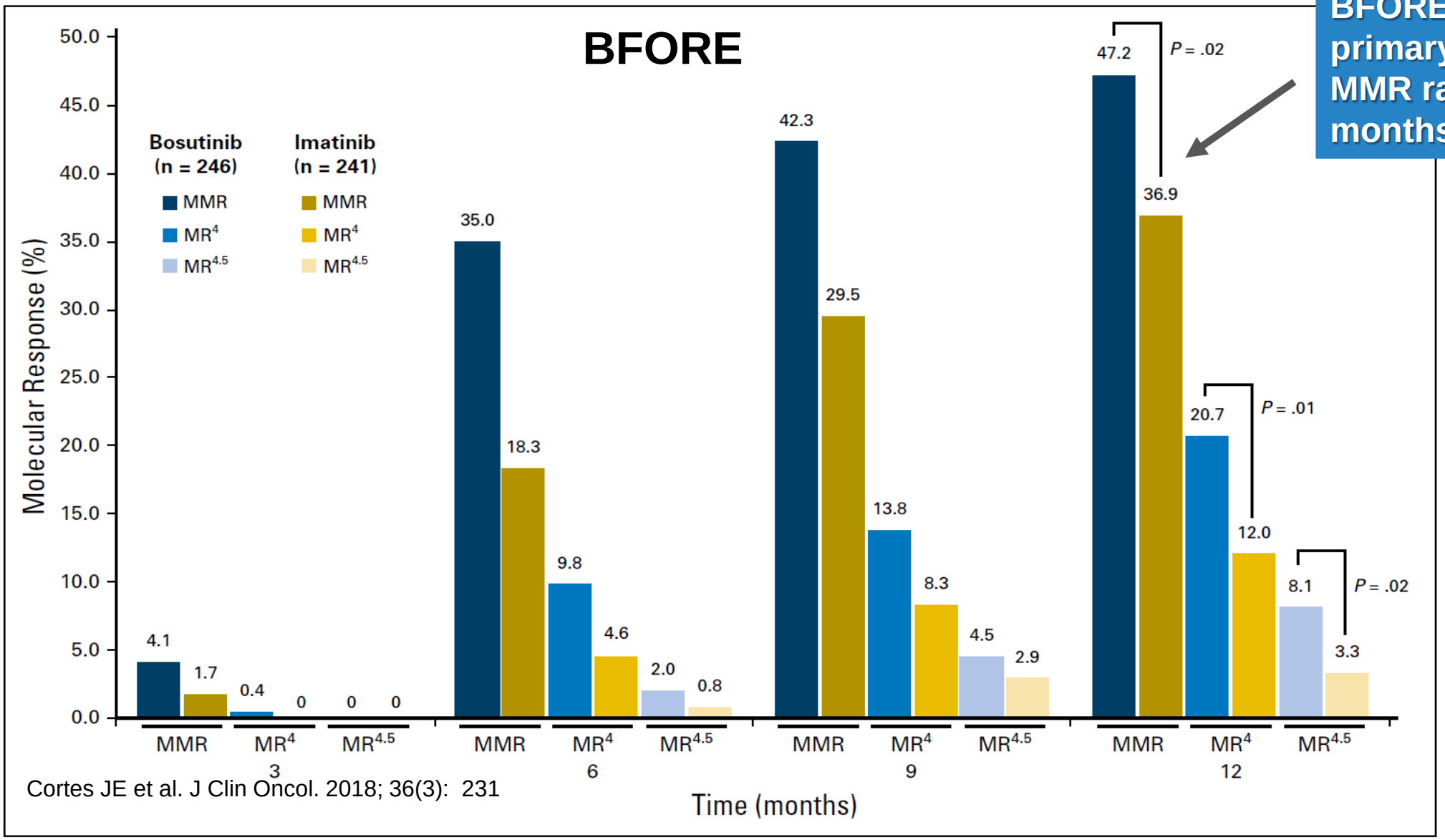
Table 1. Long-term patient outcomes

	Nilotinib 300 mg twice daily (n = 282)	*Nilotinib 400 mg twice daily (n = 281)*	*Imatinib 400 mg once daily (n = 283)*
Progression to AP/BC			
Progression to AP/BC on core treatment, *n*	2	3	12
Estimated 5-year freedom from progression to AP/BC on core treatment, % (95% CI)[a]	99.3 (98.2–100)	98.7 (97.2–100)	95.2 (92.6–97.9)
HR vs imatinib (95% CI)[b]	0.1599 (0.0358–0.7143)	0.2457 (0.0693–0.8713)	—
P vs imatinib[c]	0.0059	0.0185	—
Progression to AP/BC on study, *n*	10	6	21
Estimated 5-year freedom from progression to AP/BC on study, % (95% CI)[a]	96.3 (94.1–98.6)	97.8 (96.0–99.5)	92.1 (88.8–95.3)
HR vs imatinib (95% CI)[b]	0.4636 (0.2183–0.9845)	0.2753 (0.1111–0.6821)	—
P vs imatinib[c]	0.0403	0.0028	—

- *On core treatment: 69 (59.9%), 174 (61.9%) and 141 (49.8%) patients in the nilotinib 300-mg twice-daily, nilotinib 400-mg twice-daily and imatinib arms, respectively, remained on core treatment*
- *On study: on treatment or in follow-up after discontinuation of study treatment*

Hochhaus A et al. Leukemia (2016) 30, 1044-1054.

Benefits of first-line 2nd generation TKI use: more rapid MMR and deeper MR



BFORE study primary endpoint MMR rate at 12 months

Cortes JE et al. J Clin Oncol. 2018; 36(3): 231

Risks of 2nd generation TKI use: pleural effusions with dasatinib - increasing incidence with age

- DASISION and 034/Dose-optimization randomized studies and a pooled population of 11 trials
  - N= 2712
- Annual risk of pleural effusion ~5-15%
  - **<u>Continued risk over time</u>**
  - At 5 years DASISION: pleural effusion in 28%
  - At 7 years 034/Dose-optimization: 33%
- AGE is the main risk factor
  - *Up to 50% of patients > 60 may develop pleural effusion on doses of 100 mg or higher*
  - *Consider starting patients > 60 years on lower doses*

Porkka K et al. Cancer. 2010 Jan 15;116(2): 377-86
Hughes TP et al. Haematologica. 2019 Jan;104(1):93-101.

Increased risk for pulmonary arterial hypertension on dasatinib

- Incidence estimated at less than 1%
- 41 cases of PAH confirmed by right heart catheterization
- 68% presented with synchronous pleural effusion
- No clear relationship with dasatinib dose
- Occurred anywhere from < 1 month to 7 years
- 36 cases with follow-up demonstrated that most improved or resolved off therapy (N=34, 94%)

Shah et al. Am J Hematol. 2015 Nov;90(11):1060-4

Nilotinib and increased risk for arterial vascular events

ENESTnd 6-year Update

Patients With an Event, n (%)	Nilotinib 300 mg BID n = 279	Nilotinib 400 mg BID n = 277	Imatinib 400 mg QD n = 280
	Total, n (%)	Total, n (%)	Total, n (%)
Peripheral arterial occlusive disease (PAOD)	12 (4.3%)	9 (3.2%)	0
Ischemic heart disease	14 (5%)	28 (10.1%)	6 (2.1%)
Ischemic cerebrovascular events	4 (1.4%)	9 (3.2%)	1 (0.4%)
Other	4 (1.4%)	3 (1.1%)	0
	28 (10%)	44 (15.9%)	7 (2.5%)

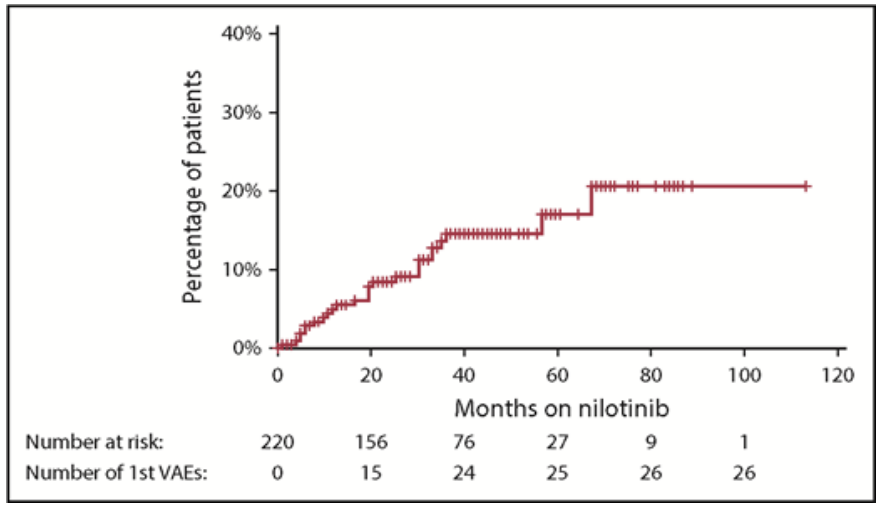
Larson RA, et al. Blood. 2014:[American Society of Hematology Meeting 2014, abstract 4541]
Hochhaus A et al. Leukemia (2016) 30, 1044–1054
Steegman JL et al. Leukemia. 2016 Aug;30(8):1648-71

Continued risk for arterial vascular adverse events over time on nilotinib in CP CML patients

Therapy line	N (%)
First	76 (35%)
Second	112 (51%)
Third	32 (14%)

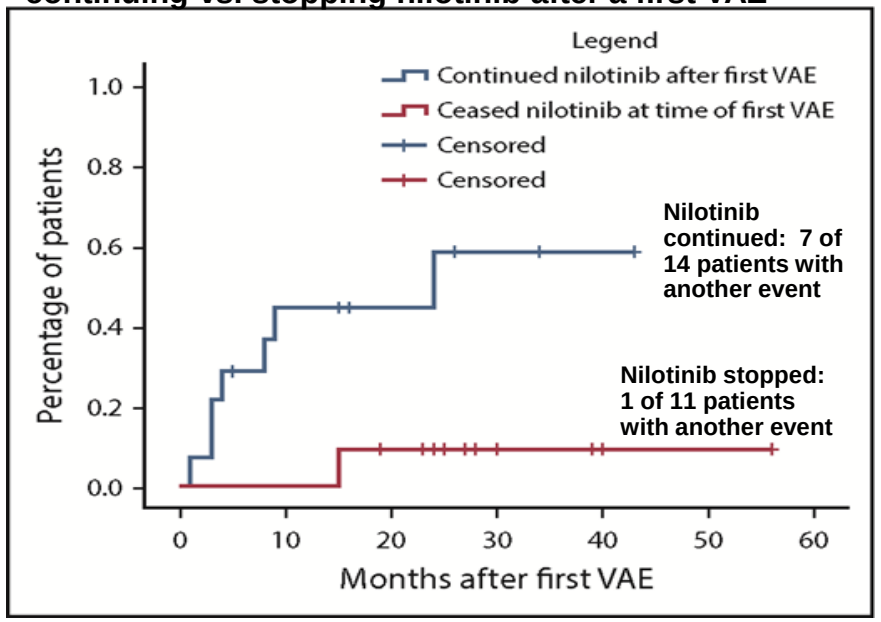
220 patients treated with nilotinib for chronic myeloid leukaemia in chronic phase at 17 Australian institutions

Cumulative incidence of first VAE



26 patients with first arterial vascular event

Cumulative incidence of second VAEs in patients continuing vs. stopping nilotinib after a first VAE



- Events more common in older patients
- Smoking history and dyslipidemia are independent risk factors for events
- High rate of recurrence if nilotinib continued after an event even with appropriate management

Minson AG et al. Blood Adv. 2019 Apr 9; 3(7): 1084–1091.

Considerations when selecting 1st line therapy

Goals:	Tyrosine kinase inhibitor:
• Life expectancy not impacted by CML	• Imatinib, 2nd generation TKI
• Overcome higher risk CML	• ***2nd generation TKI,*** imatinib
• Treatment-free remission	• **2nd generation TKI,** imatinib
• Limit impact of TKI therapy on co-morbidity outcomes	• **Imatinib,** 2nd generation TKI
• Quality of life/minimizing adverse events	• Imatinib, 2nd generation TKI
• Family planning	• **2nd generation TKI,** imatinib
• Limiting costs	• **Imatinib**

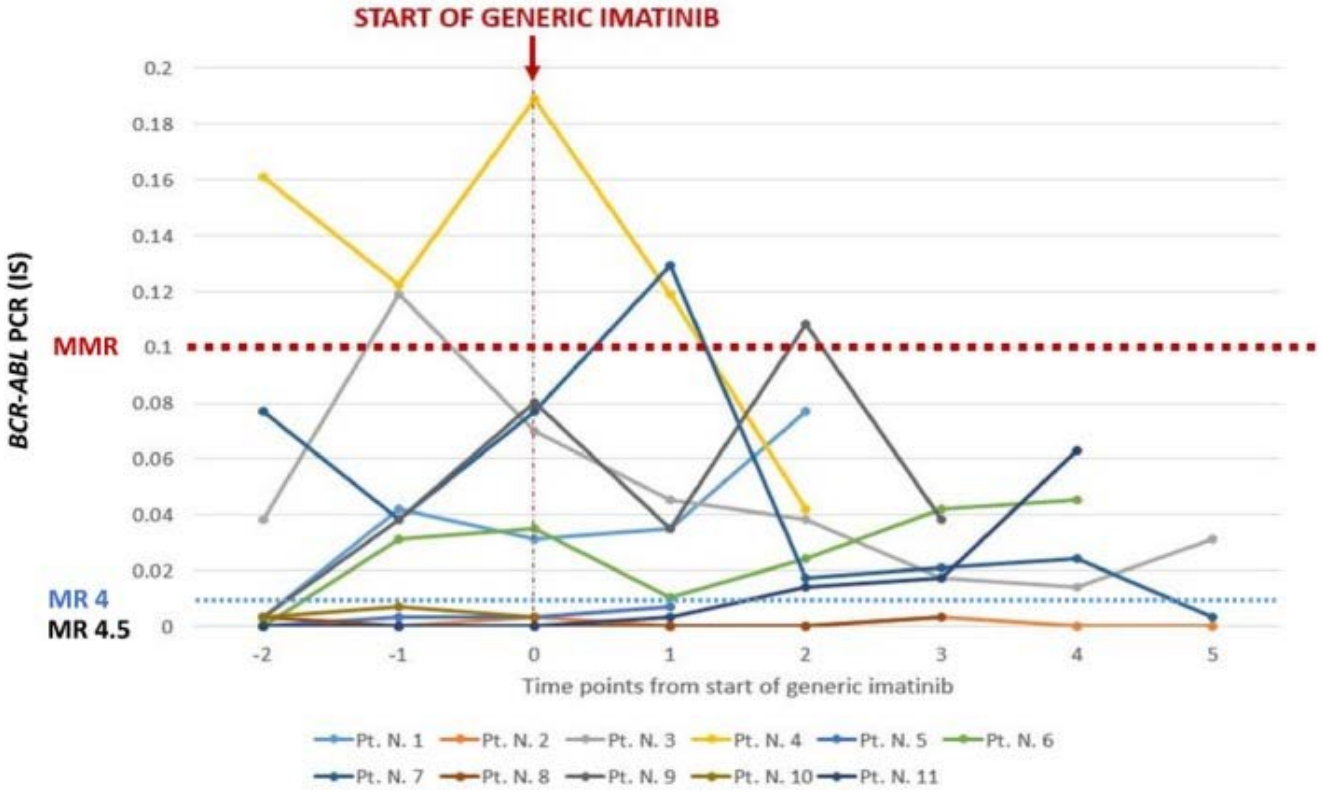
- Imatinib is generic and had an excellent safety profile
- Medical comorbidities may make nilotinib, dasatinib, or bosutinib a less optimal choice vs. imatinib
  1. Atherosclerotic cardiovascular disease, tobacco, T2DM, early family history – *increased risk with nilotinib*
  2. Pulmonary hypertension or pleural effusion – *increased risk with dasatinib*
  3. Hepatitis, liver disease, pancreatitis –*increased risk for transaminitis with nilotinib or bosutinib*
  4. IBD – *increased risk of diarrhea with bosutinib*

Requires close follow-up

1. Blood pressure
2. Fasting lipid panel
3. Hemoglobin A1c
4. ABI

Oehler VG. First Generation vs. Second Generation TKI - Which is Best At Diagnosis of Chronic Phase Chronic Myeloid Leukemia? ASH Annual Meeting 2020. CML Education Session

No difference between generic and branded imatinib after switch



- **Change from original to generic imatinib appears to maintain efficacy and safe**
- 38 patients
  - 100% CCyR
  - 95% MMR
  - 74% MR4.5
- Received generic IM for median of 19.4 mos (range 3.4-46.3 mos)
- Response after switch
  - Stable: 89%
  - Improved: 8%
  - Worsened: 3%
- Adverse events were mild, **although side effect may vary**

Dalle et al. Cancer Med. 2019 Nov;8(15):6559-6565.

Monitoring goals summary

- Early molecular response (*BCR-ABL1* IS < 10%) at 3 months
  - ~10% difference in OS or PFS
    - On either 1st or 2nd generation TKIs
  - Three months may be too early to assess response if poor adherence to therapy or multiple doses were held due to AEs early in the treatment course

- *BCR-ABL1* IS < 1% by 12 -15 months (equivalent of CCyR)
  - Associated with large OS and PFS benefits

- MMR (≤ 0.1%) (by 12 months)
  - Associated with (smaller) OS and PFS (as compared to *BCR-ABL1 < 1%*)
  - Limits likelihood of losing response
  - **Goal if treatment-free remission is desired**

- Deep molecular response
  - **Goal if treatment-free remission is desired**
  - No patient achieving MR4.5 on German CML Study IV progressed

NCCN Guidelines Version 1.2021: Early treatment response milestones

	3 months		6 months		12 months
>10%	NCCN Possible TKI Resistance		NCCN TKI-resistant		NCCN TKI-resistant
>1% - 10%	NCCN TKI sensitive		NCCN TKI sensitive		NCCN Possible TKI Resistance
>0.1 - 1%	NCCN TKI sensitive		NCCN TKI sensitive		*NCCN TKI sensitive**
≤ 0.1%	NCCN TKI sensitive		NCCN TKI sensitive		NCCN TKI sensitive

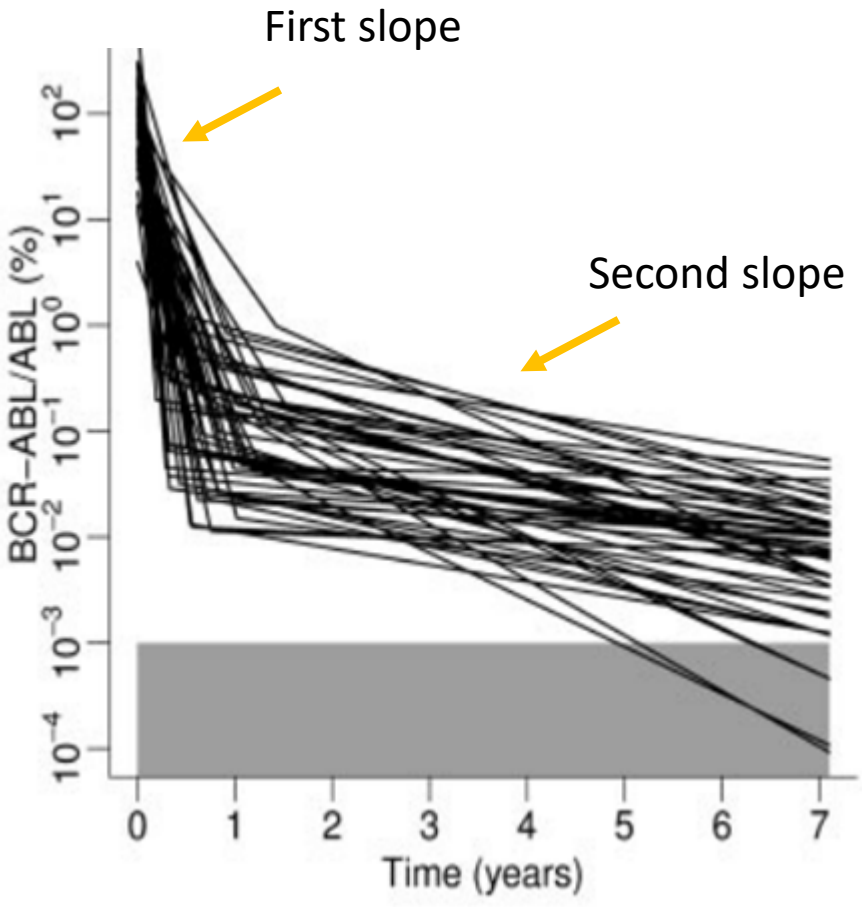
COLOR	CONCERN	CLINICAL CONSIDERATIONS	SECOND-LINE TREATMENT
RED	TKI-resistant disease	• Evaluate patient compliance and drug interactions • Consider mutational analysis	Switch to alternate TKI and evaluate for allogeneic HCT
YELLOW	Possible TKI resistance	• Evaluate patient compliance and drug interactions • Consider mutational analysis • Consider bone marrow cytogenetic analysis to assess for MCyR at 3 mo or CCyR at 12 mo	Switch to alternate TKI or Continue same TKI (other than imatinib) or Increase imatinib dose to a max of 800 mg and Consider evaluation for allogeneic HCT
LIGHT GREEN	TKI-sensitive disease	*• If treatment goal is long-term survival: >0.1%–1% optimal* *• If treatment goal is treatment-free remission: ≤0.1% optimal*	*• If optimal: continue same TKI* *• If not optimal:shared decision-making with patient*
GREEN	TKI-sensitive disease	• Monitor response and side effects	Continue same TKI

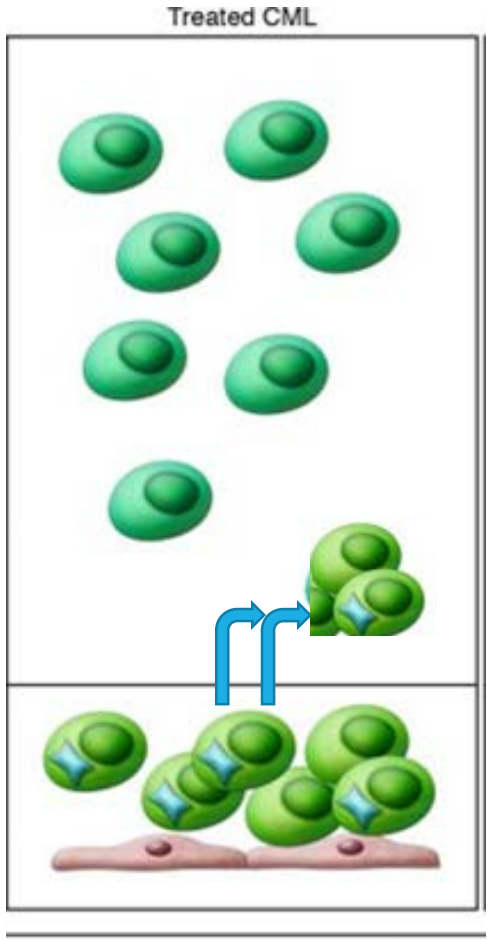
Maintaining quality of life and response: TKI cessation and dose reduction

Benefits of treatment-free remission

- Limit long-term adverse events
- Improve quality of life
- Family planning
- Minimize costs

CML stem cell eradication





Progenitor cell compartment: ***sensitive to TKI***

Stem cell eradication

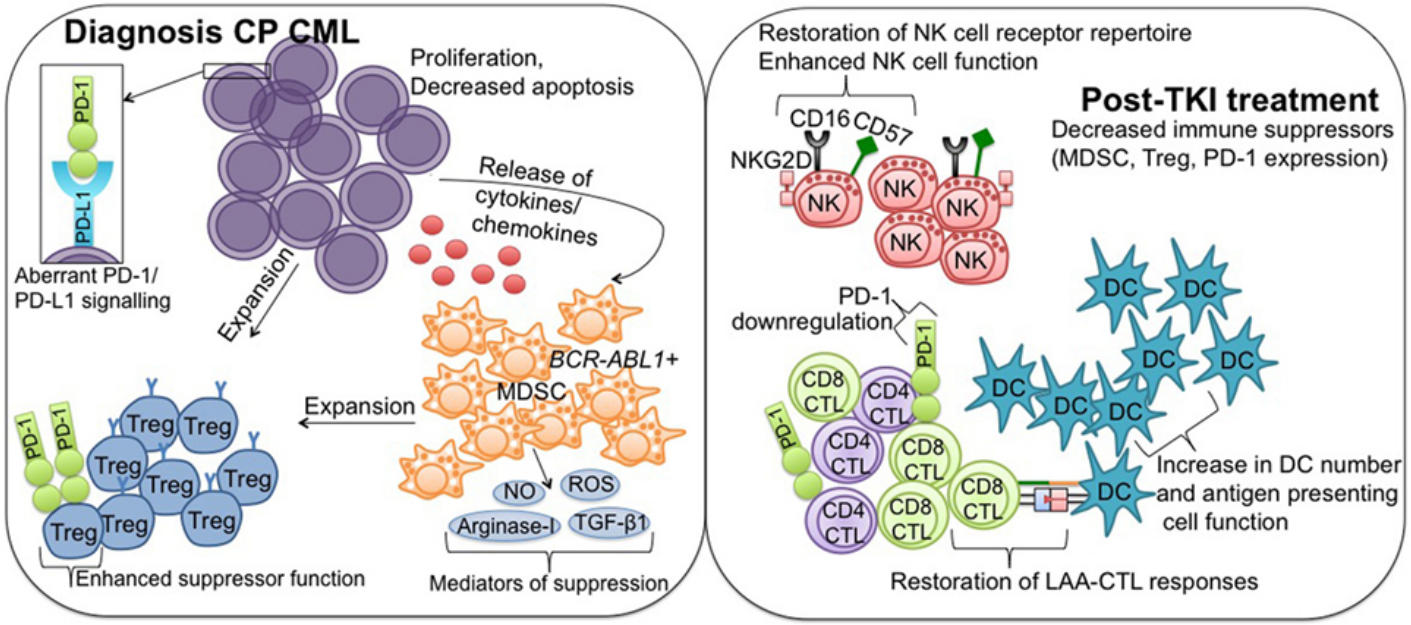
CML stem cell compartment: ***resistant to TKI***

During treatment inactive CML cells persist in the stem cell compartment

- **CML stem cell erosion/eradication on TKI therapy**
  - Over time some of the inactivated CML stem cells become activated
  - This leads to a slow eradication of CML stem cells on continued TKI treatment
  - Partly explains why longer treatment with TKI is associated with better success at stopping TKI

Horn M et al. Blood. 2013 Jan 10;121(2):378-84.
Tang M et al. Blood. 2011 Aug 11; 118(6): 1622-1631

Immunological control that helps sustain treatment-free remission

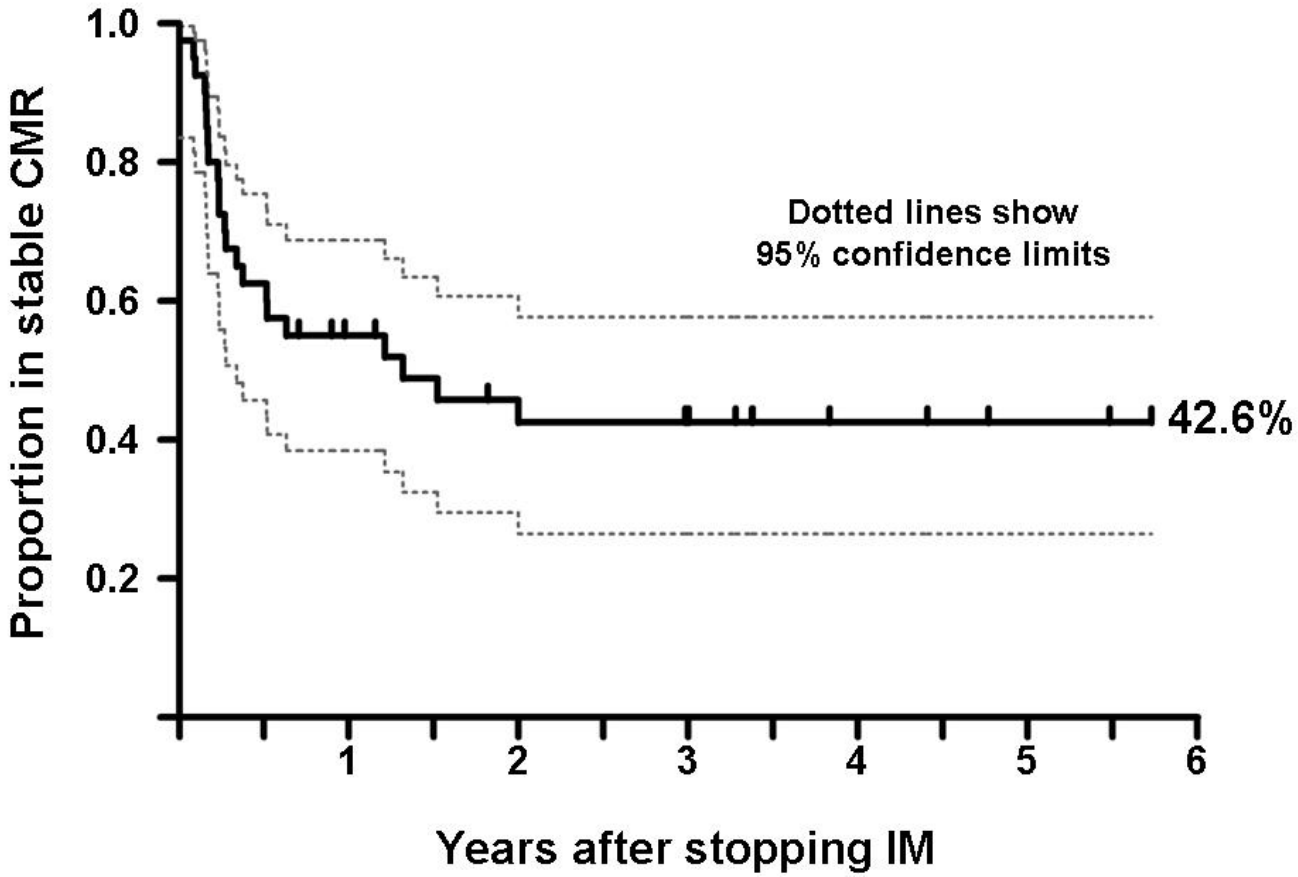


- Patients with deep molecular response have a different immune environment as compared to patients at diagnosis
  - Increased immune activators/surveillance
  - Decreased immune suppressors
- Possible immune cell signature to predict better TKI treatment response and success at stopping therapy

Hughes A and Yong ASM. Front Immunol. 2017; 8: 469.
Hughes et al. Blood. 2017 Mar 2;129(9):1166-1176
Bruck O et al. Leukemia. 2018. 32, pages1643–1656.

Stopping first-line imatinib therapy

Australian CML8 study (TWISTER)

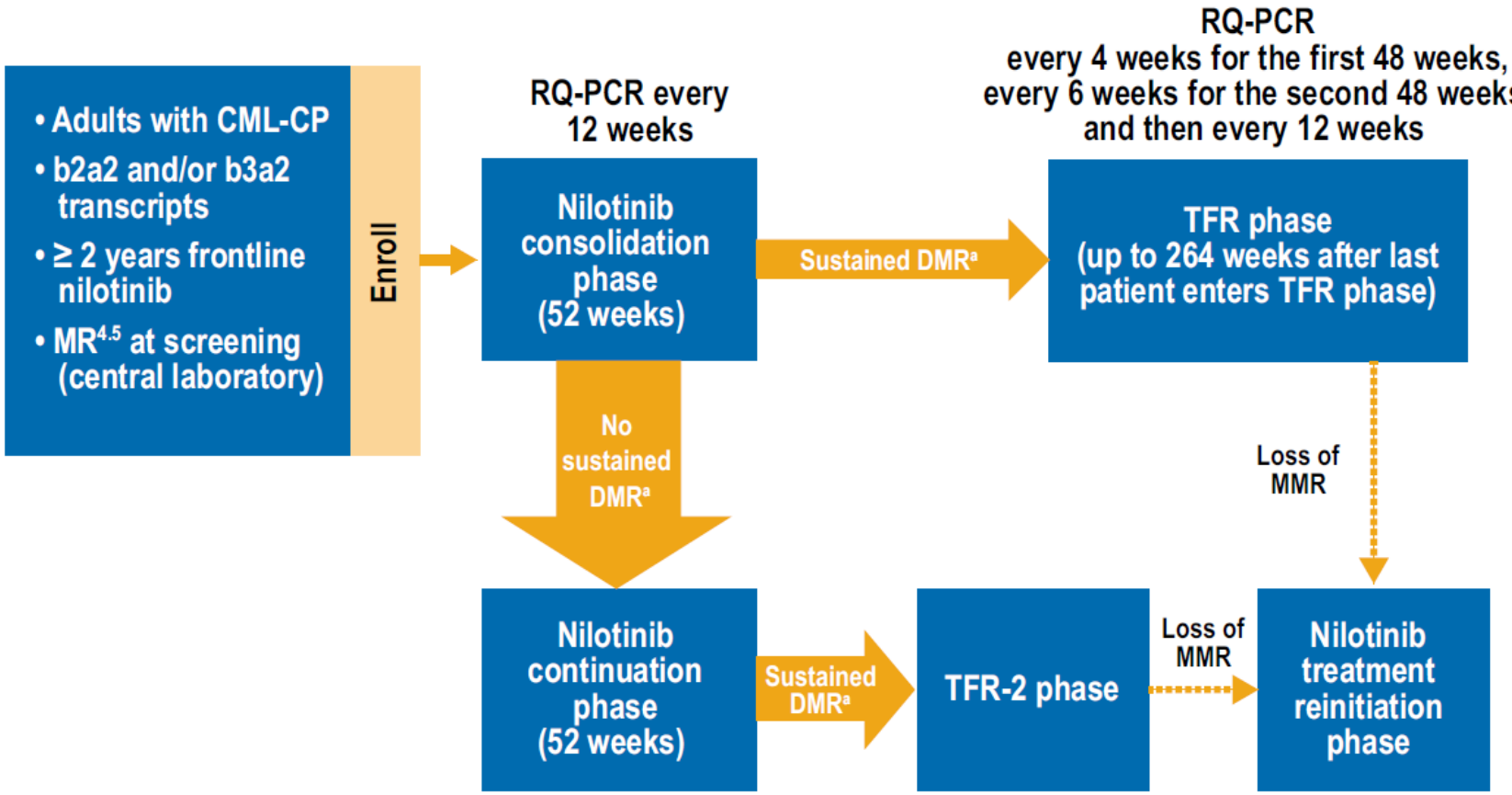


N=40
Entry criteria: BCR-ABL1 IS ≤ 0.0032% (MR4.5 for two years or longer

- Earlier studies stopping IM: **STIM1, STIM2, TWISTER**
  - Very consistent TFR rate at ~45%-50%
  - Most patients restarting therapy achieved former responses
- Stopping 2nd generation TKI
  - STOP-2G TKI: TFR at 48 months 53.6%

Ross DM et al. Blood. 2013 Jul 25;122(4):515-22. Rea D et al. Blood. 2017; 129(7): 846-854.

ENESTfreedom: Stopping 1st-line nilotinib



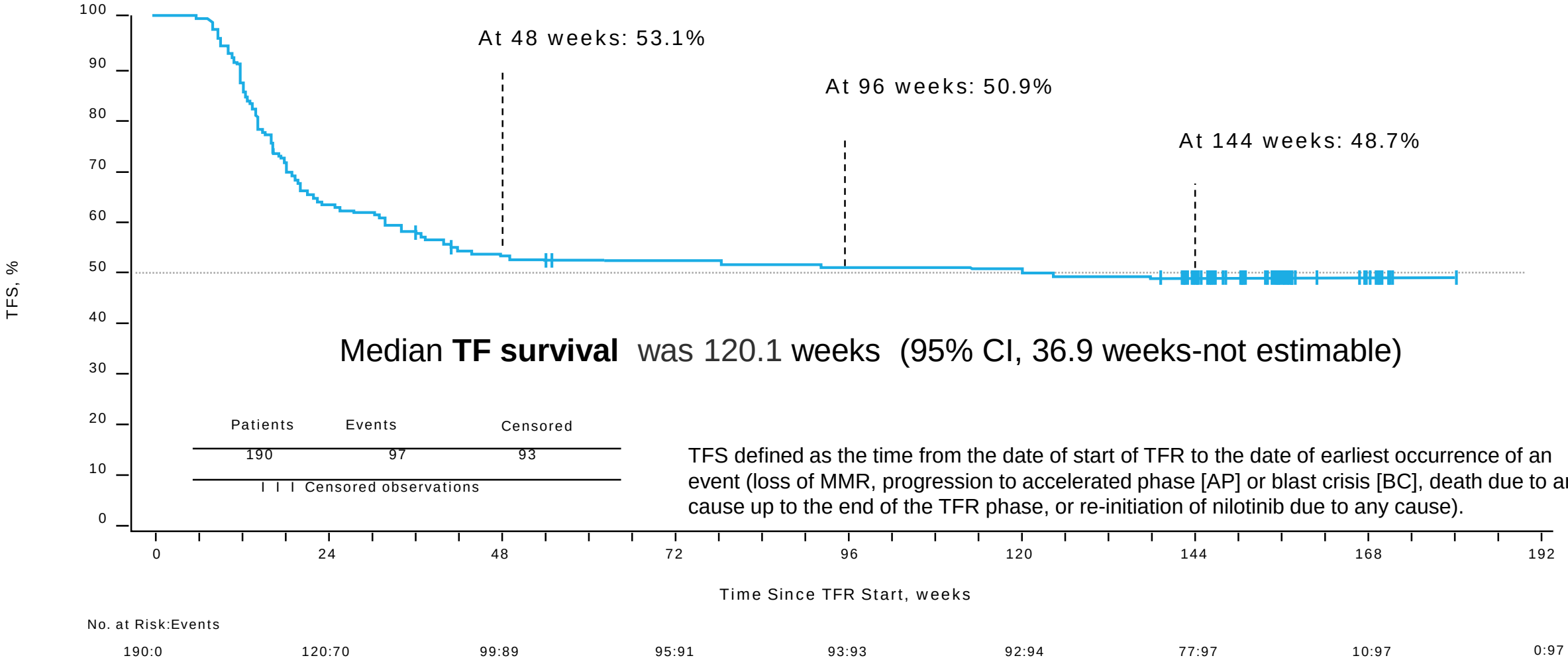
Nilotinib label update includes treatment discontinuation recommendations for CML with sustained molecular responses based on ENESTfreedom and ENESTop

1. Median total nilotinib duration prior to TFR phase was 43.5 months (range 32.9 – 88.7 months)
2. Median time from first MR4.5 to entering TFR phase was 30.4 months (range 12.3 – 83.0 months)

Sustained MR4.5 during a one-year consolidation

Ross DM et al. J Cancer Res Clin Oncol 2018 May;144(5):945-954

ENESTfreedom: Treatment-Free Survival[a]



Median **TF survival** was 120.1 weeks (95% CI, 36.9 weeks-not estimable)

TFS defined as the time from the date of start of TFR to the date of earliest occurrence of an event (loss of MMR, progression to accelerated phase [AP] or blast crisis [BC], death due to any cause up to the end of the TFR phase, or re-initiation of nilotinib due to any cause).

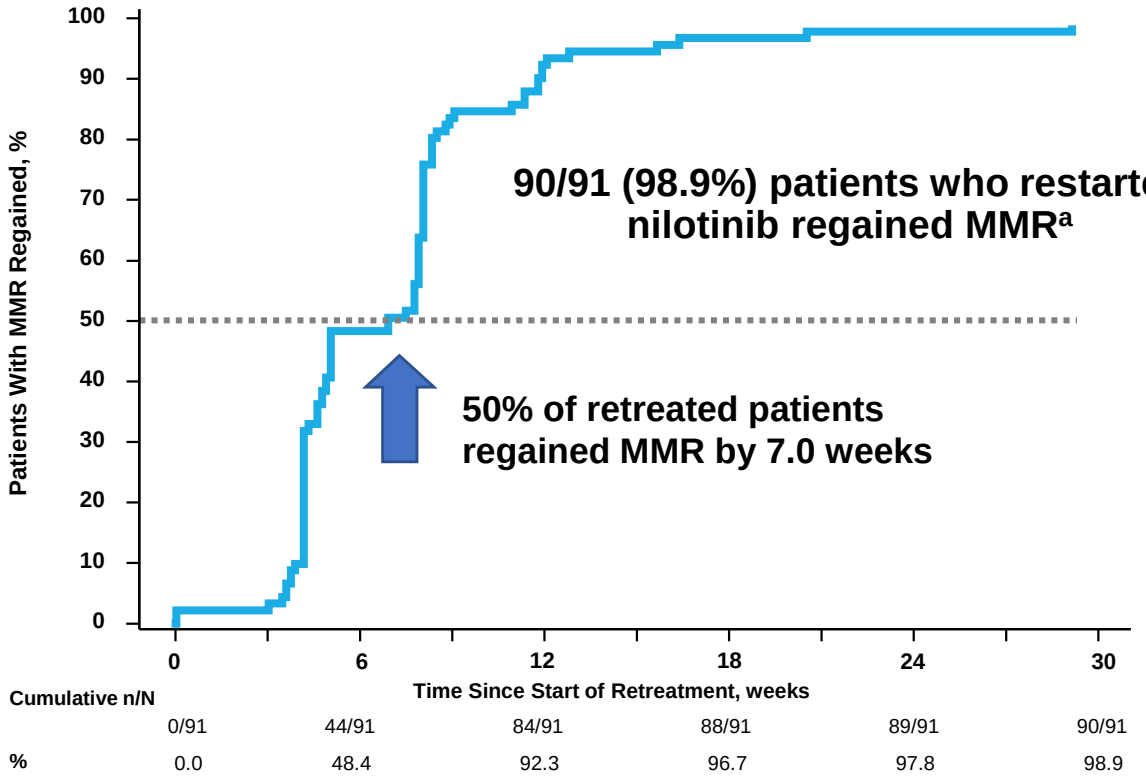
TFS, treatment-free survival.

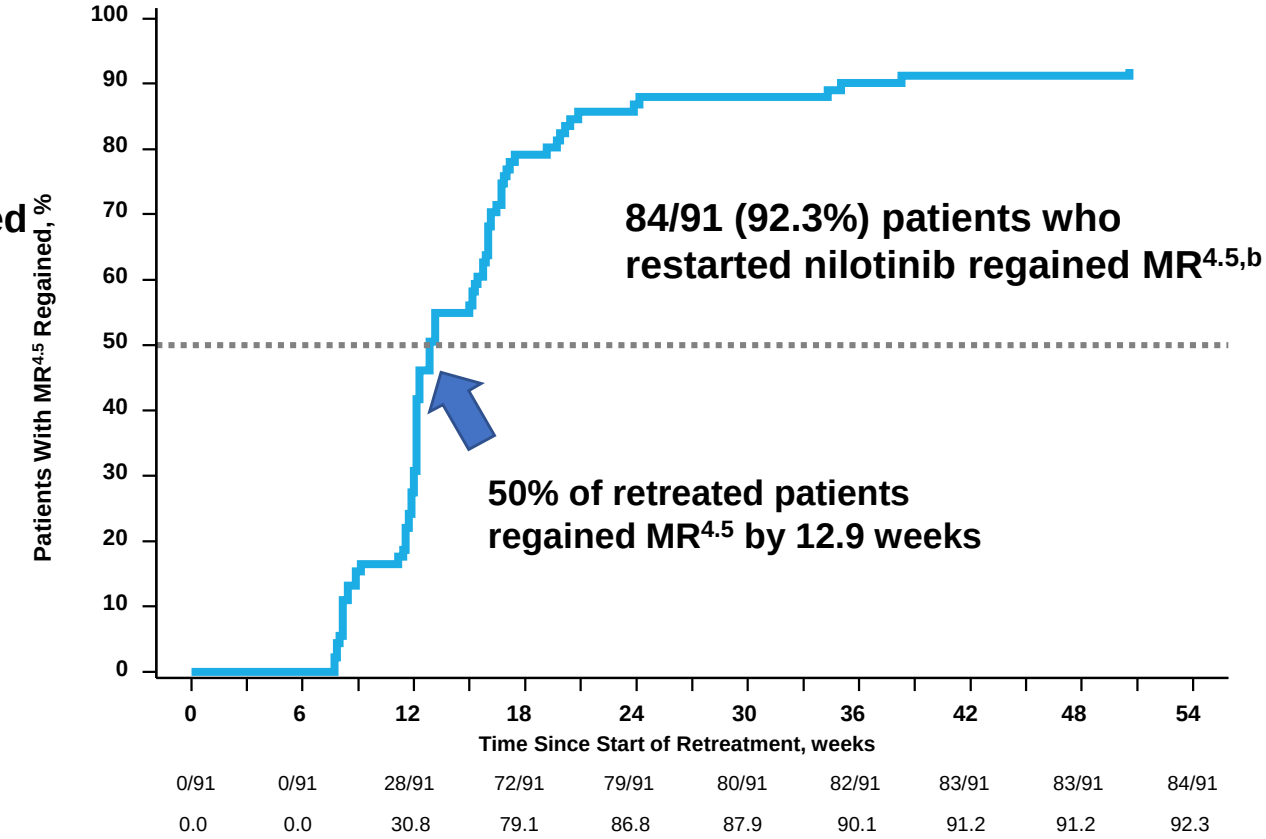
[a] TFS was estimated using the Kaplan-Meier method and was defined as the time from the date of start of TFR to the date of earliest occurrence of an event (loss of MMR, progression to accelerated phase [AP] or blast crisis [BC], death due to any cause up to the end of the TFR phase, or reinitiation of nilotinib due to any cause).

[b] Defined as no loss of MMR and no reinitiation of nilotinib in the first 48 weeks of TFR.

1. Hochhaus A, et al. *Leukemia*. 2017;31:1525-1531.

ENESTfreedom: Cumulative Rate of MMR and $MR^{4.5}$ Regained in Nilotinib Reinitiation Phase





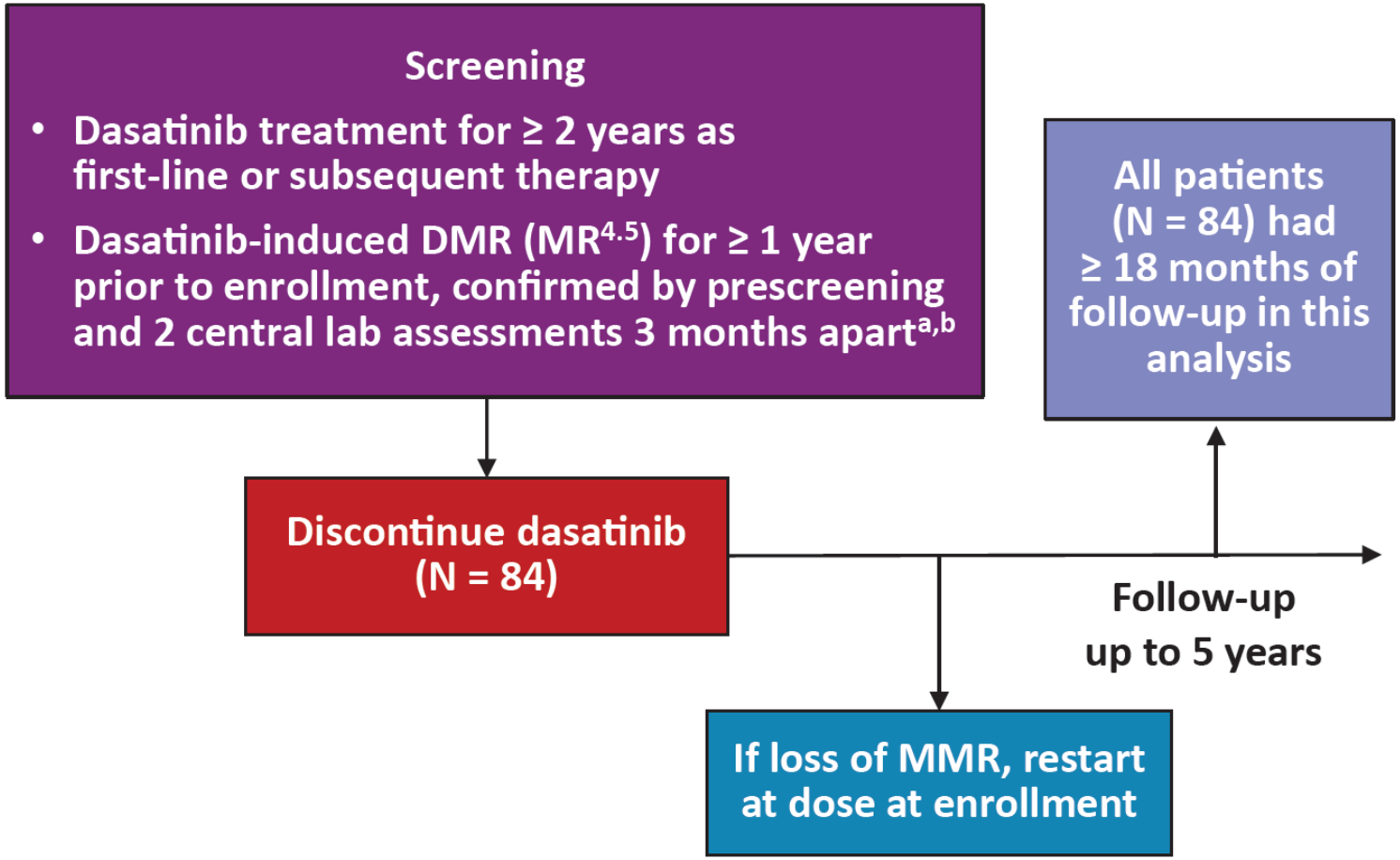
[a] 1 patient discontinued from the study after 7.1 weeks of retreatment without regaining MMR. [b] Of the 6 patients who regained MMR but not $MR^{4.5}$, 1 remained in the reinitiation phase at the data cutoff, and 5 had discontinued from the study (2 due to AEs, 1 due to physician decision, 1 due to patient decision, and 1 due to lack of efficacy [after regaining and then losing MMR; patient was found to have an F359V mutation[1]]).

1. Hochhaus A, et al. *Leukemia*. 2017;31:1525-1531.

Radich et al. Clinical Lymphoma, Myeloma, & Leukemia. 2018; 18(Supplement 1): S226

DASFREE: Stopping dasatinib 1st and 2nd line

- **DASFREE is a phase 2, open-label, single-arm study conducted in North America and Europe**
- ***TFR (proportion of subjects who maintained MMR [BCR-ABL < 0.1%])***



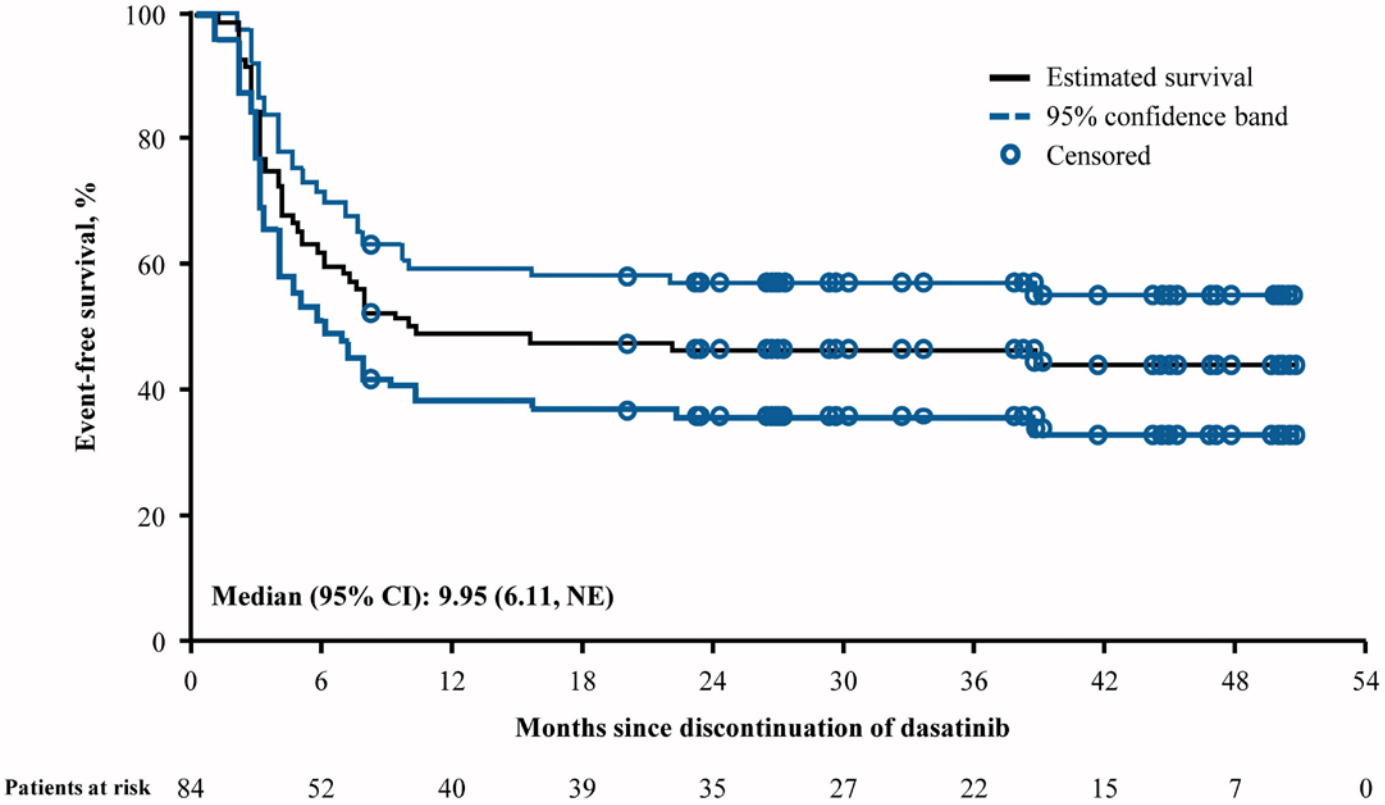
[a] Adults with dasatinib-induced stable DMR for ≥ 9 months, documented by ≥ 3 assessment conducted 2 to 6.5 months apart at a local lab were screened.

[b]For any patient not eligible for enrollment because both assessments at the central lab did not confirm DMR, rescreening was allowed ≥ 9 months after the last central lab screening failure.

DMR = deep molecular response; IS = International Scale; MMR = major molecular response; $MR^{4.5}$ = BCR-ABL1 ≤ 0.0032% on the International Scale.

Shah NP et al. *Blood.* 2018; 132: ASH Meeting Abstract 4253
Shan NP et al . Leuk Lymphoma. 2019 Oct 24:1-10

DASFREE: TFR at 2 years



	2-year TFR, % (95% CI)
Patients on first-line dasatinib	51 (35, 67)
Patients on subsequent lines of dasatinib	42 (28,57)
Resistant	44 (25, 64)
Intolerant	44 (22, 67)

French STOP-2G TKI Study

- 60-month TFR rate 29.8% for patients with prior resistance *versus* 63.6% if no such history

ENESTop stopping 2nd line nilotinib after imatinib

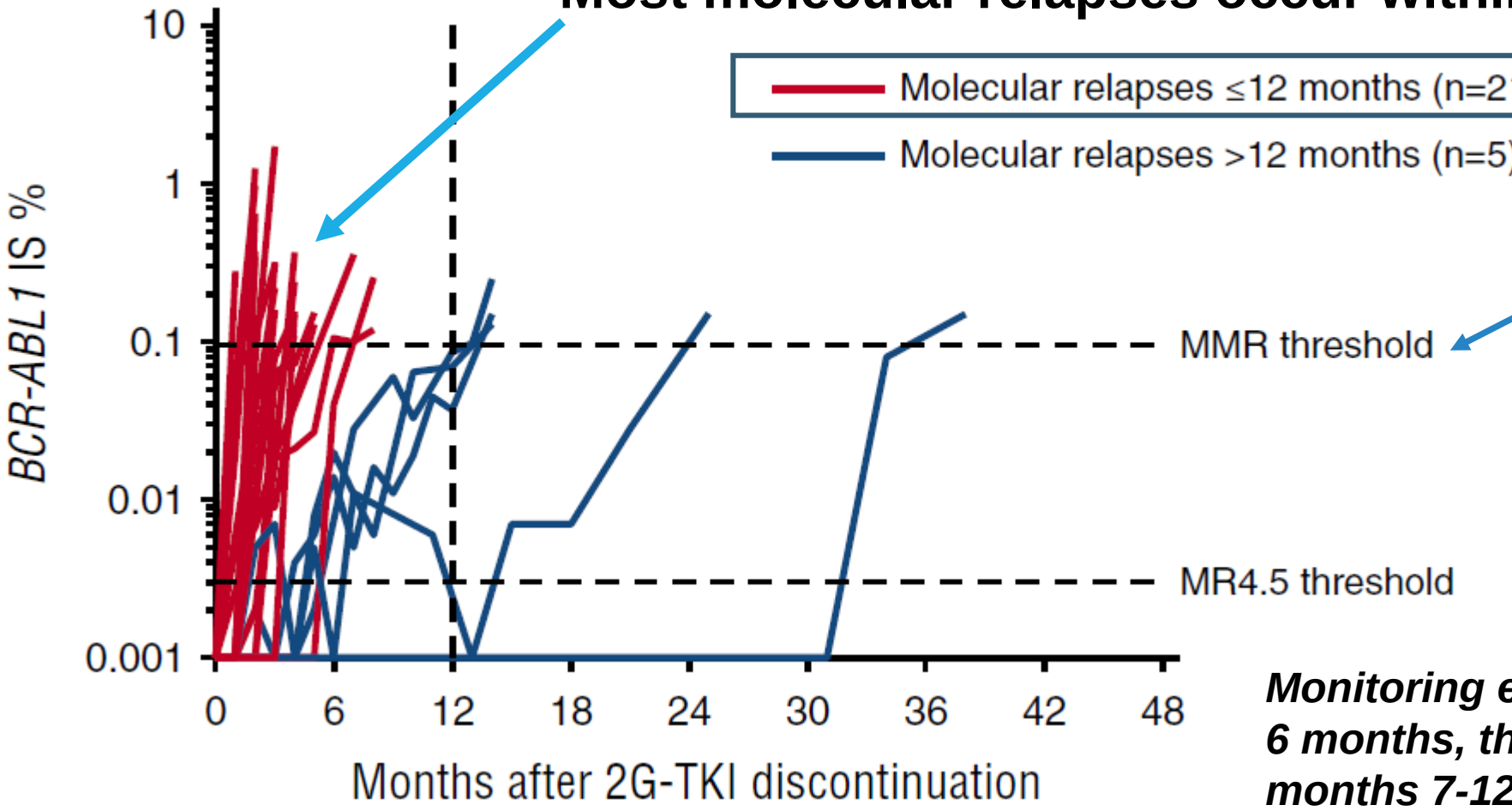
- NO difference in TFR rates if stopping for resistance or intolerance

Shah NP et al. *Blood.* 2018; 132: ASH Meeting Abstract 4253
Shan NP et al . Leuk Lymphoma. 2019 Oct 24:1-10
Rea et al. ASH Annual Meeting 2019, abstract 30

Monitoring is critical

STOP 2G-TKI study

Most molecular relapses occur within 12 months



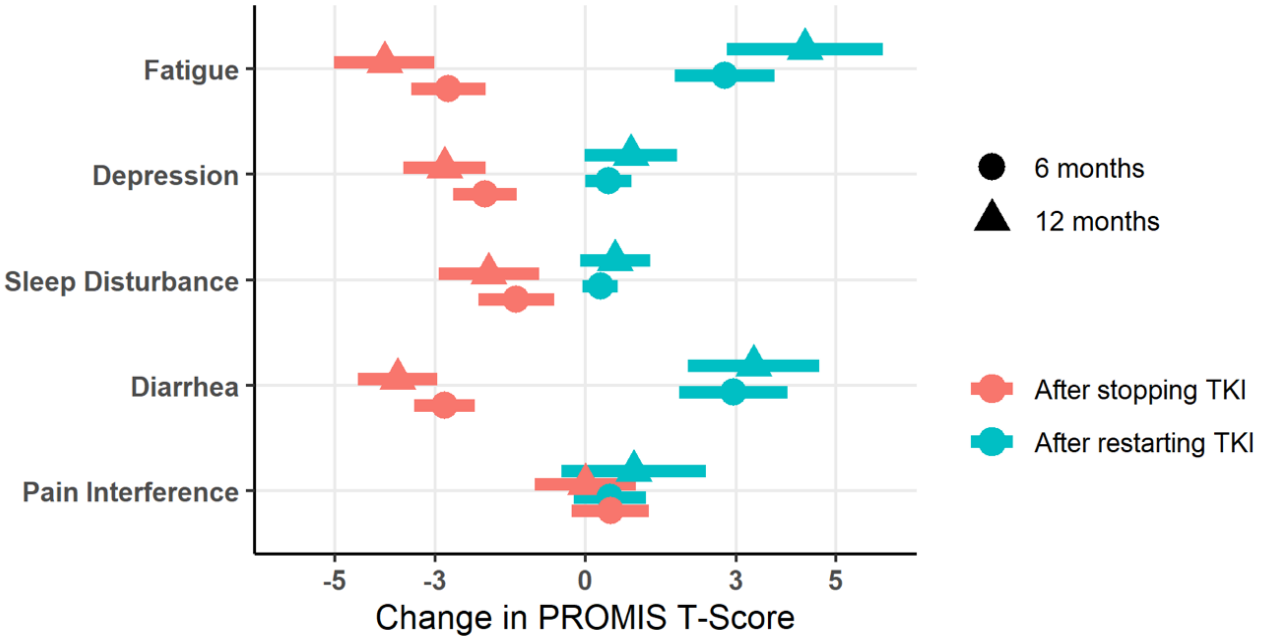
Therapy is typically resumed when MMR is lost

Monitoring every month for the first 6 months, then every 2 months for months 7-12, then every 3 months if MMR is maintained indefinitely

Rea D et al. Blood. 2017; 129(7): 846-854.

U.S. Life after Stopping TKIs (LAST) Study

First study to prospectively assess patient-reported outcomes (PROs) after stopping (and restarting) TKIs

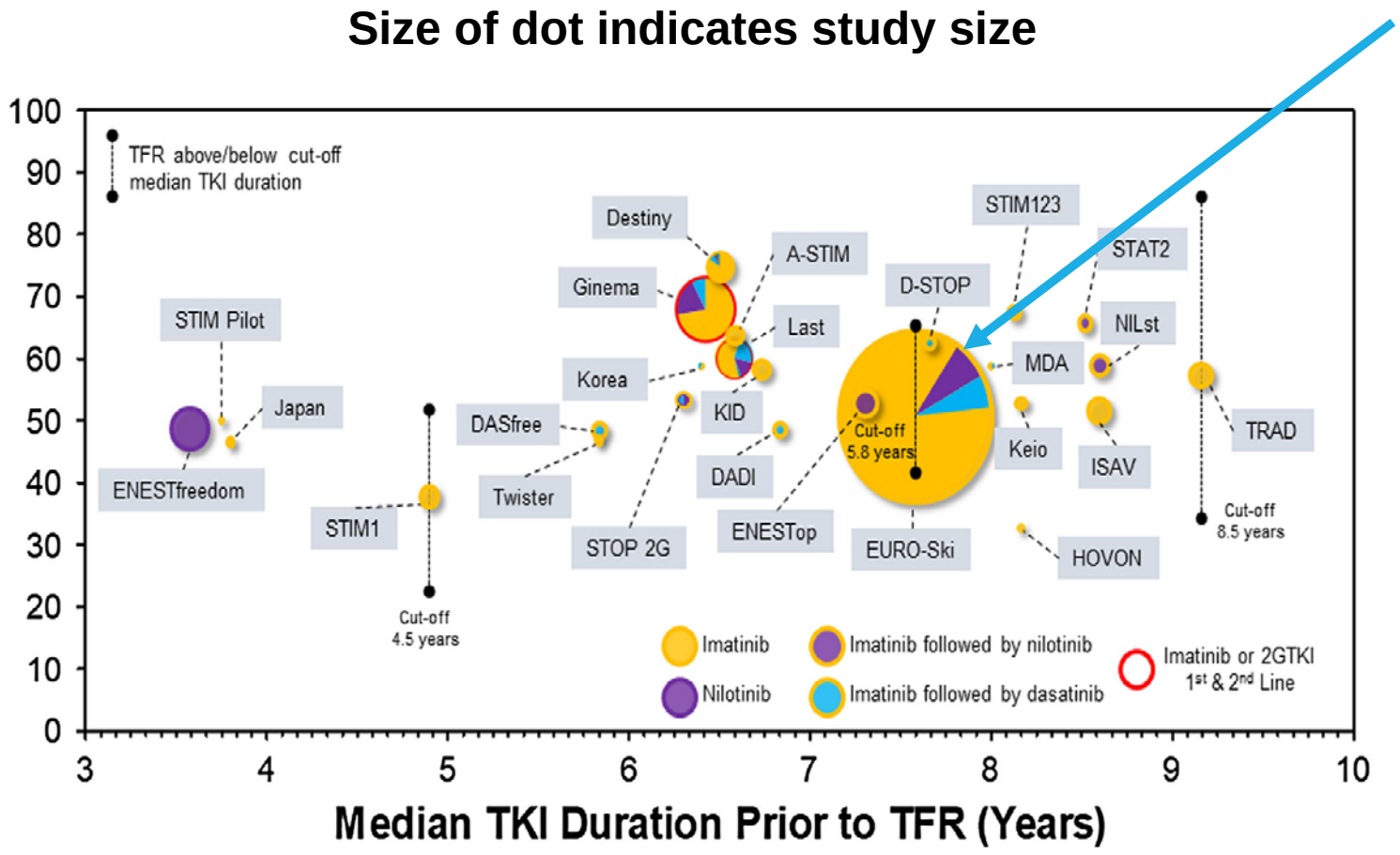


Mean changes (and 95% confidence intervals) in PROs after TKI discontinuation and TKI restart at 6 and 12 mos.

1. 172 patients at 14 US sites
2. 60% TFR at 3 years
3. Significant improvements in fatigue, depression, sleep, and GI symptoms off therapy
4. Molecular relapse occurred most frequently within the first 12 months
5. Rare late relapses were seen
   - 10.2% between 12-24 months
   - 5.1% between 24-36 months
   - 3.4% after 36 months

Atallah E et al. JAMA Oncology. 2020 *in press*

Factors associated with successful TFR



- EURO-Ski

1. **LONGER TKI use**
   - Cut-off >5.8 yrs vs < 5.8 yrs
     - TFR 57% vs. 34%
2. **LONGER period of deep molecular response**
   - For each additional year of MR 4.0 – odds of remaining in MMR by 6 months increased by 13%
3. **No difference:** depth of response when stopping TKI: MR 4.0 vs. MR4.5 v. MR5.0

Laneuville P. Curr. Treat. Options in Oncol. (2018) 19: 15

One downside of treatment-free remission: withdrawal syndrome

LAST study: 3 patients restarted therapy due to withdrawal syndrome

- 25 -30% of patients after stopping TKIs
- Low-grade musculoskeletal pain
- Typically within the first one to two months
- Duration – median 6 months, range 1-36 months (Korean Imatinib Discontinuation Study (KIDS))
- Duration of TKI use (>93 months) and prior history of osteoarticular symptoms predispose to withdrawal syndrome

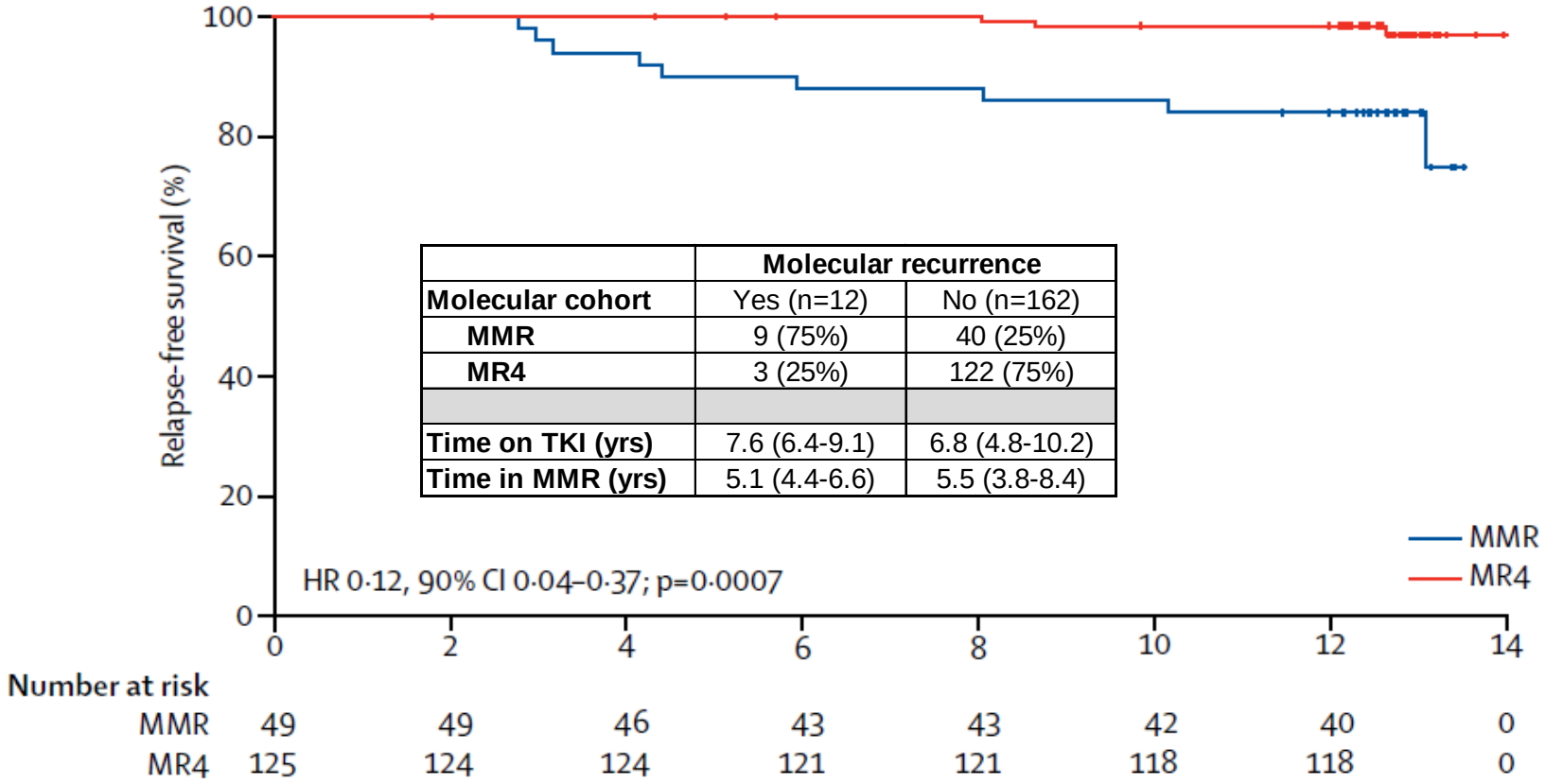
- Management:
  - NSAIDs
  - Prednisone

Lee SE et al. Haematologica. 2016; 101(6):717-723
Berger MG et al. Br J Haematol. 2019 Jul 4. doi: 10.1111/bjh.16083. [Epub ahead of print]

Dose reductions and continued durable response: DESTINY

174 patients

	MMR (n=49)	MR4 (n=125)	Overall
Time on TKI (years)	7.7 (5.1-10.7)	6.5 (4.8-10.2)	6.9 (4.8-10.2)



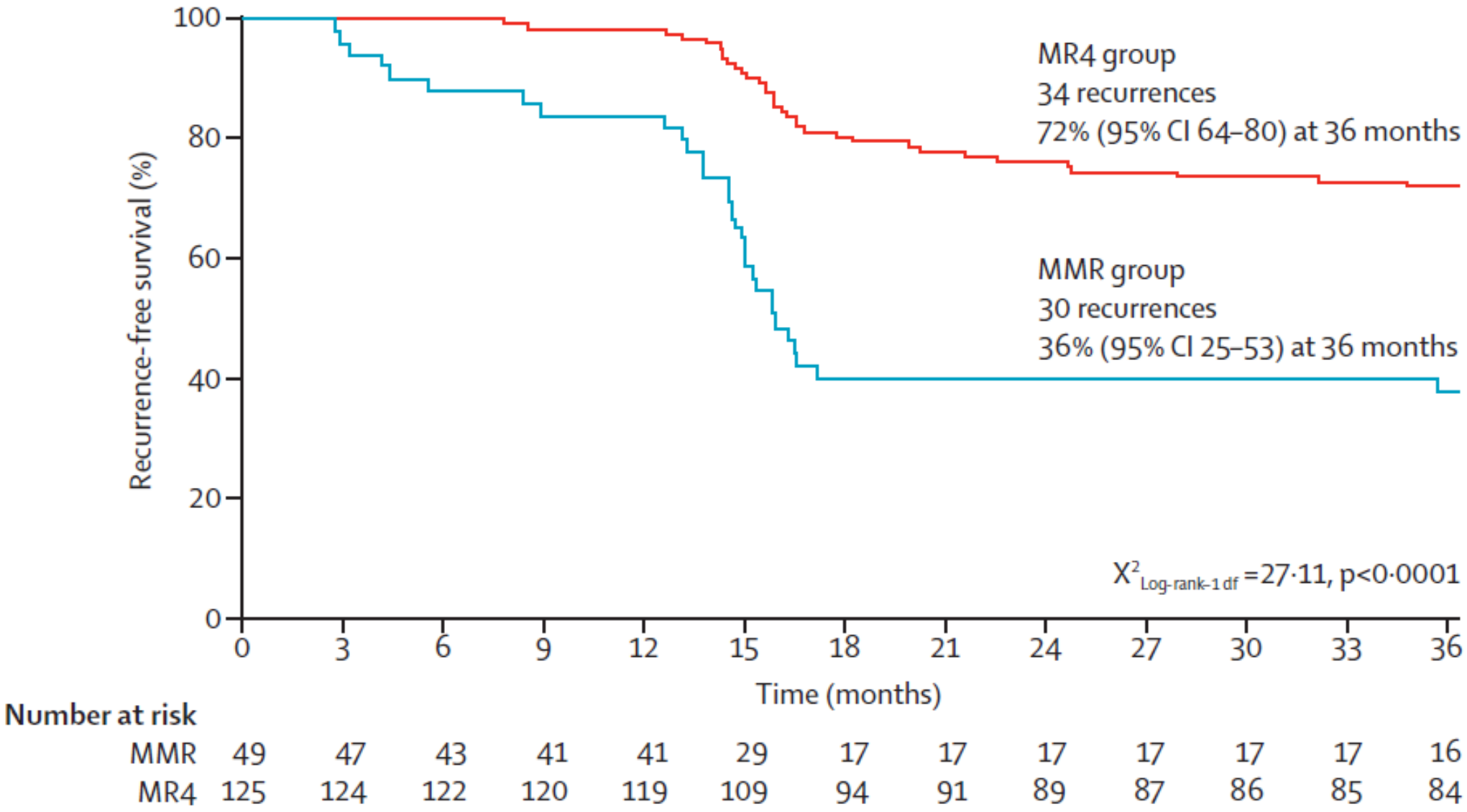
	Molecular recurrence	
Molecular cohort	Yes (n=12)	No (n=162)
MMR	9 (75%)	40 (25%)
MR4	3 (25%)	122 (75%)
Time on TKI (yrs)	7.6 (6.4-9.1)	6.8 (4.8-10.2)
Time in MMR (yrs)	5.1 (4.4-6.6)	5.5 (3.8-8.4)

1. General improvement in adverse side effects
2. Limited MSK symptoms vs. complete TKI withdrawal
3. All regained MMR within 4 months of resumption of full dose TKI

De-Escalation and Stopping Treatment with Imatinib, Nilotinib, or sprYcel (DESTINY) study: TKI treatment was deescalated to half the standard dose for 12 months, then stopped for a further 24 months

Clark RE et al. Lancet Hematol. 2017 Jul;4(7):e310-e316.
Clark RE et al. Lancet Haematol. 2019 Jul;6(7):e375-e383.

DESTINY: TKI cessation phase

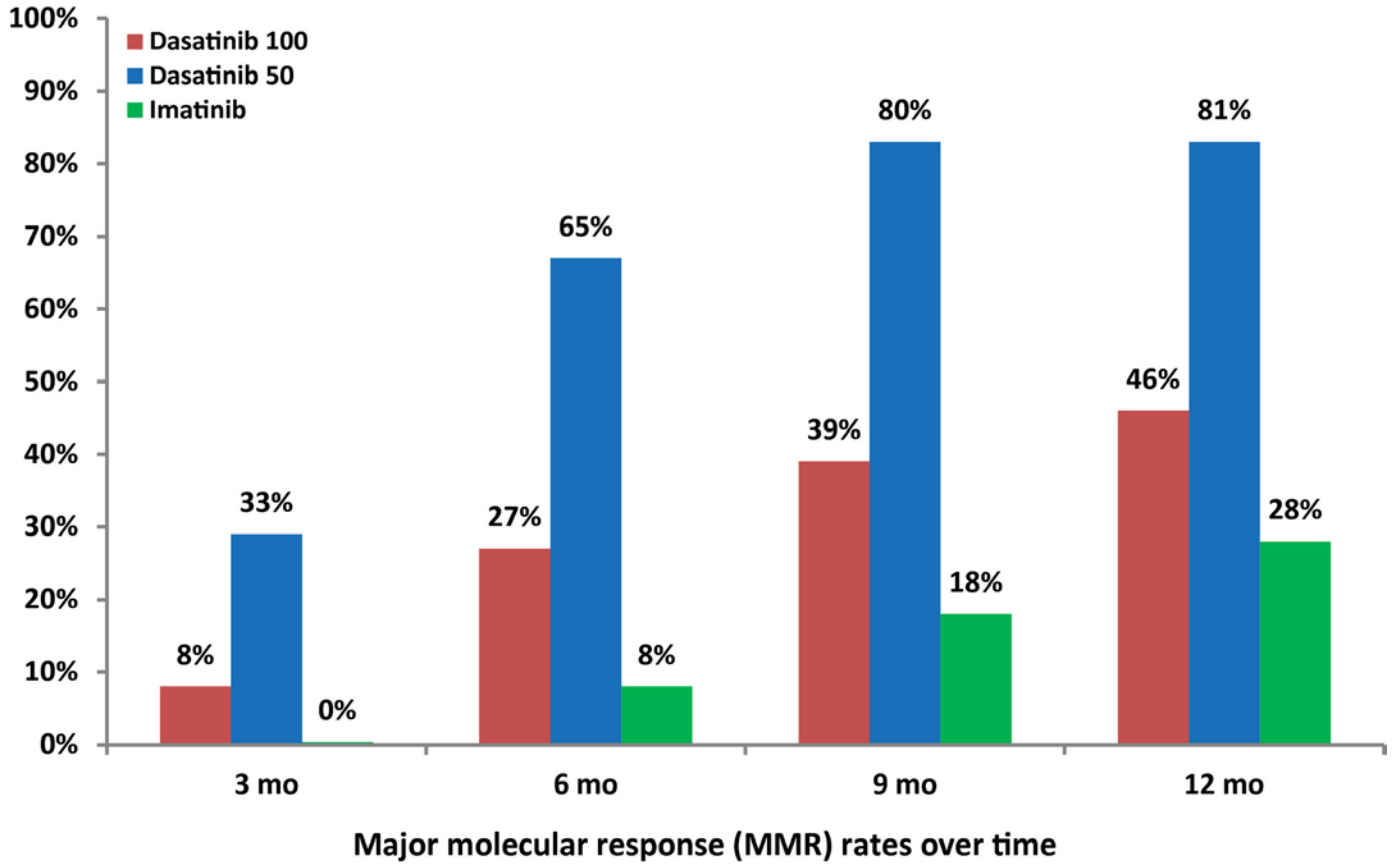


Clark RE et al. Lancet Hematol. 2017 Jul;4(7):e310-e316.
Clark RE et al. Lancet Haematol. 2019 Jul;6(7):e375-e383.

Starting lower dose first-line

- Pilot study MD Anderson of newly diagnosed CP CML
- 96% achieved early molecular response at 3 months
- At 12 months
  - 81% MMR
  - 59% MR4
- Mechanism: perhaps safety profile of lower dose dasatinib with fewer treatment interruptions and more continuous dosing
- DASISION study:
  - pleural effusion in up to 28% of the patients
- Low-dose dasatinib:
  - pleural effusion occurred in 6% of patients

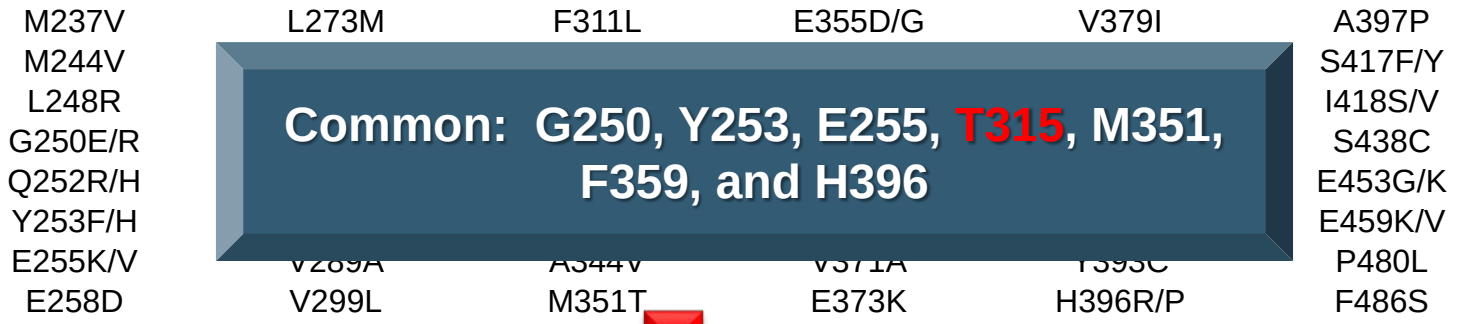
N=81
Dose: 50 mg orally daily
Minimum f/u: 12 months



Naqvi K et al. Cancer. 2020 Jan 1;126(1):67-75..

Next-line therapy

Mutations associated with tyrosine kinase inhibitor resistance



1st Generation: Imatinib

Y253H
E255K/V
T315I
F359V/I/C

Nilotinib

V299L
T315I
F317L/V/I/C

Dasatinib

L248V
G250E
E255K
V299L

T315I
F359C

Bosutinib

2nd Generation

Ponatinib
Treats T315I

3rd Generation

NCCN recommendations for next-line treatment based on BCR-ABL kinase domain mutation status

THERAPY	CONTRAINDICATED mutations[u]
Bosutinib	*T315I, V299L, G250E or F317L*[v]
Dasatinib	*T315I/A, F317L/V/I/C* or *V299L*
Nilotinib	*T315I, Y253H, E255K/V, F359V/C/I or G250E*
Ponatinib,[w] Omacetaxine,[x] allogeneic HCT (CML-6), or clinical trial	None

BUT NOT ALL RESISTANCE IS MUTATION DRIVEN

- BCR-ABL–independent mechanisms
- **Harder to treat**

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Chronic Myeloid Leukemia. Version 1.2021.

Summary response to 2nd-line therapy after imatinib

- Resistance to frontline imatinib is associated with lower CCyR rates compared with intolerance to imatinib*
  - Dasatinib (100 mg once daily, 2-year follow-up): imatinib-resistant, 44%; imatinib-intolerant, 67%
  - Nilotinib (400 mg twice daily, 2-year follow-up): imatinib-resistant, 41%; imatinib-intolerant, 51%
  - Bosutinib (500 mg once daily, 2-year follow-up): imatinib-resistant, 46%; imatinib-intolerant, 54%

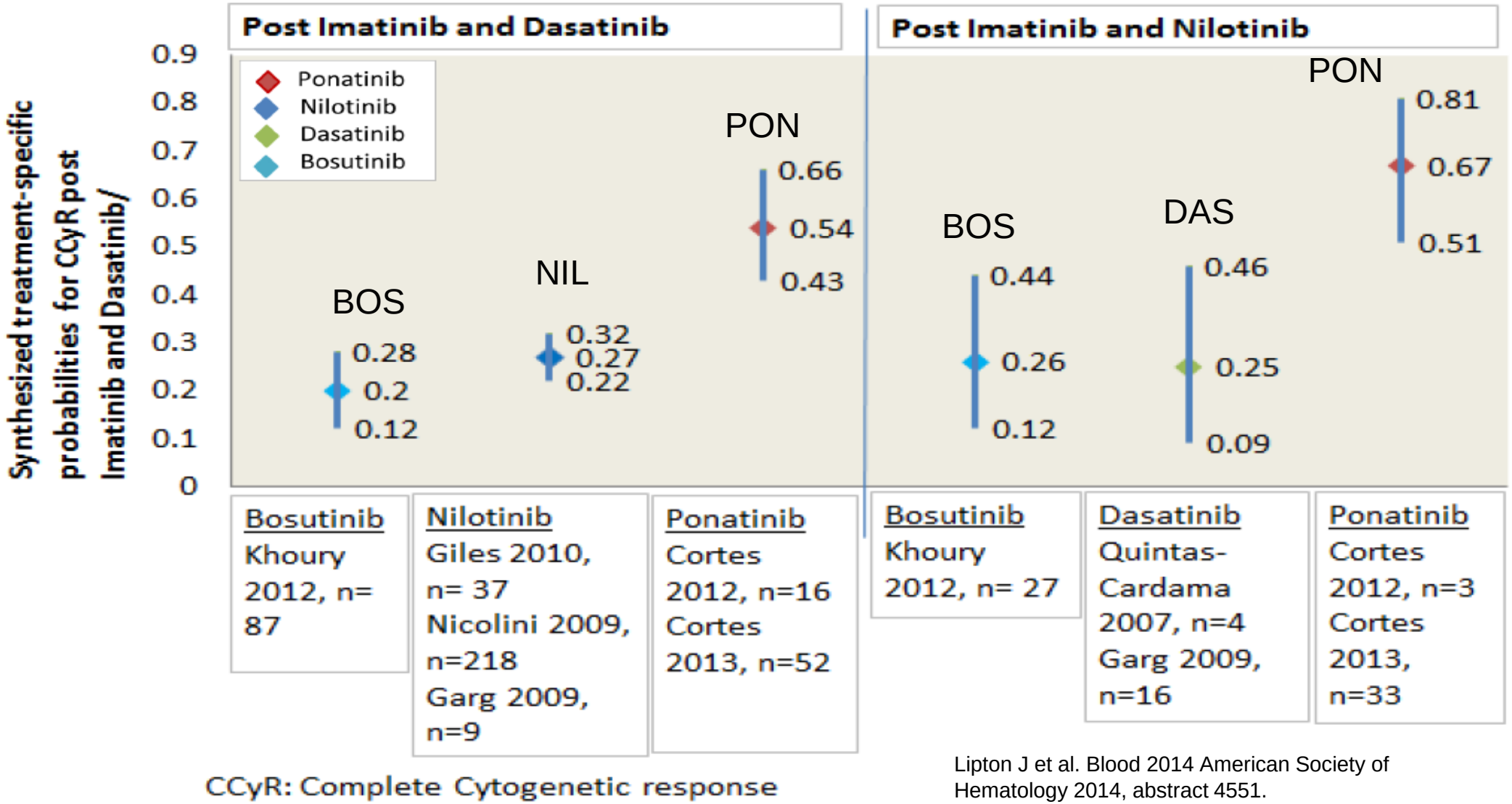
- Patients treated second-line with either dasatinib or nilotinib experience lower long-term overall survival rates compared with patients treated first-line with these TKIs*
  - Dasatinib: first-line 5-year OS, 91%; second-line 5-year OS, ~75%
  - Nilotinib: first-line 5-year OS, 96%; second-line 4-year OS, 78%
  - Overall survival at 5-year on bosutinib was 84% for the imatinib resistant group

*** These trials cannot be directly compared due to different methods of trial evaluation**

Shah NP et al. *Haematologica*. 2010;95(2):232-240.
Kantarjian HM et al. *Blood*. 2011;117(4):1141-1145.
Gambacorti-Passerini C, et al. *Am J Hematol*. 2014;89(7):732-742.
Cortes JE et al. *J Clin Oncol*. 2016;34(10):2333-2340.

Shah NP, et al. *Am J Hematol*. 2016;91(9):869-874.
Hochhaus A, et al. *Leukemia*. 2016;30(5):1044-1054.
Giles FJ, et al. *Leukemia*. 2013;27(1):107-112.
Gambacorti-Passerini C, et al. *Haematologica*. 2018;103(8):1298-1307.

Responses after 2nd generation TKI: CCyR on third-line TKI therapy



CCyR: Complete Cytogenetic response

Lipton J et al. Blood 2014 American Society of Hematology 2014, abstract 4551.
Lipton J et al. Leuk Res. 2015 Jan;39(1):58-64

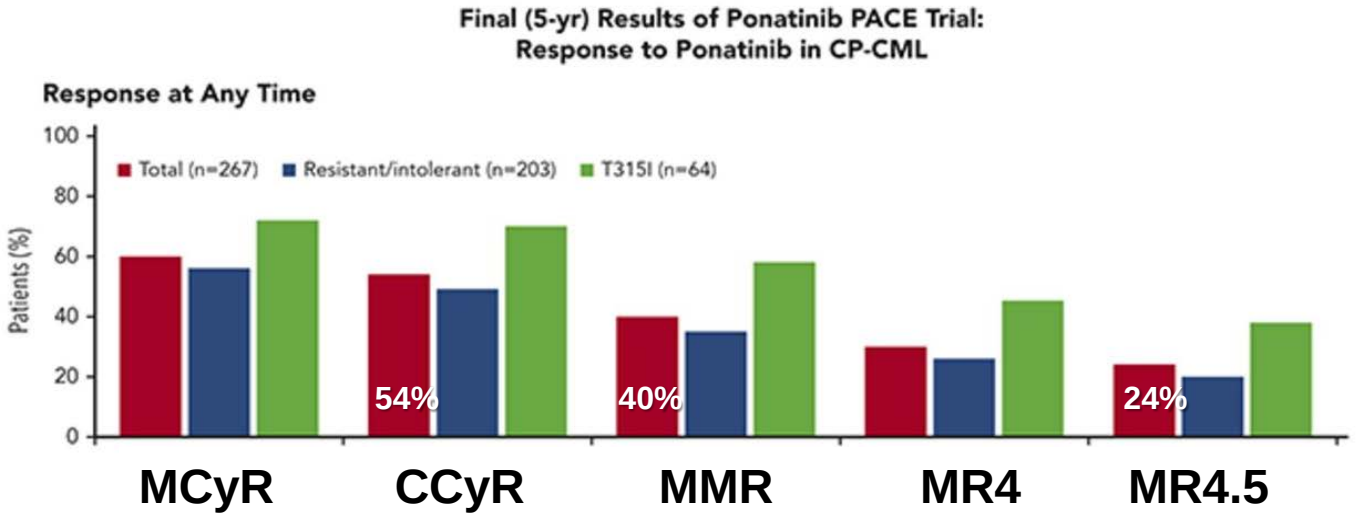
When to consider ponatinib?

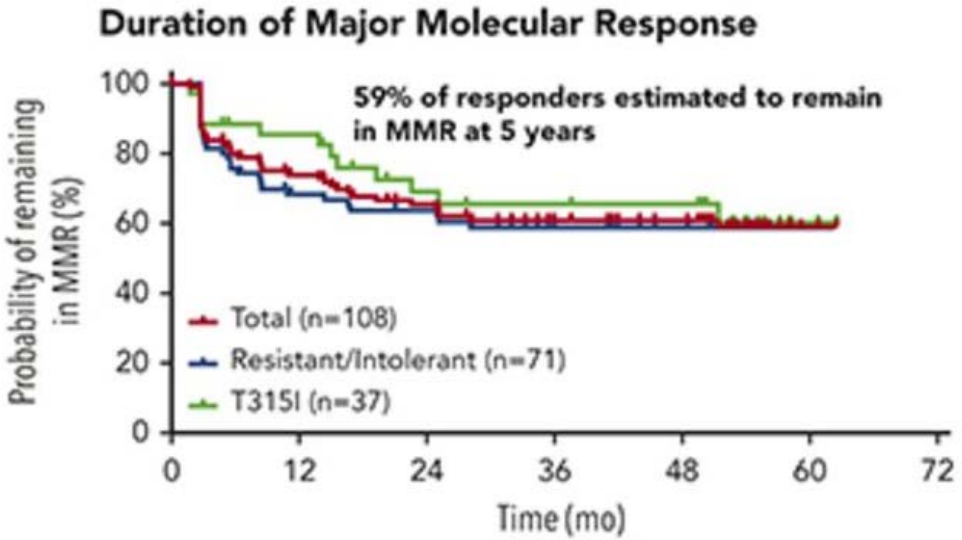
- Label: T315I mutated CML and “for whom no other tyrosine kinase inhibitor (TKI) therapy is indicated”
- Consider: Progression to advanced phase (bridge to transplant)
- Consider: after failure of two 2nd generation TKIs (NCCN)
  - Response to a third 2nd generation TKI is usually low
- *Consider: in CP CML patients who fail first-line 2nd generation TKI therapy with primary resistance* ***and no mutations***
  - *Consider brief trial of 2nd line 2nd generation TKI*
  - *Worrisome group who may need early consideration for allogeneic stem cell transplantation*

Arterial occlusion has occurred in at least 35% of ICLUSIG® (ponatinib)-treated patients including fatal myocardial infarction, stroke, stenosis of large arterial vessels of the brain, severe peripheral vascular disease, and the need for urgent revascularization procedures.

Requires close monitoring of blood pressures, glucose and lipid panel with primary care or cardiology

PACE study: final 5-year results





- Start at 30-45 mg for first 3 months and dose reduce to 30 mg if optimal response (MCyR or better)
  - Responses appear to be durable **<u>with</u>** dose reduction
  - Lower risk of arterial events *predicted* with lower dose
- Consider dose reduction to 15 mg for MMR
- *New data:* OPTIC Study: *Ponatinib in Participants With Resistant Chronic Phase Chronic Myeloid Leukemia (CP-CML) to Characterize the Efficacy and Safety of a Range of Doses* – abstract ASCO 2020
  - Starting 45 mg dose appears to be more effective in these resistant patients

Cortes JE et al. Blood 2018;132:393-404.
Cortes JE et al. Interim analysis (IA) of OPTIC: A dose-ranging study of three ponatinib (PON) starting doses. American Society of Clinical Oncology Annual Meeting. 2020, abstract 7502

Omacetaxine: CP or AP CML after failure/intolerance to 2 TKIs

- Consider for patients:
  - With increased vascular risk
  - Non-adherent

	MCyR			CCyR[a]		
	Overall (n = 76)	Patients With >3 Cycles (n = 50)	Patients With ≥12 Cycles (n = 21)	Overall (n = 76)	Patients With >3 Cycles (n = 50)	Patients With ≥12 Cycles (n = 21)
Response rate, n (%)	14 (18)	11 (22)	6 (29)	7 (9)	6 (12)	6 (29)
All patients	5/22 (23)	3/16 (19)	2/7 (29)	3/22 (14)	2/16 (13)	2/7 (29)
Patients with T315I at baseline	10/40 (25)	7/28 (25)	4/12 (33)	5/40 (13)	4/18 (22)	4/12 (33)
Patients with 2 prior TKIs	4/36 (11)	4/22 (18)	2/9 (22)	2/36 (6)	2/22 (9)	2/9 (22)
Patients with 3 prior TKIs						

vs. ~50% in ponatinib-treated patients

Response to omacetaxine in CP CML patients receiving more than 3 or 12 cycles
Duration of response is mostly < 12 months

Cortes JE et al. Cancer. 2015 May 15;121(10):1637-44.

When to consider allogeneic stem cell transplantation

CP patients →

- ≥ 3rd line therapy
  - Typing at failure or intolerance of 2nd-line therapy, consider in some when initiating 2nd line therapy (failure of 1st line 2nd gen TKI without mutations)

Progression to AP or BC →

- HCT using alternate TKI to bridge

***de novo* AP patients** →

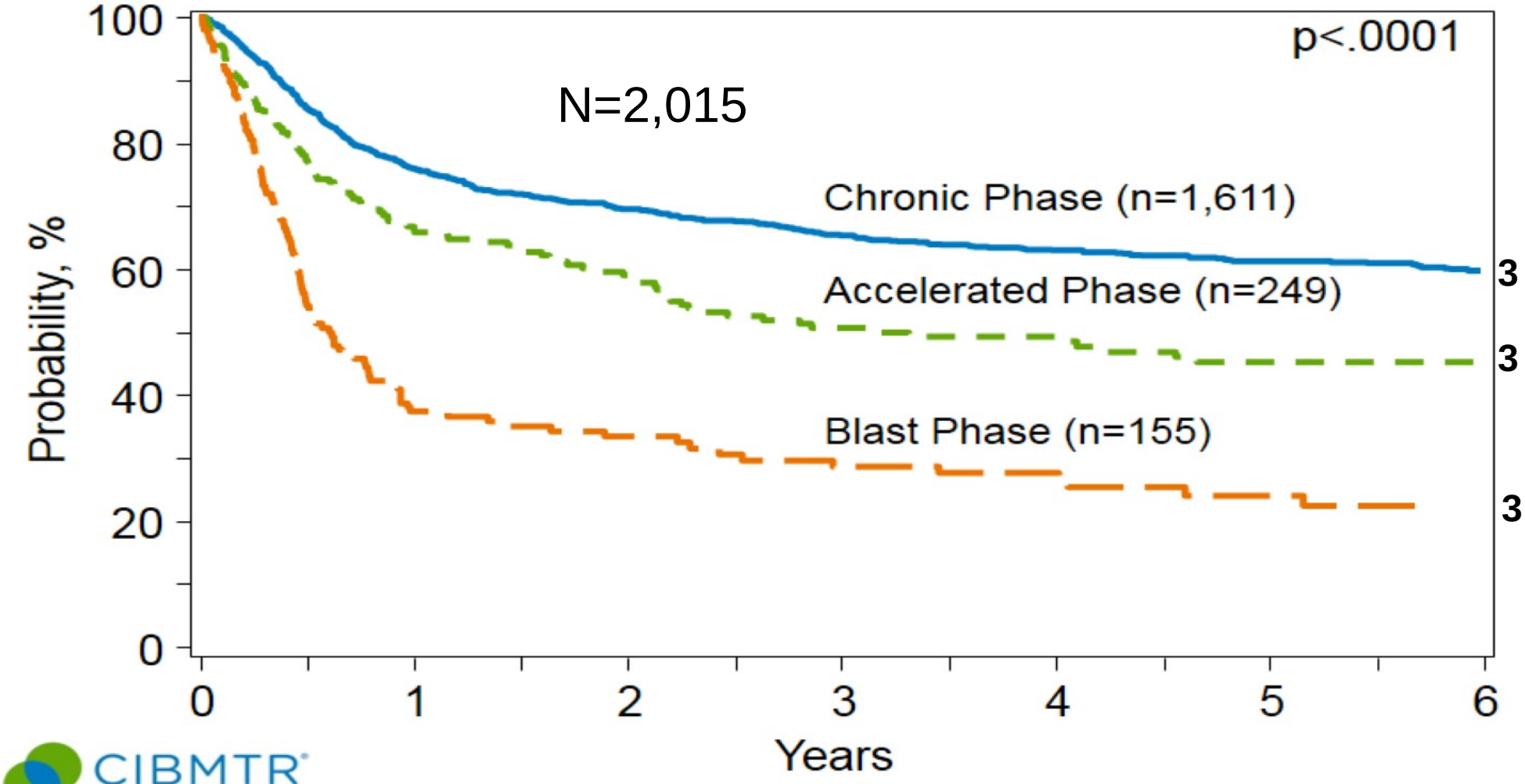
- Type patient and siblings; use first-line TKI therapy with close monitoring for optimal response as some AP patients do well. HCT in patients with worrisome ACA*; for others HCT when optimal milestones are not met.*

BP patients →

- HCT after TKI therapy +/- induction chemotherapy

Median survival is ~7-12 months with TKI-based therapy

Survival after HLA Matched Sibling HCT for CML, 2005-2015



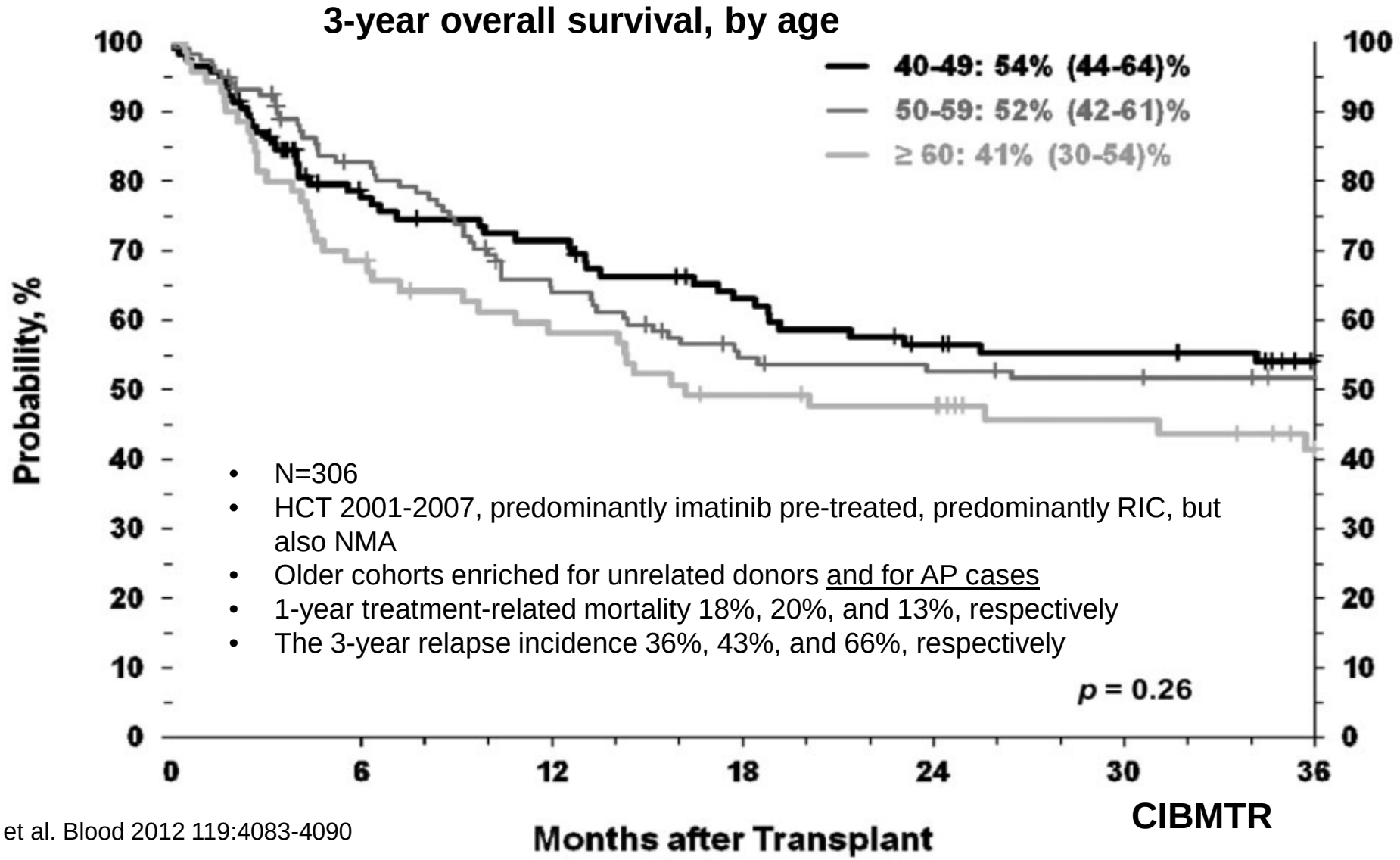
3 yr OS: 66%

3 yr OS: 51%

3 yr OS: 29%

CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Survival after reduced intensity conditioning HCT in CML



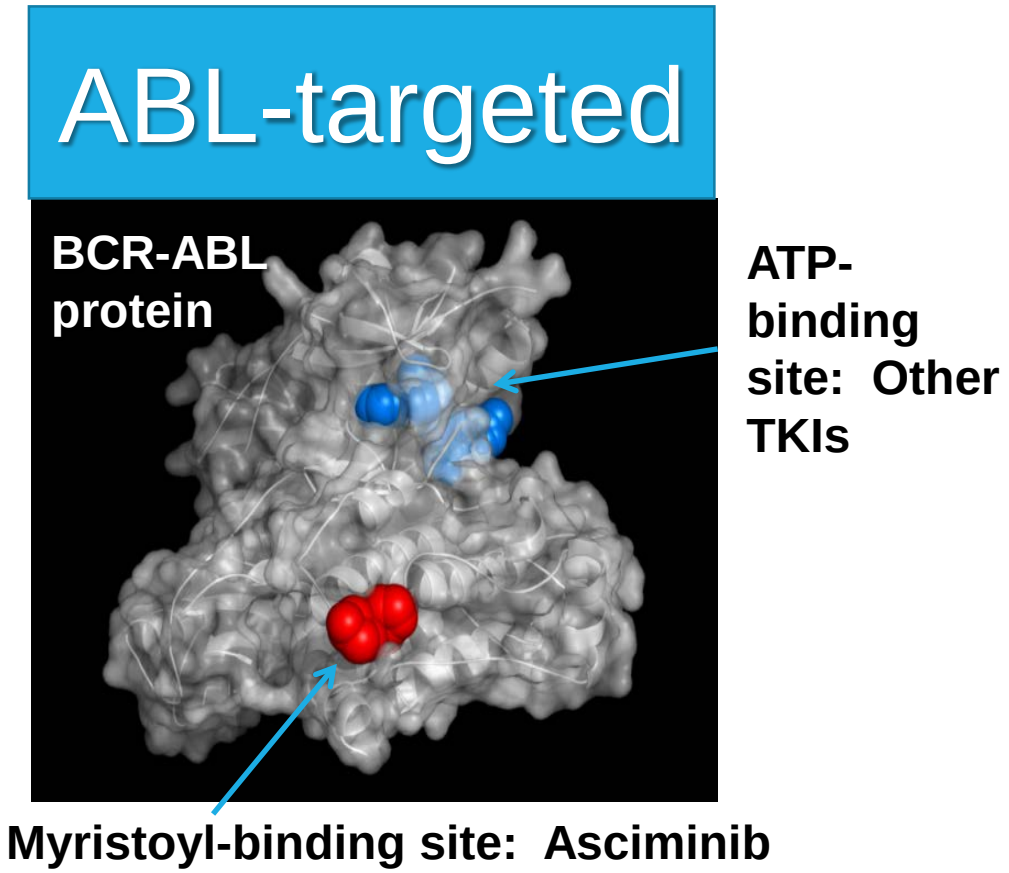
- N=306
- HCT 2001-2007, predominantly imatinib pre-treated, predominantly RIC, but also NMA
- Older cohorts enriched for unrelated donors and for AP cases
- 1-year treatment-related mortality 18%, 20%, and 13%, respectively
- The 3-year relapse incidence 36%, 43%, and 66%, respectively

Warlick E et al. Blood 2012 119:4083-4090

New therapeutic approaches

1. **Other strategies to target BCR-ABL**
2. *Targeting BCR-ABL-independent mechanisms and immune approaches*

Asciminib a potent, specific inhibitor of BCR-ABL1 with a distinct allosteric mechanism of action

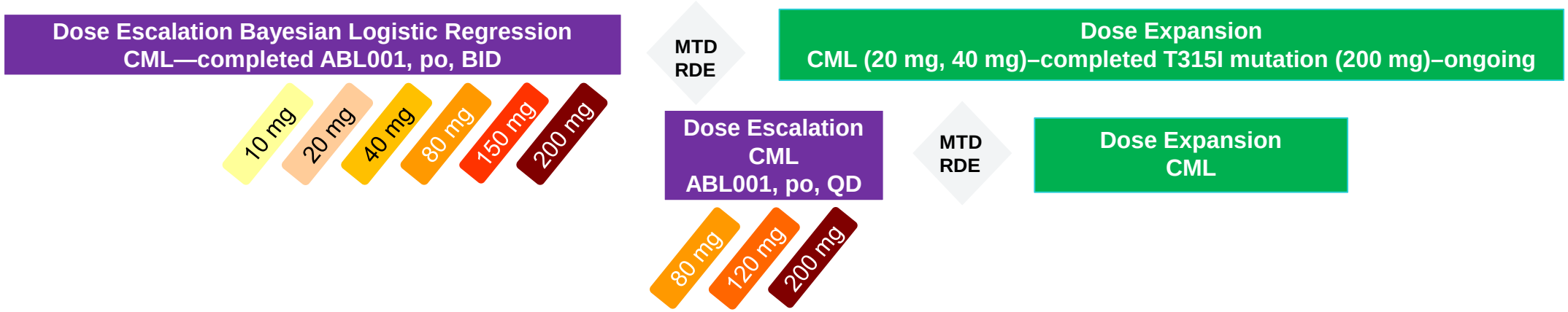


- Very high selectivity with narrow target profile
- Active against BCR-ABL1 mutations that confer resistance to TKIs
- Potential to combine with TKIs to prevent the emergence of *BCR-ABL1* mutations

TKI, tyrosine kinase inhibitor.

Hughes TP, et al. Blood 2016;128 [abstract 625].
Hughes TP et al. N Engl J Med 2019;381:2315-26.

ABL001X2101: a multicenter, phase 1, first-in-human study



- 141 CP and 9 AP patients relapsed or refractory to at least two different TKIs or who had unacceptable side effects on therapy
- Patients with a T315I mutation (33 patients) were eligible after they had received at least one TKI
- **Primary outcome:** estimation of MTD/RDE
- **Secondary outcomes:** safety, tolerability, preliminary anti-CML activity, pharmacodynamics, pharmacokinetic profile

ALL: Acute lymphocytic leukemia; BID: Twice daily; BP: Blast phase; CML: Chronic myeloid leukemia; MTD: Maximum tolerated dose; Ph+: Philadelphia chromosome–positive; po: Peroral; QD: Once daily; RDE: Recommended dose for expansion.
CABL001X2101 study protocol.

Response in CP CML patients without T315I in Phase I Asciminib Trial

Variable - NO T315I	Overall (N=113)
Median follow up (week, range)	72 (0.1-167)
Patients remaining on study N (%)	88 (78%)
CHR, N (%) evaluable	34/37 (92%)
MCyR, N(%) evaluable	85/110 (77%)
CCyR, N (%) evaluable	77/110 (70%)
MMR, N (%)	
In all patients	
By 6 mo	37/99 (37%)
By 12 mo	44/91 (48%)
In patients with 2 or fewer TKI	
By 6 mo	13/25 (53%)
By 12 mo	15/25 (60%)
In patients with more than 2 TKI	
By 6 mo	24/74 (32%)
By 12 mo	29/66 (33%)

Prior TKI	%
1 prior TKI	**2**
2 prior TKIs	**27**
≥ 3 prior TKIs	**72**

Adverse events related to study drug

- Most common all grade AEs
  - Fatigue, headache, increased lipase, nausea, arthralgias, diarrhea, rash, thrombocytopenia
- Most common grade 3/4 AEs
  - Increased lipase, hypertension and thrombocytopenia

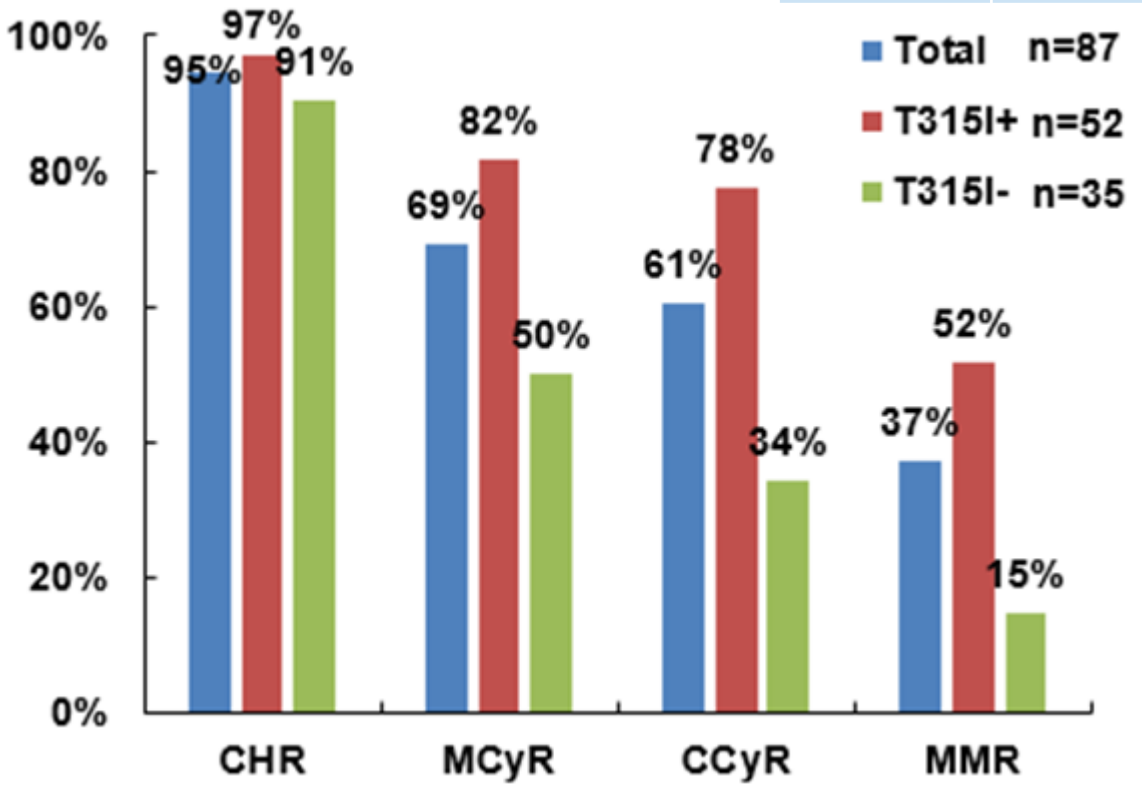
Hughes, Mauro et al N Engl J Med 2019;381:2315-26.

HQP1351 a TKI WITH efficacy against T315I

- 101 CML patients
  - 87 CP patients and 14 AP patients
  - The 18-month progression free survival (PFS) rate was 94% in CP and 61% in AP
- The most common non-hematologic adverse events were hypertriglyceridemia, transaminitis, proteinuria, hyperbilirubinemia
- The most common hematologic treatment-related adverse event that was Grade 3/4 was thrombocytopenia (50%)

Prior TKI	N (%)
1	12 (14)
2	47 (54)
3 or more	28 (32)

Responses in CP patients



Ren et al. J Med Chem. 2013 Feb 14;56(3):879-94
Liu et al. Cell Biosci. 2019 Oct 26;9:88

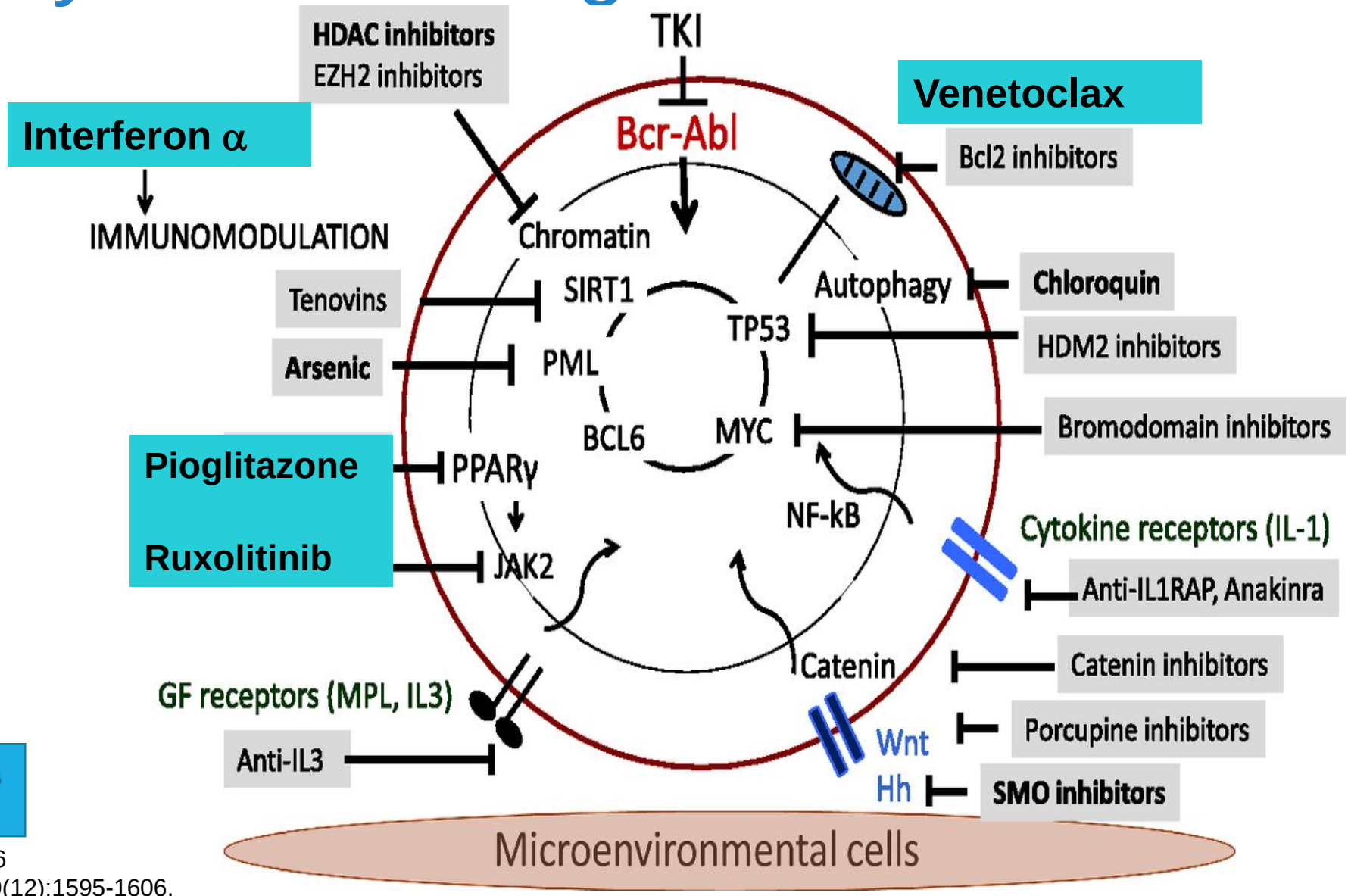
Turkina et al. American Society of Hematology Meeting 2018. Blood (2018) 132 (Supplement 1): 790.
Jiang et al. American Society of Hematology Meeting 2019. Abstract 493.

Other pathways contributing to CML

Targeting BCR-ABL-independent mechanisms to:

1. Combat resistance
2. Eradicate CML stem cells
3. Promote deep response and improve TFR rates
4. Treat advanced disease

Inteferon, JAKi, and PPARγ agonists also likely impact immune function



Massimino et al. Mol Cancer. 2018 Feb 19;17(1):56
Holyoake TL and Vetrie D. Blood. 2017 Mar 23;129(12):1595-1606.
Bhatia R. Hematology Am Soc Hematol Educ Program. 2017 Dec 8;2017(1):115-120

Clinical Trials at Fred Hutch/SCCA for CML:

1. Phase 1b Study of PK, safety and efficacy of orally administered HQP1351 (TKI, Ascentage)
2. BMS: Studying vascular events on TKIs prospectively
3. Treatment Free Remission After Combination Therapy With Ruxolitinib Plus Tyrosine Kinase Inhibitors
4. Pending: 2nd TKI stop
5. In development: asciminib first-line

Research studies:

1. Chemogenomic profiing of CML progenitor cells *in vitro* to various TKIs and other agents to identify biomarkers of clinical response and toxicity

voehler@uw.edu

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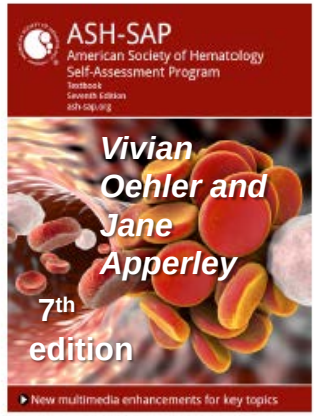


H. JEAN KHOURY CURE CML CONSORTIUM

We are a group of researchers from 17 world-class academic medical centers throughout North America committed to curing CML through innovative research. With feedback from advocates and patients, we strive to meet the needs of the CML community.

Fred Hutchinson Cancer Research Center
Huntsman Cancer Institute
H. Lee Moffitt Cancer Center & Research Institute
Medical College of Wisconsin
MD Anderson Cancer Center
Oregon Health & Science University
John Theurer Cancer Center at Hackensack University
Winship Cancer Institute of Emory University

www.curecml.org

'Galvanized by the spectacular collaboration created by the LAST study, the creation of a CML consortium was simply the next logical thing to do' -H. Jean Khoury

University of Chicago Comprehensive Cancer Center
Princess Margaret Cancer Centre
Memorial Sloan Kettering Cancer Center
Duke Cancer Institute
Weill Medical College of Cornell University
Barbara Ann Karmanos Cancer Institute
UCSF Helen Diller Family Comprehensive Cancer Center
Roswell Park Cancer Institute
Dana-Farber Cancer Institute

Extra slides

Helpful reviews and recommendations European LeukemiaNet

REVIEW

European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia

JL Steegmann[1], M Baccarani[2], M Breccia[3], LF Casado[4], V García-Gutiérrez[5], A Hochhaus[6], D-W Kim[7], TD Kim[8], HJ Khoury[9], P Le Coutre[8], J Mayer[10], D Milojkovic[11], K Porkka[12,13], D Rea[14], G Rosti[2], S Saussele[15], R Hehlmann[16] and RE Clark[17]

Leukemia (2016), 1–24

www.nature.com/leu

Most reports on chronic myeloid leukaemia (CML) treatment with tyrosine kinase inhibitors (TKIs) focus on efficacy, particularly on molecular response and outcome. In contrast, adverse events (AEs) are often reported as infrequent, minor, tolerable and manageable, but they are increasingly important as therapy is potentially lifelong and multiple TKIs are available. For this reason, the European LeukemiaNet panel for CML management recommendations presents an exhaustive and critical summary of AEs emerging during CML treatment, to assist their understanding, management and prevention. There are five major conclusions. First, the main purpose of CML treatment is the antileukemic effect. Suboptimal management of AEs must not compromise this first objective. Second, most patients will have AEs, usually early, mostly mild to moderate, and which will resolve spontaneously or are easily controlled by simple means. Third, reduction or interruption of treatment must only be done if optimal management of the AE cannot be accomplished in other ways, and frequent monitoring is needed to detect resolution of the AE as early as possible. Fourth, attention must be given to comorbidities and drug interactions, and to new events unrelated to TKIs that are inevitable during such a prolonged treatment. Fifth, some TKI-related AEs have emerged which were not predicted or detected in earlier studies, maybe because of suboptimal attention to or absence from the preclinical data. Overall, imatinib has demonstrated a good long-term safety profile, though recent findings suggest underestimation of symptom severity by physicians. Second and third generation TKIs have shown higher response rates, but have been associated with unexpected problems, some of which could be irreversible. We hope these recommendations will help to minimise adverse events, and we believe that an optimal management of them will be rewarded by better TKI compliance and thus better CML outcomes, together with better quality of life.

European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia

A. Hochhaus[1] · M. Baccarani[2] · R. T. Silver[3] · C. Schiffer[4] · J. F. Apperley[5] · F. Cervantes[6] · R. E. Clark[7] · J. E. Cortes[8] · M. W. Deininger[9] · F. Guilhot[10] · H. Hjorth-Hansen[11] · T. P. Hughes[12] · J. J. W. M. Janssen[13] · H. M. Kantarjian[14] · D. W. Kim[15] · R. A. Larson[16] · J. H. Lipton[17] · F. X. Mahon[18] · J. Mayer[19] · F. Nicolini[20] · D. Niederwieser[21] · F. Pane[22] · J. P. Radich[23] · D. Rea[24] · J. Richter[25] · G. Rosti[2] · P. Rousselot[26] · G. Saglio[27] · S. Saußele[28] · S. Soverini[2] · J. L. Steegmann[29] · A. Turkina[30] · A. Zaritskey[31] · R. Hehlmann[28,32]

Abstract

The therapeutic landscape of chronic myeloid leukemia (CML) has profoundly changed over the past 7 years. Most patients with chronic phase (CP) now have a normal life expectancy. Another goal is achieving a stable deep molecular response (DMR) and discontinuing medication for treatment-free remission (TFR). The European LeukemiaNet convened an expert panel to critically evaluate and update the evidence to achieve these goals since its previous recommendations. First-line treatment is a tyrosine kinase inhibitor (TKI; imatinib brand or generic, dasatinib, nilotinib, and bosutinib are available first-line). Generic imatinib is the cost-effective initial treatment in CP. Various contraindications and side-effects of all TKIs should be considered. Patient risk status at diagnosis should be assessed with the new EUTOS long-term survival (ELTS)-score. Monitoring of response should be done by quantitative polymerase chain reaction whenever possible. A change of treatment is recommended when intolerance cannot be ameliorated or when molecular milestones are not reached. Greater than 10% BCR-ABL1 at 3 months indicates treatment failure when confirmed. Allogeneic transplantation continues to be a therapeutic option particularly for advanced phase CML. TKI treatment should be withheld during pregnancy. Treatment discontinuation may be considered in patients with durable DMR with the goal of achieving TFR.

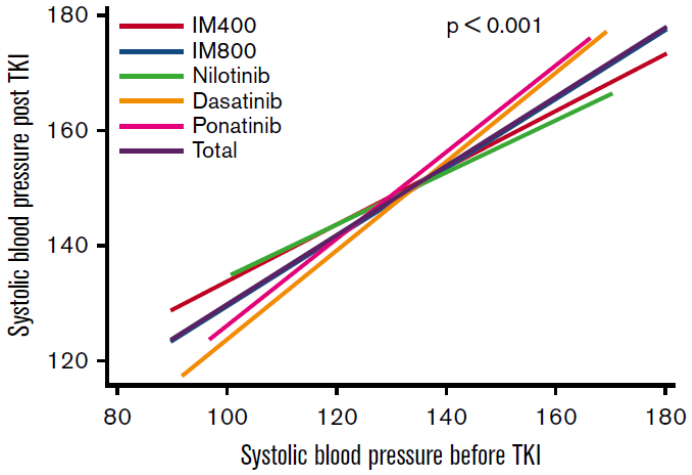
Leukemia (2020) 34:966–984
https://doi.org/10.1038/s41375-020-0776-2

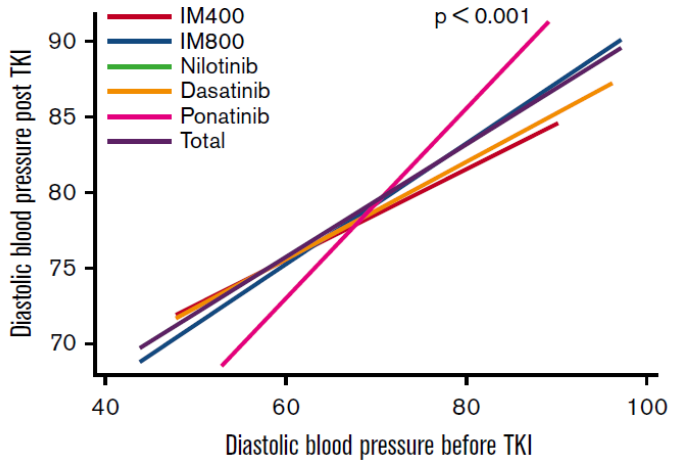
REVIEW ARTICLE

Primer of (some) CML clinical trials

- **IRIS:** Phase 3, front-line imatinib vs. Interferon-α and cytarabine CP CML
- **ENESTnd:** Phase 3, front-line nilotinib vs. imatinib CP CML
- ***ENESTFreedom:*** *Stopping first-line nilotinib*
- ***ENESTop:*** *Stopping second-line nilotinib*
- **DASISION:** Phase 3, front-line dasatinib vs. imatinib CP CML
- **DASFREE:** Stopping dasatinib
- ***BFORE:*** *Phase 3, front-line bosutinib vs. imatinib CP CML*
- **German CML-Study IV:** five-arm randomized trial CP CML comparing first-line imatinib treatment with different dosages and with or without additional non-TKI therapy
  - including - imatinib (400), imatinib (800), imatinib/ara-C, imatinib/interferon
- ***DESTINY:*** *Phase 2 study de-escalating followed by stopping imatinib, nilotinib, and dasatinib*
- **PACE:** ponatinib once daily in CML or Ph+ ALL patients with resistance or intolerance to dasatinib or nilotinib, or with the *BCR-ABL1* T315I mutation.
- **EPIC:** front-line ponatinib vs. imatinib CP CML

Cardiovascular and arteriothrombotic adverse events after frontline TKIs





NCT03045120: Determining Change in Cardiovascular and Metabolic Risks in Patients With Chronic Phase Chronic Myeloid Leukemia Receiving BCR-ABL Tyrosine Kinase Inhibitor First-Line Therapy in the United States

- Retrospective study of 531 patients treated with frontline TKIs in different prospective trials
- Hypertension was the most common AE seen across all TKIs
  - 175 patients (33%)
    - grade 3/4 in 17%
- Incidence and the risk of CV-AEs and AT-AEs is significantly increased in patients
  - taking second- and third-generation TKIs, and
  - with preexisting cardiovascular risk factors

Jain P et al. Blood Adv. 2019 Mar 26;3(6):851-861
Haguet H et al. Expert Opin Drug Saf. 2017;16(1):5-12

What to know for the Boards (1)

1. Know when to declare failure, how to assess for resistance, and select next-line therapy

2. Recognize that mutation profile is needed to select appropriate next-line therapy
   - T315I (ponatinib, omacetaxine, or transplant)
   - V299L (nilotinib is good choice)

3. Interferon can be used during 2nd and 3rd trimester
   - TKIs cause birth defects (omphalocele)

http://www.cdc.gov/ncbddd/birthdefects/omphalocele.html
Centers for Disease Control and Prevention, National Center on Birth Defects and Developmental Disabilities

What to know for the Boards (2)

Know expected/important/bad side effects

- Helps you select best therapy for a particular patient
- Early recognition AND intervention will enhance compliance and ultimately impact response

- Pleural and pericardial effusion and dasatinib
- Pulmonary hypertension and dasatinib
- Glucose intolerance and nilotinib
- Liver function test abnormalities and nilotinib and bosutinib
- Diarrhea and bosutinib (usually first 1-2 months)
- Increased vascular events (arterial – CAD, PAD, stroke)
  - Ponatinib ~27-34%
  - Nilotinib – increased, ~ 10-20%
- QTc monitoring
  - Nilotinib: weekly ECG X 3 as strongest effect on QT prolongation, keep potassium and magnesium WNL

Comparison of TKI efficacy in 3 registration phase 3 studies compared with imatinib (*note can not be compared directly)*

Endpoint	Nilotinib (300)	Imatinib	Dasatinib	Imatinib	Bosutinib	Imatinib
	ENESTnd		DASISION		BFORE	
CCyR by 12 months	80	65	85	73	77	66
CCyR by 24 months	87	77	86	82		
MMR by 12 months	53	27	46	28	47	36
MMR by 24 months	69	44	64	46		
MR4.5 by 24 months	23	10	17	8		
Transformation	2.6	6.7	3.5	5.8	1.6	2.5
Death	*3.7*	*6*	*6*	*5*	*0*	*4*
Overall survival	*95.1**	*94**	*95.3***	*95.2***	*99.6****	*97.9****

*Median f/u 36 mo, ** Median f/u 24 mo, *** Median f/u 12 mo

Manage toxicities aggressively: Common adverse events on IRIS, DASISION, ENESTnd and BFORE first-line trials

Grade	All (%)	3 /4 (%)	All %	3 /4 (%)	All %	3 / 4(%)	All %	3 / 4(%)
	imatinib 400 mg QD (n=551)		dasatinib 100 mg QD (n=258)		nilotinib 300 mg BID (n=279)		bosutinib 400 mg QD (n=268)	
Rash	34	2	11	0	31	<1	19.8	0.4
Headache	31	<1	12	0	14	1	18.7	1.1
Nausea	44	<1	8	0	11	<1	35.1	0
Alopecia	4	0			8	0		
Pruritus	7	<1			15	<1		
Myalgia	21	1.5	6	0	10	<1	3	0.4
Fatigue	35	1	8	<1	11	0	19.4	0.4
Vomiting	17	1.5	5	0	5	0	17.9	1.1
Diarrhea	33	2	17	<1	8	1	70.1	7.8
Musculoskeletal Pain	37	3	11	0			29.5	1.9
Muscle Spasm	38	1			7	0	2.2	0
Peripheral Edema	55	1	14	1	5	0	4.1	<1
Eyelid Edema					1	0		
Periorbital Edema					<1	0	1.5	0
Pleural Effusion			10	0			1.9	
Hematologic								
Neutropenia	61	14	65	21	43	12	11.2	6.7
Thrombocytopenia	57	8	70	19	48	10	35.1	13.8
Anemia	45	3	90	10	38	3	18.7	3.4

Rash: anti-histamines, steroid creams, systemic steroids (rarely)

Diarrhea: immodium
Edema: lasix

Pleural effusion: lasix, steroids, thoracentesis

Grade 3/4 : hold drugs, see NCCN, can reintroduce at same dose or if repeat event lower dose. Consider switch for severe toxicities

For hematologic toxicity as marrow recovers and CML disappears typically can slowly push drug dose to therapeutic range

Summary of common toxicities on tyrosine kinase inhibitor therapy extracted from the IRIS, DASISION, ENESTnd and BFORE first-line trials

	imatinib 400 mg QD (n=551)		dasatinib 100 mg QD (n=258)		nilotinib 300 mg BID (n=279)		bosutinib 400 mg QD (n=268)	
Grade	All (%)	3 /4 (%)	All %	3 /4 (%)	All %	3 / 4(%)	All %	3 / 4(%)
Labs								
Increased total bilirubin					53	4		
Increased alkaline phosphatase					21	0		
Decreased phosphate					32	5	43.7	4.5
Increased glucose					36	6	46.3	2.2
Increased lipase					24	6	39.6	13.1
Increased amylase					15	<1	25	2.2
Increase creatinine					5	0		0
Increased ALT	43	5			66	4	63.4	23.1
Increased AST					40	1	49.3	11.9

Mechanisms of resistance

Primary resistance: *no initial response*

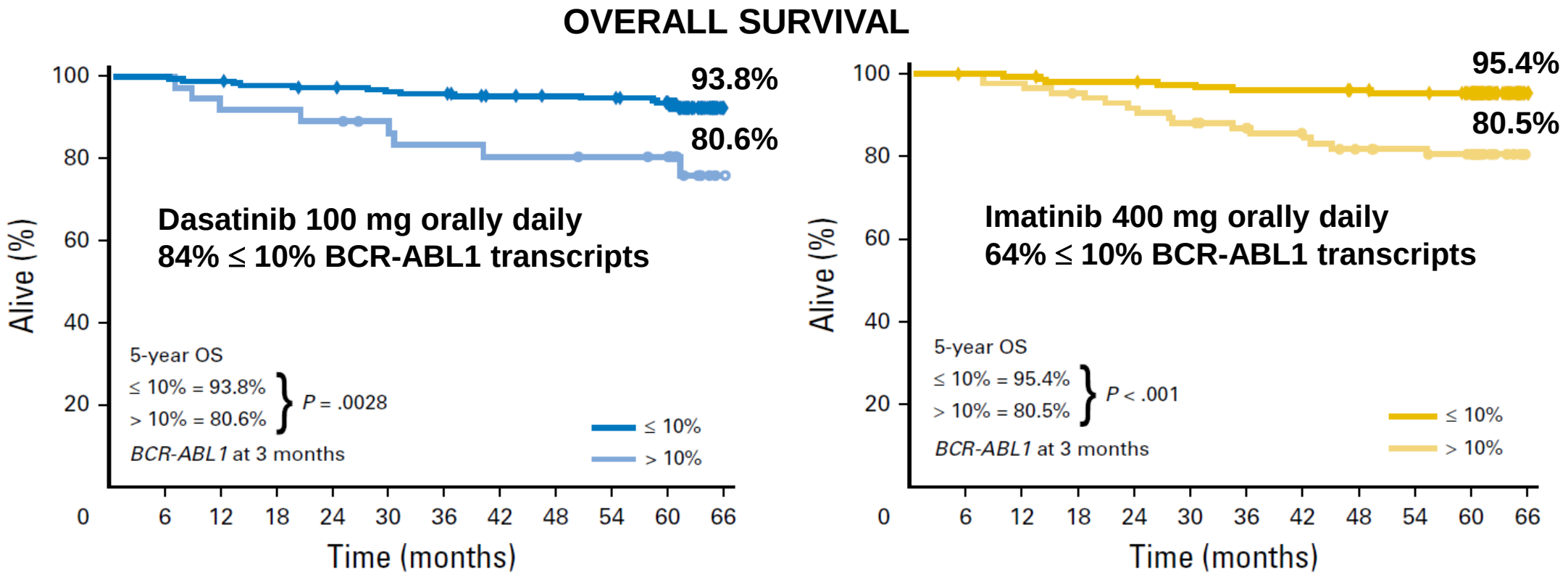
- Insufficient inhibition of Bcr-Abl
  - Low hOCT (OCT1) activity (imatinib)
- BCR-ABL–independent mechanisms
- ABL tyrosine kinase domain (TKD) mutations

Acquired (secondary) resistance: after a response

- ABL TKD mutations (common, *but many DO NOT have*)
- BCR-ABL–independent mechanisms

1. Eide CA, O'Hare T. *Curr Hematol Malig Rep*. 2015;10:158-166.

Early molecular response and outcomes



- Similar results across various studies: ~10-15% difference in OS or PFS
- Impact on outcomes is similar for 1st and 2nd generation TKIs
- However, absence of EMR may be a marker of poor adherence and not only of poor biology

Hanfstein B, et al. *Leuk* . 2012; 26:2096
Marin D, et al. *J Clin Oncol*. 2012;30(3):232
Cortes JE et al. J Clin Oncol. 2016; 34: 2333
Hochhaus A et al. Leukemia. 2016; 30: 1044

Summary of TKI discontinuation trials and retrospective series

Consistent TFR rate across studies (mostly of patients stopping first-line therapy)

Table 1. Summary of TKI discontinuation trials and retrospective series

Study	# Pts	1st-line TKI	2nd-line/ consolidation TKI	Median duration TKI (years)	Stable DMR at STOP	Median duration DMR (years)	Retreatment criteria	Follow-up (years)	Time TFR (years)	Rate TFR (%)
A-STIM [6]	80	I (100%)		6.58	UMRD	3.42	> MMR	2.58	2	64
DADI [7]	63	I (100%)	D (100%)	6.83	0.0069%^{IS}	NR	> 0.0069%^{IS}	1.67	1	48
DASFREE [23]	84	I (85%),D	D (100%)	5.91	MR4.5	NR	> MMR	NR	1	49
Destiny* [15, 29]	117	I (84%), D (8%), N (4%)		6.80	MR4.0*	NR	> MMR	NR	2	77
D-STOP [19]	54	I (61%), D (39%)	D (100%)	7.66	UMRD	4.25	> MR4.0	1.5	1	62.9
ENESTfreedom [22]	190	N (100%)	N (100%)	3.58	MR4.5	2.52	> MMR	NR	1.85	48.9
ENESTop [16]	126	I (100%)	N (100%)	7.3	MR4.5	3.65	> MR4 × 2, > MMR × 1	1.9	1.85	53.2
Euro-Ski [21]	750	I (94%), N/D	15% D/N/I	7.58	MR4.0	2.98	> MMR	0.83	2	51
Ginema [26]	293	I (72%), N (20%), D (8%)		6.42	MR4.0	3.83	Variable	2.83	1	68
Hovon [12]	15	I (100%)		8.17	MR4.5	NR	> 1 log/> MMR	3.6	2	33
ISAV [9]	112	I (100%)		8.59	UMRD	2.14	> UMRD ×2, > MMR	1.8	3	51.9
Japan [28]	43	I (100%)		3.77	UMRD	2.28	> MMR × 2	1.87	5	47
Keio [20]	53	I (91%), N (8%), D (1%)		8.16	UMRD	3.17	> 100 copies *BCRABL*	NR	2	52.8
KID [8]	90	I (100%)		6.73	UMRD	3.32	> MMR × 2	2.22	2	58.5
Korea [27]	24	I (67%), D (21%), B (12%)		6.42	UMRD	4.16	> MMR	3.04	2	59.7
LAST [14]	173	I (60%), N (23%), D (15%), B (2%)		6.58	MR4.0	NR	> MMR	1.025	1	60
MDA** [25]	27	I (77%), D (11%), N (6%), B (6%)		8.0	UMRD	5.25	> UMRD	1.33	1.5	59
NILst [17]	87	I/N	N (100%)	8.6	MR4.5	2–12 Y	> MR4.5 × 2	1.11	1	58.9
STAT2*** [24]	73	I/N	N (100%)	8.52	MR4.5	2$^{\&}$, 2.58$^{\&\&}$	> MR4.5 × 2	NR	1	67.9
STIM1 [4]	100	I (100%)		4.9	UMRD	3.03	> UMRD × 2, > MMR	6.42	5	38
STIM123 [11]	68	I (100%)		8.125	MR4.5	4.5	> MMR	NR	1	67.6
STIM-Pilot [5]	12	I (100%)		3.75	UMRD	2.67	> UMRD × 2	1.5	1.5	50
STOP 2G-TKI [10]	60	D/N 1stL 13.3%, 2ndL 66.7%, 3rdL 20%		6.3	UMRD	2.42	> MMR	3.92	4	53.6
TRAD [18]	123	I (100%)		9.16	MR4.5	NR	> MR4 × 2, > MMR	NR	1	57.5
Twister [13]	40	I (100%)		5.92	UMRD	2.5	> UMRD × 2, > MMR	3.5	2	47.1

 # Pts number of patients, *TKI* tyrosine kinase inhibitor, *DMR* deep molecular response, *TFR* treatment-free remission, *I* imatinib, *D* dasatinib, *N* nilotinib, *B* bosutinib, *UMRD* undetectable molecular residual disease, *MR* molecular response, *MMR* major molecular response, *IS* international standard, *NR* not reported

*MR4 subgroup

**UMDR subgroup

***Median duration TFR from weighted average of SG1$^{\&}$ and SG2$^{\&\&}$ patient groups

Laneuville P. Curr. Treat. Options in Oncol. (2018) 19: 15

Claudiani et al. Haematologica September 2019 : haematol.2019.234179; Doi:10.3324

National Comprehensive Cancer Network (NCCN) recommendations on TKI cessation

1. Age ≥ 18 years
2. CP CML. No prior h/o AP or BP
3. On TKI therapy for at least 3 years
4. Documentation of quantifiable *BCR-ABL1* transcript
5. Stable deep molecular response (MR 4 or better, ≤ 0.01% on at least 4 tests (at least 3 months apart) for ≥ 2 years.
6. Access to a reliable QPCR test with a sensitivity of detection of at least MR4.5 (*BCR-ABL1* ≤ 0.0032% and provides results within 2 weeks.
7. Monthly monitoring for the first 6 months, then every 2 months during months 7-12 and then every 3 months indefinitely if MMR is maintained
8. Discuss with CML Specialty Center to review the appropriateness for TKI discontinuation
9. Resumption of TKI within 4 weeks for loss of MMR with monitoring monthly until MMR is re-established, and then every 3 months

NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Chronic Myeloid Leukemia. Version 1.2020

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

CNS CANCERS

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Disclosures

None

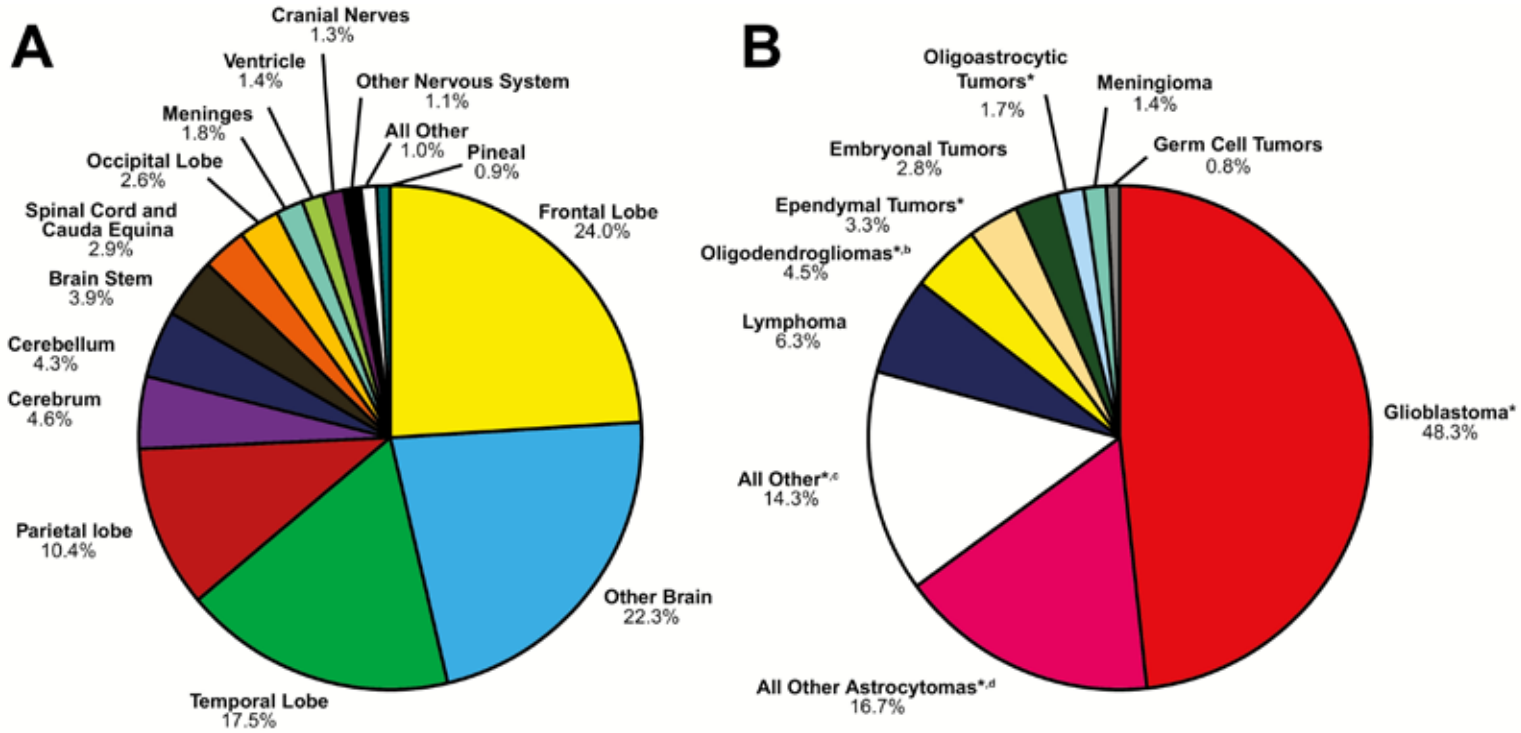
I **will** be discussion some investigational or off-label use of products during this presentation.

Outline

- Epidemiology
- Classification of Glioma
- General Management of gliomas
- Glioblastoma
- Other Glioma
- Meningioma
- Primary CNS Lymphoma
- Brain Metastases
- Leptomeningeal Metastases

Epidemiology of Brain Tumors

- Most common non- malignant CNS tumor: Meningioma (7.33/100,000)
- Most common malignant CNS tumor: Glioblastoma (3.19/100,000)
- Around 13,000 deaths/year
- 1.3% of all adult malignancies



Distribution of malignant brain tumors- CBTRUS 2019

Epidemiology of Brain Tumors-Risk Factors

- NF1, Li-Fraumeni, Lynch, tuberous sclerosis, prior radiation therapy (TBI/CSI for ALL in childhood lead to multiple meningiomas in adulthood)
- NO DEFINITIVE EVIDENCE WITH CELLPHONES/ BLUETOOTH

- NF1 diagnostic criteria:
  - Family history of NF1
  - Six or more cafe-au-lait skin lesions 5 mm or larger in pre-pubertal individuals, or 15 mm or larger in post-pubertal individuals
  - Presence of two or more neurofibromas of any type, or one or more plexiform neurofibromas
  - Axillary Freckling
  - Two or more Lisch nodules (pigmented lesions in the iris) .
  - Dysplasia of the sphenoid bone or dysplasia of long bones, often in the lower leg
  - Optic glioma

Classification of Glioma

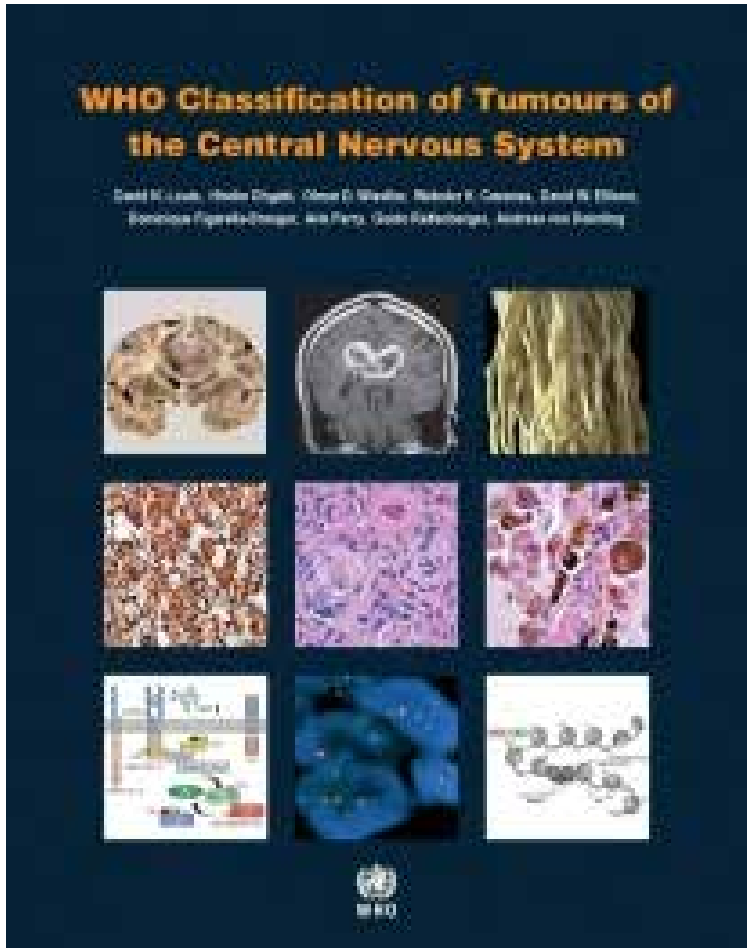
General Schema

Layer 1	**Final Integrated Diagnosis**
Layer 2	Histologic Classification
Layer 3	WHO Grade
Layer 4	Molecular Information

Specific Example

Layer 1	**Anaplastic oligodendroglioma**
Layer 2	Infiltrating glioma with oligodendroglial features by microscopy
Layer 3	WHO Grade III
Layer 4	Isocitrate dehydrogenase 1 mutation Whole-arm loss of both 1p and 19q

Figure 1. Layered diagnosis of CNS tumors. Integrated diagnosis (layer 1) comes last, only after layers 2–4 are defined. WHO grading criteria (layer 3) and relevant molecular information (layer 4) are separately defined for different histologic tumor types.



Classification of Glioma

Glioblastoma: WHO Grade IV

Histology: Marked nuclear atypia, high mitotic activity, vascular proliferation, necrosis

Molecular features: TERT promoter mutation, EGFR amplification (EGFRvIII), PTEN alterations, ?BRAF mutations

Molecular features more important than histology features

MOLECULAR GBM: *EGFR* amplification; losses of chromosome 10 (whole chromosome, 10p or 10q); gains of chromosome 7 (whole chromosome, 7p or 7q); *TERT* promoter mutations; homozygous deletion of *CDKN2A/B*

Classification of Glioma

WHO Grade I: Pilocytic astrocytoma (BRAF/KIAA fusion), Common in children, Cured by gross total resection.

WHO Grade II: aka “Low-grade glioma” diffuse Astrocytoma, diffuse oligodendroglioma, pilocytic xanthoastrocytoma (PXA) [low/no mitotic activity, no necrosis, no vascular proliferation]

WHO Grade III: Anaplastic astrocytoma, anaplastic oligodendroglioma, anaplastic PXA

[high mitotic activity (>10/hpf), no necrosis, no vascular proliferation]

Classification of Glioma-Molecular features

IDH mutation

- Present in >85% of low-grade glioma
- 5% of glioblastoma
- R132H point mutation
- Favorable prognosis
- Test by IHC for >55 years of age
- Less than 55 check PCR even if IHC negative

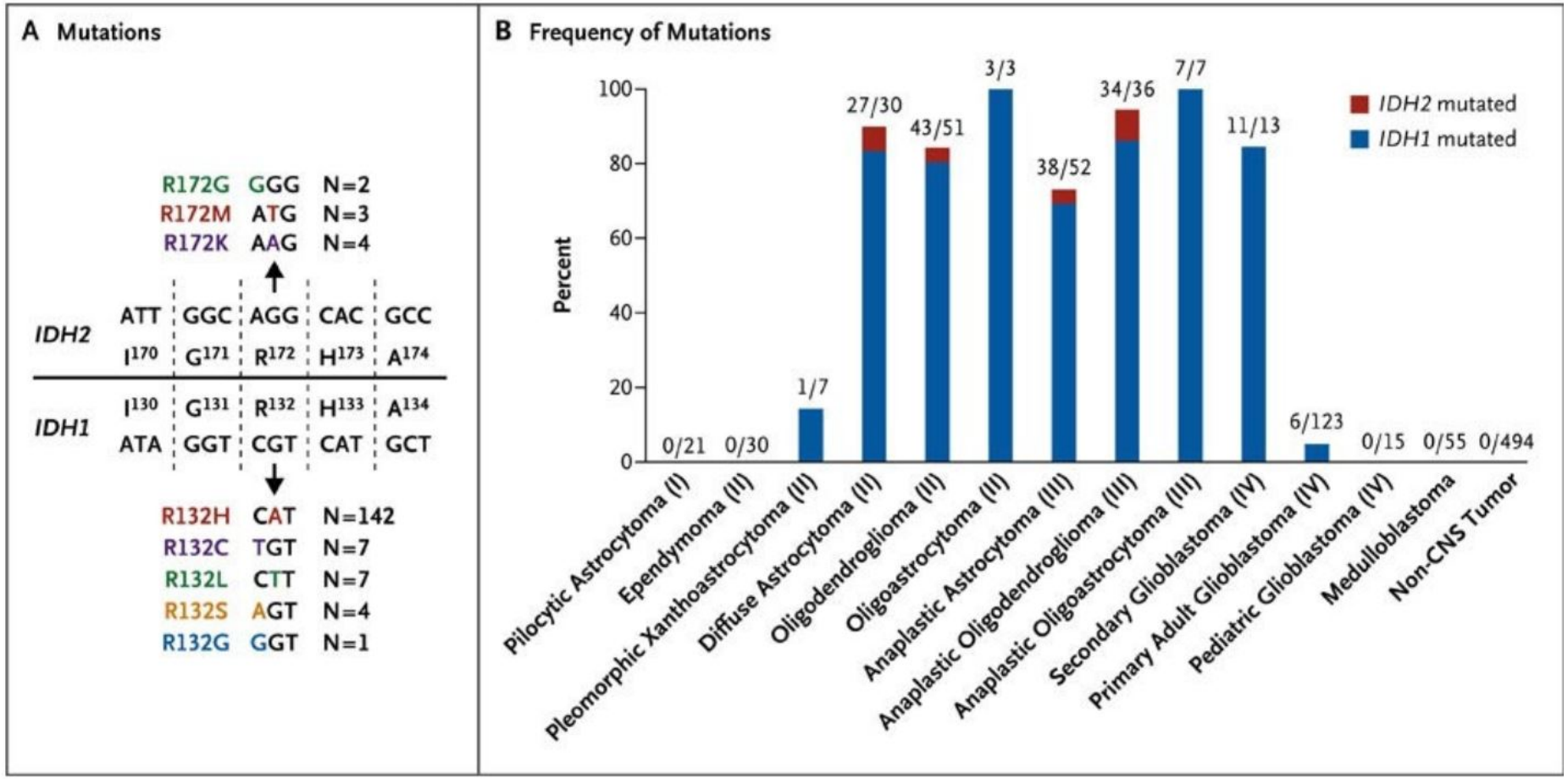
1p/19q co-deletion

- Diagnostic feature for oligodendroglioma
- Favorable prognosis
- FISH test

BRAF mutation (V600E)

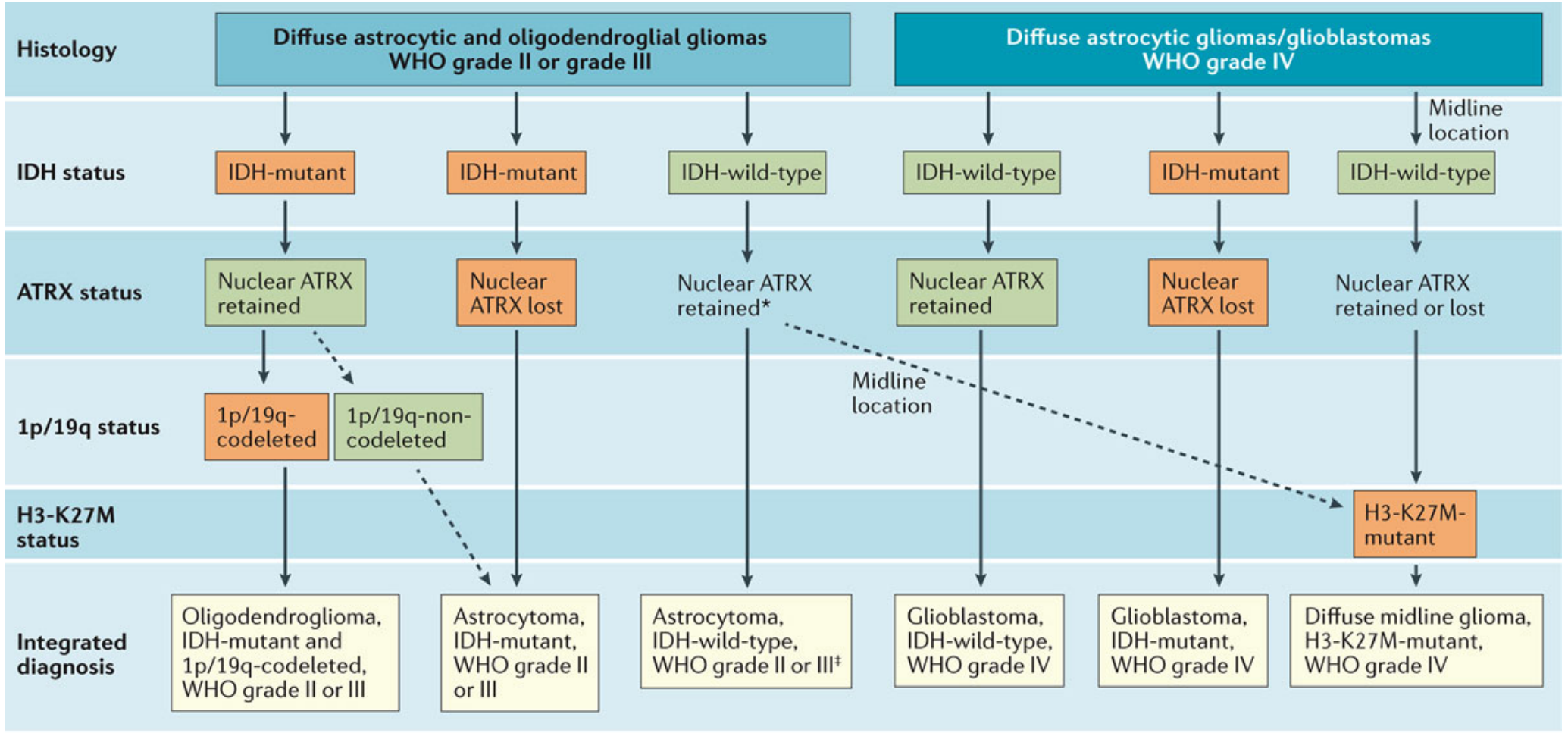
- PXA (grade II and III)
- Craniopharyngioma- papillary variant

IDH mutation



N Engl J Med 2009; 360:765-773

Classification of Glioma



Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2016.204

General guidelines- Glioma

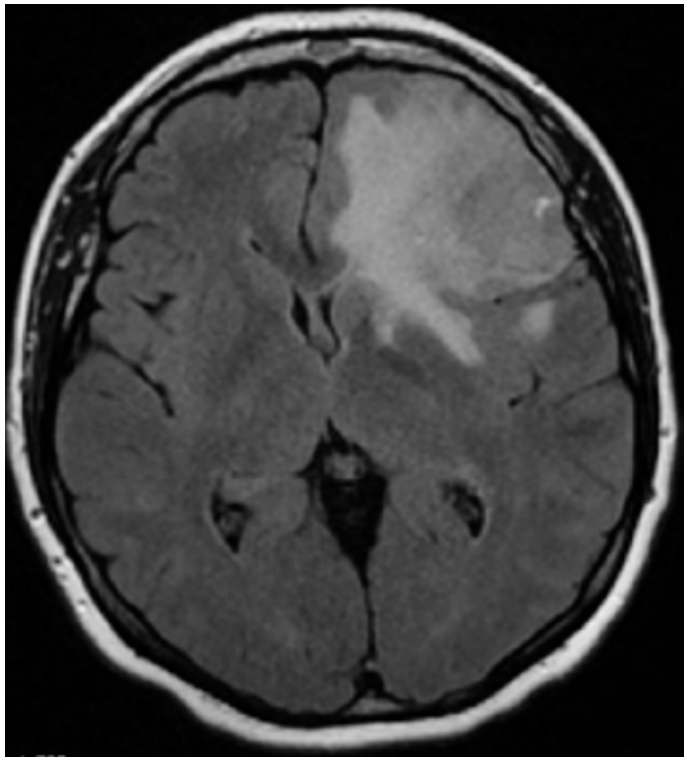
- Presentation: Focal neurologic symptoms, seizures, diffuse neuro symptoms
- Imaging of choice: MRI brain w/wo contrast
- No need for systemic imaging
- Surgery: “When tumor is the rumor, tissue is the issue”, debulking, symptom management, gross total resection has better prognosis
- Steroids: Dexamethasone is the steroid of choice. Use the lowest dose.

  Watch for hyperglycemia, insomnia, mania, PJP prophylaxis with prolong use, negative prognostic factor if prolong use necessary
- Seizure management: Non enzyme inducers like levetiracetam, lacosamide, zonisamide
- DVT/PE: ⇧frequency. Anticoagulation not contraindicated. LMWH preferred

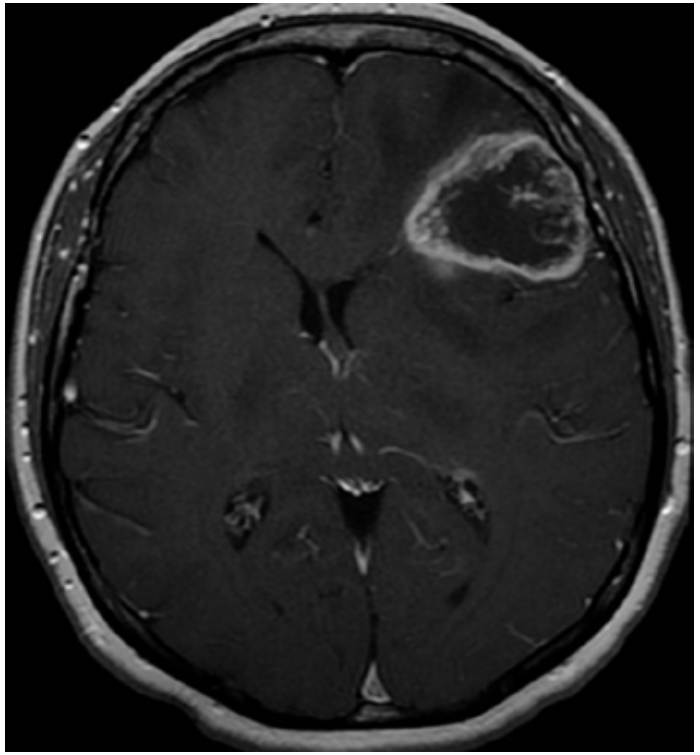
Glioblastoma (GBM)

Age of onset: 50-60 years, frequent in men

Standard Treatment: Surgery → Concurrent chemoradiation therapy (60 Gy with temozolomide) → Maintenance temozolomide 150-200 mg/m2 for five consecutive days every 28 days + TTF

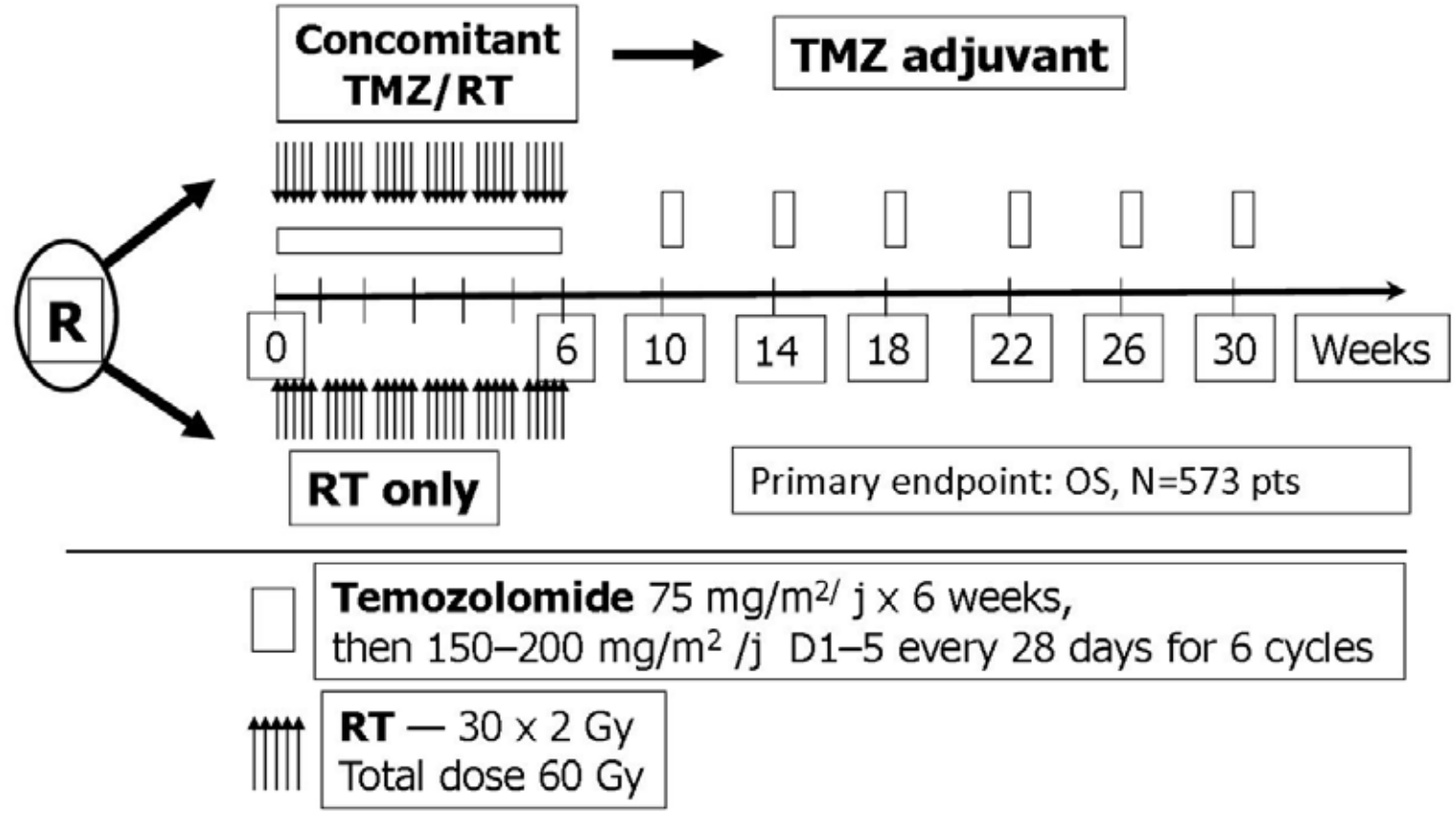


T2-FLAIR



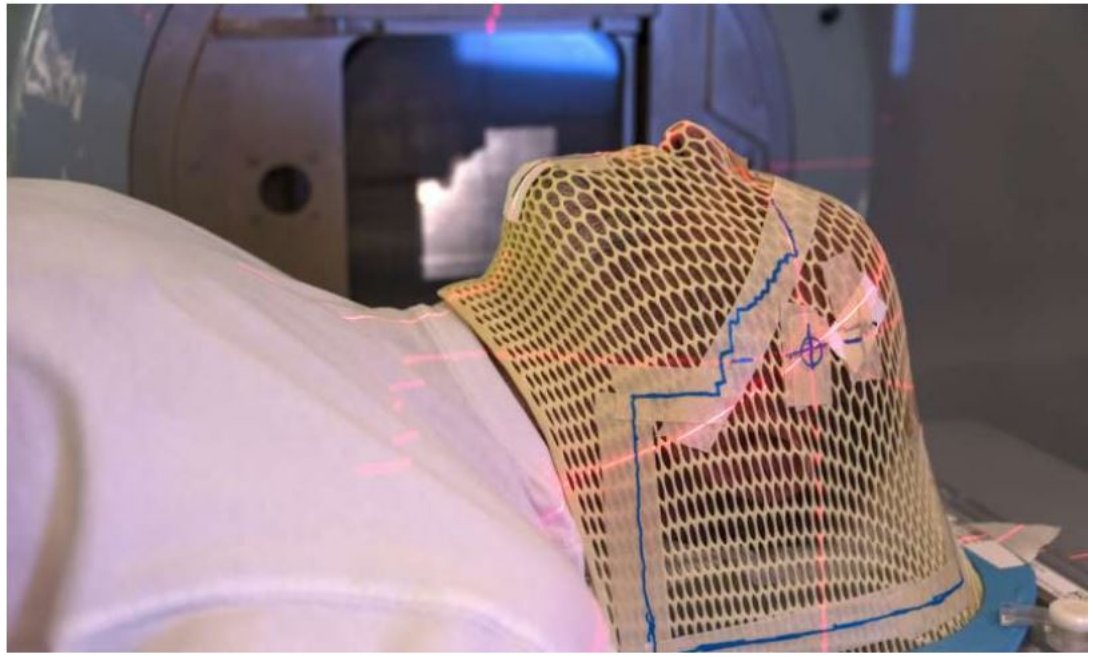
T1 post contrast

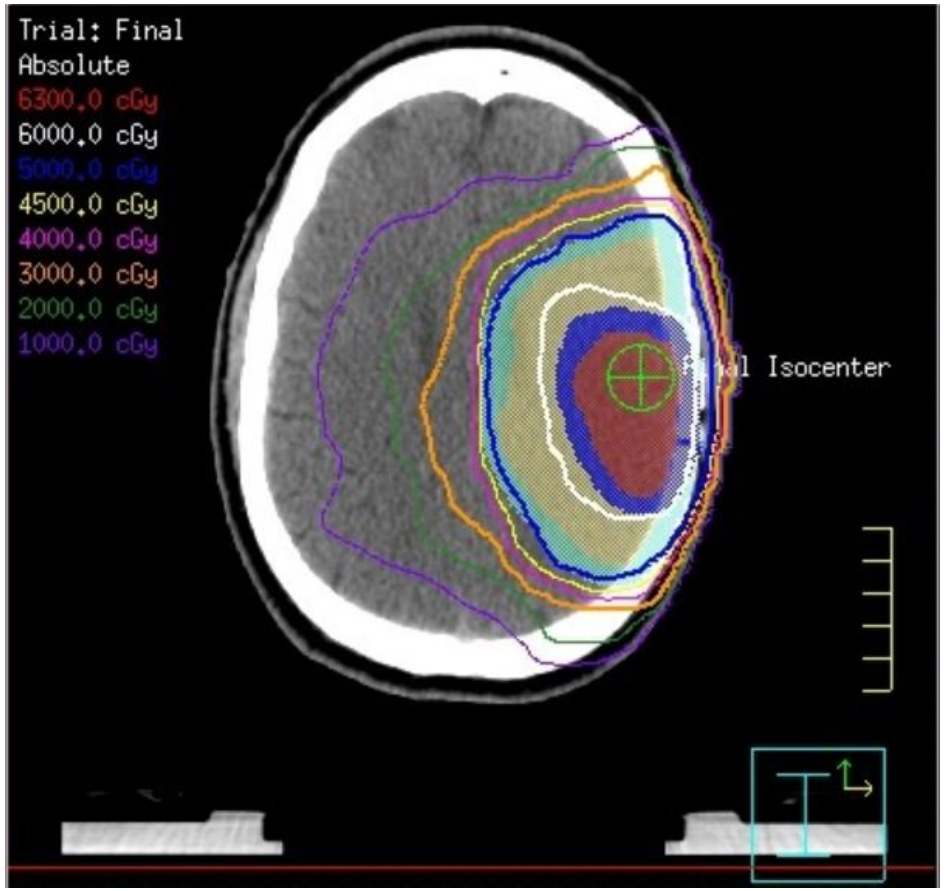
GBM-Treatment



EORTC 22981/ NCIC 26981 (**Stupp,** NEJM **2005**)

Radiation Therapy





- Focal radiation therapy for 6 weeks
- 60 Gy in 1.8-2.0 Gy/day
- Concurrently with temozolomide

GBM- Treatment

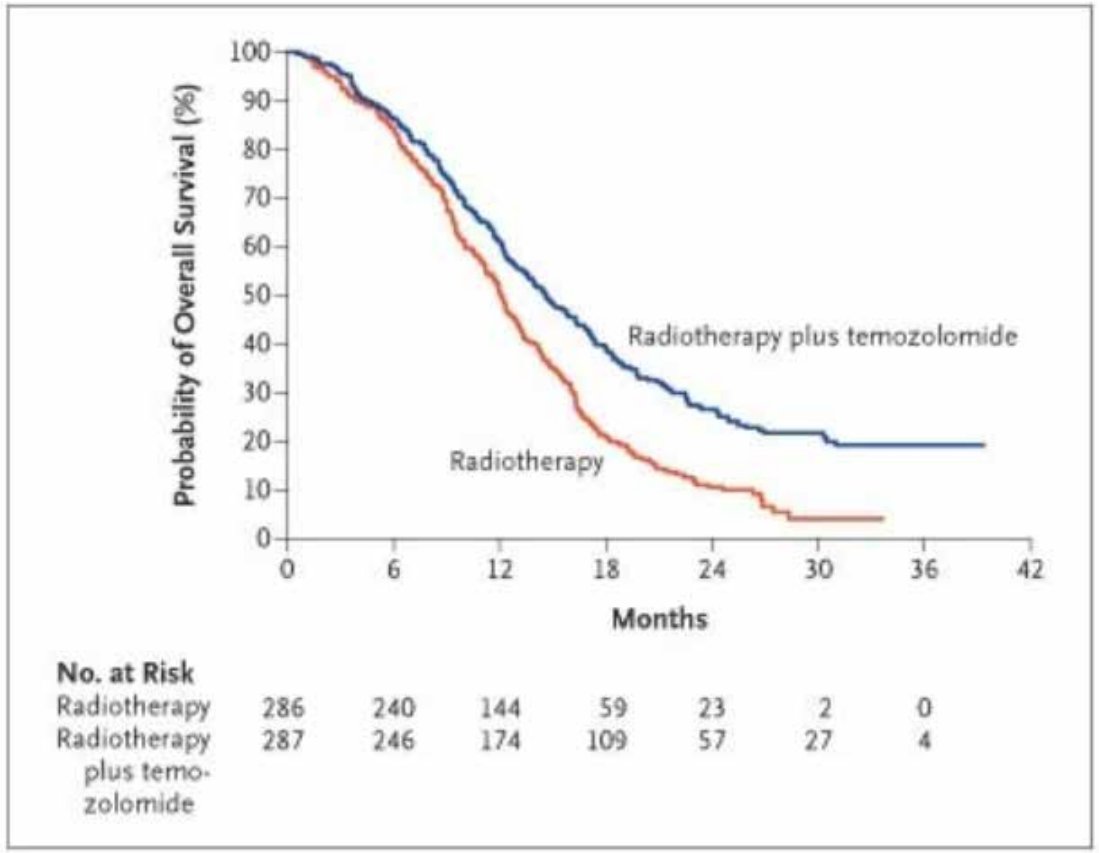


Table 3. Overall and Progression-free Survival According to Treatment Group.*

Variable	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
	value (95% CI)	
Median overall survival (mo)	12.1 (11.2–13.0)	14.6 (13.2–16.8)
Overall survival (%)		
At 6 months	84.2 (80.0–88.5)	86.3 (82.3–90.3)
At 12 months	50.6 (44.7–56.4)	61.1 (55.4–66.7)
At 18 months	20.9 (16.2–26.6)	39.4 (33.8–45.1)
At 24 months	10.4 (6.8–14.1)	26.5 (21.2–31.7)
Median progression-free survival (mo)	5.0 (4.2–5.5)	6.9 (5.8–8.2)
Progression-free survival (%)		
At 6 months	36.4 (30.8–41.9)	53.9 (48.1–59.6)
At 12 months	9.1 (5.8–12.4)	26.9 (21.8–32.1)
At 18 months	3.9 (1.6–6.1)	18.4 (13.9–22.9)
At 24 months	1.5 (0.1–3.0)	10.7 (7.0–14.3)

NEJM 2005; 352:987-996

MGMT methylation

- O6 methylguanine methyltransferase
- DNA repair enzyme
- Favorable prognosis
- Predicts response to alkylating agent

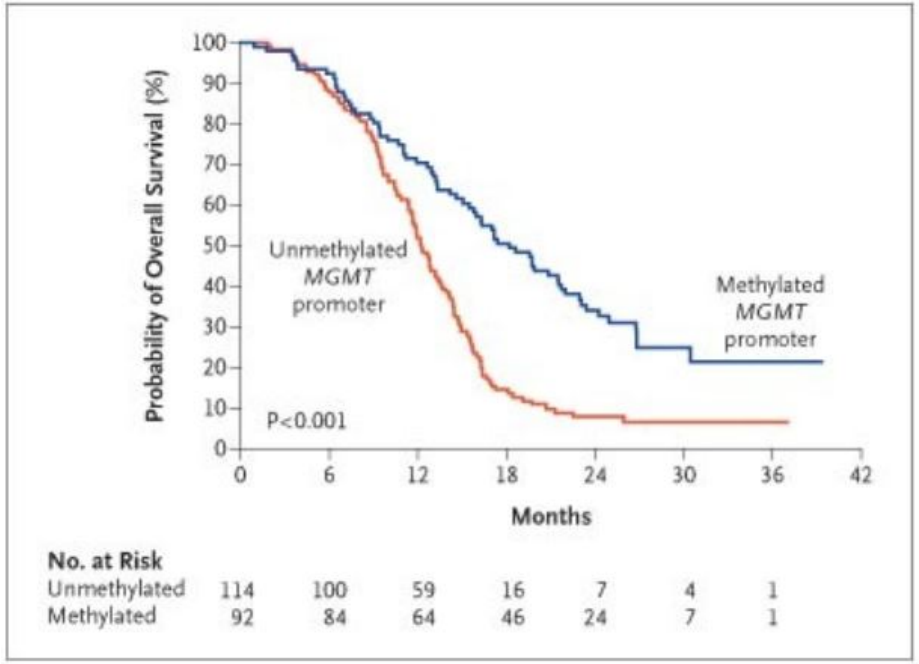


Table 1. Effect of *MGMT* Promoter Methylation Status on Survival, According to Random Treatment Assignment.*

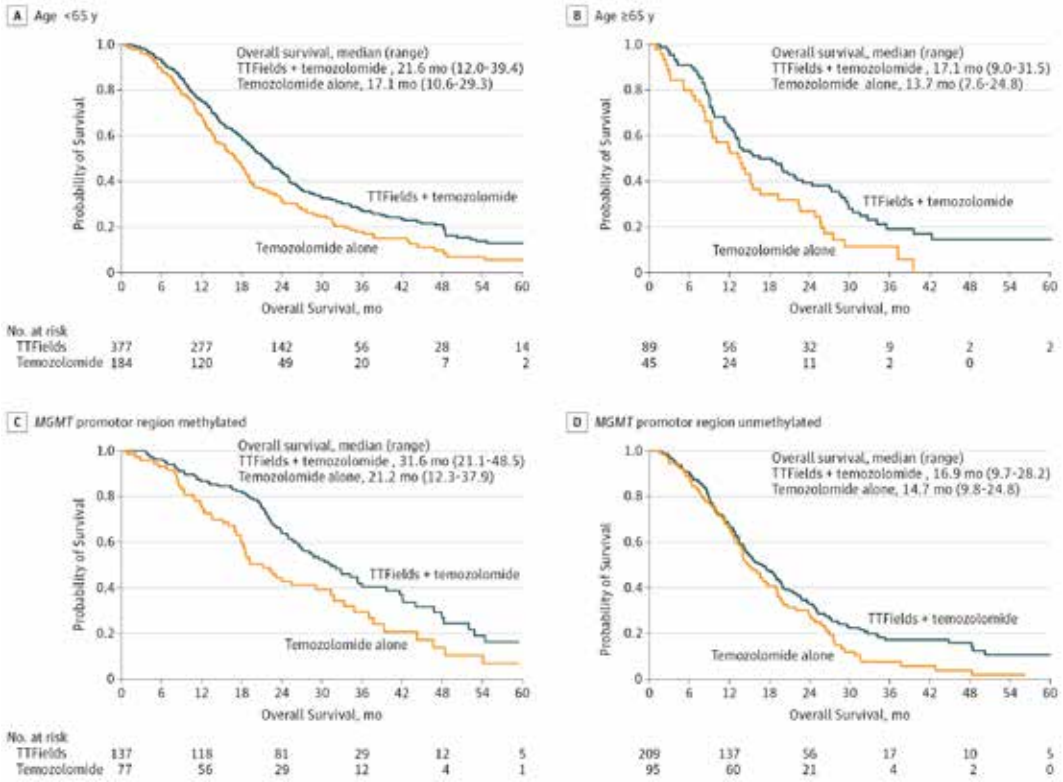
Promoter Status and Outcome	Radiotherapy (N=100)	Temozolomide plus Radiotherapy (N=106)
Methylated *MGMT* promoter		
No. of patients	46	46
Progression-free survival		
Median duration (mo)	5.9 (5.3–7.7)	10.3 (6.5–14.0)
Rate at 6 mo (%)	47.8 (33.4–62.3)	68.9 (55.4–82.4)
Hazard ratio for death	1.00	0.48 (0.31–0.75)
Overall survival		
Median duration (mo)	15.3 (13.0–20.9)	21.7 (17.4–30.4)
Rate at 2 yr (%)	22.7 (10.3–35.1)	46.0 (31.2–60.8)
Hazard ratio for death	1.00	0.51 (0.31–0.84)
Unmethylated *MGMT* promoter		
No. of patients	54	60
Progression-free survival		
Median duration (mo)	4.4 (3.1–6.0)	5.3 (5.0–7.6)
Rate at 6 mo (%)	35.2 (22.5–47.9)	40.0 (27.6–52.4)
Hazard ratio for death	1.00	0.62 (0.42–0.92)
Overall survival		
Median duration (mo)	11.8 (9.7–14.1)	12.7 (11.6–14.4)
Rate at 2 yr (%)	<2†	13.8 (4.8–22.7)
Hazard ratio for death	1.00	0.69 (0.47–1.02)

NEJM 2005; 352:997-1003

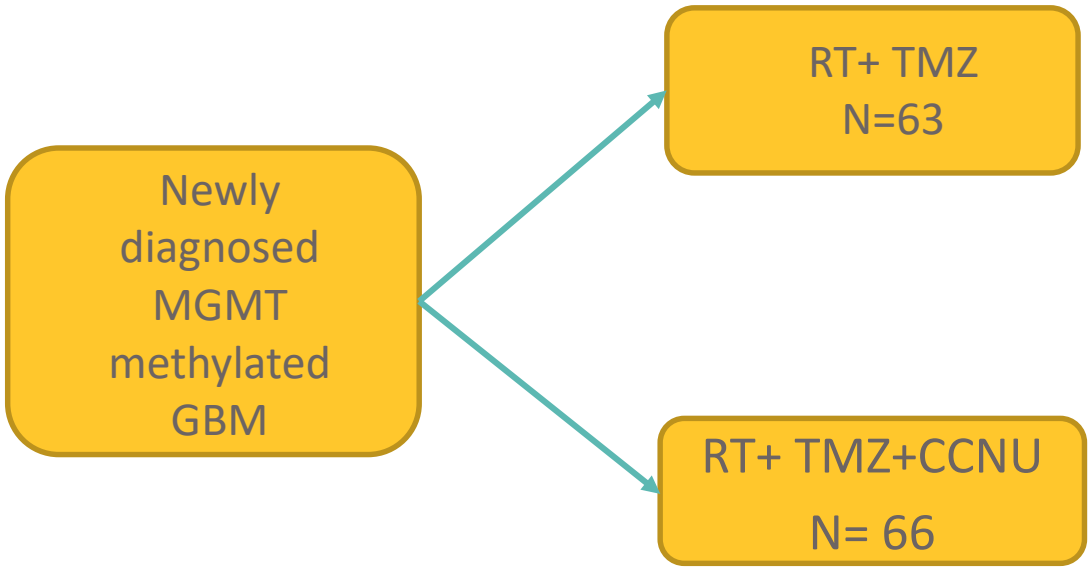
Tumor Treating Fields

- TTF used after completion of chemoRT
- With adjuvant temozolomide
- N=315 pts
- PFS: 7mo vs. 4mo
- OS: 20 mo vs. 17 mo
- Use atleast 18 hours/day
- Pros: Survival benefit,
- Cons: Non-blinded study, no placebo, QoL?
- Not yet widely accepted

Tumor Treating Fields



CeTeG/NOA-09: MGMT methylated GBM



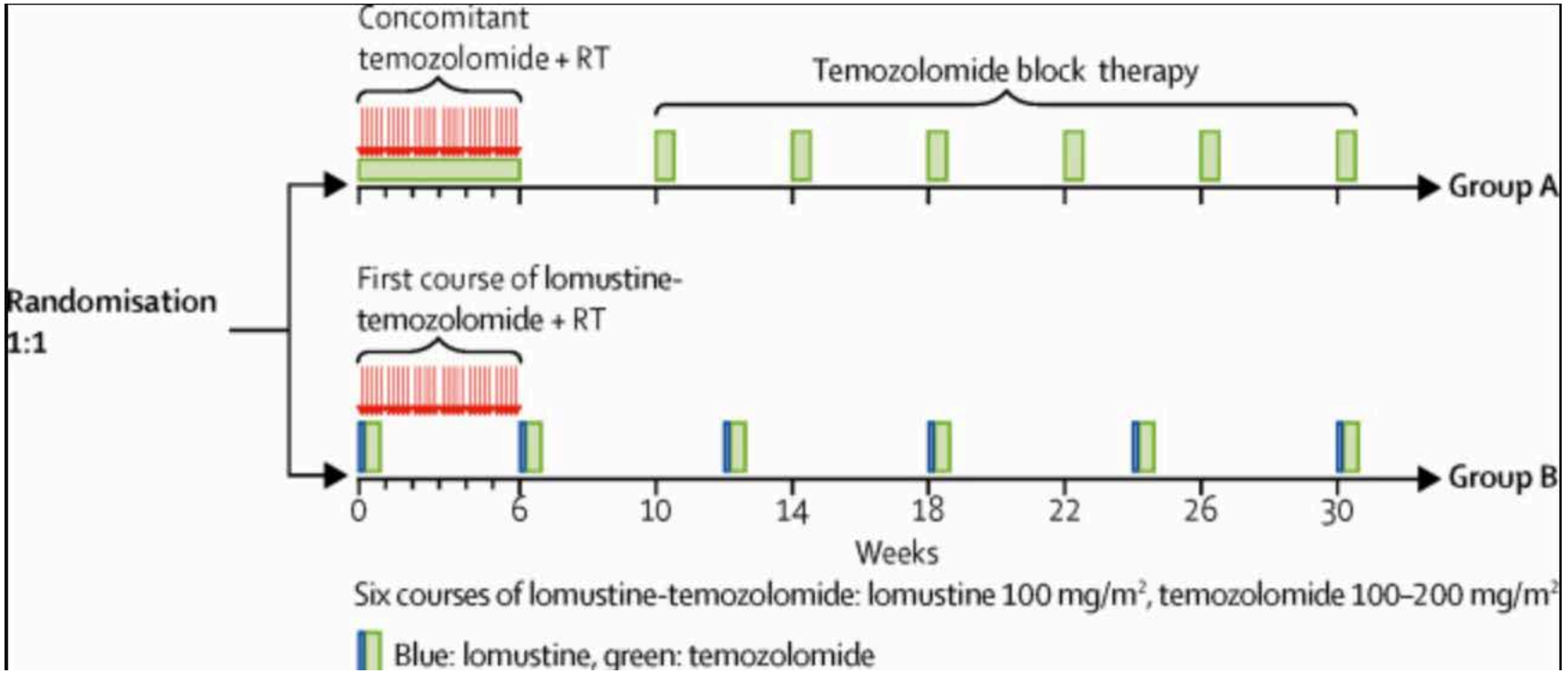
	RT+ TMZ	RT+ TMZ+CCNU
PFS	16.7 months	16.7 months
OS	30.9 months	49.6 months

Limitations:

1. Small sample size
2. No PFS benefit
3. Significant thrombocytopenia

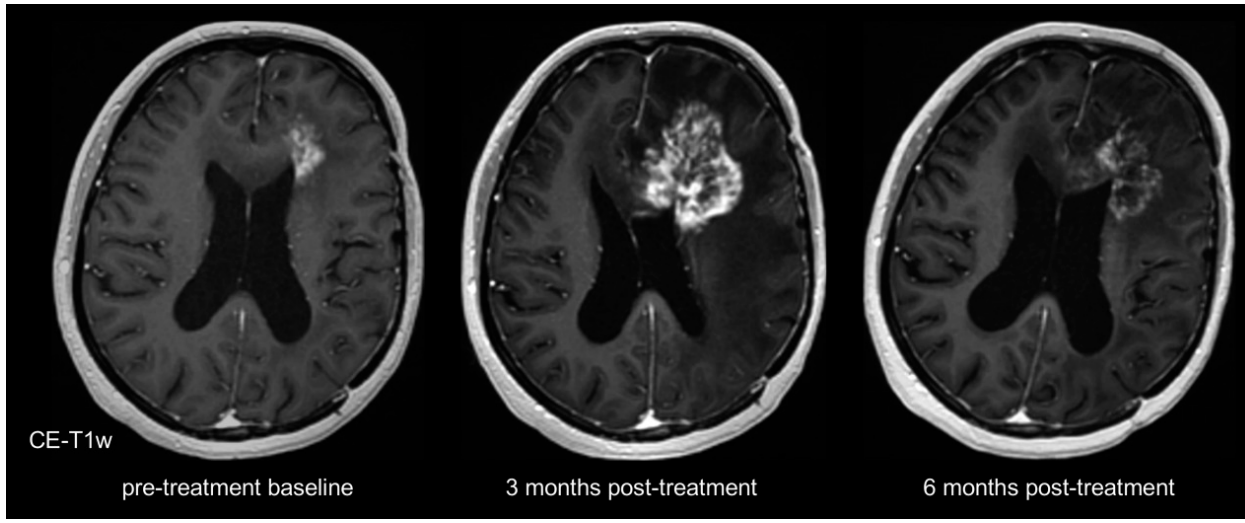
Glioblastoma Treatment: CCNU plus TMZ

CeTeG/NOA-09- MGMT Methylated newly diagnosed GBM



Pseudoprogression- Radiation Necrosis

- Upto 40% pts display radiologic worsening of disease after RT, mostly in the RT field
- Common during the first 3-4 months after RT
- Baseline MRI: 4 weeks after RT+ chemo
- Usually asymptomatic, may occasionally be symptomatic
- Avoid making changes to treatment
- Could use steroids or bevacizumab for symptom management
- Consider surgery for confirmation



JMRI, Volume: 48, Issue: 3, Pages: 571-589

Recurrent GBM

- Poor prognosis
- No standard treatment options
- Bevacizumab as a single agent
- Other chemotherapy agents: Lomustine, carboplatin, irinotecan, etoposide
- Tumor treating fields
- The correct answer: CLINICAL TRIALS

Bevacizumab

- VEFG antibody
- Decreases vascular permeability
- Improves edema and MRI
- Improves symptoms
- FDA accelerated approval in 2009 and full approval 2018
- Used for symptomatic patients
- Limited post-bev trials

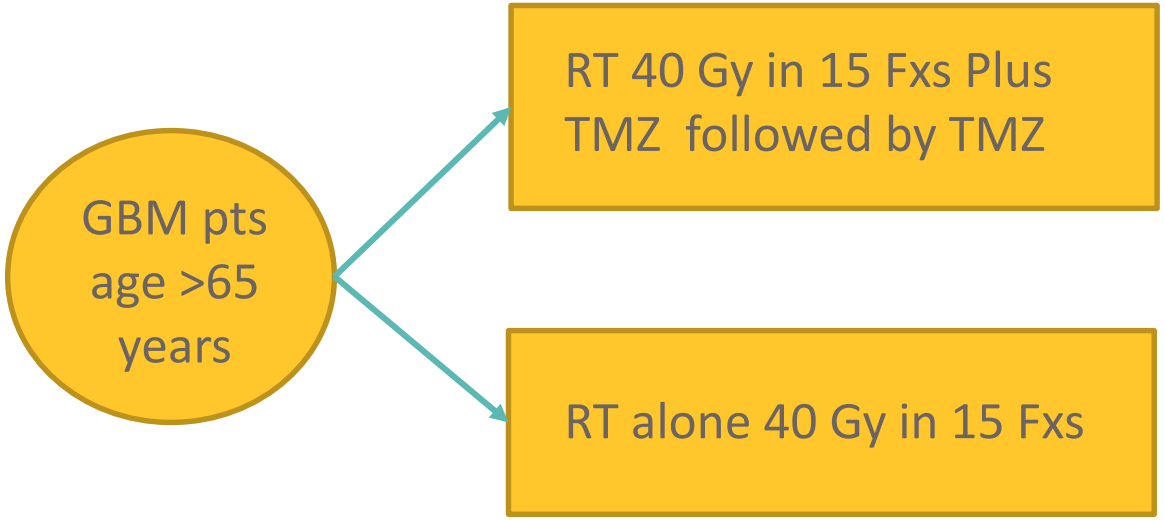
Trial	Phase	N	Intervention	Median PFS (95% CI), mo	Median OS (95% CI), mo
Recurrent GBM					
Friedman et al,[26] 2009	II	167	Bev	4.2 (2.9–5.8)	9.2 (8.2–10.7)
			Bev + irinotecan	5.6 (4.4–6.2)	8.7 (7.8–10.9)
Taal et al,[27] 2014	II	148	Lomustine	1 (1–3)	8 (6–11)
			Bev	3 (3–4)	8 (6–9)
			Bev + lomustine	4 (3–8)	12 (8–13)
Field et al,[28] 2015	II	122	Bev	3.5 (1.9–3.7)	7.5 (NR)
			Bev + carboplatin	3.5 (2.2–3.7)	6.9 (NR)
Wick et al,[29] 2017	III	437	Lomustine	1.5 (1.5–2.5)	8.6 (7.6–10.4)
			Bev + lomustine	4.2 (3.7–4.3)	9.1 (8.1–10.1)
Newly Diagnosed GBM					
Herrlinger,[30] 2016	II	170	TMZ/RT + TMZ	6.0 (2.7–7.3)	17.5 (15.1–20.5)
			Bev/RT + Bev/Iri	9.7 (8.7–10.8)	16.6 (15.4–18.4)
Gilbert et al,[31] 2014	III	621	TMZ/RT + TMZ	7.3 (5.9–7.9)	16.1 (14.8–18.7)
			Bev/TMZ/RT + Bev/TMZ	10.7 (10.0–12.2)	15.7 (14.2–16.8)
Chinot et al,[32] 2014	III	921	TMZ/RT + TMZ	6.2 (NR)	16.7 (NR)
			Bev/TMZ/RT + Bev/TMZ	10.6 (NR)	16.8 (NR)
Unresectable GBM					
Chauffert et al,[33] 2014	II	120	TMZ/RT + TMZ	5.2 (4.3–6.8)	11.1 (9.0–15.0)
			Bev/Iri + Bev/TMZ/RT + Bev/Iri	7.1 (5.5–9.2)	11.1 (9.0–15.0)

Bev indicates bevacizumab; Iri, irinotecan; NR, not reported; TMZ, temozolomide.

The Cancer Journal Issue: Volume 24(4), July/August 2018, p 180-186

GBM In Elderly

Hypofractionated RT plus TMZ vs. hypofractionated RT alone



	RT alone	RT plus TMZ
PFS	3.9 months	5.3 months
OS	7.6 months	9.3 months

NO consensus for treatment in elderly

N Engl J Med 2017; 376:1027-1037

Grade II and III glioma: Management

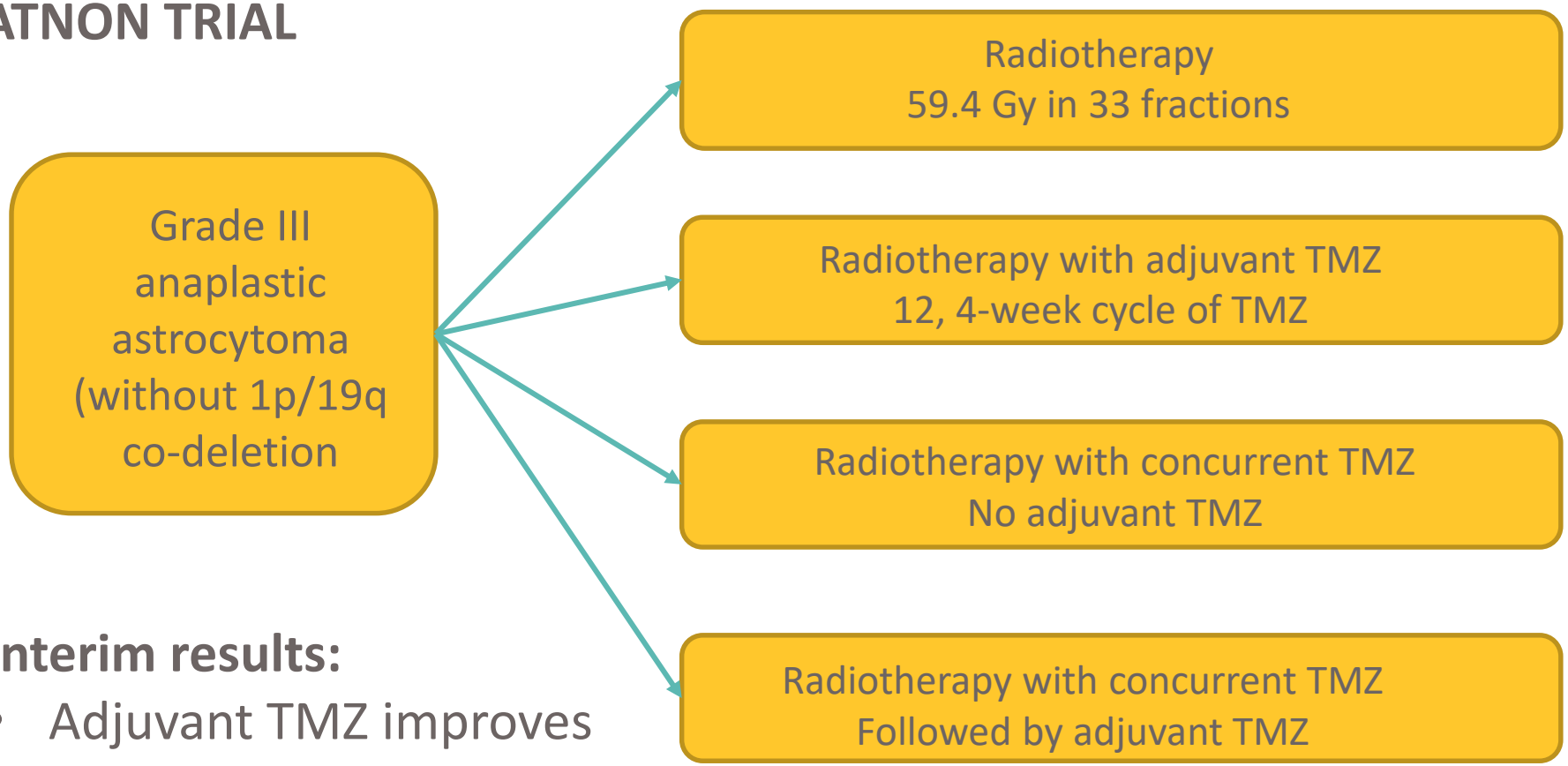
WHO grade II glioma: Younger patients 20-40 year old

- Surgery, if gross total resection, < 40: Observation
- >40 year old or less than gross total resection: Consider chemotherapy
- RT plus PCV has the most evidence
- Could consider RT plus TMZ

WHO grade III glioma: Treated like GBM

Studies to Watch out for

CATNON TRIAL



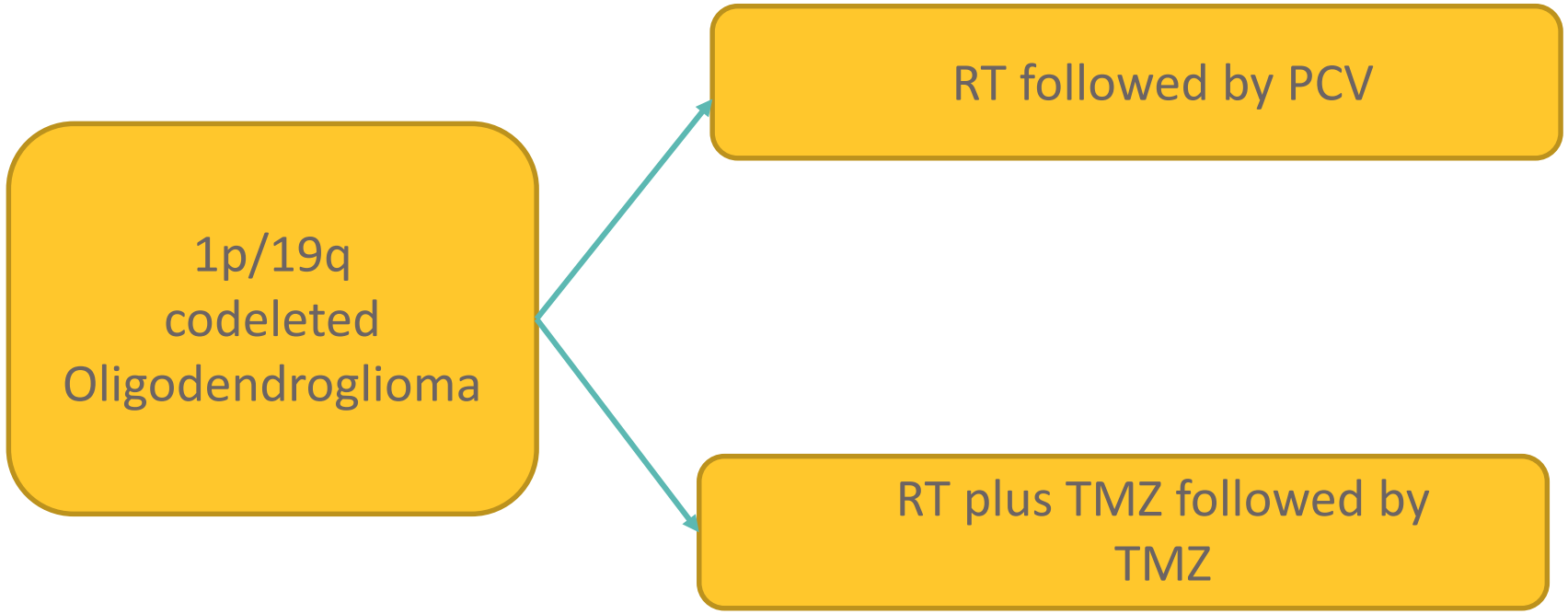
Interim results:

- Adjuvant TMZ improves survival
- Concurrent TMZ does not add to treatment

Lancet. 2017 Oct 7;390(10103):1645-1653

Studies to Watch out for

CODEL trial



Prognosis

Tumor	Median survival
Grade II, diffuse oligodendroglioma	10-15 years
Grade II, diffuse astrocytoma, IDH mutant	10-12 years
Grade II, diffuse astrocytoma, IDH wild type	1.5-3 years
Grade III, anaplastic astrocytoma, IDH mutant	8-10 years
Grade III, anaplastic oligodendroglioma	5-9 years
Grade III, anaplastic astrocytoma, IDH wild type	1.5-3 years
Grade IV, Glioblastoma	1.5-2 years

Meningioma

Arise from the meninges- most common CNS tumor

Often found in adults

Usually slow growing

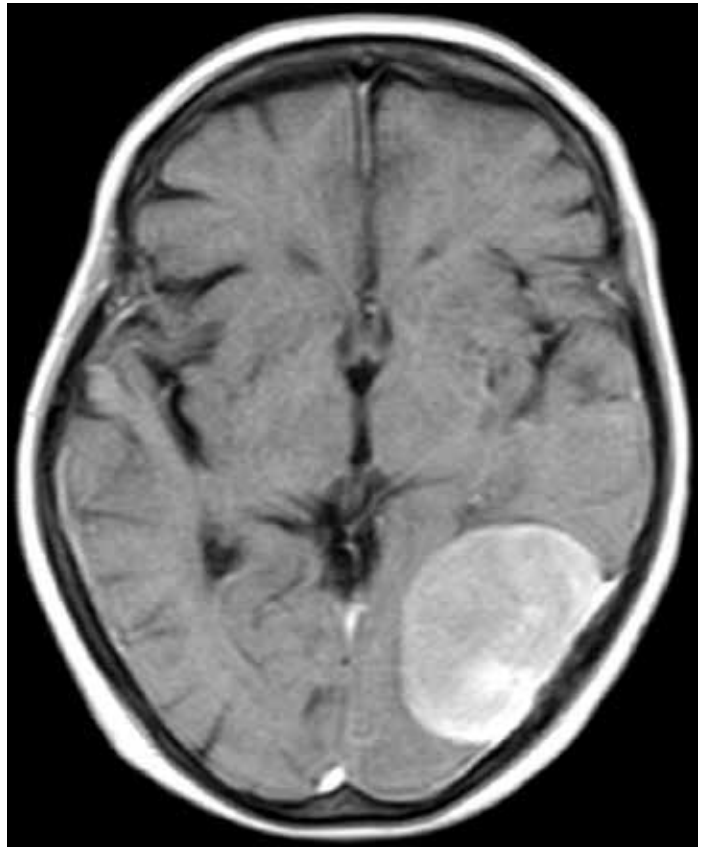
Asymptomatic: followed with periodic CT/MRI

Symptomatic: Surgery

WHO grade I: Surgical resection is curative

WHO grade II (high mitotic index): Surgery +/- RT

WHO grade III (brain invasion, bone invasion): Surgery + RT



CNS lymphoma

- NHL, aggressive, median age 60 years
- >95% DLBCL, ABC subtype, mostly immunocompetent patients (PTLD could have EBV+)
- Imaging: MRI brain w/wo contrast: periventricular, homogenous contrast enhancing, diffusion restricting
- Extent of disease evaluation: MRI spine, LP, ophthalmology eval, CT CAP, testicular US in males
- Treatment:
    - HD-MTX based regimen (3.5 gm/m2 to 8 gm/m2): MTR, MATRIX
    - Consolidation: consolidation chemotherapy: cytrabine plus etoposide/low dose RT/HDC-ASCT

Brain Metastases

- Common primaries: Lung, breast, melanoma
- Imaging: MRI brain w/wo contrast
- Factors to consider for treatment selection:
  - Patient factors: Performance status, Symptoms,
  - Local factors: Number/size/location of brain mets,
  - Primary malignancy factors: extracranial disease control, presence of targetable mutation
- Treatment options: observation, surgery, radiation therapy (SRS vs. WBRT), systemic therapy

Brain Metastases

Surgery: Solitary or large or symptomatic

Alleviates mass effect, provides tissue diagnosis, ability to taper steroids fast

Post op RT controversial: could lead to local leptomeningeal disease

RT: SRS: 1-3 lesions (? Upto 10 lesions), <3 cm, good focal control

WBRT: Improves CNS control, no OS benefit, consider hippocampal sparing WBRT and memantine to delay neurocognitive decline

Systemic therapy: Consider for targeted therapies with good CNS penetration, small, asymptomatic brain metastases.

Melanoma: BRAF inhibitors, ipilimumab plus nivolumab, pembrolizumab

Lung: Osimertinib, brigatinib, lorlatinib, pembrolizumab

Breast: tucatinib, neratinib, lapatinib all with capecitabine

Leptomeningeal metastases

- Spread to the subarachnoid space
- Imaging: MRI brain plus spine w/wo contrast
- Lumbar puncture: Cell count, glucose, protein, cytology, ?cf-DNA
- Treatment: Focal radiation, WBRT, craniospinal radiation
- IT chemotherapy: MTX, cytarabine, thiotepa, trastuzumab
- Consider shunt for hydrocephalus

Thank You

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Acute Myeloid Leukemia in 2020

Mary-Beth Percival, MD, MS

Assistant Professor, University of Washington

Assistant Professor, Fred Hutchinson Cancer Research Center

Outline

Epidemiology

Diagnosis

Treatment

- Heme emergencies
- New drugs
- Regimens at UW/FHCRC/SCCA

Relapse

Indications for transplant

Older AML

APL

Epidemiology in 2020

Estimated annual new cases: 19,940

- 1.1% of all new cancer cases in the US

Estimated annual deaths: 11,180

5 year survival rate: 28.7%

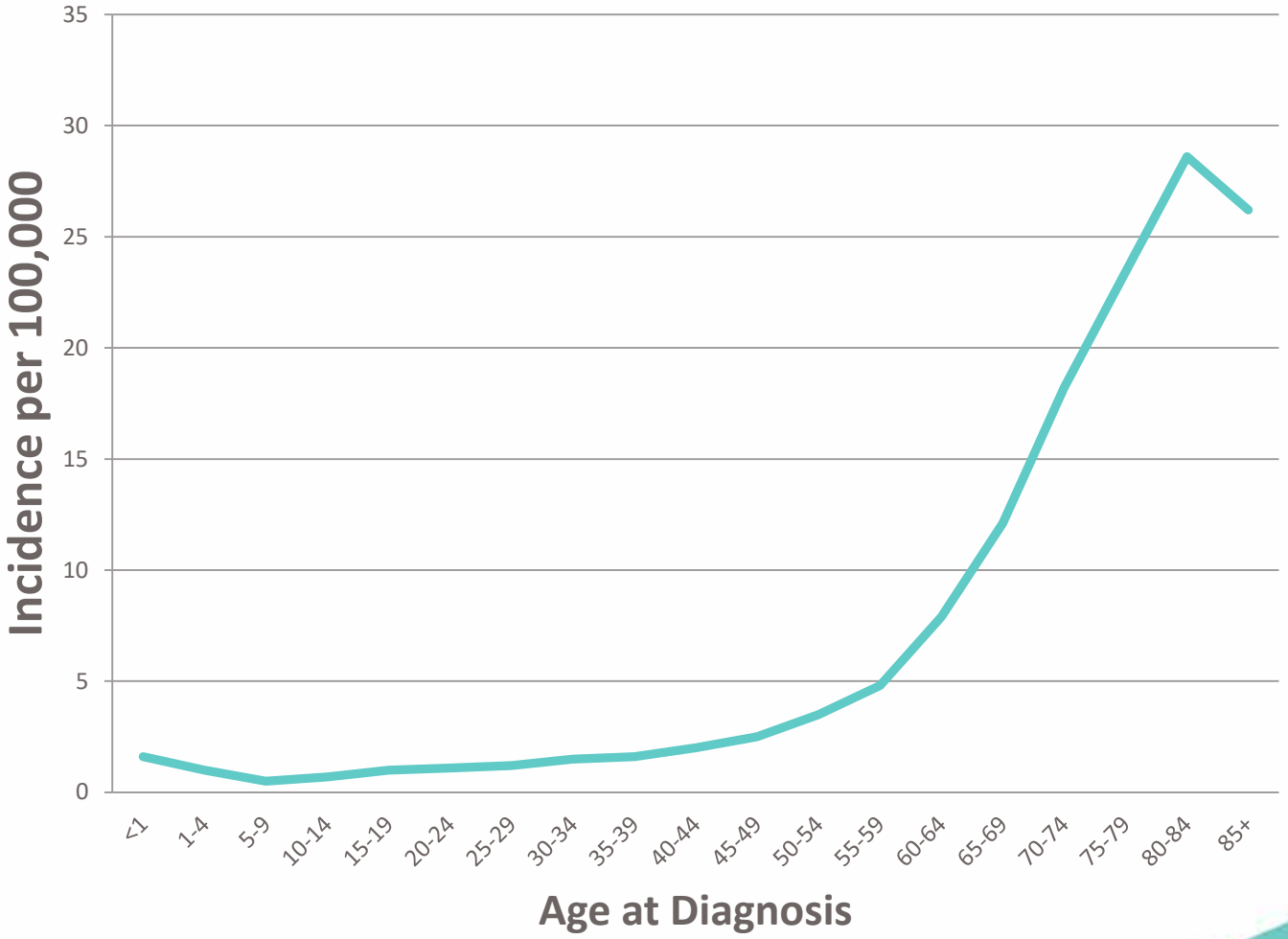
- Improving over time (6.3% survival in 1975)

M:F predominance of approximately 1.5:1

Median age at diagnosis: 68

http://seer.cancer.gov/statfacts/html/amyl.html

Incidence by age, 2011-2015



SEER Cancer Statistics Review (https://seer.cancer.gov/csr/1975_2015/)

Etiology

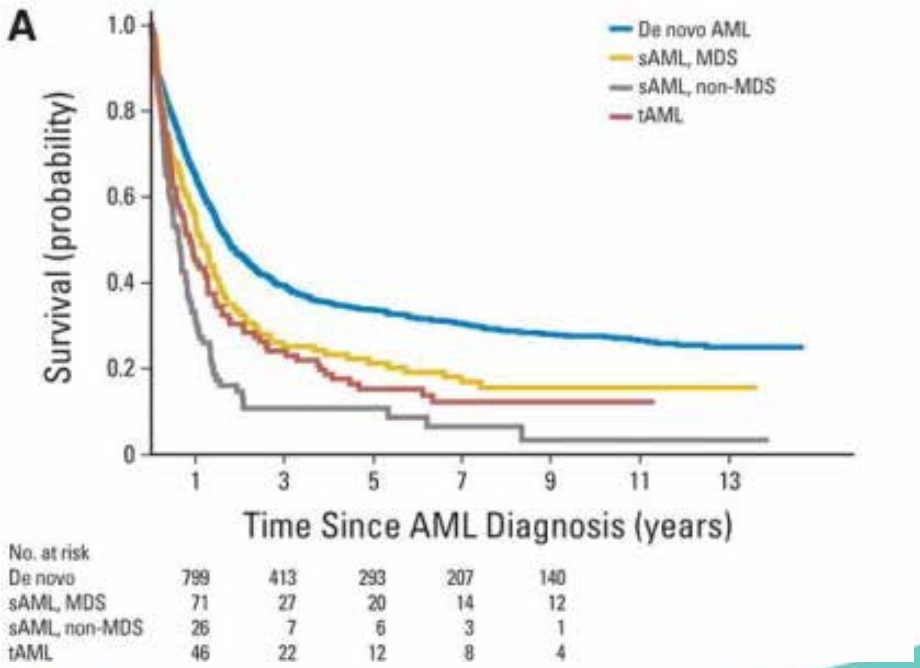
Prior chemotherapy/radiation (therapy-related, or t-AML)

Antecedent hematologic disorder (secondary, or s-AML)

Genetic predisposition

Smoking

Chemical exposures, such as benzene



Ostgard L et al *JCO* 2015

Genetic Predisposition

Many familial AML/MDS syndromes described in the past 2 decades

Most common: *GATA2*, *RUNX1*, *CEBPA*, *TERC/TERT*, Fanconi anemia, Li Fraumeni

Important to identify!

- Treatment planning
- Choice of donors for allogeneic HCT candidates
- Screening for other associated medical issues
- Counseling of family members

Consider referral to genetics clinic specializing in heme malignancy

Ongoing question: who should undergo germline testing?

"How I treat inherited AML" *Blood* 2016

Diagnosis of AML

Peripheral blood (≥20% blasts)

- <20% blasts diagnostic for recurrent genetic abnormalities: t(8;21), inv(16) or t(16;16), t(15;17)

Bone marrow aspirate/biopsy

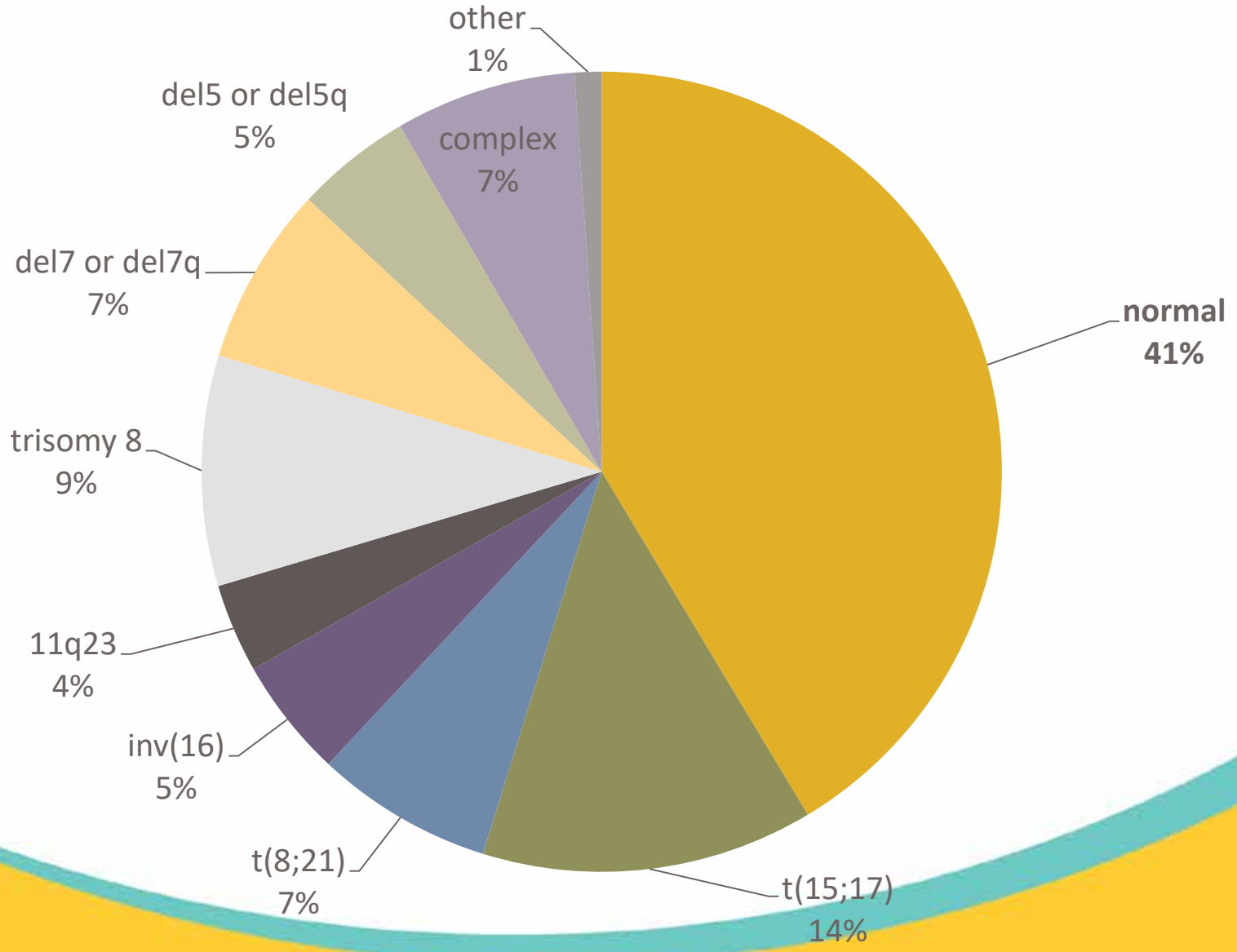
- Generally not necessary if >2K blasts in peripheral blood

Mandatory testing on blood and/or marrow at diagnosis

- Morphology
- Cytogenetics/FISH
- Molecular studies
- Immunophenotyping (a.k.a. flow cytometry)

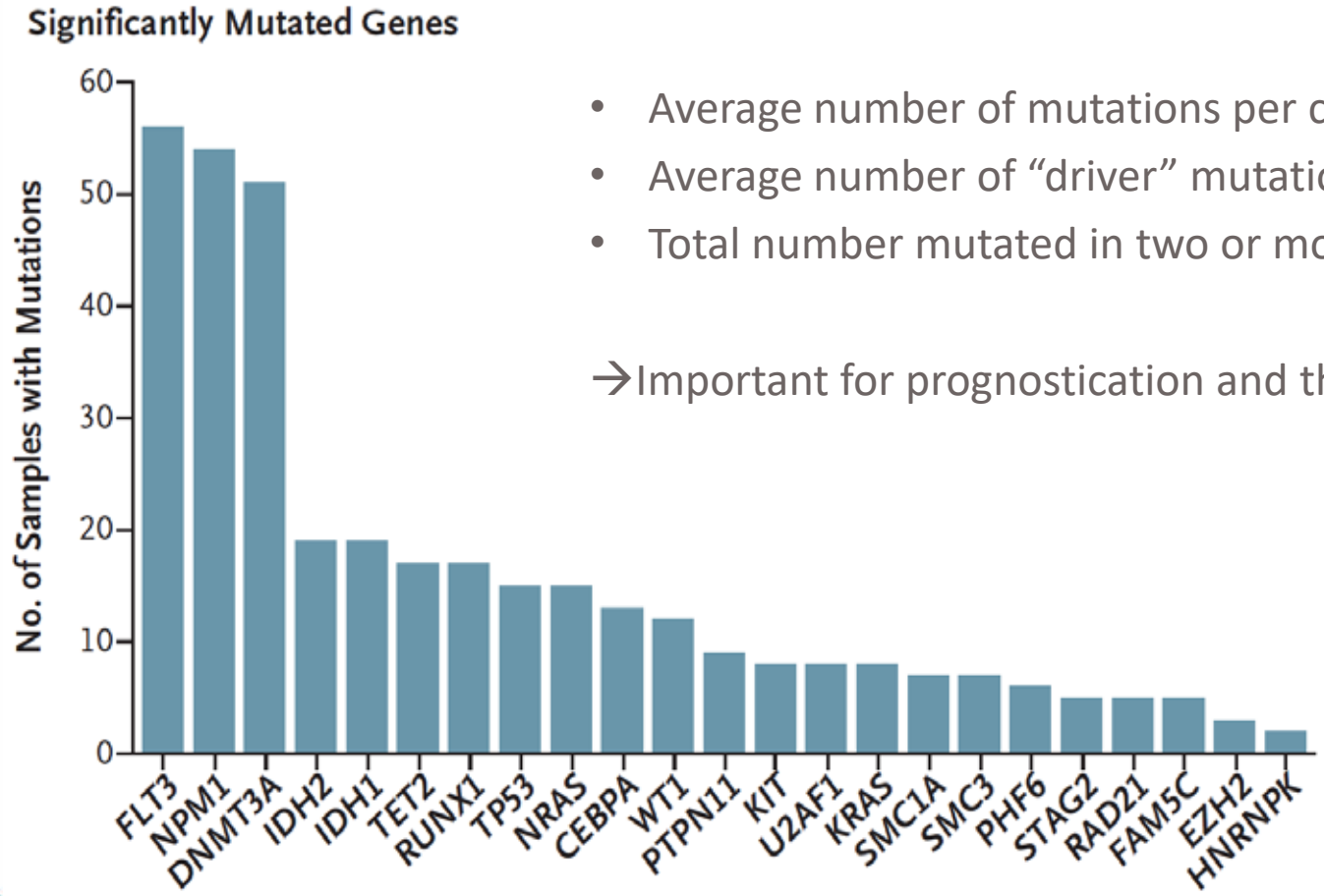
Arber DA et al, *Blood* 2016; Dohner H et al, *Blood* 2017

Common cytogenetic abnormalities



Grimwade D et al, *Blood* 2010

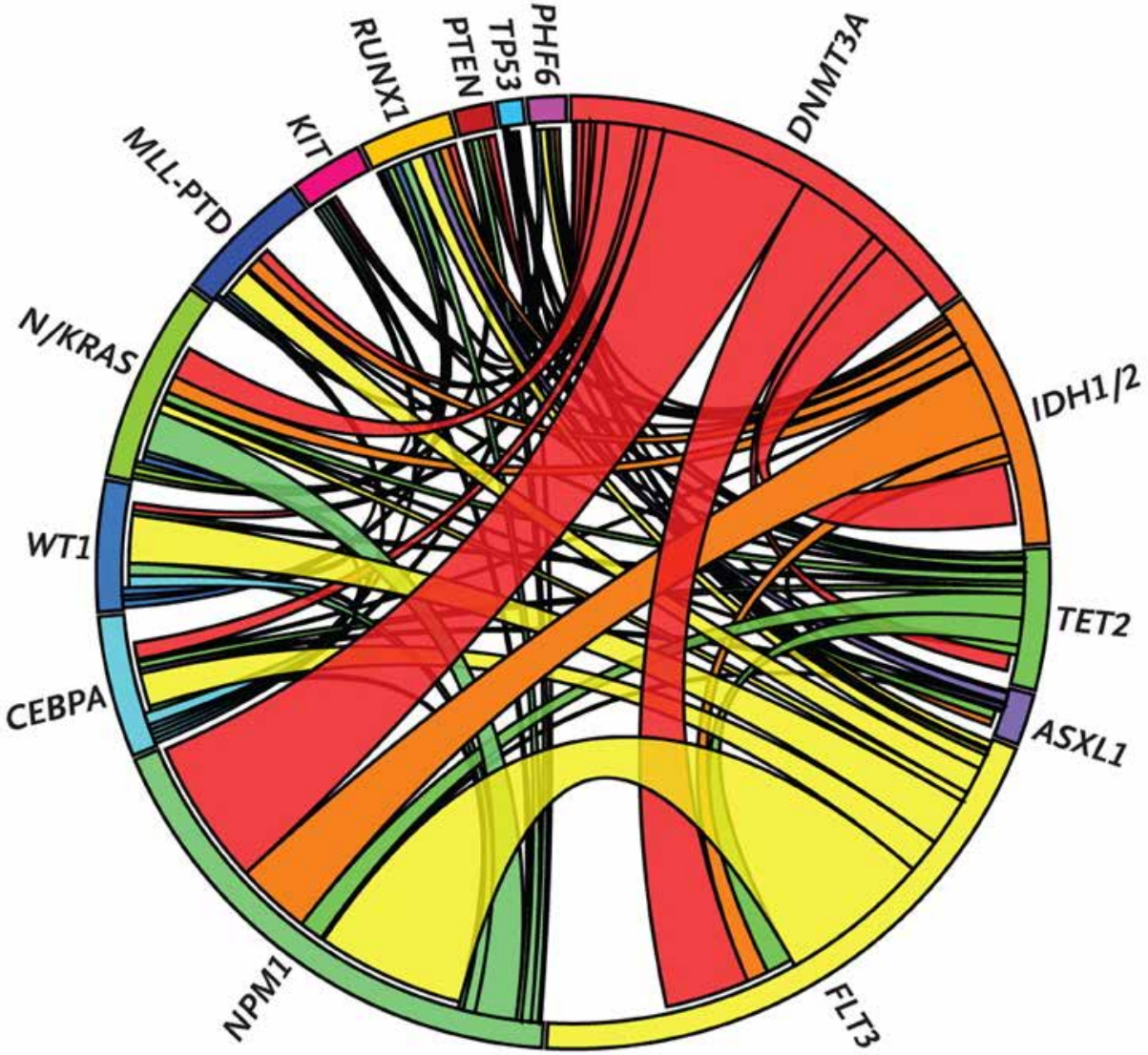
Recurrent mutations in 200 AML samples



- Average number of mutations per case: 13
- Average number of "driver" mutations per case: 5
- Total number mutated in two or more samples: 237

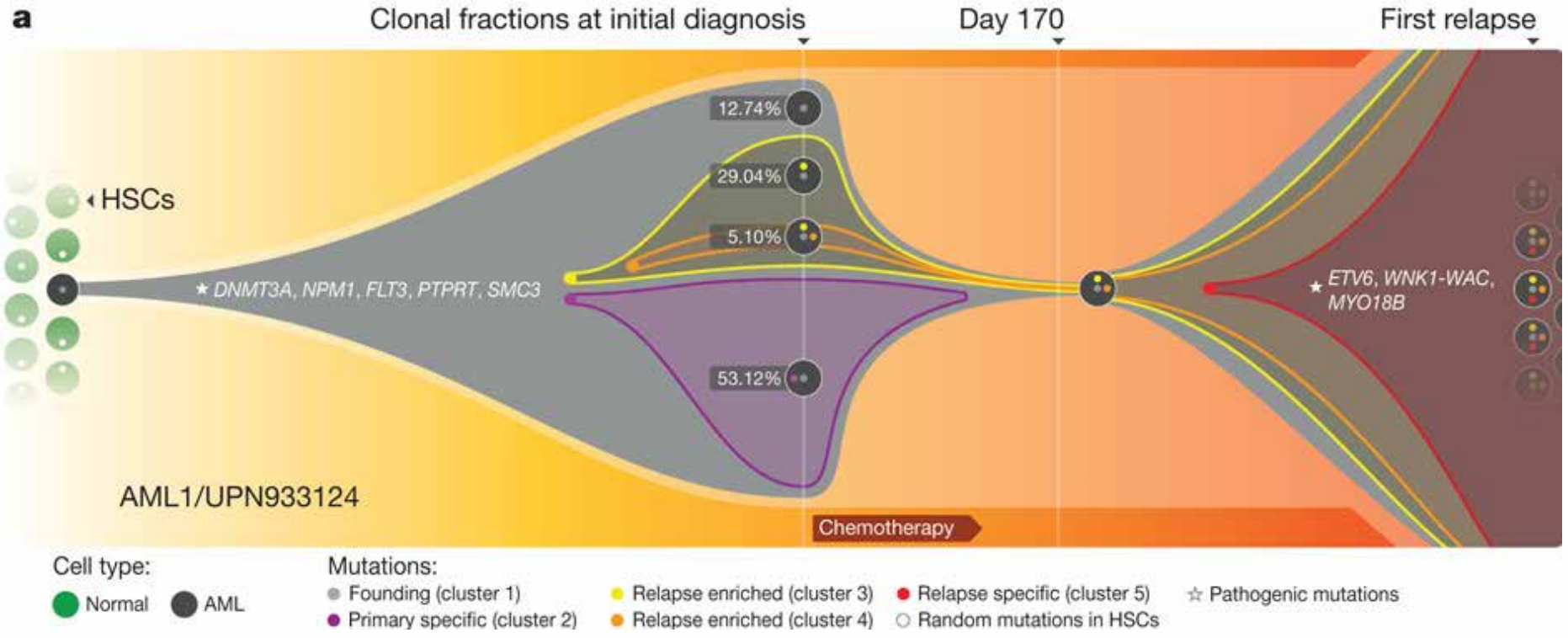
→Important for prognostication and therapeutic targets!

TCGA, *NEJM* 2013



Patel J, *NEJM* 2012

Clonal evolution



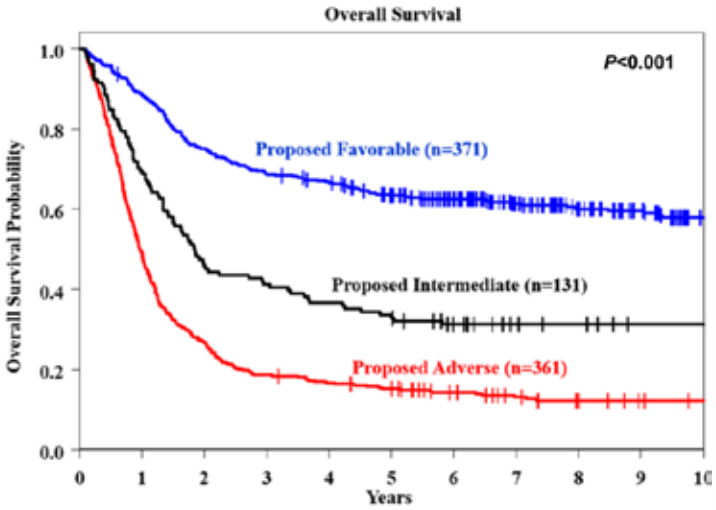
Ding *et al*. *Nature* 2012

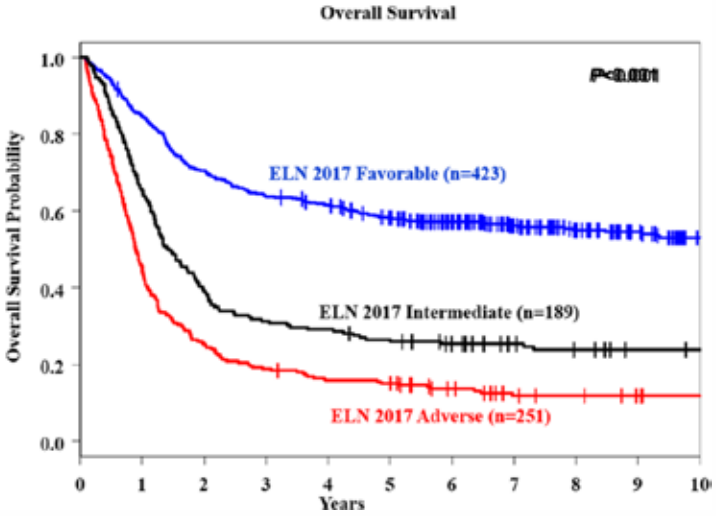
European LeukemiaNet criteria 2017

Risk status	Subsets
Favorable	t(8;21) inv(16) or t(16;16) Mutated *NPM1* without *FLT3*-ITD ~~(normal karyotype)~~ or with FLT3-ITD^{low} Biallelic mutated *CEBPA* ~~(normal karyotype)~~
Intermediate~~-I~~	Mutated *NPM1* and *FLT3*-ITD^{high} ~~(normal karyotype)~~ ~~Wild-type *NPM1* and *FLT3*-ITD (normal karyotype)~~ Wild-type *NPM1* without *FLT3*-ITD (without adverse-risk genetic lesions)
~~Intermediate-II~~	t(9;11); *MLLT3-MLL* Cytogenetic abnormalities not classified as favorable or adverse
Adverse	inv(3) or t(3;3); t(6;9); t(v;11); -5 or del(5q); -7; -17/abnl(17p); complex karyotype monosomal karyotype; wild-type *NPM1* and *FLT3*-ITD^{high}; mutated *RUNX1*; mutated *ASXL1*; mutated *TP53*

Dohner H et al, *Blood* 2017

Proposed modification for <60 years





Eisfeld AK et al, *Leukemia* 2020

Heme emergencies: leukostasis

In AML, hyperleukocytosis defined as WBC>100,000/μl

Hyperleukocytosis ≠ leukostasis

Leukostasis most commonly affects CNS and lungs

Treatment:

- Starting definitive induction chemotherapy
- Hydroxyurea 2g q6hr
- (Leukapheresis)
- +/- cytarabine 500mg/m^2 x 1-2 doses
- +/- high-dose dexamethasone for pulmonary symptoms

Heme emergencies: tumor lysis

Spontaneous or chemo-induced

Hyperkalemia, hyperphosphatemia, hypocalcemia, hyperuricemia

Treatment:

- Hydration 4-5L/day (not necessary or beneficial to alkalinize)
- “You can’t dialyze the lung”
- Allopurinol 300-600mg/day (blocks xanthine oxidase)
- Rasburicase 0.15 mg/kg (recombinant urate oxidase which metabolizes uric acid to allantoin)
    - G6PD deficiency is a contraindication

Cortes J et al, *JCO* 2010

Heme emergencies: thrombohemorrhagic syndrome

Relatively common in APL, due to DIC + fibrinolysis + fibrinogenolysis

Incidence of fatal hemorrhage in APL is 5-17%

- Highest rates are outside academic institutions

Incidence of thrombosis in APL is ~5%

Supportive care

- Transfuse platelets to keep >30-50K/μl
- Transfuse FFP to keep INR<1.5
- Transfuse cryo to keep fibrinogen >150mg/dl

Park JH et al, *Blood* 2011

Fundamentals of induction

Most common therapy for 40+ years: “7+3” x 1-2 cycles

- Anthracycline x 3 days

  Daunorubicin 60-90mg/m^2/day

  Idarubicin 10-12 mg/m^2/day

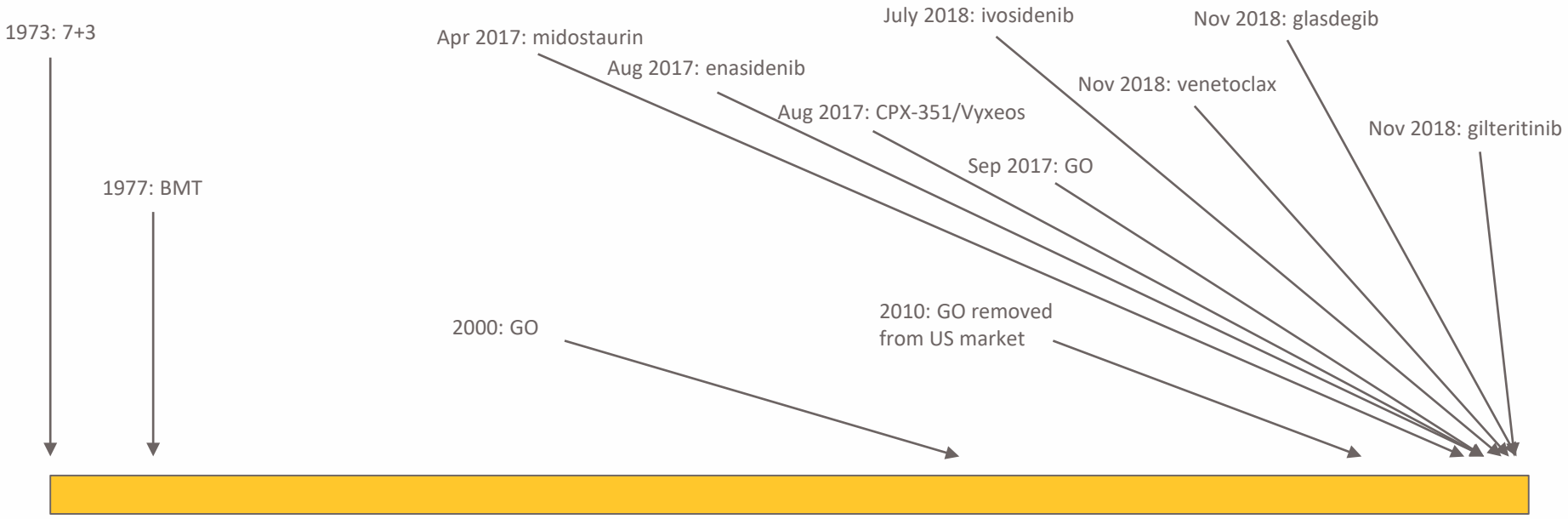
  Mitoxantrone 12-15 mg/m^2/day
- Cytarabine 100-200mg/m^2/day continuous infusion x 7 days

Other options: high-dose cytarabine containing (IA, FLAG-ida or G-CLAM)

NCCN guidelines: “The best management of any cancer patient is in a clinical trial.”

Yates JW et al, *Cancer Cehmother Rep* 1973

New AML drug approvals



Issues with recent drug approvals

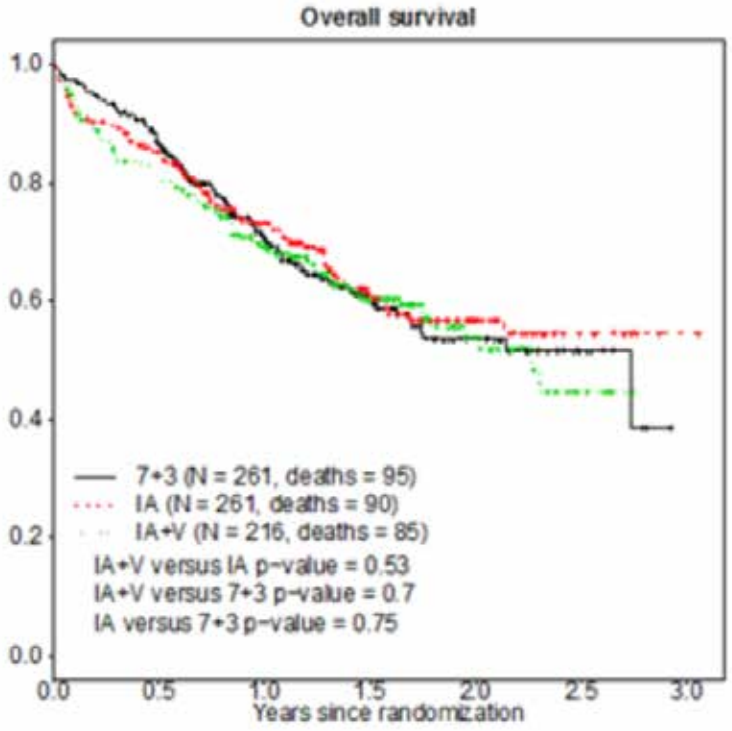
- Many single-arm phase 1/2 studies
- FDA label not always consistent with population studied
- Few drug combinations examined
- Drug hierarchy unknown (which mutation to prioritize, how to sequence treatments, etc.)
- What is the definition of “unfit”?

7+3 vs. high-dose Ara-C in induction

SWOG 1203: 738 patients randomized to 7+3 vs. IA vs. IA+vorinostat

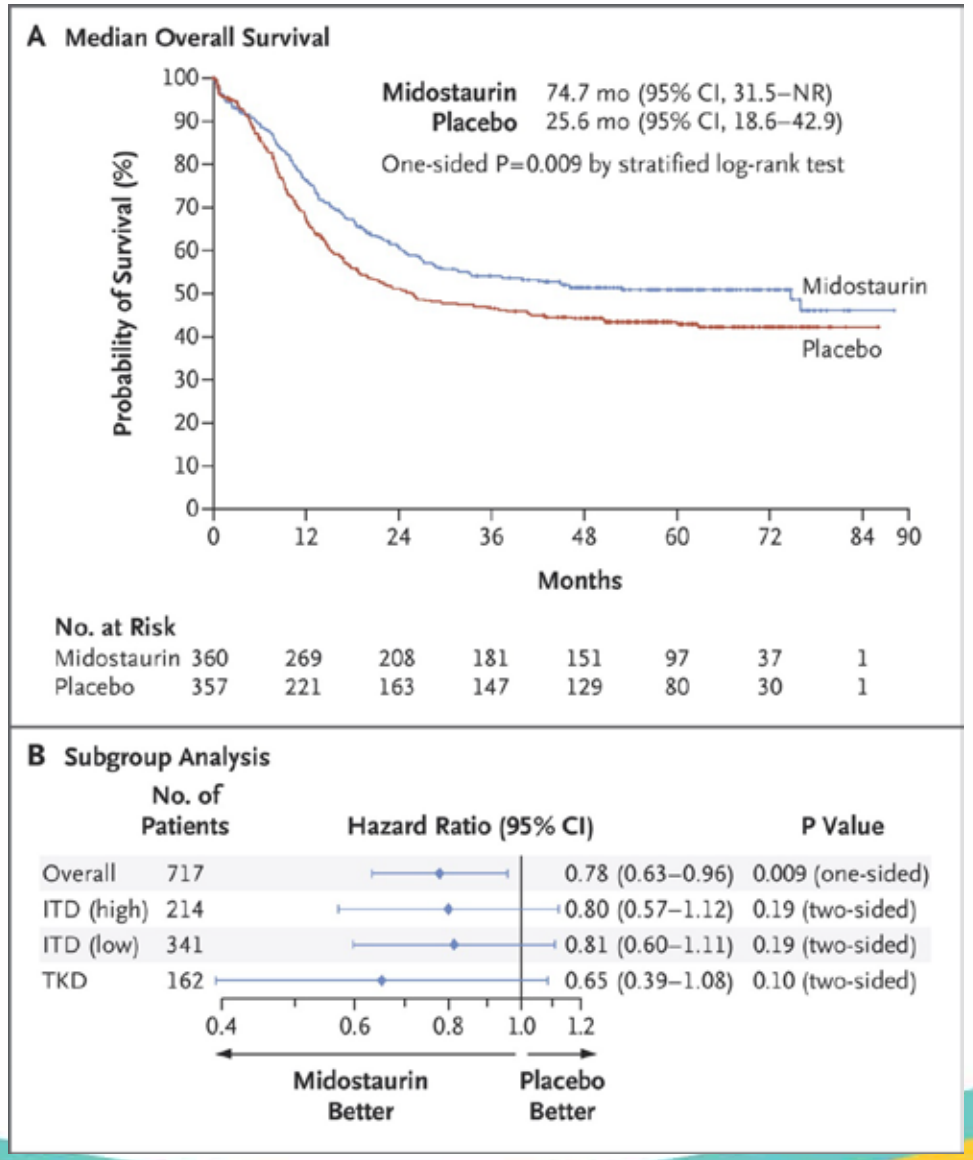
No differences in EFS, RFS, or OS

Favorable cytogenetics: outcomes were inferior with IA or IA+V (?Ara-C dose)



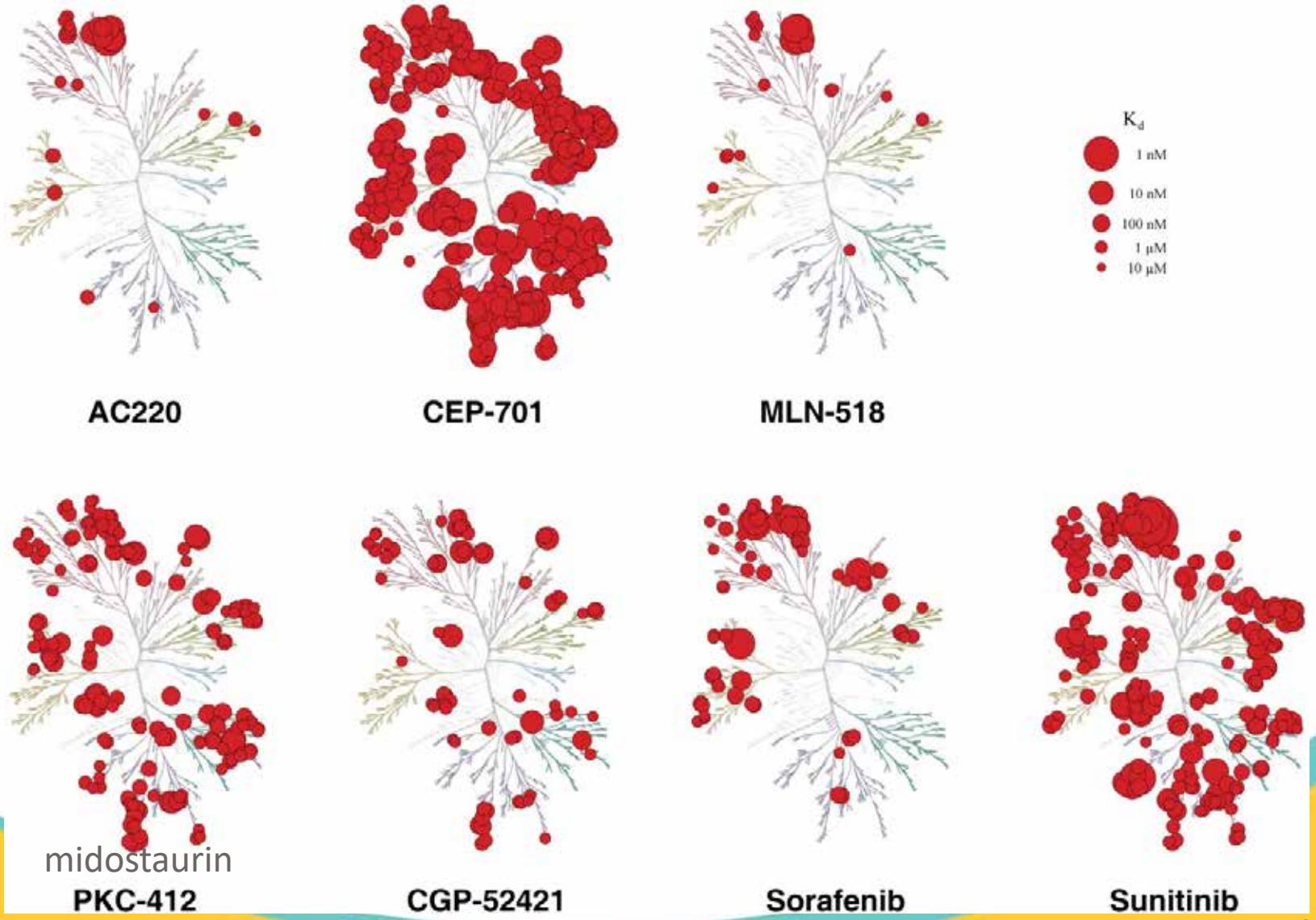
Garcia-Manero et al, *ASH annual meeting* 2016

Addition of midostaurin in *FLT3*+ AML



Stone RM et al. *N Engl J Med* 2017

Selectivity of FLT3 inhibitors



Zarrinkar PP et al, *Blood* 2009

FDA approval 2017: GO

- Gemtuzumab ozogamicin, first antibody-drug conjugate ever developed
- Targets CD33 (splice variants may be important for response)
- Approved in 2000
- Voluntarily removed from market in 2010
- Meta-analysis of RCTs suggested benefit, particularly in favorable risk
- ALFA-0701: 7+3+GO 3mg/m^2 on days 1, 4, 7
- Side effects: prolonged cytopenias (particularly thrombocytopenia) and SOS

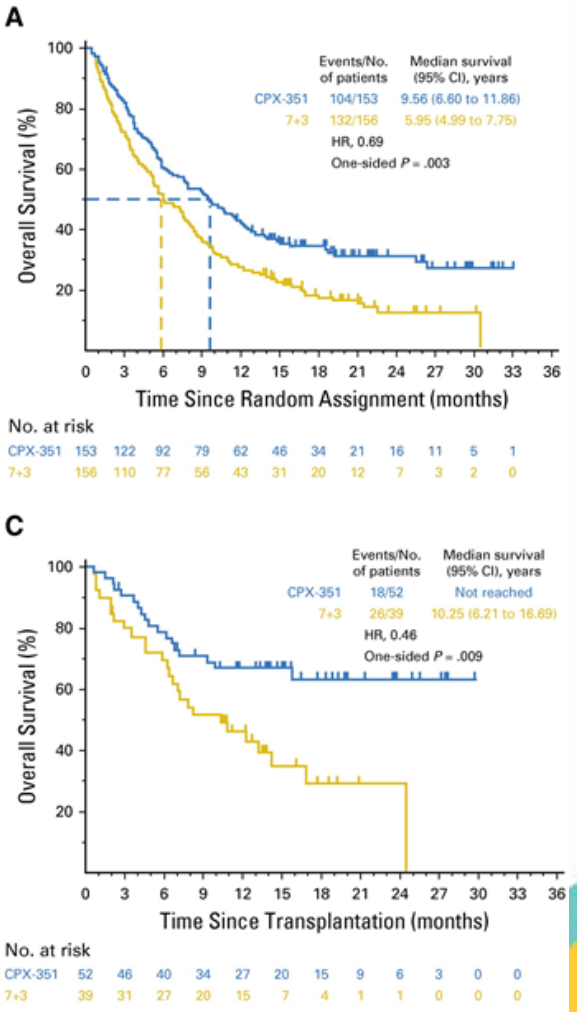
Side notes:

- APL is highly sensitive to GO
- Also approved for R/R disease as a single-agent

Hills RK et al, *Lancet Oncol* 2014; Lamba JK et al, *JCO* 2017; Lambert J, *Haematologica* 2018

FDA approval 2017: CPX-351 (Vyxeos)

- Liposomal formulation with fixed 5:1 molar ratio of cytarabine:daunorubicin
- Phase 3 randomized trial vs. 7+3
- Eligible: 60-75 years of age with untreated high-risk or sAML
- Superior overall survival (HR=0.69)
  - ➢ Median 9.56 vs. 5.95 months
  - ➢ Improved EFS and 60-day mortality
  - ➢ HIGH rate of grade 3-5 AEs (92% vs. 91%)
  - ➢ More patients underwent alloHCT, and survival better after alloHCT



Lancet JE et al, *JCO* 2018

Induction at UW/FHCRC/SCCA

Intensive

- GCLAM + sorafenib (age ≤60)
- GCLAM + GO

GCLAM vs. CPX-351 (for TRM≥13.1)

→Induction choices are frequently based on TRM score, allowing for risk-adapted therapy (https://cstaging.fhcrc-research.org/TRM/Default.aspx)

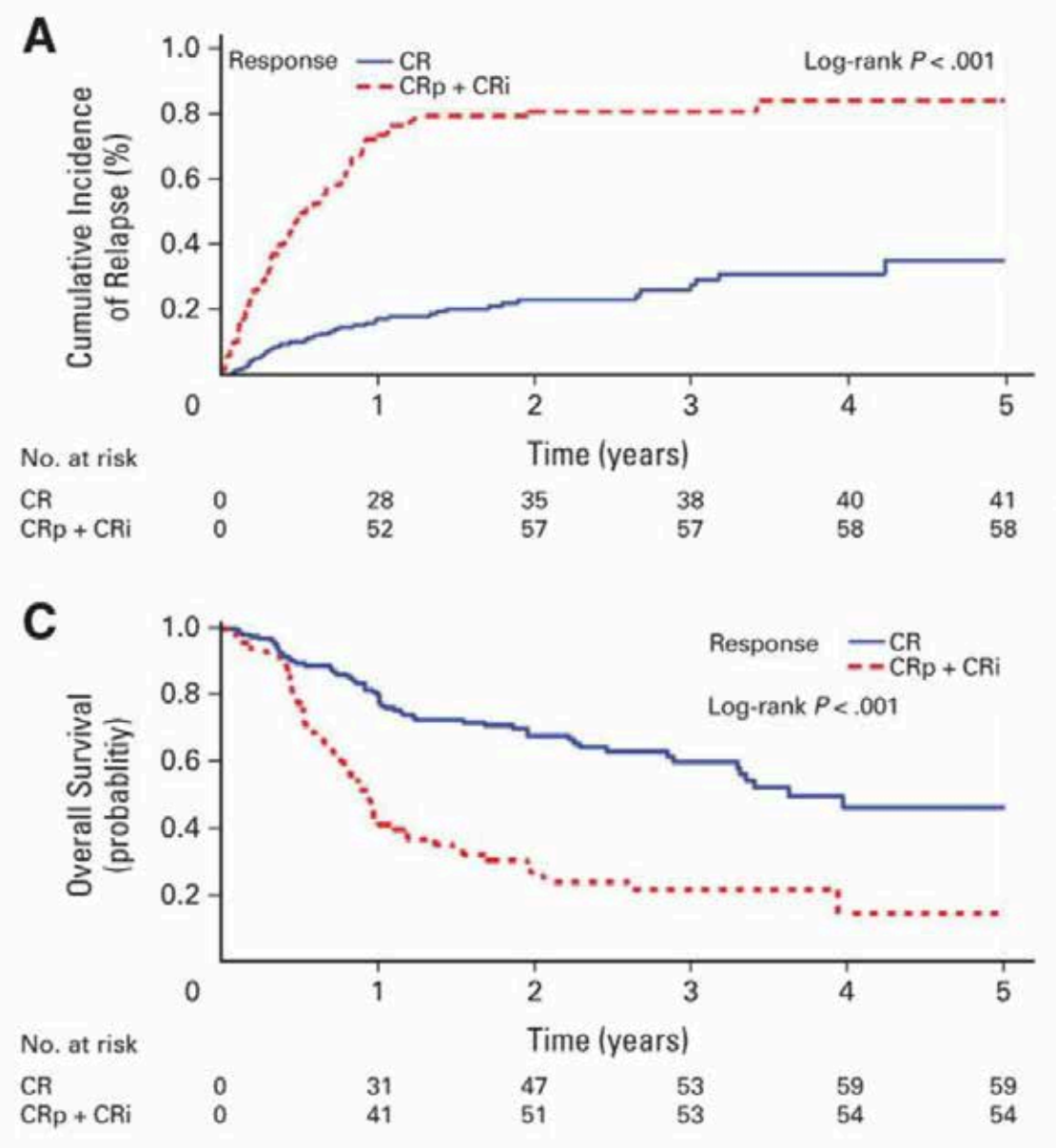
→Clinical trial options change frequently!

Response criteria (ELN 2017)

Response	Definition	Comment
CR without MRD	**CR along with pre-treatment marker by PCR or flow cytometry is negative**	**Sensitivities vary by marker tested and method used**
CR	BM blasts <5%; absence of circulating blasts; absence of extramedullary disease; ANC≥1000/μl; plt≥100K/μl	MRD+ or unknown
CRi	All CR criteria except ANC<1000/μl and/or plt<100K/μl	
MFLS	Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary disease; no hematologic recovery required	Cellularity at least 10% and/or 200 cells counted
PR	Heme criteria of CR; decrease of BM blasts to 5% to 25%; and decrease of pretreatment BM blast percentage by at least 50%	Primarily for clinical trials

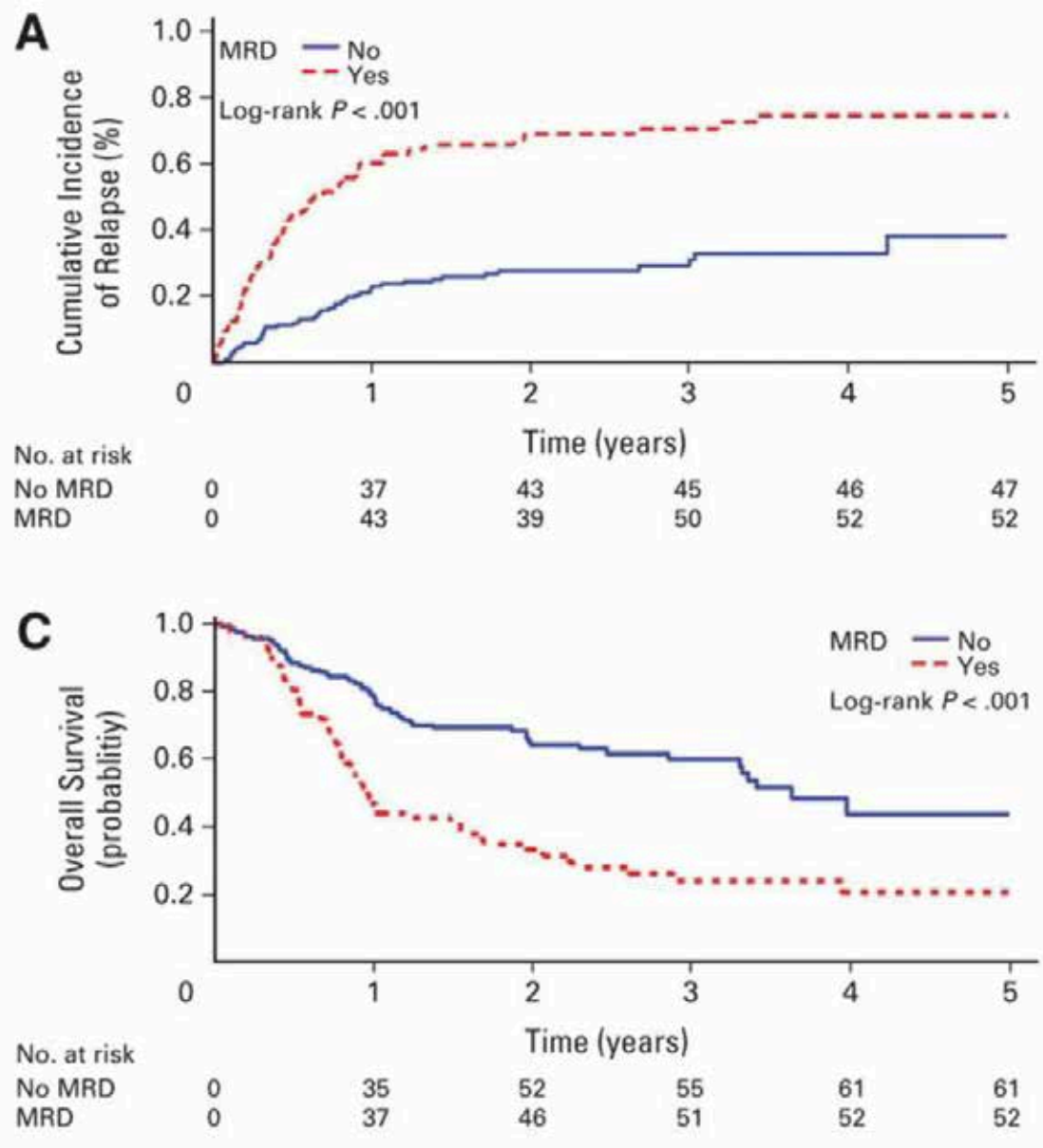
Dohner H et al, *Blood* 2017

Importance of count recovery

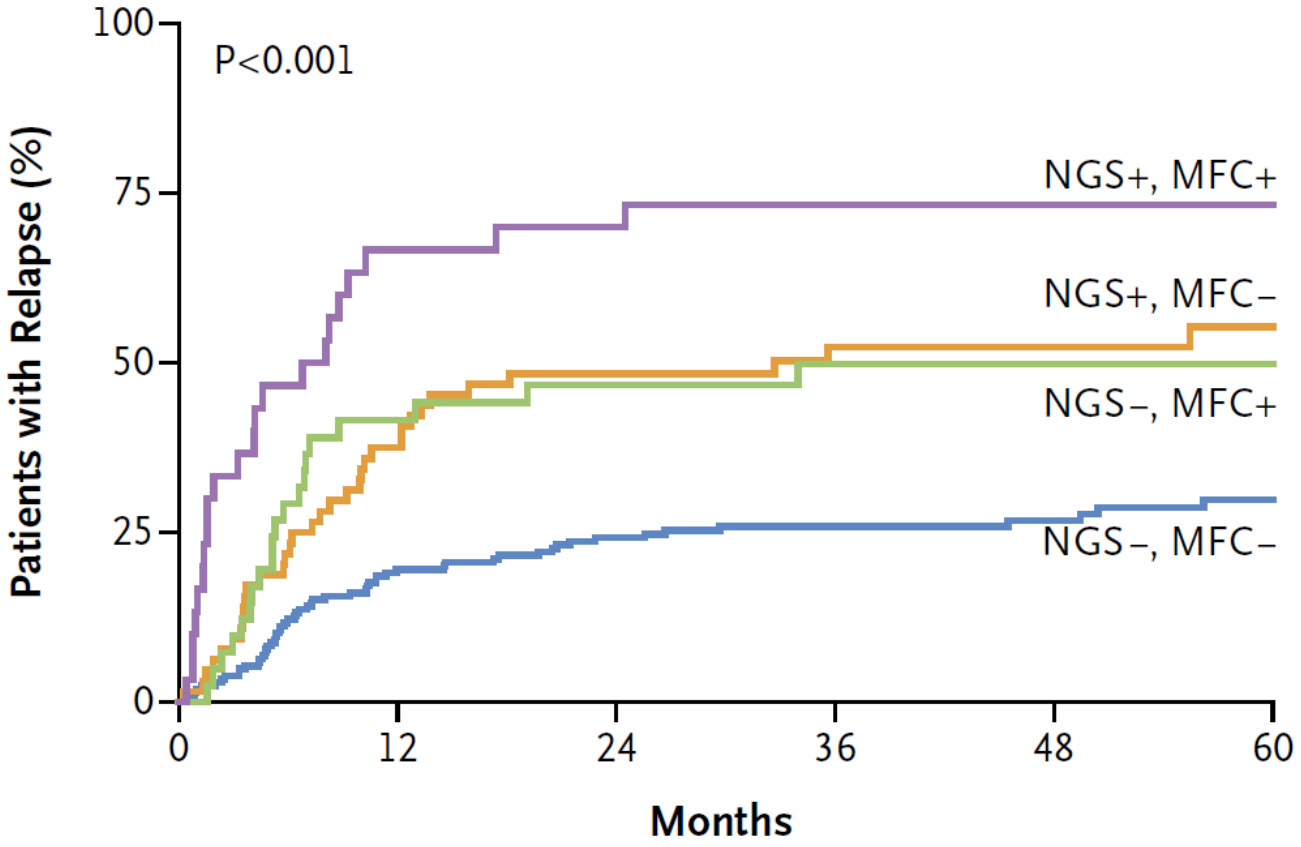


Chen X et al, *JCO* 2015

Importance of MRD



Chen X et al, *JCO* 2015



No. at Risk

NGS+, MFC+	30	8	7	5	4	4
NGS–, MFC+	41	22	18	14	11	7
NGS+, MFC–	64	39	30	22	15	11
NGS–, MFC–	205	153	130	101	69	42

Jongen-Lavrencic et al, *NEJM* 2018

What to do about MRD?

- Outcomes are clearly worse (also as a predictor of post-alloHCT outcomes)
- Clinical trials generally ignore patients with <5% morphologic blasts
- Novel therapies are needed!

Post-remission therapy

Induction x 1-2 cycles

Post-remission therapy:

- Consolidation x 3-4 cycles
  - HiDAC (3g/m^2 q12hr on days 1, 3, 5; or 1g/m^2 q12hr x 12 doses)
- Allogeneic transplant (for intermediate or high-risk AML)

Maintenance:

- midostaurin x 1 year in *FLT3*-mutated patients who do not undergo alloHCT
- 5-day azacitidine in patients >60 after 2 courses of intensive chemo

Huls G et al, *Blood* 2019

Management of relapsed AML

Survival for patients attaining CR2

Risk Group	Treatment	5 year OS
Favorable	Chemo	33%
	Allo HCT	88%
Intermediate	Chemo	31%
	Allo HCT	48%
Poor	Chemo	6%
	Allo HCT	26%

Many potential salvage regimens exist, but clinical trial is preferred

Breems DA et al, *JCO* 2005

FDA approval 2017/18: IDH inhibitors

Found in 10-20% of newly diagnosed AML, and increase in frequency with age

Ivosidenib (AG-120): selective IDH1 inhibitor

- Approved for newly diagnosed and R/R AML

Enasidenib (AG-221): selective IDH2 inhibitor

- Approved for R/R AML

Pros	Cons
CR rate 19.3%; ORR 40.3%	Comparative efficacy unknown
Oral	Combination with chemo?
Well-tolerated	Differentiation syndrome (~10%)

Stein EM et al, *Blood* 2017; DiNardo et al, NEJM 2018; Paschka P et al, *EHA annual meeting abstracts* 2016

Salvage regimens at UW/FHCRC/SCCA

Straight to alloHCT (radiolabeled antibody)

Bispecific antibodies

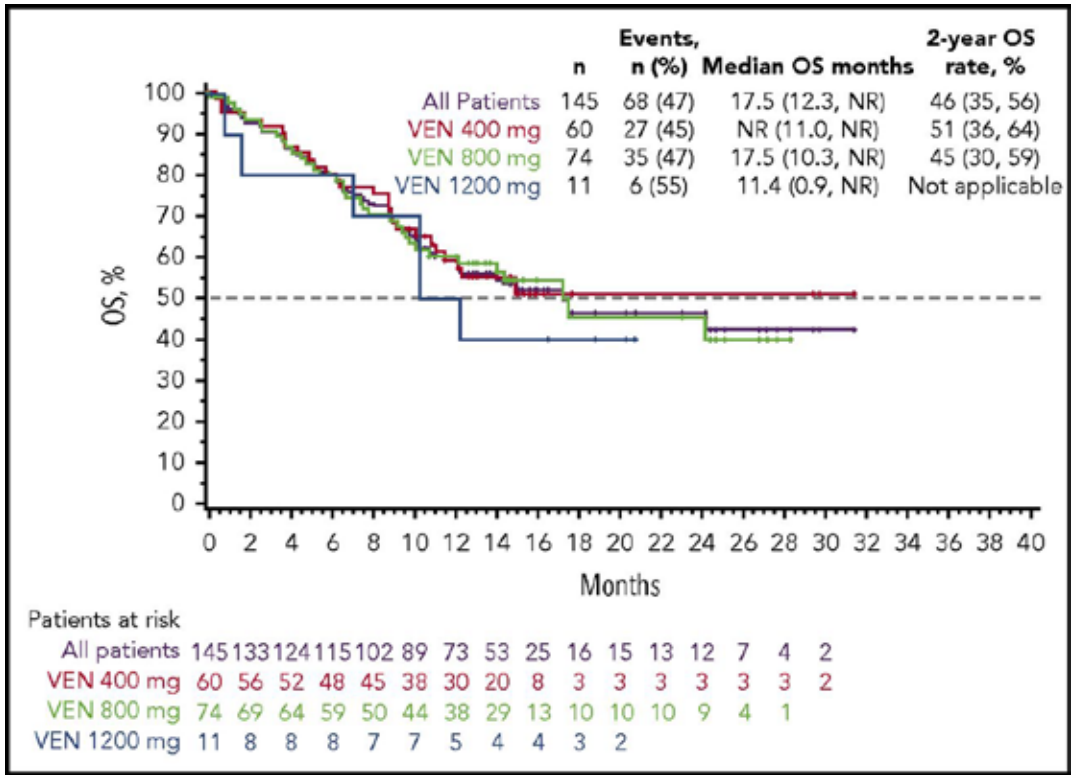
Polo-kinase inhibitor + decitabine/cytarabine

…

→Clinical trial options change frequently!

FDA approval 2018: venetoclax

- Venetoclax for ND older AML (plus azacitidine or decitabine)
- CR rate 30%; CRi rate 37%



Courtney D. DiNardo et al. Blood 2019;133:7-17

FDA approval 2018: gilteritinib

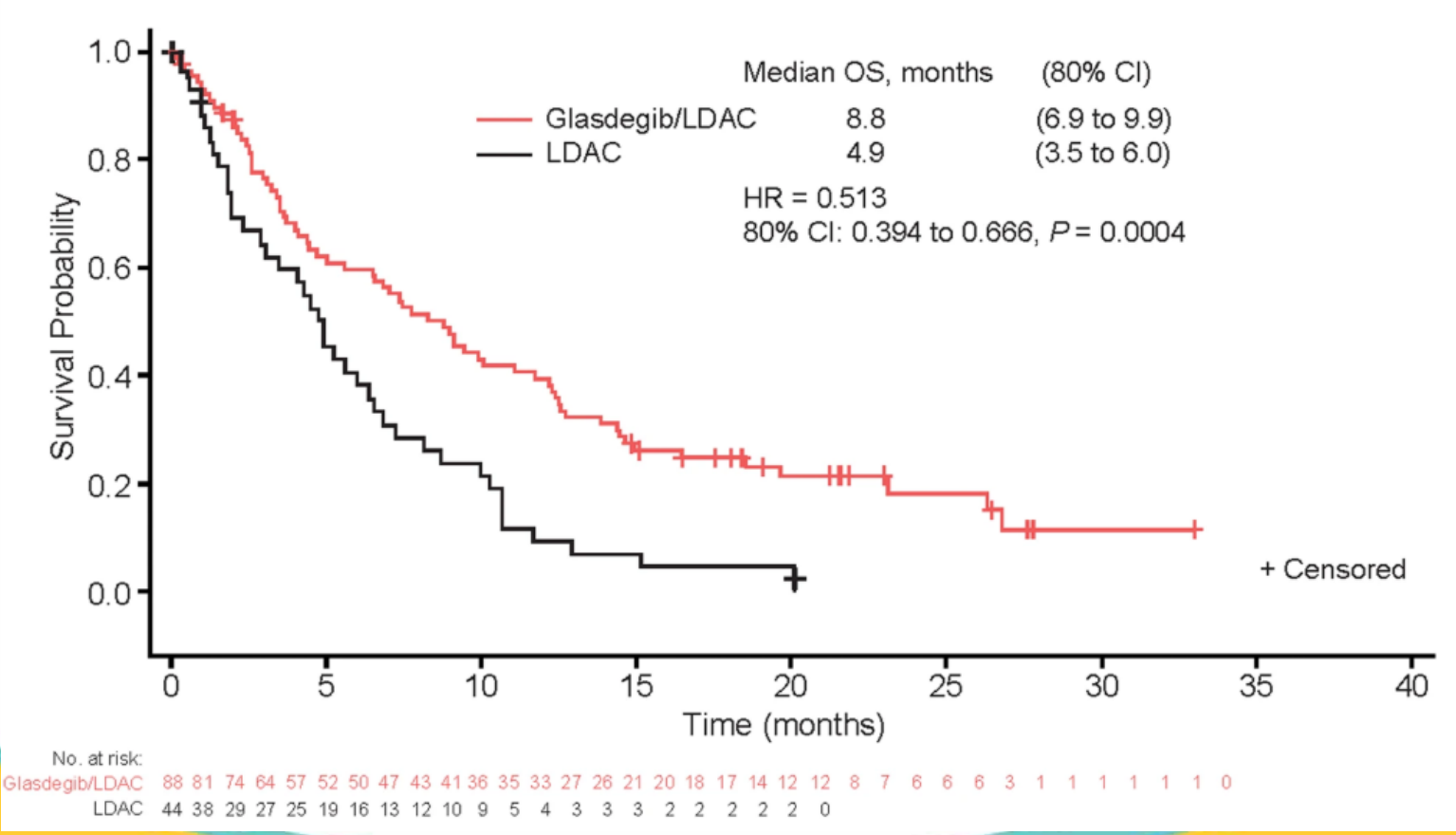
- ADMIRAL trial: phase 3 RCT of gilteritinib vs. salvage in R/R *FLT3*-mutated AML
- 371 patients randomized 2:1
  - Gilteritinib: n=247
  - Salvage: n=124 (MEC 25.7%, FLAG-ida 36.7%, LoDAC 14.7%, aza 22.9%)
- OS favored gilteritinib (HR 0.637, p = 0.0007)
  - Median OS 9.3 months vs. 5.6 months

Ongoing trials:

- Gilteritinib + induction/consolidation (NCT02236013)
- Gilteritinib vs. aza vs. combo (NCT02752035)
- Gilteritinib maintenance post-chemo (NCT02927262) and post-HCT (NCT02997202)
- Gilteritinib + venetoclax (NCT03625505)
- Gilteritinib vs. midostaurin (NCT03836209)

FDA approval 2018: glasdegib

- Hedgehog pathway inhibitor
- Approved +/- low dose cytarabine



Cortes JE et al, *Leukemia* 2019

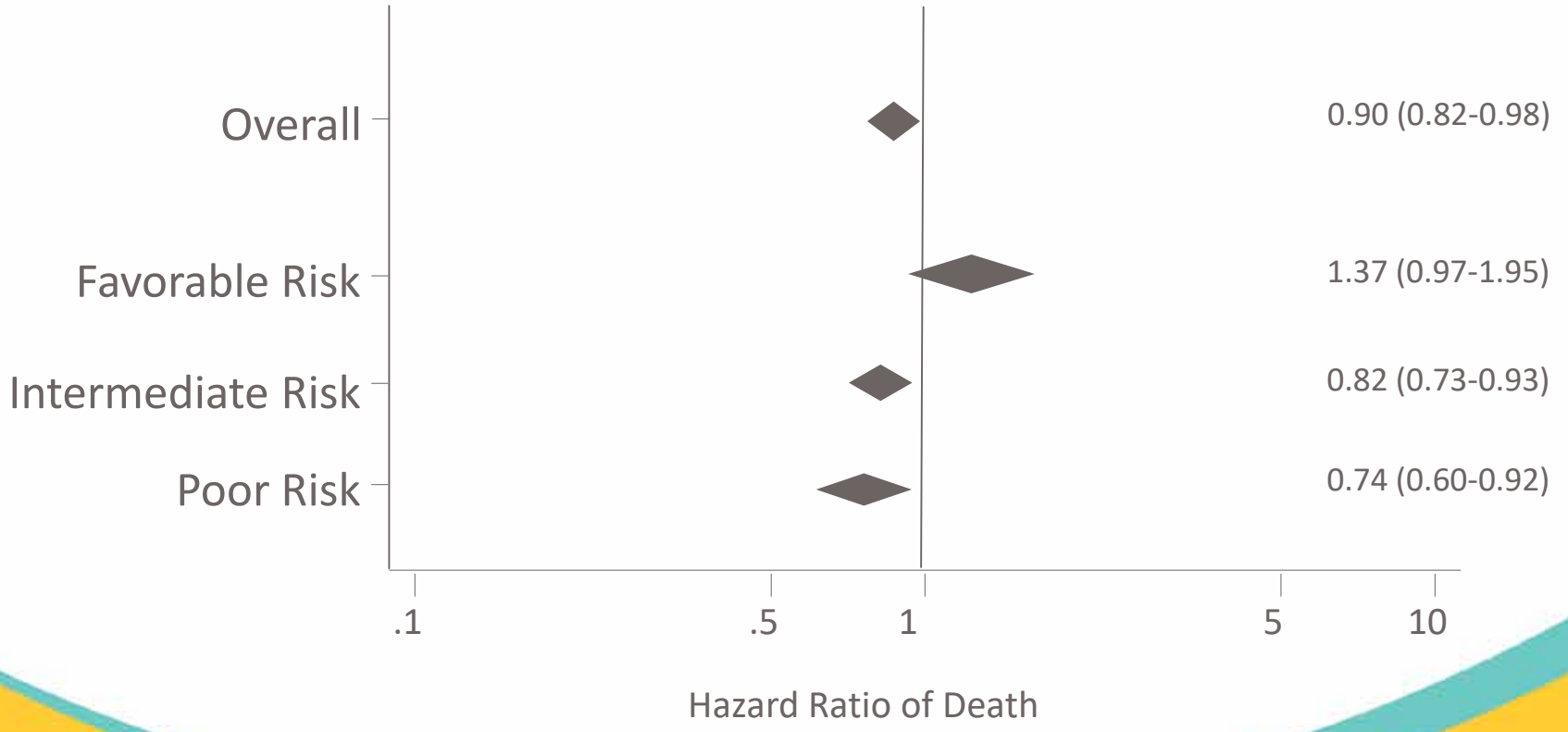
Indications for transplant referral

- Intermediate or adverse risk AML in CR1
- AML in CR2
- Primary refractory AML

- ?CR with incomplete count recovery
- ?CR or CRi with MRD

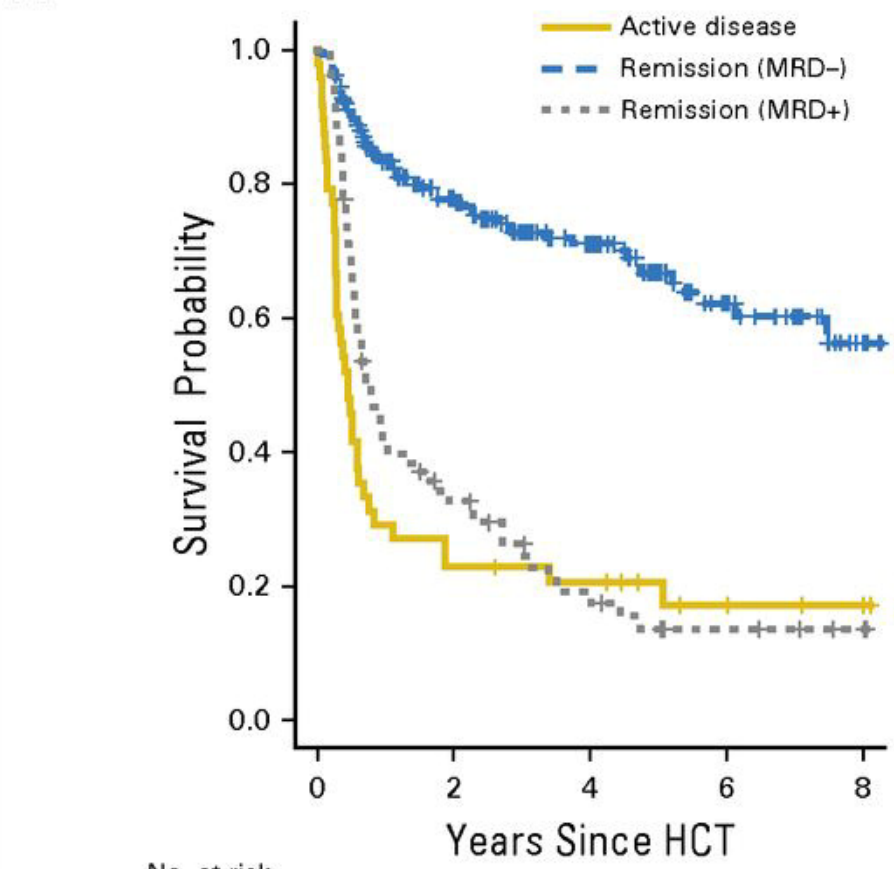
Meta-analysis of survival using allo HCT in CR1

- **Randomized trials = 23**
- **Patients = 5,839**



Koreth, et al JAMA 301:2349, 2009

Post-transplant survival with MRD



No. at risk					
Active disease	48	11	9	4	2
Remission (MRD–)	235	136	80	34	8
Remission (MRD+)	76	22	11	5	2

Araki D et al, *JCO* 2016

Older AML

Is age just a number?

- TRM score can be helpful in stratifying risk of death during induction

Retrospective analyses: older patients benefit from higher-intensity therapy

ELN 2017: older age *plus* another factor for non-intense therapy

- Patient-related factors, such as ECOG PS 3-4 or significant co-morbidities not related to AML
- Disease-related factor, such as adverse-risk genetics

Juliusson G et al, *Blood* 2009; Dohner H et al, *Blood* 2017

Alternatives to intensive induction

- Azacitidine (+/- venetoclax)
- Decitabine (10-day induction)→?particularly in *TP53*-mutated AML
- Low dose cytarabine (+/- glasdegib, venetoclax)
- Clofarabine
- Lenalidomide (5q-)
- CPX-351, a.k.a. Vyxeos (is it really less intense?)

- InDACtion study (NCT02172872)

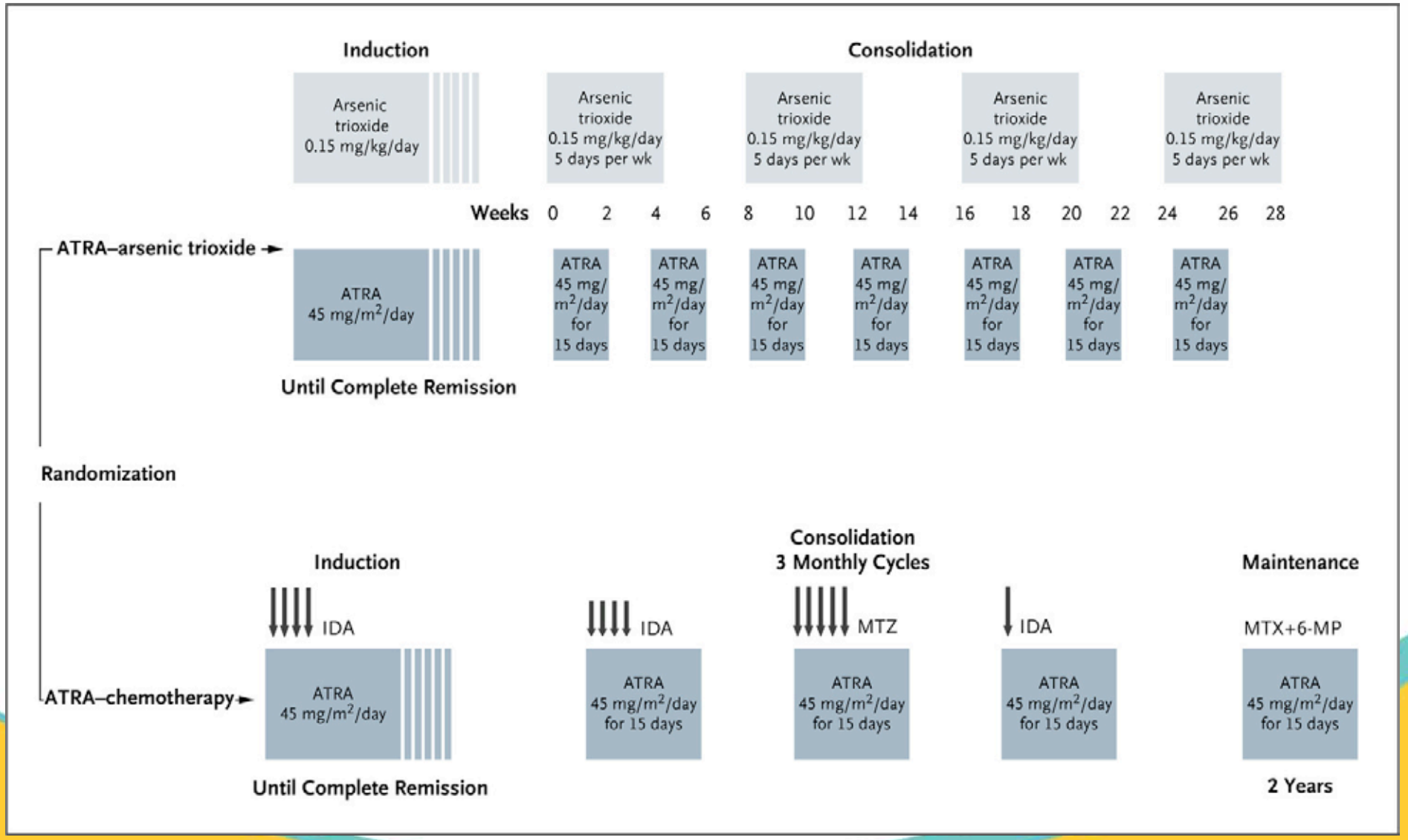
Blum W et al, *PNAS* 2010; Welch JS et al, *NEJM* 2016

Acute promyelocytic leukemia

- ~10% of new AML (1200 pts/year in US)
- Leukopenia in 85%
- Divided into low vs. high-risk depending on WBC count at diagnosis

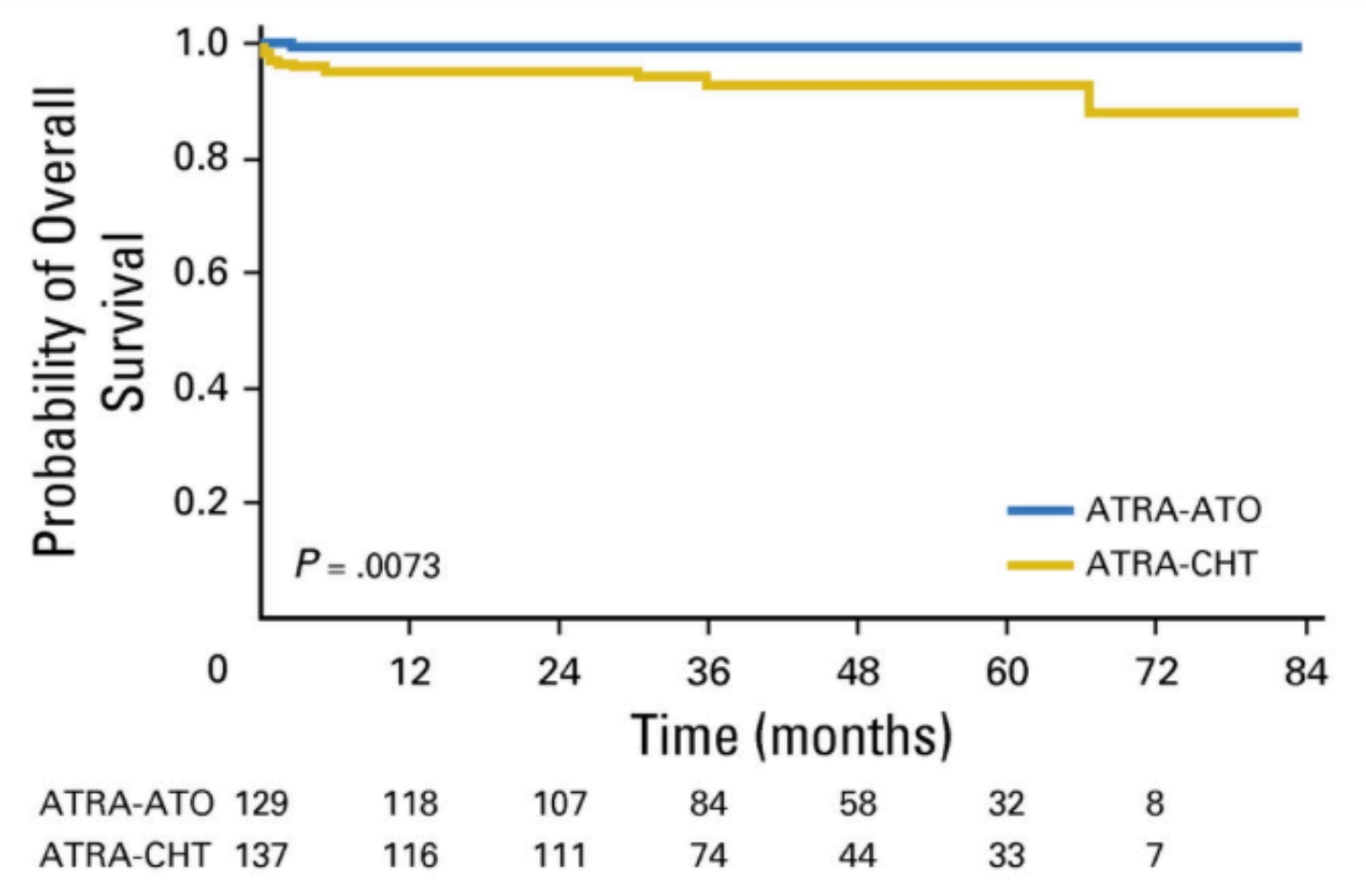
  →high risk = ≥10,000/μl
- Common to have coagulopathy at diagnosis
- t(15;17)→PML-RARα fusion transcript
- Differentiation syndrome can happen with ATRA or ATO (treat promptly with dexamethasone)

“Lo-Coco regimen”



Lo-Coco F et al, *NEJM* 2013

APL 0406 trial: ATRA + ATO



Platzbecker U et al, *JCO* 2017

Contact with questions

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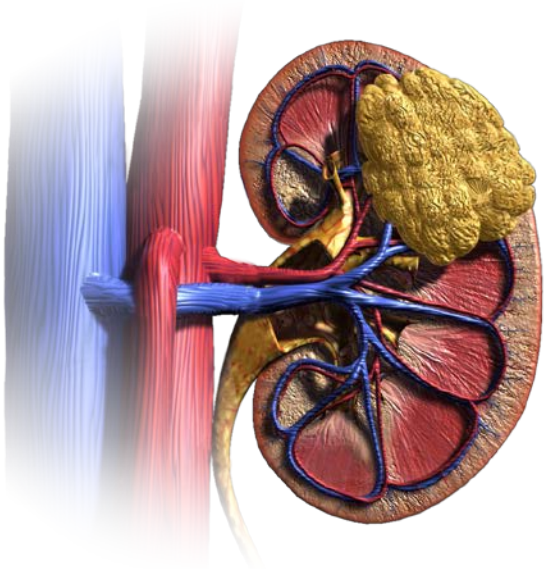
Comprehensive HemOnc Review:
Renal Cell Carcinoma



Scott S. Tykodi, MD, PhD

October 4, 2020

Seattle Cancer Care Alliance

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- **Research Funding**
  - Bristol-Myers Squibb
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  - Exelixis
  - Jounce Therapeutics
  - Merck
  - Nektar Therapeutics
  - Pfizer
- **Consulting**
  - Merck

Learning Objectives

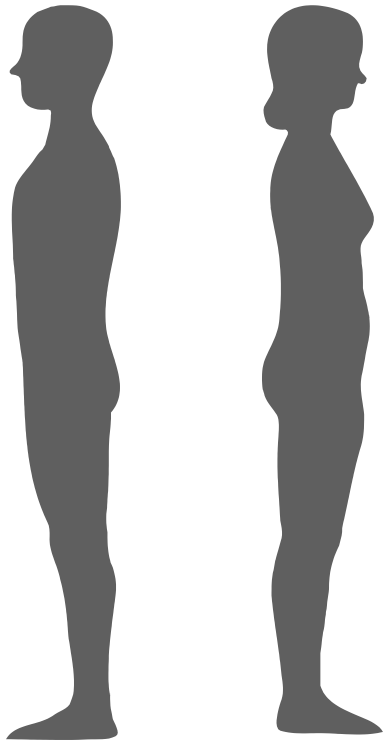
- RCC Epidemiology
- Hereditary RCC cancer syndromes
- Risk Stratification
- Cytoreductive Nephrectomy
- Systemic Treatments Overview
  - Local RCC - Adjuvant therapy
  - Metastatic RCC
    - → 1st line
    - → 2nd line
    - → Clinical subsets

Epidemiology

2020 - Estimated US New Cancer Cases*

2020 US Estimates:
- **73,750 new cases**
- **14,830 deaths**

Men 893,660		Women 912,930	
Prostate	21%	30%	Breast
Lung & bronchus	13%	12%	Lung & bronchus
Colon & rectum	9%	8%	Colon & rectum
Urinary bladder	7%	7%	Uterine corpus
Melanoma of skin	7%	4%	Melanoma of skin
Kidney & renal pelvis	5%	4%	Thyroid
Non-Hodgkin lymphoma	5%	4%	Non-Hodgkin lymphoma
Oral cavity & pharynx	4%	3%	Kidney & renal pelvis
Pancreas	3%	3%	Pancreas
Liver and bile duct	3%	2%	Ovary
All Other Sites	23%	23%	All Other Sites



*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder.
American Cancer Society: www.cancer.org.

Why Me?

Associations and Risk Factors for RCC

- **Male > female 2:1**
- **Age – median 64**
- **Genetic predisposition**
- **Smoking**
- **Obesity**
- **Uncontrolled hypertension**

3 modifiable RF's associated with 49% of cases

- Occupational exposure to toxins - Organic solvents (Benzene, TCE), cadmium, asbestos
- Disease associations: Long-term dialysis for acquired renal cystic disease; Chronic Hepatitis C; Sickle cell anemia (medullary carcinoma of the kidney); Solid organ transplant recipient
- Drug associations: Phenacetin, aspirin abuse (renal pelvis tumors); Prior cytotoxic chemotherapy (translocation RCC)

Staging system for RCC

AJCC 8th ed., 2017

Stage I
Tumor < 7 cm in greatest dimension and limited to kidney

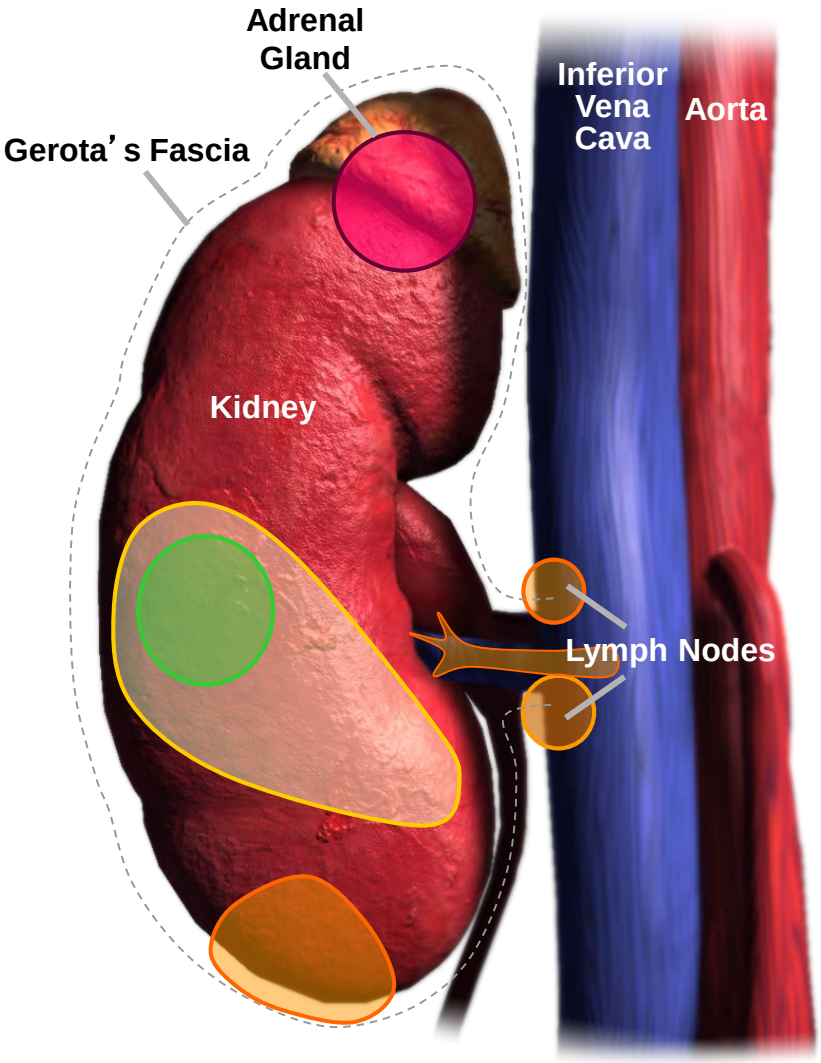
- **Ia** < 4 cm
- **Ib** > 4 to < 7 cm

Stage II
Tumor > 7 cm in greatest dimension and limited to kidney

- **IIa** > 7 to < 10 cm
- **IIb** > 10 cm

Stage III
Tumor major veins, tumor within Gerota's fascia, or regional lymph node involved

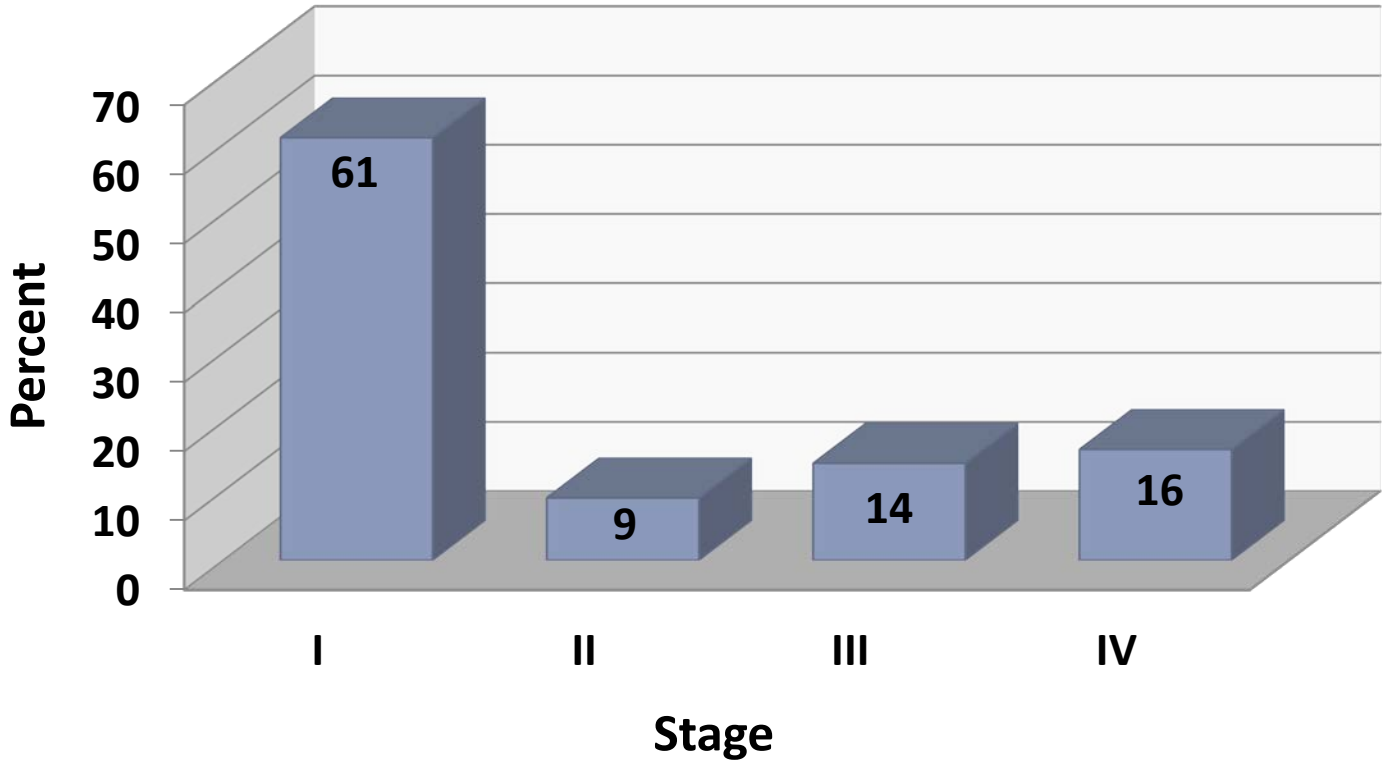
Stage IV
Tumor invasion beyond Gerota's fascia, adrenal or distant metastases



AJCC Cancer Staging Manual, 8th edition. New York: Springer; 2017.

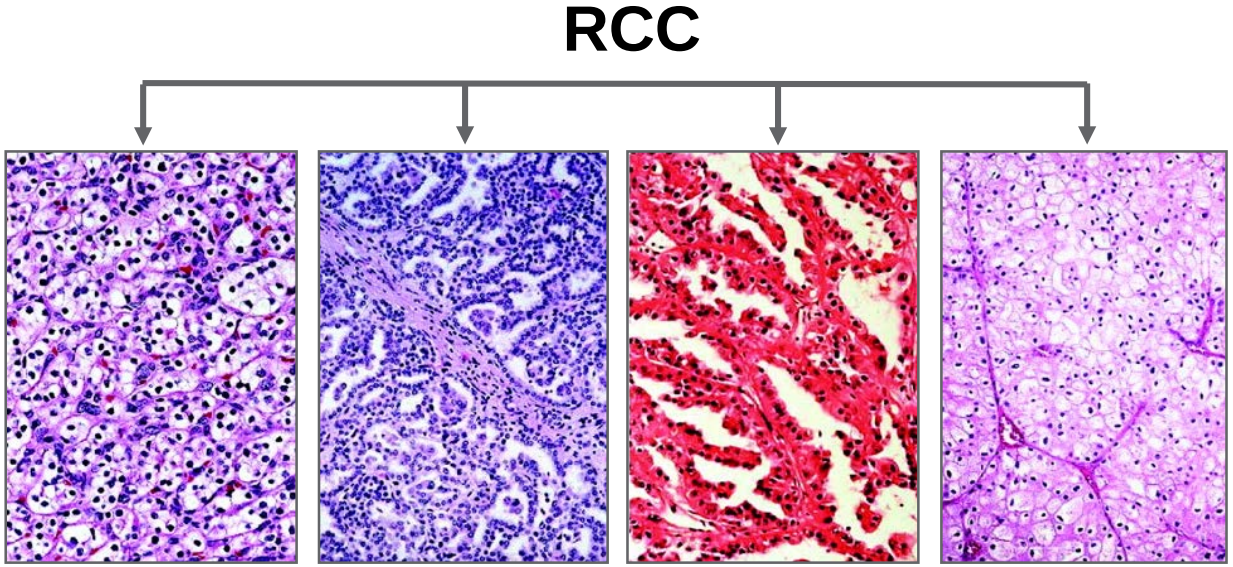
RCC Stage at Diagnosis, 2004-2014

National Cancer Database (NCDB),
1442 hospitals; N=371,851



https://oliver.facs.org/BMPub/Docs/

Common histologic subtypes of RCC



Type	Clear cell	Papillary type 1	Papillary type 2	Chromophobe	*Unclassified*
Incidence	75%	5%	10%	5%	2-6%
Associated Germline Mutations	*VHL* *SDH* *BAP1* *TSC1/2*	*Met*	*FH*	*FLCN* *TSC1/2* *PTEN*	

Plus

- Translocation RCC
- Medullary
- Collecting Duct

VHL = von Hippel-Lindau;
SDH = succinate dehydrogenase;
FH = fumarate hydratase;
FLCN = folliculin;
TSC = tuberous sclerosis complex

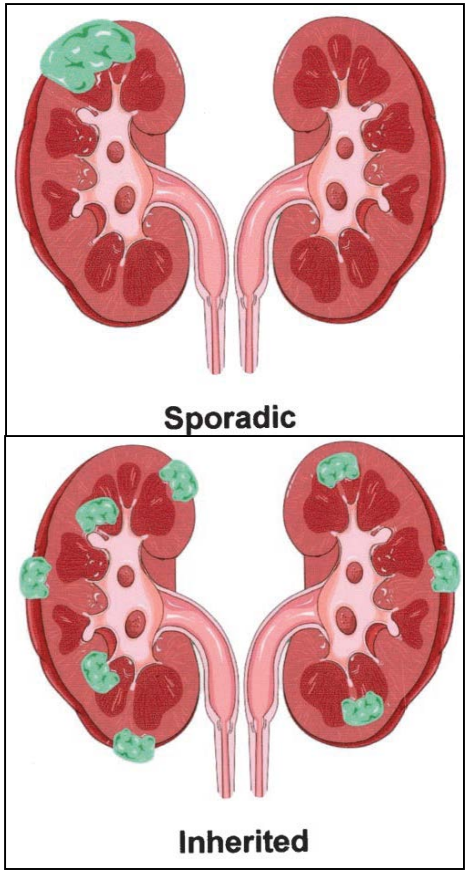
Modified from Linehan *et al*. J Urol. (2003) 170:2163-2172.
Ho and Jonasch. JNCCN. (2014) 12:1347.

Hereditary RCC

Referral criteria for genetic counseling

- All common histologic subtypes of RCC can be associated with a hereditary syndrome
- Kidney cancer age of onset ≤ 46 years (mean 37 years)
- Bilateral/multifocal kidney tumors
- Family history of kidney cancer
- Association with other clinical features of a recognized cancer syndrome

- Germline mutation incidence in unselected RCC patients with advanced disease – 16%



Linehan *et al*. J Urol. (2003) 170:2163-2172.
Carlo, MI *et al*. JAMA Oncol. (2018) 4:1228-1235.

Risk Stratification

(for Newly Diagnosed Metastatic RCC)

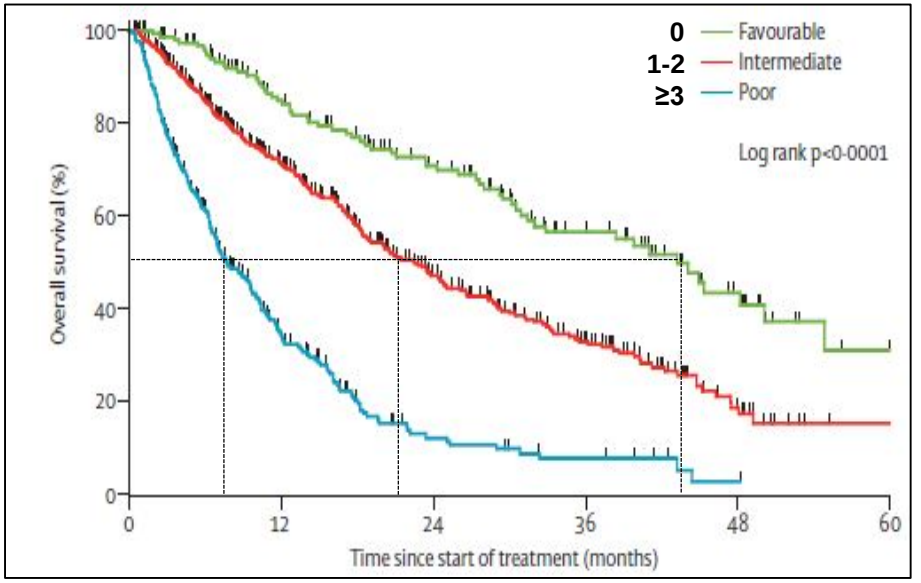
IMDC (Heng) Risk Model for mRCC Treated by Targeted Therapy

International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) Risk Model:

6 Baseline Risk Factors Predict Diminished Overall Survival (OS) in mRCC:

- Diagnosis to systemic treatment < 1 year* (DxTx<1yr)
- Diminished performance status (PS)*
- Elevated corrected calcium*
- Anemia*
- Elevated neutrophils (new)
- Elevated platelets (new)

*Same as MSKCC risk model[3]



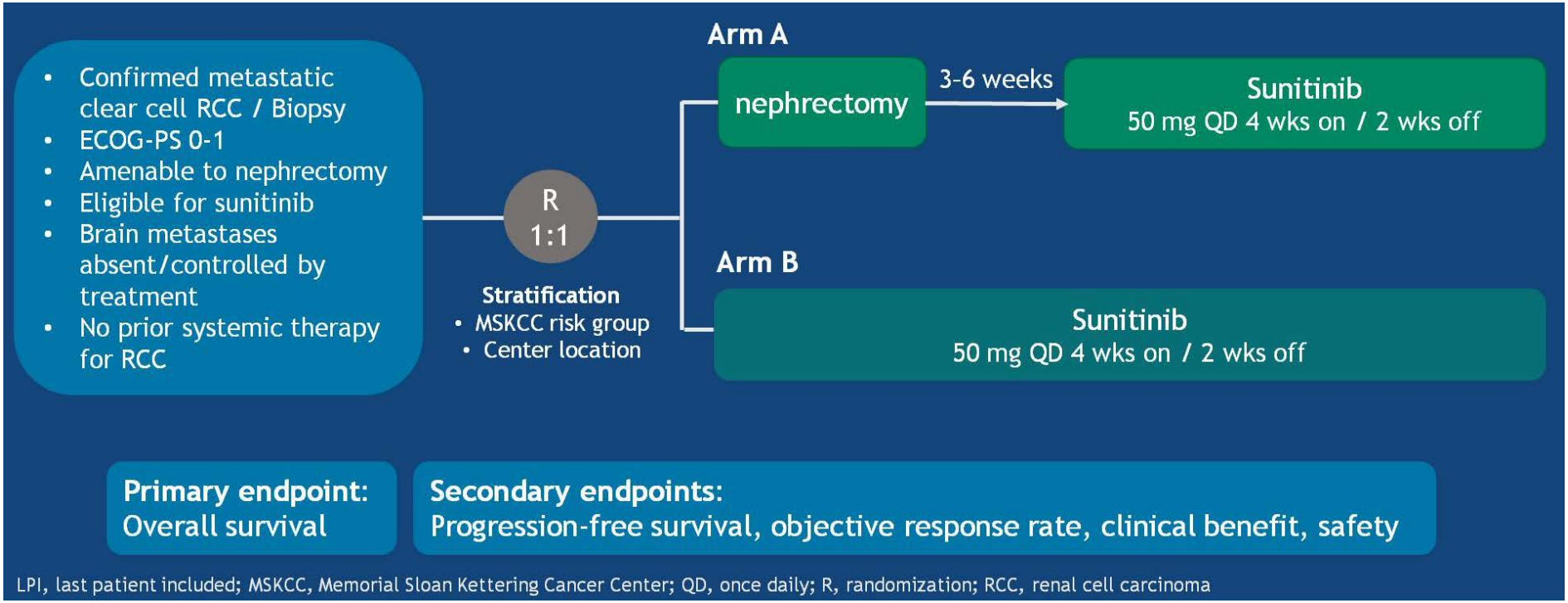
Median OS by IMDC risk group:

- Favorable risk: 43 months
- Intermediate risk: 22.5 months
- Poor risk: 7.8 months

1. Heng, D *et al*. JCO (2009) 27:5794
2. Heng, D *et al*. Lancet Oncology. (2013) 14:141
3. Motzer, RJ *et al*. JCO (2002) 20:289-296

Cytoreductive Nephrectomy (CN)

CARMENA: Prospective, multicenter, open-label, randomized, phase 3 non-inferiority study

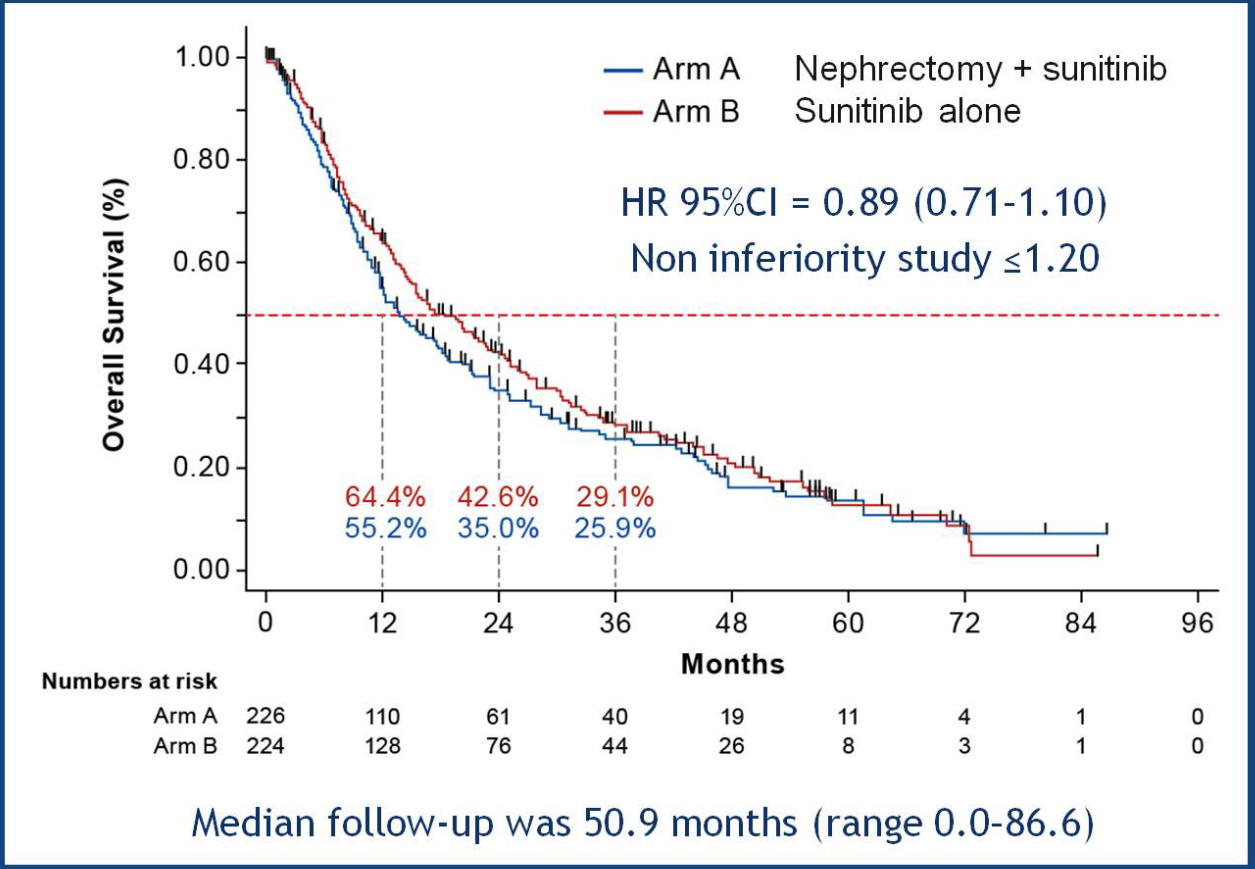


LPI, last patient included; MSKCC, Memorial Sloan Kettering Cancer Center; QD, once daily; R, randomization; RCC, renal cell carcinoma

CARMENA – Primary Endpoint

Overall survival (ITT)

Total enrollment = 450



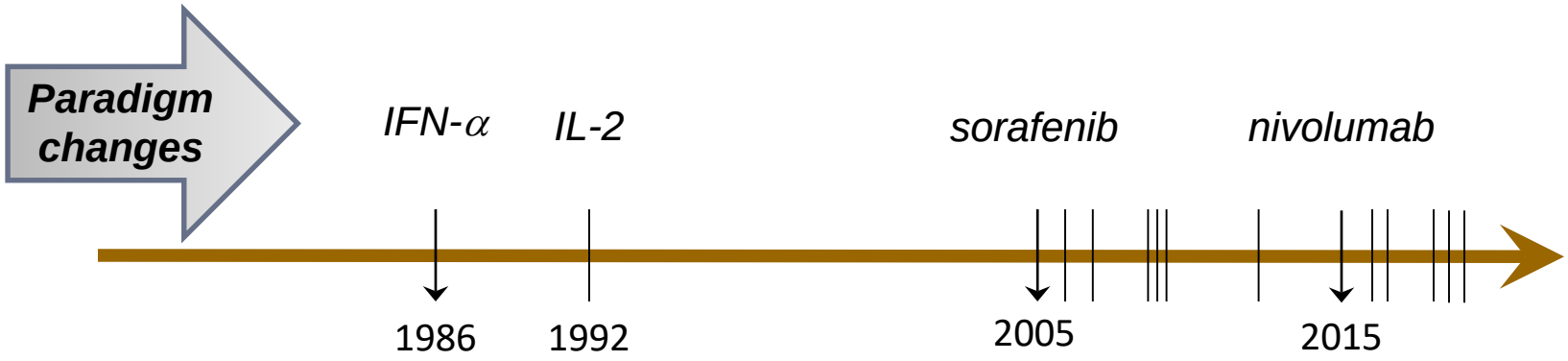
Post CARMENA Role for Initial CN with mRCC?

NO	YES
▪ Patients with similar clinical profile to CARMENA population	▪ Palliation – Hematuria – Flank pain – LUQ mass and weight loss – IVC thrombus ▪ With metastatectomy to surgical NED status

- Can we extrapolate to immune checkpoint blockade?
- ***Consider Multispecialty consultation***

Systemic Therapy Overview

Timeline of Systemic RCC Therapies



No Standard Therapy	Cytokine Immunotherapy	Targeted Therapy	Checkpoint Immunotherapy
cytotoxics	Interferon alfa Interleukin-2	TKI's Sorafenib (2005) Sunitinib (2006) Pazopanib (2009) Axitinib (2012) Cabozantinib (2016) Lenvatinib (2016) Bevacizumab mTOR-Inhibitors	Immune Checkpoint-Blocking Abs Nivolumab (2015) Ipilimumab (2018) Pembrolizumab (2019) Avelumab (2019)

Tools in the Tool Box:
15 FDA-Approved Drugs for Metastatic RCC

Immunotherapy		Targeted Therapy		
		VEGF-Pathway		
Cytokines	Immune Checkpoint Blocking Abs	Antibody	Tyrosine-kinase Inhibitor (TKI)	mTOR Inhibitor
IFN-α (1986) IL-2 (1992)	Nivolumab (2015) Ipilimumab* (2018) Pembrolizumab* (2019) Avelumab* (2019)	Bevacizumab* (2009)	Sorafenib (2005) Sunitinib (2006) Pazopanib (2009) Axitinib (2012) Cabozantinib (2016) Lenvatinib* (2016)	Temsirolimus (2007) Everolimus (2009)

*FDA approval as part of combination therapy

Adjuvant Therapy

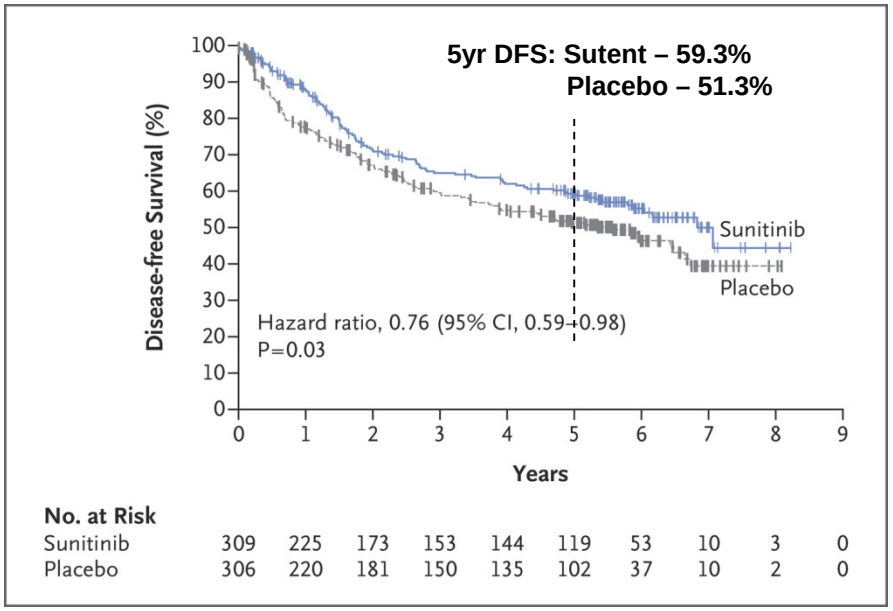
Key Comparisons for Reported Adjuvant Targeted Therapies

Trial	N	Drug	Patients	Histology	DFS	OS
ASSURE	1943	Sunitinib Sorafenib Placebo	pT1b,N0,Gr>2, M0 pT2-4,N0,G(any), M0 pT(any),N1,G(any), M0	80% cc	5.8 yr 6.1 yr 6.6 yr	5yr 77.9% 5yr 80.5% 5yr 80.3%
S-TRAC	720	Sunitinib Placebo	≥ Stage 3, M0	100% cc	6.8 yr 5.6 yr *HR 0.76, P=0.03*	5.4yr 79.3% 5.4yr 79.1%
PROTECT	1500	Pazopanib Placebo	pT2,N0,Gr>2, M0 pT3-T4 N0, G(any), M0 pT(any),N1,G(any), M0	100% cc	ITT_{600mg} *HR 0.862* *P=0.1649*	*HR 0.79* *P=0.16*
ATLAS	722	Axitinib Placebo	≥pT2, any N, M0	100% cc	*Stopped for futility*	NA

Haas, NB *et al*. Lancet (2016) 387:2008–16.
Ravaud, A *et al*. NEJM (2016) 375:2246-54.
Motzer, RJ et al. JCO (2017) 35:3916-3923.
www.clinicaltrials.gov

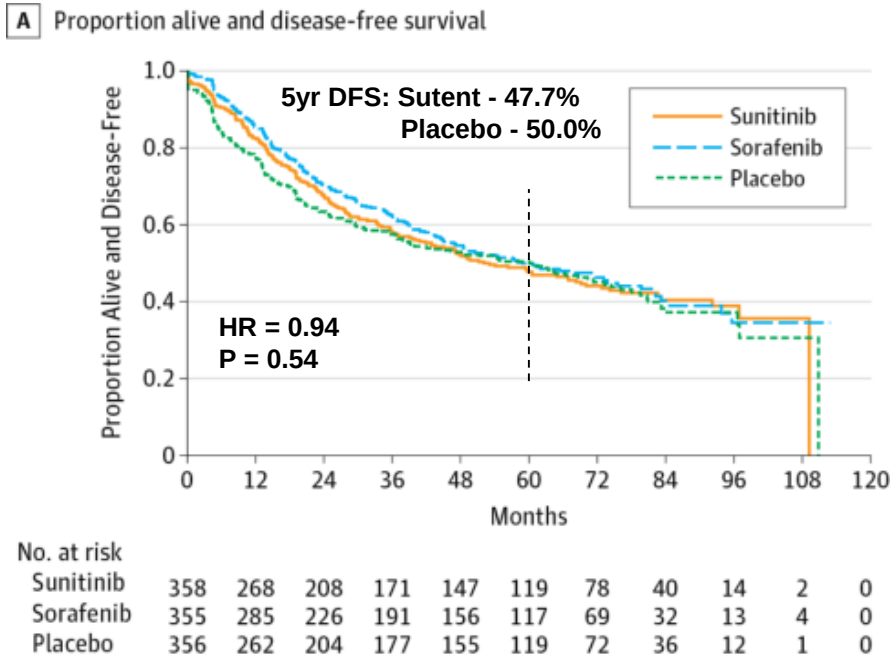
S-TRAC vs ASSURE Subset - DFS Outcomes

S-TRAC



Median DFS: Sutent - 6.8 yrs
Placebo - 5.6 yrs

ASSURE High Risk ccRCC (≥ Stage 3)



Ravaud, A *et al*. NEJM (2016) 375:2246-54.
Haas, NB *et al*. JAMA Oncol. (2017) 3:1249-1252.

First FDA Approval of Adjuvant Treatment for RCC

- Based on S-TRAC results, FDA approved adjuvant Sunitinb November 16, 2017
- Package Insert language - “SUTENT is indicated for the adjuvant treatment of adult patients at high risk of recurrent RCC following nephrectomy.”

  (underlining added for emphasis – no FDA stage or histology requirement)

What are we Doing with Adjuvant Sunitinib in 2020?

- Discordant randomized trials, no OS endpoint, and no data for non-clear cell histology or stage IV NED
- NCCN Category 2B indication for stage III, clear cell RCC

Yes?	No?

• Young patients
• Highest risk
  – Poor prognostic variables
• Good PS (ECOG 0)
	• Elderly
	• Unlikely to maintain dose intensity
	  – Renal dysfunction
	  – Heart disease
	  – GI syndromes
	  – Poor PS
	• ? Non-clear cell histology

Front-Line Systemic Therapy

CheckMate 214 (RCC): Pivotal Phase III Study of IPI + NIVO vs Sunitinib

Key Eligibility Criteria

- Clear cell histology
- No prior treatment
- Tumor tissue available for PD-L1 testing
- Stratification
  - IMDC Risk
  - Geographic location

1:1

N=550

NIVO 3 mg/kg + IPI 1 mg/kg Q3W x 4 doses Followed by NIVO 3 mg/kg Q2W

N=546

Sunitinib 50 mg PO daily, d1-28 Q6W

IMDC RFs (6)

- Diagnosis to tx < 1yr
- PFS < 70%
- Elevated Ca
- Elevated neutrophil
- Anemia
- Elevated plt

IMDC Risk Group

- Good (0 RF)
- Intermediate (1-2 RF)
- Poor (≥ 3 RF)

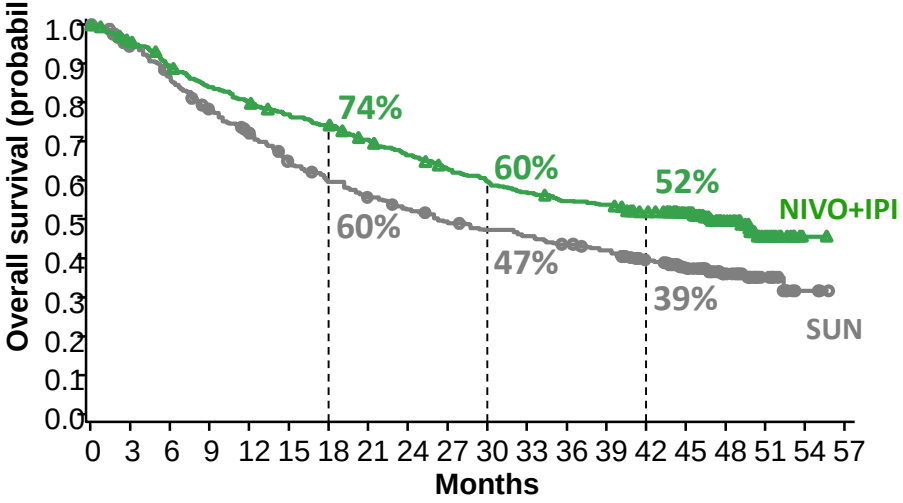
– **Co-primary end points: OS, ORR, PFS in Intermediate and Poor Risk patients**

Motzer, RJ *et al*. NEJM (2018) 378:1277-90.

CheckMate 214: Overall Survival by IMDC Risk

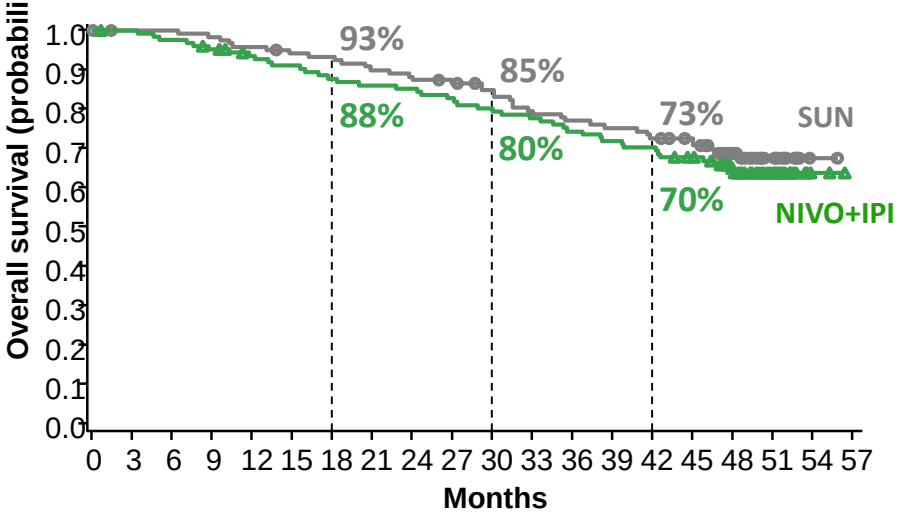
42-Month Follow-Up

Intermediate/poor risk



Minimum follow-up	OS	NIVO+IPI N = 425	SUN N = 422
42 mo	Median, mo (95% CI)	47.0 (35.6–NE)	26.6 (22.1–33.5)
	HR (95% CI)	0.66 (0.55–0.80) *P* < 0.0001	

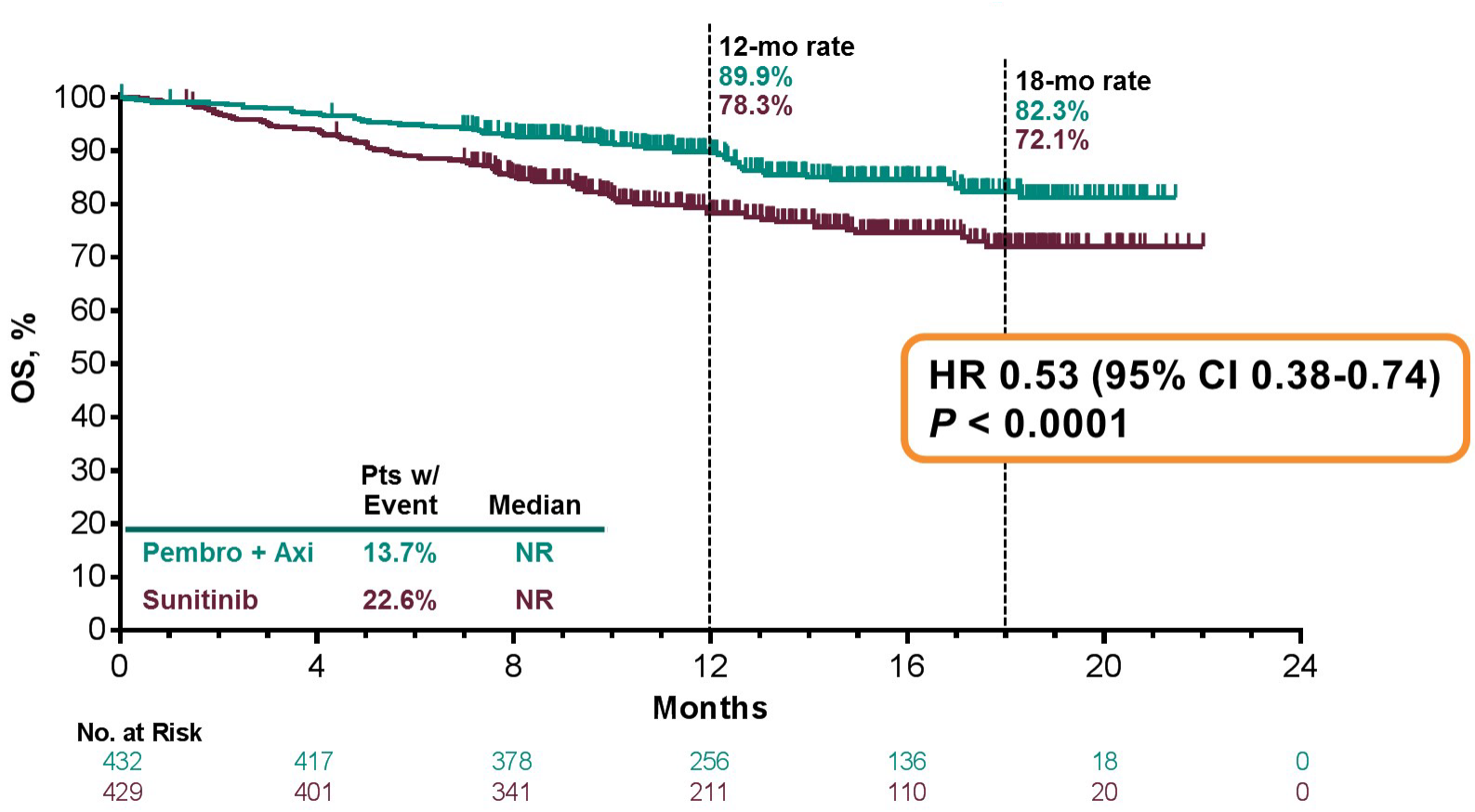
Favorable risk



Minimum follow-up	OS	NIVO+IPI N = 125	SUN N = 124
42 mo	Median, mo (95% CI)	NR (NE)	NR (NE)
	HR (95% CI)	1.19 (0.77–1.85) *P* = 0.4383	

Presented By Nizar Tannir at 2020 Genitourinary Cancers Symposium

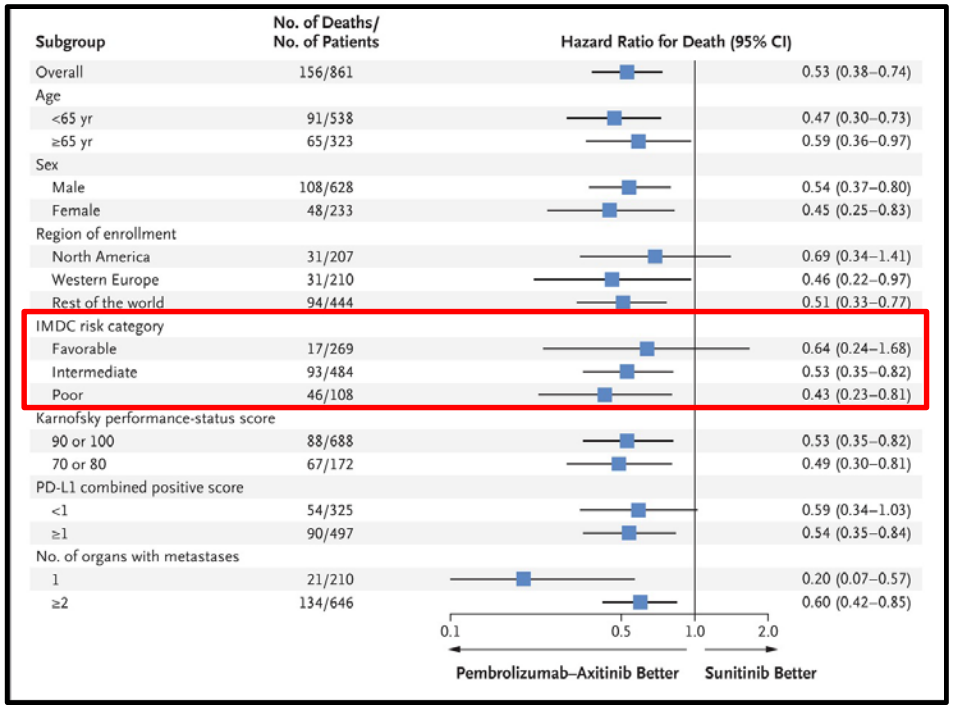
KeyNote 426: Axitinib + Pembrolizumab Survival Outcomes



Rini, BI *et al*. NEJM (2019) 380:1116-1127

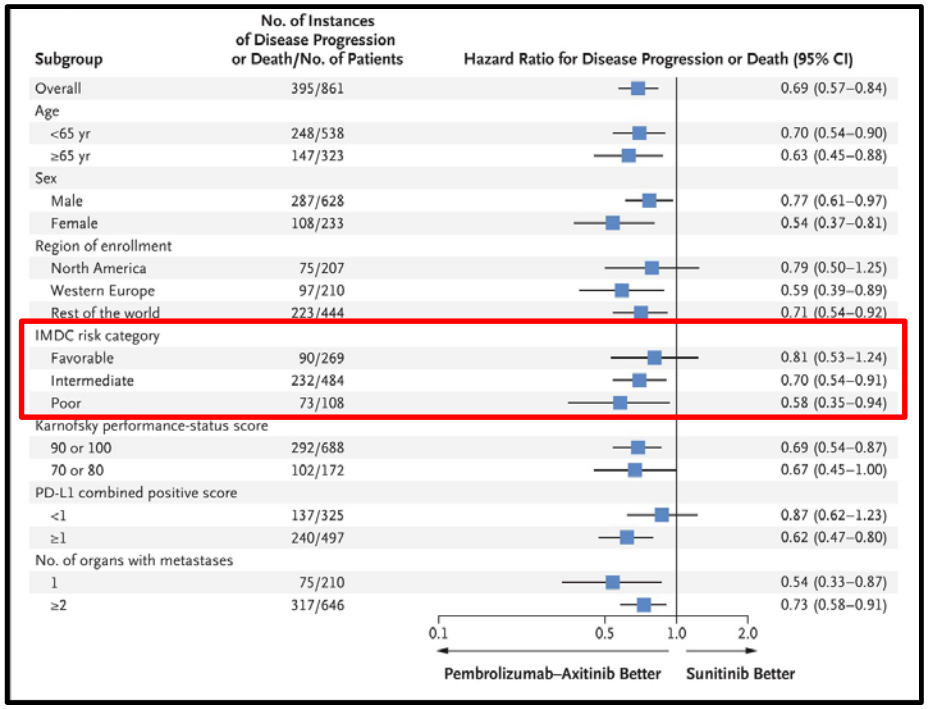
KeyNote 426:
Outcomes by Clinical Subsets

OS



Subgroup	No. of Deaths/ No. of Patients	Hazard Ratio for Death (95% CI)
Overall	156/861	0.53 (0.38–0.74)
Age		
<65 yr	91/538	0.47 (0.30–0.73)
≥65 yr	65/323	0.59 (0.36–0.97)
Sex		
Male	108/628	0.54 (0.37–0.80)
Female	48/233	0.45 (0.25–0.83)
Region of enrollment		
North America	31/207	0.69 (0.34–1.41)
Western Europe	31/210	0.46 (0.22–0.97)
Rest of the world	94/444	0.51 (0.33–0.77)
IMDC risk category		
Favorable	17/269	0.64 (0.24–1.68)
Intermediate	93/484	0.53 (0.35–0.82)
Poor	46/108	0.43 (0.23–0.81)
Karnofsky performance-status score		
90 or 100	88/688	0.53 (0.35–0.82)
70 or 80	67/172	0.49 (0.30–0.81)
PD-L1 combined positive score		
<1	54/325	0.59 (0.34–1.03)
≥1	90/497	0.54 (0.35–0.84)
No. of organs with metastases		
1	21/210	0.20 (0.07–0.57)
≥2	134/646	0.60 (0.42–0.85)

PFS



Subgroup	No. of Instances of Disease Progression or Death/No. of Patients	Hazard Ratio for Disease Progression or Death (95% CI)
Overall	395/861	0.69 (0.57–0.84)
Age		
<65 yr	248/538	0.70 (0.54–0.90)
≥65 yr	147/323	0.63 (0.45–0.88)
Sex		
Male	287/628	0.77 (0.61–0.97)
Female	108/233	0.54 (0.37–0.81)
Region of enrollment		
North America	75/207	0.79 (0.50–1.25)
Western Europe	97/210	0.59 (0.39–0.89)
Rest of the world	223/444	0.71 (0.54–0.92)
IMDC risk category		
Favorable	90/269	0.81 (0.53–1.24)
Intermediate	232/484	0.70 (0.54–0.91)
Poor	73/108	0.58 (0.35–0.94)
Karnofsky performance-status score		
90 or 100	292/688	0.69 (0.54–0.87)
70 or 80	102/172	0.67 (0.45–1.00)
PD-L1 combined positive score		
<1	137/325	0.87 (0.62–1.23)
≥1	240/497	0.62 (0.47–0.80)
No. of organs with metastases		
1	75/210	0.54 (0.33–0.87)
≥2	317/646	0.73 (0.58–0.91)

Rini, BI *et al*. NEJM (2019) 380:1116-1127

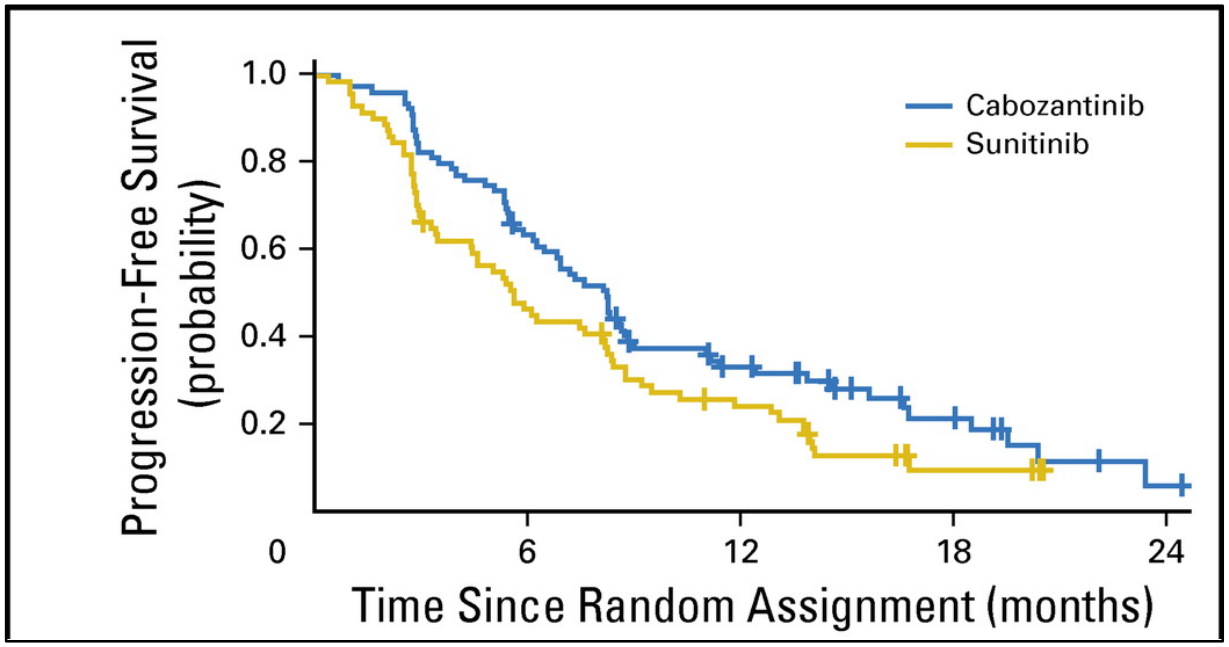
Summary – PD-L1 as Biomarker for Selecting Immune Checkpoint Blocking Therapy

PD-L1 Expression in Tumor	RCC
Prognostic	Unfavorable
Association with ICI treatment – OS ▪ Ipi+Nivo vs SUN ▪ Axi+Pembro vs SUN	No comparative outcome difference for OS
Companion Diagnostic	No
Clinical role for testing	No

Selecting Between First-Line Checkpoint Containing Regimens

- **Nuances between checkpoint regimens**
  - ORR
  - Depth of response (CR)
  - Treatment free survival
  - Toxicity / discontinuation rate
  - Frequency of visits
- **Await more mature OS data**
- **No consensus for “best choice”**

CABOSUN (Randomized, phase II) – Front-line Treatment of Intermediate and Poor Risk ccRCC



Endpoint	CABO	SUN	HR (P)
PFS	8.2 mo	5.6 mo	0.66 (P=0.012)
OS	30.3 mo	21.8 mo	0.80 (NS)
ORR	46%	18%	Not stated

Choueiri, T.K. *et al*. JCO (2017) 35, 591-597.

Current NCCN Guidelines for First-Line Therapy for clear cell RCC

FIRST-LINE THERAPY FOR CLEAR CELL HISTOLOGY			
Risk	**Preferred regimens**	Other recommended regimens	Useful in certain circumstances
Favorable[a]	• **Axitinib + pembrolizumab**[b] • **Pazopanib** • **Sunitinib**	• Ipilimumab + nivolumab[b] • Axitinib + avelumab[b] • Cabozantinib (category 2B)	• Active surveillance[c] • Axitinib (category 2B) • High-dose IL-2[d]
Poor/ intermediate[a]	• **Ipilimumab + nivolumab**[b] **(category 1)** • **Axitinib + pembrolizumab**[b] **(category 1)** • **Cabozantinib**	• Pazopanib • Sunitinib • Axitinib + avelumab[b]	• Axitinib (category 2B) • High-dose IL-2[d] • Temsirolimus[e]

What's Coming to First-Line Therapy?

- Axitinib + avelumab
  - FDA approval May, 2019
  - Await OS data
- Nivolumab + cabozantinib (CheckMate 9ER)
  - Press release - study was positive for PFS, OS, ORR versus sunitinib

www.nccn.org – Kidney Cancer Guidelines version 1.2021

Second-Line Systemic Therapy and Select Clinical Subsets

Comparison of Current Second-Line Treatment Options for RCC

	Axitinib	Nivolumab	Cabozantinib	Lenvatinib/Eve
Patient Population	TKI refractory*	TKI refractory	TKI refractory	TKI refractory
Comparator	Sorafenib	Everolimus	Everolimus	Everolimus
ORR	9%*	22%	17%	35%
PFS, months	6.5*	4.6	7.4	12.8
OS, months	15.2*	25.0	21.4	25.5
Dose reductions	30%	n/a	60%	71%
D/C due to AE	7%	8%	9%	29%
Toxicity	G3 50%	18%	63%	57%
	G4 6%	1%	8%	14%

Modified from B. Rini, 2016 ASCO Annual Meeting

Rini, BI et al. Lancet. (2011) 378:1931. Motzer, RJ et al. NEJM. (2015) 373:1803.
Choueiri, T et al. NEJM (2015) 373:1814.
Motzer, RJ et al. Lancet Oncol. (2015) 16:1473.

Clinical Outcomes for Sarcomatoid RCC

Treatment	Chemo	Targeted Tx	Immunotherapy			
Regimen (N)	**Dox+Gem[1] 39**	**Sun+Gem[2] 39**	**Ipi/Nivo[3] 60**	**Atezo/Bev[4] 68**	**Pembro/Axi[5] 51**	**Pembro[6] 11**
ORR, %	16	26	57	49	59	64
CR, %	3	3	18	10	12	0
PR, %	13	23	38	39	47	64
Median PFS, mo	3.5	5	8.4	8.3	NR	—
Median OS, mo	8.8	10	31.2	NR	NR	—

[1]Haas, NB *et al*. Med Oncol (2012) 29:761-7
[2]Michaelson, MD *et al*. Cancer (2015) 121:3435-43
[3]ASCO 2019, abstr #4513
[4]ASCO 2019, abstr #4512
[5]ASCO 2019, abstr #4500
[6]ASCO 2019, abstr #4570

KeyNote 427: First-Line Pembrolizumab for non-clear cell RCC

Group (N)	TOTAL 165	Papillary 118	Chromophobe 21	Unclassified 26	Sarcomatoid 38
ORR, %	25	25	10	35	45
CR, %	5	—	—	—	—
PR, %	20	—	—	—	—
12-mo PFS, %	23	—	—	—	—
12-mo OS, %	72	—	—	—	—
Median DOR	NR[1]	NR	NR	NR	NR

[1]Median follow-up 11.1 mo

Conclusions

- Immune checkpoint inhibitors appear to be the drug class of choice for sarcomatoid RCC tumors
- Immune checkpoint inhibitors have clinically significant activity in most subtypes of non clear cell RCC

SEATTLE CANCER CARE ALLIANCE, UW MEDICINE and FRED HUTCH

Thank you for your attention

Aggressive B-Cell Non-Hodgkin Lymphomas

Stephen Smith MD

Associate Professor, Division of Hematology, UW
Associate Member, Clinical Research Division, FHCRC

Disclosures

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Ignyta (spouse)
Incyte Corporation
Merck Sharp and Dohme Corp.
Pharmacyclics

Portola Pharmaceuticals

Seattle Genetics

Consultancy OR Advisory Board

Astrazeneca

Millenium/Takeda

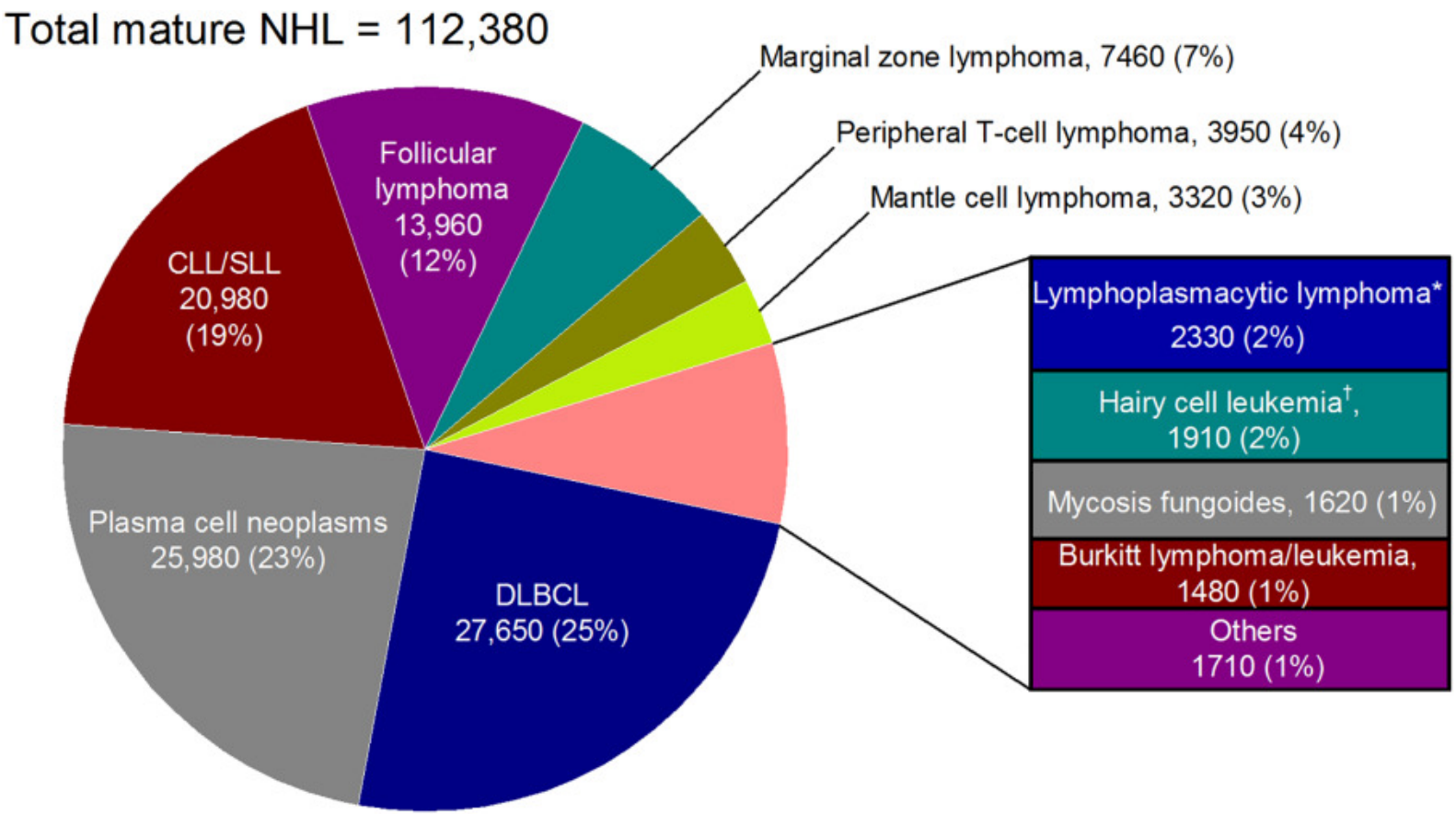
Beigene

Karyopharm

Outline

- Incidence of B-NHL
- Diffuse Large B-Cell Lymphoma
  - Staging and Pretreatment Evaluation
  - Limited-Stage Disease
  - Advanced-Stage Disease
  - Biologic Risk Stratification
  - Relapsed/Refractory Disease
- Primary Mediastinal Large B-Cell Lymphoma
- High-Grade B-Cell Lymphoma
- Mantle Cell Lymphpoma

Estimated Cases and Distribution of Mature Non-Hodgkin Lymphomas: 2016



DLBCL incidence: 7 per 100k

Table 1 WHO classification of mature large B-cell lymphoid neoplasms

Diffuse large B-cell lymphoma (DLBCL), NOS – Germinal centre B-cell type[a] – Activated B-cell type[a]
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
EBV+ DLBCL, NOS[a]
EBV+ mucocutaneous ulcer[a]
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal/thymic large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK+ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
HHV8+ DLBCL, NOS[a]
Burkitt lymphoma
Burkitt-like lymphoma with 11q aberration[a]
High grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements[a]
High grade B-cell lymphoma, NOS[a]
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma

The provisional entities are listed in italics
[a]Changes from the 2008 classification
NOS not otherwise specified, *EBV* Epstein Barr virus

80% of DLBCL are "NOS"

Diffuse Large B-Cell Lymphoma: Staging and Pretreatment Evaluation

DLBCL: Initial Work-Up

- Diagnosis
  - Incisional or excisional biopsy is preferred
  - Core needle biopsy can be considered if above not feasible
- Patient evaluation
  - B-symptoms: temp > 101°F (38.3°C), drenching NS, unexplained weight loss > 10% over 6 months
  - Comorbidities and functional assessment
  - Laboratory studies (e.g., LDH, Hep B serologies)
  - Consider fertility preservation
  - Consider assessment of LVEF

Cheson, *et al. J Clin Oncol.* 2014; 32:3059-3067.
Zelenetz, et al. *NCCN Guidelines* (Version 2.2017). Accessed 3/20/2017.

DLBCL Pathology - Key testing

Question 1- Adequacy of sample for Dx? Morphology, clonality, other

Assay	Role	Notes
Flow	Clonality, cell surface markers	DLBCL can be flow negative
IHC	Biologic risk stratification	Hans criteria for Cell of Origin (COO) Double Expressor: MYC >40% **and** BCL2 >50%
FISH	Diagnosis - MYC breakapart, then BCL2/6	("Double hit" is now high-grade B-cell lymphoma)

Pretreatment evalution

- Echo/MUGA (especially if cardiac risk factors, HTN)
- Fertility evaluation and preference
- Laboratory workup (Hep B, HIV, LDH)
- Imaging and other staging
- Venous access

Defining “nodal sites” ; benefit of PET

PET-CT vs CT- in roughly 20%:

- Detection of more *extranodal* sites (GI, head+neck, skin+soft tissue most common)

- Upstaging: stage migration in light of IPI shift

Ann-Arbor → Lugano nodal sites

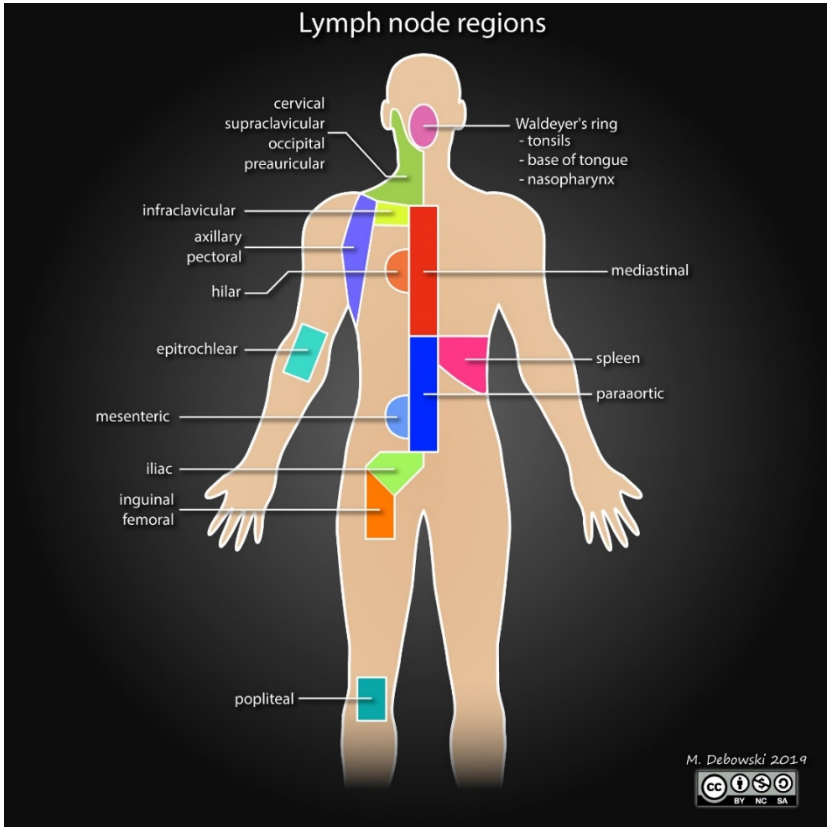


Image -Dr Maciej Debowski, Radiopaedia.org, rID: 65530

Is BM Bx necessary in the PET era?

Guidelines still say yes, but:

- BM Bx utilization in staging is decreasing in practice*
- PET-CT sensitivity high (meta-analysis: 88%)**
- Impact on Px debatable (marrow often detects low-grade dz)

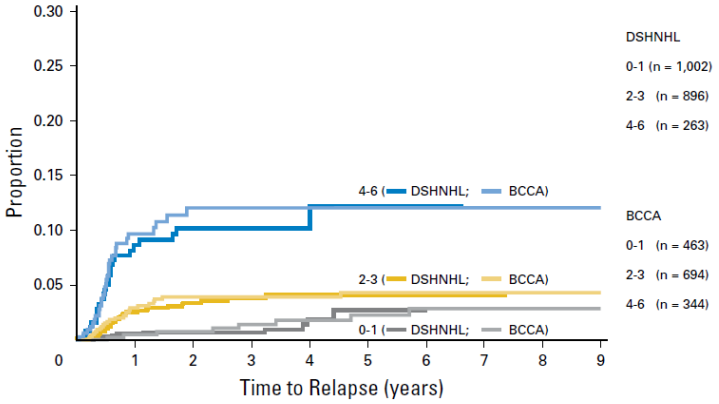
Consider marrow for:

- Key treatment decisions (stage/therapy change)
- Required in clinical trials
- Baseline cytopenias
- Uncertain PET result

*Bischin PMID 31993568
**Adams E J Nuc Med 2014

DLBCL: Role of Lumbar Puncture

- CNS IPI:
  - Risk factors: same as standard IPI plus kidney or adrenal involvement
  - Low (0-1) or intermediate (2-3) risk: defer LP
    - Risk of CNS relapse < 5%
  - **High (4-6) risk: intervene**
    - **Risk of CNS relapse > 10%**



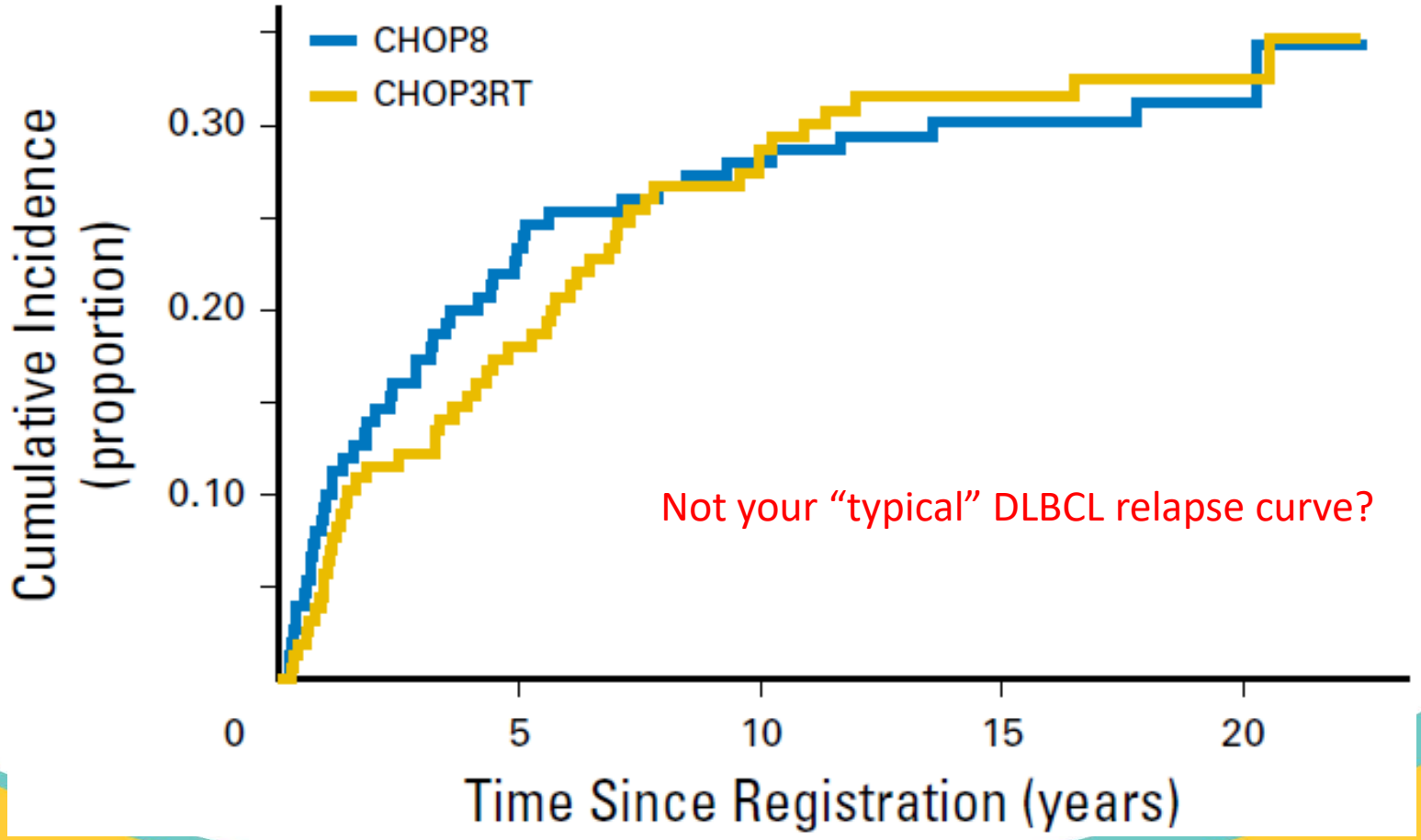
ALSO

- HIV-associated
- Testicular involvement
- Breast DLBCL
- ?MYC and BCL2 over-expression (i.e., “double-expressor lymphoma”)- not a validated risk factor (Klanova Blood 2019)

Cheson, *et al. J Clin Oncol*. 2014; 32:3059-3067.
Schmitz, et al. *J Clin Oncol*. 2016;34:3150-3156.
Zelenetz, et al. *NCCN Guidelines* (Version 2.2017

Diffuse Large B-Cell Lymphoma: Limited Stage Disease

Limited stage DLBCL: Long-Term Risk of Relapse



Stephens, *et al*. *J Clin Oncol*. 2016;34(25):2997-3004.

Limited stage DLBCL case study

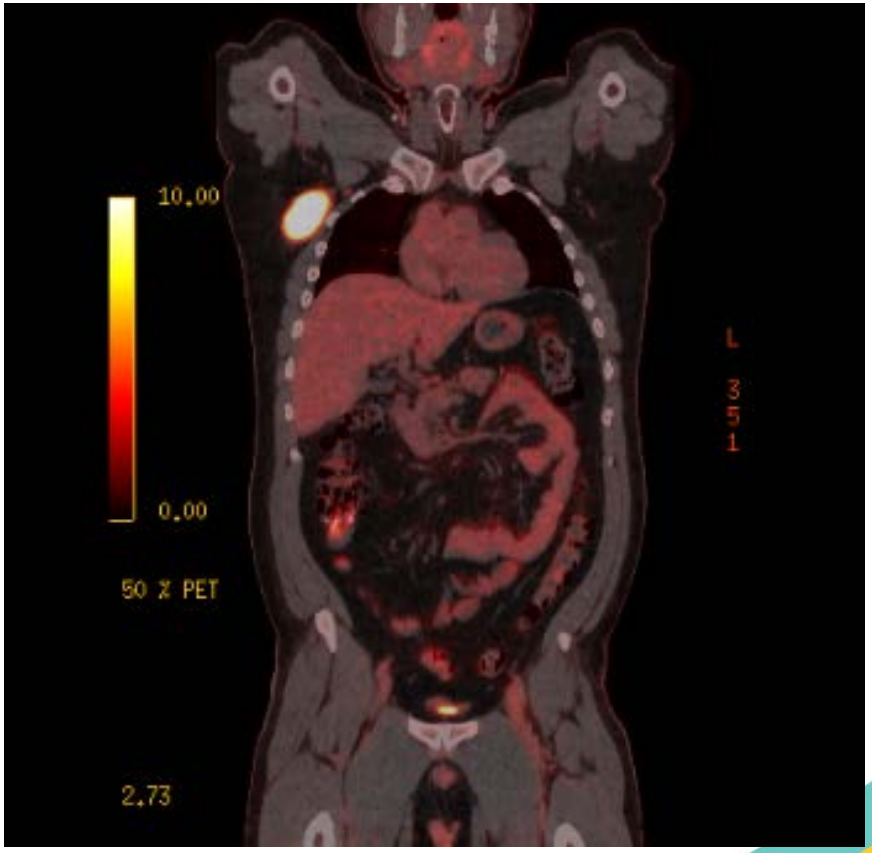
40 M previously healthy male developed R armpit swelling

R axillary Bx Path- GCB DLBCL
Flow cytometry: negative
Morphology: Diffuse sheets of large atypical cells
IHC: CD10+ (GCB subtype), MYC 5%

FISH: BCL6 rearrangement (only)

PET**:** 1. FDG avid right axillary LAD, Deauville 5. Size 4.5 cm
2. No other sites.

BM Bx - negative

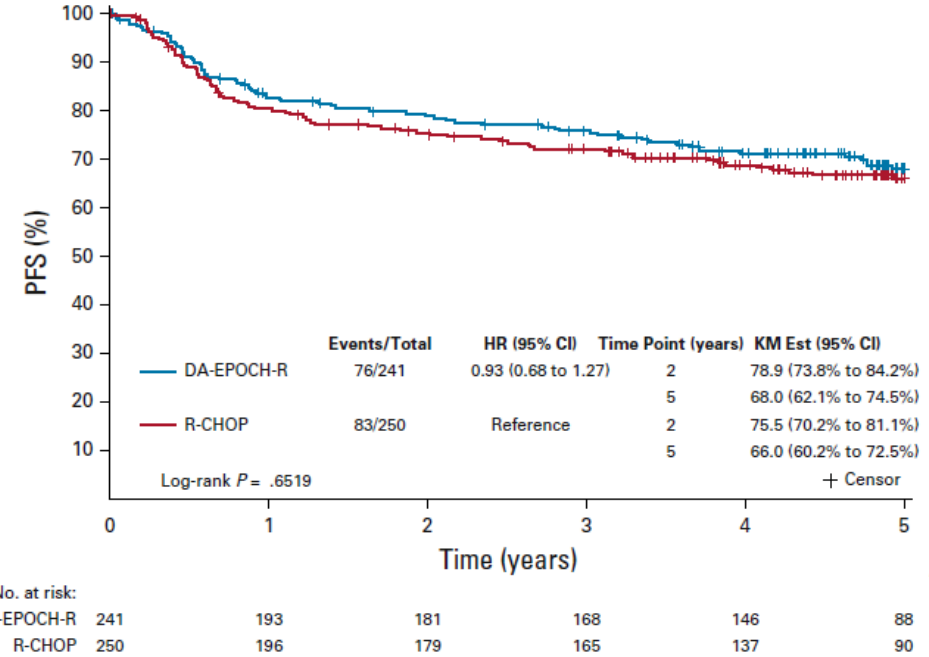


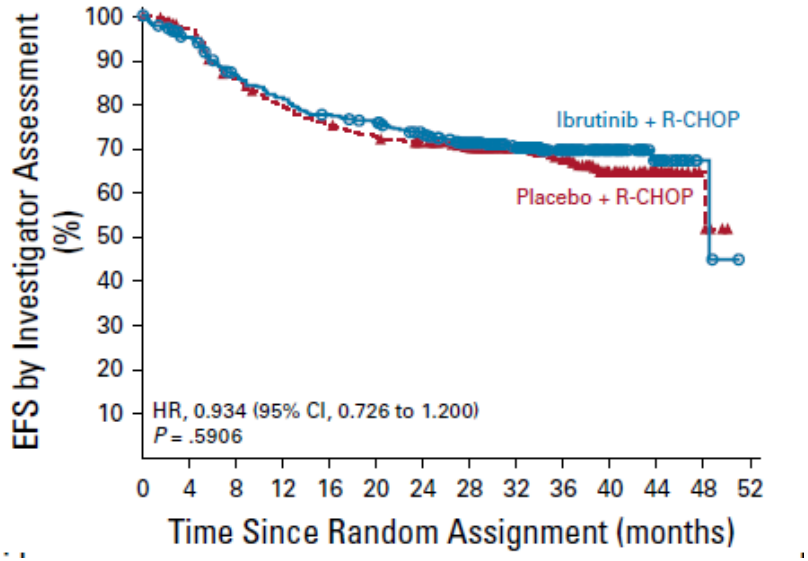
Therapy for Limited Stage DLBCL: Short-course options

Regimen	Population/findings	Downsides	Consider In (presenter opinion)
RCHOP x 3 + IFRT Miller NEJM 1998, Persky JCO 2008, Stephens JCO 2016	***Int-High grade NHL***	RT acute/late effects (40-46 Gy)	IPI risks present; elderly/frail with optimal XRT field-
- OPTIONS WITHOUT RADIOTHERAPY-			
RCHOP-14 x 4-6 Lamy Blood 2018 Randomized PET-4 CR pts: XRT vs observation	***Lower risk DLBCL***; PET-CR after 4 cycles **89% 5 yr EFS w/RCHOP alone**	q14 day RCHOP needs GCSF	**No IPI risks** + desire a brief treatment course could do RHCOP-14 x 4
RCHOP-21 x 4 + 2 R FLYER: Poeschel Lancet 2019 Randomized: 4 RCHOP + 2R vs 6 RCHOP	***Lowest risk DLBCL*** (stage 2 OK / no IPI risks, no bulk 7.5cm) **96% 3 yr PFS w/4 RCHOP**	May undertreat stage II? Extra 2 R needed?	**Young/no IPI risks**
R-CHOP-21 x 4 S1001: Perksy JCO 2020 Stratified: RCHOP x 3 - PET negative DV 1-3: 1 more - PET positive: XRT + RIT	**All limited stage DLBCL** (nonbulky 10 cm) **89% 5 yr PFS in PET neg w/4 RCHOP**	Too few PET + pts to judge that arm. Inferior for non-GCB and double expressor	**PET-3 negative** - May be best in low biologic risk pts

Diffuse Large B-Cell Lymphoma: Advanced-Stage Disease

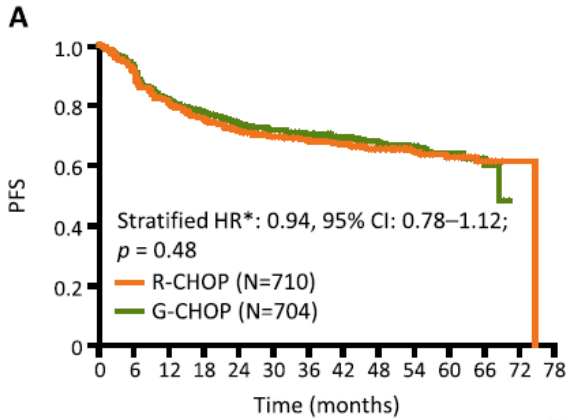
Randomized trials for 1L DLBCL- Outcome of “typical” studies





RCHOP ibrutinib vs RCHOP
Younes JCO 2019

DA-EPOCH+R vs RCHOP
Bartlett JCO 2019



GCHOP vS RCHOP
Sehn J Hem Onc 2020

NCCN – IPI: Zhou *Blood* 2014

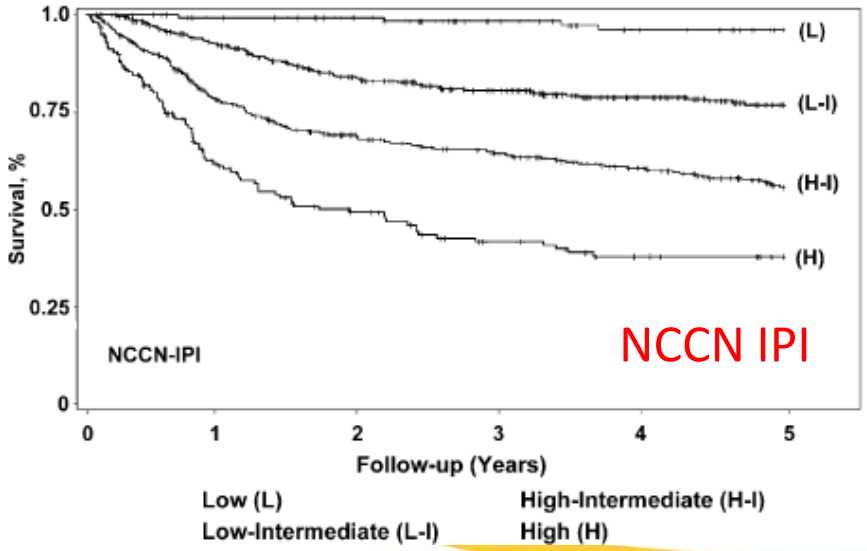
Table 3. The NCCN-IPI

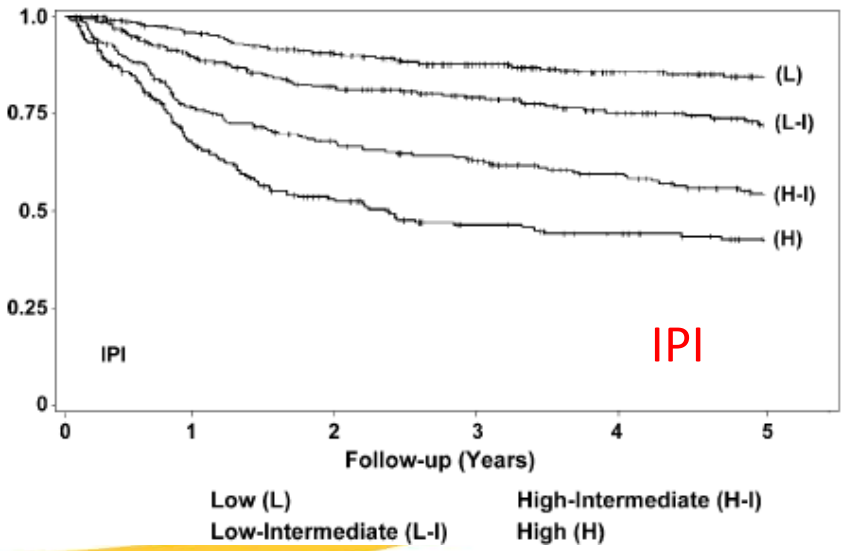
NCCN-IPI	Score
Age, y	
>40 to ≤60	1
>60 to ≤75	2
>75	3
LDH, normalized	
>1 to ≤3	1
>3	2
Ann Arbor stage III-IV	1
Extranodal disease*	1
Performance status ≥2	1

*Disease in bone marrow, CNS, liver/GI tract, or lung.

Benefits to NCCN IPI

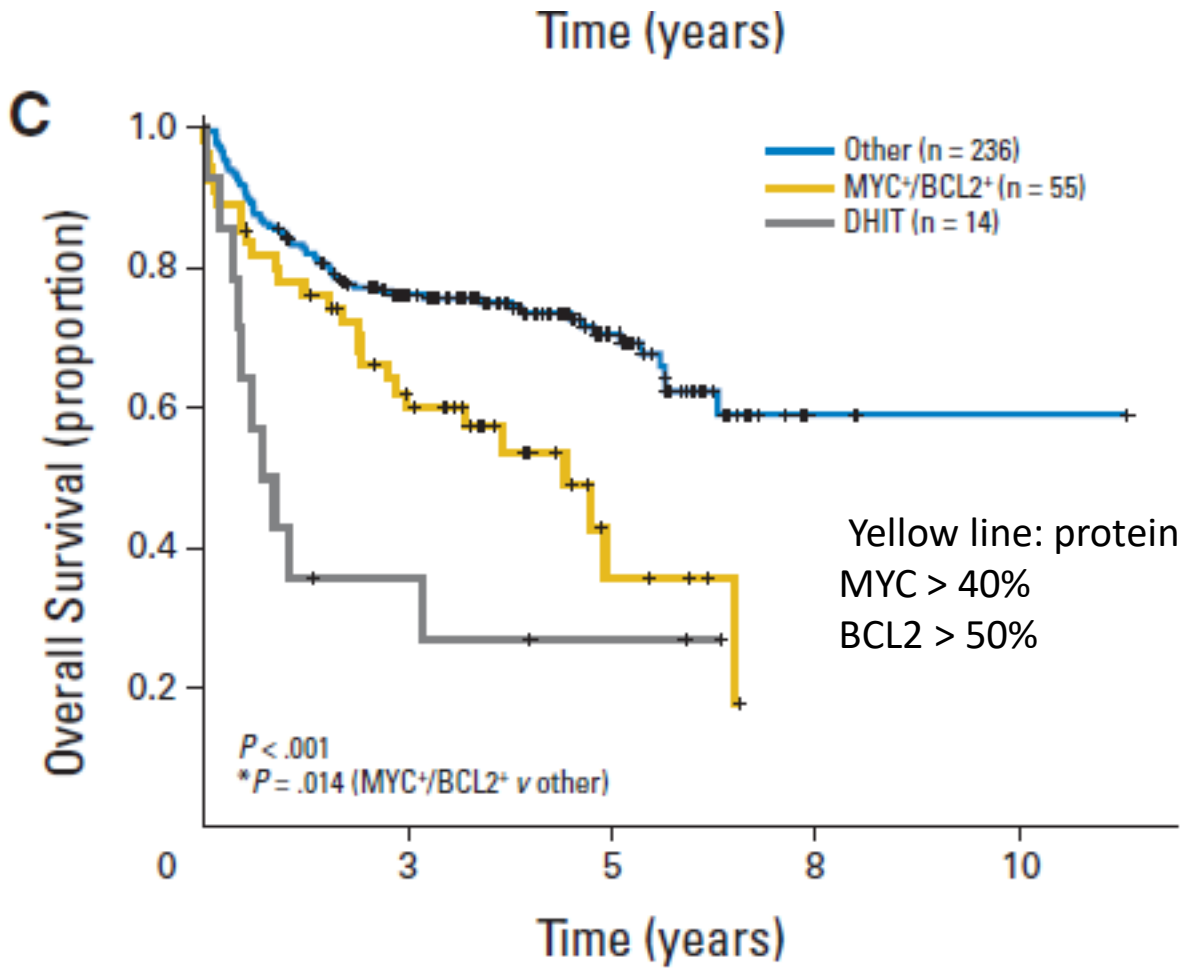
- DLBCL pt specific
- High LDH elevations represented
- Slightly wider range/better discrimination of groups





MYC dysregulation: protein and translocation

Double expressor (protein) ≈ 30%
Double hit ≈ 10 %

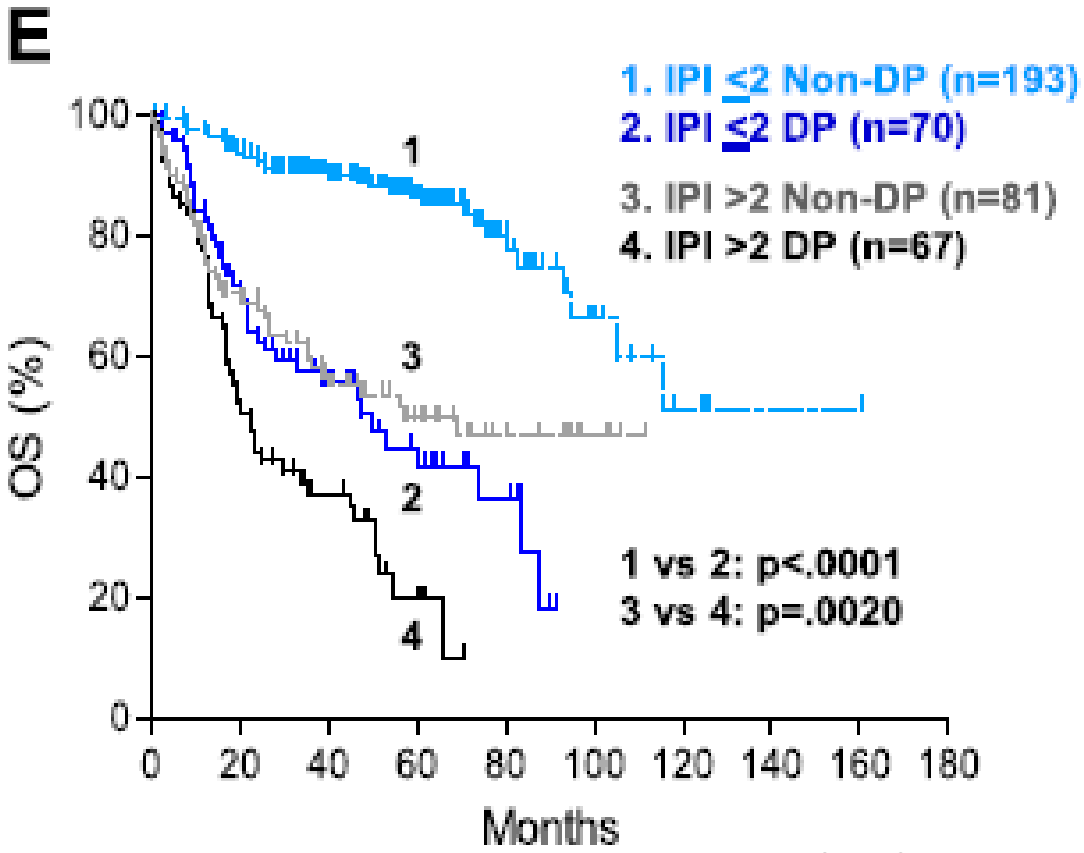


Yellow line: protein overexpression
MYC > 40%
BCL2 > 50%

Johnson (BCCA) JCO 2012

Double expression of MYC and BCL2

≈ 30% of new DLBCL



Hu Blood 2013

"double positive" = DP

IHC cutoffs

40% for MYC

70% for BCL2 (50% in 1 study)

Green (Denmark), Johnson (BCCA) JCO 2012, Hu (MD Anderson) Blood 2013

How urgent is DLBCL treatment?

Accelerated workup and treatment:

- SVC syndrome
- Neurologic compromise or involvement
- Tumor lysis syndrome
- Poor PS, disease-related or unclear
- Very high (3x or greater) LDH elevations
- Metabolic- lactic acidosis, hyperCa

Randomized First-Line DLBCL Trials vs R-CHOP

- RCH-P with polatuzumab (Polarix): Fully accrued
- RCHOP + Enzastaurin (ENGINE): IPI 3-5
- RCHOP+ tafasitamab (MOR208, CD19 MoAb)
- RCHOP + acalabrutinib for non-GCB

___

- Nonrandomized- RCHOP + checkpoint blockade

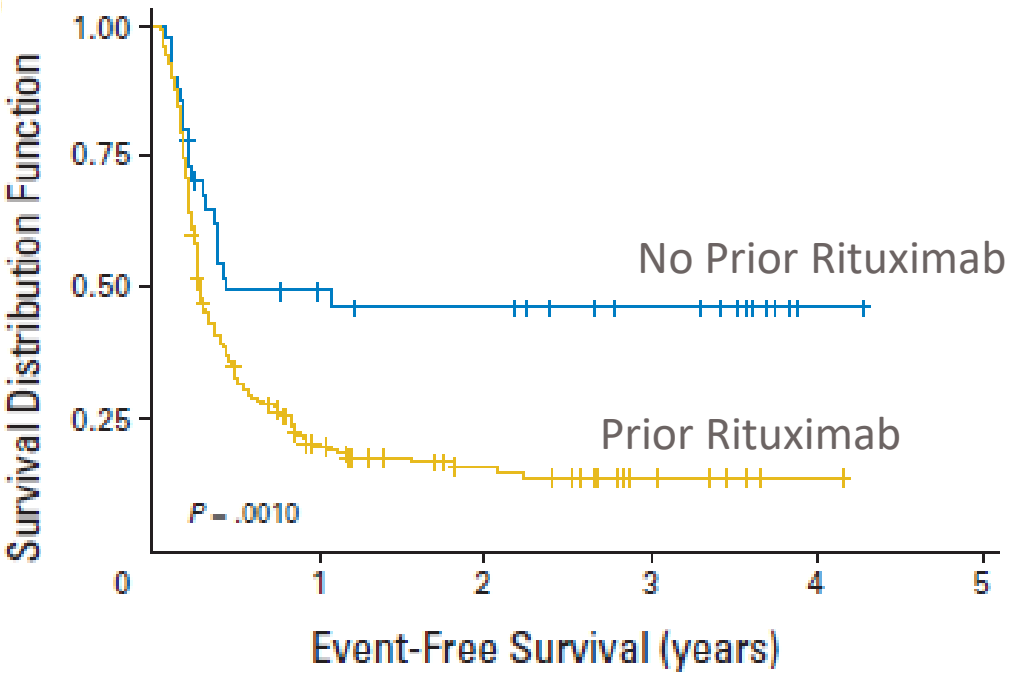
DLBCL: Post-Treatment Surveillance

- **Relapses** occur mostly in the first 2 years
- **Limited utility** of surveillance imaging[1]
  - Most relapses (60%) identified BEFORE a schedule follow up visit
    - **Imaging detects** few relapses in asymptomatic pts
  - **Survival** no different in relapses detected in planned follow up vs not

1. Thompson, *et al*. *J Clin Oncol*. 2014;32(31):3506-3512.1

Diffuse Large B-Cell Lymphoma: Relapsed/Refractory Disease

CORAL: Impact of Early Relapse (& prior rituximab)



- ***CONCLUSION: For relapse < 12 mo from diagnosis, salvage therapy followed by auto transplant yields relatively poor outcome.***

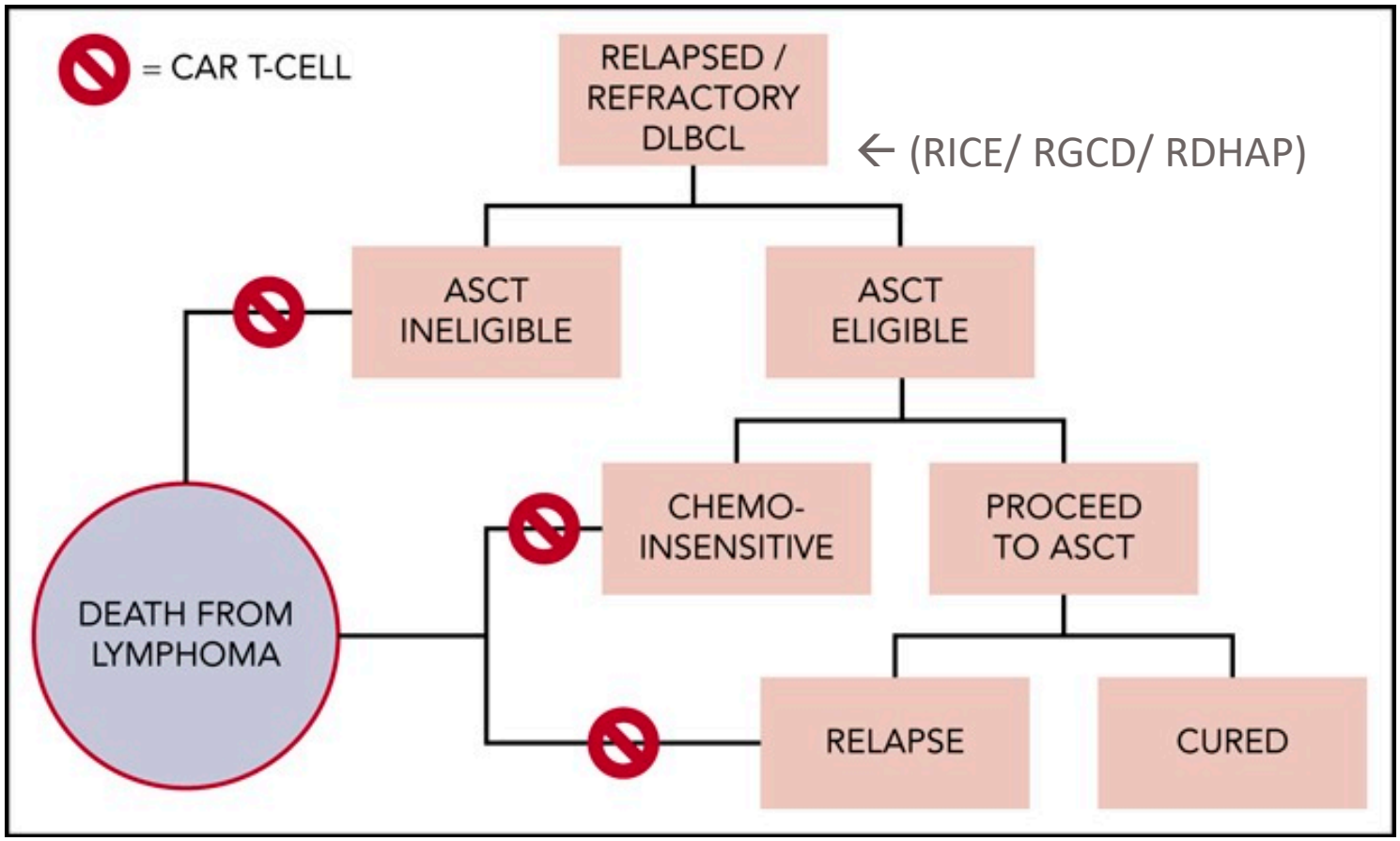
Gisselbrecht C, *et al. J Clin Oncol.* 2010;28:4184–4190

Strategy in Treating Relapsed DLBCL

1. Goal setting: Bridge to cellular therapy vs. Stand-alone tx)
    - Fitness for auto, Car T-cell; allo
    - Address high risk: early relapse, high sIPI, MYC+

2. Select specific therapy
    - Expected toxicities (organ/hematologic)
    - preferences/logistics

Strategy in Treating Relapsed DLBCL: ASCT and Car-T therapy



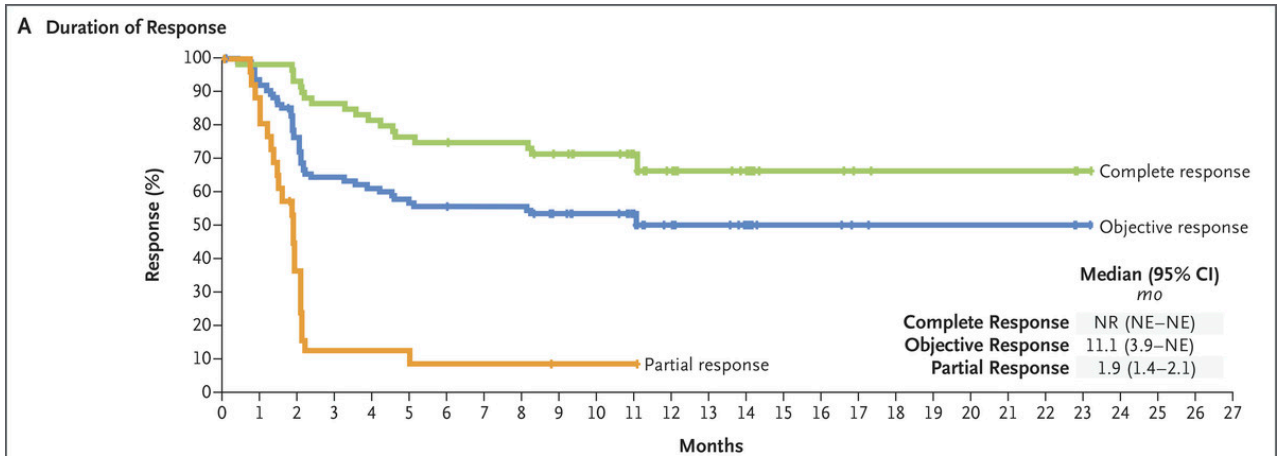
Adapted from Chow/Gopal Blood 2018

Chimeric antigen receptor T (CAR-T) Therapy

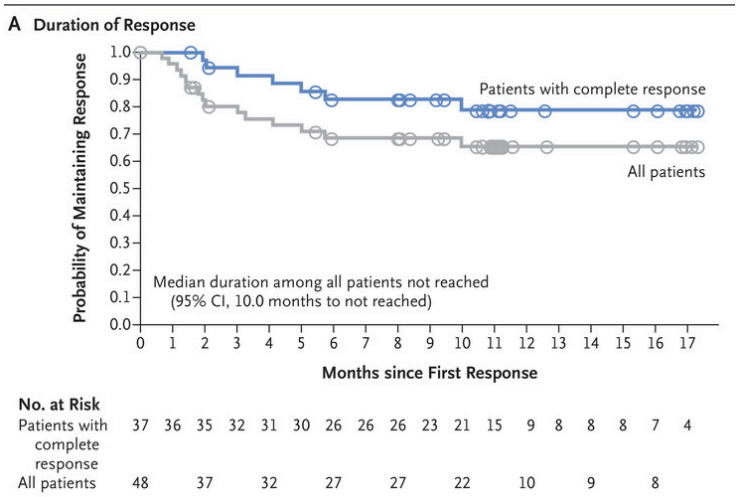
Approved for relapsed/ref DLBCL failing ≥2 lines:

- Yescarta (axicabtagene ciloleucel, axi-cel): Kite, Oct 2017
- Kymriah (tisagenlecleucel): Novartis, May 2018

CD19 CAR-T cells: CR's appear to be *cured*



Axi-cel



Tisagenlecleucel

Axi-cel: Neelapu SS et al. N Engl J Med 2017;377:2531-2544.
Tisagen: SJ Schuster et al. N Engl J Med 2019;380:45-56.

DLBCL Relapsed After, or Ineligible for, auto/Car-T

- Polatuzumab + BR- approved 6/2019
- Selinexor- approved 6/23/20 (after 2 prior tx)
- Lenalidomide+ Tafasitamab- approved 7/31/20 (

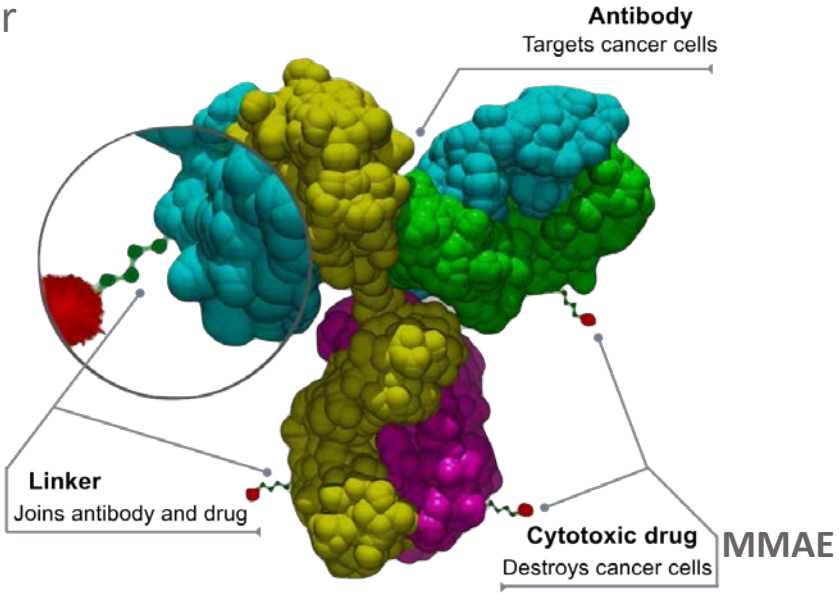
Polatuzumab vedotin: CD79b-targeted Ab with MMAE payload

CD79b

- A component of the B-cell receptor
- Expressed on mature B cells

Published data for pola in B-NHL

- Single agent phase I
- Randomized phase 2:
  - Pola+R vs pina+R
- Pola + RCHOP phase I/II
- Randomized phase II
  - Pola BR vs BR



Polatuzumab vedotin+ BR

Pivotal trial design/accrual: (phase Ib/expansion) +

- *Randomized phase 2* : Pola BR vs BR, 40 pts per arm
- Objective: 65% CR rate w/pola BR (c/w 40%)

Dose: 1.8 mg/kg polatuzumab + BR (90 mg/m2)

Notable eligibility criteria:

- No transformed disease
- "Ineligible for second-line stem cell transplant (SCT)"
- 6 month life expectancy
- No car T-cells within 100 days, no prior allo

Sehn JCO 2019

Polatuzumab vedotin+ BR

Efficacy: CR 40% with pola BR vs. 18%

- Median PFS: 9.5 months in pola BR vs 3.7 in BR
- OS 12.4 vs 4.7 mo

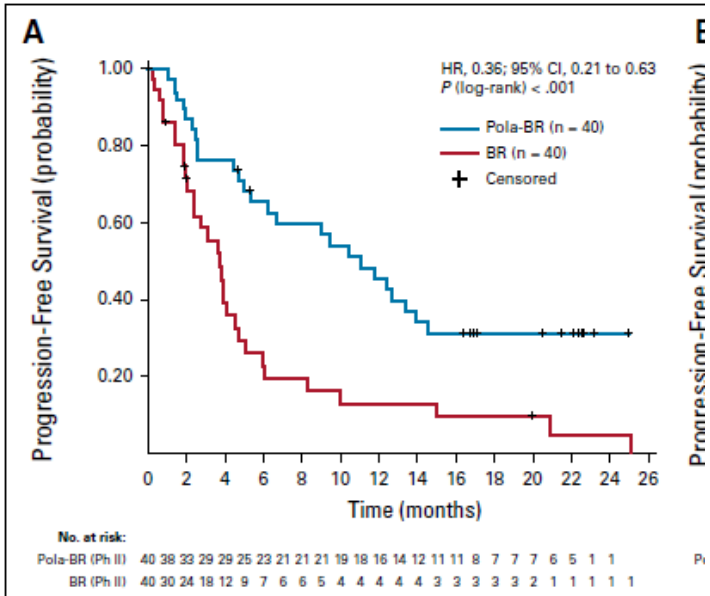
- Toxicity: 23% grade 3-4 infection
  - 42% received all 6 cycles
  - 33% d/c therapy due to AE
  - 54% had a treatment delay

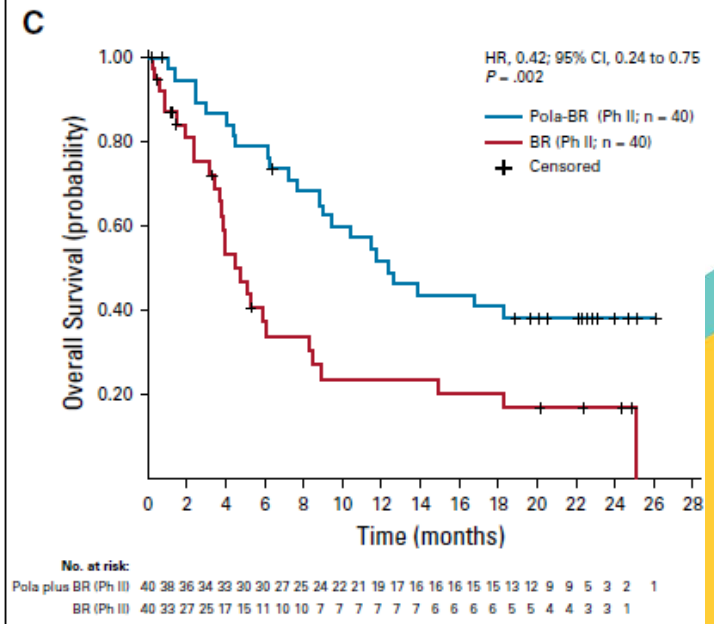
Limitations

- BR as a backbone
- Uncertain impact if bridging for future car T-cell therapy

PFS

OS





Sehn JCO 2019

Selinexor: Oral small molecule targeting nuclear export (exportin)

Pivotal trial design/Accrual: Single arm phase 2. Accrued 267 over 4 yrs @ 59 sites

Dose: 60 mg PO, Days 1 and 3 of each week

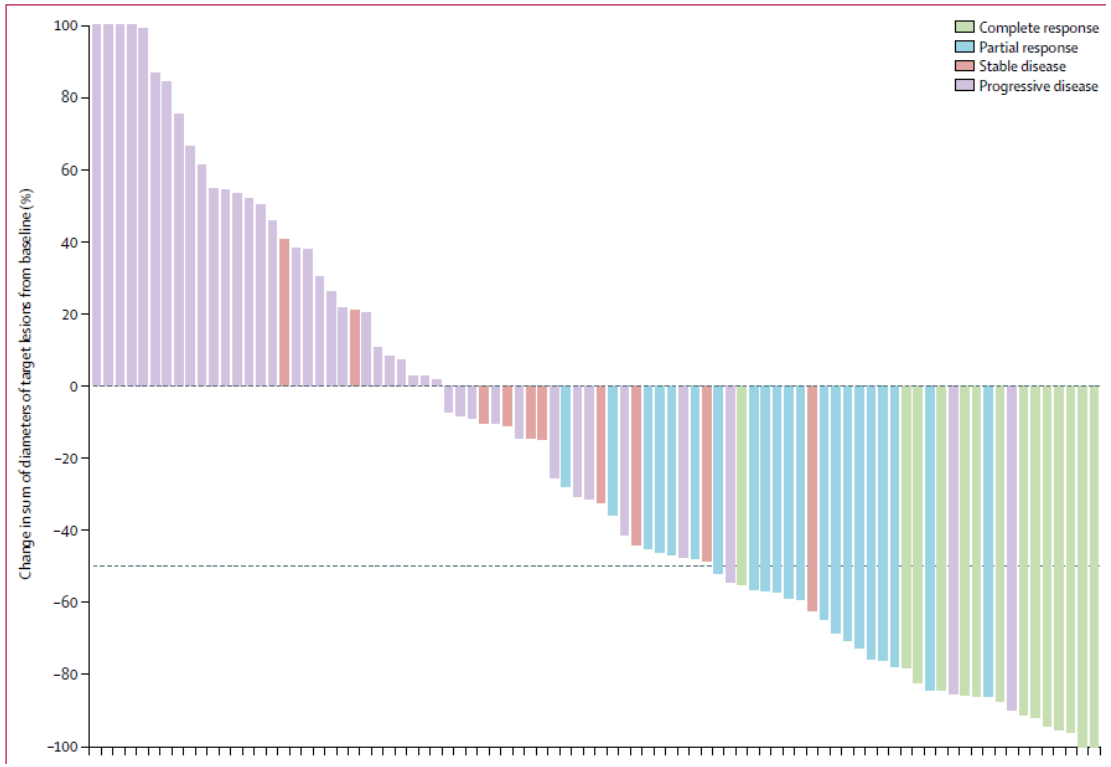
Notable eligibility criteria

- 60 day “washout” from prior therapy

Selinexor: Oral small molecule targeting nuclear export (exportin)

Efficacy
28% ORR; 2.6 mo PFS/9 mo OS
12% CR (15 pts)

Toxicity: fatigue/nausea (mostly grade 1-2); cytopenias (plts) most common grade 3 or higher AE



Limitations:
Efficacy and durability limited. Pt selection.

Tafasitamab (CD19 Mo Ab) + lenalidomide:

Design/accrual: single arm phase 2; 156 screened/81 treated over 23 mo.

Dosing: Tafasitamab: 12 mg/kg IV over 2 h, 28 day cycles

- Cycles 1–3 weekly 1, 8, 15, and 22
  - an additional loading dose C1 D4
- Cycle 4 onward: IV q 14 days

Lenalidomide: 25 mg for 3 out of 4 weeks for **up to 12 cycles**

Notable eligibility:

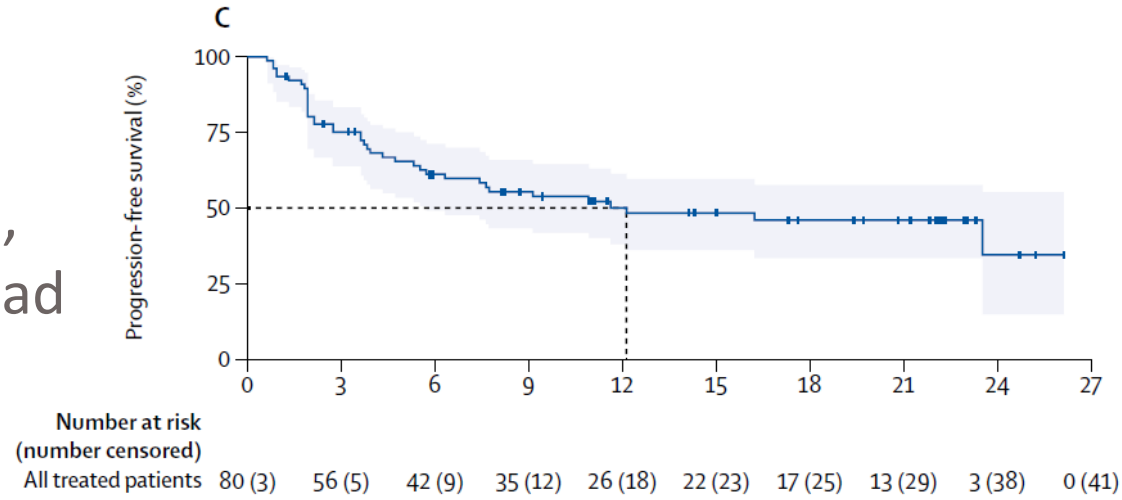
- Ineligible for transplant (age > 70 or other reasons)
- At MOST, 3 prior regimens
- Primary refractory disease excluded

Salles Lancet Onc 2020

Tafasitamab (CD19 Mo Ab) + lenalidomide:

Efficacy: 13 month follow:
ORR 60% including 43 % PR/
18 % CR

Toxicity: neutropenia/plts, F+N in 12%. 51% of pts had an SAE.



Limitations: Small, single arm trial; pt selection (half screened were ineligible) . Chronic therapy. PFS needs more follow-up.

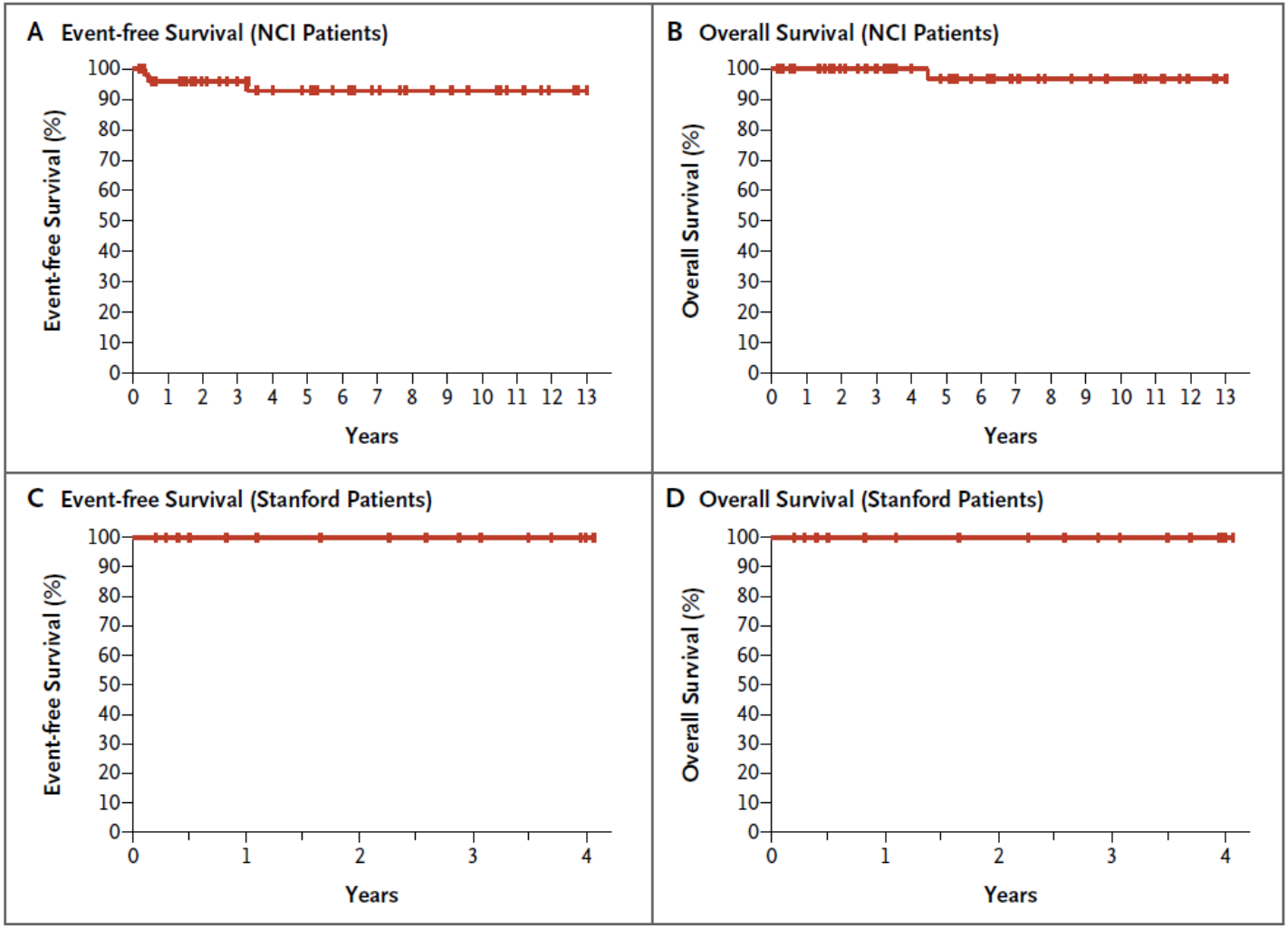
Salles Lancet Onc 2020

Primary Mediastinal Large B-Cell Lymphoma

Phase II Study of DA-EPOCH-R (no XRT)

NCI:
N = 51
Prospective

Stanford:
N = 16
Retrospective



Dunleavy, *et al*. *New Engl J Med*. 2013;368:1408-1416.

High-Grade B-Cell Lymphomas

- **HGBL, with *MYC* and *BCL2* and/or *BCL6* rearrangements**
  - Double (DHL) or triple-hit lymphomas (THL)
  - Gene rearrangements by FISH/cytogenetics
  - Copy-number abnormalities DO NOT COUNT
  - Protein over-expression is NOT included

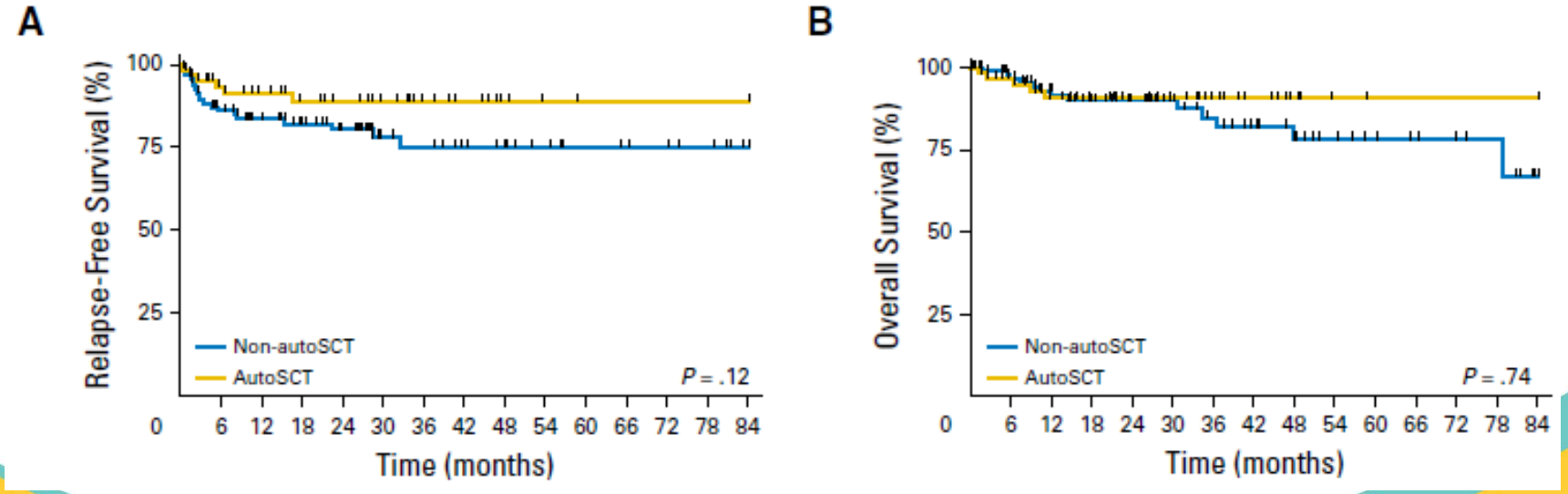
- **HGBL, not otherwise specified**

- **<u>Treatment</u>: Intensified regimens are recommended**
  - No randomized trials
  - Low IPI patients may be an expcetion

Swerdlow, *et al*. *Blood.* 2016; 127(20):2375-2390.

DHL in CR1: Role of Auto SCT

- 159 patients with DHL who achieved CR1
- Compared outcomes by initial regimen and use of stem cell transplant vs observation in CR1
- Median f/u = 26.5 months (range, 0.2-114.6)



Landsburg, Cassaday *et al*. *J Clin Oncol*. 2017

Mantle Cell Lymphoma

- **Features**
  - Male predominance, EN disease/stage IV usual
  - CD5+ CD23- typical.
  - **t11;14 by FISH** and /or cyclin D1+ by IHC.
- **Treatment**
  - Initially observe in some cases
  - Young/Fit: Consider intensive induction (Nordic, R+HyperCVAD)→auto SCT
  - Older: BR or VR-CAP (>RCHOP)
- **Special Subgroups**
  - Leukemic Variant: watch/wait
  - TP53 *mutation* : clinical trial and early incorporation of novel agents; ASCT unlikely to benefit

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

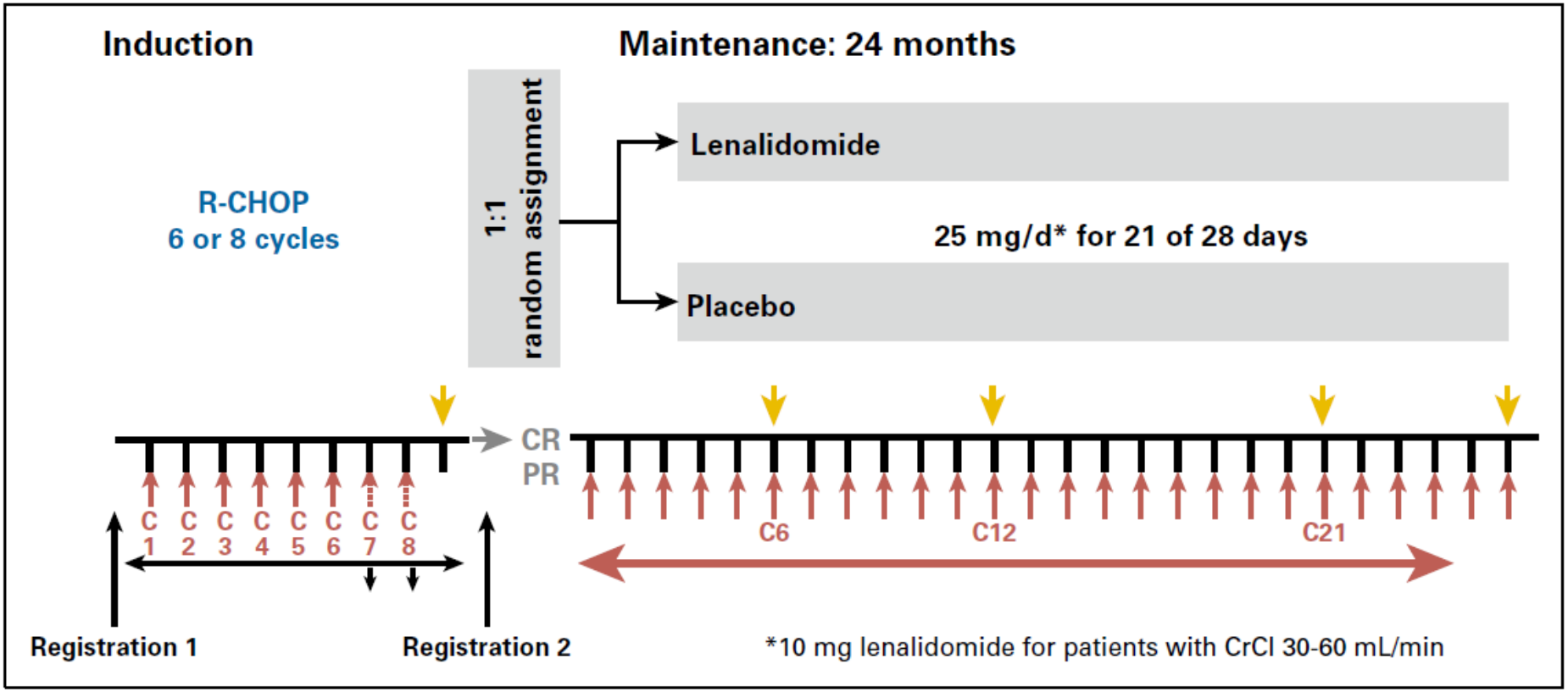
Thank You

DLBCL in First Remission… Maintenance?

- Maintenance rituximab
  - After R-CHOP, **no benefit** with R maintenance in DLBCL[1]
- Maintenance lenalidomide- REMARC study
  - **DLBCL > 60 years old[2]**

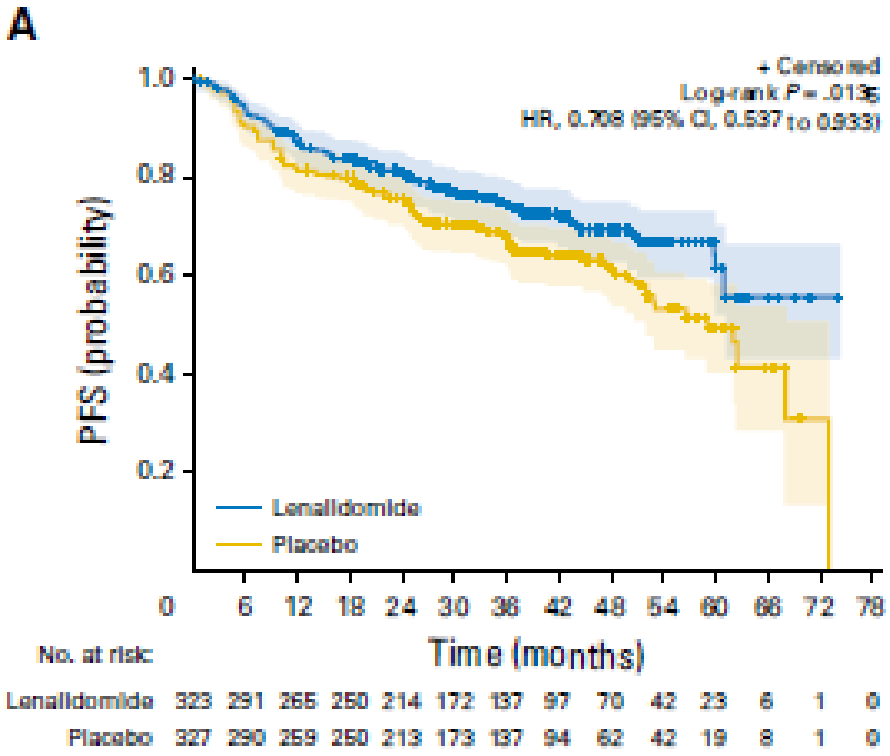
[1]Haberman, *et al*. *J Clin Oncol*. 2006;24(19):3121-3127.
[2]ThieblemontJ Clin Oncol. 2017 Aug 1

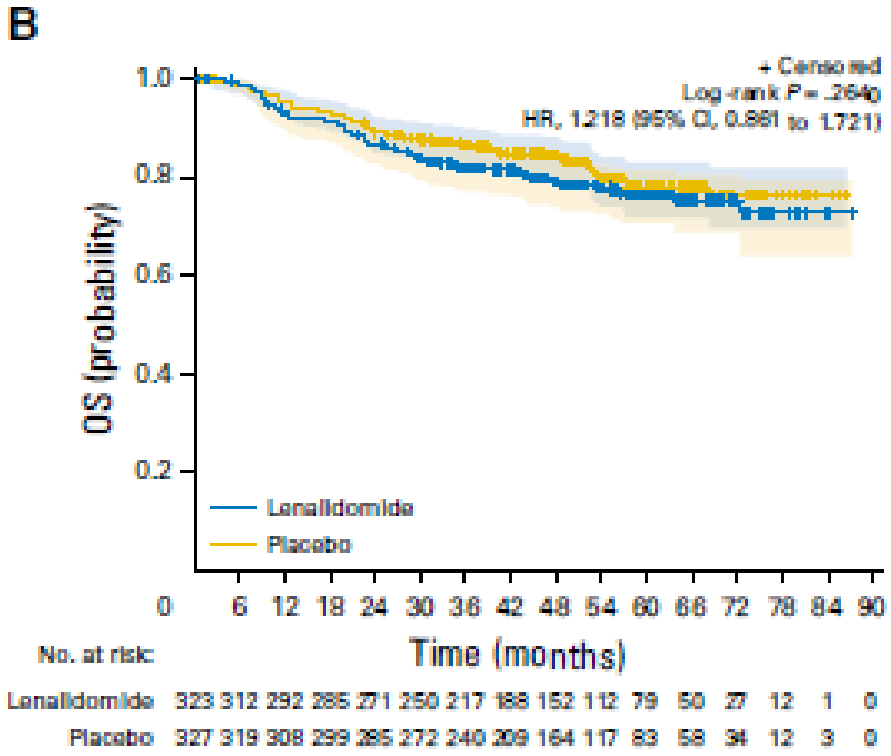
Maintenance with Lenalidomide: REMARC



Thieblemont J Clin Oncol. 2017

Len Maintenance – REMARC PFS and OS





- Not FDA approved, unclear impact on salvage therapy, NCCN Category 2B

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Esophageal and Gastric Cancer

SCCA Comprehensive Oncology Review

September 2020

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University of Washington School of Medicine
Fred Hutchinson Cancer Research Center

Objectives

- Epidemiology and Risk Factors
- Pathology, Diagnosis, and Staging
- Stage I-III Esophageal Cancer
- Stage I-III Gastric Cancer
- Advanced Esophageal and Gastric Cancer

Epidemiology and Risk Factors

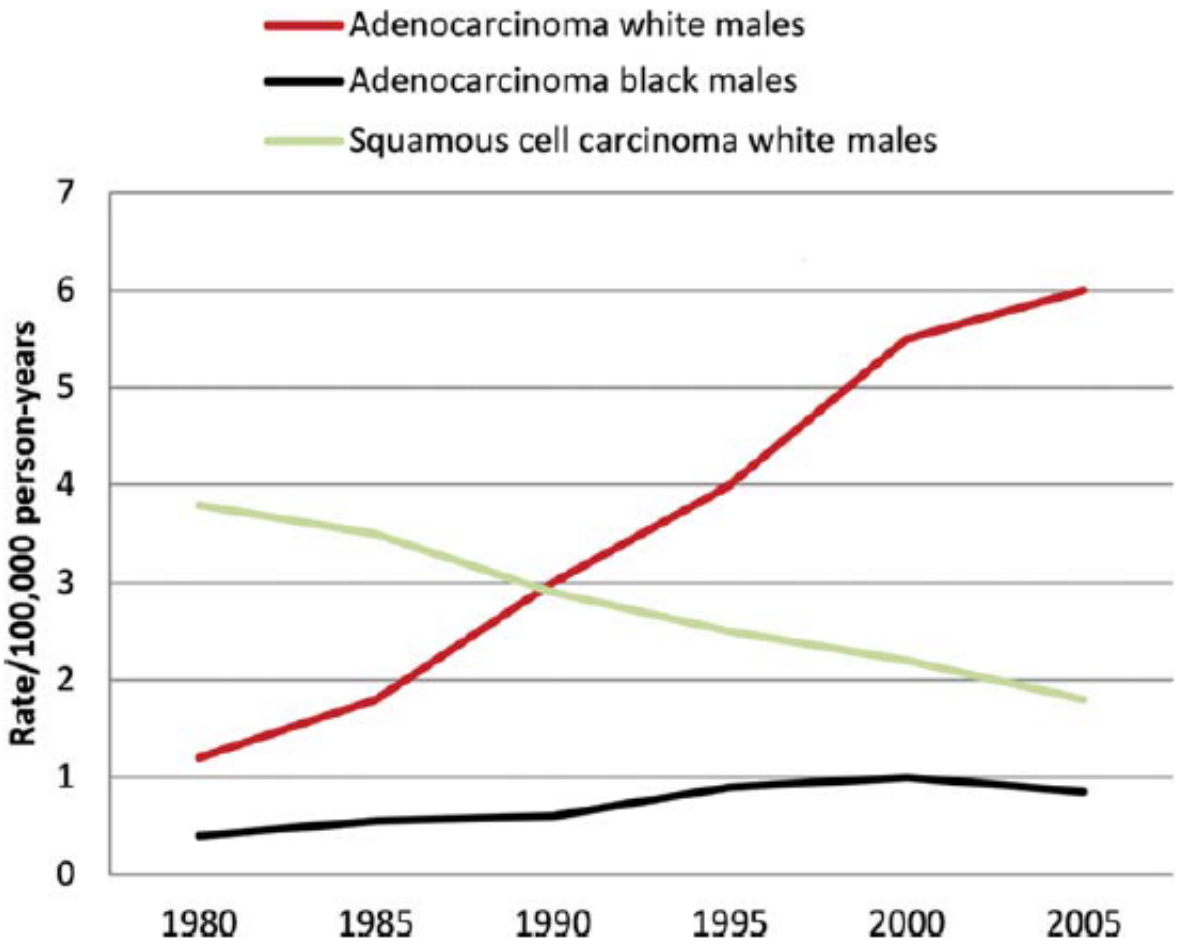
Incidence and Mortality - 2020

	Estimated new cases			Estimated deaths		
	Male	Female	**TOTAL**	Male	Female	**TOTAL**
Esophageal	14,350	4,090	**18,440**	13,100	3,070	**16,170**
Gastric	16,980	10,620	**27,600**	6,650	4,360	**11,010**

Esophageal Cancer: 6th most common cause of cancer death worldwide
Gastric Cancer: 3rd most common cause of cancer death worldwide

American Cancer Society, Facts & Figures, 2020

Esophageal Cancer Epidemiology



FRED HUTCH

Lagergren J and Lagergren P. *Cancer*. 2013; 64: 232-248.

Esophageal Cancer: Risk Factors

Squamous Cell Carcinoma	Adenocarcinoma
•***Tobacco (5-10 x risk)***	•Tobacco (2 x risk)
•***EtOH (3-7 x risk)***	•EtOH (1.2 x risk)
•Betel nut	•***GERD (7.7 x risk)***
•Hot liquids – burns	•***Obesity (3 x risk)***
•Nitroso compounds	

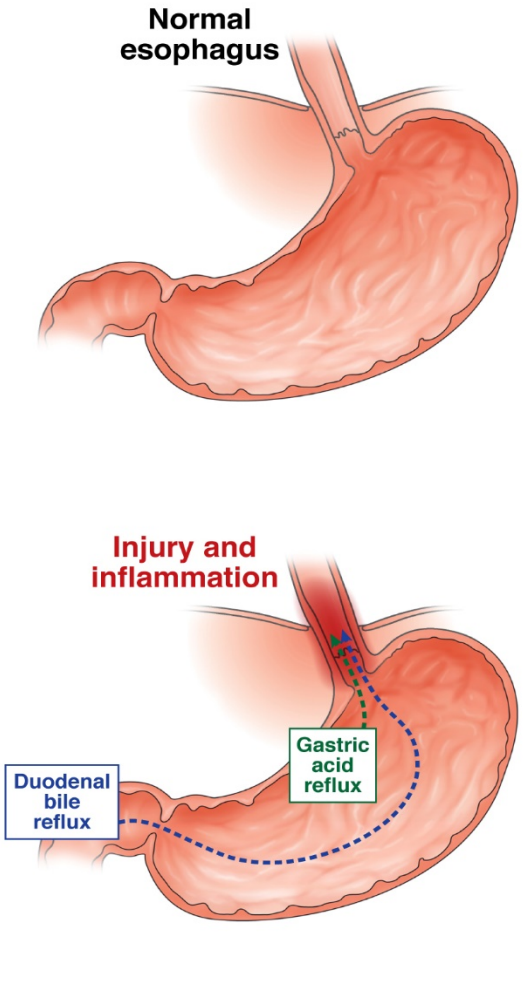
Crew, KD and Neuget AI. *World J Gastroenterology*. 2006 Jan; 12(3): 354-62
Lagergren, J et al. *NEJM*. 1999; 340(11): 825.
Lagergren, J et al. *Ann Intern Med*. 1999: 883-890

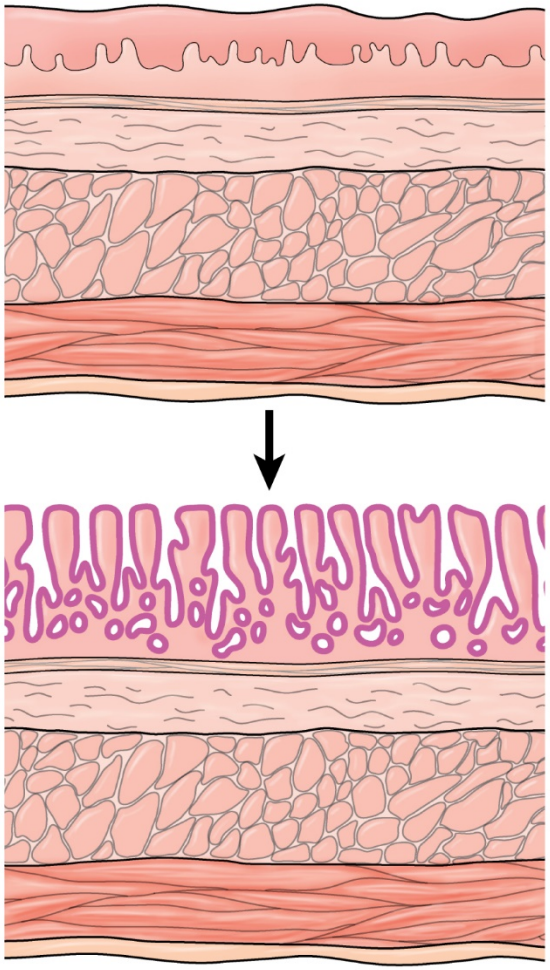
Symptomatic GERD

	Adjusted odds ratio (95% CI)		
	Esophageal adenocarcinoma	**Gastric cardia adenocarcinoma**	**Esophageal squamous cell ca**
No symptoms	1.0	1.0	1.0
Heartburn +/or regurgitation at least once a week	7.7 (5.3-11.4)	2.0 (1.4 – 2.9)	1.1 (0.7-1.9)
Heartburn +/or regurgitation at night at least once a week	10.8 (7.0-16.7)	2.4 (1.5 – 3.8)	0.9 (0.4-2.0)

Lagergren et al, N Eng J Med 340:825, 1999.

Barrett's Esophagus





A Normal squamous epithelium

B Metaplastic columnar tissue (BE)

6.6% Annual risk for adenocarcinoma with HIGH GRADE DYSPLASIA

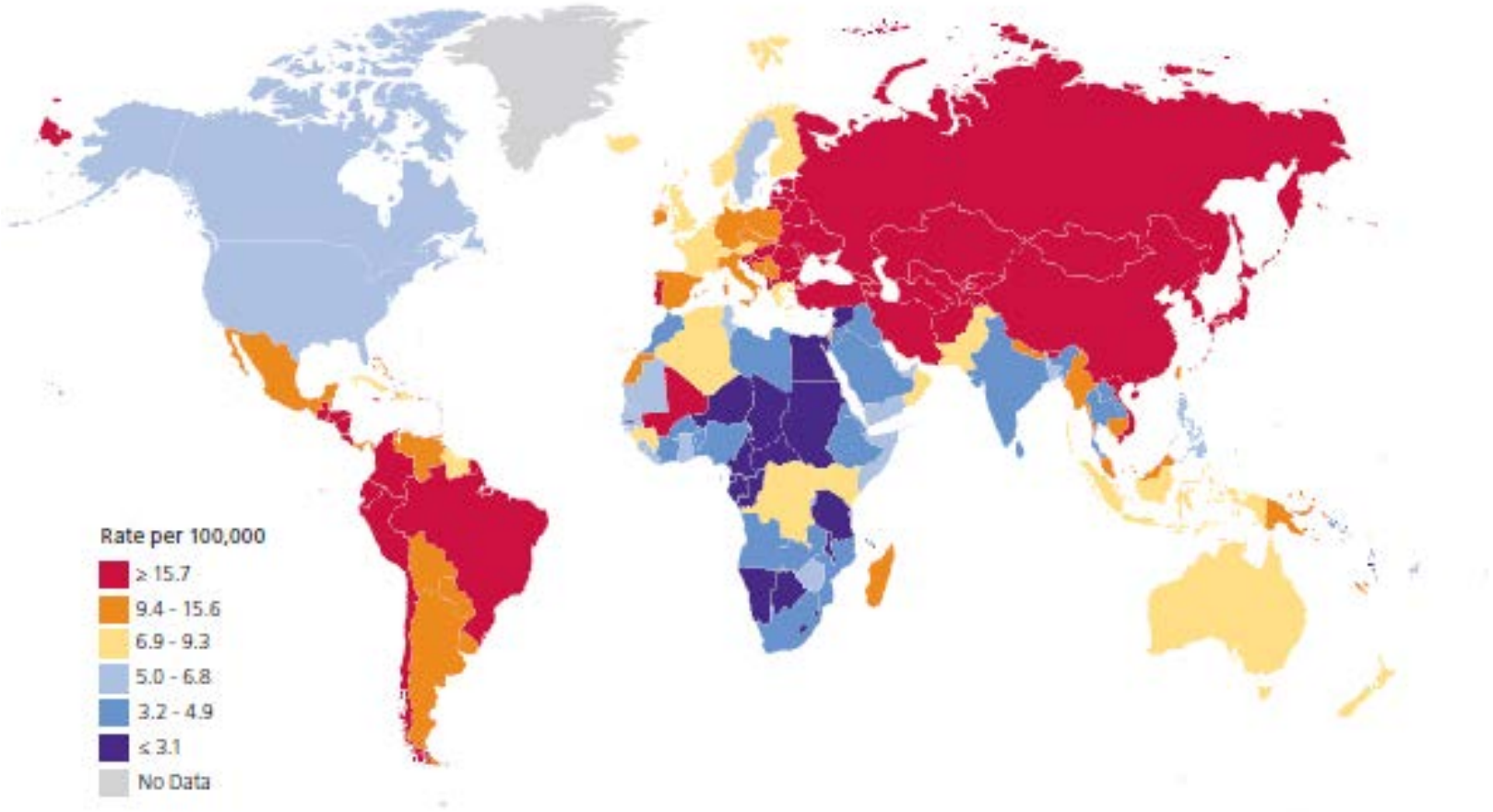
Morales CP et al. *Lancet*. 360: 9345, 2002
American Gastroenterological Association

Gastric Cancer: Risk Factors

Gastric Cancer
•Nitrite-containing, salt preserved foods •Smoking (distal gastric cancers) (OR 2.1 vs. nonsmoker) •GERD (cardia tumors) (OR 2.0) •Obesity (2-3x higher risk in obese vs. normal BMI) •**H. pylori** (intestinal subtype; body/distal) (1.2-16.7 fold increased risk, particularly CagA strain) •**Familial** (Hereditary diffuse gastric cancer (CDH1 mut; E. cadherin loss); HNPCC (Lynch); Peutz-Jehgers (STK11); Li-Fraumeni (p53); FAP (APC)

Gastric Cancer Trends

International variation in age-standardized gastric cancer incidence globally



FRED HUTCH

American Cancer Society, Global Facts & Figures 2nd ed, 2008

Gastric Cancer: Asian vs. Western

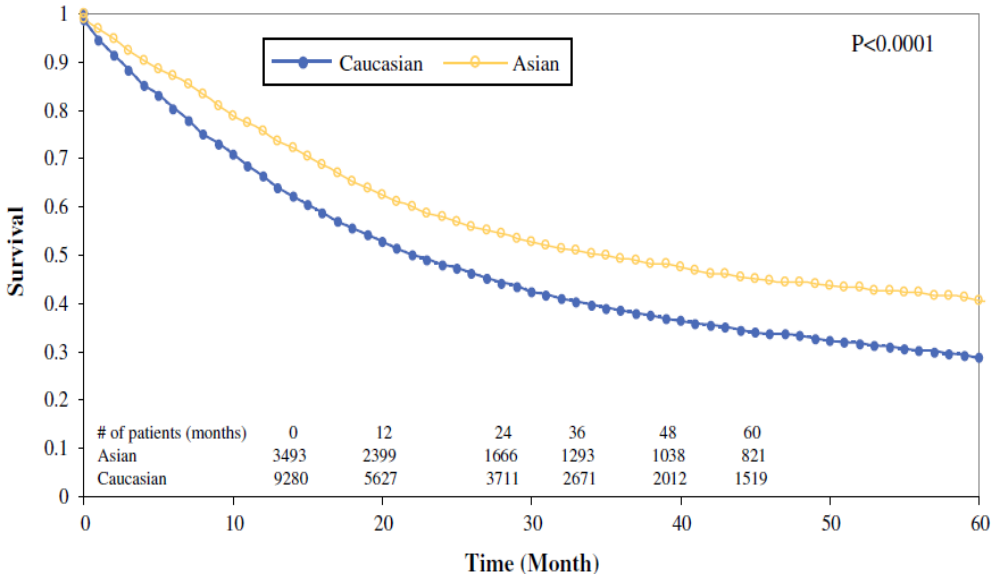
In Asia:

- Younger age at diagnosis
- More localized disease at presentation (53% in Japan vs. 27% in US) – screening programs
- More common in distal stomach
- More aggressive surgical resection
- More lines of systemic therapy

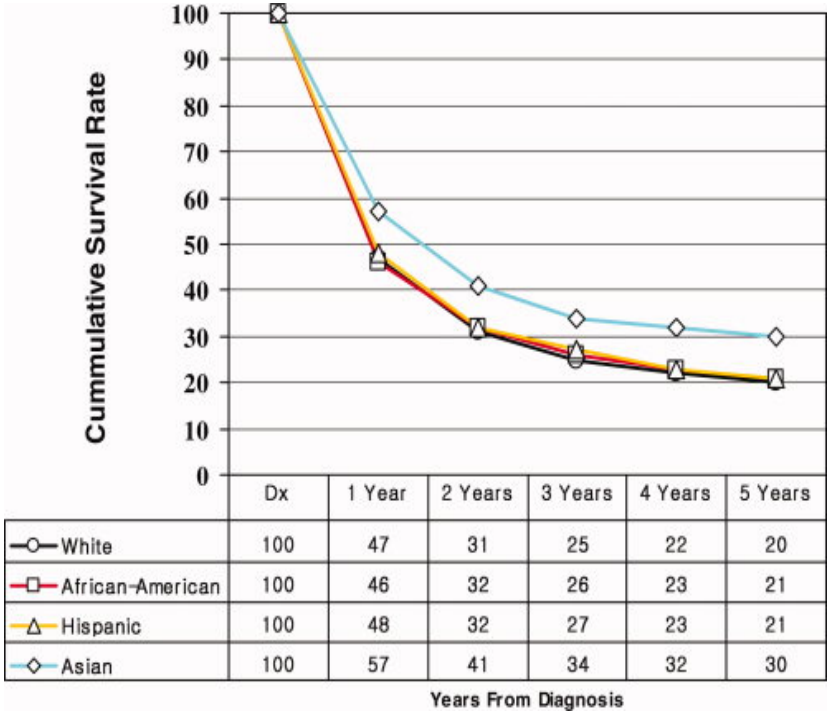
- ***Better Survival in Asia***

Gastric Cancer: Outcomes by Ethnicity

SEER-Medicare



National Cancer Database



	Dx	1 Year	2 Years	3 Years	4 Years	5 Years
White	100	47	31	25	22	20
African-American	100	46	32	26	23	21
Hispanic	100	48	32	27	23	21
Asian	100	57	41	34	32	30

Wang J. et al. Ann Surg Oncol, 2015; 22: 2965-2971
Al-Refaie W. et al. Cancer, 2008; 113(3): 461-469

Diagnosis, Staging, and Pathology

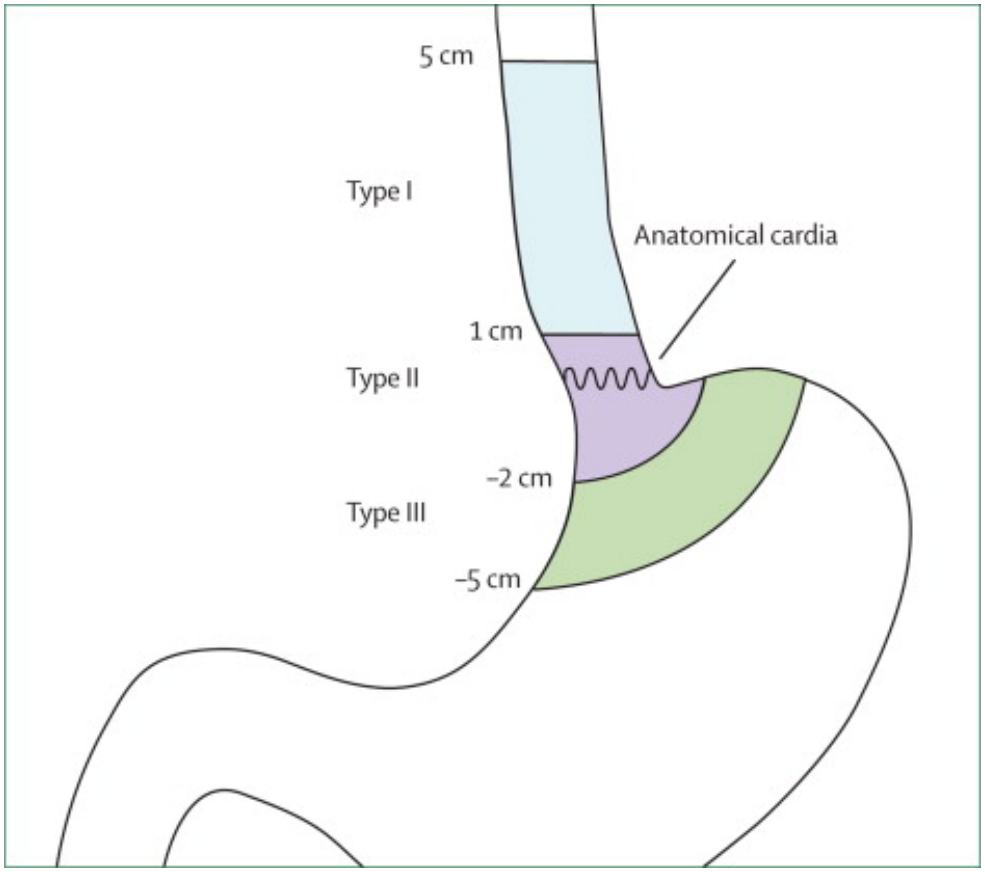
Esophageal Cancer Staging Workup

T-stage: EUS, Bronchoscopy (if above carina)

N-stage: EUS (FNA if possible), PET

M-stage: CT, PET, staging laparoscopy (GE jxn or cardia)

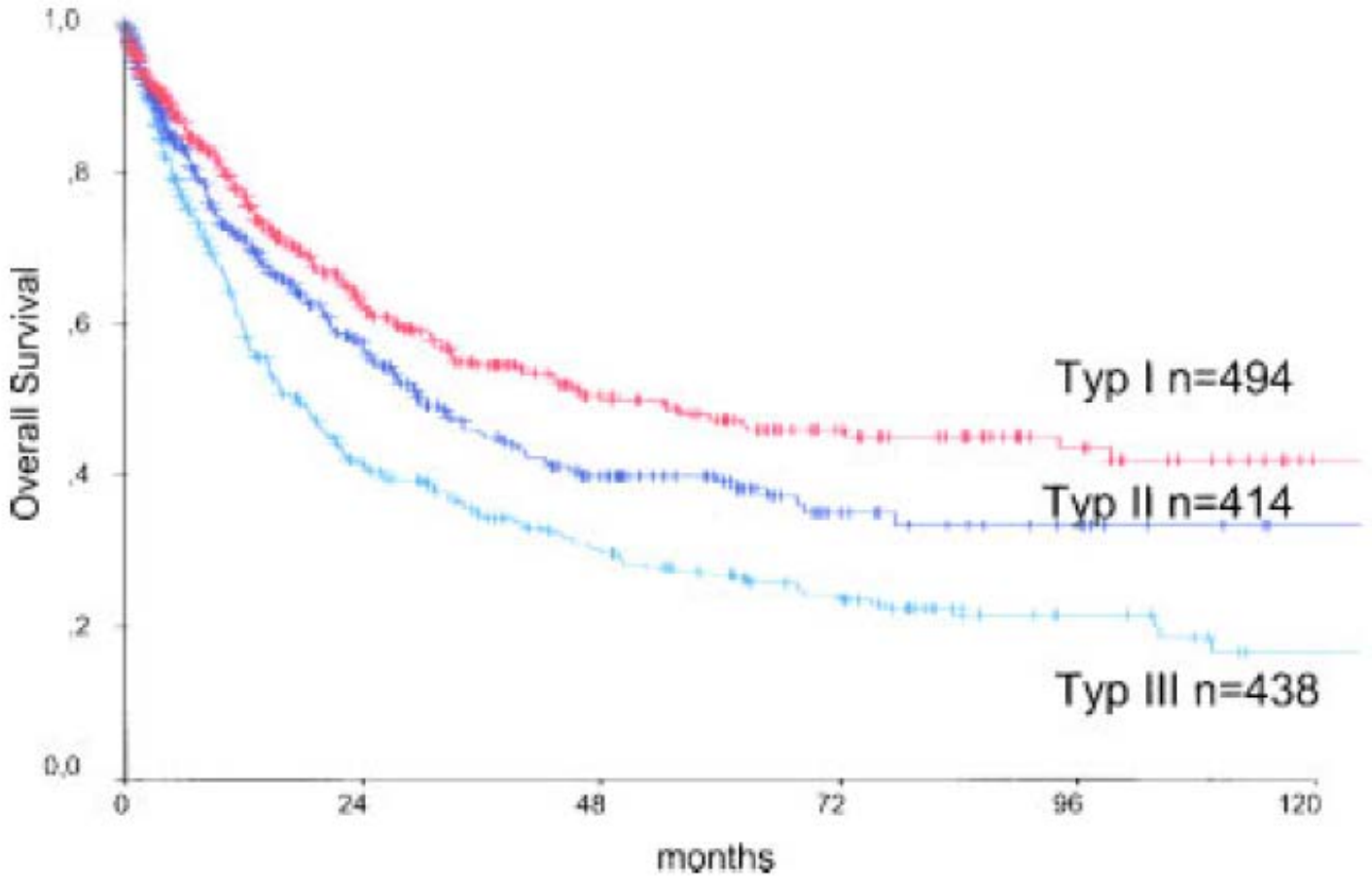
GE Junction– Siewert Classification



Type 1	Located between 1-5cm proximal to anatomic cardia
Type 2	Located between 1cm proximal and 2cm distal to anatomic cardia
Type 3	Located between 2 and 5cm distal to anatomic cardia

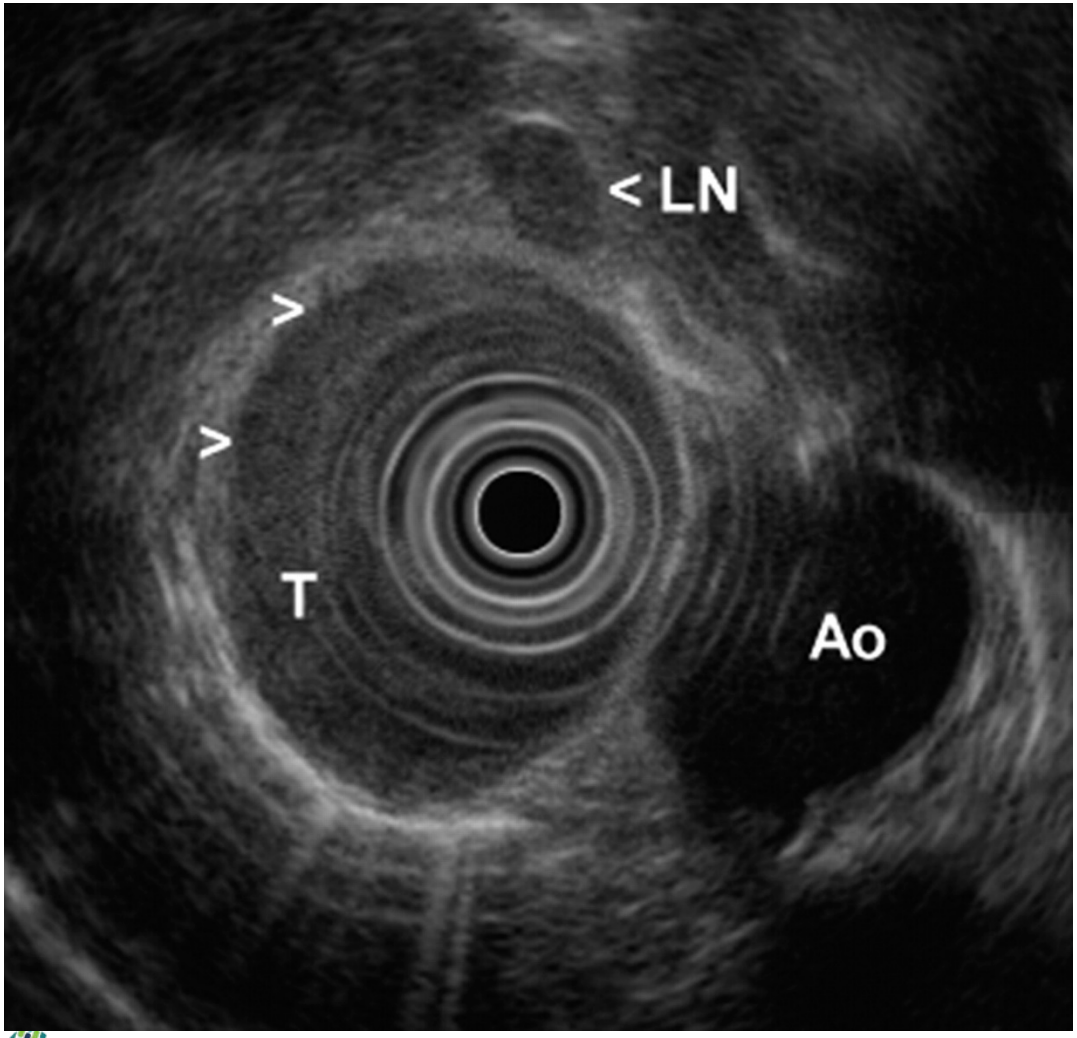
Gronnier C, et al. *Journal of Visceral Surgery*. 149:1, Feb 2012

Siewert Classification



Siewert R et al. *J Surg Onc*. 90; 139-46, 2005

Endoscopic Ultrasound



Malignant lymph nodes

- Round
- Hypoechoic
- Smooth borders
- 1cm or greater

Lennon A M , Penman I D Br Med Bull 2007;84:81-98

Esophageal Cancer Staging Principles

- Squamous cell and Adenocarcinoma = Different stage groupings
- TNM, Grade, Location (Squamous only)
- Clinical staging (u or c prefix)
- Pathologic staging after chemoRT (yp prefix)
- Example: uT3N1 (stage IIIB) distal esophageal adeno → chemoRT → surgery → ypT1N0

Esophageal Cancer Staging: AJCC 8th ed

AJCC 8th Edition - Esophageal Cancer Staging	
T stage	Tis = high grade dysplasia T1a = Tumor invades lamina propria or muscularis mucosae T1b = Tumor invades submucosa) T2 = Tumor invades muscularis propria T3 = Tumor invades adventitia T4a = Resectable tumor invading pleura, pericardium, or diaphragm T4b = Unresectable tumor invading other adjacent structures, such as aorta, vertebral body, trachea, etc.)
N stage	N0 = No lymph node metastases N1 = Metastases in 1-2 regional lymph nodes N2 = Metastases in 3-6 regional lymph nodes N3 = Metastases in 7 or more regional lymph nodes
M stage	M0 = no distant metastases M1 = distant metastases

Squamous Cell Ca: AJCC 8th ed

Stage Groupings: Squamous Cell Carcinoma

Stage	T	N	M	G	Location
Stage 0	Tis	N0	M0#	N/A	Any
Stage IA	T1a	N0	M0	1 or X	Any
Stage IB	T1a	N0	M0	2 or 3	Any
	T1b	N0	M0	Any	Any
	T2	N0	M0	1	Any
Stage IIA	T2	N0	M0	2, 3, or X	Any
	T3	N0	M0	Any	Lower
	T3	N0	M0	1	Upper, middle
Stage IIB	T3	N0	M0	2 or 3	Upper, middle
	T3	N0	M0	X	Any
	T3	N0	M0	Any	location X
	T1	N1	M0	Any	Any
Stage IIIA	T1	N2	M0	Any	Any
	T2	N1	M0	Any	Any
Stage IIIB	T2	N2	M0	Any	Any
	T3	N1-2	M0	Any	Any
	T4a	N0-1	M0	Any	Any
Stage IVA	T4a	N2	M0	Any	Any
	T4b	N0-2	M0	Any	Any
	Any	N3	M0	Any	Any
Stage IVB	Any T	Any N	M1	Any	Any

Adenocarcinoma: AJCC 8th ed

Stage Grouping: Adenocarcinoma

Stage	T	N	M	G
Stage 0	Tis (HGD#)	N0	M0	N/A
Stage IA	T1	N0	M0	1 or X
Stage IB	T1a	N0	M0	2
	T1b	N0	M0	1, 2, or X
Stage IC	T1	N0	M0	3
	T2	N0	M0	1 or2
Stage IIA	T2	N0	M0	3 or X
Stage IIB	T1	N1	M0	Any
	T3	N0	M0	Any
Stage IIIA	T1	N2	M0	Any
	T2	N1	M0	Any
Stage IIIB	T2	N2	M0	Any
	T3	N1-2	M0	Any
	T4a	N0-1	M0	Any
Stage IVA	T4a	N2	M0	Any
	T4b	N0-2	M0	Any
	Any	N3	M0	Any
Stage IVB	Any T	Any N	M1	Any

Gastric Cancer Staging

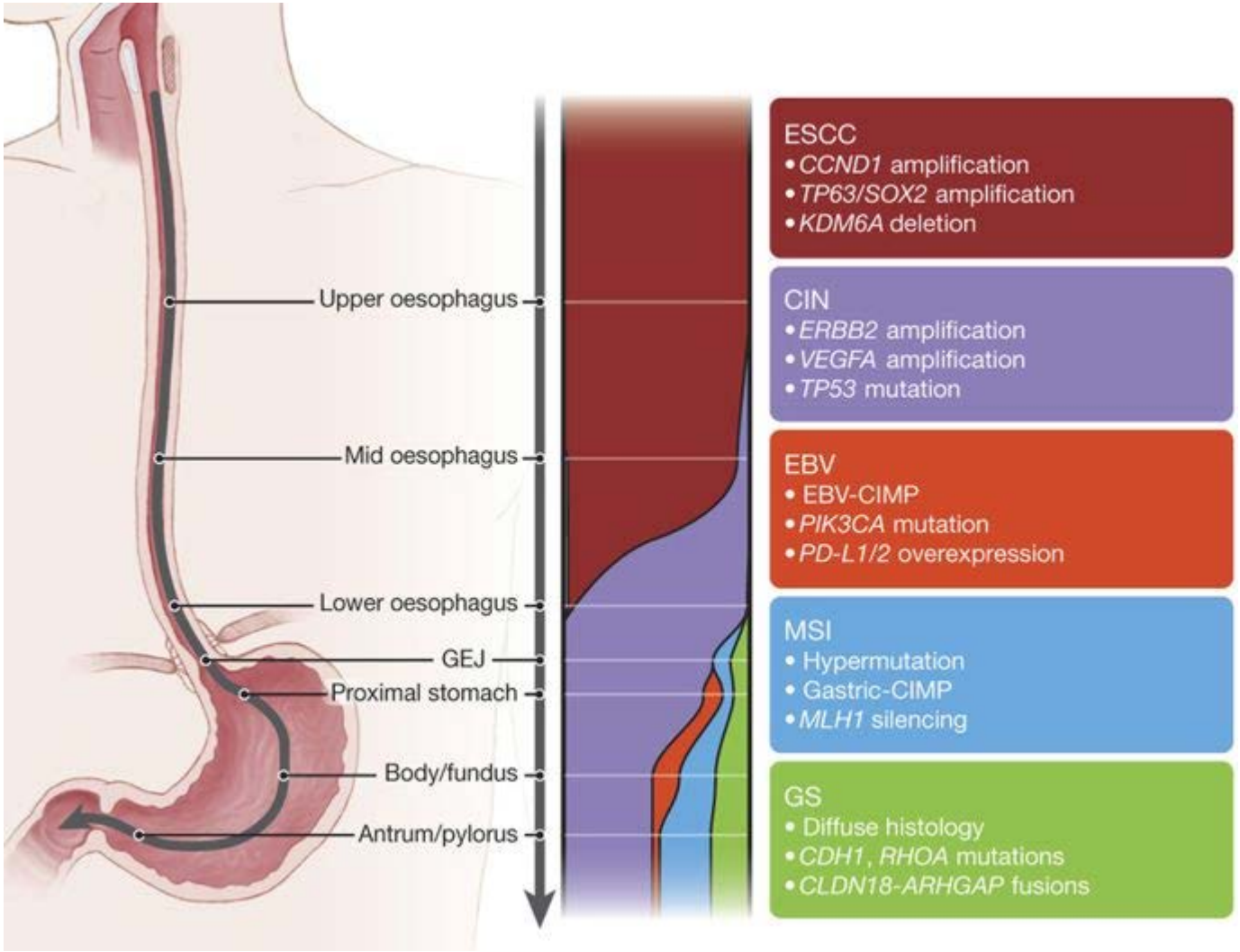
Incorporates diagnostic laparoscopy

- Evaluation of the peritoneum
- + cytology = pM1

Stage Groupings for pTNM			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage 1B	T1	N1	M0
	T2	N0	M0
Stage IIA	T1	N2	M0
	T2	N1	M0
	T3	N0	M0
Stage IIB	T1	N3a	M0
	T2	N2	M0
	T3	N1	M0
	T4a	N0	M0
Stage IIIA	T2	N3a	M0
	T3	N2	M0
	T4a	N1-2	M0
	T4b	N0	M0
Stage IIIB	T1-2	N3b	M0
	T3	N3a	M0
	T4a	N3a	M0
	T4b	N1-2	M0
Stage IIIC	T3	N3b	M0
	T4a	N3b	M0
	T4b	N3a or N3b	M0
Stage IV	Any T	Any N	M1

College of American Pathologists June 2017

Upper GI Cancer Molecular Subtypes



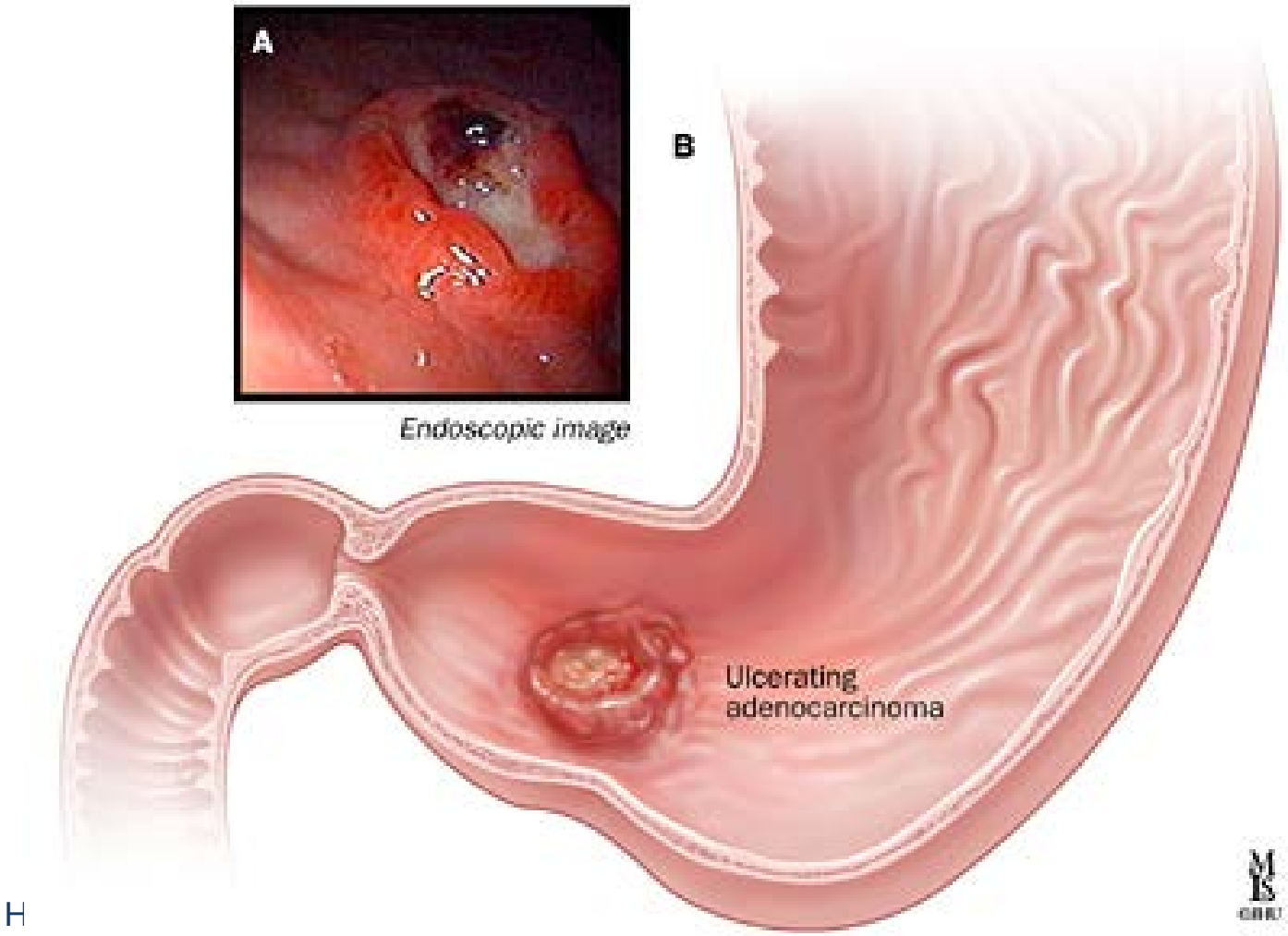
The Cancer Genome Atlas Research Network. *Nature*, 2017. 541: 69–175

Lauren Classification - Adenocarcinoma

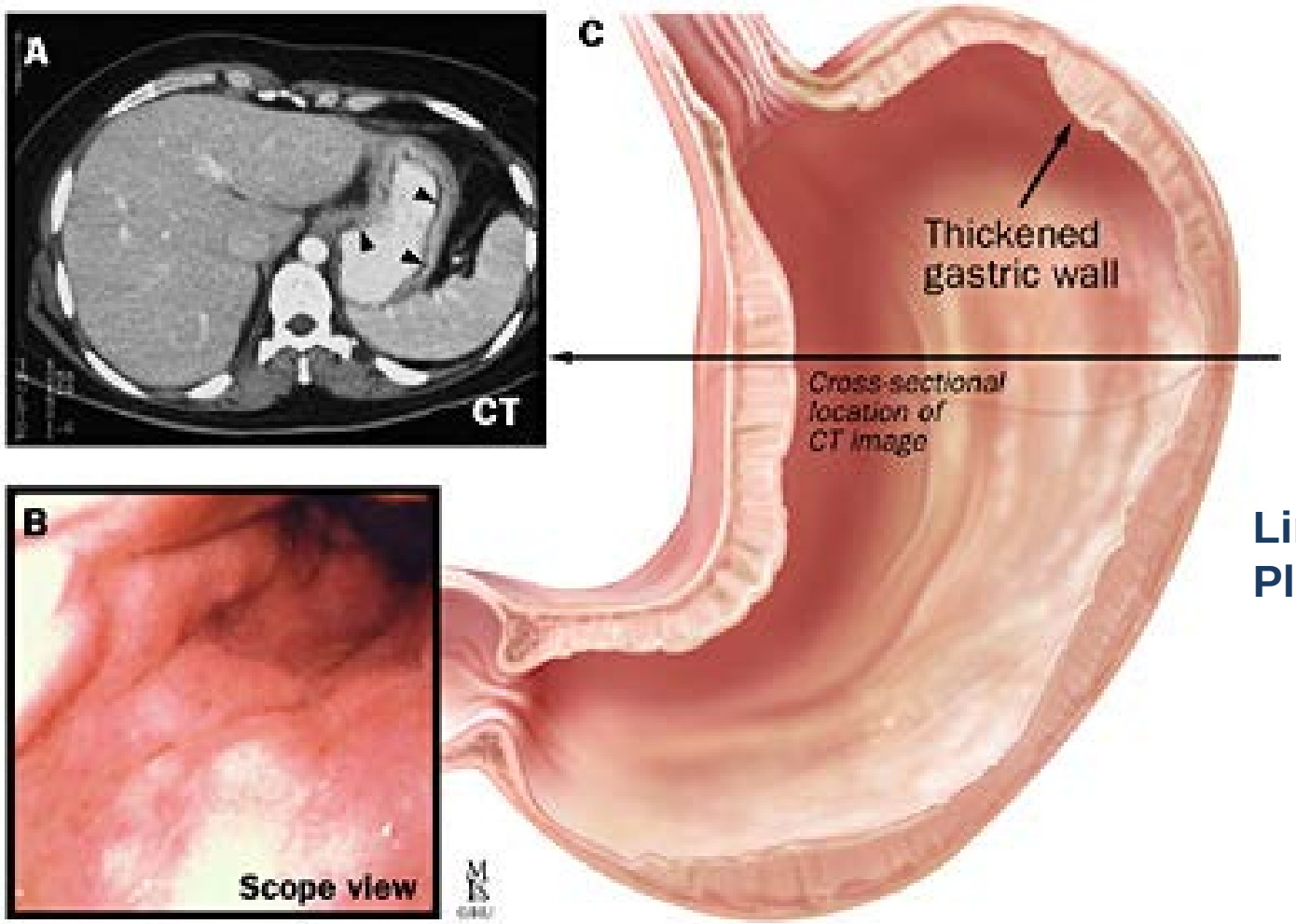
Intestinal	Diffuse
• **Inflammation** present *(H. pylori, atrophic gastritis, glandular dysplasia)* • '**Cascade**' of events: inflammation → intestinal metaplasia → dysplasia → invasive carcinoma • **Mucosal mass** • Develop over years, **better prognosis**	• **No inflammation** • Loss of E-cadherin **-- no clear precancerous lesion** • No clear mucosal mass - **Invades gastric wall** (e.g. linitis plastica) • Highly metastatic, invasive, **poor prognosis**

Lauren, P. *Acta Pathol Microbiol Scand*. 1965; 64(31).
Shah, M. et al. *Clin Cancer Research*. 2011; 17: 2693-2701

Intestinal Type Adenocarcinoma



Diffuse Type Adenocarcinoma



Linitis Plastica

Hereditary Diffuse Gastric Cancer

Germline mutations in CDH1 gene (leading to loss of E-cadherin)

- Autosomal dominant with > 70% penetrance
- Diffuse, signet ring type adenocarcinoma
- Increased incidence lobular breast cancer
- Prophylactic gastrectomy should be considered

Huntsman, et al. New England Journal of Medicine. 344;1904, 2001

Her2 + Esophageal and Gastric Cancers

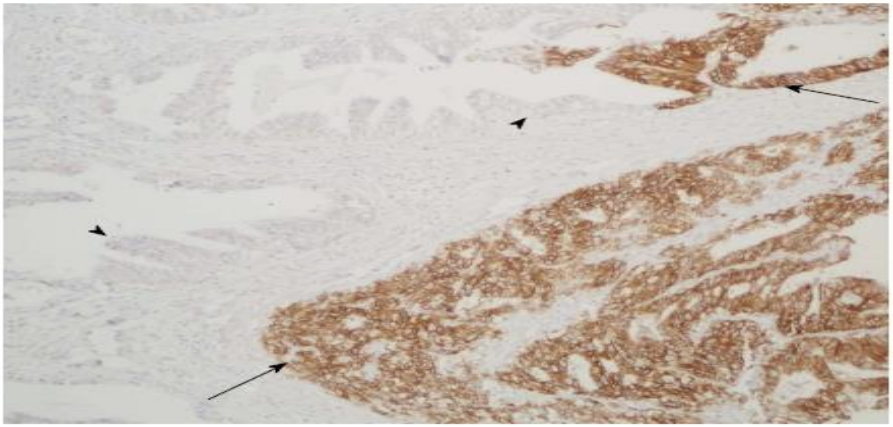
- **15-20%** of all gastric/esophageal adenocarcinoma (distal esophageal, GE junction, intestinal-type)

- Her2 3+ OR FISH + (*HER2*/CEP17 ratio ≥2.0) considered eligible

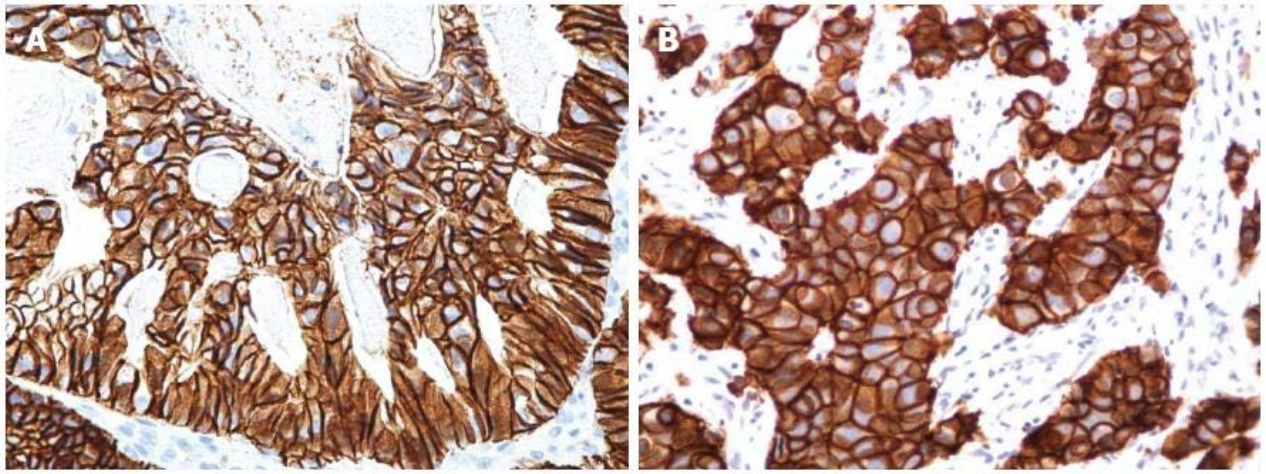
Gastric / Eso	**Breast**
• Heterogeneous expression • Interpretation criteria differs between biopsy and resection • Apical membrane often does not stain - + result requires only lateral / basolateral staining	• Uniform expression • Same interpretation criteria regardless of specimen • Complete circumferential staining required for positive result.

College of American Pathologists 2013; Questions Relating to Immunohistochemistry for Her2 on Gastric and Gastroesophageal Junction Adenocarcinoma

Her2 + Esophageal and Gastric Cancers



Heterogeneity

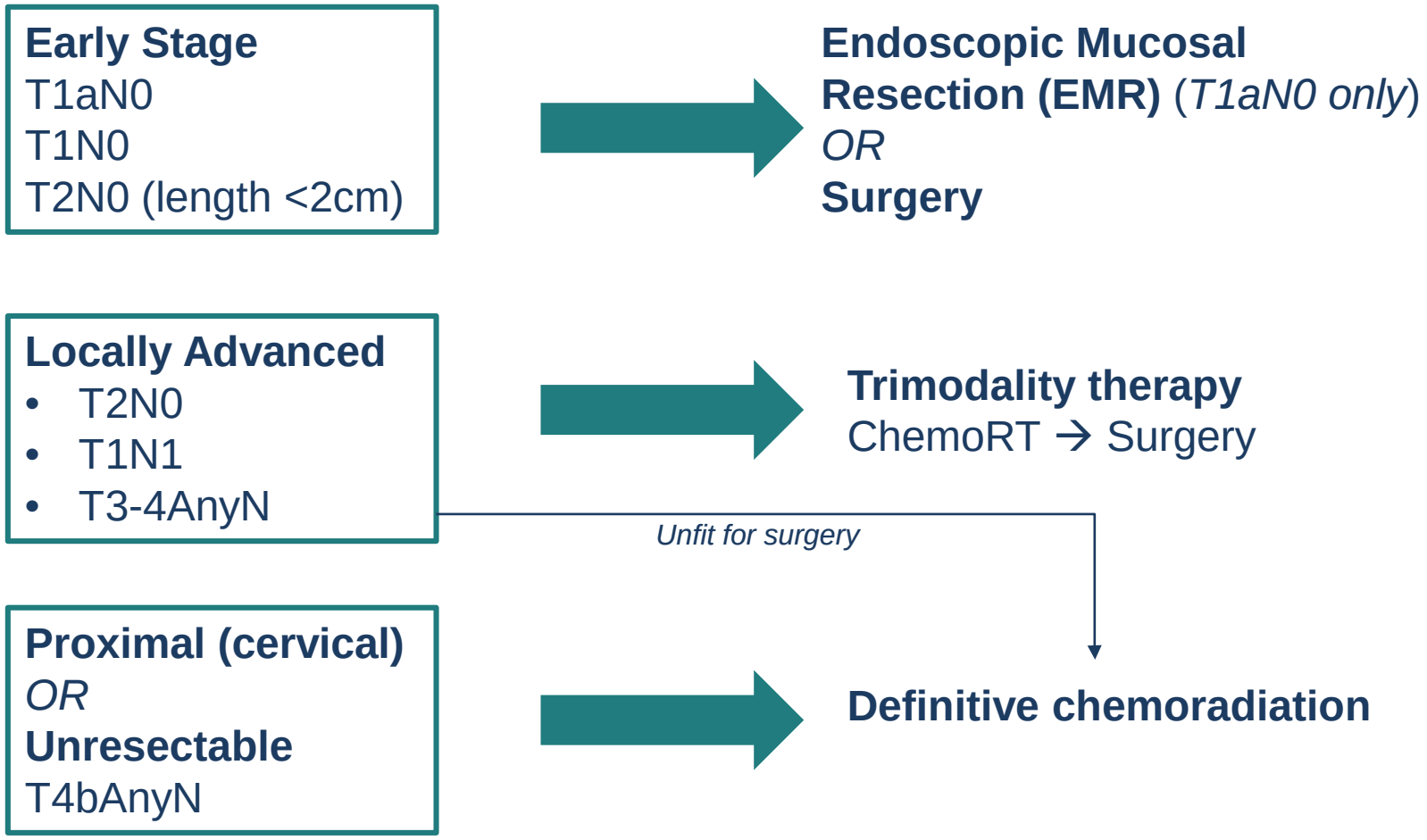


Basolateral vs. Circumferential and Apical staining

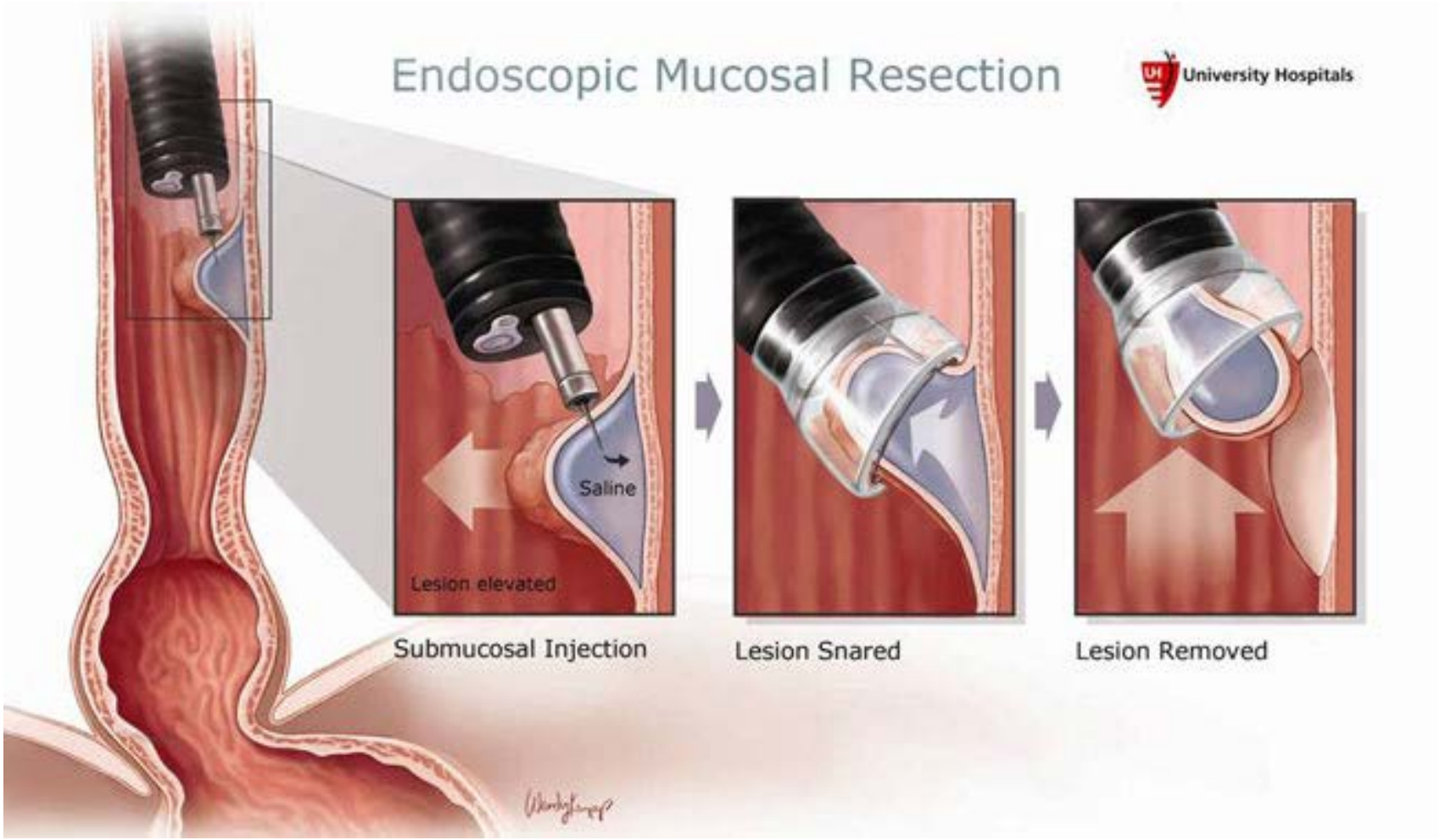
Abrahao-Machado, et al. World J Gastroenterol. 2016; 22(19): 4619-4625.

Stage I-III Esophageal Cancer

Esophageal Cancer Treatment Algorithm



Endoscopic Mucosal Resection – T1a lesions



Surgery (Esophagectomy)

Transhiatal approach	Transthoracic (Ivor Lewis)
• Blind dissection of tumor	• Direct visualization of tumor
• **Thoracotomy not required**	• **Thoracotomy required**
• Anastomotic leak more common, but easier to manage	• Anastomotic leak less common, but mediastinal leaks difficult to manage – higher morbidity
• Abdominal and cervical incisions	• Abdominal and thoracic incisions
• Shorter ICU / hospital stay	

Surgery should be done at a high volume center

FRED HUTCH

Barreto and Posner. *World J Gastroenterol*. Aug 2010
Chang AC, et al. Ann Thoracic Surgery. 85(2), 2008.

Neoadjuvant ChemoRT: Randomized Trials

Citation	# Pts	Preoperative Treatment	Path CR	Survival
Walsh, TN *NEJM* 1996	113 (adeno only)	Cis/5-FU/RT (40 Gy)	25%	16 vs. 11 months (p=0.01)
Bosset, JF *NEJM* 1997	282 (SCC only)	Cis/RT (37 Gy)	26%	18.6 months both groups
Urba, SG *JCO* 2001	100 (75% adeno)	Cis/5FU/ Vinblastine/RT (45 Gy)	28%	17.6 vs. 16.9 months (p=0.15)
Burmeister, BH *Lancet Oncol* 2005	256 (60% adeno)	Cis/5FU/RT (35 Gy)	16%	21.7 vs. 18.5 months (p=NS)
Tepper, J *JCO* 2008	56 (75% adeno)	Cis/5FU/RT (50.4 Gy)	40%	4.48 years vs 1.79 years (p=0.02)
Van Hagen, P *NEJM* 2012	363 (75% adeno)	Paclitaxel/Carbo/RT (41.4 Gy)	32.6%	49 vs. 24 months (p=0.011)

Neoadjuvant Chemoradiation: Meta-Analyses

Citation	# Studies	# Pts	Result
Urschel, JD Am J Surg, 2003	9 RCTs	1,116 pts	3-year survival HR 0.66 (p=0.016)
Gebski, V Lancet Oncol 2007	10 RCTs	1,209 pts	HR 0.81, p=0.002 (benefit seen in both histologies)
Jin, HL World J Gastroenterol 2009	11 RCTs	1,208 pts	5-year survival OR 1.46 (p=0.02) (benefit seen only in adenocarcinoma)
Sjoquist, KM Lancet Oncol 2011	12 RCTs	1,854 pts	HR 0.78 (p<0.001) Adeno HR 0.75, p=0.02 SCC HR 0.80, p=0.004

Dutch CROSS Trial

ORIGINAL ARTICLE

Preoperative Chemoradiotherapy for Esophageal or Junctional Cancer

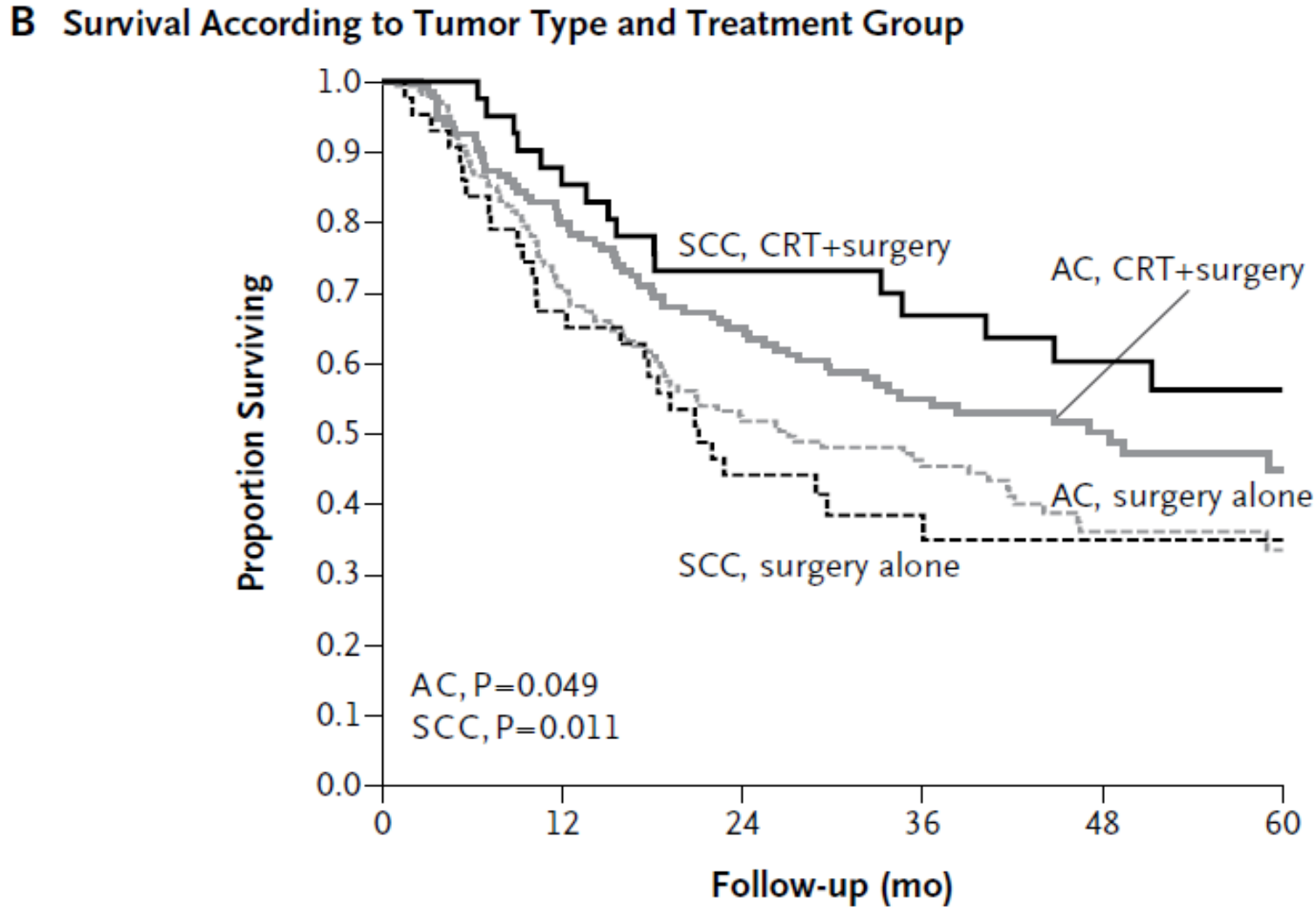
P. van Hagen, M.C.C.M. Hulshof, J.J.B. van Lanschot, E.W. Steyerberg, M.I. van Berge Henegouwen, B.P.L. Wijnhoven, D.J. Richel, G.A.P. Nieuwenhuijzen, G.A.P. Hospers, J.J. Bonenkamp, M.A. Cuesta, R.J.B. Blaisse, O.R.C. Busch, F.J.W. ten Kate, G.-J. Creemers, C.J.A. Punt, J.T.M. Plukker, H.M.W. Verheul, E.J. Spillenaar Bilgen, H. van Dekken, M.J.C. van der Sangen, T. Rozema, K. Biermann, J.C. Beukema, A.H.M. Piet, C.M. van Rij, J.G. Reinders, H.W. Tilanus, and A. van der Gaast, for the CROSS Group*

Dutch CROSS Trial

Rationale	• Does **preoperative chemoradiation** add to benefit of surgery?
N = 368	• 188 surgery vs 180 chemoRT + surgery
Inclusion	• **Adenocarcinoma or SCC** • Esophagus and GE Junction (Siewert 3 excluded); T1N1, T2-3N0-1
Treatment Arms	• **Surgery alone** (Transthoracic for mid-thoracic tumors, Transhiatal for distal tumors) • **Preoperative chemoRT→ surgery** o Total Radiation Dose = 41.4 Gy o Weekly Carboplatin AUC 2 + Paclitaxel 50mg/m2

Van Hagen P et al. *NEJM*. 366;22, 2012

Histologic Subtype and Survival



Dutch CROSS Trial – Key Results

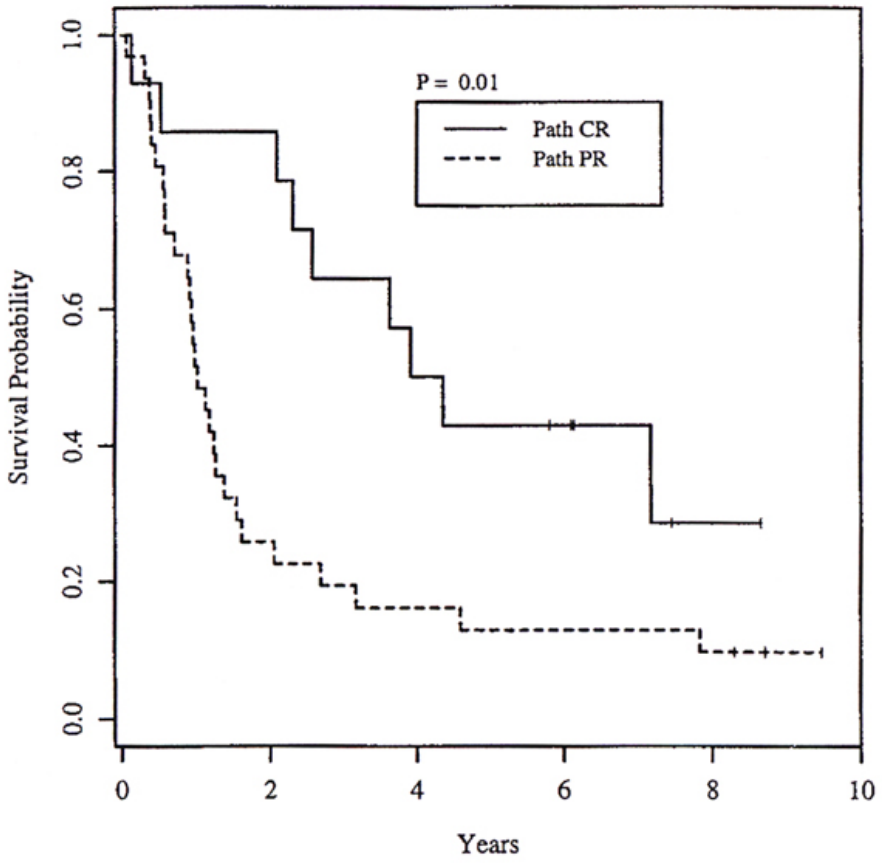
	Surgery alone	CRT + surgery
N	188	175
R0 resection rate	67%	92.3%
Path complete response	N/A	32%
Med survival	**26 months**	**49 months**
1-year survival	70%	82%
3-year survival	48%	59%
Anastomotic leakage	25%	22%
In-hospital mortality	3.8%	3.4%

Tumor Regression Grading

Modified Ryan Scheme	
Description	**Tumor Regression Score**
No viable cancer cells (complete response)	0
Single cells or rare small groups of cancer cells (near complete response)	1
Residual cancer with evident tumor regression, but more then single or rare groups of cancer cells (partial response)	2
Extensive residual cancer with no evident tumor regression (poor or no response)	3

Ryan, R. et al. *Histopathology*. 2005; 47(2): 141-146

Pathologic Response after Trimodality Therapy



Path CR vs. Residual Disease

Median Survival (49.7 vs. 12 months)

3-yr survival (64% vs. 19%)

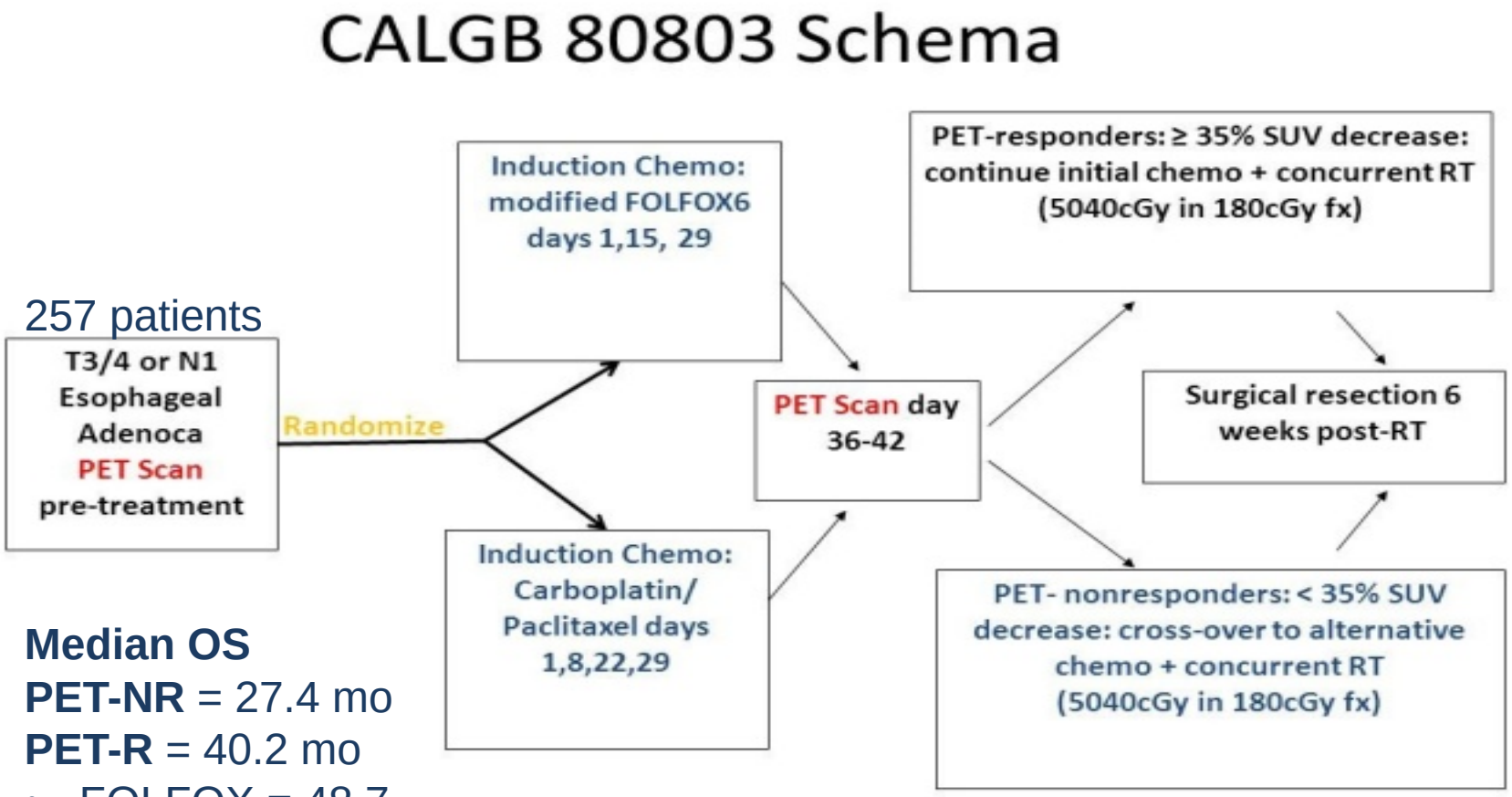
Urba S. *J Clin Oncol*. 19(2), 2001

Trimodality Therapy: Completed Trials

CALGB 80803: Randomized Phase II Trial of PET Scan-Directed Combined Modality Therapy in Esophageal Cancer

RTOG 1010: A Phase III Trial Evaluating the Addition of Trastuzumab to Trimodality Treatment of Her2-Overexpressing Esophageal Adenocarcinoma

CALGB 80803



Median OS
PET-NR = 27.4 mo
PET-R = 40.2 mo
- FOLFOX = 48.7

FRED HUTCH

Goodman, KA et al. J Clin Oncol. 2018: 36 (suppl; abstr 4012)

RTOG 1010

Step 1: Registration

Mandatory Central Her2 Testing

Step 2: Randomization (stratification by celiac lymphadenopathy > or ≤ 2cm (n=571)

Arm 1

1. Radiation (50.4 Gy), paclitaxel, carboplatin, and **trastuzumab**
2. Surgery
3. Maintenance trastuzumab, q3 wks x 13

Arm 2

1. Radiation (50.4 Gy), paclitaxel, carboplatin
2. Surgery

ASCO 2020: Addition of trastuzumab does not improve DFS – HR 0.97, 95% CI 0.69, 1.36)

Safran H. et al. *Journal of Clinical Oncology* 38, no. 15_suppl (May 20, 2020) 4500-4500.

What to do after Trimodality therapy?

Routine Surveillance

NCCN Guidelines

- Years 1-2: q3-4 month clinical assessment and labs
- Years 3-5: q6 month clinical assessment and labs
- Years 1-5: Annual CT imaging

Poor Responders (Extensive residual disease – tumor regression scores 2-3)

- Adjuvant chemotherapy?
- Immune checkpoint inhibition being studied

Nutrition / Dietary Counseling – Learning how and what to eat!

Do we need all 3 components of trimodality therapy?

Maybe not in certain scenarios …

Definitive Chemoradiation: RTOG 8501

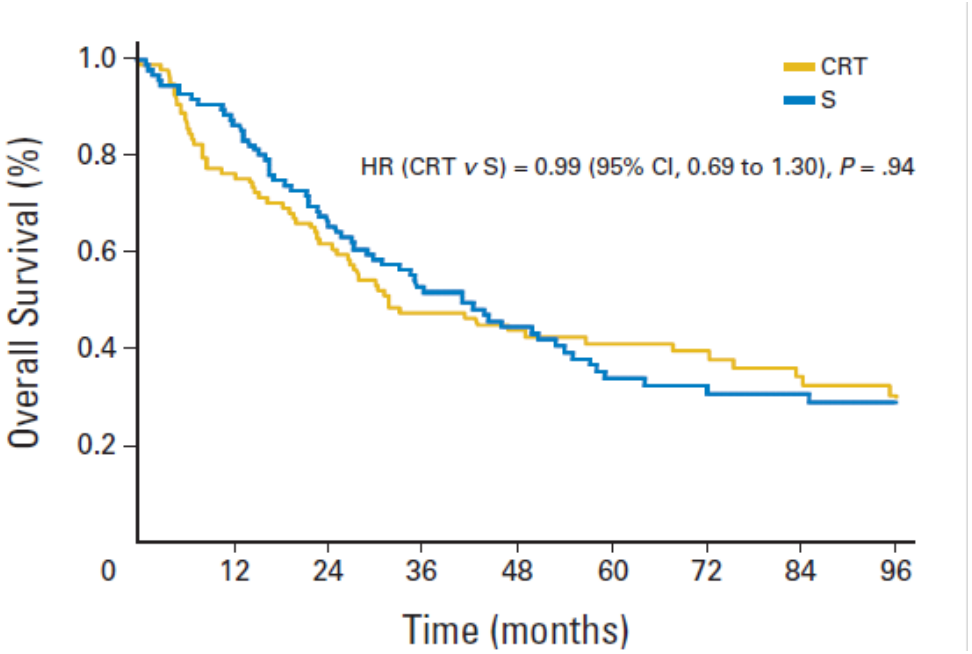
Survival Estimates by Histologic Type after Combined Modality Therapy		
Year	Adenoca (% alive)	Squamous Cell (% alive)
0	100%	100%
1	52%	59%
2	22%	38%
3	17%	30%
4	13%	26%
5	13%	21%

Is ChemoRT Mandatory ?

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Surgery Alone Versus Chemoradiotherapy Followed by Surgery for Stage I and II Esophageal Cancer: Final Analysis of Randomized Controlled Phase III Trial FFCD 9901

Christophe Mariette, Laetitia Dahan, Françoise Mornex, Emilie Maillard, Pascal-Alexandre Thomas, Bernard Meunier, Valérie Boige, Denis Pezet, William B. Robb, Valérie Le Brun-Ly, Jean-François Bosset, Jean-Yves Mabrut, Jean-Pierre Triboulet, Laurent Bedenne, and Jean-François Seitz



Mariette C, et al. J Clin Oncol. 2014; 32(23): 2416-22

Radiation Esophagitis

- **Topical anesthetics** (e.g. viscous lidocaine)
- **Analgesics and antiinflammatories** (narcotics, dex elixir, carafate)
- **Dietary modification** (bland, soft, pureed, less acidic, room temp, converting to liquid medication when possible
- **Supplementary nutrition**
  - Avoid PEG/G tubes in surgical candidates; NG / Dobhoff tube feedings preferred in the short term preoperatively

Take-home points: Esophageal Cancer

- Endoscopic resection for T1a lesions
- For T2+ or N1+ tumors, **trimodality therapy** is still the standard of care
- How can we improve path response to chemoRT?
- PET response may be prognostically useful and may guide treatment
- No additional therapy after trimodality, regardless of pathologic response

Stage I-III Gastric Cancer

Gastric Cancer Treatment Algorithm

Early Stage
- T1-T2N0

→ **Surgery**

Locally Advanced
- T1-2N1
- T3-4AnyN

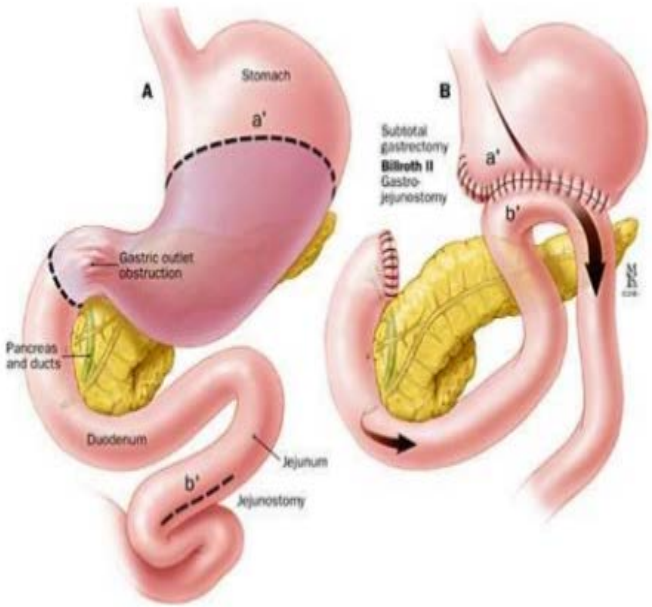
→ **Perioperative chemo**
OR
Postoperative chemo *(Asia)*
OR
Postoperative chemoRT
(margin positive)

Peritoneal washings positive
AnyTAnyNpM+ (cytology)

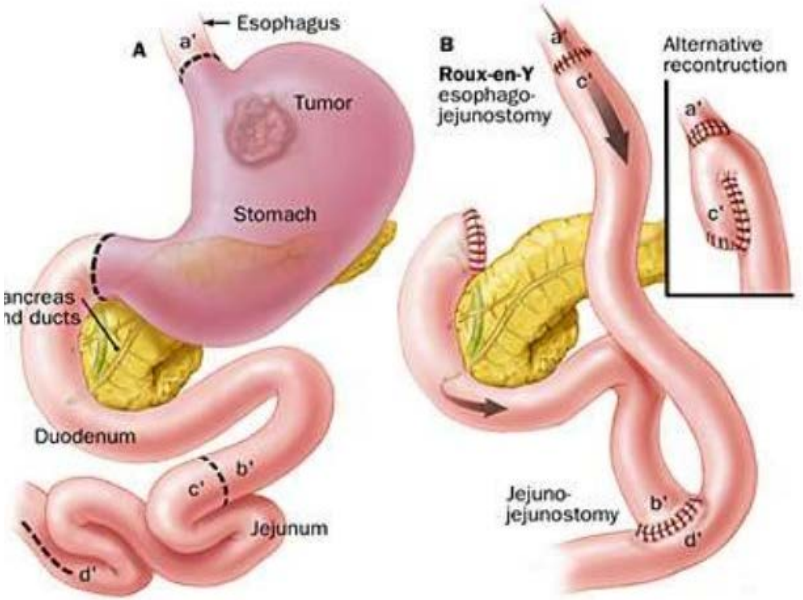
→ **Chemotherapy alone**
(consider surgery in very fit patients who clear peritoneal cytology after upfront chemo)

Gastric Resection

Distal Gastrectomy



Total Gastrectomy



Post-Gastrectomy Considerations

- Inability to store and break down food – frequent SMALL meals
- Vitamin B12 deficiency – lack of instrinsic factor production (cardia)
- Iron deficiency – decreased gastric acid
- Dumping syndrome – rapid emptying into small bowel – lightheadedness, nausea, diarrhea

Gastric Cancer Lymph Node Dissection

Lymph Node Dissection	Description
D1	lesser and greater curvature, paracardial
D2	Left gastric, hepatic, celiac, splenic (could require pancreatectomy or splenectomy to access these nodes)
D3	D2 + portahepatic, hepatoduodenal
D4	retropancreatic, root of mesentery, transverse mesocolon, paraaortic

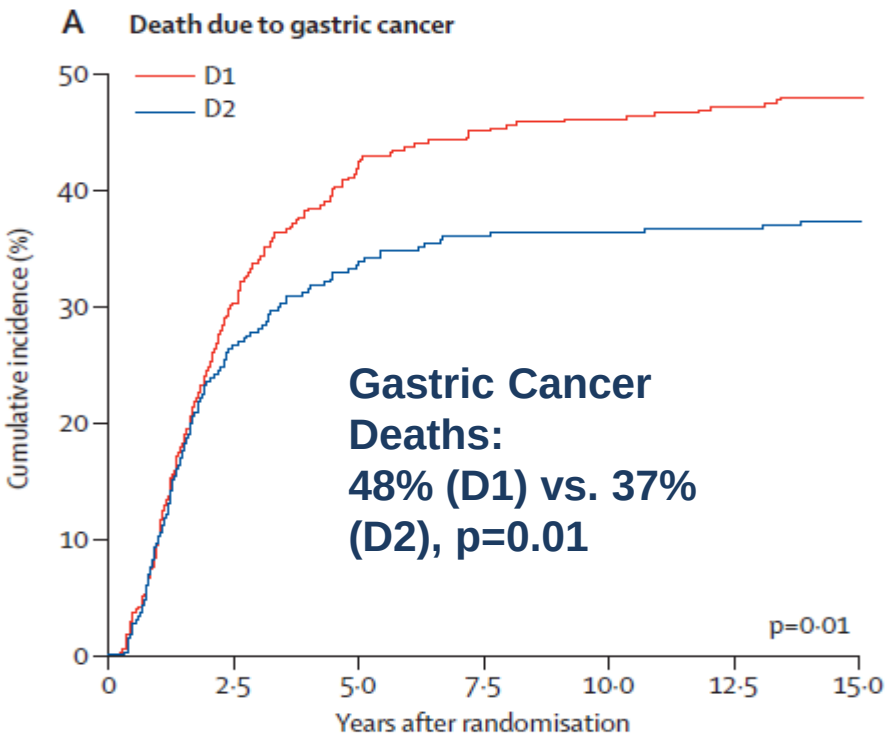
The Dutch Gastric Cancer Group: D1 vs. D2

711 patients undergoing curative resection of gastric cancer

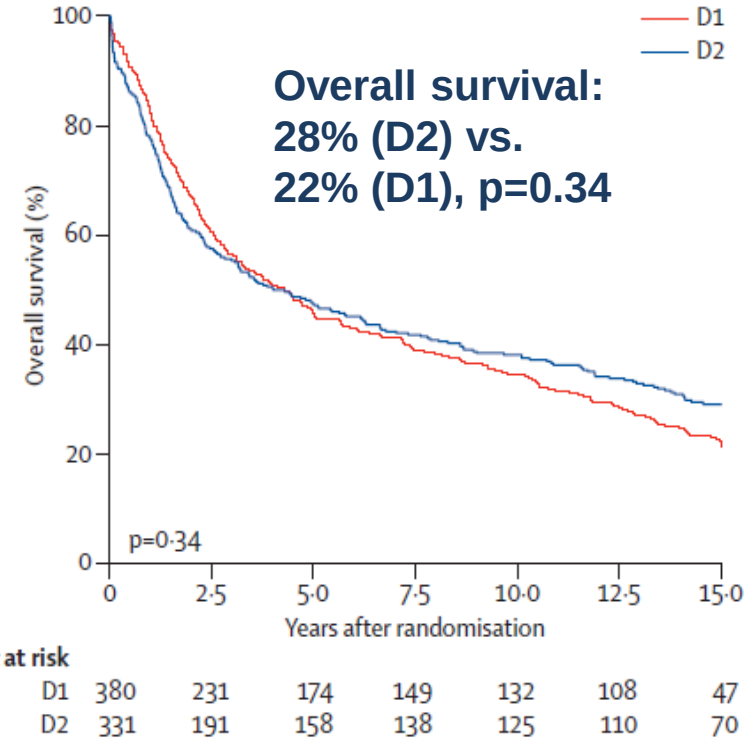
	Peri operative morbidity	Peri operative mortality	5-yr survival
D1	25%	4%	45%
D2	43%	10%	47%

Bonenkamp JJ et al, NEJM 1999; 340:908-914

15 Year Follow Up



Gastric Cancer Deaths: 48% (D1) vs. 37% (D2), p=0.01



Overall survival: 28% (D2) vs. 22% (D1), p=0.34

Number at risk

D1	380	231	174	149	132	108	47
D2	331	191	158	138	125	110	70

Songun, I et al. Lancet Oncology. 2010; 11:439-49.

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The Dutch Gastric Cancer Group: D1 vs. D2

	D2	D1
N stage		
N0	**144 (44%)**	**171 (45%)**
N1	113 (34%)	138 (36%)
N2	47 (14%)	50 (13%)
N3	27 (8%)	21 (6%)

- High rates of over and under dissection
- Higher than anticipated number of node negative cases

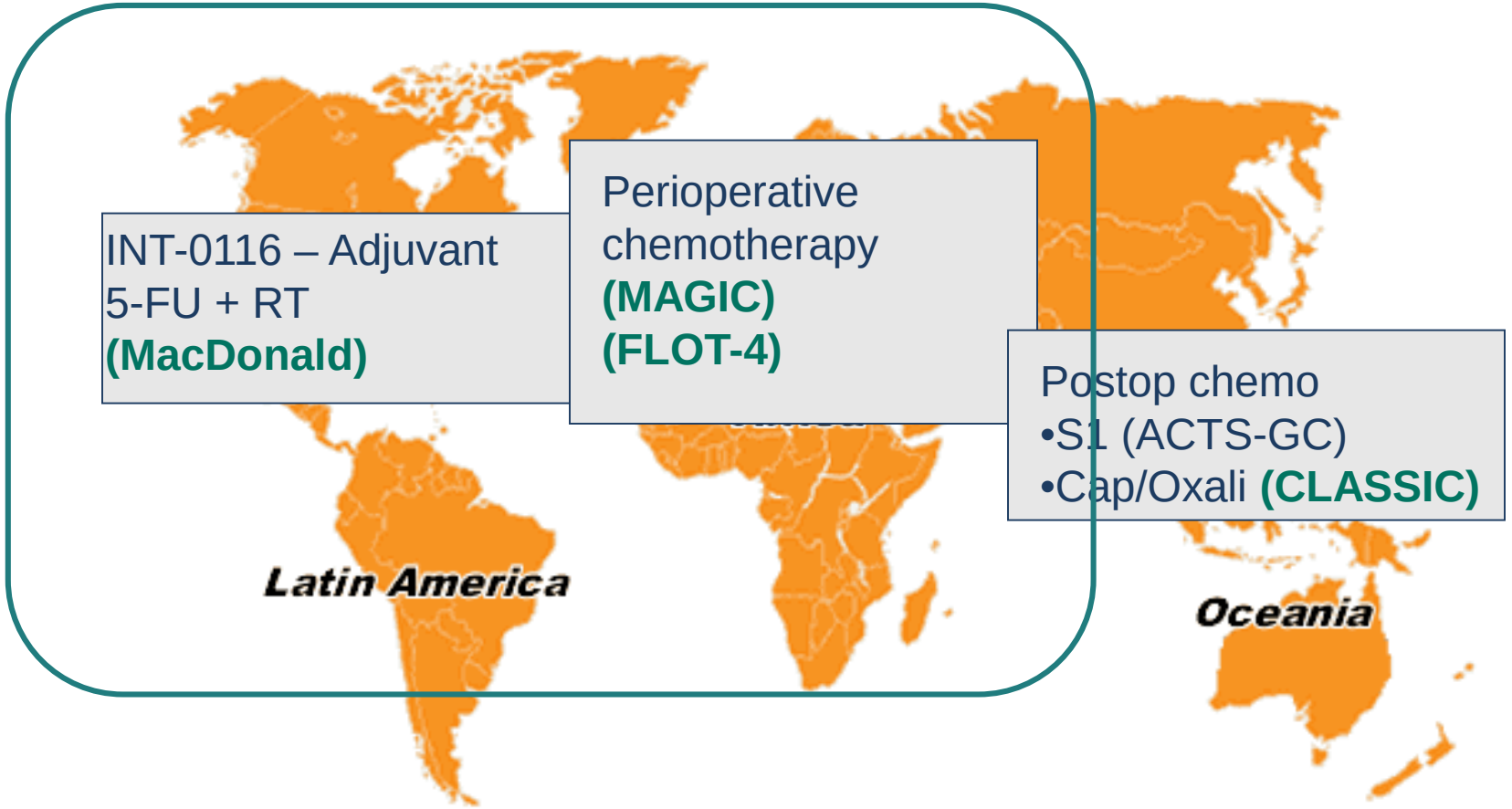
Songun, I et al. Lancet Oncology. 2010; 11:439-49.

D1 vs. D2 Lymph Node Dissection

D2 lymph node dissection is preferred over D1 dissection, only when the surgery can be performed without increasing morbidity

Pancreas and spleen – preserving D2 dissection is generally preferred

Adjuvant and Neoadjuvant Treatment



Sasako, M. et al. *J Clin Oncol*. 2011; 29(33): 4387
Cunningham, D et al. *NEJM*. 2006; 355(1): 11
MacDonald, JS et al. *NEJM*. 2001; 345(10): 725

Adjuvant ChemoRT: INT 0116/SWOG 9008

SCHEMA

20% GE Junction

Resected
Stage IB-IV (M0)
Gastric
Adenocarcinoma
N=603

Stratified
T stage
N 0, 1-3, ≥4

RANDOM

→ **OBSERVATION**

→ **5-FU/LV** → RADIATION → 5-FU/LV x2

5-FU/LV 5-FU/LV

4,500 cGy

Macdonald *NEJM* 2003; 345: 725-730

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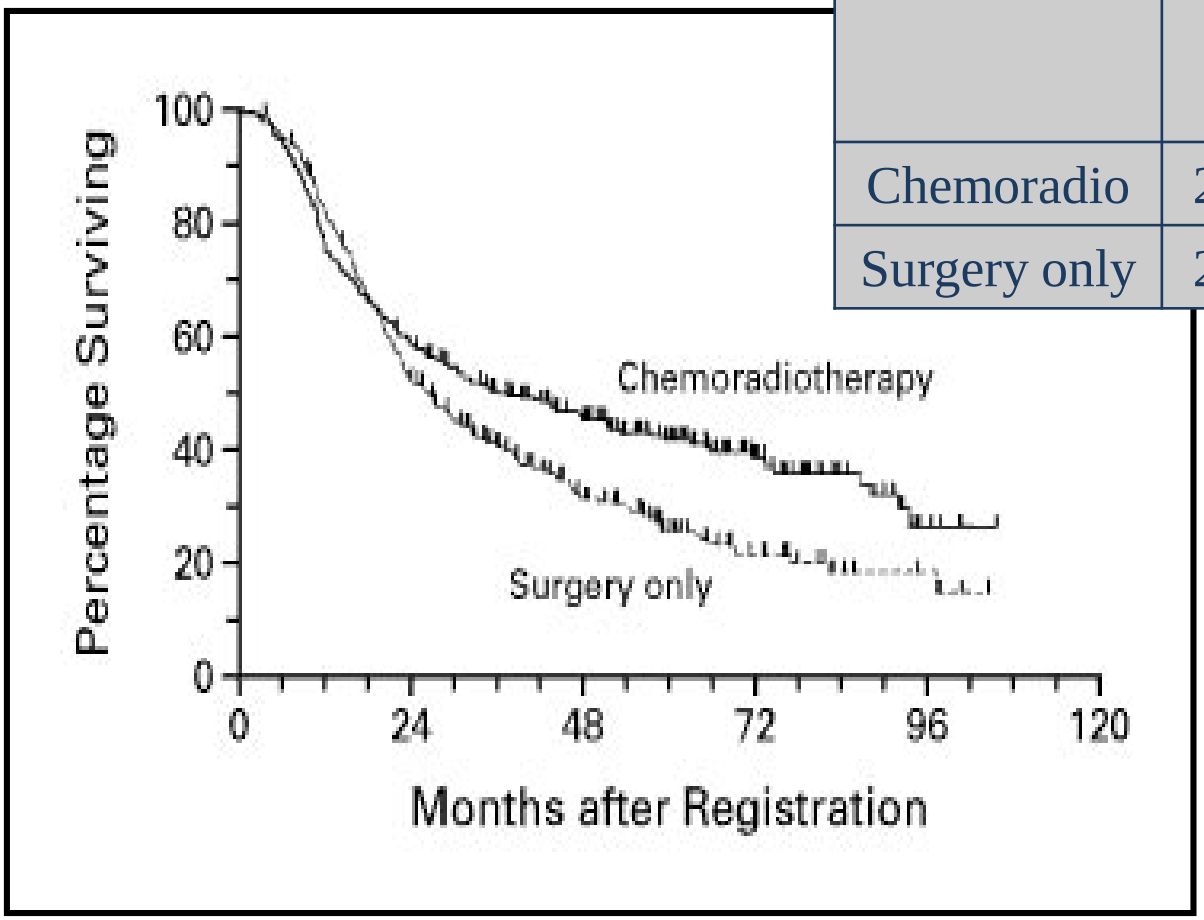
Adjuvant ChemoRT: INT 0116/SWOG 9008



	N	Events	Median (mos)
Chemoradio	282	192	35
Surgery only	277	214	27

P = .006

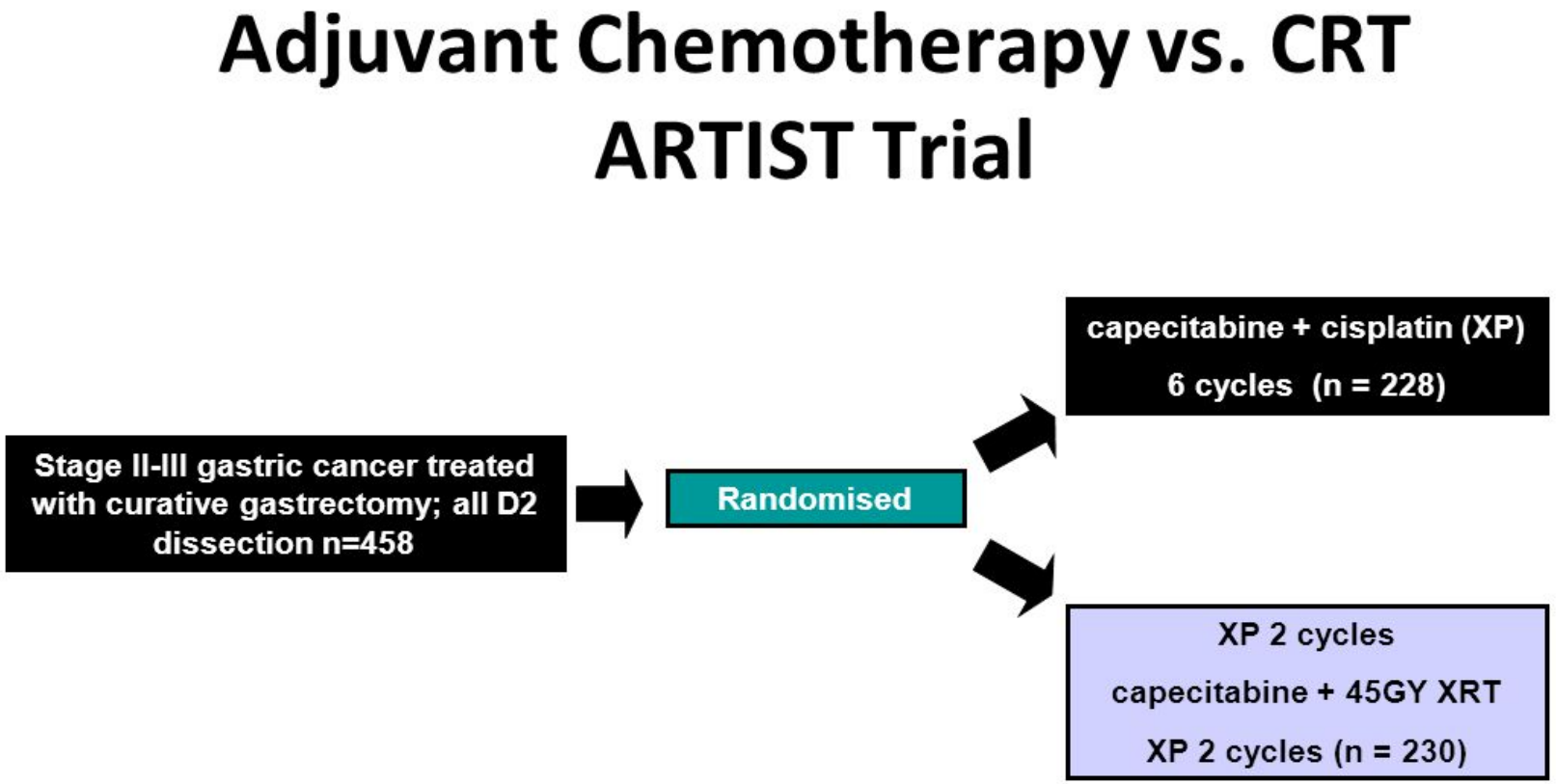
Macdonald *NEJM* 2003; 345: 725-730

Adjuvant ChemoRT: INT 0116/SWOG 9008

Level of lymph node dissection	%
< D1	**54%**
D1	36%
D2	10%

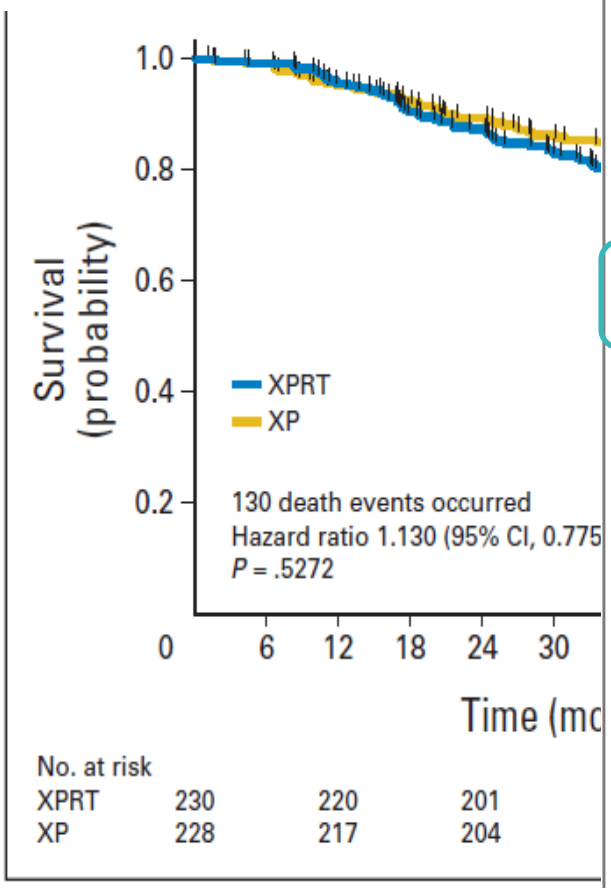
Macdonald *NEJM* 2003; 345: 725-730

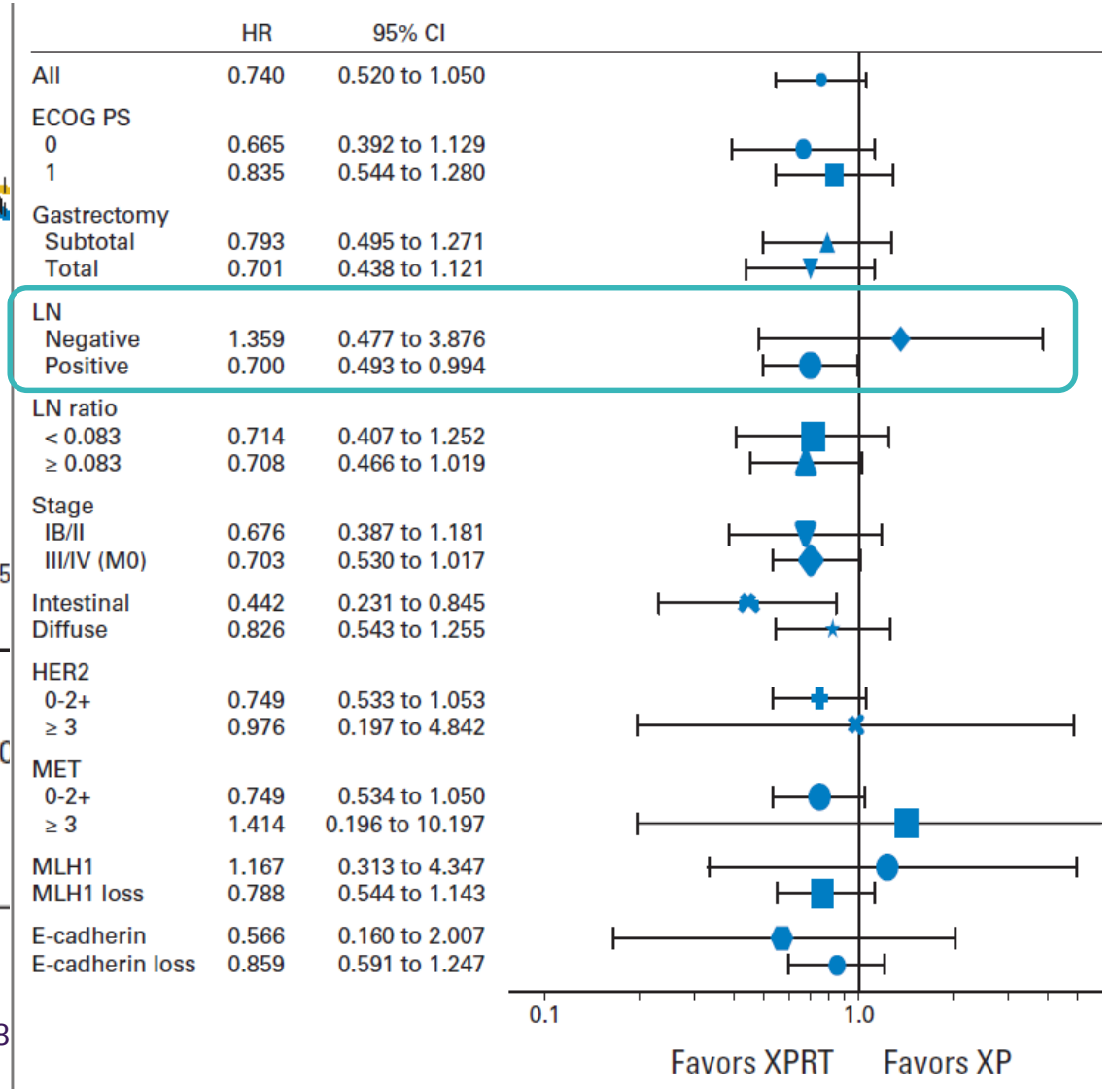
ARTIST Trial: Adjuvant Chemo vs. RT



Park, S. et al. J Clin Oncol. 2015; 33(28)

ARTIST: Adjuvant Chemo vs. chemoRT





Park, S. et al. J Clin Oncol. 2015; 33(28

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ARTIST-II: Adjuvant chemo vs. chemoRT (Node+)

Randomize 900 patients
with D2 resected NODE
POSITIVE Gastric Cancrer

Key Results

- SOX and SOXRT >> S1 alone
- **No difference in DFS between SOX and SOXRT** (HR 0.91, p=0.67)

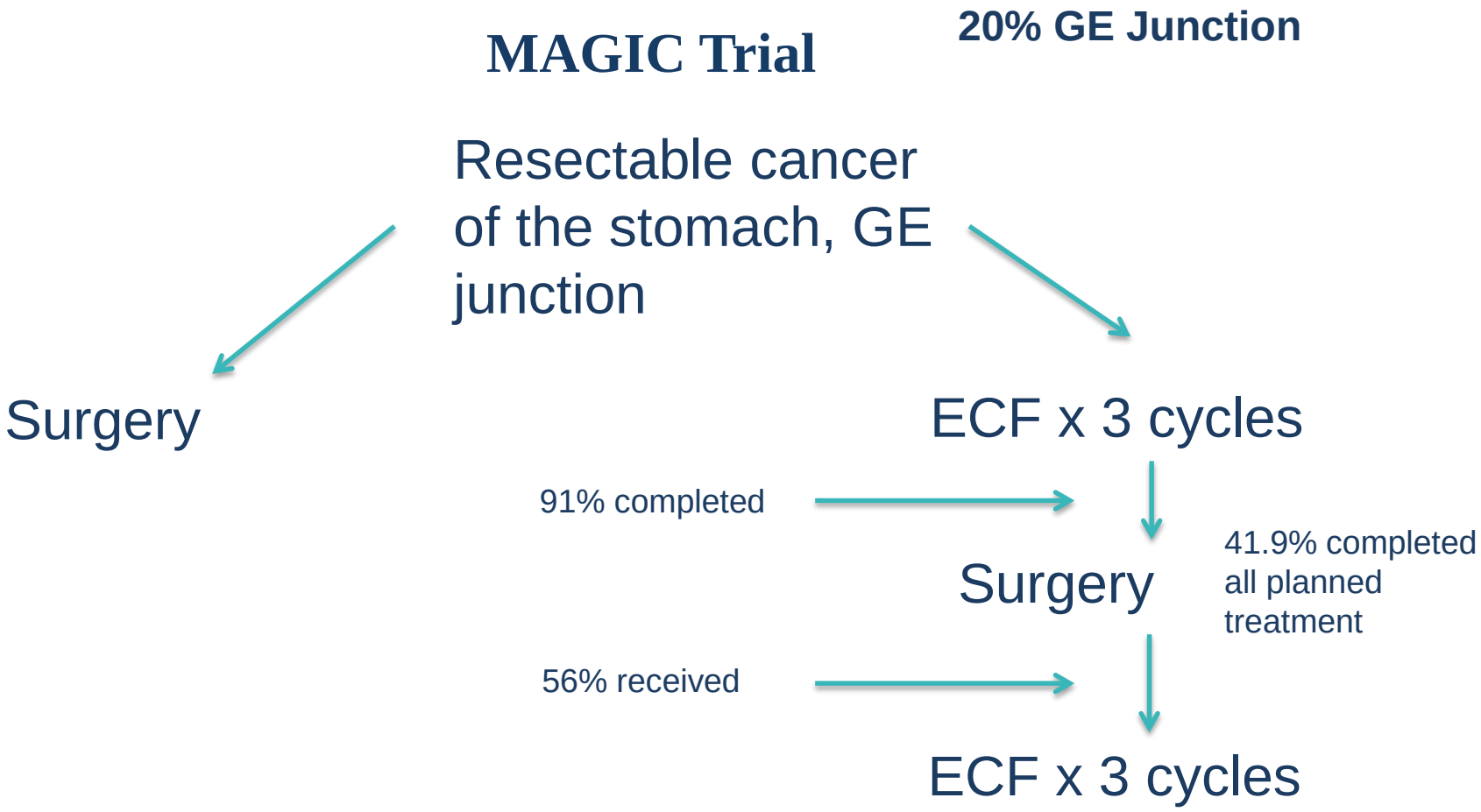
Park, SH et al. 2019 May ASCO / J Clin Oncol

Is there a role for Postoperative Radiation?

NO, except …

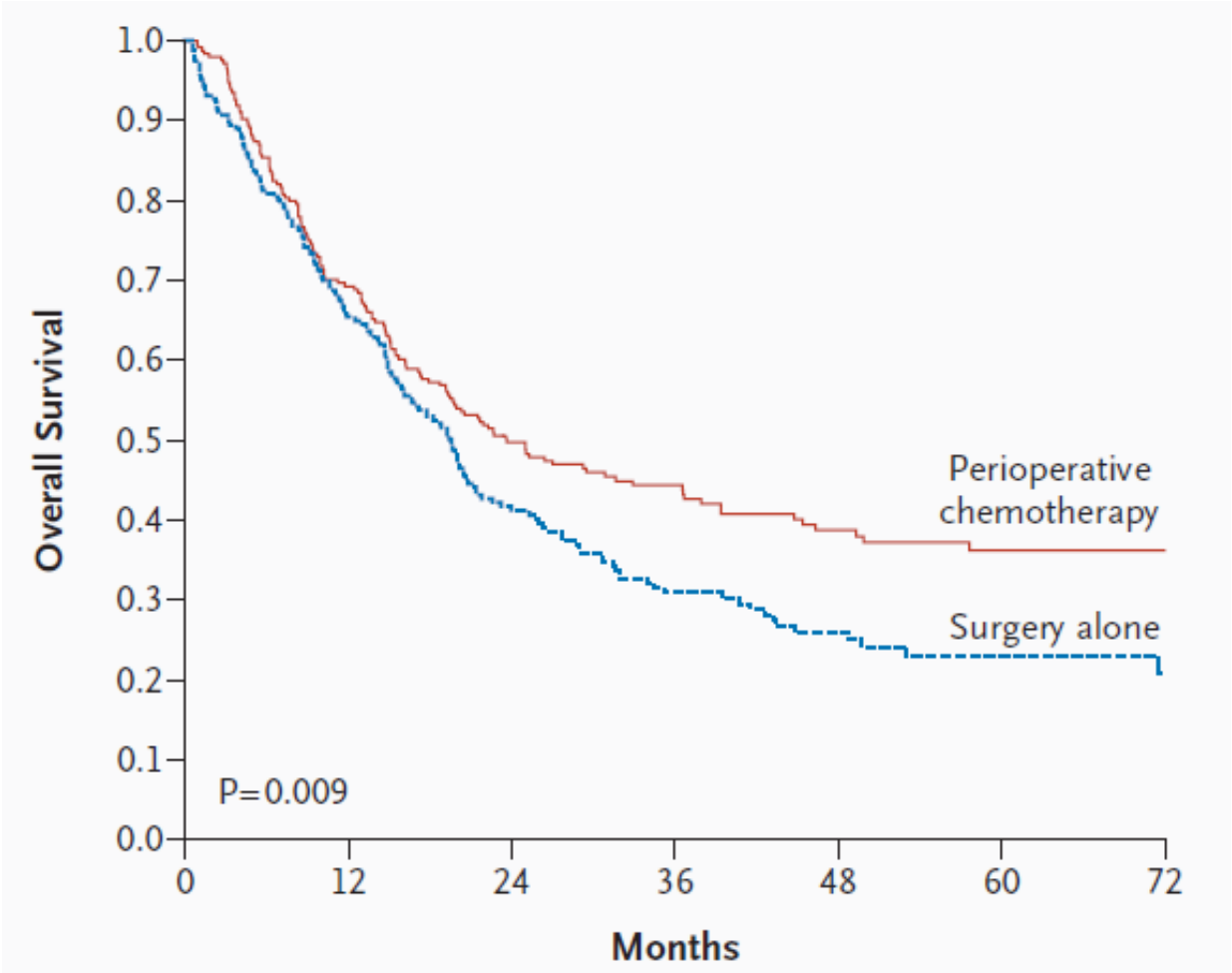
- Inadequate resections / lymph node dissection
- Positive margin (R1 resection)

Perioperative Chemotherapy: MAGIC Trial



Cunningham D, et al. *NEJM* July 2006

Perioperative Chemotherapy: MAGIC Trial

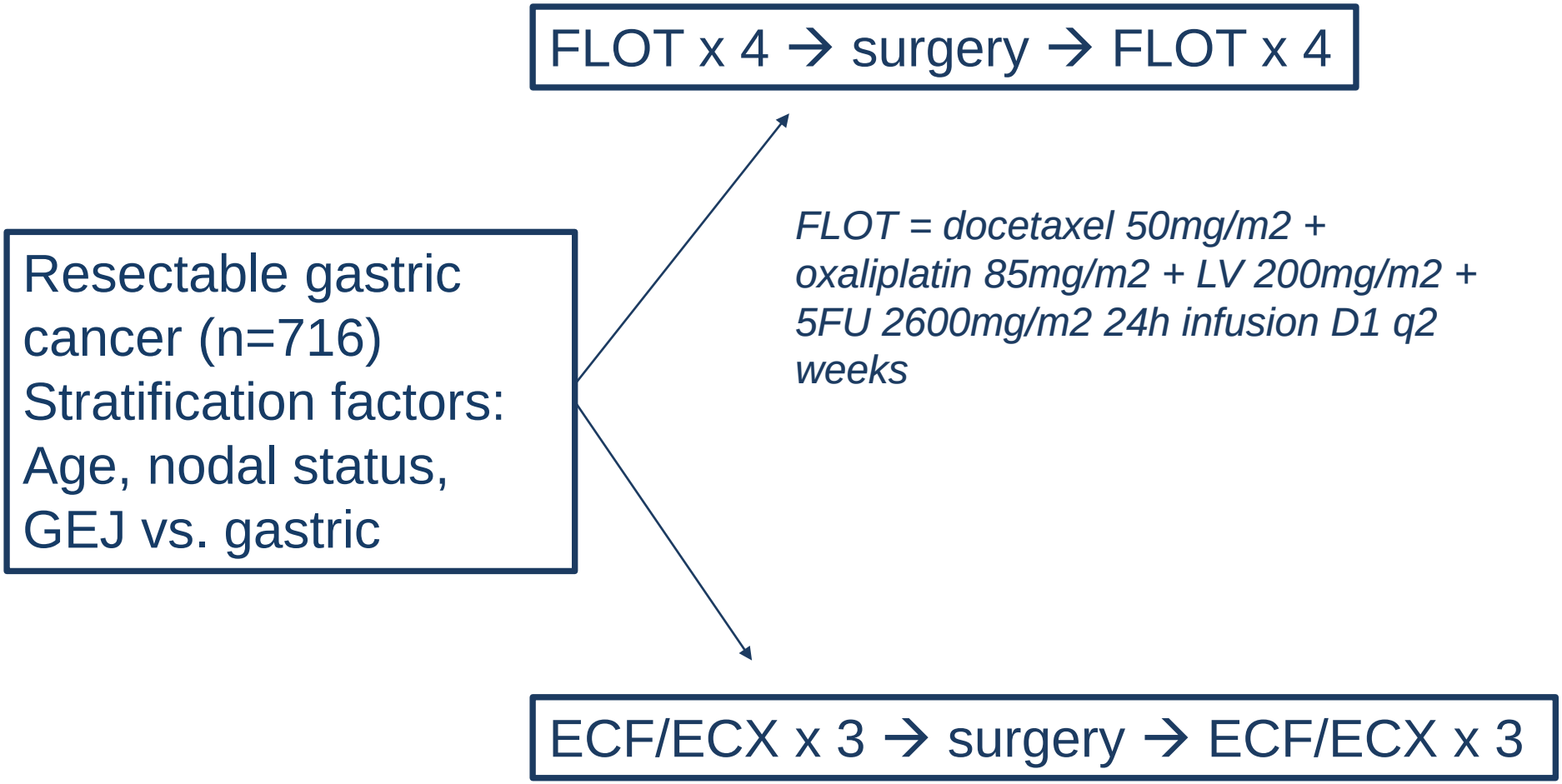


5-year survival
- 36.3% (Chemo)
- 23.0% (Surgery)

Median Survival
- 24 months (Chemo)
- 20 months (Surgery)

Cunningham D, et al. *NEJM* July 2006

Perioperative Chemotherapy: FLOT-4



Al-Batran S, et al. ASCO 2017 Annual Meeting.

Perioperative Chemotherapy: FLOT-4

Key Results:

- 50% FLOT vs. 37% ECF/X completed post-operative chemotherapy
- Median OS 50 months vs. 35 months (HR 0.77, p=0.012)
- 3yr OS 57% FLOT vs. 48% ECF/X
- Postop complications and 30/90 day mortality were similar

Al-Batran S, et al. ASCO 2017 Annual Meeting.

FLOT-4 – ASCO 2020 Updates

PETRARCA study (phase II/III)

- 81 patients randomized
- No benefit with addition of trastuzumab to FLOT – path CR, R0 resection rate, DFS, OS
- Study ended early and did not proceed to phase III

FLOT-4 +/- Ramucirumab (phase II/III)

- 180 patients randomized
- Endpoints: Path response, R0 resection rate, safety
- Findings: Increased AEs, Improved R0 resection rate (97% vs. 83%, p=0.0049), similar path response

Hofheinz, RD et al. ASCO 2020
Al Batran, SE et al. ASCO 2020

Take Home Points: Localized and Locally Advanced Gastric Cancer

Post-gastrectomy B12 and iron supplementation

D2 gastrectomy should be performed when possible

Perioperative chemotherapy – general approach for Western patient

Vanishing role of radiation therapy in gastric cancer treated with D2 lymph node dissection

Metastatic Esophageal and Gastric Cancer

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Initial Diagnostic Evaluation

Clinical Assessment

- ECOG PS
- Comorbidities
- Nutritional status
  - Stent
  - G or J tube

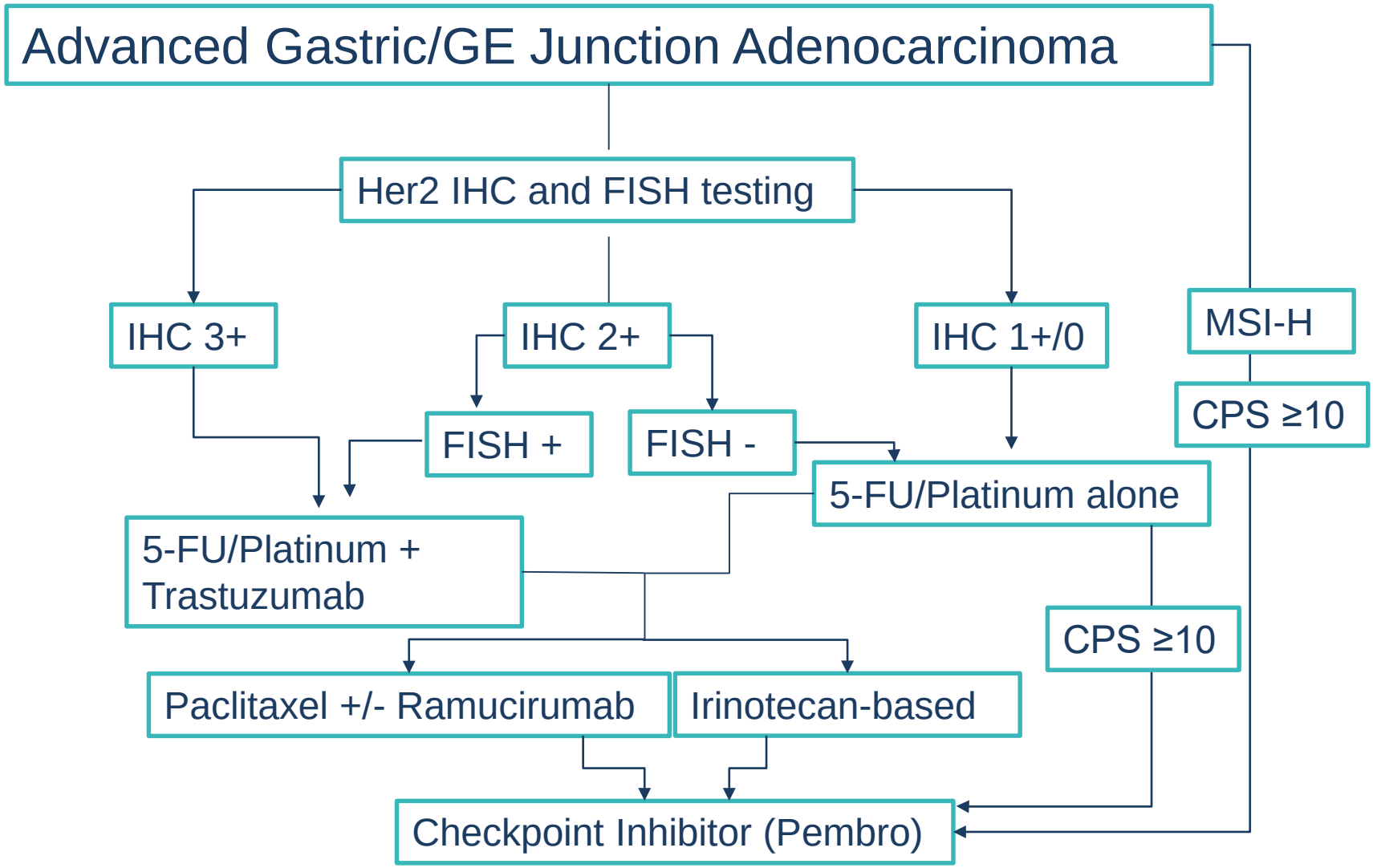
Labs and Imaging

- CT C/A/P w/ IV contrast (peritoneal dz)
- CEA
- CA 19-9

Molecular testing

- Her2 IHC and FISH (3+ or FISH+)
- PDL1 (CPS score)
- MSI
- EBV (Gastric)
- *NGS for most – tumor mutational burden (Pembro for TMB-high)*

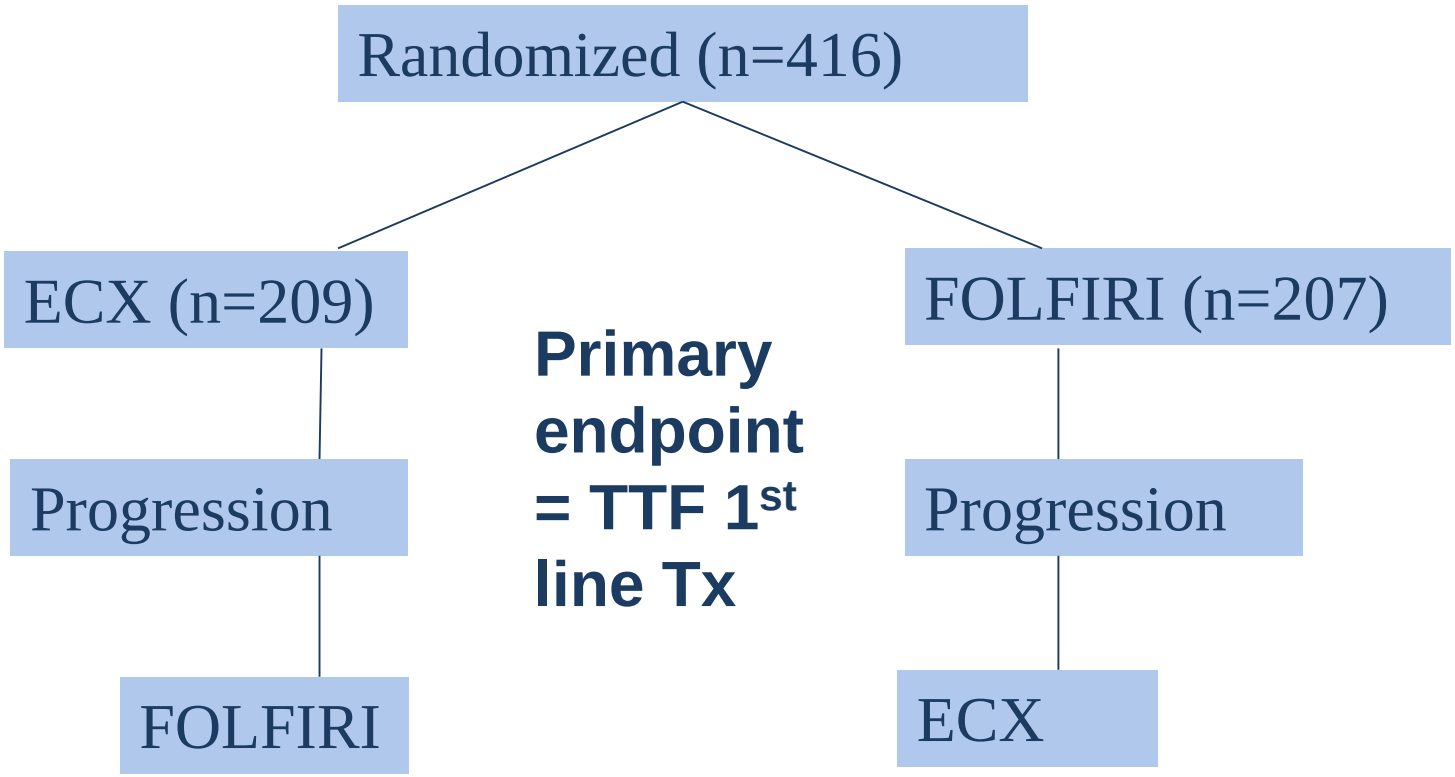
Initial Treatment Algorithm



First-Line Chemotherapy Backbones

Author	Regimen	RR	Median OS (months)
Van Cutsem, 2006	DCF	37%	9.2
Cunningham, 2008	ECF ECX EOF EOX	40.7% 46.4% 42.4% 47.9%	9.9 9.9 9.3 11.2
Al Batran, 2008	FLO	41.3%	10.7
Shah, 2010	Modified DCF	50%	14.9
Boku, 2009	Cisplatin/Irinotecan	38%	12.3
Narahara, 2011	Irinotecan/S-1	41.5%	12.8

2 Drugs vs. 3 Drugs



TTF = Time between randomization and treatment d/c, progression, death

Guimbaud, R et al. J Clin Oncol. 2014, Nov 1; 32(21): 3250-6.

2 Drugs vs. 3 Drugs

Table 3. Maximum Severity Grade for Toxicities

Toxicity and Grade	ECX Arm No.	ECX Arm %	FOLFIRI Arm No.	FOLFIRI Arm %	*P**
First-line	200		203		
Nonhematologic					.81
Grade 0 to 2	85	42.5	90	44.3	
Grade 3 to 4	107	53.5	108	53.2	
Missing	8	4.0	5	2.5	
Hematologic					< .001
Grade 0 to 2	60	30.0	120	59.1	
Grade 3 to 4	129	64.5	78	38.4	
Missing	11	5.5	5	2.5	
Overall					< .001
Grade 0 to 2	25	12.5	58	28.6	
Grade 3 to 4	167	83.5	140	69.0	
Missing	11	5.5	5	2.5	

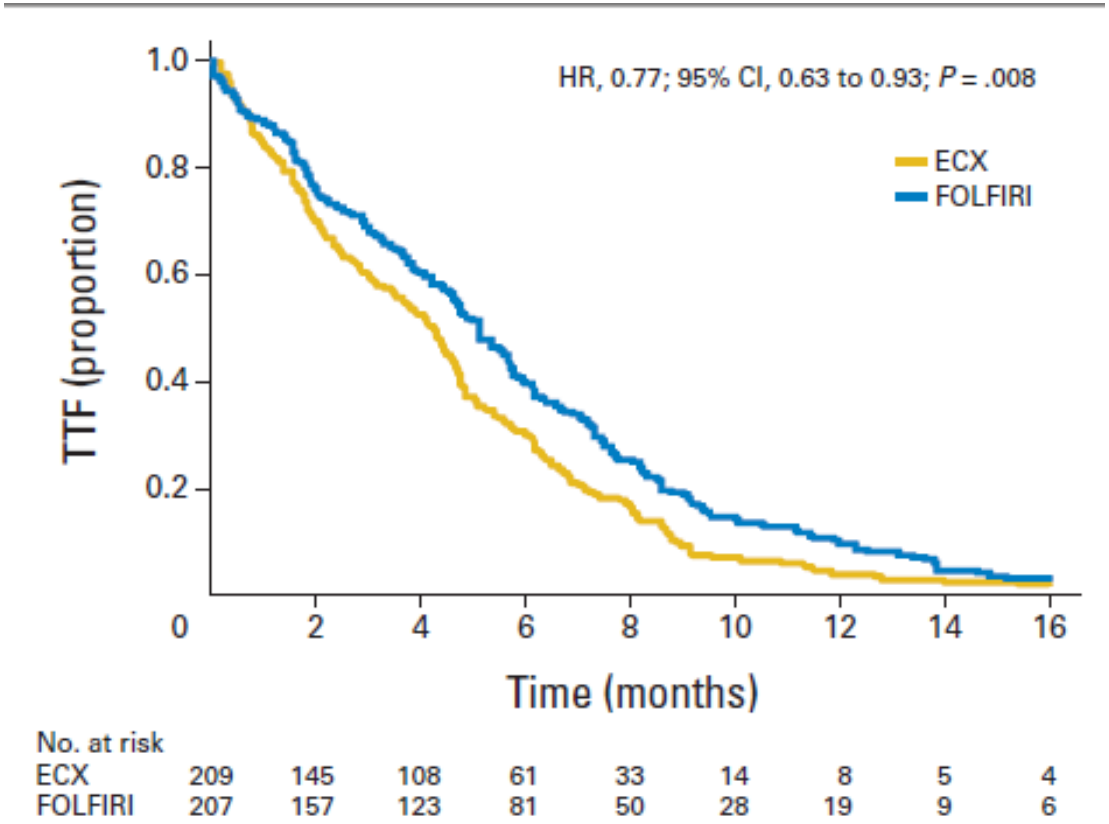
Guimbaud, R et al. J Clin Oncol. 2014, Nov 1; 32(21): 3250-6.

2 Drugs vs. 3 Drugs

TTF:
4.24 mo (ECX)
5.08 mo (FOLFIRI)
P=0.008

PFS:
5.29 mo (ECX)
5.75 mo (FOLFIRI)
P=0.96

OS:
9.49 mo (ECX)
9.72 mo (FOLFIRI)
P=0.95



In U.S., most typical 2-drug first-line regimen is FOLFOX

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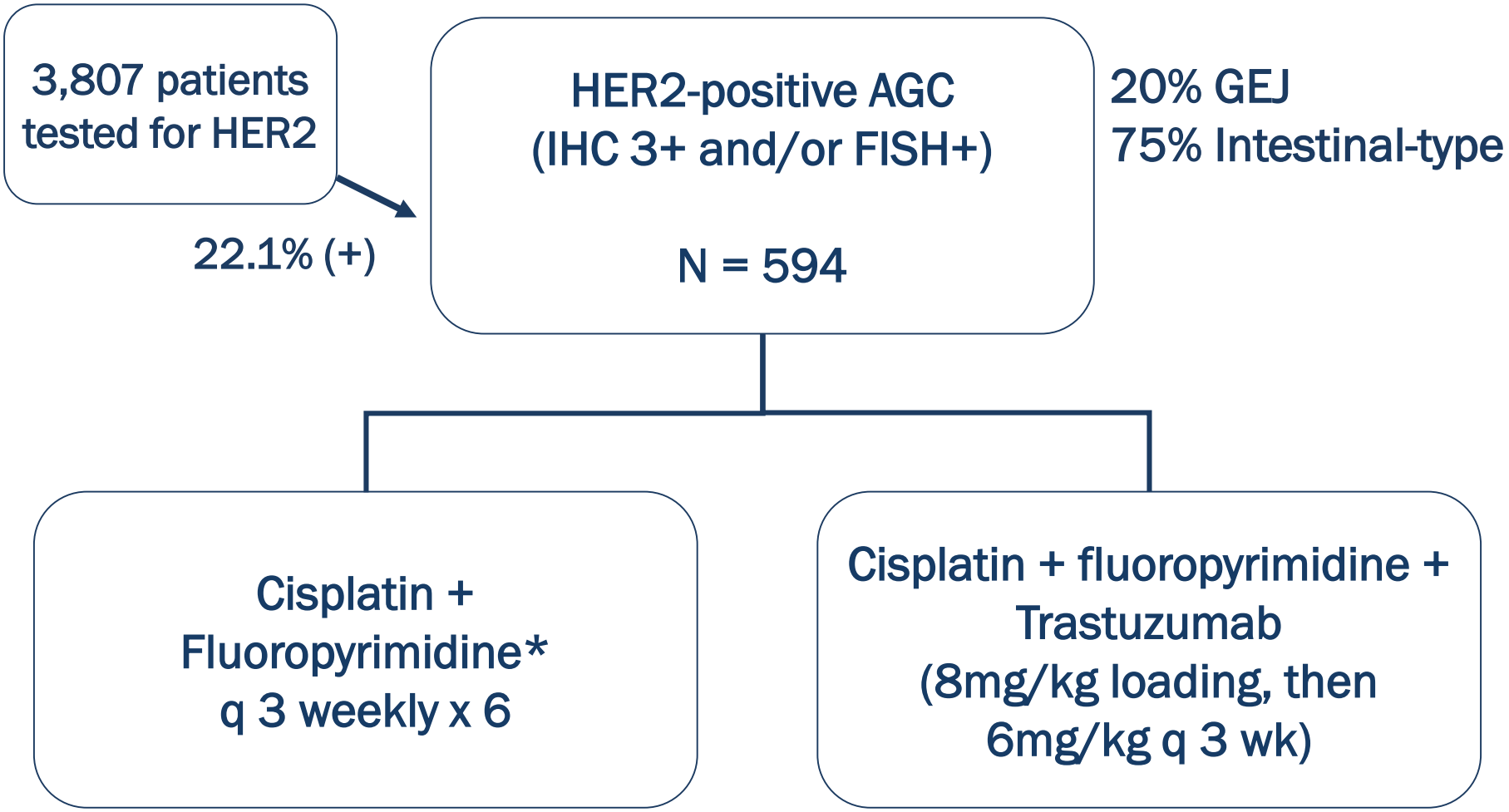
Targeting Her2 – TOGA Trial



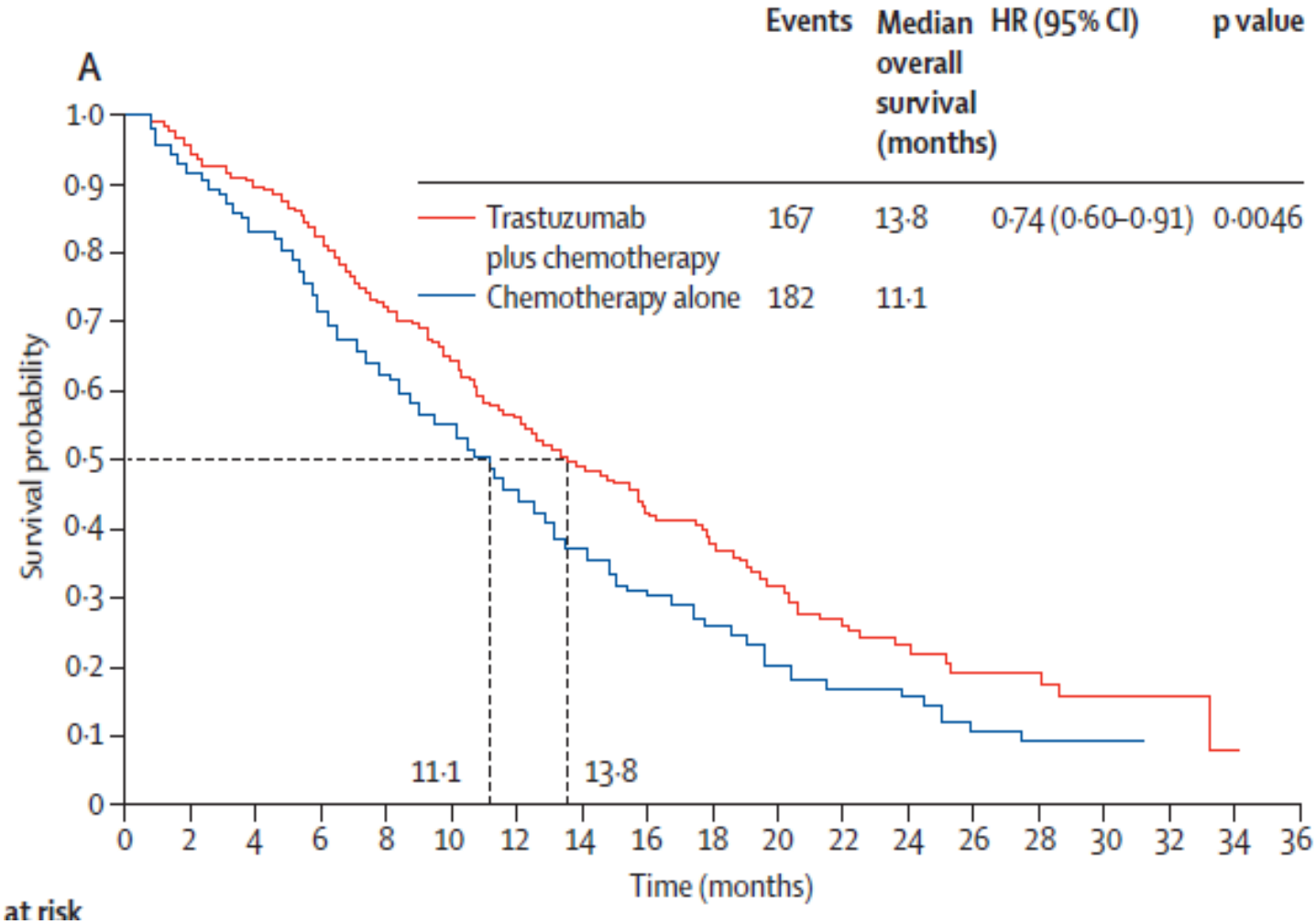
Bang, YJ et al. *Lancet* 2010; 376: 698-97

TOGA Trial - Results

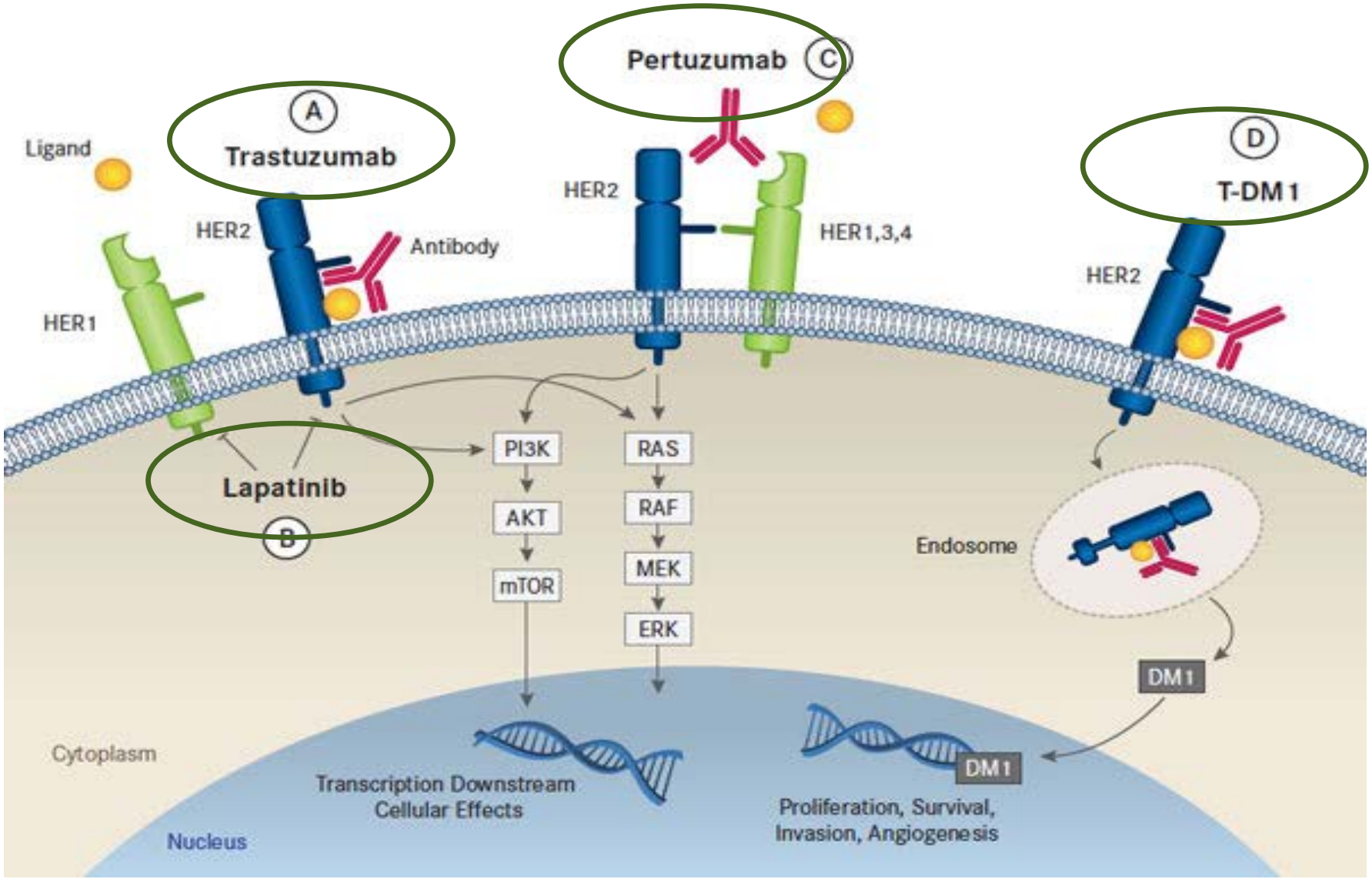
	Chemo alone	Chemo + trastuzumab	P value
ORR	34.5%	47.3%	P=0.0017
Median PFS	5.5 months	6.7 months	P=0.0002, HR 0.71
Median survival	11.1 months	**13.8 months**	P=0.0048, HR 0.74

Bang, YJ et al. *Lancet* 2010; 376: 698-97

TOGA Trial - Results



Anti-Her2 agents – Mechanism of Action



Her2 Agents in Gastric Cancer

TRIO-013/LOGiC 1st line: CapOx +/- **Lapatinib**

JACOB Trial 1st line: FU+Cis+Trastuzumab +/- **Pertuzumab**

TyTAN study 2nd line: Paclitaxel +/- **Lapatinib**

GATSBY trial 2nd line: Taxane vs. **TDM-1**

Hecht, R et al. J Clin Oncol. 2016, 34(5): 443-451.
Satoh, T et al. J Clin Oncol. 2014, 32(19): 2039-49
Thuss-Patience, PC et al. Lancet Oncol. 2017, 18(5): 640-53
Tabernero, J et al. ESMO 2017.

Trastuzumab Deruxtecan

- Randomized phase II study in Japan and Korea
- Patient population: Her2 positive gastric and GE jxn cancer patients who received at least 2 prior lines of therapy (including prior trastuzumab)
- 188 patients randomized (2:1) to trastuzumab deruxtecan versus physician's choice (irinotecan or paclitaxel)
- Primary endpoint = objective response

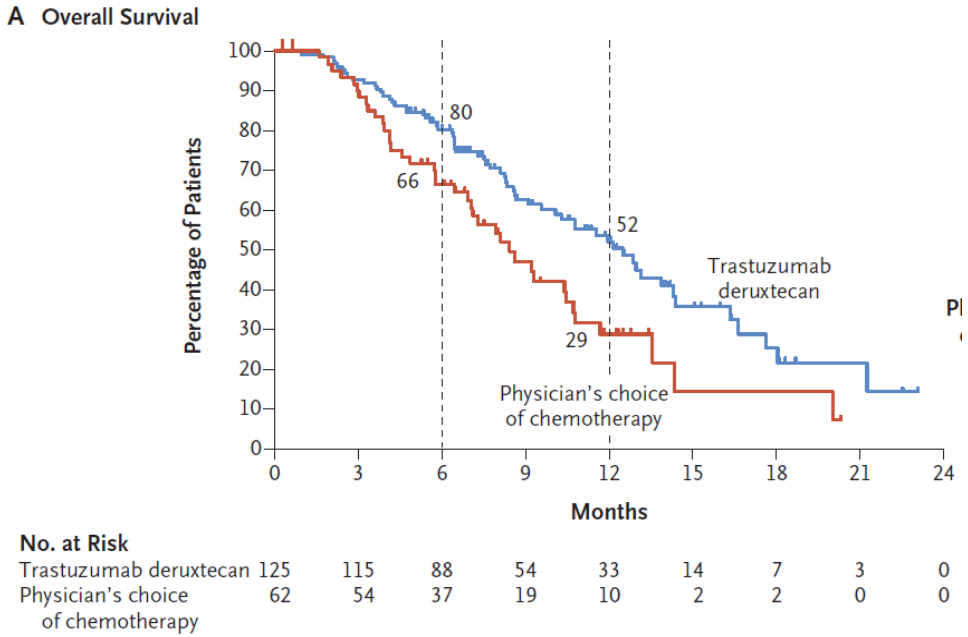
Shitara, K. et al. NEJM 2020; 382:2419-30.

Trastuzumab Deruxtecan

OR: 51% vs. 14%

PFS: 5.6 vs. 3.5 months (HR 0.47, 95% CI 0.31, 0.71)

Safety: neutropenia (51% vs. 24%) and ILD or pneumonitis (10%)



Median OS: 12.5 vs. 8.4 months

HR 0.59, 95% CI 0.39-0.88)

Shitara, K. et al. NEJM 2020; 382:2419-30.

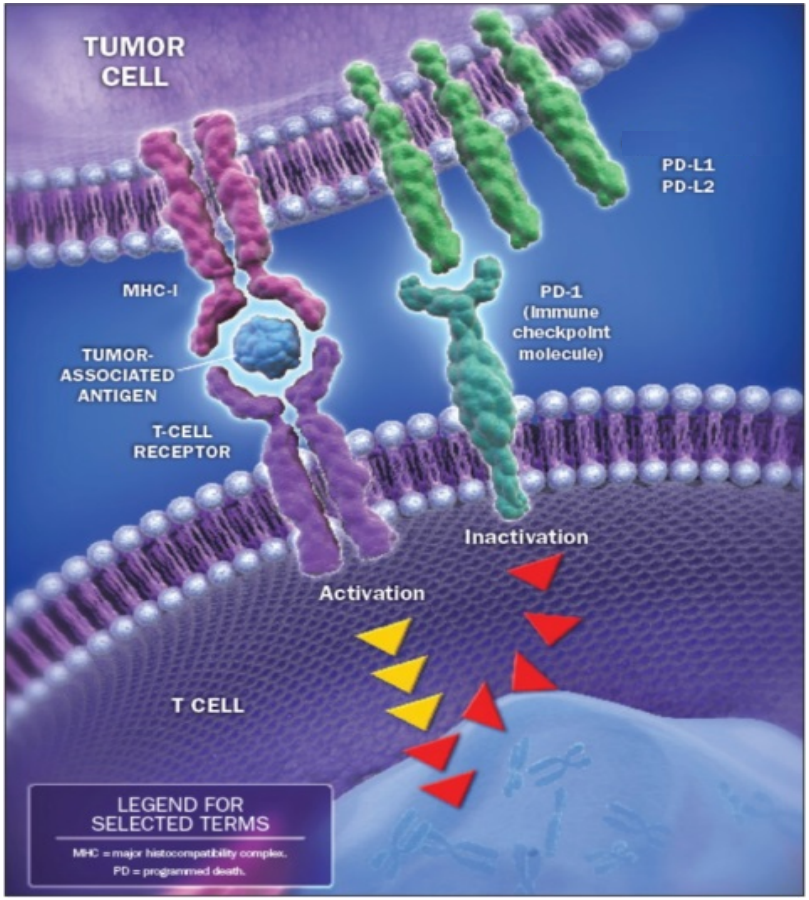
Trastuzumab “Beyond Progression”

WJOG Study: 2nd line paclitaxel +/- trastuzumab *(in Her2+ pts who progressed on 5-FU/platinum + trastuzumab)*

- No PFS benefit with trastuzumab
- In cases where pre-treatment biopsies could be performed, only 1/3 retained Her2 positivity (IHC 2/3+)

Sukawa, Y. et al. ASCO 2018

First-Line Checkpoint Inhibitor ?



- **Pembrolizumab** was approved by the FDA in Sept 2017 for PDL1 overexpressing (CPS ≥ 1) gastric and esophagogastric cancers progressed on 2 or more prior lines of therapy
- In Japan, **Nivolumab** approved for refractory gastric cancer (3rd line and beyond) in October 2017

Keir ME, et al. *Annu Rev Immunol*. 2008;26:677-704.
Pardoll DM, et al. *Nat Rev Cancer*. 2012;12:252-64.

Immune Checkpoint Inhibitors

Study	Drug	Population	N	RR	OS
Keynote 012	Pembro 10mg/kg q2 wks	Refractory PDL1+	39	22%	11.4 mo
Attraction-2	Nivolumab 3mg/kg q2 wks vs. Placebo	Refractory any PDL1	493	11.2%	5.32 vs. 4.14 mo (HR 0.63, p<0.0001)
Keynote 059 (cohort 1)	Pembro 200mg q3 wk	Refractory any PDL1	259	11.2% *PDL1+ 15.5%* *PDL1- 5.5%*	NR
Checkmate 032	• Nivo 3mg/kg q2 • Nivo 1mg/kg + Ipi 3mg/kg • Nivo 3mg/kg + Ipi 1mg/kg	Refractory any PDL1	160	16% Overall 14% N3 26% N1+I3 10% N3+I1	 5.0 mo 6.9 mo 4.8 mo

Muro, K et al. *Lancet Oncology*. 17(7), 2016.
Al-Batran, S. et al. ACSO 2017 Annual Meeting
Janjigian, E. et al. ASCO 2016
Fuchs, CS et al. ASCO 2017.

Pembrolizumab – Keynote 059

Advanced gastric cancer, progressed after 2 or more prior therapies

Table 1. Objective Tumor Response

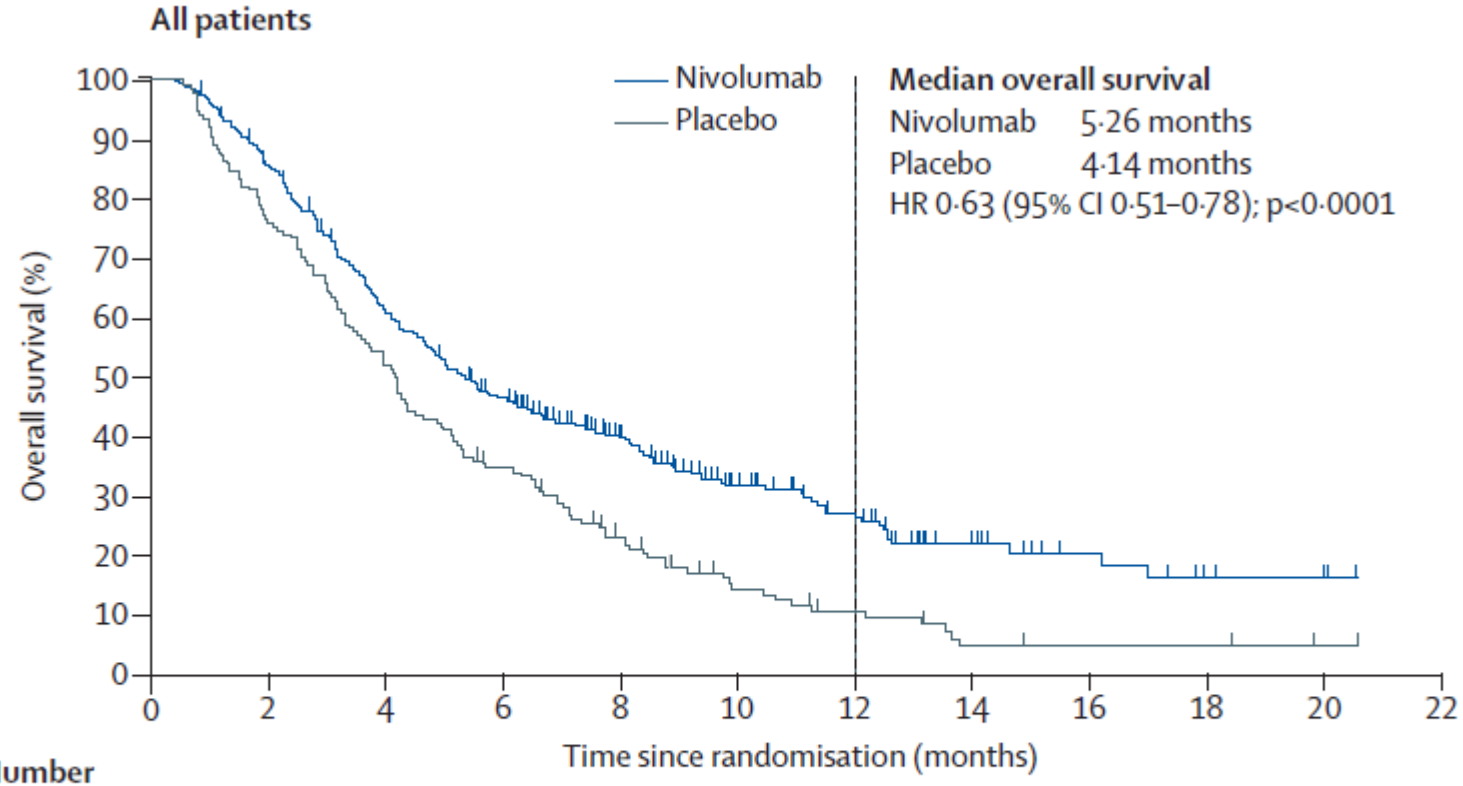
Best Overall Response[a]	Participants (n = 259) No.	% (95% CI)
Objective response (CR+PR)	30	11.6 (8.0-16.1)
Disease control (CR+PR+SD ≥2 mo)	70	27.0 (21.7-32.9)
CR	6	2.3 (0.9-5.0)
PR	24	9.3 (6.0-13.5)
SD	42	16.2 (11.9-21.3)
Progressive disease	145	56.0 (49.7-62.1)
Nonevaluable	7	2.7 (1.1-5.5)
No assessment[b]	35	13.5 (9.6-18.3)
Duration of response, median (range), mo	8.4 (1.6+ to 17.3+)[c]	

15.5% PDL1 +

6.4% PDL1 -

Fuchs, C et al. JAMA Oncology. 2018, 4(5): e180013

Nivolumab vs. BSC: ATTRACTION 2 Trial



Number at risk (censored)												
Nivolumab	330 (0)	275 (6)	192 (10)	141 (16)	94 (45)	56 (65)	38 (75)	19 (88)	10 (96)	5 (99)	3 (101)	0 (104)
Placebo	163 (0)	121 (3)	82 (4)	53 (6)	32 (10)	16 (15)	10 (17)	4 (18)	3 (19)	3 (19)	1 (21)	0 (22)

Kang, Y et al. Lancet. 2017, 390: 2461-2471.

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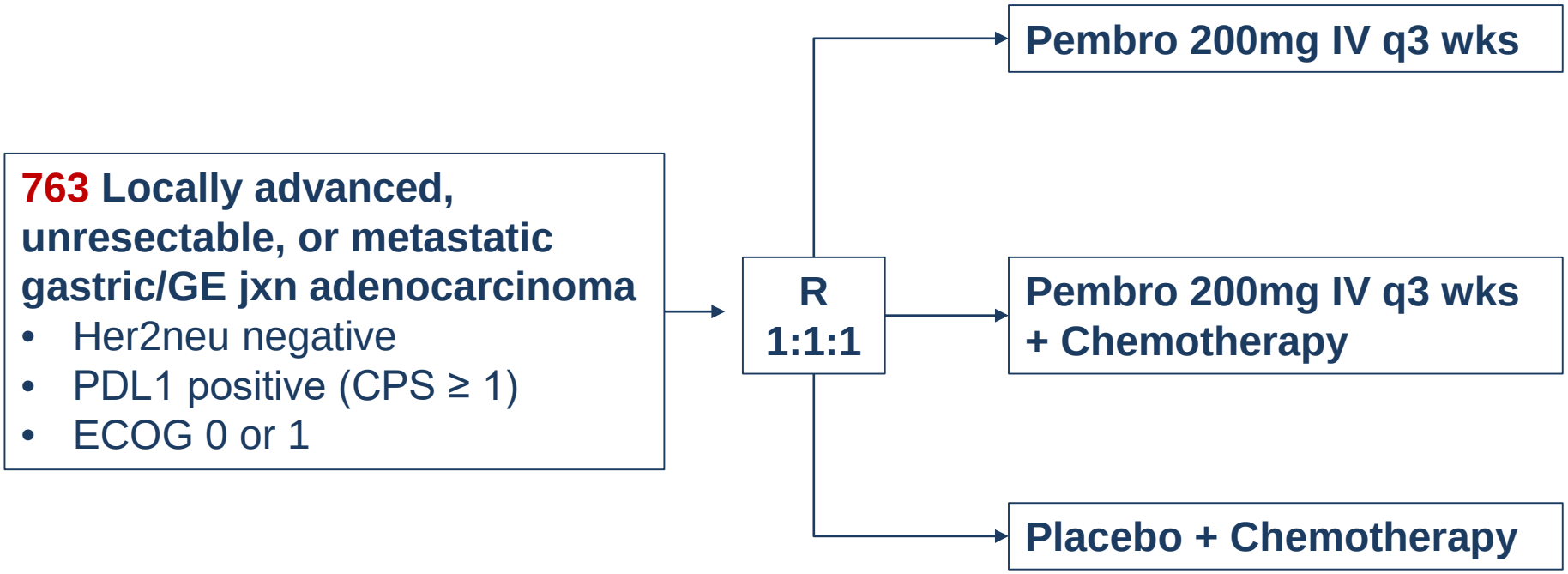
First-line pembrolizumab – Keynote 062



Primary endpoints = noninferiority OS (pembro vs. chemo) ; superiority OS (pembro+chemo vs. chemo)
Chemotherapy = 5-FU or capecitabine + cisplatin

Tabernero, J. et al. 2019. ASCO Annual Meeting

First-line pembrolizumab – Keynote 062

Pembro versus Chemotherapy

- Noninferior OS Pembro vs. Chemo (10.6 months vs. 11.1 months) HR 0.91, p=NS
- Superior OS in CPS ≥ 10 subgroup (17.4 vs. 10.8 months) HR = 0.69
- Lower Grade 3 or higher AEs (17% P, 71% pembro +chemo, 68% chemo)

Pembro + Chemo versus Chemo

- OS ***not*** superior Pembro + chemo vs. chemo (12.5 mo vs. 11.1 mo) HR 0.85
- ORR slightly better in pembro + chemo vs. chemo alone (48.6% vs. 36.8%
- OS not superior in CPS ≥ 10 subgroup (12.3 mo vs. 10.8 mo) HR 0.85

Tabernero, J. et al. 2019. ASCO Annual Meeting

When to use first-line pembrolizumab?

Monotherapy in CPS ≥ 10 (if you can get this information quickly and if covered by insurance

Lower burden of disease, lower symptom burden

Elderly or frail patients with CPS ≥ 10 who cannot tolerate chemo

Second Line Therapy

For patients who retain good PS

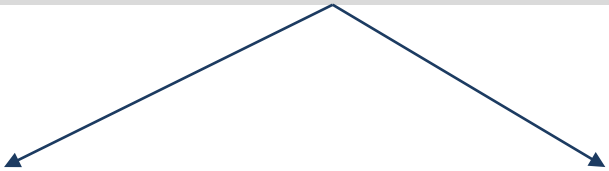
- Paclitaxel (+ Ramucirumab)
- Docetaxel
- Irinotecan
- Ramucirumab
- Pembrolizumab (CPS ≥ 10)

???????

- Neuropathy
- Bleeding from primary tumor
- Pace and extent of disease progression

WJOG 4007: 2nd Line Irinotecan vs. Paclitaxel

Advanced Gastric Cancer without Severe Peritoneal Metastases – After Progression through 5-FU + Platinum (n=223)

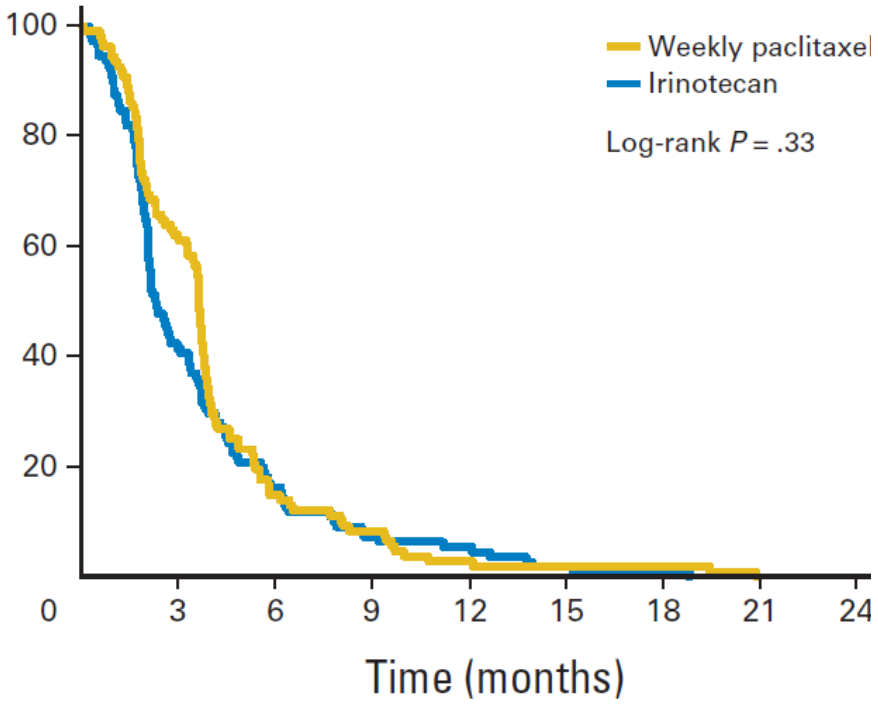


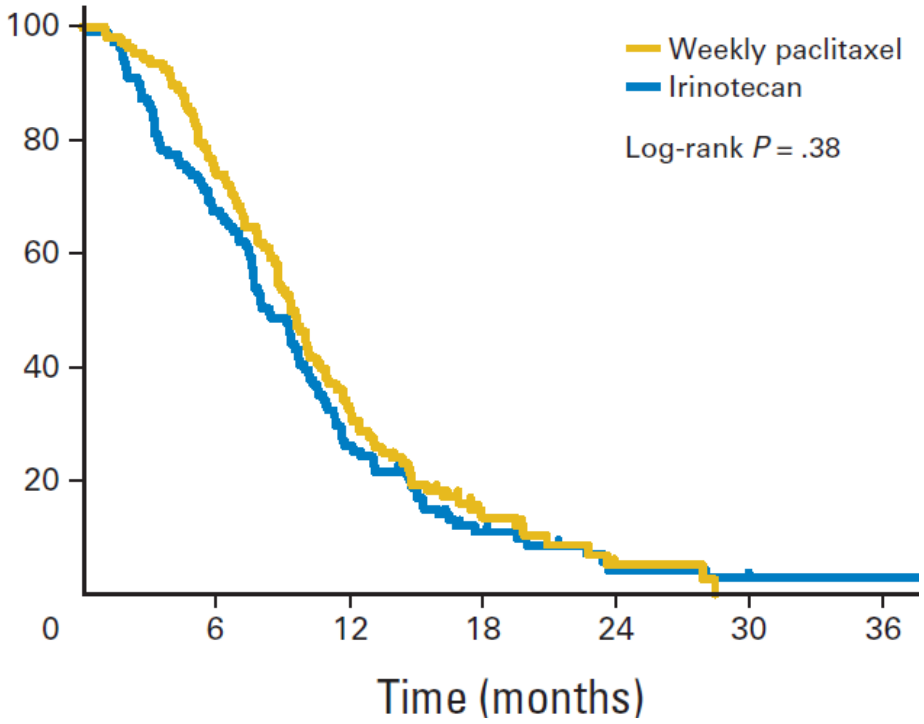
Weekly Paclitaxel 80mg/m2 Days 1, 8, 15 q28 days (n=111)

Irinotecan 150 mg/m2 Days 1,15 q28 days (n=112)

Hironaka S et al. J Clin Oncol, 2013; 31: 4438-4444.

WJOG 4007: 2nd Line Irinotecan vs. Paclitaxel





PFS: 3.6 mo (paclitaxel) vs. 2.3 mo (irinotecan)

OS: 9.5 mo (paclitaxel) vs. 8.4 mo (irinotecan)

Versus 5.2 mo in docetaxel arm of Cougar-2 study

Hironaka S et al. J Clin Oncol, 2013; 31: 4438-4444.

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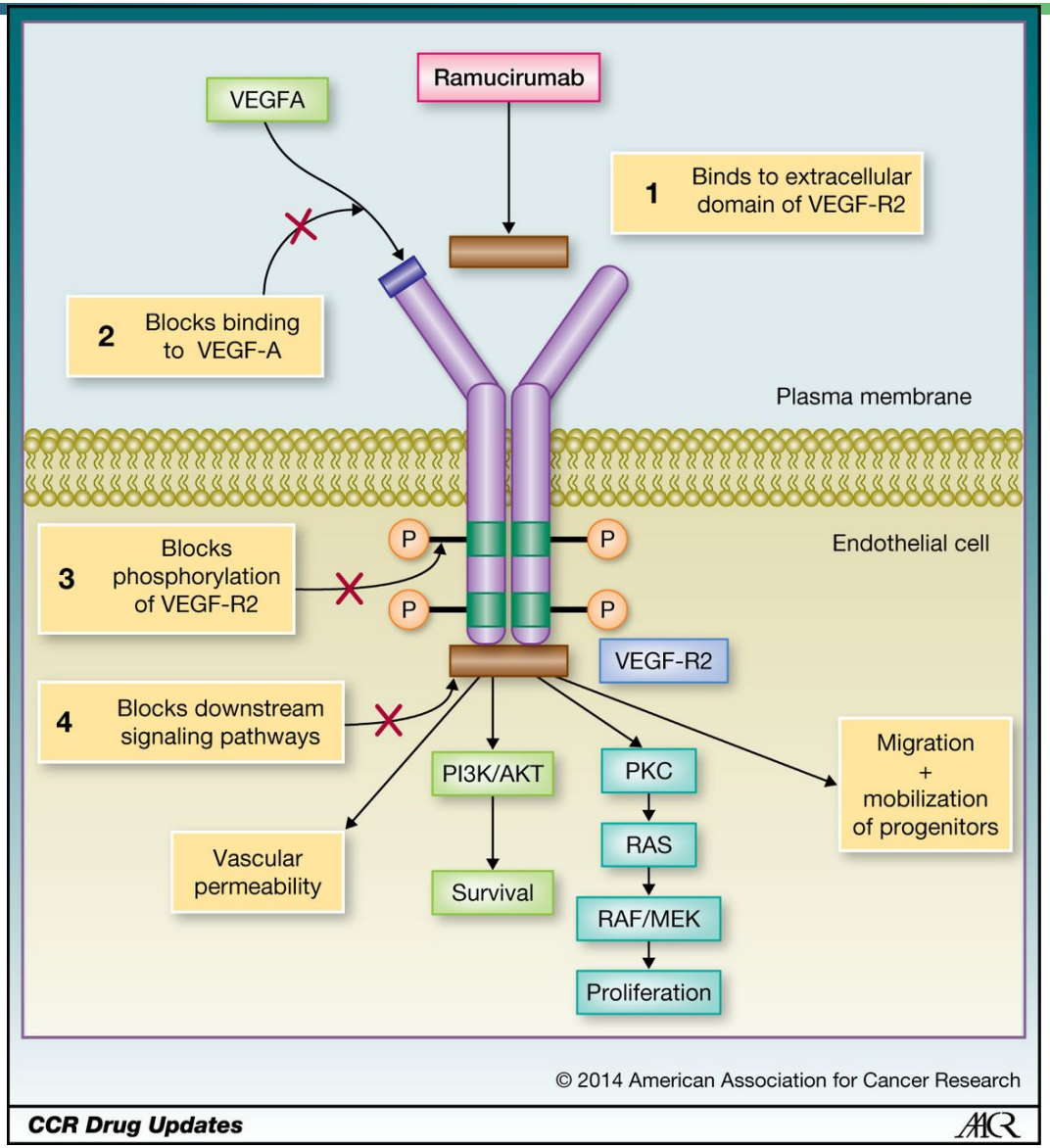
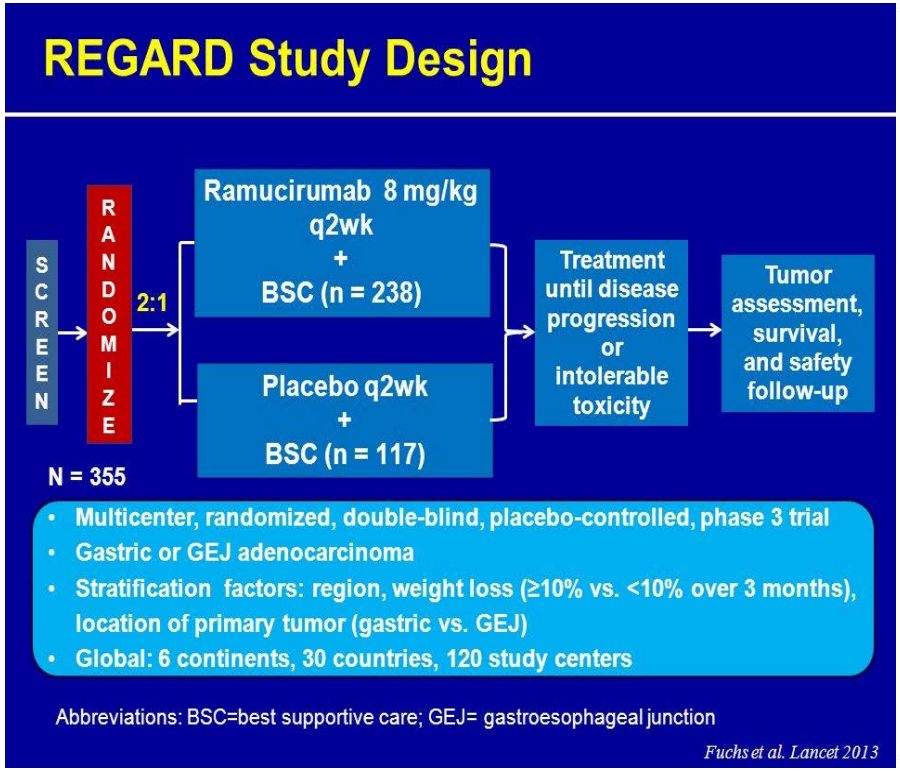
Ramucirumab and VEGF Pathway

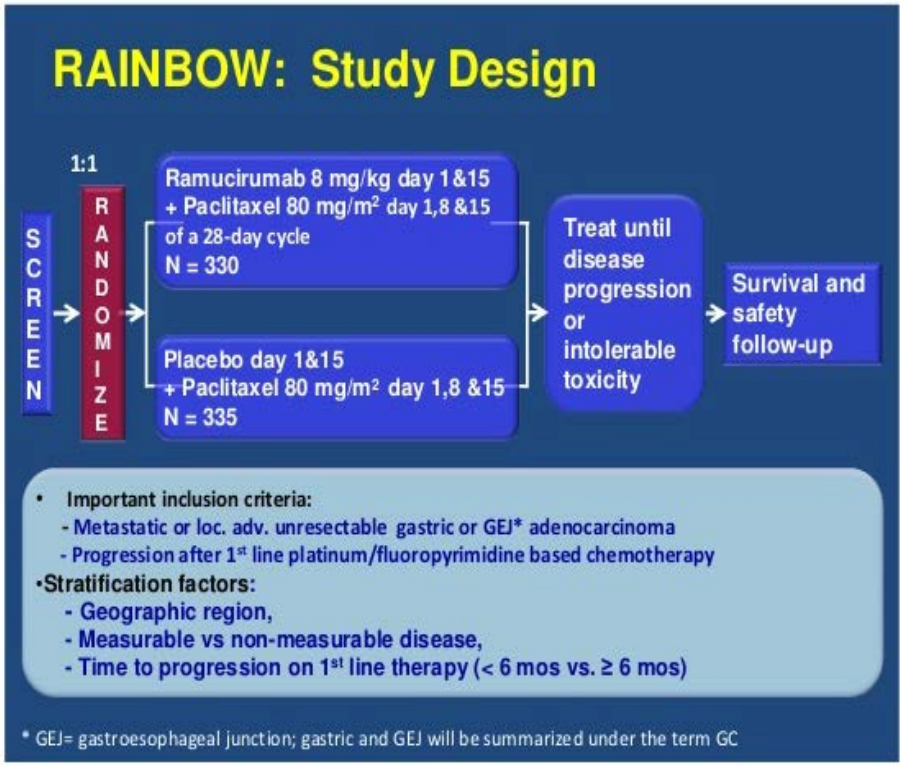


Javle, M et al. Clinical Cancer Research. 2014. 20(23)

REGARD and RAINBOW

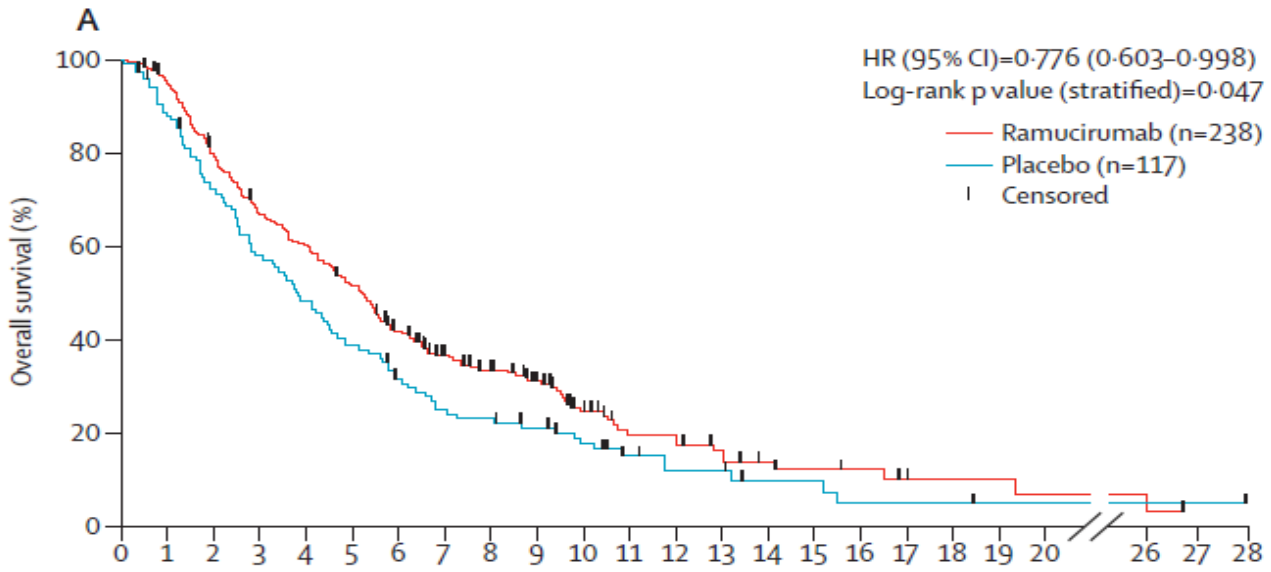


Fuchs, C et al. *Lancet*. Oct 3, 2013



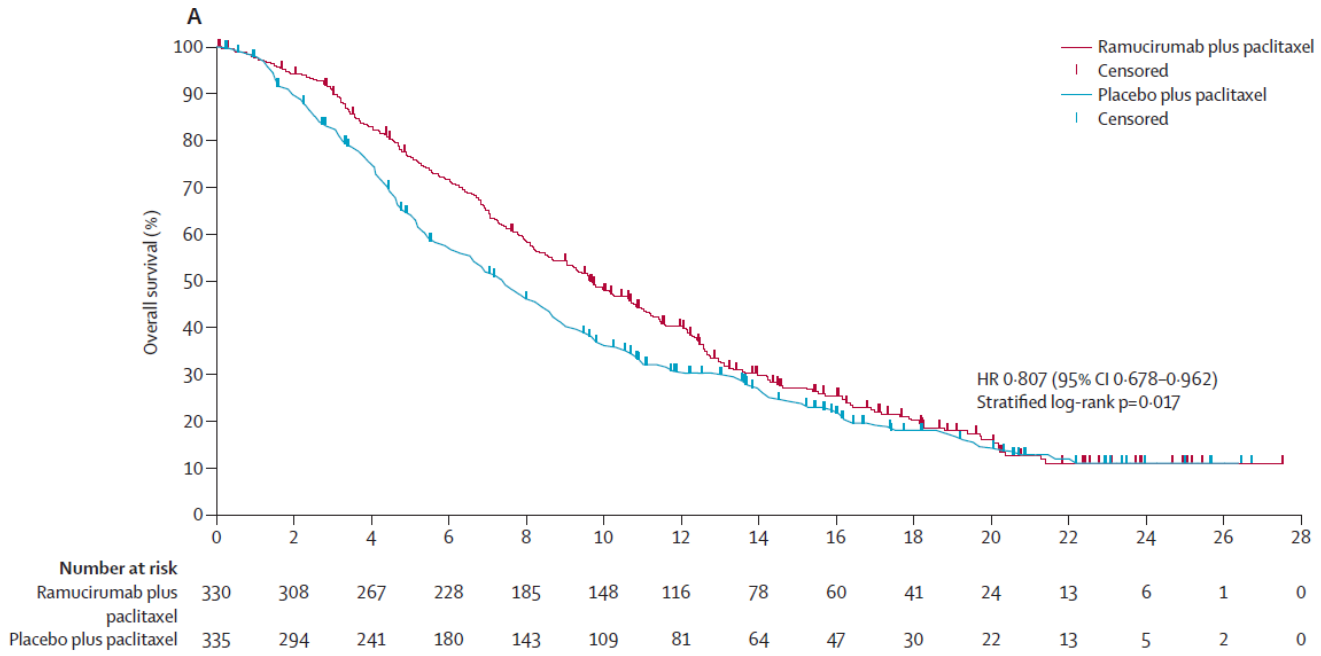
Wilke, H et al. Lancet Oncology. 2014, 15(11): 1224-35.

Ramucirumab: REGARD Study



	Ram	Placebo	P
PFS	2.1 mo	1.3 mo	<0.001
OS	**5.2 mo**	**3.8 mo**	**0.047**

Ramucirumab: RAINBOW



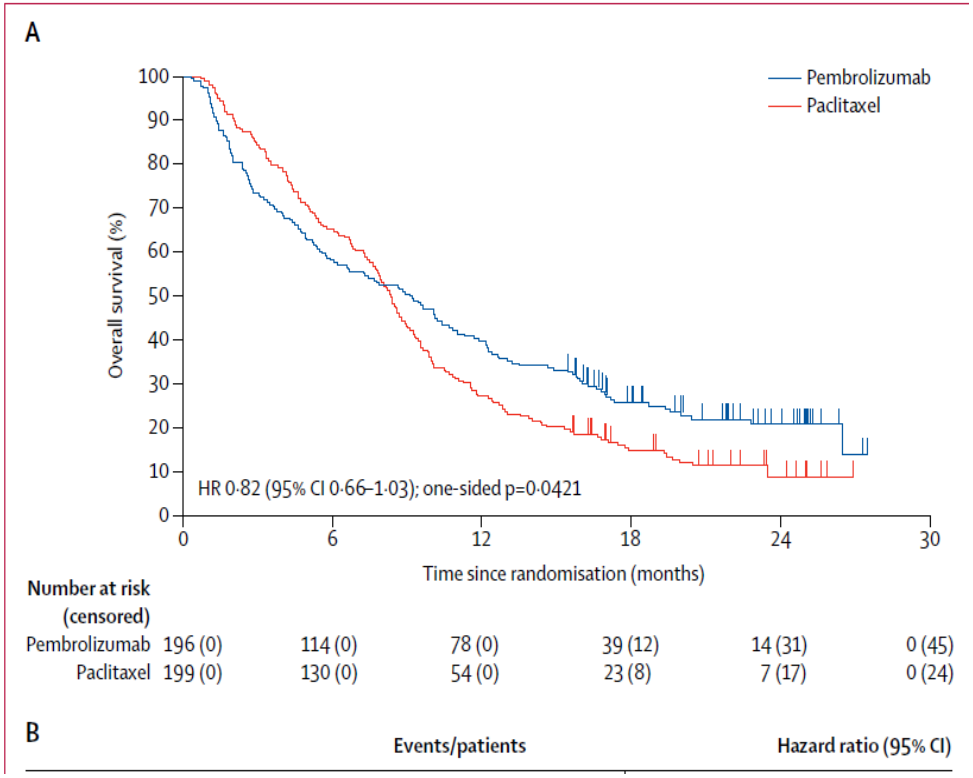
Endpoint	Ram + Paclitaxel	Placebo + Paclitaxel	Δ	p value
RR	28%	16%	12%	0.0001
DCR	80%	64%	16%	<0.0001
PFS	4.4 mo	2.86 mo	1.5	<0.0001
OS	9.63 mo	7.36 mo	2.3	0.0169

Ramucirumab Adverse Events

	Ramucirumab plus paclitaxel (n=327)				Placebo plus paclitaxel (n=329)			
	Grades 1–2	Grade 3	Grade 4	Grade 5	Grades 1–2	Grade 3	Grade 4	Grade 5
Bleeding or haemorrhage	123 (38%)	12 (4%)	1 (<1%)	1 (<1%)	51 (16%)	4 (1%)	2 (<1%)	2 (<1%)
Proteinuria	51 (16%)	4 (1%)	0	0	20 (6%)	0	0	0
Liver injury or failure	39 (12%)	12 (4%)	3 (<1%)	0	28 (9%)	11 (3%)	2 (<1%)	0
Hypertension	34 (10%)	48 (15%)	0	0	10 (3%)	9 (3%)	0	0
Gastrointestinal haemorrhage†	21 (6%)	10 (3%)	1 (<1%)	1 (<1%)	15 (5%)	3 (<1%)	1 (<1%)	1 (<1%)
Infusion-related reaction	17 (5%)	2 (<1%)	0	0	12 (4%)	0	0	0
Renal failure	16 (5%)	4 (1%)	2 (<1%)	0	11 (3%)	0	1 (<1%)	2 (<1%)
Congestive heart failure	6 (2%)	2 (<1%)	0	0	2 (<1%)	1 (<1%)	0	1 (<1%)
Venous thromboembolic events	5 (2%)	7 (2%)	0	1 (<1%)	7 (2%)	8 (2%)	1 (<1%)	2 (<1%)
Arterial thromboembolic events	3 (<1%)	1 (<1%)	2 (<1%)	0	2 (<1%)	2 (<1%)	0	1 (<1%)
Gastrointestinal perforation	0	1 (<1%)	2 (<1%)	1 (<1%)	1 (<1%)	0	0	0

Second-line Pembrolizumab: Keynote 061

592 pts with advanced gastric cancer randomized to paclitaxel weekly versus pembro 200mg IV q3 wks. Trial amended to include only PDL1 CPS ≥1 pts.



- **Pembro did not significantly prolong OS** (9.1 vs 8.3 mo, HR 0.82, 95% CI 0.66-1.03). ORR was similar (16 versus 14 %)
- P threshold 0.0135 for superiority
- **Pembro toxicity profile favorable** (14% vs. 35% grade ≥ 3 AE)
- Potentially greater effect in CPS ≥10 and MSI-h

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Shitara, K. et al. Lancet. 2018; 392: 123-133.

Second-line Pembrolizumab: Keynote 061

Efficacy Outcomes.

	Pembrolizumab CPS ≥1 n = 196	Paclitaxel CPS ≥1 n = 199	Pembrolizumab CPS ≥5 n = 95	Paclitaxel CPS ≥5 n = 91	Pembrolizumab CPS ≥10 n = 53	Paclitaxel CPS ≥10 n = 55
OS, deaths, n (%)	176 (89.8)	190 (95.5)	84 (88.4)	86 (94.5)	44 (83.0)	51 (92.7)
OS, months, median (95% CI)	9.1 (6.2-10.7)	8.3 (7.6-9.0)	10.4 (6.7-15.5)	8.3 (6.8-9.4)	10.4 (5.9-18.3)	8.0 (5.1-9.9)
HR (95% CI)	0.81 (0.66-1.00)	—	0.72 (0.53-0.99)	—	0.69 (0.46-1.05)	—
P	0.03	—	0.02	—	0.04	—
PFS, months, median (95% CI)	1.5 (1.4-2.0)	4.1 (3.2-4.3)	1.6 (1.4-2.8)	4.0 (2.8-4.4)	2.7 (1.4-4.3)	4.0 (2.7-4.4)
HR (95% CI)	1.25 (1.02-1.54)	—	0.98 (0.71-1.34)	—	0.79 (0.51-1.21)	—
ORR, % (n)	16.3 (32)	13.6 (27)	20.0 (19)	14.3 (13)	24.5 (13)	9.1 (5)
DOR, months, (range)	19.1 (1.4+ to 47.1+)	5.2 (1.3+ to 16.8)	32.7 (4.1 to 47.1+)	4.8 (1.3+ to 15.3)	NR (4.1 to 47.1+)	6.9 (2.6 to 6.9)

Fewer drug-related AEs with Pembrolizumab

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Fuchs, C et al. ASCO 2020

Second-line Pembrolizumab: Keynote 181

401 pts with SCC and 222 pts with CPS ≥10

628 patients with advanced or metastatic **squamous cell cancer** of the esophagus or **adenocarcinoma** of the esophagus / GE jxn

- Progressed on 1L therapy
- ECOG 0 or 1

R
1:1

Pembrolizumab 200mg q3wk

Investigator choice chemo

- Paclitaxel 80mg/m2 D 1,8,15 q28d
- Docetaxel 75mg/m2 q3wk
- Irinotecan 180mg/m2 q2wk

Primary endpoints: OS in SCC, CPS ≥10, and total population

Kojima, T. et al. 2019 GI Cancers Symposium

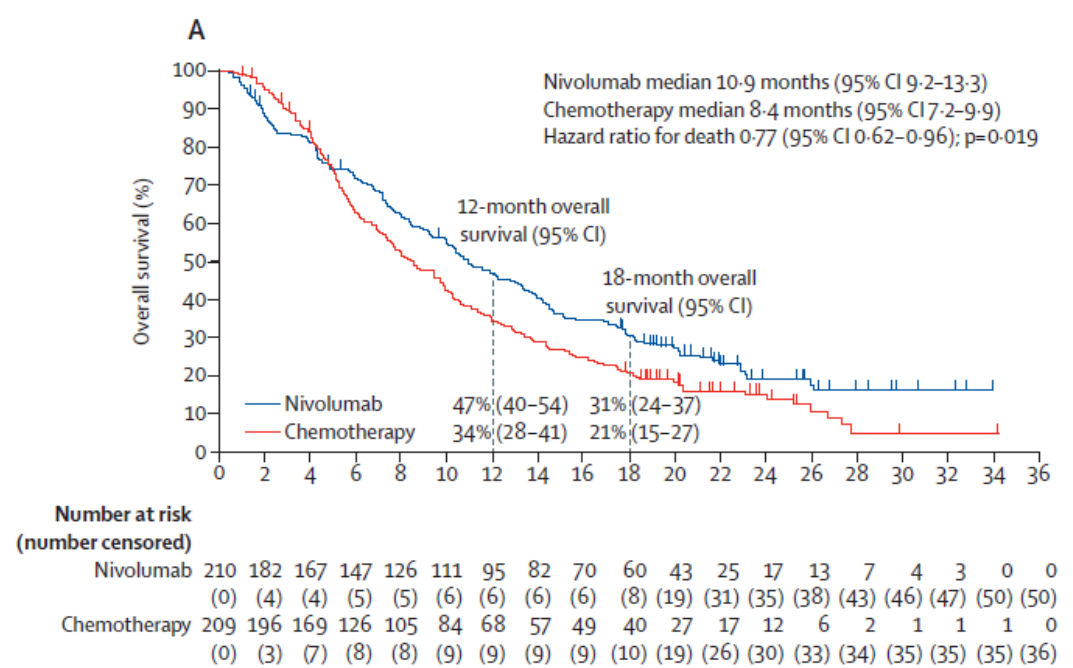
Pembro approved in July 2019 for 2nd line treatment of SCC esophagus with CPS ≥ 10 based on results from Keynote 181

Key Results

- Pembrolizumab was superior to chemo for OS in CPS ≥10 (9.3 vs. 6.7 mo; HR 0.69; 95% CI 0.52-0.93; *P*=0.0074).
- SCC subgroup: Improvement in OS with pembrolizumab vs chemo, (8.2 mo vs 7.1 mo; HR 0.78; 95% CI 0.63, 0.96; *P*=0.0095).
- Fewer any-grade (64% vs 86%) or grade 3-5 (18% vs 41%) drug-related AEs with pembrolizumab vs chemo.

Nivolumab 2nd line – ATTRACTION 3

- Open-label phase 3 randomized trial Nivolumab vs. Chemotherapy
- Patient population: Advanced squamous cell carcinoma ; 1 prior line of therapy
- Primary endpoint: Overall survival



Kato K, et al. Lancet Oncology. 2019; 20: 1506-17

What didn’t work?

CMET Inhibitors -- (RILOMET 1 – worse survival in Txarm)

EGFR Inhibitors – Cetuximab, Panitumumab (REAL3, E1206/CALGB 80403)

mTOR inhibitors – Everolimus vs. BSC

Napabucasin (BRIGHTER trial)

Take-home points: Metastatic Gastric/Eso

- 2 drug combinations rather than 3 drug combinations (5-FU+platinum) represents a standard of care worldwide in 1st line therapy
- Trastuzumab in 1st line for Her2 positive tumors
- In 2nd line, irinotecan, paclitaxel, docetaxel all viable standard chemotherapeutic options
- Ramucirumab in 2nd line therapy (alone or with Paclitaxel)
- Pembrolizumab in PDL1 + or MSI-high tumors (3rd line)
  - First line monotherapy, particularly in CPS ≥10
  - Second line, in CPS ≥10 (SCC) and MSI-H

THANK YOU

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Extra Slides

Siewert Classification

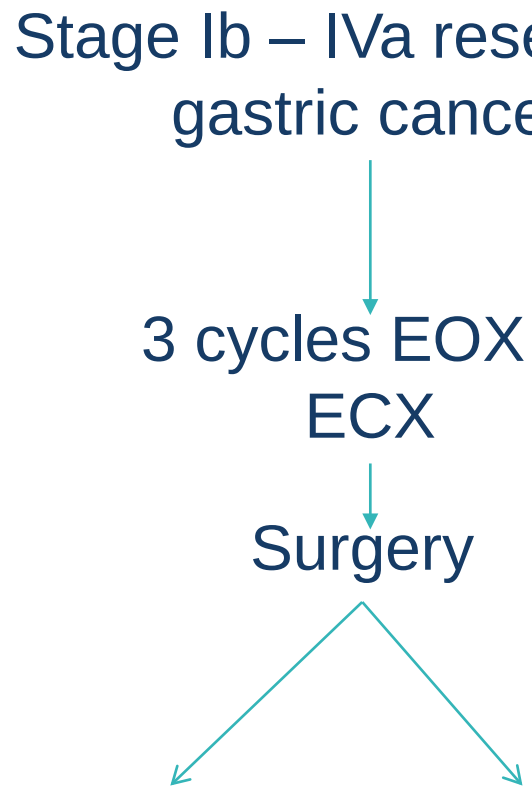
	Type 1 (n= 494)	Type II (n= 414)	Type III (n= 438)
Mean age at presentation	60.1 ± 10.3	60.7 ± 11.4	62.7 ± 12.0
Male: Female Ratio	9.9 : 1	4.8 : 1	2.1 : 1
Associated Barrett's	76.9%	9.8%	2.0%
Prevalence of Grade 3/4 tumors	52.6%	58.7%	72.6%
Intestinal type histology	81.1%	41.3%	39.1%

Siewert R et al. *J Surg Onc*. 90; 139-46, 2005

Chemo (PeriOp vs. PostOp) vs. ChemoRT

Citation	# Pts	Treatment	3 or 5 year OS in Treatment Arm
MacDonald, JS 2001 (INT-0116)	**556**	**Arm A: Surgery alone** **Arm B: Surgery → 5-FU/LV + RT**	**50%**
Fuchs, CS 2011 (CALGB 80101)	546	Arm A: Surgery → 5-FU/LV/RT Arm B: Surgery → ECF/RT	52%
Cunningham, D 2006 (MAGIC)	**503**	**Arm A: Surgery alone** **Arm B: ECF(3) → surgery → ECF(3)**	**36%**
Sasako, M 2011 (ACTS-GC)	1,059	Arm A: Surgery (D2) Arm B: Surgery → S1 x 1 year	71.7%
Bang, Y. 2011 (CLASSIC)	**1,035**	**Arm A: Surgery (D2)** **Arm B: Surgery (D2) →XELOX x 8 cycles**	**83%**

CRITICS Trial: (MAGIC vs. MacDonald?)



KEY RESULTS

5-year survival: 41.3 % (chemo) vs. 40.9% (RT), p=0.99

87% underwent D2 dissection

Poor postoperative treatment compliance in both arms

Cats, A. et al. Lancet Oncology. 2018, 19(5): 616-628

2nd Line Therapy --- Cougar-2 Study

Advanced Esophagogastric Cancer (n=168)

Progression within 6 mo of 5FU/platinum

ECOG 0-2

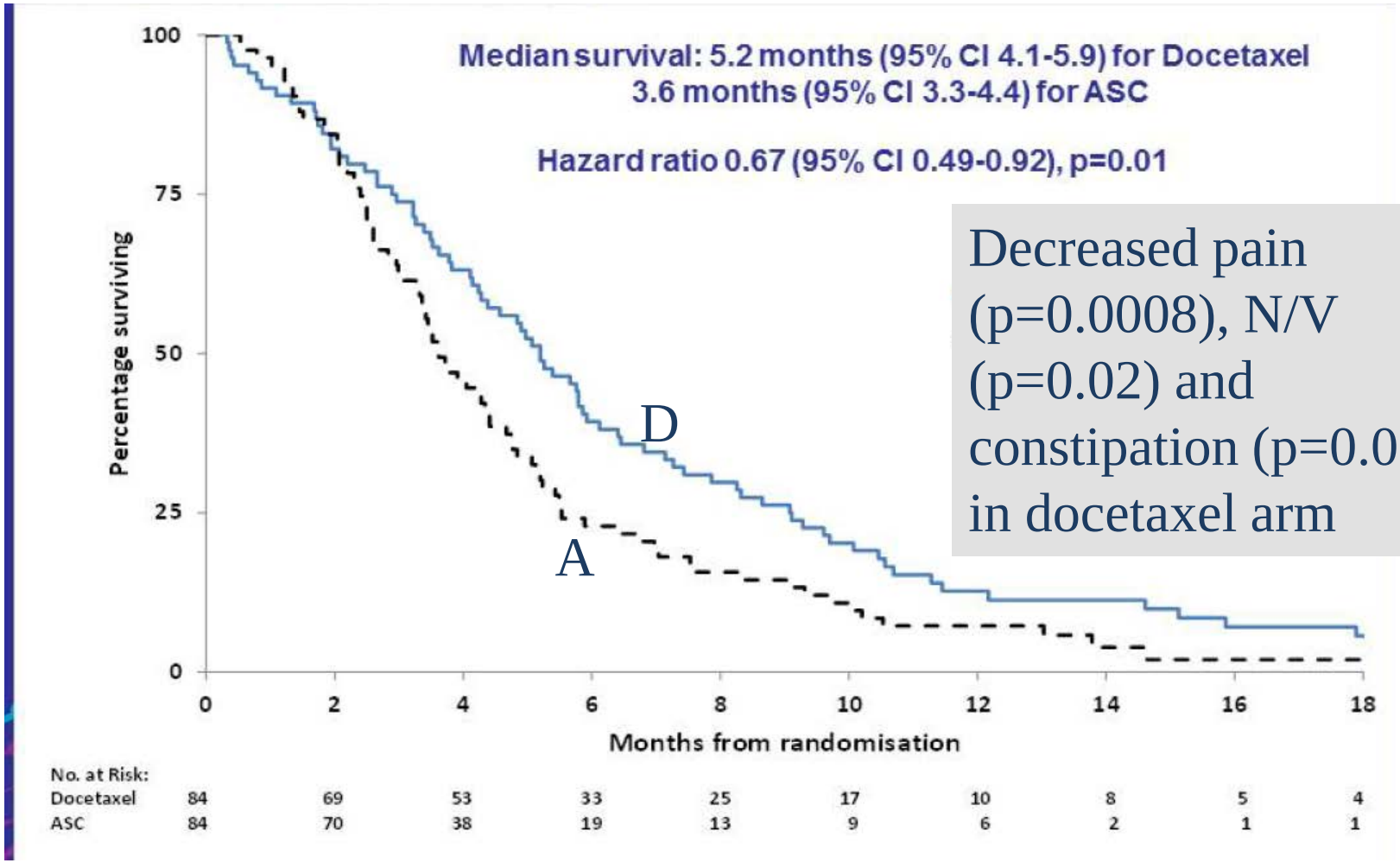
→ Docetaxel 75mg/m2 q3w X 6 cycles

→ Active symptom control

OS (primary endpoint),
HRQOL (secondary endpoint)

Ford H et al. Lancet Oncology 2014; 15: 78-86

2nd Line Therapy --- Cougar-2 Study



Decreased pain (p=0.0008), N/V (p=0.02) and constipation (p=0.02) in docetaxel arm

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Ford H et al. Lancet Oncology 2014; 15: 78-86

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Iron metabolism disorders and hemolytic anemias

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Director, Hemolytic Anemias and Iron Disorders Program

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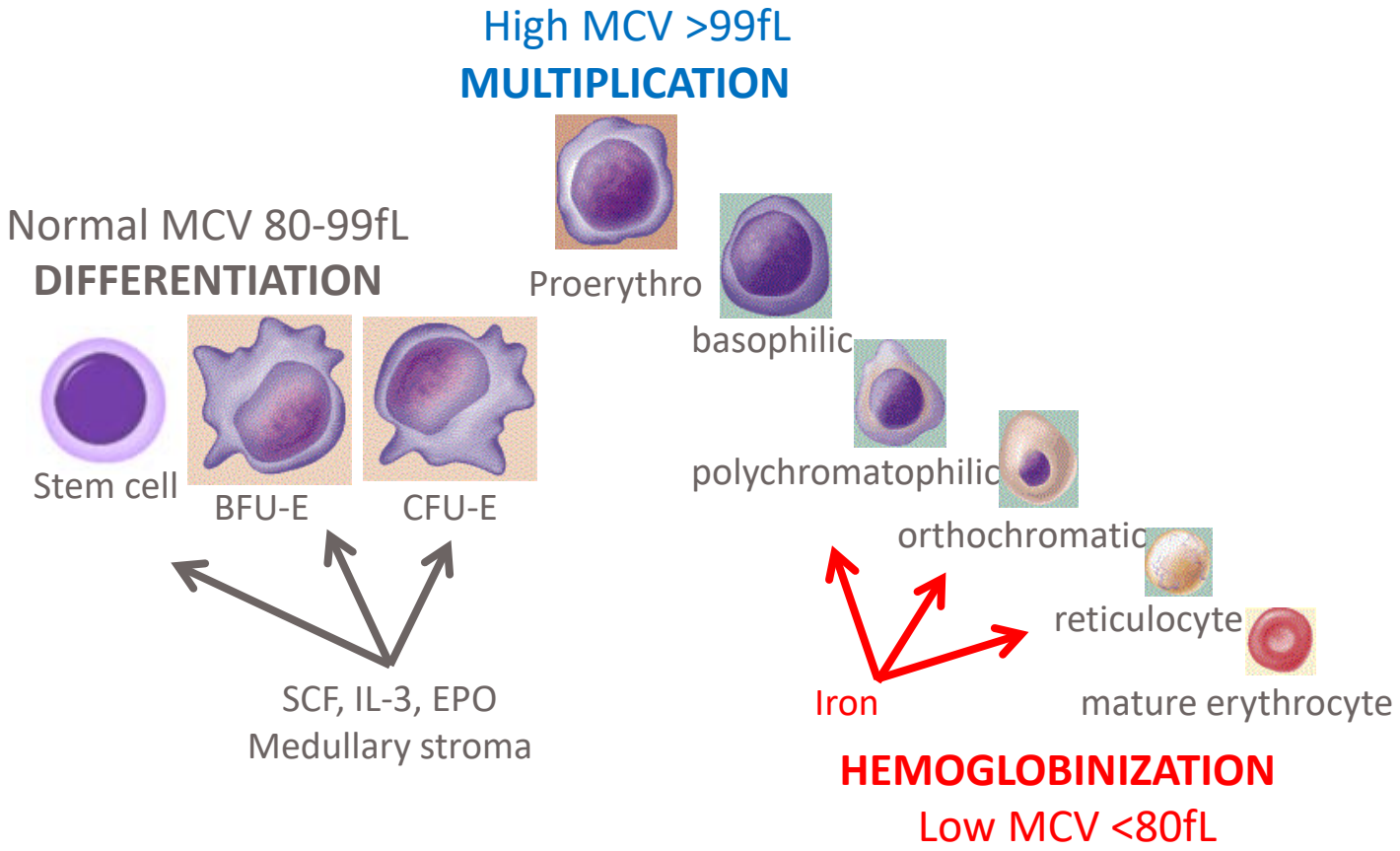
ABIM Hematology exam blueprint

		Diagnosis	Testing	Treatment/ Care Decisions	Risk Assessment/ Prognosis/ Epidemiology	Pathophysiology/ Basic Science
Red blood cell production disorders *(4% of exam)*						
Nutritional deficiencies		✓	✓	✓	/	/
Anemia of chronic inflammation		✓	✓	✓	/	✓
Red blood cell destruction disorders *continued...*						
Autoimmune hemolytic anemias (AIHA)						
Warm antibody-mediated autoimmune hemolytic anemia		✓	✓	✓	✓	/
Cold antibody-mediated autoimmune hemolytic anemia	LF	✓	/	✓	/	/
Drug-induced hemolysis	LF	/	/	/	/	/
Metabolic abnormalities and enzyme deficiency hemolytic anemias						
Oxidant hemolysis, including glucose-6-phosphate dehydrogenase (G6PD) deficiency	LF	/*	/*	/*	/*	/*
Pyruvate kinase deficiency and other metabolic deficiencies	LF	/*	/*	✗*	✗*	✗*

ABIM Hematology exam blueprint

	Diagnosis	Testing	Treatment/ Care Decisions	Risk Assessment/ Prognosis/ Epidemiology	Pathophysiology/ Basic Science
Paroxysmal nocturnal hemoglobinuria LF	✓	/	/	/	/
Red blood cell membrane disorders LF	/	/	/	/	✗
Microangiopathic hemolytic anemias (other than TTP, HUS, or DIC)	✓	✓	✓	✓	/
Non-autoimmune, acquired hemolytic anemias LF	/	/	/	/	/
Hemochromatosis	✓	✓	✓	/	/

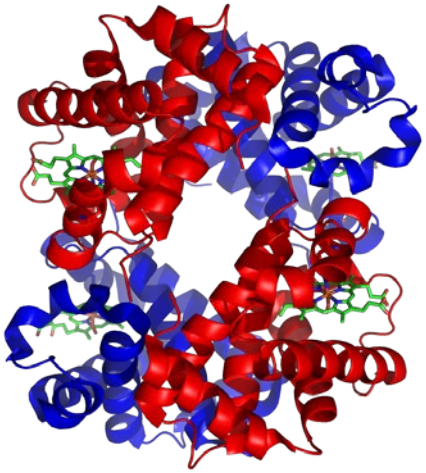
Stages of erythropoiesis



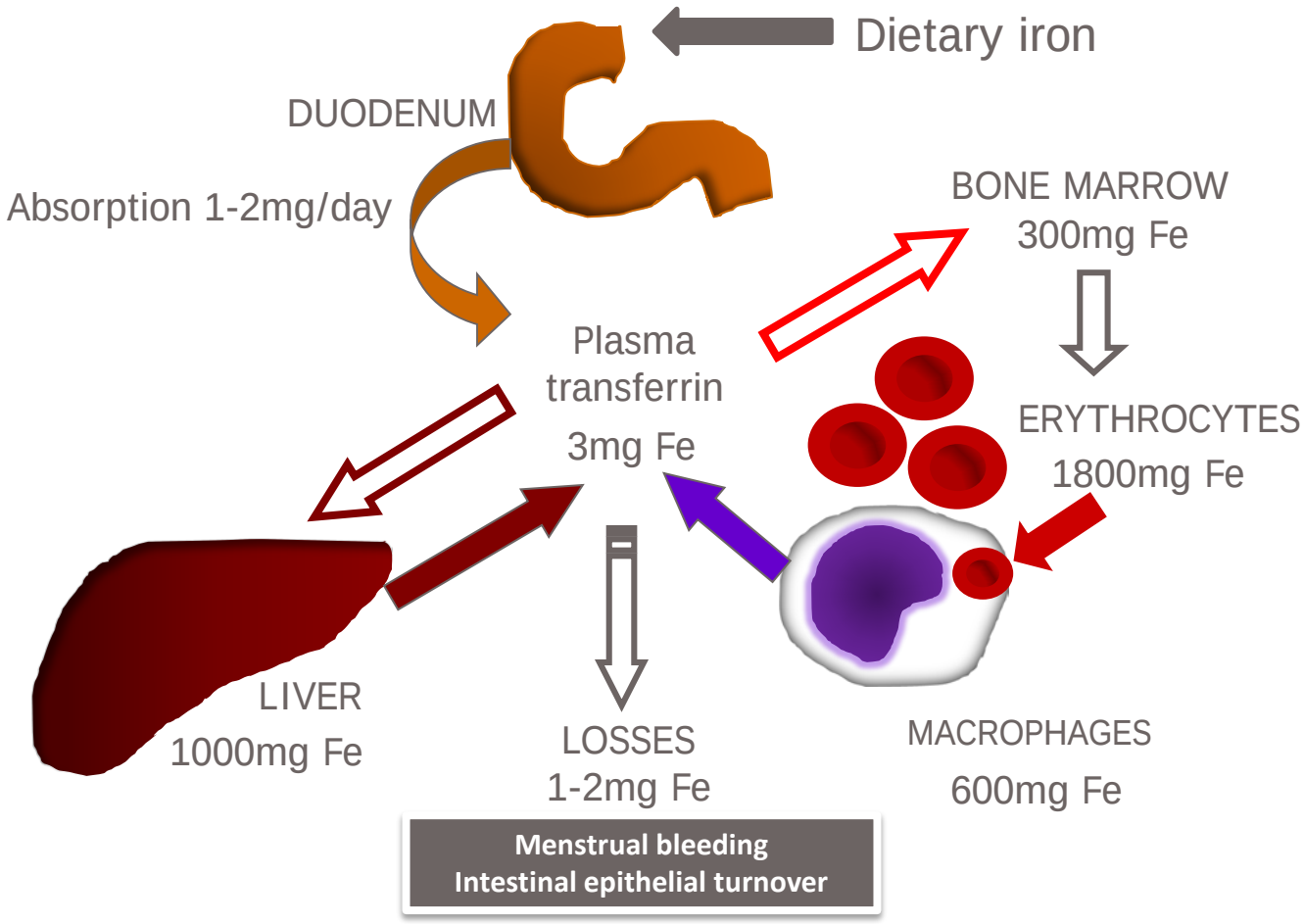
Anemias of the hemoglobinization stage (microcytic, MCV<80fL)

Lack of a component of hemoglobin

1. **Iron** deficiency
   - Absolute: iron deficiency anemia
   - Functional: anemia of inflammation /chronic disease
2. **Globin** deficiency
   - Thalassemias (see other lecture)
3. **Heme** deficiency
   - Hereditary sideroblastic anemia
     - ALA synthase mutation (*ALAS2* gene)
   - Chronic lead poisoning
     - ALA synthase inhibition



Physiology of iron metabolism



Common “iron studies”

Test	Usual reference ranges
Serum ferritin (mcg/L)	20-200 (female) 30-300 (male)
Serum iron (mcg/dL)	60-180
Total iron binding capacity (mcg/dL)	270-535 (female) 250-460 (male)
Serum transferrin (mg/dL)	192-382 (female) 180-329 (male)
Transferrin saturation (TSAT) (Serum iron/TIBC) (%)	20-45 (female) 20-50 (male)

Diagnosis of iron deficiency anemia

- **Anemia = low RBC production:** low Hb, Hct, and RBCs
  - Beta thal trait has normal or elevated RBCs
- **Hypoproliferative:** reticulocytes are normal or low
  - High reticulocytes (>100k) – think acute bleeding or hemolysis!
- Biochemical evidence of **iron deficiency**
  - Ferritin <30mcg/L (men) or <20mcg/L (women)
  - Low serum iron with high TIBC = low transferrin saturation <20% (typically <16%)
- **Work up for causes**

Causes of iron deficiency

- Always investigate bleeding (GI, Gyn, epistaxis, hematuria)
- Malabsorption
  - Surgical (gastric bypass, resections…)
  - Inflammatory bowel diseases
  - Parasites (hookworm)
  - Atrophic gastritis
  - Prolonged use of medications (e.g. PPI)
- Vegetarian/vegan diet DOES NOT cause iron deficiency by itself

Treat or control the underlying cause!

Treatment of iron deficiency anemia - 1

Goals of iron supplementation:

1. **Normalize CBC** (first phase, takes about 4-6 months)
   - Hb>12g/dL women, Hb>13g/dL men **AND**
   - Normal MCV (>80fL) and MCH (>28pg)
2. **Normalize iron stores** (usually 3-4 more extra months)
   - Ferritin >20ug/L for women, >30ug/L for men **AND**
   - Transferrin saturation > 20%

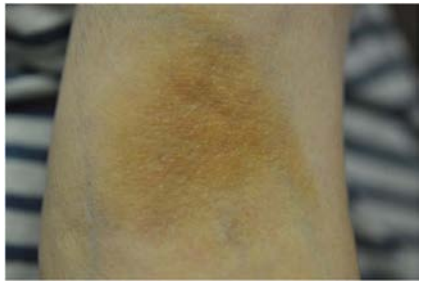
Oral iron: ferrous sulfate, fumarate, gluconate

- **First line of therapy**
- **Single, lower (100-150mg elemental iron) dose qod favored** (e.g. ferrous sulfate 325mg 2 tab qod)
- Side effects: GI symptoms (>50%), dark stools

Treatment of iron deficiency anemia - 2

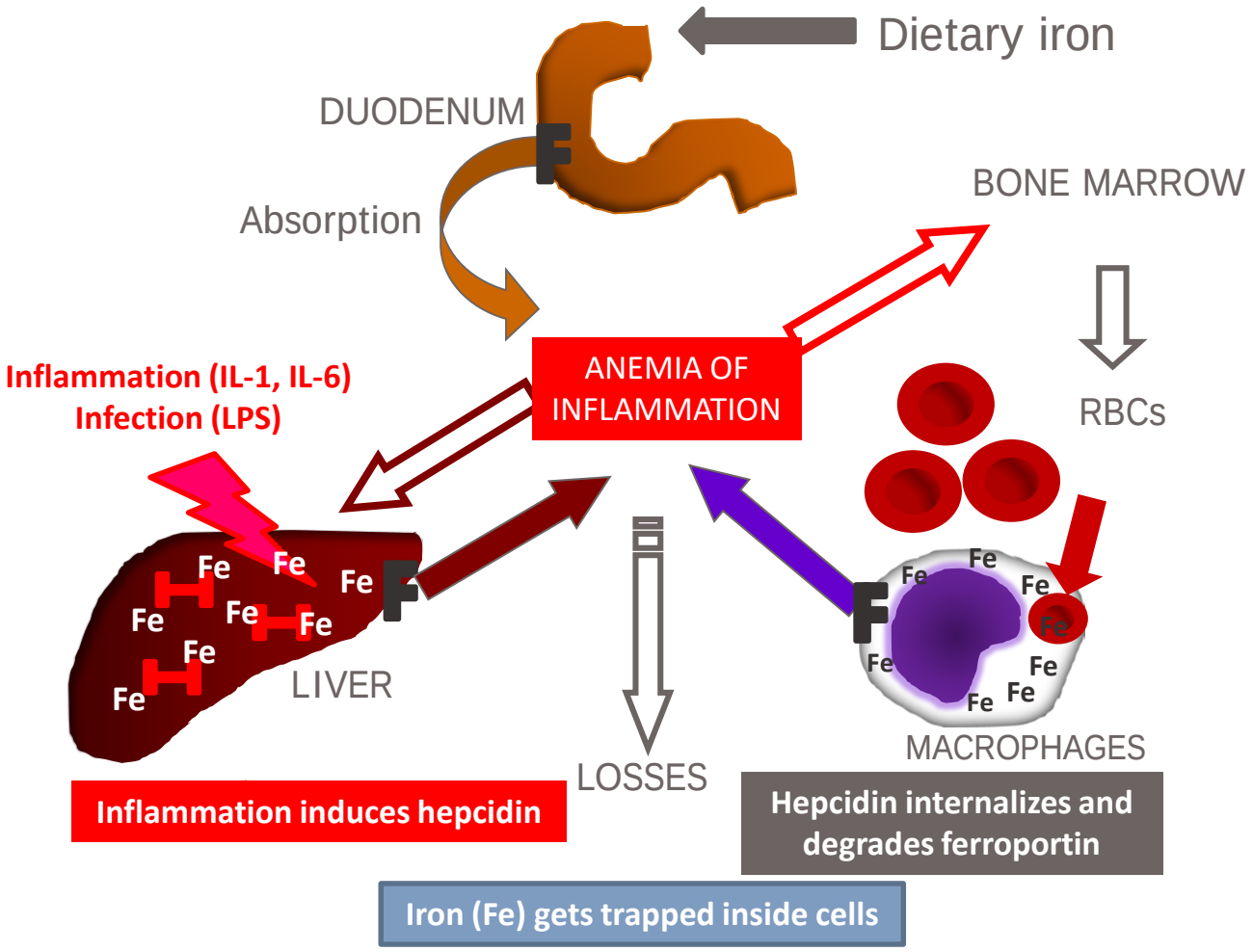
Intravenous iron

- Formulations: Iron sucrose, low molecular weight iron dextran, iron gluconate, ferric carboxymaltose, ferumoxytol, iron isomaltoside
- Consider if :
  - Intolerance/failure to oral iron
  - Malabsorption (e.g gastric bypass, IBD)
  - CKD
- Side effects:
  - **Anaphylaxis**: RARE these days, mostly associated with HIGH-molecular weight dextran (discontinued);
  - **Skin hyperpigmentation**
  - **Hypophosphatemia** (ferric carboxymaltose, isomaltoside)



Gan & Orringer, Dermatol Surg 2015

Pathophysiology of anemia of inflammation



Diagnosis of anemia of inflammation

- History of **underlying chronic disease**:
  - Inflammatory: RA, SLE, IBD, Castleman's disease
  - Infections: Tb, osteomyelitis, endocarditis
  - Malignancy: lymphoma and other hematologic
  - Other chronic conditions: CHF, COPD

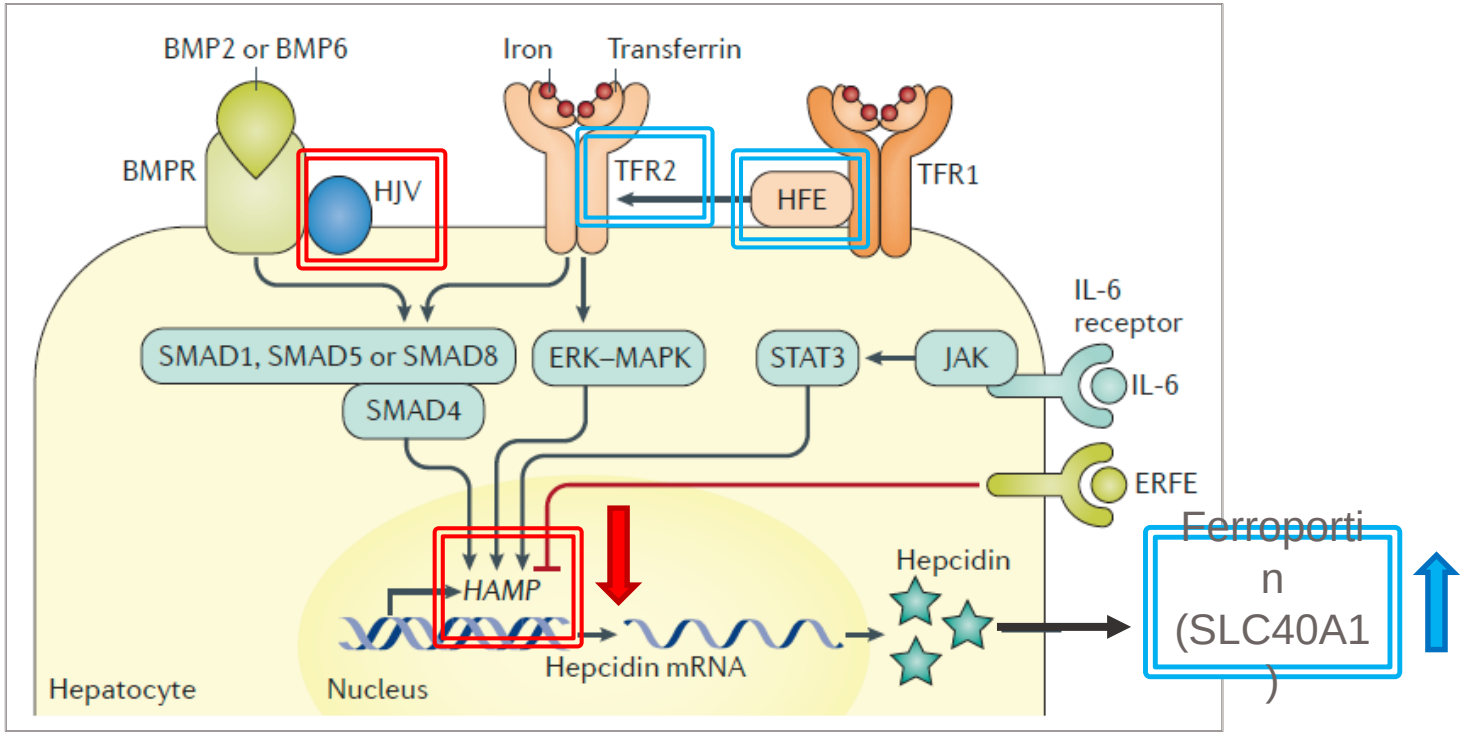
- Lab findings:
  - Mild to moderate **hypoproliferative N/N anemia** (occasionally microcytic)
  - Low serum iron with low TSAT <20%
  - Normal to increased serum ferritin (>100 mcg/L)
  - May have elevated CRP>5 mg/L but not required
  - Investigational: hepcidin levels

Management of anemia of inflammation

- **Treatment of the underlying disorder** is usually best;
- **Iron supplementation**: usually NOT indicated unless combined iron deficiency exists (e.g. if ferritin <100ug/L), or if patient on ESA for CKD;
- **Erythropoiesis-stimulating agents**: consider if CKD-associated, or in some patients undergoing chemotherapy for malignancy
- **Transfusions**: only if symptomatic, life-threatening anemia
- Investigational: hepcidin blockers

Pathophysiology of Hereditary Hemochromatoses

Uncontrolled iron absorption due to hyperactivity of ferroportin (mostly due to hepcidin deficiency)



Adapted from Brissot et al., Nat Rev Dis Primers 2018

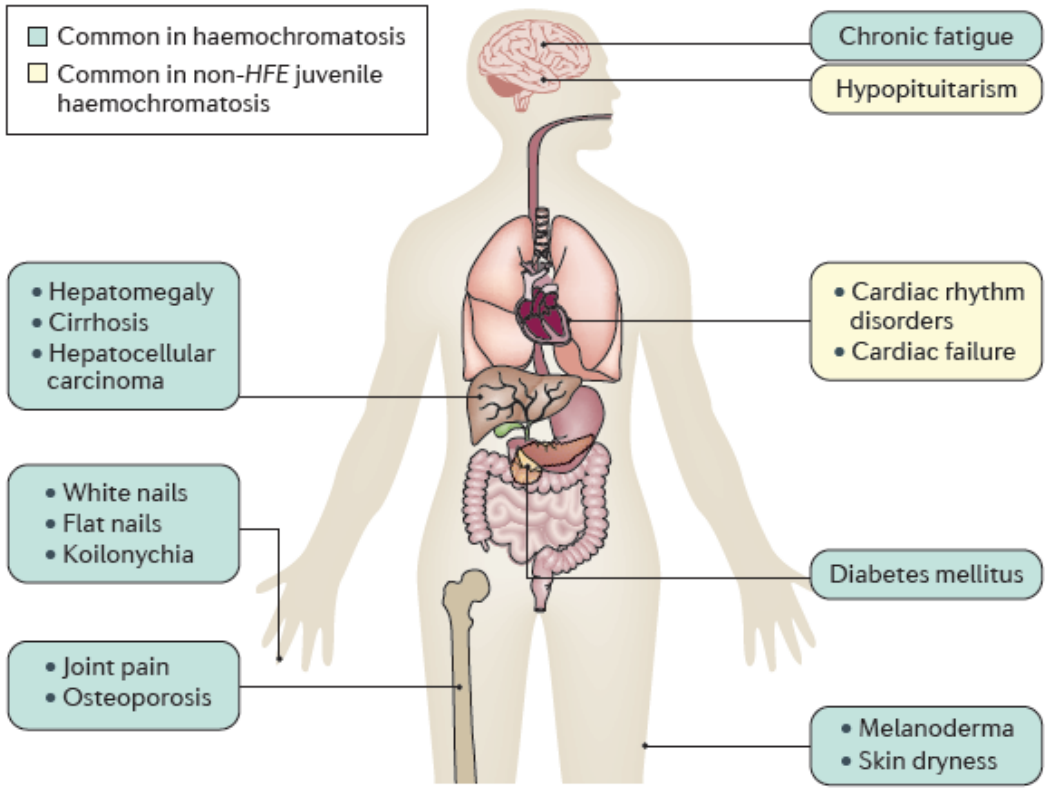
Hemochromatosis – Clinical features

Classical HH

- type 1, *HFE* mutation (Northern Europe origin)
- type 3, *TFR2* mutation (rare, may have earlier onset)
- type 4B, *SLC40A1* mutation (gain-of-function ferroportin)

Juvenile HH

- type 2A, hemojuvelin mutation
- type 2B, hepcidin mutation (extremely rare)



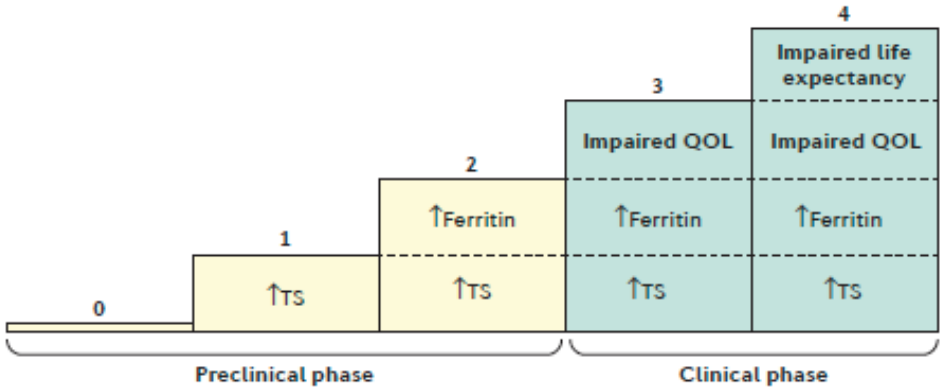
Brissot et al., Nat Rev Dis Primers 2018

Hemochromatosis - Diagnosis

Labs:

No anemia

high ferritin AND TSAT>45%



- Northern European ascent: start with ***HFE* testing**
  - *HFE* C282Y/C282Y or heterozygote C282Y/H63D: diagnosis of HH
  - *HFE* H63D/H63D: diagnosis is debatable; low penetrance
  - Other genotypes: non-diagnostic, pursue other causes
- No obvious Northern European ascent: **start with MRI T2*** to confirm iron overload; if positive for liver iron overload:
  - If age<30, consider testing for *HAMP, HJV, TFR2* genes
  - If age>30, consider testing for *HFE, TFR2, SLC40A1* genes

Hemochromatosis - treatment

- Avoid iron supplements and alcohol;
  - Tea, coffee comsumption and use of PPI can decrease absorption
  - No need to follow iron-poor diet
- **Phlebotomy** – GOAL: ferritin 50-100mcg/L
  - Induction: 400-500mL weekly provided Hb>11g/dL
  - Maintenance : maximum interval to keep ferritin at goal
  - Blood donation: acceptable in some countries
- **Erythrocytapheresis**: allows faster iron removal; higher cost; side effects of procedure (hypocalcemia, longer procedure)
- **Iron chelation**: low dose deferasirox may be used for those intolerant to phlebotomy
- **Liver transplantation** may be required and is curative

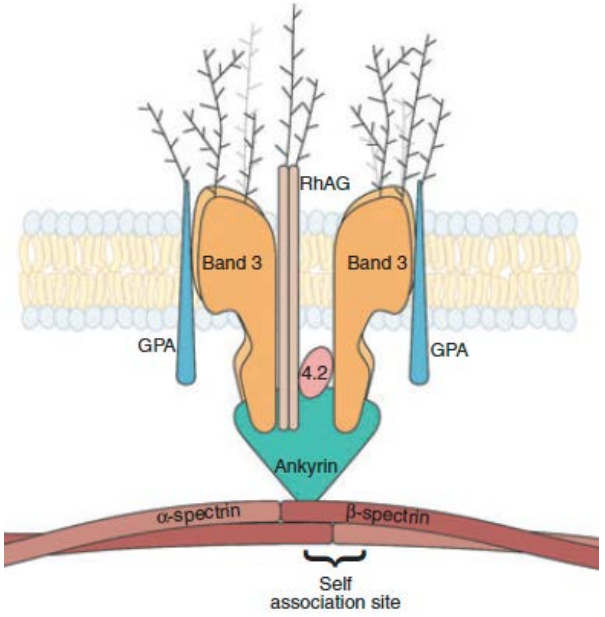
Hemolytic anemias

CAUSES

- **Ma**laria (and other infections- Clostridium, Babesia)
- **Me**dications (drug-induced or oxidative)
- **Mi**croangiopathies
- **Mo**therhood (think antibodies: hemolytic disease of the newborn; transfusion reactions; don't forget **autoimmune**)
- **Mu**tations
  - Acquired mutation → PIG-A: paroxysmal nocturnal hemoglobinuria
  - Congenital (think COMPONENTS OF A RED CELL):
    - Hemoglobin (other lecture)
    - Membrane: HS, elliptocytosis, stomatocystosis, xerocytosis...
    - Enzyme: G6PDD, PKD

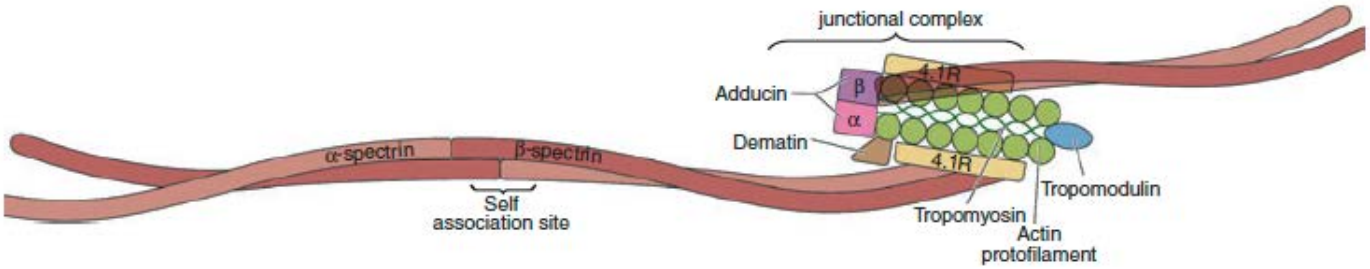
Red cell membranopathies - HS

- **Hereditary spherocytosis** is the most common inherited hemolytic anemia due to membrane defects (1/3,000, all racial groups)
- AD in 75%; mutation in ankyrin, spectrin or band 3 (VERTICAL linkages); may occur *de novo;*
- Family history of **gallstone and/or splenectomy**;
- Clinical features: hemolysis with **high MCHC**; negative DAT; may have hypersplenism
- Diagnosis:
  - osmotic fragility test with right shift of the curve; reduced fluorescence with **eosin-5'-maleimide (flow cytometry)**
  - Treatment: splenectomy is curative



Na & Mohandas, Br J Haematol 2008;141(3):367-375op

Other red cell membranopathies



Brissot et al., Nat Rev Dis Primers 2018

1. **Hereditary elliptocytosis**
   - AD, more common in malaria endemic regions
   - Alpha spectrin (65%), beta spectrin or protein 4.1R mutations (LATERAL linkages)
   - Hereditary pyropoikilocytosis – homozygous or compound heterozygous spectrin mutations causing severe form of HE
2. Southeast Asian Ovalocytosis: mild or no hemolysis with ovalocytes causes by unique 27bp deletion in band 3
3. Hereditary stomatocytoses: AD defects in volume control
   1. xerocytosis (compensated hemolysis, macrocytosis, <10% stomatocytes)
   2. overhydrated stomatocytosis (frank stomatocytosis with hemolytic anemia)

Red cell enzymopathies

- **Glucose-6-phosphate dehydrogenase (G6PD) deficiency**
  - Recessive X-linked inheritance
  - Variable phenotype: mostly episodic hemolytic crises; may present as chronic non-spherocytic hemolytic anemia
  - Diagnosis: Heinz bodies during hemolysis; low G6PD activity outside of hemolytic episode (false normal G6PD with reticulocytosis)
  - Triggers: infections, medications (dapsone, primaquine)

- **Pyruvate kinase deficiency (PKD)**
  - Most common defect of the glycolytic pathway; AR
  - Chronic non-spherocytic anemia with variable severity
  - Macrocytosis and extreme reticulocytosis (>50%) postsplenectomy
  - May develop spontaneous iron overload

Autoimmune hemolytic anemias

- Acquired hemolytic conditions with production of abnormal antibodies reacting against red cell epitopes
- **Positive hemolytic markers** (increase in reticulocyted, LDH, indirect bilirubin, with low haptoglobin)
- **Direct antiglobulin test**: detects immunoglobulins and complement bound to red blood cells ("direct Coombs' test)

    - IgG+: warm AIHA (typically with spherocytes in peripheral blood smear)
    - Complement (C3b) and/or IgM: cold AIHA
    - IgG and C3b: mixed AIHA

Warm autoimmune hemolytic anemia - management

- **Transfusions**: if severe anemia (Hb<6), instability; beware of history of alloimmunization; failure to respond may indicate IVIg.

- **First line of therapy is glucocorticosteroids** (e.g. prednisone 1-2mg/kg/day with taper after 2-3 weeks if response)

- Second line therapy:
  - **Rituximab** (may be used as first line)
  - Splenectomy (often third line)
  - Other immunosuppressants
    - MMF, cyclophosphamide, azathioprine, cyclosporine
    - sirolimus – may be preferred in children/young adults with ALPS

Cold agglutinin disease – clinical features

- Cold-induced symptoms
  - Acrocyanosis
  - Livedo reticularis / skin ulcers
  - Raynaud's phenomenon
  - Dysphagia or pain upon ingesting cold food

- Extravascular hemolytic anemia (may be precipitated by cold or infections)
  - Spurious macrocytosis
  - *In vitro* agglutination

- Venous thromboembolism

Cold agglutinin disease – diagnosis

- Evidence of hemolysis
- DAT positive for complement (C3d)
- Cold agglutinin titer 1:64 or higher at 4°C
    - IgM with specificity anti-I (often linked to *Mycoplasma*) or anti-i (often linked to mononucleosis)

Classification:

- **Primary CAD**: typically associated with a monoclonal IgM kappa not meeting criteria for a lymphoproliferative disorder (MGUS)
- **Secondary CAD**: infections, autoimmune disorder, or lymphoid malignancy

Cold agglutinin disease – treatment

- **Cold avoidance**
- **Transfusions**: avoid cooling down patient's sample for crossmatch; use of blood warmers
- **Plasmapheresis and IVIg** can be used as temporizing measures in severe cases
- For secondary CAD, treatment of the underlying disorder is appropriate
- For primary CAD:
  - Consider first line with rituximab containing regimen (e.g. rituximab + bendamustine); may associated with fludarabine, prednisone, interferon, or monotherapy;
  - Alternative regimen: bortezomib.
  - Investigational: anti-complement therapies (sutimlimab)

Drug-induced hemolysis

- **Most common: diclofenac, ceftriaxone, piperacillin, oxaliplatin**
- **Mechanisms:**
  - DAT-positive (IgG and/or C3)
    - Hapten formation: penicillin, ceftriaxone
    - Drug-independent: methyldopa
  - **Oxidative hemolysis:** primaquine, dapsone, phenazopyridine – worse if associated with G6PD deficiency
  - **Methemoglobinemia:** anesthetics, nitrites
  - Drug-induced thrombotic **microangiopathy:** quinine, Bactrim, oxaliplatin, gemcitabine, mitomycin, bevacizumab, sunitinib, proteasome inhibitors, quetiapine, cyclosporine, tacrolimus, sirolimus
  - Other mechanisms: ribavirin, artesunate (for malaria), interferon alpha

Paroxysmal nocturnal hemoglobinuria (PNH)

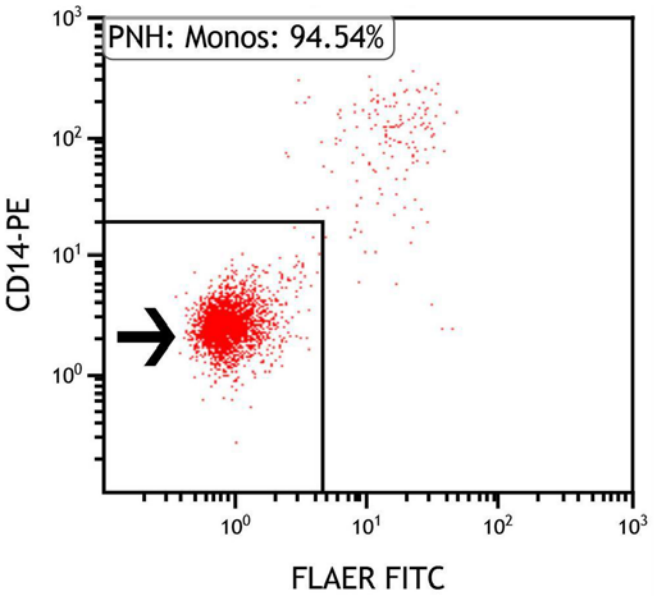
- Acquired clonal disorder with *PIGA* gene mutation → loss of GPI-anchored proteins → susceptibility to complement destruction

1. **Classical PNH**
   - **P**ancytopenia
   - **N**on-autoimmune hemolytic anemia
     - Fatigue, jaundice, hemoglobinuria
     - Smooth muscle dystonia: dysphagia, erectile dysfunction
   - **H**emostasis activation: venous thromboembolic events in unusual vessel beds
     - Abdominal VTE (Budd-Chiari syndrome)
     - Upper extremity
     - Venous sinuses

2. **PNH clone in the context of another hematologic disorders** (aplastic anemia, MDS, PMF)

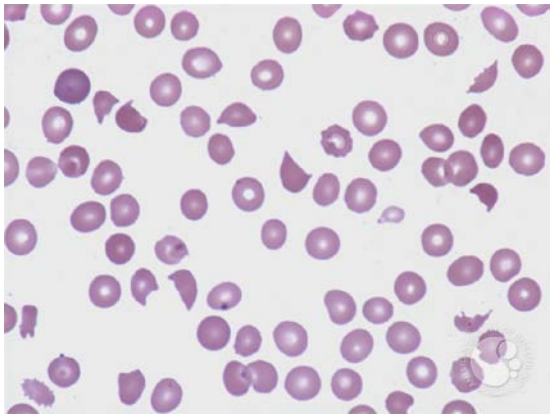
Paroxysmal nocturnal hemoglobinuria

- Diagnosis: **Peripheral blood flow cytometry**
  - lack of at least 2 GPI-anchored proteins in at least 2 different lineages
- Treatment:
  - **Support** for anemia: folic acid, iron supplementation if iron deficient due to hemoglobinuria, transfusions
  - Symptomatic disease: **complement inhibitors** eculizumab or ravilizumab
    - prophylaxis for meningococcal infections
  - **Allogeneic hematopoietic cell transplant** for AA/MDS, refractory disease, or severe disease without access to anti-complement therapy



Microangiopathic hemolytic anemias

1. Thrombotic microangiopathy: TTP, HUS
2. Systemic conditions:
   - DIC
   - Pre-eclampsia / HELLP syndrome
   - Malignancy
   - Scleroderma renal crisis
   - Malignant hypertension
   - Antiphospholipid syndrome
3. Localized hemolysis:
   - Hemangioma (Kasabach-Merritt syndrome)
   - TIPS
   - Malfunctioning cardiac valve or assist device
   - March hemoglobinuria (includes extreme running, bongo drumming)



Educational resources

- American Society of Hematology Self-Assessment Program 6th Ed. (ASH SAP)
- ASH Pocket Guides (download from App store)
- Hematology/Oncology question bank http://hemeoncquestions.com/
- Hematology-Oncology board review questions www.turner-white.com/brm/bonco.htm

THANK YOU

NSCLC. Adjuvant/Locally Advanced

Rafael Santana-Davila.

Associate Professor Of Medicine.

University of Washington/Fred Hutchinson Cancer Center.

SCCA

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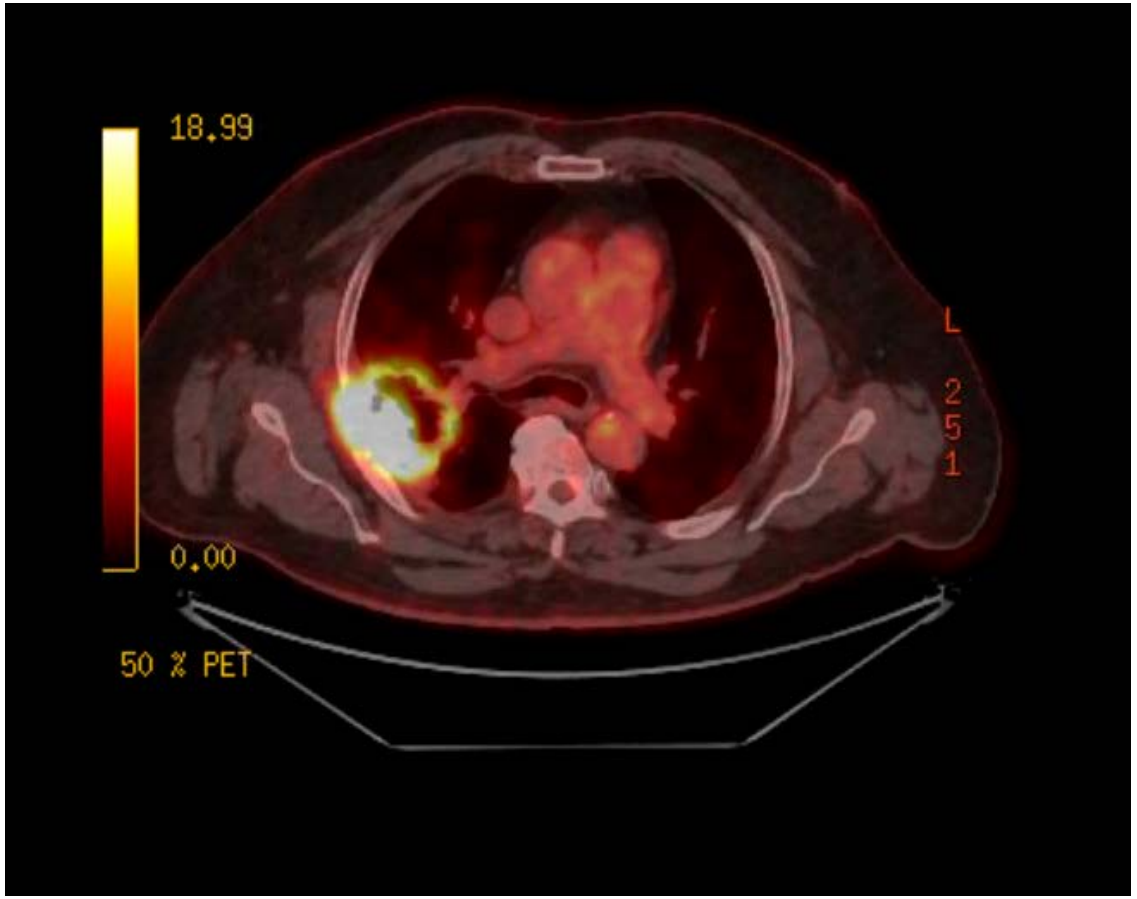
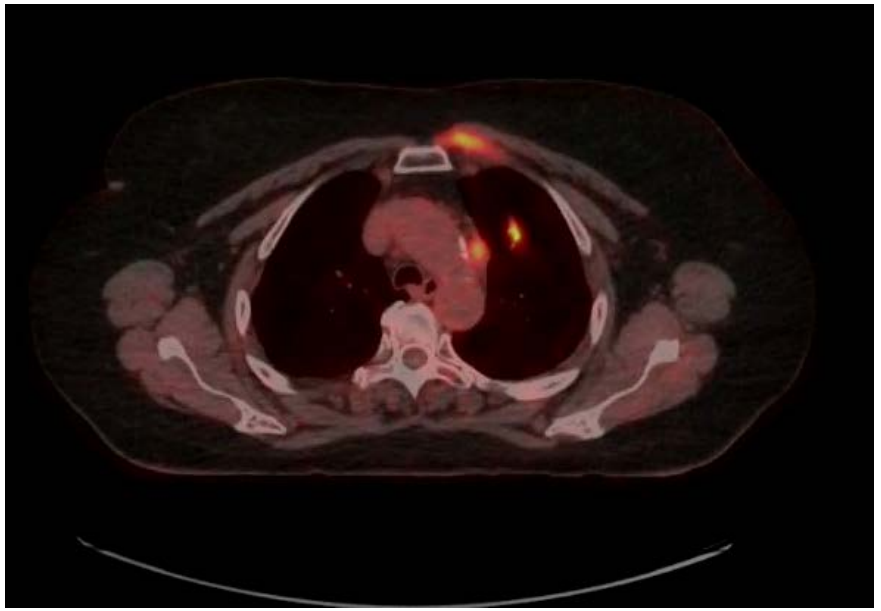
Stage I to stage IIIA

- Treatment goal for patients with stage I to III is curative. Although prognosis is still dismal.
- Between 40-50% of patients with stage IB, 55-70% of patients with stage II and and the great majority of patients with stage IIIA will have recurrent disease if surgery is the only modality of treatment.
- Important to remember that this is a very heterogenous group with likely different prognosis.
- The role of adjuvant chemotherapy was been widely studied and although the benefits are small they have been consistent.

Heterogenous group



T4, NO, MO Stage IIIA



T2, N2, MO Stage IIIA

Staging of the mediastinum.

- Essential to stage via endoscopic bronchial ultrasound or mediastinoscopy prior to a resection.
- Invasive mediastinal staging is indicated for all patients with central tumors; those with potentially resectable T2, T3, and T4 tumors; and those with tumors with enlarged hilar lymph nodes by CT and/or clinical N1 involvement by PET, even if the mediastinum appears clean by both CT and PET criteria.

Clinical evidence for adjuvant treatment.

- Lung Adjuvant Cisplatin Evaluation (LACE) group performed a pooled analysis of individual patient data from the largest cisplatin-based adjuvant trials performed since 1995, including 5 trials, with a total of 4584 patients.
- Established a reduction in mortality of 5.4% at 5 years in patients who received chemotherapy compared with those who did not (hazard ratio [HR] = 0.89; 95% CI, 0.82–0.96; *P* = .005).
- No benefit in stage IA. But present in stage IB (0.93; 95% CI, 0.78 to 1.10) stage II (HR= 0.83; 95% CI, 0.73 to 0.95) and stage III (HR= 0.83; 95% CI, 0.72 to 0.94)

Pignon, JCO, 2008

Clinical evidence

- A follow-up meta-analysis in 2010 confirmed the benefits of adjuvant chemotherapy after evaluating 34 trials and 8447 patients and showing an increase in overall survival by 4% at 5 years with the addition of adjuvant chemotherapy.
- Currently the recommendation is for a platinum doublet.
- Vinorelbine is the most widely studied partner but pemetrexed is preferred for non-squamous and gemcitabine or docetaxel for squamous.
- Cisplatin is preferred. Concern for less activity for carbo. Use of carboplatin is controversial and should only be reserved for patients in special circumstances.

Arriagada, Lancet, 2010.

Stage IB

- Controversial.
- Only study using carboplatin and paclitaxel was negative. Subgroup analysis showed only benefit in patients with large tumors (>more then 4 cm).

Strauss, JCO, 2008.

Stage II and III with N0 disease

- Another area of controversy.
- If there is no lymph node metastasis likely lower risk of distal metastasis.
- Most analysis come from restrospective studies with mixed results.
- However bias plays an important roles in this setting
- Important to know how much lymph nodes were actually resected.

Ahmand, Ann Thorac Surg. 2017

PORT

- If margins are negative there is no role for patients with stage II disease .
- In patients with stage IIIA/IIIB disease, there is a benefit for mediastinal radiation. Most is done sequentially to diminish toxicity after surgery.

Neoadjuvant treatment

- Benefits include prognostication, potential for downstaging.
- However is difficult to establish in which patients this should be the standard.
- Best subset of patients such as those with single station stage IIIA disease, superior sulcus tumors or those with chest wall invasion in the setting of N1 nodal involvement.
- Key, as in the management of all patients with early stage disease, is the use of a multidisciplinary team.

Immunotherapy

- Several clinical trials are establishing the role of immunotherapy both in the neoadjuvant and adjuvant studies.
- Several early phase studies have shown an increase in the rate of complete responses when neoadjuvant immunotherapy is used.
- Nivo or Nivo/Ipi. NCT01822496
- Pembrolizumab. NCT03425643
- Durvalumab. NCT03800134.
- Atezolizumab. NCT03456063

Special populations

- EGFR

ADAURA Phase III double-blind study design

Patients with completely resected stage* IB, II, IIIA NSCLC, with or without adjuvant chemotherapy†

Key inclusion criteria:
- ≥18 years (Japan / Taiwan: ≥20)
- WHO performance status 0 / 1
- Confirmed primary non-squamous NSCLC
- Ex19del / L858R‡
- Brain imaging, if not completed pre-operatively
- Complete resection with negative margins§
- Max. interval between surgery and randomization:
  - 10 weeks without adjuvant chemotherapy
  - 26 weeks with adjuvant chemotherapy

Stratification by:
stage (IB vs II vs IIIA)
EGFRm (Ex19del vs L858R)
race (Asian vs non-Asian)

Randomization 1:1 (N=682)

- Osimertinib 80 mg, once daily
- Placebo, once daily

Planned treatment duration: 3 years

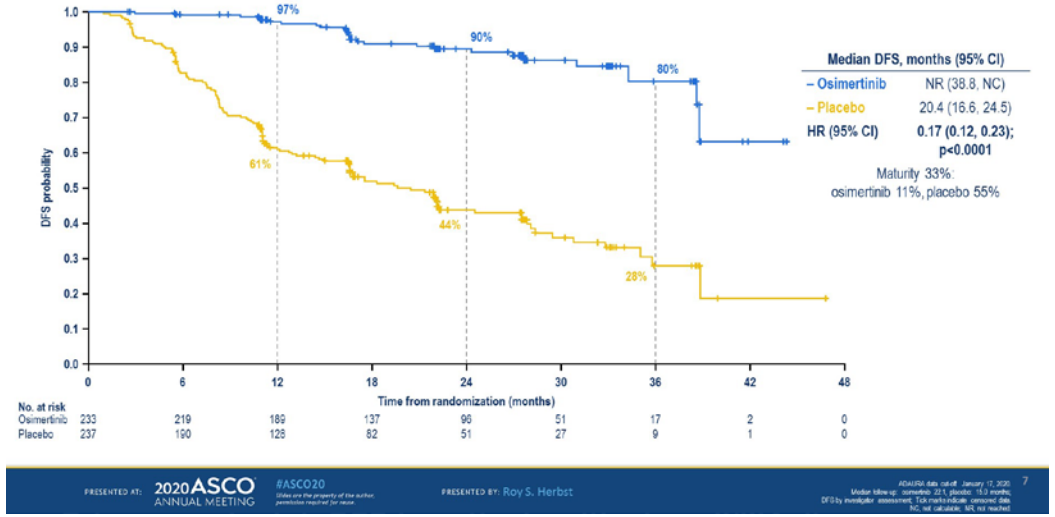
Treatment continues until:
- Disease recurrence
- Treatment completed
- Discontinuation criterion met

Follow up:
- Until recurrence: Week 12 and 24, then every 24 weeks to 5 years, then yearly
- After recurrence: every 24 weeks for 5 years, then yearly

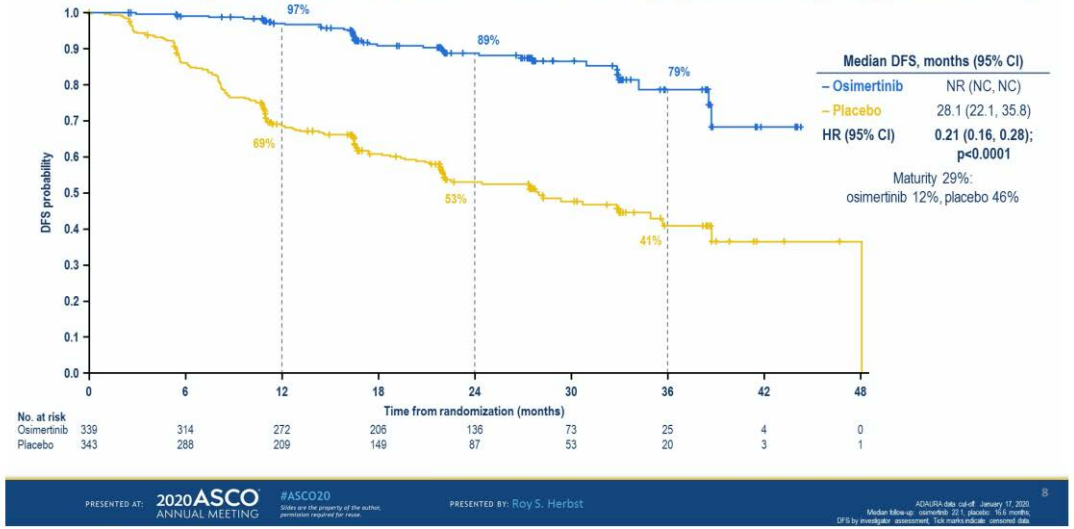
Endpoints
- **Primary**: DFS, by investigator assessment, in stage II/IIIA patients; designed for superiority under the assumed DFS HR of 0.70
- **Secondary**: DFS in the overall population¶, DFS at 2, 3, 4, and 5 years, OS, safety, health-related quality of life

- **Following IDMC recommendation, the study was unblinded early due to efficacy; here we report an unplanned interim analysis**
- **At the time of unblinding the study had completed enrollment and all patients were followed up for at least 1 year**

Primary endpoint: DFS in patients with stage II/IIIA disease



Secondary endpoint: DFS in the overall population (stage IB/II/IIIA)



Presented By Roy Herbst at TBD

So, now what?

- How will OS be affected, how many patients will cross-over?
- Currently designated as a breakthrough therapy by the FDA.
- Osimertinib is well tolerated and has an impressive DFS advantage.
- What is the role of chemotherapy? 😉
- In an ideal world (where consideration for costs doesn't exist) it would be a clear standard.
- Cost is $1,200,000 for 3 years of therapy.
- Gulp. 😳
- This evidence should not be extrapolated to other cancers that have mutations drivers.

Conclusion regarding adjuvant therapy.

- Benefit is small but exists.
- Proper staging is essential.
- Patients should be managed by a multidisciplinary team.
- Cisplatin doublet is the preferred regimen for patients that are candidates.
- Immunotherapy and targeted therapy are likely to play a role in the near future.

Locally advanced disease

- For patients with inoperable stage II disease, multistation stage IIIA or stage IIIB disease the standard of care is chemotherapy and radiation.
- Several clinical trials have established that concurrent therapy offers a survival advantage over sequential treatment. At the price of increase adverse events.
- Important for patients who have poor PS.

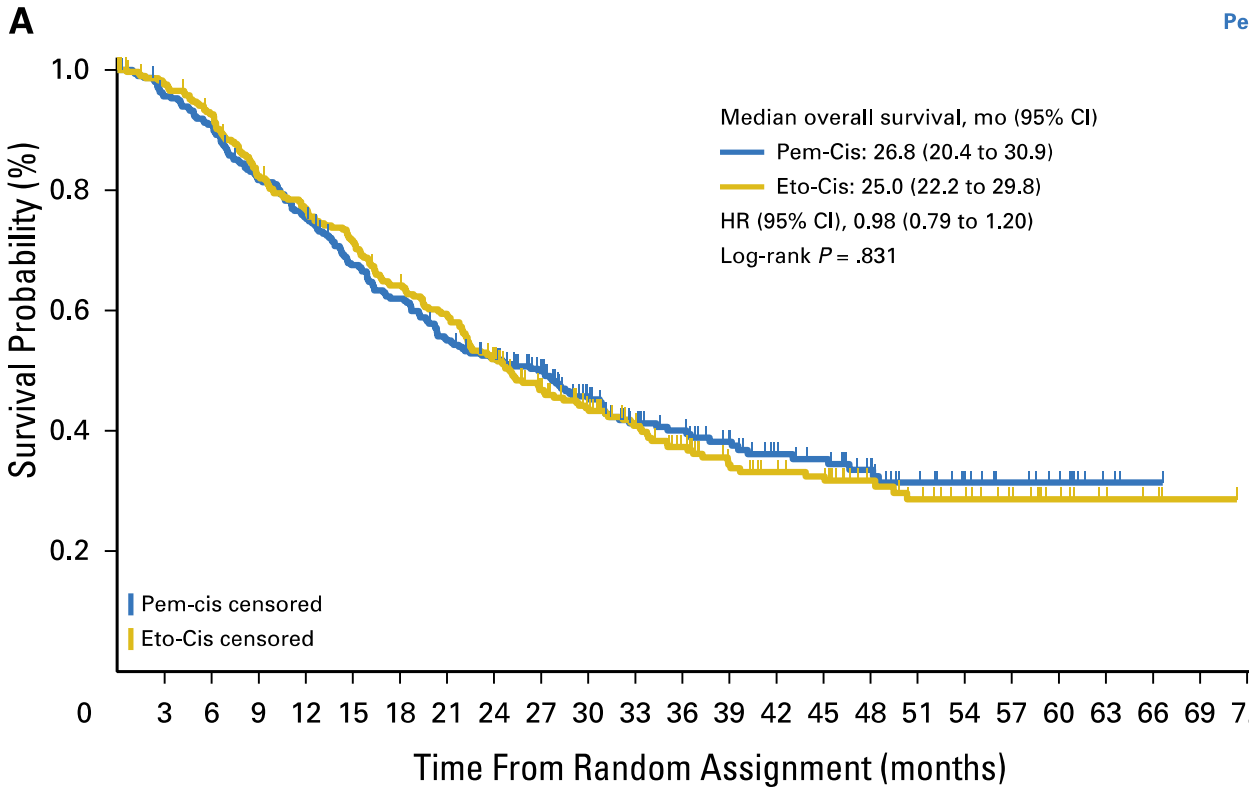
Role of higher dose of radiation

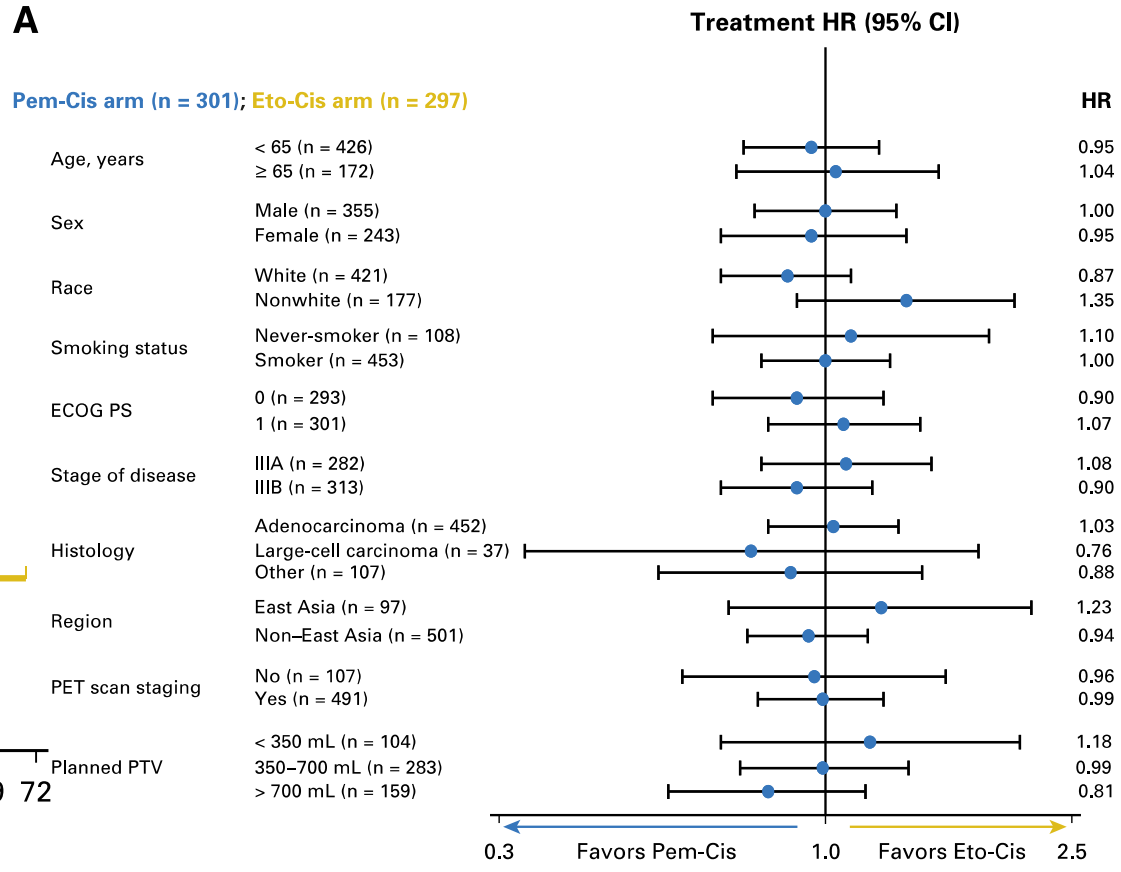
- Increased dose of radiation is not beneficial. RTOG 0617 randomized patients to either standard-dose (60 Gy/30 daily fractions) or high-dose RT (74 Gy/37 daily fractions).
- High-dose (74 Gy) RT was associated with a shorter survival and an increased risk of death compared with conventional-dose (60 Gy) RT (median, 20 versus 29 months; HR 1.38, 95% CI 1.09-1.76).

Chemotherapy

- Platinum-doublet is the standard.
- Long debate as to what chemotherapy is the best partner along side with radiation.
- Before the era of immunotherapy:
- Cisplatin-etoposide likely equal to carboplatin and paclitaxel.
- More adverse events in the former and need for additional consolidation in the latter.
- Few randomized studies have actually been conducted.
- PROCLAIM. Compared EP vs cisplatin-pemetrexed in 598 patients

PROCLAIM





Senana, JCO, 2016

Adverse events

- Patients in the pemetrexed arm received consolidation pemetrexed alone.

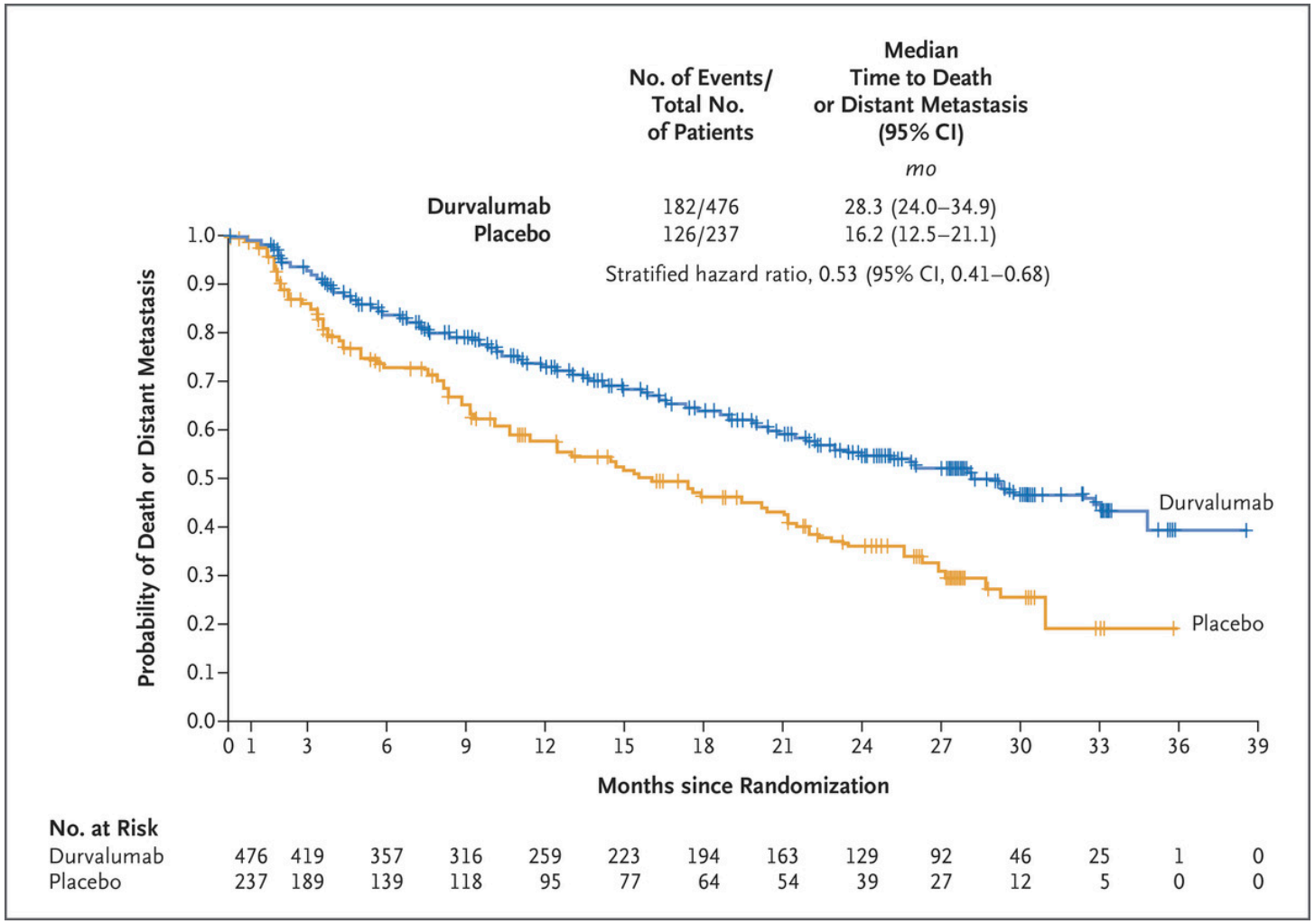
Senana, JCO, 2016

	Overall Study			
	Arm A (n = 283)		Arm B (n = 272)	
CTCAE Term	Any Gr*	Gr 3–4	Any Gr*	Gr 3–4
≥ 1 CTCAE	281 (99.3)	181 (64.0)	269 (98.9)	**209 (76.8)**
Laboratory				
Neutrophils/granulocytes (ANC/AGC)	121 (42.8)	69 (24.4)	**149 (54.8)**	**121 (44.5)**
Hemoglobin	114 (40.3)	25 (8.8)	124 (45.6)	37 (13.6)
Leukocytes (total WBC)	104 (36.7)	64 (22.6)	111 (40.8)	82 (30.1)
Lymphopenia	61 (21.6)	51 (18.0)	52 (19.1)	40 (14.7)
Platelets	55 (19.4)	19 (6.7)	**85 (31.3)**	29 (10.7)
Potassium, serum low	18 (6.4)	8 (2.8)	29 (10.7)	9 (3.3)
Nonlaboratory				
Nausea	**170 (60.1)**	10 (3.5)	137 (50.4)	11 (4.0)
Fatigue	154 (54.4)	17 (6.0)	146 (53.7)	13 (4.8)
Dysphagia	143 (50.5)	23 (8.1)	115 (42.3)	18 (6.6)
Esophagitis	136 (48.1)	44 (15.5)	138 (50.7)	56 (20.6)
Vomiting	110 (38.9)	11 (3.9)	90 (33.1)	17 (6.3)
Anorexia	91 (32.2)	11 (3.9)	79 (29.0)	10 (3.7)
Rash: dermatitis associated with radiation‡	77 (27.2)	0 (0.0)	64 (23.5)	4 (1.5)
Constipation	71 (25.1)	1 (0.4)	72 (26.5)	4 (1.5)
Mucositis/stomatitis‡	**62 (21.9)**	3 (1.1)	40 (14.7)	5 (1.8)
Pneumonitis	**48 (17.0)**	5 (1.8)	29 (10.7)	7 (2.6)
GI pain‡	**46 (16.3)**	5 (1.8)	23 (8.5)	2 (0.7)
Weight loss	46 (16.3)	3 (1.1)	45 (16.5)	1 (0.4)
Cough	46 (16.3)	1 (0.4)	33 (12.1)	1 (0.4)
Infection‡	42 (14.8)	8 (2.8)	33 (12.1)	7 (2.6)
Dyspnea	**42 (14.8)**	6 (2.1)	23 (8.5)	4 (1.5)
Diarrhea	38 (13.4)	3 (1.1)	40 (14.7)	5 (1.8)
Heartburn/dyspepsia	38 (13.4)	4 (1.4)	30 (11.0)	1 (0.4)
Neuropathy, sensory	37 (13.1)	0 (0.0)	**56 (20.6)**	0 (0.0)
Pulmonary/upper respiratory pain‡	35 (12.4)	6 (2.1)	34 (12.5)	5 (1.8)
Pain other than pulmonary or GI‡	33 (11.7)	1 (0.4)	**53 (19.5)**	4 (1.5)
Rash‡	33 (11.7)	0 (0.0)	27 (9.9)	1 (0.4)
Renal event‡	**30 (10.6)**	5 (1.8)	16 (5.9)	4 (1.5)
Fever (in the absence of neutropenia)	29 (10.2)	0 (0.0)	24 (8.8)	1 (0.4)
Dizziness	29 (10.2)	2 (0.7)	21 (7.7)	1 (0.4)
Dysgeusia	29 (10.2)	0 (0.0)	21 (7.7)	0 (0.0)
Alopecia	23 (8.1)	0 (0.0)	**98 (36.0)**	1 (0.4)
Febrile neutropenia	16 (5.7)	15 (5.3)	28 (10.3)	26 (9.6)

Role of immunotherapy

- PACIFIC study was the most important game changer.
- 713 patients were randomized 2:1 to receive durvalumab after the concurrent phase of radiation.
- Chemotherapy partners was dealer’s choice but no consolidation treatment was allowed.

Updated Analysis of Time to Death or Distant Metastasis in the Intention-to-Treat Population.



SJ Antonia et al. N Engl J Med 2018;379:2342-2350.

Adverse Events of Any Cause.

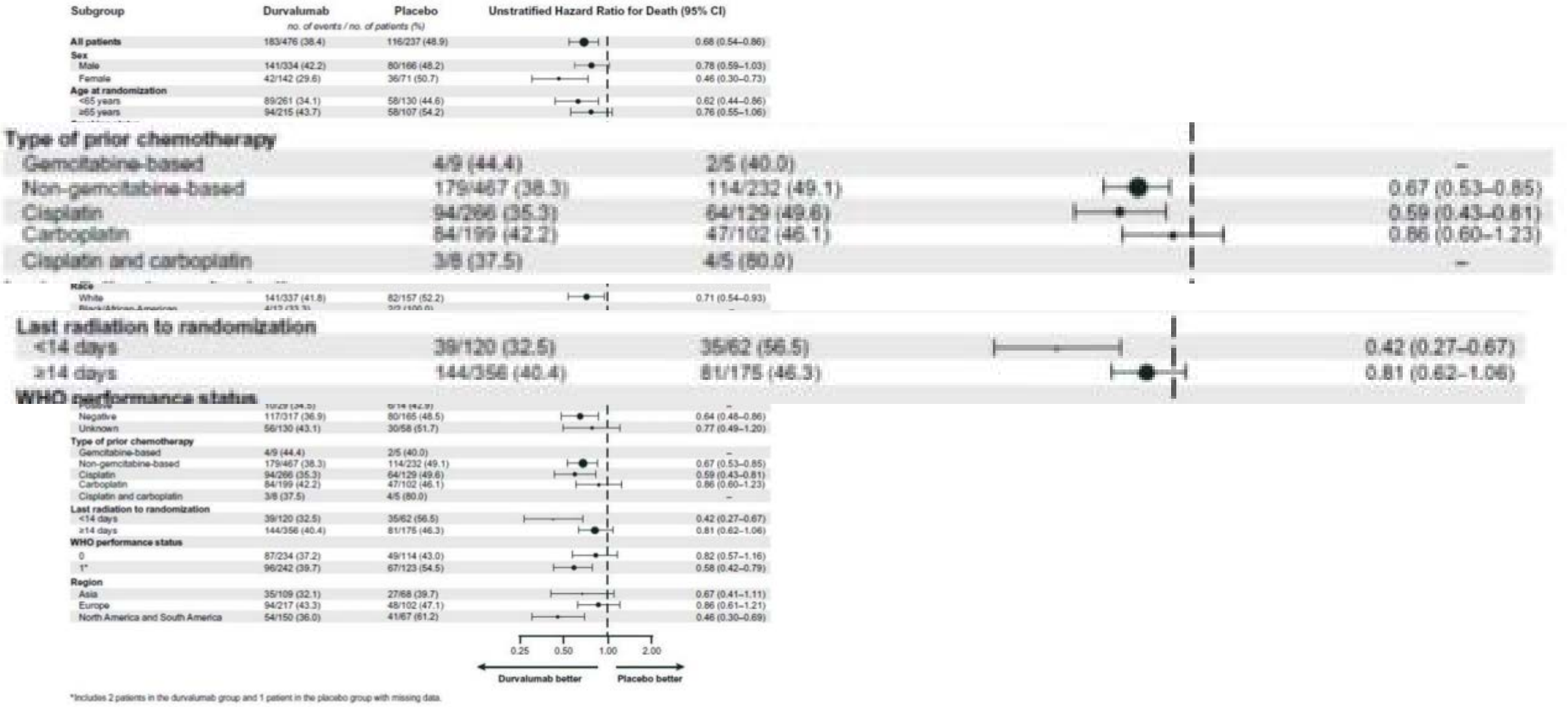
Table 3. Adverse Events of Any Cause.

Event	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade*	Grade 3 or 4	Any Grade*	Grade 3 or 4
	number of patients with event (percent)			
Any event	460 (96.8)	142 (29.9)	222 (94.9)	61 (26.1)
Cough	168 (35.4)	2 (0.4)	59 (25.2)	1 (0.4)
Pneumonitis or radiation pneumonitis†	161 (33.9)	16 (3.4)	58 (24.8)	6 (2.6)
Fatigue	113 (23.8)	1 (0.2)	48 (20.5)	3 (1.3)
Dyspnea	106 (22.3)	7 (1.5)	56 (23.9)	6 (2.6)
Diarrhea	87 (18.3)	3 (0.6)	44 (18.8)	3 (1.3)
Pyrexia	70 (14.7)	1 (0.2)	21 (9.0)	0
Decreased appetite	68 (14.3)	1 (0.2)	30 (12.8)	2 (0.9)
Nausea	66 (13.9)	0	31 (13.2)	0
Pneumonia	62 (13.1)	21 (4.4)	18 (7.7)	9 (3.8)
Arthralgia	59 (12.4)	0	26 (11.1)	0
Pruritus	58 (12.2)	0	11 (4.7)	0
Rash	58 (12.2)	1 (0.2)	17 (7.3)	0
Upper respiratory tract infection	58 (12.2)	1 (0.2)	23 (9.8)	0
Constipation	56 (11.8)	1 (0.2)	20 (8.5)	0
Hypothyroidism	55 (11.6)	1 (0.2)	4 (1.7)	0
Headache	52 (10.9)	1 (0.2)	21 (9.0)	2 (0.9)
Asthenia	51 (10.7)	3 (0.6)	31 (13.2)	1 (0.4)
Back pain	50 (10.5)	1 (0.2)	27 (11.5)	1 (0.4)
Musculoskeletal pain	39 (8.2)	3 (0.6)	24 (10.3)	1 (0.4)
Anemia	36 (7.6)	14 (2.9)	25 (10.7)	8 (3.4)

Event†	Durvalumab (N=475)		Placebo (N=234)	
	Any Grade‡	Grade 3 or 4	Any Grade‡	Grade 3 or 4
	number of patients with an event (percent)			
Any event	115 (24.2)	16 (3.4)	19 (8.1)	6 (2.6)
Pneumonitis	51 (10.7)	8 (1.7)	16 (6.8)	6 (2.6)
Hypothyroidism	44 (9.3)	1 (0.2)	3 (1.3)	0
Hyperthyroidism	13 (2.7)	0	0	0
Rash	5 (1.1)	2 (0.4)	1 (0.4)	0
Dermatitis	5 (1.1)	0	0	0

Antonia SJ et al. N Engl J Med 2017;377:1919-1929.

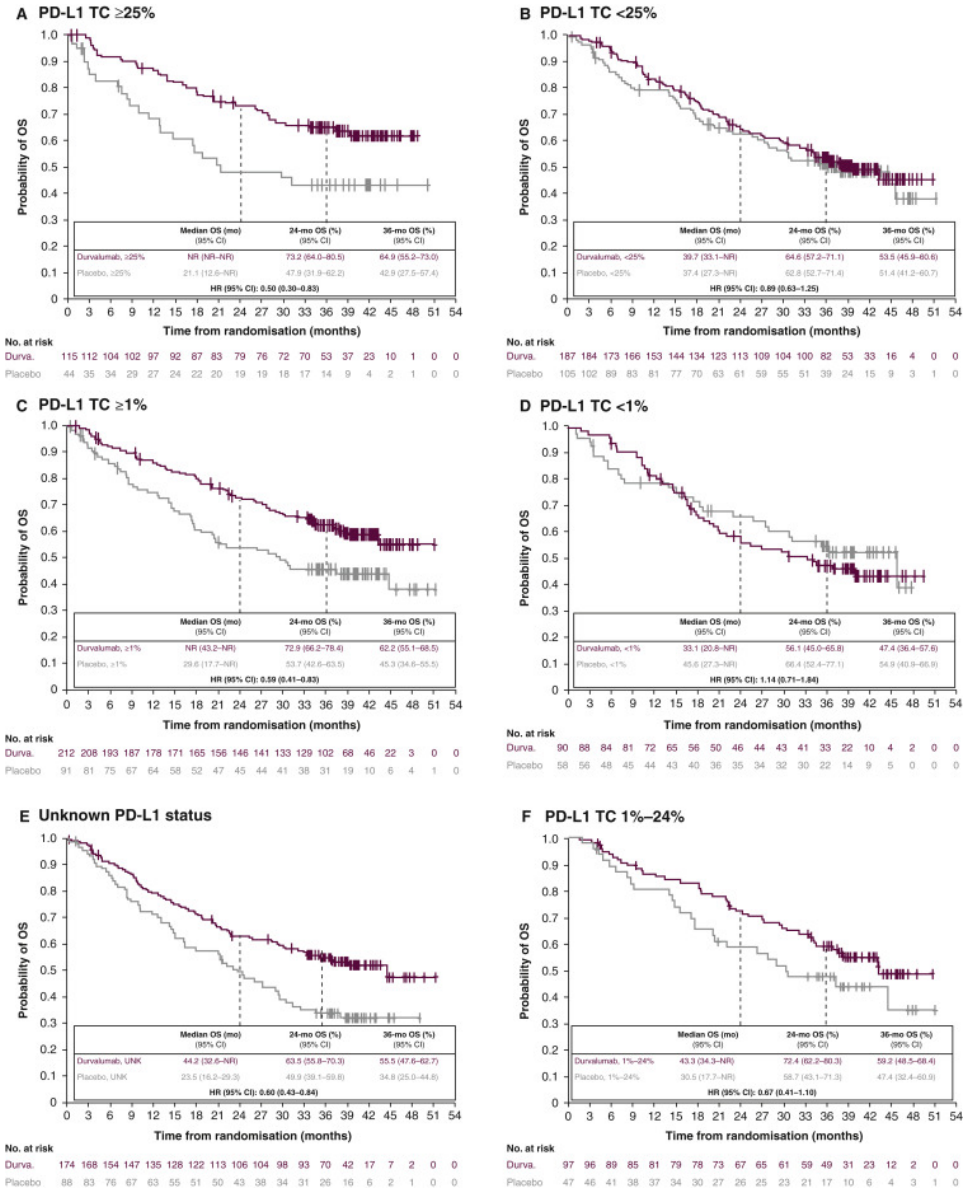
Subgroup analysis.



*Includes 2 patients in the durvalumab group and 1 patient in the placebo group with missing data.

PDL1 status.

- OS favored durvalumab, versus placebo, across all PD-L1 subgroups but one, patients with TC <1% (HR, 1.36; 95% CI, 0.79–2.34).
- However this is not a proper endpoint and was done post-hoc.



Paz-Ares. Ann Oncol. 2020

Special populations.

EGFR mutation				
Positive	10/29 (34.5)	6/14 (42.9)		–
Negative	117/317 (36.9)	80/165 (48.5)		0.64 (0.46–0.86)
Unknown	56/130 (43.1)	30/58 (51.7)		0.77 (0.49–1.20)

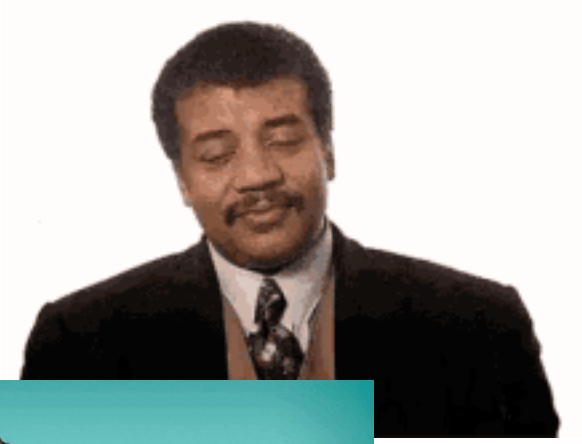
- Patients with driver mutations.
- Really controversial area.
- Do this patients benefit from immunotherapy?
- Does prior immunotherapy put patients at risk for pneumonitis if a TKI is subsequently needed?
- Is there any role for using targeted therapy in this setting?

New trials are being done.

- NCT01822496. An NRG trial was designed that used crizotinib and erlotinib before chemoradiaiton.
- NCT03521154. LAURA study. Osimertinib after chemoradiation.
- Patients with less common drivers. ROS1, BRAF, MET. Data free zone.

Post treatment surveillance.

- No consensus as to what is ideal.
- Could be tailored to what is received as the risk of recurrence.
- Our groups typical schedule is q3 months visit with labs and PE and imaging done q 6 months during the first 2 years.



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Small Cell Lung Cancer. The basics

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SCCA

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Small Cell Lung Cancer

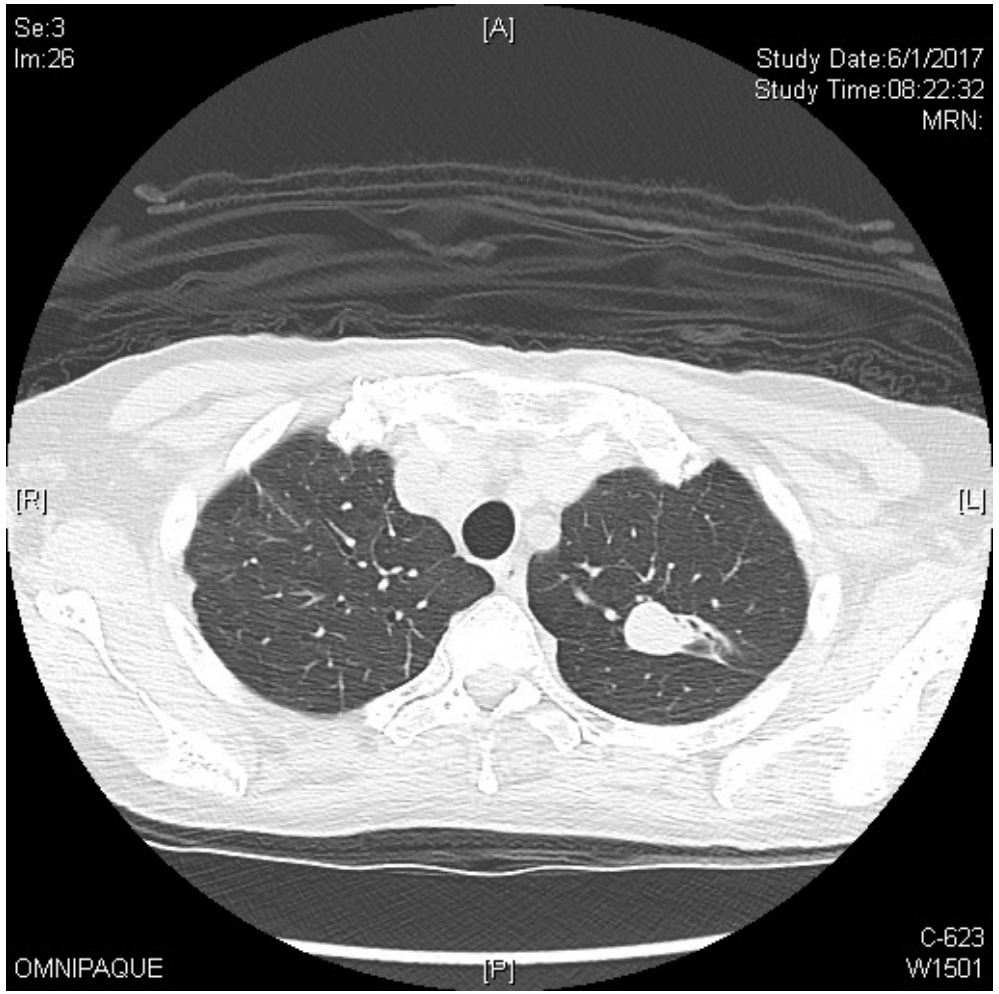
- Accounts for 10-15% of lung tumors.
- >30 K patients diagnosed every year in the US.
- Most patients present with metastatic disease.
- Survival of untreated disease with weeks-months.
- Most patients respond well to chemotherapy initially
- With treatment median OS 8-13 months. With <5% of patients alive within 2 years.

Staging

- For treatment purposes its divided between limited and extensive stage. Depending on the radiation field.
- TNM follows that of NSCLC.

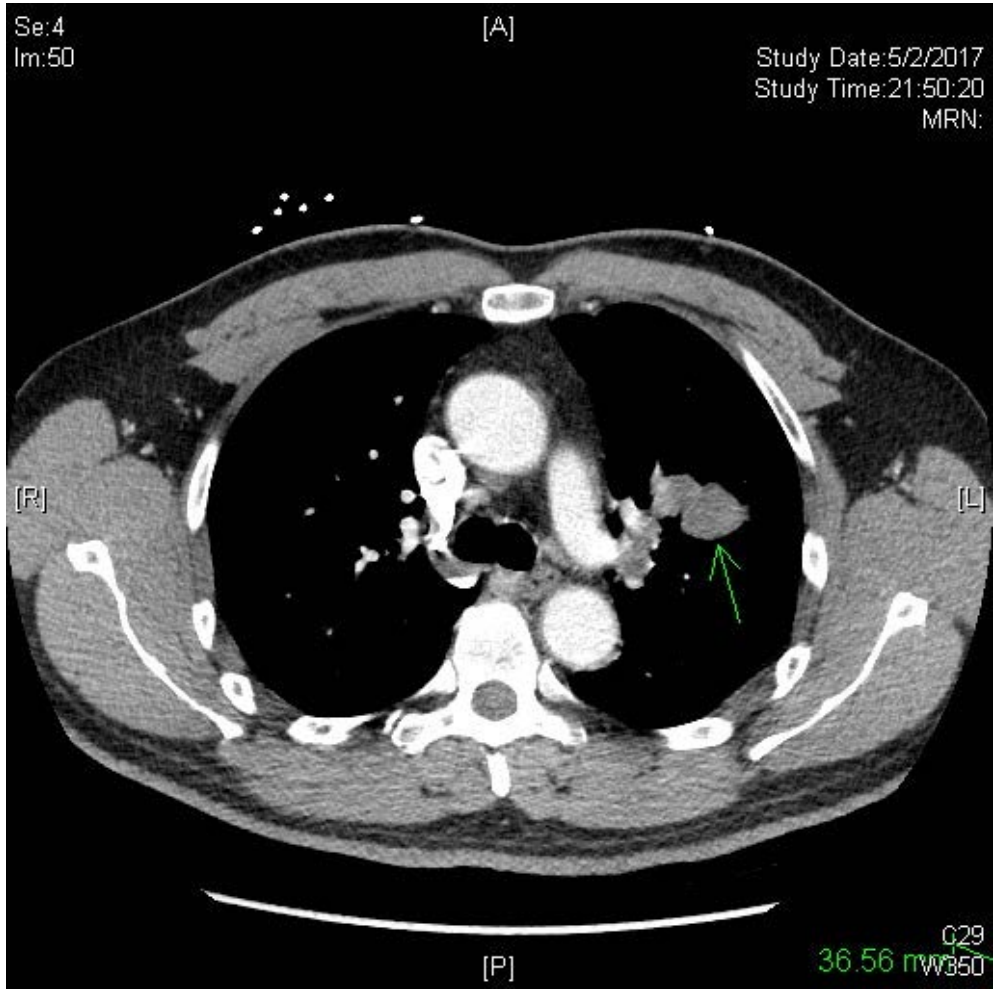
Stage 1

- 78 yo M, no symptoms. Incidental nodule found for unrelated reasons.
- PET no evidence of disease elsewhere.
- Taken to surgery.
- Histology reveals SCLC
- Now what?
- Adjuvant platinum based treatment.



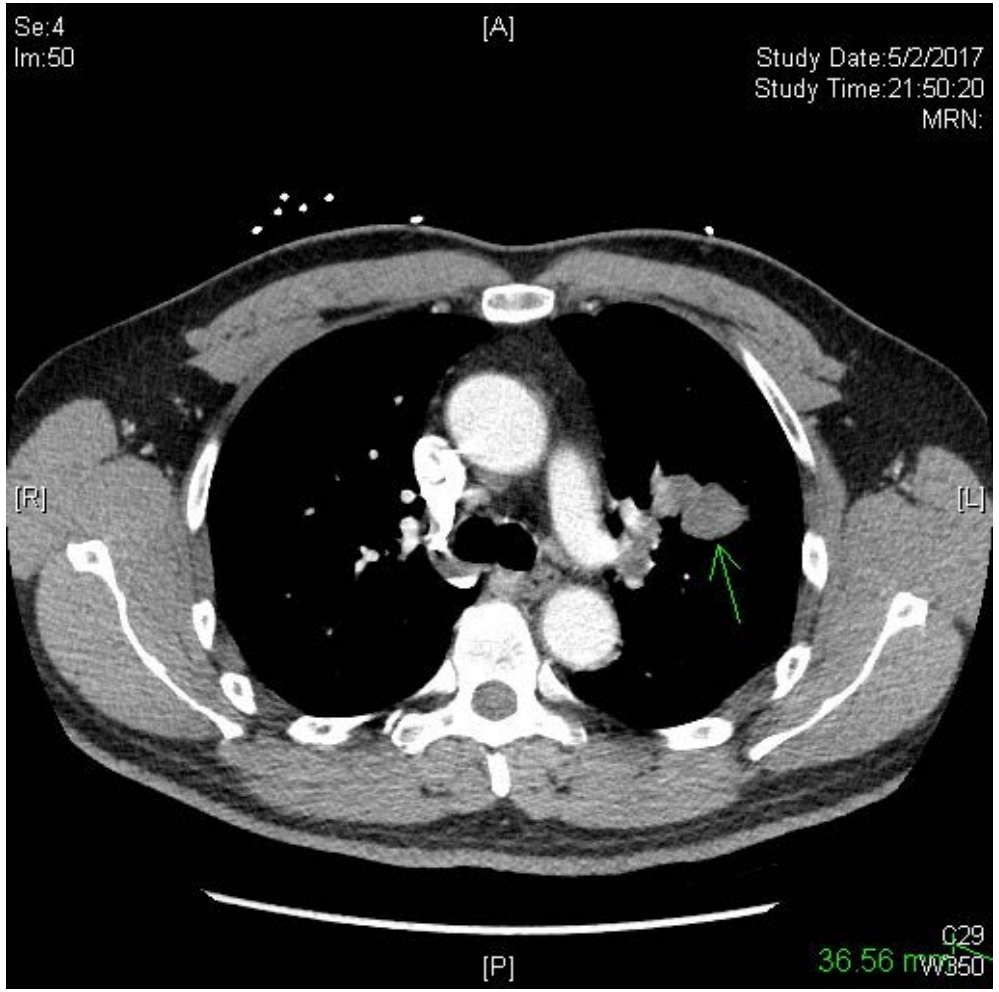
Limited stage

- 58 yo M presents with hemoptysis. Imaging reveals a midlung mass.
- Biopsy shows SCLC

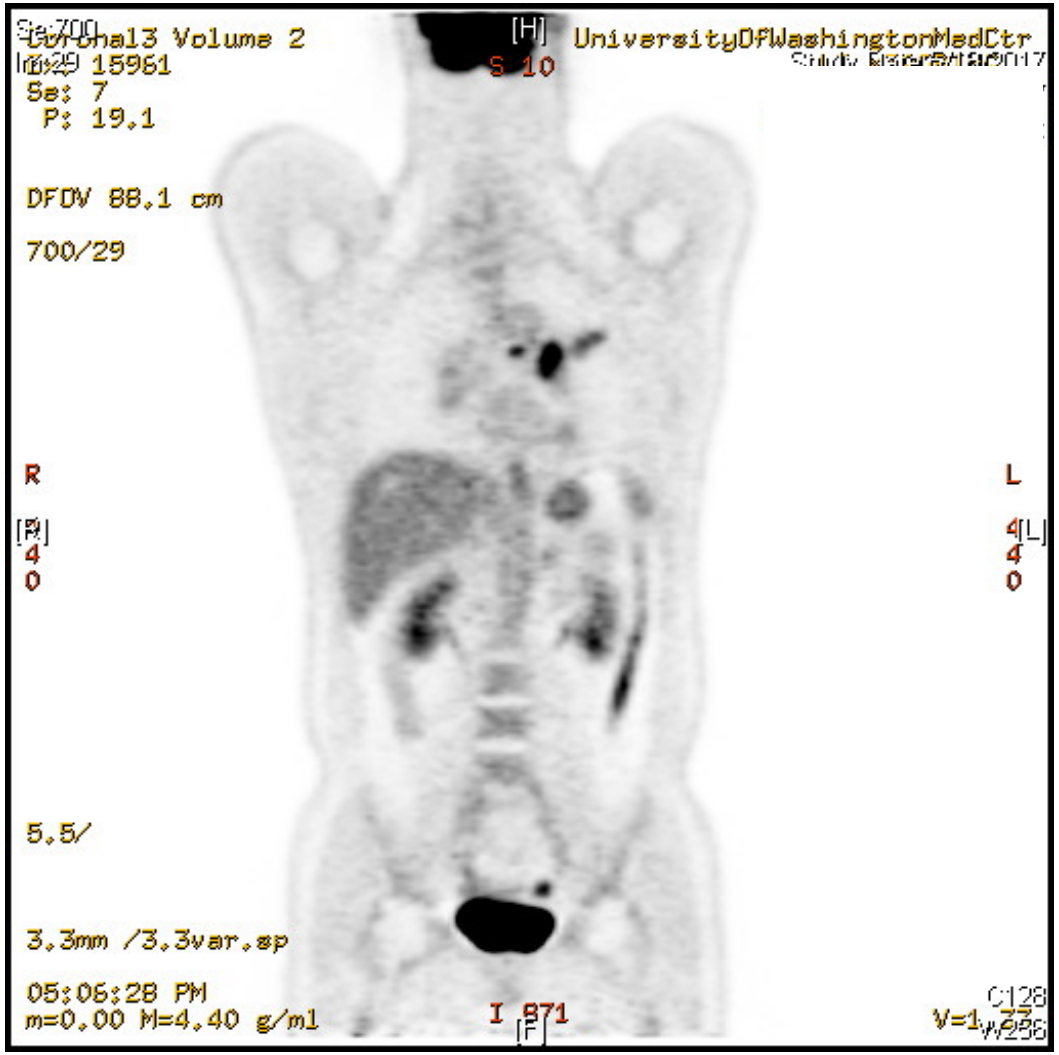


Workup should include

- CT scan: Chest and abdomen
- PET scan/Bone scan.
- If there is no evidence of distant metastatic disease.
- MRI brain.
- Bone marrow if unexplained hematologic abnormality is present.



PET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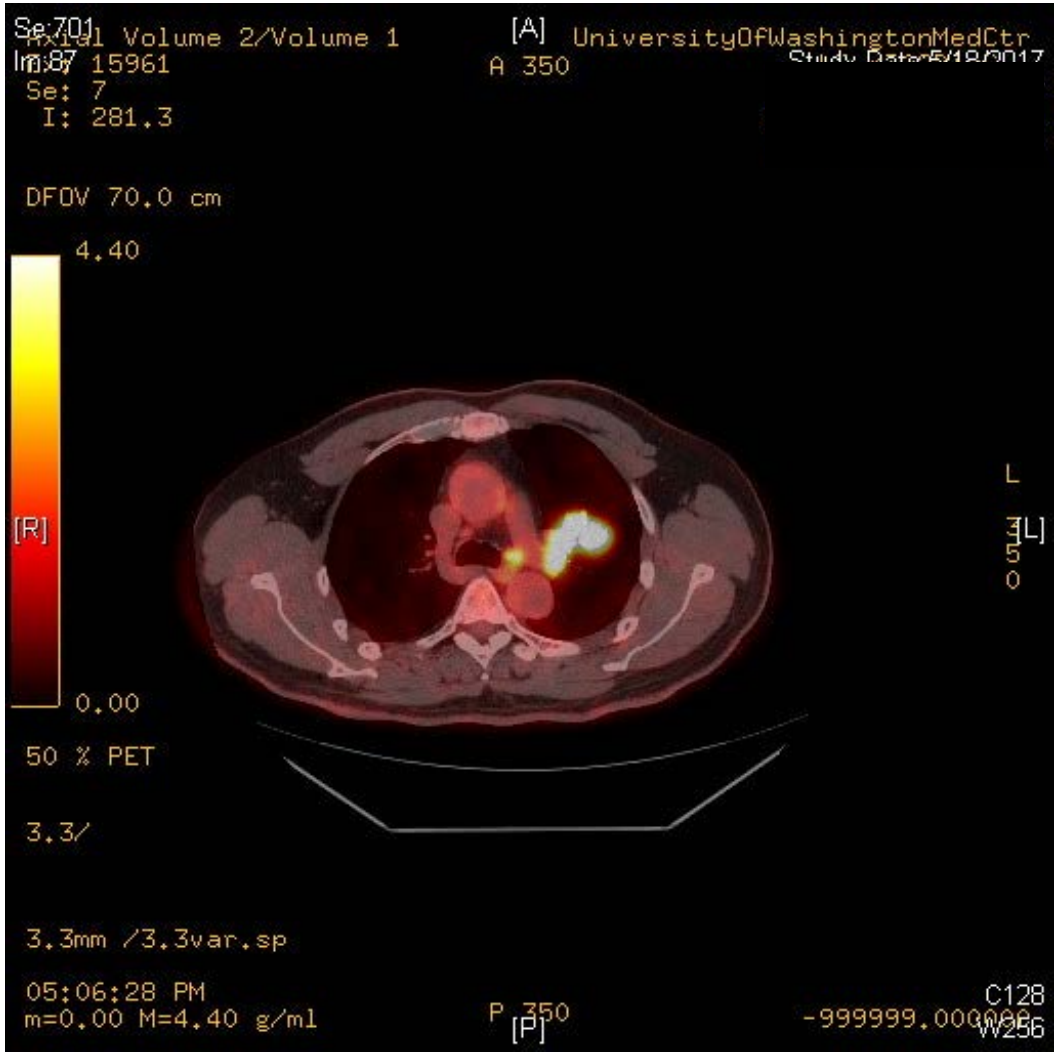
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P 350
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C128
W256

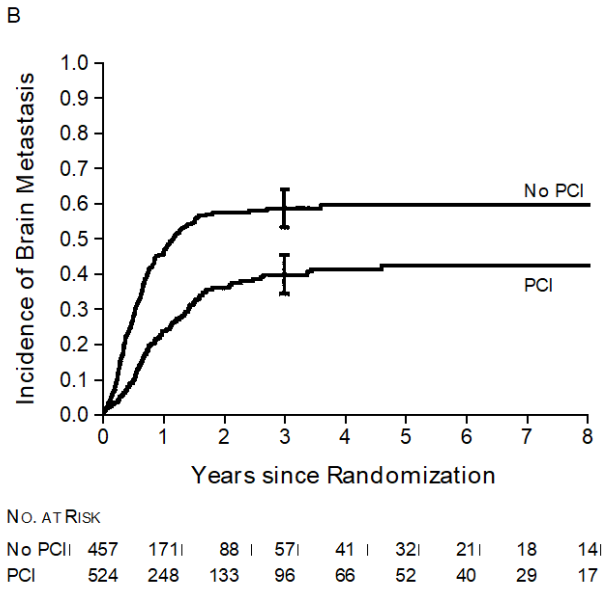
Treatment

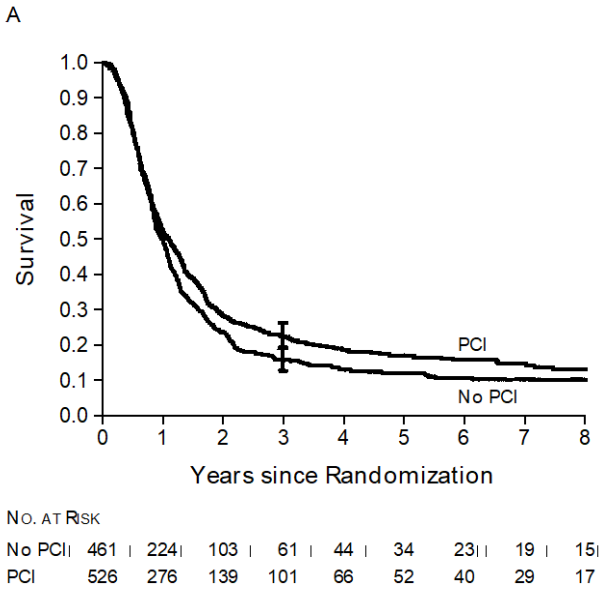
- Main stay of treatment should be chemotherapy and radiation.
- Cisplatin and Etoposide is SOC.
- Cis day 1. Etop Days1-3 q 21 days
- Carboplatin can be considered. Although controversial.
- Radiation can start during second cycle.
- Once vs twice daily radiation is currently controversial.

Rossi, et. al Carboplatin- or cisplatin-based chemotherapy in first-line treatment of small-cell lung cancer: the COCIS meta-analysis of individual patient data. JCO. 2012. PMID. 22473169

After Chemoradiation

- PCI. Associated with a clear survival benefit. RR 0.84; 95% CI 0.73-0.97, which corresponded to an increase in the three-year survival rate from 15.3 to 20.7





Auperin, N Engl J Med. 1999. PMID 10441603

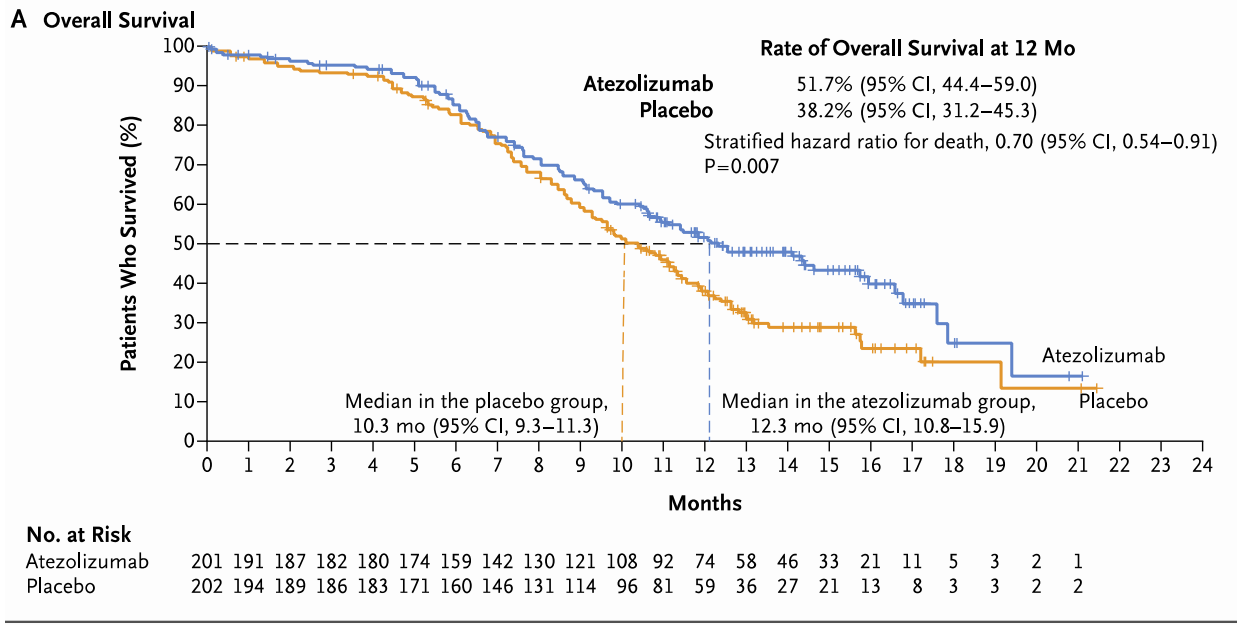
Extensive Stage.

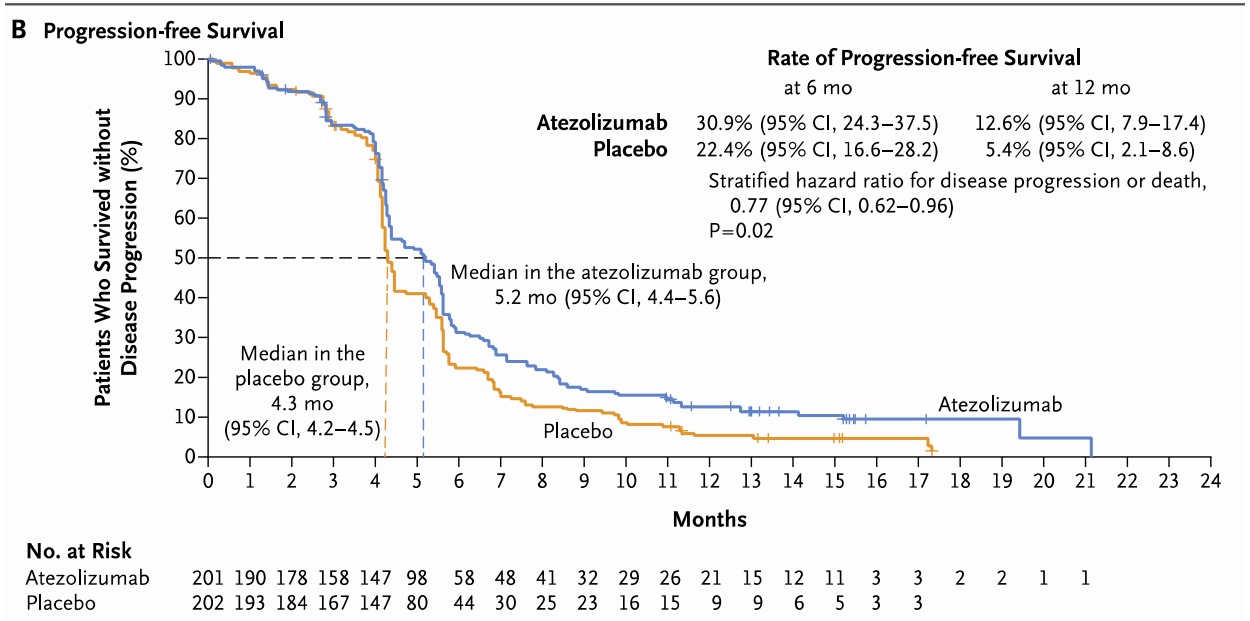
- Rapidly growing disease.
- Post obstructive pneumonia.
- SVC Syndrome.
- Para neoplastic phenomena
  - Hyponatremia
  - Eaton-Lambert
  - ACTH secretion
- Bone marrow infiltration.

Treatment for extensive stage.

- Main treatment challenge is decide when to start treatment.
- Are symptoms due to disease vs poor overall health.
  - Poor PS.
  - Liver failure.
  - BM infiltrations
- New current standard of care is chemotherapy and immunotherapy concurrently.

Chemoimmunotherapy





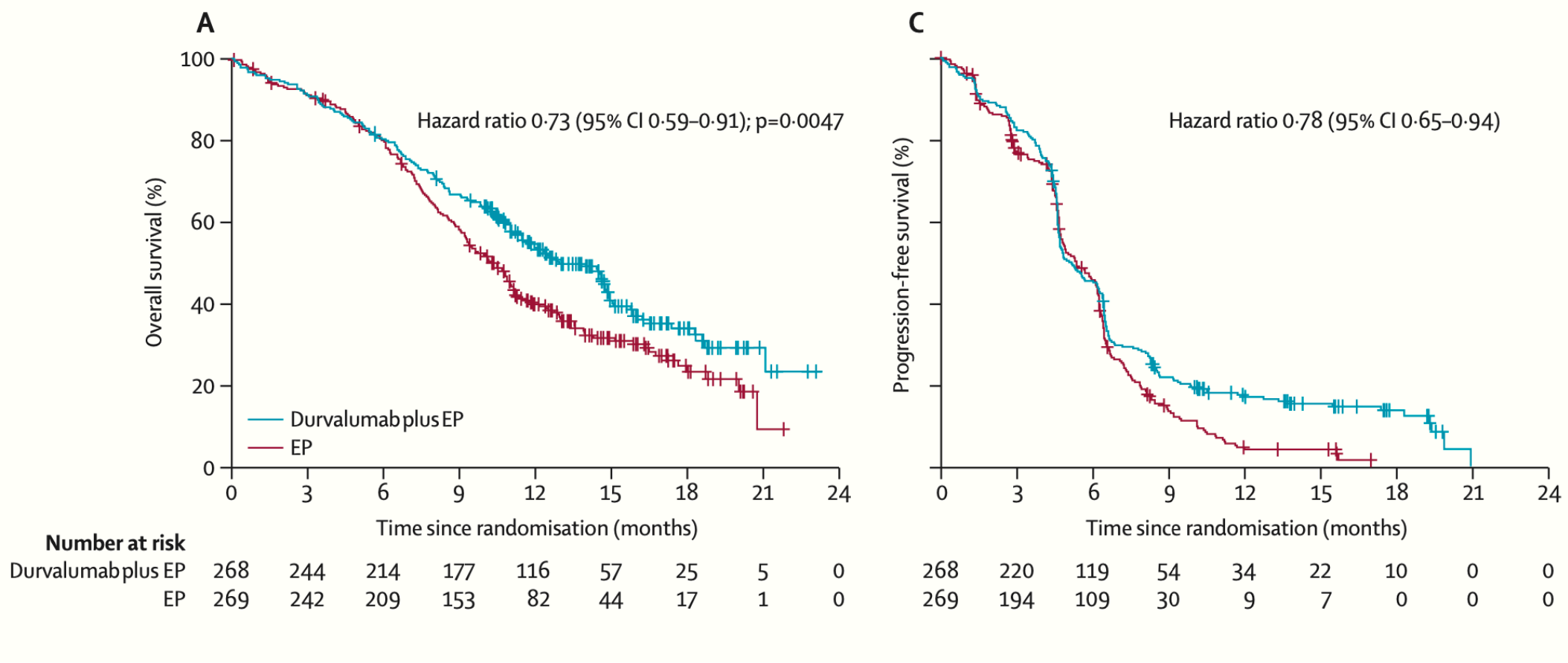
Horn, NEJM 2018

- No increase in AE in patients treated with atezo.

Table 3. Adverse Events Related to the Trial Regimen.*

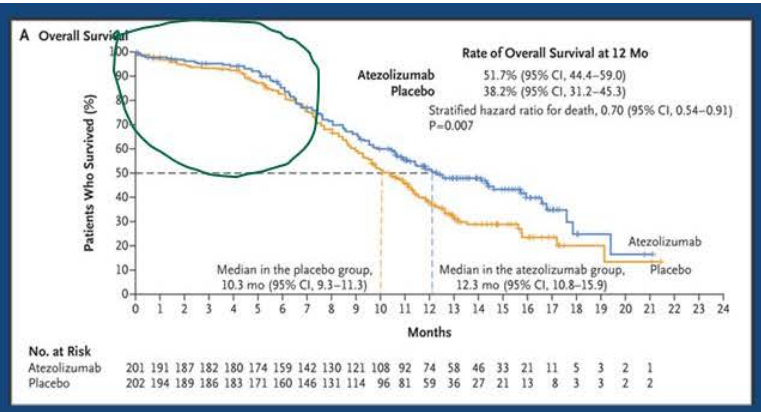
Event	Atezolizumab Group (N = 198)			Placebo Group (N = 196)		
	Grade 1 or 2	Grade 3 or 4	Grade 5	Grade 1 or 2	Grade 3 or 4	Grade 5
	number of patients (percent)					
Any adverse event	73 (36.9)	112 (56.6)	3 (1.5)	68 (34.7)	110 (56.1)	3 (1.5)
Adverse events with an incidence of ≥10% in any grade category or events of grade 3 or 4 with an incidence of ≥2% in either group						
Neutropenia	26 (13.1)	45 (22.7)	1 (0.5)	20 (10.2)	48 (24.5)	0
Anemia	49 (24.7)	28 (14.1)	0	41 (20.9)	24 (12.2)	0
Alopecia	69 (34.8)	0	0	66 (33.7)	0	0
Nausea	62 (31.3)	1 (0.5)	0	58 (29.6)	1 (0.5)	0
Fatigue	39 (19.7)	3 (1.5)	0	37 (18.9)	1 (0.5)	0
Decreased neutrophil count	7 (3.5)	28 (14.1)	0	12 (6.1)	33 (16.8)	0
Decreased appetite	39 (19.7)	2 (1.0)	0	26 (13.3)	0	0
Thrombocytopenia	12 (6.1)	20 (10.1)	0	14 (7.1)	15 (7.7)	0
Decreased platelet count	17 (8.6)	7 (3.5)	0	21 (10.7)	7 (3.6)	0
Vomiting	25 (12.6)	2 (1.0)	0	19 (9.7)	3 (1.5)	0
Constipation	19 (9.6)	1 (0.5)	0	25 (12.8)	0	0
Leukopenia	15 (7.6)	10 (5.1)	0	10 (5.1)	8 (4.1)	0
Decreased white-cell count	10 (5.1)	6 (3.0)	0	16 (8.2)	9 (4.6)	0
Diarrhea	15 (7.6)	4 (2.0)	0	18 (9.2)	1 (0.5)	0
Febrile neutropenia	0	6 (3.0)	0	0	12 (6.1)	0
Infusion-related reaction	6 (3.0)	4 (2.0)	0	9 (4.6)	1 (0.5)	0

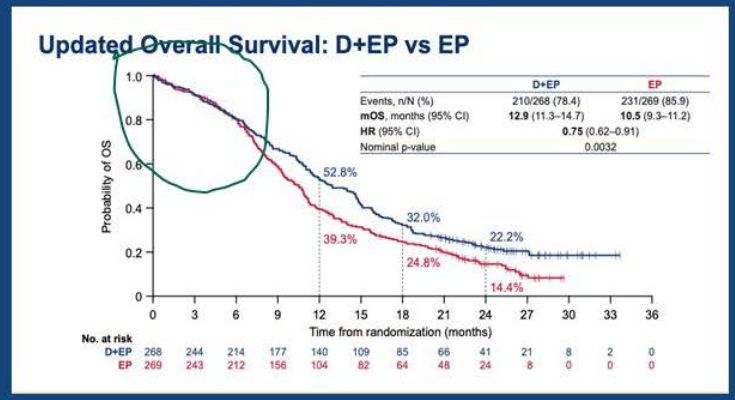
Results confirmed with durvalumab

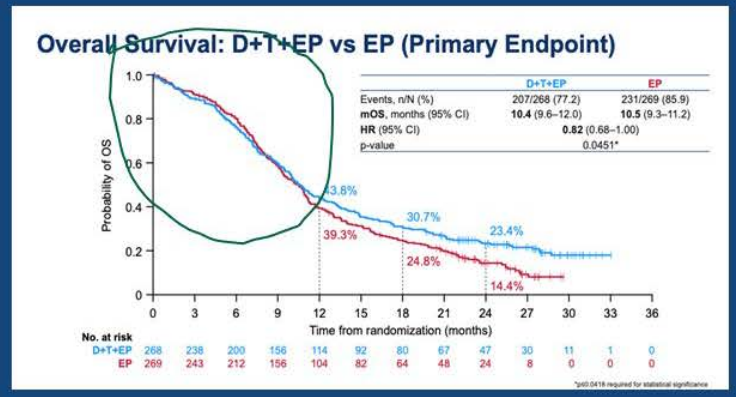


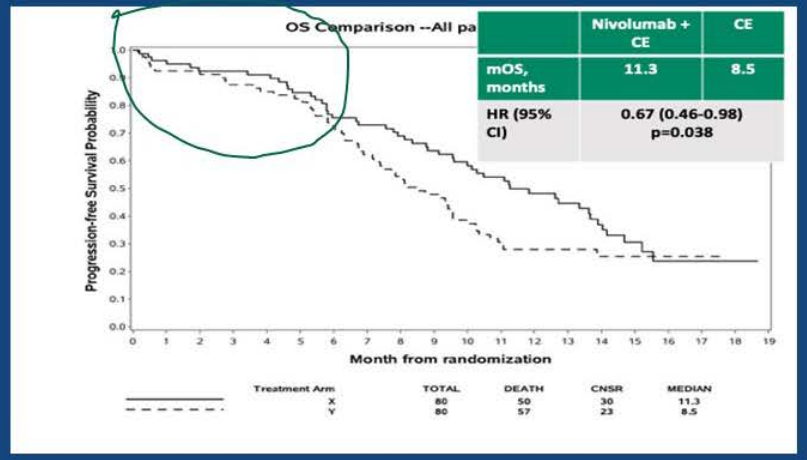
Paz-Ares, Lancet 2019

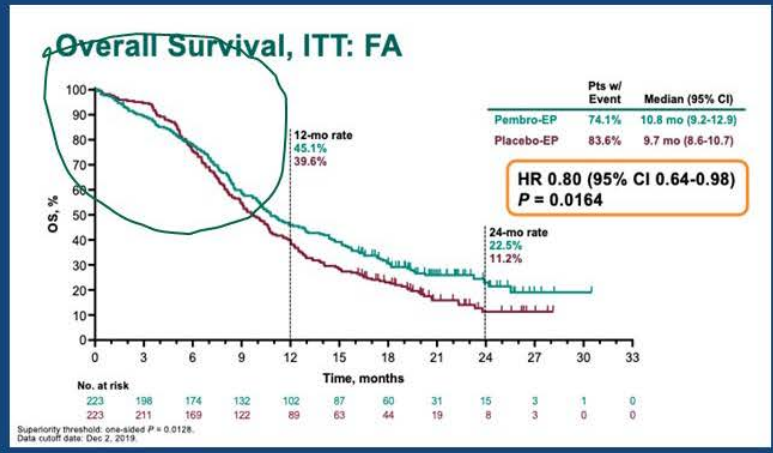
And Nivo and Pembro











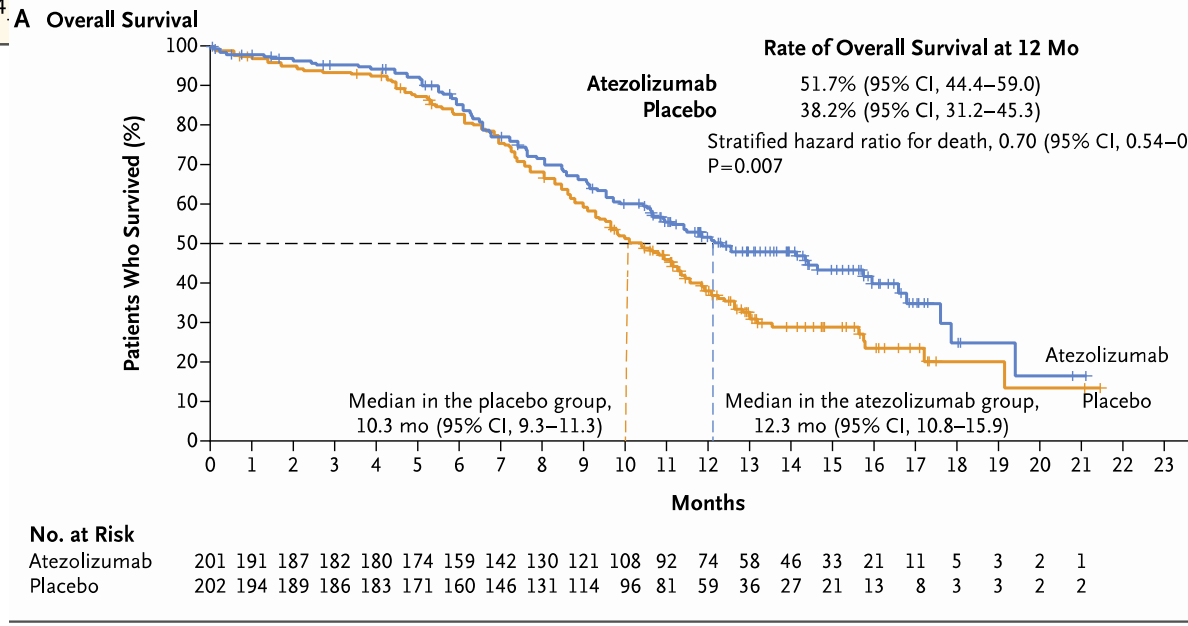
Chemoimmunotherapy

Table 2. Response Rate, Duration of Response, and Disease Progression.*

Variable	Atezolizumab Group (N = 201)	Placebo Group (N = 202)
Objective confirmed response†	121 (60.2 [53.1–67.0])	130 (64.4 [57.3–71.0])
Complete response — no. (% [95% CI])	5 (2.5 [0.8–5.7])	2 (1.0 [0.1–3.5])
Partial response — no. (% [95% CI])	116 (57.7 [50.6–64.6])	128 (63.4 [56.3–70.0])
Median duration of response (range) — mo‡	4.2 (1.4§–19.5)	3.9 (2.0–16.1§)
Ongoing response at data cutoff — no./total no. (%)	18/121 (14.9)	7/130 (5.4)
Stable disease — no. (% [95% CI])	42 (20.9 [15.5–27.2])	43 (21.3 [15.9–27.6])
Progressive disease — no. (% [95% CI])	22 (10.9 [7.0–16.1])	14 (6.9 [3.8–11.4]

Concerns:

- No “tail” at the end of the curve (although early data)
- No increase in response rate (although 60% RR is tough to beat)
- Unlike NSCLC curves don’t begin to separate until after the chemotherapy period



Horn, NEJM 2018

Chemoimmunotherapy

- Is the new current standard with the addition of atezolizumab or durvalumab to platinum based therapy.
- Carboplatin is associated with less toxicities in the metastatic setting, no decrease in efficacy compared to carboplatin.
- In real life most patients receive a dose of chemotherapy alone before adding immunotherapy

Slotman Study

- Patients needed to have “responsive therapy”.
- ECOG 0-2.
- No evidence of brain metastasis.
- No MRI required.
- 286 patients
- No follow-up imaging

Slotman, B. N Engl J Med. 2007

Table 2. Scores on Quality-of-Life Assessment.*

Quality-of-Life Score	Assessment Time	Prophylactic Cranial Irradiation	Control	P Value†
Primary end points				
Global health status	0–9 mo‡			0.10
Role functioning	0–9 mo‡			0.17
Cognitive functioning	0–9 mo‡			0.07
Emotional functioning	0–9 mo‡			0.18
Fatigue	6 wk	43.2±2.56	29.3±2.47	<0.001
	3 mo	53.6±3.03	38.5±3.24	<0.001
Hair loss	6 wk	36.5±3.96	11.7±3.73	<0.001
Exploratory results				
Appetite loss	6 wk	28.9±3.25	10.6±3.06	<0.001
	3 mo	43.9±3.87	14.8±4.18	<0.001
Nausea and vomiting	6 wk	15.0±1.73	5.3±1.64	<0.001
	3 mo	26.9±2.92	8.2±3.15	<0.001
Leg weakness	6 wk	25.2±2.71	11.8±2.48	<0.001
	3 mo	32.2±3.62	16.0±3.93	0.003

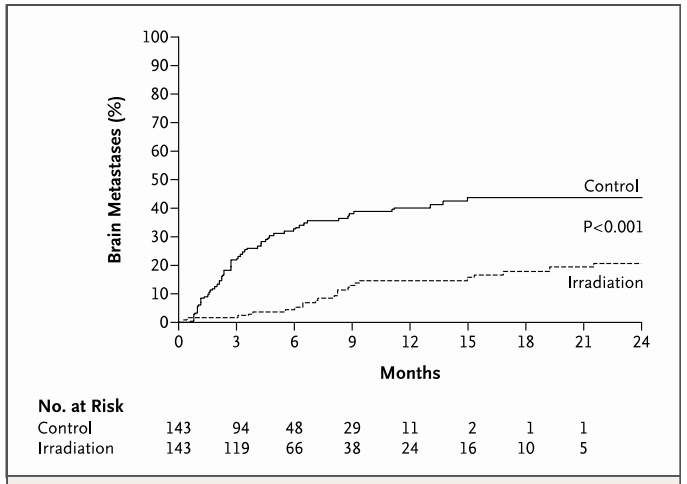


Figure 1. Cumulative Incidence of Symptomatic Brain Metastases.
The difference in the cumulative incidence of brain metastases between the irradiation group and the control group was significant (P<0.001, by Gray's method).

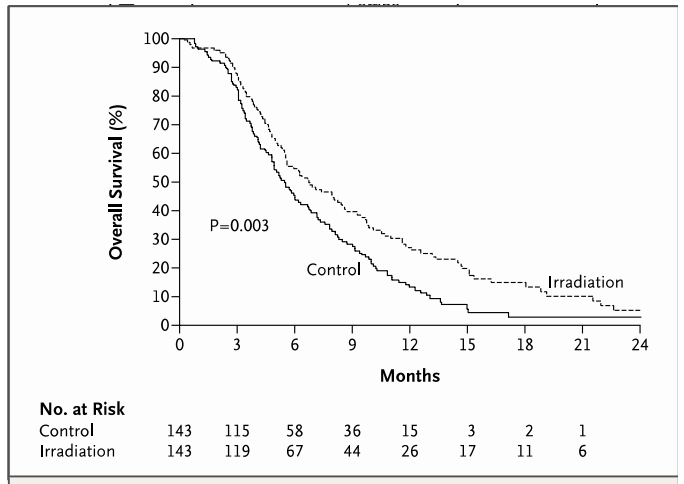
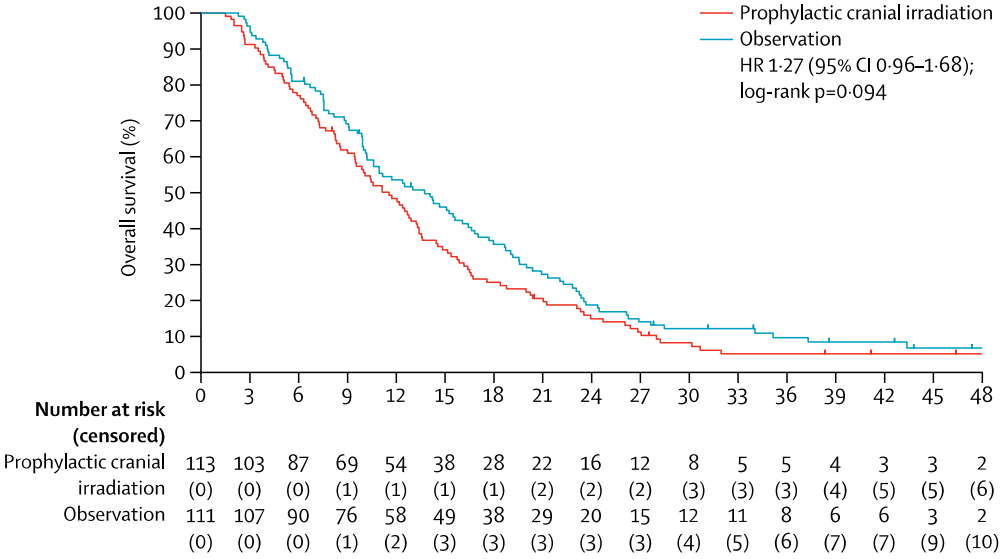
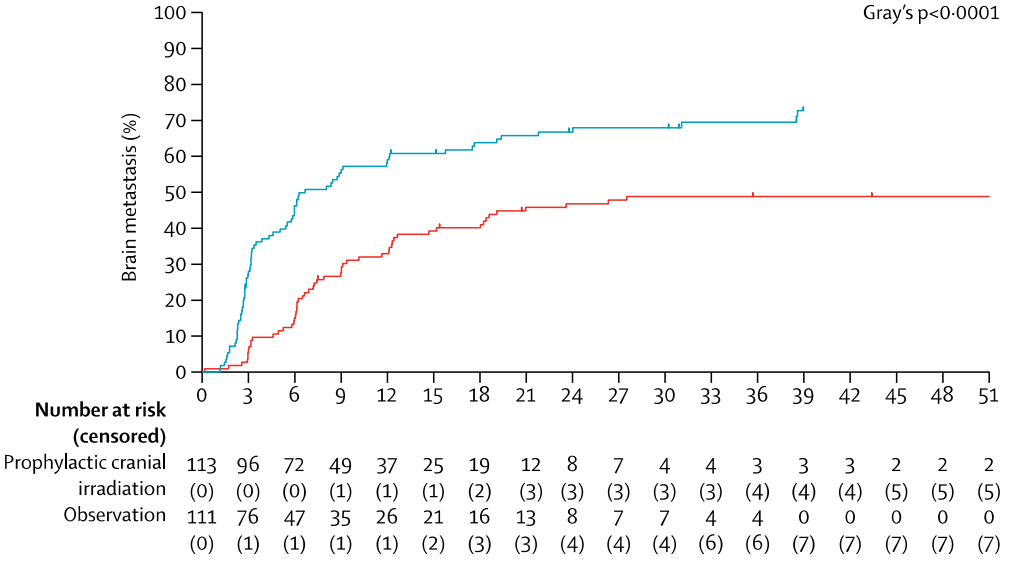


Figure 3. Overall Survival.
Patients in the irradiation group had a longer median overall survival (6.7 months) than did those in the control group (5.4 months) (P=0.003; hazard ratio, 0.68; 95% CI, 0.52 to 0.88).

Takahashi study

- Patients needed to have “responsive therapy”.
- ECOG 0-2.
- No evidence of brain metastasis with a screening MRI.
- Follow up MRI q 3 months <u>required</u>.





Takahashi et. al. Lancet Oncol. 2017. PMID 28343976

Thoracic radiation.

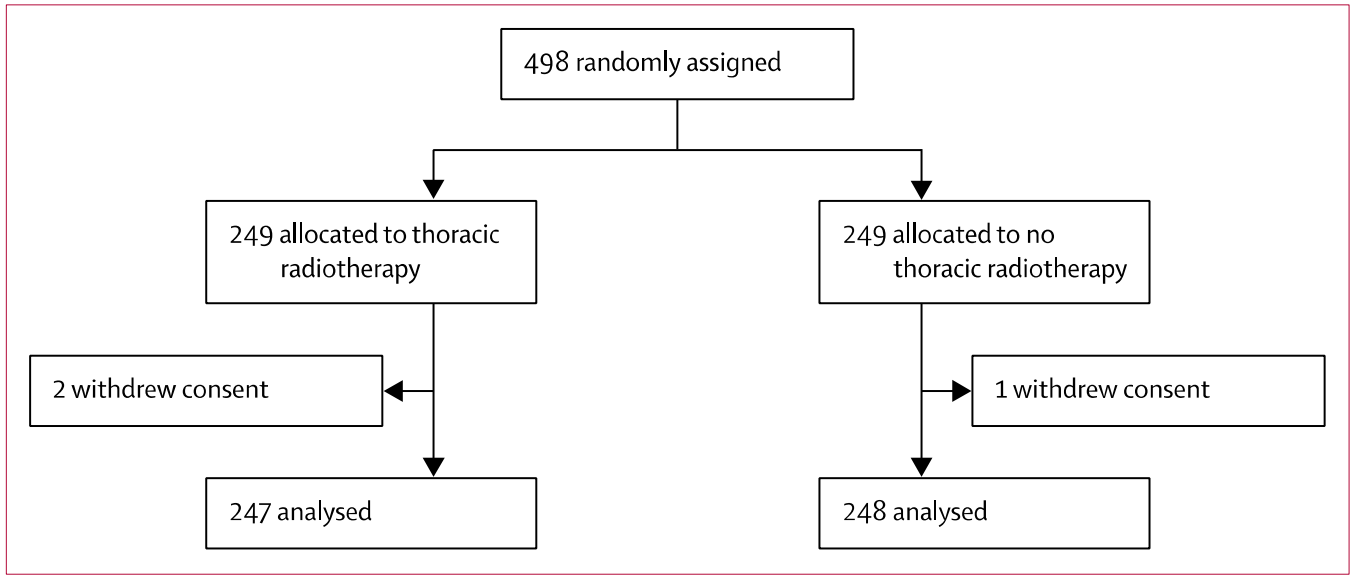
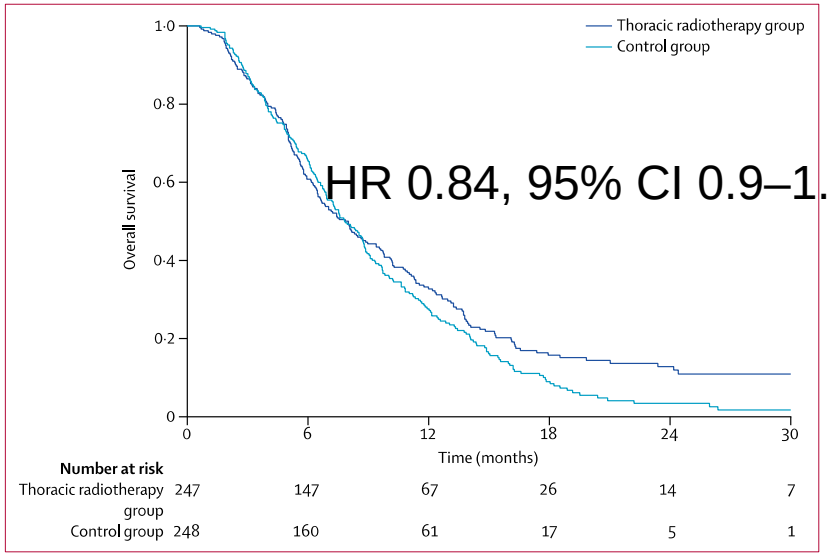


Figure 1: **Trial profile**



HR 0.84, 95% CI 0.9–1.01, p=0·066

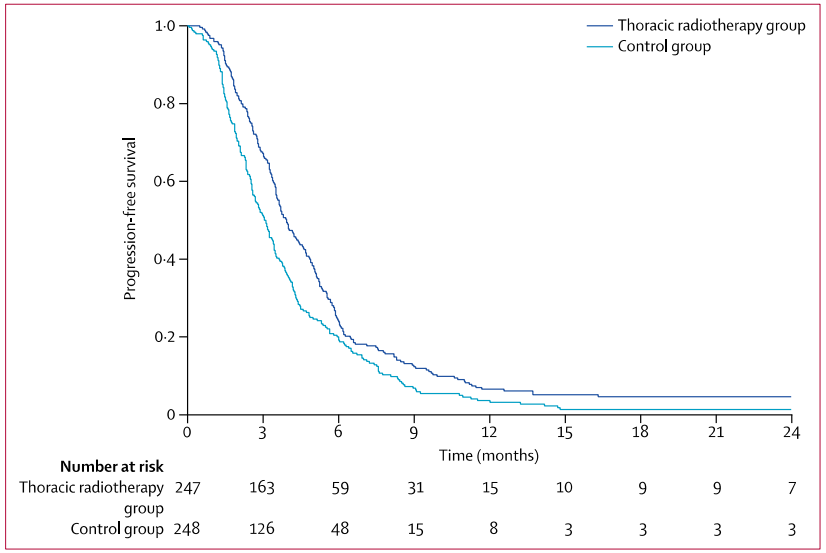


Figure 4: **Kaplan-Meier curves for progression-free survival**

Slotman et. al. Lancet Oncol. 2015.

Thoracic and extratoracic radiation

- RTOG 0937. Phase 2 study. PCI vs PCI vs ”consolidative” xrt up to 4 metastatic lesions.
- Interim analysis showed no difference in 1 year survival rate (60.1 PCI alone vs 50.8 in PCI + XRT (p=0.21) and the study was stopped for futility.
- With the current standard of chemoimmunotherapy and maintenance immunotherapy there is no data as to what to do with the PD1/PDL1 agent.

What to do at relapse? Second line chemotherapy

Phase III Trial Comparing Supportive Care Alone With Supportive Care With Oral Topotecan in Patients With Relapsed Small-Cell Lung Cancer

Mary E.R. O'Brien, Tudor-Eliade Ciuleanu, Hristo Tsekov, Yaroslav Shparyk, Branka Čučeviá, Gabor Juhasz, Nicholas Thatcher, Graham A. Ross, Graham C. Dane, and Theresa Crofts

A B S T R A C T

Purpose
For patients with small-cell lung cancer (SCLC), further chemotherapy is routinely considered at relapse after first-line therapy. However, proof of clinical benefit has not been documented.

Patients and Methods
This study randomly assigned patients with relapsed SCLC not considered as candidates for standard intravenous therapy to best supportive care (BSC) alone (n = 70) or oral topotecan (2.3 mg/m^2/d, days 1 through 5, every 21 days) plus BSC (topotecan; n = 71).

Results
In the intent-to-treat population, survival (primary end point) was prolonged in the topotecan group (log-rank P = .0104). Median survival with BSC was 13.9 weeks (95% CI, 11.1 to 18.6) and with topotecan, 25.9 weeks (95% CI, 18.3 to 31.6). Statistical significance for survival was maintained in a subgroup of patients with a short treatment-free interval (≤ 60 days). Response to topotecan was 7% partial and 44% stable disease. Patients on topotecan had slower quality of life deterioration and greater symptom control. Principal toxicities with topotecan were hematological: grade 4 neutropenia, 33%; grade 4 thrombocytopenia, 7%; and grade 3/4 anemia, 25%. Comparing topotecan with BSC, infection ≥ grade 2 was 14% versus 12% and sepsis 4% versus 1%; other grade 3/4 events included vomiting 3% versus 0, diarrhea 6% versus 0, dyspnea 3% versus 9%, and pain 3% versus 6%. Toxic deaths occurred in four patients (6%) in the topotecan arm. All cause mortality within 30 days of random assignment was 13% on BSC and 7% on topotecan.

Conclusion
Chemotherapy with oral topotecan is associated with prolongation of survival and quality of life benefit in patients with relapsed SCLC.

J Clin Oncol 24:5441-5447. © 2006 by American Society of Clinical Oncology

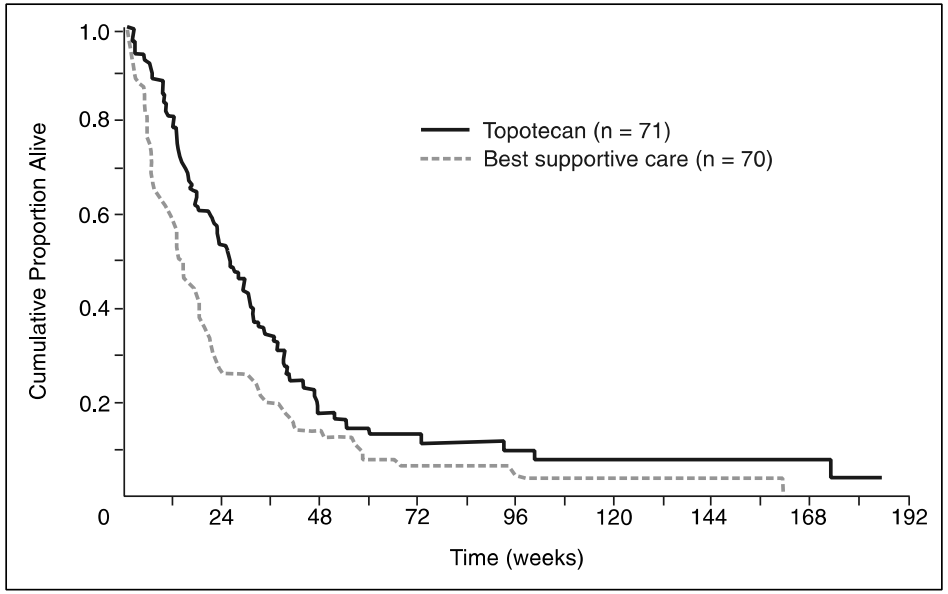


Fig 1. Kaplan-Meier estimates for overall survival in the intent-to-treat population (log-rank P = .01). The unadjusted hazard ratio for overall survival was 0.64 (95% CI, 0.45 to 0.90) for topotecan relative to best supportive care alone. Adjusted for stratification factors, the hazard ratio was 0.61 (95% CI, 0.43 to 0.87).

Lurbinectedin

- Is a selective inhibitor of transcription that binds preferentially to guanines located in the GC-rich regulatory areas of DNA gene promoters.
- Found to have activity on early Phase 1 studies.
- Phase 3 in combination with doxorubicin versus topotecan or CAV has finished accrual.
- Phase 2 confirmed activity as a single agent.

Lurbinectedin

- 105 patients enrolled.
- No active CNS metastasis.
- 45 had <90 days chemotherapy free interval and 60 had more.
- Most except 7 patients were treated after only 1 line of therapy.
- ORR. 35% (n=35).
- PFS 3.5 months
- OS 9.3 months.
- This led to its FDA approval.

Second line chemotherapy

- Other second line agents are also effective.
  - Paclitaxel.[1]
  - Gemcitabine.[2]
  - Irinotecan.[3]
- Response rates single digits
- Immunotherapy should not be given if first line contained a PD1/PDL1 agent.

1. Smit. Br J Cancer. 1998. PMID. 9461009
2. Masters. J Clin Oncol. 2003. PMID. 12697880
3. Masuda. J Clin Oncol. 1992. PMID. 1321891


Questions

The Myelodysplastic Syndromes

Aaron T. Gerds, MD, MS
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@AaronGerds

Cleveland Clinic
Taussig Cancer Institute

L&MD
Leukemia & Myeloid Disorders Program

Disclosures

“It troubles me that we’re being led into battle by a person wearing a bow tie.”

-New Yorker | September 10, 2018

Overview – Myelodysplastic Syndromes

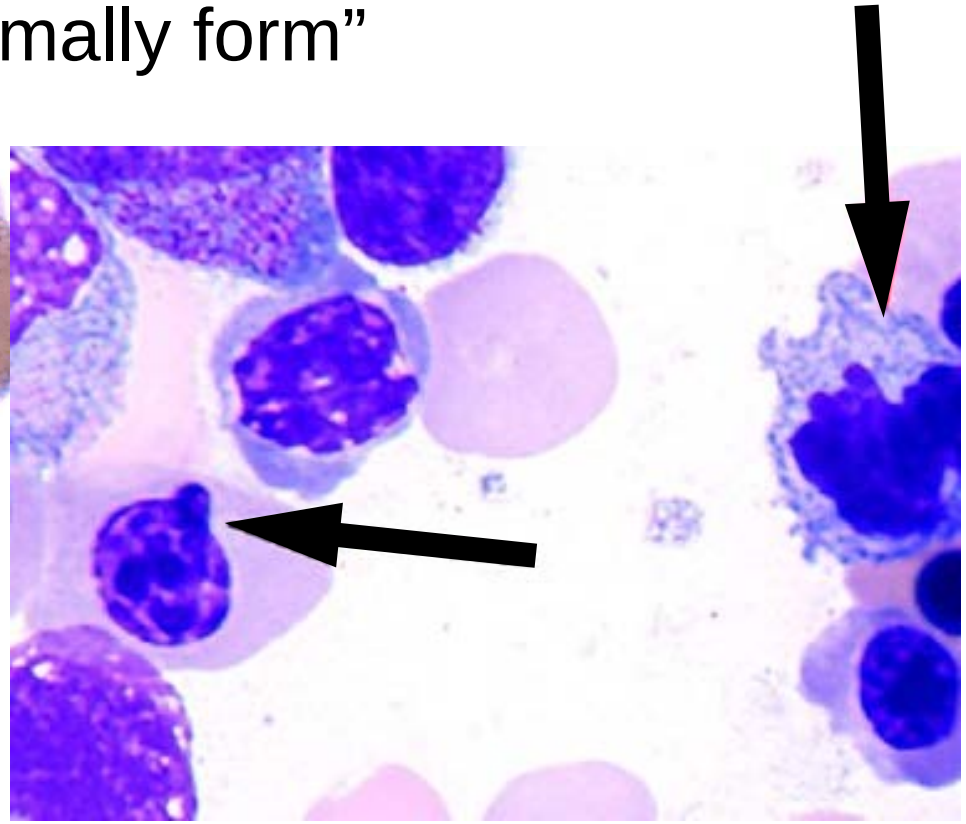
1. Organization, in general
2. Diagnosis and Classification
3. Epidemiology
4. Pathogenesis
    a. Clonal Process
    b. Secondary MDS
5. Risk stratification
    a. IPSS-R
6. Treatment of Lower-risk MDS
    1. ESAs
    2. IMIDS
    3. Immunosuppressive therapy
7. Treatment of Higher-risk MDS
    1. Hypomehtylating agents
8. Transplantation for MDS
9. Discussion

Cleveland Clinic
Taussig Cancer Institute

What is MDS?

The Myelodysplastic Syndromes

- Gr. *myelos* – “marrow”
- Gr. *dys* + *plassein* – “abnormally form”



Maslak P, Pelger Huet Cell - 1. ASH Image Bank. 2011; 2011-2117.

Maslak P, Dysplastic Red Cell Changes (Bone Marrow Aspirate) I - 2. ASH Image Bank. 2011; 2011-3269.

MDS is a cancer?

Oxford dictionary: The disease caused by an uncontrolled division of abnormal cells in a part of the body (from Latin *cancr* meaning crab)

Mural Study for Cancer, 1948; Clarence Van Duzer (1920-2009)

Diagnosis and Classification of MDS

WHO Diagnostic Criteria

Minimal Morphologic Criteria

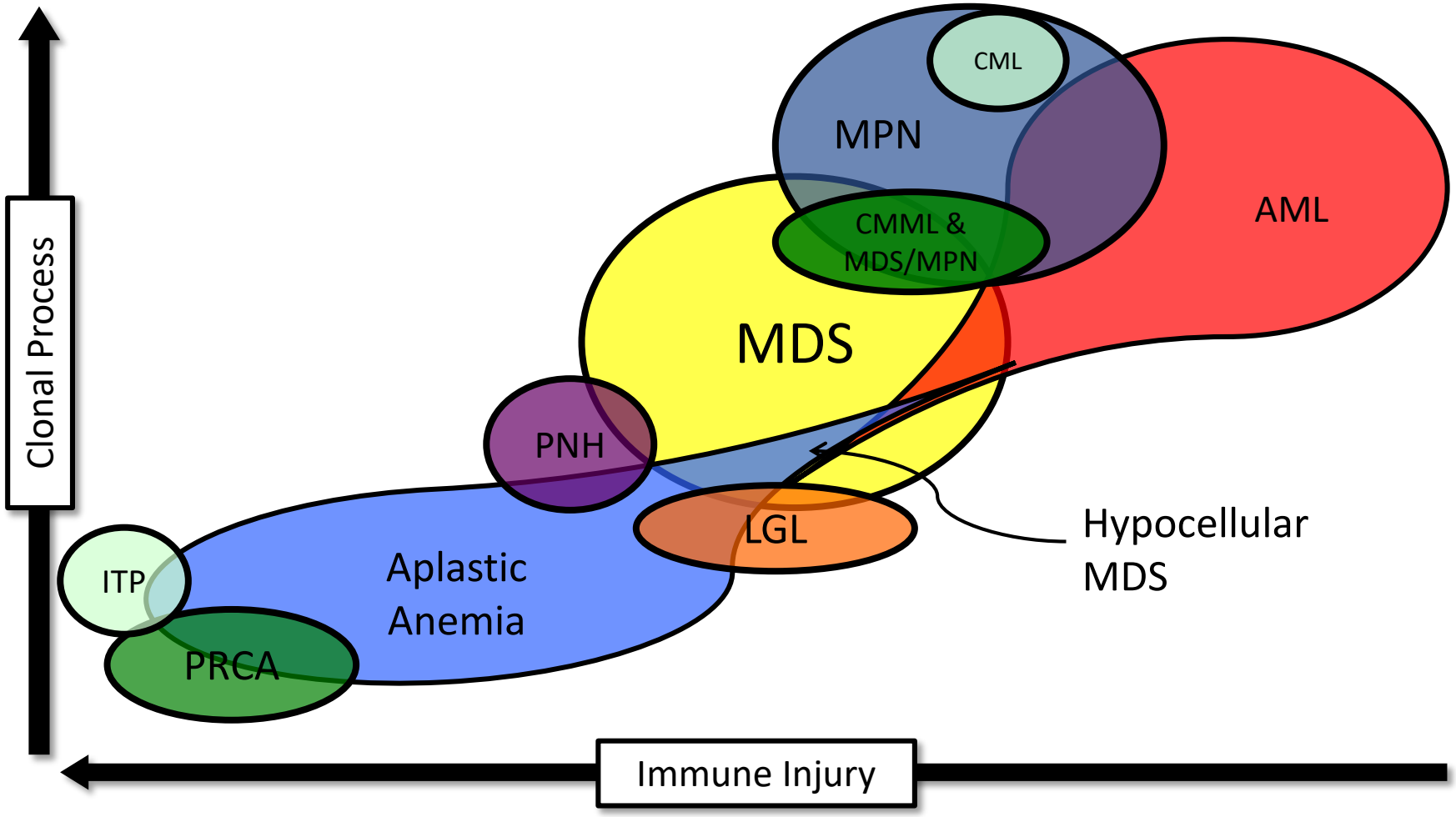
- ≥10% of the cells ≥1 lineage must show dysplasia
- Dysplasia not required if:
  - Defining cytogenetics
  - BM blasts ≥ 5%, PB blasts ≥ 2%, or Auer rods
- At least one cytopenia present
- Causes of secondary dysplasia must be excluded

Defining Cytogenetics

- -7 or del(7q)
- -5 or del(5q)
- del(13q)
- del(11q)
- del(12p) or t(12p)
- del(9q)
- idic(X)(q13)
- t(17p) or i(17q)
- t(11;16
- t(3;21)
- t(1;3)
- t(2;11)
- inv(3)
- t(6;9)
- Complex

Swerdlow SH et al (Eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 4th ed., IARC, Lyon 2017Press

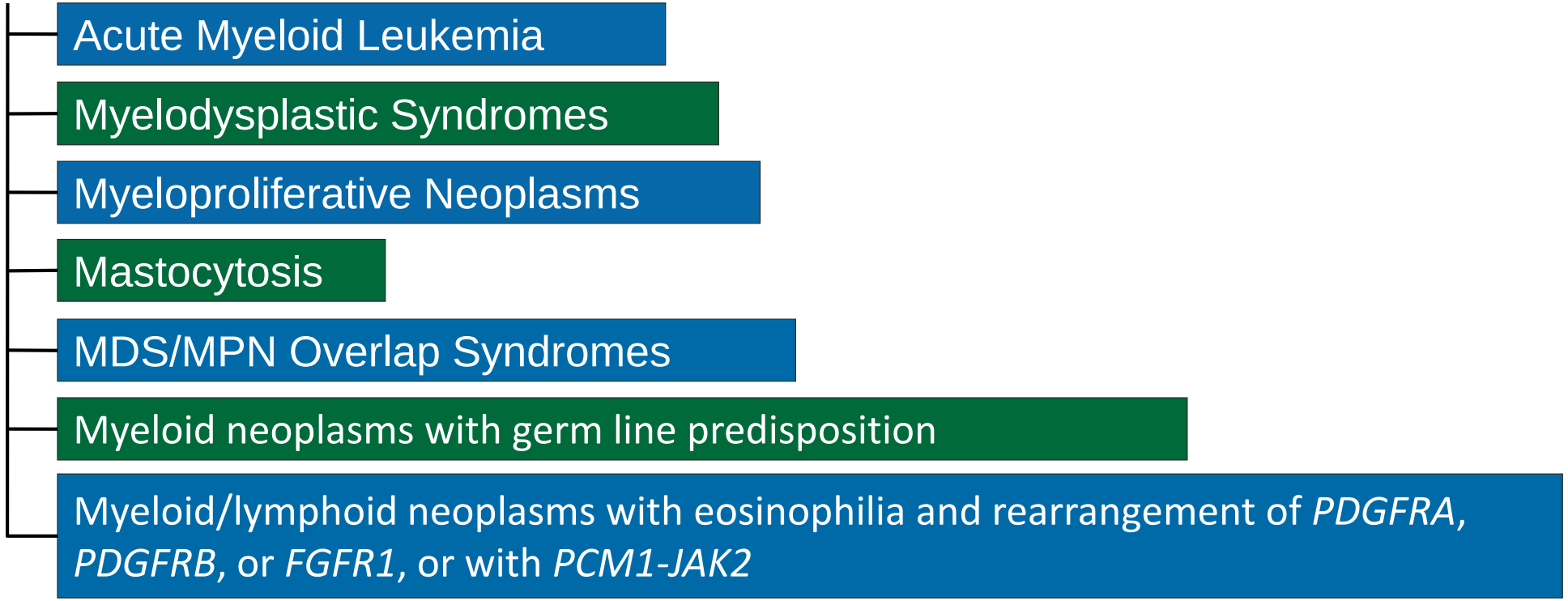
Spectrum of Marrow Failure



Gerds, AT. *Curr Hematol Malig Rep*. 2014 Dec;9(4):400-6

WHO Classification

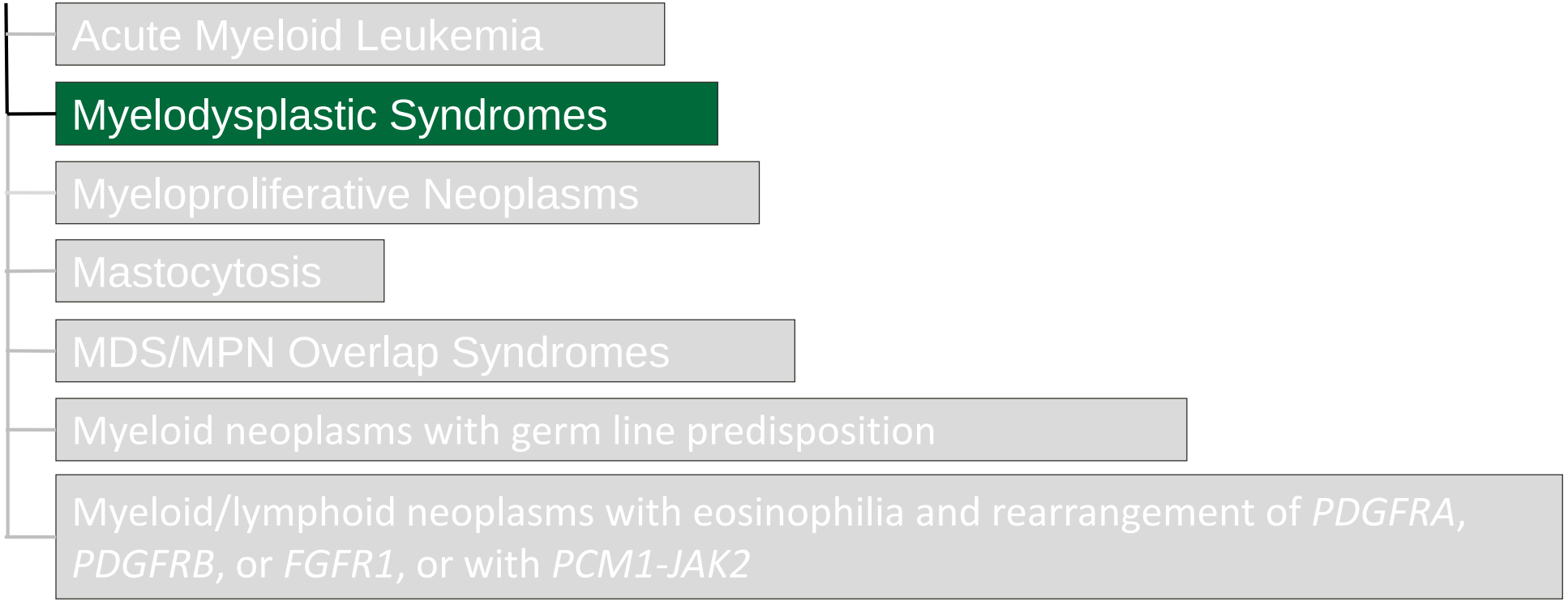
Myeloid Neoplasms



Swerdlow SH et al (Eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 4th ed., IARC, Lyon 2017Press

WHO Classification

Myeloid Neoplasms



Swerdlow SH et al (Eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 4th ed., IARC, Lyon 2017Press

Name	Dysplastic lineages	Cytopenias*	Ringed sideroblasts as % of marrow erythroid elements	Bone marrow (BM) and peripheral blood (PB) blasts	Cytogenetics by conventional karyotype analysis
MDS with single lineage dysplasia (MDS-SLD)	1	1 or 2	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with multilineage dysplasia (MDS-MLD)	2 or 3	1-3	<15%/<5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with ring sideroblasts (MDS-RS)					
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	1	1 or 2	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS-RS with single lineage dysplasia (MDS-RS-SLD)	2 or 3	1-3	≥15%/≥5%†	BM <5%, PB <1%, no Auer rods	Any, unless fulfills all criteria for MDS with isolated del(5q)
MDS with isolated del(5q)	1-3	1-2	None or any	BM <5%, PB <1%, no Auer rods	del(5q) ± 1 additional abnormality except -7 or del(7q)
MDS with excess blasts (MDS-EB)					
MDS-EB-1	0-3	1-3	None or any	BM 5%-9% or PB 2%-4%, no Auer rods	Any
MDS-EB-2	0-3	1-3	None or any	BM 10%-19% or PB 5%-19% or Auer rods	Any
MDS, unclassifiable (MDS-U)					
With 1% blood blasts	1-3	1-3	None or any	BM <5%, PB = 1%,‡ no Auer rods	Any
with single lineage dysplasia and pancytopenia	1	3	None or any	BM <5%, PB <1%, no Auer rods	Any
based on defining cytogenetic abnormality	0	1-3	<15%§	BM <5%, PB <1%, no Auer rods	MDS-defining abnormality
Refractory cytopenia of childhood	1-3	1-3	None	BM <5%, PB <2%	Any

Swerdlow SH et al (Eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 4th ed., IARC, Lyon 2017Press

Name	Dysplastic lineages	Cytopenias*	Ringed sideroblasts as % of marrow erythroid elements	Bone marrow (BM) and peripheral blood (PB) blasts	Cytogenetics by conventional karyotype analysis

MDS with < 5% blasts

MDS with excess (≥ 5%) blasts

MDS, unclassifiable

Swerdlow SH et al (Eds). WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues 4th ed., IARC, Lyon 2017Press

Epidemiology of MDS

MDS Epidemiology

Age-Adjusted Incidence Rates[a] for the 18 SEER Geographic Areas by Age and Race, 2009-2013

Site	Both Sexes Rate	Both Sexes Count	Males Rate	Males Count	Females Rate	Females Count
Myelodysplastic Syndromes (MDS)						
By age						
Ages <40	0.1	335	0.1	164	0.1	171
Ages 40-49	0.7	459	0.8	233	0.7	226
Ages 50-59	2.4	1,406				
Ages 60-69	9.3	3,653				
Ages 70-79	30.2	6,539				
Ages 80+	59.8	8,946				
By race						
All Races	4.9	21,338				
White	5.1	17,978				
Black	4.1	1,617				
Asian/Pacific Islander	3.7	1,420				
American Indian/Alaska Native[b]	3.4	76	3.6	38	3.2	38
Hispanic[c]	3.5	1,644	4.4	866	2.9	778

Incidence Rate = 4.9/100,000 per year

Howlader et al. SEER Cancer Statistics Review, 2009-2013, http://seer.cancer.gov/csr/1975_2013/.

MDS Epidemiology

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Ages 40-49	0.7	459	0.8	233	0.7	226
Ages 50-59	2.4	1,406	2.7	781	2.0	625
Ages 60-69	9.3	3,653	11.5	2,131	7.4	1,522
Ages 70-79	30.2	6,539	40.3	3,861	22.2	2,678
Ages 80+	59.8	8,946	90.0	4,928	42.3	4,018
By race						
All Race		21,338	6.7	12,098	3.7	9,240
White		17,978	7.0	10,351	3.8	7,627
Black	4.1	1,617	5.3	806	3.4	811
Asian/Pacific Islander	3.7	1,420	4.8	777	2.8	643
American Indian/Alaska Native[b]	3.4	76	3.6	38	3.2	38
Hispanic[c]	3.5	1,644	4.4	866	2.9	778

Men > Women

Howlader et al. SEER Cancer Statistics Review, 2009-2013, http://seer.cancer.gov/csr/1975_2013/.

MDS Epidemiology

Age-Adjusted Incidence Rates[a] for the 18 SEER Geographic Areas by Age and Race, 2009-2013

Site	Both Sexes Rate	Both Sexes Count	Males Rate	Males Count	Females Rate	Females Count
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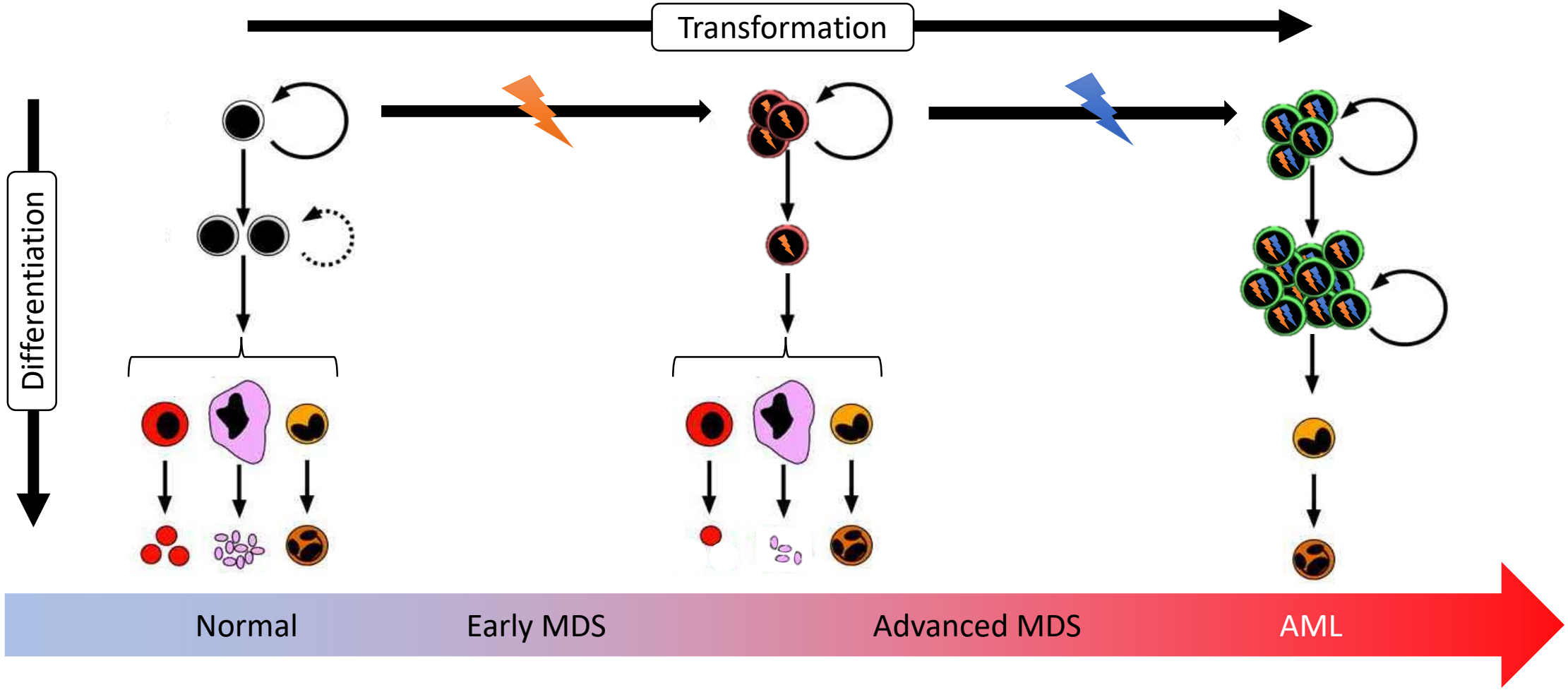
White > African-American

Howlader et al. SEER Cancer Statistics Review, 2009-2013, http://seer.cancer.gov/csr/1975_2013/.

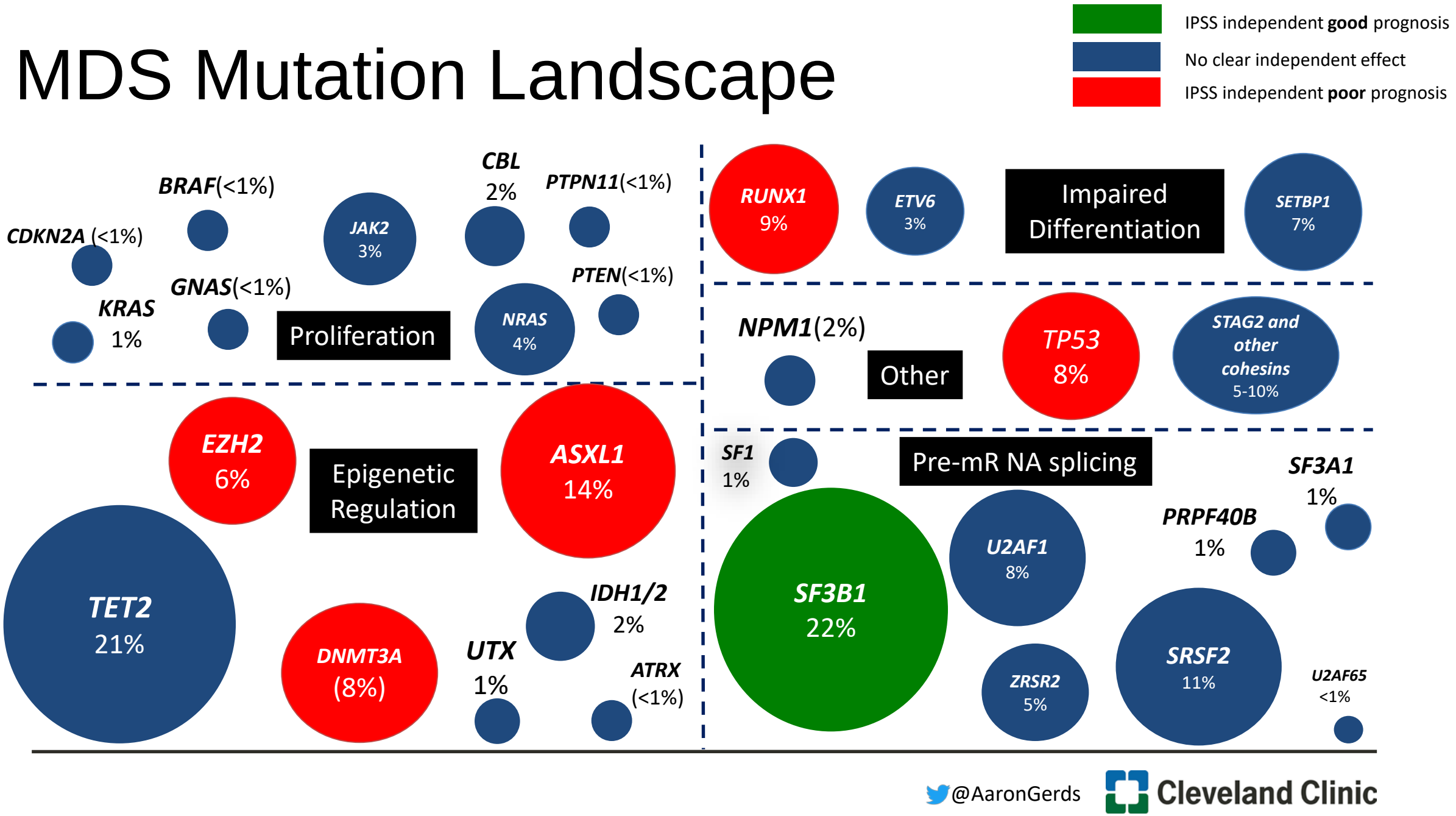
Pathogenesis of MDS

Pathogenesis of MDS



Adapted from: Passegué E, et al., Proc Natl Acad Sci. 2003 Sep 30;100 Suppl 1:11842-9.

MDS Mutation Landscape



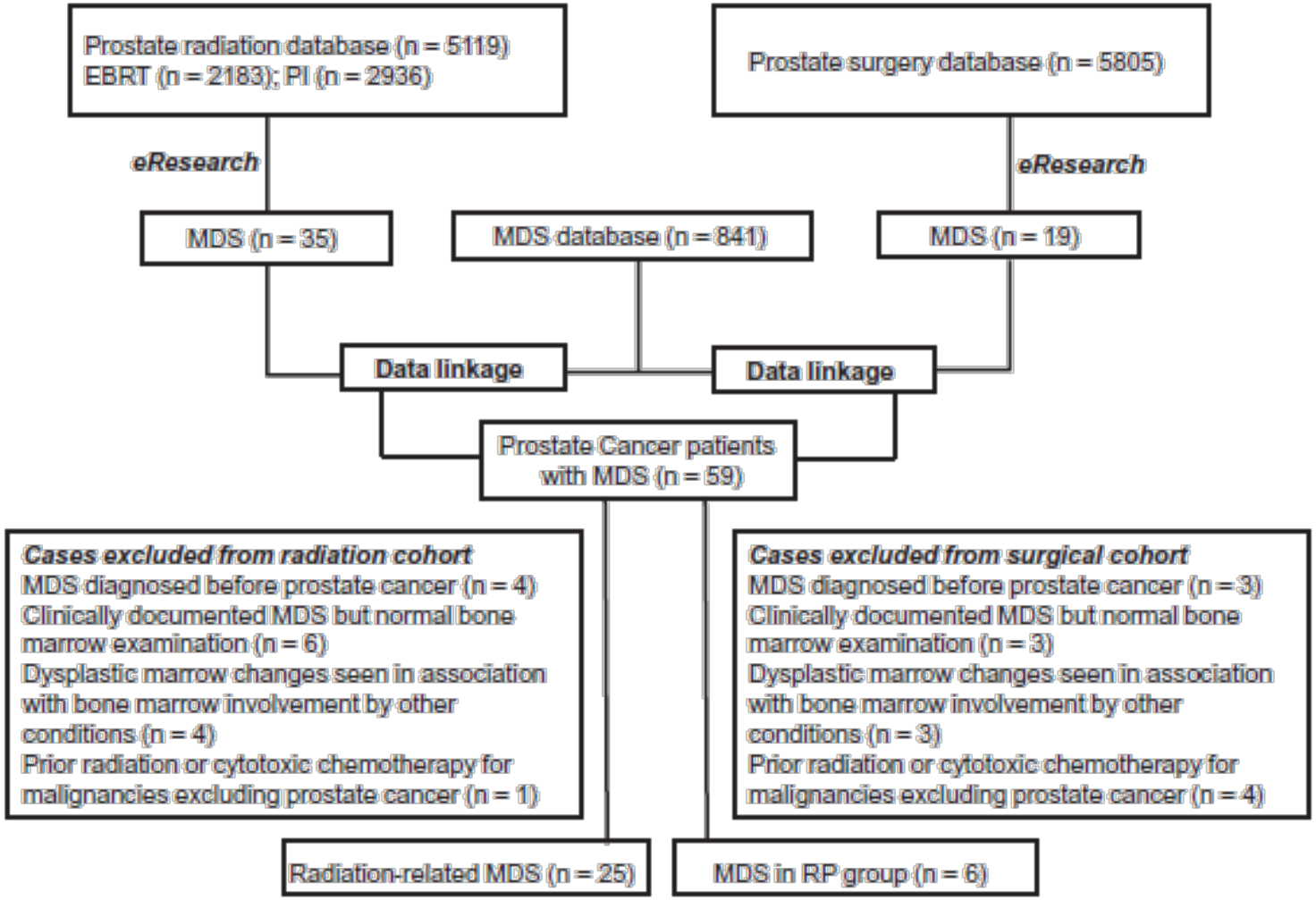
@AaronGerds Cleveland Clinic

Cross-sectional analysis of 4,514 MDS patients in the U.S. in 2005-2007

Age (Median)	**Newly diagnosed**	**71 years**
	Established	**72-75 years**
Sex (Mean)	**Male (Newly diagnosed)** **(Established)**	**55%** **51-57%**
Duration of MDS (Median)		**13-16 months**
MDS Status	**Primary**	**88 – 93%**
	Secondary	**7 – 12%**
Secondary	**Chemotherapy**	**55 – 80%**
Cause	**Radiation**	**6 – 21%**
	Chemical exposure	**2 – 9%**

Sekeres et al. *J National Cancer Inst* 2008;100:1542.

MDS and Prostate Cancer Radiotherapy



Mukherjee et al. J National Cancer Inst 2014;106:462

MDS and Prostate Cancer Radiotherapy

	Risk regression model 2§		Risk regression model 4ll	
Age	1.13 (1.06 to 1.19)	<.001	1.20 (1.12 to 1.29)	<.001
BMI			1.12 (1.03 to 1.23)	.01
Radiation vs RP	1.63 (0.59 to 4.53)	.35	1.40 (0.26 to 7.67)	.70

Mukherjee et al. J National Cancer Inst 2014;106:462

MDS Risk Stratification

IPSS-R Cytogenetic Classification

Risk Group	Included karyotypes (19 categories)	Patients in group	Median survival (months)
Very good	del(11q), -Y	2.9%	60.8
Good	Normal, del(20q), del(5q) alone or with 1 other anomaly, del(12p)	65.7%	48.6
Intermediate	+8, del(7q), i17(q), +19, +21, any single or double anomaly not listed, two or more independent clones	19.2%	26.1
Poor	der(3q), -7, double with del(7q), complex (3 abnormalities)	5.4%	15.8
Very poor	Complex with ≥ 4 abnormalities	6.8%	5.9

Schanz J, et al., J Clin Oncol. 2012 Mar 10;30(8):820-9.; Greenberg PL, et al. Blood. 2012 Sep 20;120(12):2454-65.

Scoring the IPSS-R

Parameter	Categories and associated score				
Cytogenetic risk group	Very Good	Good	Int	Poor	Very Poor
	0	1	2	3	4
Marrow blasts	≤ 2%	> 2% - < 5%	5% - 10%	>10%	
	0	1	2	3	
Hemoglobin	≥ 10 g/dL	8 - < 10 g/dL	< 8 g/dL		
	0	1	2		
Platelet count	≥ 100	50 - < 100	< 50		
	0	0.5	1		
ANC	≥ 0.8	< 0.8			
	0	0.5			

Greenberg PL, et al. Blood. 2012 Sep 20;120(12):2454-65.

Scoring the IPSS-R

Prognostic variable	0	0.5	1	1.5	2	3	4
Cytogenetics	Very Good		Good		Int	Poor	Very Poor
BM Blast %	<=2		>2-<5%		5-10%	>10%	
Hemoglobin	=>10		8-<10	<8			
Platelets	=>100	50-<100	<50				
ANC	=>0.8	<0.8					

Greenberg PL, et al. Blood. 2012 Sep 20;120(12):2454-65.

IPSS-R Risk Groups

Risk group	Points	Patients	Median Survival (years)	Time until 25% develop AML (yr)
Very low	0 - 1.5	19%	8.8	NR
Low	> 1.5 - 3	38%	5.3	10.8
Intermediate	> 3 - 4.5	20%	3.0	3.2
High	>4.5 - 6	13%	1.6	1.4
Very High	> 6	10%	0.8	0.73

http://www.ipss-r.com

Greenberg PL, et al. Blood. 2012 Sep 20;120(12):2454-65.

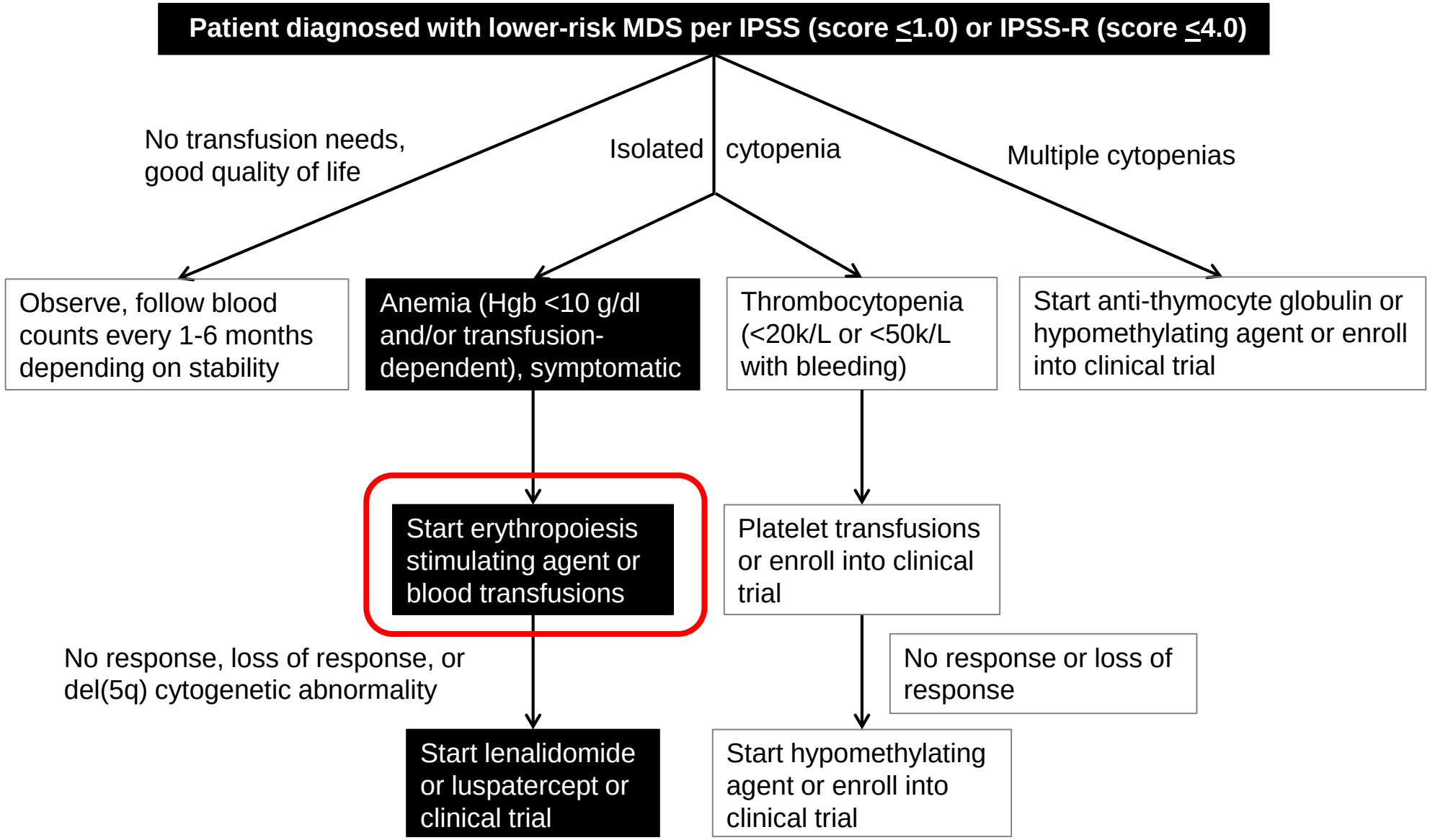
MDS Prognosis Made Easy!

- **Lower Risk**
  - MDS-SLD/MLD (*RA, RCMD, RCUD*)
  - MDS-RS (*RARS*)
  - MDS del (5q)
  - MDS-U
  - IPSS Low/Intermediate-1 (0-1.0)
  - IPSS-R Very Low/Low/Intermediate (<3.5)

- **Higher Risk**
  - MDS-EB-1, MDS-EB-2 (*RAEB-1, RAEB-2*)
  - IPSS Int-2/High (>1.5)
  - IPSS-R Intermediate/High/Very High (>3.5)

Slide courtesy of Mikkael Sekeres

Treatment of Lower-risk MDS



Adapted from Sekeres MA, Gerds AT. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):82-9.

Erythropoiesis Stimulating Agents

- Number of published regimens:
  - Erythropoietin 150 to 300 U/kg daily
  - Erythropoietin ≥150 U/kg three times weekly
  - Erythropoietin 40,000 U once per week
  - Darbepoetin alpha 75-400 mcg once/week
  - Darbepoetin alpha 500 mcg every 2-3 weeks

- Higher doses may be more effective than lower doses
- Responses may take up to 12-26 weeks

Mundle S, et al., Cancer. 2009 Feb 15;115(4):706-15.
Terpos E, et al., Br J Haematol. 2002 Jul;118(1):174-80.

ORR for ESAs in MDS

	Patients (%)	Response rate	IWG response			Duration of response (median months, range)
			CR/PR	HI-E	HI-N/P	
Growth factors	100	39·5	9·1	66·8	24·1	18 (1–116)
EPO	57·3	39·4	6·1	93·9	–	17 (1–93)
EPO + GCSF	23·4	47·8	23·2	60·6	7·1	19 (2–62)
GMCSF	6·2	37·8	–	–	100	6 (1–18)
EPO + GMCSF	5·8	33·7	–	81·3	18·7	24 (1–116)
GCSF	3·0	47·9	–	4·5	95·5	3 (1–6)
IL3	3·0	17·0	–	–	100	3 (1–12)
IL6	1·3	38·1	–	–	100	5 (2–14)

Overall Response Rate ~40%

Golshayan AR. et al. Br J Haematol. 2007 Apr;137(2):125-32.

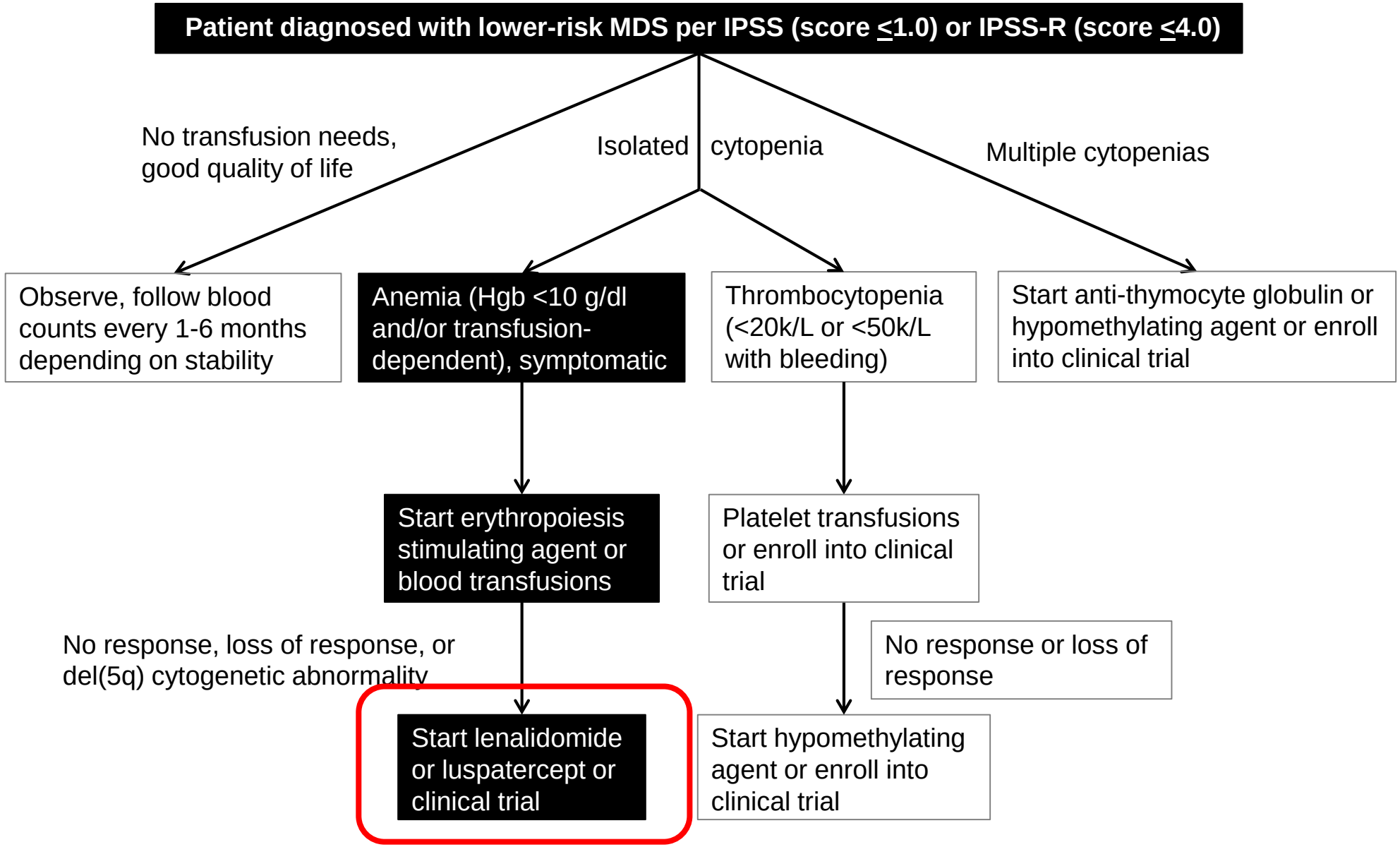
Predictive Model for ESA + GCSF

- Nordic MDS Group [N = 98]

Parameter	Points			
	+2	+1	-2	-3
Serum Epo (mU/mL)	< 100	100 - 500		> 500
RBC Transfusions	< 2 units/mo		≥ 2 units/mo	

Points	Patients	% Response
≥ 2	29	74%
-1 to 1	31	23%
< -1	34	7%

Hellstrom-Lindberg et al, Br J Haematol 1997; 99: 344.



Sekeres MA, Gerds AT. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):82-9.

Luspatercept (Approved 4/3/2020)

- For the treatment of anemia
  - After ESA *AND*
  - Requiring >/=2 RBC units over 8 weeks *IN*
  - Very low- to intermediate-risk MDS-RS *OR* MDS/MPN-RS-T

Fenaux P et al. *N Engl J Med*. 2020 Jan 9;382(2):140-151.

MEDALIST: Study Design

- ≥ 18 yrs of age with non-del(5q) MDS and ring sideroblasts
- IPSS-R: very low/low/intermediate
- Refractory, intolerant, or ineligible for ESAs
- RBC transfusion dependent

(N = 229)

Randomized 2:1

*Could be titrated up to 1.75 mg/kg if needed.

Primary endpoint: RBC TI for ≥ 8 wks between Wk 1 and Wk 24

Fenaux P et al. *N Engl J Med*. 2020 Jan 9;382(2):140-151.

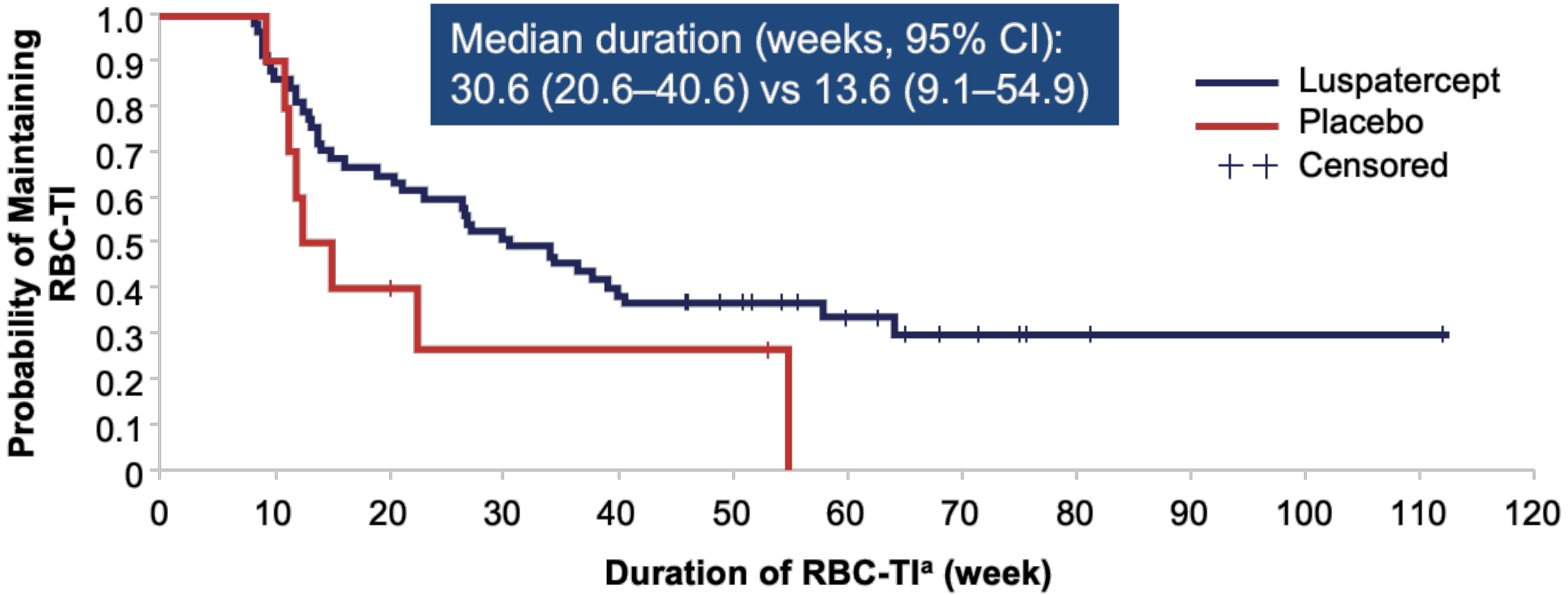
MEDALIST Trial: Primary Endpoint: RBC Transfusion Independence ≥ 8 Weeks

RBC-TI ≥ 8 weeks	Luspatercept (n = 153)	Placebo (n = 76)
Weeks 1–24, n (%)	**58 (37.9)**	**10 (13.2)**
95% CI	30.2–46.1	6.5–22.9
P-value[a]	< 0.0001	

[a] Cochran–Mantel–Haenszel test stratified for average baseline RBC transfusion requirement (≥ 6 units vs < 6 units of RBCs/8 weeks) and baseline IPSS-R score (Very Low or Low vs Intermediate).
CI, confidence interval.

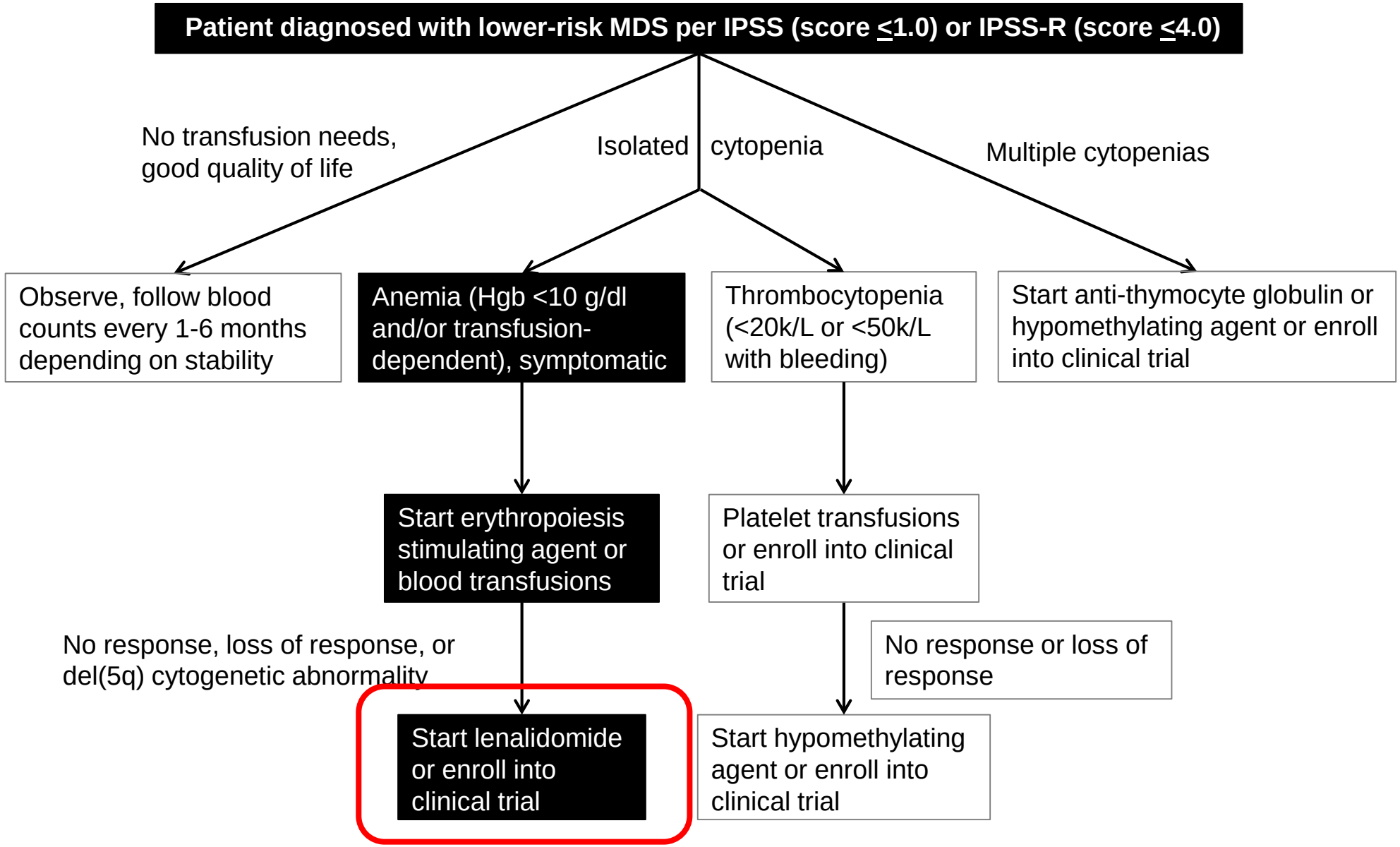
Fenaux P et al. *N Engl J Med*. 2020 Jan 9;382(2):140-151.

MEDALIST Trial: Duration of RBC-TI Response in Primary Endpoint Responders



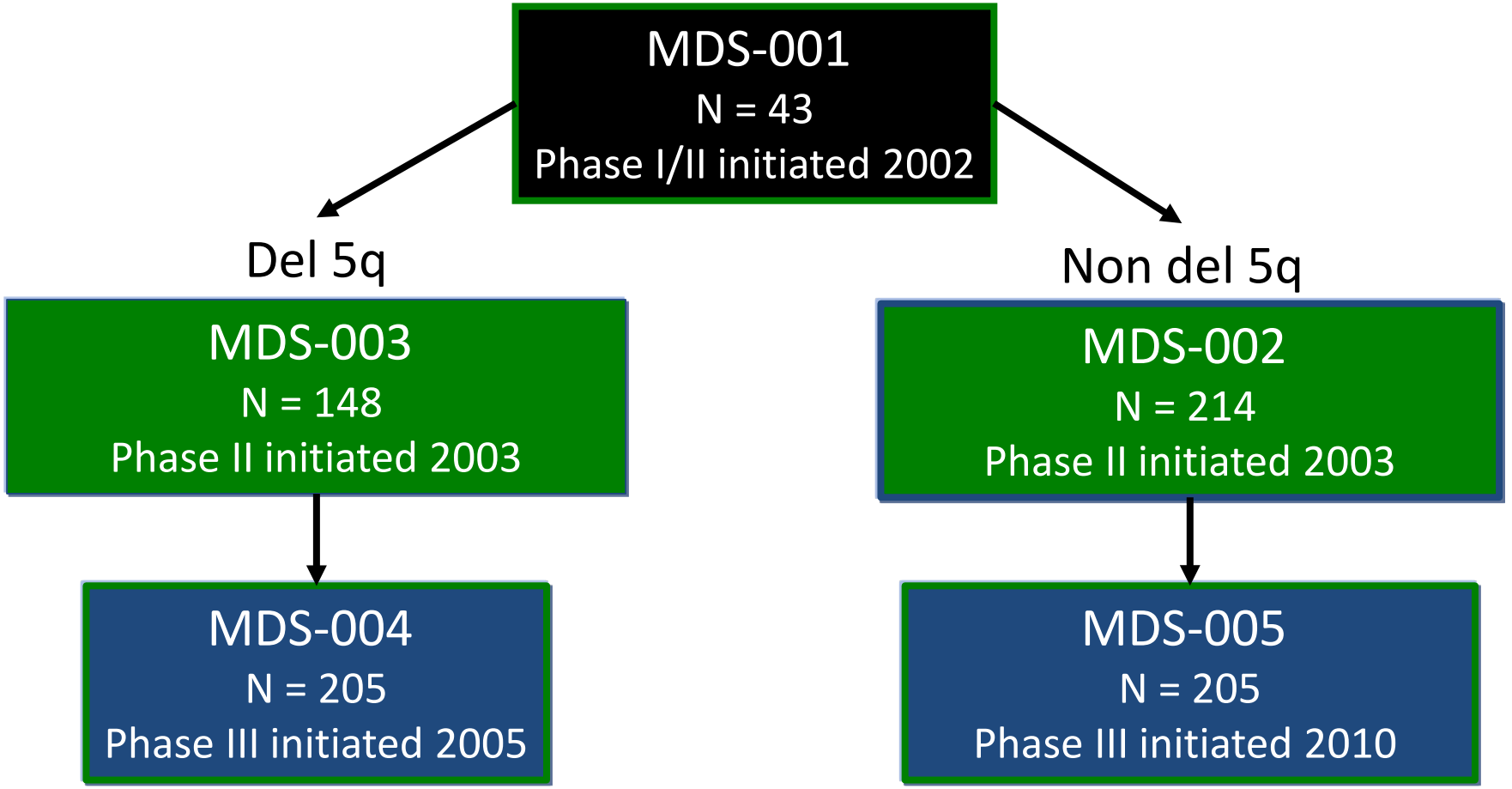
Number of patients												
Luspatercept	58	49	37	29	22	18	10	6	3	2	1	1	0
Placebo	10	9	3	2	2	2	0						

Fenaux P et al. *N Engl J Med*. 2020 Jan 9;382(2):140-151.
Fenaux P et al. ASH 2018. Abstr 1. NCT02631070.



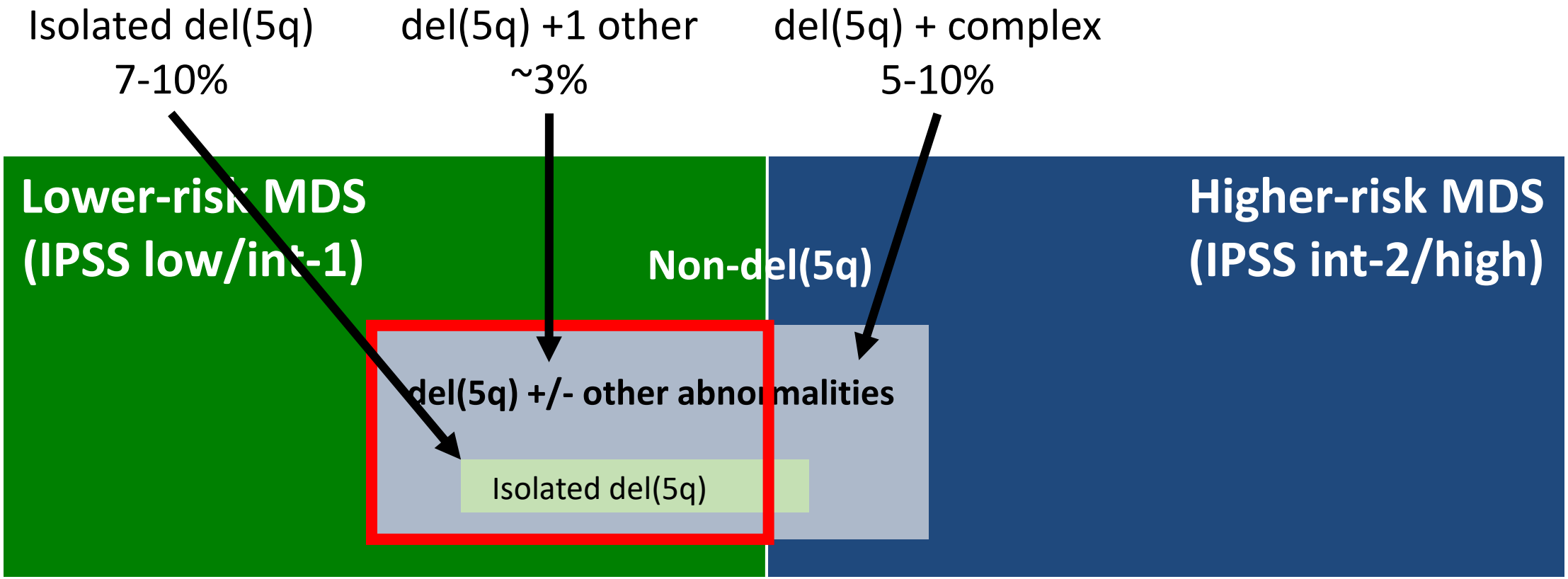
Adapted from Sekeres MA, Gerds AT. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):82-9.

Development of IMIDs for MDS



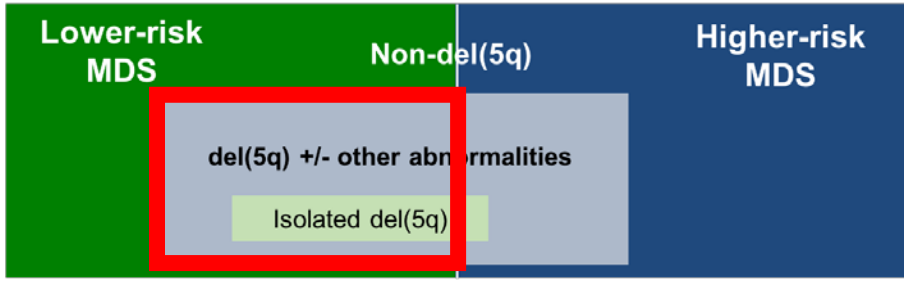
US FDA Indication for Lenalidomide

Warning: This figure is not to scale!



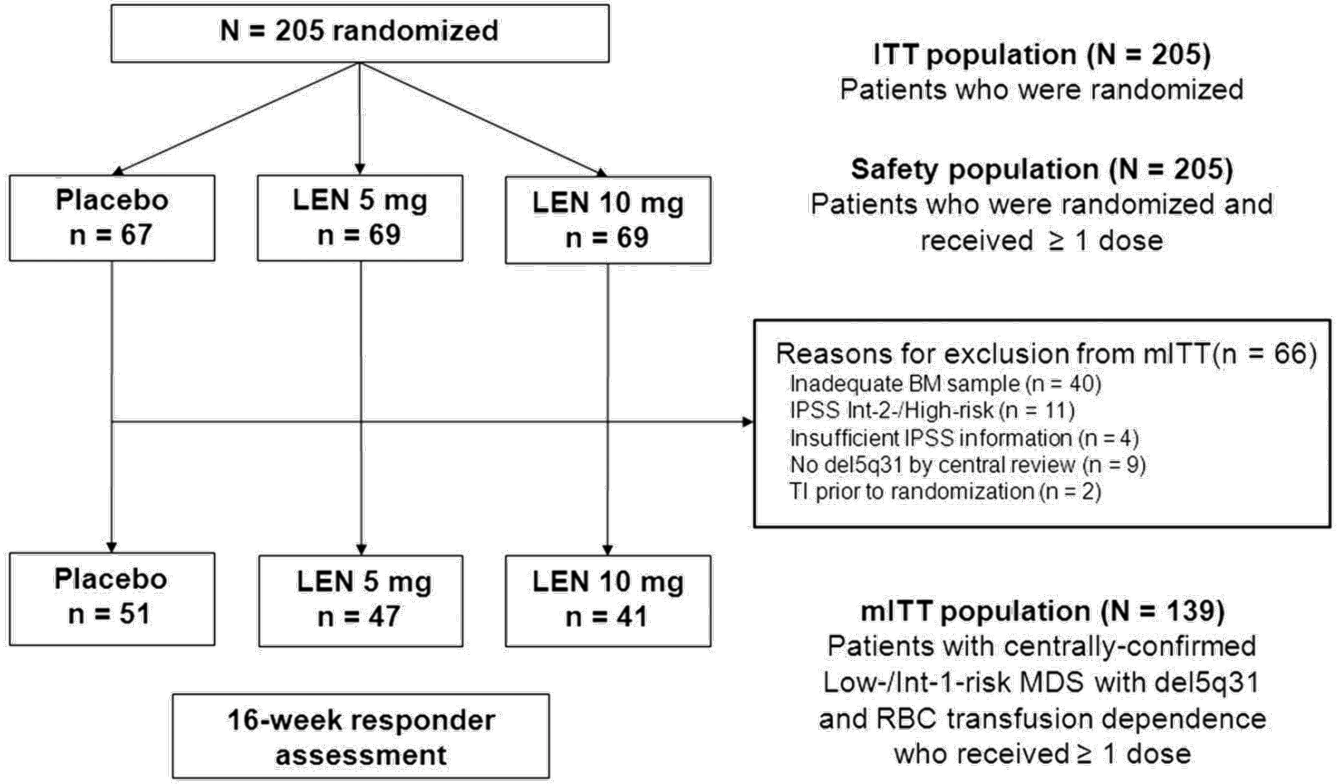
Schanz J et al. J Clin Oncol. 2012 Mar 10;30(8):820-9.
Komrokji RS, Padron E, Ebert BL, List AF. Best Pract Res Clin Haematol. 2013 Dec;26(4):365-75

MDS-004 Study



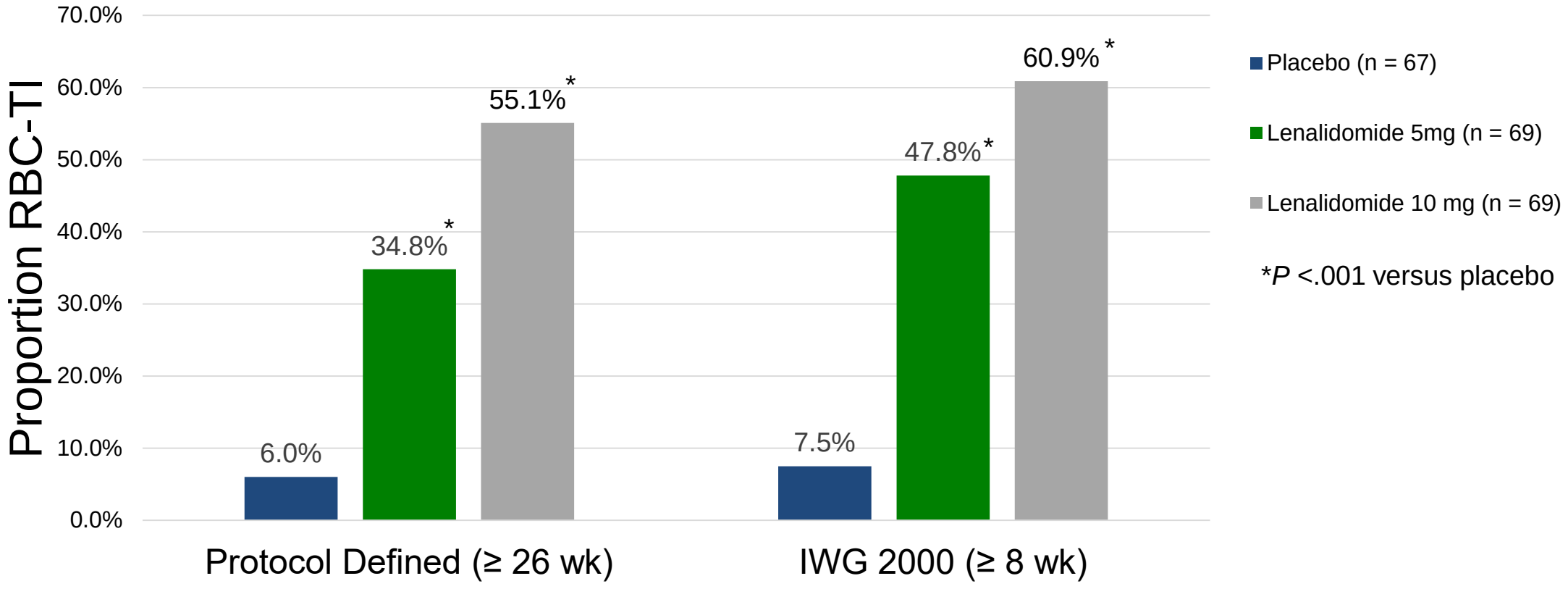
- RBC-Transfusion dependent anemia

- Lenalidomide
  - 10 mg/day days 1 - 21
  - 5 mg/day days 1 - 28
  - Placebo



Fenaux P et al. Blood. 2011 Oct 6;118(14):3765-76.

MDS-004 Study: Erythroid Response by RBC-TI

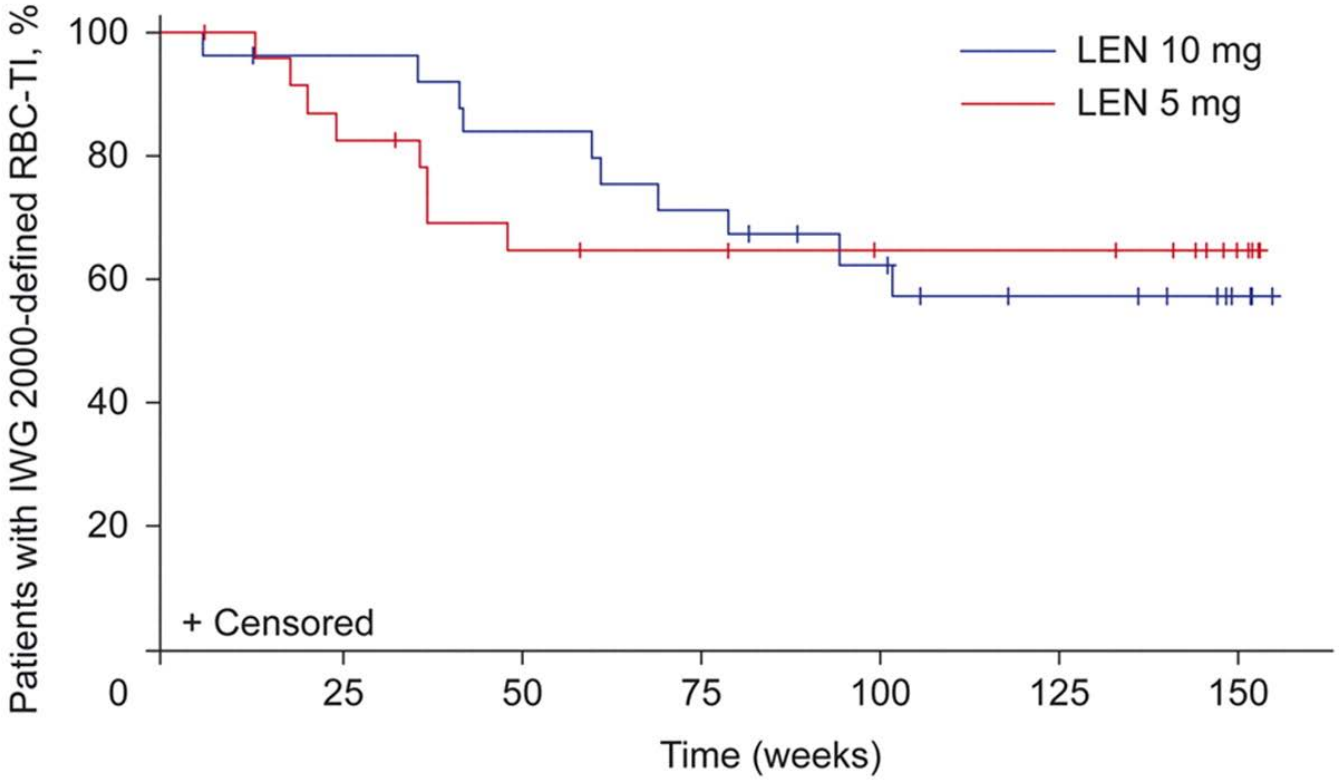


52% pre-treated with ESA, median time from diagnosis to enrolment 2.7 years (0.2-17.2)

Fenaux P et al. Blood. 2011 Oct 6;118(14):3765-76.

MDS-004 Study: Response Duration

- Median (95% CI) duration of RBC-TI:
  - LEN 5mg: NR weeks (41.3-NR)
  - LEN 10mg: NR weeks (82.9-NR)
- 30% patients on LEN 10mg had a major cytogenetic response (20% minor)

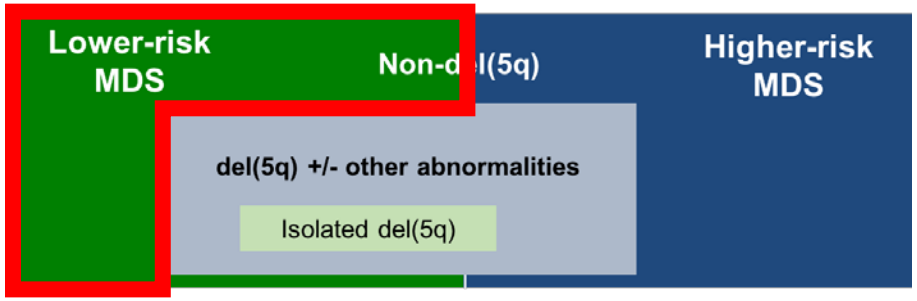


Patients at risk, n

LEN 10 mg	25	23	20	17	13	9	7
LEN 5 mg	24	20	15	13	12	11	7

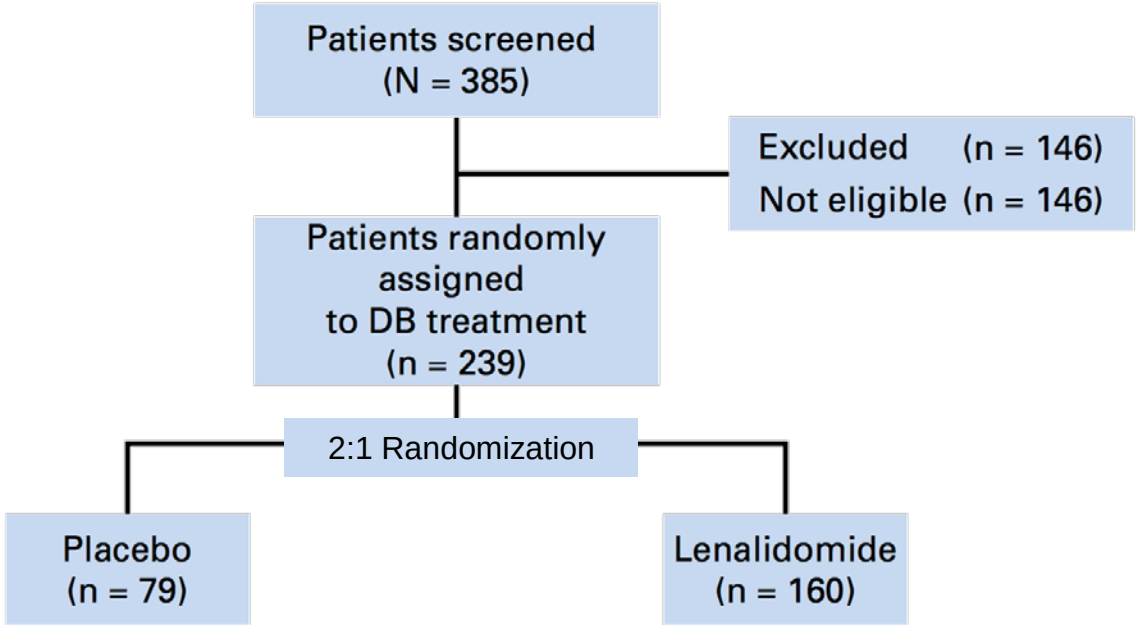
Fenaux P et al. Blood. 2011 Oct 6;118(14):3765-76.

MDS-005 Study



- RBC-Transfusion dependent anemia
- R/R or unlikely to respond to ESA

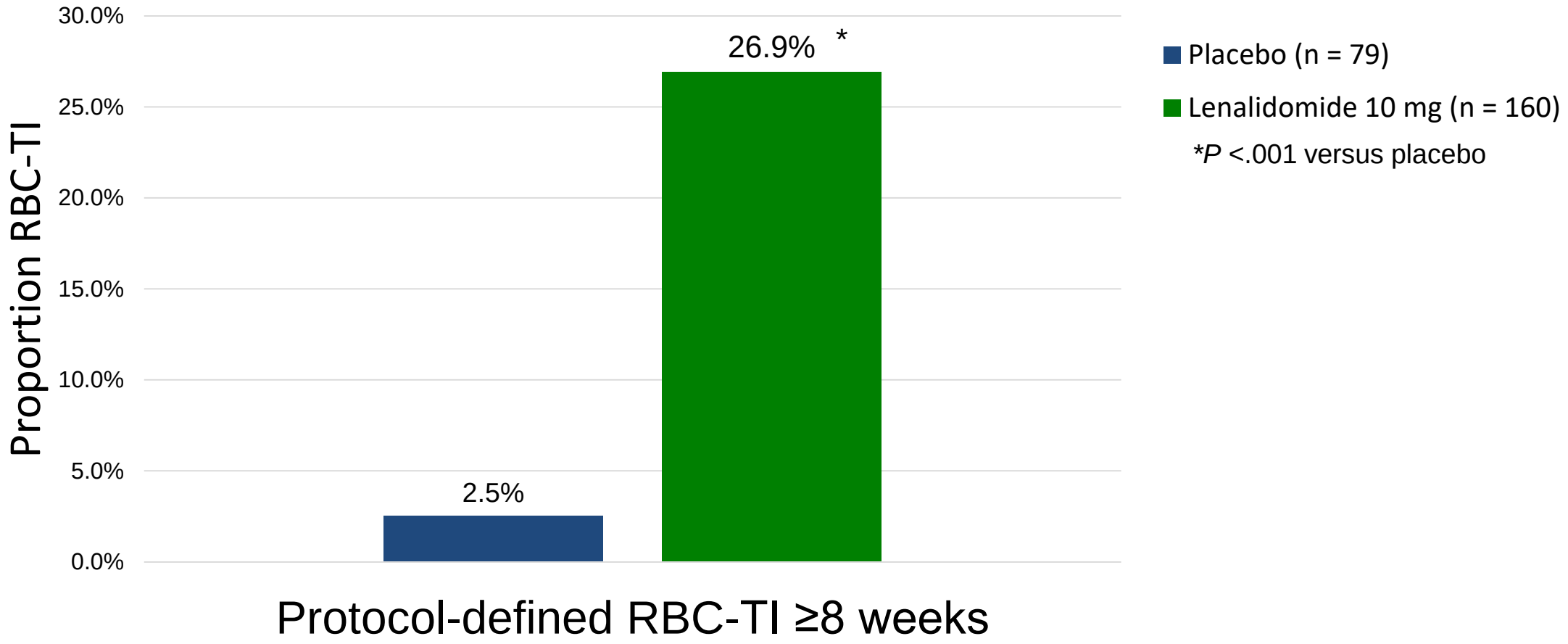
- Lenalidomide
  - 10 mg/day days 1 - 28
  - Placebo



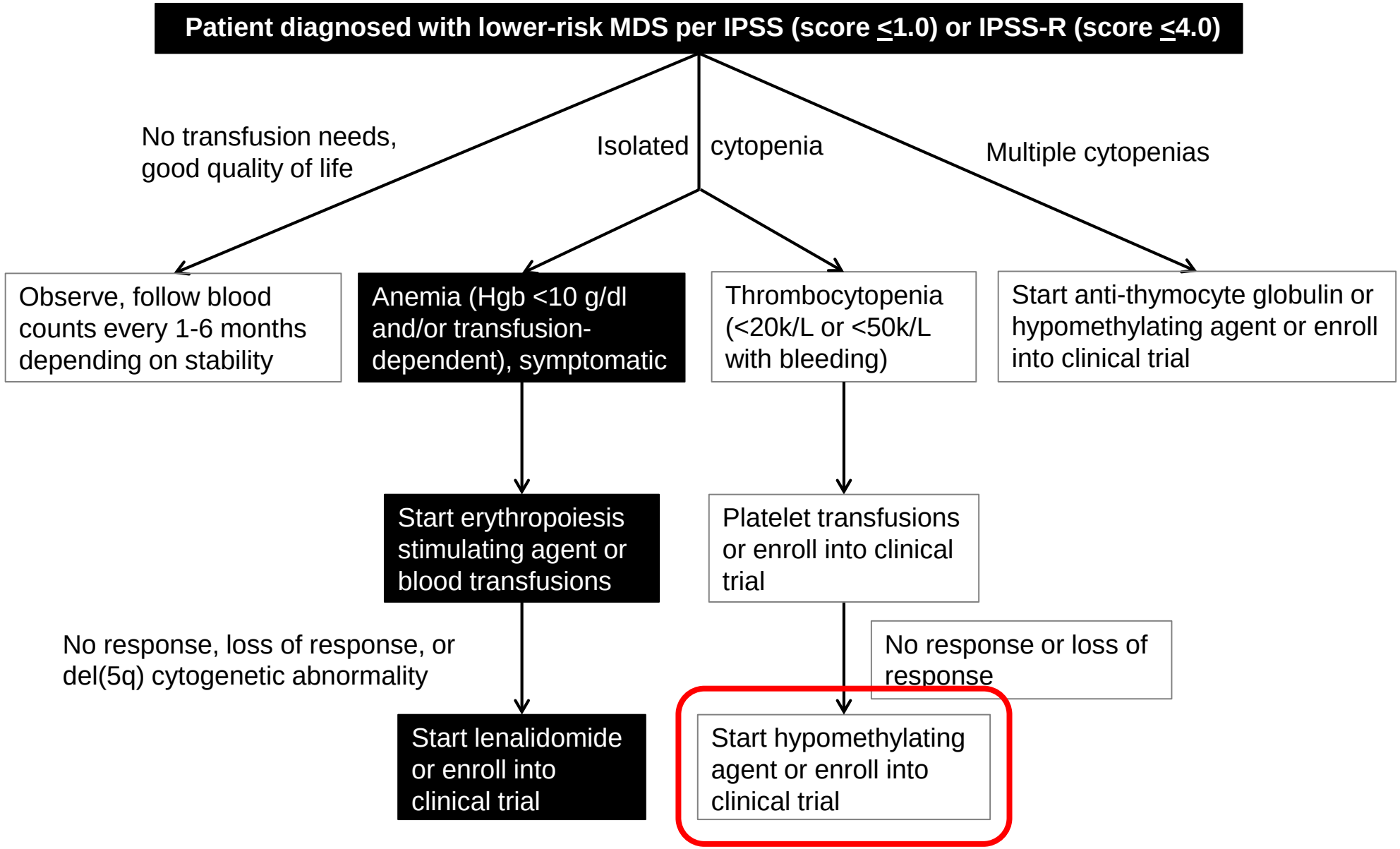
Somatic mutations (n = 198)	
SF3B1	58.6%
TET2	33.3%
ASXL1	23.2%
DNMT3A	13.6%

Santini V et al. J Clin Oncol. 2016 Sep 1;34(25):2988-96.

MDS-005 Study: Erythroid Response by RBC-TI



Santini V et al. J Clin Oncol. 2016 Sep 1;34(25):2988-96.



Sekeres MA, Gerds AT. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):82-9.

Low-Dose HMA for LR-MDS

- Regimens:
  - DAC 20 mg/m2 IV D1-3 every 4 weeks
  - AZA 75 mg/m2 IV/SC D1-3 every 4 weeks
- Response assessment by modified IWG 2006
- Between 11/2012 and 10/2015, 91 pts with LR-MDS treated and evaluable for response
- Median duration of follow-up = 14 months (range: 2-30 months)

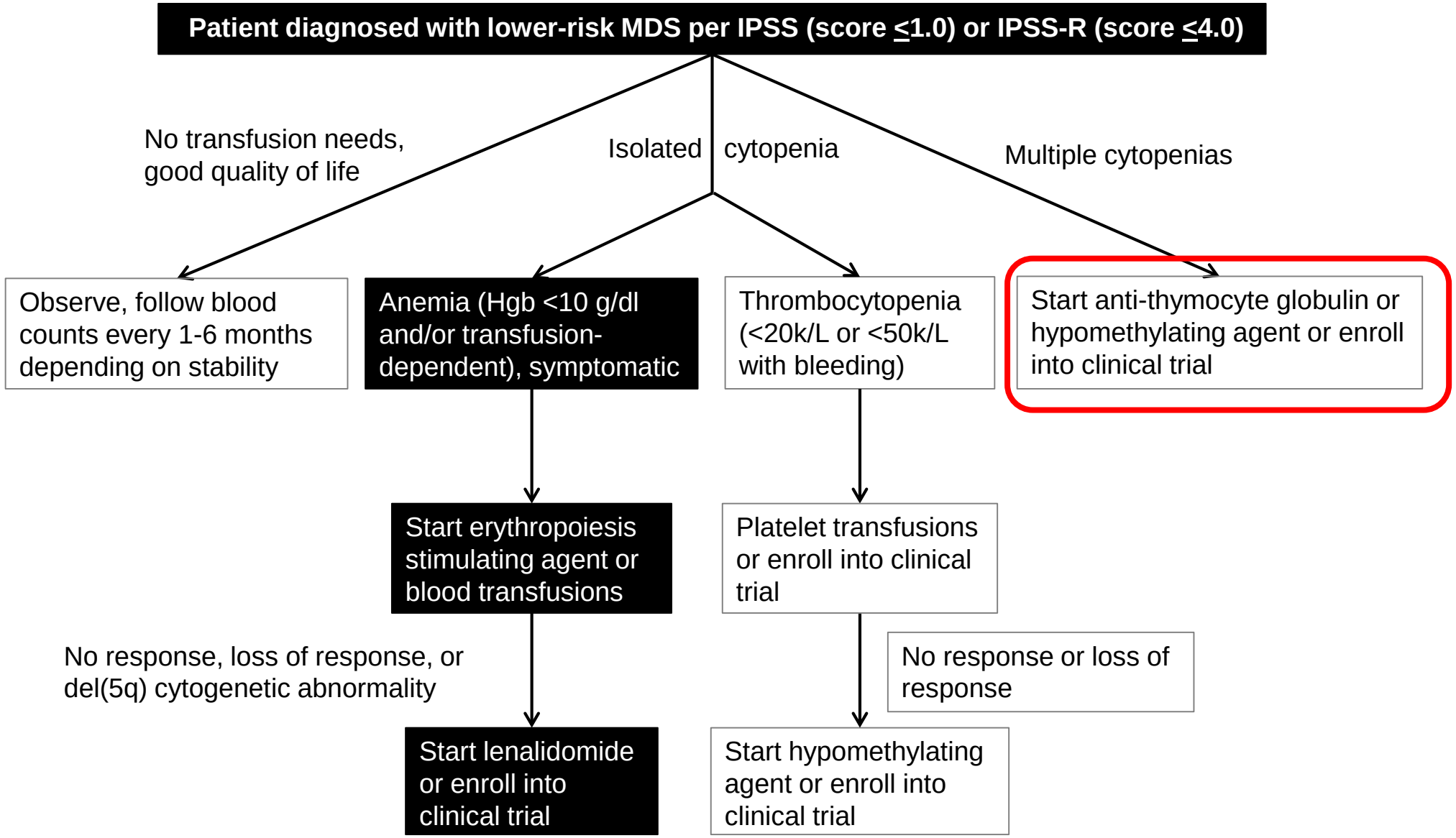
Jabour and Short et al. Blood. 2017 Sep 28;130(13):1514-1522.

Low-Dose HMA for LR-MDS

Response	N (%)
CR	33 (36)
mCR	8 (9)
HI	13 (14)
ORR	54 (59)
SD	31 (34)
PD	6 (7)

- Median time to best response: 2 months (range: 1-20)
- Median number of cycles received: 9 (range: 2-32)

Jabour and Short et al. Blood. 2017 Sep 28;130(13):1514-1522.

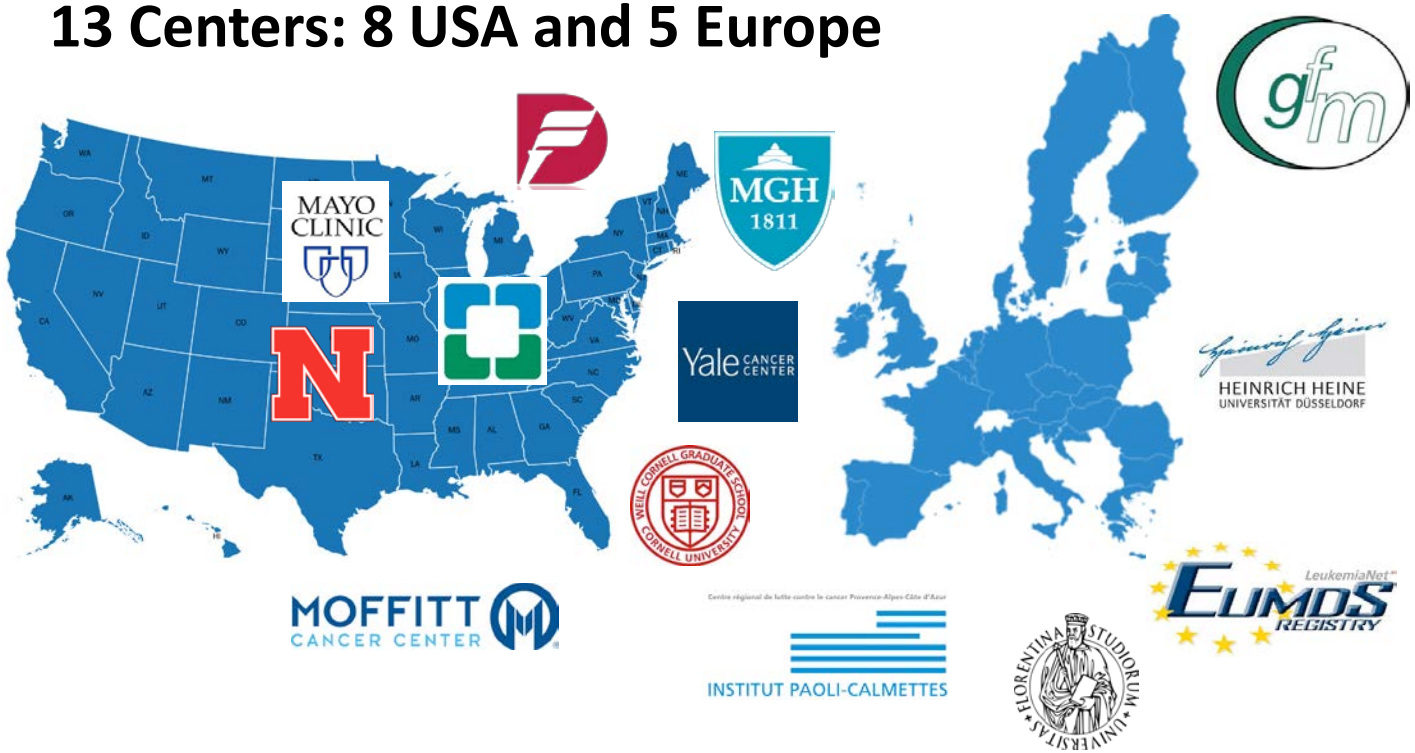


Sekeres MA, Gerds AT. Hematology Am Soc Hematol Educ Program. 2014 Dec 5;2014(1):82-9.

Anti-thymocyte Globulin for MDS

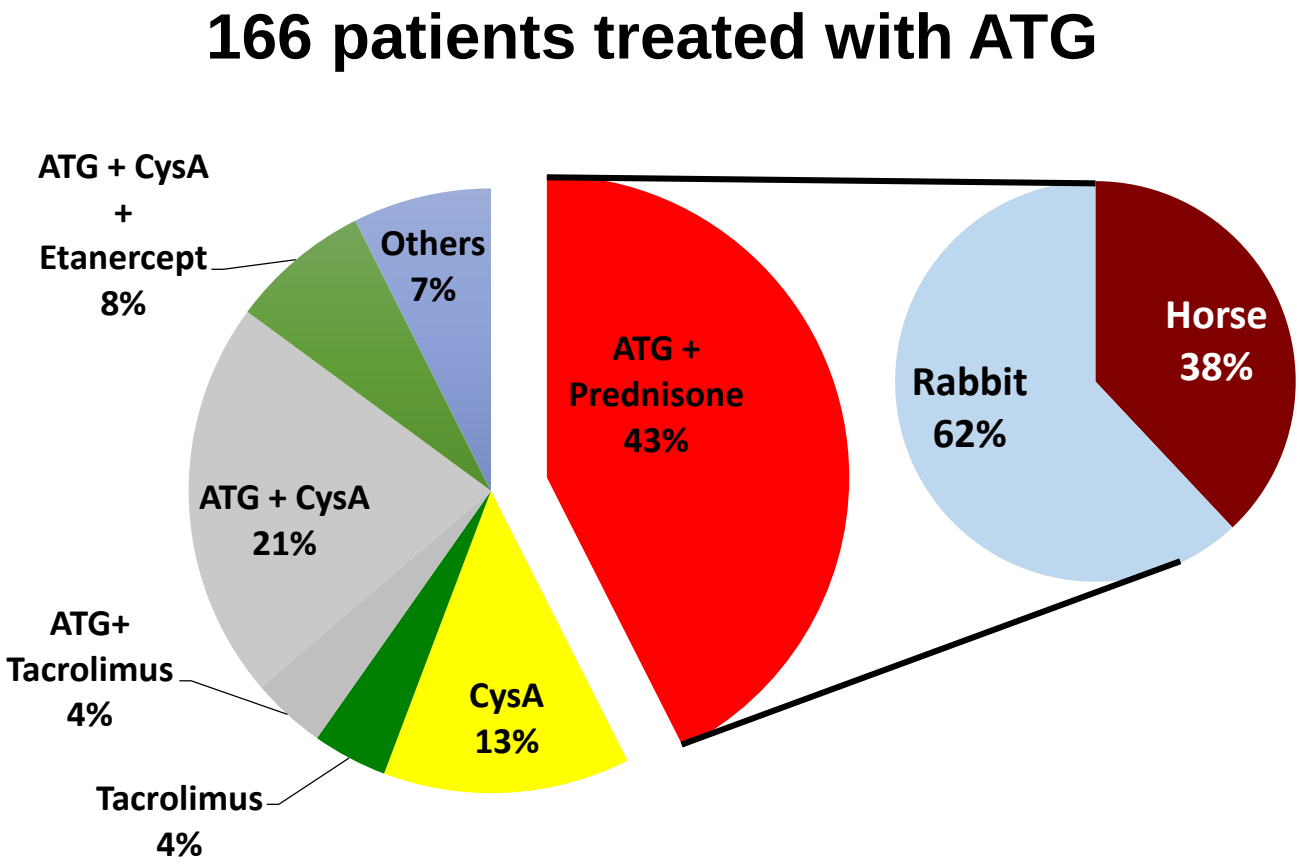
A retrospective cohort, International, multi-center, study

13 Centers: 8 USA and 5 Europe



Stahl et al. Blood Adv. 2018 Jul 24;2(14):1765-1772.

Anti-thymocyte Globulin for MDS

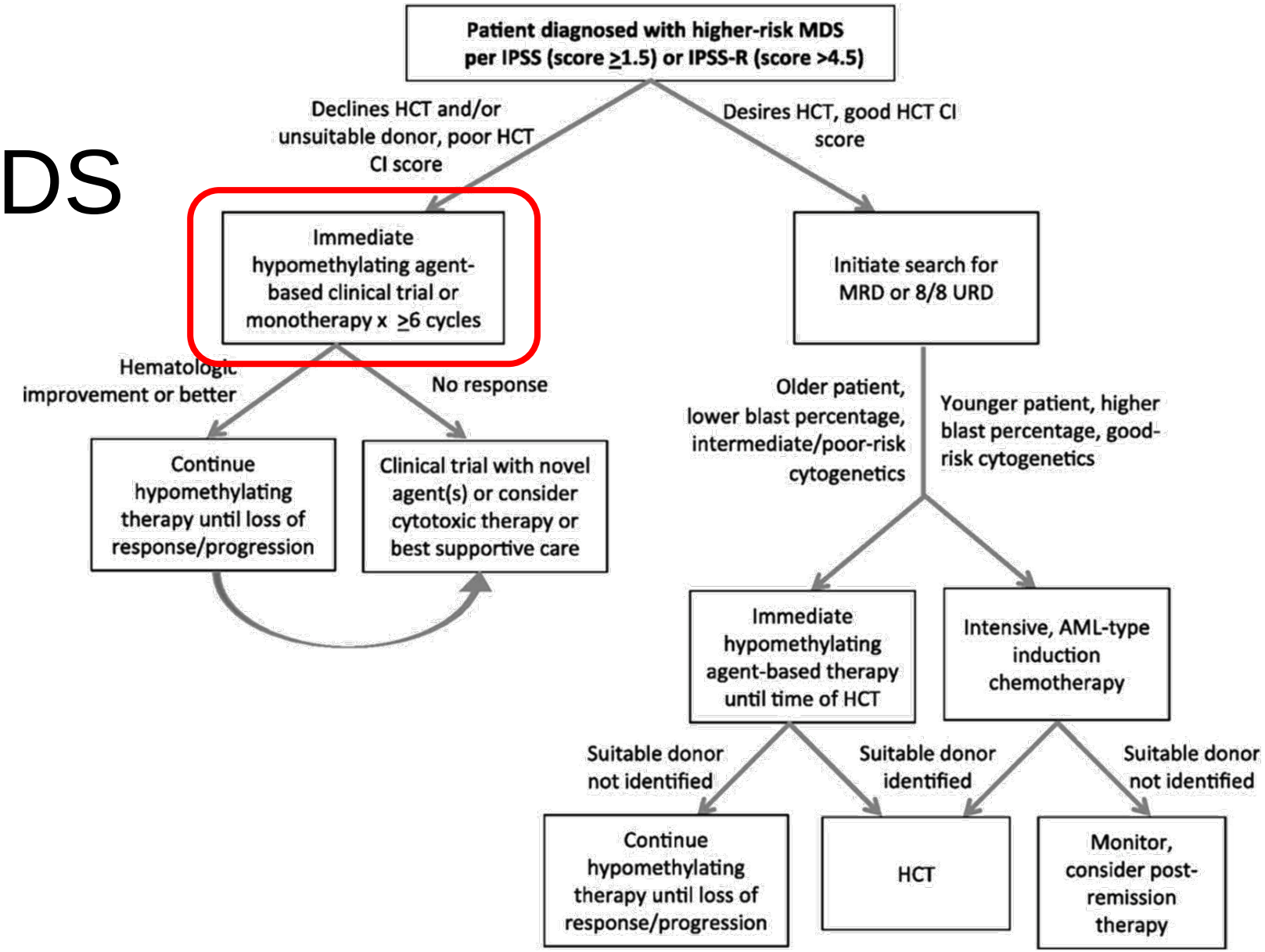


Response	%	95%CI
CR	11.2	6.5-18.4
PR	5.6	2.5-11.6
HI	32.0	24.1-41.0
SD	39.2	30.7-48.4
PD	12.0	7.1-19.3
ORR	48.8	39.8-57.9

Stahl et al. Blood Adv. 2018 Jul 24;2(14):1765-1772.

Treatment of Higher-risk MDS

Treatment of Higher-risk MDS

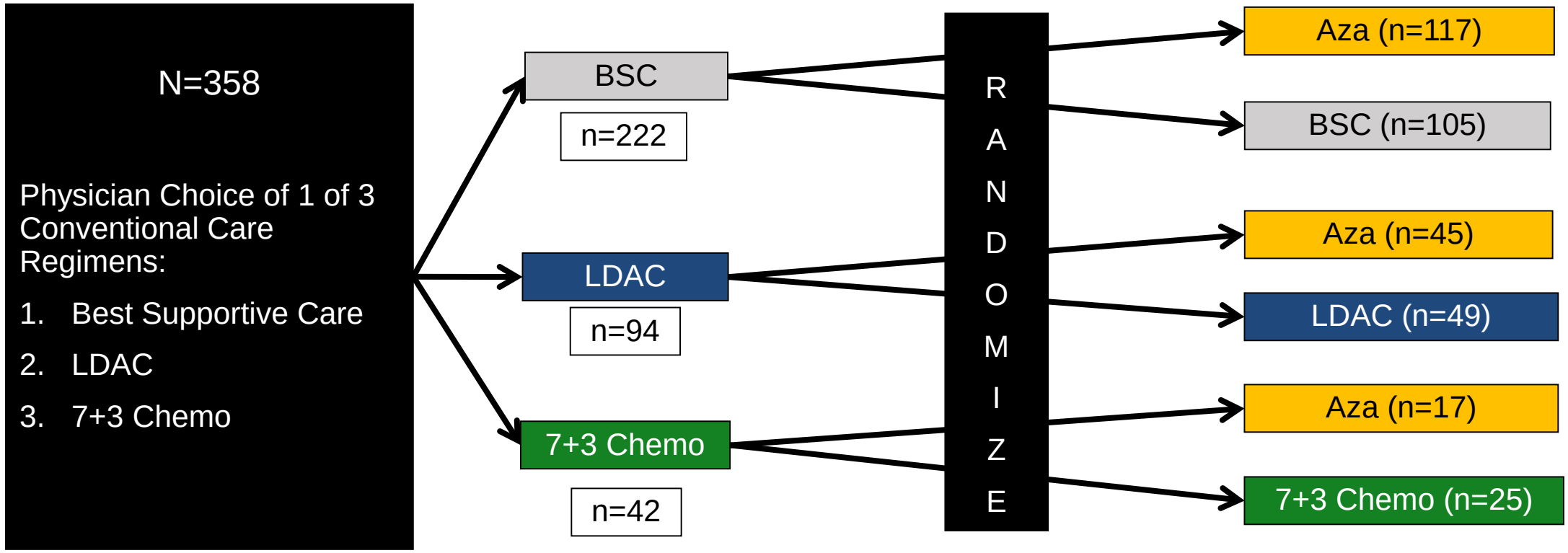


Sekeres MA., Cutler C. *Blood*. 2014 Feb 6;123(6):829-36.

Hypomethylating Agents

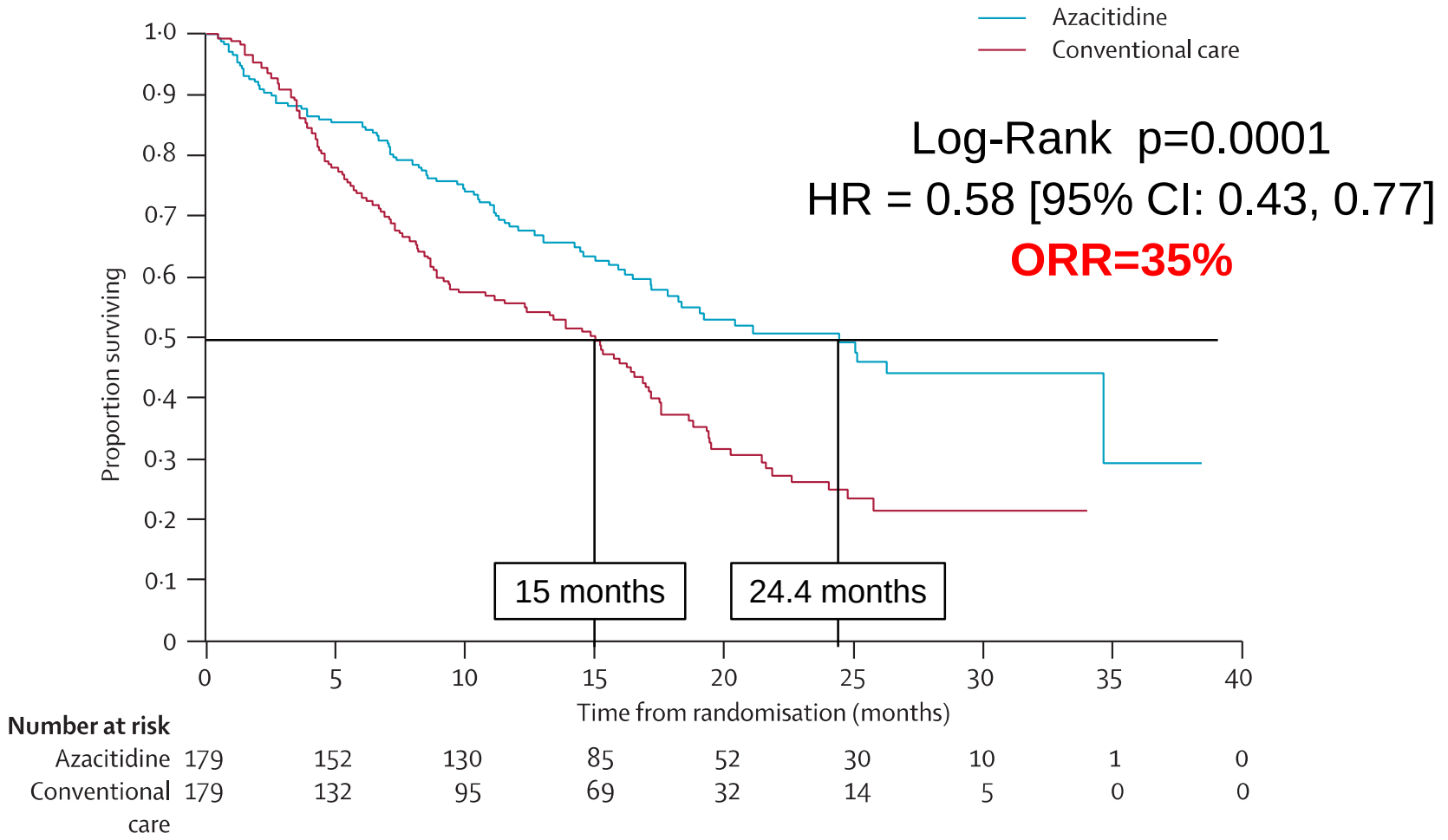
- Azacitidine and decitabine
  - Favorable toxicity profile
  - Outpatient administration
  - Delay progression of MDS to AML
  - Shown survival advantage over conventional care (azacitidine)

AZA-001 Randomization Schema



Fenaux P, et al. Lancet Oncol. 2009 Mar;10(3):223-32.

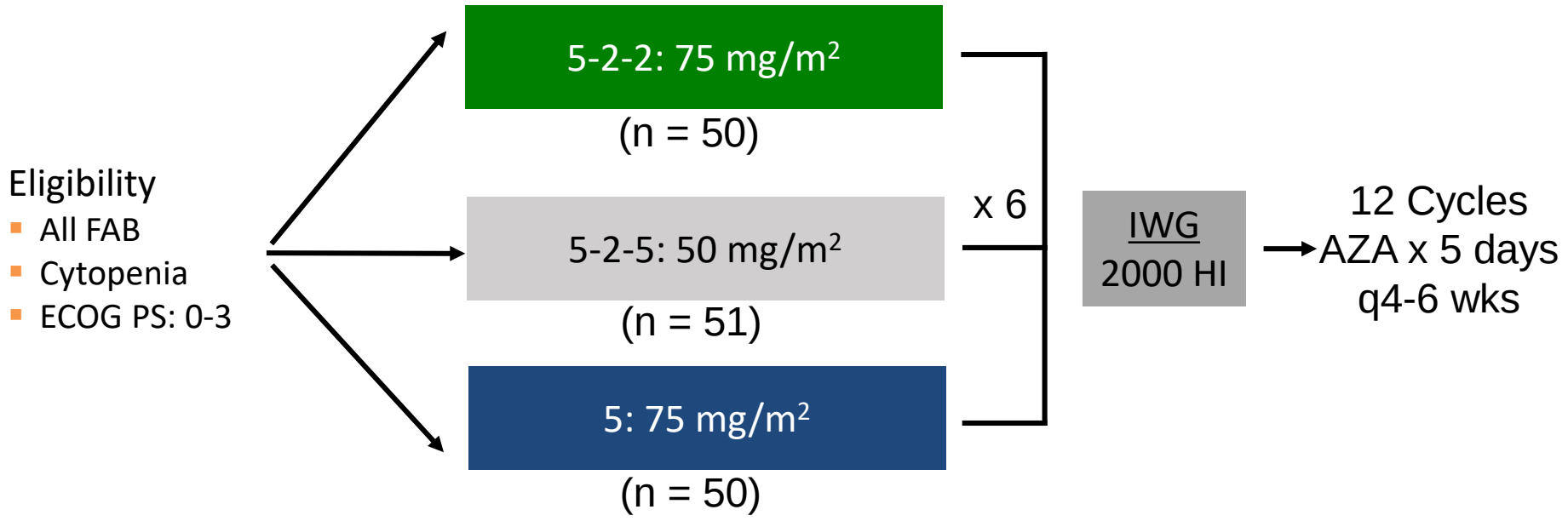
AZA-001 Overall Survival



Fenaux P, et al. Lancet Oncol. 2009 Mar;10(3):223-32.

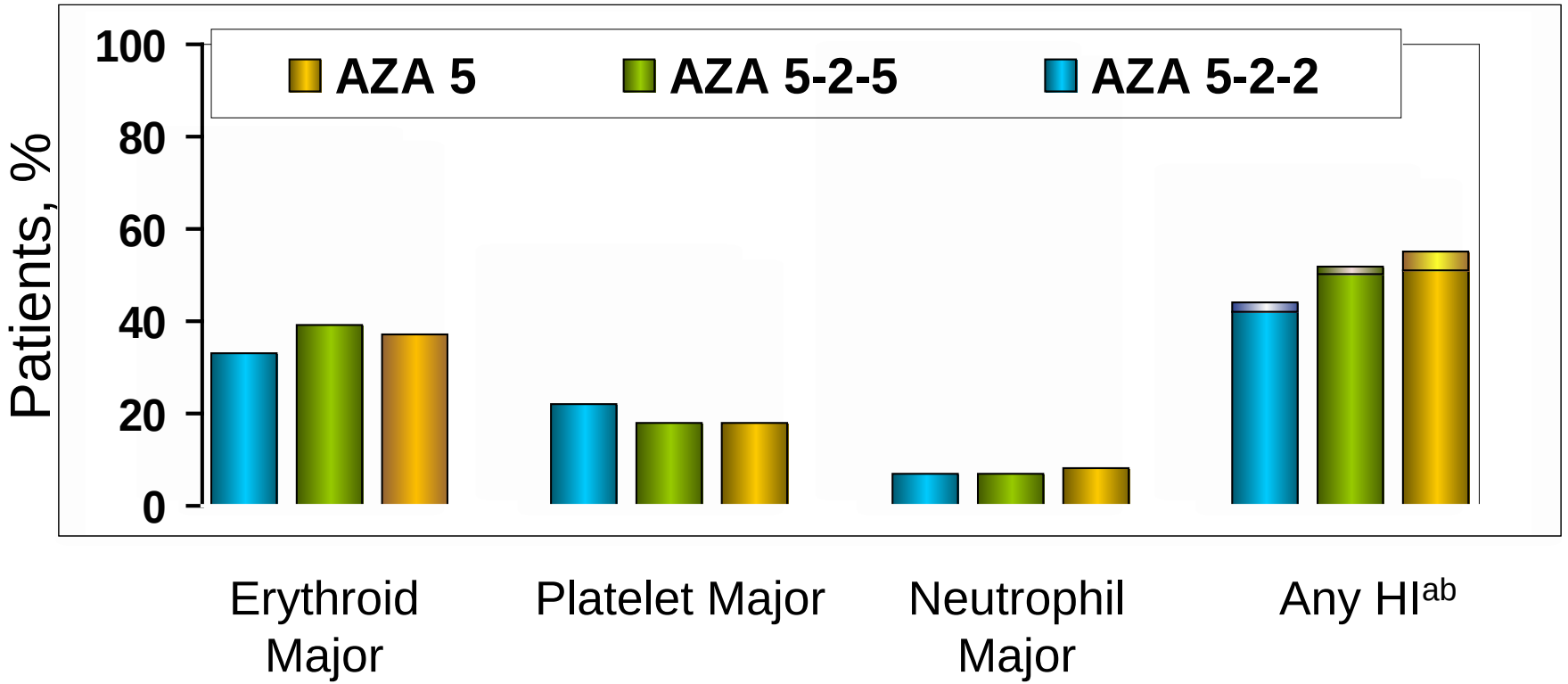
Randomized Phase II Study of Alternative AZA-002 Dose Schedules

Study Design (N = 151)



Lyons RM et al. *J Clin Oncol.* 2009;27:1850-1856.

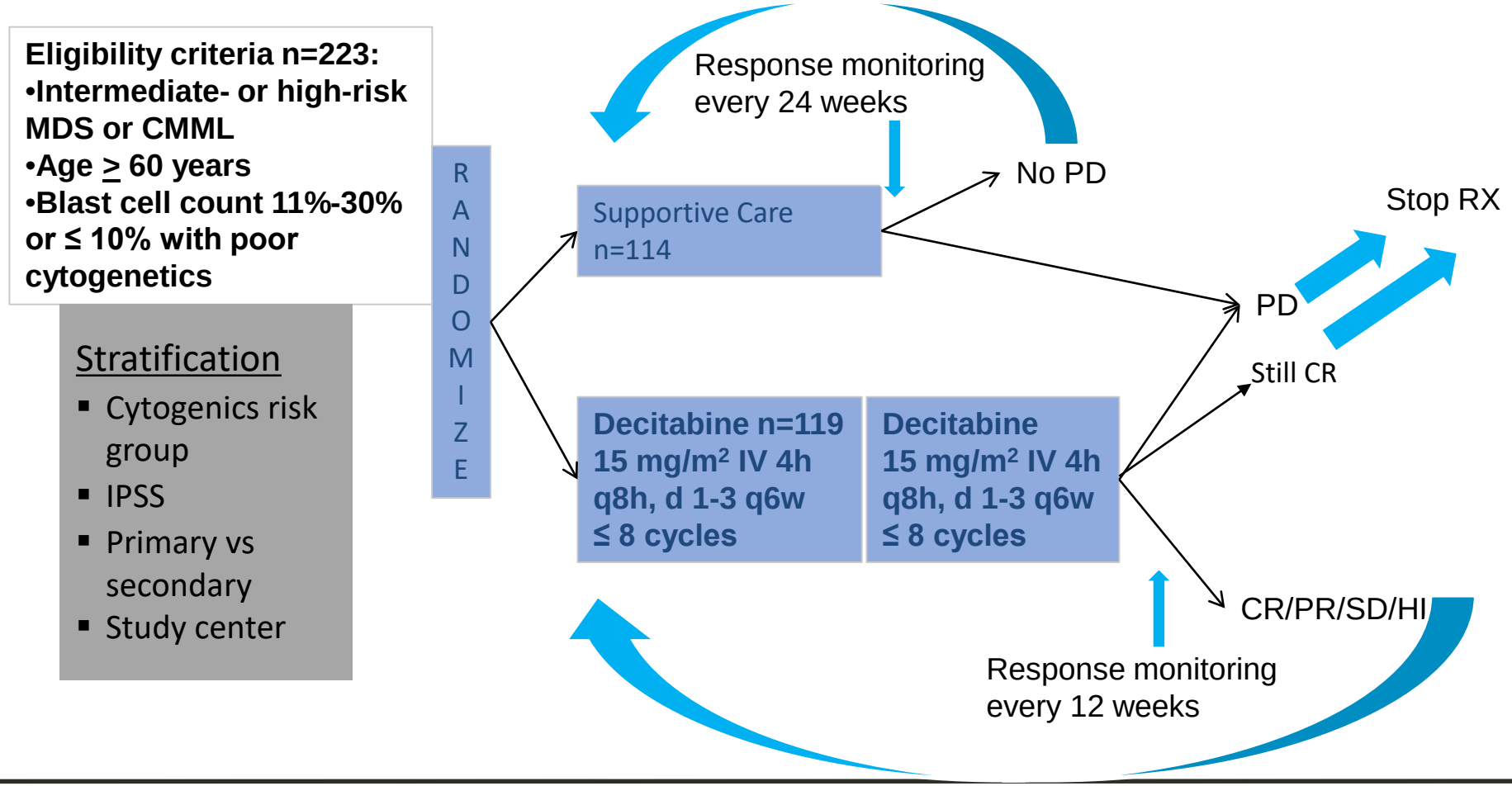
AZA-002: Hematologic Improvement



[a] Patients counted only once for best response in an improvement category.
[b] Minor improvement at top of HI columns.

Lyons RM et al. *J Clin Oncol.* 2009;27:1850-1856.

Randomized Phase III Study of Low-Dose Decitabine for Patients With Higher-Risk MDS EORTC-06011



Lübbert M, et al. J Clin Oncol. 2011;29:1987-1996

EORTC-06011 Reason for going off-protocol

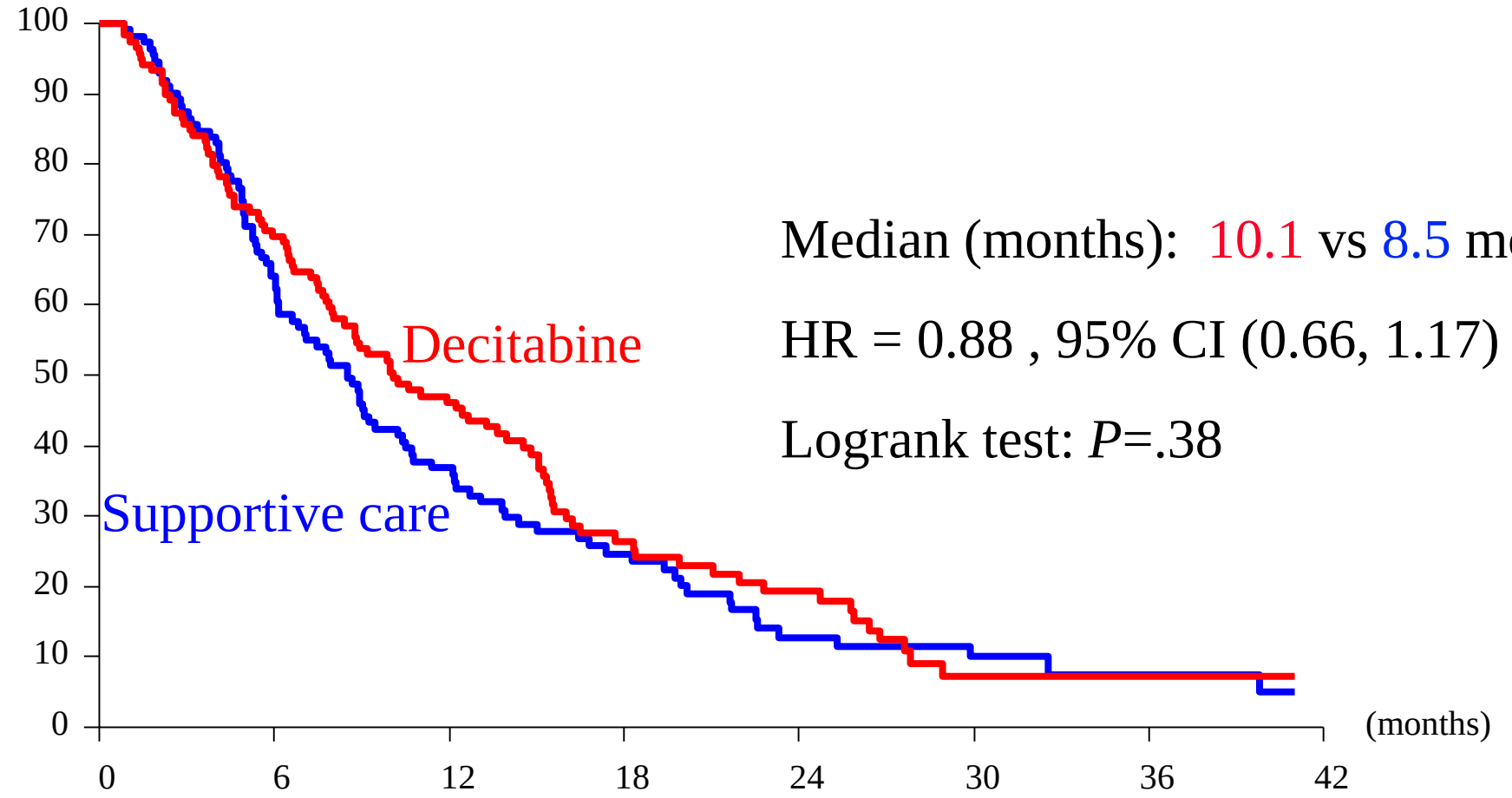
	Supportive care N=114 (100%)	Decitabine N=119 (100%)
Normal completion	19 (16.7%)	31 (26.1%)
Progression of disease	55 (48.2%)	40 (33.6%)
Toxicity	NA	19 (16.0%)
Prolonged cytopenia	NA	5 (4.2%)
Death	17 (14.9%)	11 (9.2%)
Refusal	14 (12.3%)	6 (5.0%)
Protocol violations	5 (4.4%)	3 (2.5%)
Ineligible	1 (0.9%)	1 (0.8%)
Other	3 (2.6%)	3 (2.5%)

Median time to off-study: 112 days vs 180 days

Lübbert M, et al. J Clin Oncol. 2011;29:1987-1996

Cleveland Clinic

EORTC-06011 Overall Survival



Median (months): 10.1 vs 8.5 months

HR = 0.88 , 95% CI (0.66, 1.17)

Logrank test: *P*=.38

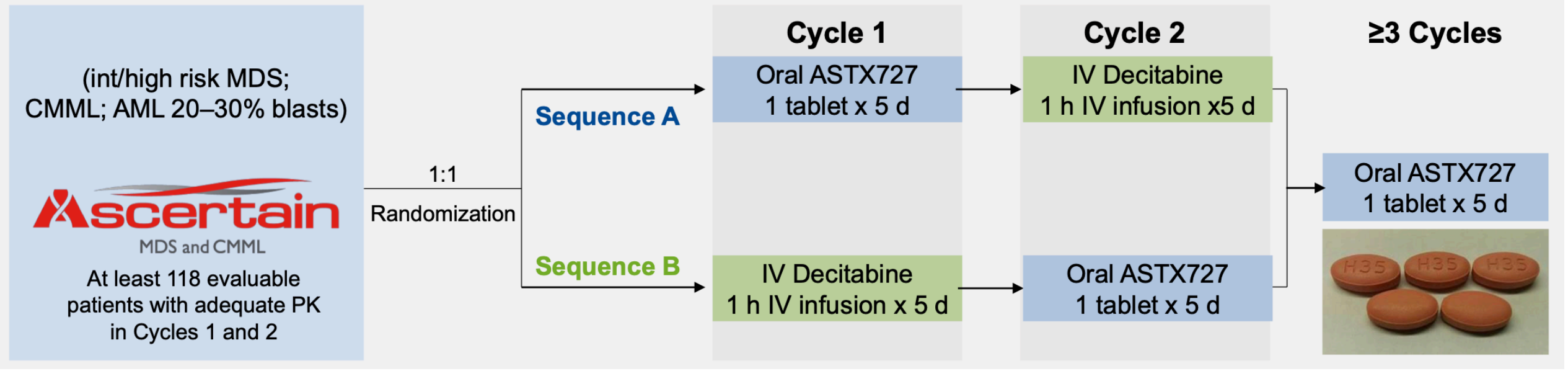
Lübbert M, et al. J Clin Oncol. 2011;29:1987-1996

No survival advantage for DAC?

- Number of treatments courses given
- Different populations and comparator groups
  - MDS duration
  - Cytogenetic risk groups
  - Performance status
- How the drug was given
- There is a true difference between aza and dac

Oral Decitabine (Approval 7/7/2020)

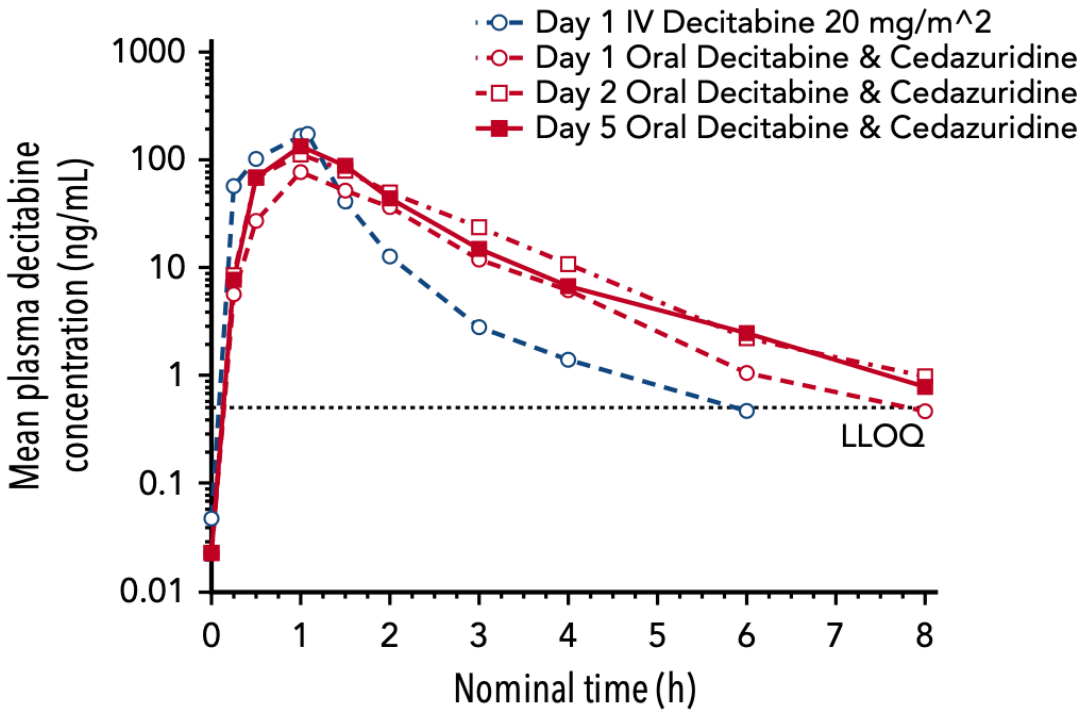
- 35mg decitabine/100mg cedazuridine vs deciatibine (20 mg/m^2)
  - ASTX727-01-B (N=80) – Phase 1/2
  - ASTX727-02 (N=133) – Phase 3



Savona M, et al. *Lancet Haematol*. 2019 Apr;6(4):e194-e203.
Garcia-Manero, G et al. *Blood*. 2020 Aug 6;136(6):674-683.

Oral Decitabine

- ASTX727-01-B
  - CR rate of 18% (95% CI, 10%-28%)
  - Median duration of CR 8.7 (range, 1.1-18.2) months
- ASTX727-02 (Ascertain)
  - CR rate of 21% (95% CI, 15%-29%)
  - Median duration of CR 7.5 (range, 1.6-17.5) months
- Both studies showed similar:
  - Side effect profiles/toxicity
  - PK data between oral and IV formulation

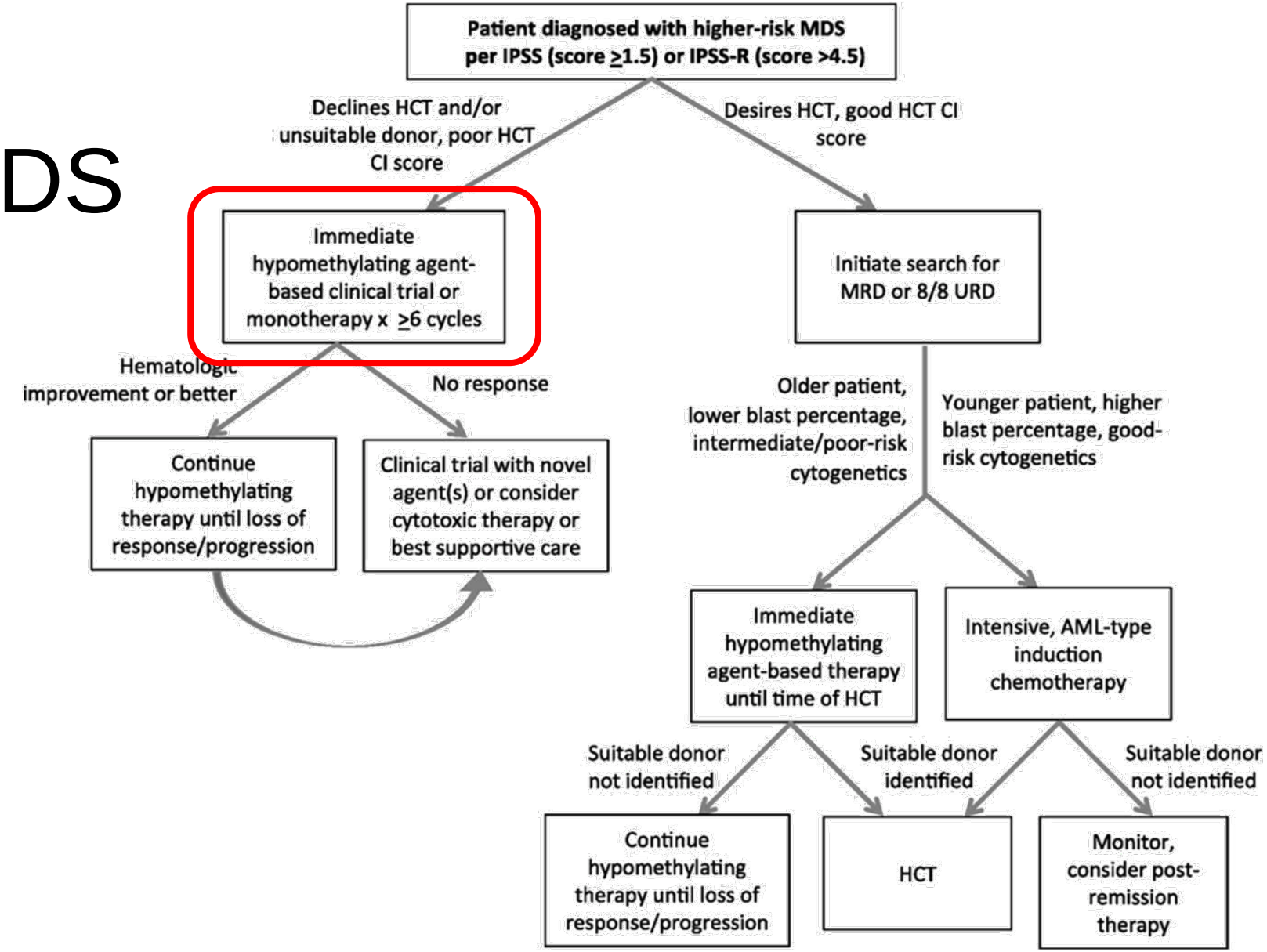


- Comparison of disease response between oral and IV was not possible because all patients received decitabine-cedazuridine starting in cycle 3

Savona M, et al. *Lancet Haematol*. 2019 Apr;6(4):e194-e203.
Garcia-Manero, G et al. *Blood*. 2020 Aug 6;136(6):674-683.

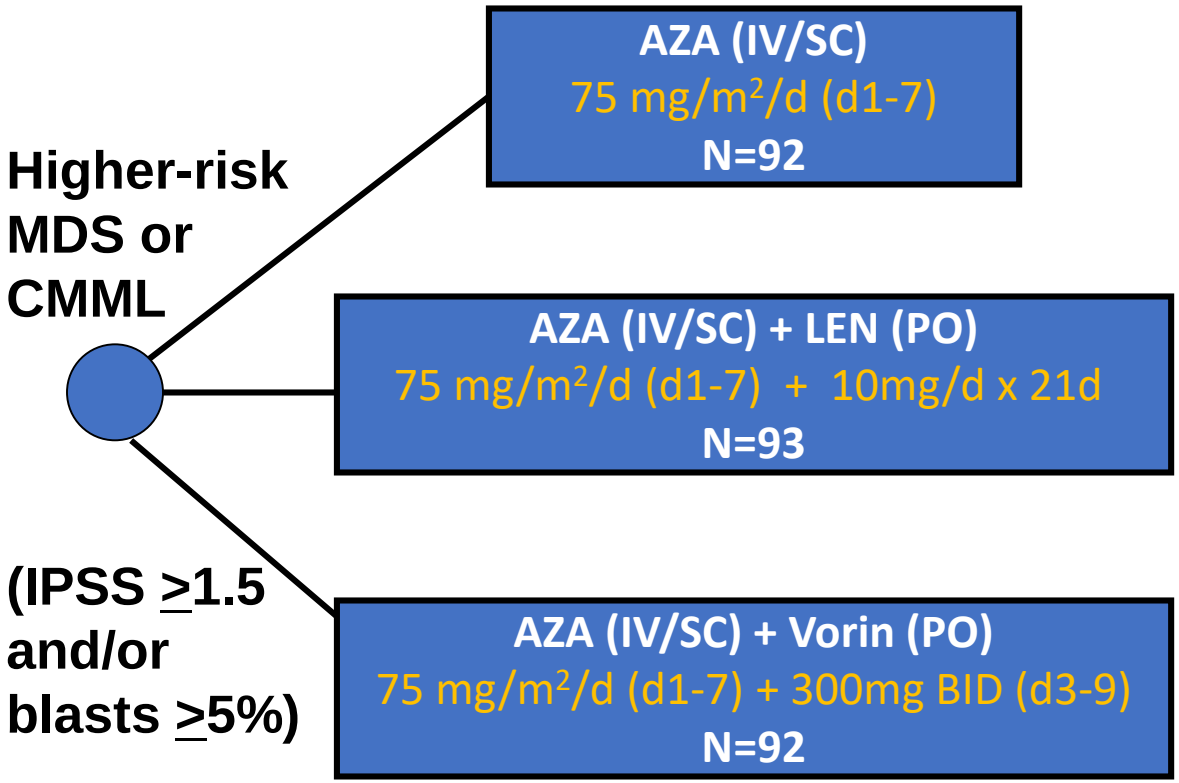
Treatment of Higher-risk MDS

Oral C-DEC?



Sekeres MA., Cutler C. *Blood*. 2014 Feb 6;123(6):829-36.

North American Intergroup Randomized Phase 2 MDS Study S1117: Study Design



Groups: SWOG, ECOG, Alliance, NCIC

Total Sample Size: 282/277

Primary Objective: 20% improvement of ORR (CR/PR/HI) based on 2006 IWG Criteria

Secondary Objectives: OS, RFS, LFS

Power 81%, alpha 0.05 for each combo arm vs. AZA

06/2012 – 06/2014

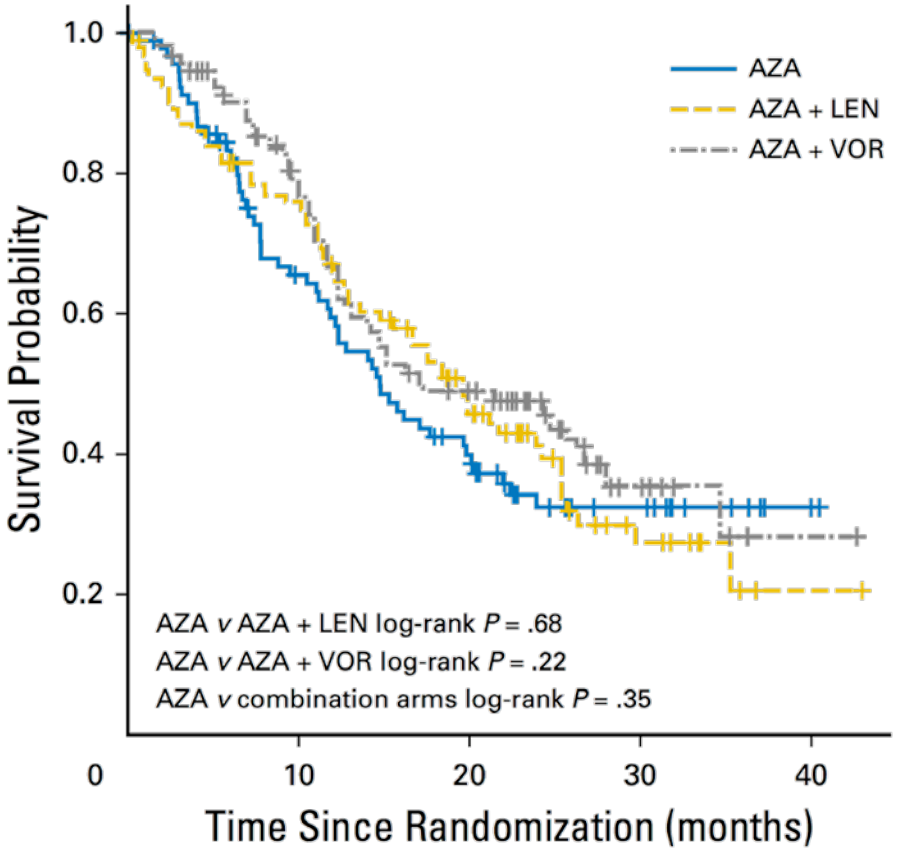
Sekeres MA et al, J Clin Oncol. 2017 Aug 20;35(24):2745-2753

North American Intergroup Randomized Phase 2 MDS Study S1117: Response

Response Variable	AZA	AZA+LEN (P-value vs. AZA)	AZA+VOR (P-value vs. AZA)	Total n=277
Median Tx Duration (Wks)	25	24	20	22
Overall Response Rate (%)	38	49 (.16)	27 (.16)	38%
CR/PR/HI (%)	24/0/14	24/1/25	17/1/9	22/1/16%
CMML ORR (%)	5 (28)	13 (68) (.02)	2 (12) (.41)	37%
ORR Duration (median)	10 months	14 months (.41)	15 months (.31)	14 months

Sekeres MA et al, J Clin Oncol. 2017 Aug 20;35(24):2745-2753

North American Intergroup Randomized Phase 2 MDS Study S1117: OS All Patients

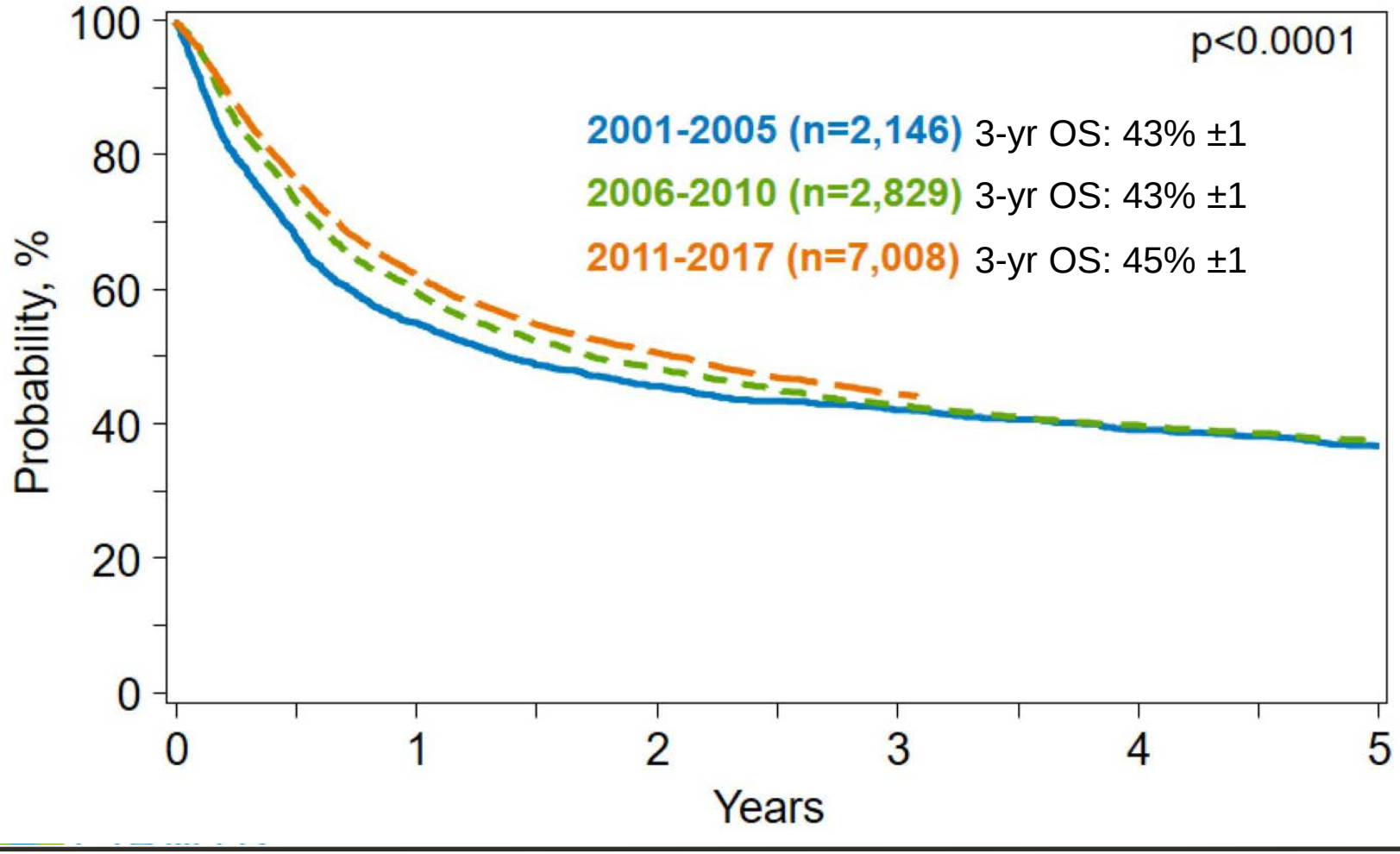


Sekeres MA et al, J Clin Oncol. 2017 Aug 20;35(24):2745-2753

Blood and Marrow Transplantation for MDS

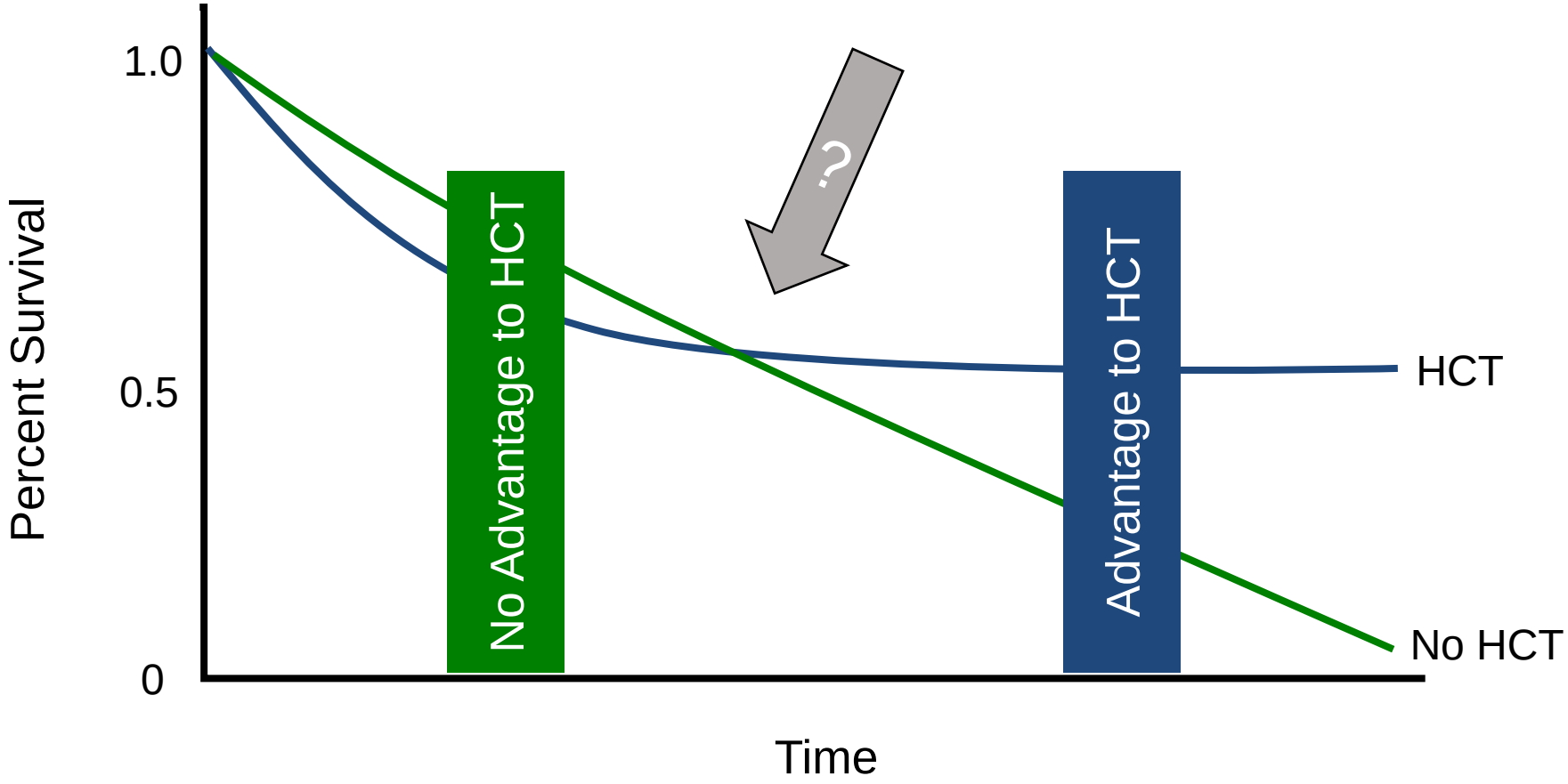
Cleveland Clinic
Taussig Cancer Institute

OS after HCT for MDS, 2001-2017

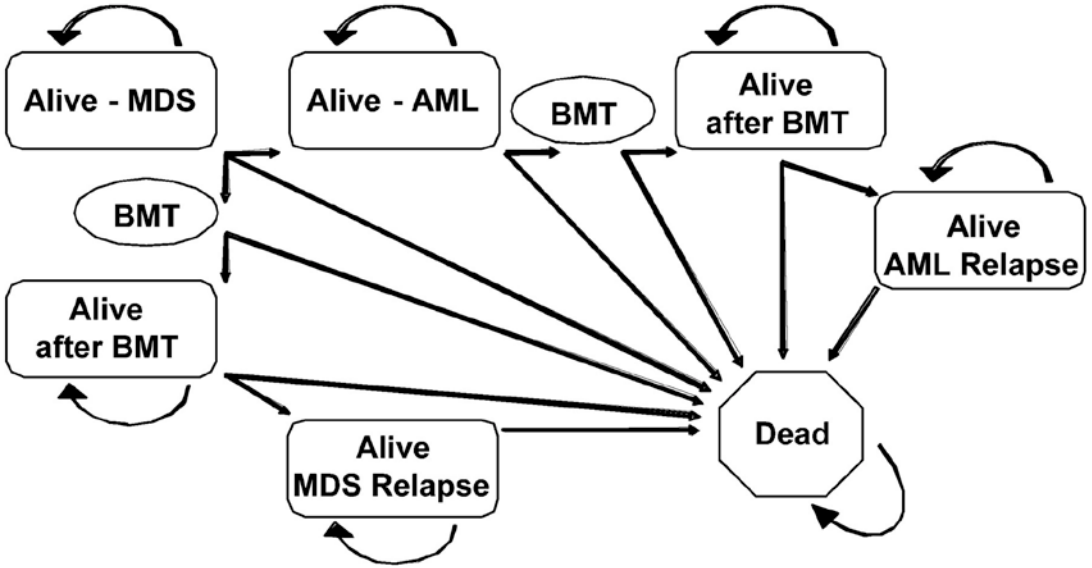


D'Souza A, Fretham C. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2019. Available at https://www.cibmtr.org

Allogeneic HCT for MDS



Markov Modeling in HCT



- Retrospective comparison
  - All Primary MDS
  - Marrow Grafts
  - HLA-identical donors
  - Myeloablative
- 184 Delayed transplant MDS
- 260 Transplant MDS at time of diagnosis
- 230 Transplant at progression to tAML

Cutler C, et al. Blood. 2004 Jul 15;104(2):579-85.

Decision Analysis

Estimated Life expectancy (years) after HCT for MDS (age < 60)

IPSS RISK	Immediate HCT	HCT in 2 years	HCT at progression
Low	6.51	6.88	**7.21**
Int-1	4.61	4.74	**5.16**
Int-2	**4.93**	3.21	2.84
High	**3.20**	2.75	2.75

Cutler C, et al. Blood. 2004 Jul 15;104(2):579-85.

Decision Analysis

Estimated Life expectancy (years) after RIC-HCT for MDS (age ≥ 60)

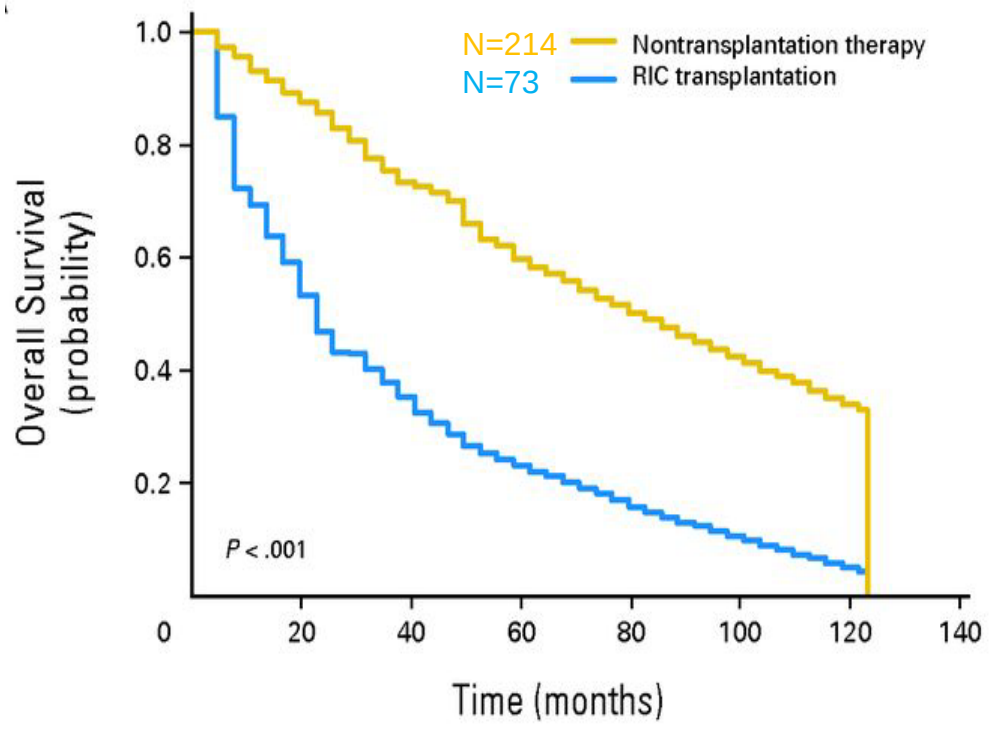
IPSS RISK		Non-HCT	Early HCT
Low/Int-1	Overall LE	6.42	3.17
	QALE: TI	5.42	2.92
	QALE: TD	3.83	2.92
Int-2/High	Overall LE	0.24	3.00
	QALE: HR-MDS	1.25	2.75
	QALE: GvHD	1.25	1.83

Koreth J, et al. Blood 2011; ASH Annual Meeting Abstracts 2011 118: 115.

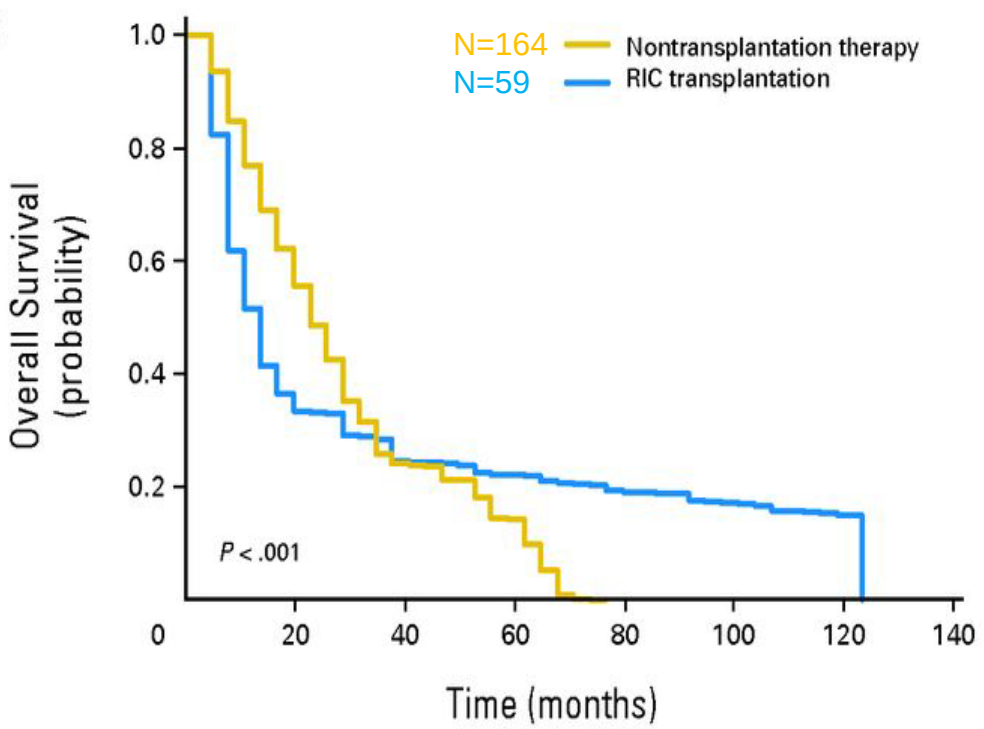
Timing of HCT by IPSS Using RIC

- *de novo* MDS 60-70 years of age
- Survival measured from start of therapy
- HLA Matched Donors
- Bu x 2 days or 2-4 Gy TBI (no T-cell depletion)

Low/Int-1



Int-2/High



Koreth et al. *J Clin Oncol* 2013;31:2662-2670

Summary – Myelodysplastic Syndromes

1. Organization, in general
2. Diagnosis and Classification
3. Epidemiology
4. Pathogenesis
    a. Clonal Process
    b. Secondary MDS
5. Risk stratification
    a. IPSS-R
6. Treatment of Lower-risk MDS
    1. ESAs
    2. IMIDS
    3. Immunosuppressive therapy
7. Treatment of Higher-risk MDS
    1. Hypomehtylating agents
8. Transplantation for MDS
9. Discussion

Cleveland Clinic
Taussig Cancer Institute

Discussion

Thanks!

Mikkael Sekeres, MD, MS
Jaroslaw Maciejewski, MD, PhD
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Matt Kalaycio, MD
Ronald Sobecks, MD
Betty Hamilton, MD
Aziz Nazha, MD
Bhumika Patel, MD
Yogen Saunthararajah, MD
Babal Jha, PhD

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And Our Patients!!!

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Comprehensive Oncology Review: Colorectal Cancer - Adjuvant

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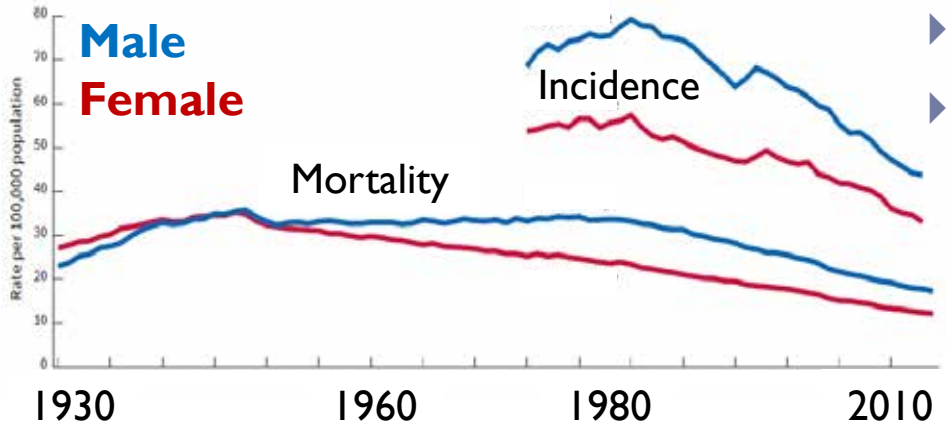
Outline

- Epidemiology and risk factors
- Evaluation and initial management
- Adjuvant chemotherapy for colon cancer
- Localized rectal cancer

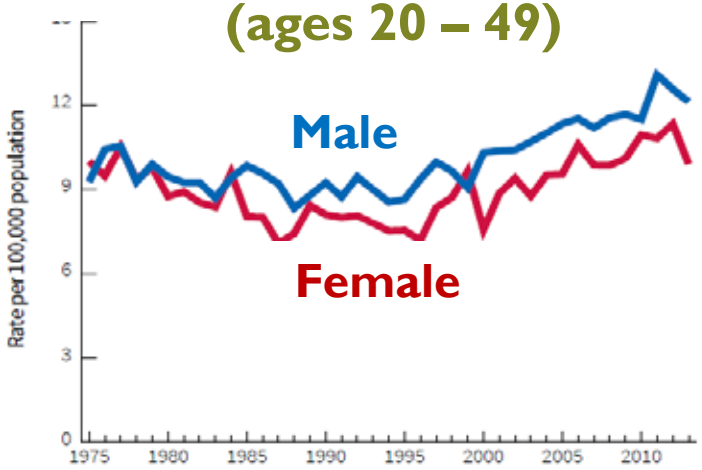
Epidemiology and Risk Factors

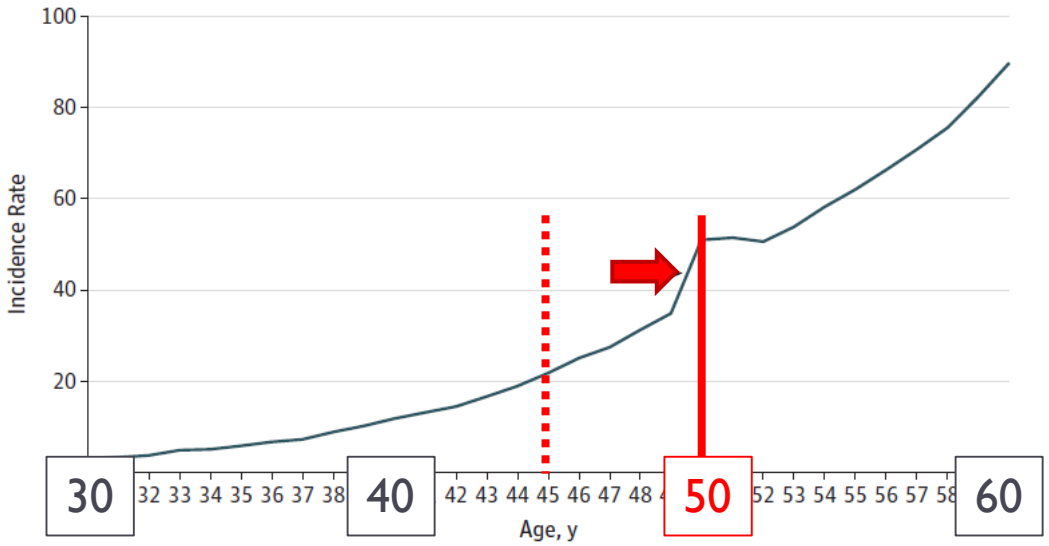
Epidemiology



- 90% are diagnosed after age 50
- But rising incidence in younger individuals
  - Diet? Environment? Microbiome? (in unscreened population)
  - Start screening earlier?
    50 (NCCN, ASCO, USPSTF) ⇨ ?45 (ACS)

Rising in the unscreened (ages 20 – 49)





- SEER: 1930 – 2016; Abualkhair *JAMA Network Open* 2020; Yarden, *AACR* 2019

Risk factors for colorectal cancer

Environmental

(*Increase*)

- Tobacco
- Alcohol
- Low fiber
- Red meat
- Antibiotics
- Sedentary lifestyle

(*Decrease*)

- Aspirin
  - *PIK3CA* mutations?
- NSAIDs
- Post-menopausal hormones
- Calcium
- Vitamin D

Genetic

- Estimated 12-35% is familial
  - Higher risk for siblings than a parent-child
- 5-10% due to highly penetrant cancer family syndromes
  - Lynch syndrome (2-5%)
  - Familial Adenomatous Polyposis (1%)

  …and others

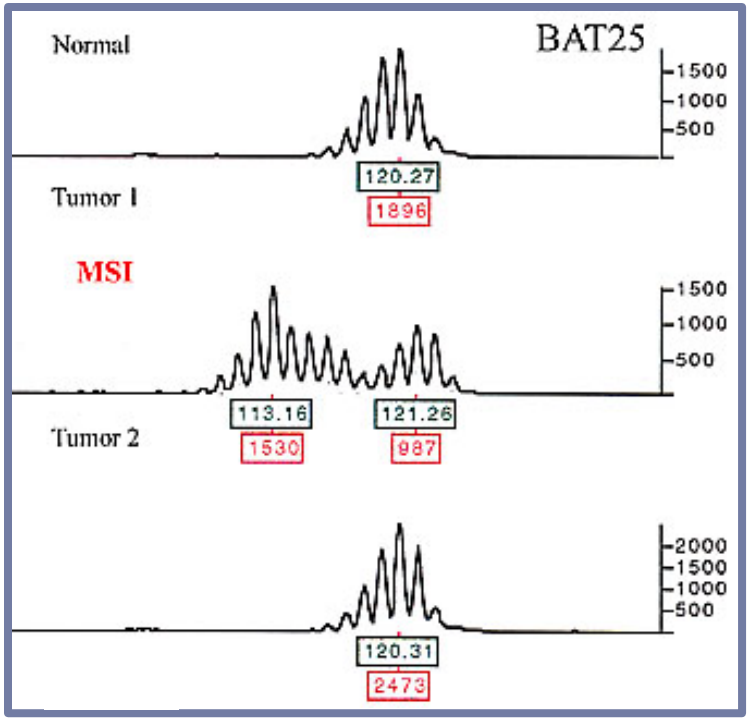
Inflammatory bowel disease

Chan, *Gastro* 2010; Jiao, *Hum Mol Genet* 2014; Hemminki, *CEBP* 2004; Chubb *JCO* 2015; Seigel *JNCI* 2017, Zhang, Gut 2019

Microsatellite instability (MSI)

- 15% of colorectal cancers are MSI-high
  - Detect with PCR, IHC, and/or next-generation sequencing
  - Prognostic and predictive biomarker
- 20% MSI-high = germline
  - Lynch syndrome (formerly: HNPCC)
- 80% MSI-high = somatic
  - Typically due to *MLH1* promoter hypermethylation
  - Often also *BRAF* mutated
- **Universal testing recommended**

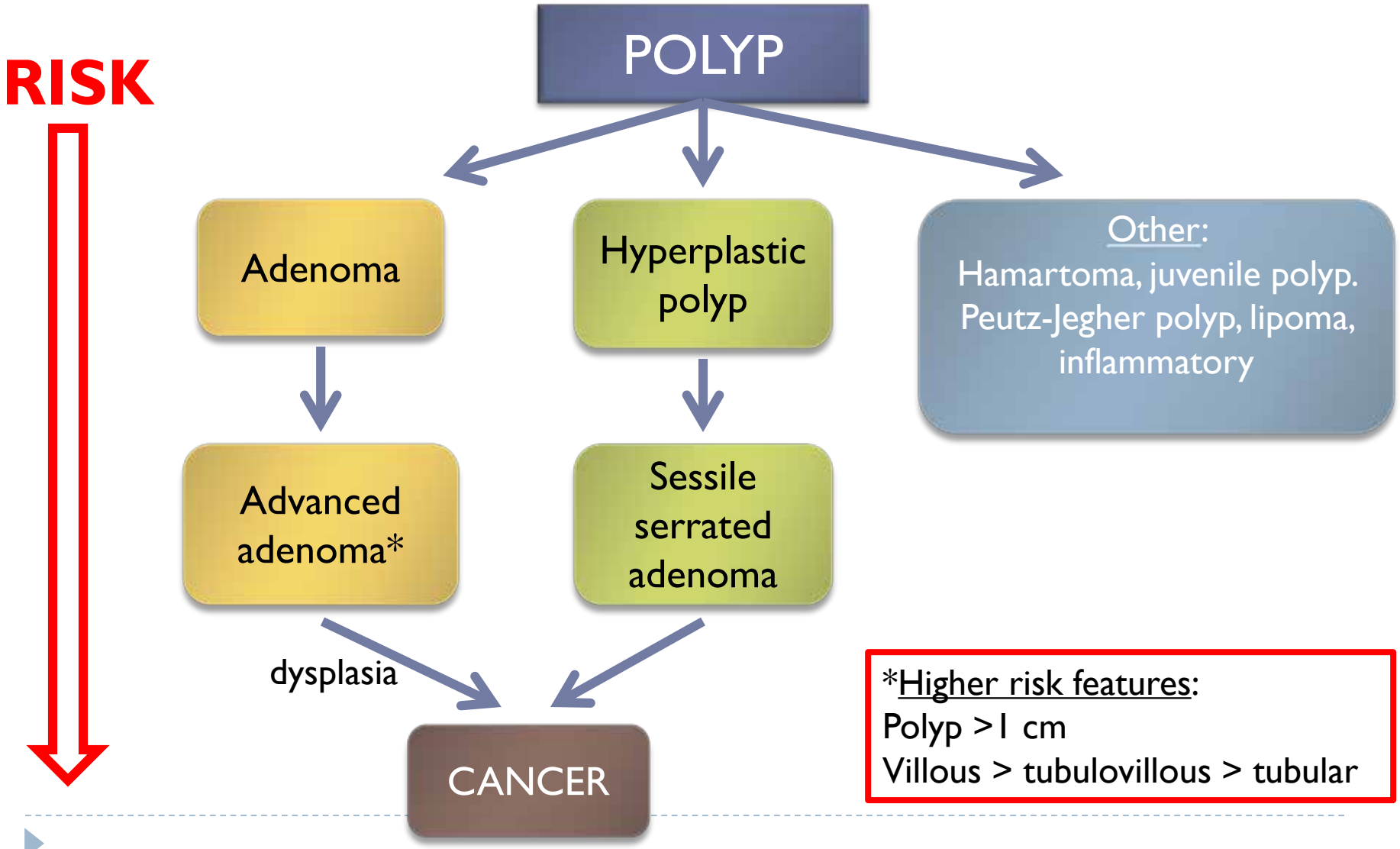
MSI-H = ≥30% loci instable



Hampel, *NEJM* 2005

www.ous-research.no/home/lothe/methods/2766

Polyps as precancerous lesions



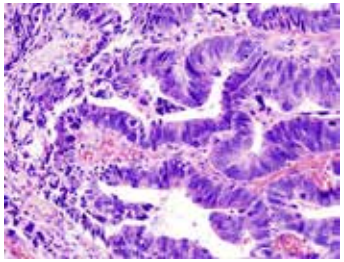
Key points

- Lynch syndrome
  - Most common hereditary CRC syndrome
  - Due to germline mismatch repair mutations → tumor MSI
  - But, not all MSI is due to Lynch (esp. *BRAF*-mutant)

- >1cm and villous adenomas have the highest likelihood of devolving into cancer

Evaluation and Initial Management

Work-up of suspected cancer



Colonoscopy to terminal ileum

Pathology (CK7- CK20+ CDX2+ villin+)

Labs (including CEA)

Tumor molecular testing (MSI, ± extended RAS/RAF)

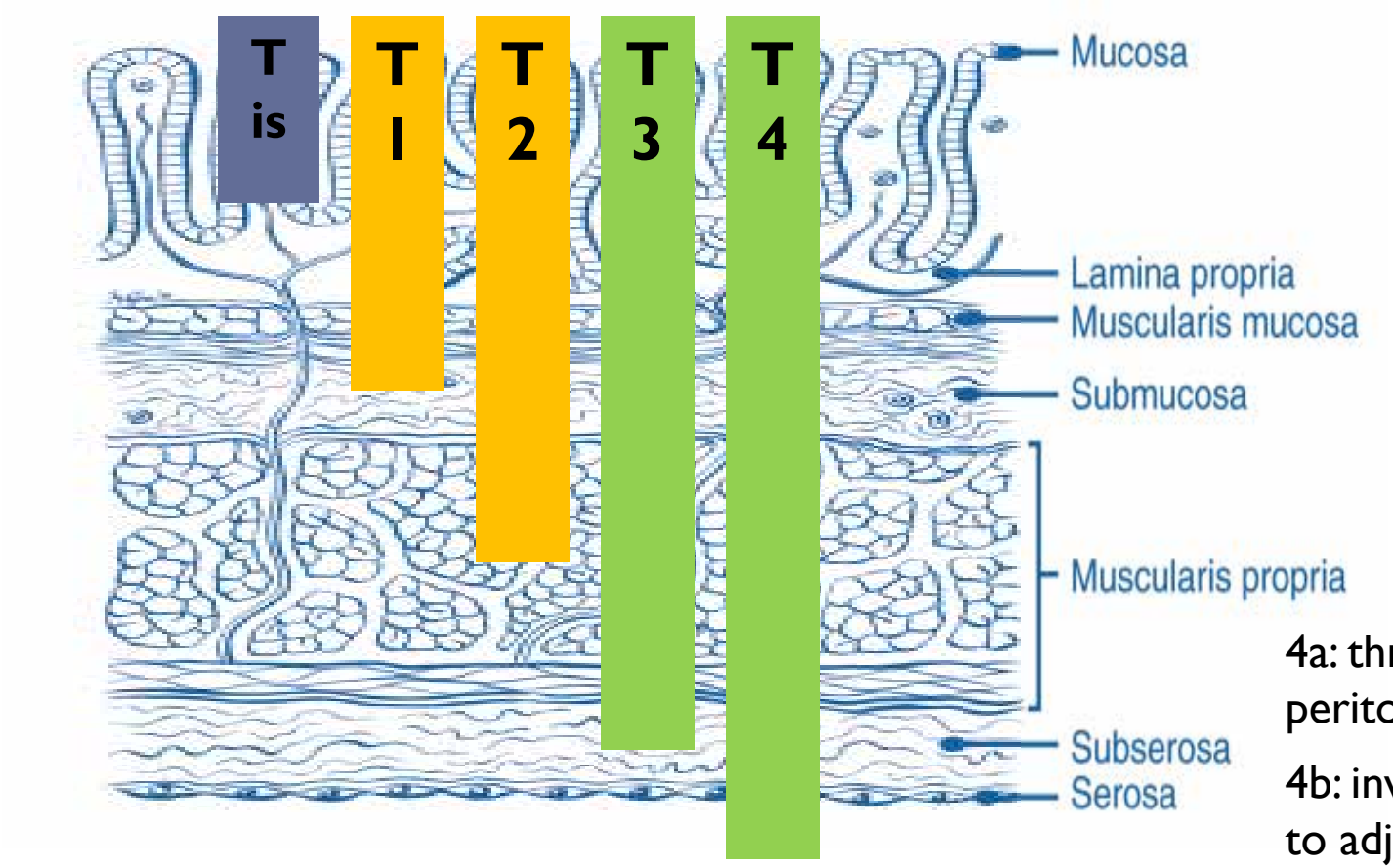
CT chest, abdomen, pelvis with contrast
(and rectal MRI for rectal primary)

PET scans are NOT routinely part of staging

- Use to evaluate equivocal CT findings, or
- if IV contrast contraindicated

Colorectal cancer staging

"TNM" score: T (tumor)



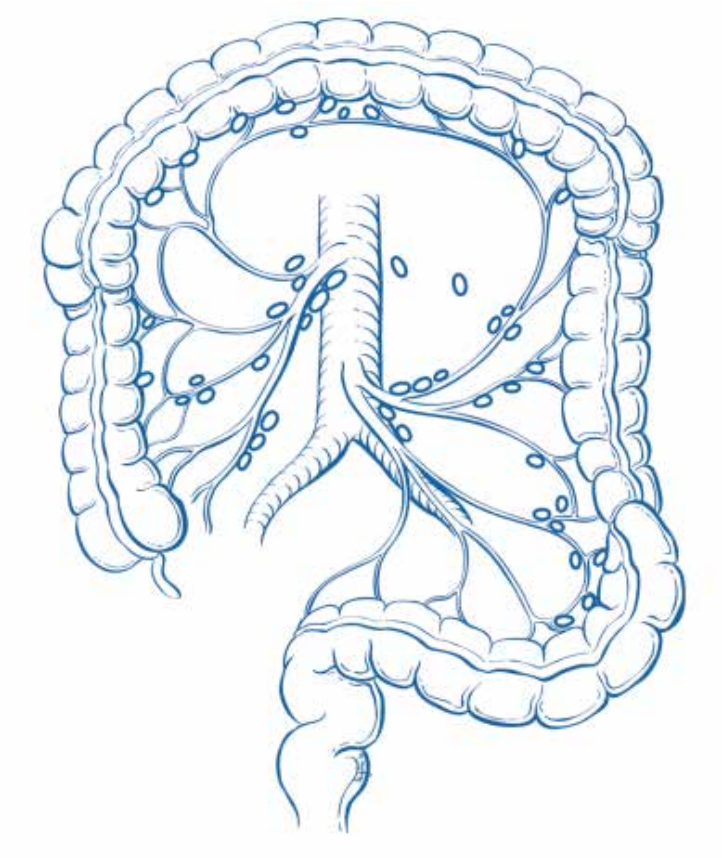
4a: through visceral peritoneum

4b: invade/adherent to adjacent organs or structures

- AJCC 7: www.cancerstaging.org

Colorectal cancer staging

"TNM" score: N (nodes)*



N0	**0**	
N1	**1-3**	N1a = 1 N1b = 2-3 N1c = deposits
N2	**≥ 4**	N2a = 4-6 N2b = 7+

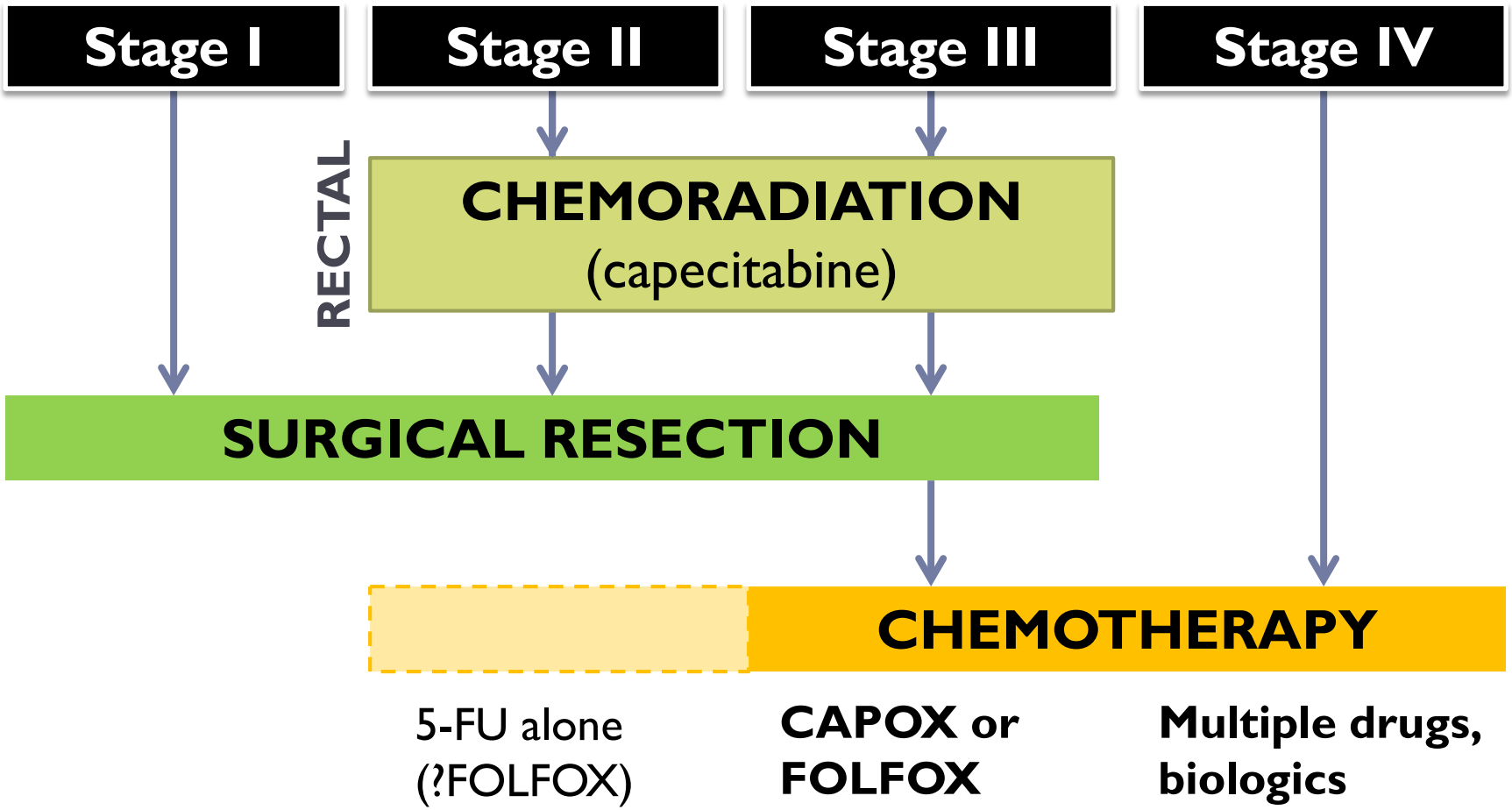
*Non-regional nodes are considered M1a

Colorectal cancer staging

TNM	AJCC Stage	Sub-stage
T1-2 N0 M0	I	
T3-4 N0 M0	II	IIA: T3 N0 IIB: T4a N0 IIC: T4b N0
T **N1-2** M0	III	IIIA: T1-2 N1, T1 N2a IIIB: T3-4a N1, T2-3 N2a, T1-2 N2b IIIC: T4a N2a, T3-4a N2b, T4b N1-2
Tx Nx **M1**	IV	IVA: Tx Nx M1a (single site/organ) IVB: Tx Nx M1b (2+ sites)

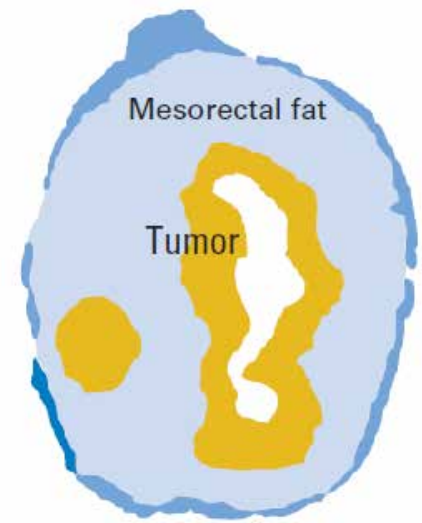
- AJCC 8th edition; SEER data 2004-2010: colon

Treatment overview



Surgery: Partial colectomy with en bloc lymph node removal

- Sufficient margins
  - >5cm proximal and distal to the tumor
- Lymph node sampling
  - En bloc resection with removal of regional LN
  - Minimum 12 removed
- Total mesorectal excision (TME) for rectal
  - Low anterior (LAR) or abdominoperineal (APR)
  - Follows anatomic guidelines
  - Improved circumferential margin clearance
  - Reduced local recurrence with complete TME



Nagtegaal, JCO 2008

Endoscopic colon polyp resection

Endoscopic polypectomy

- Complete polyp removal (not fragmented)
- Negative margins
  - Controversial, but ideally >1mm
- Favorable histologic features
  - Grade 1-2, no angiolymphatic invasion
- Pedunculated
  - Consider for sessile polyp, but higher risk of recurrence

- Otherwise full oncologic bowel surgery

Rectal Transanal Excision*

NCCN Criteria for Transanal Excision

- T1 tumors only (limited to submucosa), N0 M0
- < 30% circumference of bowel
- < 3 cm in size
- Mobile, non-fixed lesion within 8 cm of anal verge
- Favorable histologic features
  - Grade 1-2, no angiolymphatic or perineural invasion
- Clear margin (>3mm) obtainable

- Less complications
  - Sphincter, bladder, sexual dysfunction
- Higher risk of local recurrence

*Modern transanal excision microsurgery (TEM) outperforms classic transanal excision (TAE)

Monson, *Dis Colon Rectum* 2013

Key points

- PET-CT should not routinely be part of the work up of colorectal cancer
- Surgical removal of ≥12 LN is a benchmark metric
- Standard surgery includes colorectal resection with en bloc LN removal
  - Total mesorectal excision improves recurrence rates
  - Polypectomy, transanal excision are options in select cases

Adjuvant Chemotherapy for Colon Cancer

Stage **II**: Adjuvant chemotherapy

- Historically, use is controversial
  - 3% overall benefit based on Cochrane review
- May be beneficial for tumors with "high-risk" features:

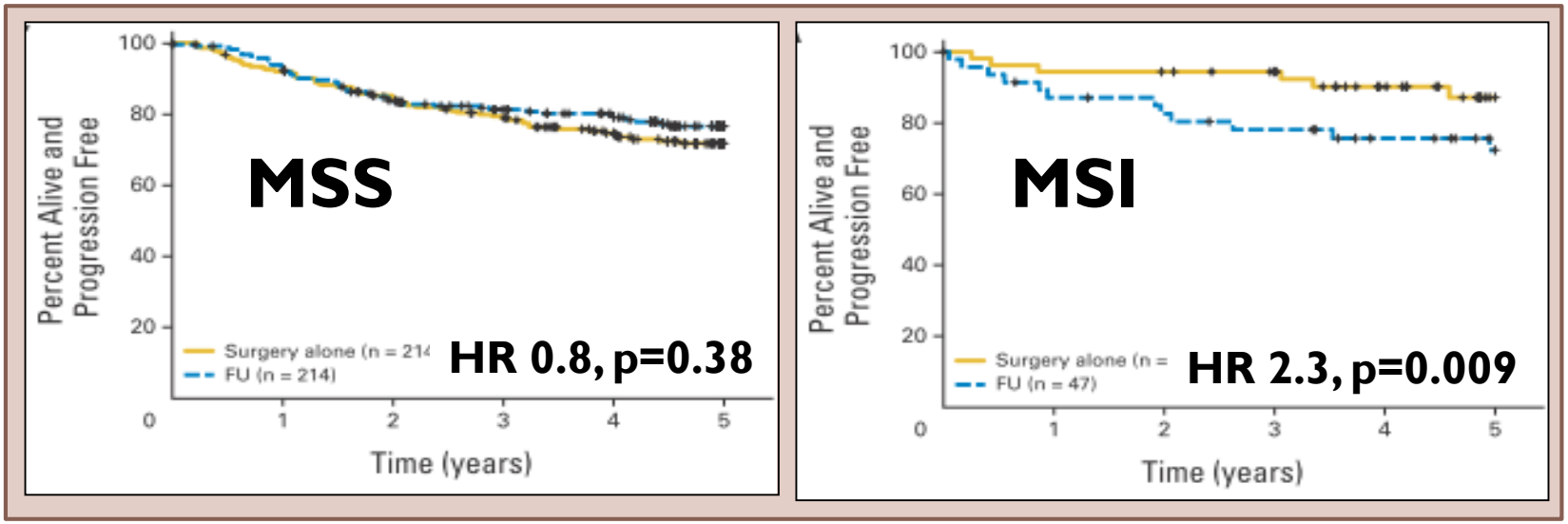
pT4	Bowel obstruction / perforation
Poorly differentiated	< 12 lymph nodes evaluated
Lymphovascular or perineural invasion	Close, indeterminate, or positive margins
Tumor budding	

- Newer data may support adjuvant therapy in high-risk MSS stage II, but observation is also acceptable
  - Regimen and duration are debatable

Meyers, ASCO 2015; Meyers, *Curr Oncol* 2016; Seymour, ASCO 2019; Iveson, ASCO 2019

Stage II guided by molecular sub-types

- ~~Use of multigene assays? (Oncotype DX)~~
  - Validation study did not show predictive benefit
- Microsatellite instability is a useful biomarker
  - Retrospective data of adjuvant **5-FU** vs. **observation**



- Adjuvant chemotherapy is currently NOT recommended in stage II colon cancer that is MSI-H (and this outweighs "high-risk" features)

QUASAR: Gray, *JCO* 2011; Sargent, *JCO* 2010; Yothers, *JCO* 2011

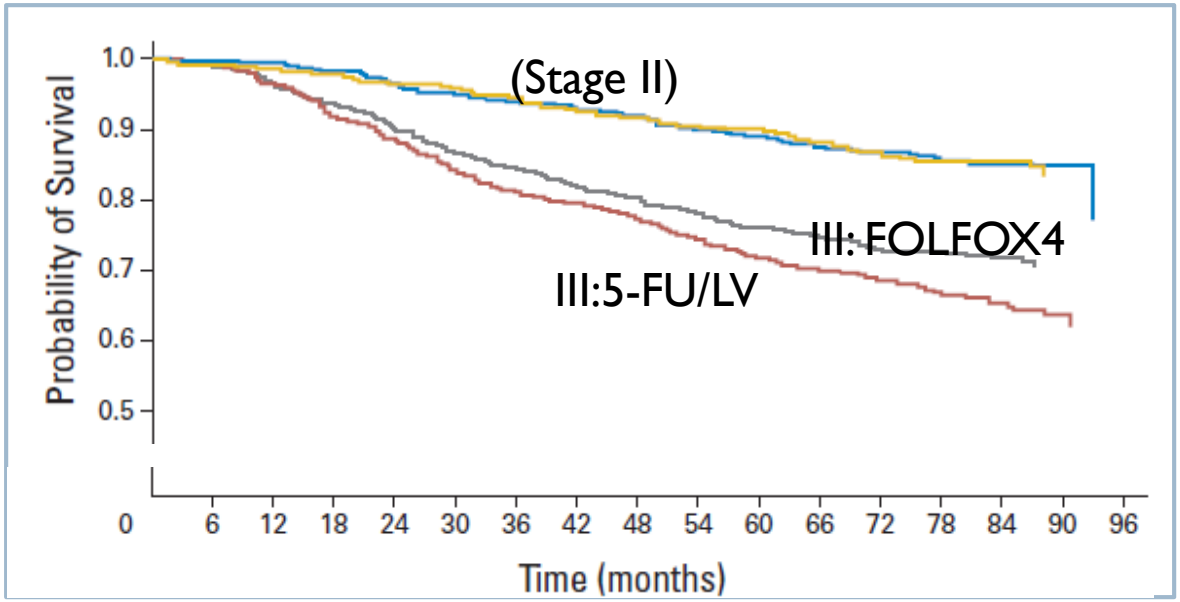
Stage **III**: Adjuvant chemotherapy

Recommendation

- FOLFOX x 3-6 months
  - CAPOX (capecitabine + oxaliplatin) generally considered equivalent
  - ?Benefit for oxaliplatin if ≥70yo (up to 85 included in IDEA)

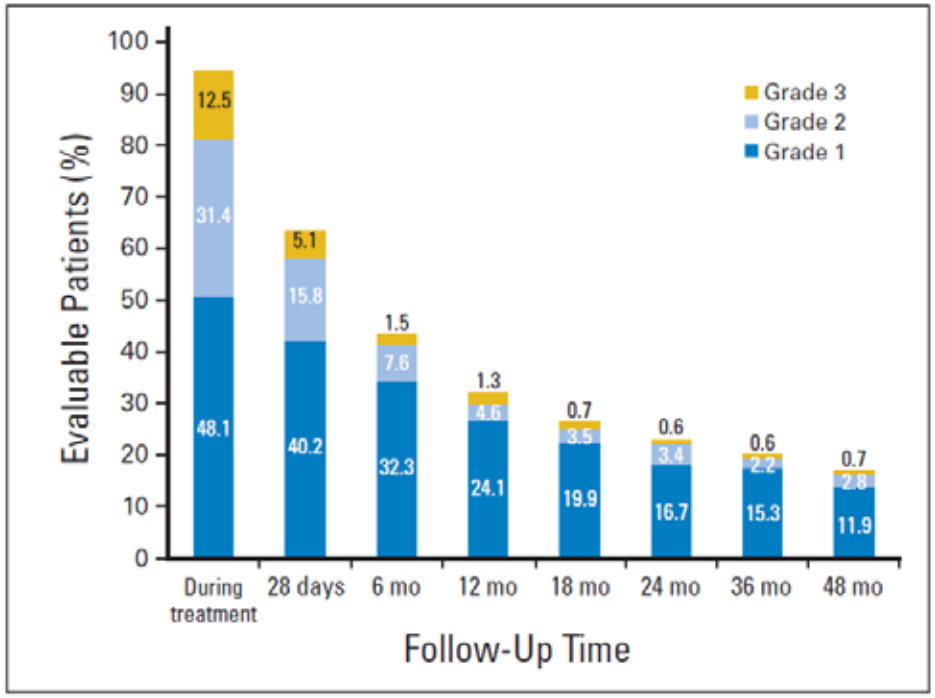
Benefit (vs. 5-FU)

- 3-year DFS:
  - 78 vs. 73%, p=0.002
  - HR 0.76 (24% better)
- 6-year OS:
  - 73 vs. 68%, p=0.02



MOSAIC: Andre, *JCO* 2004, 2009; Tournigand, *JCO* 2012

Oxaliplatin neuropathy



>90% get neuropathy from oxaliplatin
15% is "permanent," but usually mild

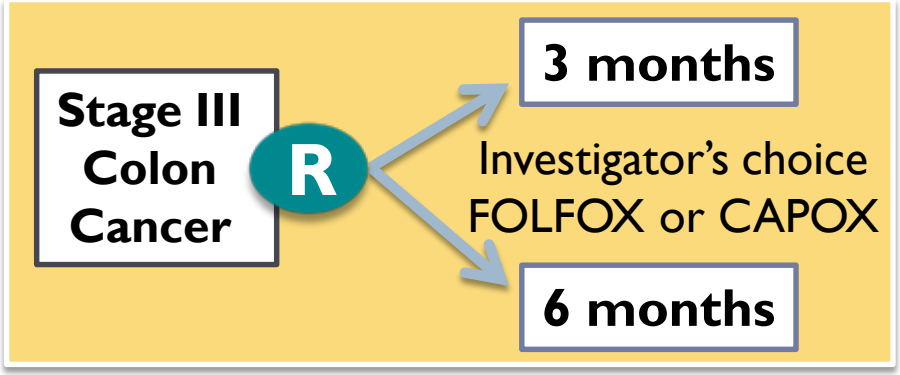
Longer duration of oxaliplatin is associated with greater neuropathy

Neuropathy	3 months		6 months	
	FOLFOX	CAPOX	FOLFOX	CAPOX
Grade 2	9%	14%	26%	29%
Grade 3-4	1%	2%	9%	8%

- MOSAIC: Andre, *JCO* 2009; IDEA: Iveson, *ASCO* 2019

Is 3 months sufficient?

- IDEA consortium
  - 6 trials, 12,800 participants
    - 60% FOLFOX
    - 66% T3, 21% T4; 28% N2



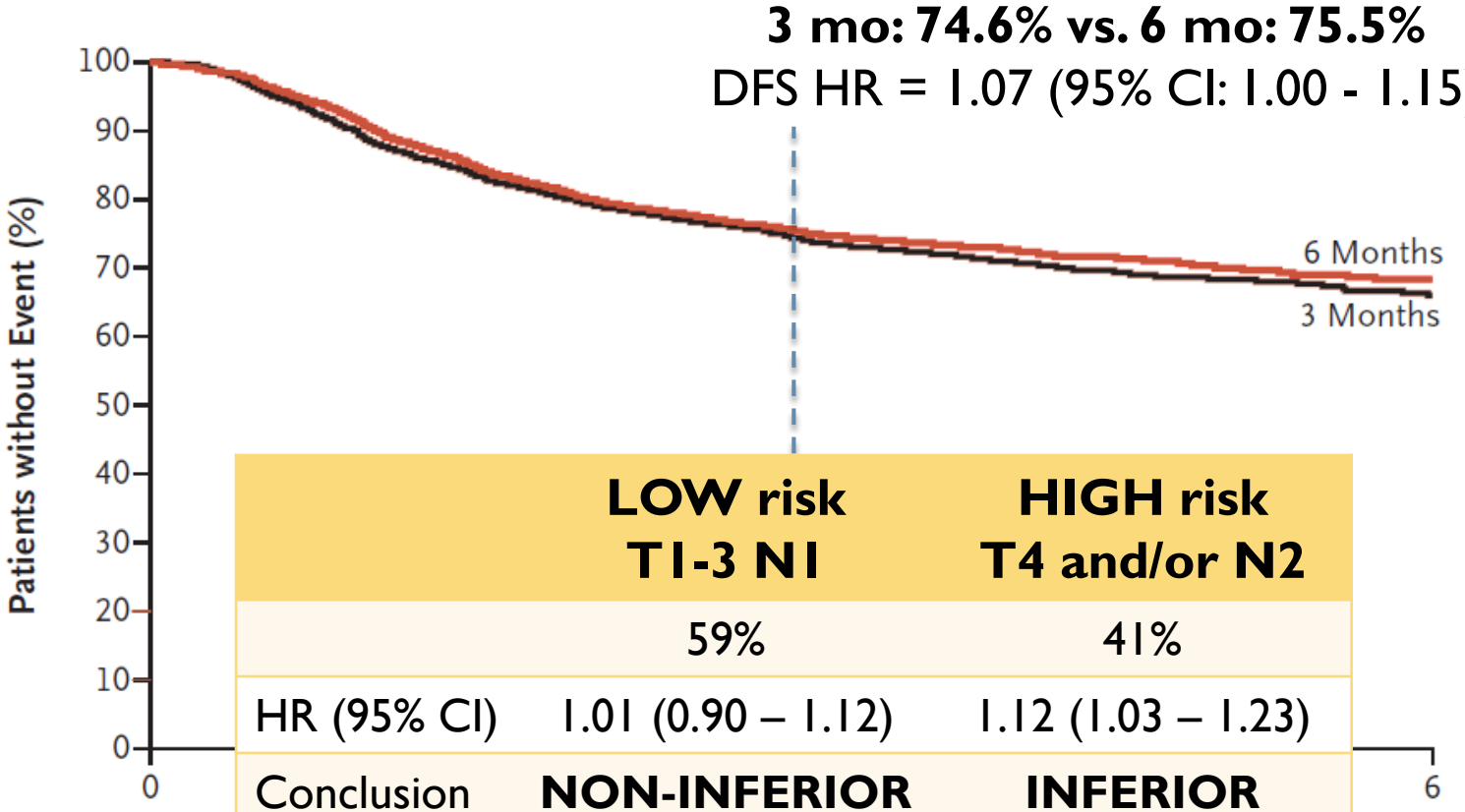
  - C80702 (n=2440) was the trial conducted in North America
    - And all participants were required to receive FOLFOX

  - Designed as a non-inferiority trial with DFS HR 1.12
    - 12% "harm" arbitrarily decided to be acceptable to change to 3 mo.

Sobrero, *JCO* 2018; Andre, *JCO* 2018; Grothey, *NEJM* 2018

Primary outcome: disease-free survival

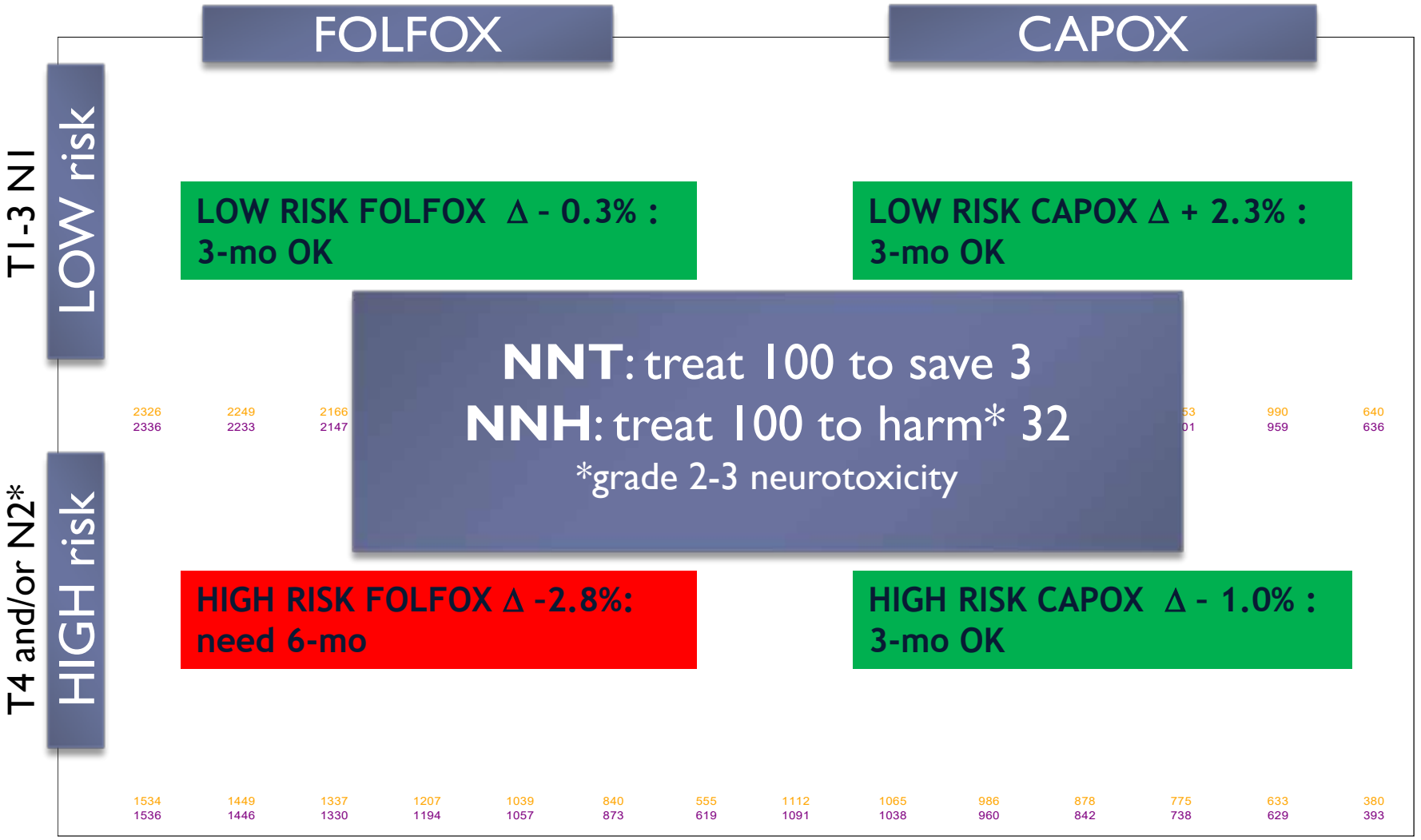
- NOT non-inferior



	LOW risk T1-3 N1	HIGH risk T4 and/or N2
	59%	41%
HR (95% CI)	1.01 (0.90 – 1.12)	1.12 (1.03 – 1.23)
Conclusion	**NON-INFERIOR** 3 mo likely ok	**INFERIOR** 6 mo needed

Grothey, *NEJM* 2018

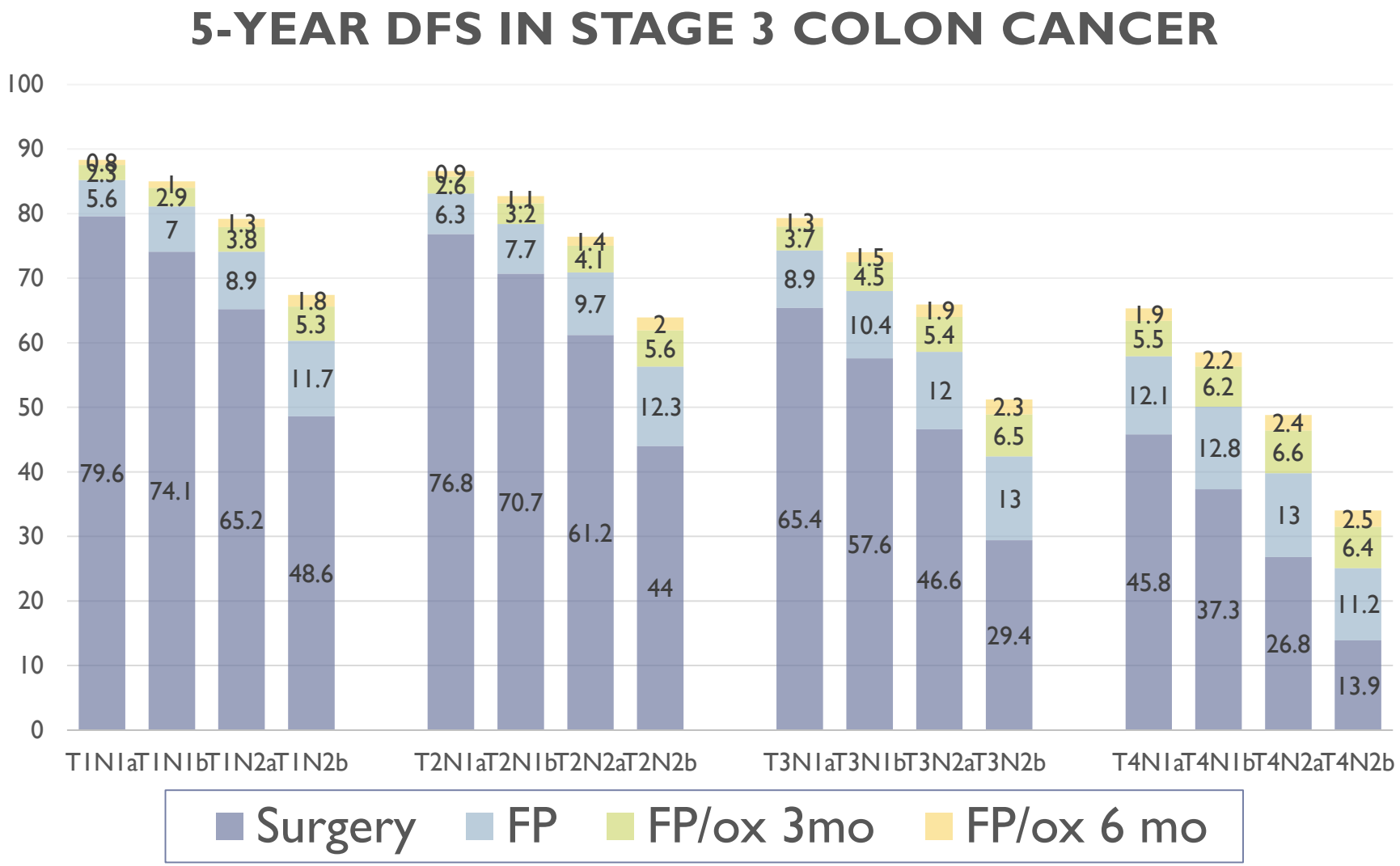
OS outcomes by risk and by regimen



Sobrero, *ASCO* 2020; Yamanaka, *ASCO* 2020

*T4 risk > N2

Incremental benefits in adjuvant therapy



Adapted from: Sobrero, *ASCO* 2020

The future of adjuvant therapy

- NO benefit to irinotecan
  - Benefit in CIMP+ MMR-intact?
- NO benefit to cetuximab
  - Benefit in T4 N2?
- NO benefit to bevacizumab

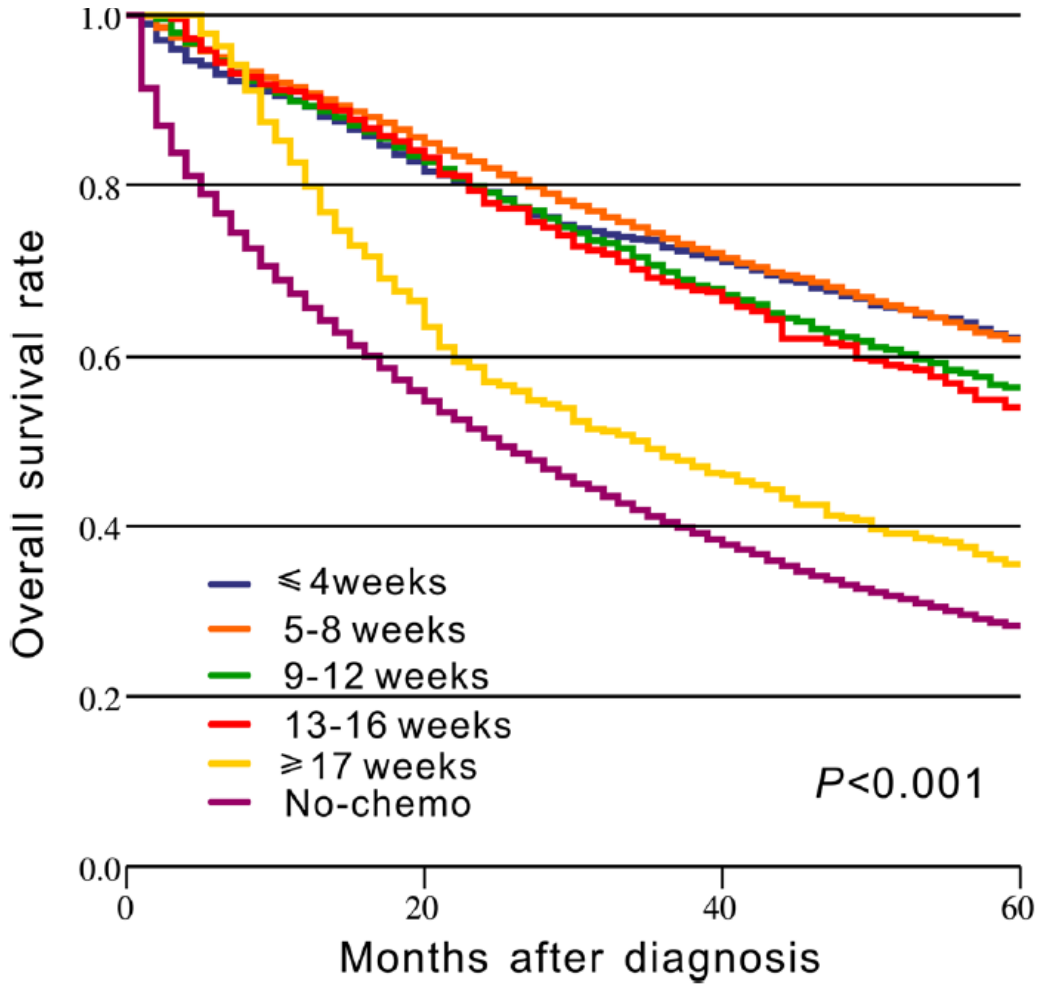
Biomarkers are needed to better tailor therapy

- Expect future (exploratory) subgroup analyses within the IDEA 3 vs. 6 mo trials
  - MSI (dMMR)?
  - Elderly (≥70yo)?
  - Right vs. left?

And what about 3 mo FOLFOX or CAPOX and then just 5-FU/capecitabine alone through 6 mo?

CALGB 89803; N0147, PETACC-8; NSABP C-08, AVANT

Time to adjuvant chemotherapy vs. survival



- Meta-analysis of >18,000 patients
- Most benefit from adjuvant <8 weeks post-op
  - But still some benefit up to +16 weeks
- Prior analysis suggested 14% mortality increase for each 4-week delay after 8 weeks

Gao, *BMC Cancer* 2018; Biagi, *JAMA* 2011

Key points

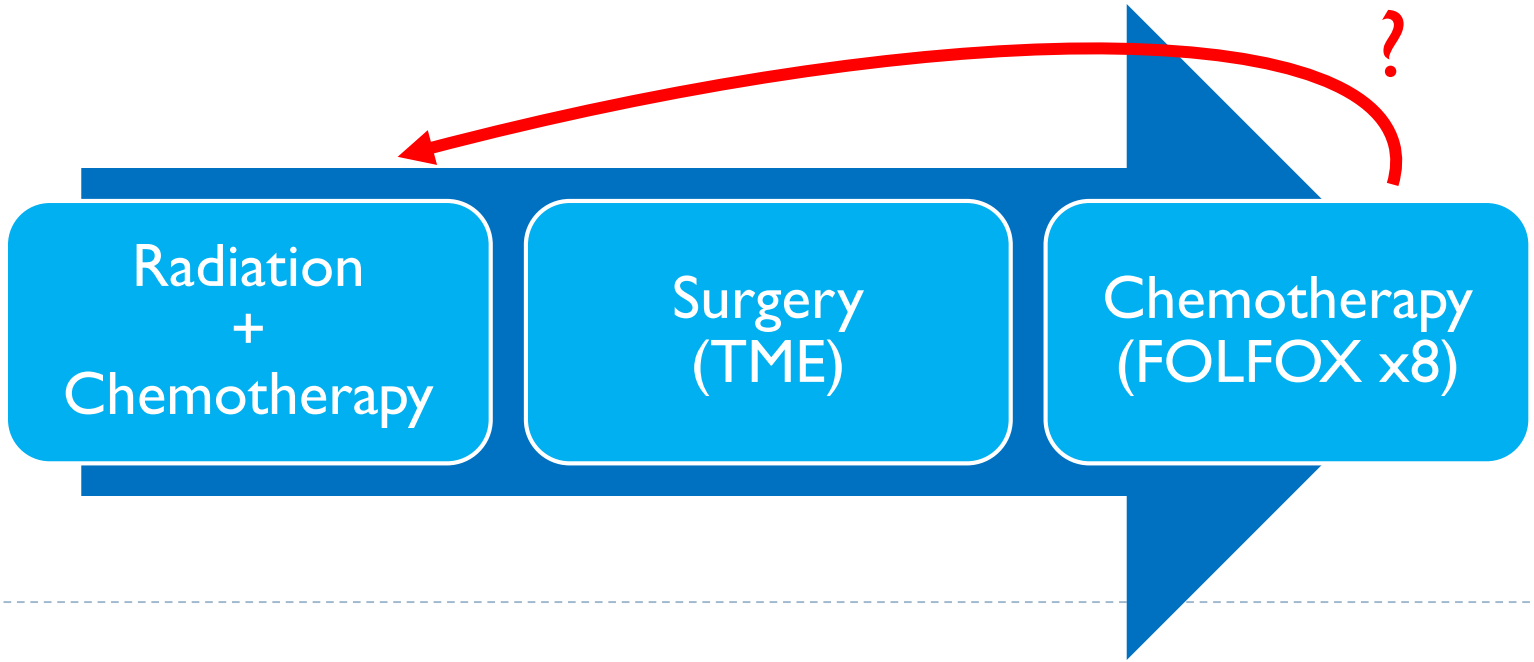
- Overall, no benefit for adjuvant chemotherapy in stage II
  - Consider for select "high-risk" MSS patients
  - Avoid adjuvant chemotherapy in MSI-high stage II
- 3 months of adjuvant chemotherapy is becoming the new standard for stage III
  - 6 months is still recommended for high-risk (T4 or N2) patients who receive FOLFOX
    - And potentially for all high-risk patients?
  - CAPOX may be more effective (though not studied in the US population)
- No indication for irinotecan, cetuximab, or bevacizumab

Localized Rectal Cancer

Rectal cancer: General principles

- Definition: primary lesion within 12 cm of anal verge by rigid proctoscopy
  - Consider treating cancers entirely above the anterior peritoneal reflection "as colon" (i.e. upfront surgery)

- Higher rates of local recurrence compared to colon



Neoadjuvant radiation therapy

- German CAO/ARO/AIO-94 trial:
  - 5-FU/RT → TME vs. TME → 5-FU/RT
  - All T3-4 or N+ (n=823)

	Pre-op radiation	Post-op radiation	
Pelvic Relapse (10-yr)	7%	10%	p=0.048
5-year DFS	68%	65%	NS
5-year OS	76%	74%	NS
Sphincter preservation	39%	13%	p=0.006
Toxicity	27%	40%	p=0.001

- Neoadjuvant therapy may allow sphincter-preserving surgery and reduces risk of local recurrence

Sauer, *NEJM* 2004; Sauer, *JCO* 2012

Neoadjuvant chemotherapy with radiation

NSABP R-04: stage II-III rectal (n=1608)

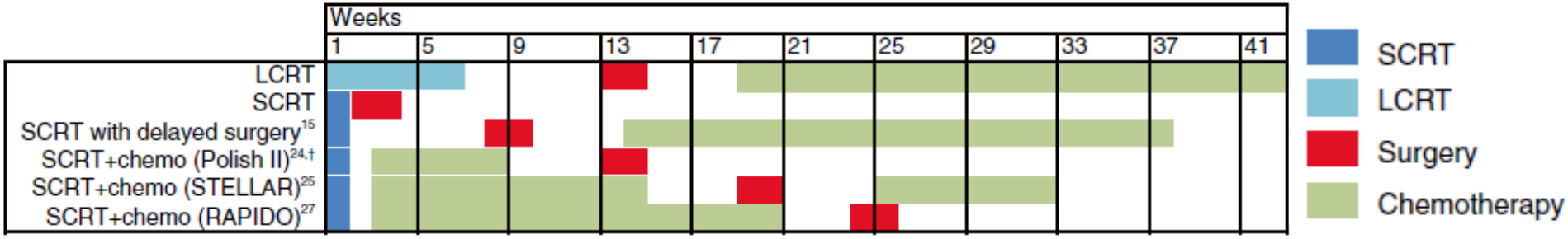
5-FU	Capecitabine	5-FU + oxaliplatin	Cape + oxaliplatin

- Conclusions:
  - No benefit to addition of oxaliplatin
  - Capecitabine appears as good as 5-FU
  - No difference in surgical outcomes
- 5-year OS about 80%
  - Oxaliplatin trended to better DFS, but similar OS
- Today: Recommend capecitabine alone

NSABP R-04: O'Connell, *JCO* 2014; Allegra, *JNCI* 2015

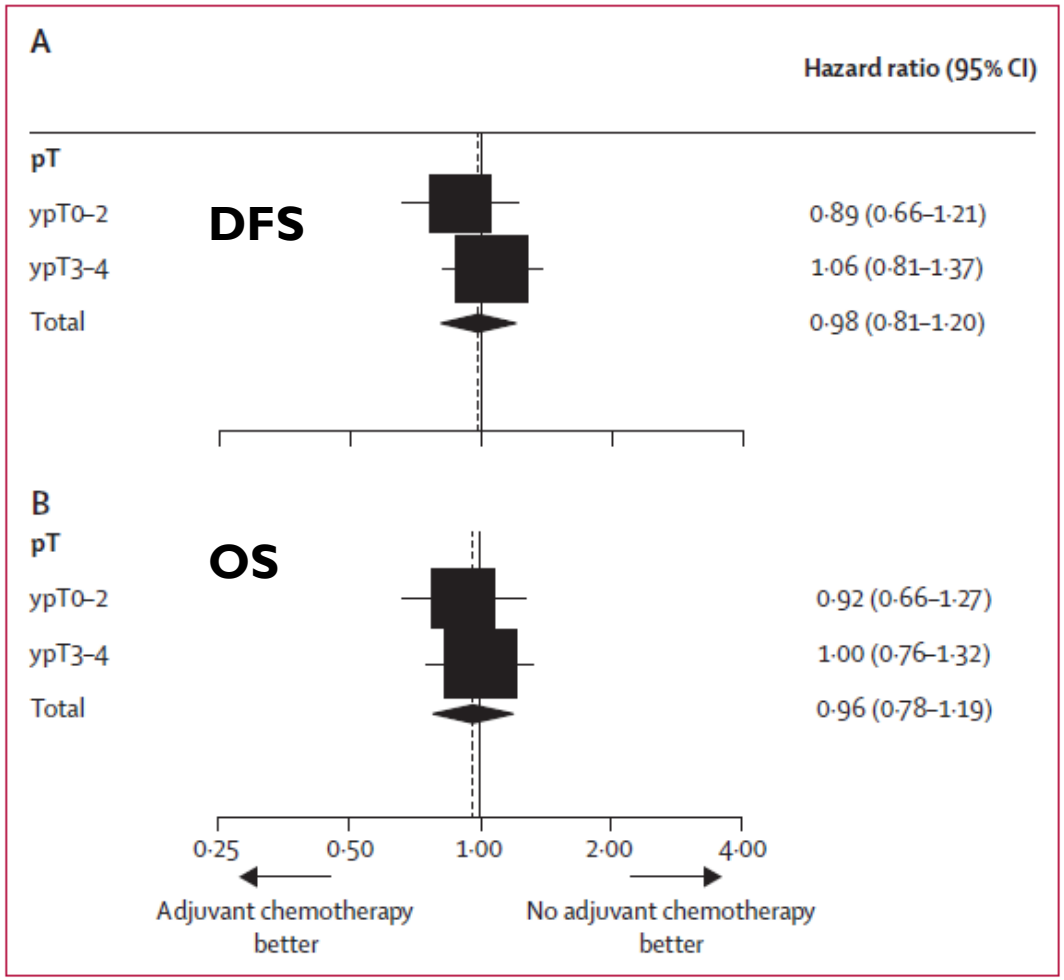
Short-course radiation

- Hypofractionated 25Gy (5Gy x 5 days), NO chemo
  - (Standard/long-course: 28 fractions over 5.5 weeks, 50.4 Gy)
  - Surgery 1 or 4+ weeks later
- If plan for surgery soon after, best when primary tumor down-staging is not required, limited/no nodal disease
  - Lower pCR rate (unless wait a similar interval as long-course)
  - Sequencing with surgery, systemic chemotherapy needs to be further elucidated



Mullen, *Curr Colorectal Cancer Rep* 2017; Bahadoer, *ASCO* 2020

Rectal: Adjuvant chemotherapy



- cT3-4 (n=1101)
  - Neoadjuvant 5-FU/RT → Surgery
  - RCT to adjuvant 5-FU vs. surveillance
- Trend to benefit only in ypT0-2

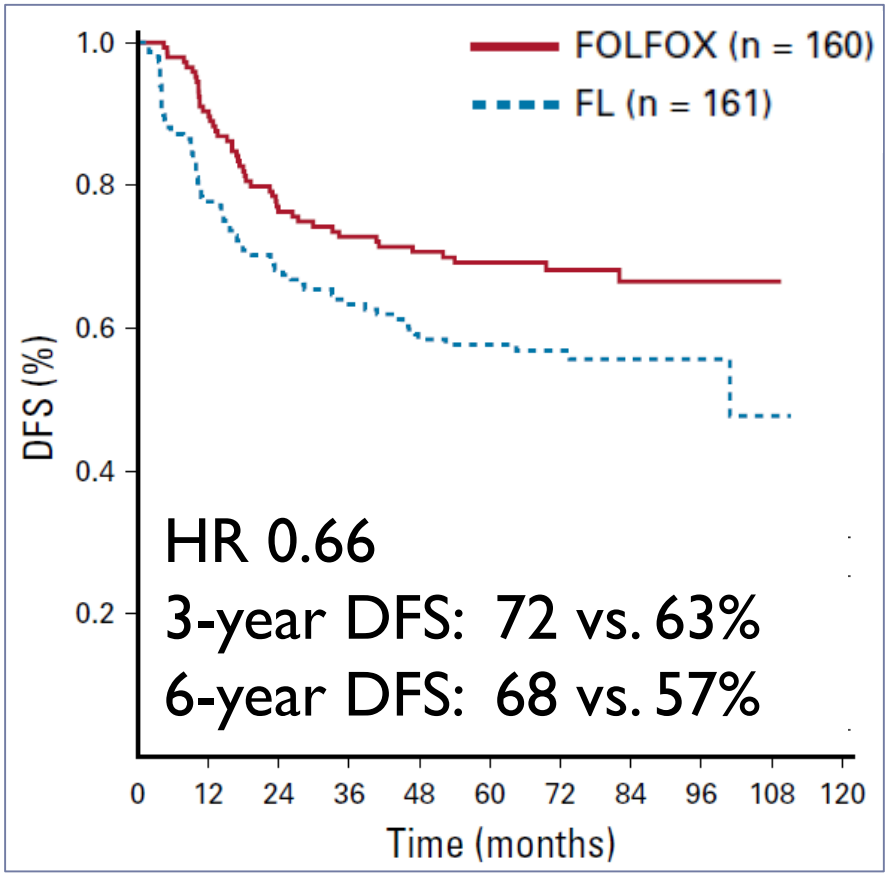
- EORTC 22921: Bosset, *Lancet Onc* 2014

Adjuvant FOLFOX

- ADORE: 5-FU/RT → TME → **ypT3-4** N0 or Tx **ypN1-2**

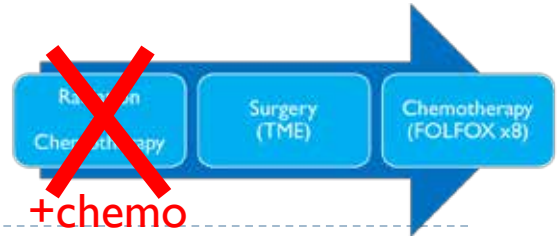
- FOLFOX improved DFS
  - ypN+ > ypN0
  - Not significantly better for very good tx response

- Today, FOLFOX is recommended for all stage 2-3 rectal cancer
  - ?benefit of oxali in ≥70yo



Hong, *Lancet Onc* 2014, *JCO* 2019; Rodel, *JCO* 2005

Omit radiation?

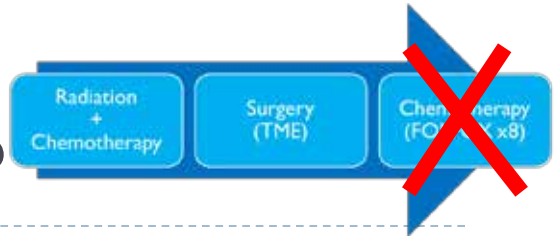


- Most patients dying from rectal cancer have distant metastases, not local recurrence
- Some patients may never start adjuvant chemotherapy because of surgical complications, or it is quite delayed
  - So are we doing patients a disservice by placing high-dose chemotherapy at the end of therapy?

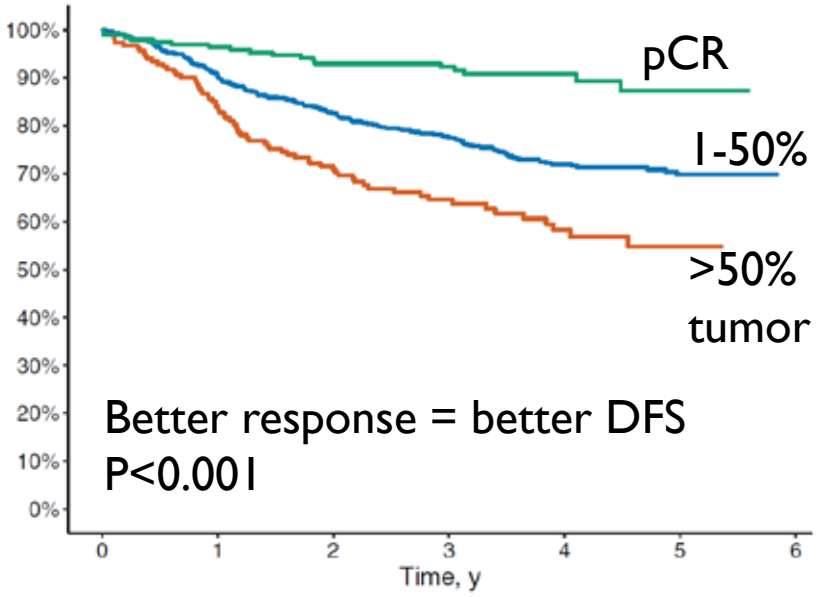
- PROSPECT trial:
  - Phase 3 trial of peri-operative FOLFOX + selective RT for poor responders or positive margins
  - Completed accrual and awaiting results (2022?)

Bosset, *NEJM* 2006; Fernandez-Martos, *JCO* 2010; Rodel, *Lancet Onc* 2012

Skip adjuvant chemotherapy?

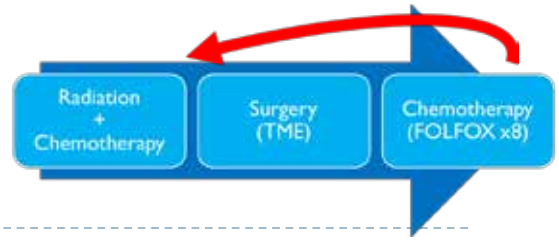


- May be delayed/omitted in patients with surgical morbidity
- Helpful if poor risk disease
- pathologic Complete Response
  - Associated with better outcomes
  - Unclear if this should affect adjuvant therapy
- Ok to use 5-FU/capecitabine alone? Observe?

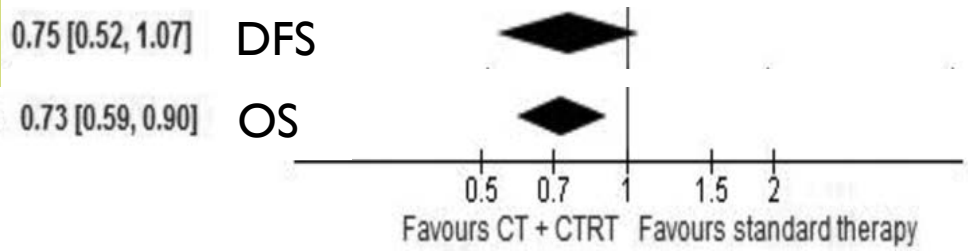


Fokas, *JNCI* 2017; Rodel, *JCO* 2005; Loree, *Clin Colorectal Cancer* 2016

Total neoadjuvant therapy



- Concept of sequencing both chemoRT and systemic chemotherapy PRIOR to surgery
  - Removes the need for adjuvant therapy
  - Could be done with short- or long-course RT



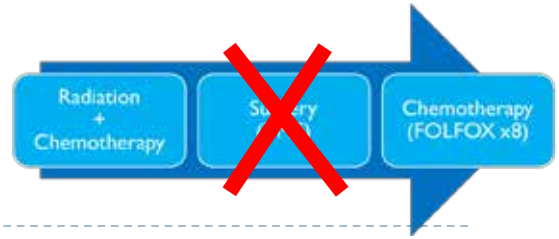
Highly consider TNT if:

- Unresectable or may convert from APR to LAR
- T4 and/or N2
- Involved circumferential margin

- Need more prospective, randomized data
- Newer studies suggest higher pCR rate (25-45% vs. 15-20%)
  - Especially if chemoRT done first?
  - Possible role for FOLFIRINOX in the neoadjuvant setting?

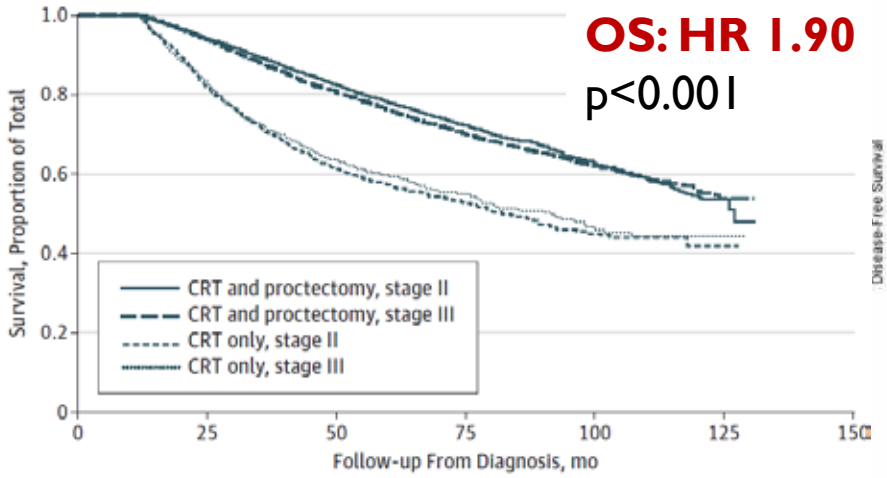
Petrelli, *Ann Surg* 2020; Garcia-Aguilar, *ASCO* 2020; Conroy, *ASCO* 2020

Nonoperative management?

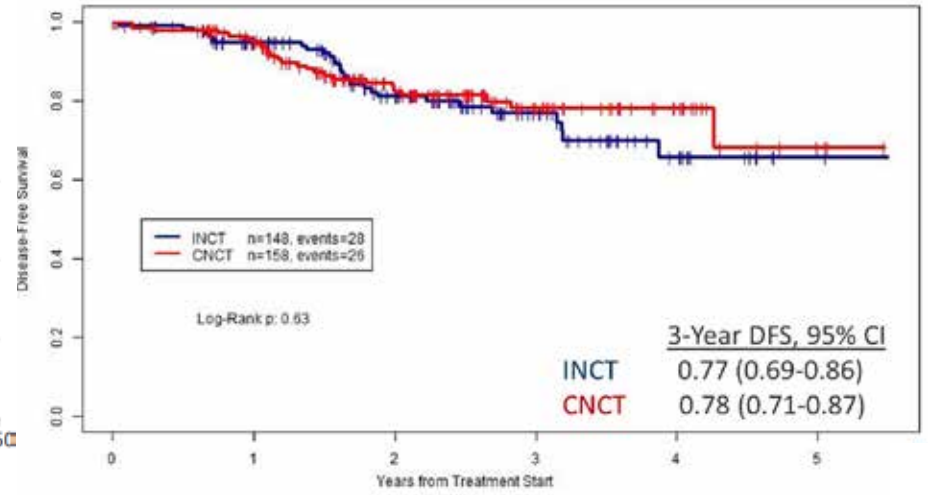


- "Watch and wait" approach
  - Avoid surgical morbidity in poor candidates
  - Avoid permanent ostomy in those that decline
- Higher rates of local and possibly distant failure
- Need a complete clinical response (by CT, MRI, flex sig)

NCDB 2004-2008



OPRA trial: 2013-2020



Ellis, *JAMA Onc* 2017; Garcia-Aguilar, *ASCO* 2020

Key points

- Preoperative chemoradiation therapy is standard-of-care for T3-4 or node-positive rectal cancers
  - Reduces local recurrence
  - Improves likelihood of sphincter-sparing surgery
  - Does not improve survival (vs. adjuvant RT)
- Do NOT use oxaliplatin with preoperative chemoradiation
- 5-FU/oxaliplatin is recommended for all stage 2-3 patients
  - Neoadjuvant systemic chemotherapy (TNT) is a growing trend

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Comprehensive Oncology Review: Colorectal Cancer - Metastatic

Stacey Cohen, MD

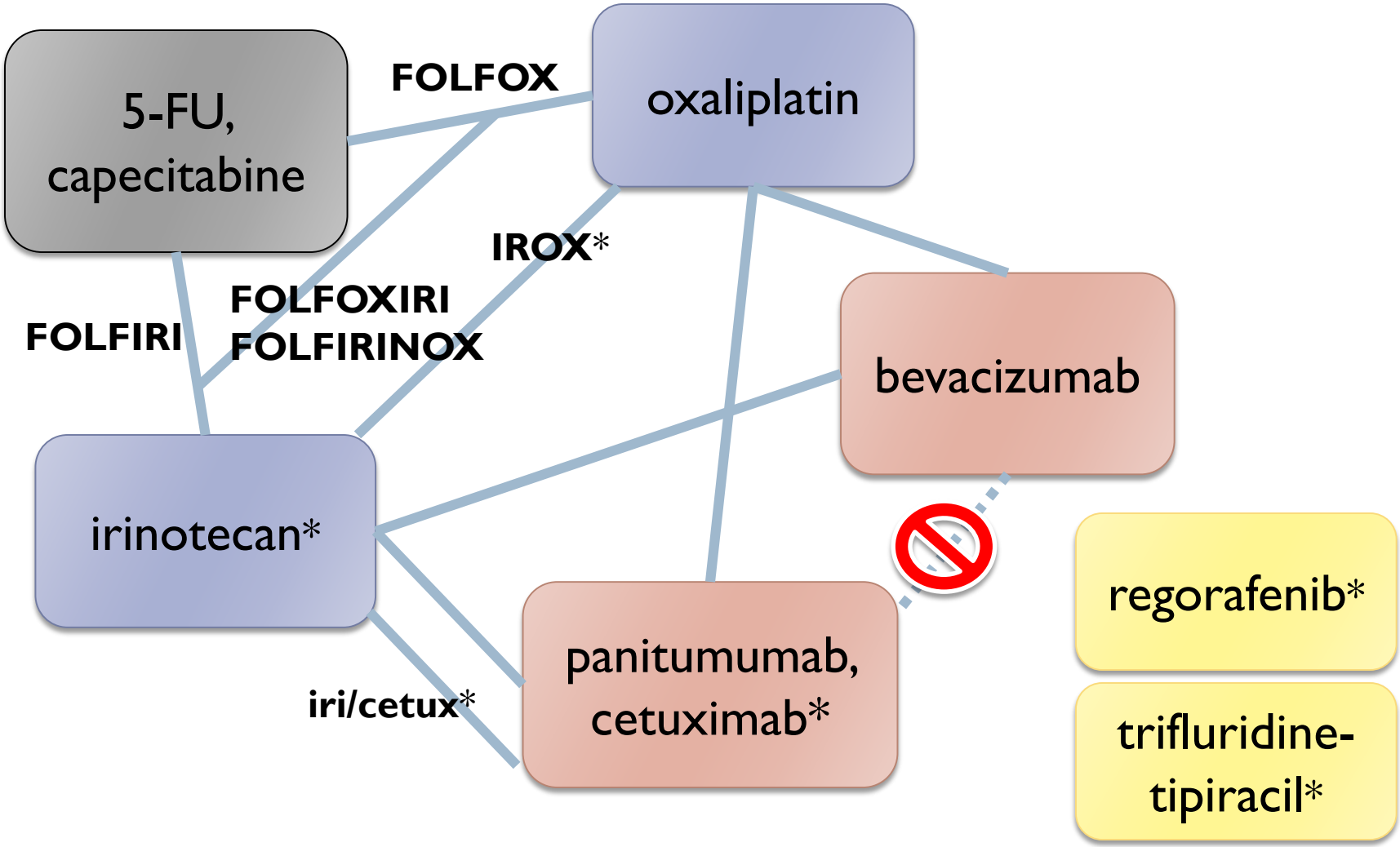
shiovitz@uw.edu

Outline

- Standard cytotoxic chemotherapy
- Tailored chemotherapy strategies
- Targeting molecular alterations

Standard cytotoxic chemotherapy

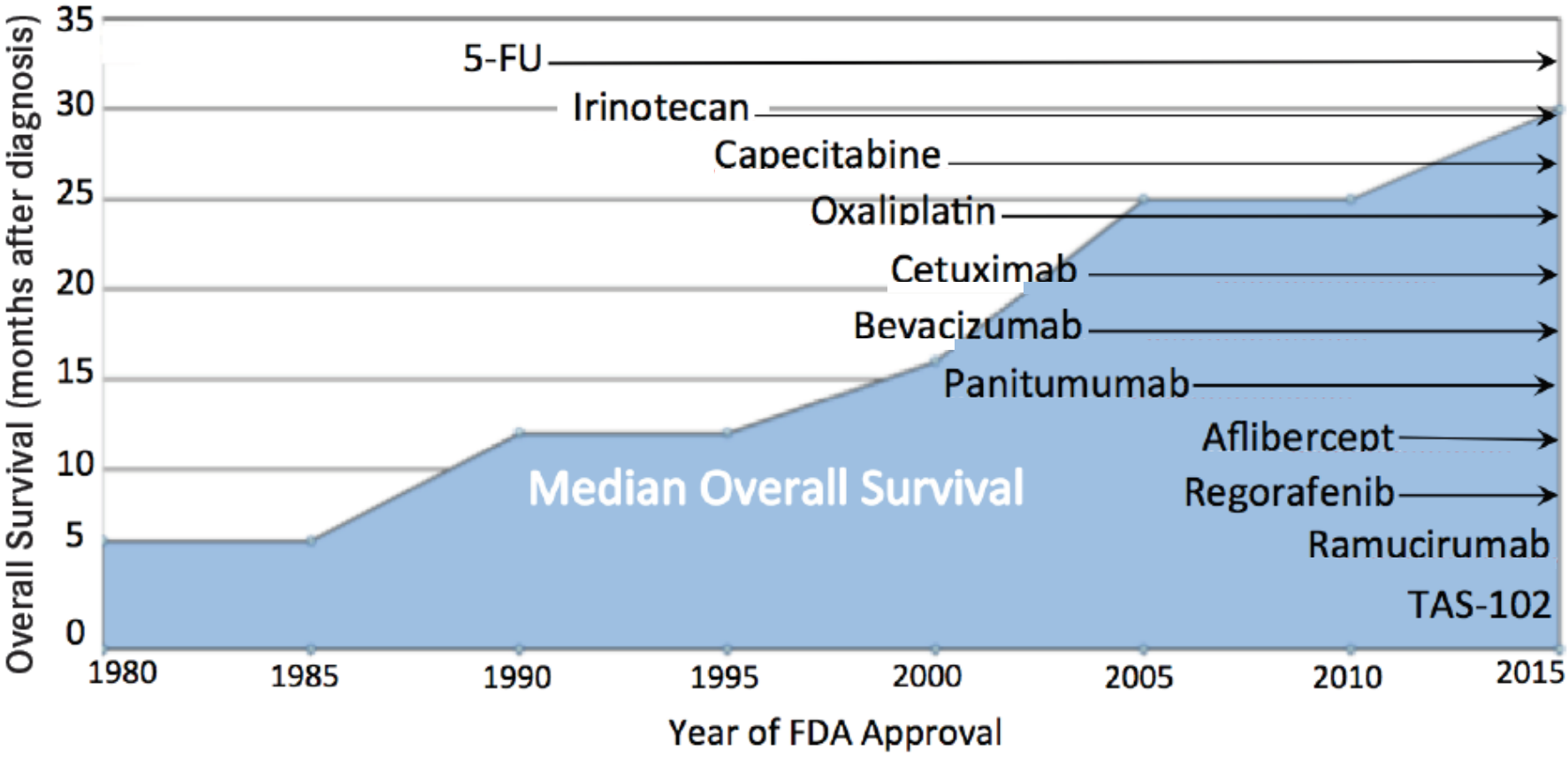
Multiple chemotherapy options



*Has activity without 5-FU

Growing repertoire of drug choices

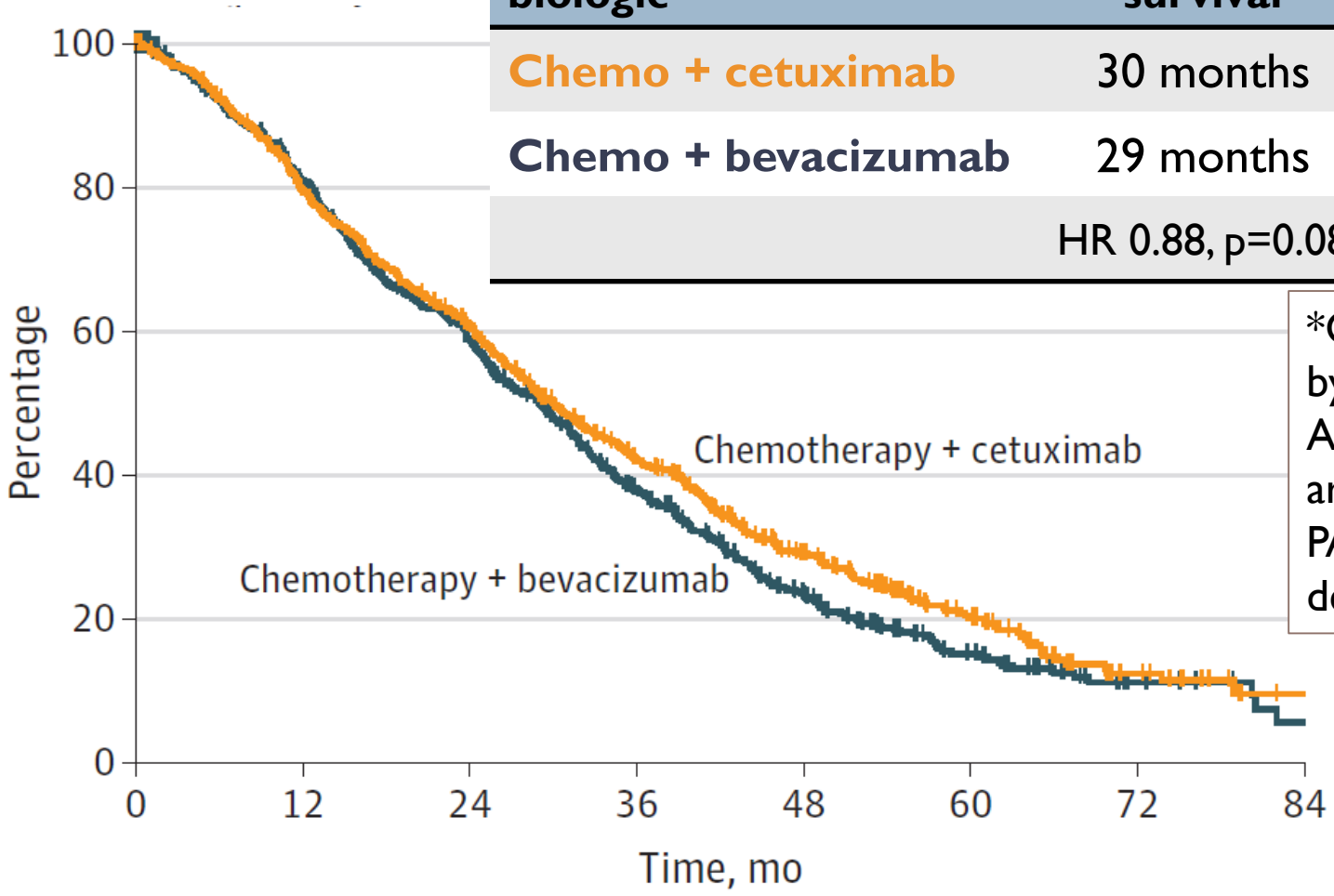
- Increase in drug options has improved mOS to ~30 mo



- Mody, *Am J Hematol Oncol* 2017

Optimal first-line therapy in KRASwt: CALGB/SWOG 80405

FOLFOX/FOLFIRI + biologic*	Overall survival	Progression-free survival
Chemo + cetuximab	30 months	10.5 months
Chemo + bevacizumab	29 months	10.6 months
	HR 0.88, p=0.08	HR 0.95, p=0.45



*Chemo backbone by physician choice. Additional bev/cetux arm dropped after PACCE, CAIRO-2 demonstrated harm

- Venook, *JAMA* 2017

Differences by side?

- Updated analysis classifying patients by left (distal/rectal) vs. right (proximal) primary colon site

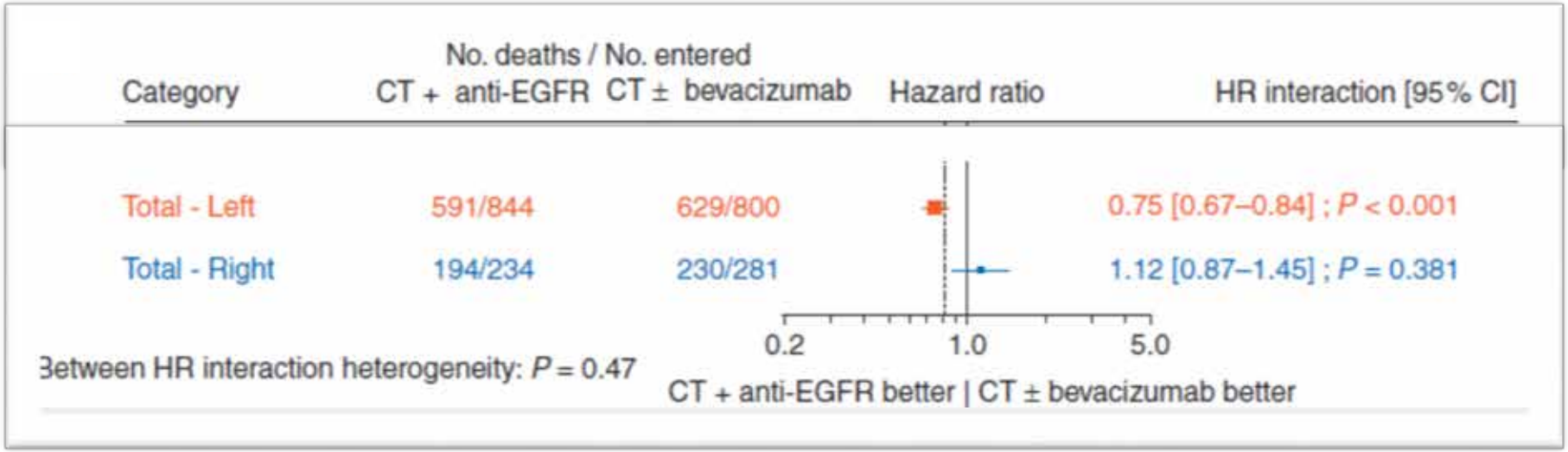
OS (months)	Overall
Left	33
Right	19
	p<0.0001

- Likely driven by different molecular profiles
  - But no difference when accounting for age, race, gender, synch/metachronous, MSI, *BRAF*, *RAS*, CMS

Venook, *ASCO* 2016, *ASCO* 2017

Differences by side?

- Pooled analysis of 80405 and 5 other RCT, classified by left (distal/rectal) vs. right (proximal) primary site

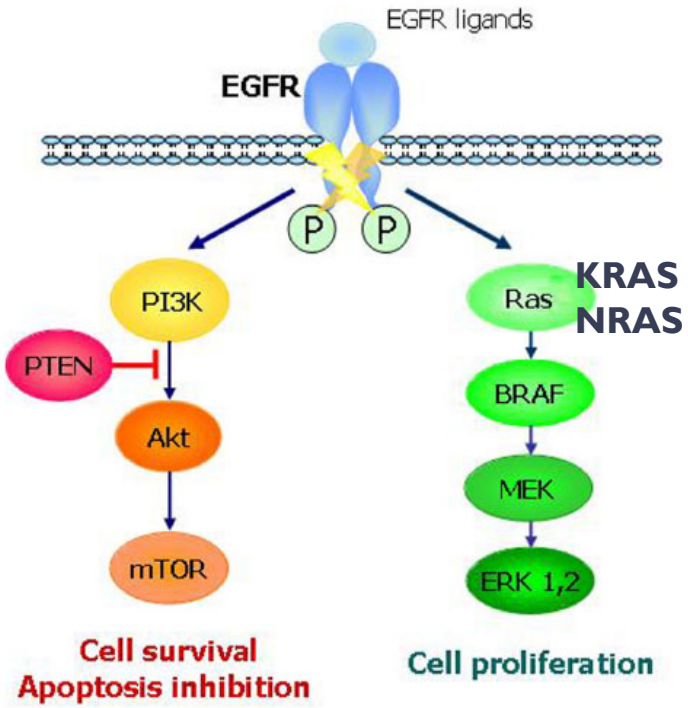


Thus, when *RAS* status is known…

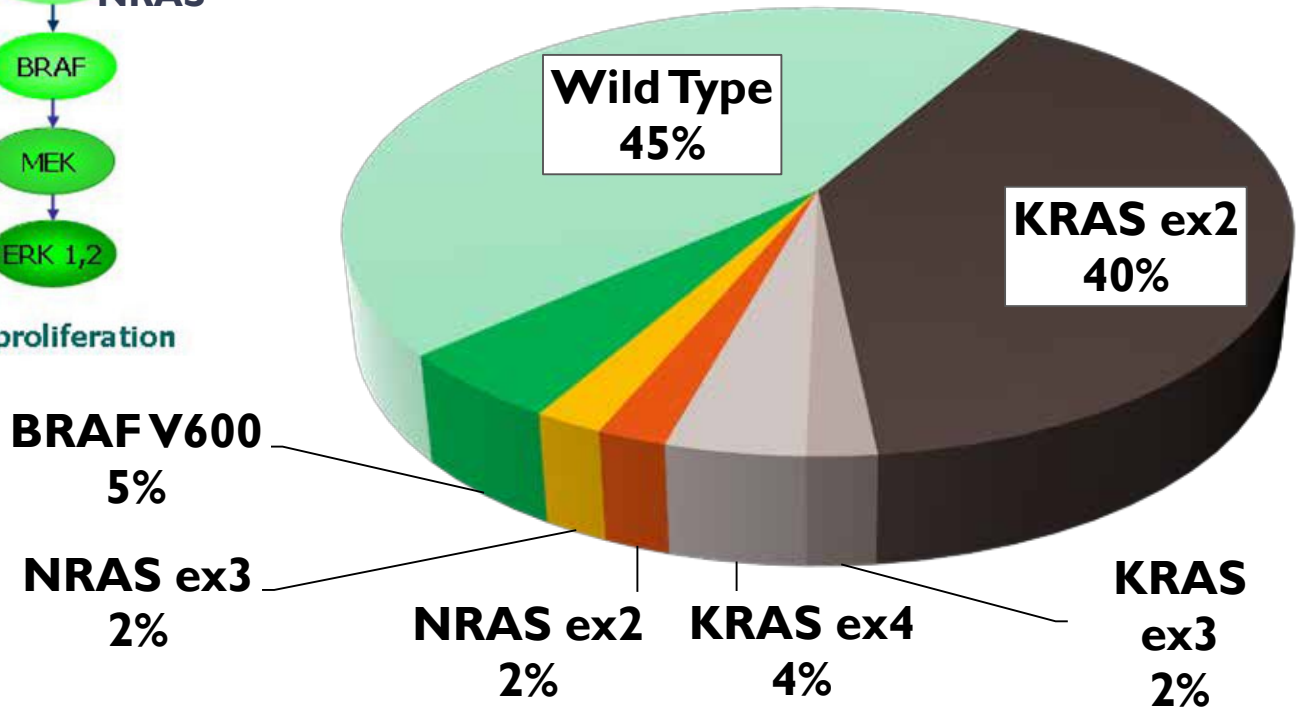
- Left-sided: consider starting with EGFR-targeted therapy
- Right-sided: may use EGFR therapy, but reserve for later line

Arnold, *Ann Oncol* 2017

Anti-EGFR: no benefit in RAS mutants



- Mut KRAS does not respond to silencing by EGFR inhibition (cetuximab, panitumumab)



15-17% wild-type for KRAS exon 2 have a different *RAS/RAF* mut

- Saletti, *GI Cancer: Targets and Therapy* 2015; Douillard, *NEJM* 2013; Heinemann, *Lancet Onc* 2014

EGFR inhibitor-induced rash

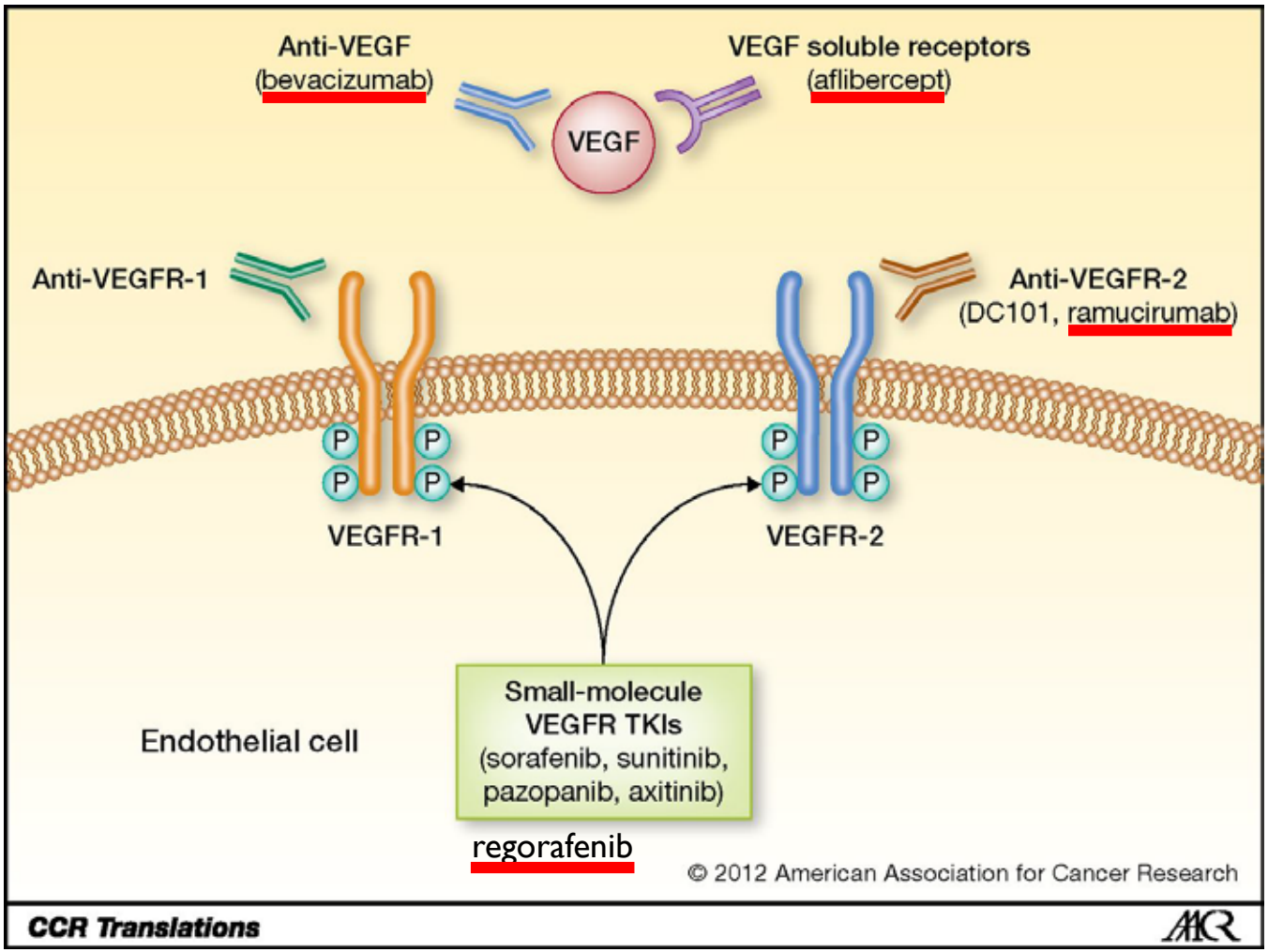
Cetux	Pani
Any rash: 85%	Any rash: 90%
Grade 3: 10%	Grade 3: 16%

Prevention:

- Sunscreen
- Topical hydrocortisone 1%
- Oral doxycycline or minocycline

- Lacouture, *Br J Derm* 2006; Shepherd, *NEJM* 2005; Rosell, *Ann Onc* 2008; Van Cutsem, *JCO 2007*; Geyer, *NEJM* 2006

Anti-VEGF therapy: no biomarkers



- Bevacizumab
  1st or later line
- Aflibercept
  2nd line
- Ramucirumab
  2nd line
- Regorafenib
  3rd line

- Trials: NO16966, TREE-2; VELOUR; RAISE; CORRECT

Should we be using a triplet?

- FOLFOXIRI / FOLFIRINOX
  - Improved response rate, progression-free survival
  - BUT…
    - Increased toxicity
    - Benefit on OS lacking (until TRIBE2)
    - And how do you approach second-line therapy?

- There is increasing support. Especially consider for patients with (*my opinion*):
  - Excellent performance status
  - Patient wants aggressive care
  - And/or need for significant down-staging (i.e. attempt to convert metastases to resectable disease)

Cremolini, *Lancet Oncol* 2015; Cremolini, *Lancet Oncol* 2020; Gruenberger, *Ann Oncol* 2015; Sastre, *ASCO* 2019

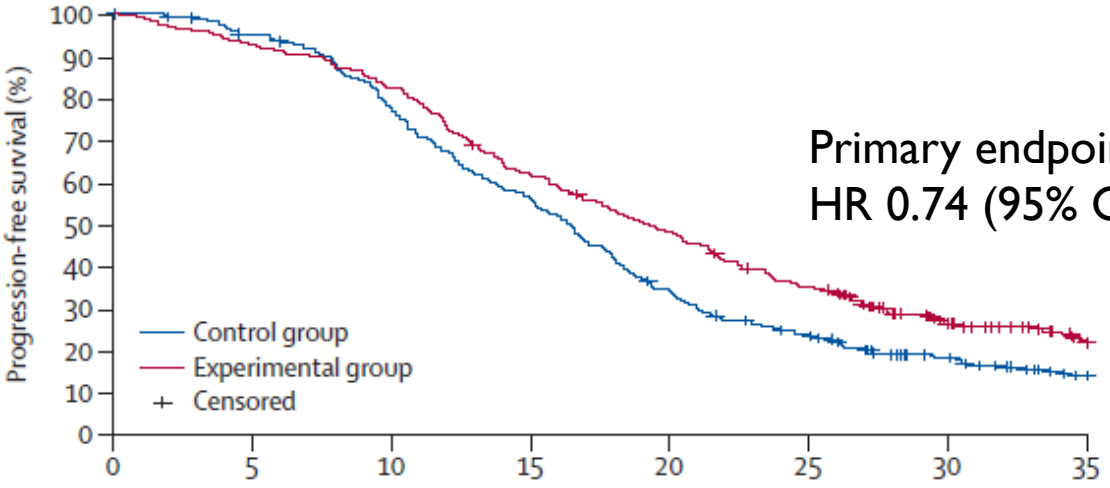
Growing support for triplet therapy

- TRIBE-2 study
  - Phase 3 of 679 patients

12.0 mo 19.2 mo

FOLFOXIRI + bev x8	5-FU + bev maint	FOLFOXIRI + bev
FOLFOX + bev x8	5-FU + bev maint	FOLFIRI + bev

9.8 mo 16.4 mo



Primary endpoint: PFS2
HR 0.74 (95% CI: 0.63-0.88), p=0.0005

Cremolini, *Lancet Oncol* 2020

Second-line therapy

- All of the same options
  - FOLFOX with bevacizumab or cetuximab*
  - FOLFIRI with bevacizumab or cetuximab*

* RAS wildtype

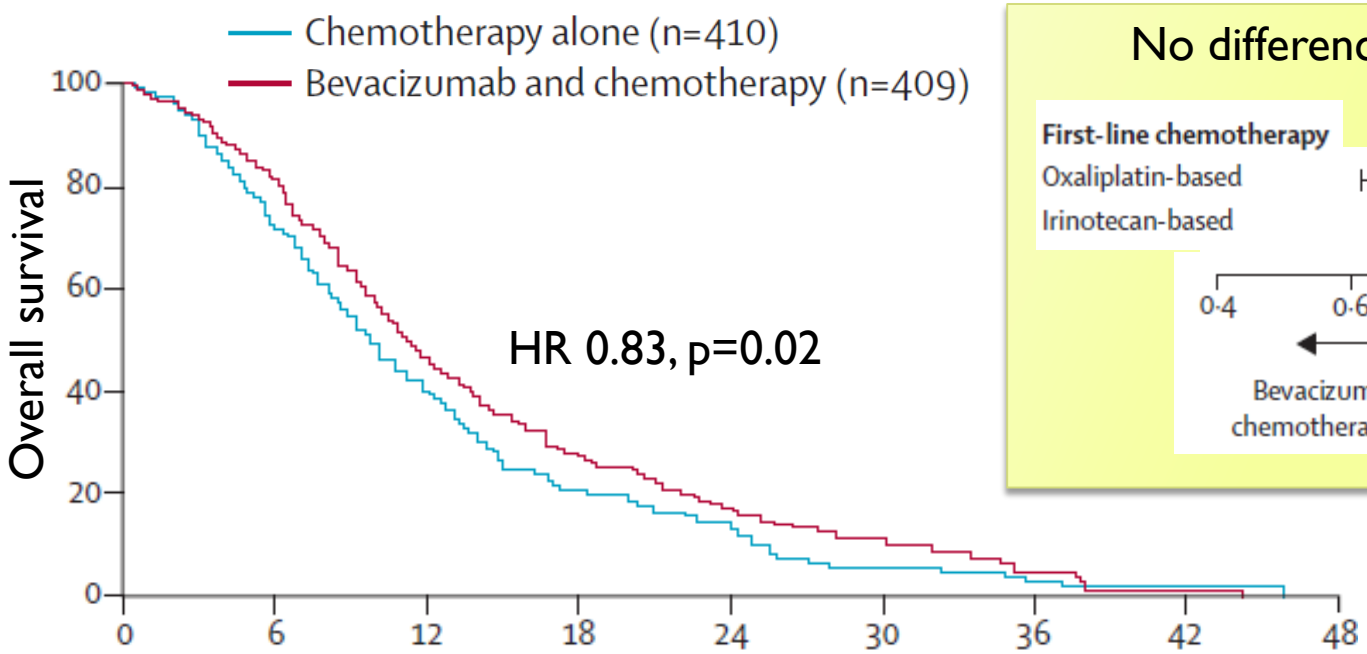
- Sequencing trials show no "correct" order

- Evidence supports continuation of biologic at progression
  - Ex. FOLFOX + bev → FOLFIRI + bev
    FOLFIRI + cetux* → FOLFOX + cetux*

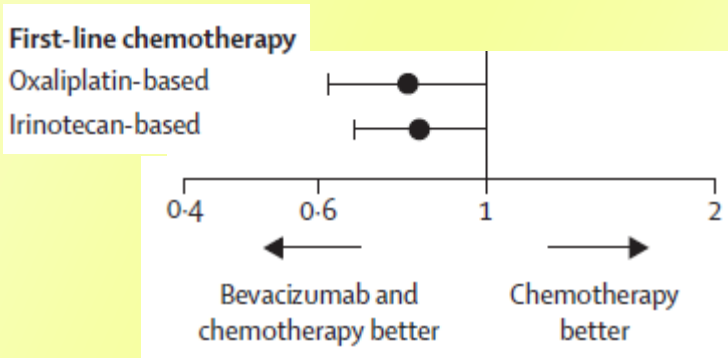
Tournigand, *JCO* 2004; Seymour, *Lancet* 2007; Grothey, *JCO* 2008; Ciardiello, *Ann Onc* 2015

Bevacizumab at progression

- ML 18147: randomized to **continuation of bevacizumab** at progression vs. **chemotherapy alone**
  - All switched FOLFOX ⇔ FOLFIRI
  - Capecitabine allowed



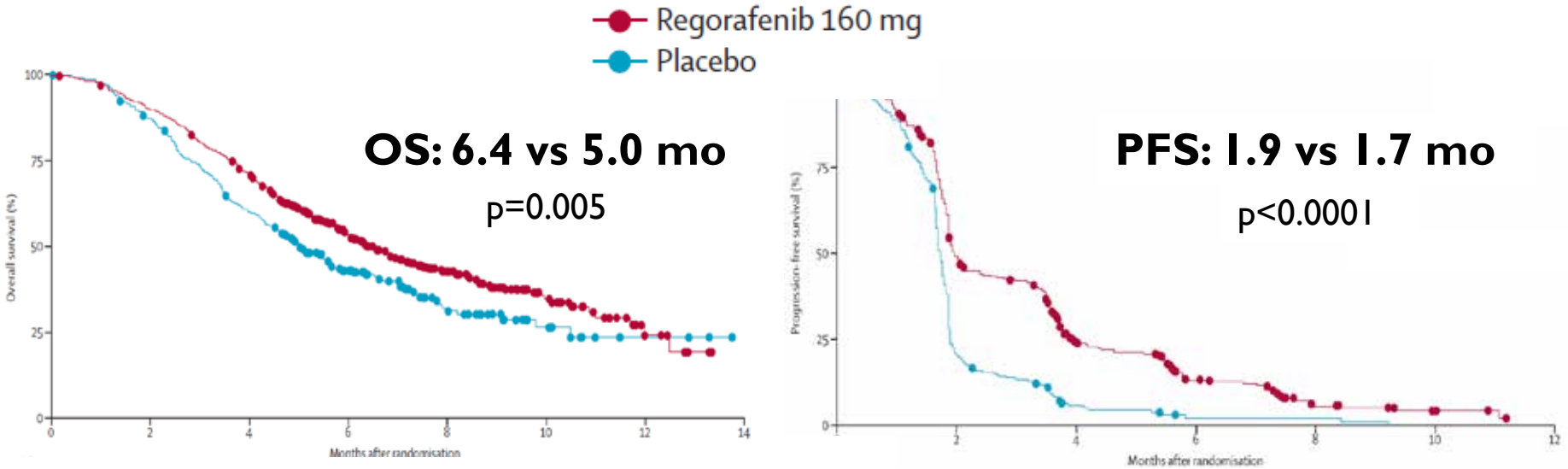
No difference in subgroups:



Bennouna, *Lancet Onc* 2013

Regorafenib

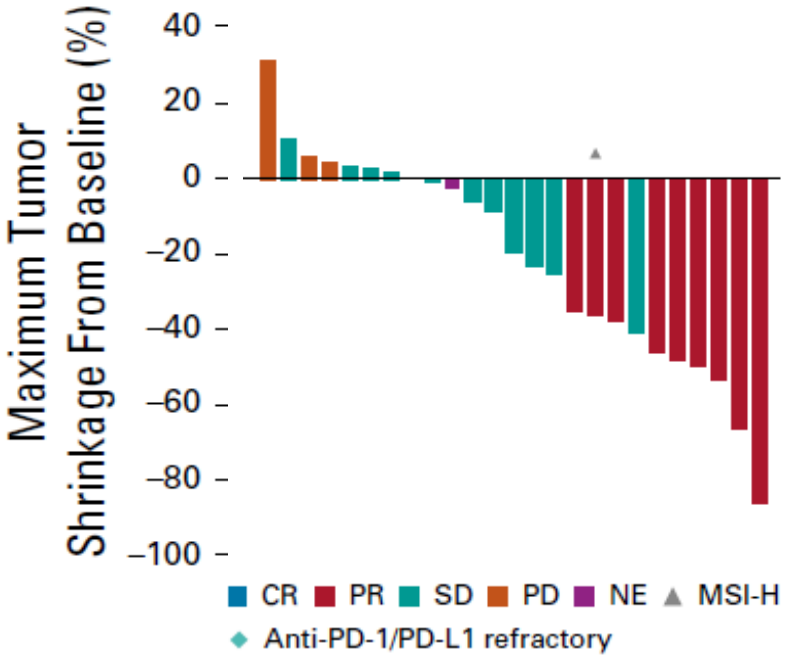
- Oral multi-kinase inhibitor (approved dose: 160mg)
  - REDOS: rPh2 80mg escalated to 160mg vs. upfront 160mg
    - Superior OS, PFS with starting at a lower dose, less toxicity
- CORRECT: RCT 2:1 to **regorafenib** vs. **placebo**
  - 53% grade 3/4 toxicity: hand-foot syndrome, fatigue, HTN, rash, GI

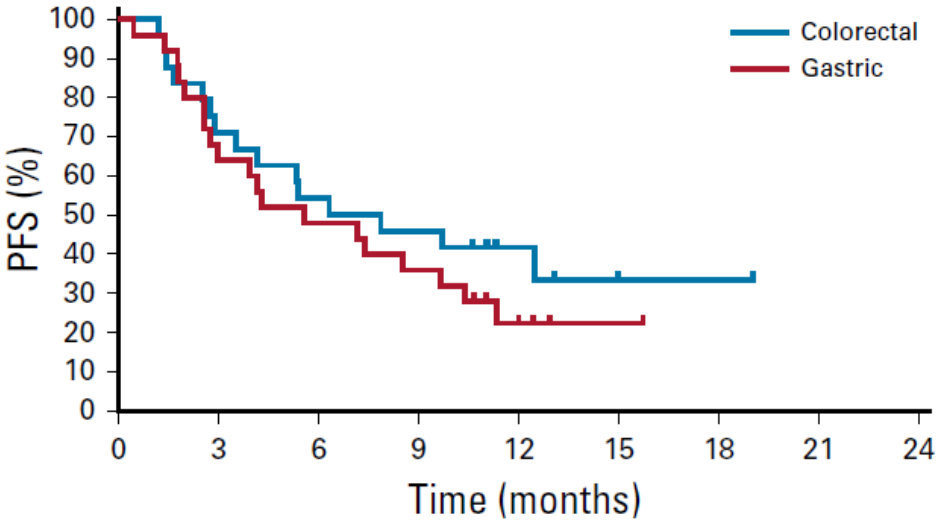


CORRECT: Grothey, *Lancet* 2013; Bekaii-Saab, *Lancet Oncol* 2019

Regorafenib with immunotherapy

- Phase I studies suggest benefit when combining regorafenib 80mg with nivolumab





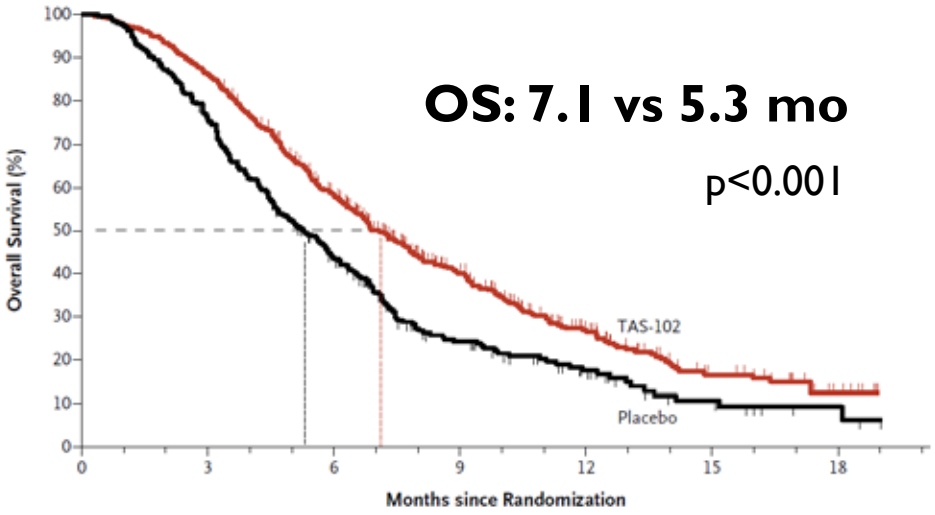
PFS 7.9 mo
1-year PFS: 42%

Fukoka, *J Clin Oncol* 2020; Kim, *ESMO GI* 2020

Trifluridine-tipiracil (TAS-102)

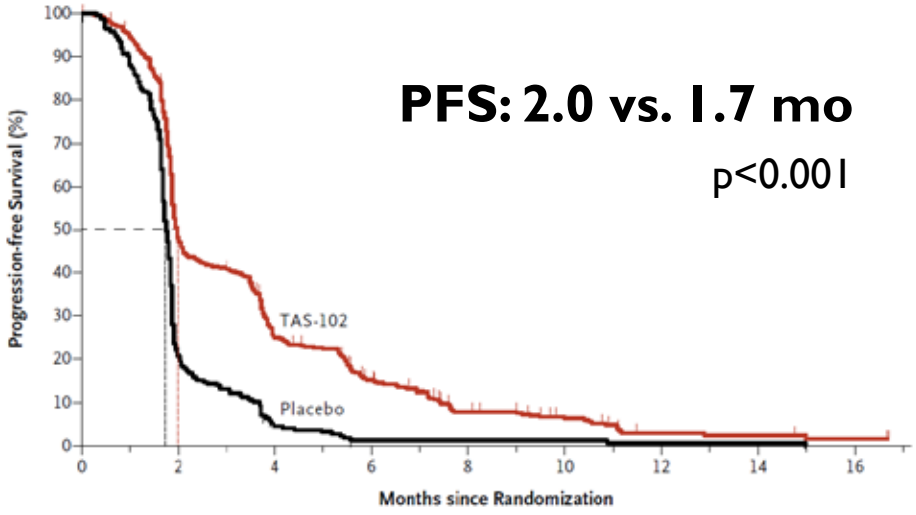
- Oral thymidine analog

- RECOURSE: RCT 2:1 to **TAS-102** vs. **placebo**
  - >90% 5-FU-refractory
  - Benefit irrespective of prior regorafenib
  - 38% neutropenia; low rates of hand-foot syndrome



OS: 7.1 vs 5.3 mo

p<0.001



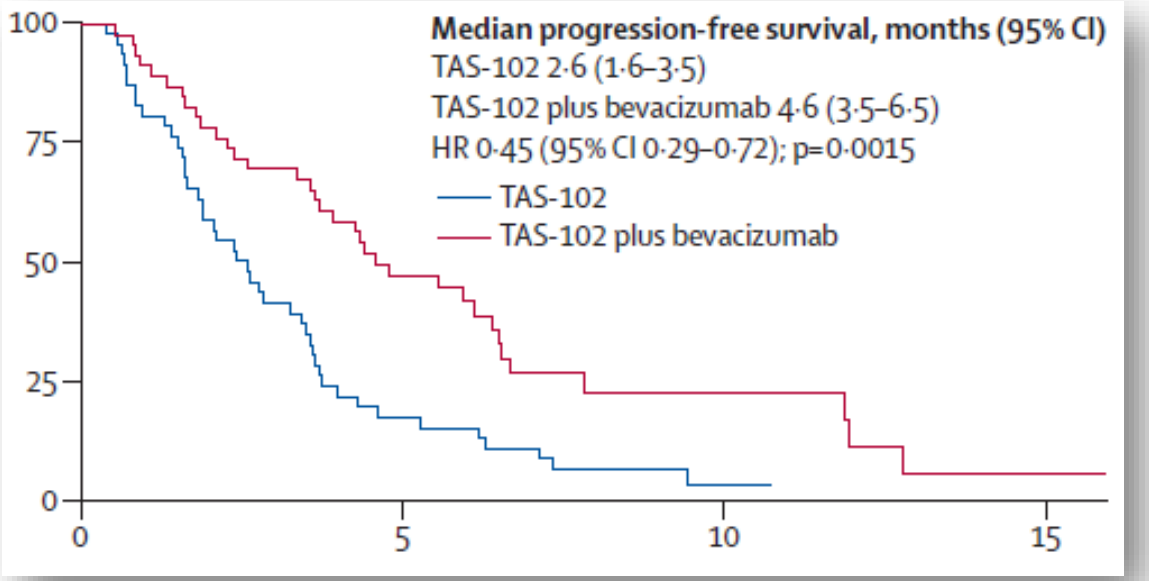
PFS: 2.0 vs. 1.7 mo

p<0.001

- Mayer, *NEJM* 2015

Trifluridine-tipiracil combinations

- C-TASKFORCE
  - Improved benefit in combination with bevacizumab



- Anticipate that it will be evaluated earlier in treatment and/or combination with other agents
  - Ex. trifluridine/tipiracil + irinotecan ± bevacizumab

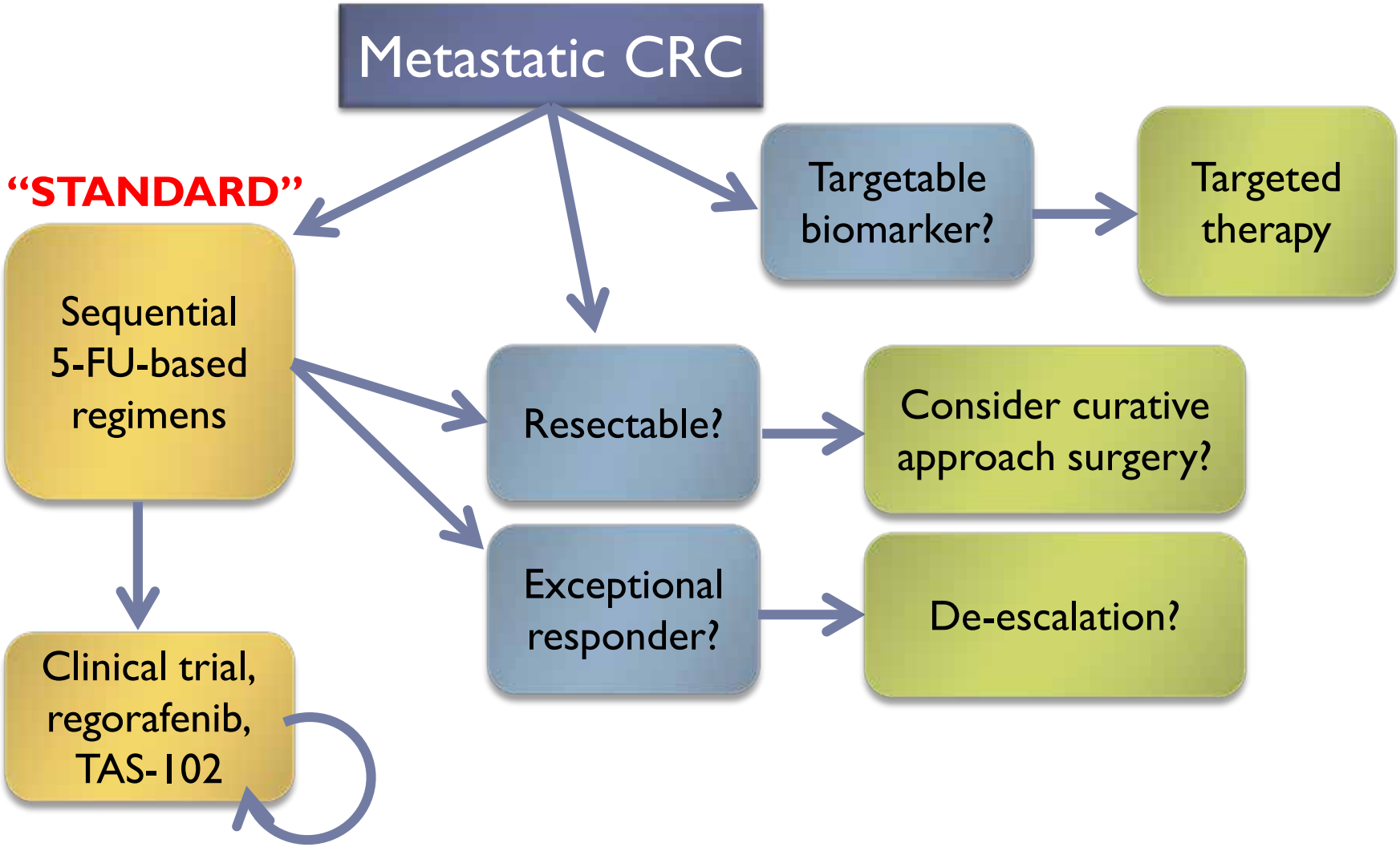
Pfeiffer, *Lancet Oncol* 2020

Key points

- No "correct" first-line chemotherapy regimen
  - Any chemo doublet (or triplet) + biologic is acceptable
  - Cetuximab may be less effective for right-sided tumors
- Extended RAS + BRAF testing should be part of every stage IV CRC work-up
- Regorafenib and TAS-102 are approved, but of limited clinical benefit (OS ~2 months) as monotherapy

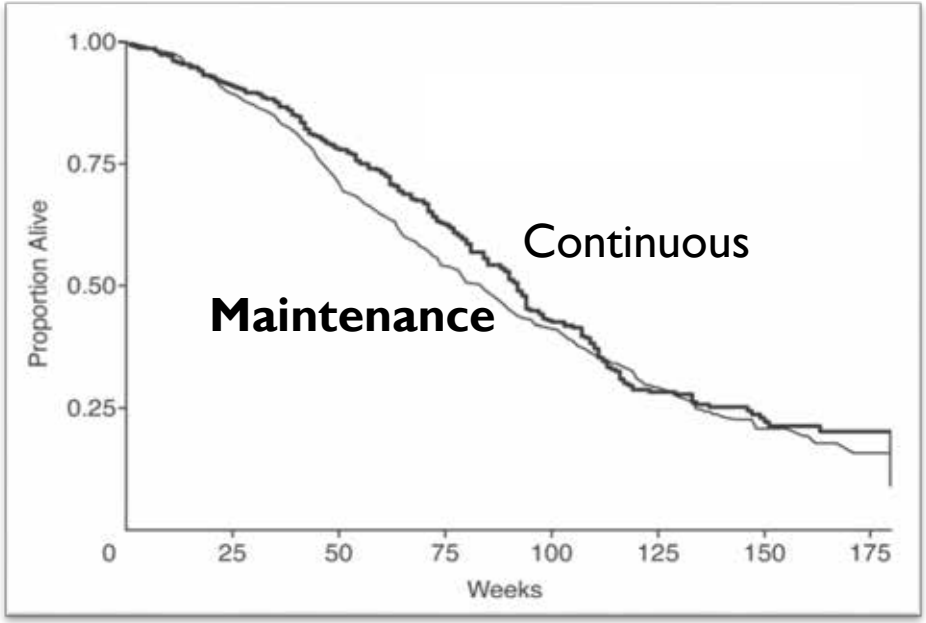
Tailored chemotherapy strategies

Approaches to longitudinal treatment



Maintenance / de-escalation

- OPTIMOX-1
  - RCT to de-escalating to **5-FU** vs. continuous FOLFOX
  - PFS, OS similar
  - Less toxicity with 5-FU



- Multiple "correct" maintenance strategies

5-FU + bevacizumab*	CAIRO3, AIO KRK 0207
Bevacizumab	AIO KRK 0207, PRODIGE-9
5-FU + panitumumab*	VALENTINO
Cetuximab	MACBETH, (PANAMA), (ERMES)

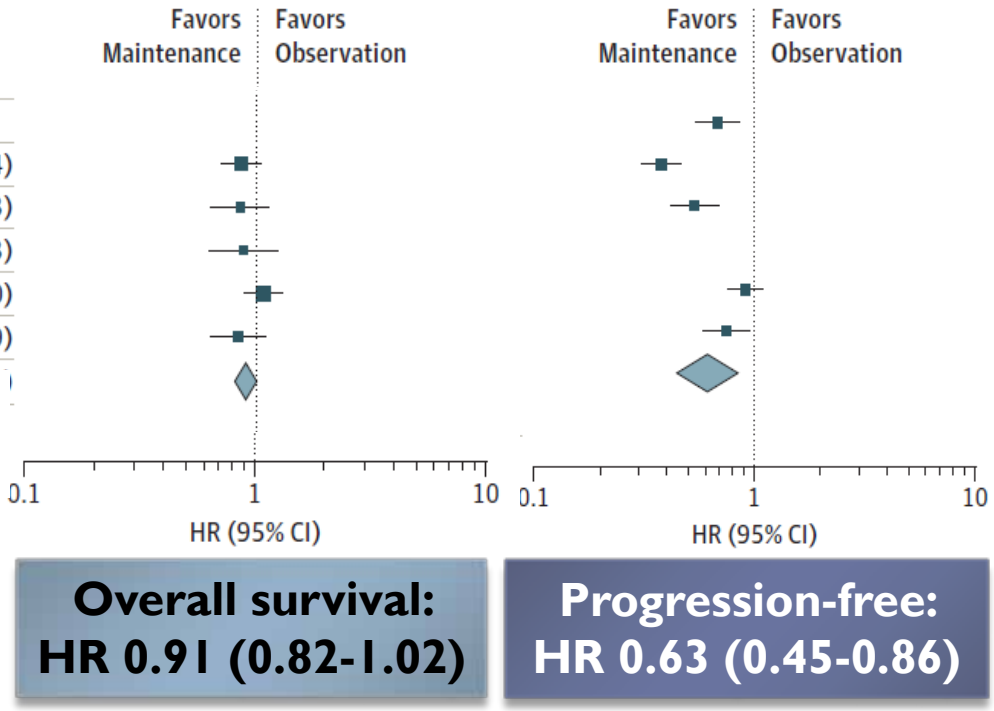
*Numerically, maintenance with 5-FU + biologic has best outcomes

Tournigand, *JCO* 2006; Simkens, *Lancet* 2015; Hegewisch-Becker, *Lancet Onc* 2015; Aparicio, *J Clin Oncol* 2018; Cremolini, *JAMA Oncol* 2018; Pietrantonio, *JAMA Oncol* 2019

Treatment holiday

- Meta-analysis

Hegewisch-Becker et al,[19] 2015	0	0	Not estimable
Simkens et al,[16] 2015	-0.1508	0.0978	0.86 (0.71-1.04)
Luo et al,[21] 2016	-0.1625	0.1448	0.85 (0.64-1.13)
Chibaudel et al,[7] 2009	-0.1278	0.1705	0.88 (0.63-1.23)
Aparicio et al,[14] 2018	0.0677	0.0997	1.07 (0.88-1.30)
Koeberle et al,[20] 2015	-0.1863	0.1407	0.83 (0.63-1.09)



Overall survival: HR 0.91 (0.82-1.02)

Progression-free: HR 0.63 (0.45-0.86)

- Complete treatment breaks often associated with worse short-term outcomes
- No clear detriment in the overall survival

Sonbol, *JAMA Oncol* 2019

Metastasectomy

- Retrospectives of carefully selected patients suggest improved 5-year OS: 25-58% (vs. 10% with just chemotherapy)
- Only 10-15% of stage IV patients qualify
  - Limited metastatic sites that are amenable to localized treatment (resection, ablation, etc.)
  - Thorough multi-disciplinary review
- Do not over-treat patients beforehand
  - Irinotecan: steatohepatitis
  - Oxaliplatin: sinusoidal obstructive syndrome
  - If upfront resectable, typically give ~2 months of chemo before reassessment and surgery

Folprecht, *Ann Onc* 2014; Karoui, *Ann Surg* 2006; Vauthey, *JCO* 2006; Adams, *HPB* 2013; Kim, *JKSS* 2011; Verwaal, *Ann Surg Onc* 2008

"Adjuvant" therapy after metastasectomy

- Controversial with limited data, but often done
- EORTC 40983: RCT to 6 cycles FOLFOX pre/post surgery vs. surgery alone

	Peri-op chemo	Surgery alone	
PFS	20.9 mo	12.5 mo	p=0.04
OS (all pt)	63.7 mo	55.0 mo	p=0.30
OS (resected)	77.5 mo	73.3 mo	p=0.35

- Like stage III, no demonstrated benefit to irinotecan or biologics
  - FOLFOX alone recommended

    (5-FU/capecitabine alone in an older person or residual neuropathy)
  - Guidelines allow for continuation of a biologic if it was helpful in converting to resectable disease

Nordlinger, *Lancet Onc* 2013; Primrose, *Lancet Onc* 2014

Key points

- Maintenance therapy is acceptable in good responders, without compromising PFS or OS
  - 5-FU/capecitabine ± biologic is recommended
- Full chemotherapy holidays compromise PFS, but may be appropriate for certain patients
- Curative intent treatment of oligometastatic disease greatly improves long-term survival in the correct patient

Targeting molecular alterations

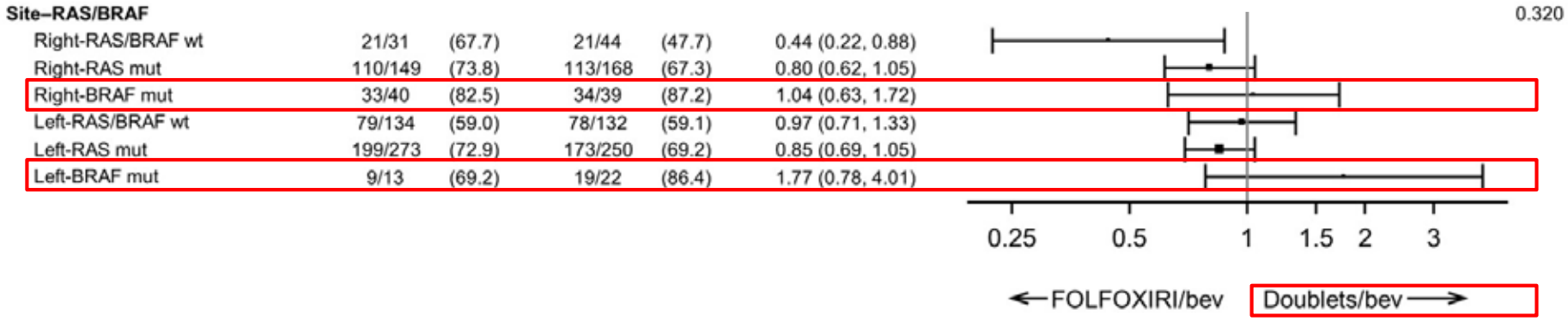
Tailoring to biomarkers

* BRAF	~~FOLFOXIRI~~ Encorafenib + cetuximab ~~Vemurafenib + irinotecan + cetuximab~~
* HER2	Trastuzumab + lapatinib Trastuzumab + pertuzumab Trastuzumb-deruxtecan
* MSI, hypermutation	PD-1 inhibitor, immune therapy
NTRK, ALK	Entrectanib, larotrectanib
ERCC1	~~Avoid oxaliplatin~~ → *Failed to show prospective difference*
CIMP (epigenetic hypermethylation)	Demethylating agents? Irinotecan-based regimen?

- Kopetz, *NEJM* 2019; Sartore-Bianchi, *Lancet Onc* 2015, MyPathway; Lenz, *ASCO 2016*; Overman, *Oncotarget* 2016, Shiovitz, *Gastro* 2014; Le, *NEJM* 2016; Drilon, *NEJM* 2018

BRAF+ colorectal cancer

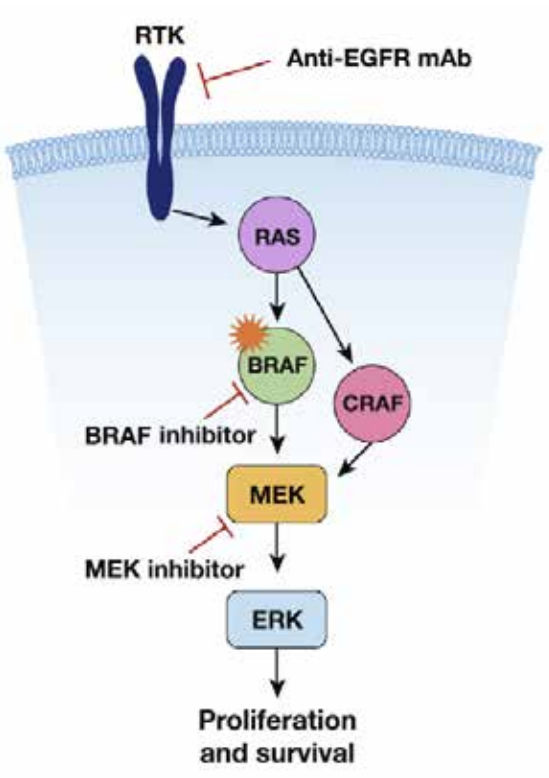
- Poor prognostic marker, resistant to anti-EGFR
- Benefit from more intensive first-line chemotherapy?
  - TRIBE trial suggested improved PFS from FOLFOXIRI/bev in the BRAF mutant subgroup
  - Meta-analysis of 5 trials (TRIBE, TRIBE2, CHARTA, OLIVIA, STEAM) was not supportive

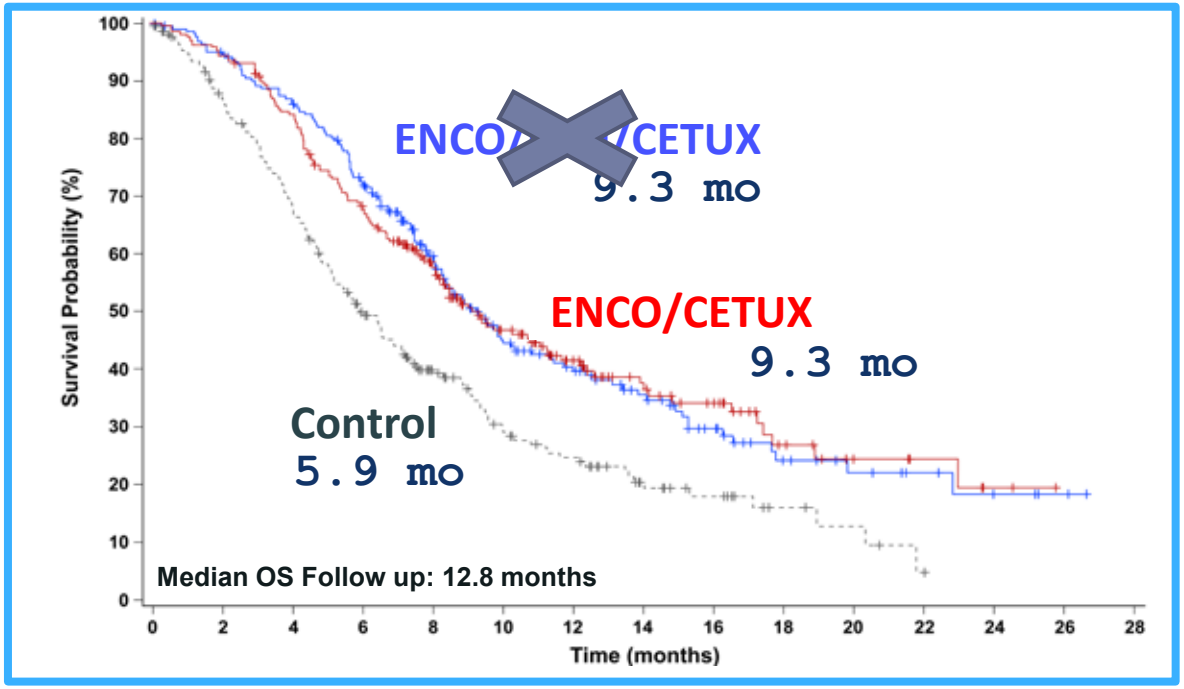


Cremolini, *ASCO* 2020

Targeted BRAF inhibition

- BRAF-inhibitor monotherapy ineffective
- Multi-pathway is necessary against BRAF and EGFR





New standard: encorafenib + cetuximab/panitumumab

MEK inhibition adds no meaningful benefit to BRAF/EGFR

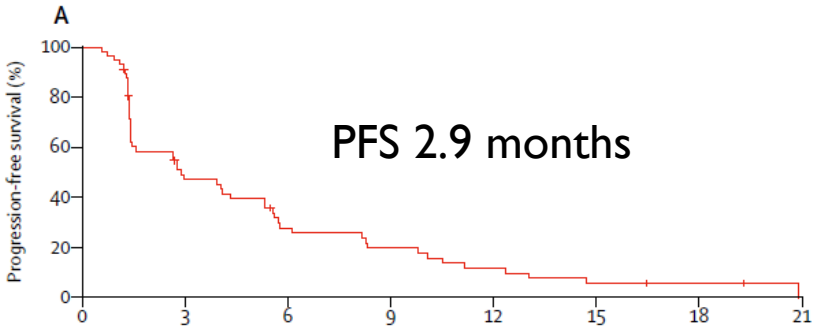
Future: BRAF/EGFR/PD1? BRAF/MEK/PDI?

Strickler, *Cancer Treat Rev* 2017; Kopetz, *NEJM* 2019; Kopetz, *ASCO* 2020

HER2 targeted therapy

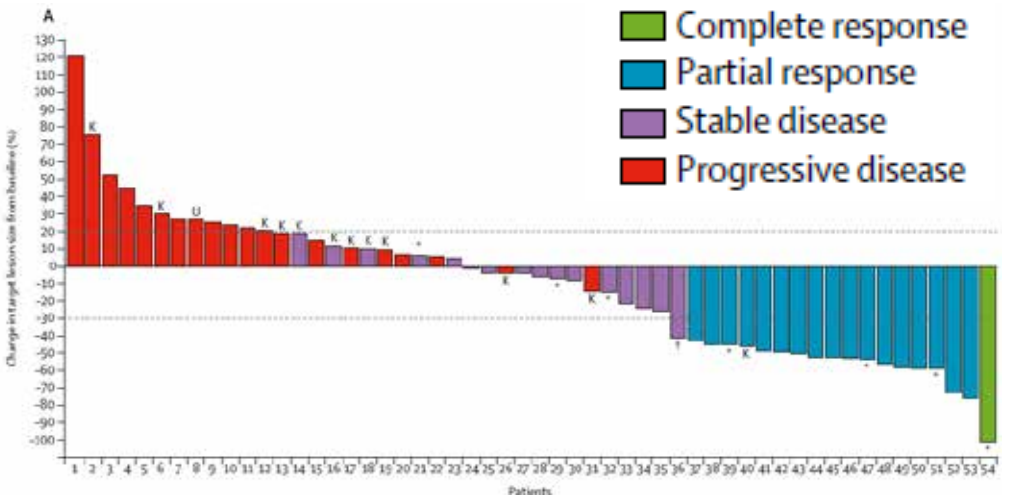
- 4-6% of mCRC; associated with MSI, wild-type RAS/RAF

- Trastuzumab + pertuzumab
  - ORR 14-32%



- Trastuzumab + lapatinib
  - ORR 30%

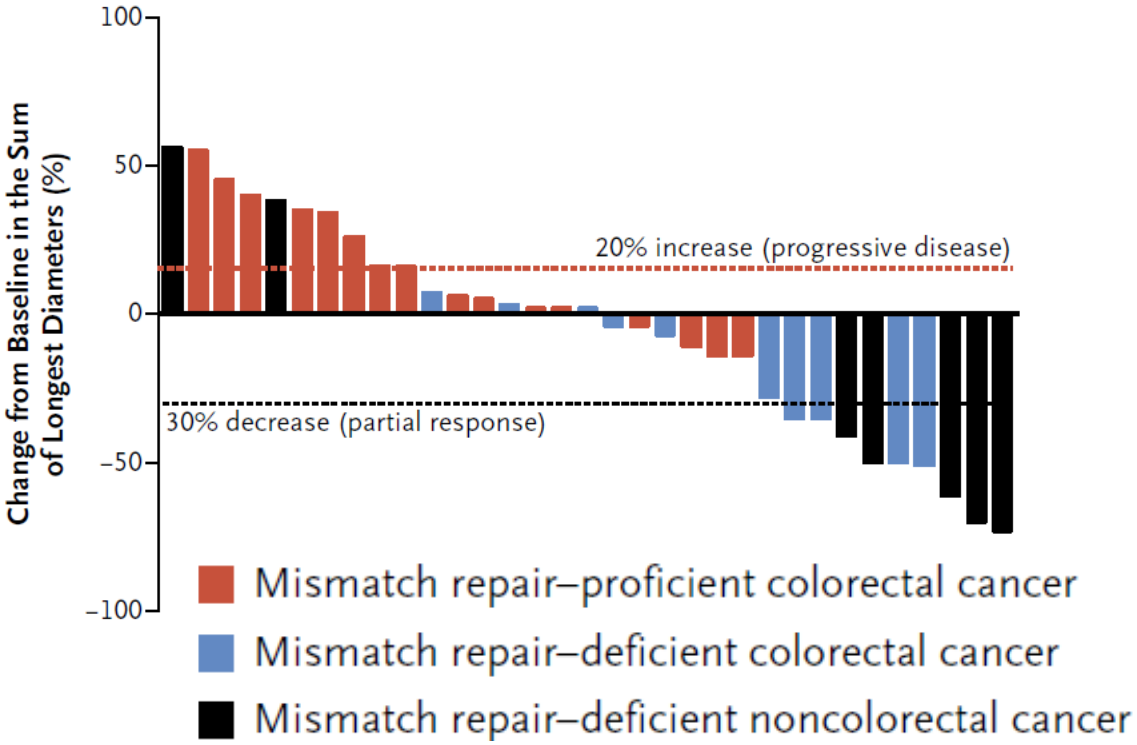
- Trastuzumab deruxtecan
  - ADC w/ topo-I derivative
  - ORR 45%



Meric-Bernstam, *Lancet Onc* 2019; Gupta, *ASCO GI* 2019; Sartore-Bianchi, *Lancet* 2016; Siena, *ASCO* 2020

Anti-PD1 therapy in MSI

- Phase 2 trial of pembrolizumab in mCRC or other cancers
- Response: MSI (MMR-deficient) >> MSS (MMR-proficient)

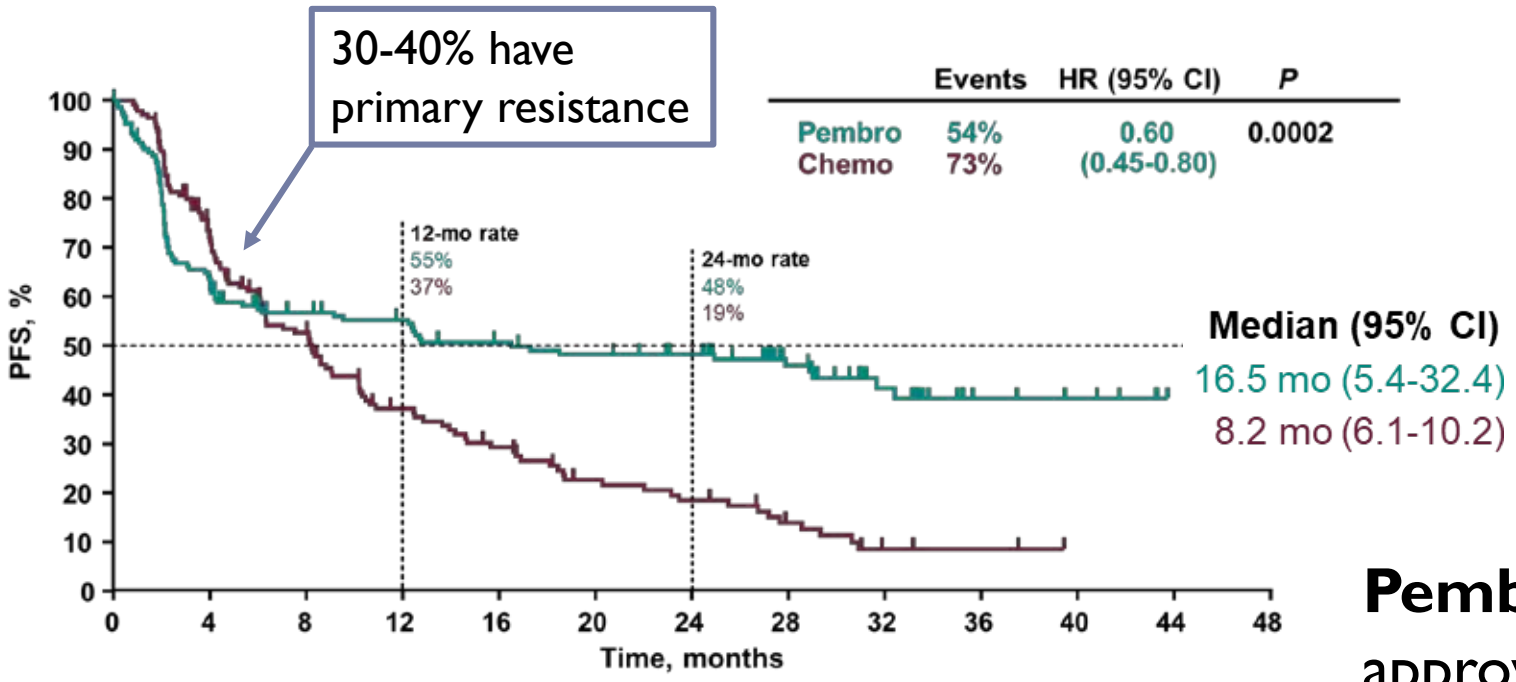


- Somatic MSI did better than germline (Lynch)
- **Pembrolizumab** approved 5/2017
- **Nivolumab** approved 8/2017
- **Nivo/ipilimumab** approved 8/2018

Le, *NEJM* 2015; Overman, *Lancet Onc* 2017

Use of anti-PD1 in first-line therapy

- Keynote-177
  - MSI CRC randomized to pembrolizumab vs. chemotherapy (any doublet ± biologic) allowed



Pembrolizumab approved 6/2020

Andre, *ASCO* 2020

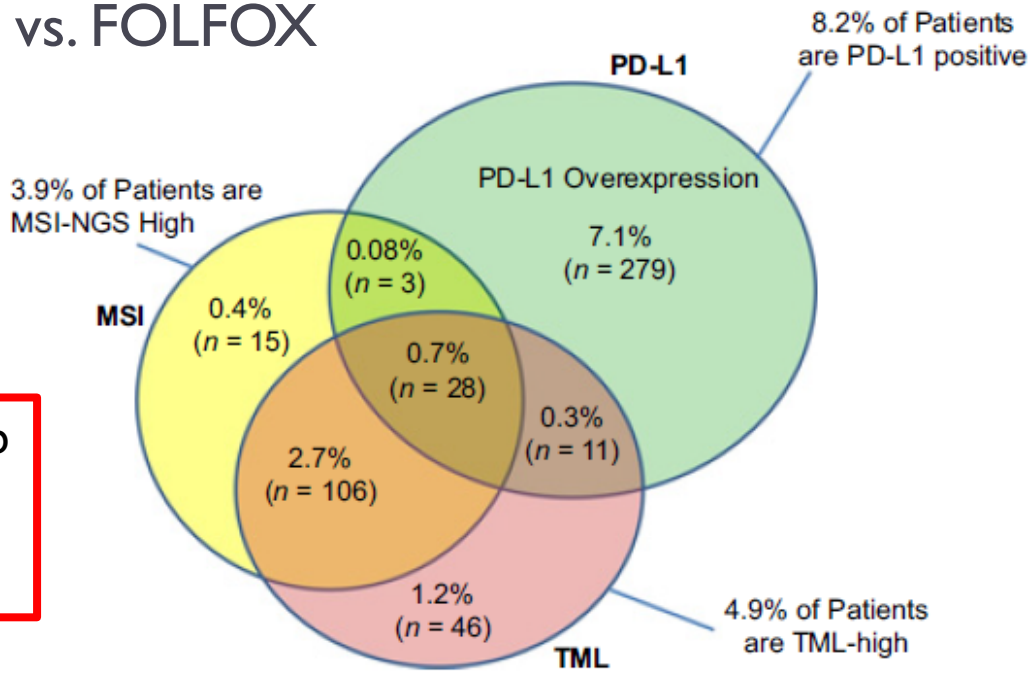
Ongoing investigation (examples)

- First-line therapy
  - SWOG 1610: atezolizumab vs. FOLFOX/bev/atezo vs. FOLFOX/bev
- Adjuvant therapy
  - ATOMIC: FOLFOX/atezo vs. FOLFOX

…but how to identify and/or induce MSS responders?

6/2020: FDA approves pembrolizumab for TMB ≥10 mut/Mb

… too low for CRC?



Salem, *Mol Cancer Res* 2018; Keynote-158: Marabelle, *J Clin Oncol* 2020

Key points

- Targeting BRAF requires multi-pathway blockade
  - At this point, encorafenib + cetuximab (panitumumab) is standard
- HER2 should be evaluated in RAS/RAFwt as targeted options are available
- MSI is a biomarker for response to immunotherapy
  - Now indicated in first or later line
  - Role in combination with chemotherapy is unproven

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Thrombotic Microangiopathies (TTP/aHUS)

Allyson Pishko, MD MSCE

Assistant Professor

University of Pennsylvania, Division of Hematology/Oncology

Disclosures

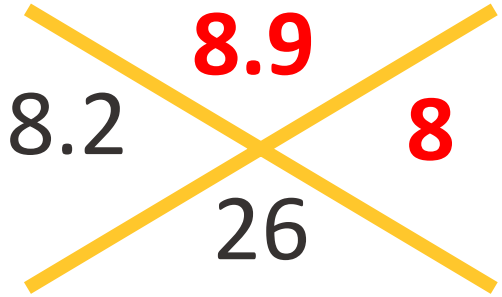
- Research support from Sanofi Genzyme

Outline

- Case-based
- Differential of Thrombotic Microangiopathies
- Brief Review of Pathogenesis
- Management
  - Diagnosis
  - Treatment
  - Follow-up

Case #1

23 yo F presents with dyspnea, fatigue and petechiae



137	107	15
3.8	22	1.06

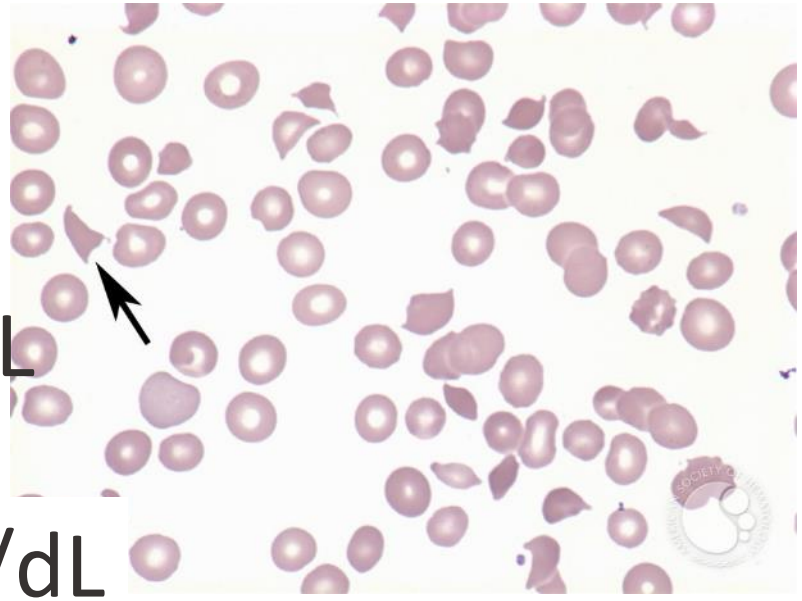
PT 12 s

PTT 32 s

Fibrinogen 250 mg/dL

LDH 865 U/dL

Haptoglobin <30 mg/dL



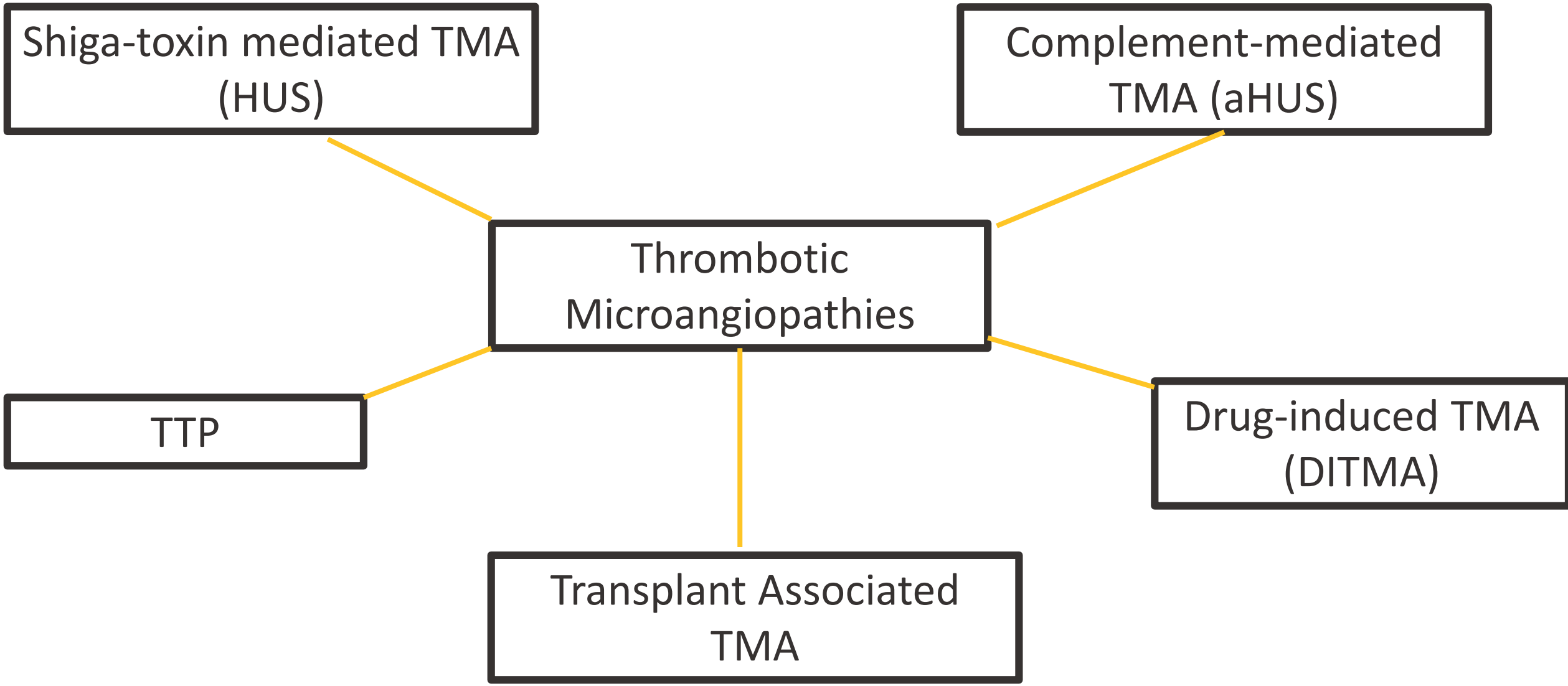
Authors: Peter Maslak; Lisa Southern;

ASH | Image Bank

Thrombotic Microangiopathies-*Diagnosis*

- Hemolytic Anemia
  - ↓HgB + ↑LDH + ↓haptoglobin
- Thrombocytopenia
- +/- renal dysfunction
- Neurologic Symptoms

TMA-*Types*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Complement-mediated TMA (aHUS)
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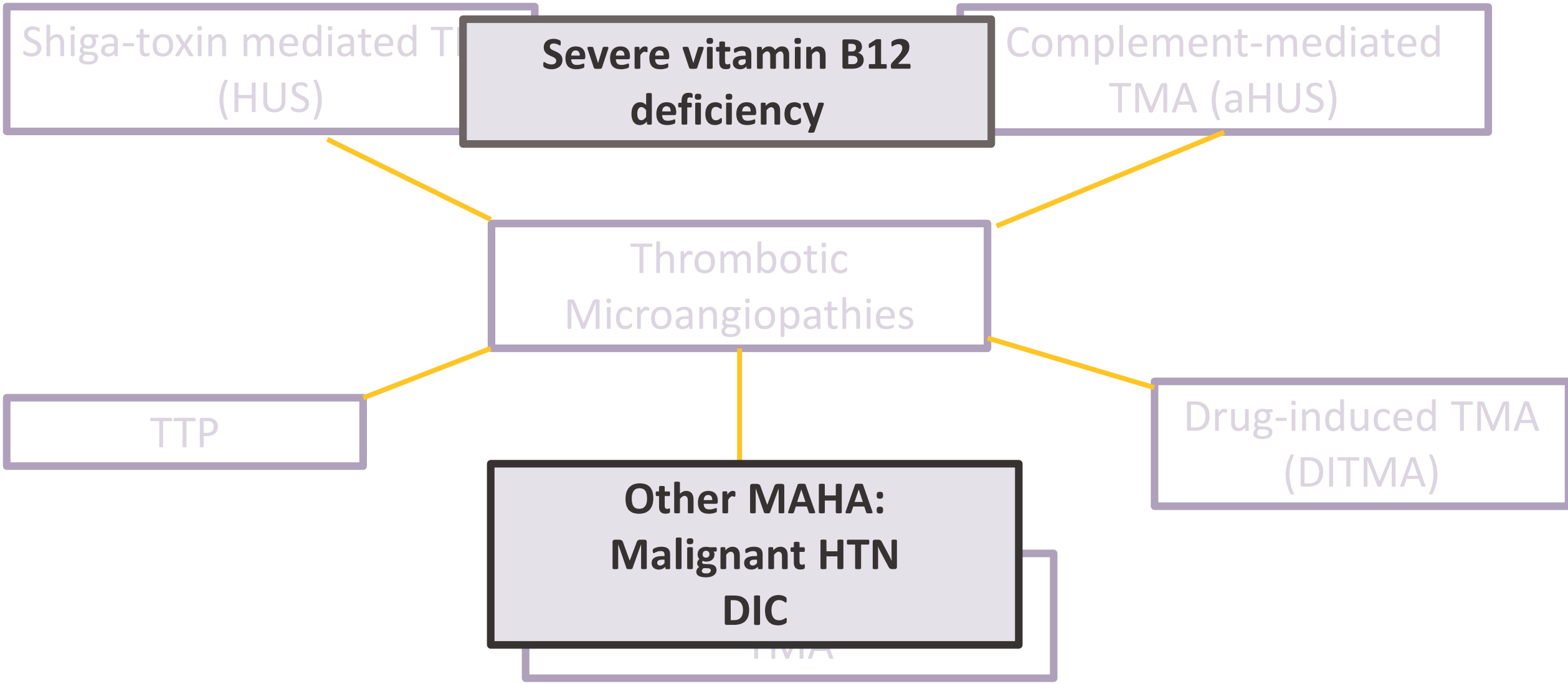
Transplant Associated TMA

TMA-*Mimickers*



Case #1

23 yo F presents with dyspnea, fatigue and petechiae

8.2	**8.9**	**8**
	26	

137	107	15
3.8	22	1.06

PT 12 s

PTT 32 s

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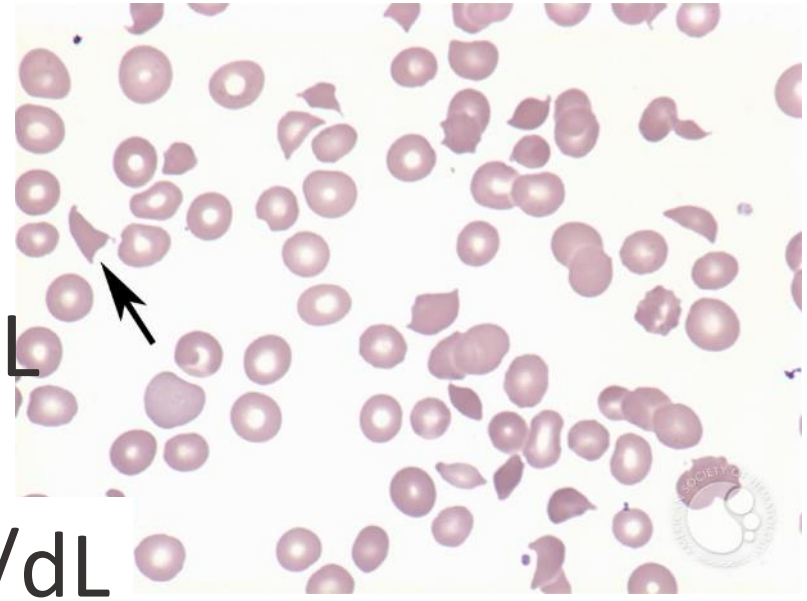
LDH 865 U/dL

Haptoglobin <30 mg/dL



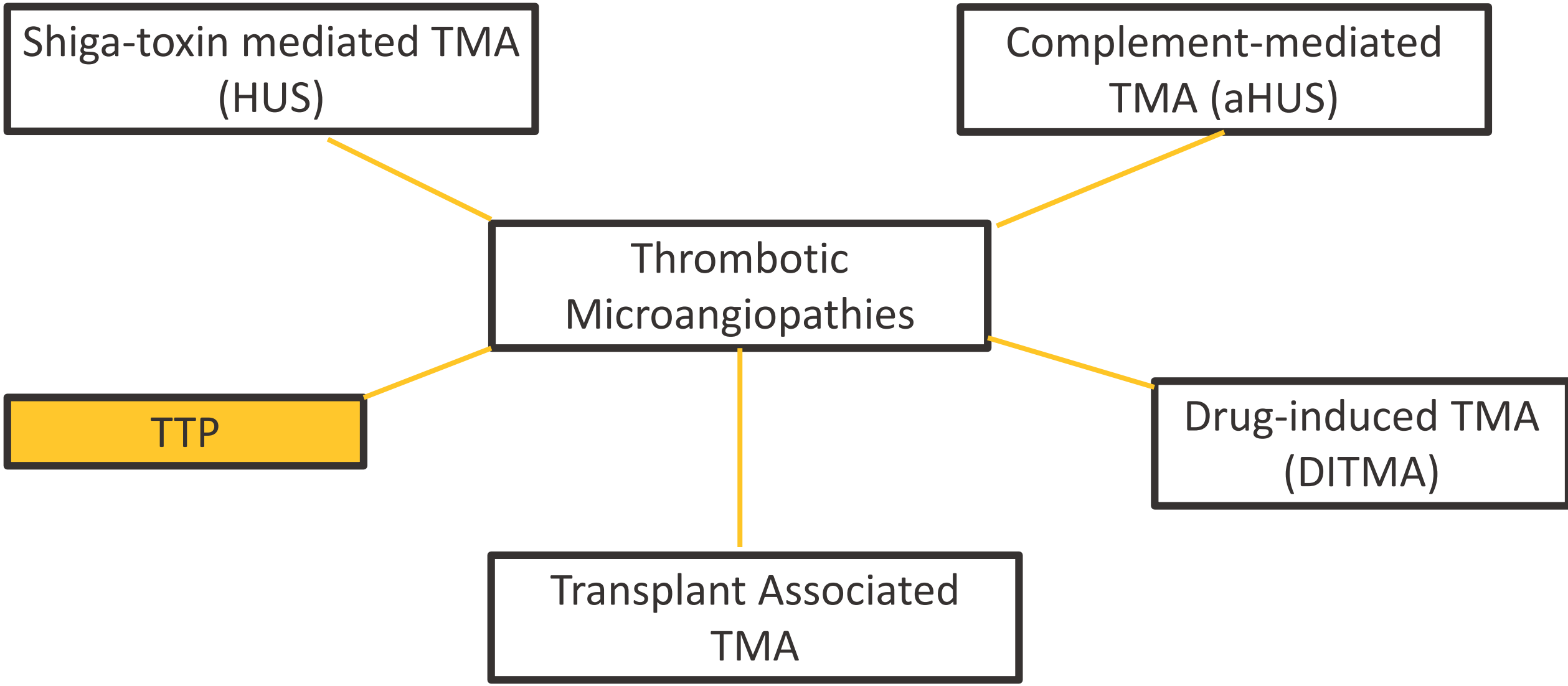
Authors: Peter Maslak; Lisa Southern;

ASH | Image Bank

PLEX initiated…….

ADAMTS13 <10%

TMA-*Types*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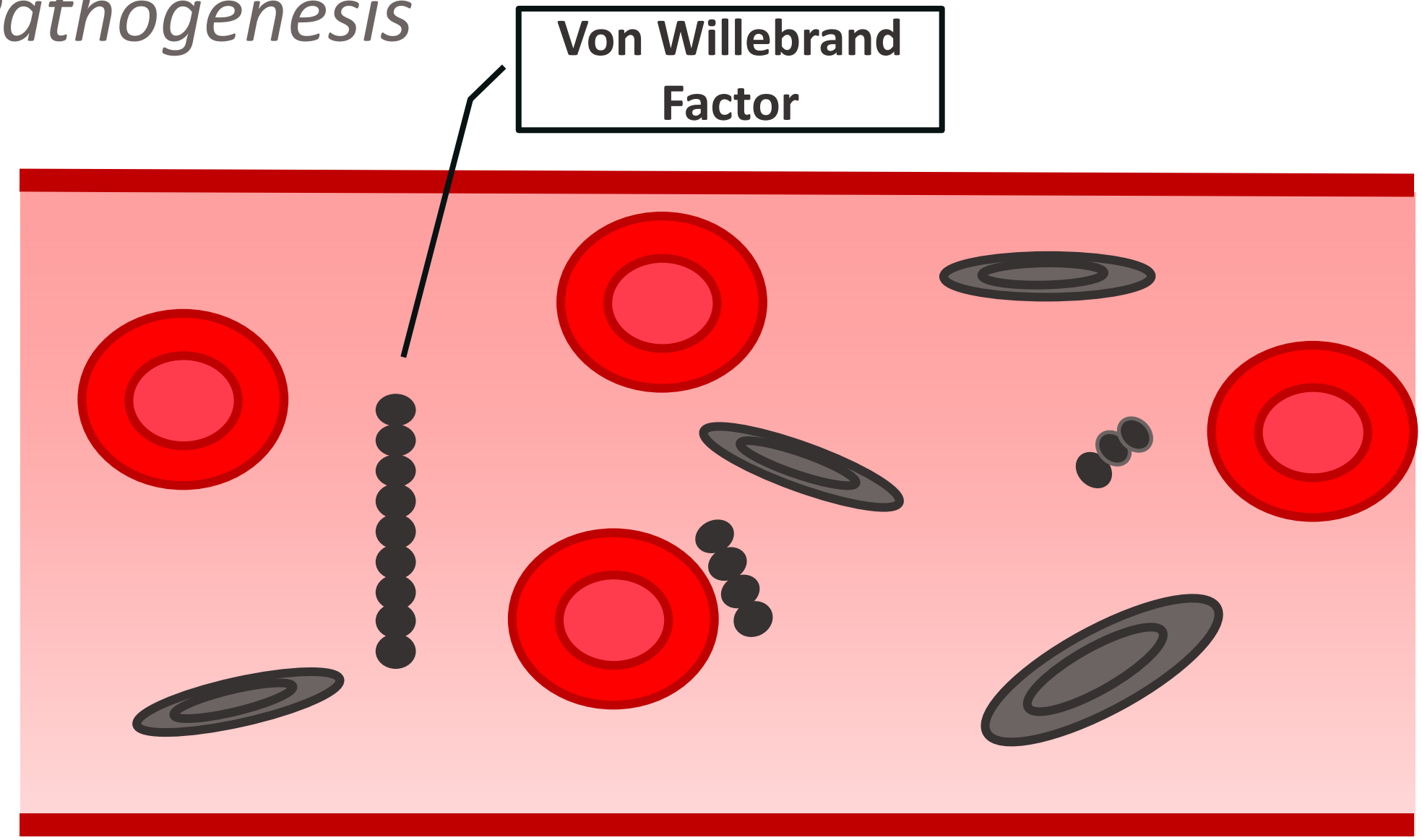
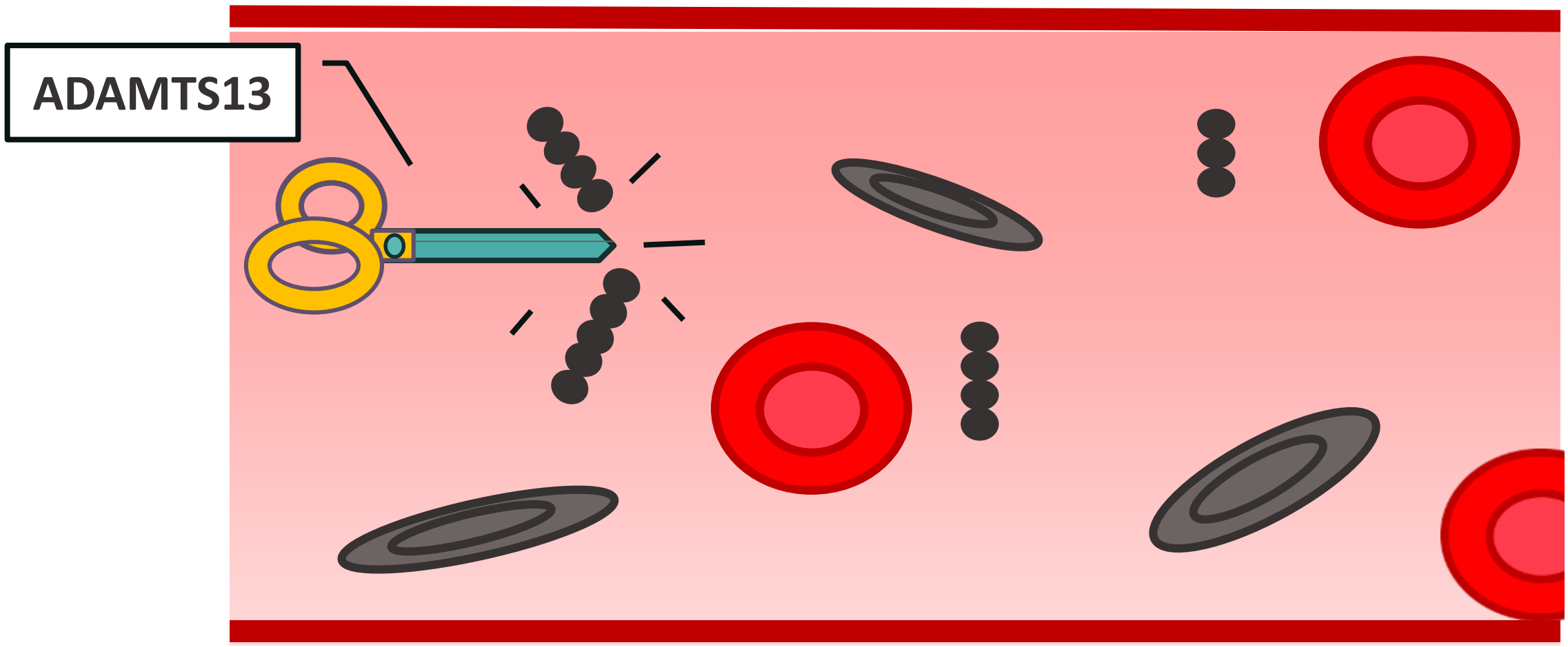
TTP: *Pathogenesis*



TTP: *Pathogenesis*



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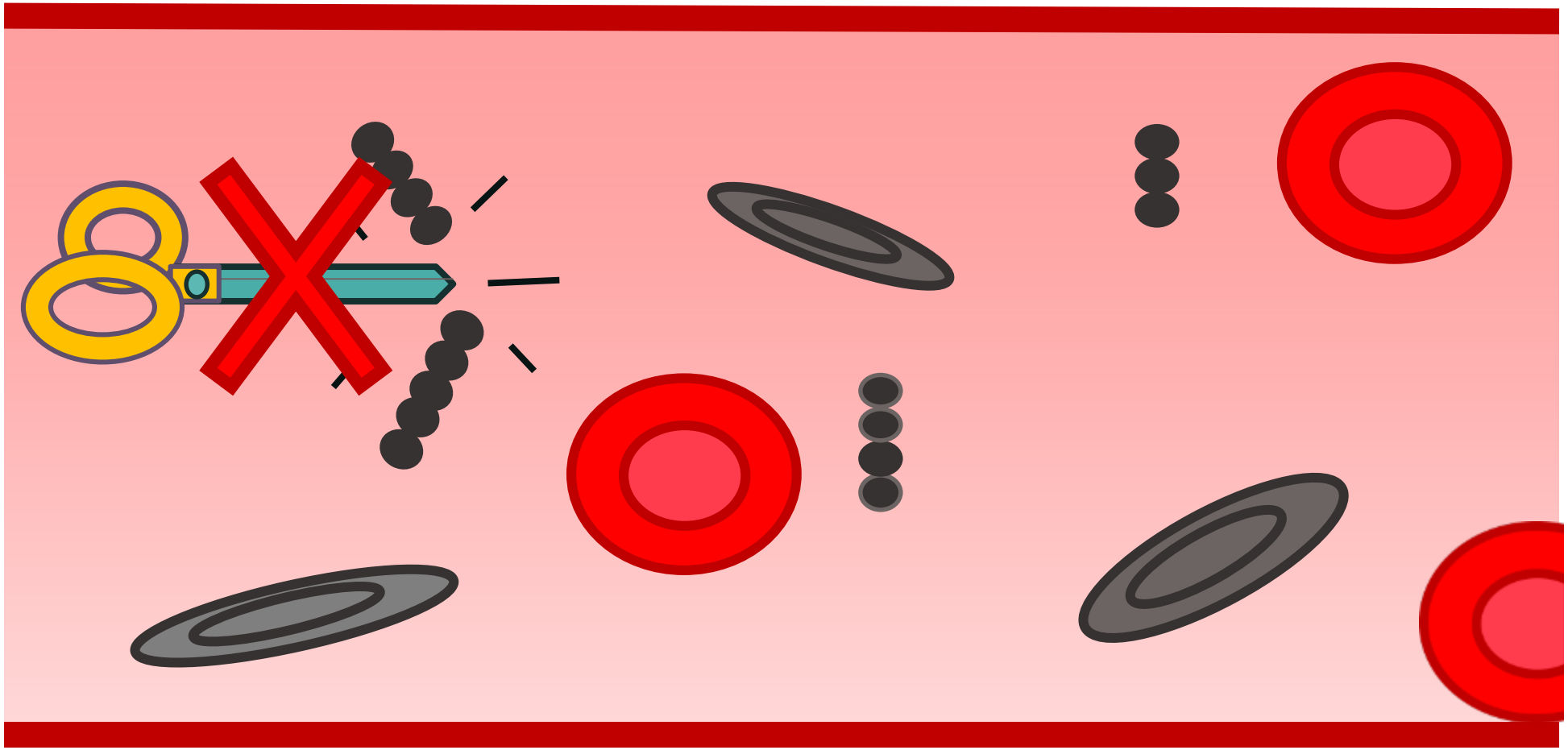
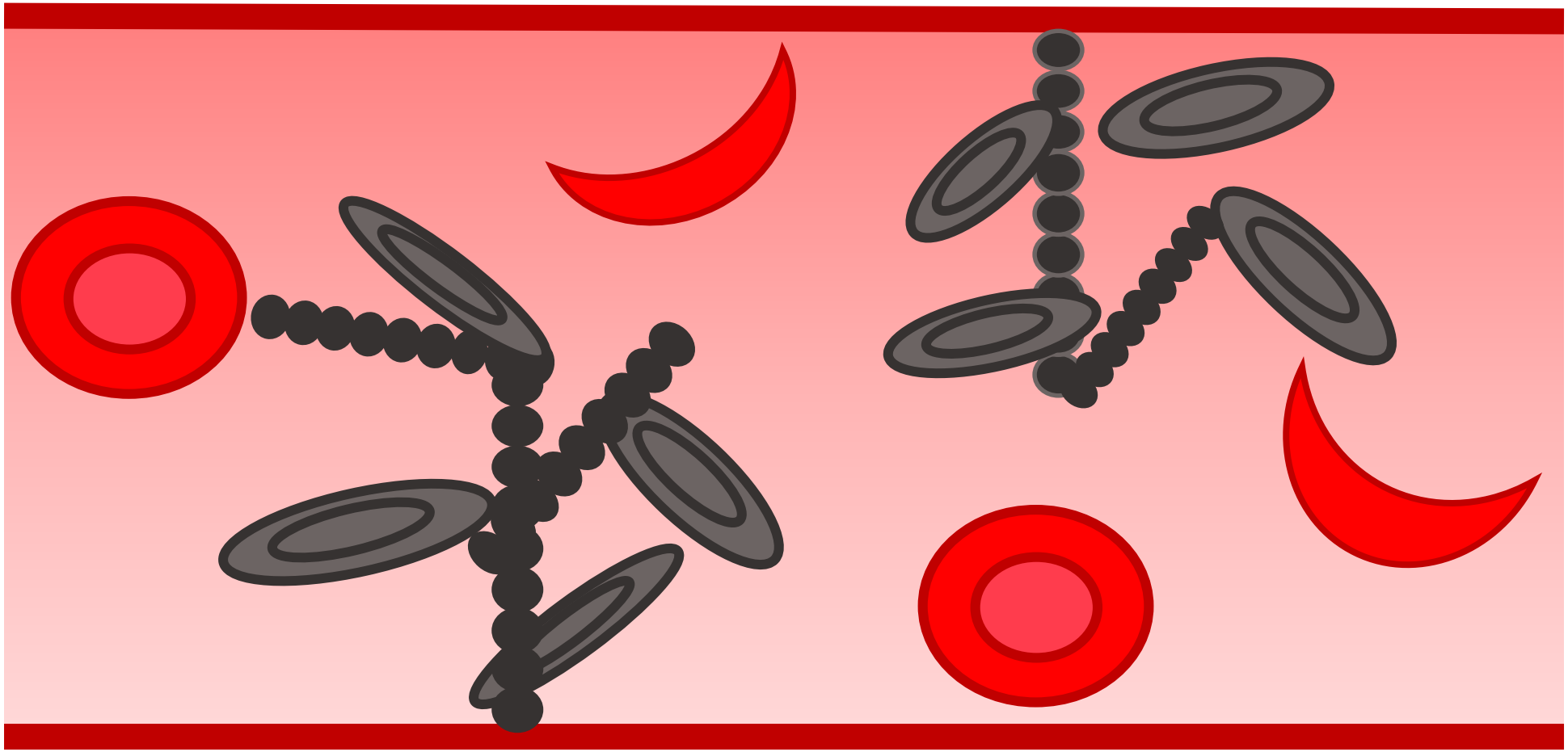


TTP: *Pathogenesis*



Shearing, Thrombi, Vascular occlusion

TTP: *Management*

- Thrombocytopenia
- Hemolytic Anemia
- PLASMIC score
- ADAMTS13 <10%* (send prior to PLEX)

George et al *Blood*. 2010;116(20):4060-4069

TTP: *Management*

- Thrombocytopenia
- Hemolytic Anemia
- **PLASMIC score**
- ADAMTS13 <10%* (send prior to PLEX)

George et al *Blood*. 2010;116(20):4060-4069

TTP: *Management*

Diagnosis → Treatment → Follow-up

	Yes	No
Platelet Count <30k/uL	+1	0
Hemolysis	+1	0
Active Cancer	0	+1
MCV <90 fL	1+	0
INR <1.5	1+	0
Cr <2.0 mg/dL	1+	0

Bendapudi PK etl al . *Lancet Haematol*. 2017; Li et al. *J Thromb Haemost*. 2018;16(1):164-169.

TTP: *Management*

Diagnosis → Treatment → Follow-up

	Yes	No
Platelet Count <30k/uL	+1	0
Hemolysis	+1	0
Active Cancer	0	+1
MCV <90 fL	1+	0
INR <1.5	1+	0
Cr <2.0 mg/dL	1+	0

Total Score	Risk of ADAMTS13 <10%
Low (0-4)	0%
Intermediate (5)	6%
High (6-7)	72%

Bendapudi PK etl al . *Lancet Haematol*. 2017; Li et al. *J Thromb Haemost*. 2018;16(1):164-169.

TTP: *Management*

Diagnosis → **Treatment** → Follow-up

- Plasma exchange
- Steroids (1 mg/kg prednisone for standard risk)
- Rituximab
- +/- Caplacizumab

Zeng et al. JTH 2020

TTP: *Management*

Diagnosis → **Treatment** → Follow-up

- **Plasma exchange**
- Steroids (1 mg/kg prednisone for standard risk)
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RECOMMENDATIONS AND GUIDELINES | Free Access

ISTH Guidelines for Treatment of Thrombotic Thrombocytopenic Purpura

X. Long Zheng ✉, Sara K. Vesely, Spero R. Cataland, Paul Coppo, Brian Geldziler, Alfonso Iorio, Masanori Matsumoto, Reem A. Mustafa, Menaka Pai, Gail Rock, Lene Russell ... **See all authors**

Zeng et al. JTH 2020

TTP: *Management*

- **Plasma exchange (PLEX)**
  - 1 – 1.5 Plasma volume daily
  - Replace with FFP
  - Adverse events w/ PLEX:
    - Transfusion Reactions
    - Citrate-induced Hypocalcemia
    - Hypotensive reaction with ACE-inhibitors (discontinue)
    - Catheter-related complications

Mokrzyck et al. Am J Kidney Dis. 1994;23(6):81

TTP: *Management*

Diagnosis → **Treatment** → Follow-up

- Plasma exchange
- Steroids (1 mg/kg prednisone for standard risk)
- **Rituximab**
- +/- Caplacizumab

Zeng et al. JTH 2020

TTP: *Management*

- **Rituximab**
  - Weekly 375 mg/m2 x 4 (administered after PLEX session)
  - Initially used for refractory TTP, now with benefit shown when used up-front
    - Decrease time to recovery*
    - Reduced exacerbation and relapse rates*

*Based on retrospective/prospective cohort studies (see Dane et al. for review TTP 2019: STATE OF THE ART)

Scully et al. Blood. 2011;118(7):1746; Page et al Blood 2016; 127(24):3092

TTP: *Management*

Diagnosis → **Treatment** → Follow-up

- Plasma exchange
- Steroids (1 mg/kg prednisone for standard risk)
- Rituximab
- **+/- Caplacizumab**

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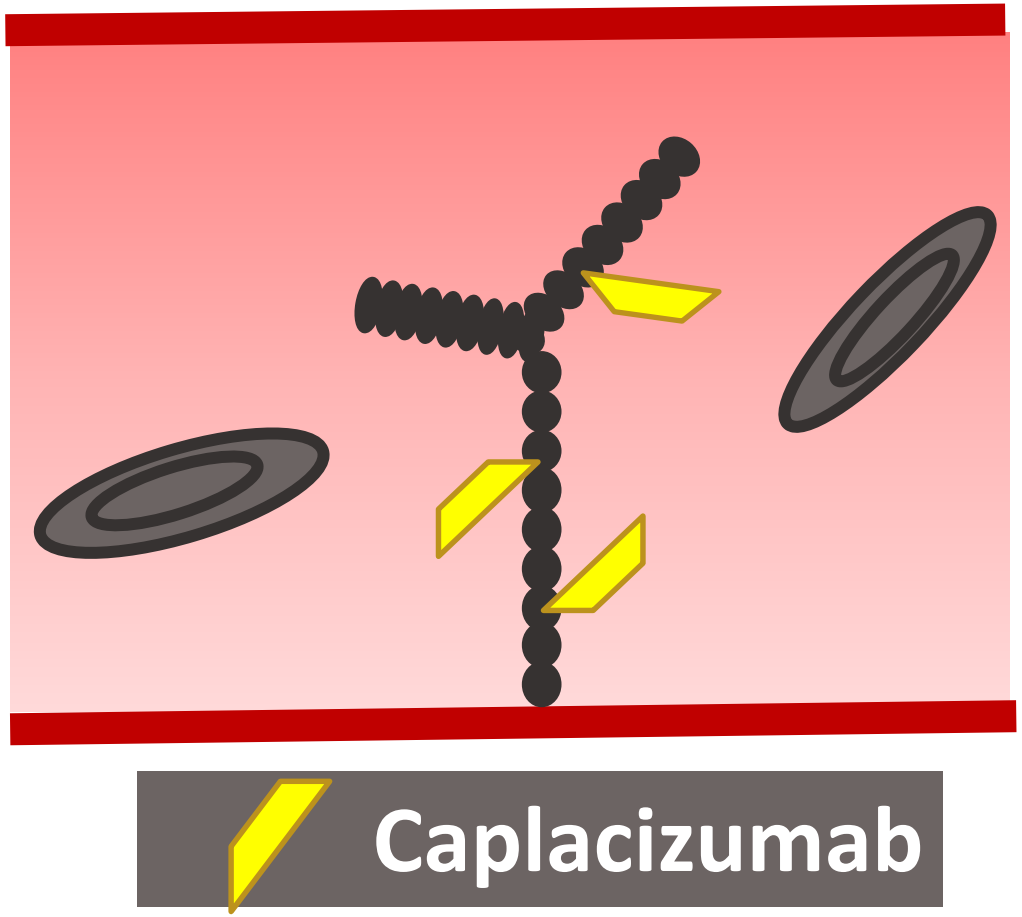
Zeng et al. JTH 2020

TTP: *Management*

Diagnosis → **Treatment** → Follow-up

- **Caplacizimumab**
  - Nanobody blocks platelet binding to vWF
  - TITAN & Hercules Trials
    - Reduced time to normalization of platelet count
    - Decreased # of PLEX sessions
    - Reduced Relapse Rate
  - Risks: Bleeding complications



Peyvandi et al. N Engl J Med 2016; 374:511-522
Scully et al. N Engl J Med 2019; 2019; 380:335-346

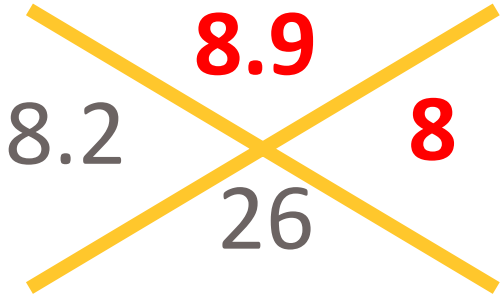
TTP: *Management*

- **Approx 40%** of acquired TTP will relapse
- Consider rituximab if ADAMTS13 <20% to prevent relapse
- Long-term complications:
  - Increased risk of pre-eclampsia
  - Stroke
  - Hypertension
  - PTSD/depression

Page et al. Blood. 2016;127(24):3092
Deford et al. Blood. 2013 Sep;122(12):2023-9
Upreti et al. *Blood* (2019) 134 (13): 1037–1045.

Case #2

23 yo F with presents with dyspnea, fatigue and petechiae……



LDH 865

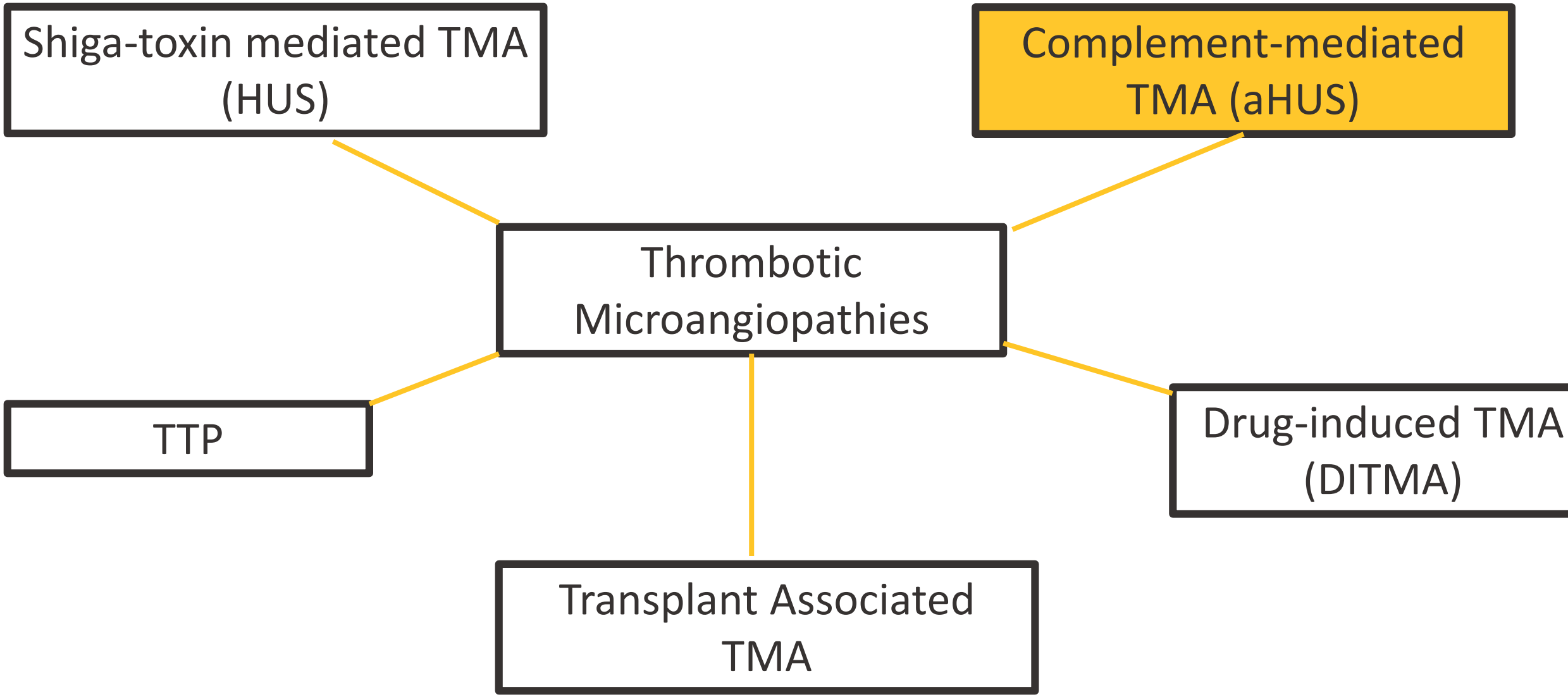
Haptoglobin <30

137	107	15
3.8	22	3.0

Started on daily PLEX and 3 days later…..

137	107	40
3.8	22	3.5

TMA-*Types*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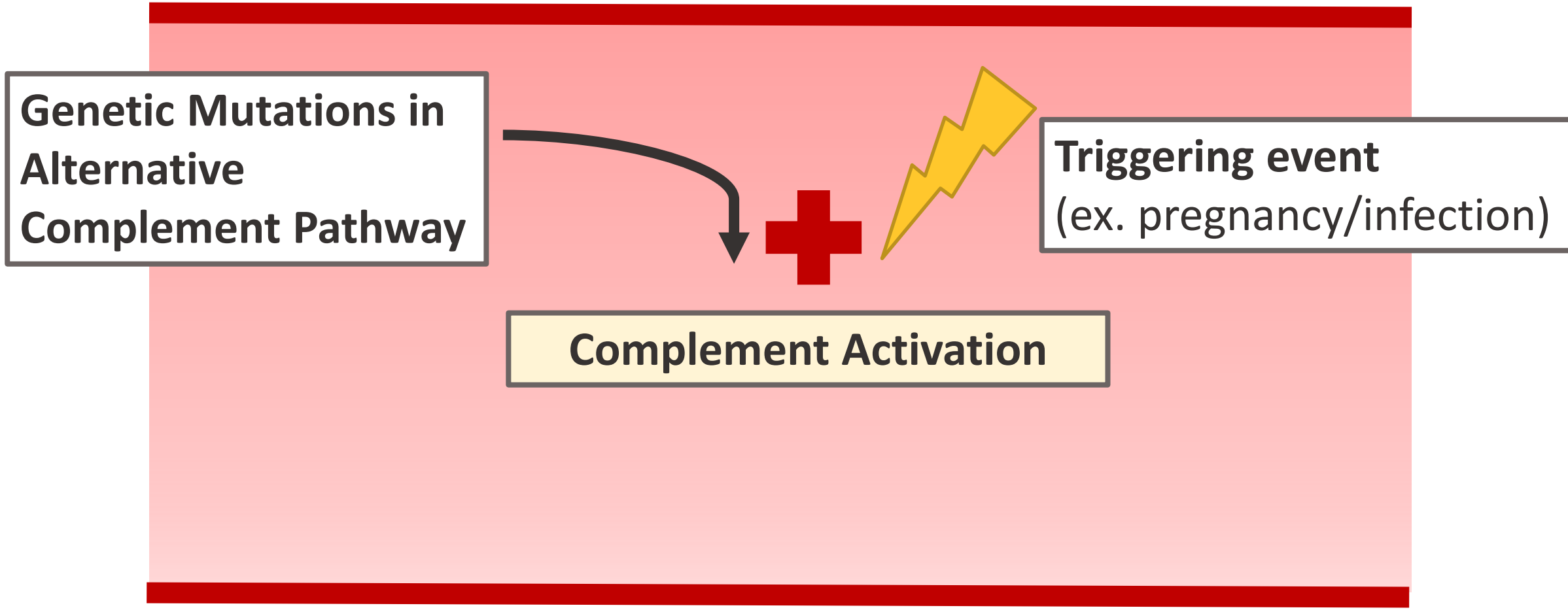
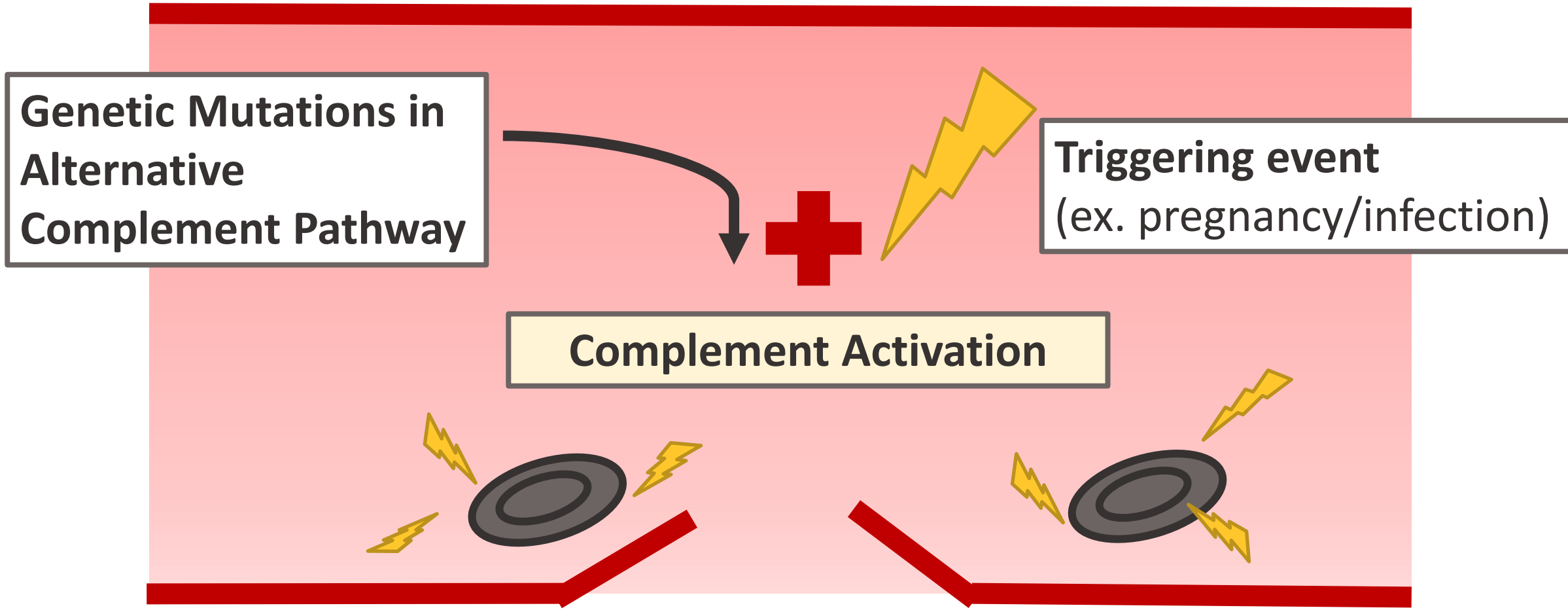
Complement-mediated TMA: *Pathogenesis*



Jokiranta. *Blood* (2017) 129 (21): 2847–2856

Complement-mediated TMA: *Pathogenesis*



Jokiranta. *Blood* (2017) 129 (21): 2847–2856

Complement-mediated TMA: *Management*

- ADAMTS13 >10%
- Lack of improvement with PLEX over 3-4 days
- Complement testing (C3,C4, CH50)
- Genetic testing + inhibitory antibodies (specialized centers- Versitas and Cinicinati Children's Hospital

Jokiranta. *Blood* (2017) 129 (21): 2847–2856

Complement-mediated TMA: *Management*

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- **Genetic testing + inhibitory antibodies (specialized centers- Versitas and Cinicinati Children's Hospital**

Jokiranta. *Blood* (2017) 129 (21): 2847–2856

Complement-mediated TMA: *Management*

- **Genetic testing + inhibitory antibodies**
  - Loss of function mutation in CHB, CFI, CD46
  - Gain of function mutation in CFB or C3
  - Complement factor H auto-antibody

Noris et al. N Engl J Med 2009;361:1676-87

Complement-mediated TMA: *Management*

- **Eculizumab**
  - Complement blockade
    - C5-monoclonal antibody
  - Risks: Infectious
    - Meningicoccal Vaccination
    - + Antimicrobial prophylaxis (at least for 2 weeks if not vaccinated prior)

Noris et al. N Engl J Med 2009;361:1676-87

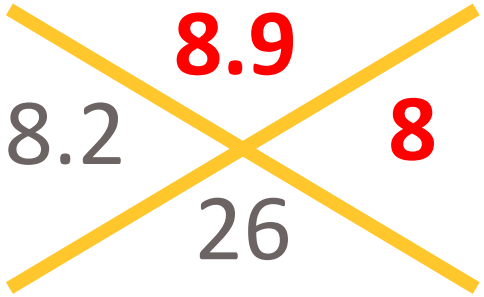
Complement-mediated TMA: *Management*

- Maintenance dosing of eculizumab every 2 weeks
- Data regarding safety of eculizumab discontinuation lacking

Jokiranta. *Blood* (2017) 129 (21): 2847–2856

Case

40 yo F with metastatic ovarian cancer receiving bevacizumab maintenance therapy presents with fatigue and petechiae.



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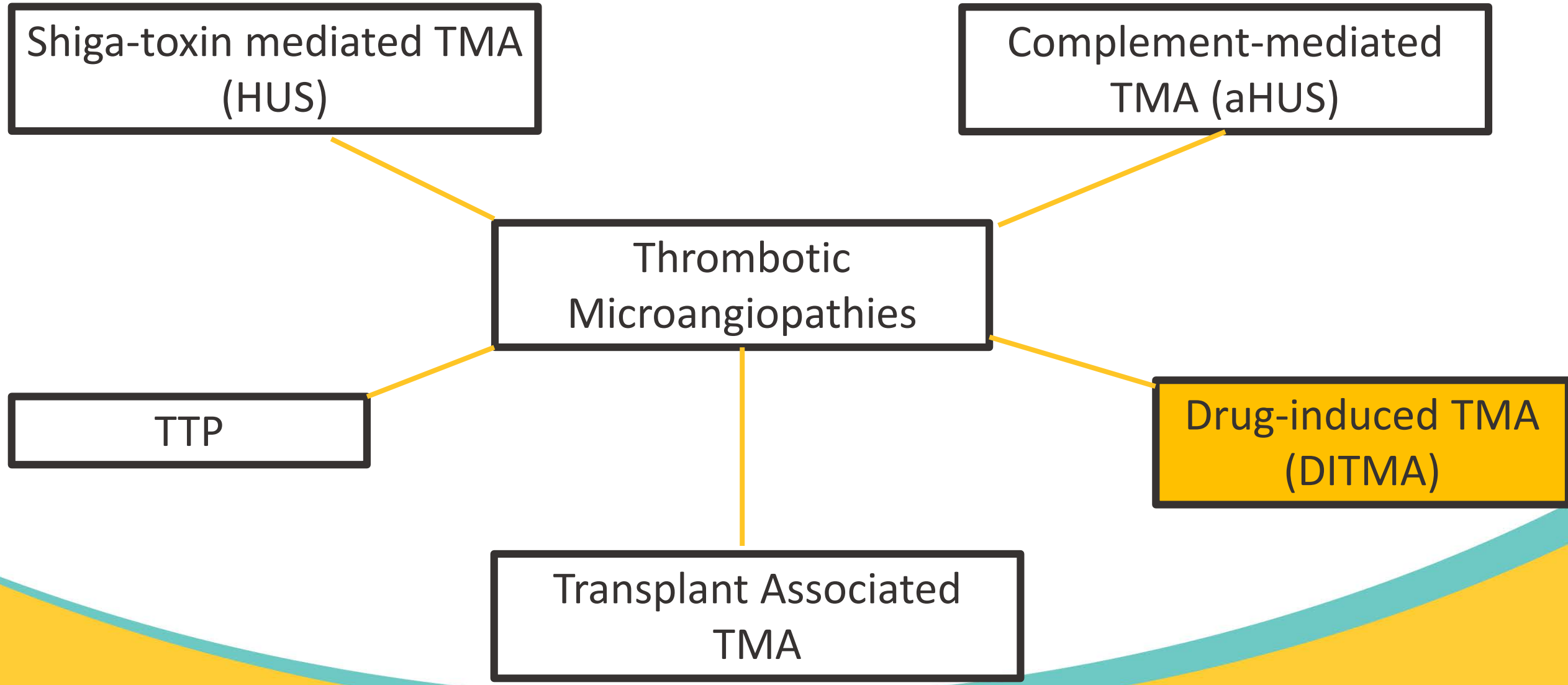
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Drug-induced TMA: *Diagnosis*

- Drugs
  - Mitomycin-C
  - VEGF
  - Gemcitabine
  - Immunosuppressive agents (tacrolimus/sirolimus/cyclosporine)
  - Emicizumab (+ FEIBA)
- Drugs of Abuse
  - Opana ER (extended release oxymorphone) administered IV

Al-Nouri et al. *Blood*. 2015;125(4):616-618

Drug-induced TMA: *Diagnosis*

- Discontinue offending agent
- Supportive Care
- Generally not responsive to PLEX

Al-Nouri et al. *Blood*. 2015;125(4):616-618

Drug-induced TMA: *Diagnosis*

- Drug Avoidance (immune cases)
- Non-immune causes
  - Decreased doses (ex. supratherapeutic cyclosporine levels)

Al-Nouri et al. *Blood*. 2015;125(4):616-618

Review of Key Points

- Differential for TMA
  - TTP, complement-mediated, transplant/drug-effect
- ADAMTS13 useful for distinguishing etiology, but not readily available
  - Clues to alternate diagnosis: Lack of responsive PLEX/severe kidney injury
- Developing Role of Novel Therapies for TTP
- Risks of eculizumab therapy & prevention
- Recognize drug-associated TMA

Thank you

Questions:

allyson.pishko@pennmedicine.upenn.edu

@PishkoMD

UPDATES IN OVARIAN CANCER

Renata Urban, MD
Associate Professor
Division of Gynecologic Oncology
Department of Obstetrics & Gynecology
University of Washington

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

Disclosures

- UpToDate.com – Royalties, Editorial responsibilities
- I have no other financial disclosures

Objectives

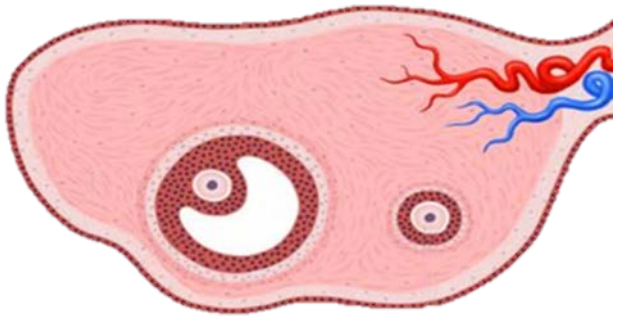
- Describe the treatments available for ovarian cancer and discuss how care can be personalized for patients
- Define new approved therapeutic approaches for the treatment of ovarian cancer patients
- Review histology specific indications for ovarian cancer therapies

Review & Update

2020
21,750 new cases of ovarian cancer
13,940 deaths due to ovarian cancer

• Epithelial ovarian cancer
  • Fallopian tube carcinoma
  • Primary peritoneal carcinoma
	95%

• Germ cell cancers of the ovary	3%
• Sex cord/stromal cancers of the ovary	1-3%

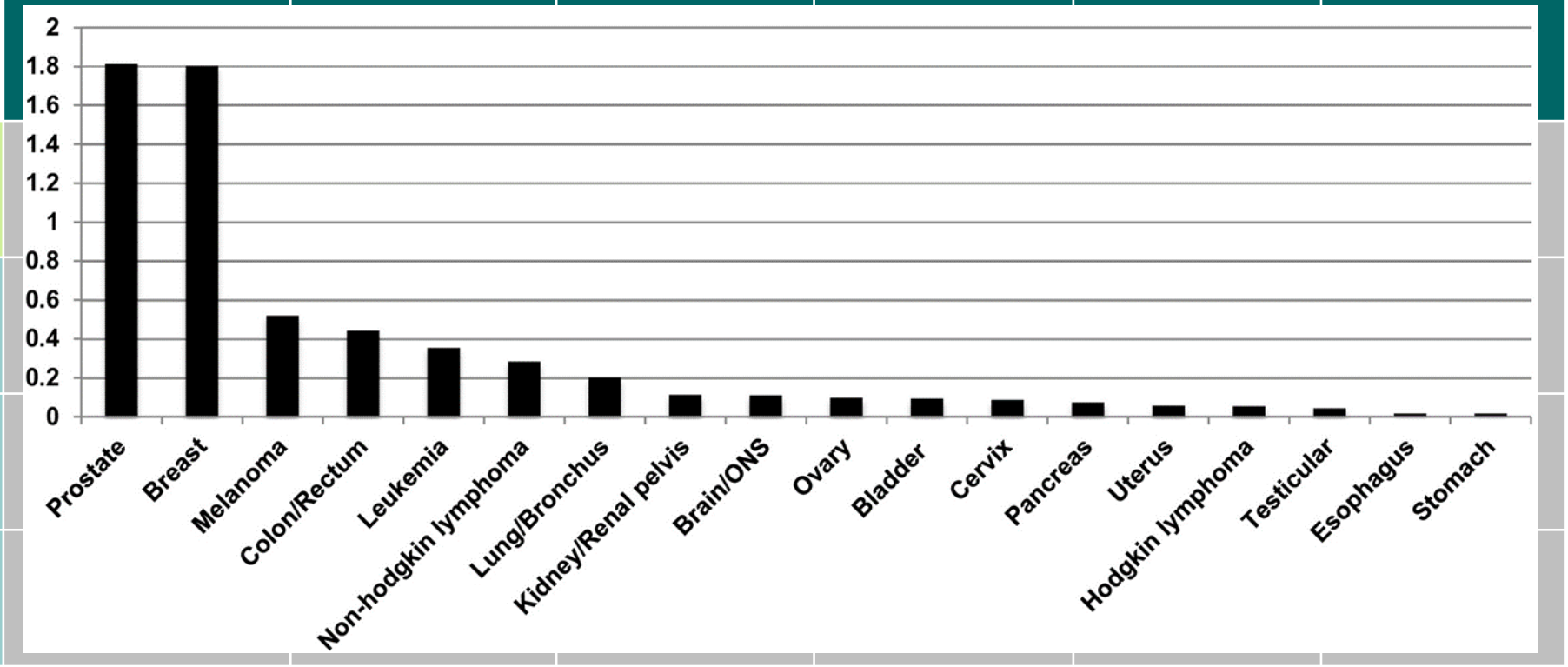


Cell Types within Ovary

Fallopian tube Endosalpingiosis	▶	Epithelial ovarian cancer
Germ cells (oocytes)	▶	Germ cell cancers
Sex hormone producing and stromal cells	▶	Sex cord stromal cancers

Ovarian Cancer Patterns of Care

	Incidence/100,000	Age-Adjusted Cancer Death Rate
OVARY		
Breast		
Colorectal*		
Prostate		



Goff BA. *Gynecol Oncol* 2015.
Spencer RJ et al. *Gynecol Oncol* 2019.

Treatment

- **Surgery**
  - Diagnosis
  - Staging
  - Cytoreduction

- **Chemotherapy**
  - Recommended for nearly all patients

- Referral to a **gynecologic oncologist** has been associated with:
  - Increased surgical management
  - Improved survival

Mercado C et al. Gynecol Oncol 2010.
Chan JK et al. Obstet Gynecol 2003.

Surgical Staging

Staging of disease via surgery especially important

In an evaluation of 100 patients believed to have **early stage disease:**

- 31% upstaged
- 77% actually were Stage III
- A more recent review showed 13% of "early" stage patients had positive lymph nodes

Young RC et al. JAMA 1983.
Powless CA et al. Gynecol Oncol 2011.

Postoperative Chemotherapy

Cycles of Chemo by Stage

	Platinum & Paclitaxel
Stages IA and IB *(grades 1 and 2 **only**)*	No further treatment
Stages IA & IB *(grade 3)*, and IC–II disease	3–6 cycles
Stages III–IV disease	6–8 cycles

Early Stage (Stage I-II)

A subset of women with early stage disease benefit from additional adjuvant treatment:

- **High-grade/serous tumors**
  - 6 cycles of adjuvant chemo associated with progression-free survival benefit
- **Clear cell histology**
- **Stage IC or greater disease**

Chan JK et al. Gynecol Oncol 2010.

Advanced Stage Disease

- Regimen should include a taxane and platinum
  - Carboplatin = cisplatin, but less toxicity
  - Docetaxel alternative, if neuropathy or hypersensitivity
- Response rate **70-80%**
- Encourage clinical trial participation

Modifications

Intraperitoneal chemotherapy

Dose-dense paclitaxel

Weekly carbo & taxol

Maintenance

Treatment Options

NCCN

PRINCIPLES OF SYSTEMIC THERAPY
Primary Systemic Therapy Regimens[a] - Epithelial Ovarian (including LCOC)/Fallopian Tube/Primary Peritoneal

Primary Systemic Therapy Recommended Dosing

IV/IP Paclitaxel/cisplatin
- Paclitaxel 135 mg/m² IV continuous infusion[g] Day 1; Cisplatin 75–100 mg/m² IP Day 2 after IV paclitaxel; Paclitaxel 60 mg/m² IP Day 8
- Repeat every 21 days x 6 cycles

Paclitaxel 175/carboplatin[h]
- Paclitaxel 175 mg/m² IV followed by carboplatin[i] AUC 5–6 IV Day 1
- Repeat every 21 days x 3–6 cycles[h]

Paclitaxel weekly/carboplatin q3weeks
- Dose-dense paclitaxel 80 mg/m² IV Days 1, 8, and 15 followed by carboplatin[i] AUC 5–6 IV Day 1
- Repeat every 21 days x 6 cycles

Paclitaxel weekly/carboplatin weekly
- Paclitaxel 60 mg/m² IV followed by carboplatin AUC 2 IV
- Days 1, 8, and 15; repeat every 21 days x 6 cycles (18 weeks)[f]

Docetaxel/carboplatin[h]
- Docetaxel 60–75 mg/m² IV followed by carboplatin[c] AUC 5–6 IV Day 1
- Repeat every 21 days x 3–6 cycles[h]

Carboplatin/liposomal doxorubicin[h]
- Carboplatin AUC 5 IV + pegylated liposomal doxorubicin 30 mg/m² IV
- Repeat every 28 days for 3–6 cycles[h]

Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab[e] (ICON-7)
- Paclitaxel 175 mg/m² IV followed by carboplatin[i] AUC 5–6 IV, and bevacizumab 7.5 mg/kg IV Day 1
- Repeat every 21 days x 5–6 cycles
- Continue bevacizumab for up to 12 additional cycles

Paclitaxel/carboplatin/bevacizumab + maintenance bevacizumab[e] (GOG-218)
- Paclitaxel 175 mg/m² IV followed by carboplatin[i] AUC 6 IV Day 1. Repeat every 21 days x 6 cycles
- Starting Day 1 of cycle 2, give bevacizumab 15 mg/kg IV every 21 days for up to 22 cycles

Elderly Patients (age >70 years) and/or those with comorbidities

Paclitaxel 135/carboplatin[1]
- Paclitaxel 135 mg/m² IV + carboplatin AUC 5 IV given every 21 days x 3–6 cycles[h]

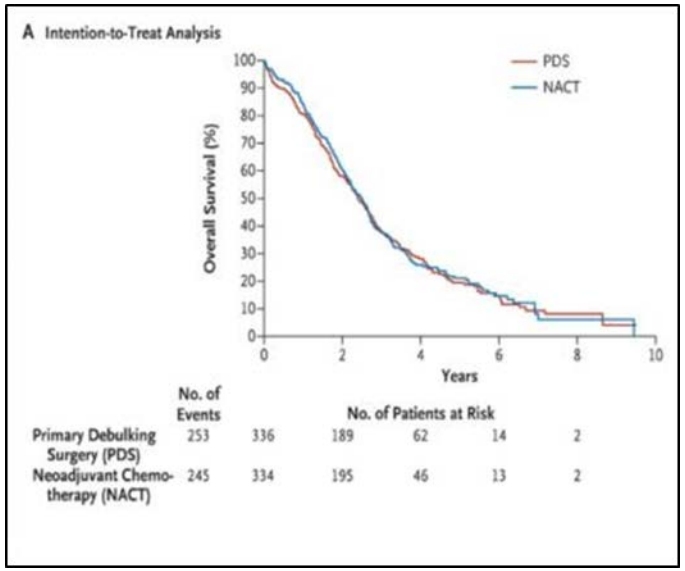
Paclitaxel weekly/carboplatin weekly
- Paclitaxel 60 mg/m² IV over 1 hour followed by carboplatin AUC 2 IV over 30 minutes
- Days 1, 8, and 15; repeat every 21 days x 6 cycles (18 weeks)

Carboplatin[1]
- Carboplatin AUC 5 IV given every 21 days

Neoadjuvant Chemotherapy

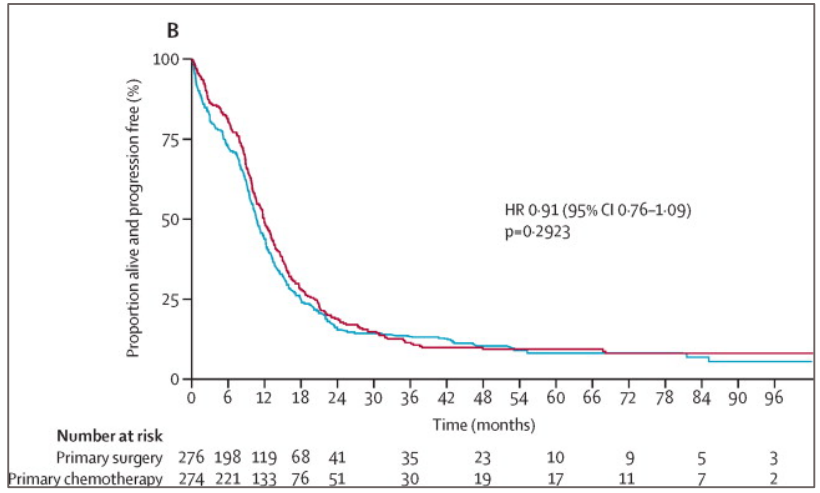
EORTC

- Neoadjuvant chemo followed by interval debulking surgery versus primary debulking & chemo
- Platinum-based chemotherapy
- Decreased surgical morbidity, increased rates of successful cytoreduction
- Similar PFS, OS



CHORUS

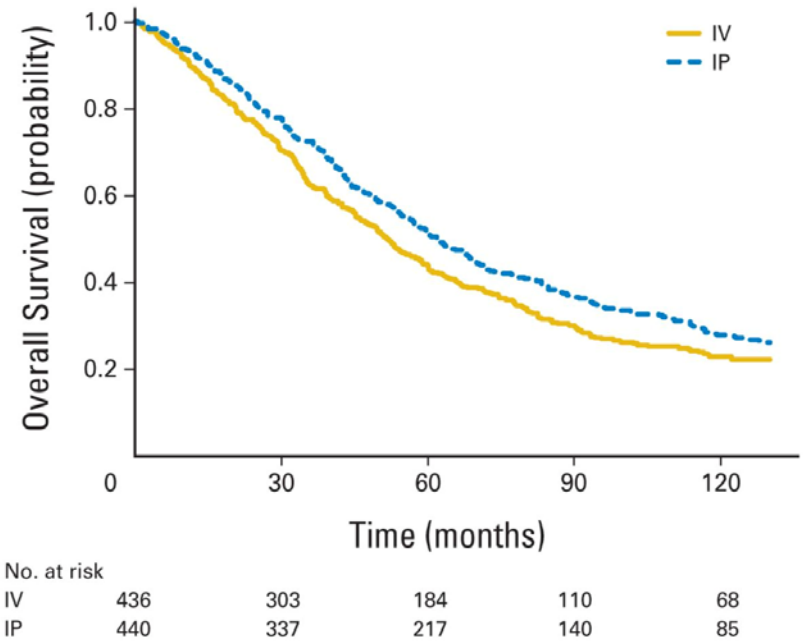
- Non-inferiority phase 3 trial
- Carbo/taxol either postoperatively or neoadjuvant (3:3)
- Decreased rates of surgical complication and postoperative deaths
- Similar PFS, OS



Vergote I et al. N Engl J Med 2010.
Kehoe S et al. Lancet 2015.

Intraperitoneal (IP) Chemotherapy

- Long-term survival analysis of GOG 114 and 172
- Among 876 patients, IP treatment associated with 17% ↓ risk of death
- Survival advantage evident in microscopic and gross residual disease



GOG 114

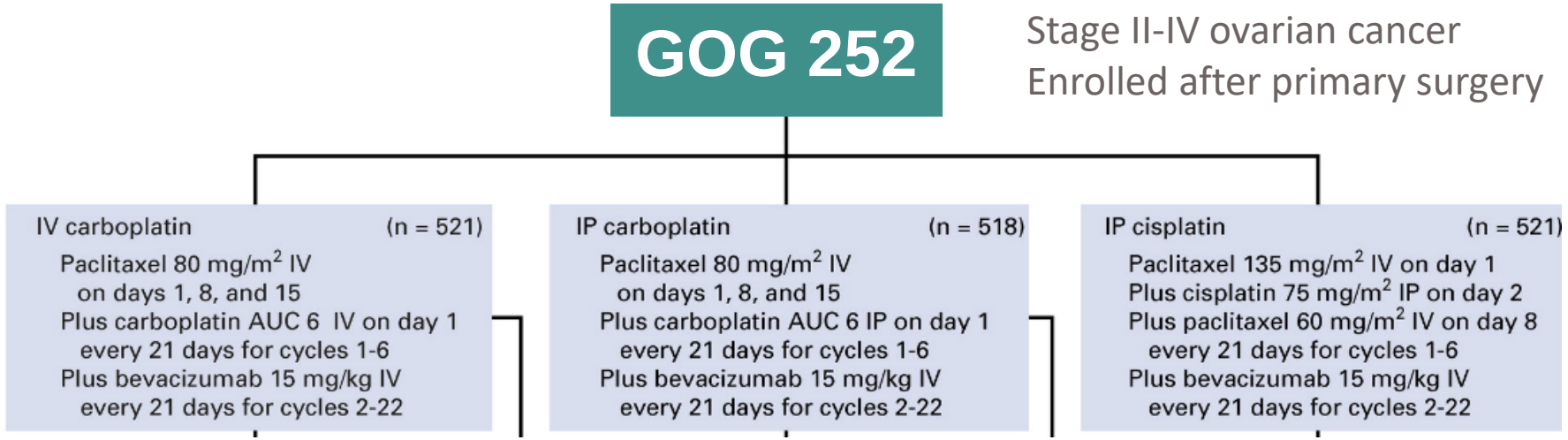
IV Cis / IV Taxol
vs.
IP Cis / IV Taxol / IV Carbo

GOG 172

IV Cis / IV Taxol
vs.
IP Cis / IV & **IP** Taxol

Tewari D et al. J Clin Oncol 2015.
Landrum L et al. Gynecol Oncol 2013.

Intraperitoneal (IP) Chemotherapy

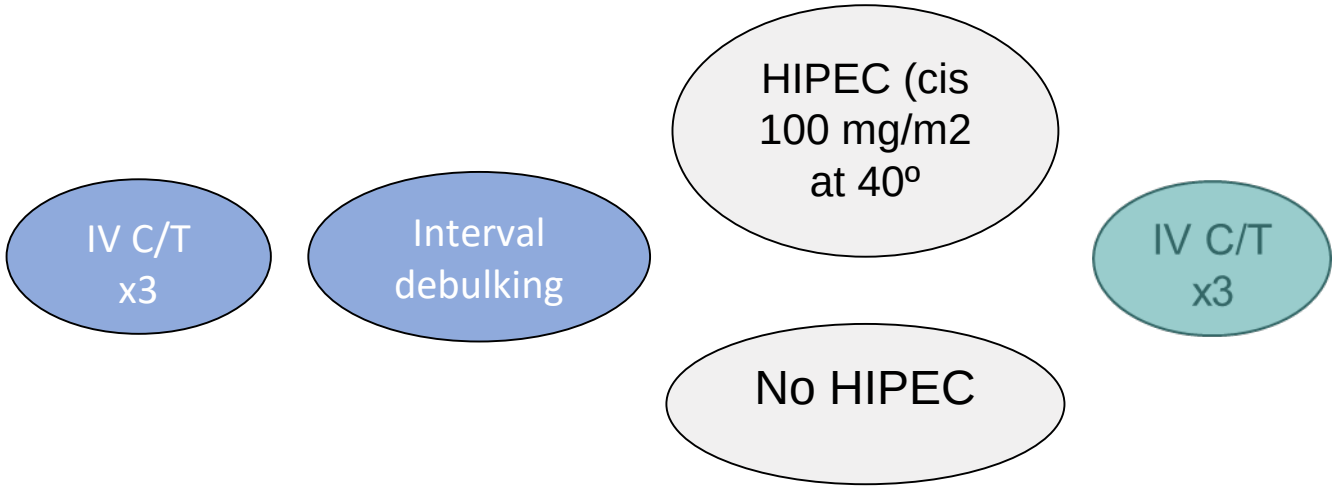


- Impact of bevacizumab
- Similar neurotoxicity scores for all arms
  - Worse FACT-TOI in IP cisplatin arm
- Similar PFS and OS
  - Median OS 75.5 mos (IV C), 78.9 (IP C), 72.9 (IP cis)

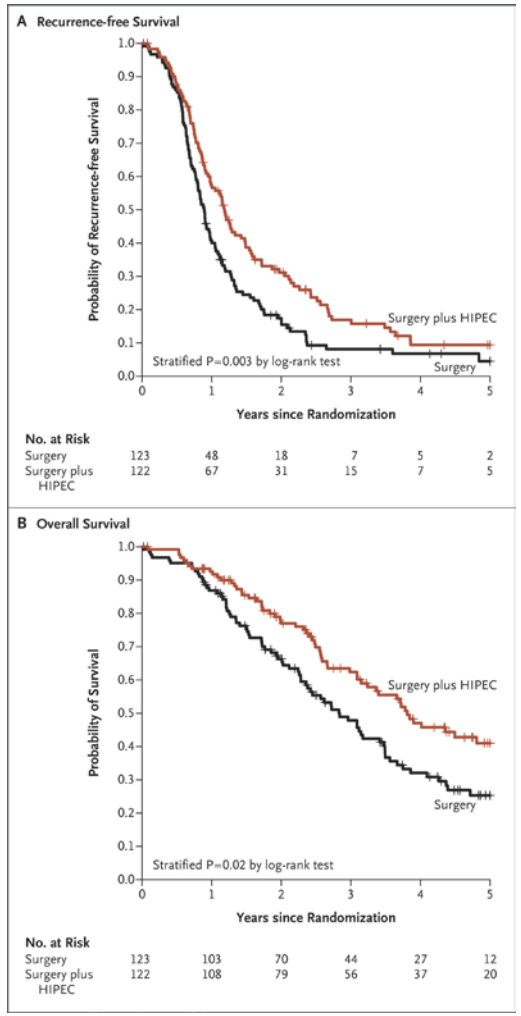
Walker JL et al. J Clin Oncol 2019.

Heated Intraperitoneal Chemotherapy (HIPEC)

- Randomized phase III trial



- No significant difference in adverse events
- Significant improvement in progression-free (14.2 vs 10.7 months) and overall survival 45.7 vs 33.9 months)
- ASCO 2020: randomized phase II trial of HIPEC after secondary cytoreductive surgery revealed no impact on survival



Van Driel WJ et al. N Engl J Med 2018
Zivanoic O et al. ASCO 2020

“Dose-Dense” Paclitaxel

JGOG 2016

- RCT: q3 wks carbo/Taxol vs carbo/weekly Taxol
- Improved 5-year OS (100.5 mos in weeklyT vs 62.6 mos on standard therapy)
- Controversy on generalizability of findings

GOG 262

- Bevacizumab optional, 84% providers/patients opted in
- No difference in PFS
- For cohort who did not receive bev (n=88), significant improvement in PFS (14.2 mos for weeklyT vs 10.2 mos, p=0.03)

ICON 8

- RCT: C/T q3w vs C/T q1w vs Cq3w/Tq1w
- Similar PFS in each arm
- Slight increase in heme toxicity in weekly arm

Katsumata N et al. Lancet 2009; Katsumata N et al. Lancet 2013
Chan JK et al. N Engl J Med 2016.; Clamp AR et al Lancet 2019.

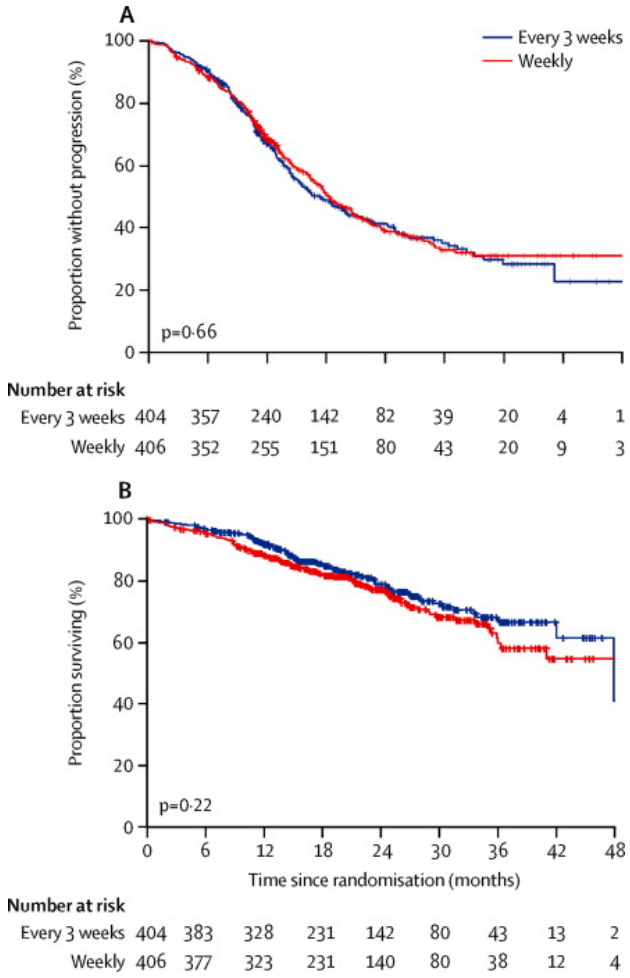
Tolerability of Chemotherapy

MITO-7

Weekly Carbo (AUC 2)
and Taxol (60 mg/m^2)
vs.
Every 3 week Carbo (AUC 6)
and Taxol (175 mg/m^2)

Eligibility: Stage IC-IV EOC
ECOG PS ≥ 2

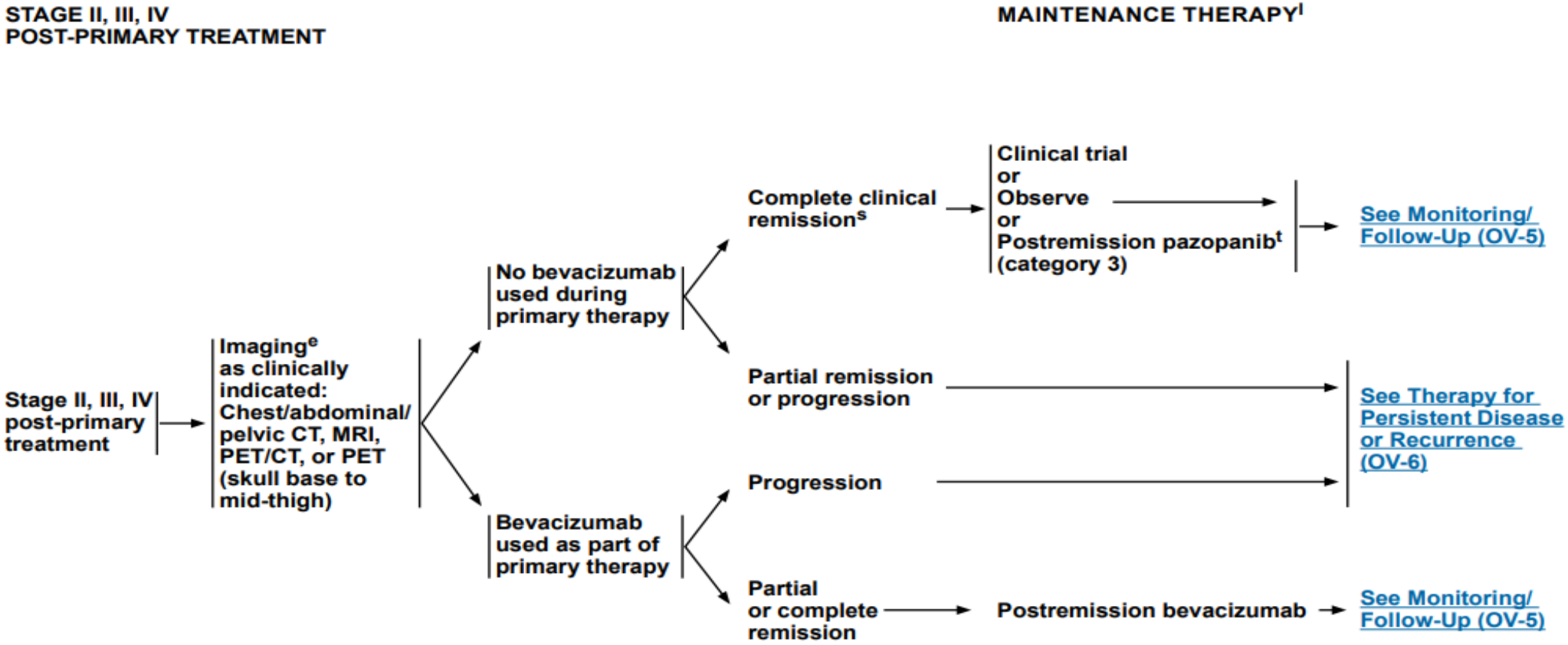
Outcomes: Similar PFS & OS in patients receiving weekly treatment



Pignata S et al. Lancet Oncol 2014.

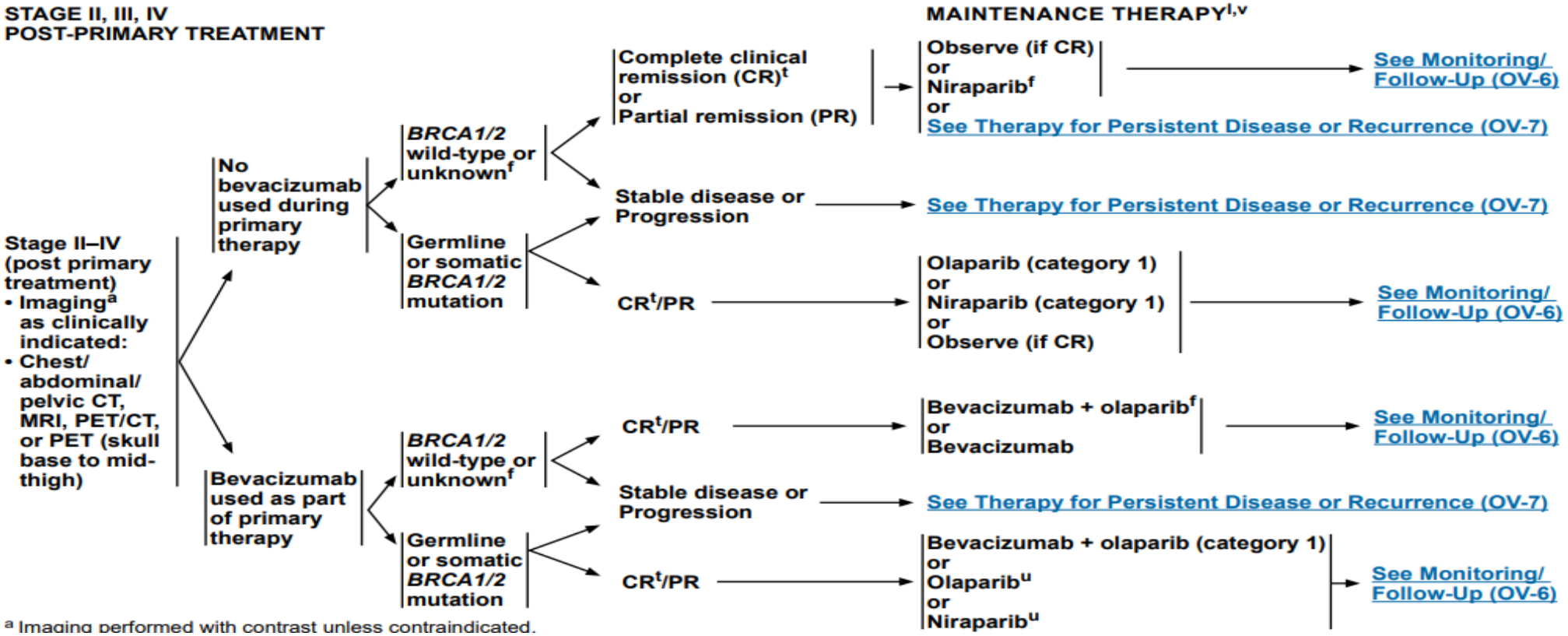
Maintenance Treatment

NCCN recommendations (2018)



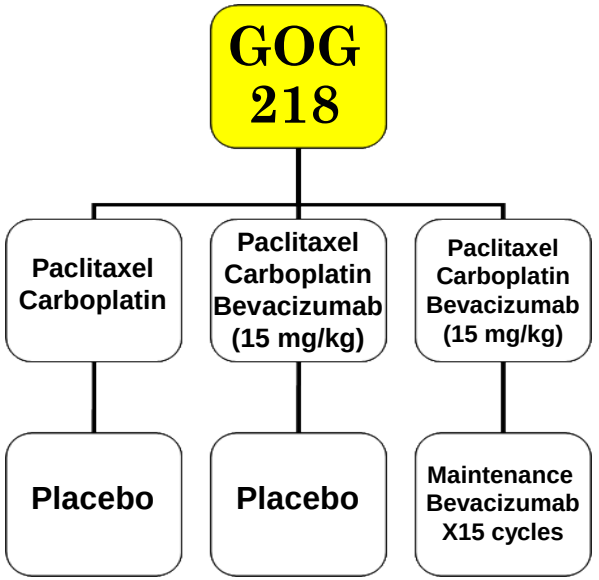
Maintenance Treatment

NCCN recommendations (2020)



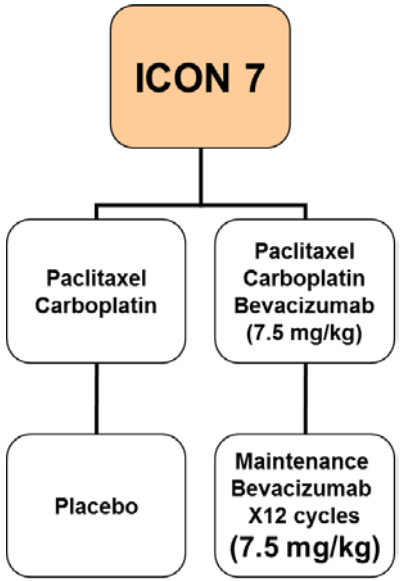
Maintenance Treatment

Role of Bevacizumab



Phase III RCT showed PFS of 6.2 months with C/T/B + B, no difference in OS

Burger RA et al. NEJM 2011.



European phase III RCT showing PFS of 1.7 months with C/T/B + B

Perren TJ et al. NEJM 2011.

June 13, 2018: FDA approved bevacizumab for treatment of Stage III-IV ovarian cancer in combination with carbo/taxol followed by maintenance bevacizumab

Candidates for Bevacizumab

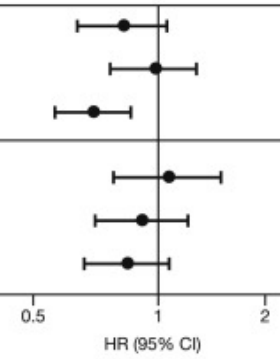
GOG 218

- PFS improvement, but no overall improvement in OS
- For stage IV patients, OS 42.8 mos (chemo/bev+bev) vs 32.6 mos (chemo alone) (HR 0.75, CI 0.59-0.95)

ICON-7

- Improved PFS seen in "high risk" group (Stage IV disease, >1 cm residual disease at surgery)
- Trend towards improved OS

	Stage and residuum	No. of events/ patients (%)	Median, months		Restricted mean, months		HR (95% CI)
			Reference	Bevacizumab	Reference	Bevacizumab	
PFS	III/IV 0 cm	240/461 (52)	21.9	25.9	26.2	28.6	0.82 (0.64–1.06)
	III/IV >0–≤1 cm	260/340 (76)	12.9	17.4	19.1	20.0	0.98 (0.77–1.25)
	III/IV >1 cm	324/388 (84)	10.6	16.4	15.1	19.6	0.69 (0.56–0.86)
OS	III/IV 0 cm	166/461 (36)	NR	NR	49.3	49.0	1.06 (0.78–1.44)
	III/IV >0–≤1 cm	211/340 (62)	43.1	44.1	40.8	41.6	0.91 (0.70–1.20)
	III/IV >1 cm	258/388 (66)	31.3	38.9	35.2	39.2	0.84 (0.66–1.07)



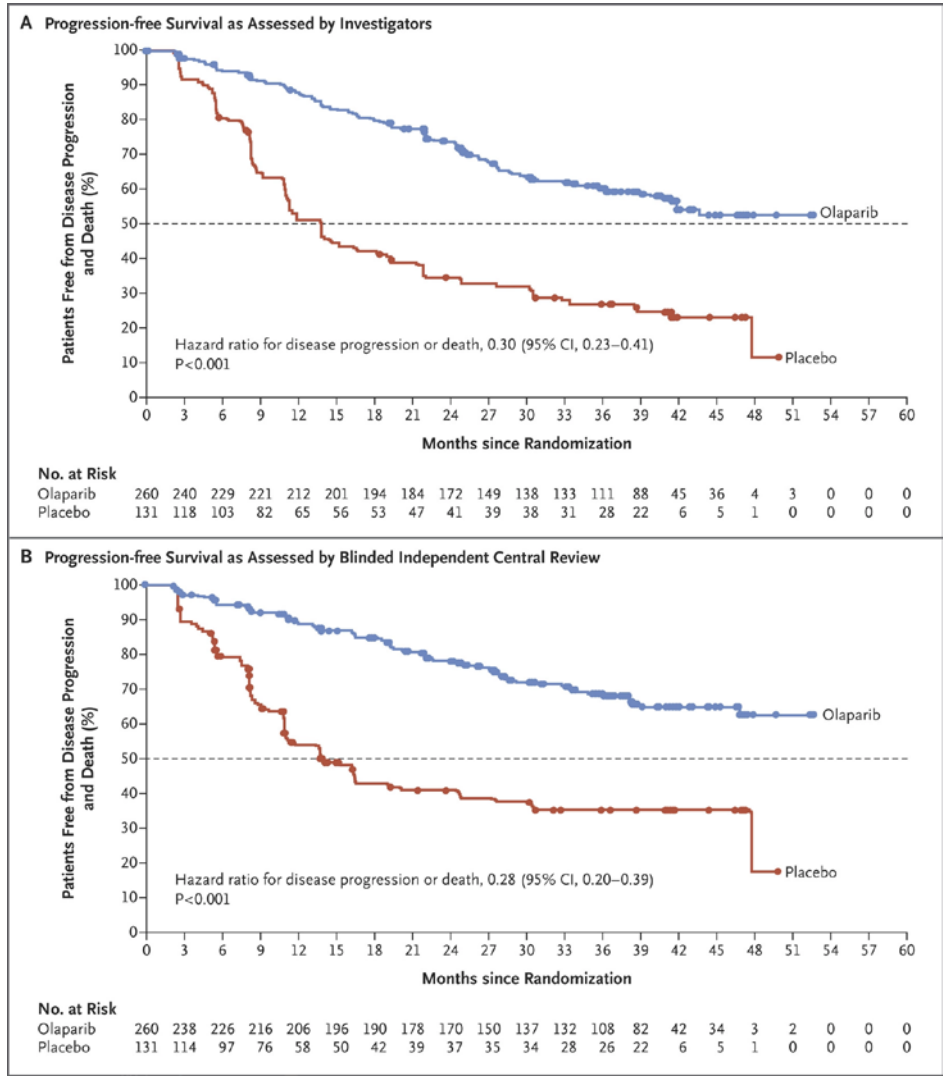
Tewari KS et al. J Clin Oncol 2019.
Gonzalez Martin A et al. Gynecol Oncol 2019.

Maintenance Treatment

PARP Inhibitors

SOLO-1

- Randomized (2:1), placebo-controlled trial of **olaparib**
- Newly diagnosed stage III-IV high-grade serous or endometrioid ovarian cancer, germline BRCA 1 or 2 mutation
- Median PFS 36 mos longer in olaparib group
- **70% risk in reduction of progression or death**
- 1% patients on olaparib developed AML



Moore K et al, N Engl J Med 2018

Maintenance Treatment

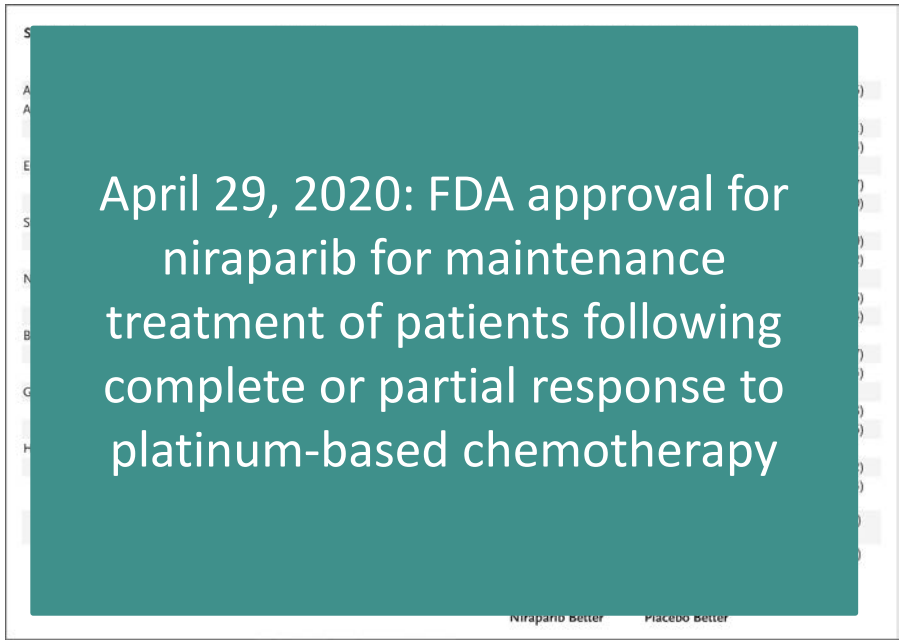
PARP Inhibitors

VELIA

- Randomized (1:1:1), placebo-controlled trial of chemo +- **veliparib** followed by placebo or veliparib maintenance
- Significant improvement in PFS seen in chemo/veliparib + veliparib cohort
- Bulk of benefit in patients with BRCA mutation (germline OR somatic) or tumors with homologous recombination deficiency (HRD)

PRIMA/ENGOT-OV26/GOG-3012

- Randomized (2:1), placebo-controlled trial of chemo +- **niraparib maintenance**
- Significant improvement in PFS seen in niraparib maintenance cohort
  - Pronounced benefit in patients with HRD tumors



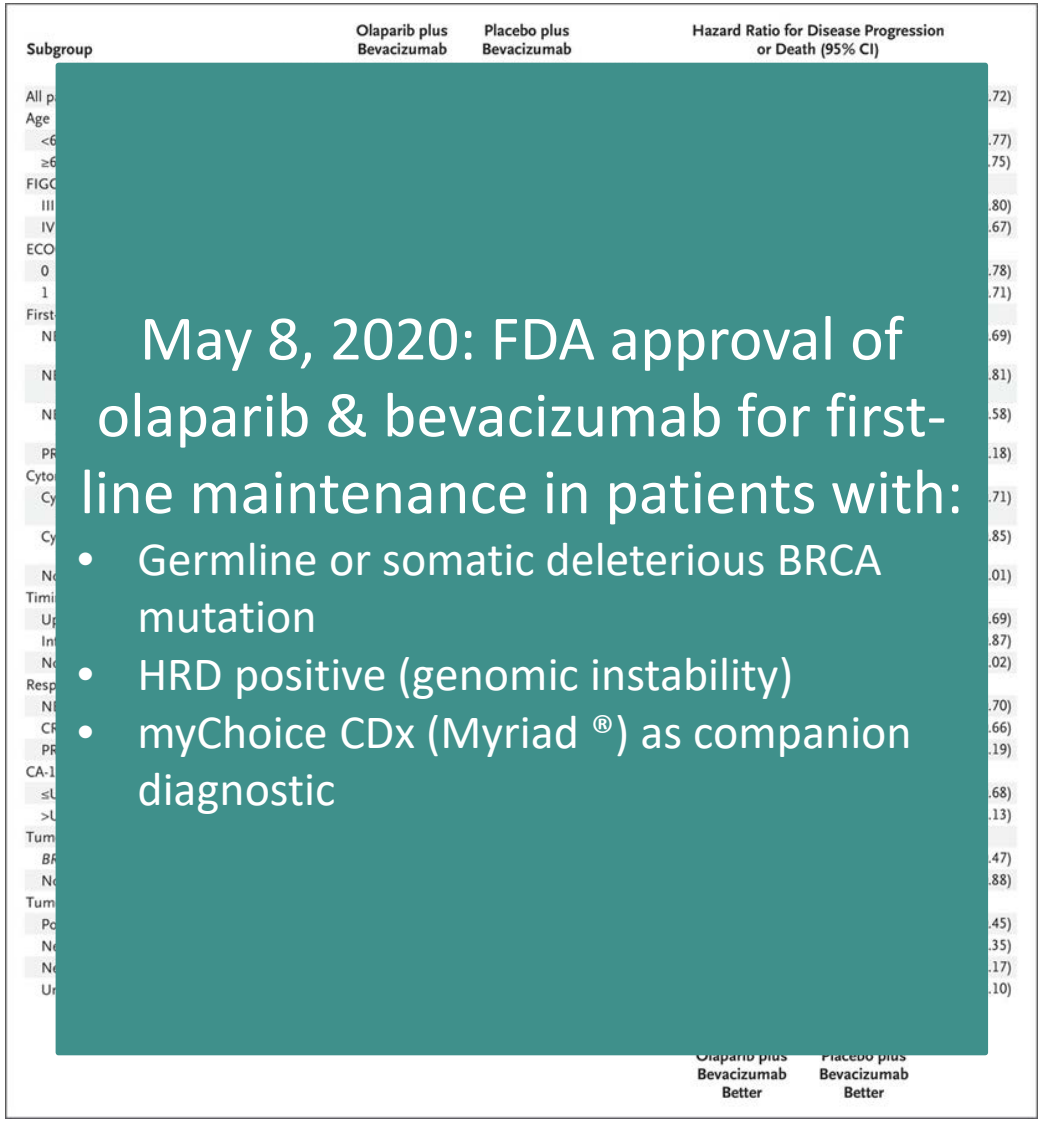
Coleman RL et al. N Engl J Med 2019.
Gonzalez-Martin A et al. N Engl J Med 2019.

Maintenance Treatment

PARP Inhibitors

PAOLA

- Randomized (2:1), placebo-controlled trial of carbo/taxol/bev +- **olaparib**
- Allowed to have primary surgery or interval following neoadjuvant chemo
- Significant improvement in PFS
  - HR 0.33 (HRD +BRCAm)
  - HR 0.43 (HRD, -BRCAm)
  - HR 0.92 (no/unknown HRD)



May 8, 2020: FDA approval of olaparib & bevacizumab for first-line maintenance in patients with:

- Germline or somatic deleterious BRCA mutation
- HRD positive (genomic instability)
- myChoice CDx (Myriad ®) as companion diagnostic

Ray-Coquard I et al. N Engl J Med 2019

Maintenance Treatment

PARP Inhibitors

Table 1. A Comparison of Three PARP Inhibitors in Patients with Ovarian Cancer.*

Trial Drug	Overall Population†			Mutated *BRCA*‡			HRD§			No HRD¶		
	Control	Treatment	Hazard Ratio (95% CI)	Control	Treatment	Hazard Ratio (95% CI)	Control	Treatment	Hazard Ratio (95% CI)	Control	Treatment	Hazard Ratio (95% CI)
	median			*median*			*median*			*median*		
Niraparib												
Duration of progression-free survival	8.2 mo	13.8 mo	0.62 (0.50–0.75)	10.9 mo	22.1 mo	0.40 (0.26–0.62)	10.4 mo	21.9 mo	0.43 (0.31–0.59)	5.4 mo	8.1 mo	0.68 (0.49–0.94)
P value			<0.001						<0.001			
Veliparib												
Duration of progression-free survival	17.3 mo	23.5 mo	0.68 (0.56–0.83)	22.0 mo	34.7 mo	0.44 (0.28–0.68)‖	20.5 mo	31.9 mo	0.57 (0.43–0.76)	NR	NR	0.81 (0.60–1.09)
P value			<0.001			<0.001			<0.001			
Olaparib plus bevacizumab												
Duration of progression-free survival	16.6 mo	22.1 mo	0.59 (0.49–0.72)	21.7 mo	37.2 mo	0.31 (0.20–0.47)	17.7 mo	37.2 mo	0.33 (0.25–0.45)	16.2 mo	16.6 mo	1.00 (0.75–1.35)**
P value			<0.001									

* Evaluations were performed in 733 patients who received niraparib in the PRIMA trial,[4] in 1140 patients who received veliparib in the VELIA trial,[5] and in 806 patients who received olaparib in the PAOLA-1 trial.[6] HRD denotes homologous-recombination deficiency, PARP poly(adenosine diphosphate [ADP]–ribose) polymerase, and NR not reported.
† In all three trials, patients with *BRCA* mutations were overrepresented, as compared with the overall population of patients with ovarian cancer. The outcome for the overall population was favorable for each of the PARP inhibitors listed here.
‡ In all three trials, the PARP inhibitor substantially improved the duration of progression-free survival in patients with *BRCA* mutations.
§ In all three trials, the PARP inhibitor substantially improved the duration of progression-free survival in the HRD cohort.
¶ The effect of the PARP inhibitor among patients in the no-HRD cohort was more limited than in the other subgroups, and the size of the between-group difference was modest.
‖ The patients who were included in this comparison could have either tumor (somatic) or germline *BRCA* mutations.
** Patients who had unknown HRD status were excluded from this comparison.

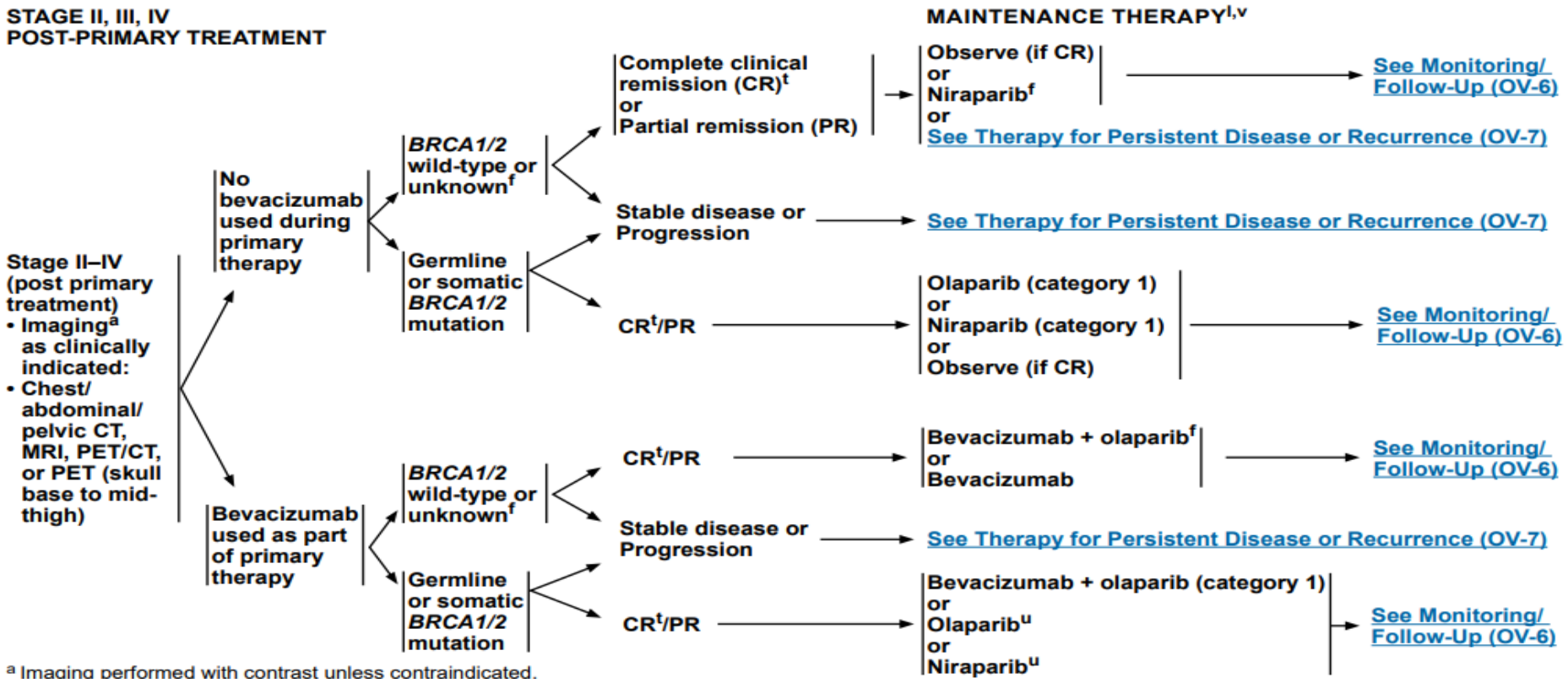
Longo DS. N Engl J Med 2019.

Candidates for PARP Inhibitors

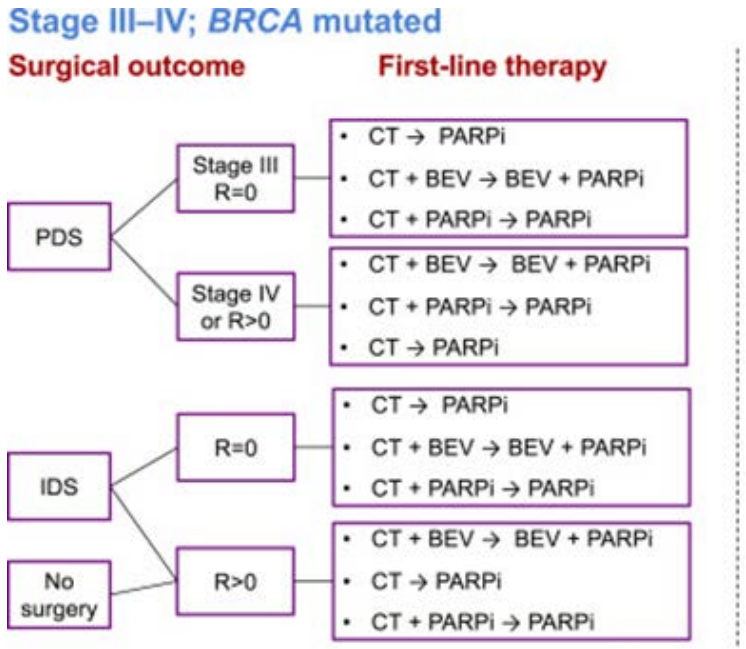
- Germline or somatic carriers of BRCA 1 or 2 mutation
  - ➡ Carriers of other gene mutations causing HRD (e.g. CHEK2, ATM, PALB2)
- Patients with tumors exhibiting HRD
  - ➡ How to best assess for HRD?
  - ➡ Recent trials utilized Myriad myRisk, cut-off varies between trials

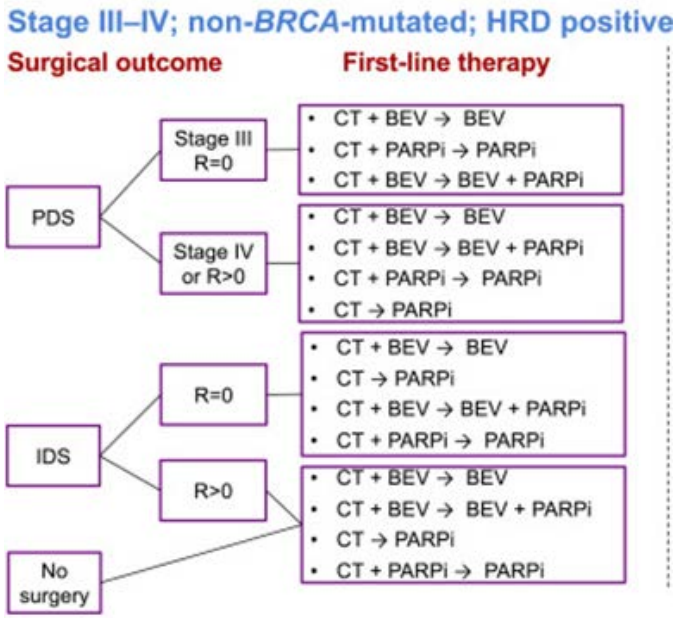
Maintenance Treatment

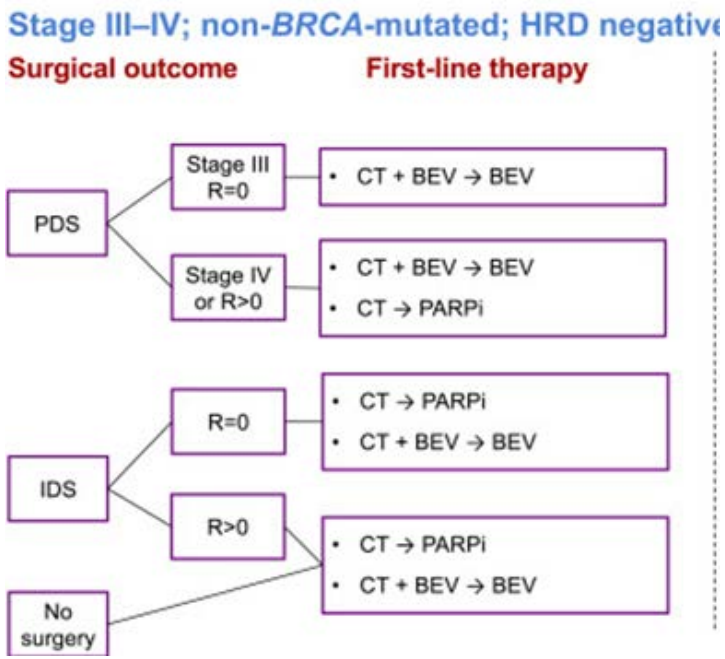
- **NCCN recommendations (2020)**



Maintenance Treatment







Mirza MR et al. Ann Oncol 2020

Current & Future Issues

- Further work on benefit of IP versus IV

JGOG 3016

IV carbo & IV dose-dense paclitaxel

IP carbo & IV dose-dense paclitaxel

- Combining PARP inhibitors with immunotherapy

FIRST Primary OC

Platinum-based chemo + placebo

Platinum-based chemo + niraparib

Platinum-based chemo + niraparib + anti-PD1

- Modifying neoadjuvant treatment

NRG GY007

Carbo/taxol + placebo

Carbo/taxol + ruxolitinib

Tumor reductive surgery

Genetic Testing

- Patients with EOC MUST be offered genetic counselling & testing
- ***15-20% Rate of HRD mutations (BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2, BARD1 and MMR genes)***
- Unfortunately, referral rates for genetic counseling are low – 10-30% in recent review
  - In retrospective review from Brown, of those referred, 70.8% consulted with genetics

Referral based on family hx alone may miss 1/3 cases of mutation carriers

NCCN *recommends*

Genetic risk evaluation and germline & somatic testing for all patients with a new diagnosis of ovarian, fallopian tube or primary peritoneal cancer

Febbraro T et al. Gynecol Oncol 2015.
Hospins PJ and Gotlieb WH. CA Cancer J Clin 2017.

Pat T et al. Cancer 2005. Pennington & Swisher. Gynecol Oncol 2012.
NCCN Clinical Practice Guidelines in Oncology: Genetic/Familial High-Risk Assessment: Breast and Ovarian. Version 1.2020.

Recurrence

Likelihood of recurrence:

- >80% with advanced disease will recur

Timing of relapse:	*Treatment-free Interval*
Platinum-sensitive	≥6 mos
Platinum-resistant	<6 mos

Prognosis - cure unlikely following recurrence

Numerous trials open through SCCA for recurrent epithelial ovarian cancer

Platinum Sensitive Recurrent EOC

Re-treat with:

- Carboplatin/paclitaxel
- Carboplatin/Gemcitabine
- Carboplatin/Doxil
- Superior platinum regimen?

Gemcitabine thought to reverse platinum resistance

Rose PG et al. Gynecol Oncol 2003.

CALYPSO:
Phase III comparison C/D vs C/T: equivalent outcomes, but less toxicity in C/D arm

Pujade-Lauraine E et al. J Clin Oncol 2010.

ENGOT-ov 18:
C/G/B +B vs C/D/B + B

Significant improvement PFS, OS with C/D/B + B arm

Global QOL slightly superior in C/D/B+B

Pfisterer J et al. Lancet Oncol 2020.

Maintenance Treatment Recurrent Disease

PARP inhibitors

ENGOT-OV16/NOVA

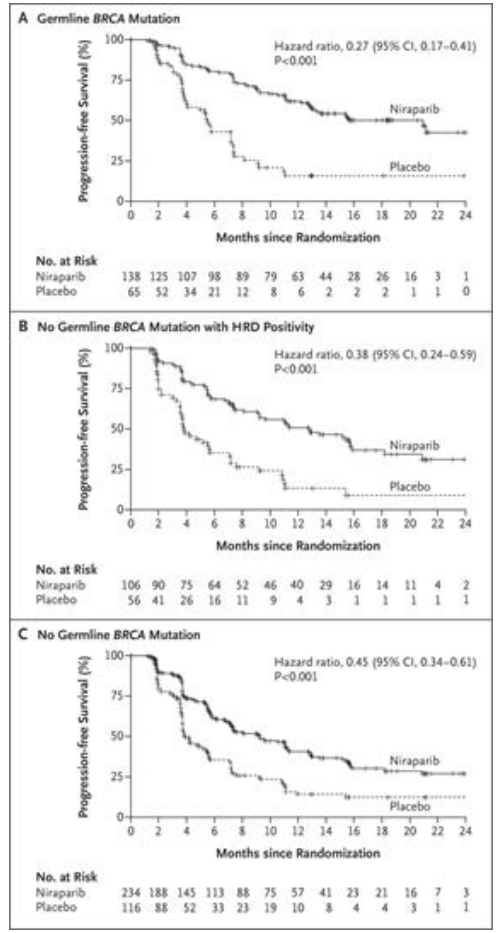
RCT phase 3 of maintenance niraparib

Most improvement seen in patients with BRCA mutations and evidence of HRD

Improved PFS compared to placebo in all groups

Niraparib FDA-approved for maintenance following complete or partial response to platinum-based chemo for recurrent disease (olaparib, rucaparib also approved)

Mirza MR et al. N Engl J Med 2016.



SOLO-3

RCT phase 3 of olaparib vs non-platinum-chemo for BRCA 1 or 2 mutation carriers

Significant improvement in ORR and PFS

Penson RT et al. J Clin Oncol 2020.

Maintenance Treatment Recurrent Disease

Bevacizumab

OCEANS:

C/G vs C/G/B + maintenance B showed significant improvement in PFS

Aghajanian C et al. J Clin Oncol 2012.

GOG 213

C/T or C/G vs C/T/B or C/G/B showed PFS survival benefit with addition of bevacizumab, trend towards OS benefit (42.2 vs 37.3 mo)

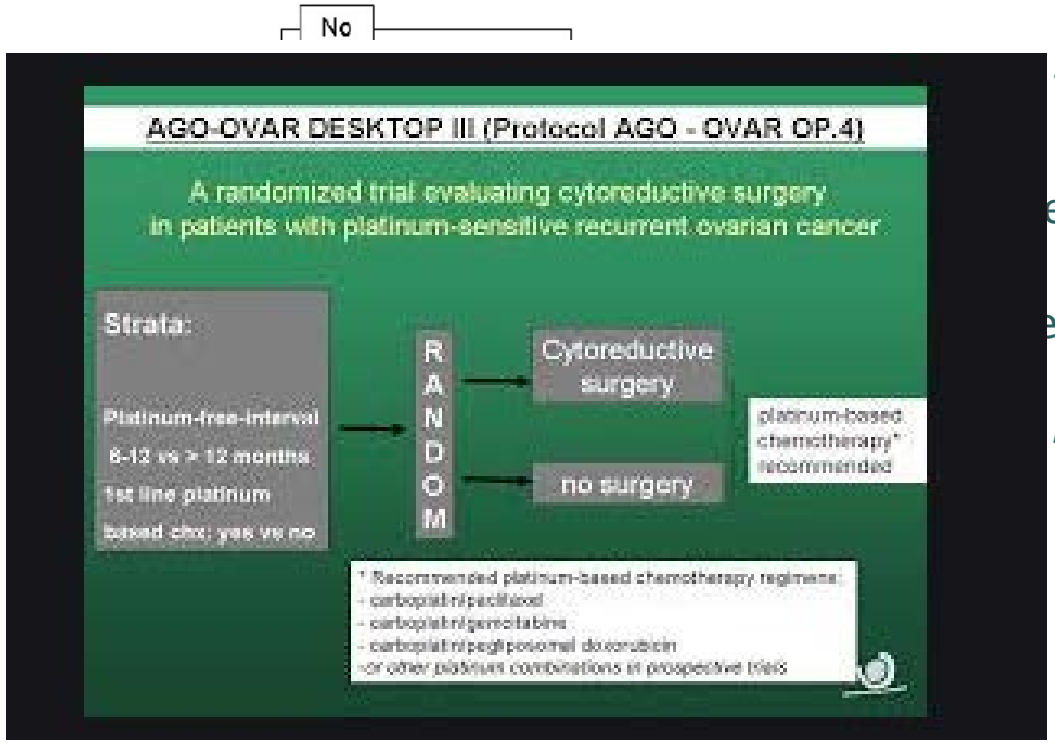
Coleman RL et al. Lancet Oncol 2017.

Platinum Sensitive Disease Secondary Cytoreduction?

- Historically considered for patients with recurrent disease
  - Long disease-free interval
  - Limited sites of disease
- Retrospective studies suggest survival benefit

GOG 213

DESKTOP III



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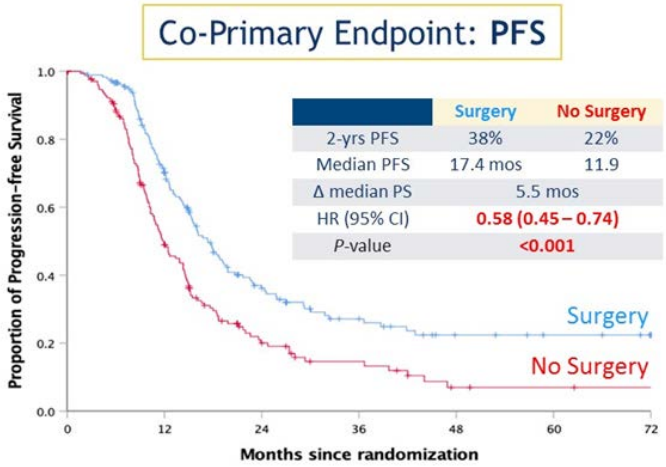
Med 2019.

Platinum Sensitive Disease Secondary Cytoreduction?

SOC-1



Secondary cytoreduction associated with improved PFS & OS

- Standardized means of patient selection (iMODEL)
- No maintenance therapy used

Zang R et al. ASCO 2020

GOG-213, DESKTOP III and SOC-1 Comparison: PFS

	GOG-213	AGO Desktop III	SGOG SOC-1
PFS - Surgery (median)	18.2 mos	18.4 mos	17.4 mos
PFS - No Surgery (median)	**16.5 mos**	14.0 mos	11.9 mos
HR, 95% CI	0.88 (0.70-1.11)	0.66 (0.54-0.82)	0.58 (0.45-0.74) P < 0.001

- Secondary cytoreduction may be appropriate, but careful patient selection using validated models is crucial

Platinum Resistant Options

Multiple treatment options:

- Topotecan
- Doxil
- Oral VP16
- Tamoxifen
- Abraxane
- Pemetrexed
- Gemcitabine
- Bevacizumab
- Cyclophosphamide
- Paclitaxel, docetaxel
- Hexamethamelamine

Encourage clinical trial participation!

- Phase III AURELIA trial showed PFS benefit of adding bevacizumab to chemotherapy (topo, taxol, Doxil), as well as improvement in QOL

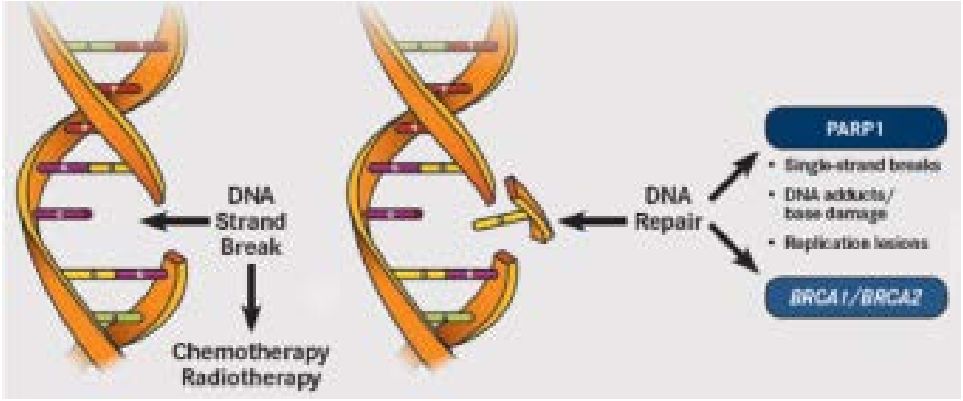
Pujade-Lauraine et al. J Clin Oncol 2014
Stockler MR et al. J Clin Oncol 2014.

- Recent Australian data suggest that our definition of "platinum resistance" may need revision
  - In patients with platinum-free interval of 3-6 months, improved outcomes were seen with platinum-based chemo compared with no platinum

Lindemann K et al. Gynecol Oncol 2018

PARP Inhibitors

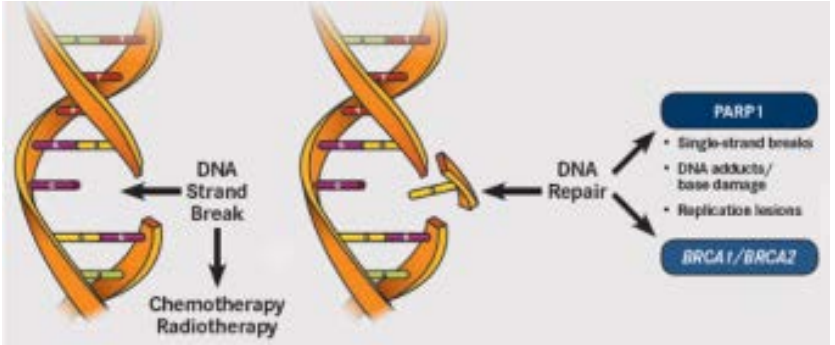
- Current FDA-approved PARP inhibitors
  - Olaparib (Lynparza)
  - Rucaparib (Rubraca)
  - Niraparib (Zejula)



- Approved indications
  - Maintenance following platinum-based primary treatment in BRCA-mutated ovarian cancer
  - Maintenance following platinum-based treatment of platinum sensitive recurrence
  - Monotherapy in patients with platinum-sensitive recurrent disease (>2 lines of treatment) and germline or somatic BRCA 1 or 2 mutation and/or HRD+ tumor

Moore K et al. N Engl J Med 2018.
Mirza MR et al. N Engl J Med 2016.
Kaufman B et al. J Clin Oncol 2015.
Swisher EM et al. Lancet Oncol 2017.
Coleman RL et al. Lancet 2017.

PARP Inhibitors



- Consider PARPi in patients with germline BRCA 1 or 2 mutation with platinum resistant disease

Domchek SM et al. Gynecol Oncol 2016.

- Management of toxicities
  - Upfront dose modification of niraparib in patients with baseline weight of <77 kg or baseline platelets <150K
  - Aggressive use of antiemetics when starting PARP inhibitor

Moore KN et al. Gynecol Oncol 2018.
Mirza MR et al. N Engl J Med 2016.

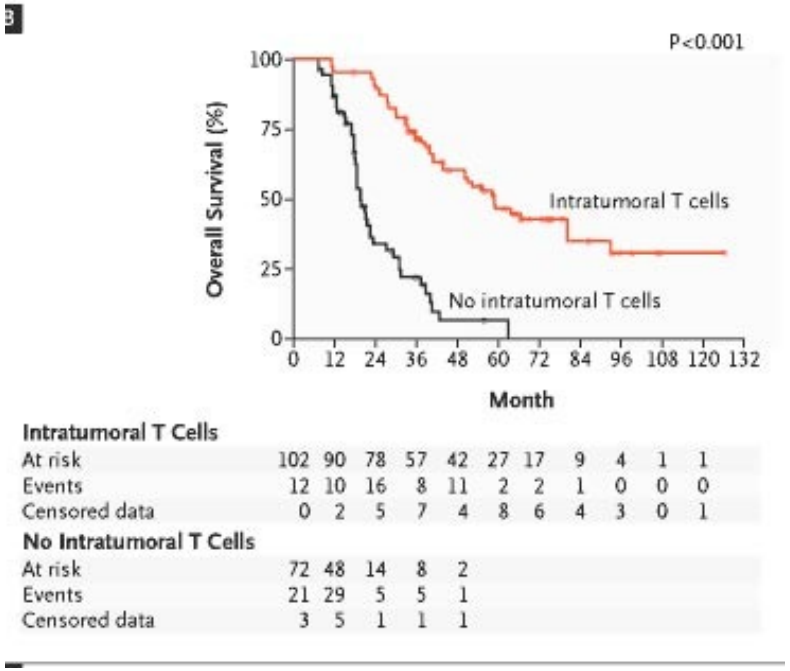
- Future directions
  - Combination with antiangiogenic agents (olaparib & cediranib)
  - Combination with immunotherapy
    - TOPACIO/KEYNOTE-16: niraparib & pembrolizumab, ORR 18%, DCR 65%
    - MOONSTONE: niraparib + anti-PD-1 antibody

Washington C et al. Curr Op Obst Gyn 2019.
Konstantinopoulos PA et al. JAMA Oncol 2019

Immunotherapy in EOC/FTC/PPC

Rationale for approach:

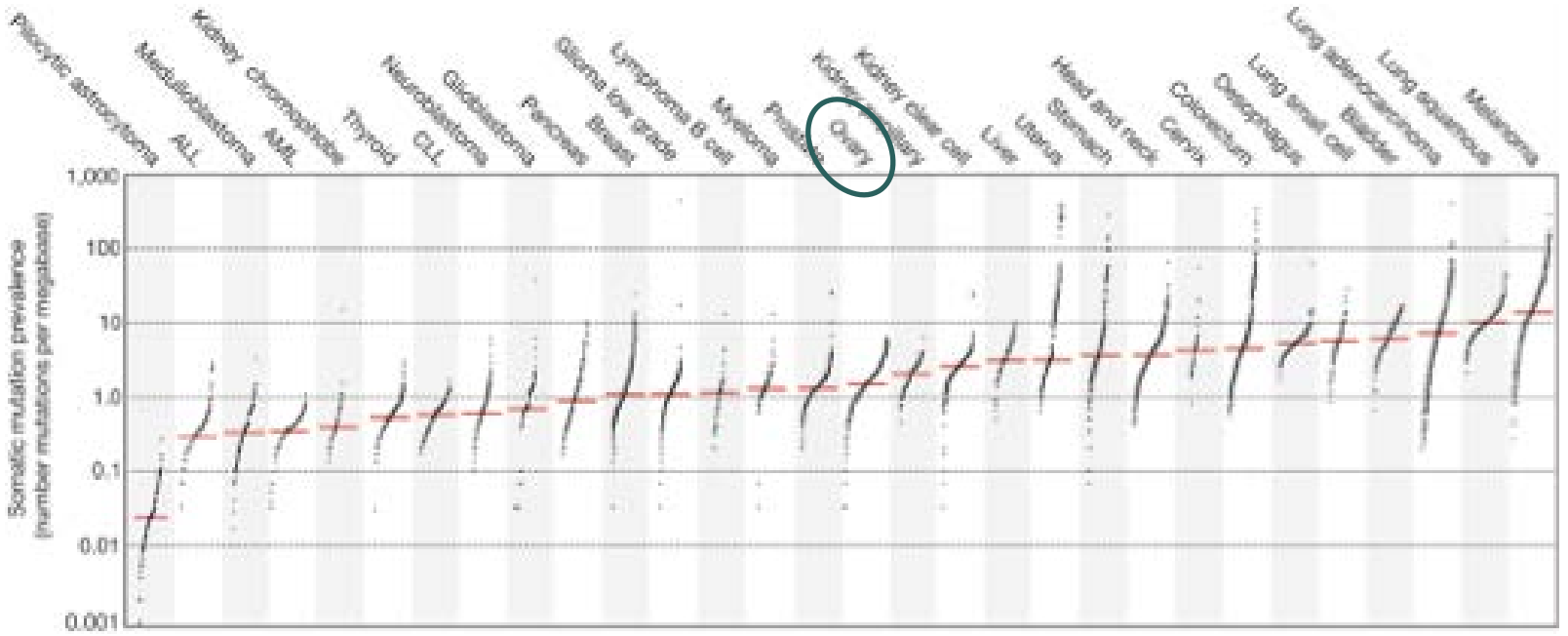
- Overall survival in ovarian cancer found to correlate to presence/absence of tumor-infiltrating lymphocytes
- Analysis of the TCGA has shown “immunoreactive-like" subtype of ovarian cancer to have improved survival
  - 20% of samples fit profile



Zhang L et al. NEJM 2003.
Konecny GE et al. J Natl Cancer Inst 2014.

To date, modest response in clinical trials → **currently no approved immune therapies for ovarian cancer**

Prevalence of Somatic Mutations



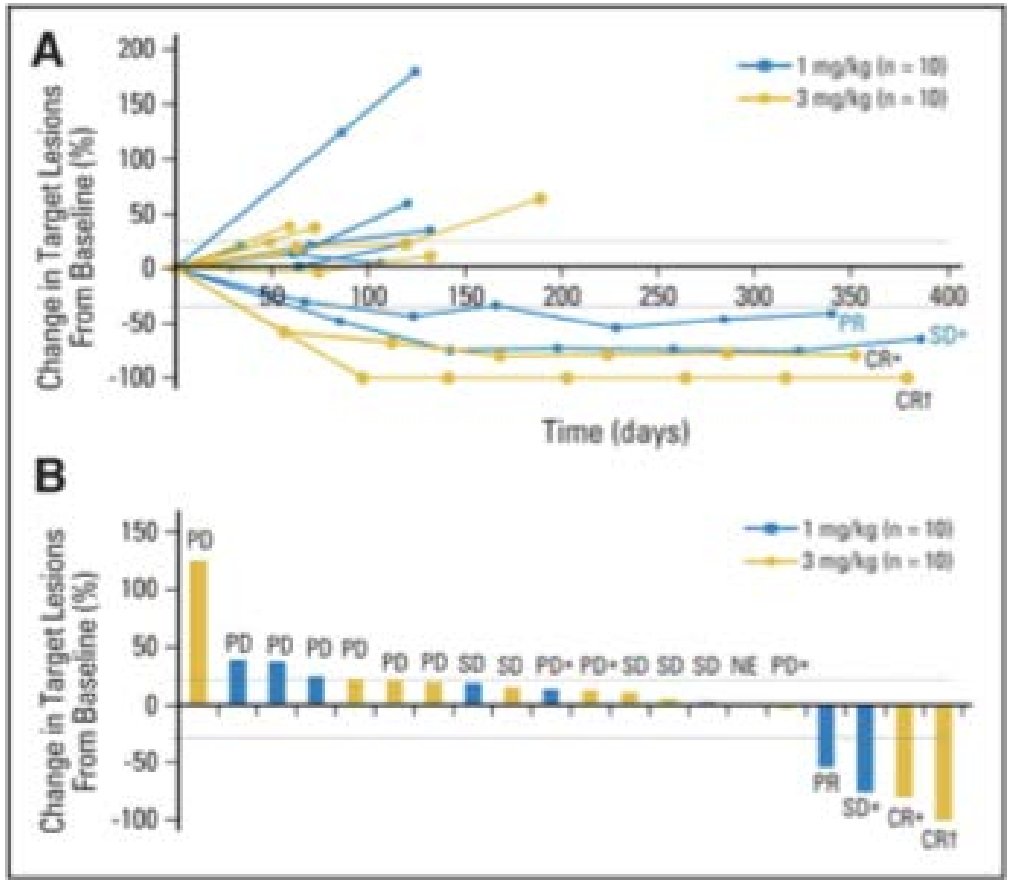
Why limited benefit to immunotherapy in ovarian cancer?

1. Low mutational burden
2. Expression of multiple co-inhibitory receptors on infiltrating T-cells
3. Upregulation of immune checkpoints if another is blocked
4. Redundant immune suppressive mechanisms

Alexandrov LB et al. Nature 2013.
Odunsi K. Ann Oncol 2017.

Immune Checkpoint Inhibition

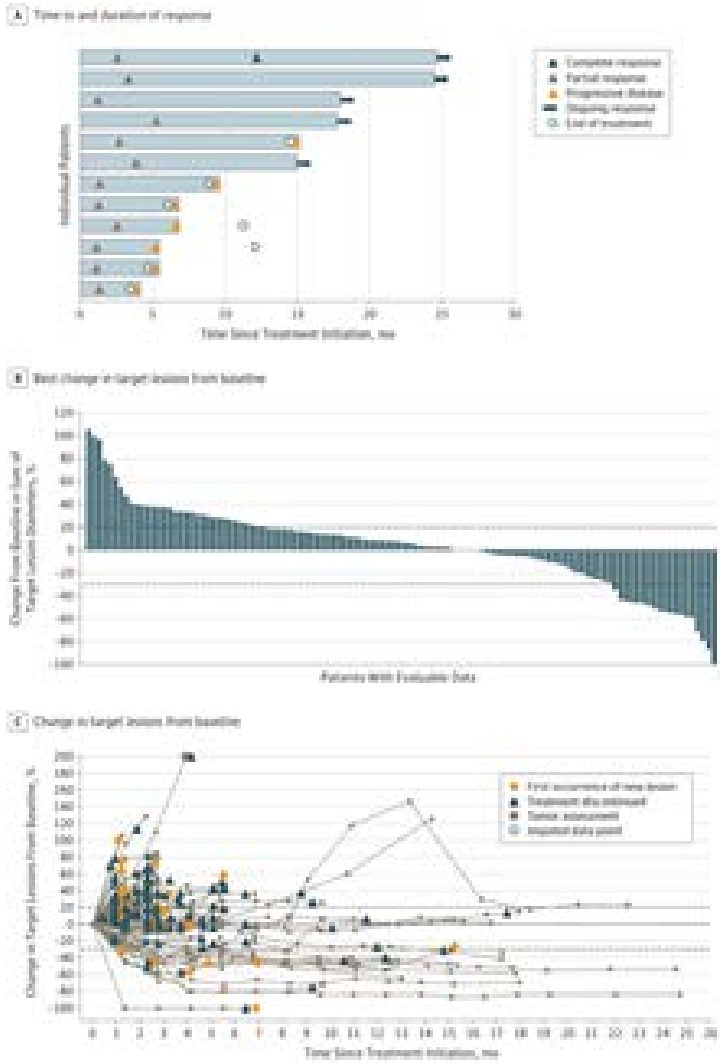
- Phase 2 study of nivolumab in platinum resistant ovarian cancer with ORR of 15%
- Two durable complete responses, one partial response, one stable disease
- Response to therapy did not correlate with tumor PD-L1 IHC



Hamanishi J et al. J Clin Oncol 2015.

Immune Checkpoint Inhibition

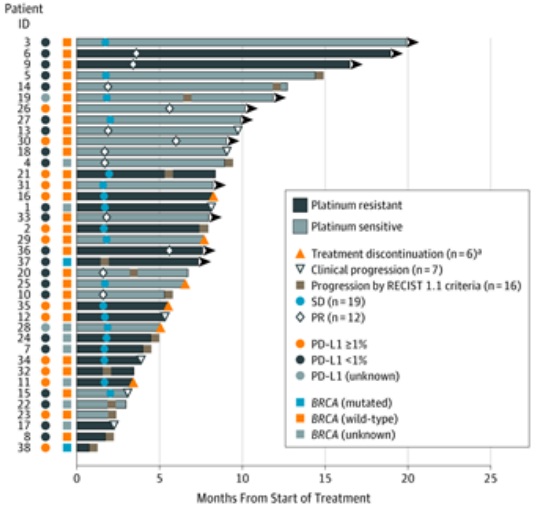
- Phase 1B KEYNOTE-100 – RR of 7.4-9.9% with pembrolizumab in recurrent ovarian cancer
  - ASCO 2020: Final analysis showed trend towards increased ORR with higher PD-L1 expression
- Phase 1b KEYNOTE-028 – pembrolizumab for PD-L1+ recurrent ovarian cancer reported ORR of 11.5%
- Phase 1b JAVELIN – ORR 9.6% with avelumab in recurrent ovarian cancer, DCR 54%

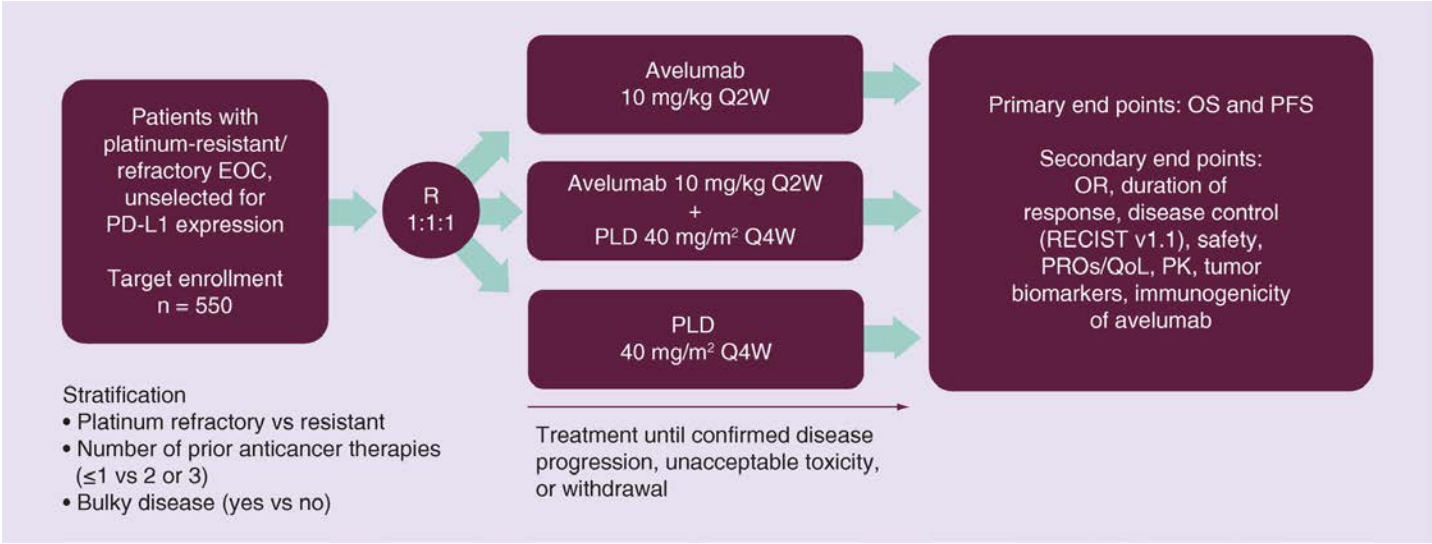


Matulonis UA et al. Ann Oncol 2019.
Matulonis U et al. ASCO 2020.
Varga A et al. Gynecol Oncol 2019
Disis ML et al. JAMA Oncol 2019.

Immune Checkpoint Inhibition

- Phase 2 combination therapy with nivolumab and bevacizumab
  - 38 patients with recurrent ovarian cancer (relapse within 12 months of last platinum)
  - ORR 28.9% (40.0% pt-sensitive, 16.7% pt-resistant)
  - Response not correlated with PD-L1 staining
- JAVELIN OVARIAN 200





Liu JF et al. JAMA Oncol 2019.
Pujade-Lauraine E et al. Future Oncol 2018.

Immunotherapy

- Vaccination studies: CA 125, NY-ESO-1
- Recent pilot clinical trial of “personalized vaccine” generated by autologous DCs

Berek J et al. J Clin Oncol 2009,
Sabbatini P et al. J Clin Oncol 2010.
Tanyi JL et al. Sci Transl Med 2018.

- Future studies testing agents in combination with chemo, antiangiogenic agents and PARP inhibitors

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2019
Ovarian Cancer

NCCN Ovarian Cancer Panel Members
Summary of the Guidelines Updates

Epithelial Ovarian Cancer/Fallopian Tube Cancer/Primary Peritoneal Cancer:
Clinical Presentation, Workup, Clinical Stage, Primary Treatment (OV-1)
Poor Surgical Candidate or Low Likelihood of Optimal Cytoreduction (OV-2)
Diagnosis by Previous Surgery: Findings and Primary Treatment (OV-3)
Pathologic Staging, Primary Chemotherapy/Primary Adjuvant Therapy (OV-4)
Post-Primary Treatment: Maintenance Therapy (OV-5)
Monitoring/Follow-Up, Recurrent Disease (OV-6)
Disease Status, Therapy for Persistent Disease or Recurrence (OV-7)

Less Common Ovarian Histopathologies:
Diagnosis (LCOH-1)
Carcinosarcoma (Malignant Mixed Müllerian Tumors) (LCOH-2)
Clear Cell Carcinoma of the Ovary (LCOH-3)
Mucinous Carcinoma of the Ovary (LCOH-4)
Grade 1 Endometrioid Carcinoma (LCOH-5)
Low-Grade Serous Carcinoma (LCOH-6)
Ovarian Borderline Epithelial Tumors (Low Malignant Potential) (LCOH-7)
Malignant Sex Cord-Stromal Tumors (LCOH-10)
Malignant Germ Cell Tumors (LCOH-11)

Principles of Surgery (OV-A)
Principles of Pathology (OV-B)
Principles of Systemic Therapy (OV-C)
- Primary Systemic Therapy Regimens (OV-C, 3 of 9)
- Acceptable Recurrence Therapies (OV-C, 6 of 9)

Management of Drug Reactions (OV-D)
WHO Histologic Classification (OV-E)
Staging (ST-1)

“One Size No Longer Fits All”

Low-grade Serous (LGS)
LG Endometrioid
Clear Cell
Mucinous

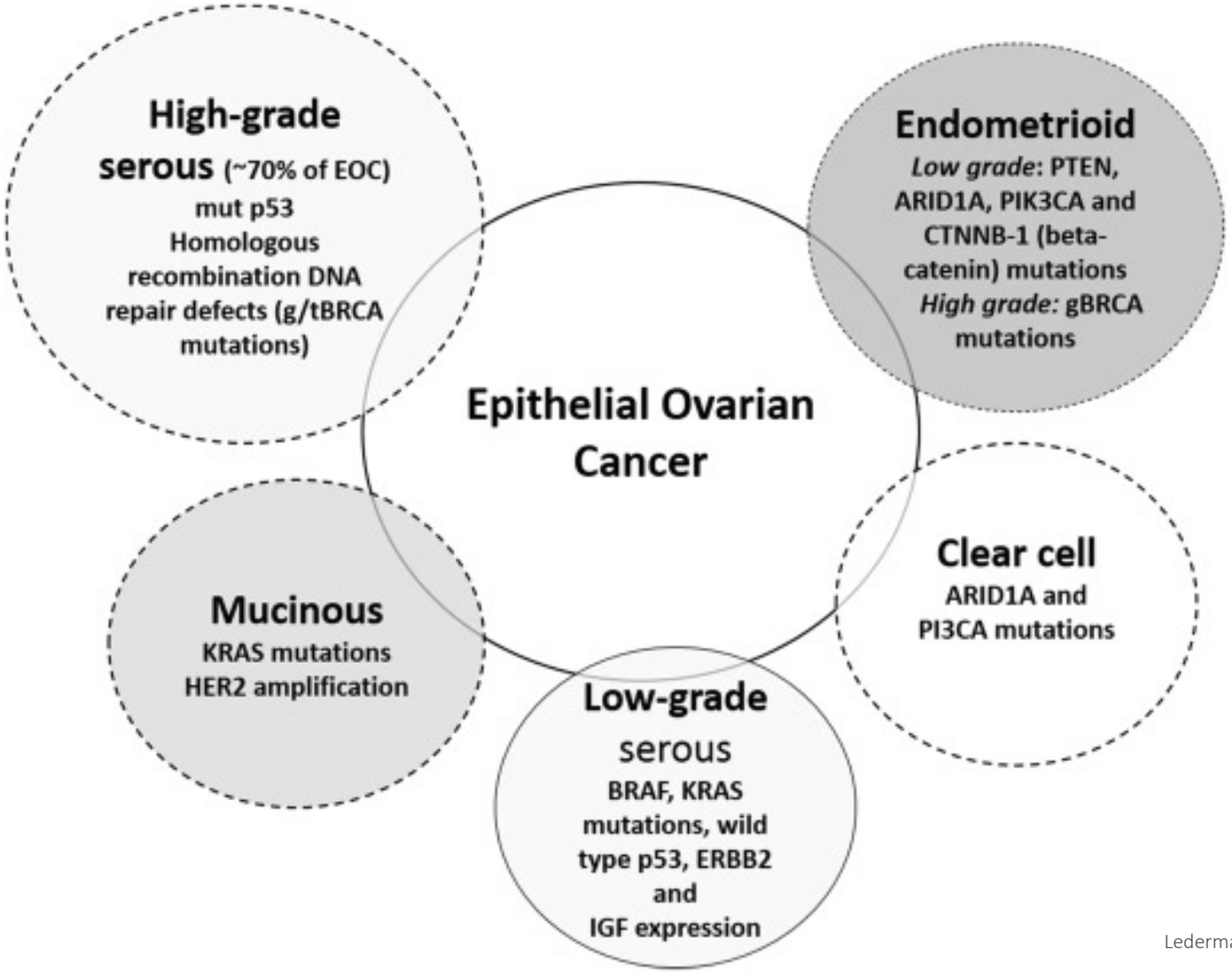
- Develop in stepwise fashion
- Activating mutations in:
  - PTEN
  - KRAS
  - BRAF
  - P13KCA

High-grade Serous (HGS)
HG Endometrioid
Carcinosarcoma
Undifferentiated

- Present with **ADVANCED** disease
- May have mutations in BRCA 1 & 2, nearly universal p53 mutations

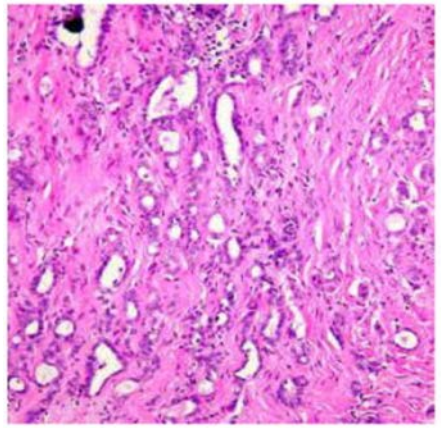
Groen RS et al. Gynecol Oncol 2015.
Kurman & Shih. Am J Surg Pathol 2010.

Molecular Subtypes

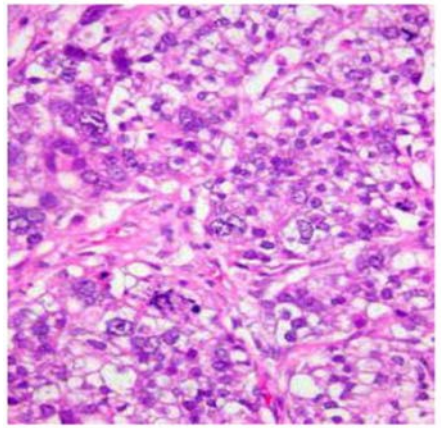


Ledermann JA et al. Eur J Cancer 2016.

Histology-Specific Therapy
Low Grade Serous (LGS)



1A Low Grade Serous Carcinoma

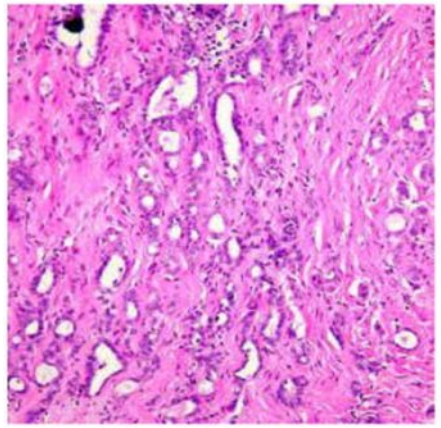


1B High Grade Serous Carcinoma

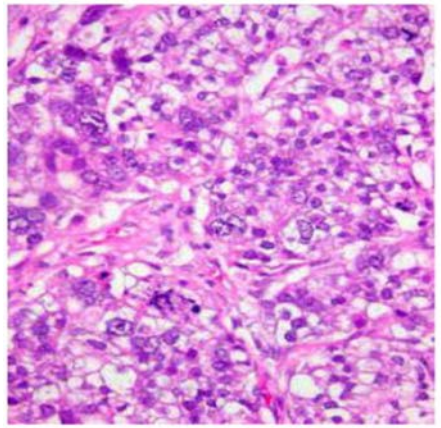
- Represents 5% of all ovarian cancers, and a minority of all serous cancers
- Such patients are often younger & survive longer
- Review of patients with LGS on phase III clinical trial showed that only residual disease after surgery was associated with improvement in survival

Fader AN et al. Obstet Gynecol 2013.
Gershenson DM et al. Obstet Gynecol 2006.

Histology-Specific Therapy
Low Grade Serous (LGS)



1A Low Grade Serous Carcinoma



1B High Grade Serous Carcinoma

Lack response to chemotherapy compared to high-grade serous tumors

- Often have activating mutations in PTEN, KRAS, BRAF, PI3KCA
- Higher expression of ER, PR receptors

MEK inhibitors

- 15% ORR, 65% SD with selumetinib
- GOG 281: ORR 26.2% trametinib vs 6.2% with IC chemo

Hormonal therapy

- Recent MDACC review of hormonal maintenance therapy showed significant improvement in PFS

Farley J et al. Lancet Oncol 2013.
Gershenson DM et al. J Clin Oncol 2017.
Gersenson DM et al. SGO 2020.

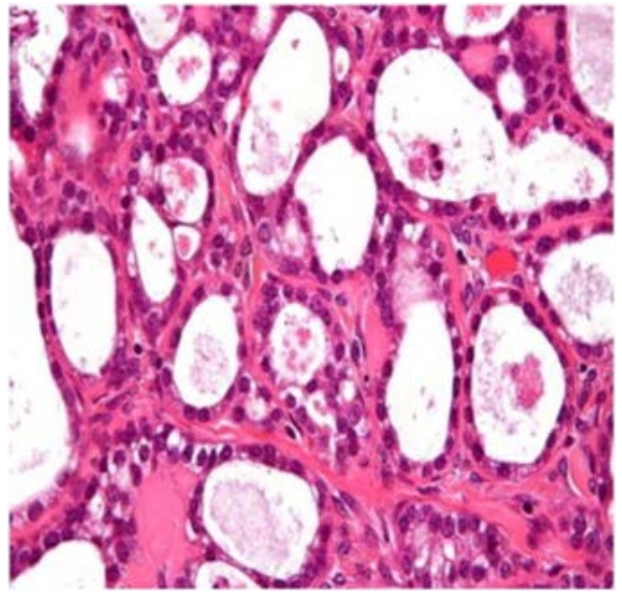
NRG GY 019

Debulking surgery

Carbo/taxol + letrozole

Letrozole

Histology-Specific Therapy
Clear Cell



- 3-12% of all ovarian cancers, higher prevalence in Asian patients
- Lower response to platinum-based chemotherapy compared to high-grade serous cancers
- Use of antiangiogenic agents
  - Used in renal clear cell carcinoma
  - Such cancers have very high VEGF expression
- Consider checking for mismatch repair protein expression (11.5%)
- Use of radiation?
  - Improved DFS in patients with high-risk early stage disease
  - Improved outcomes in patients with recurrent ovarian clear cell cancer

Mabuchi S et al. Mol Cancer Ther 2010.
Hoskins PJ et al. J Clin Oncol 2012.
Brown AP et al. Gynecol Oncol 2013.

Histology-Specific Therapy Endometrioid Ovarian Cancer

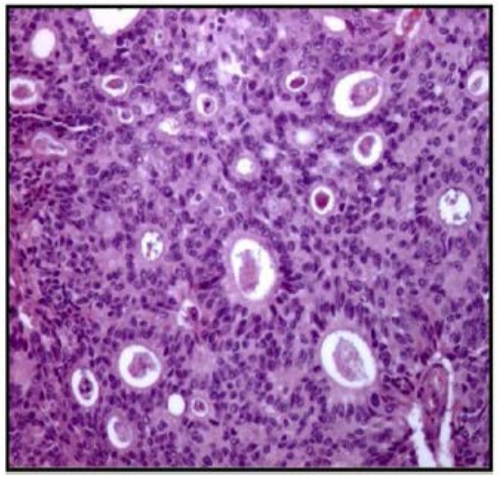


Fig. 3. Grade 2 endometrioid carcinoma demonstrating atypical crowded, back-to-back glands, little intervening stroma and few mitotic figures.

- 11% of epithelial ovarian cancers
- Often found in association with endometriosis
  - High rate of estrogen, progesterone expression
- Check for microsatellite instability (19.2%)
  - In patients with Lynch syndrome, have a strong association with synchronous endometrial cancer
  - Consider checking for microsatellite instability
- No benefit of chemotherapy in *low grade* early stage disease
  - High grade endometrioid ovarian cancers behave similarly to high-grade serous

Trimbos JB et al. J Natl Cancer Inst 2003.

Histology-Specific Therapy Mucinous Ovarian Cancer

- 3–5% of ovarian cancers
  - Incidence hard to estimate given overlap with primary GI sites
- May be low- or high-grade
- In advanced stages, significantly worse prognosis than high-grade serous cancers
- Consideration of “GI-type” chemotherapy regimens (e.g. CAPOX), given similar molecular profiles
  - Studies to date suggest survival benefit
  - Interpretation difficult given use of bevacizumab

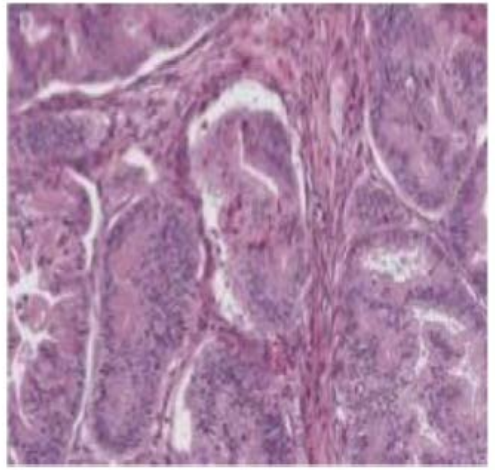


Fig. 4. Mucinous carcinoma exhibiting an expansive pattern with few mitotic figures. All figures were borrowed with permission from David M. Gershenson and Anais Malpica, MD Anderson Cancer Center.

Zaino RJ et al. Cancer 2011.
Ledermann JA et al. Int J Gynecol CA 2014.
Kurnit KC et al. Obstet Gynecol 2019.
Gore M et al. Gynecol Oncol 2019.

Conclusions

- Ovarian cancer is a heterogenous disease & histology is key in management
- Maintenance treatment following primary therapy for all?
  - Upfront molecular profiling is essential to determine potential benefit of maintenance
- Consult with gynecologic oncologists at diagnosis and throughout the disease continuum

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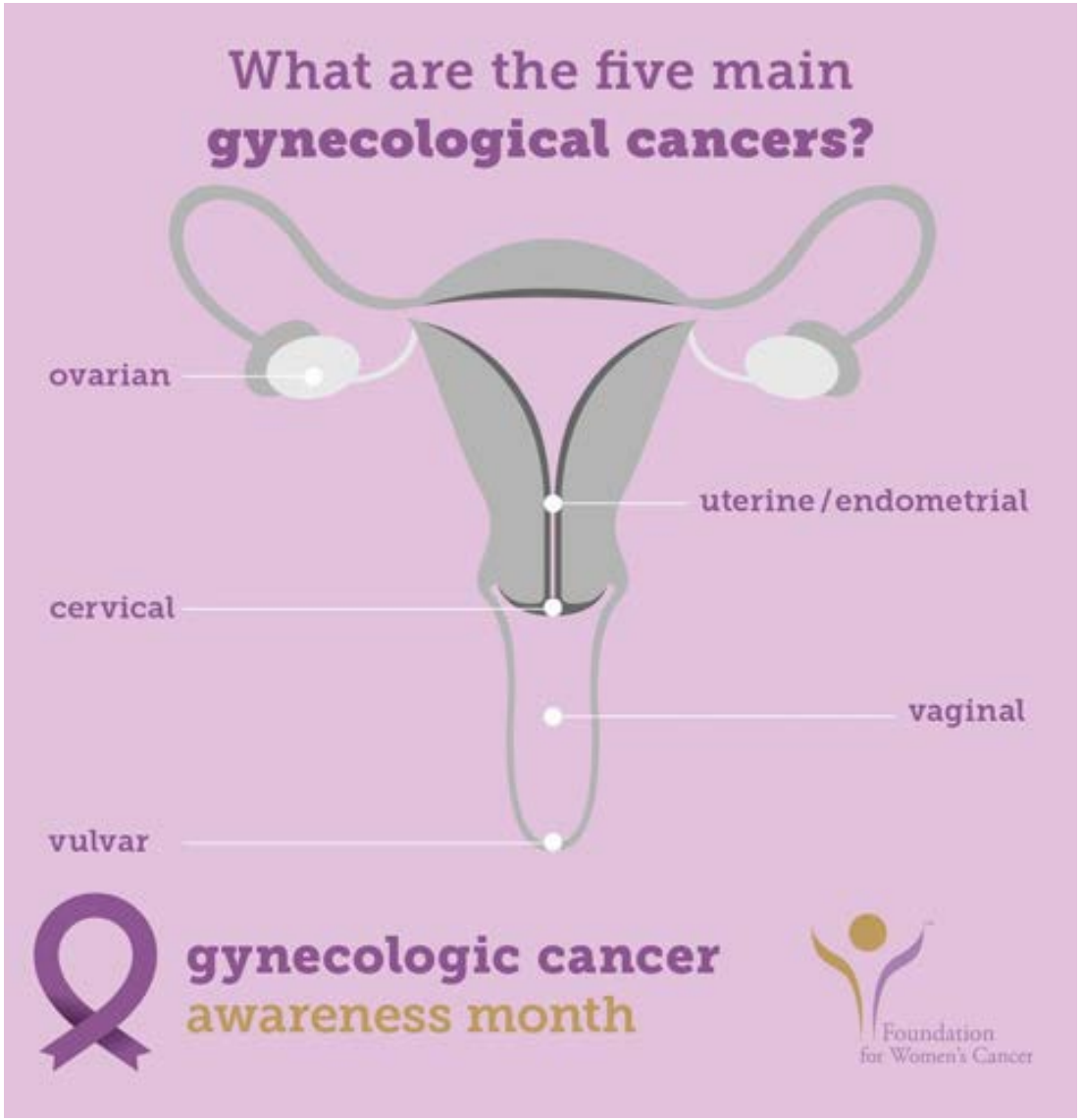


Genetic Testing

Expanded panel testing – 30 genes panel

- BROCA(UW panel), Foundation One, Myriad, Ambry
- Insurance will only pay for one $$$

Color genomics

$249, need Dr. to approve

19 gene panel (including BRCA1 & 2)

Sample Case

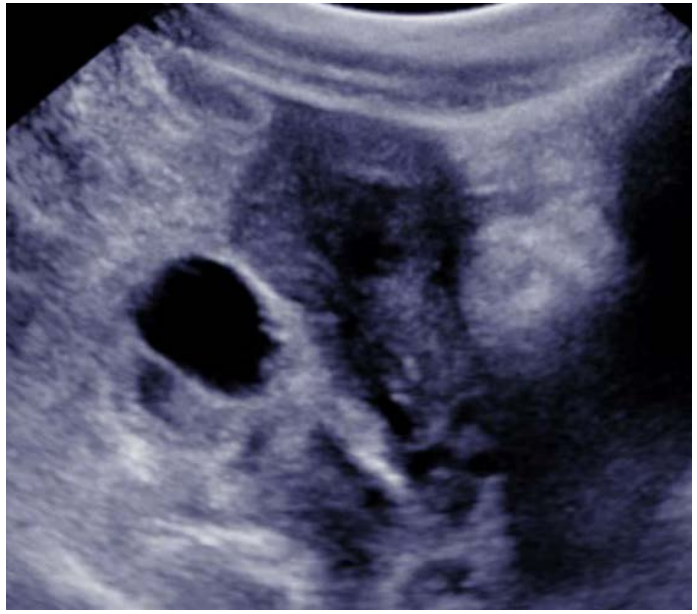
ZA, 65 yo, referred to your office by her PCP:

- 3 months of abdominal bloating
- CT showed a pelvic mass and ascites
- CA 125 = 1,031; CEA = 0.9

How to proceed with a presumed advanced ovarian cancer?

Diagnostic Approaches - Imaging

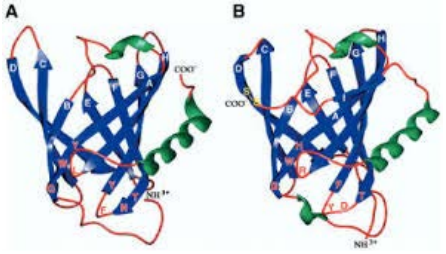
- Pelvic (transvaginal) ultrasound
  - Useful for gynecologic tract
  - Cheapest
- CT abdomen/pelvis ± chest
  - If concerned about abdominal disease or exam findings
- MRI
  - Good for distinguishing solid ovarian tumors
- Role of PET?
  - Not cost-effective for primary disease
  - May be useful in recurrent disease



Tumor Markers

CA-125 (normal <35 U/mL)

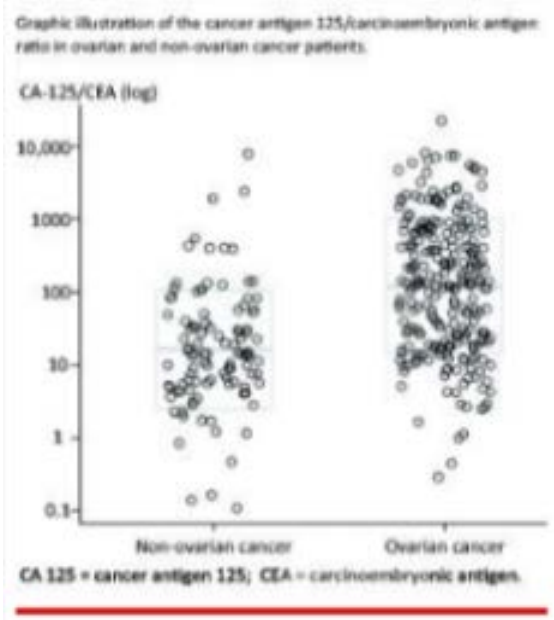
- Expressed by cells of coelomic (pleura, peritoneum) and Mullerian (gyn) epithelia
- Sensitivity 70%, specificity 80% (lower in premenopausal)
- Not as useful in mucinous or clear cell tumors
- If find a pelvic mass/abnormal ovary – order CA125



HE-4 (human epididymis protein 4) (normal <150 pM/mL)

- FDA Approved for monitoring recurrent or progressive EOC
- Part of ROMA (Risk of malignancy algorithm) score
  - CA125, HE4 & menopausal status
  - Assess likelihood of malignancy in women undergoing surgery for adnexal mass
- Generic price at UW: $184

Modes of Diagnosis



- Biopsy-proven (preferable)
- If biopsy specimen unavailable, FNA specimen acceptable if:
- presence of pelvic (ovarian) mass
- presence of metastases outside pelvis measuring ≥2 cm
- regional lymph node metastasis or proof of stage IV disease (+ pleural effusion, + parenchymal liver mets)
- Ratio of CA 125:CEA ≥ 25

Ratio of CA 125:CEA <25 requires evaluation for primary gastrointestinal malignancy

Surveillance?

Modalities

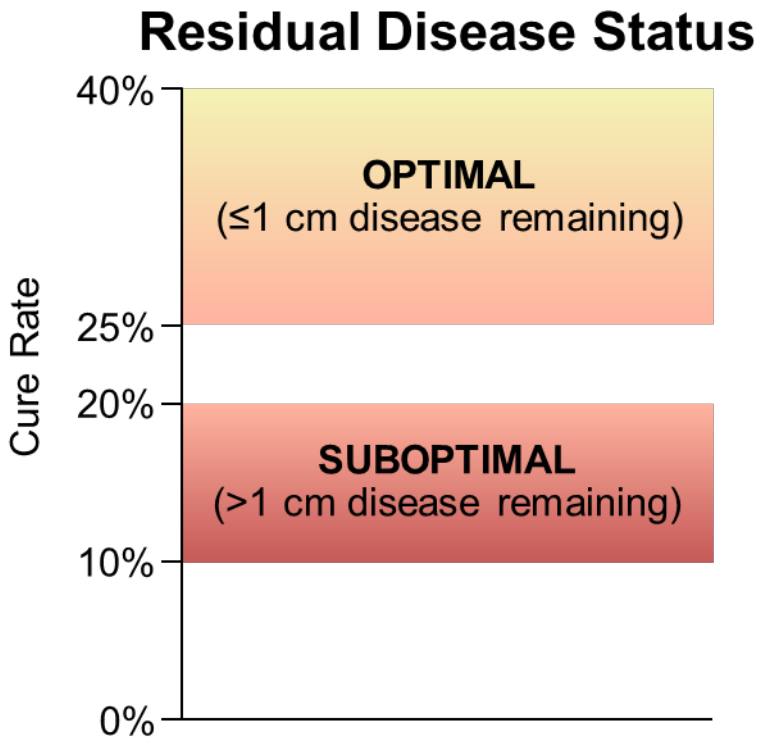
- Clinical exam, including pelvic, q 3-6 mos
- CA 125 every visit, if initially elevated
- Imaging, as clinically indicated
- HE4 - newly discovered glycoprotein, overexpressed by serous and endometrioid adenocarcinomas
  - FDA-approved marker to monitor for recurrence

Evidence

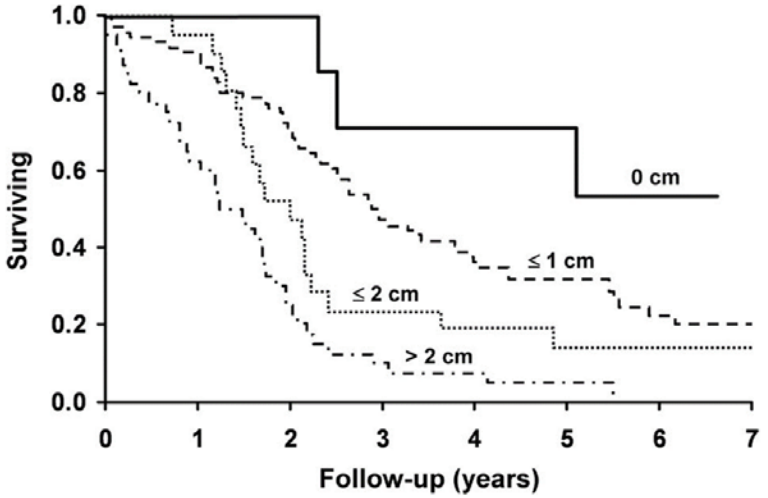
- Detection of early recurrence may extend lifespan; however, that benefit not derived from routine F/U Exams
- Randomized EORTC trial: No survival benefit when Rx on basis of CA 125 alone vs clinical recurrence

NCCN Guidelines. Ovarian Cancer. V1.2019
Geurts SM et al. Int J Gynecol Cancer 2011
Rustin GJ et al. Lancet 2010.

Importance of Cytoreduction



Survival by volume of residual disease remaining after surgery



Questions?

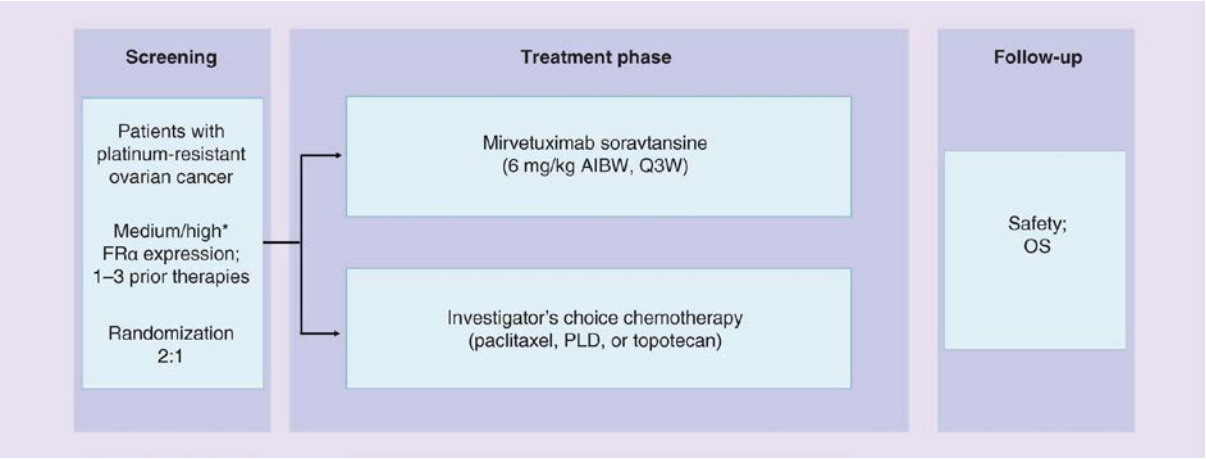
Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Platinum Resistant Disease
Future Directions

Folate receptor (FR)

- Capacity to internalize large molecules
- Mirvetuximab (coupled to DM4)
- FORWARD I: Mirvetuximab vs IC chemo in patients with tumors having FRα expression



Encourage clinical trial participation!

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Hemoglobin disorders

Kleber Y. Fertrin, MD, PhD

Assistant Professor, University of Washington

Director, Hemolytic Anemias and Iron Disorders Program

kleber@uw.edu

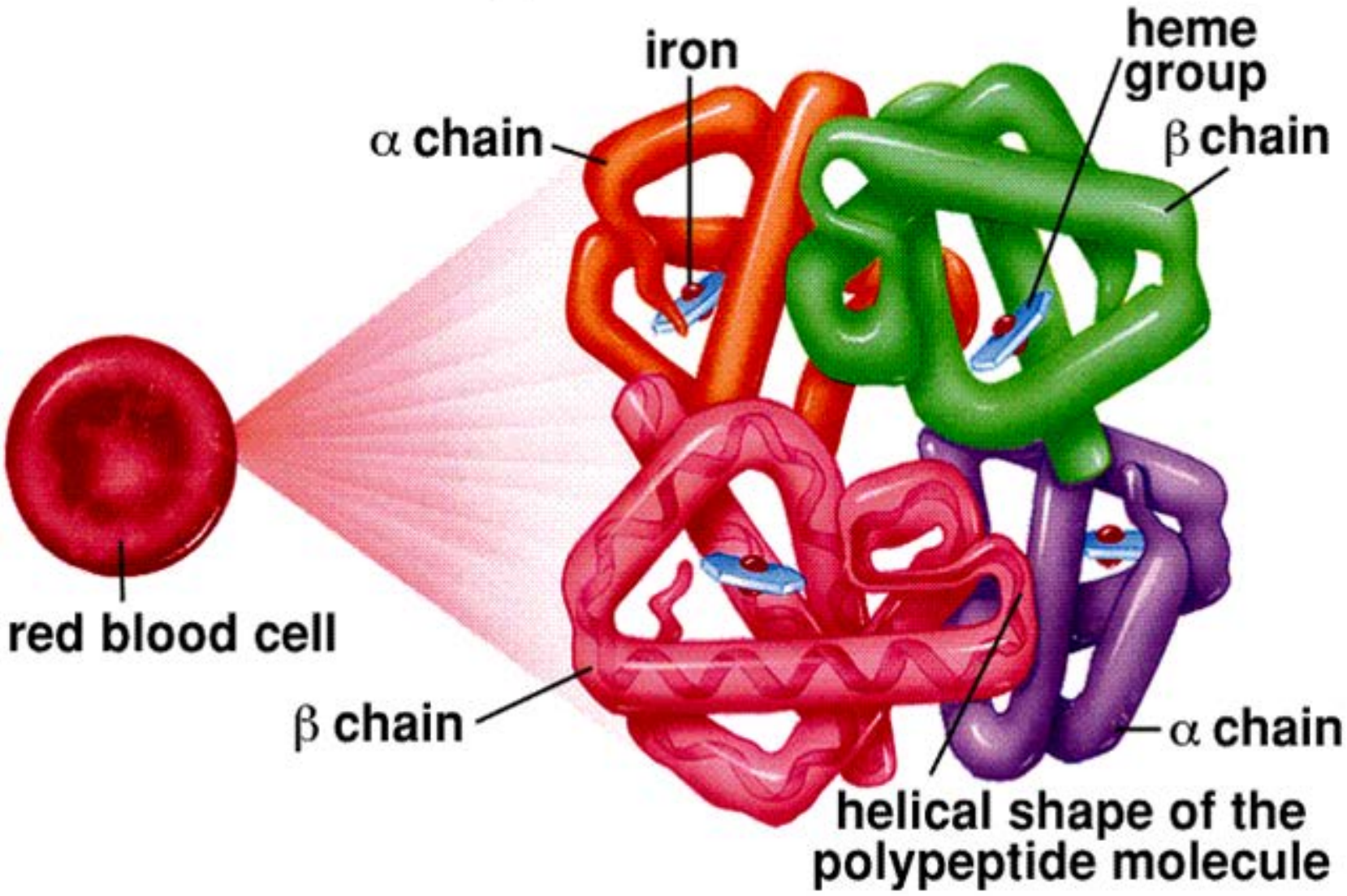
DISCLOSURES

Agios Pharmaceuticals – Research funding, Advisory Board

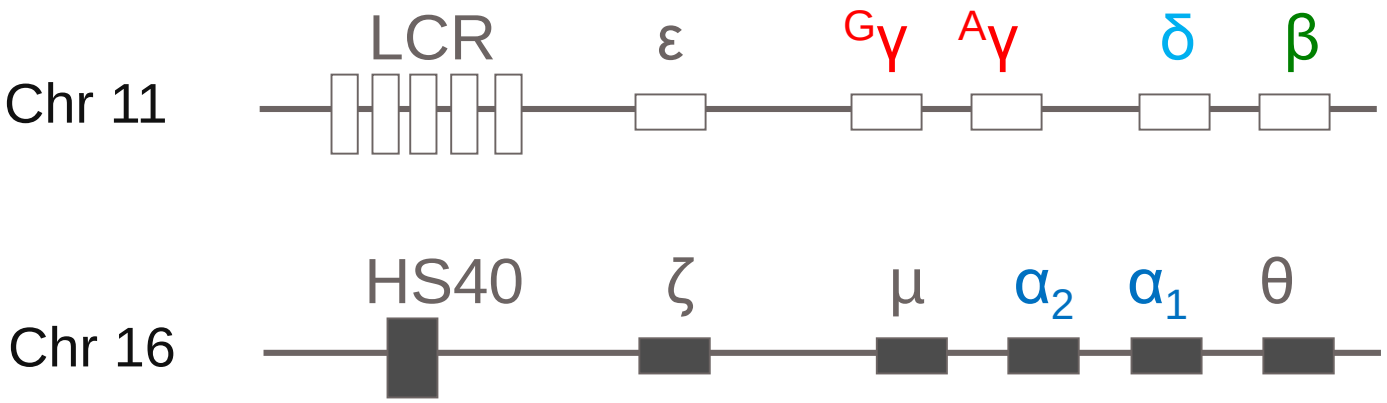
ABIM Hematology exam blueprint

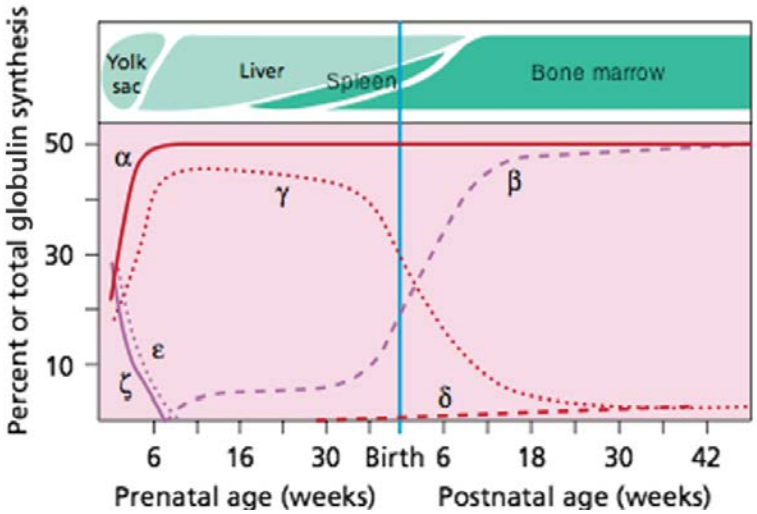
Red blood cell destruction disorders *(15% of exam)*						
Thalassemias						
Alpha thalassemia	LF	⊘	⊘	⊘	⊘	⊘
Beta thalassemia	LF	⊘	⊘	⊘	⊘	⊘
Hemoglobin E disorders	LF	⊘	⊘	⊗	⊗	⊗
Sickle cell disorders *(4.5% of exam)*						
Sickle cell trait		⊘	⊘	⊘	⊘	⊘
Sickle cell anemia (hemoglobin SS disease)		✓	✓	✓	✓	⊘
Hemoglobin SC disease	LF	⊘	⊘	⊘	⊘	⊘
Sickle cell-beta zero and sickle cell-beta plus-thalassemias	LF	⊘	⊘	⊘	⊘	⊘
Non-sickle hemoglobinopathies	LF	⊘	⊘	⊘	⊗	⊗

Hemoglobin Molecule



Globin genes and hemoglobins





Postembryonic hemoglobin species

A	$\alpha_2\beta_2$	(97%)
A2	$\alpha_2\delta_2$	(3%)
F	$\alpha_2\gamma_2$	(<1%)

Figure from ASH SAP 2013 Chapter 7.

Hemoglobin disorders

Thalassemias:

- Named after the reduced/absent *structurally normal* globin chain
- α-thalassemia: excess β-chains
- β-thalassemia: excess α-chains

Hemoglobinopathies:

Amino acid substitution results in *structurally abnormal* hemoglobin
→ **Hb S**, Hb C, HbSC, Hb G-Philadelphia, Hb D, Hb O-Arab, etc.

Thalassemia-hemoglobinopathy:

- HbS-β thalassemia, HbE-β thalassemia, etc.

Genetics of thalassemias

α-thalassemias

- expressed in fetus and at birth
- Predominantly gene deletion(s)

β-thalassemias

- expressed several months after birth (γ-globin → β-globin)
- Predominantly point mutations

β-thalassemias

Causative mutations

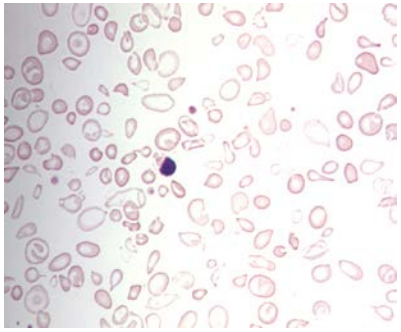
β^0 (null) = No gene product

β^+ = reduced production

- **Excess α-globin chains → <u>INEFFECTIVE ERYTHROPOIESIS</u>**
  - α-globin aggregates in erythroid precursors → intramedullary death
- **Excess free intracellular iron:**
  - membrane lipid oxidation
  - membrane protein damage
- **Membrane damage → PS* exposure and hypercoagulability**
  - decreased RBC deformability
  - increased clearance from circulation

PS phosphatidylserine

Pathophysiology and complications of thalassemias



Impaired α:ß globin ratio

↓

Red cell pathology

↓

Inneffective erythropoiesis

Hemolysis → **Gall stones**

↓

Iron overload

Anaemia

↓ Tissue oxygenation

↓

Erythroid marrow expansion

↓

Hypercoagulable state

- Diabetes mellitus
- Growth deficiency
- Hypothyroidism
- Hypoparathyroidism
- Hypogonadism
- Hepatic cancer
- Renal disease

- Leg ulcers
- Thrombotic events
- Pulmonary hypertension

- Bone deformities
- Osteoporosis

- Hepatosplenomegaly
- Extramedullary hematopoietic psuedotumors

From Guidelines for the Managements of Nontransfusion dependent Thalassemia. Thalassemia International Federation publication 2013.

Hoffbrand & Pettit Color Atlas of Clinical Hematology; © Harcourt, 2000

Clinical classification of β-thalassemias

Phenotype	Hb (g/dL)	Transf	Clinical features	Most common genotype
Thalassemia minor (trait)	**10-12**	**No**	No hemolysis or symptoms, **RBC>5million**, **HbA_2>3.5%**	**β^0/β or β^+/β**
Thalassemia intermedia	7-10	+/-	**high Hb F,** bone disease, **transfusion and/or spontaneous** iron overload, splenomegaly*, pulm HTN, leg ulcers	**β^+/β^+ or β^+/β^0**
Thalassemia major	<7	Age<2	**>95% HbF**, bone disease, **transfusion** iron overload, splenomegaly*	**β^0/β^0 or β^0/β^+**

*splenomegaly due to increased hemolysis, extramedullary hematopoiesis

β-thalassemia major: current treatment

Referral to comprehensive medical center

- Hematology, Genetics, Cardiology, Hepatology, Endocrinology, Ob/Gyn

Palliative care:

- **Transfusion:** typically 2-3 pRBCs q 3-4weeks
  - Goals:
    - pre-transfusion Hb: 9-10.5 g/dL
    - post-transfusion Hb: 12-15g/dL
- **Iron chelation**
  - Initiate **after 10-20 pRBCs or ferritin>1000ug/L**
  - **Single chelator or combination therapy**
  - **Goals:**
    - liver iron concentration (LIC) < 3mg/g
    - cardiac T2* >20ms
      - **Cardiac iron → consider combination therapy (e.g. DFO+DFP)**

Iron chelators

Medication	Brand name	Dose	Route/form	Comments
Deferoxamine (DFO)	Desferal®	50-60mg/kg/d 5-7 days per week	**SQ/IV** 8-24h	Local reaction, **hearing loss, retinopathy, growth delay**
Deferiprone (DFP)	Ferriprox®	25-33mg/kg/d **q8h**	PO tablets	**Neutropenia,** n/v/d, elevated LFTs, arthralgia
Deferasirox (DFX)	Exjade®	20-40mg/kg/d **q24h**	PO dispersible	**elevated creat**, rash, n/v/d
	Jadenu®	14-28mg/kg/d **q24h**	PO tablets or sprinkles	**elevated creat**, rash, n/v/d, less diarrhea (**no lactose**)

β-thalassemia major: current treatment

- **Splenectomy**
  - Indications: transfusion >200-220mL/kg/year; untransfusable due to alloimmunization, severe cytopenias, symptomatic splenomegaly
  - **less used than before due to complications**
    - post-op pancreatitis, pleural effusion, portal vein thrombosis;
    - long term risk for sepsis and VTE; need for antibiotic ppx

- **Luspatercept**
  - FDA-approved for TD beta thal in April 2020
  - Activin receptor ligand trap → improves ineffective erythropoiesis
  - Dose: 1-1.25mg/kg SQ q 3 weeks
  - >33% reduction in transfusion burden in 72% patients
  - AE: bone pain, headache, asthenia

Piga et al. Blood 2019; 133(12):1279-1289

β-thalassemia major: current treatment

Curative treatments:

- **Allogeneic hematopoietic cell transplantation**
  - Ideally: age<14; HLA-matched sibling donor; no significant iron overload.
    - **Pesaro system: predicts post-BMT 3-year OS in children<16yo**

      Adverse factors:

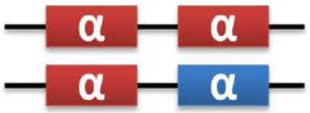
      1. Hepatomegaly >2cm from costal arch
      2. Liver fibrosis on biopsy
      3. Irregular iron chelation

      - Class I: 0 adverse factors → 94%
      - Class II: 1 or 2 adverse factors → 80%
      - Class III: all adverse factors → 61%

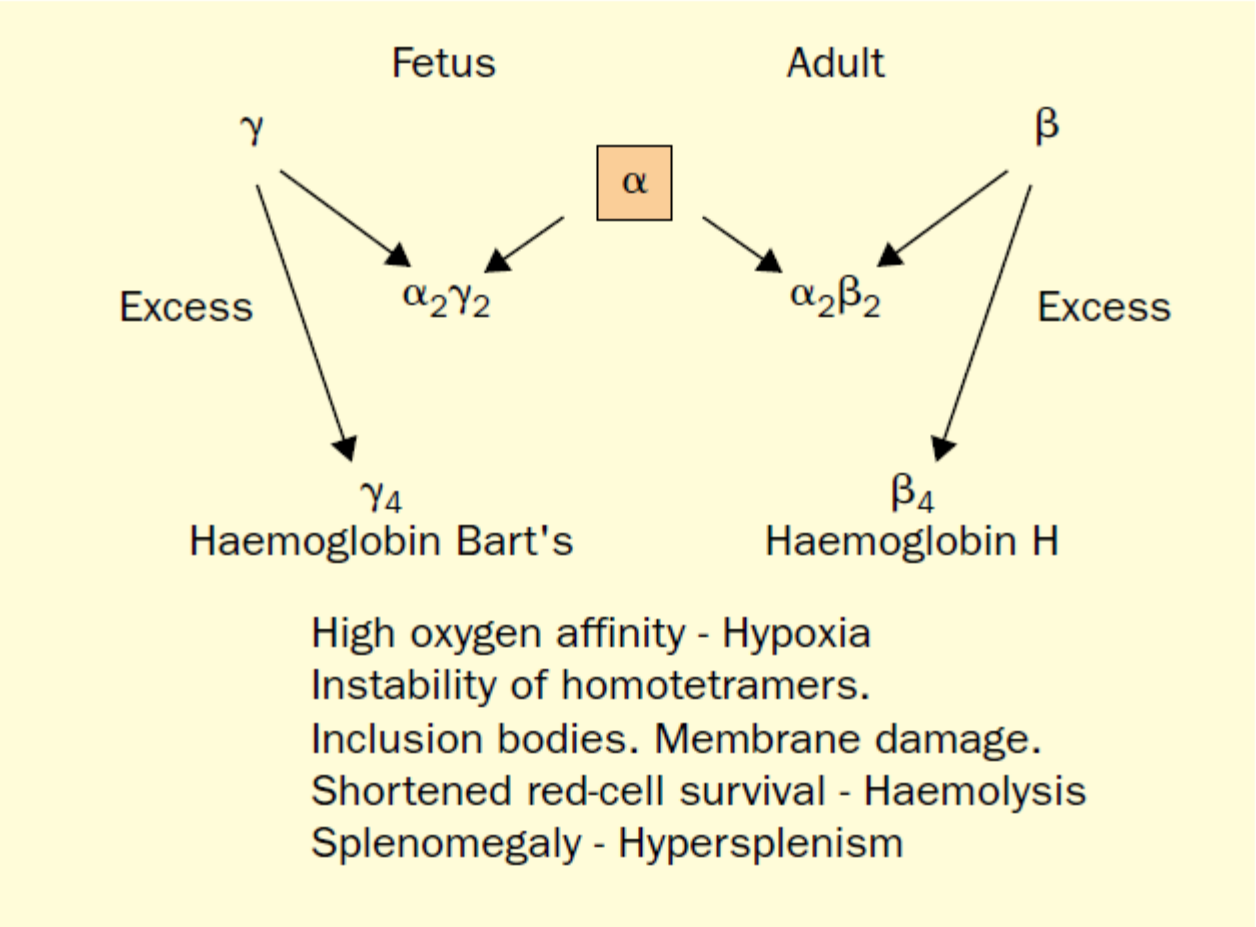
- *Investigational: LentiGlobin gene therapy*
  - Thompson et al. N Engl J Med. 2018 Apr 19;378(16):1479-1493

α thalassemia genetics

Chromosome 16

Normal		**Normal αα/αα**
Carrier: Asymptomatic WNL or isolated microcytosis		**α^+ trait: α-/αα**
α-thal minor: Asymptomatic Mild microcytic anemia	**homozyg α^+ trait** -α/-α  or **α^0 trait** --/αα 	
Hb H Disease: Symptomatic Hemolytic and Microcytic anemia Splenomegaly		**Hb H disease --/-α**
Incompatible with Life Hydrops Fetalis		**Hydrops fetalis --/--**

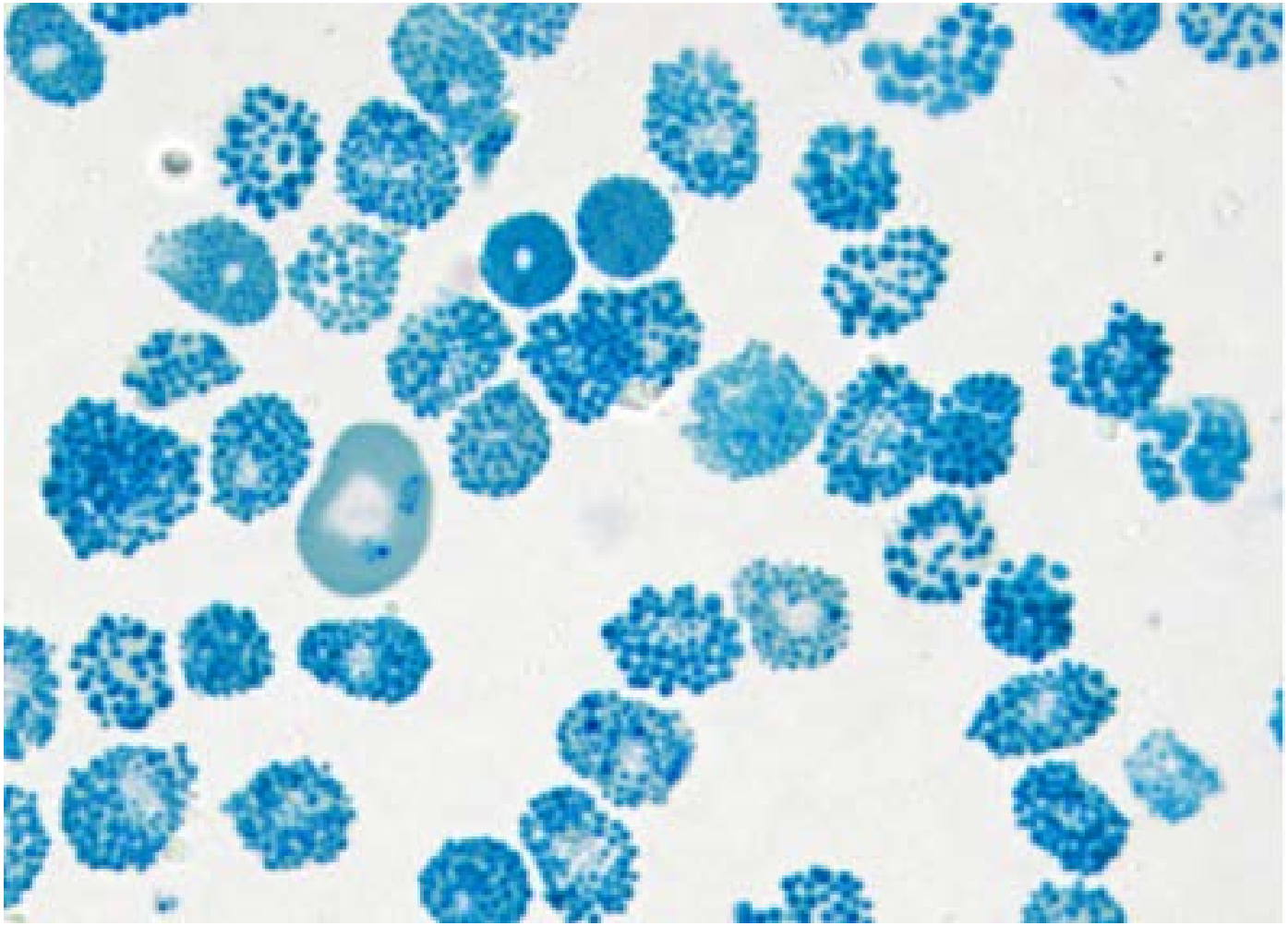
Pathophysiology of α-thalassemias



- excess of γ-like globin chains – Hb Bart's
- excess of β-like globin chains – Hb H

Weatherall and Proven. *Lancet* 2000;355:1169-1175

RBC inclusions in Hb H disease



Additional information on α thalassemia

- **If suspecting α thalassemia carrier state or trait:**
  - Consider compatible ethnicity and clinical picture (no hemolysis, family history of HbH or hydrops)
  - **Rule out the following conditions:**
    - Iron deficiency
    - β thalassemia trait
  - Newborn screening: may show Hb Bart's or HbH
  - Adults: confirmed if positive for HbH inclusions in peripheral blood or confirm with genetic testing for deletions

- **Unusual α thalassemias:**

  <u>α thalassemia-intellectual disability syndromes</u>
  - ATR-16 syndrome : large deletions in α-globin genes on chromosome 16
  - ATR-X syndrome: mutations in ATRX gene (chromatin-associated protein)

  <u>α thalassemia associated with myeloid malignancy (ATMDS)</u>
  - acquired α thalassemia mostly in MDS, very rarely MPN or AML
  - ATRX mutation with low MCV/MCH; HbH inclusions can be present

Treatment for α thalassemias

- **Hb Bart's hydrops fetalis (--/--)**
  - Intrauterine transfusions followed by chronic transfusions and chelation
  - screening, genetic counseling in high risk populations
  - hematopoietic cell transplantation has been done

- **HbH disease (α-/--)**
  - Splenomegaly may lead to hypersplenism
  - Hemolytic crises →RBC transfusions +/-iron chelation
  - Complications: gallstones, leg ulcers

- **Milder α thalassemias (α-/α- or αα/--)**
  - genetic counseling
  - avoid unnecessary iron supplementation

ABIM Hematology exam blueprint

- **Thalassemias**
  - β-thalassemia
  - α-thalassemia
  - Hemoglobin E disorders

- **Sickle cell disorders**
  - Sickle cell trait
  - Sickle cell anemia (hemoglobin SS disease)
  - Hemoglobin SC disease and C hemoglobinopathy
  - Sickle cell-β^0 and sickle cell-β^+ thalassemias

- **Non-sickle hemoglobinopathies**

- **Educational resources**

Hemoglobin E

- **Thalassemic hemoglobinopathy**
  - amino acid substitution *HBB* p.Glu26Lys
  - decreased β^E-mRNA production
  - precipitation of α-globin chains in cytoplasm of erythroid precursors and RBCs
  - increased oxidant stress

- **2nd most prevalent Hb variant in the world**
  - 30 million worldwide with > 80% in Southeast Asia

Hemoglobin E disorders

Condition	Genotype	Hb EP	Clinical features
Hb E trait	β^A/β^E	HbE 30%	Normal or low MCV
Hb E disease	β^E/β^E	HbE 90%	**Mild** microcytic anemia
Hb E/β thal **(Very common in SE Asia)**	β^E/β^0 or β^E/β^+	HbE 40-85%, **HbF 10-60%**	**Moderate to severe** microcytic anemia, ineffective erythropoiesis, iron overload
Hb SE disease	β^S/β^E	HBE 30% HbS 65%	**Mild sickling disorder**, similar to HbS/β^+ thalassemia

ABIM Hematology exam blueprint

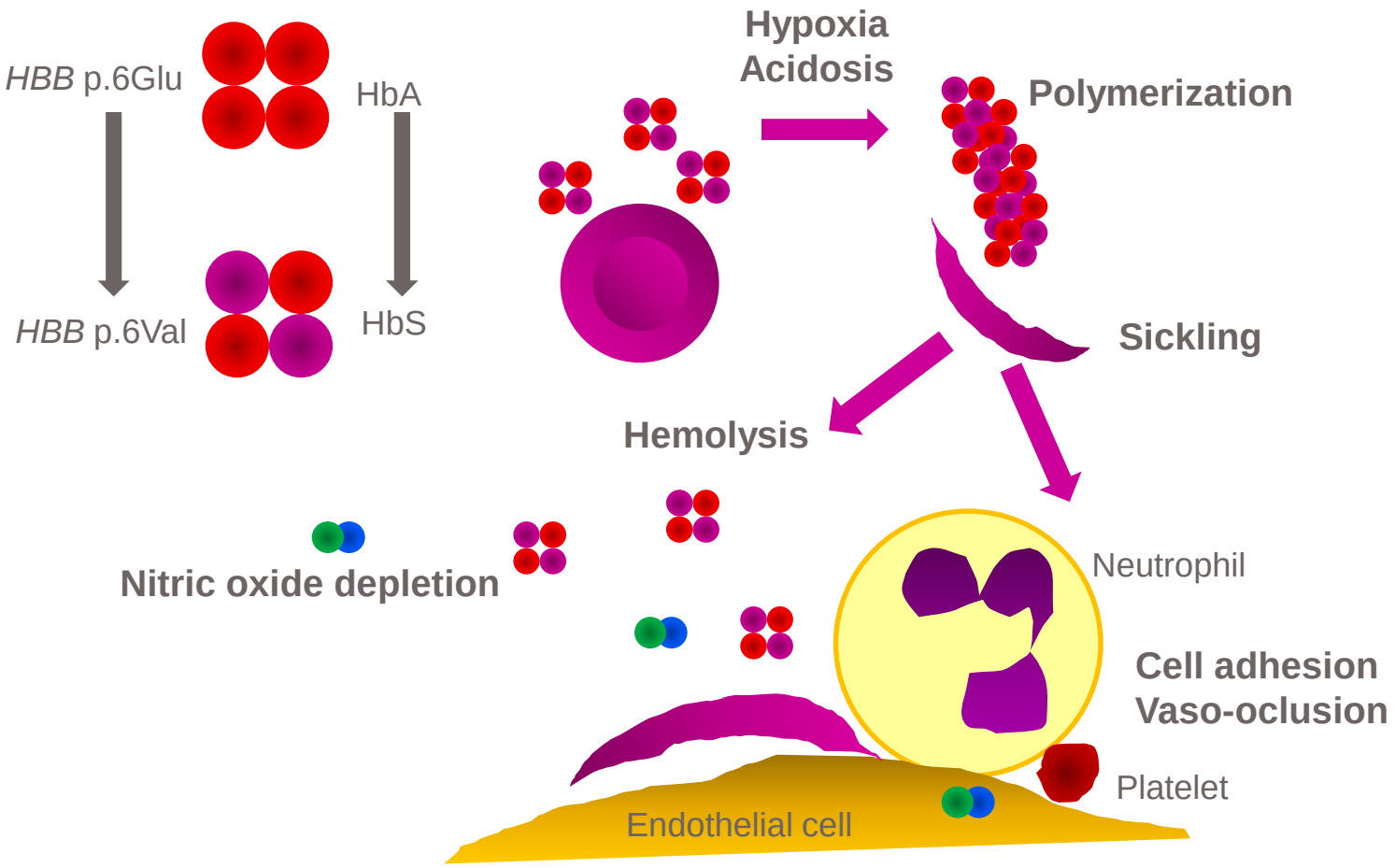
- Thalassemias
  - β-thalassemia
  - α-thalassemia
  - Hemoglobin E disorders

- **Sickle cell disorders**
  - Sickle cell trait
  - Sickle cell anemia (hemoglobin SS disease)
  - Hemoglobin SC disease and C hemoglobinopathy
  - Sickle cell-β^0 and sickle cell-β^+ thalassemias

- Non-sickle hemoglobinopathies

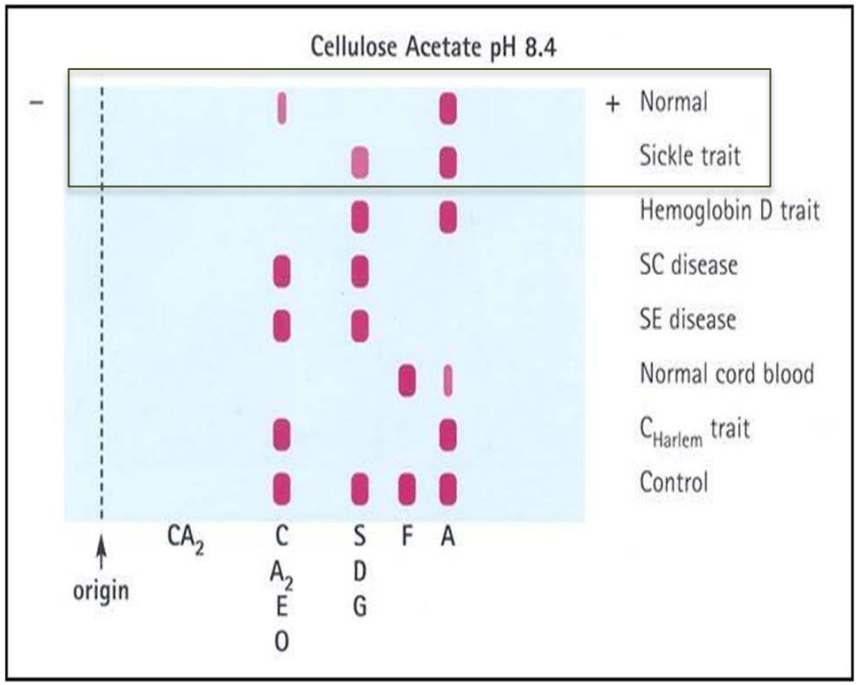
- Educational resources

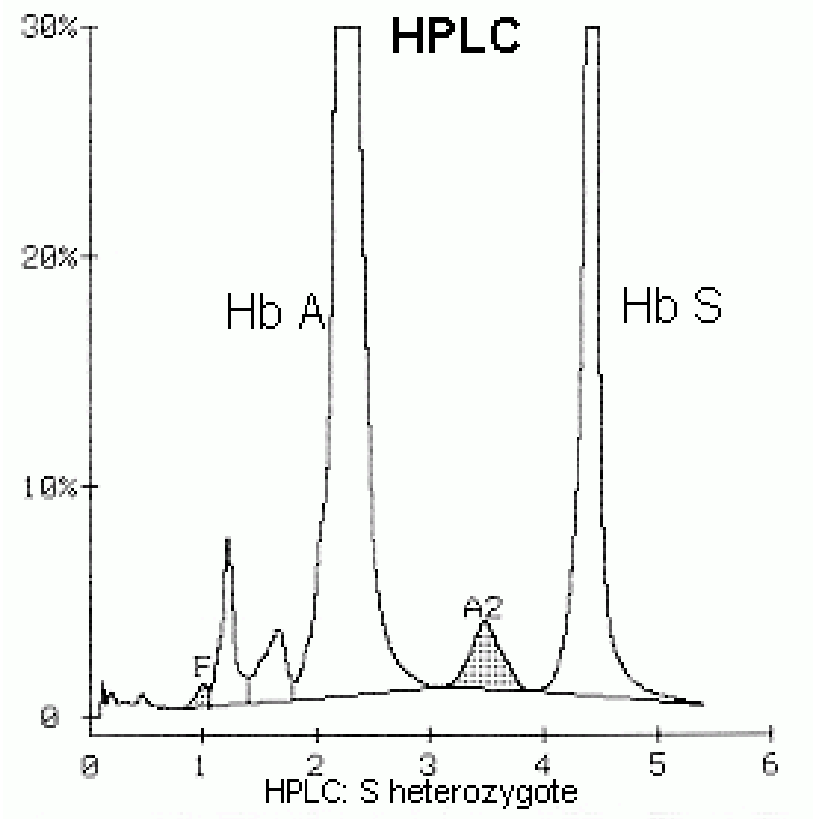
Pathophysiology of sickle cell disease (SCD)



Laboratory diagnosis

- **Hemoglobin electrophoresis**
  - cellulose acetate (alkaline)
  - citrate agar (acidic)
- **High performance liquid chromatography (HPLC)**
  - currently most common test
- **Molecular biology**
  - PCR, gene sequencing





Sickling syndromes

Table 1. Genotypes of Sickling Syndromes and Their Relative Severities

Genotype	Severity	Characteristics
HbSS	Severe	Most common form
HbSβ^0	Severe	Clinically indistinguishable from HbSS[6]
HbSO-Arab	Severe	Relatively rare[6]
HbSD-Punjab	Severe	Mostly in northern India[6]
HbSC-Harlem	Severe	Migrates like HbSC, but rare double β-globin mutation[7]
HbCS-Antilles	Severe	Rare double β-globin mutation[8]
HbSC	Moderate	25% of SCD[9]
HbSβ+, Mediterranean	Moderate	5%–16% HbA[6]
HbAS-Oman	Moderate	Dominant rare double β-globin mutation[10]
HbSβ+, African	Mild	16%–30% HbA[6]
HbSE	Mild	HbE found mostly in Southeast Asia[11]
HbS-HPFH	Very mild	Large deletions in β-globin gene complex; > 30% HbF[6]

HbA = hemoglobin A; HbE = hemoglobin E; HbF = fetal hemoglobin; HbS-HPFH = HbS and gene deletion HPFH; HbSC = heterozygous hemoglobin SC; HbSS = homozygous hemoglobin SS; HbSβ^0 = hemoglobin S-β thalassemia^0; HbSβ+ = hemoglobin S-β thalassemia+; SCD = sickle cell disease.

Vivien A. Sheehan. Hematology-Oncology 12:1, 2-15

Sickle cell trait

- HbAS → 35-40% HbS and 55-60% HbA, no anemia

Clinical manifestations

- Renal disease:
  - Hematuria due to renal papillary necrosis
  - Hyposthenuria
  - CKD
  - UTI
  - Renal medullary carcinoma
- Splenic infarction or sequestration
  (high altitude / scuba diving / dehydration)
- Exertional sudden death / rhabdomyolysis
- Higher risk of PE (OR 3.9)
- Traumatic hyphema may lead to acute glaucoma

Tsaras et al. *Am J Med.* 2009;122(6):507-512.

Hemoglobin SC disease

Clinical manifestations

- CBC:
  - Hemolytic anemia or compensated hemolytic state
  - Sickled cells and HbC crystals

- Milder disease; 30% may have frequent VOC
- Splenomegaly frequent – may have mild thrombocytopenia due to hypersplenism
- Higher incidence of AVN and retinopathy

Question

A healthy African immigrant woman with sickle cell trait brings her 19 and 21-year old sons by the same father for evaluation. Neither has ever had a blood transfusion. You find on hemoglobin HPLC that the younger son has a report of $ASFA_2$ and the older $SAFA_2$. You suspect:

A. Both sons have sickle cell trait
B. One son has sickle cell trait and the other has sickle cell anemia with α-thalassemia
C. One has sickle cell trait and the other has sickle-β-thalassemia
D. Lab error in reporting S and A out of order for in the older son
E. Incongruent paternity

Sickle cell disease (SCD)

- Acute manifestations
  - Vaso-occlusive crisis
  - Acute chest syndrome
  - Stroke (isch/hemorrh)
  - Sequestration (hepatic/splenic)
  - Acute intrahepatic cholestasis
  - Aplastic crisis
  - Priapism

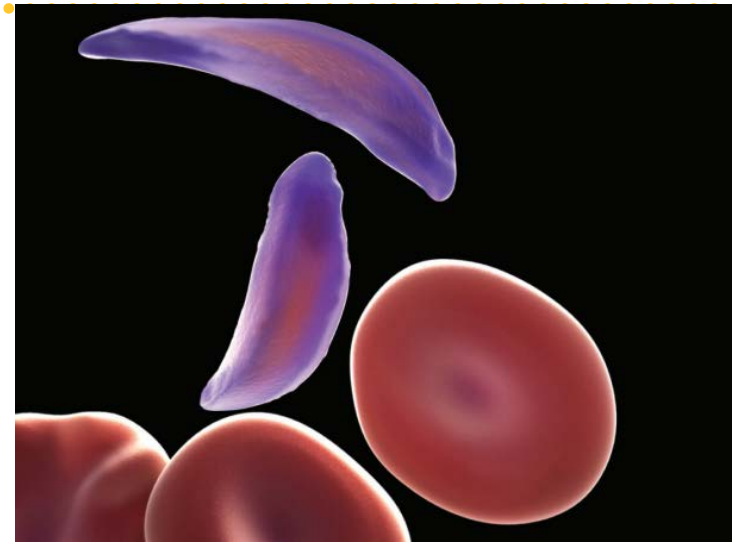


Image courtesy of National Institute of Health

Sickle cell disease (SCD)

- Chronic complications and end-organ damage
  - Retinopathy
  - Heart failure
  - Pulmonary hypertension
  - Gallstones
  - Hypersplenism/Asplenia
  - Avascular necrosis
  - Osteopenia/osteoporosis
  - CKD
  - Recurrent or stuttering priapism
  - Leg ulcers / osteomyelitis

Image courtesy of National Institute of Health

Question

A 22-yo F with history of sickle cell anemia (HbSS) presents to the ED with severe chest pain and shortness of breath. She has copious sputum production, severe pain and low-grade fever. CXR reveals a RLL infiltrate. She is also hypoxic. She is started on broad spectrum antibiotics, IVF and a morphine PCA. She receives 2 units of packed RBCs. Despite these interventions, she remains in respiratory distress.

What additional therapy should be initiated at this time?

A. BiPAP

B. Albuterol

C. Hydroxyurea

D. RBC exchange

E. Sildenafil

Acute chest syndrome (ACS)

- Leading cause of death and 2nd most common cause of admission in adult SCD patients
- Diagnosis:
  - Fever,
  - Respiratory sx (dyspnea/cough/sputum)
  - New infiltrate on CXR
  - ±Hypoxia
- Triggers:
  - Infection (mostly children)
  - in-situ thrombosis
  - fat emboli (more frequent in adults)

ST Miller. How I treat acute chest syndrome in children with sickle cell disease. Blood 2011; 117(20)

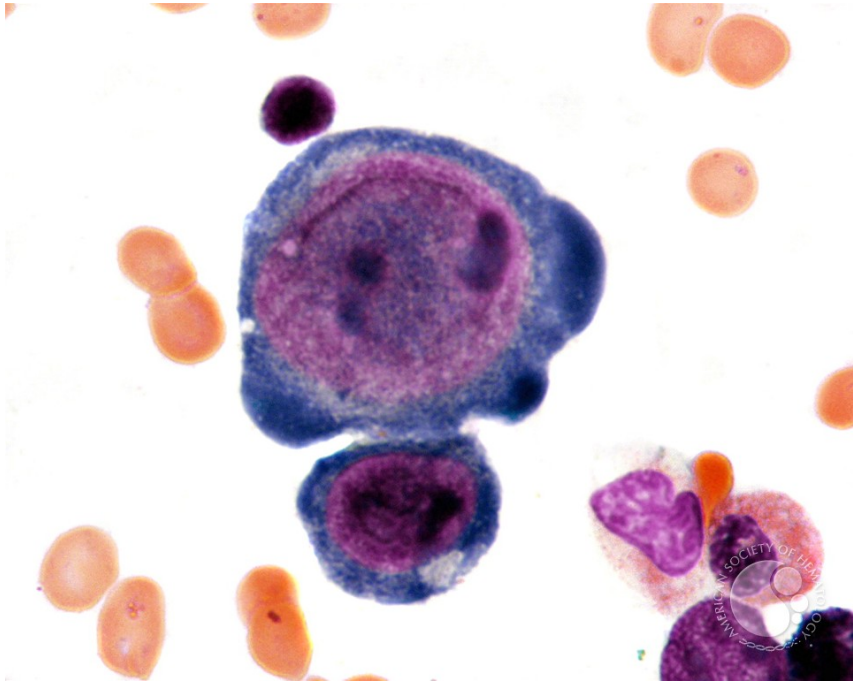
VOC and ACS management

- VOC:
  - Aggressive analgesia
  - Appropriate hydration
  - Check for triggers (infection, dehydration, acidosis)
- ACS → also add:
  - Empiric broad-spectrum antibiotics
  - Supplemental oxygen if SpO2<92%
  - Incentive spirometer, bronchodilators PRN
  - **Simple or exchange red cell transfusions**
- **DISCUSS STARTING HYDROXYUREA!**

ST Miller. How I treat acute chest syndrome in children with sickle cell disease. Blood 2011; 117(20)

Question

A 17 yo F with sickle cell anemia presents with profound fatigue and weakness. Her labs show Hb 4.3 g/dl (baseline 7.5 g/dl), MCV 84fL, and retic 1%. Her bone marrow core biopsy shows:



What is the most likely cause of her severe anemia?

A. Splenic sequestration
B. Hyperhemolysis syndrome
C. Iron deficiency
D. Parvovirus infection
E. Folate deficiency

Aplastic crisis

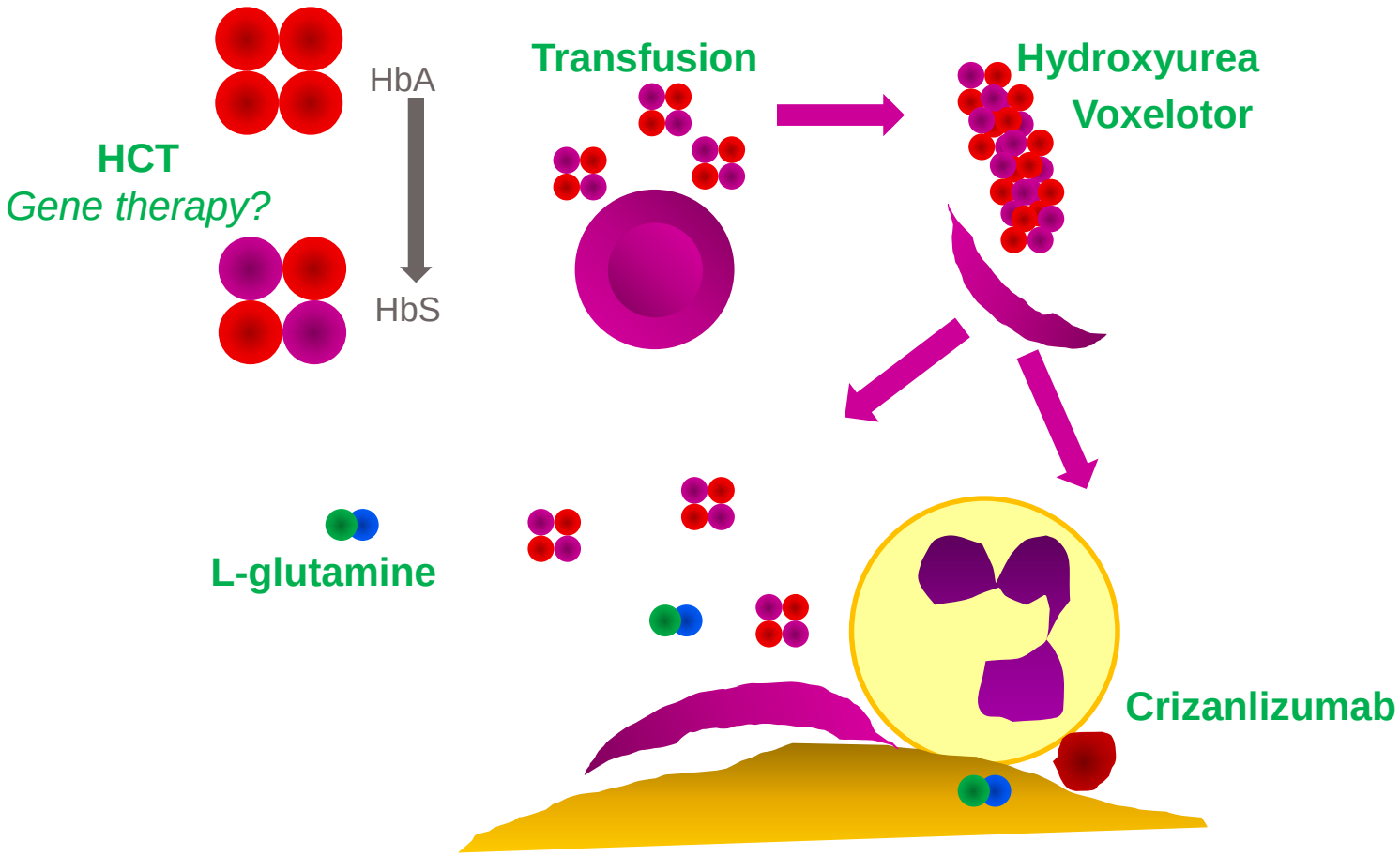
- Cause: parvovirus B19 infection
- May happen in ANY chronic hemolytic anemia
- Diagnosis:
  - Anemia with **reticulocytopenia**
  - Marrow: giant **proerythroblasts** with viral inclusions
  - **PCR+ for parvovirus** (serology is not useful)

- Management: transfusions for support; avoid Hb overcorrection

ST Miller. How I treat acute chest syndrome in children with sickle cell disease. Blood 2011; 117(20)

Treatment of sickle cell disease (SCD)

Children<5y: penicillin; All: folate supplementation



Hydroxyurea

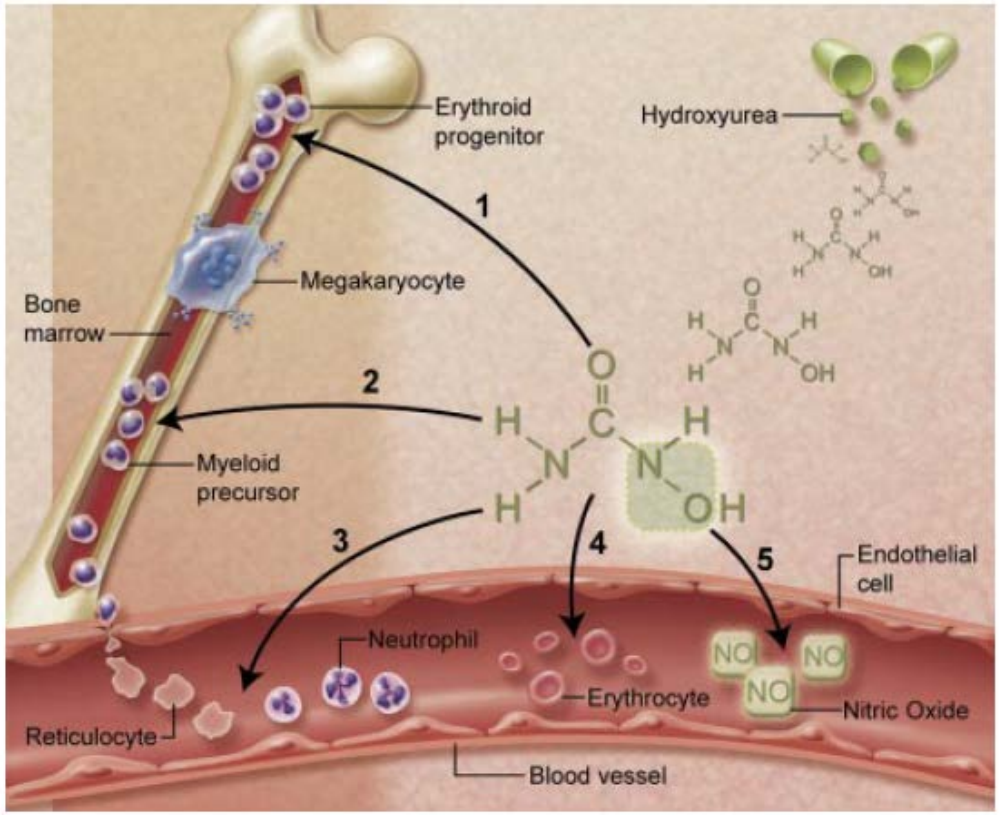
Mechanisms of action:

1. HbF induction
2. Lower WBC, plt, retic
3. Decrease adhesion
4. Reduce hemolysis, improve RBC hydration, increase MCV
5. Nitric oxide donor

Decreases:

- Mortality
- Frequency of VOC
- Frequency of ACS
- Red cell transfusion

Dose: 15-35mg/kg/day



Charache et a. *N Engl J Med.* 1995;332(20):1317-1322

Russell E. Ware. *Blood* 2010 115:5300-5311;

When should you consider hydroxyurea?

Table 4. Indications for Hydroxyurea in Adult Patients with Sickle Cell Disease

Indication	Strength of Recommendation
SCA with ≥ 3 pain crises per year	Strong
SCA with pain that interferes with ADL and QoL	Strong
History of severe or recurrent ACS	Strong
Chronic kidney disease on epoetin	Weak
HbSβ+ and HbSC with pain that interferes with ADL and QoL; consult sickle cell disease expert	Moderate

ACS = acute chest syndrome; ADL = activities of daily living; QoL = quality of life; SCA = sickle cell anemia.

Vivien A. Sheehan. Hematology-Oncology 12:1, 2-15

Question

A 16-yo F with sickle cell anemia (HbSS) is admitted to the hospital for an acute ischemic stroke. Her baseline hemoglobin is 9 g/dL (Hb S 85-90%). What should be recommended to prevent further cerebral ischemia?

A. Simple transfusion to Hb>10g/dL

B. Simple transfusion to Hb>10g/dL and heparin drip

C. Red cell exchange transfusion to Hb>10g/dL

D. Red cell exchange transfusion to HbS<30%

E. Red cell exchange transfusion to HbS<20%

Question

She receives the RBC exchange transfusion and makes a full neurologic recovery from her acute cerebrovascular infarct.

Which of the following interventions should be recommended upon discharge?

A. Continue red cell exchange

B. Initiate hydroxyurea

C. High dose folic acid (5 mg daily)

D. Simples transfusion to keep Hb>10g/dL

E. Erythropoietin to keep Hb > 10 g/dL

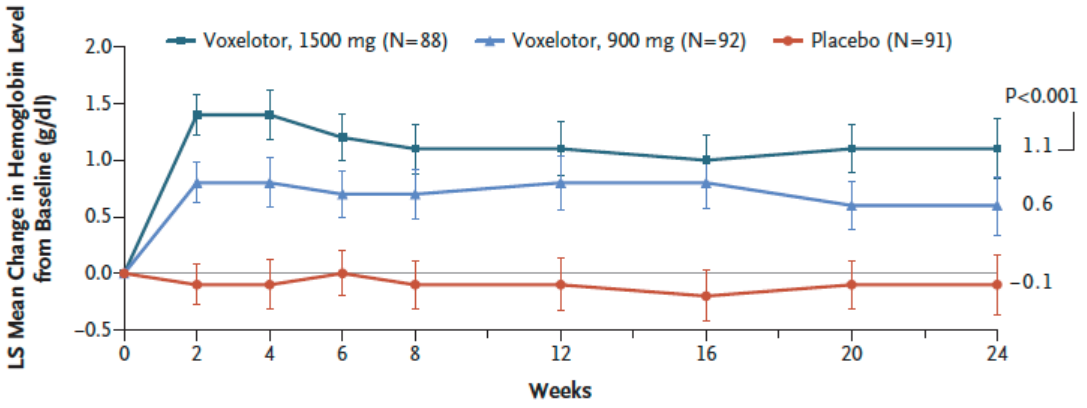
Novel agent to improve anemia in SCD

- Voxelotor (Oxbryta®, previously GBT440)

  Vichinsky et al. *N Engl J Med*. 2019 381(6):509-519. doi:10.1056/NEJMoa1903212

  - small molecule that stabilizes R state binding to amino-terminus of alpha chain of Hb

B **LS Mean Change in Hemoglobin Level from Baseline to Wk 24**



No. at Risk

Voxelotor, 1500 mg	76	78	74	74	71	76	77	72
Voxelotor, 900 mg	82	78	69	74	76	77	73	78
Placebo	82	79	81	74	81	77	78	72

Novel agents to decrease VOC in SCD

L-glutamine (Endari®)

Niihara et al. N Engl J Med 379;3 July 19, 2018

- Increases NADH and improves anti-oxidative defense
- No change in Hb or hemolysis
- Decrease in VOC frequency

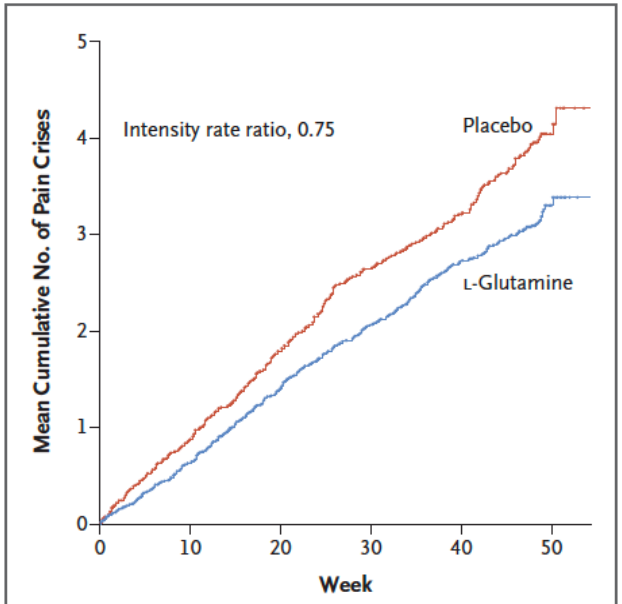


Figure 1. Recurrent Events of Sickle Cell–Related Pain Crisis over Time, According to Trial Group.

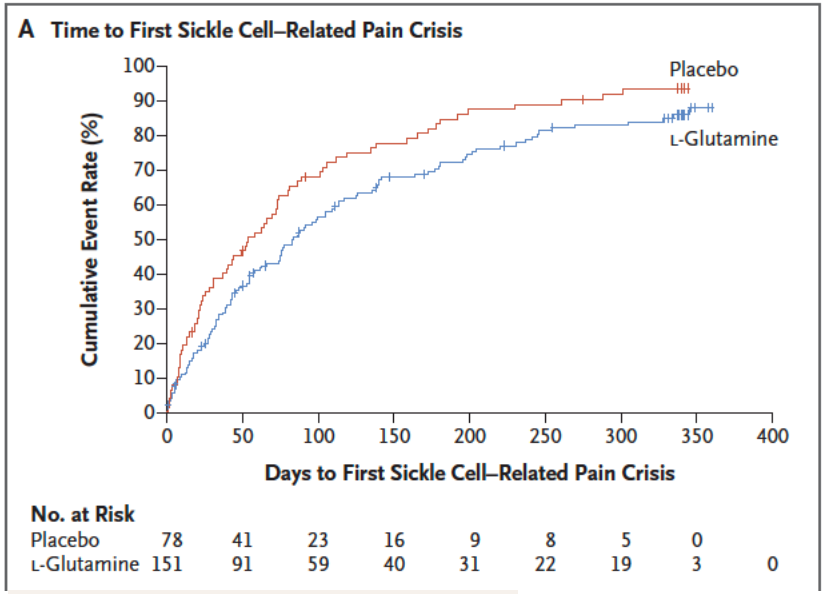


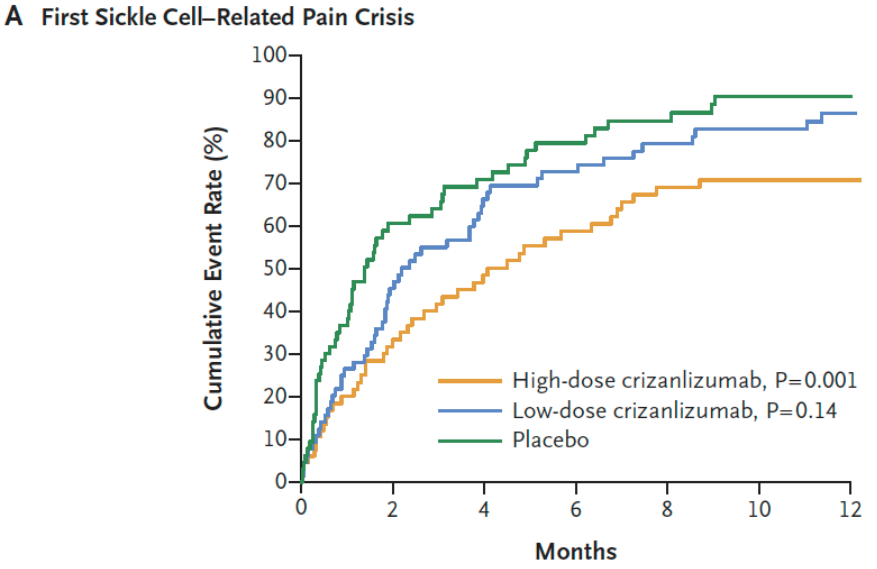
Figure 2. Time to Sickle Cell–Related Pain Crisis.

Novel agents to decrease VOC in SCD

Crizanlizumab (Adakveo®, previously SelG1)

Ataga et al. N Engl J Med 376;5 Feb 2, 2017

- Humanized monoclonal anti-P-selectin antibody that reduces cell adhesion



No. at Risk													
High-dose crizanlizumab	67	49	41	35	30	26	24	20	18	17	16	15	7
Low-dose crizanlizumab	66	47	34	28	21	19	17	15	12	10	10	10	3
Placebo	65	37	23	21	17	13	12	9	8	6	5	4	1

Question

A 32-yo male with sickle cell anemia (HbSS) is diagnosed with acute cholecystitis. He has not been compliant with his daily folic acid and hydroxyurea. He is slated for a cholecystectomy under general anesthesia. CBC shows his baseline hemoglobin level of 8.2 g/dL.

Which of the following should be done preoperatively?

A. Simple RBC transfusion
B. Folic acid
C. Hydroxyurea
D. Enoxaparin
E. RBC exchange transfusion

Question

An 18-year-old woman with HbSS on chronic transfusion therapy for primary stroke prevention develops back pain and fever 6 days after a routine pRBC transfusion. Her pre-transfusion Hb was 8.3 g/dL; current Hb is 5.7 g/dL. Her electrophoresis shows HbA 40%, HbS 60%, HbF 5%, and HbA_2 5%. Direct antiglobulin test (DAT) and screen are negative; LDH level is elevated at 1200 U/L. Absolute reticulocyte count (ARC) is high at 450,000/µL.

What is the most likely diagnosis?

a. Aplastic crisis
b. New alloantibodies
c. Delayed hemolytic transfusion reaction (DHTR)
d. Hyperhemolysis syndrome
e. Splenic sequestration

Novel therapies for sickle cell disease

Gene therapy - investigational

Ribeil et al. N Engl J Med 2017;376:848-55

- Gene addition

  e.g. anti-sickling Hb (HbA^{T87Q})
- Gene editing (zinc-finger nucleases, CRISPR-Cas9)

  e.g. Disruption of BCL11A
- Gene editing and addition
- Base pair editing

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  - α-thalassemia
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  - Sickle cell anemia (hemoglobin SS disease)
  - Hemoglobin SC disease and C hemoglobinopathy
  - Sickle cell-β^0 and sickle cell-β^+ thalassemias

- **Non-sickle hemoglobinopathies**

- **Educational resources**

Hemoglobin Lepore

- **Fusion** of β and δ globin genes
- Decreased synthesis of β-like globins
- **Homozygote: β-thal major phenotype**
  - 8-30% Hb Lepore
  - 70-92% Hb F
- **Heterozygote: β-thal minor (trait) pheno**type

Hemoglobin Constant Spring

- Non-deletional form of α-thalassemia
- Mutation in stop codon of α_2-globin adds 31 additional aminoacids → 1% normal α-globin
- Homozygotes: more severe Hb H disease, but ~normal MCV

Hereditary persistence of HbF (HPFH)

- Clinically silent (e.g. found in blood donation)
- Up-regulation of γ chain synthesis

- Caused by:
  - deletions involving β and δ genes (nearly 100% HbF);
  - point mutations in γ chain promoter (variable HbF);
  - decreased expression of *KLF1*, transcription factor that activates HbF suppressor gene *BCL11A*

- Significantly modifies clinical outcomes when co-inherited with Hb S

Unstable hemoglobin disease

- Congenital chronic non-spherocytic anemia
  - variable severity
  - ± low MCV
- Rare, AD mutations →defective heme binding by globin chains
- Diagnosis:
  - Heinz bodies precipitation in RBCs on isopropanol test
  - About 200 “unstable” Hb variants → DNA sequencing
- Hb Köln most common: anemia, retics (10-25%), splenomegaly
- Treatment: avoid oxidant drugs, RBC transfusions as needed, splenectomy

Hemoglobin M disorders

Hereditary methemoglobinemias:

- Asymptomatic cyanosis, slate grey/brownish skin, no dyspnea or hypoxia
- Autosomal dominant

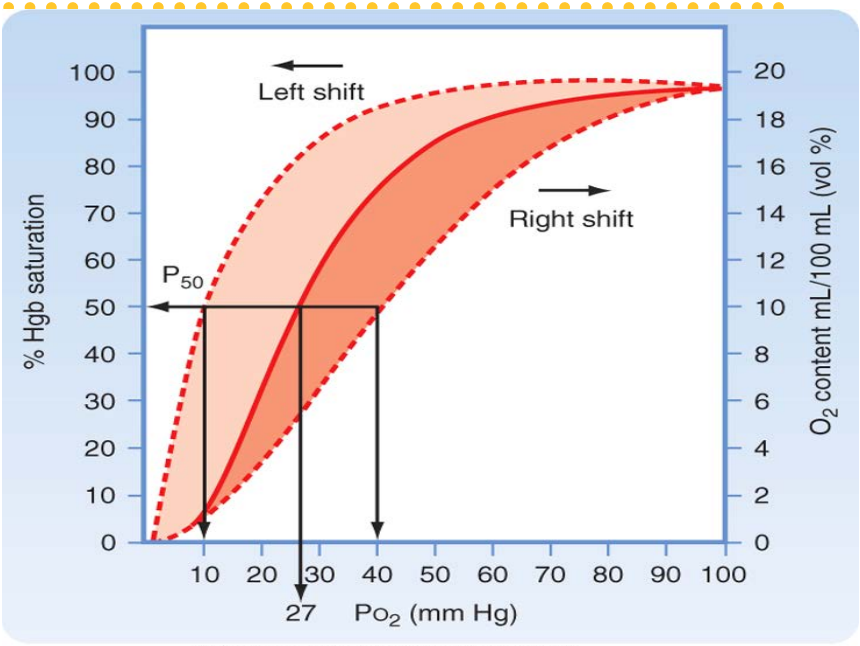
- Amino acid substitution in heme pocket: $Fe^{2+} \rightarrow Fe^{3+}$, cyanosis

- Diagnosis: abnormal SpO2, Hb electrophoresis/spectra, **metHb < 30%**
- No tx needed, cyanosis ***not*** reversible with methylene blue or vitamin C

- Distinguish from other metHbemias (treat with methylene blue)
  - **Toxins:** nitrites, sulfanilamide, dapsone, primaquine, etc.
    - Symptomatic with metHb> 30% (> 50% is lethal!)
  - **Congenital deficiency in cytochrome b5 reductase:** $Fe^{3+} \rightarrow Fe^{2+}$
    - cyanosis improves with methylene blue or vitamin C

Other hemoglobin disorders

- **Hb with high O_2 affinity:**
  - AD, familial **erythrocytosis**,
  - α or β-chains can be affected
  - Diagnosis: low P_{50} (left shifted on O_2 dissociation curve), variant Hb in electrophoresis, DNA sequencing
  - No phlebotomy unless Ht>60%
  - Differential dx: polycythemia vera, secondary polycythemias



- **Hb with low O_2 affinity:**
  - Right shift on O_2 dissociation curve (high P_{50} ~ 30-40 mmHg)
  - Cyanosis, but otherwise asymptomatic (depending on degree of right shift)
  - No treatment required

Educational resources

- NHBLI Evidence-based Management of Sickle Cell Disease- Expert Panel Report (2014)
- Thalassemia International Foundation (TIF) publications www.thalassaemia.org.cy
- American Society of Hematology Self-Assessment Program 6th Ed. (ASH SAP)
- ASH Pocket Guides (download from App store)
- Hematology/Oncology question bank hemeoncquestions.com/
- Hematology-Oncology board review questions www.turner-white.com/brm/bonco.htm

- Special thanks: Drs. Oyebimpe Adesina, Victor Gordeuk, Ravin Garg, and Vivien Sheehan

THANK YOU

General Principles of Radiation Oncology

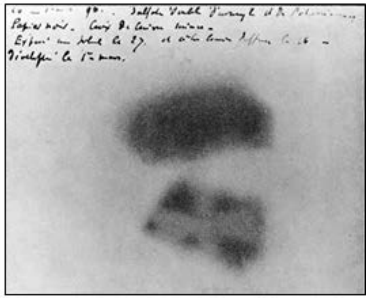
Jonathan Chen, MD, PhD
Assistant Professor
Department of Radiation Oncology
University of Washington / SCCA

Overview

- Basics of radiation therapy
  - History
  - Mechanism
  - Particle types: photons, protons, neutrons, heavy ions
- Definition of common lingo
  - IGRT, IMRT, VMAT, SBRT, SABR, CyberKnife, Gamma Knife
- A few specific clinical points of interest
  - Palliative RT
  - Hypofractionation
  - Protons
- What’s on the frontier
  - Metastatic cancer treatment
  - MR-guided RT
  - FLASH

Radiation Oncology: A Brief History

- **1895** – Röntgen discovers x-rays (Nobel Prize 1901)
- **1896** – First patients with cancer treated with x-rays by Emil Grubbe in Chicago and Victor Despeignes in France
- **1896** – Becquerel discovers natural radioactive decay. Marie and Pierre Curie further characterize radioactive compounds. (All three win Nobel Prize in 1903)
- **1901** – First use of brachytherapy
- **1952** – First “linear accelerator” used for treatment (USA in 1957)
- **1967** – Invention of the Gamma Knife
- **1970s** – Computed Tomography (CT)
- **1980s** – Intensity modulated radiation treatment (IMRT), Proton therapy
- **2000s** – Image-guided RT (IGRT), MR-based RT



Marie Curie (1867-1934)

Radiation Oncology: A Brief History

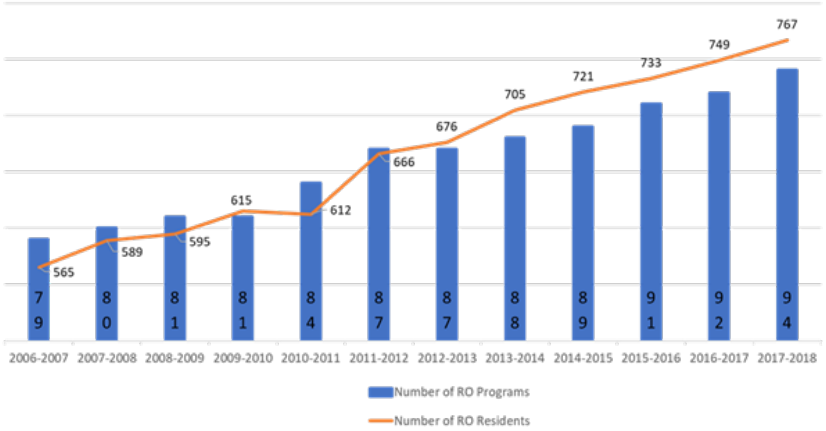
- Cyclotron (Ernest Lawrence, UC Berkeley)
- Linear Accelerator (Henry Kaplan, Stanford)

Radiation Oncology: A Brief History

- Treatment of malignant and non-malignant conditions
  - Tinea capitis
  - Tonsillitis
  - Enlarged thymus
  - Ankylosing spondylitis
  - Acne
  - Peptic ulcers
  - Keloids
  - Heterotopic ossification prophylaxis
  - Graves opthalmopathy
  - Orbital pseudotumor
  - Dupuytren's disease
  - Gynecomastia

Radiation Oncology: A Brief History

- Radiation oncologists initially trained as diagnostic radiologists and then pursued “Therapeutic Radiology” afterwards
- Still under American Board of Radiology, American College of Radiology, etc.
- 1970’s: dedicated radiation therapy residency programs began to proliferate



“Allied Disciplines”

One of the tines in the trident of oncology

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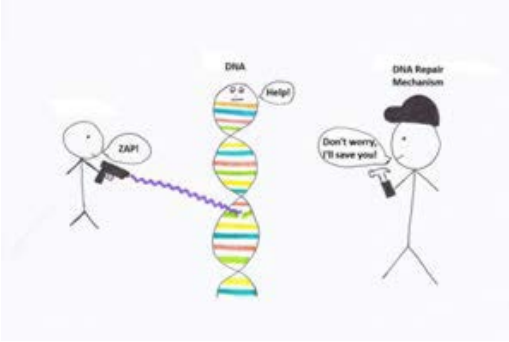
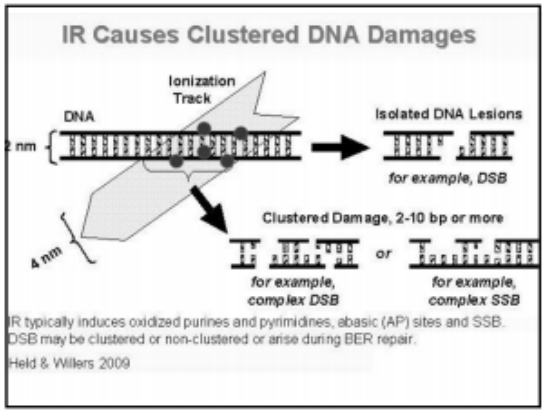
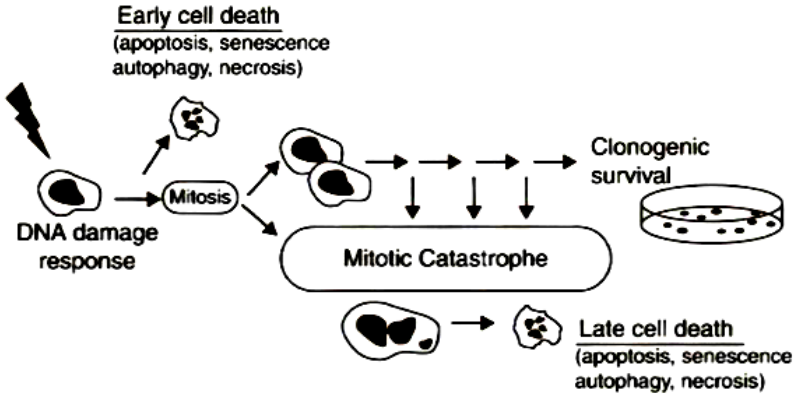
Radiation Biology 101

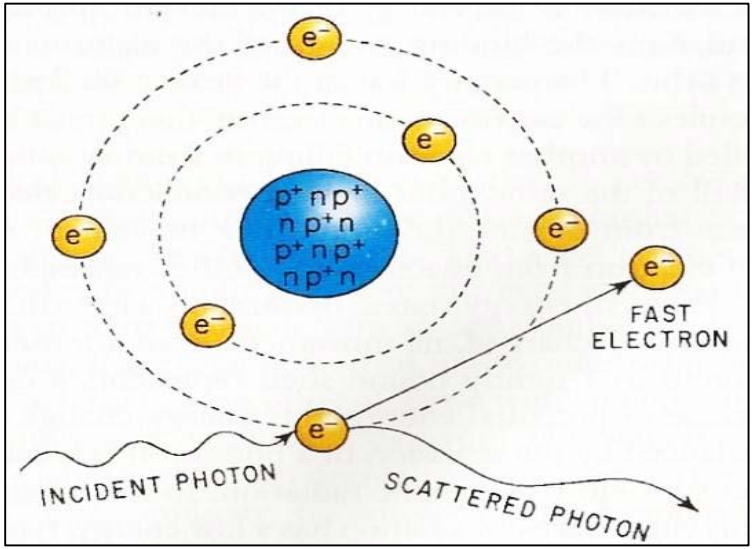


- Radiation treats cancer by directly killing tumor cells
- DNA damage → Mitotic catastrophe
- Preferentially affects rapidly proliferating cells
- Tumor Control Probability based on dose-dependent killing of all cells in a tumor

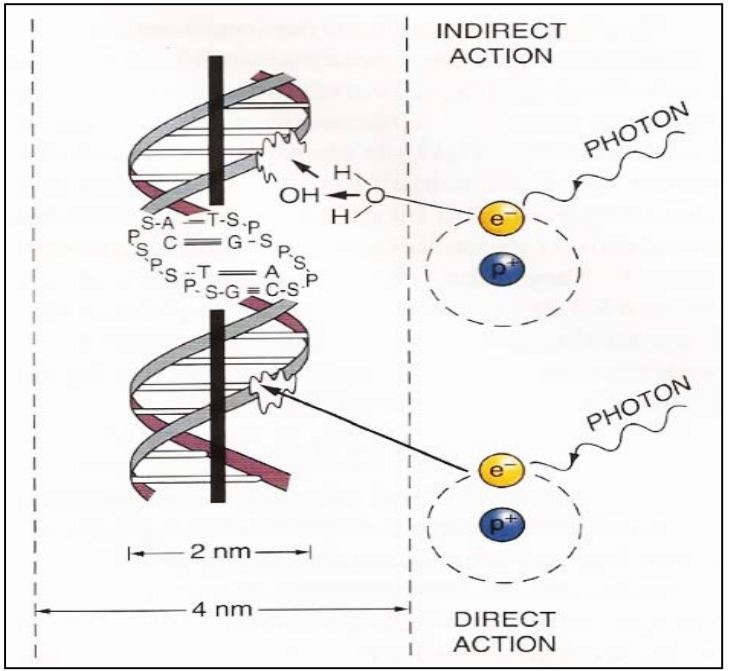




Radiation Oncology: Mechanism



Hall Figure 1.6



Hall Figure 1.8

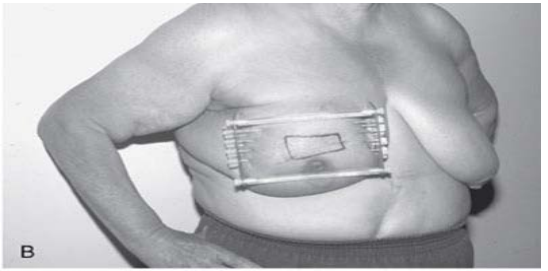
Radiation Oncology: Mechanism

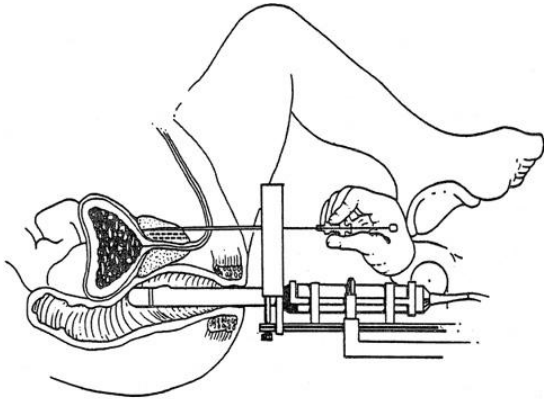
- Radiation’s primary effects have been thought to be mediated by DNA damage leading directly to cell death
- However, other mechanisms may be more important than we originally realized as well...
  - Effects on vasculature, especially tumor vasculature
  - Very high dose or high LET radiation may affect cell membrane integrity and protein structures
  - Modulation of the immune response

Different RT Options and Definition of Common Lingo

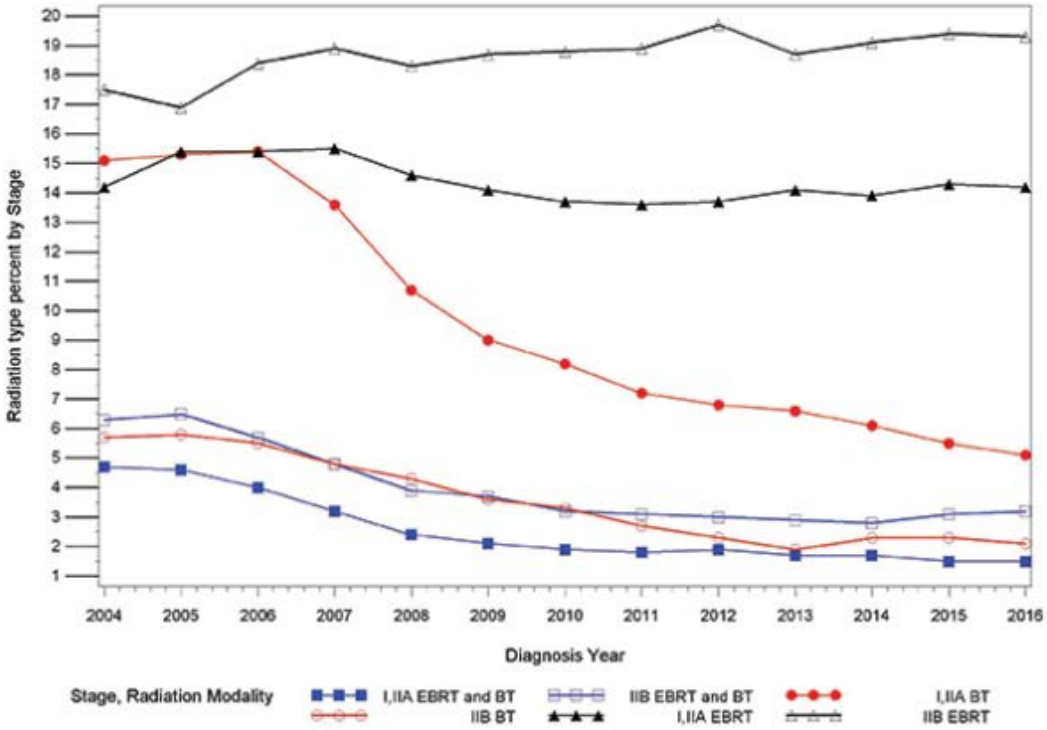
Radiation Oncology: Brachytherapy

- Brachytherapy
  - Low dose rate = < 2 Gy/hr
  - High dose rate = > 12 Gy/hr
  - Pulsed dose rate (uncommon) = 2-12 Gy/hr





Brachytherapy: A Dying Art?



External Beam Radiation Treatment Options

- The linear accelerator or LINAC

Modality	Energies
Photons MV	6, 10, 15, 18
Electrons MeV	6, 9, 12, 16

- 3DCRT, IMRT, IGRT, VMAT, SBRT, SABR, SRS
- Gamma Knife
- Cyberknife
- Tomotherapy

Common RT Terms

3DCRT - 3-D conformal RT

IMRT - intensity modulated RT

VMAT - volumetric modulated arc therapy

IGRT - image-guided RT

SBRT - stereotactic body RT

SABR - stereotactic ablative radiation

SRS - stereotactic radiosurgery

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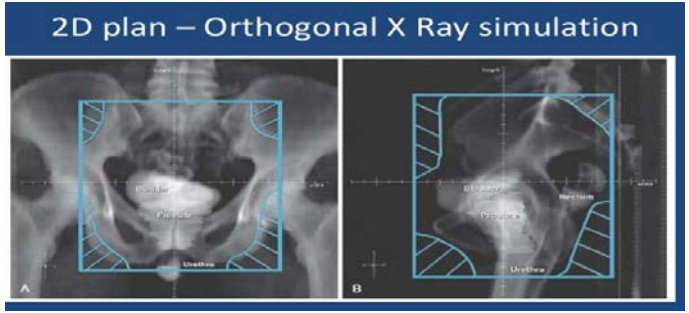

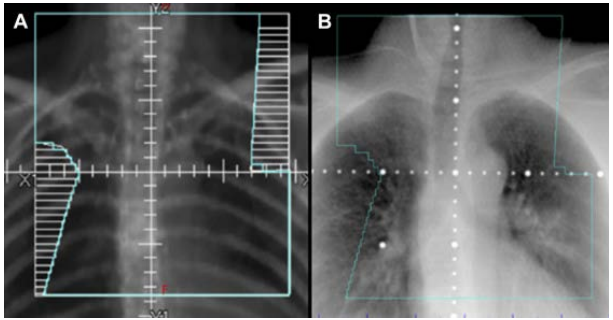

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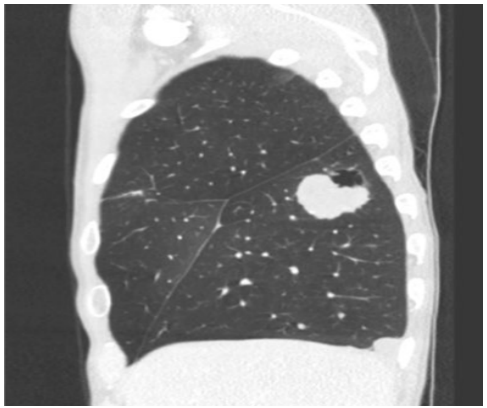

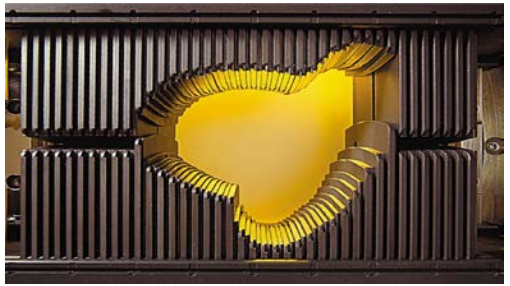

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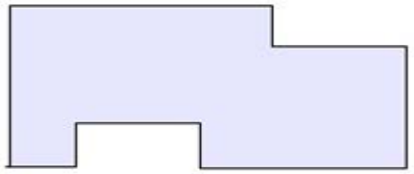

Geometrical Field shaping

With intensity modulation

Common RT Terms

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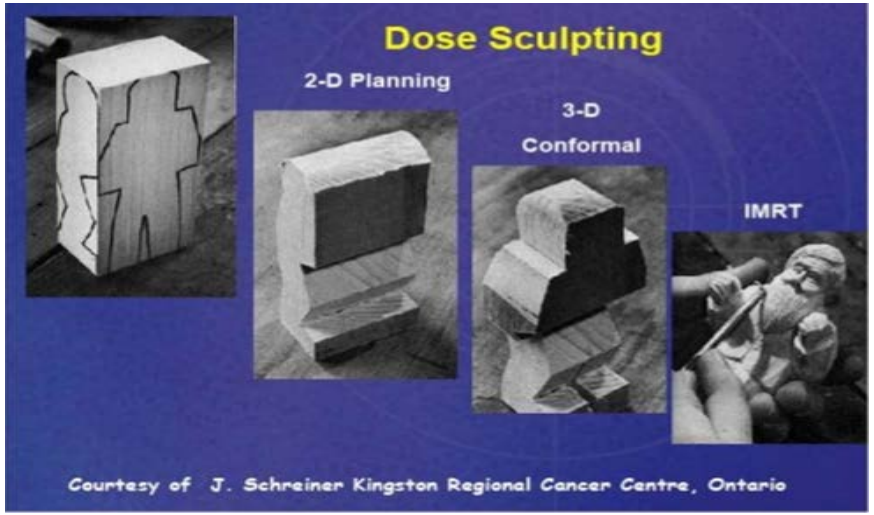

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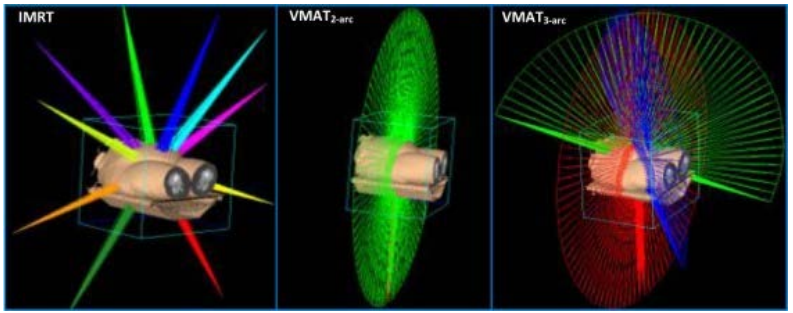

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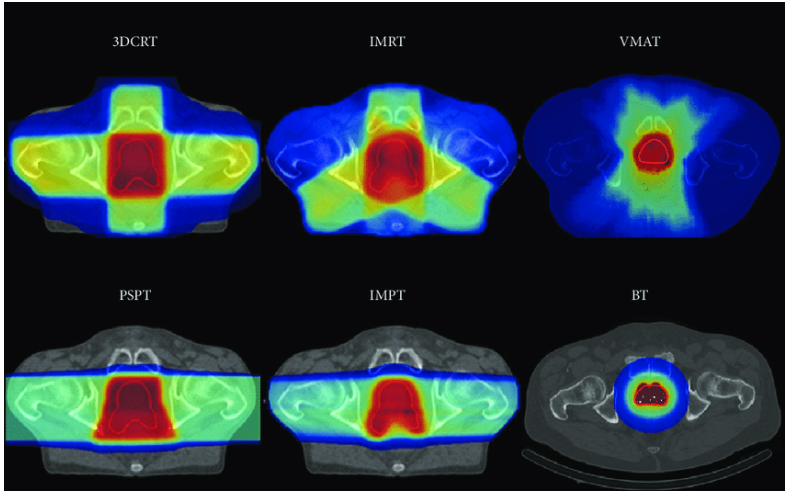

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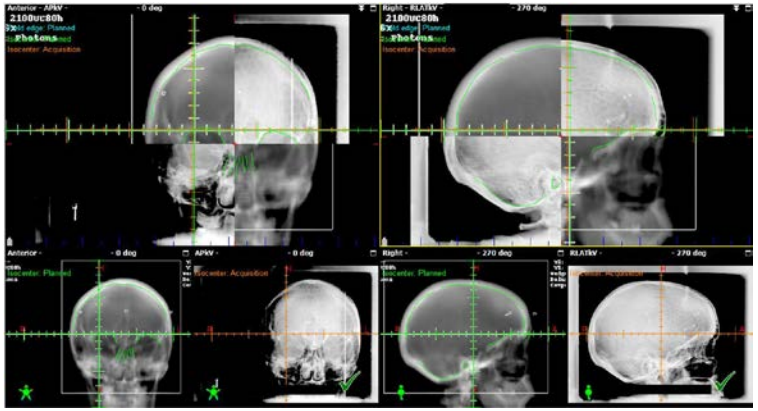

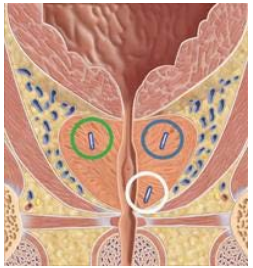

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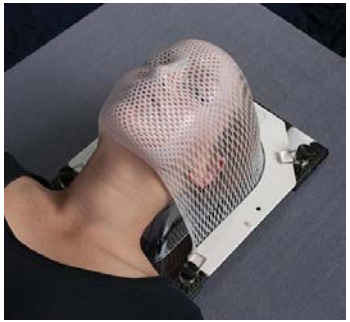
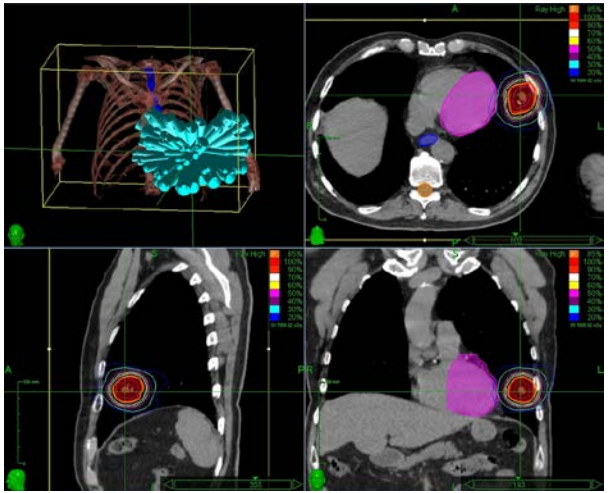
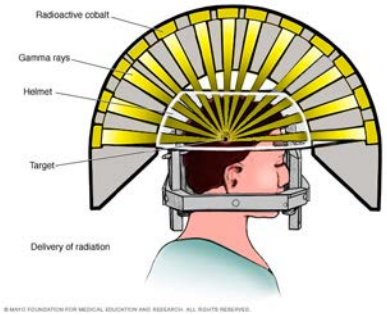
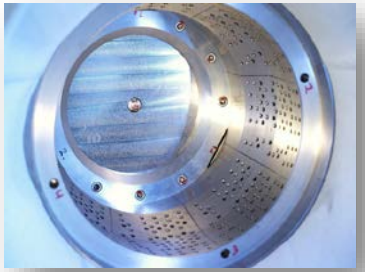




Radiation Treatment Machines: Gamma Knife

- Radiosurgery
  - Single high-dose radiation fraction
  - Very conformal (i.e. tight margins)



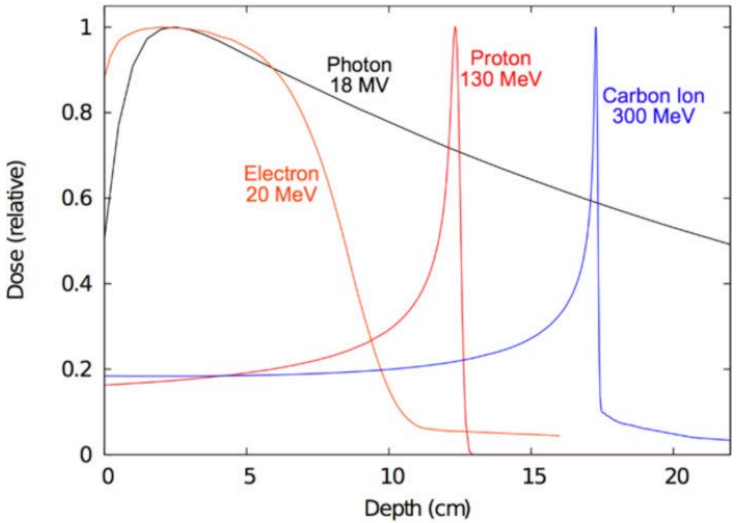


Radiation Treatment Machines: CyberKnife

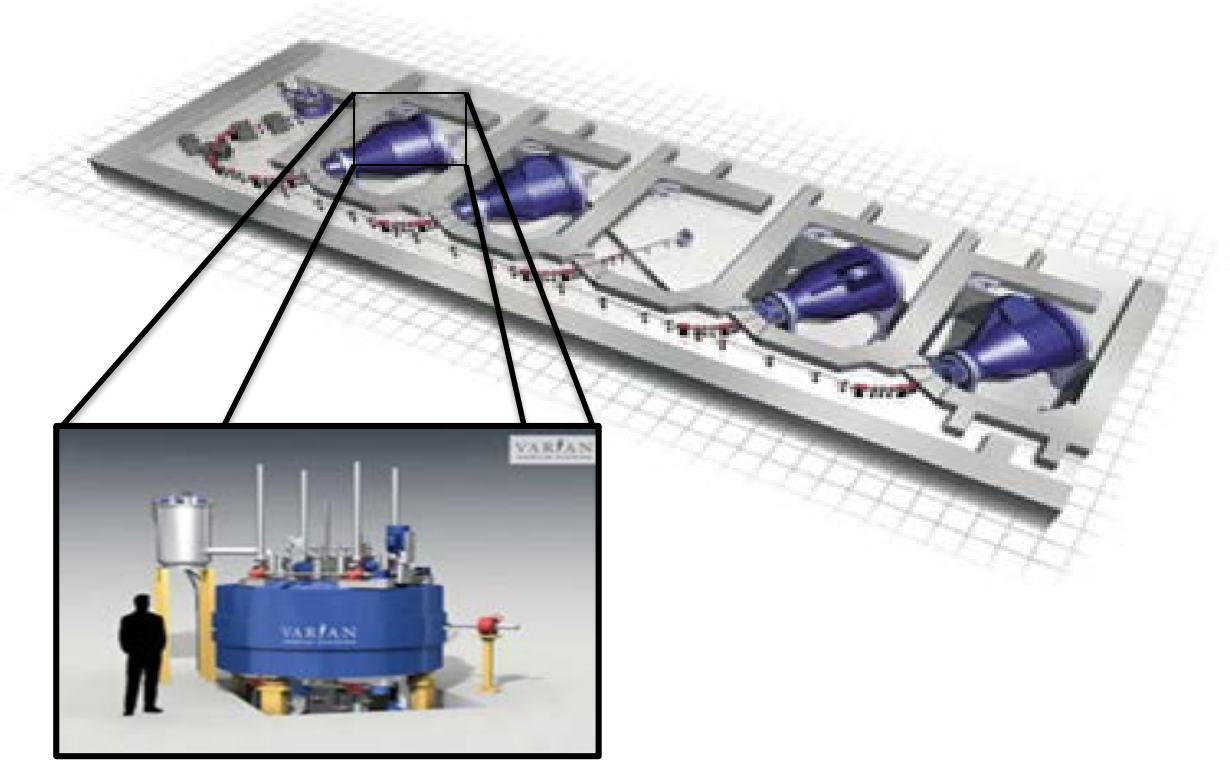
Radiation Treatment Machines: Tomotherapy

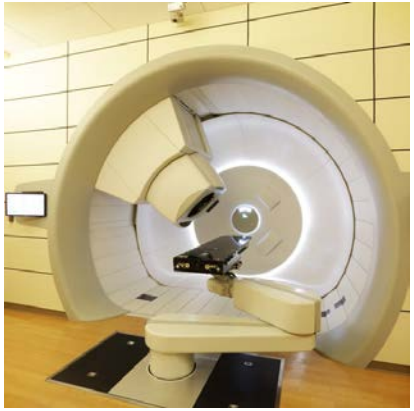
Radiation Oncology: Particle Options

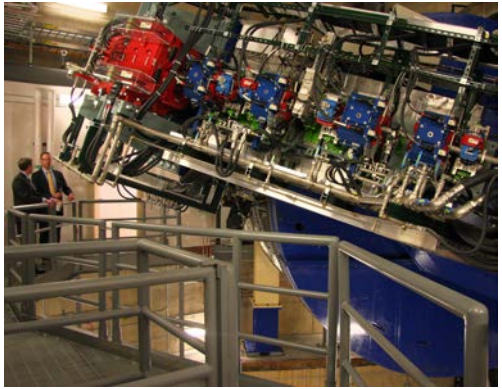
- Particle therapy
  - Photons
  - Electrons
  - Protons
  - Neutrons
  - Heavy ions



Radiation Treatment Machines: Protons

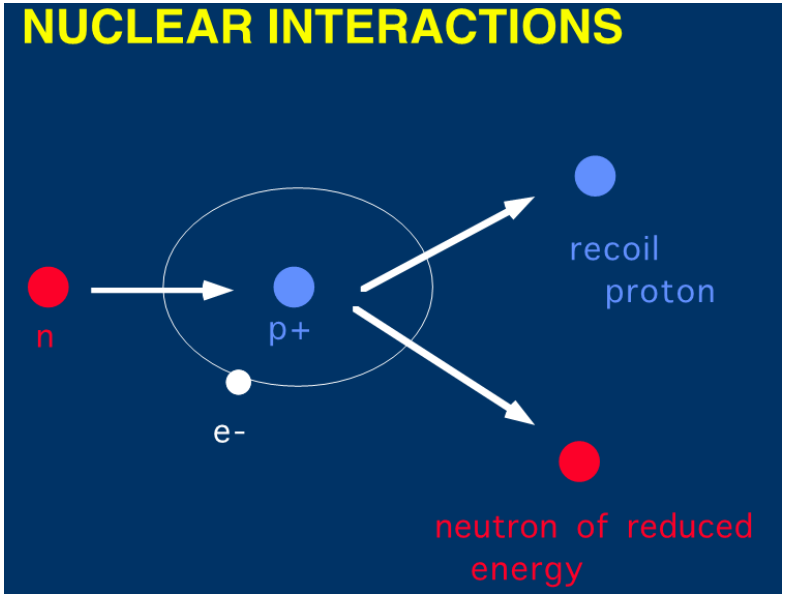






Radiation Treatment Machines: Neutrons

- Potentially lower toxicities
- Better able to kill hypoxic tumor cells
- Cells less able to repair radiation damage
- Less variation in radiosensitivity across cell cycle
- Potentially greater non-traditional anti-cancer mechanisms



A Few Clinical Points of Interest

What is the Deal with Protons?

- Proton radiation is a type of radiation
- FDA approved technology 1988
- Delivers radiation to tumors while reducing radiation exposure to surrounding normal tissues
- Confers a clinical advantage for some patients compared to conventional X-ray (photon) treatment
- Another tool for the radiation oncologist
- Useful only when radiation therapy is indicated

What is the Deal with Protons?

- Unique dose depth profile due to the Bragg peak
- Spread-out Bragg peak used to treat a clinical volume (overlap individual proton beams of variable intensities)

FIGURE 1

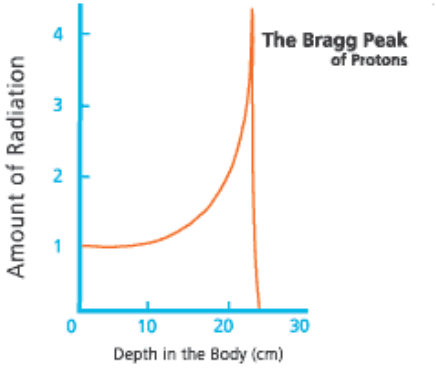
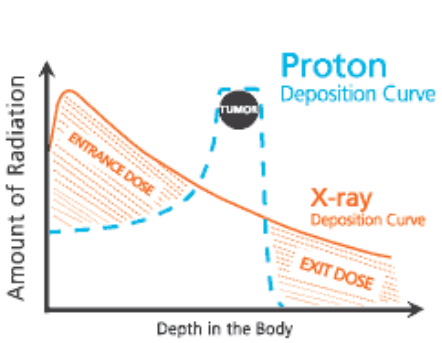
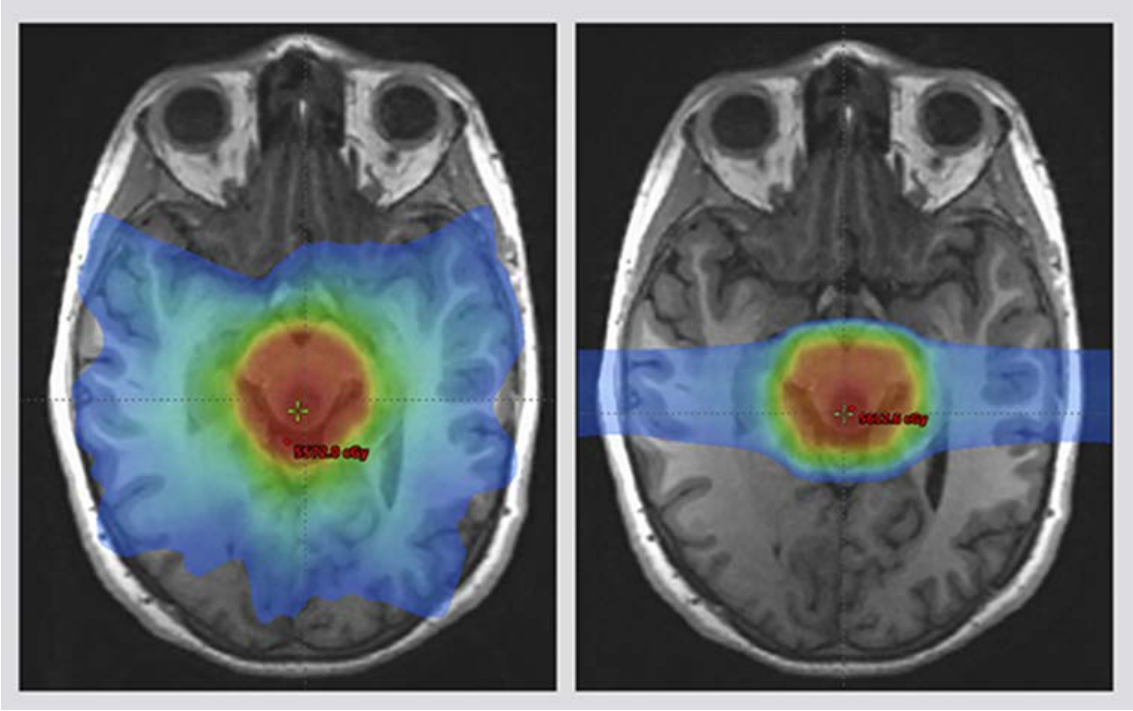


FIGURE 2



Proton Therapy



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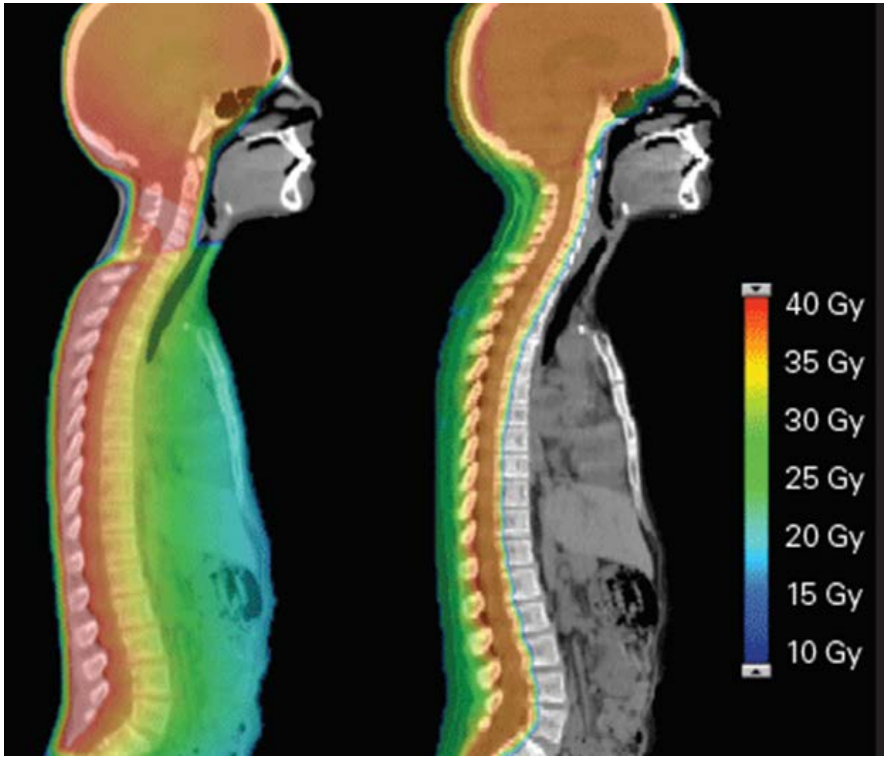

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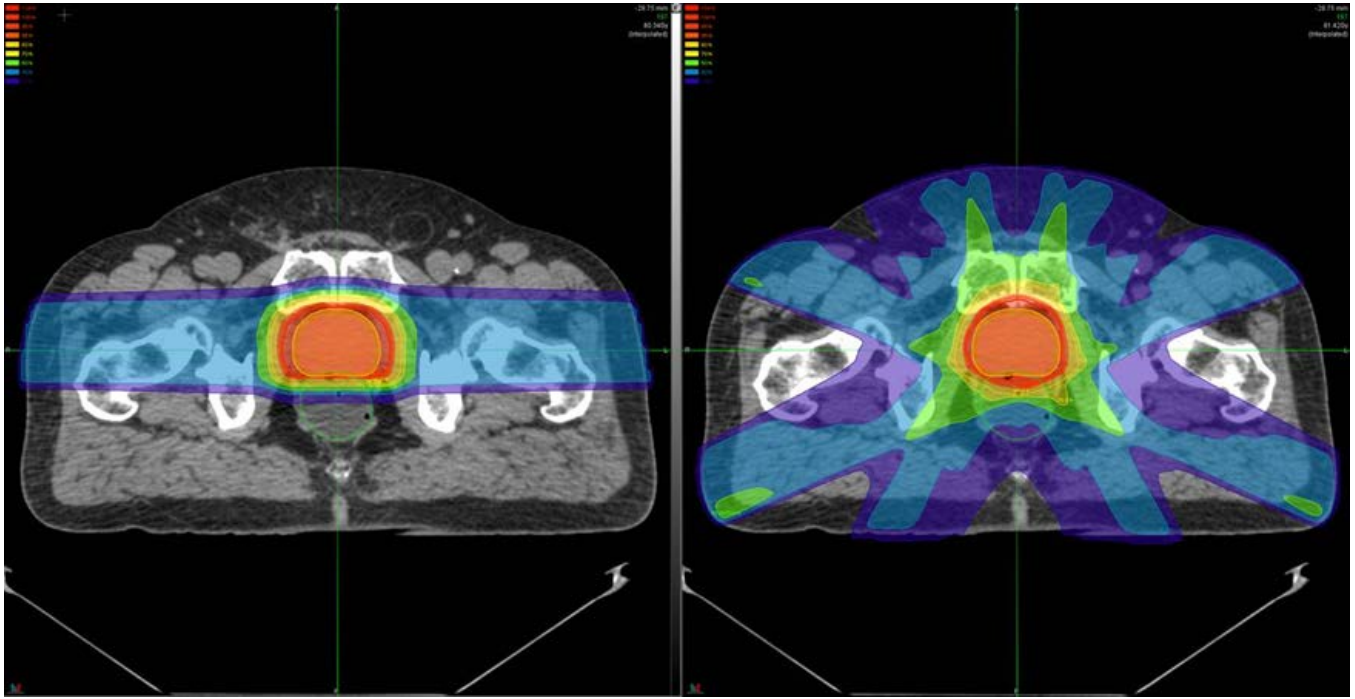


Proton Therapy

Proton Therapy

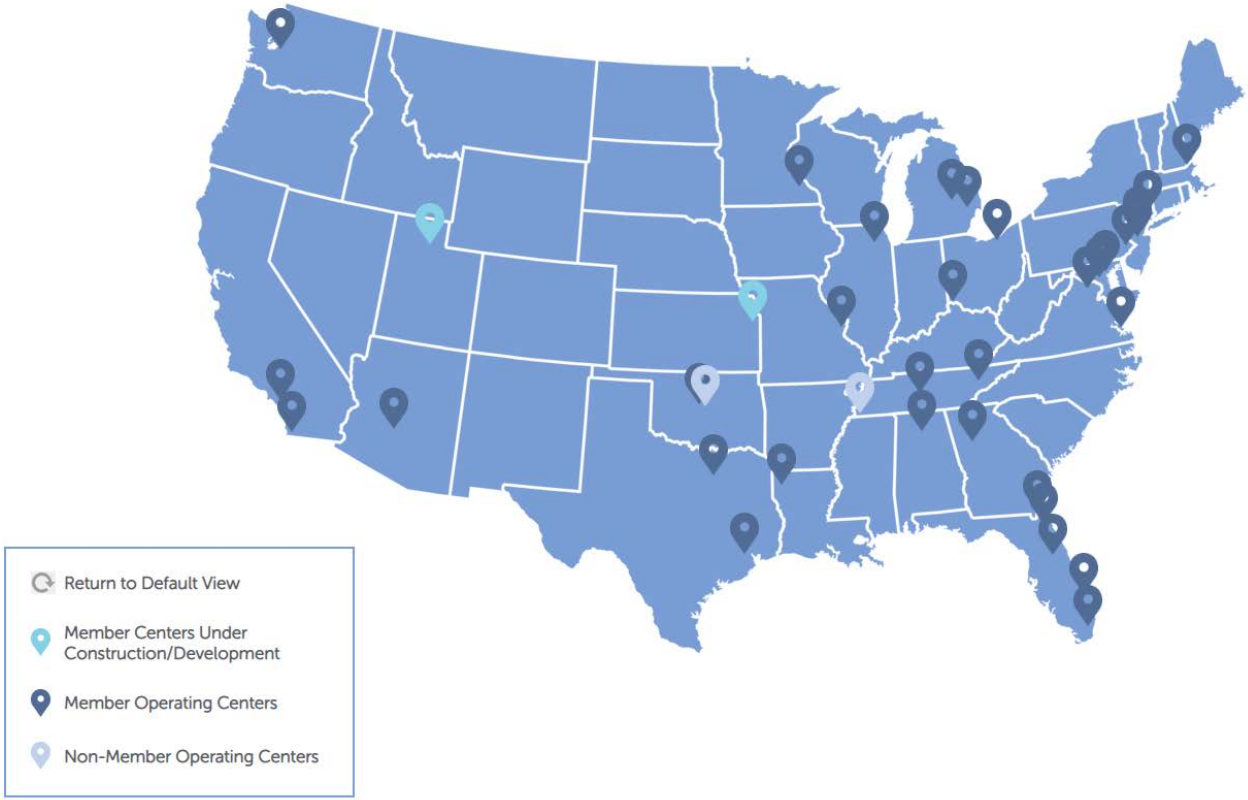
ASTRO Group 1

- Ocular tumors
- Base of skull tumors
- CNS tumors, including spinal tumors near the cord
- HCC
- Pediatric tumors
- Patients with genetic syndromes with RT hypersensitivity (e.g. NF-1, Rb)
- T4 and/or unresectable H&N cancers
- Paranasal sinus tumors
- RP sarcomas
- Re-RT

ASTRO Group 2

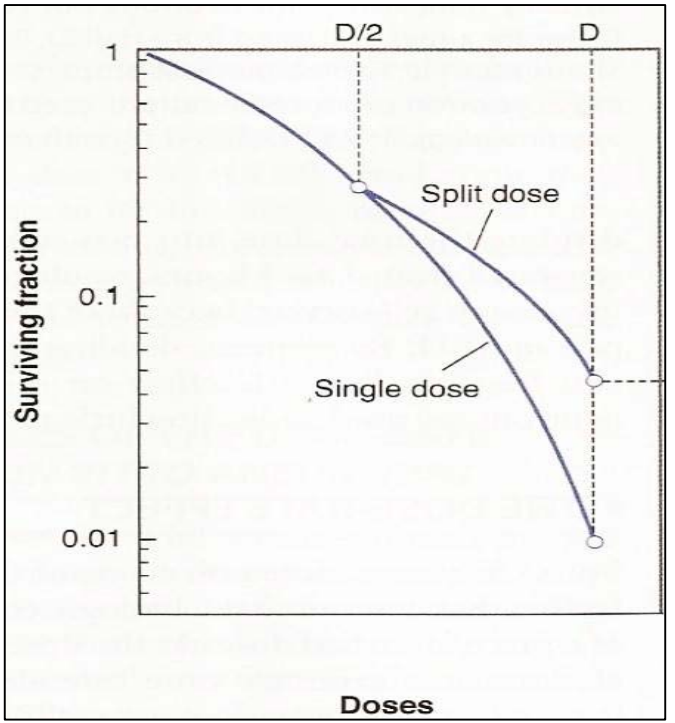
- Other H&N cancers
- Thoracic malignancies
- Abdominal malignancies
- Pelvic malignancies
- Prostate cancer
- Breast cancer

Proton Therapy Centers



Radiation Oncology: Fractionation

- Radiation therapy has traditionally been a “fractionated” treatment course spread over several weeks.
- Takes advantage of differential repair abilities of normal and malignant tissues.



Hall Figure 5.6a

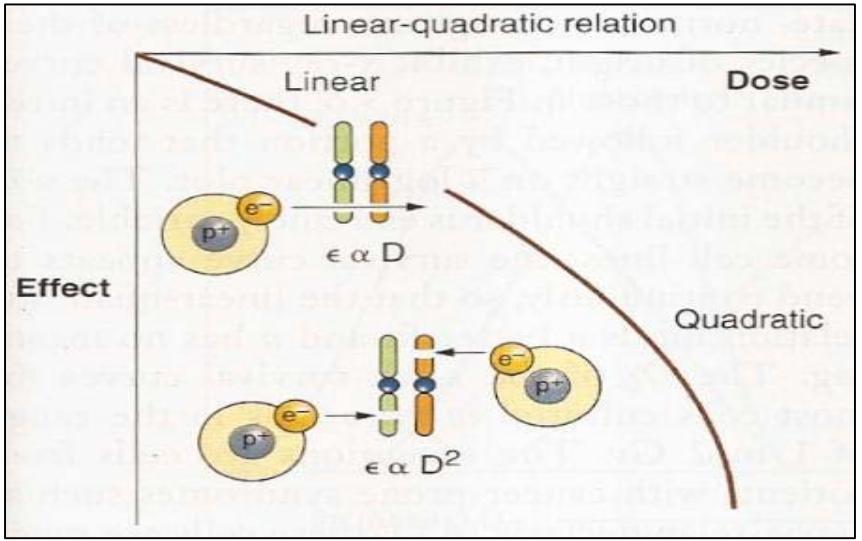
Radiation Oncology: Fractionation

- Regaud and The French Ram
  - A single dose of radiation that is sufficient to sterilize a ram also causes significant skin toxicity
  - If the same dose is delivered in several fractions, the ram is sterilized, but there is no skin toxicity
- 1920's – 1930's
  - Regaud – extended treatment time for uterine cancer improved outcomes
  - Coutard – fractionated treatment for head and neck cancer reduced toxicity with better outcomes

Hall Figure 23.1

Radiation Oncology: Fractionation

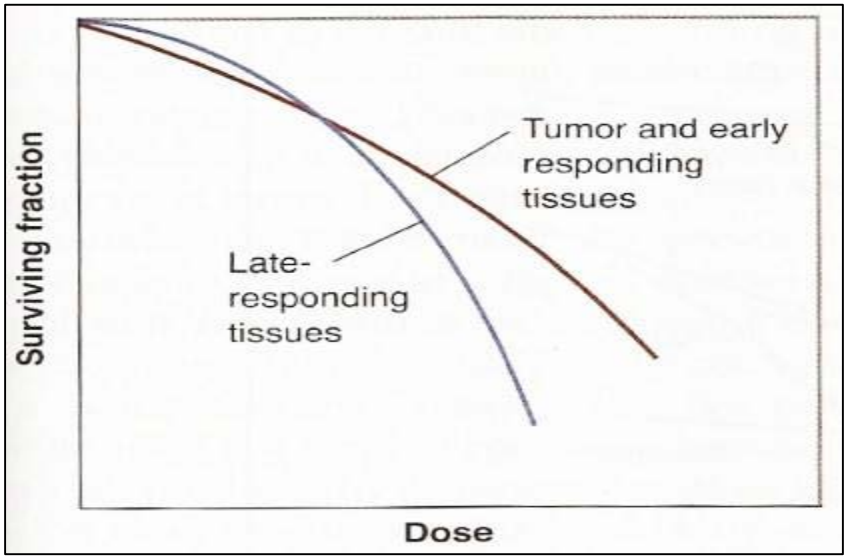
- Linear quadratic (α/β) model
  - Alpha = single hit kills
  - Beta = double hit kills



Hall Fig 3.5

Radiation Oncology: Fractionation

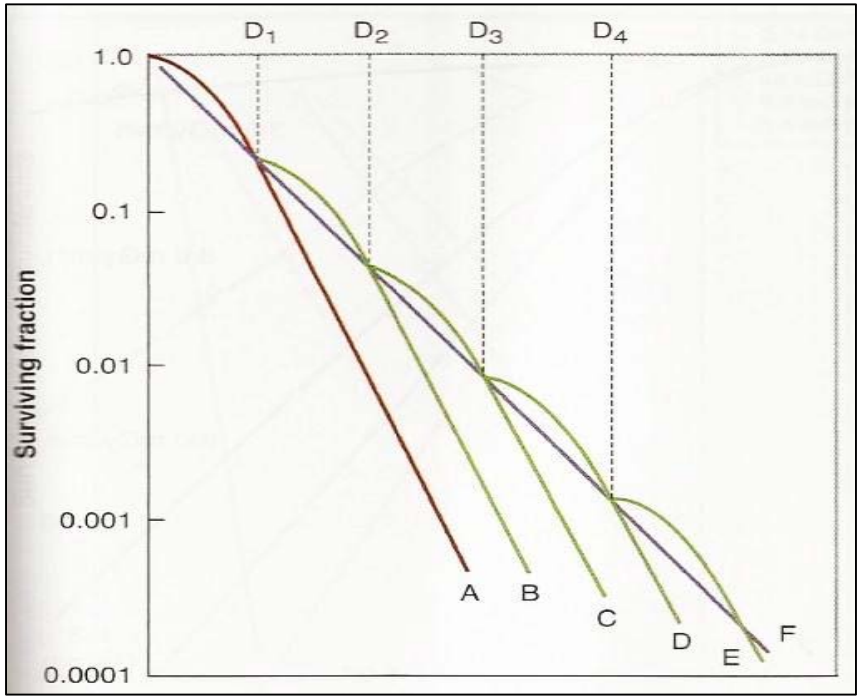
- Different cell lines, tissues, and tumors have different α/β values
  - α/β defines the dose of radiation at which the number of cells killed by a single hit equals the number killed by two hits
  - High α/β = most tumors, early responding normal tissues
  - Low α/β = late responding tissues, some tumors (eg. prostate)



Hall Figure 23.6

Radiation Oncology: Fractionation

- Radiation prescription can be modified to take advantage of different dose response curves.
  - Change number of fractions, keep same “biologically effective dose” (BED).
- BED = nd(1+d/[α/β])
  - n = number of fractions
  - d = dose/fraction



Hall Figure 5.8

Hypofractionation vs Hyperfractionation

- Hypofractionation
  - Convenience for patient
  - Potentially more effective for tumors with low a/B
  - E.g. prostate cancer, RCC
- Hyperfractionation / Accelerated
  - Potentially more favorable toxicity profile
  - May also be more effective for tumors with quick repopulation rates
  - E.g. head and neck cancers

Palliative RT

- 30 Gy in 10 fractions has been the standard for years
- 8 Gy in 1 fraction was directly compared to the standard in treating painful bone metastases
- No difference in rate of pain relief
- Higher rate of requiring re-treatment
- Other palliative situations
  - Bleeding
  - Radioresistant tumors
  - “Durable palliation”

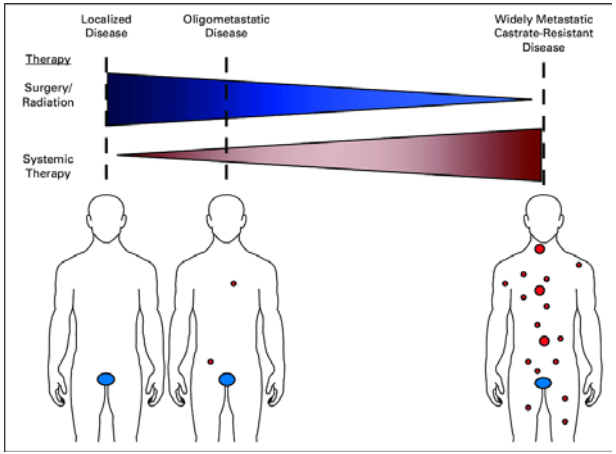
Looking to the Future

RT in the Metastatic Cancer patient

- Radiation typically restricted to palliation
- Emphasis of treatment is on systemic therapy
- Theory that cancer cells have already spread throughout the entire body, so local ablation has no curative benefit

Oligometastatic Disease

- First popularized by Hellman and Weichselbaum in 1995
- A distinct state from non-metastatic and widely metastatic disease
- Also referred to as “low metastatic burden” or “low volume disease”
- Possible benefit of definitive therapy



Can RT Do More in Metastatic Cancer?

SABR-COMET

Palma et al. (IJROBP 2018)

- Phase II multi-national study w/ patients with 1-5 mets and controlled primary
- Palliative SOC vs SOC + SABR to all mets
- Trial designed with two-sided alpha of 0.20, 1o endpoint OS
- n=99 with breast, lung, CRC, and prostate cancer
- 92/99 had 1-3 mets
- At median f/u 27 mo, median OS was 28 vs 41 mo (p=0.09), PFS was 6 vs 12 mo (p=0.001)
- Grade 2+ AEs 9% vs 30% (p=0.02), mostly fatigue, dyspnea, pain
- Three treatment-related grade 5 AEs in SABR arm

STAMPEDE

Parker et al. (Lancet 2018)

- Phase III RCT in 117 hospitals across Switzerland and the UK
- n=2061 patients w/ newly diagnosed metastatic PCa
- Median PSA 97 ng/ml
- Randomized to lifelong ADT +/- RT to prostate
- Docetaxel allowed with ADT in 2016 (18% received)
- Randomization stratified for hospital, age, nodal involvement, WHO performance status, planned ADT, and regular aspirin or NSAID use, and later docetaxel use
- RT = 55 Gy/20 fx QD or 36 Gy/6 fx weekly
- 1o endpoint: Overall Survival

STAMPEDE

Definition of “high metastatic burden” = ≥4 bone mets w/ ≥1 outside the vertebral bodies/pelvis or visceral mets

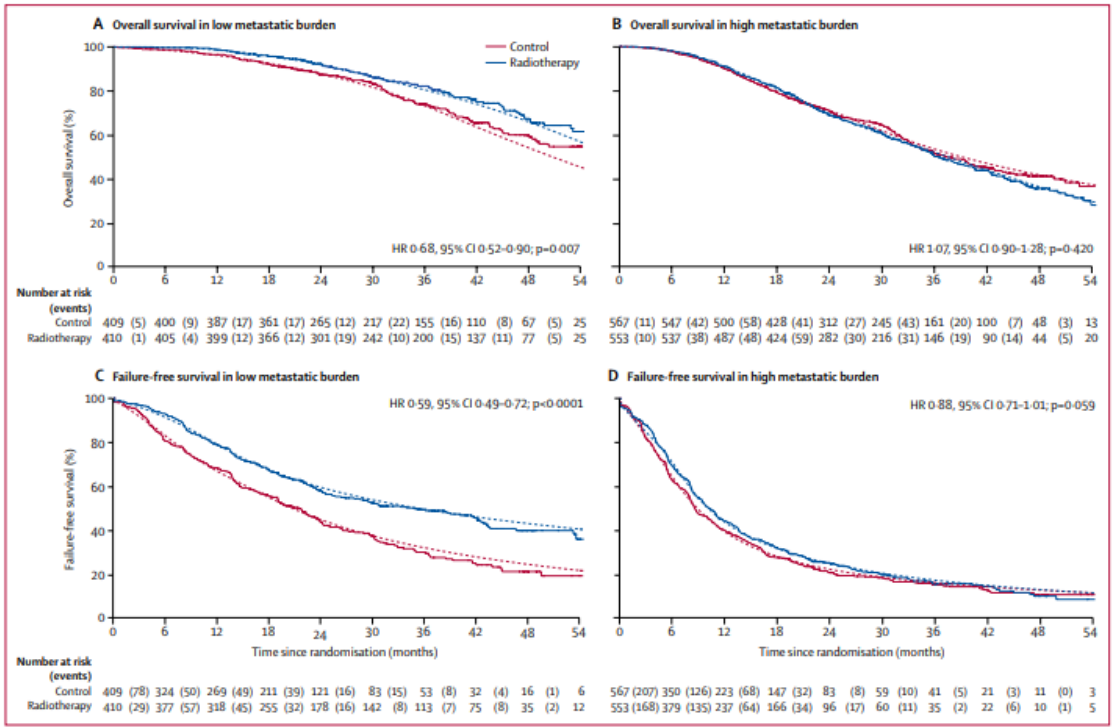


Figure 4: Overall survival and failure-free survival by treatment and metastatic burden
HR=hazard ratio. Solid lines show the Kaplan-Meier analysis and dotted lines show the flexible parametric model.

Why Does Local Therapy Help?

- Diminishes tumor burden
- Durable LC important as systemic control improves
  - Preventing morbidity/mortality from local growth
- Disrupts complex interplay between primary tumor and microenvironment of potential metastatic sites (“priming the premetastatic niche”)
- Disrupts metastasis-to-metastasis communication and spread
- SBRT may have different effects on cancer biology
- Enhances immune response

MR-Guided Radiation Therapy

- The best soft-tissue contrast
- Real-time imaging
- Automated gating
- Adapting planning

- First system launched commercially in 2014, the ViewRay MRIdian
- Other systems currently in early stages of use and testing

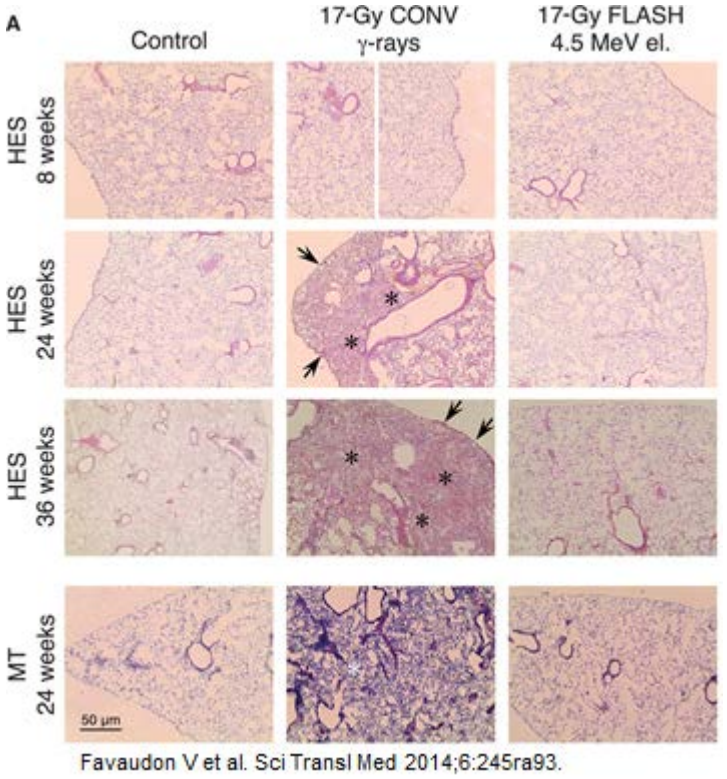
MR-Guided Radiation Therapy

- The best soft-tissue contrast
- Real-time imaging
- Automated gating
- Adapting planning

- First system launched commercially in 2014, the ViewRay MRIdian
- Other systems currently in early stages of use and testing

FLASH-RT

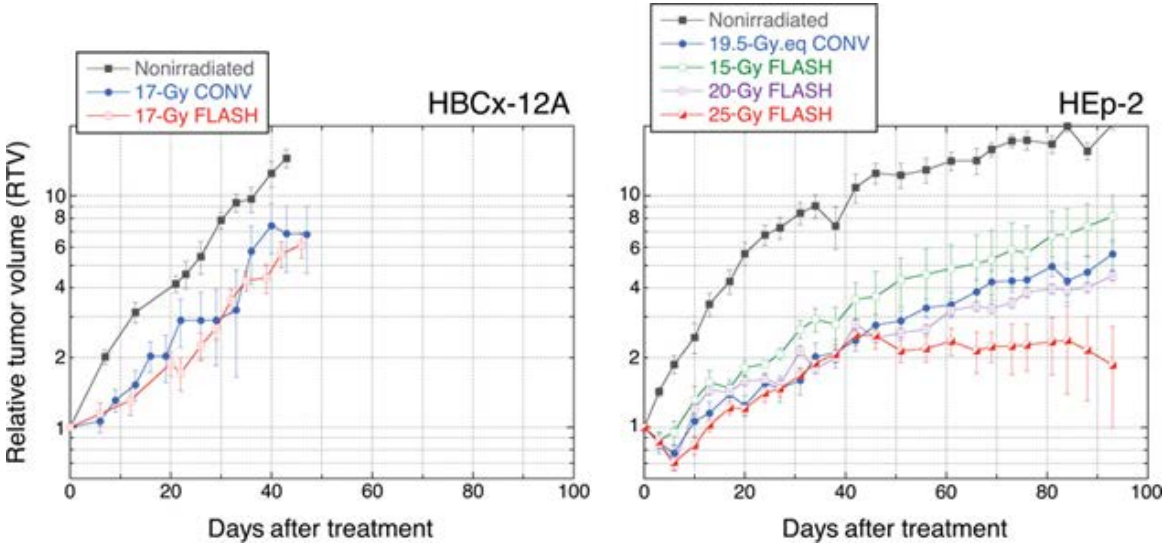
- Ultrahigh dose rate (>40 Gy/s)
  - Regular radiation treatments are typically 1-5 Gy/minute
  - Total body radiation is given 0.06-0.25 Gy/min
- Whole lung radiation in mice
  - Less pulmonary fibrosis
  - Hair depigmentation, no epilation or ulceration 36 weeks post FLASH RT



Favaudon V et al. Sci Transl Med 2014;6:245ra93.

FLASH-RT

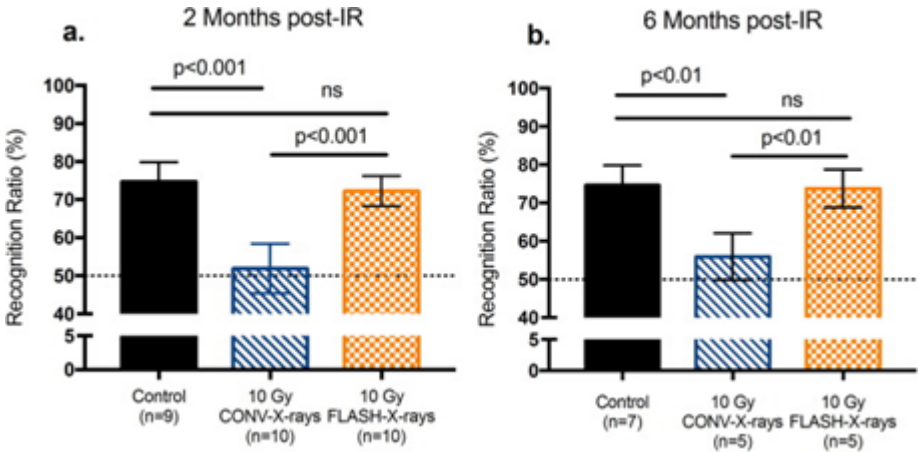
- Potentially the same or better tumor control but less toxicity



Favaudon V et al. Sci Transl Med 2014;6:245ra93.

FLASH-RT

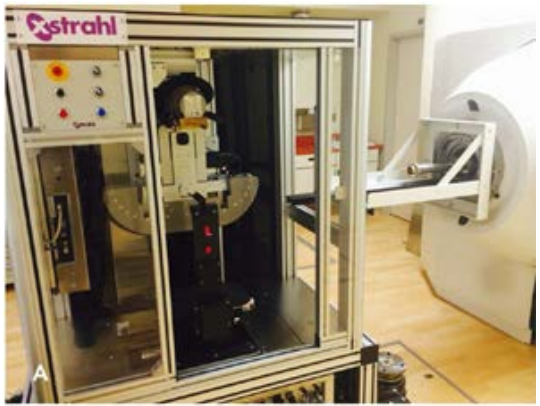
- Similar results seen with whole brain radiation (10 Gy CONV dose rate or FLASH rate)
- Blinded assessment of mice videotaped performing Novel Object Recognition tests showed better memory skills post FLASH RT
  - Better preservation of cellular division in the hippocampus subgranular zone
  - Less astrogliosis

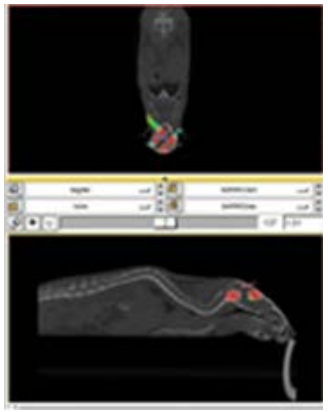


Montay-Gruel P et al. Radiother Oncol. 2018 Dec;129(3):582-588.

FLASH-RT at UW

- Small animal x-ray and proton radiator, beam sizes 1-40 mm, on board CT scan for positioning
- In process of being adapted to deliver proton FLASH-RT
- Existing linear accelerators cannot deliver FLASH-RT to patients, but proton centers could!





Ford E et al. Phys Med Biol. 2017 Jan 7;62(1):43-58.

Thank you for your attention!

An Update in Thromboembolism

David A. Garcia, MD

September 2020

Declaration of Interest

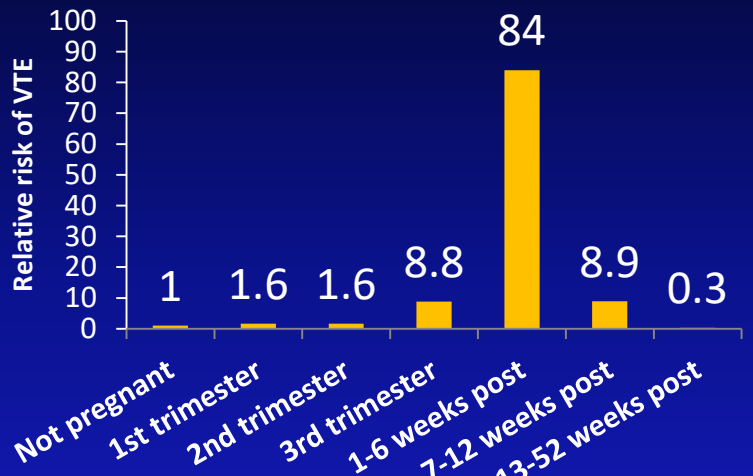
- Research funding
  - Incyte

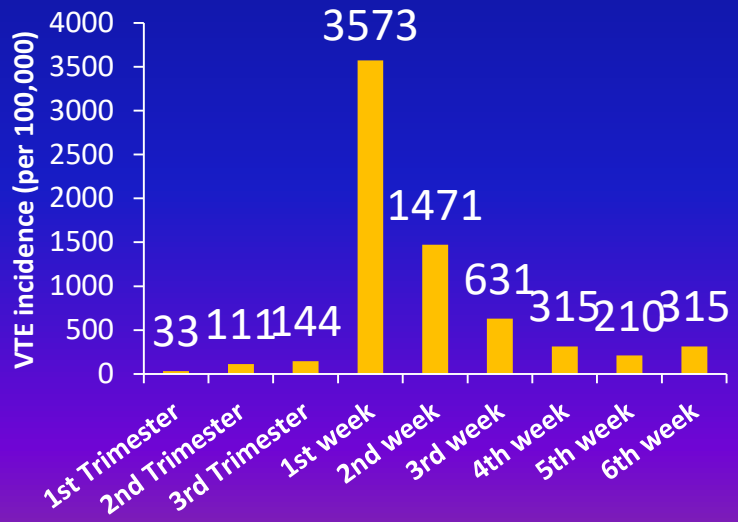
Outline

- Risks/mechanisms
- Pregnancy
- Cancer
- New acute treatment options
- Duration issues
  - Thrombophilia testing
  - Aspirin, target-specific oral agents
- Catheters
- Anticoagulation ‘failure’
- ‘Reversal’

Epidemiology of VTE in pregnancy

- Incidence of VTE– 0.76 to 1.72 per 1000 pregnancies
- Incidence of fatal PE- 1.1-1.5 per 100,000 deliveries
- VTE increases with age
  - < 20- 1.47 per 1000 deliveries
  - 20-29 years- 1.63
  - 30-39 years- 1.93
  - 40 + years- 2.75





Marik and Plante N Engl J Med 2008;James AH, et al. Am J Obstet Gyne 2006; Heit J et al. Ann Intern Med 2005; Pomp ER et al. J Thromb Haemost 2008

Antepartum PRIMARY Prophylaxis*

- AT deficiency + FH
- Homozygous FVL or PG** mutation +/- FH
- “Combined thrombophilias” +/- FH

*All are “conditional suggestions”
**Prothrombin gene

Postpartum PRIMARY Prophylaxis

- "Combined thrombophilias" +/- FH
- Homozygous for PG or FVL mutation +/- FH
- AT*, proC, proS deficiency + FH
- *Suggests against* for
  - FH + heterozygous FVL or PG mutation

*Strong recommendation

BATES et al. 2018 Nov 27;2(22):3317-3359.

Women with prior VTE not on AC therapy

- Unprovoked or estrogen-associated
  - Antepartum *and* Postpartum LMWH
- Provoked (e.g. after surgery)
  - Postpartum LMWH

Initial VTE Treatment

- Anticoagulation
  - Unfractionated heparin
    - Bolus 80 U/kg IV
    - Infusion 18 U/kg/h adjusted to aPTT 50-80 seconds
  - LMWH
    - Dalteparin 200 IU/kg sc qday
    - Enoxaparin 1 mg/kg sc q12h
  - Fondaparinux 5-10 mg sc qday (depends on weight)
  - Rivaroxaban 15 mg PO BID x 21 days, then 20 mg QD
  - Apixaban 10 mg PO BID x 7 days, then 5 mg PO BID

Initial VTE Treatment

- Anticoagulation
  - Warfarin (must overlap with parenteral agent for minimum 4-5 days)
  - Dabigatran 150 mg po BID – after 5-day heparin “lead-in”
  - Edoxaban 60 mg PO QD - after 5-day heparin “lead-in”
- Other
  - ~~Vena caval filter (retrievable or permanent)~~
  - Pharmacomechnical Thrombolysis?
  - ~~Elastic compression stockings~~

Thrombolysis for ilio-femoral clot:

Vedantham et al. N Engl J Med. 2017 Dec 7;377(23):2240-2252

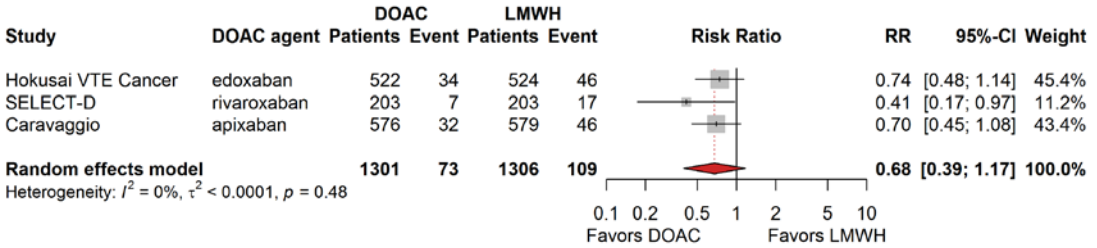
Table 3. Binary Trial Outcomes.

Outcome	Pharmacomechanical-Thrombolysis Group (N=336)	Control Group (N=355)	Risk Ratio (95% CI)	P Value
	number of patients (percent)			
Post-thrombotic syndrome between 6 and 24 mo*				
Ulcer at any follow-up assessment	12 (4)	17 (5)		
Villalta score ≥5 without ulcer	144 (43)	154 (43)		
Late endovascular procedure only	1 (<1)	0		
Total	157 (47)	171 (48)	0.96 (0.82–1.11)†	0.56
Post-thrombotic syndrome according to follow-up visit‡				
At 6 mo	78/291 (27)	113/285 (40)	0.68 (0.53–0.86)	
At 12 mo	92/272 (34)	88/258 (34)	0.99 (0.78–1.26)	
At 18 mo	85/245 (35)	76/222 (34)	1.01 (0.79–1.30)	
At 24 mo	79/258 (31)	86/239 (36)	0.85 (0.66–1.09)	
Major non–post-thrombotic syndrome treatment failure	4 (1)	7 (2)	0.58 (0.17–1.98)§	0.38¶
Any treatment failure‖	158 (47)	176 (50)	0.94 (0.80–1.09)†	0.39¶
Moderate-to-severe post-thrombotic syndrome**	60 (18)	84 (24)	0.73 (0.54–0.98)†	0.04¶
Major bleeding††				
First 10 days	6 (1.7)	1 (0.3)	6.18 (0.78–49.2)§	0.049
Total over 24 mo	19 (5.7)	13 (3.7)	1.52 (0.76–3.01)§	0.23
Any bleeding				
First 10 days	15 (4)	6 (2)	2.64 (1.04–6.68)§	0.03

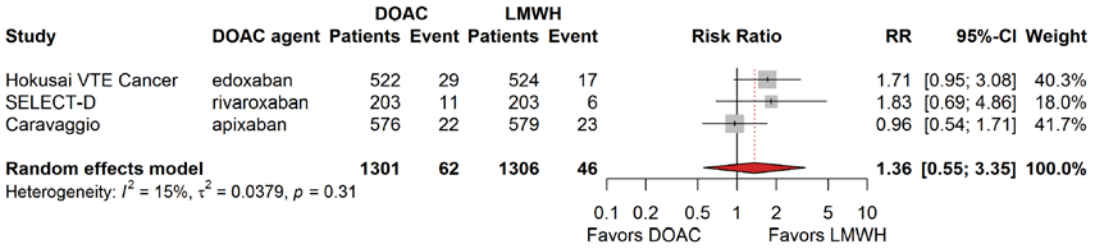
Also see: Haig et al Lancet Haematol 2016;3:e64-e71

Pooled Analysis of DOAC Trial Results Using Homogenized Endpoint Definitions

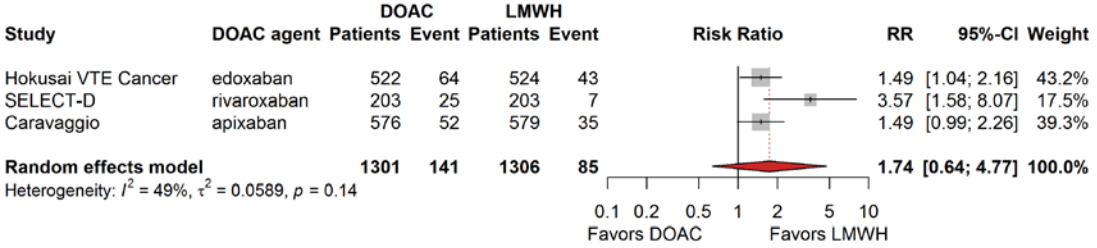
Recurrent VTE



Major bleeding



Clinically relevant non-major bleeding



Mulder F et al. *Blood.* 2020; blood.2020005819.

DOAC Trial Baseline Characteristics for the Treatment of Cancer-Associated VTE

	HOKUSAI-VTE CANCER		SELECT-D		ADAM-VTE		CARAVAGGIO	
	Edoxaban (n=522)	Dalteparin (n=524)	Rivaroxaban (n=203)	Dalteparin (n=203)	Apixaban (n=150)	Dalteparin (n=150)	Apixaban (n=576)	Dalteparin (n=579)
Age, years	64.3 ± 11.0	63.7 ± 11.7	67[†]	67[†]	64	64	67.2±11.3	67.2±10.9
Male sex, %	53.1	50.2	57	48	48	49	50.7	47.7
Metastatic disease, %	52.5	53.4	58	58	65[‡]	66[‡]	67.5*	68.4*
Active chemo, %	71.6[‖]	73.1[‖]	81	85	74	74	85.6[‖]	85.8[‖]
GI tumors, %								
Colorectal	15.9	15.1	27	23	12.2	19.6	21.0	19.5
Upper	6.3	4.0	7[§]	12[§]	4.8	2.7	4.0	5.4
Pancreatic or hepatobiliary	9.4	7.6	10[¶]	6.4[¶]	15.6	16.2	7.6	7.4
ECOG PS, %								
0	29.7	28.2	29	30	40.0	41.3	32.3	29.4
1	46.6	46.9	44	47	46.7	50.7	48.8	47.8
2	23.6	23.7	26	21	13.3	8.0	18.9	22.8
Qualifying VTE diagnosis, %								
PE ± DVT	62.8	62.8	–	–	56	51	52.8	57.7
DVT only	37.2	37.2	–	–	37	35	47.2	42.3
Symptomatic DVT or PE	68.0	67.0	47	48	–	–	79.9	80.3
Incidental DVT or PE	32.0	33.0	53	52	–	–	20.1	19.7

*Recurrent locally advanced or metastatic disease. [†]Median age. [‡]Distant metastases. [§]Includes gastric and esophageal/gastroesophageal cancers. [‖]Includes any anticancer drug therapy (cytotoxic, hormonal, targeted, or immunomodulatory), radiotherapy, surgery, or a combination of these therapies. [¶]Includes pancreatic and gallbladder cancers.
DOAC=direct-acting oral anticoagulant; DVT=deep vein thrombosis; ECOG PS=Eastern Cooperative Oncology Group performance status; GI=gastrointestinal; NR=not reported; PE=pulmonary embolism; VKA=vitamin K antagonist; VTE=venous thromboembolism.

DOAC Trial Results for the Treatment of Cancer-Associated VTE

	HOKUSAI-VTE CANCER Edoxaban	SELECT-D Rivaroxaban	ADAM-VTE Apixaban	CARAVAGGIO Apixaban
Randomized patient numbers	1050	406	300	1170
Trial duration, months	12	6	6	6
Primary endpoint	Composite of recurrent VTE or ISTH major bleeding	Recurrent VTE	ISTH major bleeding	Recurrent VTE
VTE recurrence				
Oral agent (O)	7.9%	4%	0.7%	5.6%
Dalteparin (D)	11.3%	11%	6.3%	7.9%
HR (95% CI); O vs D	0.71 (0.48-1.06)	0.43 (0.19-0.99)↓	0.099 (0.013-0.78)	0.63 (0.37-1.07)
Major bleeding				
Oral agent	6.9%	6%	0%	3.8%
Dalteparin	4.0%	4%	1.4%	4.0%
HR (95% CI); O vs D	1.77 (1.03-3.04) ↑	1.83 (0.68-4.96)	NE	0.82 (0.40-1.69)
Fatal bleeding				
Oral agent	0%	0.5%	0%	0%
Dalteparin	0.2%	0.5%	0%	0.3%
HR (95% CI); O vs D	NR	NR	NE	NR
Major GI bleeding				
Oral agent	3.8%	3.9%	0%	1.9%
Dalteparin	1.1%	2.0%	0%	1.7%
HR (95% CI); O vs D	NR	NR	NE	1.05 (0.44-2.50)
CRNM Bleeding				
Oral agent	14.6%	13%	6.2%	9.0%
Dalteparin	11.1%	4%	4.2%	6.0%
HR (95% CI); O vs D	1.38 (0.98-1.94)	NR	NR	1.42 (0.88-2.30)

Yellow highlights denote statistically significant results.

Can we use DOACs in patients with gastrointestinal cancer?

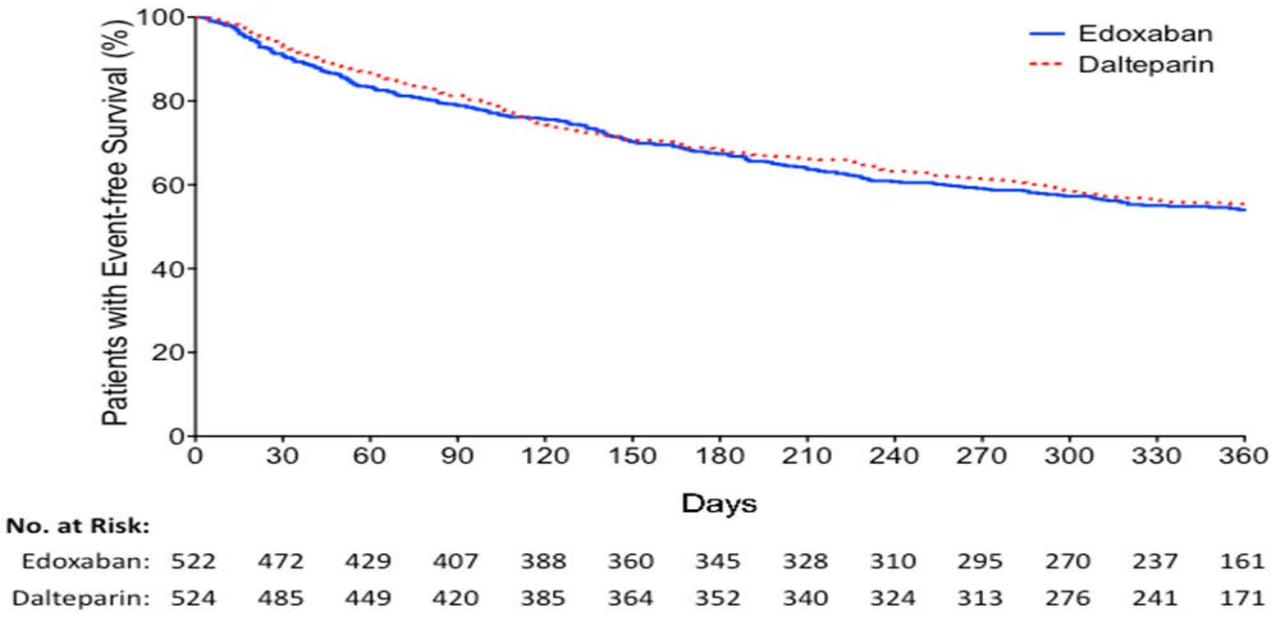
- 2018 ISTH Guidance Statement:

- We suggest the use of specific DOACs (edoxaban and rivaroxaban) for cancer patients with an acute diagnosis of VTE, a low risk of bleeding, and no drug–drug interactions with current systemic therapy.

- We suggest the use of LMWHs for cancer patients with an acute diagnosis of VTE and a high risk of bleeding, including patients with luminal gastrointestinal cancers with an intact primary, patients with cancers at risk of bleeding from the genitourinary tract, bladder, or nephrostomy tubes, or patients with active gastrointestinal mucosal abnormalities such as duodenal ulcers, gastritis, esophagitis, or colitis. Edoxaban and rivaroxaban are acceptable alternatives if there are no drug–drug interactions with current systemic therapy.

* Khorana A, et al, *JTH* 2018

Event-free Survival
Freedom from Recurrent VTE, Major Bleeding and Death



Raskob G et al. *N Engl J Med*. 2018 Feb 15;378(7):615-624.

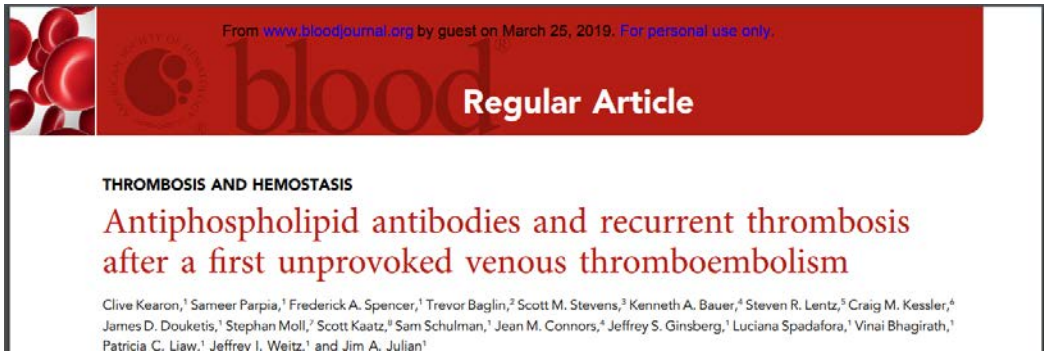
Duration of AC after VTE

Thrombophilia - Why test?

- **Because the results will influence the intensity of anticoagulation**
  - **No evidence in any setting**
- **Because the results will influence the duration of anticoagulation**
  - **Little evidence, except for specific circumstances**
- **Because it might influence future decisions for the patient or their family**
  - **Selected patients**
- **Curiosity**
  - **A legitimate reason IF the patient is fully aware of the implications**

- **Because we can or we didn't bother to think about it**
  - **The most frequent reason, unfortunately**

Important APS Papers



blood

Regular Article

THROMBOSIS AND HEMOSTASIS

Antiphospholipid antibodies and recurrent thrombosis after a first unprovoked venous thromboembolism

Clive Kearon,[1] Sameer Parpia,[1] Frederick A. Spencer,[1] Trevor Baglin,[2] Scott M. Stevens,[3] Kenneth A. Bauer,[4] Steven R. Lentz,[5] Craig M. Kessler,[6] James D. Douketis,[1] Stephan Moll,[7] Scott Kaatz,[8] Sam Schulman,[1] Jean M. Connors,[4] Jeffrey S. Ginsberg,[1] Luciana Spadafora,[1] Vinai Bhagirath,[1] Patricia C. Liaw,[1] Jeffrey I. Weitz,[1] and Jim A. Julian[1]

2018;131(19):2151-2160

blood

Plenary Paper

CLINICAL TRIALS AND OBSERVATIONS

Rivaroxaban vs warfarin in high-risk patients with antiphospholipid syndrome

Vittorio Pengo,[1] Gentian Denas,[1] Giacomo Zoppellaro,[1] Seena Padayattil Jose,[1] Ariela Hoxha,[2] Amelia Ruffatti,[2] Laura Andreoli,[3] Angela Tincani,[3] Caterina Cenci,[4] Domenico Prisco,[4] Tiziana Fierro,[5] Paolo Gresele,[5] Arturo Cafolla,[6] Valeria De Micheli,[7] Angelo Ghirarduzzi,[8] Alberto Tosetto,[9] Anna Falanga,[10] Ida Martinelli,[11] Sophie Testa,[12] Doris Barcellona,[13] Maria Gerosa,[14] and Alessandra Banzato[1]

2018;132(13):1365-1371


Annals of Internal Medicine

ORIGINAL RESEARCH

Rivaroxaban Versus Vitamin K Antagonist in Antiphospholipid Syndrome

A Randomized Noninferiority Trial

Josep Ordi-Ros, MD, PhD; Luis Sáez-Comet, MD, PhD; Mercedes Pérez-Conesa, MD; Xavier Vidal, MD, PhD; Antoni Riera-Mestre, MD, PhD; Antoni Castro-Salomó, MD, PhD; Jordi Cuquet-Pedragosa, MD; Vera Ortiz-Santamaria, MD; Montserrat Mauri-Plana, MD, PhD; Cristina Solé, PhD; and Josefina Cortés-Hernández, MD, PhD

2019;171:685-694

Thrombophilia: Summary

- Antiphospholipid antibody testing is probably appropriate for many patients with unprovoked VTE if/when d/c therapy contemplated
  - May also be appropriate if clinical features suggest APS (mild thrombocytopenia, livedo reticularis, late pregnancy loss)

- More comprehensive testing may be indicated with strong family history

- Special situations
  - Splanchnic vein thrombosis: consider JAK2 V617F and PNH testing

- For most patients, *don't do it*.

A Suggested Approach

Treat Proximal DVT or PE (unprovoked*) *at least* 3 months

- Ensure the patient is up-to-date on age-appropriate cancer screening and perform careful physical exam and review of systems.
- Discuss risks/benefits of extended therapy with all patients.
- Encourage extended therapy for patients who:
  - are male
  - have had previous VTE
  - had PE (rather than DVT) as their index event
  - have poor cardiopulmonary reserve
  - have low risk of AC-related bleeding (see next slide)
- Test patients for antiphospholipid syndrome before permanently discontinuing.
- Consider d-dimer testing in women if other factors equivocal.

*Kearon C et al. J Thromb Haemost. 2016 Jul;14(7):1480-3.

Factors Associated with Increased Major Bleeding Risk

Table 1: The VTE-BLEED score.

Factor	Score
Active cancer[a]	2
Male with uncontrolled arterial hypertension[b]	1
Anaemia[c]	1.5
History of bleeding[d]	1.5
Age ≥60 years old	1.5
Renal dysfunction[e]	1.5
Classification of patients with the VTE-BLEED score	
Low bleeding risk	Total score <2
High bleeding risk	Total score ≥2

Klok et al. Thromb Haemost 2017; 117: 1164–1170

You Have Decided to "Extend" Antithrombotic Tx

- What are the options besides warfarin?

Comparison of the DOAC Agents

- Dabigatran
  - Direct thrombin inhibitor
  - Taken twice daily (150 mg)
  - 5 days of parenteral (LMWH) treatment needed
- Rivaroxaban
  - Direct FXa inhibitor
  - 15 mg twice daily for 3 wks, then 20 mg **once daily**
  - Can be used as monotherapy
- Apixaban
  - Direct FXa inhibitor
  - 10 mg twice daily for seven days; then 5 mg **BID**
  - Can be used as monotherapy
- Edoxaban
  - Direct FXa inhibitor
  - Daily (60 mg; or 30 mg for renal impairment or low weight)
  - 5 days parenteral (LMWH) treatment needed

Long-term (secondary) VTE Prevention

Trial Name	Drug	Year Published (or presented)	Comparator	VTE Prevented per 1,000/yr vs. comparator	*Extra* Major Bleeds per 1,000/yr vs. comparator
EINSTEIN CHOICE†	Riva (10 QD)	2010	ASA	> 20	Fewer than 10
RE-SONATE*	Dabi (150 BID)	2012	placebo	> 50	Approximately 10
AMPLIFY** Extension	Apix (2.5 BID)	2013	placebo	> 50	Fewer than 10?

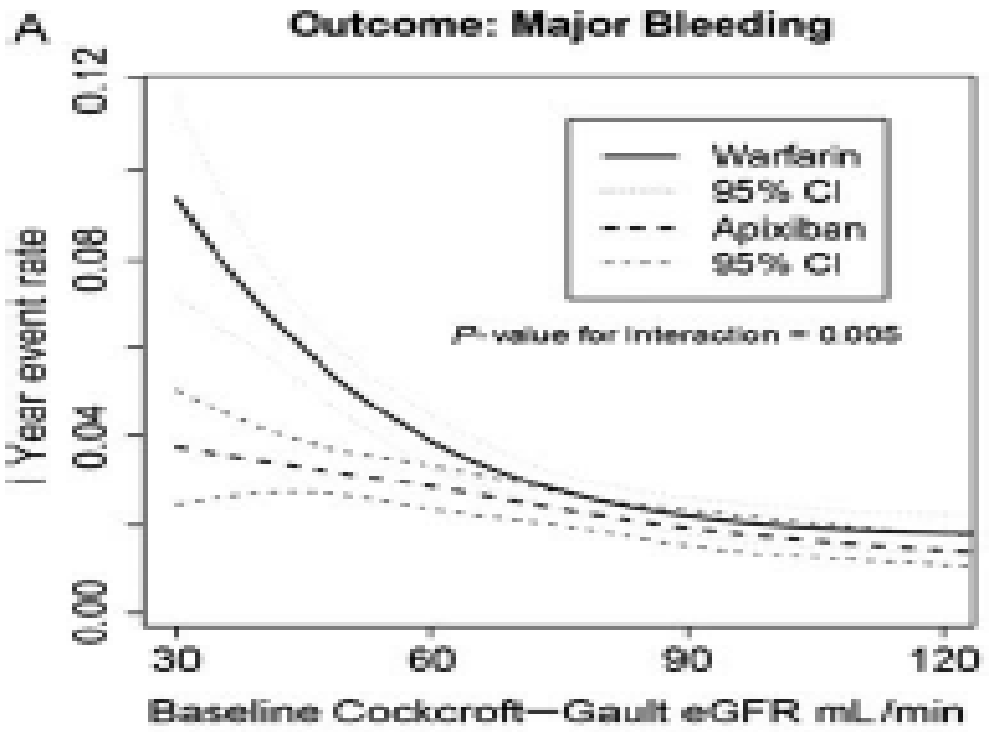
† Weitz et al. NEJM 2017; 376:1211-1222.
* Schulman et al. NEJM 2013; 368:709-18.
** Agnelli et al. NEJM 2013 Feb 21;368(8):709-18

Do NOT Prescribe DOACs For Patients Who:

- Are likely to skip doses
- Weigh more than ____ kg*
- Take medicines likely to interact
- Are “triple positive” for APL
- Cannot afford them

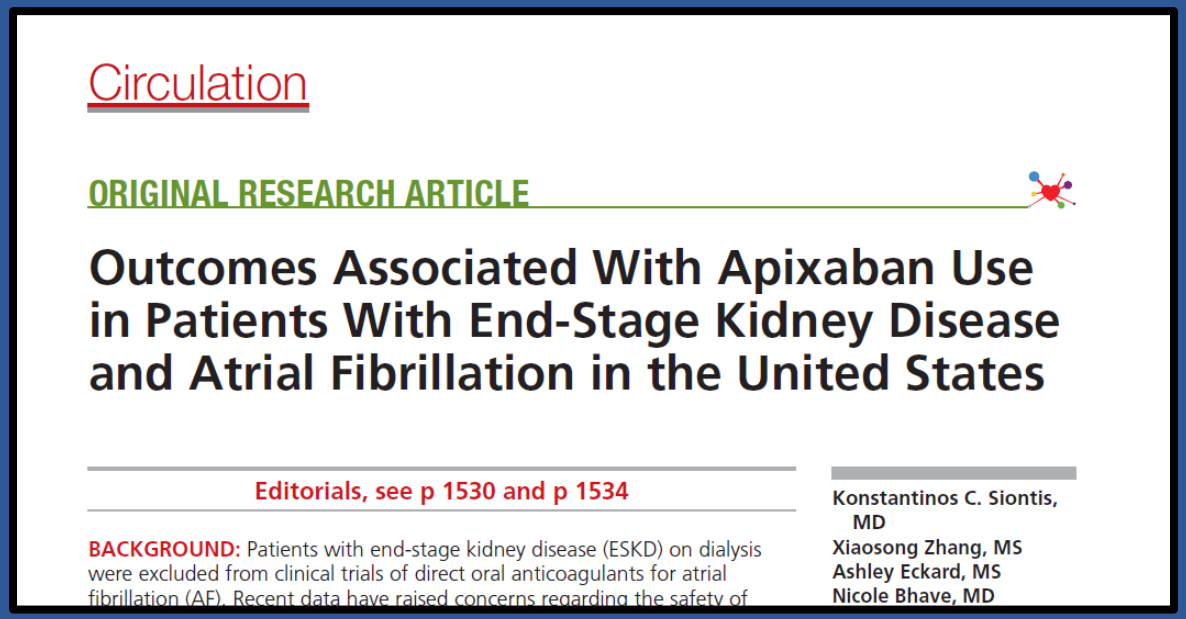
*see Wang, T.F. Blood. 2020 Mar 19;135(12):904-911.

Risk of Anticoagulant-associated Major Bleeding Increases with Lower GFR



Hohnloser et al. Eur Heart J. 2012 Nov;33(22):2821-30

Apixaban vs. warfarin in ESRD: cohort study of approx, 9,400 Medicare beneficiaries



Circulation

ORIGINAL RESEARCH ARTICLE

Outcomes Associated With Apixaban Use in Patients With End-Stage Kidney Disease and Atrial Fibrillation in the United States

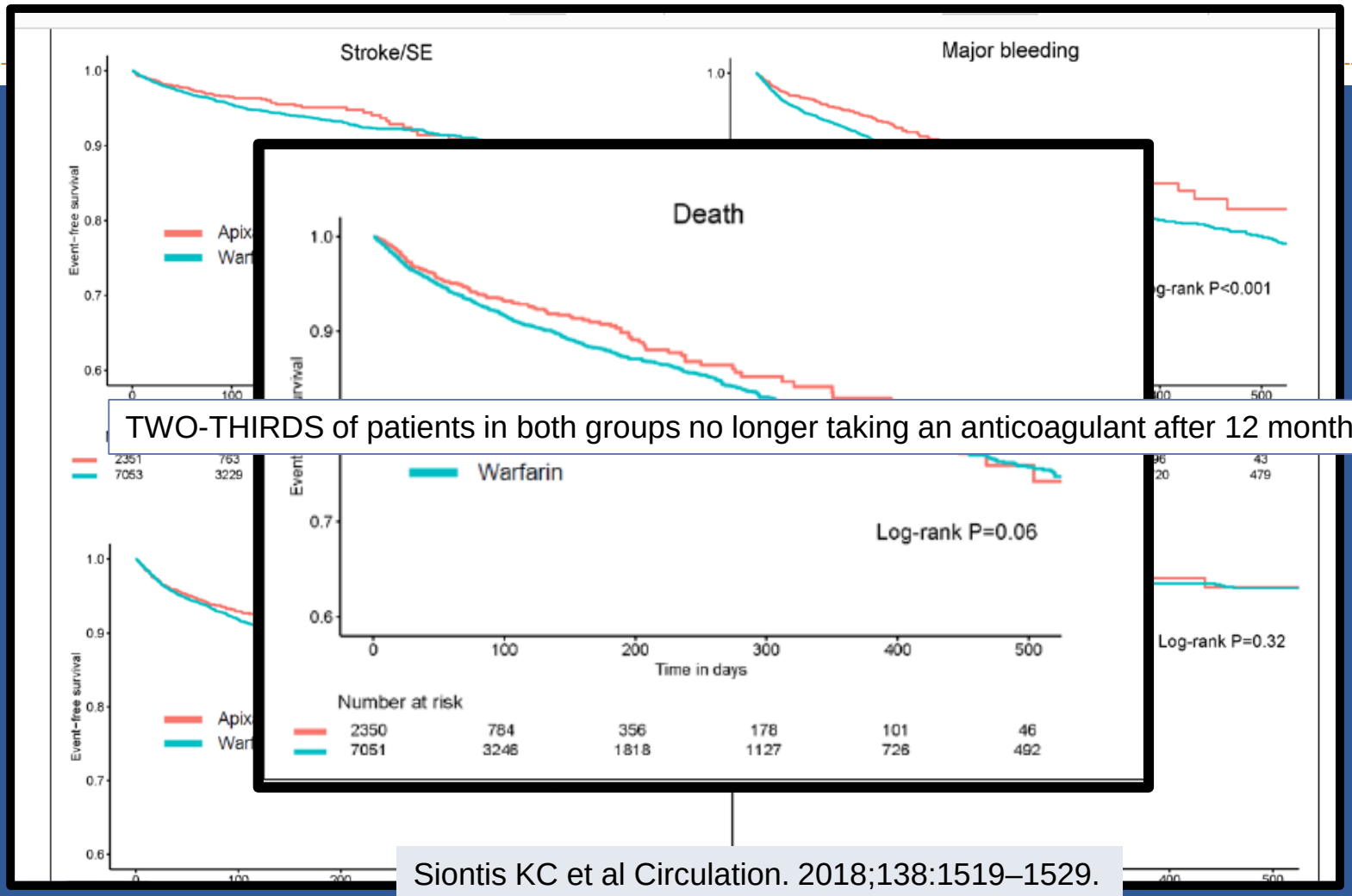
Editorials, see p 1530 and p 1534

Konstantinos C. Siontis, MD
Xiaosong Zhang, MS
Ashley Eckard, MS
Nicole Bhave, MD

BACKGROUND: Patients with end-stage kidney disease (ESKD) on dialysis were excluded from clinical trials of direct oral anticoagulants for atrial fibrillation (AF). Recent data have raised concerns regarding the safety of

Time period: 2010-2015

Siontis KC et al Circulation. 2018;138:1519–1529.



TWO-THIRDS of patients in both groups no longer taking an anticoagulant after 12 months!

Siontis KC et al Circulation. 2018;138:1519–1529.

For moderate renal impairment see: Harel et al. J Am Soc Nephrol 25: 431–442, 2014

New 2018 ASH Clinical Practice Guidelines on Venous Thromboembolism:

What You Should Know

Warfarin Reversal

INR	Response
INR 5-9	Hold warfarin 1-2 days, follow INR, consider vit K 1-2.5 mg PO
INR > 9	Hold warfarin, follow INR, consider vit K 2.5-5 mg PO
Serious bleeding	Hold warfarin, follow INR, give IV vit K 5-10 mg + Kcentra (4-factor PCC) – dose depends on INR

PCC = prothrombin complex concentrate (contains large amounts of all vit K dependent clotting factors).

Holbrooke et al. Chest. Feb 2012.

Anticoagulation Reversal

Anticoagulant	Reversal	Additional considerations
Unfractionated Heparin (Half-life ~ 60 min)	Protamine 1 mg/100 units UFH Infuse slowly (< 5mg/min)	Max dose = 50 mg Risk of anaphylaxis
LMWH (Half-life 3.5-7 hrs)	Within 8 hrs: Protamine 1mg/1mg Enoxaparin More than 8 hrs: Protamine 0.5mg/mg Enox	Max dose = 50 mg Risk of anaphylaxis
Fondaparinux (Half-life 17-21 hrs)	FVIIa 90 mcg/kg IV or FEIBA 50-100 u/kg	Risk of thromboembolic events
Dabigatran	1. Idarucizumab 5 gm IV 2. Hemodialysis	
Rivaroxaban or apixaban or edoxaban	1. Kcentra 2000 units IV *or* 2. FEIBA 3. Andexanet alpha	Risk of thromboembolic events

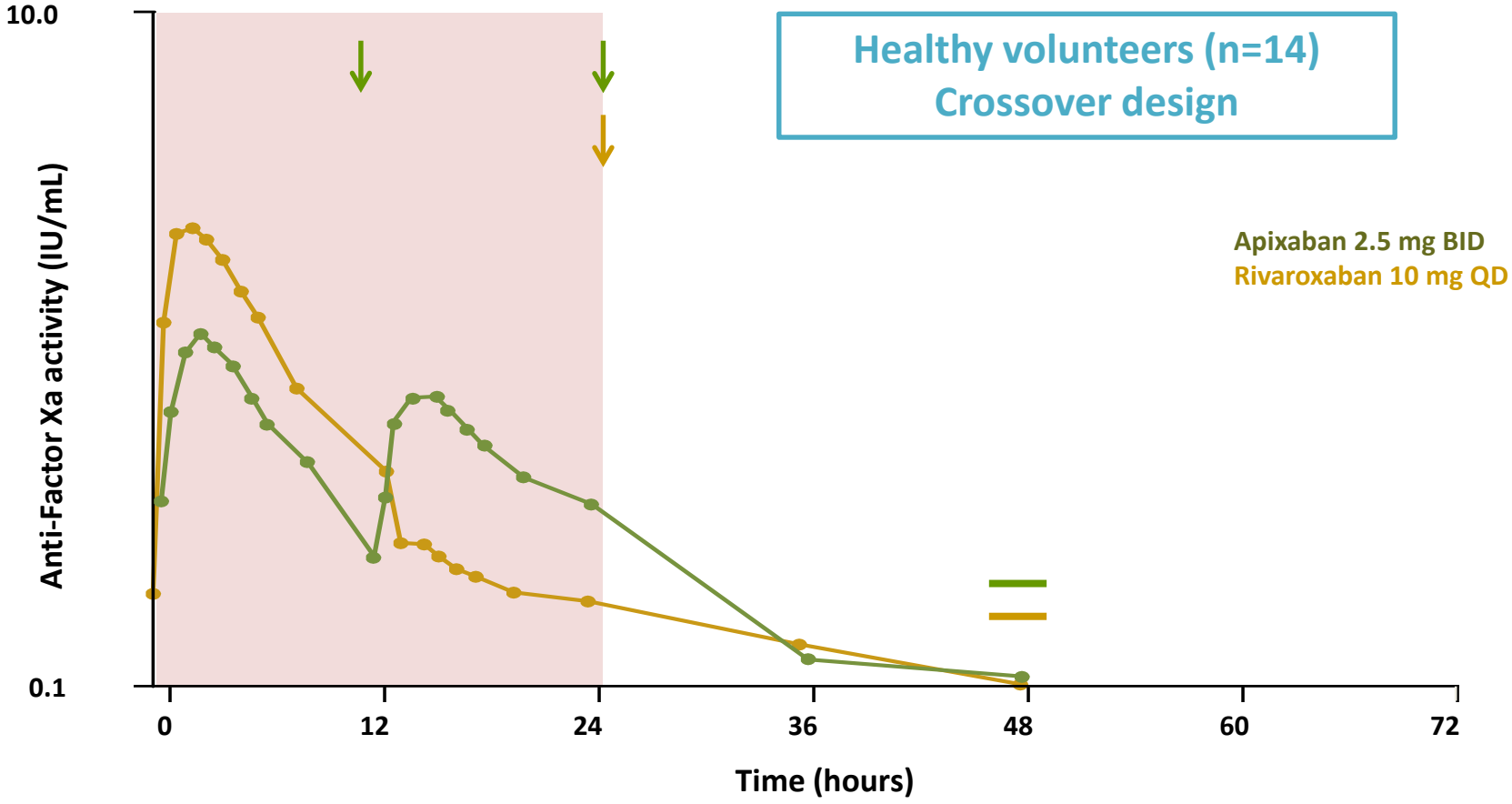
Anticoagulation Reversal

- Key papers:
  - **Pollack et al. N Engl J Med 2017;377:431-41**
    - **(idaucizumab for dabigatran)**
  - **Connolly et al. N Engl J Med. 2019 Feb 7. [Epub ahead of print]**
    - **(andexanet alpha for FXa inhibitors)**
  - **Piran S, et al. Blood Adv. 2019 Jan 22; 3(2): 158–167.**
    - **(4-factor PCC for FXa inhibitors)**

How Emergent is the need to Reverse?

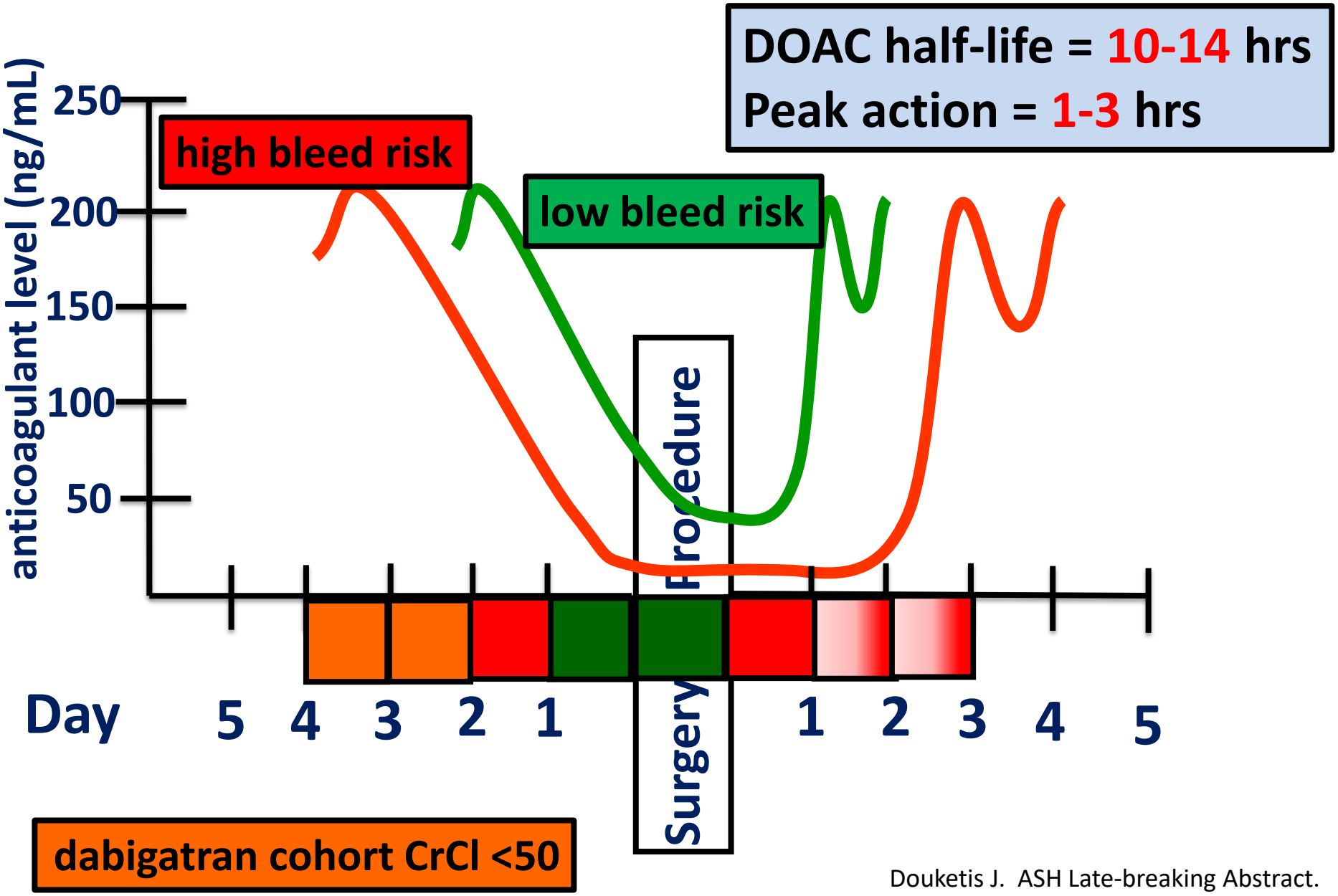
- *Critical to discuss risk of delay*
  - *Because:*
- *Drug effect will dissipate quickly*
- *"Prohemostatic" interventions carry risk*

Pharmacodynamics of apixaban and rivaroxaban



Frost et al. *J Thromb Haemost* 2011;9(Suppl 2): ISTH abstract no. P-WE-159.

DOACs: Perioperative Management



Douketis J. ASH Late-breaking Abstract.

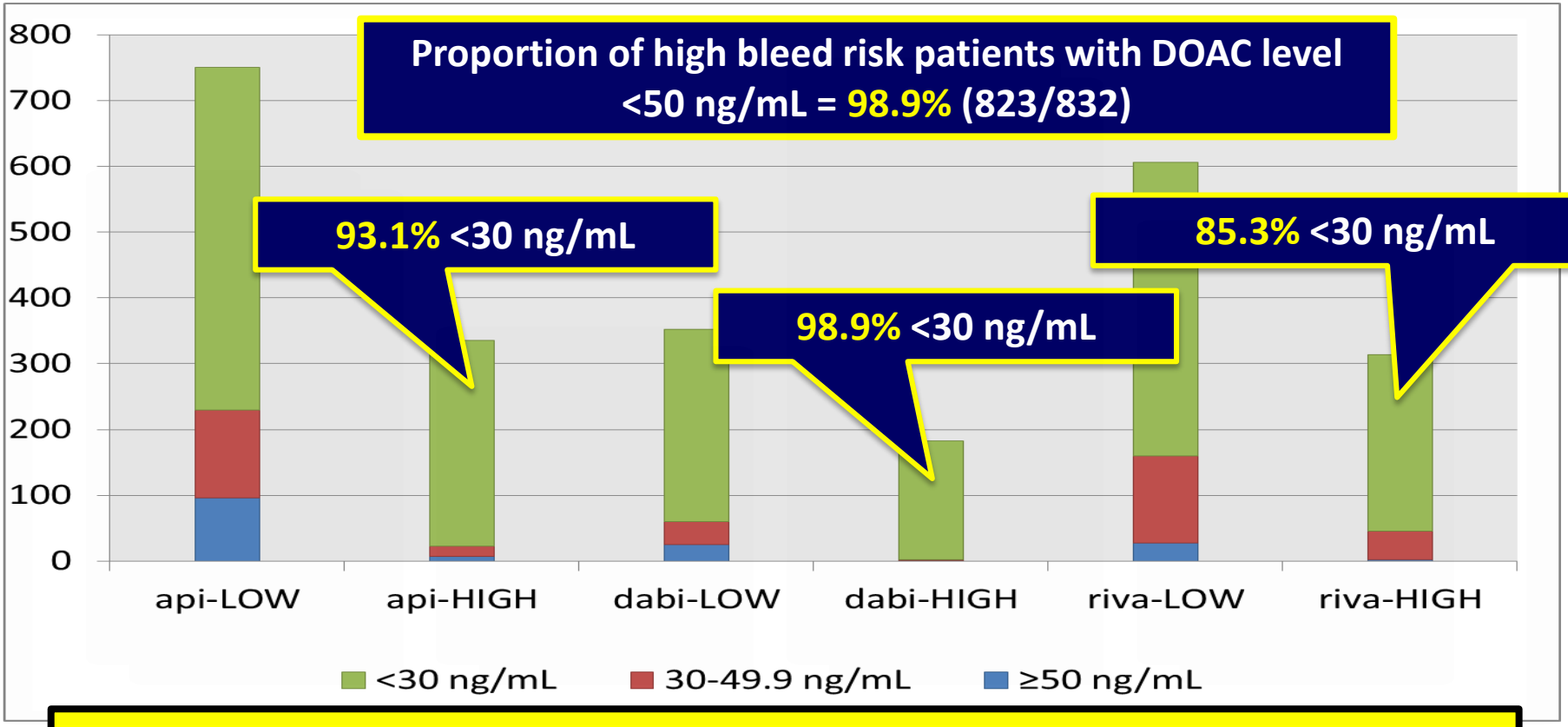
Results: Primary Outcomes (ITT Analysis)

Outcome (%, 95% CI) (expected)	Cohort		
	Apixaban *n=1257*	Dabigatran *n=668*	Rivaroxaban *n=1082*
*Arterial thromboembo-lism (0.5%)	0.16 (0-0.48) *n=2*	0.60 (0-1.33) *n=4*	0.37 (0-0.82) *n=4*
**Major bleeding (1.0%)	1.35 (0-2.00) *n=17*	0.90 (0-1.73) *n=6*	1.85 (0-2.65) *n=20*

*Ischemic stroke, TIA, systemic embolism, **ISTH definition

Douketis J. ASH Late-breaking Abstract.

Results: Residual Preoperative DOAC Levels



DOAC levels measured in 2,541 (85%) patients

Lab Measurement for DOACs

- DOACs can (but do not always) prolong “traditional” clotting times (PTT or PT)

- Thrombin time (TT) is very sensitive to (even low concentrations of) dabigatran – a normal thrombin time excludes dabigatran

Best tests for DOACs

- Dabigatran: dilute thrombin time (*calibrated for dabigatran*)

- FXa inhibitors: anti-Xa assay (*calibrated for a particular DOAC*)
  - mPT (at UWMC and HMC) also sensitive

- "expected" trough: ~ 50 ng/mL
- "expected" peak: 150 – 250 ng/mL

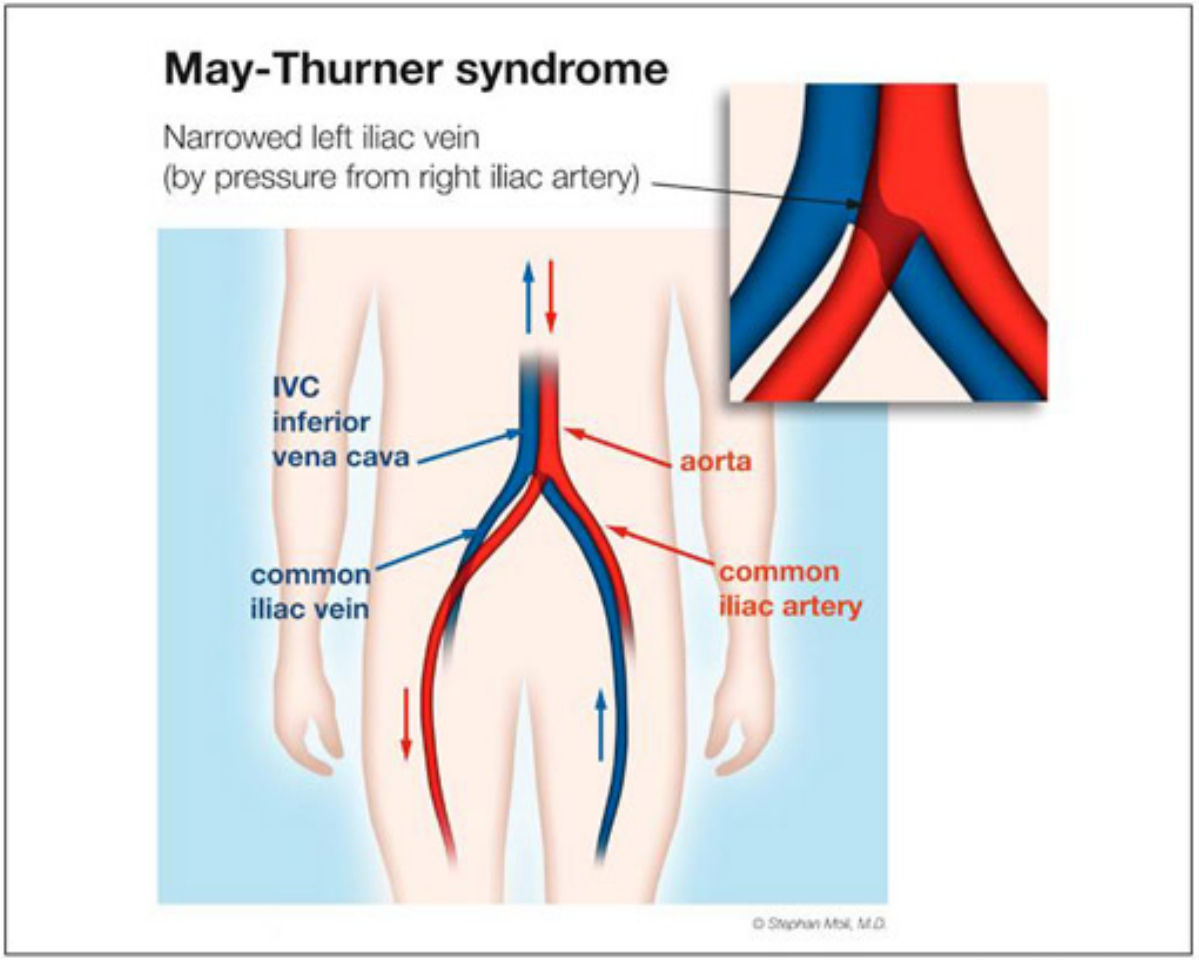
Samuelson et al. Chest. 2017 51(1):127-138.

“Recurrent VTE” on anticoagulation

Question the diagnosis! Interview the patient re: adherence. Look up INR results, interview radiologists and compare images (old vs. new)

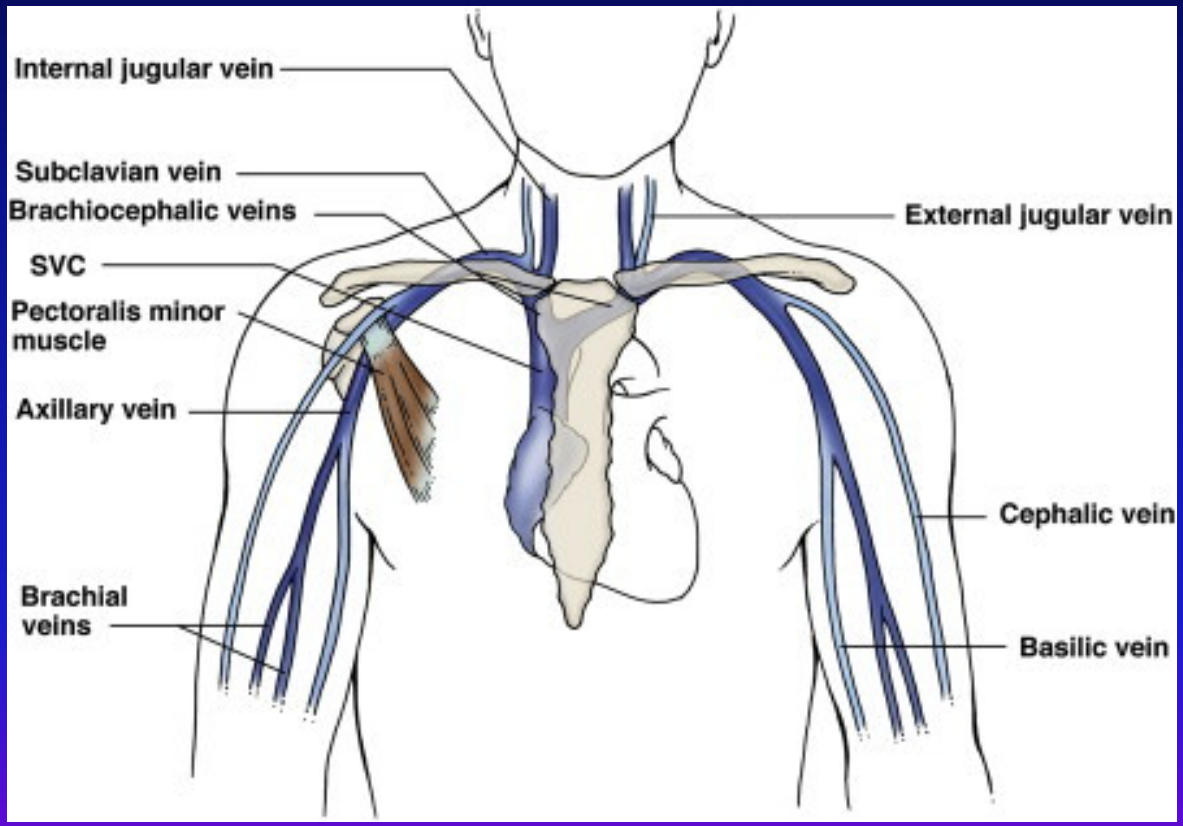
Clinical Scenario	Management
Therapeutic AC	On VKA- consider LMWH or fondaparinux or rivaroxaban On LMWH- empiric 25% dose escalation or fondaparinux or rivaroxaban
Anatomic Compression	Relieve compression, reinstitute AC
Underlying Cancer	Switch to LMWH
Heparin-induced thrombocytopenia	DTI or fondaparinux
Antiphospholipid syndrome	Higher INR target (3-4) or alternative anticoagulation (LMWH, fonda)

Recommended paper: Schulman S. Blood. 2017 Jun 22;129(25):3285-3293.



Graphic assistance: Jeff Harrison, Wilmington, N.C.

Thoracic Outlet Syndrome



What About Arterial Thrombosis?

- Most of the inherited deficiencies (Pro C/S, FVL, AT, etc.) have *not* been associated with an increased risk of arterial thrombosis.
- Look for cardiac source
- Look for vasculitis or other vessel wall problem
- Tests that *might* be helpful [might impact management decisions]
  - HCY
  - Antiphospholipid antibodies
  - PNH, JAK-2

Moll, S. "How I Treat": Patients with Unexplained Arterial Thrombsosis Blood (2020) 2020 Jun 25:blood.2019000820. doi: 10.1182/blood.2019000820.

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Testicular cancer

Todd Yezefski, MD

Clinical Assistant Professor

Disclosures

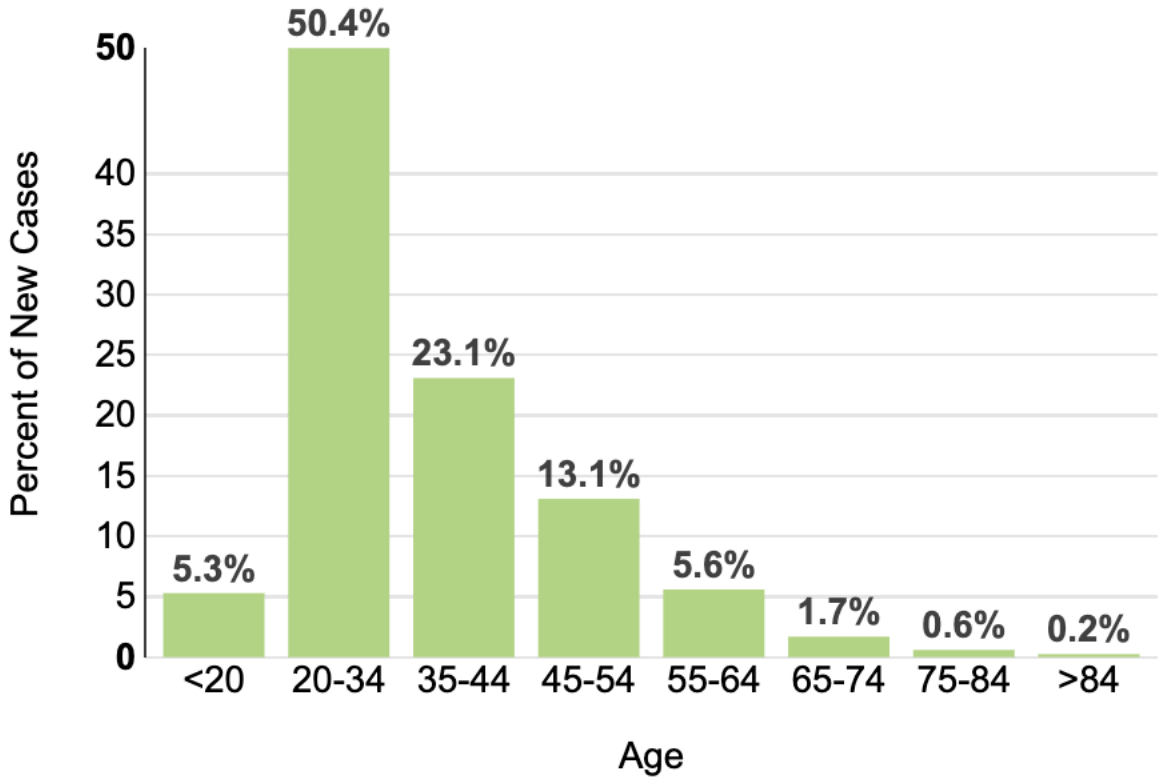
None

Epidemiology

- In 2019, estimated 9,560 new diagnoses
  - 410 deaths from testicular cancer

- Increasing incidence over the last several decades
  - Particularly in Hispanic Americans

Epidemiology



Epidemiology

- Risk Factors
  - Cryptorchidism (RR=10-15, absolute risk 2-3%)
  - Klinefelter's syndrome
  - Personal history (2-3% risk of contralateral 2nd primary)
  - Infertility
  - Family history (Brother RR=8-10, Father RR=4)
    - Germline CHEK2 mutations

Pathology

- Seminoma
- Non-seminoma
  - Embryonal – worse prognosis for stage I
  - Choriocarcinoma
  - Yolk sac tumor – better prognosis for Stage I
  - Teratoma
- If any histology other than seminoma → non-seminoma
- If alpha-fetoprotein is elevated → non-seminoma
- Other rare histologies – lymphoma (>70yr), sex cord/stromal

Pathology

- Teratoma
  - Higher malignant potential in men than women or children

- Isochromosome 12p
  - Occurs in 50% of germ cell tumors
  - Excess copies of 12p can help identify some poorly differentiated carcinomas as GCT through FISH/cytogenetics

Presentation

- Painless testicular mass is pathognomonic
- Testicular pain or discomfort
- Testicular swelling
- Growth or shrinkage of testicle

- Abdominal pain/mass
- Back pain
- Gynecomastia and/or gynecodynia
- Supraclavicular and/or cervical lymphadenopathy
- Renal failure
- Lower limb edema
- Infertility

Evaluation

- H&P
- Scrotal ultrasound
- Tumor markers

  B-HCG, AFP, LDH
- Chemistry panel
- Radical inguinal orchiectomy
- Consider sperm banking

Evaluation

- Pure seminoma
  - CT AP
  - CXR
    - CT chest if RP LAD or abnormal CXR
  - Repeat tumor markers
  - Brain MRI
    - HCG >5,000
    - Extensive lung mets
    - Symptoms

Evaluation

- Non-seminoma
  - CT CAP
  - Repeat tumor markers
    - Staging is based off post-orchiectomy values
  - Brain MRI
    - HCG >5,000, AFP >10,000
    - Choriocarcinoma
    - Extensive lung mets
    - Liver mets
    - Symptoms

AFP

- Half-life 5-7 days
- Not produced by seminoma
- Can be associated with numerous cancer, but mostly hepatocellular carcinoma and non-seminomatous germ cell tumor
- AFP levels <20 ng/mL can be non-specific and treatment decisions should not be based on this alone
- Can be produced by teratoma at low levels
- May be elevated due to liver disease or hepatotoxicity (any liver regenerative state)

β HCG

- Half-life 1-3 days
- Can be made by any type of germ cell tumor
- Extremely high levels suggest choriocarcinoma
- False positives
  - Cross reactivity with luteinizing hormone
  - Can test for this by administering exogenous testosterone
  - Pituitary production in hypogonadal men
  - Marijuana consumption may lead to elevated B-HCG

Lactate Dehydrogenase

- Many conditions can elevate LDH
- Useful only for staging of disseminated disease
- The only important LDH is the level on day 1 of the first cycle of first-line chemotherapy for disseminated disease
- Treatment decisions should never be made on elevated LDH alone

Serum Tumor Markers

	Good (S1)	Intermediate (S2)	Poor (S3)
AFP (ng/mL)	<1,000	1,000-10,000	>10,000
BHCG (IU/L)	<5,000	5,000-50,000	>50,000
LDH*	<1.5x ULN	1.5-10x ULN	>10x ULN

* In practice, cutoff of >3x ULN is generally used

Staging

- Stage I
  - Limited to testis, scrotum, and spermatic cord
- Stage II
  - Metastases to retroperitoneal lymph nodes only
  - Tumor markers normal (S0) or S1
- Stage III
  - Distant metastases (including pelvic nodes)
  - RP nodal mets only but S2/S3

Risk stratification for advanced disease

	Good	Intermediate	Poor
Seminoma	Primary Site: Any Mets to nodes and/or lung	Non-pulmonary visceral mets	None
Non-seminoma	Primary Site: testis or RP Mets to nodes and/or lungs S0-1	Primary Site: testis or RP Mets to nodes and/or lungs S2	Primary site: Mediastinum Non-pulmonary visceral mets S3

Survival Based on Risk Categories for Stage III Disease

Risk Group	Percent of Patients	5 year survival
Good risk	60%	91%
Intermediate risk	26%	79%
High risk	14%	48%

International Germ Cell Cancer Collaborative Group. J Clin Oncol. 1997;15:594-603.

Important Considerations

- Testis masses necessitate urgent workup
- Do not biopsy the testis
- Radical inguinal orchiectomy is the standard since transcrotal orchiectomy can lead to seeding of disease and increased local recurrence rates
- Discuss sperm banking prior to surgery, radiation, or chemotherapy (~20% risk of infertility)
- The testis is a sanctuary site
  - Even in patients with metastatic disease at diagnosis, radical inguinal orchiectomy should be performed, either before or after chemotherapy

Stage I Seminoma

- Active Surveillance - preferred
  - Risk of relapse~15%
  - Tumor size >4cm and rete testis involvement are risk factors for recurrence
- Adjuvant chemotherapy
  - 1-2 doses carboplatin AUC 7
  - ~2% recurrence rate
  - May decrease risk of contralateral primary
- Adjuvant radiation therapy
  - 25-30 Gy to infradiaphragmatic LNs
  - ~4% relapse rate
  - Risk of secondary cancer, GI complications, cardiovascular disease

Oliver et al, JCO 2011;29(8):957-962
Solberg et al, Ann Onc 2016;27(7):1299-1304
Aparicio et al, JCO 2011;29:4677-4681

Stage I Seminoma

- With any option, survival ~100%
- Relapse with tumor markers or measurable disease is treated as the stage at recurrence
- Caution with Stage IS
  - Generally portends occult disease
  - Consider false positive BHCG

Stage II Seminoma

- Nodes <3cm (IIA/IIB)
  - Radiation therapy or chemotherapy (BEPx3 or EPx4)
    - BEP – Bleomycin, etoposide, cisplatin; EP – etoposide, cisplatin

- Nodes >3cm (IIB/IIC)
  - Chemotherapy BEPx3 or EPx4

- No randomized trials

Stage I Non-seminoma

- Surveillance - preferred
  - 25% relapse
  - LVI, >pT2, and high % embryonal histology predictive of relapse

- Retroperitoneal lymph node dissection
  - 20% likelihood of finding residual disease
    - Unclear who benefits from adjuvant chemo – typically given for >5 nodes or >2cm in size
  - 11% risk of relapse
  - 10-20% of patient get chemotherapy
  - 10% risk of retrograde ejaculation

Stage I Non-seminoma

- Chemotherapy
  - 1-2 cycles BEP
  - 2% risk of relapse

- Stage IS – treat as advanced disease with chemotherapy

Stage II Non-seminoma

- IIA with normal markers
  - RPLND
    - 30% will be benign
    - Use of adjuvant chemo based on amount/size of nodes
  - BEP x3 or EP x4
  - If borderline LAD, consider short interval repeat imaging

- IIA with S1, IIB/IIC
  - BEP x3 or EP x4

Good Risk Disease

- BEP x3
  - Equivalent to BEP x4
  - Less cisplatin – anorexia, nausea, vomiting, neurotoxicity, ototoxicity, infertility
  - Less risk of etoposide-induced leukemia
    - Dose-dependent
- EP x4
  - EP x4 superior to EP x3
  - Bleomycin can cause pulmonary fibrosis
  - Post-chemo RPLND is more difficult after bleomycin
  - Consider in >50yr, renal insufficiency, pre-existing lung disease

De Wit et al, JCO 2001;19(6):1629-1640
Culine et al, Ann Onc 2007;18(5):917-924

BEP x3 vs EP x4

GETUG T93BP – 257 patients, 1:1 randomization

	BEP x3 (127)	EP x4 (124)	P-value
G3-4 Neutropenia	47%	62%	<0.001
G1-3 Neurotoxicity	2	7	<0.001
Adverse Events*	13%	22%	0.05
PFS	91%	86%	0.135
4yr OS	96%	92%	0.096

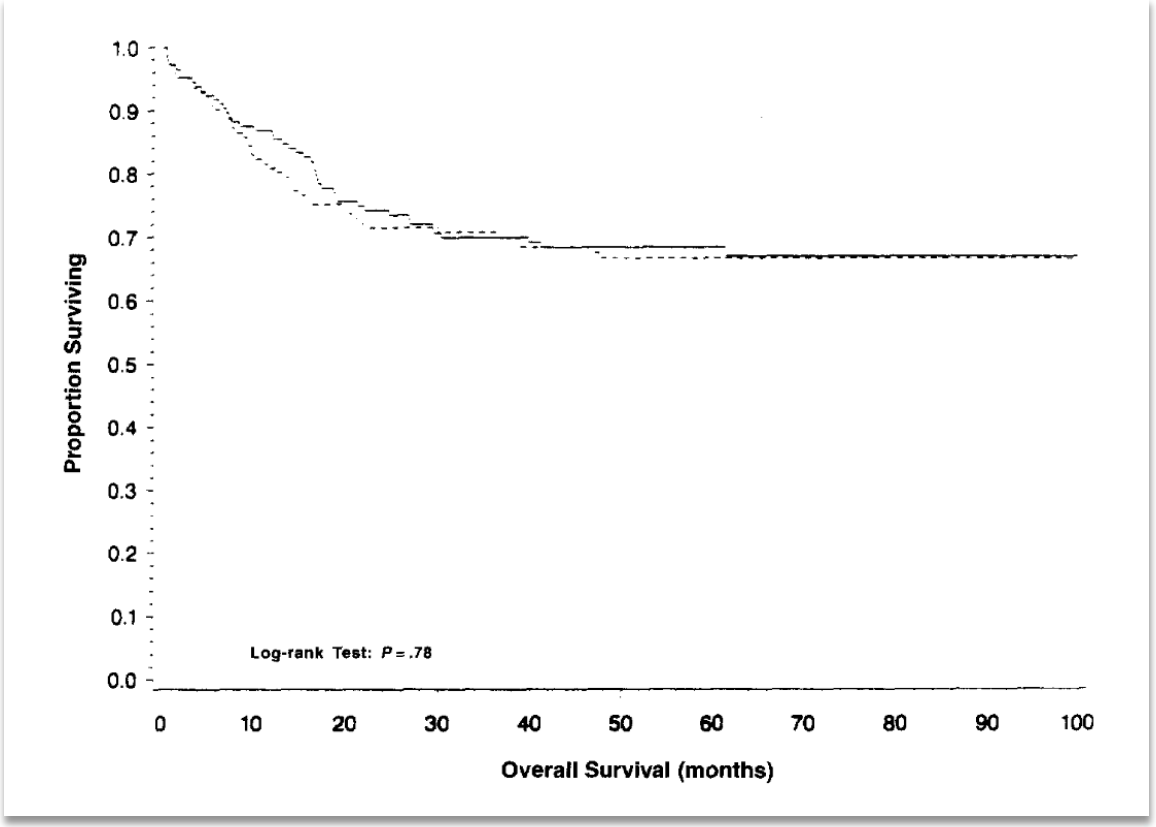
Indiana University Testis Cancer Database – 223 patients

	BEP x3 (178)	EP x4 (45)	P-value
10yr OS	98%	91%	<0.01

Culine et al, Ann Onc 2007;18(5):917-924
Cary et al, Clin GU Cancer 2018;16(2)e307-e313

Intermediate and Poor Risk Disease

- BEP x4 or VIP x4
  - VP-16 (etoposide), ifosfamide, cisplatin
  - VIP for patients with concern for bleomycin pulmonary toxicity
  - Increased hematologic toxicity with VIP
  - VIP given inpatient



Nichols et al, JCO 1998;16(4)1287-1293

Post-chemotherapy management

- Seminoma
  - Most residual masses are benign
    - <3cm – 3% carcinoma (path+ or relapse)
    - >3cm – 30% carcinoma
  - Observe
  - Observe masses <3cm, resect/biopsy if >3cm
  - Observe <3cm, PET if >3cm → resect/biopsy if PET+
    - Generally wait until at least 6-8 weeks post-chemo for PET
      - Improved sensitivity and specificity

Post-chemotherapy management

- Non-seminoma
  - Resect residual masses when possible
  - Residual mass histology
    - Viable carcinoma: 10%
    - Teratoma: 40%
    - Fibrosis/necrosis: 50%
  - Teratoma needs to be removed
    - Growing teratoma syndrome
    - Malignant transformation
      - Chemo resistant

Recurrent/Relapsed Disease

- For Stage I surveillance and Stage I/II treated with RPLND or RT, treat based on stage at time of recurrence

- Post-chemo recurrence
  - Most often <2 yrs for NSGCT, <3yr for seminoma
  - Salvage chemotherapy
    - VIP x4
    - VeIP x4 (vinblastine, ifosfamide, cisplatin)
    - TIP x4 (paclitaxel, ifosfamide, cisplatin)
    - High-dose chemotherapy with autologous stem cell rescue

HDC with Autologous Stem Cell Rescue

- No benefit over standard chemotherapy for 1st line treatment
- No high-quality studies comparing HDC to standard salvage chemotherapy
- Retrospective analysis from Indiana University
  - Tandem transplant with carboplatin 700mg/m2 and etoposide 750mg/m2 qd x3d
  - 364 patients
  - 2yr OS 66%
  - 2nd line – 2yr PFS 63%; 3rd line – 2yr PFS 49%
- TIGER Trial – salvage chemo for HCD with TI-CE

Adra et al, JCO 2017;35(10):1096-1102

Late Relapse

- Often can be cured
- Resection is integral to the plan
- At risk for subsequent relapse

Seminoma Stage I	NSGCT Stage I	Pathological stage II*	Good-risk disease	Intermediate- or poor-risk disease
Carboplatin 1 or 2 doses	BEP x 1 or BEP x 2	BEP x 2 or EP x 2	BEP X 3 or EP X 4	BEP X 4 or VIP X 4

	Relapsed after first-line chemotherapy
Salvage Treatment	VeIP x 4 or TIP x 4 or HDCT x 2

*Pathological stage II refers to patients who had positive nodes with GCT after undergoing primary RPLND for Stage I/II disease.

Surveillance

- Clinic visit, tumor markers, imaging
  - Decrease frequency over time away from treatment
- Less intense follow-up for patient who have had systemic therapy
- Trend to using less imaging due to concern over radiation exposure
  - MRI can be used in place of CT; CXR in place of CT chest
- Consult NCCN guidelines as recommendations change frequently

Survivorship

- Cardiovascular disease risk increases ~2X
- Metabolic syndrome up to 10X risk
- Infertility
- Hypogonadism
- Erectile dysfunction – often with normal testosterone levels and may be a neuropathy
- Secondary malignancy risk increases 1.5-2X
- Contralateral primary testicular cancer – 2-3%
  - Testicular self-exam, exam at clinic visits

Survivorship

- Restrictive pulmonary disease - may be more related to cisplatin than bleomycin
- Hearing loss, tinnitus
- Peripheral neuropathy
- Renal dysfunction
- Raynaud's phenomenon

Key Points

- Affects young men and is highly curable, even with advanced disease
- Tumor markers are critical for diagnosis, staging, prognosis, treatment response, and surveillance
- For Stage I, surveillance is preferred
- Chemo-sensitive: don’t dose reduce or delay!
- High-dose chemotherapy with autologous stem cell rescue can be curative
- Patients can have significant long-term side effects from treatment

Things to Remember for the Boards

- Diagnosis
  - Seminoma vs non-seminoma
  - Staging
  - Risk stratification for Stage III disease
- Use of serum tumor markers for staging, prognosis, treatment response, and surveillance
  - Know the half-lives of AFP (5-7 days) and BHCG (1-3 days) and causes of false positives
- Treatment options by stage and risk

Things to Remember for the Boards

- Management of residual masses
  - PET for seminoma >3cm
  - Resection for NSGCT
    - Risk of teratoma and persistent disease

- Complications and toxicity of treatment

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Thrombocytopenia: Updated Review

Terry Gernsheimer, MD

Seattle Cancer Care Alliance

University of Washington School of Medicine

Fall, 2020

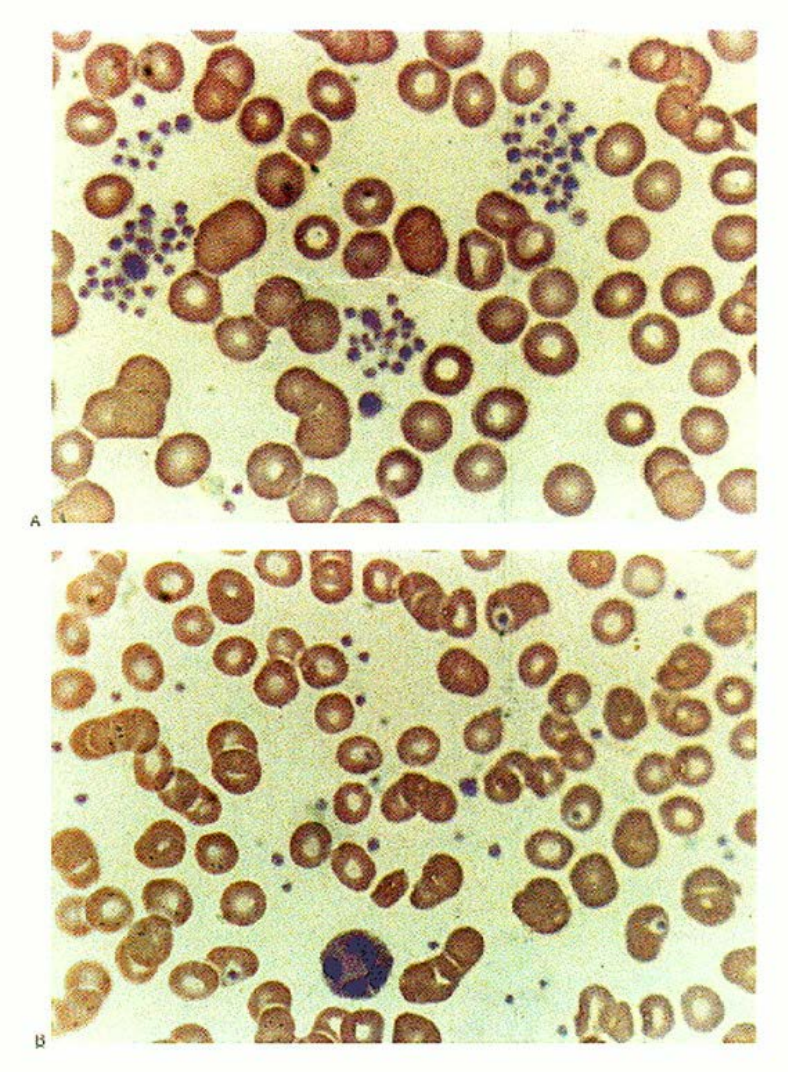
Discussion of off-label drug use:

Rituximab, mycophenolate, vincristine, azathioprine, cyclosporine, cyclophosphamide, danazol, dapsone, sirolimus, pentasacharides, antifibrinolytic agents, anti-RhD, prostacycline, tirofiban, aspirin

Approach to thrombocytopenia

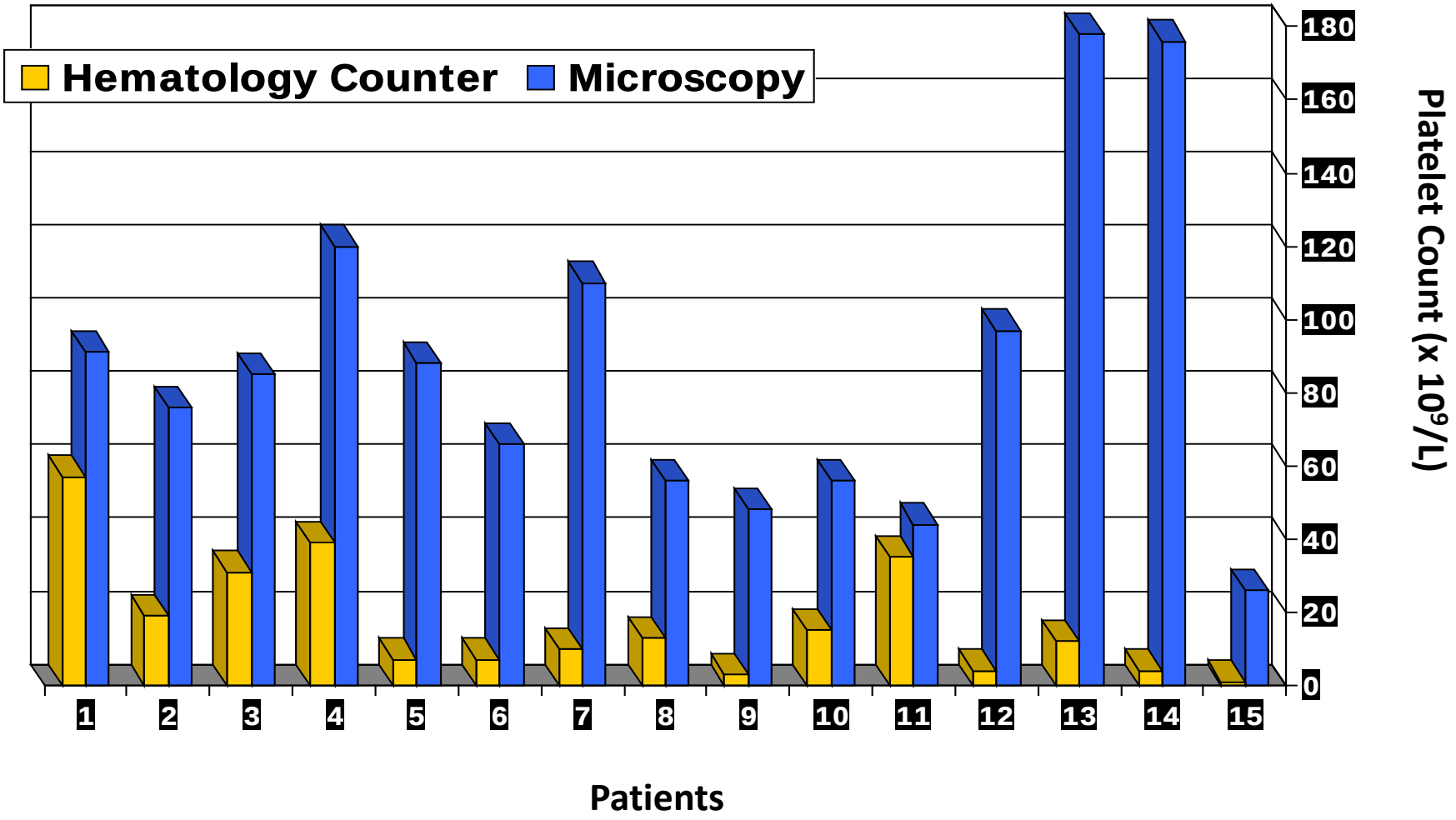
- History
- Physical examination
- Complete blood count
- Peripheral blood smear

Pseudo-thrombocytopenia



Shalev, O. et. al. N Engl J Med 1993;329:1467

Platelet count errors in macrothrombocytopenia



Noris, P. et al., Am. J. Medicine, 1998; 104: 355-360

Mechanisms of thrombocytopenia

- Decreased production
- Increased destruction
- Increased splenic sequestration
- Dilutional

Disorders of production: MYH9-related platelet disorders

Clinical features	May-Hegglin	Sebastian	Fechner	Epstein
Macrothrombocytopenia	Yes	Yes	Yes	Yes
Leukocyte inclusions	Yes	Yes	Yes	No
Hearing impairment	No	No	Yes	Yes
Cataracts	No	No	Yes	No
Nephritis	No	No	Yes	Yes

From Seri, M., et al., *Medicine*, 2003, 82(3):203-215

Hereditary thrombocytopenia

- Autosomal dominant
  - MYH9 Gene mutations e.g. May Hegglin
    - Tpenia, large platelets, neutrophil inclusions
  - Gray Platelet Syndrome – large, ↓ α granules, pmn granules
- Autosomal recessive
  - Congenital amegakaryocytic thrombocytopenia
  - Thrombocytopenia with Absent Radii
  - Bernard Soulier syndrome large plts w/ ↓ GPIb
- Sex-linked recessive
  - Wiskott-Aldrich syndrome –
    - small plts, immunodefic, eczema

Congenital thrombocytopenias

- Macrothrombocytopoenia
  - MyH9
  - GP1B
  - GATA1-X-linked
- Microthrombocytopenias
  - WAS
- Normal platelet size
  - ANDRD26
    - Predisposition to MDS and AML (30 X increase)
  - RUNX1
  - MPL
  - ADAMTS13

Acquired thrombocytopenia: ↓ Production

Are other Cell Lines Affected?

- Intrinsic marrow abnormalities
- Vitamin deficiencies
- Toxins
- Drugs
- Infection
- Marrow infiltration
- Liver disease

Thrombocytopenia in liver disease

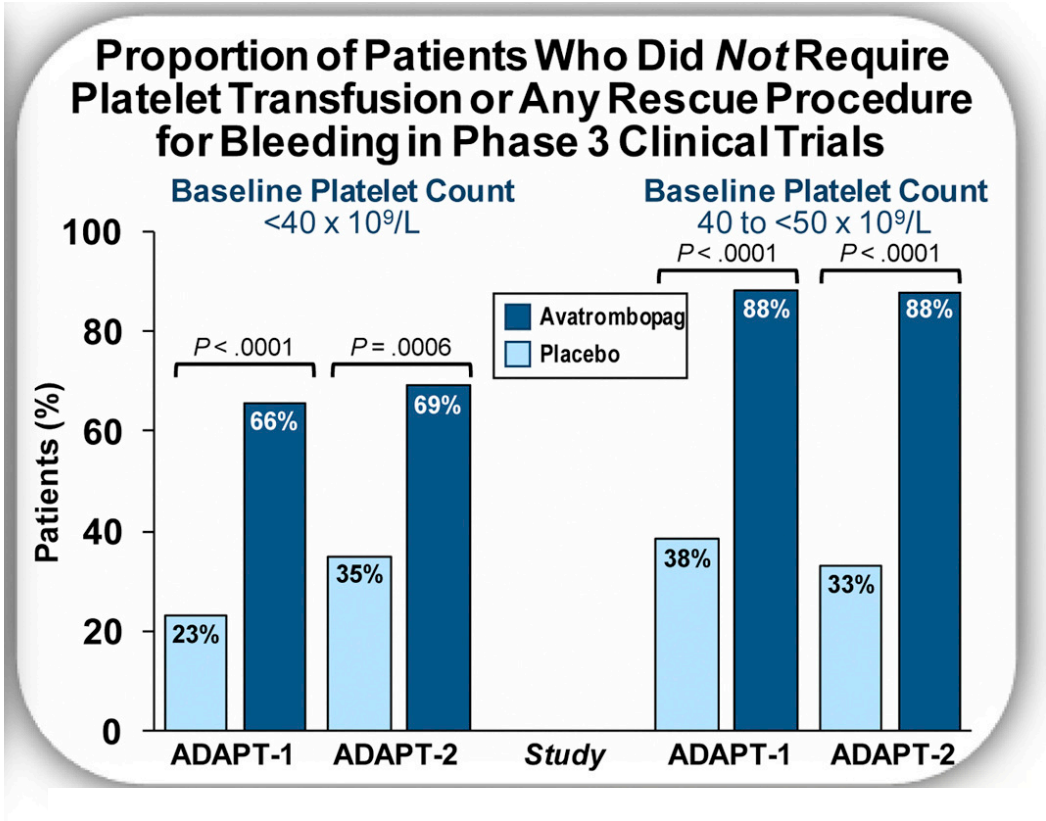
- Multifactorial
  - Splenomegaly
  - Decreased TPO
  - Increased turnover
  - Immune
    - Hepatitis C
    - Autoimmune hepatitis
- Therapy
  - Transfusion
  - Eltrombopag (HCV)
  - Avatrombopag for procedures

Increasing platelet production for procedures in cirrhosis

N= placebo 158, Avatrombopag 277

Procedure

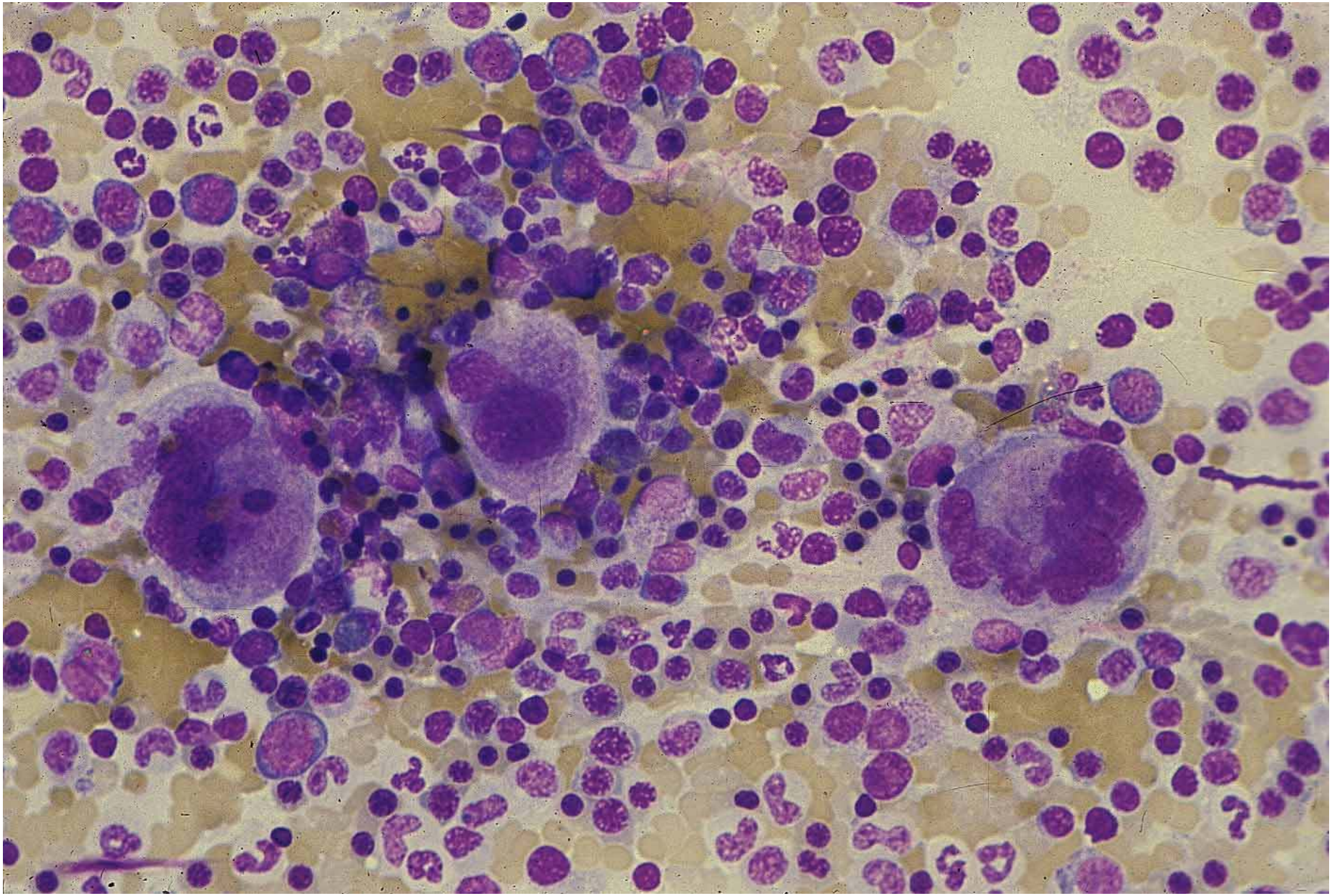
- Paracentesis
- Endoscopy
- Colonoscopy
- Liver biopsy
- Ablation
- Chemoembolization
- Dental procedures
- TIPS
- Laparoscopic
- Vascular catheterizaton



Gastroenterology 2018; 155:705-718

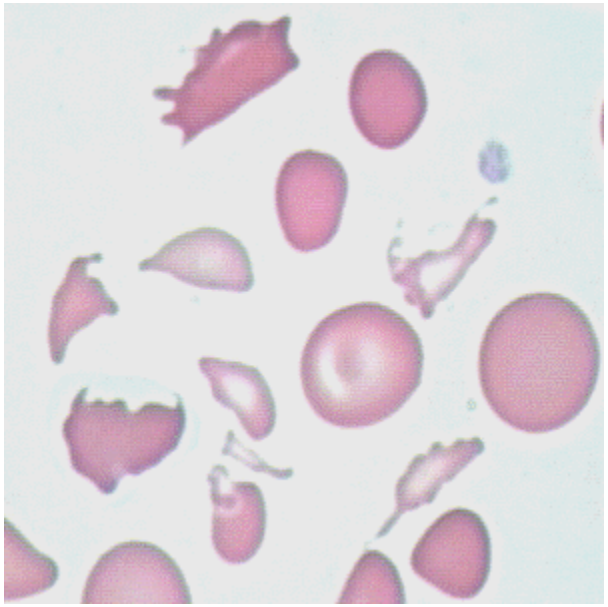
Thrombocytopenia due to increased platelet destruction and consumption

- Platelet lifespan < 10 Days
  - Increased platelet turnover
- Normal or increased megakaryocytes
- Immune or non-immune



Isolated platelet consumption: MAHA

- Disruption of laminar flow
- Vasculitis
- Malignancy
- Malignant hypertension
- Cryoglobulinemia
- Infection
  - Septic emboli, rickettsia



- Thrombotic Thrombocytopenic Purpura & Hemolytic Uremic Syndrome

Is platelet transfusion contraindicated?

Goel et al. Blood. 2015; 125(9):1470-1476

Isolated platelet consumption

- Thrombotic Thrombocytopenic Purpura
  - Adults
  - Classic pentad
  - Rx - plasma exchange
- Secondary TTP
  - Drugs, HIV, pregnancy, malignancy
- Congenital TTP
- Thrombotic microangiopathies with acute kidney injury
  - Complement mediated –C-TMA (HUS)
  - Shigatoxin (Stx HUS) 0157:H7 Ecoli

TTP & atypical HUS

	TTP	C-TMA
Pathophysiology	ADAMTS13 Deficiency	Aberrant activation of alternative C' pathway Factor H gene mutations (25%), others
Clinical	Tpenia/anemia more severe	Renal insufficiency more prominent
Therapy High risk disease	Plasma Plasma exchange + corticosteroids, rituximab Caplacizumab	Chronic C5 inhibition Eculizumab, ravulizumab

Immune platelet destruction

- Auto-Immune
  - Primary – "ITP"
  - Secondary
    - Collagen-Vascular Disease
    - Malignancy
    - Infection
    - HIV
- Drug induced
  - vanc, pcns, quinine
- Allo-immune
  - Post-Transfusion Purpura
  - Neonatal Alloimmune Thrombocytopenia

Recommendations for diagnosis of primary ITP

- Diagnosis principally one of exclusion
- History & PE
- Full blood count, retic & peripheral blood examination
- Helicobacter pylori infection detection by breath test or stool antigen (regional)
- HBV, HIV, HCV
- Quantitative Immunoglobulins
- DAT
- Other testing in selected individuals (ab, imaging)
- Bone marrow in selected individuals only

Provan D et al. *BloodAdvances* 2019;3: 3780-3817.

Summary of recommendations for initial treatment of ITP

	ASH 2020[1]	**ICR Recommendations[2]**
Platelet count threshold for treatment	≤30 × 10^9/L	<20-30× 10^9/L Individualize to patient & phase
First-line treatment	Corticosteroids (prednisone, methyprednisolone or dexamethasone) taper off by 6 weeks	same
First-line treatment if corticosteroids are contraindicated	IVIg or anti-D	same
Emergency treatment	IVIg plus corticosteroids	High-dose IV corticosteroids plus IVIg platelet transfusions antifibrinolytic drugs

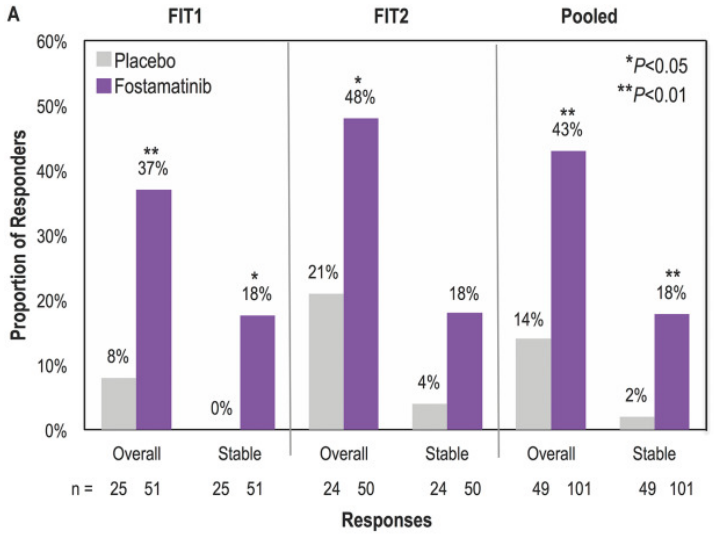
Neunert C et al. *BloodAdvances* 2019;3:3829–66; Provan D et al. *BloodAdvances* 2019;3: 3780-3817

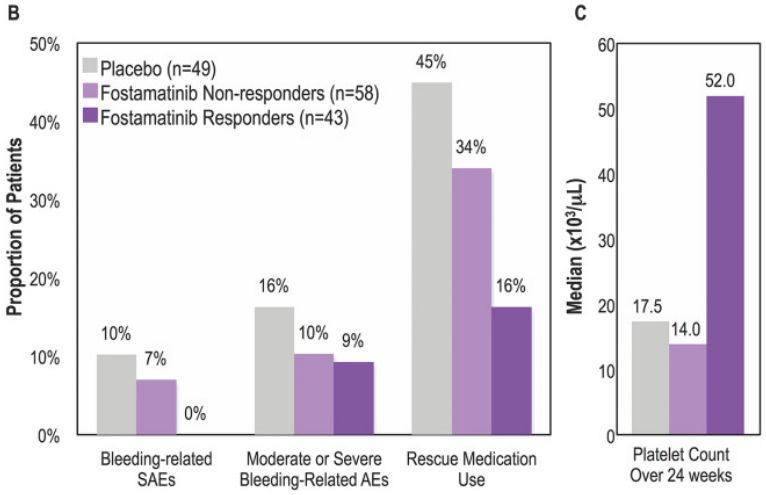
Summary of recommendations for treatment of persistent (>3 months) ITP

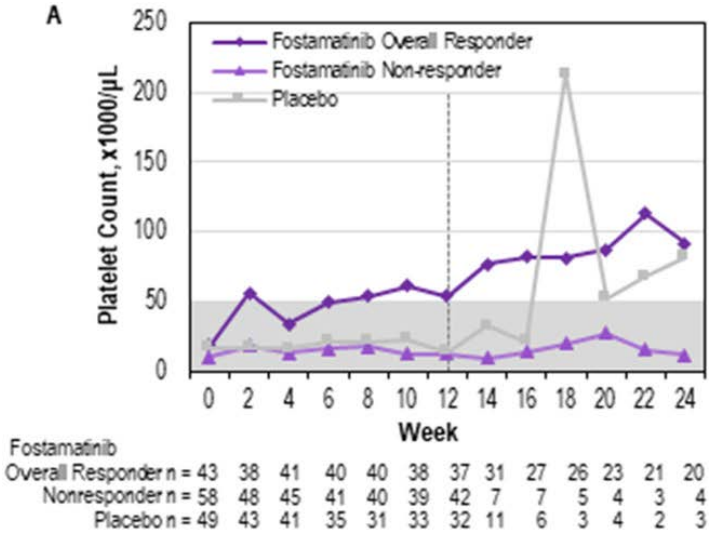
Treatment type/parameter	ASH 2020[1]	ICR Recommendations[2]
Platelet count threshold for treatment	≤30 × 10^9/L	Treat to maintain platelet count >20-30× 10^9/L Individualize to patient & phase Minimize toxicity
Subsequent Therapy	TPO receptor agonists Rituximab Splenectomy	TPO receptor agonists Rituximab Fostamatinib Splenectomy
Agents with less robust evidence /subsequent treatment	Azathioprine Cyclosporin A Cyclophosphamide Danazol	Dapsone Mycophenolate mofetil Vinca alkaloids TPO RA switch

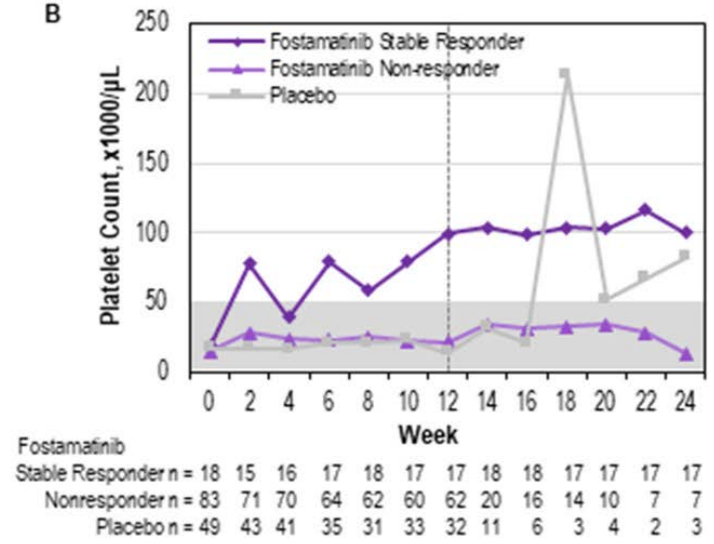
Neunert C et al. *BloodAdvances* 2019;3:3829–66; Provan D et al. *BloodAdvances* 2019;3: 3780-3817

Syk kinase inhibition:
Fostamatinib for refractory persistent/chronic ITP









Bussel J, et al. Hematology. 2018; 93: 921-930

Treatment of drug induced thrombocytopenia

- Stop offending agent(s)
- Severe: IVIg
- Severe refractory: Plasma exchange
  Dialysis
- Severe adjunctive therapy
  - Platelet transfusions
  - Antifibrinolytic agents

- Testing for drug dependent antibody

Clinical diagnosis of HIT

- History of heparin exposure
- Thrombocytopenia during and after heparin exposure (<150,000)
  - Drop in platelet count (>50%) rather than absolute thrombocytopenia
  - Thrombocytopenia recovers after heparin withdrawal
- With or without thrombotic complications
- Unusual presentations
  - Absence of expected increase, skin necrosis, delayed onset

Laboratory tests for HIT

Functional (activation)

- **Serotonin release**
- **ATP release**

- **Platelet aggregation**
- **Flow cytometry**

Antigen

- **Heparin-PF4 ELISA**
- **Other IA**

Clinical scoring system for HIT pretest probability:

"The 4Ts"

4T's	2 points	1 point	0 point
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥20*	Platelet count fall 30–50% or platelet nadir 10–19	Platelet count fall <30% or platelet nadir <10
Timing of platelet count fall	Clear onset between days 5–10 or platelet fall ≤1 day (prior heparin exposure within 30 days)†	Consistent with days 5–10 fall, but not clear (e.g. missing platelet counts); onset after day 10‡; or fall ≤1 day (prior heparin exposure 30–100 days ago)	Platelet count fall <4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed); skin necrosis§; acute systemic reaction postintravenous unfractionated heparin (UFH) bolus	Progressive or recurrent thrombosis¶; Non-necrotizing (erythematous) skin lesions§; Suspected thrombosis (not proven)**	None
Other causes for thrombocytopenia	None apparent	Possible††	Definite††

0-3 Points: Low pretest probability of HIT; lab testing not indicated

4-5 Points: Intermediate pretest probability of HIT

6-8 Points: High pretest probability of HIT

Lo et al (2006) *Journal of Thrombosis and Hemostasis.*

Alternate thrombotic therapy

Low Molecular Wt Heparin

<u>Anti-platelet agents</u>

Prostacycline, tirofiban, aspirin

<u>Direct Thrombin Inhibitors</u>

Argatroban

Bivalirudin

DOACs?

<u>Pentasacharides</u>

Fondaparinux

Cardiac surgery with history of HIT

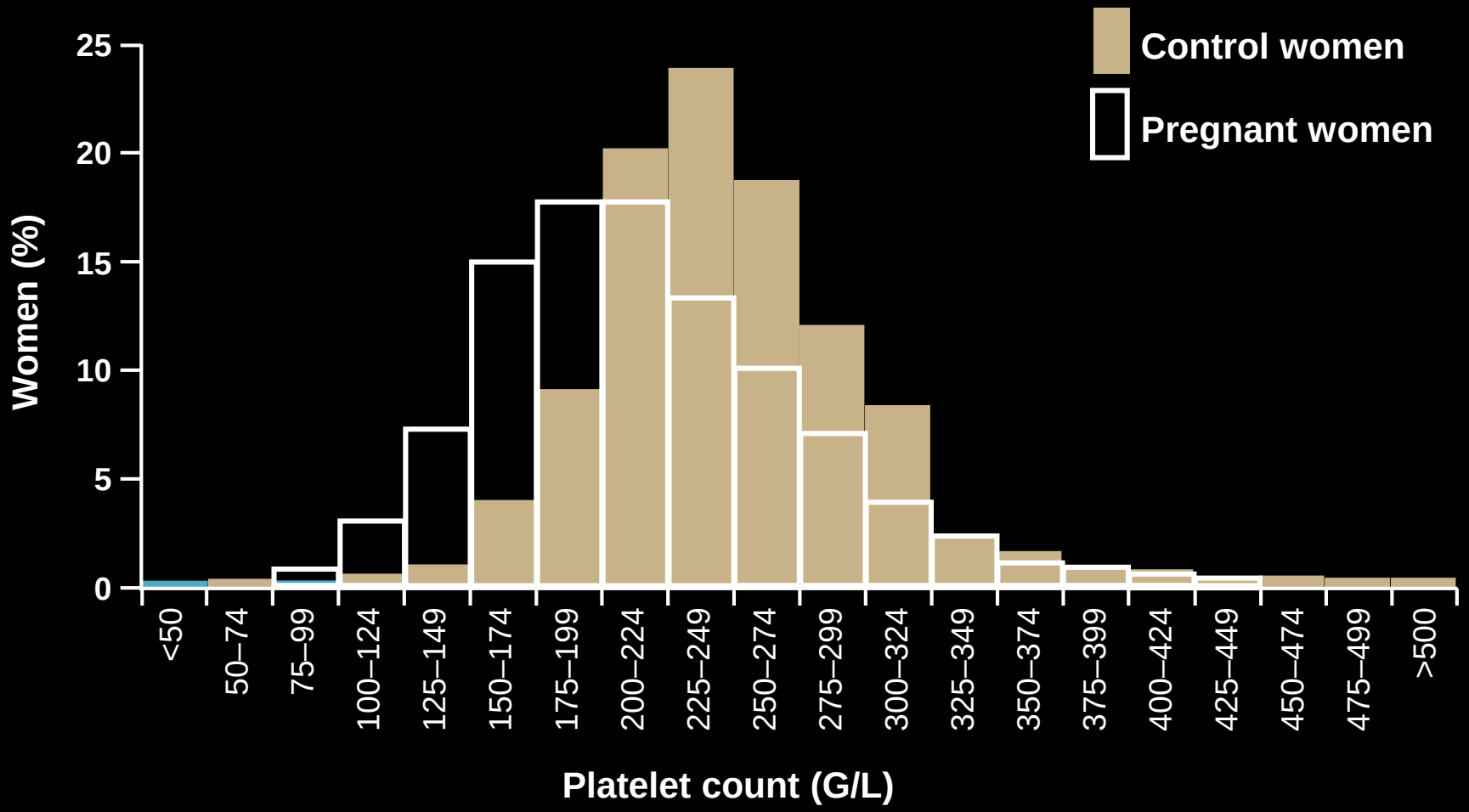
- Delay 3-6 months
- Antibody (ELISA) Neg
- Expose during CPB only
- Use alternate anticoagulation post-op

- Experimental:
  - Plasma Exchange
  - IVIg

Warfarin in HIT

- Contraindicated until platelet count recovery (or >100,000) due to decreased Protein C
- Use with a thrombin inhibitor
  - Associated with progression of DVT to venous limb gangrene
  - Caution if INR >4
- Do not use loading dose

Platelet count at term in healthy pregnancy



Boehlen F et al. *Obstet Gynecol* 2000;95:29–33

Pregnancy-associated thrombocytopenia

- Isolated Thrombocytopenia
  - Incidental (Gestational)
  - Immune (ITP)
  - Drug-induced
    - HIT
  - Congenital
  - Type IIb vWD

- Systemic Disorders
  - Preeclampsia
  - HELLP syndrome
  - Acute fatty liver
  - Thrombotic microangiopathies
  - SLE / Antiphospholipid antibodies
  - DIC
  - Viral infection
  - Nutritional deficiencies
  - Hypersplenism
  - Bone marrow dysfunction

Evaluation of thrombocytopenia in pregnancy

Clinical History & Physical Exam	History of thrombocytopenia Bleeding history Hypertension
Review blood smear	Pseudothrombocytopenia Large platelets Fragments
Laboratory evaluation	Coagulation testing, vWF Thyroid testing LFTs Virus – HIV, HCV, H Pylori ANA, Lupus anticoagulant, ACLA

Gernsheimer T , James A, Stasi R. *Blood* 2013 ;121:38-47

Immune thrombocytopenia (ITP) in pregnancy

- Incidence: 1 in 1,000 to 1 in 10,000 pregnancies
- Most common cause of thrombocytopenia in 1st trimester
- Pathogenesis--autoantibodies targeting platelet gp's or T cell dysregulation and direct toxicity
- 31% require intervention
- Incidence of neonatal thrombocytopenia ~20%
  - 4% severe

1. Gill KK & Kelton JG. *Semin Hematol* 2000;37:275–289; 2. Won YW et al. *Korean J Intern Med* 2005;20:129–134; 3. Fujimura K et al. *Int Hematol* 2002;75:426–433

Management of ITP in pregnancy

- Indications for therapy
  - First and second trimesters
    - Symptomatic
    - Platelet count 20–30,000x10^9/L
    - Procedures
- Monitor more frequently in third trimester
- Therapy based on risk of maternal haemorrhage
  - Therapy of mother does not affect fetal platelet count
- First-line therapy
  - Corticosteroids
  - IVIg
- Combine first-line therapies in refractory patients

Gernsheimer T , James A, Stasi R. *Blood* 2013 ;121:38-47

Management of refractory ITP in pregnancy

Second-line therapies

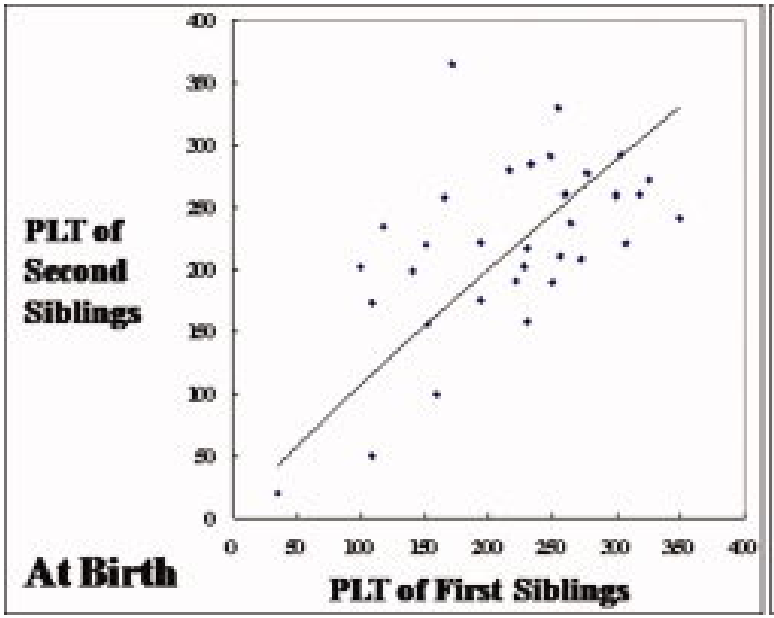
- IV anti RhD
- Splenectomy
  - Rarely performed, best performed in the second trimester
- Azathioprine
- Cyclosporine
- HDMP with IVIg or azathioprine if refractory to oral corticosteroids or IVIg

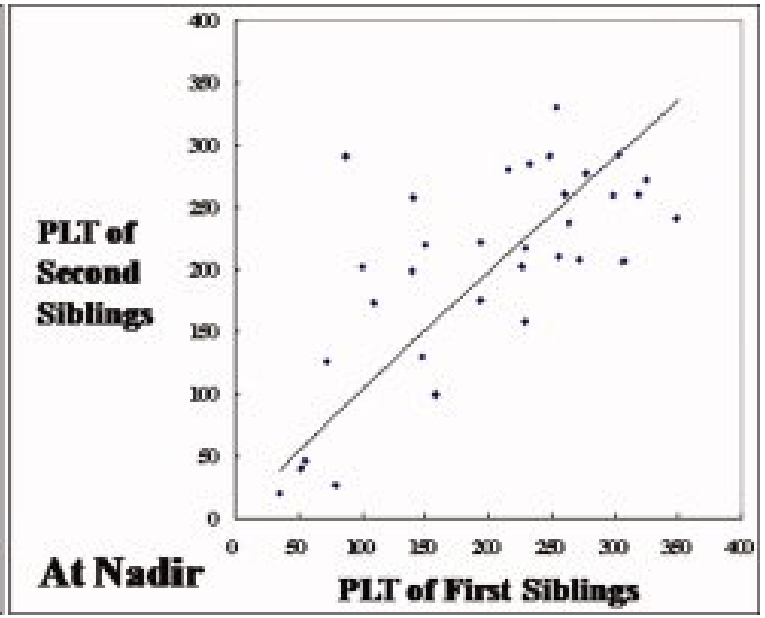
Should not be used

- Other immunosuppressive drugs
- +/- rituximab
- Vinca alkaloids, danazol
- TPO receptor agonists, TPO

Gernsheimer T , James A, Stasi R. *Blood* 2013 ;121:38-47

Correlation of sibling platelet counts at birth and at nadir





$P = 0.001$ $P < 0.0001$

Koyama S, et al. Am J Hematol. 87:15-21, 2012

Management of delivery

- Mode of delivery determined by obstetric indications
  - Most neonatal haemorrhage occurs at 24–48 hrs
  - Fetal platelet count measurement not recommended
  - Avoid procedures with increased fetal bleeding risk

- Epidural anaesthesia
  - Risk of spinal hematoma unknown
  - Platelets of 70,000/μL
  - Consider other hemostatic parameters and history
  - Usefulness of thromboelastography unclear

Gernsheimer T , James A, Stasi R. *Blood* 2013 ;121:38-47

Thanks for your attention!

Pancreatic Cancer

E. Gabriela Chiorean, MD
Professor of Medicine
GI Medical Oncology
University of Washington

Objectives

Pancreatic cancer:

- epidemiology
- diagnosis
- treatments

Pancreatic Cancer

- Projected 57,600 new cases of pancreatic cancer in US with 47,000 deaths in 2020
- 5-yr OS 9%
- Stage for stage, it is associated with the lowest survival rates of any major cancer type
- By 2030 it is expected to rise to the 2nd leading cause of cancer death in the US (behind lung cancer)

Siegel RL, et al. Cancer Statistics 2020

Risk Factors

- Age
- Gender (men slightly higher than women)
- Race
- Smoking
- Obesity
- Diet
- Chronic pancreatitis
- Exposures (pesticides, benzene, dyes, petrochemicals)
- Family history / genetic mutations

Number of 1st Degree Relatives	Standardized Incidence Ratio (95% CI)	Incidence (per 100,000 in U.S. population)
General U.S. Population	-	9
1	4.5 (0.54 - 16.3)	41
2	6.4 (1.8 – 16.4)	58
3 or more	32 (10.4 – 74.7)	288

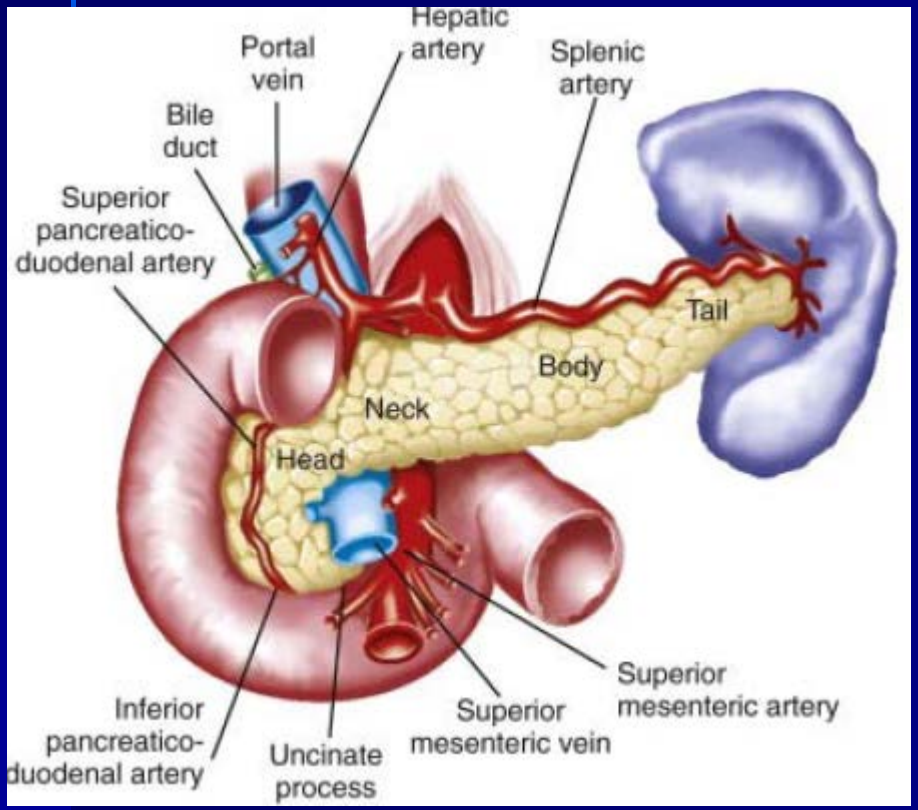
Klein AP et al. Cancer Research 2004; 64; 2634-2638

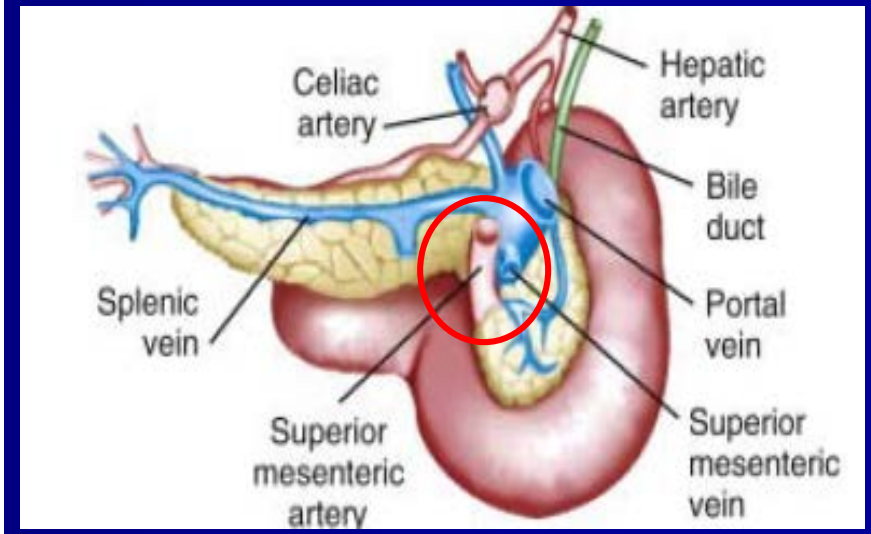
Risk Factor: Genetics

Syndrome	Mutation	Relative Risk of Pancreatic Cancer	Other Malignancies
Hereditary Breast and Ovarian Cancer (HBOC)	*BRCA1, BRCA2*	2-9	Ovary, prostate, melanoma
	PALB2	Increased	Breast, ovarian, prostate
Ataxia Telangiectasia	*ATM*	3	Breast
Familial Atypical Multiple Mole Melanoma (FAMMM)	*CDKN2A/P16*	13-39	Multiple nevi, dysplastic nevi, melanomas
Peutz-Jeghers Syndrome	*STK11*	132	Hamartomatous polyps, breast, colon, small intestine, ovarian
Lynch Syndrome	*MLH1, MSH2, MSH6, PMS2, EPCAM*	9-11	Colon, endometrial, ovary, gastric, small bowel, renal pelvis, brain, sebaceous
Hereditary Pancreatitis	*PRSS1*	53	
Familial Polyposis	*APC*	5	Colon, small bowel, fundic gland polyps, desmoid, thyroid, hepatoblastoma, brain

Summarized in: Syngal et al. American Journal Gastroenterology 2015
Screening recommendations: Syngal et al. American Journal Gastroenterology 2015, Canto et al. Gut 2012.

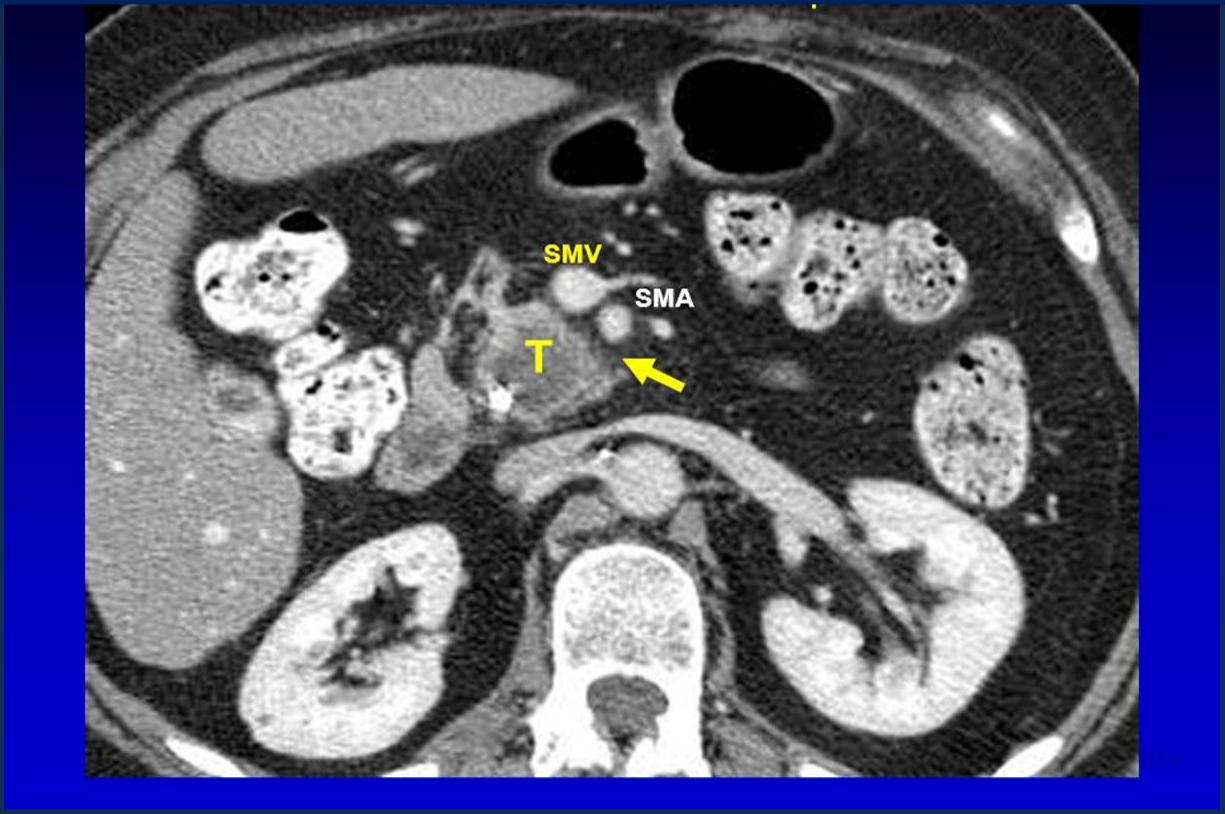
Defining Resectability





Sleisinger and Fordtran's Gastrointestinal and Liver Disease, 9th edition

Resectable Pancreatic Adenocarcinoma



Case 1: What is the standard of care after surgery for pancreatic cancer?

55 yo woman underwent R0 resection for pT3N2 pancreatic adenocarcinoma. She recovered well after surgery with no post-operative complications.

CA19-9 after surgery is 19 (normal 0-54)

CT scans show no evidence of metastatic disease.

She has a history of hypertension.

Which of the following would you consider the most appropriate adjuvant treatment?

A. Gemcitabine

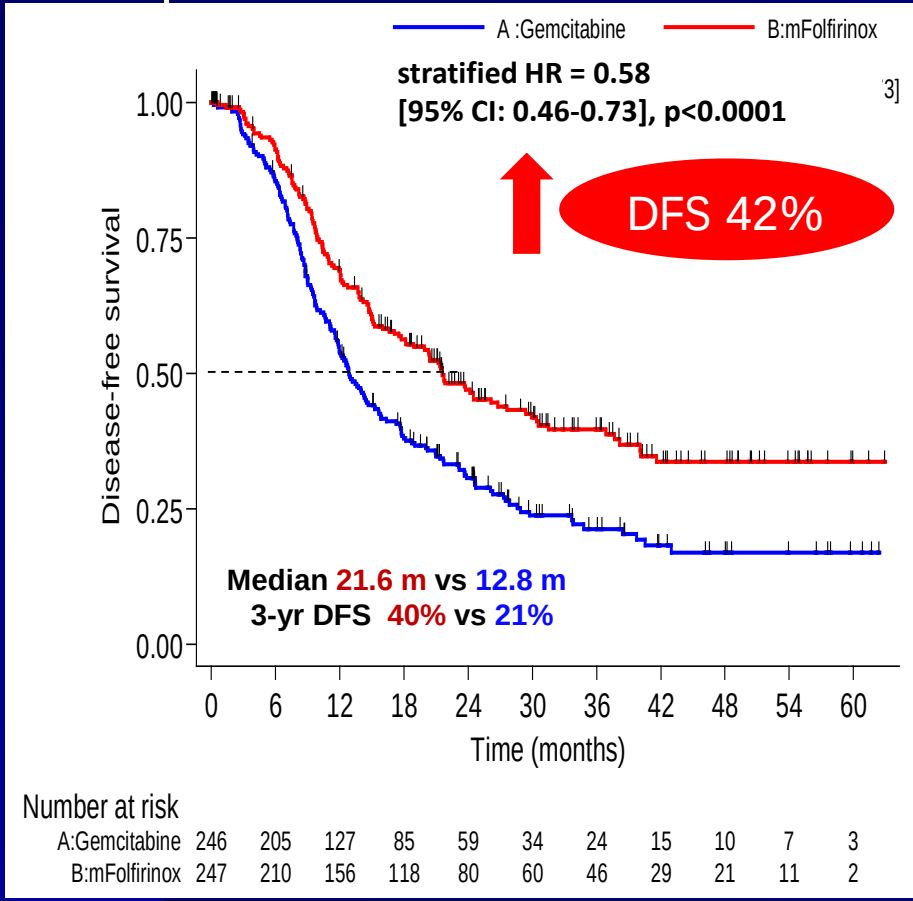
B. Gemcitabine + capecitabine

C. modified FOLFIRINOX

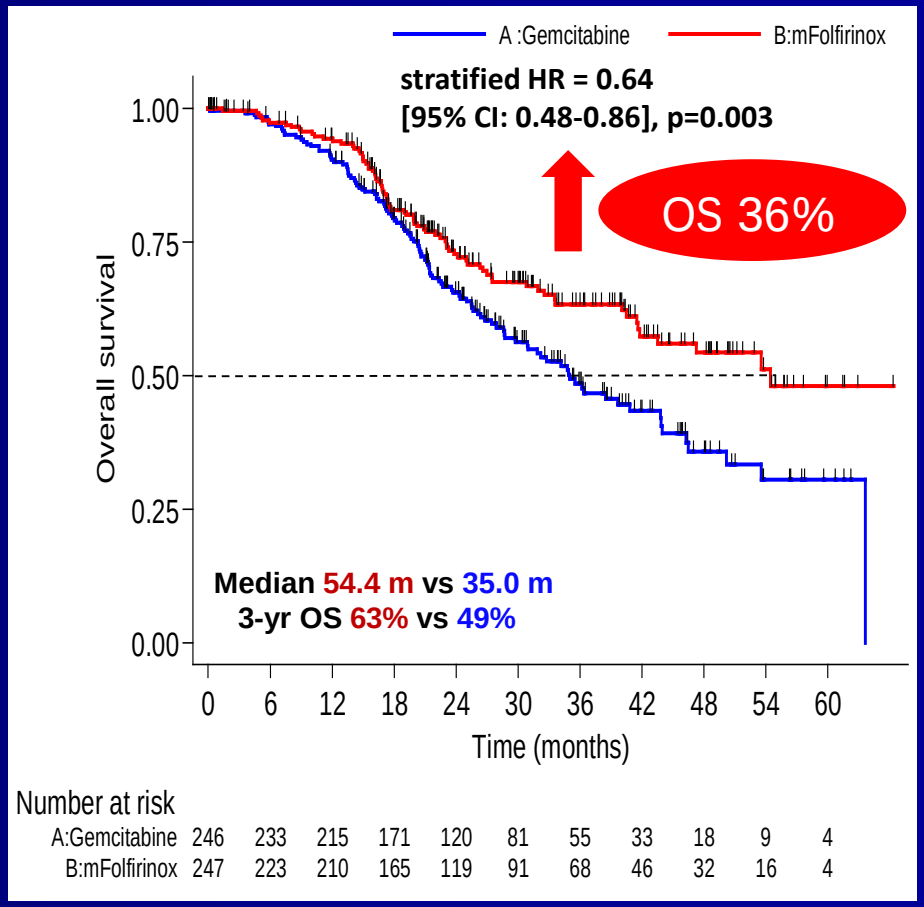
D. Gemcitabine/*nab*-paclitaxel

PRODIGE 24: mFOLFIRINOX vs Gemcitabine

DFS



OS



DFS = first occurrence of any tumor recurrence or metastases, second cancer or death from any cause

Conroy T, et al N Engl J Med 2018

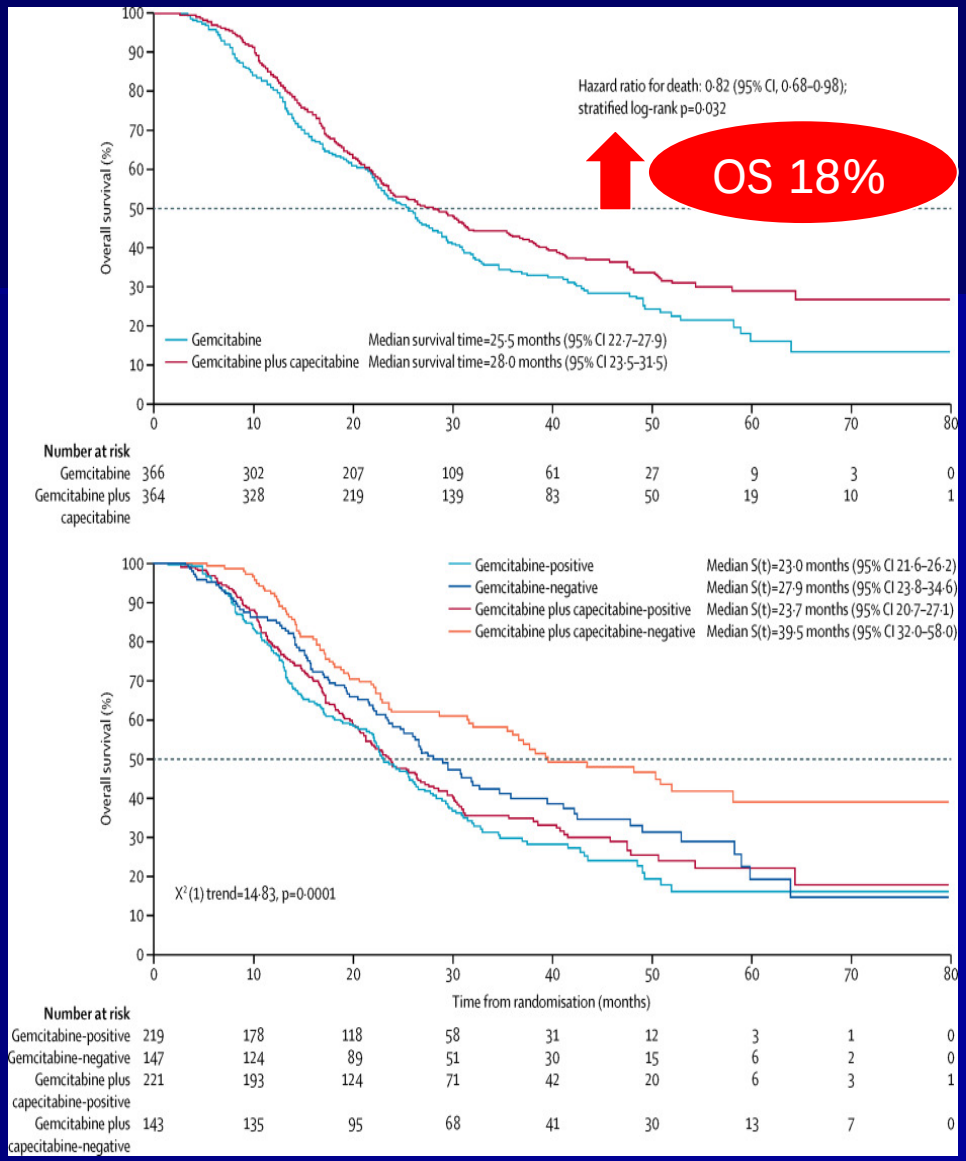
ESPAC 4

Gemcitabine + Capecitabine vs Gemcitabine

OS: 28 vs 25.5 mos

RFS: 13.9 vs 13 mos

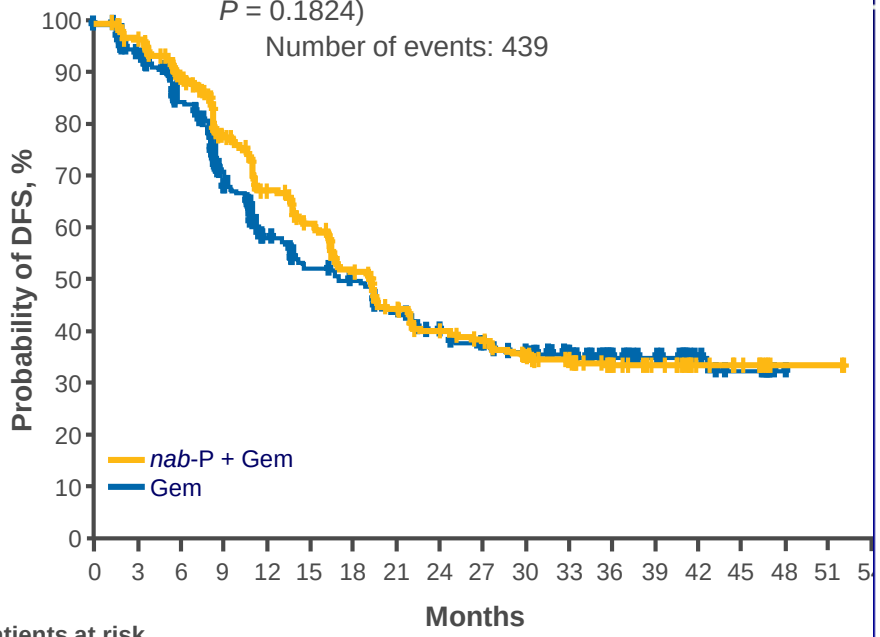
3-year RFS: 24% vs 21%



Neoptolemos JP, et al Lancet 2017 389:1011

APACT: Gemcitabine / nab-Paclitaxel

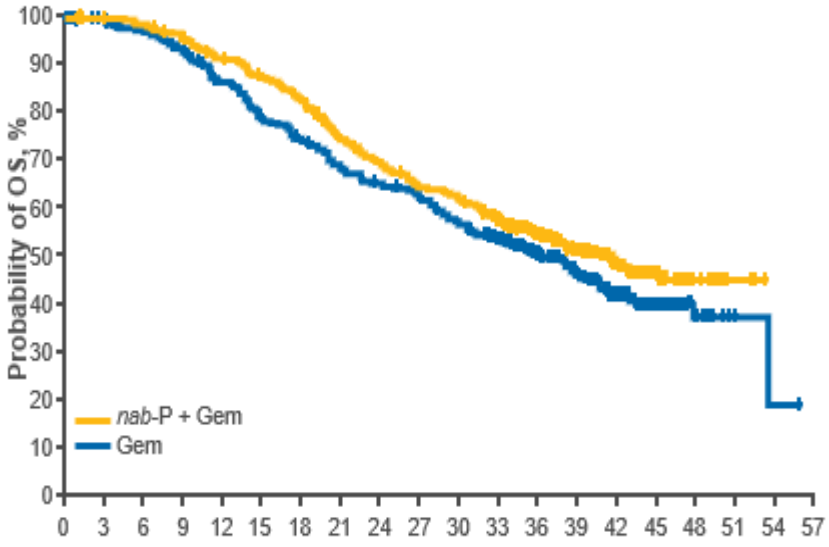
Median independently assessed DFS
nab-P + Gem: **19.4** months
Gem: **18.8** months
(HR 0.88; 95% CI, 0.729 - 1.063; stratified log-rank *P* = 0.1824)
Number of events: 439



Patients at risk

nab-P + Gem	432	391	338	279	236	204	167	138	121	112	99	88	54	43	20	14	2	2
Gem	434	368	309	235	183	157	147	127	116	105	98	88	59	42	15	10	1	

Median interim OS (68% mature)
nab-P + Gem: **40.5 mo**
Gem: **36.2 mo**
(HR 0.82; 95% CI, 0.680 - 0.996; nominal *P* = 0.045)
Number of events: 427; Median follow-up, 38.5 months



Patients at risk

nab-P + Gem	432	427	420	406	385	366	344	307	284	264	252	219	162	113	73	40	12	3
Gem	434	415	404	384	354	320	301	275	262	249	228	198	153	101	64	29	12	2	1

Tempero M et al ASCO 2019

Case 1: What is the standard of care after surgery for pancreatic cancer in fit patients?

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A. Gemcitabine alone

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C. modified FOLFIRINOX

D. Gemcitabine/*nab*-paclitaxel

Neoadjuvant / Perioperative Chemotherapy

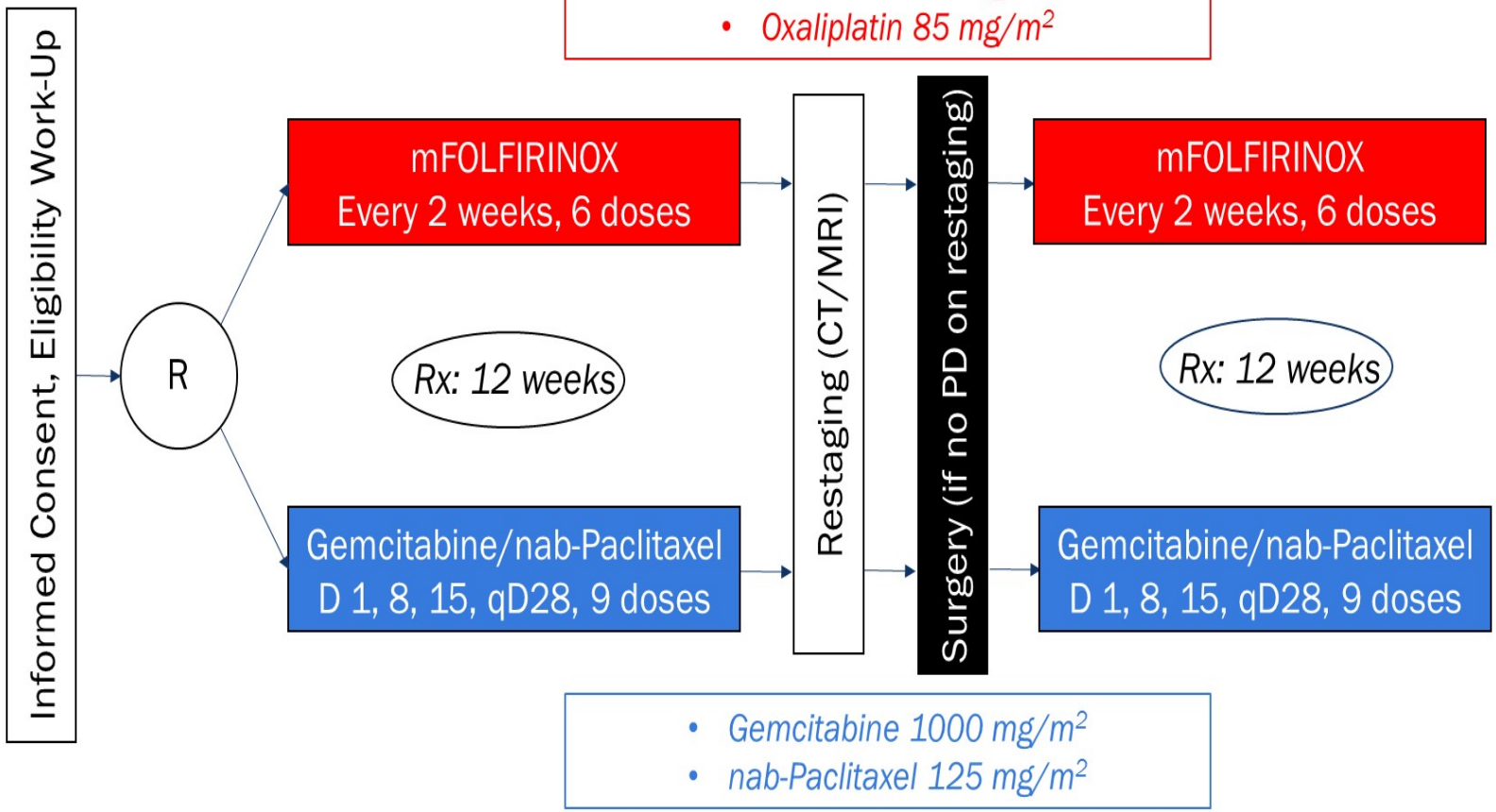
SWOG S1505: Results of Perioperative Chemotherapy with mFOLFIRINOX vs Gemcitabine/nab-Paclitaxel for Resectable Pancreatic Ductal Adenocarcinoma

Davendra P. S. Sohal, Mai Duong, Syed A. Ahmad, Namita S. Gandhi, M. Shaalan Beg, Andrea Wang-Gillam, James L. Wade III, E. Gabriela Chiorean, Katherine A. Guthrie, Andrew M. Lowy, Philip A. Philip, Howard S. Hochster

Presented By: Davendra Sohal, MD, MPH
Associate Professor of Medicine
Director of Experimental Therapeutics, Clinic Medical Director
Hematology and Oncology, University of Cincinnati

Study Schema

- *5-Fluorouracil 2400 mg/m^2, over 46 hrs*
- *Irinotecan 180 mg/m^2*
- *Oxaliplatin 85 mg/m^2*

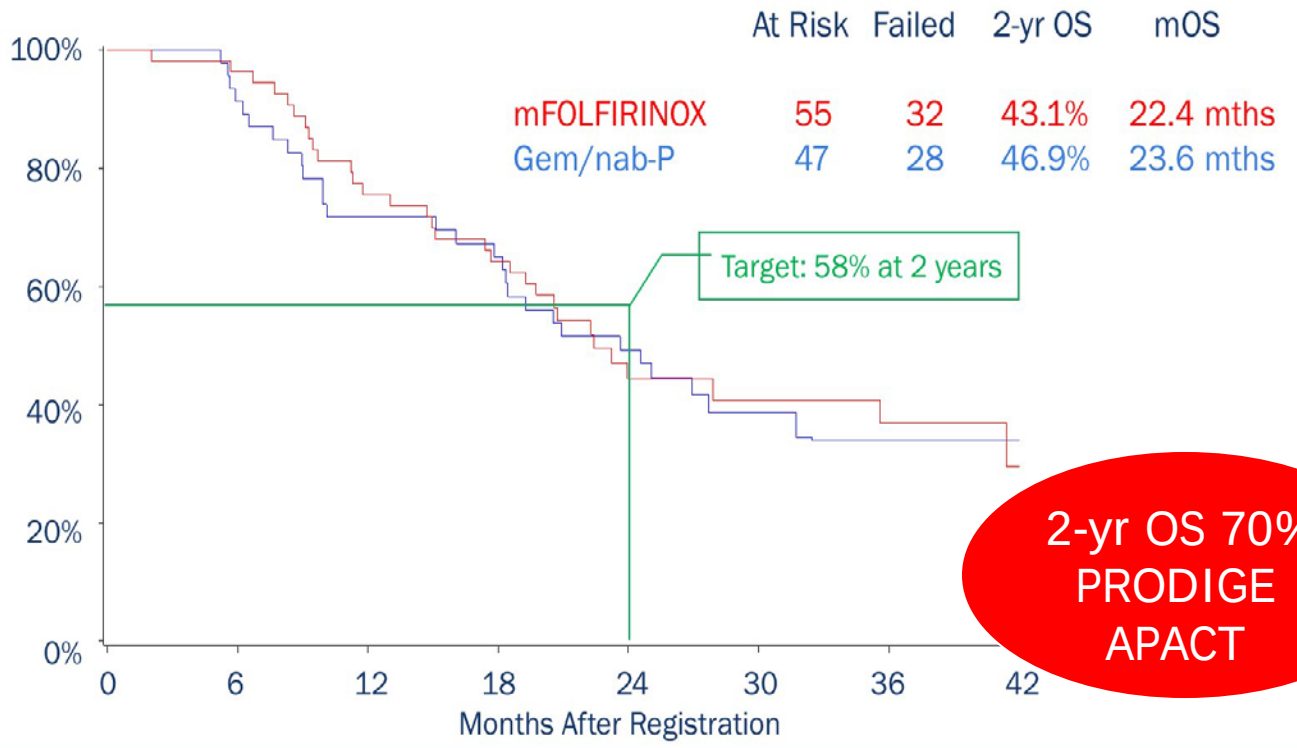


- *Gemcitabine 1000 mg/m^2*
- *nab-Paclitaxel 125 mg/m^2*

Both Regimens were Similar and Did Not Reach 58% 2-Yr OS

Patients who qualify for adjuvant chemotherapy trials are very selected

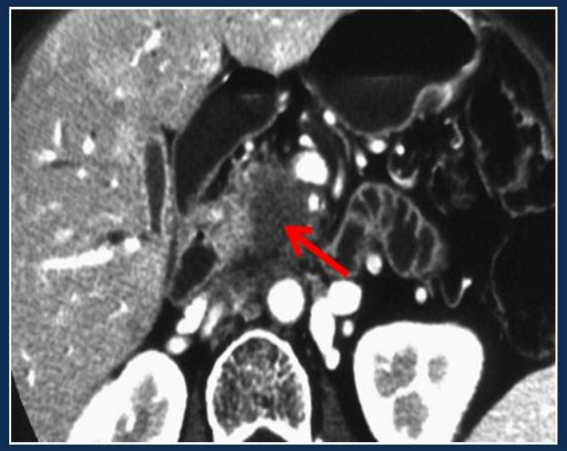
Primary Endpoint: Two-year OS



2-yr OS 70%
PRODIGE
APACT

BRPC and LAUPC

<180°



≥180°

- Locally advanced pancreatic cancer: involvement of a major arterial axis (superior mesenteric artery, celiac trunk)
- LAUPC = stage 3 (T4NxM0)
- Treatment of BRPC/LAUPC: like metastatic disease +/- CRT

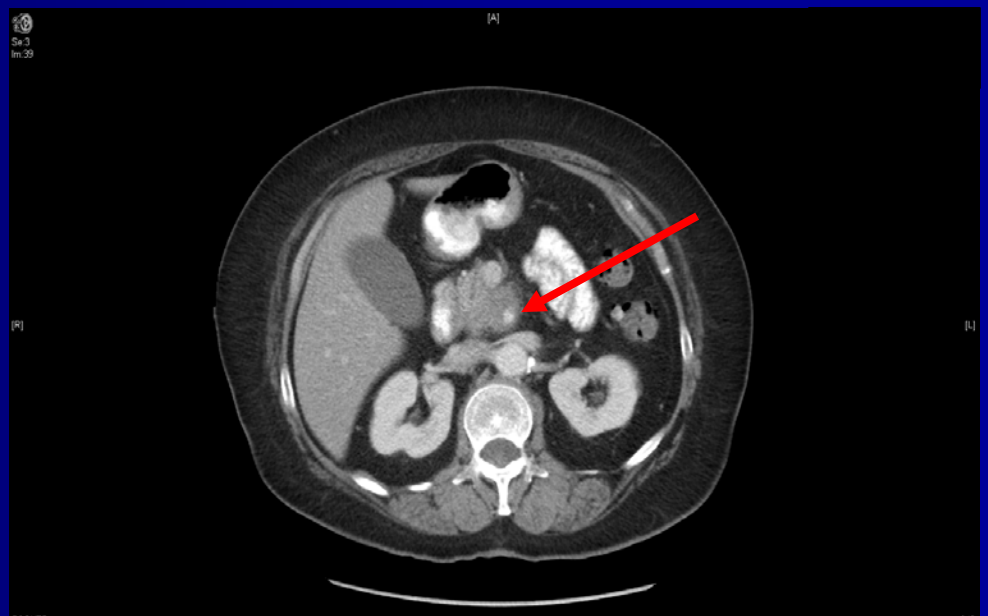
Case 2: Management of LAPC

- 64 y/o woman presents with dull LLQ pain and fatigue x 1 month
- Refractory to metamucil and proton pump inhibitor

- CT scan shows a 3.5cm pancreatic mass in uncinate process encasing SMA
- PMH: small fiber idiopathic peripheral neuropathy; diabetes, GERD
- FH: maternal aunts breast cancer x2 (50, 60), maternal cousin breast cancer at 64

- ECOG PS 1
- CA19-9 = 87 U/mL (0-54)
- Genetics:

  germline no pathogenic mutations



Presented by: E. Gabriela Chiorean at ASCO 2017 meeting

Post 2 months of mFOLFIRINOX:
- continued SMA encasement
- decreased tumor size

Post 4 months of mFOLFIRINOX:
- decreased SMA encasement
- decreased tumor size

- Grade 4 N/V/D after Cycle 1
- C Diff colitis after Cycle 2

20% 5FU and oxaliplatin dose reduction
40% irinotecan reduction

Next Steps

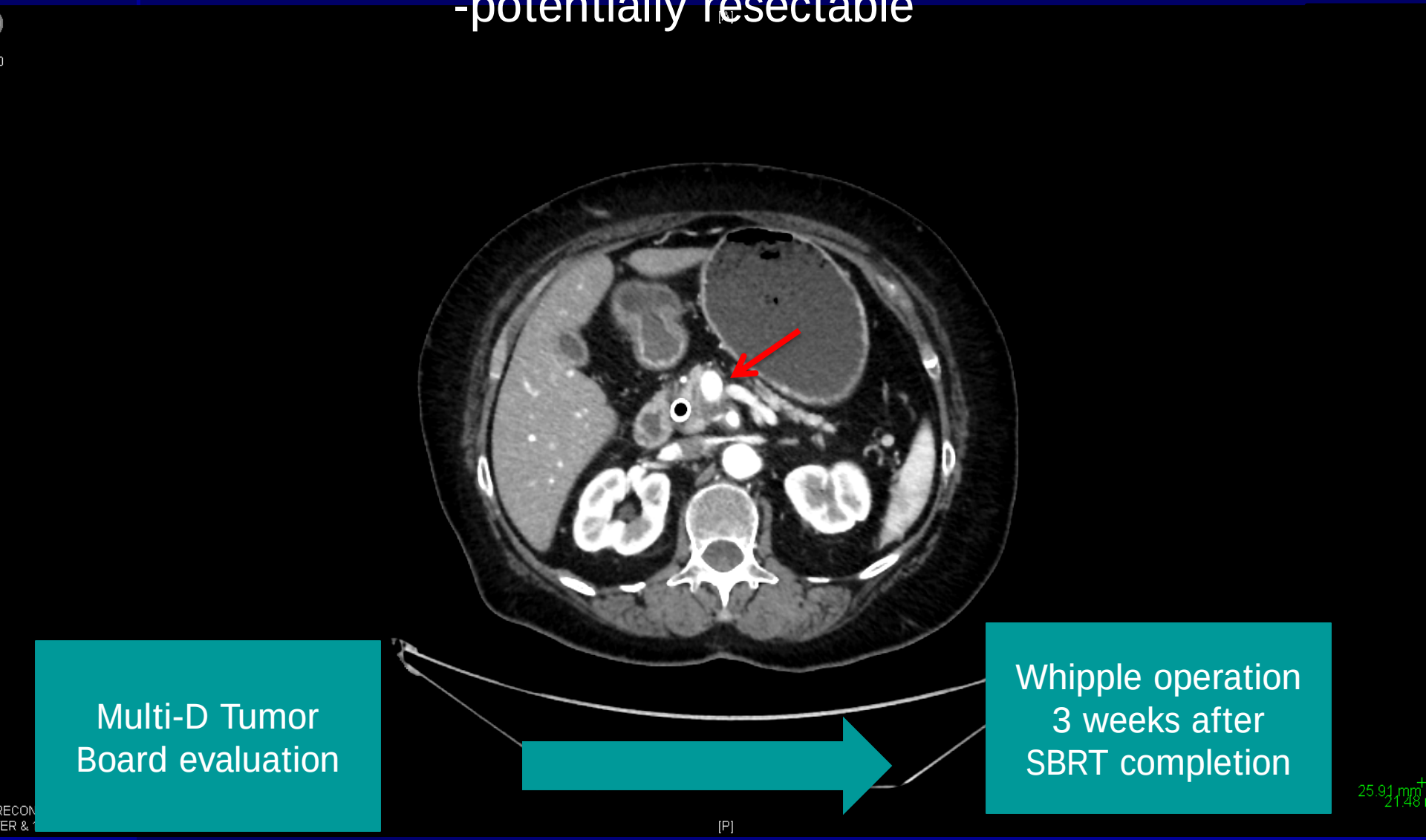
Would you recommend:

a. continue mFOLFIRINOX

b. chemoradiotherapy or SBRT

c. surgical exploration

Post SBRT
-more tumor shrinkage
-potentially resectable



Multi-D Tumor Board evaluation

Whipple operation 3 weeks after SBRT completion

Pathology

- Grade 1 well differentiated ductal adenocarcinoma
- 5.5 cm mass with chronic pancreatitis
- few small foci of residual adenocarcinoma largest <0.1cm
- Viable adenocarcinoma <5% of mass
- 16 lymph nodes negative for metastatic carcinoma
- No lympho-vascular invasion
- Margins negative (R0)
- PanIN-3 present

Sequencing of Chemotherapy and RT

Table 4 Recommendations for sequencing of chemotherapy and RT in patients receiving RT

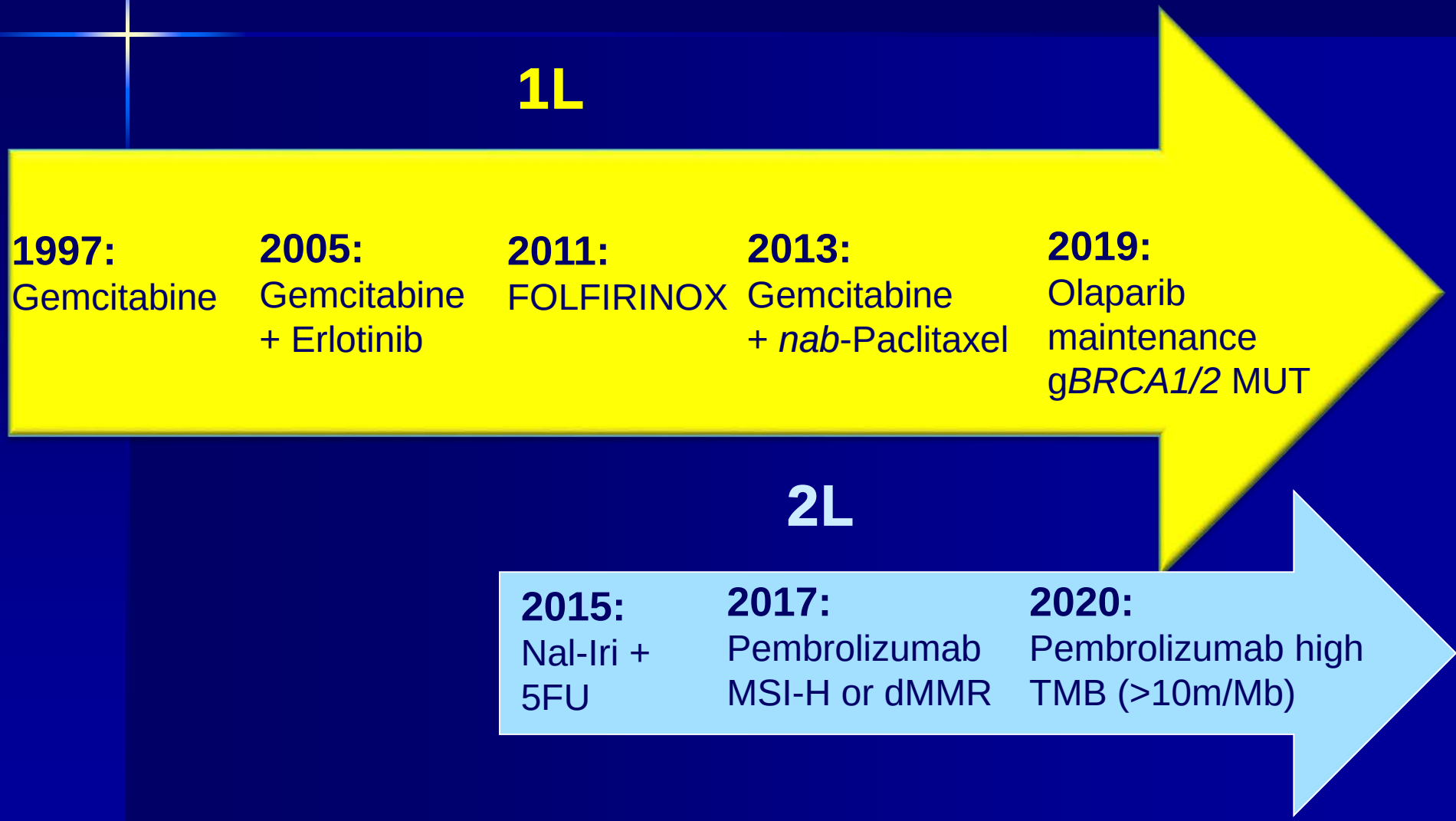
KQ 3 recommendations	Strength of recommendation	Quality of evidence	Consensus
1. For patients with resected pancreatic cancer receiving adjuvant therapy, delivery of chemoradiation following 4-6 months of systemic chemotherapy is recommended.	**Strong**	**Moderate**	92%*
2. For patients with borderline resectable pancreatic cancer receiving neoadjuvant therapy, delivery of RT following 2-6 months of systemic chemotherapy is recommended.	**Strong**	**Moderate**	92%*
3. For patients with unresectable or locally advanced pancreatic cancer without systemic progressionfollowing 4-6+ months of chemotherapy, definitive RT is recommended.	**Strong**	**Moderate**	85%*

Abbreviations: KQ = key question; RT = radiation therapy.

* The medical physics representative abstained from rating these recommendations.

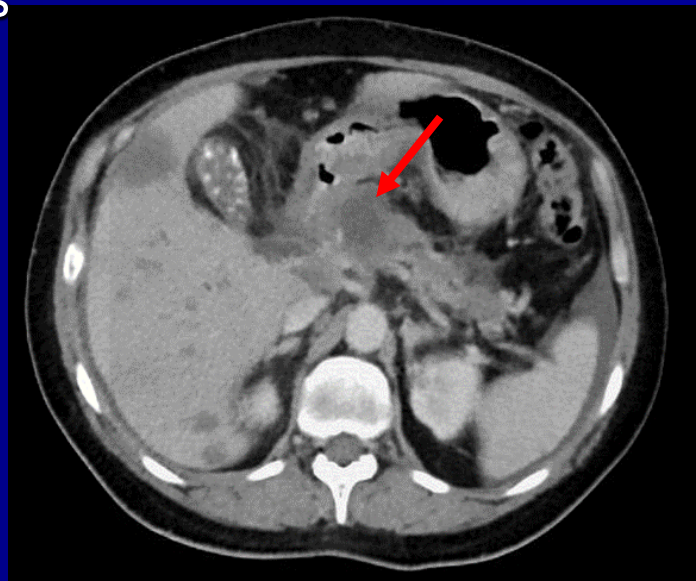
Palta M et al Practical Rad Oncol 2019
ASTRO guidelines

Metastatic Pancreatic Cancer



Case 3: Management of Metastatic Disease

- 66-yr-old man with 2 mos of epigastric pain, 15-lb weight loss, and gradual jaundice and clay-colored stools
  - total bilirubin 4.5 mg/dL, ALK 273, AST/ALT 85/90
- CT: mass in the head of pancreas and multiple liver metastases
- ERCP: metallic biliary stent through a malignant common bile duct stricture
- Liver biopsy: adenocarcinoma CK7+, CDX2+, CK20-
- Bilirubin 10 days later: 0.8 mg/dL
- No family history of pancreatic or other cancers
- ECOG PS 1



Question: What would you choose as the optimal 1L treatment option for this patient?

a. Gemcitabine alone

b. Gemcitabine + nab-paclitaxel

c. FOLFOX

d. FOLFIRINOX

e. Either b or d are preferred 1st line options

What genetic and molecular markers would you order to help with treatment decisions?

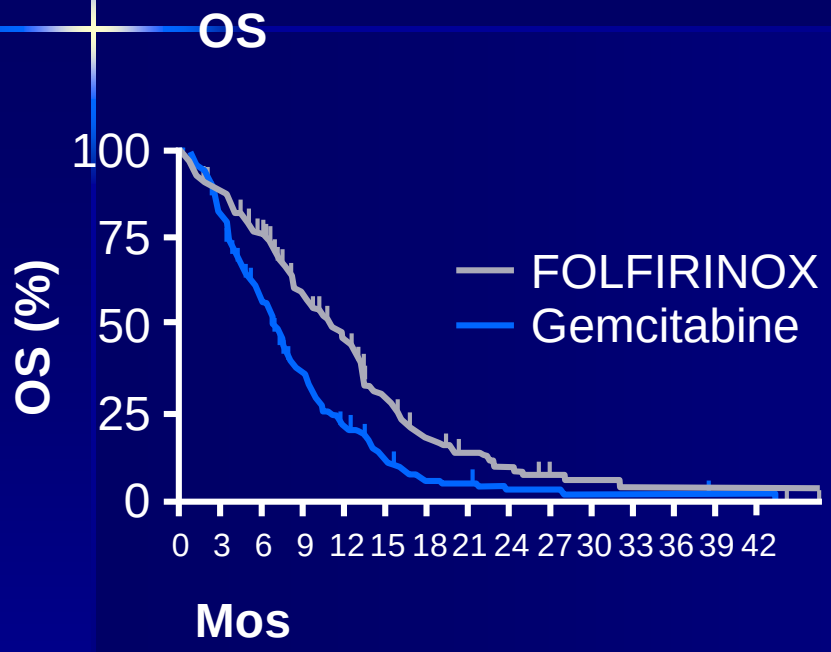
a. Microsatellite instability (MSI) germline (blood) test

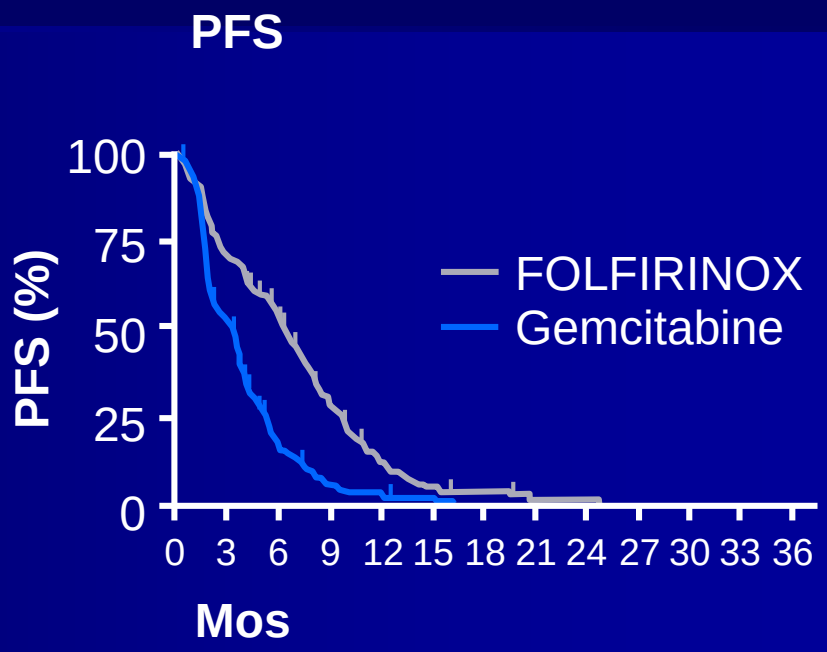
b. BRCA1, BRCA2 germline testing

c. Comprehensive somatic (tumor) gene profiling

d. a, b and c

FOLFIRINOX vs Gemcitabine: OS and PFS



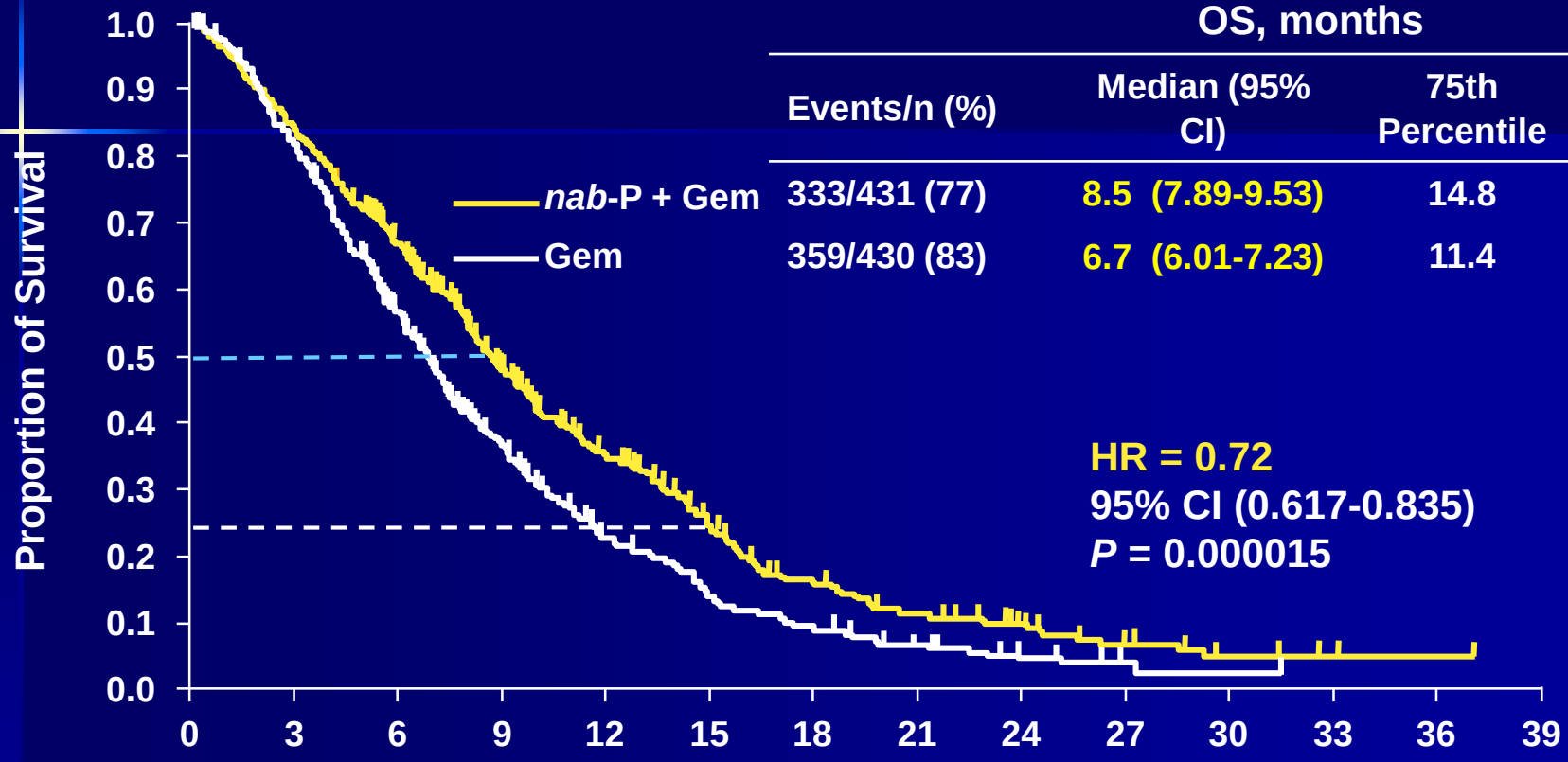


Median OS: 11.1 vs 6.8 mos
HR: 0.57 (95% CI: 0.45-0.73; *P* < .001)

Median PFS: 6.4 vs 3.3 mos
HR: 0.47 (95% CI: 0.37-0.59; *P* < .001)

Conroy T, et al. N Engl J Med. 2011;364:1817-1825.

Gemcitabine/*nab*-Paclitaxel vs Gemcitabine



	OS, months	
Events/n (%)	Median (95% CI)	75th Percentile
333/431 (77)	8.5 (7.89-9.53)	14.8
359/430 (83)	6.7 (6.01-7.23)	11.4

HR = 0.72
95% CI (0.617-0.835)
P = 0.000015

Pts at risk

nab-P + Gem:	431	357	269	169	108	67	40	27	16	9	4	1	1	0
Gem:	430	340	220	124	69	40	26	15	7	3	1	0	0	0

Von Hoff et al. NEJM 2013

Question: What would you choose as the optimal 1L treatment option for this patient?

a. Gemcitabine alone

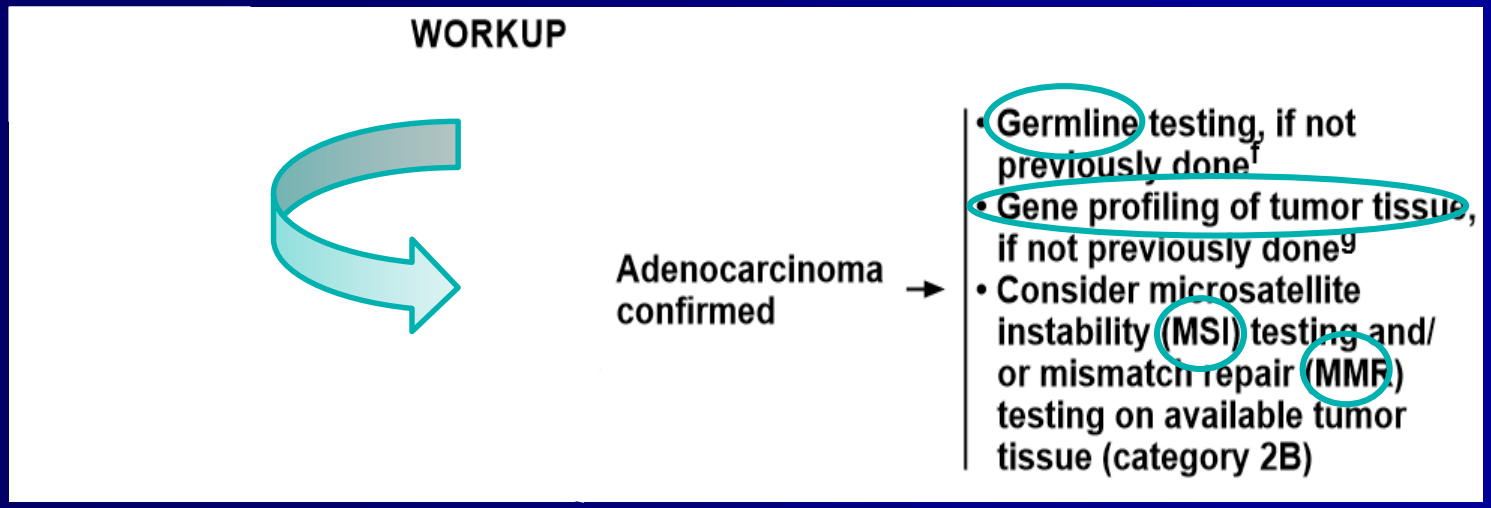
b. Gemcitabine + nab-paclitaxel

c. FOLFOX

d. FOLFIRINOX

e. Either b or d are preferred 1st line options

Genetic Testing for Pancreatic Cancer



Tempero, M, Malafa MP, Chiorean EG, NCCN Guidelines 2019, JNCCN 2019

What genetic markers would you order to help with treatment decisions?

a. Microsatellite instability (MSI) germline (blood) test

b. BRCA1, BRCA2 germline testing

c. Comprehensive somatic (tumor) gene profiling

d. a, b and c

Case 4: 2L Treatment for metastatic disease

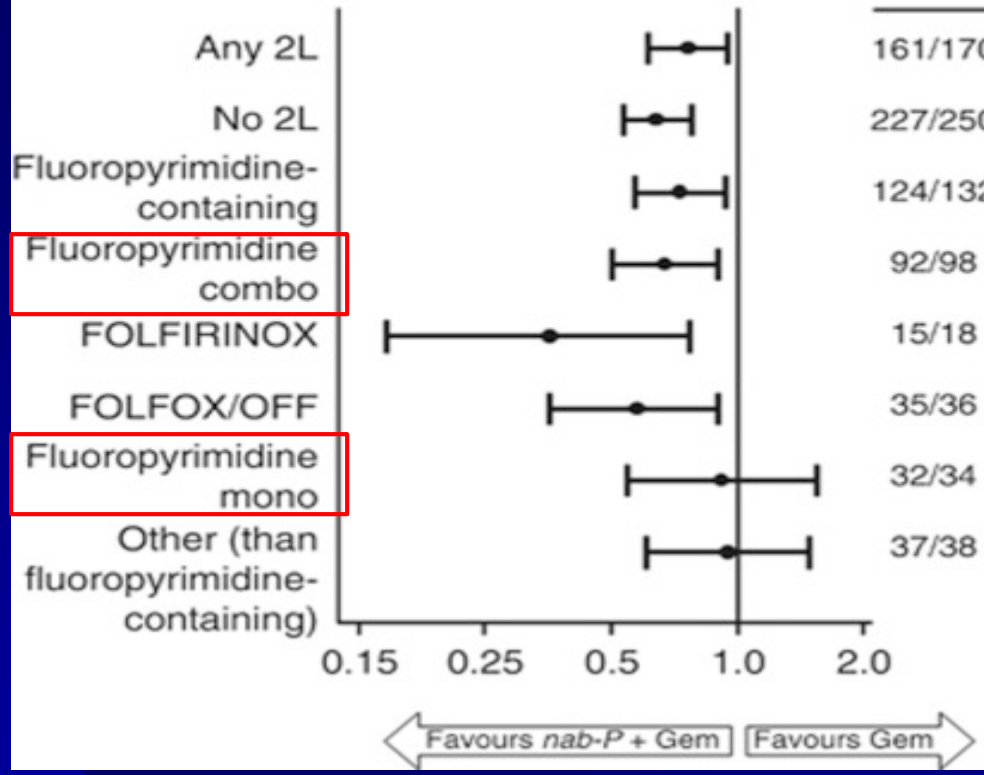
- 69-yr-old female with metastatic pancreatic adenocarcinoma to the liver
- Initial treatment consisted of gemcitabine and *nab*-paclitaxel
  - Achieved a PR lasting for 8 mos

- CT scan at 8 mos shows new peritoneal nodules
- ECOG PS at 1
- She has persistent mild peripheral sensory neuropathy (gr 2)

Question: What would you choose as the best treatment option for this patient?

a. 5-FU/LV
b. FOLFOX
c. FOLFIRINOX
d. 5-FU/LV + nanoliposomal irinotecan

OS after Gem / nab-Paclitaxel Depending on 2nd line Therapy



	nab-P + Gem		Gem		HR	*P*-value
	Events/ *n*	Median OS, months	Events/ n	Median OS, months		
Any 2L	161/170	12.8	166/177	9.9	0.76	0.015
No 2L	227/250	6.3	218/226	4.3	0.64	< 0.001
Fluoropyrimidine-containing	124/132	13.5	124/135	9.5	0.73	0.012
Fluoropyrimidine combo	92/98	14.0	99/107	9.5	0.67	0.006
FOLFIRINOX	15/18	15.7	15/17	7.2	0.36	0.007
FOLFOX/OFF	35/36	13.7	46/49	9.8	0.57	0.015
Fluoropyrimidine mono	32/34	11.9	25/28	9.4	0.92	0.746
Other (than fluoropyrimidine-containing)	37/38	10.9	42/42	11.3	0.95	0.806

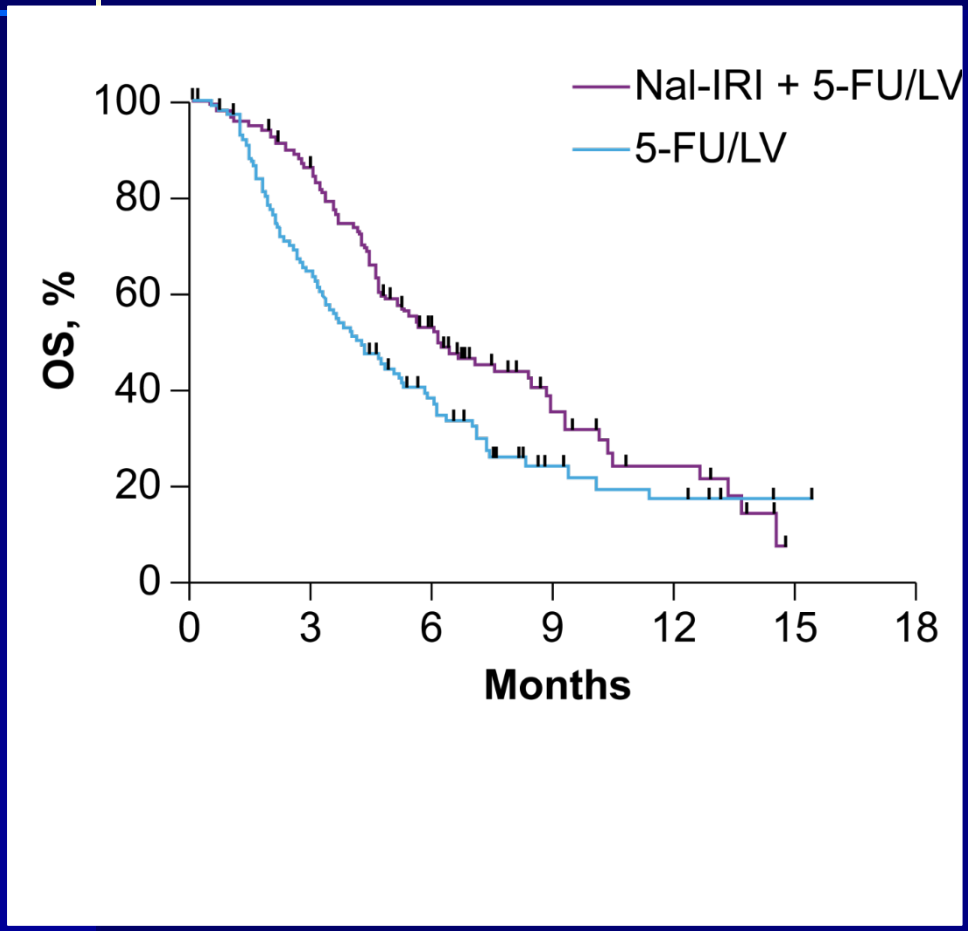
Chiorean EG, et al *Br J Cancer* 2016

Comparison of 2nd Line Studies with Oxaliplatin-Based Chemo

	CONKO-003 (OFF vs. 5-FU/FA)	PANCREOX (mFOLFOX-6 vs. 5-FU/LV)
Sample size	160	108
Median survival	**5.9 vs. 3.3 months** (HR 0.66)	**6.1 vs. 9.9 months** (HR 1.78)
Median PFS	2.9 vs. 2.0 months (HR 0.68)	3.1 vs. 2.9 months (HR 1.0)
Objective response rate	N/A	13.2 vs. 8.5%
Grade 3/4 AEs (for experimental arm)	Pain (32%) Paresthesias (4%) Anemia (4%)	Neutropenia (33%) Fatigue (14%) Thrombocytopenia (8%) Dehydration (8%)

Oettle H et al, *J Clin Oncol* 2014 Aug, 32:2423-9; Gill S et al, *J Clin Oncol* 2016 Nov, 34:3914-3920.

NAPOLI-1 Trial
5FU +/- Nanoliposomal Irinotecan



- **Median OS: 6.1 vs 4.2 months**
  HR = 0.67, p = .012
- Median PFS 3.1 vs 1.5 months
- ORR 16% vs 1%

Wang-Gillam A et al, Lancet 2015

Treatment Sequencing for Metastatic Pancreatic Cancer

Gemcitabine-based

(e.g. gemcitabine, **gem/nab-paclitaxel**, gemcitabine /erlotinib)

(PS 0-1): Fluoropyrimidine-based regimen (+/- nal-IRI, oxaliplatin)

(PS 2): Fluoropyrimidine alone; BSC

(PS 0-1): Irinotecan- or platinum-based regimen

(if no prior exposure)

FOLFIRINOX

(PS 0-1): Gemcitabine/nab-paclitaxel

(PS 2 or less): Gemcitabine monotherapy; BSC

Clinical trial if available

Question: What would you choose as the best treatment option for a patient who progressed after gemcitabine/nab-paclitaxel and has grade 2 neuropathy?

a. 5-FU/LV

b. FOLFOX

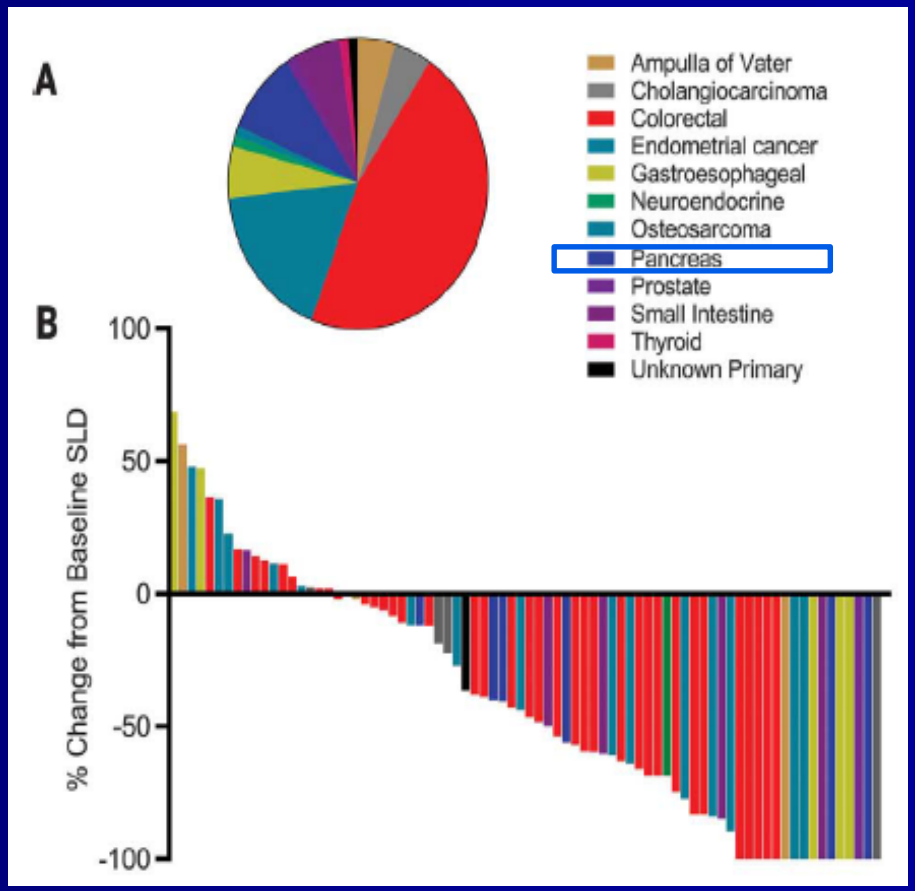
c. FOLFIRINOX

d. 5-FU/LV + nanoliposomal irinotecan

Treatment for Specific Patient Subgroups: MSI-High

- **<1%** of pancreatic cancers are associated with defective mismatch repair (dMMR/MSI-high)

- Immune checkpoint inhibitors (anti-PD1 mAbs, e.g., pembrolizumab) now approved for this indication (disease-agnostic)



Le DT et al. *Science* 2017 Jul ; 357(6349):409-413.

Olaparib maintenance following 1st -line platinum-based chemotherapy in mPC patients with a gBRCA mutation: Phase III POLO trial

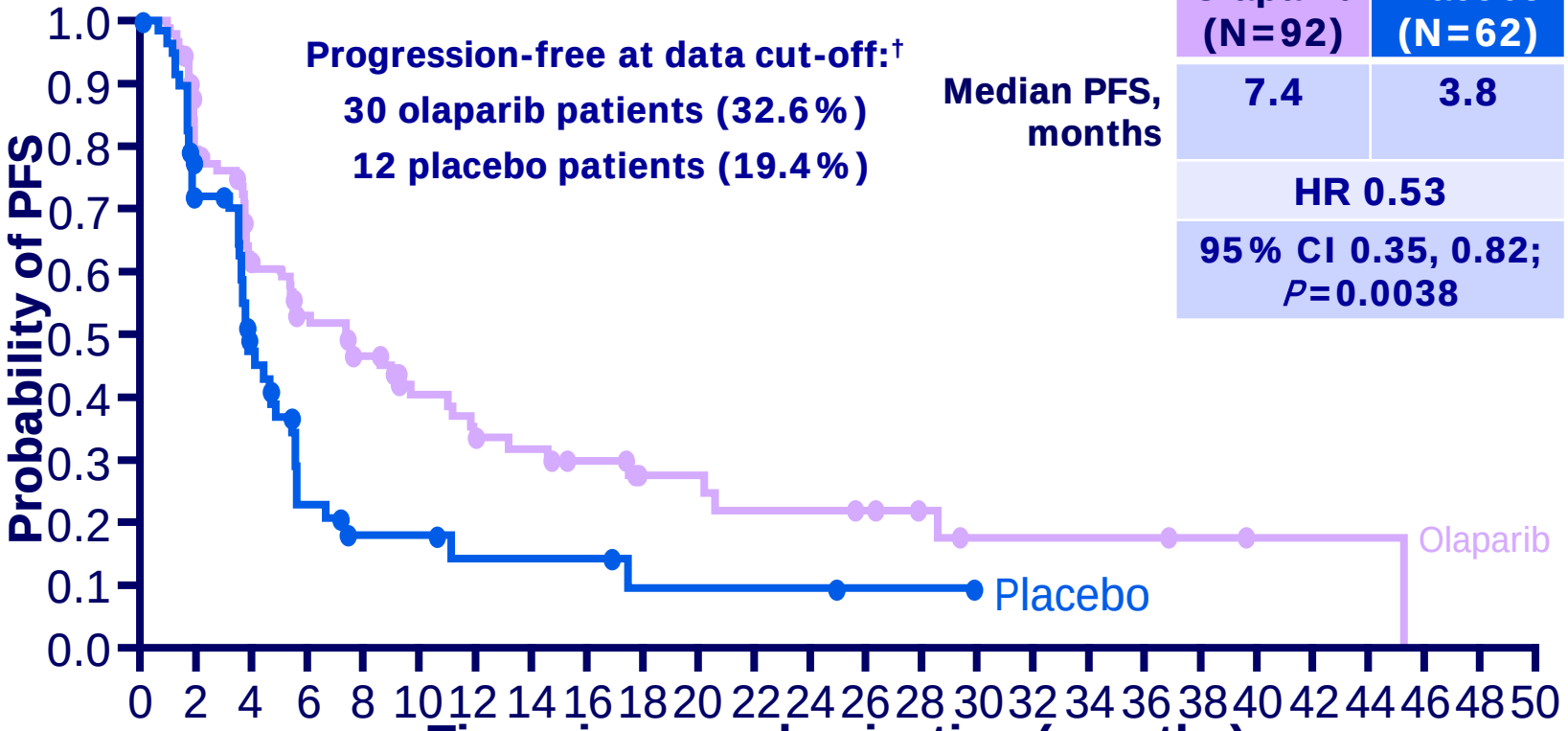
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Maintenance Olaparib for Germline *BRCA*-Mutated Metastatic Pancreatic Cancer

Talia Golan, M.D., Pascal Hammel, M.D., Ph.D., Michele Reni, M.D., Eric Van Cutsem, M.D., Ph.D., Teresa Macarulla, M.D., Ph.D., Michael J. Hall, M.D., Joon-Oh Park, M.D., Ph.D., Daniel Hochhauser, M.D., Ph.D., Dirk Arnold, M.D., Ph.D., Do-Youn Oh, M.D., Ph.D., Anke Reinacher-Schick, M.D., Ph.D., Giampaolo Tortora, M.D., Ph.D., Hana Algül, M.D., Ph.D., M.P.H., Eileen M. O'Reilly, M.D., David McGuinness, M.Sc., Karen Y. Cui, M.D., Ph.D., Katia Schlienger, M.D., Ph.D., Gershon Y. Locker, M.D., and Hedy L. Kindler, M.D.

Primary endpoint: PFS by blinded independent central review*



*Dots indicate censorship. †January 15, 2019. CI, confidence interval

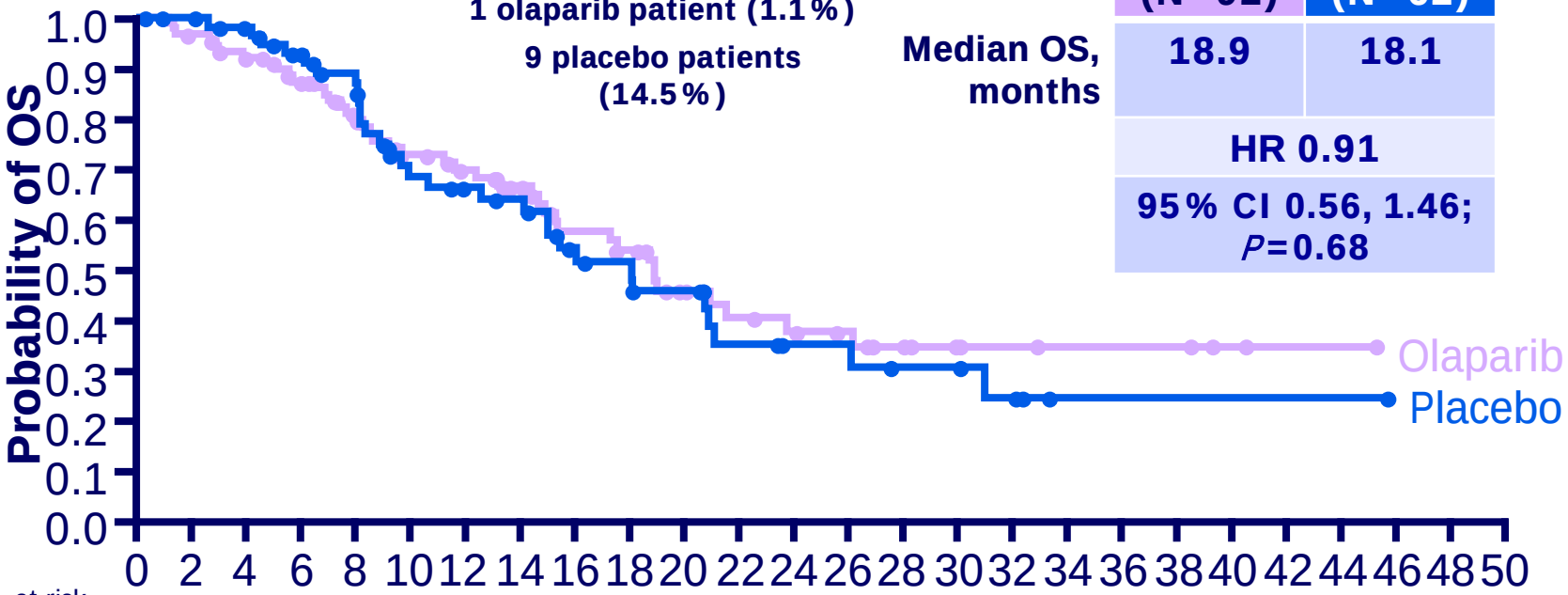
OS: interim analysis, 46% maturity*

Subsequent treatment with a PARP inhibitor:†

1 olaparib patient (1.1%)

9 placebo patients (14.5%)

	Olaparib (N=92)	Placebo (N=62)
Median OS, months	18.9	18.1
HR 0.91		
95% CI 0.56, 1.46; *P*=0.68		



No. at risk

Olaparib	92	87	80	71	61	51	46	39	31	28	20	16	14	12	9	6	5	4	4	4	2	1	1	0
Placebo	62	60	56	50	44	32	29	27	20	18	14	10	8	8	6	6	4	1	1	1	1	1	1	0

*Dots indicate censorship. †Crossover to olaparib was not permitted during this study; subsequent therapies were given at the investigators' discretion

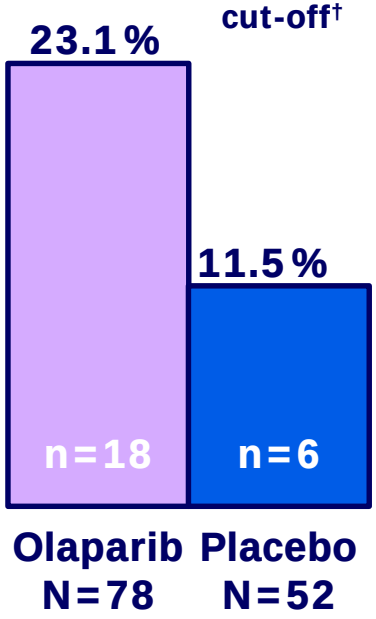
Time since randomization (months)

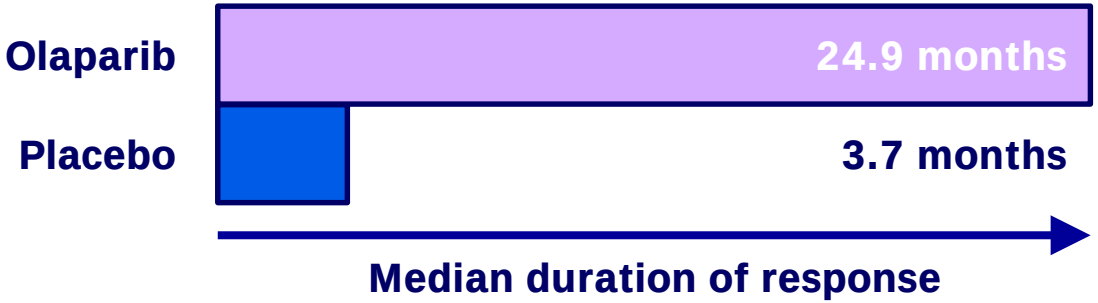
Final OS analysis planned at 106 events

Objective response* in patients with measurable disease

Two olaparib arm patients had a complete response

Both complete responses were ongoing at the data cut-off†

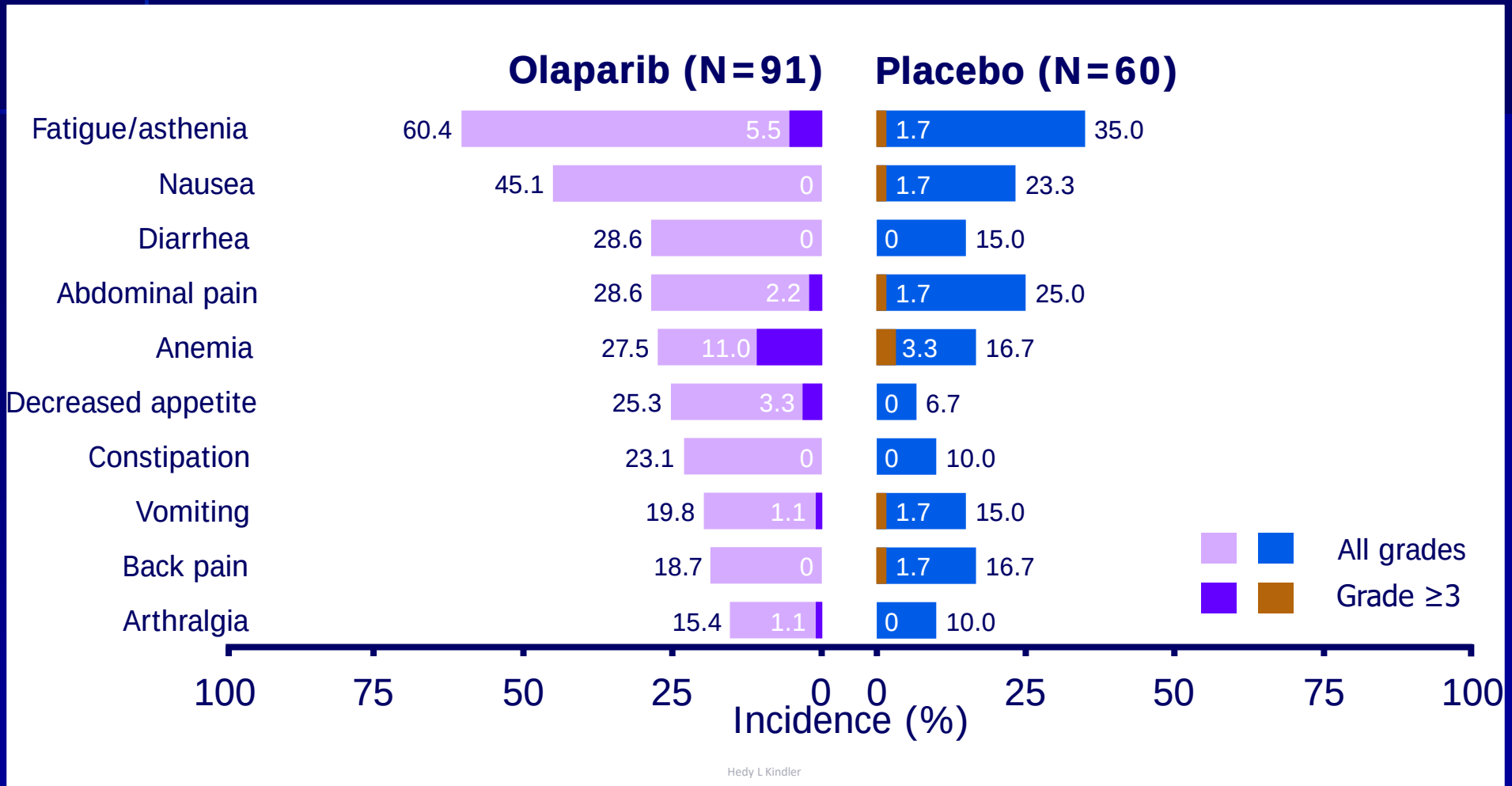




*By modified RECIST v1.1. †January 15, 2019

Hedy L Kindler

Most common AEs



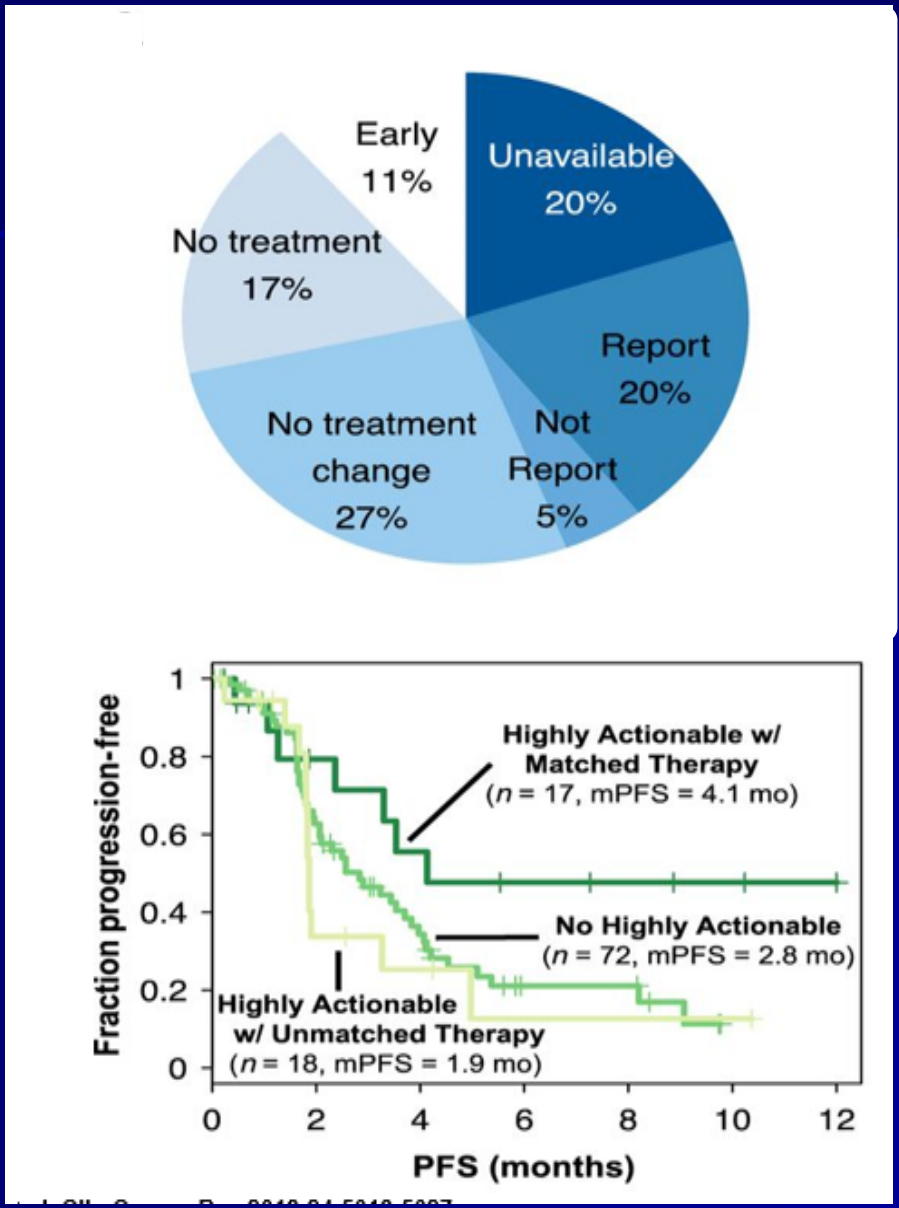
PanCan Know Your Tumor Project Genomics

N=640
had Know Your Tumor NGS

N=126
utilized a report-listed therapy

N=35 (5%)
had highly actionable mutations

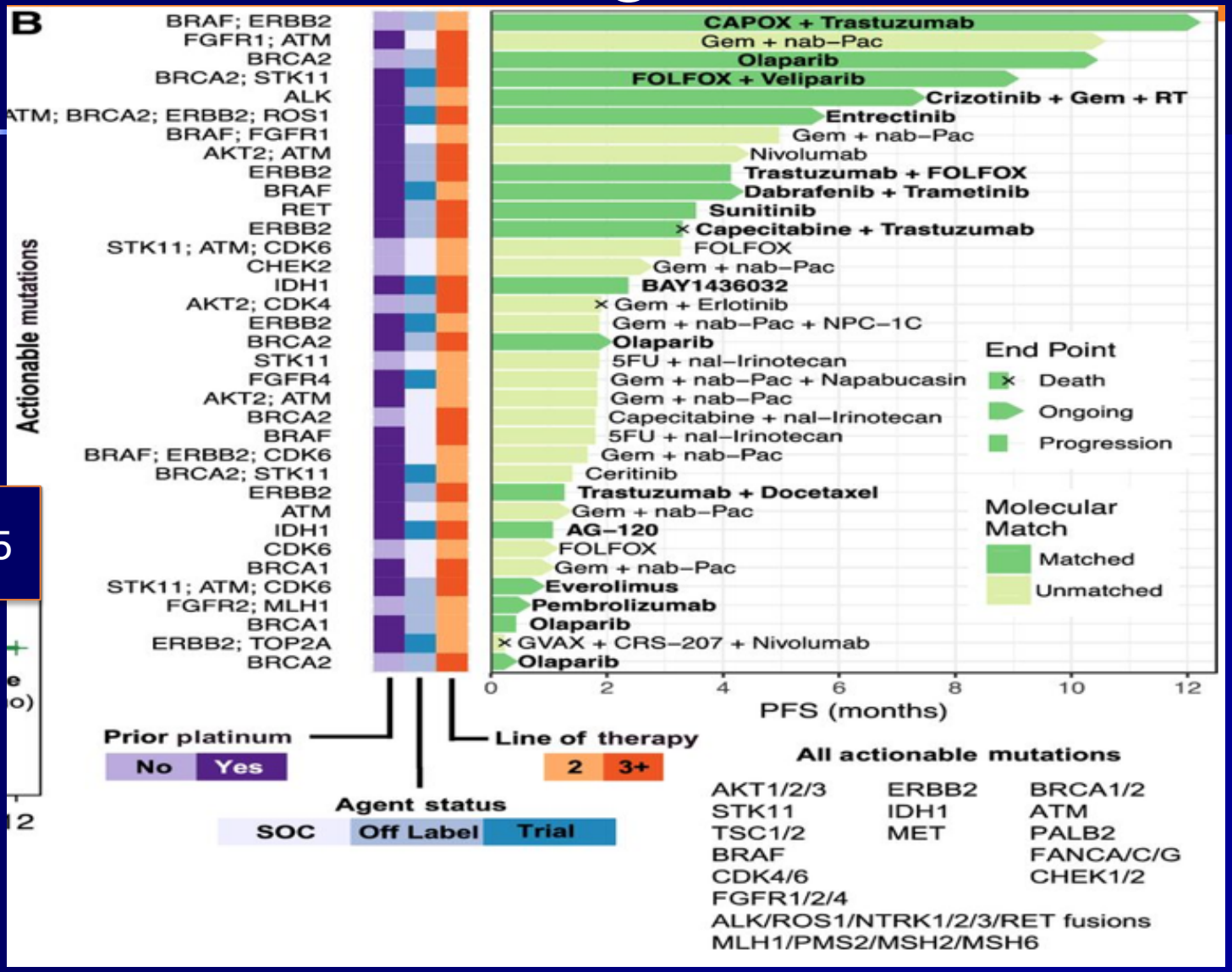
N=17 (2.6%)
utilized molecularly targeted therapies



Pishvaian MJ et al. Clin Cancer Res 2018;24:5018-5027

Outcomes in Patients with Actionable Targets

N=35



Pishvaian MJ et al. Clin Cancer Res 2018;24:5018-5027

Case 5: Palliative Care

A 45-year-old male recently diagnosed with metastatic pancreatic cancer is going to initiate first-line palliative chemotherapy and reports mild, vague abdominal pain. When should this patient be referred to palliative care?

A. When his symptoms become intolerable
B. When all cancer-directed therapies have been exhausted
C. There is no role for palliative care in this setting
D. As soon as possible
E. When he decides he is ready for hospice care

Pancreas Cancer: Palliative Care

- Biliary obstruction (70-85% patients present with pancreatic head tumors): in unresectable patients, metal stent preferred (covered or uncovered)
- Pancreatic insufficiency: Pancreatic enzyme supplementation (Creon)
- Diabetes: Insulin
- Nutrition: appetite stimulants, dietary counseling
- Abdominal pain: Narcotics, celiac plexus neurolysis –
  - 60-80% of pancreas cancer patients report some degree of pain relief with celiac block

Summary

- **mFOLFIRINOX**: remains standard of care after surgery for good PS patients
- Chemotherapy alone is standard for localized unresectable PC, but CRT remains an option for select patients after 4-6 mos of induction chemo
- FOLFIRINOX and Gemcitabine-nab/paclitaxel are 1st line options for mPC
- 2nd line therapy: nanoliposomal irinotecan +5FU (~ FOLFIRI)
- Pembrolizumab for MSI-H/dMMR pancreatic cancer (<1%)
- Maintenance Olaparib for germline BRCA1/2 MUT
- Germline testing for all PC patients
- Somatic genomic testing: for LAPC and Metastatic
- Palliative Care: essential

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Inherited and Acquired Marrow Failure

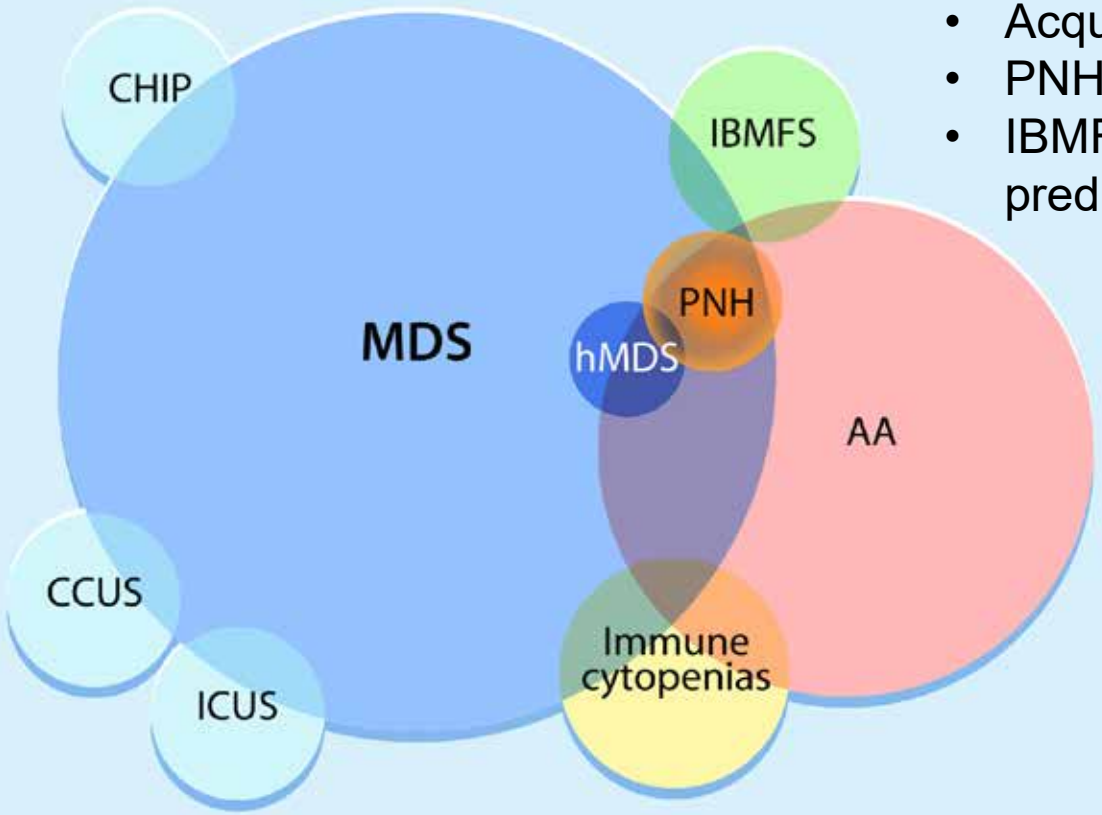
Comprehensive Hematology & Oncology Review Course

Siobán Keel, MD
Associate Professor of Medicine

August 2020

Marrow failure

- Inability of hematopoiesis to meet physiologic demands for the production of healthy blood cells.



- Acquired aplastic anemia
- PNH
- IBMF/hematopoietic malignancy predisposition syndromes

Diagnostic work-up of hypocellular marrow + cytopenias

Pancytopenia
Exclude known causes, e.g, B12/ folate deficiency, medication

↓

BM aspirate/biopsy
(chromosome analysis, cytology, flow cytometry, iron stain)

↓

Hypocellullar

↓

Peripheral blood
- HSCT candidate consider HLA typing
- **Chromosomal breakage study**
  (+ skin fibroblast testing if suspicion is high)
- Reticulocyte count
- Flow cytometry for GPI-anchored proteins
- Consider telomere length testing
- Consider genetic testing

Consider underlying genetic cause

- Younger age
- Personal history of congenital anomalies or extra-hematologic manifestations
- Family history
- Member of family with genetically defined IBMF/AL-MDS
- Antecedent macrocytosis or cytopenias
- Monosomy 7 & trisomy 8 MDS in peds/young adults
- Absence of a PNH clone[1]

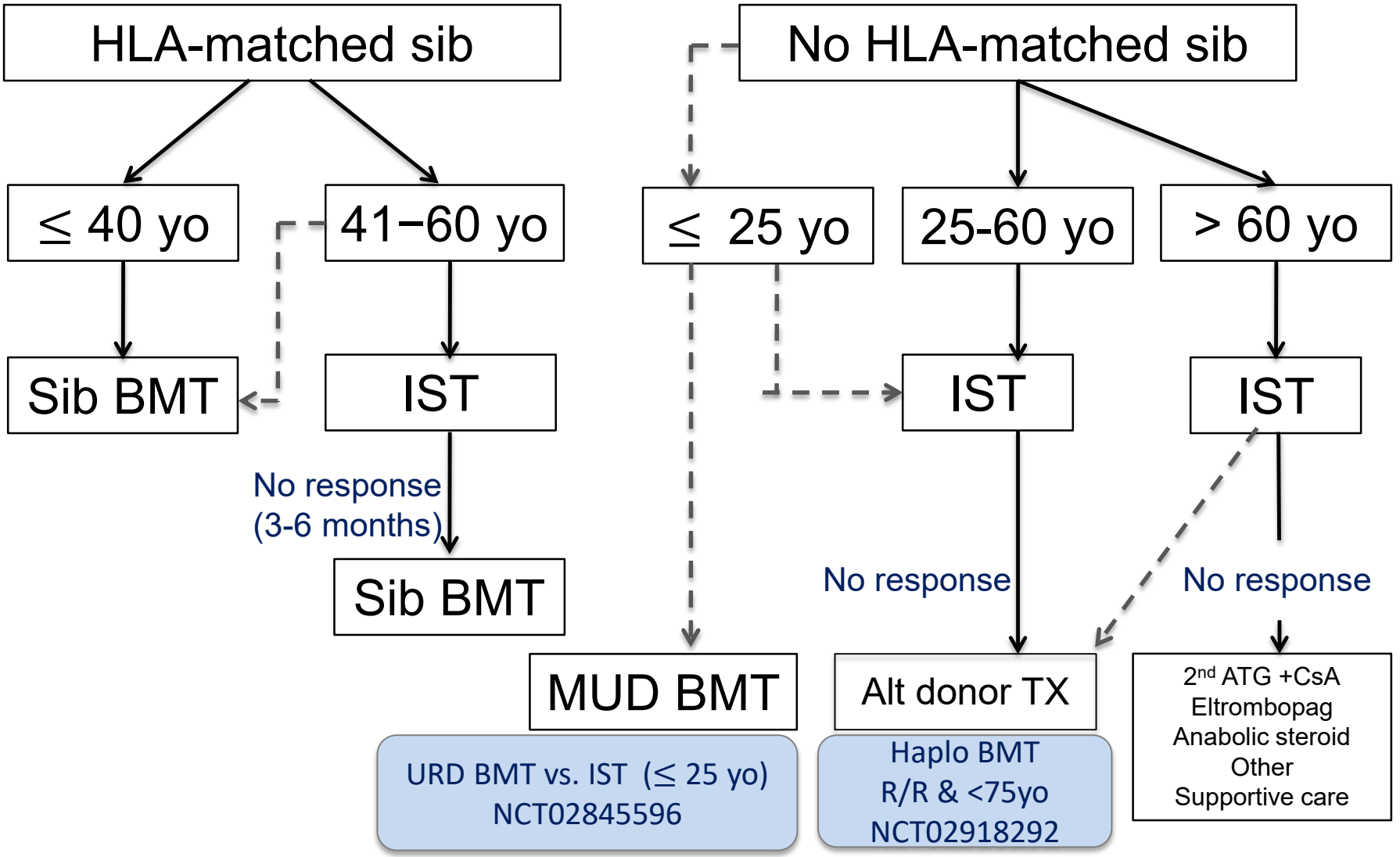
1. DeZern A. et al. Eur Journal Hematology 2014: 92.

Idiopathic acquired aplastic anemia

- Biphasic age distribution
  - Young adults and > 60 yo
- Presumed 2^{ndary} to immunologic destruction of hematopoietic stem cells
- Severity - Camitta's criteria[1]
  - Severe
    - BM cellularity <25% or 25-50% w/ <30% residual hemat. cells
    - 2/3 of the following
      - ANC <500/uL
      - Plts < 500/uL
      - Absolute retic count <20,000/uL (some use <60,000/uL[2])
  - Very severe - ANC<200/uL
  - Non-severe (moderate) - better than severe

1. Camitta BM. Blood 1976: 48(1). 2. Killlick S. BJH 2016: 172.

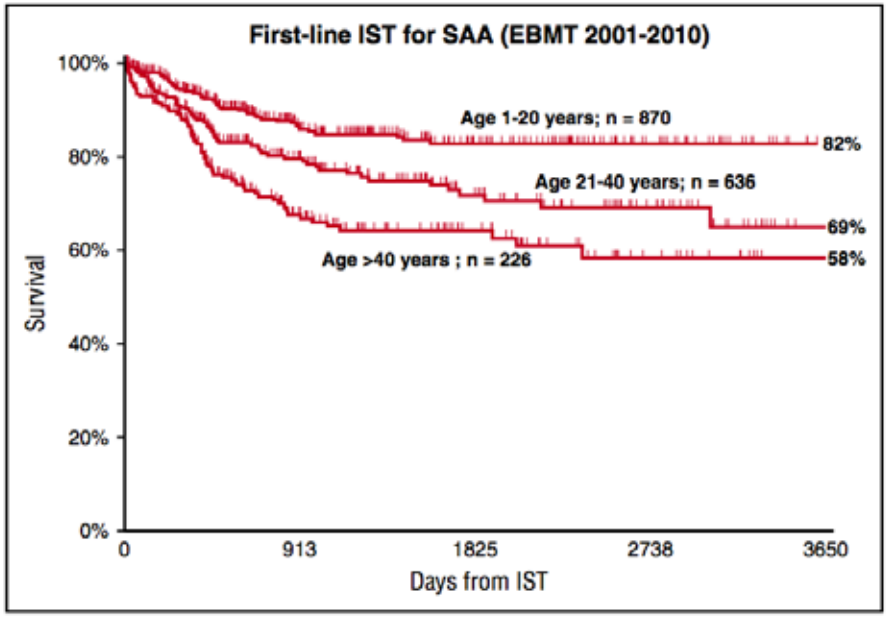
Severe idiopathic acquired aplastic anemia

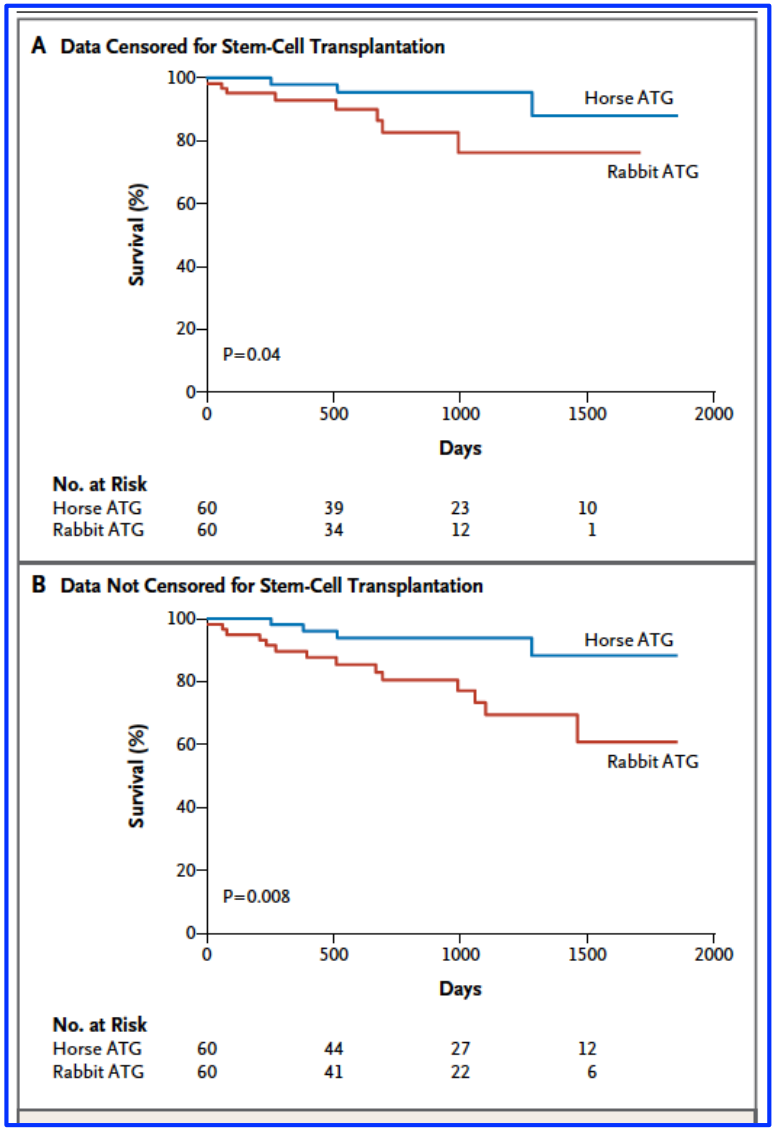


Nice review in Georges G. et al. Blood Advances 2018: 2(15).

Immune suppressive therapy (IST)

- **Horse is better than rabbit ATG[1]**
- **Response to IST is age-dependent[2]**
- Adding GM-CSF, G-CSF, and IL-3 doesn't improve response or survial[3]





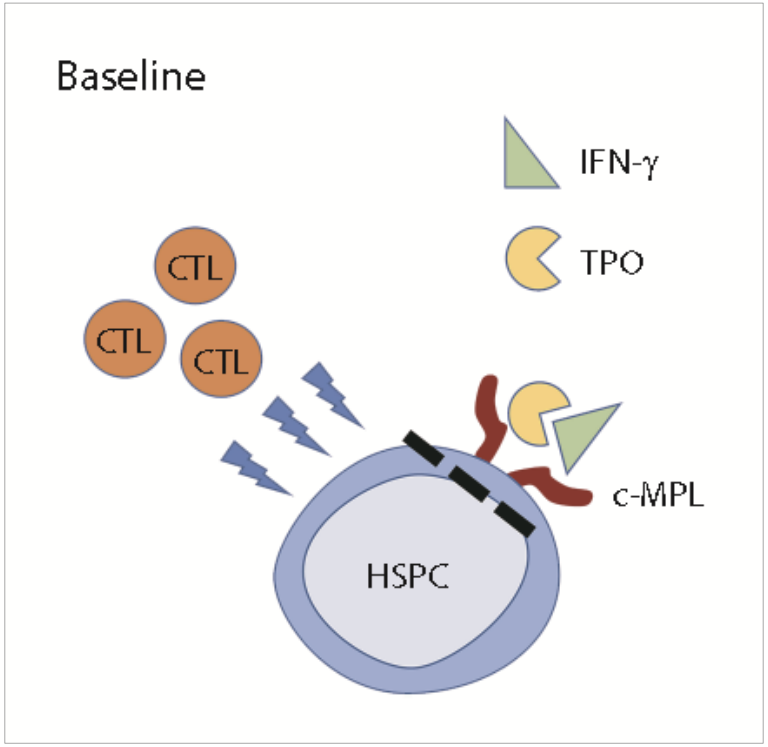
1.Scheinberg P et al. NEJM 2011: 365(35). 2. Bacigalupo A. Blood 2017: 129 (11).
3. Gurion R. et al. Haematologica 2009: 94(5). 4. Young N. et al. Blood 2006: 108(8).

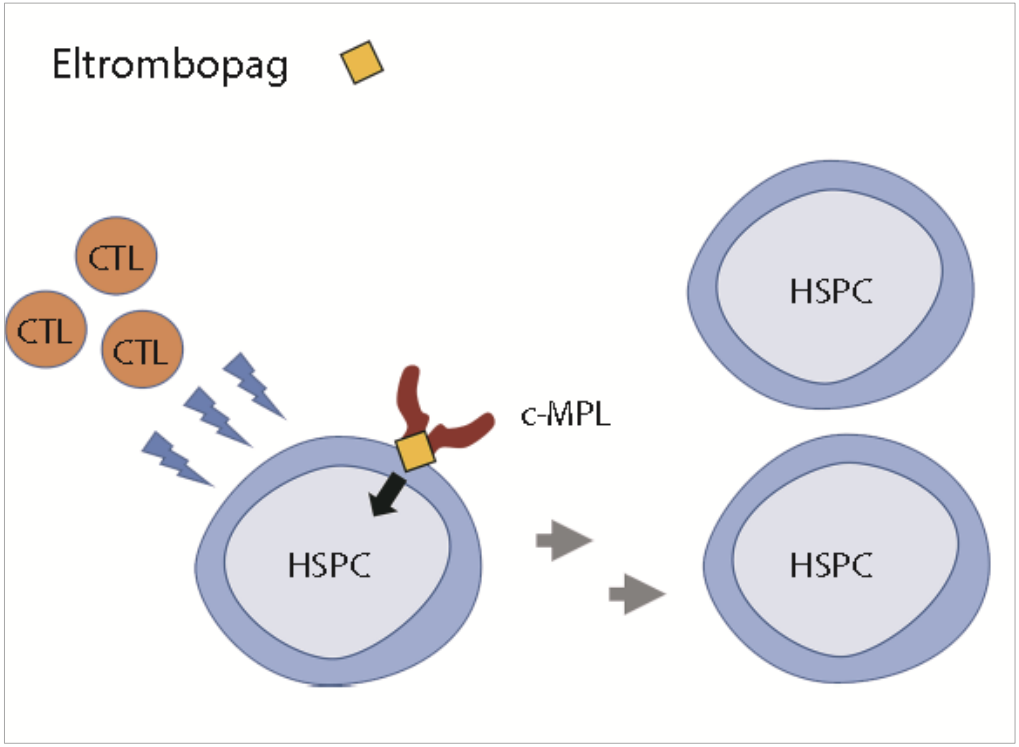
Late complications of IST treated patients

- Relapse in ~ 1/3 of responders[1]
- MDS/AML evolution in 10-15% of cases[1,2]
- Only 29% (24/84) with normal blood counts and off all IST after long-term follow-up (median follow-up 11.3 yrs)[2]

1. Young N. et al. Blood 2006: 108(8). 2. Frickenhofen N. et al. Blood 2003: 101(4).

Eltrombopag (Epag) improves trilineage hematopoiesis in patients with acquired AA





From Bubushok DV. Blood 2019: 133(24).
Mechanism in Alvarado et al. Blood 2019: 139(19).

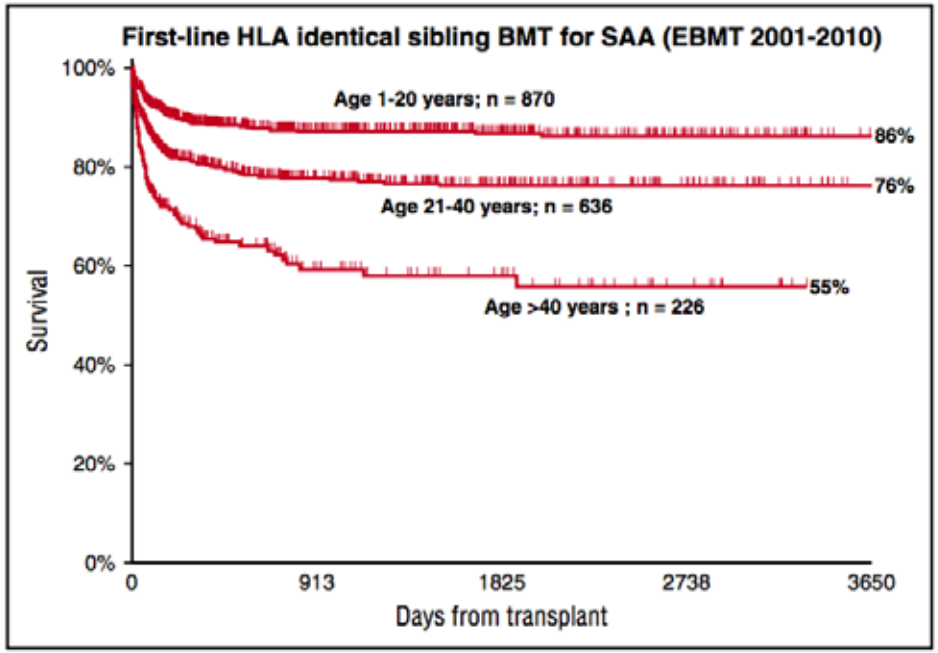
Epag added to standard IST for AA

- Relapsed/refractory[1]
  - Phase 2 study; 25 patients
  - Epag 150 mg po daily
    - Hematologic response 44% @ 12 wks
- Upfront therapy[2]
  - Phase 1-2 study; 92 patients; median f/up 2 yrs
  - Epag 150 mg po daily D1-6 months + hATG/CsA
    - CR 58% and OR 94% @ 6 months
  - **RCT IST vs IST+Epag (NCT02099747, >15 yo)**
- Impact on malignant evolution uncertain
  - 19% (16/83) of rSAA treated with single-agent Epag early cytogenetic clonal evoluation[3]

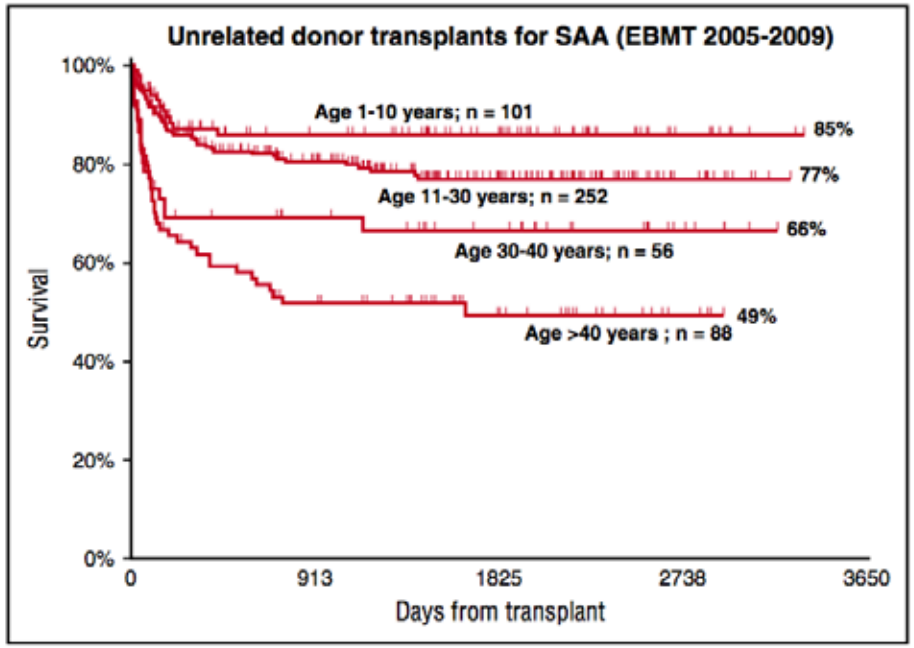
1. Olnes MJ. et al. NEJM 2011: 371(1). 2. Townsley M et al. NEJM 2017: 376(16). 3. Winkler T. et al. Blood 2019; 133(24).

BMT for severe AA

HLA-matched sib



MURD



Data from EBMT Registry reviewed in Bacigalupo A. Blood 2017: 129 (11).

Hopkins Phase II trial of Haplo BMT for SAA

Relapsed/refractory trial (20 patients)

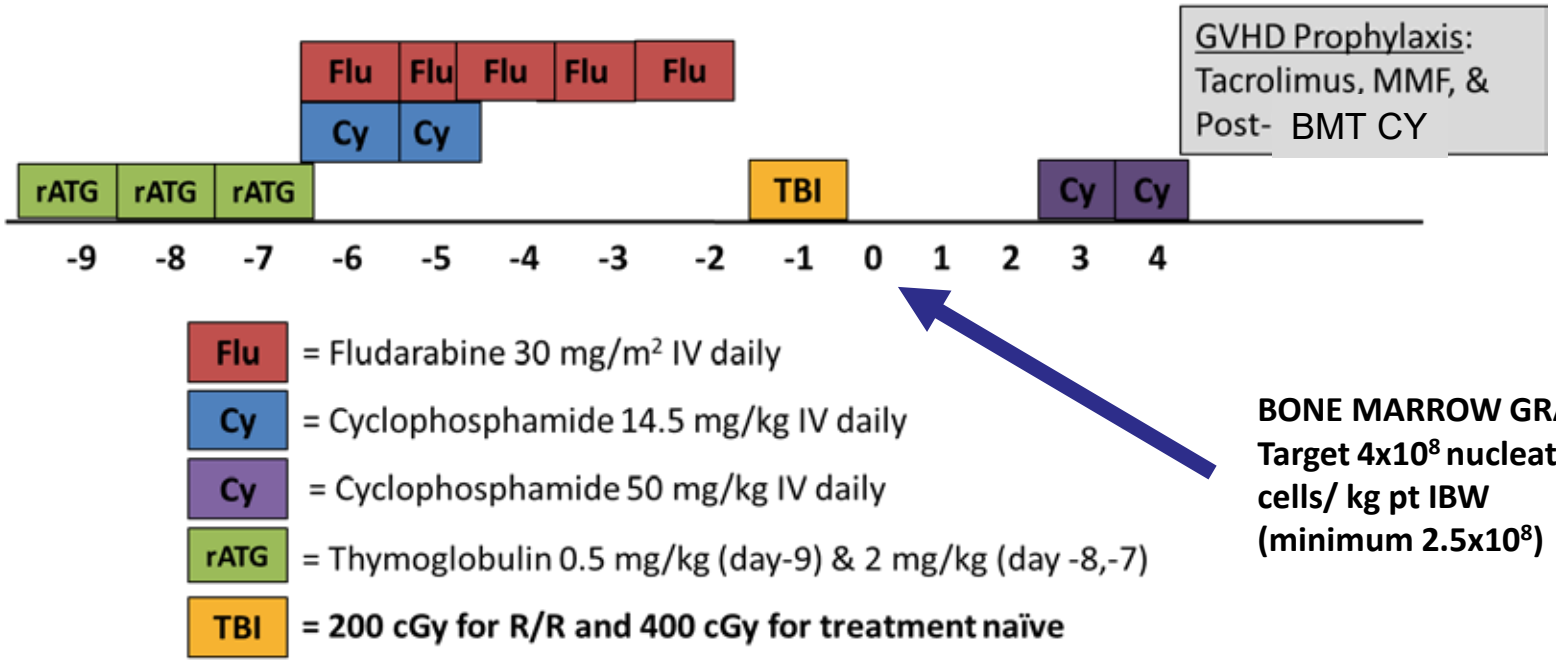
- SAA and ≥3 months after IST & no sib donor
- Median age 29 yo (5-69)

Treatment naïve trial (17 patients)

- SAA and untreated & no sib donor
- Median age 22 yo (3-63)

DeZern A. Blood Adv 2020: 8(4).

Conditioning and GVHD Prophylaxis

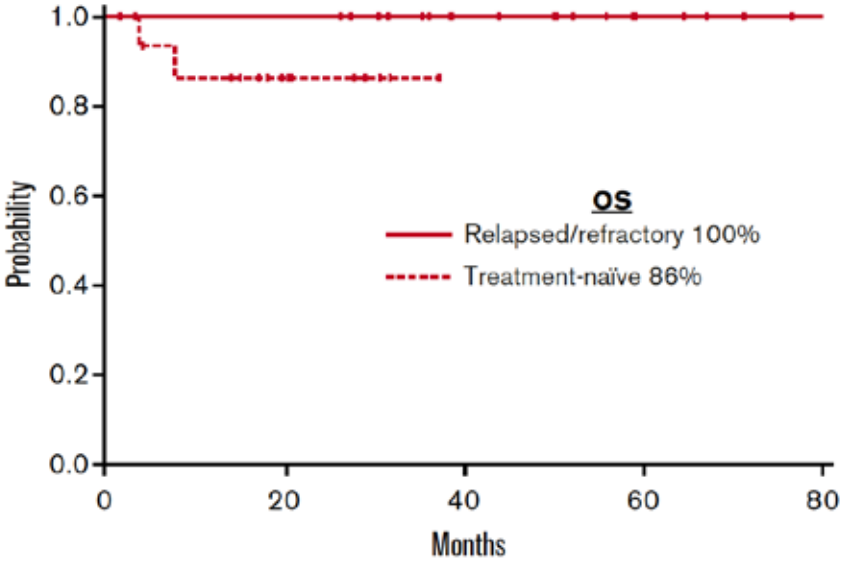


BONE MARROW GRAFT:
Target $4x10^8$ nucleated cells/ kg pt IBW (minimum $2.5x10^8$)

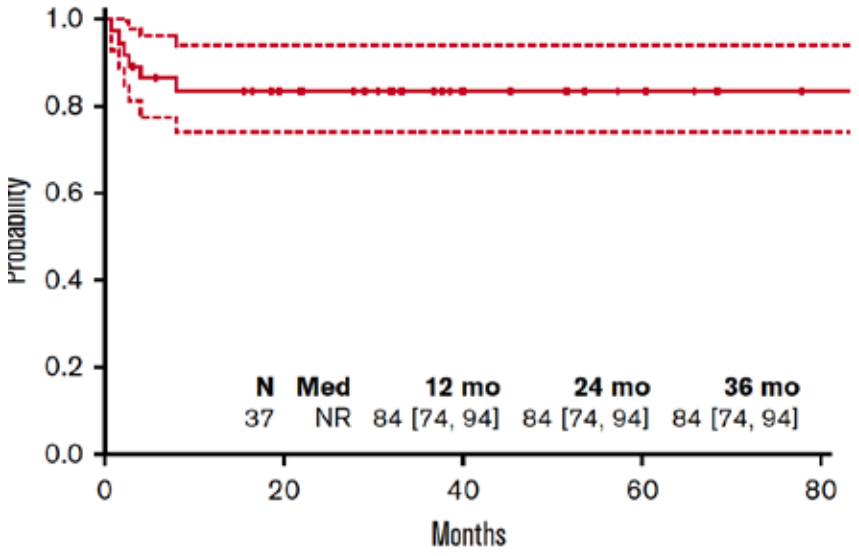
**** After initial 7 treatment-naïve patients treated at 200 cGy, increase TBI to 400 cGy**

DeZern A. Blood Adv 2020: 8(4).

Overall survival



GVHD-free survival



DeZern A. Blood Adv 2020: 8(4).

- CTN 1502 CHAMP study NCT02918292 (relapsed/refractory SAA up to 75 yo)

Paroxysmal nocturnal hemoglobinuria

- Nonmalignant clonal expansion of HSCs with a somatic mutation of *PIGA*
- PNH cells lack surface proteins that require a GPI anchor which normally protect against complement-mediated hemolysis

CD59

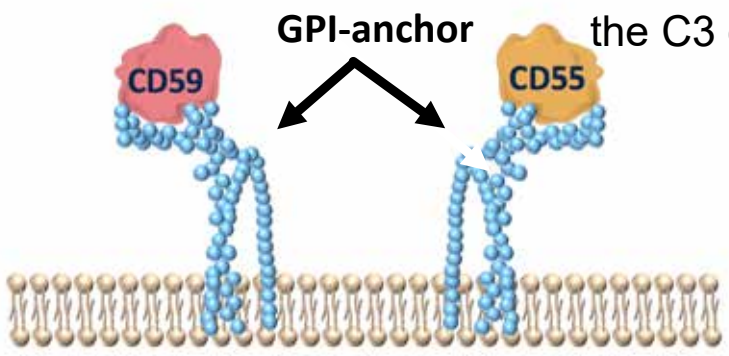
Membrane inhibitor of reactive lysis (MIRL)

Inhibits assembly of the membrane attack complex

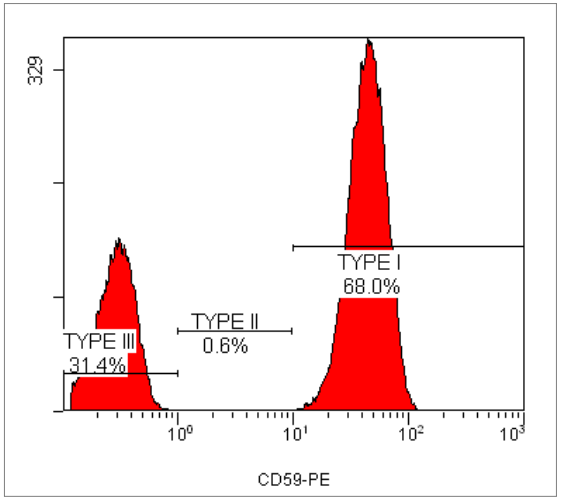
CD55

Decay accelerating factor (DAF)

Inhibits the formation and stability of the C3 convertases



Classical PNH



Clinical triad

1. Intravascular hemolysis
2. Thrombosis
3. Bone marrow failure

Diagnosis - Absent or reduced GPI-linked proteins

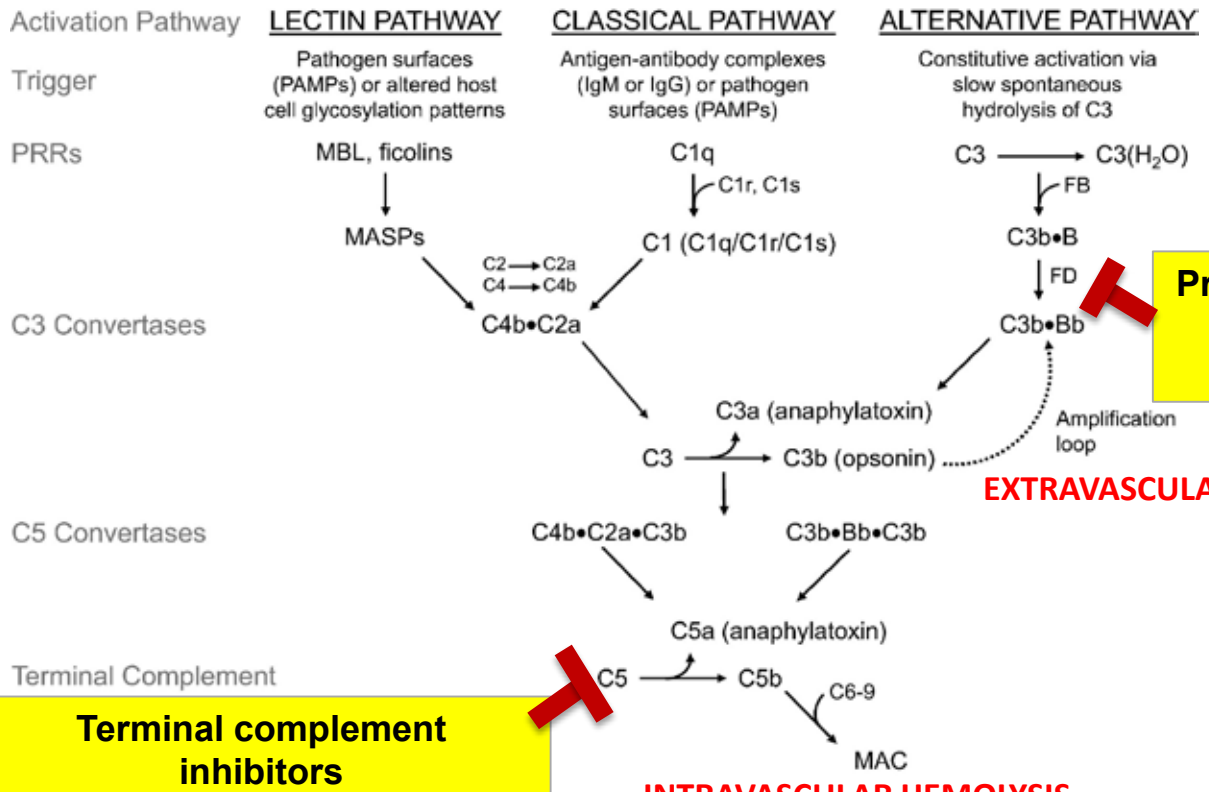
Treatment

- Folic acid ± iron supplementation, role for prophylactic anticoagulation unclear

- Eculizumab or ravulizumab[1,2] treatment indicated for significant disease manifestations attributable to hemolysis
  - Consider d/c anticoagulation in patients on therapy
  - **ACIP recommends meningococcal vaccination**
    MenACWY and MenB vaccines
    Consider antimicrobial prophylaxis for duration of ecu/ravulizumab txt
    Vaccination does not eliminate risk

1. Lee JW. Blood 2019; 133(6). 2. Kulasekararaj AG. et al. Blood 2019; 133(6).

Complement pathways and PNH



Proximal complement inhibitors in clinical trials
(target C3, factor B, factor D)

Terminal complement inhibitors
(target C5)
Eculizumab, **Ravulizumab**

Baines and Brodsky, Blood Reviews 2017: 31.

Potential causes of persistent anemia on eculizumab

- ~70% of patients on eculizumab do not normalize their hemoglobin[1]

Cause	Mechanism	Therapeutic approach
Intravascular hemolysis	Inherited C5 variants (rare)	Switch agent
	Inadequate plasma level of eculizumab	Decrease dosing interval
	Massive complement activation	Avoid triggers, maybe switch agent
Extravascular hemolysis	**C3-mediated (C3-fragment opsonization)***	Maybe proximal complement inhibitors
Bone marrow Disorders	Bone marrow failure	Aplastic anemia treatment
	Clonal evolution	Myeloid malignancy treatment

* Not uncommon and significantly contributes to the residual anemia

Modified from Ristano et al. Frontiers in Immunology 2019: 10.

IBMF/AL-MDS predisposition syndromes

Classical inherited bone marrow failure syndromes

- Congenital neutropenia
- Diamond Blackfan anemia
- Fanconi anemia
- Telomere biology disorders
- Shwachman-Diamond syndrome

Germline predisposition for hematopoietic malignancy

- *CEPBA*
- *DDX41*
- *14q32.2* genomic duplication *(ATG2B/GSKIP)*

Germline predisposition for hematopoietic malignancy with pre-existing cytopenia(s) and/or other organ dysfunction prior to hematopoietic malignancy presentation

- *ANKRD26*
- *ETV6*
- GATA2 Deficiency Syndrome
- *RUNX1* - Familial platelet disorder with associated myeloid malignancy
- *SAMD9* - MIRAGE syndrome; *SAMD9L* - Ataxia Pancytopenia Syndrome
- *SRP72*

Germline predisposition for myeloid neoplasms and solid tumor cancers

- Constitutional mismatch repair deficiency
- Hereditary breast and ovarian cancer (e.g., *BRCA1, BRCA2*)
- Li-Fraumeni syndrome
- RASopathies
- Other rare DNA repair syndromes (e.g., *BLM)*

Modified from 2019 NCCN MDS Guidelines (mutations associated with hereditary myeloid malignancy)

NCCN National Comprehensive Cancer Network®

Inherited BMF syndrome	Genetics	Classical findings	Hematology & oncology	Diagnostic tests	Solid tumors
Fanconi anemia	AR and x-linked recessive DNA repair genes (e.g., *FANCA*)	Congenital anomalies (1/3 lacking)	Macrocytosis, cytopenias, hypocellular marrow/AA, MDS, leukemia, solid tumors	Increased chromosome fragility	SCC (head/neck/ vulva/vagina) Hepatocellular carcinoma
Dyskeratosis congenita/ Telomere biology disorders	AD, AR, x-linked recessive Telomere maintenance genes (e.g., *DKC1*,*TERC, TERC*)	Dystrophic nails, lacey reticular rash, oral leukoplakia Adult presentations – immune deficiency, liver cirrhosis, premature graying, pulmonary AVMs, pulmonary fibrosis	Macrocytosis, cytopenias, hypocellular marrow/AA, MDS, leukemia, solid tumors	Very short telomeres for age	SCC (head & neck) ,
Diamond-Blackfan anemia	AR Ribosomal proteins (e.g. *RPS19*)	Short stature, Cathie's facies	Macrocytosis, erythroid hypoplasia, MDS, leukemia, solid tumors	Elevated erythrocyte adenosine deaminase	Sarcomas
Shwachman-Diamond syndrome	AR *SBDS, EFL1, DNAJC21*	Exocrine pancreatic insufficiency, short stature, skeletal abnormalities	Macrocytosis, cytopenia (especially neutropenia), hypocellular marrow/AA, MDS, leukemia	Low pancreatic isoamylase (adults) and serum trypsinogen (children) Low fat soluble vitamin levels	

Why care about IBMF/AL-MDS predisposition syndromes?

- Not so rare
- Informs clinical care
  - HSCT donor selection, timing and preparatory regimen
  - Cancer and end organ damage surveillance programs
  - Appropriate family counseling
  - Incorporation of genetic predisposition in 2016 WHO myeloid neoplasm and AL classification[1] and NCCN MDS and European LeukemiaNet guidelines[2]
- Informs mechanisms of clonal hematopoiesis and potential MDS/leukemia treatment strategies[3,4,5,6]

1. Arber D. et al. Blood 2016: 127. 2. Dohner H. et al. Blood 2017: 129. 3. Hinds DA et al. Blood 2016: 128. 4. Loh PR et al. Nature 2018: 559. 5. Farmer H. et al. Nature 2005: 434. 6. Bryant HE. rt al. Nature 2005: 434.

Fanconi anemia

- Autosomal recessive; FANC B is x-lined recessive
- Many Fanconi genes
- Function in DNA repair
- Congenital anomalies
  - ~1/3 lack congenital anomalies
- Hypocellular marrow ± cytopenias
- Predisposition to cancer (AML; oral, esophageal, vulvar SCC, HCC)
- Radiosensitivity (DNA damage)

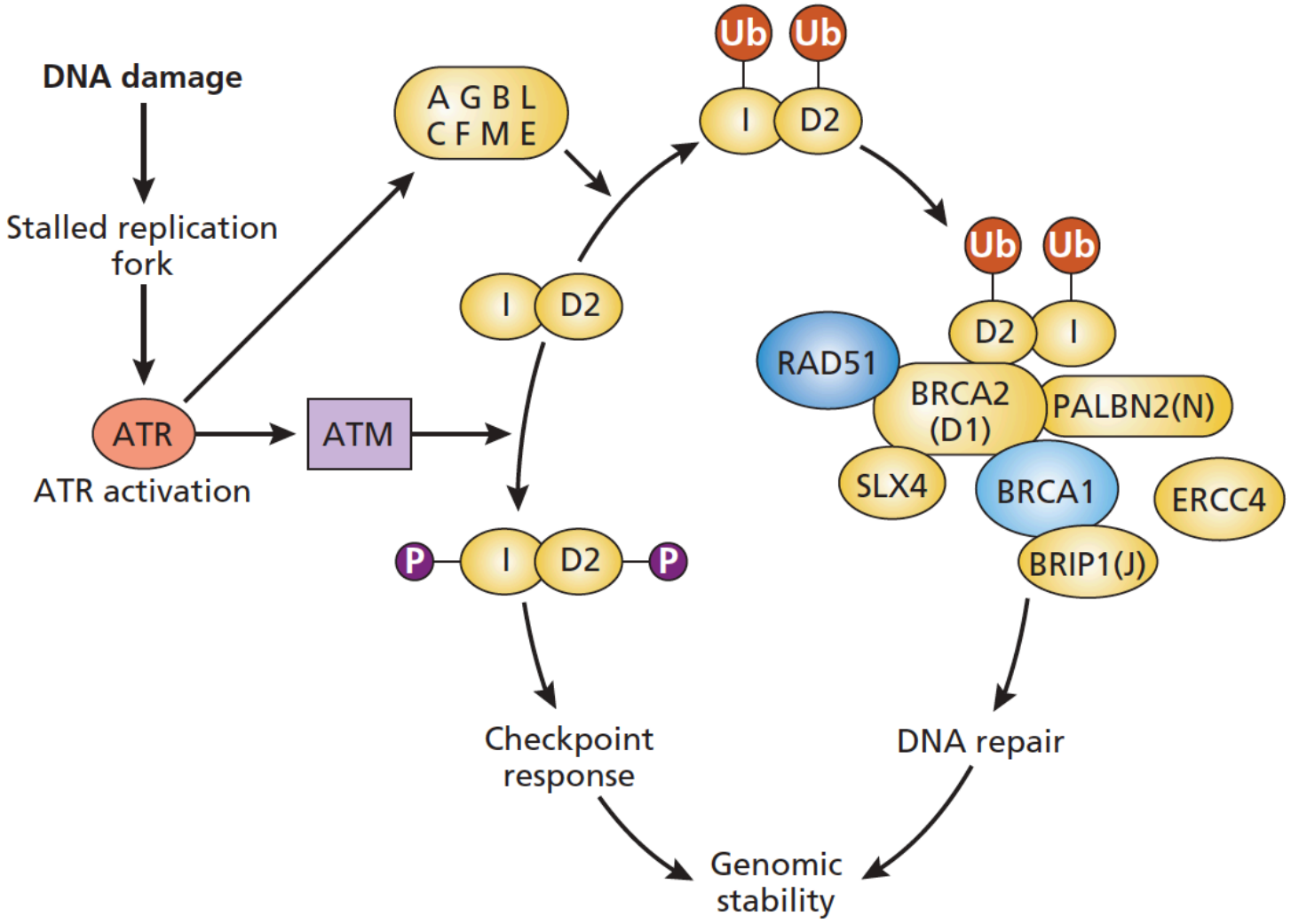
café au lait spot

thumb abnormalities

short stature

Alter BP, Young NS. In Nathan DG, Oski DA, eds. Hematology of Infancy and Childhood 1993.

Fanconi anemia – hallmark is hypersensitivity to genetic damage induced by DNA damaging and cross-linking agents



From ASH SAP 2016 Chapter 15
Berturch A. and Dokal I.

FA-diagnosis – Chromosome fragility testing

- Based on the hallmark of genomic instability in FA cells[1,2]
  - 20% have mosaic lymphocytes (genetic reversion)[3,4]

    If clinical suspicion is high → test skin fibroblasts

    Back mutation has been reported in a hematopoietic stem cell.[5]
- Genetic testing
- Flow cytometry for G2 arrest
- Western blot for ubiquitinated D2
- Retroviral FA gene correction of FA phenotype

+MMC

Image from Clinical Hematology
Edi Young N, Gerson S, High K. 2006.

1. Schroeder TM. Humangenetik 1966: 2. Sasaki MS. Et al. Cancer Res 1973: 33. 3. Soulier et al. Blood 2005: 105.
4. Lo Ten Foe JR, et al. Eur J Human Genet 1997: 5. Gregory J, et al. PNAS 2001: 98.

FA treatment and surveillance

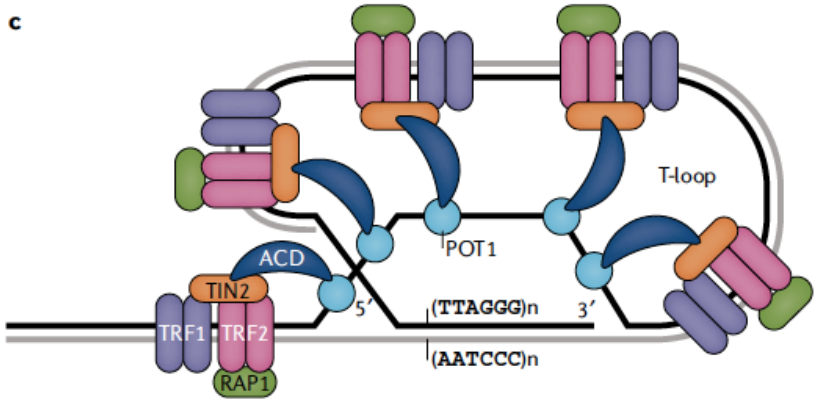
- Androgens improve hematopoiesis (oxymethalone 0.5-1 or danazol 2-4 mg/kg/day)
  - Stimulates erythroid progenitors and increases telomerase gene expression[1]
  - Erythroid and trilineage responses in ~ 60-80%[2]
  - Monitor LFTs, liver US (hepatic adenomas and peliosis hepatis), virilization
- HSCT
- Special consideration of potential treatment-related toxicities when treating solid tumors
- Monitor bone marrow failure and leukemia/MDS
- Avoid tobacco
- Surveillance for solid tumors in all adults

Fanconi anemia guidelines for diagnosis and management
https://www.fanconi.org/images/uploads/other/Guidelines_4th_Edition.pdf

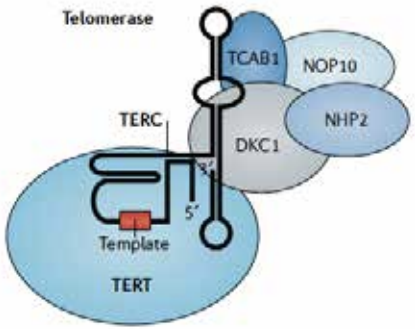
1. Calado RT et al. Blood 2009: 114. 2. Calado RT and Cle D. ASH Education Book 2017. Bone Marrow Failure: Inherited.

Human telomere complex

Telomeres



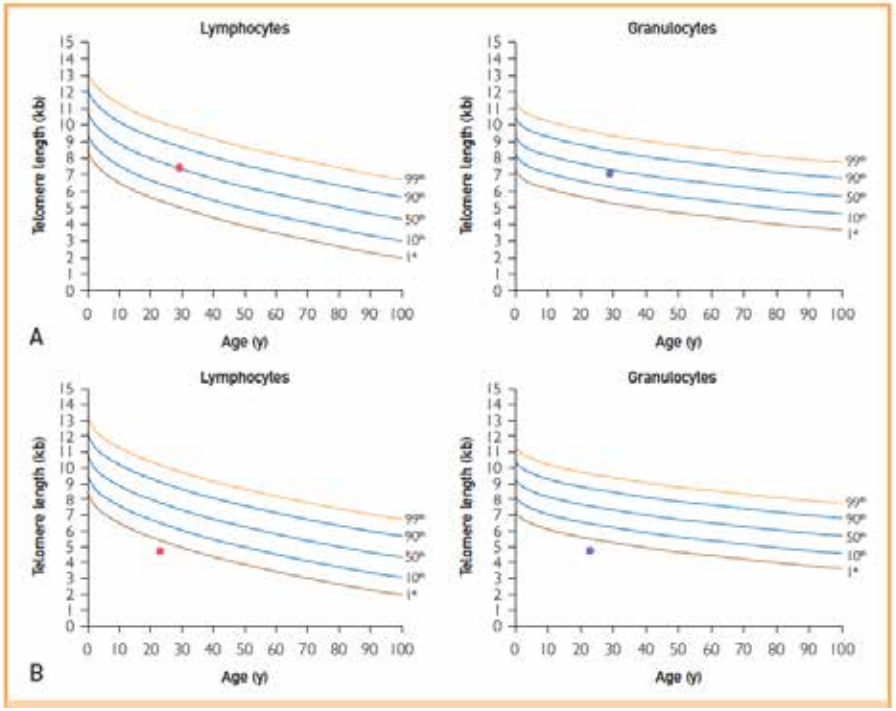
Telomerase



Clinical measurement of telomere lengths - Flow-FISH

Control

Suspected STS



From Shay JW and Wright WE Nature Reviews 2019: 20.

From Mangaonkar A. et al. Mayo Proceedings 2018: 93..

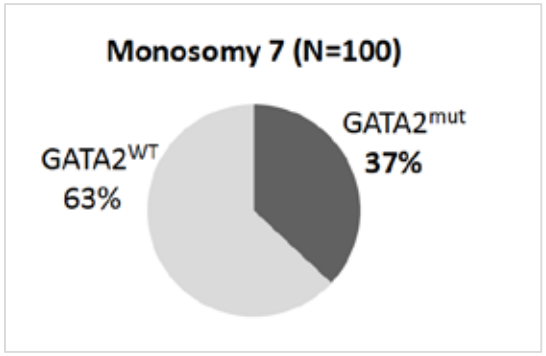
Spectrum of Telomere Biology Disorder phenotypes

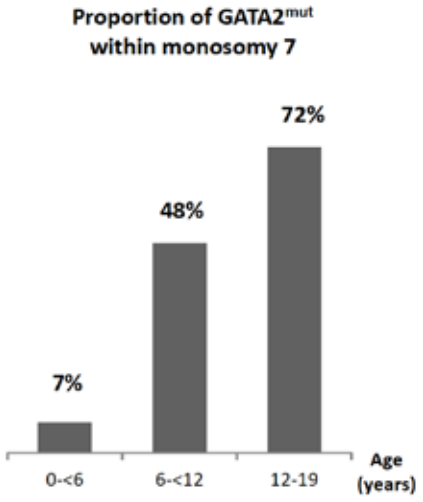
Representative disorders	Key clinical features
Dyskeratosis congenita (DC) 	Mucocutaneous triad (nail dysplasia, abnormal skin pigmentation, and oral leukoplakia), bone marrow failure, pulmonary fibrosis, pulmonary arteriovenous malformations, liver disease, avascular necrosis of hips or shoulders , urethral stenosis, lacrimal duct stenosis, esophageal stenosis, cancer, and/or developmental delay
Aplastic anemia*	Progressive multi-lineage cytopenias, non-immune mediated
MDS and AML*	
Hepatic disease*	Cryptogenic cirrhosis, noncirrhotic portal hypertension (nodular regenerative hyperplasia), hepatopulmonary syndrome
Idiopathic Pulmonary Fibrosis*	May occur in absence of DC-associated features. ~25% of familial IPF and 1–3% of sporadic IPF. Other pulmonary phenotype – pulmonary AVMs

* **May occur in absence of DC-associated features** - Important to recognize in adult patients as subclinical disease can exist concurrently in multiple organs, even when symptoms related to a single disorder predominate.

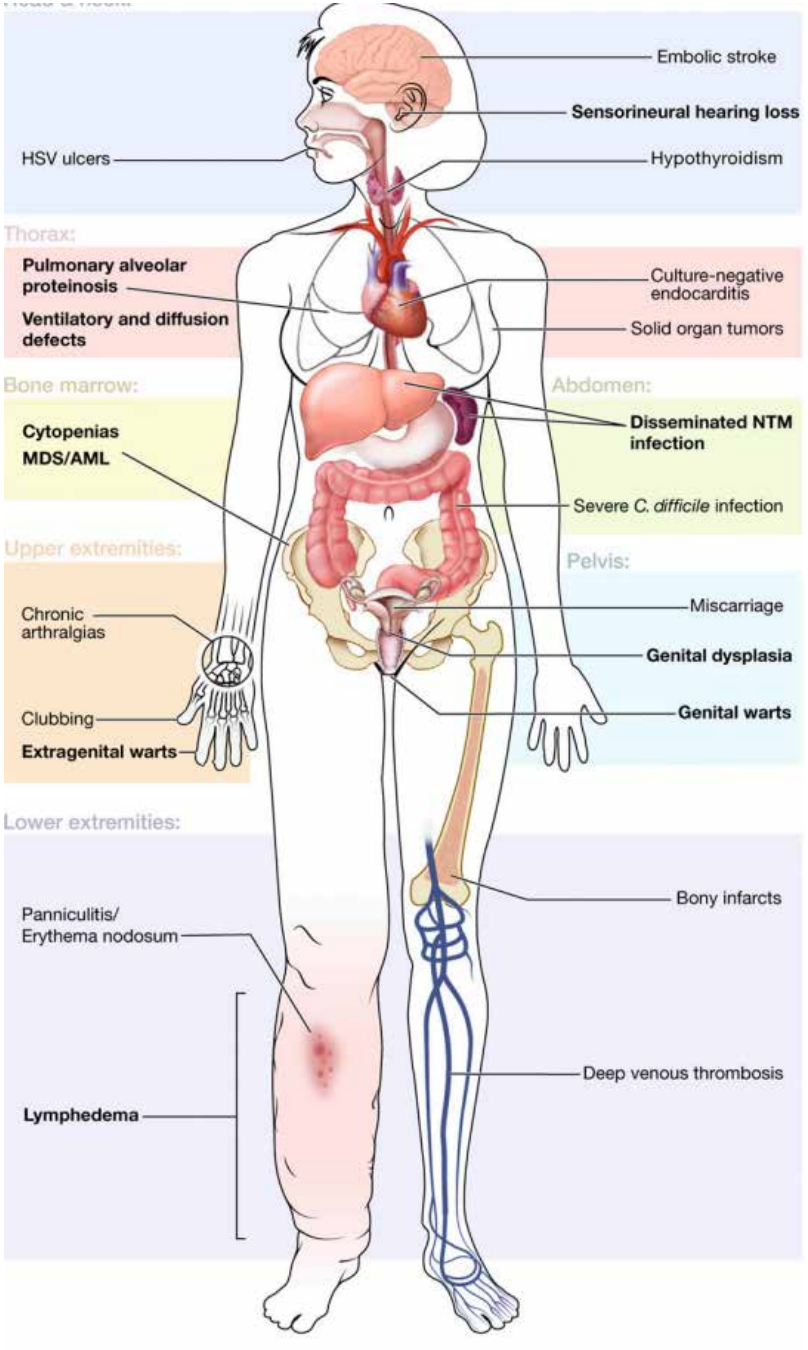
GATA2 deficiency syndrome

- Autosomal dominant familial AML/MDS
- Multiple clinical syndromes
  - MonoMac
  - Familial MDS/AML
  - Emberger's syndrome
  - Isolated cytopenias
  - Immunodeficiency (in all patients)
- Hints – disseminated NTM infection, Monosomy 7 MDS in young adults
  - Family history is not reliable - many de-novo mutations
- High risk of developing AML/MDS





Wlodarski MW et al. Blood 2016:127(11).



Spinner M et al. Blood 2014:123(6).

Familial Platelet Disorder with Associated Myeloid Malignancy: RUNX1 disorder

- Autosomal dominant
- Mild/moderate thrombocytopenia
- Hints - mild bleeding tendency – plt dense granule deficiency, family history of MDS/AL
- High risk of developing MDD/AML

High-yield pearls

- Randomized control study data demonstrates superior response and survival with horse ATG/CsA compared to rabbit ATG/CsA in upfront therapy of sAA
- Recognition of an underlying inherited myeloid malignancy predisposition syndrome is important.
- It is important to differentiate somatic from germline genetic variants in clonal hematopoietic states
- Consider GATA2 deficiency in patients presenting with disseminated nontuberculous mycobacterial infections or monosomy 7 MDS in young adults.

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Tanya Dorff, MD
Associate Clinical Professor of Medicine
Head of Genitourinary Cancer Program
City of Hope Comprehensive Cancer Center

Prostate Cancer Oncology Board Review August 2020

Disclosures

Consultant: Advanced Accelerator Applications, Abbvie, Bayer, BMS, Dendreon, Exelixis, Janssen, Seattle Genetics

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Overview: highlighting major changes in Prostate Cancer management

Early stage Prostate Cancer

- Avoid overtreatment.
- XRT and surgery equally effective. ADT + XRT >XRT

Biochemical recurrence

- Add ADT to salvage radiation – but not all of the time
- PSA doubling time is critical to choosing treatment

Metastatic hormone sensitive

- Up front intensification: abiraterone, apalutamide, docetaxel, enzalutamide are all options

mCRPC

- Sequence remains preferred over combination
- New FDA approvals: PARP inhibitors

Epidemiology/ Risk Factors

- 1 in 9 men will be dx prostate CA
- 2x risk if 1st degree relative
  - 4x risk if ≥2 relatives affected age < 70
- Higher risk from high fat diet (α-linoleic acid)
  - Lower risk with lycopene, cruciferous vegetables
- African American
- Prostatitis, HG PIN

Siegel RL et al.
CA Cancer J Clin 2019; 69:7-34

Estimated New Cases

		Males
Prostate	174,650	20%
Lung & bronchus	116,440	13%
Colon & rectum	78,500	9%
Urinary bladder	61,700	7%
Melanoma of the skin	57,220	7%
Kidney & renal pelvis	44,120	5%
Non-Hodgkin lymphoma	41,090	5%
Oral cavity & pharynx	38,140	4%
Leukemia	35,920	4%
Pancreas	29,940	3%
All Sites	**870,970**	**100%**

Estimated Deaths

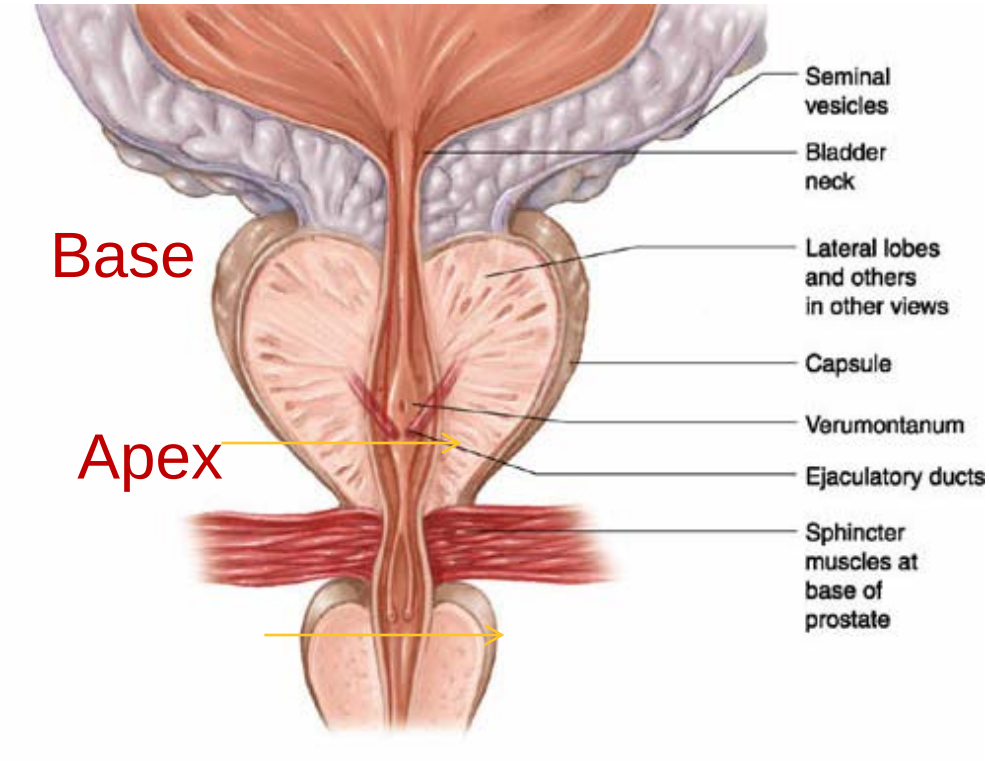
		Males
Lung & bronchus	76,650	24%
Prostate	31,620	10%
Colon & rectum	27,640	9%
Pancreas	23,800	7%
Liver & intrahepatic bile duct	21,600	7%
Leukemia	13,150	4%
Esophagus	13,020	4%
Urinary bladder	12,870	4%
Non-Hodgkin lymphoma	11,510	4%
Brain & other nervous system	9,910	3%
All Sites	**321,670**	**100%**

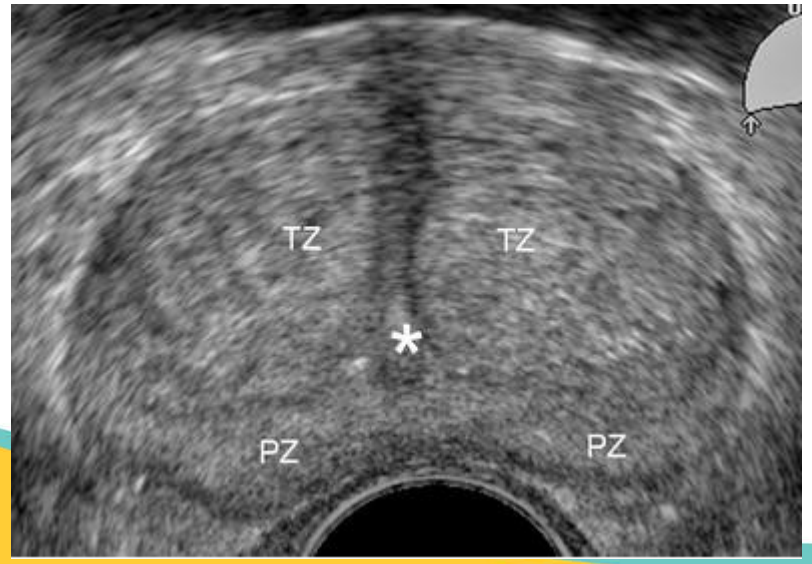
Prostate Cancer Prevention

	PCPT[1]	SELECT[2]
Number enrolled	18,000	35,553
Intervention	Finasteride 5 mg Placebo	Vit E (400 IU), Selenium, Both, or Neither
Results	22.9% risk PC for placebo vs 16.6% risk PC for finasteride RR 0.7 (0.64 – 0.76) p<0.0001	17% increased risk PC in Vitamin E group

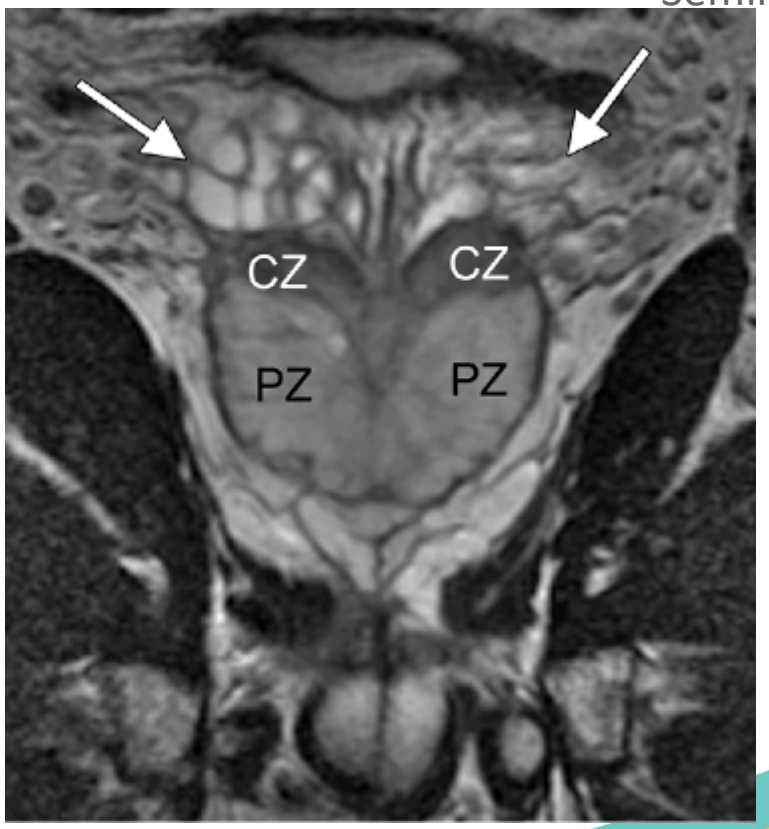
1. Thompson IM et al. NEJM 2003; 349:297
2. Lippman SM et al. JAMA 2009; 301:39

Anatomy of the Prostate Gland



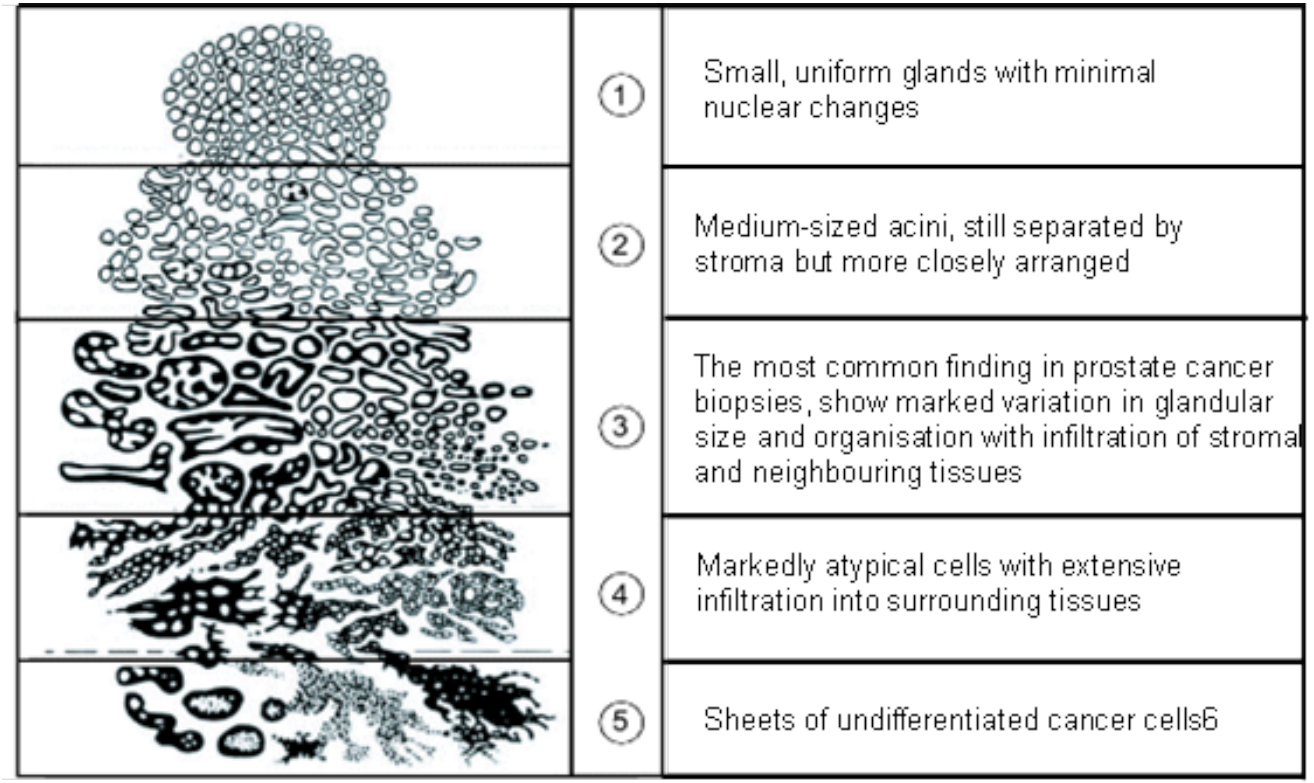


Seminal vesicle



CZ = central zone
PZ = peripheral zone

Gleason Grading



Grade Group	Gleason Score	Gleason Pattern
1	≤6	≤3+3
2	7	3+4
3	7	4+3
4	8	4+4, 3+5, 5+3
5	9 or 10	4+5, 5+4, 5+5

Prostate Cancer Staging

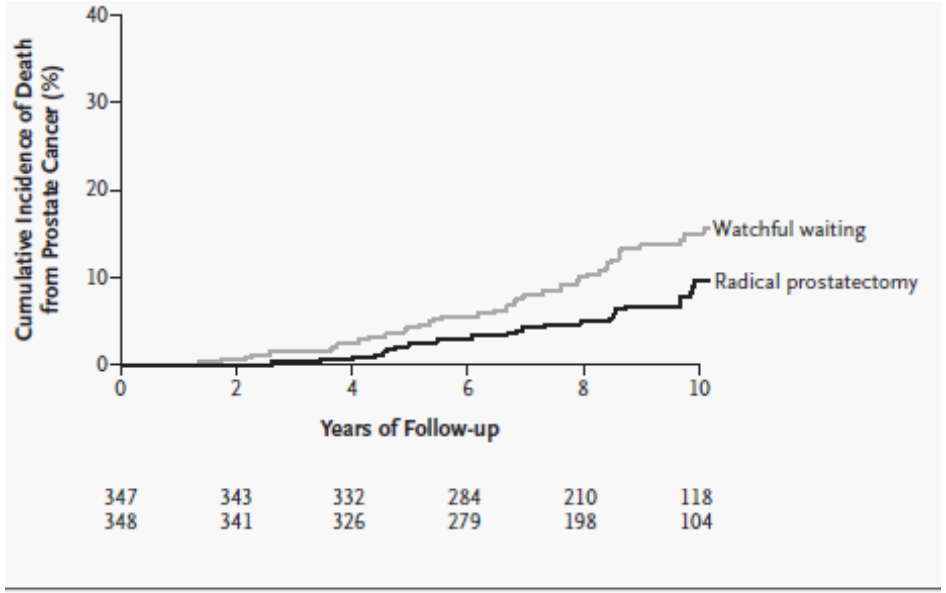
When T is...	And N is...	And M is...	And PSA is...	And Grade Group is...	Then the stage group is...
cT1a-c, cT2a	N0	M0	<10	1	I
pT2	N0	M0	<10	1	I
cT1a-c, cT2a	N0	M0	≥10 <20	1	IIA
cT2b-c	N0	M0	<20	1	IIA
T1-2	N0	M0	<20	2	IIB
T1-2	N0	M0	<20	3	IIC
T1-2	N0	M0	<20	4	IIC
T1-2	N0	M0	≥20	1-4	IIIA
T3-4	N0	M0	Any	1-4	IIIB
Any T	N0	M0	Any	5	IIIC
Any T	N1	M0	Any	Any	IVA
Any T	Any N	M1	Any	Any	IVB

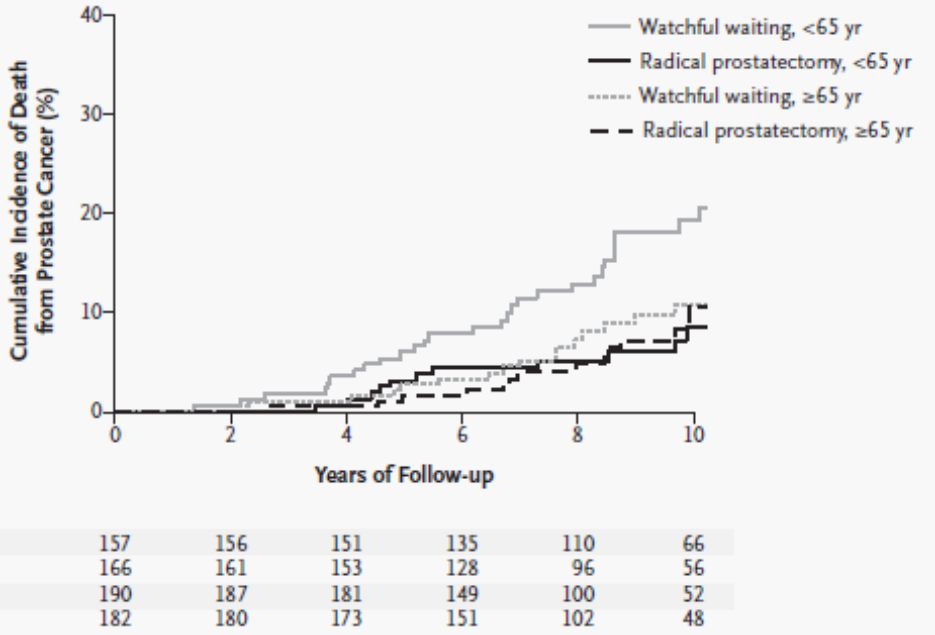
NOTE: When either PSA or Grade Group is not available, grouping should be determined by T category and/or either PSA or Grade Group as available.

INITIAL RISK STRATIFICATION AND STAGING WORKUP FOR CLINICALLY LOCALIZED DISEASE

Risk Group	Clinical/Pathologic Features			Imaging[f,g]	Germline Testing[c]	Molecular/ Biomarker Analysis of Tumor[c]	Initial Therapy
Very low[d]	Has all of the following: • T1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core[e] • PSA density <0.15 ng/mL/g			Not indicated	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Not indicated	See PROS-3
Low[d]	Has all of the following but does not qualify for very low risk: • T1–T2a • Grade Group 1 • PSA <10 ng/mL			Not indicated	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]	See PROS-4
Intermediate[d]	Has all of the following: • No high-risk group features • No very-high-risk group features • Has one or more intermediate risk factors (IRF): ▸ T2b–T2c ▸ Grade Group 2 or 3 ▸ PSA 10–20 ng/mL	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive[e]	• Bone imaging[h]: not recommended for staging • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]	See PROS-5
		Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥50% biopsy cores positive[e]	• Bone imaging[h]: recommended if T2 and PSA >10 ng/mL • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended if family history positive or intraductal/cribriform histology See PROS-1	Consider if life expectancy ≥10 y[j]	See PROS-6
High	Has no very-high-risk features and has at least one high-risk feature: • T3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL			• Bone imaging[h]: recommended • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended	Consider if life expectancy ≥10 y[j]	See PROS-7
Very high	Has at least one of the following: • T3b–T4 • Primary Gleason pattern 5 • 2 or 3 high-risk features • >4 cores with Grade Group 4 or 5			• Bone imaging[h]: recommended • Pelvic ± abdominal imaging[i]: recommended if nomogram predicts >10% probability of pelvic lymph node involvement • If regional or distant metastases are found, see PROS-8	Recommended	Not routinely recommended	See PROS-7

What is the Role of Prostatectomy for low risk prostate cancer?





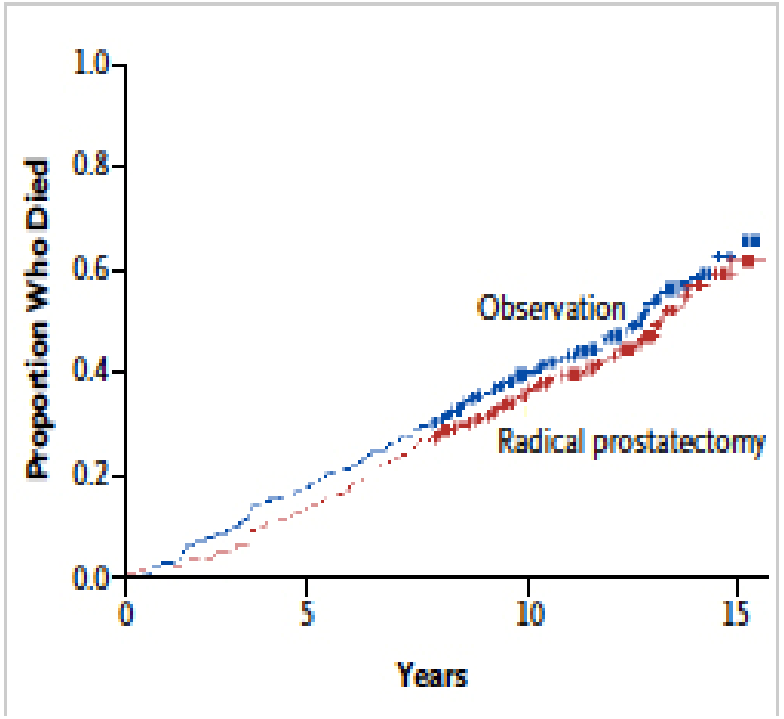
Bill-Axelson A et al.
NEJM 2005; 352:1977-84

Table 3. Probabilistic Sensitivity Analysis

Strategy	QALYs (95% Confidence Interval)	Incremental QALY
Active surveillance	11.00 (6.93-13.90)	
Brachytherapy	10.65 (5.57-14.29)	−0.35
IMRT	10.54 (5.55-14.27)	−0.09
Radical prostatectomy	10.30 (4.89-14.36)	−0.24

Abbreviations: IMRT, intensity-modulated radiation therapy; QALY, quality-adjusted life-year.

Hayes JH et al JAMA 2010 304:2373



ORIGINAL ARTICLE

Treatment or Observation for Localized Prostate Cancer

July 19, 2012 | T.J. Wilt and Others

Over 700 men were assigned to radical prostatectomy or observation after receiving a diagnosis of prostate cancer, usually on the basis of elevated PSA levels. After a median of 10 years, between-group differences in all-cause and prostate-cancer mortality were not significant.

CME | Comments

SPECIALTIES Hematology/Oncology, Surgery

Wilt TJ et al. NEJM 2012; 367:203-12

"If there is no difference in mortality [between active surveillance and immediate treatment], then quality of life is the defining issue."

— Mark Litwin, MD, MPH

Criteria for Inclusion in Active Surveillance

- **Epstein criteria for VERY low risk:**
  - **T1c, Gleason ≤ 6**
  - **PSA density <0.15 ng/cc**
  - **Fewer than 3 cores with cancer, <50% involvement of any one core**
- Other groups have criteria:
  - Gleason 3+4 becoming possible (with molec testing)
  - T2a OK in some series
  - Fewer than 2 cores or <1/3 of cores involved
  - * for boards, <10 years life expectancy

How To: Active Surveillance

Table 3. National Active Surveillance Guidelines

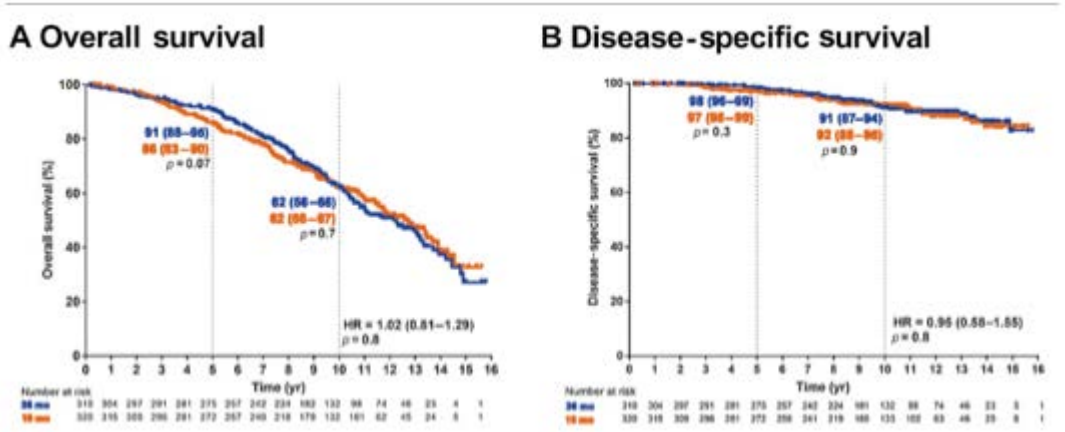
Group	Recommendations for Low-Risk Prostate Cancer	Recommendations for Intermediate-Risk Prostate Cancer	Tests Recommended for Use In Active Surveillance	Recommendations Regarding Other Tests	Role of 5-α Reductase Inhibitors
Cancer Care Ontario[27]	Active surveillance is preferred management	Active treatment; active surveillance for selected pts	PSA every 3–6 mo DRE annually Systematic bx within 6–12 mo of diagnostic bx, then every 3–5 yr	MRI when clinical and pathology findings discordant	May have a role
ASCO[28]	Active surveillance is preferred management	Active treatment; active surveillance for selected pts	PSA every 3–6 mo DRE annually Systematic bx within 6–12 mo of diagnostic bx, then every 3–5 yr	Other tests remain investigational	No clear role
NCCN[29]	Very-low-risk prostate cancer: active surveillance is preferred management Low-risk prostate cancer: all therapies are options	Active treatment; active surveillance for selected pts	PSA ≤ every 6 mo Biopsy ≤ annually	Consider MRI if aggressive cancer suspected or PSA increases with neg systematic bx	
NICE[30]	Active surveillance is preferred management	Radical treatment for disease progression	PSA every 3–4 mo, monitor kinetics; otherwise same as in Cancer Care Ontario guidelines	MRI on enrollment	

ASCO = American Society of Clinical Oncology; bx = biopsy; DRE = digital rectal examination; NCCN = National Comprehensive Cancer Network; neg = negative; NICE = National Institute for Health and Care Excellence; PSA = prostate-specific antigen; pts = patients.

Garisto and Klotz. Oncology 2017

Localized Prostate Cancer: XRT

- ADT added to radiation (EBXRT) improves survival for high risk or locally advanced patients[1]
  - 4-6 months (short course) for intermediate risk
  - Neoadjuv + concurrent + 2-3 years LHRH for hi risk[2,3]
  - 18 months may be acceptable[4]
- ADT needed even with dose escalation[5]
  - GETUG 14 – 377 pts tx 80 Gy, 5 yr RFS 84% w/ ADT vs 76% w/out (p=0.02)
- **Brachy boost** should be added when appropriate
- Doses <70 Gy inadequate
  - Unclear whether escalation >78 Gy beneficial



1. Pilepich MV et al. JCO 1997; 15:1013 (RTOG 8531)
2. Hanks GE et al. JCO 2003; 21:3972 (RTOG 9202)
3. Bolla M et al. Lancet 2002; 360:103 (EORTC)
4. Nabid A et al. Eur Urol 2018; 74:432-41.
5. Dubray M et al. ASCO 2016 (abstr 5021)

Localized Prostate Cancer: RRP

- ADT is not recommended prior to surgery
  - Neoadjuvant studies show some pCR with ADT + abi or ADT + apa
- Robotic (minimally invasive) is most common option
- Potency depends on nerve bundle preservation
  - Sacrifice of 1 side nerves ↓ chance of potency to 50%
- Adjuvant ADT for lymph node positive[1] and other high risk patients[2] "Investigational"
- **Adjuvant XRT** for +margins or T3 [3,4]

1. Messing EM et al. NEJM 1999; 341:1781
2. Dorff TB et al. JCO 2011;29:2040
3. Thompson IM et al. JAMA 2006; 296:2329 (S8794)
4. Bolla M et al. Lancet 2005; 366:13 (EORTC 22911)

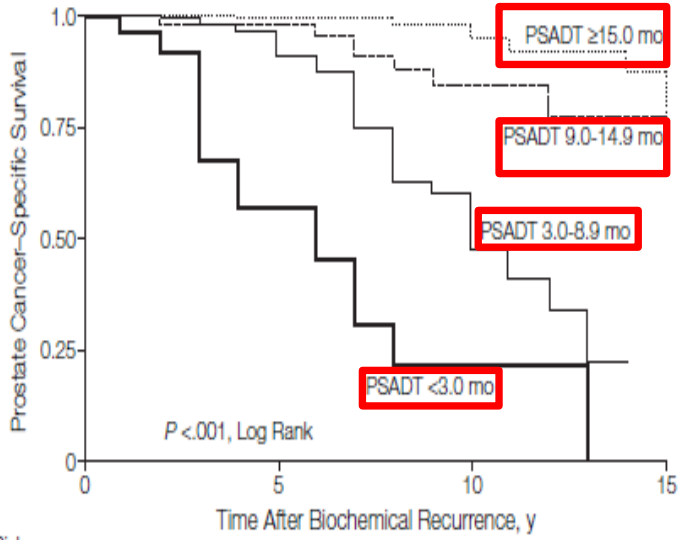
- **Definition**: PSA >0.2 after RRP, “nadir +2” after XRT
- ADT beneficial when giving salvage radiation for BCR
  - GETUG-AFU16[1] gave 6 months of goserelin with XRT 66 Gy or XRT alone; 5 year biochem RFS 80% vs 62% (HR 0.5)
  - RTOG 9601[2] gave bicalutamide 150 mg for 24 months with XRT 64.8 Gy or XRT alone; mets at 12 years 14% w/ bicalut vs 23% (p<0.001) and HR for OS 0.75 (2-sided p = 0.036).
  - SPPORT found 89% 5-year RFS for ADT + pelvic LN XRT compared to 83% w/out pelvic LN and 71% w/out ADT (i.e. prostate bed XRT only)
- BUT… minimal benefit of ADT when XRT started at PSA <0.8[4]

		Pre-RT PSA (ng/ml)		
Margin status	ISUP grade group (Gleason score)	0.1–0.5	0.6–1.0	>1.0
Negative	1 (6)	RT	RT	RT + STADT
	2, 3 (7)	RT	RT + STADT	RT + LTADT
	4, 5 (8–10)	RT [a]	RT + STADT	RT + LTADT
Positive	1 (6)	RT	RT + STADT	RT + LTADT
	2, 3 (7)	RT	RT + STADT	RT + LTADT
	4, 5 (8–10)	RT [a]	RT + LTADT	RT + LTADT

1. Carrie C. et al Lancet Oncol 2016; 17:747
2. Shipley WU et al. NEJM 2017; 376:417
3. Pollack A et al. J Urol 2019; supp (abstr MP72-01)
4. Spratt D et al. Eur Urol 2018; 73:156-65

Biochemical Recurrence (after salvage XRT): When (If) to Start ADT?

Figure 3. Fifteen-Year Actuarial Kaplan-Meier Prostate Cancer–Specific Survival Curves by PSADT



No. at Risk PSADT, mo				
<3.0	23	10	2	0
3.0-8.9	119	85	19	0
9.0-14.9	79	51	19	3
≤15	158	113	52	9

Biochemical recurrence segregated by prostate-specific antigen doubling time among patients who experienced a biochemical recurrence. PSADT indicates prostate-specific antigen doubling time.

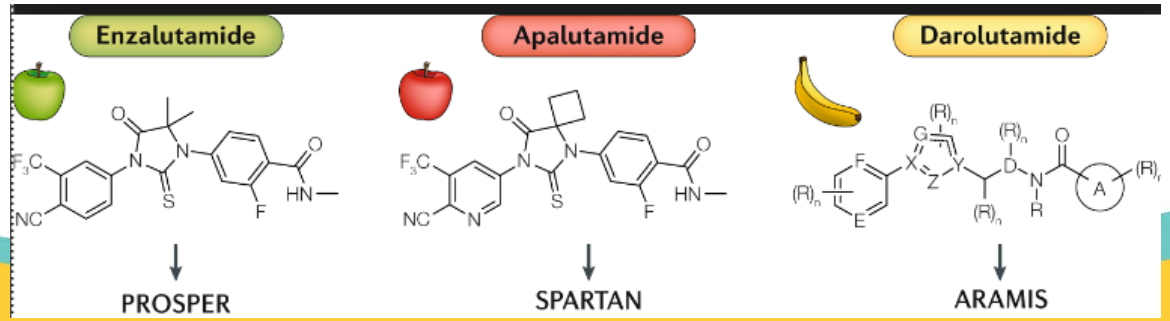
- PSA Doubling Time
- Time to Recurrence
- Gleason Grade
- COMORBIDITIES

HOW:

- Intermittent (4-12 months on)
- Degarelix vs Leuprolide/Goserelin

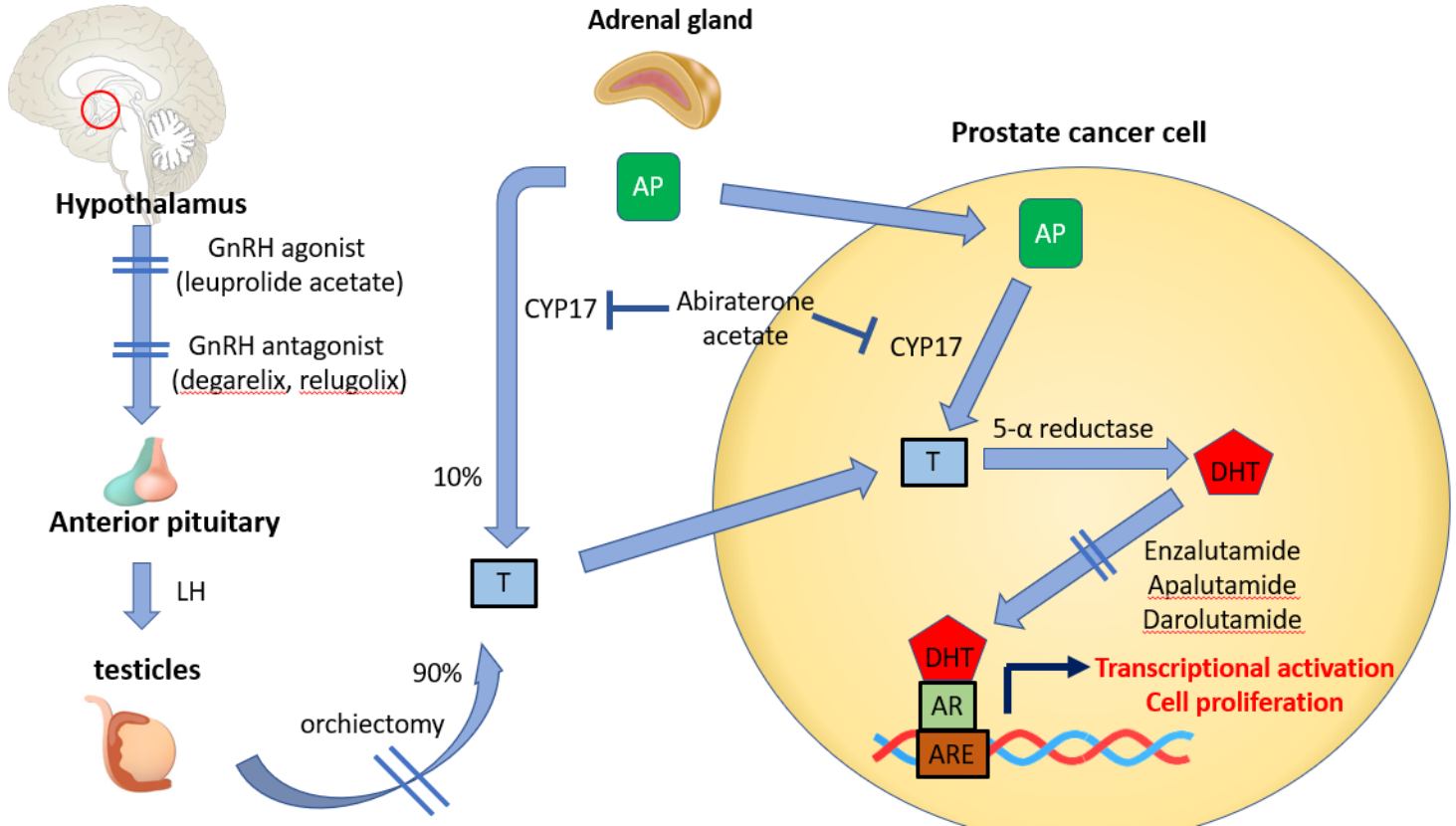
JAMA 2005; 294:433-439.

Agent	Apalutamide 240 mg daily	Darolutamide 600 mg BID	Enzalutamide 160 mg daily
Study name	SPARTAN	ARAMIS	PROSPER
Design	2:1 apa/placebo	2:1 daro/placebo	2:1 enza/placebo
Number of pts	1207	1509	1401
Inclusion:	PSA DT <10 mo Pelvic LN <2 cm OK	PSA DT ≤10 mo Pelvic LN <2cm OK bPSA ≥2	PSA DT ≤10 mo -- bPSA ≥2
Met Free Surv	40.5 mo vs 16.2 placebo (HR 0.29)	40.4 mo vs 18.4 placebo (HR 0.41)	36.6 mo vs 14.7 placebo (HR 0.07)
Discontinuation	10.7% apa, 6.3% placebo	8.9% daro, 8.7% placebo	10% enza, 8% placebo



Principles of treatment metastatic prostate cancer: Androgen Deprivation Therapy (ADT)

- **ADT is effective**
  - 60-70% will have PSA “normalization”
  - 30-50% will have >50% regression of measurable tumors
  - 60% will have palliation of symptoms
- **Castration**
  - **Surgical vs chemical**
  - Use AR antagonist (ex: bicalutamide) run-run-in to block flare
  - LHRH antagonist (degarelix) avoids flare



ADT: managing side effects

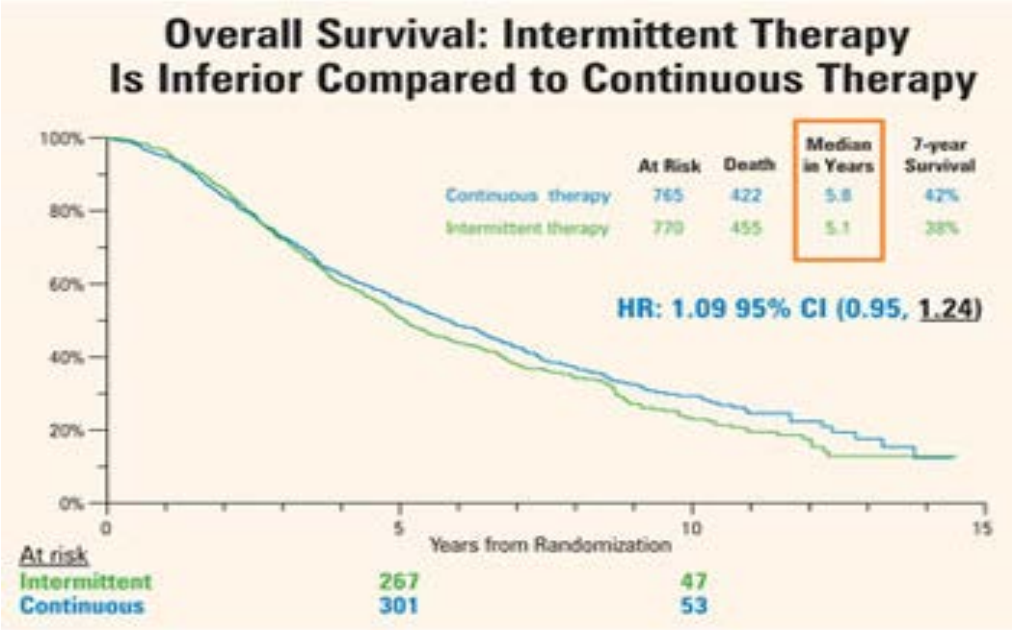
- Common: impotence, hot flashes, fatigue, gynecomastia, weight gain, muscle loss
- Metabolic: diabetes, lipids, **osteopenia**, cardiovascular disease
  - Check DEXA
  - Bisphosphonates if osteopenia or denosumab 60 mg SQ q6, which reduces vertebral fractures[1]
  - Resistance and Aerobic **Exercise** can improve muscle mass, physical function
  - **Vit D + Calcium**
  - LHRH antagonist may be safer than LHRH agonist[2]

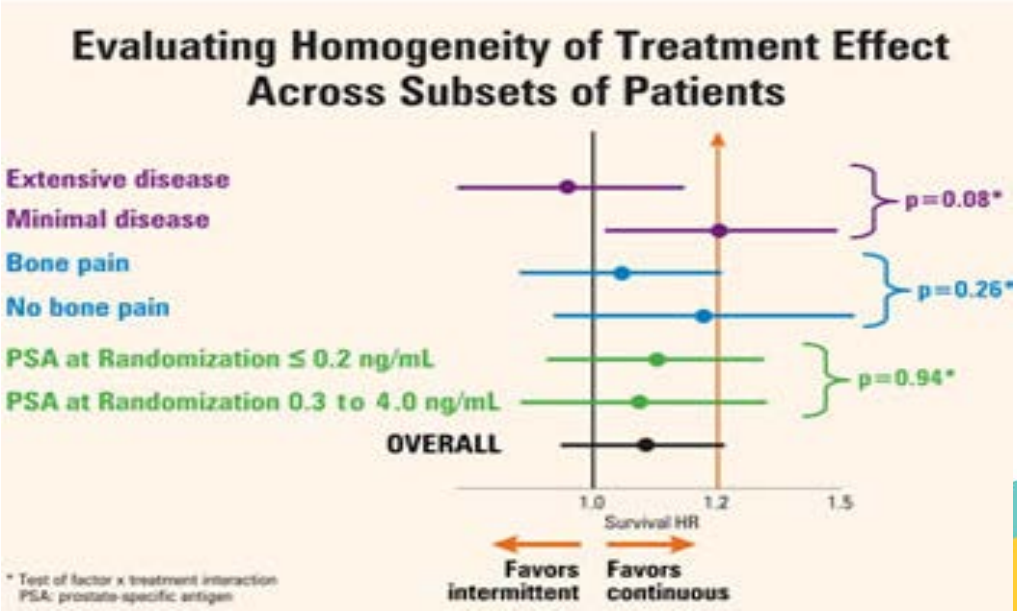
1. Smith MR et al. NEJM 2019; 361:745
2. Margel D et al. ASCO 2019; abstr 5015

mHSPC: Continuous ADT preferred over intermittent

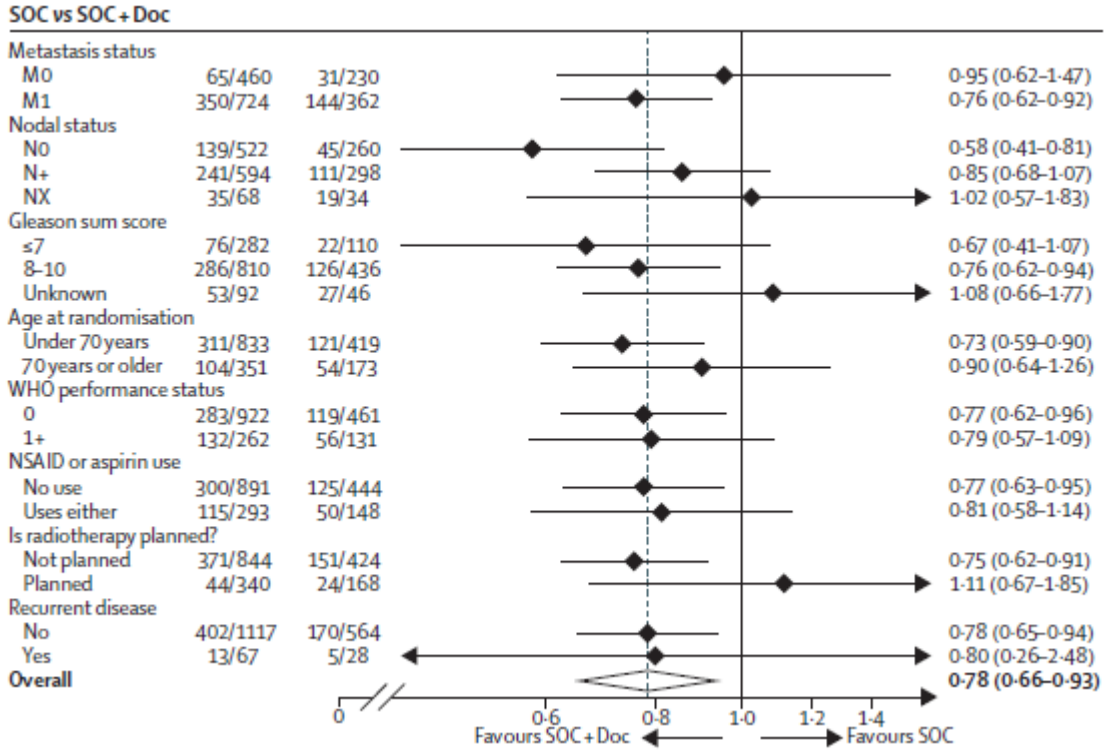
SWOG 9346

Hussain M et al,
NEJM 2013;
368:1314-25



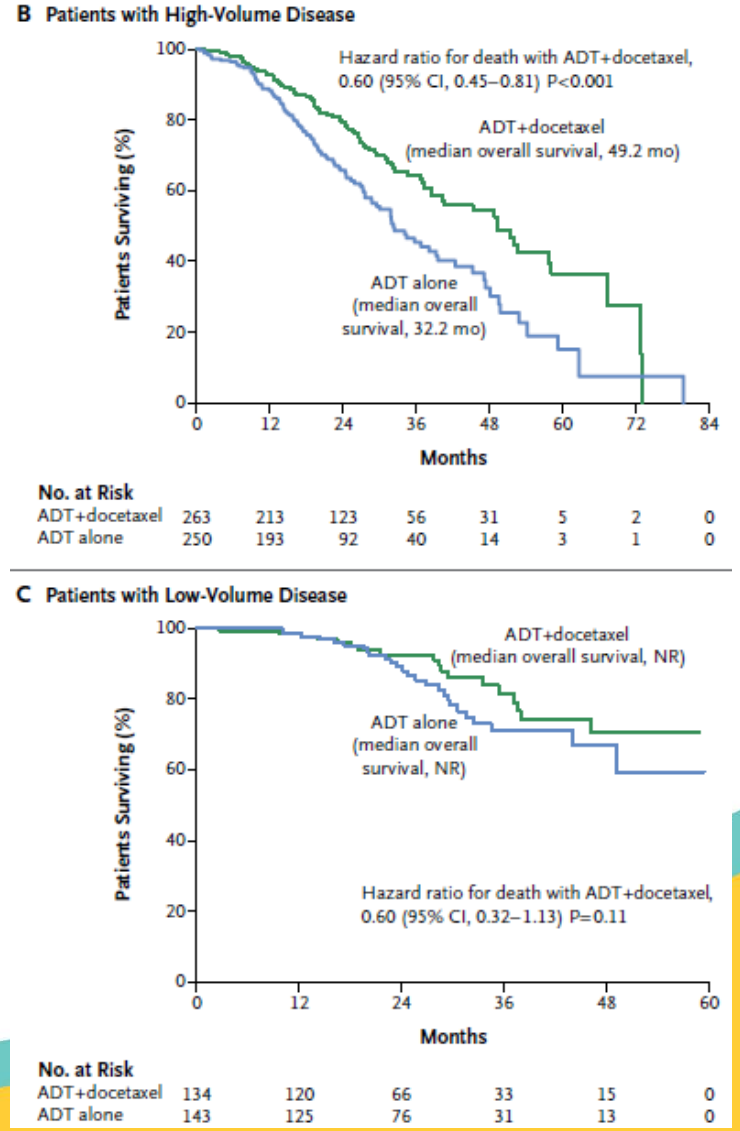


Early chemotherapy improved survival in metastatic hormone sensitive prostate cancer (HSPC)

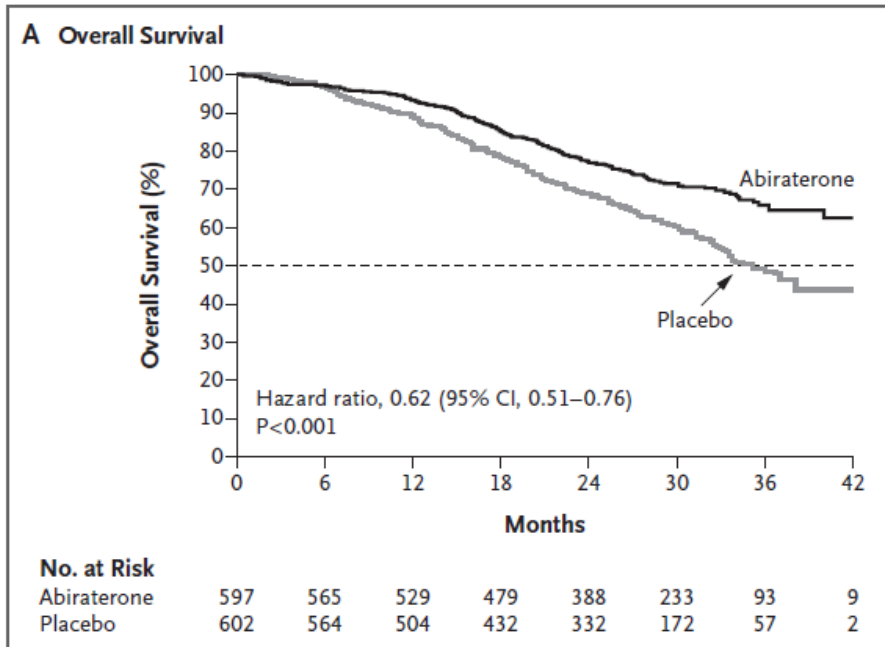


STAMPEDE (James et al, Lancet 2016; 387:1163-77)

CHAARTED (Sweeney CJ et al. NEJM 2015; 373:737-46)



Early abiraterone improves survival in mHSPC



LATITUDE 2 of 3 high risk features:

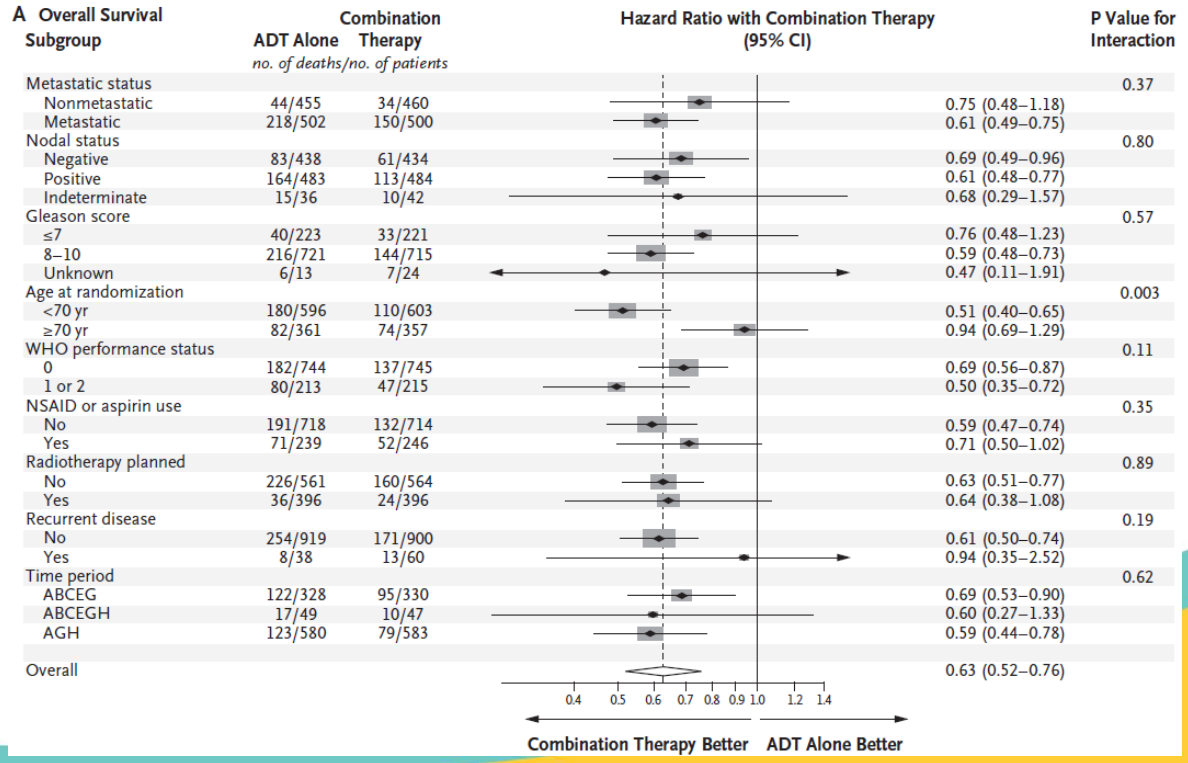
- Gleason 8-10
- 2+ bone metastases
- Visceral metastases

Fizazi K et al. NEJM 2017
DOI:10.1056/NEJMoa1704174

STAMPEDE:
Hi risk localized if 2/3:
Gleason 8-10 T3/T4 PSA >40

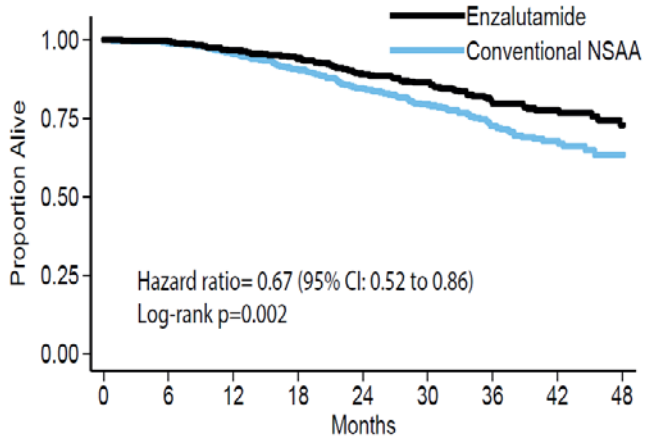
Biochemically recurrent if
PSA >4 and PSA DT <6 mo

James ND et al. NEJM 2017;
DOI: 10.1056/NEJMoa1702900



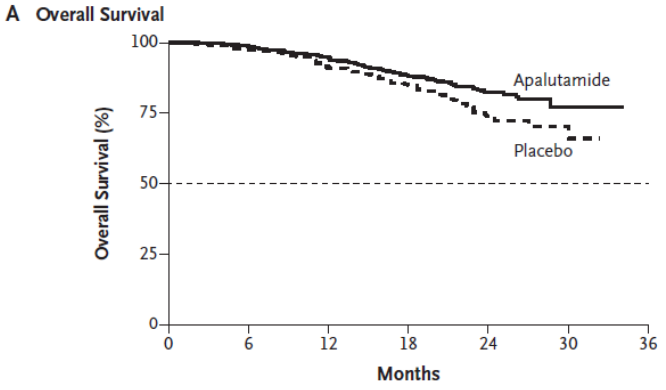
AR antagonists in mHSPC: ENZAMET and TITAN

- Up-front enzalutamide increased 3 year OS from 72% to 79% in ENZAMET[1], HR 0.67.
  - Bicalutamide allowed in control arm
  - No apparent advantage for enza after docetaxel; toxicity was noted
- TITAN[2] found improved OS at 24 months for apalutamide in mHSPC (82.4% vs 73.5%) compared to placebo



Number at risk

Conventional NSAA	562	551	531	501	452	311	174	86	32
Enzalutamide	563	558	541	527	480	340	189	106	45



No. at Risk

Apalutamide	525	513	490	410	165	14	0
Placebo	527	509	473	387	142	16	0

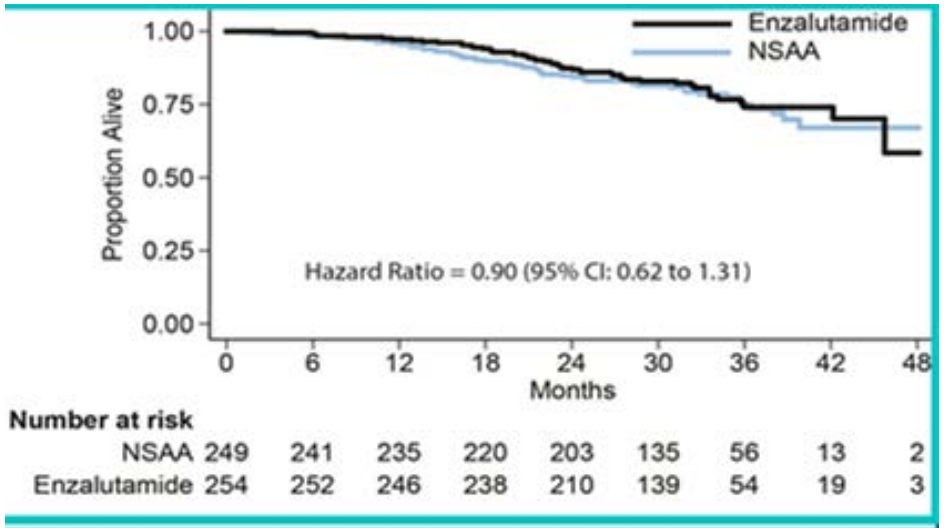
	No. of Patients	Median Overall Survival (95% CI)	Patients with Overall Survival at 24 Mo (95% CI)
		mo	%
Apalutamide	525	NE	82.4 (78.4–85.8)
Placebo	527	NE	73.5 (68.7–77.8)

Hazard ratio for death, 0.67 (95% CI, 0.51–0.89)
P=0.005

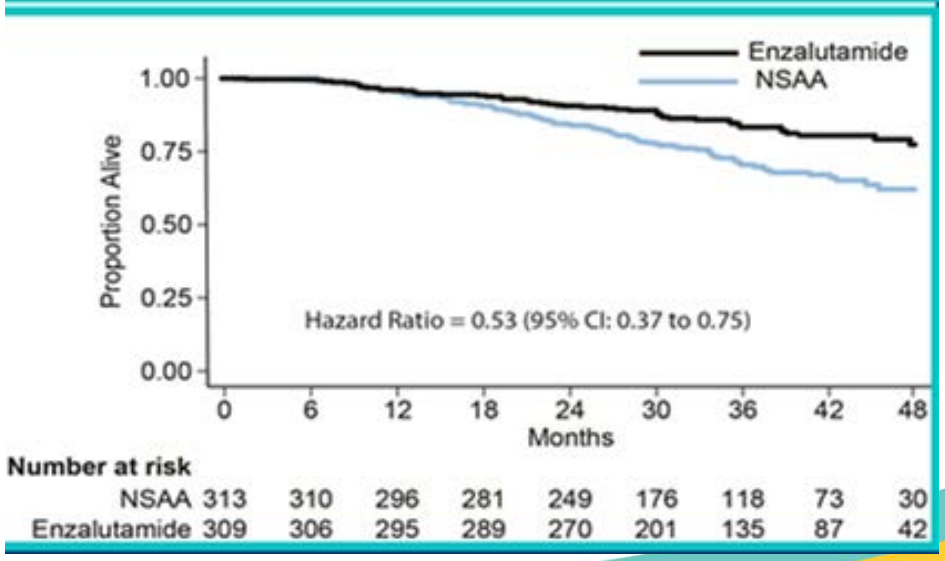
1. Davis ID et al. NEJM 2019; 381:121-31
2. Chi KN et al. NEJM 2019; 381:13-24

No apparent benefit for using both docetaxel and enza in ENZAMET

Testosterone Suppression + Docetaxel N=503 (71% High Volume)



Testosterone Suppression + No Docetaxel N=622 (37% High Volume)



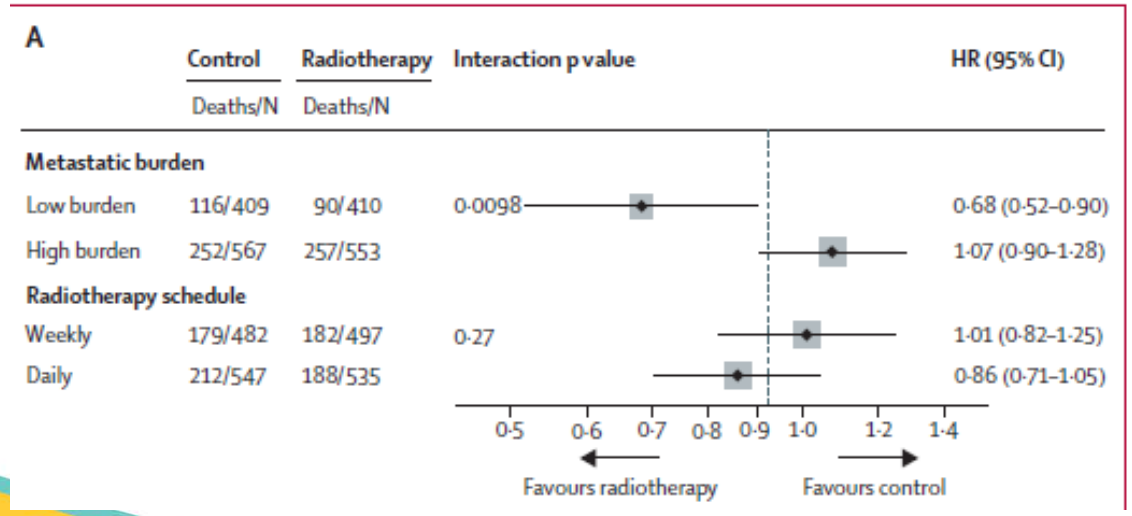
How will we choose between available agents?

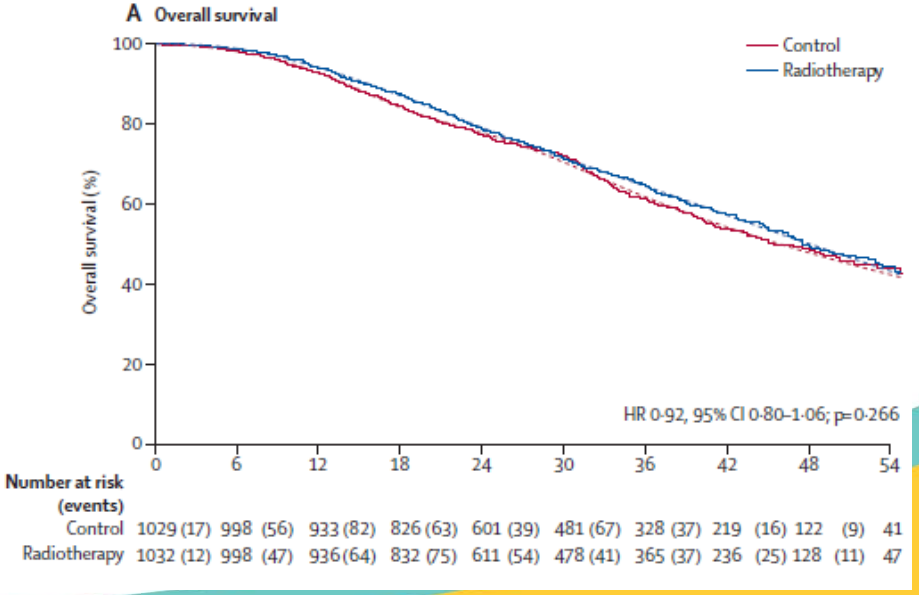
	DOCETAXEL	ABIRATERONE	ENZA/APA
Length of Treatment	**Short term** (approx 4.5 months)	Long term (approx 33 mo)	Long term (>36 months)
Financial	possible time off work	Prescription co-pays; **generic**	Prescription co-pays
Toxicities	Peripheral neuropathy, hair loss	Liver enzymes, electrolytes, HTN	CNS (seizures/ cognitive), falls
Corticosteroids	YES	YES	**NO**
Subsets	High-volume*	Any	Any

*≥4 bone mets with 1 outside axial skeleton OR visceral mets

- STAMPEDE: radiation to the prostate primary improves survival
  - only in low-volume subset

Characteristic		SOC (n=1029)	SOC+RT (n=1032)
Age (years)	Median (IQR) Range	68 (63–73) 37–86	68 (63–73) 45–87
PSA (ng/ml)	Median (IQR) Range	98 (30–316) 1–20590	97 (33–313) 1–11156
Metastatic burden	Low High Not classified	409 (42%) 567 (58%) 53	410 (43%) 553 (57%) 69
Site of metastases	Bone Liver Lung Distant lymph nodes Other	919 (89%) 23 (2%) 42 (4%) 294 (29%) 35 (3%)	917 (89%) 19 (2%) 48 (5%) 304 (29%) 33 (3%)
Docetaxel use	No Yes	845 (82%) 184 (18%)	849 (82%) 183 (18%)



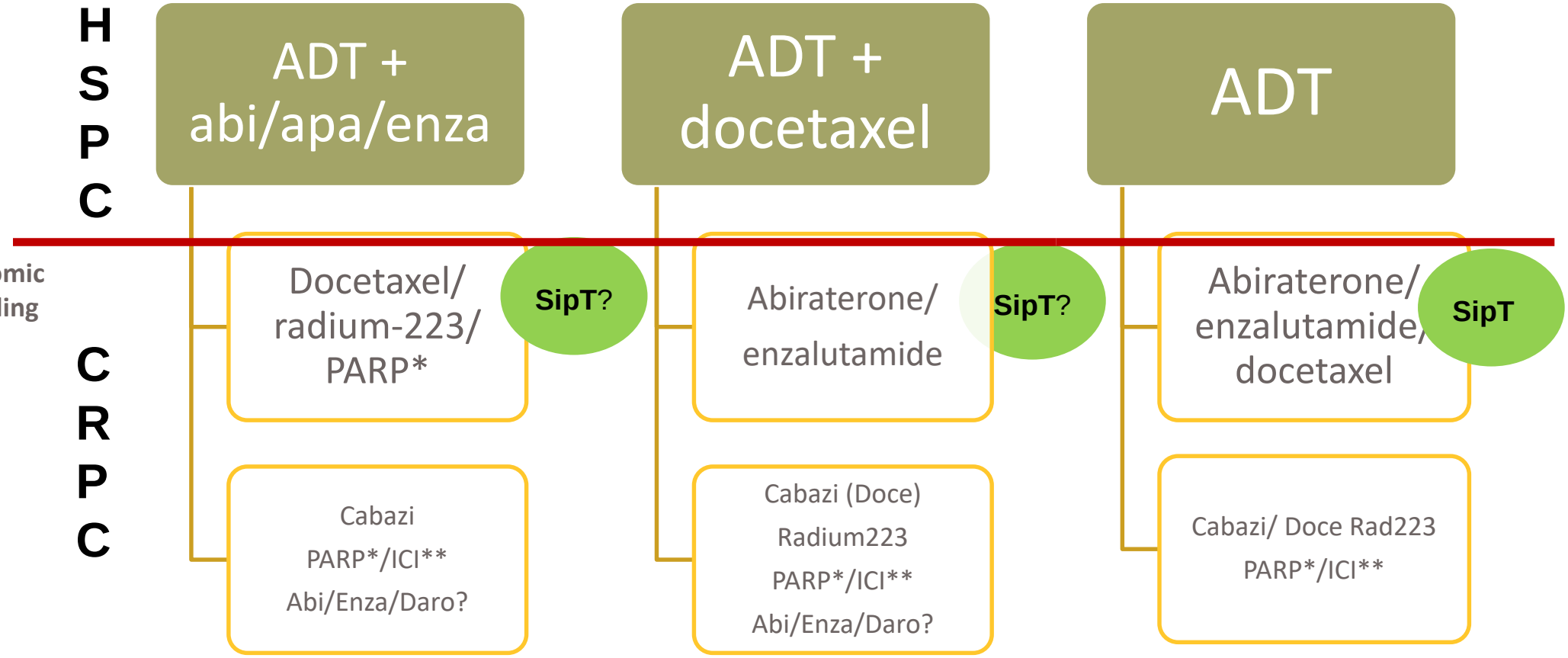


"Life Extending Therapies" for mCRPC

- **Abiraterone**
  - COU301: med OS 14.8 mo vs 10.9 mo for placebo (post TAX)[1]
  - COU 302: PFS 8.3 months → 16.5 months (pre TAX) [2]
- **Cabazitaxel**
  - Med OS 15.1 months vs 12.7 months mitoxantrone (post TAX)[3]
- **Docetaxel**
  - TAX327: med OS 18.9 months (16.5 mitoxantrone) [4]
- **Enzalutamide**
  - AFFIRM: med OS 18.4 months vs 13.6 for placebo [5] (post TAX)
  - PREVAIL: med OS 32.4 mo vs 30.2[6] pre TAX
    - (17 mo delay in chemo)
- **Radium223**
  - ALSYMPCA: med OS 14.9 months[7] (11.3 mo placebo)
- **Sipuleucel-T**
  - IMPACT: med OS 23.2 months[8] (18.9 placebo)

1. deBono J et al, NEJM 2011; 364:1995
2. Rahtkopf D et al, ASCO 2013; abstr 5
3. deBono JS et al, Lancet 2010; 376:1147
4. Tannock IF et al. NEJM 2004; 351:1502-12
5. Scher HI et al, NEJM 2012; 367:1187
6. Beer TM et al. Proc ASCO 2014
7. Parker C et al, ASCO 2013
8. Higano CS, et al. Cancer 2009; 115:3670

Current Paradigms for M1



- **Genomic Profiling**

AR = androgen receptor antagonist
PARP = *if DNA repair mutation identified
ICI = immune checkpoint inhib (**i.e pembrolizumab if MSI high)

There Is Not ONE Optimal Sequence…

- Clinical Factors may Impact Decision

Consider abiraterone first

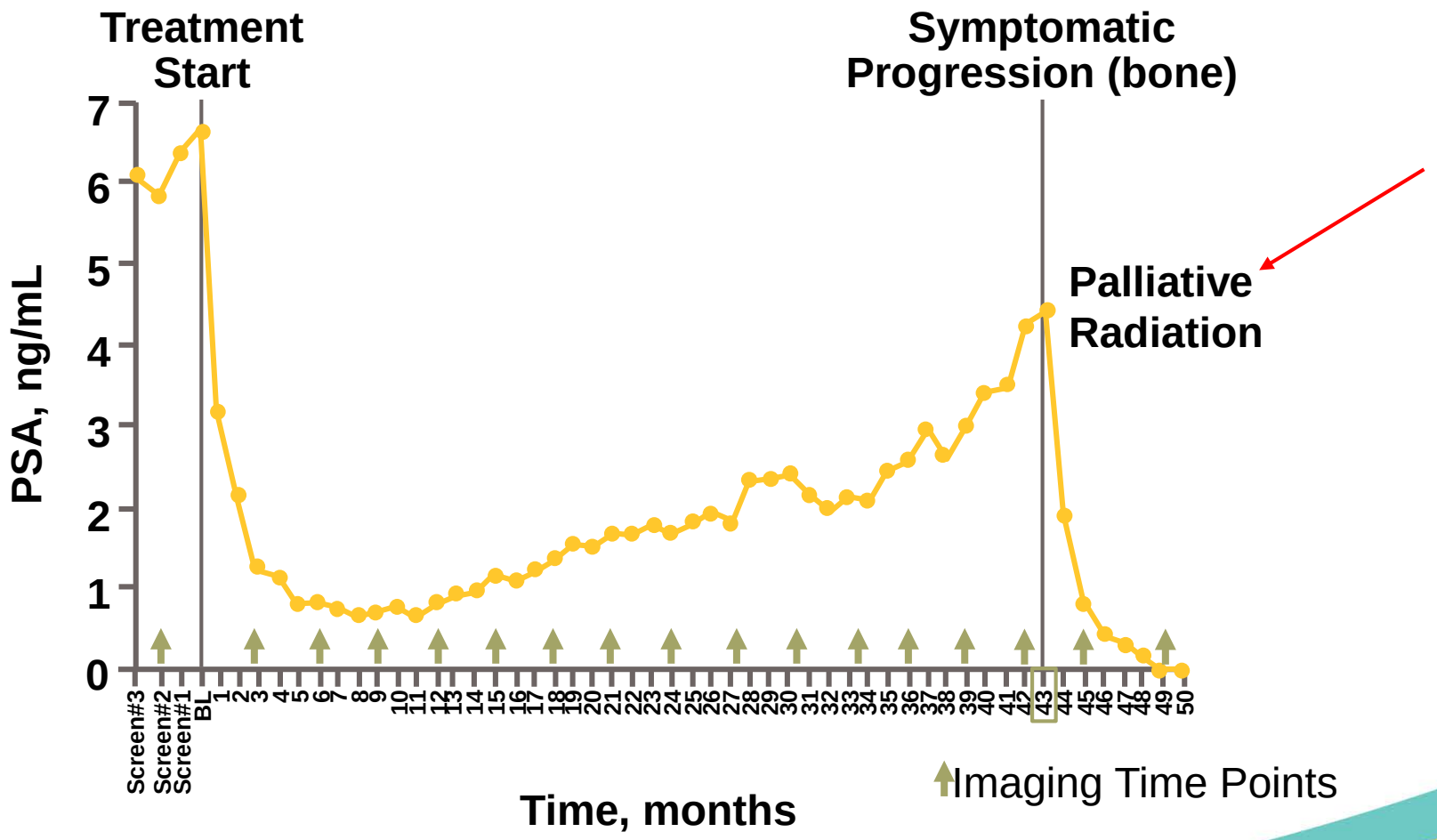
- Mild baseline pain; steroids may help
- Significant baseline fatigue
- Falls, gait, or neurological issues
- Older patients

Consider enzalutamide first

- Fragile diabetes
- Remote living
- Visceral metastases (pre TAX)
- Baseline edema

Keep in mind that the steroids with abiraterone are not supraphysiologic

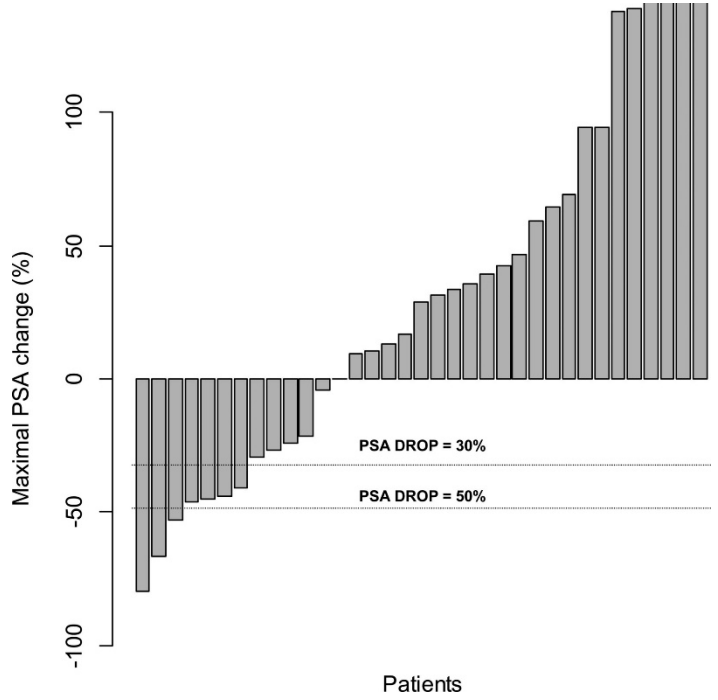
Optimizing use of existing therapies: Ensure Drug Is No Longer Working Before Stopping



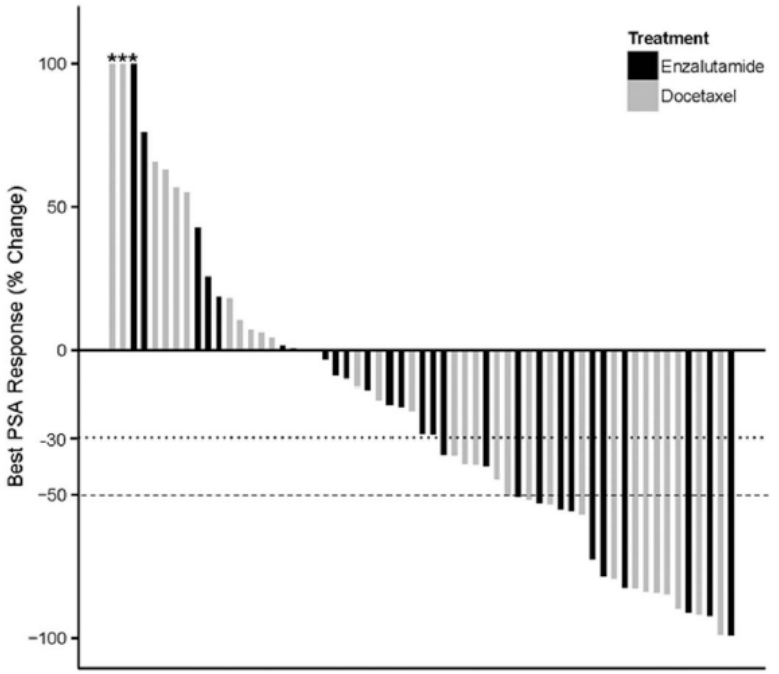
•Scher HI, et al. *J Clin Oncol*. 2011;29:3685-3704.

Sequencing: less effect of abi after enza, and enza after abi

Abiraterone response after prior treatment with enzalutamide[1]



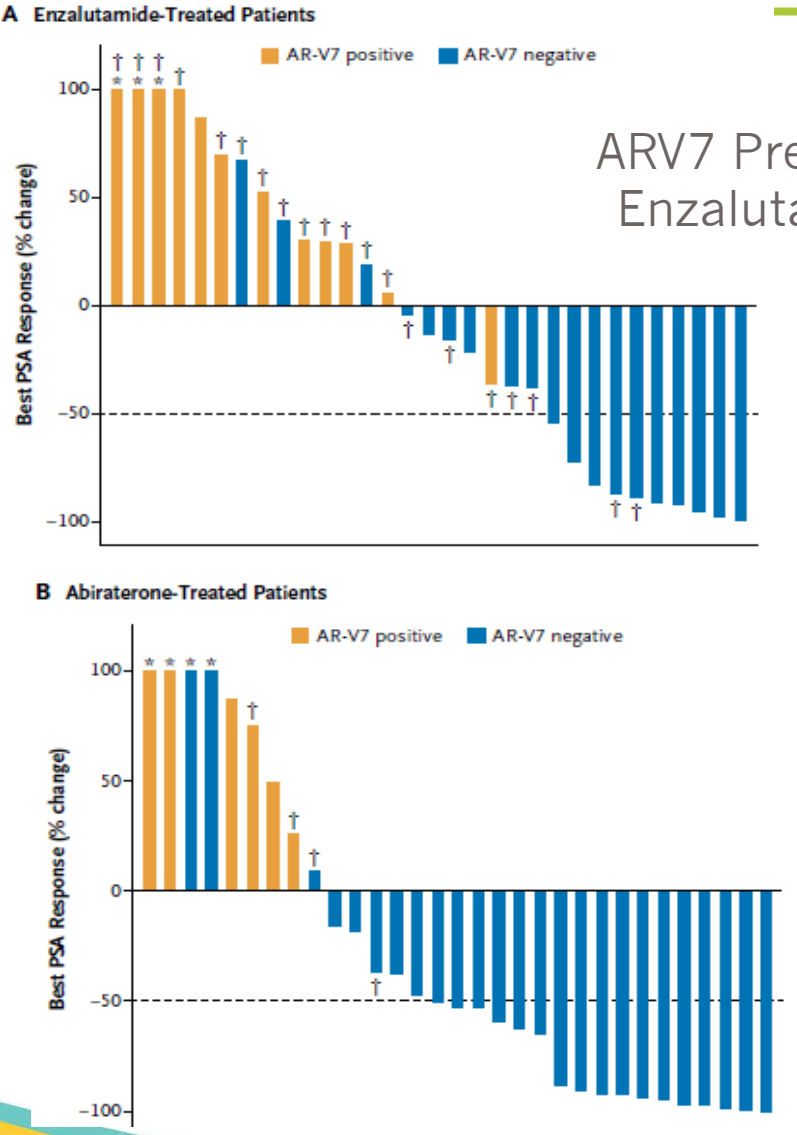
Enzalutamide versus docetaxel in men with CRPC progressing after abi[2]



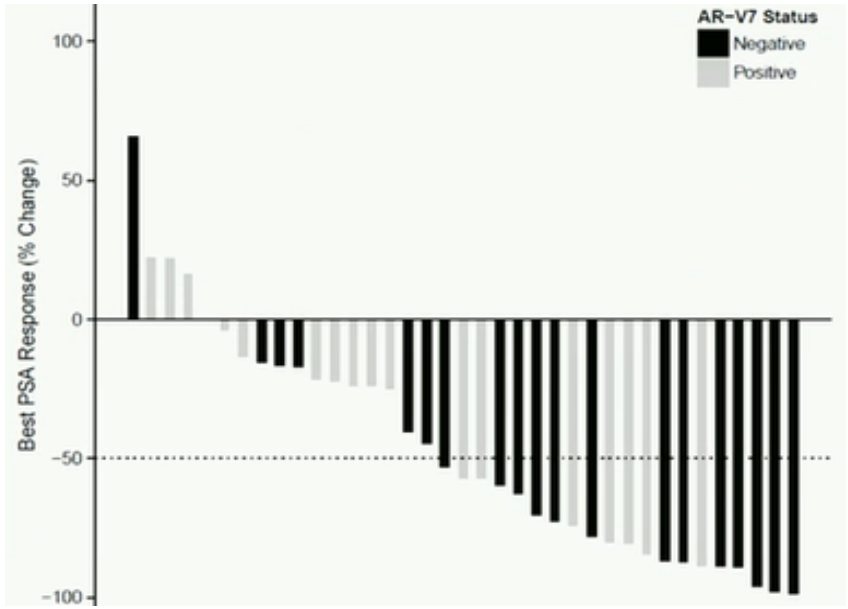
1. Loriot Y, et al. Ann Oncol 2013;24:1807-1812.
2. Suzman DL, et al. Prostate. 2014; 74:1278-1285.

Antonarakis et al, NEJM 2014.

ARV7 explains some cross-resistance



ARV7 Predicts Less Response to Enzalutamide and Abiraterone

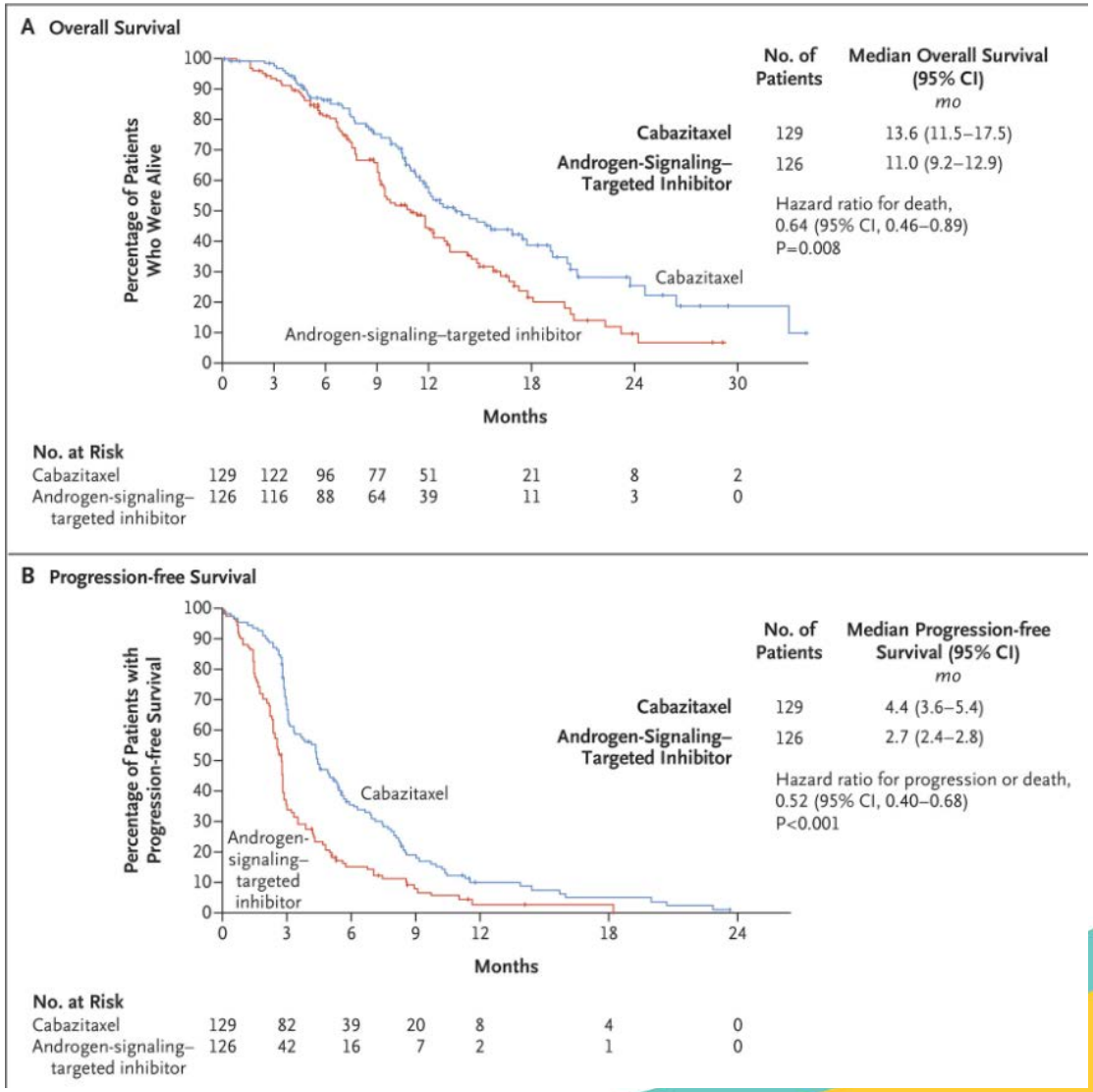


But response to Docetaxel is not impacted by ARv7

Antonarakis et al, 2015.

CARD: cabazitaxel more effective than abi/enza (ASTI) post abi/enza

- Men previously treated with both docetaxel and abi or enza
  - Median age 70 (46-85)
  - 70% had pain progression
- ORR 37% cabazi, 12% ASTI
- Grade ≥ 3 Adverse events in 56.3% with Cabazi, 52.4% with ASTI
  - 44.7% grade 3+ neutropenia- 3.2% febrile
  - Grade 3+ Cardiac disorders 4.8% with ASTI

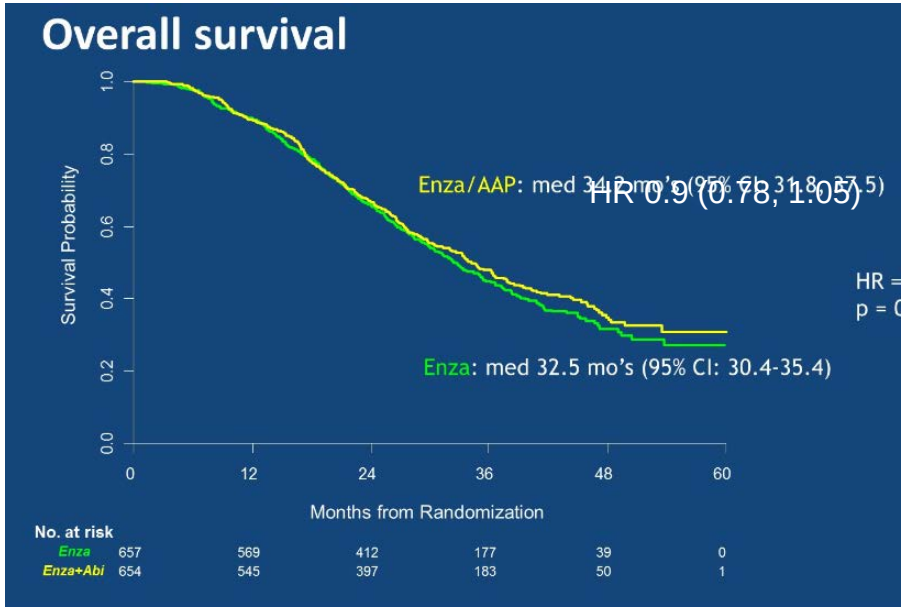


deWit R et al, NEJM 2019; 381:2506-18

Combinations have not been successful

- A031201 enza +/- abiraterone in mCRPC[1]
  - No diff in OS
  - Higher rate grade 3-5 Aes

- Neoadjuvant (ASCO 2020[2])
  - LHRH + Abi + Apa no better than LHRH + Abi (pathologic response)



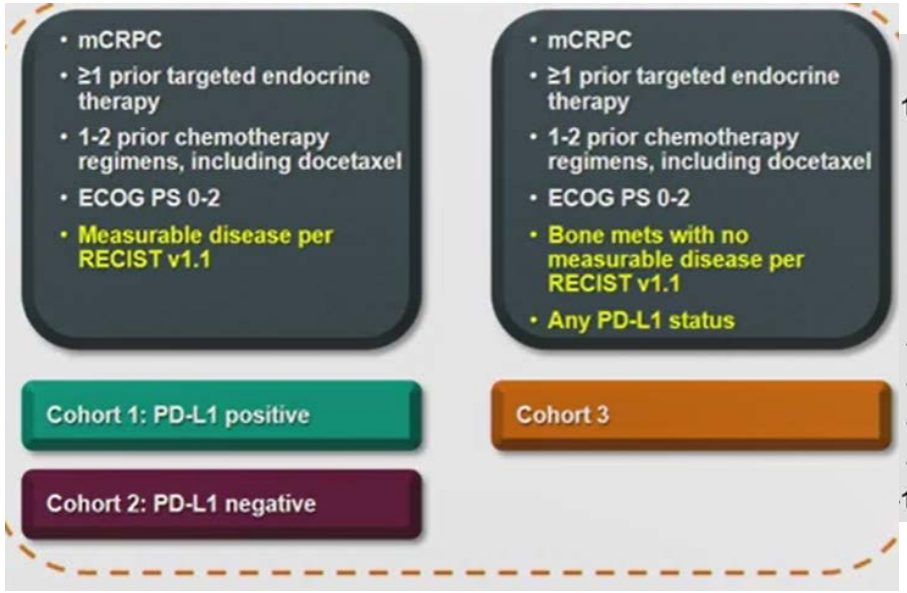
		APL (n=59)	APAL (n=55)
Pathologic Response	pCR	6 (10%)	7 (13%)
	MRD (≤5 mm)*	6 (10%)	5 (9%)
	pCR or MRD	12 (20%)	12 (22%)

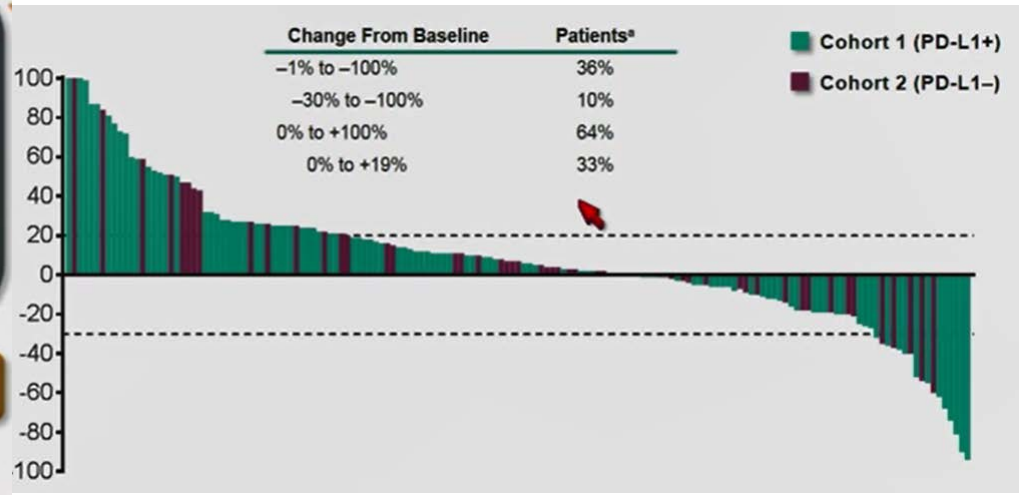
1. Morris MJ et al. ASCO 2019 abstr 5008 NCT01949337
2. McKay R et al. ASCO 2020 abstr 5503 NCT

- ERA223 identified increased fracture risk when abiraterone is used together with radium223[1]
- Shore et al (ASCO 2020) found this varied based on concurrent vs “layered” use[2]
  - bone support mitigated the risk
- EORTC 1333/ PEACE III[3]
  - Excess fractures for combination of enza + rad223
  - bone support eliminated the increased risk
  - Unclear yet whether advantage for enza w/rad223

1. Smith M et al, Lancet Oncol 2019; 20:408-19.
2. Shore N et al, ASCO 2020 abstr
3. Tombal BF et al. ASCO 2019 abstr 5007 NCT02194842

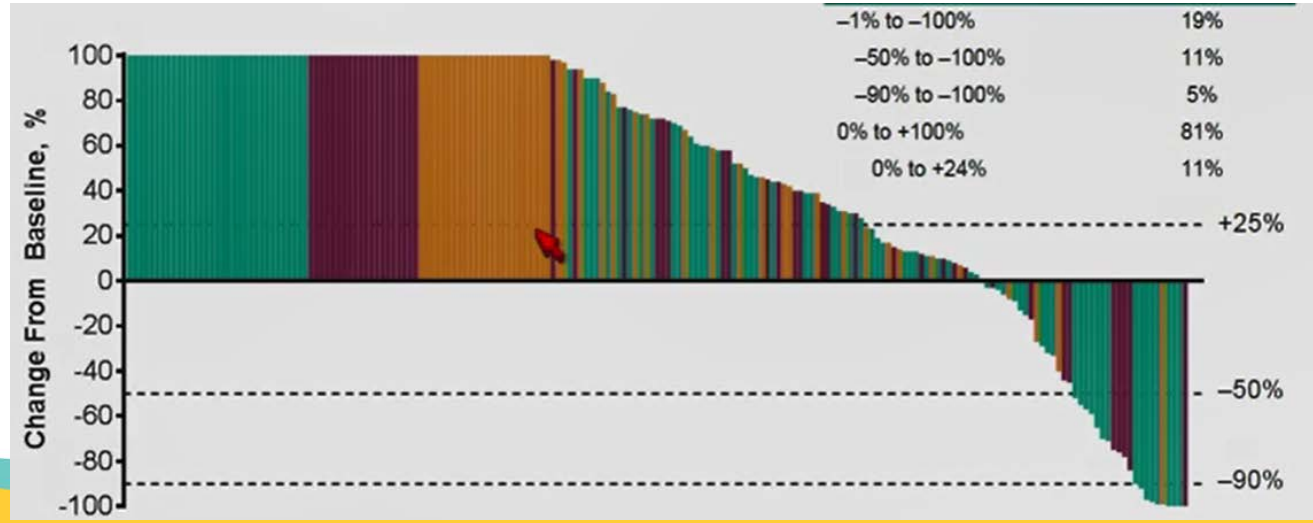
New agents: Pembrolizumab in mCRPC (KEYNOTE-199)



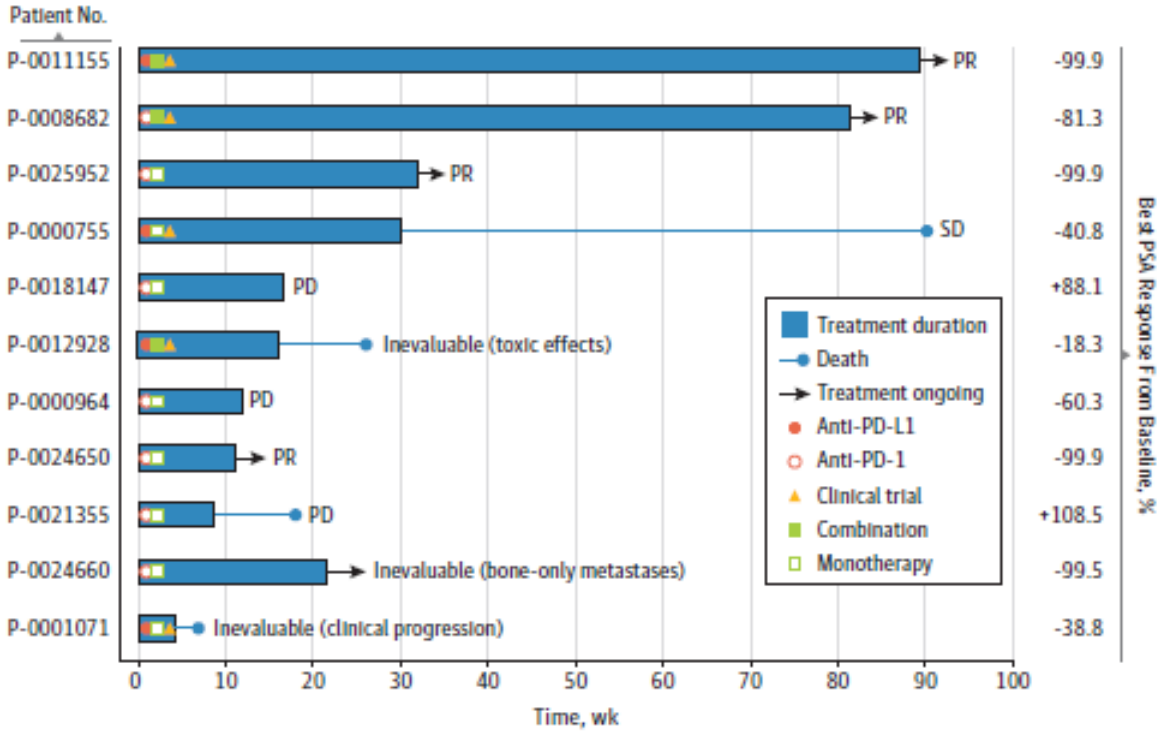


Top right: objective response
Bottom right: PSA changes

DeBono JS. ASCO 2018; oral present



- 32 of 1033 (3.1%) of prostate cancer patients tested with germline + somatic DNA sequencing had MSI-high or mismatch-repair status.
- 6 of 11 treated with PD-1/PD-L1 antibody therapy had >505 PSA decline and 4 of 11 had objective radiographic response.
- Duration of response up to 89 weeks

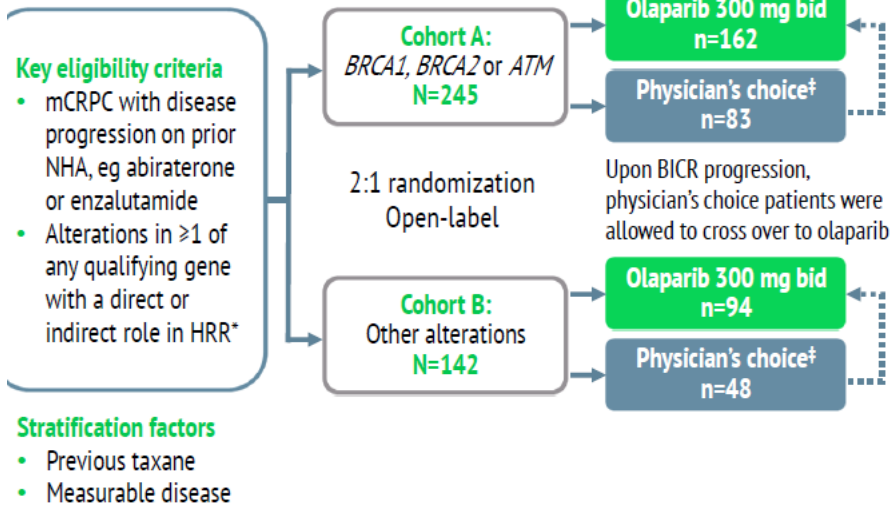


Abida W et al. JAMA oncol 2019; 5:471-8

- High response rate for olaparib in men with DNA repair deficiency
  - BRCA 1/2 , ATM, Fanconi, CHEK2
- TOPARP- B (ASCO 2019) olaparib 300 vs 400 BID
  - ORR 54% with **400 BID**. mPFS 5.4 months
  - Highest ORR BRCA 1/2 (80%), PALB2 (57%), ATM 37%, CDK12 25%, others 20%
- Rucaparib approved for BRCA1 and BRCA2
  - 54% PSA response and 47.5% objective response in BRCA patients[3]
  - Other mutations had limited benefit; 10.5% objective response in ATM, 0 with CDK12 and 11% with CHEK2[4]
- Awaiting data from additional agents (niraparib, talazoparib)

1. Mateo J et al. NEJM 2015; 373: 1697
2. Mateo J et al. ASCO 2019; abstr 5005
3. Abida W et al. Ann Oncol 2019; 30 (supp) abstr 846PD
4. Abida W et al. Clin Cancer Res 2020; 26:2487-96

PROFOUND: phase III data with PARP inhibitors



Primary endpoint

Radiographic progression-free survival (rPFS) in Cohort A (RECIST 1.1 & PCWG3 by BICR)

Key secondary endpoints

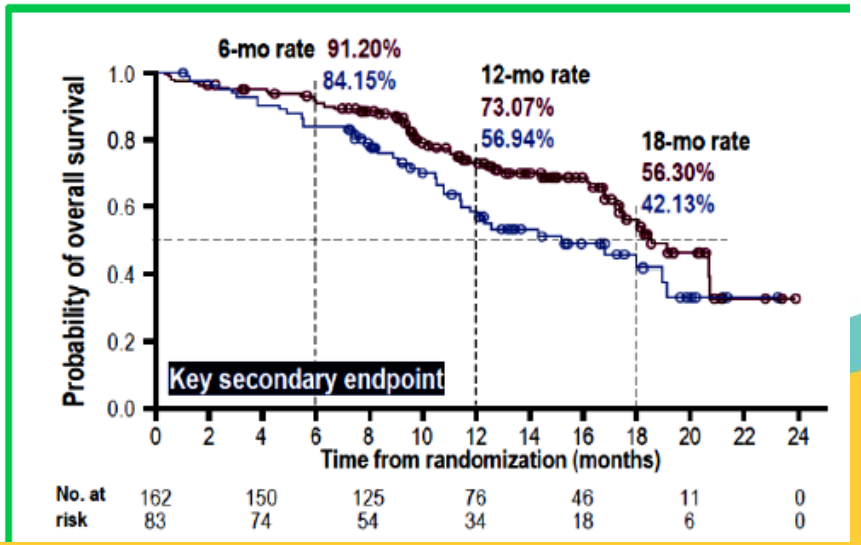
- rPFS in Cohorts A+B
- Confirmed radiographic objective response rate (ORR) in Cohort A
- Time to pain progression (TTPP) in C
- O

rPFS 7.39 months vs 3.55 mo in cohort A

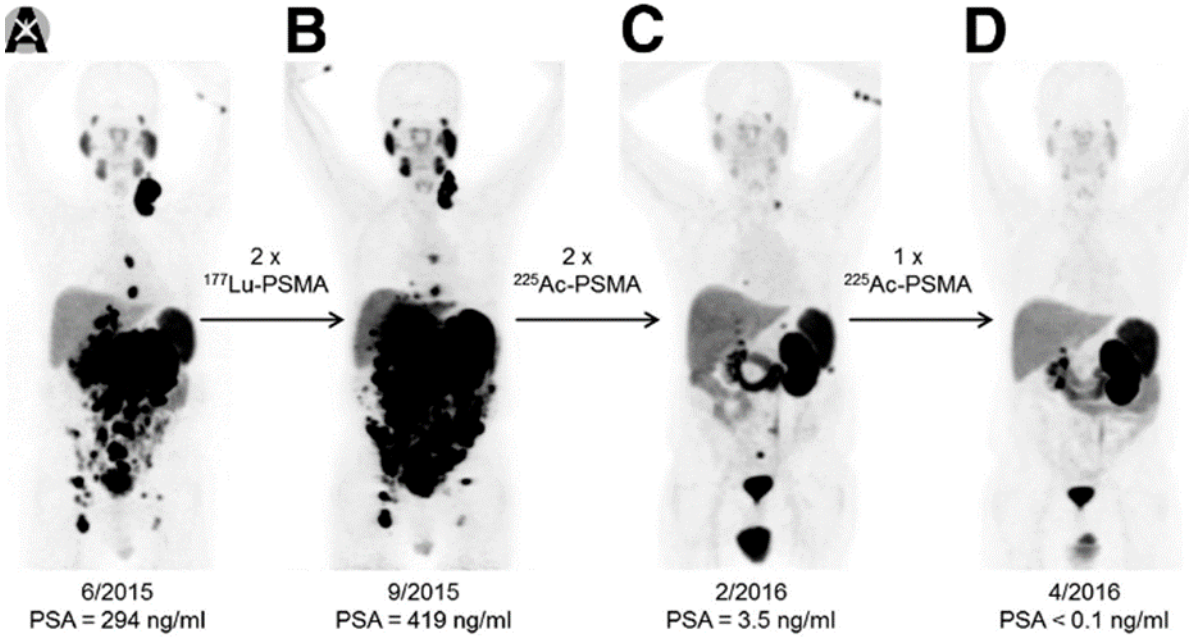
COHORT A	Olaparib (N=162)	Physician's choice (N=83)
Median OS (months)	18.50	15.11
Hazard ratio (95% CI)	0.64 (0.43-0.97) P=0.0173‡	

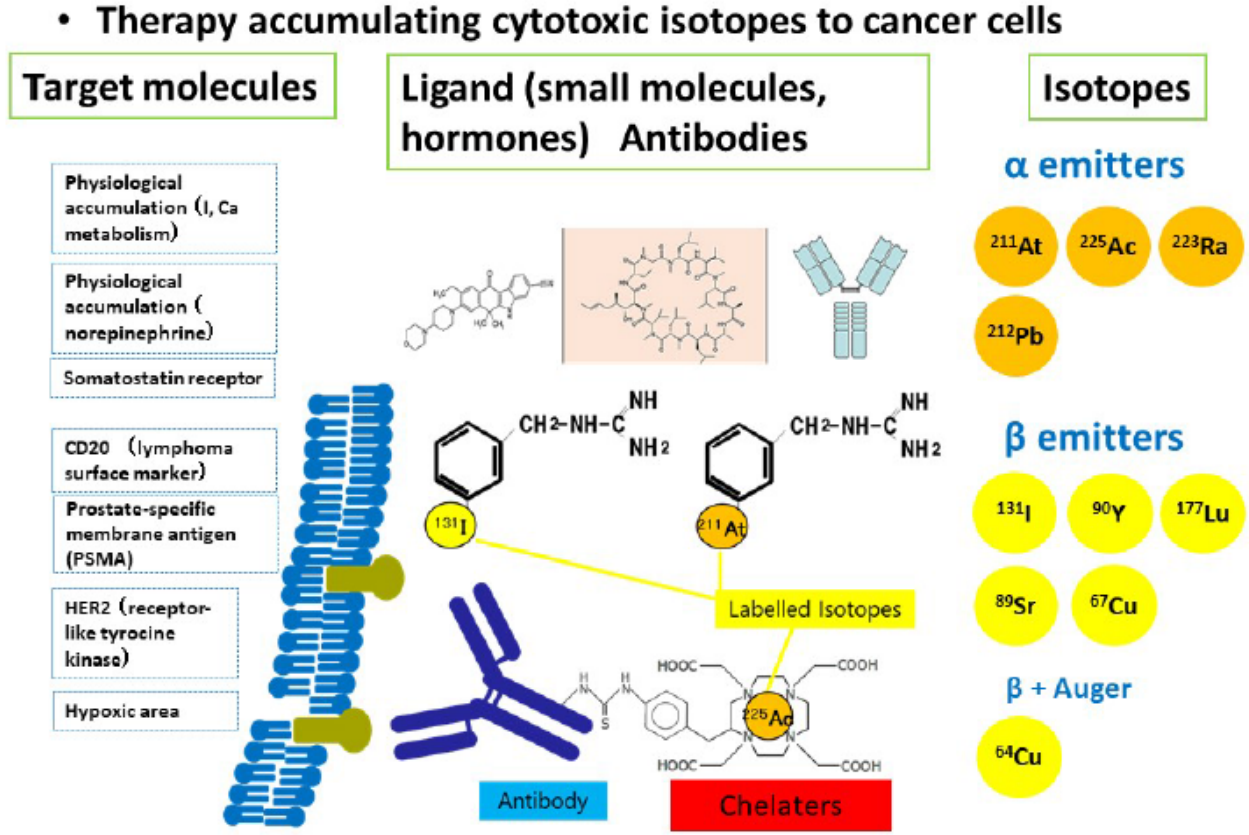
Hussain M, et al. Presented at ESMO 2019 Abstract #LBA12.

>80% crossover!



Radiopharmaceutical future: theranostics

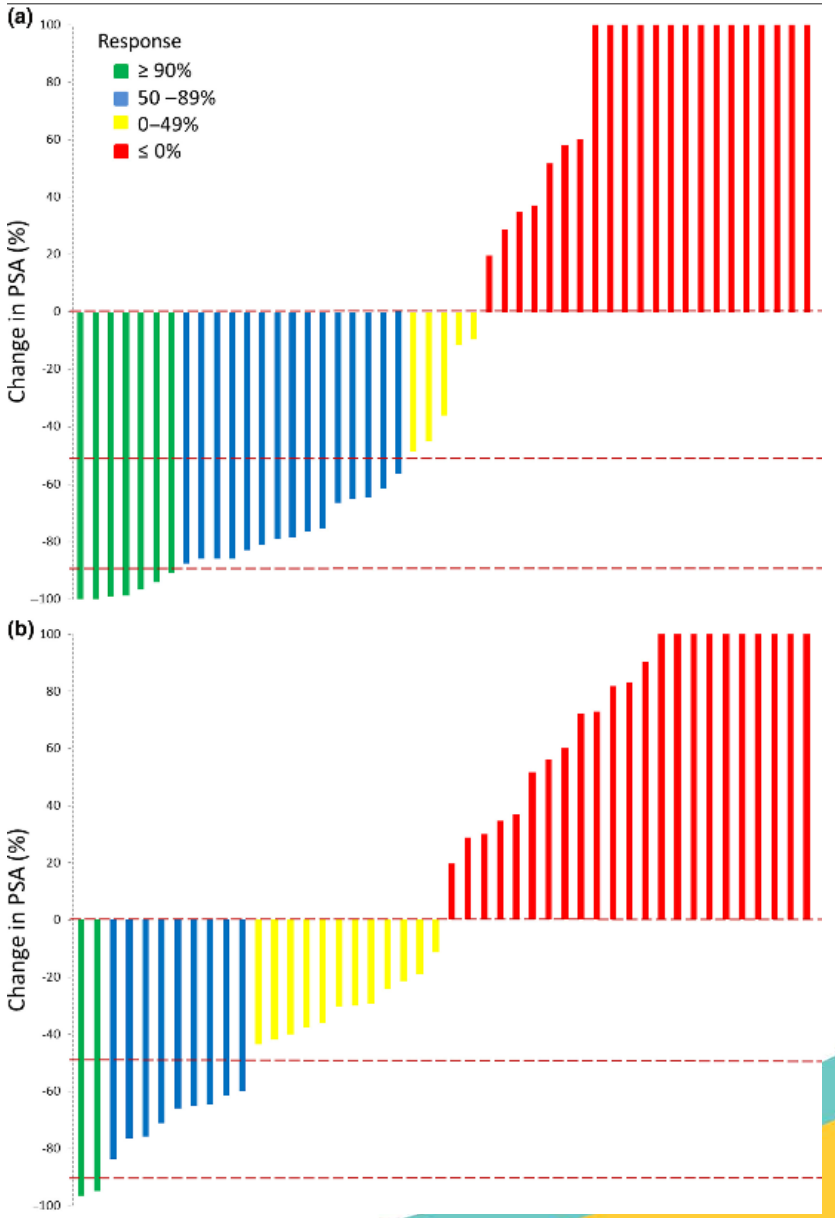




Limitations:

- Expression of the ligand (heterogeneity, downregulation)

- Australian experience[1]
  - 50 patients
  - Median 3 doses
  - 22 (45%) had PSA decline >50%
  - Main AEs: fatigue, nausea
- German experience[2]
  - 52 patients
  - 81% “any” PSA decline (44% >50%)
  - Med OS 60 weeks (i.e. 13.8 mo)
- VISION trial = randomized phase III
  - ongoing



1. McBean R et al.J Med Imag Rad Onc 2019; 63:538
2. Ahmadzadehfar H et al. Eur J Nucl Med Mol Imag 2017; 44:1448

- Other abiraterone dosing schedules
  - 500 mg w/ or w/out food - microparticle (YONSA)
  - 250 mg w/low-fat food (ZYTIGA)
  - Prednisone 5 mg daily mHSPC, 5 mg BID mCRPC
- Cabazitaxel dosing
  - 25 mg/m2 original approval, need GCSF
  - 20 mg/m2 similar efficacy in PROSELICA, ?need GCSF
- Side effects/ monitoring
  - Abiraterone: LFTs, electrolytes, blood pressure
  - Apalutamide: thyroid, rash
  - Radium223: CBC prior to each dose
- Oligomets SBRT: not prime-time yet, not likely on boards

- Localized
- Staging (imaging) only for high risk
- Increased emphasis on genetic and molecular testing
- Biochemical recurrence
  - add ADT to salvage XRT
  - Individualize based on PSA and margins
- metastatic prostate cancer (mHSPC)
  - Abiraterone, Docetaxel, Enza/Apalutamide… most men should get more than just LHRH
  - Consider XRT to prostate (STAMPEDE)
  - No benefit yet for combining or “switch maintenance” with doce followed by ARTI
- non-metastatic CRPC (m0CRPC or nmCRPC)
  - Apalutamide, Darolutamide, Enzalutamide
  - PSA DT <10 months
- Adding enza + abi doesn’t give benefit
- Sequencing abi → enza or enza → abi with limited benefit
- Individualized therapy
  - Pembro only in MSI high (?addl mutations)
  - PARP inhibitors with genomic selection
  - Lu177-PSMA ? with PET selection

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Bleeding Disorders

Rebecca Kruse-Jarres, MD/MPH

Professor of Medicine and Pediatrics, University of Washington

Medical Director, Washington Center for Bleeding Disorders

Disclosures

Consulting Fees (e.g., advisory boards)

Chugai, Biomarin, CSL Behring, CRISPR Therapeutics, Genentech

Fees for Non-CME/CE Services Received Directly from a Commercial Interest or their Agents (e.g., speakers' bureaus)

Roche

Contracted Research

CSL Behring, Genentech, Spark

Objectives

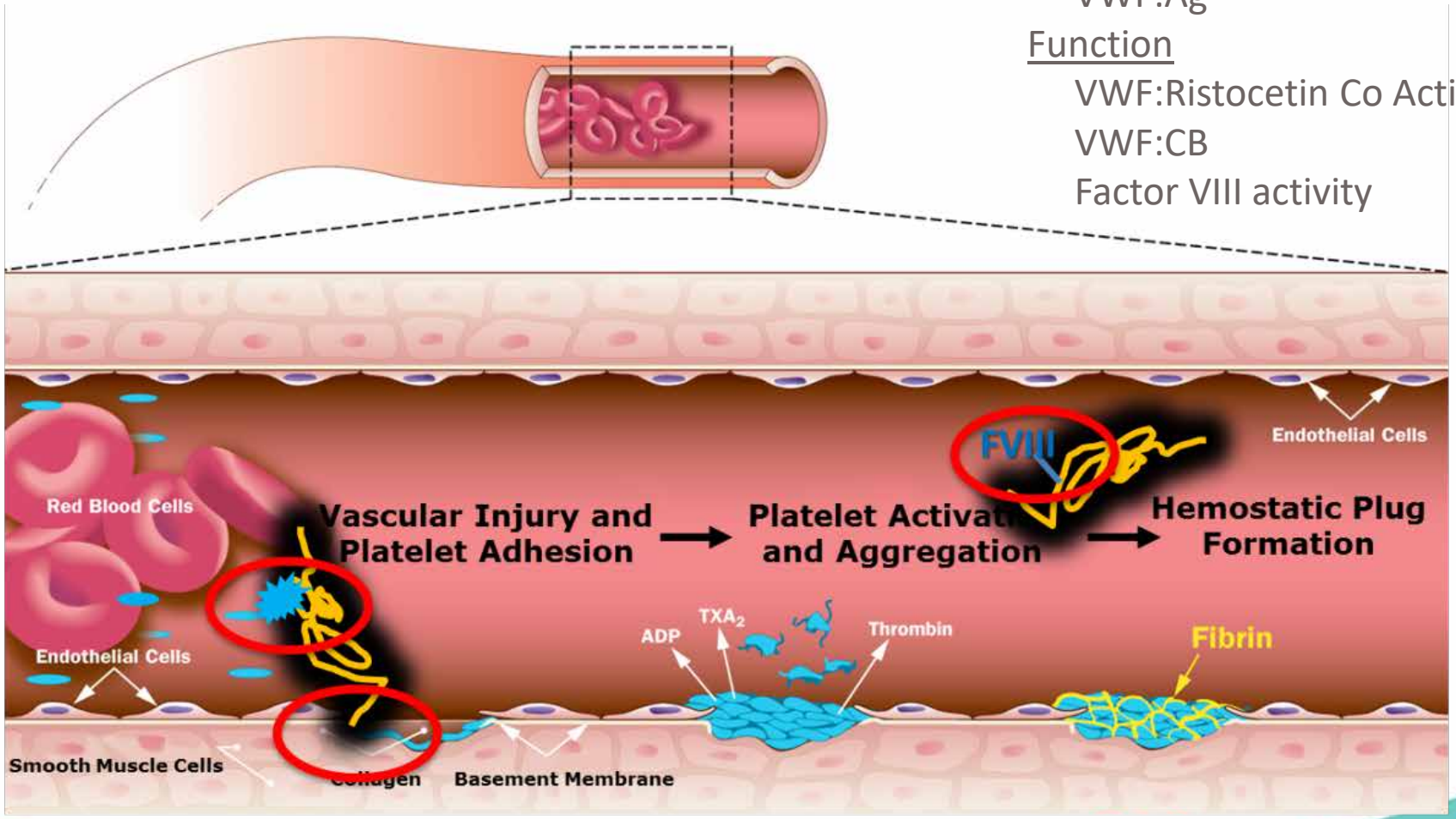
- To discuss **von Willebrand disease**
  - Treatment option
  - Acquired von Willebrand syndrome
- To describe new treatment options for **congenital hemophilia**
- To recognize **acquired hemophilia** and describe potential 1st line treatment options
- To describe some **rarer factor deficiencies** and their treatment approaches

Von Willebrand Disease

Von Willebrand Factor

Quantity
- VWF:Ag

Function
- VWF:Ristocetin Co Activity (RCo)/ VWF:Act
- VWF:CB
- Factor VIII activity



Collagen binding

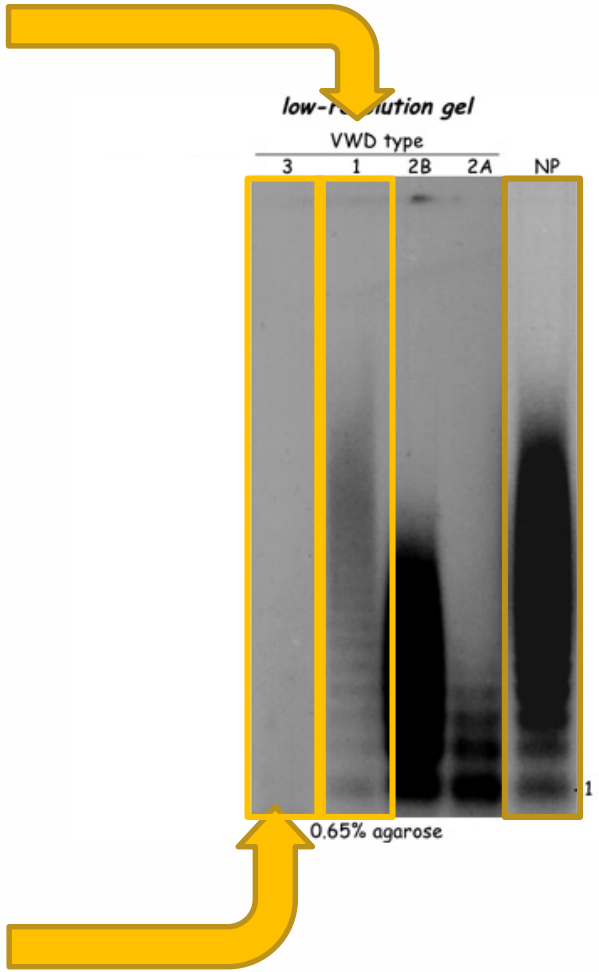
Platelet binding

Factor VIII binding

Image adjusted from Victor S. Blanchette

Quantitative defects

- Type 1
- Type 2
  - 2A
  - 2B
  - 2M
  - 2N
- Type 3



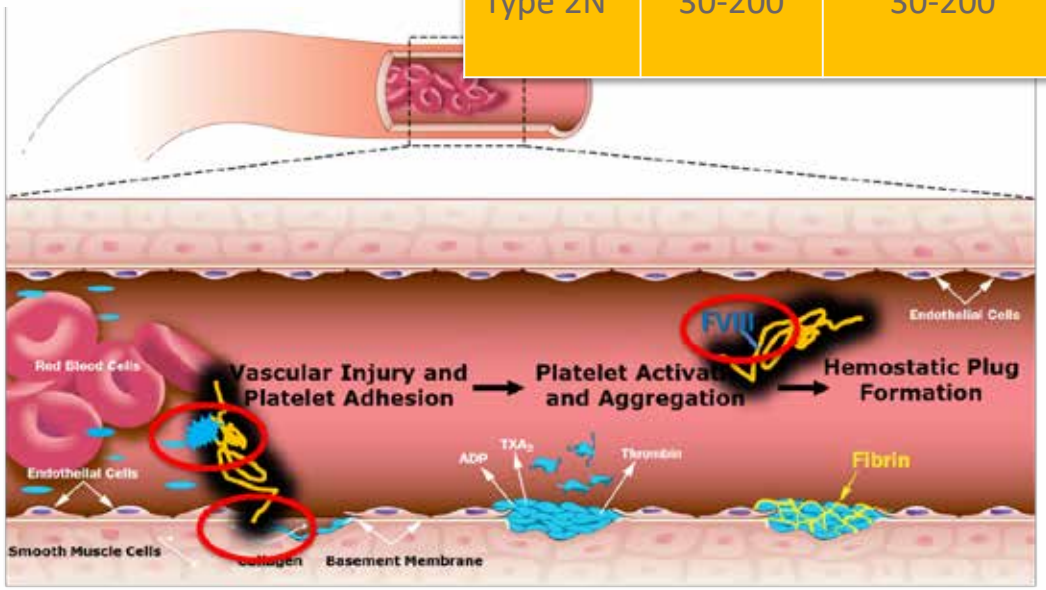
- Decreased VWF production
- Most common (75%)
- Mild bleeding symptoms

- Very decreased VWF production
- Very rare (<5%)
- Severe bleeding symptoms

Qualitative defects

- Type 2
  - 2A
  - 2B
  - 2M
  - 2N

VWD type	VWF:RCo (IU/dL)	VWF:Ag (IU/dL)	FVIII	Ratio of VWF:RCo/ VWF:Ag	
Type 2A	<30*	<30-200*?	↓or Normal	<0.5-0.7	Abnormal multmers Abnormal Ag/RCo ratio
Type 2B	<30*	<30-200*?	↓ or Normal	Usually <0.5-0.7	Abnormal multmers Abnormal Ag/RCo ratio Increased plt. binding
Type 2M	<30*	<30-200*?	↓ or Normal	<0.5-0.7	Normal multimers Abnormal Ag/RCo ratio
Type 2N	30-200	30-200	↓↓	>0.5-0.7	Normal multimers Normal Ag/RCo ratio Decreased FVIII binding



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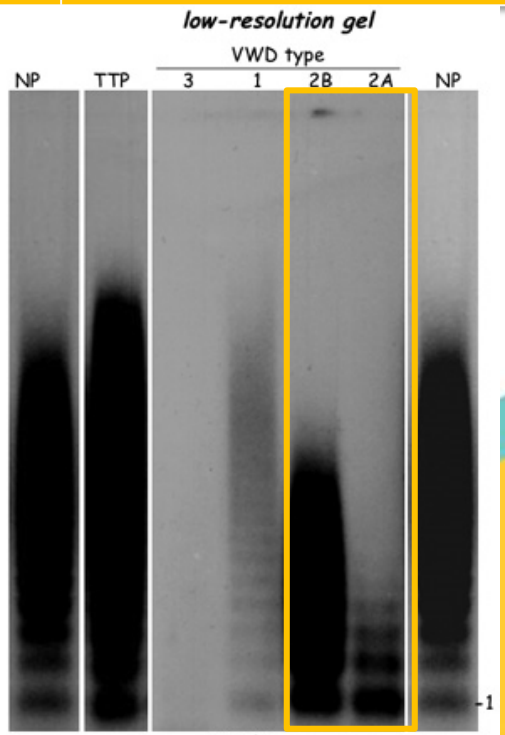
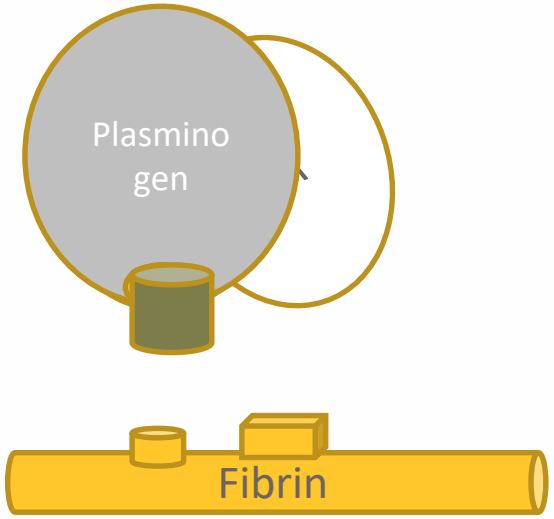


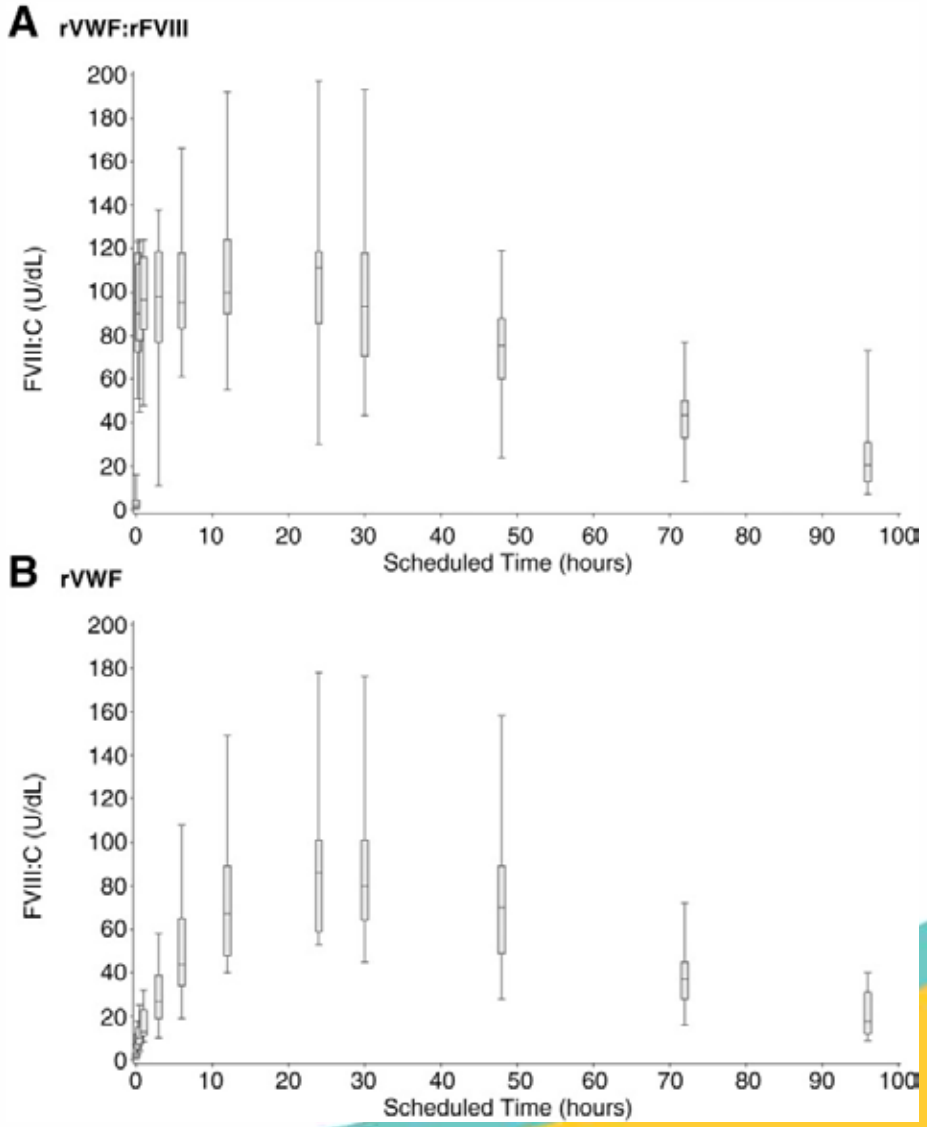
Treatment of VWD

- Desmopressin (DDAVP, Stimate)
  - Releases endogenous VWF and factor VIII
- Antifibrinolytic
  - ε-aminocaproic acid, tranexamic acid
  - Lysine analog
  - Binds to plasminogen and prevents conversion to plasmin and thus fibrin degradation



Treatment of VWD

- Factor concentrate
  - Plasma derived - all contain factor VIII as well
  - Recombinant von Willebrand factor (rVWF)
    - Phase III trial in severe VWD
    - 50 U/kg with or without FVIII
    - Terminal half life not affected by co-infusion of FVIII
    - Single infusion was effective in 81.8% of bleeds
    - 100% of bleeds (n=192) were controlled



Gill et al. Blood. 2015 Oct 22;126(17):2038-46

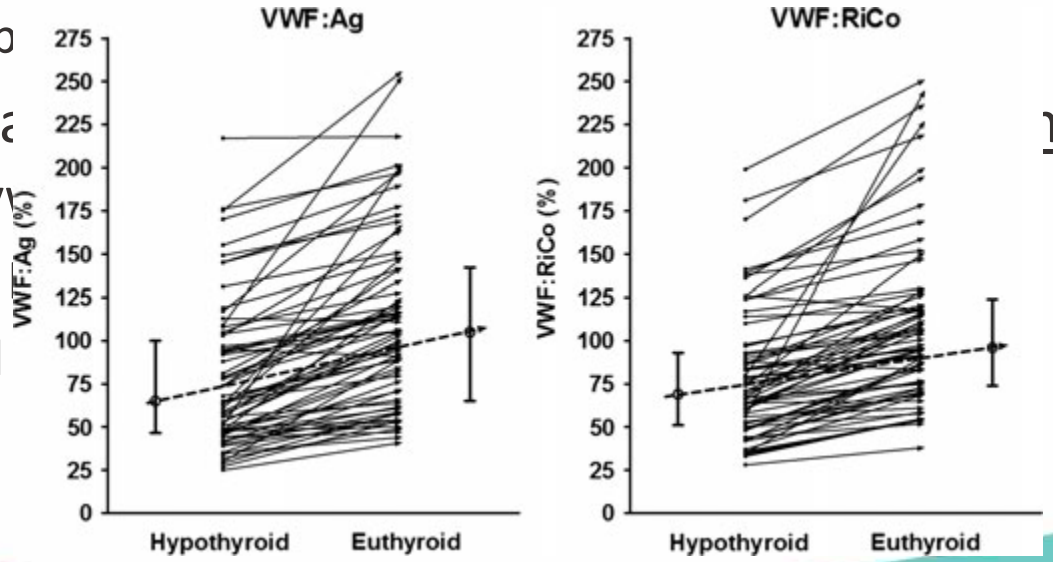
Acquired von Willebrand syndrome (AVWS)

- Rare
  - underreported
- Paucity of data
  - largest data collection on the disorder today, the International Society of Thrombosis and Haemostasis International Registry on AVWS

AVWS due to decreased production

Decreased production of thyroid hormone → Decreased synthesis of von Willebrand factor

- Looks like a type 1 VWD (quantitative)
  - Low VWF:Ag and VWF:Activity
  - Normal multimers
  - Low VWF p
- Study of 90 a n
  - **33%** had V
  - Most with
  - Correlated



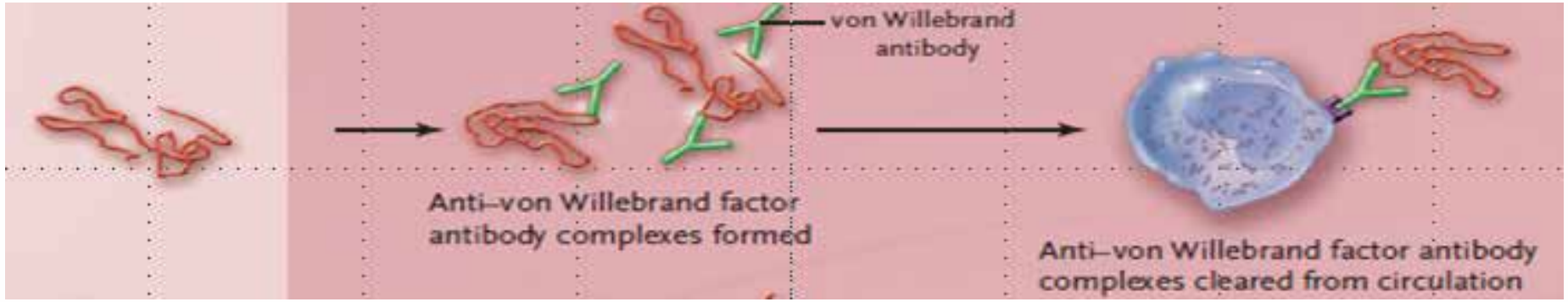
Stuijver et al. Haemophilia 2014

AVWS due to adsorption

- Lymphoproliferative disorders (MM, WM, NHL, HCL), Myeloproliferative disorders (ET, PV), other thrombocytosis, malignancy
- Treat the underlying disease

Cuker et al, N Eng J Med 2009

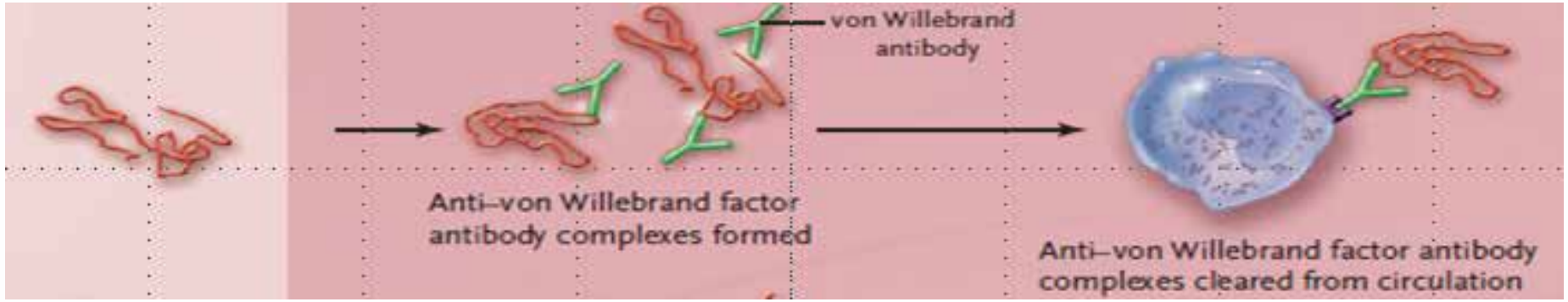
AVWS due to antibodies



- Associated conditions:
  - monoclonal gammopathy of undetermined significance (MGUS)
  - lymphoproliferatve disorders
  - systemic lupus erythematous
- Detection of actual antibodies remains challenging and not well standardized

Cuker et al, N Eng J Med 2009

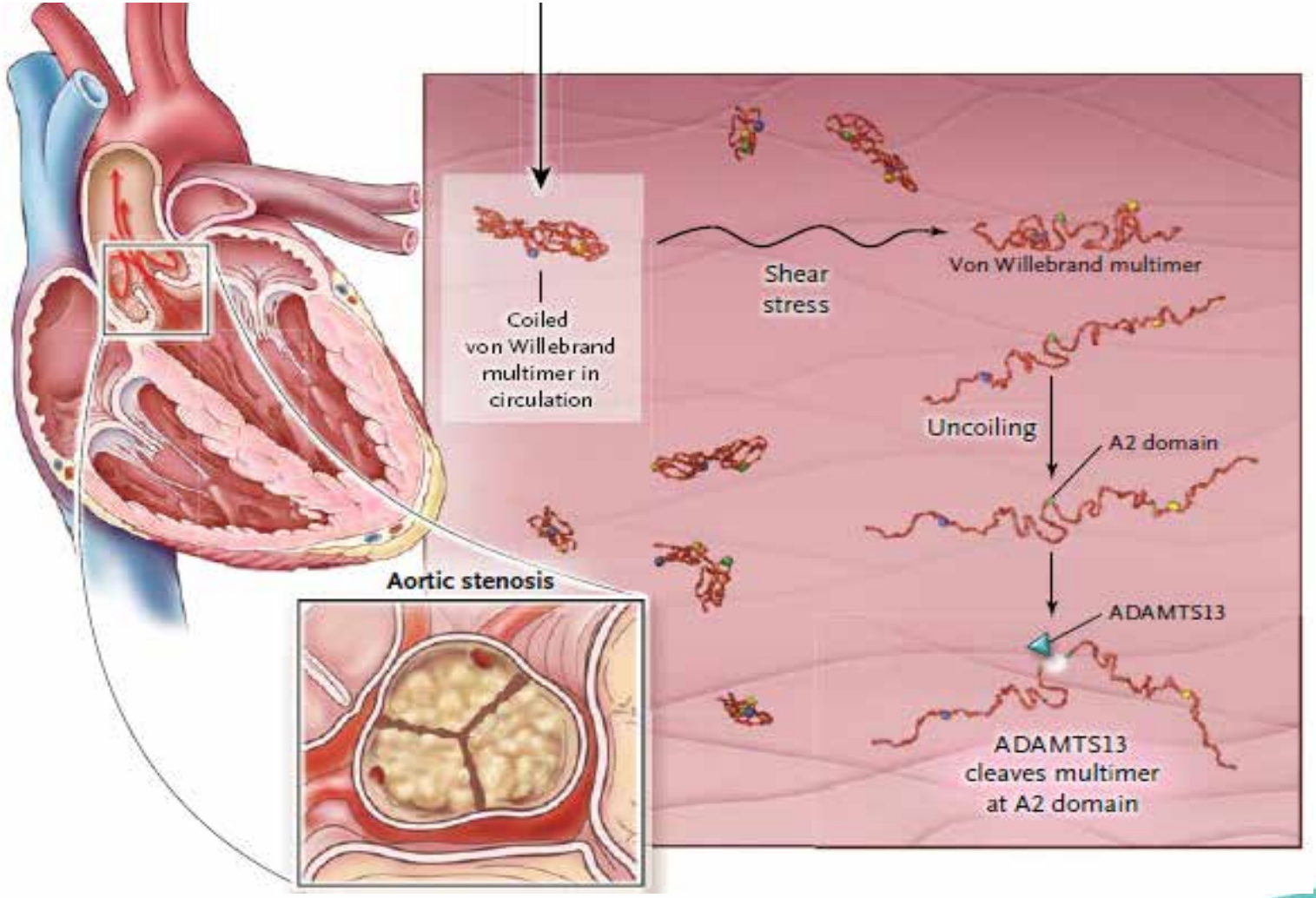
AVWS due to antibodies



- Immunosuppression
  - Intravenous immunoglobulin[1]
    - Corrects laboratory abnormalities within 24-48 hours
    - Alleviates bleeding symptoms in IgG-MGUS but not IgM-MGUS.
    - Response can be seen for about 21 days and periodic re-dosing can achieve long-term control
  - Prednisone and other immunosuppressant and rituximab
    - Varying results

Cuker et al, N Eng J Med 2009

AVWS associated with cardiovascular abnormalities



Loscalzo. N Eng J Med 2012

AVWS associated with cardiovascular abnormalities

- Etiology
  - acquired valve and other structural abnormalities
  - hypertrophic cardiomyopathy
  - intra-cardiac devices
- About 20% of adults with congenital heart disease have AVWS

Laboratory

  - Often normal VWF:Ag, VWF:RCo, or VWF:CB levels
  - But reduced VWF:RCo/Ag and VWF:CB/Ag ratio

Waldow et al. 2014

AVWS associated with cardiovascular abnormalities

- Mitral valve regurgitation:

Variable	Mild (N = 13)	Moderate (N = 14)	Severe (N = 26)	P-value
HMWM loss	1 (8)	9 (64)	22 (85)	< 0.001*
PFA-CADP (s)	84 (73–96)	156 (104–181)	190 (157–279)	< 0.001
VWF multimers > 15	0.21 (0.18–0.23)	0.15 (0.14–0.18)	0.12 (0.10–0.14)	< 0.001
VWF multimers > 10	0.50 (0.46–0.54)	0.43 (0.37–0.45)	0.37 (0.32–0.44)	< 0.001
VWF:Act (%)	109 (93–124)	101 (61–133)	83 (77–140)	0.56
VWF:Ag (IU dL^{-1})	123 (97–146)	116 (76–167)	107 (93–195)	0.67
VWF:Act/VWF:Ag	0.92 (0.83–0.97)	0.85 (0.76–0.89)	0.79 (0.75–0.82)	< 0.001
BNP (pg mL^{-1})	48 (27–60)	112 (72–193)	156 (77–329)	< 0.001
BNP/ULN	0.42 (0.31–0.55)	1.10 (0.79–1.61)	1.92 (1.04–3.78)	< 0.001

Blackshear et al. J Thromb Haemost 2014; 12: 1966–74.

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VWF:Act/VWF:Ag	0.92 (0.83–0.97)	0.85 (0.76–0.89)	0.79 (0.75–0.82)	< 0.001
BNP (pg mL^{-1})	48 (27–60)	112 (72–193)	156 (77–329)	< 0.001
BNP/ULN	0.42 (0.31–0.55)	1.10 (0.79–1.61)	1.92 (1.04–3.78)	< 0.001

Blackshear et al. J Thromb Haemost 2014; 12: 1966–74.

AVWS associated with cardiovascular abnormalities

- Mitral valve regurgitation:

Variable	Mild (N = 13)	Moderate (N = 14)	Severe (N = 26)	P-value
HMWM loss	1 (8)	9 (64)	22 (85)	< 0.001*
PFA-CADP (s)	84 (73–96)	156 (104–181)	190 (157–279)	< 0.001
VWF multimers > 15	0.21 (0.18–0.23)	0.15 (0.14–0.18)	0.12 (0.10–0.14)	< 0.001
VWF multimers > 10	0.50 (0.46–0.54)	0.43 (0.37–0.45)	0.37 (0.32–0.44)	< 0.001
VWF:Act (%)	109 (93–124)	101 (61–133)	83 (77–140)	0.56
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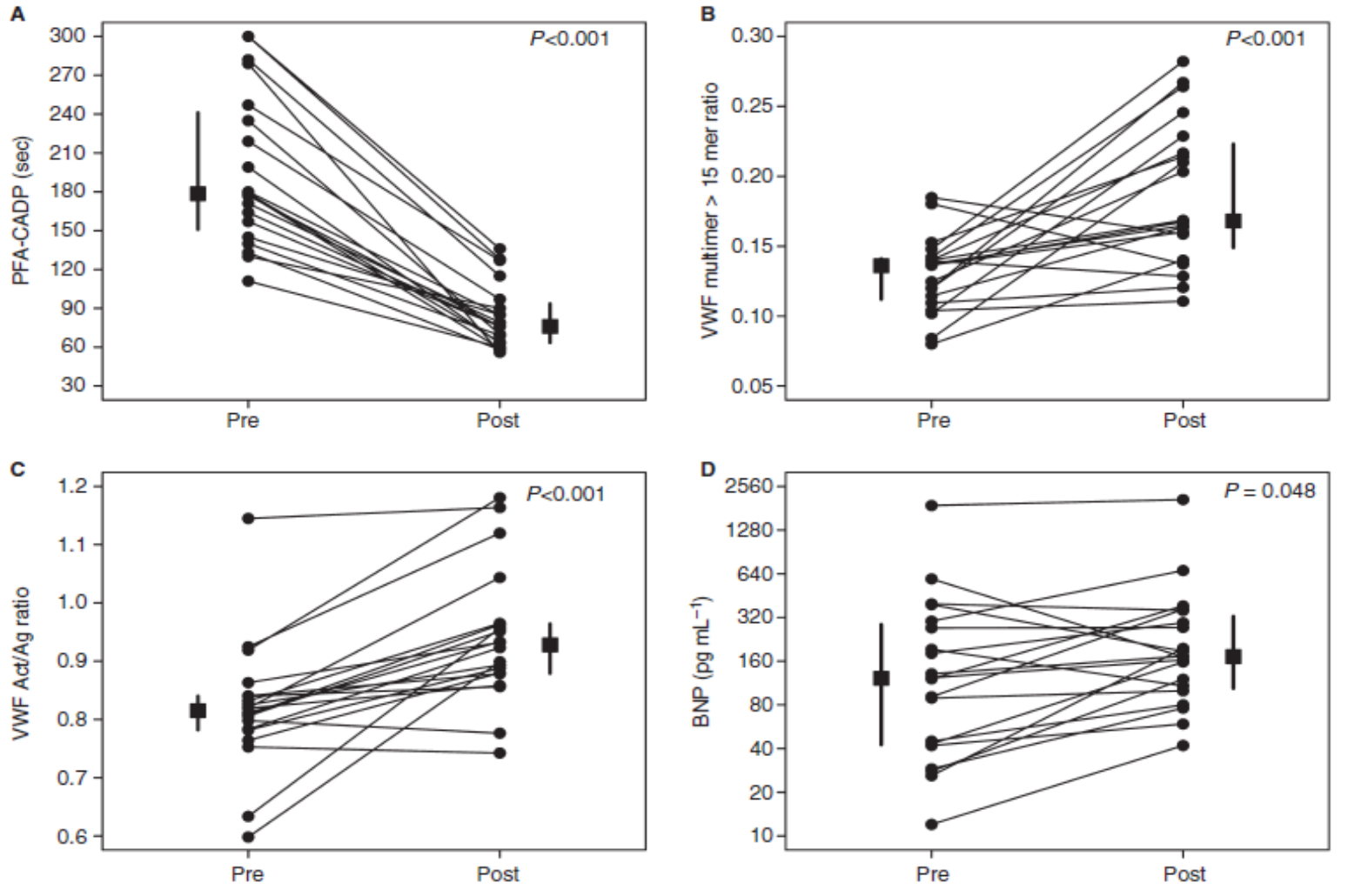
Blackshear et al. J Thromb Haemost 2014; 12: 1966–74.

AVWS associated with cardiovascular abnormalities

Effect of mitral valve repair



Blackshear et al. J Thromb Haemost 2014; 12: 1966–74.

Hyde's Syndrome

Correspondence in NJEM 1958 by EC Heyde

- Gastrointestinal Bleeding in Aortic Stenosis

In Blacksmith study in hypertrophic cardiomyopathy

- 8/20 (40%) had AVM's

Etiology is poorly understood

- normal vascular aging and an impairment of platelets to maintain vascular endothelium

Bleeding symptoms resolve after valve replacement

Loscalzo. N Eng J Med 2012

Congenital Hemophilia

Prophylaxis In U.S.

First Recombinant Factor Concentrates

First Monoclonal Factor Concentrates

First Factor Concentrates

Cryoprecipitate discovered by Dr. Judith Pool

First Plasma Transfusion

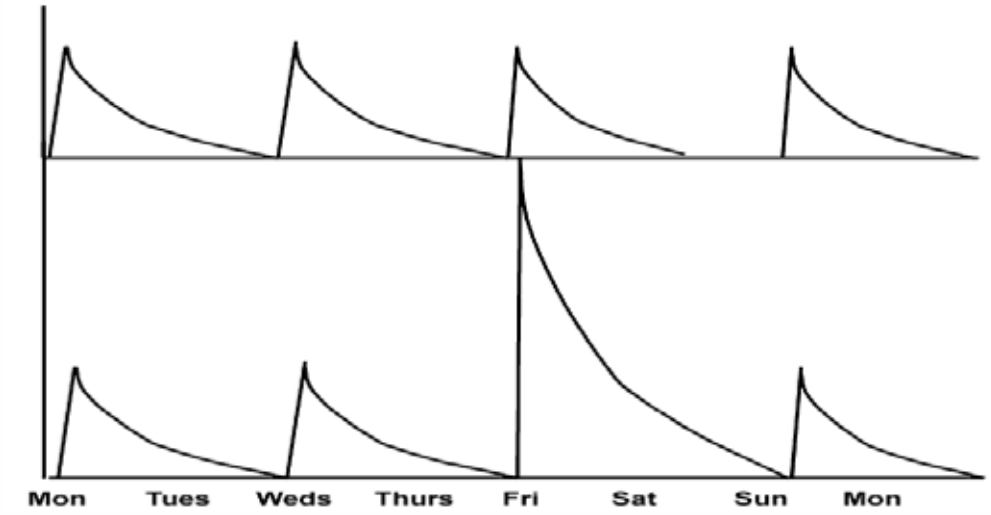
First Blood Transfusion for Hemophilia

1803 **1823** **1840** **1936** **1964** **1960/70's** **1987** **1993** **2007** **2014** **2017**

The biggest challenges for hemophilia #1

Factor replacement is standard of care

- Prophylactic factor given several times weekly for severe hemophilia
- As needed for moderate/mild hemophilia
- Has to be given **IV**
- Factor has a relatively **short half life**
  - ~ 6-10 hours for factor VIII
  - ~12-18 hours for factor IX
  - Has to be given frequently
  - Difficult to achieve troughs to maintain an active lifestyle



Loscalzo. N Eng J Med 2012

1803 First Blood Transfusion for Hemophilia

1823 First Plasma Transfusion

1840 Cryoprecipitate discovered by Dr. Judith Pool

1936 First Factor Concentrates

1964 First Monoclonal Factor Concentrates

1960/70's First Recombinant Factor Concentrates

1987 Prophylaxis In U.S.

1993 Extended half-life factors (EHL)

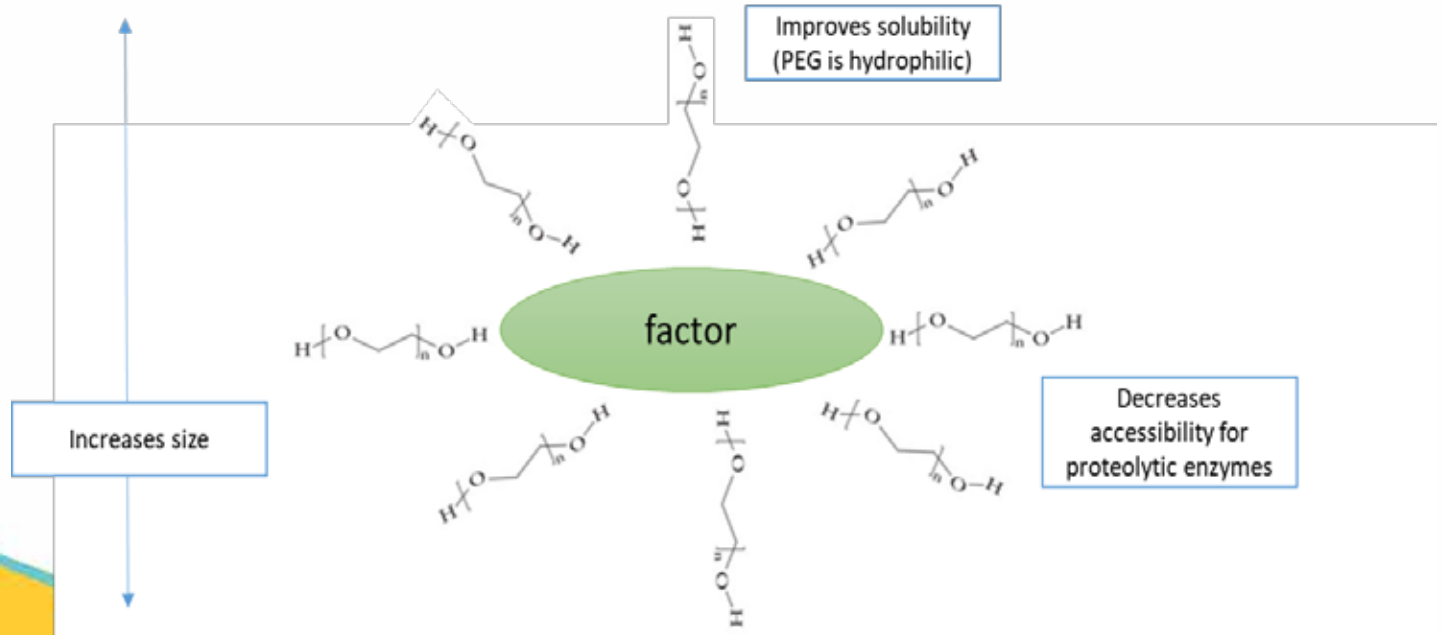
2007 Bi-specific Ab

2014 Gene therapy

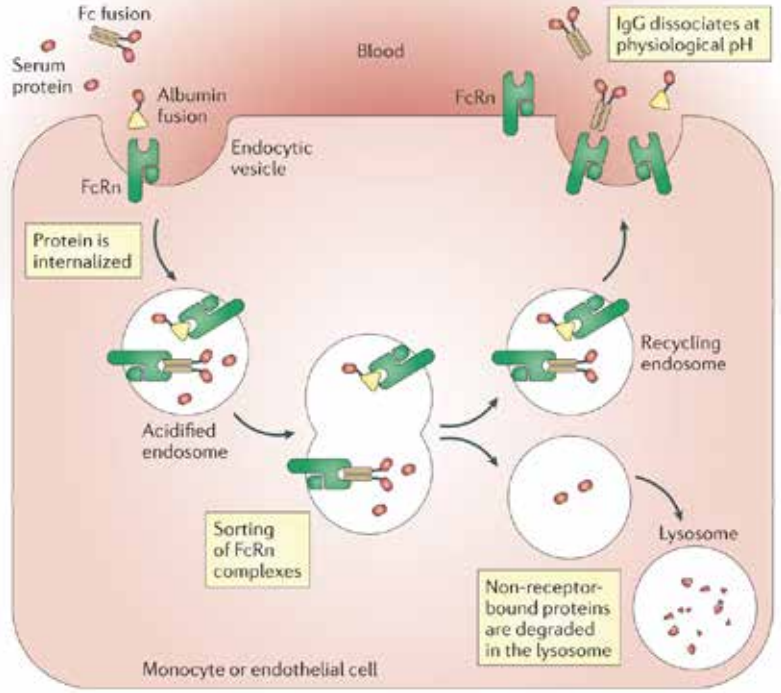
2017

Mechanism of extended half-life factors

Pegylation

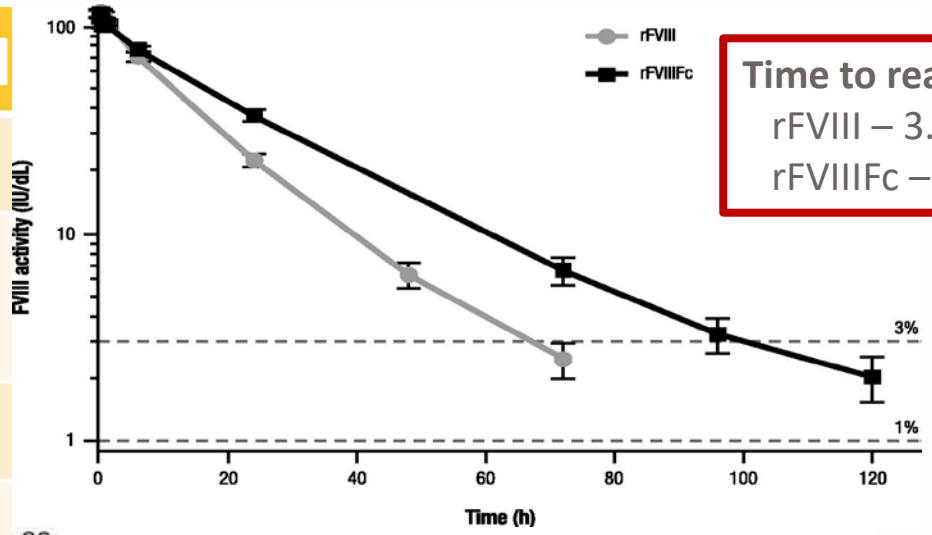


Fc or albumin fusion

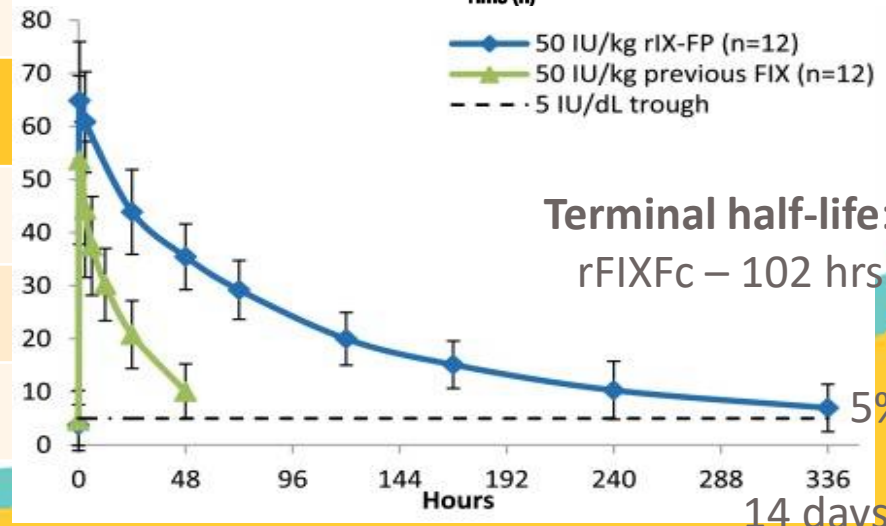


Products with phase III data in the U.S.

	Factor VIII
rFVIIIFc (Eloctate)	1.5 fold
rFVIII pegylated (BAX855, Adynovate)	1.5 to 2-fold
N8-GP (Esperoct)	2-fold
BAY94-9027 (Jivi)	1.8-fold
	Factor IX
rIXFc (Alprolix)	2.4 fold
rIX-FP (Idelvion)	> 5 fold
N9-GP (Rebinyn)	> 5 fold



Time to reach 1%:
rFVIII – 3.3 days
rFVIIIFc – 4.9 days



Terminal half-life:
rFIXFc – 102 hrs
14 days

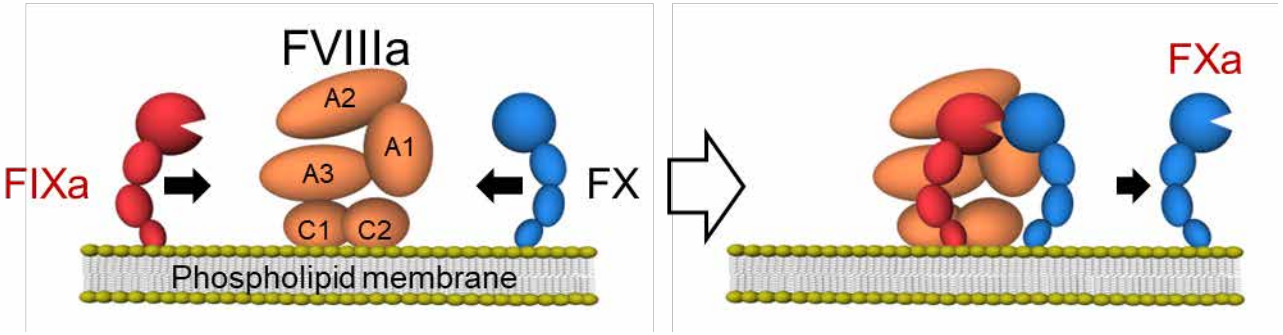
Santagostino et al. Blood 2016

The biggest challenges for hemophilia #2

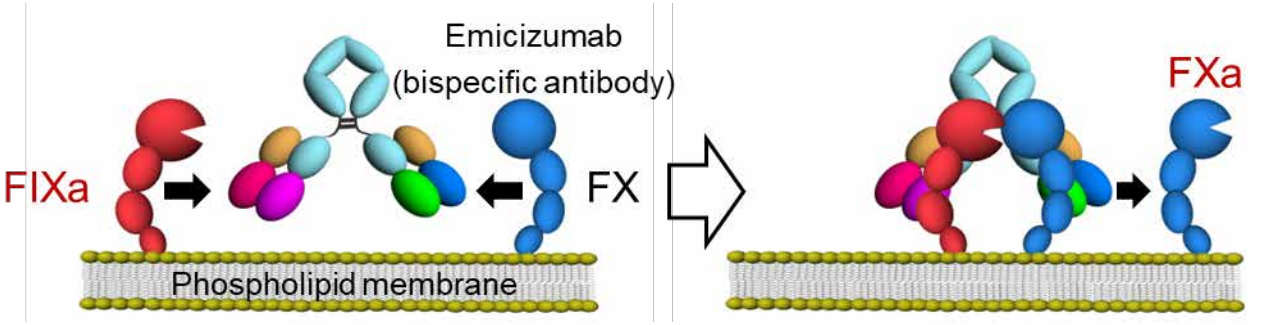
Antibody (**inhibitor**) formation is the most problematic side effect of factor replacement

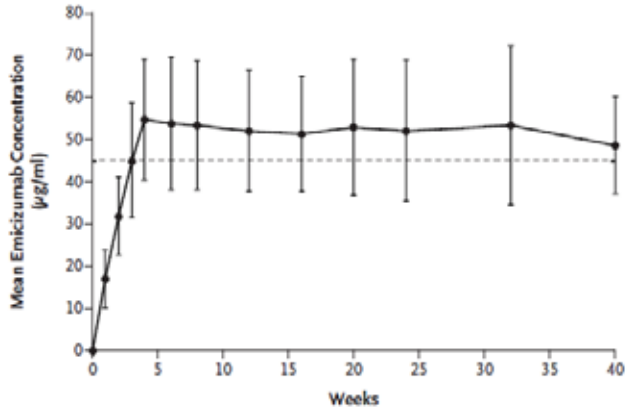
- 30% of people with severe hemophilia A develop antibodies
- High titer inhibitors do not respond to FVIII replacement
  - Need to treat bleeding with **bypassing agents**
    - recombinant factor VII activated (rFVIIa)
    - activated prothrombin complex concentrate (aPCC, contains factor II, VII, IX, X)
  - Need lengthy **immune tolerance therapy** (ITT) to eradicate inhibitor
    - Daily high dose factor VIII infusion for months

Concept of FVIIIa-Mimetic Bispecific Antibody



IV
$T_{1/2}$ ~ 8 hours





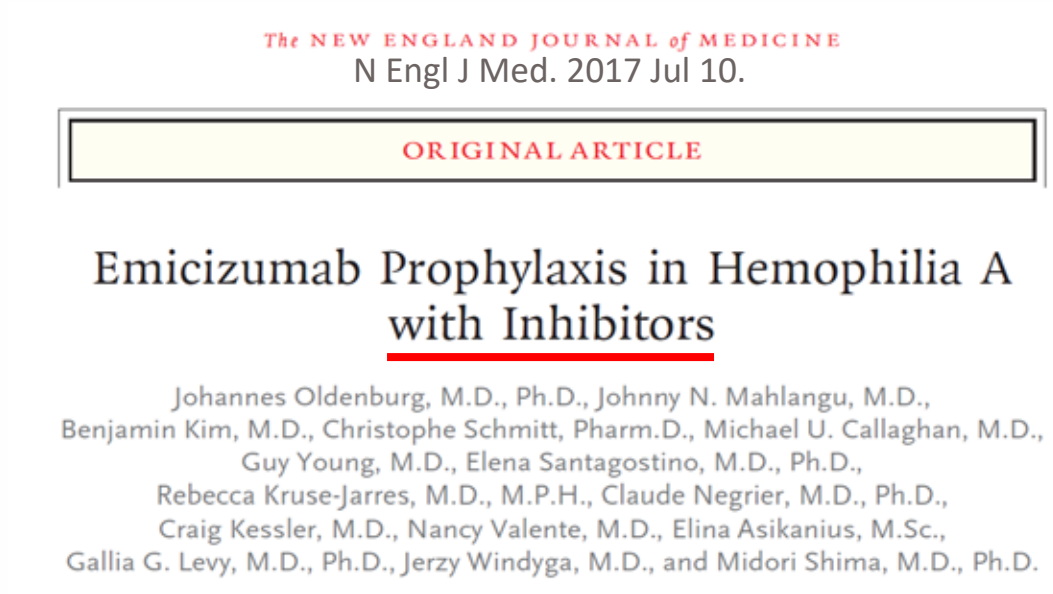
SQ
$T_{1/2}$ ~ 28 days

- SQ every 1-4 weeks
- Hemophilia A ONLY
- With and without inhibitors

FVIIIa=activated factor VIII; FIXa=activated factor IX; FX=factor X.

Kitazawa T et al. *Nat Med.* 2012;18:1570-1574; Sampei Z et al. *PLoS One.* 2013;8:e57479;
Muto A et al. *J Thromb Haemost.* 2014;12:206-213; Shima M et al. *N Engl J Med.* 2016;374:2044-2053.

Emicizumab approval

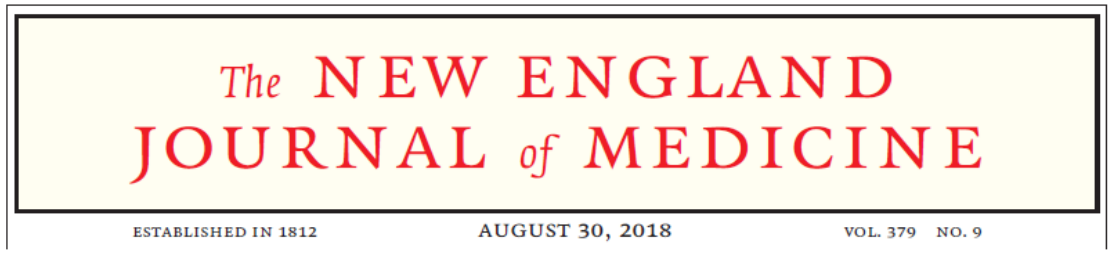


The NEW ENGLAND JOURNAL of MEDICINE
N Engl J Med. 2017 Jul 10.

ORIGINAL ARTICLE

Emicizumab Prophylaxis in Hemophilia A with Inhibitors

Johannes Oldenburg, M.D., Ph.D., Johnny N. Mahlangu, M.D., Benjamin Kim, M.D., Christophe Schmitt, Pharm.D., Michael U. Callaghan, M.D., Guy Young, M.D., Elena Santagostino, M.D., Ph.D., Rebecca Kruse-Jarres, M.D., M.P.H., Claude Negrier, M.D., Ph.D., Craig Kessler, M.D., Nancy Valente, M.D., Elina Asikanius, M.Sc., Gallia G. Levy, M.D., Ph.D., Jerzy Windyga, M.D., and Midori Shima, M.D., Ph.D.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 AUGUST 30, 2018 VOL. 379 NO. 9

Emicizumab Prophylaxis in Patients Who Have Hemophilia A without Inhibitors

J. Mahlangu, J. Oldenburg, I. Paz-Priel, C. Negrier, M. Niggli, M.E. Mancuso, C. Schmitt, V. Jiménez-Yuste, C. Kempton, C. Dhalluin, M.U. Callaghan, W. Bujan, M. Shima, J.I. Adamkewicz, E. Asikanius, G.G. Levy, and R. Kruse-Jarres

FDA Approval in USA for on November 16, 2017

to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A who have developed antibodies called Factor VIII (FVIII) inhibitors

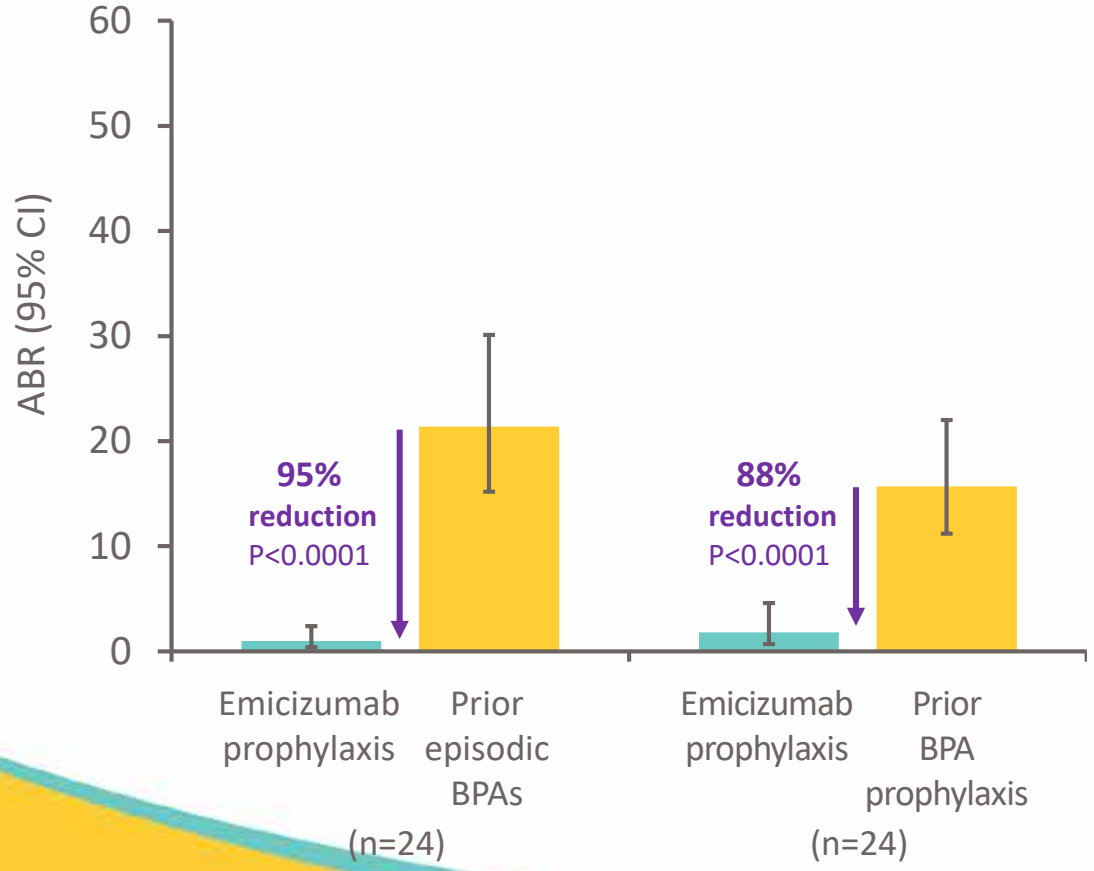
FDA Approval in USA for on October 4, 2018

for prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients (ages newborn and older) with hemophilia A with or without factor VIII (FVIII) inhibitors

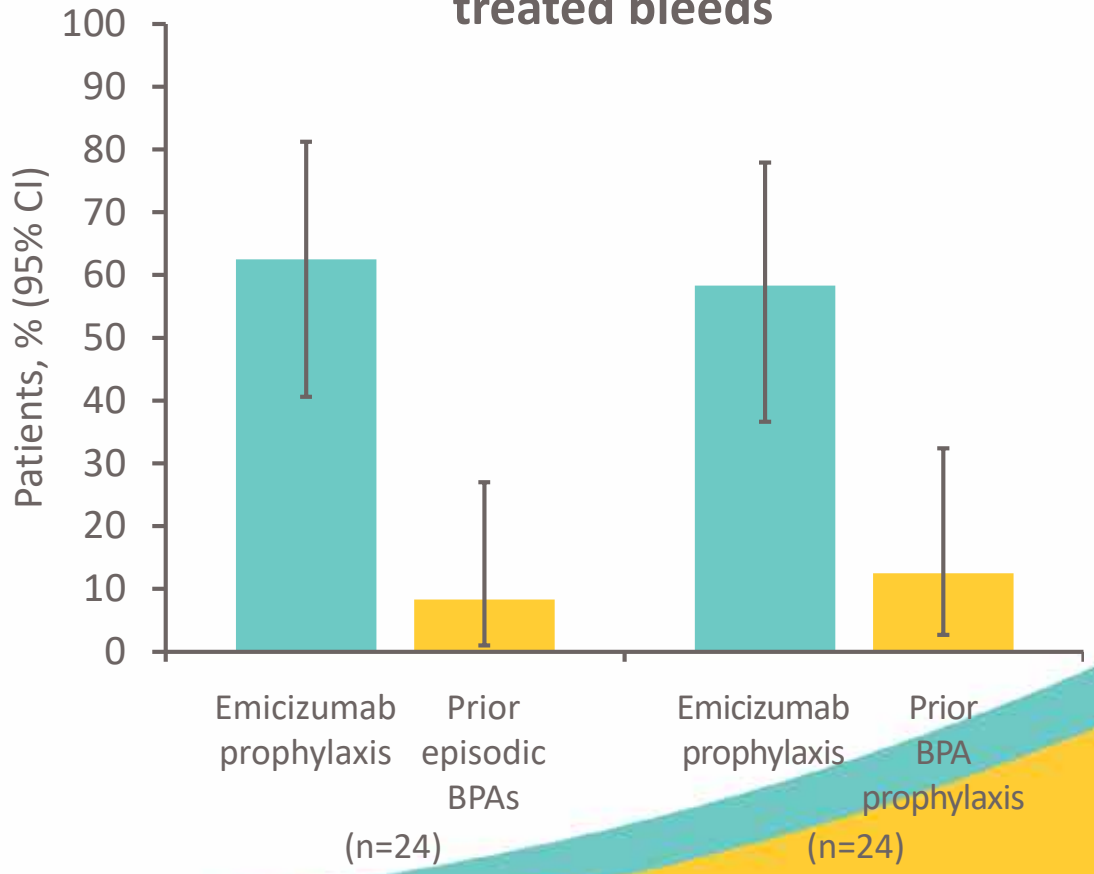
Intra-individual comparison

Comparing BPA prophylaxis to Emicizumab - ≥12 years old

Annualised bleeding rate*



Percentage of patients with zero treated bleeds

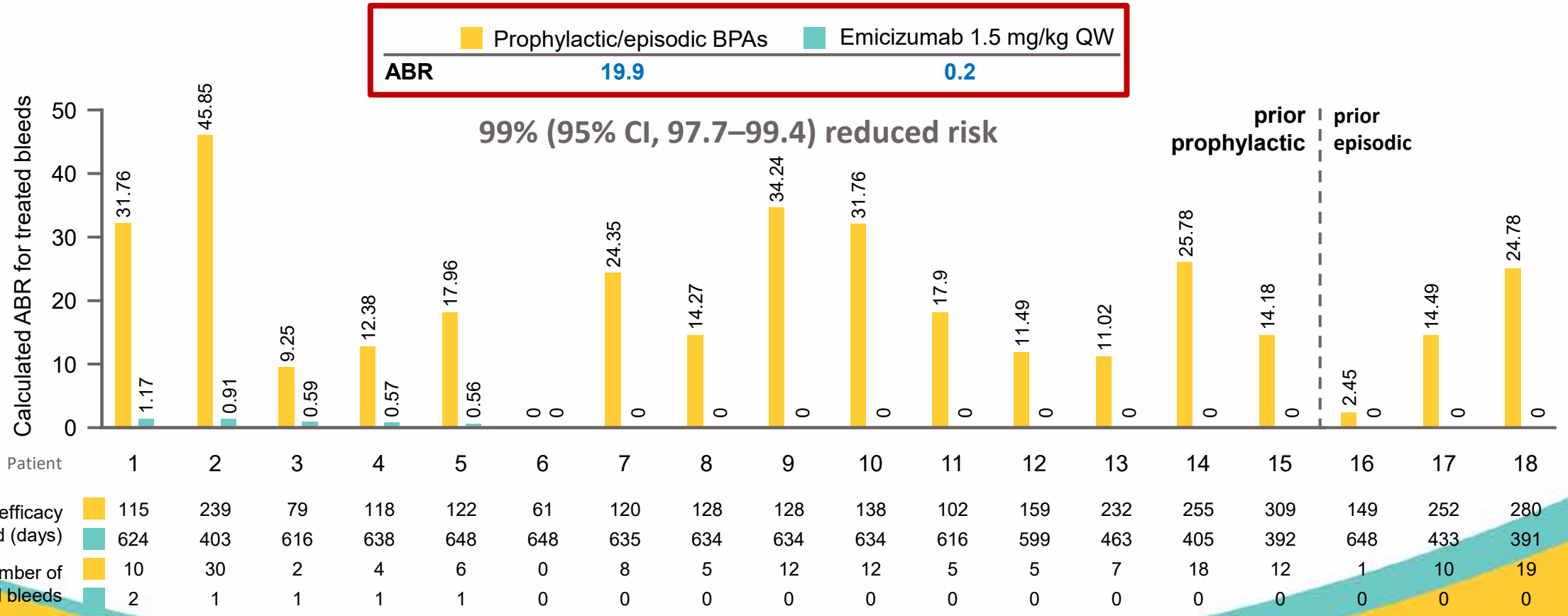


*Negative binomial regression model.
ABR, annualised bleeding rate; BPA, bypassing agent.

Mancuso et al. 2nd International Conference on Inhibitors in Coagulation Disorders 2018, Milan

Efficacy of Emicizumab – Inhibitor <12 yo (HAVEN 2)

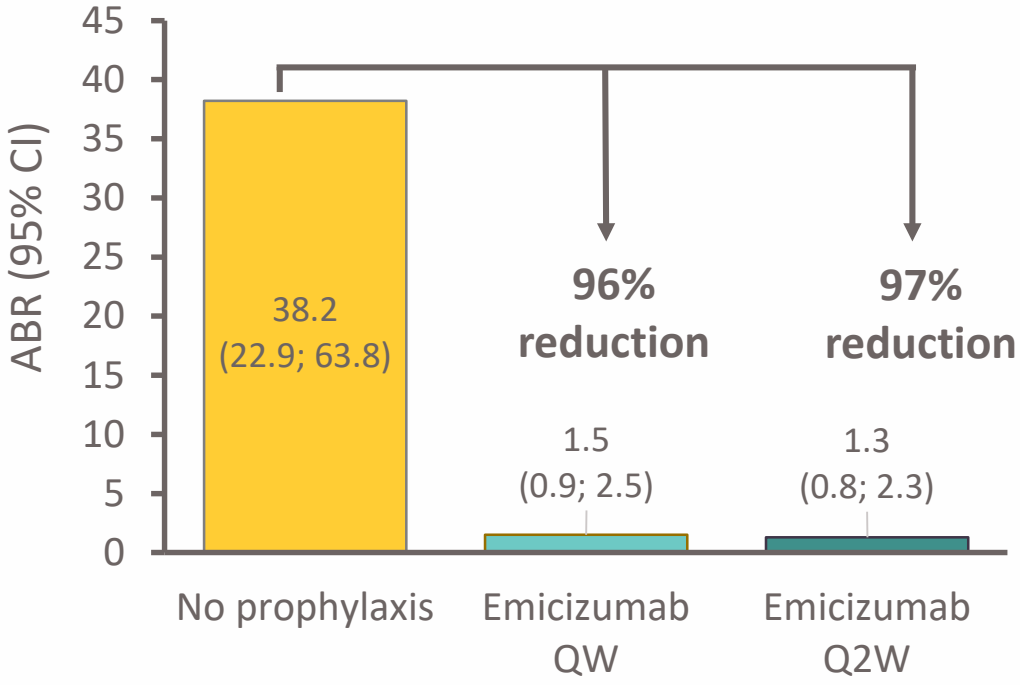
Intra-individual comparison



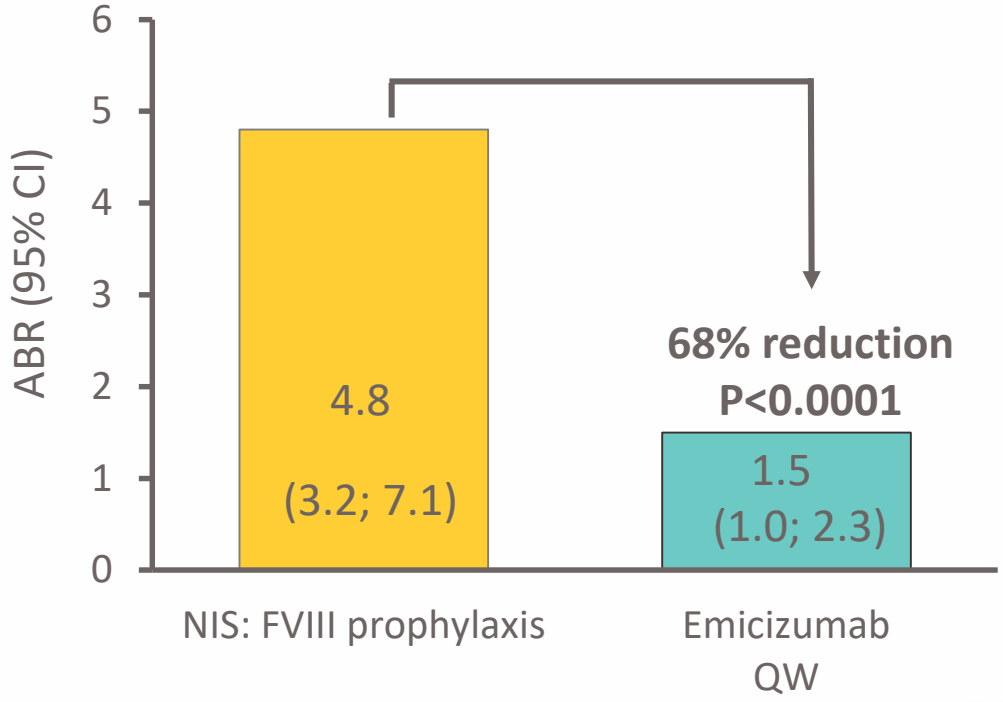
Young G, et al. ASH 2018 – oral presentation

Efficacy of emicizumab – Non-Inhibitor (HAVEN 3)

On demand FVIII



Prophylactic FVIII



Mahlangu et al. *NEJM*. 2018.

HAVEN 1: Overall Safety with Emicizumab

	Total (N=103)
Total number of adverse events (AEs), n	198
Total patients with ≥1 AE, n (%)	73 (70.9)
Serious AE*	9 (8.7)
Thrombotic microangiopathy (TMA)**	3 (2.9)
Thrombotic event	2 (1.9)
Death**	1 (<1)
AEs leading to withdrawal	2 (1.9)
Grade ≥3 AE	8 (7.8)
Related AE	23 (22.3)
Local injection site reaction	15 (14.6)

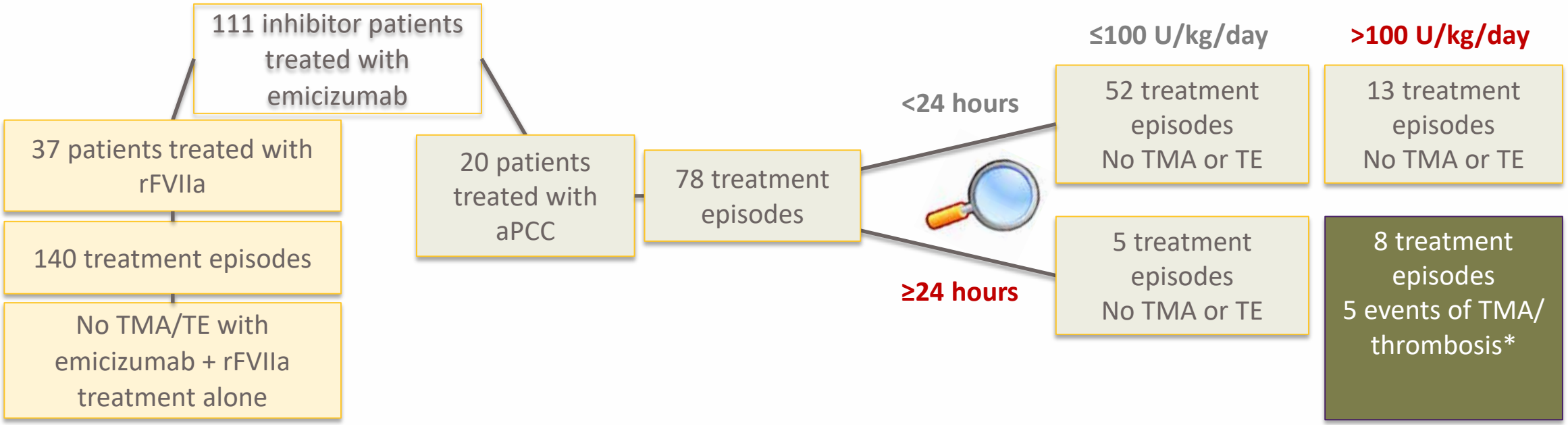
Serious adverse

Most common

*Additional serious AEs included one event each of: iron deficiency anaemia, sepsis, haemarthrosis, muscle haemorrhage, gastric ulcer haemorrhage, headache and haematuria. **Third TMA event occurred after primary data cut-off; patient also experienced fatal rectal haemorrhage
Two additional withdrawals not related to AEs; one withdrawal by patient, one withdrawal due to physician decision

Oldenburg J, et al. ISTH 2017

HAVEN 1: assessment of interaction between emicizumab and aPCC

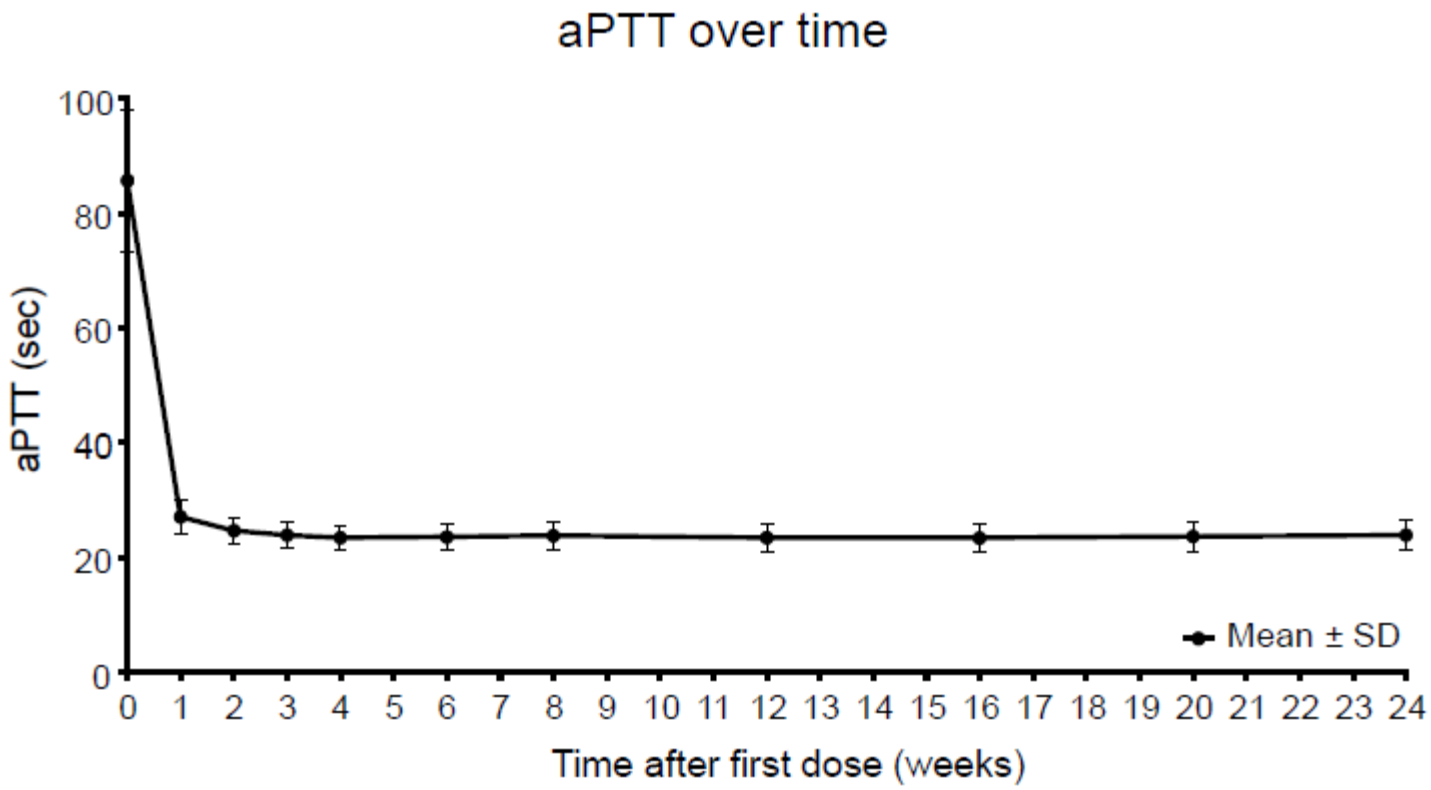


- aPCC contains activated and non-activated coagulation factors, including FII, FVII, **FIX** and **FX**, which can accumulate with repeat dosing
- Risk may be mitigated with clear dosing guidance
- No further SAEs of TE/TMA in >350 patients treated in emicizumab development program to date

*Two patients also received rFVIIa prior to/during the event
Updated data cutoff – April 21, 2017, including 8 additional patients

Oldenburg J, et al. ISTH 2017

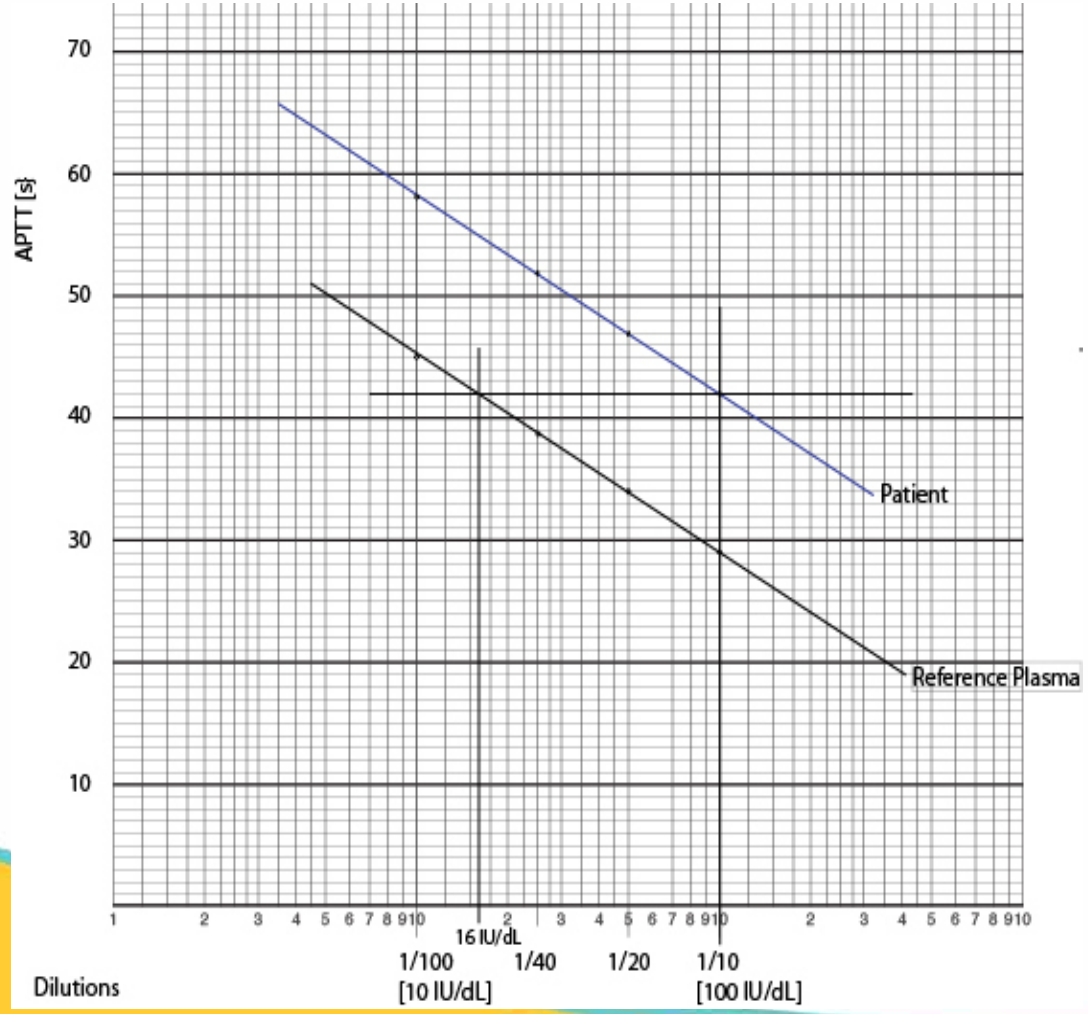
Emicizumab has a strong effect on aPTT



- aPTT is not an accurate measure of hemostatic potential in the presence of emicizumab

Adamkewicz et al – data from HAVEN 1 study

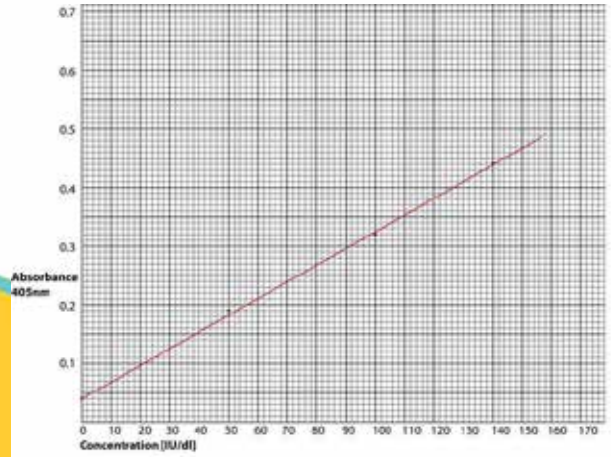
Effect on one stage assay (OSA) factor VIII assay…

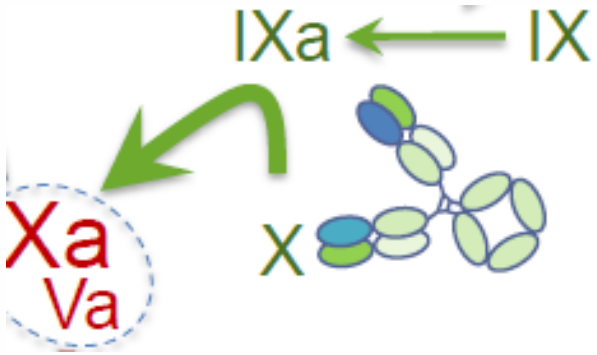


- OSA is based on aPTT
- Not a reliable assay to measure FVIII on emicizumab

Chromogenic Factor VIII Assay

- Incubation step to generate FXa -> determine the amount of FXa produced
- Amount of FXa is measured by its action on a highly specific chromogenic substrate -> color intensity produced is directly proportional to the amount of Fxa -> directly proportional to the amount of FVIII

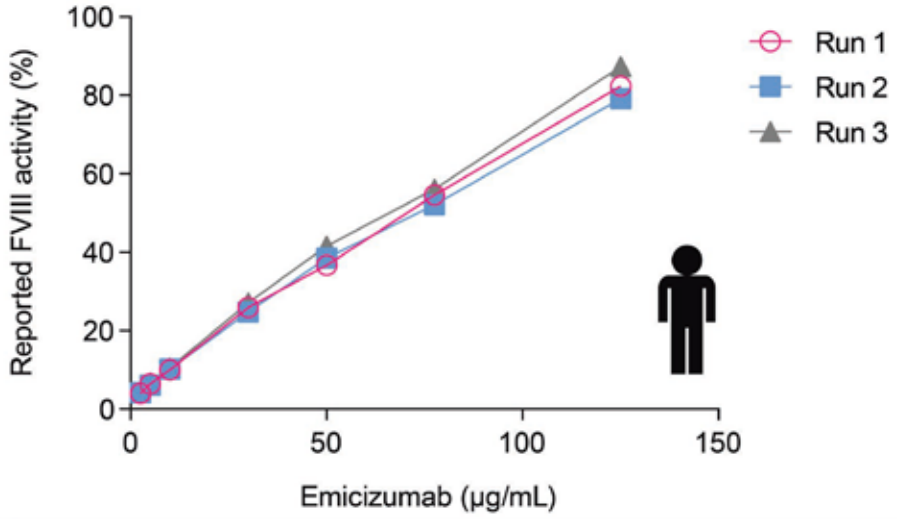




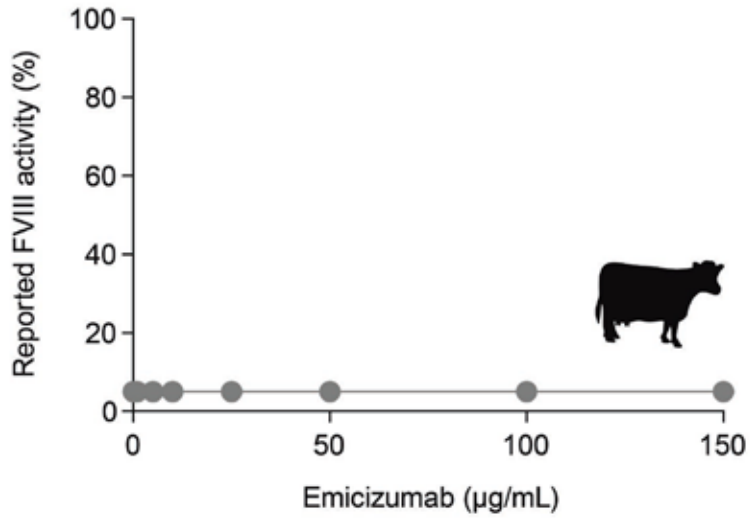
Works with **human** or **bovine** reagent

Effect of emicizumab on chromogenic factor VIII activity

Human reagent
– detects emicizumab



Bovine reagent
– does NOT detect emiczumab

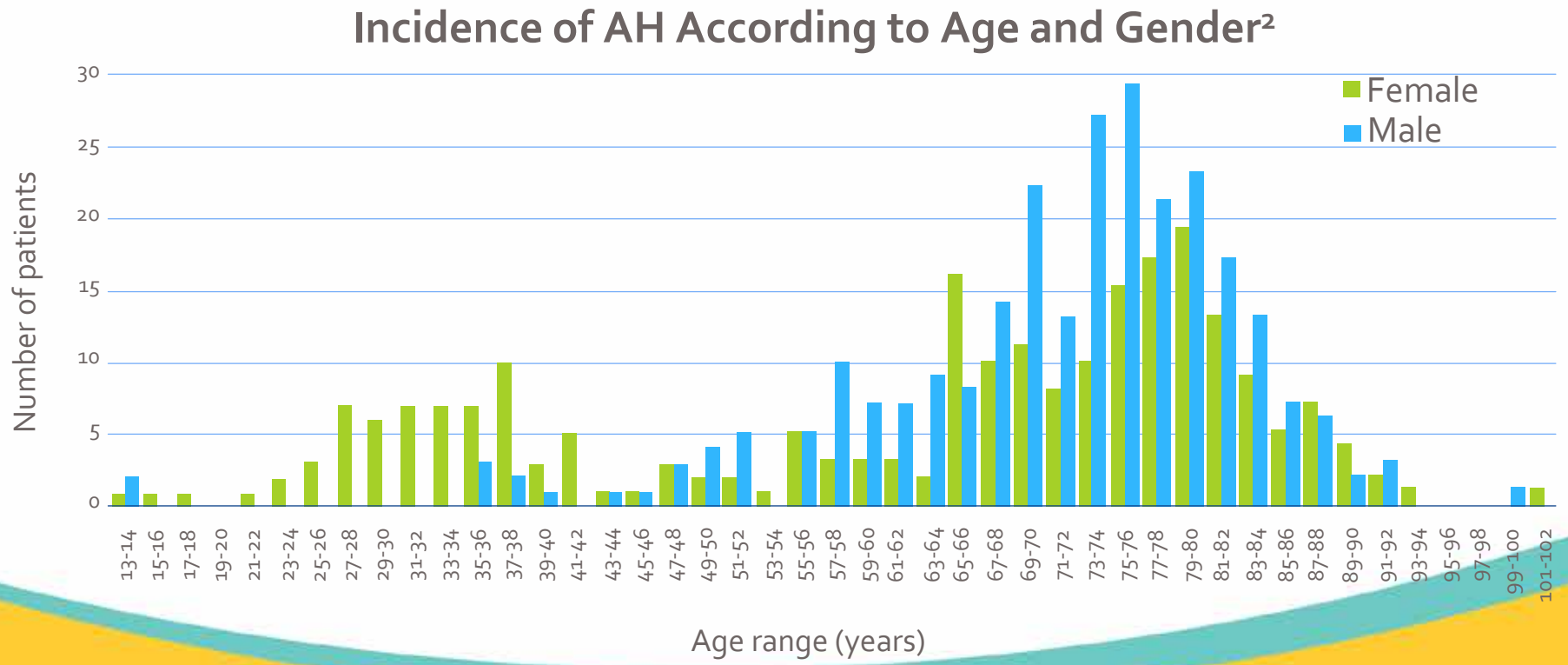


Adamkewicz et al – poster presentation – HTRS 2017

Acquired Hemophilia A

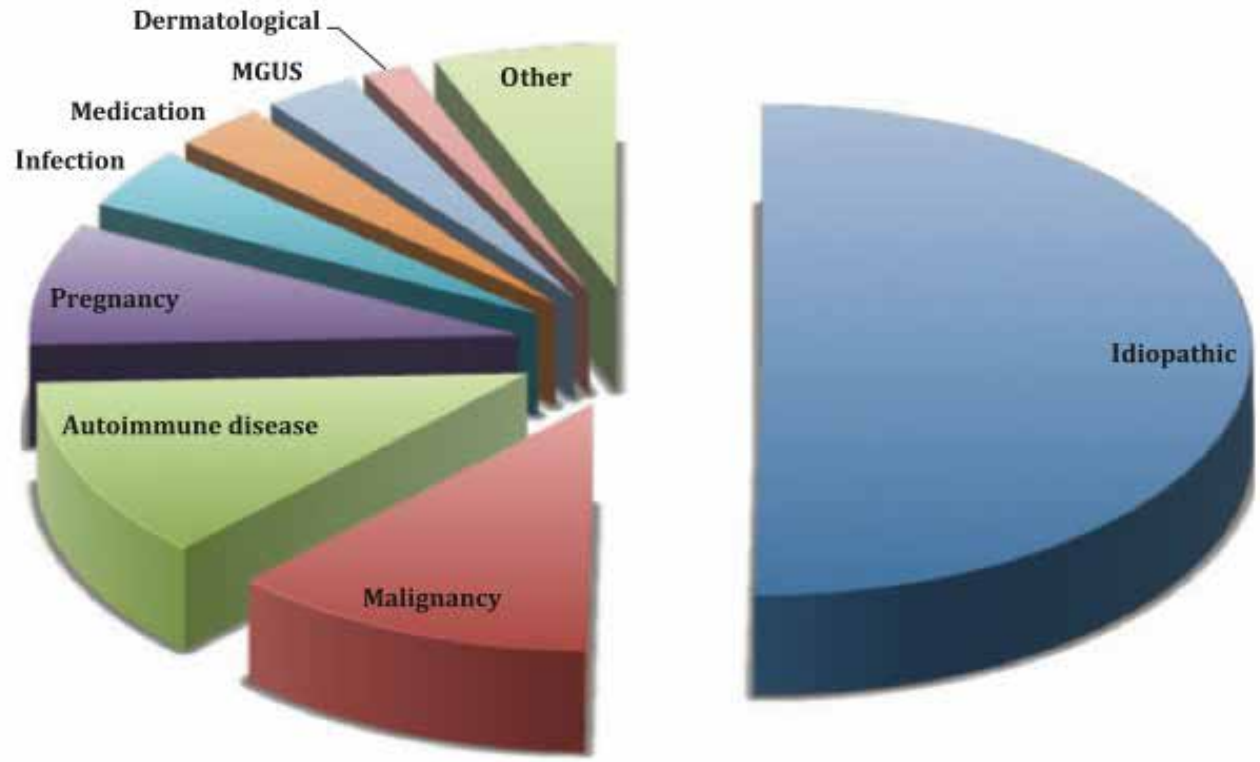
Epidemiology of Acquired Hemophilia

- Rare bleeding condition caused by an autoantibody (inhibitor) to coagulation factor VIII (FVIII)
  - Incidence: 1.5 cases per million/year[1]



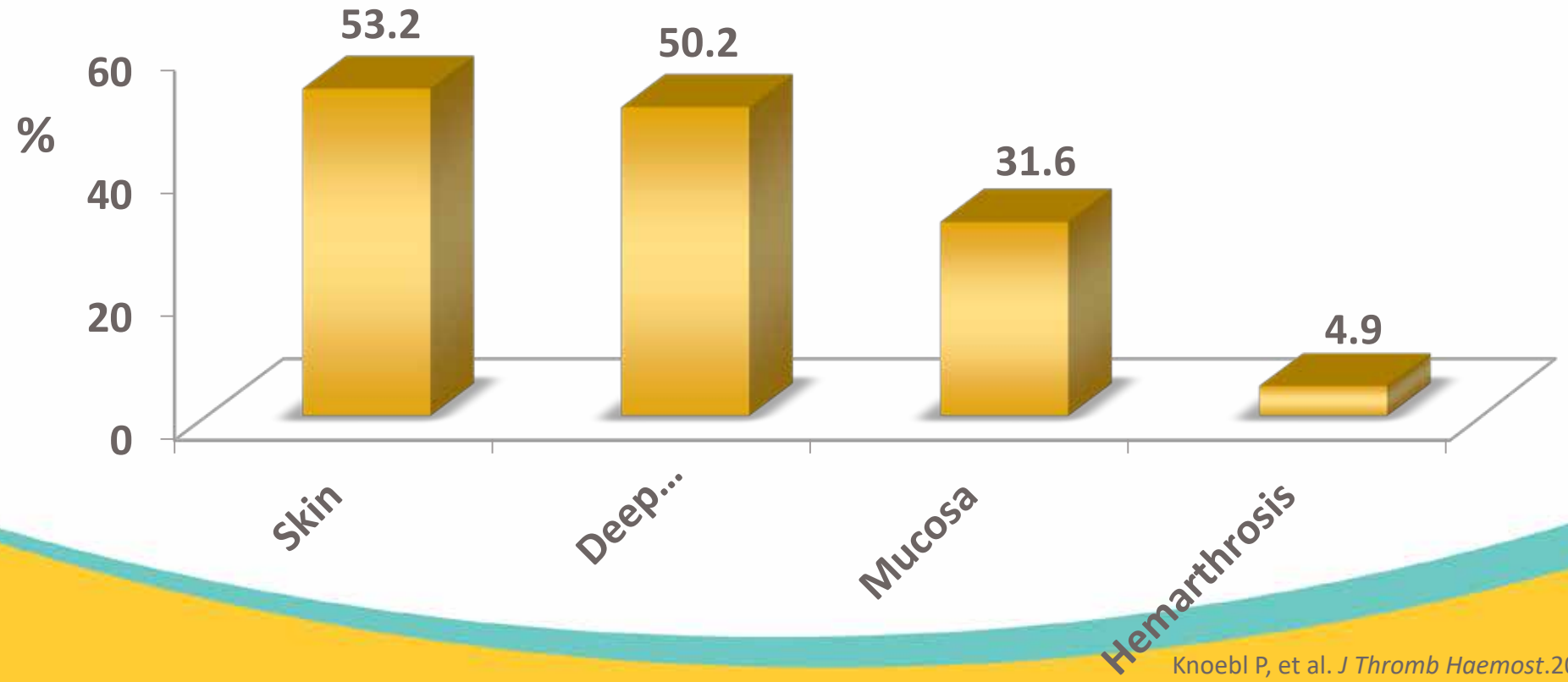
1. Collins et al Blood 2007, 2. Knoebl, et al.

Associated Conditions



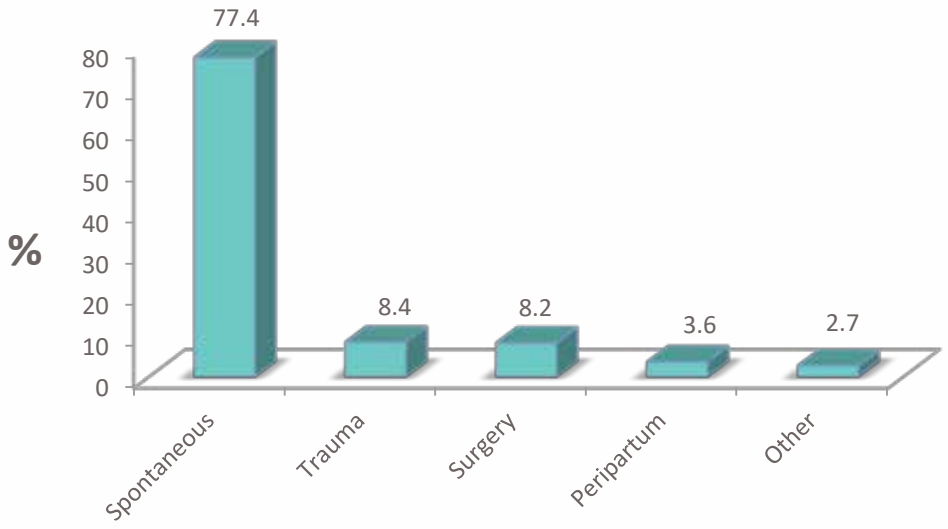
Adapted from: Knoebl P, et al. *J Thromb Haemost*. 2012;10:622-631.

Bleeding Pattern in AHA



Knoebl P, et al. *J Thromb Haemost*.2012

Bleeding Severity in AHA



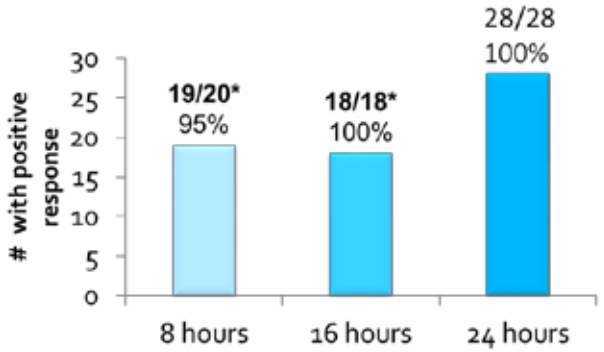
73% severe
Mortality - 8% to 22%

Collins P, et al. *BMC Res Notes*. 2010;3:161.

Zeitler H, et al. *Atheroscler Suppl*. 2013.

Principles of Treatment

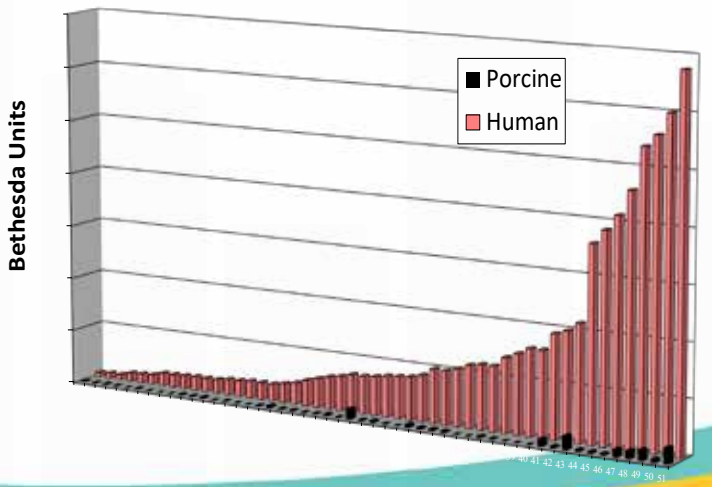
Principles of Treatment

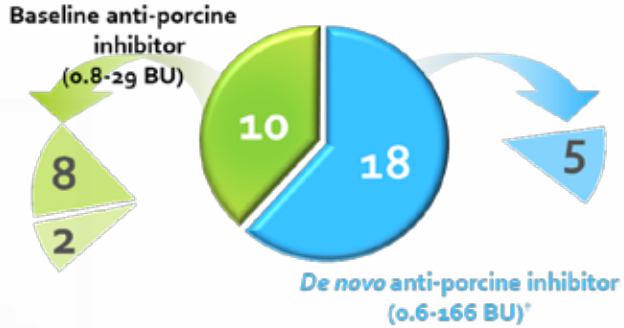


Rates of Control for First Bleeding Episodes by First-line Therapy

	First-line Bleeding Control	
	n	%
Bypassing Agent	219	91.8
- Recombinant factor VIIa	159	91.2
- Activated prothrombin complex concentrate (aPCC)	60	93.3
Replacement Therapy	69	69.6
- FVIII	55	70.1
- DDAVP	14	64.3

Porcine factor VIII concentrate





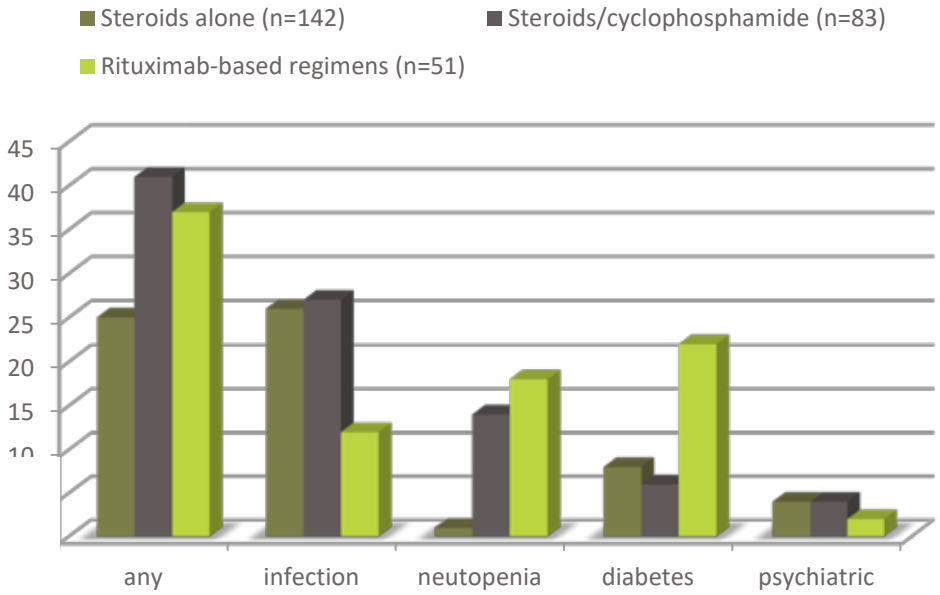
Adapted from Baudo et al - Blood 2012.

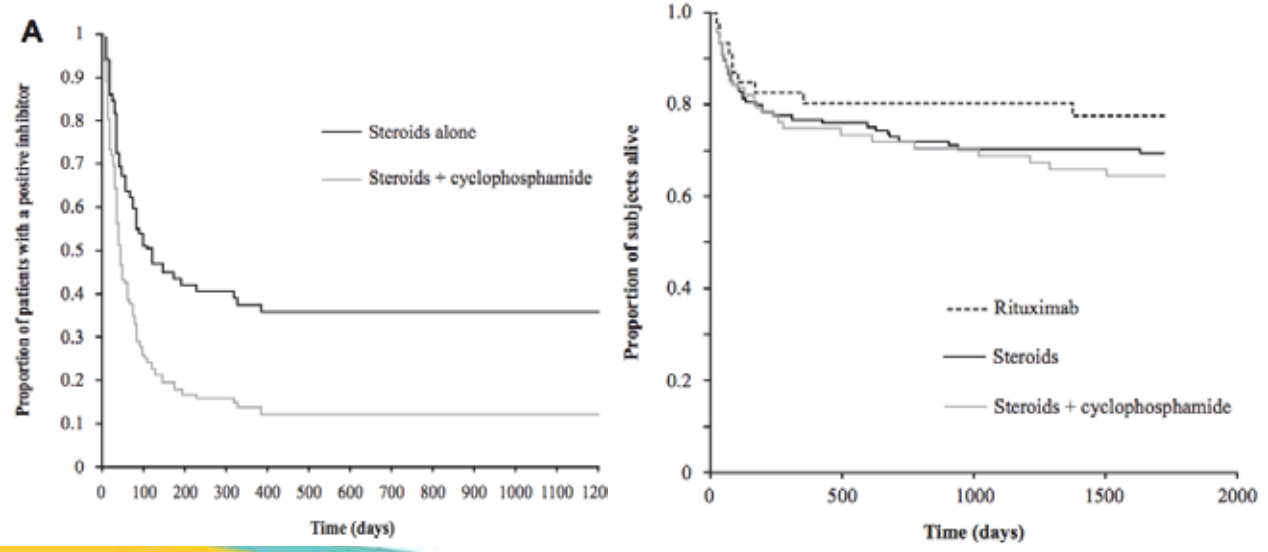
Adapted from Morrison et al. Blood 1993; 81: 1513

Kruse-Jarres et al. Haemophilia 2015

Immunosuppressive therapy (IST)

- Autoantibodies rarely disappear spontaneously
- Higher risk of mortality if they persist





- Rate of complications from IST is about 30%
- Mortality as high as 16-30%

Collins et al. Blood. 2012 .

Other Clotting Factor Deficiencies

Factor V Deficiency

Pathophysiology

- Inherited as an autosomal recessive disease
  - 75% quantitative, 25% qualitative
- Acquired as a result of autoantibody formation
  - Spontaneously or secondary to exposure to bovine thrombin or medications
    - autoimmune disorders, human immunodeficiency virus, bacterial infections, malignancy, and medications such as beta-lactam or aminoglycoside antibiotics

Treatment

- 25% of FV is stored within platelet alpha granules
- FFP or platelet transfusion
- There is no factor V concentrate

Lippi et al. Blood Coagul Fibrinolysis 2011;22:160-6
Bouchard et al. Blood 2015;125:3647-51
Franchini et al. J Thromb Thrombolysis 2011;31:449-57

Factor VII Deficiency

Pathophysiology

- Inherited – autosomal

Clinical

- Bleeding correlates poorly with factor level
  - less likely if FVII > 10%
  - patient with undetectable levels can be asymptomatic
- Excessive bleeding after invasive procedures, intracranial, umbilical cord, joint and muscle bleeding

Treatment

- rFVIIa concentrate 15 to 30 mcg/kg every 12 hours
- Goal to keep FVII > 15-20%

Factor X Deficiency

Pathophysiology

- Inherited as an autosomal recessive disease
- Acquired associated with amyloidosis

Clinical

- Bleeding correlates well with factor level, usually < 10%
- Excessive bleeding after invasive procedures, intracranial, umbilical cord, joint and muscle bleeding

Treatment

- Half-life of factor X is 40 to 60 hours
- FFP or prothrombin complex concentrate (Factor II, VII, IX, X)
- High-purity, human plasma-derived FX concentrate (pdFX; Coagadex®)
- Goal – to keep FX>20%

Austin et al. Haemophilia. 2016 May;22(3):419-25

Factor XI Deficiency

Pathophysiology

- Inherited as an autosomal recessive disease
  - Higher prevalence in Ashkenazi Jews (8-9% are heterozygous)
- Acquired associated with liver dysfunction, DIC, factor XI inhibitors (allo or auto)

Clinical

- Poor correlation between plasma level and bleeding
- Not usually spontaneous bleeding but bleeding provoked by trauma or surgery (especially mucosal surfaces)

Treatment

- Half-life of factor XI is 50 to 80 hours
- Fresh Frozen Plasma - 10 - 20 mL/kg, followed by 5 - 10 mL/kg every 24 to 48 hours
- Antifibrinolytic agents, fibrin sealant (fibrin glue), desmopressin (DDAVP), and low dose recombinant activated factor VII (rFVIIa)
- Factor XI concentrates not available in the United States

Factor XIII Deficiency

Pathophysiology

- Inherited as an autosomal recessive disease
- A or B subunit deficiency (A more severe)
- Factor XIII A subunit in anchoring the cytotrophoblast
  - Unlikely to have successful pregnancy without replacement

Clinical

- Bleeding correlates well with factor level, bleeding usually if < 5%

Treatment

- Half-life of factor XIII is 11-14 days
- FFP or cryoprecipitate
- Factor XIII concentrate
  - Recombinant factor XIII A subunit (Tretten)
  - Plasma derived factor XIII (Corifact)

International registry of 104 patients with factor XIII deficiency[2]	
Subcutaneous bleeding	57%
Delayed umbilical cord bleeding	56%
Muscle hematoma	49%
Postoperative bleeding	40%
Hemarthrosis	36%
Intracerebral bleeding	34%
Gastrointestinal bleeding	6%

1. Austin et al. Haemophilia. 2016 May;22(3):419-25
2. Ivaskevicius et al. Thromb Haemost. 2007;97(6):914.

Summary

- Reviewed von Willebrand disease
  - New treatment option – recombinant VWF
  - Acquired von Willebrand syndrome – always an underlying etiology
- New treatment options for congenital hemophilia
  - Extended half-life factor: FXI more than FVIII
  - Bispecific antibody
- Treatment options for Acquired hemophilia A
  - Bypassing agents (rFVIIa, aPCC, porcine FVIII)
- Some rarer factor deficiencies and their treatment approaches


Thank you for attention!

Seattle Cancer Care Alliance

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UNIVERSITY OF WASHINGTON 1861

Hepatocellular Carcinoma

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Disclosures:

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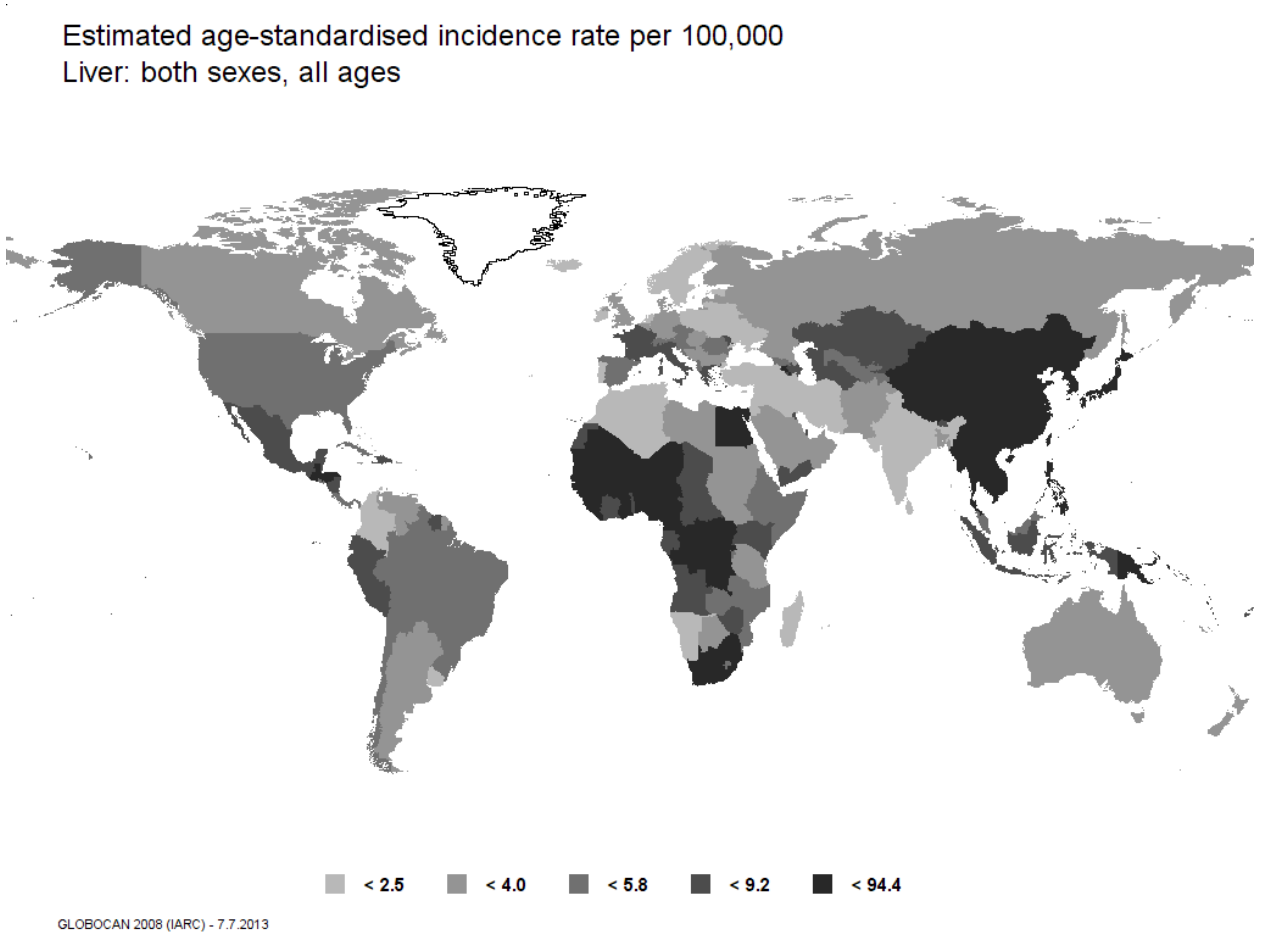
- Consulting: Eisai, Zymeworks
- Other Unpaid Affiliations: GI Cancer Alliance, ASCO, Fibrolamellar Cancer Foundation

HCC: Global incidence



3rd leading cause of global cancer related death
Incidence and mortality is rising in the United States

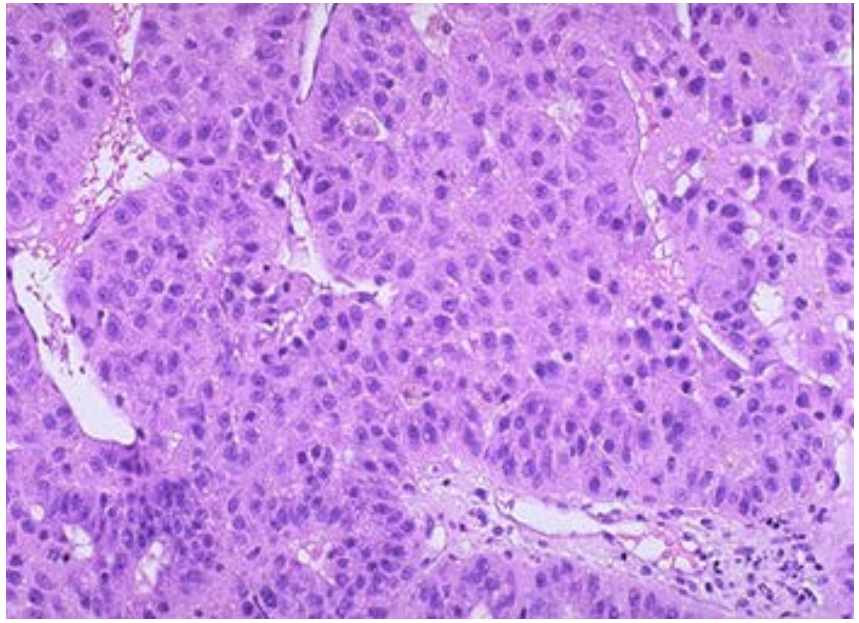
El-Serag HB. N Engl J Med 2011; 365:1118-1127.

Bray et al. Cancer 2018:68(6) 394-424

HCC: Risk Factors

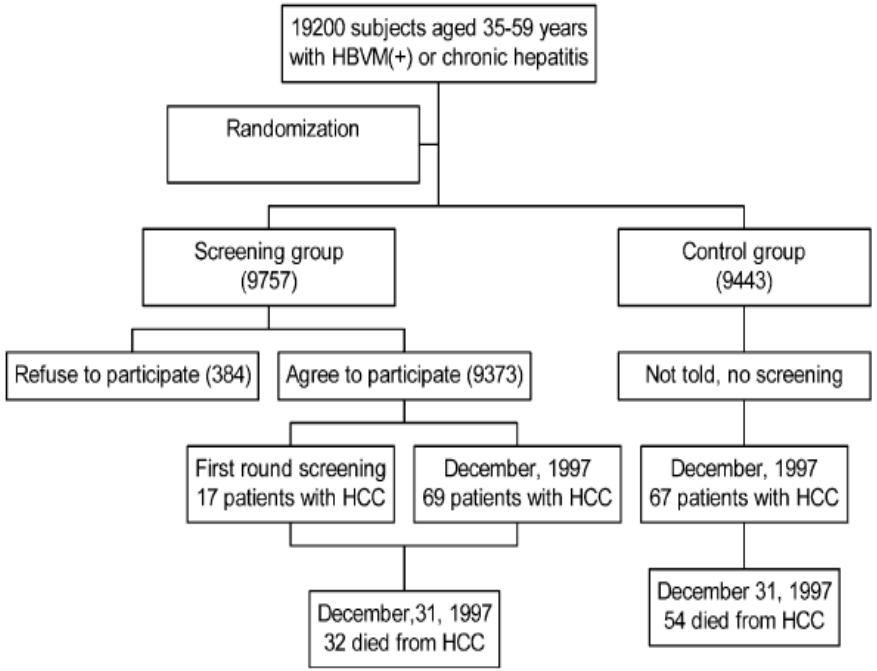
- **Cirrhosis from any cause**
  (3-4%annual risk of HCC)
  - HCV
  - HBV
  - Heavy alcohol consumption
  - Non-alcoholic steatohepatitis (NASH)
  - Aflatoxins
- **HBV Chronic Hepatitis**
  (0.4% annual risk of HCC)
- **Inherited metabolic diseases**
  - Hemochromatosis
  - Alpha-1 antitrypsin deficiency
  - Glycogen storage disease
  - Porphyria cutanea tarda
  - Tyrosinemia
  - Autoimmune hepatitis

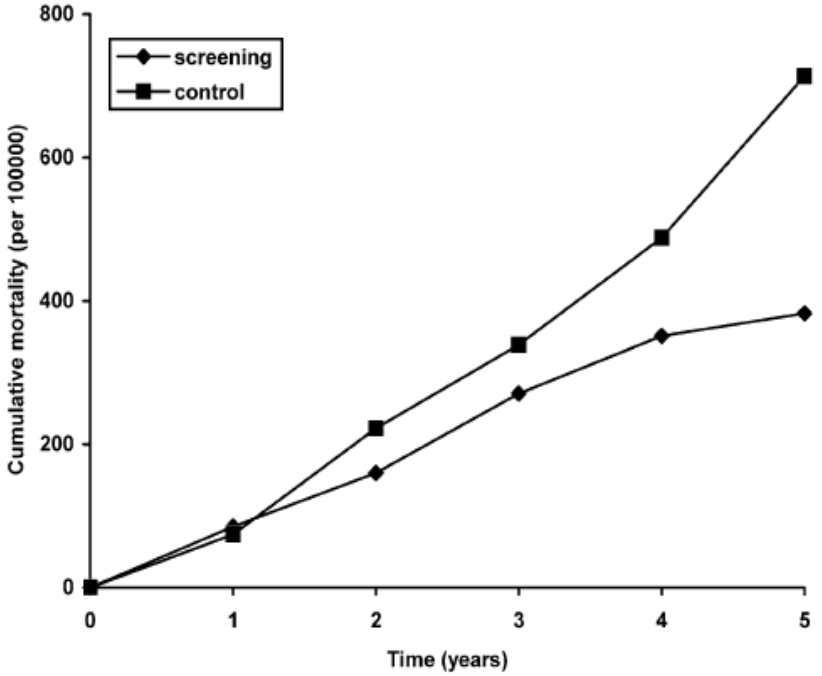
Diabetes Mellitus
Obesity



HCC: Screening and Early Detection

- Approximately 19,000 patients with chronic hepatitis/chronic HBV randomized to: Ultrasound every 6 months and AFP vs. control (no screening)
- **37% HCC mortality reduction** – **mortality rate ratio 0.63** (95% CI 0.41, 0.98)





Zhang BH et al. Randomized controlled trial of screening in hepatocellular carcinoma. *J Can Research Clin Oncol*. July 2004.

Who should be screened for HCC? AASLD Guidelines

TABLE 1. PATIENTS AT THE HIGHEST RISK FOR HCC

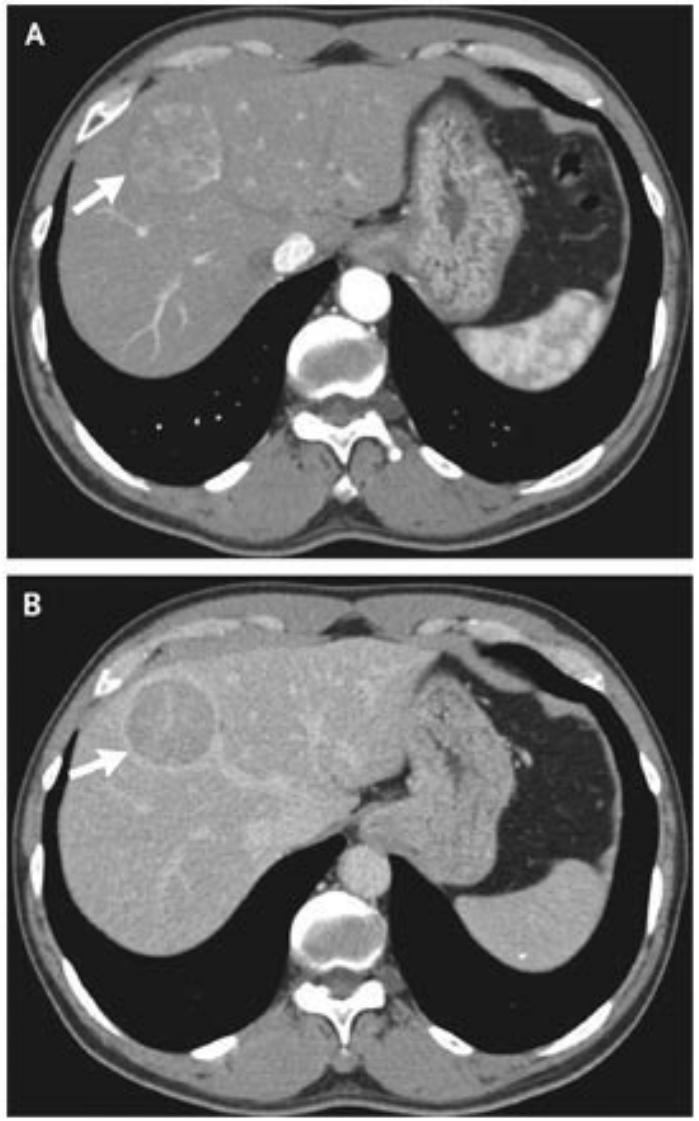
Population Group	Threshold Incidence for Efficacy of Surveillance (>0.25 LYG; % per year)	Incidence of HCC
Surveillance benefit		
Asian male hepatitis B carriers over age 40	0.2	0.4%-0.6% per year
Asian female hepatitis B carriers over age 50	0.2	0.3%-0.6% per year
Hepatitis B carrier with family history of HCC	0.2	Incidence higher than without family history
African and/or North American blacks with hepatitis B	0.2	HCC occurs at a younger age
Hepatitis B carriers with cirrhosis	0.2-1.5	3%-8% per year
Hepatitis C cirrhosis	1.5	3%-5% per year
Stage 4 PBC	1.5	3%-5% per year
Genetic hemochromatosis and cirrhosis	1.5	Unknown, but probably >1.5% per year
Alpha-1 antitrypsin deficiency and cirrhosis	1.5	Unknown, but probably >1.5% per year
Other cirrhosis	1.5	Unknown
Surveillance benefit uncertain		
Hepatitis B carriers younger than 40 (males) or 50 (females)	0.2	<0.2% per year
Hepatitis C and stage 3 fibrosis	1.5	<1.5% per year
NAFLD without cirrhosis	1.5	<1.5% per year

Abbreviation: LYG, life-years gained.

Marrerro et al. Hepatology 68(2) 2018.

Diagnosis

- **Diagnostic** imaging indicated for lesion 1 cm or greater or AFP > 20
- Typically no biopsy required
- LIRADS scoring system used to characterize lesions
  - Applies to patients with cirrhosis or chronic hepatitis B infection and incorporates:
    - Size of arterially enhancing lesion
    - Washout
    - Capsule
    - Threshold growth
- Contrast enhanced **multiphase** MRI or CT



Burrel et al. Hepatology 2003; 38
Marrerro et al. Hepatology 68(2) 2018

LIRADS: Standardized radiology reporting system

LR-1 = definitely benign LR-2 = probably benign

LR-3 = indeterminate LR-4 = suspicious LR-5 = definite

CT/MRI Diagnostic Table

Arterial phase hyperenhancement (APHE)		No APHE		APHE (not rim)		
Observation size (mm)		< 20	≥ 20	< 10	10-19	≥ 20
Count major features: • "Washout" (not peripheral) • Enhancing "capsule" • Threshold growth	None	LR-3	LR-3	LR-3	LR-3	LR-4
	One	LR-3	LR-4	LR-4	LR-4 / LR-5	LR-5
	≥ Two	LR-4	LR-4	LR-4	LR-5	LR-5

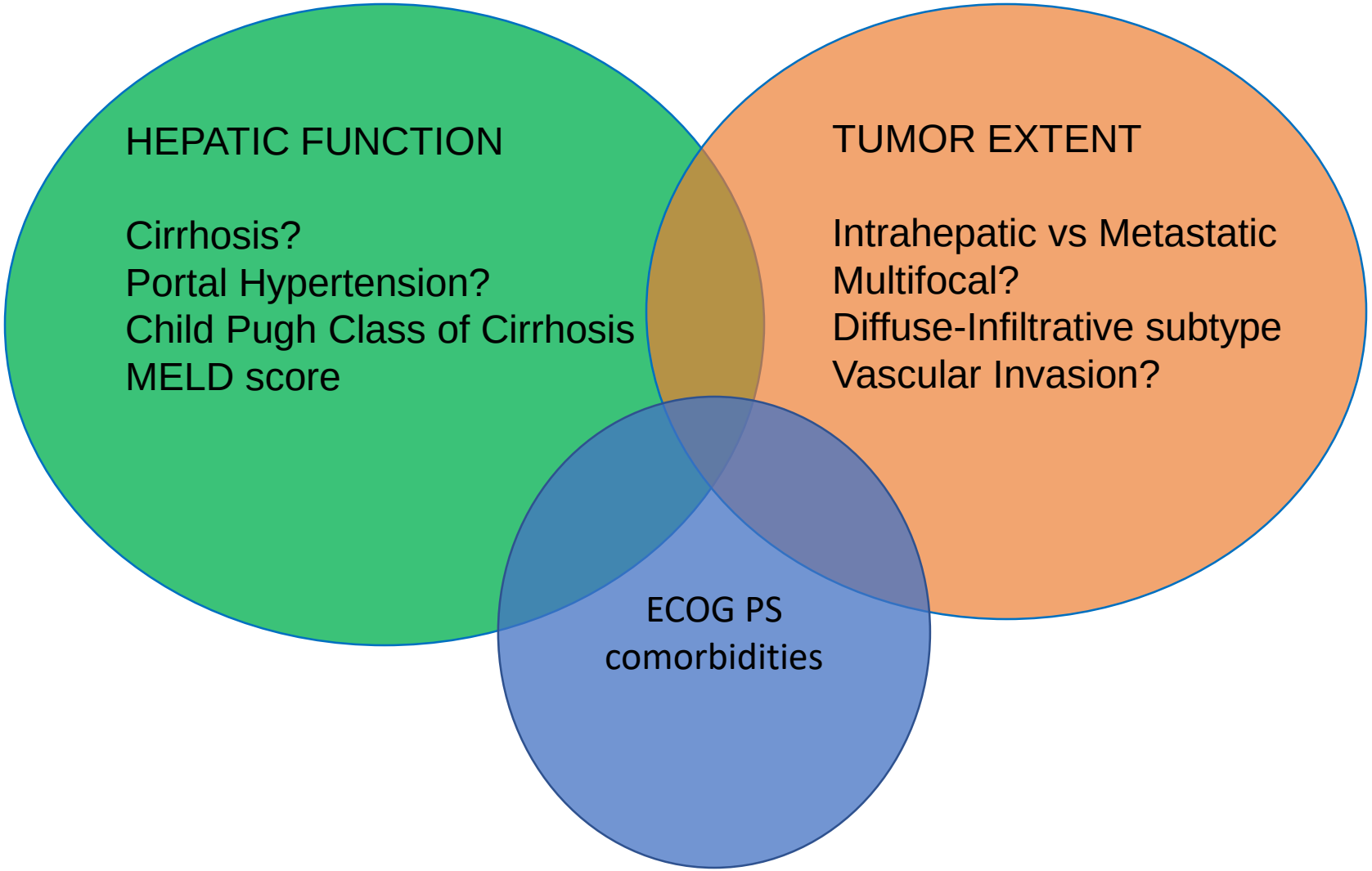
LR-4 / LR-5

Observations in this cell are categorized LR-4, except:
- LR-5g, if ≥ 50% diameter increase in < 6 months (equivalent to OPTN 5A-g)
- LR-5us, if "washout" and visibility at screening ultrasound (per AASLD HCC criteria)

ACR website: derived from LIRADS v2017

Separate LIRADS criteria for Contrast Enhanced Ultrasound exist

HCC: Considerations in staging and selection of therapeutic options



Hepatocellular Carcinoma: Staging

Multiple Complex staging systems incorporate:

- Size
- Multifocality
- Vascular invasion (e.g. portal vein tumor thrombus)
- Underlying liver function (Child-Pugh, MELD)
- Performance status
- Alpha fetoprotein levels

BCLC (Barcelona Clinic Liver Cancer) Staging

	BCLC stage				
	Very early stage (0)	Early stage (A)	Intermediate stage (B)	Advanced stage (C)	Terminal stage (D)
Child–Pugh classification	A	A–B	A–B	A–B	C
Performance status	0	0	0	1–2	3-4
Tumor status	1 HCC <2cm *Carcinoma in situ*	1 HCC or 3 nodules <3cm	Multinodular	Portal invasion or N1/ M1	Terminal stage

Llovet, JM et al. Design and Endpoints of Clinical Trials in Hepatocellular Carcinoma. *Journal of National Cancer Institute*. 100: 10, May 21, 2008

Modified BCLC Treatment Algorithm:
Early Stage Disease

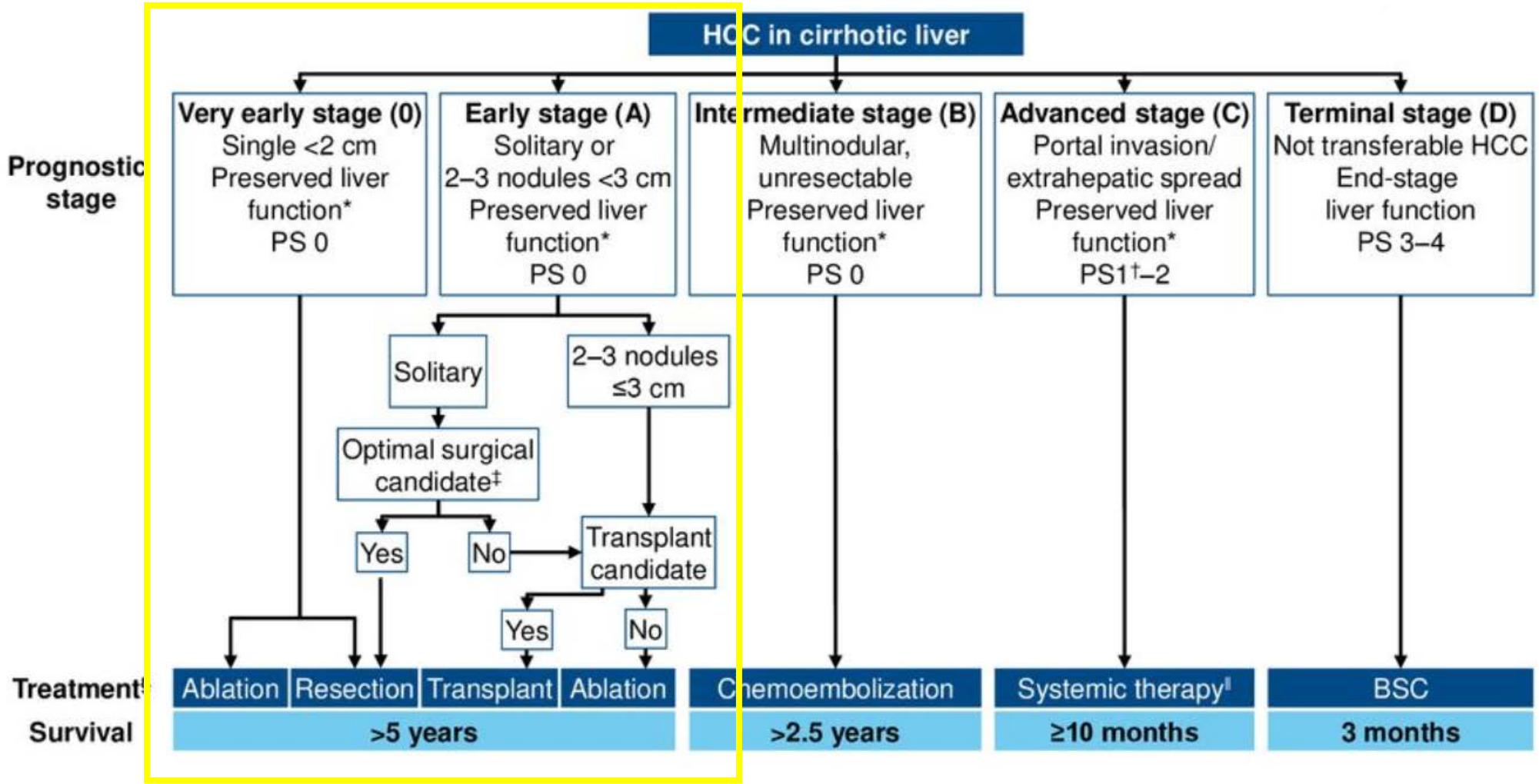


Figure: EASL CPG HCC. J Hepatol 2018

Early Stage Hepatocellular Carcinoma → BCLC Stage 0/A Local Options

Well-preserved liver function (non-cirrhotic, Child-Pugh A amenable to surgery)

- Surgical resection: no specific tumor size cut-off; no vascular invasion
- Accepted surgical outcome goal targets include:
  - Perioperative mortality 2-3%
  - 5-year overall survival of 60%

Underlying cirrhosis, poorer baseline liver function

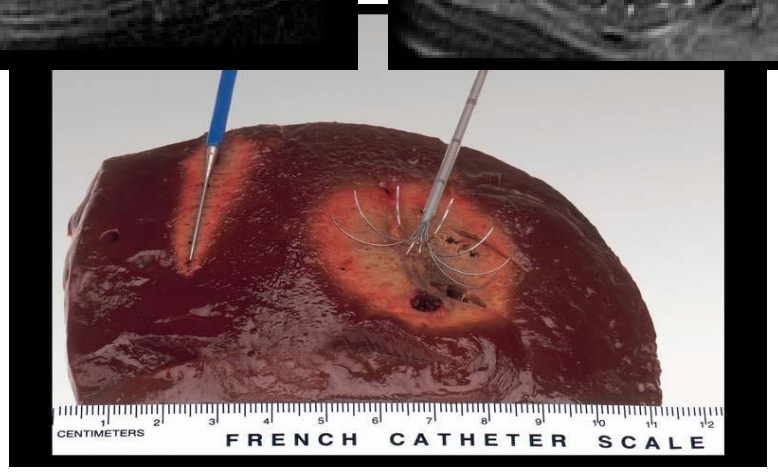
- Liver transplantation: Milan criteria; strict eligibility criteria
- Radiofrequency ablation (RFA): Best in tumors < 3 cm; associated with similar survival to surgery.
- Stereotactic Radiation, focal radioembolization and other local interventions promising in multiple phase II trials

Hong SN, et al. Comparing the Outcomes of Radiofrequency Ablation and Surgery in Patients with a Single Small Hepatocellular Carcinoma and Well-Preserved Hepatic Function

Local Treatment for Early Stage HCC: Radiofrequency Ablation

Pre-Radiofrequency Ablation

1-month post-RFA



Images from Dr. Siddharth Padia, UW Interventional Radiology

Early Stage Hepatocellular Carcinoma

- In well-selected patients with early stage HCC, 5-year survival 60-75% with local treatments.

  (Llovet JM et al. Hepatocellular Carcinoma. *Lancet*. December, 2003)

- No standard adjuvant chemotherapy following surgical resection, radiofrequency ablation (RFA) or other definitive local therapies

Orthotopic Liver Transplant: MELD Exception Points

Milan Transplant Criteria (1996)

- **Strict Criteria**
  - Solitary tumors ≤ 5cm

    or
  - 2-3 tumors all < 1-3 cm

    and
  - No macrovascular invasion/ mets

New Transplant Criteria (2017)

- **Downstaging to Milan allowed**
  - Solitary tumors 5-8 cm
  - 2-3 lesions
    - Each < 5 cm, sum < 8 cm
  - 4-5 lesions
    - Each < 3 cm, sum < 8 cm
- **AFP Criteria**
  - AFP > 1000 within Milan require locoregional therapy to achieve AFP < 500

Transplantation based on these guidelines has been shown to result in a 5-year post-transplant survival of ~80%

1) Llovet JM et al. Liver transplantation for small hepatocellular carcinoma: the tumor-node-metastases classification does not have prognostic power. *Hepatology*. June 1998. 2) Kalra A and Biggins SW. New paradigms for organ allocation and distribution in liver transplantation. Gastroenterology volume 34, 2018

Modified BCLC Treatment Algorithm:
Intermediate/Advanced Stage Disease

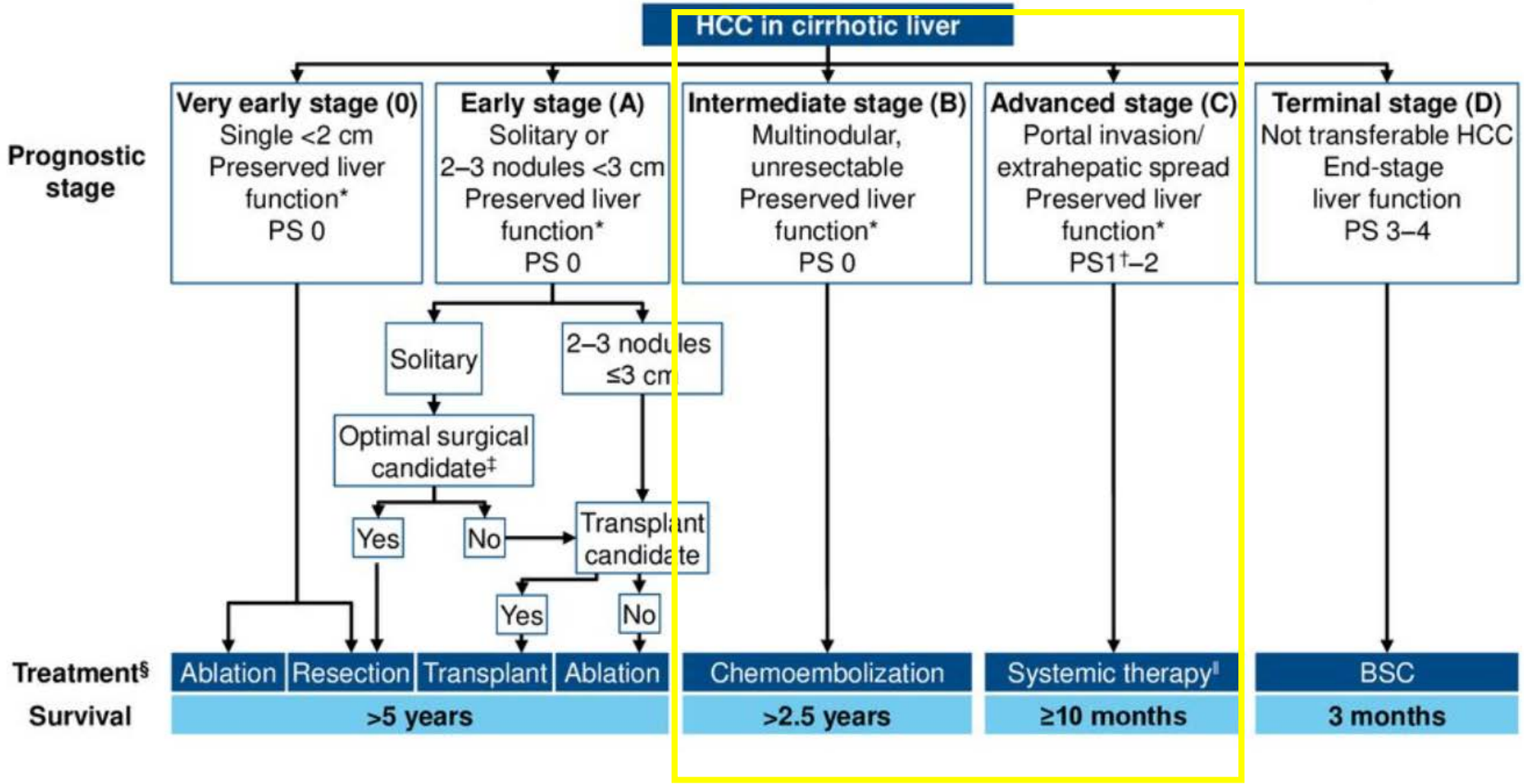


Figure: EASL CPG HCC. J Hepatol 2018

Intermediate/Advanced Hepatocellular Carcinoma: Standard Approaches

Liver-confined disease (tumors > 5cm, multifocal):

- Transarterial embolization (TAE/bland embolization) and chemoembolization (TACE)
- Radioembolization with Y^{90} beads (TARE, SIRT)
- External Beam Radiation (SBRT)
- Can be used as 'bridge' therapy while awaiting transplant

Metastatic disease or vascular invasion (BCLC C)

- Systemic therapy (boards answer); Y90 a consideration in less extensive portal venous invasion

Hepatocellular Carcinoma: Updated Algorithms

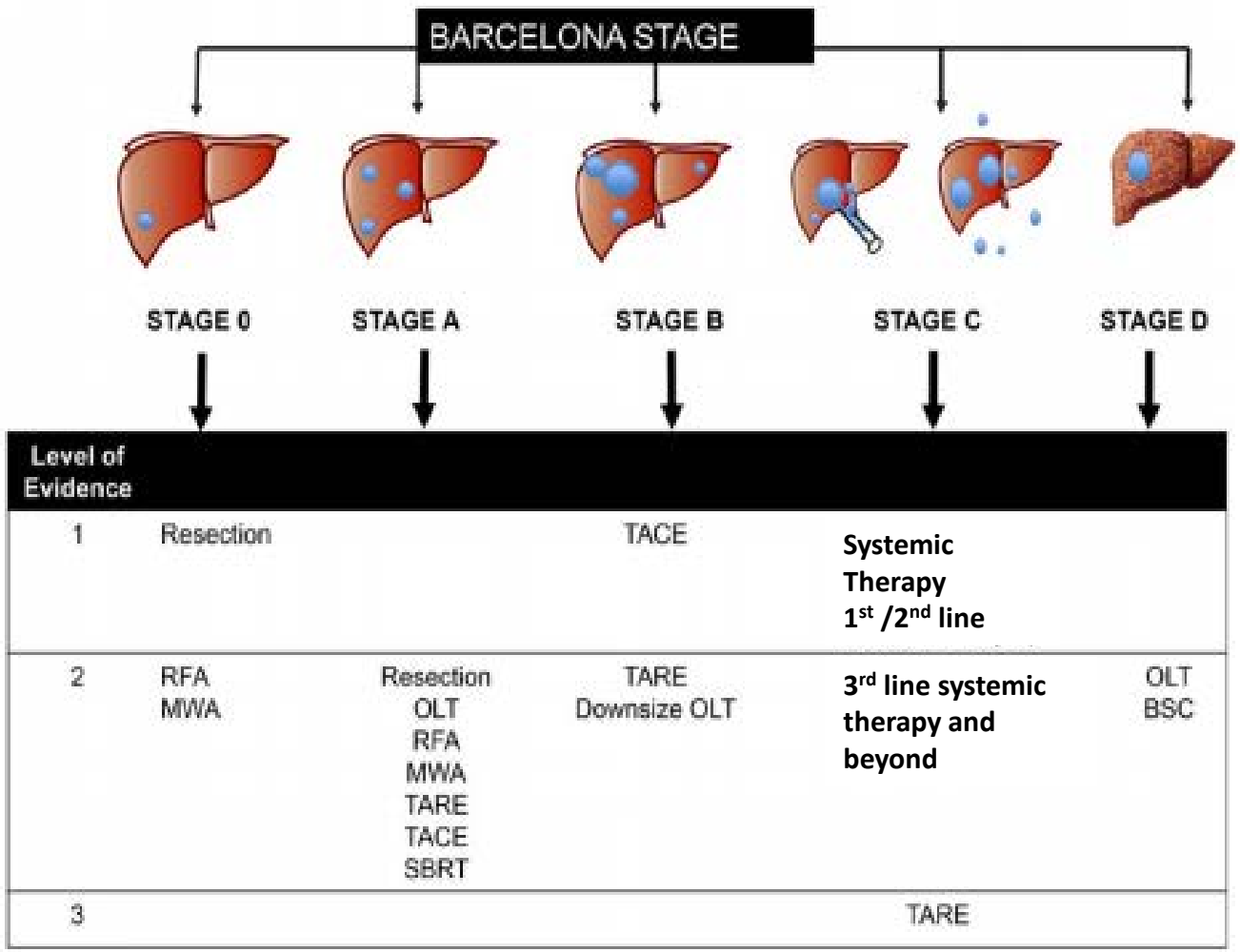


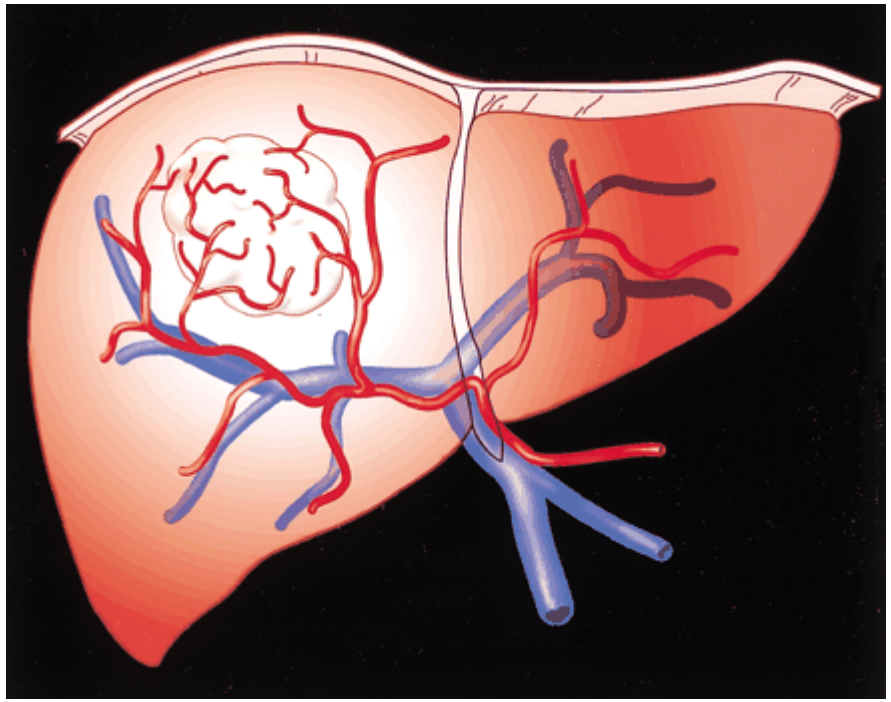
FIG. 3. Treatment recommendations according to BCLC Stage. Abbreviations: MWA, microwave ablation; BSC, best supportive care; 1L, first-line therapy; 2L, second-line therapy.

Modified from Marrero et al. Hepatology 68(2); 2018

Hepatocellular Carcinoma – Blood Supply to Tumor

Hepatocellular carcinomas derive 95% of their blood supply from branches of the hepatic artery.

Normal liver parenchyma: derives 75% of its blood supply from the portal vein

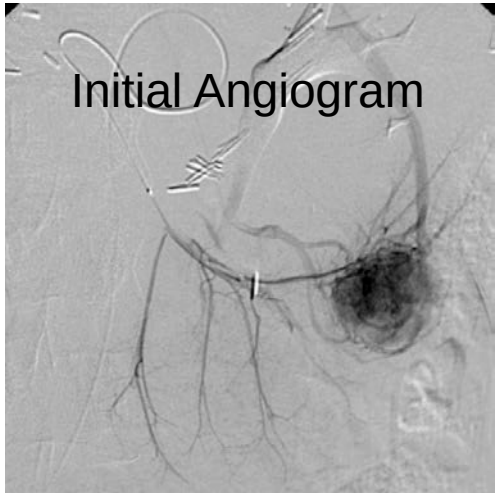


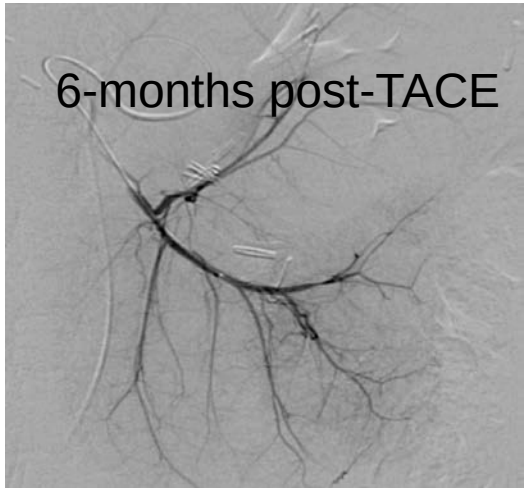
Intermediate/Advanced HCC: Transarterial Embolization

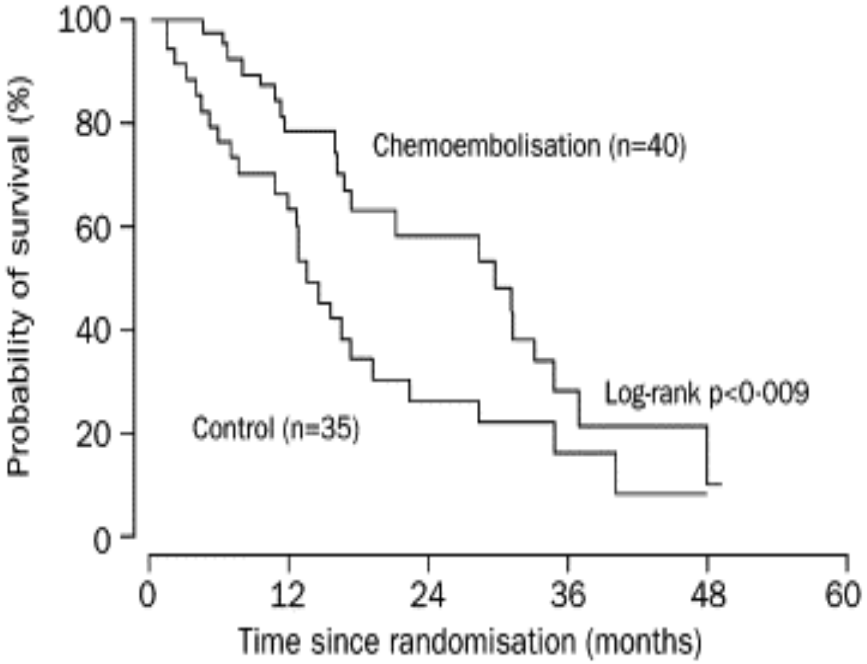
Two components of therapy:

1) Acute arterial obstruction

2) Local administration of chemotherapeutic agents







Llovet et al. Lancet 2002 359(9319)

TACE vs. Best Supportive Care – Asian vs. Western Population

	Lo et al *Hepatology* 2002		**Llovet et al *Lancet* 2002**	
Etiology	80% Hepatitis B		87% Hepatitis C	
Tumor characteristics	60% multinodular, mean tumor size 7cm		71% multinodular, mean tumor size 5cm	
Treatment (TACE)	Cisplatin (chemo) Gelatin sponge (embolic)		Doxorubicin (chemo) Gelatin sponge (embolic)	
Survival	TACE	BSC	TACE	BSC
1 year	57%	32%	82%	63%
2 year	**31%**	**11%**	**63%**	**27%**
3 year	26%	3%	29%	17%
HR for death TACE vs. BSC	**HR 0.49** (95% CI 0.28-0.81), p=0.006		**HR 0.45** (95% CI 0.25-0.81), p=0.02	

Lo C, et al. Randomized controlled trial of transarterial lipiodol chemoembolization for unresectable hepatocellular carcinoma. *Hepatology*. May, 2002.

Llovett JM, et al. Arterial embolisation or chemoembolisation versus symptomatic treatment in patients with unresectable hepatocellular carcinoma: a randomised controlled trial. *Lancet*. May, 2002

TACE/TAE: Adverse Events

Expected toxicities:

- Post-embolization syndrome: Fatigue, nausea, pain, liver enzyme elevation, low grade fever
- Chemotherapy side effects: pancytopenia, alopecia, nausea

Contraindications:

- Bilirubin >3 mg/dL
- Main portal vein thrombosis – hepatic ischemia
- Child-Pugh C cirrhosis

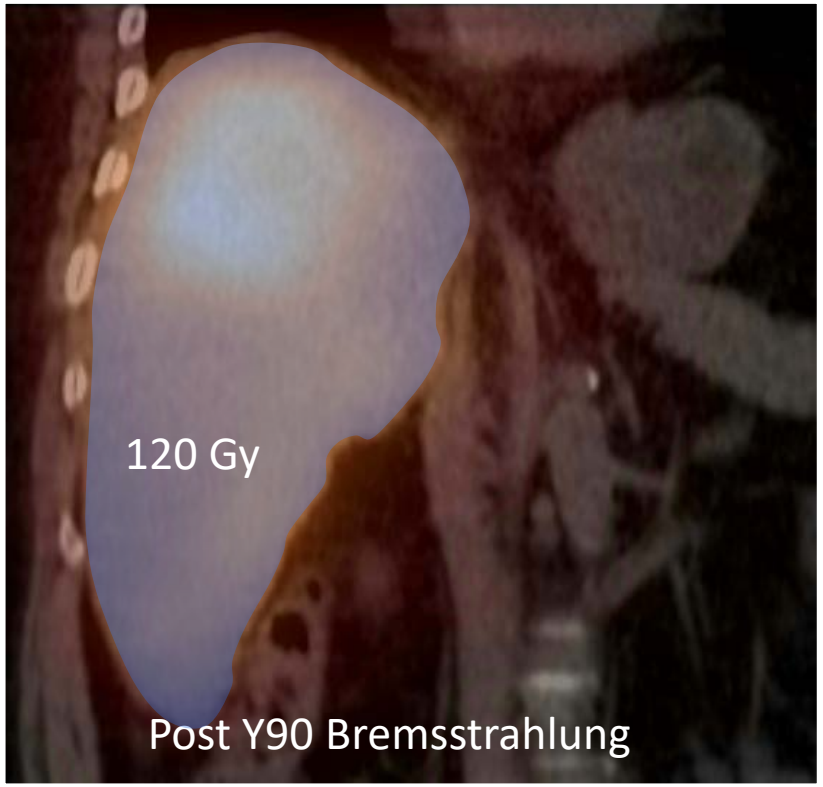
TACE/TAE – Conclusions and Questions

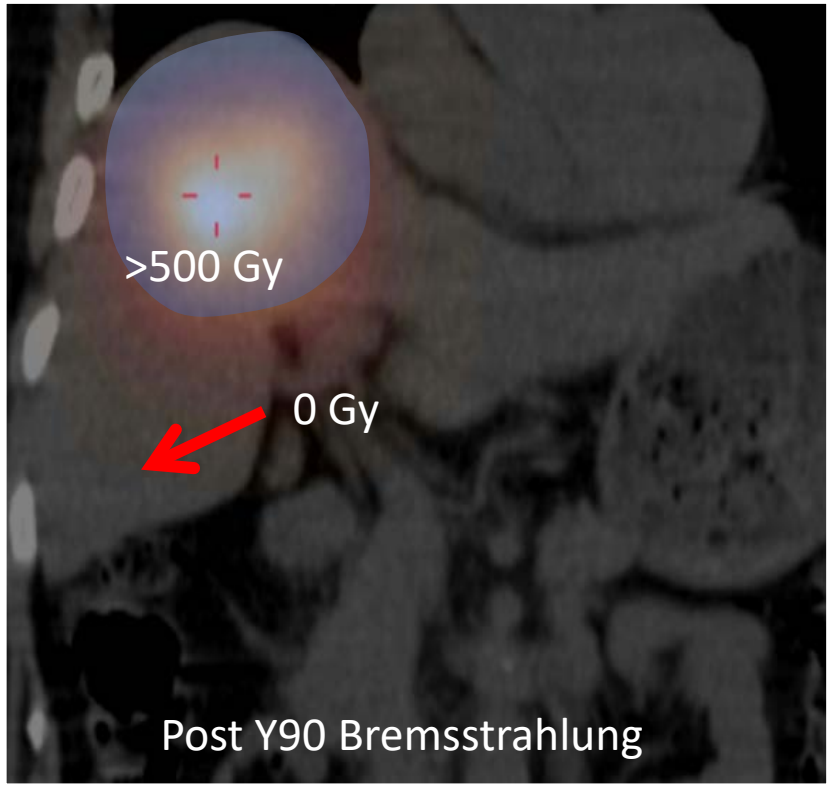
- Large systematic reviews / meta-analyses have demonstrated a benefit from TACE
  - Large contemporary series show median OS of 2.5-3.0 years with catheter-based therapy

(Bruix J et al. Chemoembolization for hepatocellular carcinoma. *Gastroenterology*. November, 2004).

- No definitive advantage of TACE over bland embolization.
- Is TACE/TAE superior to systemic therapy in BCLC B patients?
- How often should TACE/TAE be performed?
- When to move on to systemic therapy?

Y90 Radioembolization: Evolving Segmental Approaches for HCC

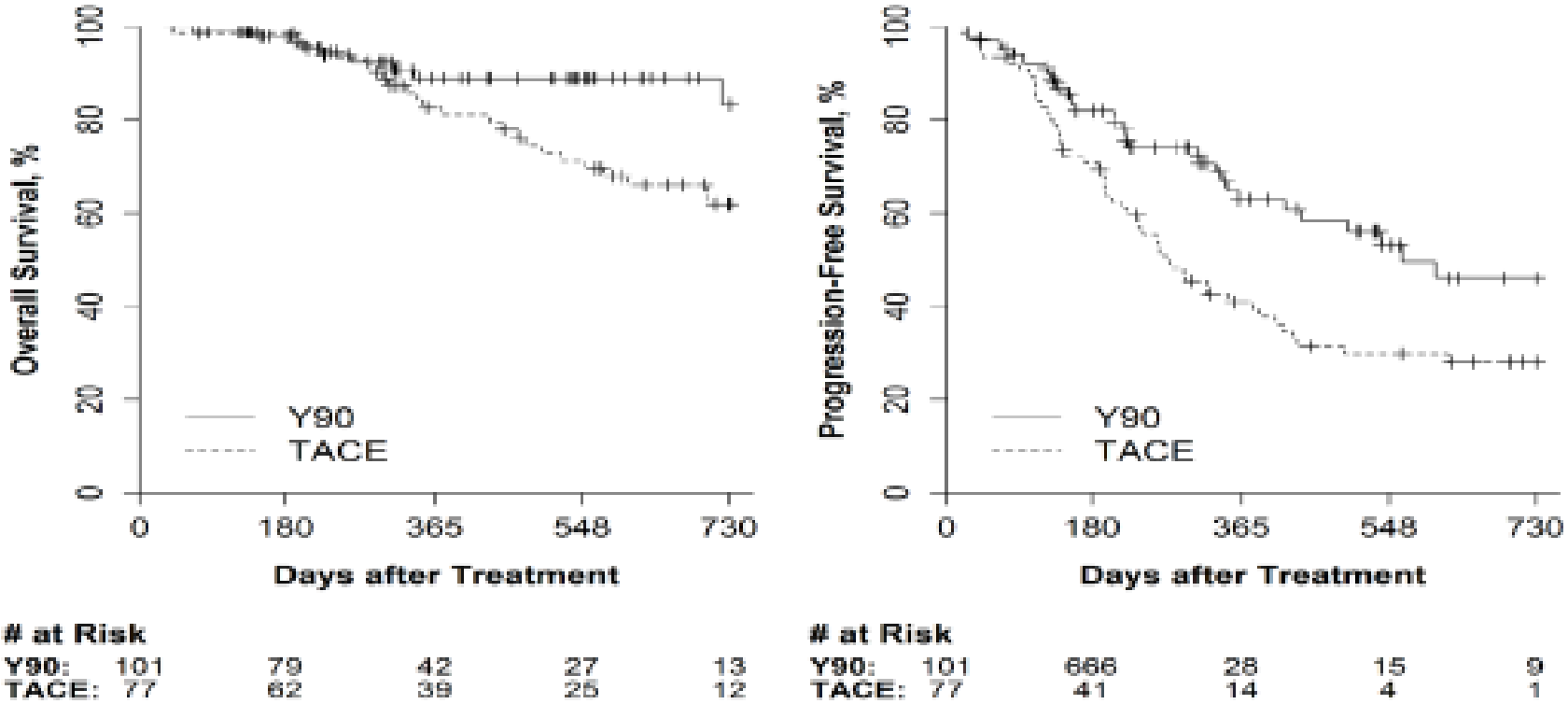




Improved targeting
Higher intra-tumoral radiation doses → Improved response?
Decreased collateral damage

High dose localized radioembolization: (radiation segmentectomy)

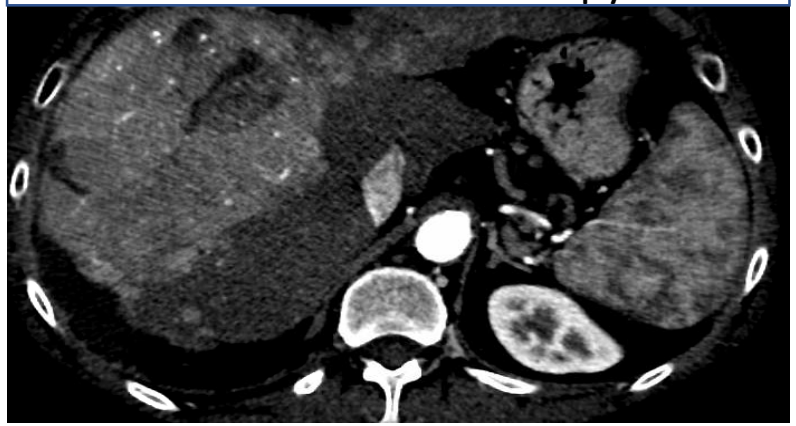
Figure 2. Kaplan-Meier curves of overall survival and progression-free survival.

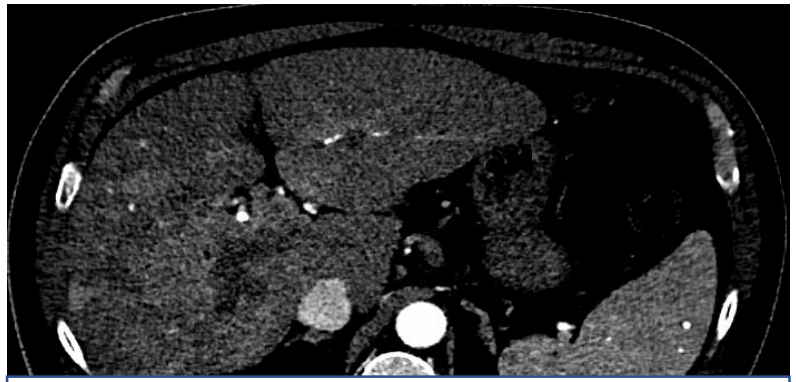


Padia et al. ASCO 2016 Poster, JCO 34, (suppl. Abstract 4084)

Background:
Systemic Therapy for Advanced Hepatocellular Carcinoma

BCLC B (ineligible/refractory to catheter-based therapy





BCLC C (Vascular Invasion/Metastatic Disease)

FDA APPROVED AGENTS

1st Line	2nd Line	3rd Line
Sorafenib SHARP/ASIA PACIFIC	Cabozantinib CELESTIAL TRIAL	Cabozantinib CELESTIAL TRIAL
Lenvatinib REFLECT TRIAL	Regorafenib (sorafenib tolerant) RESOURCE	
Atezolizumab + Bevacizumab IMBRAVE150 TRIAL	Ramucirumab (AFP>400) REACH-2	
	Nivolumab* CHECKMATE 040	
	Pembrolizumab* KEYNOTE 224	
	Nivolumab + Ipilimumab CHECKMATE 040	

*Accelerated Approval based upon ORR and DOR

Advanced/Metastatic Hepatocellular Carcinoma: SHARP Trial

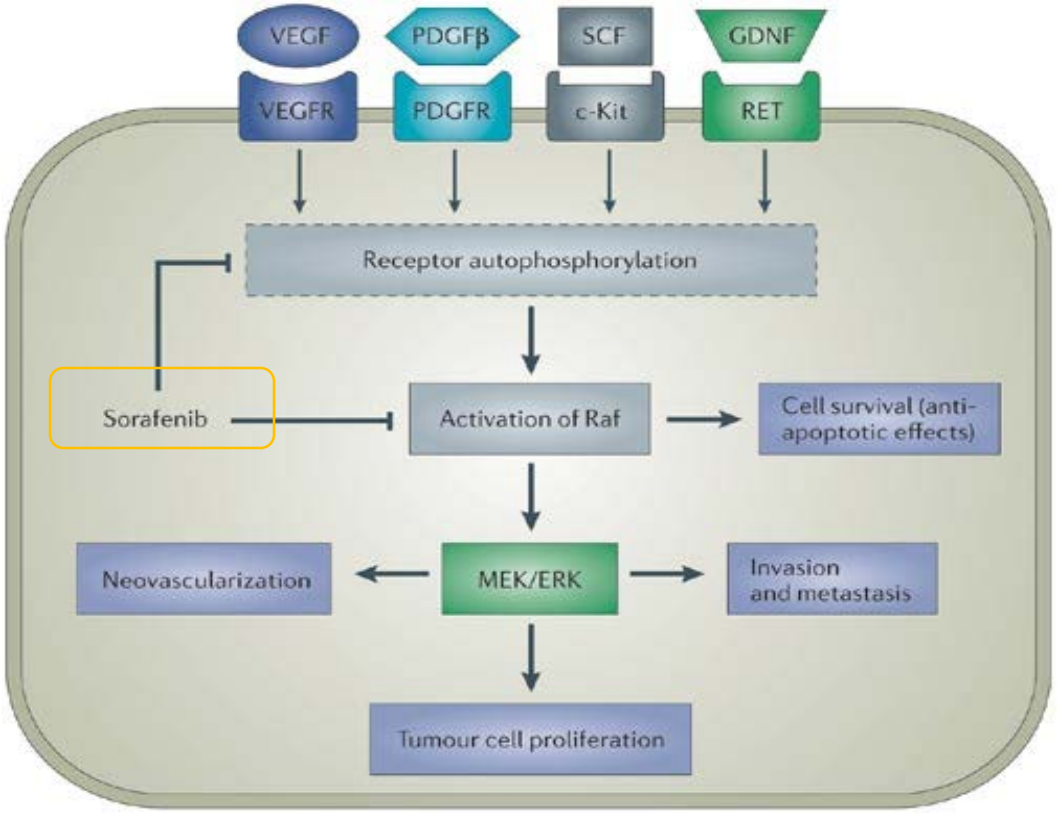
ORIGINAL ARTICLE

Sorafenib in Advanced Hepatocellular Carcinoma

Josep M. Llovet, M.D., Sergio Ricci, M.D., Vincenzo Mazzaferro, M.D., Philip Hilgard, M.D., Edward Gane, M.D., Jean-Frédéric Blanc, M.D., Andre Cosme de Oliveira, M.D., Armando Santoro, M.D., Jean-Luc Raoul, M.D., Alejandro Forner, M.D., Myron Schwartz, M.D., Camillo Porta, M.D., Stefan Zeuzem, M.D., Luigi Bolondi, M.D., Tim F. Greten, M.D., Peter R. Galle, M.D., Jean-François Seitz, M.D., Ivan Borbath, M.D., Dieter Häussinger, M.D., Tom Giannaris, B.Sc., Minghua Shan, Ph.D., Marius Moscovici, M.D., Dimitris Voliotis, M.D., and Jordi Bruix, M.D., for the SHARP Investigators Study Group*

Sorafenib approved by the FDA for advanced HCC in November 2007

Advanced/Metastatic HCC: Sorafenib



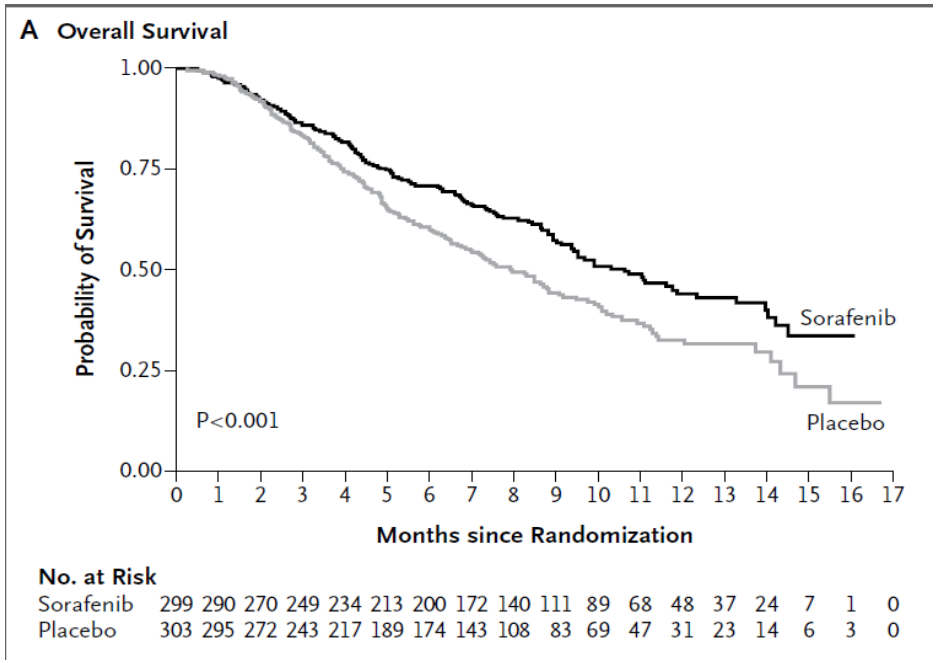
Wilhelm et al. Discovery and development of sorafenib: a multikinase inhibitor for treating cancer. *Nature Reviews Drug Discovery*. October, 2006.

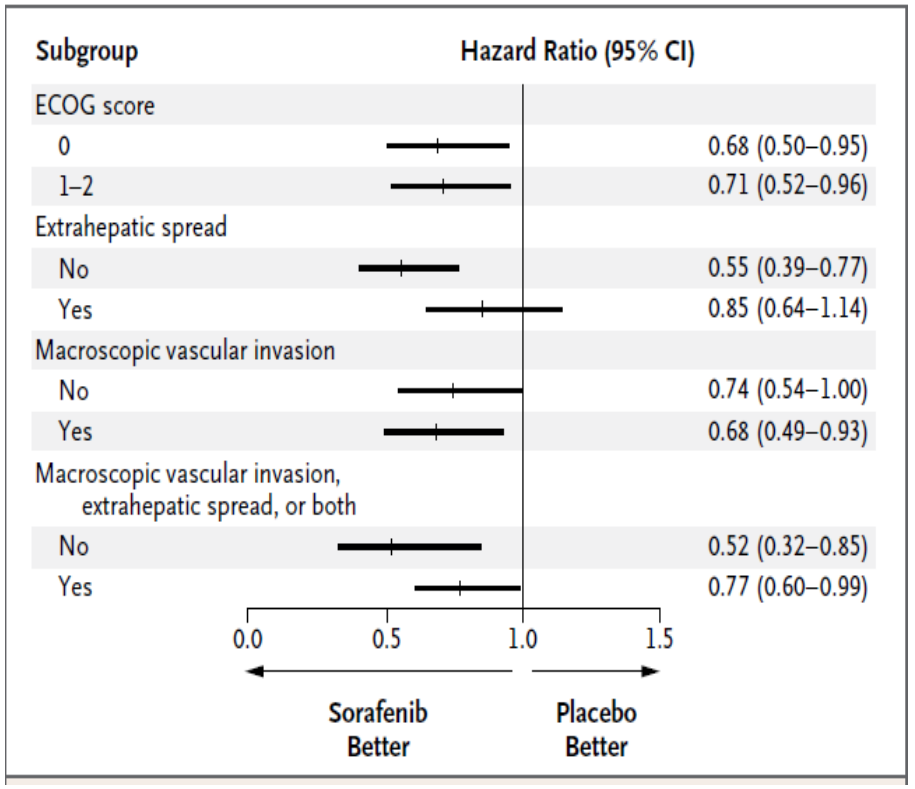
SHARP: Patient Characteristics

	Sorafenib (n=299)	Placebo (n=303)
Age	65	66
Male/Female	87/13	87/13
Region (Europe/N. America/Other %	88/9/3	87/10/3
Etiology (HCV/HBV)	29/19	27/18
(Alcohol/Other)	26/26	26/29
Child Pugh (A/B %)	95/5	98/2
Prior Therapies:		
Surgical resection	19%	21%
Loco-regional therapies	39%	41%
ECOG PS:		
O	54%	54%
1	38%	39%
2	8%	7%
Vascular Invasion/Extrahepatic spread		
Present	70%	70%
Absent	30%	30%

Llovet ASCO 2007

SHARP Trial: Results





Median survival: 10.7 vs. 7.9 months
(HR 0.69 (95% CI 0.55, 0.87) p<0.001

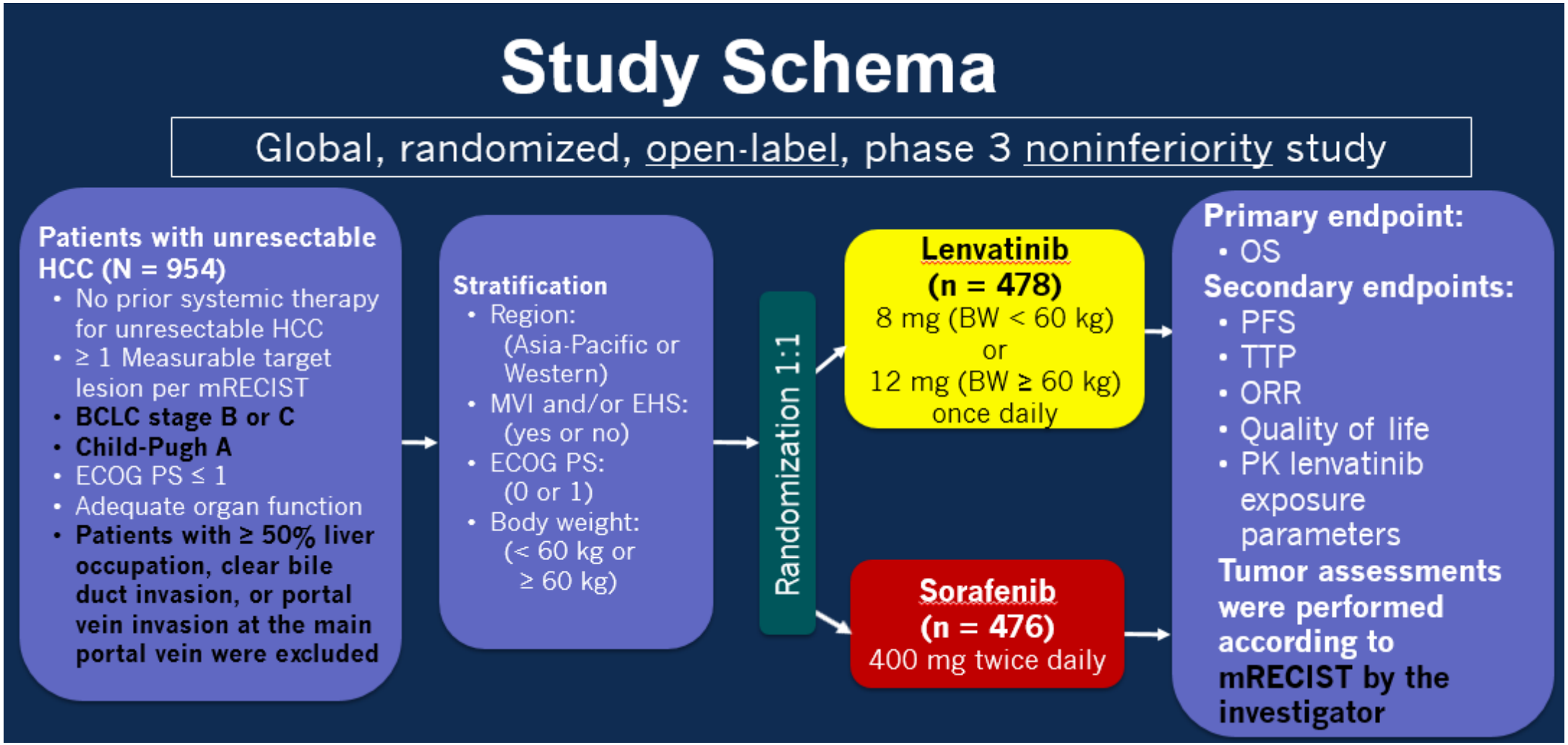
Disease control rate: 43% vs. 32%
(p=0.002) – largely stable disease

SHARP Trial: Safety

- Overall incidence of any grade adverse event: 80% (sorafenib) vs. 52% (placebo)
- Grade 3-4 toxicities: Hand-foot syndrome, diarrhea.
- Of note, prophylactic urea-based lotions decrease severity of hand-foot syndrome

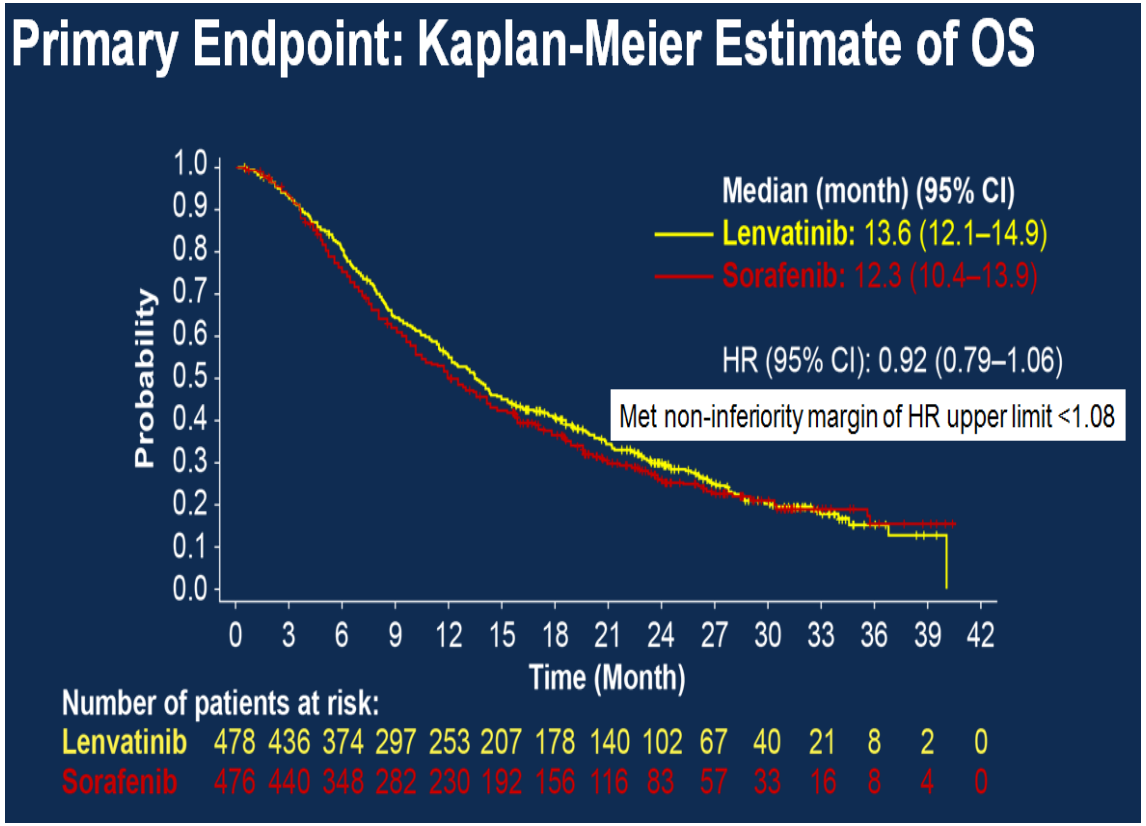
Benomar, et al. *Dermatology online journal*. Nov 2008

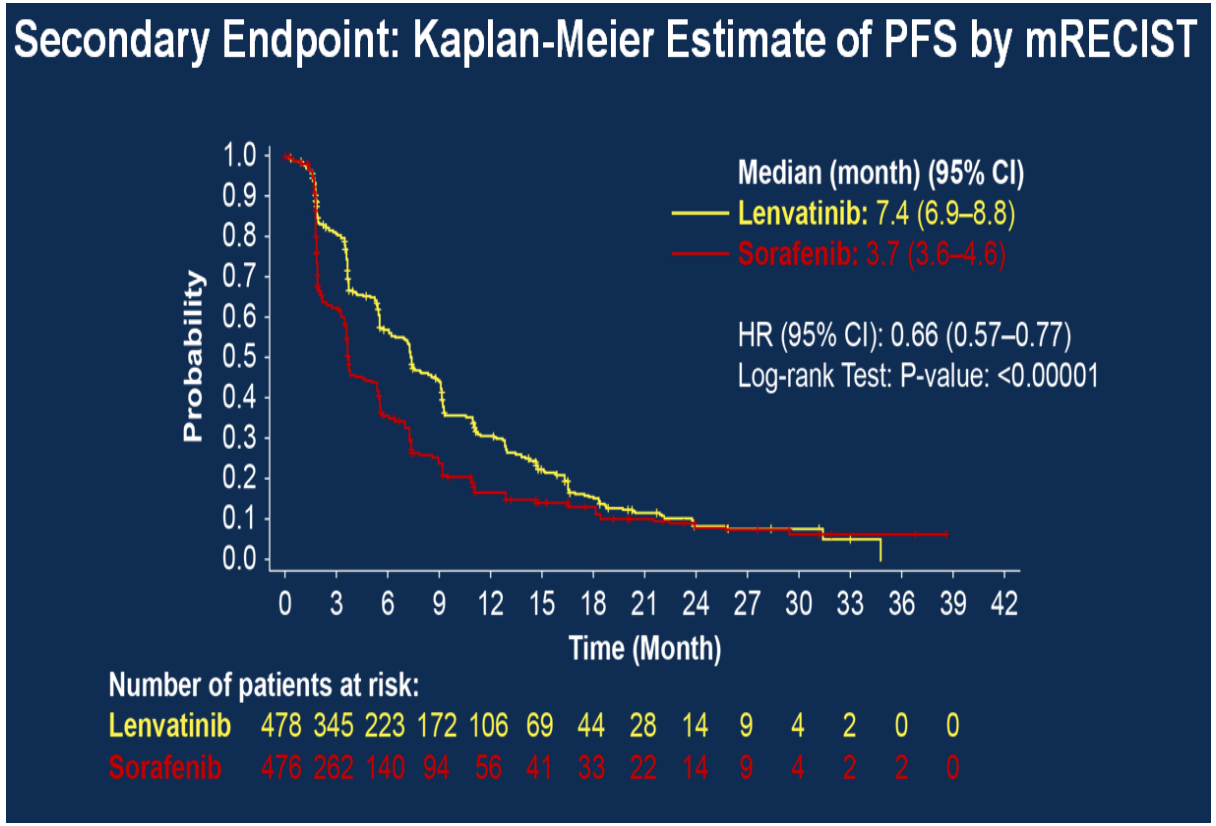
Lenvatinib: First-Line HCC Trial



Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial [published online February 9, 2018]. *Lancet.* doi:10.1016/S0140-6736(18)30207-1.

Lenvatinib First-Line HCC Trial





Lenvatinib non-inferior to sorafenib as 1st line therapy

- Multi-TKI: anti VEGF, FGFR, PDGFRα, RET, KIT
- FDA approved August 2018 for Child-Pugh A patients
- ORR: 24% vs 9% by mRECIST

Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial [published online February 9, 2018]. *Lancet.*

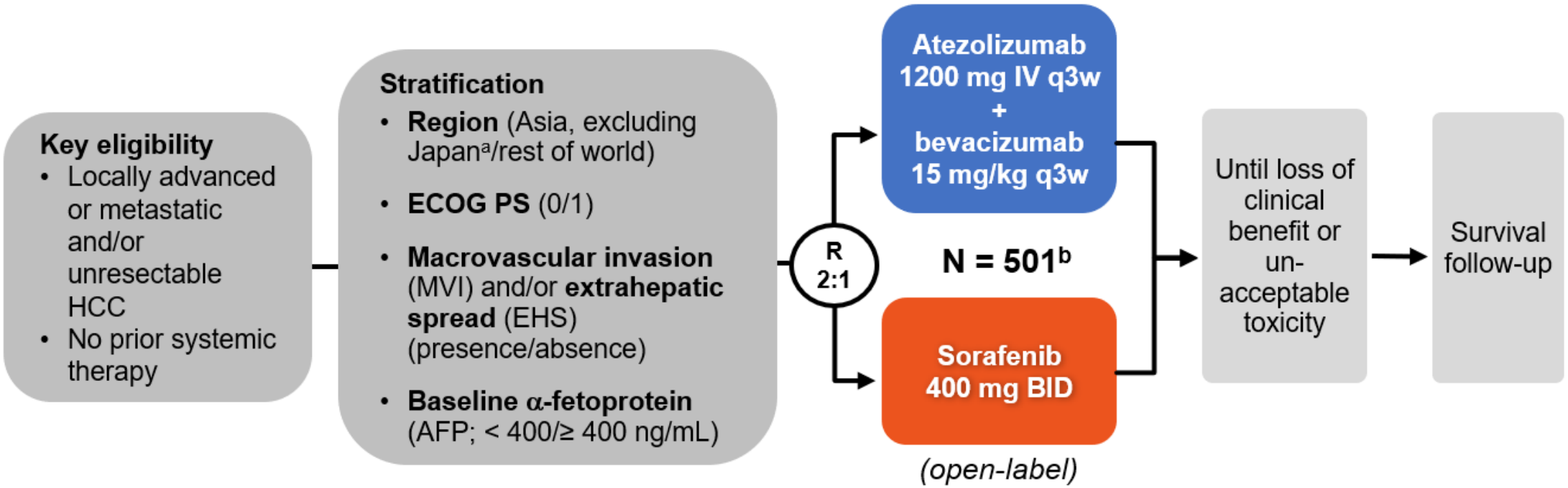
Lenvatinib: First-Line HCC Trial

Adverse event, n (%)	Lenvatinib (n = 476)		Sorafenib (n = 475)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Hypertension	201 (42)	111 (23)	144 (30)	68 (14)
Diarrhea	184 (39)	20 (4)	220 (46)	20 (4)
Decreased appetite	162 (34)	22 (5)	127 (27)	6 (1)
Decreased weight	147 (31)	36 (8)	106 (22)	14 (3)
Fatigue	141 (30)	18 (4)	119 (25)	17 (4)
Palmar-plantar erythrodysesthesia	128 (27)	14 (3)	249 (52)	54 (11)
Proteinuria	117 (25)	27 (6)	54 (11)	8 (2)
Dysphonia	113 (24)	1 (0)	57 (12)	0 (0)
Nausea	93 (20)	4 (1)	68 (14)	4 (1)
Decreased platelet count	87 (18)	26 (6)	58 (12)	16 (3)
Abdominal pain	81 (17)	8 (2)	87 (18)	13 (3)
Hypothyroidism	78 (16)	0 (0)	8 (2)	0 (0)
Vomiting	77 (16)	6 (1)	36 (8)	5 (1)
Constipation	76 (16)	3 (1)	52 (11)	0 (0)
Elevated aspartate aminotransferase	65 (14)	24 (5)	80 (17)	38 (8)
Rash	46 (10)	0 (0)	76 (16)	2 (0)
Alopecia	14 (3)	0 (N/A)	119 (25)	0 (N/A)

Kudo M, Finn RS, Qin S, et al. Lenvatinib versus sorafenib in first-line treatment of patients with unresectable hepatocellular carcinoma: a randomised phase 3 non-inferiority trial [published online February 9, 2018]. *Lancet.* doi:10.1016/S0140-6736(18)30207-1.

Practice Changing Trial: IMBRAVE 150 Trial

Atezolizumab + Bevacizumab for 1st Line HCC



Co-primary endpoints
- OS
- IRF-assessed PFS per RECIST 1.1

Key secondary endpoints (in testing strategy)
- IRF-assessed ORR per RECIST 1.1
- IRF-assessed ORR per HCC mRECIST

Slide modified from Cheng, AL et al. ESMO ASIA 2019 Oral Presentation

Key Inclusion/Exclusion Criteria

Notable Inclusion Criteria

- Child Pugh A hepatic function
- Advanced HCC (not a candidate for surgery or transplant)
- ECOG 0-1
- Extensive portal vein and hepatic venous invasion allowed
- AST/ALT < 5x ULN
- Platelet count >75,000

Notable Exclusion Criteria

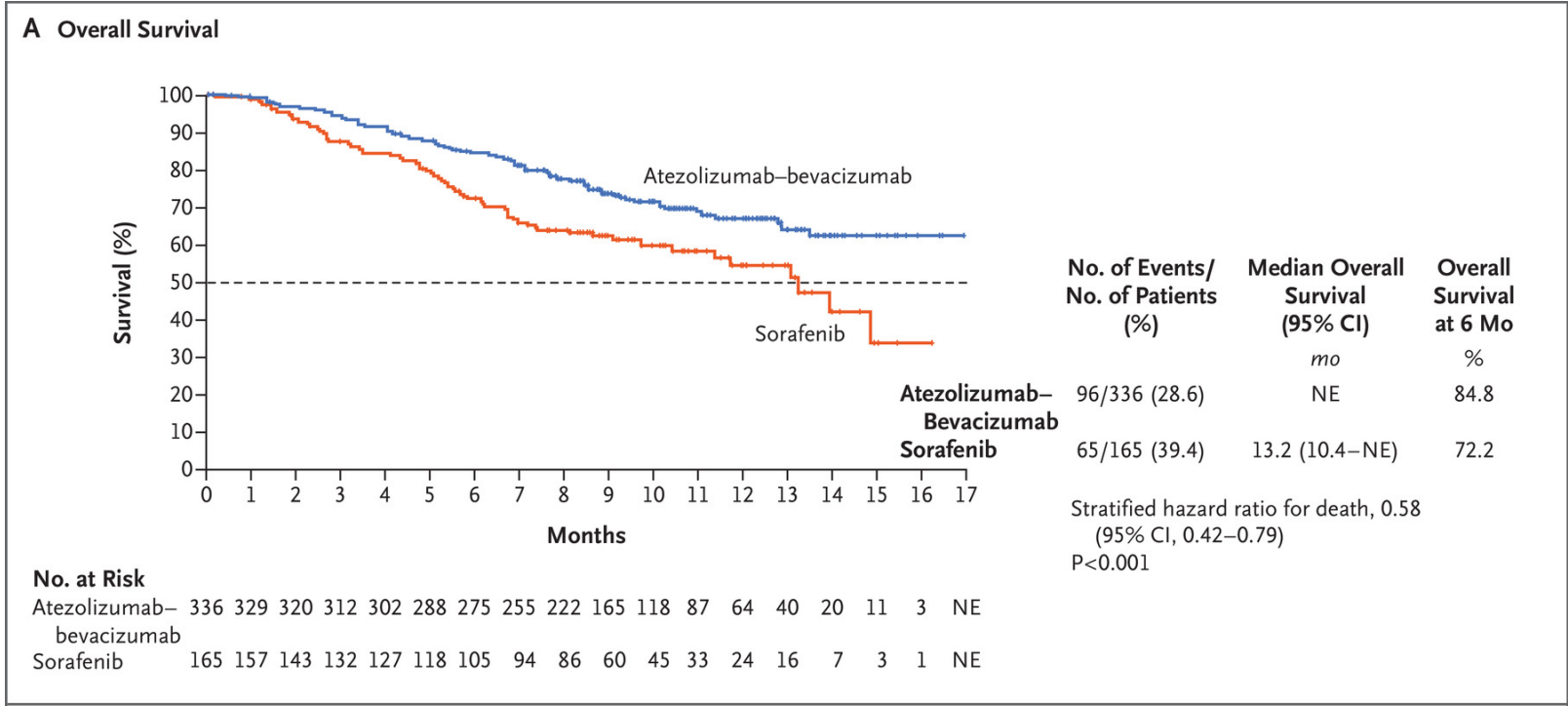
- Untreated/incompletely treated esophageal/gastric varices
- History of autoimmune disease
- Hepatitis B/C co-infection
- Anticoagulation or antiplatelet therapy (ASA 81 mg allowed)
- Uncontrolled hypertension (>150/100)

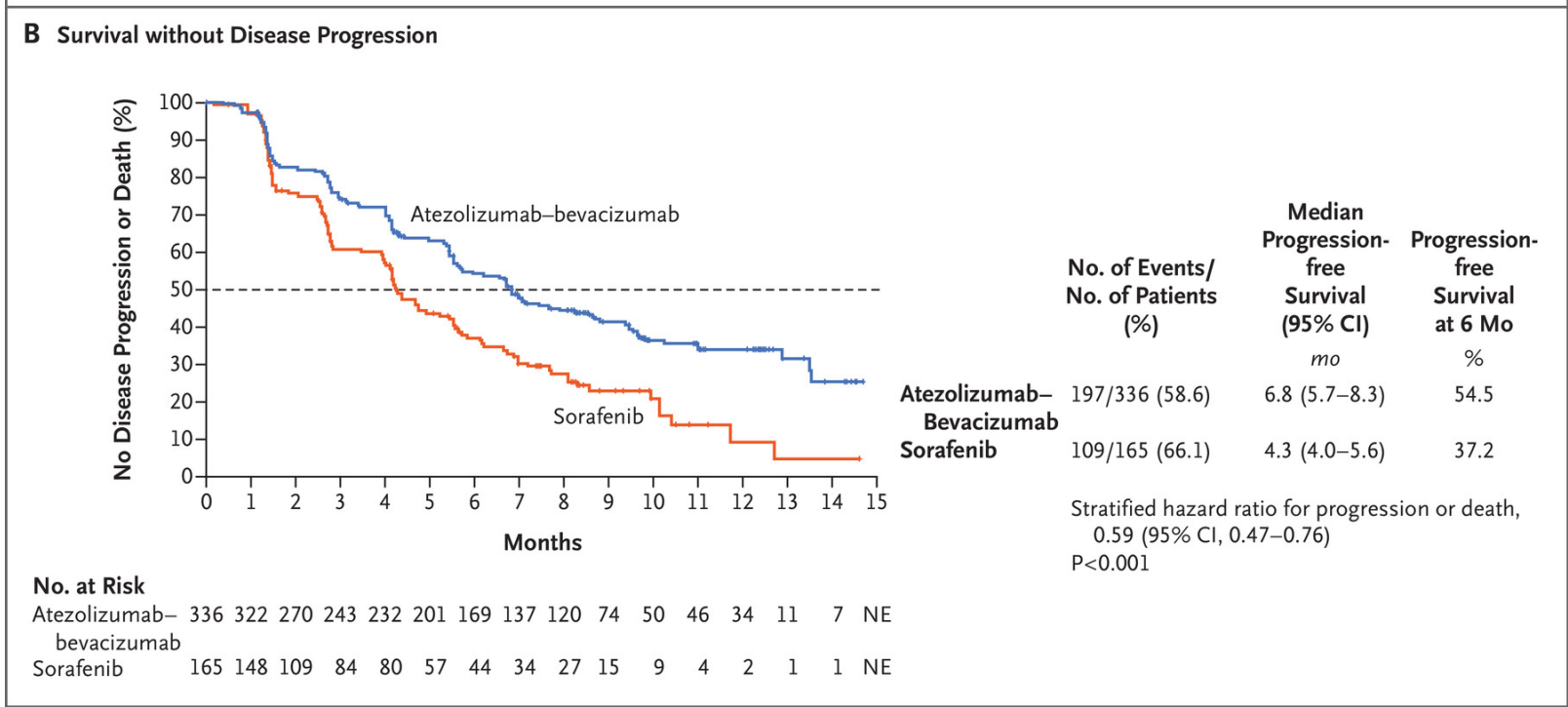
IMBRAVE 150 RESULTS

Comments:

- Trial stopped at first interim analysis due to clear efficacy
- Met both co-primary endpoints
  - **OS HR 0.58 p<.001**
  - **PFS HR .59 p<.001**
- mOS not yet reached, longer follow-up needed
- ORR 27.3% vs 11.9%
- Favorable mPFS of 6.8 months

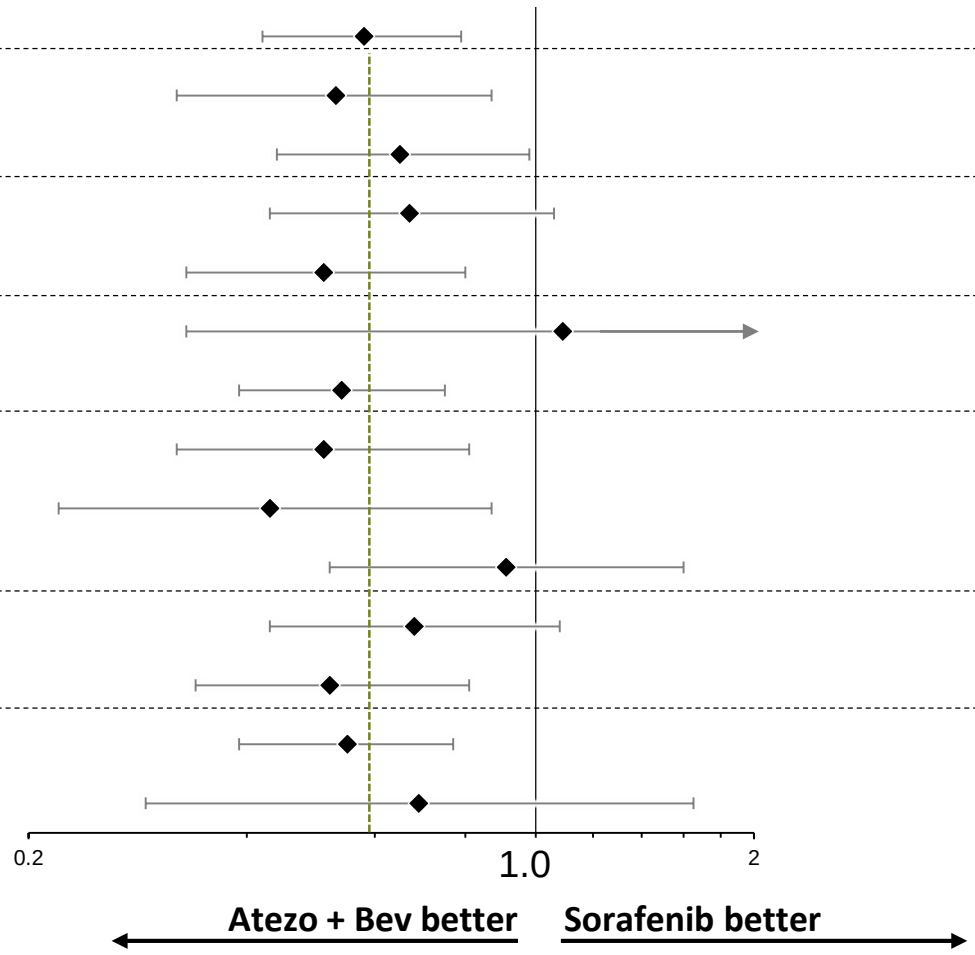
Finn et al. NEJM 2020 382:1894-1905





OS subgroups

Characteristic (n)	Atezo + Bev mOS, mo (n = 336)	Sorafenib mOS, mo (n = 165)	HR (95% CI)[a]
All patients (501)	NE	13.2	0.58 (0.42, 0.79)
Asia (excluding Japan[b]) (201)	NE	13.1	0.53 (0.32, 0.87)
Rest of world (300)	NE	13.2	0.65 (0.44, 0.98)
ECOG PS 0 (312)	NE	13.9	0.67 (0.43, 1.06)
ECOG PS 1 (189)	NE	7.4	0.51 (0.33, 0.80)
BCLC stage B[c] (78)	NE	14.9	1.09 (0.33, 3.53)
BCLC stage C[c] (409)	NE	11.4	0.54 (0.39, 0.75)
HBV HCC (240)	NE	13.9	0.51 (0.32, 0.81)
HCV HCC (108)	NE	13.1	0.43 (0.22, 0.87)
Non-viral HCC (153)	NE	14.9	0.91 (0.52, 1.60)
AFP ≥ 400 ng/mL (187)	12.8	9.1	0.68 (0.43, 1.08)
AFP < 400 ng/mL (314)	NE	13.9	0.52 (0.34, 0.81)
EHS and/or MVI (378)	NE	10.4	0.55 (0.39, 0.77)
No EHS and MVI (123)	NE	14.9	0.69 (0.29, 1.65)



NE, not estimable.
[a] Unstratified HR shown for all characteristics except for "All patients," where stratified HR is shown. [b] Japan is included in rest of world.
[c] BCLC stage A not shown, as there were only 14 patients; thus, estimation is not meaningful.
Data cutoff, 29 Aug 2019; median survival follow-up, 8.6 mo.

Slide derived from Cheng, AL et al. ESMO ASIA 2019 Oral Presentation

IMBRAVE 150 - AEs

Comments:

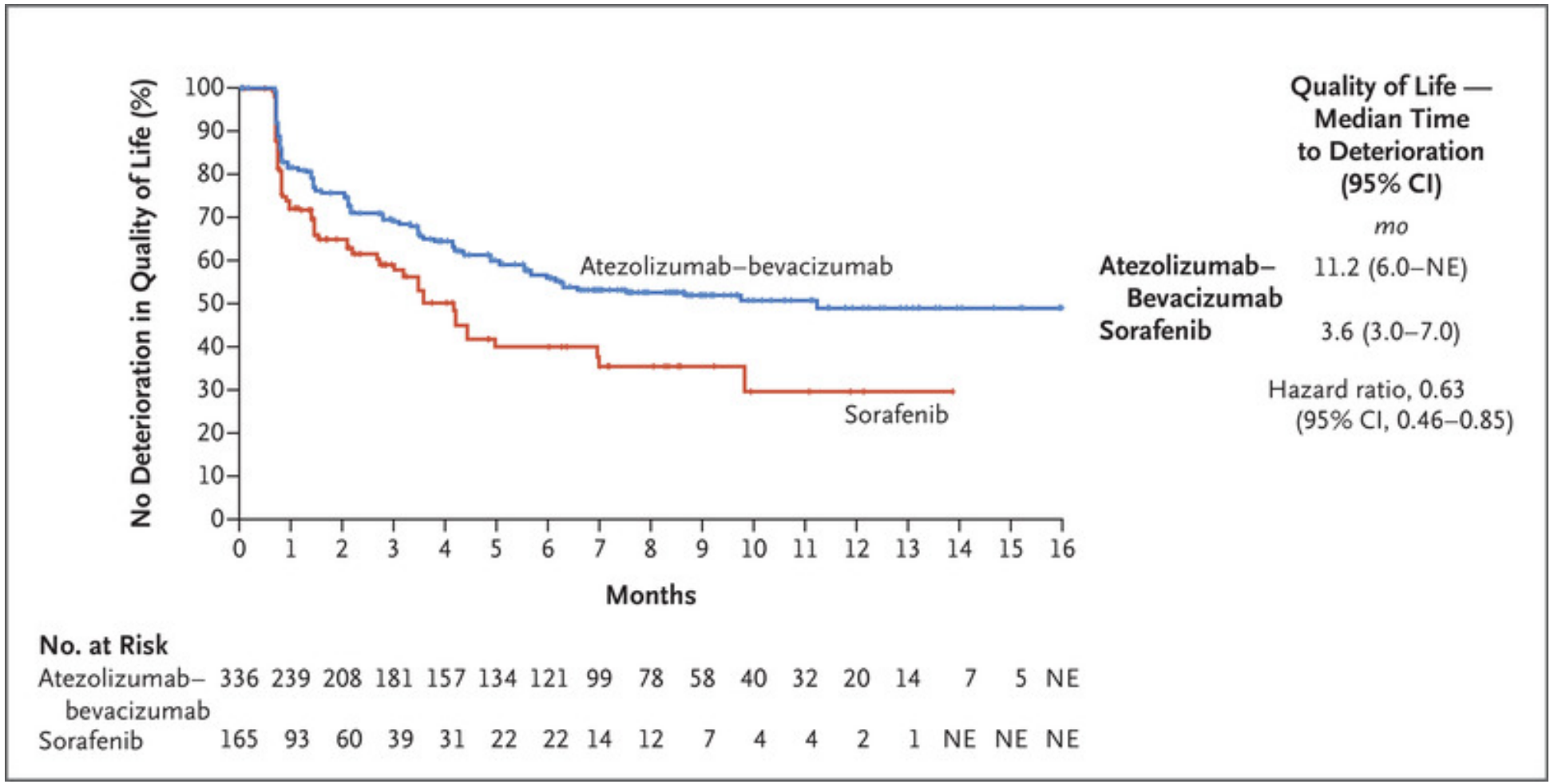
- Serious Adverse Events increased in Atezo/Bev arm slightly (38% vs. 30.8%)
    - No one clear toxicity stands out
    - Less PPE, severe diarrhea, asthenia noted
- Gastrointestinal (usually variceal) bleeding rates consistent with known risk
    - 7% vs 4.5% overall
    - Fatal bleeding/Perforation Atezo/Bev (n=6) vs sorafenib (n=1)

Finn et al. NEJM 2020 382:1894-1905

Table 4. Adverse Events with an Incidence of More Than 10% in Either Group.

Event	Atezolizumab–Bevacizumab (N=329)		Sorafenib (N=156)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number (percent)			
Hypertension	98 (29.8)	50 (15.2)	38 (24.4)	19 (12.2)
Fatigue	67 (20.4)	8 (2.4)	29 (18.6)	5 (3.2)
Proteinuria	66 (20.1)	10 (3.0)	11 (7.1)	1 (0.6)
Aspartate aminotransferase increase	64 (19.5)	23 (7.0)	26 (16.7)	8 (5.1)
Pruritus	64 (19.5)	0	15 (9.6)	0
Diarrhea	62 (18.8)	6 (1.8)	77 (49.4)	8 (5.1)
Decreased appetite	58 (17.6)	4 (1.2)	38 (24.4)	6 (3.8)
Pyrexia	59 (17.9)	4 (1.2)	15 (9.6)	2 (1.3)
Alanine aminotransferase increase	46 (14.0)	12 (3.6)	14 (9.0)	2 (1.3)
Constipation	44 (13.4)	0	22 (14.1)	0
Blood bilirubin increase	43 (13.1)	8 (2.4)	22 (14.1)	10 (6.4)
Rash	41 (12.5)	0	27 (17.3)	4 (2.6)
Abdominal pain	40 (12.2)	4 (1.2)	27 (17.3)	4 (2.6)
Nausea	40 (12.2)	1 (0.3)	25 (16.0)	1 (0.6)
Cough	39 (11.9)	0	15 (9.6)	1 (0.6)
Infusion-related reaction	37 (11.2)	8 (2.4)	0	0
Weight decrease	37 (11.2)	0	15 (9.6)	1 (0.6)
Platelet count decrease	35 (10.6)	11 (3.3)	18 (11.5)	2 (1.3)
Epistaxis	34 (10.3)	0	7 (4.5)	1 (0.6)
Asthenia	22 (6.7)	1 (0.3)	21 (13.5)	4 (2.6)
Alopecia	4 (1.2)	0	22 (14.1)	0
Palmar–plantar erythrodysesthesia syndrome	3 (0.9)	0	75 (48.1)	13 (8.3)

IMBRAVE 150 – Quality of Life Assessments



Finn et al. NEJM 2020 382:1894-1905

SUMMARY: FIRST-LINE SYSTEMIC THERAPY FOR HCC

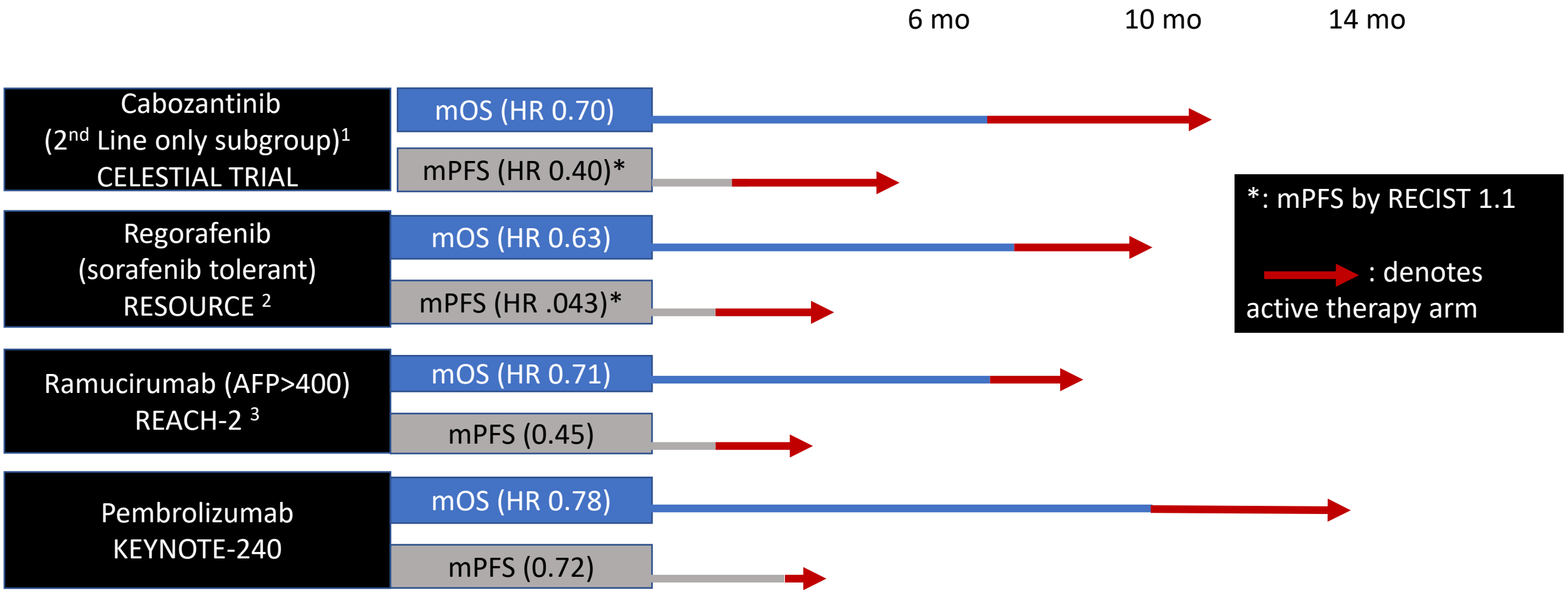
- Atezolizumab and Bevacizumab represents the favored 1st line therapy for advanced HCC for eligible patients
    - **Patients require EGD for variceal screening and treatment as indicated prior to initiation of therapy**

- In patients with advanced, unresectable HCC with Child-Pugh A cirrhosis, treatment with sorafenib resulted in a 3-month survival benefit compared to placebo.

- Lenvatinib demonstrated non-inferiority to sorafenib as 1st line therapy, with superior response rates, TTP and PFS.

- The benefit/safety of current 1st line therapy for routine use in Child-Pugh B cirrhosis is unclear.

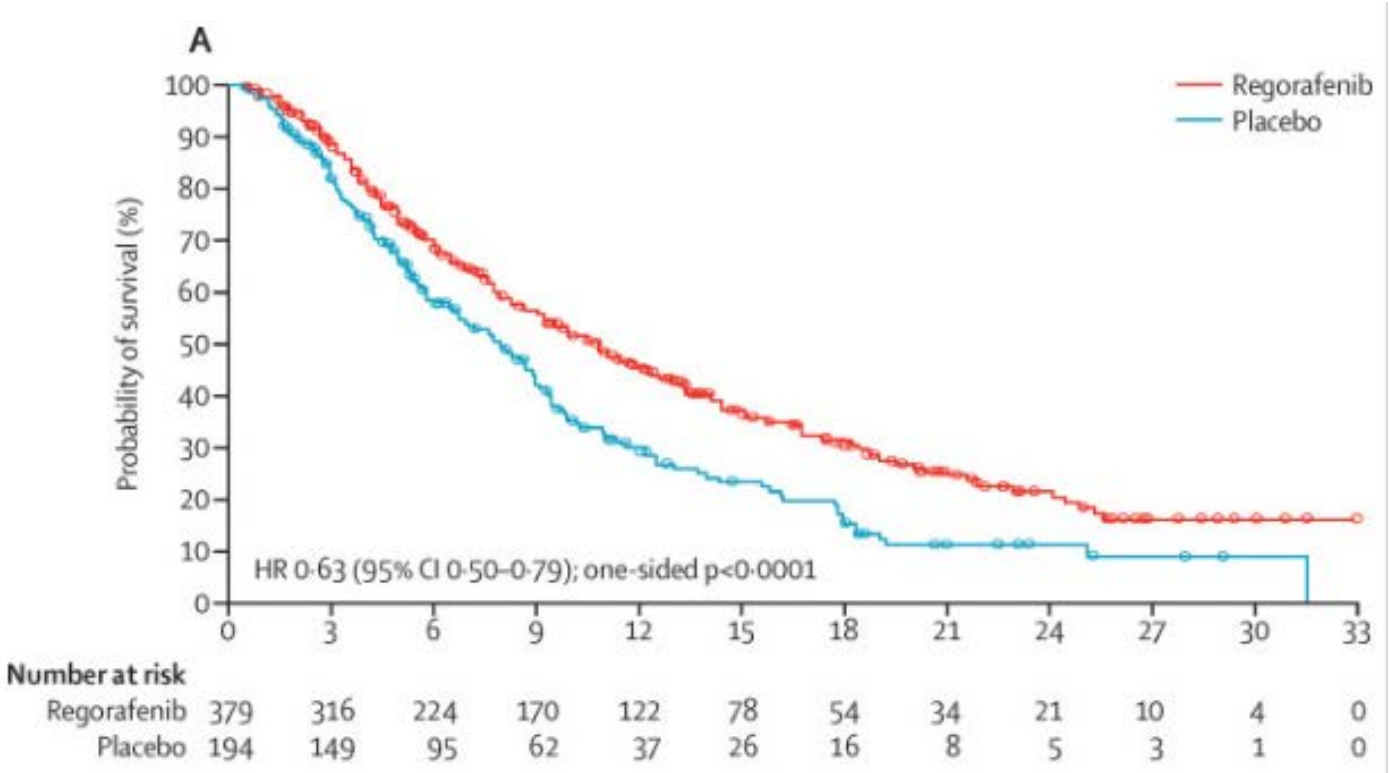
Phase III HCC Trials: Second-Line Therapy Outcomes



1. Kelley et al. ASCO 2018 Abstract 4088
2. Bruix et al. Lancet 2017 389(10064):56-66
3. Zhu et al. Lancet Oncology 2019 20(2):282-292

Regorafenib vs. Placebo (2nd line) Positive Phase III Trial Results

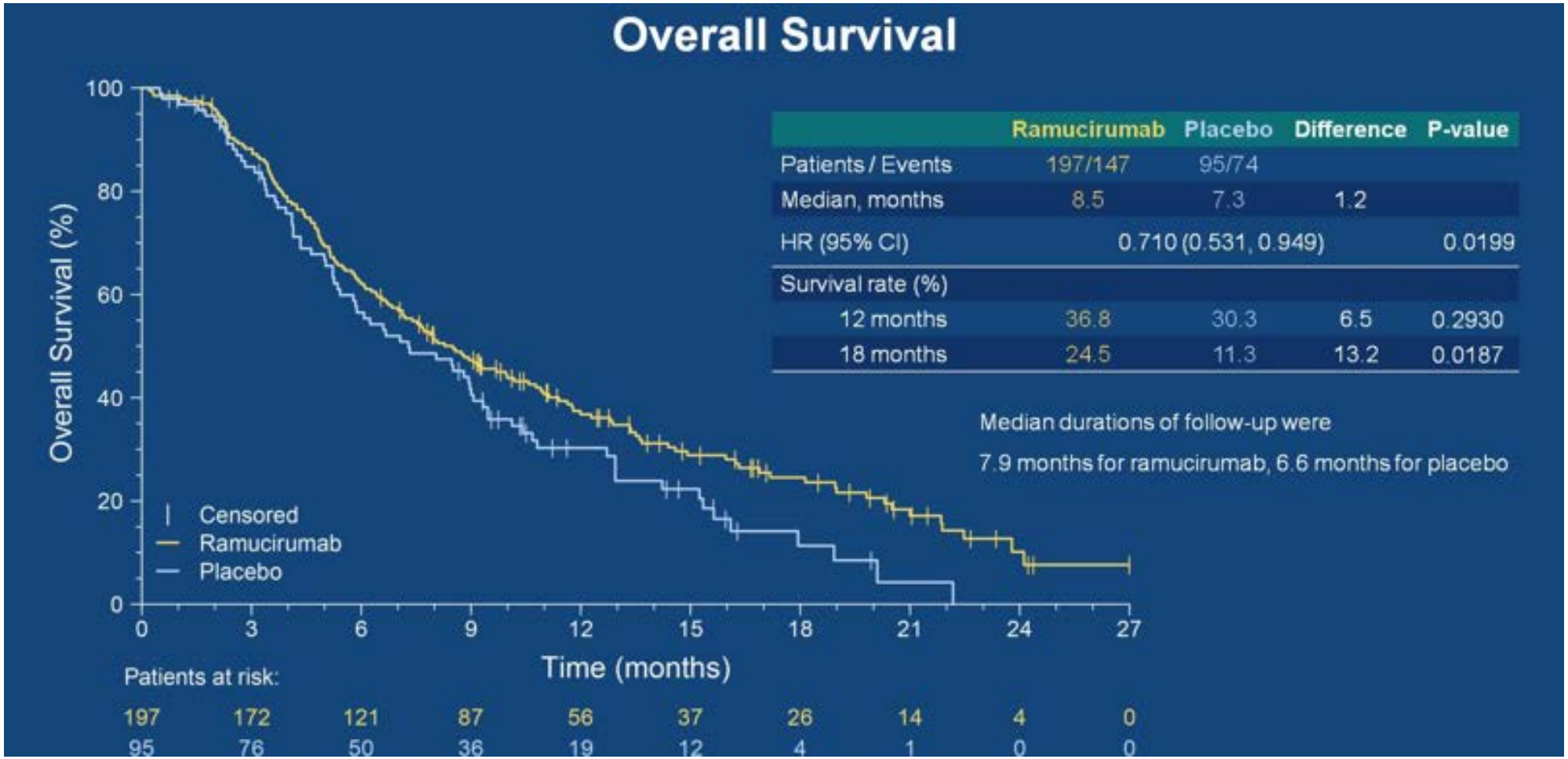
- Multi-TKI with broad activity
  - VEGFR1-3, TIE2
  - FGFR1, PDGFR-B, KIT, RET
  - C-RAF, B-RAF
- Key Patient Characteristics
  - Child Pugh A, ECOG 0-1
  - **Tolerant but progressing on sorafenib**
- Design
  - 2:1 randomized placebo-controlled trial
  - Regorafenib 160 mg days 1-21 monthly
  - Primary endpoint: improved OS
- Outcome
  - **mOS 10.6 vs 7.8 months (HR .63, p<.0001)**
  - Grade >3 Toxicity compared to placebo:
    - 10% increased HTN
    - 12% hand-foot syndrome
    - 4% fatigue
    - 3% diarrhea



FDA approved for second line HCC

Bruix J et al. Lancet Jan 2017. 389(10064):56-66

Ramucirumab as 2L therapy for HCC (in patients with AFP >400)



	Ramucirumab	Placebo	Difference	P-value
Patients / Events	197/147	95/74		
Median, months	8.5	7.3	1.2	
HR (95% CI)	0.710 (0.531, 0.949)			0.0199
Survival rate (%)				
12 months	36.8	30.3	6.5	0.2930
18 months	24.5	11.3	13.2	0.0187

FDA approved as second line therapy if AFP > 400

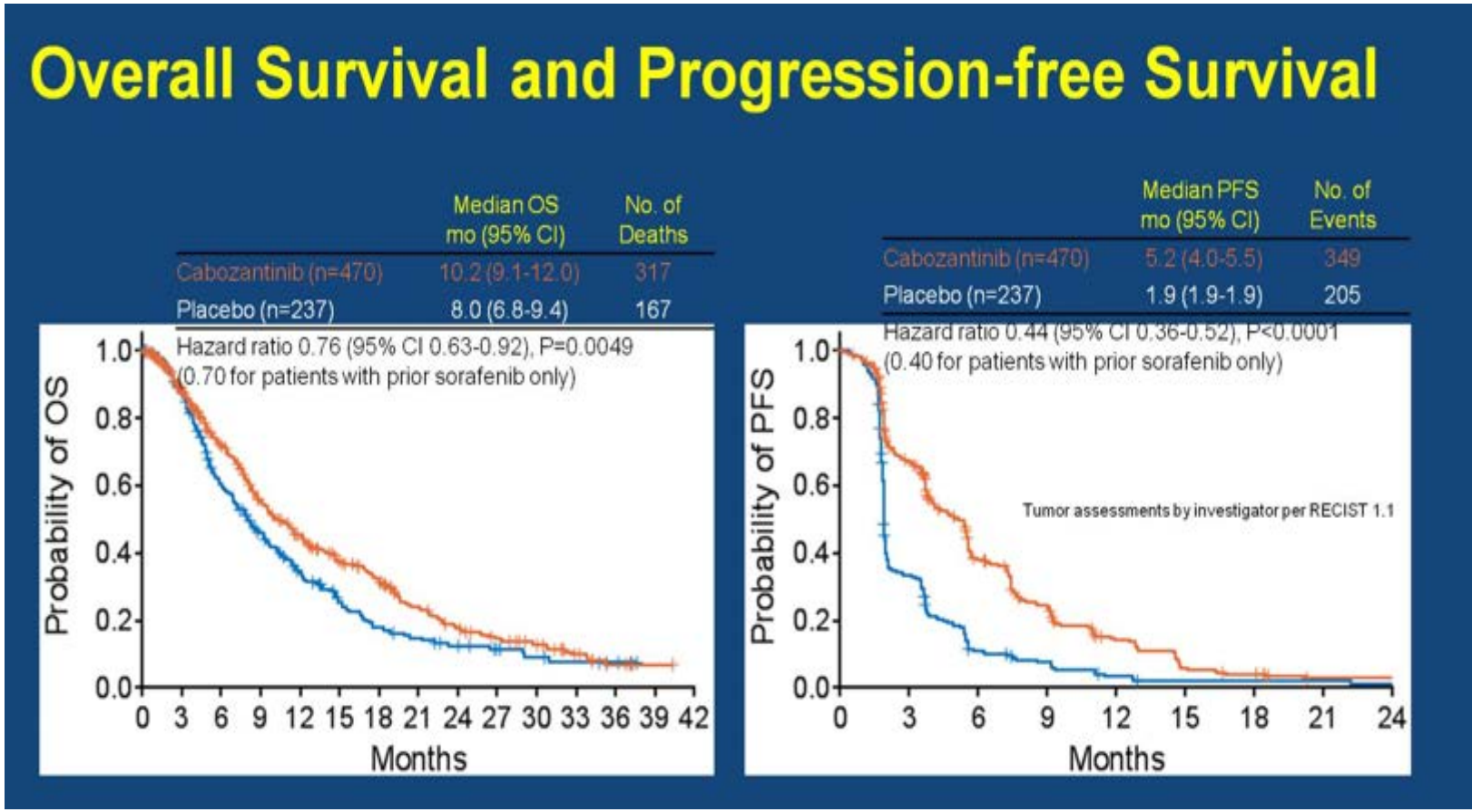
Main Grade 3-4 Toxicities: HTN (12%), Ascites (4%), encephalopathy (3%)

Zhu et al. REACH-2 Trial Oral Presentation, ASCO 2018 Annual Meeting

Cabozantinib in Refractory HCC
Positive Phase III Data in 2nd / 3rd line

Randomized Phase III trial of cabozantinib vs. placebo
→ sorafenib refractory / intolerant patients with HCC

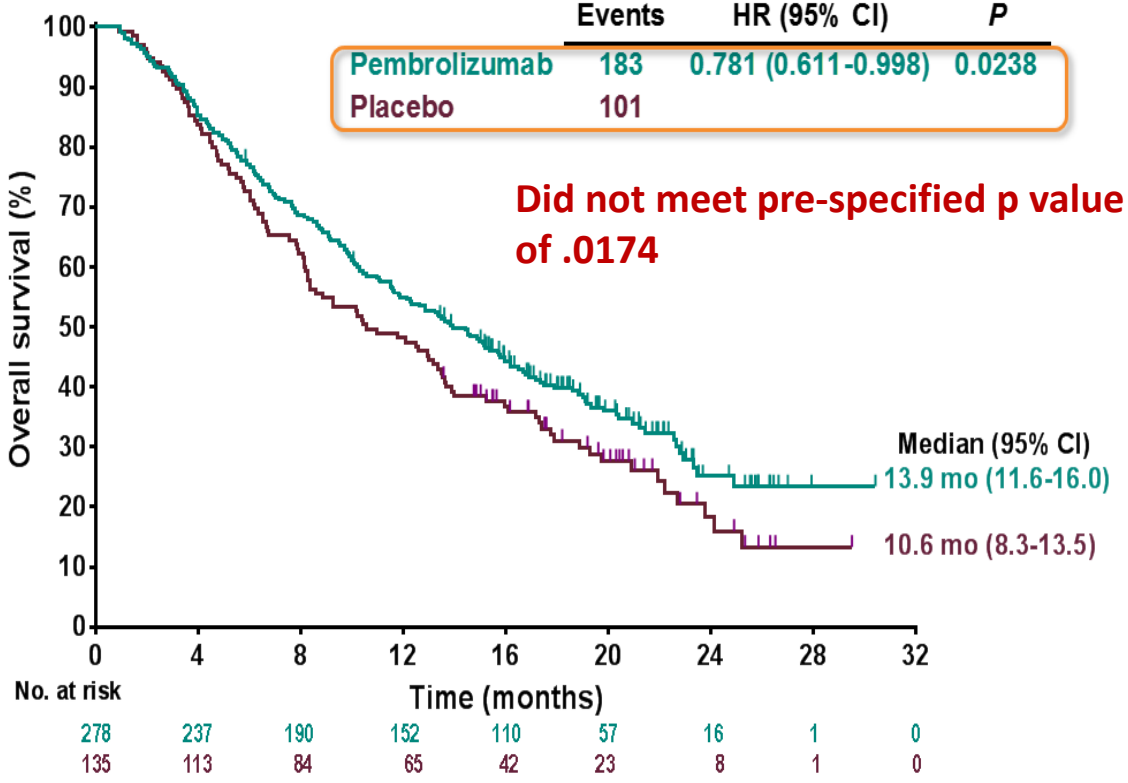
- 707 patients randomized 2:1 against placebo
- 2nd /3rd line therapy; Child-Pugh A
- mOS 10.2 vs 8.0 months (HR .76, p=.005)
- Not selected based upon c-met status
- FDA approved



Abou-Alfa GK et al. GI ASCO 2018 oral presentation; JCO 36:4s Abstr 207

Recent results: KEYNOTE-240 Trial (2nd Line Pembrolizumab vs. Placebo)

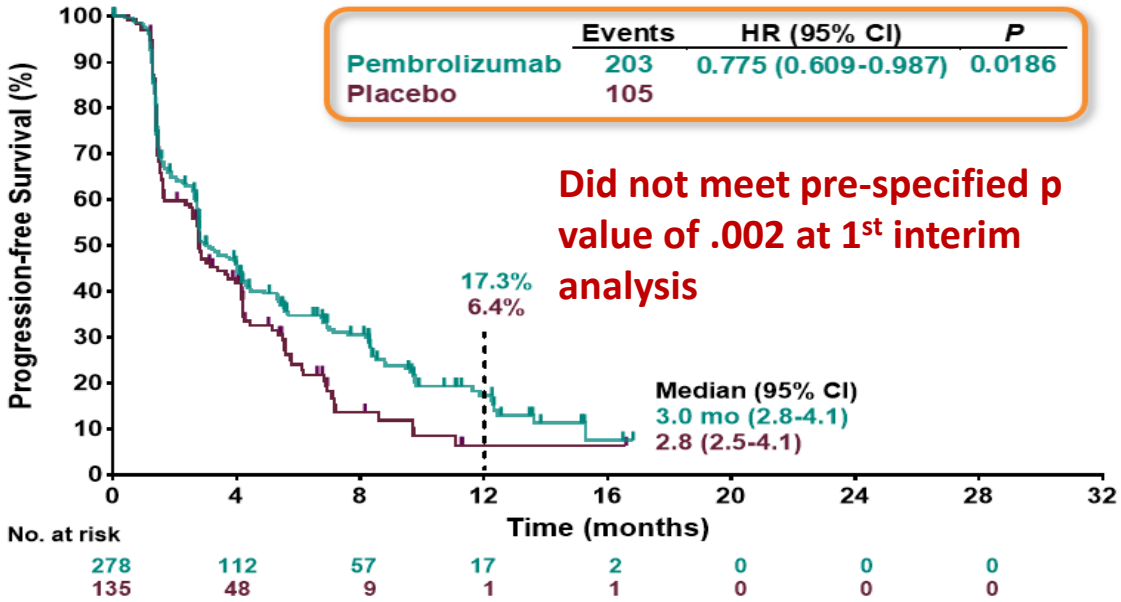
Overall Survival



Did not meet pre-specified p value of .0174

Progression-free Survival

First interim analysis



Did not meet pre-specified p value of .002 at 1st interim analysis

FDA approved 2nd Line irrespective of PD-L1 status despite just missing statistical endpoints in Phase III trial.

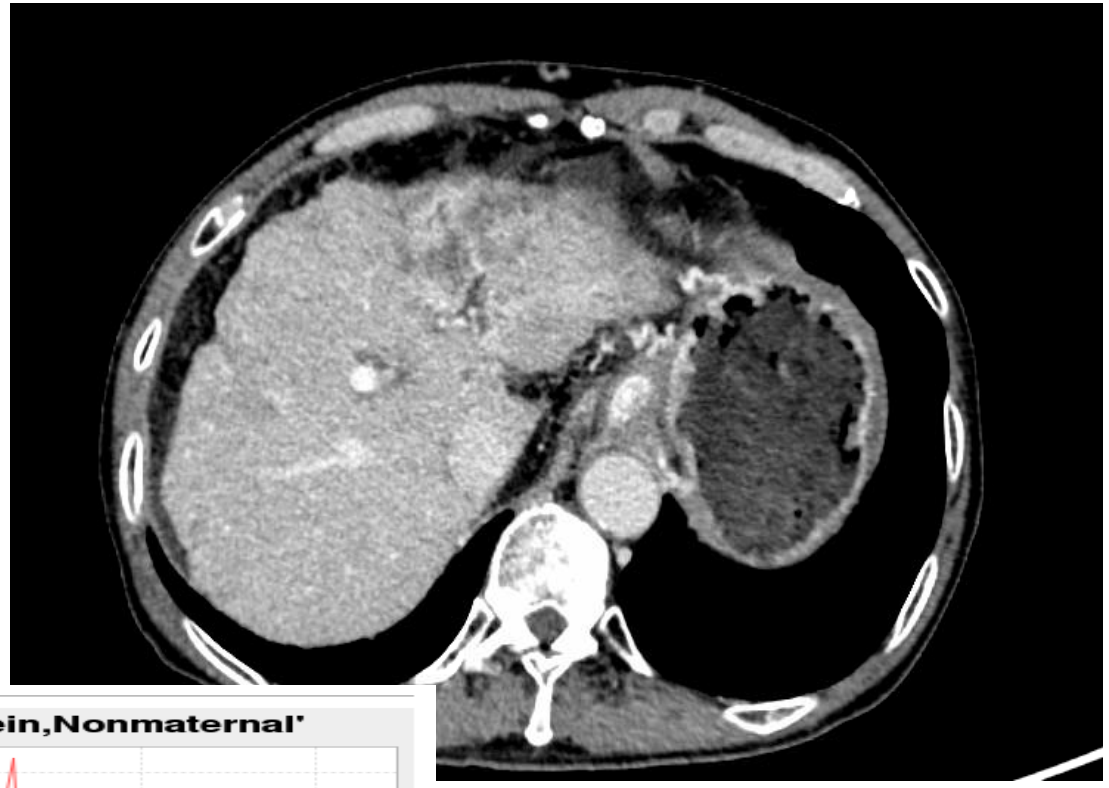
ORR 18.3% by RECIST 1.1 **Median DOR 13.8 months** **mOS 13.9 months**

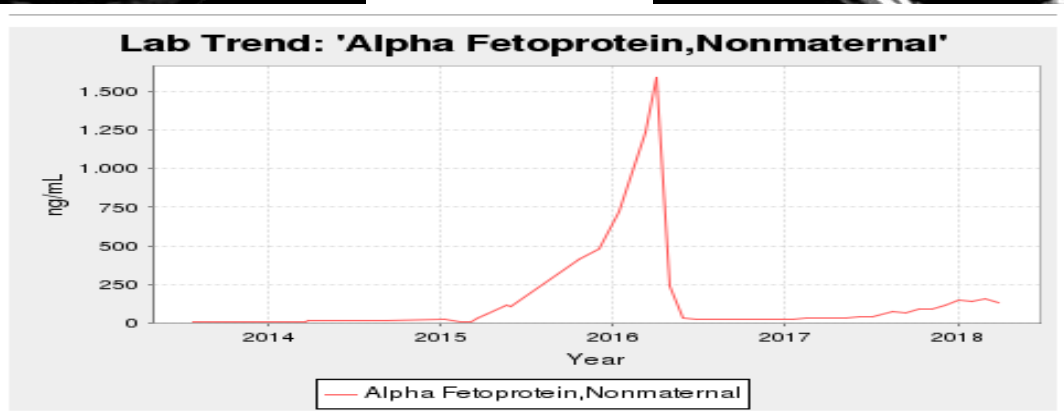
Finn et al. ASCO 2019 JCO 37(suppl; abstr 4004)

Second-Line Systemic Therapy: Case

Progressive Disease 1 year after sorafenib initiation

Scans 2 years after PD1 inhibition



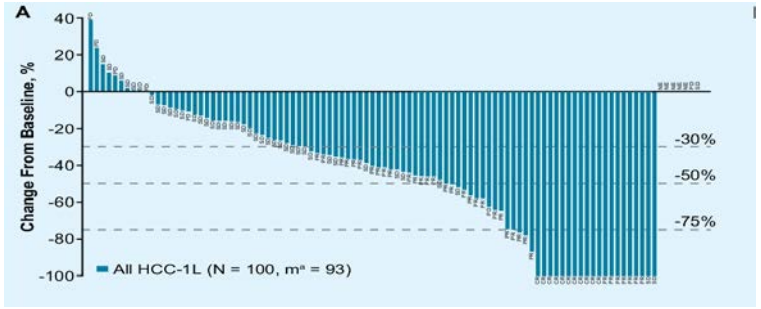


Future Directions/Questions: HCC

- **Optimal sequencing of currently approved agents unclear**
  - **Especially with no data to guide next steps after atezo/bev 1st line therapy**
- **Optimizing Immunotherapy approaches**

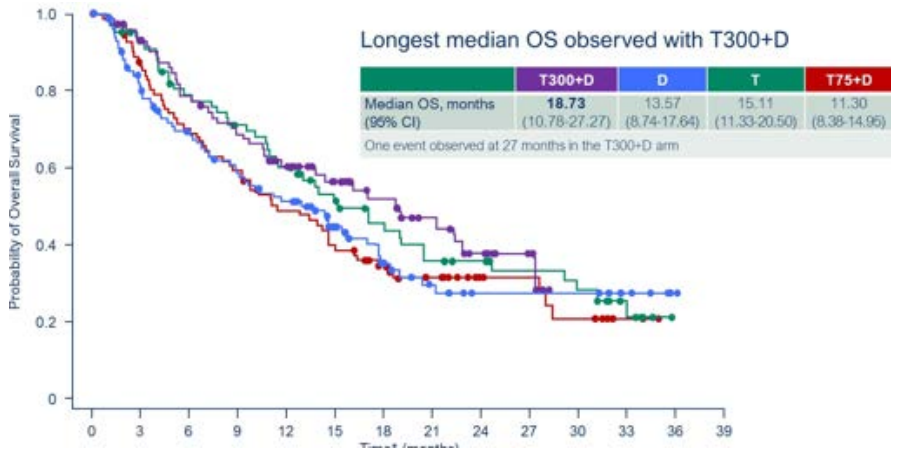
Promising combination strategies show high response rates in early phase trials; Phase III 1st line trials ongoing

TKI + α-PD1/PDL1 (n=100)
Lenvatinib + Pembro: 36% ORR
88% DCR, mPFS 8.6 mo.



α-CTLA4 + α-PD1/PDL1 (2nd Line)
Nivo(1)/Ipi(3): 32% ORR
8% CR; 23-month mOS

One Priming Dose α-CTLA4 + α-PDL1
Tremelimumab + Durvalumab



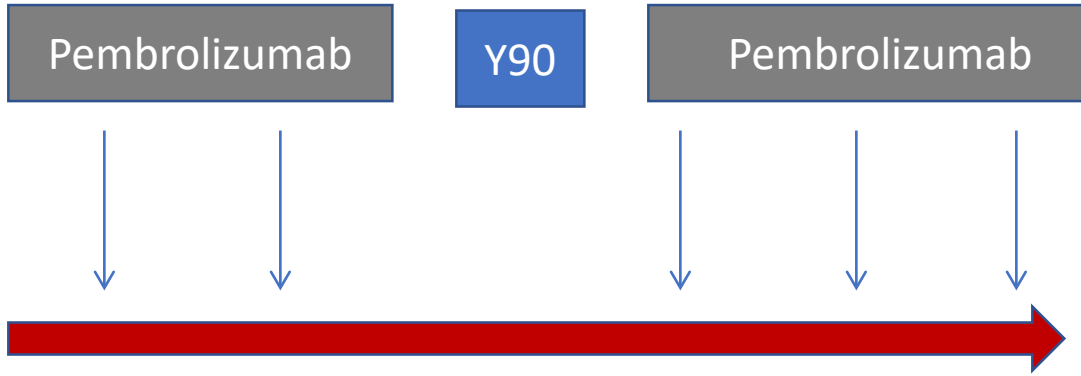
1. Zhu et al. ASCO 2020 Abstr 4519
2. Kelley et al ASCO 2020 Abstr 4508.
3. Yau et al. ASCO 2019 J Clin Oncol. 2019; 37(suppl) Abstr 4012

Future Directions: Local Interventions + Immune Checkpoint Inhibition

Phase II: SBRT + PD1 inhibitor (NCT03316872)
Phase II: Radioembolization + PD1 inhibitor (NCT03099564)
Phase III: TACE + PD-L1 inhibitor (+/- Bevacizumab) (NCT03778957)

Ongoing phase 2 Single arm Pilot study (n=30), 3 institution study

- **HCC not amenable to Resection/Transplant**
- **No prior radioembolization**
- **Child Pugh A, ECOG 0-1**
- **BCLC Stage B/C**

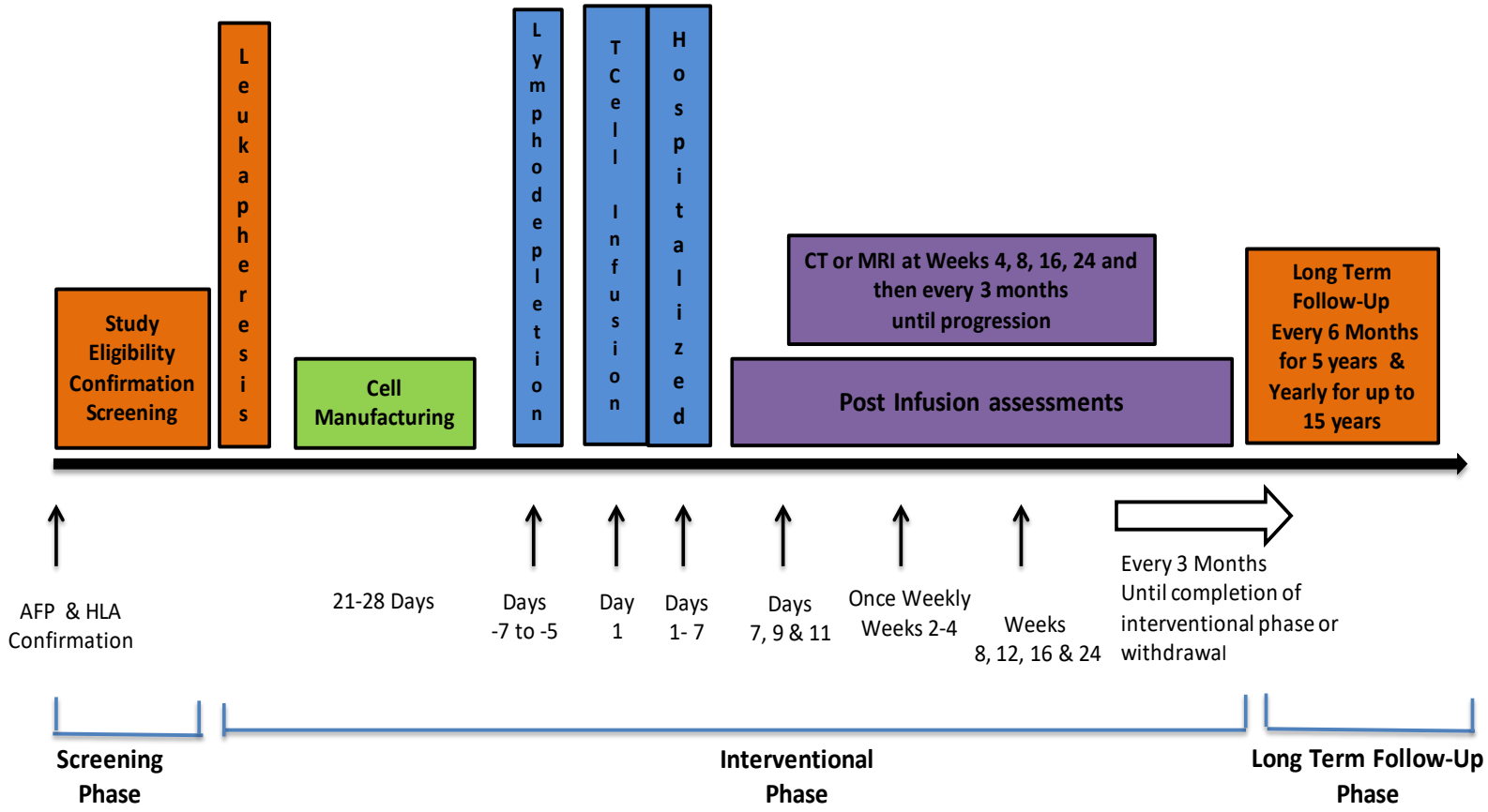


<u>Outcomes:</u>
Immunologic correlates
Toxicity assessment
Response rates, mOS, TTP

Future Directions: Adoptive T-cell Therapy
AFP-directed chimeric T-cell Receptor Therapy (TCR)

- Advanced HCC, any-line
- Child Pugh A
- ECOG 0-1
- HLA-A*02:01 + (~35%)
- Tumor AFP + by IHC (~40%) or elevated serum AFP
- Liver Parenchyma AFP – by IHC (most)
- Mandatory biopsies
- Requires chemotherapy conditioning

First in Human Studies, currently accruing



HCC: Final Take-home messages

- Localized therapy and liver transplantation for early stage disease (BCLC stage A) can be curative
- For Child-Pugh A/B unresectable HCC (without vascular involvement or metastatic disease): TACE has been shown to prolong survival compared with best supportive care
- For vascular involvement/metastatic HCC or select patients with bulky intermediate stage disease (Child-Pugh A), atezolizumab and bevacizumab is standard of care as first-line therapy.
- For advanced/metastatic HCC (Child-Pugh B), the benefit of systemic therapy is less defined but may be considered in select patients.
- Multiple recently FDA approved systemic therapies in the refractory setting, with no current consensus regarding optimal selection. Many GI Oncologists would attempt TKI (Lenvatinib, sorafenib) after atezo/bev.

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Hematopoietic Stem Cell Transplantation

Rachel B. Salit

Fred Hutchinson Cancer Research Center

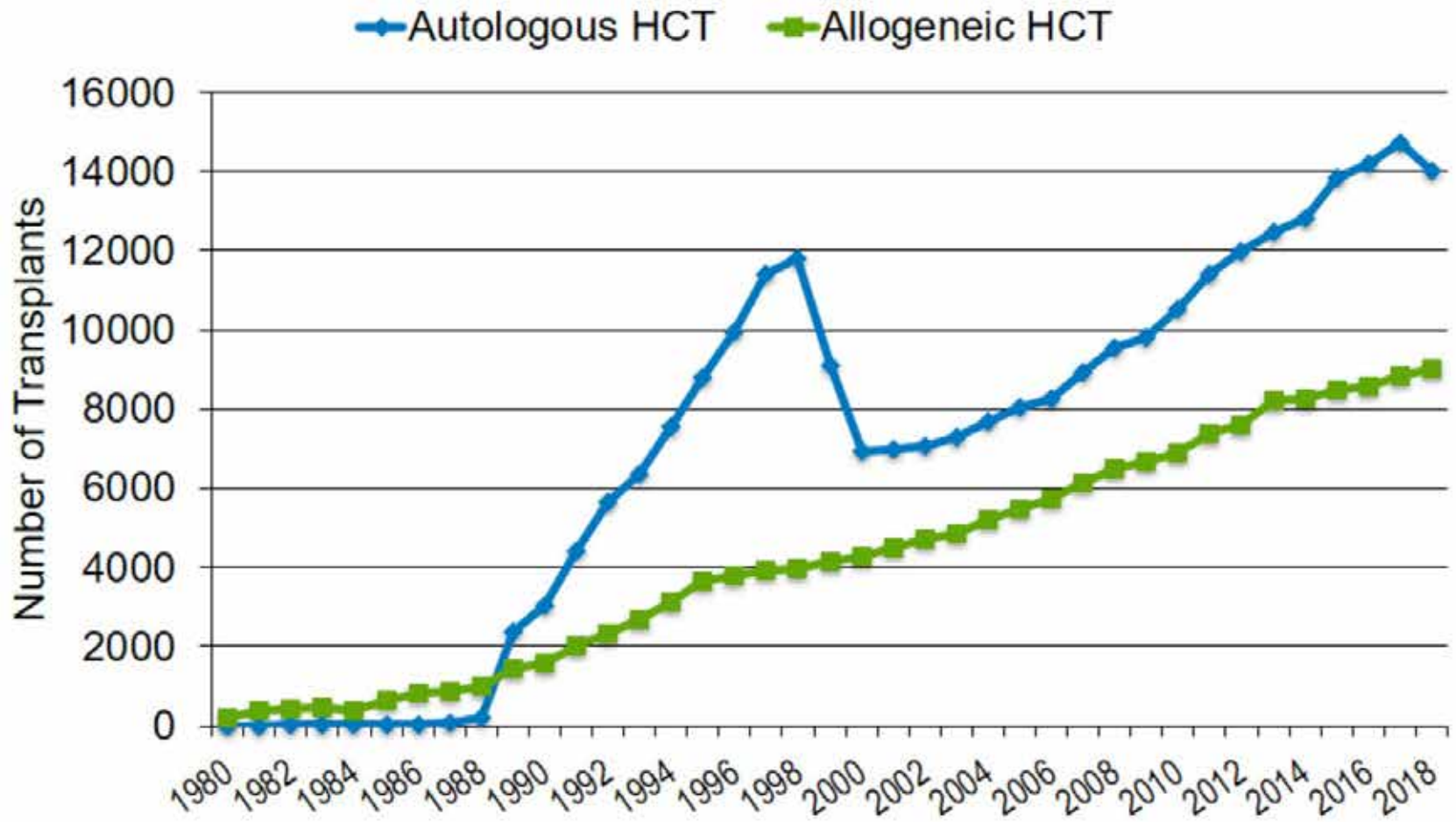
Seattle, WA

=

Outline

- Indications for Hematopoietic Stem Cell Transplant (HCT)
- Donor and Cell Sources
- Conditioning Regimens
- Complications
  - Regimen Related Toxicity
  - GVHD
  - Infections
  - Late Effects
  - Relapse

Annual Number of HCT Recipients in the US by Transplant Type



CIBMTR
CENTER FOR INTERNATIONAL BLOOD & MARROW TRANSPLANT RESEARCH

Indications for Transplant

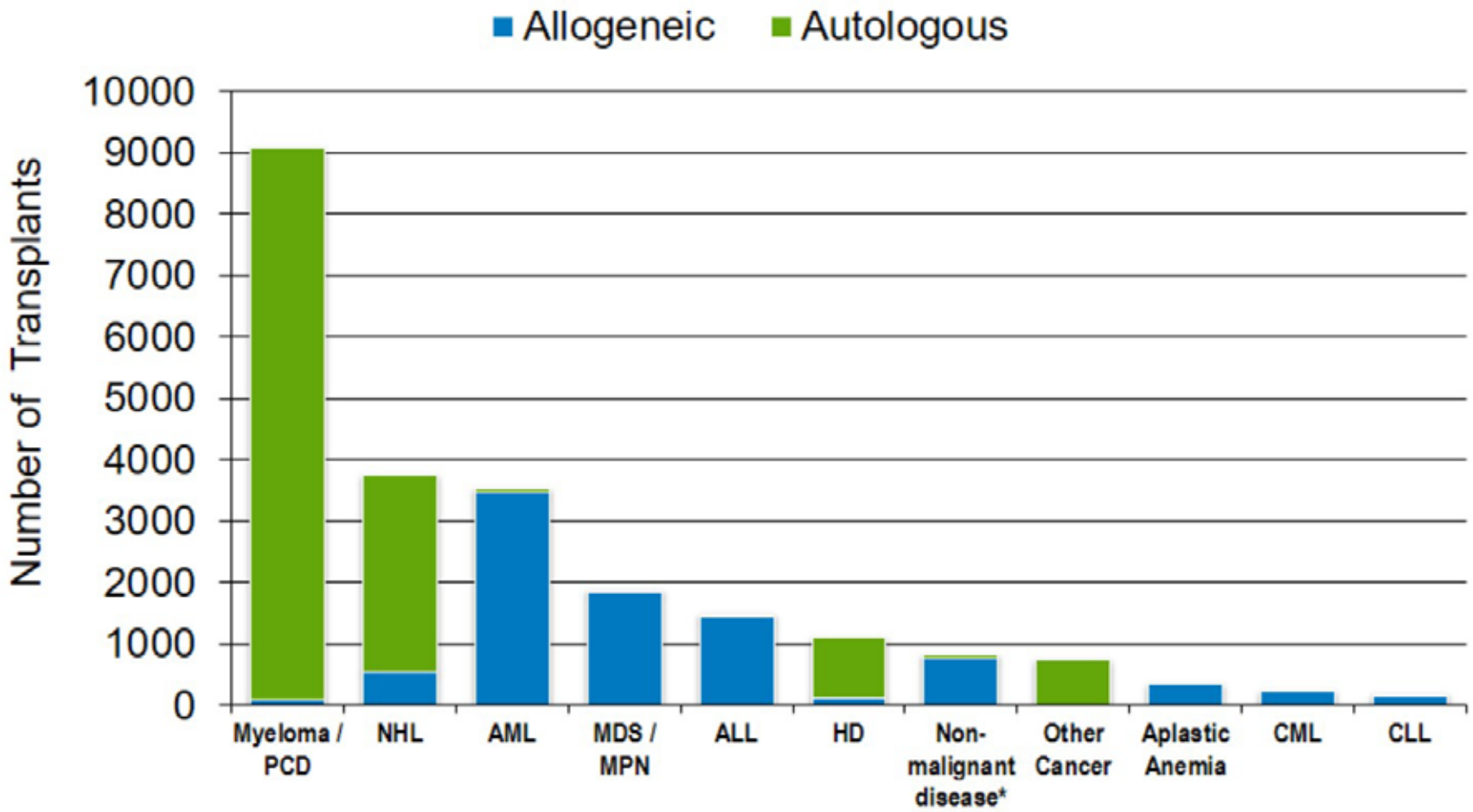
Malignant

- Acute Myeloid Leukemia
- Acute Lymphocytic Leukemia
- Myelodysplastic Syndrome
- Chronic Myeloid Leukemia
- Myeloproliferative Disease
- Chronic Lymphocytic Leukemia
- Multiple Myeloma
- Hodgkin Lymphoma
- Non-Hodgkin's Lymphoma

Non-Malignant

- Immunodeficiencies
- Aplastic Anemia
- Hemoglobinopathies
- Enzymatic Disorders
- Autoimmune Diseases

Indications for Hematopoietic Cell Transplant in the US, 2018



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*excludes aplastic anemia.

Autologous Transplant

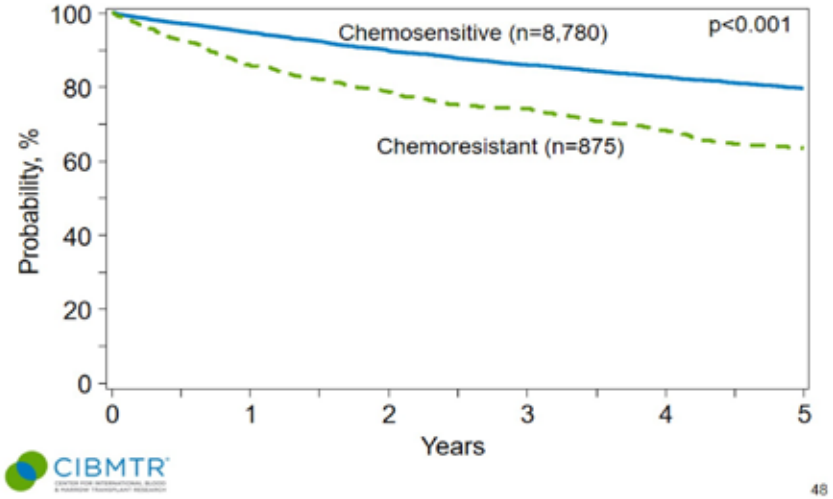
- Disease targeted myeloablative chemotherapy and followed by rescue with their own previously saved stem cells.
- Auto-stem cells are collected from GCF or chemo-mobilized peripheral blood.
- If the patient fails to mobilize, plerixafor may be administered
- Frozen cells may be used more than 10 years later without change in CD34+ viability.
- Treatment-related mortality rate < 1%-3%.

Multiple Myeloma

- Auto HCT improves survival in patients < 65 years old with newly diagnosed multiple myeloma.
- Progression free survival is longer if patients have HCT earlier rather than waiting for first relapse.
- Maintenance with lenalidomide or bortezomib further improves PFS.

Lymphoma

Survival after Autologous HCT for Hodgkin Disease, 2007-2017



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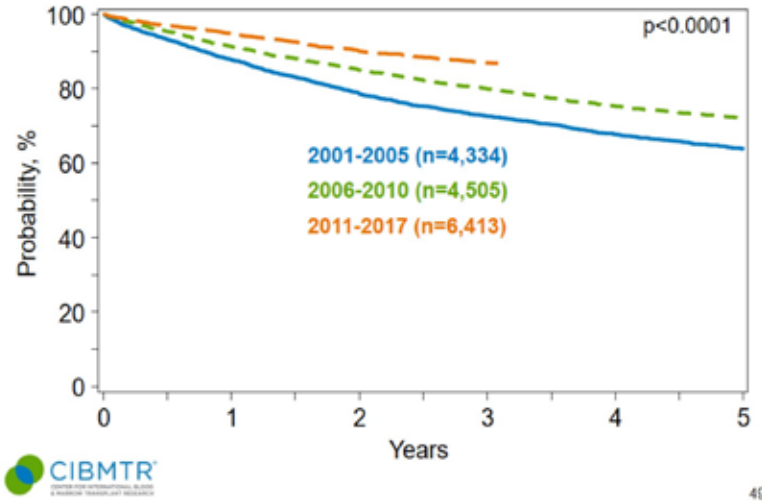
Trends in Survival after Autologous HCT for HD, 2001-2017



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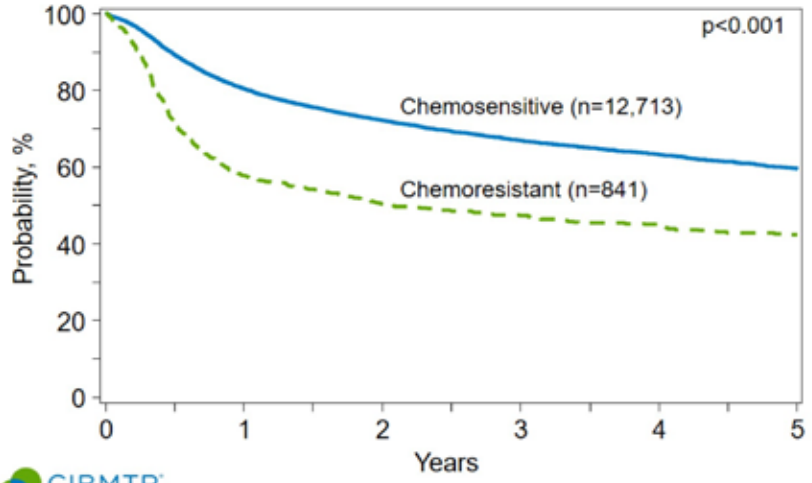
Survival after Autologous HCT for Diffuse Large B-Cell Lymphoma (DLBCL), 2007-2017



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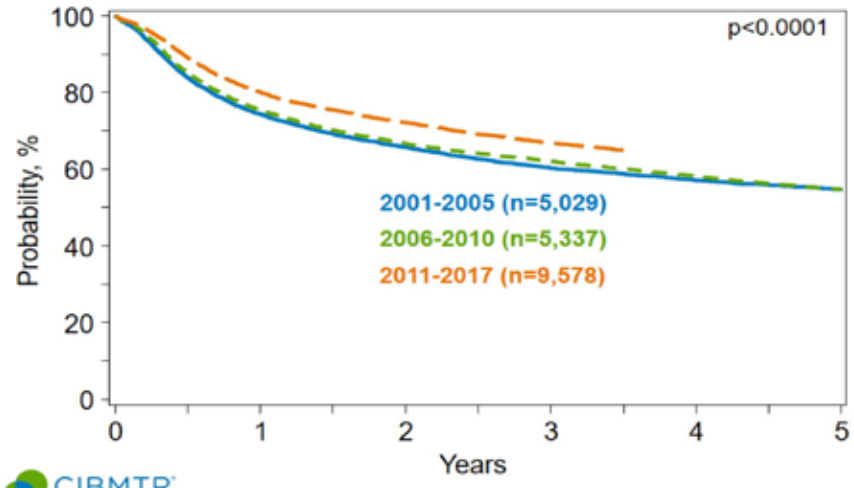
Trends in Survival after Autologous HCT for DLBCL, 2001-2017



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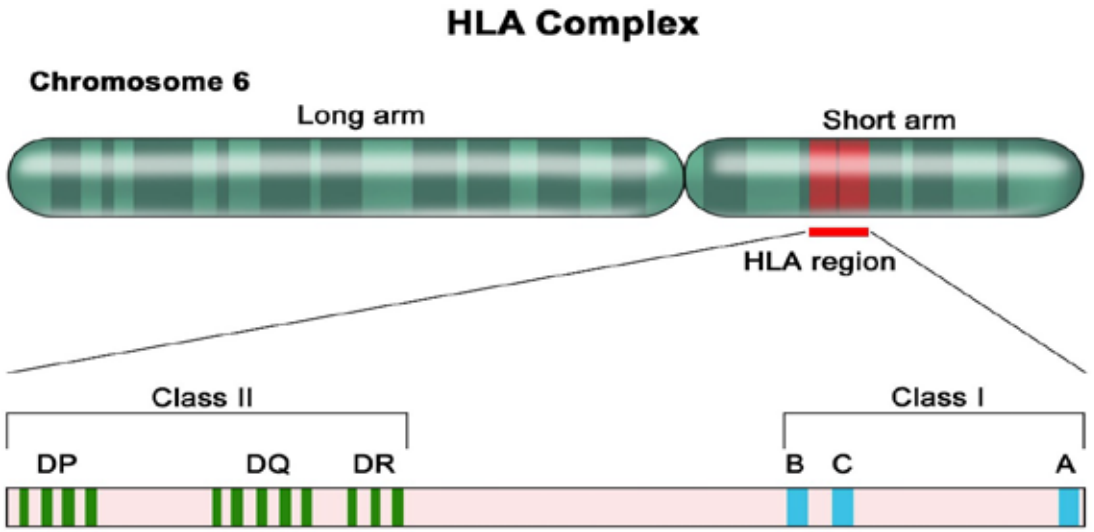
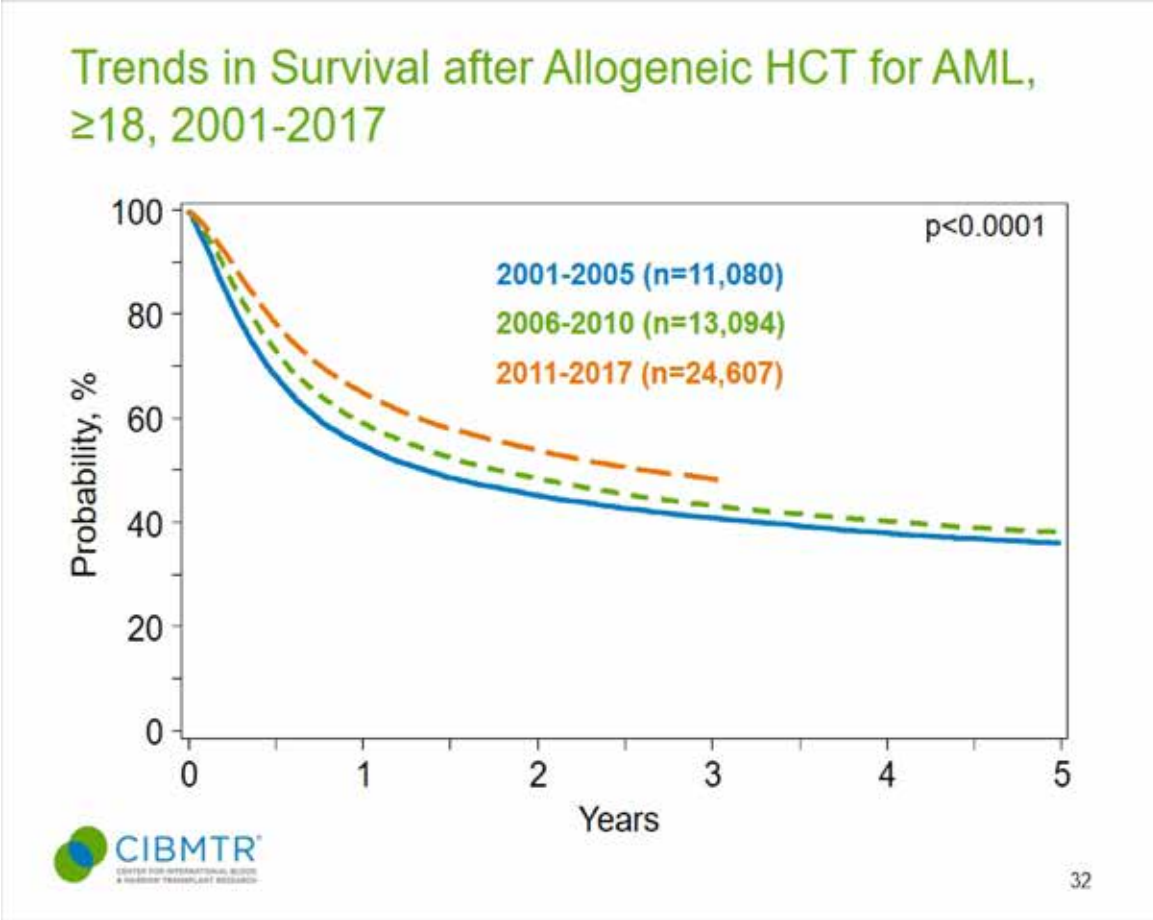
Allogeneic Transplant

- Utilizes both chemo/radiotherapy and graft versus tumor effect.
- HLA is encoded by the Major Histocompatibility Complex on chromosome 6.
- Even if individuals are HLA matched at major antigens (10 of 10), they are likely to be mismatched at the minor antigens.



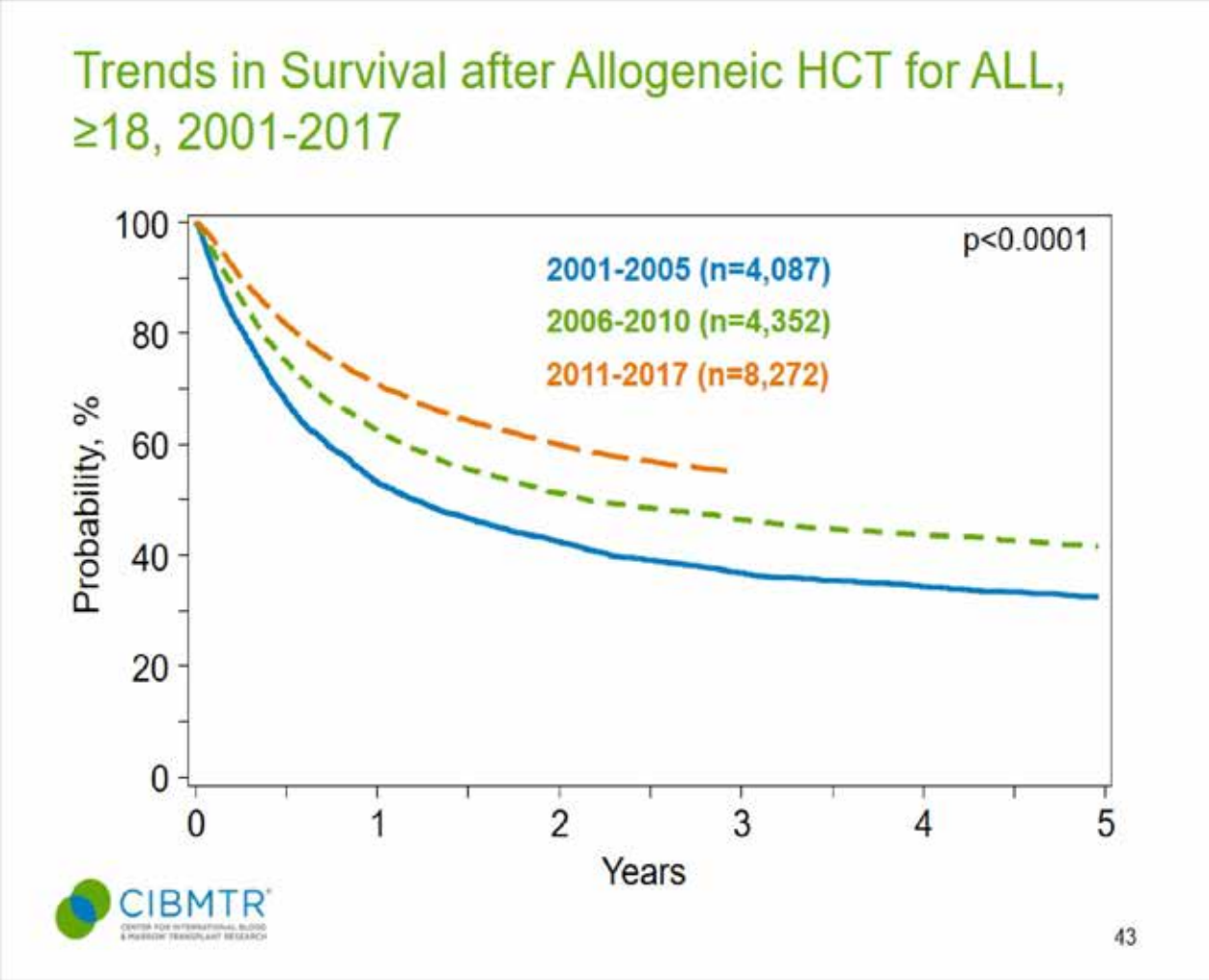
Acute Myeloid Leukemia (AML)

- Allo-HCT consistently achieves 5-year disease free survival of 50-70% for patients in first remission.
- Advantages of transplantation are most apparent for patients with unfavorable and intermediate risk leukemia.
- Cure rates decrease if patients are transplanted in second complete remission but are still better than expected for chemotherapy alone.



Allo HCT for ALL

- Long-term survival is improved with allo-HCT for patients with high-risk disease including MLL, Philadelphia chromosome positive (Ph+) and patients who are delayed in achieving remission beyond the first cycle of induction chemotherapy.
- Results with Ph+ ALL have improved with the availability of tyrosine kinase inhibitors (TKIs), but HCT remains superior to chemotherapy.



Allo-HCT for Myelodyplastic Syndrome (MDS) and Myeloproliferative Disease (MPN)

- MDS and MPN are generally incurable except with Allo-HCT
- HCT is reserved for patients with advanced stage disease.
- Current guidelines recommend allo-HCT be considered for:
  - Patients up to age 65
  - Intermediate 2 or higher risk according to the D(IPSS(R)).
- Patients with MPN have higher rates of graft failure than more other malignant diseases.

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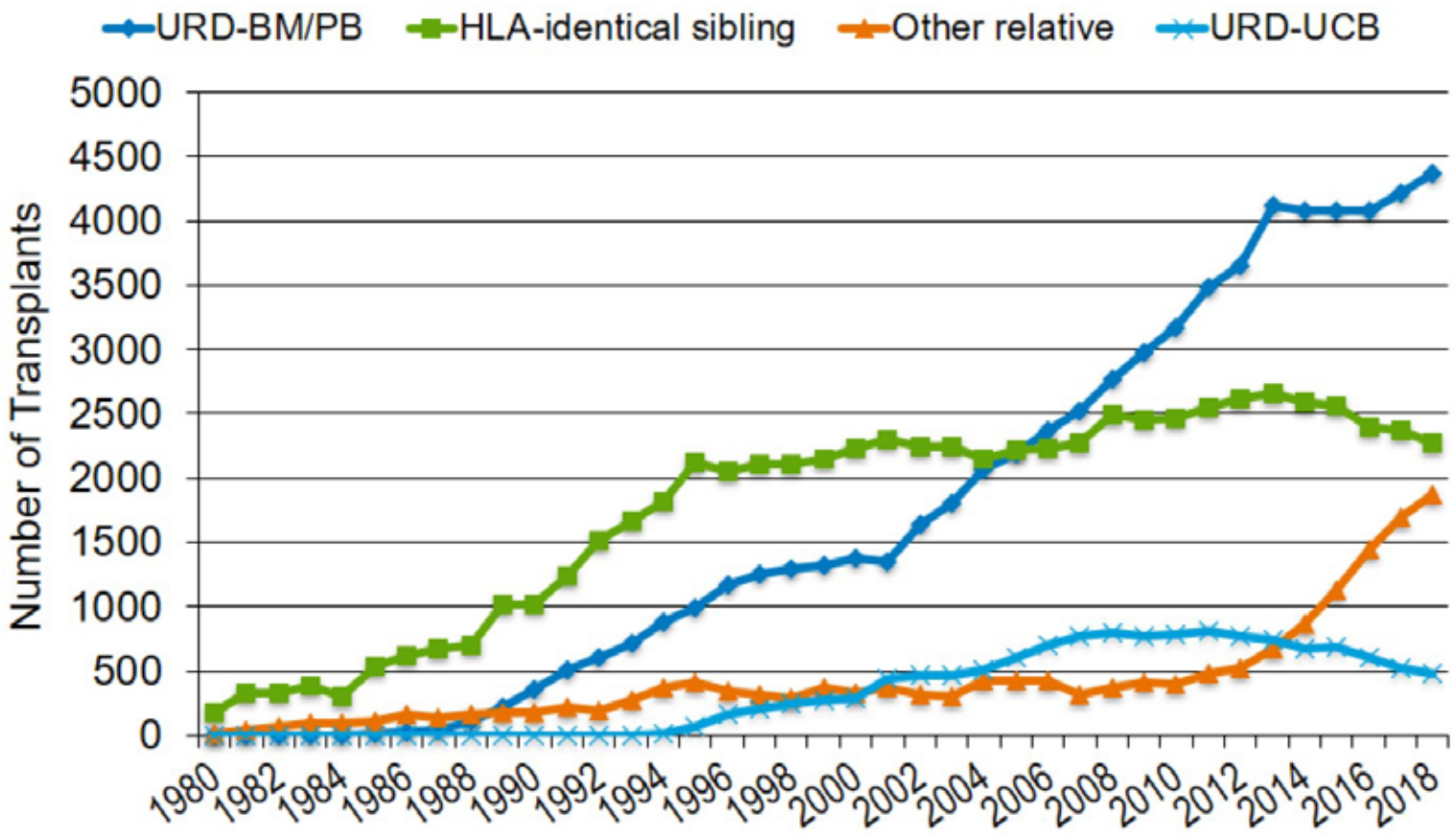
Donor and Cell Sources

Allogeneic HCT Recipients in the US, by Donor Type



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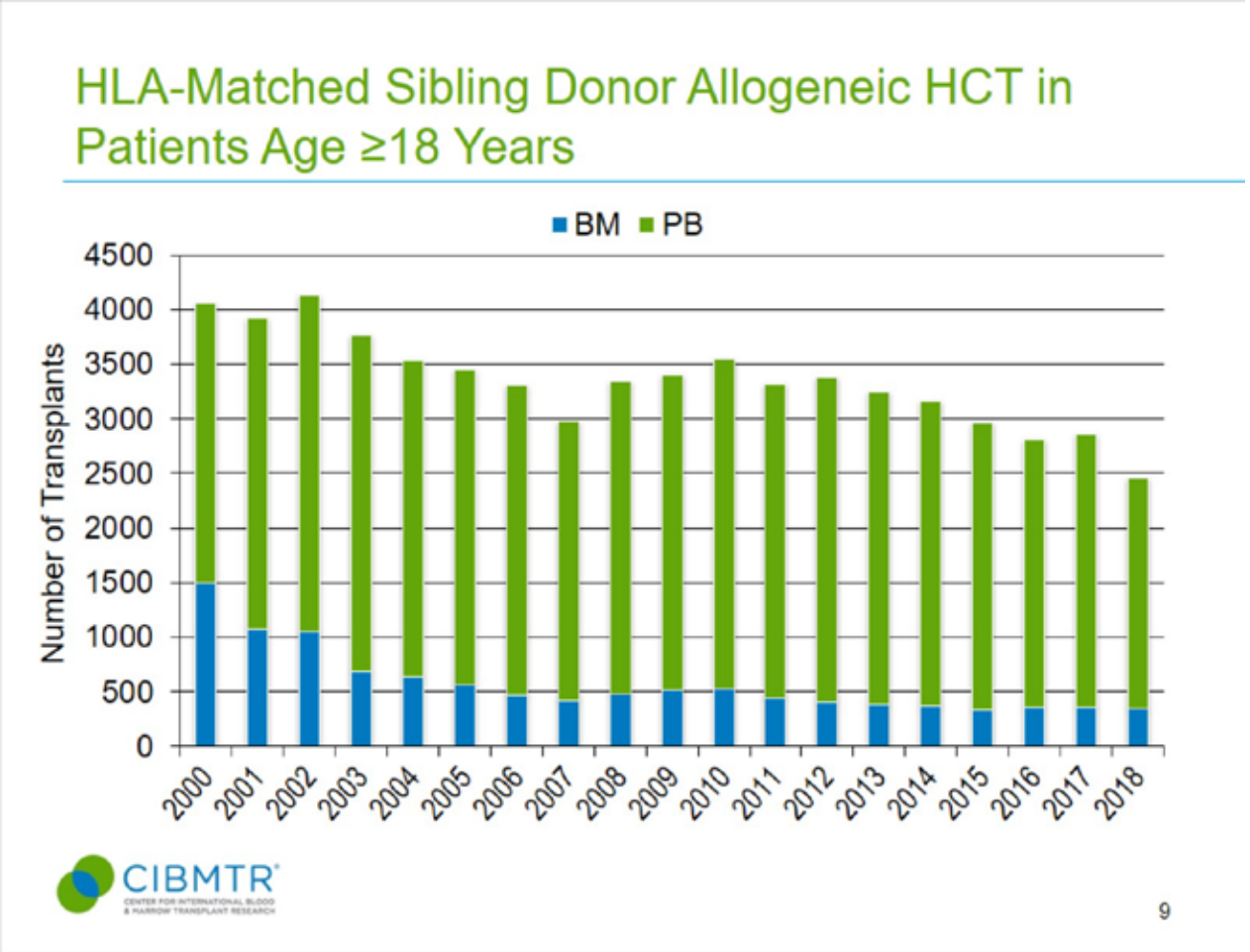
Bone marrow (BM) vs PB (Peripheral Blood)

- Use of PB accelerates engraftment by about 7 days without increasing acute GVHD.
- PB has a higher proportion of T-cells than marrow.
- Chronic GVHD may be higher with PB than BM but disease recurrence appears to be less and survival equivalent

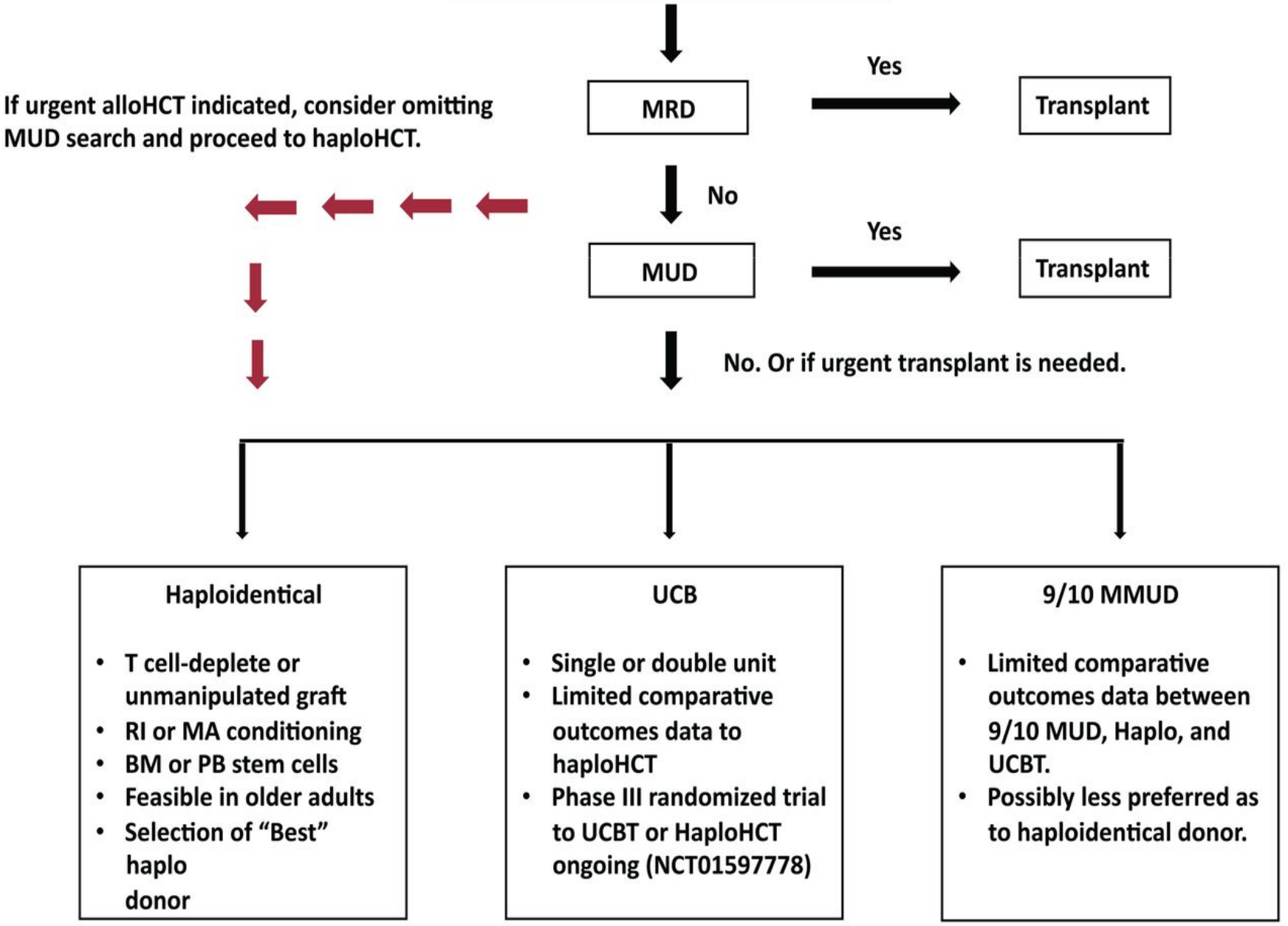


BMT vs PBSCT in Unrelated Donors

- BMT with PBSCT following myeloablative regimen and methotrexate/calcineurin inhibitor for GVHD prophylaxis.
- Faster engraftment but more chronic GVHD with PBSCT.
- Survival was equivalent, but given the higher incidence of chronic GVHD, this study would favor the use of marrow.
- However, this is not being done in clinical practice.

Anasetti C, Logan BR, Lee SJ, et al. Peripheral-Blood Stem Cells versus Bone Marrow from Unrelated Donors. New Engl J Med 2012;367:1487-96.

Patient in need of transplant



Umbilical Cord Blood

- Fewer mature T-cells = less stringent matching criteria
- Allow HLA 4/6 with antigen matches at A and B and allele match at DR
- Data looking at HLA-C suggest improved OS with 5/8 or greater.
- Other advantages include:
  - Rapid availability
  - Potential GVT effect especially when 2 cords are used.
- Disadvantages include:
  - Slower engraftment and immune recovery.
  - Increased viral, bacterial and fungal infections early.
  - Higher incidence of graft failure.
  - Inability to go back to the donor in the event of relapse.

Haploidentical Donors

- Any patient with a living parent or child has a potential Haplo donor.
- Siblings or half-sibling have 50% chance of sharing a haplotype with the patient.
- Advantage of Haplo donors:
  - –Ability to go back to the donor.
  - –Very low chronic GVHD with post transplant Cytoxan.
- Disadvantage of Haplo donors:
  - Higher relapse rate.
  - Increased risk of infections due to T-Cell depletion.
  - Increased graft failure.

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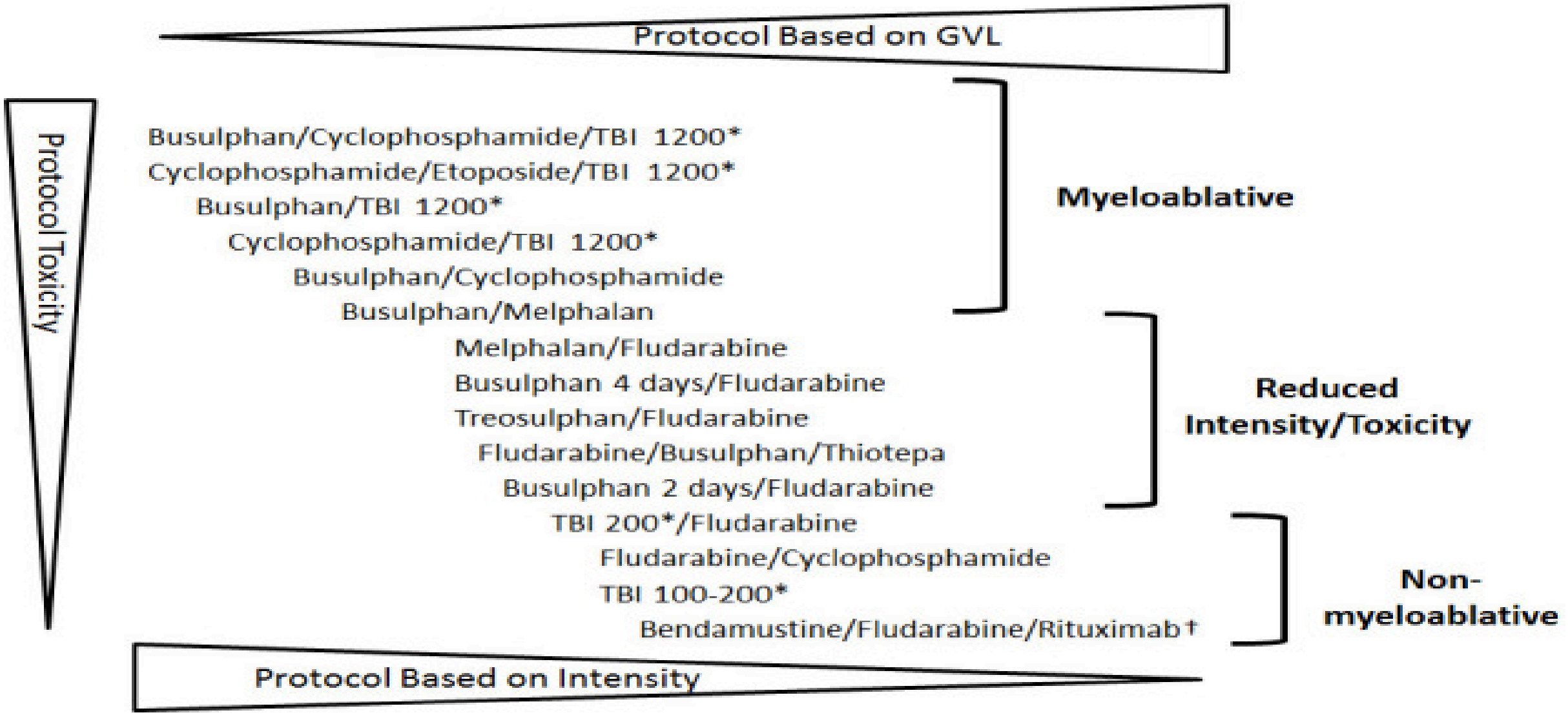
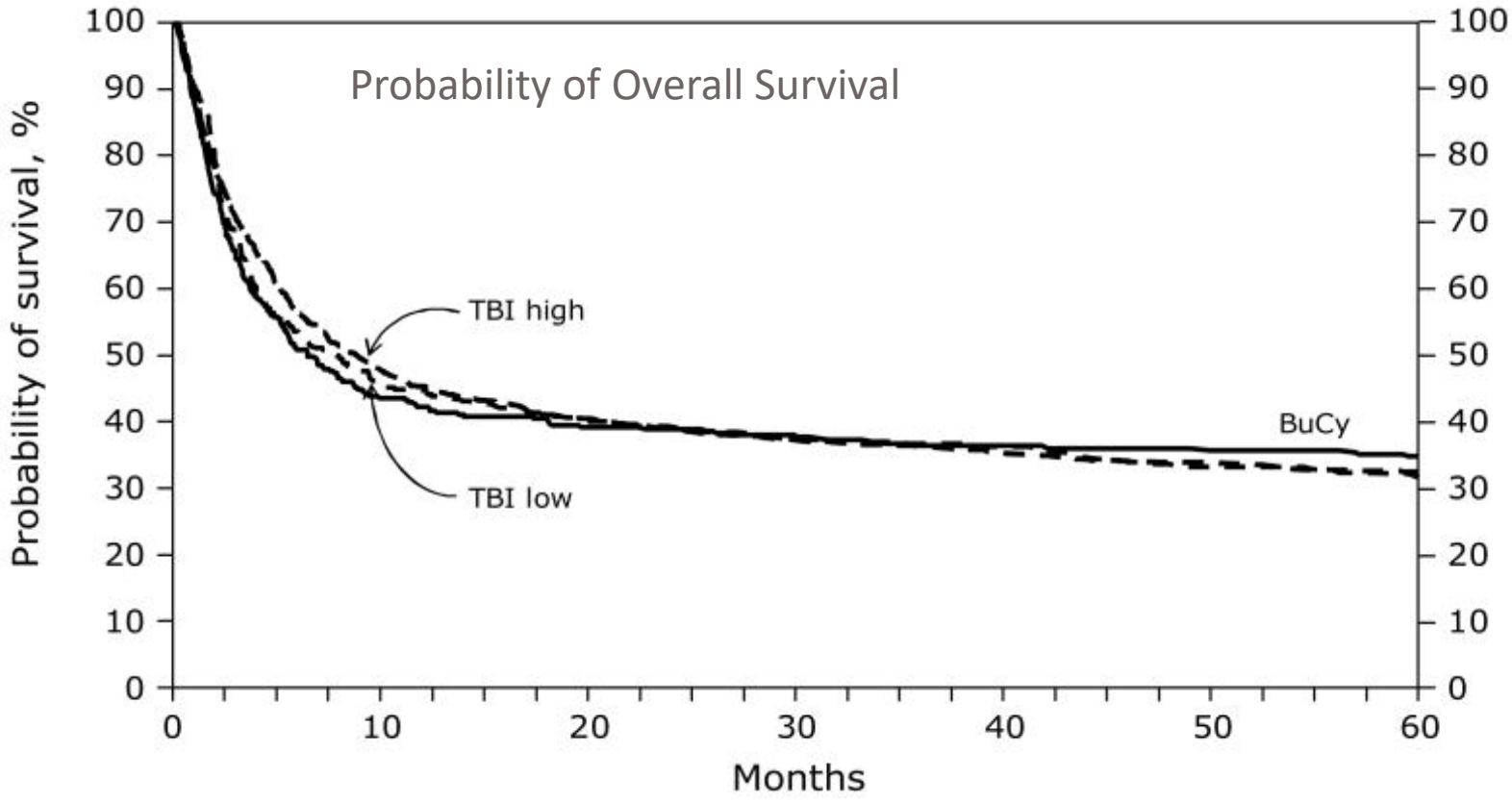
Conditioning Regimens


Protocol Based on GVL
Protocol Toxicity
Busulphan/Cyclophosphamide/TBI 1200*
Cyclophosphamide/Etoposide/TBI 1200*
Busulphan/TBI 1200*
Cyclophosphamide/TBI 1200*
Busulphan/Cyclophosphamide
Busulphan/Melphalan
Myeloablative
Melphalan/Fludarabine
Busulphan 4 days/Fludarabine
Treosulphan/Fludarabine
Fludarabine/Busulphan/Thiotepa
Busulphan 2 days/Fludarabine
Reduced Intensity/Toxicity
TBI 200*/Fludarabine
Fludarabine/Cyclophosphamide
TBI 100-200*
Bendamustine/Fludarabine/Rituximab†
Non-myeloablative
Protocol Based on Intensity

Myeloablative Conditioning (MAC)

- Cytoxan 120mg/kg + 1200 CGy total body irradiation (TBI).
- Busulfan 16mg/kg + Cyclophosphamide 120mg/kg
  - Targeting Busulfan levels in the plasma may decrease the risk of relapse and severe regimen related toxicities.



Uberti et al BMT 2010

Reduced Intensity Conditioning (RIC)

- RIC regimens are selected for:
  - –Older patients
  - –Those with significant comorbidities
  - –Those who have received prior therapy thought to limit their ability to tolerate high dose regimens.
- RIC is associated with less toxicity than MAC but higher relapse rates
- Recovery of hematopoiesis would be expected without the support of hematopoietic progenitor cells.

3 yr Nonadjusted Outcomes

	FluBu2 (N=71)	FluBu4 (N=51)	p-value
TRM	24%	10%	0.06
Relapse	43%	36%	0.5
OS	39%	62%	0.02
DFS	34%	54%	0.04

Non-Myeloablative Conditioning

- Examples of NMA conditioning include:
  - Fludarabine 90mg/m2 + 200cGy or
  - 200-300 cGy TBI alone.
- NMA regimens cause minimal marrow suppression
- Depend on pre and post transplant immune suppression to prevent graft rejection.
- Efficacy of the treatment is largely from a graft versus tumor response.
- Relapse risk is lowest in patients who develop acute or chronic GVHD.

Engraftment

- Defined as the first day of three days of ANC > 500.
- Approximately day +14 post HCT with peripheral blood.
- Delayed by 4-6 days if bone marrow or CB is the source.
- Rate of myeloid recovery can be accelerated by ~7 days with GCSF with marrow and CB.
- GCSF has less of an effect with peripheral blood.
- Chimerism refers to the percent donor or recipient DNA found in the marrow or peripheral blood.
  - Whole marrow
  - CD3, CD33, and CD56 in the peripheral blood

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Complications

Chemotherapy regimen related toxicities

- Nausea, vomiting, diarrhea
- Oral mucositis (Patients may require TPN and PCA)
- Alopecia
- Cytopenias
- Sinusoidal obstruction syndrome
- Idiopathic pneumonia syndrome
- Renal Dysfunction

Sinusoidal obstruction syndrome (SOS)

- Timing: 1-4 weeks following conditioning.
- Characterized by: weight gain, ascites, hepatomegaly, jaundice
- Overall incidence 5-15%
- Risk of severe SOS is higher for patients with:
  - Abnormal liver function tests before the HCT
  - Pre-transplant hepatitis
  - High intensity conditioning
  - Use of Busulfan
- Defibrotide may be effective both as prophylaxis and therapy.
  - Used in cases of severe SOS

Idiopathic pneumonia syndrome (IPS)

- Occurs within 30-90 days after conditioning
- 4-12% of patients.
- Thought to be a toxicity related to chemotherapy or radiation
- Risk factors:
  - High dose TBI
  - Pre-existing lung disease
  - Older age
  - Prior chest radiation
- Mortality rate is about 50%
- No available treatments are clearly effective
  - Usually treated with steroids

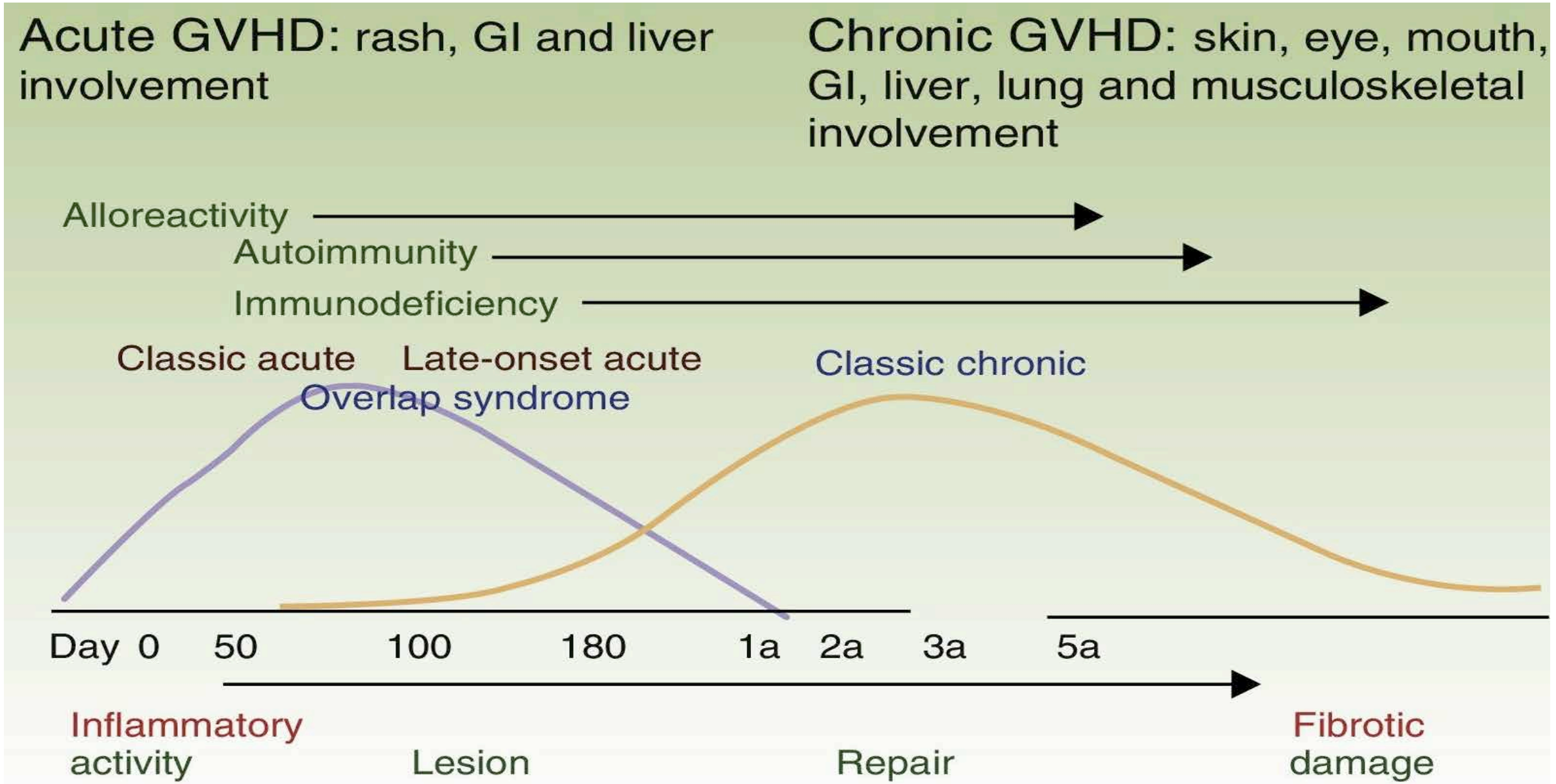
Graft Rejection

- Loss or failure to achieve donor chimerism.
- Result of residual host immune cells rejecting the donor.
- Risk Factors:
  - Increased disparity between donor and recipient.
  - Patients with multiple transfusions and little prior chemotherapy ie. aplastic anemia.
  - T-cell depletion leading to persistence of host immunity.
  - NMA HCT resulting from persistence of host immunity.
  - CBT due to decreased numbers of donor T-cells.

Graft Failure and Poor Graft Function

- Full donor chimerism without recovery of counts.
- Causes include:
  - Prior exposure to stem cell toxins
  - Cell damage during processing and cryopreservation
  - Viral infections
  - Large Spleen
- Patients with graft failure can respond to GCSF.

Graft versus Host disease


Acute GVHD: rash, GI and liver involvement
Chronic GVHD: skin, eye, mouth, GI, liver, lung and musculoskeletal involvement
Alloreactivity
Autoimmunity
Immunodeficiency
Classic acute
Late-onset acute
Overlap syndrome
Classic chronic
Day 0
50
100
180
1a
2a
3a
5a
Inflammatory activity
Lesion
Repair
Fibrotic damage

Acute GVHD Prevention

- Immune Suppression
  - Cyclosporine or tacrolimus + methotrexate
  - MMF + cyclosporine in the NMA setting
  - Addition of sirolimus may further reduce GVHD risk
- T-cell Depletion
  - Positive selection for CD34+
  - Negative selection of CD3+
  - Horse or rabbit ATG
  - Post transplant cyclophosphamide

Acute GVHD characteristics

- Acute (a)GVHD: First 3 months post transplant
- Late Acute GVHD: After 3 months
  - Most commonly when immune suppression is withdrawn.
  - NMA/RIC transplant with late complete donor chimerism.
- Occurs in 30% of patients with HLA-matched sibs and 50-60% with unrelated donors
- Factors associated with increased aGVHD include:
  - HLA-mismatching
  - Older age of patient
  - Multiparous female donor
  - Peripheral blood and
  - More intense conditioning

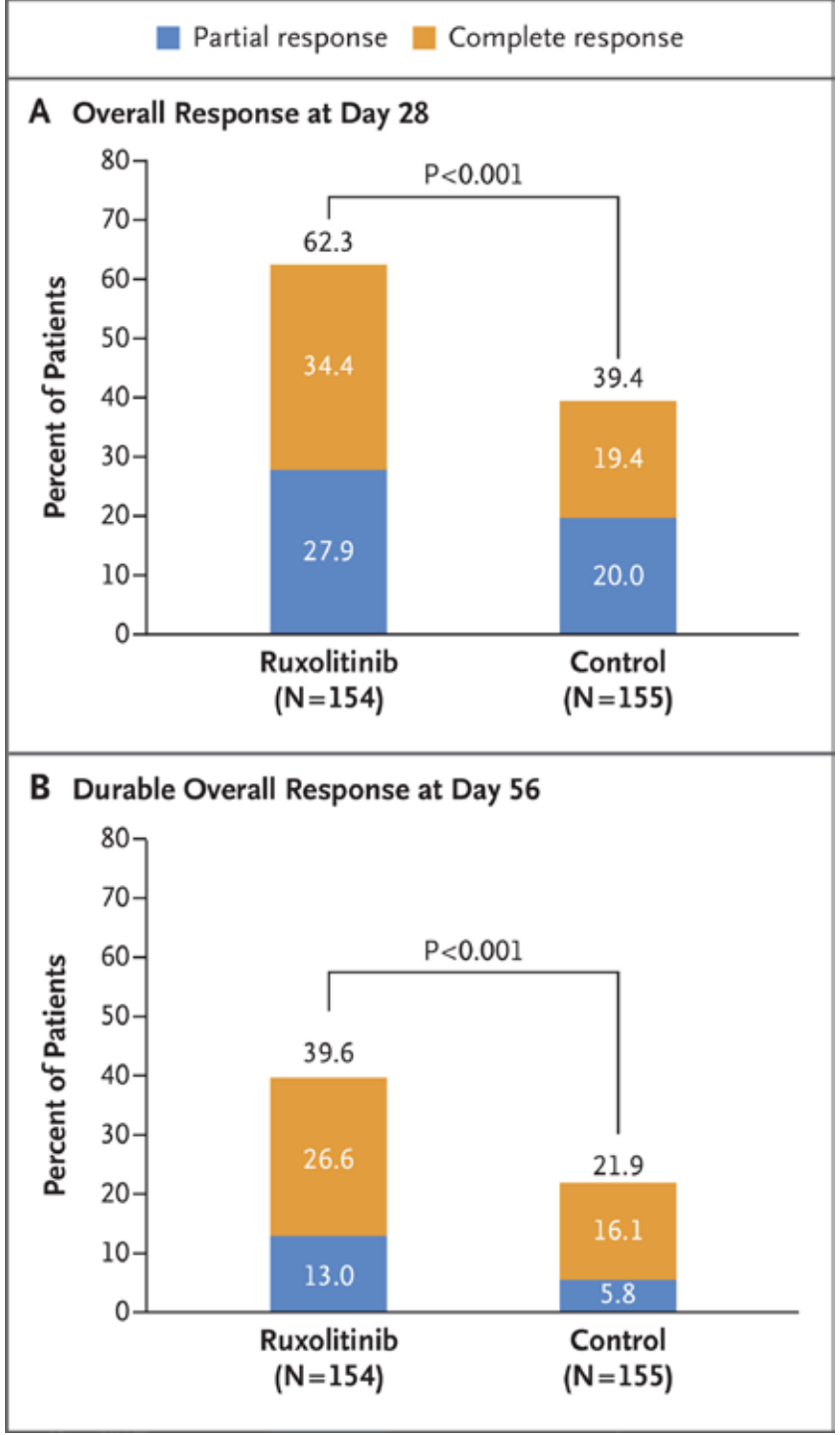
Acute GVHD Manifestations and Scoring

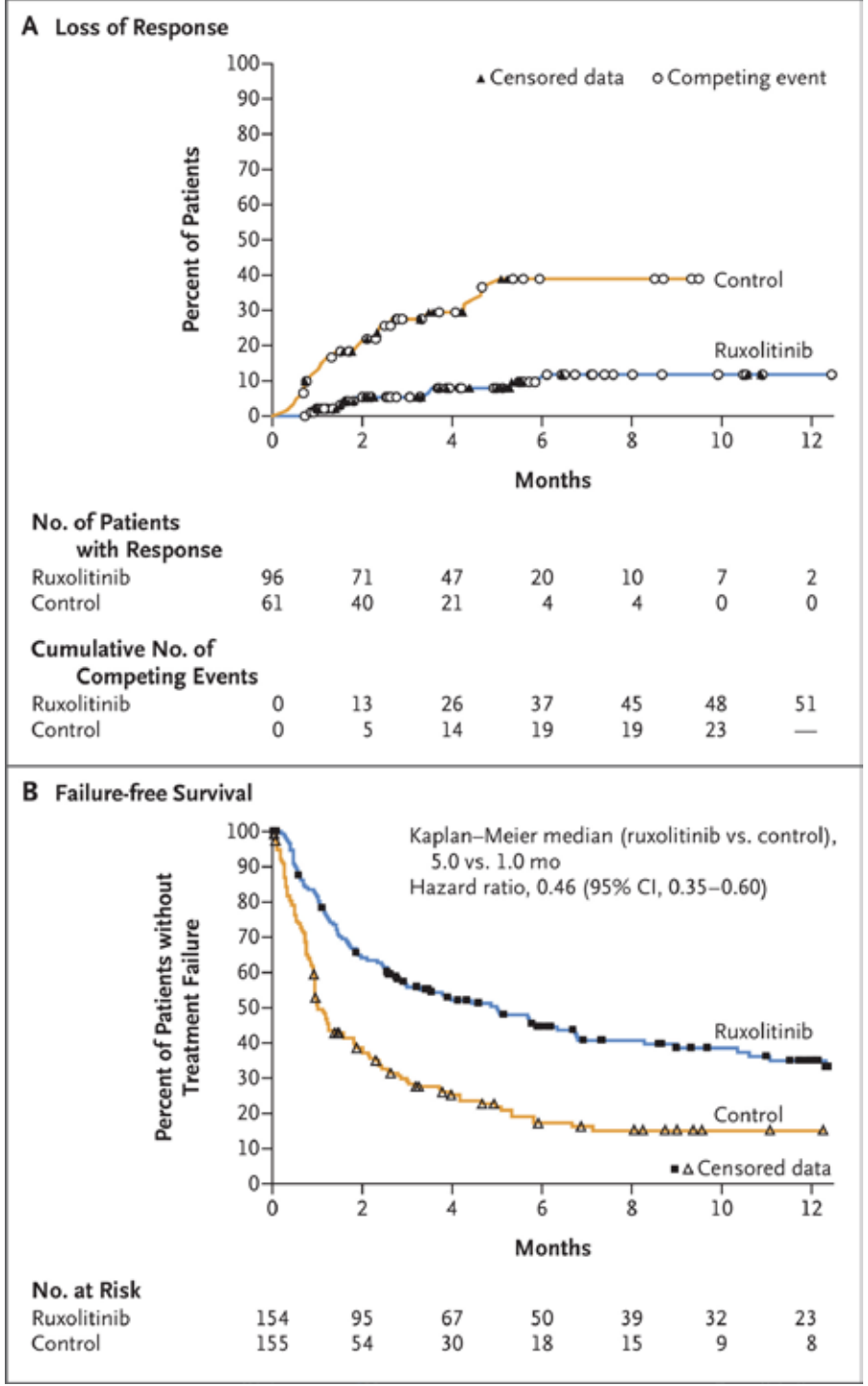
GVHD Staging			
Stage	Skin	Liver (total bilirubin)	GI tract (diarrhea output/day)
0	No GVHD rash	<2 mg/dl	Adult: <500 ml/d *Child: <10 ml/kg/d
1	Maculopapular rash <25% body surface area	2-3 mg/dl	Adult: 500-999 ml/d Child: 10-19.9 ml/kg/d -or- persistent nausea, vomiting, or anorexia with a positive upper GI biopsy
2	Maculopapular rash 25-50% BSA	3.1-6 mg/d	Adult: 1000-1500ml/d Child: 20-30 ml/kg/d
3	Maculopapular rash >50% BSA	6.1-15 mg/dl	Adult: >1500ml/d Child: >30 ml/kg/d
4	Generalized erythroderma (>50% BSA) plus bullous formation or desquamation >5% BSA	>15 mg/dl	Severe abdominal pain with or without ileus, or grossly bloody diarrhea
*Use adult values for patients ≥ 50 kg			
Overall Clinical Grade: Grade 0: No GVHD of any organ Grade 1: Stage 1-2 skin and no liver OR GI tract involvement Grade2: Stage 3 skin and/or stage 1 liver and/or stage 1 GI tract Grade 3: Stage 0-3 skin with stage 2-3 liver and/or stage 2-3 GI tract Grade 4: Stage 4 skin, liver, and/or GI tract			

Acute GVHD Treatment

- Standard Treatment is 2mg/kg of prednisone.
- 1mg/kg may be used for grade I-II aGVHD.
- Therapy given for 5-7 days prior to taper.
- Beclomethasone and Budesonide added for acute GVHD of upper and lower GI tract.
- 40-70% of patients are steroid responsive.
- No standard second line (Ruxolitinib)???
- Other options: ATG, ECP, MMF, Sirolimus, TNF inhibitors.

Reach-2 Trial of Ruxolitinib for Steroid Refractory GVHD





Zeiser R NEJM 2020

Chronic GVHD Characteristics

- As early as 50-60 days or as late as 400 days after transplant.
- 30-70% of patients
- Associated with increased TRM and decreased relapse.
- More frequent with:
  - Unrelated Donor Transplant
  - Peripheral blood
  - Older patients
  - Patients with history of acute GVHD

Chronic GVHD manifestations

- Oral and Ocular Sicca
- Serositis
- Fasciitis
- Esophageal and Vaginal Strictures
- Systemic Sclerosis
- Bronchiolitis Obliterans Syndrome

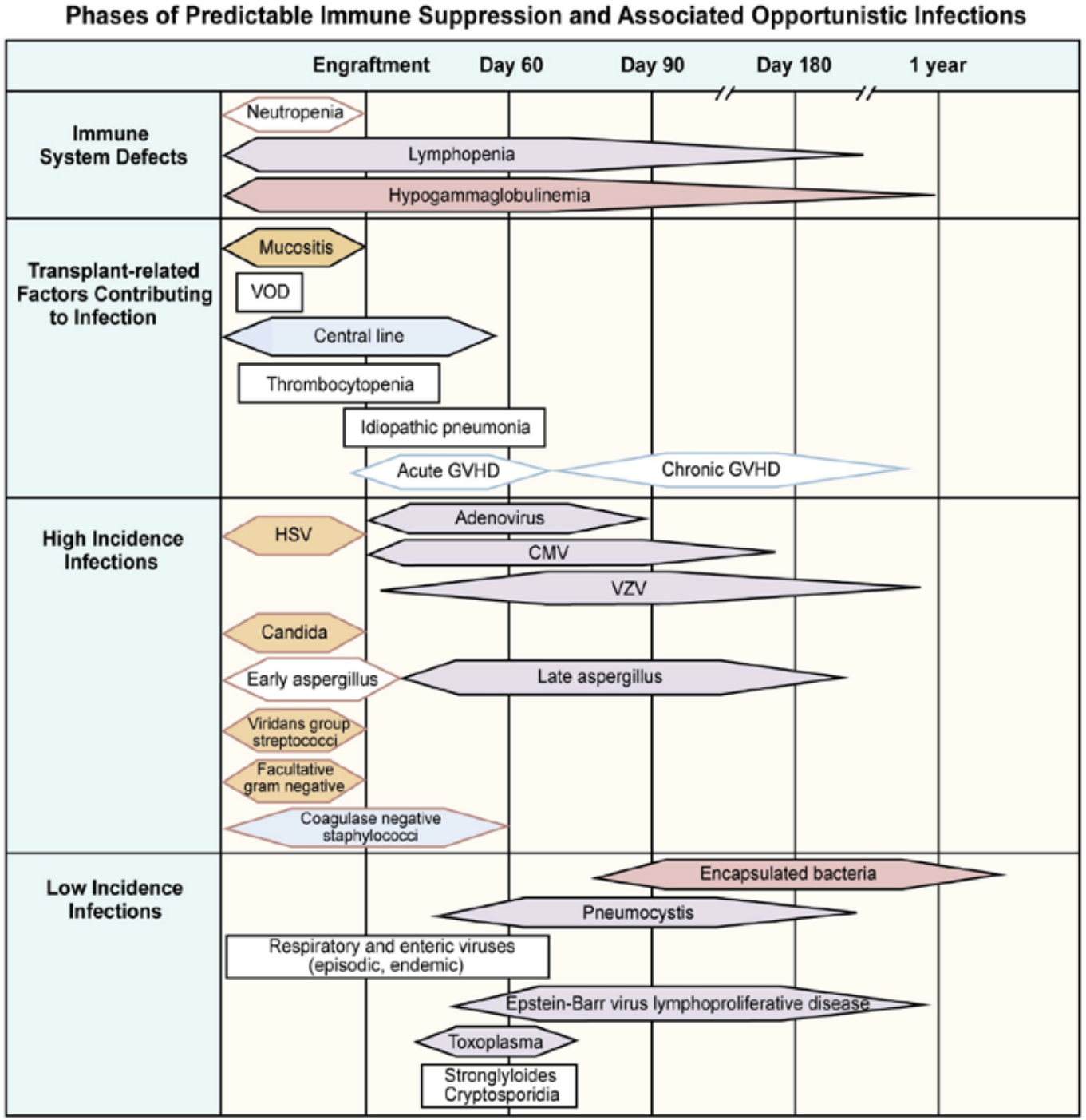
Bronchiolitis Obliterans Syndrome

- Bronchiolitis obliterans syndrome (BOS)
  - Non-productive cough
  - Progressive dyspnea
  - Obstructive changes on PFTs (FEV1/FVC < 70)
  - Air trapping on high res inspiratory/expiratory CT scan
  - Pathology: deposition of collagen and granulation tissue.
- Treat with FAM therapy (Fluticasone, Azithromycin and Montelukast)
  - Can prevent deterioration but rarely regain normal lung function

Chronic GVHD Treatment

- Mild
  - Oral-dexamethasone swishes
  - Ocular- preservative free artificial tears or CSA eye drops (Restasis)
- Moderate
  - Prednisone alone or in combination with a calcineurin inhibitor
  - Second line: Sirolimus, Ibrutinib, Ruxolitinib, ECP, clinical trial
- Average duration of therapy after PBSCT is 2-3 years.
- Increased risk of infections with encapsulated bacteria due to functional asplenia.
  - Prophylaxis with PCN VK

Infections


Phases of Predictable Immune Suppression and Associated Opportunistic Infections
Engraftment
Day 60
Day 90
Day 180
1 year
Immune System Defects
Neutropenia
Lymphopenia
Hypogammaglobulinemia
Transplant-related Factors Contributing to Infection
Mucositis
VOD
Central line
Thrombocytopenia
Idiopathic pneumonia
Acute GVHD
Chronic GVHD
High Incidence Infections
HSV
Adenovirus
CMV
VZV
Candida
Early aspergillus
Late aspergillus
Viridans group streptococci
Facultative gram negative
Coagulase negative staphylococci
Low Incidence Infections
Encapsulated bacteria
Pneumocystis
Respiratory and enteric viruses (episodic, endemic)
Epstein-Barr virus lymphoproliferative disease
Toxoplasma
Stronglyloides
Cryptosporidia

Infectious Prophylaxis

- Fungal
  - Fluconazole for patients at standard risk
  - Voriconazole or posaconazole for patients with prior fungal infection or pulmonary nodules on CT scan.
- Viral
  - Acyclovir or valacyclovir for reactivation of herpes simplex virus and varicella zoster
  - Letermovir for CMV
- PJP
  - Bactrim is first choice
  - Dapsone (check G6PD) (will not cover toxo)
  - Atovaquone
  - Inhaled pentamidine (will not cover toxo)

Early Infectious complications

- Neutropenic fever
  - Add Ceftazidime or Cefepime
  - If suspicion of gram positive-add Vancomycin
  - If Anaerobic due to intra-abdominal infection-add meropenem or metronidazole
  - Persistent fever > 72 hours consider antifungal therapy

CMV

- Patients who are CMV positive with CMV negative donors are most likely to reactivate.
- To prevent CMV disease, patients are started on letermovir
- Monitoring is done by PCR on a weekly basis.
- As soon as the virus is detected at a certain level of copies, ganciclovir or valgancyclovir is preemptively started.
- Foscarnet can also be used.

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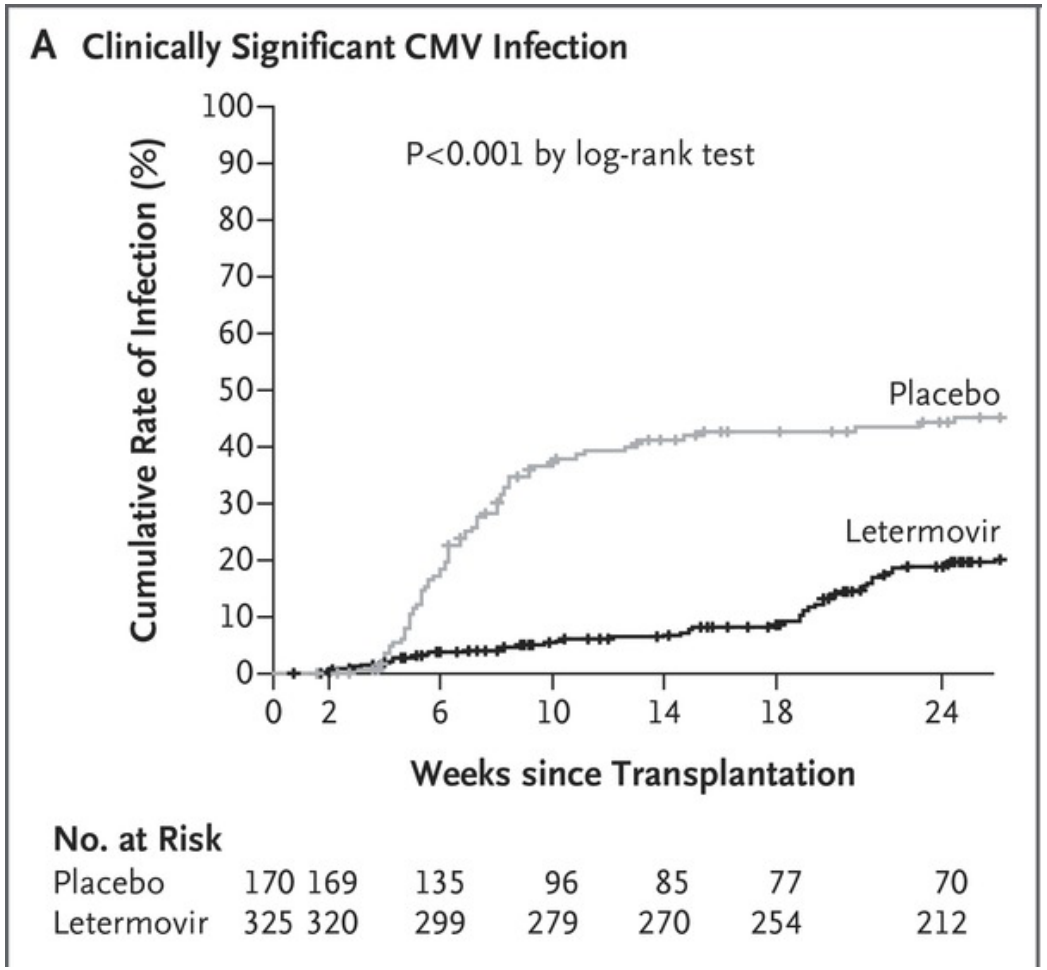

Marty FM et al NEJM 2017

Viral infections

- RSV, influenza, parainfluenza, metapneumovirus can cause upper or lower tract respiratory infections and can be life threatening.
- Patients with URI symptoms pretransplant should get NPT.
- Transplant is delayed for RSV, influenza or parainfluenza.
- Inhaled or oral ribavirin for parainfluenza and RSV.
- Tamiflu can shorten the course of influenza.

Fungal Infections

- Invasive candida should be considered in patients with neutropenia, mucositis or an indwelling catheter.
- Invasive aspergillus should be considered in patients with fevers, respiratory or sinus symptoms or new CNS or skin disease.
- Fungal disease should be confirmed by biopsy or BAL.
- Galactomannan often used in suspected aspergillus.
- Treatment is most frequently with voriconazole or posaconazole.
- Isavuconazonium (Cresemba) for resistant disease.

Late Effects

- 50% of long-term survivors report at least 1 late effect.
- Most common late effects:
  - Osteoporosis
  - Hypothyroid
  - Diabetes
  - Cataracts (10-20%)
  - Avascular Necrosis (10%)
  - Autoimmune disorder (3-5%)
- Among those living 5 years post HCT, there is 30% lower life expectancy than age matched controls.
- Leading cause of death of 5-year survivors: recurrent disease, secondary malignancy, chronic GVHD, respiratory ailments, and cardiovascular events.

Cryptogenic organizing pneumonia (COP)

- Can be seen both early and late.
- Characterized by fever, dry cough, shortness of breath.
- Chest imaging shows diffuse fluffy infiltrate.
- Pathology shows patchy fibrosis, granulation tissues and small airways.
- COP usually responds well to lengthy course of steroids (4-6 months) and is reversible (unlike BOS).

Secondary Malignancies

- Patients receiving high dose chemotherapy and radiation are at highest risk.
- Patients receiving T-cell depleted grafts are at higher risk of PTLD.
- Increase in solid tumors of 6-11% at 15 years.
- Incidence of MDS after Auto transplant can be as high as 10%.

Relapse after Auto Transplant

- Higher risk of relapse when performed after failure of initial chemotherapy.
- Patients who relapse after Auto may respond to conventional chemotherapy.
- RIC Allo-HCT has been found to be safe in those who relapse after Auto.
- Results are better in those with chemo-sensitive disease.

Relapse after Allo Transplant

- May have complete response with discontinuation of immune suppression
  - 25% response
  - 97% GVHD
- Donor Lymphocyte Infusion (DLI) can also result in complete remission
  - Response 60% with CML, 18% with ALL, 15% with AML
  - Patients with active disease should be reinduced prior to DLI
  - May result in GVHD (60%) of patients
  - Starting with low cell dose and increasing can lessen toxicity

Kekre et al Haematologica 2015; Dazzi et al Blood 2000

Newer treatments for relapse

- Chimeric Antigen receptor T-cells.
  - Most common in ALL.
  - Clinical trials for AML and Multiple Myeloma.
- Second Transplant
  - Younger patients
  - Patients who have at least a year interval from first transplant to relapse.
  - Controversial about whether it is beneficial to change donors.

Thank you and Questions???

Systemic therapy in the treatment of bladder cancer

Michael Schweizer, MD
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University of Washington / Fred Hutch Cancer Research Center

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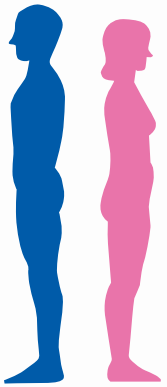
Bladder Cancer - Objectives

- Describe the epidemiology and staging of bladder cancer
- Describe the evidence for the use of neoadjuvant and adjuvant chemotherapy with surgery in the treatment of localized bladder cancer
- Describe the evidence for the use of chemotherapy, anti-PD1/PDL1 therapy and FGFR inhibitors in metastatic bladder cancer

Bladder Cancer - Epidemiology

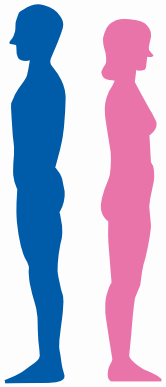
Estimated New Cases

Males			Females		
Prostate	191,930	21%	Breast	276,480	30%
Lung & bronchus	116,300	13%	Lung & bronchus	112,520	12%
Colon & rectum	78,300	9%	Colon & rectum	69,650	8%
Urinary bladder	62,100	7%	Uterine corpus	65,620	7%
Melanoma of the skin	60,190	7%	Thyroid	40,170	4%
Kidney & renal pelvis	45,520	5%	Melanoma of the skin	40,160	4%
Non-Hodgkin lymphoma	42,380	5%	Non-Hodgkin lymphoma	34,860	4%
Oral cavity & pharynx	38,380	4%	Kidney & renal pelvis	28,230	3%
Leukemia	35,470	4%	Pancreas	27,200	3%
Pancreas	30,400	3%	Leukemia	25,060	3%
All Sites	**893,660**	**100%**	**All Sites**	**912,930**	**100%**



Estimated Deaths

Males			Females		
Lung & bronchus	72,500	23%	Lung & bronchus	63,220	22%
Prostate	33,330	10%	Breast	42,170	15%
Colon & rectum	28,630	9%	Colon & rectum	24,570	9%
Pancreas	24,640	8%	Pancreas	22,410	8%
Liver & intrahepatic bile duct	20,020	6%	Ovary	13,940	5%
Leukemia	13,420	4%	Uterine corpus	12,590	4%
Esophagus	13,100	4%	Liver & intrahepatic bile duct	10,140	4%
Urinary bladder	13,050	4%	Leukemia	9,680	3%
Non-Hodgkin lymphoma	11,460	4%	Non-Hodgkin lymphoma	8,480	3%
Brain & other nervous system	10,190	3%	Brain & other nervous system	7,830	3%
All Sites	**321,160**	**100%**	**All Sites**	**285,360**	**100%**



- 62,100 new cases/year
- 13,050 deaths/year
- Lower incidence and risk in women
- Slight decrease in incidence over time

Siegel R et al. Cancer J Clin. 2020

Risks - Bladder cancer

- Tobacco
  - ~ 50% of bladder cancer deaths are due to tobacco use
- Occupational exposures
  - Benzene, aniline dyes, polycyclic hydrocarbons
  - Painters, metal workers, firemen
- Diet

  Carcinogens in water (e.g. arsenic)
  Coffee
  Fluid intake → increased is possibly protective
  Fruits and vegetables → increased is possibly protective
- Chronic inflammation/cystitis
  - Schistosomiasis, indwelling urinary catheters, bladder stones
- Cyclophosphamide
- Prior urothelial carcinoma of the upper tract
- Lynch syndrome

Pathology

- Urothelial carcinoma
  - Majority of cases (~90%)
  - Some element of differentiation to other subtypes is present in 20-50% (Squamous, adenocarcinoma – not pure histology)
  - Micropapillary variant
- Depth of invasion is the most important element in pathologic staging of localized disease
  - Implications for treatment and prognosis
- Treatment paradigm based on invasion
  - Ta, CIS, T1 → non-muscle invasive (~70% of cases)
  - ≥T2 → Muscle invasive
  - Metastatic

Systemic therapy in localized bladder cancer

Neoadjuvant therapy

Advantages

- Early therapy of micrometastatic disease
- Performance status is clearly better prior to cystectomy – better tolerance
- Randomized trial data indicate an OS benefit

Disadvantages

- Delay of potentially curative therapy (cystectomy)

Adjuvant therapy

Advantages

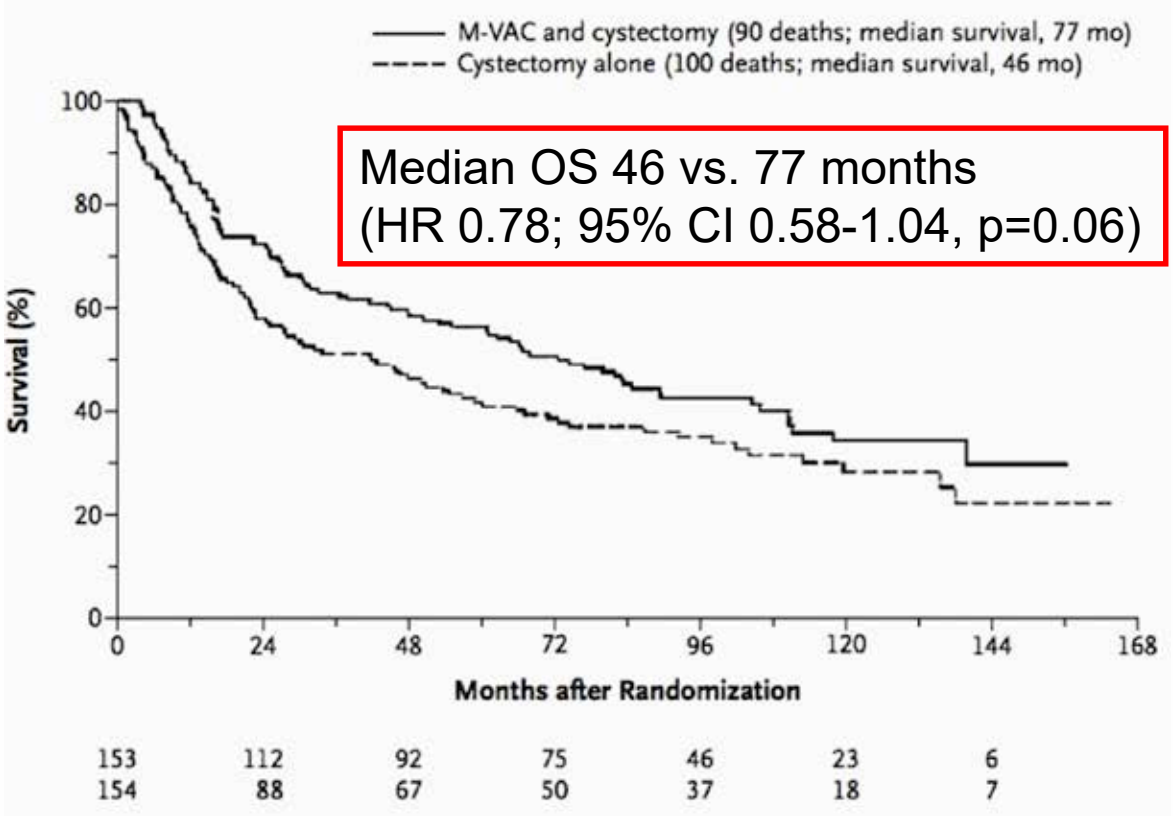
- Better staging and risk assessment

Disadvantages

- Evidence for benefit of adjuvant therapy is not robust

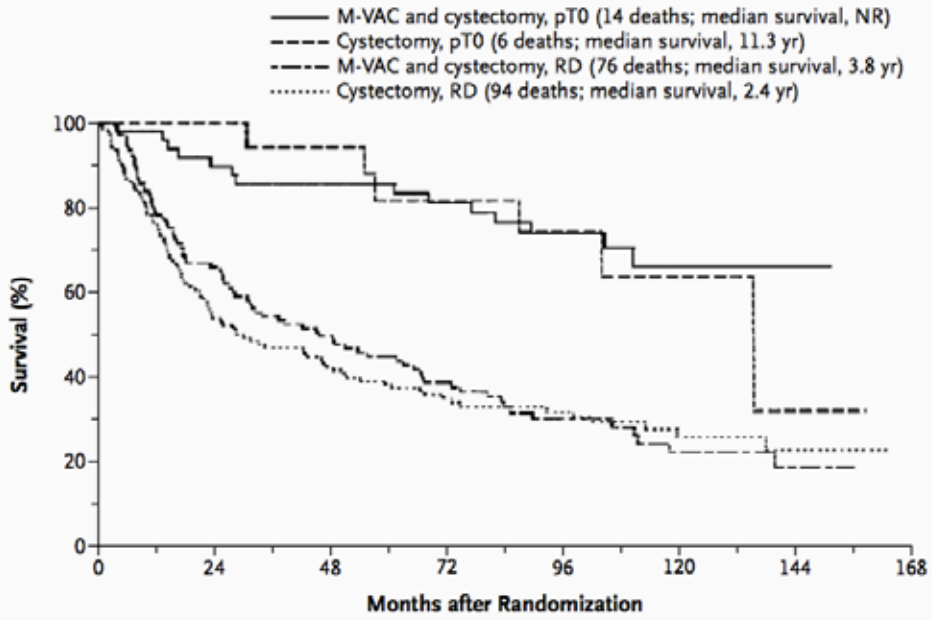
Perioperative Chemotherapy

- SWOG-8710: Neoadjuvant MVAC + Surgery vs. Surgery
- N = 317
- Patients with T2-T4, N0
- 3 cycles of neoadjuvant MVAC (methotrexate, vinblastine, adriamycin, cisplatin)



Grossman, et al. N Engl J Med 2003;349:859

SWOG 8710: Complete Responses Matter



No. at Risk							
M-VAC and cystectomy, pT0	48	43	40	37	26	12	2
Cystectomy, pT0	18	17	15	12	10	4	1
M-VAC and cystectomy, RD	105	69	52	38	20	11	4
Cystectomy, RD	136	71	52	37	27	14	6

Figure 2. Survival According to Treatment Group and Whether Patients Were Pathologically Free of Cancer (pT0) or Had Residual Disease (RD) at the Time of Cystectomy.

M-VAC denotes methotrexate, vinblastine, doxorubicin, and cisplatin, and NR not reached.

- Improved pCR rate with MVAC: 38% vs. 15%
- No clear benefit unless pCR is achieved
- No accurate way to identify patients with 'platinum-sensitive' tumors prior to therapy
  - *ERCC2*, *FANCC*, *ATM*, *RB1?*

Grossman, et al. N Engl J Med 2003;349:859
Allen E, et al. Ca Discovery 2014
Plimack E, et al. Eur Urol 2015

Support for neoadjuvant chemotherapy

Advanced Bladder Cancer (ABC) meta-analysis

- Muscle invasive bladder cancer (T2-4N0)
- Analyzed 3055 patients from 11 randomized trials
- Intervention included cystectomy or radiotherapy
- Platinum **combination chemotherapy** had significant survival benefit (HR= 0.86 (95% CI 0.77 to 0.95, P = 0.003)
  - 5% absolute benefit at 5 years (95% CI 1% to 7%)
  - Overall survival increased from 45% to 50%.
  - All clinical subgroups benefited (cT2-T4)
  - Single agent platinum alone is not recommended (no statistically significant benefit)
- Most common regimens: ddMVAC or gemcitabine + cisplatin

Advanced Bladder Cancer Meta-analysis Collaboration. Lancet. 2003; 361:1927
Update 2008 – Cochrane Library

Problems with Adjuvant Chemotherapy Studies

- Split results in the existing studies
- Small under-powered studies
- Serious methodological flaws
- Early stopping of patient entry
- Confusing statistical analyses
- Reporting of questionable results

Sylvester R and Sternberg C. Ann Oncol. 2001; 11:851-856.

Support for Adjuvant Chemotherapy

Advanced Bladder Cancer (ABC) meta-analysis

- Analyzed 945 patients from 9 randomized trials
- Most with T3-4 or N1
- Platinum combination chemotherapy had statistically significant survival benefit (HR= 0.77, 95% CI 0.59-0.99, p = 0.049)
  - Effect most pronounced in studies where patients had node positive disease
- “However, the impact of trials that stopped early, of patients not receiving allocated treatments or not receiving salvage chemotherapy is less clear.”

Leow, et al. European Urology 2014

Bladder sparing - chemoradiotherapy

- Best performed by teams experienced with this approach
  - Complete TURBT is critical
- Ideal candidate: small tumor size (<5 cm), T2 disease, no hydronephrosis, unifocal disease (i.e. no diffuse CIS)
- Neoadjuvant chemotherapy is not recommended (based on small randomized studies)
  - Benefit of adjuvant chemo unclear
- Concurrent radiation with platinum chemotherapy or mitomycin/5-FU
- Re-evaluation with cystoscopy and biopsy:
  - If residual tumor consider cystectomy
- Poor prognosis if patients have hydronephrosis or lack CR after induction
- Outcomes
  - Outcomes similar compared to cystectomy in select patients
  - 50-60% long-term survival (comparable to cystectomy).
  - Bladder function retained in 75-80% of patients

Shipley, J Clin Oncol. 1998;16:3576
James, N Engl J Med. 2012;366(16):1477-88
Efstathiou, J Clin Oncol. 2009;27:4055
Kulkarni, J Clin Oncol 2017; 35(20): 2299-99

Bladder Cancer – Treatment of localized disease

Conclusion for localized disease

- Meta-analysis supports the use of neoadjuvant chemotherapy prior to cystectomy. NCCN recommends neoadjuvant therapy for appropriate patients.
- Meta-analysis suggests benefit for adjuvant chemotherapy after cystectomy but is limited by the number of randomized studies. NCCN recommends adjuvant therapy (category 2B) if ≥T3 or N+.
- Bladder sparing chemoradiotherapy is an alternative approach, with evidence suggesting similar outcomes to cystectomy in highly selected patients treated by experienced teams.

Metastatic Disease

- Sites of metastasis
  - Lungs
  - Pelvic and abdominal lymph nodes
  - Liver
  - Bone
  - CNS
- Median overall survival likely 24+ months since the approval of immune checkpoint inhibitors
- Metastatic disease has variable prognosis
  - Poor performance status, bone and liver metastasis decrease median survival significantly

Chemotherapy for metastatic disease

- No good randomized studies performed to compare multi-agent chemotherapy to supportive care
- Cisplatin is the most active drug
  - Carboplatin is inferior
  - Meta-analysis of RCTs comparing carboplatin vs. cisplatin regimens
  - Advanced disease, only 4 studies (N=286 patients)

Response*	HR	95% CI	P-value
Objective Response	1.34	1.04 – 1.71	0.02
Complete Response	3.54	1.48 – 8.49	0.005

*Cisplatin compared to carboplatin

- Patients unable to tolerate cisplatin (GFR < 50-60, PS 2)
  - Options: split dose gemcitabine + cisplatin, gemcitabine + carboplatin, anti-PD1/PDL1 drugs (PDL1+ only)

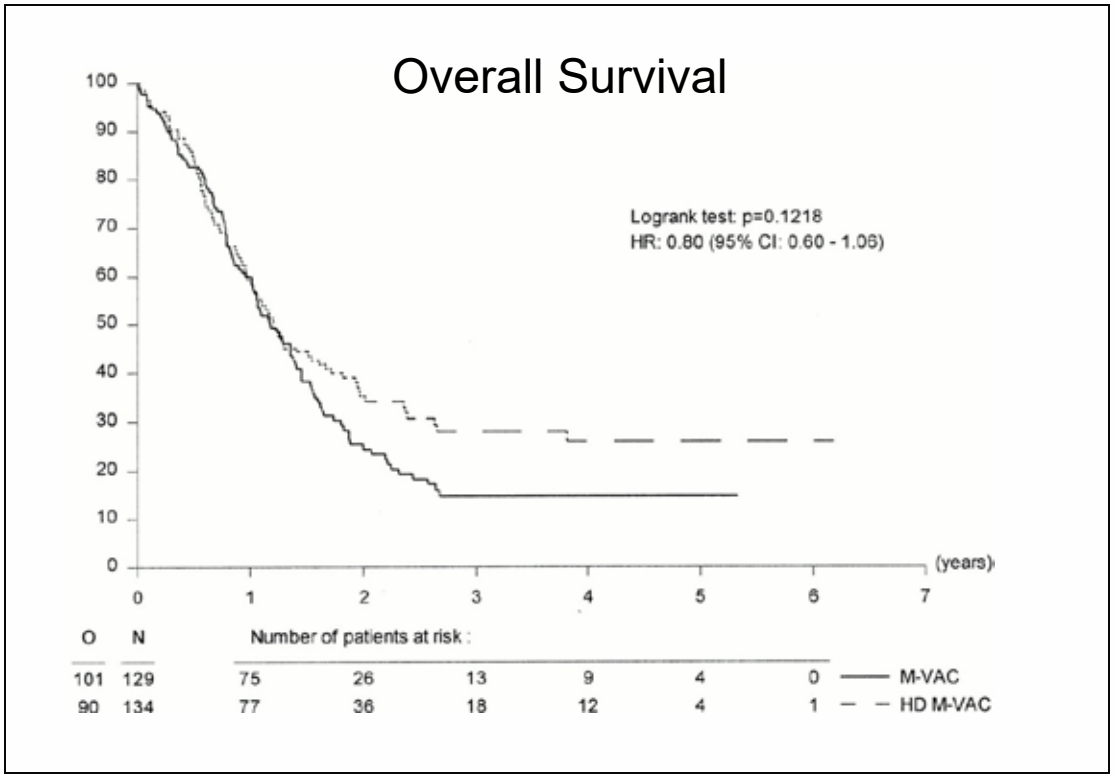
Petrioli, Cancer. 1996;77(2):344-51.
Sternberg, Cancer. 1989; 64(12):2448-58.
Loehrer J Clin Oncol. 1992 ;10:1066
Bajorin J Clin Oncol 17: 3173.
Galsky, et al. Annals of Oncology 23: 406–410, 2012

The MVAC Story

- Methotrexate, vinblastine, doxorubicin, cisplatin
- Survival advantage (12.5 months) over single agent cisplatin (8.2 months)
  - Response rate 39% vs. 12%
  - Toxic death rate 3%
- MVAC superior to CISCA (cisplatin, cytoxan, doxorubicin)
- CMV (cisplatin, methotrexate, vinblastine) less toxic than MVAC, but no randomized study

1. Loehrer PJ et al. J Clin Oncol. 1992; 10:1066-1073.
2. Logothetis CJ et al. J Clin Oncol. 1990; 8:1050-1055.
3. Mead GM et al. Br J Cancer. 1998; 78:1067-1075.

MVAC vs. dose dense/accelerated MVAC - metastatic

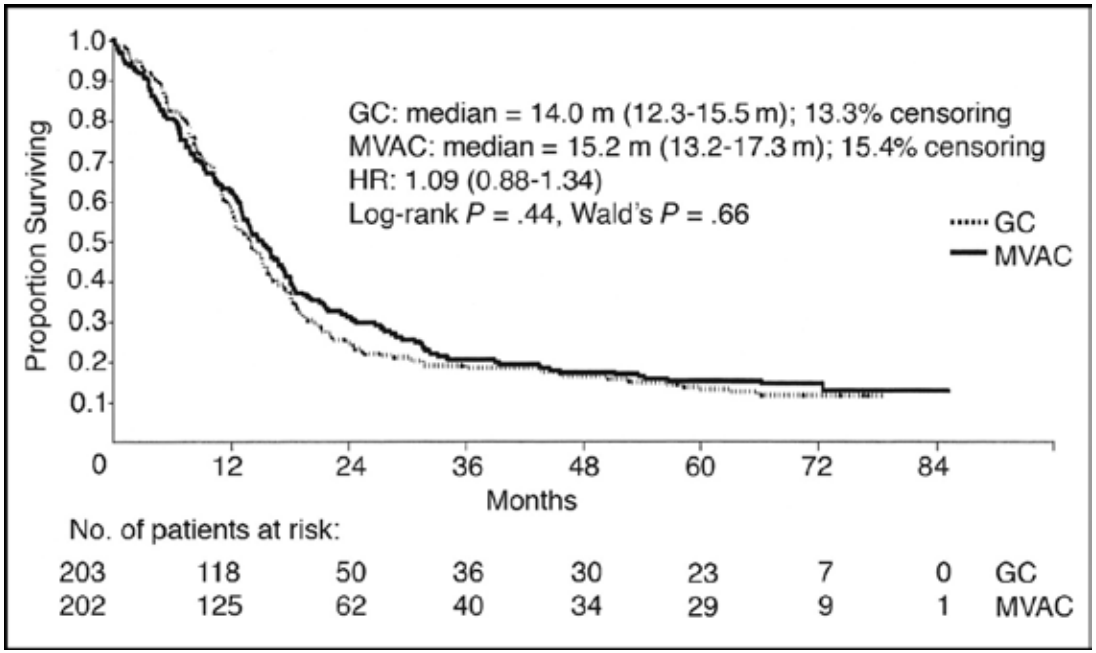


- Dose dense MVAC
  - Same dose as day 1&2 of MVAC, but given every 2 weeks
  - GCSF support
- Overall response rate 62 vs. 50% (p=0.06)
- CR 21% vs. 9% (p=0.009)
- PFS 9.1 vs. 8.2 months (p=0.037)
- Overall survival equivalent
- Standard MVAC more toxic

- <u>ddMVAC is recommended over MVAC by NCCN.</u>

Sternberg CN et al. J Clin Oncol. 2001; 19:2638

MVAC vs. Gemcitabine/cisplatin – metastatic



- N=405
- Median OS 14 vs. 15.2 months
- Less grade 3-5 hematologic toxicity in patients receiving GC

- No bone or visceral metastases:
  Med OS 18.4 vs. 10.3 months
  5-year survival 20.9% vs. 6.8%.
- Karnofsky 80-100:
  Med OS 16 vs. 8.3 months.

von der Maase H et al. JCO 2005;23:4602-4608

Bladder cancer – Second line and beyond

Immune checkpoint inhibitors (CPI)

- Multiple agents approved now: pembrolizumab, atezolizumab, nivolumab, durvalumab, avelumab

Antibody drug conjugates: Enfortumab vedotin

FGFR inhibitors

- Erdafitinib approved; other approvals likely in the future

Multiple chemotherapeutics have activity

- Docetaxel, paclitaxel, pemetrexed, others

Response Rates to Chemo Post-Platinum are Low

Author	Agent	Patients	RR (%)	PFS (months)	OS (months)
Witte[1]	Ifosfamide	56	20	2	5
McCaffrey[2]	Docetaxel	30	13	4	9
Lorusso[3]	Gemcitabine	31	23	4	5
Vaughn[4]	Paclitaxel	31	10	2	7
Sweeney[5]	Pemetrexed	47	28	3	10
Galsky[6]	Pemetrexed	13	8	NR	NR
Bambury[7]	Pemetrexed	129	5	2	7
Dreicer[8]	Ixabepilone	45	12	3	8
Bellmunt[9]	Vinflunine	253	9	3	7
Dreicer[10]	Sorafenib	22	0	2	7
Wulfing[11]	Lapatinib	59	2	2	4
Gallagher[12]	Sunitinib	77	5	2	7
Ko[13]	Nab-paclitaxel	48	28	6	11

[1]JCO 1997;15(1):589-93 / [2]JCO 1997;15(5):1853-7 / [3]Eur J Can 1998;34(8)1208-12 / [4]JCO 2002;20(4):937-40 / [5]JCO 2006;24(21):3451-7 / [6]Invest New Drugs 2007;25(3):265-70 / [7]The Oncologist 2015;20(5):508-15 / [8]Cancer 2007;110(4):759-63 / [9]JCO 2009;27(27):4454-61 / [10]Cancer 2009;115(18):4090-5 / [11]Cancer 2009;115(13):2881-90 / [12]JCO 2010;28(8)1373-79 / [13]Lancet Oncol 2013;14(8):769-76.

Slide courtesy of Noah Hahn from ASCO 2015 Discussion

Checkpoint Inhibitors Approved for Platinum-Treated Patients

Drug	Target	N	ORR (%)	CR (%)	PFS (mos)	OS (mos)	1yr Sur (%)	FDA approval
Atezolizumab	PDL1	310	15	6	2.1	7.9	36	2016
Pembrolizumab	PD1	27	26	11	2	13	50	2017
Nivolumab	PD1	265	20		2	8.7		2017
Durvalumab	PDL1	191	18	4		18.2		2017
Avelumab	PDL1	161	17	6	3	13.7	51	2017

Summary- All CPI inhibitors active in Post platinum disease; ORR-15-26%; Small fraction with CR; Pembrolizumab demonstrating superior OS to chemotherapy

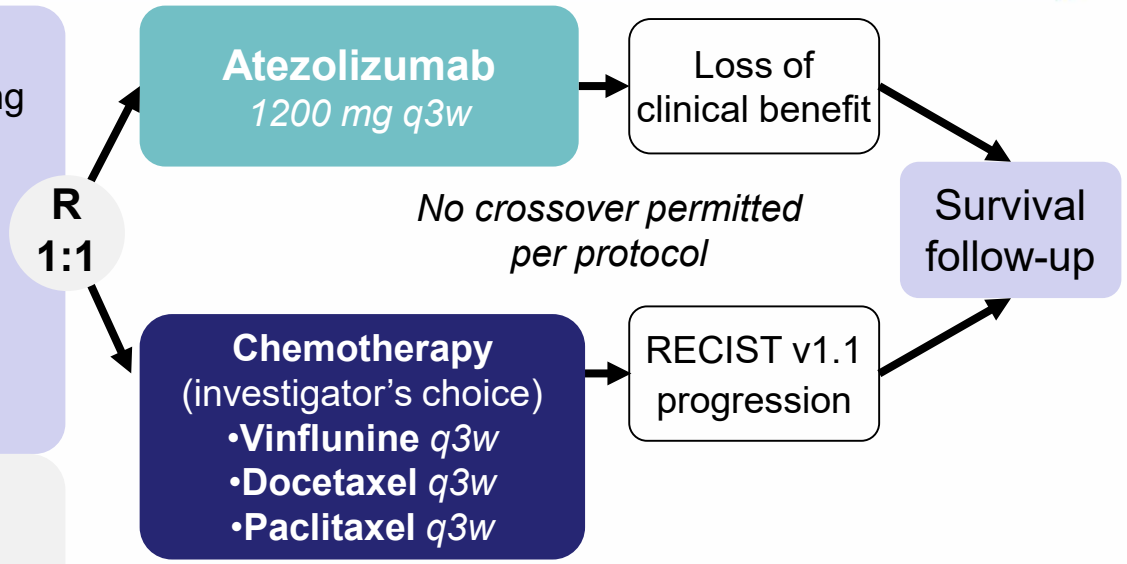
Rosenberg JE et al. Lancet 2016; 387:1909-20. Sharma P et al. Lancet Oncol 2017; 18:312-22. Apolo AB et al. J Clin Oncol 2017; 35:2117-24. Powles T et al. JAMA Oncol 2017; 3:e172411.

Imvigor 211 Randomized Phase 3 Trial Design

Key Eligibility Criteria[a]
- mUC with progression during or following platinum-based chemotherapy
  - ≤ 2 prior lines of therapy
- Measurable disease per RECIST v1.1
- ECOG PS 0-1
- Evaluable sample for PD-L1 testing
- TCC histology as primary component

(N = 931)

Stratification Factors
- No. of risk factors[b] (0 vs. 1/2/3)
- Liver metastases (yes vs. no)
- PD-L1 status (0/1 vs. 2/3)
- Chemotherapy (vinflunine vs. taxanes)



- **Primary endpoint**
  - OS, tested hierarchically in pre-specified populations

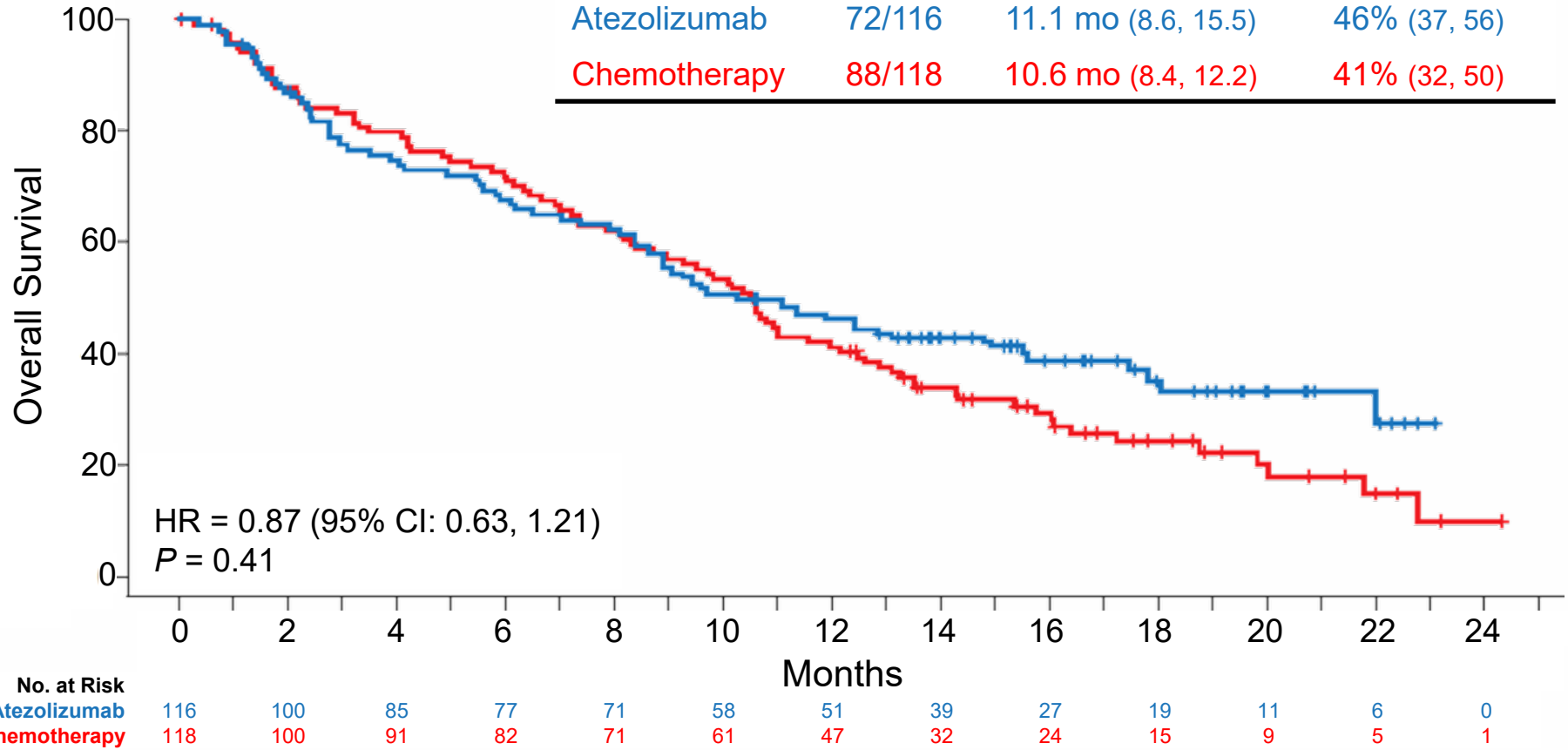
- **Additional endpoints**
  - Efficacy: RECIST v1.1 ORR, PFS and DOR[c]
  - Safety
  - PROs: EORTC QLQ-C30

DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; EORTC, European Organisation for Research and Treatment of Cancer; PRO, patient-reported outcome; q3w, every three weeks; RECIST, Response Evaluation Criteria In Solid Tumors; TCC, transitional cell carcinoma. [a] ClinicalTrials.gov, NCT02302807. [b] Defined by time from prior chemotherapy < 3 mo, ECOG performance status > 0 and hemoglobin < 10 g/dL. [c] Confirmed response was not required for secondary efficacy endpoints. This analysis reports exploratory confirmed responses.

Powles T et al. Lancet 2018; 391:748-57.

Overall Survival: IC2/3 Population

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	72/116	11.1 mo (8.6, 15.5)	46% (37, 56)
Chemotherapy	88/118	10.6 mo (8.4, 12.2)	41% (32, 50)

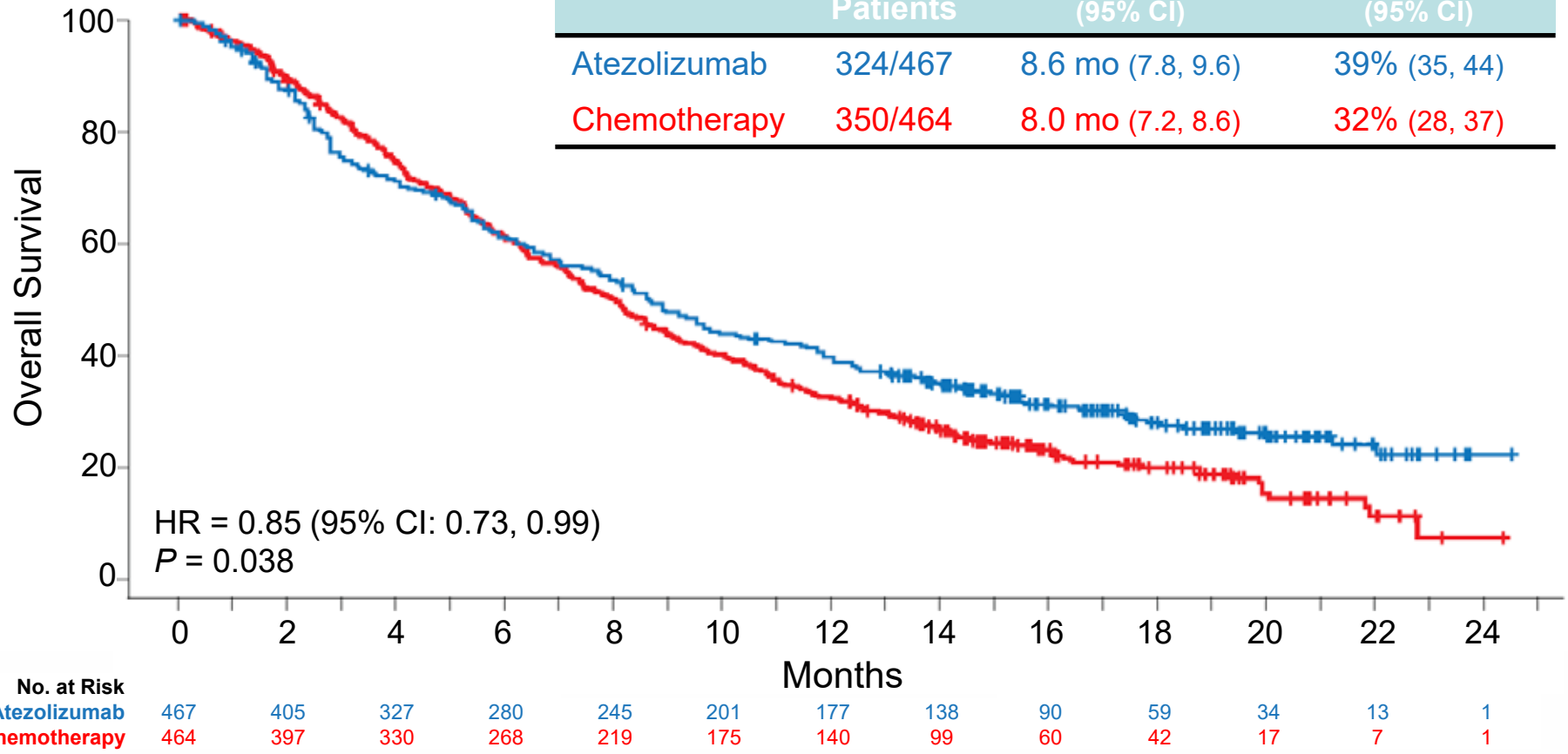


No. at Risk													
Atezolizumab	116	100	85	77	71	58	51	39	27	19	11	6	0
Chemotherapy	118	100	91	82	71	61	47	32	24	15	9	5	1

Powles T et al. Lancet 2018; 391:748-57.

Overall Survival: ITT Population

	Events/ Patients	Median OS (95% CI)	12-mo OS Rate (95% CI)
Atezolizumab	324/467	8.6 mo (7.8, 9.6)	39% (35, 44)
Chemotherapy	350/464	8.0 mo (7.2, 8.6)	32% (28, 37)

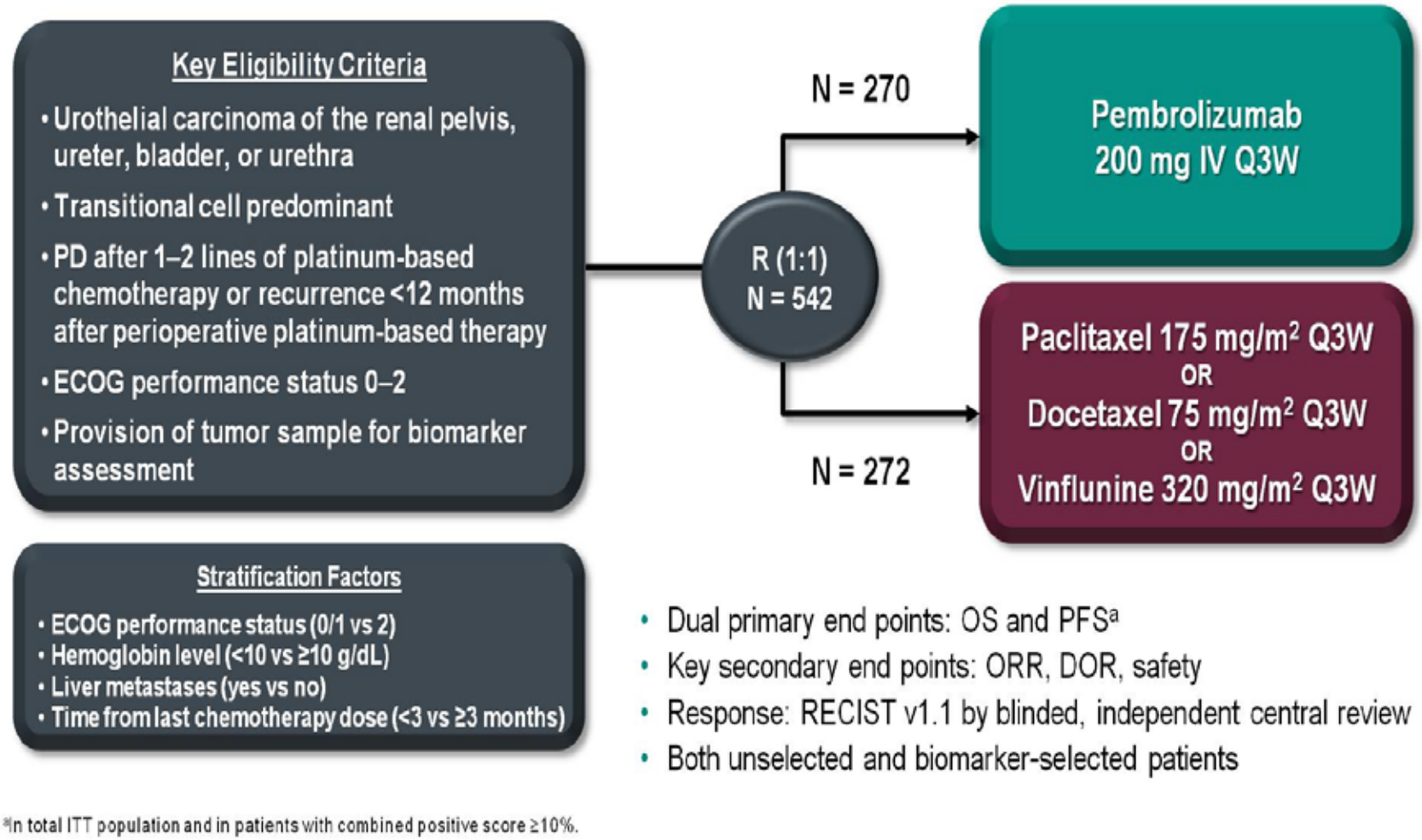


No. at Risk													
Atezolizumab	467	405	327	280	245	201	177	138	90	59	34	13	1
Chemotherapy	464	397	330	268	219	175	140	99	60	42	17	7	1

- Median follow-up duration in ITT population: 17.3 mo (range, 0 to 24.5 mo)

Powles T et al. Lancet 2018; 391:748-57.

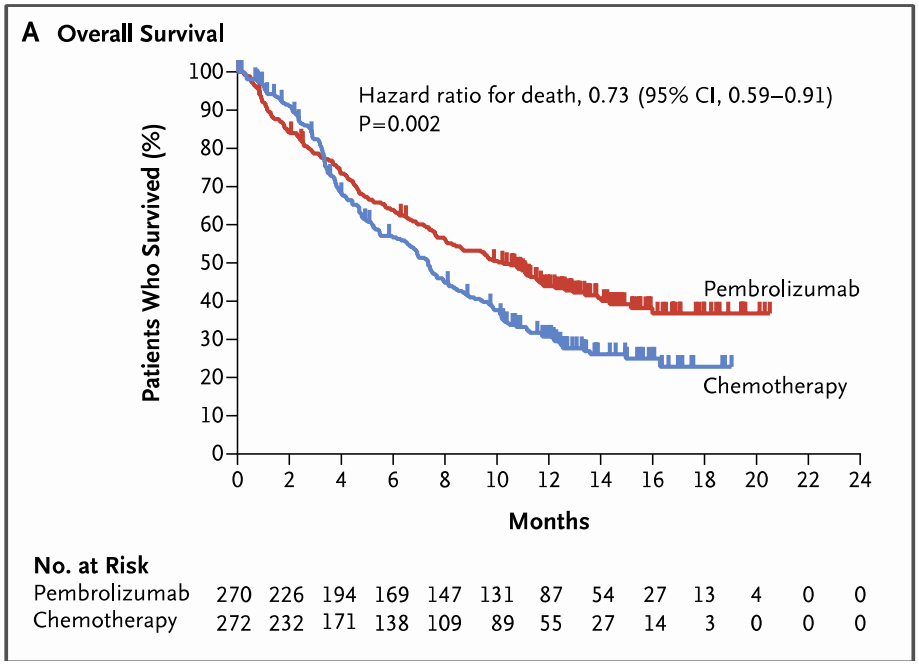
KEYNOTE-045: Phase 3 Post-Platinum Trial Design

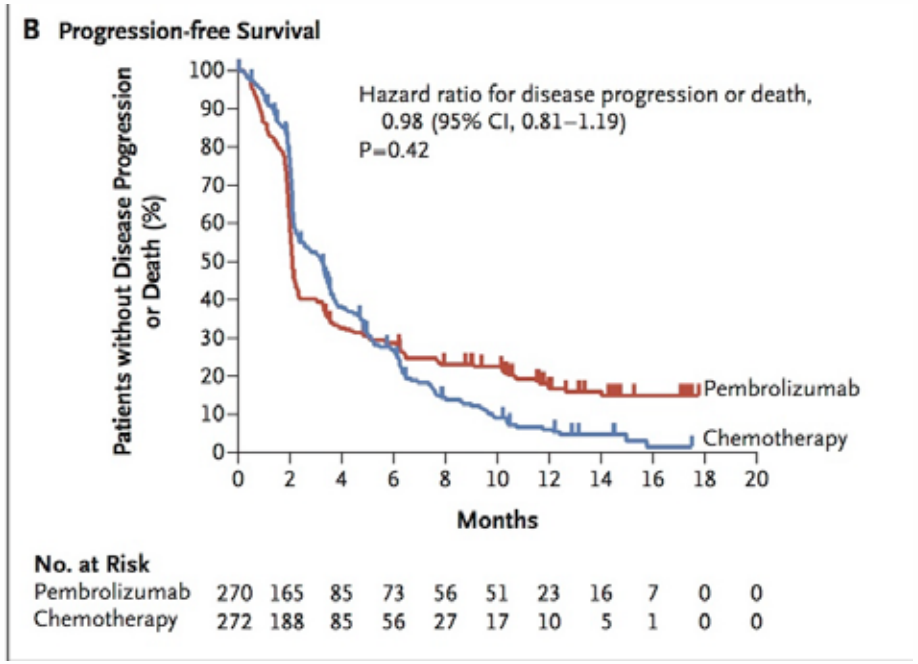


[a]In total ITT population and in patients with combined positive score ≥10%.

Bellmunt J et al. N Engl J Med 2017; 376:1015-26.

KEYNOTE-045: Pembrolizumab vs Chemo

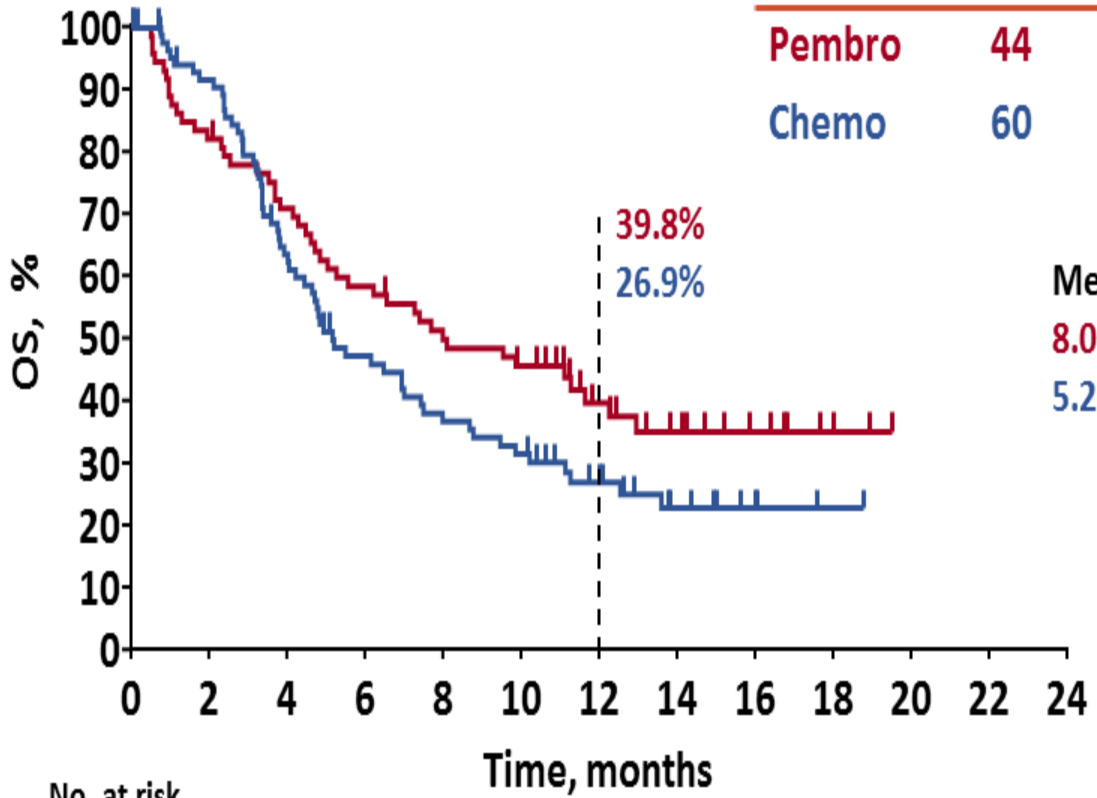




- Median OS (pembro vs. chemo): 10.3 mos vs. 7.4 mos (P=0.002)
- Median PFS: 2.1 mos vs. 3.3 mos (P=NS)
  - 18 mos PFS: 16.8% vs. 3.5%
- Response rate: 21.1% vs. 11% (P=0.001)

Overall Survival: CPS ≥10%

	Events, n	HR (95% CI)	*P*
Pembro	44	0.57 (0.37-0.88)	0.0048
Chemo	60		



Median (95% CI)
8.0 mo (5.0-12.3)
5.2 mo (4.0-7.4)

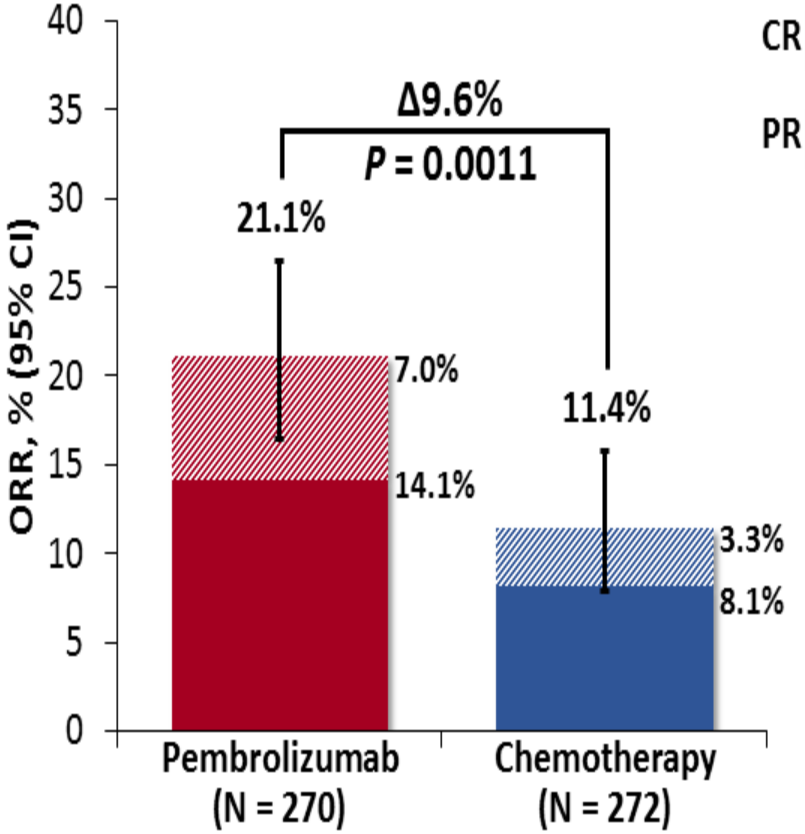
No. at risk

74	60	51	42	35	31	18	12	7	3	0	0	0
90	76	51	36	28	24	16	8	4	1	0	0	0

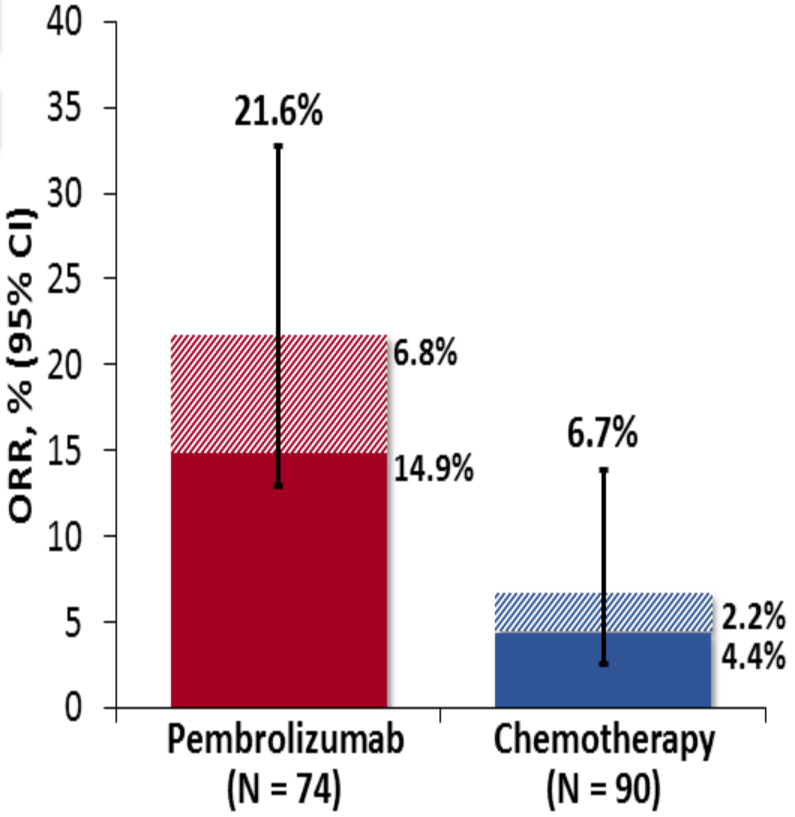
Data cutoff date: Sep 7, 2016.

Confirmed Objective Response Rate

Total Population



CPS ≥10% Population



No alpha allocated to the comparison of ORR in the CPS ≥10% population.
Assessed per RECIST v1.1 by blinded, independent central review.
Data cutoff date: Sep 7, 2016.

Checkpoint Inhibitors with Regulatory Approval in Cisplatin Ineligible Patients

Drug	N	ORR (%)	CR (%)	PFS	OS
Atezolizumb ImVigor 210	119	24	7	2.7	14.8
Pembrolizumab Key Note 052	370	29	7		6 mos OS: 67%

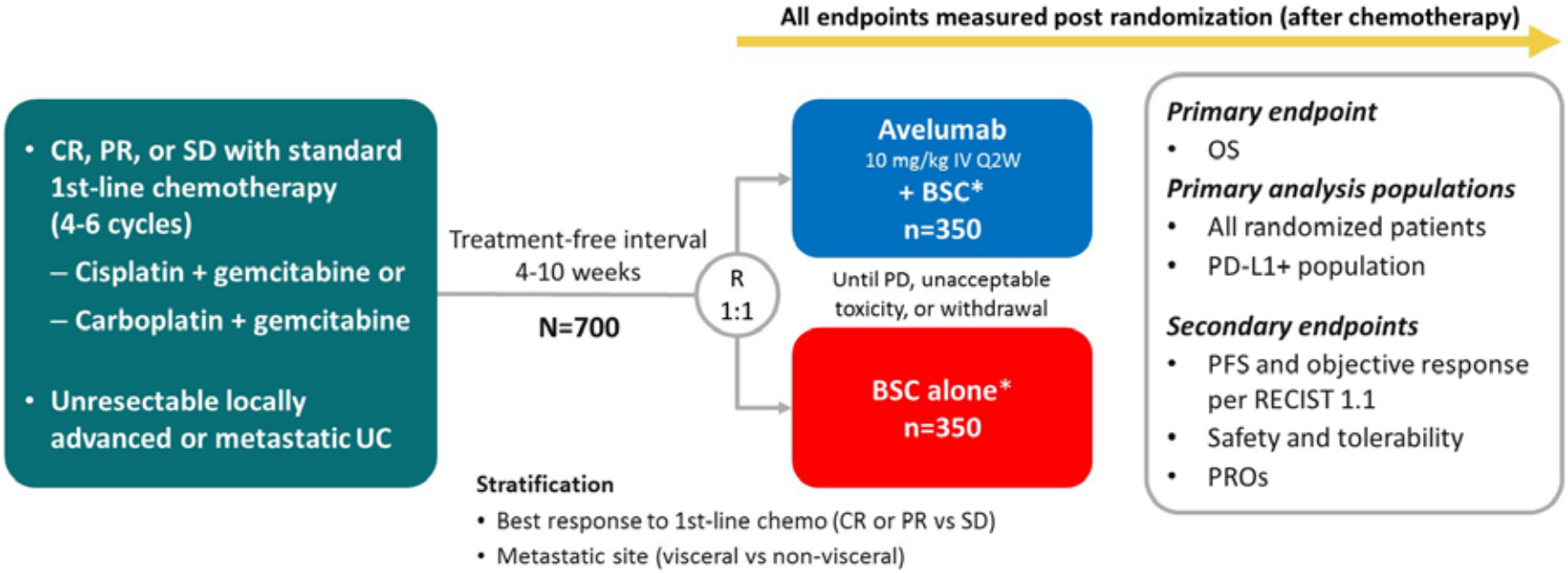
- Carboplatin/Gemcitabine:
  - ORR 36%; PFS-5.8 mos; OS-9.3 mos

Balar AV et al. Lancet 2017; 389:67-76. Balar AV et al. Lancet Oncol 2017; 18:1483-92.

FDA Alert: May 18, 2018 and Subsequent Label Changes

- In two ongoing trials, low PD-L1 expressing patients receiving pembrolizumab (KEYNOTE-361) or atezolizumab (IMVIGOR-130) monotherapy were found to have inferior survival to cisplatin or carboplatin
- Label now restricted to mandate PD-L1 testing for patients planning to receive monotherapy with either agent in the first-line who are *cisplatin*-ineligible
- If ineligible for *any* platinum chemo, PD-L1 testing is not mandated
- Label does not change for previously platinum-treated patients

JAVELIN Bladder 100 study design (NCT02603432)



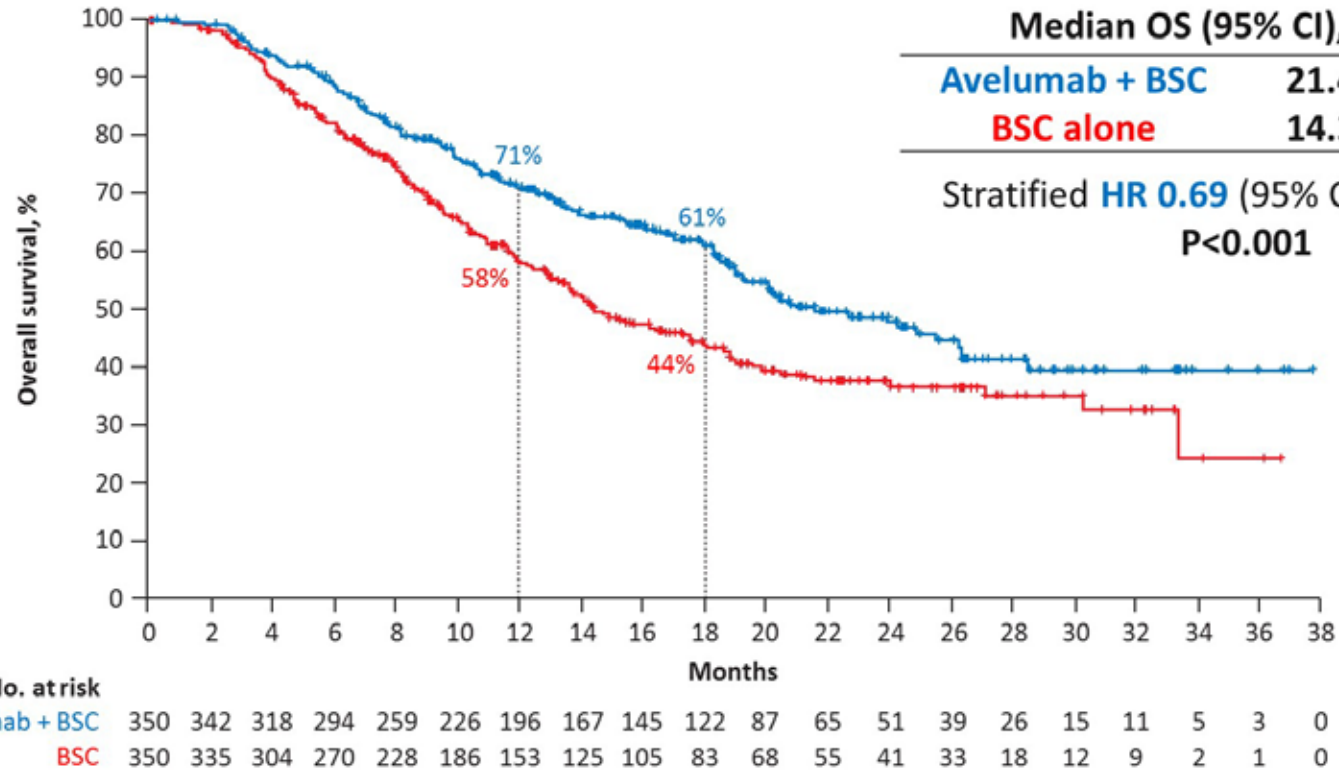
PD-L1+ status was defined as PD-L1 expression in ≥25% of tumor cells or in ≥25% or 100% of tumor-associated immune cells if the percentage of immune cells was >1% or ≤1%, respectively, using the Ventana SP263 assay; 358 patients (51%) had a PD-L1–positive tumor

BSC, best supportive care; **CR**, complete response; **IV**, intravenous; **PR**, partial response; **PRO**, patient reported outcome; **Q2W**, every 2 weeks; **R**, randomization; **RECIST 1.1**, Response Evaluation Criteria in Solid Tumors version 1.1; **SD**, stable disease

*BSC (eg, antibiotics, nutritional support, hydration, or pain management) was administered per local practice based on patient needs and clinical judgment; other systemic antitumor therapy was not permitted, but palliative local radiotherapy for isolated lesions was acceptable

Powles, et al. ASCO 2020

OS in the overall population



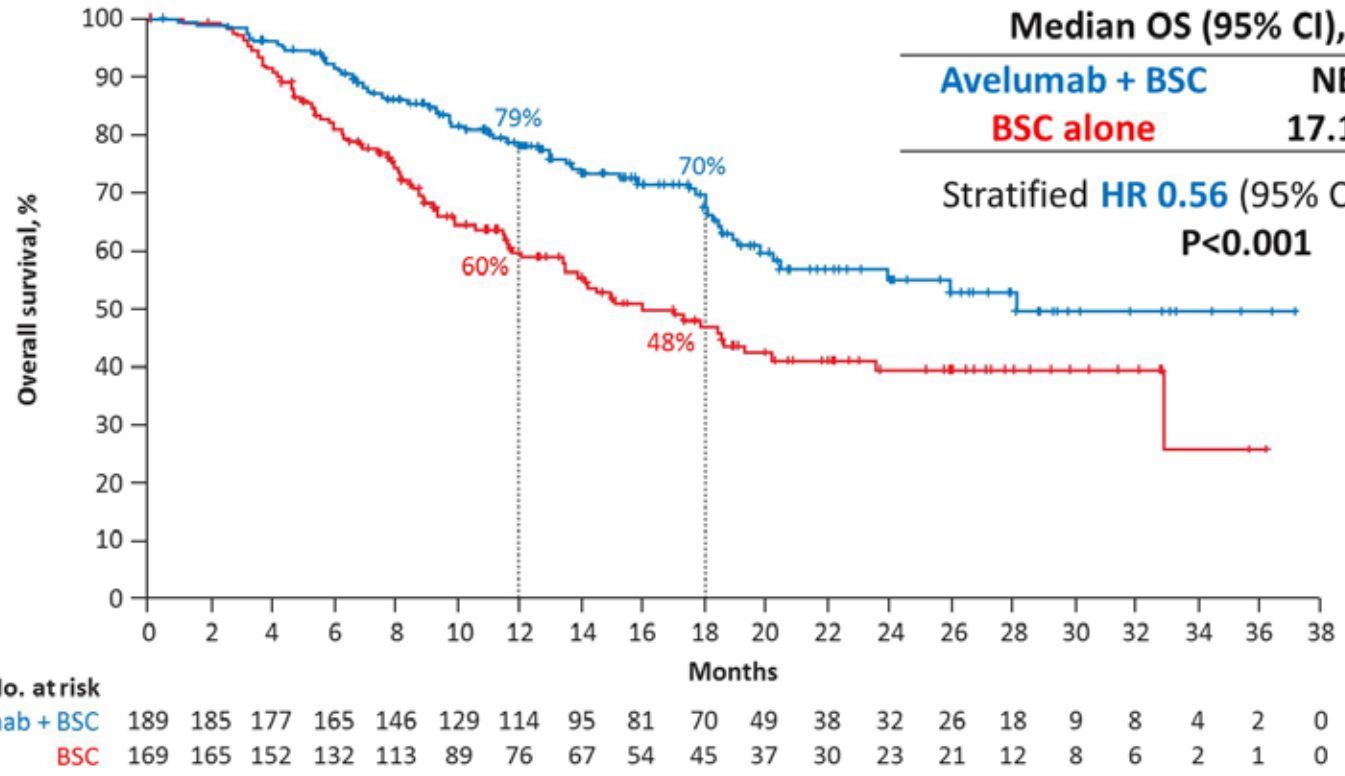
Median OS (95% CI), months	
Avelumab + BSC	**21.4** (18.9, 26.1)
BSC alone	**14.3** (12.9, 17.9)

Stratified **HR 0.69** (95% CI, 0.56, 0.86)

P<0.001

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0053)

OS in the PD-L1+ population



Median OS (95% CI), months	
Avelumab + BSC	**NE** (20.3, NE)
BSC alone	**17.1** (13.5, 23.7)

Stratified **HR 0.56** (95% CI, 0.40, 0.79)

P<0.001

OS was measured post randomization (after chemotherapy); the OS analysis crossed the prespecified efficacy boundary based on the alpha-spending function (P<0.0014). **NE**, not estimable

Presented By Thomas Powles at TBD

Confirmed objective response

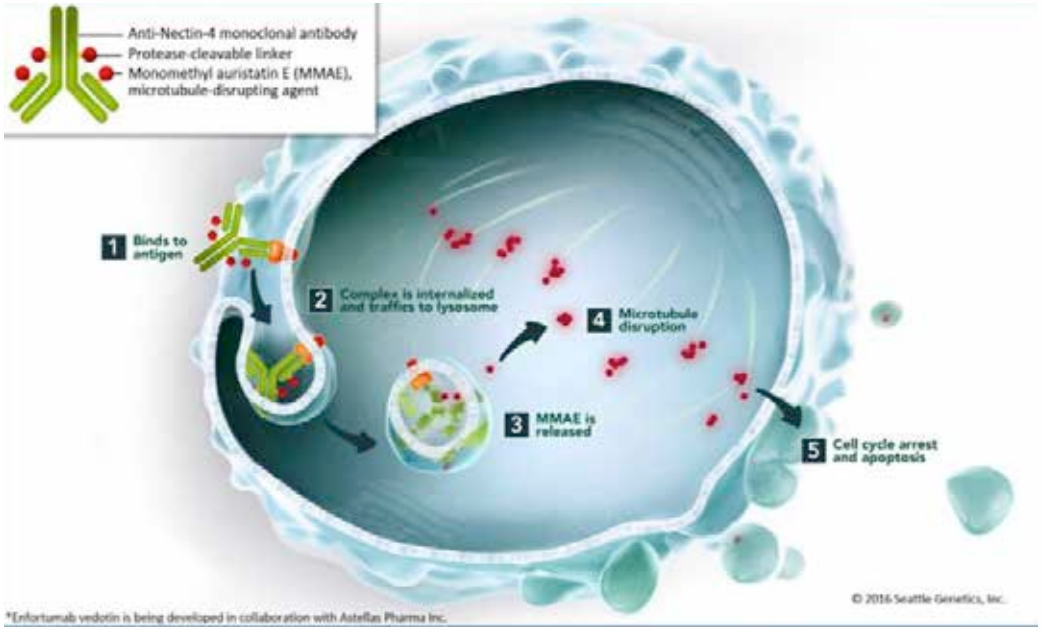
Response to maintenance therapy post randomization

	Overall population		PD-L1+ population	
	Avelumab + BSC (N=350)	BSC alone (N=350)	Avelumab + BSC (N=189)	BSC alone (N=169)
ORR, %	**9.7**	**1.4**	**13.8**	**1.2**
(95% CI)	(6.8, 13.3)	(0.5, 3.3)	(9.2, 19.5)	(0.1, 4.2)
Stratified odds ratio (95% CI)	7.464 (2.824, 24.445)		12.699 (3.160, 114.115)	
Best overall response, %				
Complete response	6.0	0.9	9.5	0.6
Partial response	3.7	0.6	4.2	0.6
Stable disease	12.6	13.1	10.1	13.6
Non-CR/non-PD	18.9	12.9	20.1	13.0
Progressive disease	37.1	48.3	31.2	48.5
Not evaluable*	21.7	24.3	24.9	23.7
Disease control, %†	41.1	27.4	43.9	27.8

PD, progressive disease
Objective response was assessed by independent radiology review; in patients with a CR after chemotherapy, best overall response was not evaluable if no evidence of disease at baseline was maintained after randomization, or PD if disease progression occurred after randomization
*Reasons for not evaluable included no evidence of disease at baseline; no post-baseline assessments; SD <6 weeks after randomization; PD >12 weeks after randomization; new anticancer therapy started before first post-baseline assessment; or all post-baseline assessments have objective response of not evaluable
†Patients with a best overall response of CR, PR, SD, or non-CR/non-PD

Enfortumab Vedotin

- Enfortumab vedotin: antibody-drug conjugate targeting Nectin-4
- Nectin-4 is a transmember cell adhesion molecule that is highly expressed (>90%) on urothelial carcinomas
- Accelerated FDA approval in 12/2019 → post-platinum chemo and anti-PD1/PDL1



Adapted from Rosenberg, et al. 2018 ASCO Annual Meeting

EV-101: Phase 1 Study of Enfortumab Vedotin Monotherapy (NCT02091999)

- The data presented here are updated results from all patients with mUC treated with 1.25 mg/kg[1]

Part A (closed to accrual)

Dose-escalation/-expansion adaptive trial design utilizing a Continual Reassessment Method to determine RP2D

- Cohort 1: 0.5 mg/kg
- Cohort 2: 0.75 mg/kg
- Cohort 3: 1 mg/kg
- **Cohort 4: 1.25 mg/kg**

Nectin-4 expressing tumors, including mUC

RP2D
1.25 mg/kg

Part B (enrolling)*

Dose expansion: 3 cohorts

- **Cohort 1:** mUC with severe renal insufficiency (0.75 mg/kg escalating to 1.25 mg/kg)
- **Cohort 2:** NSCLC (1.25 mg/kg)
- **Cohort 3:** Ovarian cancer (1.25 mg/kg)

*Only Cohort 1 is actively recruiting

Part C (closed to accrual)

Dose expansion: 1 cohort

- **CPI-treated mUC patients (1.25 mg/kg)**

[1]Petrylak DP et al. *J Clin Oncol*. 2017;35:106-106.

Rosenberg, et al. JCO 2019
Rosenberg, et al. 2018 ASCO Annual Meeting

Radiopraphic Responses

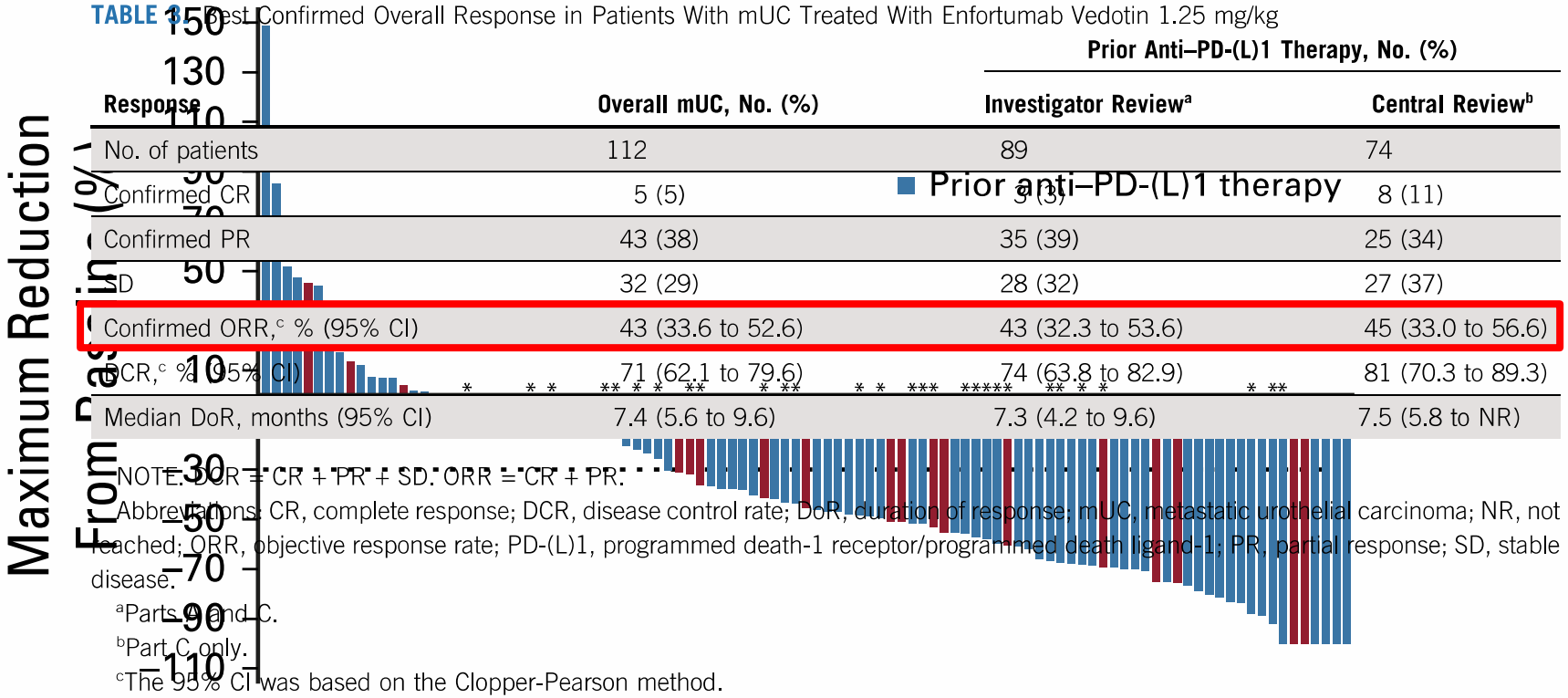


TABLE 3 Best Confirmed Overall Response in Patients With mUC Treated With Enfortumab Vedotin 1.25 mg/kg

Response	Overall mUC, No. (%)	Prior Anti–PD-(L)1 Therapy, No. (%)	
		Investigator Review[a]	Central Review[b]
No. of patients	112	89	74
Confirmed CR	5 (5)	3 (3)	8 (11)
Confirmed PR	43 (38)	35 (39)	25 (34)
SD	32 (29)	28 (32)	27 (37)
Confirmed ORR,[c] % (95% CI)	43 (33.6 to 52.6)	43 (32.3 to 53.6)	45 (33.0 to 56.6)
DCR,[c] % (95% CI)	71 (62.1 to 79.6)	74 (63.8 to 82.9)	81 (70.3 to 89.3)
Median DoR, months (95% CI)	7.4 (5.6 to 9.6)	7.3 (4.2 to 9.6)	7.5 (5.8 to NR)

NOTE: DCR = CR + PR + SD. ORR = CR + PR.

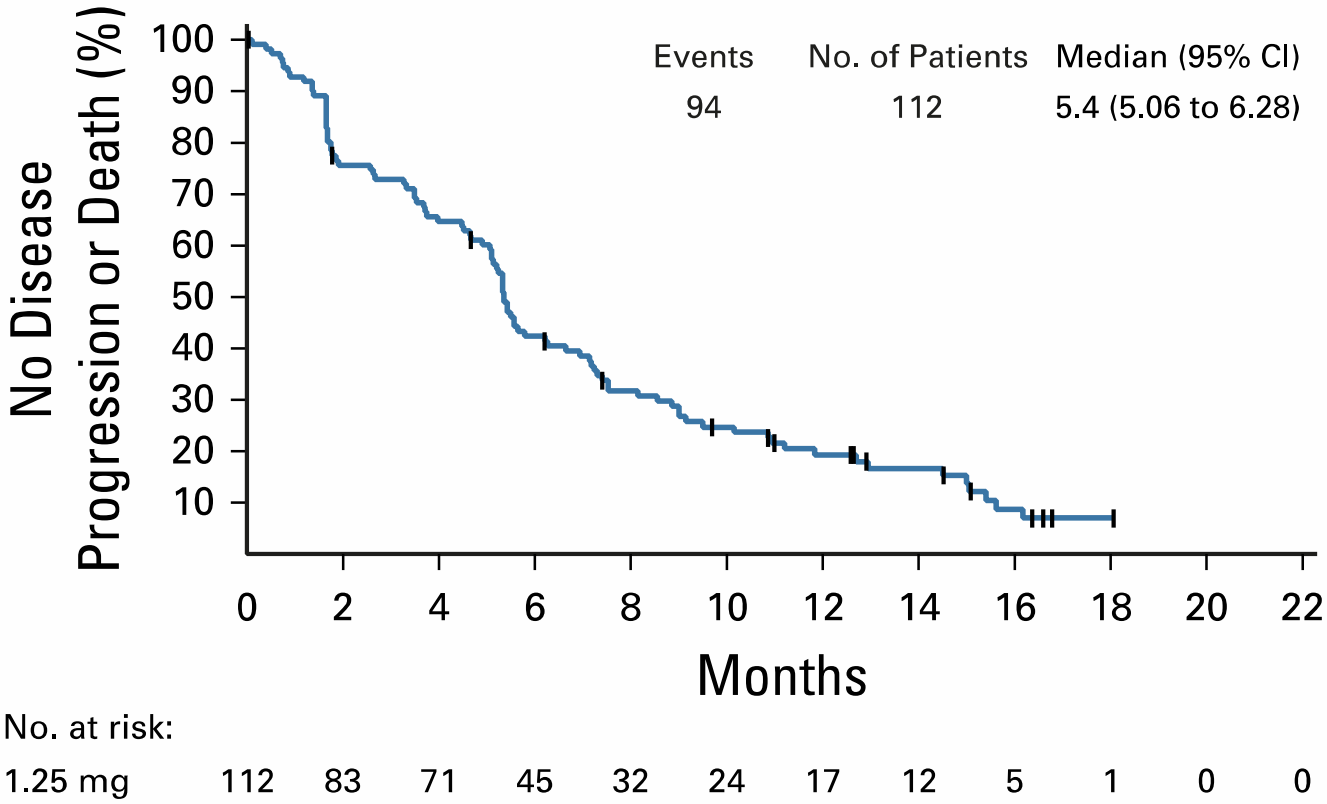
Abbreviations: CR, complete response; DCR, disease control rate; DoR, duration of response; mUC, metastatic urothelial carcinoma; NR, not reached; ORR, objective response rate; PD-(L)1, programmed death-1 receptor/programmed death ligand-1; PR, partial response; SD, stable disease.

[a]Parts A and C.

[b]Part C only.

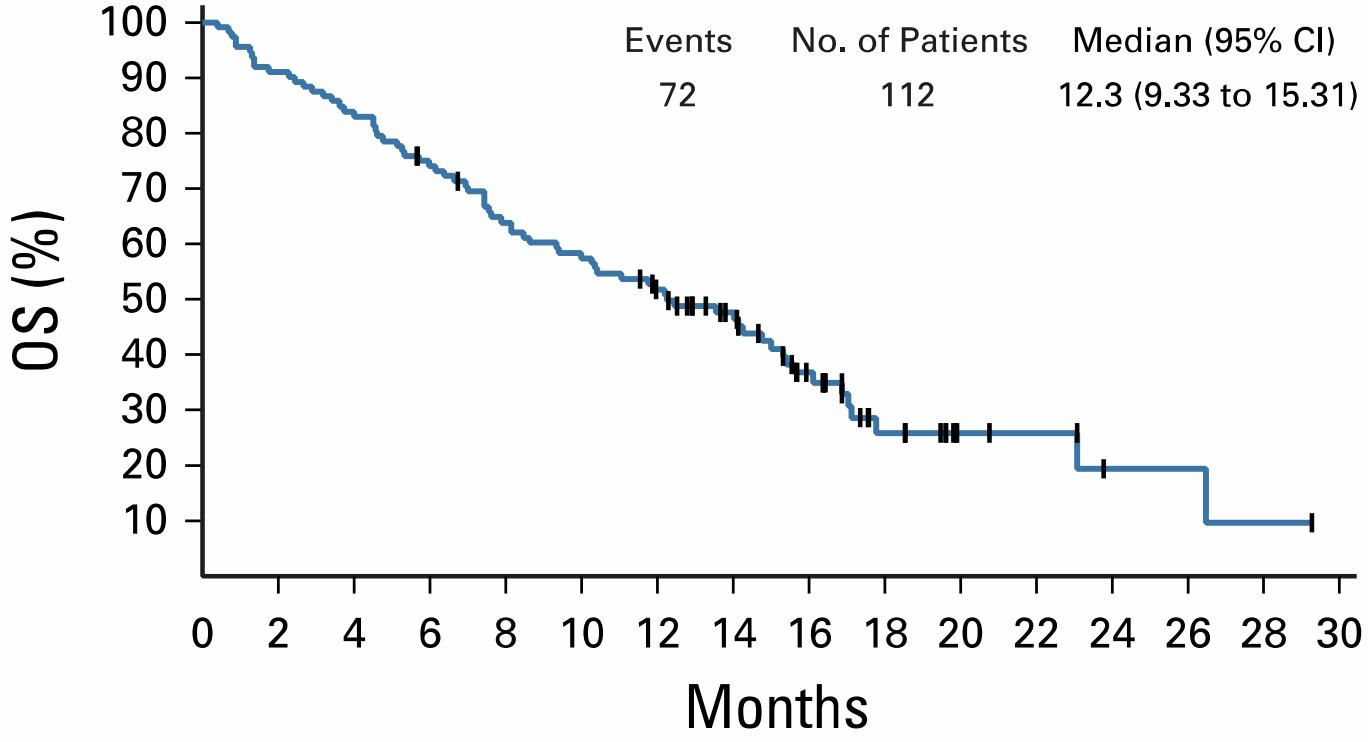
[c]The 95% CI was based on the Clopper-Pearson method.

Progression Free Survival



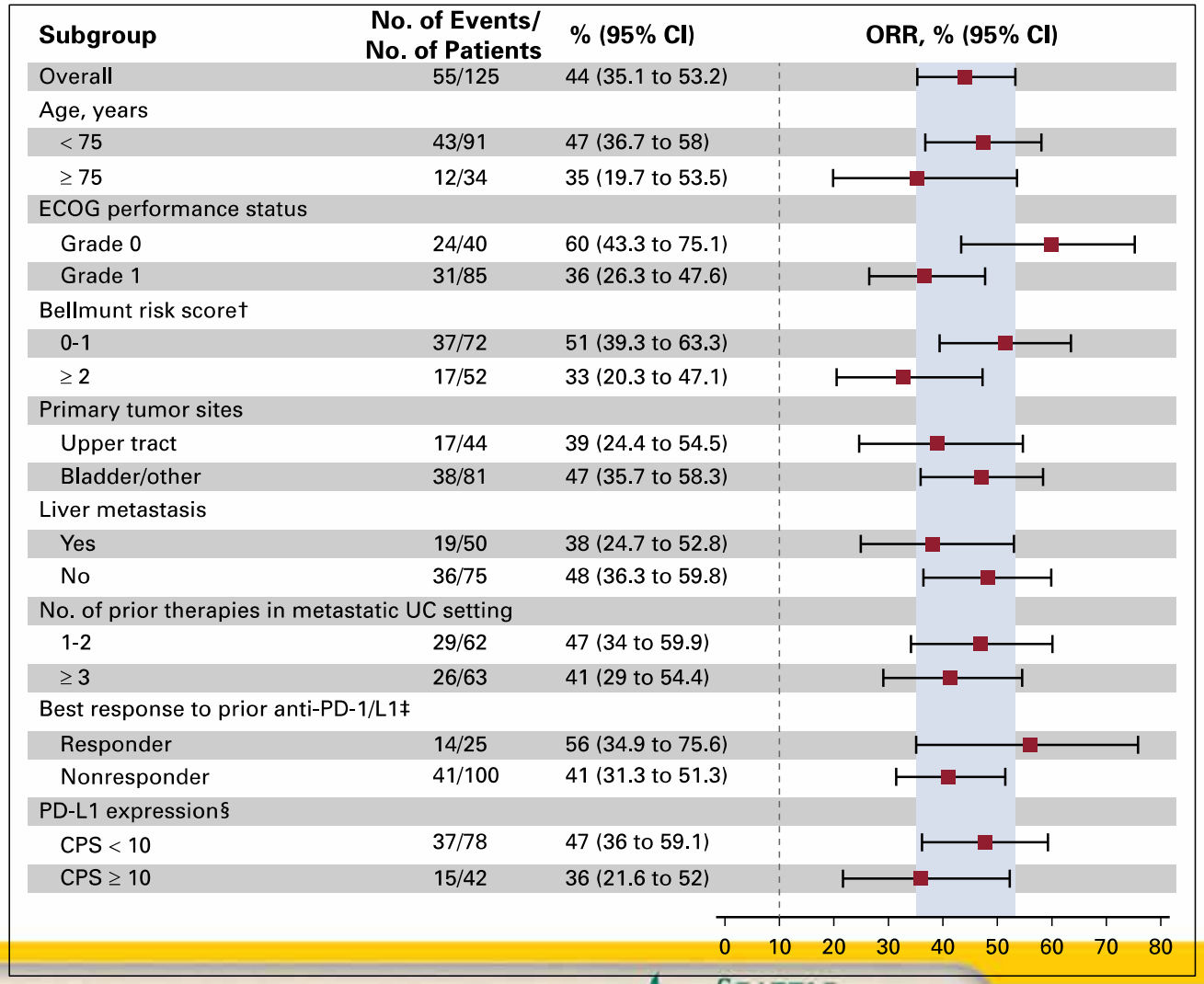
Rosenberg, et al. JCO 2019
Rosenberg, et al. 2018 ASCO Annual Meeting

Overall Survival



Rosenberg, et al. JCO 2019
Rosenberg, et al. 2018 ASCO Annual Meeting

ORR Forest Plot



Rosenberg, et al. JCO 2019

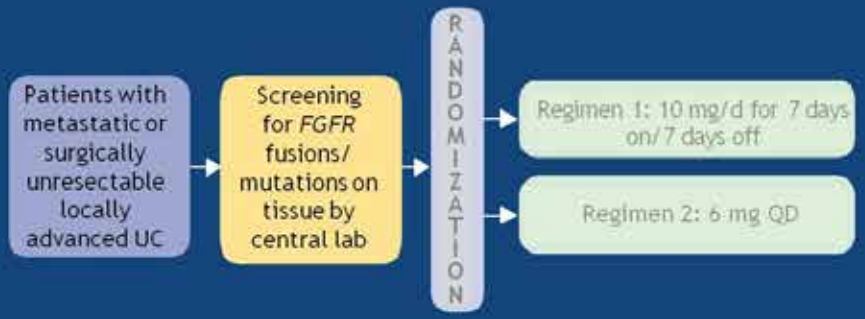
Adverse Events

Any adverse event	125 (100)	
Treatment-related adverse events	117 (94)	
Grade ≥ 3 treatment-related adverse events	68 (54)	
Treatment-related serious adverse events	24 (19)	
Treatment-related adverse events resulting in treatment discontinuation	15 (12)	
Treatment-related adverse events leading to death*	0 (0)	
Treatment-related adverse events occurring in ≥ 20% (preferred term)	Any Grade	Grade ≥ 3
Fatigue	62 (50)	7 (6)
Alopecia	61 (49)	0
Decreased appetite	55 (44)	1 (1)
Dysgeusia	50 (40)	0
Peripheral sensory neuropathy	50 (40)	2 (2)
Nausea	49 (39)	3 (2)
Diarrhea	40 (32)	3 (2)
Rash maculopapular	27 (22)	5 (4)
Weight decreased	28 (22)	1 (1)
Dry skin	28 (22)	0

Rosenberg, et al. JCO 2019

Phase 2 BLC2001 Study Design

Erdafitinib: FGFR 1/2/3 inhibitor



Regimen 3[a]:
8 mg QD with PD
Uptitration to 9 mg QD
n = 99

Primary end point

ORR

Secondary end points

PFS, DoR, OS, safety, predictive biomarker evaluation, and PK

Patients

- Progression on ≥ 1 line prior systemic chemo or within 12 months of (neo)adjuvant chemo OR
- Chemo-naïve: cisplatin ineligible per protocol criteria[b]
- Prior immunotherapy was allowed

Primary hypothesis:

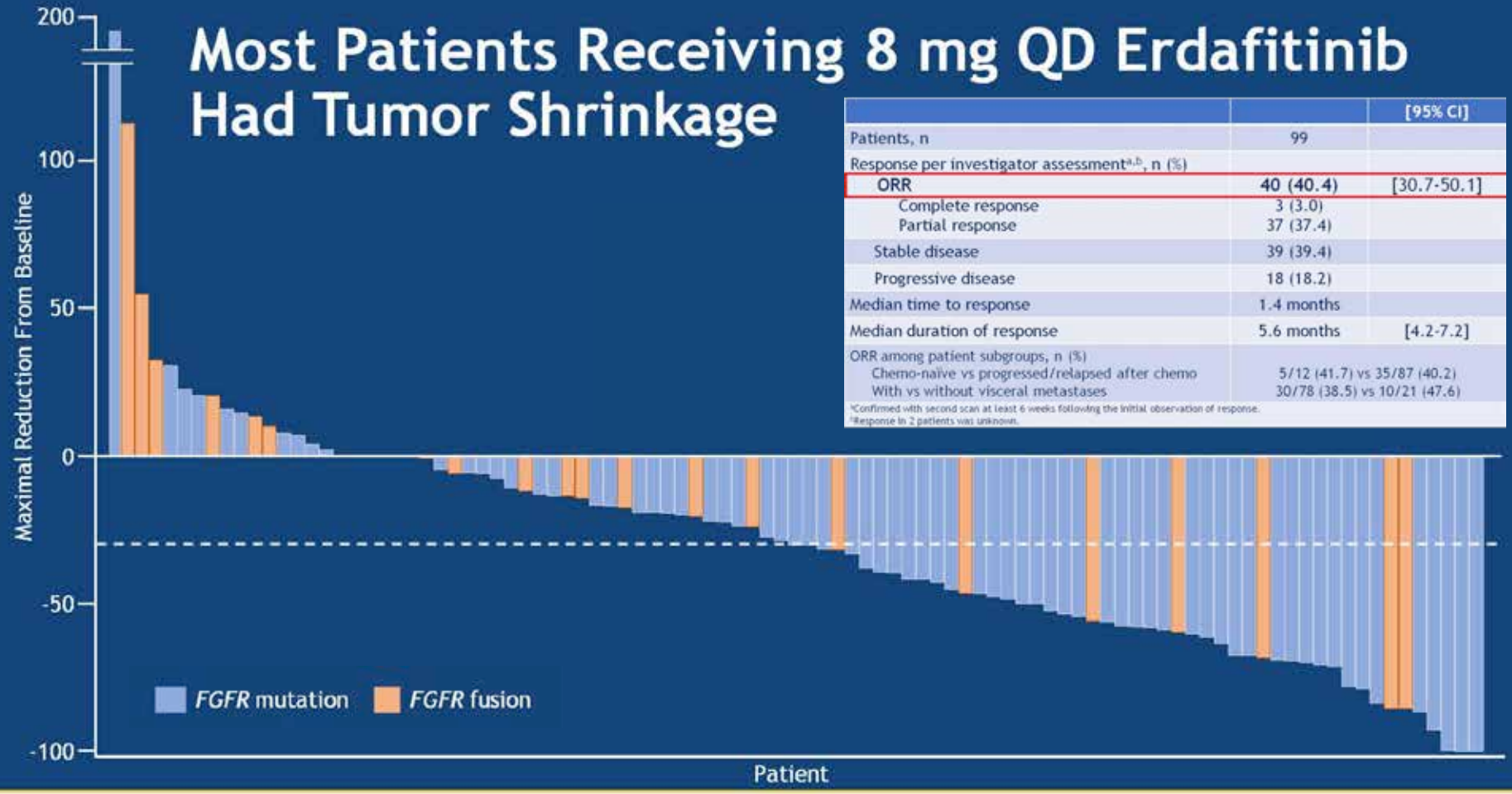
- ORR in Regimen 3 is > 25%
- One-sided α = 0.025
- 85% power

[a]Dose uptitration if ≥ 5.5 mg/dL target serum phosphate not reached by Day 14 and if no TRAEs.
[b]Ineligibility for cisplatin: impaired renal function or peripheral neuropathy.

Abbreviations: DoR, duration of response; PD, pharmacodynamics; PFS, progression-free survival; PK, pharmacokinetics; QD, daily; TRAEs, treatment-related adverse events.

Siefker-Radtke, et al. 2018 ASCO Annual Meeting
Loriot, et al. NEJM 2019

Most Patients Receiving 8 mg QD Erdafitinib Had Tumor Shrinkage



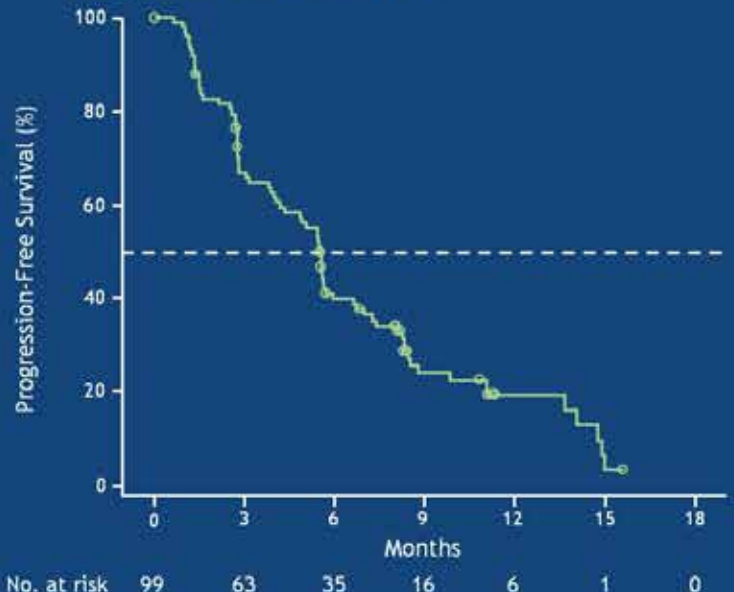
		[95% CI]
Patients, n	99	
Response per investigator assessment[a,b], n (%)		
ORR	40 (40.4)	[30.7-50.1]
Complete response	3 (3.0)	
Partial response	37 (37.4)	
Stable disease	39 (39.4)	
Progressive disease	18 (18.2)	
Median time to response	1.4 months	
Median duration of response	5.6 months	[4.2-7.2]
ORR among patient subgroups, n (%)		
Chemo-naïve vs progressed/relapsed after chemo	5/12 (41.7) vs 35/87 (40.2)	
With vs without visceral metastases	30/78 (38.5) vs 10/21 (47.6)	

[a]Confirmed with second scan at least 6 weeks following the initial observation of response.
[b]Response in 2 patients was unknown.

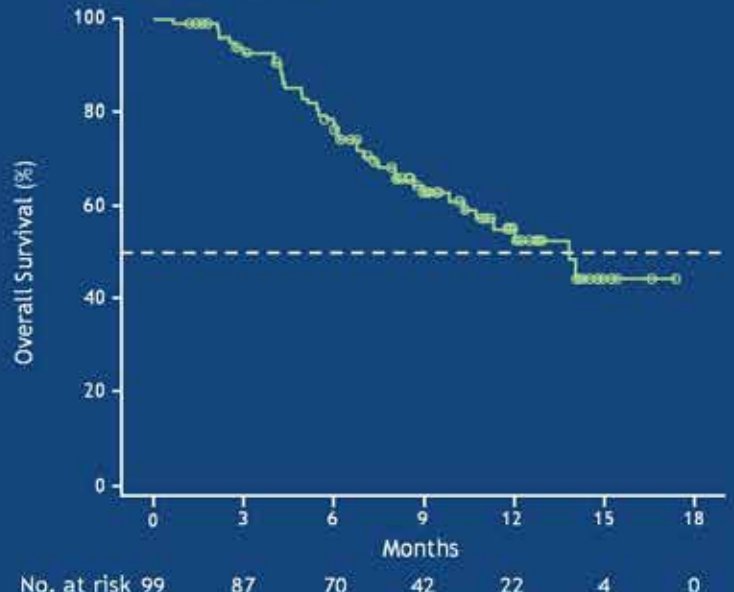
Siefker-Radtke, et al. 2018 ASCO Annual Meeting
Loriot, et al. NEJM 2019

Progression-Free Survival ~6 Months
Overall Survival > 1 Year

Median PFS = 5.5 months (95% CI, 4.2-6.0)
Progression/death events = 77



Median OS = 13.8 months (95% CI, 9.8-NE)
Survival events = 40



8 mg

Abbreviation: NE, not estimable.

Siefker-Radtke, et al. 2018 ASCO Annual Meeting
Loriot, et al. NEJM 2019

Most Common Treatment-Related AEs (TRAEs)

Reported in >20% of patients	8 mg continuous dose (n = 99)	
Patients with TRAEs, n (%)	**Any grade**	**Grade 3**
Hyperphosphatemia	72 (73)	2 (2)
Stomatitis	54 (55)	9 (9)
Dry mouth	43 (43)	0
Diarrhea	37 (37)	4 (4)
Dysgeusia	35 (35)	1 (1)
Dry skin	32 (32)	0
Alopecia	27 (27)	0
Decreased appetite	25 (25)	0
Hand-foot syndrome	22 (22)	5 (5)
Fatigue	21 (21)	2 (2)

Most were grade 1 or 2

There were no grade 4 or 5 TRAEs

Serious TRAEs were reported in 9 patients (9%); none was reported in more than 1 patient

Siefker-Radtke, et al. 2018 ASCO Annual Meeting
Loriot, et al. NEJM 2019

Bladder Cancer - Conclusions

- Chemotherapy plays no role in patients with less than T2 disease
  - Muscle needs to be in TURBT specimen to establish T2 disease
- Patients with extensive CIS, hydronephrosis or bulky disease are NOT chemo-radiotherapy candidates
- For neoadjuvant therapy, CISPLATIN based regimens are the only drugs with data to support them (ddMVAC, Gem/Cis)
- Gemcitabine/cisplatin is the standard first line option for metastatic urothelial CA
- Immune checkpoint inhibitors, enfortuamb and erdafitinib are standard ≥2nd line treatment metastatic urothelial CA

Thank You!

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Peripheral T-cell Lymphomas

Including Primary Cutaneous Subtypes

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PROFESSOR OF MEDICINE

UNIVERSITY OF WASHINGTON

FRED HUTCHINSON CANCER RESEARCH CENTER

COI Disclosure

- Research Funding: SPECTRUM Pharmaceuticals, Inc.
- Consultancy: Kyowa-Hakko-Kirin, Verastem Oncology, Celgene/Bristol-Myers-Squibb, Portola Pharmaceuticals.

PTCL/CTCL Landscape in 2019

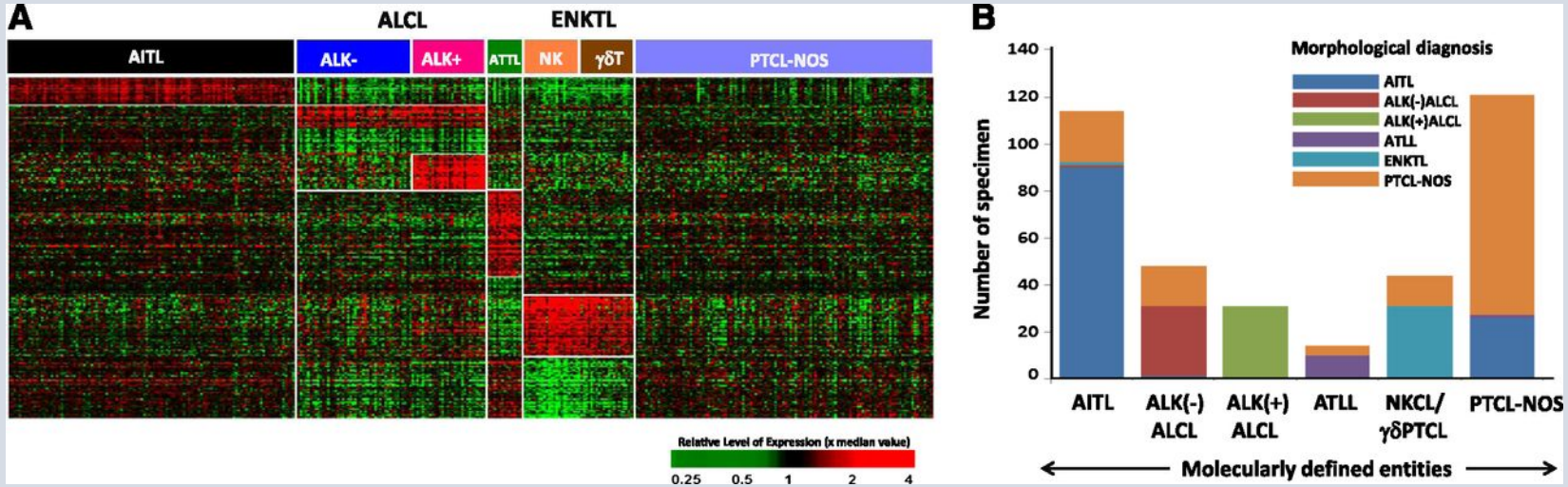
- WHO – 2016 Classification
- Clinical Outcomes in PTCL
- Front Line PTCL Therapy
    - Management of Selected Unique T-cell Malignancies
- New FDA-Approved Agents for Relapsed and Refractory PTCL
- CTCL Overview Including Management
- Recent Advances in CTCL Therapy

2016 - WHO Classification of PTCL

CTCL	Extranodal	Nodal	Leukemic
Mycosis Fungoides	NK/TCL Nasal Type	Peripheral TCL-NOS	Adult T-cell Leukemia/ Lymphoma
Sézary Syndrome	Enteropathy- Associated TCL	Anaplastic Large Cell Lymphoma, ALK +	Aggressive NK-Cell Leukemia
Primary Cutaneous CD30+ T-cell Disorders	Hepatosplenic TCL	Angioimmunoblastic TCL	T-cell Prolymphocytic Leukemia
Primary Cutaneous Gamma/Delta TCL	Subcutaneous Panniculitis-like TCL	Anaplastic Large Cell Lymphoma, ALK -	T-cell Large Granular Lymphocytic Leukemia
Hydroa vacciniforme-like Lymphoproliferative Disorder	Monomorphic Epitheliotropic Intestinal T-cell Lymphoma	Follicular TCL	Chronic Lymphoproliferative Disorder of NK-cells
Primary Cutaneous CD8+ Aggressive Epidermotropic TCL	Systemic EBV+ T-cell Lymphoma of Childhood	Nodal Peripheral TCL with TFH phenotype	
Primary Cutaneous Acral CD8+ TCL	Indolent T-cell Lymphoproliferative Disorder of the GI Tract		
Primary Cutaneous CD4+ Small/Medium T-cell Lymphoma			

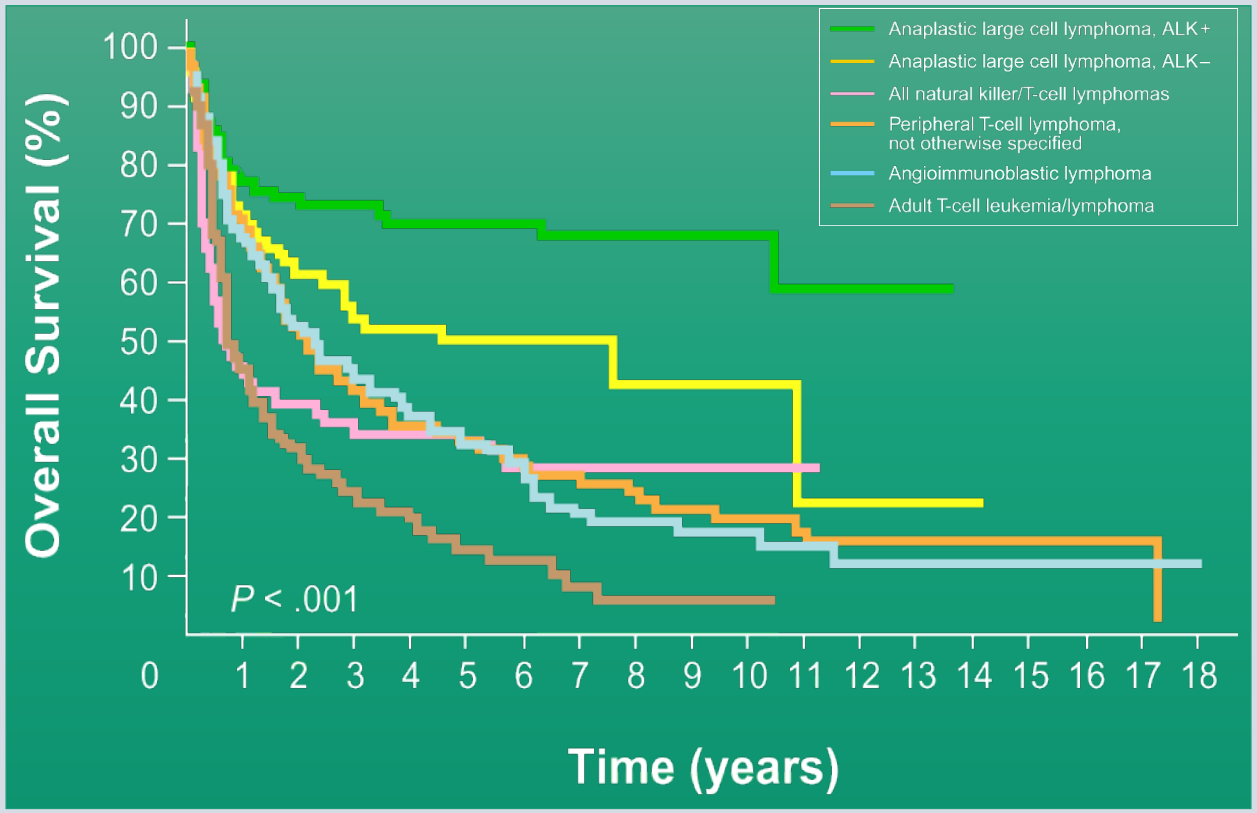
Molecular Diagnosis of PTCL Subgroups.

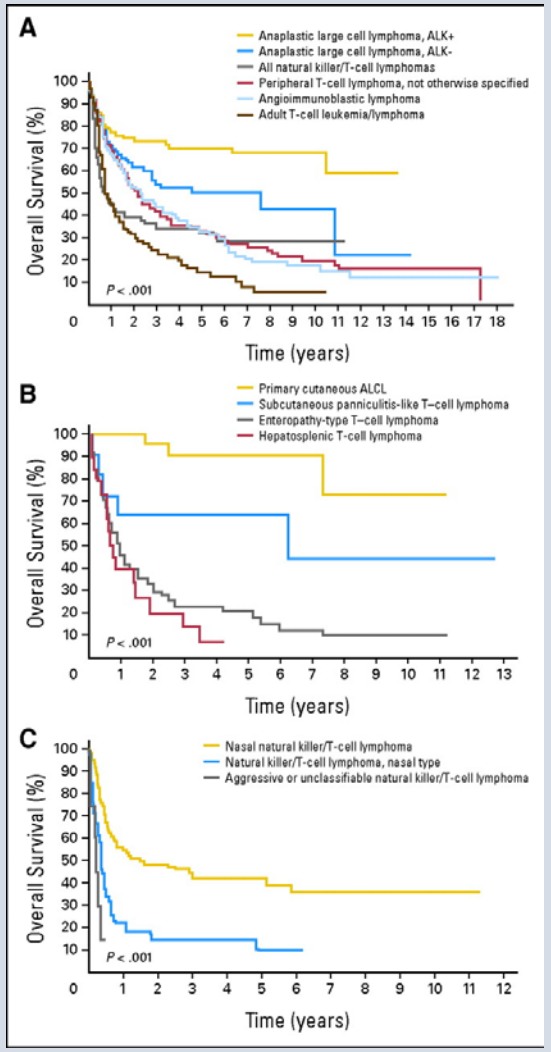
PTCL is not a single disease
Diverse genomic landscape => diverse biology/behavior



Iqbal J et al. *Blood* 2014;123:2915-2923

PTCL Prognosis is Indicative of Diverse Biology



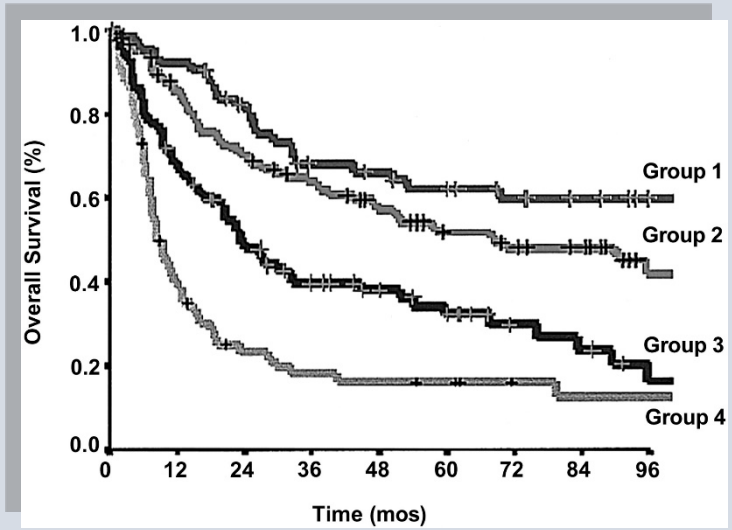


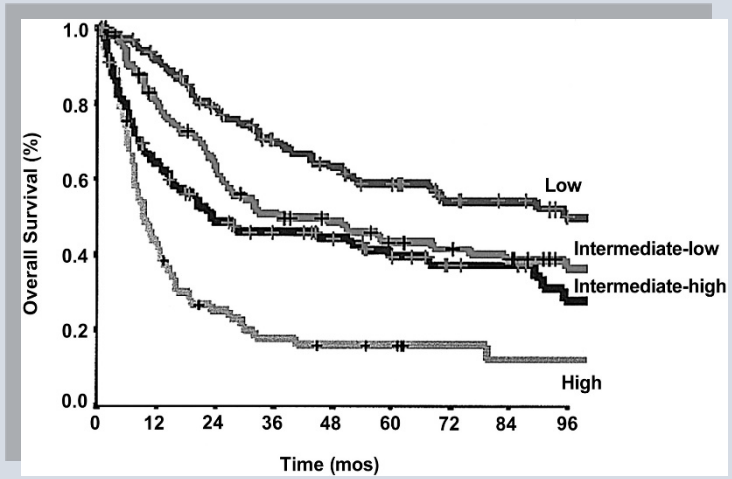
Armitage J, et al. *J Clin Oncol.* 2008;26:4124–4130.

Clinical Prognostic Models in PTCL

Clinical Variables	IPI	PIT	PIAI	KPI
Age	X	X	X	
Stage	X			X
LDH	X	X		X
ECOG PS	X	X	X	
X-nodal sites	X		X	
BM involvement		X		
Platelet count			X	
B-symptoms			X	X
Regional LN+				X

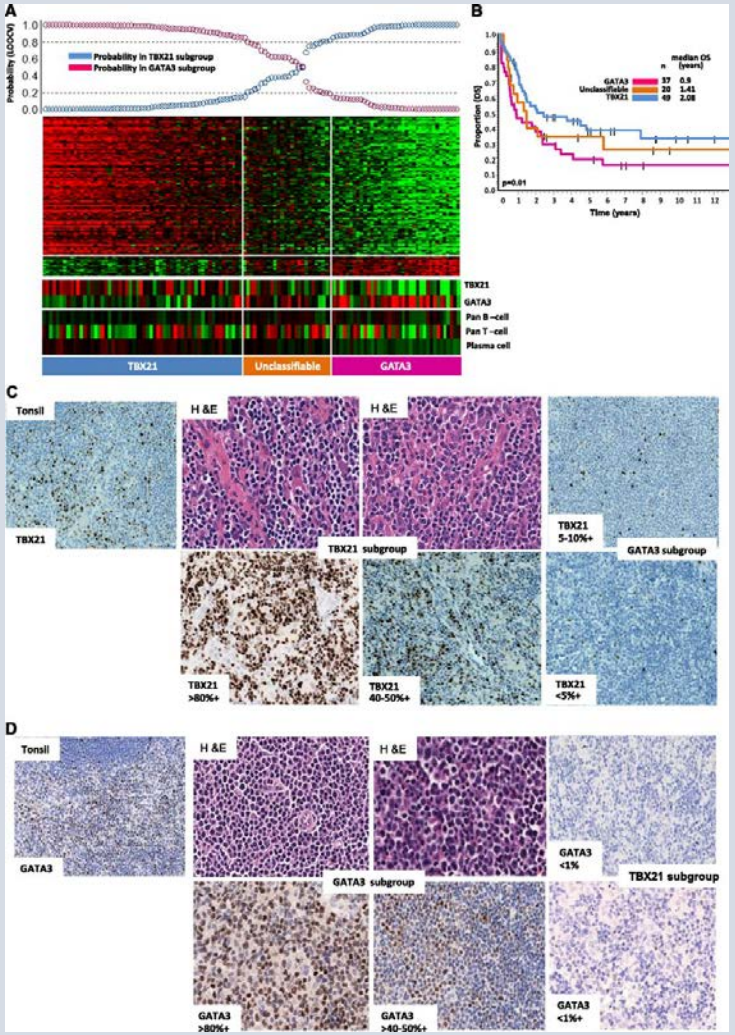
Prognosis of PTCL-NOS by Clinical Features: IPI and PIT





Gallamini A et al. *Blood* 2004;103:2474-2479

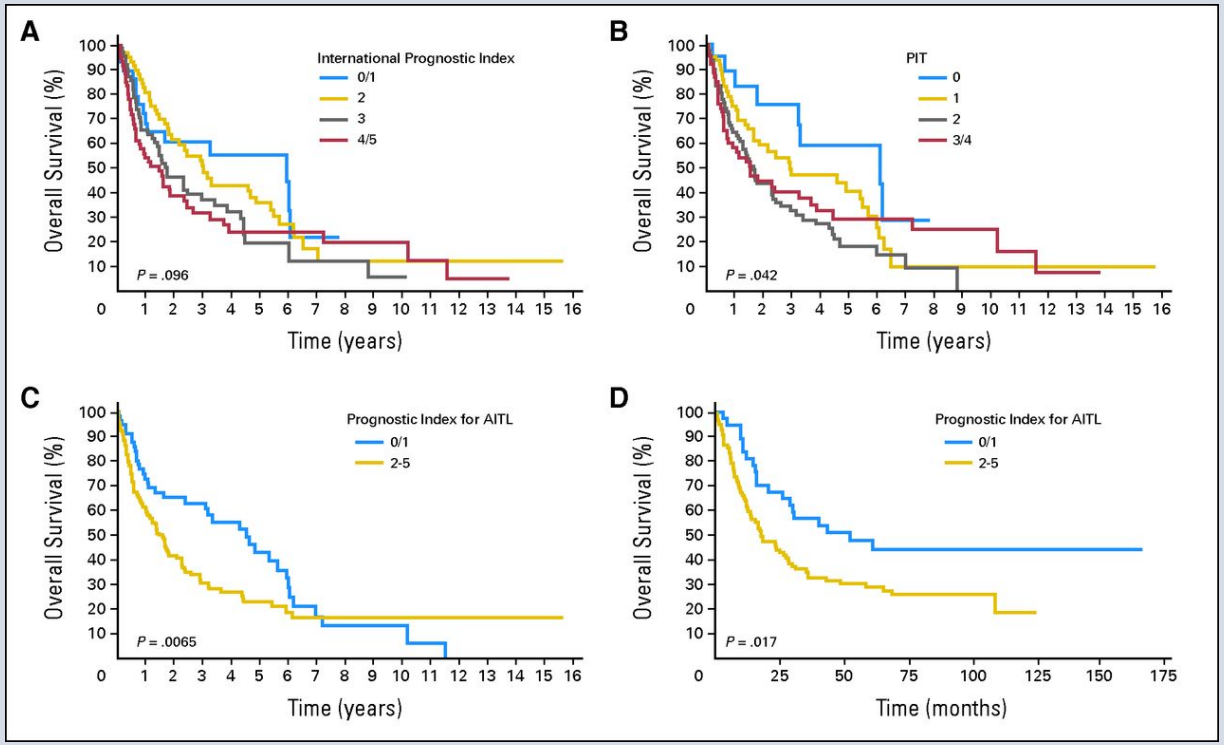
Prognosis of PTCL-NOS by Molecular Subgroups



Iqbal J et al. *Blood* 2014;123:2915-2923

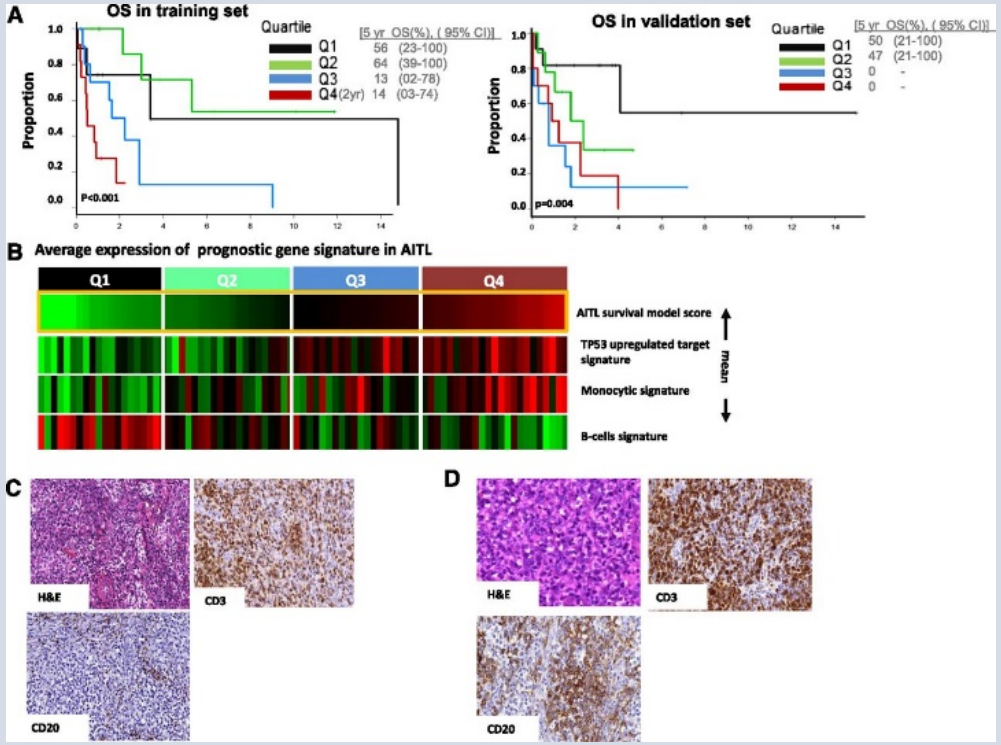
blood

Prognosis of AITL by Clinical Features: PIAI



Federico M. et al. *J Clin Oncol*. 2013 31:240-246

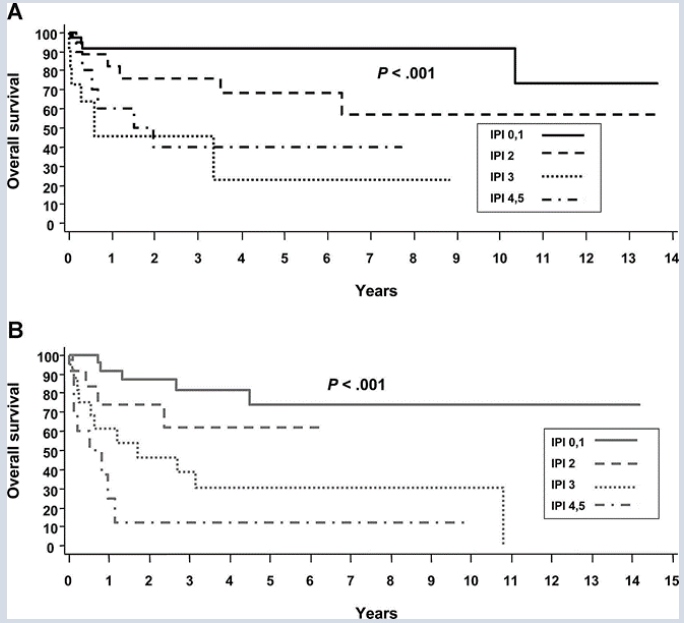
Prognosis of AITL by Molecular Subgroups



Iqbal J et al. *Blood* 2014;123:2915-2923

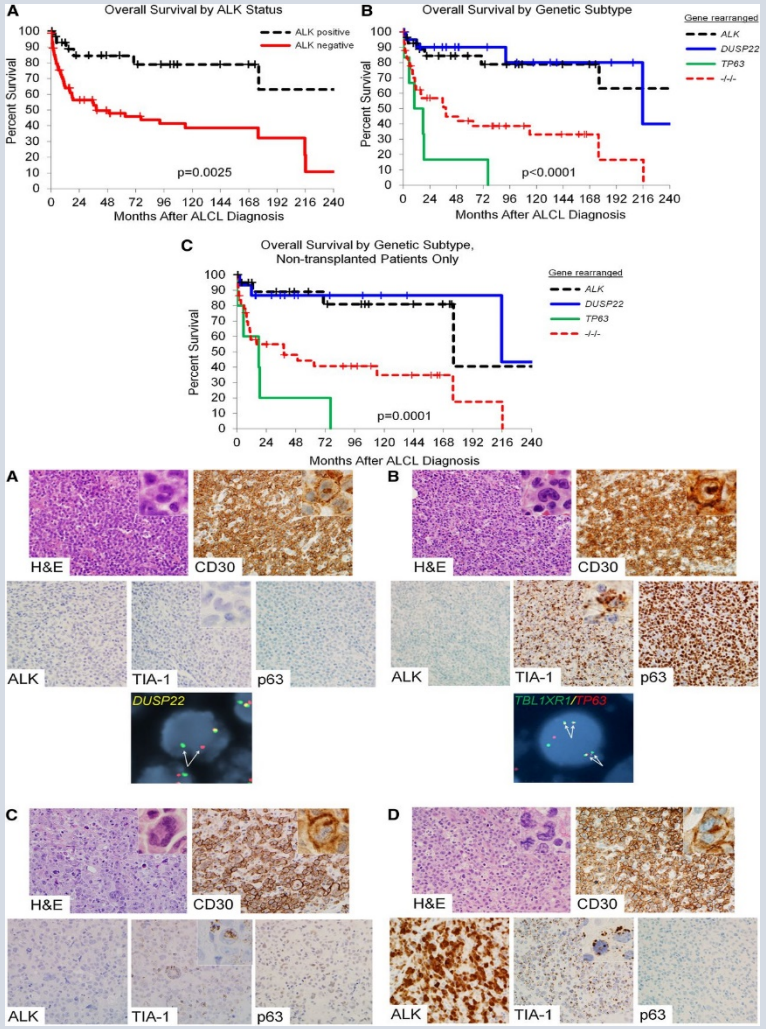
blood

Prognosis of ALCL by Clinical Features: IPI



Savage K J et al. *Blood* 2008;111:5496-5504

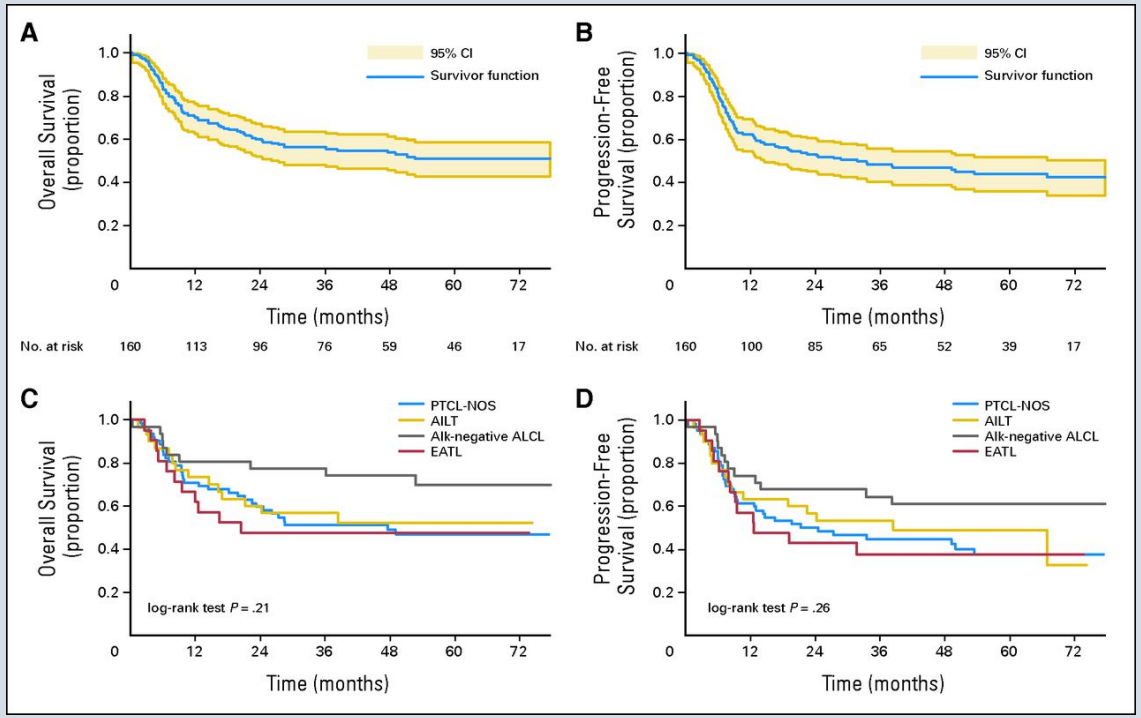
Prognosis of ALCL by Molecular Subgroups



Iqbal J et al. *Blood* 2014;123:2915-2923

blood

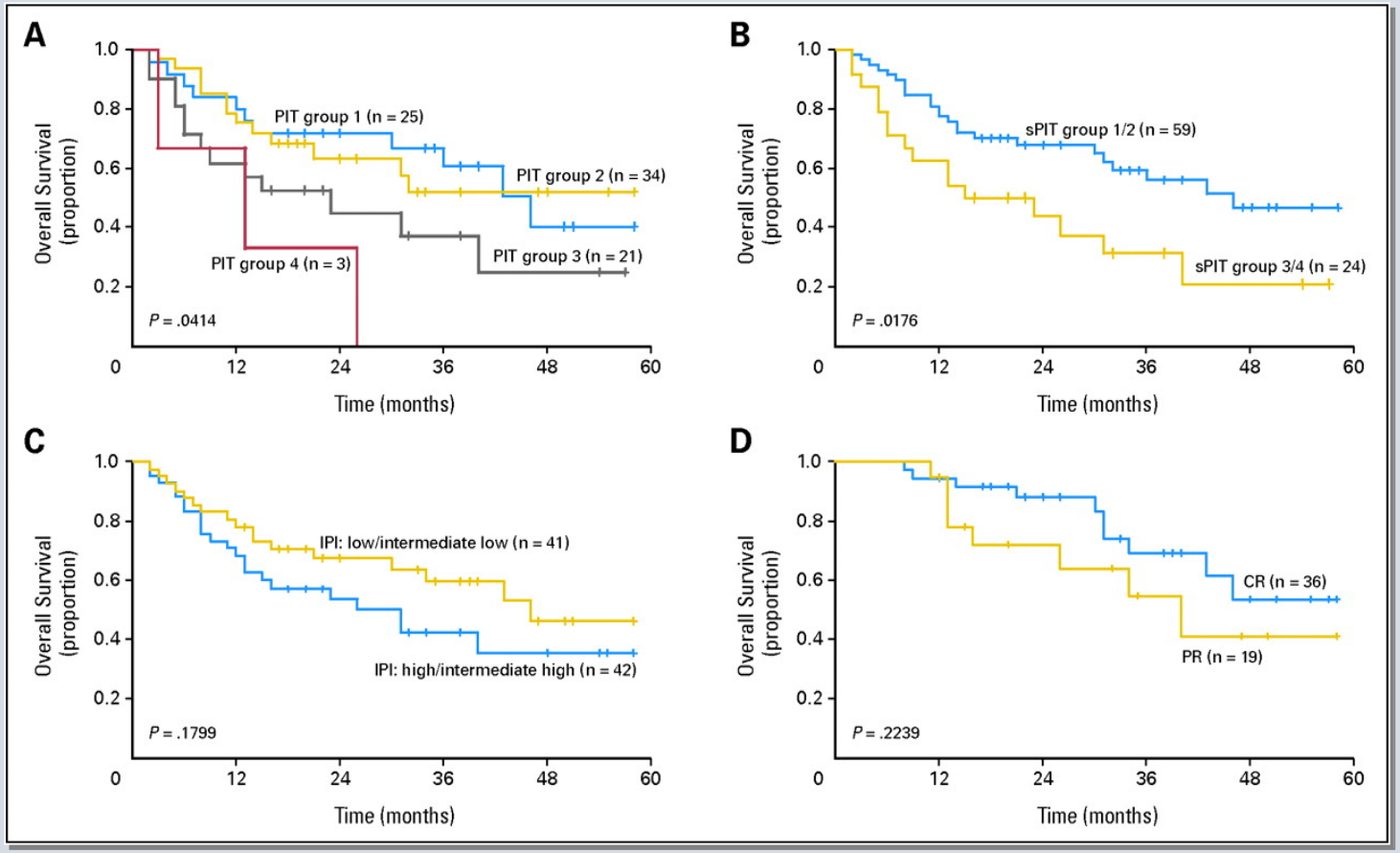
PTCL Prognosis: High-Dose Therapy



	OS		PFS	
Subtype	3-yr	5-yr	3-yr	5-yr
PTCLu (n=62)	51%	45%	43%	34%
AIL (n=30)	57%	50%	54%	47%
ALCL alk-neg (n=31)	77%	73%	64%	64%
Enteropathy (n=21)	52%	44%	47%	40%

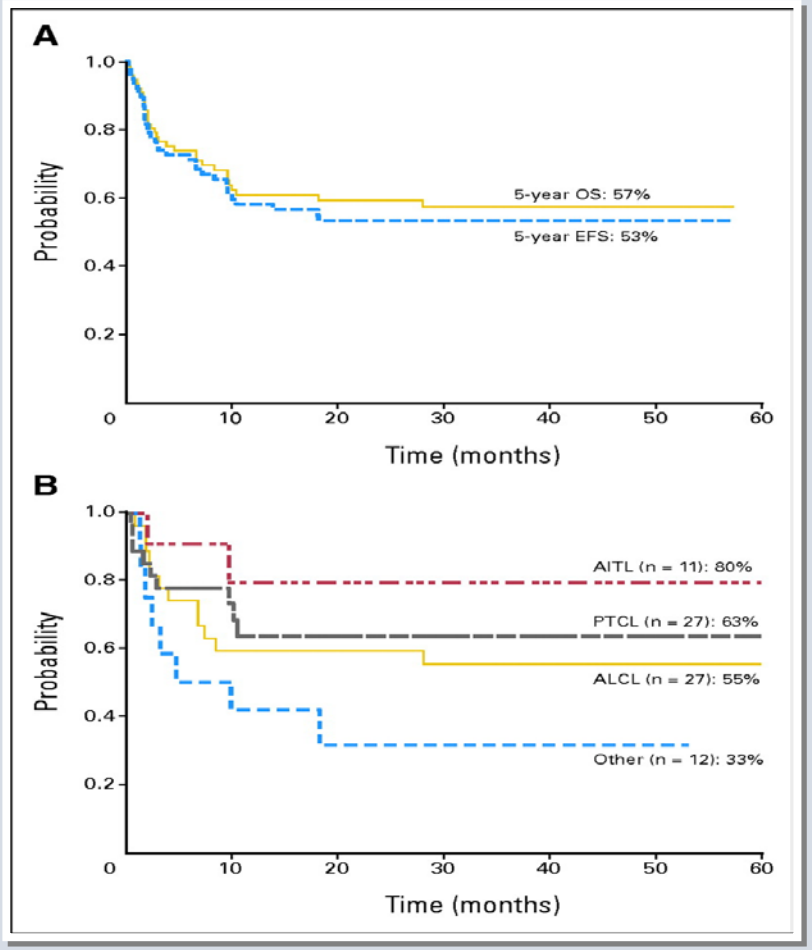
D'Amore F. et al. *J Clin Oncol*. 2012 30:3093-3099

PTCL Prognosis: High-Dose Therapy

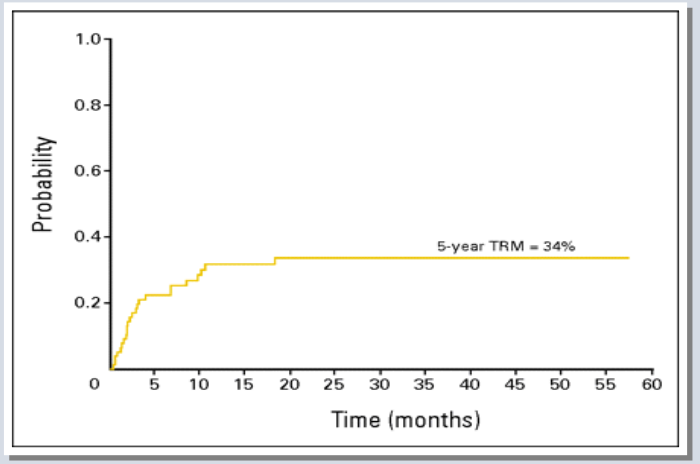


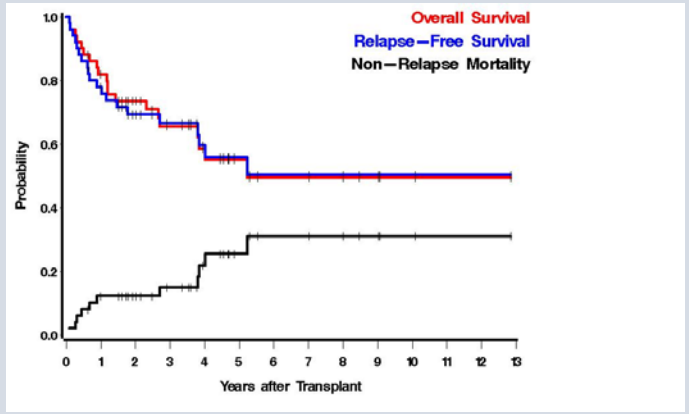
Reimer P. et al. *J Clin Oncol*. 2009 27:106-113

PTCL Prognosis: Allo-HCT



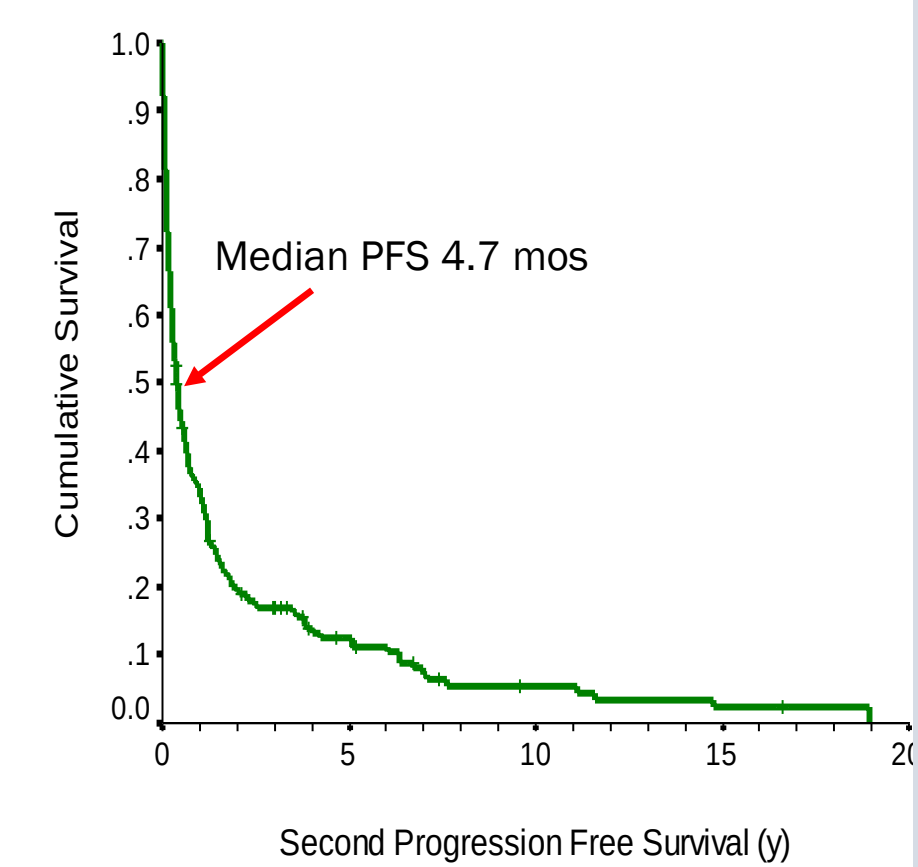
Le Gouill S. et al. *J Clin Oncol*. 2008 26:2264-2271

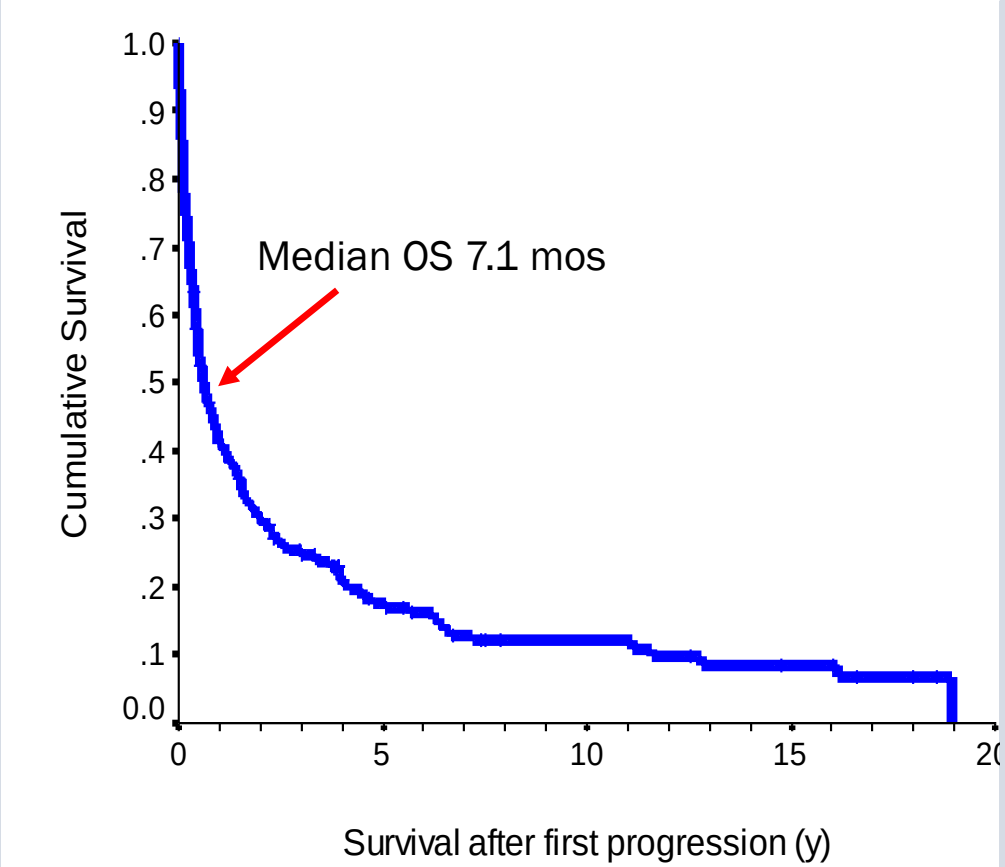




Shustov A. et al. *Br J Haem*. 2010 150:170-178

Survival in PTCL Post 1st Relapse or Progression



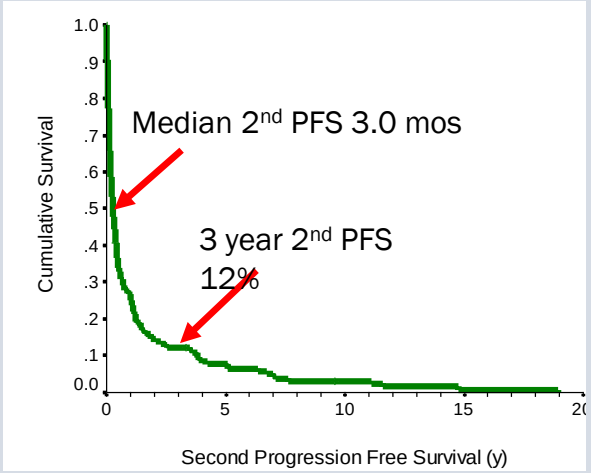


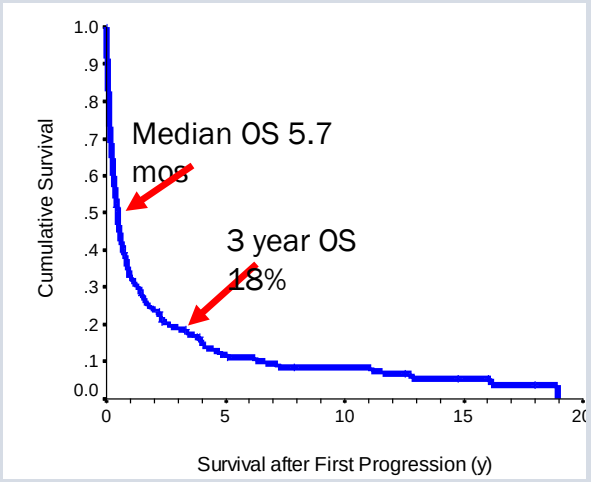
Savage K. et al. *J Clin Oncol*. 2013; 31:1970-1976

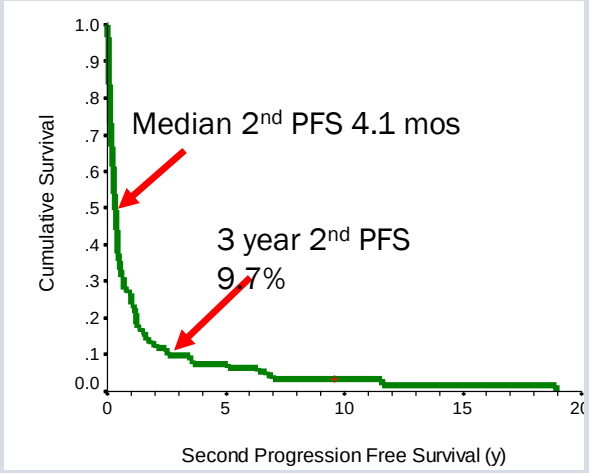
Survival in PTCL Post 1st Relapse or Progression

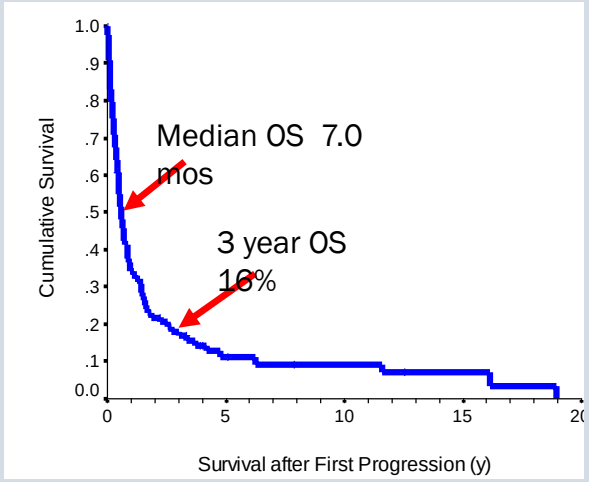
Historical Chemotherapy does not improve outcomes in relapsed or refractory PTCL

Patients not treated with chemotherapy









Patients treated with chemotherapy

Savage K. et al. *J Clin Oncol*. 2013; 31:1970-1976

PTCL Therapy: NCCN Guidelines

First-Line Therapy:

- Clinical trial
- ALCL, ALK+ histology
  - CHOP-21 (cyclophosphamide, doxorubicin, vincristine, prednisone)
  - CHOEP-21 (cyclophosphamide, doxorubicin, vincristine, etoposide, prednisone)
- Other histologies (ALCL, ALK–; PTCL, NOS; AITL; EATL), regimens that can be used include:
- Preferred regimens (in alphabetical order)
  - CHOEP
  - CHOP-14
  - CHOP-21
  - Dose-adjusted EPOCH (etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin)
- Alternative regimens (in alphabetical order)
  - CHOP followed by IVE (ifosfamide, etoposide, epirubicin) alternating with intermediate-dose methotrexate [Newcastle Regimen] [studied only in patients with EATL]
  - HyperCVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with high-dose methotrexate and cytarabine

First-Line Consolidation:

- Consider consolidation with high-dose therapy and stem cell rescue
  - Patients with low IPI ALCL, ALK+ disease in remission do not need consolidative transplant

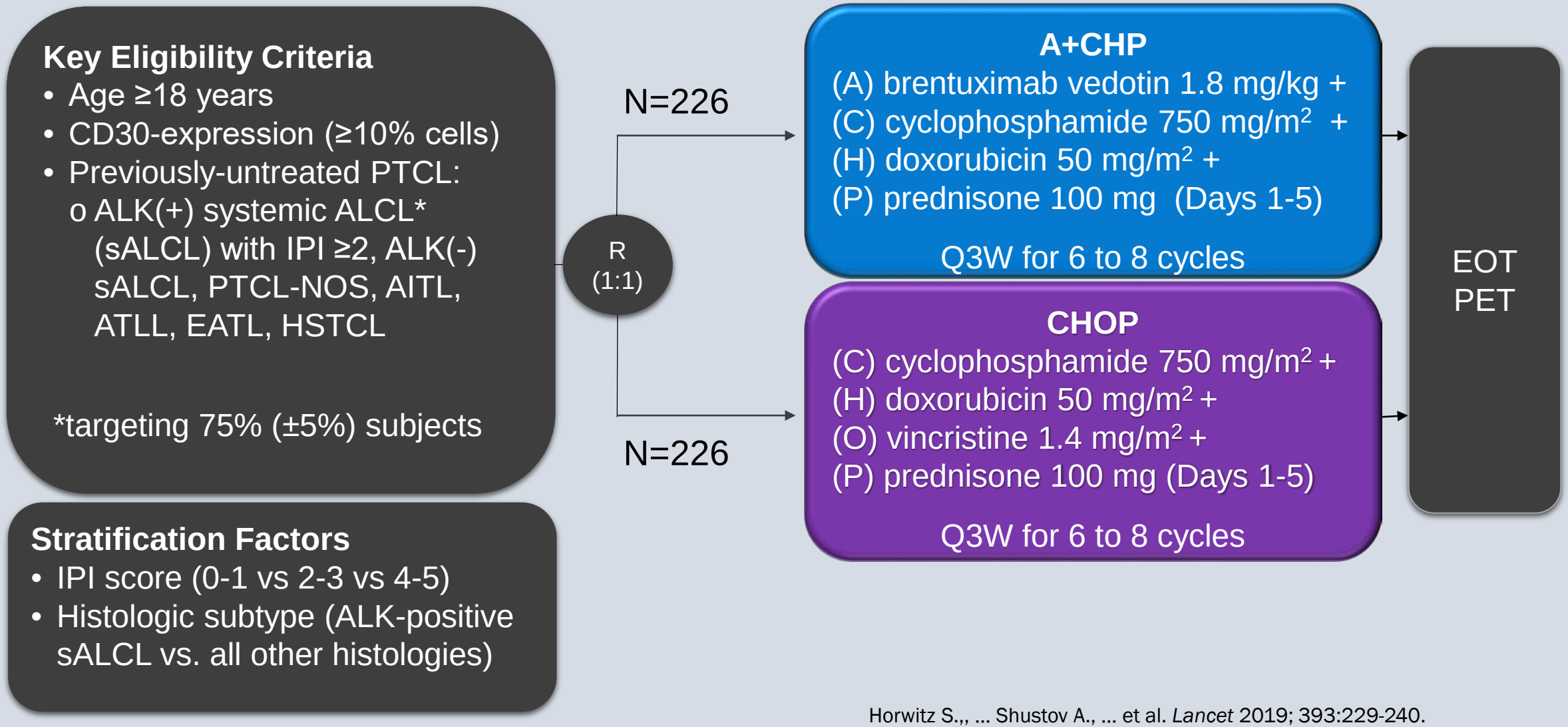
Horwitz S., ... Shustov A., et al. 2018 *J Natl Compr Canc Netw* 16(2):123-135

The Phase 3 ECHELON-2 Trial: Results of a Randomized, Double-Blind, Active-Controlled Study of Brentuximab Vedotin and CHP (A+CHP) Versus CHOP in Previously Untreated Subjects with CD30-Expressing Peripheral T-Cell Lymphomas (PTCL)

Steven Horwitz, Owen A O'Connor, Barbara Pro, Tim Illidge, Michelle Fanale, Ranjana Advani, Nancy L Bartlett, Jacob Haaber Christensen, Franck Morschhauser, Eva Domingo-Domenech, Giuseppe Rossi, Won Seog Kim, Tatyana Feldman, Anne Lennard, David Belada, Árpád Illés, Kensei Tobinai, Kunihiro Tsukasaki, Su-Peng Yeh, Andrei Shustov, Andreas Hüttmann, Kerry J Savage, Sam Yuen, Swaminathan Iyer, Pier Luigi Zinzani, Zhaowei Hua, Meredith Little, Shangbang Rao, Joseph Woolery, Thomas Manley, Lorenz Trümper

American Society of Hematology Annual Meeting; San Diego, California, December 1-4, 2018, Abstract #997

ECHELON-2 Study Design



Horwitz S.,, ... Shustov A., ... et al. *Lancet* 2019; 393:229-240.

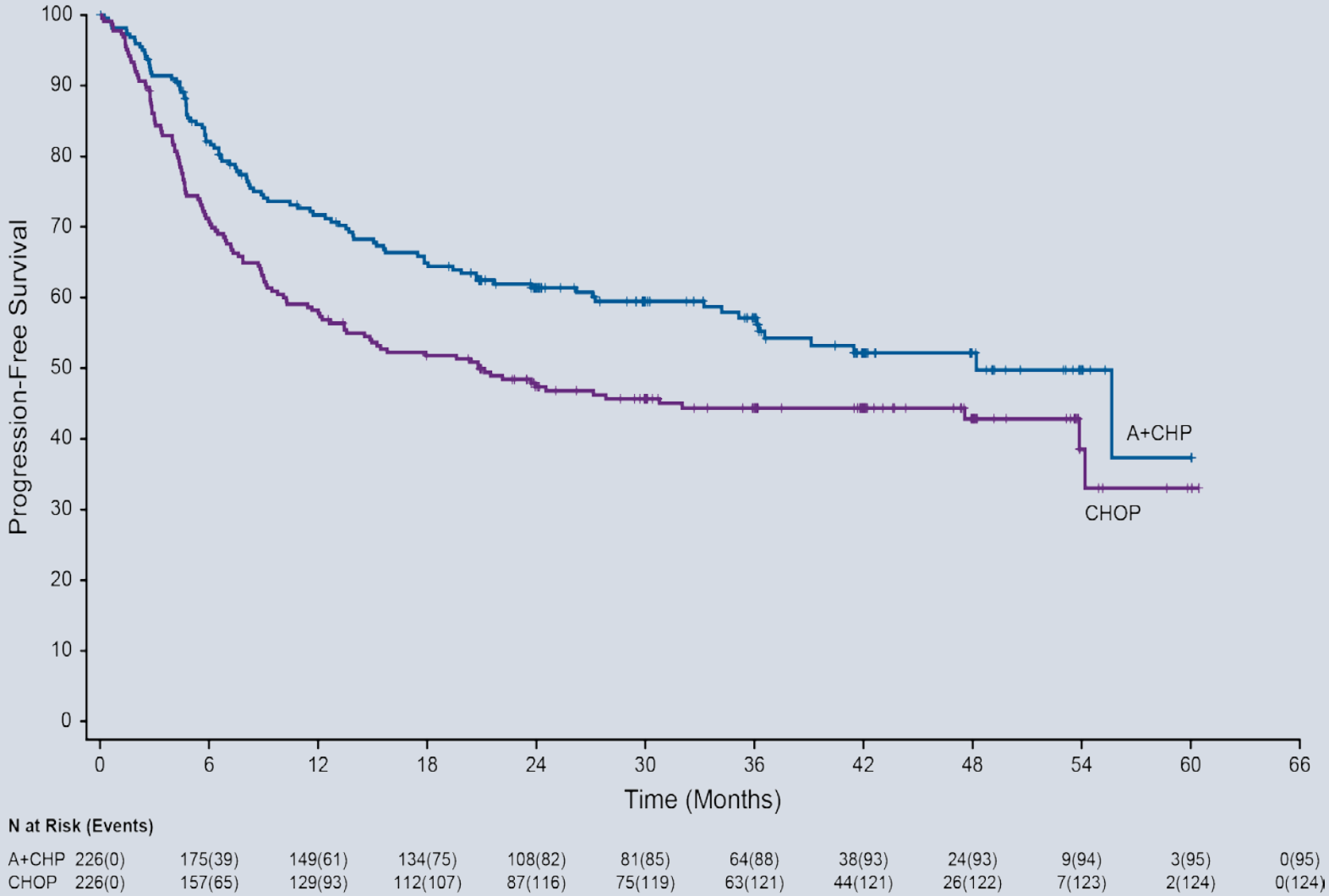
ECHELON-2: Baseline Characteristics

	A+CHP (N=226)	CHOP (N=226)
Male, n (%)	133 (59)	151 (67)
Age in years, median (range)	58 (18-85)	58 (18-83)
IPI score, n (%)		
0-1	52 (23)	48 (21)
2-3	141 (62)	145 (64)
4-5	33 (15)	33 (15)

	A+CHP (N=226)	CHOP (N=226)
Stage III/IV disease, n (%)	184 (81)	180 (80)
Disease Diagnosis, n (%)		
sALCL	162 (72)	154 (68)
ALK+	49 (22)	49 (22)
ALK-	113 (50)	105 (46)
PTCL-NOS	29 (13)	43 (19)
AITL	30 (13)	24 (11)
ATLL	4 (2)	3 (1)
EATL	1 (0)	2 (1)

Horwitz S.,, ... Shustov A., ... et al. *Lancet* 2019; 393:229-240.

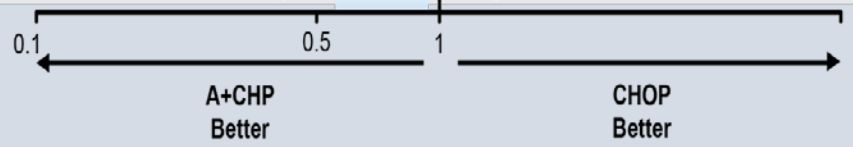
ECHELON-2: PFS



Horwitz S.,, ... Shustov A., ... et al. *Lancet* 2019; 393:229-240.

ECHELON-2: Prespecified Subset Analyses

ITT Subgroups	Event/N A+CHP	Event/N CHOP	Hazard Ratio (95% CI)
Overall	95/226	124/226	0.71 (0.54, 0.93)
IPI Score			
0–1	18/52	27/48	0.53 (0.29, 0.97)
2–3	56/141	77/145	0.71 (0.50, 1.00)
4–5	21/33	20/33	1.03 (0.55, 1.92)
Age			
<65 years	54/157	75/156	0.67 (0.47, 0.95)
≥65 years	41/69	49/70	0.70 (0.46, 1.08)
Gender			
Male	59/133	80/151	0.80 (0.57, 1.13)
Female	36/93	44/75	0.49 (0.31, 0.78)
Baseline ECOG Status			
0/1	76/174	105/179	0.66 (0.49, 0.89)
2	19/51	19/47	0.98 (0.51, 1.87)
Disease Stage			
I/II	15/42	19/46	0.95 (0.48, 1.88)
III	29/57	35/67	0.69 (0.42, 1.14)
IV	51/127	70/113	0.64 (0.45, 0.93)
Disease Indication			
ALK-positive sALCL	5/49	16/49	0.29 (0.11, 0.79)
ALK-negative sALCL	50/113	60/105	0.65 (0.44, 0.95)
AITL	18/30	13/24	1.40 (0.64, 3.07)
PTCL-NOS	19/29	31/43	0.75 (0.41, 1.37)



Horwitz S.,, ... Shustov A., ... et al. *Lancet* 2019; 393:229-240.

Special Management Scenarios

- Subcutaneous Panniculitis-Like T-cell Lymphoma
  - Never CHOP
  - Bexarotin, Pralatrexate, Combination ±Prednisone
  - Cyclosporin A, Hydroxychloroquine
- T-cell Prolymphocytic Leukemia
  - Never CHOP
  - Alemtuzumab ±Pentostatin; Allogeneic SC Transplant
  - Bendamustin

Special Management Scenarios

- Hepatosplenic T-cell Lymphoma; Other Gamma-Delta T-cell Lymphomas
  - Never CHOP
  - DHAP, ESHAP followed by Allogeneic SC Transplant
  - Hyper-CVAD followed by Allogeneic SC Transplant
- Large Granular Lymphocyte Disorder with Autoimmune Cytopenias
  - Never CHOP
  - Low-dose oral Methotrexate, Cyclosporine A, Prednisone, Growth Factors
  - Alemtuzumab in low doses

Special Management Scenarios

- Indolent Lymphoproliferative Disorder of the GI tract
  - Never CHOP
  - DO NOT TREAT asymptomatic patients
- Management of older patients with newly Dx PTCL
  - Strongly consider palliative intent from the time of Dx (Ex. ALCL)
  - AITL is a paradigm of the epigenetic malignancy

Special Management Scenarios

- Early stage extranodal NK-cell lymphoma, nasal-nasal type
  - Concurrent DEVIC + XRT
  - Concurrent VIPD + XRT
  - XRT ± Cisplatin in older patients.
- Advanced stage extranodal NK-cell lymphoma, nasal type
  - SMILE in younger fit patients, L-Aspa-Dex in older patients
  - Autologous or allogeneic HCT could be considered.

Special Management Scenarios

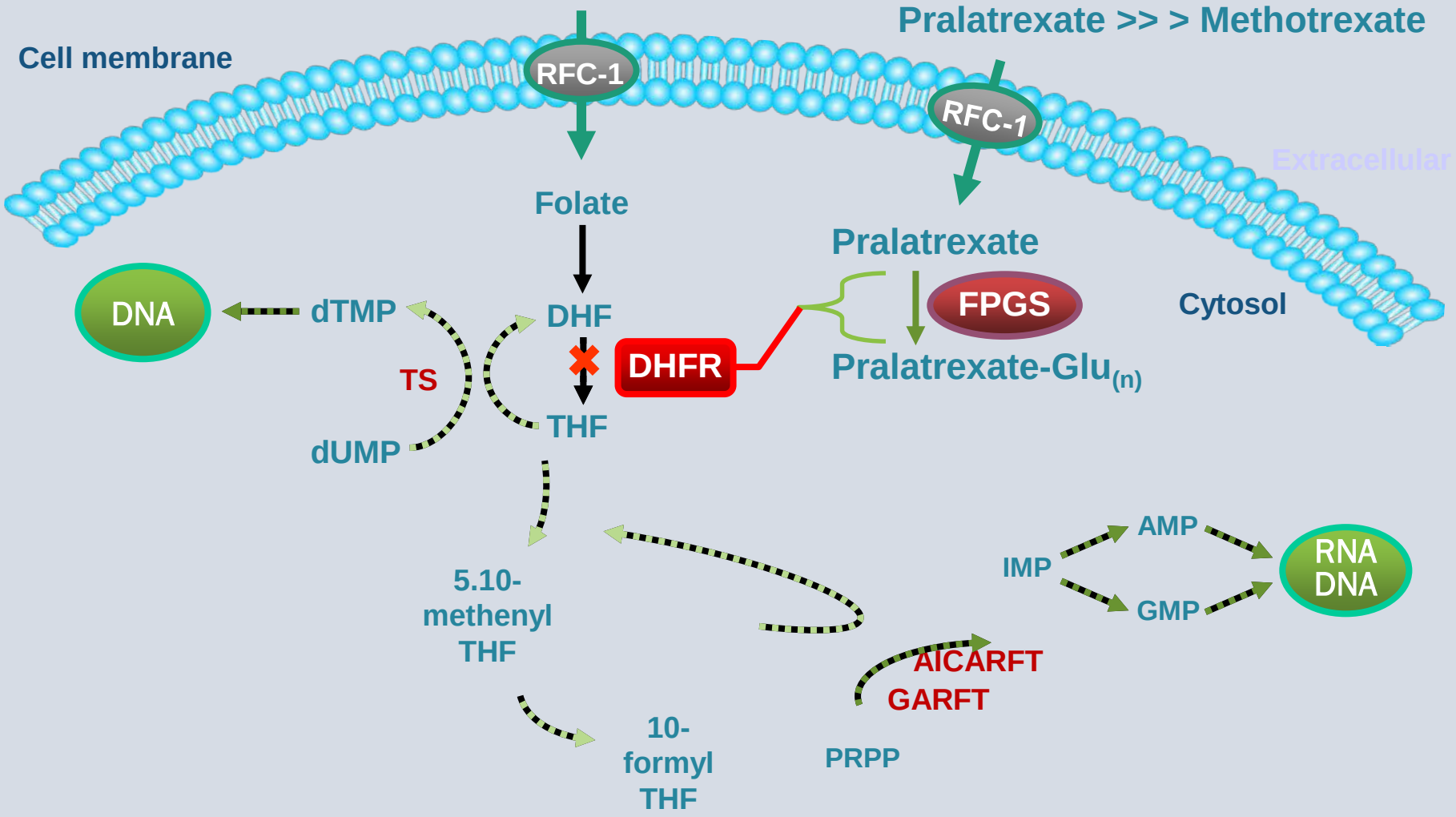
- Genomic or Targeted Genomic Testing
  - AITL: TET2, IDH1/2, RHOA
  - ALK- ALCL: DUSP22, TP63
  - LGL: STAT3, STAT5
  - PTCL-NOS: Full panel (?)
  - Other PTCLs: Full panel (?)

FDA-Approved Agents in PTCL

- PTCL
  - Pralatrexate
  - Romidepsin
  - Brentuximab Vedotin (ALCL)
  - Belinostat

- CTCL
  - Vorinostat
  - Bexarotin
  - Romidepsin
  - Brentuximab Vedotin (CD30+ CTCL)
  - Mogamulizumab (CTCL)

Pralatrexate: Mechanism of Action



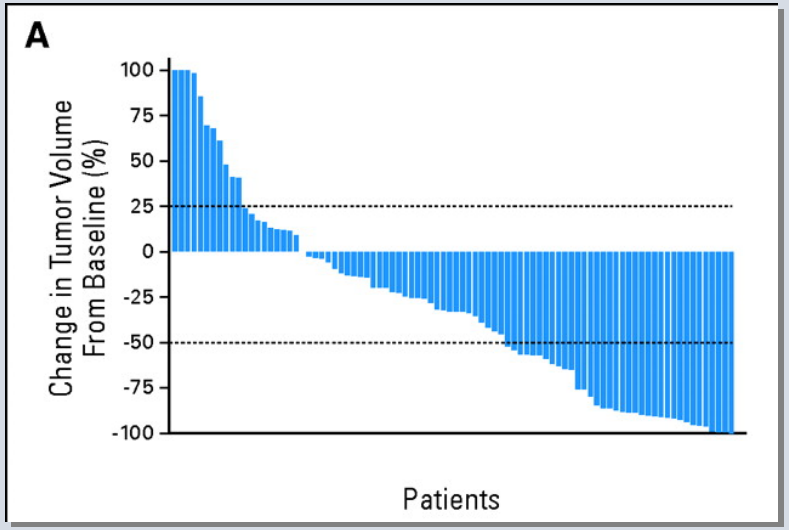
Phase II Trial of Pralatrexate in Relapsed or Progressive Peripheral T-Cell Lymphoma Following Prior Systemic Therapy

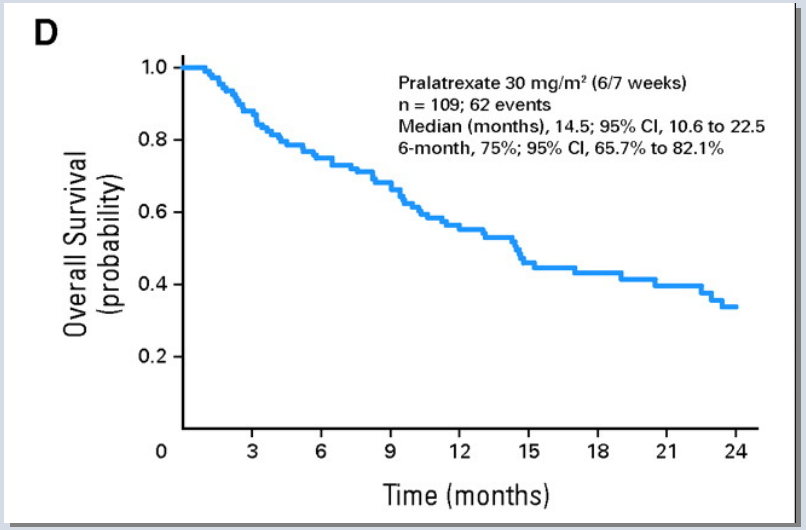
- Patient population:
  - 113 enrolled
  - 109 with confirmed PTCL
  - Failed ≥1 prior systemic therapy
- Treatment regimen: Pralatrexate 30 mg/m^2, weekly X 6 / 7 weeks
- Primary endpoint: CR/CRu by independent review
- Secondary endpoints including: ORR, duration of response, TTP, tolerability, and safety

O'Connor O., ... Shustov A., et al. *J Clin Onc* 2011; 29:1182-89

Pralatrexate in Relapsed/Refractory PTCL

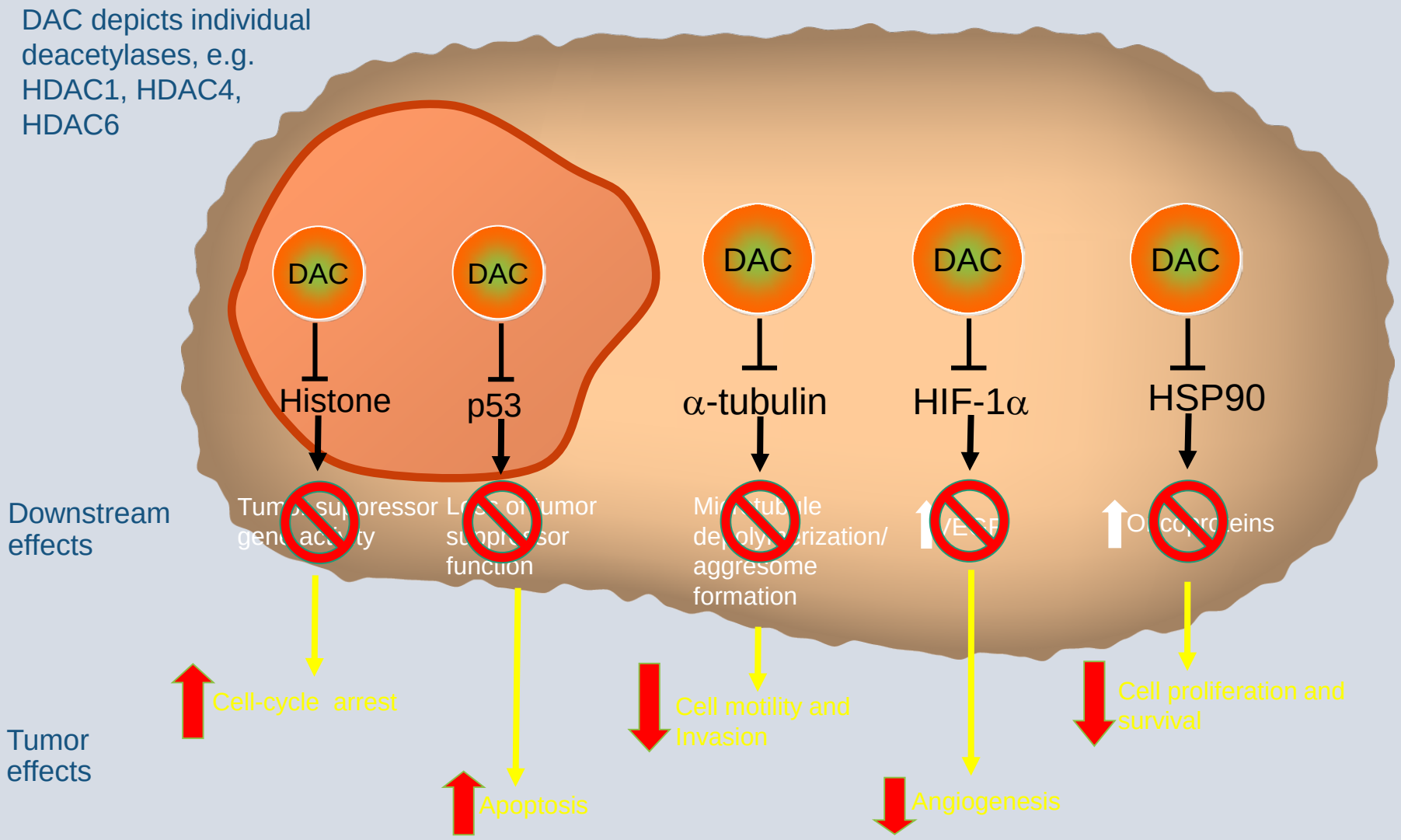
Response	Independent Review Committee Analysis (n = 109)
Overall Response Rate	32 (29%)
Complete response	12 (11%)
Partial response	20 (18%)
Median DOR, mo (95% CI)	10.1 (3.4-NE)
Median PFS, mo (95% CI)	3.5 (1.7-4.8)





O'Connor O., ... Shustov A., et al. *J Clin Onc* 2011; 29:1182-89

HDAC Inhibition



Phase II Trial of Romidepsin in Relapsed or Progressive Peripheral T-Cell Lymphoma Following Prior Systemic Therapy

- Patient population:
  - 131 enrolled
  - 130 with confirmed PTCL
  - Failed ≥1 prior systemic therapy
- Treatment regimen: romidepsin 14 mg/m^2, days 1, 8, and 15 q 28 days × 6 cycles; continued beyond 6 cycles in responding patients at investigator and patient discretion
- Primary endpoint: CR/CRu by independent review
- Secondary endpoints including: ORR, duration of response, TTP, tolerability, and safety

Coiffier B. ... Shustov A., ... et al. *J Clin Oncol.* 2012;30(6): 631-636.

Romidepsin in Relapsed Peripheral T-Cell Lymphoma

Response	Independent Review Committee Analysis (n = 130)
Overall Response Rate	34 (26%)
Complete response	10 (8%)
Unconfirmed complete response	7 (5%)
Duration of Response	**Median (Range)**
Overall	12 (<1.0-26.0+) months
Complete response/unconfirmed complete response	Not reached (<1.0-26.3+) months)

- Responses reported in PTCL (not otherwise specified) (29%), angioimmunoblastic TCL (33%), and ALK1$^-$ ALCL (24%)
- Similar response rates in patient subgroups according to number of prior therapies (<3 vs ≥3), prior SCT (yes vs no), and refractory to most recent therapy (yes vs no)

Coiffier B. … Shustov A., … et al. *J Clin Oncol.* 2012;30(6): 631-636.

BELIEF: Belinostat Phase 2 Trial in Relapsed and Refractory PTCL

- Patient population:
  - 129 enrolled
  - 120 evaluable PTCL
  - Failed ≥1 prior systemic therapy
- Treatment regimen: belinostat 1,000 mg/m^2, IV days 1-5, q 21 days
- Primary endpoint: ORR by independent review
- Secondary endpoints including: CR, DOR, TTP, tolerability, and safety

O'Connor O., ..., and Shustov, A. *J Clin Oncol.* 2015;33(23):2492-2499.

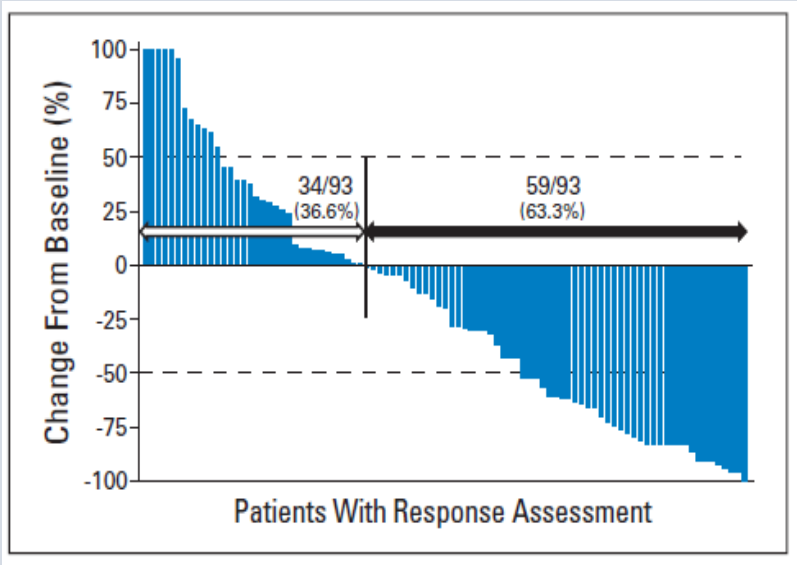
BELIEF: Belinostat Phase 2 Trial

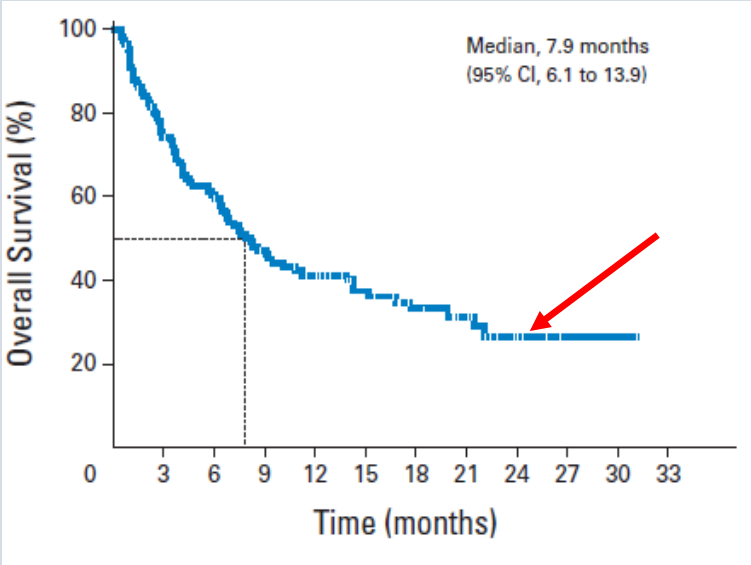
	Efficacy Analysis Set (N=120)	
Response	n (%)	(95% CI)
ORR	31 (26)	(18-35)
CR	13 (11)	(6-18)
PR	18 (15)	
SD	18 (15)	
PD	48 (40)	
NE	23 (19)	

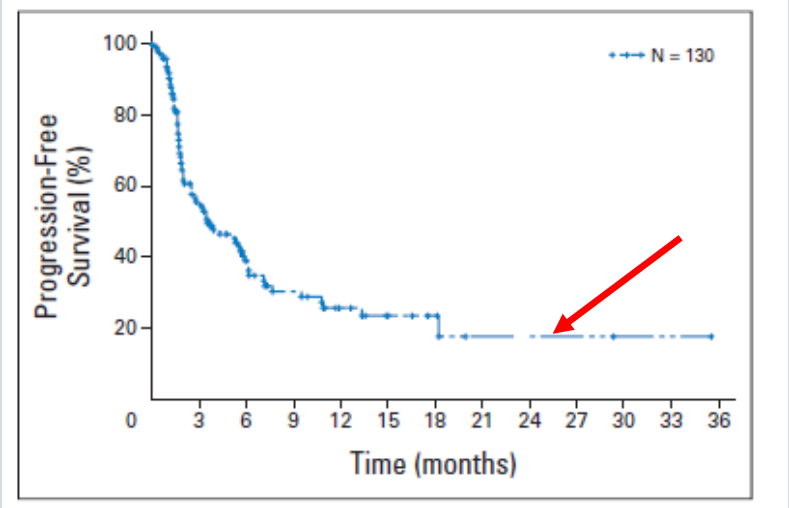
NE= not evaluable due to death (n=7), clinical progression (n=10), patient withdrawal (n=5), or lost to follow-up (n=1) prior to first radiologic assessment.

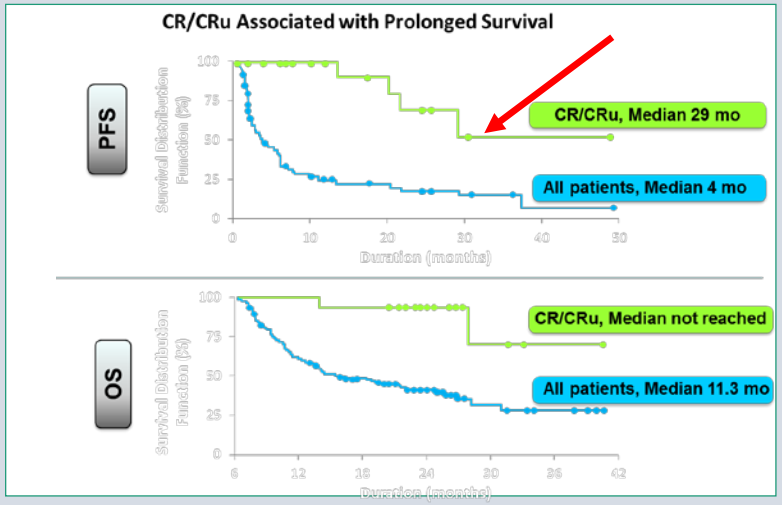
O'Connor O., ..., and Shustov, A. *J Clin Oncol.* 2015;33(23):2492-2499.

HDACi Are Not Fully Understood

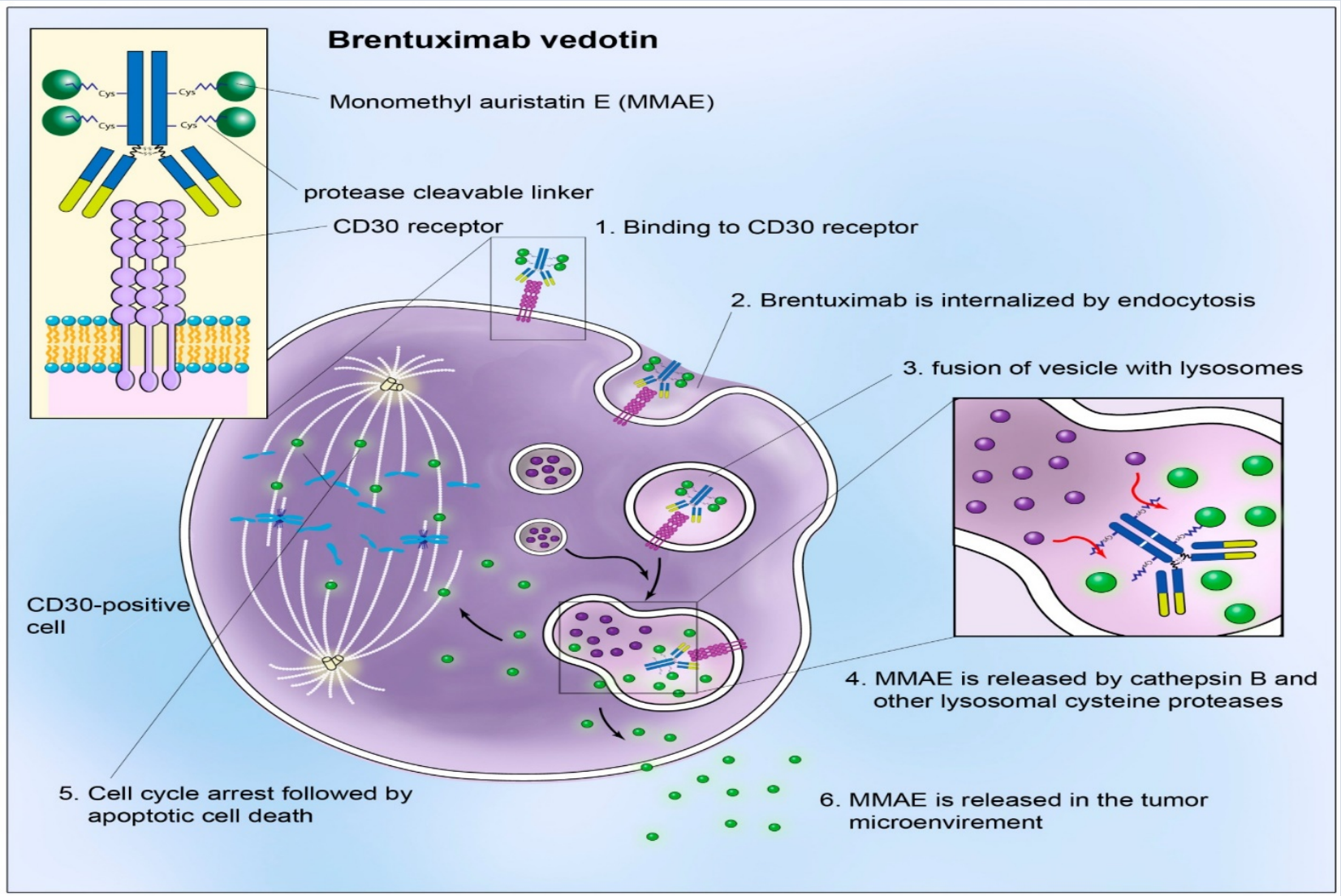








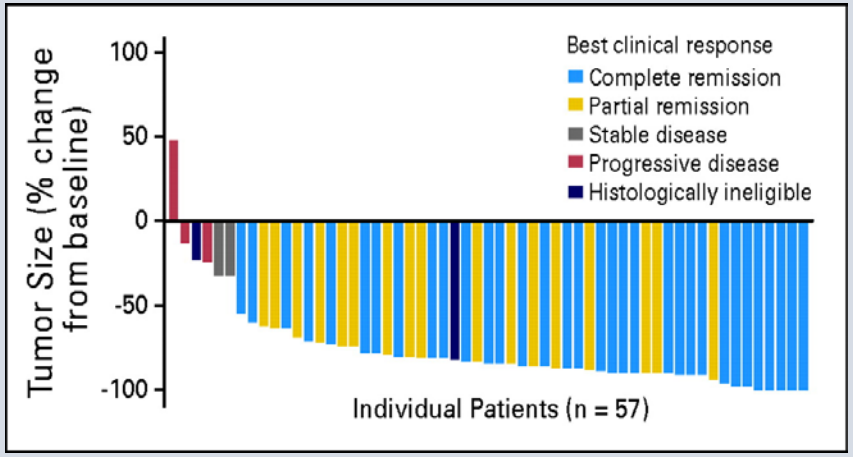
Brentuximab Vedotin: Mechanism of Action

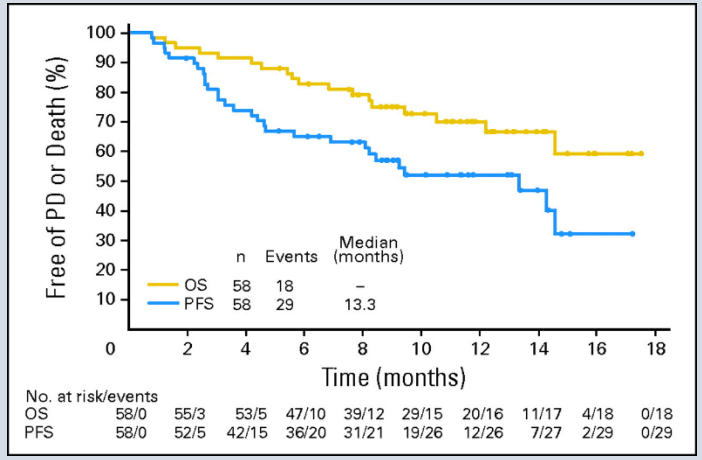


Repr. from Shustov A. *Ther Adv Hematol*. 2013

B-Vedotin in Relapsed/Refractory ALCL

Measure	Central Review (IWC)	
	N (58)	% (95% CI)
Overall response (CR + PR)	50	86 (75-94)
Complete response (CR+CRu)	33	57 (43-70)
Partial response (PR)	17	29 (NE)
Median DOR, mo (95% CI)	12.6	5.7 - NE
Median PFS, mo (95% CI)	13.3	6.9 - NE





Pro B., …., and Shustov, A. *J Clin Onc* 2012;30(18):2190-96

CD30 Across Most PTCL Subtypes vs ALCL: International PTCL Study

Subtype (n)	CD30 Expression (%)			
	0-5%	6-49%	50-80%	>80%
PTCL-NOS (168)	54	32	7	7
AITL (167)	55	42	2	1
EATL (27)	74	11	4	11
ATLL (120)	50	37	8	5
Nasal NK/T (73)	53	34	6	7
Extranasal NK/T (30)	27	27	23	23

Courtesy of Dennis Weisberger, University of Nebraska.

Brentuximab Vedotin in Relapsed Non-ALCL PTCL

	AITL (n=13)	PTCL-NOS (n=21)	Total (N=34)
ORR	7 (54%)	7 (33%)	14 (41%)
Complete remission	5 (38%)	3 (14%)	8 (24%)
Partial remission	2 (15%)	4 (19%)	6 (18%)
Stable disease	3 (23%)	3 (14%)	6 (16%)
Progressive disease	3 (23%)	11 (52%)	14 (41%)
Progression-free survival	6.74 mo	1.61 mo	2.6 mo

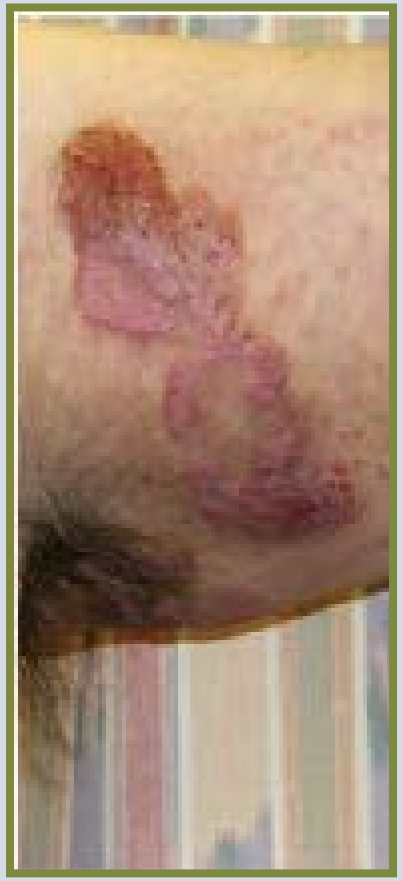
- Comparatively restricted patient population (PTCL-NOS and AILT **ONLY**)
- Short duration of DOR/PFS compared to other agents (DOR ~2 months)
- Not a heavily treated patient population (median prior therapies=2)

Horwitz S, et al. *Blood*, 2014; 123(20):3095-3100.

CTCL

Cutaneous T-Cell Lymphoma
Cutaneous Manifestations

Patch



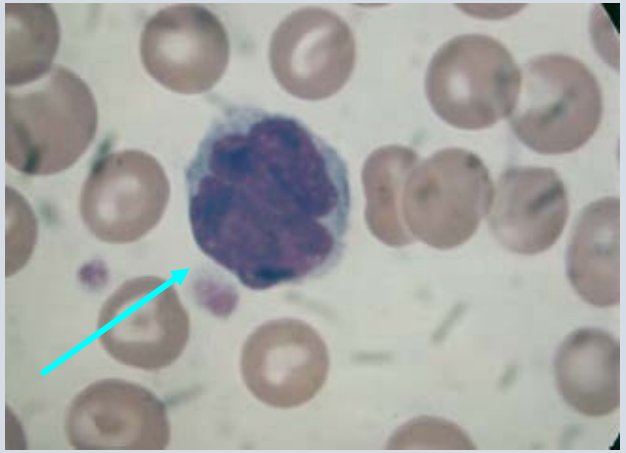
Plaque

Tumor

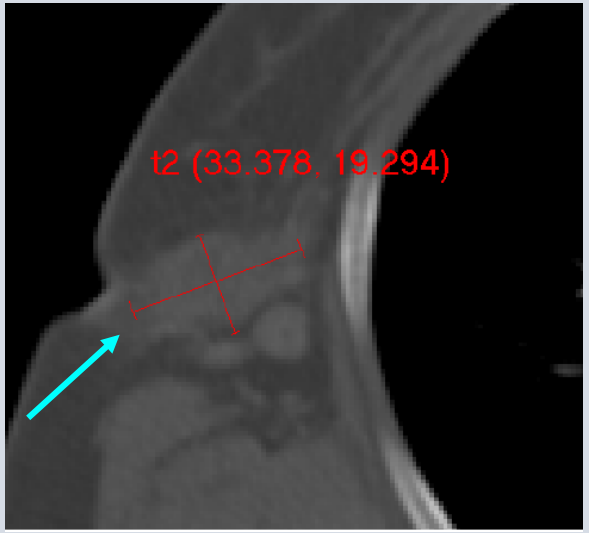
Erythroderma

Kim EJ, et al. *J Clin Invest*. 2005;115:798-812.

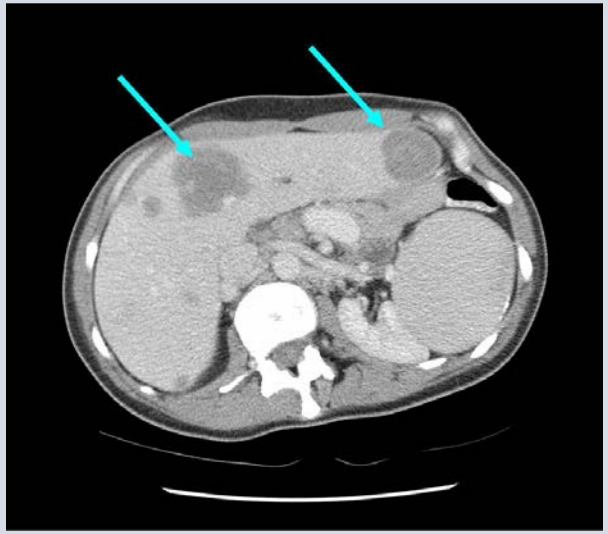
Cutaneous T-Cell Lymphoma
Extracutaneous Manifestations



Blood (Sézary cell)



Lymph node



Viscera

Cutaneous T-cell Lymphoma
ISCL/EORTC Updated Staging System

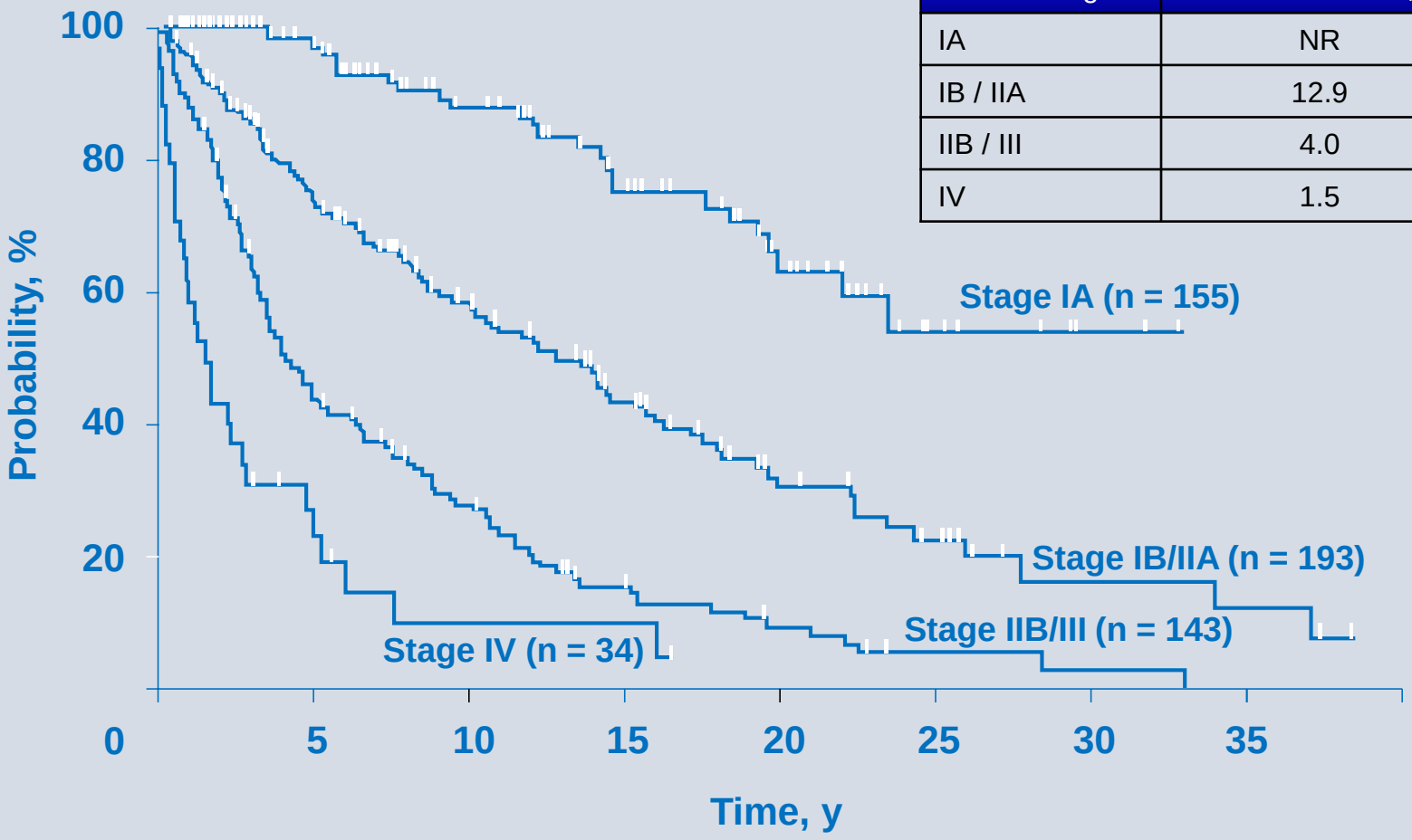
Clinical Stage	T	N	M	B
IA	1	0	0	0,1
IB	2	0	0	0,1
II	1,2	1,2	0	0,1
IIB	3	0-2	0	0,1
III	4	0-2	0	0,1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA_1	1-4	0-2	0	2
IVA_2	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

Olsen E, et al. *Blood*. 2007;110:1713-1722.

CTCL, cutaneous T-cell lymphoma; EORTC, European Organization of Research and Treatment of Cancer; ISCL, International Society for Cutaneous Lymphomas.

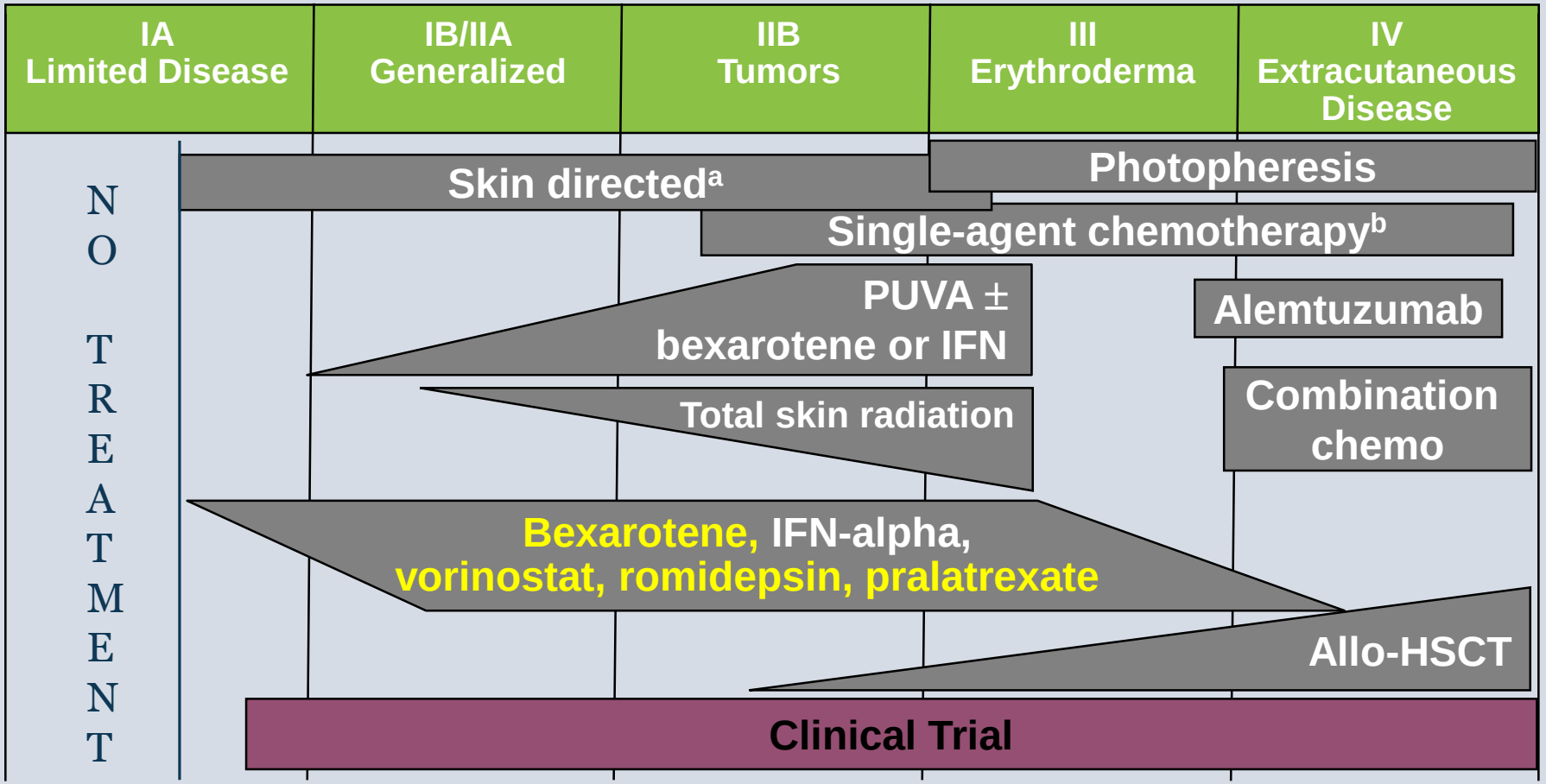
Overall Survival by Clinical Stage

Clinical Stage	Median Survival, y	5-yr OS,%
IA	NR	96
IB / IIA	12.9	73
IIB / III	4.0	44
IV	1.5	27



Kim YH, et al. *Arch Dermatol*. 2003;139:857-866.

CTCL: NCCN Practice Guidelines 2018



NCCN Clinical Practice Guidelines in Oncology: Non-Hodgkin's Lymphomas. V.1.2018.

FDA Approved Systemic Agents in Cutaneous T-Cell Lymphoma

Agent (Class)	CTCL Indication	Study	N	Stage	ORR	DOR
Bexarotene (Retinoid x-receptor activator)[1]	Cutaneous manifestations	Pivotal	62	IIB-IVB	32%	5+ mo
Vorinostat (HDAC inhibitor)[2,3]	Cutaneous manifestations	Pivotal	74	IA-IVB	30%	6+ mo
		Supportive	33	IA-IVB	24%	4 mo
Romidepsin (HDAC inhibitor)[4]	Cutaneous TCL	Pivotal	96	IB-IVA	34%	15 mo
		Supportive	71	IA-IVB	35%	11 mo

[1]Miller V, et al. *J Clin.Onc.,* 1997; 15(2): 790-95

[2]Duvic M, et al., *Blood*, 2007; 109(1): 31-39

[3]Olsen E, et al. *J Clin.Onc.,* 2007; 25(21): 3109-15

[4]Piekarz R, et al. *J Clin.Onc.,* 2009; 27(32): 5410-16

Non-Approved Systemic Agents in Cutaneous T-Cell Lymphoma

Agent (Class)	Use in CTCL	Study	N	Stage	ORR	DOR
Pralatrexate (Anti-folate)[1]	Advanced CTCL	Phase I-II	54	IB-IVA	45%	NR mo
Liposomal Doxorubicin (Anthracycline)[2]	Advanced CTCL	Phase II	49	IIB-IVB	41%	6 mo
Gemcitabine (Anti-metabolite)[3]	Advanced CTCL	Phase II	44	IIB-IVB	70%	12 mo

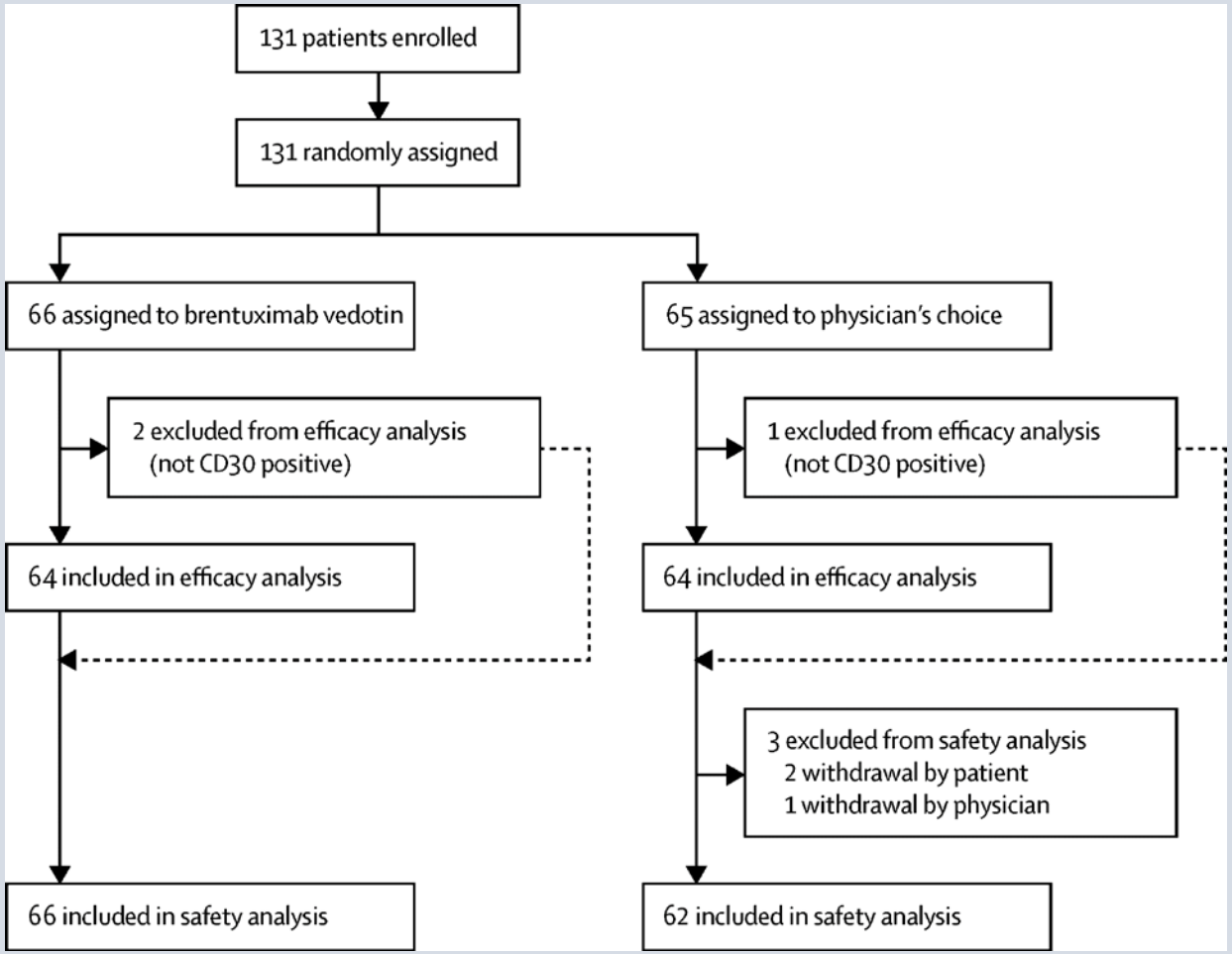
[1]Horwitz S.,... Shustov A, et al., *Blood*, 2012; 119(18): 4115-22

[2]Dummer R. et al., *J Clin. Onc.*, 2012; 30(33): 4091-97

[3]Zinzani PL, et al. *J Clin.Onc., 2000; 18(13): 2603-06*

CTCL: 2019 Update

Phase III Randomized Trial of Brentuximab Vedotin vs. Physician's Choice in Cutaneous CD30+ T-Cell Lymphoma (ALCANZA)



- Dx: CD30+ MF or pcALCL (>10% CD30+ cells)
- ≥ 1 prior systemic therapy failure
- Treatment regimen: B-vedotin 1.8 mg/kg q 21 days; MTX 5-50 mg PO QW; Bexarotene 300 mg/sqm PO QD
- Primary endpoint: OGR lasting ≥ 4 months per independent review
- Secondary endpoints including: CR, DOR, PFS, Symptom Improvement, and safety/tolerability

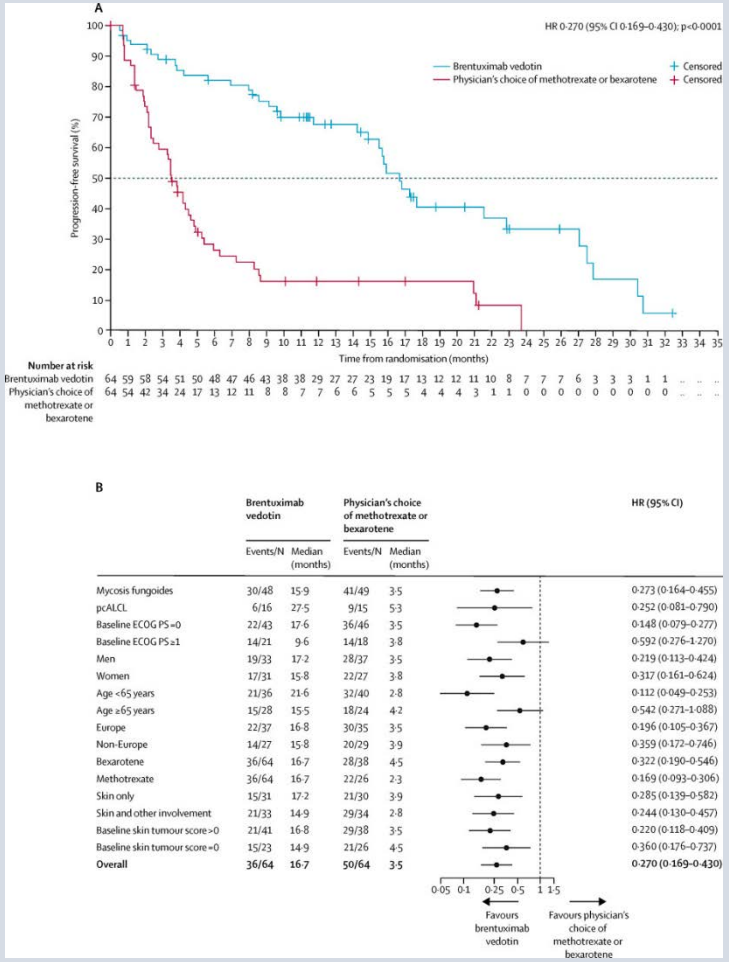
Miles P, et al. *Lancet* 2017;390: 555-566.

Phase III Randomized Trial of Brentuximab Vedotin vs. Physician's Choice in Cutaneous CD30+ T-Cell Lymphoma (ALCANZA)

	Brentuximab vedotin				Physician's choice of methotrexate or bexarotene			
	Total (n=64)	ORR4	ORR	CR	Total (n=64)	ORR4	ORR	CR
ITT population	64 (100%)	36 (56%)*	43 (67%)	10 (16%)	64 (100%)	8 (13%)†	13 (20%)	1 (2%)
Mycosis fungoides	48 (75%)	24 (50%)	31 (65%)	5 (10%)	49 (77%)	5 (10%)	8 (16%)	0
Stage‡§								
IA–IIA	15 (31%)	6 (40%)	8 (53%)	1 (7%)	18 (37%)	4 (22%)	5 (28%)	0
IIB	19 (40%)	12 (63%)	13 (68%)	3 (16%)	19 (39%)	1 (5%)	3 (16%)	0
IIIA–IIIB	4 (8%)	2 (50%)	3 (75%)	0	2 (4%)	0	0	0
IVA	2 (4%)	2 (100%)	2 (100%)	1 (50%)	9 (18%)	0	0	0
IVB	7 (15%)	2 (29%)	4 (57%)	0	0	NA	NA	NA
pcALCL	16 (25%)	12 (75%)	12 (75%)	5 (31%)	15 (23%)	3 (20%)	5 (33%)	1 (7%)
Disease involvement‡								
Skin only	9 (56%)	8 (89%)	8 (89%)	4 (44%)	11 (73%)	3 (27%)	5 (45%)	1 (9%)
Extracutaneous disease	7 (44%)	4 (57%)	4 (57%)	1 (14%)	4 (27%)	0	0	0

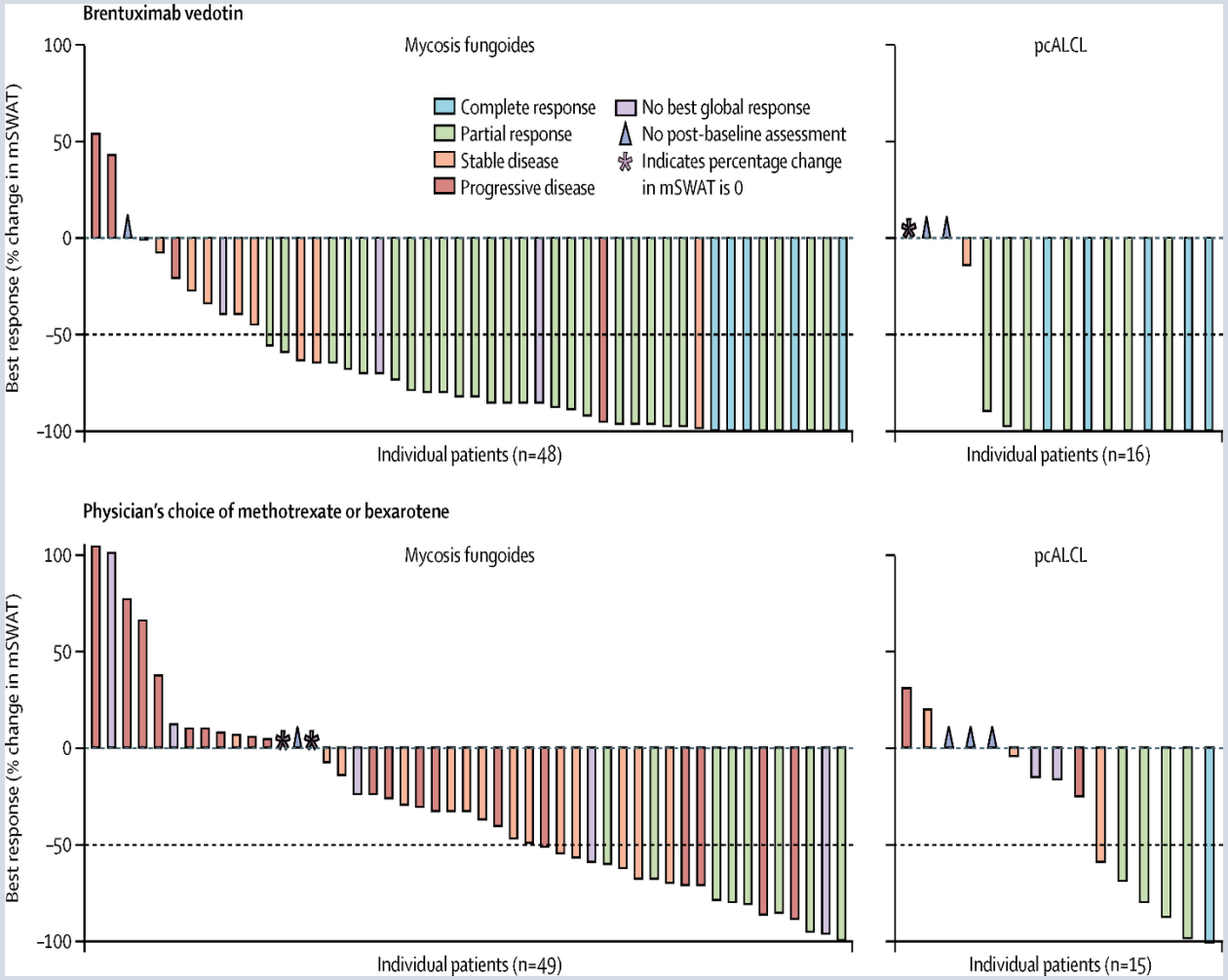
Data are n (%). ORR4, ORR, and CR percentages are based on the number of patients in the total column. ORR4=achieved an objective response lasting at least 4 months. ORR=achieved an objective response. CR=achieved a complete response. ITT=intent to treat. NA=not applicable. pcALCL=primary cutaneous anaplastic large-cell lymphoma. *One patient with mycosis fungoides in the brentuximab vedotin group achieved a partial response after C1, C2, and C3, and discontinued because of an adverse event. About 4·3 months later the patient received chemotherapy (gemcitabine) before end-of-treatment visit. Total duration of response, including after receipt of gemcitabine, was 4·8 months. †One patient with pcALCL in the bexarotene group who achieved partial response after C2 and sustained it at C5 chose to withdraw from treatment. The patient received subsequent therapy (methotrexate) about 3·5 months into the response to bexarotene but before end-of-treatment visit. Total duration of response, including after receipt of methotrexate, was 4·4 months. ‡Percentage in each subcategory in the total column is based on the number of patients in each disease subtype. §One patient in each group had incomplete staging data and are not included in the table: one patient in the brentuximab vedotin group had partial response and one patient in the physician's choice group had no response.

Table 2: **Patient responses by clinical stage at baseline**

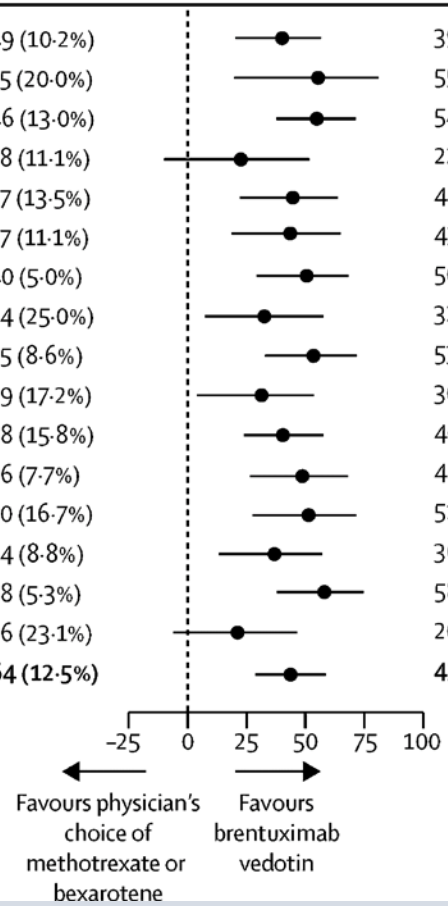


Miles P, et al. *Lancet* 2017;390: 555-566.

Phase III Randomized Trial of Brentuximab Vedotin vs. Physician's Choice in Cutaneous CD30+ T-Cell Lymphoma (ALCANZA)

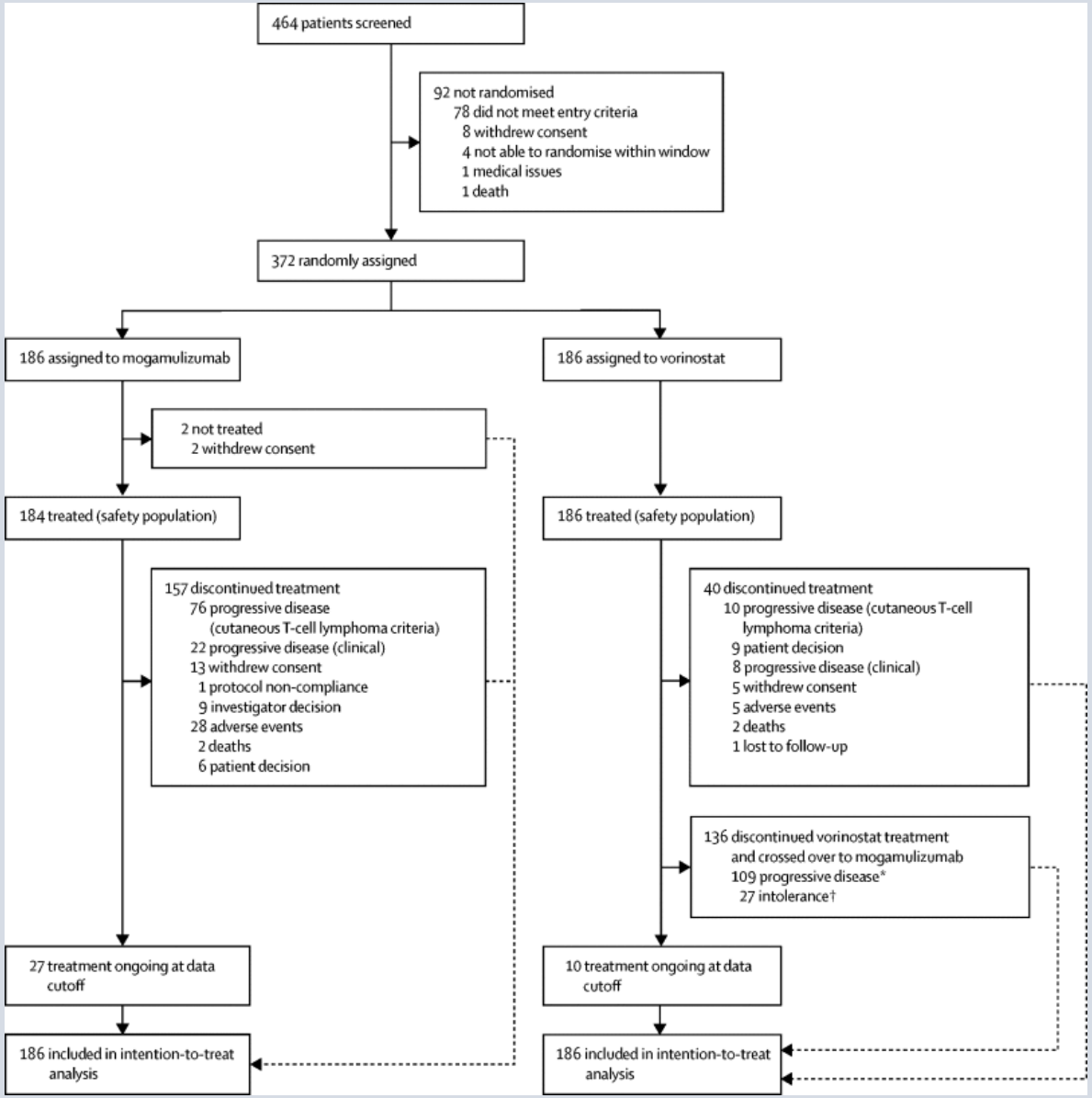


	Brentuximab vedotin, n/N (%)	Physician's choice of methotrexate or bexarotene, n/N (%)	Difference in percentages (95% CI)
Mycosis fungoides	24/48 (50·0%)	5/49 (10·2%)	39·8 (19·9 to 56·2)
pcALCL	12/16 (75·0%)	3/15 (20·0%)	55·0 (19·7 to 80·4)
Baseline ECOG PS=0	29/43 (67·4%)	6/46 (13·0%)	54·4 (37·3 to 71·5)
Baseline ECOG PS≥1	7/21 (33·3%)	2/18 (11·1%)	22·2 (–10·2 to 51·2)
Men	19/33 (57·6%)	5/37 (13·5%)	44·1 (21·3 to 63·3)
Women	17/31 (54·8%)	3/27 (11·1%)	43·7 (18·5 to 64·7)
Age <65 years	20/36 (55·6%)	2/40 (5·0%)	50·6 (29·3 to 68·3)
Age ≥65 years	16/28 (57·1%)	6/24 (25·0%)	32·1 (6·9 to 57·4)
Europe	23/37 (62·2%)	3/35 (8·6%)	53·6 (32·7 to 71·3)
Non-Europe	13/27 (48·1%)	5/29 (17·2%)	30·9 (4·2 to 53·5)
Bexarotene	36/64 (56·3%)	6/38 (15·8%)	40·5 (23·7 to 57·3)
Methotrexate	36/64 (56·3%)	2/26 (7·7%)	48·6 (26·7 to 67·7)
Skin only	21/31 (67·7%)	5/30 (16·7%)	51·1 (27·3 to 71·0)
Skin and other involvement	15/33 (45·5%)	3/34 (8·8%)	36·6 (12·3 to 56·3)
Baseline skin tumour score >0	26/41 (63·4%)	2/38 (5·3%)	58·2 (38·1 to 74·1)
Baseline skin tumour score =0	10/23 (43·5%)	6/26 (23·1%)	20·4 (–5·5 to 46·3)
Overall	**36/64 (56·3%)**	**8/64 (12·5%)**	**43·8 (29·1 to 58·4)**



Miles P, et al. *Lancet* 2017;390: 555-566.

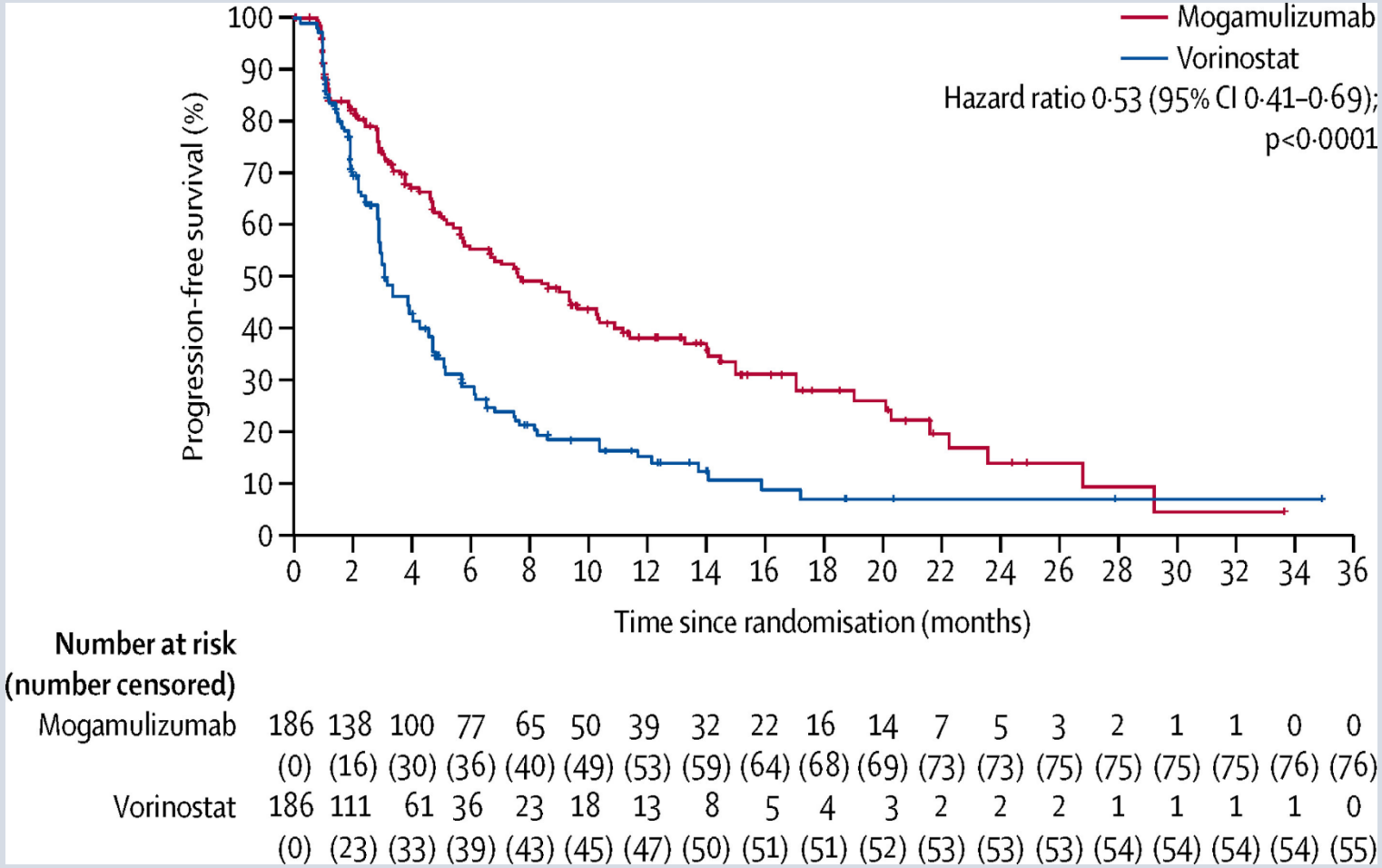
Phase III Randomized Trial of Mogamulizumab vs. Vorinostat in Previously Treated Cutaneous T-cell Lymphoma (MAVORIC)

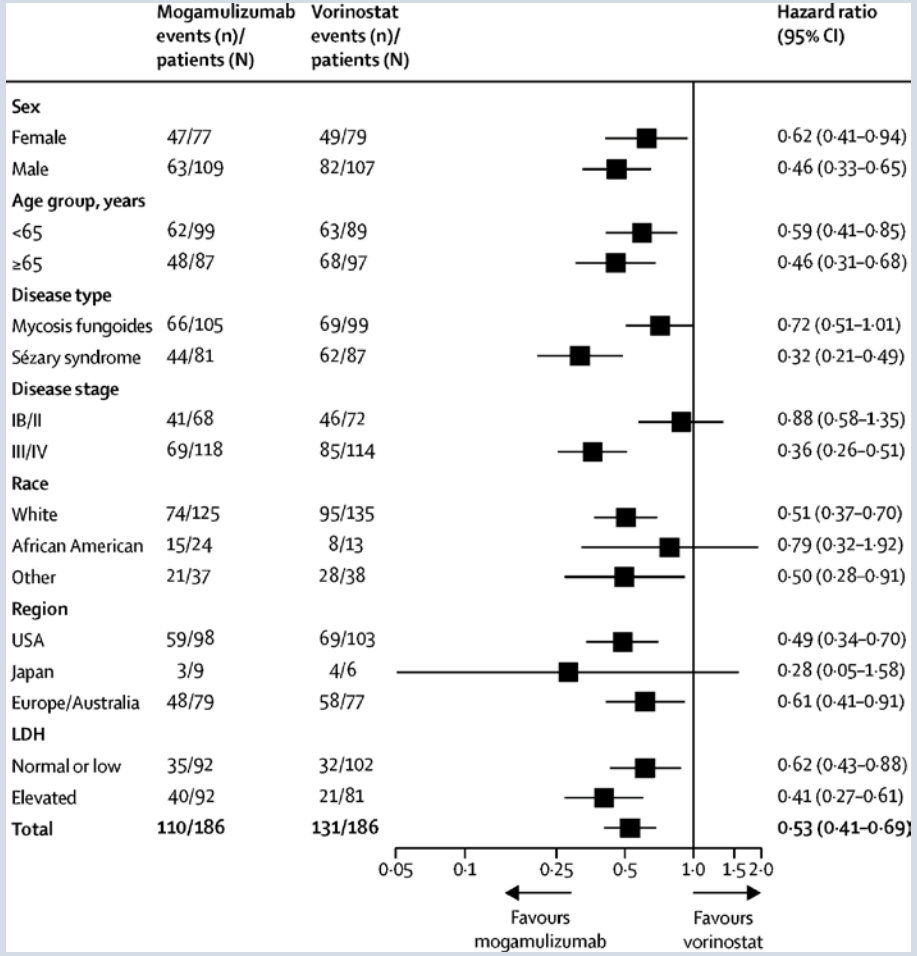


- Dx: stage IB-IVB MF or SS
- ≥ 1 prior systemic therapy failure
- Treatment regimen: Mogamulizumab 1 mg/kg IV QW -> Q2W; Vorinostat 400 mg PO QD; crossover allowed.
- Primary endpoint: PFS per investigator
- Secondary endpoints including: OGR, coOGR, DOR, Symptom Improvement, and safety/tolerability

Kim Y, … Shustov A., … et al. *Lancet Onc* 2018; 19(9):1192-1204.

Phase III Randomized Trial of Mogamulizumab vs. Vorinostat in Previously Treated Cutaneous T-cell Lymphoma (MAVORIC)





Kim Y, … Shustov A., … et al. *Lancet Onc* 2018; 19(9):1192-1204.

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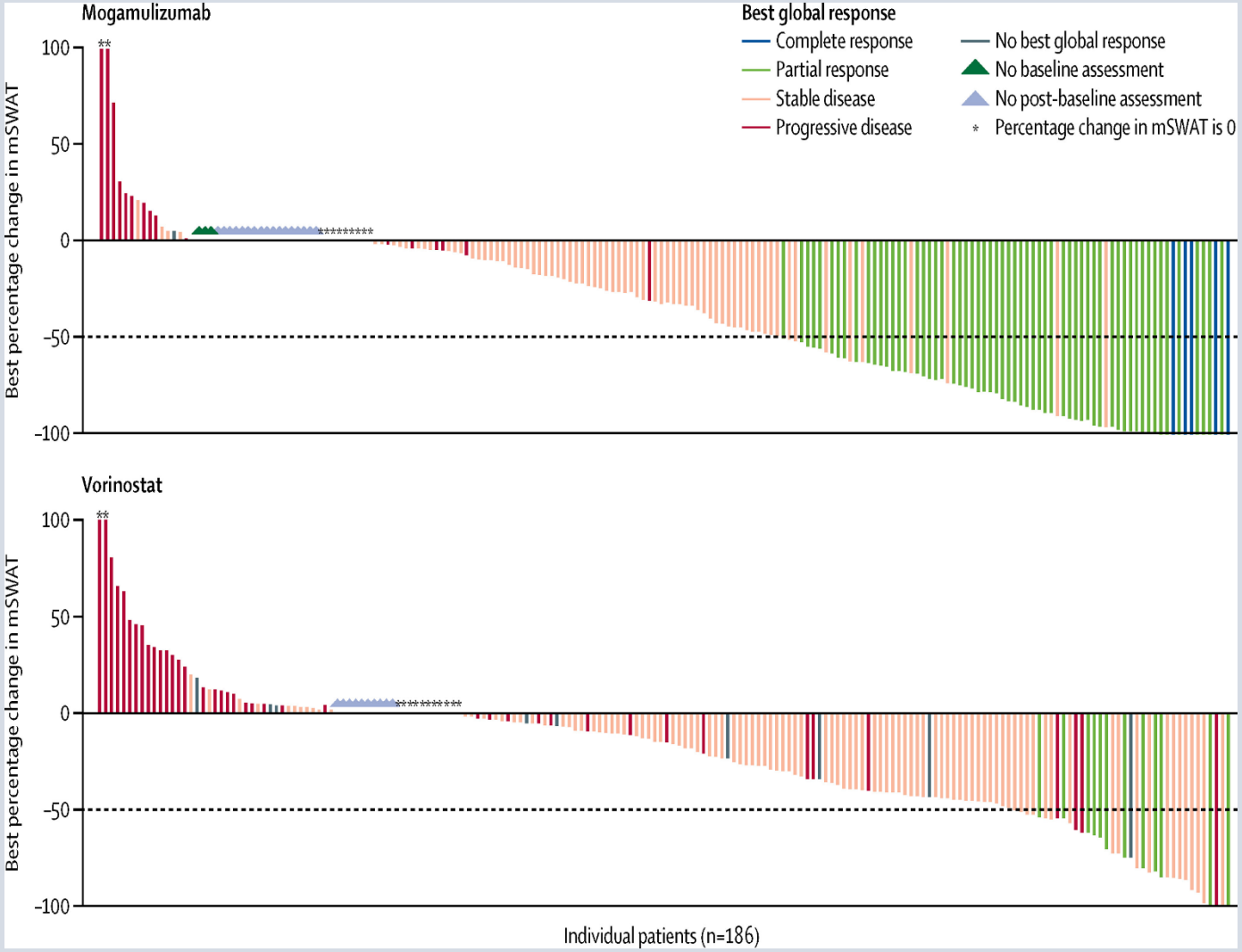

	Mogamulizumab (n=184)				Vorinostat (n=186)			
	Grade 1–2	Grade 3	Grade 4	Grade 5	Grade 1–2	Grade 3	Grade 4	Grade 5
Blood and lymphatic system disorders								
Thrombocytopenia [†]	25 (14%)	0	0	0	63 (34%)	11 (6%)	2 (1%)	0
Gastrointestinal disorders								
Abdominal pain	7 (4%)	0	0	0	21 (11%)	0	0	0
Constipation	20 (11%)	1 (1%)	0	0	32 (17%)	2 (1%)	0	0
Diarrhoea	42 (23%)	1 (1%)	0	0	106 (57%)	9 (5%)	0	0
Nausea	27 (15%)	1 (1%)	0	0	76 (41%)	3 (2%)	0	0
Vomiting	11 (6%)	0	0	0	23 (12%)	1 (1%)	0	0
General disorders and administration-site conditions								
Asthenia	10 (5%)	0	0	0	23 (12%)	4 (2%)	0	0
Fatigue	40 (22%)	3 (2%)	0	0	59 (32%)	11 (6%)	0	0
Peripheral oedema	27 (15%)	0	0	0	26 (14%)	1 (1%)	0	0
Pyrexia	30 (16%)	1 (1%)	0	0	11 (6%)	0	0	0
Infections and infestations								
Cellulitis	2 (1%)	3 (2%)	1 (1%)	0	6 (3%)	4 (2%)	0	0
Pneumonia [†]	2 (1%)	6 (3%)	1 (1%)	1 (1%)	0	1 (1%)	0	2 (1%)
Sepsis	1 (1%)	2 (1%)	0	1 (1%)	1 (1%)	0	4 (2%)	1 (1%)
Upper respiratory tract infection	19 (10%)	0	0	0	7 (4%)	2 (1%)	0	0
Injury, poisoning, and procedural complications								
Infusion-related reaction	58 (32%)	3 (2%)	0	0	1 (1%) [‡]	0	0	0
Investigations								
Aspartate aminotransferase increased	6 (3%)	2 (1%)	0	0	11 (6%)	1 (1%)	0	0
Blood creatinine increased	6 (3%)	0	0	0	52 (28%)	0	0	0
Weight decreased	10 (5%)	1 (1%)	0	0	31 (17%)	2 (1%)	0	0
Metabolism and nutrition disorders								
Decreased appetite	12 (7%)	2 (1%)	0	0	44 (24%)	2 (1%)	0	0
Musculoskeletal and connective tissue disorders								
Muscle spasms	9 (5%)	0	0	0	27 (15%)	2 (1%)	0	0
Nervous system disorders								
Dizziness	12 (7%)	0	0	0	19 (10%)	0	0	0
Dysgeusia	6 (3%)	0	0	0	53 (28%)	1 (1%)	0	0
Headache	23 (13%)	0	0	0	28 (15%)	1 (1%)	0	0
Respiratory, thoracic, and mediastinal disorders								
Pulmonary embolism	0	0	0	0	0	4 (2%)	1 (1%)	2 (1%)
Skin and subcutaneous tissue disorders								
Alopecia	13 (7%)	0	0	0	36 (19%)	0	0	0
Drug eruption [‡]	36 (20%)	8 (4%)	0	0	1 (1%)	0	0	0
Vascular disorders								
Hypertension	9 (5%)	8 (4%)	0	0	13 (7%)	12 (6%)		

Kim Y, … Shustov A., … et al. *Lancet Onc* 2018; 19(9):1192-1204.

FDA Approved Systemic Agents in Cutaneous T-Cell Lymphoma, 2019 Update

Agent (Class)	CTCL Indication	Study	N	Stage	ORR	DOR
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Bexarotene (Retinoid x-receptor activator)	Cutaneous manifestations	Pivotal	62	IIB-IVB	32%	5+ mo
Vorinostat (HDAC inhibitor)	Cutaneous manifestations	Pivotal Supportive	74 33	IA-IVB IA-IVB	30% 24%	6+ mo 4 mo
Brentuximab Vedotin	CD30+ MF, pcALCL	Randomized Ph3	131	IB-IVB	50% 75%	15+ mo
Mogamulizumab	Cutaneous TCL	Randomized Ph3	372	IB-IVB	24%	25 mo 20 mo

THANK YOU

Therapy for Non-Invasive Breast Cancer & Prevention

Rachel Yung, MD
Assistant Professor, UWSOM
Fall 2020

Seattle Cancer Care Alliance

No Disclosures

Objectives

1) Differentiate local and systemic therapy for LCIS from DCIS.

2) Evaluate who should we consider for chemoprevention.

3) Compare and contrast SERMs and Aromatase Inhibitors.

4) Understand the importance of lifestyle on Breast Cancer risk.

Epidemiology: Breast Cancer Incidence and Mortality

- Most common cancer in women
- 29% of all new cancers
- 2nd leading cause of cancer death in US
- 249,260 cases diagnosed
- 40,890 died of breast cancer

American Cancer Society. Breast Cancer Facts & Figures at www.cancer.org. Surveillance, Epidemiology, and End Results Program, 1976-2006, Division of Cancer Control and Population Sciences, NCI 2009. http://seer.cancer.gov. Combined data from National Program of Cancer Registries as submitted to CDC and from SEER as submitted to NCI in November 2014. http://www.cdc.gov/cancer/breast/statistics/race.htm

Major Risk Factors

Factor	Relative risk (RR)
Female sex	100
Age (30 vs. 70)	10
Intraepithelial neoplasia (DCIS, LCIS, ADH, etc.)	2 to 10
Prior breast/ovarian cancer	2 to 10
1° relative younger than age 60 at diagnosis	2
Germ-line mutations responsible for hereditary breast cancer	10 to 20
Breast Density (slightly increased vs. extremely dense)	1.79 to 4.64

ASCO Curriculum Cancer Prevention and Breast Cancer Prevention (PDQ®) July 2017.

Modifiable Factors with Increased Risk

Factor	Relative risk (RR) or Effect
Combined Hormone Therapy	~26% increase
Ionizing radiation to chest < 30	5 to 20
Obesity (>82 kg vs. <59 kg)	2.85
Alcohol intake (4 drinks/day vs. non-drinkers)	1.32
Parity (Nulliparous vs. parous)	2

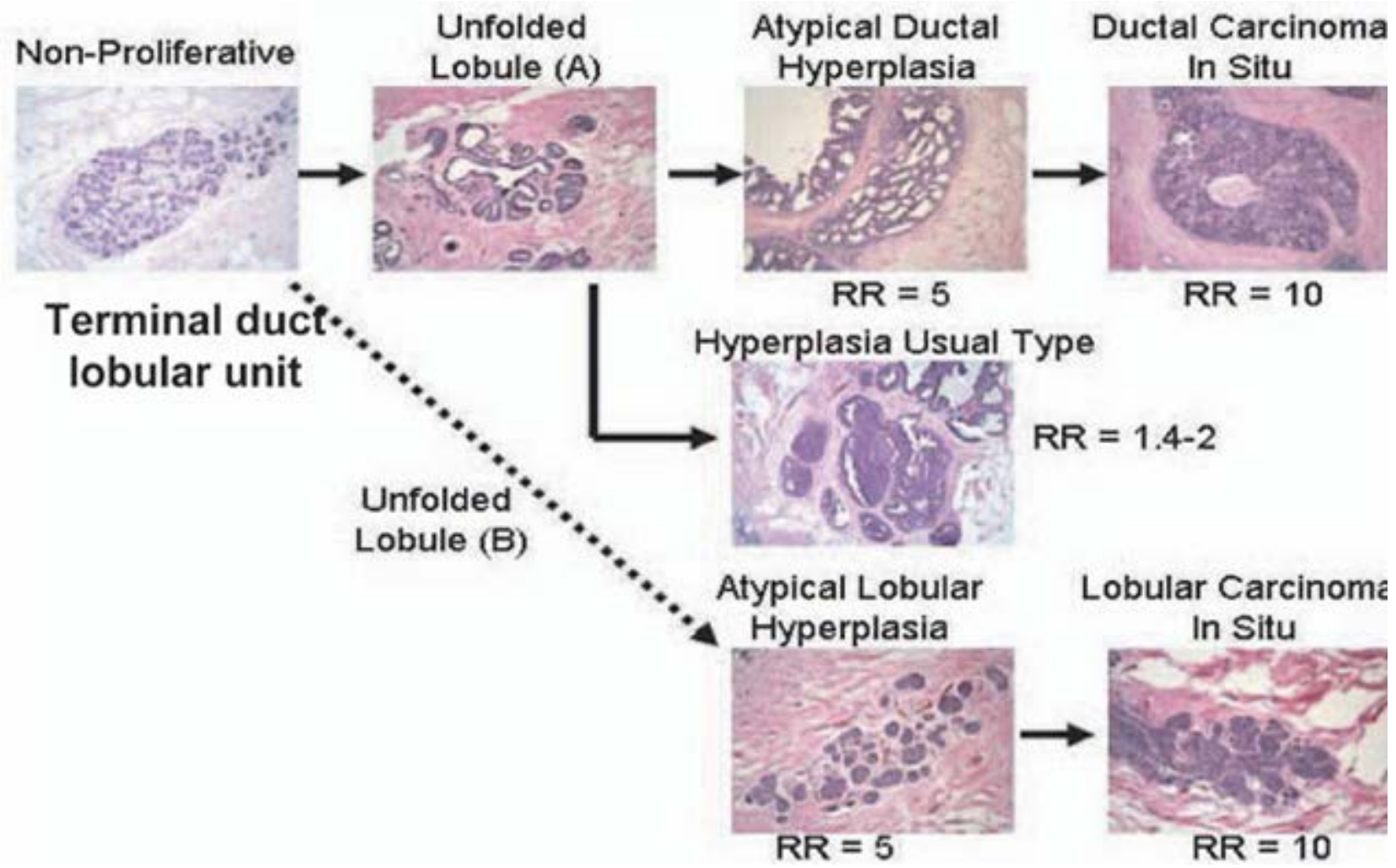
ASCO Curriculum Cancer Prevention and Breast Cancer Prevention (PDQ®) July 2017.

Modifiable Factors with Decreased Risk

Factor	Magnitude of Effect
Early pregnancy	50% decrease in risk compared to nulliparous women or women who give birth >35 years
Breast Feeding	4.3% decrease in RR for every 12 months, in addition 7% for every birth
Exercise (strenuous exercise ≥ 4 hrs/week)	Average RR reduction is 30% to 40%. The effect may be greatest for premenopausal women of normal or low body weight.

ASCO Curriculum Cancer Prevention and Breast Cancer Prevention (PDQ®) July 2017.

Proliferative lesions & Intraepithelial Neoplasia



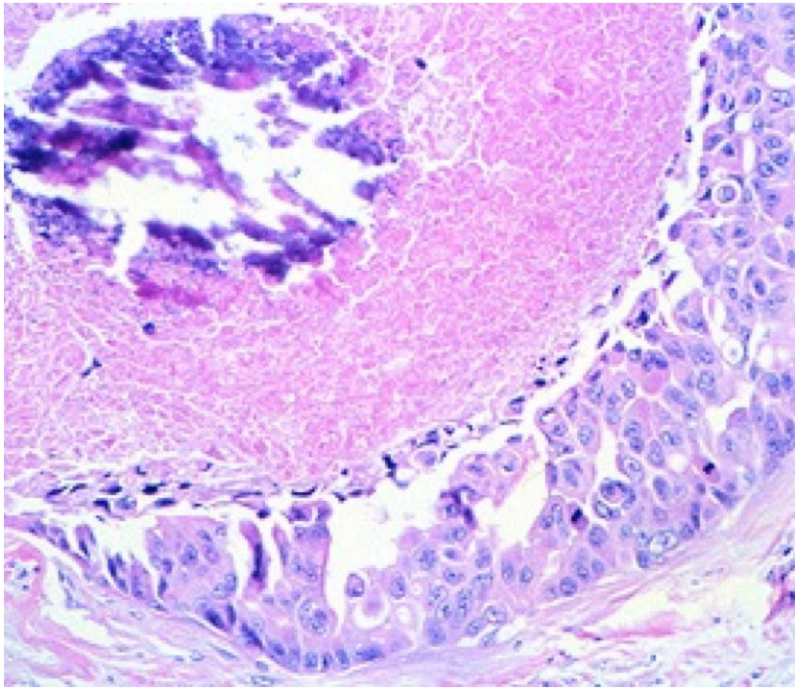
Fabian, *Endocr Relat Cancers* 2005 12:185-213

Management of DCIS & Proliferative Breast Disease

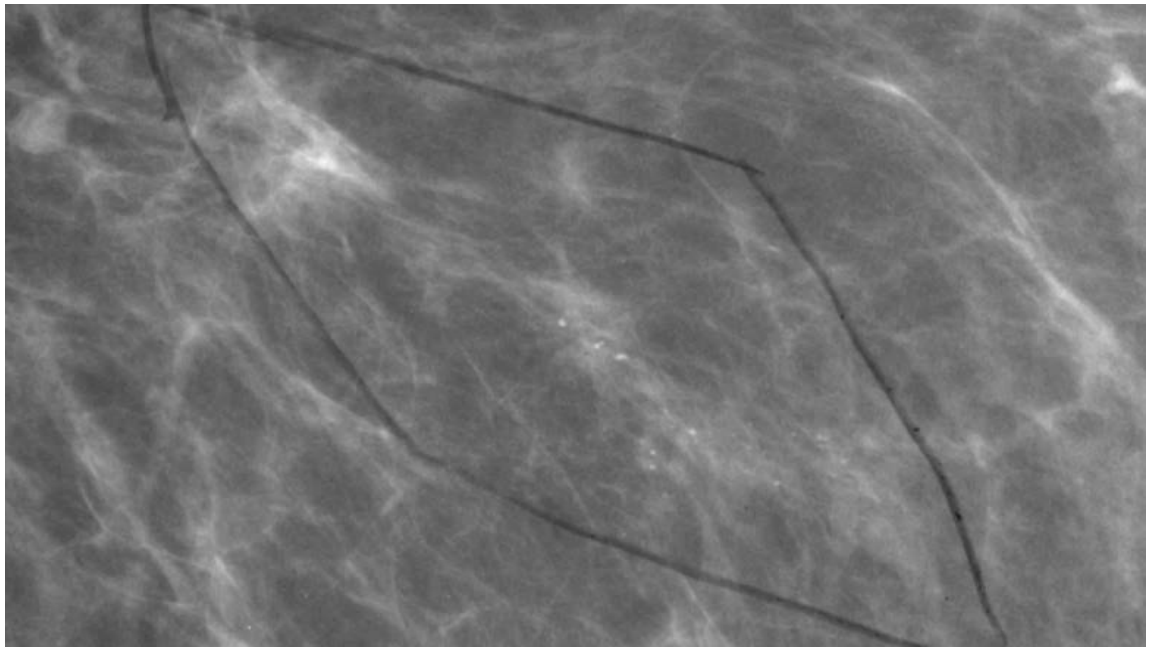
	Risk for Invasive Ca	Upstaging	Surgery for Diagnosis/Tx	Treatment & Prevention
DCIS	Precursor	10-30% to IBC	Excision Clear margins (2mm)	Treatment
pLCIS	?precursor	~malignant	Excisional Bx/ clear margins	Treatment
LCIS	Risk	<5%	Concordance with Core Bx	Chemoprevention
ADH	Risk	>20% to DCIS	Excisional Biopsy	Chemoprevention
ALH	Risk	<5%	Concordance with Core Bx	Chemoprevention

Non-invasive Breast Cancer: *DCIS*

- *Ductal carcinoma in situ* (DCIS) is a proliferation of malignant cells of the ducts not breaching basement membrane
- 50-75% is ER+ or PR+
- 1970 = 5.8/100k, 2004 = 32.5/100k
- 25% of new breast cancers
- 60K new cases each year
- Precursor lesion for invasive breast cancer
- Equal in risk to IBC for genetic mutations
- Seen in BRCA mutation carriers
- Increases risk of IBC 2 fold



Diagnosis of *DCIS*



90% with DCIS have suspicious microcalcifications on mammography
DCIS accounts for 80% of all breast cancers with calcifications

Treatment of *DCIS:* Surgery

- Surgery either mastectomy or lumpectomy
  - For mastectomy, failure rate 1-2% with 97-98% DFS
- Surgical Margins, 2 mm now standard
  - lower rates of IBTR
  - decrease re-excision rates
  - improve cosmetic outcomes
  - decrease health care costs.
- Contraindications to breast conserving therapy
  - Persistent positive margins
  - Multi-centric disease
  - Prior breast irradiation
- Sentinel node biopsy done for mastectomy or features in needle biopsy concerning for risk of invasive disease

Morrow M et al., *Pract Radiat Oncol*. 2016 Sep-Oct;6(5):287-95. doi: 10.1016/j.prro.2016.06.011. Epub 2016 Jun 24.

Treatment of *DCIS*: Benefit of Radiation

- Evaluated in 3 trials: NSABP B-17, EORTC 10853, UK trial
- In NSABP B-17, patients with *DCIS* were randomized to lumpectomy or lumpectomy + breast radiation
  - With 12 years follow up, radiation after lumpectomy was decreased in ipsilateral breast tumor recurrence by **50%**
  - Approximately 50% of recurrences are invasive
  - **No benefit in overall survival**
- Need for radiation in all patients with *DCIS* after lumpectomy is controversial

Fisher B, *et al. Semin Oncol* 2001;**28**:400. Julien JP, *et al. Lancet* 2000;**355**:528. Fisher ER, *et al. Cancer* 1999;**86**:429. Bijker N, *et al. JCO* 2006;**24**:3381. Houghton J, *et al. Lancet* 2003;**362**:95.

Original Investigation

Breast Cancer Mortality After a Diagnosis of Ductal Carcinoma In Situ

Steven A. Narod, MD, FRCPC; Javaid Iqbal, MD; Vasily Giannakeas, MPH; Victoria Sopik, MSc; Ping Sun, PhD

Rethinking the Standard for Ductal Carcinoma In Situ Treatment

Laura Esserman, MD, MBA; Christina Yau, PhD

Original Investigation

Survival Benefit of Breast Surgery for Low-Grade Ductal Carcinoma In Situ
A Population-Based Cohort Study

Yasuaki Sagara, MD; Melissa Anne Mallory, MD; Stephanie Wong, MD; Fatih Aydogan, MD; Stephen DeSantis, BS; William T. Barry, PhD; Mehra Golshan, MD

Invited Commentary

No Surgery for Low-Grade Ductal Carcinoma In Situ?

Julie A. Margenthaler, MD; Aislinn Vaughan, MD

Narod SA, *et al. JAMA Oncology* Published online August 20, 2015. Esserman L and Yau C. *JAMA Oncology* Published online August 20, 2015. Sagara Y *et al., JAMA Surgery* 2015;150(8):739-745. Margenthaler JA and Vaughan A. *JAMA Surgery* 2015;150.

Treatment of *DCIS*: BCS without Radiation

Surgical Excision Without Radiation for Ductal Carcinoma in Situ of the Breast: 12-Year Results From the ECOG-ACRIN E5194 Study

Lawrence J. Solin, Robert Gray, Lorie L. Hughes, William C. Wood, Mary Ann Lowen, Sunil S. Badve, Frederick L. Baehner, James N. Ingle, Edith A. Perez, Abram Recht, Joseph A. Sparano, and Nancy E. Davidson

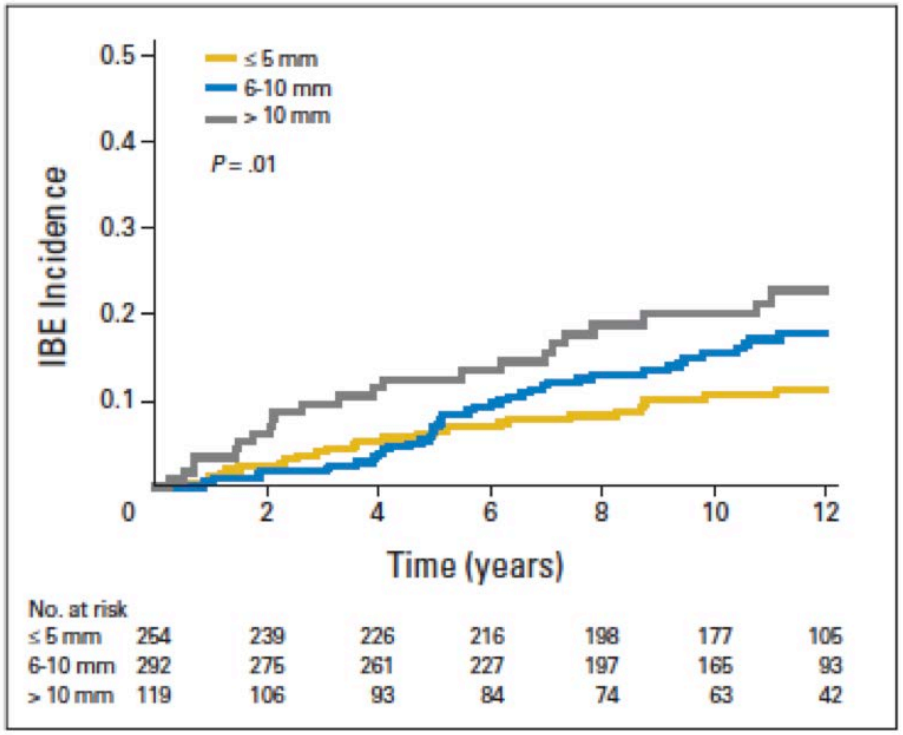
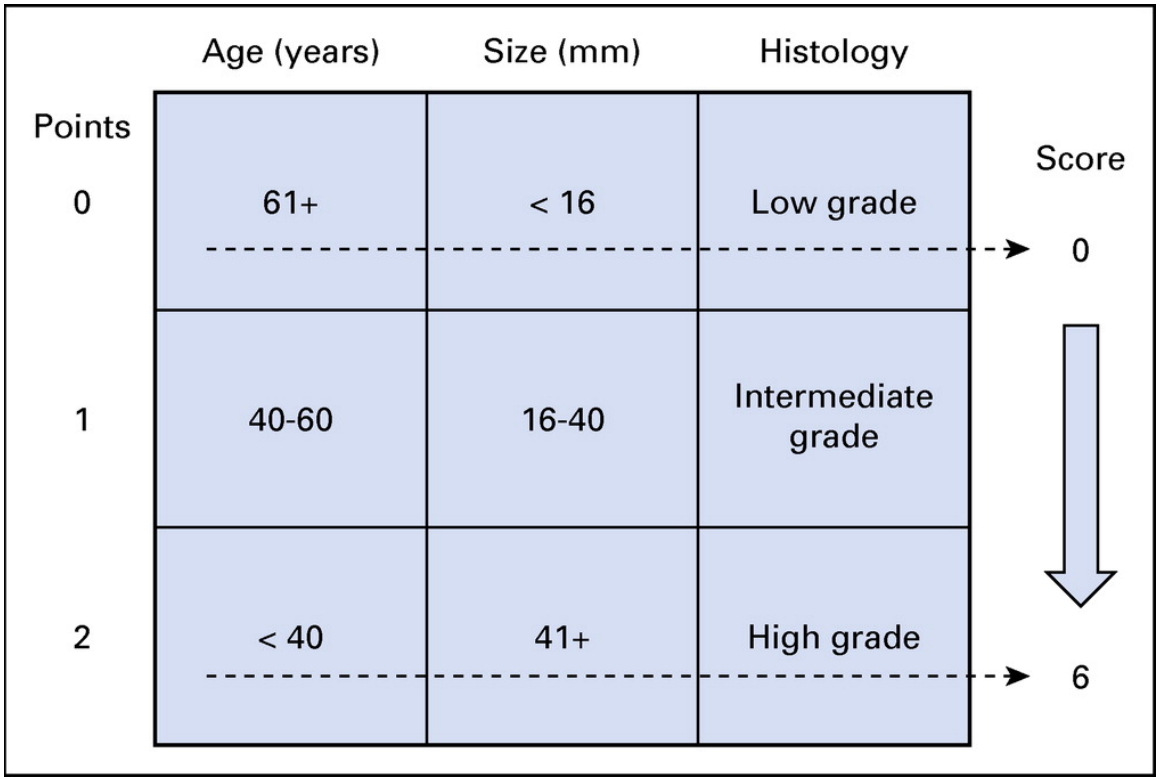


Fig 2. Ipsilateral breast events (IBEs) according to tumor size. The numbers at risk are given beneath the *x*-axis.

- Prospective trial of women with DCIS selected for lumpectomy without radiation in 2 cohorts
  1) low-int grade <2.5 cm
  2) high grade ≤ 1 cm
- Tamoxifen used in 30% of patients
- 12 yr rate of IBE 14.4% for cohort 1 and 24.6% for cohort 2
- Study cohort and tumor size associated with developing IBE

DCIS s/p BCS SEER analysis: Radiation or not

- 32,177 women with DCIS from 1988-2007



Published in: Yasuaki Sagara; Rachel A. Freedman; Ines Vaz-Luis; Melissa Anne Mallory; Stephanie M. Wong; Fatih Aydogan; Stephen DeSantis; William T. Barry; Mehra Golshan; *Journal of Clinical Oncology* **2016,** 34, 1190-1196.
DOI: 10.1200/JCO.2015.65.1869

DCIS s/p BCS SEER analysis: Radiation or not

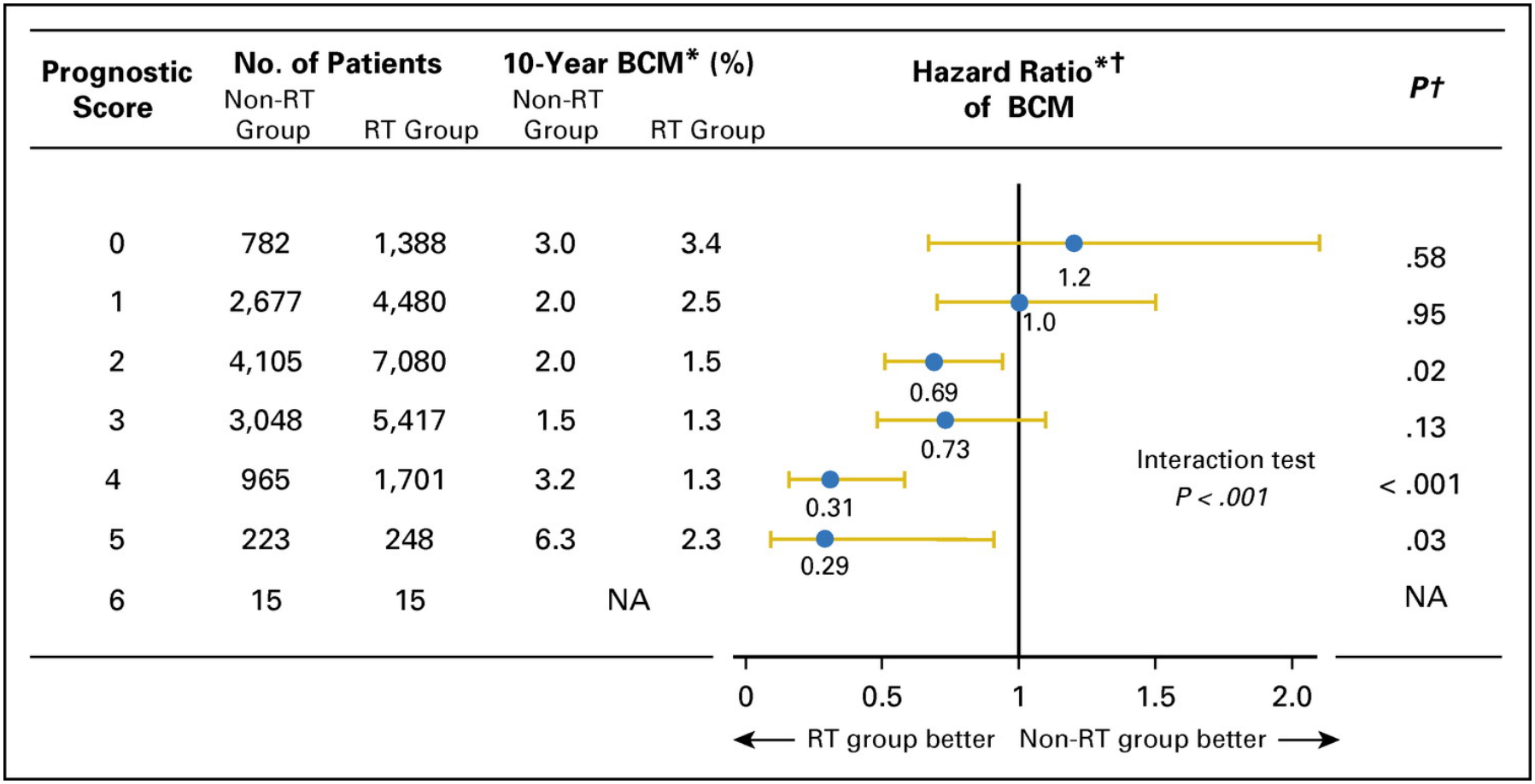


Fig 2. Hazard ratio comparing breast cancer mortality (BCM) between radiotherapy (RT) group and non-RT group according to prognostic score. (*) Weighted by inverse propensity score. (†) Multivariate analysis adjusted by age of patients, year of diagnosis, race, tumor size, nuclear grade, and marital status. NA, not applicable.

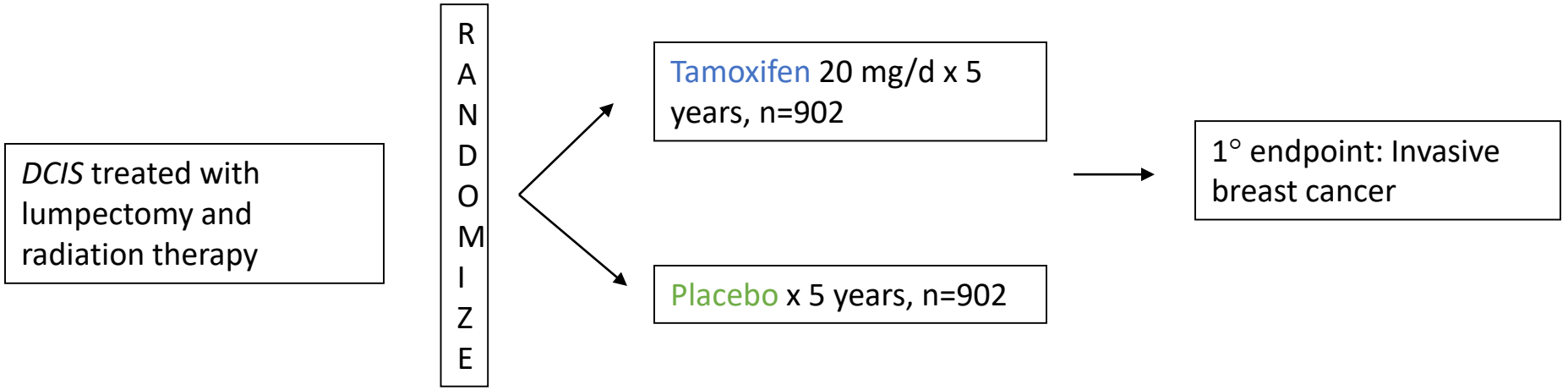
Published in: Yasuaki Sagara; Rachel A. Freedman; Ines Vaz-Luis; Melissa Anne Mallory; Stephanie M. Wong; Fatih Aydogan; Stephen DeSantis; William T. Barry; Mehra Golshan; *Journal of Clinical Oncology* **2016,** 34, 1190-1196.
DOI: 10.1200/JCO.2015.65.1869

Treatment of DCIS: Radiation

- Radiation is used for most DCIS

- Omission of Radiation in low risk patients can be considered:
  - Low or Intermediate grade DCIS
  - <1.6-2.5 cm of disease
  - Older Age (>60)
  - 1cm margins (less data on this)

Treatment of *DCIS*: Tamoxifen NSABP B-24



- 1804 women randomized between May 1991 and April 1994
- Microscopic margin-positive *DCIS* or *LCIS* was allowed (16%)
- ER- disease was allowed
- Median follow up was 74 months

Fisher B *et al*. 1999 *Lancet* **353**:1993.

NSABP B-24 results

	Placebo (n=899)	Tamoxifen (n=899)	RR (95% CI)
Breast cancer (total)	130	84	0.63 (0.47-0.83)
Invasive	70	41	0.57 (0.38-0.85)
Non-invasive	60	43	0.69 (0.46-1.04)
Contralateral breast cancer	36	18	0.48 (0.26-0.87)
Breast cancer at regional or distant sites	7	3	0.42 (0.07-1.82)
Endometrial cancer	2	7	3.39 (0.64-33.42)
Deaths, NED	11	10	0.88 (0.33-2.28)

Fisher B *et al*. 1999 *Lancet* **353**:1993.

Treatment of DCIS: Tamoxifen
Meta-Analysis of B-24 and UK/ANZ DCIS

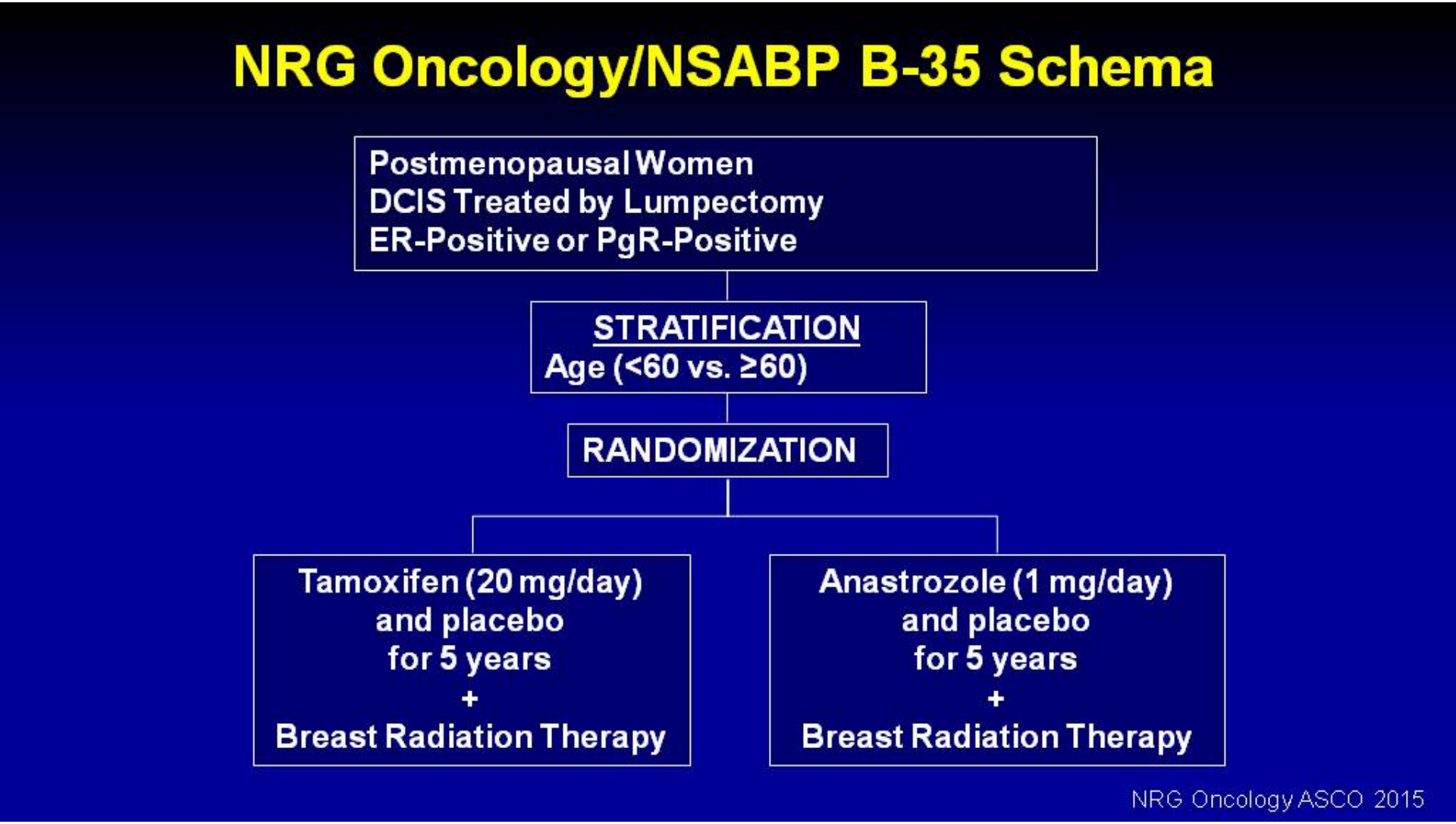
	DCIS (HR)	IBC (HR)
Ipsilateral side	0.75 (0.61-0.92)	0.79 (0.61-1.01)
Contralateral side	0.50 (0.28-0.87)	0.57 (0.39-0.83)

Included 3375 women

No OS benefit HR = 1.11 (0.89-1.39)

Staley H, *et al*. 2012 *Cochrane* 23076938

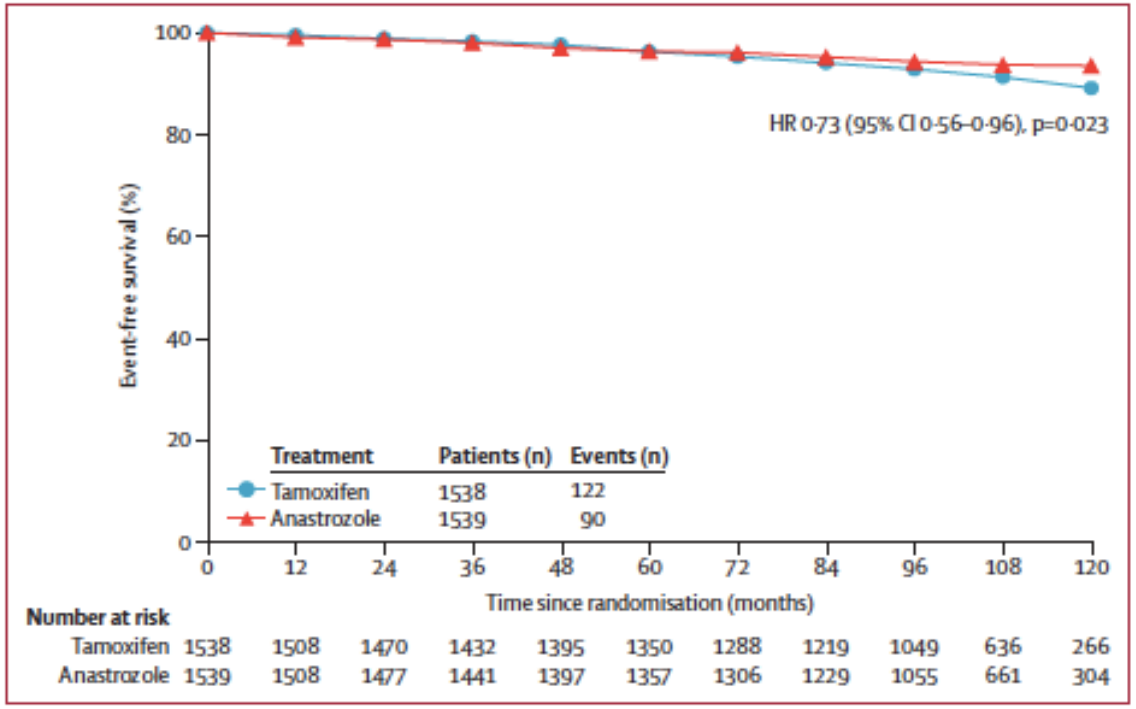
Treatment of *DCIS*: Tamoxifen vs AI



3104 patients randomized between January 2003 and June 2006
Primary Endpoint: Breast Cancer-Free Interval (BCFI)
Median Follow up 9 years

Margolese RG et al., Lancet. 2016 Feb 27;387(10021):849-56. doi: 10.1016/S0140-6736(15)01168-X. Epub 2015 Dec 11.

NSABP B-35 Results



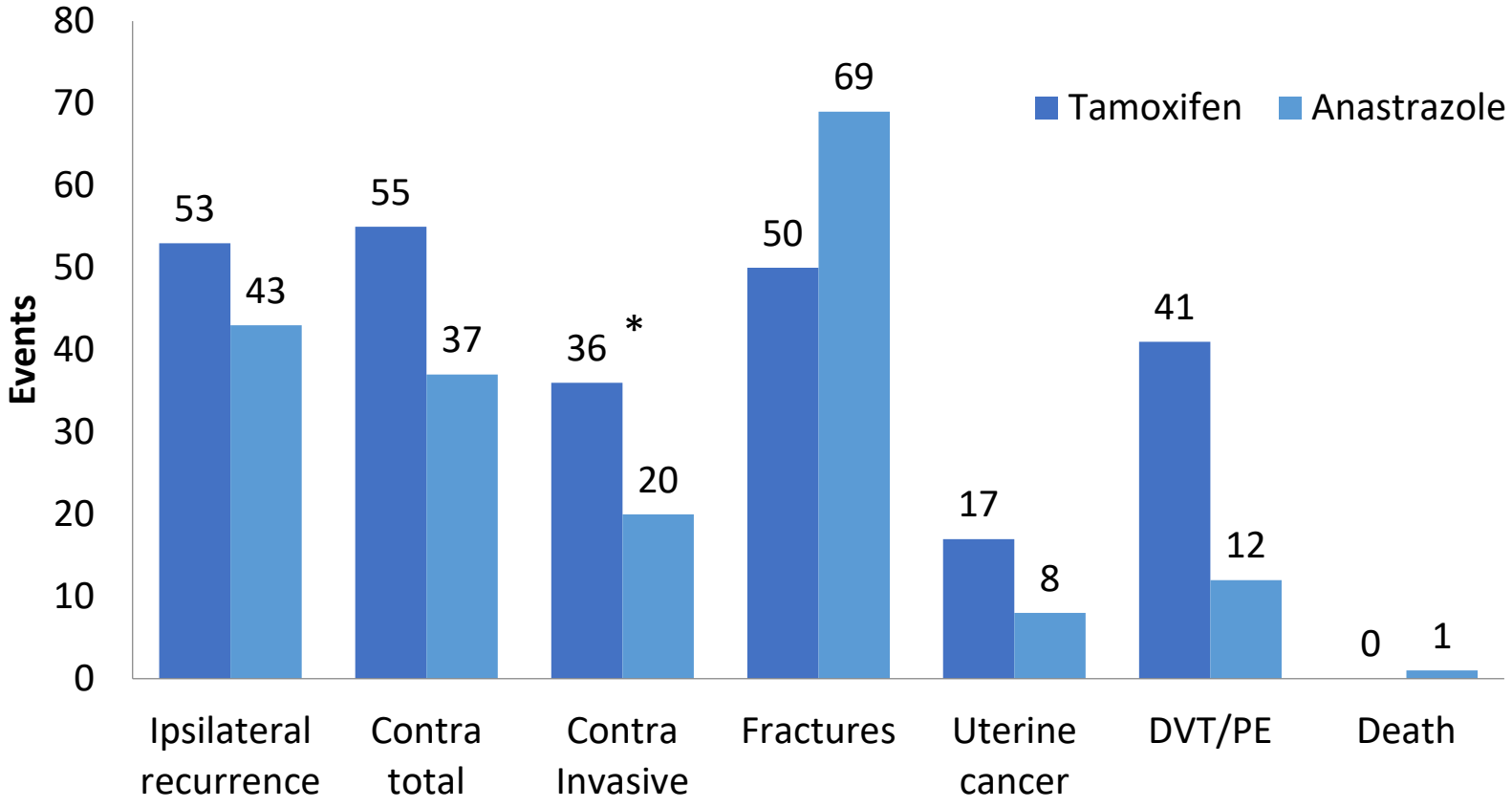
Breast Cancer Free Interval, B-35

	Tamoxifen (n=1535)	Anastrozole (n=1535)
Overall toxicity		
Grade 0/1	312 (20%)	318 (21%)
Grade 2	771 (50%)	771 (50%)
Grade 3	380 (25%)	384 (25%)
Grade 4	59 (4%)	50 (3%)
Grade 5 (death)	13 (1%)	12 (1%)
Thromboembolic events		
Grade 0/1 (none/superficial thrombosis)	1494 (97%)	1522 (99%)
Grade 2 (deep-vein thrombosis)	4 (<1%)	1 (<1%)
Grade 3 (uncomplicated pulmonary embolism)	20 (1%)	8 (1%)
Grade 4 (life-threatening pulmonary embolism)	17 (1%)	3 (<1%)
Grade 5 (death)	0	1 (<1%)
Arthralgia		
Grade 0/1 (none/mild pain)	1177 (77%)	1031 (67%)
Grade 2 (moderate pain)	302 (20%)	427 (28%)
Grade 3 (severe pain)	55 (4%)	77 (5%)
Grade 4 (disabling)	1 (<1%)	0
Myalgia		
Grade 0/1 (none/mild pain)	1367 (89%)	1317 (86%)
Grade 2 (moderate pain)	150 (10%)	187 (12%)
Grade 3 (severe pain)	18 (1%)	30 (2%)
Grade 4 (disabling)	0	1 (<1%)

Table 5: **Adverse events by treatment group**

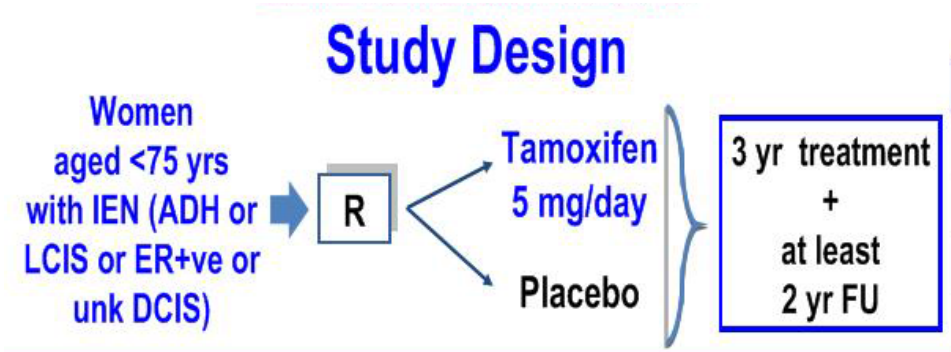
Margolese RG et al., Lancet. 2016 Feb 27;387(10021):849-56. doi: 10.1016/S0140-6736(15)01168-X. Epub 2015 Dec 11.

NSABP B-35 Results



Adapted from presentation by Richard Margolese at 2015 ASCO Annual Meeting

Randomized placebo controlled phase III trial of **low-dose tamoxifen** to prevent local and contralateral recurrence in breast intraepithelial neoplasia (JCO, 2019, DeCensi)



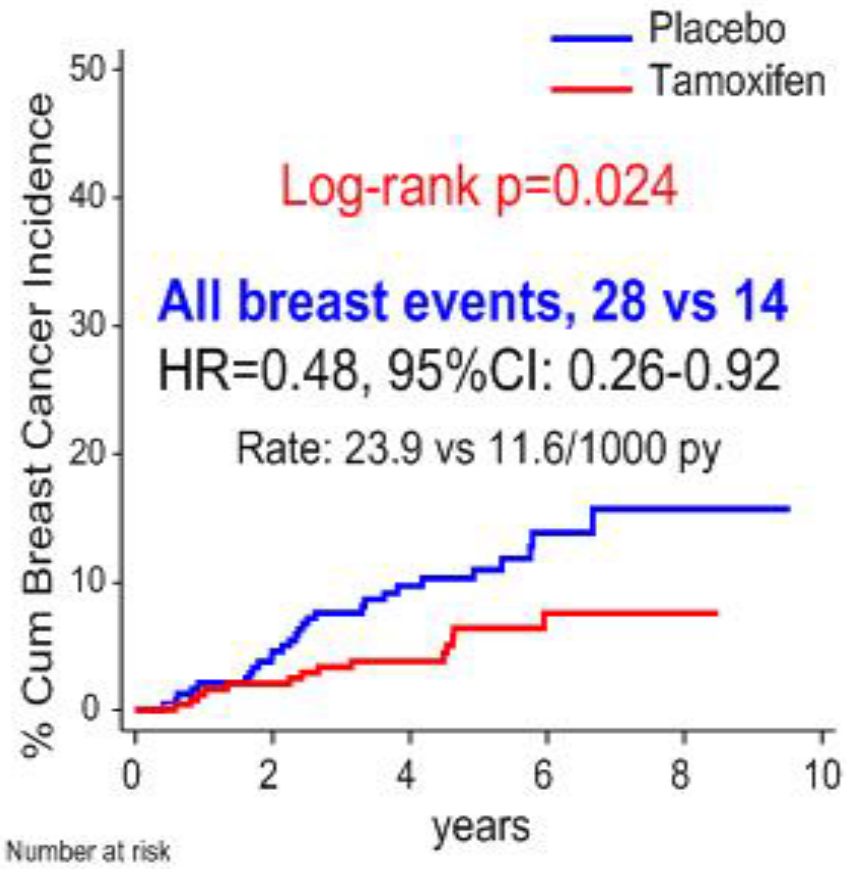
Primary endpoint: Incidence of invasive breast cancer or DCIS

- 500 participants enrolled from 14 centers in Italy
- Visit and QoL every 6 months, Mx every year
- Median follow up = 5.1 years (IQR 3.9-6.3)
- Primary events: 42

Main subject and tumor characteristics (n = 500)

	Tamoxifen N=253	Placebo N=247
Age, mean (SD)	54 (9.6)	54 (9.1)
Pre-menopausal, %	46	44
BMI, mean (SD)	25.7 (4.8)	25.3 (4.2)
ADH, %	20	20
LCIS, %	11	10
DCIS, %	69	70
ER/PR+ve/unknown, %	66 / 34	67 / 33
HER 2-neu 3+, %	8	9
Quadrantectomy/Mastectomy %	84 / 16	82 / 18
Radiotherapy, %	43	43

Results: Low Dose Tamoxifen



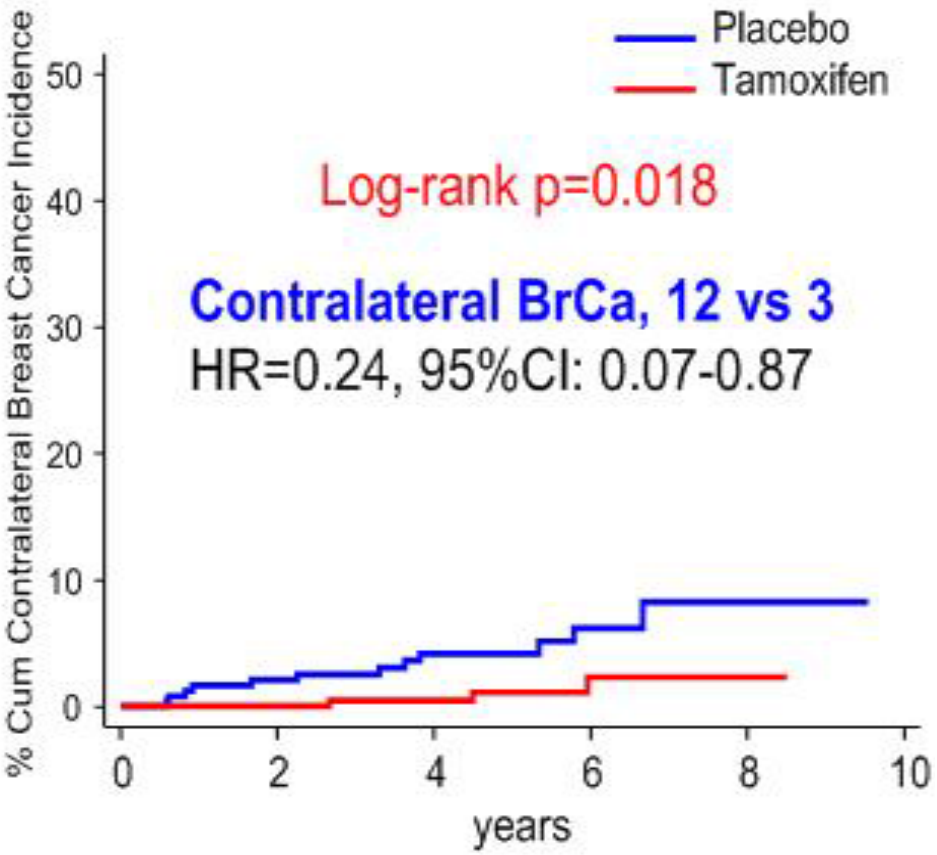


TABLE 3. Serious Adverse Events by Allocated Arm

Adverse Event	Tamoxifen (n = 249)	Placebo (n = 246)
Endometrial cancer	1 (0.4)	—
Deep vein thrombosis or pulmonary embolism	1 (0.4)	1 (0.4)
Other neoplasms	4 (1.6)	6 (2.4)
Coronary heart disease	2 (0.8)	2 (0.8)
Infection	2 (0.8)	2 (0.8)
Saphenous varices	1 (0.4)	
Temporal angioma	—	1 (0.4)
Tibial fracture	—	1 (0.4)
Gallbladder stones	—	1 (0.4)
Death	1 (0.4)	2 (0.8)
Total	12 (4.8)	16 (6.5)

NOTE. Data are presented as No. (%). The safety analysis included all patients who received at least one dose of drug or placebo (495 patients).

Risk and Results by Pathology

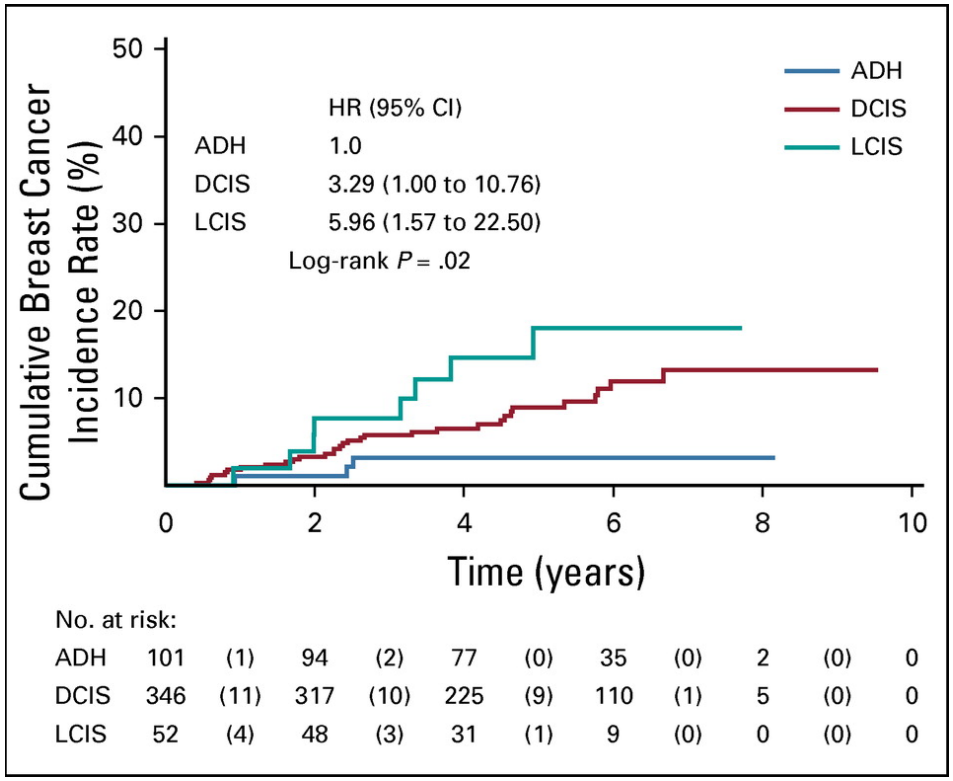
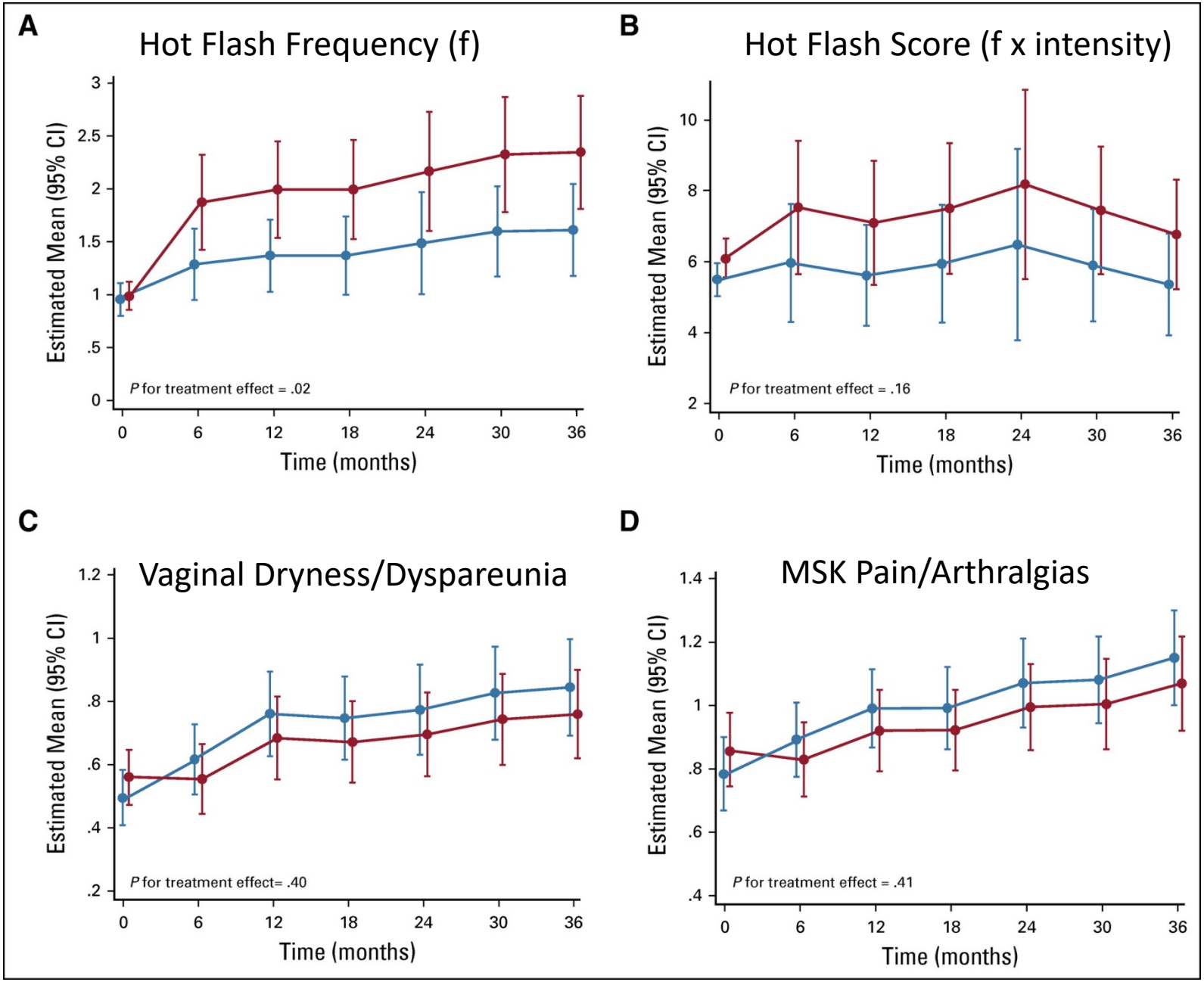


TABLE A1. Prespecified Subgroup Analyses

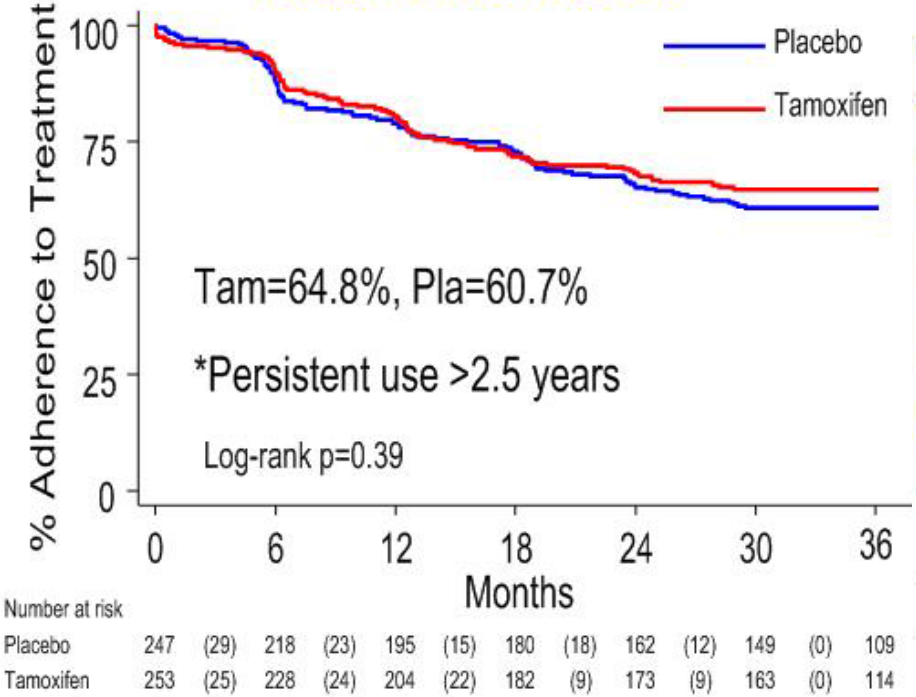
Subgroup	No. of Patients	*P**	HR (95% CI)
Diagnosis within 12 months since random assignment	458	.16	0.41 (0.20 to 0.82)
Diagnosis between 12 and 60 months	42		1.59 (0.27 to 9.53)
ADH + DCIS	447	.54	0.53 (0.26 to 1.08)
LCIS	52		0.31 (0.06 to 1.51)
ER positive	333	.84	0.51 (0.24 to 1.10)
ER unknown	166		0.45 (0.14 to 1.49)

Abbreviations: ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; ER, estrogen receptor; HR, hazard ratio; LCIS, lobular carcinoma in situ.

*For interaction with treatment arm.


A
Hot Flash Frequency (f)
Estimated Mean (95% CI)
P for treatment effect = .02
Time (months)
B
Hot Flash Score (f x intensity)
Estimated Mean (95% CI)
P for treatment effect = .16
Time (months)
C
Vaginal Dryness/Dyspareunia
Estimated Mean (95% CI)
P for treatment effect= .40
Time (months)
D
MSK Pain/Arthralgias
Estimated Mean (95% CI)
P for treatment effect = .41
Time (months)

Treatment adherence*



Number at risk													
Placebo	247	(29)	218	(23)	195	(15)	180	(18)	162	(12)	149	(0)	109
Tamoxifen	253	(25)	228	(24)	204	(22)	182	(9)	173	(9)	163	(0)	114

Estimate of treatment impact at 5 years

Number needed to treat*	22 (95% CI, 20-27)
Number needed to harm**	218 (95% CI, 193-265)
Likelihood of benefit	10 (218/22)

*5 year cumulative incidence of breast events: 6.4% on T and 11.0% on P
**5 year cumulative incidence of SAE: 0.87% on T and 0.41% on P

Summary:

5mg Tamoxifen/day for 3 years with 5 years of follow up

- ↓50% risk of a breast cancer (DCIS/IC)
- ↓75% risk of a contralateral breast cancer
- No difference in DVT or Endometrial cancers with placebo
- Hot Flashes worse than placebo, but compliance was good

But how does this compare to standard of care?

- 500 patients (compared to >3000 in 5 years at 20mg)

Conclusions, Implications B-35

- Anastrazole is more effective than Tamoxifen in reducing incidence of invasive breast cancer in patients with DCIS
- Expected side effects for Anastrazole and Tamoxifen seen
- Both Anastrazole and Tamoxifen are effective treatments for women with ER+ DCIS who desire adjuvant therapy

Margolese RG et al., Lancet. 2016 Feb 27;387(10021):849-56. doi: 10.1016/S0140-6736(15)01168-X. Epub 2015 Dec 11.

Summary of Treatment for DCIS

- Surgical resection (2mm margin)
  - Mastectomy
  - BCS
  - SLNB indicated in mastectomy
- Radiation
  - Most get radiation
  - Omission possible for low risk patients
- Endocrine therapy (only indicated for ER+ disease)
  - Treatment for BCT with Tamoxifen or AI
  - Consideration Chemoprevention for Mastectomy
  - Contraindicated after Bilateral mastecomies

Management of DCIS & Proliferative Breast Disease

	Risk for Invasive Ca	Upstaging	Surgery for Diagnosis/Tx	Treatment & Prevention
DCIS	Precursor	10-30% to IBC	Excision Clear margins (2mm)	Treatment
pLCIS	?precursor	~malignant	Excisional Bx/ clear margins	Treatment
LCIS	Risk	<5%	Concordance with Core Bx	Chemoprevention
ADH	Risk	>20% to DCIS	Excisional Biopsy	Chemoprevention
ALH	Risk	<5%	Concordance with Core Bx	Chemoprevention

Chemoprevention

Possible public health impact of chemoprevention

Question:

- What would effect be if tamoxifen was taken by all women meeting FDA criteria for prevention and also in all subset with anticipated net benefit (using Gail models)?

Methods:

- Used data from the year 2000 NHIS to determine both proportion eligible and proportion with favorable risk benefit—5% of women aged 35-79.
- Matching this to age composition of US population with census data estimated

Results:

- 2,431,911 white women would be GOOD candidates for tamoxifen
- Expected breast cancer incidence at 5 years ~58,148 without tamoxifen
- 28,492 cases prevented with tamoxifen.

Freedman et al J Natl Cancer Inst 2003;95:526–32

Cost of Survivorship

- Cost of local therapy: 15.5K (in 1998$)

  (Barlow, JNCI 2001)

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- Side effects: Pain after local therapy
  - 47% of Danish patients with some pain
  - 52% of these with moderate/severe pain

  (Gartner, JAMA, 2009)

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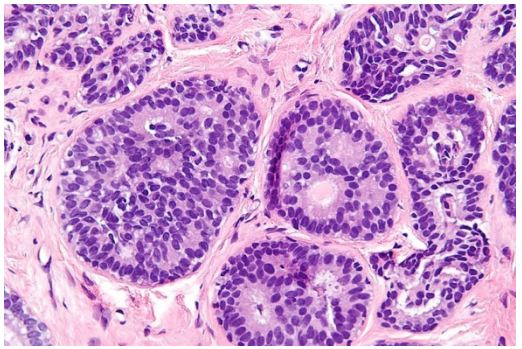
- Side effects: Pain after local therapy
  - 47% of Danish patients with some pain
  - 52% of these with moderate/severe pain

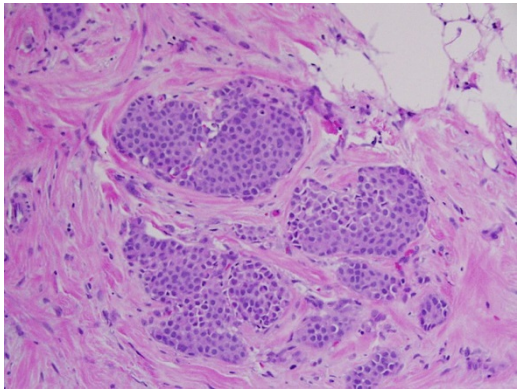
  (Gartner, JAMA, 2009)

- Risk of death: 89.7% 5 year survival

  (https://seer.cancer.gov/statfacts/html/breast.html)

Who should we consider chemoprevention in?





ASCO/NCCN guidelines:

- Age >35 with life expectancy of 10yrs
  - **h/o Atypical Hyperplasia, LCIS**
  - ≥ 1.7 Gail model
  - >20% Lifetime risk

Gaps in our recommendations?

- Consider in BRCA2 mutation carriers
- Not strong/specific recommendations for less penetrant mutations
- No data in those with chest RT < 30 (ongoing trials)

Breast Cancer Risk Assessment Models

Gail Model

- Derived from a prospective study of women undergoing mammographic screening
- Incorporates family history (1st degree), benign breast disease, age of menarche, age of first pregnancy, and race
- http://www.cancer.gov/bcrisktool/

Tyrer-Cuzick, IBIS Breast Cancer Risk Evaluation Tool

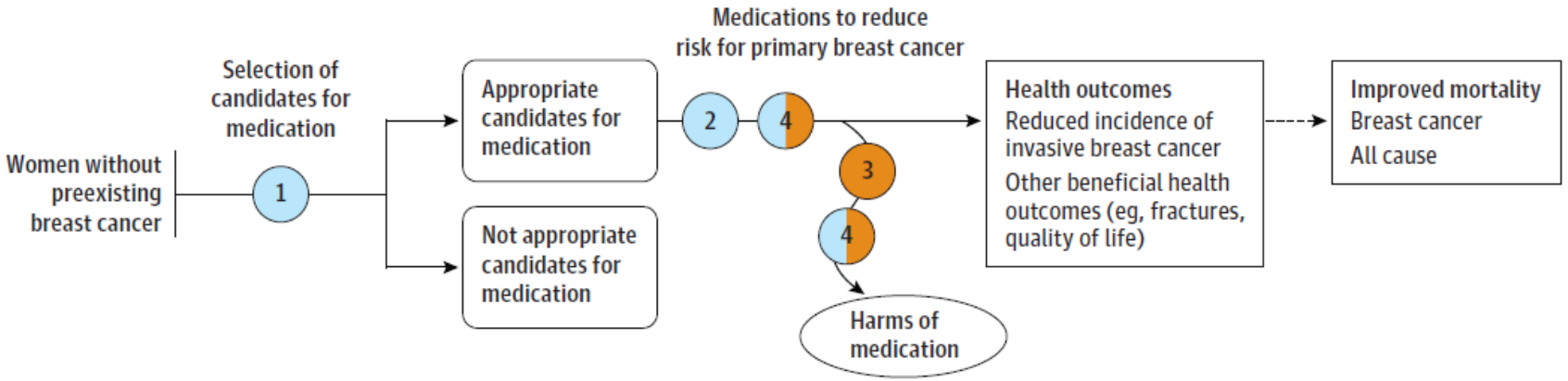
- Incorporates 1st and 2nd degree relatives, reproductive factors, BMI, atypical hyperplasia, LCIS
- http://www.ems-trials.org/riskevaluator/

Breast Cancer Surveillance Consortium Risk Calculator

- Estimates 5 year and 10 year breast cancer risk based on age, race/ethnicity, family history of breast cancer, history of breast biopsy, and BI-RADS breast density
- https://tools.bcsc-scc.org/BC5yearRisk/intro.htm

Gail MH *et al*. 1989 *J Natl Cancer Inst* **81**:1879. Tyrer, Statist. Med. 2004; **23**:1111–1130. Tice JA *et al., J Clin Oncol* 2015, published online August 17, 2015.

USPSTF schema



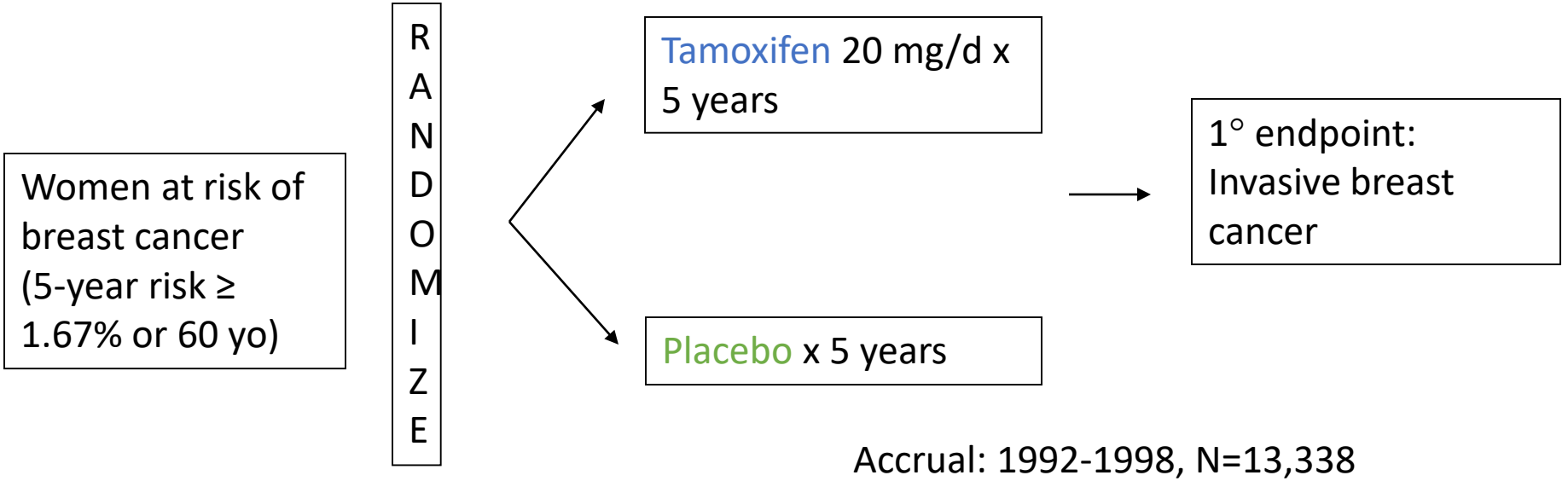
USPSTF recommendations and guidelines updated in 2019

Nelson, *JAMA onc,* 2019

The Chemoprevention Trials

Trial	Agent	Year	N	RR/HR	notes
STAR	Ral vs Tam	2006	19747	**1.24 (1.05-1.47)**	Postmen, No LCIS (50% prior TAH)
IBIS-I	Tam vs placebo	2007	7154	0.74 (0.58-0.94)	
NSABP P-1	Tam vs placebo	2005	13388	0.57 (0.46-0.70)	Pre and post
Royal Marsden	Tam vs placebo	2007	2471	0.78 (0.58-1.04)	
Italian Tamoxifen	Tam vs placebo	2007	5408	0.80 (0.56-1.15)	
USPSTF meta	**Tamoxifen**	2013		**0.70 (0.59-0.82)**	
MORE/CORE	Ral vs placebo	2004	5129, 2576 (2:1)	0.34 (0.22-0.50)	
RUTH	Ral vs placebo	2006	10101	0.56 (0.27-0.71)	
USPSTF meta	**Raloxifene**	2013		**0.44 (0.27-0.71)**	
IBIS-II	Anastrozole vs placebo	2014	3864	0.47 (0.32-0.68)	40-70 yo (postmen) Avg Tyrer-Cuzick 7.7%
MAP-3	Exemestane vs placebo	2011	4050	0.35 (0.18-0.70)	Avg age 62.5, 35+ Avg Gail 2.3%

Tamoxifen Breast Cancer Prevention Trial (NSABP P-1)

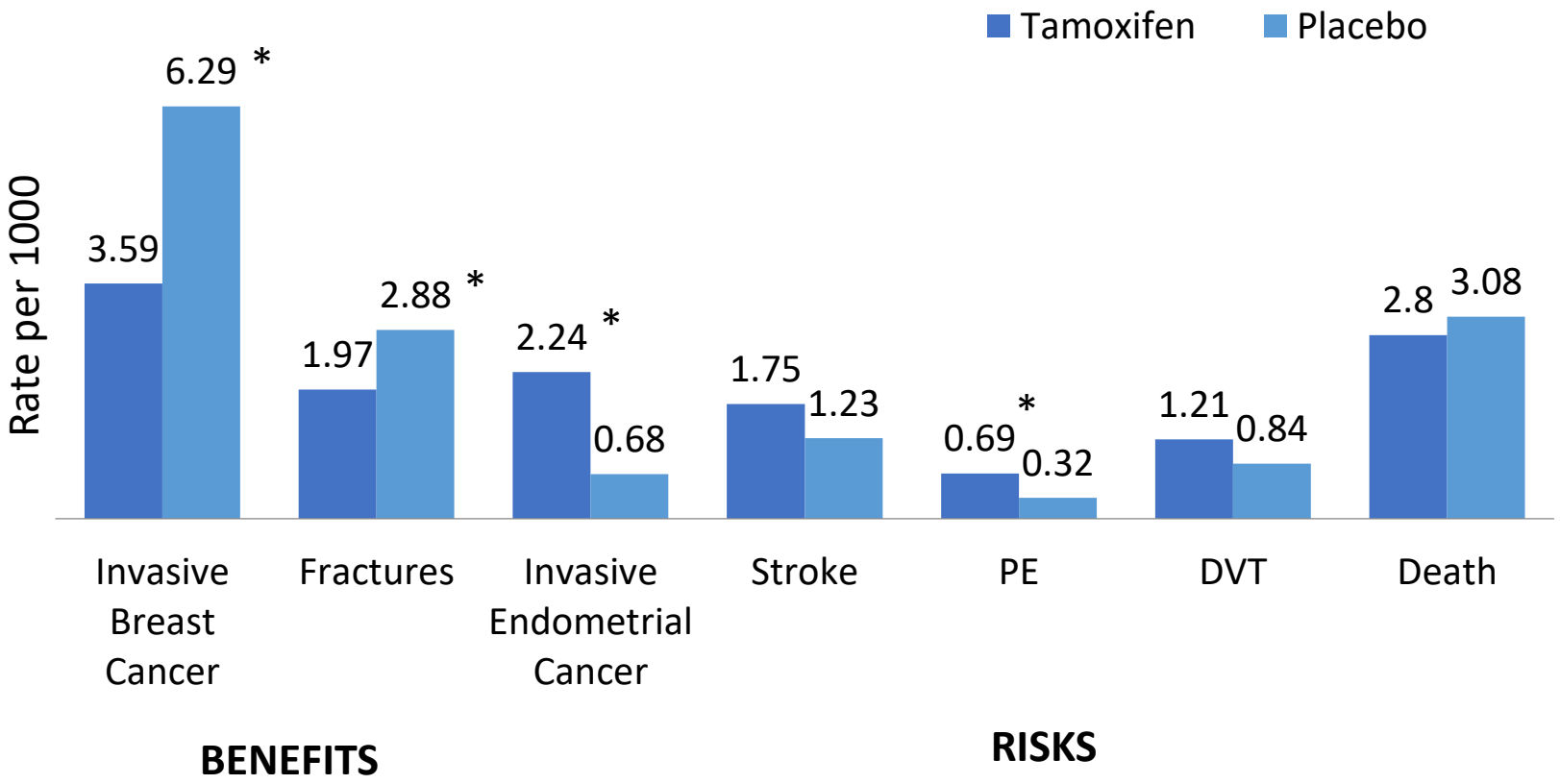


Accrual: 1992-1998, N=13,338
Closed early after interim analysis
Median follow-up 54.6 months

Analysis showed a 49% reduction in incidence of invasive breast cancer in participants treated with tamoxifen

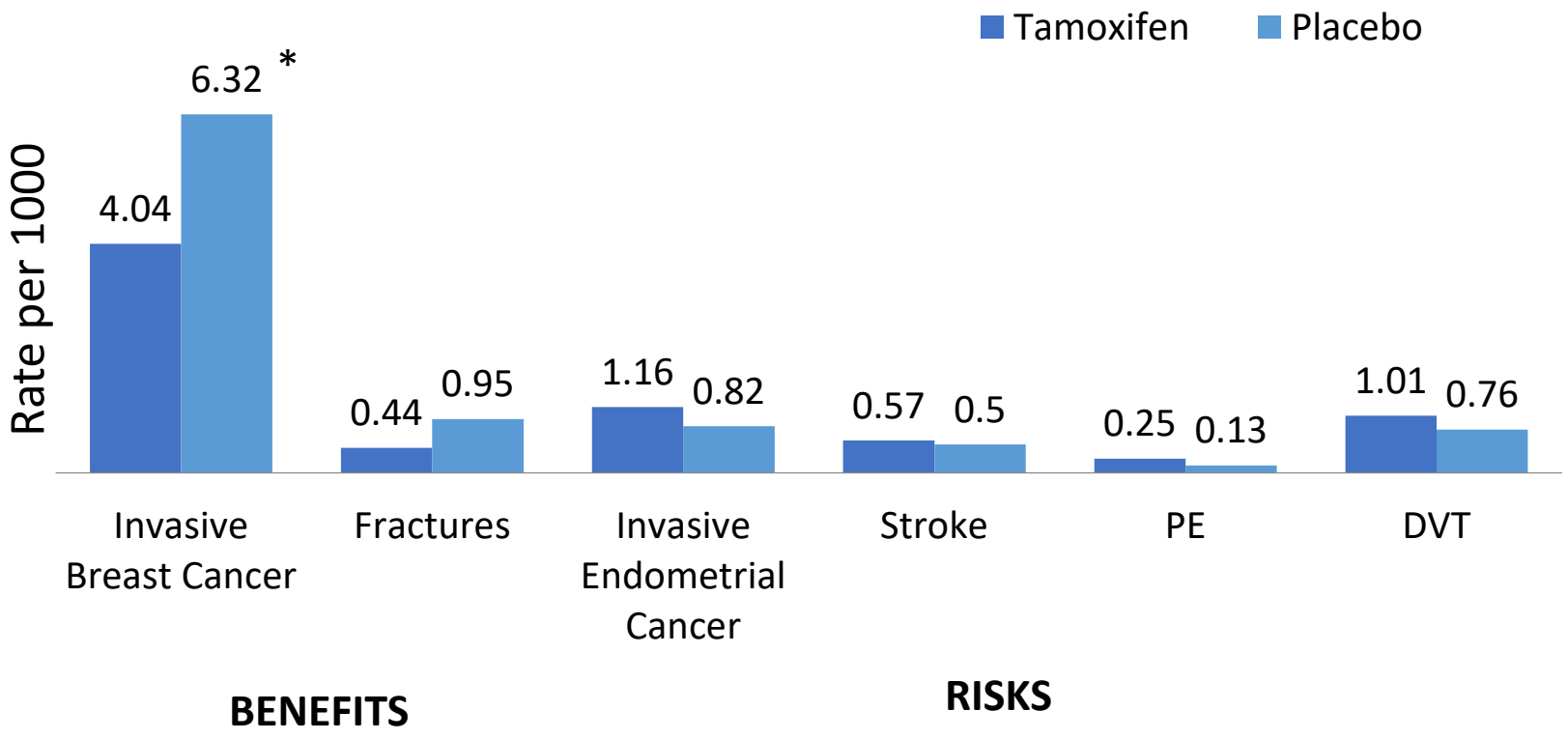
Fisher B *et al*. 1998 *J Natl Cancer Inst* **90**:1371.

NSABP P-1, All High-Risk Women



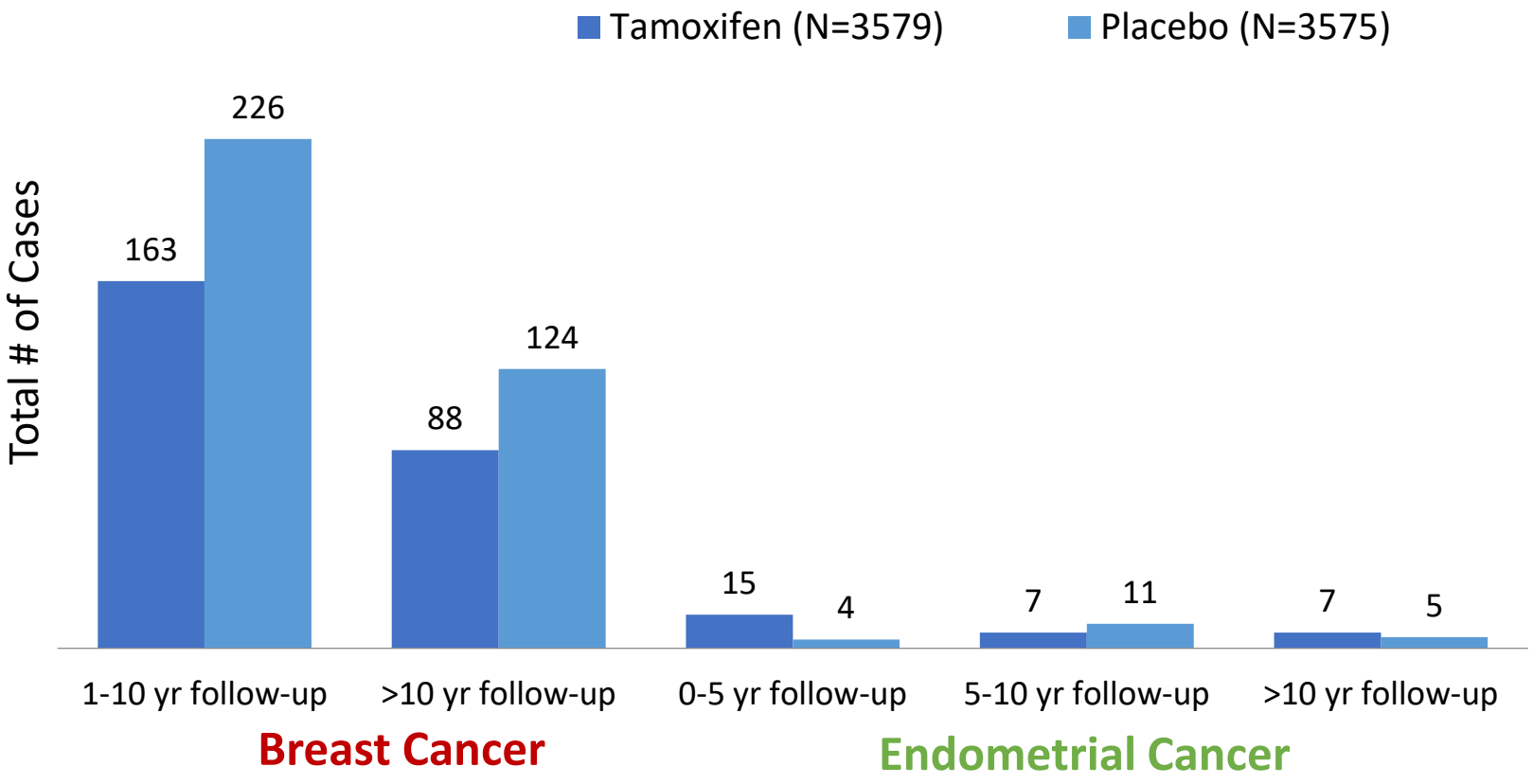
Fisher B *et al. Journal of the National Cancer Institute*, Vol. 97, No. 22, November 16, 2005

NSABP P-1 Women <50



Fisher B *et al., Journal of the National Cancer Institute*, Vol. 97, No. 22, November 16, 2005

IBIS-I Long-Term Follow-Up with Tamoxifen



Cuzick J *et al., Lancet Oncol*. 2015 Jan;16(1):67-75. doi: 10.1016/S1470-2045(14)71171-4. Epub 2014 Dec 11.

STAR Trial (NSABP P-2)

Post-menopausal women at increased risk of breast CA
(5 yr risk ≥1.7%)

RANDOMIZE

Tamoxifen 20 mg/d x 5 years

Raloxifene 60 mg/d x 5 years

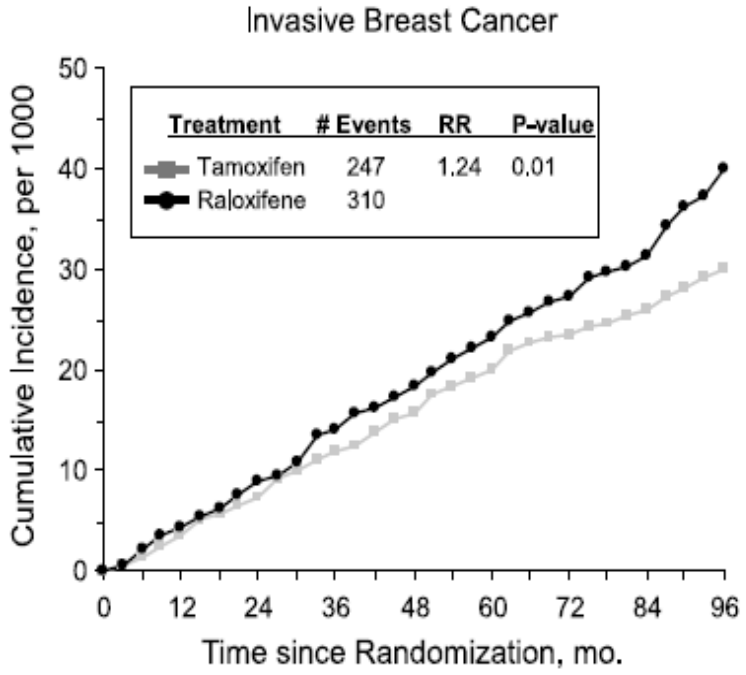
1° endpoint: Invasive breast cancer

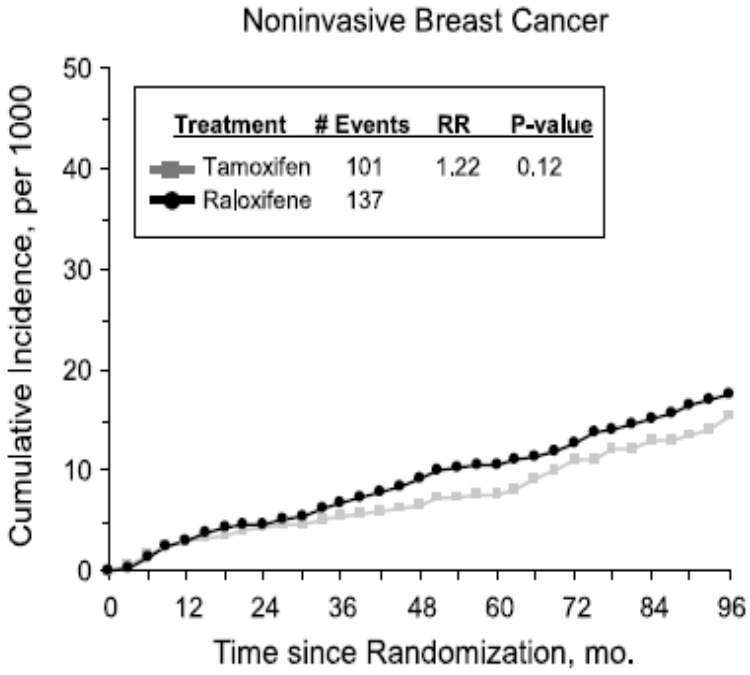
- Accrued 19,471 patients between July 1999-Nov 2004
- Mean age participants at randomization 58.5 years
- 93% of participants were white
- Mean predicted 5-year risk of IBC was 4.03%

STAR
Study of Tamoxifen And Raloxifene

Vogel VG *et al*. 2006 *JAMA* **295**:2727. Vogel VG *et al. Cancer Prev Res (Phila)* **3**:696-706, 2010.

STAR Update 2010: Tamoxifen is more effective



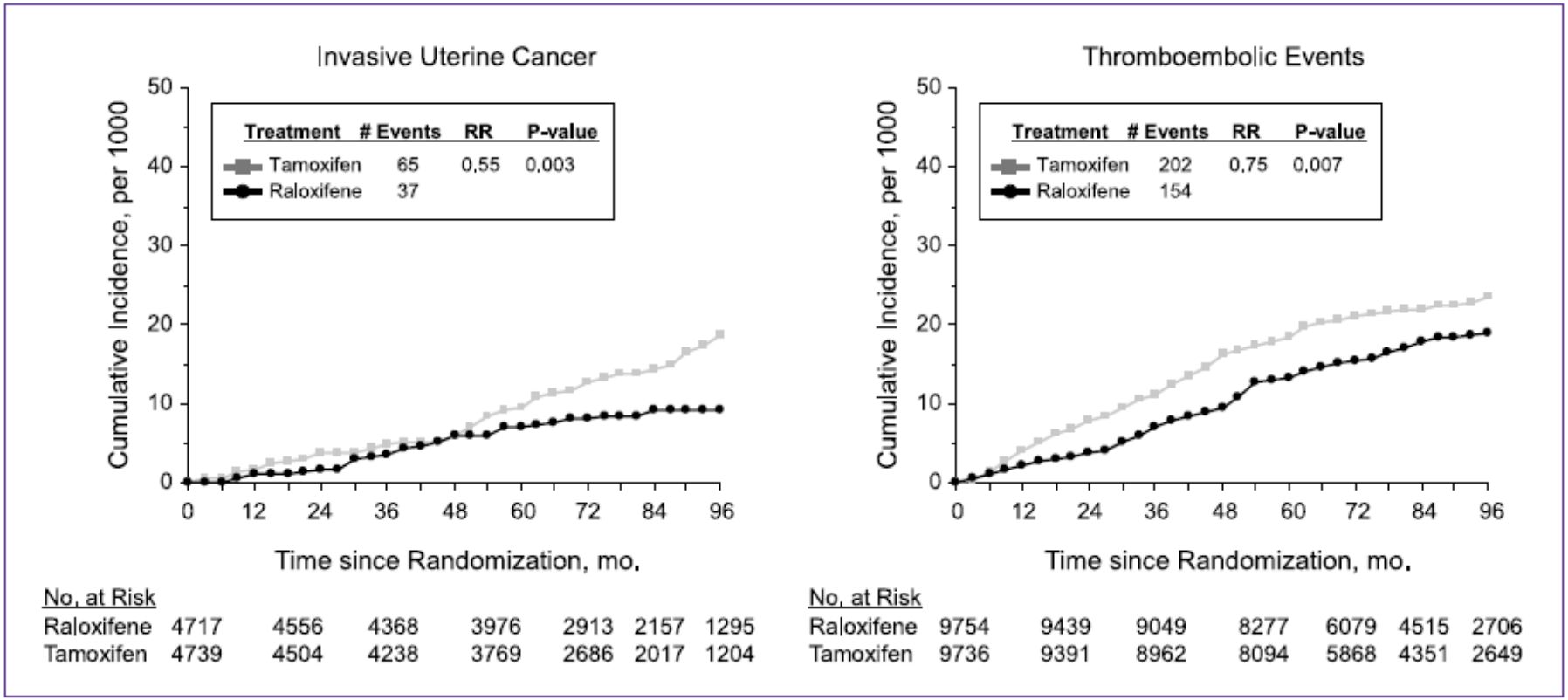


No. at Risk							
Raloxifene	9754	9398	8973	8196	5999	4453	2650
Tamoxifen	9736	9387	8939	8059	5833	4326	2621

No. at Risk							
Raloxifene	9754	9365	8925	8125	5938	4405	2616
Tamoxifen	9736	9359	8901	8019	5793	4290	2593

Vogel et al *Cancer Prevention Research* 3(6) 696-706 2010

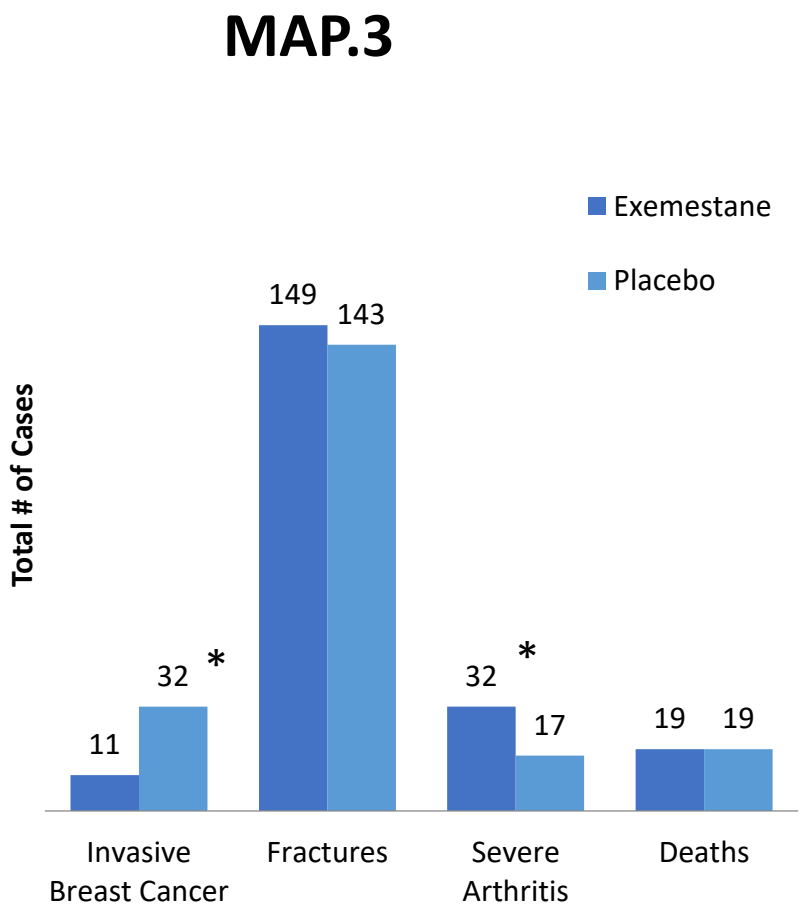
…and more toxic

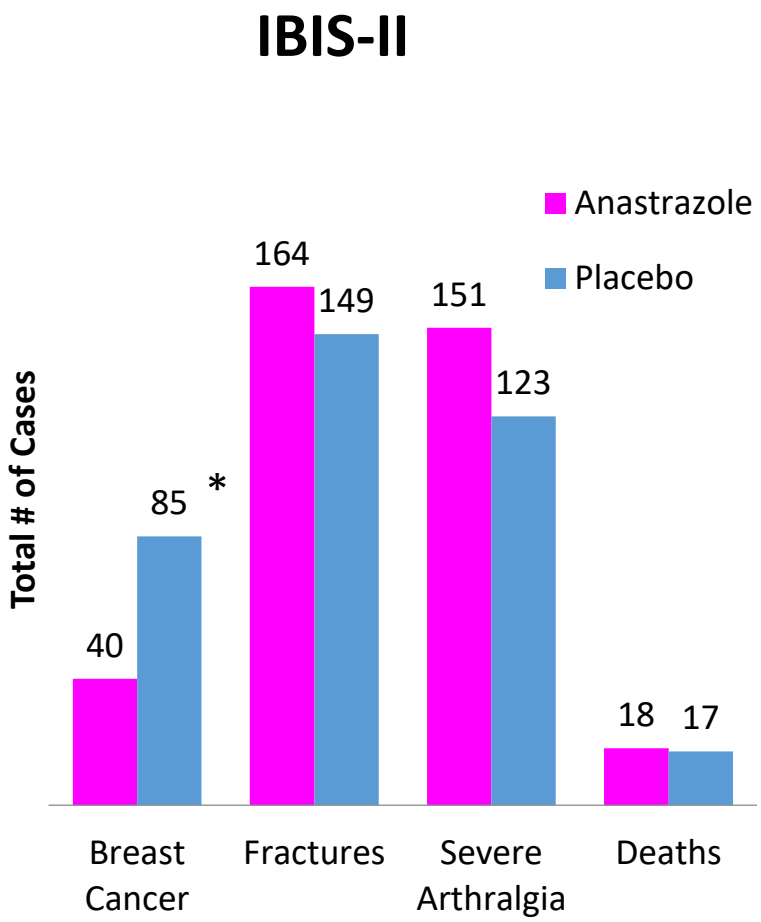


*Hysterectomy for benign disease was double in Tamoxifen group, RR = 0.45 (0.37-0.54)

Vogel et al *Cancer Prevention Research* 3(6) 696-706 2010

Risks and Benefits of AIs

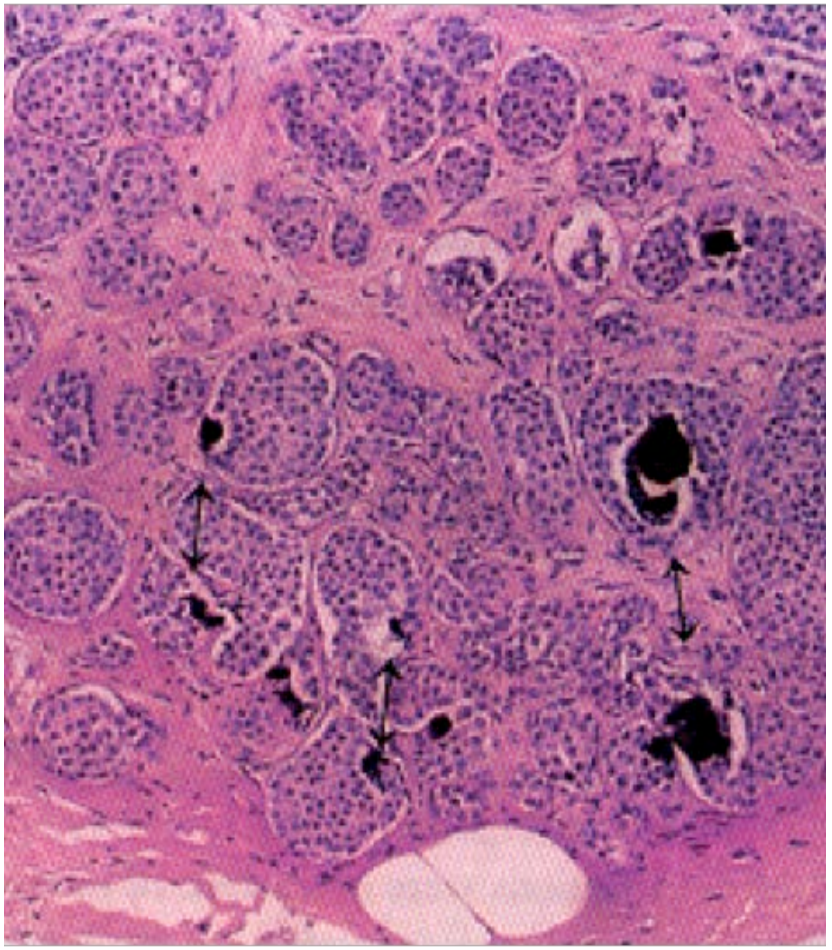




Goss PE, Ingle JN, Ales-Martinez JE, *et al. NEJM* 2011;364(25):2381-91. Cuzick J *et al., Lancet* 2014;383:1041-48.

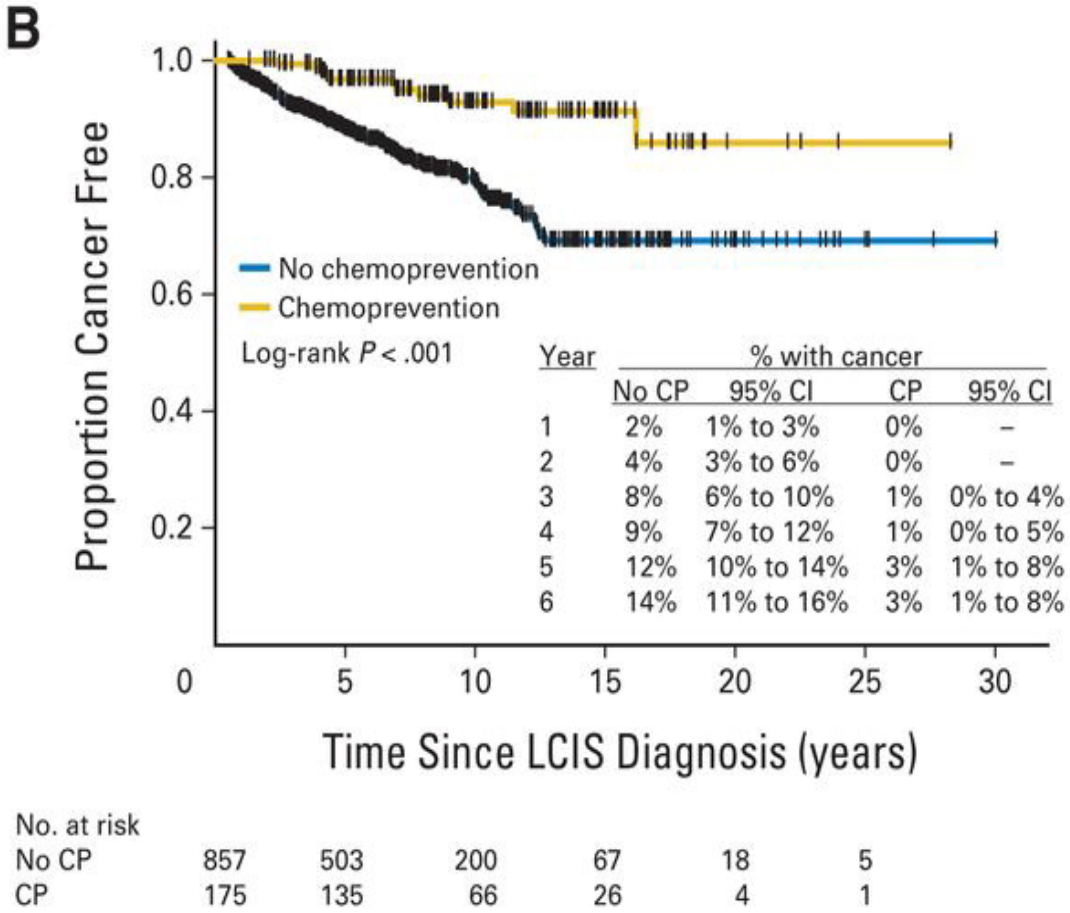
LCIS: Proliferative Breast Disease

- Risk factor not a direct precursor lesion for invasive carcinoma
- Restaged by AJCC
  - NOT a Cancer
- 7-11 Fold increase of Cancer
  - Increases risk of IDC, ILC, Mixed IC and DCIS
- Usually incidental finding on Bx
- Mean age 44-46
- 80-90% in premenopausal
- Strongly ER+ typically
- Increased incidence in HRT users



LCIS: Longitudinal Experience and Breast Cancer Risk

- 29 year study
- 1060 patients
- LCIS at MSKCC
- Incidence 2% per year
- Cumulative 26% at 15 yrs
- Chemoprevention reduced incidence of breast cancer
  - 7% vs. 21% at 10 yrs
  - HR 0.27



King TA, *et al.* *J Clin Oncol* 2015;33.

What’s the reality?
Who is getting it and actually taking it?

Shared decision making-Patient perspective

Life experiences

"they said, "Oh, but this is like a 50 percent reduction." Well, all I know is my sister said what bad side effects she had and she attributed it a lot to tamoxifen."

STAR decliner, 52 years old, Gail score 3.94

"What happened is I come from an extraordinarily long line of breast cancer victims. I say "victims" because they haven't all been survivors, unfortunately."

STAR participant, 48 years old, Gail score 4.17

Understanding the risk/benefits

"Well, I might not get breast cancer but I might get uterine cancer. What good is that?" And actually breast cancer I think is a lot easier to detect a lot of times, especially when you're getting mammogram on a regular basis, as I am."

STAR decliner, 58 years old, Gail score 5.34

"I looked at what was told was the risks of taking tamoxifen, I looked at what my own known personal risk of developing the disease is, and I also looked at what the consequences of not doing anything would be, and the benefits—possible benefits—of participation, for me, so far outweighed any detrimental possible effects of possibly taking tamoxifen"

STAR participant, 48 years old, Gail score 4.7

Holmberg, *Med Decis Making*, 2015

Shared decision making-Provider stats

350 PCP (FM, IM, Gyn) survey

- 27% prescribed Tam last 12 month
- Prescribers more likely to
  - have family member with breast cancer (20 vs 9%)
  - Believe that the benefits outweigh risks (63% vs 39%)
  - Easy to determine who is eligible (28 vs 11%)
  - Colleagues that are prescribing it (33% vs 17%)

Armstrong, *Arch Internal Med*, 2006

Shared decision making-Results

12+ studies evaluating decision guides, process

Range of Chemoprevention uptake 0.9%-56%

Higher rates of chemoprevention:

- In person discussion
- Oncology/High Risk specialty clinics
- Opportunity for clinical trials
- Higher risk of breast cancer

Nelson, *Ann Inter Med*, 2013

Adherence

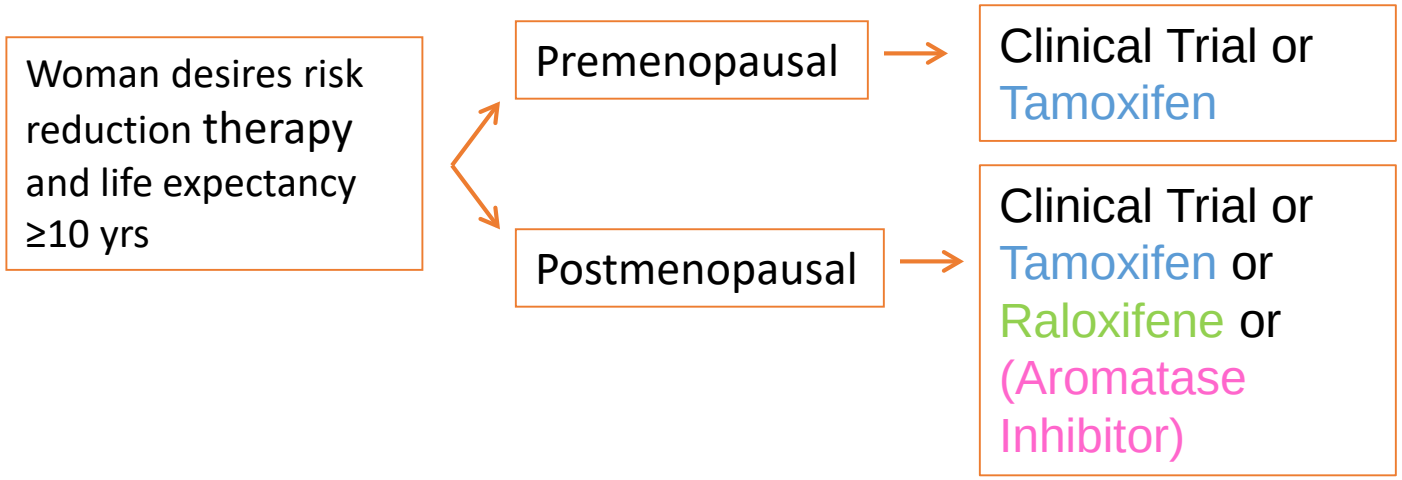
Difference in Adherence between arms in Placebo trials is 1-8%

Difference in STAR was 72% (Raloxifene) vs 68% (Tamoxifen)

Similar rates to adherence in breast cancer treatment studies

Nelson, *Ann Inter Med*, 2013

Options for Chemoprevention for Breast Cancer (Including proliferative breast disease)



Adapted from NCCN Guidelines Version 1.2016.

Who should get chemoprevention?

Offer/Consider

- motivated women with above average risk (Risk models)
- BRCA2 mutation carriers who are considering screening rather than risk reducing surgery, or significantly delayed risk reducing surgery

More strongly encourage (Ideal candidates)

- Tamoxifen
  - Premenopausal (40-50) women with high risk (risk reduction of ~50%)
  - Postmenopausl women <60 with high risk of cancer and low risk of SAE
- Raloxifene
  - Postmenopausal women at above average risk with osteopenia who are considering medication for either (risk reduction of ~38%)
- AI
  - Postmenopausal women who are unable to take Tamoxifen or Raloxifene or who have had DCIS and BCT (risk reduction of ~50-60%).

Remember:

- Shared decision making is important
- Consider medications for the best fit

Can we change risk with lifestyle modifications?

How do we treat the whole woman?

Modifiable Factors with Increased Risk

Factor	Relative risk (RR) or Effect
Combined Hormone Therapy	~26% increase
Ionizing radiation to chest < 30	5 to 20
Obesity (>82 kg vs. <59 kg)	2.85
Alcohol intake (4 drinks/day vs. non-drinkers)	1.32
Parity (Nulliparous vs. parous)	2

ASCO Curriculum Cancer Prevention and Breast Cancer Prevention (PDQ®) July 2017.

Obesity - Nurses Health Study

- Initially enrolled 121,700 married women RN's ages 30-55 in 1976 and has been collecting survey data on health status since.
- Identified a subset of 87,000+ pre/postmenopausal women at entry(95% followup) without prior history of cancer
- Identified a smaller subset of women who joined the study when premenopausal and have since become menopausal (49,514)
  - Assessed effect of postmenopausal weight gain exclusively in this group.

Weight gain substudy in NHS

Table 2. Relative Risk of Postmenopausal Breast Cancer According to Weight Change Since Age 18 Years

Weight Change Since Age 18 y, kg	Simple Update*			Stable Change†	
	No. of Cases	Age-Adjusted RR	MV-Adjusted RR (95% CI)‡	No. of Cases§	MV-Adjusted RR (95% CI)‡
Overall					
Loss					
≥10.0	53	0.72	0.84 (0.62-1.13)	48	0.80 (0.58-1.11)
5.0-9.9	99	0.88	0.94 (0.75-1.18)	84	0.90 (0.69-1.17)
2.0-4.9	152	0.97	1.00 (0.82-1.21)	109	1.05 (0.83-1.33)
Loss or gain <2.0	317	1.00	1.00	190	1.00
Gain					
2.0-4.9	420	1.12	1.10 (0.95-1.28)	315	1.08 (0.90-1.29)
5.0-9.9	798	1.17	1.15 (1.01-1.31)	749	1.13 (0.96-1.33)
10.0-19.9	1357	1.16	1.15 (1.01-1.30)	1320	1.13 (0.97-1.32)
20.0-24.9	429	1.18	1.21 (1.05-1.40)	411	1.17 (0.99-1.40)
≥25.0	768	1.36	1.45 (1.27-1.66)	749	1.43 (1.22-1.68)
P for trend‖		<.001	<.001		.001
P for weight loss trend¶		.02	.02		.02

Elliason et al. *JAMA* 2006; 296:193-201

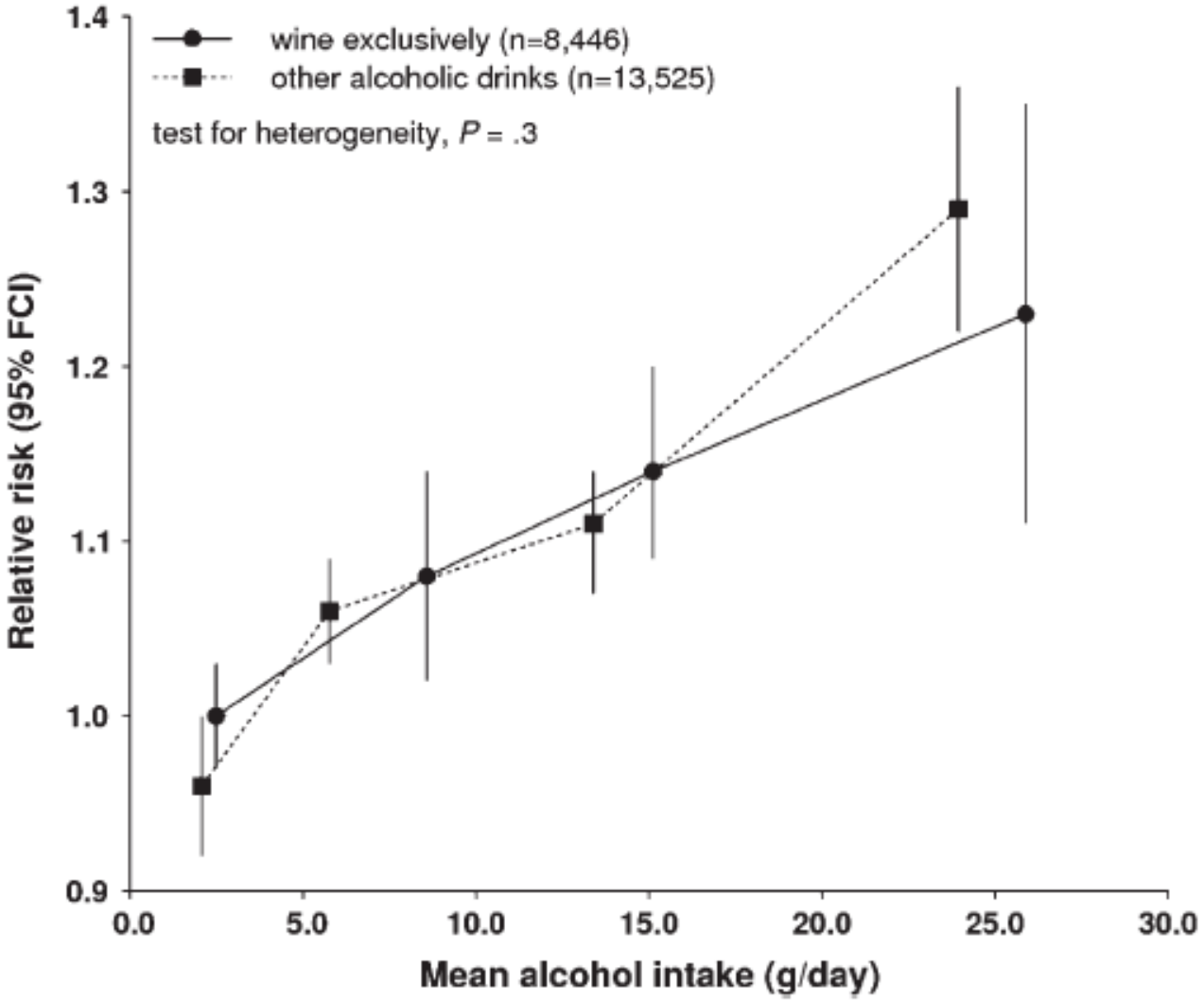
Obesity and Breast Cancer

- Study shows not only that BMI corresponds to breast cancer risk, but also (limited by observational nature of study) *shows the MODIFYING BMI* can both positively and negatively influence breast cancer risk.

Alcohol and risk of breast cancer: Million Women Study

- Study of 1,280,296 women who completed a survey on demographics and lifestyle aspects upon presentation to UK breast cancer screening clinics between 1996 and 2001
- Cohort followed prospectively for development of variety of cancers, including breast cancer, via the NHS registry
- Alcohol intake categorized as 0, 2 or less, 3-6, 7-14 or $\geq$ 15 drinks per week
- Women resurveyed at three years
- Median Follow up 7.2 years.

Million Women Study Results



For every 10g/d alcohol consumed, relative risk for breast cancer was increased by 12%

Take home points

1) DCIS requires surgery to a clear margin (BCT or mastectomy for local therapy) and treatment with Tamoxifen or AI should be considered for ER+ DCIS s/p BCT

2) LCIS is a risk factor for developing Breast Cancer and surgical removal is not required, but chemoprevention should be considered.

3) Women at above average risk should be offered chemoprevention
   - Extrapolated Effectiveness: AI > Tam > Raloxifene
   - Side effects: Raloxifene > Tamoxifen > AI

4) Survivorship has costs

5) Counsel on lifestyle choices: Exercise, Weight, and alcohol.

Breast and Ovarian
Cancer Prevention Program

The Women's Center

SEATTLE CANCER CARE ALLIANCE

Women's Wellness Clinic

The Women's Center

SEATTLE CANCER CARE ALLIANCE

Thanks!

Malignant Pleural Mesothelioma

Bernardo Goulart MD, MS
Associate Professor
2020 UW/SCCA Oncology Board Review Course

Definition & Epidemiology

- **Malignant neoplasm arising from mesothelial cells.**
- **80% pleural; 20% from peritoneum, pericardium, tunica vaginalis testis.**
- **Rare: 2,400 incident cases/year.**
- **Median age = 72 years.**
- **Male predominance.**
- **Risk factors: Asbestos (60%); ionizing radiation; erionite; Germline mutations (12%).**
- **Median OS = 12 to 18 months.**

2015 WHO Classification of Pleural Tumors

Diffuse MPM

- Epithelioid (60%)
- Sarcomatoid (20%)
- Biphasic (20%)

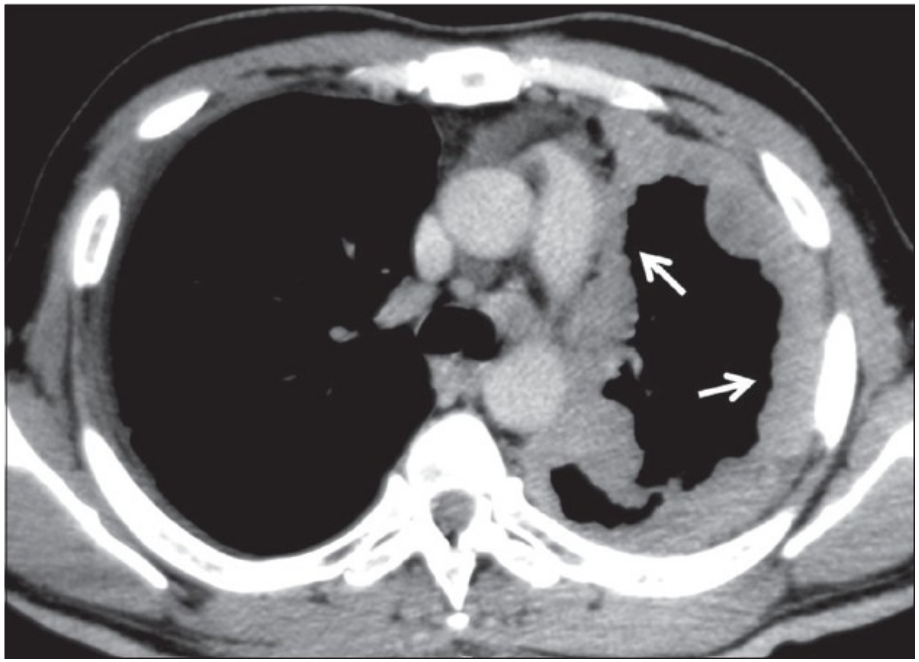
Other

- Localized MPM
- Well differentiated papillary mesothelioma

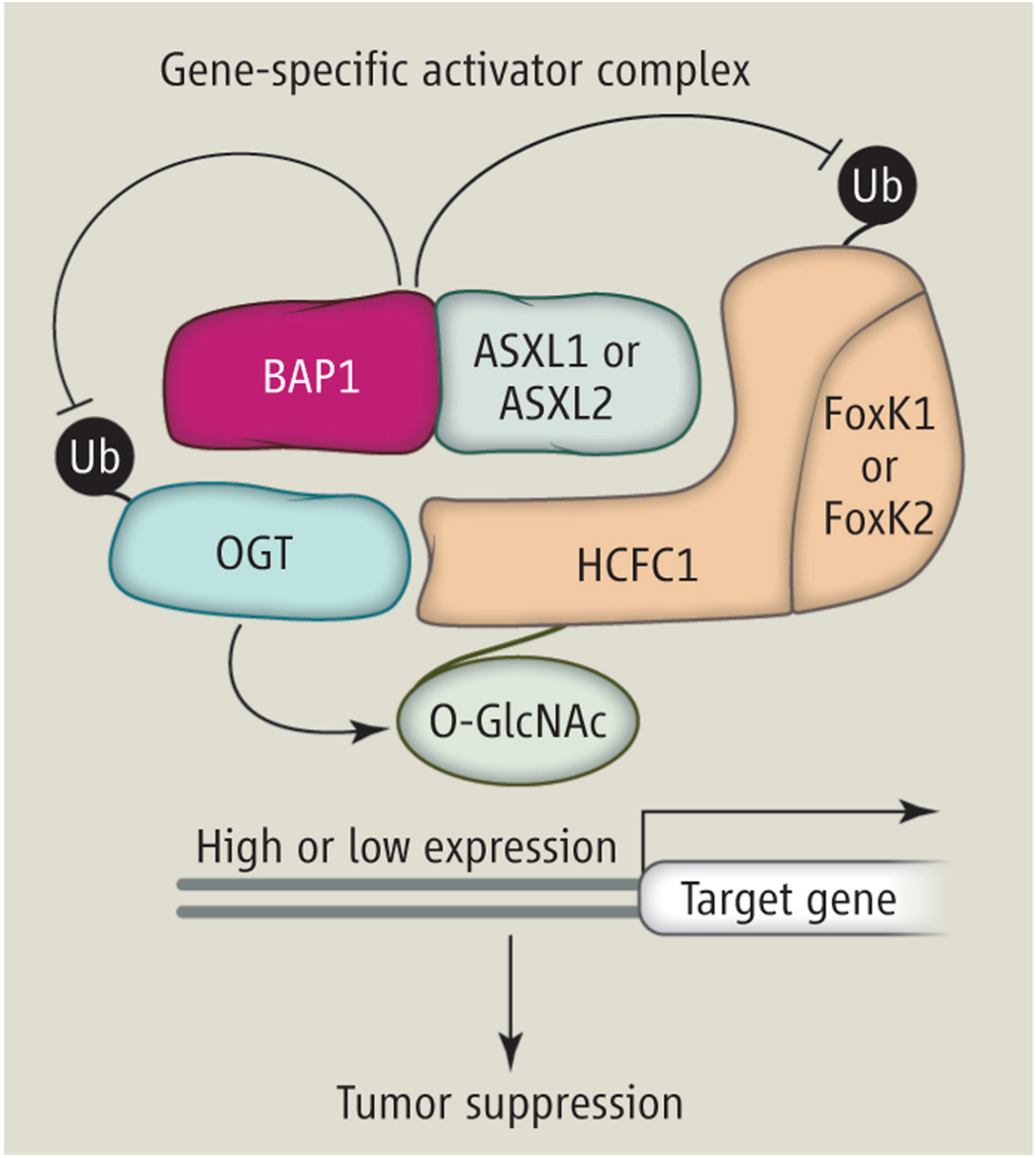
Journal of Thoracic Oncology Vol. 11 No. 2: 142-154

Clinical and Radiographic Presentation

- **Dyspnea; chest pain.**
- **Pleural effusion on initial chest x-ray.**
- **Chest CT: loculated effusion with pleural nodularities.**

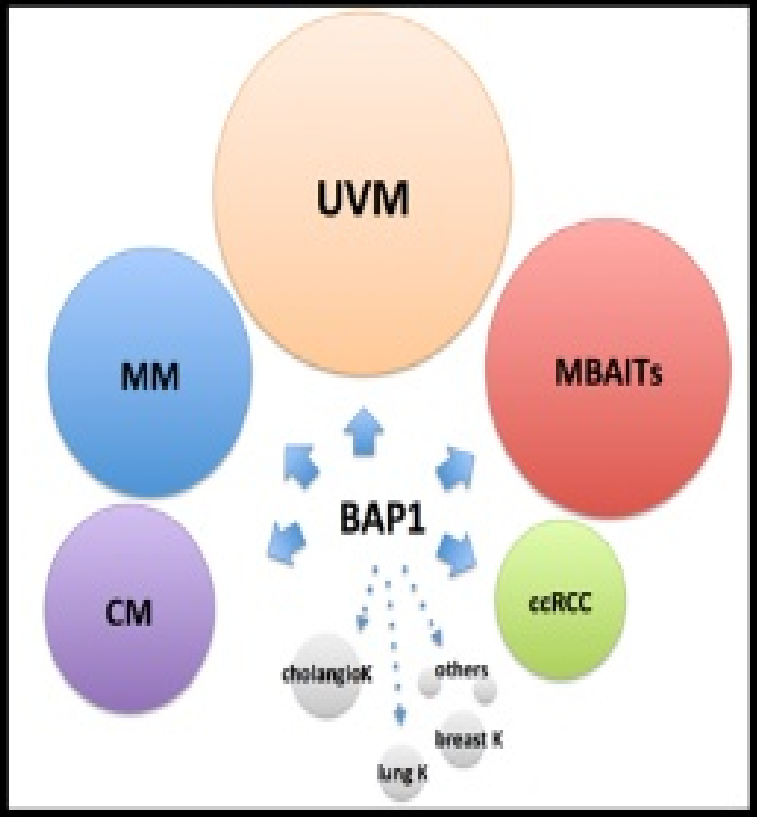


BAP-1



White AE; Harper JW. Science; Sep 2012; 337:1463-4

The BAP1 Cancer Syndrome



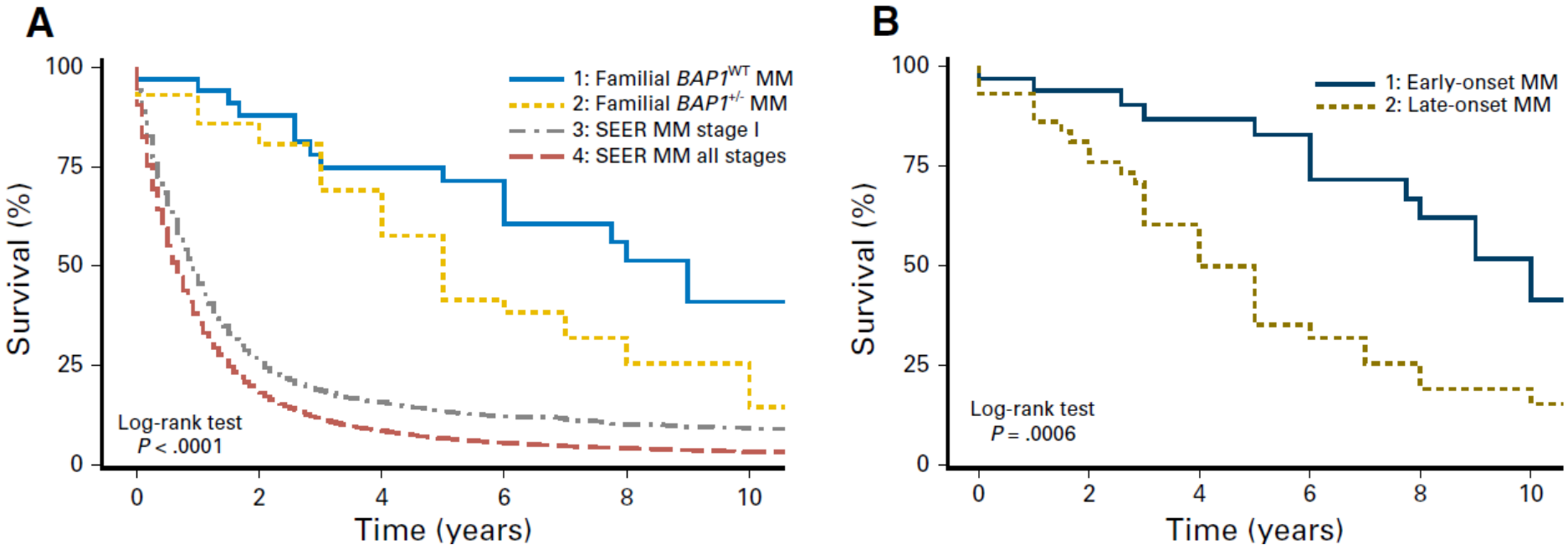
Carriers of BAP1 mutations are predisposed to different tumors:

- Malignant mesothelioma
- Uveal and cutaneous melanoma
- Renal Cell carcinoma, clear cell type
- Basal cell and squamous carcinomas
- Cholangioca and other cancers
- MBAITS (benign melanocytic tumors)

- Nature Reviews Cancer, Progess: BAP1 and Cancer, March 2013, Carbone M, et al.
- Journal of Translational Medicine, BAP1 cancer syndrome: malignant mesothelioma, uveal and cutaneous melanoma, and MBAITS, August 2012, Carbone M, ..., Harvey I Pass and Yang H

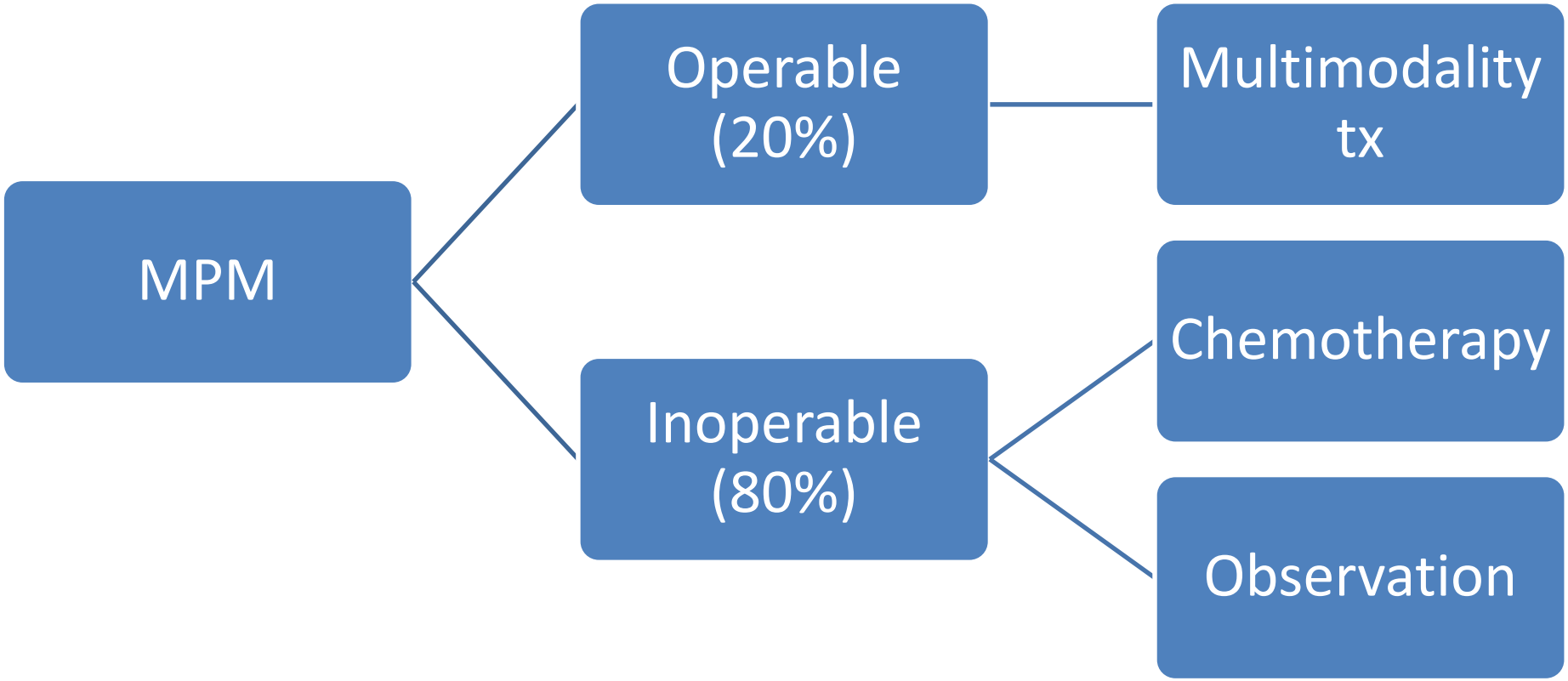
A Subset of Mesotheliomas With Improved Survival Occurring in Carriers of *BAP1* and Other Germline Mutations

Sandra Pastorino, Yoshie Yoshikawa, Harvey I. Pass, Mitsuru Emi, Masaki Nasu, Ian Pagano, Yasutaka Takinishi, Ryuji Yamamoto, Michael Minaai, Tomoko Hashimoto-Tamaoki, Masaki Ohmuraya, Keisuke Goto, Chandra Goparaju, Kavita Y. Sarin, Mika Tanji, Angela Bononi, Andrea Napolitano, Giovanni Gaudino, Mary Hesdorffer, Haining Yang, and Michele Carbone



J Clin Oncol 36:3485-3494.

Treatment Stratification



Important for Board Exam!

How to Define Inoperable MPM?

- Stage IV (M1)
- Sarcomatoid histology.
  Biphasic?
- Poor candidates for surgery.

Operable MPM: Principles

Treatment intent is "curative".

Survival benefit from surgery is uncertain.

- **Extrapleural pneumonectomy (EPP).**
- **Pleurectomy with decortication (P/D).**

Surgical goal: macroscopic complete resection (MCR).

Three potential strategies:

- **Surgery → Adjuvant chemotherapy → Hemithoracic Radiation (if EPP).**
- **Neoadjuvant chemotherapy → Surgery → Hemithoracic Radiation (if EPP).**
- **IMRT → EPP (investigational).**

Operable MPM: Principles

EPP vs. P/D:

- EPP: higher morbidity, higher likelihood of MCR.
- Optimal surgery is unclear.
- BOARD: Both EPP and P/D are acceptable.

Cisplatin and Pemetrexed.

- Regimen of choice in the neoadjuvant and adjuvant settings (BOARD).

Inoperable MPM

Observation

Minimally symptomatic.

Small tumor burden.

Favorable prognosis. Examples:

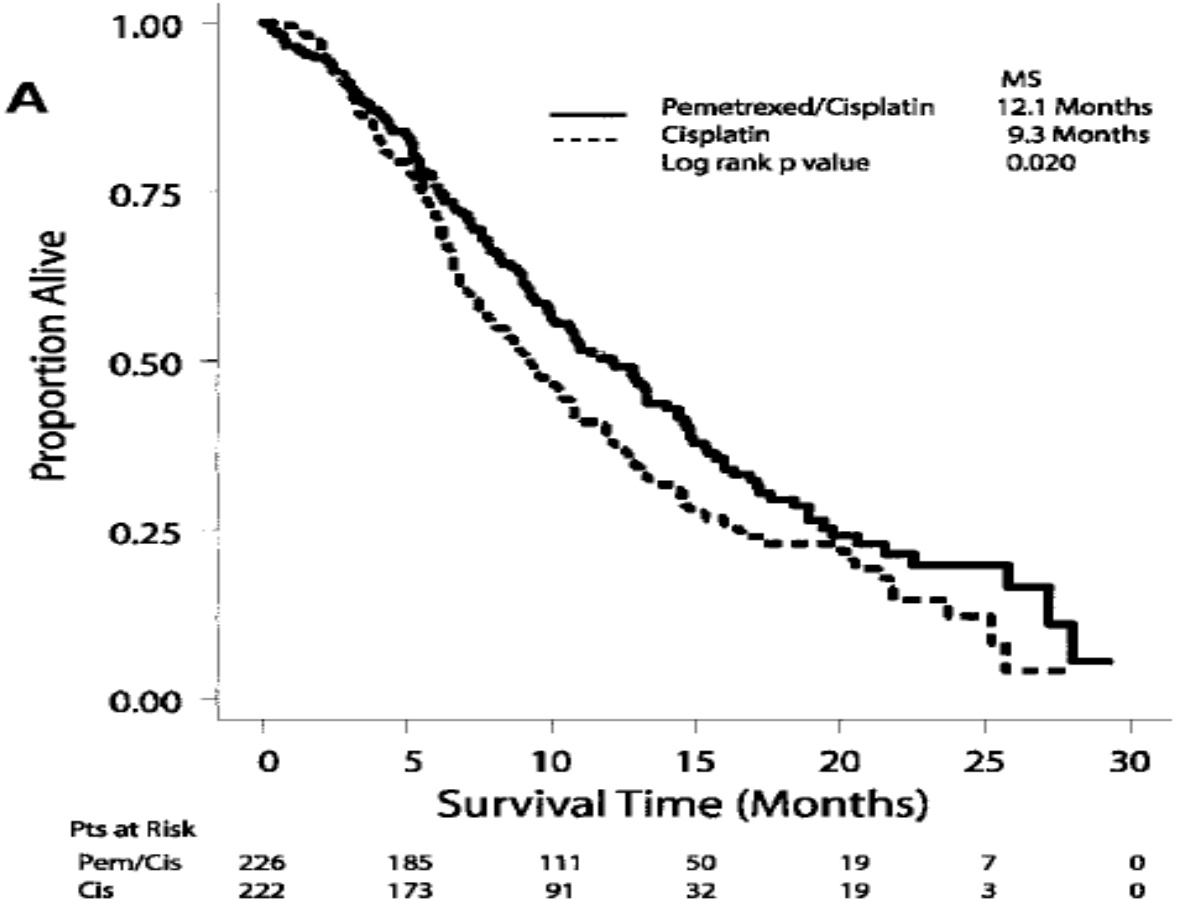
- Germline BAP-1+.
- Other familial MPM.

Older age w/ borderline PS.

First-Line Chemotherapy

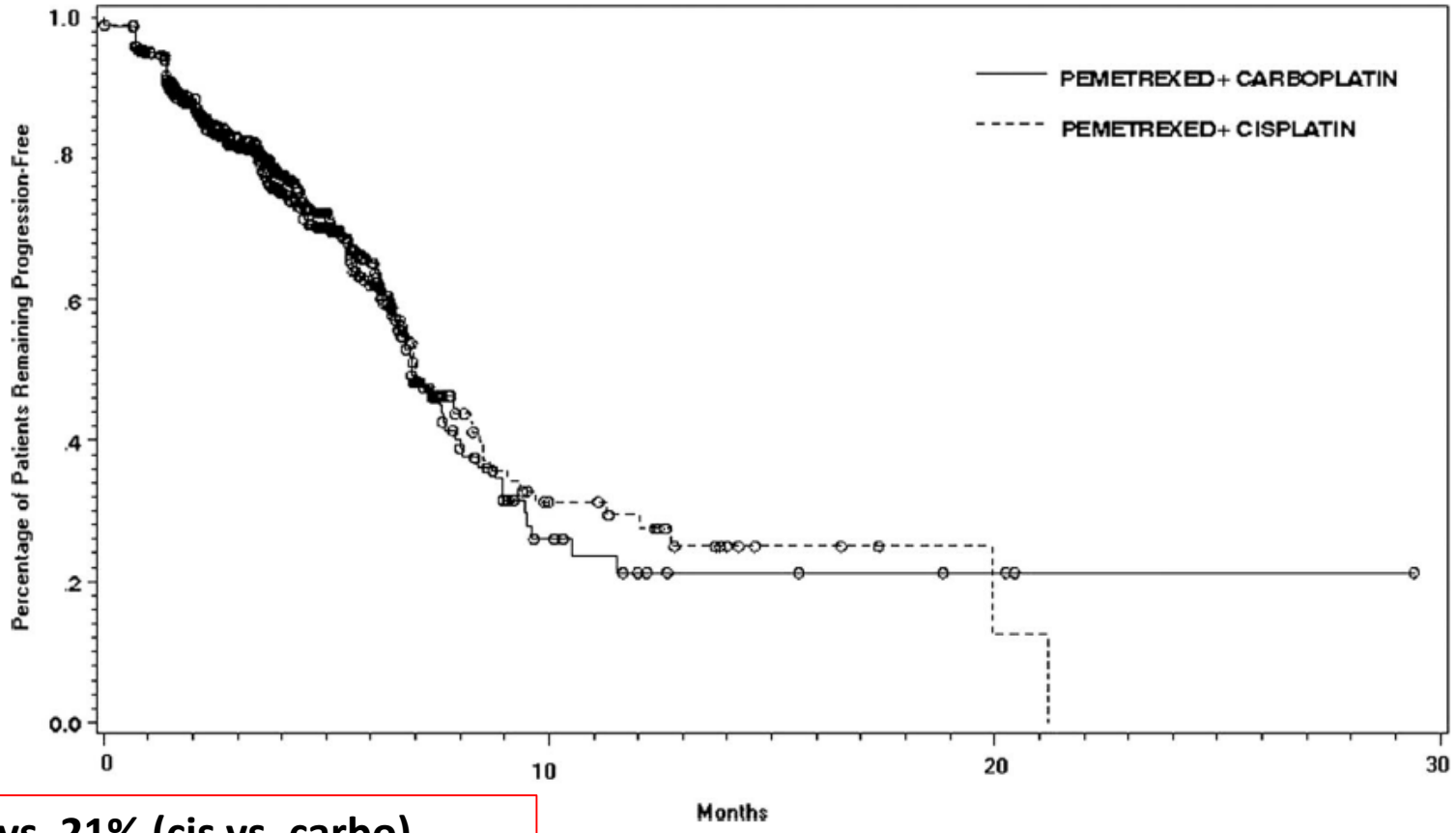
Phase III Study of Pemetrexed in Combination With Cisplatin Versus Cisplatin Alone in Patients With Malignant Pleural Mesothelioma

- N=448
- RR 41% vs. 17%.
- N/V and fatigue.



Journal of Clinical Oncology, Vol 21, No 14 (July 15), 2003: pp 2636-2644

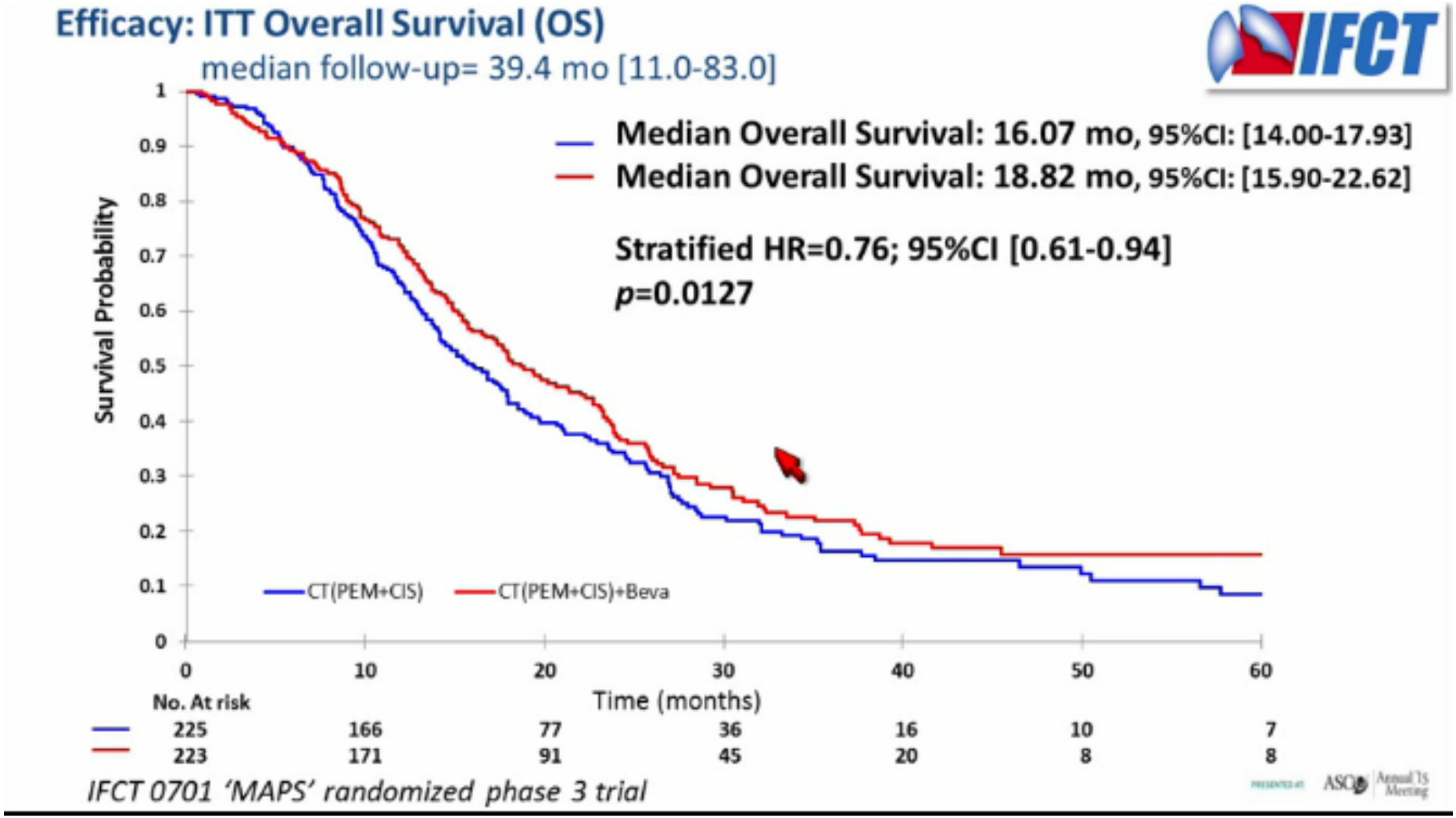
Pemetrexed Plus Cisplatin or Pemetrexed Plus Carboplatin for Chemonaïve Patients with Malignant Pleural Mesothelioma: Results of the International Expanded Access Program



RR: 26% vs. 21% (cis vs. carbo).
1-yr OS: 63% vs. 64% (cis vs. carbo).

(*J Thorac Oncol.* 2008;3: 756–763)

MAPS Trial



2015 ASCO meeting; abstract 7500

FIRST-LINE COMBINATION CHEMOTHERAPY REGIMENS

- Pemetrexed* 500 mg/m² day 1
  Cisplatin 75 mg/m² day 1
  Administered every 3 weeks (category 1)[1]

- Pemetrexed 500 mg/m² day 1
  Cisplatin 75 mg/m² day 1
  Bevacizumab 15 mg/kg day 1
  Administered every 3 weeks for 6 cycles followed by maintenance bevacizumab 15 mg/kg every 3 weeks until disease progression (category 1)[2,**]

- Pemetrexed* 500 mg/m² day 1
  Carboplatin AUC 5 day 1
  Administered every 3 weeks[3-5,†]

- Gemcitabine 1000–1250 mg/m² days 1, 8, and 15
  Cisplatin 80–100 mg/m² day 1
  Administered in 3- to 4-week cycles[6,7]

- Pemetrexed* 500 mg/m² every 3 weeks[8]

- Vinorelbine 25–30 mg/m² weekly[9]

"Board" 1st-line regimens

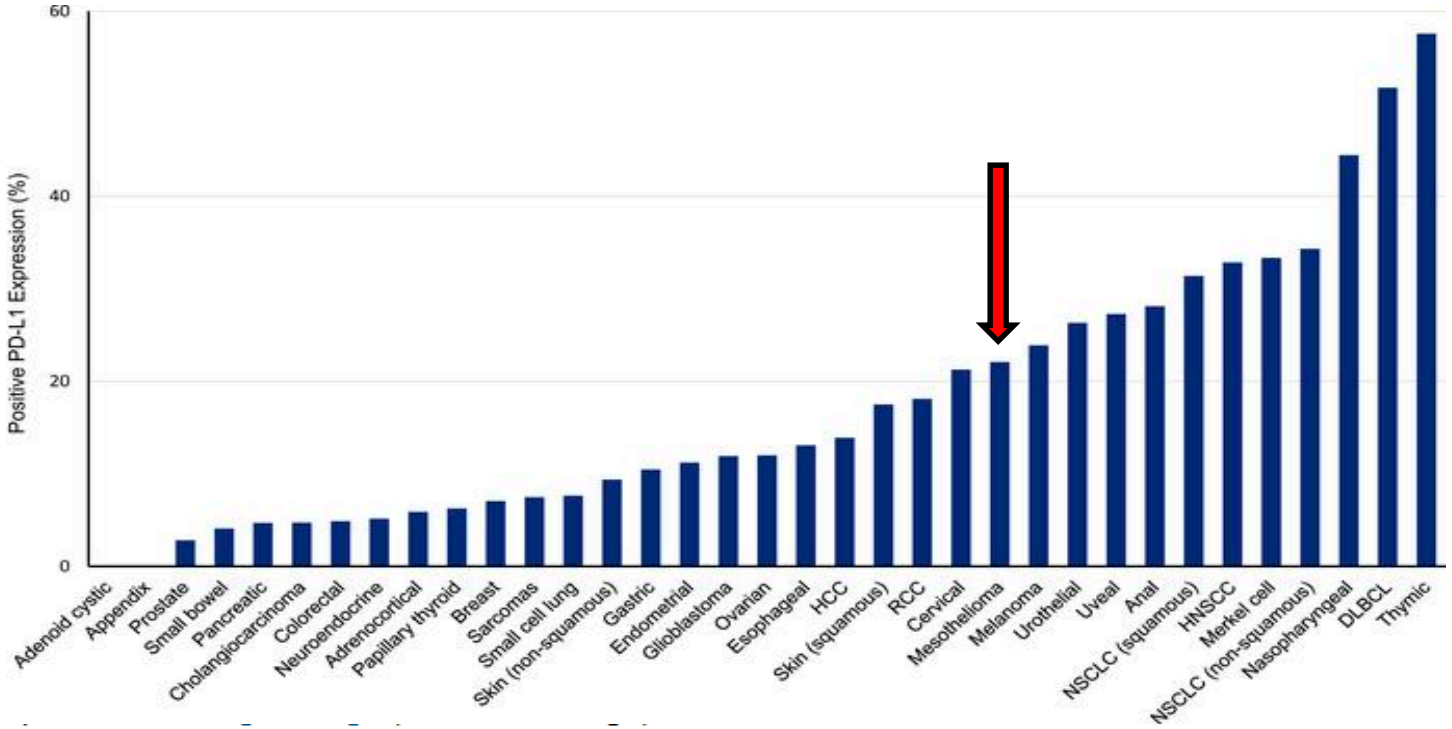
NovoTTF™-100L System - H180002

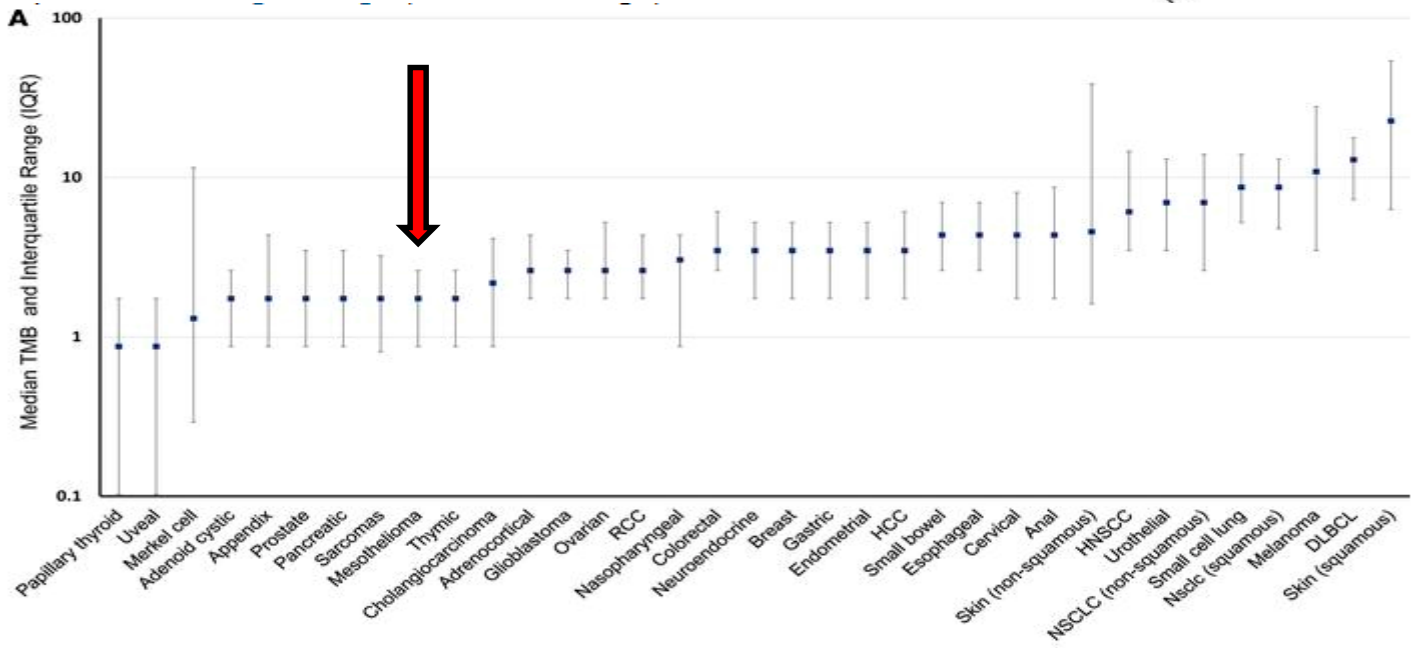
?

Stellar phase II trial with cisplatin and pemetrexed: Median OS = 18 months.

https://www.fda.gov/medical-devices/recently-approved-devices/novottftm-100l-system-h180002

Immune Checkpoint Inhibitors in 1st Line Systemic Therapy





JCI Insight. 2019;4(6):e126908. https://doi.org/10.1172/jci.insight.126908.

Abstract 9003

PrE0505

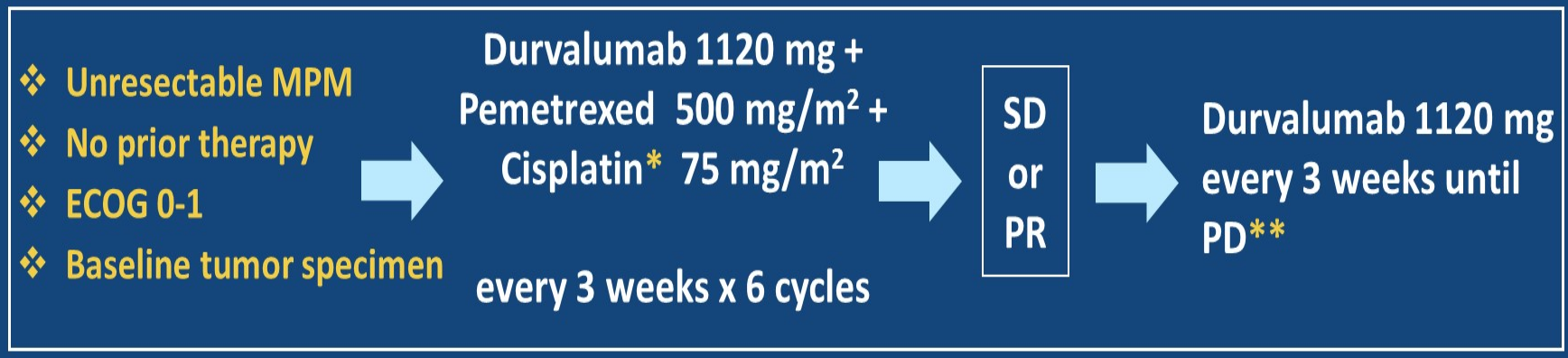
Phase 2 Multi-Center Study of anti-PD-L1 Durvalumab, in Combination with Cisplatin and Pemetrexed for the First-Line Treatment of Unresectable Malignant Pleural Mesothelioma (MPM)

Patrick Forde[1], Zhuoxin Sun[2] , Valsamo Anagnostou[1], Hedy Kindler[3], Thomas Purcell[4], Bernardo Goulart[5], Arkadiusz Z. Dudek[6], Hossein Borghaei[7], Julie Brahmer[1], Suresh Ramalingam[8]

[1]Johns Hopkins University; [2]Dana-Farber Cancer Institute; [3]University of Chicago; [4]University of Colorado; [5]University of Washington; [6]Metro-Minnesota Community Oncology Research Consortium; [7]Fox Chase Cancer Center; [8]Winship Cancer Institute of Emory University

Patients and Methods

Between June 2017 and June 2018, 55 patients were enrolled at 15 US sites

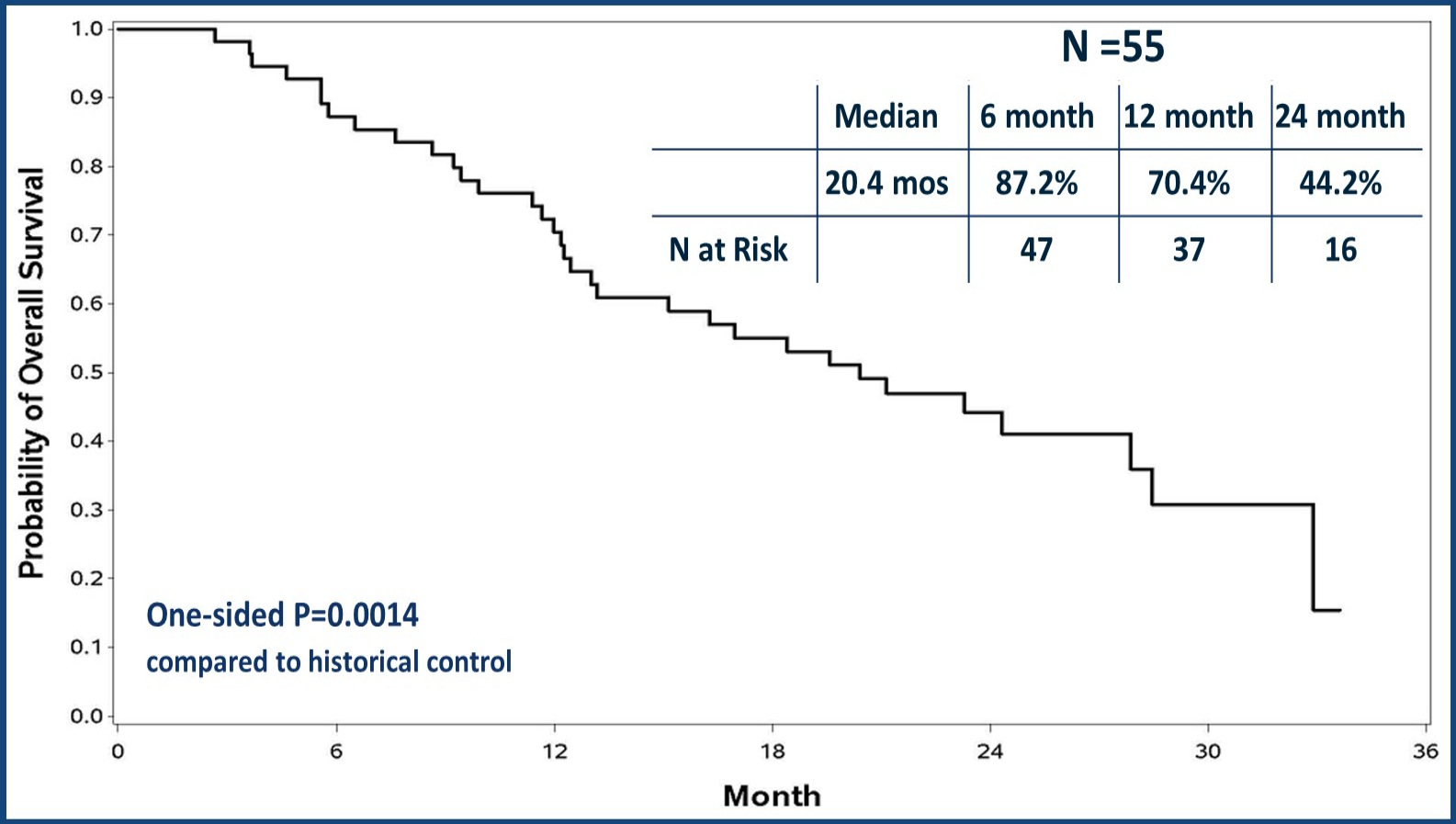


- 90% power to detect a 37% reduction in the OS hazard rate of 0.058 to 0.037 based on Wald test for the log failure rate parameter (one-sided type I error rate of 10%)
- To correspond to a 58% improvement in the median OS from 12 months (historical control) to 19 months (goal)
- Pre-specified safety review after enrollment of the first 6 and 15 patients. No DLTs noted for the combination with durvalumab 1120 mg

* Carboplatin was substituted if cisplatin was contraindicated, or due to toxicity during treatment

** Max duration 1 year from start of study

Results: Overall Survival



CheckMate-743 Trial of Nivolumab, Ipilimumab Meets Primary Endpoint in Mesothelioma Trial

April 21, 2020
Hannah Slater

The trial evaluating nivolumab in combination with ipilimumab in previously untreated malignant pleural mesothelioma met its primary endpoint of overall survival.

The CheckMate-743 trial evaluating nivolumab (Opdivo) in combination with ipilimumab (Yervoy) in previously untreated malignant pleural mesothelioma met its primary endpoint of overall survival (OS), according to Bristol-Myers Squibb, the agent's developer.[1]

Based on a pre-specified interim analysis conducted by an independent data monitoring committee, the combination treatment was also found to result in a statistically significant and clinically meaningful improvement in OS compared to chemotherapy (pemetrexed and cisplatin or carboplatin). Additionally, the safety profile of nivolumab plus ipilimumab observed in the trial reflects the known safety profile of the combination.

"Malignant pleural mesothelioma is a devastating disease that has seen limited treatment advances over the past decade," Sabine Maier, MD, development lead of thoracic cancers at Bristol Myers Squibb, said in a press release. "These topline results from the CheckMate-743 trial demonstrate the potential of Opdivo plus Yervoy in previously untreated patients with malignant pleural mesothelioma and is another example of the established efficacy and safety of the dual immunotherapy combination seen in multiple tumor types."

"We would like to thank the patients who participated in this trial, as well as the investigators and site personnel for their perseverance during the conduct of this study and in delivering this important result for patients in the midst of the COVID-19 pandemic," Maier added. "We look forward to working with investigators to present the results at a future medical meeting, and to discussing them with health authorities."

First-Line Therapy: Key Points

Standard

- Cisplatin/Carboplatin + Pemetrexed ± Bevacizumab.

Consider Observation

- Minimally symptomatic, low disease burden, favorable prognosis (e.g., germline BAP-1 germline +)

Evolving role for ICIs.

- DREAM3R: Cis/Pem/Durva vs. Cis/Pem. Ongoing.
- Promising role of Nivo/Ipi, data release pending.

Second-Line therapy

NO FDA APPROVED 2L REGIMENS (BOARD)

Chemotherapy	Evolving Role of ICIs	Evolving role for anti-VEGF MoAb
• Vinorelbine • Gemcitabine • Repeat pemetrexed • RR ≈ 10%	• Pembrolizumab • Nivolumab ±Ipilimumab	• Gemcitabine + Ramucirumab. • 2020 ASCO abst #9004.

Pembrolizumab

Keynote 028

	Full-analysis set (n=25)
Objective response	5 (20%; 95% CI 6·8–40·7)
Complete response	0
Partial response	5 (20%)
Stable disease	13 (52%)
Progressive disease	4 (16%)
Not evaluable or no assessment*	3 (12%)
Duration of follow-up (months)	18·7 (10·4–24·0)
Time to response (months)	1·9 (1·7–3·8)
Duration of response (months)	12 (3·7–NR)
Duration of stable disease (months)	5·6 (3·6–12·0)
Clinical benefit (complete response + partial response + stable disease ≥6 months)	40% (21·1–61·3)
Progression-free survival	
Events	21 (84%)
Median (months)	5·4 (3·4–7·5)
6 months	45·8% (25·6–64·0)
12 months	20·8% (7·6–38·5)
Overall survival	
Deaths	14 (56%)
Median (months)	18 (9·4–NR)
6 months	83·5% (61·7–93·5)
12 months	62·6% (40·4–78·5)

Lancet Oncol 2017; 18: 623–30

Popat et al, 2019 ESMO

2L Phase III trial Pembro vs. Gemcitabine or Vinorelbine		
	Pembro	**Gem or Vin**
PFS (months)	2.5	3.4
OS (months)	10.7	11.7

NCCN category 2A

Nivolumab or nivolumab plus ipilimumab in patients with relapsed malignant pleural mesothelioma (IFCT-1501 MAPS2): a multicentre, open-label, randomised, non-comparative, phase 2 trial

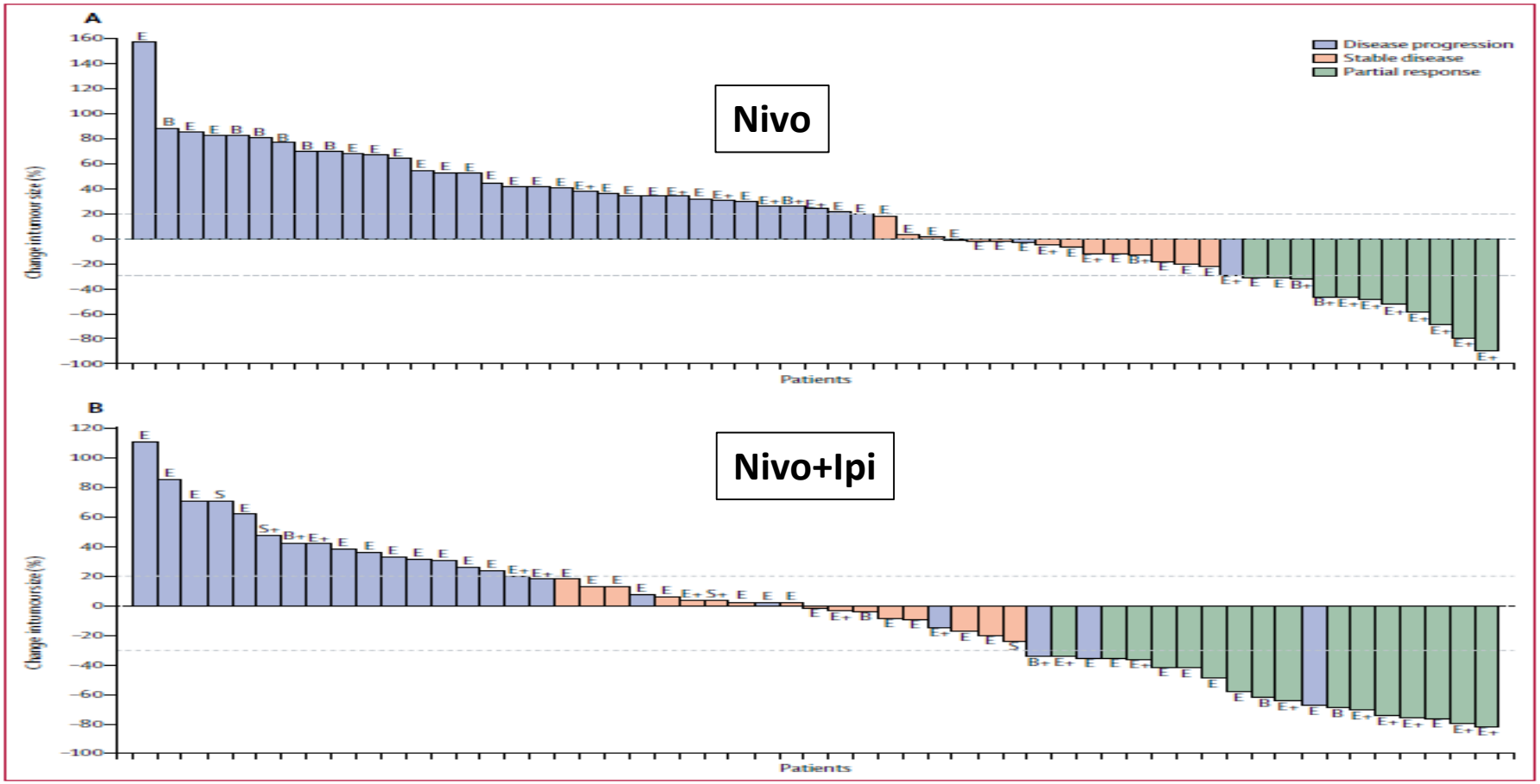
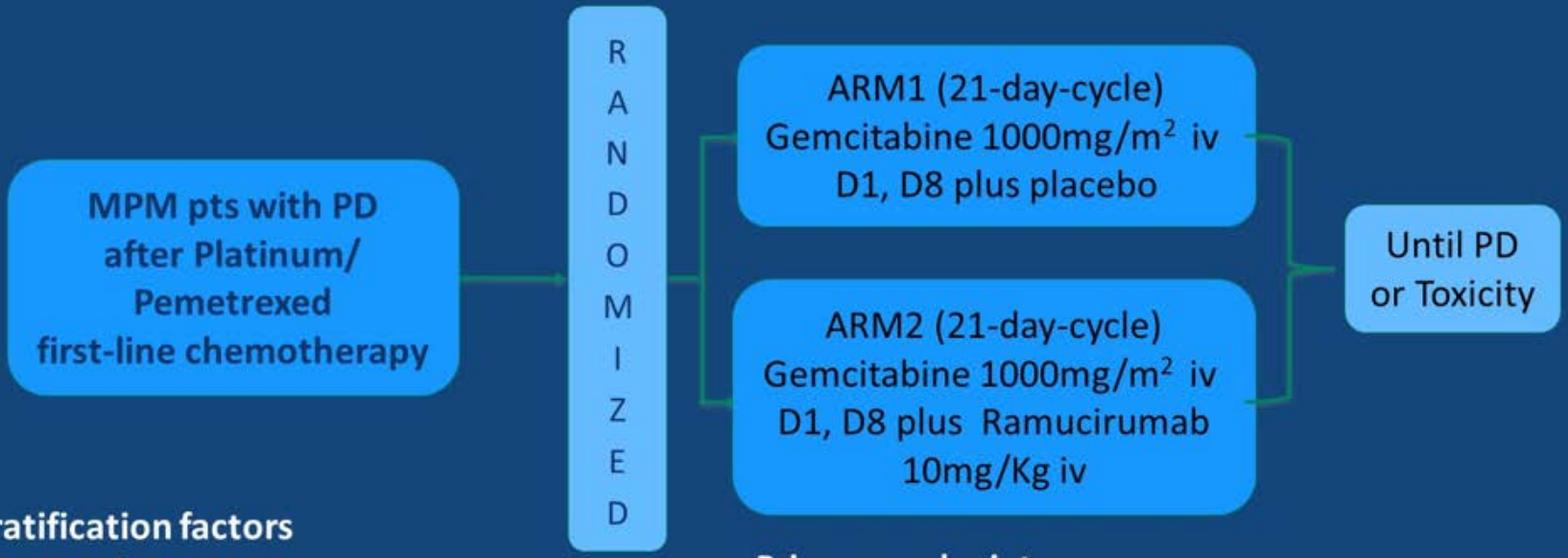


Figure 2: Percentage changes in tumour size, baseline to week 12

Lancet Oncol 2019; 20: 239–53

RAMES Study: Phase II comparative design



Stratification factors

- ECOG/PS 0-1 vs 2
- Age ≤ 70 vs > 70
- Histological subtype
- TTP

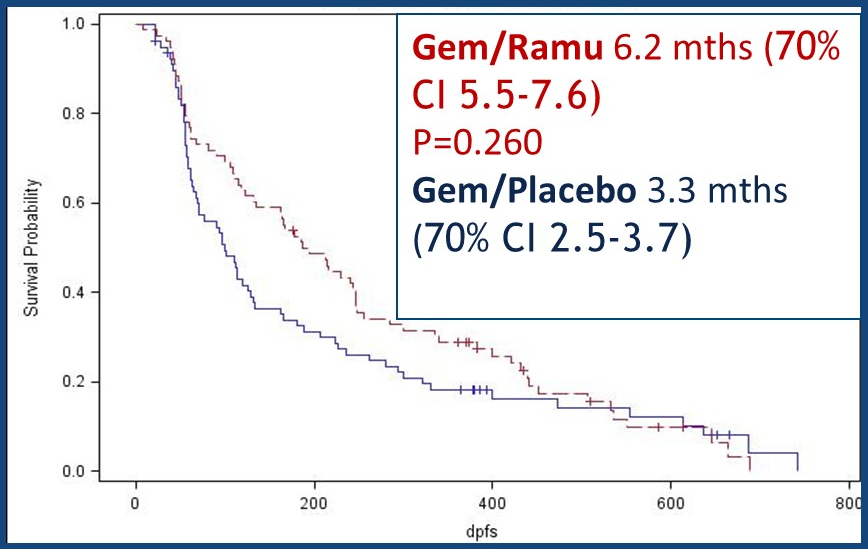
Primary endpoint

- OS

Secondary endpoints

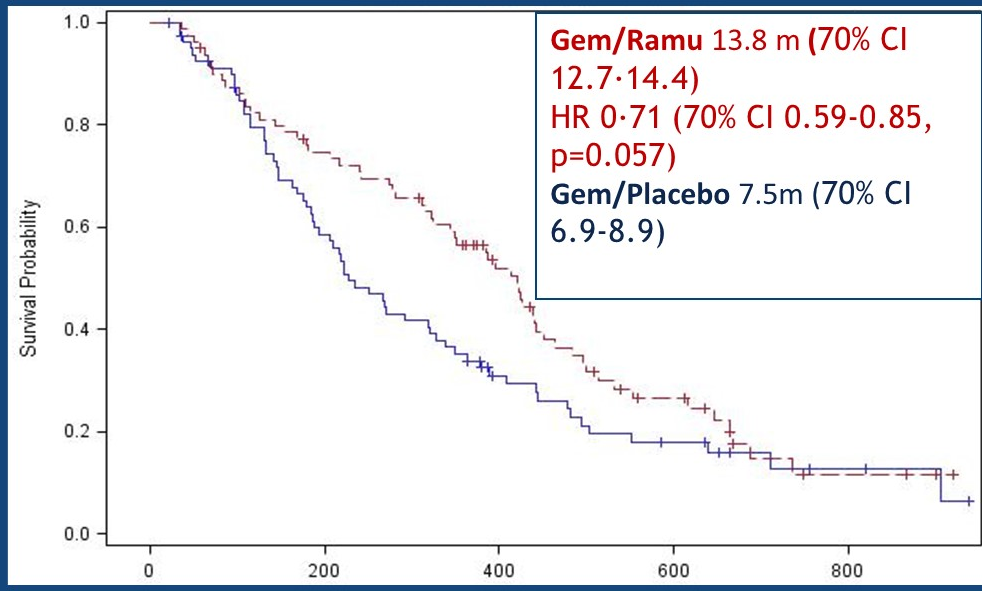
- PFS, ORR, Safety, QoL
- Predictive markers

PFS



Gem/Ramu 6.2 mths (70% CI 5.5-7.6)
P=0.260
Gem/Placebo 3.3 mths (70% CI 2.5-3.7)

OS



Gem/Ramu 13.8 m (70% CI 12.7·14.4)
HR 0·71 (70% CI 0.59-0.85, p=0.057)
Gem/Placebo 7.5m (70% CI 6.9-8.9)

2L Therapy: Keypoints

Main message

No FDA-approved 2nd line therapies (Board).

Chemotherapy

Vinorelbine, gemcitabine, pemetrexed

- RR ≈ 10%.

Checkpoint inhibitors

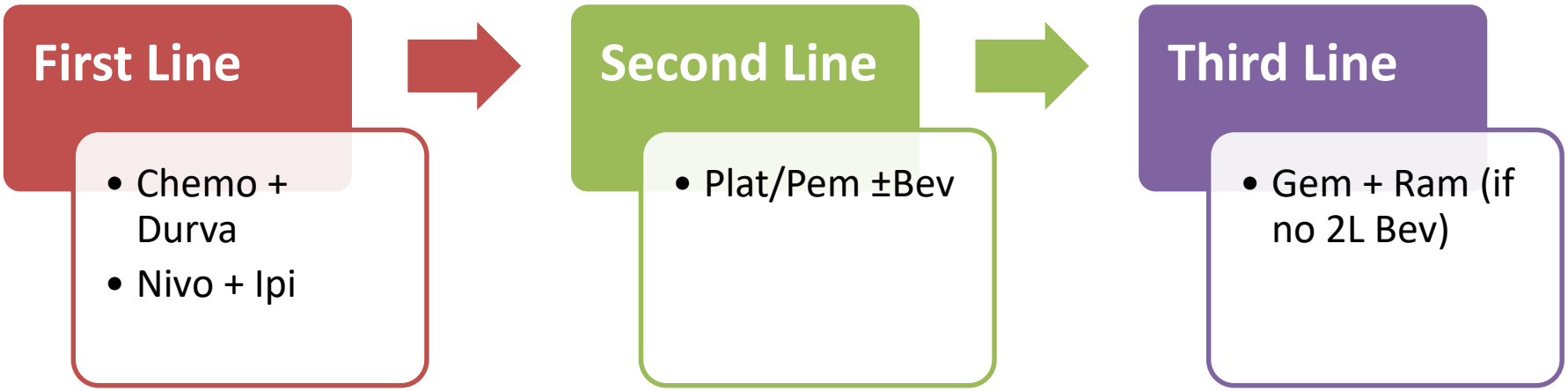
Evolving role of PDL1 CIs.

- Consider 2L pembrolizumab, gemcitabine, vinorelbine, or re-challenge pemetrexed*.
- Data is immature for nivo or nivo/ipi.

Gem/Ram

Deserves at least a phase III. Stay tuned.

Final Thoughts on Future Directions



Questions

Supportive Care

Keith Eaton, MD, PhD

September 2020

What is supportive care?

- Encompasses significant amount of what an oncologist does – widely applicable
- Not specific to any oncologic disease
- Aimed at improving symptoms and tolerance of therapy
- Multiple topics
- Guidelines by NCCN, MASCC, ASCO, and others
- Supportive Care, Survivorship, and Communication = 10% boards

Topics – covered today

Antiemesis

Anemia

Myeloid growth factors

Skeletal

Fatigue

Brief reviews – neuropathy, cachexia

Not covered: pain, mucositis, GI, distress, palliative care, infections, survivorship, chemotherapy dosing, IV access, immunotherapy toxicity management, communication …

Antiemesis

CINV Introduction

- N/V are the most common and feared symptoms of cancer chemotherapy
- Management of these symptoms is the most important determinant of the patient experience
- Innovation in this area has undoubtedly improved QOL and likely survival though improved adherence

Potential problems due to N/V:

- Metabolic disturbances
- Dehydration
- Anorexia
- Decline in PS
- Wound complications, esophageal tears
- Withdrawal from treatment

Definitions

- Acute onset N/V usually occurs within minutes to hours after chemotherapy administration and , it peaks after ~ 6 hours and commonly resolves within 24 hours

Delayed CINV

- Delayed = (>24hrs)
- Common with platins, cyclophosphamide, doxorubicin
- Cisplatin – peaks at 48-72 hours, can last up to a week
- The risk of N/V extends to at least 4 days after drug is given for agents of moderate to high emetogenic potential and patients should be protected through this period

Anticipatory CINV

- N/V before next chemotherapy
- a conditioned response
- estimates range from 20-60%
- main indication for benzodiazepines (lorazepam) in CINV

Refractory/Breakthrough CINV

- Breakthrough emesis occurs despite prophylactic treatment and/or requires “rescue” antiemetics

- Refractory emesis may occur during subsequent cycles following ineffective treatment in earlier cycles

CINV Risk Factors

Acute

Patient-related factors

- Age
- Gender
- Alcohol use
- previous CINV
- History of anxiety
- Prone to motion sickness
- Morning sickness during pregnancy

Chemotherapy-related factors

- Emetogenicity
- Combination regimens, dose
- Number of cycles
- Unfractionated regimens
- Infusion time

Delayed

Any predictive factor for acute CINV

Poor control of acute CINV

Concomitant drugs after chemotherapy (i.e. opioids, antibiotics)

Low QOL score

Am J Health-Syst Pharm. 1999;56:729. J Clin Oncol. 1999;17:2971.

Emetogenicity of Chemotherapy

- No universal classification system, NCCN guidelines
- High (> 90%) of patients experience emesis
- Moderate (30-90%)
- Low (10-30%)
- Minimal (< 10%)

EMETOGENIC POTENTIAL OF PARENTERAL ANTICANCER AGENTS[a]

LEVEL	AGENT		
High emetic risk (>90% frequency of emesis)[b,c,d]	• AC combination defined as any chemotherapy regimen that contains an anthracycline and cyclophosphamide • Carboplatin AUC ≥4	• Carmustine >250 mg/m² • Cisplatin • Cyclophosphamide >1,500 mg/m² • Dacarbazine • Doxorubicin ≥60 mg/m²	• Epirubicin >90 mg/m² • Ifosfamide ≥2 g/m² per dose • Mechlorethamine • Streptozocin
Moderate emetic risk (>30%–90% frequency of emesis) [b,c,d]	• Aldesleukin >12–15 million IU/m² • Amifostine >300 mg/m² • Azacitidine • Bendamustine • Busulfan • Carboplatin AUC[e] <4 • Carmustine[e] ≤250 mg/m² • Clofarabine • Cyclophosphamide[e] ≤1500 mg/m² • Cytarabine >200 mg/m² • Dactinomycin[e]	• Daunorubicin[e] • Dual-drug liposomal encapsulation of cytarabine and daunorubicin • Dinutuximab • Doxorubicin[e] <60 mg/m² • Enfortumab vedotin-ejfv • Epirubicin[e] ≤90 mg/m² • Fam-trastuzumab deruxtecan • Idarubicin[e] • Ifosfamide[e] <2 g/m² per dose • Interferon alfa ≥10 million IU/m²	• Irinotecan[e] • Irinotecan (liposomal) • Melphalan • Methotrexate[e] ≥250 mg/m² • Oxaliplatin[e] • Temozolomide • Trabectedin[e]

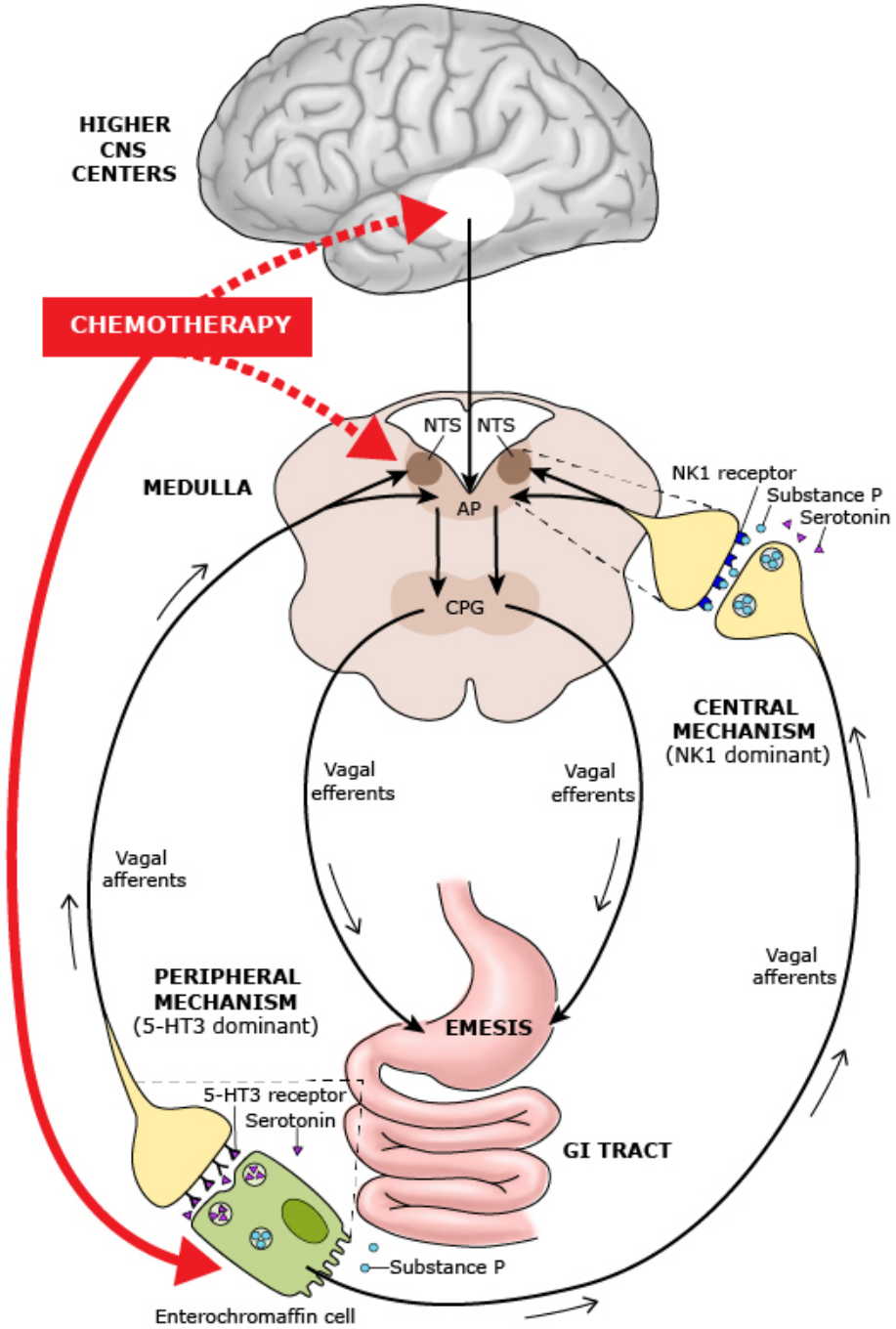
EMETOGENIC POTENTIAL OF PARENTERAL ANTICANCER AGENTS[a]

LEVEL	AGENT			
Low emetic risk (10%–30% frequency of emesis)[b,d,f]	• Ado-trastuzumab emtansine • Aldesleukin ≤12 million IU/ m^2 • Amifostine ≤300 mg/m^2 • Arsenic trioxide • Axicabtagene ciloleucel[g] • Belinostat • Brentuximab vedotin • Cabazitaxel • Carfilzomib • Copanlisib	• Cytarabine (low dose) 100–200 mg/m^2 • Docetaxel • Doxorubicin (liposomal) • Eribulin • Etoposide • 5-Fluorouracil (5-FU) • Floxuridine • Gemcitabine • Gemtuzumab ozogamicin • Inotuzumab ozogamicin • Ixabepilone	• Methotrexate >50 mg/m^2 - <250 mg/m^2 • Mitomycin • Mitoxantrone • Mogamulizumab • Moxetumomab • Necitumumab • Olaratumab • Omacetaxine • Paclitaxel • Paclitaxel-albumin	• Pemetrexed • Pentostatin • Polatuzumab vedotin • Pralatrexate • Romidepsin • Tagraxofusp • Talimogene laherparepvec • Thiotepa • Tisagenlecleucel[g] • Topotecan • Ziv-aflibercept
Minimal emetic risk (<10% frequency of emesis)[b,d,f]	• Alemtuzumab • Atezolizumab • Avelumab • Asparaginase • Bevacizumab • Bleomycin • Blinatumomab • Bortezomib • Cetuximab • Cemiplimab • Cladribine • Cytarabine <100 mg/m^2 • Daratumumab	• Decitabine • Denileukin diftitox • Dexrazoxane • Durvalumab • Elotuzumab • Fludarabine • Ipilimumab • Methotrexate ≤50 mg/m^2 • Nelarabine • Nivolumab	• Obinutuzumab • Ofatumumab • Panitumumab • Pegaspargase • Peginterferon • Pembrolizumab • Pertuzumab • Ramucirumab • Rituximab • Rituximab and hyaluronidase human injection, for subcutaneous use	• Siltuximab • Temsirolimus • Trastuzumab • Trastuzumab and hyaluronidase injection, for subcutaneous use • Valrubicin • Vinblastine • Vincristine • Vincristine (liposomal) • Vinorelbine

Adapted with permission from: Hesketh PJ, Kris MG, Grunberg SM, et al. Proposal for classifying the acute emetogenicity of cancer chemotherapy. J Clin Oncol 1997;15:103-109.
Grunberg SM, Warr D, Gralla RJ, et al. Evaluation of new antiemetic agents and definition of antineoplastic agent emetogenicity--state of the art. Support Care Cancer 2011;19:S43-S47.

EMETOGENIC POTENTIAL OF ORAL ANTICANCER AGENTS[a]

LEVEL	AGENT			
Moderate to high emetic risk[b,z] (≥30% frequency of emesis)	• Altretamine • Avapritinib • Binimetinib • Busulfan (≥4 mg/d) • Ceritinib • Crizotinib	• Cyclophosphamide (≥100 mg/m²/day) • Dabrafenib • Enasidenib • Encorafenib • Estramustine	• Etoposide • Lenvatinib • Lomustine (single day) • Midostaurin • Mitotane	• Niraparib • Olaparib • Procarbazine • Rucaparib • Selinexor • Temozolomide (>75 mg/m²/day)
Minimal to low emetic risk[b] (<30% frequency of emesis)	• Abemaciclib • Acalabrutinib • Afatinib • Alectinib • Alpelisib • Axitinib • Bexarotene • Brigatinib • Bosutinib • Busulfan (<4 mg/day) • Cabozantinib • Capecitabine • Chlorambucil • Cobimetinib • Cyclophosphamide (<100 mg/m²/day) • Dacomitinib • Dasatinib	• Duvelisib • Entrectinib • Erdafitinib • Erlotinib • Everolimus • Fludarabine • Gefitinib • Gilteritinib • Glasdegib • Hydroxyurea • Ibrutinib • Idelalisib • Imatinib • Ixazomib • Ivosidenib • Lapatinib • Larotrectinib • Lenalidomide	• Lorlatinib • Melphalan • Mercaptopurine • Methotrexate • Nilotinib • Neratinib • Osimertinib • Palbociclib • Panobinostat • Pazopanib • Pomalidomide • Ponatinib • Regorafenib • Ribociclib • Ruxolitinib • Sonidegib • Sorafenib	• Sunitinib • Talazoparib tosylate • Temozolomide (≤75 mg/m²/day)[aa] • Thalidomide • Thioguanine • Topotecan • Trametinib • Tretinoin • Trifluridine/tipiracil • Vandetanib • Vemurafenib • Venetoclax • Vismodegib • Vorinostat • Zanubrutinib



Biology of CINV

NTS: nucleus tractus solitarius
AP: area postrema
CPG: central pattern generator

From: UpToDate

Pharmacologic options for CINV

- $5HT_3$ antagonists (ondansetron, dolasetron, granisetron, palonosetron)
- Corticosteroid (dexamethasone)
- Benzodiazepines (lorazepam)
- Phenothiazines** (prochlorperazine, promethazine)
- Butyrophenones** (droperidol, haloperidol)
- Olanzapine
- Cannabinoids (dronabinol)**
- Substituted benzamides (metoclopramide)**
- Antihistamine/Anticholinergics (diphenhydramine, scopolamine)**
- Substance P/NK_1 receptor antagonist (aprepitant, netupitant)

** low therapeutic index agents not discussed in this lecture

- No final common pathway has been discovered
- Current agents act on different receptor families

  (M1, D2, H1, 5-HT3, NK1)
- No single agent expected to provide complete protection

Serotonin ($5HT_3$) in CINV

- Closely associated with acute phase CINV
- Chemotherapy administration causes release of serotonin from the GI tract, thereby stimulating emesis via vagus and greater splanchnic nerves, as well as the area postrema of the brain
- In early trials, $5HT_3$ release was not found in delayed phase of CINV
- Palonosetron has efficacy for prevention of delayed emesis, but role of other $5HT_3$ is debated

5-HT3 receptor antagonists

- ondansetron (1991), granisetron, dolasetron, palonsetron (2003)
- Numerous studies have demonstrated the 5-HT3 agents have same SE profile and efficacy*
- SE are mild – HA, constipation – counsel patients
- Steroids improve efficacy
- QTc prolongation (except palonosetron and ER formulations)
- Limited role in treatment of delayed phase N/V

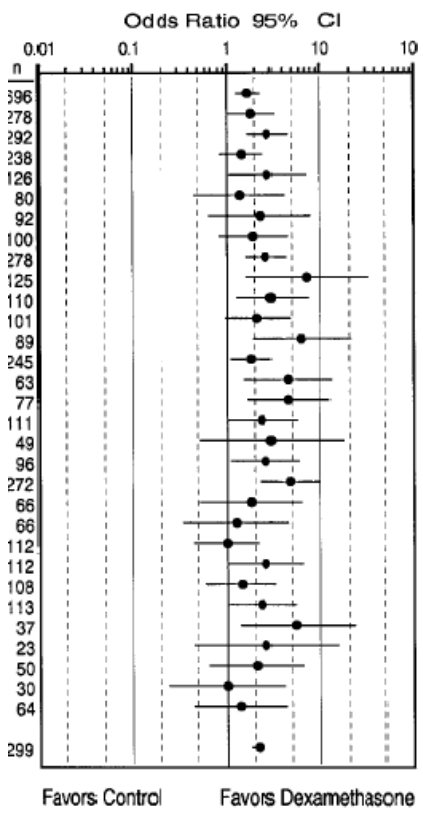
Palonsetron

- pharmacologically distinct
- 100-fold higher binding affinity for 5-HT3R
- T ½ ~ 40 hours
- As effective as traditional 5-HT3 agents for acute CINV (single dose)
- Superior in preventing delayed emesis (single dose)

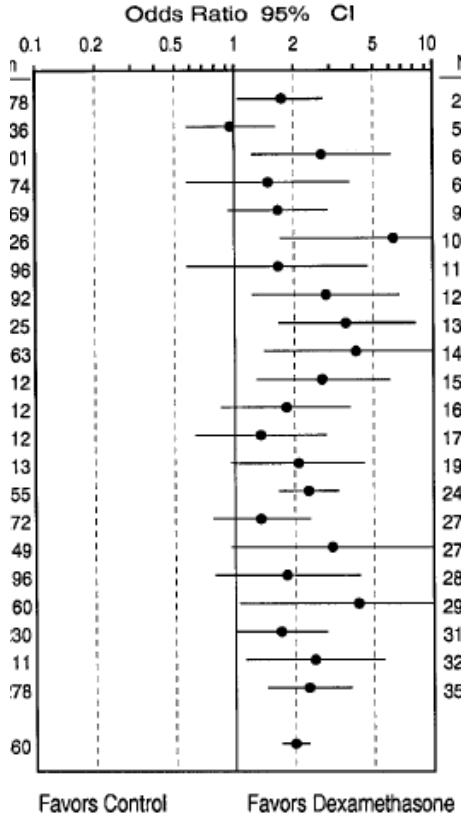
Dexamethasone addition to 5HT3

Meta-analysis of 32 studies showing OR of 2 vs 5HT3 monotherapy for acute and delayed phase

Acute Phase



Delayed Phase



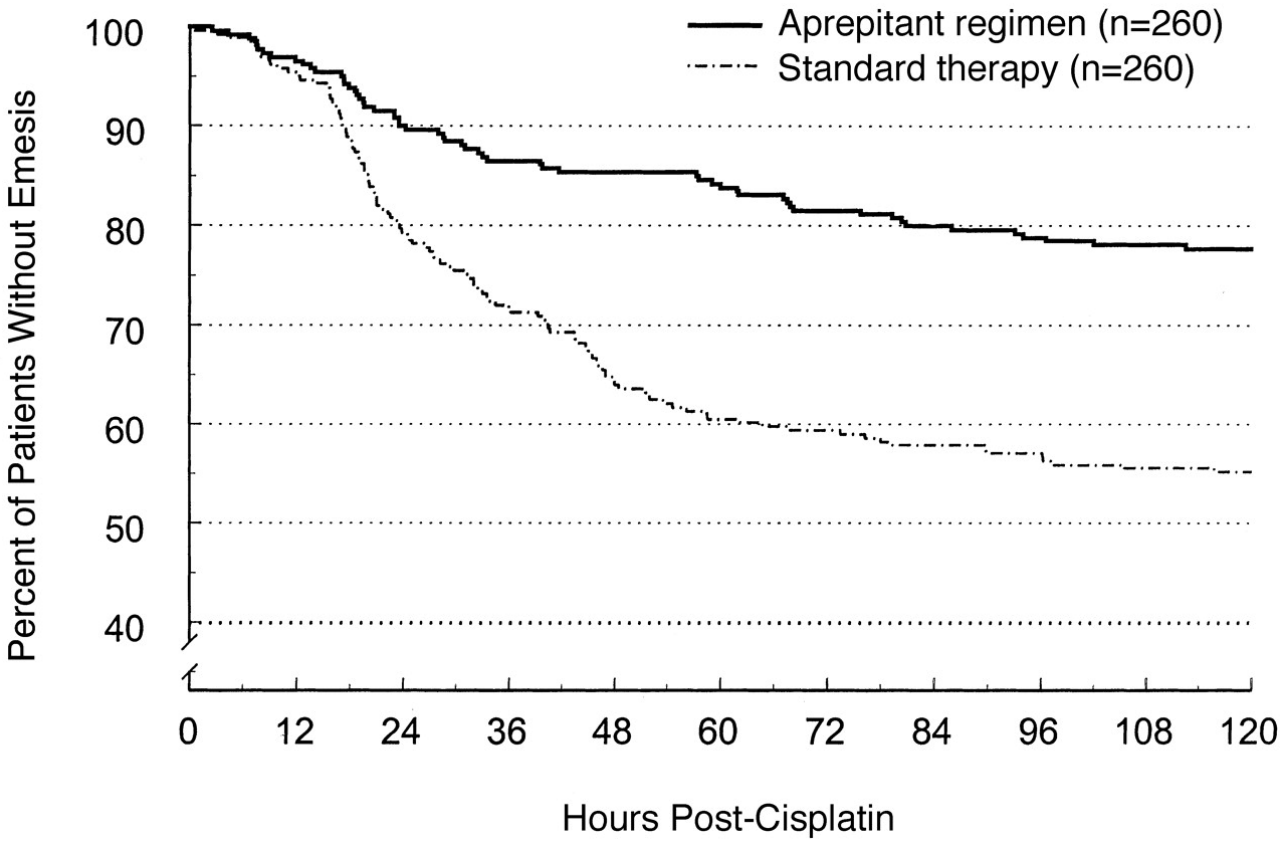
(side note – dexamethasone induced hiccup -> prednisone)

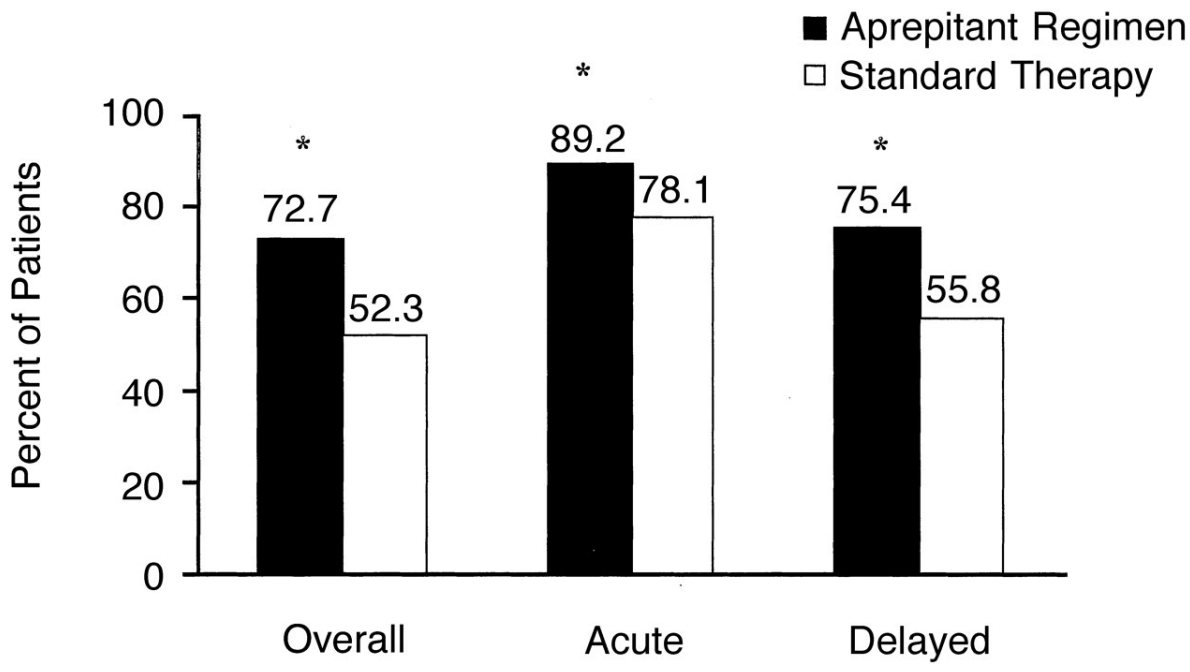
Ioannidis et al. JCO. PMID 11013282

Substance P / Neurokinin Receptors Aprepitant/fosaprepitant

- Substance P: a member of the tachykinin family of neuropeptides
- Biological activity mediated by neurokinin (NK-1) receptor
- Substance P and NK-1 receptors located in brain stem dorsal vagal complex – nucleus tractus solitarus (NTS) and area postrema
- Also located in the GI tract
- Beneficial in delayed > acute CINV, but use is in prevention
- New non-polysorbate-80 IV formulation for aprepitant

Kaplan-Meier curves demonstrating percentages of patients without emesis during the 120-hour study period.





Standard therapy – ondansetron d1, dexamethasone d1-4

Hesketh et al. JCO 2003;21:4112-4119

RCT: (**olanzapine**10mg vs placebo) + fosaprepitant, 5HT3, Dex

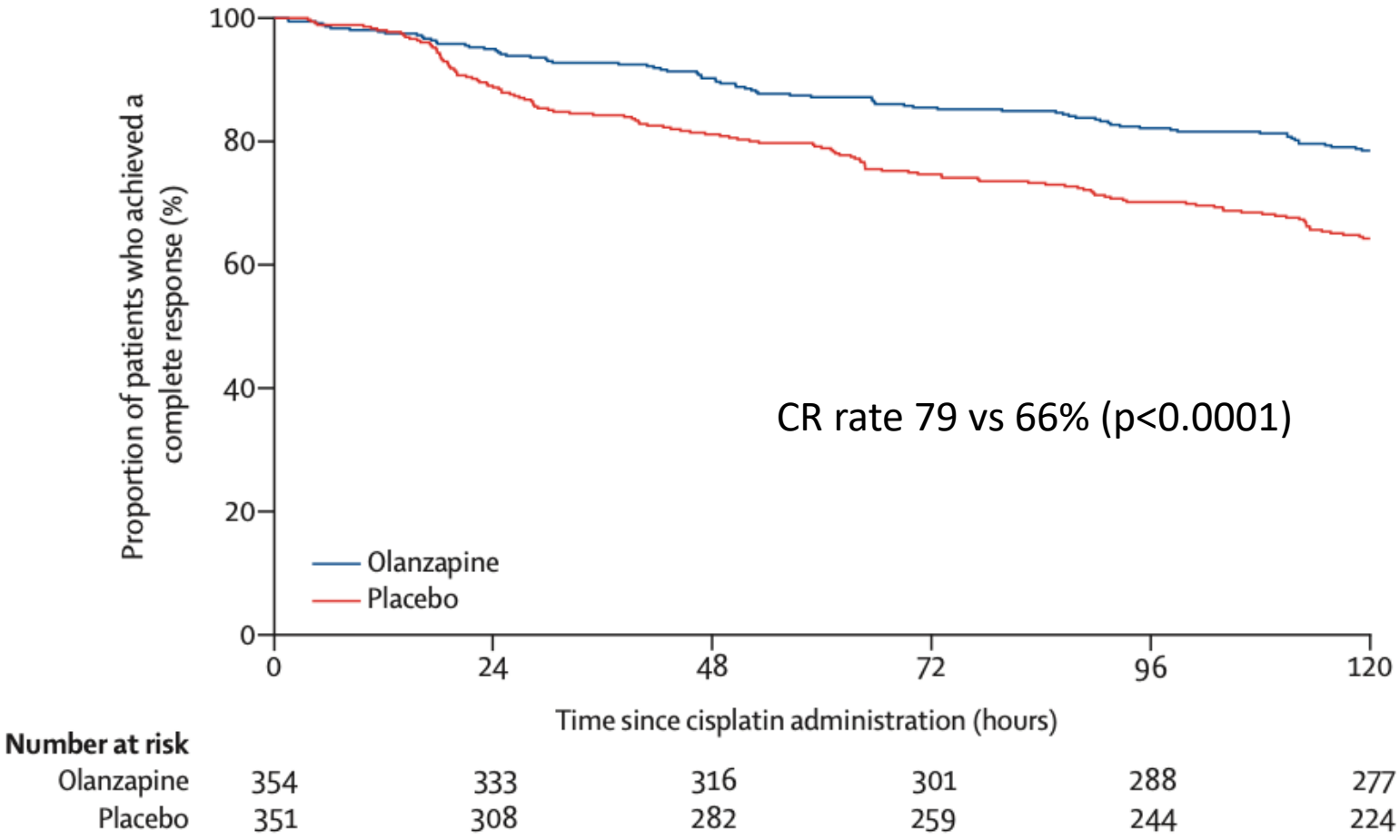
	CR Rate=no emesis or rescue(%)		No nausea (%) = primary endpt	
	Olanz	PCO	Olanz	PCO
0-24 hr	86	65	74	55
0-120 hr	64	40	37	22

All $P < 0.01$, N= 380

Side Effects: mild increase in **sedation** at day 2 (2/10 vs. 1/10) and increased appetite

Navari RM et al. NEJM 2016: 375: 134-142

Olanzapine 5 mg plus standard antiemetic therapy for the prevention of chemotherapy-induced nausea and vomiting (J-FORCE):



CR rate 79 vs 66% (p<0.0001)

cisplatin (≥50 mg/m2)
age 20 - 75 years,
ECOG 0–2.

oral olanzapine 5 mg or placebo d1–4
aprepitant, palonosetron, and dexamethasone

Less sedation than 10mg
mixed effect on sleep

Hashimoto H. Lancet Oncol. 2020;21(2):242-249

Principles

- Prophylactic therapy should be given before chemotherapy to prevent adverse outcomes
- Routes of administration: PO, PR, IV, IM
- PO route is preferred as it is most convenient /cost effective
- Often IV is needed due to inability to take PO
- Lowest maximally effective dose should be used
- Once daily dosing
- Delayed N/V therapy incorporated proactively
- Avoid using concomitant drugs in same class

Guidelines – see NCCN website

- In contrast to other guidelines that are often based on expert opinion - there is a significant amount of clinical trials data supporting the recommendations

- USE THE GUIDELINES

HIGH EMETIC RISK PARENTERAL ANTICANCER AGENTS — ACUTE AND DELAYED EMESIS PREVENTION[h,i,j,k,l]

DAY 1: Select treatment option A, B, or C All treatment options are category 1 and should be started before chemotherapy[j]	DAYS 2, 3, 4:
Treatment option A (preferred), use the following combination: • Olanzapine 5–10 mg PO once[m,n] • NK1 RA (choose one): ▸ Aprepitant 125 mg PO once ▸ Aprepitant injectable emulsion 130 mg IV once[o] ▸ Fosaprepitant 150 mg IV once ▸ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[p] ▸ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[p] ▸ Rolapitant 180 mg PO once[q] • 5-HT3 RA (choose one):[r,s] ▸ Dolasetron 100 mg PO once ▸ Granisetron 10 mg SQ once,[t] or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of chemotherapy. ▸ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ▸ Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[u,v]	Treatment option A: • Olanzapine 5–10 mg PO daily on days 2, 3, 4[m] • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • Dexamethasone 8 mg[u,v] PO/IV daily on days 2, 3, 4
Treatment option B, use the following combination: • Olanzapine 5–10 mg PO once[m] • Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[u,v]	Treatment option B: • Olanzapine 5–10 mg PO daily on days 2, 3, 4[m]
Treatment option C, use the following combination: • NK1 RA (choose one): ▸ Aprepitant 125 mg PO once ▸ Aprepitant injectable emulsion 130 mg IV once[o] ▸ Fosaprepitant 150 mg IV once ▸ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[p] ▸ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[p] ▸ Rolapitant 180 mg PO once[q] • 5-HT3 RA (choose one):[r,s] ▸ Dolasetron 100 mg PO once ▸ Granisetron 10 mg SQ once,[t] or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of chemotherapy. ▸ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ▸ Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[u,v]	Treatment option C: • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • Dexamethasone 8 mg[u,v] PO/IV daily on days 2, 3, 4

MODERATE EMETIC RISK PARENTERAL ANTICANCER AGENTS — ACUTE AND DELAYED EMESIS PREVENTION[h,i,j,k,l]

DAY 1: Select treatment option D, E, or F. All treatment options are category 1 and should be started before chemotherapy:[j]	DAYS 2, 3:
Treatment option D, use the following combination: • 5-HT3 RA (choose one): ▸ Dolasetron 100 mg PO once ▸ Granisetron 10 mg SQ once[t] (preferred), or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of chemotherapy. ▸ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ▸ Palonosetron 0.25 mg IV once (preferred) • Dexamethasone 12 mg PO/IV once[u,v]	Treatment option D: • Dexamethasone 8 mg[u,v] PO/IV daily on days 2, 3 OR • 5-HT3 RA monotherapy[w]: ▸ Granisetron 1–2 mg (total dose) PO daily or 0.01 mg/kg (max 1 mg) IV daily on days 2 and 3 ▸ Ondansetron 8 mg PO twice daily or 16 mg PO daily or 8–16 mg IV daily on days 2, 3 ▸ Dolasetron 100 mg PO daily on days 2, 3
Treatment option E, use the following combination:[x] • Olanzapine 5–10 mg PO once[m] • Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[u,v]	Treatment option E: • Olanzapine 5–10 mg PO daily on days 2, 3[m]
Treatment option F, use the following combination:[x] • NK1 RA (choose one): ▸ Aprepitant 125 mg PO once ▸ Aprepitant injectable emulsion 130 mg IV once[o] ▸ Fosaprepitant 150 mg IV once[p] ▸ Netupitant 300 mg / palonosetron 0.5 mg (available as fixed combination product only) PO once[p] ▸ Fosnetupitant 235 mg / palonosetron 0.25 mg (available as fixed combination product only) IV once[p] ▸ Rolapitant 180 mg PO once[q] • 5-HT3 RA (choose one):[r,s] ▸ Dolasetron 100 mg PO once ▸ Granisetron 10 mg SQ once,[t] or 2 mg PO once, or 0.01 mg/kg (max 1 mg) IV once, or 3.1 mg/24-h transdermal patch applied 24–48 h prior to first dose of chemotherapy. ▸ Ondansetron 16–24 mg PO once, or 8–16 mg IV once ▸ Palonosetron 0.25 mg IV once • Dexamethasone 12 mg PO/IV once[u,v]	Treatment option F: • Aprepitant 80 mg PO daily on days 2, 3 (if aprepitant PO used on day 1) • ± Dexamethasone 8 mg[u,v] PO/IV daily on days 2, 3

LOW AND MINIMAL EMETIC RISK PARENTERAL ANTICANCER AGENTS - EMESIS PREVENTION[h,i,j,l]

Low →

Start before chemotherapy[i,j,y]
Repeat daily for multiday doses of chemotherapy

- **Dexamethasone 8–12 mg PO/IV once[l,y]**
  or
- **Metoclopramide 10–20 mg PO/IV once[l,y]**
  or
- **Prochlorperazine 10 mg PO/IV once[l,y]**
  or
- **5-HT3 RA[l,y] (select one):**
  - ◊ **Dolasetron 100 mg PO once**
  - ◊ **Granisetron 1–2 mg (total dose) PO once**
  - ◊ **Ondansetron 8–16 mg PO once**

→ Breakthrough Treatment for Chemotherapy-Induced Nausea/Vomiting (AE-10)

Minimal → **No routine prophylaxis** →

ORAL CHEMOTHERAPY - EMESIS PREVENTION[i,j,bb,cc]

High to moderate emetic risk →

Start before chemotherapy and continue daily (order does not imply preference)[y]
- **5-HT3 RA (choose one):[l]**
  - **Dolasetron 100 mg PO daily**
  - **Granisetron 1–2 mg (total dose) PO daily or 3.1 mg/24-h transdermal patch every 7 days**
  - **Ondansetron 8–16 mg (total dose) PO daily**

→ **Breakthrough Treatment for Chemotherapy-Induced Nausea/Vomiting (AE-10)**

Low to minimal emetic risk → **PRN recommended** → **Nausea/ vomiting** →

Start before chemotherapy and continue daily (order does not imply preference)[y]
- **Metoclopramide 10–20 mg PO and then every 6 h PRN[l]**

  or
- **Prochlorperazine 10 mg PO and then every 6 h PRN (maximum 40 mg/day)[l]**

  or
- **5-HT3 RA (choose one):[l]**
  - ◊ **Dolasetron 100 mg PO daily PRN**
  - ◊ **Granisetron 1–2 mg (total dose) PO daily PRN**
  - ◊ **Ondansetron 8–16 mg (total dose) PO daily PRN**

→ **Breakthrough Treatment for Chemotherapy-Induced Nausea/Vomiting (AE-10)**
and
Consider changing antiemetic therapy to higher level primary therapy for the next cycle

Breakthrough Treatment

- assess what was actually taken (medication reconciliation)
- add agents from a different drug class
  - Additional steroid for prolonged nausea in delayed phase
  - (don’t use additional 5HT3 for 3 days post-palonosetron)
  - (5HT3 likely minimally effective in delayed phase)
- use multiple concurrent agents
- IV therapy often needed (drugs, IVF)
- round-the-clock administration
- remember this for the next cycle, assess for other causes

Consider non-CINV causes

- bowel obstruction
- constipation
- vestibular dysfunction
- brain metastases
- electrolytes, dehydration
- uremia
- other drugs (opiates)
- gastro paresis (tumor or vincristine)
- anxiety, anticipatory N/V

Take Home Points

- 5-HT3 agents are the mainstay for the prevention of acute CINV in moderate to highly emetogenic regimens
- The benefit of the 5-HT3 agents (except palonset.) in delayed CINV is debated
- Steroids significantly augment 5-HT3s and should almost always be used
- NCCN recommends avoiding steroids in immunotherapy
- Aprepitant and/or olanzapine (~5mg) are indicated for highly emetogenic chemotherapy
- High therapeutic index agents: 5HT3, NK1, olanzapine
- CW: Don’t give patients starting on a chemotherapy regimen that has a low or moderate risk of causing nausea and vomiting antiemetic drugs intended for use with a regimen that has a high risk of causing nausea and vomiting.

Erythropoiesis-Stimulating Agents (ESA)

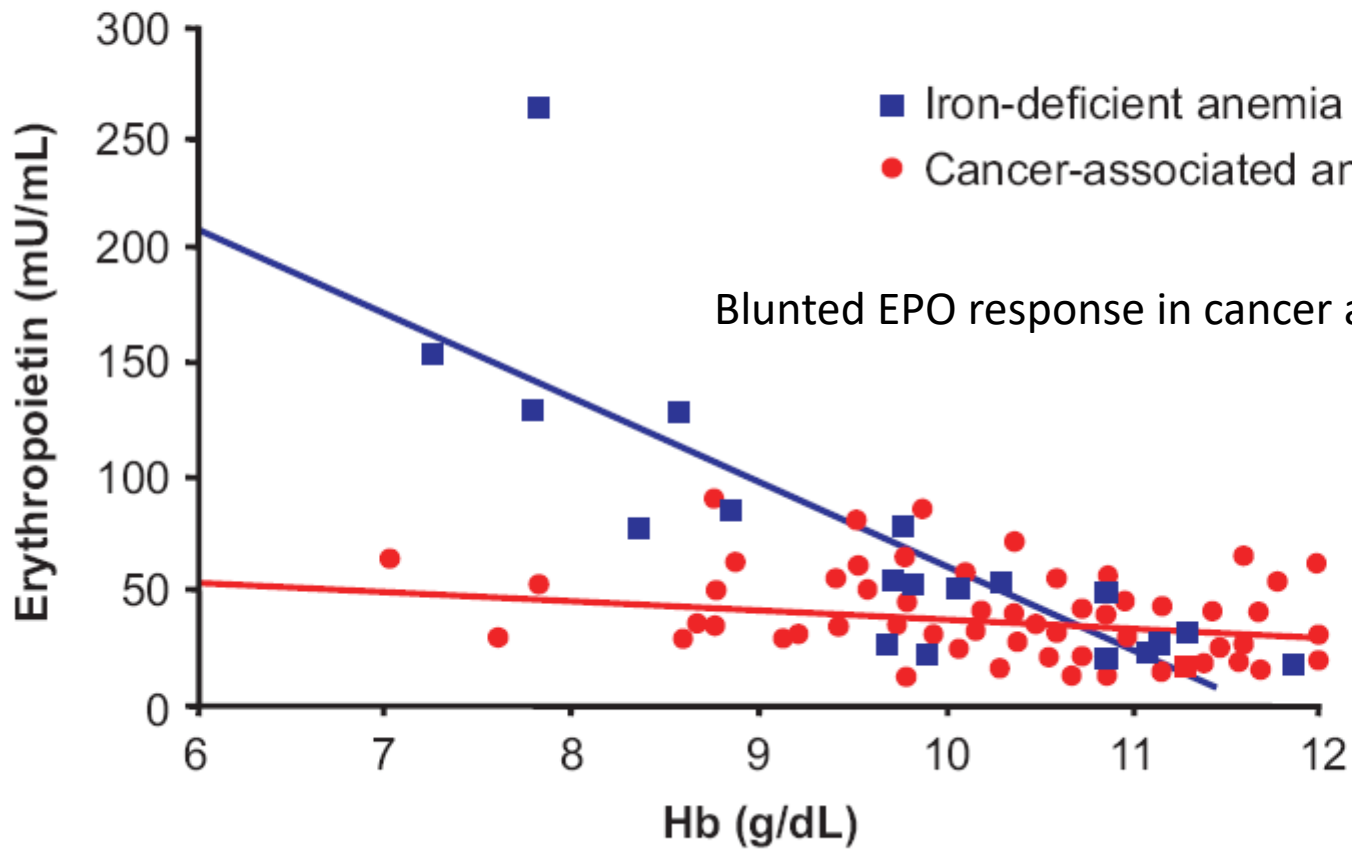
Cancer Related Anemia

- High prevalence among cancer patients
- Multifactorial
  - Inflammatory state related to cancer
  - Treatment related myelosuppression
  - BM infiltration
  - Paraneoplastic
  - Other (bleeding, nutritional, hemolysis, congenital,…)

Workup of Anemia in Ca Patients

- Screen for anemia in cancer patients
- Complete workup not always needed
- Consider: smear, BM, B12, folate, guaiac, Creat, retics
- EPO levels not recommended as they are not predictive of response
- Screening iron studies: ferritin, Fe, TIBC, TSAT

Erythropoietin Response to Anemia



Blunted EPO response in cancer associated anemia

Miller et al. *N Engl J Med*. 1990;322:1689-1692.

ESAs in solid tumor oncology

- Anemia is very common in cancer
- Linked to worse prognosis
- Worse outcomes with radiation
  - hypoxia leads to radio-resistance

- ESAs initially used in CRF, use extended to oncology
  - Reduction of transfusions, HR =0.64 in chemo patients
  - Difference between placebo was ~1 unit, NNT = 6
  - Marginal effects on QOL and fatigue
  - Utilization was quite high, but has decreased due to safety concerns

This is a controversial subject, with a vast literature

ESAs: Risks/Benefits

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Management of Cancer- and Chemotherapy-Induced Anemia

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COMPARISON OF RISKS AND GOALS OF ESA USE VERSUS RBC TRANSFUSION[h]

Discuss the following risks and goals with patients when considering anemia treatment options:

	ESA in the Cancer Setting	RBC Transfusion
Risks	• Increased thrombotic events • Possible decreased survival • Time to tumor progression shortened	• Transfusion reactions (eg, hemolytic, febrile, non-hemolytic, lung injury) • Transfusion-associated circulatory overload (TACO) • Virus transmission (eg, hepatitis, HIV) • Bacterial contamination • Iron overload • Increased thrombotic events • Possible decreased survival • Alloimmunization • Increased risk of poor response to future platelet transfusions due to HLA immunization
Goals	• Transfusion avoidance • Gradual improvement in anemia-related symptoms	• Rapid increase of Hb and hematocrit levels • Rapid improvement in anemia-related symptoms

See Erythropoietic Therapy - Dosing, Titration, and Adverse Effects (ANEM-A)

When considering ESAs:
- **Discuss the risks of ESAs with patients including the potential for tumor growth, death, blood clots, and serious heart problems.**
- **Refer patients to the following medication guides for more information on the benefits and risk of ESAs: Epoetin Alfa Medication Guide, Epoetin Alfa-epbx Medication Guide and Darbepoetin Alfa Medication Guide**

When considering RBC transfusion, see AABB Clinical Practice Guidelines: Tobian AA, Heddle NM, Wiegmann TL, Carson JL. Red blood cell transfusion: 2016 clinical practice guidelines from AABB. Transfusion 2016;56:2627-2630.

Iron deficiency

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2020
Management of Cancer- and Chemotherapy-Induced Anemia

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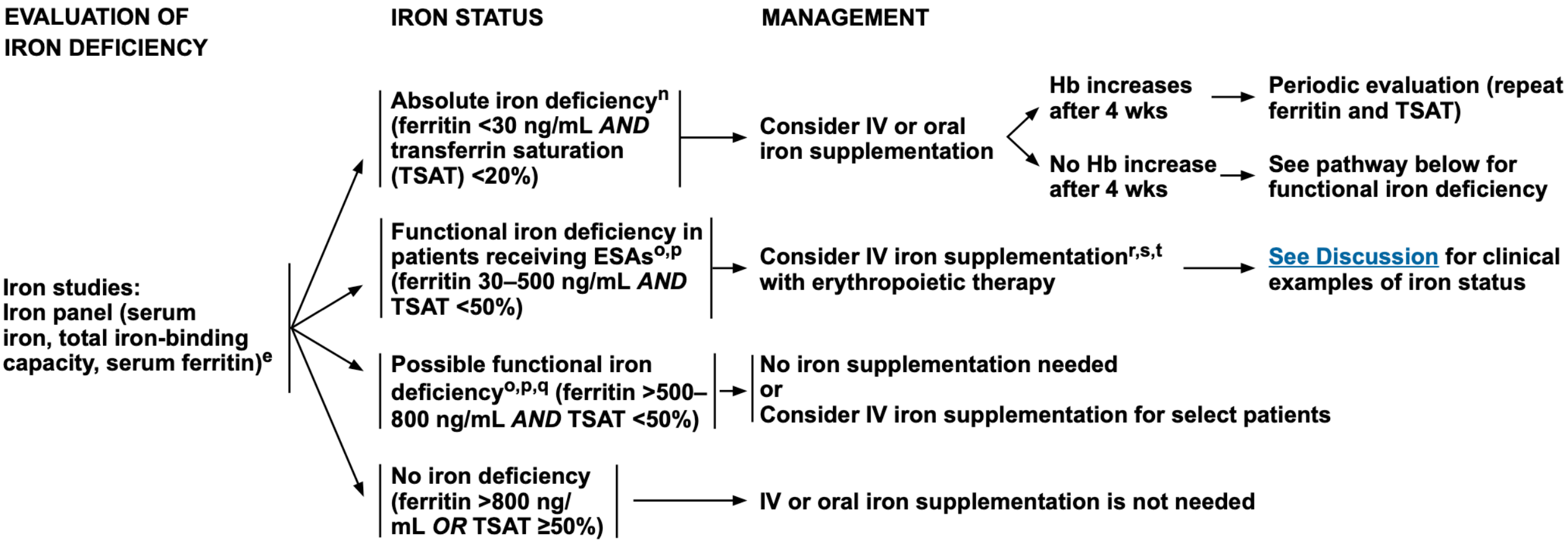
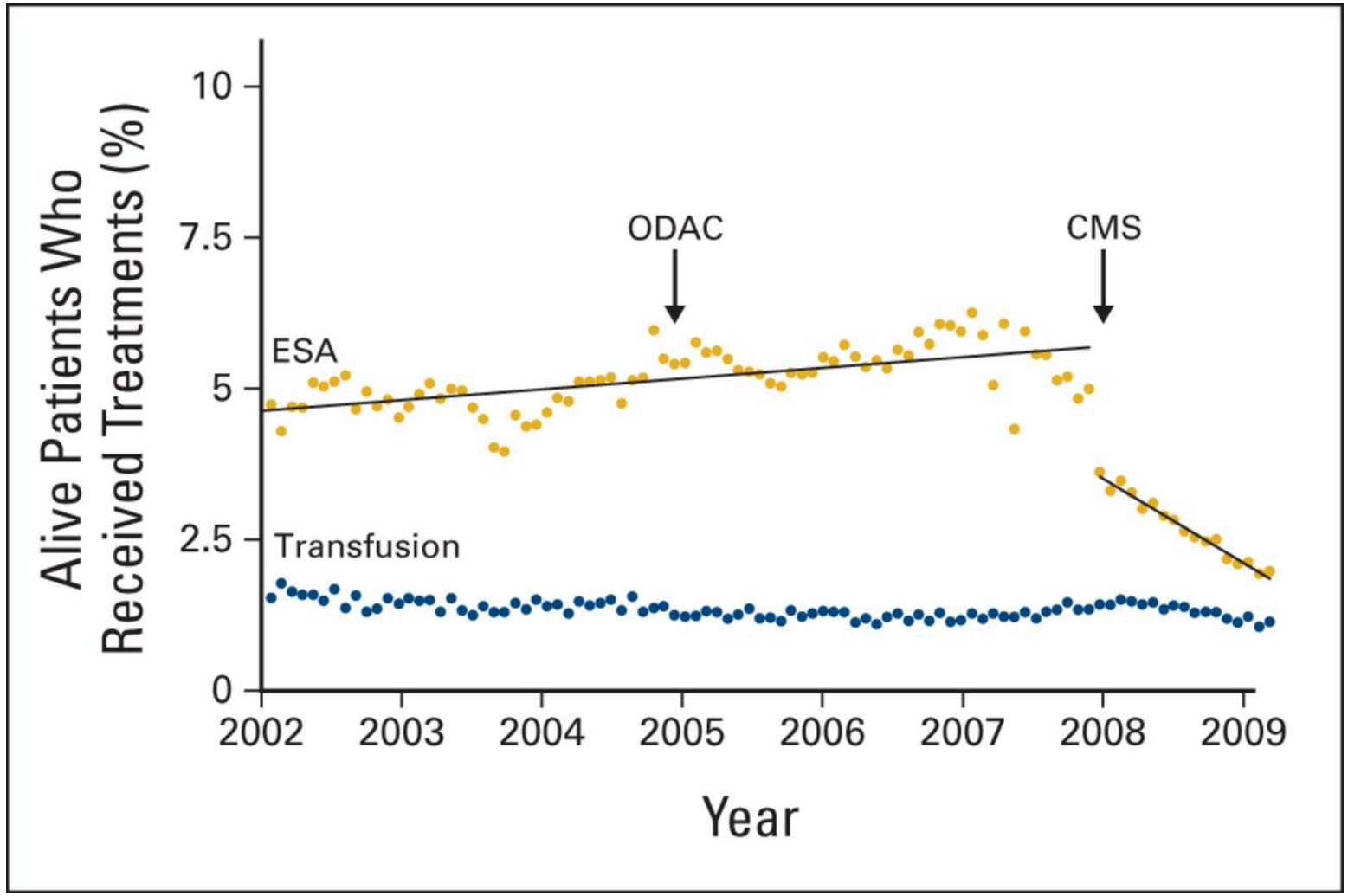


Recommendations

- No use of ESA for anemia not associated with chemotherapy
- For chemotherapy related anemia, weigh risks/benefits
- Start Hgb < 10, goal = avoid transfusion, increase < 1gm/2w
- CMS start Hgb < 10, DC for >10
- FDA indications and dosing should be used, NCCN lists alternative regimens

Percentage of patients with cancer who received erythropoiesis-stimulating agents (ESAs) per month in relation to regulatory changes.



Hershman D L et al. JOP 2014;10:264-269

Myeloid Growth Factors

Myeloid Growth Factors

- Neutropenia is a common DLT of chemotherapy
- Febrile neutropenia (FN) results in hospitalization, IV antibiotic use, decreased QOL, and morbidity
- FN risk is highest with first two cycles of a regimen
- Neutropenia may result in reductions in dose-density and intensity which can compromise outcomes
- This all can be reduced with use of myeloid CSFs

Myeloid CSFs

- Reduce risk (by ~50% for FN), severity and duration of neutropenia
- Cost-benefit threshold is now at 20% risk of FN, previously was at 40%
- Many common regimens have 25-40% FN risk in treatment naïve patients

Risk of FN – chemotherapy

- Risk is hard to define precisely
- Published trials are informative
- Guidelines (NCCN) have been published which estimate risk for regimens

Patient risk factors for neutropenia

Treatment-related

- Previous history of severe neutropenia with similar chemotherapy
- Type of Chemotherapy (anthracyclines)
- Planned relative dose intensity > 80%
- Preexisting neutropenia (< 1000) or lymphocytopenia
- Extensive prior chemotherapy
- Concurrent or prior radiation therapy to marrow containing bone

Patient-related

- Age (> 65 y)
- Female gender
- Poor performance status (ECOG ≥ 2)
- Poor nutritional status (eg, low albumin)
- Decreased immune function

Cancer-related

- Bone marrow involvement with tumor
- Advanced or uncontrolled cancer
- Elevated Lactate Dehydrogenase (Lymphoma)
- Leukemia
- Lymphoma
- Lung cancer

Conditions associated with risk of serious infection

- Open wounds
- Active tissue infection

Comorbidities

- COPD
- Cardiovascular disease
- Liver disease (elevated bilirubin, alkaline phosphatase)
- Diabetes mellitus
- Low baseline hemoglobin

From NCCN guidelines

Use of myeloid CSFs

- Risk of FN
  - >20% recommended
  - 10-20% consider
  - <10% generally not recommended
  - CW: Don’t use white cell stimulating factors for primary prevention of febrile neutropenia for patients with less than 20 percent risk for this complication.
- Also consider intent of treatment: curative, adjuvant, palliative
- Prior FN is an indication for CSFs
- Prior FN w/CSF-> dose reduction or change regimen
- Do not use with chemoradiation
- (antibiotics not recommended)

Myeloid CSF regimens

- Filgrastim
  - 5mcg/kg/d rounded to 300 or 480mcg
  - Start 1-3 days after chemo
  - Treat through post-nadir recovery
- Tbo-filgrastim, filgrastim-sndz, other biosimilars
- Pegfilgrastim, other biosimilars, OnPro®
  - 6mg/cycle
  - Start 1-3 days after chemo
  - Data for q3wk regimens, phase II data for q2wk
  - Dosing on day 1 safe, but less efficacious*
  - NCCN recommends administration on day 2

*Lyman, GH. Support Care Cancer (2017) 25:2619–2629

Adverse Effects

- Bone pain (common)
- Allergic reactions
- ARDS
- Splenic rupture (transplant setting)
- Precipitate sickle cell crisis
- MDS/AML* (increased AR 0.4%, RR 1.9)
- Cutaneous vasculitis (Sweet’s syndrome)

Bone Supportive Care

Skeletal Morbidity

- Cancer treatment induced bone loss
  - Androgen deprivation
  - Estrogen deprivation
  - Corticosteroids, TSH suppression
  - These will not be discussed further
- Bone metastases
  - Common in many cancer
  - Lung, breast, and prostate are most common

Measuring Skeletal Morbidity

- “Skeletal related event” – SRE
  - Fracture, spinal cord compression
  - Need for surgery or radiation
  - (some definitions) hypercalcemia
- QOL and pain are other outcomes of interest
- SREs are quite common, estimates are > 50% of metastatic breast cancer patients will have a SRE

Bisphosphonates

- Analogs of pyrophosphate – a major constituent of bone
- Decrease bone resorption and increase mineralization by inhibiting osteoclast activity
- Induce apoptosis in osteoclasts
- Zoledronic acid (ZA) and pamidronate are potent bisphosphonates

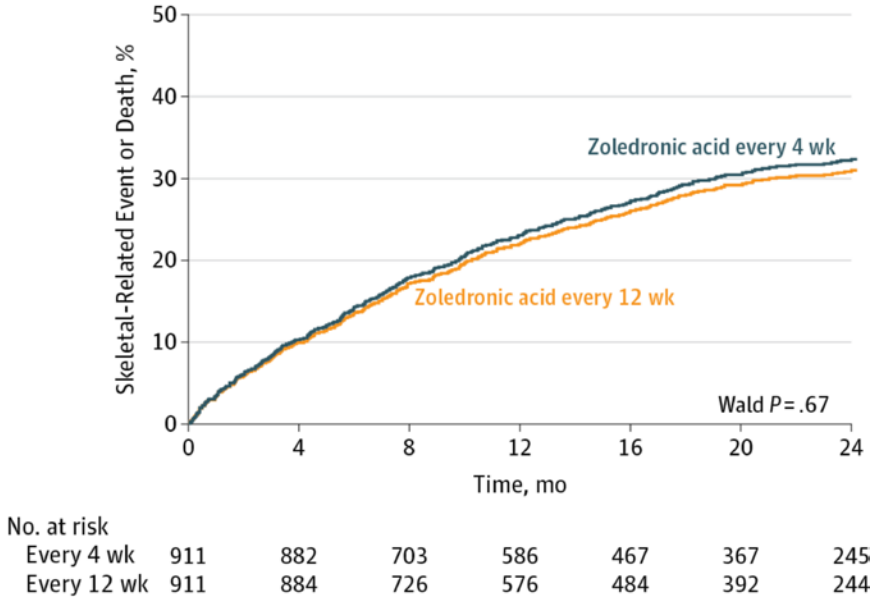
Bisphosphonates in solid tumors with established bone metastases

- Positive data is primarily for zoledronic acid (ZA)
- ZA vs. placebo in AR-prostate cancer
  - Incidence of SRE 38% vs. 49% median FU 2yrs
  - TTE was 488 vs. 321 days, benefit in pain control
- ZA vs. placebo in solid tumor
  - (no breast/prostate, mostly NSCLC)
  - Incidence of SRE 38% vs. 47%
  - TTE was 230 vs. 163 days

The JAMA Network

From: **Effect of Longer-Interval vs Standard Dosing of Zoledronic Acid on Skeletal Events in Patients With Bone MetastasesA Randomized Clinical Trial**

JAMA. 2017;317(1):48-58. doi:10.1001/jama.2016.19425



Cause-Specific Cumulative Incidence of Skeletal-Related EventsThere were 256 patients with skeletal-related events in the zoledronic acid every 4-week dose group and 246 patients in the every 12-week dose group (hazard ratio, 0.96 [95% CI, 0.81-1.15]).

Denosumab

- Monoclonal antibody targeting the RANKL which is involved in osteoclast formation and activation
- Has indications for osteoporosis and prevention of SREs in solid tumors
- Denosumab does not have renal toxicity
- Given as 120mg SQ injection q 4 weeks
- Goodrx: $2400 vs $33 for ZA

Denosumab efficacy

- All have ZA as comparator arm
- Three positive trials: breast, AR-prostate, “other”
- Denosumab vs. ZA
- Other (N=1176) MM and solid tumors (not breast or prostate), 40% were NSCLC)
  - TTE 20.6m vs. 16.3 mo.
  - P=0.03, but 0.06 after correction for multiple comparisons

ONJ - osteonecrosis of the jaw

- Presents as infection with exposed necrotic maxillary or mandibular bone
- Risks: poor dental hygiene, dental extractions/implants, chemotherapy?, anti-angiogenics?
- Incidence is ~2% for both ZA and denosumab
- Most patients who get ONJ have a risk factor (~80%)
- “Dental” exam prior to initiation
- Avoid invasive dental procedures

Comparison

Denosumab

- Expensive
- Monthly
- Ok in renal dysfunction
- Mildly improved SRE
- Rebound vertebral fractures after DC
- Hypersensitivity, neutralizing Abs
- Mild increase in infections (skin, UTI)

ZA

- Cheap
- Q 3 month
- Avoid if CrCl < 30, dose adjust; potential for renal injury
- Acute phase reaction – flu like ~50%
- conjunctivitis, uveitis, scleritis, and orbital inflammation
- Afib/flutter , stroke – RR~1.3 in SEER
- MSK pain

Common to both: hypocalcemia , ONJ, atypical fractures

Conclusions

- Use agents in patients with established bone metastases
- Aggregate data favors denosumab over ZA, but cost is high
- Among bisphosphonates ZA is the preferred agent
- Screen for ONJ risk factors prior to use
- Adverse events are similar between agents
- Supplement Ca, D, replete if deficient prior to therapy

Fatigue

- High symptom burden among cancer patients
- Some nihilism regarding treatment
- I will focus on NCCN guidelines and trials data
- “Cancer-related fatigue is a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning.”

Sources – NCCN Guidelines and Cancer-related fatigue; UpToDate

Fatigue Evaluation

- Medications
- Pain
- Emotional distress -depression
- Anemia
- Sleep disturbance
- Comorbidities – endocrine disorders, organ dysfunction
- Assessment on 0-10 scale

Interventions: non – pharmacologic

- Different interventions for different milestones in cancer treatment
- Management strategies (delegation, prioritize)
- physical activity (cat 1)
- massage therapy, CBT, educational therapies (cat 1)
- Sleep hygiene – structure, naps

Pharmacologic Interventions

- Stimulants – methylphenidate
- Modafinil
- Corticosteroids
- Ginseng

- Overall evidence is weak or mixed for these interventions, but downside is relatively low

Methylphenidate

- Of 8 RCTs, only 2 have demonstrated benefit
- Most rigorous studies were negative
- Trials were small and populations heterogeneous
- Suggestion of greater benefit with
  - Higher levels of fatigue
  - More advanced disease
  - Opioid related fatigue
  - Higher dose

Modafinil

- “Wake-promoting” agent for narcolepsy
- Initial pilot studies were encouraging
- Subsequent studies did not show overall benefit
  - N=631 evaluable, any level of fatigue, only patients with score ≥ 7 showed benefit
  - N=160 in ITT, NSCLC no benefit over placebo

Corticosteroids

- Studied in terminal stage of cancer
- Long-term side effects limit utility in patients with longer life expectancy
- N=84 RCT of advanced cancer patients with fatigue(≥4) and high symptom burden, dexamethasone 4mg bid vs. placebo
- Improved QOL and fatigue scores

J Clin Oncol. 2013 Sep 1;31(25):3076-82.

Ginseng

- N=364 cancer patients with curative intent therapy and fatigue(≥4) , RCT of ginseng 2000mg vs. PCO
- Improved fatigue at 8 week (but not 4 week)
- No discernable toxicities
- Potential for drug interactions, inhibitor of CYP3A4

J Natl Cancer Inst. 2013 Aug 21;105(16):1230-8.

Chemotherapy Induced Peripheral Neuropathy (CIPN)

- Common side effect of many agents
  - Most common in breast and colon cancer
  - Platins, taxanes, vincas, bortezomib
- Can be dose-limiting
- Potential for significant impact on QOL

CIPN

- Prevention – despite some reports demonstrating benefit, NO agent has been useful for prevention of CIPN
- Preliminary data suggests possible beneficial effect of limb cooling
- Prevention strategies are dose reduction, dose delays, and treatment breaks
- Bortezomib: Weekly vs. 2x/week and SQ vs IV is preferred
- Treatment – the only agent that has demonstrated efficacy is duloxetine
- 59% vs 38% (PCO) reported pain decrease
- Difference in decrease of pain was modest: 0.7 on a 1-10 scale
- RCT: Smith EM. JAMA. 2013 Apr 3;309(13):1359-67. PMID: 23549581

Cancer Cachexia

- Pharmacologic interventions:
- Only corticosteroids and progesterone analogs have demonstrated benefit
- Increased appetite, modest weight gain
- No effect on survival or overall QOL

Treatment of Cancer Cachexia

For patients with short life expectancy (~weeks) dexamethasone (4mg daily)

- Side effects: myopathy, Cushingoid, PUD

Megestrol 400-800mg daily for longer term

- Side effects: edema, VTE, increased mortality with doses >800mg/d
- Effect is weak, 16% of patients with >15# gain

No benefit of dronabinol in RCTs

Sources for further study

- ASCO Guidelines: Supportive Care and Treatment Related Issues; Patient and Survivor Care
- NCCN Guidelines for Supportive Care
- ESMO Clinical Practice Guidelines: Supportive and Palliative Care
- MASCC, Multinational Association for Supportive Care in Cancer
- UpToDate – multiple topics covered

thank you!

Melanoma and other skin cancers

August, 2020

UW CME Board Review Lecture

Shailender Bhatia, MD

Associate Professor, Medical Oncology

University of Washington

Fred Hutchinson Cancer Research Center, Seattle, WA

Disclosures

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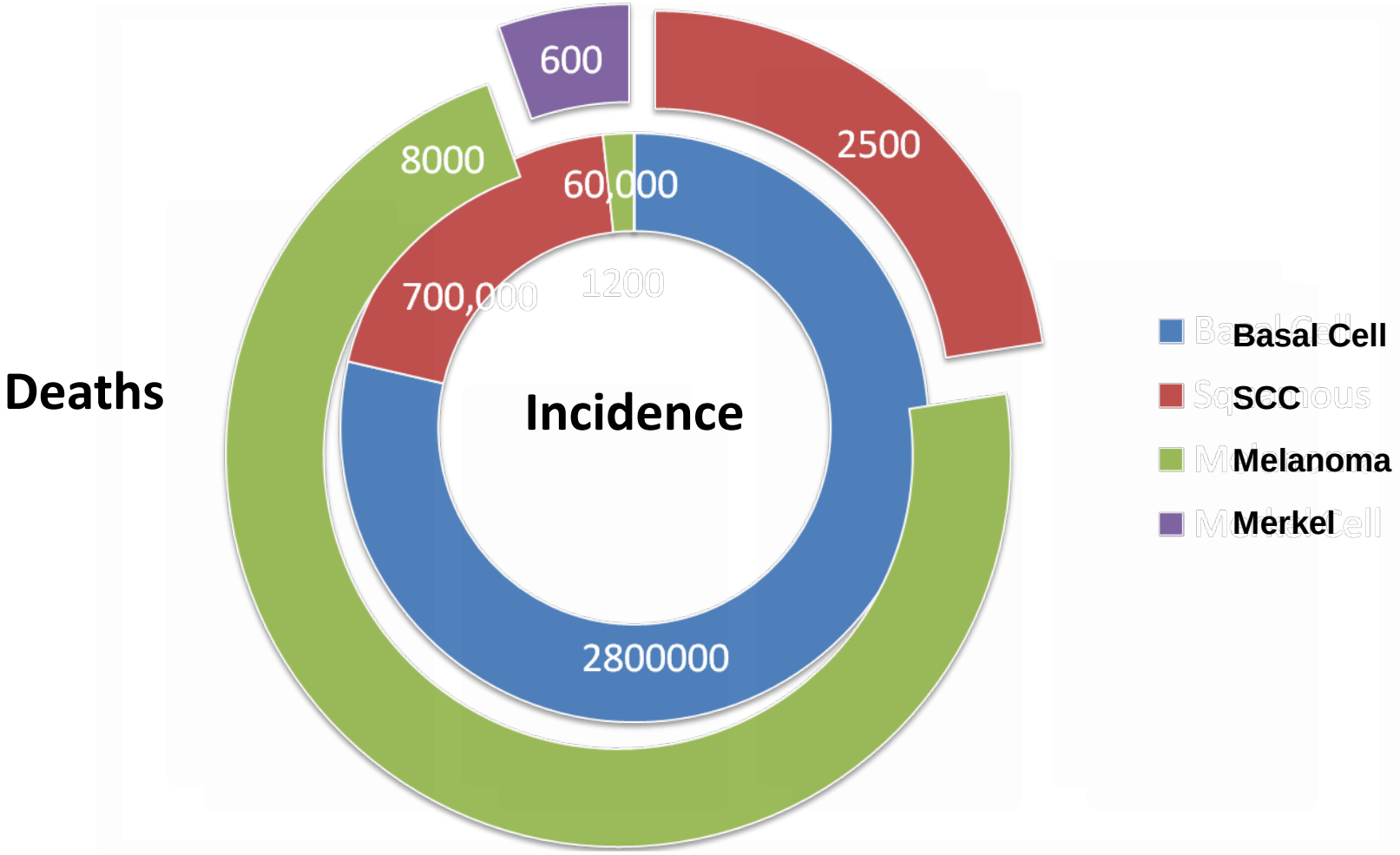
  BMS, EMD-Serono, Immune Design, Merck, Novartis, Oncosec, Nantkwest, Exicure, Nektar.

- **Advisory Board**:

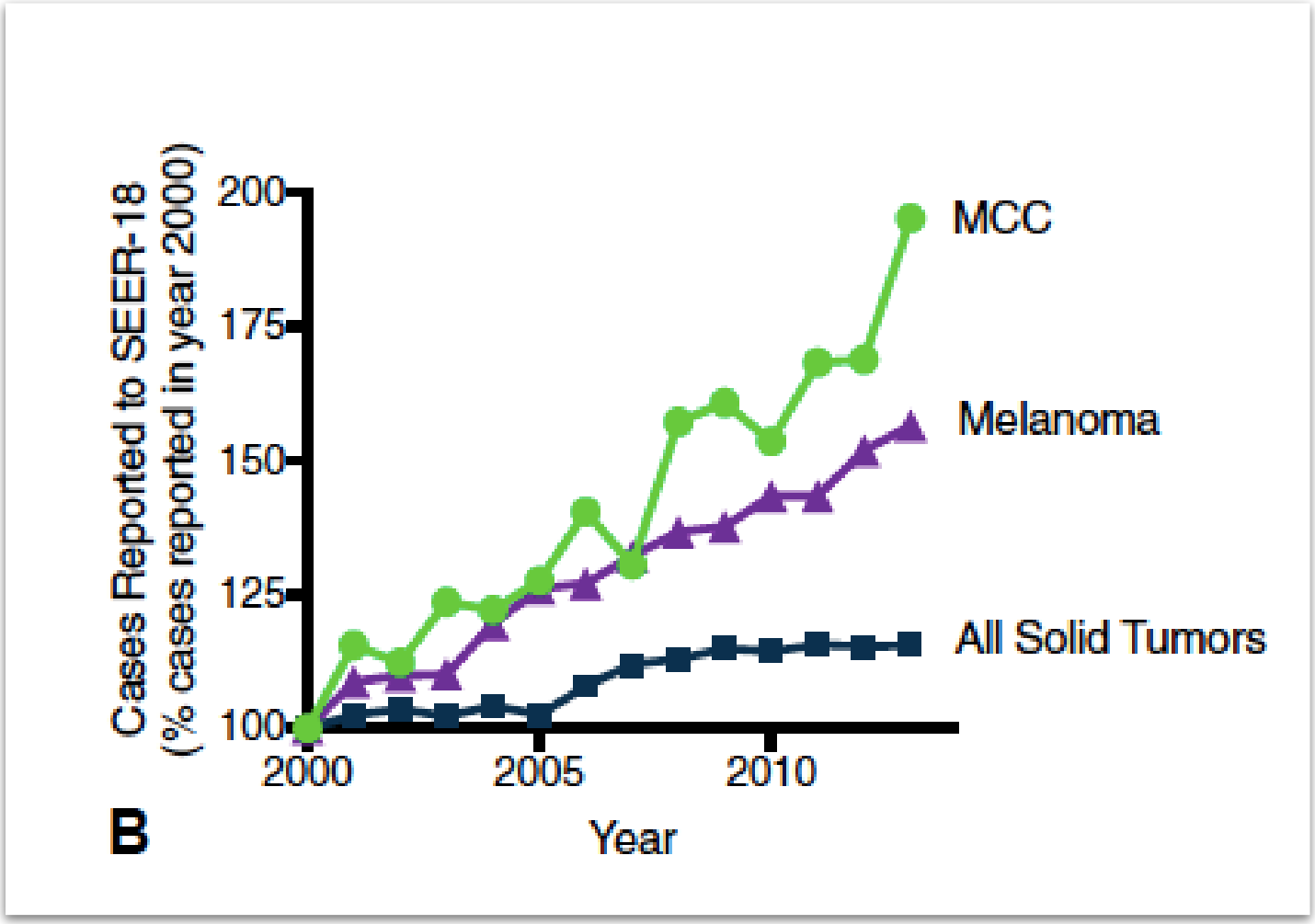
  Genentech, BMS, EMD-Serono, Sanofi-Genzyme

Skin, the largest organ, is also the most vulnerable to cancer development



NOTE: The numbers listed in this figure do not reflect the most up-to-date statistics.

The incidence of skin cancers is increasing steadily.

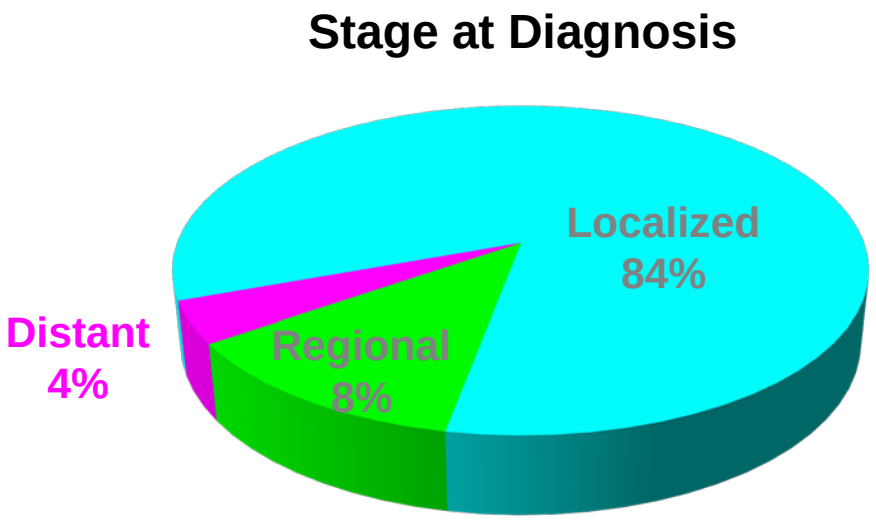


Paulson K et al. *JAAD* 2017

I. Melanoma

Incidence, Mortality and Stage Distribution of Melanoma

- 91,270 new cases of cutaneous melanoma in U.S. in **2018**
  - ~9,320 deaths
- 100,350 new cases of cutaneous melanoma in U.S. in **2020**
  - ~6,850 deaths



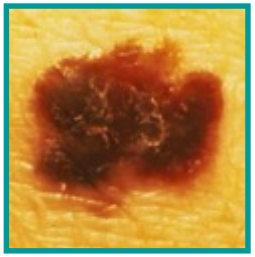
American Cancer Society. Cancer.org 2020
Siegel R. *CA Cancer J Clin*. 2018 and 2020.

The ABCDEs of Melanoma Diagnosis

Asymmetry

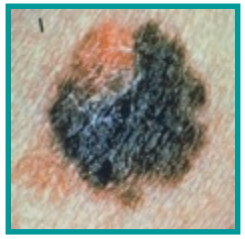
One half of the lesion is shaped differently than the other

Border



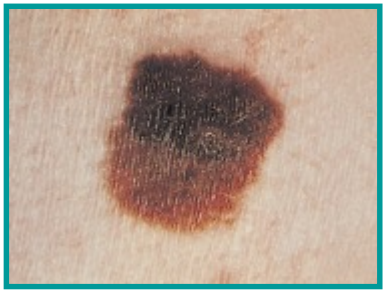
The border of the lesion is irregular, blurred, or ragged

Color



Inconsistent pigmentation, with varying shades of brown and black

Diameter



>6 mm, or a progressive change in size

Evolution

History of change in the lesion

Photos courtesy of the American Cancer Society.

Morphologic Types of Melanoma

	Type	*Frequency*	*Features*
	**Superficial spreading**	**60%-70%**	**Flat during early phase; notching, scalloping, areas of regression**
	**Nodular**	**15%-30%**	**Darker and thicker than superficial spreading, rapid onset; commonly blue-black or blue-red (5% amelanotic)**
	**Lentigo maligna**	**~5%**	**Enlarge slowly; usually large, flat, tan or brown**
	**Acral lentiginous**	**Uncommon Asians (46%), Blacks (70%)**	**On soles, palms, beneath nail beds; usually large, tan or brown; irregular border; subungual melanoma more common in older, dark-skinned people**
	**Desmoplastic**	**1.7%**	**Rare, locally aggressive, occur primarily on head and neck in elderly**

Data from Lotze MT, et al. *Cutaneous Melanoma.* In: DeVita VT Jr,. et al, eds. *Cancer: Principles & Practice of Oncology.* 6th ed. Philadelphia, PA: Lippincott-Raven; 2001.

Wide Local Excision (WLE)

PRINCIPLES OF SURGICAL MARGINS FOR WIDE EXCISION OF PRIMARY MELANOMA

Tumor Thickness	Recommended Clinical Margins[2]
In situ[1]	0.5–1.0 cm
≤1.0 mm	1.0 cm (category 1)
>1.0–2 mm	1–2 cm (category 1)
>2.0–4 mm	2.0 cm (category 1)
>4 mm	2.0 cm (category 1)

Margins may be modified to accommodate individual anatomic or functional considerations.

NCCN Guidelines version 3.2018

Sentinel Lymph Node Biopsy (SLNB)

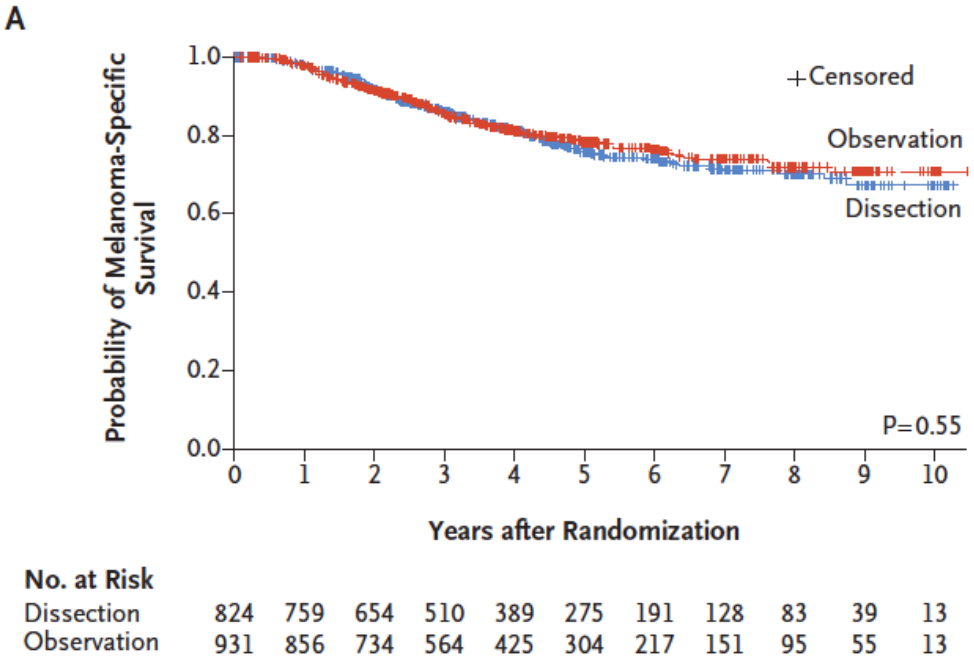
In patients with clinical stage I/II melanoma, SLN status is the strongest predictor of, but does not impact, survival.

Breslow Thickness (mm)	Mitotic rate		Ulceration		Adverse factors*	
	$<1/mm^2$	$\geq 1/mm^2$	No	Yes	No	Yes
≤ 0.8	No	Consider	No	Consider	No	Consider
0.8-1.0	Consider	Consider	Consider	Consider	Consider	Consider
>1.0	Offer	Offer	Offer	Offer	Offer	Offer

* Adverse features include positive margins, Lympho-vascular invasion (LVI), or a combination of these factors

NCCN Guidelines version 3.2018

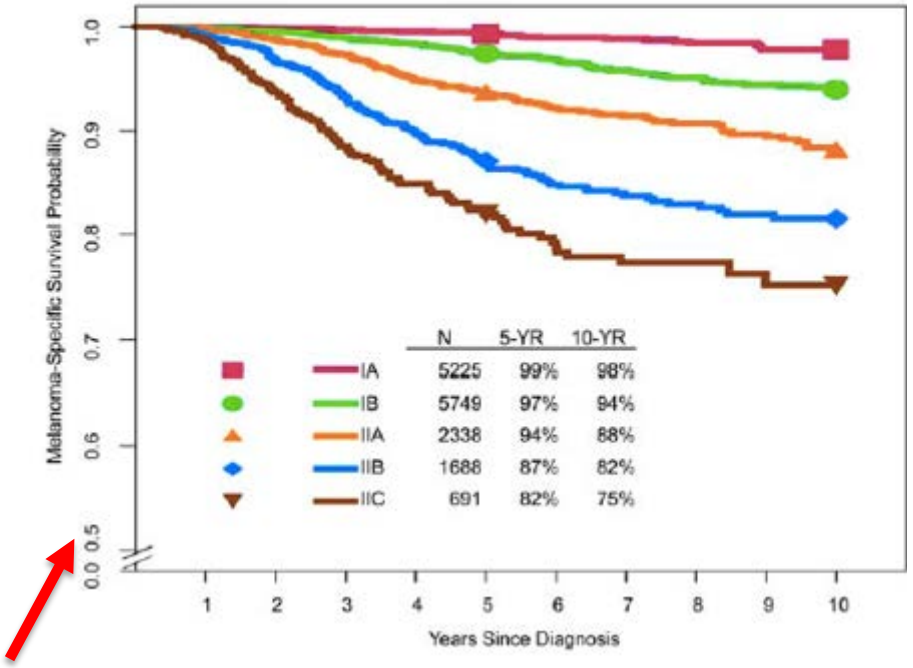
Completion Lymph Node Dissection (CLND)

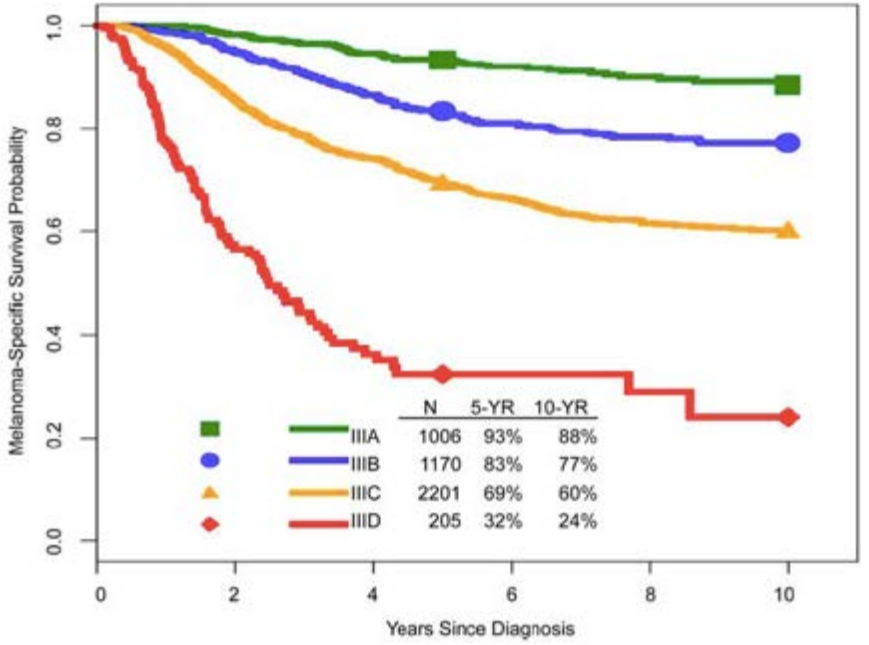


CONCLUSIONS

Immediate completion lymph-node dissection increased the rate of regional disease control and provided prognostic information but did not increase melanoma-specific survival among patients with melanoma and sentinel-node metastases. (Funded by the National Cancer Institute and others; MSLT-II ClinicalTrials.gov number, NCT00297895.)

Despite aggressive surgery, metastatic disease is frequent and life-threatening.





NOTE: These figures include data reflected in the **AJCC 8th edition staging** system

[Gershenwald J et al. *CA Cancer J Clin* 2017]

Metastatic Melanoma (Stage IV)

Until 2011, few effective systemic therapy options existed.

US-FDA approved therapies for metastatic melanoma prior to 2011.

Dacarbazine (1975)

High-dose IL-2 (1998)

} No proven OS benefit

Treatment of Metastatic Melanoma: An Overview
Bhatia S et al. ONCOLOGY. 2009; 23:6; 488-500

Since 2011, multiple new drugs have been FDA-approved.

IMMUNOTHERAPY

Ipilimumab (2011)

Pembrolizumab (2014)

Nivolumab (2014)

Ipilumumab + Nivolumab (2015)

TVEC (2015)

CHEMOTHERAPY

Vemurafenib (2011)

Dabrafenib (2013)

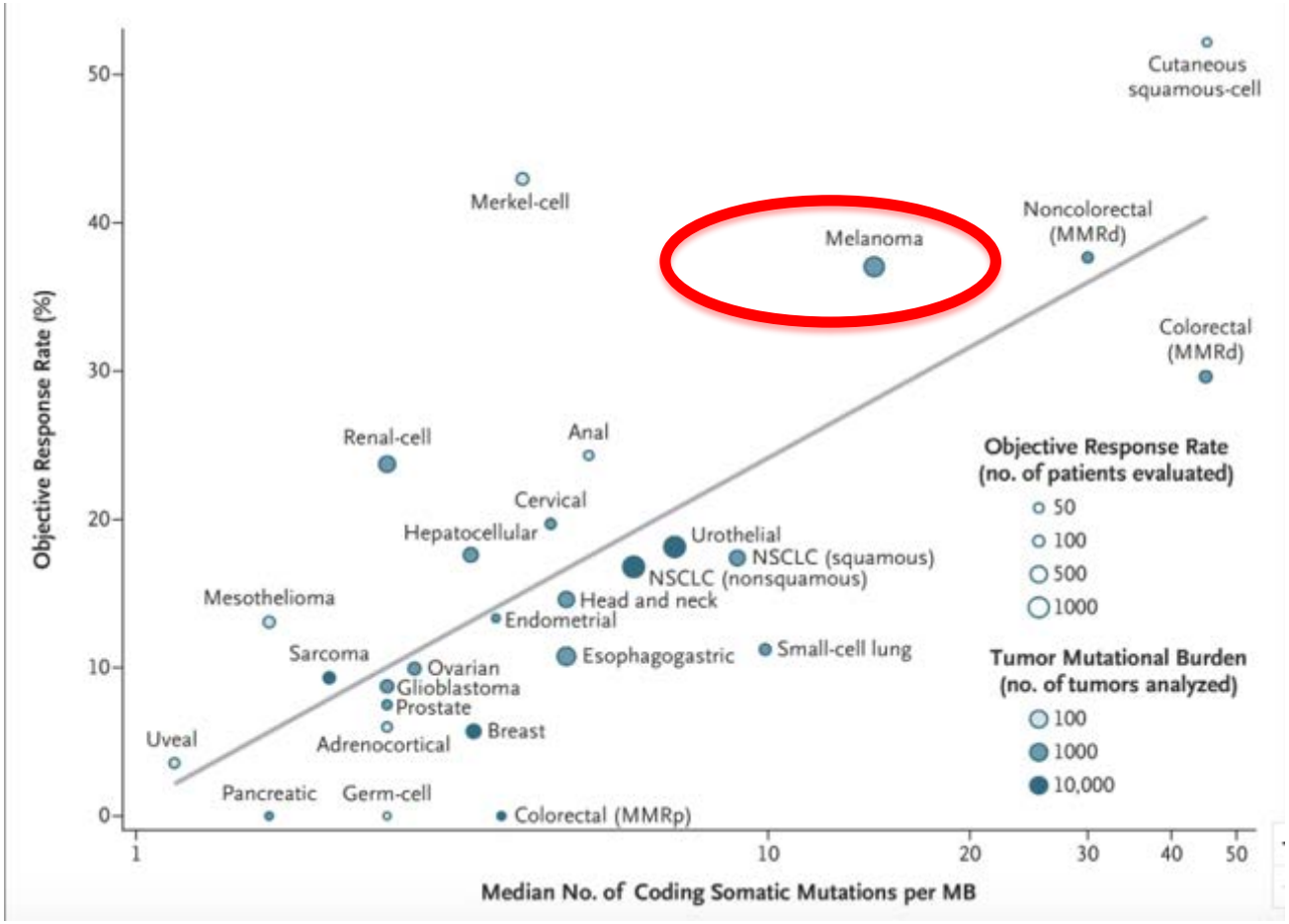
Trametinib (2013)

Dabrafenib + Trametinib (2014)

Vemurafenib + Cobimetinib (2015)

Encorafenib + Binimetinib (2018)

Immunogenicity of melanoma: High mutational burden (Neoantigens)



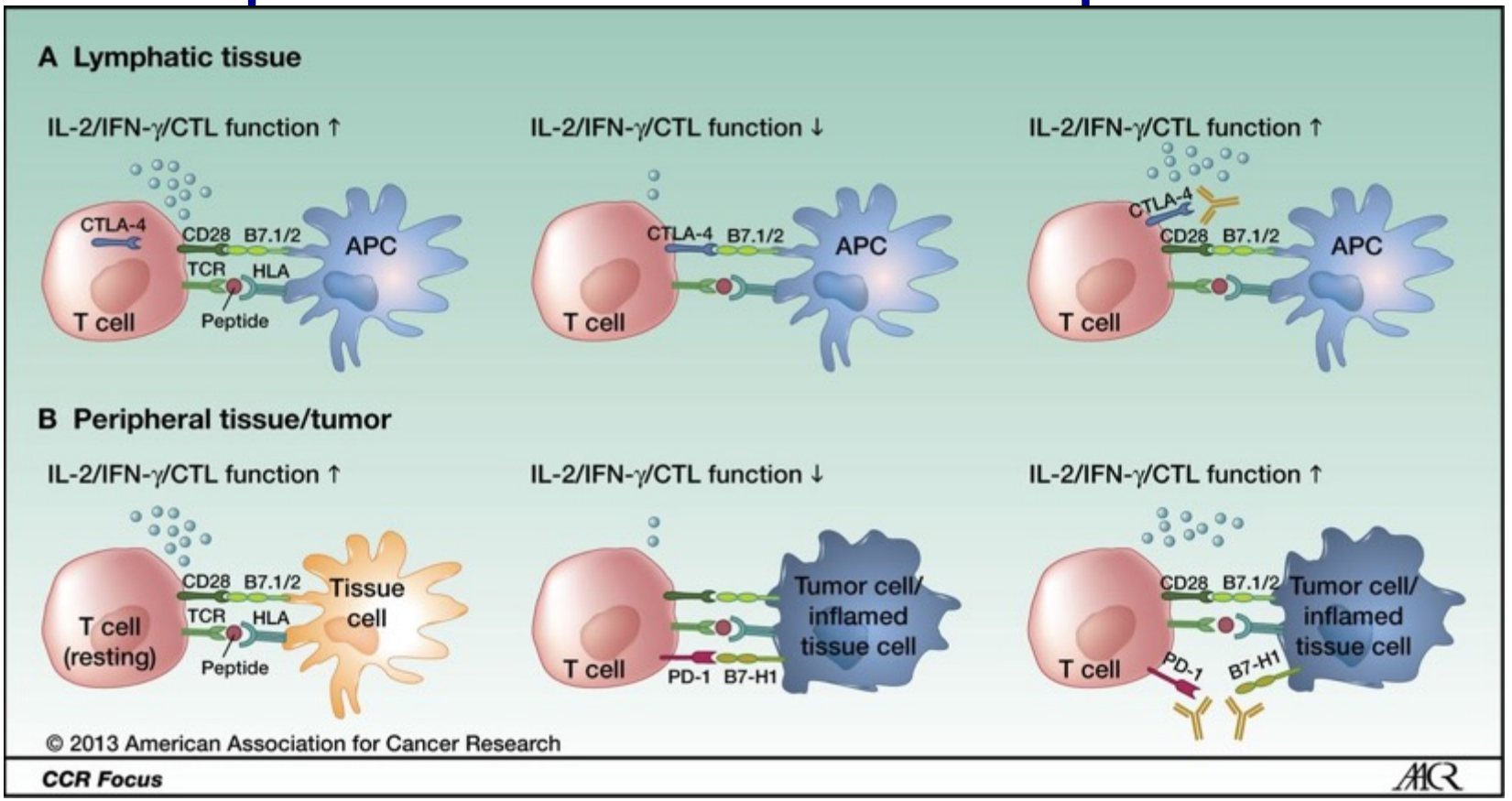
[Yarchoan M *NEJM* 2017]

IMMUNOTHERAPY

Anti-PD-1 agents (as monotherapy or in combination with ipilimumab) are regarded as the current standard-of-care for immunotherapy of metastatic melanoma.

- Pembrolizumab
- Nivolumab

CTLA-4 and PD-1 modulate different aspects of the T-cell response

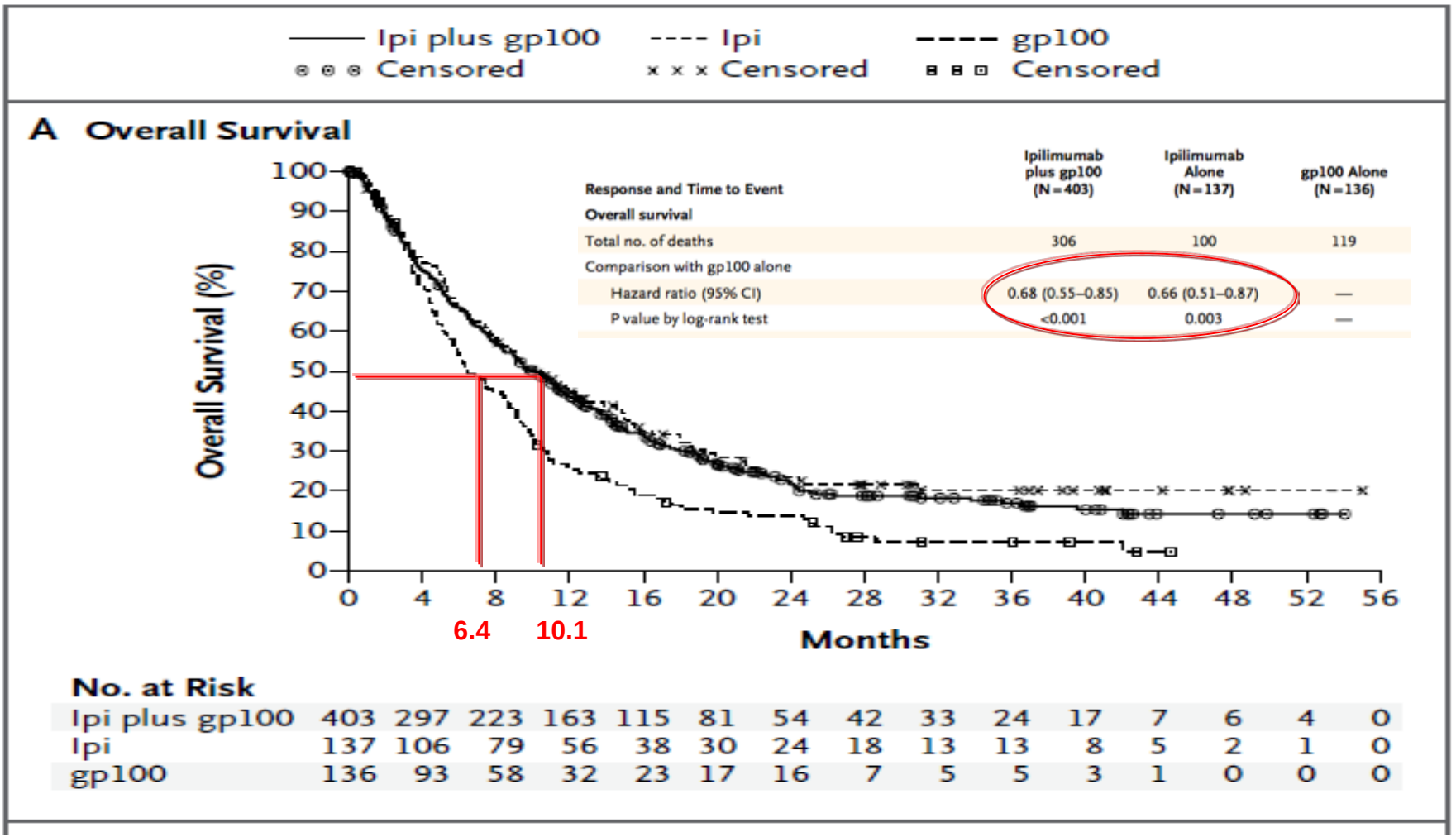


A, CTLA-4 is upregulated after antigen-specific activation of a naïve or memory T cell in lymphatic tissue, leading to decreased effector function (early activation phase).

B, PD-1 is mainly expressed on antigen-experienced memory T cells in peripheral tissues cells. Tumor cells use this regulatory mechanism to evade a tumor-directed T-cell response by upregulating the PD-1 ligands.

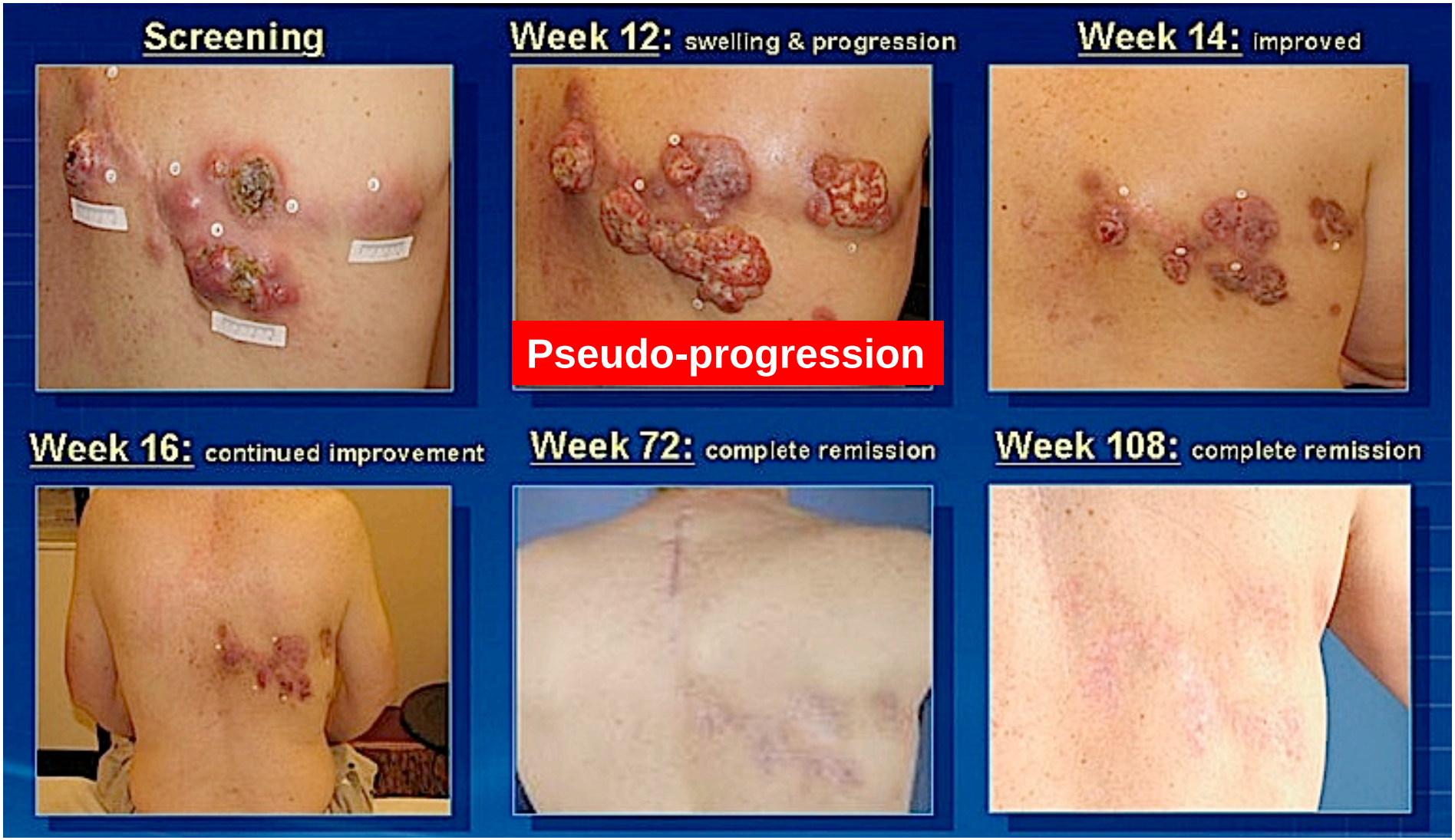
[Patrick A. Ott et al. Clin Cancer Res 2013;19:5300-5309]

Improved Overall Survival was seen in both the Ipilimumab arms (3 mg/kg q3 wks x4)



Hodi FS et al. NEJM. 2010

Ipilimumab: Impressive clinical responses



Pembrolizumab versus Ipilimumab: Improved efficacy with Lower toxicity

	Response rate (%)	Grade 3 or higher IRAE (%)
Ipilimumab	12	20
Pembrolizumab	33	10

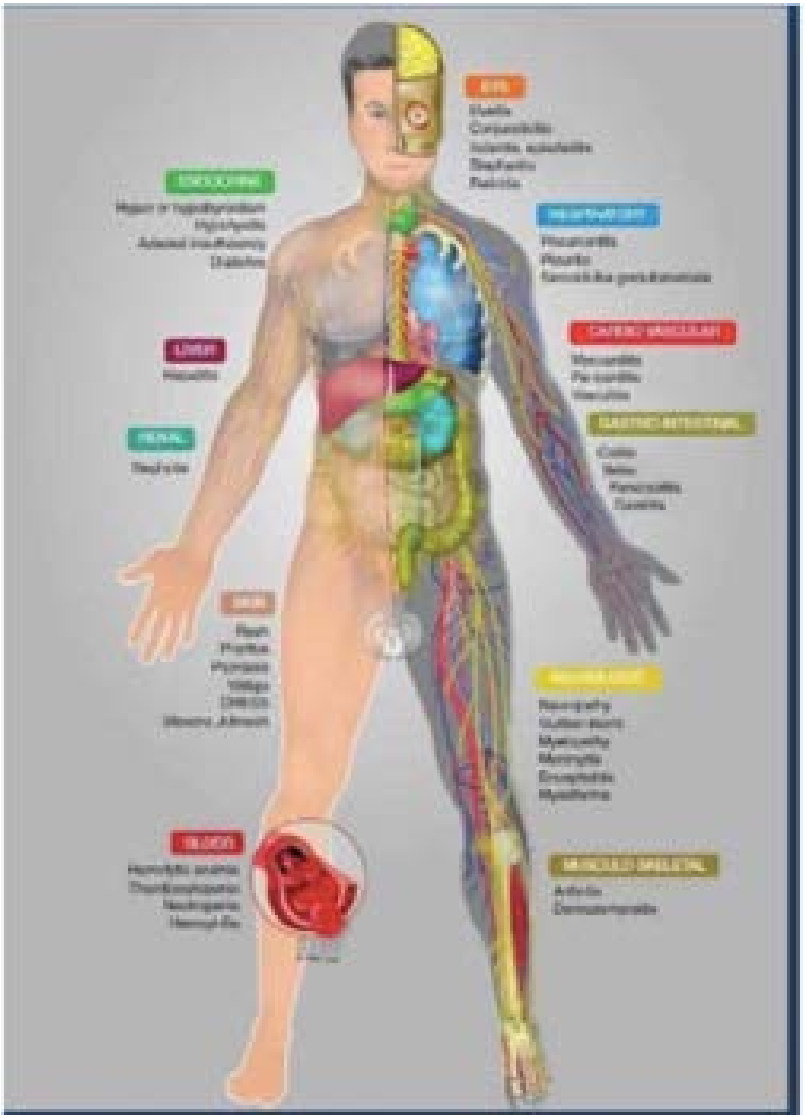
[Robert C et al. NEJM]

Nivolumab versus Ipilimumab

	Response rate (%)	Grade 3 or higher IRAE (%)
Ipilimumab	19	27
Nivolumab	44	16

[*Larkin J et al* NEJM *2015*]

Immune-related Adverse events (IRAEs)



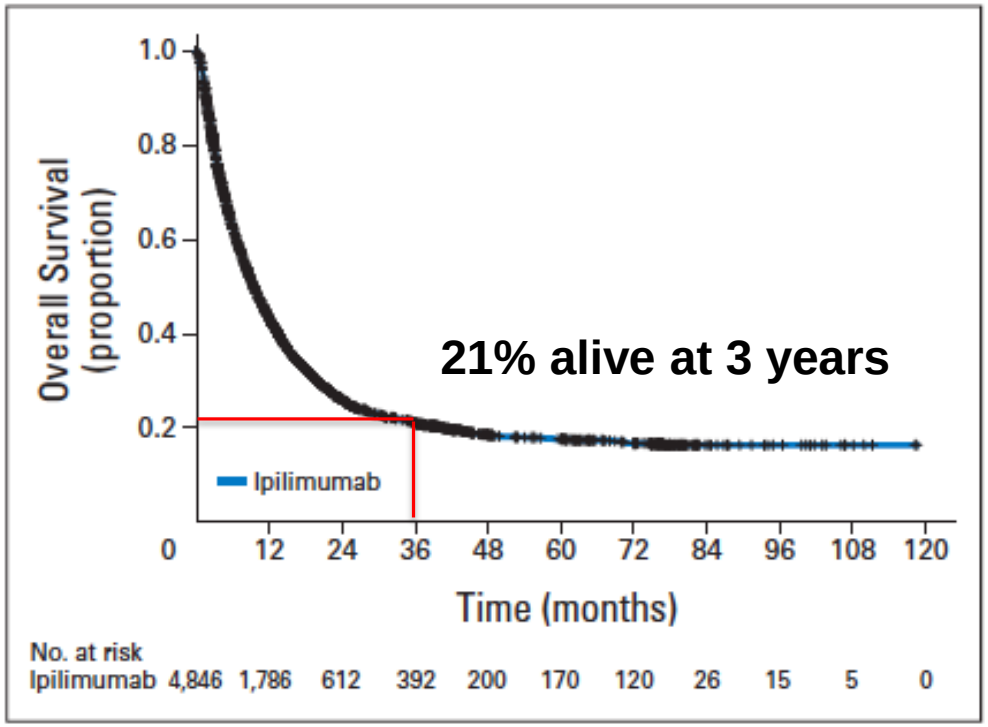
- Risk of Death (~1%)
- Permanent side-effects affecting QoL (hypophysitis, type I DM, neuropathy)
- Require careful counseling, close monitoring, and aggressive management.
- NCCN guidelines exist.

Efficacy of nivolumab is comparable in BRAF-mut and BRAF-WT melanoma

Variable	*BRAF* WT (n = 217)	*BRAF* Mut (n = 74)
Best overall response, No. (%)		
Complete	9 (4.1)	2 (2.7)
Partial	66 (30.4)	20 (27.0)
Stable disease	53 (24.4)	13 (17.6)
Progressive disease	74 (34.1)	33 (44.6)
Unknown	15 (6.9)	6 (8.1)
Objective response rate, % (95% CI)[a]	34.6 (28.3-41.3)	29.7 (19.7-41.5)
Mut over WT, OR (95% CI)	0.8 (0.5-1.4)	
Time to objective response, mo		
Median (range)	2.2 (1.6-14.8)	2.2 (1.7-7.9)
Mean (SD)	3.3 (2.2)	3.0 (1.7)
Duration of objective response, median (95% CI) [range], mo[b]	14.8 (11.1-24.0) [1.4-30.5]	11.1 (7.3-22.9) [2.8-27.6]

[*Larkin J et al* JAMA Oncol *2015*]

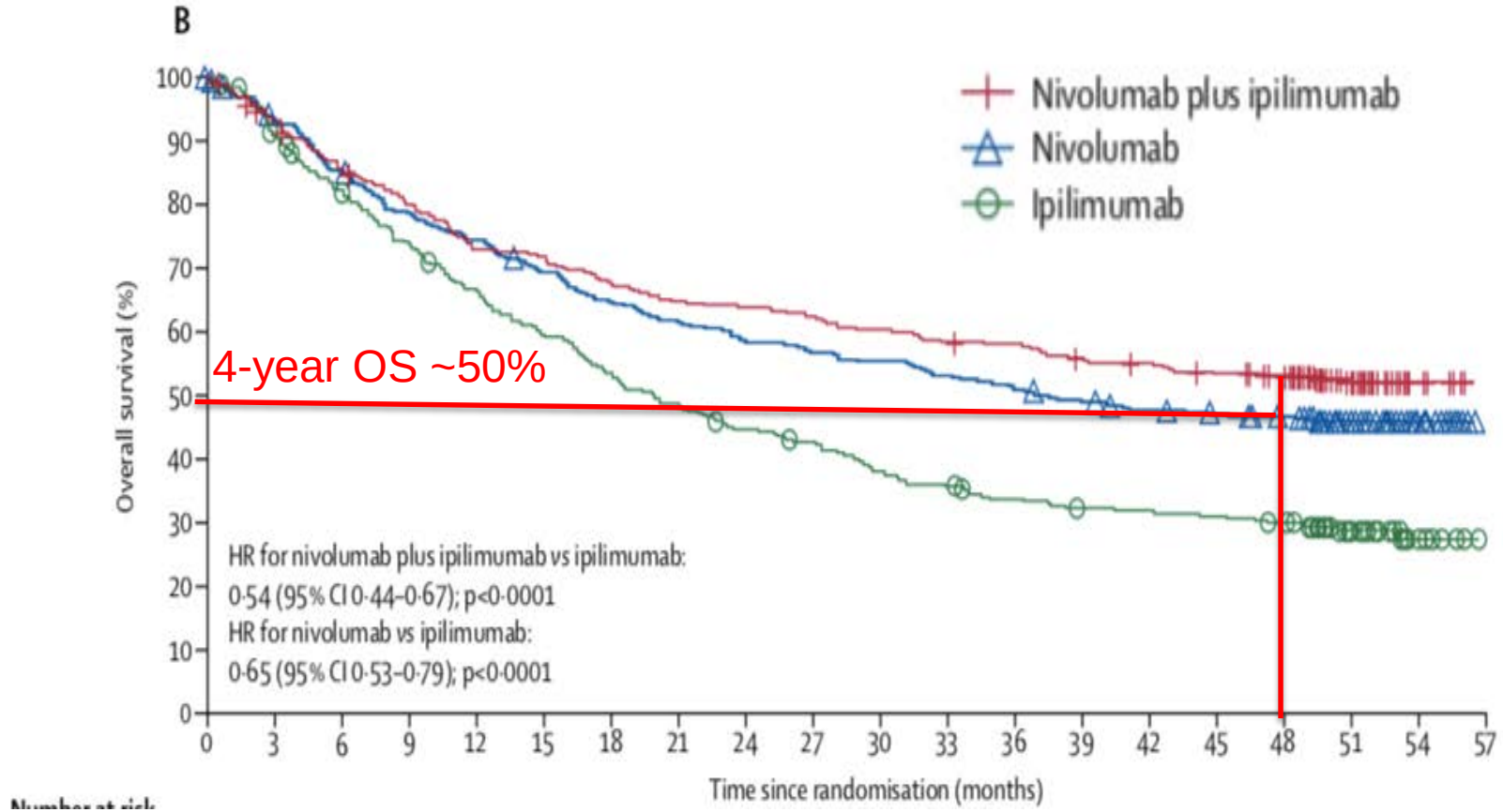
Potential for long-term survival with immunotherapy



- Retrospective analysis of 4,846 patients treated with Ipilimumab on several clinical trials.

[Schadendorf D et al. 2015 *JCO*]

Long-term survival with PD-1-blockade



[*Hodi FS et al* Lancet Oncol *2018*]

Ipilimumab *plus* Nivolumab combination

Combination was approved by the US FDA in **September 2015**

Approved dose is Ipilimumab 3 mg/kg plus Nivolumab 1 mg/kg administered IV every 3 weeks x 4 doses [**Induction**] followed by Nivolumab 3 mg/kg administered IV every 2 weeks [**Maintenance**].

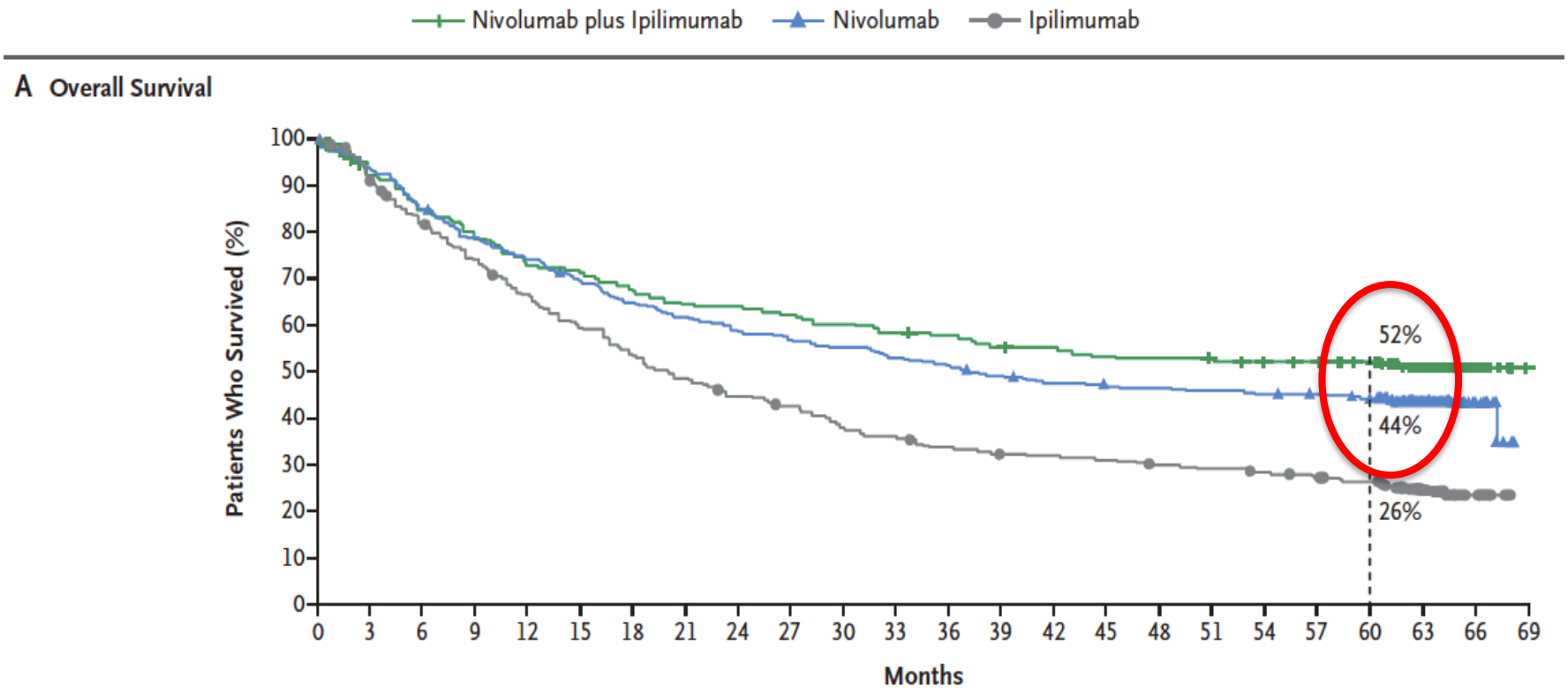
Systemic immunotherapy: Outcomes in melanoma

	Response rate (%)	Grade 3 or higher IRAE (%)
Ipilimumab	19	27
Nivolumab	44	16
Ipi plus Nivo	58	**55**

[*Larkin J et al* NEJM *2015*]

Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.-J. Grob, P. Rutkowski, C.D. Lao,

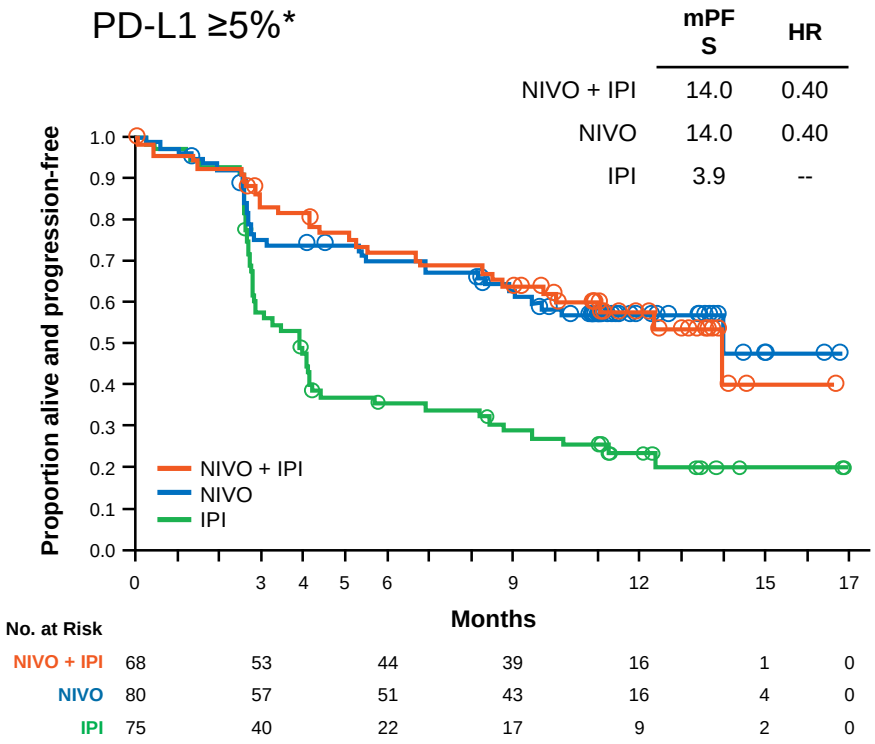


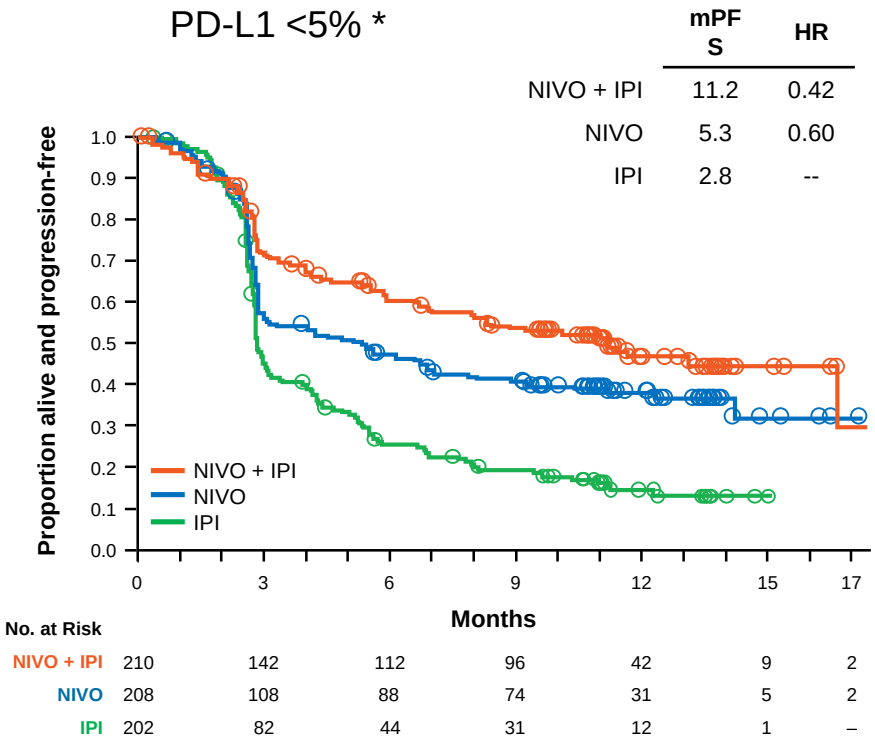
No. at Risk

Nivolumab plus ipilimumab	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
Nivolumab	316	292	266	245	231	214	201	191	181	175	171	164	158	150	145	142	141	139	137	135	130	78	14	0
Ipilimumab	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

DOI: 10.1056/NEJMoa1910836

Ipi plus Nivo: PFS by PD-L1 Expression Level





*Per validated PD-L1 immunohistochemical assay with expression defined as ≥5% of tumor cells showing PD-L1 staining in a section of at least 100 evaluable tumor cells.

My conclusions on Immunotherapy

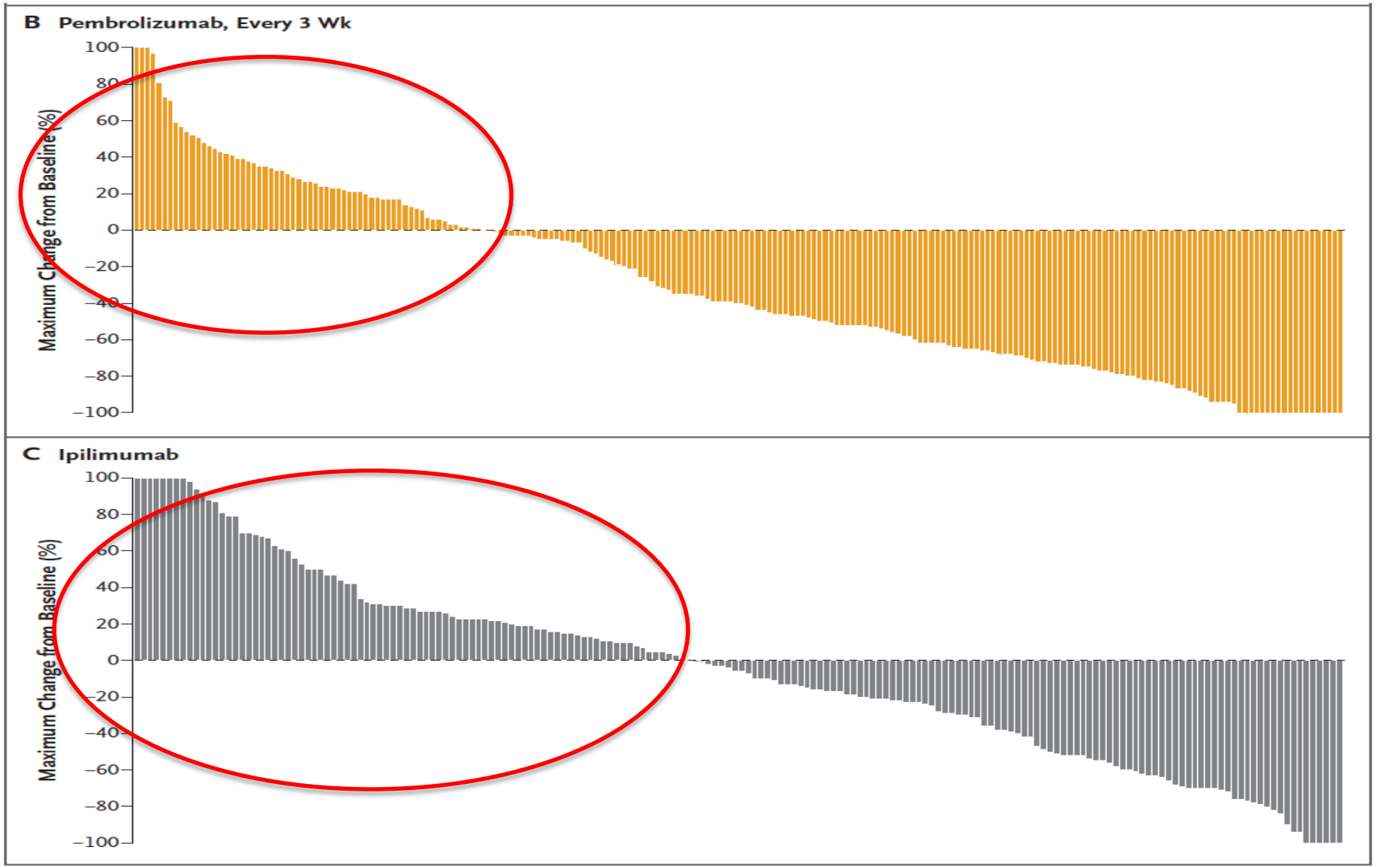
1. Immunotherapy leads to **durable responses and long-term survival** in a subset of melanoma patients, regardless of BRAF status.

2. **PD-1 monotherapy is superior to Ipilimumab** (better efficacy; lesser toxicity)

3. **Ipi-Nivo has higher ORR (and toxicity), but no significant survival benefit** over nivolumab; utility of PDL-1 for selecting patients warrants further confirmation.

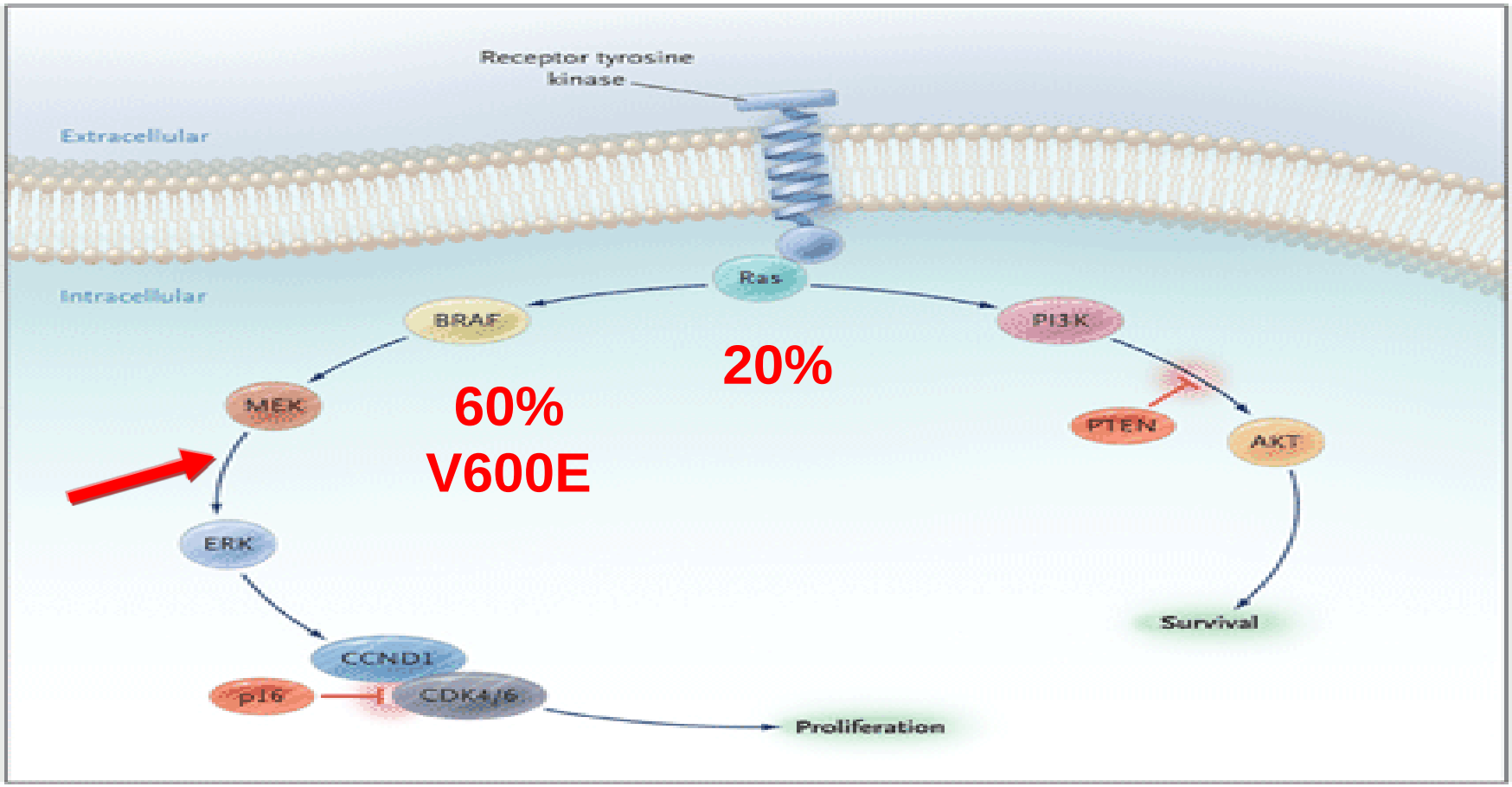
4. Clinical decisions must be individualized based on patient's desire for aggressive therapy and risk tolerance.

Immunotherapy does not work all the time



[Robert C et al. NEJM]

Mutations in BRAF and NRAS are frequent in cutaneous melanomas



[Curtin JA et al. NEJM 2005]

Multiple targeted agents are efficacious in BRAF-mutated melanoma

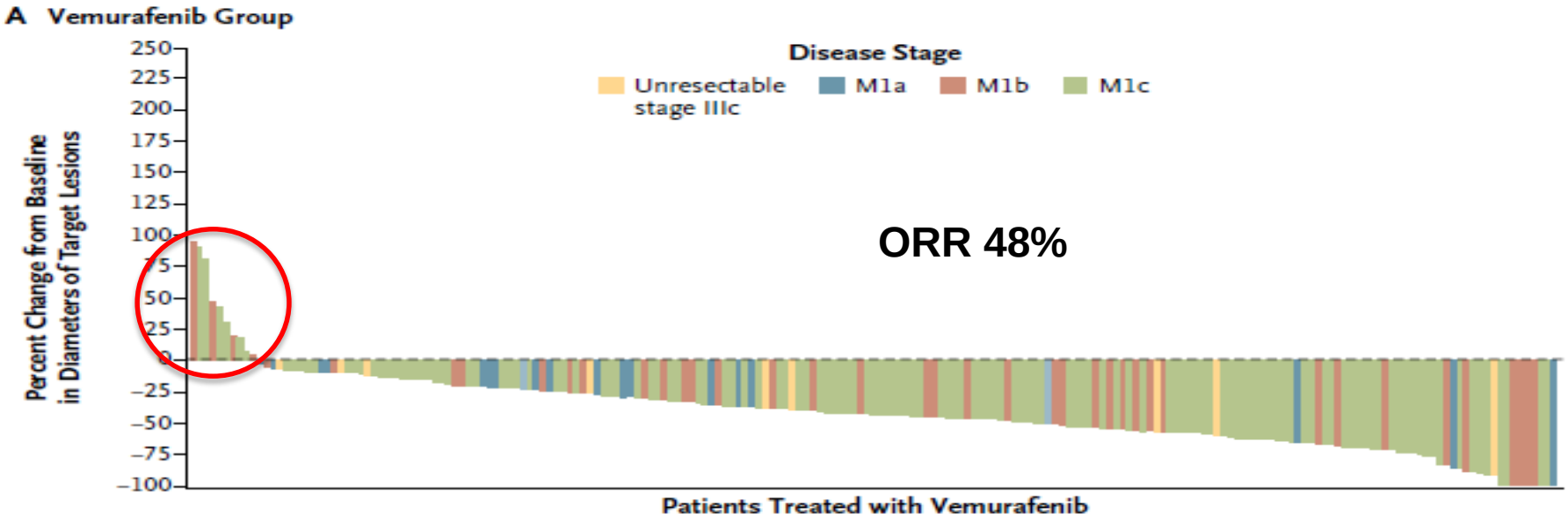
BRAFi

- Vemurafenib
- Dabrafenib
- Encorafenib

MEKi

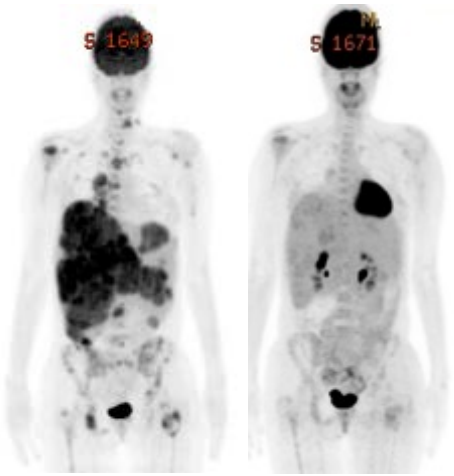
- Trametinib
- Cobimetinib
- Binimetinib

BRAFi (+/-MEKi) are associated with tumor regressions in **vast majority** of patients with BRAF-mutant melanoma

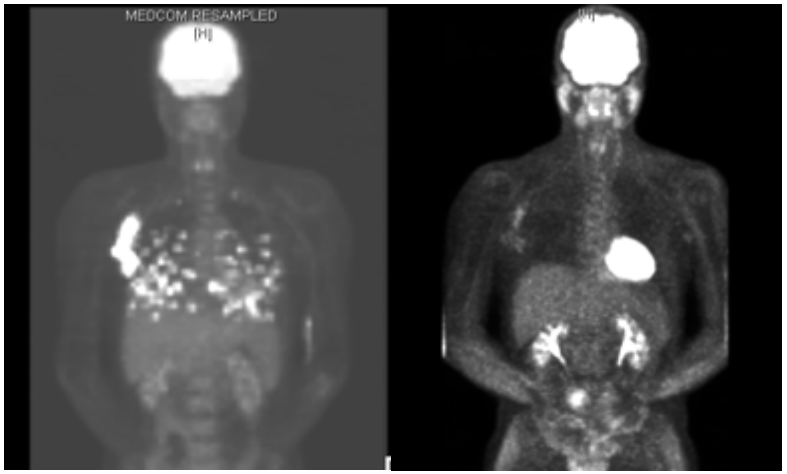


[Chapman P et al. NEJM. 2011]

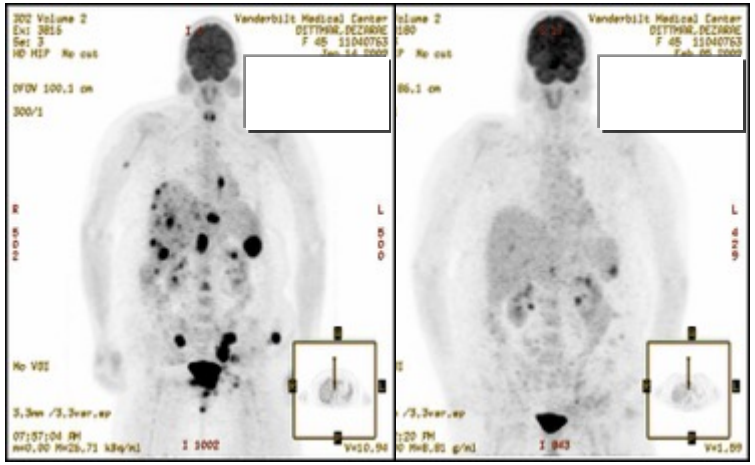
Onset of tumor regression is **fairly rapid** with BRAFi (median TTR ~6 weeks)

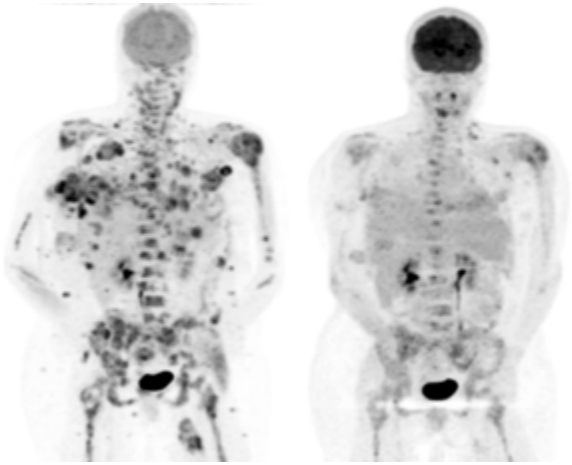


Baseline Day 15

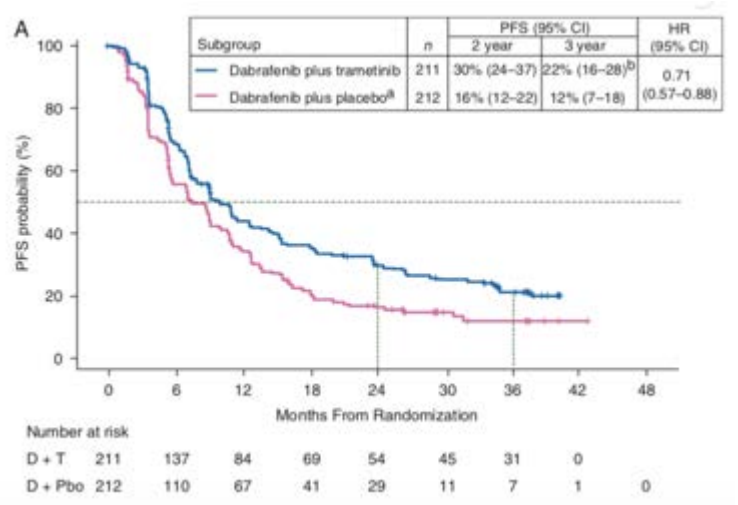


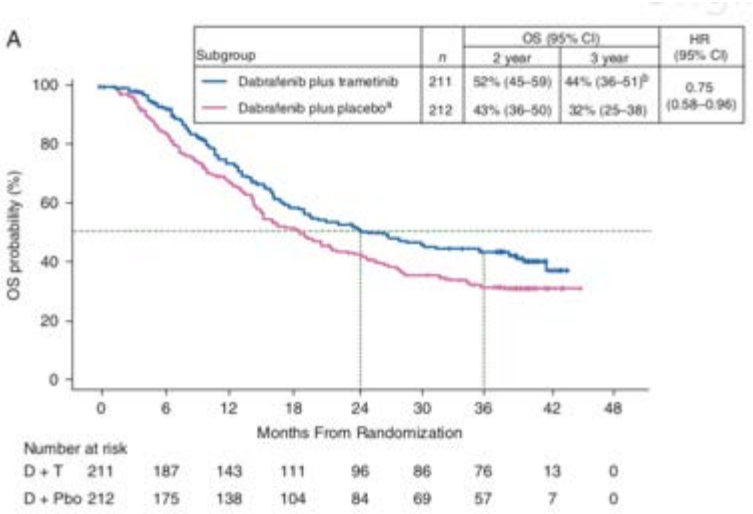
Baseline Day 15





BRAFi + MEKi more efficacious (and not more toxic) than BRAFi alone



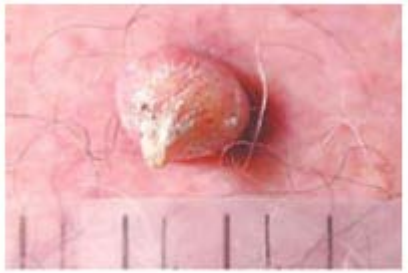


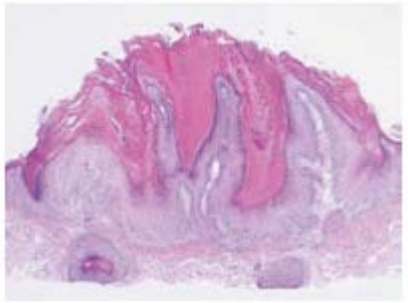
TOXICITY

- Rate of Grade 3 or higher AEs similar in D+T (48%) vs D (50%) arms
- Pyrexia/chills, GI toxicities, edema higher in D+T arm
- SCC/KA, hyperkeratosis, Skin papillomas higher in D arm

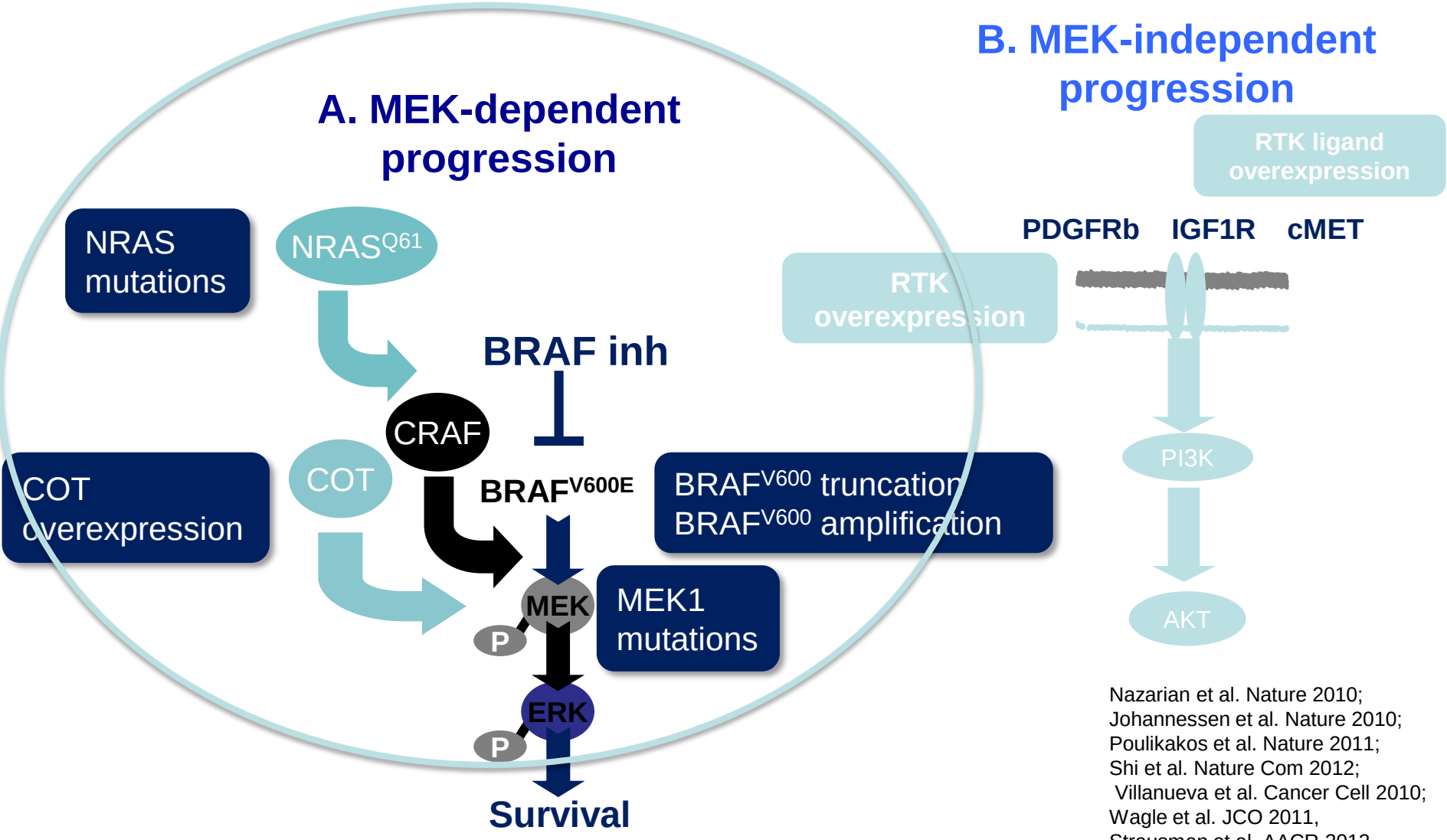
[Long G et al. Ann Oncol. 2017]

Also, toxicity can be substantial and continues for the duration of the treatment with effects on QoL





Unfortunately, resistance develops after initial benefit in the majority of patients



Nazarian et al. Nature 2010;
Johannessen et al. Nature 2010;
Poulikakos et al. Nature 2011;
Shi et al. Nature Com 2012;
Villanueva et al. Cancer Cell 2010;
Wagle et al. JCO 2011,
Strausman et al. AACR 2012

How to choose amongst therapeutic options?

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2019
Cutaneous Melanoma

FIRST-LINE THERAPY[2]

Metastatic or unresectable disease →

- **Preferred regimens**
  - **Anti PD-1 monotherapy[3,4]**
    - ◊ **Pembrolizumab (category 1)**
    - ◊ **Nivolumab (category 1)**
  - **Combination targeted therapy if *BRAF* V600-activating mutation;[6] preferred if clinically needed for early response[7,8,9,10]**
    - ◊ **Dabrafenib/trametinib (category 1)**
    - ◊ **Vemurafenib/cobimetinib (category 1)**
    - ◊ **Encorafenib/binimetinib (category 1**
- **Useful in certain circumstances**
  - **Nivolumab/ipilimumab (category 1)[3,4,5]**

How to choose amongst therapeutic options?

1. **Establish goals of care**
   - Durable disease-control
   - Rapid symptom palliation
   - Quality-of-life

2. **Match desired goals to the safety/efficacy characteristics of the therapy**
   - Rate of tumor regression (ORR) or clinical benefit
   - Kinetics of response (rapid vs delayed)
   - Duration of response
   - AEs
   - ?Cost

Table Treatment Characteristics and Endpoints to Consider in Tailoring Treatment for a Patient With Metastatic Melanoma

Desired Goal(s) of Care	Relevant Clinical Trial Endpoint to Consider	Treatment [Study]					
		High-dose IL-2[74,77,78]	Ipilimumab [18,27,36]	Pembrolizumab, Nivolumab [19,21,23,24,30,79]	Ipilimumab Plus Nivolumab [25,26]	BRAFi [4,53,54,56-59]	BRAFi Plus MEKi [56-58]
Cure (tumor eradication)	CR rate (%)	6	2	3–7	5 (Near CR: 31%)	4–9	9–13
	Median CR duration	NR (> 3.5 yr)	NA	NA	NA	NA	NA
Prolonged survival (improved disease control)	Median OS	11 mo	10–12 mo	17 mo	39 mo	14–17 mo	NR
	2-year OS (%)	25	30	43–48	75	NA	NA
	5-year OS (%)	NA	18	NA	NA	NA	NA
	Median PFS	1.6 mo	< 3 mo	4–7 mo	NA	5–9 mo	9–11 mo
	1-year PFS (%)	5	20–25	30–40	40	30–35	35–45
Symptom palliation (rapid tumor regression)	ORR (%)	10–15	10	28–40	53	45–51	64–76
	Median time to response	NA	Slow (14–16 wk)	9 wk	< 12 wk	Rapid (< 8 wk)	Rapid (< 8 wk)
Improved quality of life (less toxicity)	Grade 3+ drug-related AE rate (%)	80	15	11-22	53	37-63	35-65
	Drug discontinuation rate (%)	NA	NA	7	21	5-12	9-13

AE = adverse events; BRAFi = BRAF-inhibitors; CR = complete response; IL-2 = interleukin-2; MEKi = MEK-inhibitor; NA = not available; NR = not reached; ORR = objective response rate; OS = overall survival; PFS = progression-free survival.

Bhatia S *et al,* 2015 Oncology (Williston Park)

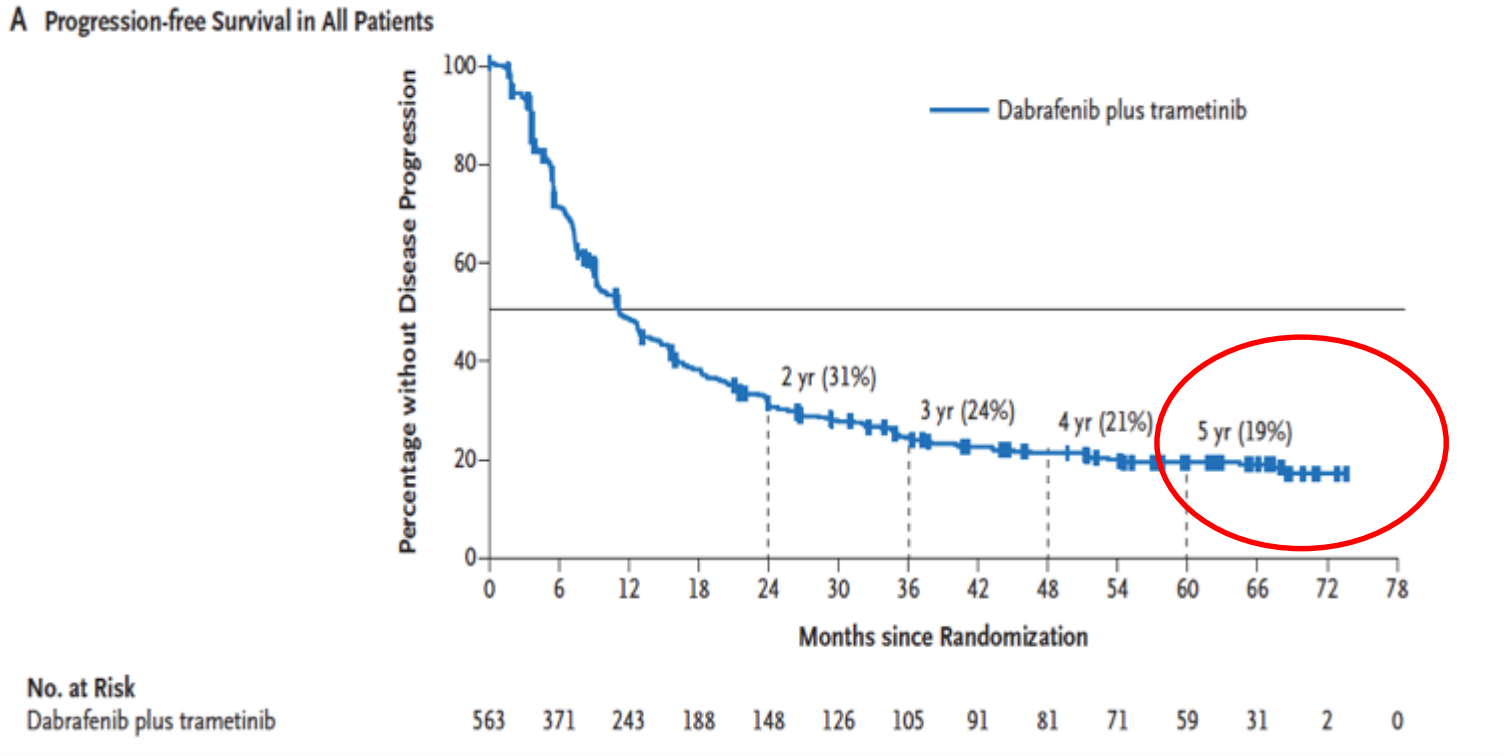
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Five-Year Outcomes with Dabrafenib plus Trametinib in Metastatic Melanoma

C. Robert, J.J. Grob, D. Stroyakovskiy, B. Karaszewska, A. Hauschild, E. Levchenko, V. Chiarion Sileni, J. Schachter, C. Garbe, I. Bondarenko, H. Gogas, M. Mandalá, J.B.A.G. Haanen, C. Lebbé, A. Mackiewicz, P. Rutkowski, P.D. Nathan, A. Ribas, M.A. Davies, K.T. Flaherty, P. Burgess, M. Tan, E. Gasal, M. Voi, D. Schadendorf, and G.V. Long

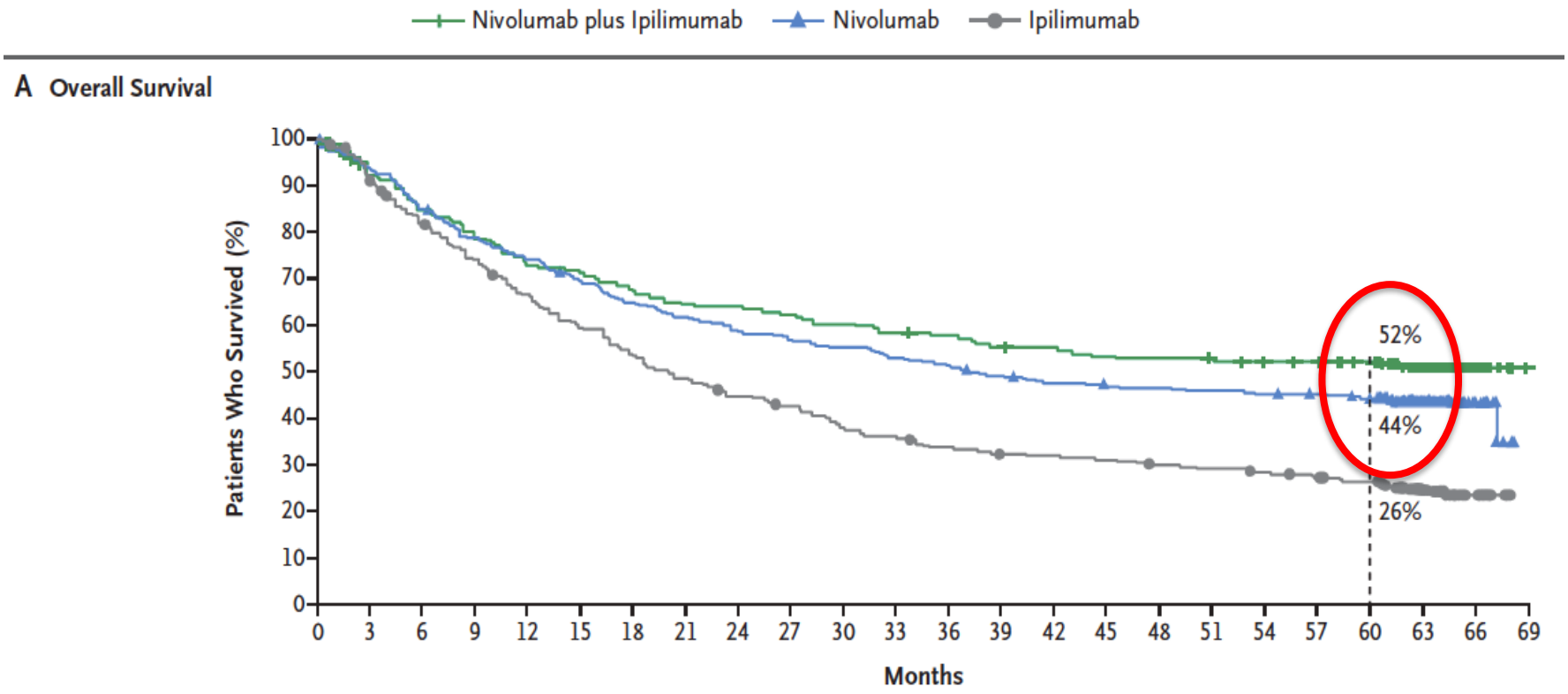
Durable PFS with BRAF-MEKi in some pts



88% (52/59) of patients, who were ongoing on trial and progression-free at 5-years, were **still receiving treatment (Dab or Tram or both).**

Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma

J. Larkin, V. Chiarion-Sileni, R. Gonzalez, J.-J. Grob, P. Rutkowski, C.D. Lao,



No. at Risk

Nivolumab plus ipilimumab	314	292	265	248	227	222	210	201	199	193	187	181	179	172	169	164	163	159	157	155	150	92	14	0
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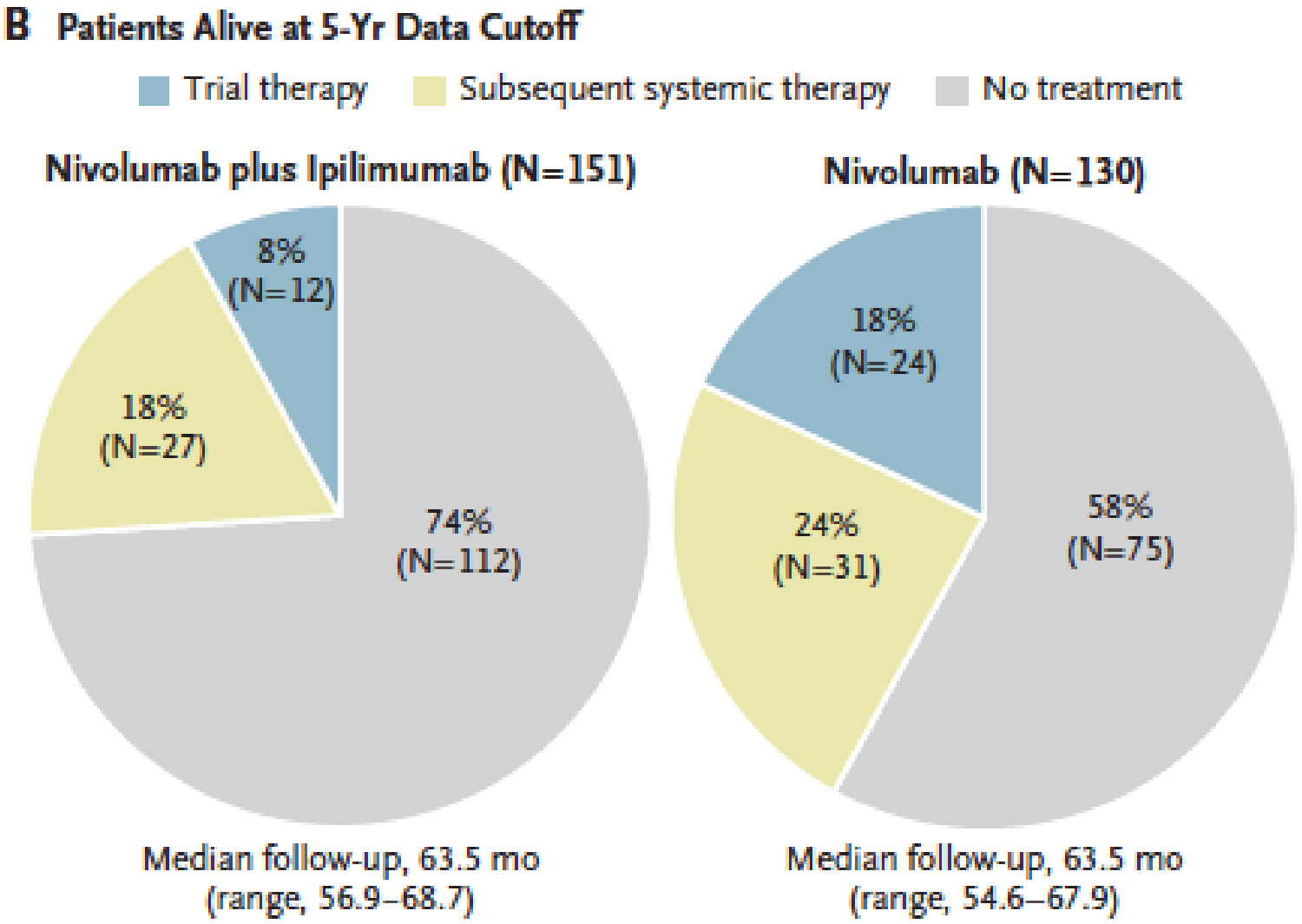
Ipilimumab	315	285	253	227	203	181	163	148	135	128	113	107	100	95	94	91	87	84	81	77	73	36	12	0

DOI: 10.1056/NEJMoa1910836

Treatment-free status after Immunotherapy



DOI: 10.1056/NEJMoa1910836

Immunotherapy vs BRAF-MEKi: LTFU

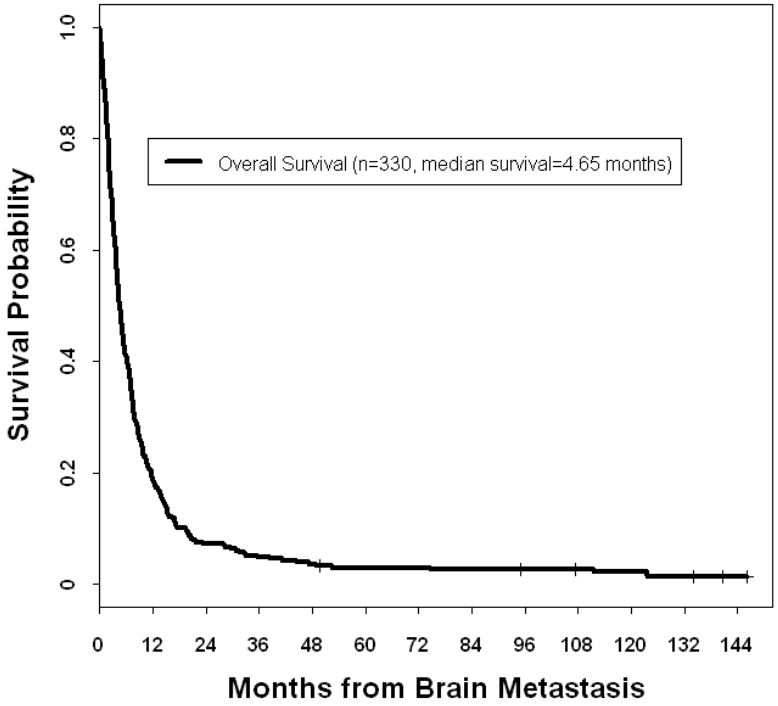
	BRAF-MEKi (Combi-D and -V)	Ipi-Nivo (Checkmate 067)
ORR	**68%**	58%
CR	19%	21%
4-yr PFS	21%	37%
4-yr OS	37%	**62%**
Ongoing Study Treatment	**88%**	**11%**

How to choose amongst therapeutic options?

SB approach	**BRAF wild type**	**BRAF mutated**
Low Volume, Asymptomatic disease	**Immunotherapy** (anti PD-1 alone or in combination)	**Immunotherapy (preferred)** **BRAFi +/- MEKi (acceptable)**
Bulky disease, Symptomatic	**Immunotherapy** (anti PD-1 alone or in combination) **Chemotherapy**	**BRAFi +/- MEKi followed by Immunotherapy**

Melanoma Brain Metastases (MBMs)

- Among the highest risk of brain metastases among common solid tumors
  - 10-20% at diagnosis of stage IV
  - Up to 50% over course of disease
  - Up to 70% in autopsy studies
- Common site of treatment failure for systemic therapies
- Historically median OS ~ 4 months



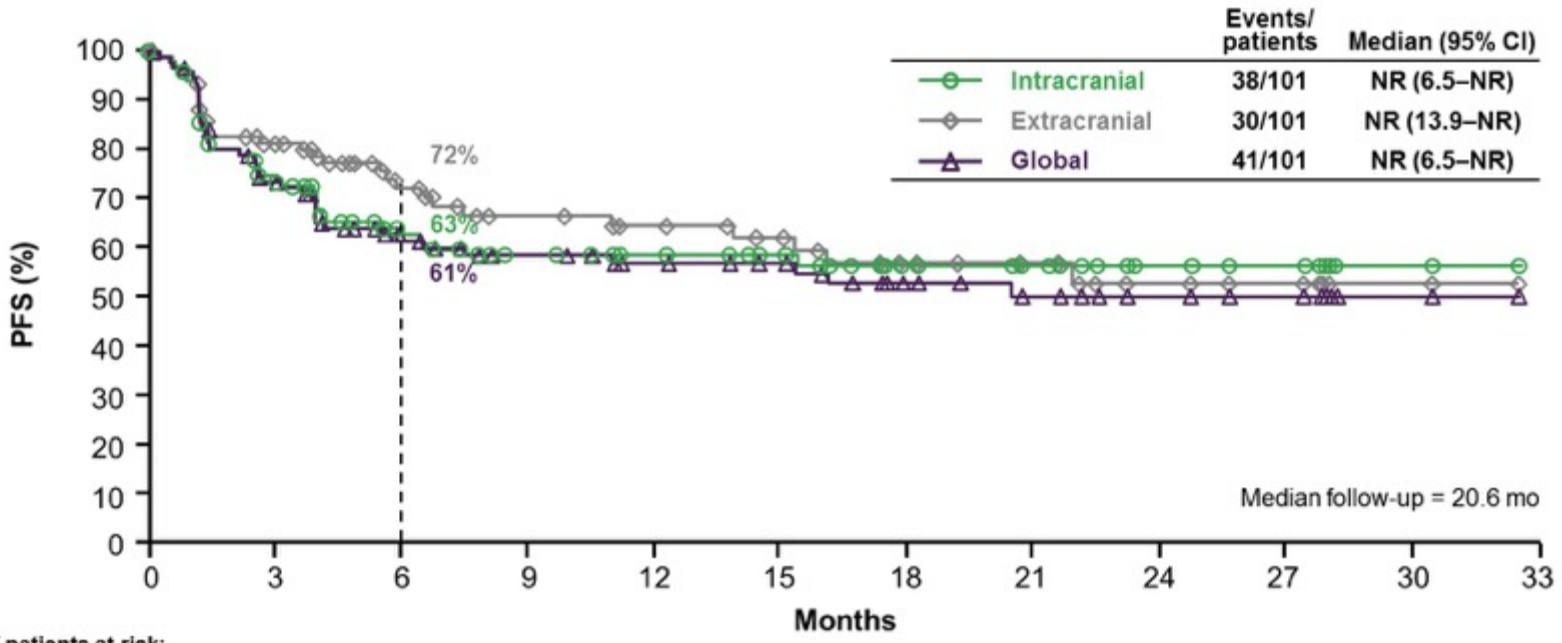
Davies, *Cancer,* 2011
Cohen et al, *PCMR,* 2016

ORIGINAL ARTICLE

Combined Nivolumab and Ipilimumab in Melanoma Metastatic to the Brain

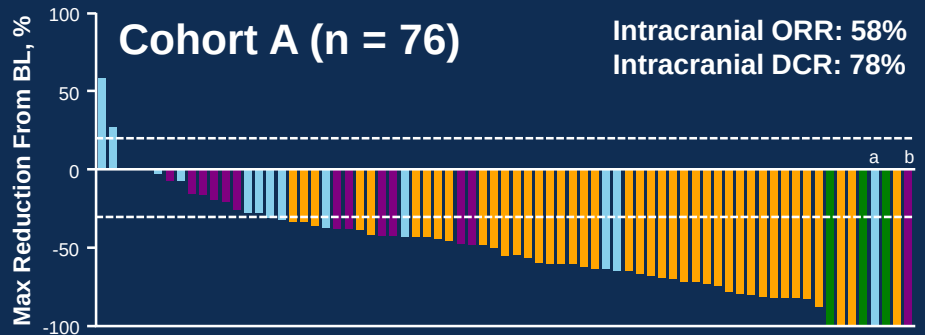
CheckMate 204

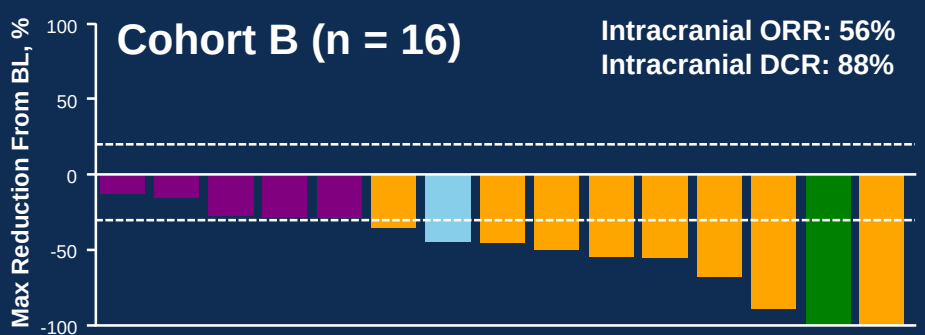
Progression-Free Survival – Asymptomatic Patients

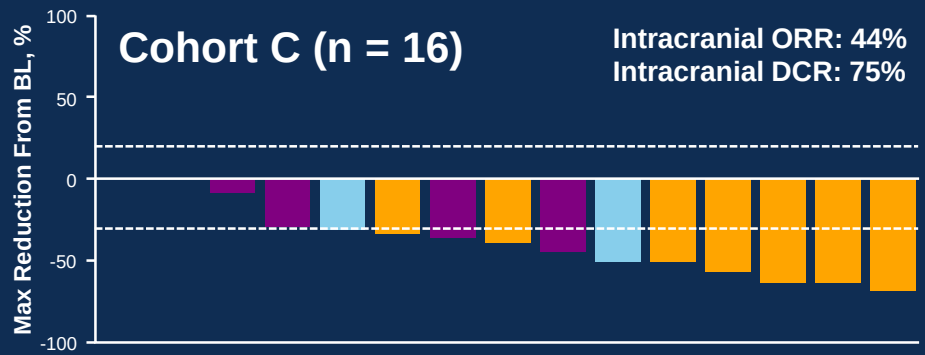


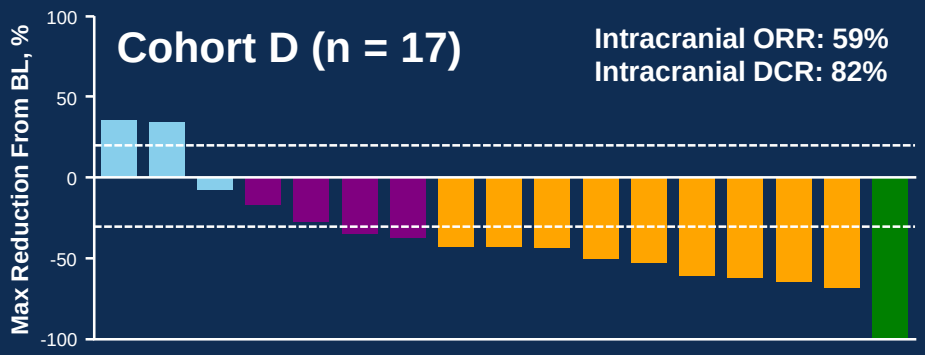
BRAF-MEKi in MBMs

Intracranial Response









Best Confirmed IR[c]: CR PR SD PD

CR, complete response; SD, stable disease.
[a] Patient had a CR in the target lesion, but best confirmed response was determined to be PD due to development of an unequivocal new lesion; [b] Patient had an unconfirmed CR, but best confirmed response was SD; [c] Investigator assessed; these results were supported by independent review.

MBMs: Conclusions

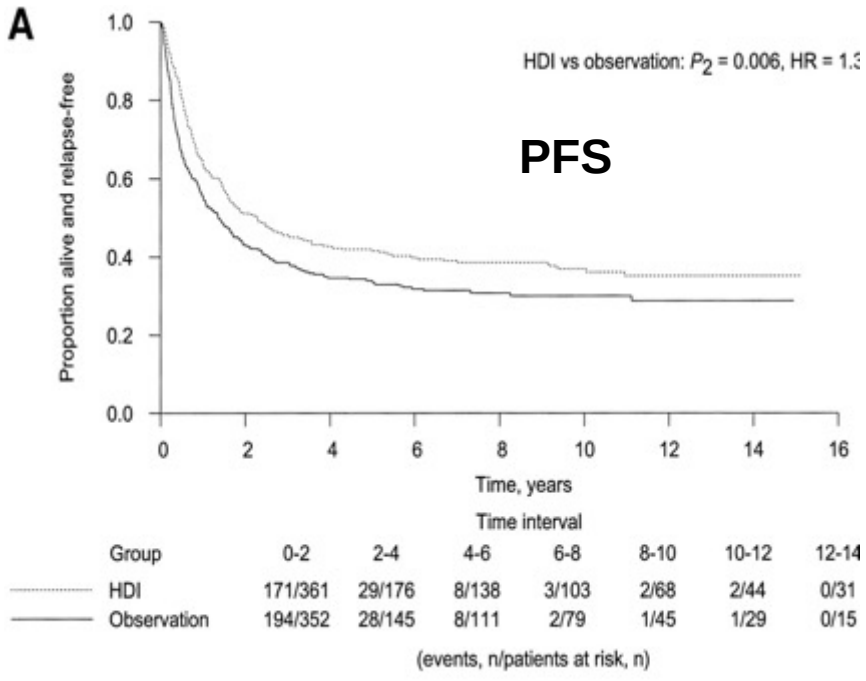
- MBMs need **systemic** therapy for long-term control.

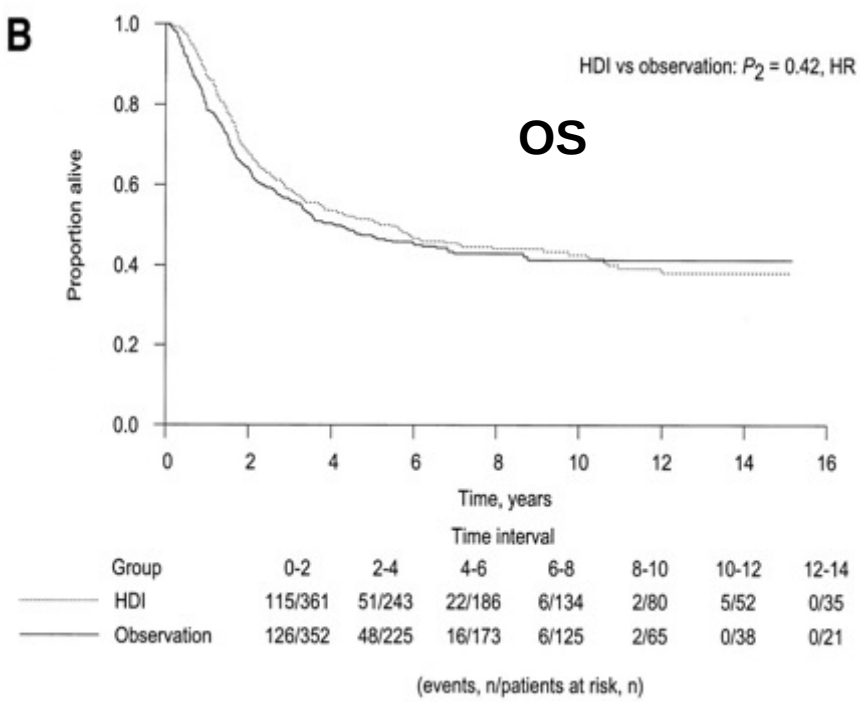
- The durable intracranial responses observed in patients with asymptomatic brain metastases supports the use of NIVO+IPI as first-line therapy.

- Symptomatic patients remain difficult to treat, but can benefit from the high rate of initial intra-cranial responses with BRAF-MEKi in the BRAF-mutant melanoma, although duration of responses shorter than in extracranial sites.

Adjuvant therapy in high-risk melanoma

Adjuvant interferon-alfa was the (poor) standard-of-care for decades





Dubious efficacy

<u>Considerable toxicity</u>

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Prolonged Survival in Stage III Melanoma with Ipilimumab Adjuvant Therapy

A.M.M. Eggermont, V. Chiarion-Sileni, J.-J. Grob, R. Dummer, J.D. Wolchok, H. Schmidt, O. Hamid, C. Robert, P.A. Ascierto, J.M. Richards, C. Lebbé, V. Ferraresi, M. Smylie, J.S. Weber, M. Maio, L. Bastholt, L. Mortier, L. Thomas, S. Tahir, A. Hauschild, J.C. Hassel, F.S. Hodi, C. Taitt, V. de Pril, G. de Schaetzen, S. Suciu, and A. Testori

- **Toxicity**: Grade 3 or higher IRAEs rate > 40%

- **Approximate cost of 3-year course at current prices:** $1.5 million

However, toxicity and cost remain concerns to utilization

- **Toxicity**: Grade 3 or higher IRAEs rate > 40%
- **Approximate cost of 3-year course at current prices:** $1.5 million

The NEW ENGLAND JOURNAL of MEDICINE

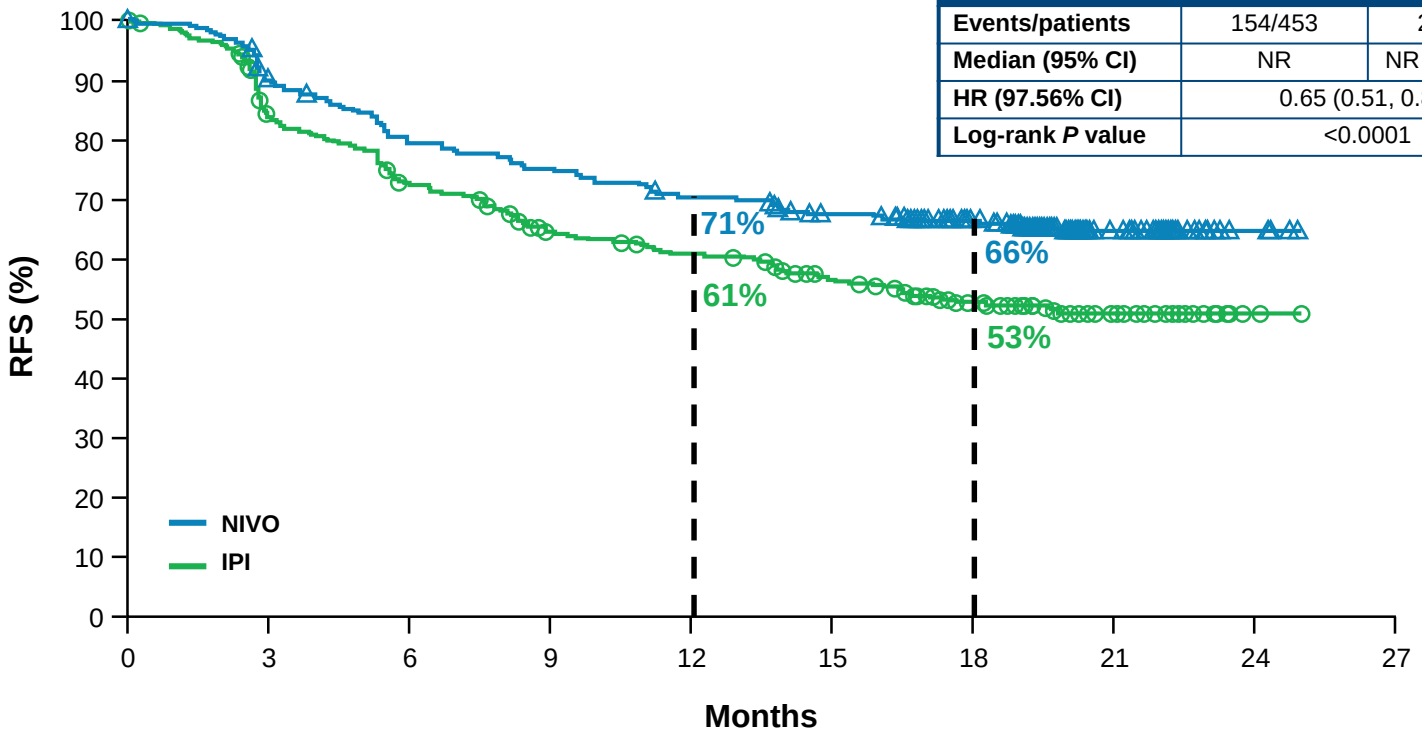
ORIGINAL ARTICLE

Adjuvant Nivolumab versus Ipilimumab in Resected Stage III or IV Melanoma

J. Weber, M. Mandala, M. Del Vecchio, H.J. Gogas, A.M. Arance, C.L. Cowey, S. Dalle, M. Schenker, V. Chiarion-Sileni, I. Marquez-Rodas, J.-J. Grob, M.O. Butler, M.R. Middleton, M. Maio, V. Atkinson, P. Queirolo, R. Gonzalez, R.R. Kudchadkar, M. Smylie, N. Meyer, L. Mortier, M.B. Atkins, G.V. Long, S. Bhatia, C. Lebbé, P. Rutkowski, K. Yokota, N. Yamazaki, T.M. Kim, V. de Pril, J. Sabater, A. Qureshi, J. Larkin, and P.A. Ascierto, for the CheckMate 238 Collaborators*

Primary Endpoint: RFS

	NIVO	IPI
Events/patients	154/453	206/453
Median (95% CI)	NR	NR (16.6, NR)
HR (97.56% CI)	0.65 (0.51, 0.83)	
Log-rank *P* value	<0.0001	

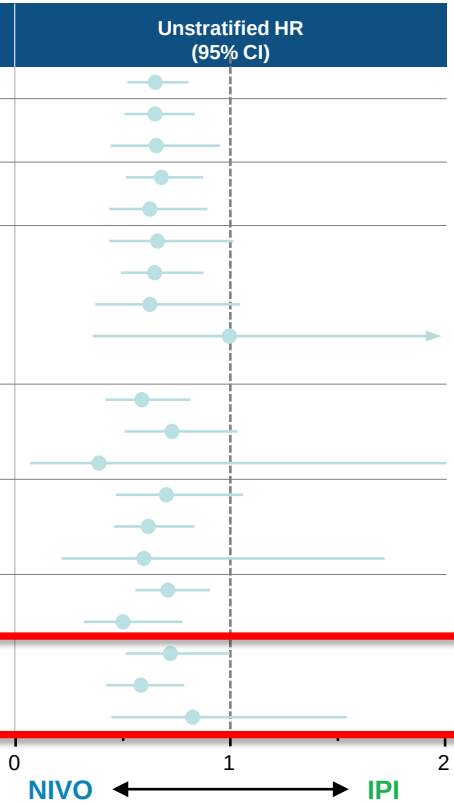


Number of patients at risk

NIVO	453	399	353	332	311	291	249	71	5	0
IPI	453	364	314	269	252	225	184	56	2	0

RFS: Prespecified Subgroups

Subgroup		No. of events/no. of patients		Unstratified HR (95% CI)
		NIVO 3 mg/kg	IPI 10 mg/kg	
Overall	Overall	154/453	206/453	0.66 (0.53, 0.81)
Age	<65 years	106/333	147/339	0.65 (0.51, 0.84)
	≥65 years	48/120	59/114	0.66 (0.45, 0.97)
Sex	Male	99/258	133/269	0.68 (0.53, 0.88)
	Female	55/195	73/184	0.63 (0.44, 0.89)
Stage (CRF)	Stage IIIb	41/163	54/148	0.67 (0.44, 1.00)
	Stage IIIc	79/204	109/218	0.65 (0.49, 0.87)
	Stage IV M1a-M1b	25/62	35/66	0.63 (0.38, 1.05)
	Stage IV M1c	8/20	8/21	1.00 (0.37, 2.66)
	Not reported	1/2	0/0	
Stage III: Ulceration	Absent	58/201	94/216	0.59 (0.42, 0.82)
	Present	60/153	64/135	0.73 (0.51, 1.04)
	Not reported	2/15	5/15	0.39 (0.07, 2.00)
Stage III: Lymph node involvement	Microscopic	41/125	55/134	0.71 (0.47, 1.07)
	Macroscopic	72/219	101/214	0.62 (0.46, 0.84)
	Not reported	7/25	7/18	0.60 (0.21, 1.72)
PD-L1 status	<5%/indeterminate	123/300	149/299	0.71 (0.56, 0.90)
	≥5%	31/152	57/154	0.50 (0.32, 0.78)
***BRAF* mutation status**	Mutant	63/187	84/194	0.72 (0.52, 1.00)
	Wild-type	67/197	105/214	0.58 (0.43, 0.79)
	Not reported	24/69	17/45	0.83 (0.45, 1.54)

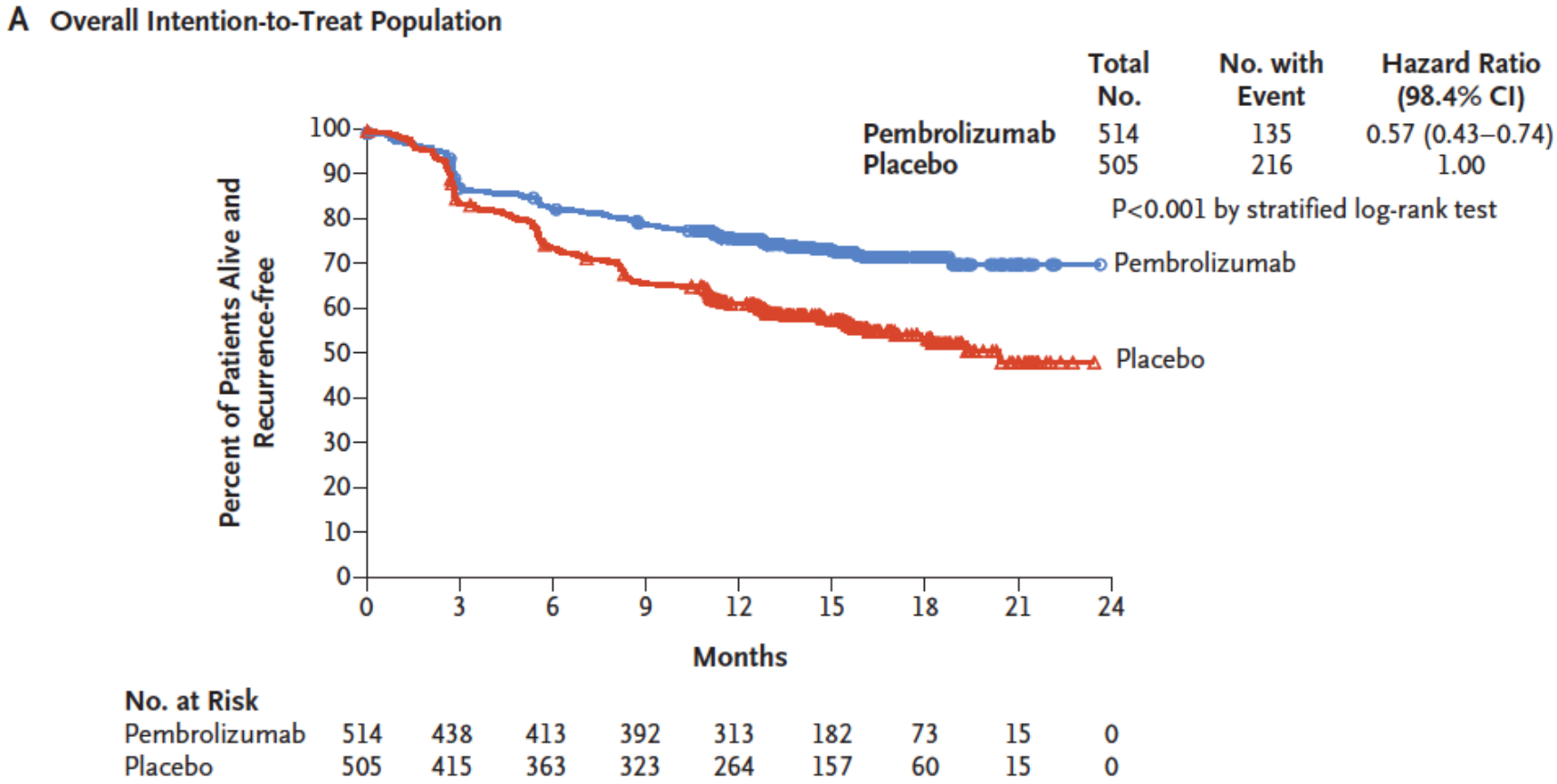


Safety Summary

AE, n (%)	NIVO (n = 452)		IPI (n = 453)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Any AE	438 (97)	115 (25)	446 (98)	250 (55)
Treatment-related AE	385 (85)	65 (14)	434 (96)	208 (46)
Any AE leading to discontinuation	44 (10)	21 (5)	193 (43)	140 (31)
Treatment-related AE leading to discontinuation	35 (8)	16 (4)	189 (42)	136 (30)

- There were no treatment-related deaths in the NIVO group
- There were 2 (0.4%) treatment-related deaths in the IPI group (marrow aplasia and colitis), both >100 days after the last dose

Adjuvant Pembro in Melanoma



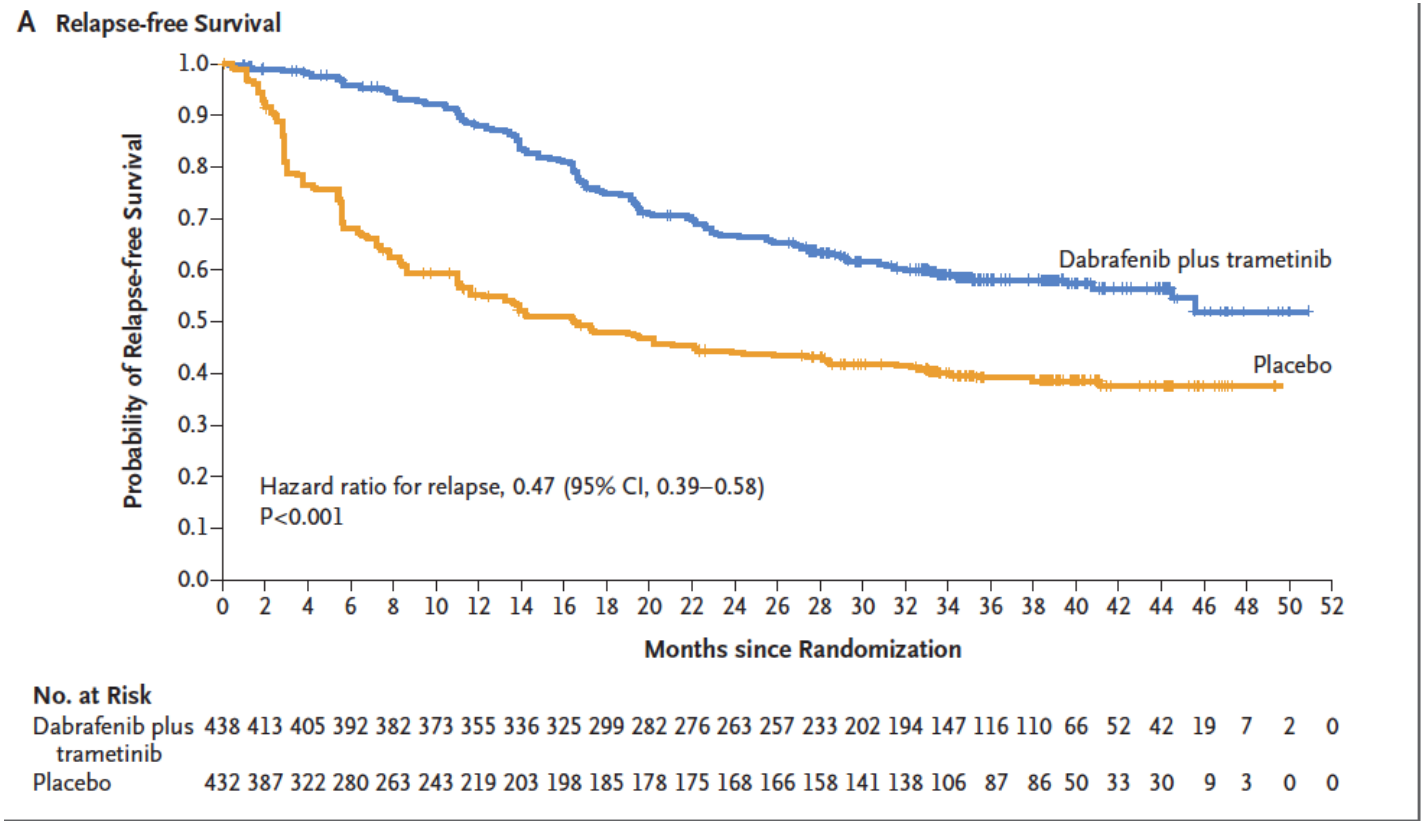
{Eggermont AM et al *NEJM* 2018}

The NEW ENGLAND JOURNAL of MEDICINE

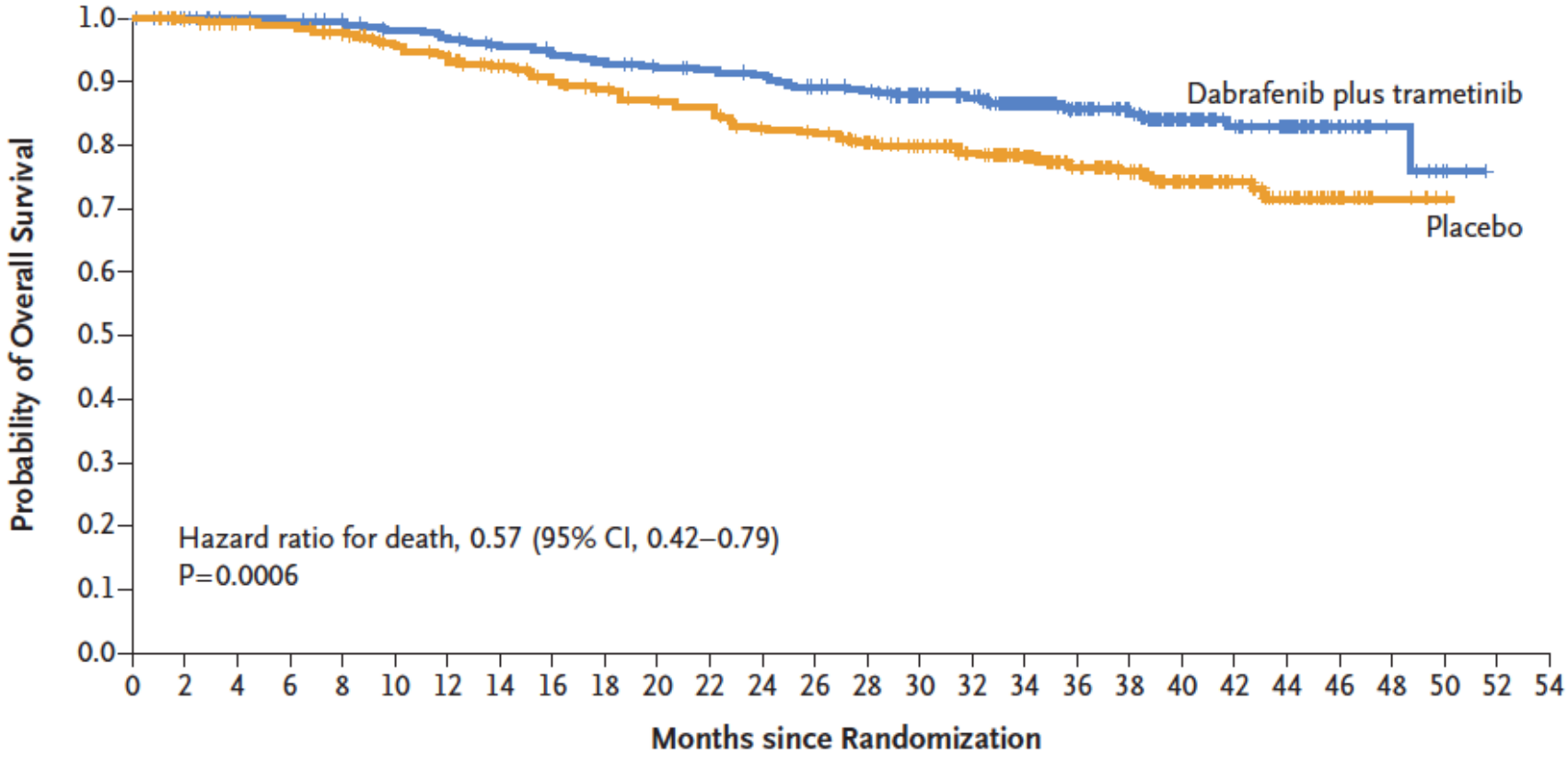
ORIGINAL ARTICLE

Adjuvant Dabrafenib plus Trametinib in Stage III *BRAF*-Mutated Melanoma

G.V. Long, A. Hauschild, M. Santinami, V. Atkinson, M. Mandalà, V. Chiarion-Sileni, J. Larkin, M. Nyakas, C. Dutriaux, A. Haydon, C. Robert, L. Mortier, J. Schachter, D. Schadendorf, T. Lesimple, R. Plummer, R. Ji, P. Zhang, B. Mookerjee, J. Legos, R. Kefford, R. Dummer, and J.M. Kirkwood



B **Overall Survival**



No. at Risk

Dabrafenib plus trametinib	438	426	416	414	408	401	395	387	381	376	370	366	362	352	328	301	291	233	180	164	105	82	67	28	12	5	0	0
Placebo	432	425	415	410	401	386	378	362	346	337	328	323	308	303	284	269	252	202	164	152	94	64	51	17	7	1	0	0

What should we do in clinic?

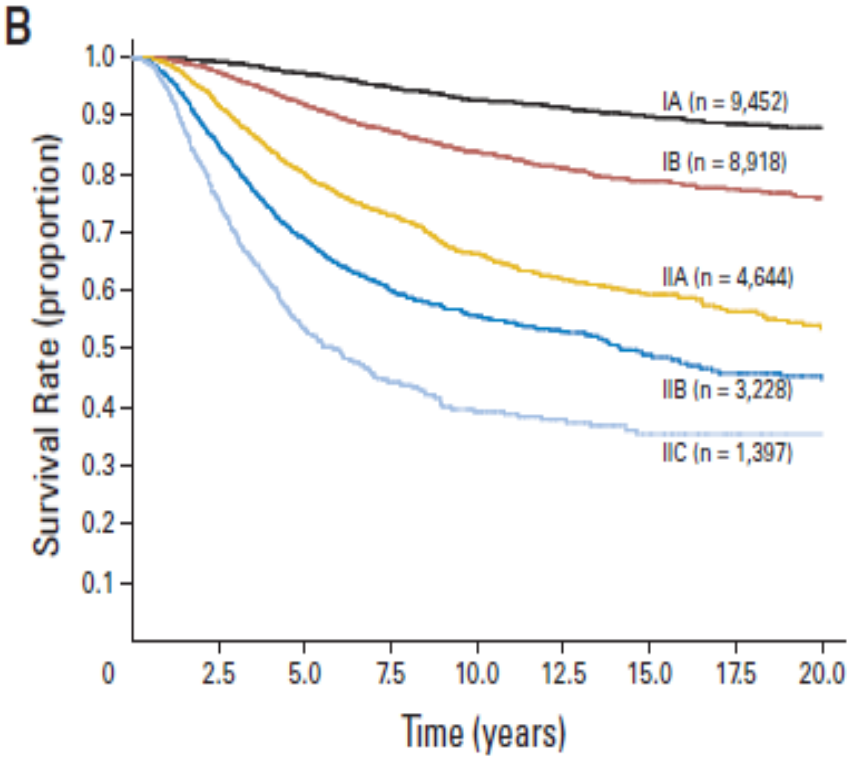
For BRAF-WT patients, PD-1 monotherapy is most appropriate at this time.

Better efficacy, lower toxicity than HD-Ipi

For BRAF-mutant patients, should we use anti-PD-1 or Dab-tram?

	2-year RFS (%)	Toxicity > Gr 3 AEs (%)
All melanoma		
Placebo	43	
Ipilimumab	51	42
Nivolumab	66	9
BRAF-mutant melanoma		
Placebo	44	
Dab-Tram	67	41

High-risk stage II patients are finally getting attention



Safety and Efficacy of Pembrolizumab Compared to Placebo in Resected High-risk Stage II Melanoma (MK-3475-716/KEYNOTE-716)

ClinicalTrials.gov Identifier: NCT03553836

N=954

Open at SCCA

Balch , J Clin Oncol 2009; 27(36):6199-6206

Melanoma Subtypes

Ocular (uveal) melanoma

Frequent somatic mutations of *GNAQ* in uveal melanoma and blue naevi

Catherine D. Van Raamsdonk[1], Vladimir Bezrookove[2], Gary Green[2], Jürgen Bauer[3,4], Lona Gaugler[2], Joan M. O'Brien[3], Elizabeth M. Simpson[5], Gregory S. Barsh[6] & Boris C. Bastian[2]

Local therapy options: Proton RT; Plaque Brachytherapy; Enucleation)

High-risk of **liver metastases**; can have **prolonged dormancy**

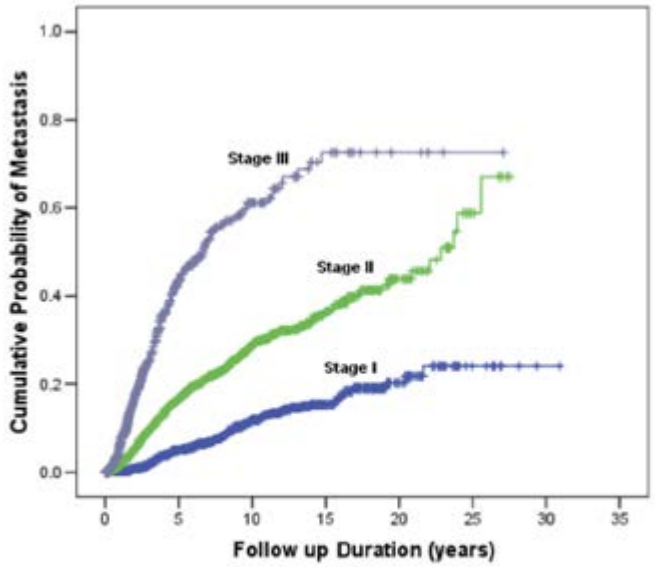


Figure 2. Kaplan–Meier estimate of metastasis from posterior uveal melanoma in 7731 patients, based on the American Joint Cancer Committee (AJCC) tumor staging.

Frequent Mutation of *BAP1* in Metastasizing Uveal Melanomas

J. William Harbour,[1,3*] Michael D. Onken,[1] Elisha D. O. Roberson,[2] Shenghui Duan,[2] Li Cao,[2] Lori A. Worley,[1] M. Laurin Council,[2] Katie A. Matatall,[1] Cynthia Helms,[2] Anne M. Bowcock[2,3*]

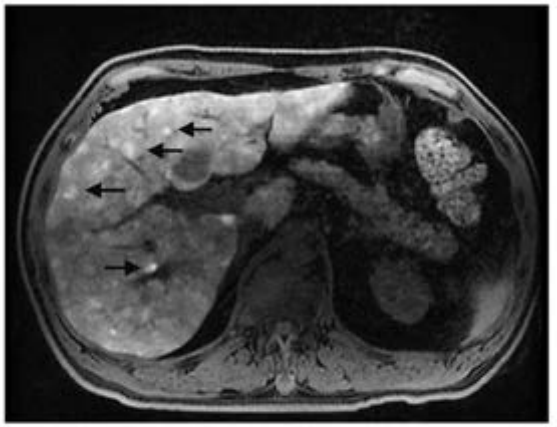
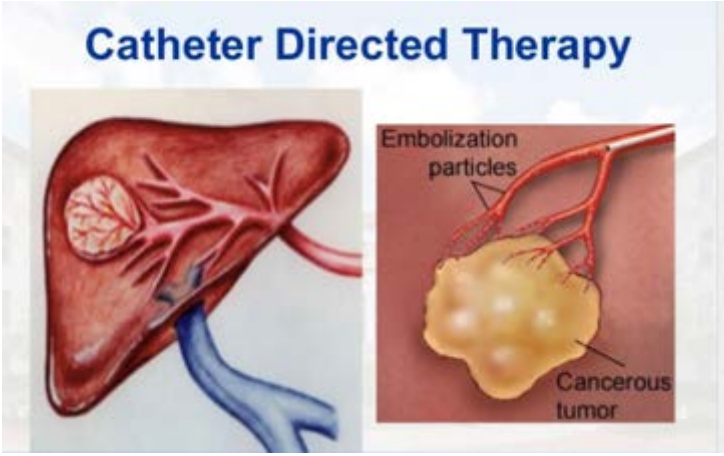


Fig. 3. Numerous T1-weighted fat suppressed hyperintense lesions on MRI compatible with melanoma metastases (arrows).



Imatinib for Melanomas Harboring Mutationally Activated or Amplified *KIT* Arising on Mucosal, Acral, and Chronically Sun-Damaged Skin

F. Stephen Hodi, Christopher L. Corless, Anita Giobbie-Hurder, Jonathan A. Fletcher, Meijun Zhu, Adrian Marino-Enriquez, Philip Friedlander, Rene Gonzalez, Jeffrey S. Weber, Thomas F. Gajewski, Steven J. O'Day, Kevin B. Kim, Donald Lawrence, Keith T. Flaherty, Jason J. Luke, Frances A. Collichio, Marc S. Ernstoff, Michael C. Heinrich, Carol Beadling, Katherine A. Zukotynski, Jeffrey T. Yap, Annick D. Van den Abbeele, George D. Demetri, and David E. Fisher

Hodi FS. JCO 2013

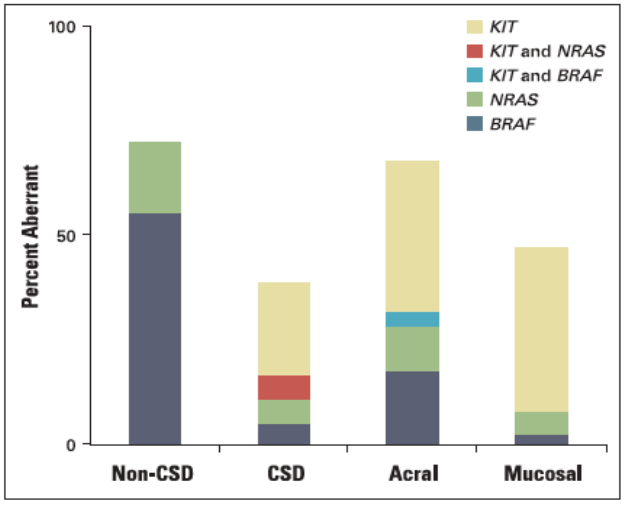
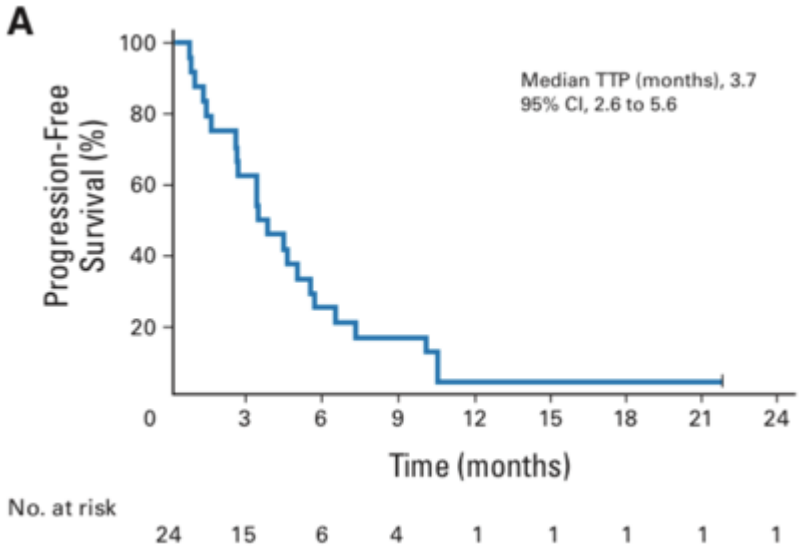


Fig 2. Frequency distribution of genetic alterations in BRAF, *NRAS*, and *KIT* among four groups of melanoma. Non-CSD, melanomas on skin without chronic sun-induced damage; CSD, melanomas on skin with chronic sun-induced as evidenced by the presence of marked solar elastosis; acral, melanomas on the soles, palms, or sub-ungual sites; mucosal, melanomas on mucosal membranes. One CSD melanoma had a *KIT* and an *NRAS* mutation, and one acral melanoma had a *KIT* and a *BRAF* mutation.

Curtin JA. JCO 2006

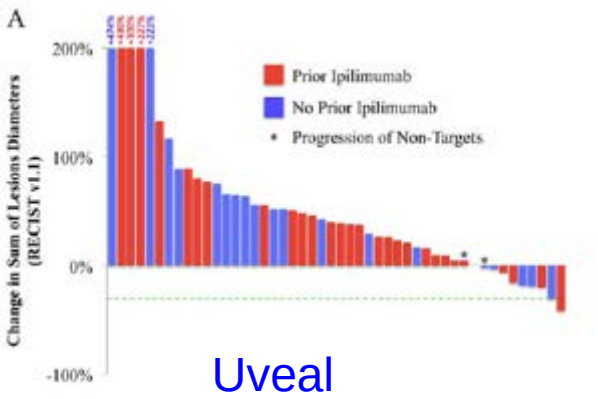
BORR was 54% (7/13) in KIT-mutant (0% in KIT-amplified)



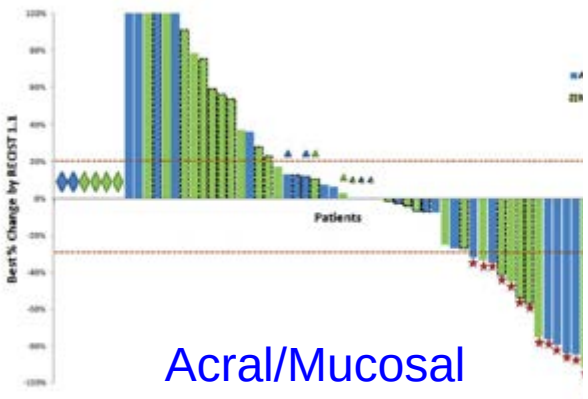
Editorial

Disparate Clinical Activity of PD-1 Blockade in Melanoma Subtypes: Know thy Enemy!

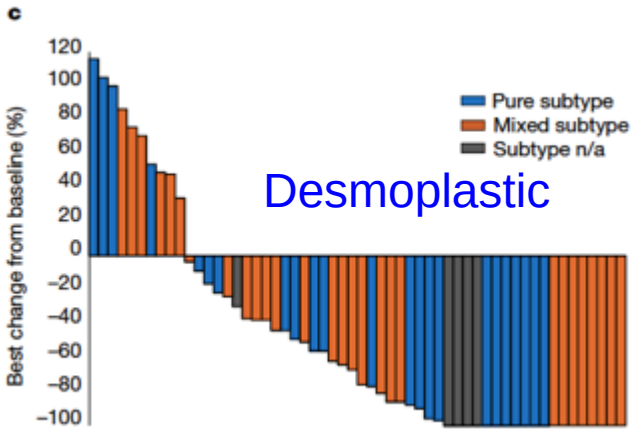
Shailender Bhatia, MD[1,2] and Kim Margolin, MD[3]



Uveal



Acral/Mucosal



Desmoplastic

LETTER

doi:10.1038/nature25187

High response rate to PD-1 blockade in desmoplastic melanomas

Zeynep Eroglu[1,2*], Jesse M. Zaretsky[1*], Siwen Hu-Lieskovan[1*], Dae Won Kim[2,3], Alain Algazi[4], Douglas B. Johnson[5], Elizabeth Liniker[6], Ben Kong[7], Rodrigo Munhoz[8,9], Suthee Rapisuwon[10], Pier Federico Gherardini[11], Bartosz Chmielowski[1], Xiaoyan Wang[1], I. Peter Shintaku[1], Cody Wei[1], Jeffrey A. Sosman[5†], Richard W. Joseph[12], Michael A. Postow[8,9], Matteo S. Carlino[6,7,13], Wen-Jen Hwu[3], Richard A. Scolyer[6,13,14], Jane Messina[2], Alistair J. Cochran[1], Georgina V. Long[6,13,15] & Antoni Ribas[1]

II. Non Melanoma Skin Cancers

Merkel cell Carcinoma (MCC)

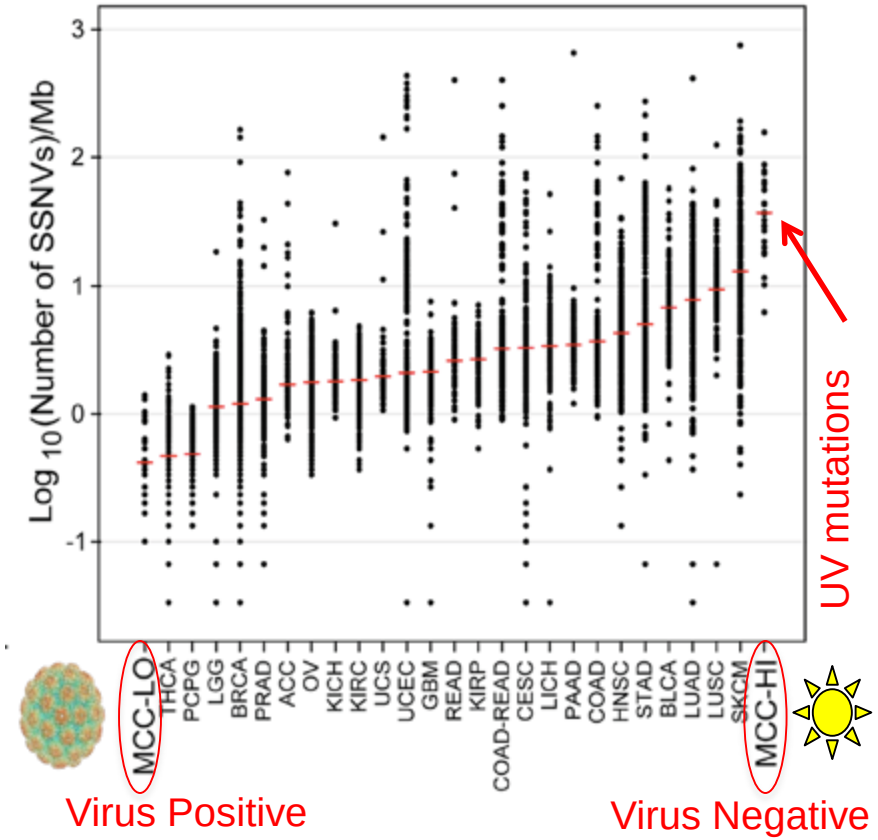
- Merkel cell polyoma virus (MCPyV) in 80% of MCC tumors

{Feng H et al *Science* 2008}

- UV-induced high mutational load (Neoantigens)

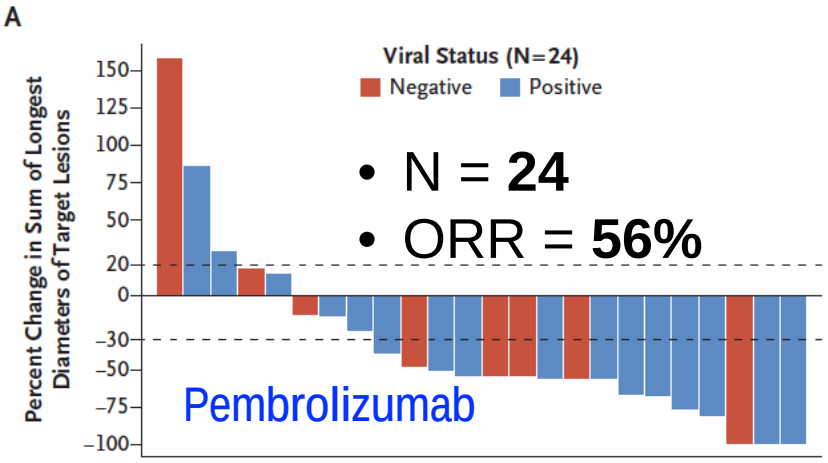
- Immune exhaustion of TILs [reversible with Immune Checkpoint Inhibitors (ICIs)]

[Afanasiev O et al. *Clin Cancer Res*. 2013]

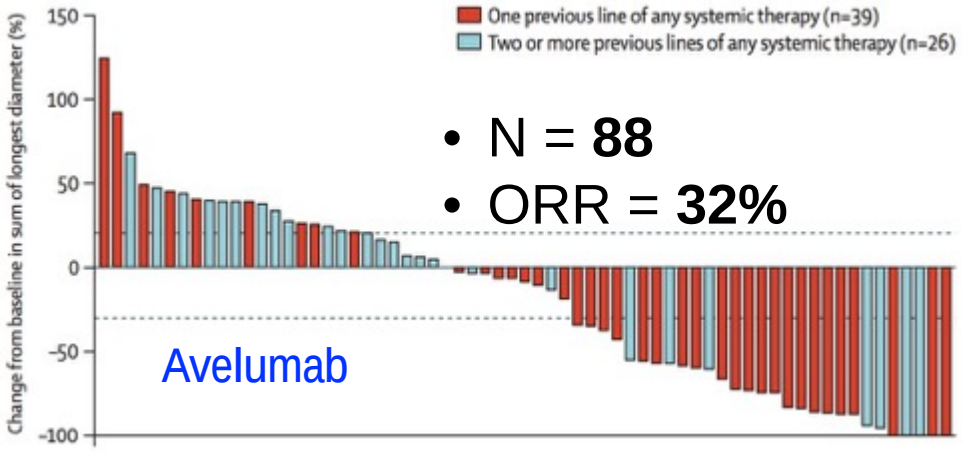


{Goh et al. Oncotarget 2015}

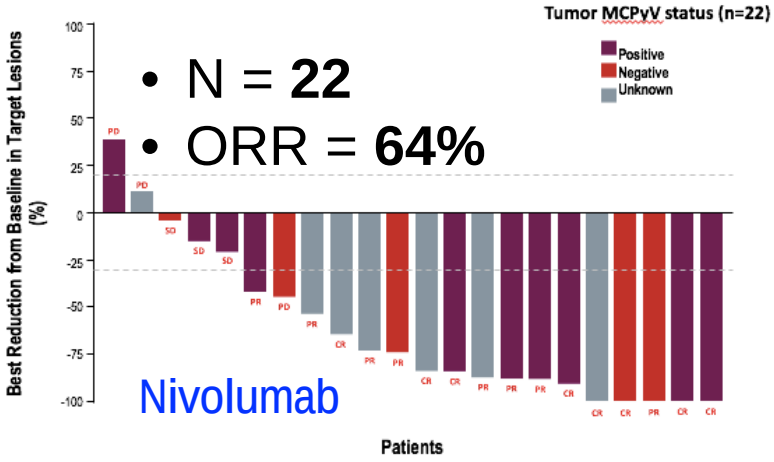
High response rates with ICIs in MCC



- N = **24**
- ORR = **56%**



- N = **88**
- ORR = **32%**



- N = **22**
- ORR = **64%**

{Nghiem P, Bhatia S et al. 2016 *NEJM*}

{Kaufman H et al. *The Lancet Oncology* 2016}

{Topalian S, Bhatia S et al. *AACR* 2017}

Lancet Oncol 2016

Published Online
September 1, 2016

Comment

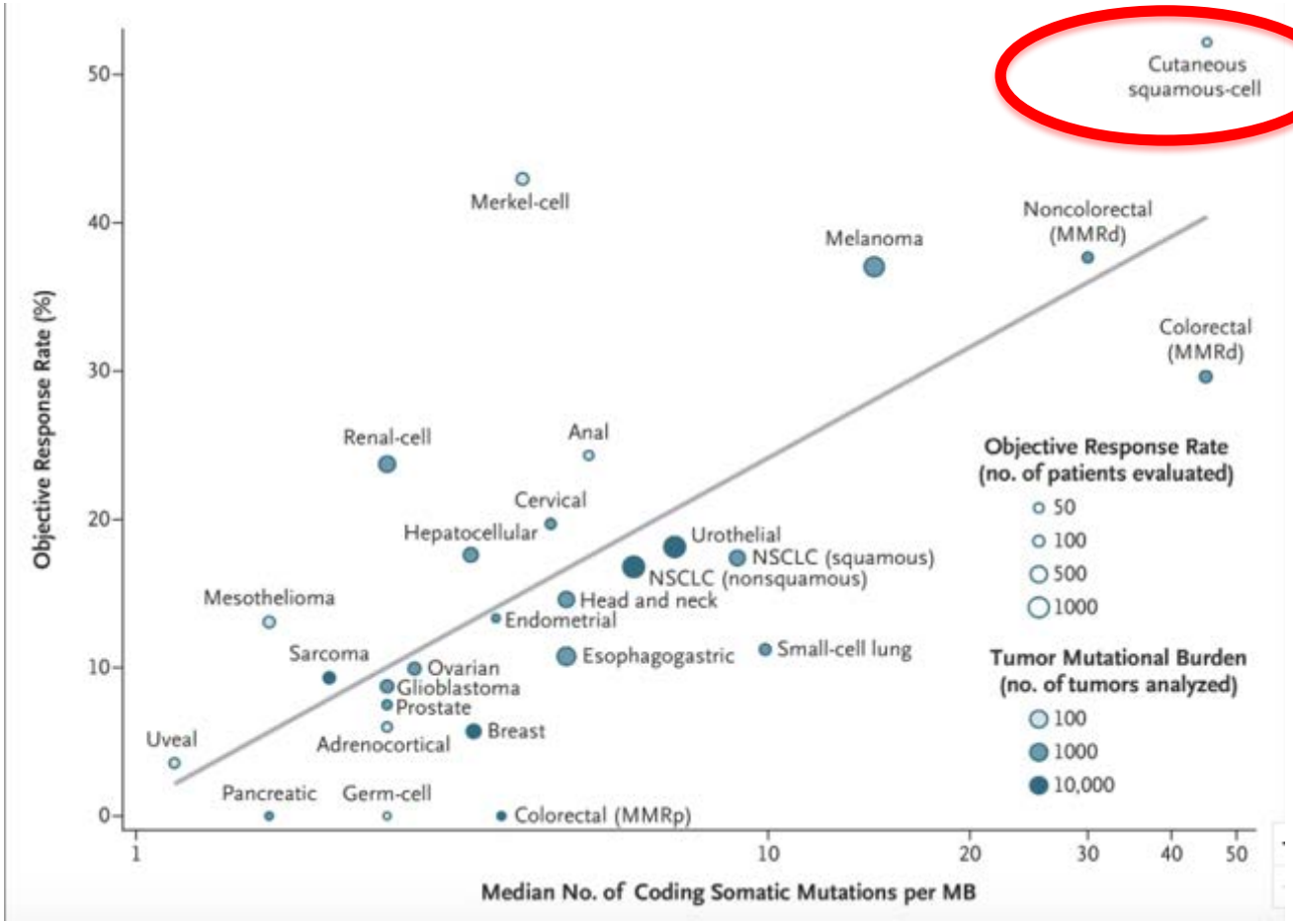
Checkpoint inhibitors: a new standard of care for advanced Merkel cell carcinoma?

*Axel Hauschild, Dirk Schadendorf
Department of Dermatology, University Hospital Schleswig-Holstein (UKSH), Kiel, Germany (AH); Department of Dermatology Comprehensive Cancer Center, University Hospital Essen, Germany (DS); and German Cancer Consortium, Heidelberg, Germany (DKTK)

"Taken together, these reports strongly suggest that checkpoint blockade is the best option to treat patients with advanced Merkel cell carcinoma…"

Cutaneous Squamous cell carcinoma (cSCC)

High mutational burden: Neoantigens



[Yarchoan M *NEJM* 2017]

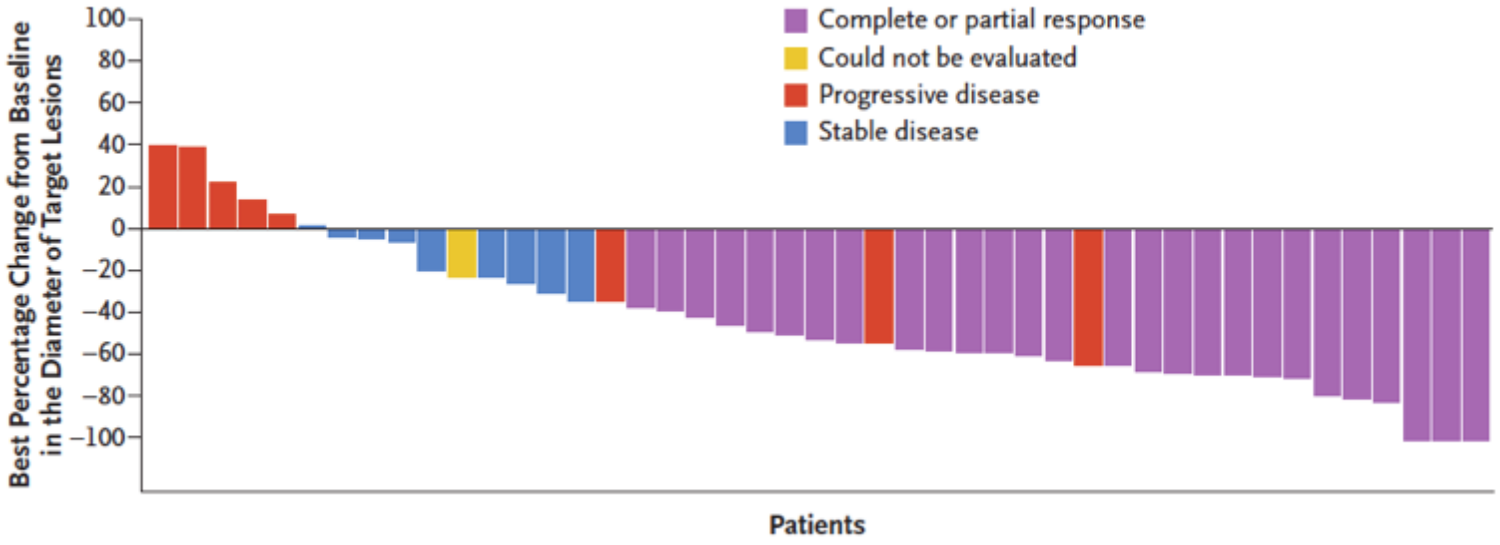
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

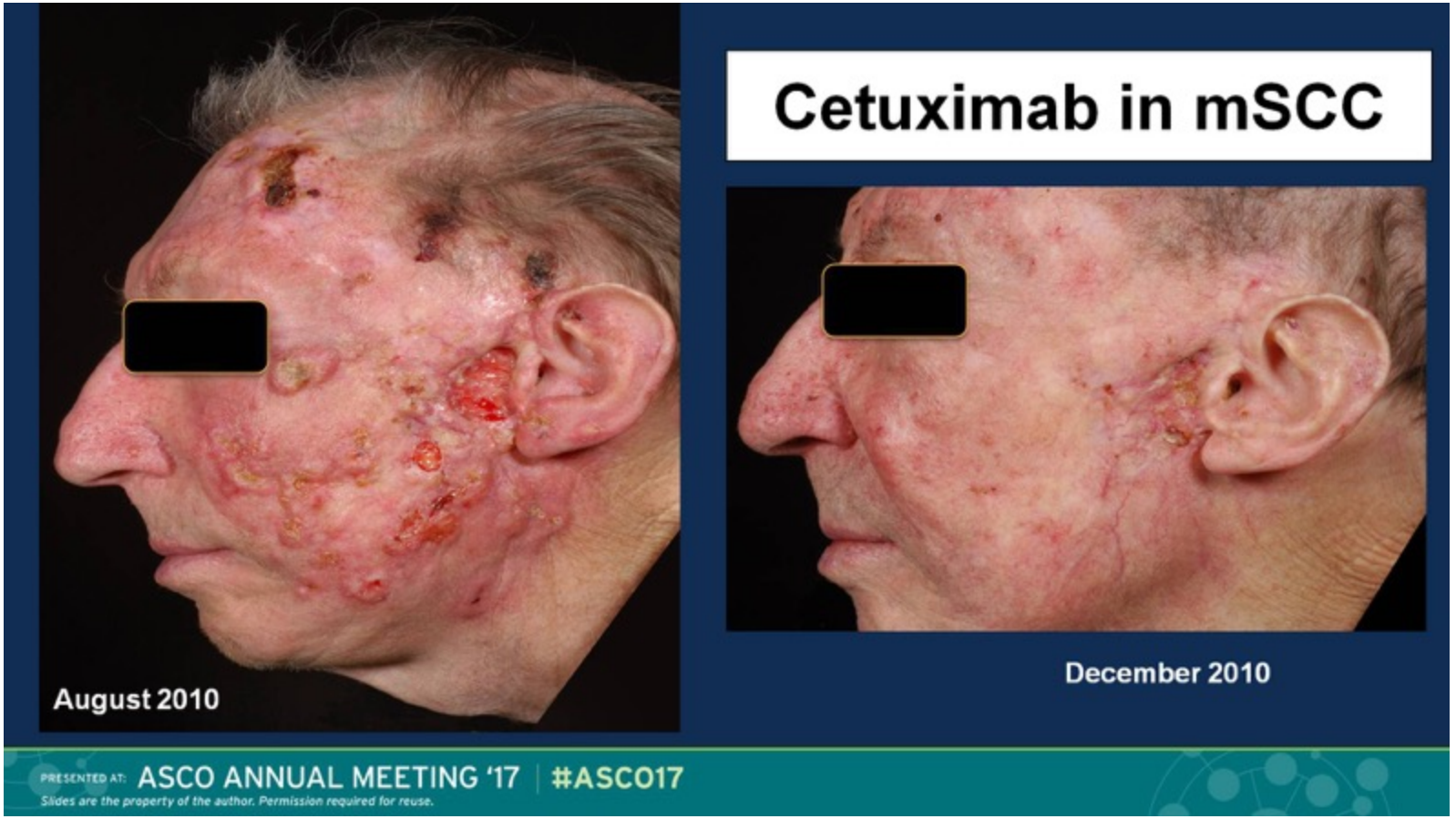
PD-1 Blockade with Cemiplimab in Advanced Cutaneous Squamous-Cell Carcinoma

M.R. Migden, D. Rischin, C.D. Schmults, A. Guminski, A. Hauschild, K.D. Lewis, C.H. Chung, L. Hernandez-Aya, A.M. Lim, A.L.S. Chang, G. Rabinowits, A.A. Thai, L.A. Dunn, B.G.M. Hughes, N.I. Khushalani, B. Modi, D. Schadendorf, B. Gao, F. Seebach, S. Li, J. Li, M. Mathias, J. Booth, K. Mohan, E. Stankevich, H.M. Babiker, I. Brana, M. Gil-Martin, J. Homsi, M.L. Johnson, V. Moreno, J. Niu, T.K. Owonikoko, K.P. Papadopoulos, G.D. Yancopoulos, I. Lowy, and M.G. Fury

A **Best Tumor Response for 45 Patients in the Phase 2 Study**



EGFR targeting in cSCC



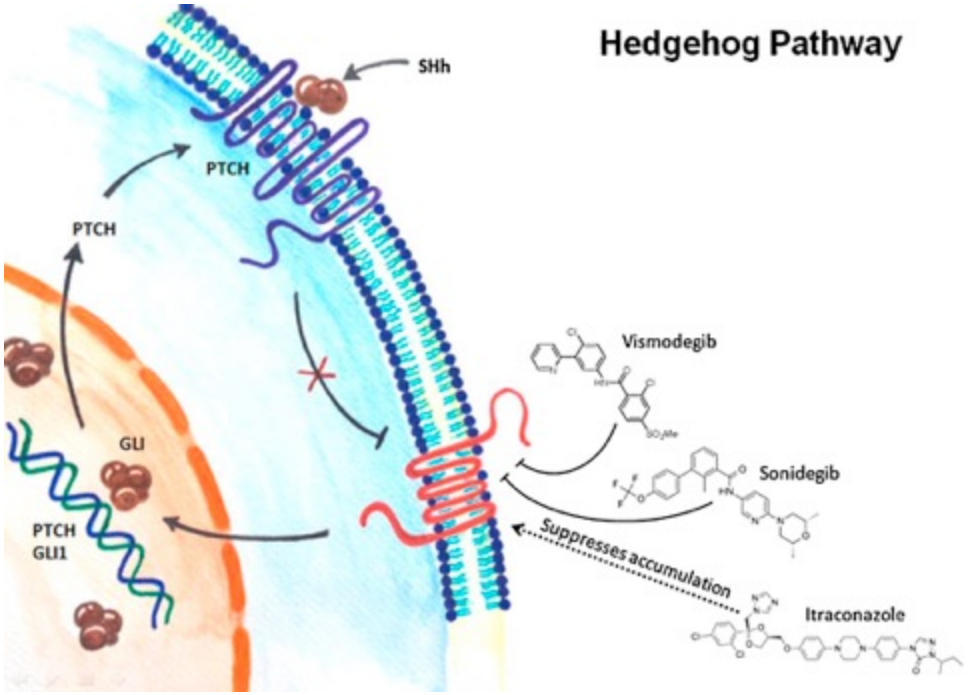
Presented By Axel Hauschild at 2017 ASCO Annual Meeting

Basal cell carcinoma (BCC)

Hedgehog inhibition in BCC: Vismodegib, sonidegib

The hedgehog pathway is active during embryonic development but thought generally to be dormant after birth

<u>Basal cell nevus syndrome</u>: Germline mutation in PTCH gene



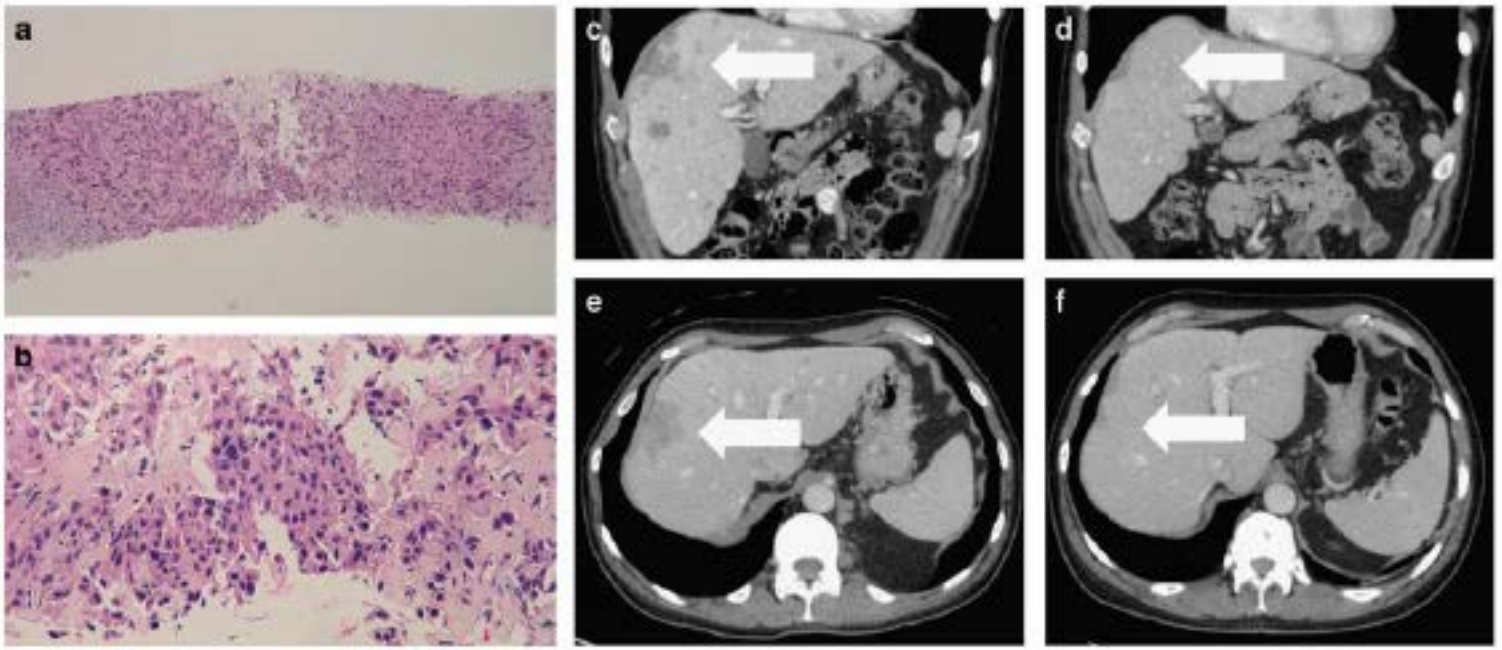
Pros	Cons
Oral	Not well tolerated
High efficacy	Primary/secondary resistance
Can get histologic clearance	

Critical Reviews in Oncology / Hematology 2016 98, 235-241

Resistant BCC: ? Immunotherapy

BCC resistant to hedgehog inhibitor treated with PD-1 antibody (nivolumab).

Baseline 4 months



Ikeda S et al. NPJ Genom Med, 2016

Case

A 75-year old man presents with progressive anorexia, weight loss, night sweats, fatigue and right-sided abdominal pain for the last few weeks.

Imaging studies show **widely disseminated metastase** in multiple organs, including **greater than 50% liver involvement**. Brain MRI showed **5 brain metastases (largest was 1.5 cm in R-frontal lobe)**; he denied neurologic symptoms and neuro exam was WNL.

Baseline

Biopsy of a liver tumor reveals **metastatic melanoma** with **BRAF V600E mutation present**.

Laboratory analyses reveal Hemoglobin 10, **AST 75, AL. 85, ALK-P 375 and Bilirubin 1.5**. His ECOG **performance score is 2**.

What will you recommend next?

A. Whole brain radiation therapy.

B. PD-1 blockade (Pembrolizumab or Nivolumab)

C. Ipilimumab plus Nivolumab

D. BRAFi + MEKi

E. Hospice

Thank you!!

Integrative Oncology – What oncology clinicians need to know

Heather Greenlee, ND, PhD, MPH

Associate Professor, Public Health Sciences/Clinical Research Divisions,
Fred Hutch Cancer Research Center
Associate Professor, Dept of Medicine, Univ of Washington School of Medicine
Medical Director, Integrative Medicine, Seattle Cancer Care Alliance

FRED HUTCH
CURES START HERE®

Comprehensive Hematology and Oncology Review
University of Washington CME
August 2020

Complementary and Integrative Medicine Use among Cancer Patients and Survivors

High use by cancer patients and survivors

- 17+ million cancer survivors in the US
- 60-80% of US cancer survivors use complementary, alternative and integrative medicine
- $6.7 Billion spent in 2012

Patient reasons for use

- Increase survival
- Increase efficacy of conventional cancer therapies
- Prevent & treat side effects of conventional therapies
- Treat existing comorbidities
- Improve quality of life
- Decrease stress

What works?
What doesn't work?
What is safe?

John...Greenlee *J Cancer Surv* 2016

Definitions

Traditional therapies

- Culturally-based health practices

Alternative therapies

- Used in place of conventional medicine

Complementary therapies

- Used with conventional medicine

Integrative medicine

- Evidence-based use of complementary and supportive therapies in conjunction with conventional therapies

What is Integrative Oncology?

Integrative oncology is a **patient-centered**, evidence-informed field of cancer care that utilizes mind and body practices, natural products, and/or lifestyle modifications from different traditions **alongside conventional cancer treatments**.

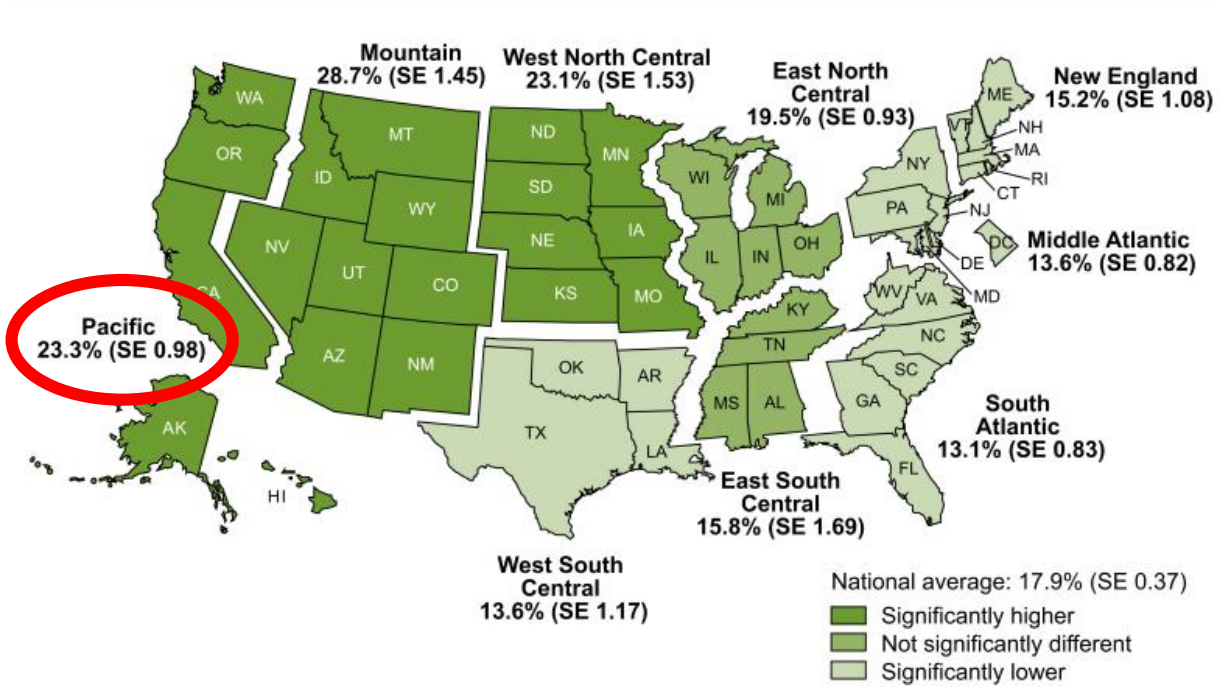
Integrative oncology aims to **optimize health, quality of life, and clinical outcomes** across the cancer continuum and to empower people to prevent cancer and become active participants before, during and beyond cancer treatment.

Society for Integrative Oncology
Witt *J Natl Cancer Inst Monogr* 2017

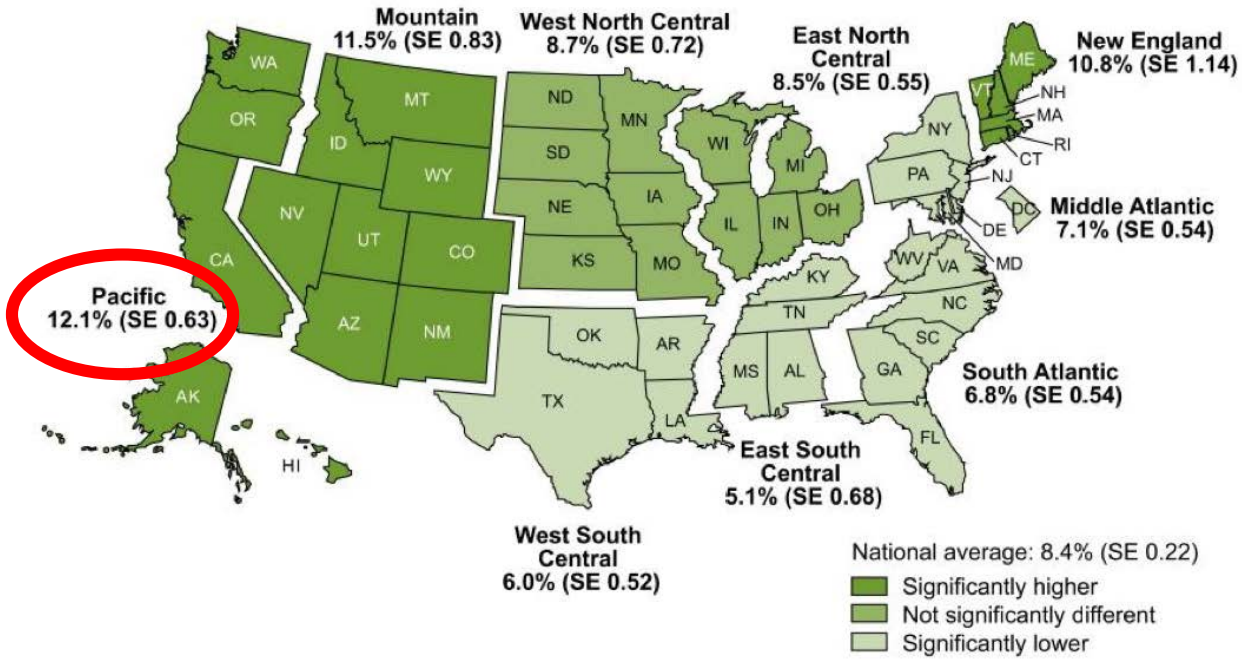
Using cohort studies to examine predictors, patterns and outcomes of use

Use of complementary health approaches in US adults

Use of non-vitamin, non-mineral **dietary supplements**



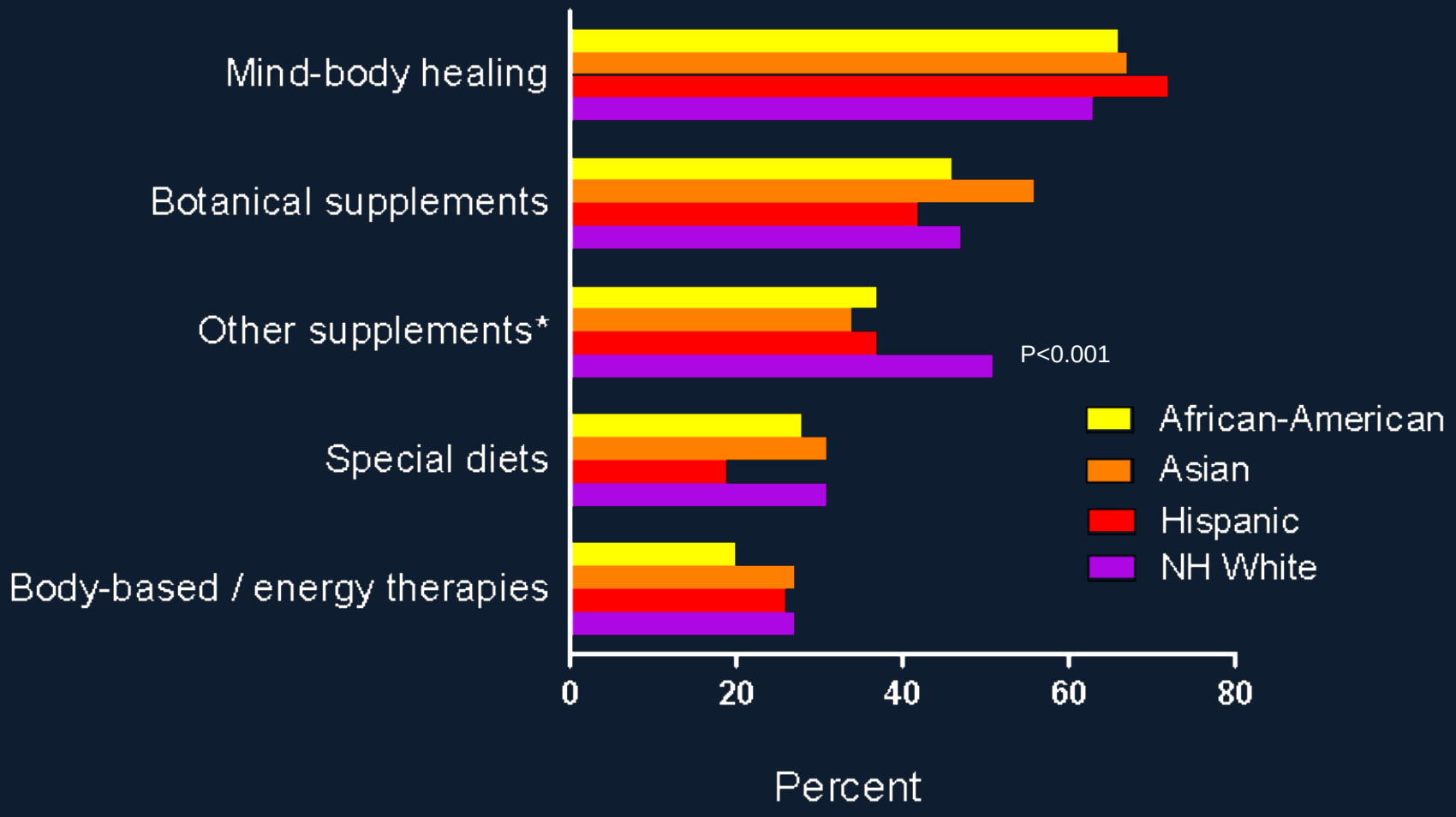
Use of **yoga** and **meditation**



Peregoy *NCHS Data Brief* 2014

CAM use in newly diagnosed Br CA patients

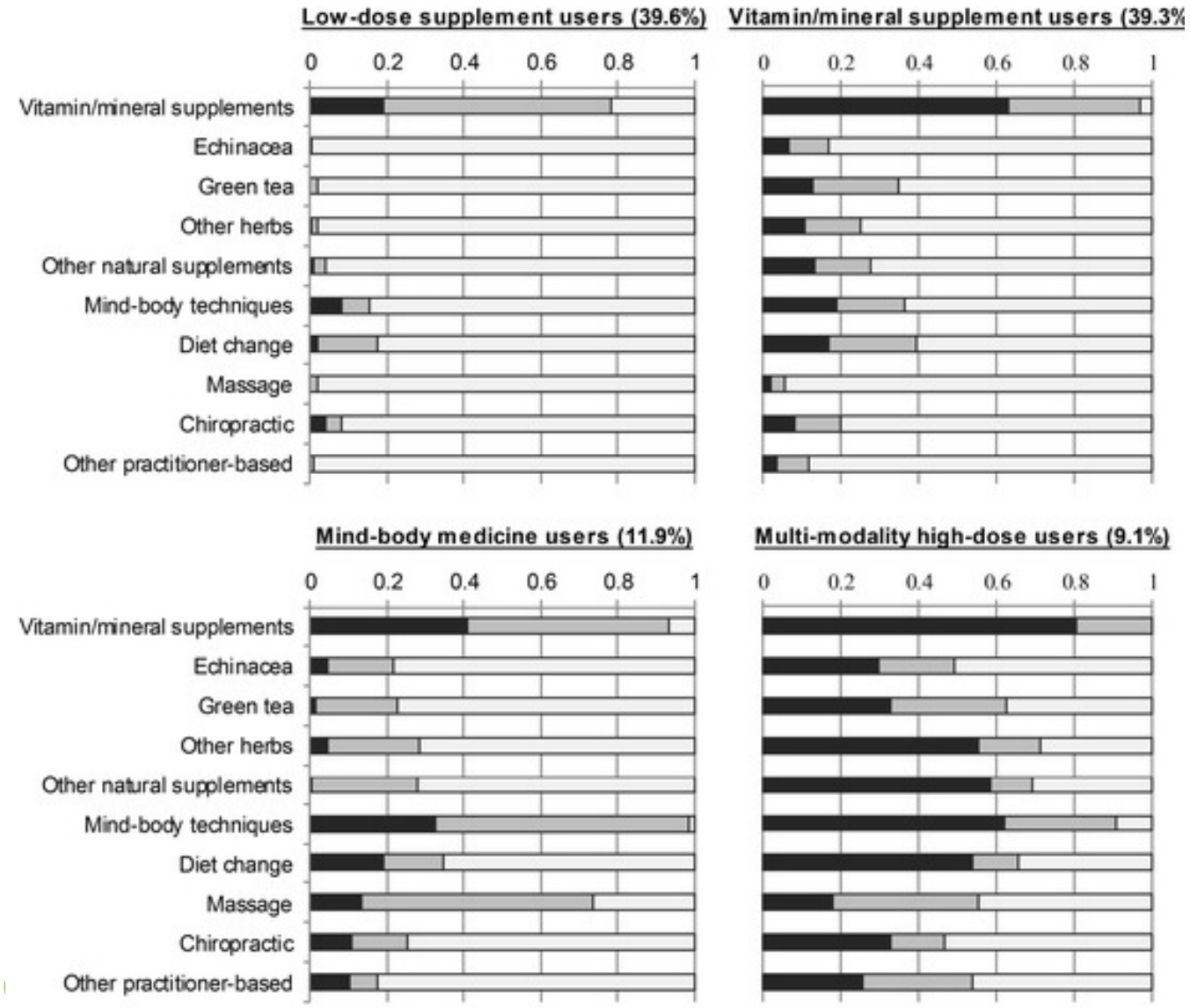
Kaiser Permanente Northern California Pathways Study (n=1,000)
PI: Kushi, R01CA105274



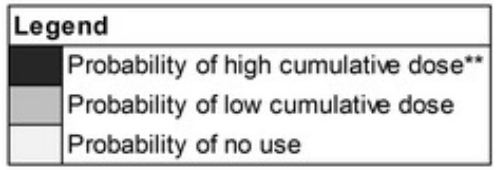
*non-botanical, non-vitamin

Greenlee *Br Cancer Res Treat* 2009

Latent class analysis: Probability of CAM use



Long Island Breast Cancer Study Project (n=764)
PI: M Gammon, UNC



Strizich *BMC Complement Altern Med* 2015

Complementary & Alternative Medicine Use by US Cancer Survivors

US National Health Interview Survey (NHIS)

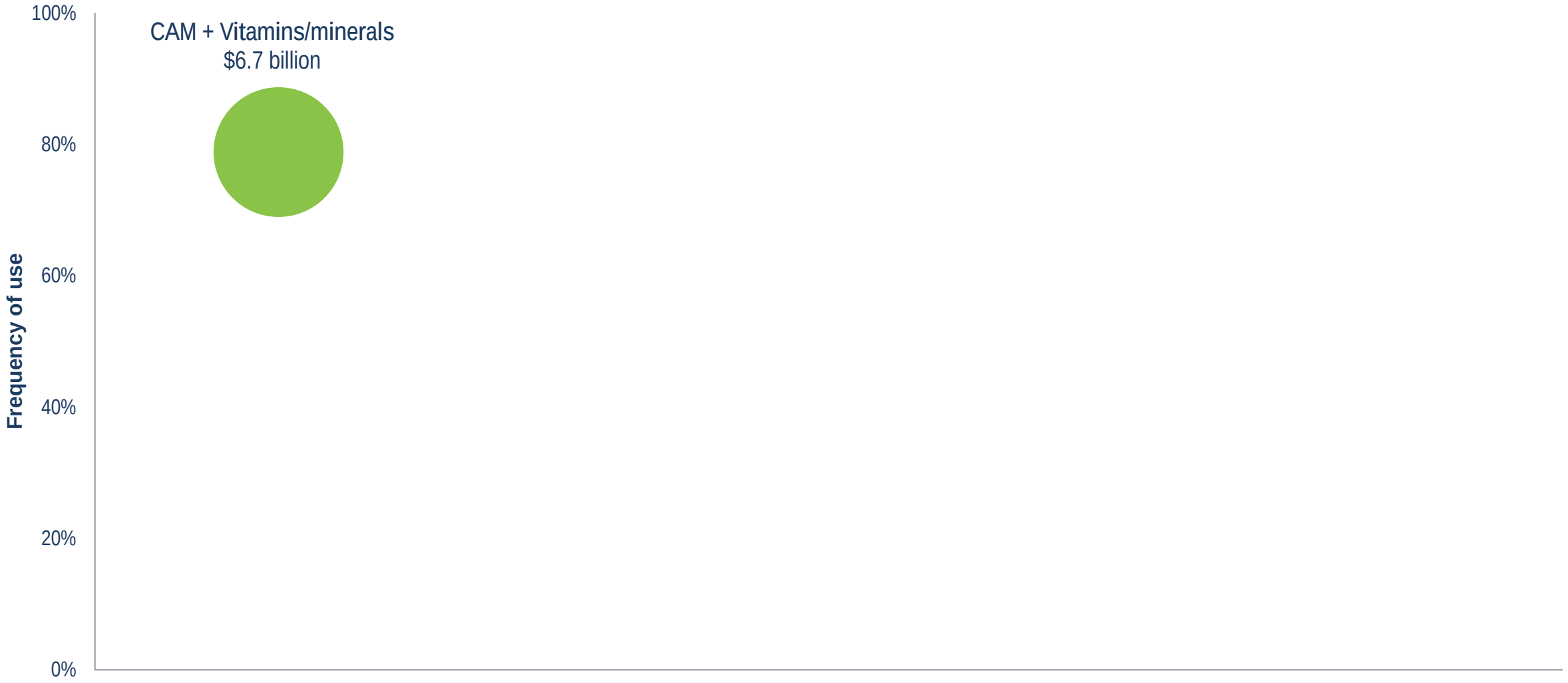
- Annual survey by CDC
- Questions on CAM use since 2002

NHIS 2012

- 2,977 adult cancer survivors and 30,551 non-cancer adults
- Self-reported CAM use in past 12 months
- **79%** of cancer survivors used ≥1 vitamin/mineral and/or CAM modality

John...Greenlee *J Cancer Surv* 2016

Cost of CAM Use by US Cancer Survivors

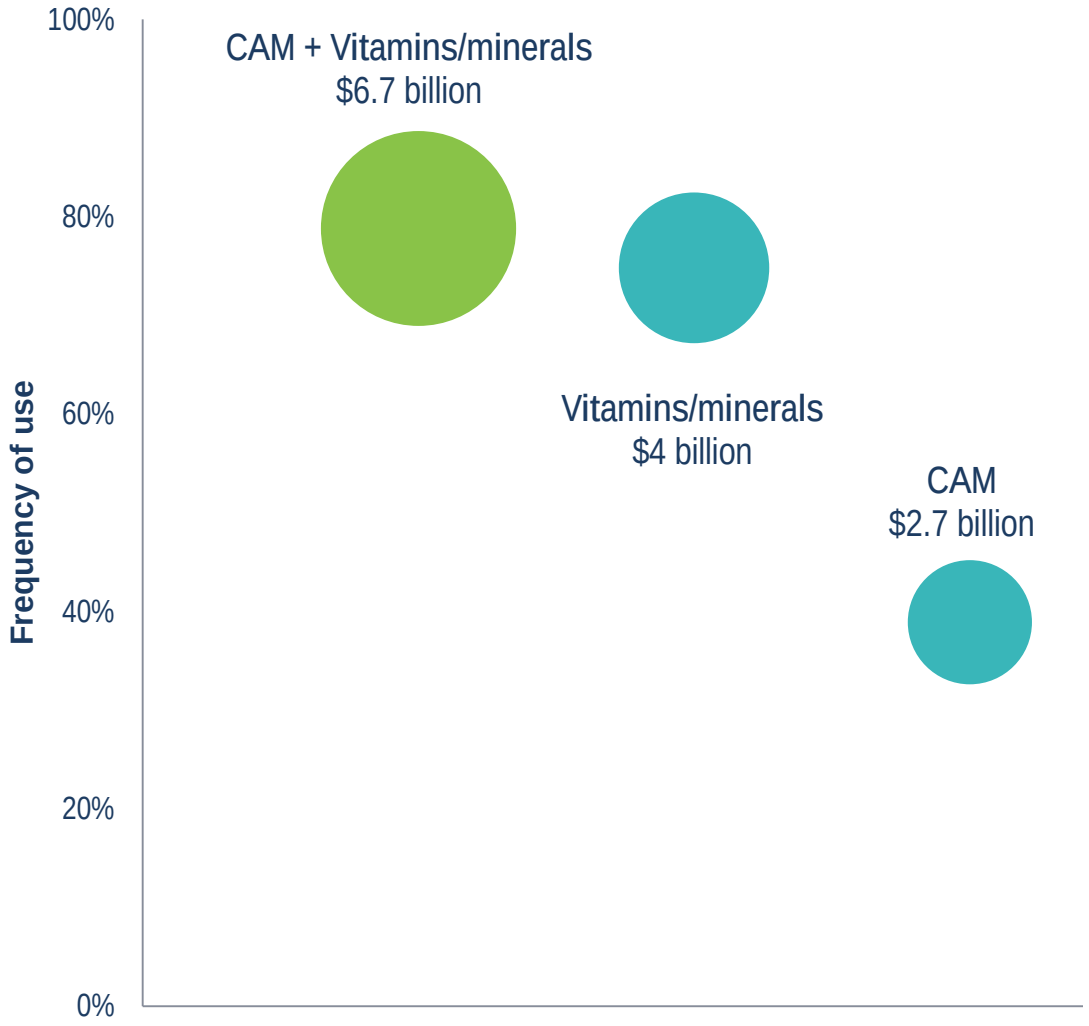


Annual expenditure by US cancer survivors (2012)

John...Greenlee *J Cancer Surv* 2016

FRED HUTCH

Cost of CAM Use by US Cancer Survivors

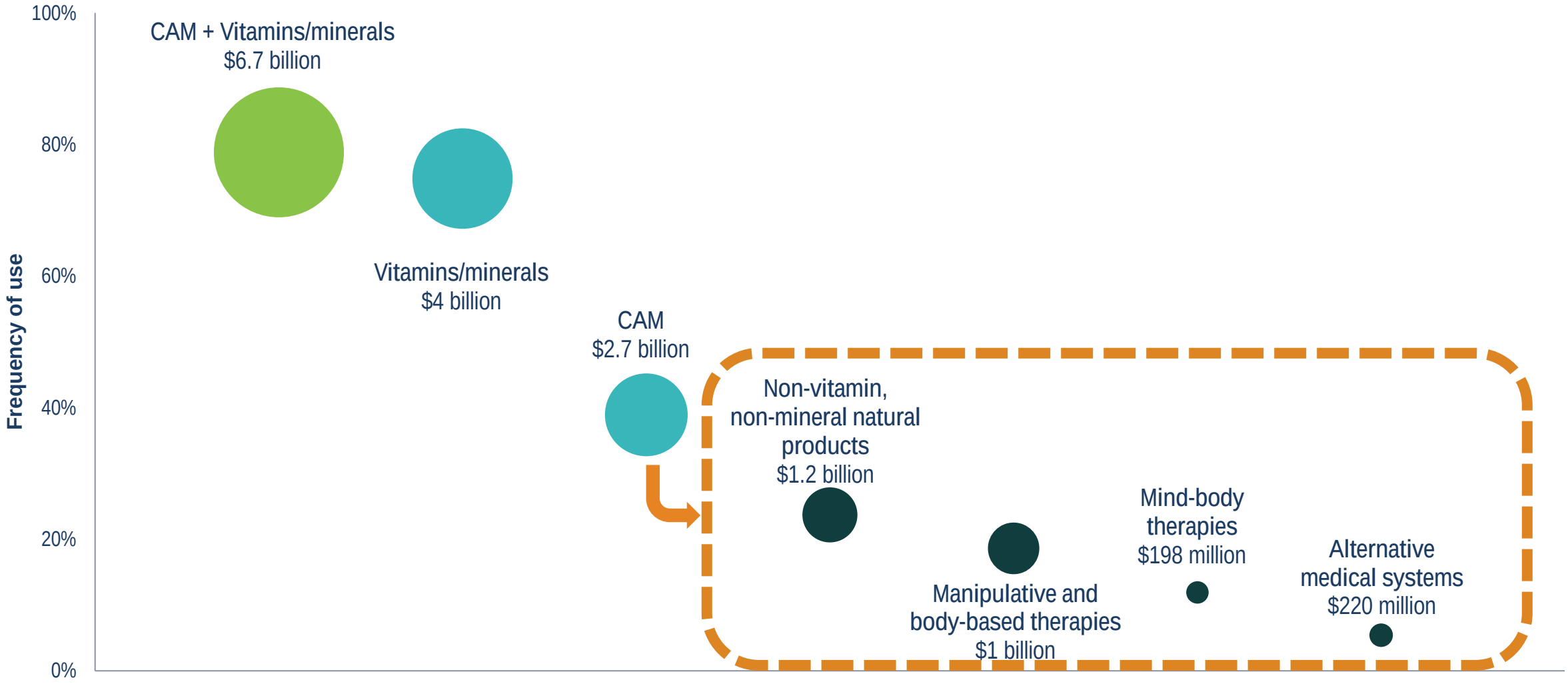


Annual expenditure by US cancer survivors (2012)

John...Greenlee *J Cancer Surv* 2016

FRED HUTCH

Cost of CAM Use by US Cancer Survivors



Annual expenditure by US cancer survivors (2012)

John...Greenlee *J Cancer Surv* 2016

FRED HUTCH

Breast Cancer Quality of Life (BQUAL) Study

Aim: To examine association of CAM use with breast cancer chemotherapy initiation

Setting

- Multi-center prospective cohort study of early stage invasive breast cancer patients
- Recruitment sites: New York (Columbia), N California (KPNC), Detroit (Henry Ford)

Methods

- Assessed baseline CAM use (2006-2010):
  - **Dietary supplements** (n=3 types): vitamin/minerals, botanicals, other products
  - **Mind-body** (n=2 types): mind-body based, and body/energy based treatments
  - **CAM use index**: sum of CAM use (1 point for each type, range 0-5)
- Data collection on clinical characteristics and treatment received
- Used NCCN guidelines/dates to determine if clinically indicated treatment was initiated
- Analyses included women <70 years eligible to receive chemotherapy (n=685)

Greenlee *JAMA Oncol* 2016

Results: CAM & Chemotherapy Initiation

CAM use at baseline

- **87%** of women reported current CAM use; **38**% reported current use of ≥3 modalities

Chemotherapy initiation of clinically indicated treatment

- **89%** initiated chemotherapy; **11%** did not initiate chemotherapy

Association between CAM use and chemo initiation

- Dietary supplement users less likely to initiate (**OR=0.16, 95% CI: 0.03-0.51**)
- High CAM index score less likely to initiate (**OR per unit CAM index=0.64, 95% CI: 0.46-0.87**)
- Mind-body practices not associated with chemotherapy initiation

Greenlee *JAMA Oncol* 2016

Antioxidant use since diagnosis & Br CA outcomes LACE Cohort (n=1,829 antioxidant users)

	All Cause Death HR (95% CI)*	Death from BC HR (95% CI)*	BC Recurrence HR (95% CI)*
Multivitamins			
No Use	Ref	Ref	Ref
Frequent use	1.0 (0.7-1.4)	0.8 (0.5-1.3)	0.9 (0.6-1.3)
Vitamin C alone			
No use	Ref	Ref	Ref
Frequent use	0.8 (0.6-1.1)	0.9 (0.6-1.3)	0.7 (0.6-0.9)
Vitamin E alone			
No use	Ref	Ref	Ref
Frequent use	0.8 (0.6-1.0)	0.9 (0.6-1.3)	0.7 (0.6-1.0)
Combination carotenoids			
No use	Ref	Ref	Ref
Frequent use	1.8 (1.1-2.7)	2.1 (1.2-3.6)	1.3 (0.8-2.2)

*Adjusted for age at diagnosis, race/ethnicity, education, stage at diagnosis, # positive lymph nodes, hormone receptor status, chemotherapy, radiation therapy, hormonal therapy, BMI, smoking, alcohol, physical activity, fruits/vegetables, and comorbidity score at enrollment.

PI: B Caan, KPNC
Greenlee, Kwan,…Caan *Cancer* 2011

Effects of integrative therapies on decreasing treatment toxicities

Effects of dietary supplements on toxicities

Aromatase inhibitor induced arthralgias in breast cancer patients

- Glucosamine & Chondroitin / Phase II single arm → Null (Greenlee *Support Care Cancer* 2013)
- Fish Oil / RCT SWOG S0927 → Null (Hershman *J Clin Oncol* 2015)

Chemotherapy-induced peripheral neuropathy in breast cancer patients

- Acetyl-L-Carnitine / RCT SWOG S0715 → Harmful (Hershman *J Clin Oncol* 2013)

Anthracycline-induced cardiotoxicity in breast cancer patients

- Coenzyme Q10 / Phase I dose-finding trial → Closed early (unpublished)

Hepatic function in liver cancer patients

- Milk thistle / Phase I dose-finding trial → Closed early (Siegel *Integr Cancer Ther* 2014)

July 10, 2018

JAMA | Original Investigation

Effect of Acupuncture vs Sham Acupuncture or Waitlist Control on Joint Pain Related to Aromatase Inhibitors Among Women With Early-Stage Breast Cancer

A Randomized Clinical Trial

Dawn L. Hershman, MD, MS; Joseph M. Unger, PhD, MS; Heather Greenlee, ND, PhD; Jillian L. Capodice, MS, LAc; Danika L. Lew, MA; Amy K. Darke, MS; Alice T. Kengla, MD; Marianne K. Melnik, MD; Carla W. Jorgensen, MD; William H. Kreisle, MD; Lori M. Minasian, MD; Michael J. Fisch, MD; N. Lynn Henry, MD; Katherine D. Crew, MD, MS

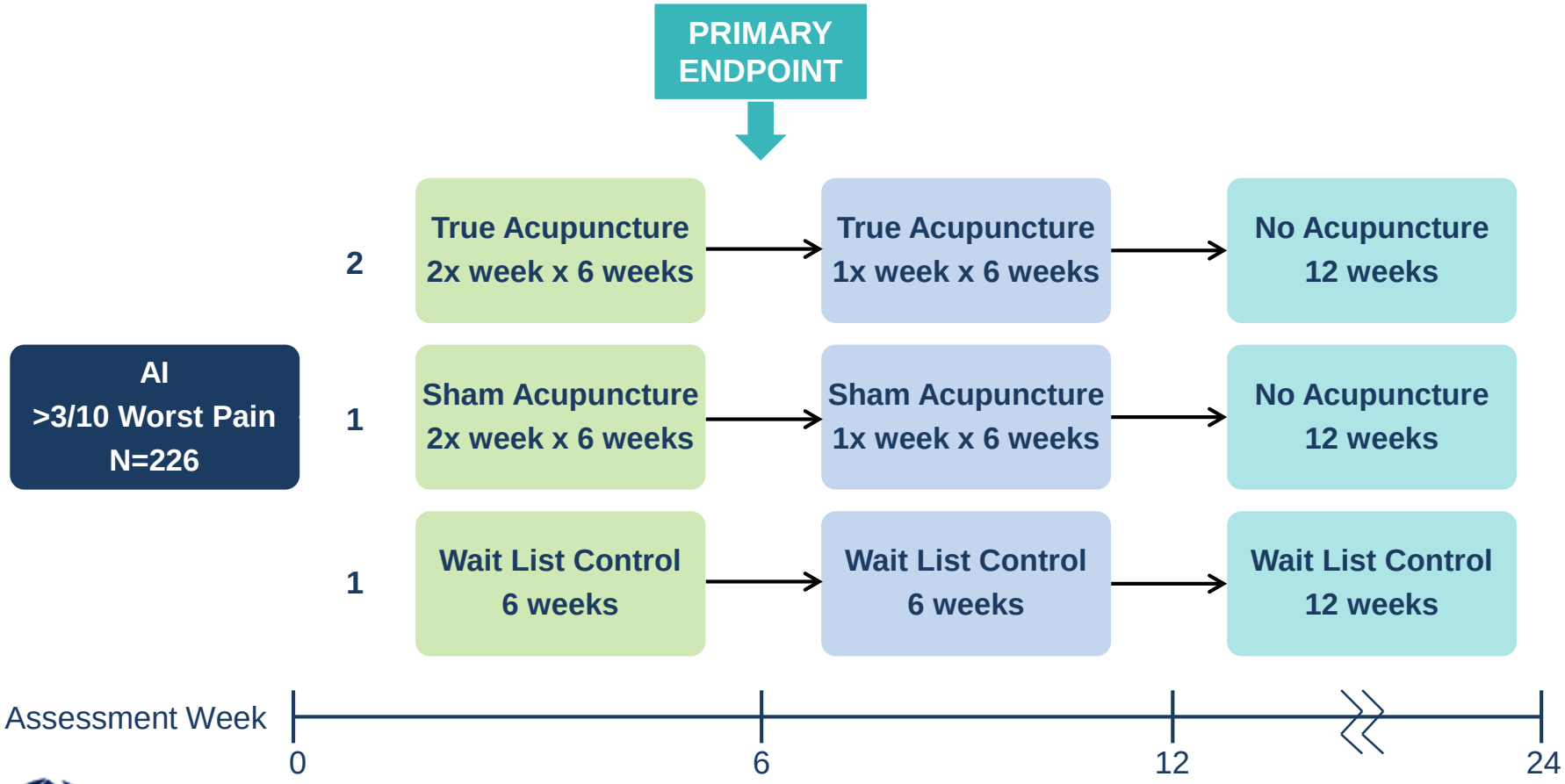
IMPORTANCE Musculoskeletal symptoms are the most common adverse effects of aromatase inhibitors and often result in therapy discontinuation. Small studies suggest that acupuncture may decrease aromatase inhibitor–related joint symptoms.

OBJECTIVE To determine the effect of acupuncture in reducing aromatase inhibitor–related joint pain.

Supplemental content

Related article at jamaoncology.com

S1200 Study design



SWOG
Leading cancer research. Together.

PI: D Hershman
Funded by NCI & NCCIH
Hershman *JAMA* 2018

Acupuncturist training

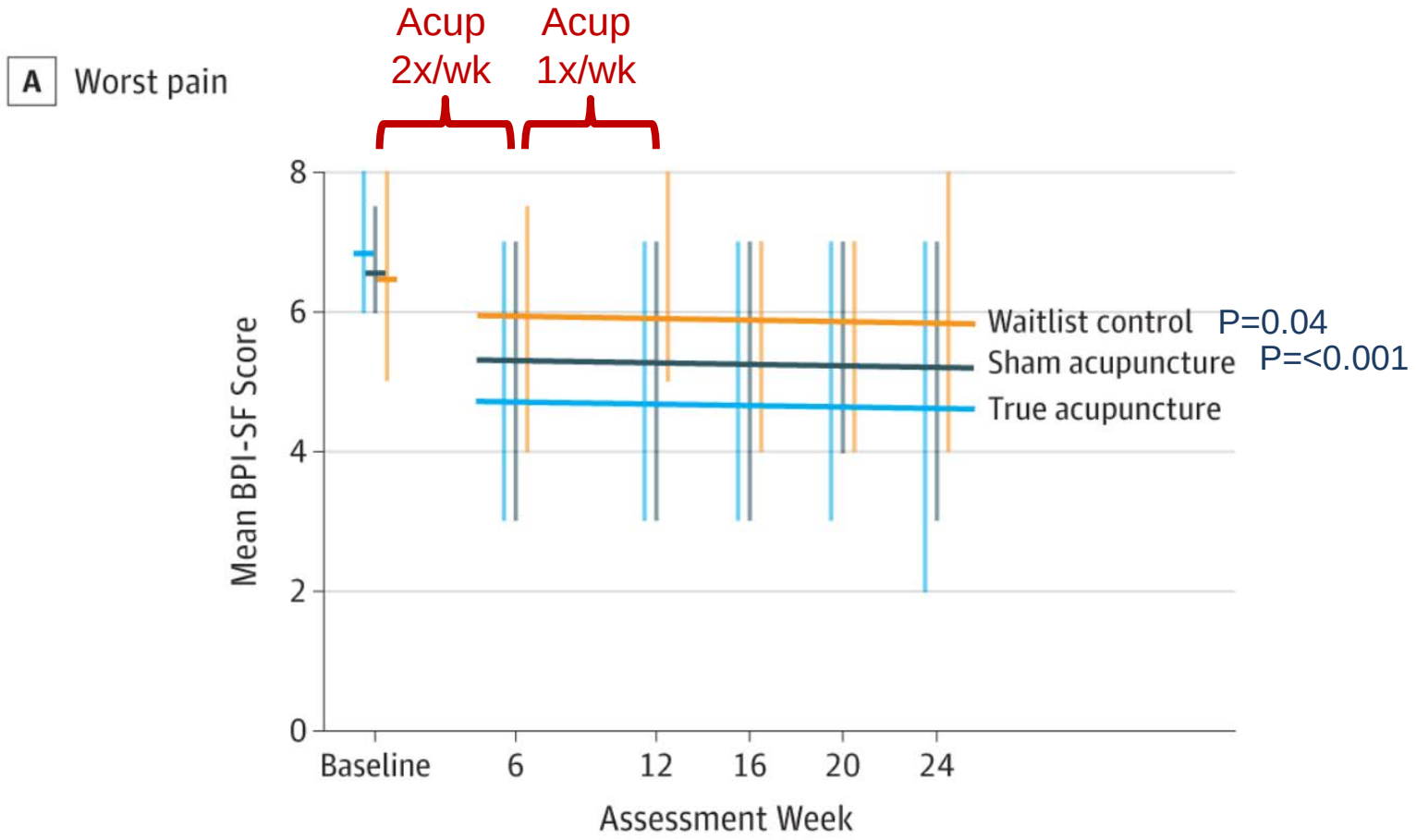
- **Interventions provided by licensed acupuncturists (n=60) at 11 sites**
- **In-person / on-site acupuncturist training**
- **Online training modules**
  - Videos
  - Visuals acupoint location
- **Training manuals**
- **Monthly teleconference**
- **Annual quality assurance**
  - Quality assurance training
  - Web-based quiz
  - Practical demonstration – video-based (Skype or Recorded)

SWOG
Leading cancer research. Together.

Greenlee *J Acupunct Meridian Stud* 2015

Randomized Blinded Sham- & Waitlist-Controlled Trial of Acupuncture for Joint Symptoms Related to Aromatase Inhibitors in Women with Early Stage Breast Cancer (SWOG S1200)

Linear Mixed Model Results



No. of patients						
Waitlist control	56	51	51	48	45	50
Sham acupuncture	59	54	54	53	52	54
True acupuncture	109	100	101	94	97	97

SWOG
Leading cancer research. Together.

Hershman *JAMA* 2018

January 2020 – CMS covers acupuncture for back pain

! CMS.gov

Centers for Medicare & Medicaid Services

Press release

CMS finalizes decision to cover Acupuncture for Chronic Low Back Pain for Medicare beneficiaries

Jan 21, 2020 | Coverage, Opioids

Today the Centers for Medicare & Medicaid Services (CMS) finalized a decision to cover acupuncture for Medicare patients with chronic low back pain. Before this final National Coverage Determination (NCD) reconsideration, acupuncture was nationally non-covered by Medicare. CMS conducted evidence reviews and examined the coverage policies of private payers to inform today's decision.

"*We are dedicated to increasing access to alternatives to prescription opioids and believe that covering acupuncture for chronic low back pain is in the best interest of Medicare patients.*"

CMS Principal Deputy Administrator of Operations and Policy Kimberly Brandt

Developing clinical practice guidelines

OUR MISSION:

TO ADVANCE EVIDENCE BASED, COMPREHENSIVE, INTEGRATIVE HEALTHCARE TO IMPROVE THE LIVES OF PEOPLE AFFECTED BY CANCER.

SIO 2020 Virtual Conference is October 16-17, 2020

Please visit our Conference Home Page for more information and to register.

SIO Offers Membership Scholarship

SIO is pleased to offer 2020 membership scholarships for patient advocates, trainees and

Navajo Nation's Regional Healthcare Facility Needs Our Help

The current COVID-19 pandemic has acutely affected the Navajo Nation, which lives in a region spanning parts of Arizona, Utah and New Mexico. Historically, the Navajo People have suffered high rates of diabetes, cardiovascular disease and cancer, all of which contribute to increased risk for poorer COVID-19 outcomes.

For decades, tribal land has been left without basic

Events Calendar

Oct 16 SIO 2020 Virtual Conference

Sep 24 SIO 2021 18th International Conference

Interventions of Interest

Natural products (e.g., botanicals, vitamins, minerals)

Mind-body practices

- Meditation
- Yoga
- Hypnosis
- Imagery/Relaxation
- Creative Therapies
- Stress Management
- Tai Chi/Qigong

Acupuncture/acupressure/electro-acupuncture

Massage therapy

Whole systems (e.g., naturopathy, traditional Chinese medicine)

* Due to previous reviews by ACS, AICR, and the American College of Sports Medicine, did not include: Diet, Physical Activity, Energy Balance

Clinically relevant outcomes of interest

Fatigue

Gastrointestinal

Gynecological

Hematological

Lymphedema

Neurological

Neuromuscular

Psychological

Quality of life

Vasomotor symptoms

Skin

Renal

Sleep

Pain

Note: Immune parameters were not included

https://integrativeonc.org/integrative-oncology-guidelines

CA CANCER J CLIN 2017;67:194–232

Clinical Practice Guidelines on the Evidence-Based Use of Integrative Therapies During and After Breast Cancer Treatment

Heather Greenlee, ND, PhD, MPH[1,2]; Melissa J. DuPont-Reyes, MPH, MPhil[3]; Lynda G. Balneaves, RN, PhD[4]; Linda E. Carlson, PhD[5]; Misha R. Cohen, OMD, LAc[6,7]; Gary Deng, MD, PhD[8]; Jillian A. Johnson, PhD[9]; Matthew Mumber, MD[10]; Dugald Seely, ND, MSc[11,12]; Suzanna M. Zick, ND, MPH[13,14]; Lindsay M. Boyce, MLIS[15]; Debu Tripathy, MD[16]

CME CNE

[1]Assistant Professor, Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY; [2]Member, Herbert Irving Comprehensive Cancer Center, Columbia University, New York, NY; [3]Doctoral Fellow, Department of Epidemiology, Mailman School of Public Health, Columbia University, New York, NY; [4]Associate Professor, College of Nursing, Rady Faculty of Health Sciences, Winnipeg, MB, Canada; [5]Professor, Department of Oncology, University of Calgary, Calgary, AB, Canada; [6]Adjunct Professor, American College of Traditional Chinese Medicine at California Institute of Integral Studies, San Francisco, CA; [7]Clinic Director, Chicken Soup Chinese Medicine, San Francisco, CA; [8]Medical Director, Integrative Oncology

Abstract: Patients with breast cancer commonly use complementary and integrative therapies as supportive care during cancer treatment and to manage treatment-related side effects. However, evidence supporting the use of such therapies in the oncology setting is limited. This report provides updated clinical practice guidelines from the Society for Integrative Oncology on the use of integrative therapies for specific clinical indications during and after breast cancer treatment, including anxiety/stress, depression/mood disorders, fatigue, quality of life/physical functioning, chemotherapy-induced nausea and vomiting, lymphedema, chemotherapy-induced peripheral neuropathy, pain, and sleep disturbance. Clinical practice guidelines are based on a systematic literature review from 1990 through 2015. Music therapy, meditation, stress management, and yoga are recommended for anxiety/stress reduction. Meditation, relaxation, yoga, massage, and music therapy are recommended for depression/mood disorders. Meditation and yoga are recommended to improve quality of life. Acupressure and acupuncture are recommended for reducing chemotherapy-induced

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline

Gary H. Lyman, Heather Greenlee, Kari Bohlke, Ting Bao, Angela M. DeMichele, Gary E. Deng, Judith M. Fouladbakhsh, Brigitte Gil, Dawn L. Hershman, Sami Mansfield, Dawn M. Mussallem, Karen M. Mustian, Erin Price, Susan Rafte, and Lorenzo Cohen

Author affiliations and support information (if applicable) appear at the end of this article.

Published at jco.org on June 11, 2018.

G.H.L. and L.C. were Expert Panel co-chairs.

Clinical Practice Guideline Committee Approved: March 8, 2018.

Editor's note: This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations,

ABSTRACT

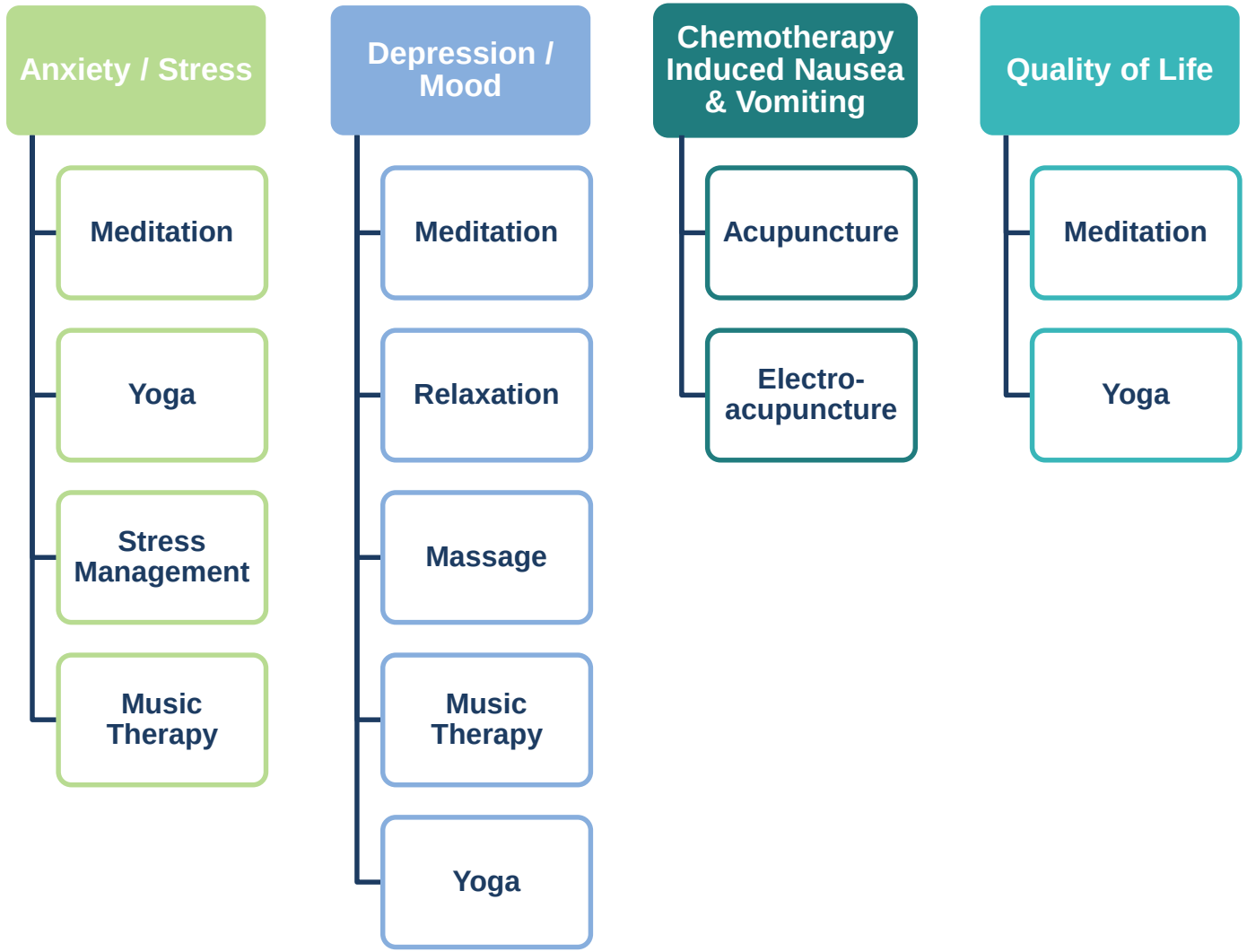
Purpose

The Society for Integrative Oncology (SIO) produced an evidence-based guideline on use of integrative therapies during and after breast cancer treatment that was determined to be relevant to the American Society of Clinical Oncology (ASCO) membership. ASCO considered the guideline for endorsement.

Methods

The SIO guideline addressed the use of integrative therapies for the management of symptoms and adverse effects, such as anxiety and stress, mood disorders, fatigue, quality of life, chemotherapy-induced nausea and vomiting, lymphedema, chemotherapy-induced peripheral neuropathy, pain,

Recommended Therapies

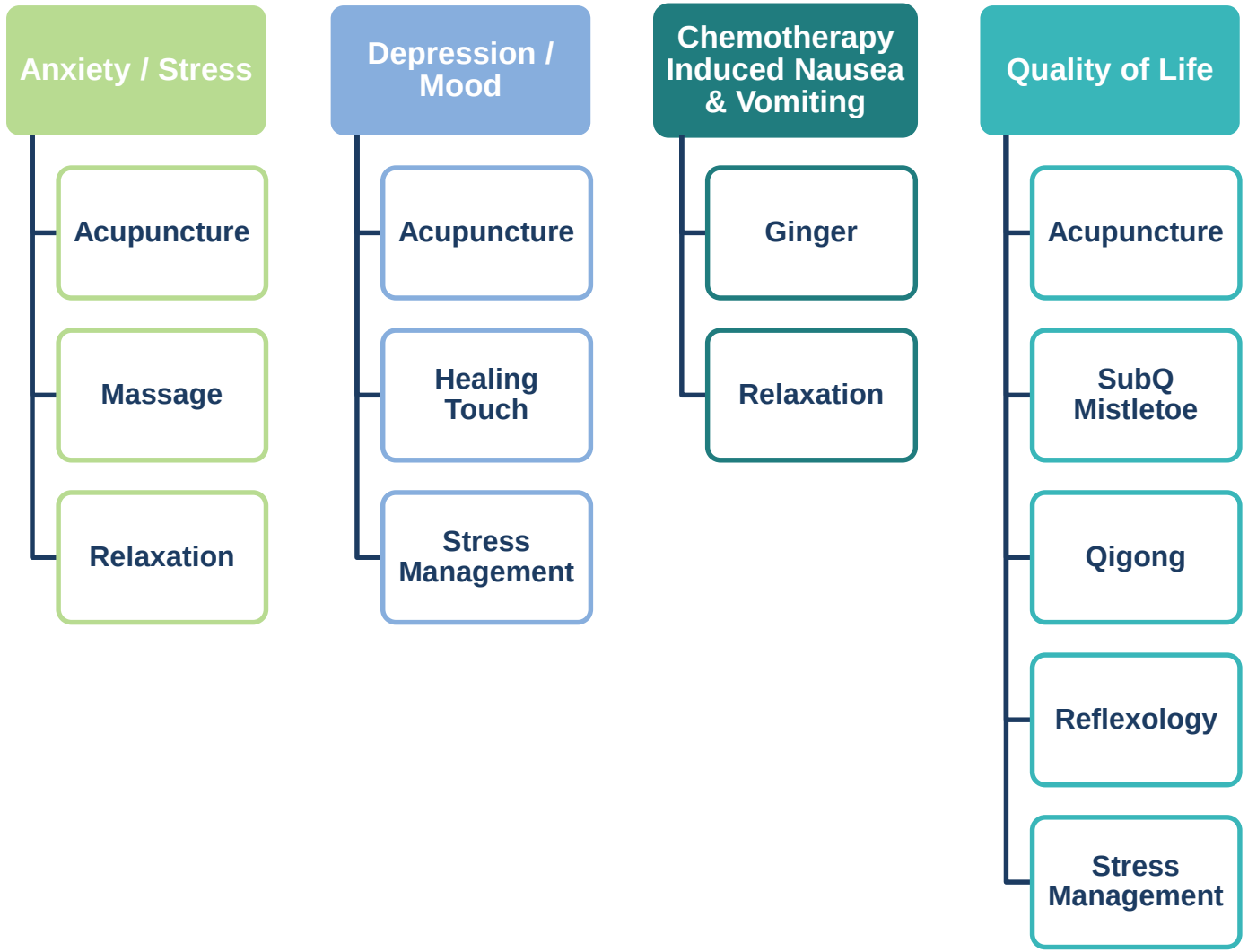


***High certainty* that the net benefit is substantial or moderate to substantial**

FRED HUTCH

Greenlee et al, *CA Cancer J Clin*, 2017

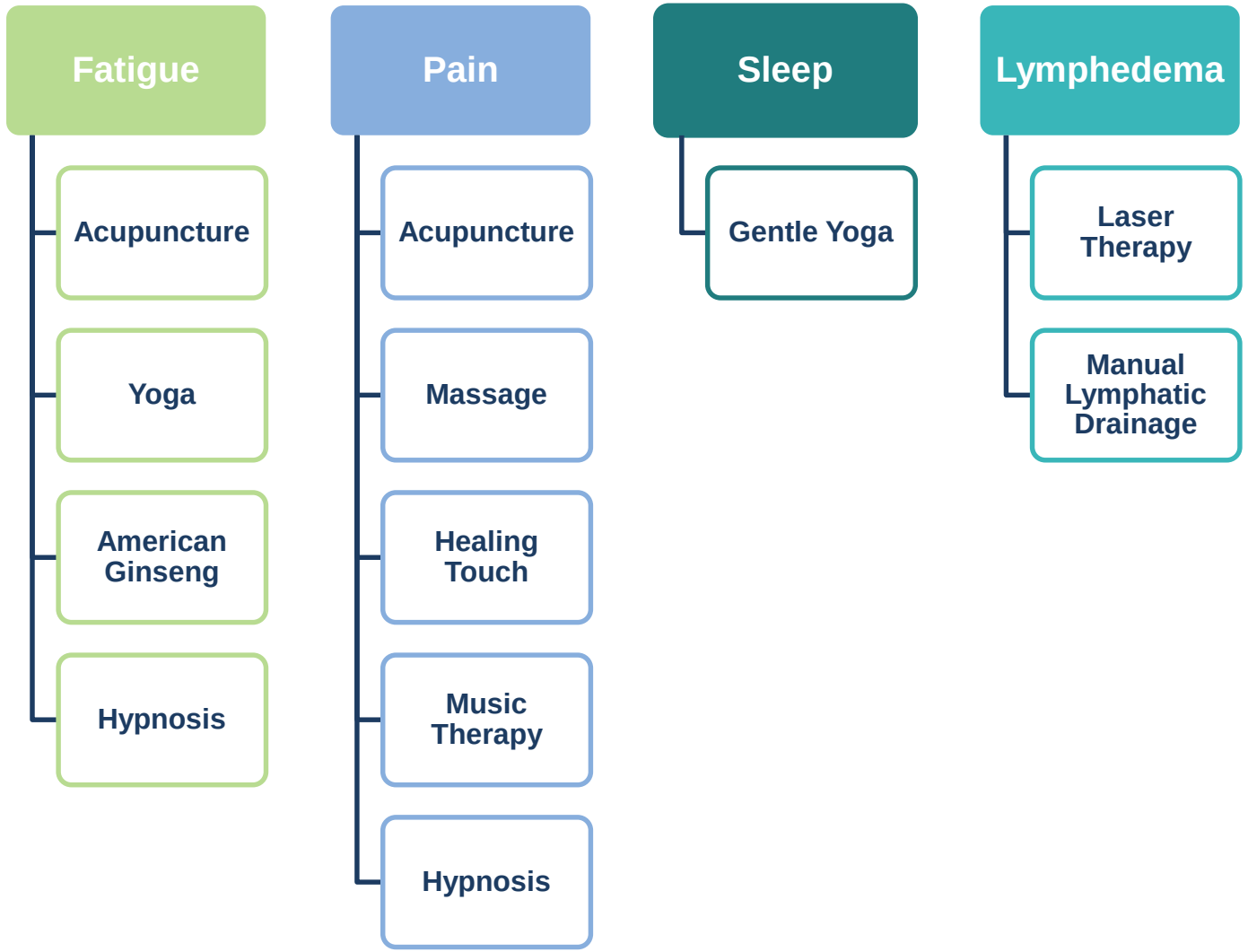
Therapies to Consider



At least moderate certainty that the net benefit is small

Greenlee et al, *CA Cancer J Clin*, 2017

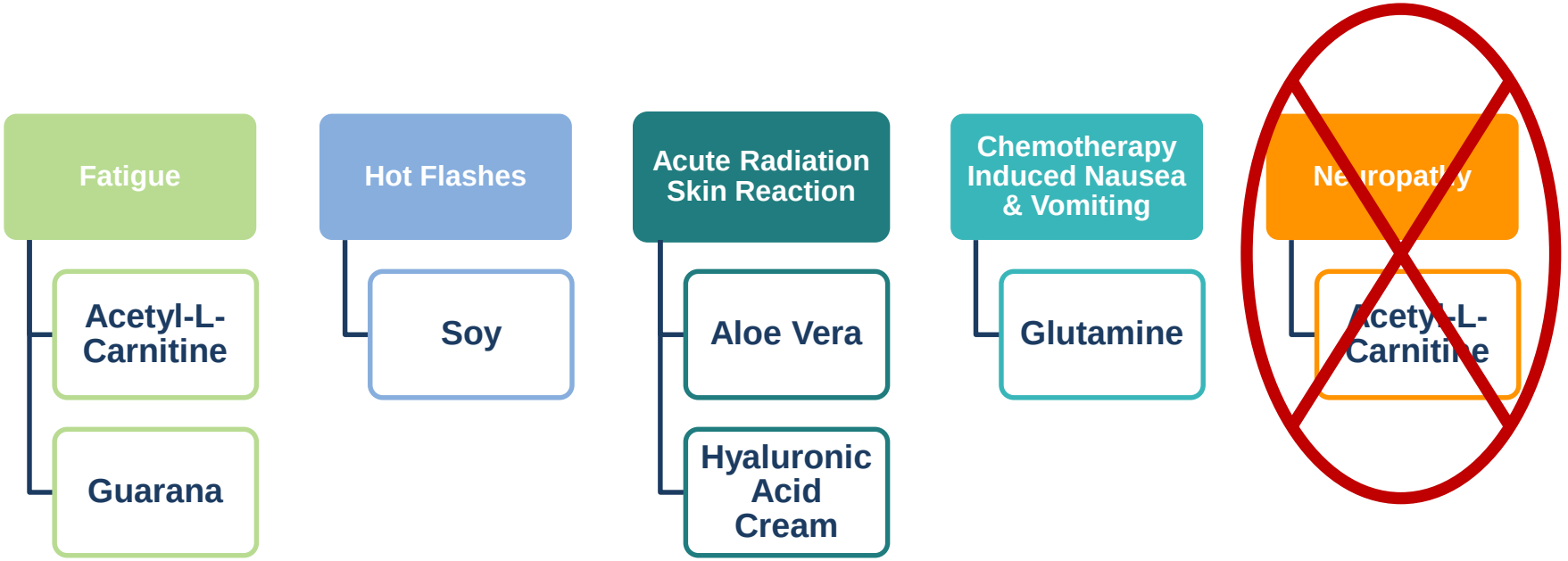
Therapies to Consider



At least moderate certainty that the net benefit is small

Greenlee et al, *CA Cancer J Clin*, 2017

Therapies with *No Benefit* or Harm



Not recommended due to no benefit or harm

Greenlee et al, *CA Cancer J Clin*, 2017

THE BOTTOM LINE

Integrative Therapies During and After Breast Cancer Treatment: ASCO Endorsement of the SIO Clinical Practice Guideline

ASCO endorses the SIO guideline, Clinical Practice Guidelines on the Evidence-Based Use of Integrative Therapies During and After Breast Cancer Treatment, with some added discussion points.

ASCO Discussion Point 1: The Grade B recommendations for **acupressure and electroacupuncture** differ from the 2017 ASCO antiemetic guideline, which states that evidence remains insufficient for a recommendation for or against complementary therapies for chemotherapy-induced nausea and vomiting. The ASCO Expert Panel feels that Grade C would be more appropriate given the limitations of the available evidence.

ASCO Discussion Point 2: The safety and efficacy of **ginseng** may vary by type of ginseng, and patients should seek guidance from a health care professional before using a dietary supplement. Some ginseng preparations may have estrogenic properties. The ginseng studies cited by the SIO guideline used American ginseng (Panax quinquefolius) that was tested for quality and potency; the duration of treatment in these studies was short (8 weeks), and the safety and efficacy of ginseng over longer periods remains uncertain.

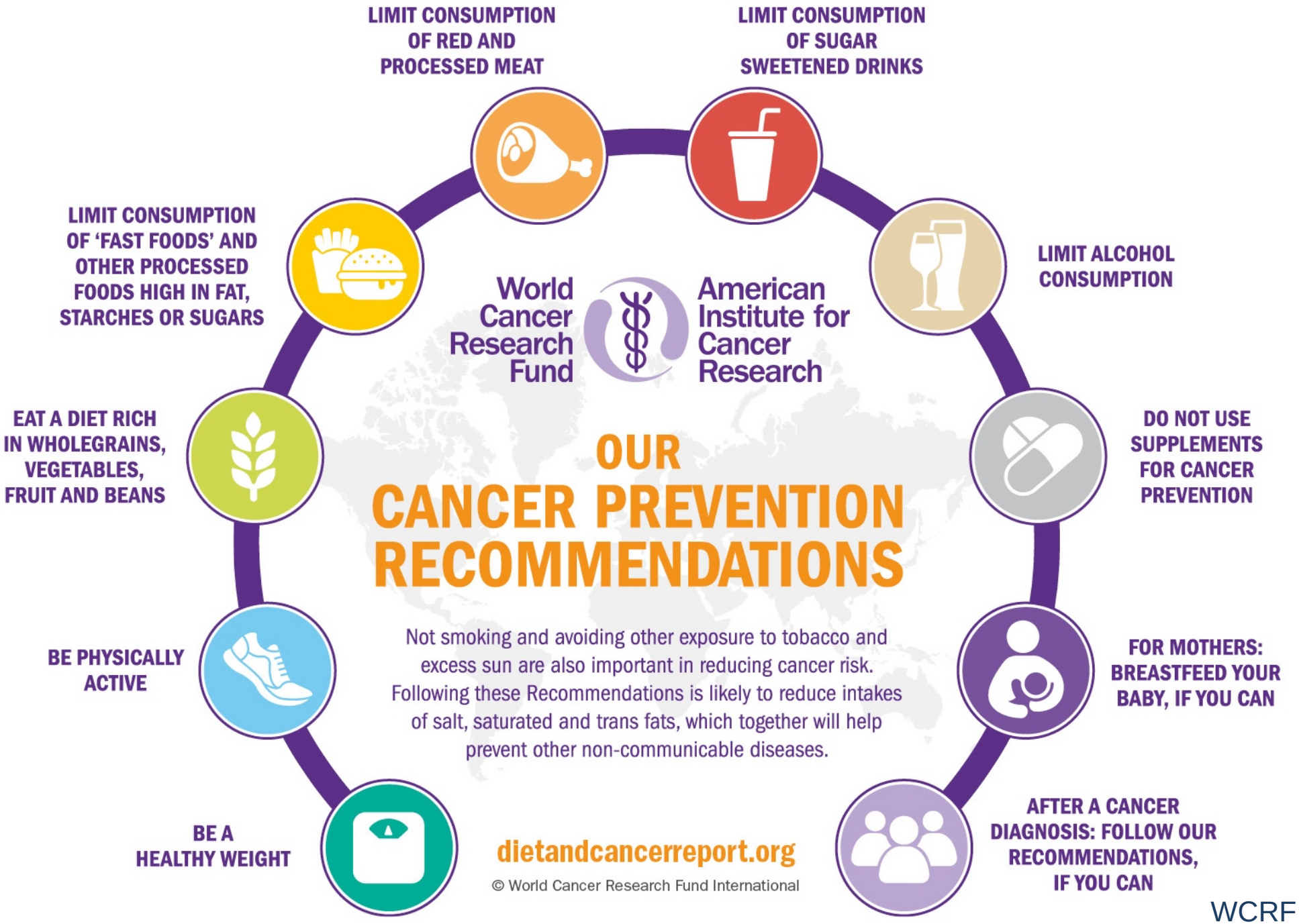
ASCO Discussion Point 3: The **mistletoe** trials cited by the SIO guideline evaluated subcutaneous delivery only. Subcutaneous mistletoe is not currently approved by the US Food and Drug Administration. Orally available mistletoe is available in the United States, but ingestion of high doses of mistletoe berry or leaf is known to cause serious adverse reactions.

Lyman et al, *J Clin Oncol,* 2018

Conclusions - clinical practice guidelines

- Guidelines improve the ability for patients and clinicians to make healthcare decisions
- Body of evidence supports routine use of selected integrative therapies in the oncology setting
- Recommended clinical practice regarding CAM use:
  - CAM use needs to be discussed upfront and monitored
  - Patients need to be advised about evidence
- Clinical practice guidelines provide an aid to making complex clinical decisions
- SIO aims to be the leader in developing trustworthy guidelines focused on integrative oncology

Identifying effective strategies to improve diet, physical activity & weight management



WCRF / AICR 2018

Effects of Exercise on Health-Related Outcomes in Those with Cancer

What can exercise do?

- **Prevention of 7 common cancers***
  Dose: 2018 Physical Activity Guidelines for Americans: 150-300 min/week moderate or 75-150 min/week vigorous aerobic exercise
- **Survival of 3 common cancers****
  Dose: Exact dose of physical activity needed to reduce cancer-specific or all-cause mortality is not yet known; Overall more activity appears to lead to better risk reduction

**bladder, breast, colon, endometrial, esophageal, kidney and stomach cancers*
***breast, colon and prostate cancers*

Outcome	Aerobic Only	Resistance Only	Combination (Aerobic + Resistance)
Strong Evidence	Dose	Dose	Dose
Cancer-related fatigue	**3x**/week for **30** min per session of moderate intensity	**2x**/week of **2** sets of **12-15** reps for major muscle groups at moderate intensity	**3x**/week for **30** min per session of moderate aerobic exercise, plus **2x**/week of resistance training **2** sets of **12-15** reps for major muscle groups at moderate intensity
Health-related quality of life	**2-3x**/week for **30-60** min per session of moderate to vigorous	**2x**/week of **2** sets of **8-15** reps for major muscle groups at a moderate to vigorous intensity	**2-3x**/week for **20-30** min per session of moderate aerobic exercise plus **2x**/week of resistance training **2** sets of **8-15** reps for major muscle groups at moderate to vigorous intensity
Physical Function	**3x**/week for **30-60** min per session of moderate to vigorous	**2-3x**/week of **2** sets of **8-12** reps for major muscle groups at moderate to vigorous intensity	**3x**/week for **20-40** min per session of moderate to vigorous aerobic exercise, plus **2-3x**/week of resistance training **2** sets of **8-12** reps for major muscle group at moderate to vigorous intensity
Anxiety	**3x**/week for **30-60** min per session of moderate to vigorous	Insufficient evidence	**2-3x**/week for **20-40** min of moderate to vigorous aerobic exercise plus **2x**/week of resistance training of **2** sets, **8-12** reps for major muscle groups at moderate to vigorous intensity
Depression	**3x**/week for **30-60** min per session of moderate to vigorous	Insufficient evidence	**2-3x**/week for **20-40** min of moderate to vigorous aerobic exercise plus **2x**/week of resistance training of **2** sets, **8-12** reps for major muscle groups at moderate to vigorous intensity
Lymphedema	Insufficient evidence	**2-3x**/week of progressive, supervised, program for major muscle groups does not exacerbate lymphedema	Insufficient evidence
Moderate Evidence			
Bone health	Insufficient evidence	**2-3x**/week of moderate to vigorous resistance training plus high impact training (sufficient to generate ground reaction force of **3-4** time body weight) for at least **12** months	Insufficient evidence
Sleep	**3-4x**/week for **30-40** min per session of moderate intensity	Insufficient evidence	Insufficient evidence

Citation: bit.ly/cancer_exercise_guidelines

serve or VO_2R) is recommended.

Exercise is Medicine® | AMERICAN COLLEGE of SPORTS MEDICINE®

cookforyourlife.org

Cook for Your LIFE

We teach healthy cooking to people touched by cancer

Cookforyourlife.org

RECIPES VIDEOS BLOG ABOUT US COVID-19 ESPAÑOL DONATE

ABOUT OUR FOUNDER, ANN

Recipe of the day

Mango Avocado Salsa

VIDEO

RECIPES

ANN'S PICKS

CANCER FIGHTER

BLOG

DONATE

Integrative Medicine at the Seattle Cancer Care Alliance (SCCA)

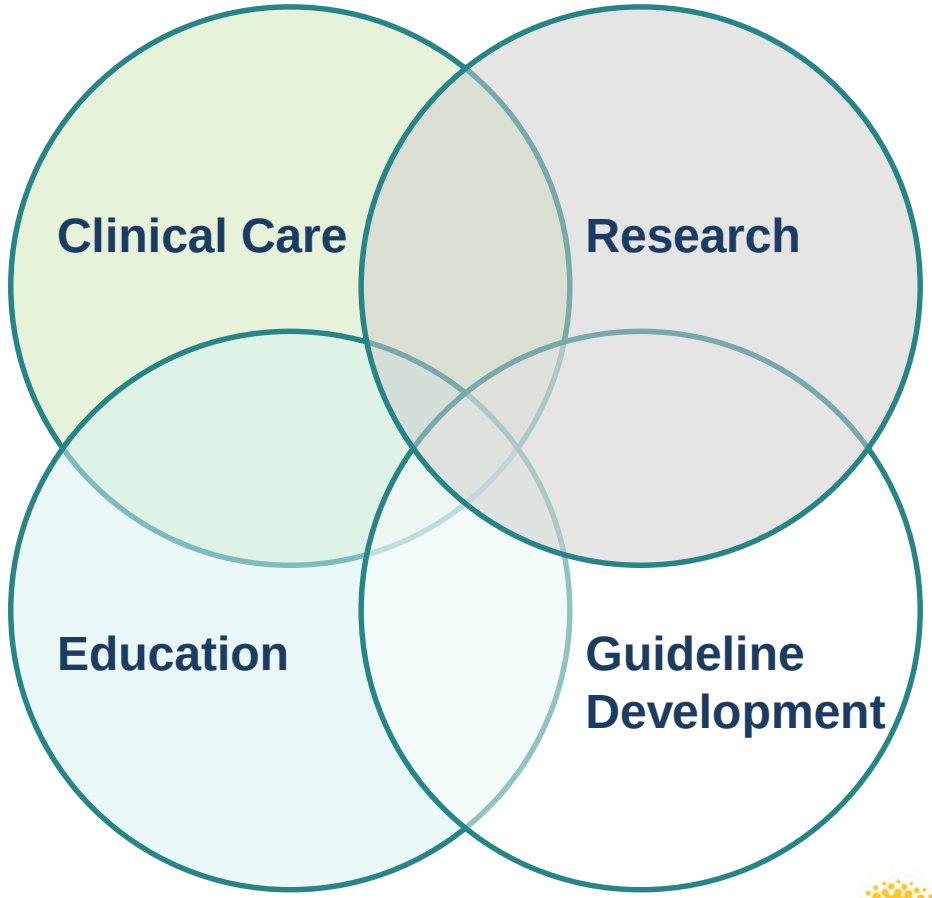
SCCA Integrative Medicine Vision

Effective Integrative Medicine therapies will be integrated into all aspects of cancer care and will become standard of care.

Focus is on improving quality of life and increasing resiliency from the time of diagnosis, through treatment, survivorship and end of life.

Emphasis on acupuncture, mind-body therapies, lifestyle behaviors, and dietary supplement counseling.

Integrative Medicine is highly interdisciplinary in the oncology setting.



Integrative Medicine at SCCA

New SCCA service – launched in January 2018

Interdisciplinary team of clinicians

- Integrative Nurse Practitioner
- Naturopathic physician
- Acupuncturists

Billable services

Shared electronic health record

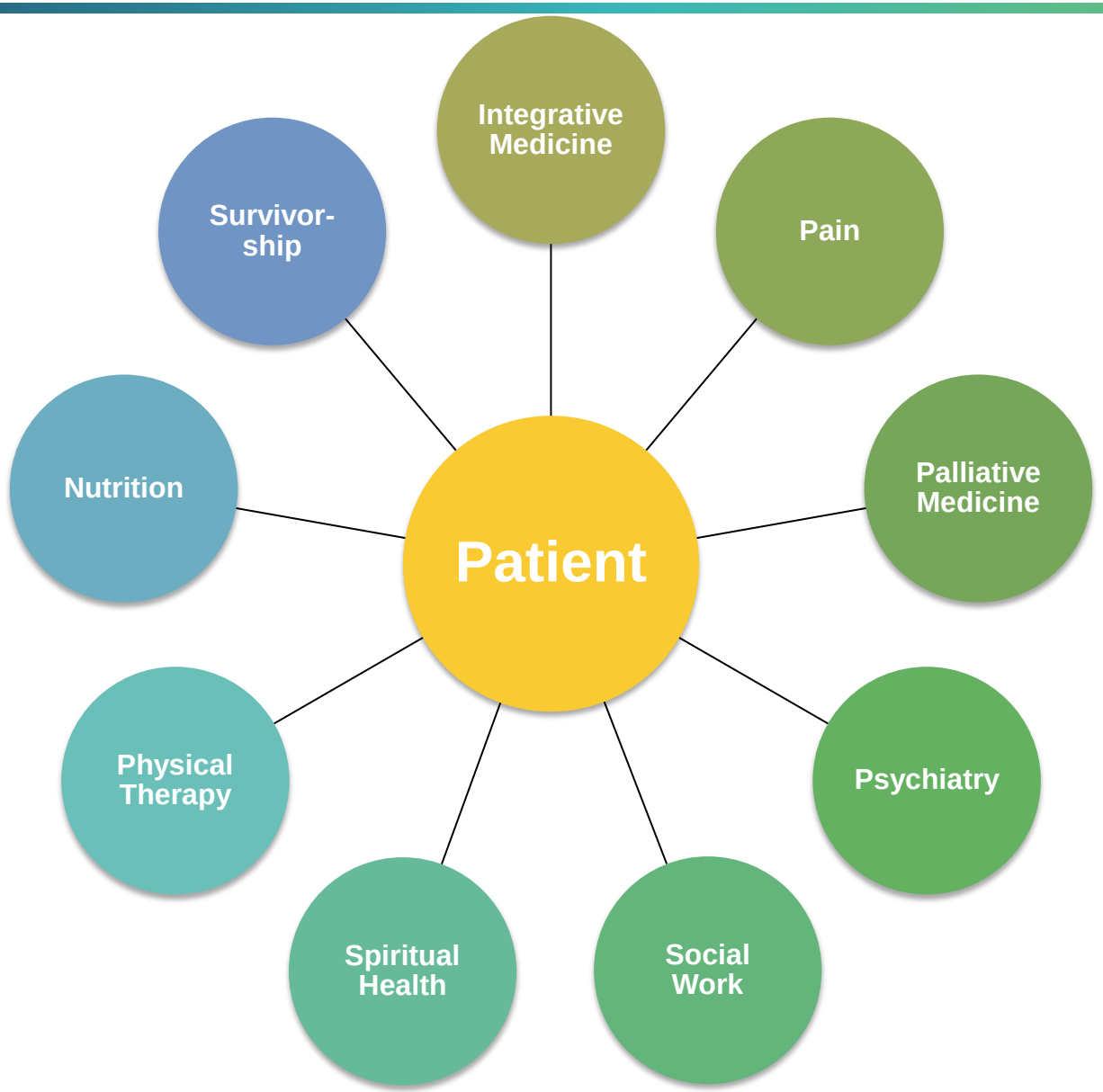
Co-located with SCCA outpatient oncology clinics

Research platform

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

Interdisciplinary Supportive Care at SCCA



FRED HUTCH

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

Dietary supplement working group

Collaboration between:

- Pharmacy
- Medical Nutrition Therapy
- Integrative Medicine

Purpose: To harmonize and publish recommendations on use of dietary supplement use by SCCA patients

Seattle Cancer Care Alliance

Fred Hutch · Seattle Children's · UW Medicine

The future of integrative oncology

- Integrative oncology is highly interdisciplinary
- Growing body of evidence supporting select use of integrative therapies for oncology symptom management
- Further need for clinical practice guidelines
- Patients are simultaneously using multiple therapies, need to understand combined use
- Need for observational studies and clinical trials with recurrence and survival endpoints
- Clinical programs and cooperative groups can provide excellent infrastructure to conduct cutting-edge research

THANK YOU

FRED HUTCH
CURES START HERE®

fredhutch.org

Anal Cancer

2020

Andrew L. Coveler, M.D.

Associate Professor
University of Washington
Fred Hutchinson Cancer Research Center

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CURES START HERE®

Seattle Cancer Care Alliance
Fred Hutch · Seattle Children's · UW Medicine

UW Medicine
UW SCHOOL OF MEDICINE

Outline

- Background
  - Pathogenesis
  - Epidemiology
  - Anatomy
- Staging and Workup
- Treatment
  - Local Disease
  - Recurrent Disease
  - Metastatic Disease

Classification

WHO classification of anal cancer

Anal canal
Squamous cell (cloacogenic) carcinoma
Large cell keratinizing
Large cell nonkeratinizing (transitional)
Basaloid
Adenocarcinoma
Rectal type
Of anal glands
Within anorectal fistula
Small cell carcinoma
Undifferentiated
Anal margin
Squamous cell carcinoma
Giant condyloma
Basal cell carcinoma
Others
Bowen's disease
Paget's disease

Epidemiology and Clinical Features

Updated, SEER, UpToDate
Glynne-Jones et al. Annals of Oncology. 2010 21(s5)

EPIDEMIOLOGY

- 8,590 cases US annually
- Increasing incidence 2-3%
- 80-85% SCC

RISK FACTORS

- Female (2:1 F:M)
- HPV (70%+ HPV related)
- Genital warts
- # sexual partners
- Cigarette use
- HIV?
- Receptive anal intercourse

CLINICAL PRESENTATION

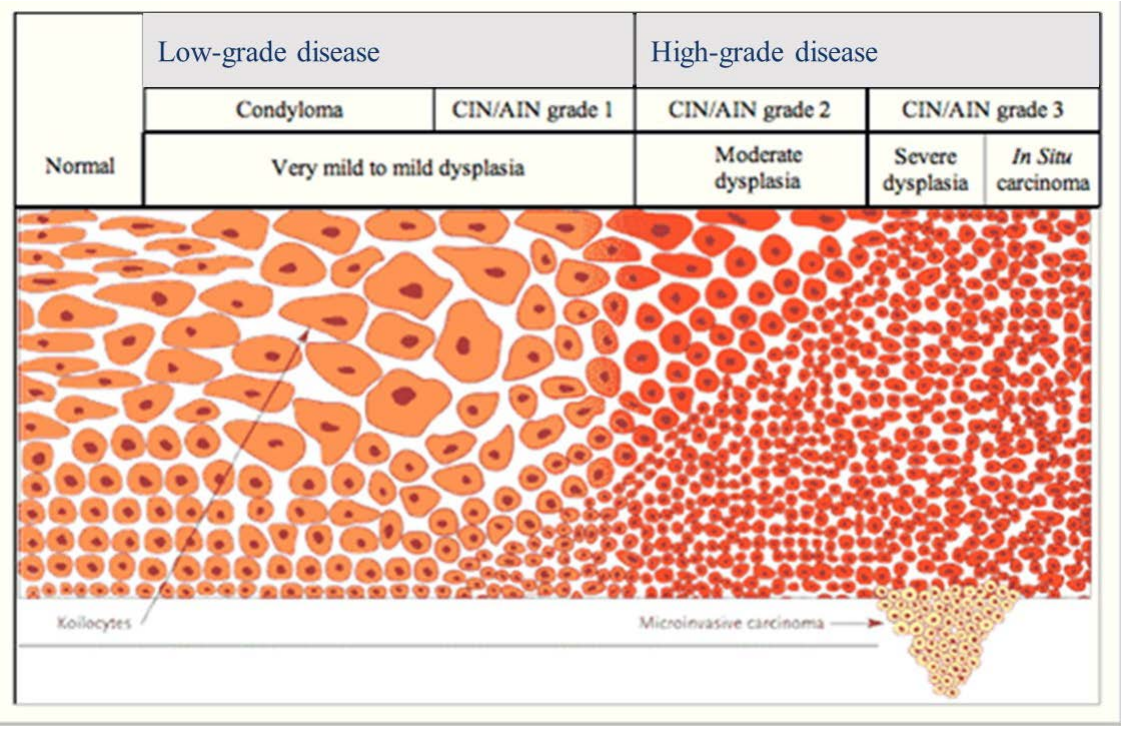
- Rectal bleeding (most common)
- Anorectal pain
- Itching
- Sensation of mass
- 20% asymptomatic
- History of anorectal condyloma
- Most patients present with T1-2 N0 disease

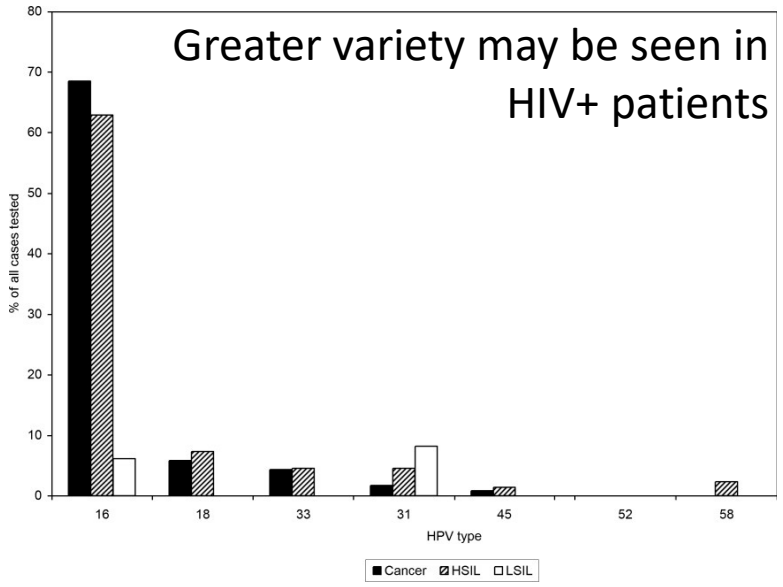
Pathogenesis

- Human Papillomavirus
  - HPV DNA has been isolated from 46 to 100 percent of in situ and invasive SCCs of the anus
  - Anal Intraepithelial Neoplasia (AIN) is the precursor lesion
- Cigarettes
  - Cigarettes increase anal cancer (and cervical)

N Engl J Med. 1997;337(19):1350

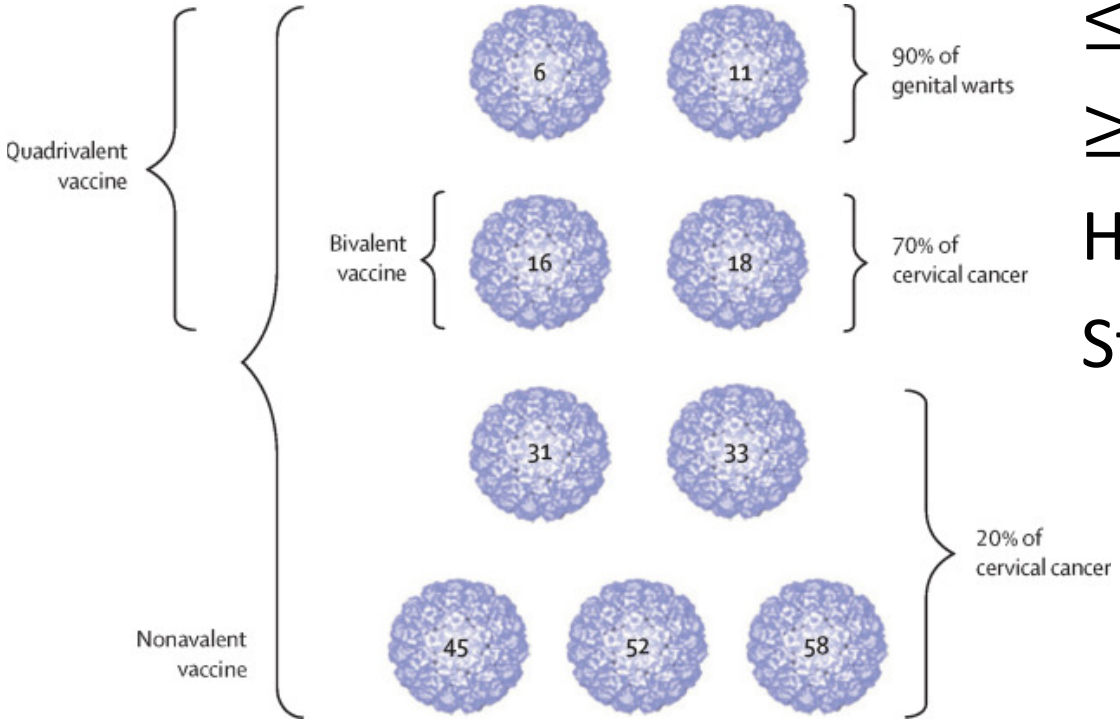
Pathogenesis





Hoots etal, Int J Cancer 2009;124:2375

Prevention: Vaccination



≦ 14 yo: 0 and 6 **or** 12 m

≧ 15 yo: 0, 2 and 6 m

HIV+: 0, 2 and 6 m

Still efficacious at 15+ yrs

Schiller, Lancet Oncol. 2015 May;16(5):e217-25.

Screening

Joel Palefsky, ASCO 2019, Educational Session

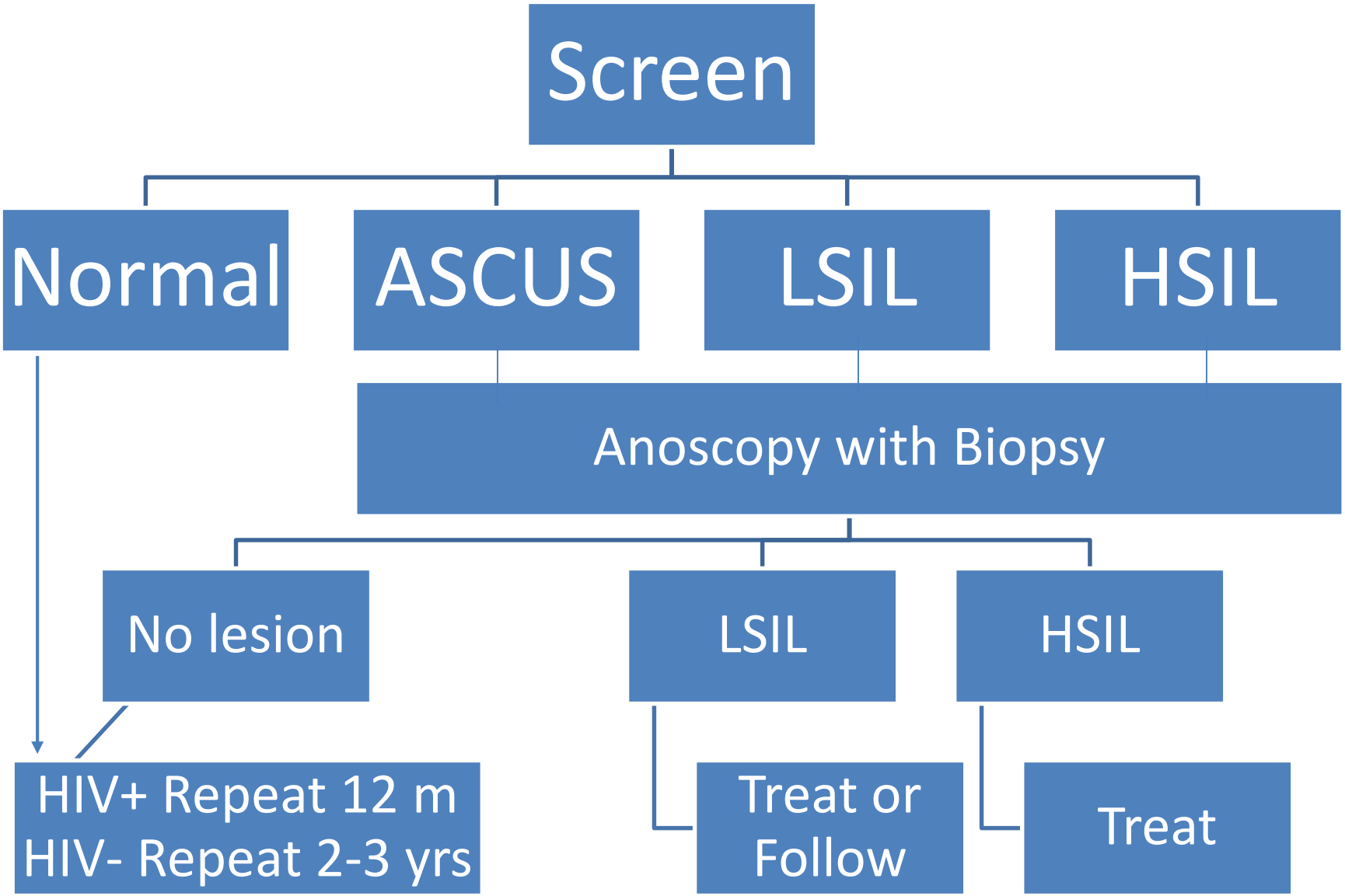
There is NOT data to support screening,
But recommended for high risk groups:

HIV-positive	Men and Women
HIV-negative	MSM
Woman with	High Grade Cervical/Vulvar Lesion/Cancer
Woman and Men	with Perianal Condyloma

Solid Organ Transplant Recipients

Over 25 if immunosuppressed

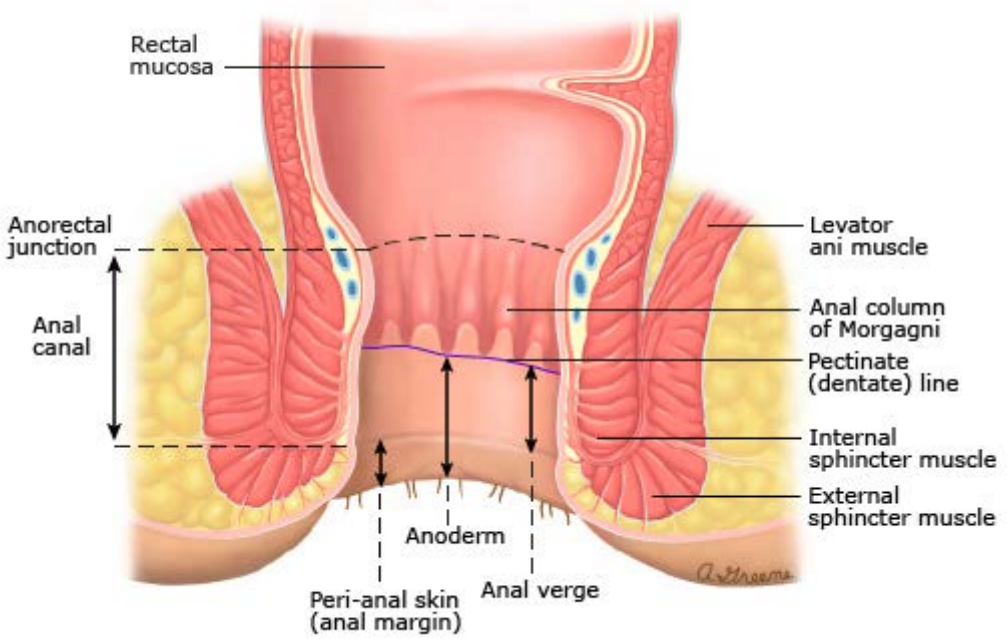
Over 40 if immunocompetent



ASCUS: Atypical Squamous Cells of Undetermined Significance
LSIL/HSIL: Low/High grade Squamous Intraepithelial Lesion

Anatomy

- 3-4 cm anal canal
- Anorectal ring to anal verge
- Dentate line located in middle of canal



- Perianal Skin Cancers are now staged and treated like anal canal cancers.

Picture from UpToDate

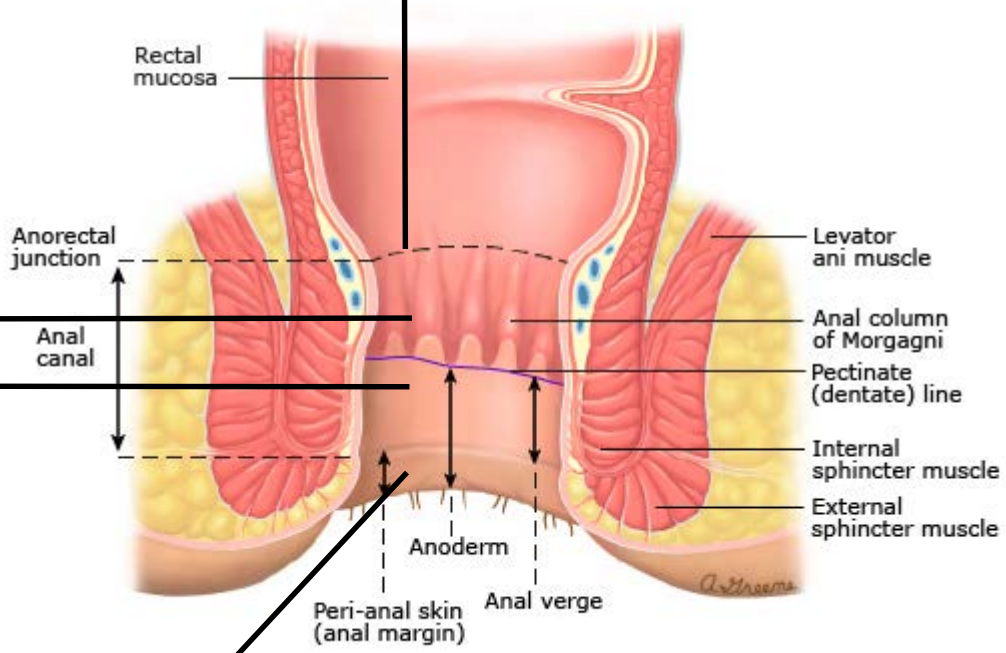
Anatomy: Nodal Drainage

Non keratinizing SCC
Perirectal Nodes

Internal Pudendal Nodes
Internal Iliac Nodes

Keratinizing SCC
Inguinal Nodes
Femoral Nodes
External Iliac Nodes

Anal Margin (Perianal) SCC
Keratinized squamous cells
~~(Treat as Primary Skin SCC)~~



Picture from UpToDate
Glynne-Jones et al. Annals of Oncology. 2010 21(s5)

Staging

T0	No evidence of primary tumor
Tis	High grade squamous epithelial lesion
T1	≤ 2 cm
T2	> 2 cm ≤ 5 cm
T3	> 5 cm
T4	Invades adjacent organs (e.g. vagina, urethra, bladder)

N0	No regional lymph node metastasis
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastasis in external iliac with any N1a nodes

M0	No distant metastasis
M1	Distant metastasis

AJCC 8th Edition

Stage Grouping

Stage	N0 (50%)	N1 (30%)
Tis	0	
T1	1	3a
T2	2a	3a
T3	2b	3c
T4	3b	3c
M1 (12%)	4	

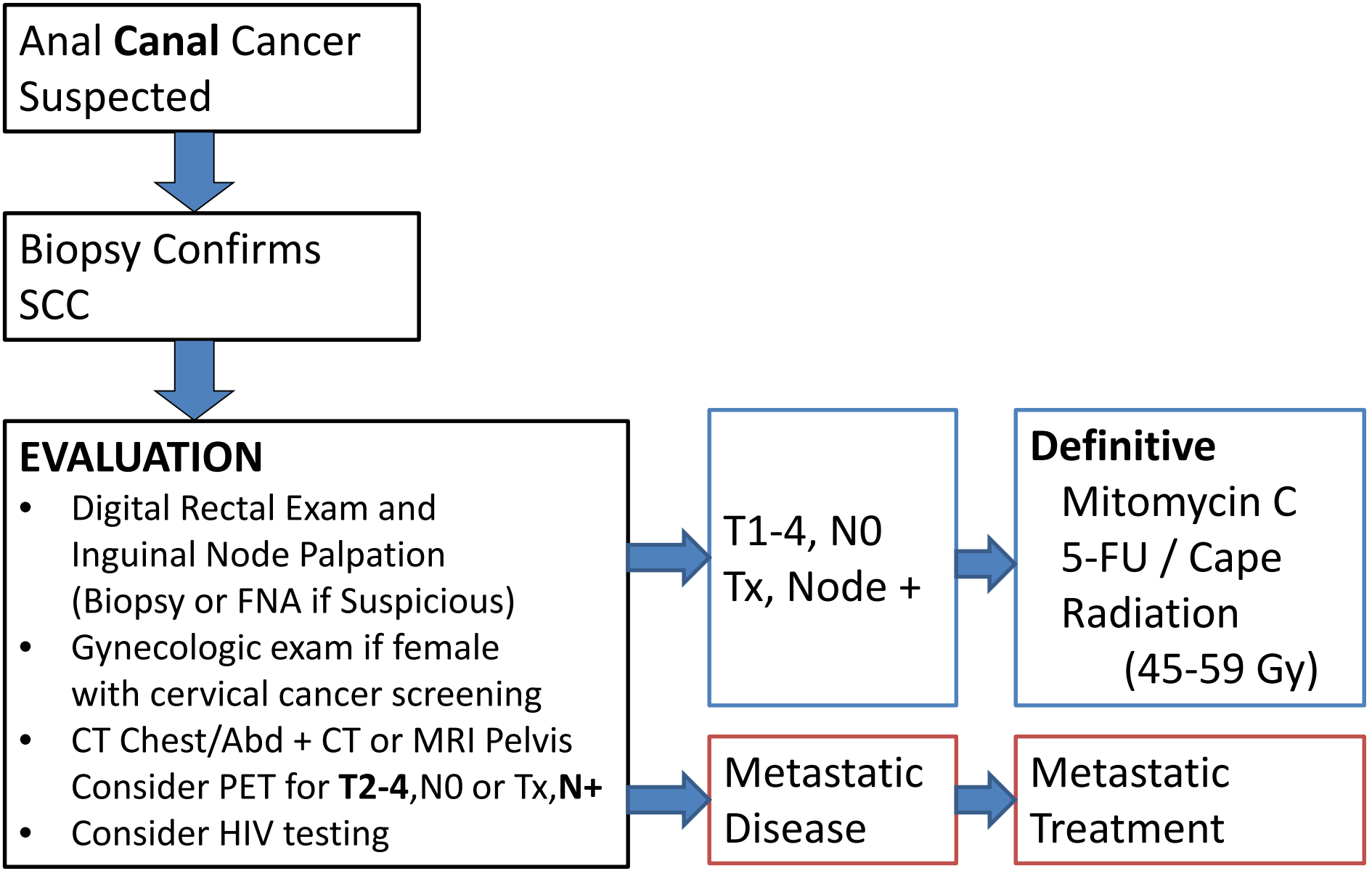
	5 y OS
T1	86%
T2	86%
T3	60%
T4	45%
N0	80%
N1	60%
M1	30%

ACTII	3 y PFS
T1	85%
T2	80%
T3	65%
T4	63%
N0	76%
N1	60%

Non-SCC do worse.

NCCN 2018

NCCN Guidelines: Anal Carcinoma



NCCN Guidelines: Anal Carcinoma

Anal **Canal** Cancer Suspected

Biopsy Confirms SCC

EVALUATION

- Digital Rectal Exam and Inguinal Node Palpation (Biopsy or FNA if Suspicious)
- Gynecologic exam if female with cervical cancer screening
- CT Chest/Abd + CT or MRI Pelvis Consider PET for **T2-4**,N0 or Tx,N+
- Consider HIV testing

PET Scan:
Sensitivity 60% Specificity 90%
Changed Nodal Status 20%
Changed TNM Stage 40%

Caldarella, et al. Sci Wrld Jrnl 2014; 1960-68
Jones, et al. Ann Surg Oncol 2015;22:3574

T1-4, N0
Tx, Node +

Definitive
Mitomycin C
5-FU / Cape
Radiation
(45-59 Gy)

Metastatic Disease

Metastatic Treatment

NCCN Guidelines: Anal Carcinoma

Anal **Canal** Cancer Suspected

Biopsy Confirms SCC

MMC Improves
- DFS at 4 years (73% vs 51%)
- Colostomy rate (9% vs 22%)
- OS at 4 years Not Different

(JCO 1996; 14:2527)

EVALUATION
- Digital Rectal Exam and Inguinal Node Palpation (Biopsy or FNA if Suspicious)
- Gynecologic exam if female with cervical cancer screening
- CT Chest/Abd + CT or MRI Pelvis Consider PET for **T2-4**,N0 or Tx,N+
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T1-4, N0
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Metastatic Disease

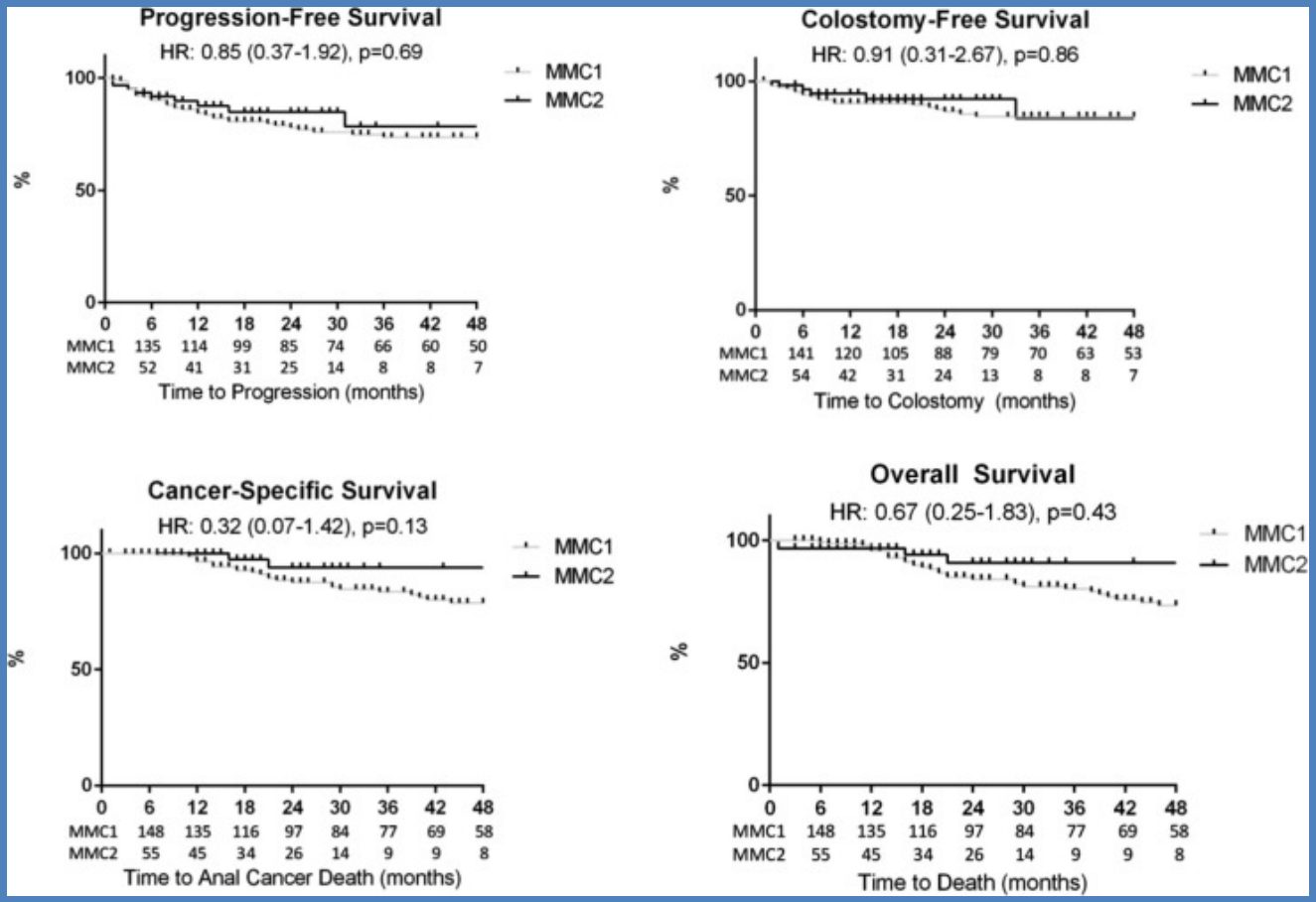
Metastatic Treatment

NCCN Guidelines: Anal Carcinoma

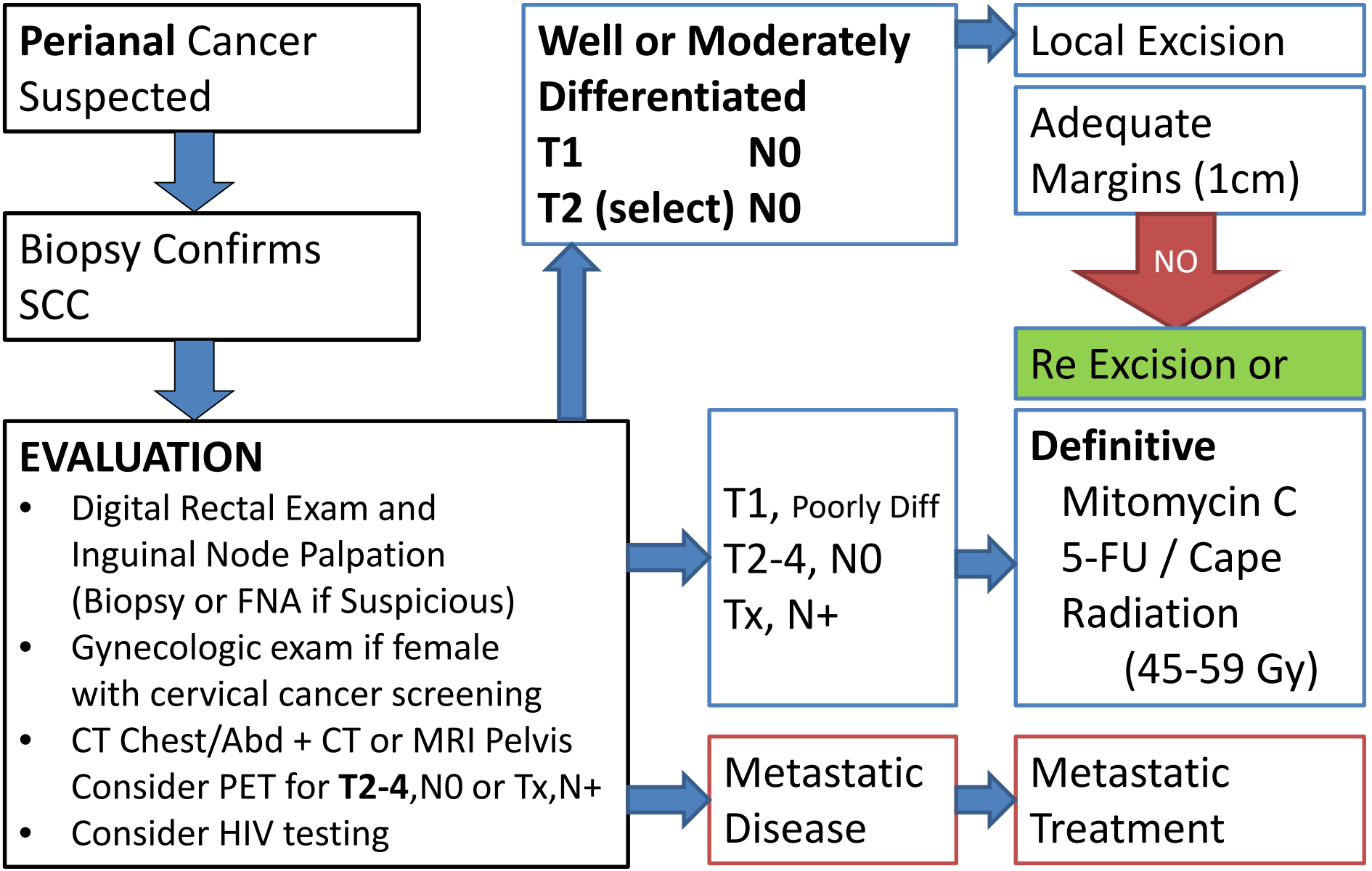
Anal **Canal** Cancer Suspected

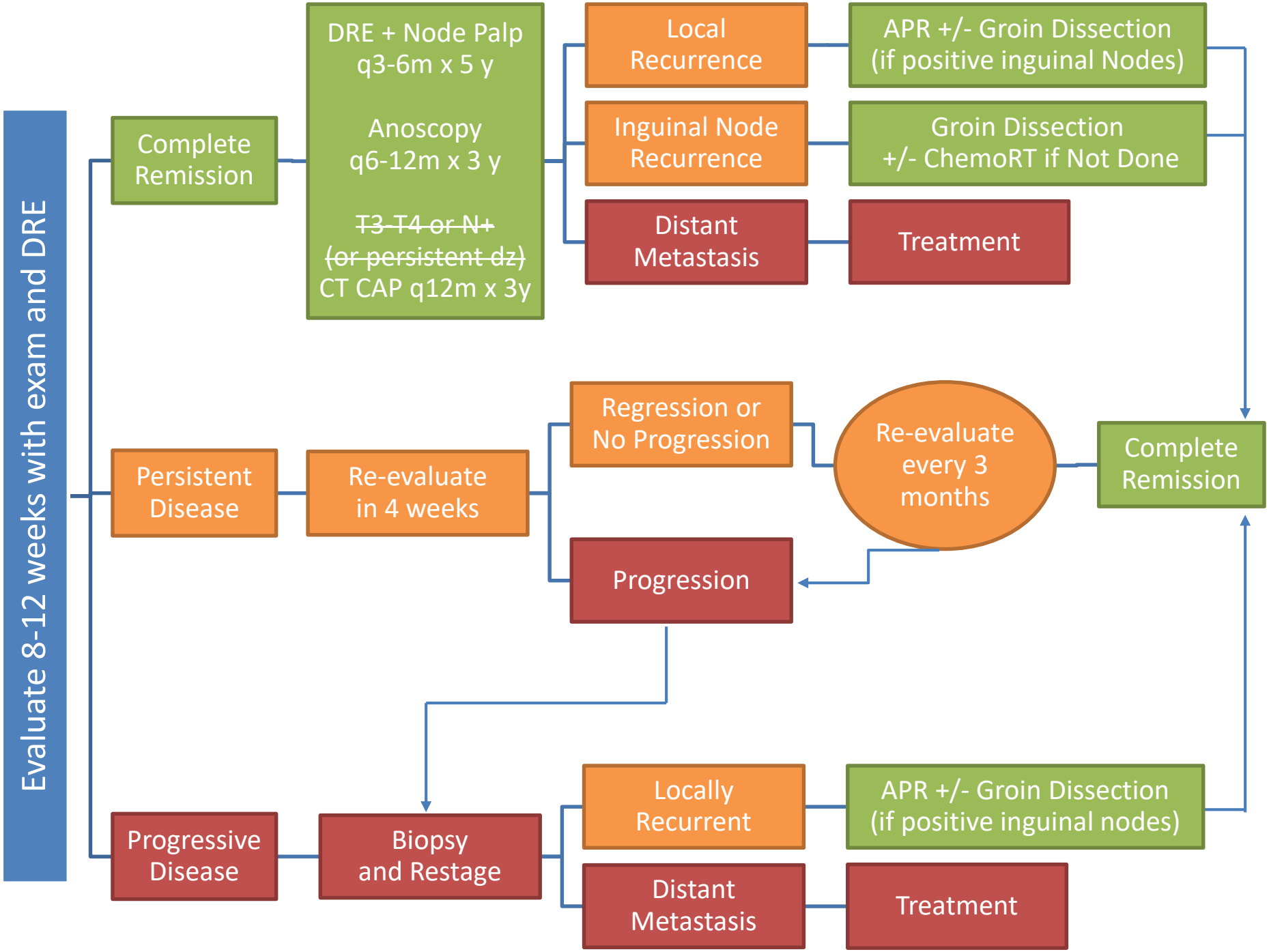
MMC Improves

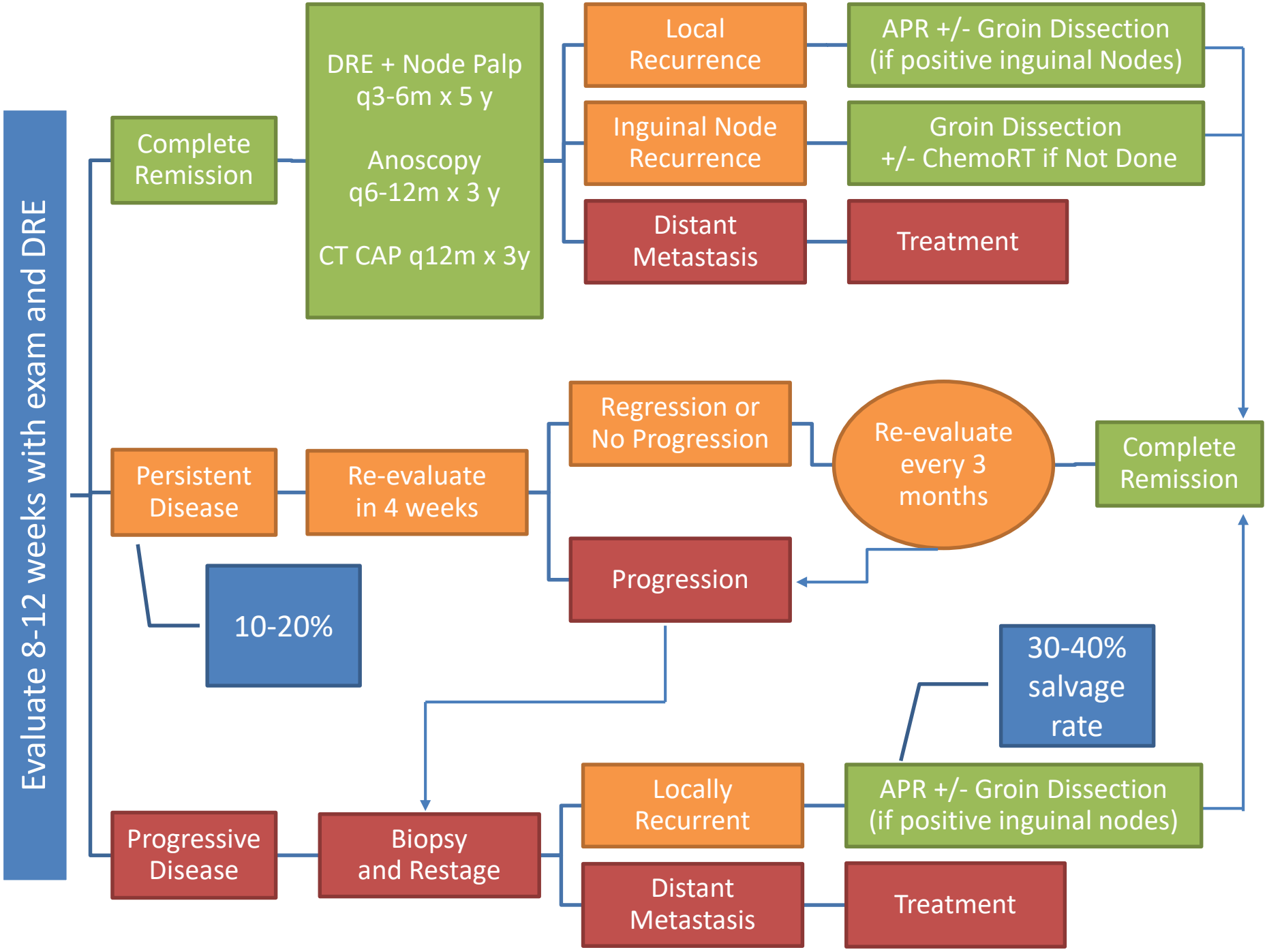
One vs Two Doses (White et al Radiother Oncol 2015)



NCCN Guidelines: Anal Carcinoma




Evaluate 8-12 weeks with exam and DRE
Complete Remission
DRE + Node Palp q3-6m x 5 y
Anoscopy q6-12m x 3 y
~~T3-T4 or N+ (or persistent dz)~~
CT CAP q12m x 3y
Local Recurrence
APR +/- Groin Dissection (if positive inguinal Nodes)
Inguinal Node Recurrence
Groin Dissection +/- ChemoRT if Not Done
Distant Metastasis
Treatment
Persistent Disease
Re-evaluate in 4 weeks
Regression or No Progression
Re-evaluate every 3 months
Complete Remission
Progression
Progressive Disease
Biopsy and Restage
Locally Recurrent
APR +/- Groin Dissection (if positive inguinal nodes)
Distant Metastasis
Treatment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Distant Metastasis
Treatment
Persistent Disease
Re-evaluate in 4 weeks
Regression or No Progression
Re-evaluate every 3 months
Complete Remission
Progression
10-20%
30-40% salvage rate
Progressive Disease
Biopsy and Restage
Locally Recurrent
APR +/- Groin Dissection (if positive inguinal nodes)
Distant Metastasis
Treatment

Treatment

APR was routinely performed

- 5 Year OS was 40-70%

Chemoradiation

- Local Failure: 15-35%
  5 Yr OS 72-90%

NCCN, Nigro et al. Dis Colon Rectum. 1974;17(3):354

Chemoradiation

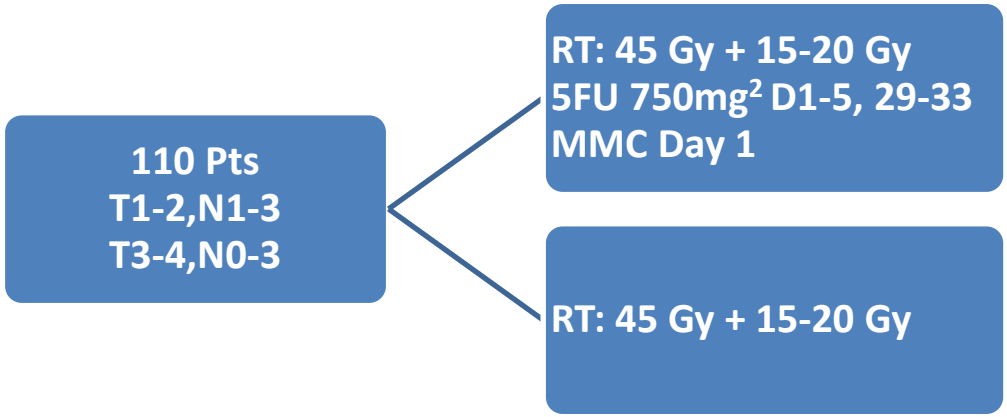
5FU/Capecitabine + Mitomycin C

5-FU 1000mg/m^2	Days 1-4, 29-32
or	
Capecitabine 825mg/m^2	M-F on RT Days
+	
Mitomycin C 10mg/m^2	Days 1 and 29
or	
Mitomycin C 12mg/m^2	Days 1

Radiation to 45-59 Gy

NCCN v2.2020

RT vs ChemoRT



After 6 weeks
If PR: 20 Gy Boost
If CR 15 Gy Boost

AEs		XRT	XRT + CT
Diarrhea	Gr 2	16	15
	Gr 3	4	10
	Gr 4	0	0
Skin	Gr 2	18	13
	Gr 3	26	28
	Gr 4	0	1

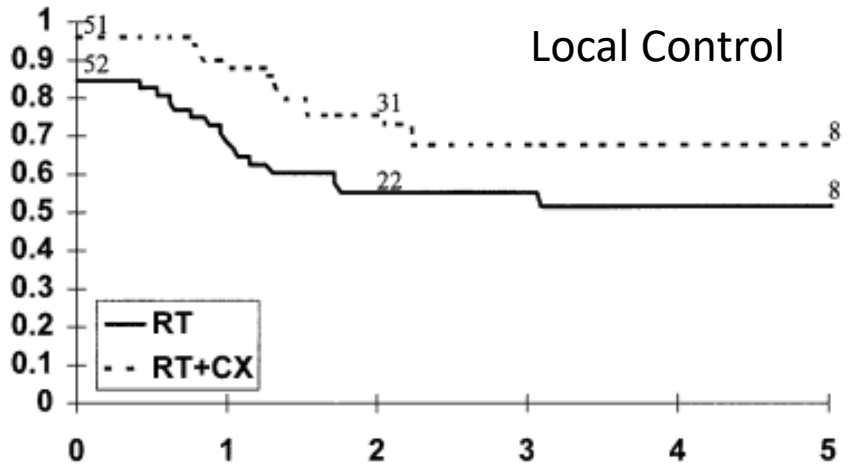
Bartelink et al. JCO 1997 15(5):2040-9

RT vs ChemoRT

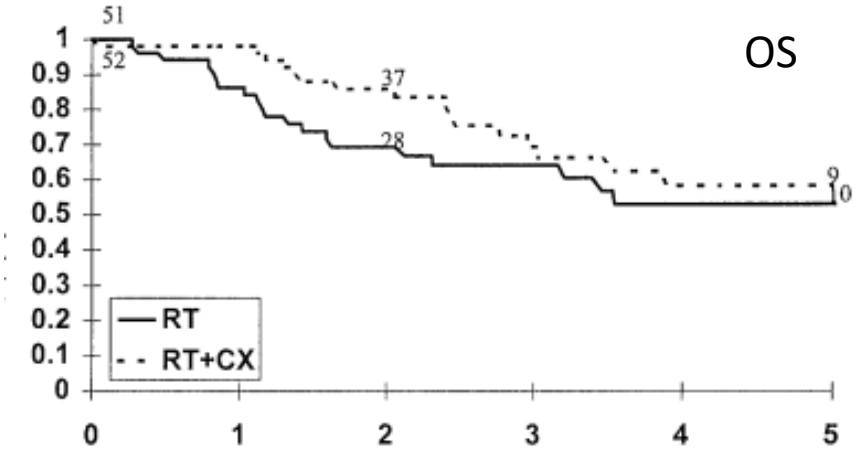
110 Pts
T1-2,N1-3
T3-4,N0-3

RT: 45 Gy + 15-20 Gy
5FU 750mg^2 D1-5, 29-33
MMC Day 1

RT: 45 Gy + 15-20 Gy



Complete Response:	80% vs 54%
CR after Surgery:	96% vs 85%
Colostomy Free Rate	32% improvement
Locoregional Control	18% improvement



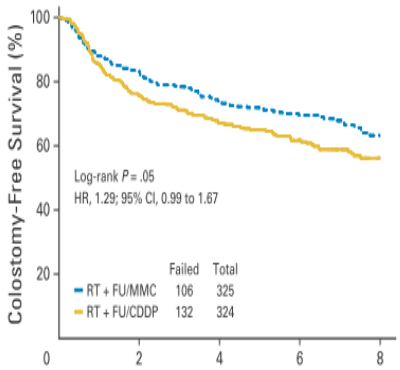
Bartelink et al. JCO 1997 15(5):2040-9

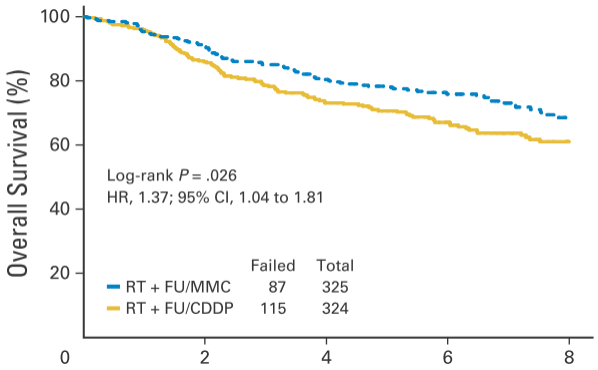
Mitomycin C vs Cisplatin

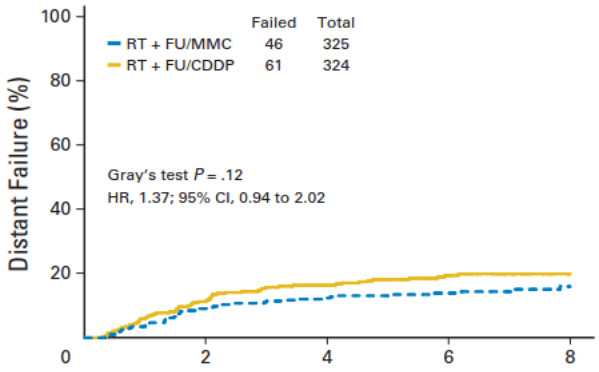
Ajani, J. A. et al. JAMA 2008;299:1914-1921
Gunderson, L et al. J Clin Oncol. 2012; 30(35)

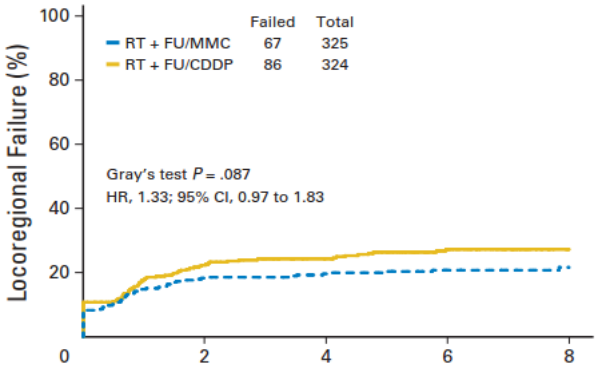
RTOG 98-11

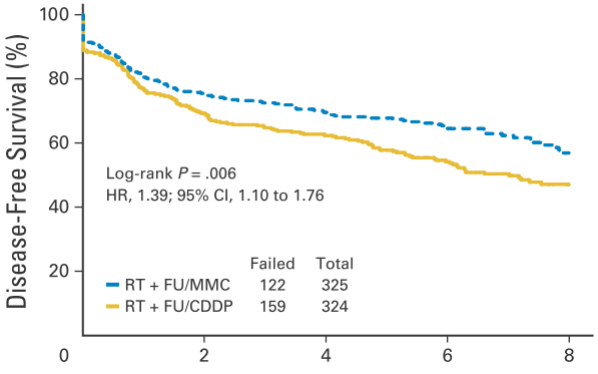
- CIS/5FU → CIS/5FU/RT
- MMC/5FU/RT





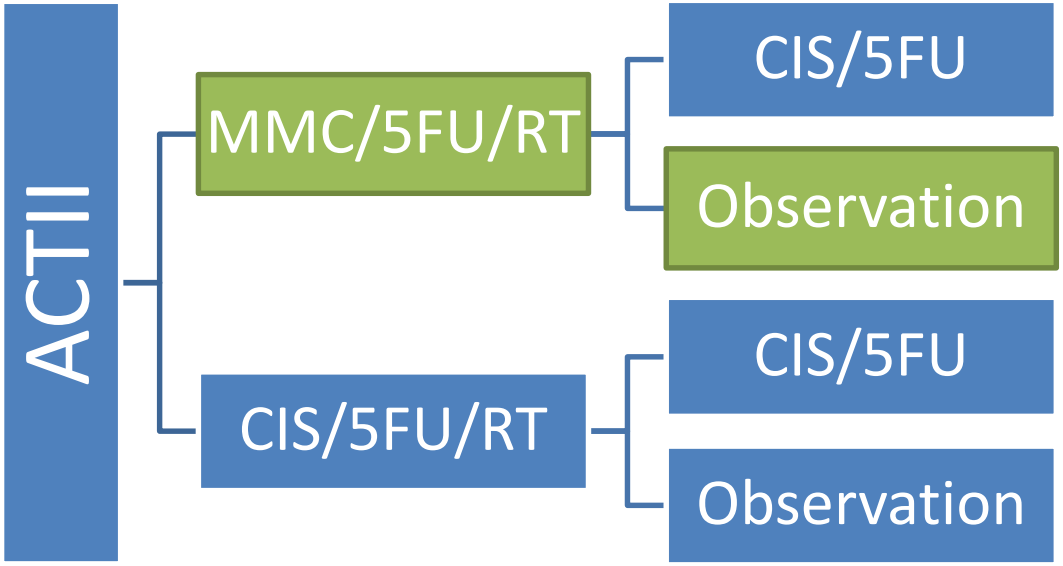




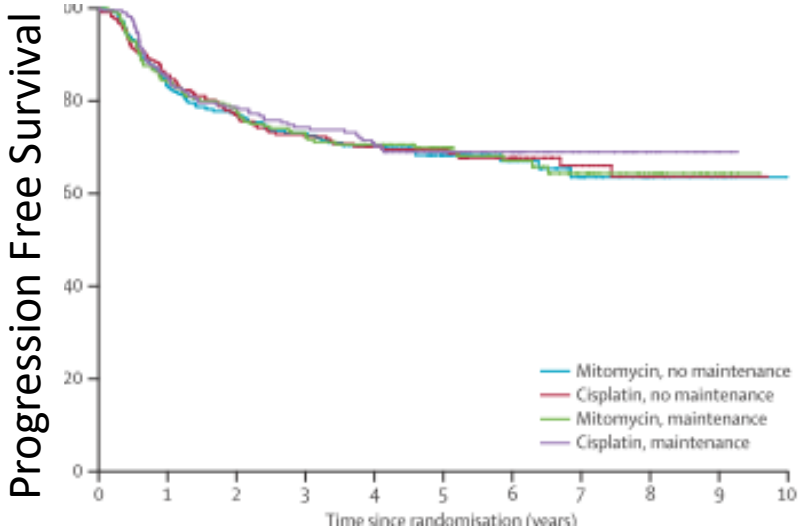


Mitomycin C vs Cisplatin

Lancet Oncol. 2013 May;14(6):516-24



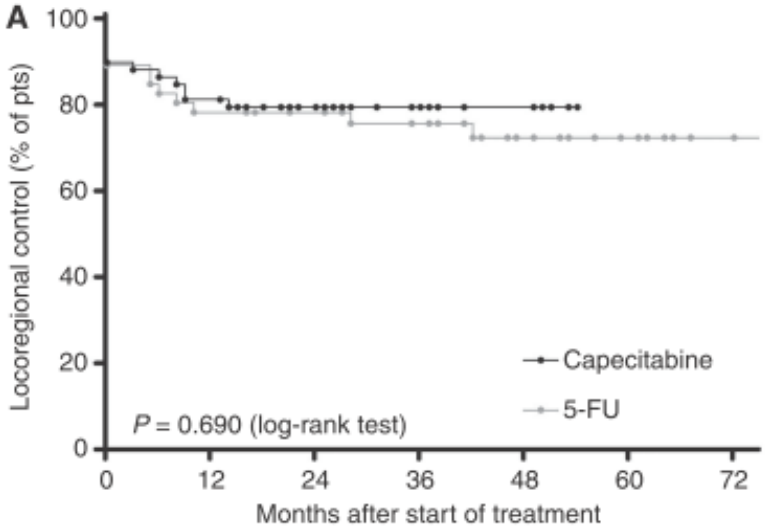
Complete Response	90%
Partial Response	5%
Stable Disease	1%
Progressive Disease	5%

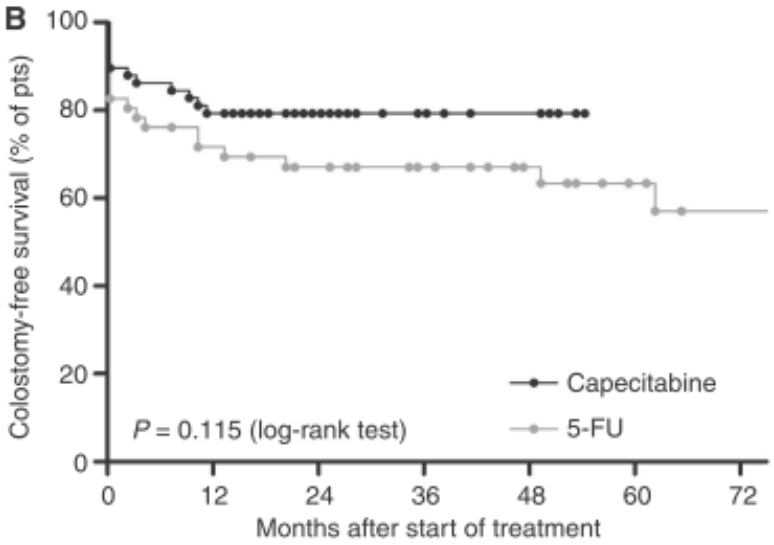


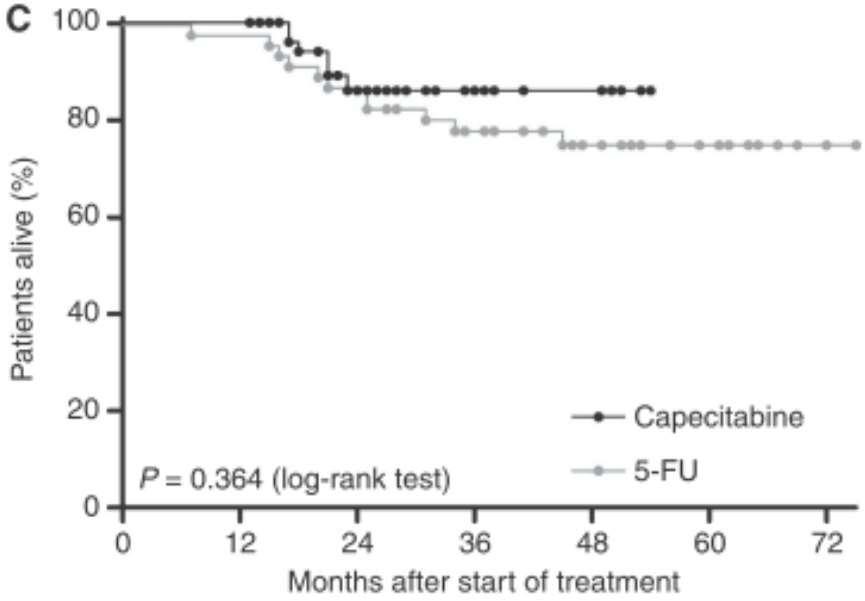
Mitomycin C vs Cisplatin

- Any Grade 3-4 Toxicity 71% vs 72%
- Hematological Grade 3-4 26% vs 16%

Capecitabine vs 5-FU







Meulendijks, BJC, 2014
Thind, Radiation Oncology, 2014,9:214

Capecitabine

Table 2. Acute toxicity according to treatment group

	5-FU + MMC (*n* = 47)		Capecitabine + MMC (*n* = 58)		
Type of toxicity	**No.**	**%**	**No.**	**%**	***P*-value[a]**
Dermatological toxicity					
No toxicity	0	0	0	0	0.035
Grade 1–2	41	87	40	69	
Grade 3–4	6	13[b]	18	31	
Gastrointestinal toxicity					
No toxicity	17	36	4	7	1.000
Grade 1–2	29	62	52	90	
Grade 3–4	1	2	2	3	
Haematological toxicity					
No toxicity	7	15	7	12	1.000
Grade 1–2	37	79	47	83	
Grade 3–4	3	6	3	6	
Genitourinary toxicity					
No toxicity	34	72	28	48	0.586
Grade 1–2	11	24	29	50	
Grade 3–4	2	4	1	2	

Meulendijks, BJC, 2014

Metastatic Disease

Bull Cancer. 1999;86(10):861.

Risk Factors for Residual/Recurrent Disease:

T > 4cm, N+

Approximately 5-20% of cases

Liver > Lung > Extra Pelvic Nodes

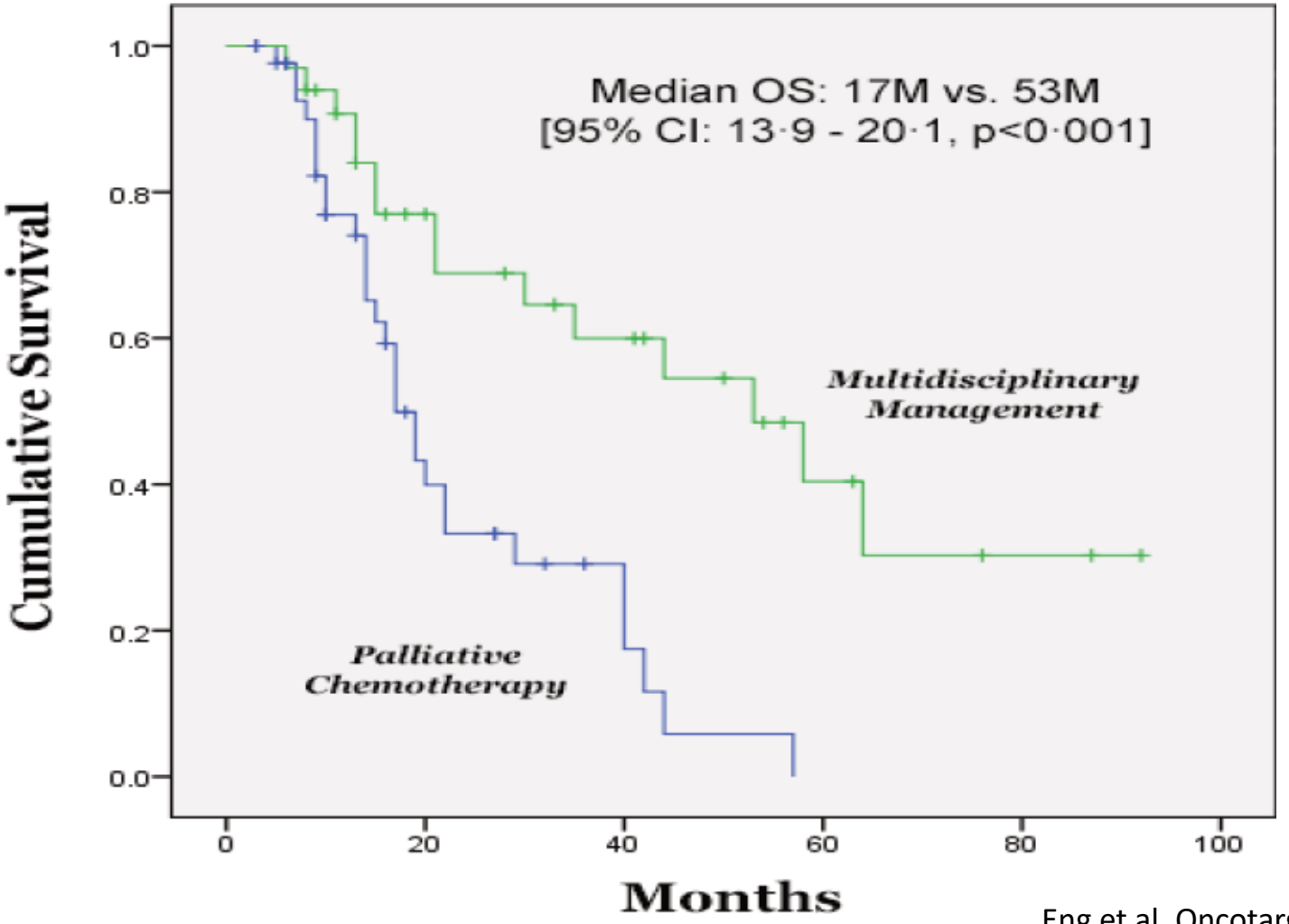
- Reports of long-term outcome with metastasectomy and radiation to oligometastatic disease

Limited data on chemotherapy

Cisplatin / fluoropyrimidine combinations most studied

- Up to 50% response rates, Median OS 15-33 months
- OS is 62% at 1 year and 32% at 5 years
- 3 patients alive at 4, 5 and 7 years benefited from local treatment

Multidisciplinary Treatment



2000 - 2012
77 patients total

5FU Cis (42)
SD 29%
PR 57%
PD 14%

Carbo Paclitaxel (24)
SD 21%
PR 33%
PD 46%

Eng et al, Oncotarget , 2014, Vol.5(22), p.11133

NCCN: Metastatic Disease

First Line Therapy +/- RT

Carboplatin + Paclitaxel (NCCN Preferred)

5FU + Cisplatin (more toxic)

FOLFOX6 (NCCN case report, adeno)

FOLFCIS

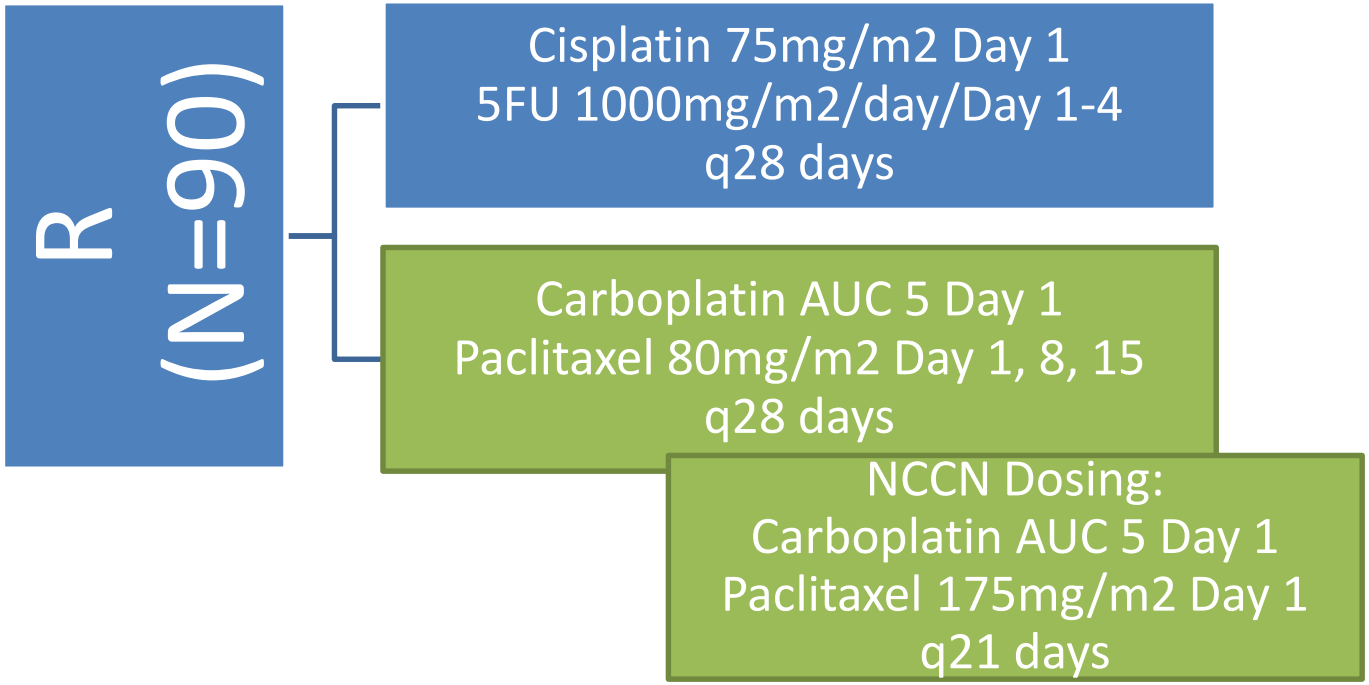
mDCF

Second Line Therapy

Nivolumab or Pembrolizumab

NCCN 2020, Modified

InterAACT: 1st Line Trial



Primary: RR

Secondary: PFS, OS, Correlatives, QOL

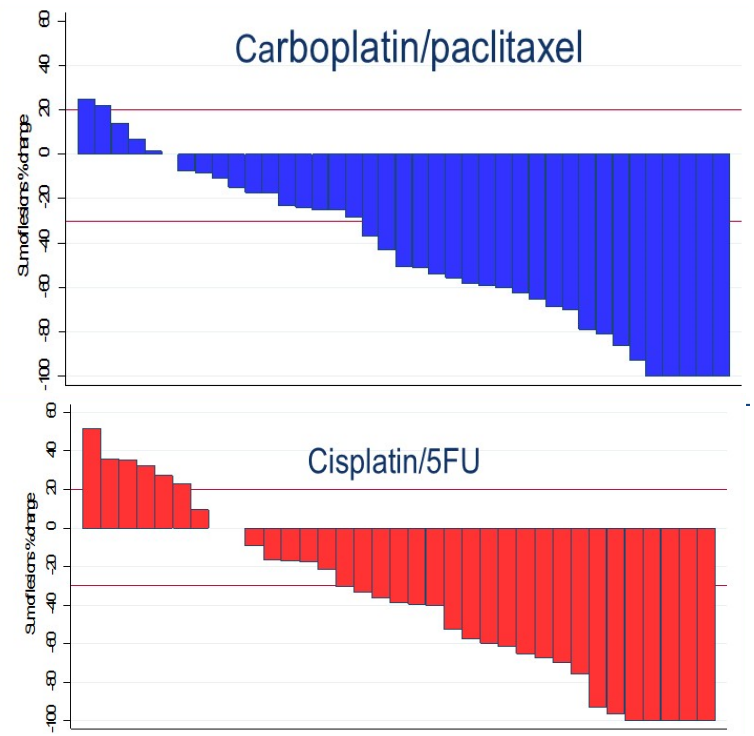
Note NCCN dosing different, ClinicalTrials.gov

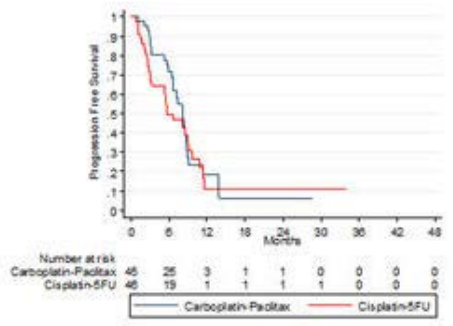
InterAACT: AEs

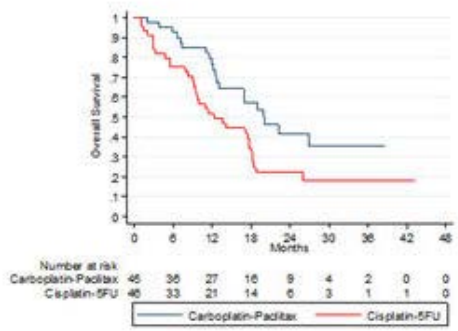
Toxicity ≥ Grade 3	Carboplatin + Paclitaxel (N=42) %	Cisplatin-5FU (N=42) %
Anemia	10	5
Diarrhea	2	5
Fatigue	10	19
Febrile Neutropenia	5	10
Mucositis	0	26
Nausea	2	17
Neuropathy	2	0
Thromboembolism	2	12
Overall	71	76
SAEs	36	62

Rao et al, ESMO 2018

InterAACT: Results







	Carboplatin Paclitaxel (N=39)	Cisplatin 5FU (N=35)
CR	13 %	14 %
PR	46 %	43 %
SD	25 %	20 %
PD	15 %	23 %
RR	59 %	57 %
DCR	84 %	77 %
PFS	8.1 months	5.7 months
OS	20 months	12.3 months

Rao et al, JCO 2020

DCF/mDCF (Epitopes HPV02)

Kim, et al. Lancet Oncol 2018

Single Arm, Multicenter, Phase 2

- 66 pts (36 DCF, 30 mDCF)
- 97 SAE (69 DCF, 28 mDCF)

Not Randomized

mDCF every 14 days

Docetaxel 40mg/m2 Day 1

Cisplatin 40mg/m2 Day 1

Fluorouracil 2400mg/m2 over 48 hours

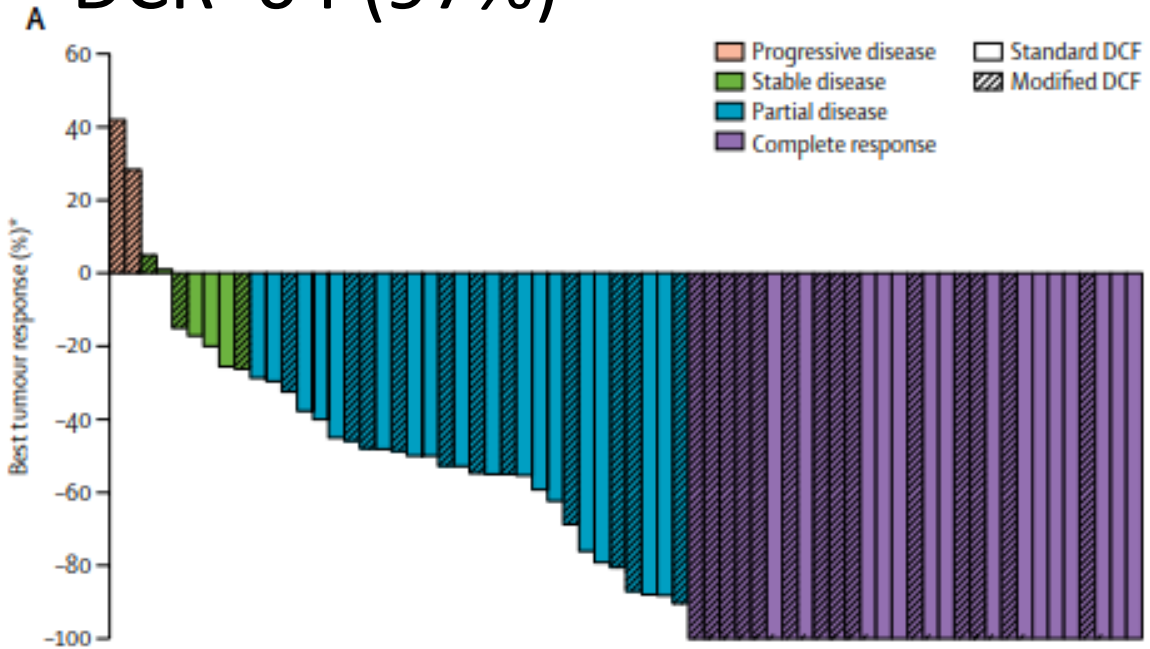
DCF/mDCF (Epitopes HPV02)

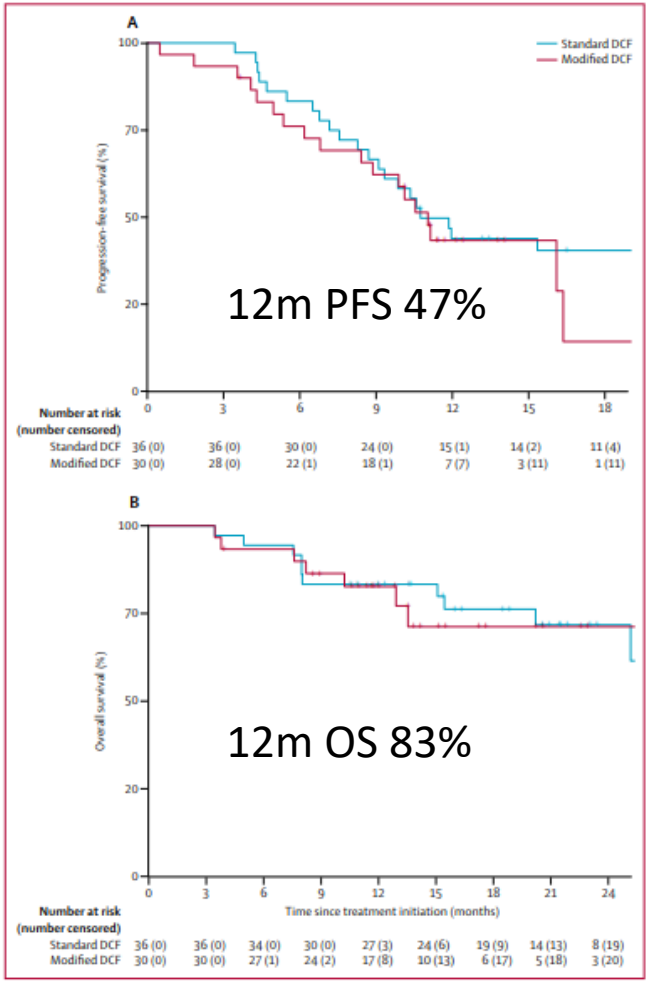
Lancet Oncol 2018

CR 30 (45%)

ORR 59 (89%)

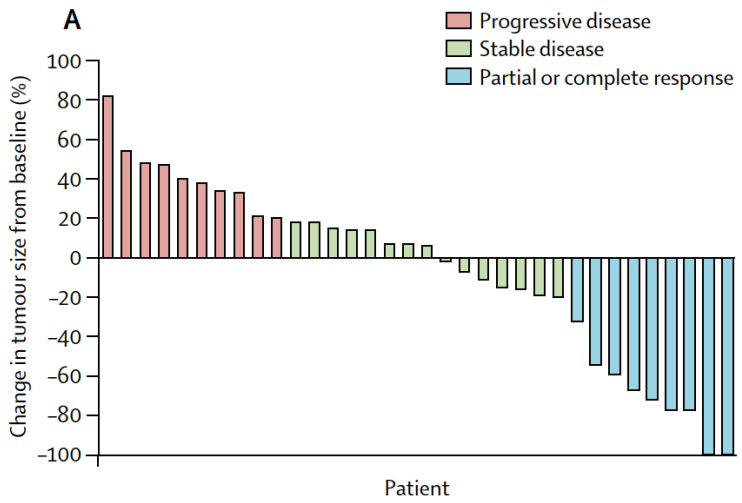
DCR 64 (97%)

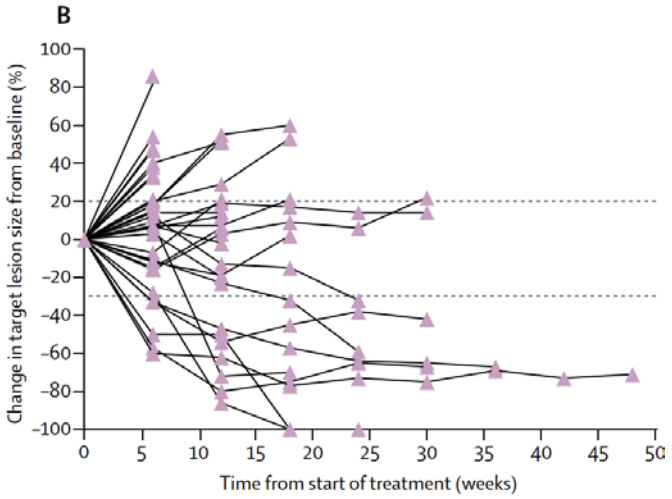




Nivolumab

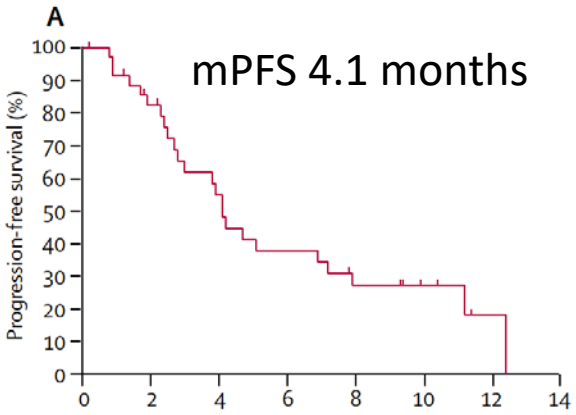
- Phase II of 37 patients.
- Primary endpoint was RECIST Response
- 9 patients (24%) responded (2 CR, 7 PR)

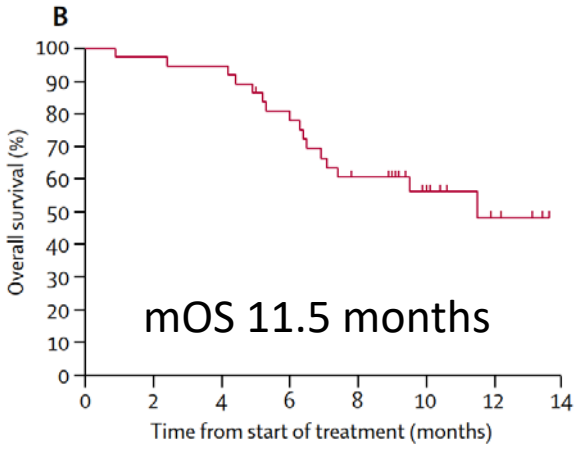




Lancet Oncol 2017; 18: 446–53

Nivolumab

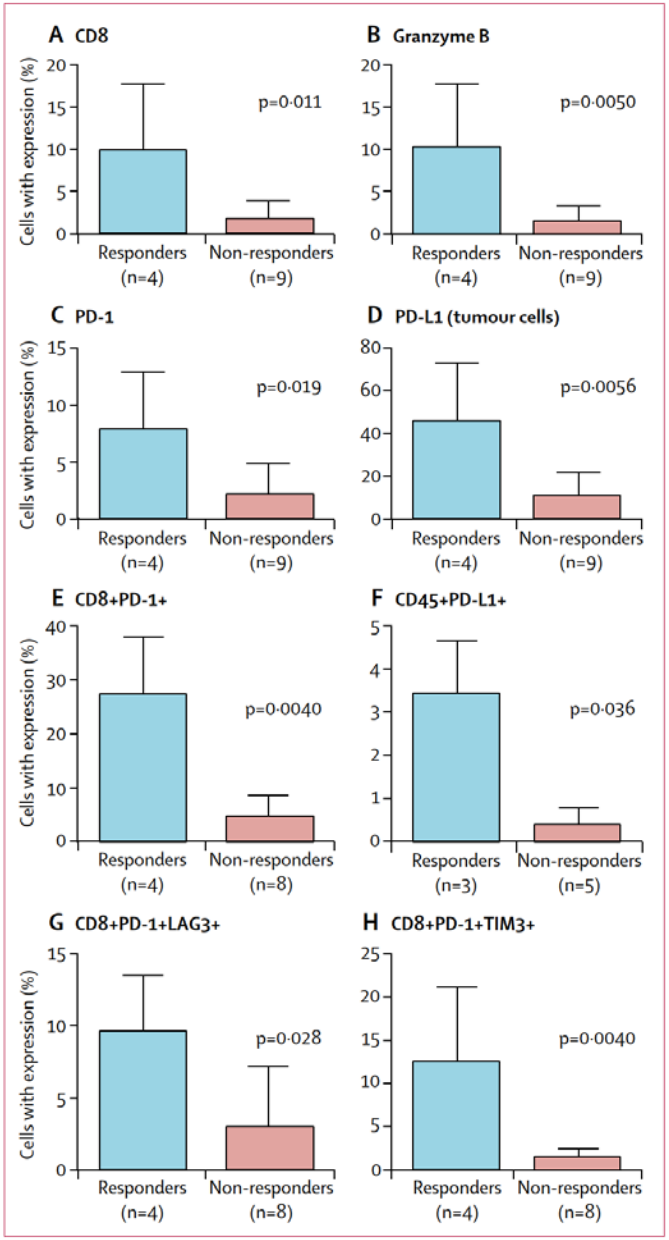




	Grade 1	Grade 2	Grade 3
Anaemia	13 (35%)	11 (30%)	2 (5%)
Fatigue	17 (46%)	7 (19%)	1 (3%)
Rash	8 (22%)	2 (5%)	1 (3%)
Constipation	8 (22%)	2 (5%)	0
Anorexia	5 (14%)	4 (11%)	0
Diarrhoea	8 (22%)	0	0
Weight loss	5 (14%)	1 (3%)	0
Arthralgia	3 (8%)	3 (8%)	0
Hyperglycaemia	3 (8%)	1 (3%)	0
Hypothyroidism	1 (3%)	1 (3%)	1 (3%)
Lymphoedema	1 (3%)	1 (3%)	0
Nausea	2 (5%)	0	0
Pneumonitis	0	1 (3%)	0

Data are n (%). n=37.

Table 2: **All adverse events**



Summary

Local Disease

- **Definitive chemoradiation** is standard.
  5-FU or Capecitabine / Mitomycin / Radiation
- Adjuvant Nivolumab trial via ECOG (at SCCA)
- Surgery is for salvage

Metastatic Disease

- **First Line:** ~~5-FU/Cis~~ Carboplatin + Paclitaxel
- **Second Line** Immunotherapy (Phase II data)
  SCCA / DFCI have Phase II Pembrolizumab Trial

Cancer Pharmacology II

Amy Ly Indorf, PharmD, BCOP

Clinical Oncology Pharmacist

Seattle Cancer Care Alliance/University of Washington Medical Center

2020

Objectives

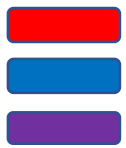
- Describe the mechanism of action and pharmacology of chemotherapy agents and targeted therapies used for the treatment of hematologic and solid tumor malignancies
- Identify the need for dose adjustments of cancer therapies based on organ dysfunction
- Recognize common and unique adverse drug reactions of cancer therapies and associated prevention and management strategies

Monoclonal Antibodies

Will not be discussed
New drugs
New drug but will not be discussed

ADO-trastuzumab emtansine
Alemtuzumab
Avelumab
Atezolizumab
Bevacizumab
Blinatumomab
Brentuximab vedotin
Caplacizumab-yhdp
Cemiplimab
Cetuximab
Daratumumab
Dinutuximab
Durvalumab
Eculizumab
Elotuzumab
Emapalumab
Emicizumab-kxwh
Enfortumab vedotin-ejfv
Gemtuzumab ozogamicin
Ibritumomab tiuxetan
Inotuzumab ozogamicin
Ipilimumab
Isatuximab
Mogamulizumab
Moxetumomab-pasudotox-tdfk
Necitumumab
Nivolumab
Obinutuzumab
~~Olaratumab~~
Ofatumumab
Olaratumab
Panitumumab
Pembrolizumab
Pertuzumab
Polatuzumab vedotin-piiq
Ramucirumab
Ravulizumab-cwvz
Rituximab
Rituximab hyaluronidase
Sacituzumab govitecan-hziy
Siltuximab
Tagraxofusp-erzs
Trastuzumab
Trastuzumab deruxtecan-nxki
Trastuzumab hyaluronidase
Trastuzumab, pertuzumab hyaluronidase
Ziv-aflibercept

Tyrosine Kinase Inhibitors



Will not be discussed
New drugs
New drug but will not be discussed

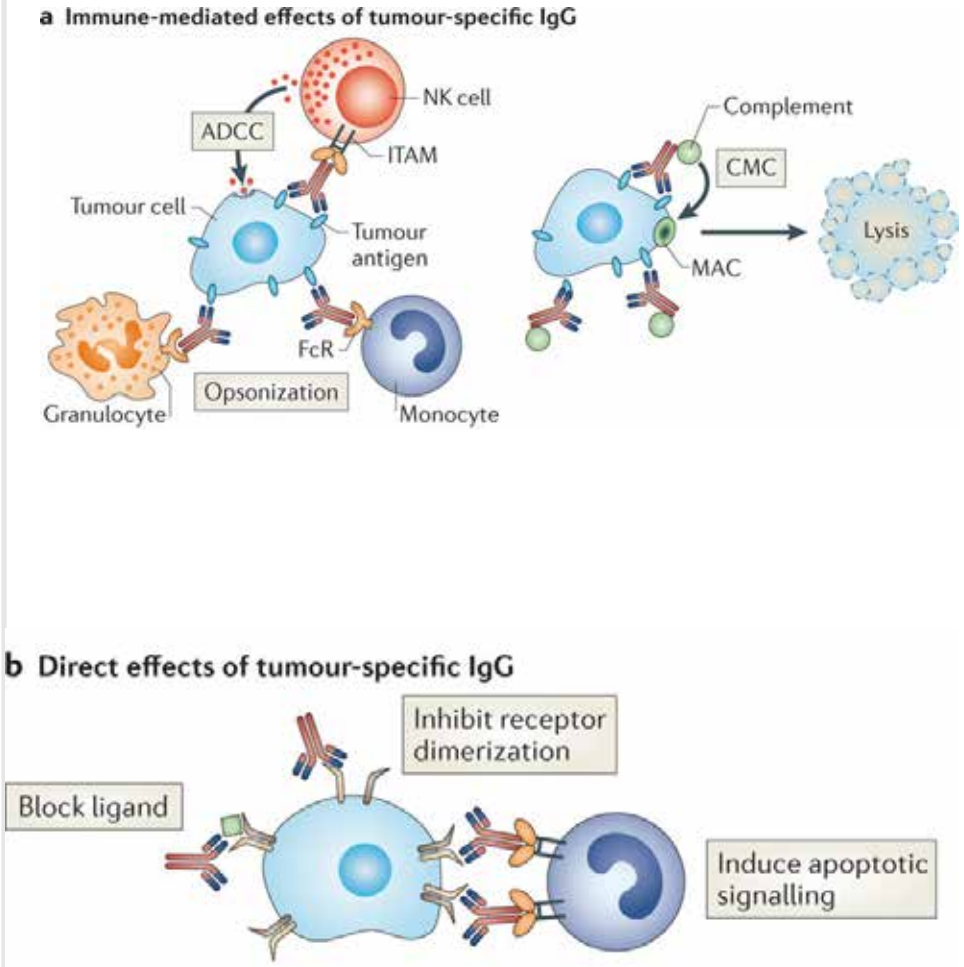
Abemaciclib
Acalabrutinib
Afatinib
Alectinib
Alpelisib
Avapritinib
Axitinib
Binimetinib
Bosutinib
Brigatinib
Cabozantinib
Capmatinib
Ceritinib
Cobimetinib
Copanlisiba
Crizotinib
Dabrafenib
Dacomitinib
Dasatinib
Duvelisib
Enasidenib
Encorafenib
Entrectinib
Erdafitinib
Erlotinib
Everolimus
Fedratinib
Gefitinib
Gilteritinib
Glasdegib
Ibrutinib
Idelalisib
Imatinib
Ivosidenib
s
Lapatinib
Larotrectinib
Lenvatinib
Lorlatinib
Midostaurin
Neratinib
Niraparib
Nilotinib
Olaparib
Osimertinib
Palbociclib
Pazopanib
Pemigatinib
Pexidartinib
Ponatinib
Regorafenib
Ribociclib
Ripretinib
Rucaparib
Ruxolitinib
Selpercatinib
Selumetinib
Sorafenib
Sonidegib
Sunitinib
Talazoparib
Tazametostat
Trametinib
Tucatinib
Vandetanib
Vemurafenib
Vismodegib
Zanubrutinib

Additional Targeted Agents

- Proteasome Inhibitors
  - Bortezomib
  - Carfilzomib
  - Ixazomib
- Immunomodulators (IMIDs)
  - Thalidomide
  - Lenalidomide
  - Pomalidomide
- Nuclear export inhibitor
  - Selinexor
- BCL-2 Inhibitors
  - Venetoclax
- CAR T-cell Therapy
  - Tisagenlecleucel
  - Axicabtagene ciloleucel

Monoclonal Antibody (mAb) Overview

- Mechanism of action
  - Engineered antibody binds target transmembrane protein
  - Direct effects on malignant/target cells to disrupt cell signaling and growth
    - Blocks binding of a ligand or inhibits dimerization of a receptor
  - Mediate antibody-dependent cellular cytotoxicity (ADCC)
  - Mediate complement mediated cytotoxicity (CMC)
  - Enhance responsiveness to chemotherapy or radiation



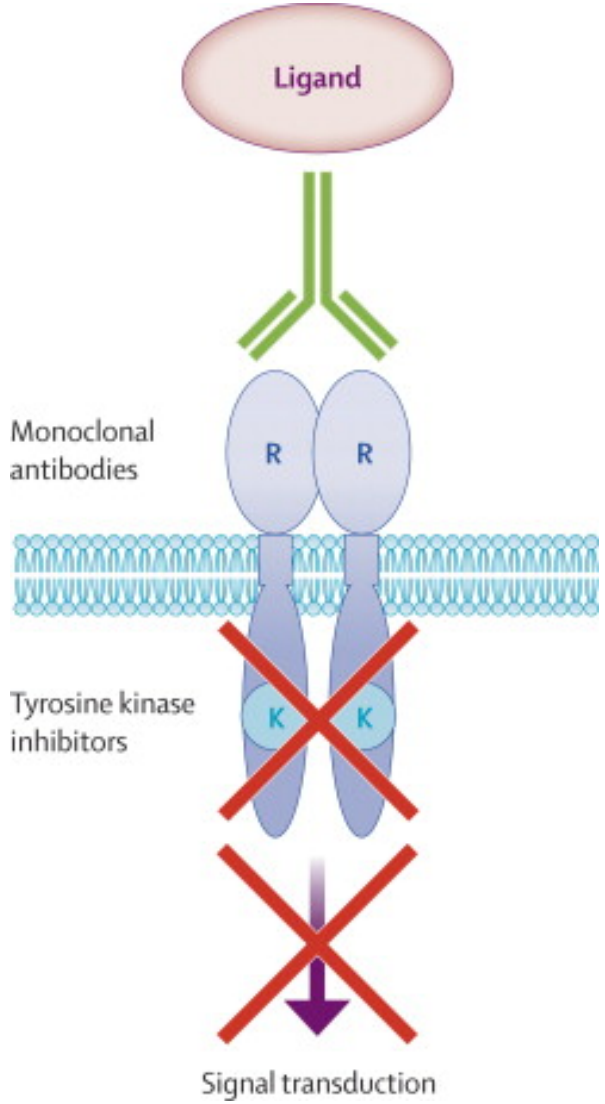
Nature Reviews Cancer. 2015. 15;361-370.

Monoclonal Antibody (mAb) Overview

- Most do not require dose adjustments (or not studied) for renal or hepatic impairment
- Most mAbs carry a **Black Box Warning** for infusion reactions
- Premedications: H1 blocker, H2 blocker, corticosteroid, acetaminophen
  - Varies by agent
  - 1st infusion vs. all infusions
- One-hour monitoring period post-infusion suggested for some agents
- Management of infusion reactions:
  - Stop infusion
  - Medication management includes agents above if not given initially, additional steroid (hydrocortisone), meperidine for rigors, oxygen, epinephrine, etc.
  - Grade 1-2: resume at 50% of previous rate after symptom resolution

Tyrosine Kinase Inhibitors (TKI) Overview

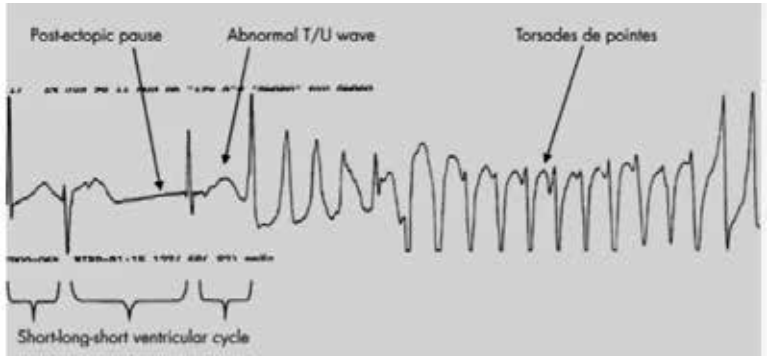
- Mechanism:
  - Inhibition of tyrosine kinase enzyme results in blockade of multiple cell signal transduction pathways
  - Affects cell proliferation, survival, and invasion
- Must consider timing of administration in relation to food
- Must consider patient compliance
  - Multiple tablets per doses
  - Multiple doses per day
  - Ability to take tablets
- Must consider drug-drug interactions (DDIs) that require specific dose adjustment



Lancet Oncol. 2007. 8(8):738-743.

TKIs and QTc prolongation

- FDA considers any drug that prolongs the QTc by 5msec to be a QTc prolonging agent
  - QTc varies by up to 60 msec in the same patient throughout the day
- Some TKIs have specific dose adjustments/parameters for QTc: Nilotinib
  - Dose dependent effect
  - Obtain baseline EKG, 7 days after any dose change, and periodically
  - Contraindicated in hypokalemia, hypomagnesemia, or long QT syndrome
  - Correct electrolyte imbalances prior to initiation



Yap YG, et al. Heart. 2003. 89:1363-1372.

TKIs as CYP P450 substrates

- Food to avoid: grapefruit juice, pomegranate juice, starfruit, Seville oranges
- Smoking is a CYP1A2 inducer
- Most common interaction is through CYP 3A4

Strong 3A4 inhibitors	Strong 3A4 inducers
Voriconazole, ritonavir, posaconazole, ketoconazole, itraconazole, clarithromycin, diltiazem, idelalisib	Rifampin, carbamazepine, enzalutamide, phenytoin, St. John's wort




CD20 Targeting mAbs

	Rituximab (Rituxan)	Rituximab hyaluronidase (Rituxan Hycela)
Target	Chimeric	
Uses	NHL, CLL, ALL, Waldenstrom's	
Dosing	375 mg/m^2 500 mg/m^2	1400mg (23,400 units) in 11.7ml over 5 min 1600mg (26,800 units) in 13.4ml over 7 min
ADRs	TLS, neutropenia	
BBW	Infusion reactions, mucocutaneous reactions, PML, HBV reactivation	
Premed	APAP, H1 blocker	
Note (s)	HBV core antibody and surface antigen testing for all patients If surface antigen positive, prophylactic therapy with entecavir recommended	
		Must have 1 full dose of IV rituximab prior to SubQ administration Hyaluronidase reversibly opens up interstitial space in SubQ tissue to deliver >2.3ml

CD20 Targeting mAbs

	Ofatumumab (Arzerra)	Obinutuzumab (Gazyva)
Target	Fully human (different epitope binding)	Humanized (glycoengineered)
Uses	CLL, Waldenstrom's	CLL, FL
Dosing	• Initial: 300mg D1, 1000mg D8 • Then: 1000-2000mg Qweek, or Q28days • Then: 1000-2000mg Q4-8weeks	• C1D1: 100mg • C1D2: 900mg • C1D8 & D15: 1000mg • Then: 1000mg Q28d • Then: 1000mg Q2monthsx2yr
ADRs	Infusion reactions, TLS	Infusion reactions, TLS, neutropenia, thrombocytopenia
BBW	HBV reactivation, PML	HBV reactivation, PML
Premed	APAP, H1 blocker, corticosteroid	
Note	HBV core antibody and surface antigen testing for all patients If surface antigen positive, prophylactic therapy with entecavir recommended	

Key Points: CD20 Targeting mAbs

- Infusion reactions and premedication
- HBV reactivation
- No SubQ Rituximab until patient tolerates IV rituximab infusion

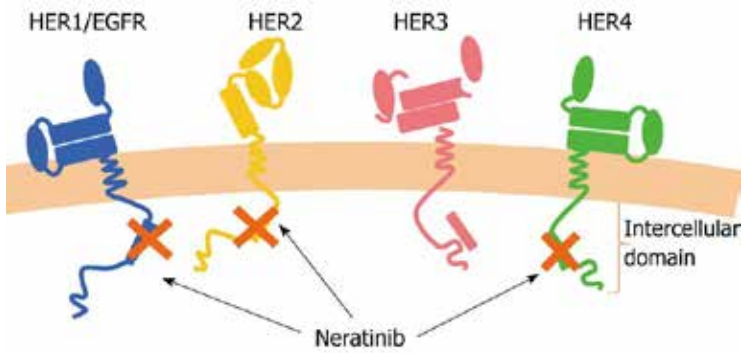
HER2 Targeting mAbs

(Human epidermal growth factor receptor 2)

	Trastuzumab (Herceptin)	Pertuzumab (Perjeta)
Target	HER2	HER2
Uses	Neoadj, adjuvant, met HER2+ breast cancer; HER2+ gastric cancer	Neoadj, adjuvant, met HER2+ breast cancer **with trastuzumab**
Dosing	4mg/kg then 2mg/kg Qweek 8mg/kg then 6mg/kg Q3week	840mg, then 420mg Q3week
Re-load	Re-load for dose delay >1 week	Re-load for dose delay ≥6 weeks
Cardiotoxicity BBW	• LVEF at baseline and periodically during treatment • Monitoring, hold/discontinuation parameters **DIFFERENT** for each agent	
Other BBW	• Infusion reactions, pulmonary toxicity, embryo-fetal toxicity	Embryo-fetal toxicity
Other ADR		Rash, diarrheas

LoRusso PM. Clin Cancer Res. 2011. 17 (20): 6437-47.

HER2 Targeting TKIs



	Lapatinib (Tykerb)	Neratinib (Nerlynx)
Target	ErbB-1 (HER1, EGFR) and ErB-2 (HER2); reversible	Pan-HER inhibitor: HER1, HER2, HER4; irreversible
Uses	HER2+, ER/PR+ met breast cancer with letrozole or capecitabine	Extended adjuvant therapy for HER2+ breast cancer
Dosing	Different dose with capecitabine vs letrozole • Child-Pugh C: dose adjust • Empty stomach	240mg daily with food • Child-Pugh C: 80mg daily • Avoid PPIs and H2 blockers • Admin 3h after antacids
DDI	Dose reduce with CYP3A4 inhibitors	Substrate of 3A4
BBW	• Hepatotoxicity – fatal deaths • AST/AST >3xULN and Tbili>2xULN • Do not rechallenge	
ADR	• **DIARRHEA** • Cardiotoxicity – hold if LVEF≥grade 2, resume if recovered (LVEF baseline and periodic) • Rash, QTc prolongation, pneumonitis	• **DIARRHEA**: Antidiarrheal prophylaxis for C1 - C2 • Titrate to 1-2 BMs/day • D1-14: loperamide 4mg TID • D15-56: loperamide 4mg BID • D57-365: loperamide 4mg PRN • Hepatotoxicity

Park Y. World J Clin Oncol. 2011. 2(2):125-134.

Tucatinib

	Tucatinib
Target	HER2 and 4, minimal inhibition of HER1
Uses	With capecitabine and trastuzumab for metastatic HER2+ breast cancer
Dose	300mg PO BID
Common adverse effects (all grades)	• Diarrhea (81%, median onset 12 days) • Hepatotoxicity • (With capecitabine) nausea, hand foot syndrome, stomatitis, rash, embryo-fetal toxicity,
Monitoring	LFTs at baseline and every 3 weeks during treatment CBC, BMP
Drug Interactions	Inhibits CYP3A4 and Pgp
Supportive care	No upfront antidiarrheal prophylaxis recommended

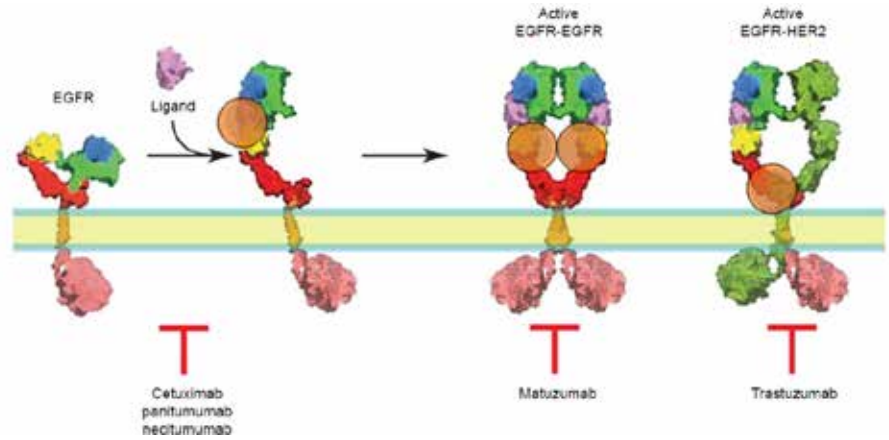
Tukysa [package insert]. Bothell, WA: Seattle genetics, Inc.; 2020.

Key Points: HER2 Targeted Therapy

- Cardiotoxicity
- Diarrhea
- Hepatotoxicity with the TKIs
- New indication for ADO-trastuzumab emtansine

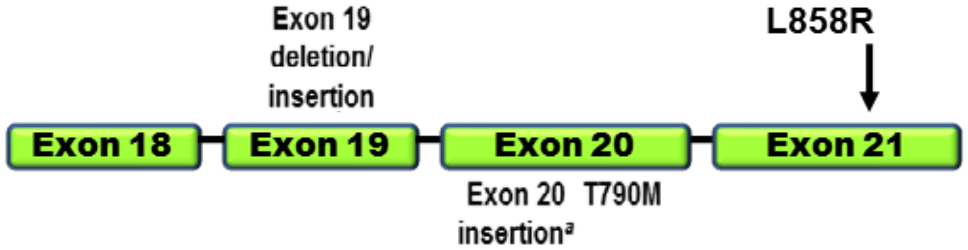
EGFR Targeting mAbs

(Epidermal growth factor receptor)



	Cetuximab (Erbitux)	Panitumumab (Vectibix)	Necitumumab (Portrazza)
Target	Binds ligand binding site of EGFR (HER1, c-ErbB-1)		
Uses	CRC, SCCHN	Metastatic CRC monotherapy; mCRC first-line with FOLFOX	Metastatic NSCLC with gemcitabine + cisplatin
Dosing	400mg/m^2 loading dose then 250 mg/m^2 weekly	6mg/kg every 14 days	800mg D1,8 Q3 weeks
ADR	Infusion reactions, acneiform rash, diarrhea, hypoMg, fatigue	Infusion reactions, acneiform rash, diarrhea, hypoMg, hypoCa, keratitis	Infusion reactions, rash, thromboembolism
BBW	Infusion reactions Cardiopulmonary arrest	Dermatologic toxicity	Cardiopulmonary arrest Hypomagnesemia
Premeds	H1 blocker		• If previous grade 1-2 inf rxn: H1 blocker with next infusion • If recurrent grade 1-2 inf rxn: H1 blocker, APAP, dex
Notes	Patients with NRAS or KRAS mutation are unlikely to benefit. Panitumumab ineffective in BRAF V600E mutation.		

EGFR Targeting TKIs



	Erlotinib (Tarceva)	Gefitinib (Iressa)	Afatinib (Gilotrif)
Targets	EGFR (reversible)		EGFR (irreversible) HER2, HER4
Uses	mNSCLC* with EGFR exon 19 or exon 21 (L858R) mutation Metastatic pancreatic cancer with gemcitabine	mNSCLC* with EGFR exon 19 or exon 21 (L858R) mutations	mNSCLC with EGFR exon 19 or exon 21 (L858R) mutations Squamous mNSCLC
Dosing	100-150mg daily Empty stomach • Caution with Tbili>3xULN	250 mg daily	40mg daily, empty stomach • Dose reduced for renal fx
ADEs	Rash, diarrhea, hemorrhage, hepatotoxicity, corneal ulcerations	Rash, diarrhea, hepatotoxicity, ocular toxicity	Cardiovascular toxicity, diarrhea, stomatitis, hepatotoxicity, ocular toxicity, paronychia
DDI	• CYP3A4, CYP1A2 inh/ind • Smoking • Acid-reducing agents	• CYP3A4 inducer • Acid-reducing agents	• Pgp inh/ind: reduce/increase by 10mg
Notes	*Higher binding affinity for EGFR exon 19 deletion or exon 21 (L858R) mutations		Consider LVEF at baseline and periodically

Lovly CM, et al. My Cancer Genome. 2015.

EGFR Targeting TKI

	Osimertinib (Tagrisso)	Dacomitinib (Vizimpro)
Target	Mutated EGFR (irreversible) (T790M, L858R, exon 19 del)	EGFR (irreversible), including exon 19del and exon 21 L858R sub HER2, HER4
Uses	**1st line NSCLC w/EGFR mut** EGFR T790M mutated mNSCLC	First line mNSCLC, EGFR mut+ exon 19 del or exon 21 L858R sub
Dosing	80mg daily W/3A4 inducer: 160mg daily	45mg daily
DDI	Rash, diarrhea, nail toxicity, ocular toxicity, nausea, QTc prolongation, bone marrow suppression (rare), cardiotox	Avoid PPI Strong CYP2D6 inhibitor; (2D6 substrates: tamoxifen)
ADR		Rash, diarrhea, pneumonitis/ILD
Notes	Consider LVEF at baseline and periodically	Take H2 blocker 10h before or 6h after dacomitinib

Wu YL. Lancet Oncol. 2017. 18;1454-66

EGFR Dermatologic Toxicity Management

- Rash correlated with drug response
  - Dose reductions only for severe reactions
- Develops within first 2 weeks of treatment
- Limit sun exposure, use sunscreen
- Moisturize
- Topical or systemic antibiotics
- May use topical corticosteroids, sparingly

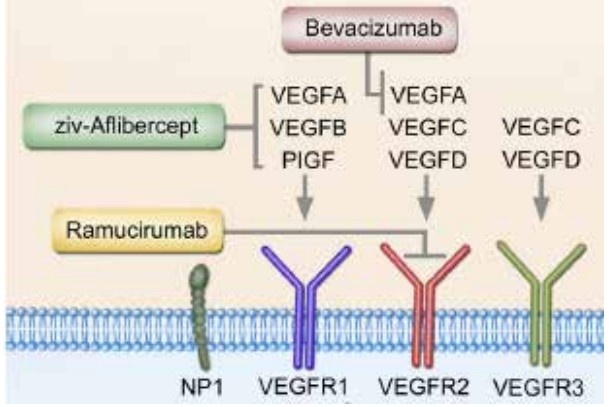
Am Fam Physician 2008;77:311-19

Key Points: EGFR Targeted Therapy

- Dermatologic toxicity – acne-like rash
- Diarrhea
- Smoking induces erlotinib clearance – need to dose adjust
- Dacomitinib interacts with tamoxifen

VEGF Targeting mAbs

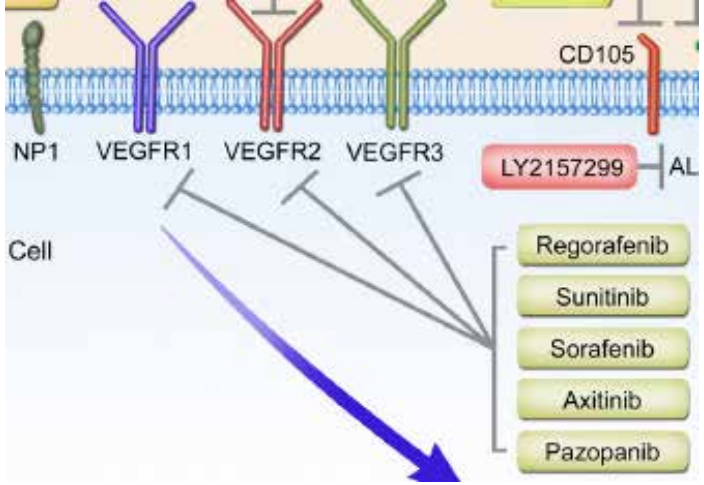
(Vascular epidermal growth factor)



	Bevacizumab (Avastin)	Ramucirumab (Cyramza)	Ziv-aflibercept (Zaltrap)
Target	VEGF (ligand)	VEGFR2 (receptor)	VEGF-A, VEGF-B, P_LGF (ligand)
Uses	Cervical, mCRC, mRCC glioblastoma, NSCLC (non-squamous), ovarian	Adv gastric/GEJ w/paclitaxel mNSCLC with docetaxel mCRC with FOLRIRI	mCRC in combination with FOLFIRI (2^{nd} line following oxaliplatin-based regimen)
Dosing	5-15 mg/kg IV every 2-3 weeks	8 mg/kg IV Q2 wks 10 mg/kg IV Q3 wks (lung)	4 mg/kg IV Q2 weeks
ADR	HTN, diarrhea, stomatitis, hand-foot syndrome, proteinuria, VTE/ATE, asthenia Ramucirumab and ziv-aflibercept: dose reductions for HTN or proteinuria		
	Myalgia, ovarian failure	Infusion reaction, thyroid dysfunction	Voice disorder
BBW	Black box warnings removed		Hemorrhage, GI perf, wound healing
Premed		IV H1 blocker Prev rxn: + APAP + steroid	
Notes	Hold for 28 days before and after surgeries	Hold prior to surgery	Hold for 28 days before and after surgeries

Clarke JM, et al. J Gastroint Oncol. 2013. 4(3): 253-63.

Antiangiogenic TKIs



	Sorafenib (Nexavar)	Sunitinib (Sutent)	Pazopanib (Votrient)	Axitinib (Inlyta)
Target	VEGFR, PDGFR, cKIT			VEGFR
	FLT3, BRAF, RET	CSFR1, RET, FLT3	FBFR1/3, Lck, etc	
Uses	RCC, HCC, DTC	RCC, GIST, PNET	RCC, STS	RCC
Dose	400 mg BID Empty stomach	50mg QD x 4wk Q6wk PNET:37.5 mg daily	800 mg QD, empty stomach, avoid acid suppression	5 mg→7mg→10mg Q12H Uptitrated Q2weeks without Grade 2 ADEs
	Lack clear dose adjustment guidelines			
DDI	Warfarin Avoid 3A4 inh/ind	3A4 inhibitor/inducer: dec/inc dose incrementally	3A4 inhibitor: 400mg 3A4 inducer: avoid	3A4 inh or Child-Pugh Class B: decrease by 50%
ADR	HTN, HFS, diarrhea, N/V, fatigue, myelosuppression, hair/skin pigment changes			
Rare ADR	Proteinuria/nephrotic syndrome, wound dehiscence, GI perforation, hypothyroidism, arterial thrombosis, hemorrhagic events, QTc prolongation			
Notes			Discontinue 7d prior to surgery	Discontinue 24h prior to surgery

Clarke JM, et al. J Gastroint Oncol. 2013. 4(3): 253-63.

VEGF Dermatologic Toxicity

Hand-foot skin reaction

Hair discoloration

Brzezniak C, et al. N Engl J Med. 2014. 370:e277.
Gomez P, et al. The Oncologist. 2011. 16:1508-1519.

Multikinase TKIs

	Regorafenib (Stivarga)	Lenvatinib (Lenvima)
Target	Antiangiogenic: VEGFR1, 2, 3; TIE-2 Anti-proliferation: PDGFR, FGFR, MAPK Anti-oncogenic: c-Kit, RAF-1 Other: BRAF, Ret, etc	Antiangiogenic: VEGFR Anti-proliferation: FGFR, PDGFR Anti-oncogenic: KIT Other: RET
Uses	HCC 2nd line treatment of mCRC, GIST	Differentiated thyroid cancer (DTC) RCC with everolimus
Dosing	160mg QD x21d (28 day cycle) • Low fat breakfast (specified) • Dose reduce by 40mg increments	24mg QD for DTC 18mg QD for RCC Adjust: CrCl<30ml/min or Child-Pugh C
ADR	Dysphonia, HFS, HTN, GI perforation, hemorrhage, wound healing, proteinuria, SCC of the skin	Moderate emetogenicity, diarrhea, ATE/MI, GI perforation, hemorrhage, proteinuria, HFS, QTc prolongation, hepatotoxicity,
BBW	Hepatotoxicity	
DDI	CYP3A4 inh/ind: no recommendations Warfarin	

LoRusso PM. Clin Cancer Res. 2011. 17 (20): 6437-47.

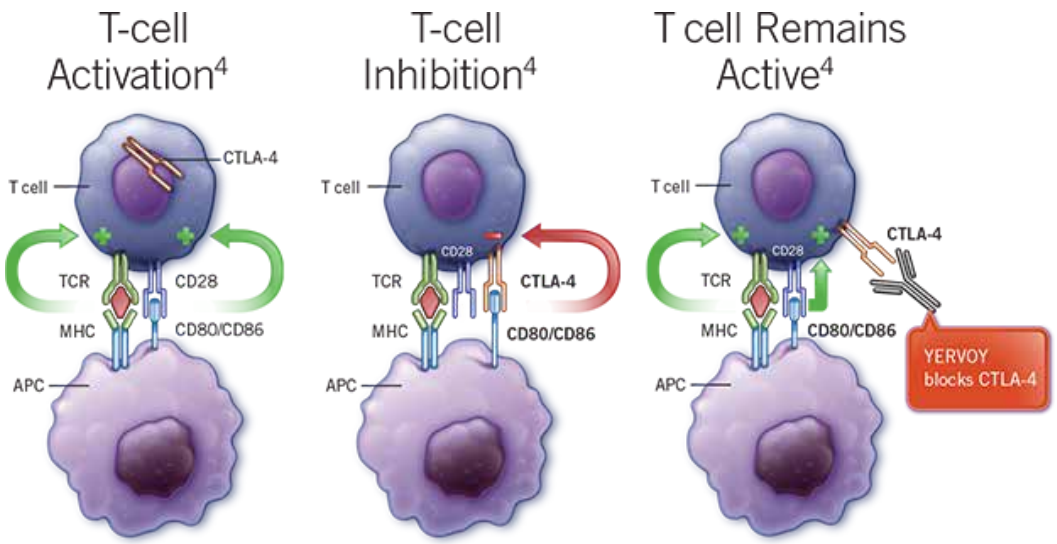
Multikinase TKIs

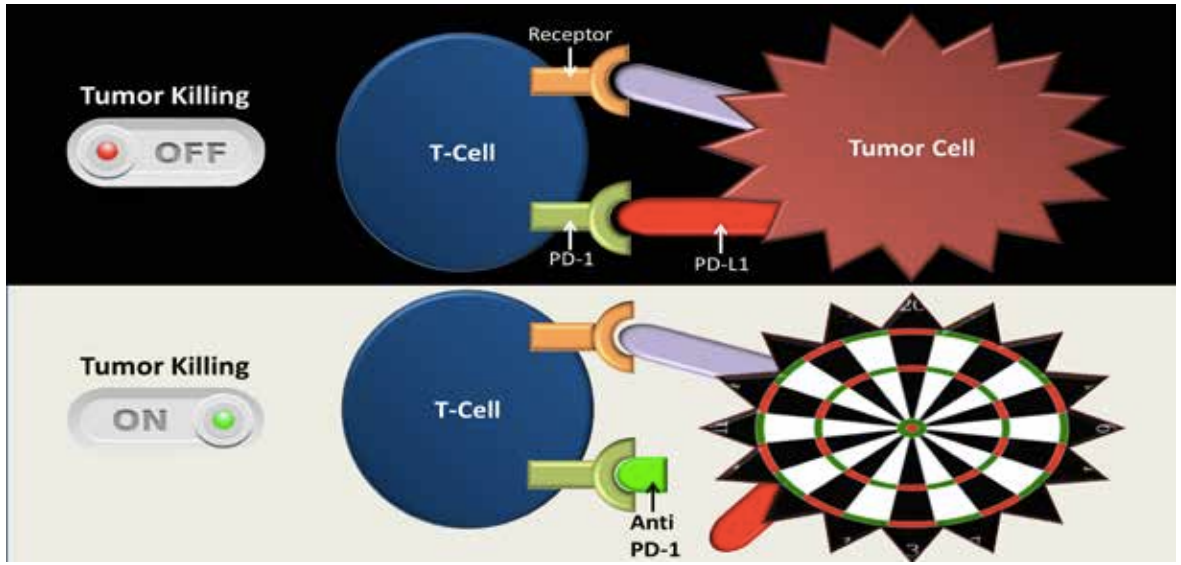
	Vandetanib (Caprelsa)	Cabozantinib (Cometriq, Cabometyx)
Target	Antiangiogenic: VEGFR1, 2, 3; TIE-2 Anti-proliferation: PDGFR, FGFR, MAPK Anti-oncogenic: c-Kit, RAF-1 Other: BRAF, Ret, etc	Antiangiogenic: VEGFR Anti-proliferation: FGFR, PDGFR Anti-oncogenic: KIT Other: RET
Uses	Medullary thyroid cancer (MTC)	RCC, MTC
Dosing	300mg daily • QTc<450msec to initiate; K^+>4mEq/L • CrCl<50ml/min: 200mg daily • Not recommended for Child-Pugh B/C • Avoid CYP3A4 inducers	Cabometyx, RCC: 60mg QD Cometriq (MTC): 140mg -180mg QD • Empty stomach • Dose adjust for 3A4 inh/ind • Dose adjust for C-P Class A/B
ADR	**Rash,** diarrhea, heart failure, HTN, CVA, hemorrhage, hypothyroidism	HFS, diarrhea, hemorrhage, HTN, proteinuria, VTE/ATE, wound healing, stomatitis, hair color change
BBW	**QTc prolongation (requires FDA REMS program)**, torsades de pointes, sudden death	Cometriq: Perforations, fistulas, hemorrhage
Notes	**Cometriq and Cabometyx not interchangeable**	
	Avoid QTc prolonging agents	Hold 28d prior to surgery

Key Points: VEGF Targeted Therapy

- Hypertension
- Proteinuria/nephrotic syndrome
- Considerations for holding therapy around the time of procedures
- Update: BBW removed for bevacizumab and ramucirumab

Checkpoint Inhibitors





CTLA4

PD-1/PD-L1

Yervoy (ipilimumab). Bristol-Myers Squibb Company. 2016. Accessed 7 Sept 2017.
Collins F. NIH Director's Blog. 2015. Accessed 3 Aug 2016.

CTLA-4 Checkpoint Inhibitor

	Ipilimumab (Yervoy)
Target	CTLA-4 (cytotoxic T-lymphocyte associated antigen 4)
Uses	Melanoma, metastatic/unresectable, adjuvant Renal cell cancer, advanced (with nivolumab) mCRC, MSI-H or dMMR (with nivolumab)
Dosing	Metastatic: 3mg/kg Q3 weeks Adjuvant: 10mg/kg Q3 weeks x4, then 10mg/kg Q12 weeks x3 years 1mg/kg Q3 weeks x4 doses with nivolumab
ADR	Immune related adverse events particularly colitis

PD-1 Checkpoint Inhibitors

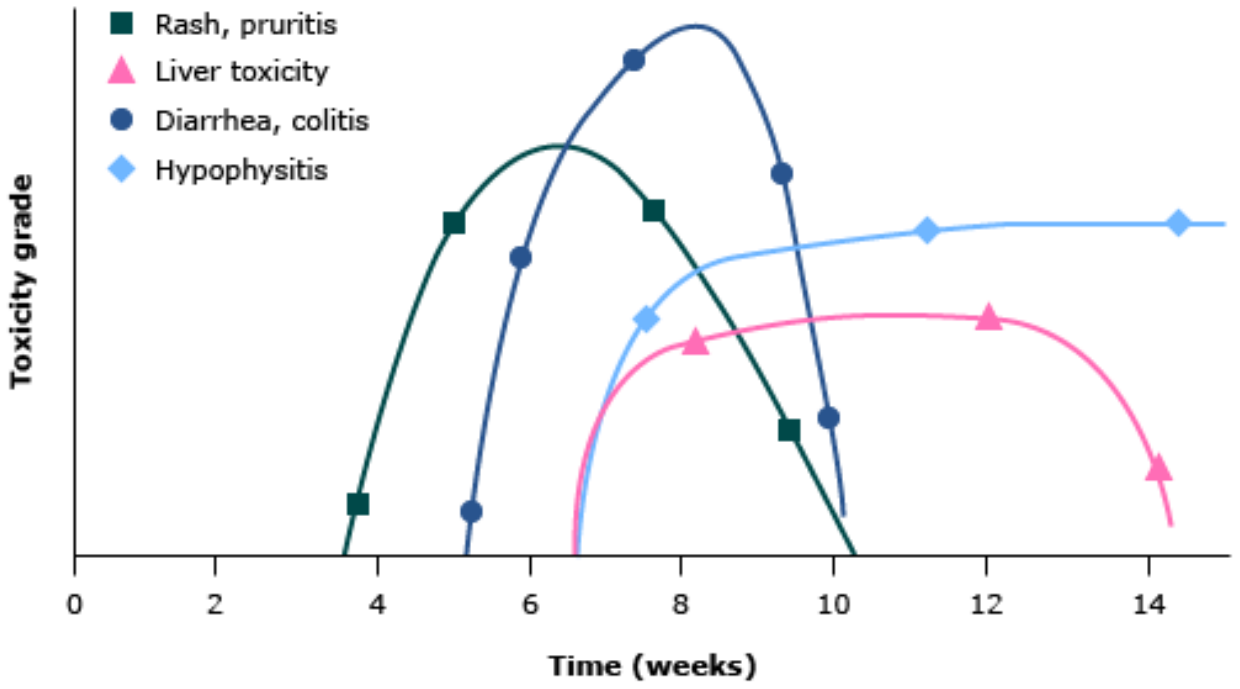
	Pembrolizumab (Keytruda)	Nivolumab (Opdivo)	Cemiplimab (Libtayo)
Target	Binds PD-1 receptor		
Use	• HNSCC, recurrent/metastatic • cHL, relapsed/refractory • Melanoma,met/unresectable • **MSI-high cancer, met/unresectable** • Met NSCLC, single agent/combo • Urothelial carcinoma, adv/met	• mCRC (MSI, MMR deficient) • HNSCC, recurrent/metastatic • cHL • Melanoma,met/unresectable • First line with ipi • Met NSCLC • Advanced RCC • Urothelial carcinoma, adv/met	• Cutaneous squamous cell carcinoma
Dose	200mg Q3 weeks	240mg Q2 weeks 480mg Q4 weeks 3mg/kg Q2 weeks	350mg Q3 weeks

PD-L1 Checkpoint Inhibitors

	Atezolizumab (Tecentriq)	Avelumab (Bavencio)	Durvalumab (Imfinzi)
Target	Binds PD-L1 receptor		
Use	• NSCLC, met • Urothelial carcinoma, advanced/metastatic	• Merkel cell, met • Urothelial carcinoma, advanced/metastatic	• Urothelial carcinoma, advanced/metastatic
Dose	1200mg Q3 weeks	10mg/kg Q2 weeks	10mg/kg Q2 weeks
	Dose adjust for toxicities: SCr, LFTs, Tbili		
Premed		H1 blocker, APAP for first 4 infusions	

Immune Related Adverse Events

- Dermatologic toxicities
  - Rash, pruritus
- GI toxicity
  - Colitis
  - Hepatitis
  - Pancreatitis
- Endocrine toxicity
  - Diabetes mellitus
  - Thyroid, adrenal, hypophysitis
- Pulmonary toxicity
- Renal Toxicity
- Ocular toxicity
- Nervous system toxicity
- Musculoskeletal toxicity



Reactions are due to T cell activation and proliferation
Treatment if severe = STEROIDS (Prednisone 1-2 mg/kg/day)

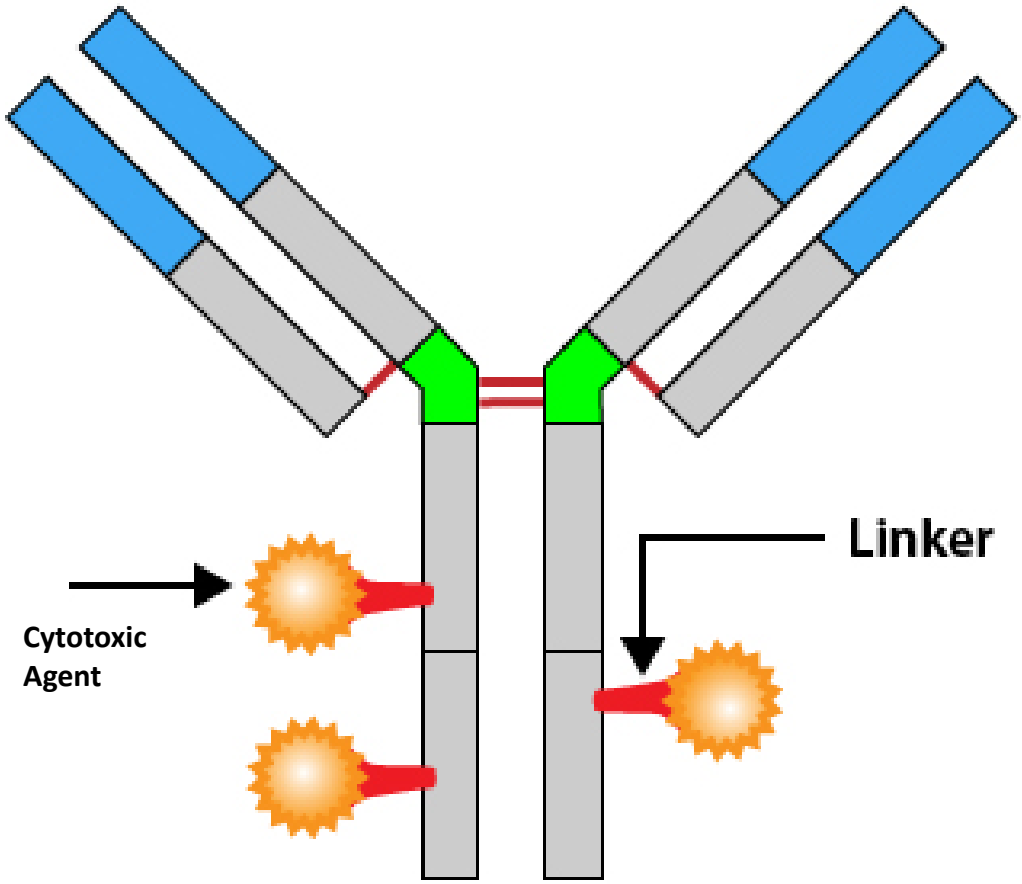
UpToDate. 2017. Accessed 7 Sept 2017.

CCR4 Targeting mAb

	Mogamulizumab (Poteligeo)
Target	CCR4
Uses	Relapsed, refractory mycosis fungoides or Sezary syndrome after ≥1 prior therapy
Dosing	1mg/kg IV D1, 8, 15, 22 C1, then 1mg/kg D1, 15 Q28 days • Premed with diphenhydramine and APAP for first infusion, then PRN
ADR	Autoimmune toxicity, lymphocytopenia, dermatologic toxicity/drug eruption (24%), infections (20%), infusion reactions (34%), diarrhea (24%)
Monitoring	Monitor closely for early evidence of transplant related complications in patients who have previously received hematopoietic transplant
Notes	Median onset of rash 15-31 weeks

Kim YH et al. *Lancet Oncol.* 2018
Poteligeo (mogamulizumab-kpkc)[package insert]. Bedminster, NJ: Kyowa Kirin, Inc; 2018

Antibody-Drug Conjugates



Cytotoxic Agent	Side effect profile
Vedotin – auristatin	Neuropathy
Ozogamicin – calicheamicin	Hepatotoxicity
Emtansine – maytansinoid	Neuropathy
Immunotoxin – Pseudomonas exotoxin, diphtheria toxin	Capillary leak syndrome

Beck A. Nature Reviews. 2017. 16;315-337
Alewine C. The Oncologist. 2015. 20;176-85

Antibody-Drug Conjugates

	Brentuximab vedotin (Adcetris)	Inotuzumab ozogamicin (Besponsa)	Gemtuzumab ozogamicin (Mylotarg)
Target	CD30	CD22	CD33
Uses	HL, relapsed/refractory HL, after HSCT anaplastic large cell lymphoma	Relapsed/refractory B-cell ALL	Newly diagnosed and relapsed/refractory AML
Dosing	1.8mg/kg Q3 weeks (max 180mg) Avoid if CrCl<30ml/min Child-Pugh A: 1.2mg/kg	0.8mg/m2 D1, 0.5mg/m2 D8&15 Q21d • CR/Cri: 0.5mg/m2 Q28d	3mg/m^2 D1, 4, 7 (max 4.5mg) with 7+3 6mg/m^2 D1, 3mg/mg^2 D8
ADR	Infusion reactions, rash, **peripheral neuropathy**, bone marrow suppression, diarrhea, hepatotoxicity	Bone marrow suppression, hepatotoxicity, QTc prolongation, embryo-fetal toxicity	Infusion rxn (anaphylaxis), hemorrhage, LFT elevations, bone marrow suppression, resp distress
BBW	PML	Hepatotoxicity (VOD); Increased risk of post-SCT non-relapse mortality	Hepatotoxicity (VOD)
Premed		APAP, H1 blocker, steroid	
Notes	MMAE – microtubule inh	Calicheamicin – causes dsDNA breaks	

Antibody-Drug Conjugates

	Polatuzumab vedotin (Polivy)	Moxetumomab pasudotox (Lumoxiti)	Tagraxofusp (Elzonris)
Target	CD79B	CD22	CD123
Uses	DLBCL, relapsed/refractory	Hairy cell leukemia, relapsed/refractory	Blastic plasmacytoid dendritic cell neoplasm
Dosing	1.8mg/kg Q21d x6 cycles w/BR	0.04mg/kg D1, 3, 5 Q28 days • Requires pre/post hydration • Consider ASA 81 daily for thromboprophylaxis	12mcg/kg D1-5 Q21 days • First cycle inpatient • Albumin >3.2 to start treatment
ADR	Infusion reactions, **peripheral neuropathy**, bone marrow suppression, hepatotoxicity	Hypocalcemia, infusion rxn, AKI, diarrhea	Hepatotoxicity, hypersensitivity, hypoalbuminemia, thrombocytopenia
BBW		Capillary leak syndrome, HUS	Capillary leak syndrome
Premed	H1 blocker, APAP	APAP, H1 blocker, H2 blocker Post-med: dex 4mg; H1 blocker + APAP for 24h after PRN	H1 blocker, H2 blocker, steroid, APAP
Notes	Need PJP and HSV prophylaxis	Made in polysorbate 80	

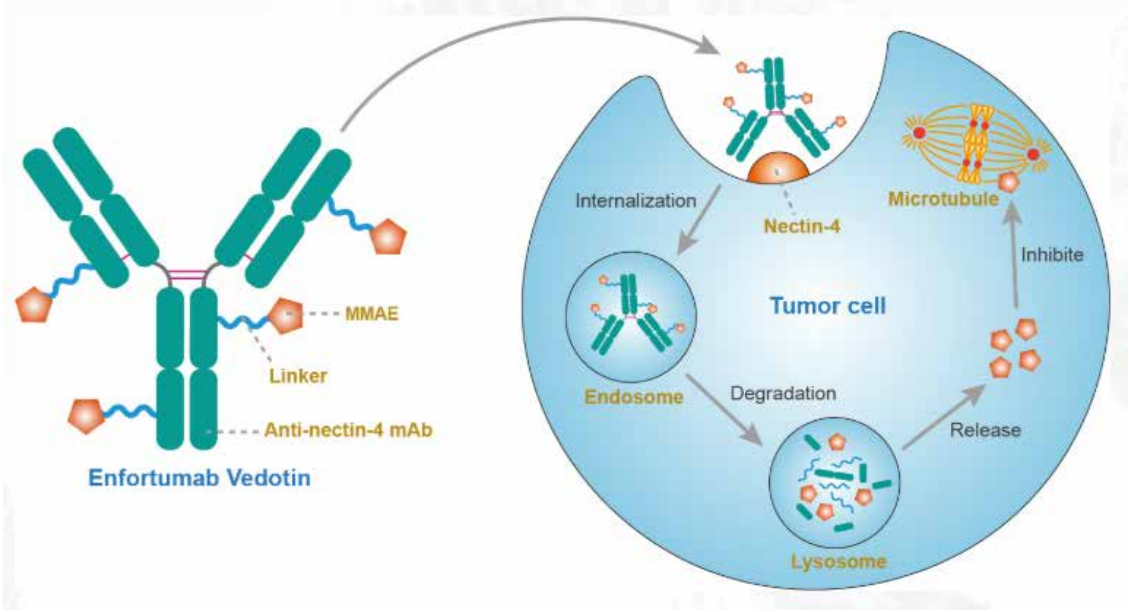
Antibody-Drug Conjugates

	ADO-trastuzumab emtansine (Kadcyla)	Trastuzumab deruxtecan (Enhertu)	Sacituzumab govitecan (Trodelvy)
Target	HER2	HER2	Trop2
Uses	Adjuvant HER2+ breast cancer for residual disease HER2+ metastatic breast cancer	Metastatic HER2+ breast cancer	Triple negative breast cancer
Dosing	3.6mg/kg Q3week • Dose adjust for liver and heme toxicities • Substrate of CYP3A4	5.4mg/kg Q3 week	10mg/kg D1, 8 Q21 days
ADR	Hepatotoxicity, embryo-fetal toxicity, stomatitis	Neutropenia, Diarrhea, Alopecia Moderate emetogenicity	Alopecia Moderate to high emetogenicity
BBW		Interstitial lung disease (9%, fatal in 2.6%)	Neutropenia Diarrhea
Premed			H1 blocker, H2 blocker, APAP
Notes			Patients with UGT1A1*28 allele at increased risk for neutropenia

Enfortumab vedotin-ejfv (Padcev)

Mechanism(s) of Action:

- Nectin-4 directed antibody conjugated to MMAE, a small molecule anti-mitotic agent



Current Indication:

- Locally advanced or metastatic urothelial cancer, after a PD1/PDL1 inhibitor and platinum-containing chemotherapy.

Padcev [package insert]. Bothell, WA: Seattle Genetics, Inc.; 2019.

Enfortumab vedotin-ejfv

Drug Topic	Detail
Common adverse effects (all grades)	• Moderate emetogenic risk • Peripheral neuropathy (49%) • Hyperglycemia (Grade ≥3 8%) • Ocular disorders (dry eyes, vision changes) (46%) • Skin reaction (54%, Grade ≥3 10%)
Monitoring	Blood glucose CBC, LFTs Eye exam

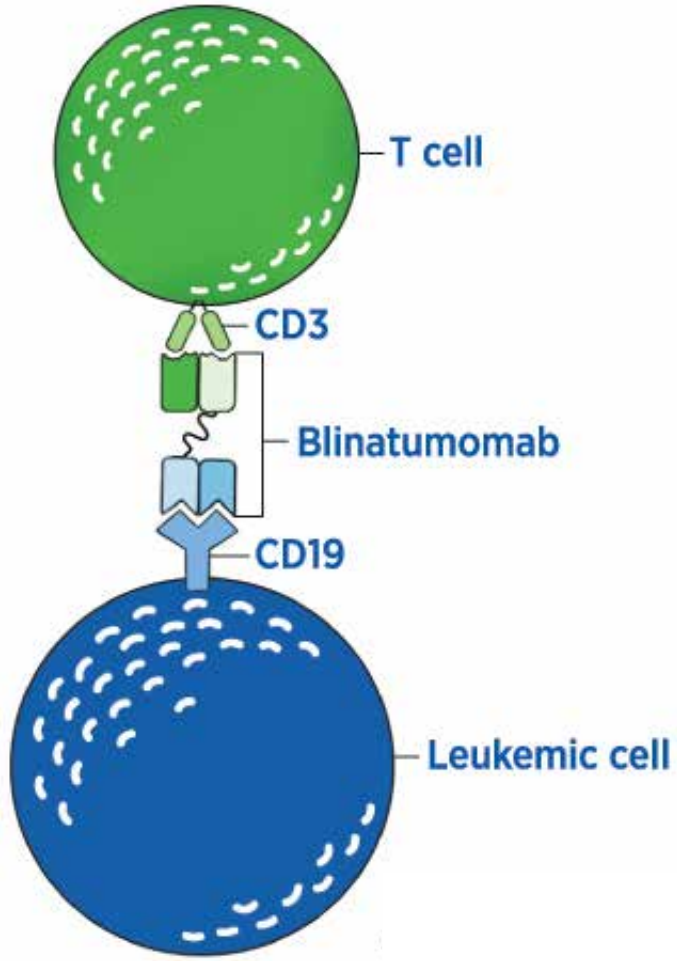
Padcev [package insert]. Bothell, WA: Seattle Genetics, Inc.; 2019.

Key Points: Antibody-drug conjugates

- No dose loading with antibody-drug conjugates
- All require premedication regimens
  - Except brentuximab vedotin
- Knowing the cytotoxic agent can predict side effect profile

Bi-specific T-cell engager: Blinatumomab (Blincyto)

	Blinatumomab
Target	CD19 B cells, CD3 T cells
Uses	Relapsed/refractory ALL, ALL MRD+
Dosing	**NEW dosing for MRD+: fixed dose starts at 28mcg daily CIVI** For relapsed/refractory: hospitalization for C1D1-9, C2D1-2
ADR	Hepatotoxicity
BBW	Cytokine Release Syndrome, neurotoxicity



Honey K. AACR. 2014.

FDA-Approved Biosimilars of mAbs

Innovator drug	Biosimilar
Trastuzumab (Herceptin)	Trastuzumab-anns (Kanjinti) Trastuzumab-qyyp (Trazimera) Trastuzumab-dttb (Ontruzant) Trastuzumab-pkrb (Herzumab) Trastuzumab-dkst (Ogiviri)
Rituximab (Rituxan)	Rituximab-pvvr (Ruxience) Rituximab-abbs (Truxima)
Epoetin alfa (Procrit)	Epoetin alfa-epbx (Retacrit)
Bevacizumab (Avastin)	Bevacizumab-bvzr (Zirabev) Bevacizumab-awwb (Mvasi)
Filgrastim (Neupogen)	Filgrastim-aafi (Nivestym) Filgrastim- sndz (Zarxio)
Pegfilgrastim (Neulasta)	Pegfilgrastim-cbqv (Udenyca) Pegfilgrastim-jmdb (Fulphila)

Note that SubQ formulations of trastuzumab and rituximab and Neulasta OnPro are NOT biosimilars

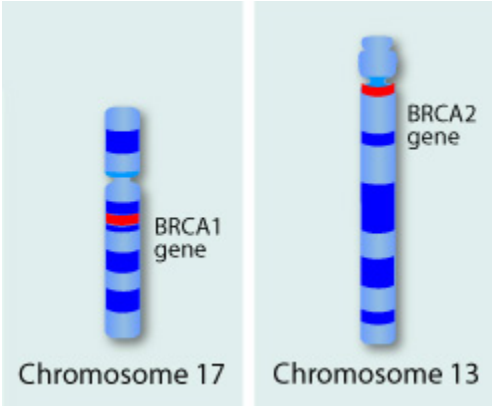
CDK Targeting TKIs

	Palbociclib (Ibrance)	Ribociclib (Kisqali)	Abemaciclib (Verzenio)
Target	Cyclin dependent kinase 4 and 6		
Uses	Breast cancer, advanced or metastatic; HR+, HER2-		
Dosing	125mg QD x21 days every 28 days with aromatase inh or ovarian suppression • Take with food • CYP3A4 inh: 75mg QD	600mg QD x 21days every 28 days with letrozole in the morning • CYP3A4 inh: 400mg QD • Child-Pugh B/C: 400mg QD	150mg BID with aromatase inh or fulvestrant • CYP3A4 inh: 100mg BID • Child-Pugh C: 150mg QD 200mg BID as a single agent • CYP3A4 inh: 150mg BID
ADR	Neutropenia, nausea, stomatitis, diarrhea	Hepatotoxicity, neutropenia, QTc prolongation, nausea, diarrhea	**Diarrhea,** neutropenia, hepatotoxicity, VTE, inc SCr
Monitoring	CBC Q2weeks x2months, then PRN	CBC, LFTs Q2weeks x2 months, then monthly Electrolytes monthly x6 months EKG Q2 weeks x3, then PRN	CBC, LFTs Q2 weeks x2 months, then monthly x2 months, then PRN
Notes	Avoid grapefruit	Avoid grapefruit	More CDK4 activity/less CDK6 = less neutropenia Avoid grapefruit

Key Points: CDK 4/6 Inhibitors

- Palbociclib = neutropenia
  - Low percentage of febrile neutropenia
- Ribociclib = neutropenia + QTc prolongation + hepatotoxicity
- Abemaciclib = diarrhea
  - Asymptomatic increase in SCr – consider using cystatin C if necessary
- All are CYP3A4 substrates and require dose reduction with a CYP3A4 inhibitor
  - Avoid grapefruit juice

PARP Inhibitors



	Olaparib (Lynparza)	Rucaparib (Rubraca)	Niraparib (Zejula)
Target	Poly-ADP ribose (PARP)		
	Ovarian cancer Met, BRCA mut, HER2- breast Prostate, Pancreatic	Ovarian cancer Prostate cancer	Ovarian cancer
Dosing	300mg BID • CYP3A4 inh: 200mg BID • Dose reduced for renal fx	600mg BID	300mg QD • Consider 200mg QD for pts <77kg and/or b/l platelet <150K
ADR	Nausea, fatigue, diarrhea, anemia, neutropenia, secondary malignancy	Nausea, constipation/diarrhea, dysgeusia, anemia, neutropenia, asymptomatic inc SCr, secondary malignancy	**Thrombocytopenia**, neutropenia, anemia, nausea, insomnia, HTN and hypertensive crisis, secondary malignancy
Notes	Tablets and capsules are not interchangeable		Begin no later than 8 weeks after platinum regimen

PARP Inhibitors

	Talazoparib (Talzenna)
Target	Poly-ADP ribose (PARP)
Uses	Breast cancer, BRCA mut, HER2-, locally advanced or metastatic
Dosing	1mg daily • Dose reduce to 0.75mg with Pgp inhibitors (amiodarone, verapamil, carvedilol) • Dose reduce for renal fx
DDI	Pgp inhibitors
ADR	Neutropenia, anemia, thrombocytopenia, nausea, transaminitis, diarrhea, secondary malignancy
Notes	**20% patients require dose reduction by Cycle 2** **50% patients require dose reduction by Cycles 4-6**

Key Points: PARP Inhibitors

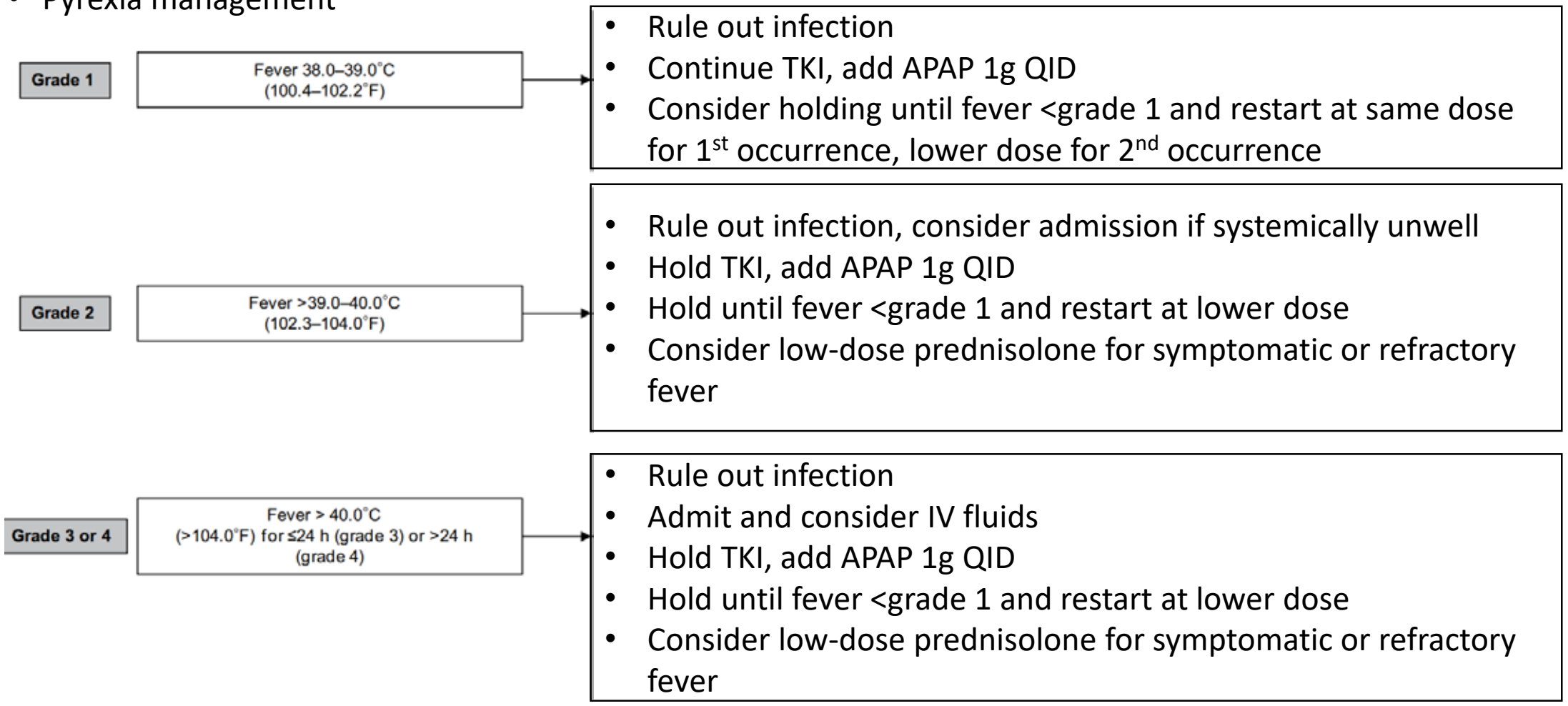
- Dose reduce for renal dysfunction: olaparib, talazoparib
- More hematologic toxicity: niraparib, talazoparib
- Olaparib FDA approved in first-line maintenance setting for BRCA mutated patients with ovarian cancer
- Olaparib and talazoparib approved for breast cancer

BRAF/MEK Targeted TKIs

	Vemurafenib | cobimetinib (Zelboraf | Cotellic)		Dabrafenib | trametinib (Tafinlar | Mekinist)		Encorafenib | binimetinib (Braftovi |Mektovi)	
Target	BRAF/MEK					
Uses	BRAF V600E or V600K mutated, unresectable or metastatic melanoma					
	Erdheim-Chester, V600E mutated		• Adjuvant melanoma • BRAF V600E mutated mNSCLC • Adv/met anaplastic thyroid ca			
Dosing	• DDI: warfarin, digoxin	• Reduce dose for short term use (<14 d) of 3A4 inhibitor	• Empty stomach • Avoid acid reducers if possible	• Empty stomach	• Reduce dose for use with CYP3A4 inhibitors	• Dose adjust for increased Tbili
Class ADR	GI toxicity (Nausea, vomiting, diarrhea) Risk for cutaneous SCC if BRAF inhibitor used alone					
Unique ADR	CK elevation, **retinal events,** photosensitivity, rash, diarrhea		**Pyrexia**, hypertension, lymphedema, hand-foot syndrome		CK elevation, **blurred vision/ocular toxicity**	
Notes	Dabrafenib - Hemolytic anemia if G6PD deficient					

Key Points: BRAF/MEK inhibitors

- Dabrafenib/trametinib approved in adjuvant melanoma with lymph node involvement after complete resection
- Pyrexia management



ALK Targeting Inhibitors

(Anaplastic lymphoma kinase)

	Crizotinib (Xalkori)	Ceritinib (Zykadia)	Alectinib (Alecensa)	Brigatinib (Alunbrig)
Target	ALK, c-MET, ROS1, RON	ALK, IGF-1R, ROS1	ALK, RET	ALK, ROS1, FLT3, EGFR
		Activity if crizotinib resistant		
Uses	mNSCLC, ALK+, ROS1+	mNSCLC, ALK+		
Dose	250mg PO BID • Dose reduce for renal fx • Avoid high fat meals	750mg PO daily • 3A4 inh: reduce by 1/3 • Empty stomach	600 mg PO BID • Take with food	• 90mg QDx7 days, then 180mg daily • Restart at initial dose if interrupted by >14d • 3A4 inh: reduce by 50%
ADR	Bradycardia, hepatotoxicity, pulmonary toxicity, QTc prolongation			**Pulmonary toxicity**, pancreatitis, hyperglycemia, visual disturbance
	Moderate emetogenicity, ocular toxicities	**Moderate emetogenicity**, neuropathy, hyperglycemia, pancreatitis	Myalgia, photosensitivity	
Notes	Avoid grapefruit juice			

ALK Targeting Inhibitors

(Anaplastic lymphoma kinase)

	Lorlatinib (Lorbrena)
Target	ALK, ROS1
Uses	ALK+ metastatic NSCLC after progression on crizotinib and ≥1 other ALK inh for mNSCLC • Active in patient with resistance to crizotinib • Activity against multiple mutant forms of ALK
Dosing	100mg daily • Dose reduce to 0.75mg with Pgp inhibitors (amiodarone, verapamil, carvedilol) • Dose reduce for renal fx
DDI	Dose reduce if given with strong CYP3A4 inhibitor
ADR	Hypercholesterolemia, peripheral edema, peripheral neuropathy, hepatotoxicity, tinnitus, cognitive effects (Slowed speech, word finding ability), AV block (rare)
Monitoring	Serum cholesterol/triglycerides (baseline, monthly x2 months) ECG at baseline, then intermittently
Notes	**Penetrates BBB**

Key Points: ALK Inhibitors

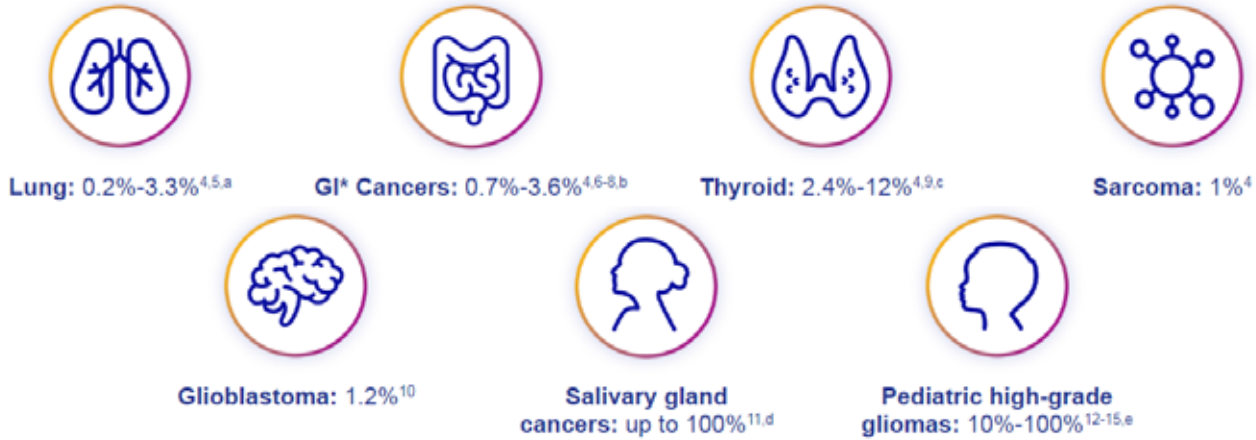
- Lorlatinib hypercholesterolemia management: statins, +/- fibrates, +/- fish oil, +/- nicotinic acid

Severity	Guidance
Mild: Cholesterol ULN–300 mg/dL OR Triglycerides 150–300 mg/dL	• Introduce or modify lipid-lowering therapy • Continue at the same lorlatinib dose
Moderate: Cholesterol >300–400 mg/dL OR Triglycerides >300–500 mg/dL	
Severe: Cholesterol >400–500 mg/dL OR Triglycerides >500–1,000 mg/dL	• Introduce lipid-lowering agent or increase dosage of ongoing lipid-lowering therapy, or change to a new lipid-lowering therapy • Continue at the same lorlatinib dose without interruption
Life threatening: Cholesterol >500 mg/dL OR Triglycerides >1000 mg/dL	• Introduce lipid-lowering agent or increase dosage of ongoing lipid-lowering therapy, or change to a new lipid-lowering therapy • Withhold lorlatinib dose until hyperlipidemia is moderate or mild before rechallenging at same dose while maximizing lipid-lowering therapy • If severe hyperlipidemia recurs despite maximal lipid-lowering therapy, reduce lorlatinib dose by one dose level (by 25 mg)

- Ceritinib has more GI toxicity (diarrhea, nausea, vomiting)
- Pulmonary toxicity with brigatinib requires up-titration

Costa RB. Oncotarget. 2018. 9;22137-46. Bauer TM. The Oncologist. 2019; 24:1103-10

NTRK Targeting Inhibitor



	Larotrectinib (Vitrakvi)	Entrectinib (Rozlytrek)
Target	Tropomyocin receptor kinase protein	
Uses	Advanced or metastatic solid tumors with *NTRK* gene fusion	*ROS1*+ metastatic NSCLC Adv or met solid tumors with *NTRK* gene fusion
Dosing	100mg BID • Dose reduce for hepatic impairment • Mg/m2 dosing for peds or if BSA <1m^2	600mg daily
DDI	Avoid (or dose reduce by 50%) with strong CYP3A4 inhibitors and avoid (or double the dose) with strong CYP3A4 inducers	Avoid with grapefruit juice Dose reduce to 100mg daily with strong CYP3A4 inh and 200mg daily with moderate CYP3A4 inh
ADR	Transaminitis Neurotoxicity (dizziness, gait disturbance, delirium, tremor, paresthesia)	Heart failure, neurotoxicity, skeletal fractures, hepatotoxicity, hyperuricemia, QTc prolongation
Monitoring	LFTs Q2 weeks during the first month, then monthly	
Notes	Oral solution available for pediatrics	

Drilon A. N Engl J Med. 2018. 378;731-9. Vitrakvi(larotrectinib)[package insert]. Stamford, CT: Loxo Oncology, Inc; 2018

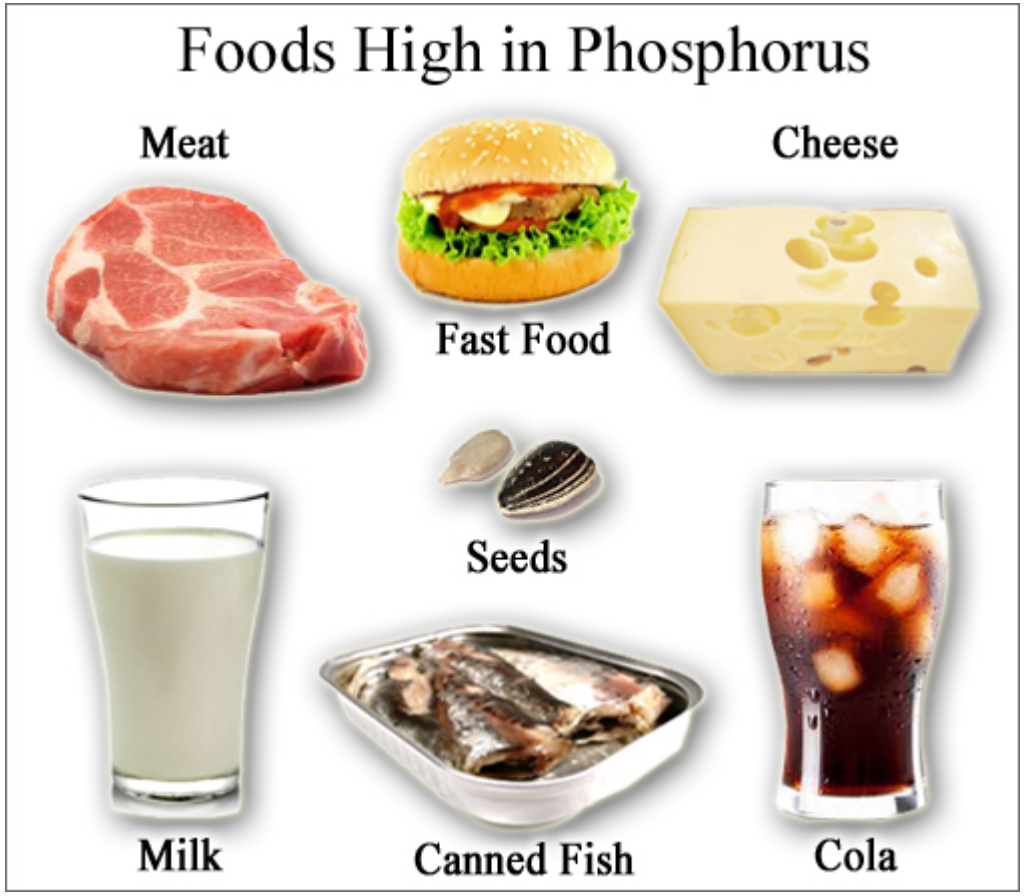
FGFR Targeting Inhibitor

	Erdafitinib (Balversa)	Pemigatinib (Pemazyre)
Target	Fibroblast growth factor receptor kinase (FGFR1/2/3/4); RET, PDGFR, KIT, FLT4, VEGFR2	FGFR1, 2, and 3
Uses	FGFR mutated urothelial carcinoma, advanced or metastatic	Metastatic cholangiocarcinoma with FGFR2 fusion
Dosing	8mg daily for 14-21 days If phosphate <5.5mg/dl and well-tolerated, increase to 9mg daily	13.5mg daily on Days 1-14, every 21 days
DDI	Substrate of CYP2C9 and CYP3A4	CYP3A4 inhibitors: avoid if possible or reduce pemigatinib dose
ADR	Hyperphosphatemia Ocular toxicity	
Monitoring	Serum phosphate level at baseline and D14-D21 Ophthalmologic exams at baseline, monthly x4 months, then Q3 months	Eye exam monthly Q2 months x6 months, then Q3 months

Pemazyre [package insert]. Wilmington, DE: Incyte Corporation; 2020.c

Hyperphosphatemia Management

- Hydration
- Low phosphate diet
  - 600-800mg daily
- Discontinue calcium supplements
- Sevelamer



http://www.nutrientsreview.com/minerals/phosphorus-phosphate.html

Hyperphosphatemia Management

- 30% patients required phosphate lower therapy with erdafitinib and pemigatinib

Lab	Erdafitinib	Lab	Pemigatinib
7-9mg/dl	Hold erdafitinib Weekly phos until <5.5 Dose reduce if phos >5.5 for >1 wk Add phosphate lowering therapy	>7mg/dl - ≤10mg/dl	Initiate phosphate lowering therapy Monitor phosphate weekly Hold if >7mg/dl w/in 2 weeks of starting phosphate lowering therapy
9-10mg/dl	Hold erdafitinib Weekly phos until <5.5 Restart at reduced dose		
>10mg/dl	Hold erdafitinib Weekly phos until <5.5 Restart at 2 dose levels lower	>10mg/dl	Initiate phosphate lowering therapy Hold if >10mg/dl w/in 1 week of starting phosphate lowering therapy

Balversa [package insert]. Horsham, PA: Janssen Products, LP; 2019.
Pemazyre [package insert]. Wilmington, DE: Incyte Corporation; 2020.

BCR-ABL Targeting TKIs

	Imatinib (Gleevec)	Dasatinib (Sprycel)	Nilotinib (Tasigna)
Target	BCR-ABL, PDGF, SCF, c-Kit	BCR-ABL, SRC family, c-Kit, EPHA2, PDGFR For imatinib resistance except T315I & F317V mut	BCR-ABL, c-Kit, PDGFR For imatinib resistance
Uses	Ph+ CML, Ph+ ALL, GIST, aggressive systemic mastocyctosis, MDS w/PDGF rearrangements	Ph+ CML, newly dx or resistant/intolerant, Ph+ ALL	Ph+ CML, newly dx or resistant/intolerant
Dose	400mg QD with food Range: 100-800mg QD • 3A4 inducer: inc 50% • CrCl<40: dec 50% • Severe hep dz: dec 25% • DDI: warfarin	100-180mg PO daily • 3A4 inh: reduce dose • 3A4 ind: increase dose • Empty stomach • Antacids 2h before/after • Avoid PPI/H2 blockers	300-400mg PO Q12 hours • 3A4 inh: reduce by 100mg • Child-Pugh A/B/C: reduce initial dose, then titrate up • Empty stomach • Antacids 2h before/after
ADR	Bone marrow suppression, cardiovascular dysfunction, edema, hypothyroidism		
	Rash, hepatotoxicity, AKI, TLS, mod emetogenicity	Rash, PAH, hemorrhage, TLS, QTc prolongation	Electrolyte abnormalities, hepatotoxicity, inc lipase
Notes	Use 400mg tabs to reduce iron exposure		BBW: QTc prolongation

BCR-ABL Targeting TKIs

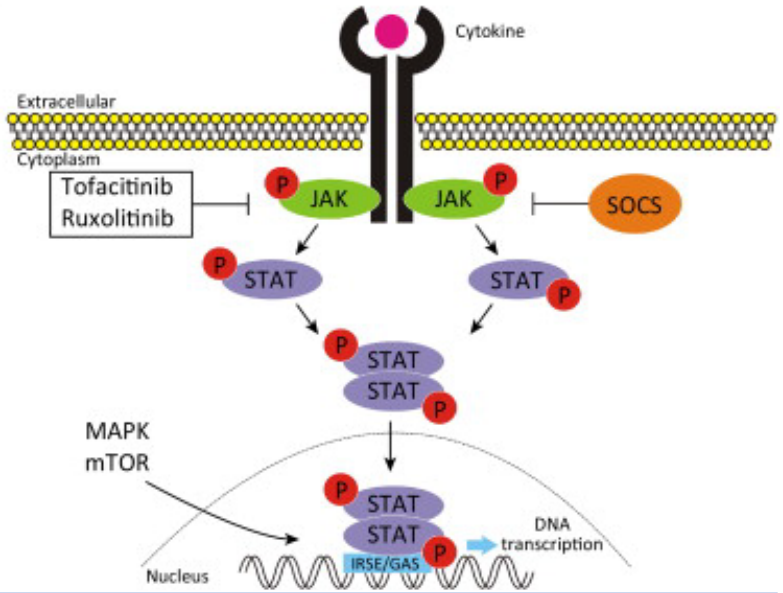
	Bosutinib (Bosulif)	Ponatinib (Iclusig)
Target	BCR-ABL, SRC family, c-Kit, PDGFR Activity in imatinib resistance except T315I and V299L	BCR-ABL, VEGFR, FGFR, PDGFR, FGFR, EPH, and SRC kinases, as well as KIT, RET, TIE2, and FLT3
Use	Ph+ CML in patients with resistance or intolerance to prior therapy	
		Resistant Ph+ ALL or with T315I mut
Dose	500-600mg PO daily with food • CrCl<50: 400mg QD • CrCl<30: 300mg QD • Child-Pugh A/B/C: 200mg QD	45mg PO daily • 3A4 inh: reduce to 30mg daily • Child-Pugh A/B/C: 30mg daily
ADR	Bone marrow suppression, edema	
	Moderate emetogenicity, nausea, diarrhea, pancreatitis, QTc prolongation	Arrhythmias, GI perf, HTN, ocular toxicity, hemorrhage, neuropathy, pancreatitis, TLS, wound healing
BBW		**Arterial occlusion (35%), heart failure, hepatotoxicity, VTE**
Notes	Antacids/H2 blockers 2h before/after	Optimal dose not identified

Key Points: BCR-ABL Targeting TKIs

- Avoid or time acid-suppressing agents with dasatinib, nilotinib, and bosutinib
- All are substrates of CYP3A4
  - Dose reduction and monitoring w/concurrent CYP3A4 inh with dasatinib, nilotinib, and ponatinib
- More fluid retention with dasatinib and imatinib
- Ponatinib has the most distinct toxicity profile

Cuellar S. J Oncol Pharm Pract. 2017. 2018. 24;433-52

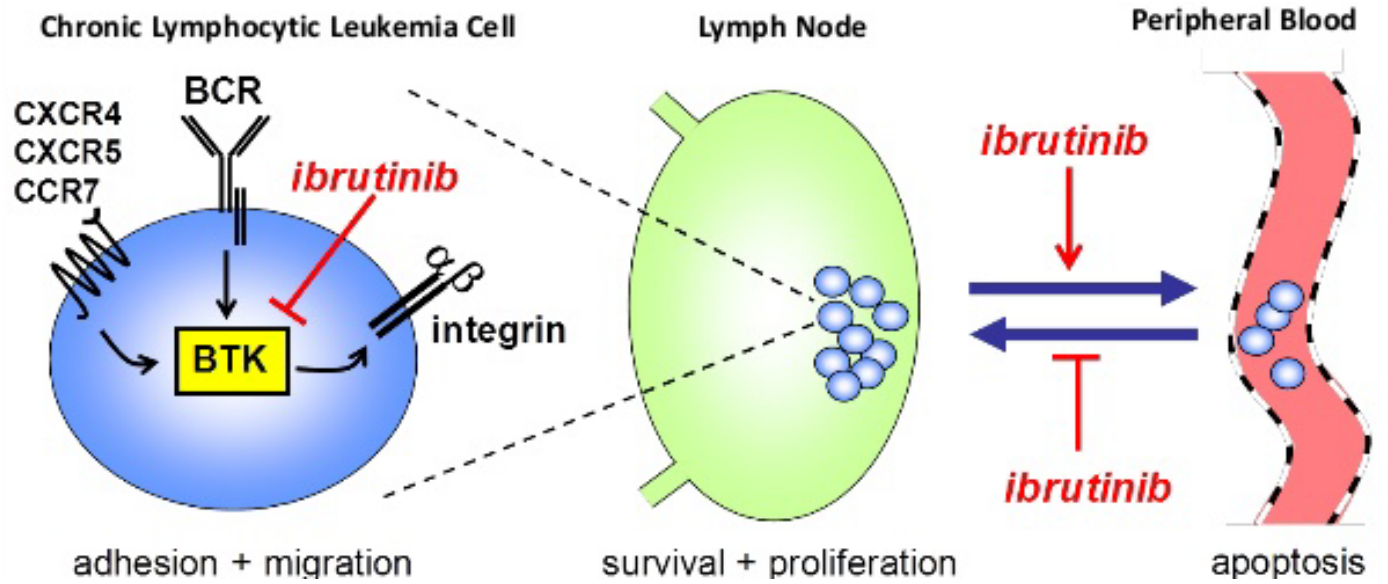
JAK Targeting TKIs



	Ruxolitinib (Jakafi)	Fedratinib (Inrebic)
Target	JAK 1 and JAK 2	JAK2 (selective) and FLT3
Use	GVHD, steroid refractory; myelofibrosis; polycythemia vera	Myelofibrosis
Dose	GVHD: 5-10mg BID MF: 5-20mg BID based on plt count • Dose reduce per CrCl <60ml/min & Tbili	400mg QD if plt >50 • Dose reduce for CrCl 15-29ml/min
DDI	Dose reduce for use w/strong CYP3A4 inhibitor	
ADR	Bone marrow suppression, edema	
	Anemia, infection, lipid abnormalities, non-melanoma skin cancer	Anemia, GI tox (N/V/diarrhea) Less common:hepatotox, amylase/lipase elevations
BBW		Encephalopathy (Wernicke's)
Notes	Taper at discontinuation d/t withdrawal syndrome	Baseline B1 (thiamine) prior to initiation

Koenders MI. Trends in Pharmacological Sciences. 2015. 36(4):189-195.

Bruton's Tyrosine Kinase Inhibitors



	Ibrutinib (Imbruvica)	Acalabrutinib (Calquence)
Target	Bruton's tyrosine kinase	
Uses	CLL/SLL, MCL, MZL, Waldenstrom's, cGVHD	MCL after 1 prior therapy
Dose	CLL/WM: 420mg daily MCL: 560mg daily	100 mg Q12 hours • Avoid PPIs; separate 2h from H2 blockers
Common ADEs	**Diarrhea**, nausea, fatigue, rash myalgias/arthralgias, myelosuppression	
Serious/Rare ADEs	**Grade 3/4 bleeding**, **AFib,** infection	Afib/flutter, bleeding, infection, secondary malignancies
Note	Avoid strong 3A4 inhibitors & inducers - dosing recommendations available	

Zanubrutinib (Brukinsa)

Mechanism(s) of Action:

- BTK inhibitor, highly selective

Current Indication:

- Mantle cell lymphoma, relapsed/refractory

Dose: 160 mg PO BID or 320 mg PO daily with food

- 80 mg tablets

Brukinsa [package insert]. San Mateo, CA: BeiGene USA, Inc.; 2019.

Zanubrutinib

Drug Topic	Detail
Common adverse effects (all grades)	• Neutropenia (G3-4, 27%), thrombocytopenia (G3-4, 10%), anemia • Hemorrhage (50%) (consider holding for 3-7d around surgeries/procedures) • Infections
Rare, but serious adverse events	Cardiovascular effects (atrial fibrillation/flutter) (2%)
Drug Interactions	CYP3A4 Inducers: Avoid CYP3A4 Inhibitors: decrease to 80mg QD (strong) or 80mg BID (moderate)
Infection prophylaxis	HSV, PJP

Brukinsa [package insert]. San Mateo, CA: BeiGene USA, Inc.; 2019.

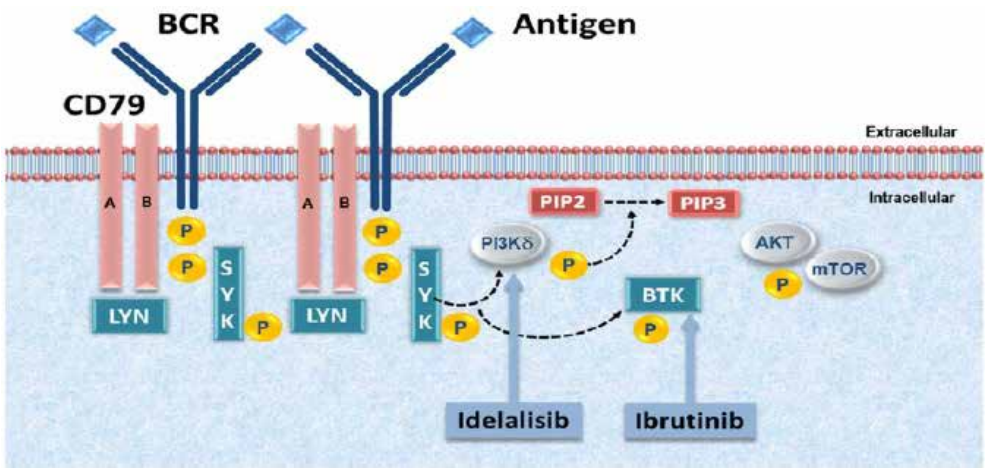
BCL-2 Targeting TKI

	Venetoclax (Venclexta)
Target	BCL-2, an anti-apoptotic protein
Uses	• Relapsed/refractory CLL, 17p deletion • AML, newly diagnosed, with azacytidine, decitabine, or cytarabine
Dosing	Dose titrated up • Adjusted for TLS and heme toxicity • Premeds: hydration and antihyperuricemic therapy
DDI	Dose reduce by 75% for concurrent strong CYP3A4 inhibitor Dose reduce by 50% for concurrent moderate CYP 3A4 inhibitor
ADR	**TLS;** neutropenia > anemia, thrombocytopenia, diarrhea, nausea

TLS Risk Assessment & Monitoring

- Start allopurinol 2-3 days prior to therapy initiation
- Outpatient hydration with 1.5 to 2L orally (or IV) for low and medium risk
  - Low risk: all lymph nodes <5 cm and ALC <25,000/mm^3
  - Medium risk: all lymph nodes <5 cm and ALC <25,000/mm^3
- INPATIENT: PO hydration as above with additional 150-200 ml/hour
  - High risk: any LN ≥10 cm OR ALC ≥25,000/mm^3 and any LN ≥5 cm
  - Consider rasburicase if baseline uric acid is high

PI3Kδ Targeting TKIs



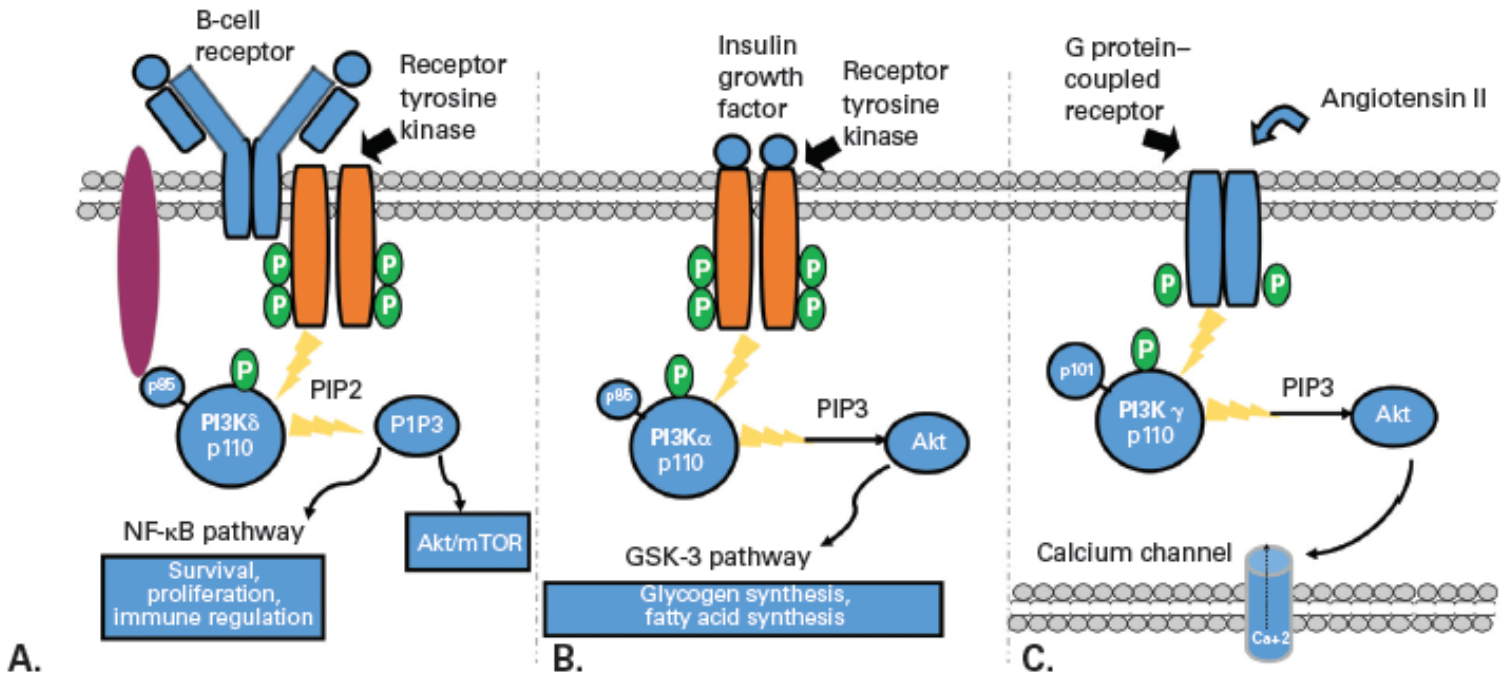
	Idelalisib (Zydelig)	Copanlisib (Aliqopa)	Duvelisib (Copiktra)
Target	Phosphatidylinositol 3-Kinase delta		
		PI3K-alpha	PI3K-gamma
Uses	CLL/SLL, relapsed FL, relapsed	FL, relapsed	CLL/SLL relapsed, refractory FL relapsed, refractory
Dose	150mg BID • Dose reduce for strong CYP3A4 inhibitor	60mg IV D1, 8, 15 Q28 days • Dose reduce to 45mg if given with strong CYP3A4 inh	25mg BID • Dose reduce for 15mg BID if given with strong CYP3A4 inh
ADR	Neutropenia, rash, diarrhea		
	Colitis, GI perf, hepatotoxicity	Hyperglycemia, hypertension	Colitis, hepatotoxicity
BBW	Hepatotoxicity, diarrhea/colitis, infection (PCP/CMV), pneumonitis, intestinal perforation		Infection (PCP/CMV), diarrhea/colitis, cutaneous reactions, pneumonitis
Notes	PCP prophylaxis during treatment and continue until CD4+>200		

Mewawalla P. Ther Adv Hematol. 2014. 5(5):139-52.

PIK3α Targeting TKIs

	Alpelisib (Piqray)
Target	Phosphatidylinositol 3-Kinase alpha
Uses	Metastatic or advanced PIK3CA mutated, HR+, HER2- breast cancer
Dosing	300mg PO daily with fulvestrant
DDI	Substrate of CYP2C9 and CYP3A4
ADR	• Hyperglycemia – start treatment with metformin +/- other diabetes medications • Rash – H1 blocker (loratadine/cetirizine) daily may decrease incidence of rash by 50% • Diarrhea
Monitoring	Fasting plasma glucose baseline, weekly x2 weeks, then monthly HbA1c Q3 months

Key Points: PI3K Targeting Agents

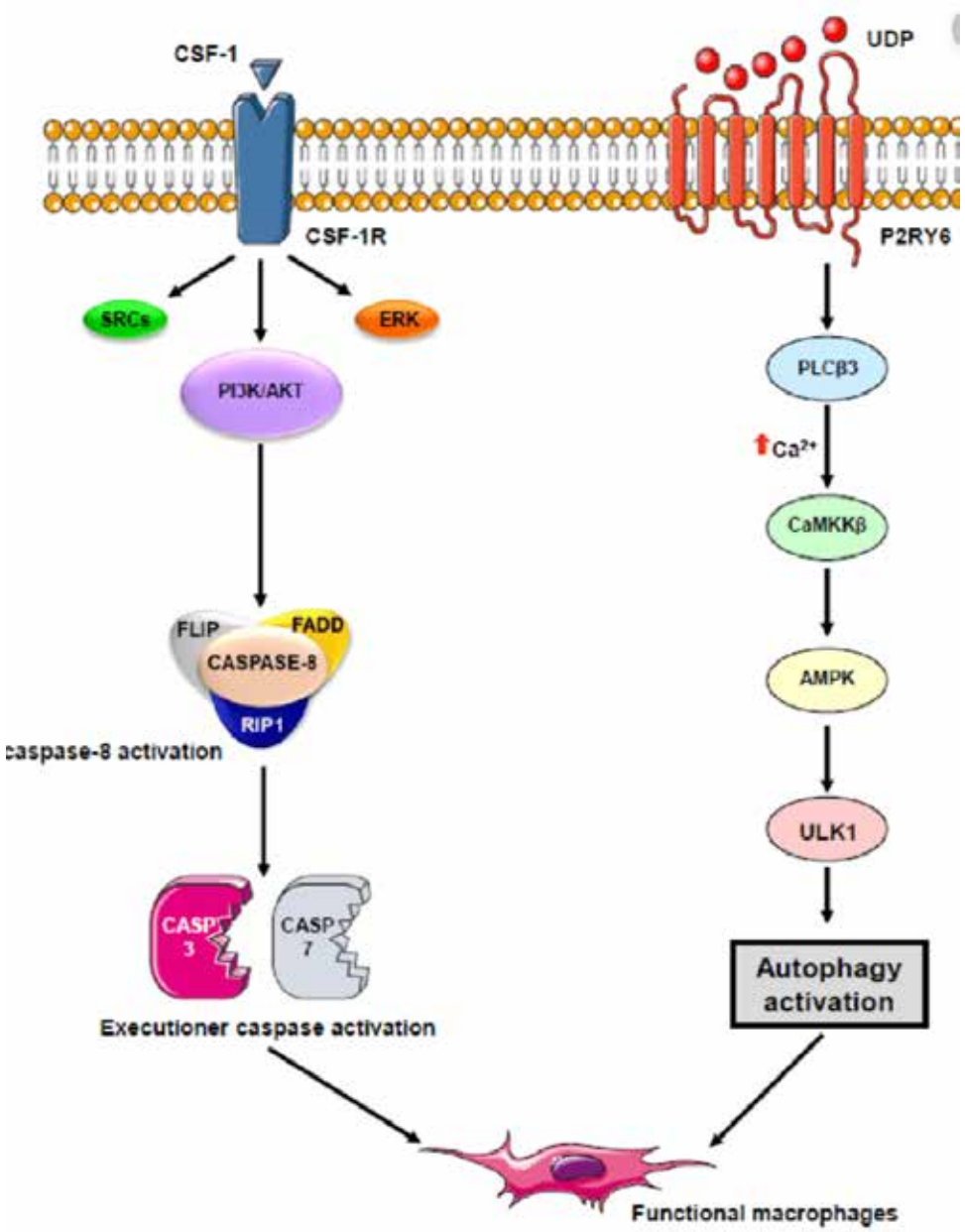


Subunit matters!

- Alpha = hyperglycemia
- Delta = autoimmune-like toxicities (hepatotoxicity, colitis, pneumonitis)
- Gamma = hypertension

Greenwell IB. Oncology (Williston Park). 2017. 31(11):821-8

Colony Stimulating Receptor



Pexidartinib (Turalio)

Mechanism of Action:

- CSF1R inhibitor, KIT, and FLT3 harboring an internal tandem duplication mutation (ITD).

Indication:

- Tenosynovial giant cell tumor (TGCT)

Dose: 400 mg PO BID on an empty stomach

- Dose reduce for CrCL <90ml/min

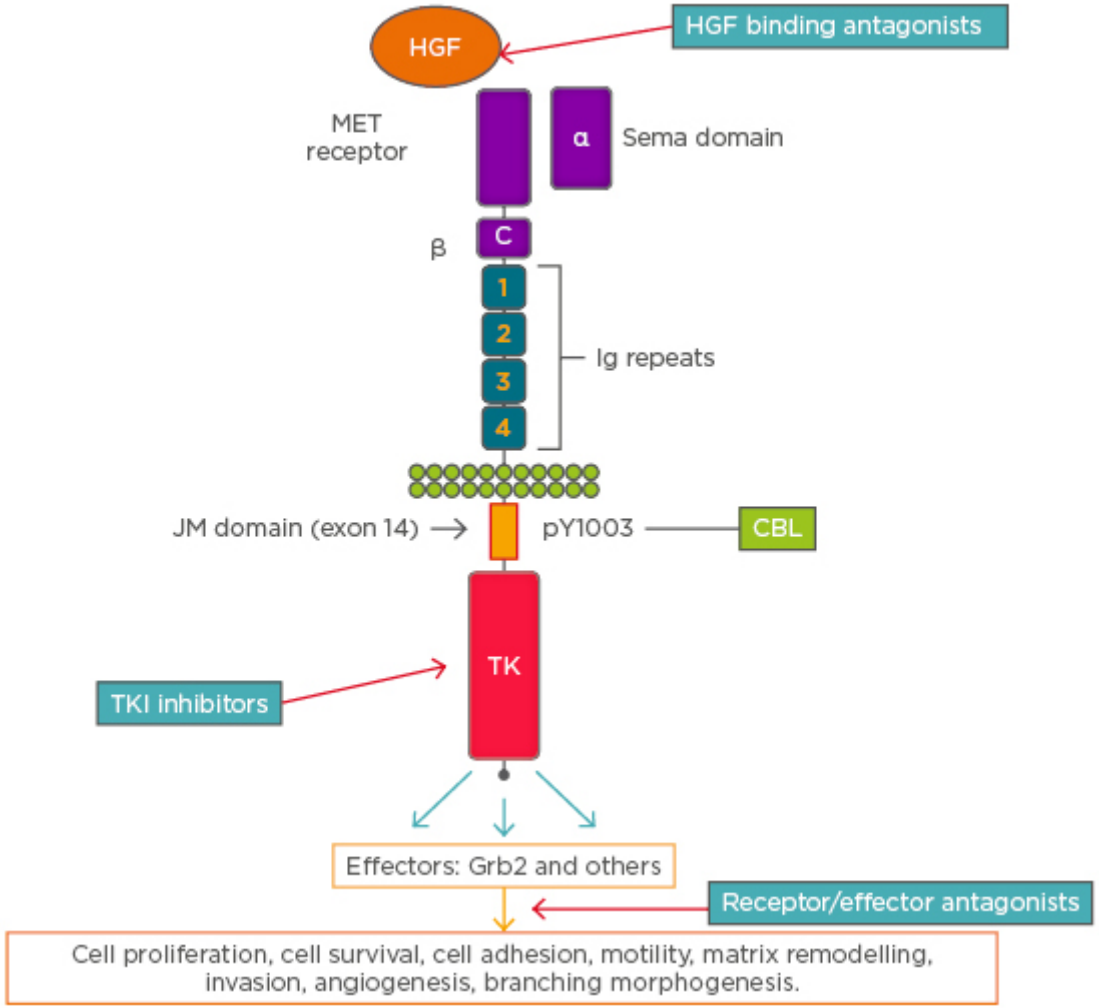
Turalio [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc..; 2019.

Pexidartinib

Drug Topic	Detail
Black Box Warning	Hepatotoxicity (**REMS Program**)
Common adverse effects (all grades)	• Hair color changes, eye edema, rash, embryo-fetal toxicity • Anemia, neutropenia ≤ grade 3
Monitoring	Liver function tests weekly x8 weeks, Q2 weeks x1 month, then Q3 months
Drug Interactions	Avoid with hepatotoxic agents CYP3A4 inhibitor: reduce dose or avoid use CYP3A4 inducer: avoid Avoid PPI Take pexidartinib 2h before or 10h after H2 receptor antagonist Separate from antacid by 2 hours

Turalio [package insert]. Basking Ridge, NJ: Daiichi Sankyo, Inc..; 2019.

MET Receptor



Rehman S. EMJ Respir. 2018. 6(1): 100-111

Capmatinib (Tabrecta)

Mechanism(s) of action:

- Inhibits MET to decrease cancer cell growth

Current indication:

- Metastatic non-small cell lung cancer, with MET exon 14 skipping mutation

Dose: 400 mg (two 200 mg tabs) PO BID

Tabrecta [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation.; 2020.

Capmatinib

Drug Topic	Detail
Common adverse effects (all grades)	• Hepatotoxicity • Photosensitivity (use sunscreen and sun protective clothing) • Likely moderate emetogenicity (5HT3 inhibitor with each dose) • Peripheral edema, Embryo-fetal toxicity
Rare, but serious adverse events	Interstitial lung disease/pneumonitis (4.5%)
Monitoring	• LFTs at baseline, Q2 weeks x 3 months, then Q month
Drug Interactions	CYP3A4 inducers: Avoid

Tabrecta [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corporation.; 2020.

Selpercatinib (Retevmo)

Mechanism(s) of Action:

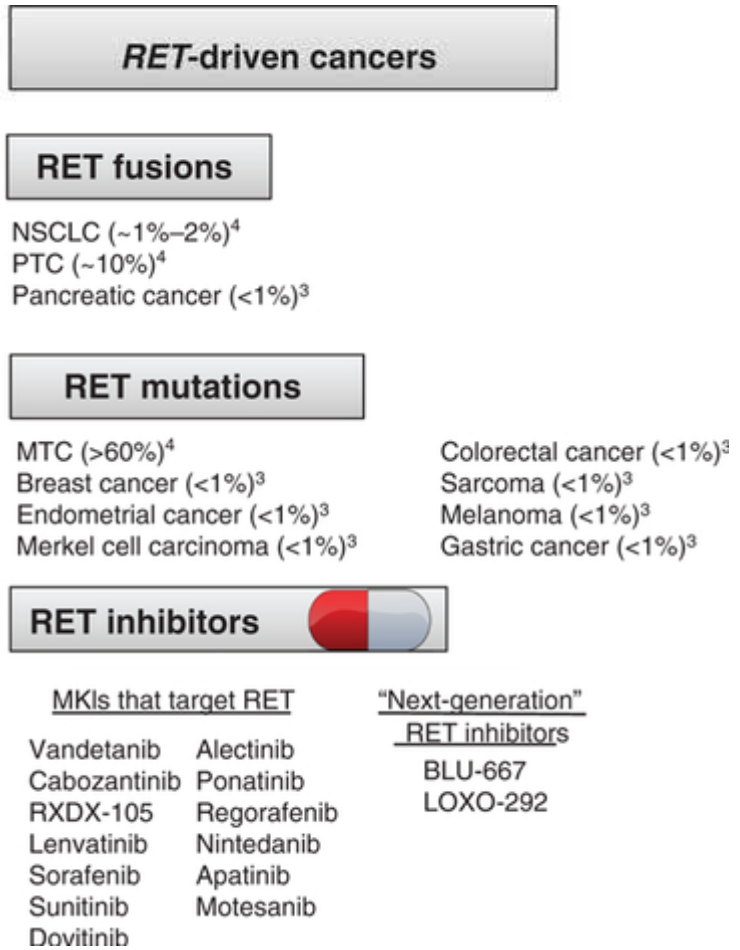
- Highly selective RET inhibitor, as well as VEGF and FGFR

Current Indication:

- Metastatic, non-small cell lung cancer, RET fusion positive
- Metastatic RET-mutant medullary thyroid cancer
- Metastatic RET fusion positive thyroid cancer

Dose: weight based dosing

- >50kg: 120 mg PO BID
- <50kg: 160 mg PO BID
- Dose reduce for hepatic impairment



Iams WT. Cancer Discov. 2018. 8(7):797-99

Retevmo [package insert]. Indianapolis, IN: Lilly USA, LLC; 2020.

Selpercatinib

Drug Topic	Detail
Common adverse effects (all grades)	• Hypertension (35%) • Hepatotoxicity (~50%, median onset 4 weeks) • Impaired wound healing (hold for 7 days before and 2 weeks after surgery) • QTc prolongation (6-15%), embryo-fetal toxicity
Rare, but serious adverse events	Hemorrhagic events (2.3%) Hypersensitivity reaction (may require steroids at 1mg/kg)
Monitoring	Blood pressure at baseline and 1 week after starting, then Q month LFTs at baseline, Q2 weeks x3 months, then monthly
Drug Interactions	Avoid PPIs, H2 antagonist, and antacids if possible OR • Administer selpercatinib with food at the same time as PPI • Administer selpercatinib 2h before or 10h after H2 antagonist • Separate selpercatinib by 2h from antacids CYP3A4 Inhibitors: avoid, or dose reduce selpercatinib CYP3A4 Inducers: Avoid

Retevmo [package insert]. Indianapolis, IN: Lilly USA, LLC; 2020.

Ripretinib (Qinlock)

Mechanism(s) of Action:

- Inhibits PDGFRA and KIT as well as PDGFRB, TIE2, VEGFR2, and BRAF

Current Indication:

- Advanced gastrointestinal stromal tumor (GIST) after ≥3 prior TKIs

Dose: 150mg (three 50 mg tabs) PO daily

- Pediatric patients: dosage is based on BSA

Qinlock [package insert]. Waltham, MA: Deciphera Pharmaceuticals, LLC; 2020.

Ripretinib

Drug Topic	Detail
Common adverse effects (all grades)	• Impaired wound healing (hold for 7 days before and 2 weeks after surgery) • HFS, nausea, hypertension, arthralgia/myalgia, alopecia, embryo-fetal toxicity
Rare, but serious adverse events	Cutaneous SCC (4.7%, median time to event 4.6 months) Cardiotoxicity (<5%)
Monitoring	LVEF at baseline and then periodically Blood pressure at baseline and routinely Dermatologic exams routinely during treatment
Drug Interactions	CYP3A inhibitors: monitor for increased adverse events CYP3A inducers: avoid

Qinlock [package insert]. Waltham, MA: Deciphera Pharmaceuticals, LLC; 2020.

Biosimilar Pearls

- Per FDA, the biosimilar product is:
  - Expected to produce the same clinical result as the reference product
  - Switching between products does not increase safety risks or decrease effectiveness
- Interchangeability depends on your health system
- Insurance coverage of the drug varies by insurance company

Current Oncology Biosimilars

Originator product	Biosimilar
Filgrastim (Neupogen)	Filgrastim-sndz (Zarxio) Filgrastim-aafi (Nivestym) Tbo-filgrastim (Granix) is *not* a biosimilar
Pegfilgrastim (Neulasta)	Pegfilgrastim-jmdb (Fulphila) Pegfilgrastim-cbqv (Udenyca) Pegfilgrastim-bmez (Ziextenzo) Pegfilgrastim-apgf (Nyvepria)
Trastuzumab (Herceptin)	Trastuzumab-dkst (Ogivri) Trastuzumab-pkrb (Herzuma) Trastuzumab-dttb (Ontruzant) Trastuzumab-qyyp (Trazimera) Trastuzumab-anns (Kanjinti)
Ritxuimab (Rituxan)	Rituximab-abbs (Truxima) Rituximab-pvvr (Ruxience)
Bevacizumab (Avastin)	Bevacizumab-awwb (Mvasi) Bevacizumab-bvzr (Zirabev)

New Formulations

- Drug with different formulations must undergo FDA approval for the specific formulation

- Hyaluronidase reversibly opens up interstitial space in SubQ tissue to deliver volumes >2.3ml

- Currently approved drugs with new formulations:
  - Rituximab hyaluronidase (Rituxan Hycela)
  - Trastuzumab hyaluronidase (Herceptin Hylecta)
  - Daratumumab hyaluronidase (Darzalex Faspro)
  - Pertuzumab, trastuzumab, hyaluronidase (Phesgo)

CANCER PHARMACOLOGY I

Zak Cerminara, PharmD, BCOP

Lead Clinical Pharmacist, Stem Cell Transplant/Immunotherapy

University of Washington Medical Center & Seattle Cancer Care Alliance

August 13, 2020

Objectives

- Describe the mechanism of action and pharmacology of chemotherapy agents and targeted therapies used for the treatment of hematologic and solid tumor malignancies
- Identify the need for dose adjustments of cancer therapies based on organ dysfunction
- Recognize common and unique adverse drug reactions of cancer therapies and associated prevention and management strategies

CELL CYCLE NONSPECIFIC AGENTS

M Phase Specific

Antimicrotubule Agents

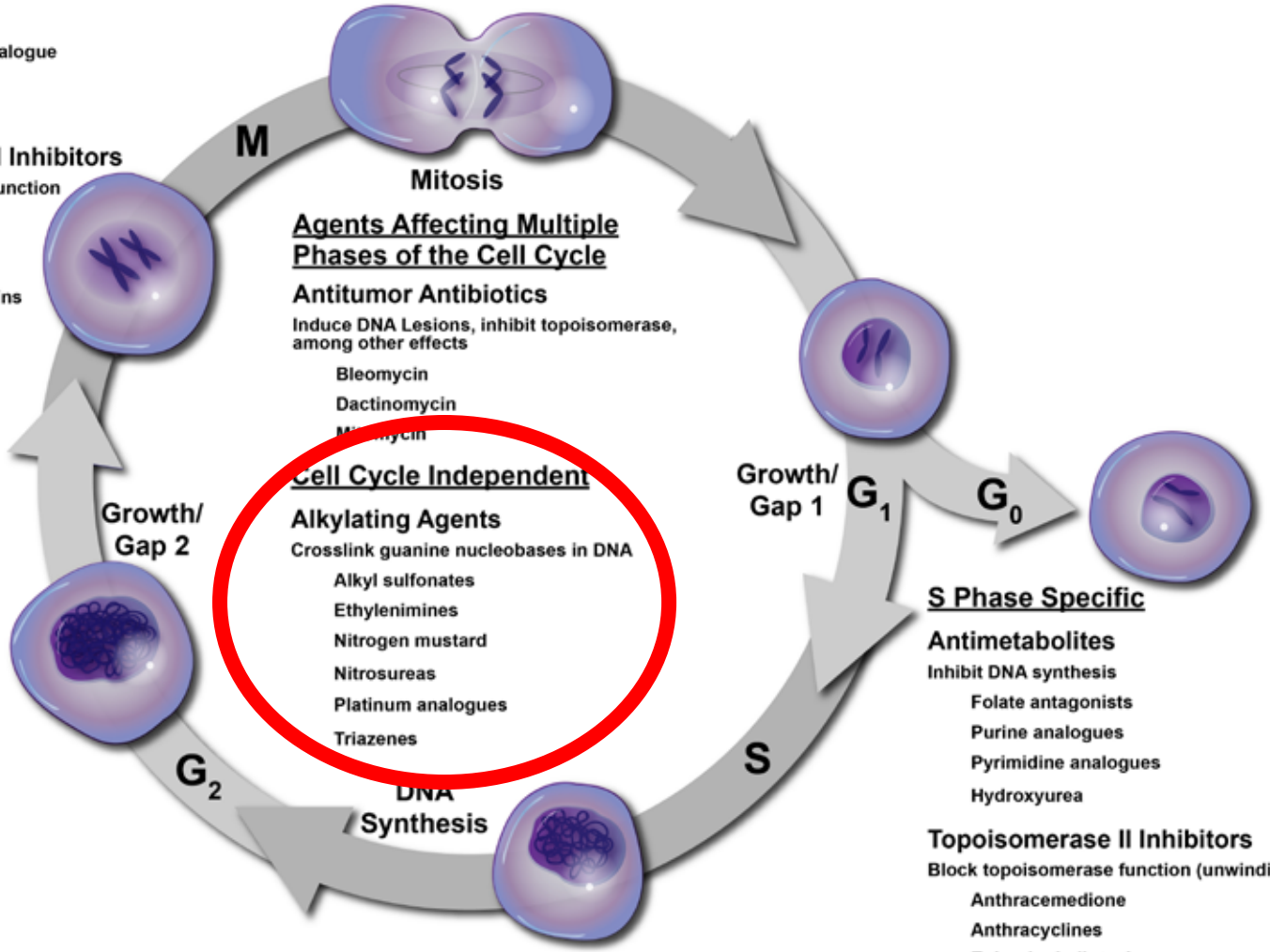
Inhibit function of microtubules

- Epothilones
- Halichondrin B analogue
- Taxanes
- Vinca alkaloids

Topoisomerase II Inhibitors

Block topoisomerase function (unwinding DNA)

- Anthracemedione
- Anthracyclines
- Epipodophyllotoxins



Agents Affecting Multiple Phases of the Cell Cycle

Antitumor Antibiotics

Induce DNA Lesions, inhibit topoisomerase, among other effects

- Bleomycin
- Dactinomycin
- [illegible]ycin

Cell Cycle Independent

Alkylating Agents

Crosslink guanine nucleobases in DNA

- Alkyl sulfonates
- Ethylenimines
- Nitrogen mustard
- Nitrosureas
- Platinum analogues
- Triazenes

S Phase Specific

Antimetabolites

Inhibit DNA synthesis

- Folate antagonists
- Purine analogues
- Pyrimidine analogues
- Hydroxyurea

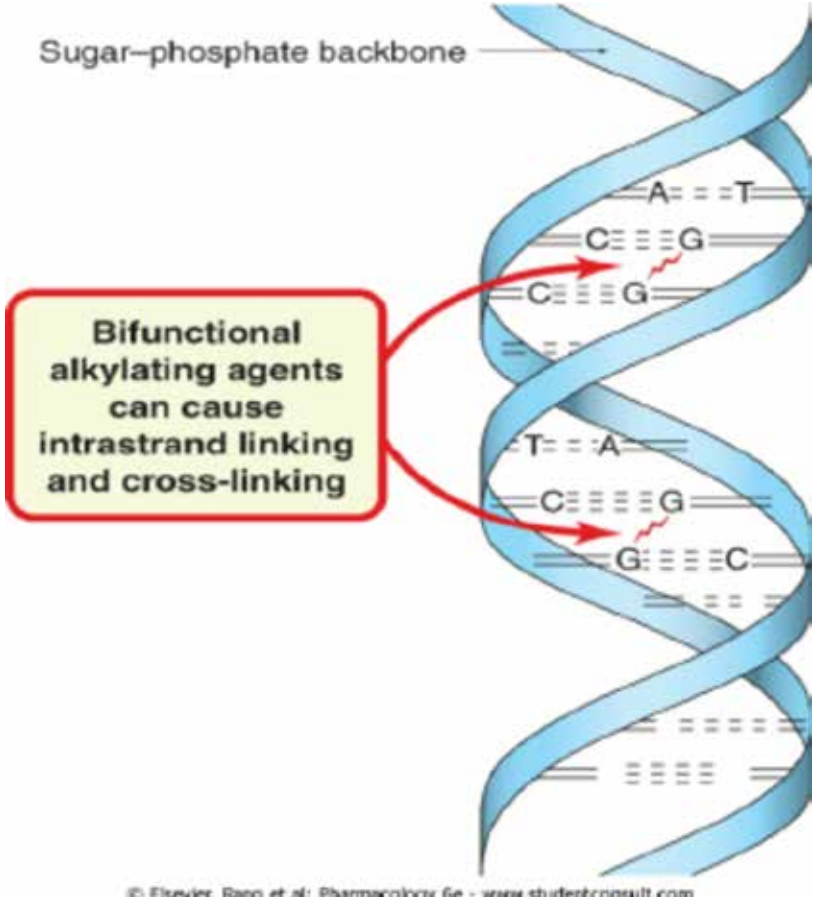
Topoisomerase II Inhibitors

Block topoisomerase function (unwinding DNA)

- Anthracemedione
- Anthracyclines
- Epipodophyllotoxins

Class	Chemotherapy Agent
Alkylating Agents (Classical)	
Nitrogen mustards	Bendamustine (Bendeka) Cyclophosphamide (Cytoxan) Ifosfamide (Ifex) Melphalan (L-phenylalanine; Alkeran, Evomela) Mechlorethamine (Mustargen) Chlorambucil (Leukeran)
Alkyl sulfonate	Busulfan (Myleran)
Aziridines	Mitomycin C (Mutamycin) Thiotepa (Thioplex)
Nitrosoureas	Carmustine (BCNU; Bicnu) Lomustine (CCNU; Ceenu)
Alkylating Agents (Non-Classical)	
Triazenes	Dacarbazine (DTIC; DTIC-Dome) Procarbazine (Matulane)
Hydrazines	Temozolamide (Temodar)
Miscellaneous	Trabectedin (Yondelis)

Alkylating Agents



https://www.researchgate.net/figure/The-effects-of-bifunctional-alkylating-agents-on-DNA-Note-the-cross-linking-of-two_fig1_221920821

Alkylating Agents: Class Toxicities

- Infertility: Oligospermia, amenorrhea
- Teratogenic: exposure in 1st trimester associated with increased risk of fetal malformations
  - Therapy in 2nd or 3rd trimester not associated w/ increased risk
- Carcinogenic
  - Melphalan >> cyclophosphamide/ifosfamide
  - Highest risk 5-10 years after exposure (MDS/AML)
  - Increased risk of bladder cancer from cyclophosphamide

Nitrogen Mustard

	Cyclophosphamide	Ifosfamide
Common uses	Breast, lymphoma, leukemia, sarcoma, HSCT, immunosuppressive tx	Sarcoma, lymphoma, testicular
Dosing	PO: 500-300mg/m^2 IV: 250-2000mg/m^2; 60-100mg/kg	IV: 1-5g/m^2/d
Common Toxicities	Myelosuppression (platelet sparing) Delayed nausea/vomiting (dose-related) Alopecia	
Rare/ Serious Toxicities	**Hemorrhagic cystitis**	
	Cardiotoxicity w/ high dose Interstitial pneumonitis SIADH	Fanconi's syndrome **Encephalopathy** (treat with methylene blue)
Notes	Drug-drug interaction with warfarin – monitor PT/INR **Dose reduce for renal dysfunction**	
	Uroprotection with mesna (Doses >1500-2000mg/m^2)	Uroprotection with mesna **ALWAYS** (60% of total ifos dose given pre and post infusion)

Alkyl Sulfonate: Busulfan

- **ADEs**
  - Severe myelosuppression (myeloid >lymphoid)
- **High dose (HSCT)**
  - Pharmacokinetic targeted dosing
  - Seizures: Pre-med with anticonvulsant
  - Hepatic sinusoidal obstruction syndrome (formerly venoocclusive disease
  - “Busulfan lung” (with chronic use)
  - “Busulfan tan” (skin hyperpigmentation)

https://www.seattlecca.org/healthcare-professionals/clinical-labs/busulfan-lab-pharmacokinetics-lab

Nitrosoureas: Carmustine, Lomustine

- **Common Uses**: Brain tumors, HSCT
- Highly lipophilic, crosses blood-brain barrier
  - CNS > 50% of plasma concentration
- **Major Toxicities**: Myelosuppression and pulmonary
  - Cycles at least 6 weeks apart due to delayed & prolonged myelosuppression
    - Neutrophil recovery in ~ 6 weeks, platelet recovery in ~ 4 weeks
  - Pulmonary function tests at baseline and periodically during therapy
    - Increased risk of pulmonary toxicity if baseline FVC or DL_{CO} < 70% of predicted
- **Dose Reductions**: Renal dysfunction

Triazenes: Procarbazine, Dacarbazine

- **Common Uses**: Lymphomas, brain tumors, pheochromocytoma (dacarbazine)

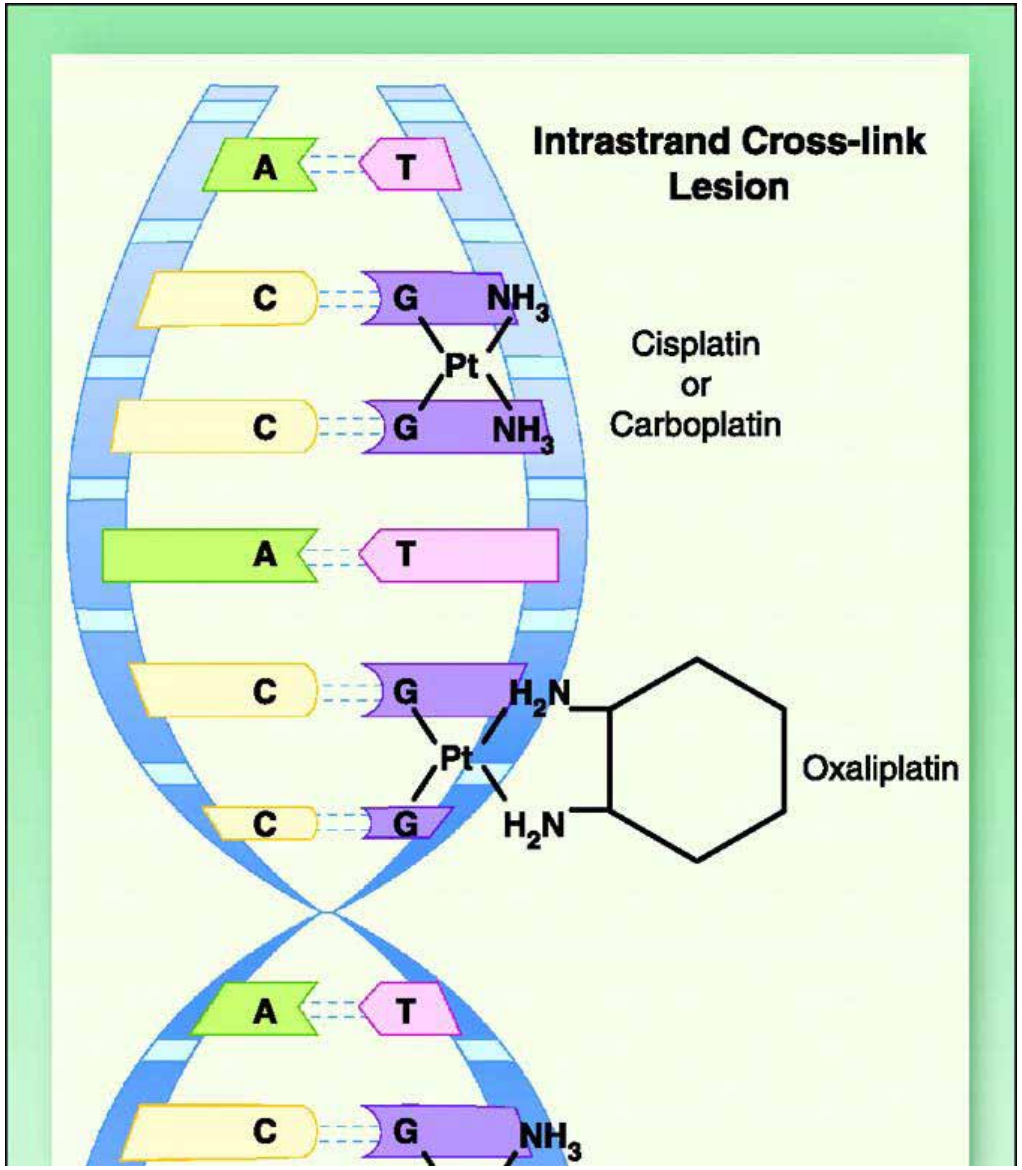
- **Major Toxicities**: Highly emetogenic, bone marrow suppression

- Procarbazine: a monoamine oxidase inhibitor (MAOI)
  - Potentiates other CNS drugs (barbiturates, opiates, antihistamines)
  - Hypertensive reactions w/ other sympathomimetics, TCAs, or tyramine-containing foods
  - Interaction with alcohol: disulfiram-like effect (sweating, flushing, headache)

Hydrazine: Temozolamide

- **Origin**: Analogue of dacarbazine, inactive in parent form
  - Crosses BBB & does not require liver for activation
- **Common Uses**: Brain tumors/with XRT, and melanoma
  - Given 5 days Q28 days or ½ dose continuously with XRT
- **Major Toxicities**:
  - Myelosuppression (anemia uncommon)
  - Lymphopenia–*PJP* (*PCP*) prophylaxis when given with XRT
  - Moderate nausea/vomiting (take at night), anorexia, flu-like sxs
  - Photosensitivity

Platinum Agents



Teicher BA. *Clin Cancer Res.* 2008.

Platinum Agents: Dosing

	Cisplatin	Carboplatin	Oxaliplatin
Common Uses	Broad spectrum activity against numerous malignancies		
Dosing	Up to 100 mg/m^2 Q21 days (50-75 mg/m^2 when used in doublet regimens) Weekly with XRT	<u>Calvert Equation</u>: Dose (mg) = AUC x (GFR* + 25) NCI recommends dose cap with max CrCl 125 mL/min	85-130 mg/m^2 Q2-3 weeks
Notes	Excreted in urine **50% dose reduction for CrCl <60 ml/min** (or split dosing)	Can give in HD	Rapid and extensive nonenzymatic metabolism

Platinum Agents: Variations in Toxicity

Cisplatin	Carboplatin	Oxaliplatin

• **Severe N/V**, acute, delayed
• **Renal dysfunction**
• Electrolyte wasting
• Peripheral Neuropathy
• Reduces clearance of other drugs (give other drug first)
• **Ototoxicity/tinnitus**, high frequency hearing loss (cumulative, irreversible)
• SIADH
	• Moderate-severe N/V
	• Peripheral neuropathy
	• **Myelosuppression** (thrombocytopenia)
	• **Hypersensitivity reaction** after dose 7-9 (can desensitize)
		• **Neuropathy**, acute & chronic (sensory/ peripheral, dose limiting)
		  • *Acute*: Triggered by cold
		  • Laryngo-pharyngeal dysesthesias with choking sensation
		• Dose-dependent neurotoxicity, typically >850mg/m^2 (reversible)

Anthracyclines

- **Drugs**: Doxorubicin/liposomal doxorubicin, daunorubicin, idarubicin, epirubicin, valrubicin, mitoxantrone
- **Mechanism**: Inhibit DNA & RNA synthesis
  - Intercalate between DNA, single and double strand breaks
  - Free radical formation → iron-anthracycline complexes bind to DNA
  - Also Topoisomerase II inhibitor
- Antitumor activity related to AUC rather than peak drug levels; administered by variety of schedules
- Metabolized in liver to active species; 40-50% of drug excreted in stool
  - **Dose reduction required for liver dysfunction** (especially with Tbili)

Anthracycline General Toxicities

- Myelosuppression: Dose-limiting neutropenia
- GI: Mucositis, N/V, diarrhea
- Alopecia
- Discoloration of bodily fluids
- Radiation recall
- Vesicant: Severe tissue damage
  - Use dexrazoxane as an antidote

Anthracycline Cardiotoxicity

- Caused by free radical damage to myocardium
- Risk factors: Bolus dosing, age, previous chest XRT, cardiac disease, HTN, concomitant chemotherapy (taxanes, cyclophosphamide, trastuzumab)
- Baseline LVEF and every 3-6 months
  - Use cautiously/avoid if LVEF < 50%
- Cardioprotectant: Dexrazoxane (controversial use)

Cumulative Dose (Doxorubicin)	Risk
< 400 mg/m^2	0.14%
500-550 mg/m^2	4%
550-600 mg/m^2	18%
> 600 mg/m^2	36%

Misc. Cell Cycle Nonspecific Agents

Class	Chemotherapy Agent
Biologic agents & other	Interferon Trabectedin mTOR inhibitors Interleukin-2 (Aldesleukin) Arsenic trioxide (Trisenox) All-*trans* retinoic acid (ATRA) Omacetaxine (Synribo) Talimogene laherparepvec (TVEC, Imlygic)

Trabectedin (Yondelis)

- **Origin**: Marine-derived alkylating agent
- **Common Uses**: Soft tissue sarcomas
- **Mechanism**: Alkylating agent, blocking cell cycle progression due to alteration of DNA transcription
- Given as 24-hr infusion (outpatient pump)
  - Pre-med with dexamethasone 20 mg IV 30 min before each infusion
- **Major Toxicities**:
  - Myelosuppression
  - Increased LFTs
  - Increased creatine phosphokinase (CPK)
  - Fatigue, hand-foot syndrome, N/V/D
  - Cardiac: LVEF at baseline and every 2-3 months

mTOR Inhibitors

- **Common Uses**:
  - Temsirolimus: Renal Cell Carcinoma (RCC)
  - Everolimus: Breast Cancer, uterine cancer, PNET, RCC
- **Mechanism**: Inhibitors of mechanistic (mammalian) target of rapamycin
  - Suppresses hypoxia-mediated angiogenesis and endothelial cell proliferation by reduced production of VEGF
- **Major Toxicities**:
  - Metabolic disturbances (hyperglycemia, hyperlipidemia)
  - Myelosuppression
  - Temsirolimus: Infusion reactions (pre-med with antihistamine)
  - Everolimus: Mucositis/stomatitis

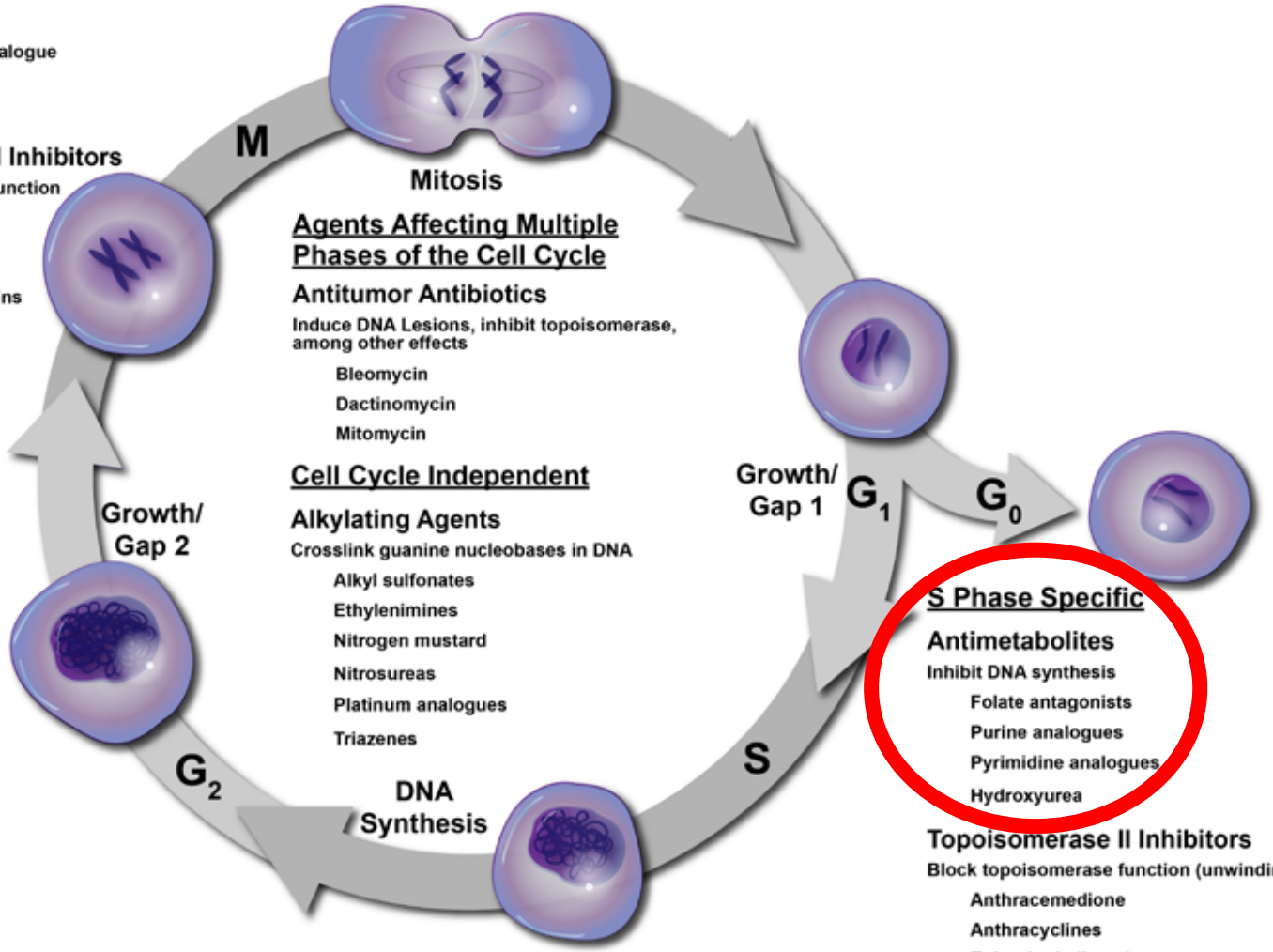
Aldesleukin (Interleukin-2; IL-2)

- **Uses**: RCC, melanoma
- **Mechanism**: Enhances lymphocyte mitogenesis and cytotoxicity, induces LAK and NK activity
- **Dose**: 600,000 units/kg Q8H for up to 14 doses; repeat after 9 days
- **Common Toxicities**:
  - Capillary leak syndrome – **dose-limiting toxicity** (hypotension)
  - Constitutional symptoms: Chills, fever, malaise
  - N/V, diarrhea, stomatitis
  - Acute liver and renal toxicity
  - Arrhythmias (Afib, Vtach)

Arsenic Trioxide

- **Common Uses:** APL (with all-trans retinoic acid)
- **Mechanism**: Induces damage and degradation of fusion protein PML/RARα
  - Direct antiproliferative activity via cell cycle arrest; inhibits angiogenesis; induces apoptosis
- **Major Toxicities**: APL differentiation syndrome
  - Fever, dyspnea, acute respiratory distress, weight gain, pulmonary infiltrates, pleural/pericardial effusions, edema, leukocytosis, multiorgan failure (usually in 1st month)
  - Treat with high-dose steroids
- **Other Toxicities**:
  - QTc prolongation (> 500msec); Baseline EKG and weekly
  - Fatigue, dizziness, headache, peripheral neuropathy
- **Use cautiously in renal insufficiency** (CrCl < 30mL/min)

CELL CYCLE SPECIFIC AGENTS



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Antimicrotubule Agents

Inhibit function of microtubules

- Epothilones
- Halichondrin B analogue
- Taxanes
- Vinca alkaloids

Topoisomerase II Inhibitors

Block topoisomerase function (unwinding DNA)

- Anthracemedione
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- Epipodophyllotoxins

Agents Affecting Multiple Phases of the Cell Cycle

Antitumor Antibiotics

Induce DNA Lesions, inhibit topoisomerase, among other effects

- Bleomycin
- Dactinomycin
- Mitomycin

Cell Cycle Independent

Alkylating Agents

Crosslink guanine nucleobases in DNA

- Alkyl sulfonates
- Ethylenimines
- Nitrogen mustard
- Nitrosureas
- Platinum analogues
- Triazenes

S Phase Specific

Antimetabolites

Inhibit DNA synthesis

- Folate antagonists
- Purine analogues
- Pyrimidine analogues
- Hydroxyurea

Topoisomerase II Inhibitors

Block topoisomerase function (unwinding DNA)

- Anthracemedione
- Anthracyclines
- Epipodophyllotoxins

Antimetabolites: Folate Antagonists

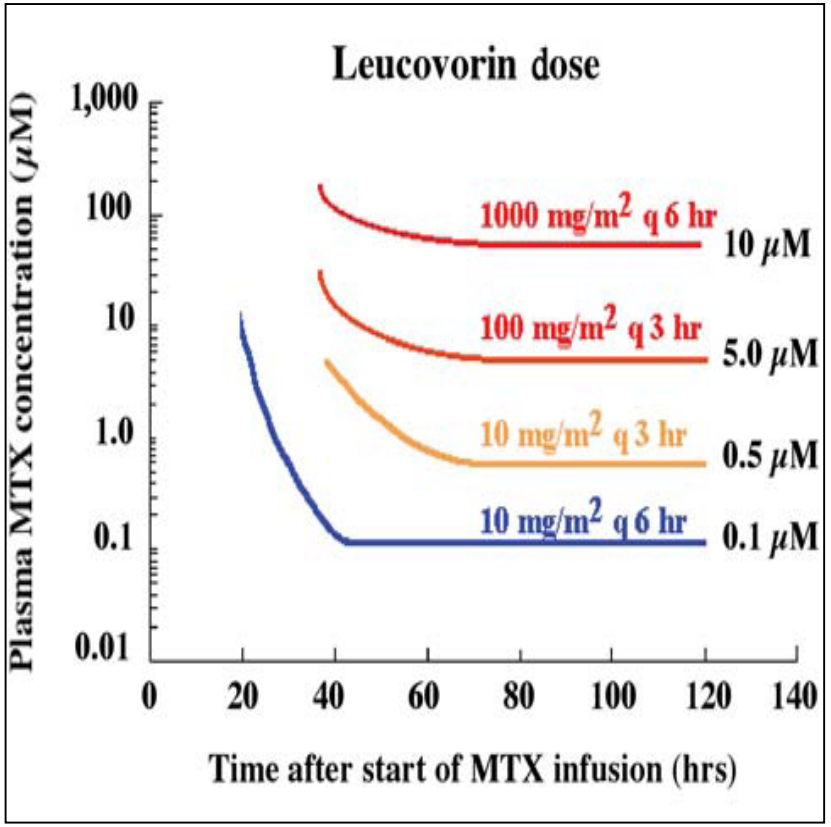
- **Mechanism** (S phase):
  - Actively transported into cell by transport proteins, metabolized to polyglutamated forms to exert cytotoxic effects
  - Inhibits dihydrofolate reductase (DHFR) = Causes depletion of intracellular reduced folate essential for thymidylate and purine synthesis
- **Drugs**: Methotrexate, Pemetrexed, Pralatrexate
- **Common Uses**: Various solid and hematologic tumors

Methotrexate

- Most widely used antifolate in cancer chemotherapy
- Penetrates and exits slowly from third-space fluids
  - Prolonged half-life of drug, leading to increased myelosuppression
- **Elimination**: Mainly renal
  - Avoid: NSAIDs, penicillins, cephalosporins, probenecid, sulfamethoxazole/trimethoprim
- **Dose reduction required in renal dysfunction**
  - Adequate hydration is key
- High-dose (>1g/m^2) therapeutic concentrations in CSF
- Intrathecal may result in myelosuppression and/or mucositis as detectable serum levels may be achieved

Methotrexate: High-Dose Therapy

- Doses ≥500 mg/m^2 require leucovorin rescue, started 24hr after start of infusion and until <0.05 micromolar
- Aggressive IV hydration with urine alkalinization (PO or IV sodium bicarbonate) prior to therapy and until drug clearance



Adapted from Bleyer WA. In: Baer DM, Dita WR, eds. c1981 American Society of Clinical Pathologists.

Methotrexate: ADEs

- **Dose-Limiting**: Myelosuppression
- Mucositis ~ 3-7 days after therapy
- Nephrotoxicity
  - Intratubular precipitation, direct toxic effects on renal tubules
- Hepatotoxicity: Acute and chronic
- Pneumonitis: Fevers, cough, interstitial pulmonary infiltrates
- Neurotoxicity with high-dose
  - Acute and chronic encephalopathy
- Neurotoxicity with intrathecal administration

- Can use glucarpidase in patients who fail to clear

Pemetrexed (Alimta)

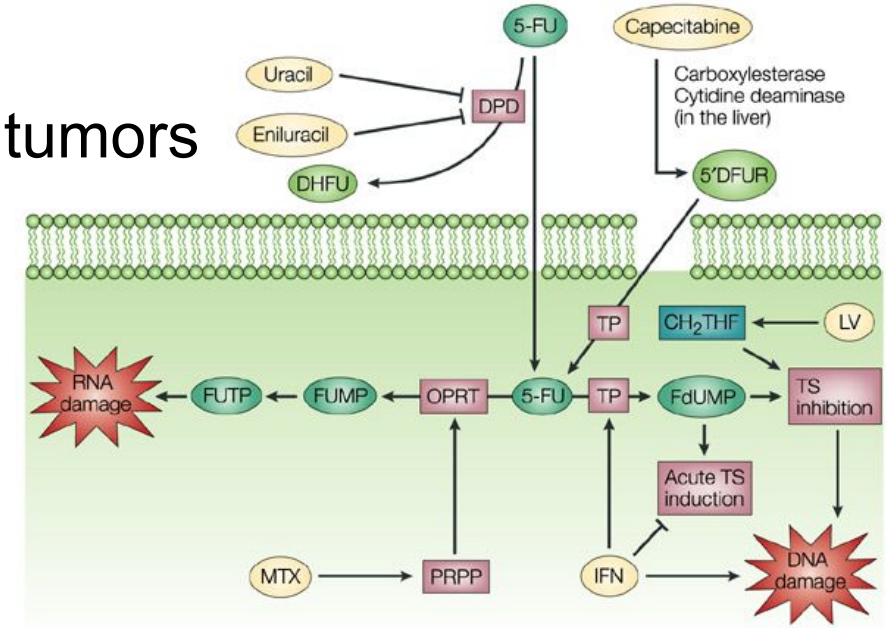
- **Common Uses**: Solid tumors
- **Elimination**: Mainly renal excretion
  - Same drug interactions as methotrexate (avoid NSAIDs)
  - **Dose reduction for renal dysfunction**
    - Not recommended if CrCl <45 mL/min
- **Major Toxicities**:
  - Myelosuppression
  - Generalized pruritic, painful rash
    - Dexamethasone 4mg BID x 3 days (day before, day of, and day after)
- Provide vitamin supplementation
  - Folic acid (400-1000 mcg) daily (start 5 days prior and continue at least 12 days after last dose)
  - Cyanocobalamin (B12) 1000mcg IM Q8-10 weeks

Pralatrexate

- **Common Uses**: Relapsed/refractory peripheral T-cell lymphoma
- Similar to methotrexate/pemetrexed
  - Mainly renal excretion
  - Use with caution in renal dysfunction
  - Same drug interactions as methotrexate
- Replenish with folic acid 1-1.25 mg daily and B12 1000mcg IM Q8-10 weeks to reduce toxicities
- Same toxicity profile as methotrexate and pemetrexed

Antimetabolites: Fluorinated Pyrimidines

- **Drugs**: Fluorouracil, capecitabine, trifluridine/tipiracil
- **Mechanism**:
  - Incorporated into RNA and DNA
  - Direct inhibitors of thymidine nucleotides via inhibition of TS by the 5-FU metabolite FdUMP
- **Common Uses**: Multiple solid tumors



Nature Reviews | Cancer

5-Fluorouracil (5-FU)

- **Dosing**:
  - IV push or continuous infusion
  - Dose reduction considered with hepatic dysfunction

- **Elimination**:
  - >80-85% metabolic conversion by dihydropyrimidine dehydrogenase (DPD), widely present outside of hepatic tissues
  - 3-5% of patients have DPD deficiency, leading to increased toxicity

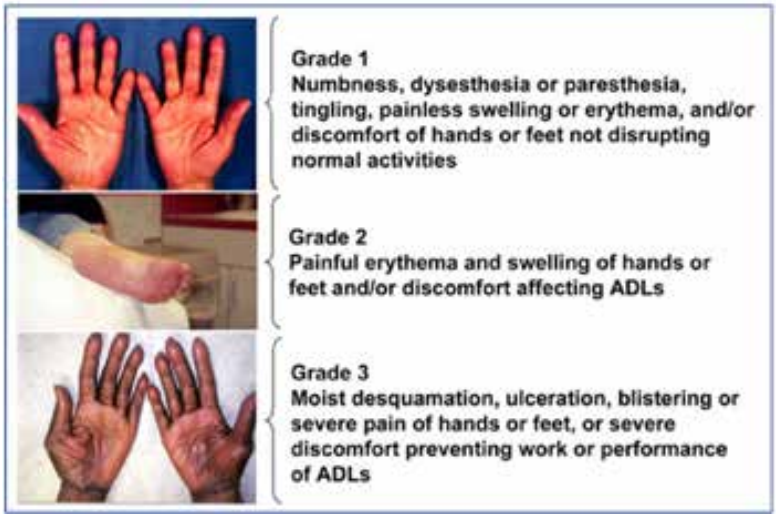
- Leucovorin increases efficacy by optimizing binding to TS

5-Fluorouracil: Toxicities

Bolus dosing	Continuous infusion
Myelosuppression (dose limiting)	Mucositis
	Diarrhea
	Hand foot syndrome (HFS/PPE)
	Myocardial ischemia

- Alopecia, hyperpigmentation, photosensitivity, ocular toxicity, N/V, cerebellar ataxia
- Uridine triacetate (Vistogard) as antidote for overdose or early onset toxicity (ie. DPD deficiency)

Capecitabine (Xeloda)



- Oral prodrug of 5-FU
  - Conversion to 5-FU in the tumor by thymidine phosphorylase
- **Dosing**:
  - 2 weeks on then 1 week off
    - Mimics continuous infusion 5FU toxicities (HFS, diarrhea)
    - HFS (onset ~2-3 months): prevention with moisturizers, lifestyle changes
  - Increased toxicity in renal dysfunction
    - Reduce dose by 25% with CrCl 30-50 mL/min
    - Contraindicated if CrCl < 30 mL/min
- **DDIs**:
  - Black box warning with warfarin – significant increases in PT/INR
  - Increased phenytoin toxicity with taken concurrently

Trifluridine/Tipiricil (Lonsurf)

- **Indication**:
  - Metastatic colon cancer after previous therapy
- **Dosing**:
  - Max 80 mg/dose given BID (based on Trifluidine component) days 1-5 and 8-12 Q28 days, with food (calendar needed for patients)
- **Toxicities**:
  - Neutropenia, thrombocytopenia (check CBC days 1 and 15 each cycle)
  - N/V/D, abdominal pain
  - Weakness, fatigue, fever

Antimetabolites: Other Pyrimidine Analogs

- **Drugs**: Cytarabine, Gemcitabine
- **Common Uses**: Multiple solid and hematologic cancers
- **Mechanism** (S phase):
  - Transports across cell membrane → phosphorylated to active triphosphate form within tumor cells → incorporated into RNA/DNA → inhibits DNA synthesis

Cytarabine: Toxicities

Conventional Dose continuous infusion (100-200 mg/m^2)

- **N/V, diarrhea**
- Alopecia
- Neutropenia & thrombocytopenia
- Rash
- Increased LFTs
- **"Ara-C syndrome"**

High-Dose bolus (1-3 g/m^2)

- Severe myelosuppression
- Mucositis
- **Cerebral & cerebellar dysfunction**: slurred speech, ataxia, confusion, coma (daily assessment of mental status)
- Pulmonary toxicities (noncardiogenic pulmonary edema)
- Hand-foot syndrome
- **Conjunctivitis** (ophthalmic corticosteroids)

Hypomethylating Agents

- **Drugs**: Azacitidine (Vidaza), Decitabine (Dacogen)
- **Common Uses**: Hematologic malignancies
  - IV and SQ dosing for Azacitidine
- **Mechanism**:
  - Inhibition of DNA methyltransferase, causes hypomethylation and apoptosis
  - Restores normal function of genes essential for cellular proliferation and growth
- **Toxicities**:
  - Myelosuppression (DAC >> AZA)
  - Fevers
  - Fatigue
  - Nausea/vomiting

Antimetabolites: Purine Analogs

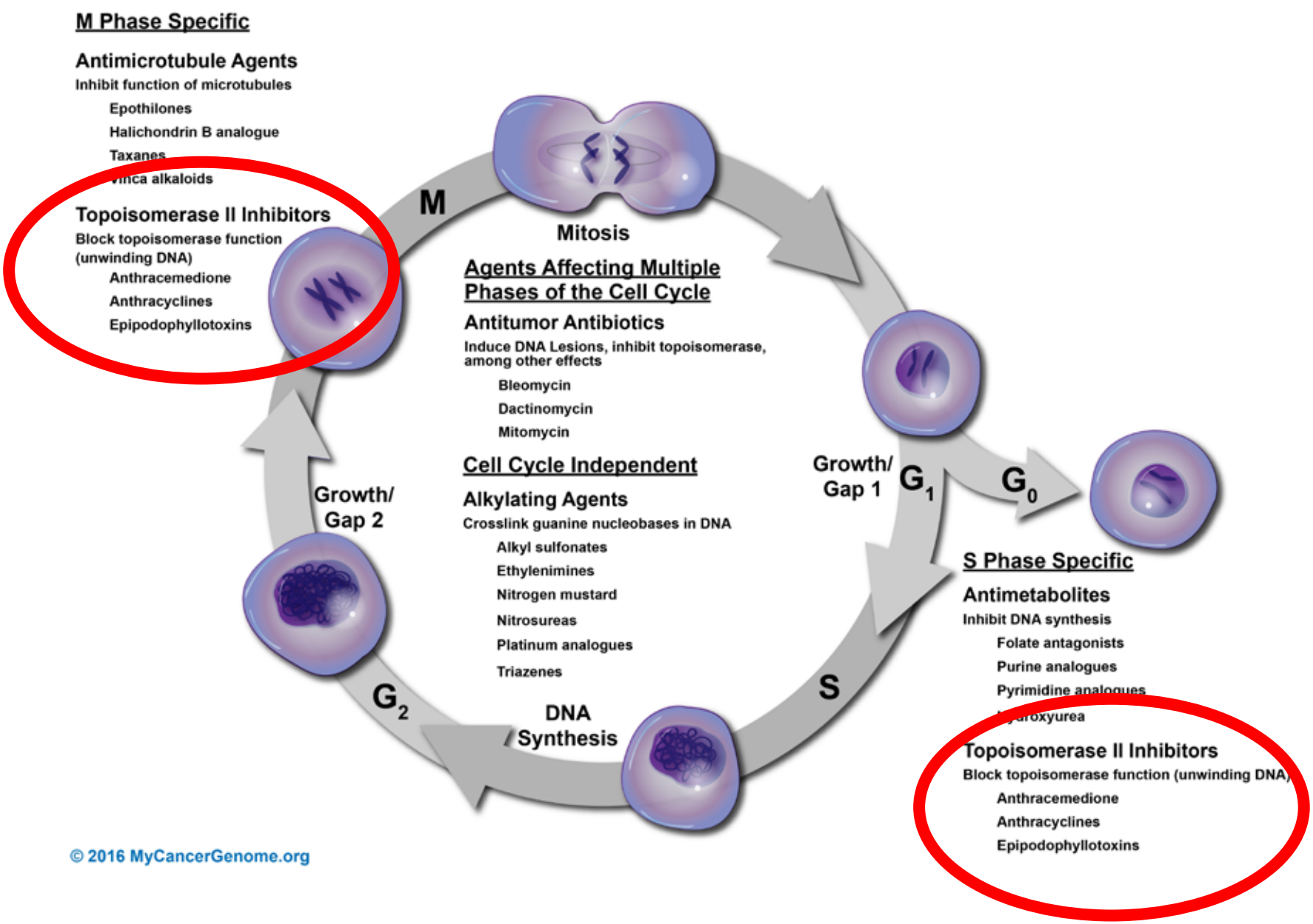
Class	Chemotherapy Agent
Purine Analogs	Mercaptopurine (6-MP) Thioguanine (6-TG) Fludarabine (Fludara) Cladribine (2-CdA) Pentostatin (Nipent) Clofarabine (Clolar) Nelarabine (Arranon)

Purine Analogs

- **Drugs**: 6-mercaptopurine (6MP) and 6-thioguanine (6TG)
- **Common Uses**: Acute leukemias
- **Mechanism**:
  - Incorporates thiopurine nucleotides into DNA & RNA → inhibition of DNA synthesis and function & RNA processing and/or mRNA translation
- **Genetics and 6MP/6TG**:
  - Thiopurine S-methyltransferase (TPMT)
  - Nudix hydrolase 15 (NUDT15)
  - Heterozygous deficiency = 30-70% of dose
  - Homozygous deficiency = 10% of dose

Fludarabine

- **Common Uses**: Lymphoid (CLL, low-grade NHL), other hematologic cancer
- Renally eliminated
  - Reduce dose for CrCl <70mL/min
  - Not recommended if CrCl < 30mL/min
- **Toxicities**:
  - Myelosuppression- Neutropenia, thrombocytopenia
  - Prolonged nadir and recovery may occur
    - CD4 and CD8 T-cells may take >1 yr to recover
    - Increased risk of opportunistic infections, e.g., herpes, fungal, PCP pneumonia (consider PCP prophylaxis)
  - Autoimmune hemolytic anemia
  - Mild and transient elevation in LFTs
  - Neurotoxicity

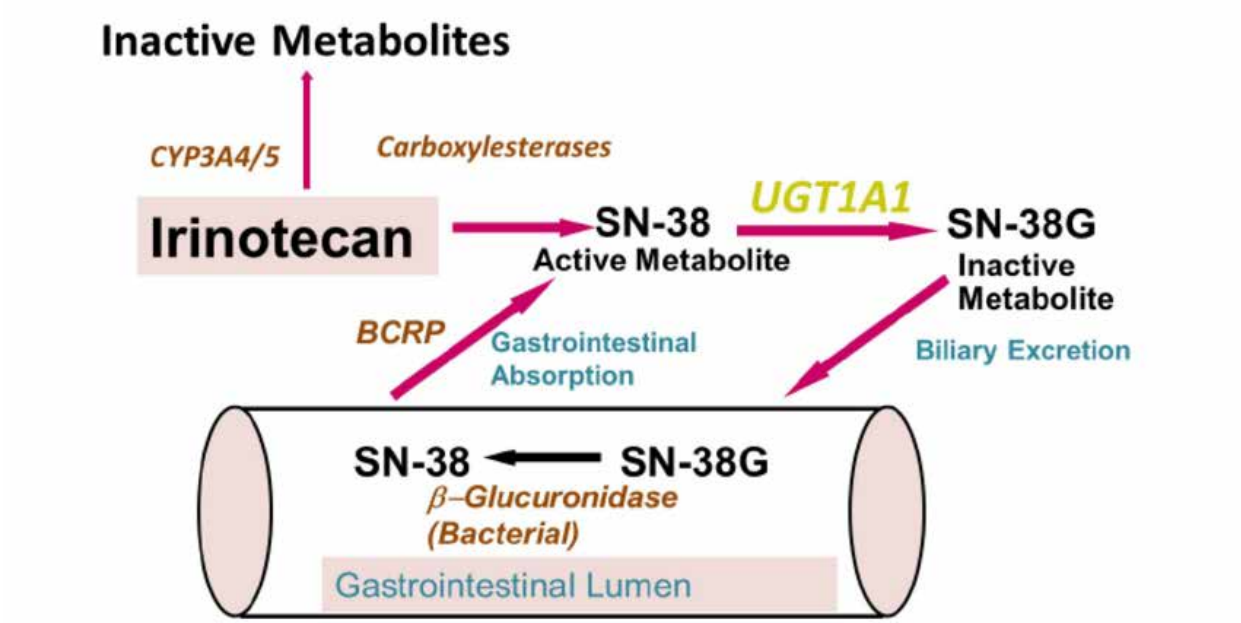


Topoisomerase I Inhibitors

- **Drugs**: Irinotecan, topotecan
- **Mechanism** (S phase):
  - Stabilize topo-I-DNA complex, preventing release of the enzyme
  - Collision of this complex with the replication fork causes double-strand DNA break → cell cycle arrest, apoptosis
- **Toxicities**:
  - Myelosuppression (neutropenia)
  - Alopecia
  - Stomatitis
  - N/V
  - Diarrhea (Irinotecan)
    - Acute (<24 hours): Cholinergic, **treat with atropine**
    - Delayed (>24 hours): Direct irritation of GI mucosa by SN-38, **treat with loperamide**

Irinotecan and SN-38

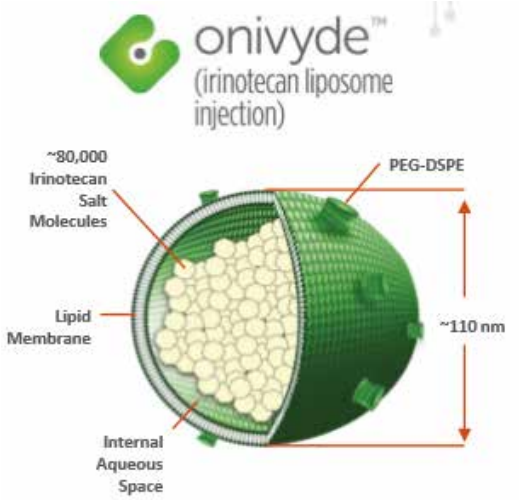
- Rapidly converted to more potent SN-38
- Conjugated and cleared by UGT1A1
- UGT1A1*28 polymorphism at increased risk for neutropenia and diarrhea



https://www.researchgate.net/figure/Irinotecan-Metabolism_fig1_221929791

Liposomal Irinotecan (Onivyde)

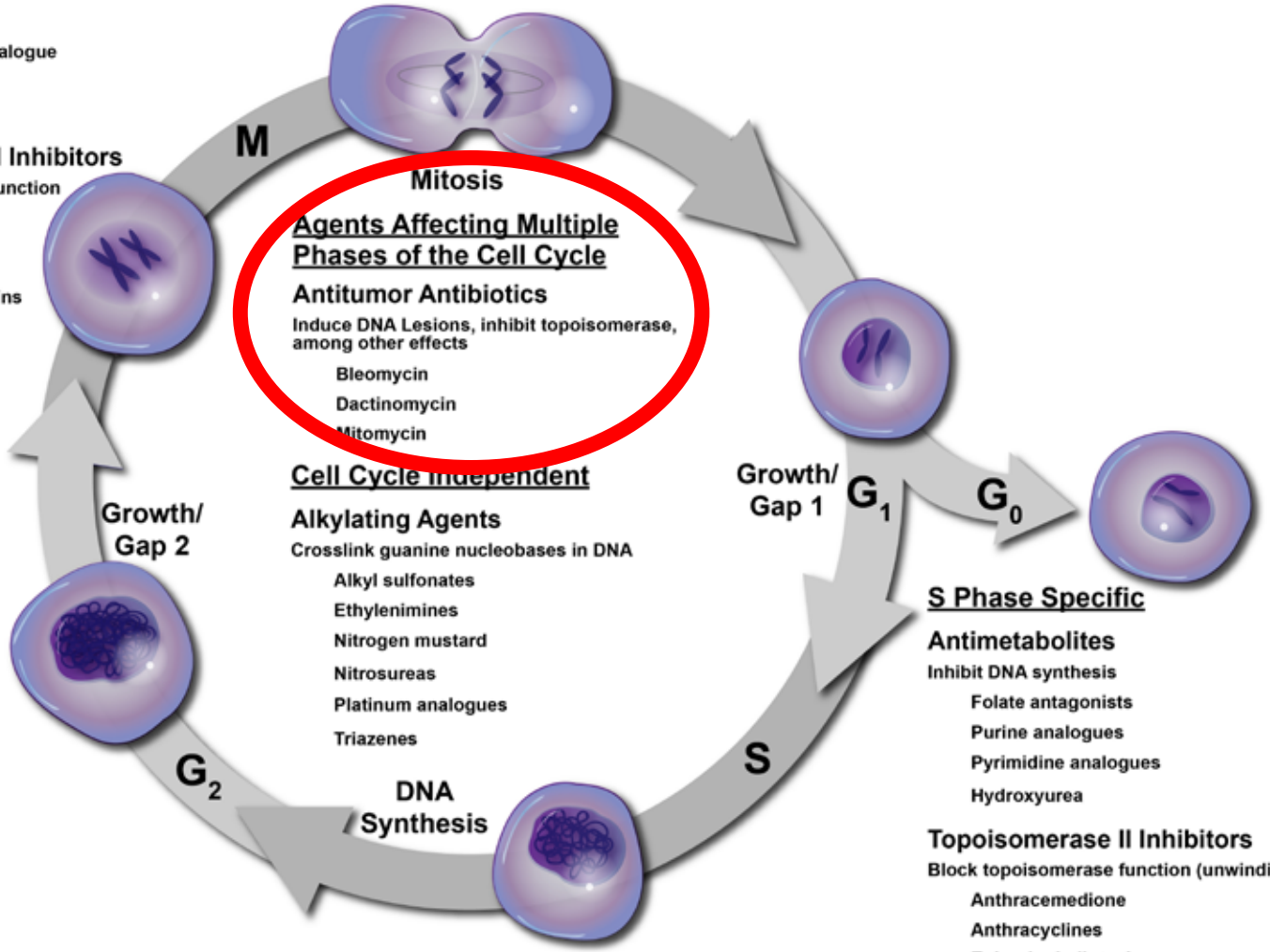
- **Common Uses**: Pancreatic cancer (with 5-FU and leucovorin)
  - Reduce starting dose if homozygous for UGT1A1*28 allele
- **Dosing**: 70 mg/m^2 Q2weeks
- **Toxicities**:
  - Diarrhea (acute and chronic):
    - Atropine for early onset; Loperamide for late onset
  - Fatigue
  - Myelosuppression
- Premedication with corticosteroid and anti-emetics
- NOT interchangeable with traditional irinotecan



https://seekingalpha.com/article/3816696-merrimack-pharmaceuticals-drive-higher-2016-onivyde-pipeline

Topoisomerase II Inhibitors: Etoposide

- **Mechanism** (S/G2 phase):
  - Stabilization of Topo-II-DNA complex causing double stranded DNA breaks
- **Common Uses**: Testicular, SCLC, NHL, BMT
- **Dose Reductions**:
  - CrCl 10-50 ml/min → give 75% of dose
  - TBili 1.5-3 or AST >3x ULN → give 50%
- **Toxicities**:
  - Myelosuppression
  - Alopecia, mucositis, secondary malignancies
  - N/V, especially with PO doses
  - Hypotension (infuse over at least 30-60 min), flushing and headache (30% EtOH in vehicle, can use etoposide phosphate)



M Phase Specific

Antimicrotubule Agents

Inhibit function of microtubules

- Epothilones
- Halichondrin B analogue
- Taxanes
- Vinca alkaloids

Topoisomerase II Inhibitors

Block topoisomerase function (unwinding DNA)

- Anthracemedione
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Agents Affecting Multiple Phases of the Cell Cycle

Antitumor Antibiotics

Induce DNA Lesions, inhibit topoisomerase, among other effects

- Bleomycin
- Dactinomycin
- Mitomycin

Cell Cycle Independent

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Crosslink guanine nucleobases in DNA

- Alkyl sulfonates
- Ethylenimines
- Nitrogen mustard
- Nitrosureas
- Platinum analogues
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Inhibit DNA synthesis

- Folate antagonists
- Purine analogues
- Pyrimidine analogues
- Hydroxyurea

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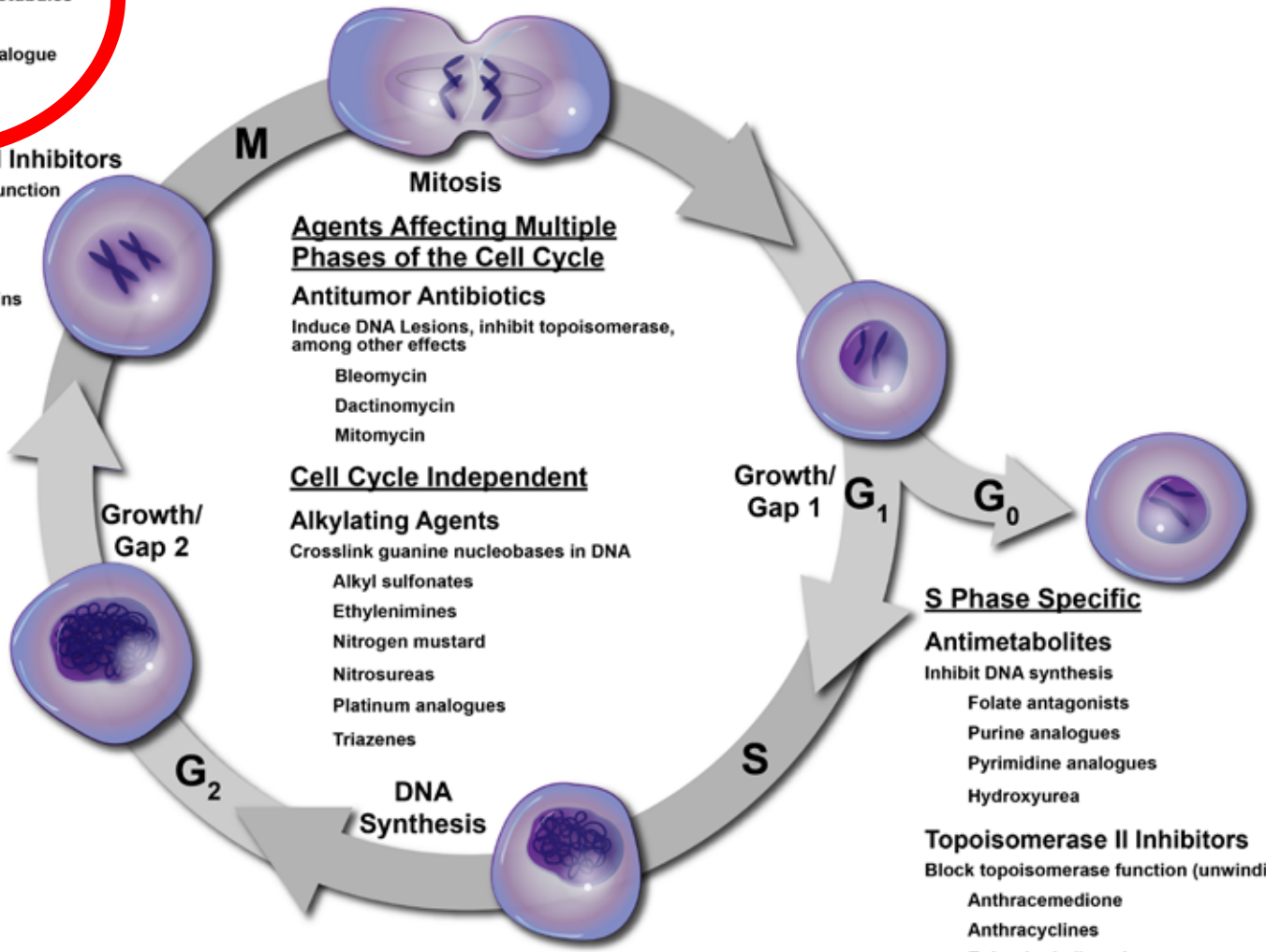
Block topoisomerase function (unwinding DNA)

- Anthracemedione
- Anthracyclines
- Epipodophyllotoxins

Antitumor Antibiotics: Bleomycin

- **Mechanism** (G2 phase):
  - Single and double stranded DNA breaks, inhibiting DNA synthesis
- **Common Uses**:
  - Testicular, Hodgkin lymphoma, NHL, squamous cell carcinoma
- **Dosing**:
  - 10-20 units/m^2 or 30 units flat dose
  - **Dose reduction for renal insufficiency** (<50 ml/min)
- **Toxicities**:
  - Hyperpigmentation, rash, fever
  - Pulmonary fibrosis (get baseline PFTs)
    - Increased risk with cumulative dose >400 units and age >70y
  - NOT myelosuppressive



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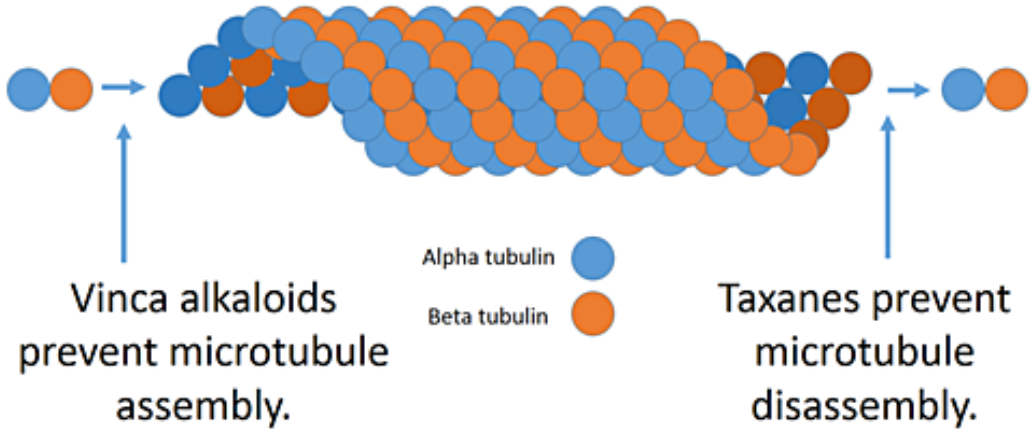
Anti-Microtubular Agents (M phase)

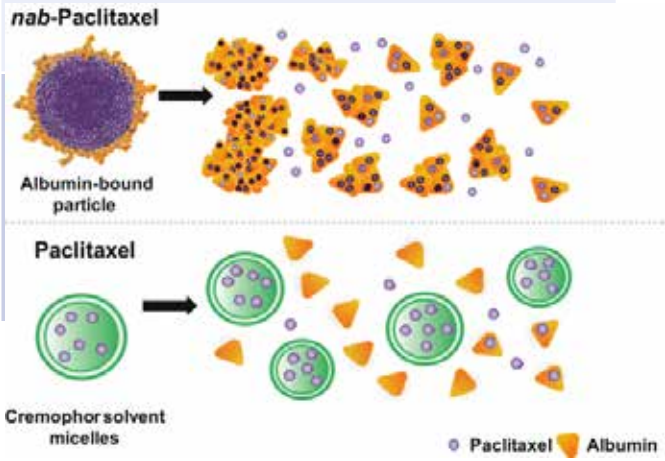


Microtubule Destabilizers	Microtubule Stabilizers
Vinca alkaloids (vincristine/liposomal vincristine, vinblastine, vinorelbine) Eribulin	Taxanes (paclitaxel/nab-paclitaxel, docetaxel, cabazitaxel) Ixabepilone

https://askhematologist.com/principles-of-chemotherapy

Paclitaxel/nab-Paclitaxel

	Paclitaxel (Taxol)	nab-Paclitaxel (Abraxane)
Uses	Multiple solid tumors	
Administration	IV; varying rates for paclitaxel (usually 1, 3, or 24 hours) Abraxane shorter 30 min infusion	
Dosing	80 – 200 mg/m^2, variable schedules	100 – 260 mg/m^2, variable schedules
Common Toxicities	Myelosuppression (↑ w/longer infusion time), Neuropathy (Abraxane > Paclitaxel, ↑ w/ shorter infusion time), mucositis, alopecia, arthralgias/myalgias	
	Hypersensitivity, to diluent	
Premedications	Diphenhydramine 25 mg IV, Ranitidine 50 mg IV , Dexamethasone 20 mg IV or 20 mg PO 12 and 6 hrs prior	



https://link.springer.com/chapter/10.1007/978-981-10-2116-9_6

Docetaxel and Cabazitaxel

	Docetaxel (Taxotere)	Cabazitaxel (Jevtana)
Uses	Prostate, NSCLC, Breast, Ovarian	Prostate
Administration	IV over one hour	
Dosing	60-100mg/m^2 Q21 days	20-25 mg/m^2 Q21 days
Common Toxicities	Myelosuppression (can be severe), neuropathy, alopecia, rash, nausea/vomiting, fatigue	
	Edema, nail changes, mucositis	Diarrhea (can be severe) Hypersensitivity
Premedications	Dexamethasone 8 mg po BID day before, of, after chemo	Diphenhydramine 25 mg IV, Ranitidine 50 mg IV , Dexamethasone 8 mg IV
Notes/Dose Adjustment	Reduce dose for ANY Tbili > ULN, or AST/ALT/Alk Phos elevations	
		Poor affinity for MDR proteins

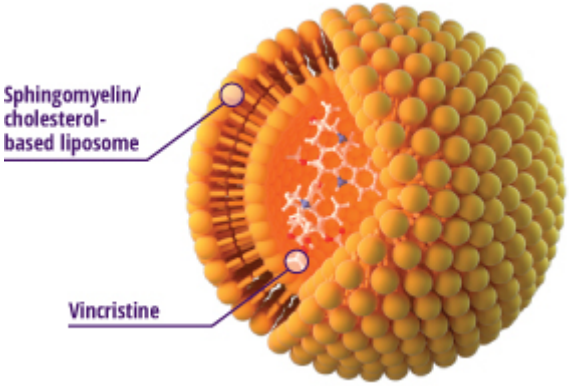
Vinca Alkaloids

- **Common Uses**:
  - Vincristine – leukemias, lymphomas, sarcomas, myeloma
  - Vinblastine – bladder, lymphomas, testicular
  - Vinorelbine – breast, lung

- **Pharmacokinetics**:
  - No CNS penetration
  - All hepatically metabolized (CYP450 3A4) and eliminated via biliary excretion

- **Reduce dose for hepatic insufficiency**

Unique Vinca Toxicities



- **Fatal if given intrathecally**
- Vesicant: Treat with heat, hyaluronidase
- VinCristine
  - **C**NS → peripheral neuropathy, autonomic neuropathy (constipation, paralytic ileus), dose cap at 2 mg
- VinBlastine
  - **B**one marrow suppression
- Vinorelbine:
  - Myelosuppression and CNS, but less severe
- Liposomal vincristine (Marqibo): NOT interchangeable
  - Increased half life vs. vincristine
  - Indicated for ALL, 2.25 mg/m^2 weekly. **No dose cap**
  - Challenging to make, requires specialized equipment

http://www.marqibo.com/hcp/treating.php

Eribulin

- **Origin**: Isolated from marine sponge
- **Common Uses**: Metastatic breast cancer, liposarcoma
- **Dose**: 1.4 mg/m^2 Days 1 and 8 Q21 days
  - **Adjustments for hepatic impairment**
- **Toxicities**:
  - Myelosuppression (neutropenia, anemia)
  - Asthenia/Fatigue
  - Alopecia
  - Peripheral neuropathy
  - QT prolongation

SELECT TARGETED AGENTS

Immunomodulatory Drugs (IMiDs)

- **MOA**: Not fully understood
  - Antiangiogenic
  - Immunomodulating
  - Antineoplastic
  - Inhibits inflammatory cytokine secretion
    - Inhibits TNFα secretion
    - Increase LF-2 and INFγ secretion

- **Black Box Warnings**
  - Teratogenicity (**REMS program required**)
  - Thromboembolism
  - Neutropenia/thrombocytopenia (lenalidomide only)

IMiDs

	Thalidomide (Thalomid)	Lenalidomide (Revlimid)	Pomalidomide (Pomalyst)
Use	MM	MM (maint.), MDS (del 5q)	MM
Dose Adjustments	None	Myelosuppression Renal/Dialysis	Myelosuppression
Common ADEs	Myelosuppression (L, P >> T), neuropathy, bowel changes, fatigue, weakness, edema, nausea, hypotension, rash		
	Sedation, bradycardia	AFib, bradycardia	AFib, dyspnea, hypercalcemia
Serious/Rare ADEs	Hypersensitivity/SJS/TEN/angioedema Secondary malignancies		
	Neuropathy (motor & sensory, may be irreversible); Seizures	Thrombocytopenia, neutropenia (80% Grade 3-4); TLS	CNS effects (dizziness, confusion)
Other		PgP substrate	Major substrate of CYP1A2, 3A4

Proteasome Inhibitors

- **MOA**:
  - 26S proteasome degrades ubiquitinated proteins within the cell thereby regulating intracellular protein concentrations and maintaining homeostasis
  - Inhibition prevents degradation → disrupts homeostasis and normal cell signaling which leads to cell death
- Bortezomib and ixazomib are reversible inhibitors
- Carfilzomib exhibits irreversible binding

Proteasome Inhibitors

	Bortezomib (Velcade)	Carfilzomib (Kyprolis)	Ixazomib (Ninlaro)
Use	MM, Mantle Cell Lymphoma	MM Combo with len/dex after 1-3 lines; Monotherapy after 1 line of therapy	MM Combo with len/dex after 1 line of therapy
Administration	SQ, IV	IV	PO
Dosing	1.3 mg/m^2 days 1, 4, 8 and 11 Q21 days 1.5 mg/m^2 days 1, 8, 15, and 22 Q28 days	Cycle 1 20 mg/m^2 days 1, 2 27 mg/m^2 days 8, 9,15,16 Q28 days Can increase up to 56 mg/m^2	4 mg Days 1, 8, and 15 Q28 days on an empty stomach
PK/PD	Not influenced by renal dysfunction, give after dialysis		Give 3 mg for CrCl < 30 ml/min Not dialyzable

Proteasome Inhibitors

	Bortezomib (Velcade)	Carfilzomib (Kyprolis)	Ixazomib (Ninlaro)
ADEs	Fatigue, malaise, N/V, diarrhea, constipation, neutropenia, **thrombocytopenia**, **peripheral neuropathy** Cardiotoxicity: orthostatic hypotension, edema, CHF		
Comparison	**Most peripheral neuropathy**: IV > SubQ	**Most cardiotoxic** Rare: pulmonary toxicity, RPLS, TLS, acute liver	Less peripheral neuropathy
Drug Interactions	CYP3A4, CYP2C19	PgP	CYP3A4; PgP
Pre-medications		Dexamethasone 4mg PO/IV	
Notes		Cap BSA at 2.2 m^2 Give fluids prior to first cycle, then PRN	

Daratumumab (Darzalex/Darzalex Faspro)

- **MOA**:
  - IgG1κ human mAB directed against CD38
  - Inhibits growth by inducing apoptosis directly through Fc mediated cross linking & immune-mediated tumor cell lysis
- **Dosing**: 16 mg/kg IV or 1800 mg SubQ
  - Weeks 1-8: once weekly
  - Weeks 9-24: Q2 weeks
  - Weeks 25+: Q4 weeks
- **Test Interference**:
  - May be detected on SPEP and immunofixation assays
  - Via binding to CD38 on RBCs, may result in a positive Coombs test
  - Daratumumab masks antibody detection to minor antigens in the serum
    - **Type and screen patients prior to therapy**

Isatuximab-irfc (Sarclisa)

- **MOA**:
  - IgG1-derived chimeric mAB directed against CD38
- **Dosing**:
  - C1: 10 mg/kg days 1, 8, 15, 22 of a 28 day cycle
  - C2+: 10 mg/kg on days 1 and 15 of a 28 day cycle
  - Given with pomalidomide
- **Test Interference**:
  - Same as daratumumab

Elotuzumab (Empliciti)

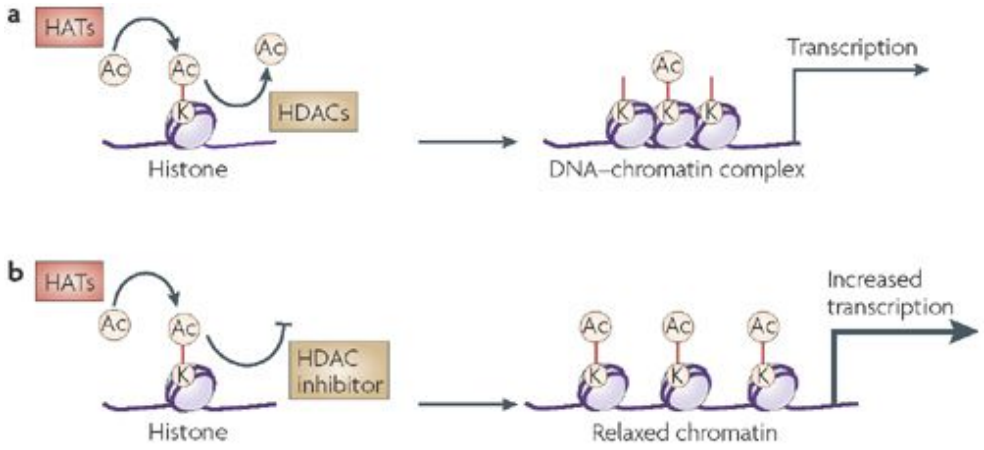
- **MOA**:
  - Antibody directed against signaling lymphocytic activation molecule family member 7 (SLAMF7), expressed on most myeloma and natural killer cells
  - Directly activates natural killer cells through SLAMF7 pathway and Fc receptors
- **Dosing**:
  - Cycles 1-2: 10 mg/kg Days 1, 8, 15, and 22 Q28 days
  - Cycle 3+: 10 mg/kg Days 1, 15 Q28 days (lenalidomide/dex combo)
  - Cycle 3+: 20 mg/kg Days 1 Q28 days (pomolidomide/dex combo)
- **Test Interference**:
  - May be detected on SPEP and immunofixation assays

Selinexor (Xopovio)

- **MOA**:
  - Reversibly inhibits nuclear export of tumor suppressor proteins, growth regulators, and mRNAs of oncogenic proteins via blockage of exportin 1
- **Dosing**:
  - 80 mg PO twice weekly
- **ADEs**:
  - Bone marrow suppression
  - GI: Nausea, diarrhea, vomiting
  - Fatigue

HDAC Inhibitor Class Overview

- Histone deacetylases catalyze the removal of acetyl groups from the lysine residues of proteins
  - Allows for accumulation of acetylated histones → changes in chromatin structure and activation of transcription factors → cell cycle arrest and/or apoptosis
- T cell lymphomas (CTCL, PTCL), myeloma
- PO and IV options
  - PO: Vorinostat, Panobinostat
  - IV: Romidepsin, Belinostat



Nature Reviews | Drug Discovery

FLT3 Inhibitors

	Midostaurin (Rydapt)	Gilteritinib (Xospata)
Use	AML, FLT-3 mutated Mast cell leukemia Systemic mastocytosis	AML, FLT-3 mutated
Dose	AML: 50 mg PO BID days 8-21 Other: 100 mg PO BID	120mg PO daily
Common Toxicities	Nausea, diarrhea, hyperglycemia, electrolyte abnormalities, increased LFTs, increased SCr, QT prolongation	
	Neutropenia, leukopenia, anemia, thrombocytopenia	Constipation, hypertriglyceridemia,
Rare/Serious Toxicities		Differentiation syndrome
Drug Interactions	CYP3A4 inducers and inhibitors	

IDH Inhibitors

	Enasidenib (Idhifa)	Ivosidenib (Tibsovo)
Use	Relapsed/refractory AML, IDH2 mutated	Relapsed/refractory AML, IDH1 mutated
Dose	100 mg PO daily	500 mg PO daily
Common Toxicities	Differentiation syndrome (treat with steroids) Electrolyte imbalances (hypocalcemia, hypokalemia)	
	Nausea, vomiting, diarrhea, anorexia Elevated bilirubin	QTc prolongation, LFT elevations
Notes		ECG monitoring weekly for first month

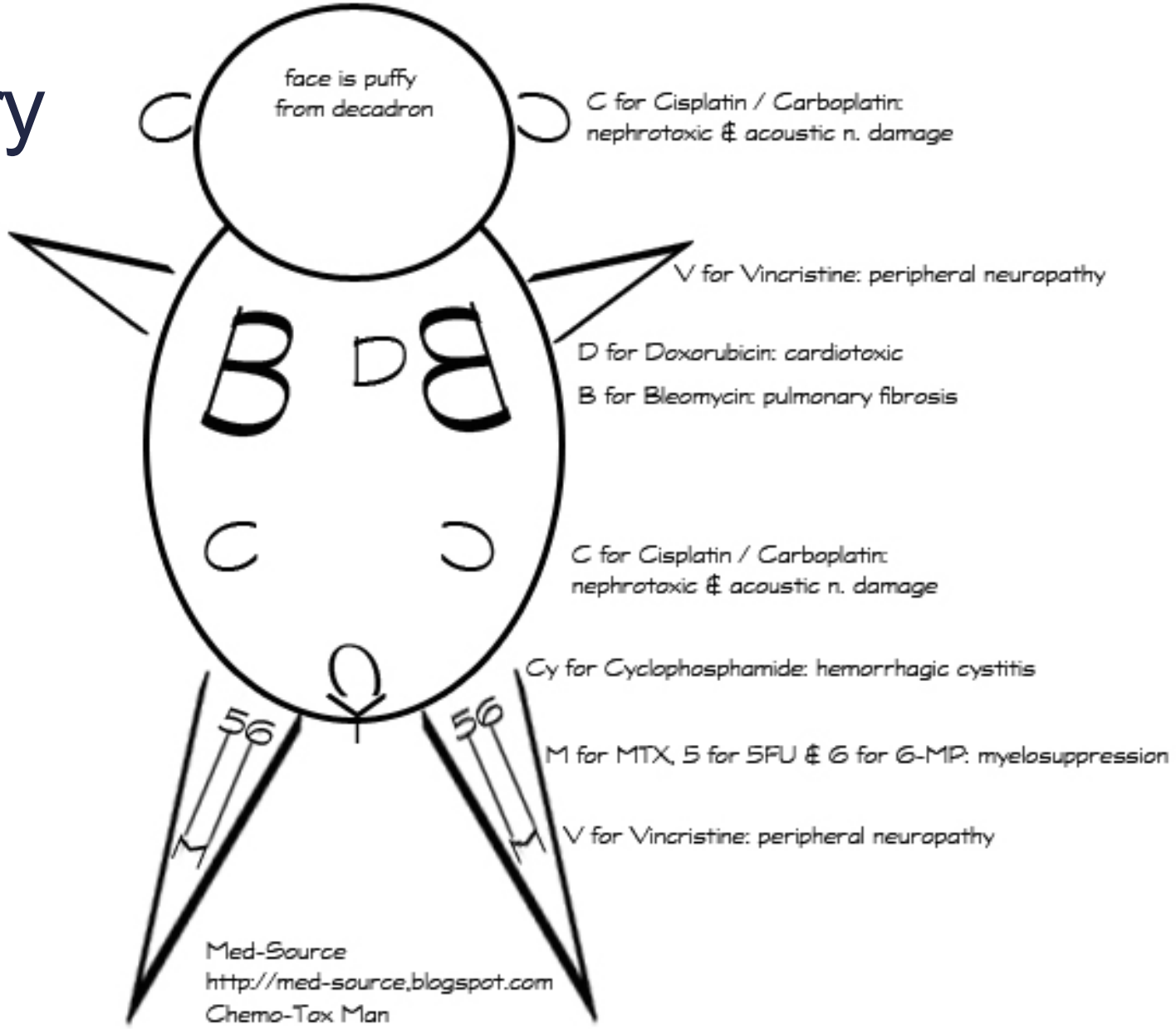
Non-Malignant Heme Drugs

- **Caplicizumab-yhdp (Cablivi)**
  - **Indication**: Thrombotic thrombocytopenic purpura, acquired (aTTP)
  - **Dose**: 11mg IV once before plasma exchange (first dose) and 11mg SubQ daily post plasma exchange (all subsequent doses)
  - **MOA**: Von Willebrand factor (vWF) – directed mAB that targets the A1-domain of vWF reducing platelet adhesion and consumption
- **Luspatercept-aamt (Reblozyl)**
  - **Indication**: Anemia due to beta thalassemia, MDS
  - **Dose**: 1 mg/kg SubQ Q3weeks
    - Max dose 1.25 mg/kg for beta thalassemia; 1.75 mg/kg for MDS
  - **MOA**: Recombinant fusion that inhibits endogenous TGF-beta superfamily, increasing differentiation/proliferation of erythroid precursors
- **Crizanlizumab-tmca (Adakveo)**
  - Indication: Sickle cell disease
  - Dose: 5 mg/kg IV Q2weeks for 2 doses, then Q4weeks
  - MOA: Antibody that binds to P-selectin, preventing adhesion of sickle erythrocytes to vessels, decreasing frequency of pain crisis

Non-Malignant Heme Drugs

- **Givosiran (Givlaari)**
  - **Indication**: Acute hepatic porphyria
  - **Dose**: 2.5 mg/kg SubQ monthly
  - **MOA**: Causes degredation of aminolevulinate synthase 1 (ALAS1) mRNA in hepatocytes, leading to reduced circulating levels of neurotoxic intermediates that lead to disease manifestations
- **Afamelanotide (Scenesse)**
  - **Indication**: Erythropoietic protoporphyria
  - **Dose**: 16 mg SubQ implant Q2months
  - **MOA**: Melanocortin receptor agonist that binds to MC1-R, increasing production of eumelanin in the skin

Summary


face is puffy
from decadron
C for Cisplatin / Carboplatin:
nephrotoxic & acoustic n. damage
V for Vincristine: peripheral neuropathy
D for Doxorubicin: cardiotoxic
B for Bleomycin: pulmonary fibrosis
C for Cisplatin / Carboplatin:
nephrotoxic & acoustic n. damage
Cy for Cyclophosphamide: hemorrhagic cystitis
M for MTX, 5 for 5FU & 6 for 6-MP: myelosuppression
V for Vincristine: peripheral neuropathy
Med-Source
http://med-source.blogspot.com
Chemo-Tox Man

Thank you!

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- Amy Indorf, PharmD, BCOP

CANCER PHARMACOLOGY I

Zak Cerminara, PharmD, BCOP

Lead Clinical Pharmacist, Stem Cell Transplant/Immunotherapy

University of Washington Medical Center & Seattle Cancer Care Alliance

August 13, 2020

APPENDICES

Selected Drugs Requiring Dose Reduction or Avoidance for Renal Dysfunction

- Cisplatin
- Carboplatin* (Calvert equation accounts for renal function)
- Methotrexate
- Capecitabine
- Etoposide
- Fludarabine
- Arsenic trioxide
- Azacitidine
- Cytarabine (high dose)
- Bleomycin
- 6-mercaptopurine
- 6-thioguanine
- Oxaliplatin
- Ifosfamide
- Topotecan
- Pemetrexed

The Oncologist 2007;12:1070 –1083

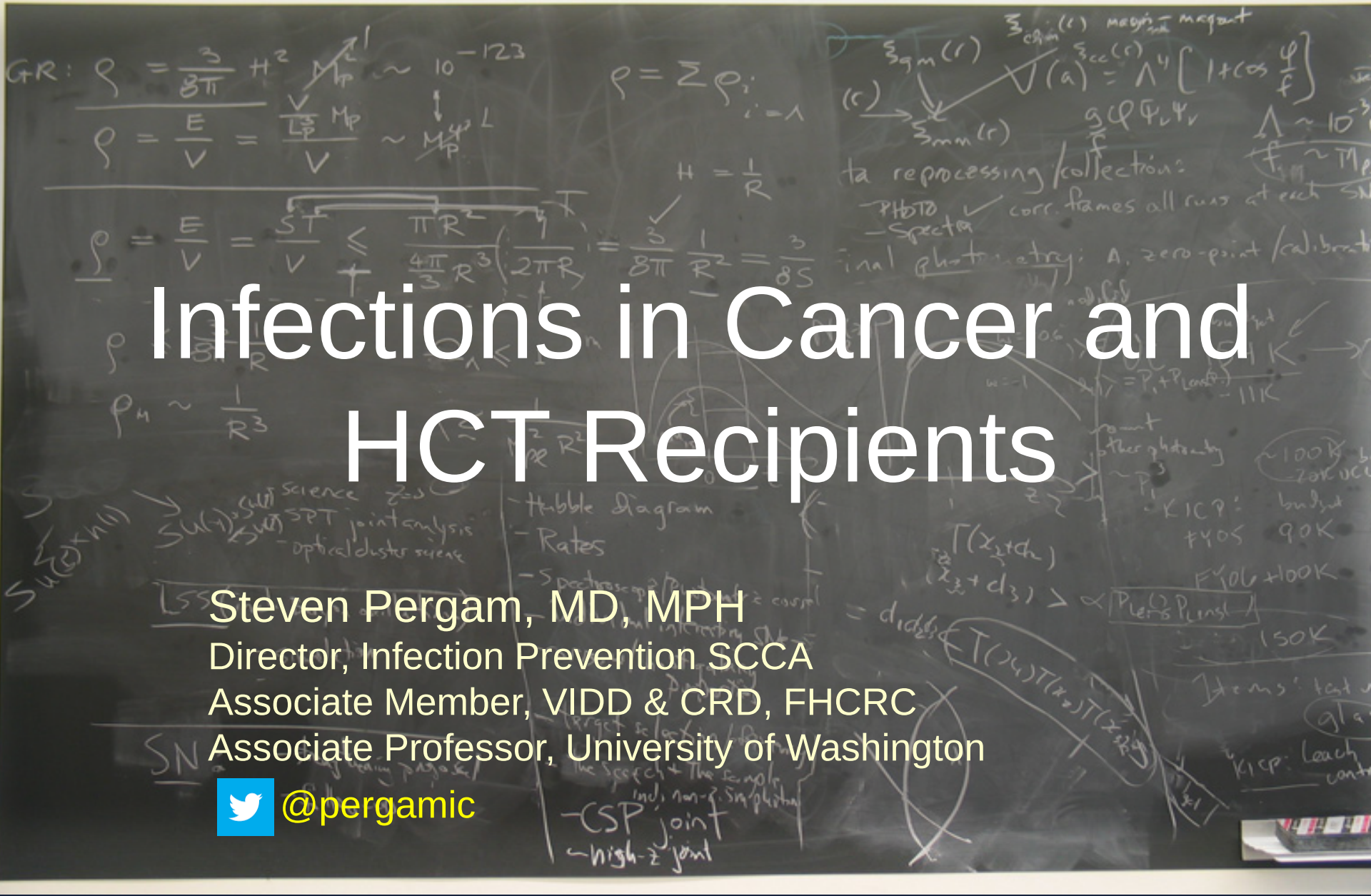
Selected Drugs Requiring Dose Reduction for Hepatic Dysfunction

- Doxorubicin
- Liposomal doxorubicin
- Irinotecan
- Etoposide
- Eribulin
- Docetaxel
- Cabazitaxel
- Ixabepilone
- Vinca alkaloids
- Methotrexate
- 5-FU
- 6-mercaptopurine
- 6-thioguanine
- Paclitaxel
- Gemcitabine

The Oncologist 2007;12:1070 –1083

Abbreviations

- BBB- Blood Brain Barrier
- DL_{CO}- Diffusing capacity for carbon monoxide
- DTIC- Dacarbazine
- FRB- FKB12-rapamycin binding
- FVC- Forced Vital Capacity
- GBM- Glioblastoma Multiforme
- LFT- Liver Function Test
- LVEF- Left Ventricular Ejection Fraction
- MOA- Mechanism of Action
- PCP/PJP- Pneumocystis carinii/jiroveci Pneumonia
- SIADH- Syndrome of Inappropriate Antidiuretic Hormone
- XRT- Radiation Therapy



Infections in Cancer and HCT Recipients

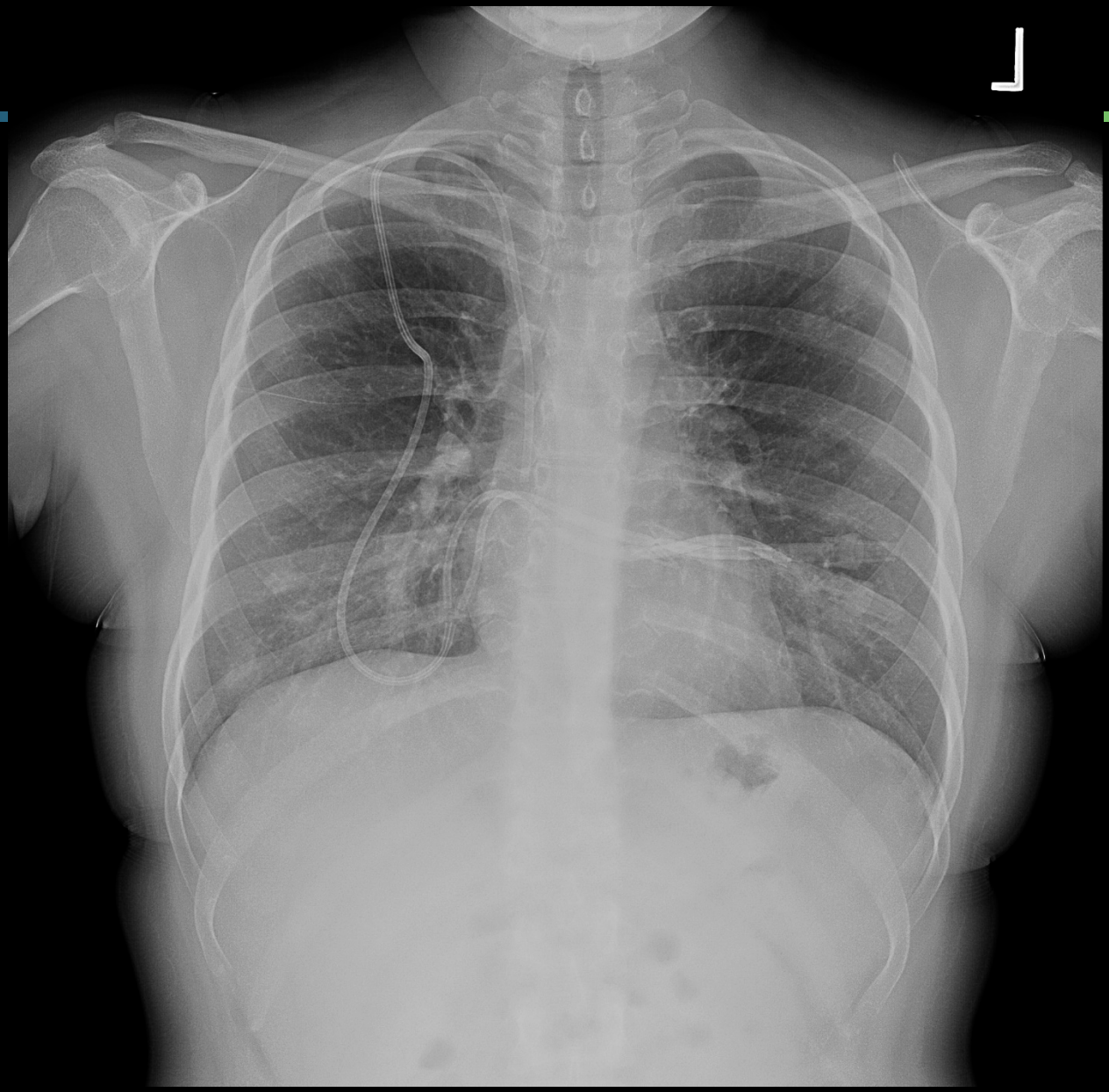
Steven Pergam, MD, MPH
Director, Infection Prevention SCCA
Associate Member, VIDD & CRD, FHCRC
Associate Professor, University of Washington
@pergamic

Case Presentation

- 27 y/o female with acute myelogenous leukemia in 1st remission
- Myeloablative conditioning with Cytoxan/TBI
- Received a double cord blood transplant
- Posttransplant period complicated by *Serratia* bacteremia, gut GVHD requiring 1 mg/kg of steroids, and low level CMV reactivation

Case Presentation

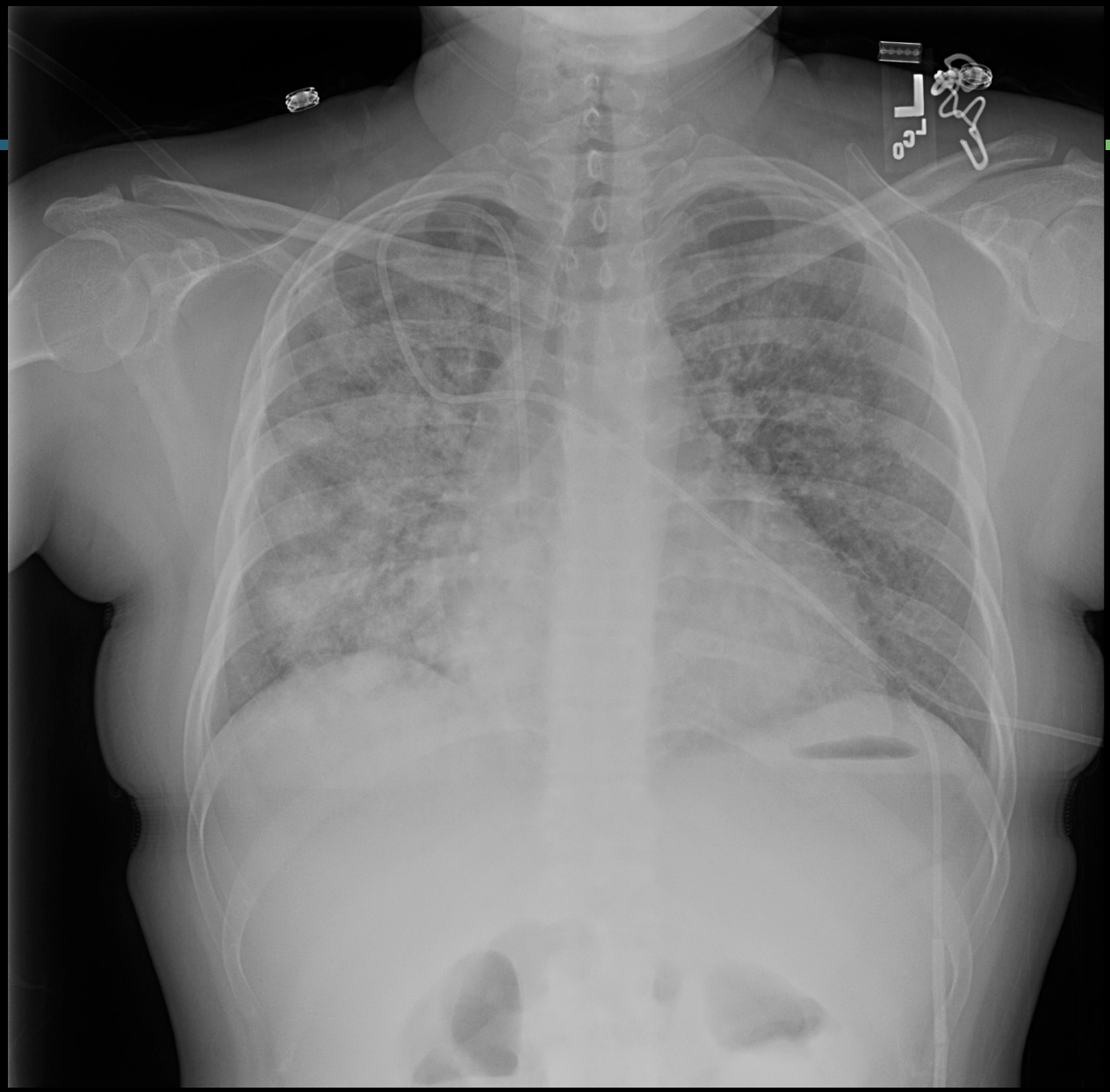
- Day +24 developed abdominal pain after discharge, seen in clinic and CT of abdomen negative
- Planned GI appointment for endoscopy
- Following day complained of fevers in clinic so admitted
- On arrival to hospital tachypnea, and hypoxic to 88% on RA



FRED HUTCH

Case Presentation

- Empiric Ceftazidime and Vancomycin started
- Continued to complain of abdominal pain and hypoxia worsened
- Moved to ICU and non-rebreather mask
- Ceftazidime changed to meropenem and ganciclovir started
- Repeat chest x-ray



Immunosuppression Pre and Post

- Radiation
- Cytotoxic chemotherapy
- Steroids
- Calcineurin inhibitors
- mTOR inhibitors
- MMF
- Antibody therapy
  - Alemtuzumab / ATG
  - Monclonal antibodies
- TNF inhibitors
- Proteasome inhibitors
- Immunotherapy

Additional Risks for Infections

- **Neutropenia (pre & post)**
- Lymphopenia
- Delayed T-cell recovery
- **Mucosal barrier injury**
- Integument breakdown
- Blood transfusions
- **Prior antibiotic use**
- **Gastric acid suppression**
- Prolonged hospitalization
- **Central lines**
- TPN/PPN use
- Colonization with MDROs
- Renal/Liver dysfunction
- Splenectomy
- Age/Obesity
- Iron overload

Taking their meds?

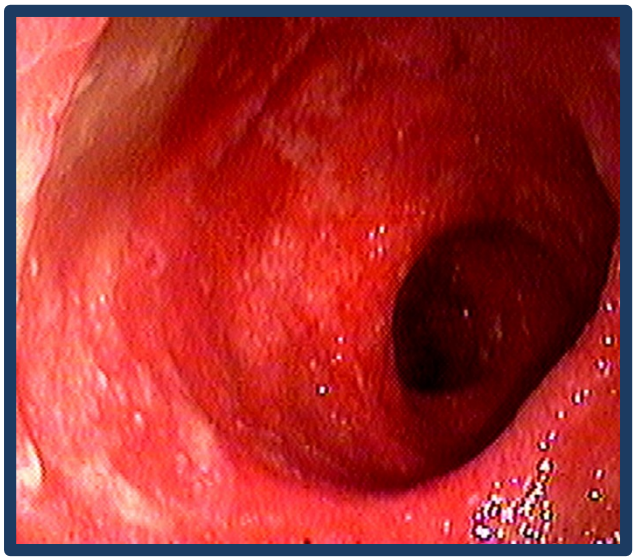
Are you sure your patient is taking their:

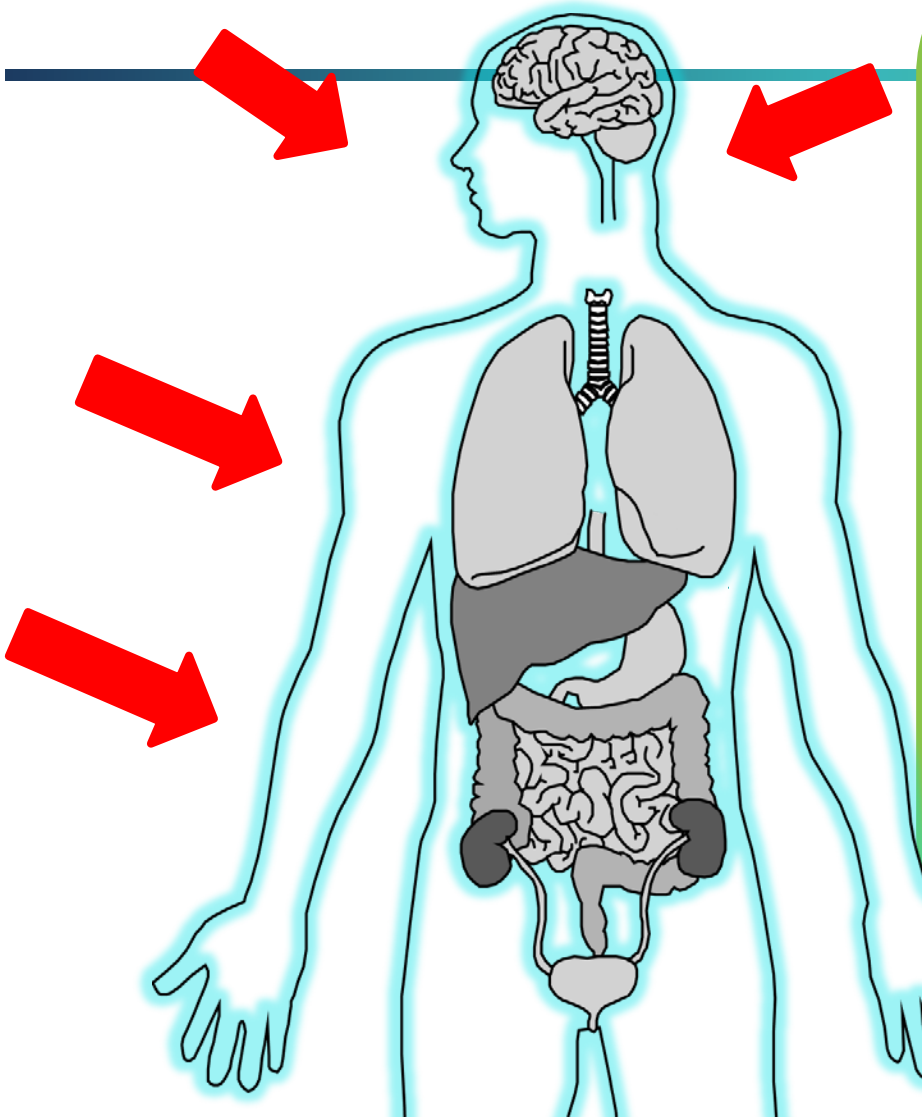
- Bactrim?
- Acyclovir?
- Fluconazole?
- Posaconazole?

From the marrowmovement.com

Complications Increase Risk

- Engraftment syndrome
- Graft-versus-host-disease
  - Need for steroids/ATG
  - Acute vs. Chronic
- Delayed engraftment/graft failure
- Rituxan/ATG
- Mucositis
- Drug side effects





External Microbial Agents

Viruses
Influenza
RSV
Paraflu
Adenovirus
Norovirus
Enteroviruses
Legionella

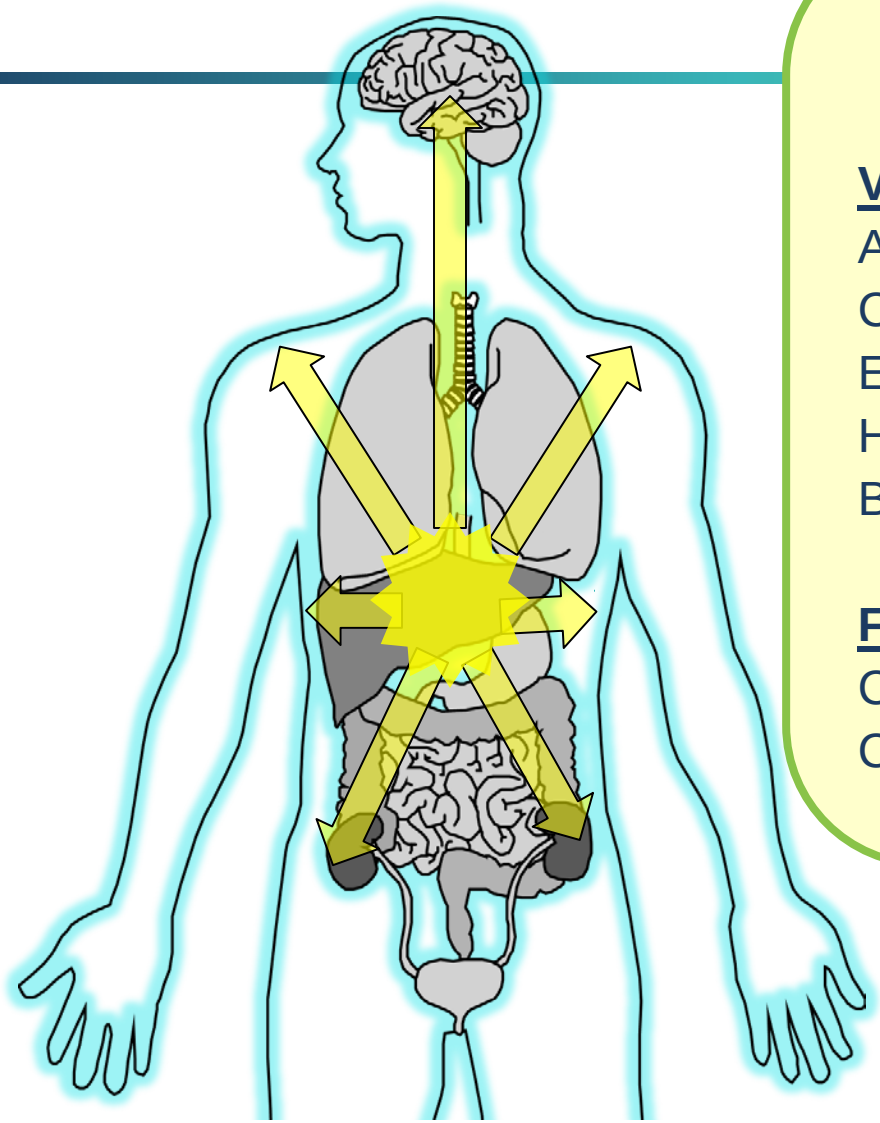
Bacteria
VRE
MRSA
Resistant GNR
Nocardia
C Difficile

Parasites
Toxoplasma

Fungi
Aspergillus
Murcorales
Cryptococcus

FRED HUTCH

Image by Kyoko Kurosawa



Internal Microbial Agents

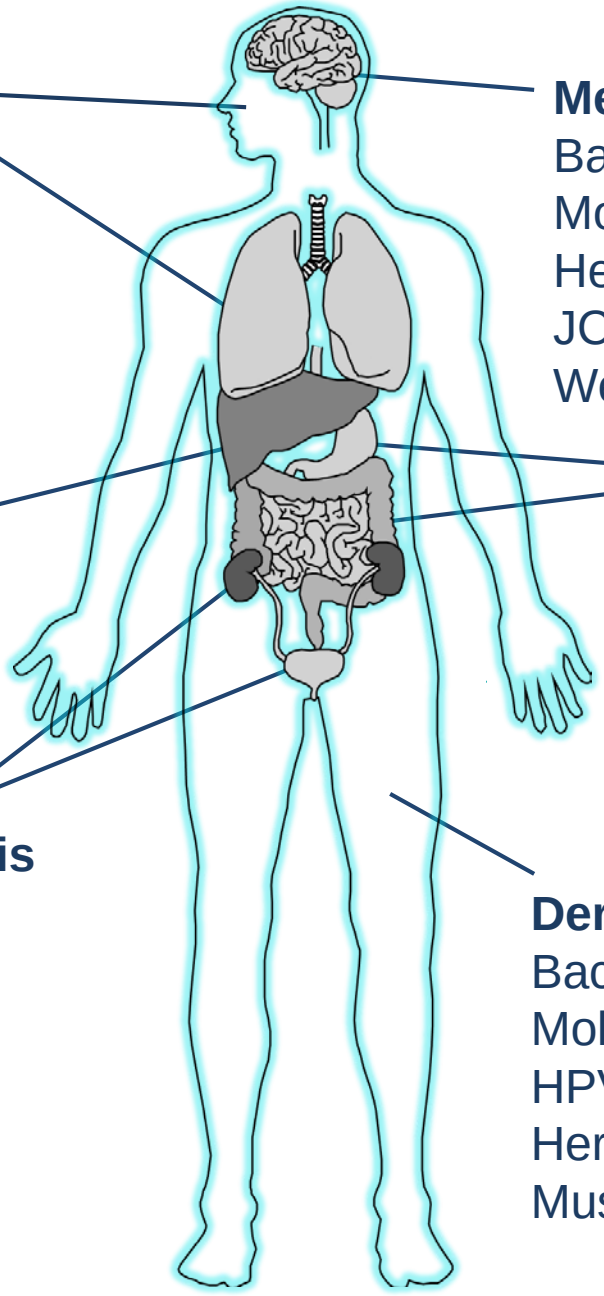
Viruses
- Adenovirus
- CMV
- EBV
- HHV-6
- BK/JC Virus

Bacteria
- Enteric GNRs
- Skin flora
- MTB
- Strep viridans/ oral flora

Fungi
- Candida
- Cocci / Histo

Parasites
- Strongylodiasis
- T cruzi
- Toxoplasma

Image by Kyoko Kurosawa



Sinopulmonary
Bacterial
Mold/Yeast
Respiratory viruses
Adenovirus
Herpesviruses (CMV)
Toxoplasmosis
PCP

Meningitis/Encephalitis
Bacteria
Mold/Yeast
Herpesviruses
JC virus
West Nile virus

Gastritis/Colitis
Bacteria
Mold/Yeast
Adenovirus
Norovirus
Herpesviruses
Parasite/Protozoa

Hepatitis
Adenovirus
Herpesviruses
Mold/Yeast

Cystitis/Nephritis
Bacterial
Mold/Yeast
Adenovirus
BK virus

Dermatologic
Bacterial
Mold/Yeast
HPV
Herpesviruses (VZV)
Musculosum contagiosum

Modified from Lennette's Laboratory Diagnosis of Viral Infections, 4th Addition

Image by Kyoko Kurosawa

Consider common infections

- Bacteria
- Fungi
- Viral infections
- **Multiple infections**
- ***Infection Mimics***

Consider timing

- Timing of neutropenia?
- How long neutropenic?
- Early during inpatient management?
- After returning to the community?
- After completing prophylaxis?
- During prophylaxis?
- Recent chemotherapy/What type?
- Steroid use?

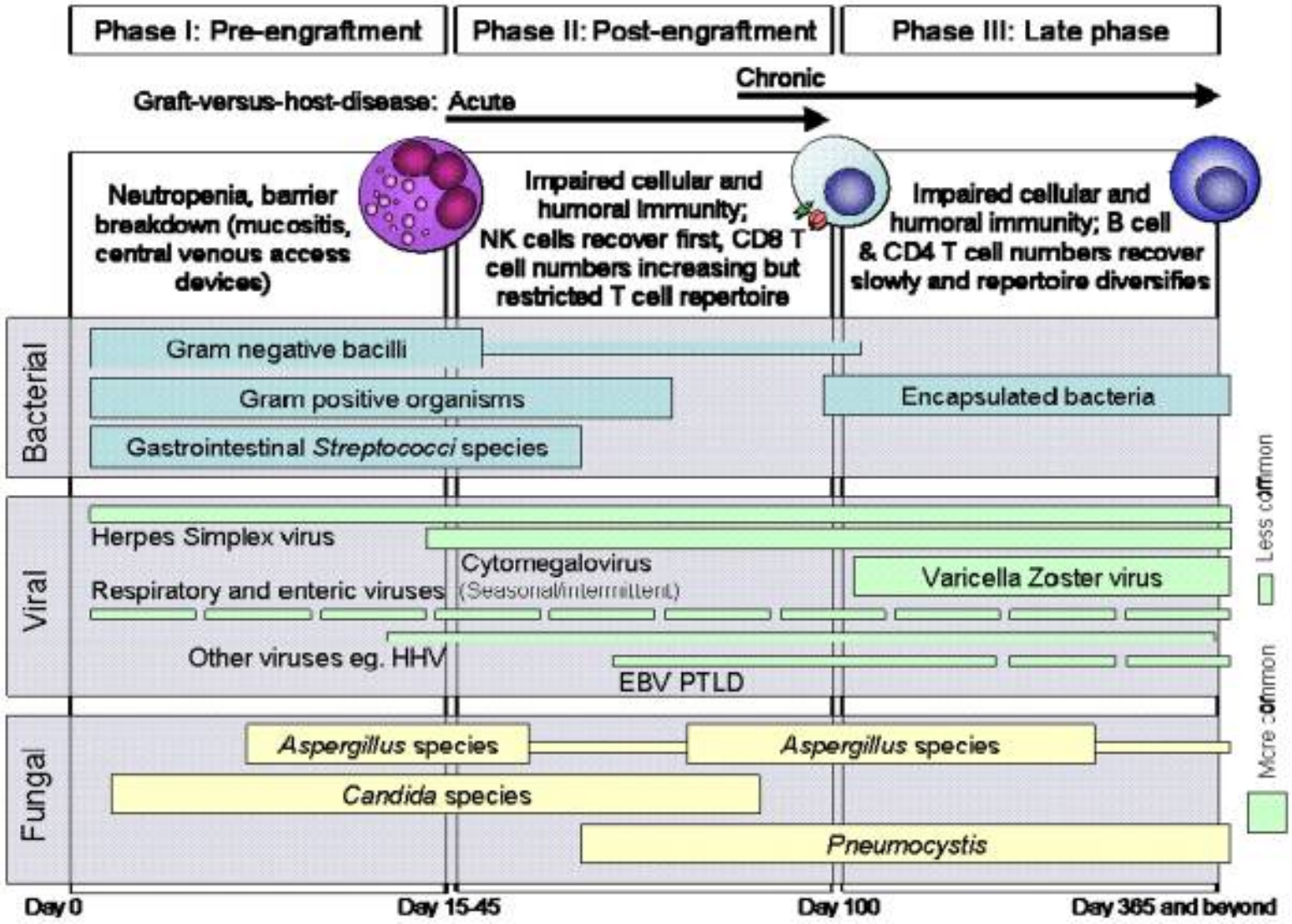
IC Hosts and Infections

- Consistent timeline for major pathogens
- Common bacteria, viruses and fungi are common
- Atypical presentations: mild presentations of major pathogens/rapidly progressive minor pathogens, uncommon symptoms
- Minor illnesses = Significant morbidity & mortality
- Unique infections / Rare presentations
- **Pay attention to symptoms**

Palatal lesion?

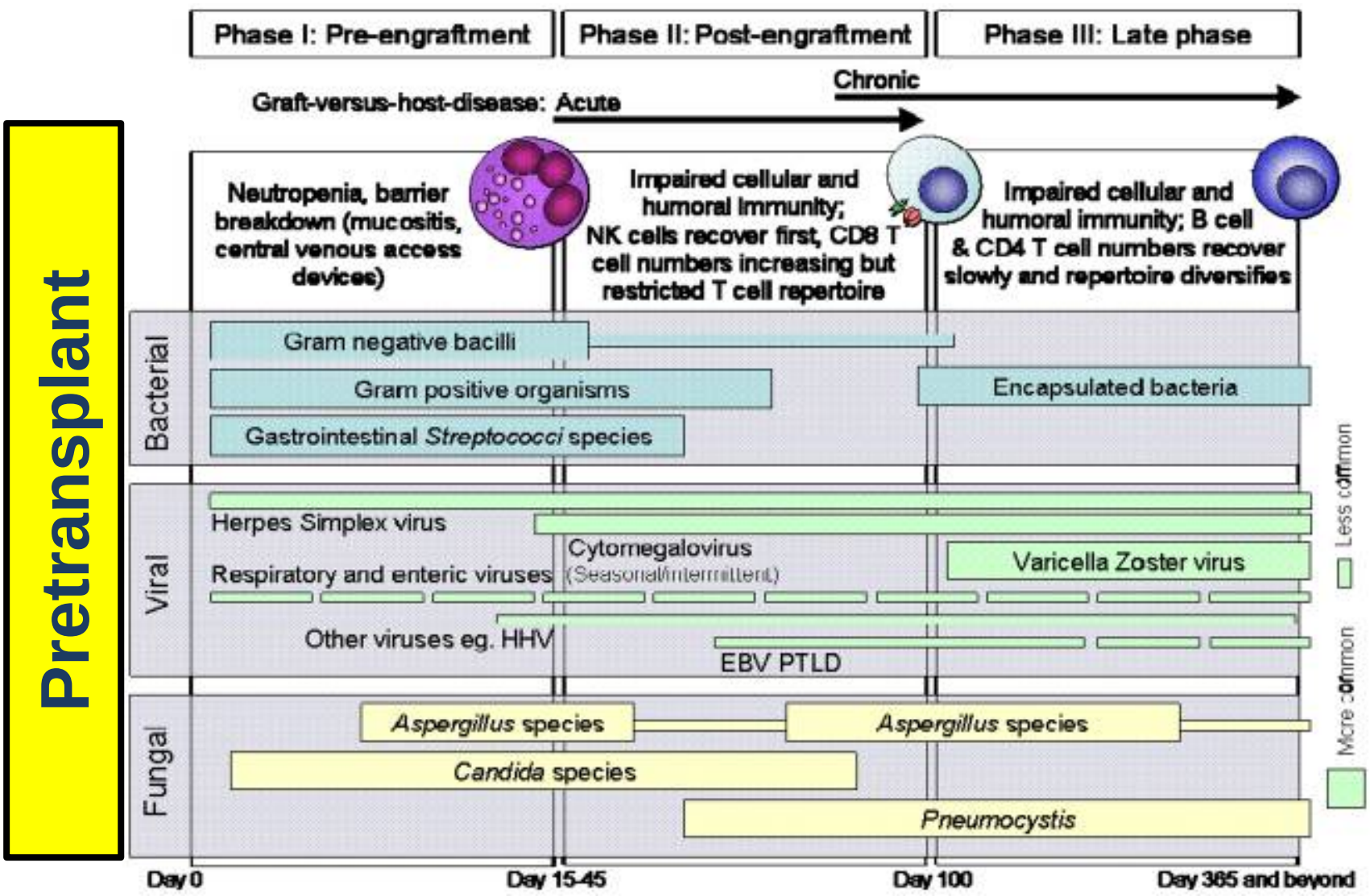
Palatal lesion? Mold

Hematopoietic Cell Tx Infection "Timeline"



Tomblyn BBMT 2011

Hematopoietic Cell Tx Infection "Timeline"



Tomblyn BBMT 2011

Prevention /Prophylaxis

CMV – Acyclovir / Ganciclovir / Valganciclovir

HSV – Acyclovir

Fungal – Fluconazole / Posaconazole / Voriconazole

PCP – Bactrim / Dapsone / Atavaquone

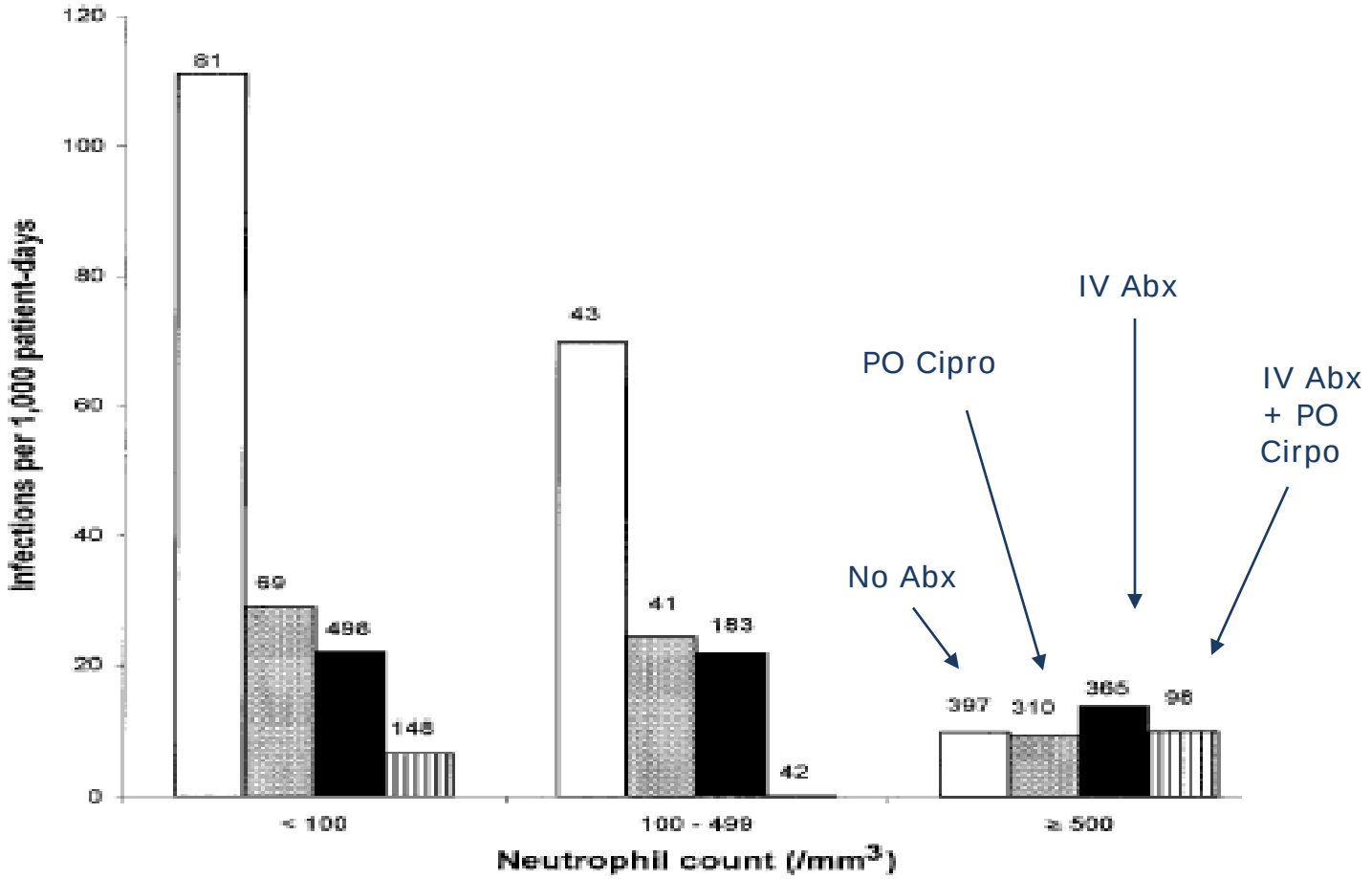
Toxoplasmosis - Bactrim

Encapsulated bacteria – Bactrim / Pen VK

Neutropenia – Flouroquinolones

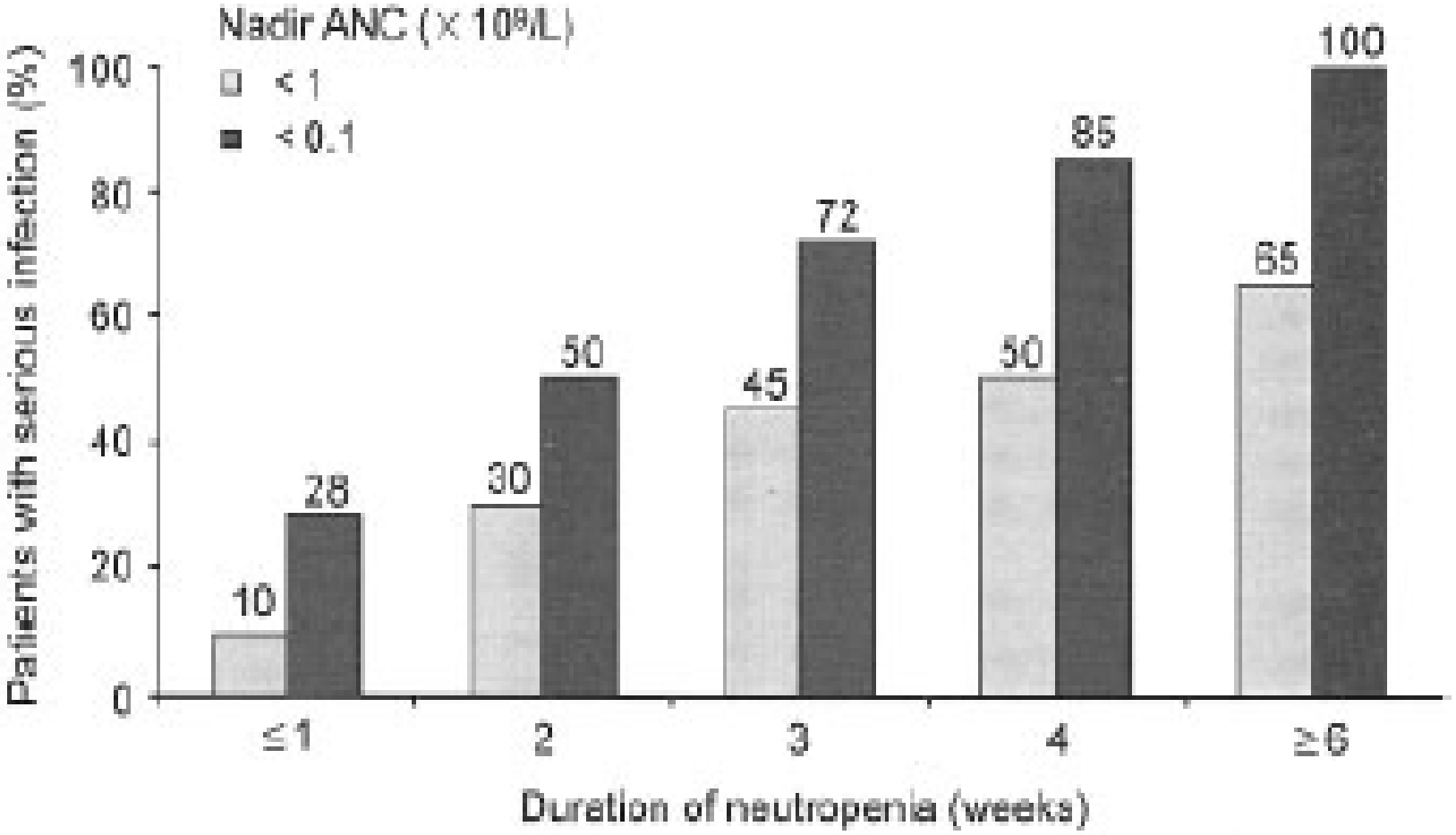
Hepatitis B – Lamivudine / Entecavir

Risk Factors for Infection: Why 500?



Engels EA (1999). *Clin Infect Dis*

Risk Factors for Infection: Duration



Viscoli C (2005), *Clin Infect Dis*

Primary prophylaxis for neutropenia

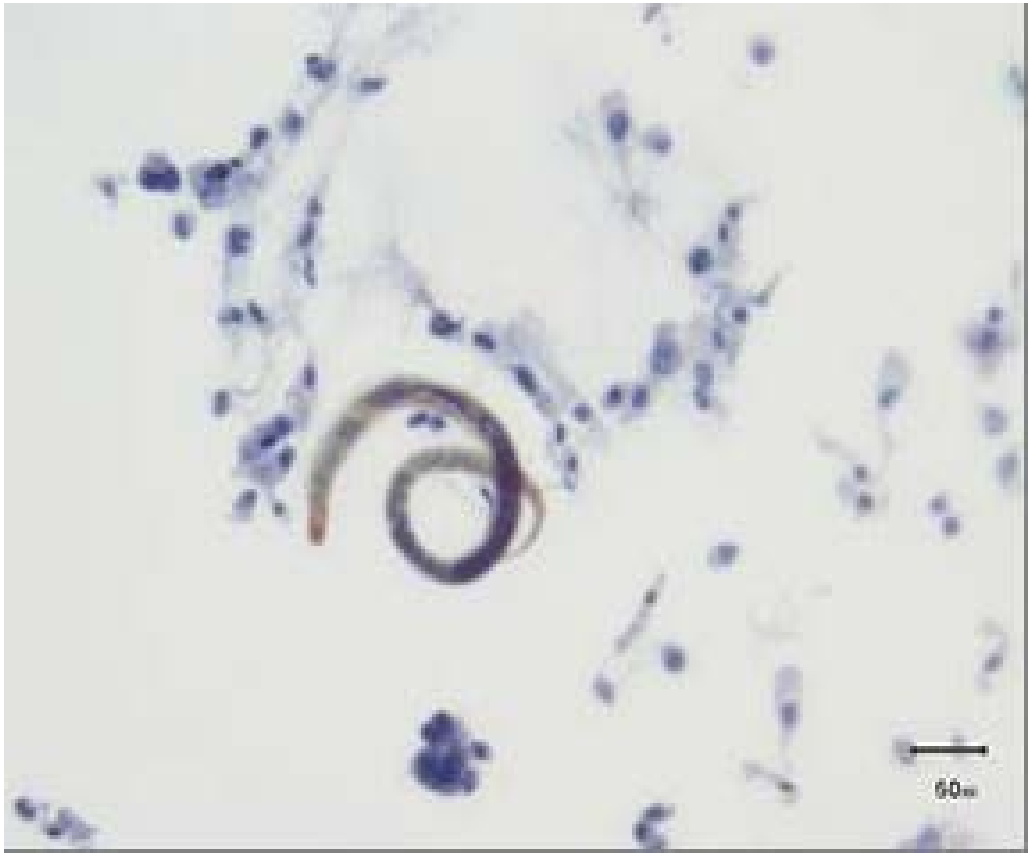
- Levofloxacin
- TMP/S
- Amox/Clav
- IV Ceftazidime
- Nothing

Emerging data suggesting potential benefits of no prophylaxis (microbiome/resistance)– but currently not policy here yet

Case

- 46 y/o Laotian man undergoing chemotherapy for ALL
- ANC 0
- Fever to 101 and shaking chills
- Started on Cefepime, hypotension moved to ICU
- Blood cultures grow *E. coli, Enterobacter cloacae,* and *Citrobacter furundii*
- Diffuse pulmonary infiltrates and acute respiratory failure, undergoes a BAL after intubation
- Diagnosis is…..

BAL results…..



Prevention /Prophylaxis

CMV – Acyclovir / Ganciclovir / Valganciclovir

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Fungal – Fluconazole / Posaconazole / Voriconazole

PCP – Bactrim / Dapsone / Atavaquone

Toxoplasmosis - Bactrim

Encapsulated bacteria – Bactrim / Pen VK

Neutropenia – Flouroquinolones

Hepatitis B – Lamivudine / Entecavir

Strongylodiasis – Ivermectin (Travel history Key!)

Pre-Engraftment (0 - ~Day +15)

- 35 y/o s/p Bu/Cy day 5
- Severe mucositis & neutropenia
- On Levofloxacin prophylaxis
- Develops fever to 101.5 and chills
- Cultures pending
- What are common cause of early fever?

Pre-Engraftment (0 - ~Day +15)

- 35 y/o s/p Bu/Cy day 5
- Severe mucositis & neutropenia
- On Levofloxacin prophylaxis
- Develops fever to 101.5 and chills
- Cultures pending
- What are common cause of early fever?

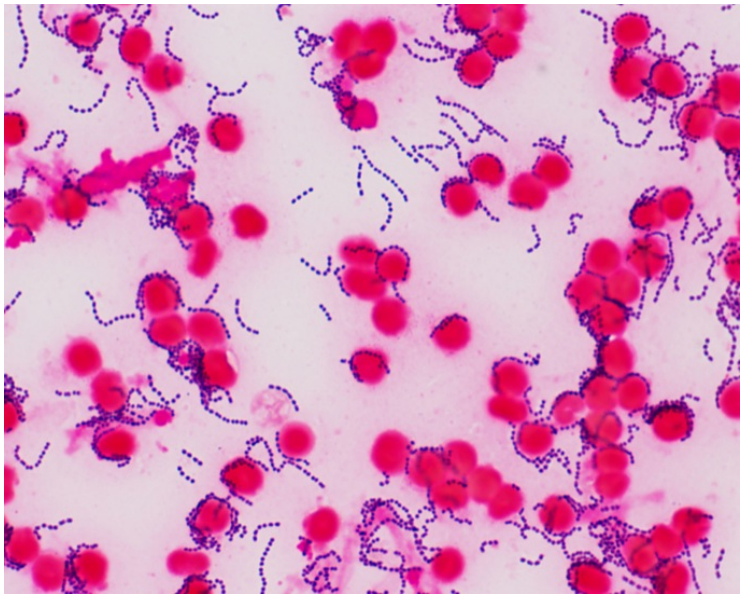
Bacteria – GPC > GNR, C diff

Fungal infections – Yeast (candida) >> Mold

Respiratory viruses

Pre-Engraftment (0 - ~Day +15)

- 35 y/o s/p Bu/Cy day 5
- Severe mucositis & neutropenia
- On Levofloxacin prophylaxis
- Develops fever to 101.5 and chills
- Cultures pending
- What are common cause of early fever?



Viridans streptococcal bacteremia = common early post-transplant phase and more often seen in patients with severe mucositis (often resistant to FQs)

Case

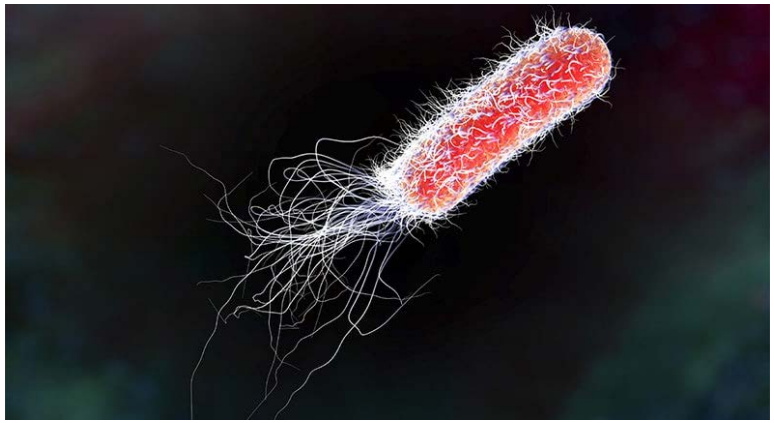
- 57 y/o male s/p MURD HCT
- Count recovery on day +22
- Now Day +57
- Course complicated by gut GVHD requiring first 1 mg/kg, and then 2 mg/kg prednisone
- Diarrhea improving, but remains on 60 mg day of prednisone on slow taper
- Over 48 hours develops hypotension and hypoxia (moved to ICU), now growing GNR in blood

Primary empiric regimens?

- IV cefepime
- IV vancomycin (if bad mucositis, or presumptive line infection)
- Meropenem in patients with:
  - known history of MDR-GNR pathogens
  - in patients with presenting with sepsis like symptoms
  - apparent GI/abdominal infection

Most common GNR in HCT patients?

- ***E coli (#1)***
- *Stenotrophomonas maltophilia*
- *Pseudomonas aeruginosa*
- *Enterobacter cloacae*
- *Klebsiella pneumonia*



Which is intrinsically resistant to Meropenem?

- *E coli*
- *Stenotrophomonas maltophilia*
- *Pseudomonas aeruginosa*
- *Enterobacter cloacae*
- *Klebsiella pneumonia*

Which is intrinsically resistant to Meropenem?

- *E coli*
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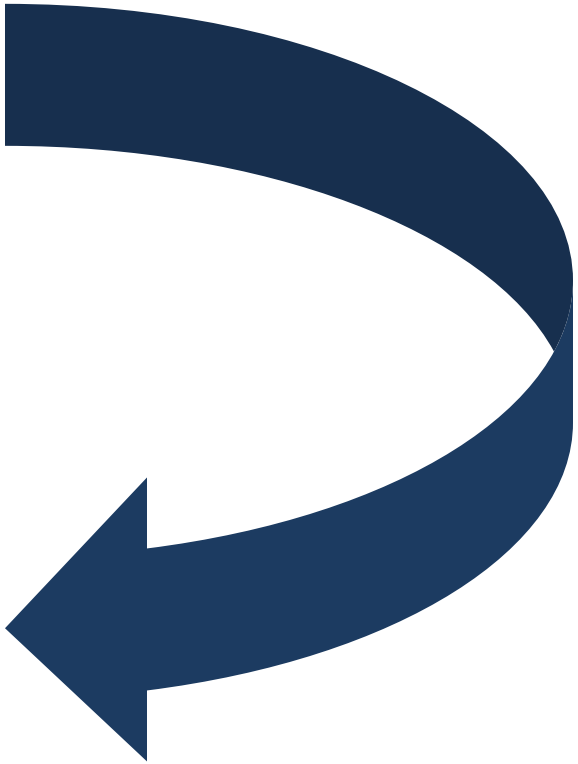


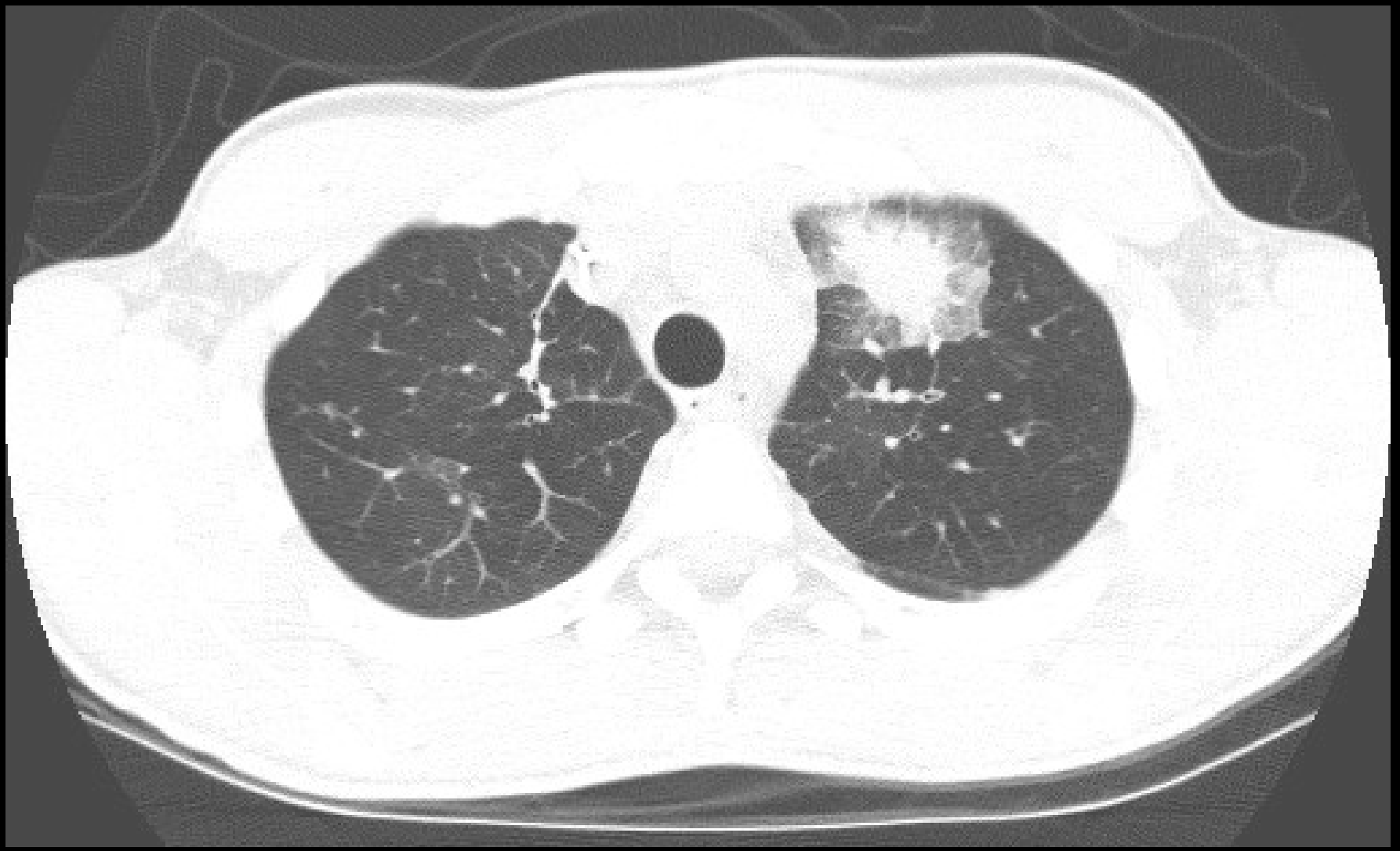
Treatment of choice = Bactrim

Higher risk for GNRs?

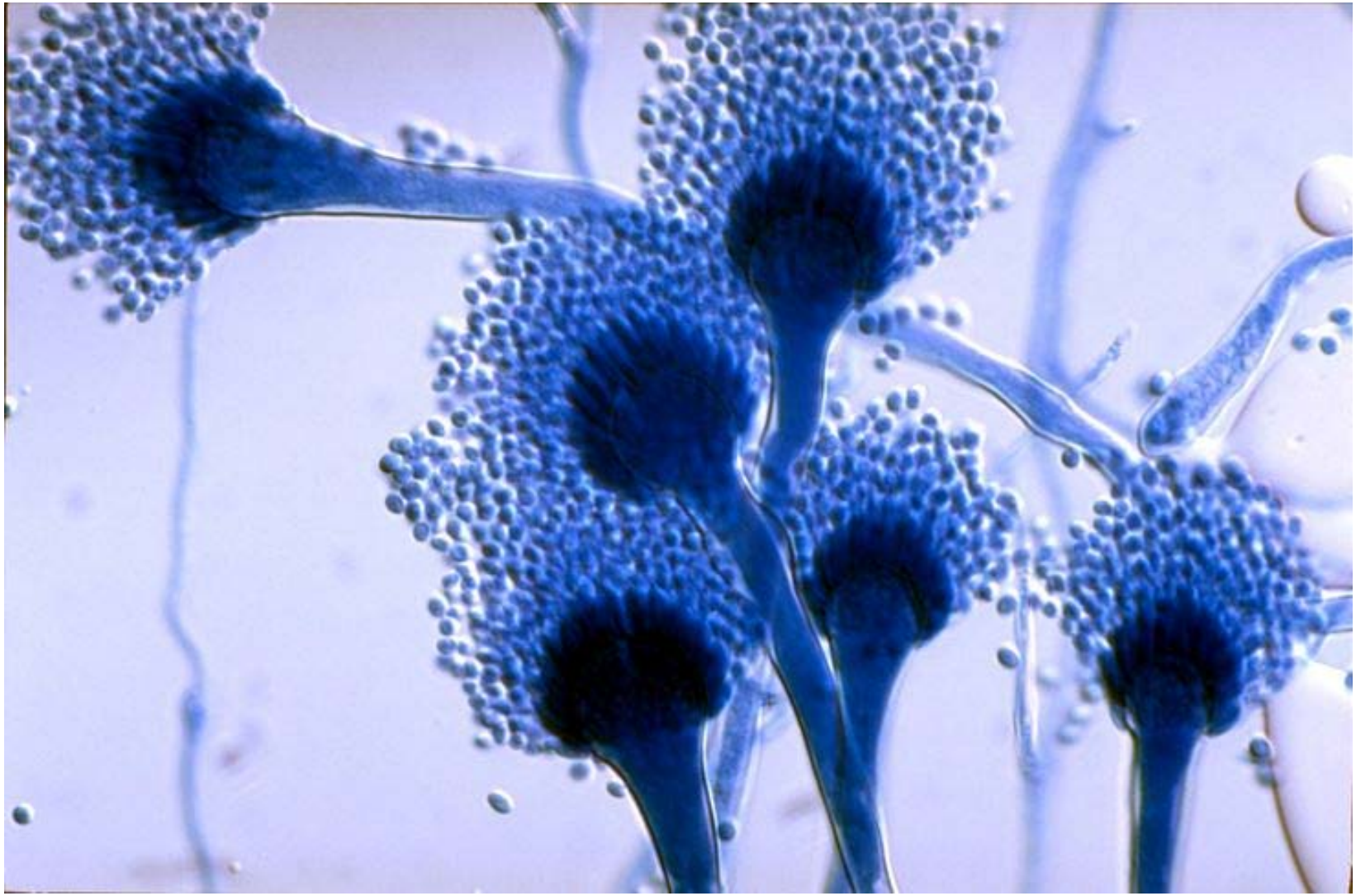
- Gut GVHD
- High-dose steroids
- Severe mucositis
- Neutropenia
- Prior colonization with MDR GNR
- Prolonged antibiotics (↑ resistance)

Case

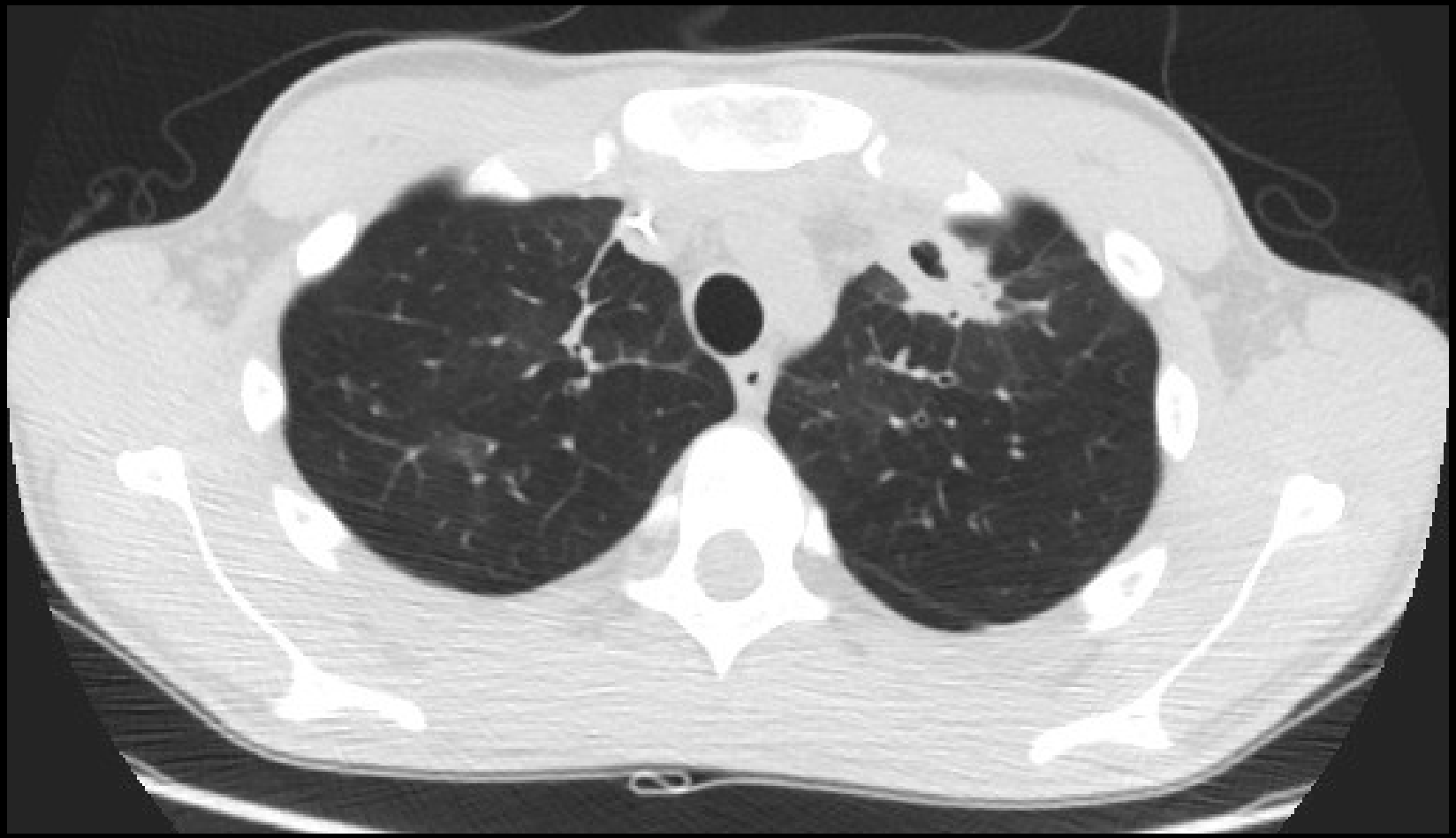
- 28 y/o male with AML, s/p G-CLAM
- Day +22 of neutropenia
- Admitted with neutropenic fever and work-up negative
- Treated with IV Cefepime
- Develops dry cough
- Abnormal chest x-ray – so gets CT scan

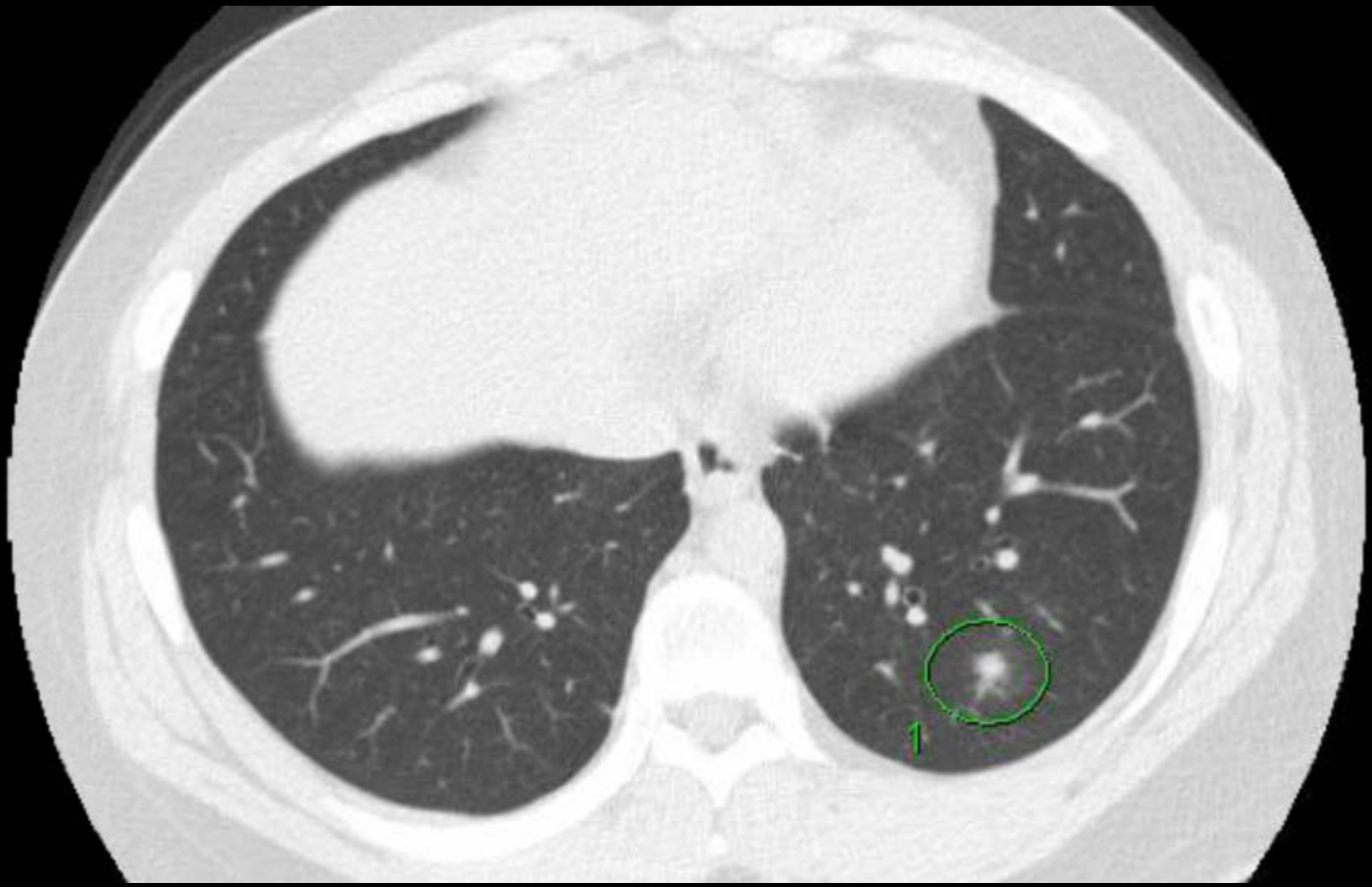


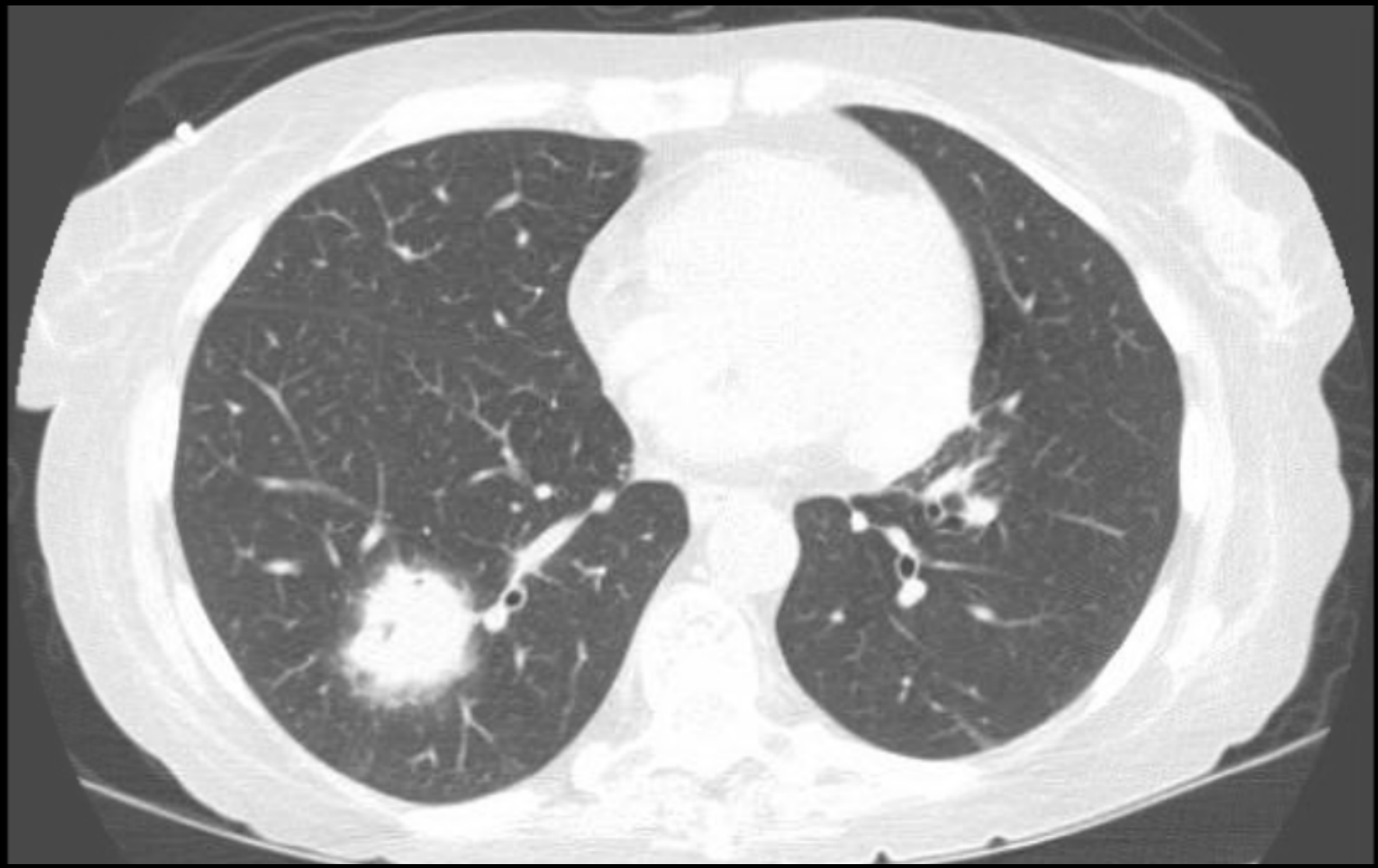
Aspergillus pneumonia

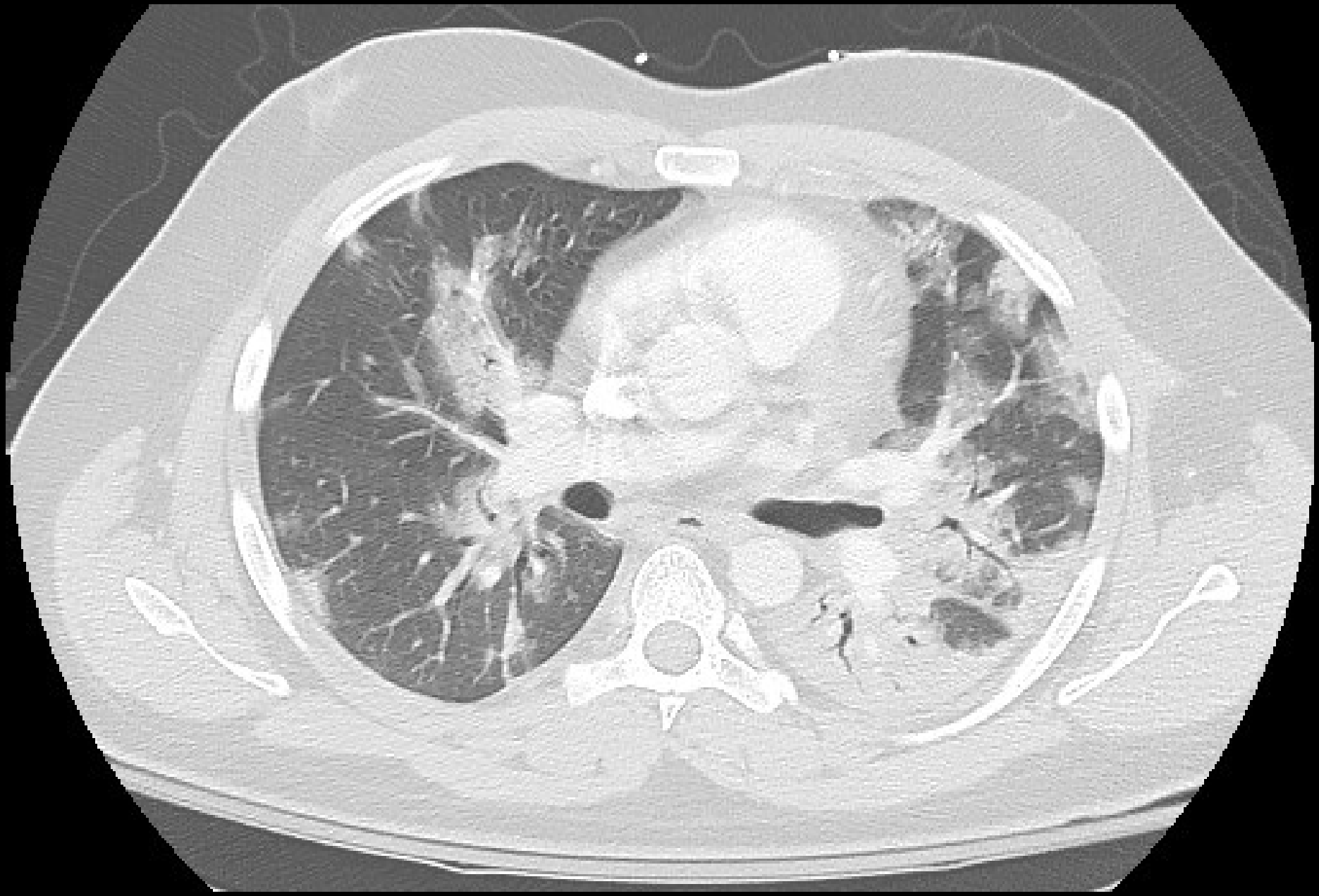


After 3 weeks of therapy with Voriconazole

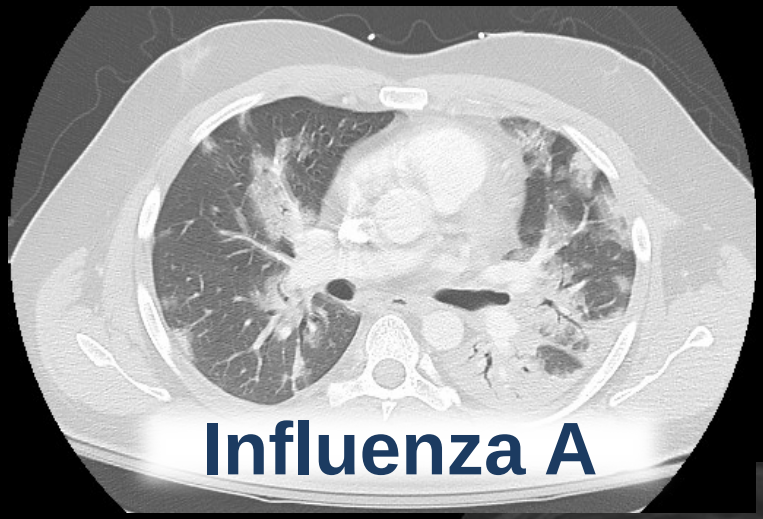


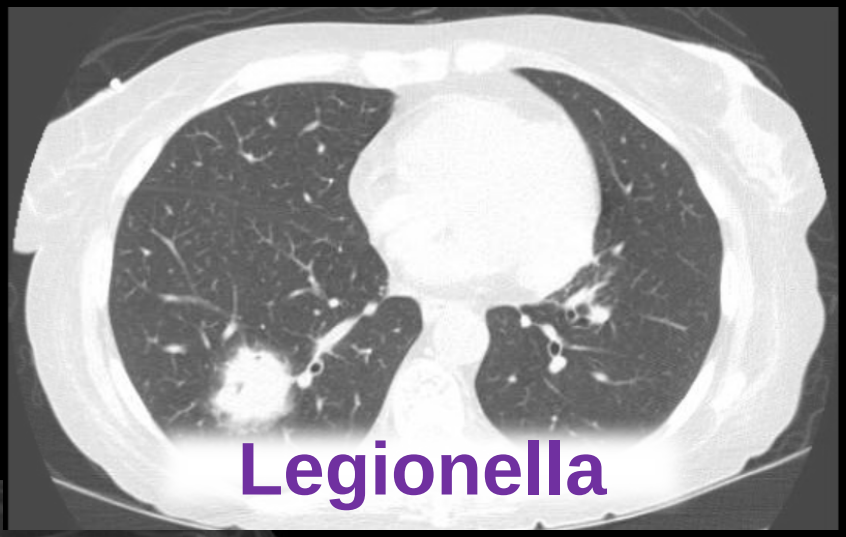





FRED HUTCH

Etiologies of Chest CTs?

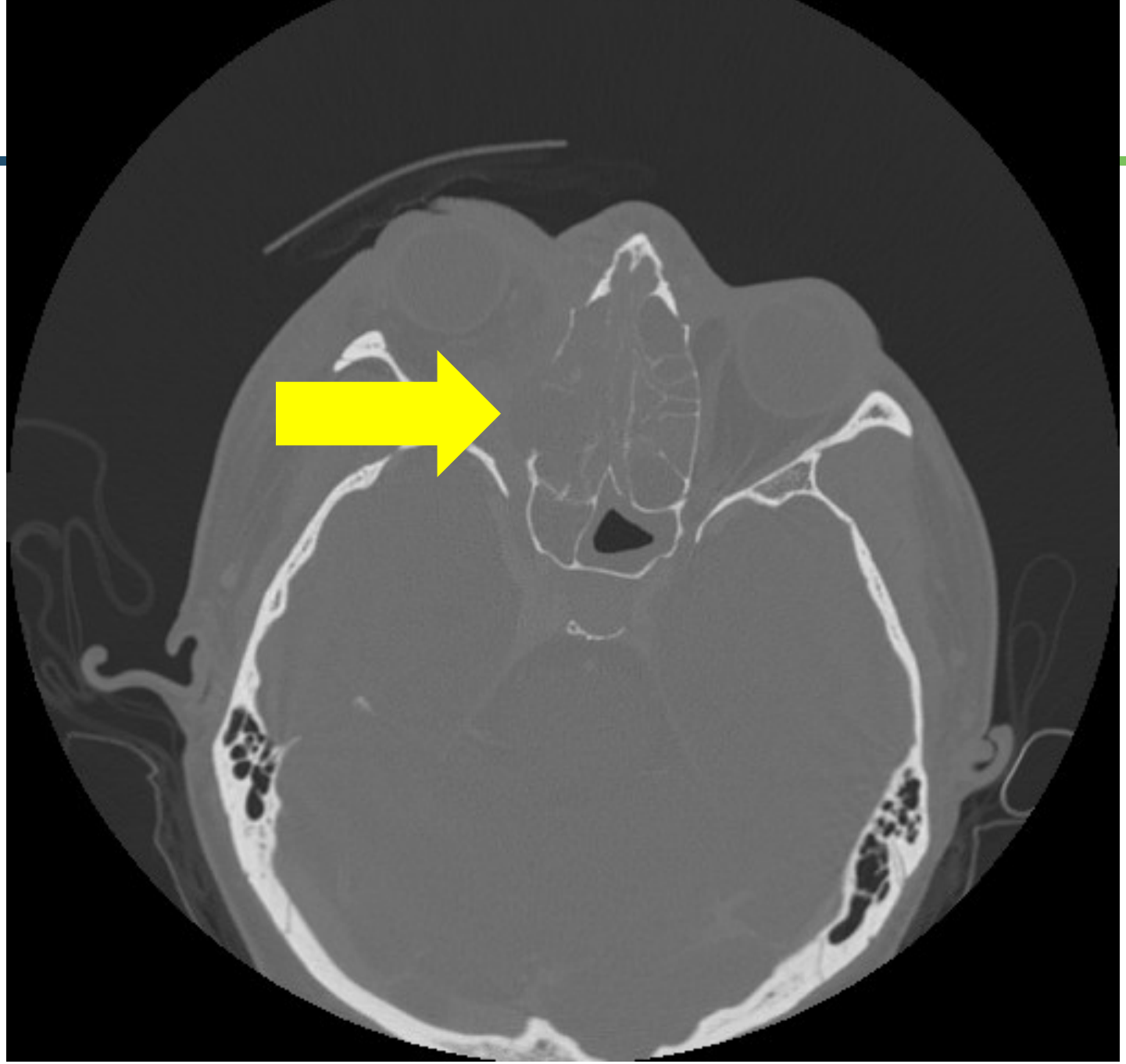




BAL important in diagnosis off pulmonary disease/nodules

Case

- 67 y/o male s/p G-CLAM X 2 with prolonged neutropenia
- Hospitalized with neutropenic fever
- On Cefepime/Vancomycin
- Develops sinus symptoms over 24 hours
- Switched to Meropenem
- Pain and numbness over “cheek”

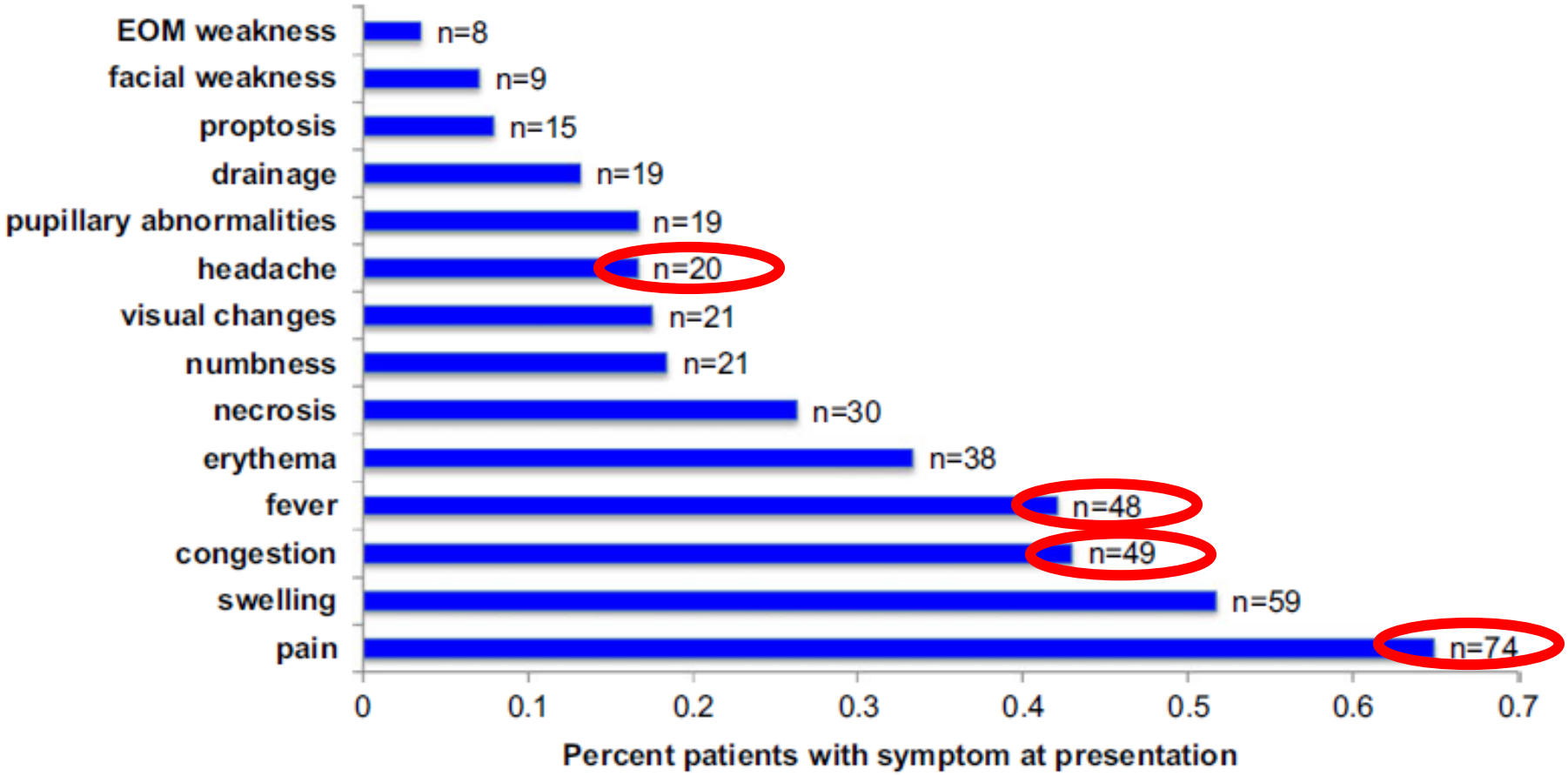


Don’t Forget Fungal sinusitis

- Prevalence 0.5-1.7% of all HCT recipients and leukemia[1,2]
- Etiologic agents:[3]
  - #1 = Aspergillus spp.
  - #2 = Mucorales spp.
  - #3 = Fusarium spp/?
  - Others: *Scedosporium, Paecilomyces, Scopulariopsis, Alternaria* [dematiaceous molds], etc.
  - ~3.5% of fungal sinusitis are mixed infections

1. Johnson Am J Rhino 1997
2. Kennedy Oto Head Neck Surgery 1997
3. Wandell Int J of Allergy & Rhinology 2018

Presenting symptoms?



From Wandell Int J of Allergy & Rhinology 2018

Diagnosis/Treatment?

- Diagnosis? Urgent ENT evaluation

  CT of sinuses

- Treatment?

  IV Ambisome +/- Azole therapy

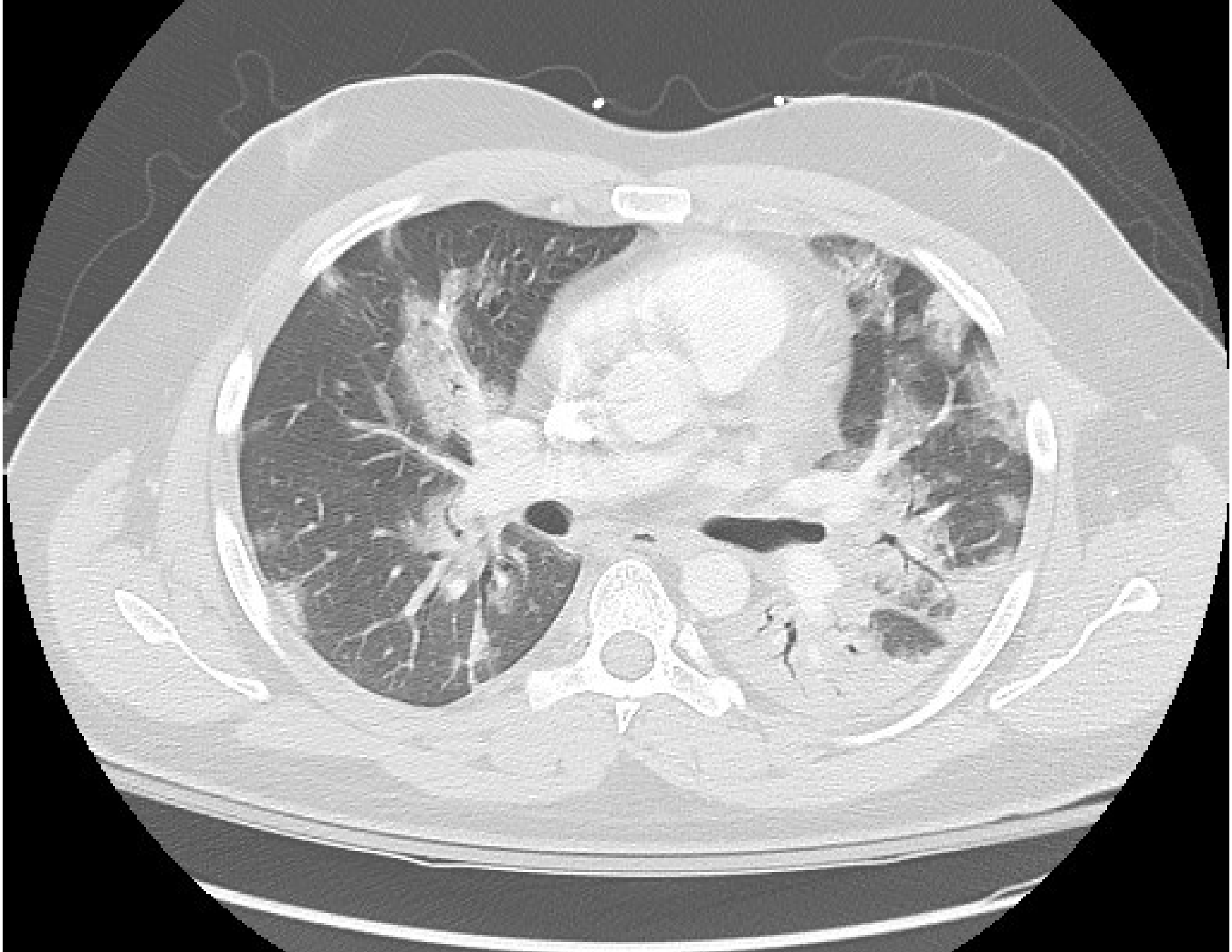
- **SURGICAL debridement and broad spectrum antifungal therapy**

Red Flags for Fungal Sinusitis

- Any CN abnormality
- Facial numbness
- Palatal eschar
- Double vision/vision loss
- Acute sudden MS changes
- Bony erosions on CT/MRI
- Significant Pain
- Prolonged symptoms

Case

- Non-Hodgkin’s Lymphoma
- Autotransplant uncomplicated, 45 days post with neutrophil recovery
- Small children at home
- Fever, myalgias and sore throat 3 days prior to admission
- Develops SOB and presents to ER with O2 sat 87%
- Acute decompensation and sent to ICU
- BAL with bronchoscopy and nasal wash



Case

- Treated with High dose Oseltamivir (150 mg BID), Ribavirin, and Amantidine
- IV Peramavir through compassionate use program
- Intubated/Proned positioning in ICU
- Renal failure dialysis
- In ICU for 3 weeks with ARDS
- Rehabilitation for 4 weeks
- Recovered

Case

- URI symptoms 3 days prior to admission
- Given “Z-pack” by Urgent Care in midst of high level Influenza in community
- Pregnant wife about to deliver, appropriately treated with oseltamivir

Prevention and Early Detection are Critical


Cost of a Transplant = $750,000


Cost of ICU admission = $250-500K
(minimum)

Respiratory Viruses –

(Days 0 to +100 and season dependent)

- Significantly higher frequency of pneumonia & death
- Atypical presentations and rapid clinical progression
- Higher risk of nosocomial transmission (cohorting)
- Persistence (shedding) after primary infection
- Important viruses seen in transplantation:

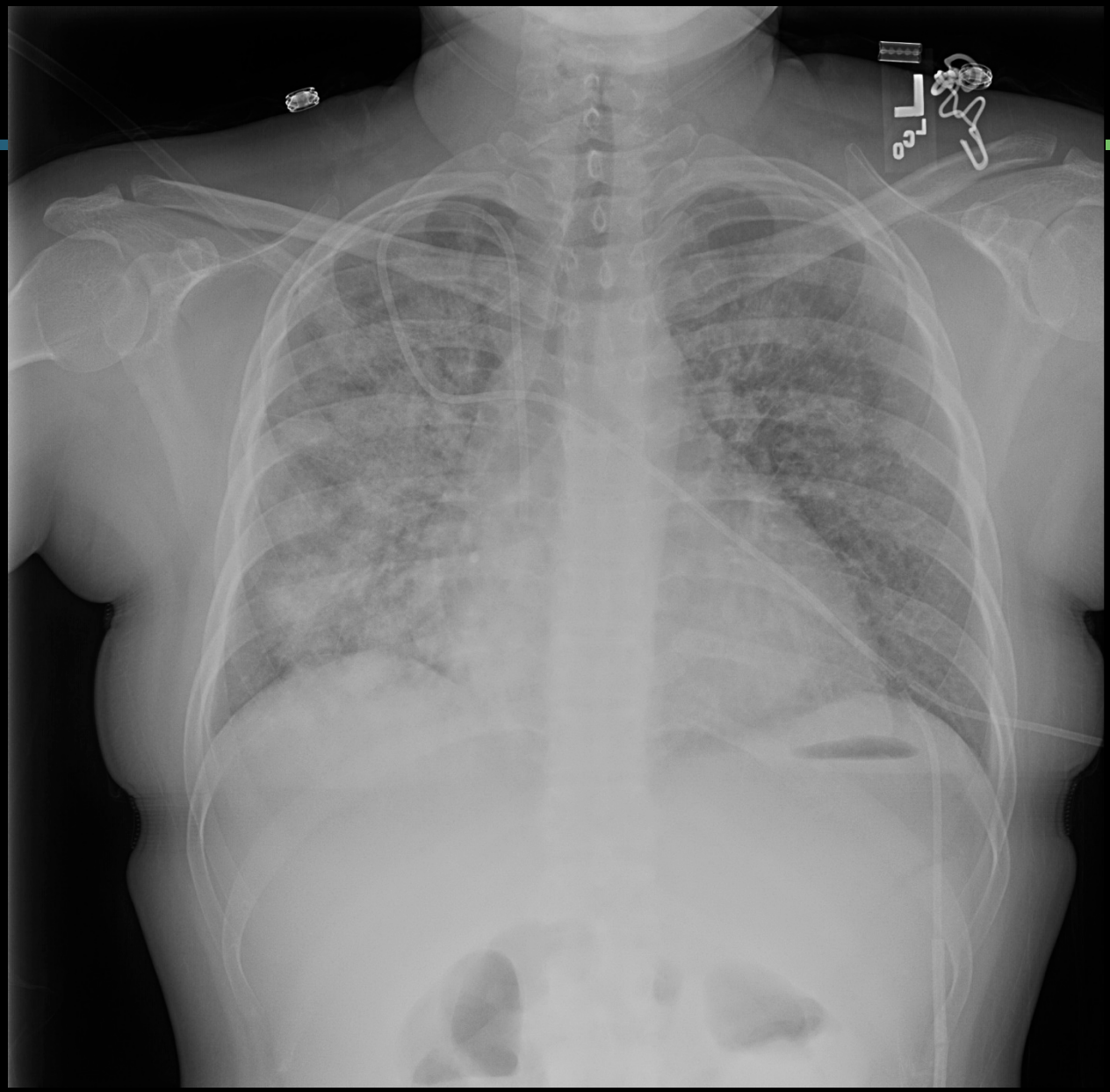
Influenza A/B Parainfluenza Metapneumovirus

Respiratory Syncytial Virus (RSV) Adenovirus

Coronavirus Rhinovirus Bocavirus

SARS-CoV-2

Heikkinen Lancet 2003



Cytomegalovirus (CMV)

- Ubiquitous, latent, herpes virus
- Major factor in determining risk: *What is the Antibody status of recipient?*
- Seronegative recipients with seronegative donors may acquire primary CMV from external sources
- Once CMV infection is established its replication is highly dynamic.
- Invasive disease reduced with routine surveillance and early tx in 1st 100 days
- Treatment Options: Ganciclovir, Valganciclovir, Foscarnet, Cidofovir

1. From Razonable and Limaye, in Transplant Infectious Diseases,3rd Edition.
2. Kalil, et al. Ann Int Med 2005;142:870-80

CMV Prevention Strategies

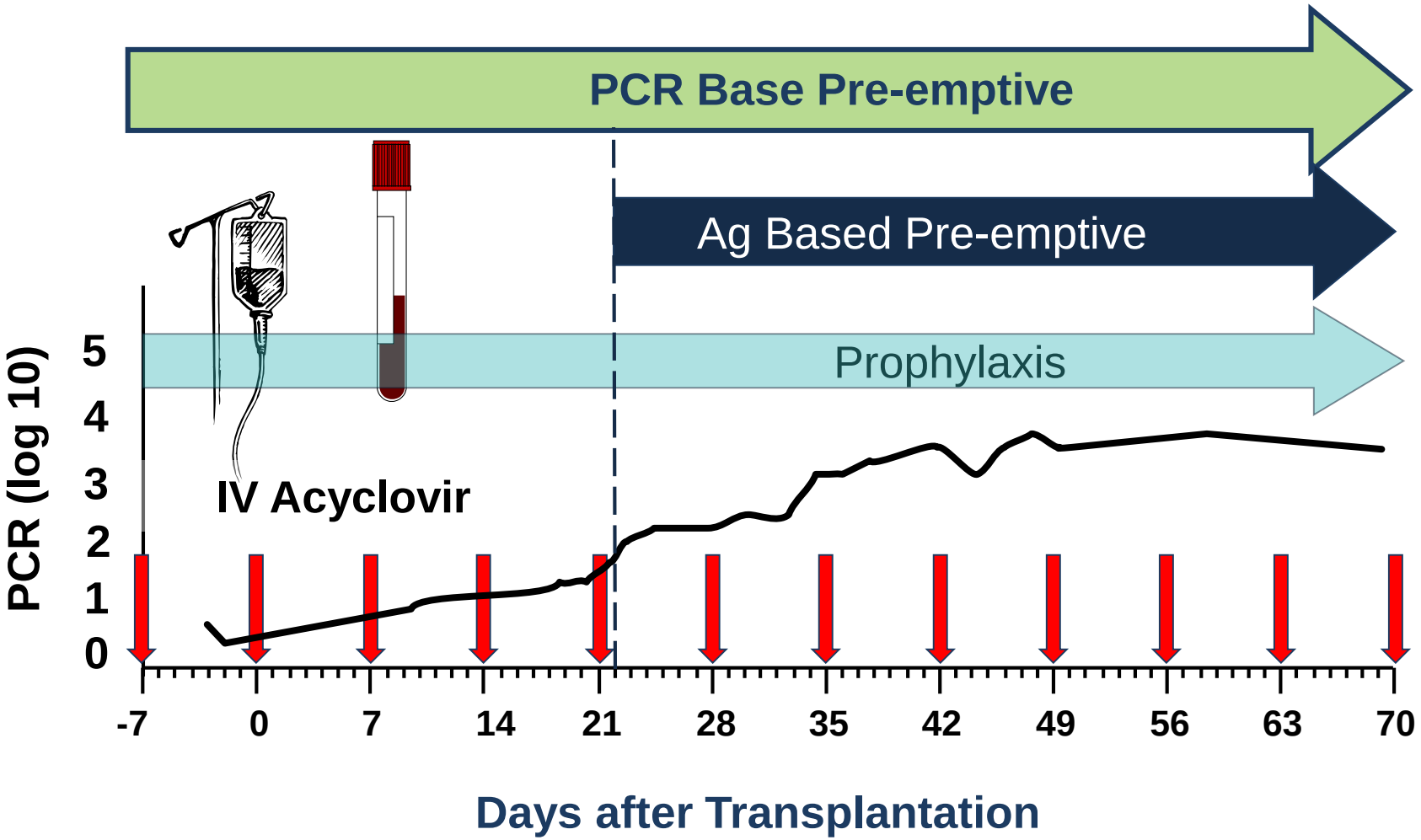
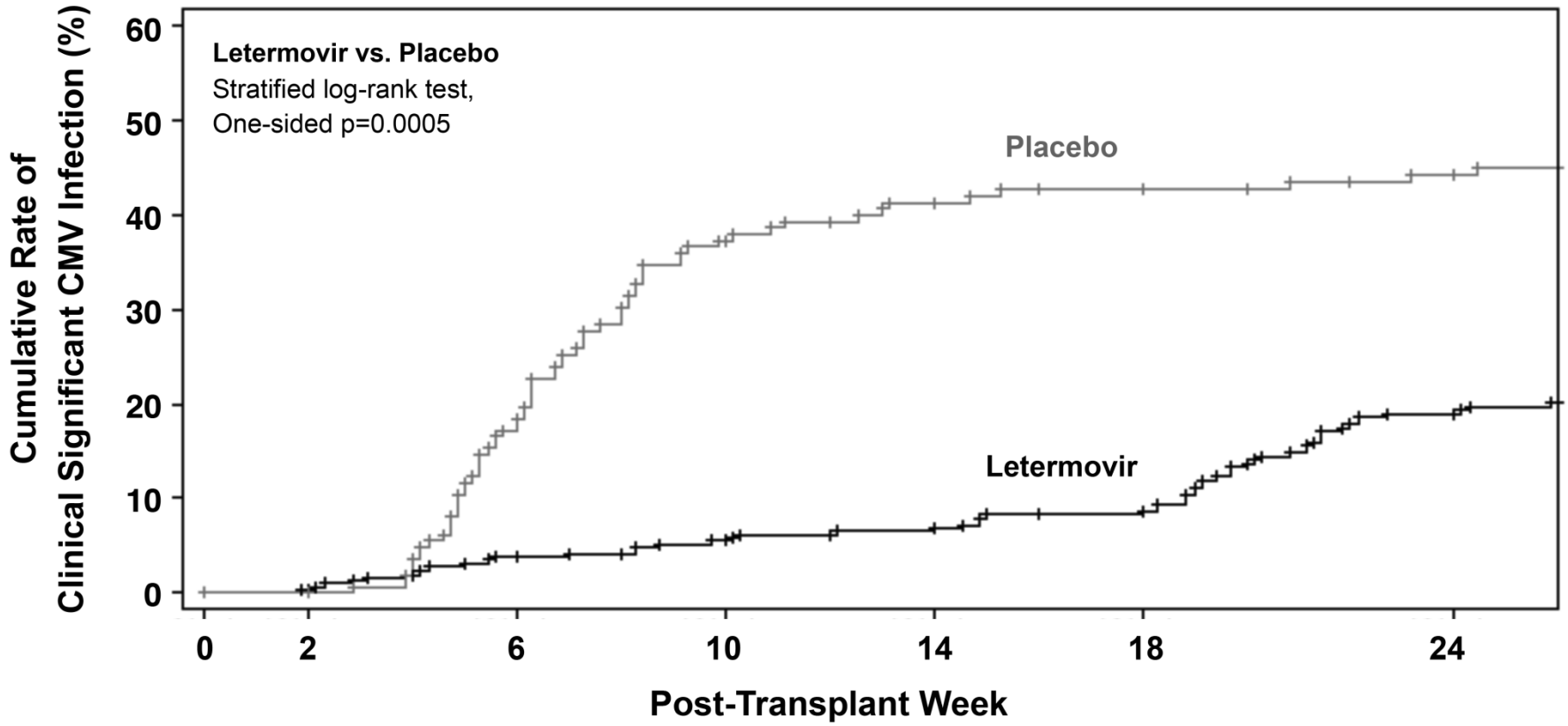


Figure 1. Time to Onset of Clinically Significant CMV Infection

Subjects with undetectable CMV DNA at Randomization



Letermovir	325	320	299	279	270	254	212
Placebo	170	169	135	96	85	77	70

Subjects at risk

Marty NEJM 2017

Direct Effects of CMV Infection

CMV Viral Syndrome

- Fever, malaise, myalgias
- Neutropenia, Leukopenia, thrombocytopenia, and other laboratory abnormalities

Tissue Invasive Disease

- Hepatitis
- Pneumonitis
- Colitis
- Carditis
- Nephritis
- Pancreatitis
- Retinitis

Late Post-Transplant Infections (>100 days)

Late Infections?

- CMV
- Herpes zoster
- Hepatitis A, Hepatitis B, Hepatitis E
- Encapsulated bacterial infections (pneumococcus)
- Fungal infections (intra-abdominal Mucor, Cryptococcus)
- EBV associated PTLD

Late Post-Transplant Infections (>100 days)

- Allotransplant patient presents at day 234, with fever, RUQ pain
- Chemistry panel, low Na
- CBC elevated WBC (13K)
- LFT's start high, but continue to rise (AST 2145 and ALT 3546)
- Hep A / Hep B and Hep C negative
- US of abdomen demonstrates small amount of ascites
- Patient's pain controlled with increasing amounts from morphine PCA
- Develops delirium

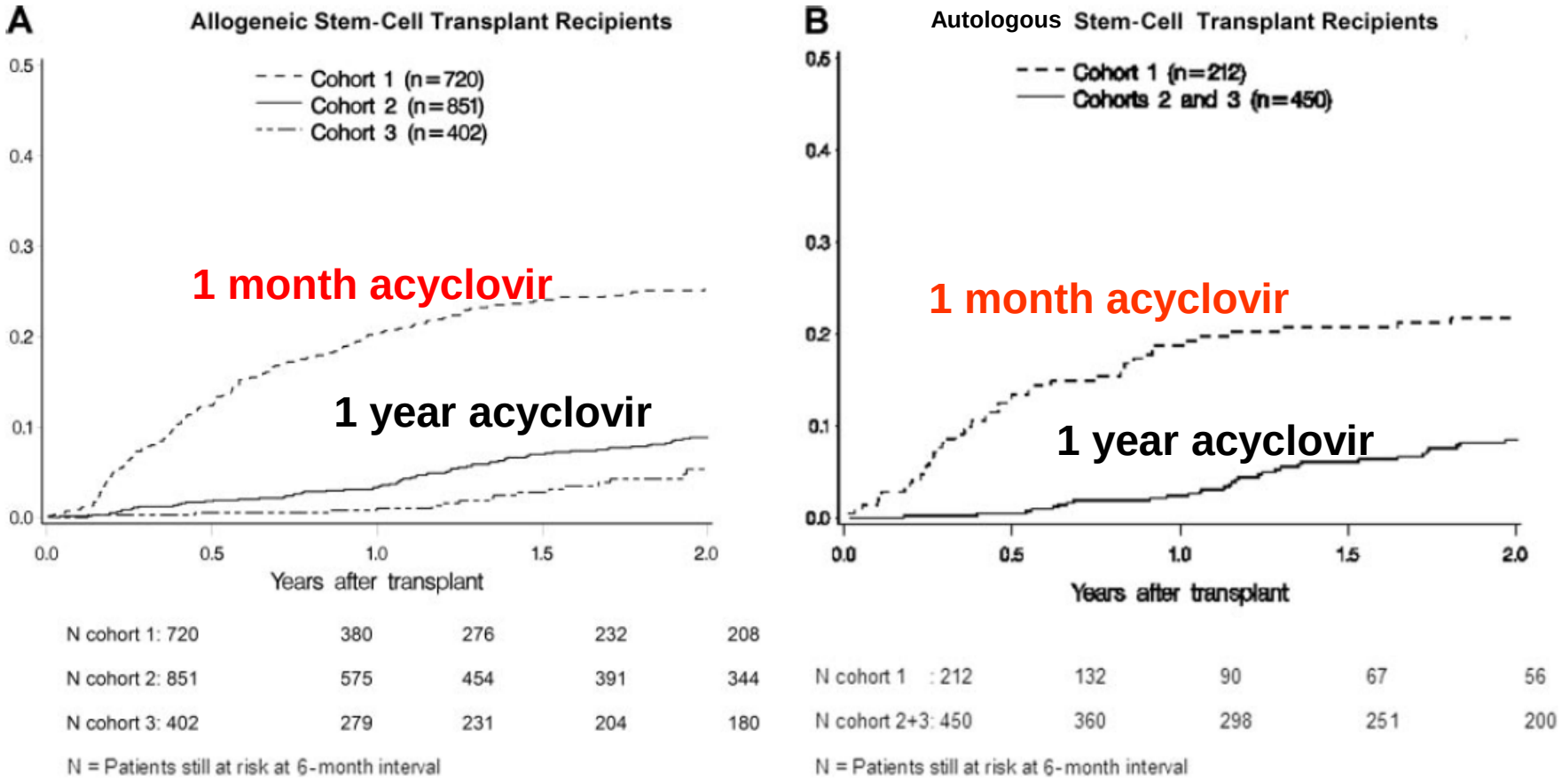
Day 2

Abdominal/Visceral Zoster

- Rare presentation of Herpes Zoster
- Triad of **severe abdominal pain, hyponatremia and elevated transaminases**
- Often presents without associated zoster rash initially
- VZV PCR diagnostic method of choice
- Treatment with high-dose acyclovir
- If treatment delayed may be associated with high rate of mortality
- Prevented with use of standard acyclovir prophylaxis

Varicella Zoster Prevention

Acyclovir Prophylaxis Post-HCT Prevents HZ after 1st year



From Erard Blood 2007;110(8):3071-7

Case

- 37 y/o female with AML, s/p G-CLAM
- Levofloxacin and voriconazole for prior pulmonary nodules
- Neutropenia for 12 days
- Develops neutropenic fever and found to have CoNS, treated with Vancomycin and Levofloxacin
- Recurrent fever at day 27
- Complains of cough and chest pain

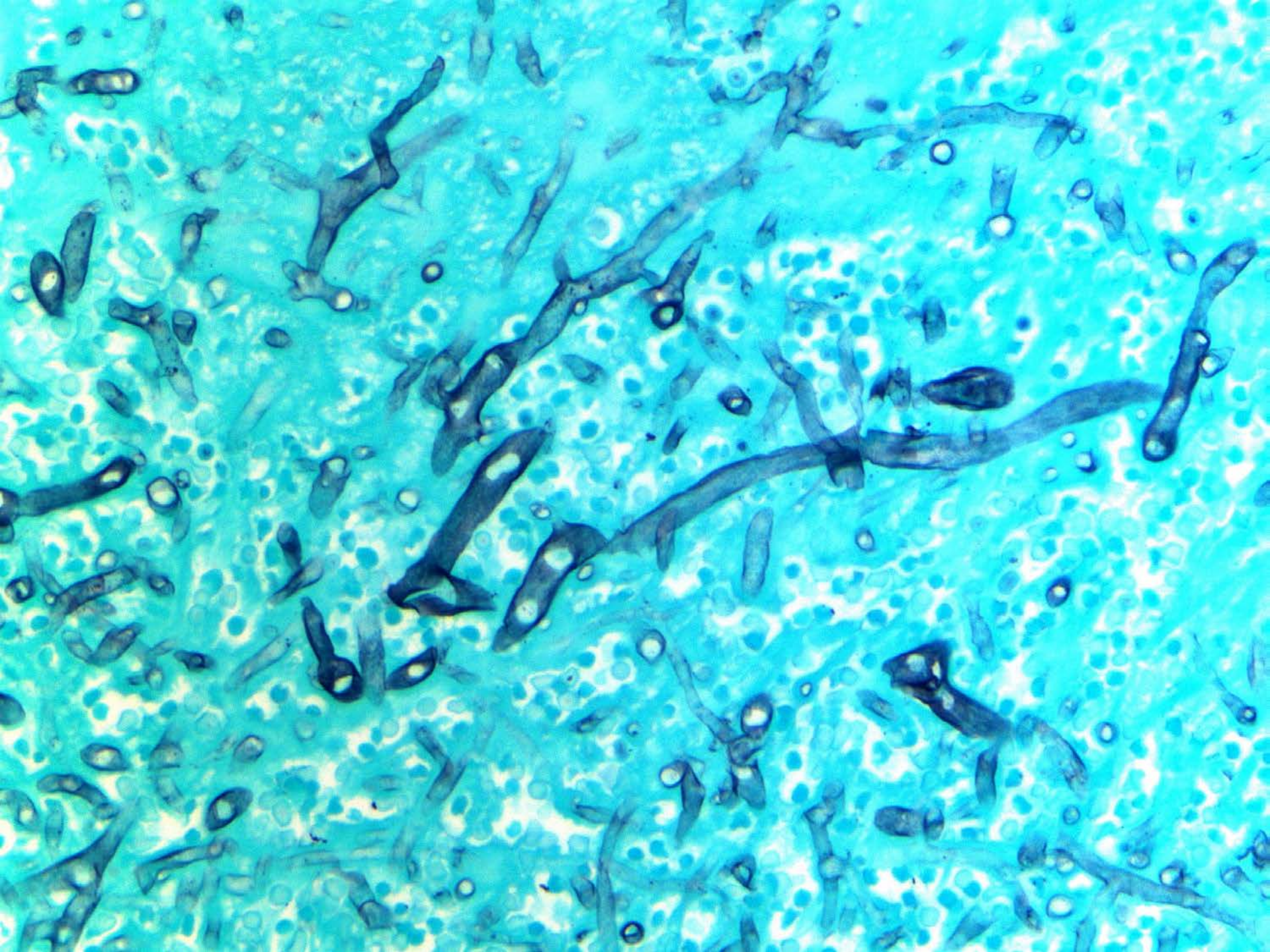
Mucorales spp.

- Fungi of the order Mucorales
- Ubiquitious mold found in dirt, decaying vegetation, decaying fruit and bread
- Grow very rapidly in petri dishes “blow lid of plates”
- Linked to severe disease
- Disease typically occurs in patients with high-risk features: trauma, high-iron levels, prolonged neutropenia, and steroids,
- Breakthrough for patients on azoles (particularly voriconazole)

Treatment

- Surgery
- Antifungal agents = particularly IV Ambisome
- Surgery
- Surgery
- Surgery

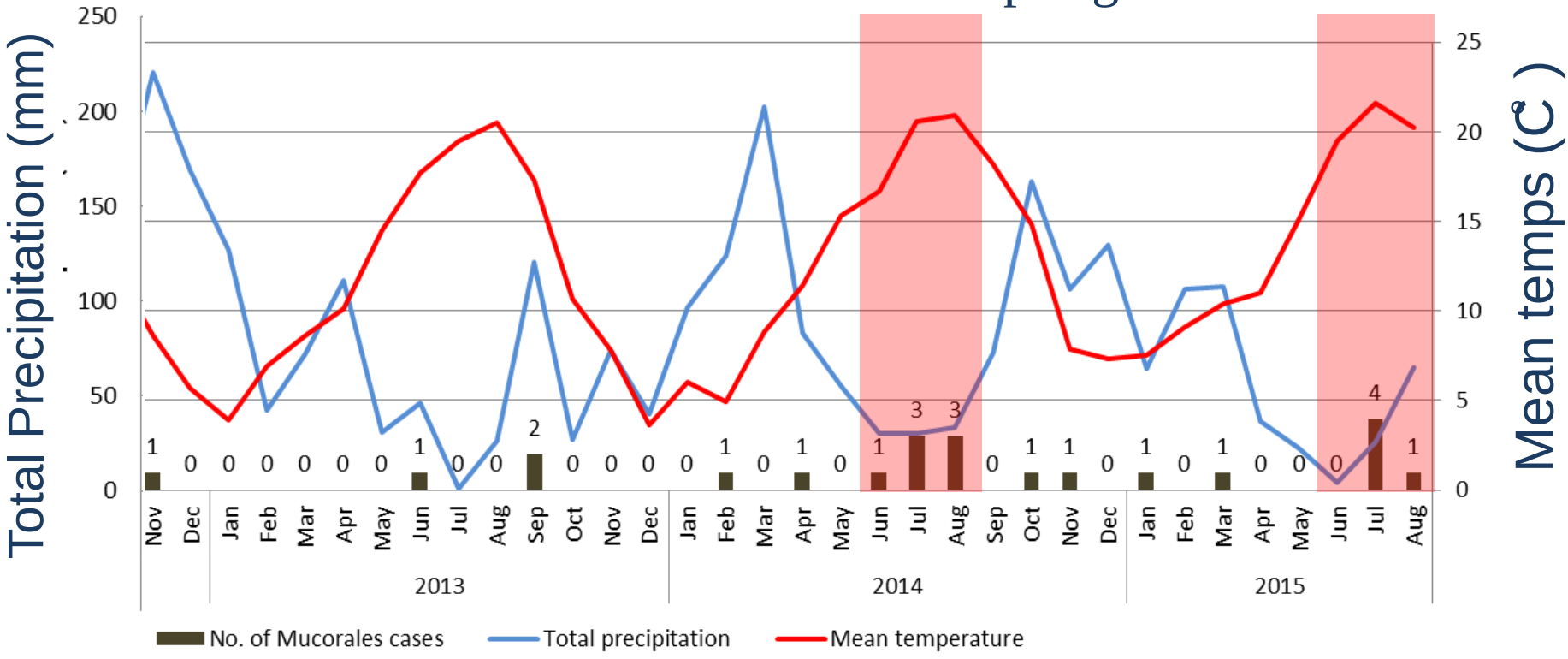

cm
1
2
3
4
5



Temperature and Mucorales?

Summer = 5.67 cases per 10,000 inpatient days

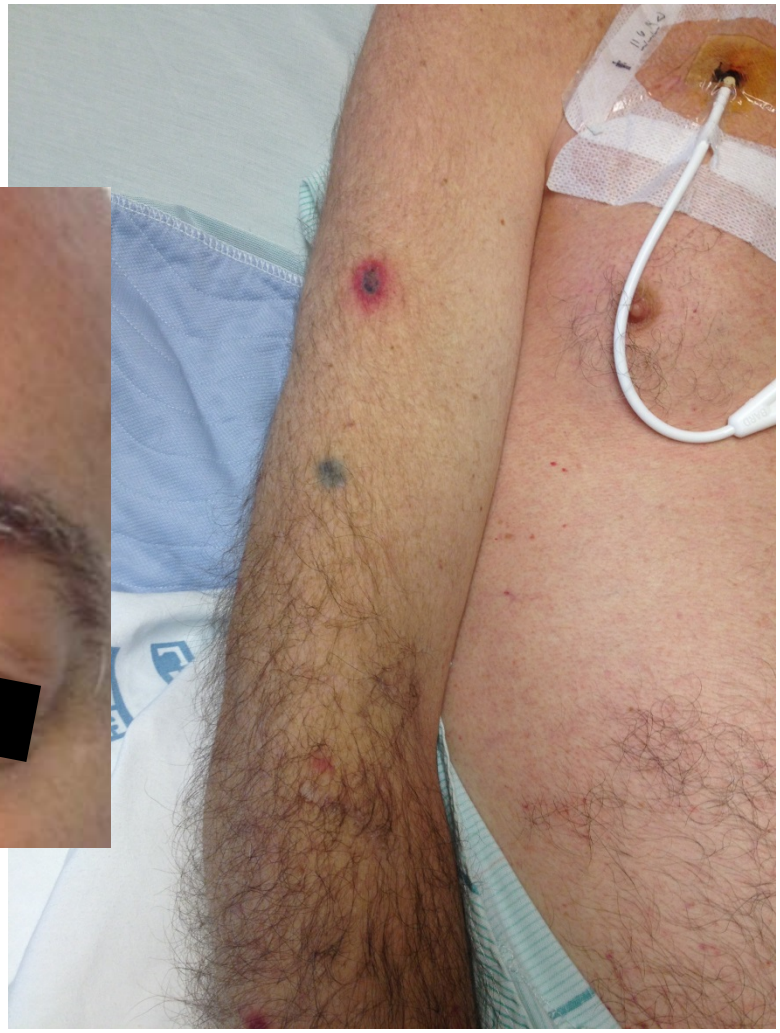
Fall = 4.10 Winter = 1.94 Spring 1.3



Sivagnanam ARIC 2017

FRED HUTCH

Case

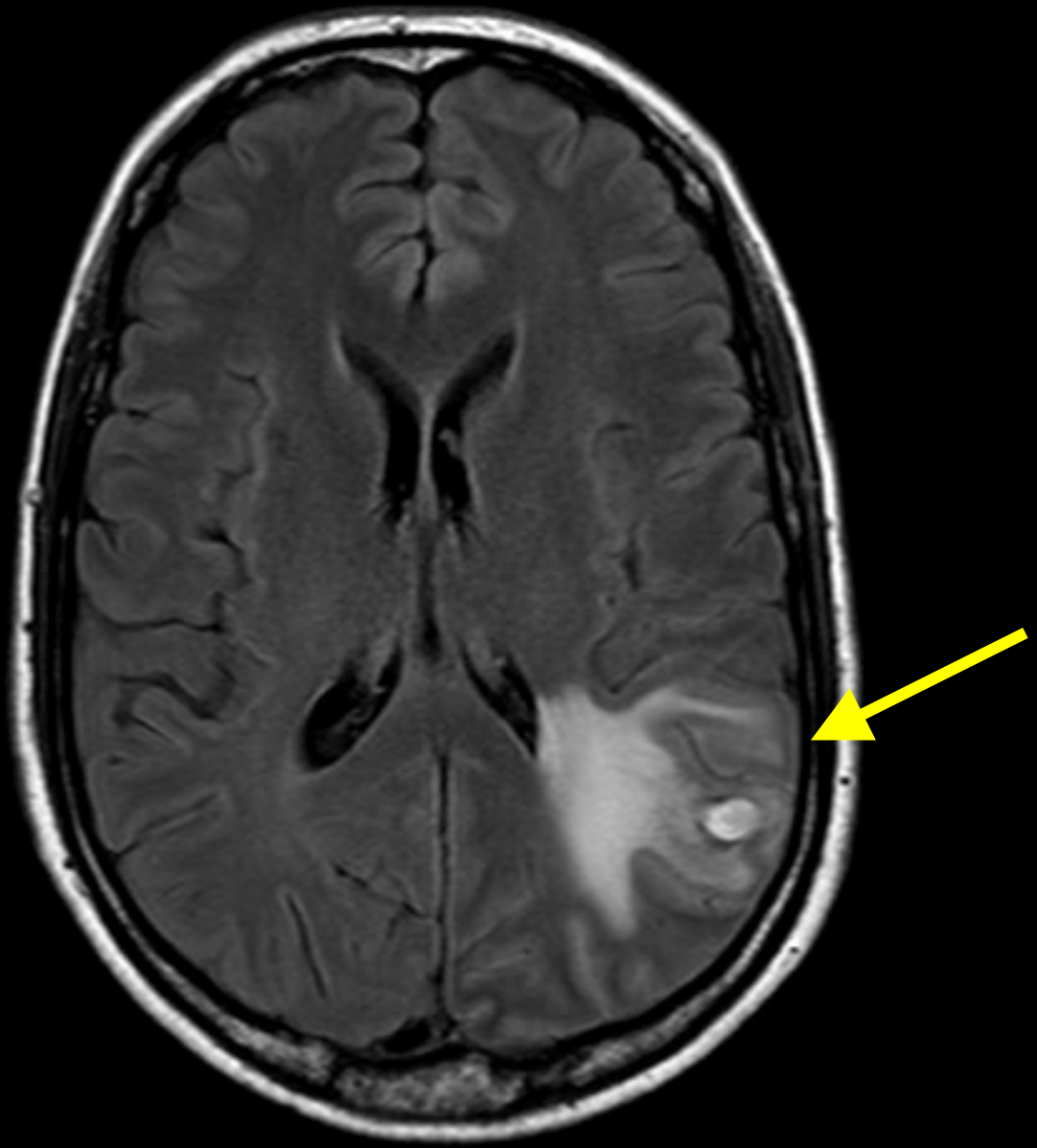


Antifungal briefly

- **Fluconazole** – Candida prophylaxis in HCT
- **Posaconazole** – standard prophylaxis for AML therapy
- **Voriconazole** – first choice for most Aspergillus species
- **Isavuconazole** – Aspergillus/Mucorales, less drug and drug/drug side-effects
- **IV liposomal Ampho B** – Breaktrough molds

56 y/o male with MM s/p autotransplant

- Had fever at home and then increasing confusion
- Developed grand mal seizure in ER during evaluation
- Transferred with abnormal brain lesion, on Ceftriaxone and Vancomycin
- Cultures reported as GNR/GPR in blood by outside hospital



Listeria monocytogenes

Epidemiology

Uncommon infection in the general population, transplant patients at increased risk

Listeria is anaerobic gram positive rod found commonly in soil, water, decaying vegetation and animals

Foodborne listeriosis is most common source for transplant recipients

In a CDC study 64% of people with listeria had at least one food source in their fridge that grew listeria[1]

Most common sources were ready-eat-foods, soft cheeses and deli meats

http://flickr.com/photo/80507002@N00/1879607602

Photo by Andre Karwath from Wikicommons

From wikicommons

1. Pinner, et al. JAMA 1992;267:2046-50

Cannabis? New Risks?

How often is MJ contaminated with mold?

- Study in Neth. found that 100% of all MJ + for fungus, compared to 64% in cigarettes[1]
  - Estimated to be 300 to 50,000 times more CFU/g mold on MJ compared to commercial cigarettes
- MJ cigarettes from 26 chronic users, found 73% grew *Aspergillus spp*, and spores easily passed into air sampler during smoking process[2]
  - 52% positive for Aspergillus precipitins in their blood, compared to 10% in controls
  - *Mucorales spp* found less frequently

Verwiej JAMA 2000 2. Kagen NEJM 1981 3. Moody NEJM 1982

New agents: Infections / Non-ID syndromes

- Bortezomib – VZV, CMV?
- Ruxolitinib – HBV, Cryptococcus, MTB
- TK inhibitors – CMV infection (e.g. disatinib)
- Ibrutinib – Aspergillus/Fungi
- Eculizimab – Meningococcal disease
- Idelalisib – CMV / PJP

New agents: Infections / Non-ID syndromes

- Bortezomib – VZV, CMV?
- Ruxolitinib – HBV, Cryptococcus, MTB
- TK inhibitors – CMV infection (e.g. disatinib)
- Ibrutinib – Aspergillus/Fungi
- Eculizimab – Meningococcal disease
- Idelalisib – CMV / PJP
- Non-infectious complications:
  - *PI3K inhibitors – pneumonitis*
  - *CAR-T cells – cytokine release syndrome*
  - Immune checkpoint inhibitor – diarrhea

Non-infectious Causes of Fever

Drug toxicity

Drug allergy

Drug fever

Underlying malignancy

Sweet's syndrome

Pulmonary embolism

Alveolar hemorrhage

Transfusion reaction

BOOP/IPS

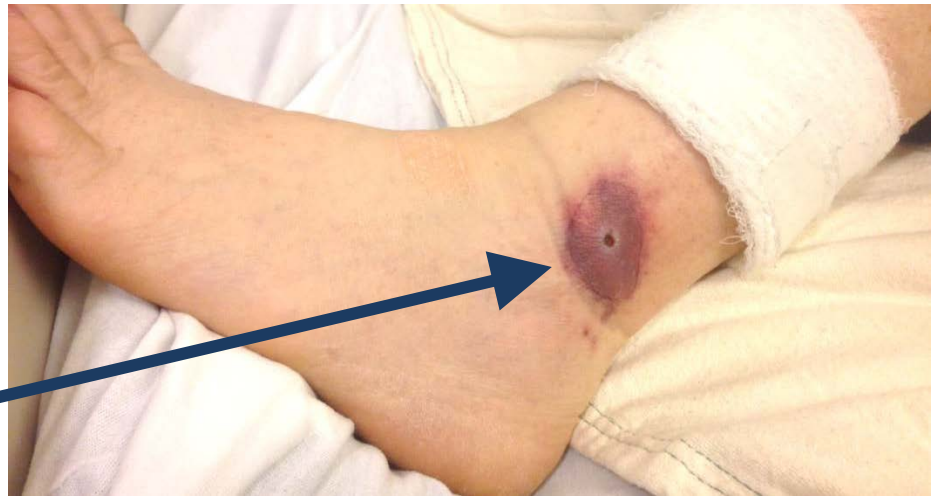
GVHD / Rejection

Don’t Forget Non-infectious Causes of Fever

Don’t Forget Non-infectious Causes of Fever

Sweet’s syndrome

Disseminated Aspergillus



Questions?

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Review Questions

11th Annual Virtual Comprehensive Hematology & Oncology Review Course
Table of Contents - Review Questions

EN2105GG Baik

A 62 year old man presented with back pain and was found to have a metastatic lesion in the L3 vertebral body without evidence of cord impingement on MRI. Biopsy showed metastatic squamous cell carcinoma with no PD-L1 expression by immunohistochemistry. CT scans of the chest, abdomen, and pelvis showed a bulky left hilar mass with bilateral mediastinal lymphadenopathy, as well as additional metastatic lesions in the left clavicle and right 8th rib. He completed palliative radiation to the L3 metastasis with good improvement of his pain. He has a non-productive cough and a 5 kg weight loss over the past 2 months. His ECOG PS is 1. Which is the most appropriate selection for first-line therapy?

1. Pembrolizumab
2. Carboplatin and pemetrexed
3. Carboplatin and paclitaxel and bevacizumab
4. Carboplatin, paclitaxel and pembrolizumab
5. Docetaxel and ramucirumab

A 70 year old woman with remote smoking history is found to have a LLL lung mass on a routine CXR obtained prior to an elective cholecystectomy. Biopsy of the lung mass reveals a TTF-1 positive adenocarcinoma and subsequent PET imaging shows FDG avid mediastinal nodes, small liver lesions and a left adrenal mass. Biopsy of the left adrenal mass confirmed the same adenocarcinoma. Molecular and PDL1 testing show that her tumor harbors EGFR exon 21 mutation (L858R) and 90% PD-L1 expressed. What is the next best step?

1. Pembrolizumab
2. Carboplatin and pemetrexed
3. Osimertinib
4. Osimertinib and pembrolizumab
5. Erlotinib and pembrolizumab

EN2105X Bhatia

A 75-year old man presents with progressive anorexia, weight loss, night sweats, fatigue and right-sided abdominal pain for the last few weeks. Imaging studies show widely disseminated metastases in multiple organs, including greater than 50% liver involvement. Brain MRI is unremarkable. Biopsy of a liver tumor reveals malignant melanoma. The patient recalls a history of primary cutaneous melanoma on the back that was diagnosed 5 years ago and treated with wide local excision. BRAF mutation analysis reveals presence of V600K mutation in the tumor tissue. Laboratory analyses reveal Hemoglobin 10, AST 75, ALT 85, ALK-P 575 and Total Bilirubin 2.2. His ECOG performance score is 2.

What will you recommend next?

1. High-dose bolus Interleukin-2 therapy
2. Anti-PD-1 monotherapy
3. Anti-PD-1 plus Anti-CTLA-4 combination
4. BRAFi plus MEKi
5. Hospice

A 62-year old woman with metastatic melanoma is currently receiving Ipilimumab plus Nivolumab therapy. She has received 3 doses every 3 weeks and is scheduled to receive the final dose today. 2 weeks ago, she started having diarrhea with 2-3 watery BMs/day, which has now progressed to 6-7 BMs/day. She reports mild pain/cramping, which is relieved after defecation. She denies blood or mucus in the stool. Her appetite is somewhat decreased, but she is trying to maintain adequate hydration and reports having a normal urine output.

What will you recommend next?

1. Administer the final dose of ipilimumab plus nivolumab today, but only after starting loperamide
2. Order stool test for Clostridium difficile; start empiric metronidazole.
3. Start corticosteroids, while trying to arrange for endoscopic evaluation
4. Inpatient hospitalization for urgent administration of infliximab

A 27-year old woman with metastatic melanoma has completed 2 doses of ipilimumab (3 mg/kg) plus nivolumab (1 mg/kg) recently. She is in clinic to discuss the results of her restaging radiologic studies performed at 6 weeks after initiation of therapy. The imaging studies show an increase in the size of her 2 pulmonary nodules (1.5 □ 2 cm and 1.2 □ 1.8 cm) and also the interval development of a new 0.8 cm nodule as compared to the baseline scans. There are no other sites of disease and she is asymptomatic except grade 1 pruritus and skin rash that started after the first dose.

What would you recommend next?

1. Start Ipilimumab at 10 mg/kg
2. Switch to Nivo 3 plus Ipi 1 mg/kg
3. Repeat imaging in 4-6 weeks
4. Start BRAFi plus MEKi, if BRAF V600 mutation is present

EN2105A Cassaday

A 21-year-old man presents with a white blood cell count of 38,000/mm^3, of which 90% are lymphoblasts, a platelet count of 110,000, and a hematocrit of 38%. Cytogenetics demonstrates the Philadelphia chromosome in 19 of 20 metaphases. He is treated with induction chemotherapy including imatinib, cyclophosphamide, vincristine, prednisone, and daunorubicin. He achieves a complete remission based on morphology, cytogenetics, and PCR assays of peripheral blood and marrow. He does not have a matched sibling. What treatment approach should be recommended?

1. Imatinib alone
2. Bosutinib alone
3. Imatinib plus consolidation and maintenance chemotherapy
4. Reduced-intensity unrelated donor hematopoietic cell transplantation
5. Standard-intensity unrelated donor hematopoietic cell transplantation

A 61-year-old man presents with a white blood cell count of 38,000/mm3, of which 90% are B lymphoblasts, a platelet count of 110,000, and a hematocrit of 38%. Cytogenetics demonstrates a complex karyotype in 19 of 20 metaphases. He is treated with induction chemotherapy including cyclophosphamide, vincristine, prednisone, pegaspargase, and doxorubicin. He achieves a complete remission based on morphology and cytogenetics, but minimal residual disease (MRD) is detected by flow cytometry. He then receives 2 cycles of Early Intensification, consisting of cyclophosphamide, vincristine, mercaptopurine, and pegaspargase. A repeat bone marrow examination now shows persistent/refractory disease, with 12% blasts by morphology. He does not have a matched sibling. What should be recommended now?

1. High-dose cytarabine based salvage chemotherapy
2. Blinatumomab
3. Ponatinib
4. Nelarabine
5. Reduced-intensity unrelated donor hematopoietic cell transplantation

EN2105Z Cerminara

KS is a 56 year old male with Philadelphia positive chronic myelogenous leukemia. He failed imatinib therapy and has been on dasatinib 100 mg daily for 9 months with evidence of complete cytogenetic response. He was recently hospitalized for fever and shortness of breath, and was found to have aspergillosis pneumonia. He was discharged on voriconazole 300 mg Q 12 hours. He presents in clinic today. You recommend:

1. Nothing at this time, continue to monitor patient's CML and pneumonia
2. Increase dasatinib to 140 mg daily
3. Decrease dasatinib to 20 mg daily
4. Decrease dasatinib to 40 mg daily

Which of the following agents do NOT need to be dose reduced for severe hepatic dysfunction?

1. Bortezomib
2. Everolimus
3. Pazopanib
4. Lenalidomide

WK is a 59 year old man with newly diagnosed ALL. He is undergoing treatment with Hyper-CVAD and high dose methotrexate/cytarabine. Upon presentation to the hospital he was started on intravenous fluids with sodium bicarbonate. He recently had a chest X-ray that showed bilateral pleural effusions. His medication list includes: multivitamin and naproxen 250mg po BID for arthritis. Pretreatment BMP and LFTs were within normal limits and urine pH was 6.4. However, recheck after infusion of methotrexate showed a bump in creatinine and creatinine clearance reduced to 40mL/min. Which of the following put the patient at risk for increased methotrexate toxicity?

1. Renal dysfunction with reduced creatinine clearance
2. Naproxen
3. Pleural effusions
4. All of the above

EN2105PP Chen

By what mechanism does radiation therapy treat malignancy?

1. Direct cytotoxicity via DNA damage
2. Disruption of tumor vasculature
3. Impairing cell membrane integrity and denaturing proteins
4. Release of neo-antigens facilitating immune recognition
5. All of the above

What characteristic of a cell indicates its sensitivity to radiation damage, and for cancers determines the theoretical optimal fractionation?

1. Oxygen enhancement ratio
2. The alpha/Beta ratio
3. Dose-depth profile
4. The Bragg peak
5. Nucleus:cytoplasm ratio

EN2105RR Chiorean

A 65-year old woman develops painless jaundice without fever. A CT scan demonstrates dilated biliary and pancreatic ducts and a hypodense mass in the head of the pancreas. There is no evidence of metastatic disease, superior mesenteric artery, or celiac axis involvement. Laboratory studies show total bilirubin of 8, CA19-9 is 200. An EUS and FNA are performed. Cytology reveals adenocarcinoma. What is the next step in management?

1. Proceed to pancreatico-duodenectomy
2. ERCP and biliary stent placement
3. Neoadjuvant chemotherapy

A 55-year old male develops abdominal pain and is found to have abnormal LFTs. An abdominal ultrasound is performed, which demonstrates multiple lesions in the liver. A CT scan shows hypodense liver lesions and a mass in the body of the pancreas measuring 5 cm and encasing the celiac axis. One of the liver masses is biopsied, with pathology returning adenocarcinoma consistent with a pancreaticobiliary primary. The patient's ECOG performance status is 0. He tells you that he wants to be aggressive. What is your treatment recommendation?

1. Gemcitabine
2. Gemcitabine + Nab-paclitaxel
3. Gemcitabine + Capecitabine
4. FOLFIRINOX (folinic acid (leucovorin), fluorouracil, irinotecan, oxaliplatin)
5. 2 or 4 are both effective options for patients with good performance status

A 58-year old female develops painless jaundice. A CT scan demonstrates dilated biliary ducts and a hypodense mass in the head of the pancreas with a dilated pancreatic duct. There is no evidence of metastatic disease, superior mesenteric artery or celiac axis involvement. A EUS and FNA are performed. Cytology reveals adenocarcinoma. The patient undergoes a "Whipple" operation. Pathology is notable for a lesion that extends outside the pancreas (T3) and 1 out of 14 nodes are positive for adenocarcinoma (N1). Following surgery, the patient recovered well, has ECOG performance status 0, and she comes to you for advice. What is the most appropriate next course of action supported by randomized clinical trials?

1. Adjuvant Gemcitabine plus Nab-paclitaxel for 6 months.
2. Adjuvant Gemcitabine plus Capecitabine for 6 months.
3. Adjuvant Gemcitabine for 6 months.
4. Adjuvant modified FOLFIRINOX (folinic acid (leucovorin), fluorouracil, irinotecan, oxaliplatin) for 6 months.

EN2105NN Cohen Adjuvant

For patients with resected stage 3 colon cancer, which of the following is NOT correct:

1. 3 months of adjuvant chemotherapy is sufficient for low-risk patients.
2. Chemotherapy-induced peripheral neuropathy leads to permanent neuropathy in a subset of patients.
3. Chemotherapy should be initiated 4-8 weeks from surgery
4. Adjuvant cetuximab is beneficial for KRAS-wildtype disease

A 56yo man presents with a low rectal mass. MR pelvis shows a T4N1 cancer that is below the peritoneal reflection and 2cm from the anal verge. The preferred treatment plan is:

1. Long-course chemoradiation, surgery, adjuvant chemotherapy
2. Short-course radiation, surgery, adjuvant chemotherapy
3. Long-course chemoradiation, neoadjuvant chemotherapy, surgery
4. Surgery, adjuvant chemotherapy, adjuvant chemoradiation

EN2105NO Cohen Metastatic

The relevant pair of biomarkers and associated targeted therapy(s) for metastatic colorectal cancer is:

1. BRAF / encorafenib + cetuximab
2. EGFR / erlotinib
3. HER2 / trastuzumab
4. NRAS / cetuximab or panitumumab

Which of the following chemotherapy regimens is useful for metastatic colorectal cancer?

1. Trifluridine-tipiracil/nivolumab for a patient refractory to 5-FU, oxaliplatin, irinotecan, and cetuximab
2. Oxaliplatin/cetuximab for a RAS/RAF wildtype patient unable to tolerate 5-FU
3. FOLFIRI + bevacizumab after progression on FOLFOX + bevacizumab
4. Maintenance oxaliplatin after 4 months of FOLFOX with a partial response

EN2105Y Coveler

InterAACT was an international randomized phase II trial in the first-line setting of advanced anal and it demonstrated that carboplatin plus paclitaxel when compared to cisplatin and fluorouracil had less toxicity and

1. A greater objective response rate with a similar PFS and OS.
2. A similar objective response rate with a greater PFS and no difference in OS.
3. A greater objective response rate with a greater PFS and OS.
4. A similar objective response rate and similar PFS with a trend towards improved OS.

In the treatment of anal cancer, studies have shown:

1. Induction cisplatin and fluorouracil followed by radiation, cisplatin and fluorouracil improved colostomy free survival.
2. Induction cisplatin and fluorouracil followed by radiation, cisplatin and fluorouracil improved disease free survival.
3. Radiation with fluorouracil and mitomycin C followed by adjuvant fluorouracil and mitomycin C demonstrated improved overall survival.
4. Induction chemotherapy, adjuvant chemotherapy and replacing mitomycin C with cisplatin was no better than radiation therapy and fluorouracil plus mitomycin C in the treatment of non metastatic anal cancer.

EN2105B Cowan

What is the best systemic treatment for a patient with newly diagnosed transplant-eligible multiple myeloma based on the results of randomized phase 3 trials?

1. Lenalidomide, bortezomib, and dexamethasone (RVd)
2. Carfilzomib, lenalidomide, and dexamethasone (KRd)
3. Daratumumab, Carfilzomib, lenalidomide, and dexamethasone (Dara-KRd)
4. None of the above

You are seeing a 56-year-old man with relapsed multiple myeloma in clinic. He was diagnosed 3 years ago, and underwent induction RVd followed by autologous stem cell transplantation, followed by lenalidomide maintenance. He is relapsing on lenalidomide maintenance, 10 mg daily. Which of the following would be the next most reasonable treatment option?

1. Increase lenalidomide to 25 mg daily
2. Daratumumab, carfilzomib, and dexamethasone (Dara-Kd)
3. Daratumumab, bortezomib and dexamethasone (Dara-Vd)
4. Carfilzomib, lenalidomide, and dexamethasone. (KRd)
5. Answers 2 & 3

Which of the following is not considered a high-risk chromosomal change in multiple myeloma?

1. 13q
2. Duplication 1q
3. t(4;14)
4. Del(17p)

EN2105SS Dorff

A 72 year old man presents with a new diagnosis of prostate cancer, with PSA of 7.5 and no palpable abnormality on digital rectal exam. Biopsy reveals Gleason 3+3 adenocarcinoma in 1 core from the right base involving 10% of the tissue; all 11 other cores do not reveal malignancy but one core from the right side does contain HG-PIN. He opts for active surveillance. Which of the following bestdescribes an appropriate surveillance plan?

1. PSA every 6 months, CT abdomen and pelvis plus bone scan annually
2. PSA every 3 months, digital rectal exam every 6 months, confirmatory biopsy after 6-12 months and biopsy every 2-5 years
3. PSA every 3 months, digital rectal exam every 6 months, multiparametric MRI annually
4. PSA every 6 months, digital rectal exam annually, and biopsy every year

A 70 year old man presents with back pain, and is found to have PSA of 150. Imaging reveals 3 osseous metastases in the pelvis and lumbar spine. Biopsy of the prostate confirms Gleason grade group 4 prostate cancer. He has no major medical comorbidities. Which of the following agents would be least likely to be beneficial based on randomized phase 3 data? '

1. Abiraterone
2. apalutamide
3. docetaxel
4. enzalutamide
5. radiation to the prostate primary

A 65 year old man presents for continued monitoring of metastatic prostate cancer, which was initially treated with LHRH + up-front docetaxel, and then abiraterone + prednisone when CRPC developed. After 15 months of good PSA response with an undetectable nadir, his PSA has started to rise. Last visit his PSA was 2.5 ng/mL. Today he reports pain at site of a known L3 bone metastasis, which is relieved with hydrocodone/acetaminophen as needed. His PSA is 8.5 ng/mL and testosterone is 20 ng/dL. Bone scan shows two new lesions in the L2 and L5 vertebral bodies and CT reveals several new 1-2 cm lung nodules, suspicious for metastatic disease. Performance status is an ECOG 1. Which of the following would be the most appropriate treatment recommendation for the patient at this time?

1. Sipuleucel-T
2. Cabazitaxel
3. Radium223
4. Niraparib

EN2105WW Eaton

Which of the following treatments should be recommended for the prevention of chemotherapy induced peripheral neuropathy?

1. Acetyl-L-carnitine
2. Calcium/Magnesium
3. Vitamin E
4. Pyridoxine (B6)
5. None of the above

Which of the following factors is predictive of increased likelihood of experiencing chemotherapy related nausea and vomiting?

1. Male gender
2. Younger age
3. History of heavy alcohol use
4. Good performance status
5. Use of antidepressants

EN2105M Fertrin Iron Metabolism Disorders and Hemolytic Anemias

A 31-yo F with sickle cell anemia (HbSS) is admitted to the hospital for vaso-occlusive crisis for the third time this year. She had been lost to follow up and had stopped all medications. All of the following therapeutic options are appropriate, EXCEPT:

1. L-glutamine
2. Hydroxyurea
3. Folic acid
4. RBC exchange transfusions

An 18-yo M knows he has sickle cell disease since childhood and has never been transfused. His CBC shows Hb 8.0, Ht 28%, MCV 71fL, MCH 24pg, reticulocyte count 12%, WBC 15,400 with neutrophilia, platelets 440,000, frequent sickled RBCs, occasional target cells. Hemoglobin electrophoresis shows HbS 87%, HbA2 5.8% (RR<4%), HbA 4%, HbF 3% (RR<1%). The correct diagnosis is:

1. Sickle cell anemia (HbSS)
2. Sickle beta zero thalassemia
3. Sickle beta plus thalassemia
4. Sickle cell anemia/alpha thalassemia

A 24-yo M with beta thalassemia major comes in for his transfusion with Hb 8.0g/dL, asymptomatic. He usually receives 2 units of packed RBCs every 3 weeks and is on iron chelation with minimum dose of deferasirox. His latest ferritin is 800ug/L. How should he be managed?

1. Increase transfusion volume to 3 RBC units aiming for pre-transfusion Hb>9g/dL and stop chelation until ferritin is above 1,000ug/L
2. Increase transfusion volume to 3 RBC units aiming for pre-transfusion Hb>9g/dL and continue chelation regardless of ferritin
3. Remain on 2 RBC units per transfusion since he is asymptomatic and stop chelation until ferritin is above 1,000ug/L
4. Remain on 2 RBC units per transfusion since he is asymptomatic and continue chelation regardless of ferritin

EN2105P Fertrin Hemoglobin Disorders

A 27-yo M with Crohn's disease is found to have Hb 8.2g/dL, MCV 73fL, MCH 22pg, WBC and platelets within normal limits, low ferritin 10ug/L, low transferrin saturation 6%, and elevated CRP 12mg/dL. How should he be managed?

1. Oral iron
2. Intravenous iron
3. Combination of oral and intravenous iron
4. It is anemia of inflammation, he should improve his control of the Crohn's disease

A 34-yo F develops progressive fatigue and dyspnea on exertion. Her labs show: Hb 5.6g/dL, Ht 16%, MCV 105fL, MCH 34pg, WBC and platelets within normal limits, reticulocytes 14%, elevated LDH 475U/L, bilirubin 4.0mg/dL with direct bilirubin 0.5mg/dL, undetectable haptoglobin. Peripheral blood smear shows frequent spherocytes and DAT is positive, so an autoimmune hemolytic anemia is suspected. What do you expect to find in the DAT and what would be an appropriate first-line treatment?

1. DAT positive for C3d; rituximab and bendamustine
2. DAT positive for C3d; corticosteroids
3. DAT positive for IgG; rituximab and bendamustine
4. DAT positive for IgG; corticosteroids

A 46-yo M is referred because of a ferritin of 500ug/L with a transferrin saturation of 85%. He is asymptomatic and is found to be a homozygote for HFE C282Y. How should he be managed?

1. Start phlebotomy immediately
2. Start phlebotomy when ferritin reaches 1,000ug/L
3. Start phlebotomy when transferrin saturation reaches 100%, regardless of ferritin
4. Start phlebotomy if there is evidence of end organ damage

EN2105Q Garcia

In patients with cancer-associated venous thromboembolism, direct oral FXa inhibitors (when compared to low molecular weight heparin):

1. cause less major bleeding
2. are at least as effective at preventing recurrent VTE
3. have been shown to improve overall survival
4. are associated with decreased patient satisfaction scores

For a patient who is taking Apixaban 5 mg PO BID and requires a low risk interventional procedure (e.g. colonoscopy), the best approach for perioperative anticoagulation would be:

1. discontinue Apixaban 5 days prior to the procedure and do not prescribe bridging
2. discontinue Apixaban 5 days prior to the procedure and initiate bridging therapy with low molecular weight heparin, to be stopped 24 hours preprocedure
3. discontinue Apixaban 24 to 48 hours prior to the procedure and do not prescribe bridging
4. perform the procedure without interruption of Apixaban

EN2105N Gerds

A 73-year-old woman with a 2-year history of anemia presents to emergency room with a hemoglobin 6.2 g/dL and severe shortness of breath. Blood counts also show a WBC of 5.2 x 109/L, ANC 1.56 x 109/L, hematocrit of 18%, MCV of 110 fL, and platelet count of 657 x109/L. On the peripheral blood smear, schistocytes are absent, and there are very few reticulocytes. TSH, vitamin b12, and folate levels are normal. A bone marrow aspiration and biopsy are performed. On the aspirate smear, bone marrow blast count was 3% by morphology, and micromegakaryocytes were seen. She received 2 units of red blood cells with immediate improvement in her symptoms. Cytogenetic testing on the marrow identifies deletion 5q 31-33 in 18/20 metaphases. Her serum erythropoietin level is 580 U/L.

Which of the following is the most appropriate next step in treatment?

1. Azacitidine 75 mg/m2, days 1-7 every 28 days
2. Decitabine 20 mg/m2, days 1-5 every 28 days
3. Allogeneic transplantation
4. Lenalidomide 10 mg/day, days 1-28 every 28 days
5. Induction chemotherapy with an anthracycline and cytarabine (7+3)

A 45-year-old man presents to his primary care doctor with easy bruising and shortness of breath. Blood counts are obtained and reveal a WBC 0.2 x109/L, absolute neutrophil count of 50 x109/L, hemoglobin of 8 g/dL, hematocrit of 24.5%, MCV of 107 fL, and a platelet count of 6 x109/L. He receives both platelet and red cell transfusions. A bone marrow aspirate and biopsy are performed. On the aspirate smear, he is found to have a bone marrow blast count of 15% by morphology. Concurrent cytogenetics show del 7q in 20/20 metaphases. Human leukocyte antigen (HLA) typing has been completed with the intent of doing a myeloablative transplant in 2 to 4 months once a donor has been identified. Which of the following are is the most appropriate next step in treatment prior to transplantation?

1. Lenalidomide 10 mg/day, days 1-28 every 28 days
2. Azacitidine 75 mg/m2, days 1-7 every 28 days
3. Anti-thymocyte globulin and cyclosporine (immunosuppressive therapy)
4. Careful observation and transfusion support
5. G-CSF and an erythropoiesis stimulating agent (growth factor support)

A 68 year-old woman was found to have anemia on a routine blood work. She denies any previous history of anemia, and had a normal colonoscopy 8 months ago. Exam shows a few ecchymoses on the arms and legs.

Laboratory studies show:
White Blood Cell Count 2,300 /uL
Absolute Neutrophil Count 980 /uL
Hemoglobin 8.3 g/dL
MCV 99 fL
Platelet Count 74,000 /uL
She then underwent a bone marrow biopsy and aspirate that did not identify any evidence of dysplasia. Approximately 2% of the cells on a 500-cell differential of the aspirate were blasts. Metaphase cytogenetics revealed an abnormal female karyotype: 46,XX,del(7q) [7]/46,XX[13].

Which of the following best describe the diagnosis?

1. Myelodysplastic syndrome
2. Clonal hematopoiesis of undetermined potential
3. Acute myeloid leukemia
4. Clonal cytopenia of undetermined potential
5. Idiopathic cytopenia of undetermined potential

EN2105R Gernsheimer

Which of the following statements about ITP is true?

1. The main cause of thrombocytopenia is antibody mediated platelet destruction
2. A lack of platelet production is the cause of thrombocytopenia in ITP
3. Increased thrombopoietin levels are found in ITP
4. Thrombocytopenia in ITP is caused by both

When considering thrombocytopenia in pregnancy

1. It is most commonly caused by autoimmune disease
2. Incidental (gestational) thrombocytopenia affects approximately 10% of pregnant women
3. Women with gestational thrombocytopenia have a 10% incidence of delivery of a thrombocytopenic baby
4. Epidural anesthesia should not be offered to women with platelet counts under 100,000

Heparin Induced Thrombocytopenia (HIT):

1. Can be adequately treated with rivaroxaban
2. Is an absolute contraindication to cardiac surgery in the future
3. The gold standard test is the serotonin release assay
4. The gold standard test is the ELISA assay

EN2105W Goulart

What histologic subtype constitutes a contraindication for surgery in malignant pleural mesothelioma (MPM)?

1. Epithelioid
2. Sarcomatoid
3. Biphasic
4. Sarcomatoid and biphasic
5. All of the above

What is the role of immune checkpoint inhibitors (ICIs) in unresectable malignant pleural mesothelioma (MPM)?

1. Investigational, with current data indicating a promising role as first-line therapy.
2. Investigational, with current data indicating a promising role as second-line therapy.
3. No role exists for ICIs in MPM.
4. ICIs have become the standard of care as second-line therapy.
5. ICIs have become the standard of care as first-line therapy.

What is the prognostic implication of detecting BAP-1 mutations in tumor specimens of patients diagnosed with epithelioid malignant pleural mesothelioma (MPM)?

1. Germline BAP-1 mutations have no prognostic role.
2. Germline BAP-1 mutations are associated with inferior overall survival.
3. Germline BAP-1 mutations are associated with superior overall survival.
4. Somatic BAP-1 mutations are associated with superior overall survival.
5. Somatic and germline BAP-1 mutations are associated with superior overall survival.

EN2105C Graf

An otherwise healthy 48 yo man with grade 1/2 follicular lymphoma was treated with 6 cycles of bendamustine and rituximab due to symptoms from bulky disease in the neck and groin. Treatment was well-tolerated and a post-treatment PET/CT showed complete metabolic response, with a 5-PS of 2. Fifteen months later he re-presented with growing lymphadenopathy in the right cervical region causing discomfort. Cross-sectional imaging showed disease in multiple lymph node chains and an excisional node biopsy showed grade 1/2 follicular lymphoma with molecular analysis confirming *EZH2* wild-type status. Which of the following is preferred?

1. Repeat course of B-R, with interim scan after 1st 3 cycles to confirm responsive disease
2. Tazemetostat, noting that *EZH2* mutation is not required for use
3. Radiation alone to the symptomatic disease
4. Obinutuzumab + CHOP followed by consideration of high dose therapy and autologous stem cell rescue

Regarding selection of an anti-CD20 antibody for initial treatment of indolent B-NHL, the following statement is correct:

1. The GALLIUM study established superior efficacy and less toxicity of obinutuzumab compared to rituximab for frontline FL treatment
2. Obinutuzumab is designed for improved natural killer cell response with antibody dependent cell-mediated cyto-toxicity
3. Both obinutuzumab and rituximab have available formulations for subcutaneous administration, but a first intravenous dose is required
4. Maintenance anti-CD20 antibody after chemoimmunotherapy induction for FL is associated with improved overall survival

EN2105XX Greenlee

What are the reasons and/or beliefs that some oncology patients use complementary, alternative and/or integrative medicine?

1. Increase survival
2. Increase efficacy, prevent and treat side effects of conventional therapies
3. Treat existing comorbidities
4. Improve quality of life
5. All of the above

What is the order of “the most evidence” to the “least evidence” supporting the use of these therapies with oncology patients:

1. Dietary/botanical supplements, mind-body therapies, acupuncture
2. Mind-body therapies, acupuncture, dietary/botanical supplements
3. Acupuncture, dietary/botanical supplements, mind-body therapies

ASCO has endorsed evidence-based guidelines on the use of specific integrative therapies during oncology care.

1. True
2. False

EN2105BB Gwin

A 33 year old woman with a BRCA1 mutation is found at lumpectomy to have a 2.5 cm high grade, ER negative and HER2 negative tumor. The sentinel node biopsy is negative. Which chemotherapy regimen is *not* appropriate?

1. AC followed by paclitaxel
2. TAC (docetaxel, Adriamycin, and cyclophosphamide)
3. Carboplatin and gemcitabine
4. CMF (cyclophosphamide, methotrexate, and 5-FU)

The previous patient now wants to have a bilateral mastectomy because she was told that her survival from breast cancer in the next 5 years will be improved compared to the lumpectomy alone followed by radiation. You tell her that this information is:

1. True
2. False

A 45-year-old woman has a clinical stage III, HER2 amplified breast cancer with palpable lymph nodes. You offer her AC-THP or TCHP. Her EF is 67% and she has no history of HTN. You tell her that the risk of symptomatic congestive heart failure if she receives AC-THP is:

1. 1-3%
2. 3-5%
3. 6-8%

EN2105G Halpern

A 68-year-old man is evaluated for a 3-year history of dyspnea on exertion. He experiences no headaches or blurred vision. Medical history is notable for a stroke 2 years ago. He is a smoker with an 80-pack-year smoking history. Medications are hydrochlorothiazide, lisinopril, aspirin, and simvastatin.

On physical examination temperature is 36.7 °C (98.0 °F), blood pressure is 145/84 mm Hg, pulse rate is 88/min, and respiration rate is 16/min. Oxygen saturation breathing ambient air is 88%. He has facial plethora. He has no carotid bruits. Cardiac sounds are distant. Pulmonary examination reveals distant breath sounds with scattered wheezing. No hepatosplenomegaly is palpated. No digital clubbing is observed.

Laboratory studies show a hemoglobin level of 18.2 g/dL (182 g/L), leukocyte count of 8000/µL (8×10^9/L) with a normal differential, and platelet count of 225,000/µL (225×10^9/L). Erythropoietin level is 30 mU/mL (30 U/L). The patient is advised to quit smoking.

Which of the following is the most appropriate next step in management?

1. Bone marrow biopsy
2. JAK2 V617F testing
3. Phlebotomy
4. Supplemental oxygen

A 67-year-old man is evaluated during follow-up consultation after thrombocythemia is discovered incidentally on a routine health maintenance examination. His medical history is notable for depression and he takes sertraline only. On physical examination, he is afebrile, blood pressure is 115/72 mm Hg, pulse rate is 72/min, and respiration rate is 18/min. Cardiac evaluation reveals a regular rate and rhythm with no murmurs. Results of laboratory studies show a hemoglobin level of 15 g/dL (150 g/L), leukocyte count of 5600/µL (5.6×10^9/L), and platelet count of 770,000/µL (770×10^9/L). Bone marrow biopsy shows megakaryocytic proliferation without fibrosis and molecular testing finds a JAK2 V16F mutation, consistent with ET.

Which of the following is the most appropriate treatment?

1. Anagrelide plus low-dose aspirin
2. Hydroxyurea plus low-dose aspirin
3. Ruxolitinib
4. Warfarin
5. Observation

EN2105HH Handford

Which statement regarding variants of uncertain significance (VUS) is false?

1. Clinically, they should be treated the same as a positive result.
2. Follow-up tests such as RNA studies may be helpful.
3. Screening recommendations should be based on the family history.
4. You will find more of them with NextGen panels than with targeted sequencing.

Which patient is least likely to need genetic testing?

1. A patient with 100 adenomatous colon polyps
2. A patient with cervical cancer diagnosed at age 35
3. A patient with MSI-high colon cancer
4. A patient with ovarian cancer and no family history of cancer

EN2105TT Harris

A 52-year old male with longstanding Hepatitis B infection on chronic antiviral therapy undergoes abdominal ultrasound, which reveals a 2.5 cm lesion in hepatic segment 8. On triple phase CT of the abdomen, this lesion demonstrates enhancement in the arterial phase and washout in the delayed venous phase, as well as pseudocapsule noted by the radiologist. Alpha-fetoprotein (AFP) measures 60 ng/mL. Additional laboratory evaluation reveals normal bilirubin, INR, albumin, and platelet count. He has no clinical or radiographic evidence of portal hypertension. The next step in management is:

1. Refer to surgery to discuss resection or ablation of presumed HCC
2. Refer to hepatology to discuss liver transplantation for presumed HCC
3. Biopsy the lesion to confirm diagnosis before proceeding with further treatment
4. Initiate planning for triple-drug transarterial chemoembolization (TACE)

A 57 year old female with documented cirrhosis related to chronic hepatitis C infection, ascites controlled on diuretic therapy and encephalopathy well controlled on lactulose is found to have two hepatic lesions (2.8 cm right hepatic lobe, 2.3 cm left hepatic lobe) on ultrasound screening. Multiphase CT demonstrates the two lesions are consistent with HCC (LR-5 on imaging) without vascular invasion or evidence of extrahepatic disease. ECOG performance status is 1, Total Bilirubin is 1.8, Albumin 3.0, AFP is 180, INR 1.4 and Platelet count is 58,000. What is the next best step in patient management?

1. Refer to local hepatologist for treatment of Hepatitis C
2. Refer for Chemoembolization
3. Initiate Systemic therapy
4. Refer to transplant center for consideration of Liver Transplant
5. Refer to surgery for Surgical Resection

EN2105AA Hunter

A 58 yo patient with a prior history of ER/PR+ breast cancer presents with back pain. Scans reveal multiple bone lesions suspicious for metastatic disease, in particular a lesion at L4 consistent with the location of her pain, as well as multiple liver lesions. As a next step, you advise:

1. Initiating a CDK4/6 inhibitor combined with an aromatase inhibitor
2. Biopsy of the L4 lesion
3. Liver biopsy
4. Radiation to the spine

A 54 year old woman with a history of stage IIIB ER/PR negative, HER2+ breast cancer presents with metastatic recurrence to liver and bone three years out from curative therapy. Liver biopsy reveals histology similar to her original tumor. Her performance status is ECOG 0-1. You recommend:

1. Trastuzumab
2. Taxane + trastuzumab
3. Taxane + trastuzumab and pertuzumab
4. Tucatinib, capecitabine and trastuzumab

43 year old woman presents with a ~5 cm left breast tumor; biopsy demonstrates a high-grade invasive ductal carcinoma, ER/PR/HER2 negative. Staging scans demonstrate liver metastases, confirmed by biopsy and consistent with the primary tumor. She is asymptomatic, ECOG 0. What will be the most important factor in choosing her first therapy?

1. ERBB2 mutation on molecular testing
2. Additional immunohistochemistry testing
3. Presence of visceral disease
4. Brain MRI results

EN2105YY Indorf

TL is a 55 year old woman with metastatic triple negative breast cancer previously treated with a taxane and capecitabine. She recently underwent her first cycle of sacituzumab govitecan and was subsequently hospitalized with febrile neutropenia and sepsis prior to Cycle 1 Day 8. Which genetic polymorphism for SN38 metabolism could have contributed to this patient's severe toxicity?

1. Glucose-6-phosphate dehydrogenase (G6PD) deficiency.
2. Dihydropyridine dehydrogenase (DPD) deficiency.
3. Uridine diphosphate glucuronosyltransferase (UGT)1A1*28.
4. No genetic polymorphisms exist for irinotecan

What is the mechanism by which olaparib and rucaparib increase serum creatinine?

1. Inhibition of MATE transporters
2. Renal tubule damage
3. Tubular necrosis
4. Nephrotic syndrome
5. Unsure

EN2105D Johnsen

You are called by the ER to consult on a 61 year old woman with profound anemia. She presented with progressing fatigue, dyspnea on exertion for several days, and new left shoulder pain. Her only medical history is hypertension. Her review of systems is suspicious for melena intermittently over the past 2-3 months. On physical exam her pulse is 90, blood pressure 110/70, and she is pale and uncomfortable. She has a II/VI systolic flow murmur at the LSB without radiation and trace bilateral pedal edema. Her laboratory testing is notable for a hemoglobin of 7.2, MCV 65, RDW 22. The remainder of her CBC and chemistries are normal. Her stool guaiac is positive. Her hs-troponin is elevated and her EKG has changes consistent with ischemia.

You recommend the next steps should be (choose one):

1. Order a type and cross, transfuse 2 units of PRBCs and reassess with a goal hemoglobin >10
2. Order a type and screen, only transfuse if she becomes hemodynamically unstable
3. Order iron studies, plan outpatient intravenous iron replacement
4. Order a type and screen, transfuse 2 units of PRBCs, 2 units of FFP, and 1 single donor platelet
5. Order a type and cross, transfuse 1 unit of PRBCs and reassess with a goal hemoglobin >8

A 23 year old woman with sickle cell disease is admitted for a pain crisis, she has been assessed on her individualized treatment plan. Her admission hemoglobin is 6.2; her baseline hemoglobin is 7.4. You order a type and screen: she is blood type B-positive, antibody screen negative. There is an EHR alert that she has a history of an anti-Jka (an antibody to an antigen in the Kidd blood group system).

You counsel her that (choose one):

1. Her current negative antibody screen means that she is not allosensitized or at increased risk for transfusion reaction
2. Transfusion is indicated now to keep her hemoglobin >8
3. Her antibody history puts her at high risk for a delayed hemolytic transfusion reaction if she receives Jka-positive blood
4. Transfusion is indicated now to improve the course of her pain crisis
5. Transfusion is indicated now to keep her hemoglobin >7

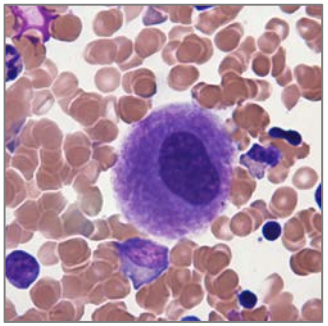
A 29 year old G1P0 woman is 41 weeks pregnant and admitted to Labor and Delivery for suspicion of labor. During consent for care, she and her spouse request more information on the risks and benefits of transfusion. You counsel them that (choose one):

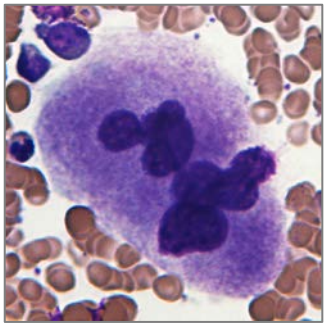
1. The most common infectious hazard of transfusion is transmission of HIV, which is still very rare
2. Mild allergic, urticarial transfusion reactions are common
3. Liberal transfusion strategies improve outcomes
4. The most common infectious hazard of transfusion is transmission of hepatitis C, which is still very rare
5. Fever is an uncommon reaction to transfusion

21 yo male referred for mild chronic thrombocytopenia and macrocytic anemia. Serum B12 and folate levels were normal. PMH notable for recurrent perineal warts. Brother was diagnosed with MDS characterized by monosomy 7 at 15 yo and is now two years post an HLA-matched sib HSCT. Sister is reportedly healthy. Mother is 45 yo and has mild thrombocytopenia. Maternal grandparents died of "old age." Father is 46 yo and healthy and has no siblings.
Exam was unremarkable.

Laboratory Test	Result	Reference Range
Hemoglobin	10.8 g/dL	12-16 g/dL
Hematocrit	32 %	36-45 %
MCV	104 fL	80-100 fL
WBC	5300/μL	4300-10,000/μL
Neutrophils	4000/μL	1800-7,000/μL
Lymphocytes	1100/μL	1000-4800/μL
Monocytes	0/μL	0-800/μL
Platelet count	125,000/μL	150,000-400,000/μL

Marrow - hypocellular for age with normal blast percentage and atypical megakaryocytes. No immunophenotypic abnormalities. Routine karyotype 46, XY.





Which of the following studies is most likely to establish a diagnosis?

1. Platelet aggregometry
2. Genetic testing (CORRECT)
3. Serum folate and B12 levels
4. Chromosomal microarray
5. Telomere length testing

Which of the following is not a feature described in the genetic syndrome affecting this family?

1. Alveolar proteinosis
2. Atypical mycobacterial infections
3. Recurrent genital HPV infections
4. Lymphedema
5. Recurrent bacterial infections

EN2105T Kruse-Jarres

You are seeing a 28 year old woman who was referred to your clinic by her primary care provider for evaluation of menorrhagia and easy bruising. The patient reports having heavy periods since menarche. She also had significant bleeding after wisdom tooth extraction several years ago, which required an evaluation in the emergency department several hours after the procedure. Her mother also has a history of heavy periods, so she had always assumed that this was "normal." She takes an oral contraceptive to manage her menorrhagia, but no other medications or supplements. She says she drinks 2-3 beers per day on average but does not use any other recreational substances. She is not sexually active. Her physical examination is notable only for some faint ecchymoses on her extremities.

Her primary physician ordered some routine tests as part of their evaluation, and these results are below:
WBC: 5600/uL (normal: 4300-10000)
Hemoglobin: 11.9 g/dL (normal: 11.5-15.5)
Hematocrit: 36% (normal: 36-45)
Platelets: 138 (normal: 150-400)
Prothrombin time: 12.6 sec (normal: 10.7-15.6)
Partial thromboplastin time: 42 sec (normal: 22-35)

Which of the following represents an appropriate panel of laboratory tests to identify the cause of these findings?

1. Peripheral blood flow cytometry for circulating malignant cells
2. Von Willebrand factor antigen and activity, and Factor VIII activity
3. Levels of Factors V, VII, and X
4. Bone marrow examination to evaluate megakaryocytes
5. No further testing is needed, as these findings can be explained by her alcohol use

Which of the following strategies is the most appropriate strategy to manage a patient with hemophilia A with a high titer of inhibiting antibody to Factor VIII?

1. Rely on bypassing agents like recombinant Factor VIIa for bleeding episodes
2. Start prophylaxis with emicizumab
3. Refer to a specialized center for gene therapy
4. Ensure the patient is receiving prophylaxis with an extended half-life formulation of recombinant factor VIII (e.g., pegylated of Fc fusion)

EN2105H Libby

You are asked to evaluate a 67 year old woman for an increased total protein level found on routine blood screening by her primary care physician. The patient is very healthy otherwise except for a history of hypothyroidism and is on chronic thyroid replacement therapy. Her total protein is 8.5 gm/dL (normal 6-8.2). Serum protein electrophoresis is 0.7 IgG kappa. Free light chains are not elevated. CBC, creatinine and calcium are all normal. The appropriate next step(s) in the evaluation of this patient are:

1. Skeletal survey
2. Bone marrow biopsy
3. Bone marrow MRI
4. 1 & 2
5. Observation

You are asked to evaluate a 66 year woman who was noted to have an elevated total protein by her primary care physician. An SPEP monoclonal spike of 3.6 IgG lambda. Serum free light chains are mildly abnormal with Kappa/Lambda ratio of 15.5. Her absolute Kappa free light chains are 16mg/dL. CBC, creatinine and calcium are all normal. The appropriate next step(s) in the evaluation of the patient are:

1. Technetium bone scan
2. Bone marrow biopsy
3. Low dose whole body computed tomography (WBLDCT)
4. Bone density test (DEXA scan)
5. 2 & 3

You have been following a 67 year old patient with low risk IgG kappa MGUS annually for several years. Over time their SPEP has slowly climbed from 0.7 to 2.5. Free light chains are normal. Skeletal survey, CBC, creatinine and calcium are all normal. A bone marrow biopsy reveals a 45% plasma cell infiltrate with a normal karyotype. Fluorescent in situ hybridization shows 1q+ and del17p.

The next step in the management of this patient should be:

1. Observation
2. Bone marrow MRI or CT/PET scan or whole body low does computed tomography (WBLDCT)
3. Start Revlimid and dexamethasone
4. Induction chemotherapy with RVD followed by upfront autologous stem cell transplantation.
5. Induction therapy followed by tandem auto-allogeneic stem cell transplantation

EN2105I Linenberger

An 18 yo male was seen by his primary MD with pharyngitis 3 mos ago. CBC at that time revealed: Hgb 14 gm/dL, Hct 40%, MCV 89 fl, WBC 2,500/mcL, ANC 450/mcL, remainder of differential normal; plt ct 300,000/mcL; monospot (–); chemistry & HIV testing and hepatitis panel were normal. Follow-up CBC 2 wks later revealed a WBC 3,000/mL, ANC 400/mcL. He was referred for Hematology consultation.

Past Medical History: Frequent otitis & tonsillitis as a young child; roughly 6 school absences/yr because of URIs; avoids sports; cellulitis secondary to acne
Medications: None
Family History: No siblings; father reports low WBC counts in past
Physical Exam: Afebrile; no skin lesions/infection; no lymphadenopathy; no organomegaly

Laboratory Data: CBC: Hgb 14.6 gm/dL, Hct 43%, MCV 90 fl, WBC 2,200/mcL, ANC 350/mcL, remainder of differential normal; plt ct 350,000/mcL

Which of the following tests will likely be most helpful in identifying the underlying cause of this patient's neutropenia?

1. Assays for mutations in genes implicated in congenital neutropenia
2. Immunophenotype analysis of peripheral blood lymphocytes by flow cytometry
3. Quantitative immunoglobulin levels
4. Marrow morphology assessment and cytogenetics
5. Granulocyte agglutinin test for antineutrophil antibodies

You are consulted on a 35 yo woman in the ICU with pancytopenia. She was admitted for evaluation of unexplained fevers and was transferred to the ICU after developing hypoxemia, pulmonary infiltrates, hypotension, delerium & coagulopathy.

Past Medical History: Systemic lupus erythematosus x 3 yrs with skin, joint and renal involvement; recently quiescent on hydroxychloroquine and prednisone.

Physical Examination: Temp 39^{o}C, BP 96/60; Stuporous; no focal deficits. Scattered ecchymoses. Diffuse, shoddy lymphadenopathy and palpable splenomegaly

Lab Data:

Hgb 9.8 gm/dL	MCV 99 fl	Plt ct 58,000/mcL
WBC 1,900 /mL	Neutrophils 900 /mL	
Bands 200 /mcL	Lymphs 300 /mcL	Monos 400 /mcL

Blood smear: RBC anisocytosis; no schistocytes

PT/INR 1.3 aPTT 43 secs Fibrinogen 100 mg/dL D-dimer 0.28

Bili T/D 3.8/2.9 mg/dL ALT 230 U/L Ferritin 5,500 mg/L

Blood & Urine Cultures: Negative

CXR: Patchy infiltrates & hilar adenopathy

Neutropenia in this patient is most likely due to which mechanism?

1. Consumption from overwhelming sepsis
2. Autoantibody-mediated destruction
3. Splenic sequestration
4. Hemophagocytic consumption
5. Drug-induced marrow suppression

EN2105E Lynch

A 21 year old female with new diagnosis of stage IA classical Hodgkin lymphoma completes 2 cycles of ABVD and 20 Gy of consolidative radiotherapy to the mediastinum. She has achieved a complete metabolic response (Deauville 2).

Which of the following would be most appropriate to recommend for follow up?

1. Surveillance CT scans every 6 months for the first 5 years
2. Post-radiation biopsy to confirm remission
3. Regular mammograms and/or breast MRI starting 7 years after radiation
4. Surveillance PET/CT at one year post treatment

A 25 year old female has been diagnosed with Stage IVA classical Hodgkin lymphoma with extensive lymphadenopathy above and below the diaphragm as well a lung involvement with bilateral pleural effusions. This patient cannot walk more than 20 feet without needing to rest due to shortness of breath. Pre-treatment echocardiogram is within normal limits. Upon further questioning, she discusses that she is a guitarist for a local band. In addition, she desires having children in the future. Given her symptomatic disease, she has been told she is not a candidate for egg retrieval prior to chemotherapy., She asks questions about potential chemotherapy regimens that will allow her to continue to work post treatment and maintain her ability to start a family in the future.

Based on this discussion, what is the most reasonable chemotherapy regimen to recommend?

1. Brentuximab + AVD
2. Escalated BEACOPP
3. ABVD
4. Pembrolizumab

A 30 year old female have presented with 6 months of intermittent fevers, drenching night sweats, dry cough, and loss of 15% of body weight. CT scan demonstrate widespread lymph adenopathy above and below the diaphragm as well as splenomegaly with multiple 2-3 cm splenic nodules. An excisional biopsy of a right axillary lymph node demonstrated lymphocyte pre-dominant Hodgkin lymphoma. What would be the most reasonable upfront treatment regimen?

1. Observation
2. ABVD
3. escalated BEACOPP
4. R-CHOP

EN2105J Oehler

Mr. Smith is a 52-year-old health care worker in good health with no other medical problems diagnosed with chronic phase CML and started on imatinib at 400mg daily. Blood counts normalize over 6 weeks. At 3 months after initiating therapy molecular response is assessed and shows 45% BCR-ABL1 transcripts. You establish that the patient is adherent to imatinib therapy and has not missed any doses. You assess for resistance by submitting mutation analysis of ABL by sequencing. The T315I mutation is identified.

The next best step in management is:

1. Stop imatinib and start dasatinib 100mg daily
2. Stop imatinib and start bosutinib at 500 mg daily
3. Stop imatinib and start ponatinib at 45 mg daily
4. Refer patient for allogenic stem cell transplant.
5. 3 or 4

A 23-year-old woman was recently diagnosed with chronic phase CML. In counseling regarding tyrosine kinase inhibitors which of the following is (are) true?

1. Tyrosine kinase inhibitors are teratogenic and consequently women should not get pregnant while taking these drugs
2. Nilotinib is associated with an increased risk of pleural effusions and pulmonary arterial hypertension.
3. Dasatinib is associated with increased glucose and lipase, and risk of QTc prolongation.
4. 1 and 2
5. 1 and 3

Indications to assess for mutations in the ABL tyrosine kinase domain and consider a switch to second-line tyrosine kinase inhibitor therapy in a 72-year-old woman with chronic phase CML include:

1. BCR-ABL1 transcripts >10% after 3 months of therapy
2. Loss of cytogenetic response or hematologic response
3. 1-log increase in BCR-ABL1 transcript levels and loss of major molecular response (MMR)
4. 1, 2, and 3

EN2105CC Pennington

A 71 year old undergoes robotic hysterectomy, bilateral salpingo-oophorectomy, and sentinel node biopsy for grade 1 endometrial cancer. Final pathology confirms grade 1, 60% myoinvasion, lymphovascular space invasion present. Sentinel nodes were negative.

Which of the following is recommended management?

1. Vaginal cuff brachytherapy
2. Whole pelvic RT
3. Chemotherapy with carboplatin and paclitaxel

A 65 year old woman underwent chemorads (pelvic RT, brachytherapy, cisplatin chemosensitization) for stage IIB cervical adenocarcinoma, with complete response. 2 years later, she presents with a 6cm pelvic mass, multiple para-aortic lymph nodes, and lung nodules, all of which are PET-avid. Biopsy confirms recurrence, PD-L1 expression is negative.

Which of the following is the next preferred treatment?

1. Total pelvic exenteration
2. Carboplatin, paclitaxel, and bevacizumab
3. Cisplatin, paclitaxel
4. Pembrolizumab

EN2105K Percival

A 46 y/o man is diagnosed with AML and begins treatment. Which of the following is the most favorable molecular pattern of mutations?

1. NPM1+, FLT3-ITD+ with high allelic ratio
2. ASXL1+
3. RUNX1+
4. RUNX1-RUNX1T1 positive

A 28 y/o woman presents with a breast mass. Biopsy confirms myeloid sarcoma. What is the next best step in treatment?

1. induction chemotherapy with 7+3
2. unilateral mastectomy with lymph node dissection
3. local radiation therapy
4. ifosfamide and epirubicin
5. allogeneic transplant

EN2105ZZ Pergam

The most common cause of early bacteremia (first week) in patients undergoing leukemia therapy is?

1. Pseudomonas aeruginosa
2. Enterococcus faecium
3. Staphylococcus aureus
4. Viridans streptococcus
5. Klebsiella pneumoniae

Which of the following is a warning symptoms/sign ("red flag symptom") for invasive fungal sinusitis?

1. Cranial nerve abnormality (e.g. sixth nerve palsy)
2. Bony erosions seen on CT/MRI of sinuses
3. Palatal eschar
4. New onset facial numbness
5. All of the above

CMV prevention with Letermovir prophylaxis in allogeneic transplant recipients (choose one):

1. Did not demonstrate a benefit in a large phase 3 trial at preventing CMV reactivation
2. Can only be given as an IV formulation
3. Does not eliminate the need for ongoing acyclovir/valacyclovir prophylaxis
4. Is associated with ganciclovir resistance
5. None of the above

EN2105O Pishko

36 year-old female with history of well-controlled type-II diabetes presents to the emergency room with menorrhagia and profound fatigue over past week. Initial labs below:

WBC 9.7k/L
HgB 8.0 g/dL, MCV 88k/uL
Platelets 18 x 10^9/L
Creatinine 2.5 mg/dL
LDH 560 U/L
Haptoglobin <30 mg/dL
PT 12.3 s *(nl 9.4-12.5 s)*
PTT 25.0 s *(nl 25.1-36.5)*
Peripheral smear- 3-4 schistocytes per hpf, low platelets without clumping, no immature white blood cells
There is concern for acquired TTP and she is started on daily plasma exchange (PLEX). An ADAMTS13 level is sent prior to initiating PLEX. Labs 3 days later show the following:
WBC 6.0 k/L
HgB 8.3 g/dL, MCV 88k/uL
Platelets 20 x 10^9/L
Creatinine 3.5 mg/dL
ADAMTS13-40% *(nl >60%)*

What is the most appropriate course of action at this time?

1. Send complement studies and complement mutation panel and continue PLEX while awaiting results
2. Patient is not responding to PLEX, add rituximab therapy 375 mg/m2 weekly x 4
3. Initiate eculizumab therapy and discontinue PLEX if she continues to have no response to PLEX
4. Initiate methylprednisone pulse (1000 mg IV x 3 days) due to concern for Evan's syndrome

33 year-old male with 10-pack year smoking history and bowel obstruction s/p extensive resection (2012) who presents after a syncopal episode. His family reports he has not been seen by a physician or taking any medications in the past decade. The patient denies any recent fevers, chills or night sweats. He denies any blood in his stools or diarrhea. His only complaint is progressive fatigue and shortness of breath over the past 2 years. Vitals on presentation show temperature 98.3ºF, blood pressure 160/90 HR 110 bpm and O2 sat 95% on room air. Initial labs are below:

WBC 2.6k/uL, no immature white blood cells on differential
HgB 5.0g/dL RDW >40.0% MCV 110fL
Platelets 31 x 10^9/L
Creatinine 0.79 mg/dL
LDH 3,000 U/dL *(nl 98-192 U/L)*
Haptoglobin <30 mg/dL *(nl 36-195 mg/dL)*
Reticulocyte count 1%, abs retic 32.0thou/uL
PT 16.1 s *(nl 9.4-12.5 s)*
PTT 25.0 s *(nl 25.1-36.5)*
Fibrinogen 261 mg/dL *(nl 170-410 mg/dL)*

In addition to sending a peripheral blood smear, what is the most appropriate next step in work-up for this patient?

1. Blood cultures, concern for sepsis-induced DIC as etiology
2. Send vitamin B12, methylmalonic acid and homocysteine levels
3. Start anti-hypertensive therapy and monitor labs in response to blood pressure control
4. Bone marrow biopsy

EN2105II Pollack

Which of the following are FDA approved specifically for GIST tumors with Exon 18 mutations notably D842V?

1. repritinib
2. avapritinib
3. regorafenib
4. desatinib

Which of the following diseases is driven by CSF-1 and is thus very sensitive to the TKI pexidartinib?

1. desmoid tumor
2. giant cell tumor of bone
3. tenosynovial giant cell tumor
4. dermatofibrosarcoma

Which sarcoma subtype is FDA approved to be treated with the drug eribulin in the metastatic setting?

1. liposarcoma
2. leiomyosarcoma
3. synovial sarcoma
4. undifferentiated pleomorphic sarcoma

EN2105DD Rodriguez

The following statements regarding HPV related oropharynx squamous cell carcinomas are true, **except:**

1. p16 IHC is an adequate method to establish HPV positivity
2. The incidence of HPV oropharyngeal cancer has increased in the last decade
3. The cure rates for locally advanced, HPV positive, oropharynx cancers are higher than in HPV negative tumor matched by stage
4. The most common HPV subtype detected in these tumors is HPV 18
5. The use of HPV vaccine may decrease HPV related oropharynx cancer

A 58 year old woman is fatigued and presents for exam. On physical examination the liver edge is palpable 2.5cm below the right costal margin. An ultrasound is performed findings multiple liver lesions. A CT scan of the chest, abdomen and pelvis is performed and finds a mass in the thyroid gland and multiple liver lesions. CEA is elevated 14. A colonoscopy is negative. A biopsy of the liver lesion is performed and is consistent with medullary thyroid carcinoma, it harbors a RET fusion mutation. You recommend meeting with a genetic counselor, and recommend:

1. Erlotinib
2. Selpercatanib
3. Cisplatin and Fluorouracil
4. Radioactive Iodine
5. Supportive care alone, since no systemic agents have activity in this disease

EN2105U Salit

A 45-year-old female is 35 days post a myeloablative allogeneic hematopoietic cell transplant from a matched unrelated donor for high-risk acute myeloid leukemia. He is currently on cyclosporine and MMF for GVHD prophylaxis. He presents to the clinic with loose watery diarrhea 7-8 times per day and a 5 kg weight loss in the last week. Stool cultures are negative. He is started on beclomethasone and budesonide and a GI consult is placed for a colonoscopy. Pathology reveals moderate to severe GVHD of the colon with many apoptotic cells and diffuse crypt dropout.

First line therapy for newly diagnosed severe acute GVHD is:

1. IV methylprednisone 2mg/kg daily.
2. IV methylprednisone 2 mg/kg plus horse ATG 15 mg/kg /day for 7 days
3. IV methylprednisolone 1mg/kg plus extracorporeal photopheresis
4. IV methylprednisolone 1mg/kg plus methotrexate 10 mg/kg/day for 7 days

A 25-year-old male is an HLA-match for his brother who requires an allogeneic transplant for acute myeloid leukemia. The donor is nervous about going to the operating room and wonders if he might elect to donate peripheral blood instead. His consenting physician tells him which of the following is an advantage to using bone marrow over peripheral blood for allogeneic hematopoietic cell transplantation?

1. Patients receiving bone marrow engraft faster since there are more stem cells in the bone marrow product than in peripheral blood.
2. Patients receiving bone marrow have a lower incidence of graft rejection because they receive a higher stem cell dose.
3. Patients receiving bone marrow have less chronic graft versus host disease due to decreased numbers of lymphocytes in the bone marrow product.
4. Donors providing bone marrow recover significantly faster because they are not exposed to G-CSF.

EN2105MM Santana-Davila NSCLC Adjuvant/Locally Advanced

85 yo old patient with a 2 cm resected NSCLC with a final stage of IB is seen in clinic. What is the role of adjuvant treatment in this setting?

1. There is no role for adjuvant treatment for patients with stage I disease.
2. Clear survival benefit for this patients and the standard is carboplatin and paclitaxel.
3. Adjuvant treatment of patient with stage IB is controversial, and treatment should be discussed and individualised.
4. patient should be referred to radiation oncology for adjuvant radiation.
5. None of the above.

After treatment with chemotherapy and radiation patients should continue with treatment with which of the following agents?

1. atezolizumab
2. nivolumab
3. durvalumab
4. infliximab
5. none of the above

The chemotherapy of choice for treatment of patients with stage IIIB cancer while undergoing chemotherapy and radiation should be:

1. carboplatin and paclitaxel
2. cisplatin and etoposide
3. cisplatin and pemetrexed
4. there is no standard chemotherapy regimen

EN2105MO Santana-Davila SCLC The Basics

For patients with stage 1 small cell lung cancer that were treated with surgery the next step in treatment should be:

1. adjuvant chemotherapy with cisplatin and etoposide
2. no treatment is necesary given that this is early stage disease
3. concurrent chemotherapy and radiation with cisplatin and etoposide
4. radiation alone to the mediastinum
5. sequential chemotherapy (with cisplatin and etoposide) followed by radiation

73 yo male treated with metastatic small cell lung cancer treated with carboplatin, etoposide and atezolizumab. with a good response for 13 months develops progressive disease in the liver and bone. Appropriate second line regimens include all of the following except.

1. Paclitaxel
2. Lurbinetedin
3. Gemcitabine
4. Nivolumab and ipilimumab
5. Topotecan

68 year old female with a history of extensive disease SCLC currently on maintenance durvalumab after initial response to chemotherapy. Has elected not to pursue PCI. Next step in treatment should be:

1. Continue durvalumab until progression. No need to image her brain.
2. Go back on chemotherapy as there is high risk that she will develop metastatic disease.
3. Continue on maintenance durvalumab with restaging MRI done every 6 months.
4. Stop all treatment given that she is not following clear PCI recommendations.

EN2105UU Schweizer

Risk factors for bladder cancer include:

1. Smoking
2. Chronic indwelling catheter
3. History of long-term cyclophosphamide use
4. History of occupational exposure to certain dye chemicals
5. All of the above

A 60 year-old man develops abdominal discomfort, fatigue, and weight loss over a 6 month period and undergoes a CT scan of the abdomen/pelvis. He is found to have a large right renal mass and other enlarged masses in the retroperitoneum felt to be lymph nodes. This tumor should be treated more like:

1. A metastatic urothelial carcinoma arising from the bladder
2. A metastatic renal cell carcinoma
3. It is important to obtain tissue to select the correct therapy
4. Tissue does not matter in this situation, as the prognosis and treatments do not significantly differ

A 65 yo woman presents with painless hematuria. She is referred to a urologist who finds a large bladder mass at the dome. She undergoes transurethral resection of the bladder tumor and the pathology report returns with a T3 urothelial carcinoma. A CXR and abdomen/pelvic CT scan are without detectable metastasis. She receives 4 cycles of neoadjuvant dose dense methotrexate, vinblastine, Adriamycin, and cisplatin (MVAC) and undergoes radical cystectomy. Her pathology from her cystectomy reveals residual tumor and no signs of necrosis or apoptosis.

What should you tell the patient at this point?

1. 4 more cycles of dose dense MVAC will improve your chances of survival
2. Changing from MVAC to gemcitabine/cisplatin will improve your chances of survival
3. Adjuvant radiation to the pelvis will improve your chances of survival
4. I’m sorry, but I don’t know of anything that will improve your chances of survival

EN2105F Shadman

A 57-year-old man with a history of small lymphocytic lymphoma (SLL) returns to the clinic for follow-up. You have been following him in the past 2 years since the time of diagnosis and he has not required treatment so far. He had stable bilateral cervical and axillary lymphadenopathy in the past but today, complains of a rapidly enlarging left supraclavicular node. In the past 3 weeks the lymph node has increased from 0.8 cm to 4 cm. Patient also reports drenching night sweats and fatigue and has lost 10 lbs in the past 2 months. His CBC shows a WBC 7.5 cells/uL with a normal differential, hematocrit 41% and platelet count 157,000/uL. Other labs include LDH 780 units/L (normal up to 210), serum creatinine 0.7 mg/dL. Patient is known to have trisomy of chromosome 12 (+12) based on the chromosome analysis at the time of diagnosis.

What is the best next step in treating this patient?

1. Combination chemoimmunotherapy with Bendamustine and Rituximab
2. Combination chemoimmunotherapy with Fludarabine , Cyclophosphamide and Rituximab
3. Combination of venetoclax and obinutuzumab for one year
4. Single agent ibrutinib treatment until progression
5. Repeat the lymph node biopsy to confirm the diagnosis

A 74-year-old woman with a 7-year history of CLL returns to the clinic for follow-up. Three years ago, patient was treated with 6 cycles of fludarabine and rituximab. In the past 4 months, she has been experiencing worsening anemia and thrombocytopenia. Her blood work 2 weeks ago showed WBC 45,000cell/uL with 90% lymphocytes, hematocrit 32% and a platelet 55,000/uL. Patient's comorbidities include a mechanical mitral valve for which she has been on warfarin therapy for 7 years, hypertension and diabetes. You performed a bone marrow biopsy 2 weeks ago which showed 80% involvement by CLL cells by flow cytometry and morphology. The CLL FISH only showed 13q14 deletion. Which one of the following treatment options is **NOT recommended**?

1. Start single agent acalabrutinib and continue until progression
2. Start treatment with duvelisib or idelalisib (with rituximab) and continue until progression
3. Start combination venetoclax and rituximab and continue for 2 years
4. All 3 options are reasonable

A 64-year-old man with history of chronic lymphocytic leukemia with normal cytogenetics returns to the clinic for clinical follow-up. Five years ago, he received chemo-immunotherapy with FCR and has been in remission until 2 months ago when he presented with worsening lymphadenopathy, an absolute lymphocyte count of 42,000 cell/uL, hematocrit 34% and platelet count of 82,000/uL. He was started on ibrutinib 420 mg daily. Today, he reports some improvement in the lymphadenopathy but his lymphocyte count is now increased to 84,000 cell/uL. His hematocrit currently is 36% and the platelets count is 95,000/uL.

What is the next best step in management of this patient?

1. Continue treatment and re-evaluate the patient in a month
2. Increase the ibrutinib dose to 560 mg daily and reassess in a month
3. Repeat CLL FISH panel looking for new cytogenetic abnormalities including 17p deletion
4. Switch the treatment to venetoclax (start the ramp-up schedule) and repeat blood work in a month
5. Switch to chemo-immunotherapy with Bendamustine and rituximab and avoid B-cell receptor (BCR) inhibitors in future

EN2105LL Shankaran

What is the standard of care treatment after trimodality therapy (chemoRT-->surgery) for locally advanced esophageal cancer?

1. FOLFOX for 4 months
2. Paclitaxel + Ramucirumab for 4 months
3. FOLFOX for 4 months only for patients who do not have pathologic complete response
4. Surveillance

In which scenario is Her2 most likely to be overexpressed?

1. 52 yo male with a proximal squamous cell esophageal carcinoma
2. 63 yo male with a GE junctional (Siewert type II) adenocarcinoma
3. 46 yo woman with a strong family history of gastric cancer and a newly diagnosed diffuse-type gastric cancer involving the entire stomach

A 71 yo male is newly diagnosed with uT3N1 GE junctional adenocarcinoma. PET/CT shows no evidence of metastatic disease. He has significant dysphagia to solids and some soft foods/liquids. He has lost a total of 20 pounds in the last 2 months and continues to lose weight. What is the next best step in management?

1. Start neoadjuvant chemoradiation immediately
2. Consult GI for placement of an esophageal stent
3. Consult GI for placement of a PEG tube
4. Referral to surgery for placement of a J tube

EN2105V Shustov

A 25 year old man presents with fevers, night sweats and weight loss. On physical exam he is noted to have enlarged cervical and bilateral axillary lymph nodes. On laboratory evaluation the patient is found to have normal blood counts and differential; LDH is elevated 2 X ULN. Excisional biopsy demonstrates strong and uniform expression of CD30. Cells are CD3- CD4-, CD8-, TIA1+, granzyme B+, and are strongly positive for ALK with cytoplasmic staining. A PET/CT is performed and demonstrates diffuse lymphadenopathy above and below the diaphragm, stage IIIB disease.

For treatment you recommend:

1. CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
2. CHOEP (cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone)
3. BV+CHP (brentuximab vedotin plus cyclophosphamide, doxorubicin, prednisone)
4. Hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone / methotrexate-cytarabine)

A 63 year old woman presented with fevers, night sweats and weight loss. On physical exam she was noted to have enlarged inguinal lymph nodes. Her LDH was greater than two times the upper limits of normal. Subsequently she was diagnosed with a peripheral T cell lymphoma, not otherwise specified. CD30 was expressed on < 1% of cells on the biopsy. She received treatment with CHOEP (cyclophosphamide, doxorubicin, etoposide, vincristine, prednisone) and after a brief remission relapsed. CHOEP was poorly tolerated two episodes of neutropenic fever and one ICU admission fir septic shock.

For treatment you recommend:

1. Pralatrexate
2. BV+CHP (brentuximab vedotin plus cyclophosphamide, doxorubicin, prednisone)
3. ICE followed by an Allogenic Stem Cell Transplant.

EN2105L Smith

Which of the following are acceptable first-line treatments for a 53 year-old with nobulky stage I DLBCL, GCB subtype with a normal DH?

1. RCHOP every 14 days for 4 cycles
2. RCHOP every 21 days for 4 cycles, and R x 3 additional doses
3. RCHOP every 21 days for 6 cycles with IFRT52 Gy
4. RCHOP x 2 cycles, if PET neg stop therapy
5. All of the above

What histologic feature is associated with inferior prognosis in 1L DLBCL treated with R-CHOP?'

1. Dual expression of BCL6 and Ki67 over 75%
2. Presence of tumor-infiltrating NK cells
3. MYC and BCL2 overexpression by IHC

Which of the following is true about the role of XRT in primary mediastinal B-cell lymphoma?

1. All young pts require XRT
2. XRT for patients in metabolic PR offers no benefit
3. RCHOP followed by XRT is a reasonable therapeutic standard

EN2105KK Tykodi

A recognized hereditary genetic syndrome is associated with an increased risk for developing renal cell carcinoma with each of the following histologic subtypes EXCEPT:

1. Clear cell
2. Papillary, type I
3. Papillary, type II
4. Chromophobe
5. *TFE3*-translocation associated RCC

In the CheckMate 025 study, the anti-PD1 antibody nivolumab dosed at 3 mg/kg intravenously every 2 weeks was compared to the mTOR inhibitor everolimus dosed at 10 mg PO daily in RCC patients who had failed 1 or 2 lines of prior anti-angiogenic therapy. The primary endpoint was OS and the study was positive in favor of nivolumab (hazard ratio for death 0.73; P=0.002). All patients were required to have archival tumor tissue submitted for PD-L1 staining by immunohistochemistry. Which statement(s) is/are true regarding the PD-L1 biomarker and CheckMate 025 outcomes?

1. In the PD-L1 negative cohort, OS was superior for nivolumab versus everolimus
2. In the PD-L1 negative cohort, OS was superior for everolimus versus nivolumab
3. In the PD-L1 negative cohort, OS did not differ between nivolumab and everolimus
4. For nivolumab treated patients, median OS was longer for PD-L1 positive tumors versus PD-L1 negative tumors.
5. Both C and D

You are evaluating a new patient referred to you for metastatic RCC. He is a 65 year old obese man with a history of hypertension, steatohepatitis, and remote 20 pack year smoking history. He presented with sudden onset gross hematuria and was found to have an 8.5 cm left renal mass. He had nephrectomy 14 months ago for a clear cell RCC pT3a, Nx tumor. Baseline imaging had shown sub-cm pulmonary nodules. He was followed by his urologist and surveillance scans revealed growth of multiple lung nodules with the largest now 12-14 mm. Needle biopsy of a lung nodule has recently confirmed metastatic RCC. The patient denies any cancer-associated symptoms and feels he is at a normal functional baseline. He is eager to start therapy for his cancer. To make a treatment recommendation, you review his lab panel below and assess his risk category according to International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria as:

Test	Value	Normal Range
Na	134	135-145
K	4.6	3.6-5.2
BUN	24	8-21
Cr	1.21	0.38-1.02
Ca	9.1	8.9-10.2

AST (SGOT)	64 U/L	9 – 38
ALT (SGPT)	55 U/L	10 – 48
Alk Phos	142 U/L	37 – 159
Total Bili	0.9 mg/dL	0.2 -1.3
Total Protein	6.9 g/dL	6.0 – 8.2
Alb	3.8 g/dL	3.5 – 5.2
LDH	268*	< 210

*hemolyzed sample

Test	Value	Normal Range
WBC	6.4	4.3-10.0
Hgb	13.7	11.5-15.5
HCT	41	36-45
PLT	364	150-400
Neutrophil	4.90	1.80-7.00
Lymphocyte	0.90	1.00-4.80
Monocyte	0.60	0.00-0.80
Eosinophil	0.00	0.00-0.50
Basophil	0.00	0.00-0.20

1. Good Risk
2. Intermediate Risk
3. Poor Risk
4. Can’t be determined; re-draw the LDH

EN2105OO Urban

Your patient presents with ascites, “omental cake,” and elevated CA 125; you suspect an advanced ovarian cancer. What are the possible diagnostic tests to confirm your suspected diagnosis?

1. Staging laparoscopy
2. Biopsy of the omental cake
3. Obtain cytology from ascites
4. Order CA 125 and CEA to assess ratio of CA 125:CEA
5. Staging laparoscopy or biopsy of the omental cake

Niraparib maintenance therapy is an option for which of the following patients?

1. Following upfront surgery & chemotherapy in a patient with a BRCA1 mutation
2. Following chemotherapy for a first recurrence in a patient with platinum-sensitive recurrent ovarian cancer; germline/somatic testing shows no BRCA mutation nor HRD
3. Following upfront surgery & chemotherapy in a patient whose tumor exhibits HRD
4. Following upfront surgery & chemotherapy in a patient with stage III disease, had an optimal surgical resection, and for whom germline/somatic testing shows no BRCA mutation nor HRD
5. All of the above

EN2105JJ Venur

A 44-year gentleman had a first-time generalized seizure while at work. He was taken to the local emergency room and as a part of his work up he had a CT head which showed a lesion in the right frontal lobe. A brain MRI w/wo contrast was obtained which confirmed a 2x2 cm lesion in the right frontal lobe, with T2 FLAIR hyperintensity and no-contrast enhancement. He was started on dexamethasone and levetiracetam and taken to the operative. A gross total resection was performed. Which of the following molecular features in the tumor would provide the best survival advantage?

1. MGMT methylation
2. IDH mutation
3. Chromosome 10p loss
4. TERT promoter mutation
5. EGFRvIII mutation

A 68-year-old male was diagnosed with left parieto-temporal glioblastoma, WHO grade IV, IDH wild type, MGMT methylated, when he presented with progressive reading and language difficulty. After complete resection of the tumor the patient received standard six -week course of radiation and temozolomide. His symptoms improved with occupational and speech therapy. His first MRI brain 4 weeks after completion of chemoradiation showed no new lesions. He was then started on maintenance temozolomide. He presents for follow up today, has no new symptoms but MRI brain shows new contrast enhancing lesion in the superior and anterior margin of the surgical cavity with surrounding T2/FLAIR hyperintensity. What is the best next step?

1. Since the patient has a new lesion on temozolomide, stop temozolomide and send the patient to hospice
2. Given the new lesion within three months of concurrent chemoradiation, radiosurgery should be considered
3. Since the new lesion is contrast enhancing on brain MRI, switch to bevacizumab
4. The patient will likely benefit with continuation of temozolomide and short interval follow up MRI brain

EN2105EE Wong

A 65-year-old man presented to his primary care provider with mild right upper quadrant pain and hematuria. A CT scan was performed and a kidney stone was found. Incidentally, it also showed a hypervascular 2 cm mass in the tail of the pancreas with multiple hypervascular liver lesions. The patient underwent liver biopsy, which revealed a well-differentiated neuroendocrine tumor (Ki67 1%, 3 mitoses/10 HPF). A gallium-68 DOTATE PET scan showed uptake in the pancreatic tail and liver lesions. Pain is currently controlled on opioids. He is very anxious and wants to start treatment.

What is the recommended treatment?

1. Temozolomide and capecitabine
2. Sunitinib or everolimus
3. Octreotide
4. Lutetium-177 dotatate (peptide radionuclide receptor therapy)
5. 2 or 3

A patient presented to ED with right lower quadrant pain and a history of diarrhea and flushing for 2 years. CT abdomen and pelvis demonstrated a 3cm right mesenteric mass and thickening of the ileum suspicious for carcinoid tumor and a solitary 1.7 cm liver lesion. Chromogranin A and 24-hour urinary 5-HIAA were elevated. Gallium-68 dotatate PET was performed, which showed uptake in the mesenteric mass and liver lesion, and no other sites of disease. Liver biopsy confirmed metastatic well-differentiated neuroendocrine tumor (Ki67 <1%, 4 mitoses/10 HFP). What is the next step in management?

1. Start octreotide
2. Refer to a neuroendocrine multidisciplinary clinic or surgical oncologist
3. Observe
4. Treatment with peptide radionuclide receptor therapy
5. 1 and 2

The following are common side effects of octreotide, except:

1. Injection site pain
2. Fever
3. Diarrhea
4. Gallstones
5. Abdominal distension and flatulence

EN2105QQ Yezefski

25yo man with a painful testicular mass x3 weeks, now s/p orchiectomy. Pathology showed a 4cm seminoma with invasion of the rete testis, and CT CAP showed enlarged retroperitoneal lymph nodes measuring up to 2.5cm. Tumor markers obtained 4 weeks after surgery were notable for LDH 140, BHCG 600, and AFP 1100. What is the best treatment?

1. RPLND
2. Radiation therapy, total dose 26 Gy.
3. BEP x4
4. EP x4

A 49yo man has just completed 3 cycles of BEP for good-risk seminoma, Stage IIIA (pT2N3M1S1). His restaging CT CAP done four weeks after finishing chemo showed several residual retroperitoneal and mediastinal masses measuring between 2-5cm. What is the best next step in management?

1. Salvage radiation therapy
2. PET-CT in 8 weeks
3. RPLND
4. Salvage chemotherapy with TIP x4

EN2105VV Yung

A 56-year-old woman is referred following a diagnosis of lobular carcinoma in situ for consideration of risk-reduction strategies. She has participated in screening mammography since age 40, and earlier this year was found to have new microcalcifications in the left upper outer quadrant. A biopsy showed lobular carcinoma in situ. She is a G2 P2, Caucasian, with last period at age 51 and has no family history of breast or ovarian carcinoma. She is a lifetime nonsmoker and exercises regularly. Relevant findings from chemoprevention trials are discussed with the patient. Based on those published results, which of the following should be recommended?

1. Referral to Medical Genetics for hereditary breast cancer gene testing
2. Yearly MRI screening in addition to yearly digital mammograms
3. Chemoprevention with tamoxifen 20 mg daily, raloxifene 60 mg daily, anastrazole 1 mg daily or exemestane 25 mg daily for five years
4. Ductal lavage with cytology

A gynecologist in your area calls to ask your advice regarding screening recommendations for a 27-year-old woman. She tells you that her patient is new to town and gave a history of treatment for Hodgkin's disease during her adolescence for which she received mantle radiation. She has no history of breast cancer. She is recently married and is considering becoming pregnant in the near future. Based on professional society recommendations for best practice you recommend frequent clinical breast examinations and which of the following at this point in time?

1. Tamoxifen for five years
2. Bilateral prophylactic mastectomies
3. Annual MRI (with interruptions during pregnancy)
4. Annual mammograms

A 31-year-old patient that is *BRCA1* positive, whose mother had breast cancer at age 35, presents with screening questions. There are no palpable breast masses. Mammogram reveals heterogeneously dense breasts. She does not desire prophylactic surgery at this time. In addition to mammography, what is the most appropriate screening method for *BRCA* positive patient?

1. Positron emission mammography
2. Contrast enhanced CT imaging of the breast
3. Breast ultrasound
4. Breast MRI

EN2105FF Zhen

A 50 year old otherwise healthy male presents to the local ED for progressive right upper quadrant abdominal pain. An abdominal ultrasound suggests findings for cholecystitis. He is taken emergently for a simple laparoscopic cholecystectomy. However, pathology identifies a pT1b gallbladder adenocarcinoma. He is referred for medical oncology evaluation. A staging CT chest/abdomen/pelvis with IV contrast shows no evidence for disease. Patient has fully recovered from his cholecystectomy and denies any further symptoms. Which of the following would you recommend at this point?

1. Surveillance
2. Obtain PET scan
3. Referral to liver surgeon for completion hepatectomy and lymph node staging
4. Start adjuvant therapy

A 60 year old woman presents with several months of progressive upper abdominal pain and unintentional weight loss. CT chest/abdomen/pelvis reveals a 4 cm mass in the R hepatic lobe with also multiple other liver lesions concerning for malignancy with also metastatic disease involving the retroperitoneal lymph nodes and lung. Ultrasound guided biopsy of the R hepatic mass shows adenocarcinoma c/w pancreaticobiliary source, and she is felt to have newly diagnosed metastatic intrahepatic cholangiocarcinoma. Her labs including creatinine and LFT's are all normal. Her ECOG is 1. She wishes to pursue palliative chemotherapy.

Which of the following treatment options would you recommend?

1. Gemcitabine/Cisplatin
2. Pemigatinib
3. FOLFOX
4. Gemcitabine alone
5. Hospice