Fred Hutch Cancer Center

Comprehensive Hematology & Oncology Review:

COLORECTAL CANCER

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UW Medicine

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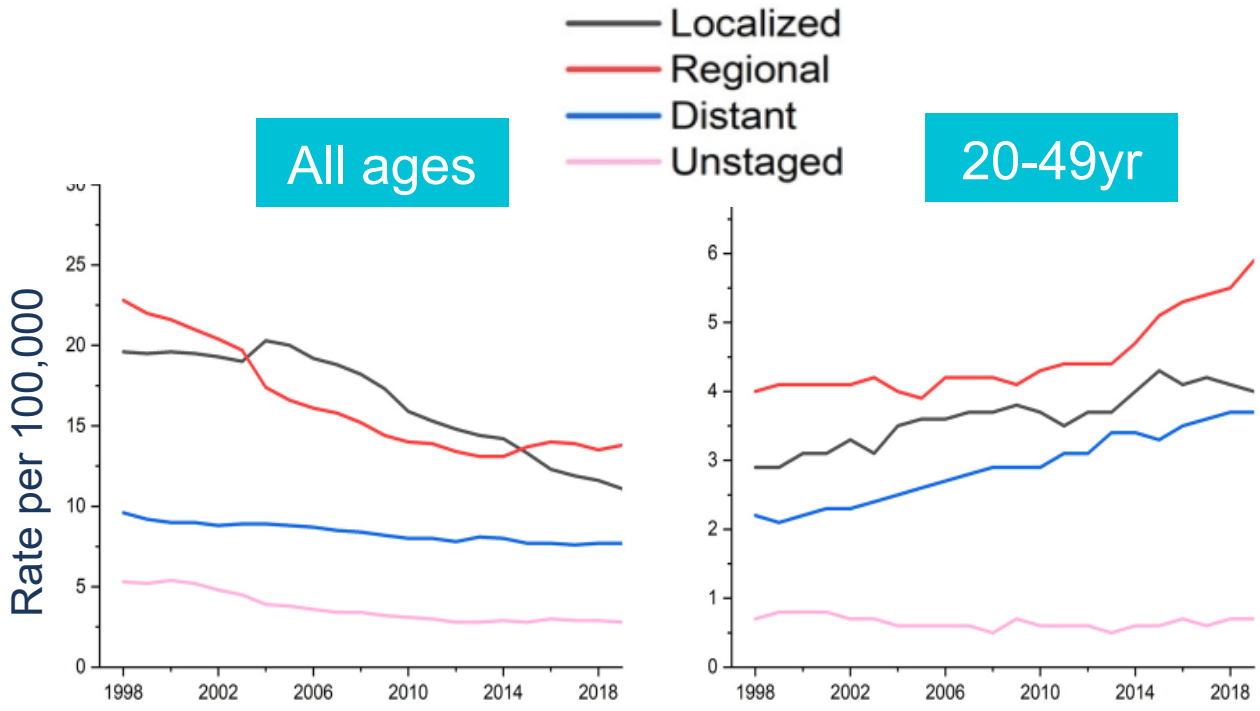
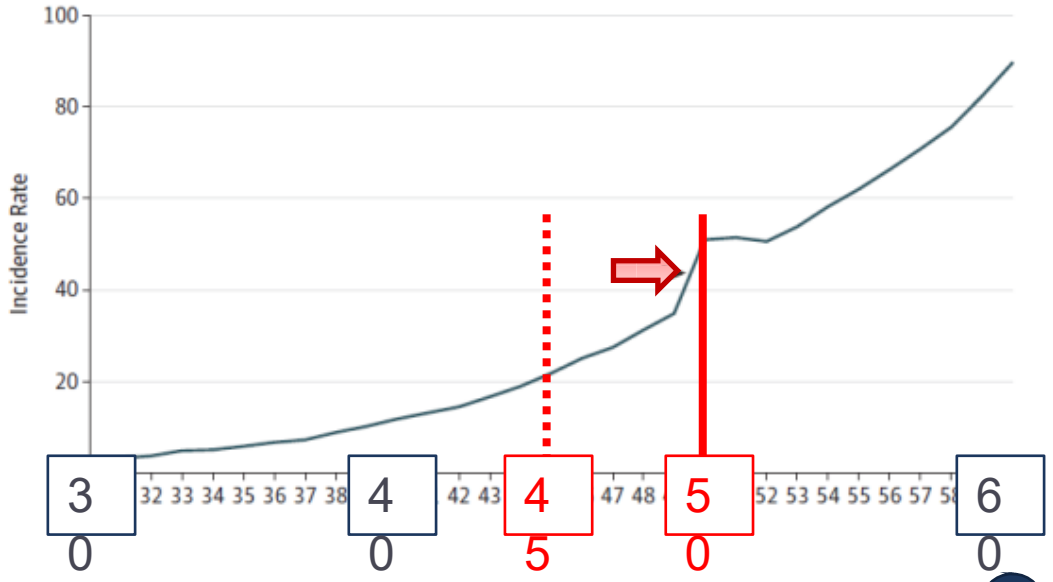
Epidemiology and Risk Factors

Epidemiology

- 90% are diagnosed after age 50, and the incidence has been declining
- But rising incidence in younger (unscreened) individuals

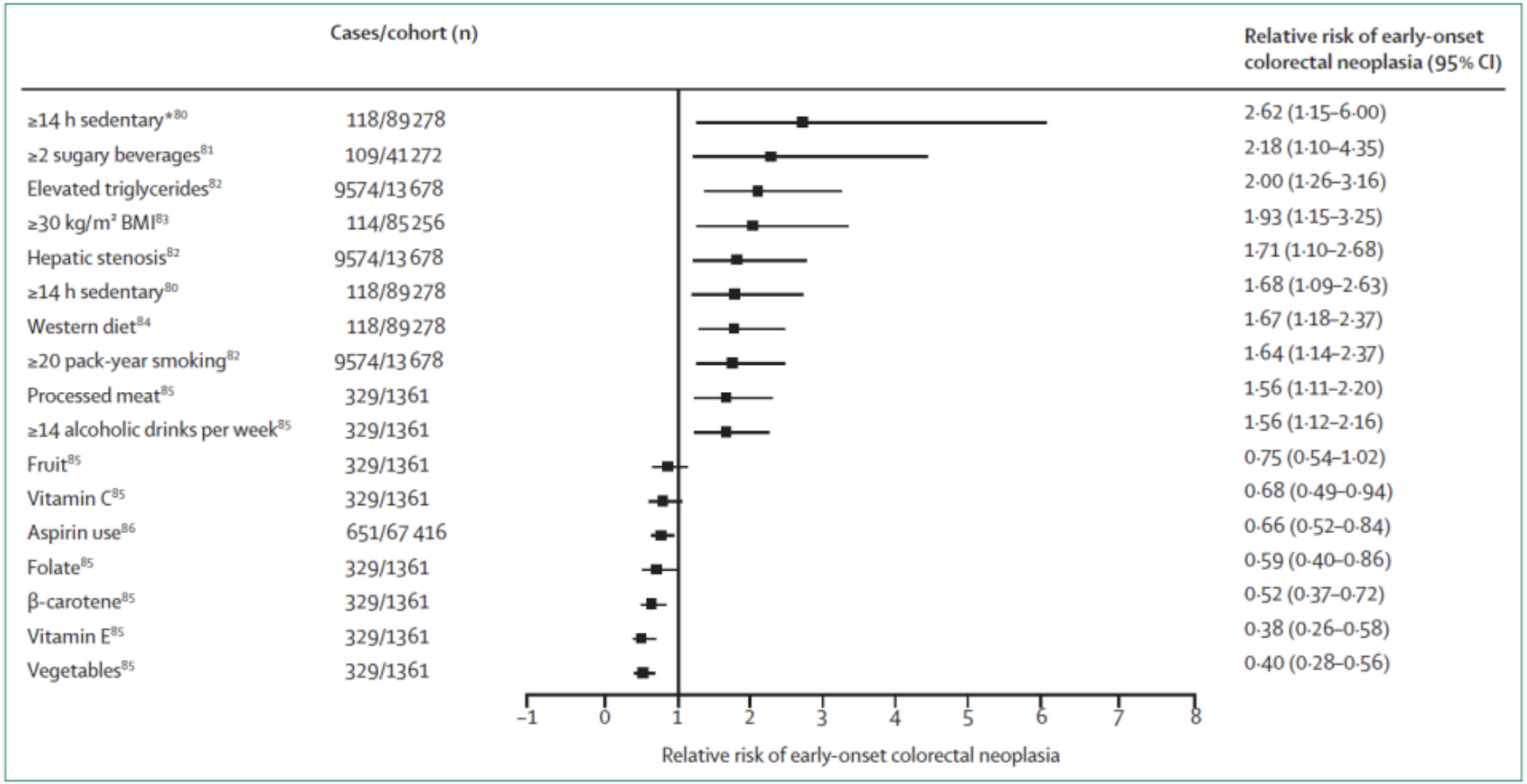


Start screening earlier: 50 ⇨ 45yo



Siegel, *CA: A Cancer J* 2023; Abualkhair, *JAMA Network Open* 2020; USPSTF, *JAMA* 2021

Environmental risk factors for CRC



- Oral antibiotics (♒)
- Microbiome (?)
- vitamin D (♓)
- Inflammatory bowel disease
  - both an environmental and hereditary risk factor

Patel, *Lancet Gastro Hep* 2022; Zhang, *Gut* 2019

Microsatellite instability (MSI) = deficient mismatch repair (dMMR)

Colorectal cancer

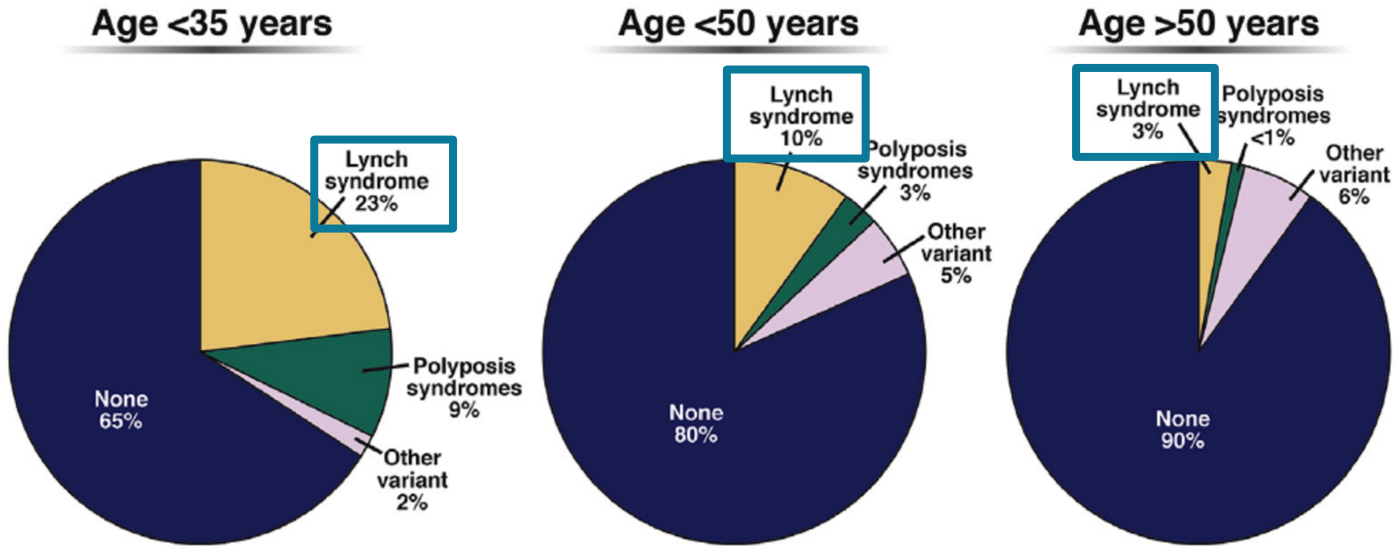
15%

MSI/dMMR*

20%

80%

Lynch syndrome: germline alteration in an MMR gene



Somatic alteration

Typically, due to MLH1 hypermethylation (often with a BRAF mutation)

*Testing can be done by PCR, IHC, and/or NGS

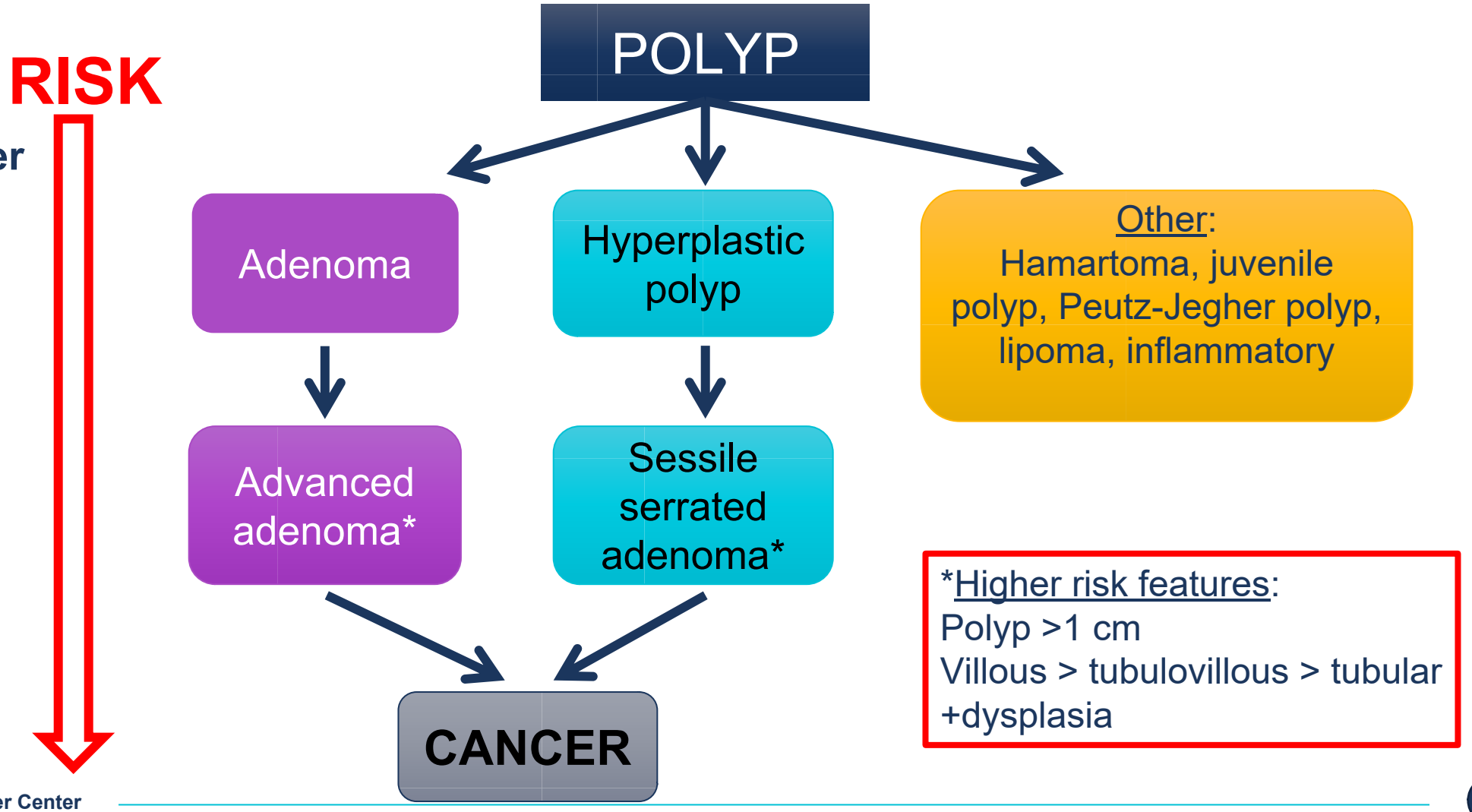
Stoffel, *Gastro* 2020

Polyps as precancerous lesions

Colorectal cancer screening:

Opportunities for prevention!

Opportunities for early detection



*Higher risk features:
Polyp >1 cm
Villous > tubulovillous > tubular
+dysplasia

Key points

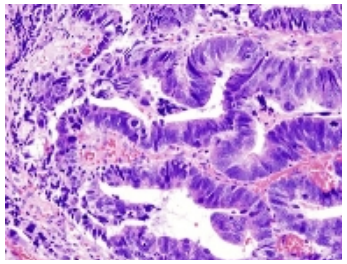
- Screening for average risk population now recommended to begin at 45yo

- Lynch syndrome
  - Most common hereditary CRC syndrome
  - Due to germline mismatch repair mutations → tumor MSI
  - Not all MSI is due to Lynch (esp. BRAF-mutant)

- >1cm and villous adenomas have the highest likelihood of devolving into cancer

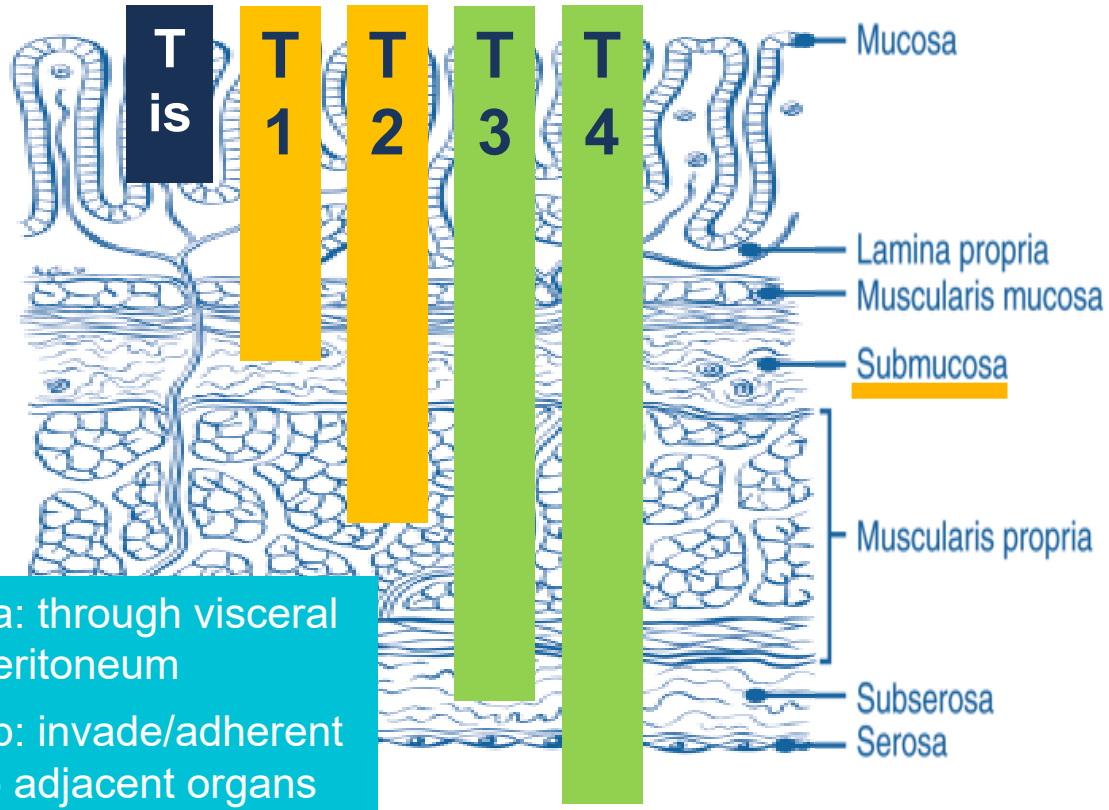
Evaluation and Initial Management

Work-up of suspected cancer



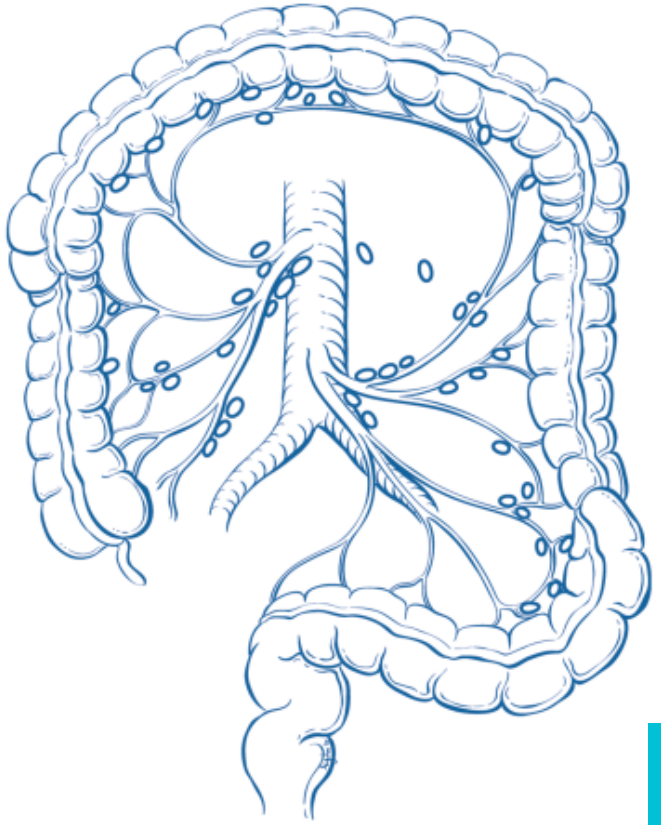
- Colonoscopy to terminal ileum
- Pathology (CK7- CK20+ CDX2+ villin+)
- Labs (including CEA tumor marker)
- Tumor molecular testing (MSI ± extended RAS/RAF/HER2)
- CT chest, abdomen, pelvis with contrast (and rectal MRI for rectal primary)
- PET scans are NOT routinely part of staging
  - Use to evaluate equivocal CT findings, or if IV contrast is contraindicated

Colorectal cancer staging: TNM score



4a: through visceral peritoneum

4b: invade/adherent to adjacent organs or structures



N0 no nodes

N1 1-3
N1a = 1
N1b = 2-3
N1c = deposits

N2 ≥ 4
N2a = 4-6
N2b = 7+

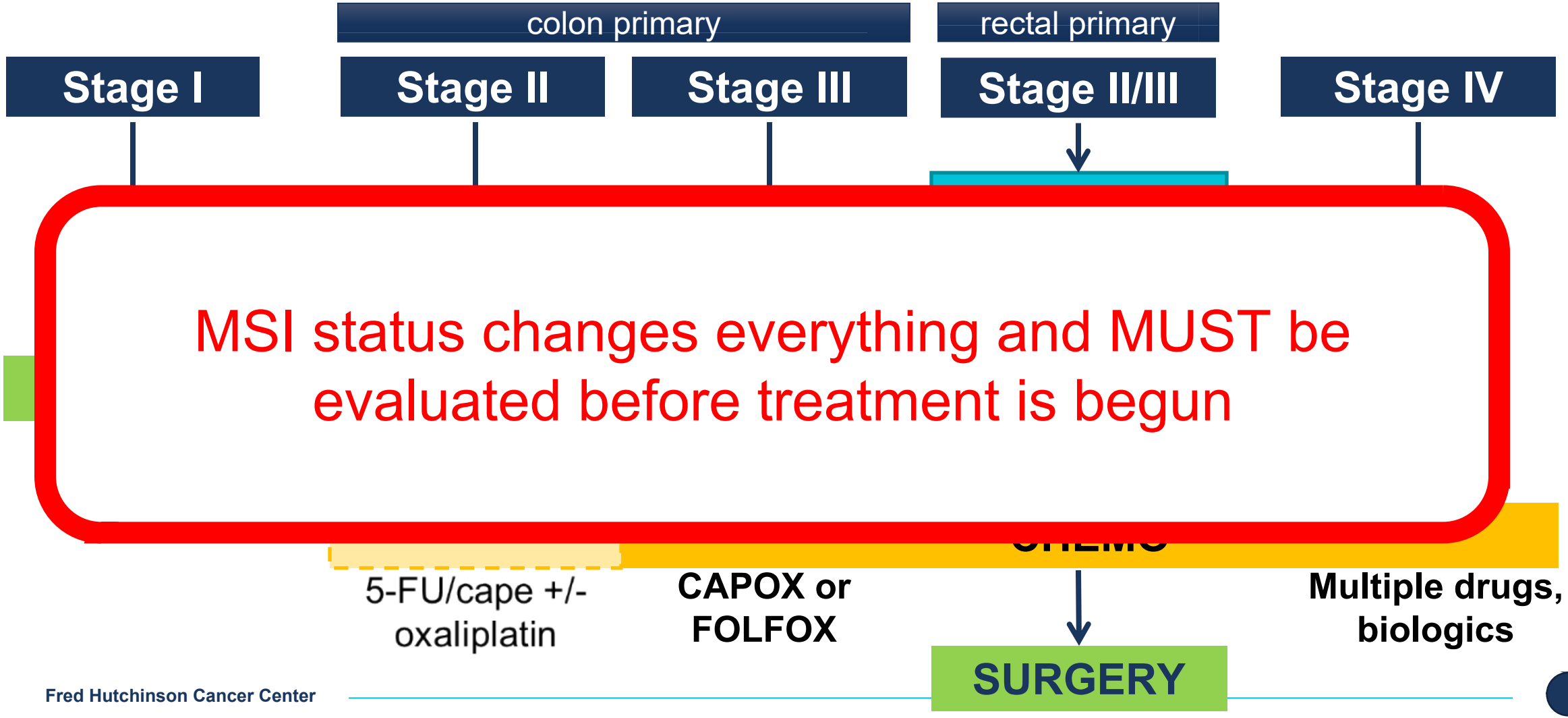
*Non-regional nodes are considered M1a

Colorectal cancer staging

	I		
	II	IIA: T3 N0 IIB: T4a N0 IIC: T4b N0	
	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	
		(2+ sites) IVC: Tx Nx M1c (peritoneal ± other)	

AJCC 8th edition; SEER data 2004-2010: colon

Treatment overview

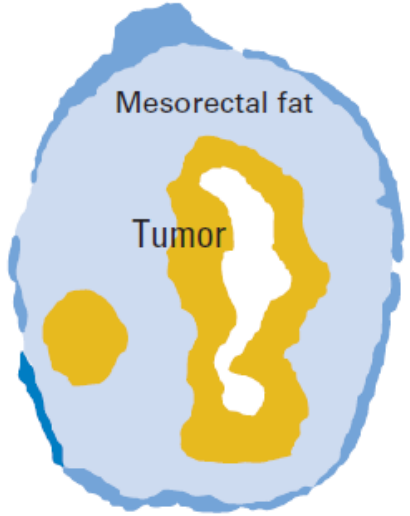


Surgery: Partial colectomy with en bloc lymph node removal

- 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 follows anatomic guidelines
  - Low anterior (LAR) or abdominoperineal (APR)
  - Improved circumferential margin clearance
  - Reduced local recurrence with complete TME



Nagtegaal, *JCO* 2008

Endoscopic resection

Endoscopic colon polypectomy

- Complete polyp removal (not fragmented)
- Negative margins
  - Controversial, but ideally >1mm
- Pedunculated
  - Higher recurrence risk if sessile
- Favorable histologic features
  - Grade 1-2, no lymphovascular or perineural invasion

Rectal transanal excision

- T1 tumors only (limited to submucosa), N0 M0
- Clear margin (>3mm) obtainable
- < 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 lymphovascular or perineural invasion

- Otherwise, full oncologic bowel resection surgery
- Local excision may have less complications (sphincter, bladder, sexual dysfunction), but has a higher risk of local recurrence

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 stage I cases

Adjuvant Chemotherapy for Colon Cancer

Stage **II**: Adjuvant chemotherapy

- Historically, use is controversial
  - 2-3% non-significant benefit
- May be beneficial for tumors with “high-risk” features:

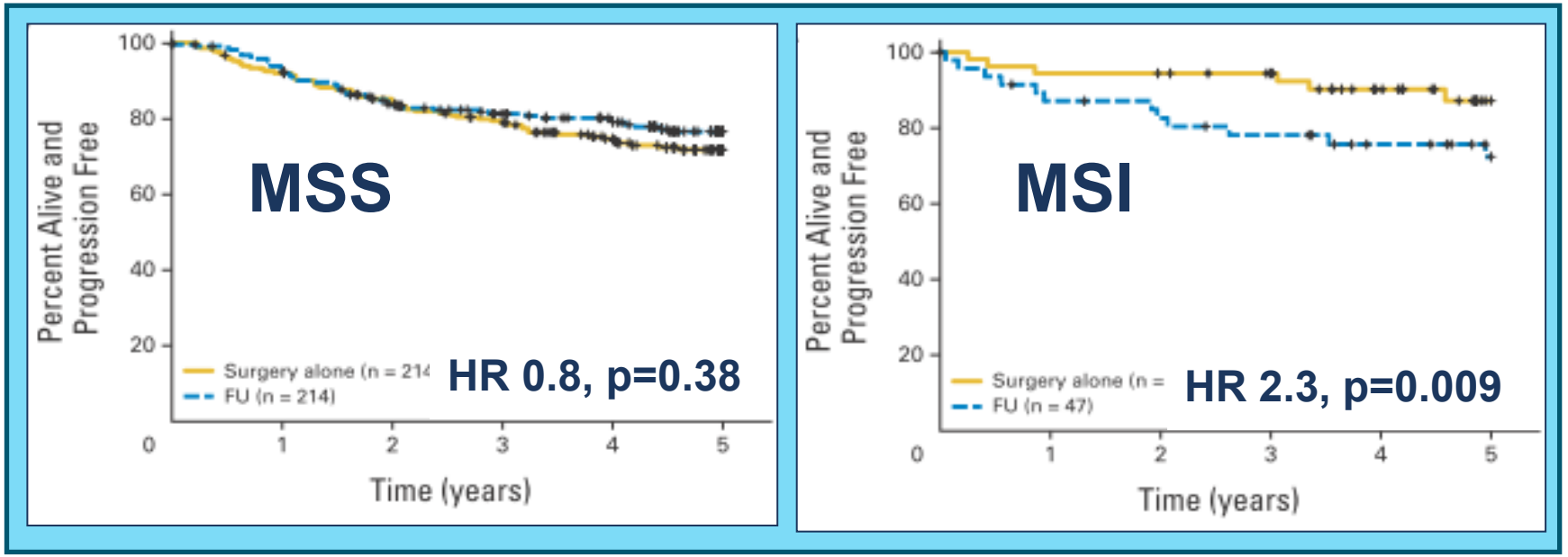
pT4	Bowel obstruction / perforation
Poorly differentiated	< 12 lymph nodes evaluated
Lymphovascular or perineural invasion	Close, indeterminate, or positive margins
High tumor budding	ctDNA positivity (controversial)

- Newer data support adjuvant therapy in high-risk MSS stage II, but observation is also acceptable
  - Regimen and duration are debated

Yothers, *JCO* 2011; Meyers, *Curr Oncol* 2016; Iveson, *JCO* 2021; Tie, *NEJM* 2022

Stage II guided by molecular sub-types

- Microsatellite instability is a useful predictive 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

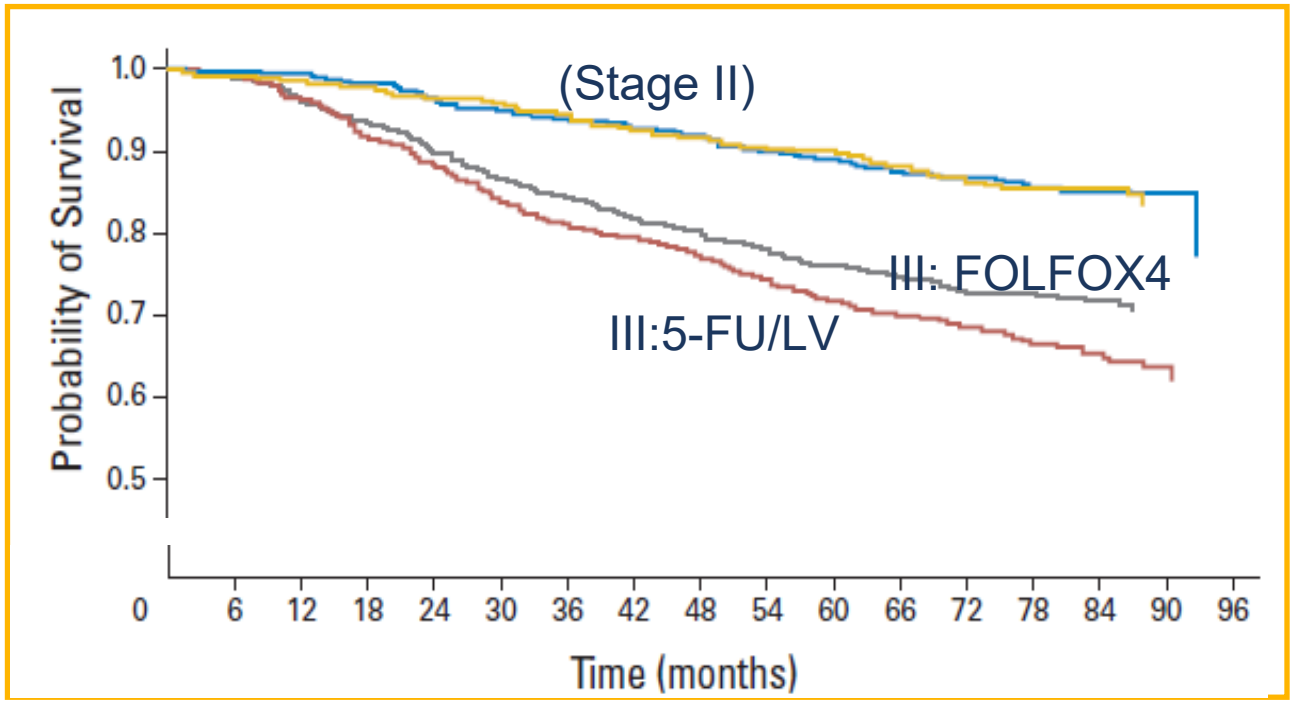
Sargent, *JCO* 2010; Yothers, *JCO* 2011; Tougeron, *JNCI* 2016

Stage III: Adjuvant chemotherapy

- Recommendation is an oxaliplatin doublet with 5-FU (FOLFOX) or capecitabine (CAPOX) x 3-6 mo
  - Data for oxaliplatin if ≥70yo had been debated, but newest data is supportive of the doublet[3]

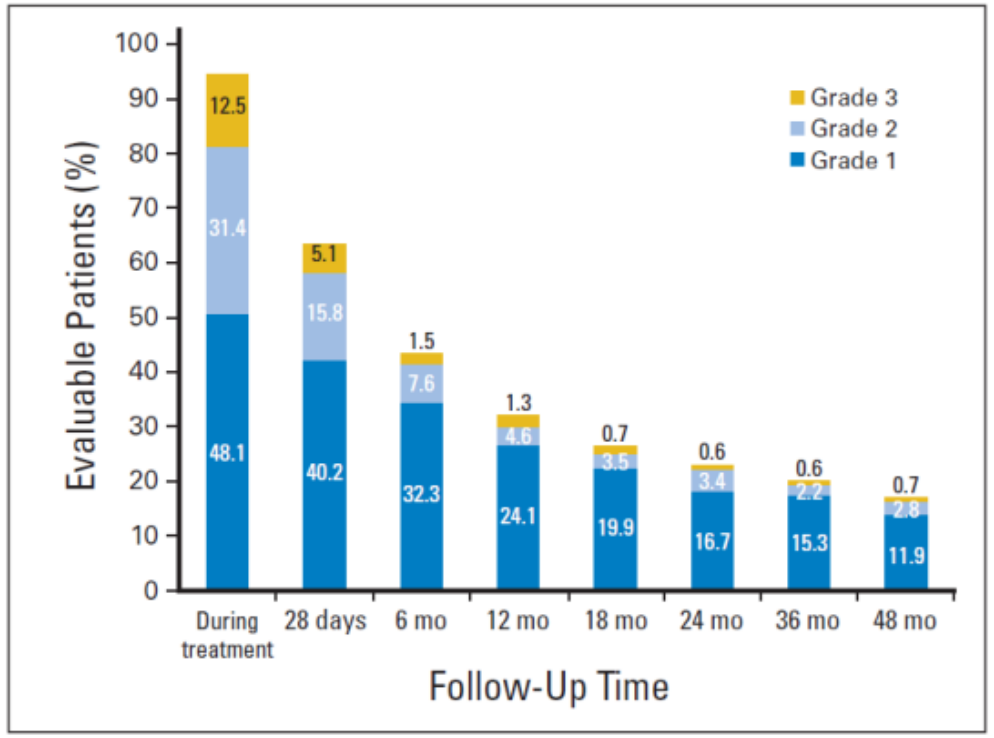
MOSAIC: FOLFOX vs 5-FU[1,2]

- 3-year DFS:
  - 78 vs. 73%, p=0.002
  - HR 0.76 (24% better)
- 6-year OS:
  - 73 vs. 68%, p=0.02



[1]Andre, *JCO* 2004; [2]Andre, *JCO* 2009; [3]Gallois, *JCO* 2024

Oxaliplatin neuropathy



Neuropathy	3 months		6 months	
	FOLFOX	CAPOX	FOLFOX	CAPOX
Grade 2	9%	14%	26%	29%
Grade 3-4	1%	2%	9%	8%

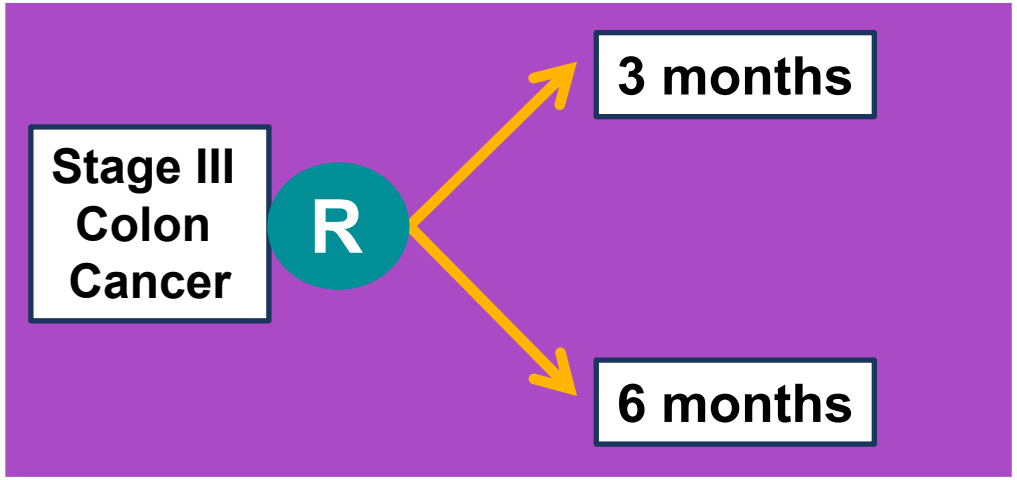
>90% get neuropathy from oxaliplatin
15% is “permanent,” but usually mild

Longer duration of oxaliplatin is associated with greater neuropathy

Andre, *JCO* 2009; Iveson, *JCO* 2021

Is 3 months sufficient?

- **IDEA** consortium
  - 6 trials, 12,800 participants
  - Investigator's choice for FOLFOX (60%) or CAPOX
  - 66% T3, 21% T4; 28% N2



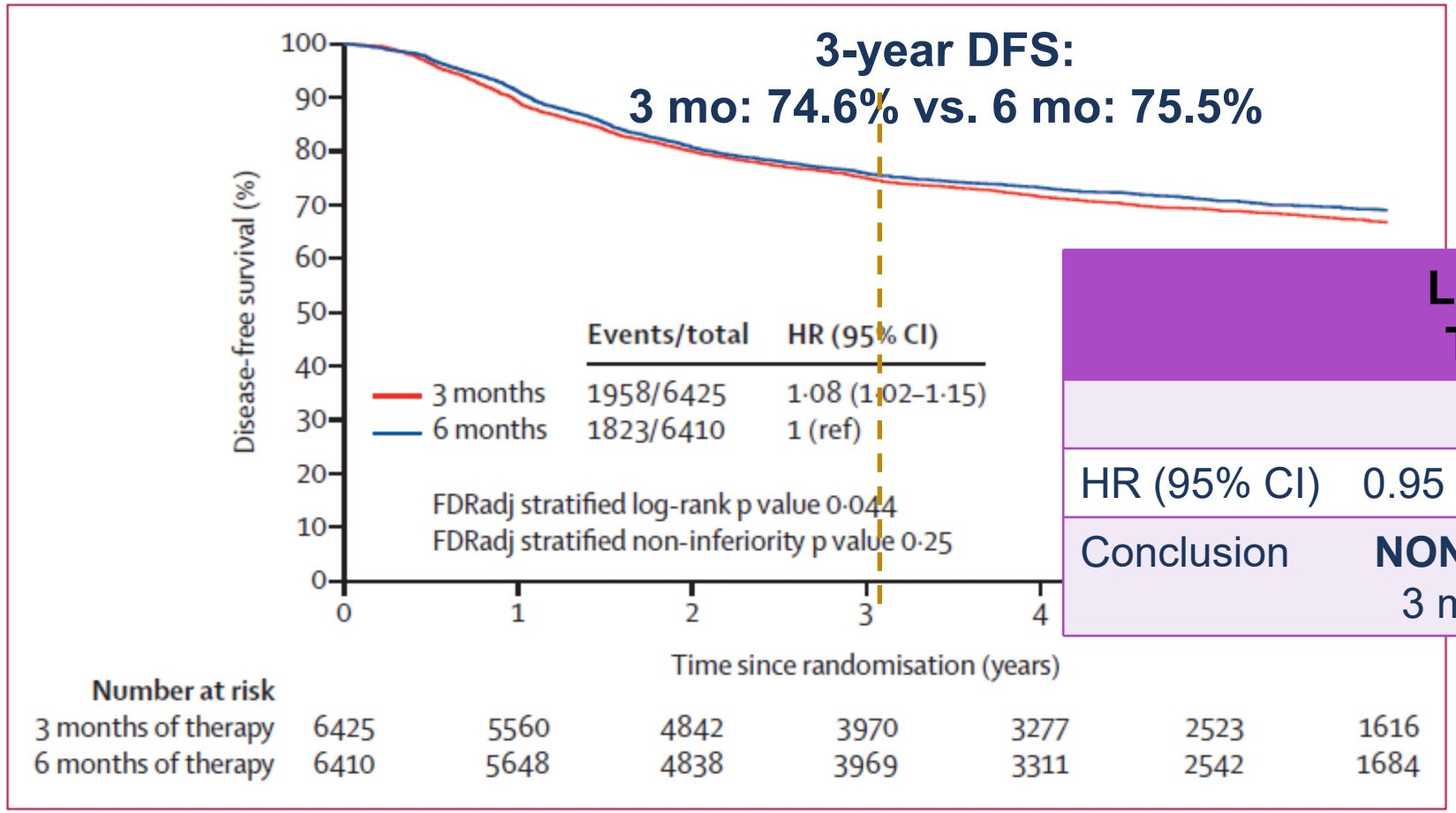
- **C80702** (n=2440) was the only trial conducted in North America
  - Protocol only allowed FOLFOX

- Designed as a non-inferiority trial with DFS HR 1.12
  - 12% "harm" arbitrarily decided to be acceptable to change to 3 months
  - Some trials permitted high-risk stage II cancers, which were analyzed separately

Sobrero, *JCO* 2018; Andre, *JCO* 2018; Grothey, *NEJM* 2018

Primary outcome: disease-free survival

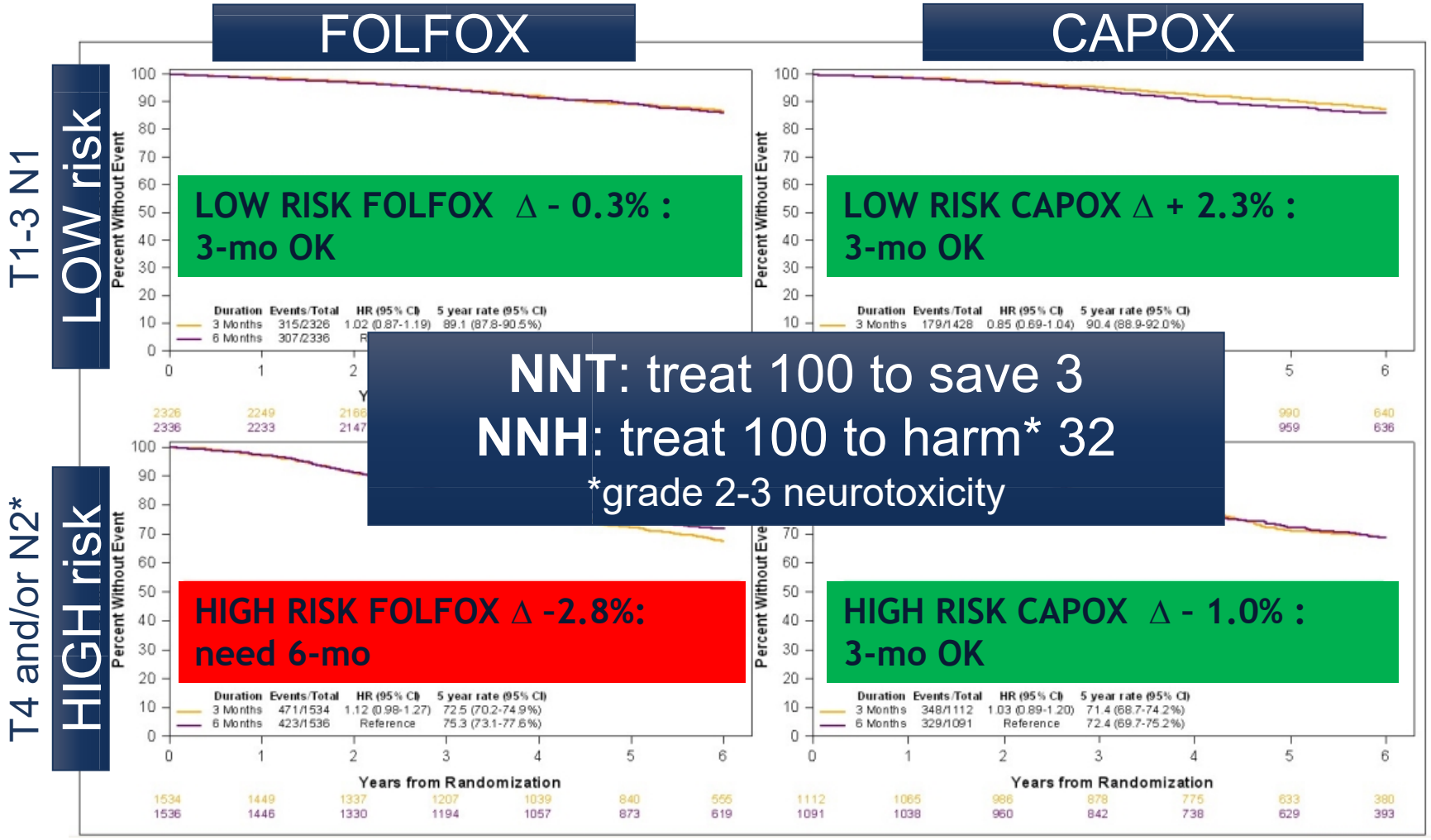
- NOT non-inferior



	LOW risk T1-3 N1	HIGH risk T4 and/or N2
	59%	41%
HR (95% CI)	0.95 (0.84 – 1.08)	1.08 (0.98 – 1.19)
Conclusion	**NON-INFERIOR** 3 mo likely ok	**INFERIOR** 6 mo needed

Andre, *Lancet Oncol* 2020

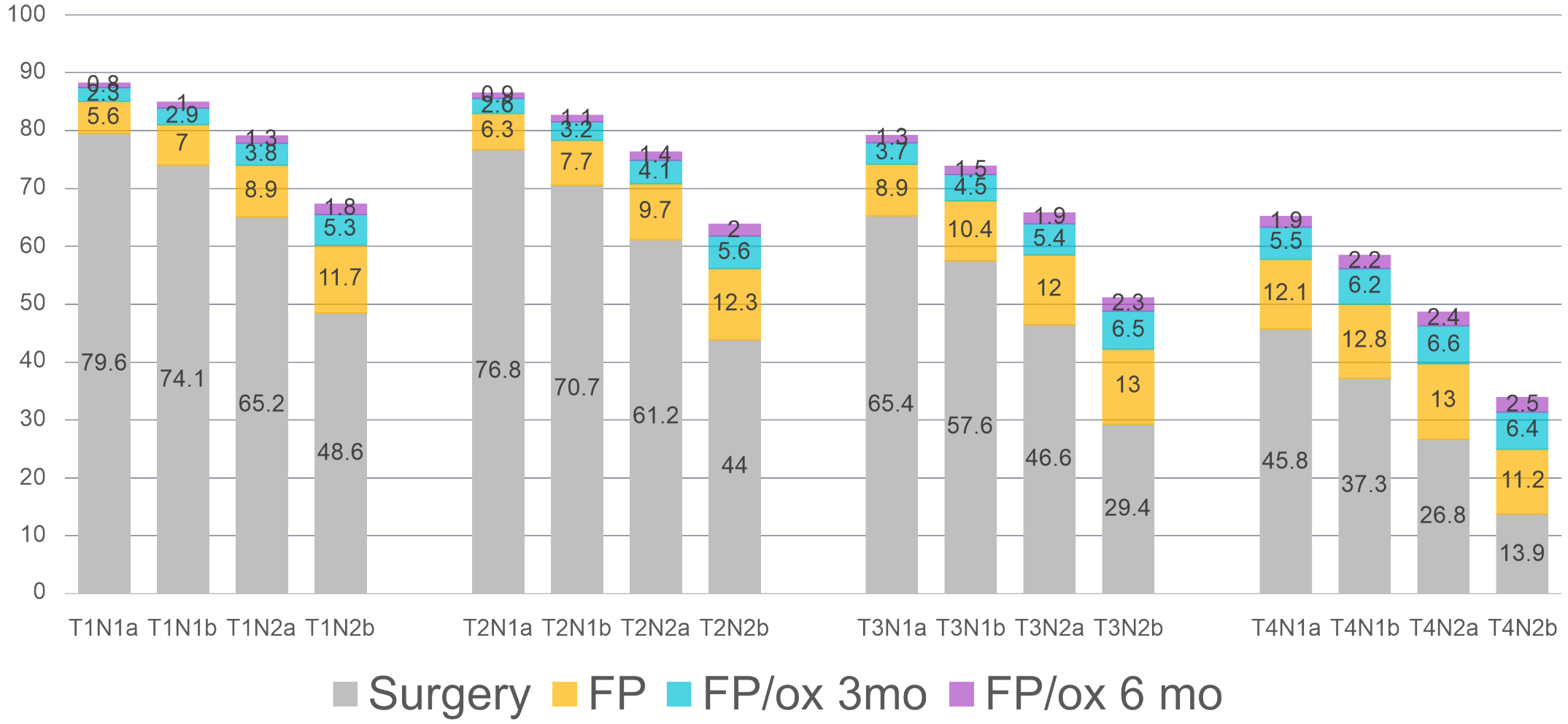
OS outcomes by risk and by regimen



*T4 risk > N2

Sobrero, *ASCO* 2020; Yamanaka, *ESMO GI* 2020; Andre, *Lancet Oncol* 2020

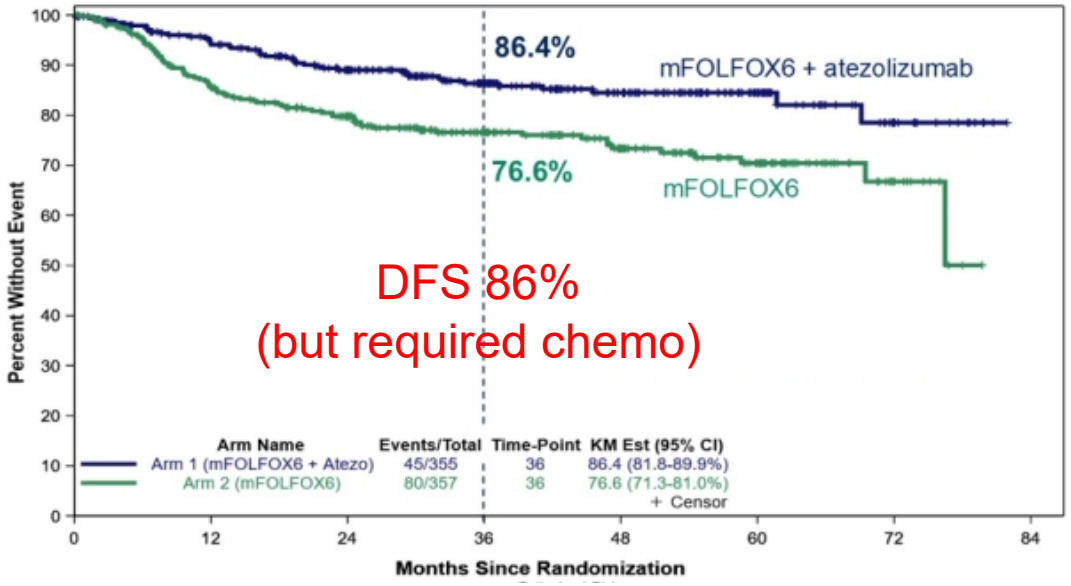
5-year disease-free survival: incremental benefits



Adapted from: Sobrero, *Eur J Cancer* 2020

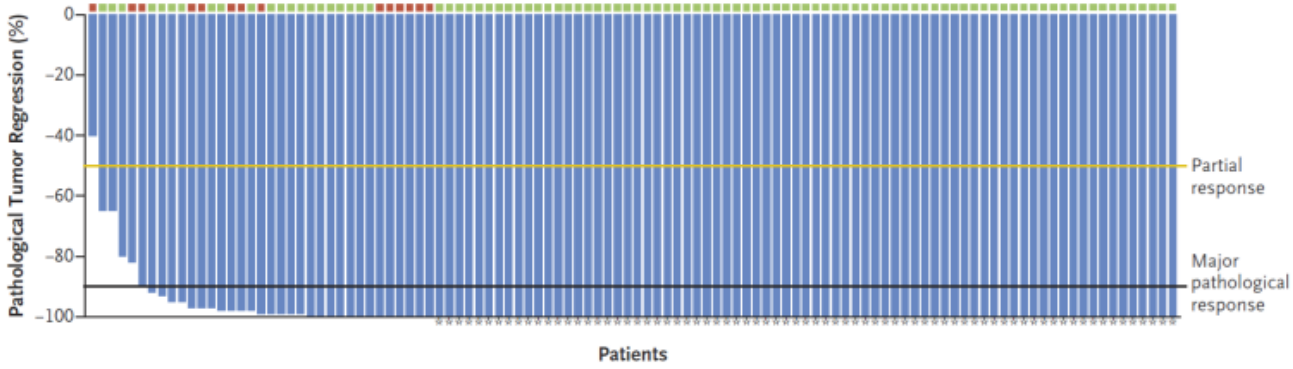
Localized MSI-high colon cancer: more options than ever

- **ATOMIC** trial: adjuvant chemoimmunotherapy
  - N=712 stage III resected MSI-H
  - Randomized 1:1 to 6 mo of
    FOLFOX vs **FOLFOX + atezo**
    (atezo x 1 year total)



DFS 86%
(but required chemo)

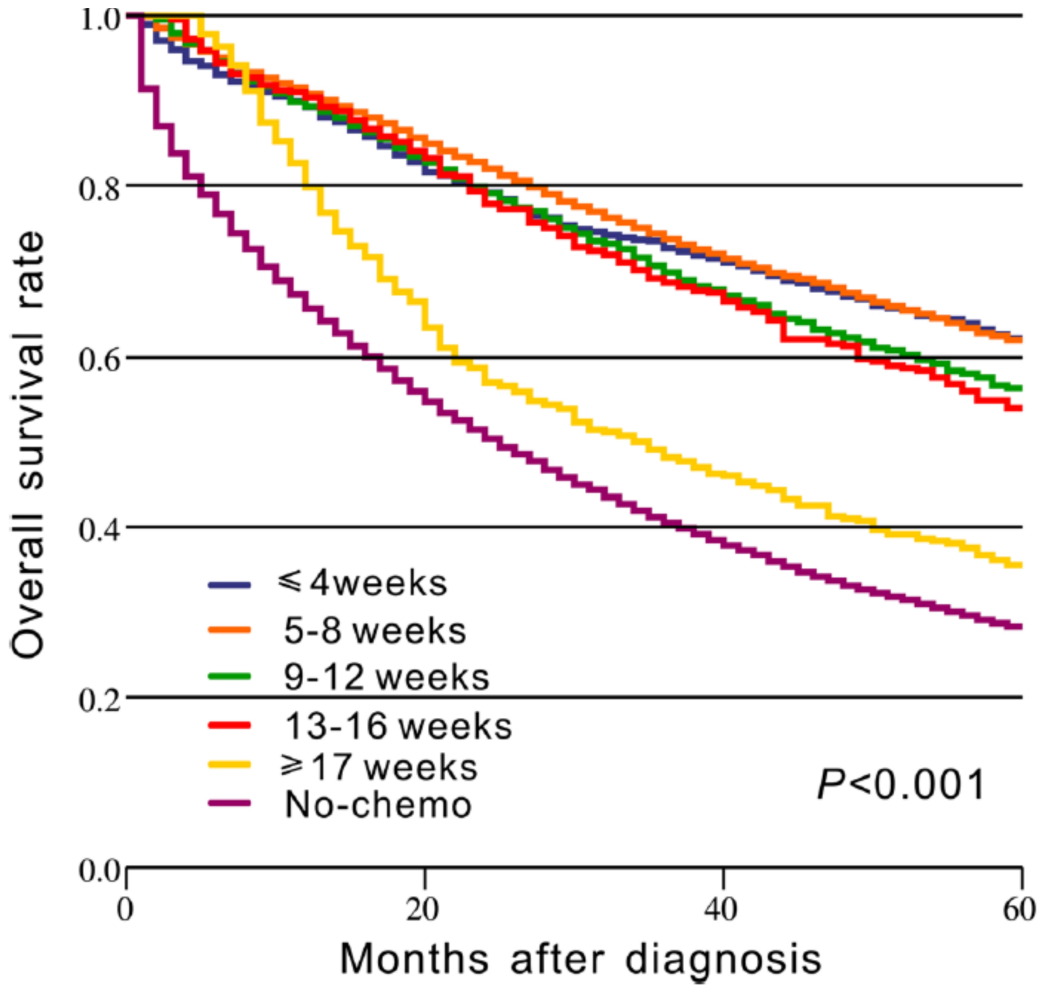
- **NICHE2** trial: neoadjuvant immunotherapy
  - N=115 untreated stage I-III MSI-H
  - Single-arm 1 mo of nivolumab/ipilimumab followed by surgery



DFS 100%
(but included earlier stages)

Sinicrope, *ASCO* 2025; Chalabi, *New Engl J Med* 2024

Time to adjuvant chemotherapy vs. survival



- Prior analysis suggested 14% decrease in OS for each 4-week delay after 8 weeks
- Meta-analysis of >18,000 patients
  - Greatest benefit <8 weeks post-op
  - But still some benefit up to +16 weeks
- Newer post hoc analysis suggests <6 weeks is preferred

Gao, *BMC Cancer* 2018; Biagi, *JAMA* 2011; Gogenur, *JAMA Surg* 2024

Emerging role of ctDNA

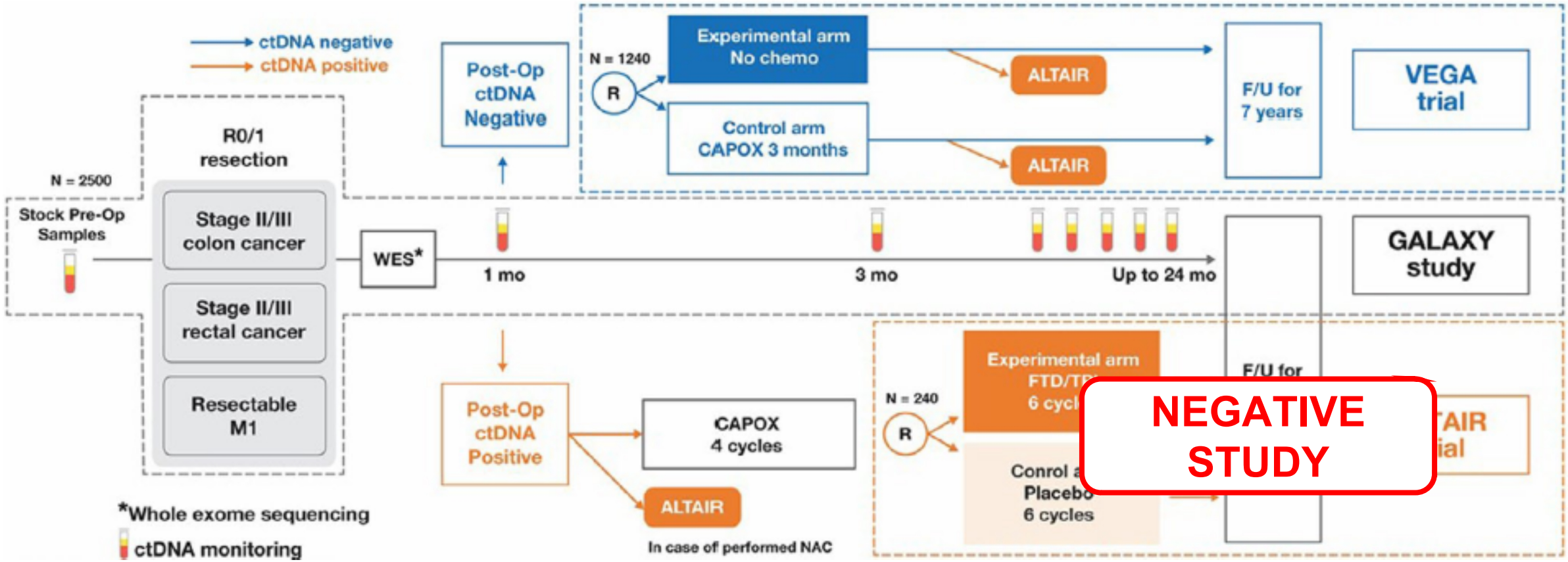
- Low levels of cell-free DNA (cfDNA) can be detected even in healthy individuals (1-10 ng/ml)

- circulating tumor DNA (ctDNA) = detecting mutations in cfDNA that are highly specific for cancer
  - Half-life: <2 hours, levels are cancer burden-dependent
  - False positives: infection, inflammation, trauma, etc.

- ctDNA is a putative biomarker to demonstrate MRD
  - Minimal/molecular residual disease (MRD) = small volume disease not appreciated radiographically or with other clinical measures

Cohen, *Nature* 2023

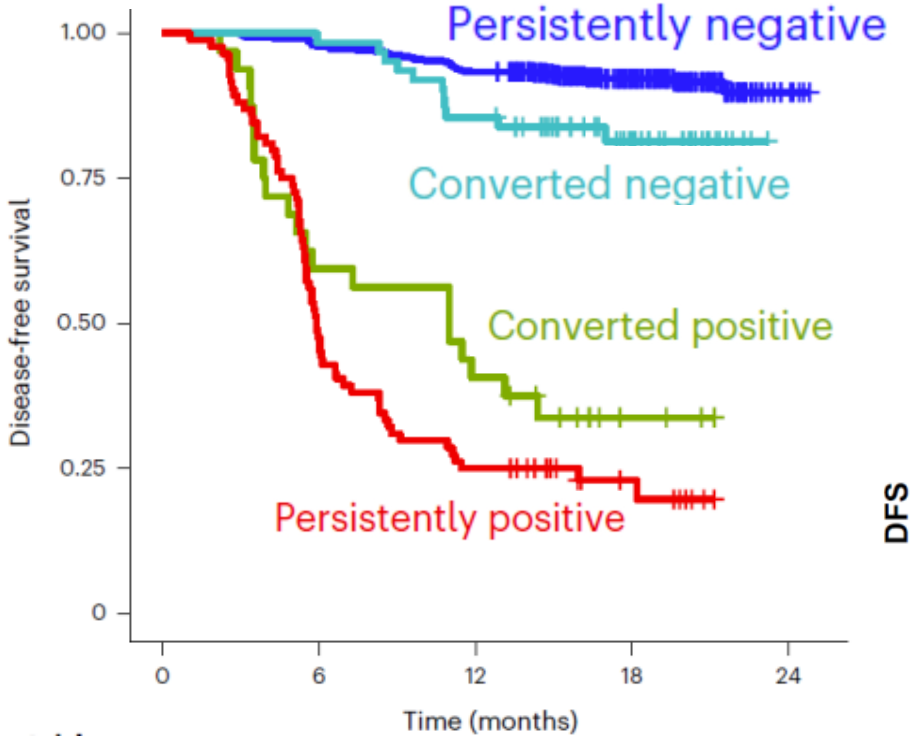
GALAXY: largest prospective observational collection

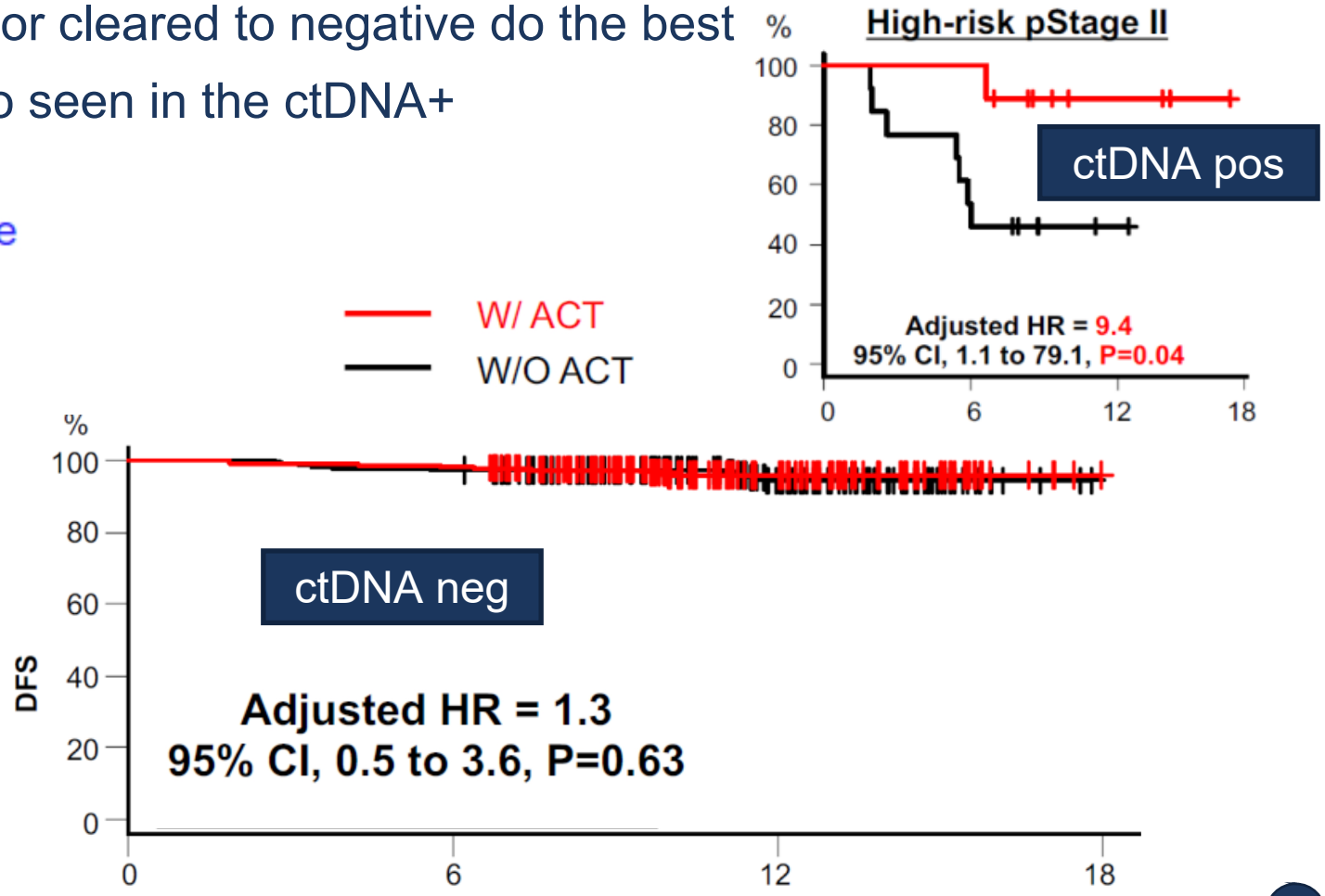


Kotani, *GI ASCO* 2022, *Nat Med* 2023

GALAXY results: DFS (in months from surgery)

- Confirm prior results that negative or cleared to negative do the best
- Greatest benefit of adjuvant chemo seen in the ctDNA+

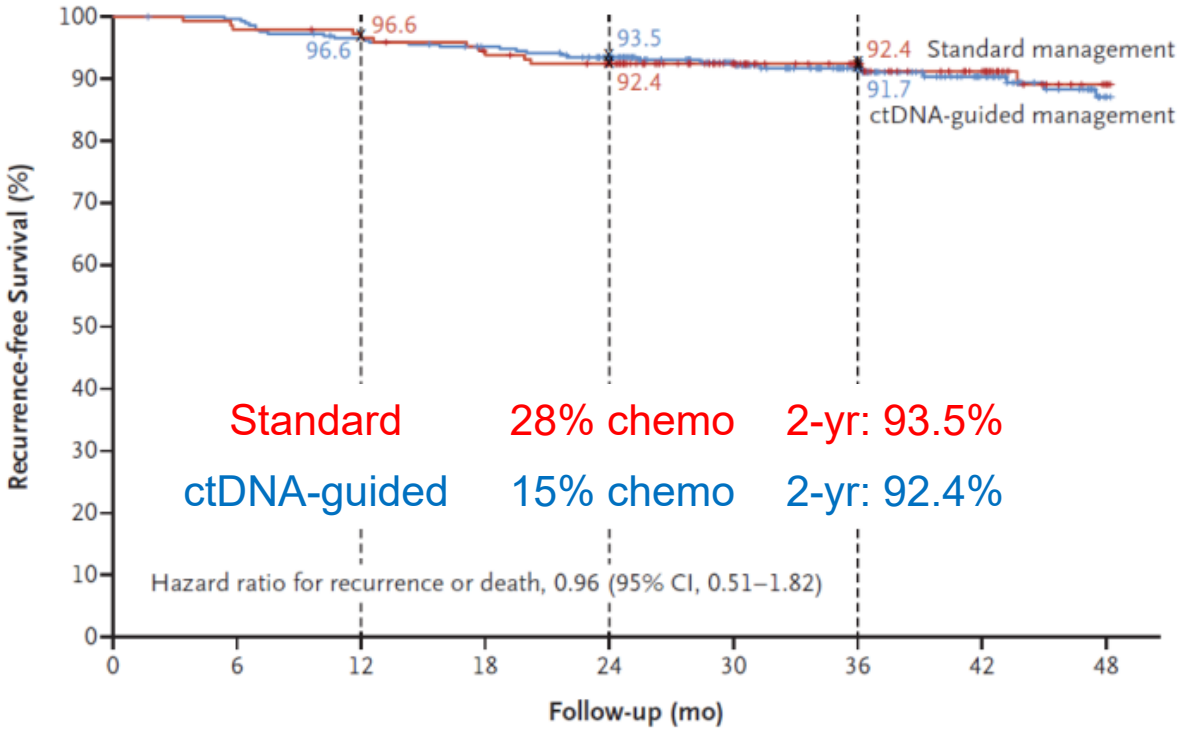


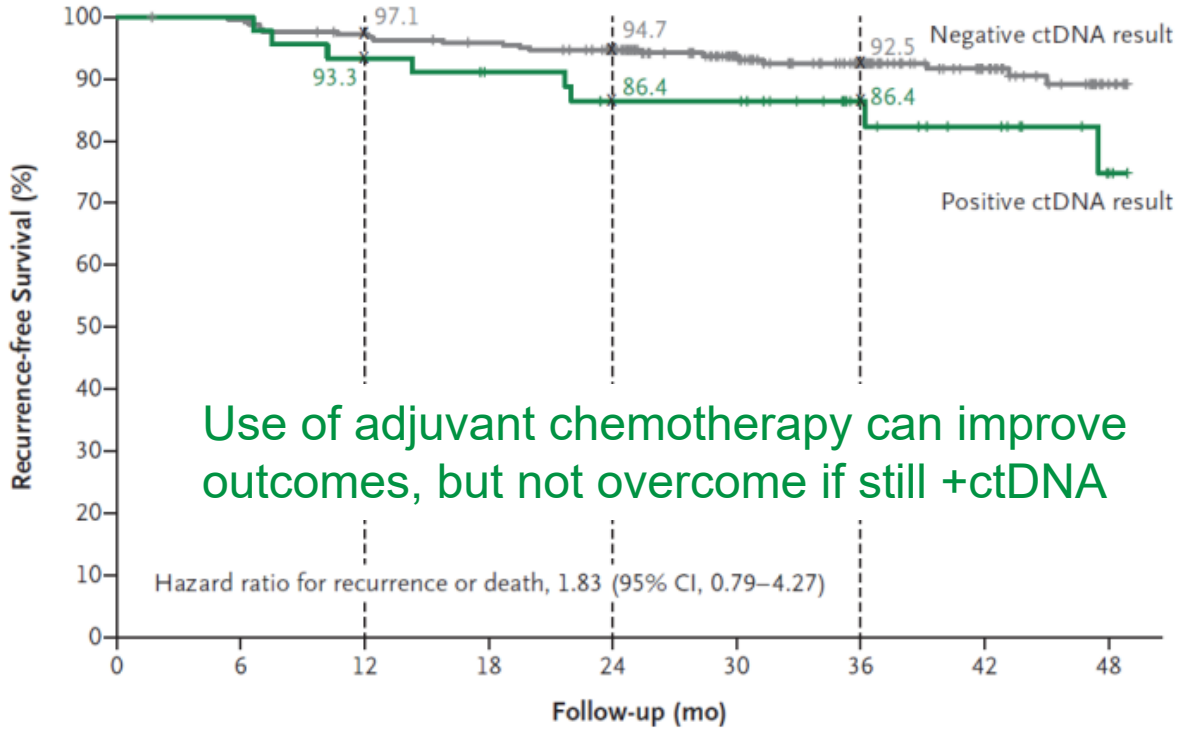


Kotani, *GI ASCO* 2022; *Nat Med* 2023

DYNAMIC: the first reported large prospective study

- 455 resected stage 2 colon cancer → randomized to ctDNA-guided management vs. standard management
  - 302 ctDNA-guided: received chemotherapy only if positive (at 4 and/or 7 weeks post-op)





Tie, *NEJM* 2022; *ESMO* 2022

Key points

- MSI status must be known upfront
  - Discuss neoadjuvant immunotherapy before surgery
  - Adjuvant chemoimmunotherapy for resected stage III is now standard

- Overall, no benefit for adjuvant chemotherapy in stage II
  - Use for T4 and consider for other “high-risk” MSS patients, but avoid in MSI

- 3 months of adjuvant chemotherapy is the new standard for stage III
  - 6 months is still suggested for high-risk (T4 or N2) patients who receive FOLFOX

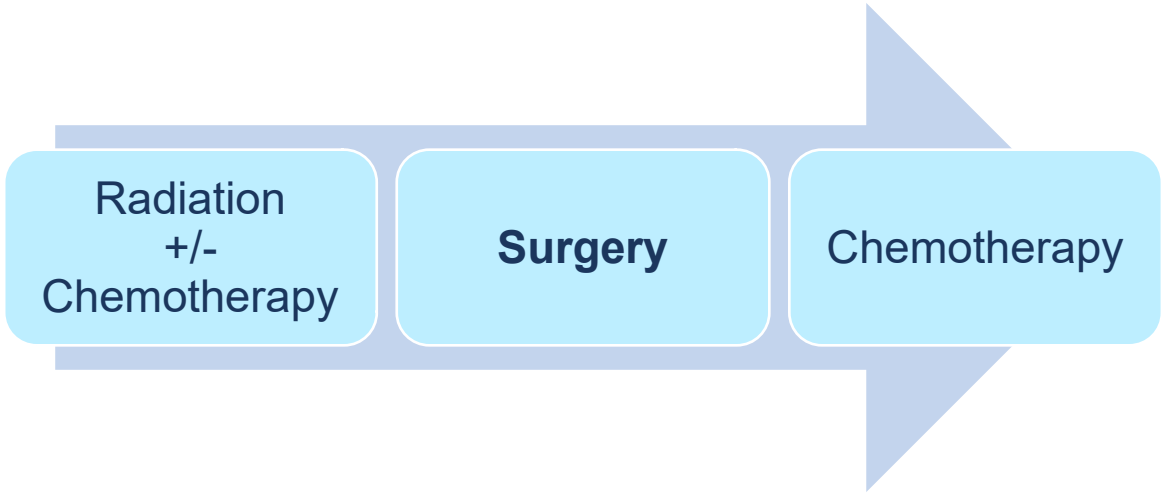
- No indication for irinotecan, cetuximab, or bevacizumab

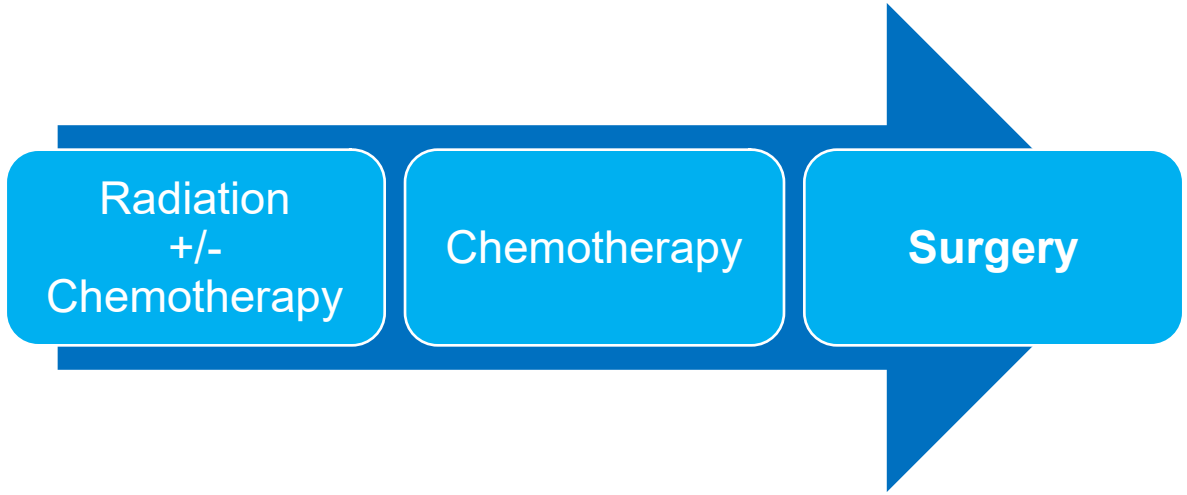
- Aim to start 4-8 weeks after surgery

Localized Rectal Cancer

Rectal cancer: General principles

- Definition: primary lesion within 12 cm of anal verge by rigid proctoscopy
  - Treating cancers entirely above the anterior peritoneal reflection “as colon” (*i.e.*, upfront surgery)
- Higher local pelvic recurrence (and morbidity) compared to colon
- Paradigms for “standard-of-care” are changing





Pelvic radiation

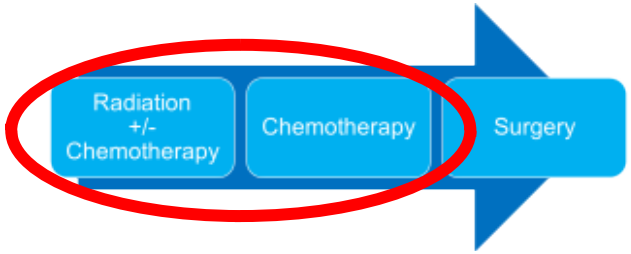
- Delivered in the neoadjuvant setting to improve survival and decrease pelvic relapse
  1) **Long-course/standard**: chemoradiation 50.4Gy over 28 fractions (5.5 weeks) with capecitabine
  2) **Short-course**: hypofractionated 25Gy (5Gy x 5 days), NO chemo

- Either way, surgery should be ~8 weeks later

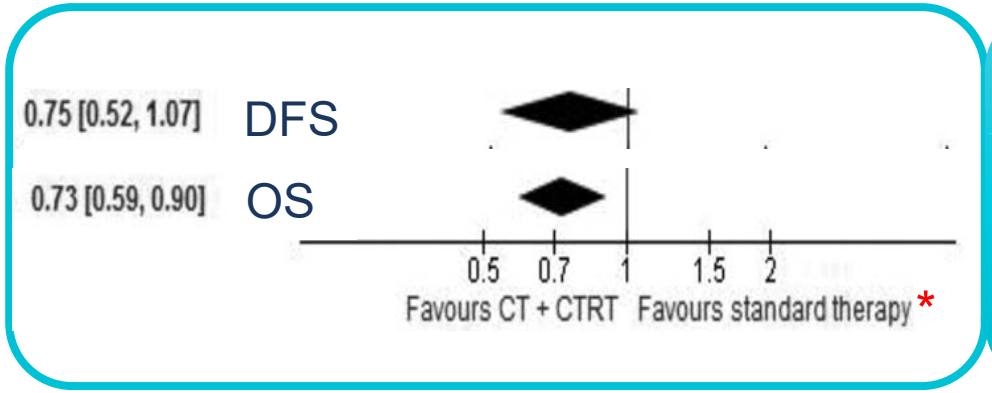
- Short-course may have inferior outcomes with non-operative management (**RAPIDO** trial)

Bahadoer, *Lancet Oncol* 2020; Dijkstra, *Ann Surg* 2023

Total neoadjuvant therapy



- Administration of both chemoRT and systemic chemotherapy PRIOR to surgery
  - Removes the need for adjuvant therapy
  - Can be done with short- or long-course RT



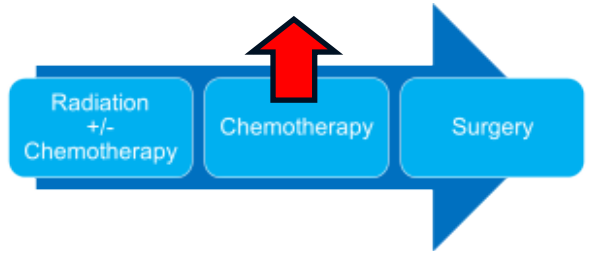
At a minimum, TNT recommended in:
- Unresectable or may convert from APR to LAR
- Bulky, T4, and/or N2
- Involved circumferential margin

- Studies suggest higher pCR rate (25-45% vs. 15-20%)
  - Especially if chemoRT done first?

*Prior standard-of-care: chemoRT → surgery → adjuvant chemo

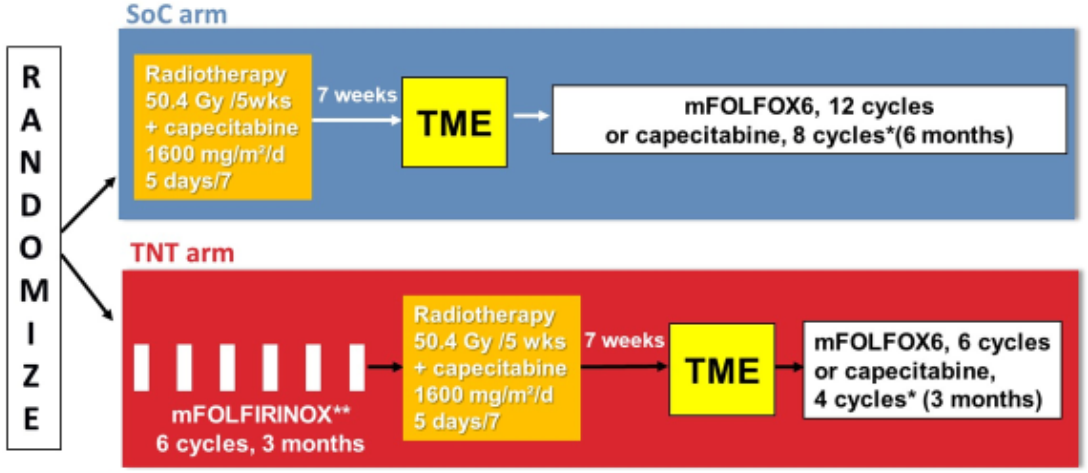
Petrelli, *Ann Surg* 2020; Garcia-Aguilar, *JCO* 2022; Conroy, *Lancet Oncol* 2021

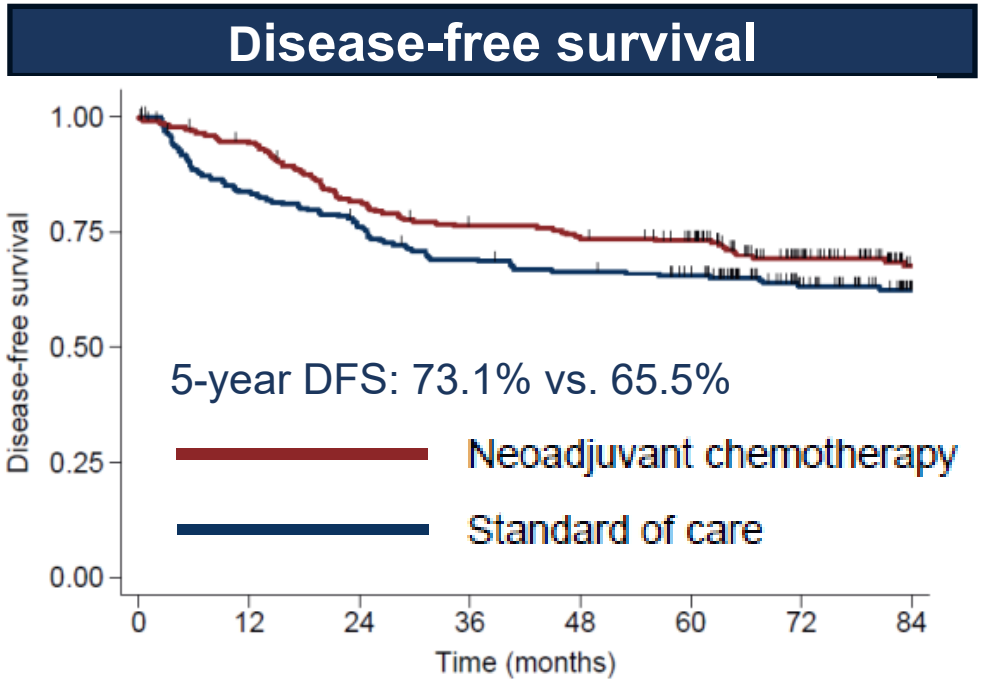
Escalation of chemotherapy



- FOLFIRINOX is associated with higher response rates → could this be used in neoadjuvant?

- **Prodige 23**: randomized TNT with FOLFIRINOX vs. neoadjuvant chemoRT alone*



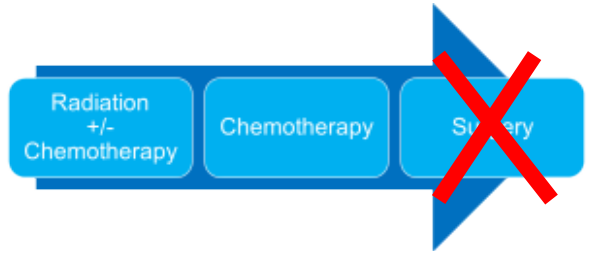


- **JANUS** study will address the chemo superiority question (completed accrual, not yet reported)

Conroy, *ASCO* 2023, *Ann Oncol* 2024

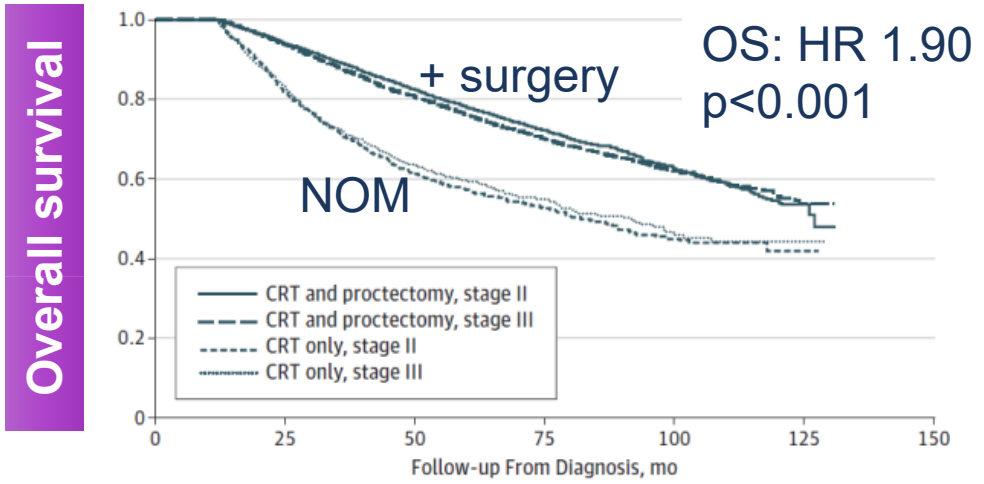
*Prior standard-of-care: chemoRT → surgery → adjuvant chemo

Non-operative management (NOM)

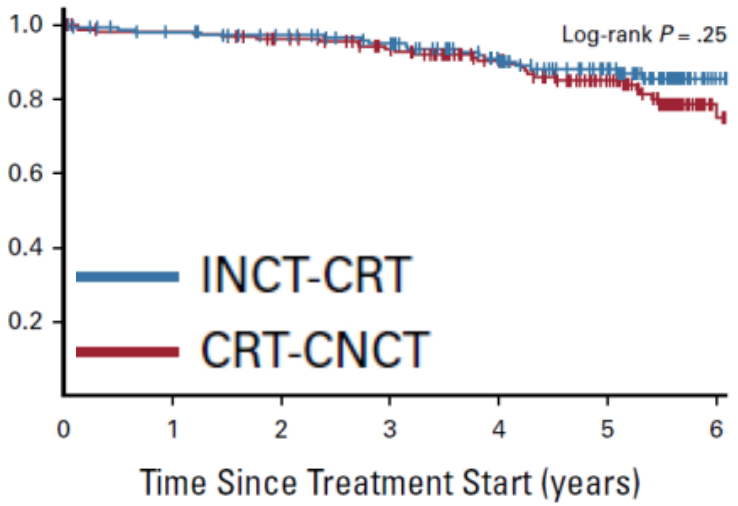


- "Watch and wait" approach
  - Avoid surgical morbidity, possibly avoid a permanent ostomy
- Higher rates of local and possibly distant failure
- Need a complete clinical response (by CT, MRI, and endoscopy)

NCDB: CRT only (2004-2008)

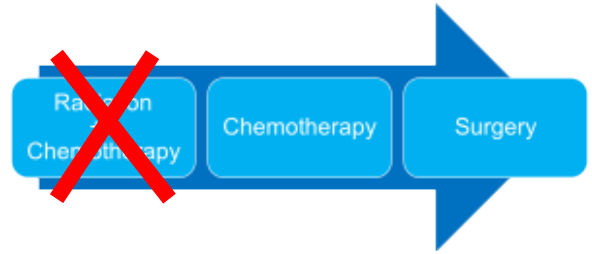


OPRA trial: TNT (2013-2020)



Ellis, *JAMA Onc* 2017; Verheij, *JCO* 2023

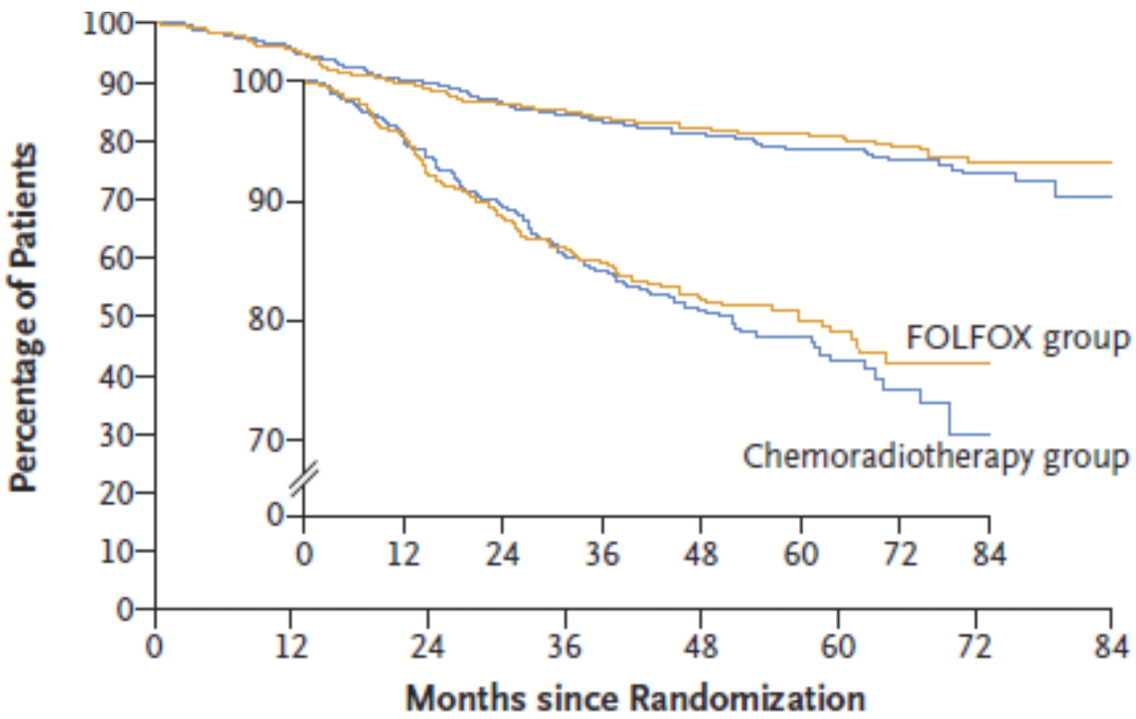
Omitting radiation



- Early chemotherapy impacts micrometastases
  - Deaths from rectal cancer usually from distant metastases, not local recurrence
- Radiation has a significant impact on fertility

- **PROSPECT** trial: T2N+, T3N0, T3N+
  - Phase III trial of **peri-operative FOLFOX** (+ selective RT for poor responders or R1) vs "**chemoradiotherapy group**"*
  - Met non-inferiority for DFS and improved QOL
- Based on IDEA, NCCN included just the 3 mo of neoadjuvant chemo

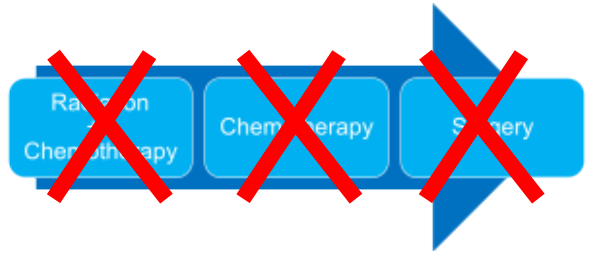
Disease-free survival



*Prior standard-of-care: chemoRT → surgery → adjuvant chemo

Schrag, *NEJM* 2023; Basch, *JCO* 2023

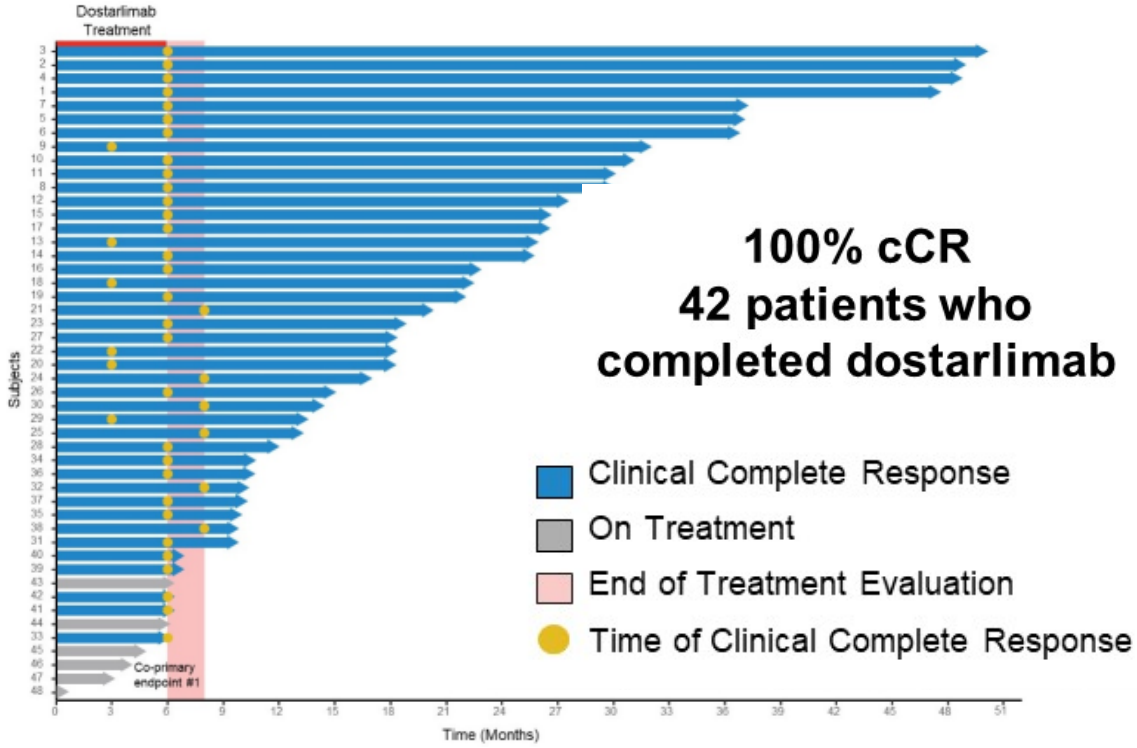
MSI status drives neoadjuvant therapy selection



MSI (dMMR) patients poorly respond to standard neoadjuvant chemotherapy

Outcome	No. of patients (%) dMMR	pMMR
FOLFOX as initial treatment	*n = 21*	*n = 63*
Progression of disease	6 (29)	0
Response or stable disease	15 (71)	63 (100)
Chemoradiation as initial treatment	*n = 16*	*n = 48*
Progression of disease	0	0
Complete pathologic response	2 (13)	8 (17)

Early data suggests impressive response to neoadjuvant immunotherapy. Long-term follow -up data is needed (currently: median 18 mo)



Cercek, *Clin Cancer Res* 2020; Cercek, *NEJM* 2022, *ASCO* 2024

Key points

- There are now many “correct” ways to treat rectal cancer

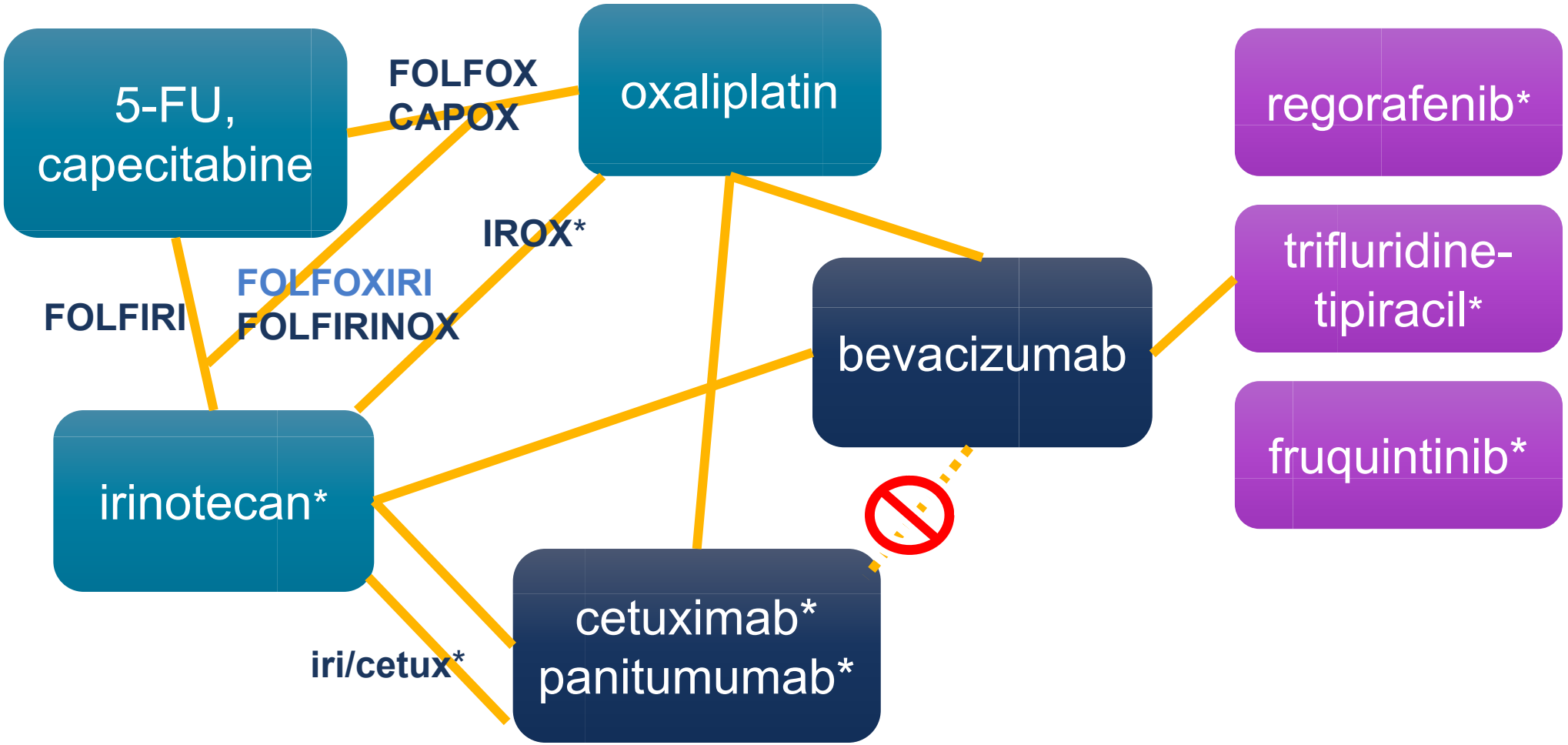
- Preoperative (chemo)radiation therapy is standard-of-care for T3-4 or node-positive rectal cancers
  - But may be omitted in low-risk patients who respond to neoadjuvant chemotherapy

- Total neoadjuvant therapy is the standard-of-care for most patients
  - Non-operative management is possible for patients who achieve a clinical complete response after TNT

- Evaluation of MSI status prior to the initiation of treatment is critical → immunotherapy only

Standard cytotoxic chemotherapy for metastatic cancer

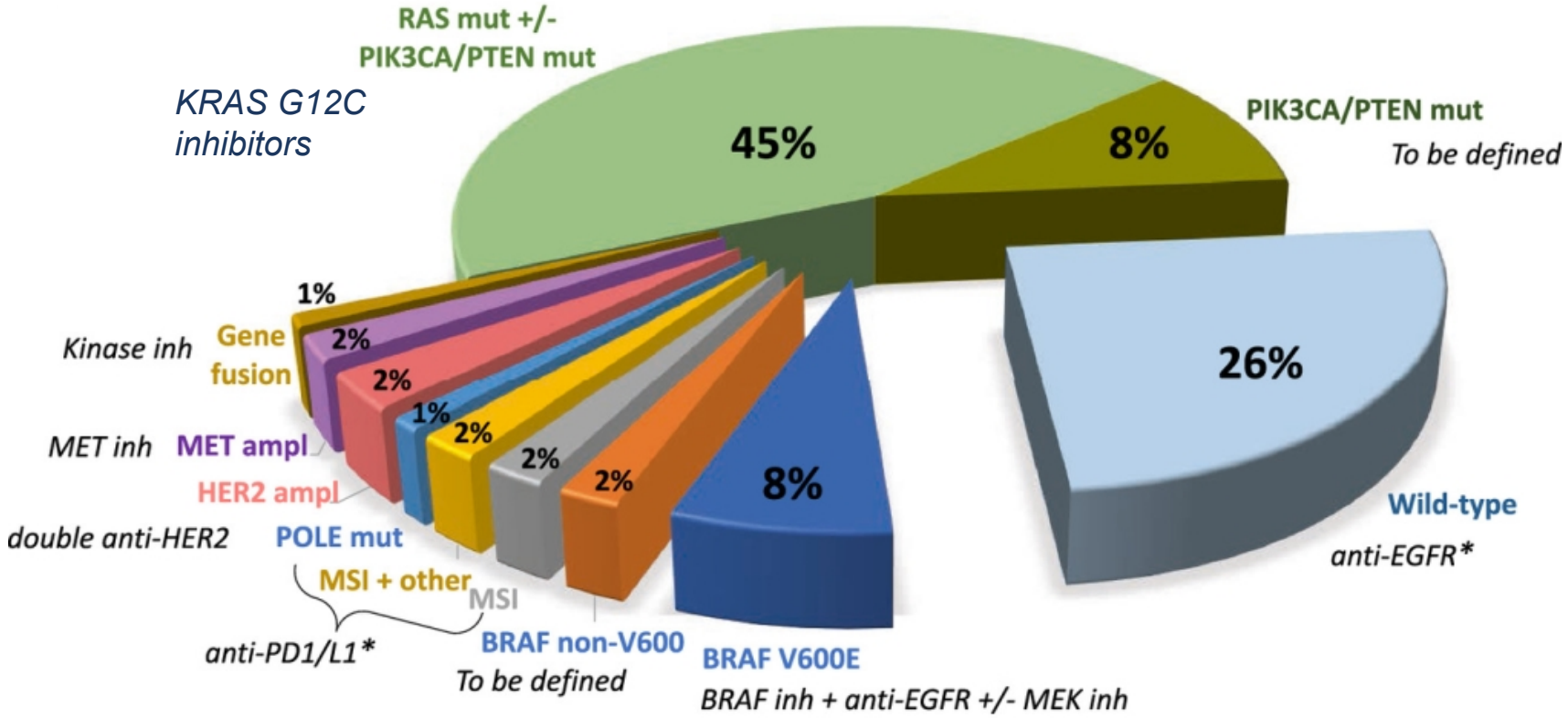
Multiple chemotherapy options

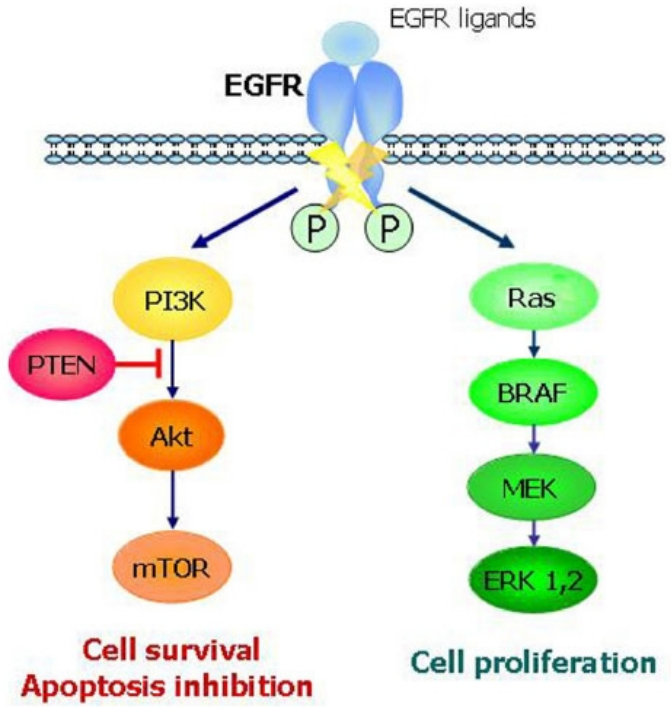


*Has activity without 5-FU

Colorectal cancer is not one disease

KRAS, NRAS, BRAF, HER2 does not respond to silencing by EGFR inhibition (cetuximab, panitumumab)





Saletti, GI Cancer: Targets and Therapy 2015

EGFR inhibitor-induced rash

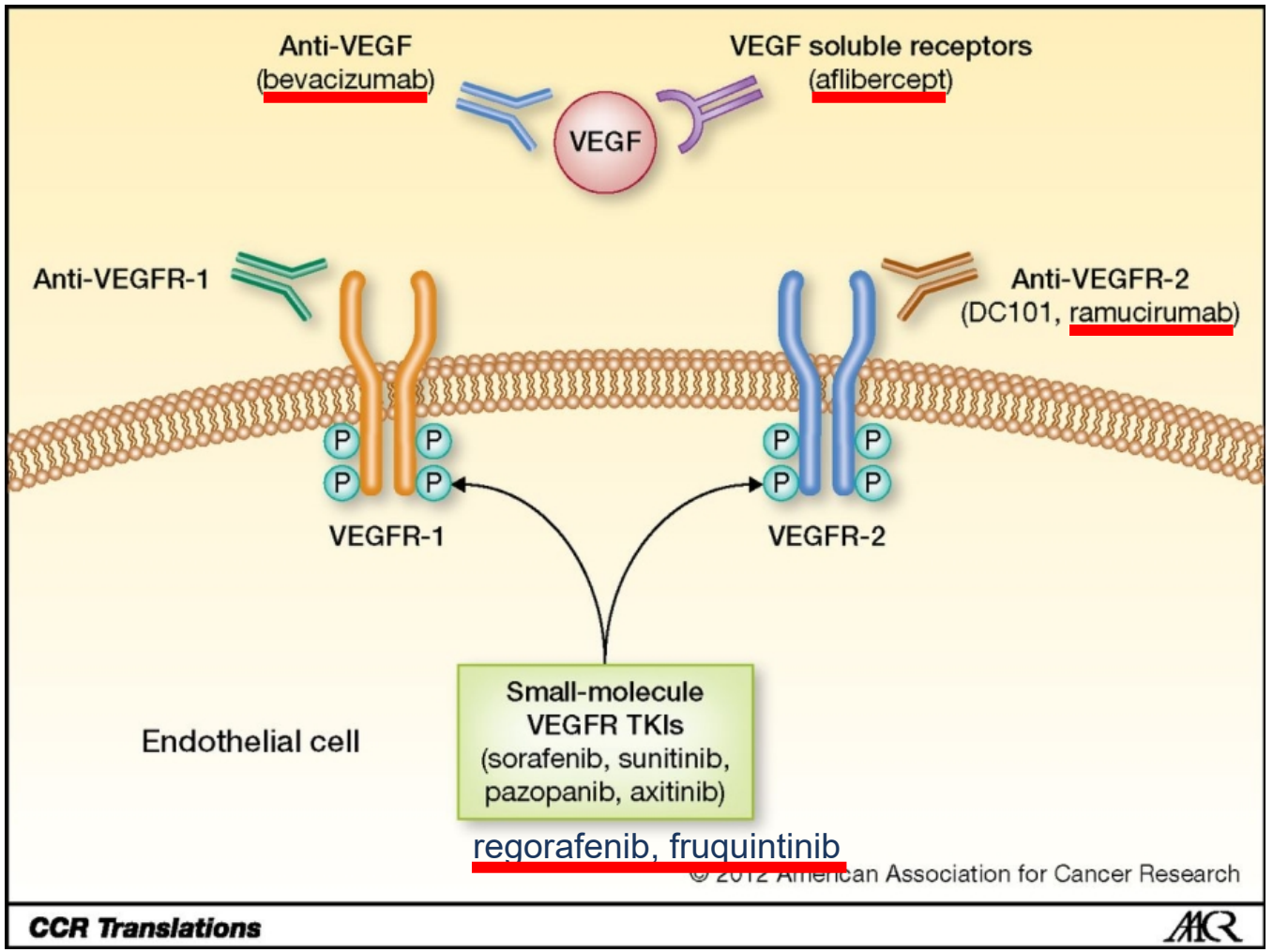
Cetuximab	Panitumumab
Any rash: 85%	Any rash: 90%
Grade 3: 10%	Grade 3: 16%

- Prevention:
  - Sunscreen
  - Topical hydrocortisone 1%
  - Oral doxycycline or minocycline
- Treatment:
  - Same agents as prevention
  - Typical clindamycin
  - If severe, treat with isotretinoin

Gorji, *Asian Pac JCO* 2021; Van Cutsem, *JCO* 2007; Geyer, *NEJM* 2006

Anti-VEGF therapy: no biomarkers

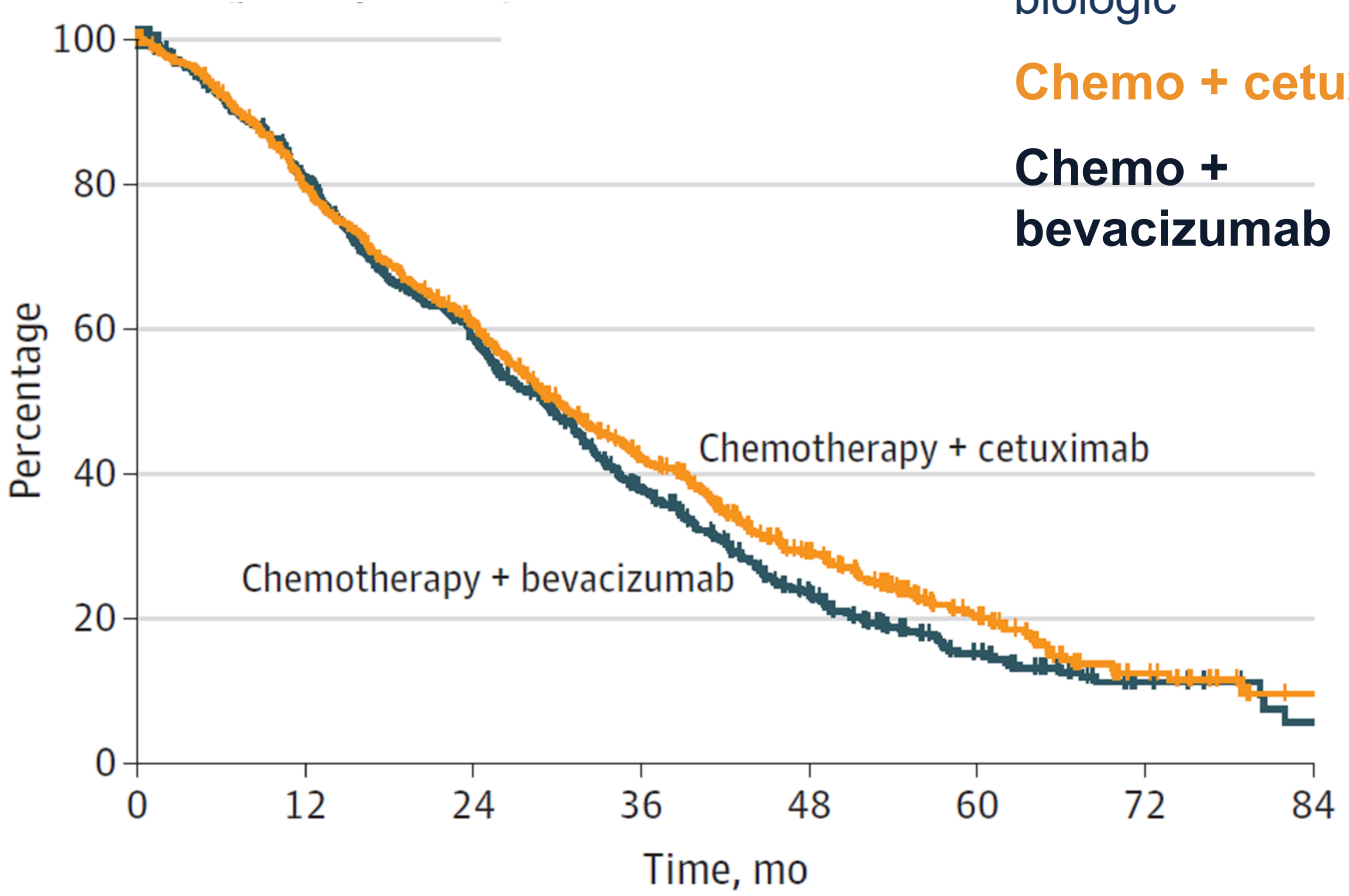
- Bevacizumab
  - 1st or later line
- Aflibercept
  - 2nd line
- Ramucirumab
  - 2nd line
- Regorafenib, fruquintinib
  - 3rd line



Trials: NO16966, TREE-2; VELOUR; RAISE; CORRECT; FRESCO-2

Optimal first-line therapy in KRAS wildtype

- **CALGB/SWOG 80405**: n=732 1L mCRC



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?

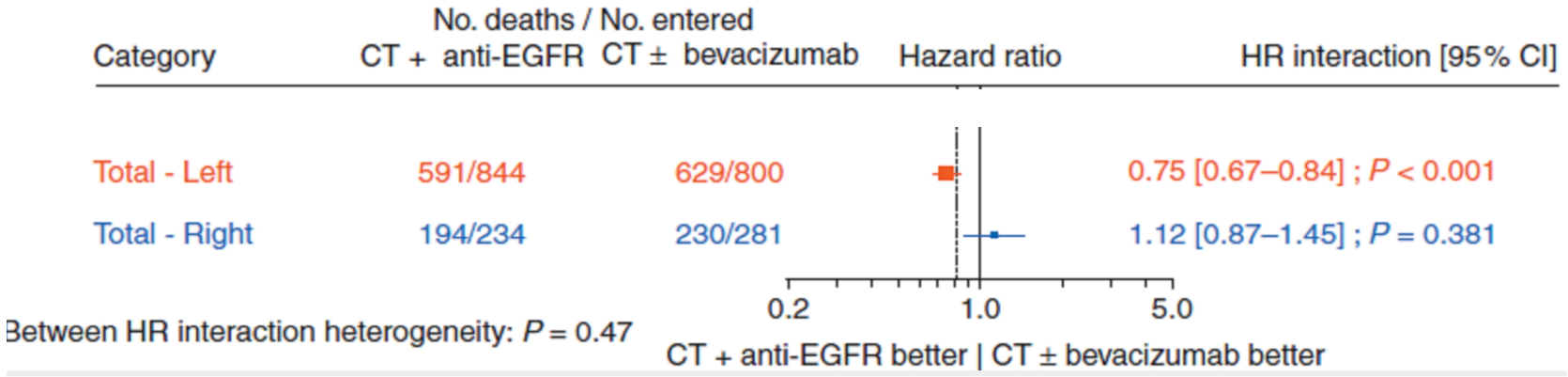
- Exploratory classification by left (distal/rectal) vs. right (proximal) primary site

OS (months)	Overall	Cetuximab	Bevacizumab
Left	33	36	31
Right	19	17	24
	p<0.0001	p<0.0001	p<0.0001

Likely driven by molecular profiles

But no difference when accounting for standard features

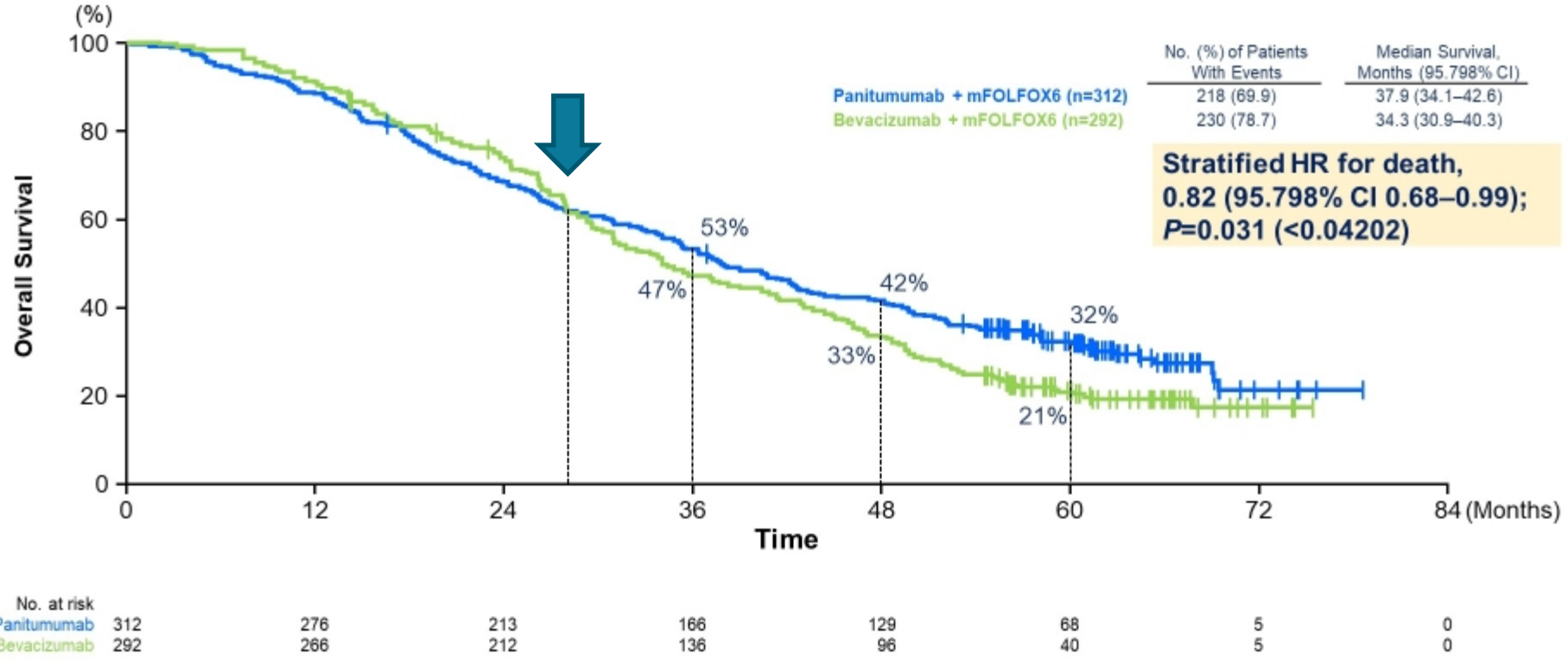
- Pooled analysis of 80405 and 5 other RCT, classified by left vs. right



Venook, *ASCO* 2016, *JAMA* 2017; Arnold, *Ann Oncol* 2017

Prospective evaluation of sidedness

- **PARADIGM**: panitumumab + FOLFOX vs. bevacizumab + FOLFOX
  - KRAS exon 2 wildtype; revised to left-sided only
  - Primary endpoint: overall survival



Similar median PFS
-13.7 vs 13.2 mo, HR 0.98

45% of bev arm did NOT get anti-EGFR in later line

33% of both arms did NOT get irinotecan in later line

Thus, fails to be practice-changing at this time

Watanabe, *JAMA* 2023

Improved survival with triplet therapy

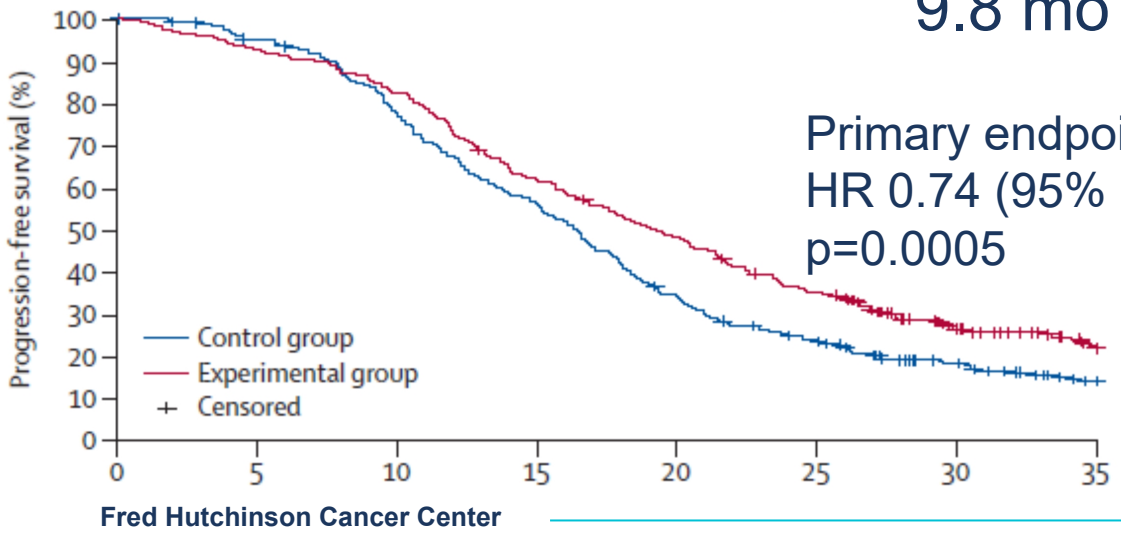
- **TRIBE-2** study: Phase 3 trial of n=679 1L patients

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

Improved PFS/ORR, but higher toxicity

Highly consider for pt with:
- Excellent performance status
- Desires aggressive care
- And/or need for significant down-staging (*i.e.*, attempt to convert to resectable mets)

*FOLFOXIRI =
same drugs as FOLFIRINOX, but different doses

Cremolini, *Lancet Oncol* 2020; Gruenberger, *Ann Oncol* 2015

Second-line therapy

* pan-RAS wildtype

- All of the same options
  - FOLFOX with bevacizumab or cetuximab*
  - FOLFIRI with bevacizumab or cetuximab*

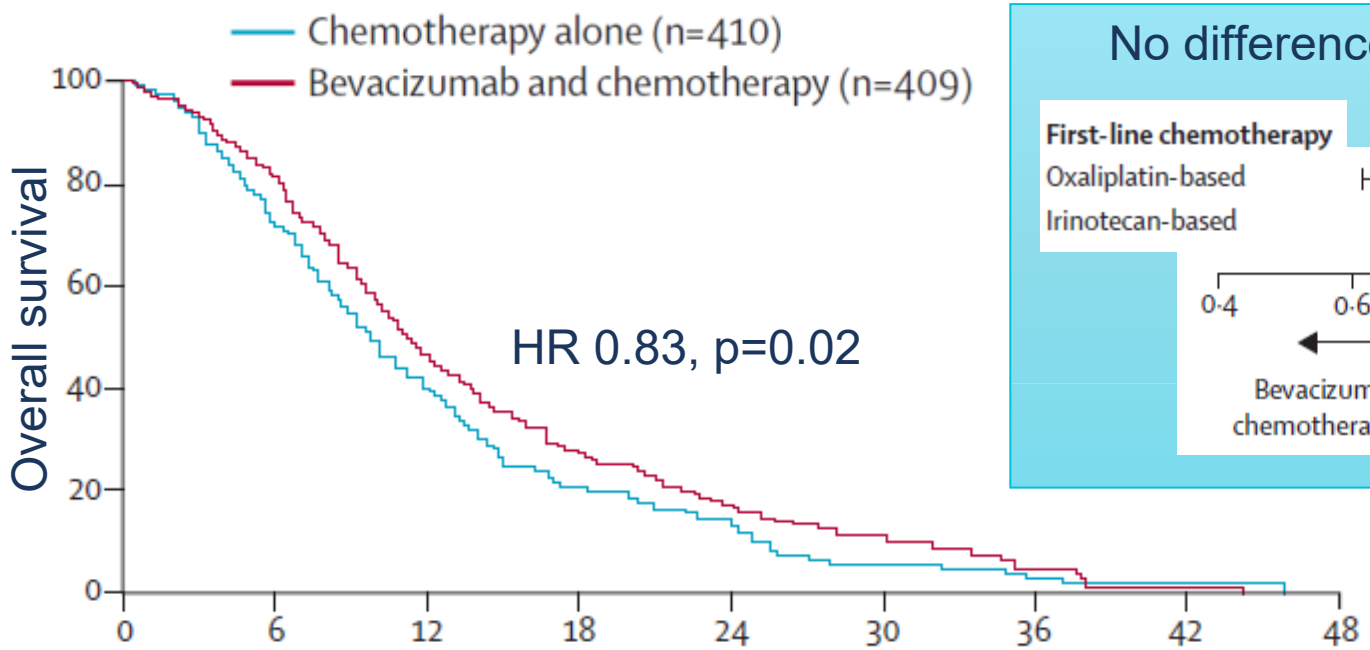
- Sequencing trials show no “correct” order

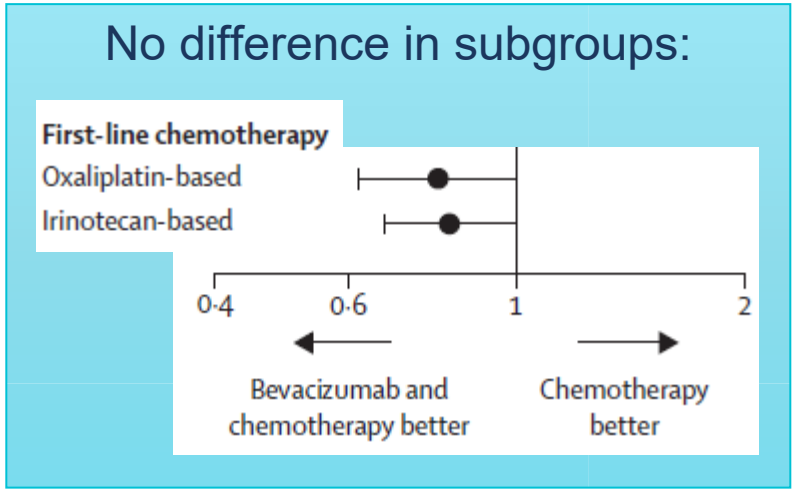
- Evidence supports continuation of biologic at progression
  - Ex. FOLFOX + bevacizumab → FOLFIRI + bevacizumab
    FOLFIRI + cetuximab* → FOLFOX + cetuximab*

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

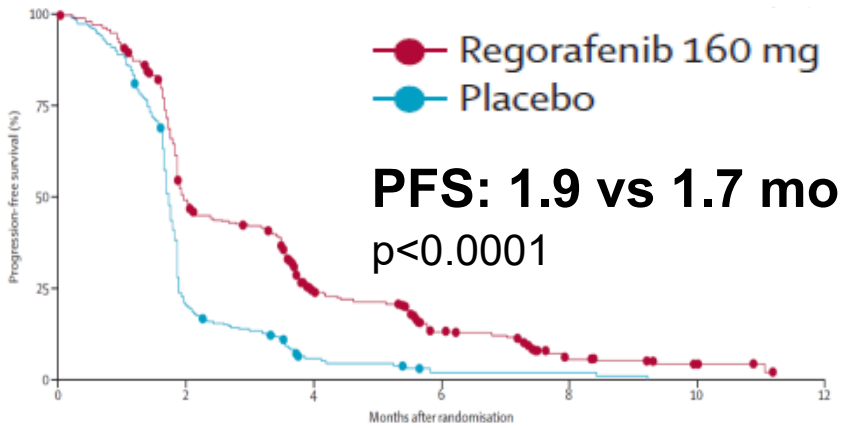




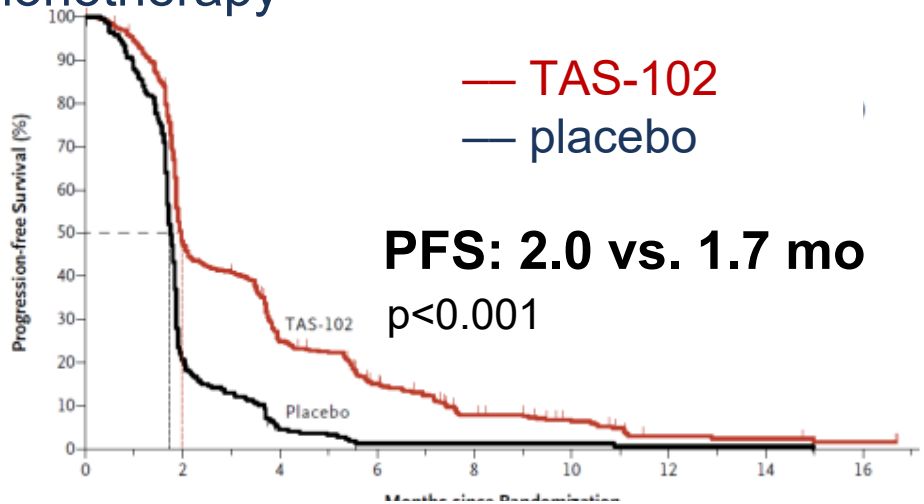
Bennouna, *Lancet Onc* 2013

Regorafenib & trifluridine-tipiracil (TAS-102)

- Oral drugs with minimal clinical benefit as monotherapy



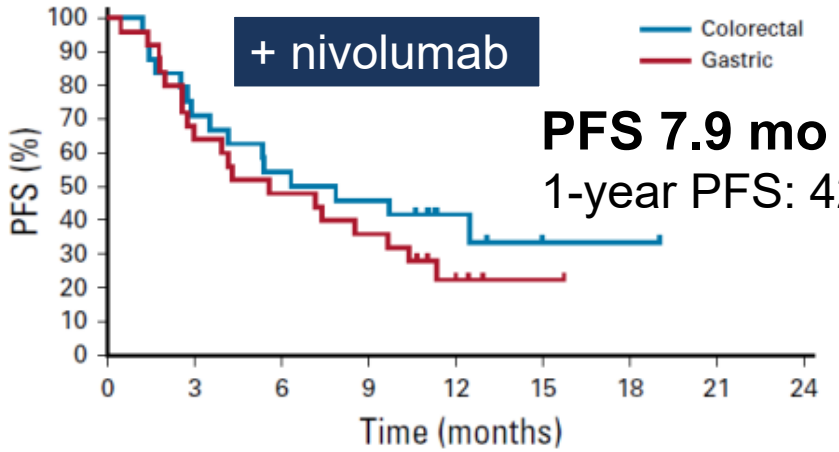
PFS: 1.9 vs 1.7 mo
p<0.0001



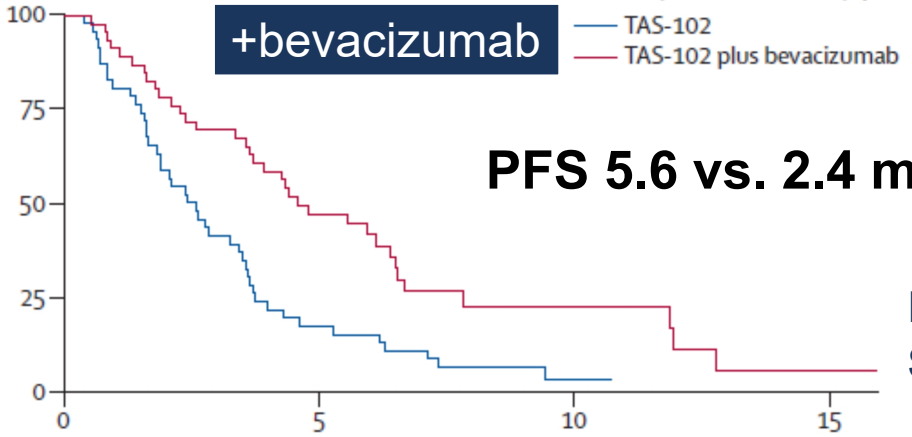
PFS: 2.0 vs. 1.7 mo
p<0.001

Emerging data

NON-liver mets only



PFS 7.9 mo
1-year PFS: 42%



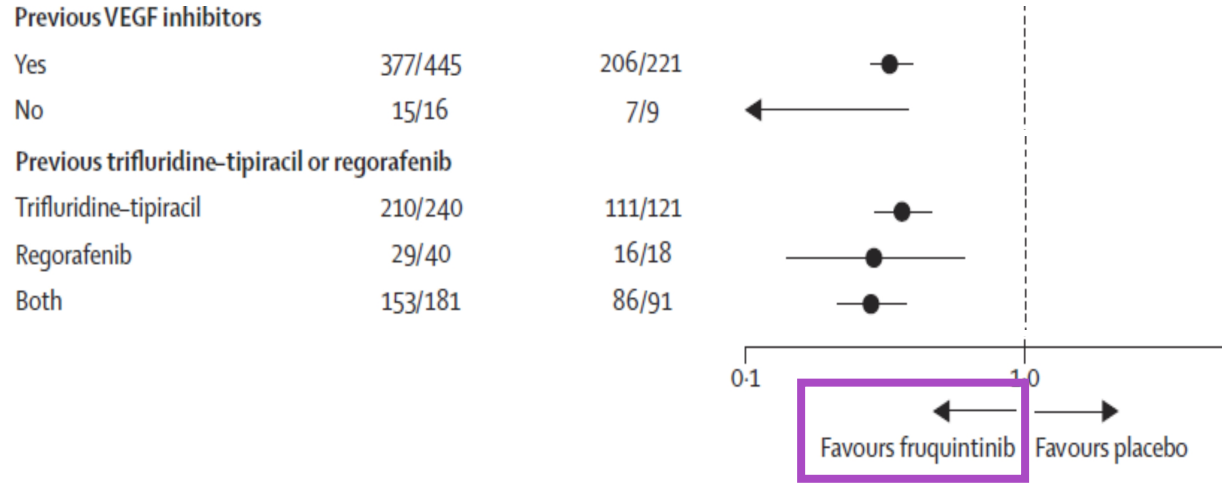
PFS 5.6 vs. 2.4 mo

Phase 3
SUNLIGHT trial

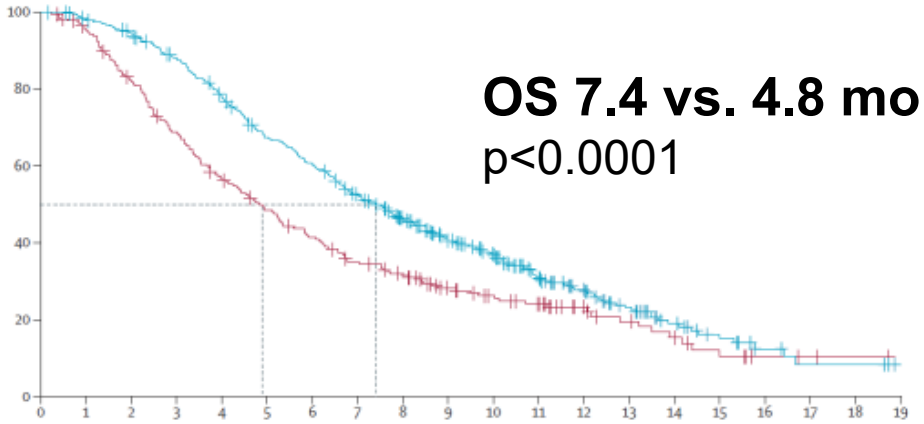
Grothey, *Lancet* 2013; Mayer, *NEJM* 2015; Fukuoka, *JCO* 2020; Pfeiffer, *Lancet Oncol* 2020; Prager, *NEJM* 2023

Fruquintinib

- Oral highly selective TKI targeting VEGF
- **FRESCO-2**: randomized to fruquintinib vs. placebo
  - FDA approved 11/2023 for 3L/4L

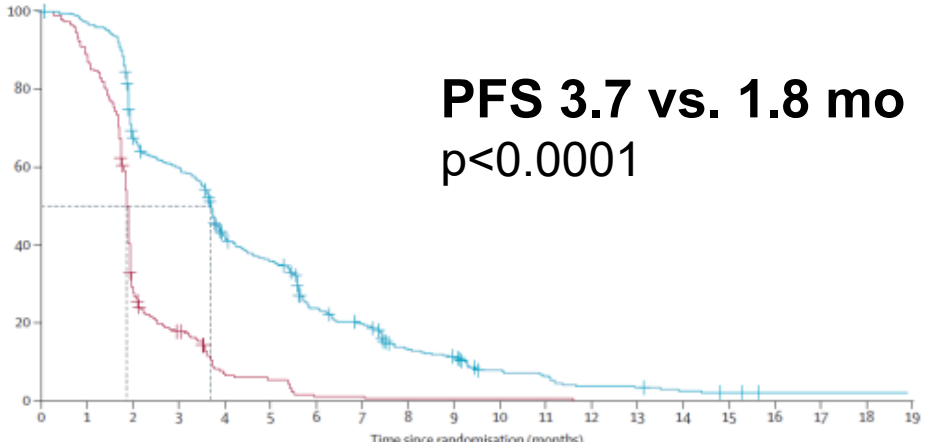


Overall survival



OS 7.4 vs. 4.8 mo
p<0.0001

Progression-free survival



PFS 3.7 vs. 1.8 mo
p<0.0001

Dasari, *Lancet* 2023

Key points

- No “correct” first-line chemotherapy regimen
  - Any 5-FU based chemo doublet (or triplet) + biologic is acceptable
  - Cetuximab is less effective for right-sided tumors

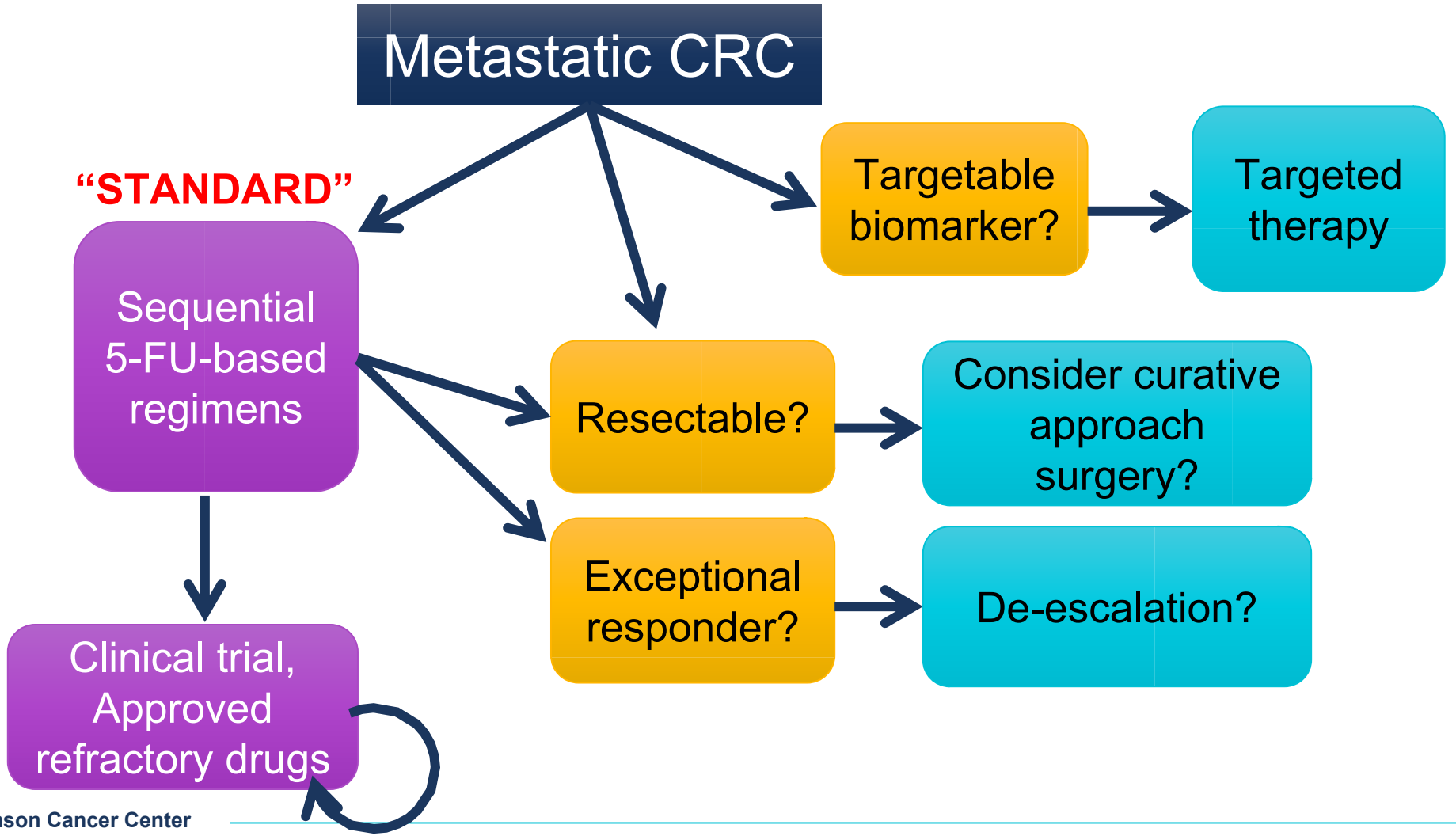
- Molecular testing should be part of every stage IV CRC work-up (more to come on that…)

- Regorafenib and trifluridine-tipiracil are approved, but of limited clinical benefit (OS ~2 months) as monotherapy, but may be more effective in combination

- Fruquintinib is now available for unselected refractory metastatic CRC

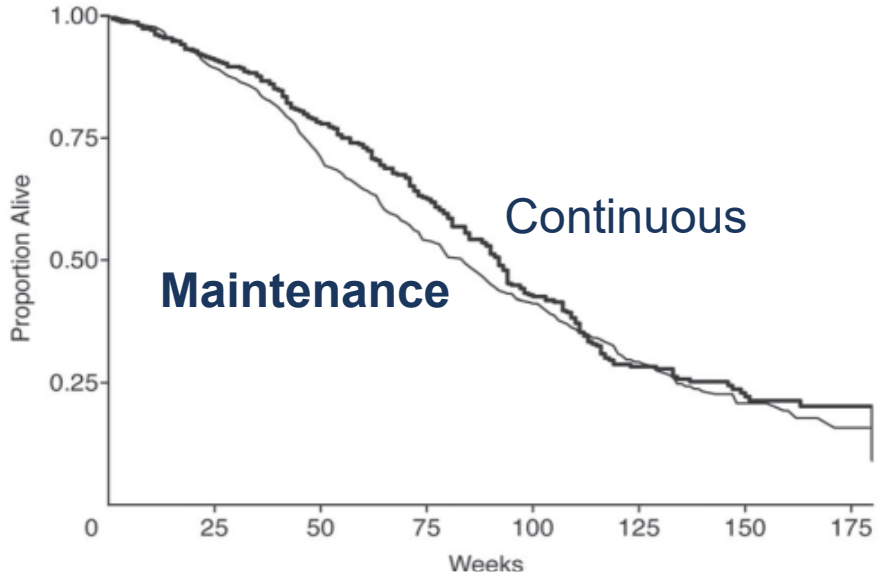
Tailored chemotherapy strategies

Approaches to longitudinal treatment



Maintenance / de-escalation

- **OPTIMOX-1** (RCT)
  - De-escalate to 5-FU s. continuous FOLFOX
  - PFS, OS similar
  - Less toxicity with 5-FU maintenance
- Done after 3-6 mo and ≥ stable disease
- Multiple “correct” strategies



5-FU/capecitabine[1,2,3,4]	1.7-5.7 mo
5-FU + bevacizumab[5,6]	6.9-8.5 mo
Bevacizumab[6,7]	3.2-6.1 mo
5-FU + panitumumab[2,9]	4.8-8.8 mo
Cetuximab / panitumumab[7,9]	4.9-6.1 mo

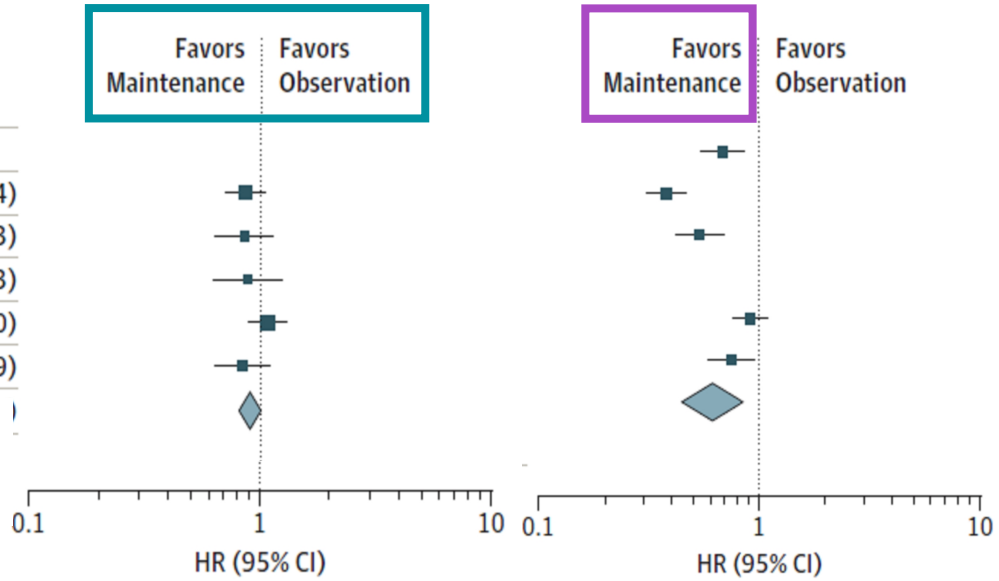
*Maintenance with 5-FU + biologic has the best PFS, which is supported by limited randomized

[1]Tournigand, *JCO* 2006; [2]Modest, *JCO* 2021; [2]Chibaudel, *JCO* 2009; [3]Simkens, *Lancet* 2015; [4]Adams, *JCO* 2021; [5]Goey, *Ann Oncol* 2017; [6]Hegewisch-Becker, *Lancet Onc* 2015; [7]Cremolini, *JAMA Oncol* 2018; [8]Aparicio, *JCO* 2018; [9]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 associated with worse short-term outcomes
- No clear detriment to overall survival

Sonbol, *JAMA Oncol* 2019; Adams, *JCO* 2021

Resectable liver metastases

- Questionable role of systemic therapy

	EORTC 40983			JCOG 0603*		
	Peri-op FOLFOX4 (n=151; resected)	Surgery alone (n=182)		Adj FOLFOX6 (n=151)	Surgery alone (n=149)	
3-yr DFS	38.2%	30.3%	p=0.04	52.7%	42.6%	p=0.006
5-yr OS	51.2%	47.8%	p=0.34	71.2%	83.1%	p=NS

- Like stage III, no demonstrated benefit to adjuvant irinotecan or biologics
  - Guidelines allow for continuation of a biologic if it was helpful in converting to resectable disease → but the data is not strong for this

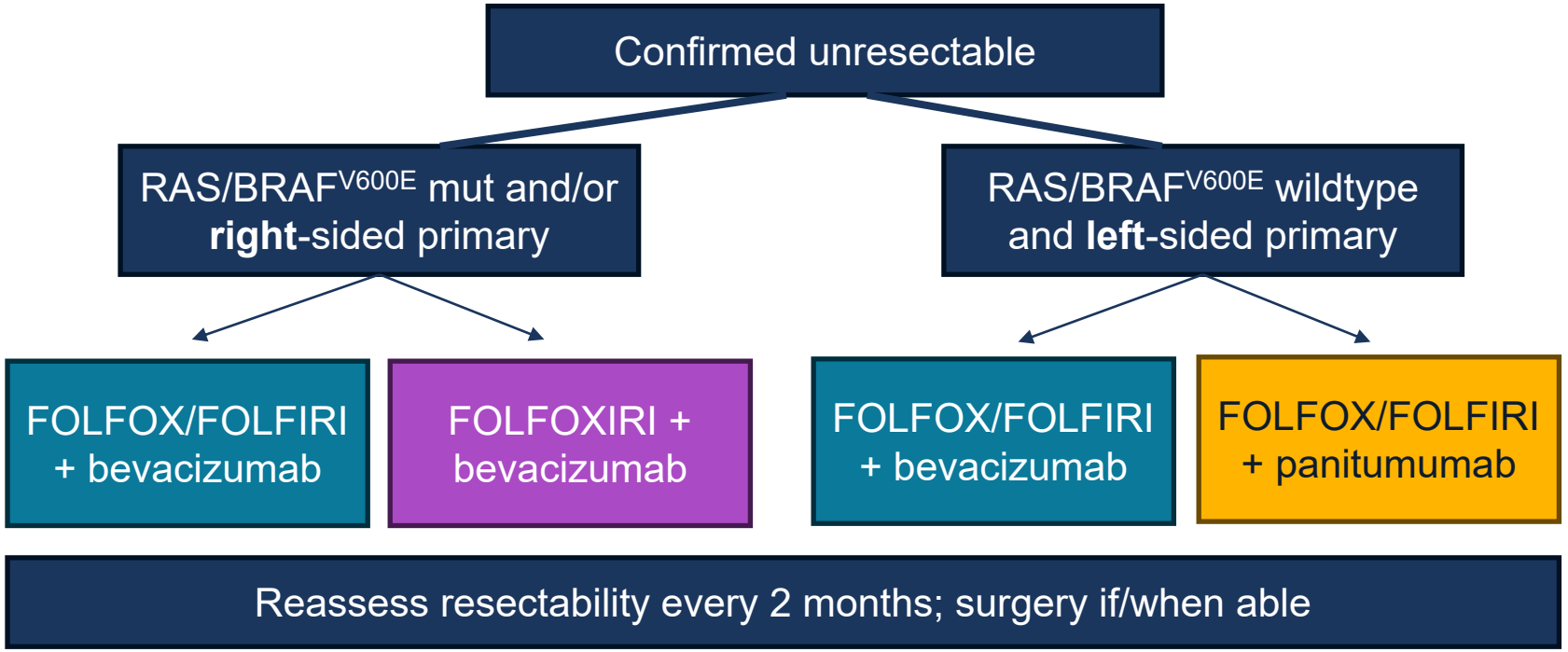
*No neoadjuvant permitted. If had prior adjuvant, could NOT have had oxali
*Terminated early due to improved DFS, but worse OS

Nordlinger, *Lancet Onc* 2013; Primrose, *Lancet Onc* 2014; Modest, *ASCO* 2021; Kanemitsu, *JCO* 2021

Unresectable liver metastases

- Chemo may convert from unresectable to resectable
- Need to balance dose-dependent side effects and hepatotoxicity
  - Irinotecan: steatohepatitis
  - Oxaliplatin: sinusoidal obstructive syndrome
- Potential for over-treatment (too small to locate) or developed resistance (progression)

CAIRO-5: n=530 patients with unresectable colorectal liver metastases randomized by molecular status



Bond, *Lancet Oncol* 2023

CAIRO-5: surprising results

- Primary outcome was PFS (…is this the correct endpoint?)

	Right and/or mutant			Left & wildtype		
	Doublet/bev	**Triplet**/bev		Doublet/**bev**	Doublet/**pani**	
PFS	9.0 mo	10.6 mo	p=0.04	10.6 mo	10.3 mo	p=0.44
ORR	33%	54%	p<0.001	52%	76%	p<0.01
OS	23.6 mo	24.1 mo	p=0.44	39.9 mo	38.3 mo	p=0.75
R0/1 resection	33%	51%	p=0.02	54%	54%	p=0.79

- Minimal differences in OS
  - Some imbalance of liver disease burden
  - Data on those who did NOT go to surgery not yet reported

Bond, *Lancet Oncol* 2023; Bond, *JAMA Oncol* 2025

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

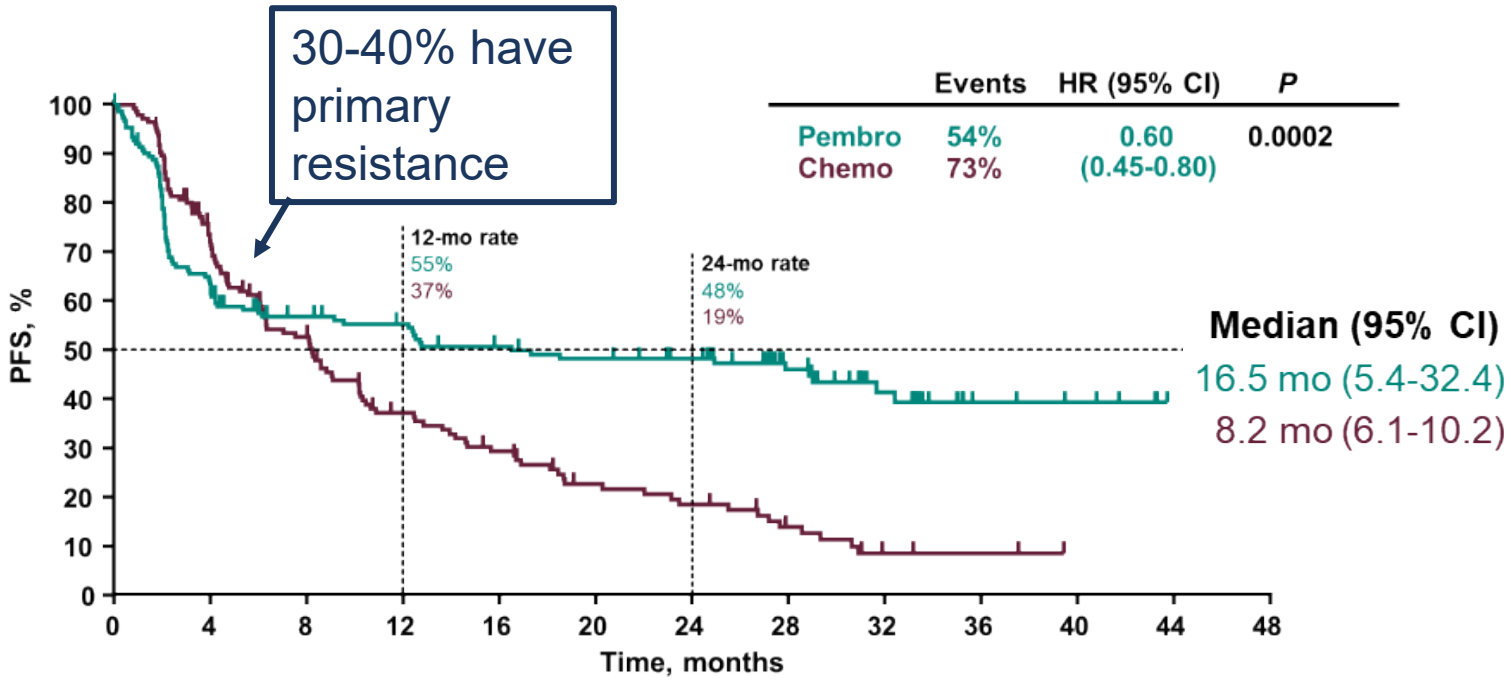
Targeting molecular alterations

Tailoring to biomarkers

* MSI (3-5%), high TMB (1%)	PD-(L)1 ± CTLA4 inhibition
* BRAF V600E (3-8%)	Encorafenib + EGFR ± chemotherapy
* HER2 (3-5%)	Trastuzumab + tucatinib Trastuzumab-deruxtecan (T-DXd)
* KRAS G12C (3%)	Sotorasib/adagrasib + EGFR
NTRK, ALK (<1%)	Entrectanib, larotrectanib, repotrectinib
ATM	*ATR inhibitor*
RET	Selpercatinib

Use of anti-PD1 in first-line therapy

- **Keynote-177** (RCT of locally tested MSI CRC)
  - Randomized to **pembrolizumab** vs. **chemotherapy** (any doublet ± biologic) allowed
  - Better QOL for pembro



Updated data demonstrate improved OS with PD-1 (HR 0.74)

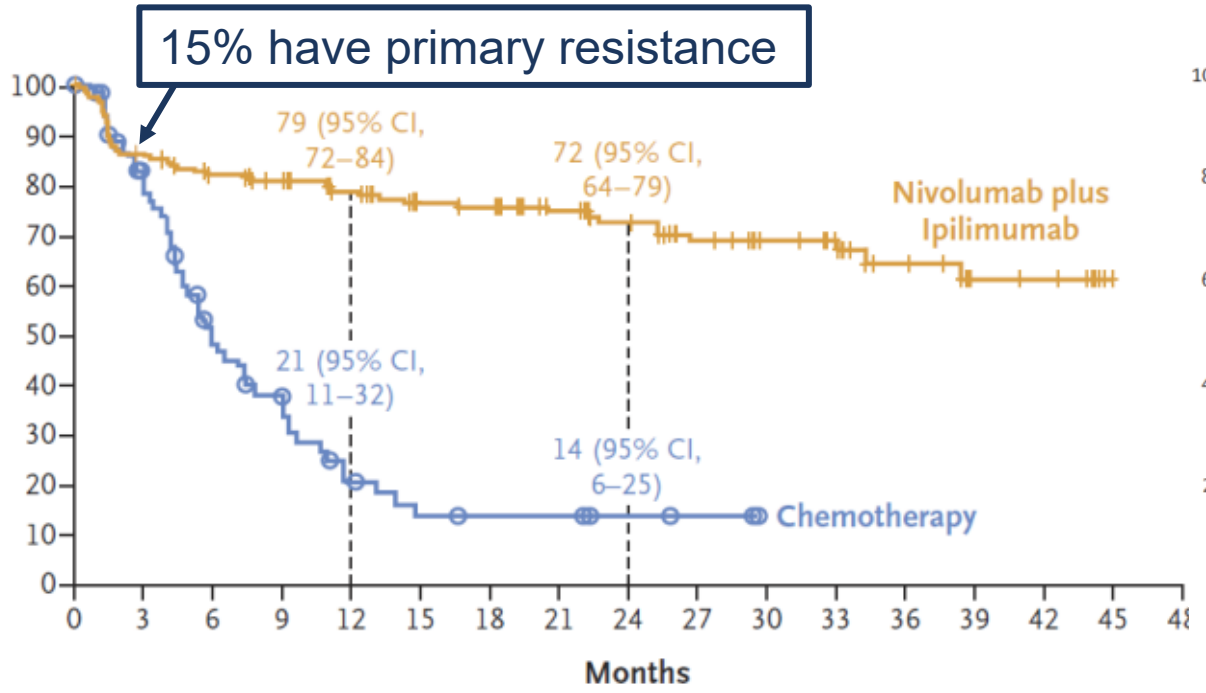
But only 60% got IO in 2L

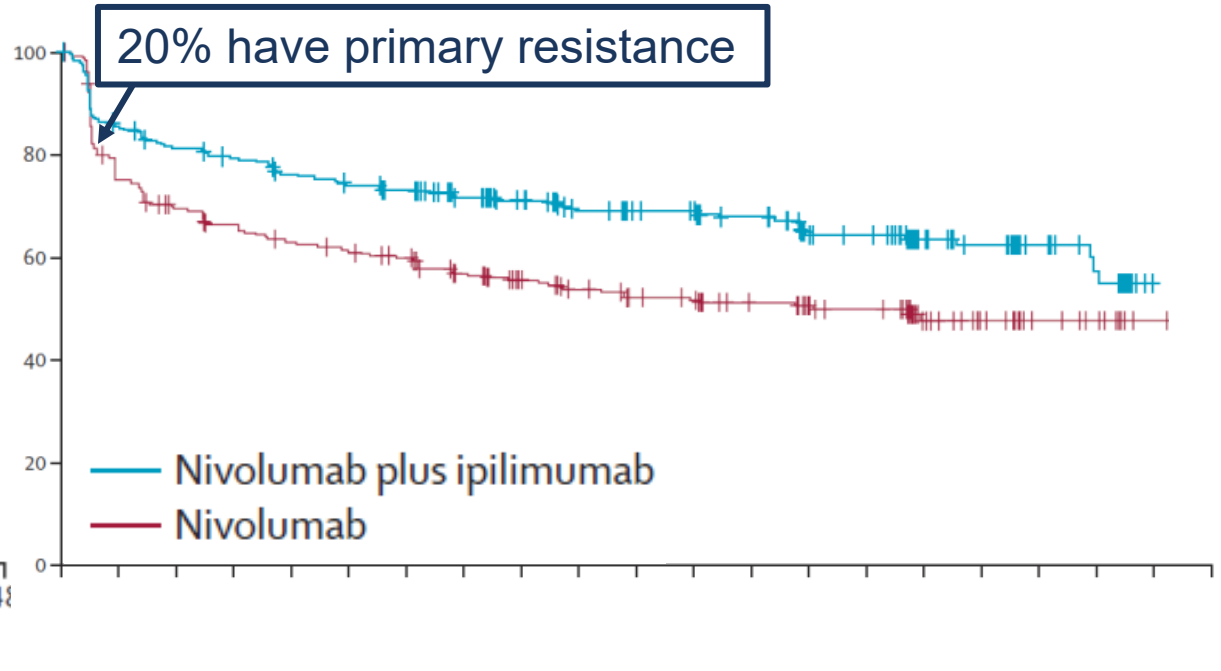
Andre, *NEJM* 2020; Andre, *Lancet Oncol* 2021

Combination therapy in first-line therapy

- **Checkmate-8HW**: randomized to nivolumab/ipilimumab vs nivolumab vs chemotherapy (doublet ± biologic)

Centrally confirmed MSI status





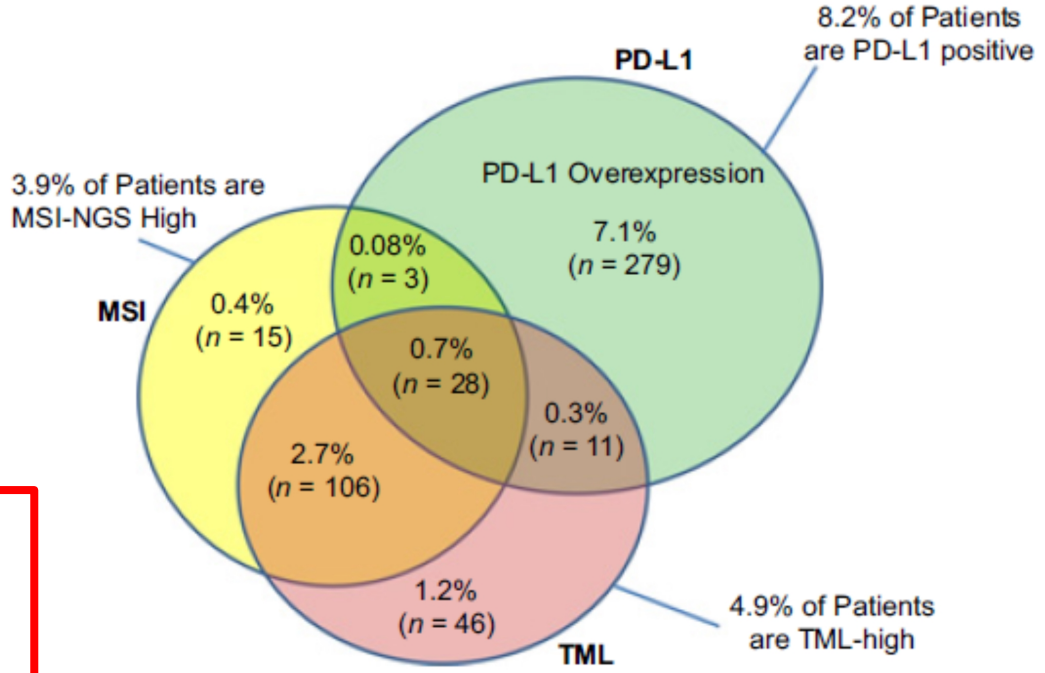
1% had prior therapy for metastatic disease

Andre, *New Engl J Med* 2024; Andre, *Lancet* 2025

Additional uses of immunotherapy

- Evaluations under way for chemo-immunotherapy
  - **COMMIT**: atezolizumab vs. FOLFOX/bev/atezo ~~vs. FOLFOX/bev~~ (study paused)
  - Evaluations in non-liver met mCRC

- But how to identify and/or induce MSS responders?



6/2020: FDA approves pembrolizumab for TMB ≥10 mut/Mb

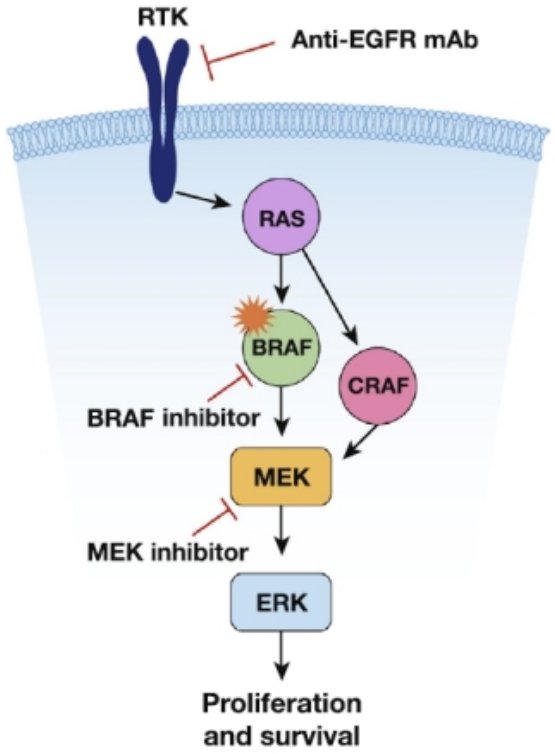
… too low for CRC?

WARNING*: TMB is over-estimated by liquid biopsy (ex. TMB 16 liquid = TMB 10 tissue)

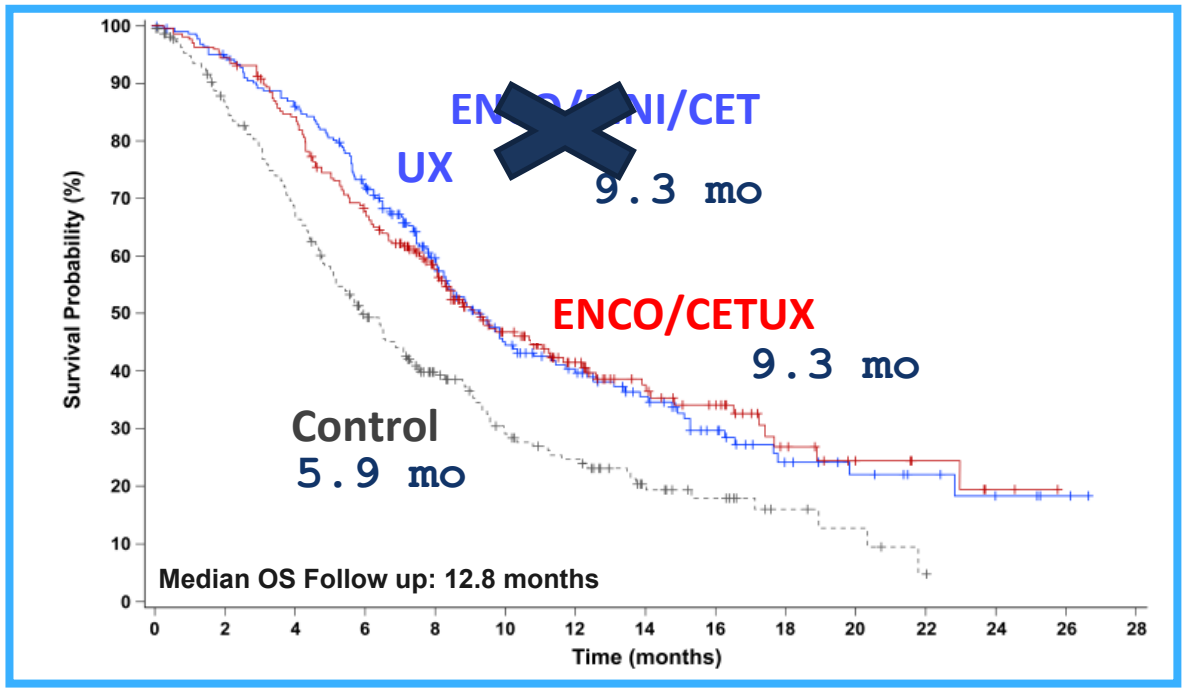
Salem, *Mol Cancer Res* 2018; Keynote-158: Marabelle, *JCO* 2020; Valero, *JAMA Oncol* 2021; *Drusbosky, *ASCO* 2021

BRAF V600E targeted therapy

- Poor prognostic marker, resistance to anti-EGFR
- BRAF-inhibitor monotherapy is ineffective → Multi-pathway blockade is necessary



BEACON: 2L+ encorafenib + cetuximab/panitumumab



MEK inhibition adds no meaningful benefit to BRAF/EGFR

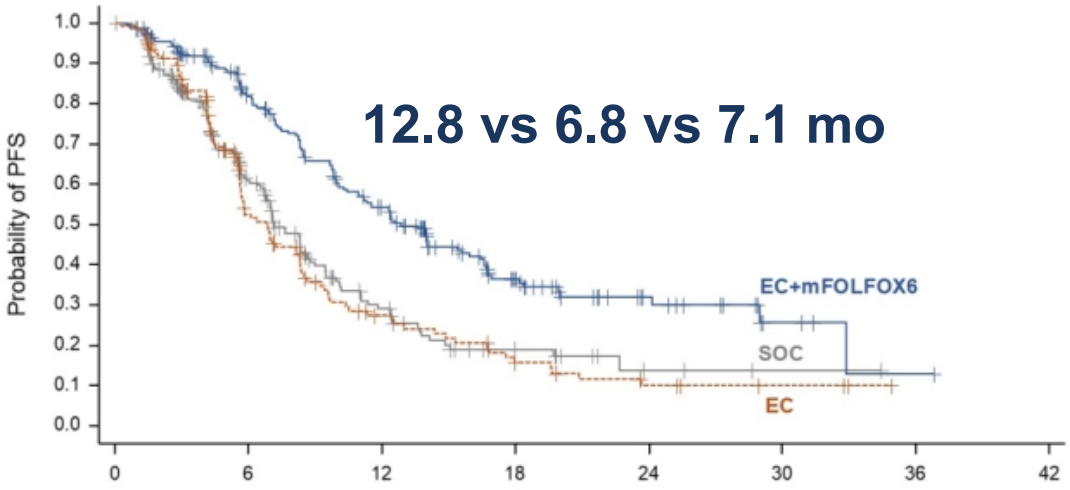
Future: add PD1?

Cremolini, *JCO* 2020; Strickler, *Cancer Treat Rev* 2017; Kopetz, *NEJM* 2019; Tabernero, *JCO* 2021

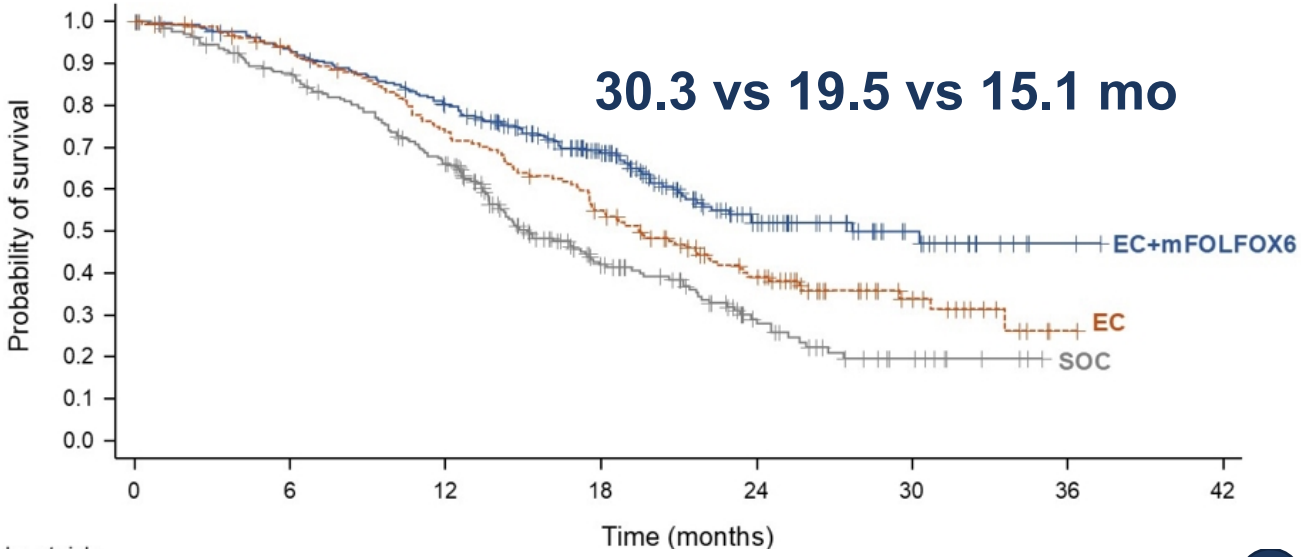
BRAF + chemotherapy

- **BREAKWATER**: 1L trial n=637 BRAF V600E MSS of encorafenib (BRAFi) + cetuximab (EGFRi) + chemo vs EC vs SOC chemo
  - Currently, only the FOLFOX backbone has been reported out
  - Patients given FOLFOX + EC had OS similar to what would be expected for mCRC overall!

Progression-free survival



Overall survival



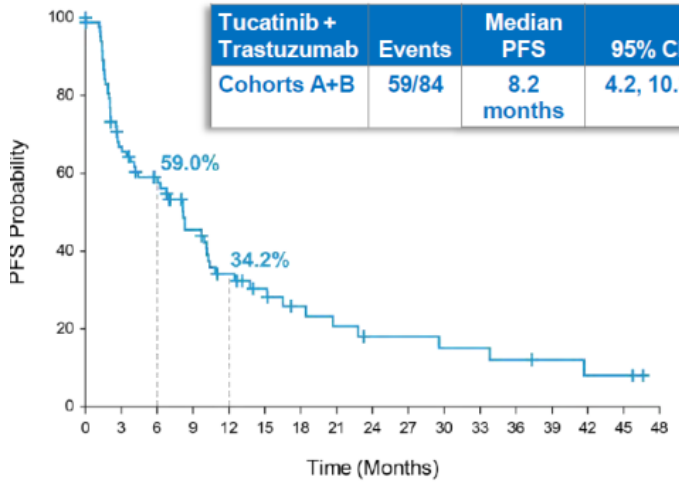
HER2 targeted therapy

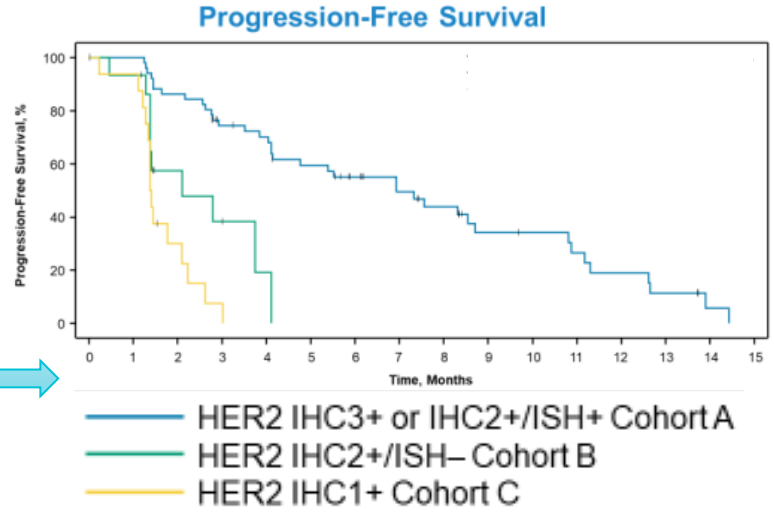
- Associated with MSI, wild-type RAS/RAF + CNS mets
- Highest responses in HER2 3+ >> 2+/FISH+ (no HER2-low)

- (trastuzumab + lapatinib/pertuzumab)
- Trastuzumab + tucatinib (**MOUNTAINEER**)
  - ORR 39%, PFS 8.2 mo

- Trastuzumab deruxtecan (**DESTINY-CRC01**)
  - ADC w/ topo-I derivative
  - ORR 28-45%, PFS 5.5-6.9 mo

Tucatinib + Trastuzumab	Events	Median PFS	95% CI
Cohorts A+B	59/84	8.2 months	4.2, 10.3



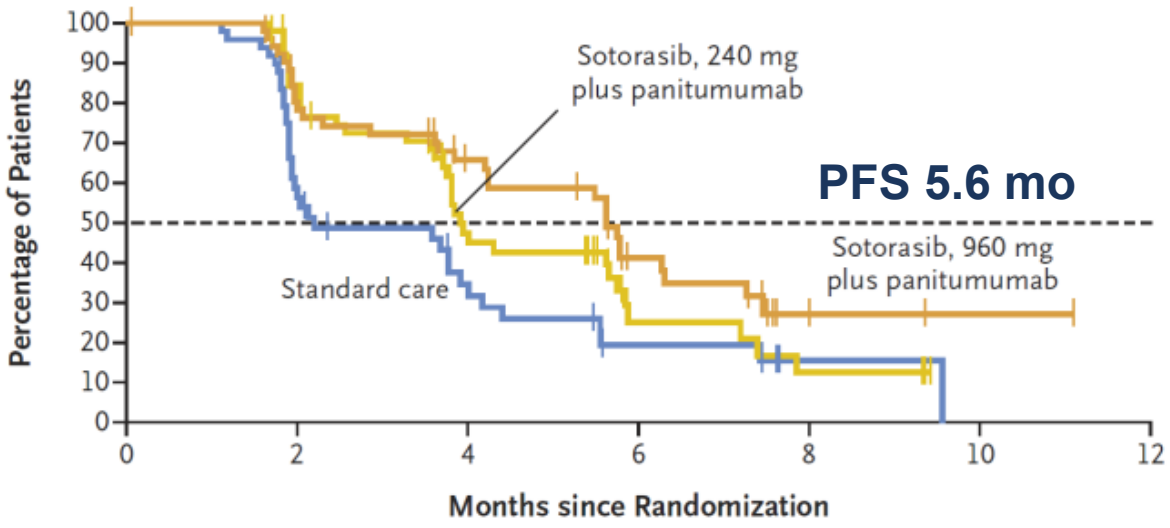


Strickler, *ASCO* 2024; Yoshino, *ASCO* 2021; Raghav, *ASCO* 2023

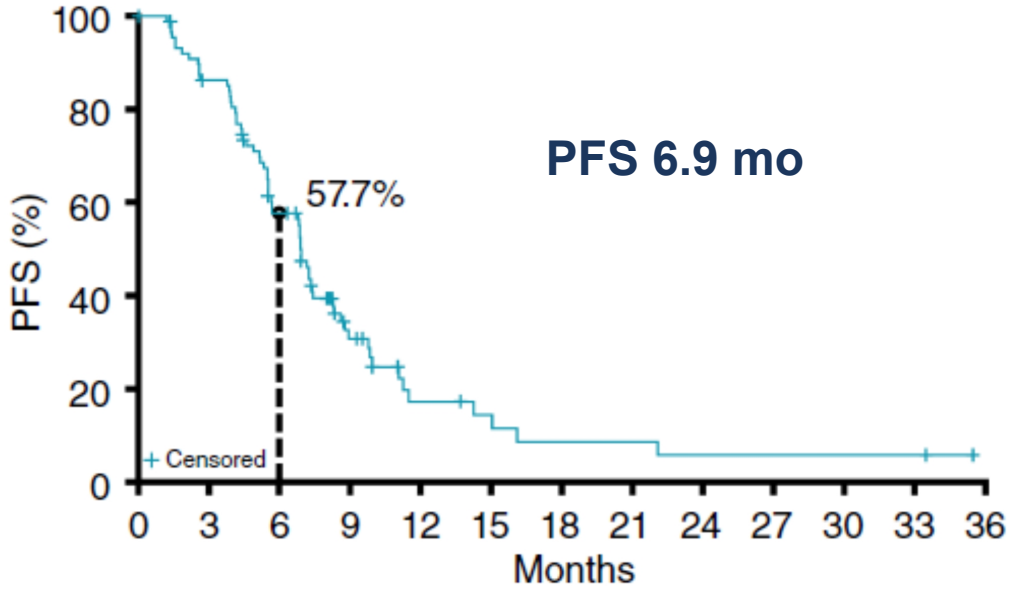
KRAS G12C: knowing which mutation matters now!

- Inhibitors have modest benefit as monotherapy (ORR 12-22%, PFS 5.6-5.7 mo)
- Improved in combination with EGFR inhibition (ORR 30-46%)
  - Future trials in combination with chemo

Sotarasib + panitumumab

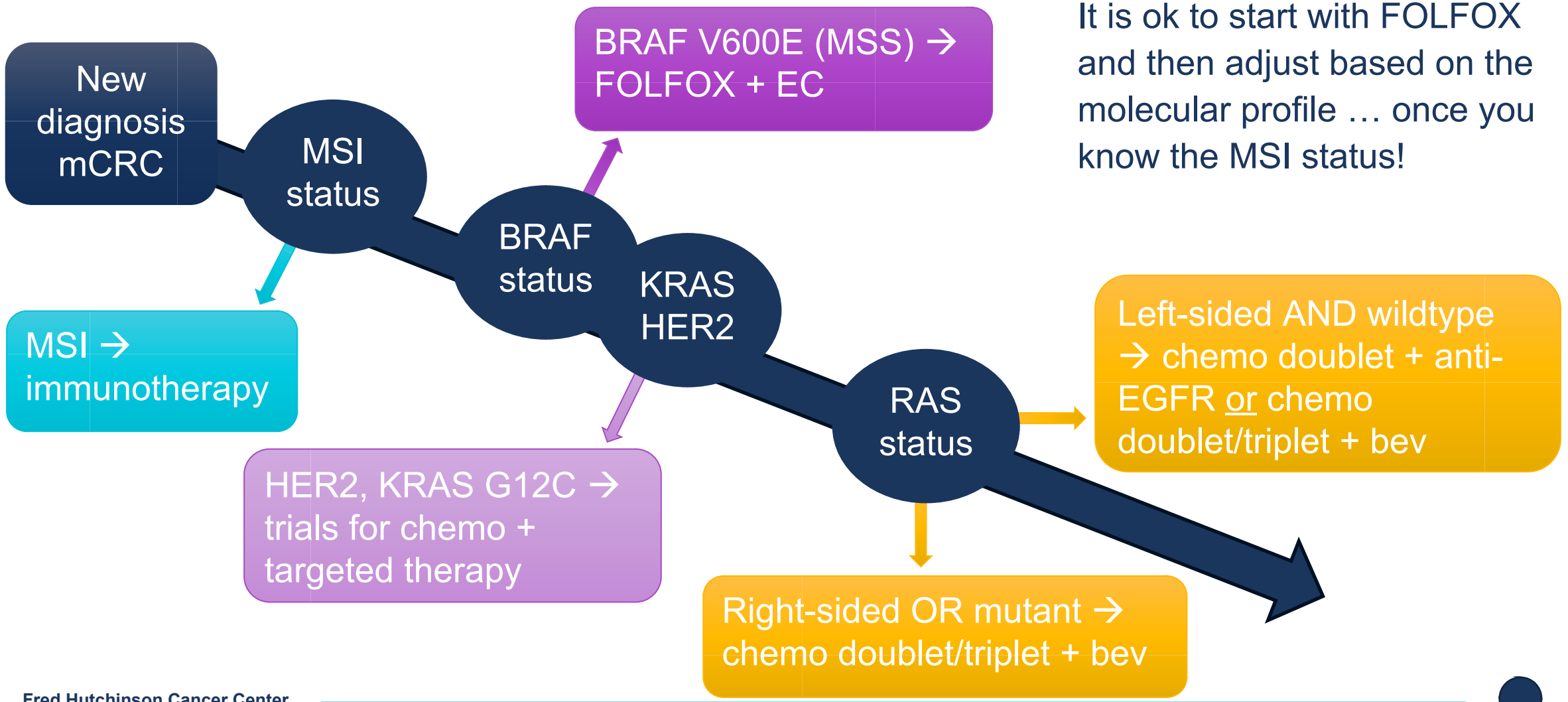


Adagrasib + cetuximab



Fakih, *NEJM* 2023; Yaeger, *Cancer Disc* 2024

1L mCRC treatment paradigm



It is ok to start with FOLFOX and then adjust based on the molecular profile … once you know the MSI status!

Key points

- MSI is a biomarker for response to immunotherapy
  - Indicated in first or later line
  - Role in combination with chemotherapy is unproven

- Targeting BRAF requires multi-pathway blockade
  - FOLFOX + encorafenib + cetuximab (panitumumab) is now standard in 1L

- HER2 should be evaluated (esp in RAS/RAFwt) as targeted options are available (currently 2L+)

- It is important to know the specific RAS mutation, as targeted options are available

Fred Hutch Cancer Center

Thank you

UW Medicine