Aggressive B-Cell Non-Hodgkin Lymphomas

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Disclosures

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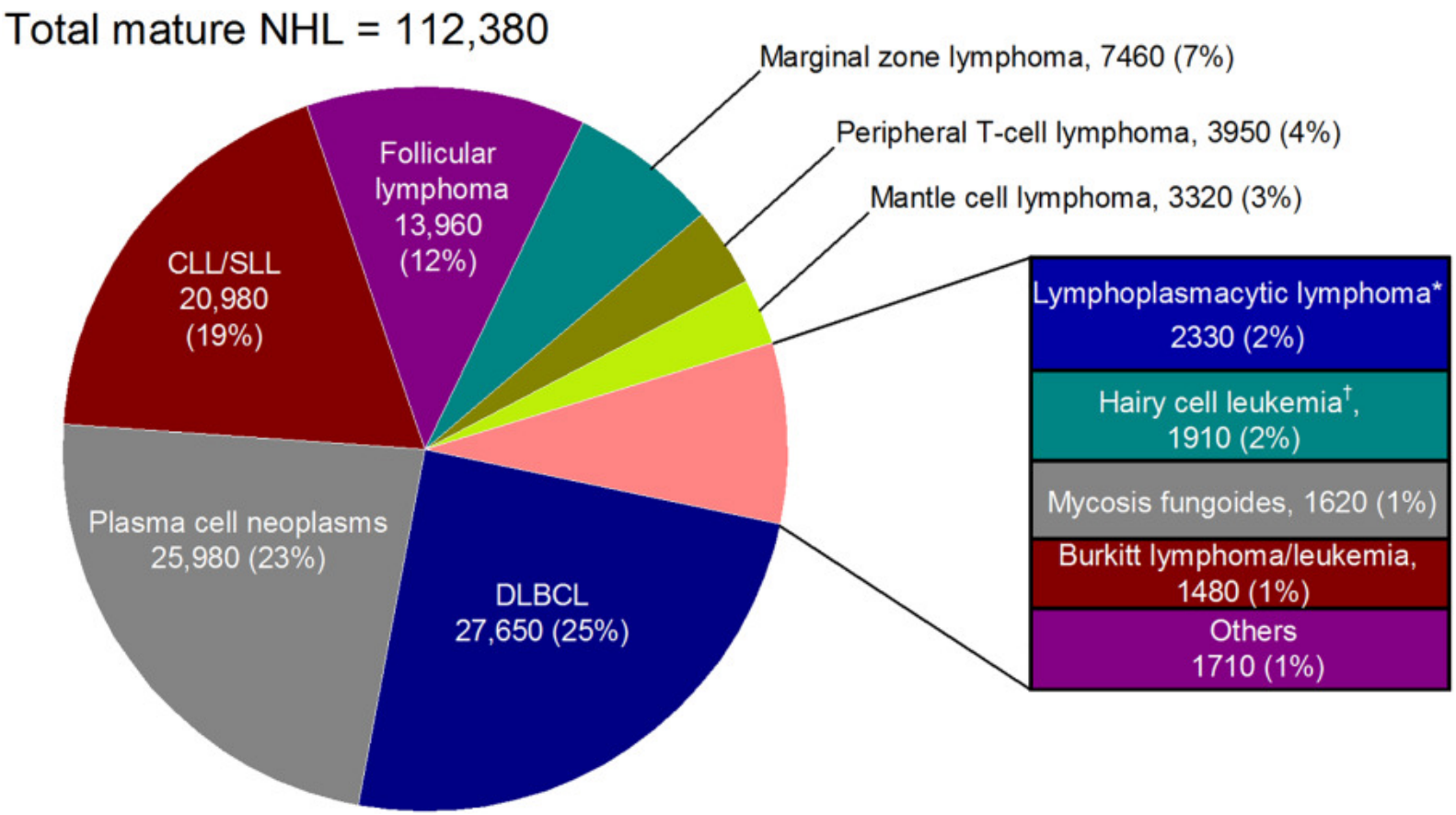
Outline

- 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

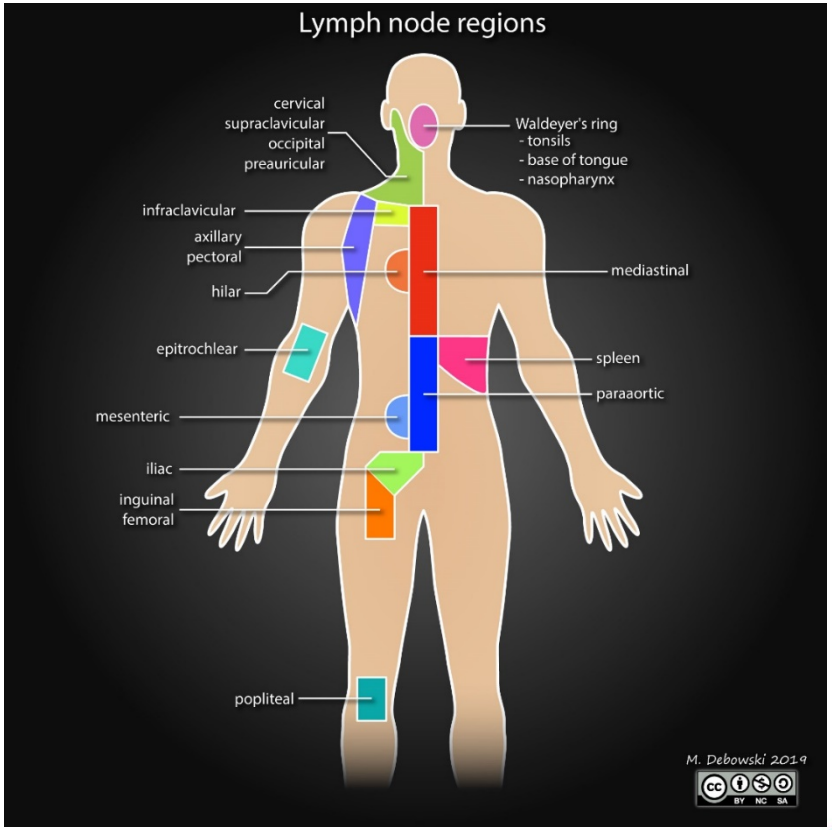


Image -Dr Maciej Debowski, Radiopaedia.org, rID: 65530

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)

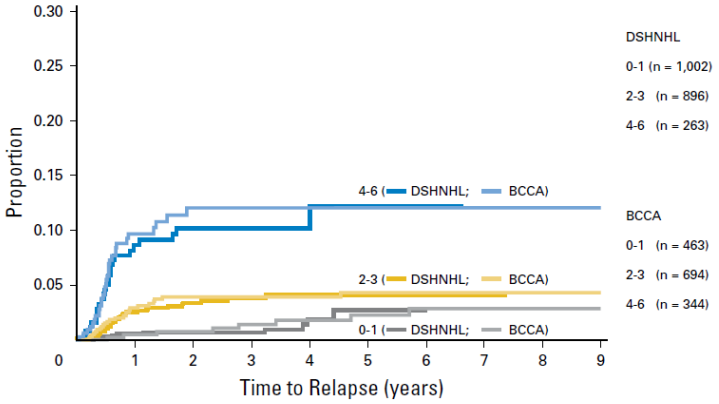
Consider marrow for:

- 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%**



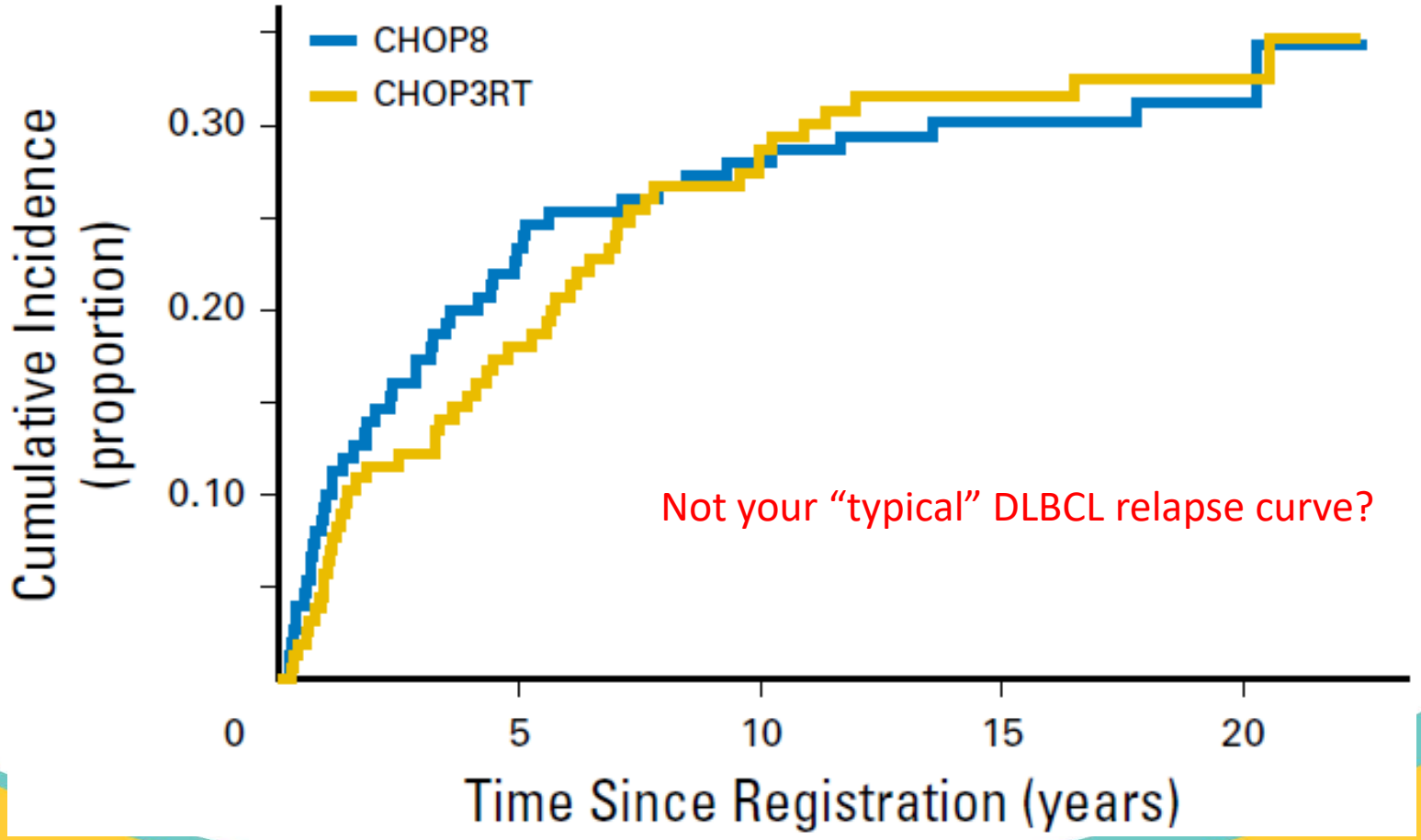
ALSO

- 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

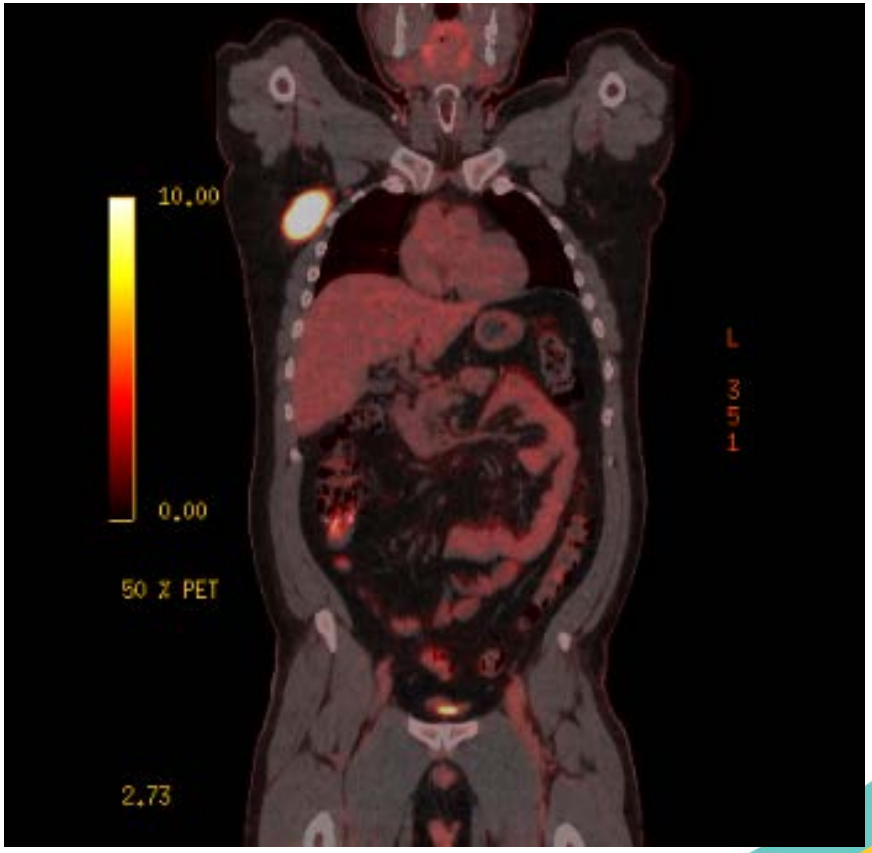
40 M previously healthy male developed R armpit swelling

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

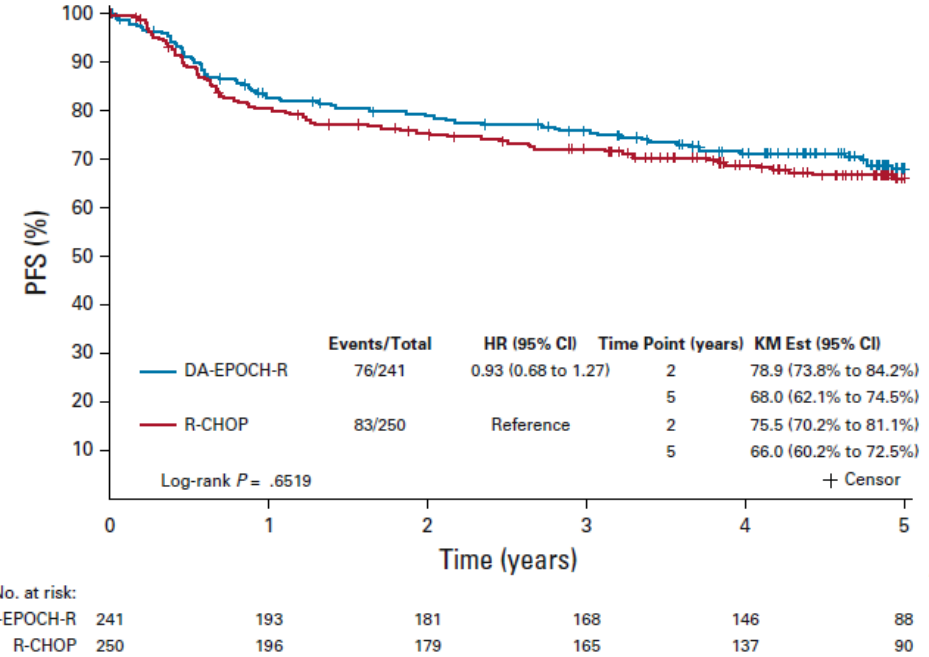


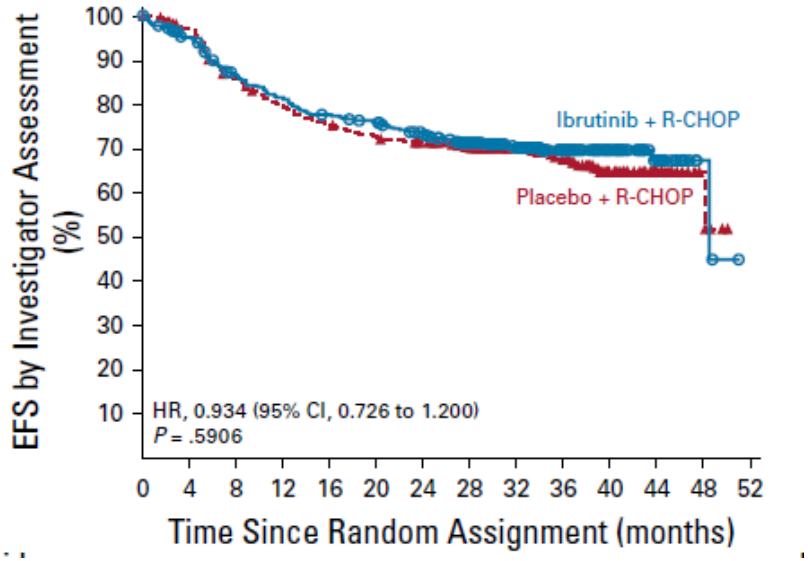
Therapy for Limited Stage DLBCL: Short-course options

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

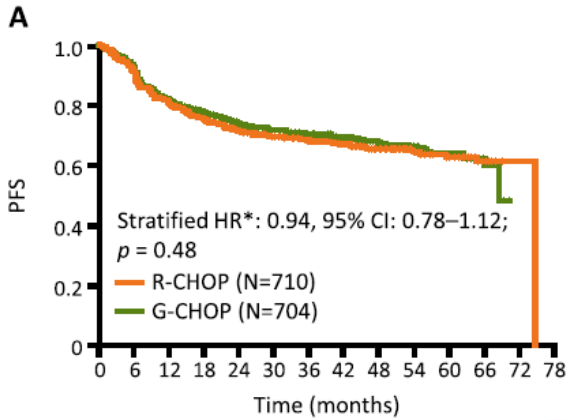
Randomized trials for 1L DLBCL- Outcome of “typical” studies





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

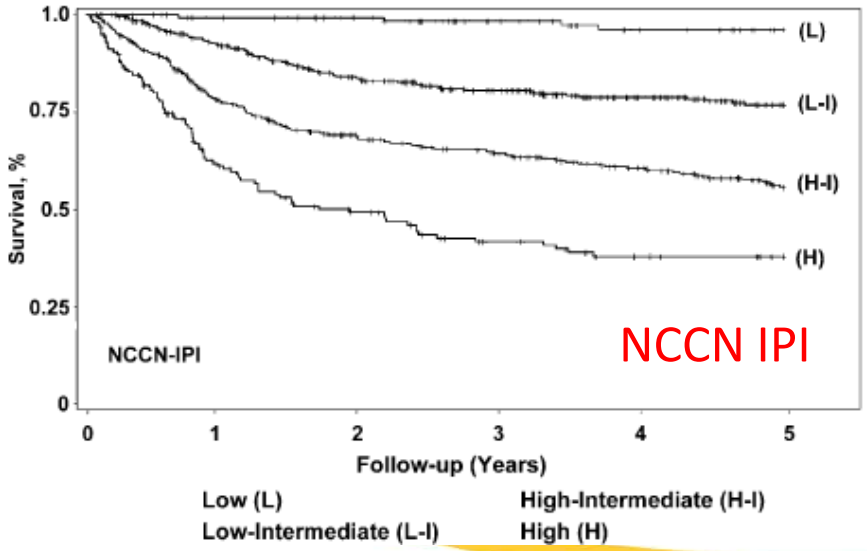
Table 3. The NCCN-IPI

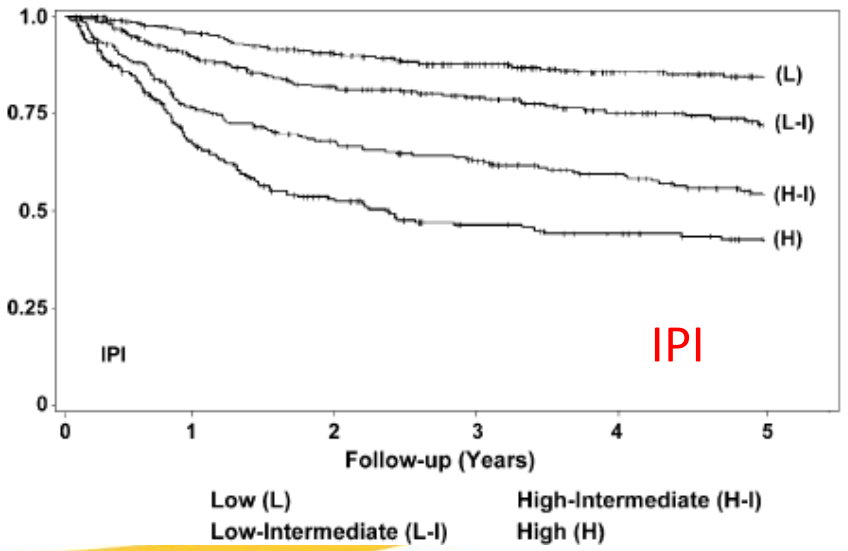
NCCN-IPI	Score
Age, y	
>40 to ≤60	1
>60 to ≤75	2
>75	3
LDH, normalized	
>1 to ≤3	1
>3	2
Ann Arbor stage III-IV	1
Extranodal disease*	1
Performance status ≥2	1

*Disease in bone marrow, CNS, liver/GI tract, or lung.

Benefits to NCCN IPI

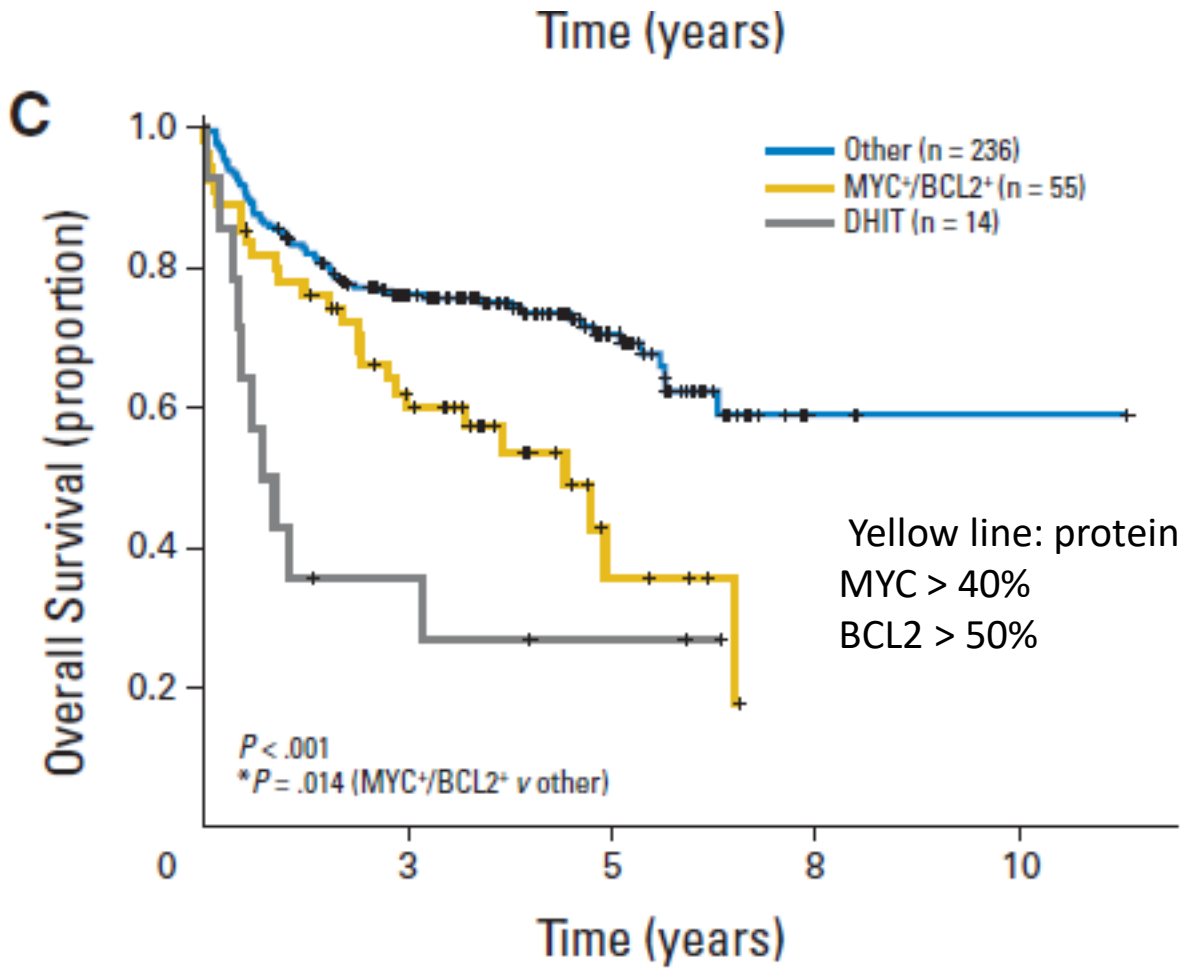
- DLBCL pt specific
- High LDH elevations represented
- Slightly wider range/better discrimination of groups





MYC dysregulation: protein and translocation

Double expressor (protein) ≈ 30%
Double hit ≈ 10 %

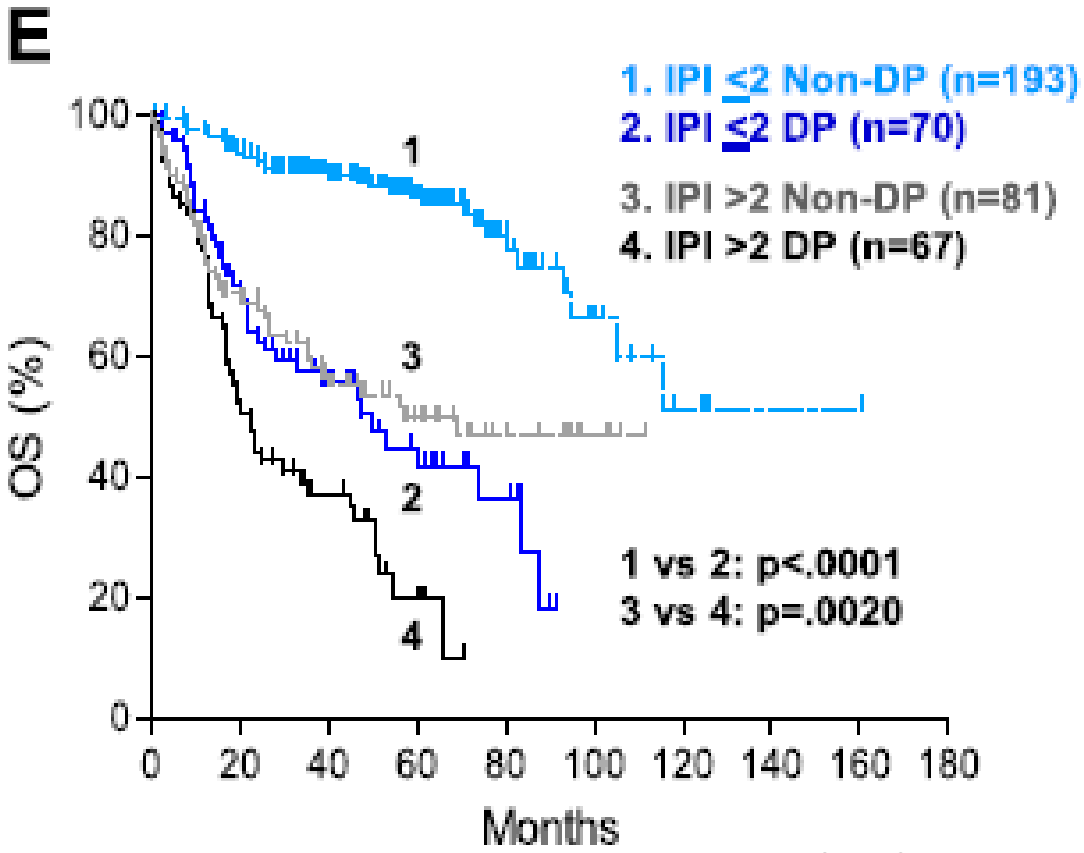


Yellow line: protein overexpression
MYC > 40%
BCL2 > 50%

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

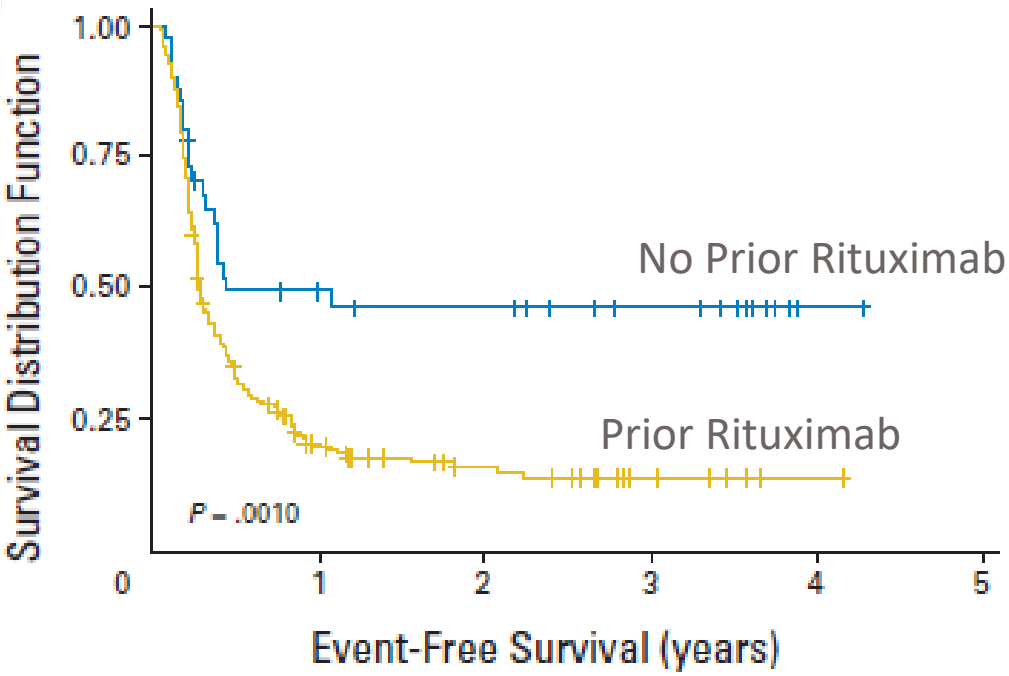
DLBCL: Post-Treatment Surveillance

- **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.***

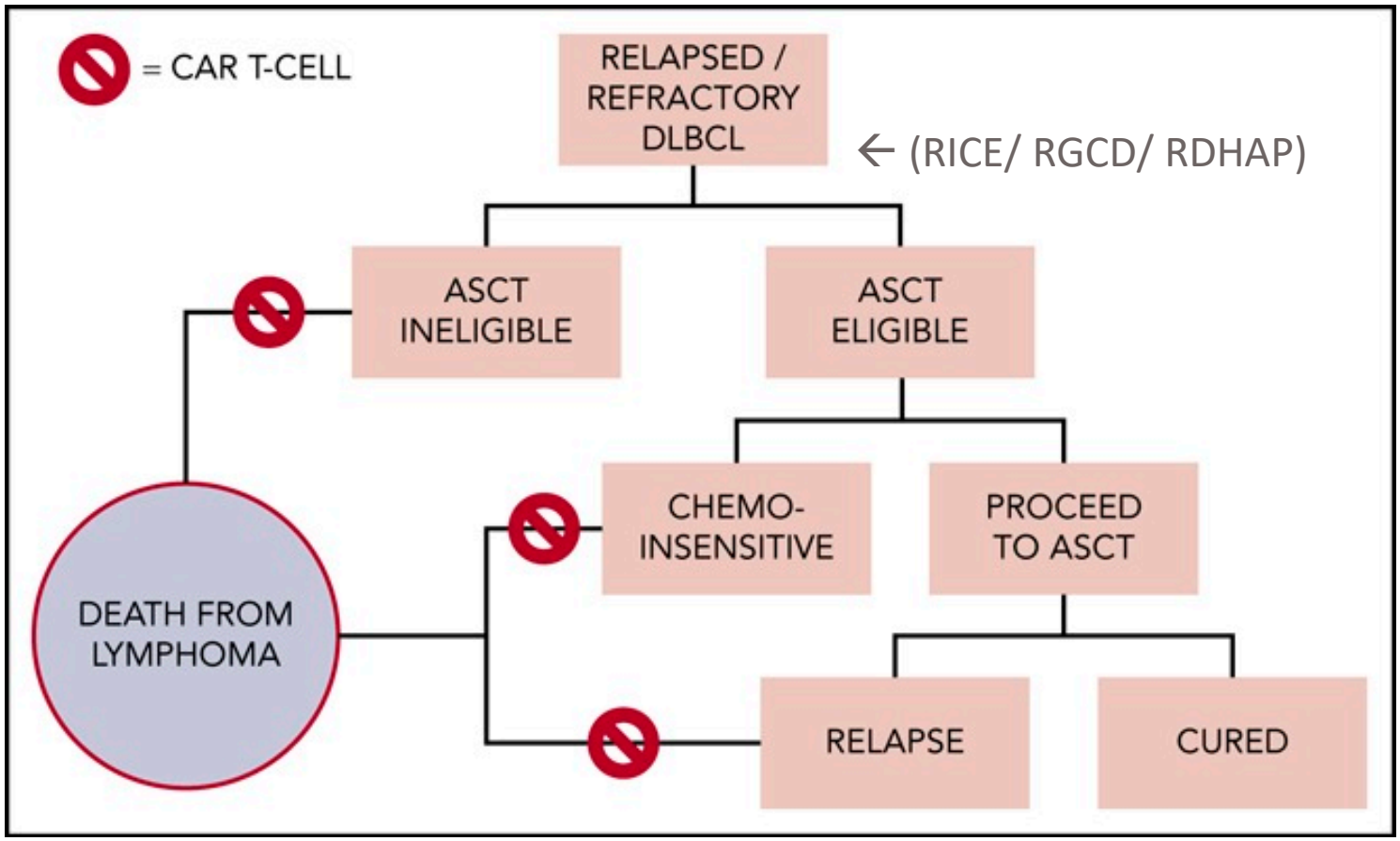
Gisselbrecht C, *et al. J Clin Oncol.* 2010;28:4184–4190

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



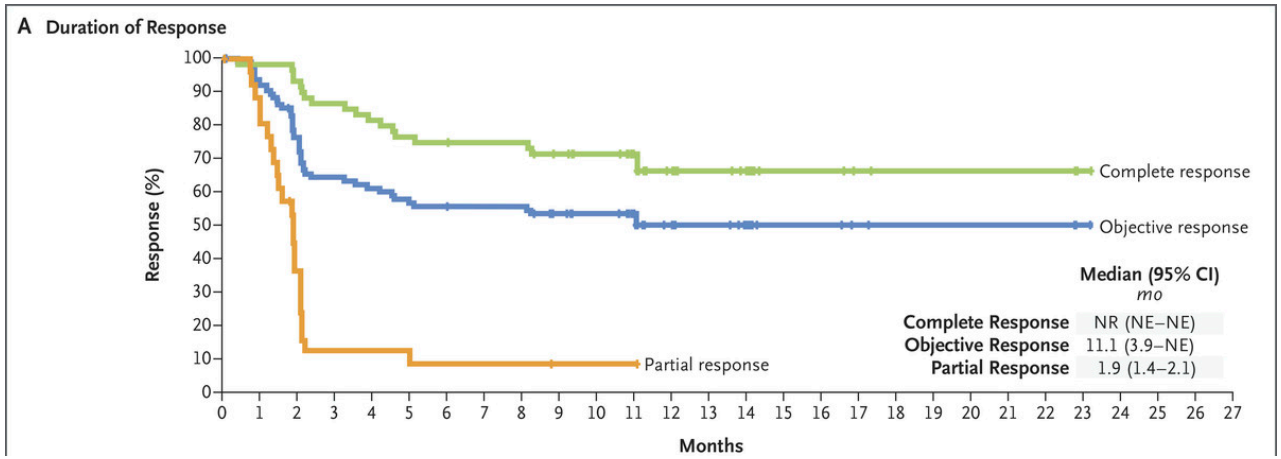
Adapted from Chow/Gopal Blood 2018

Chimeric antigen receptor T (CAR-T) Therapy

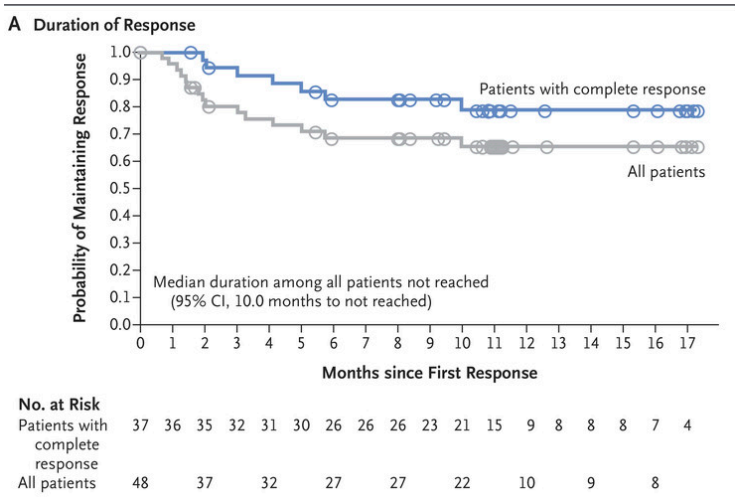
Approved for relapsed/ref DLBCL failing ≥2 lines:

- 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 (

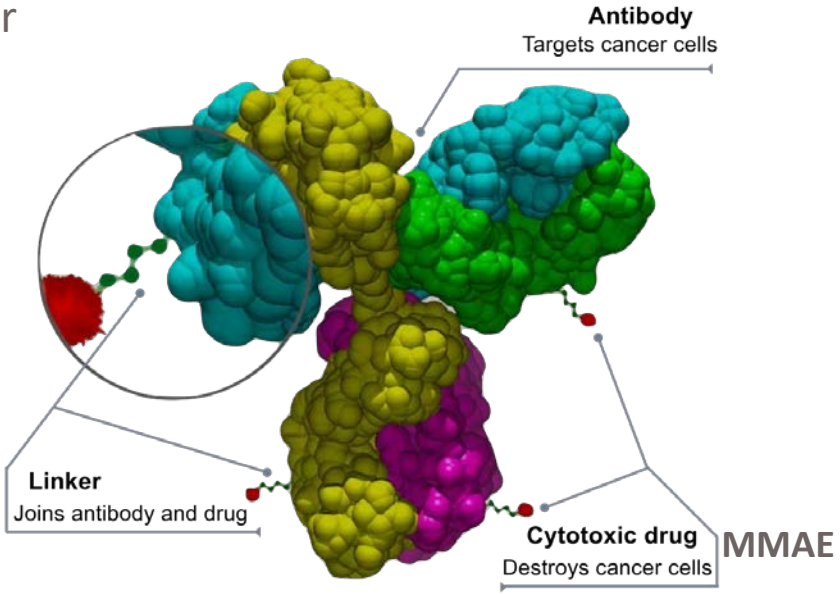
Polatuzumab vedotin: CD79b-targeted Ab with MMAE payload

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%

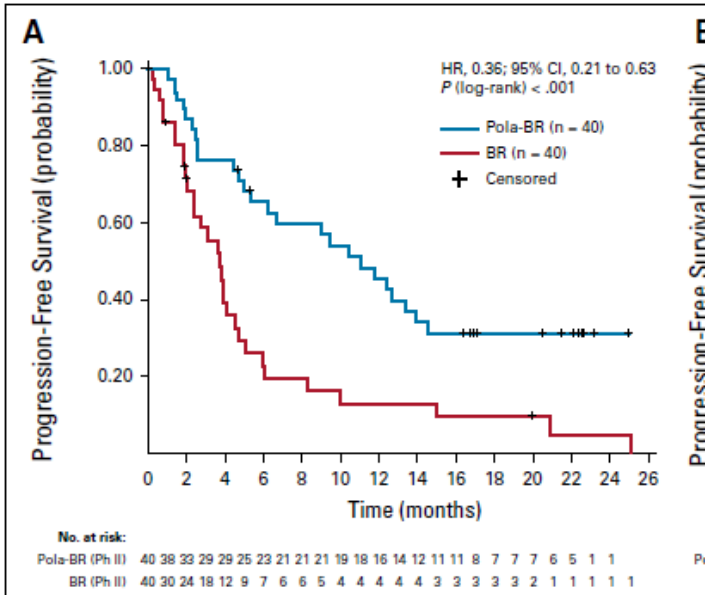
- Median PFS: 9.5 months in pola BR vs 3.7 in BR
- OS 12.4 vs 4.7 mo

- Toxicity: 23% grade 3-4 infection
  - 42% received all 6 cycles
  - 33% d/c therapy due to AE
  - 54% had a treatment delay

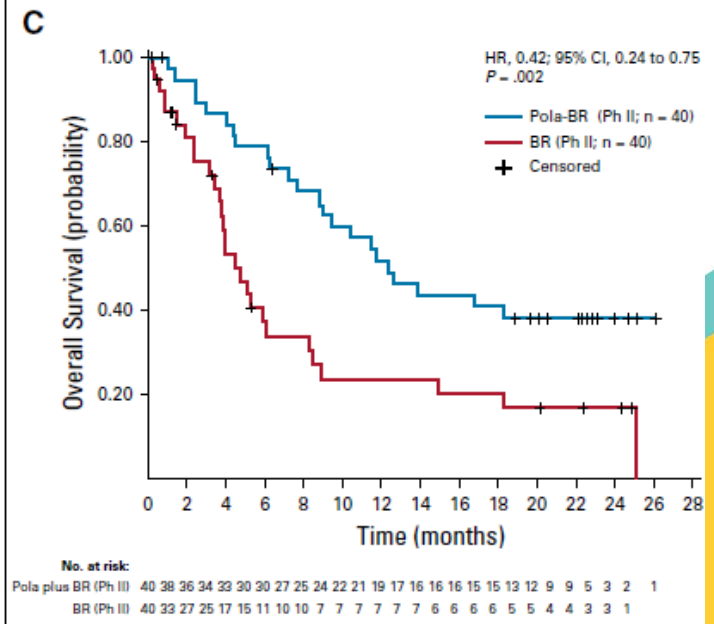
Limitations

- 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

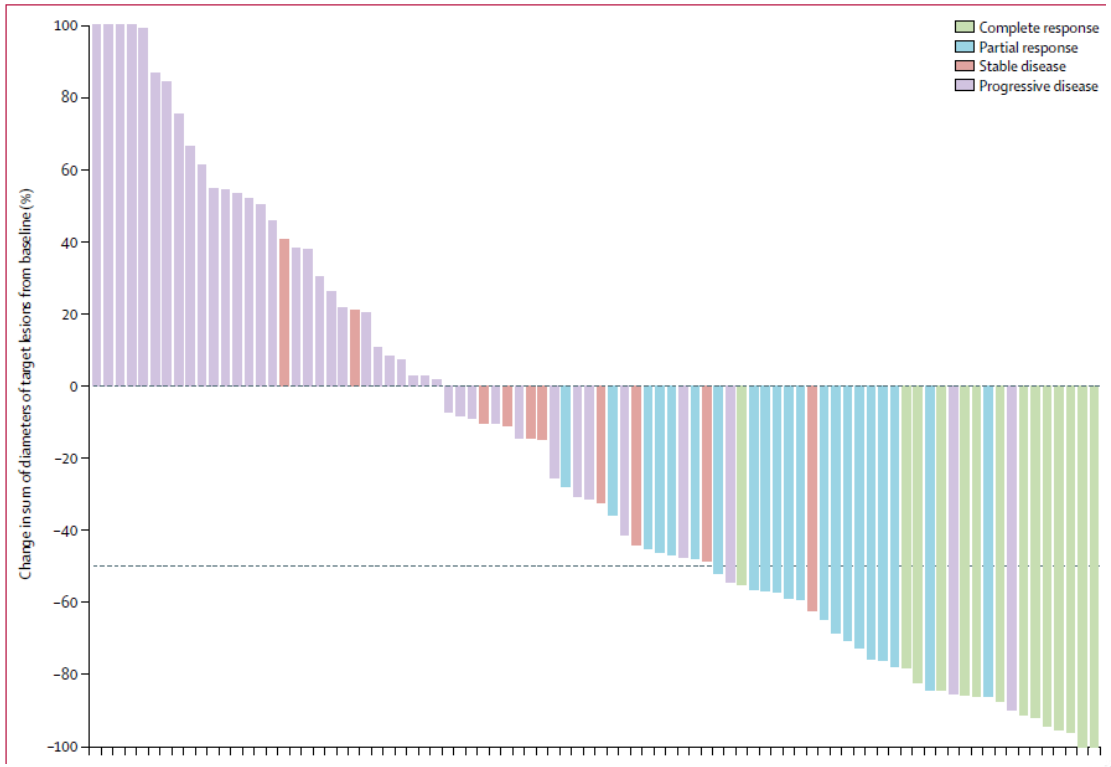
Notable eligibility criteria

- 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:

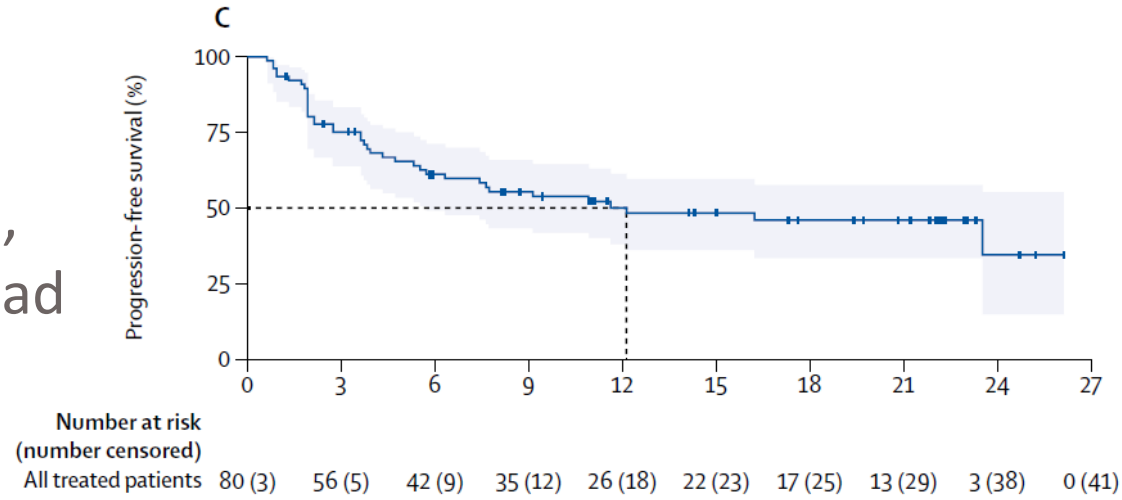
- Ineligible for transplant (age > 70 or other reasons)
- At MOST, 3 prior regimens
- Primary refractory disease excluded

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.

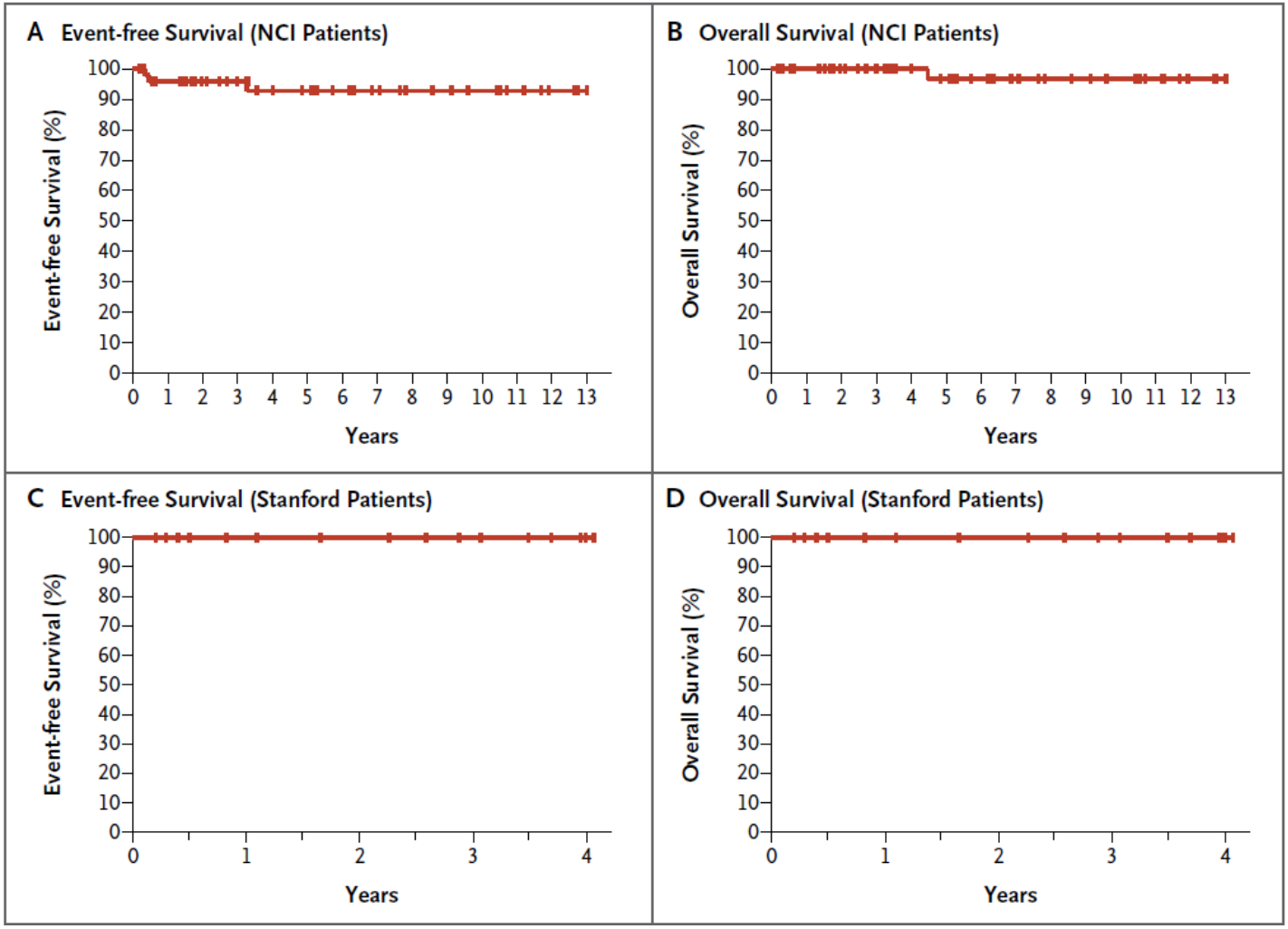
Salles Lancet Onc 2020

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

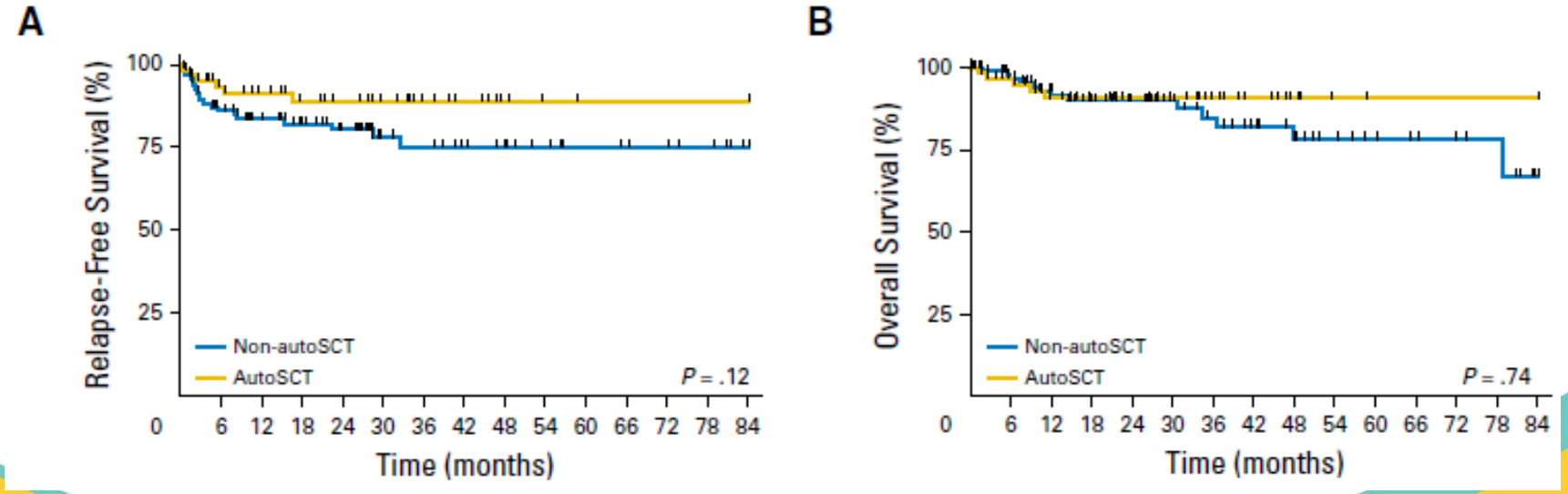
- **HGBL, not otherwise specified**

- **<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

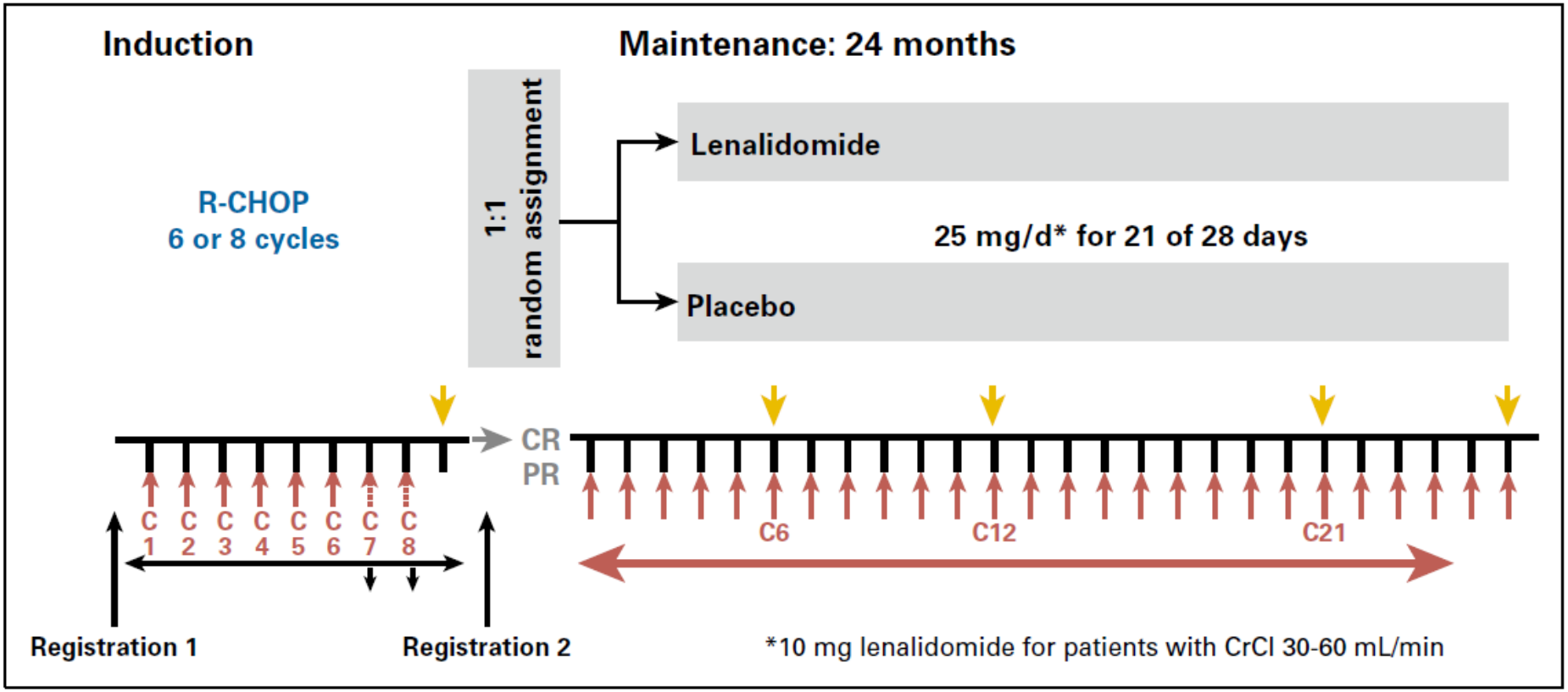
Thank You

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]**

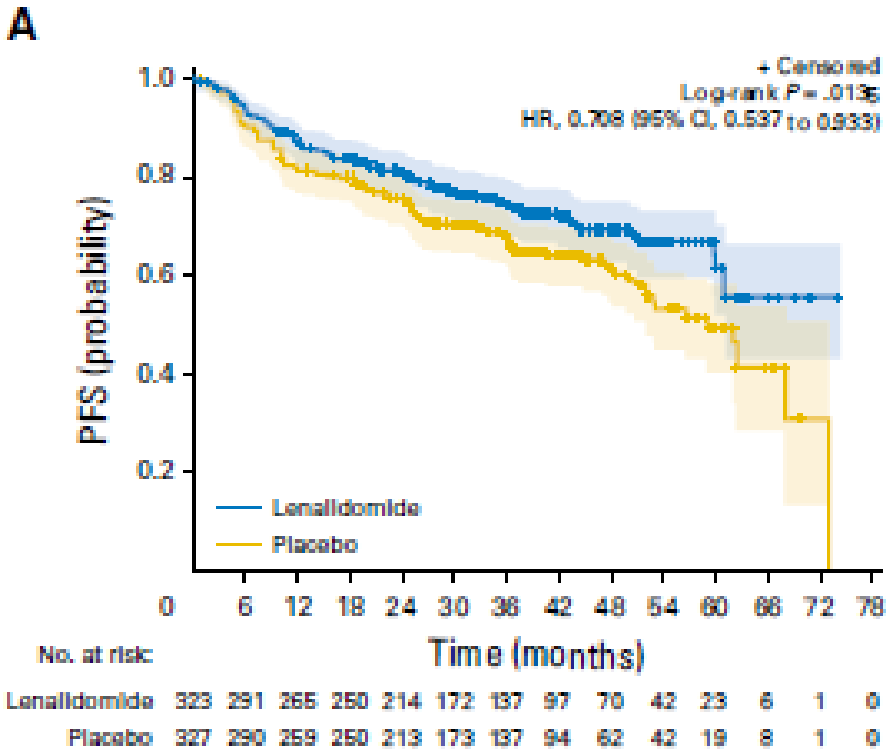
[1]Haberman, *et al*. *J Clin Oncol*. 2006;24(19):3121-3127.
[2]ThieblemontJ Clin Oncol. 2017 Aug 1

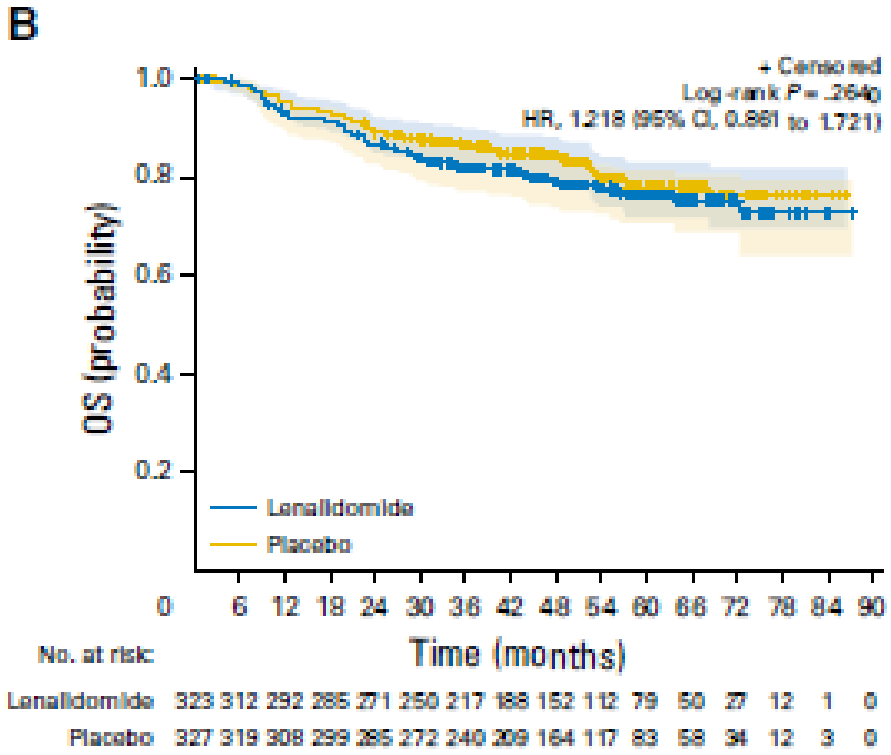
Maintenance with Lenalidomide: REMARC



Thieblemont J Clin Oncol. 2017

Len Maintenance – REMARC PFS and OS





- Not FDA approved, unclear impact on salvage therapy, NCCN Category 2B

Thieblemont J Clin Oncol. 2017