Fred Hutch Cancer Center

Aggressive B-Cell Non-Hodgkin Lymphoma

Mengyang Di, MD, PhD
Assistant Professor, Division of Hematology & Oncology
University of Washington / Fred Hutchinson Cancer Center

mydi@fredhutch.org

@DiMengyang

Disclosures

- Research Funding: Schrodinger, Inc.; BeiGene.
- Consultancy: BeiGene; Genetech.

Topics

- Diffuse Large B-Cell Lymphoma (DLBCL)
  - Limited stage
  - Advanced stage
  - Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
- Double hit (MYC/BCL2)
- Burkitt Lymphoma
- Relapsed /refractory Aggressive B-Cell Lymphomas

Topics

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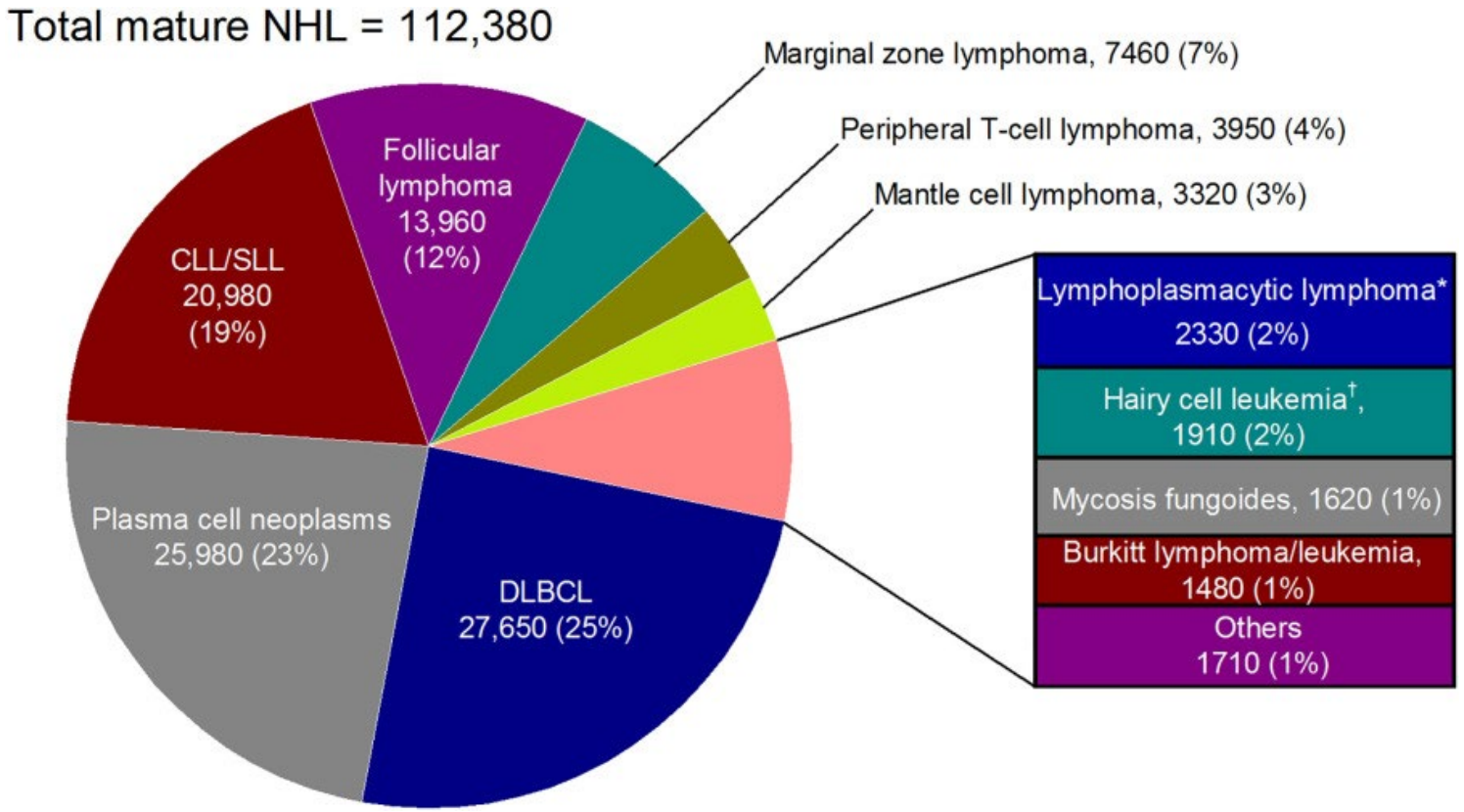
US Lymphoid Malignancy Incidence

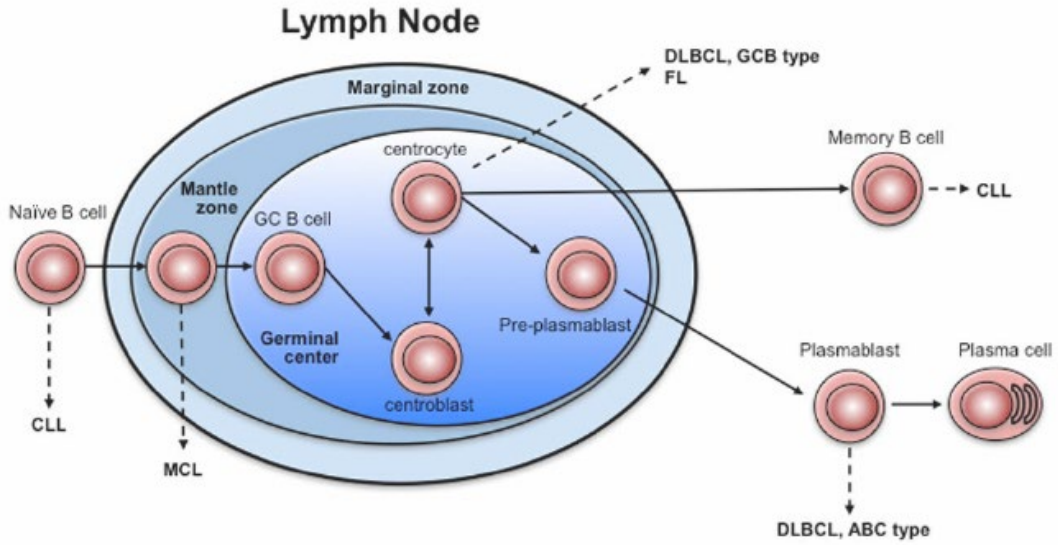


DLBCL incidence: 7 per 100k, about 30k per year

Teras Ca J Clin 2016

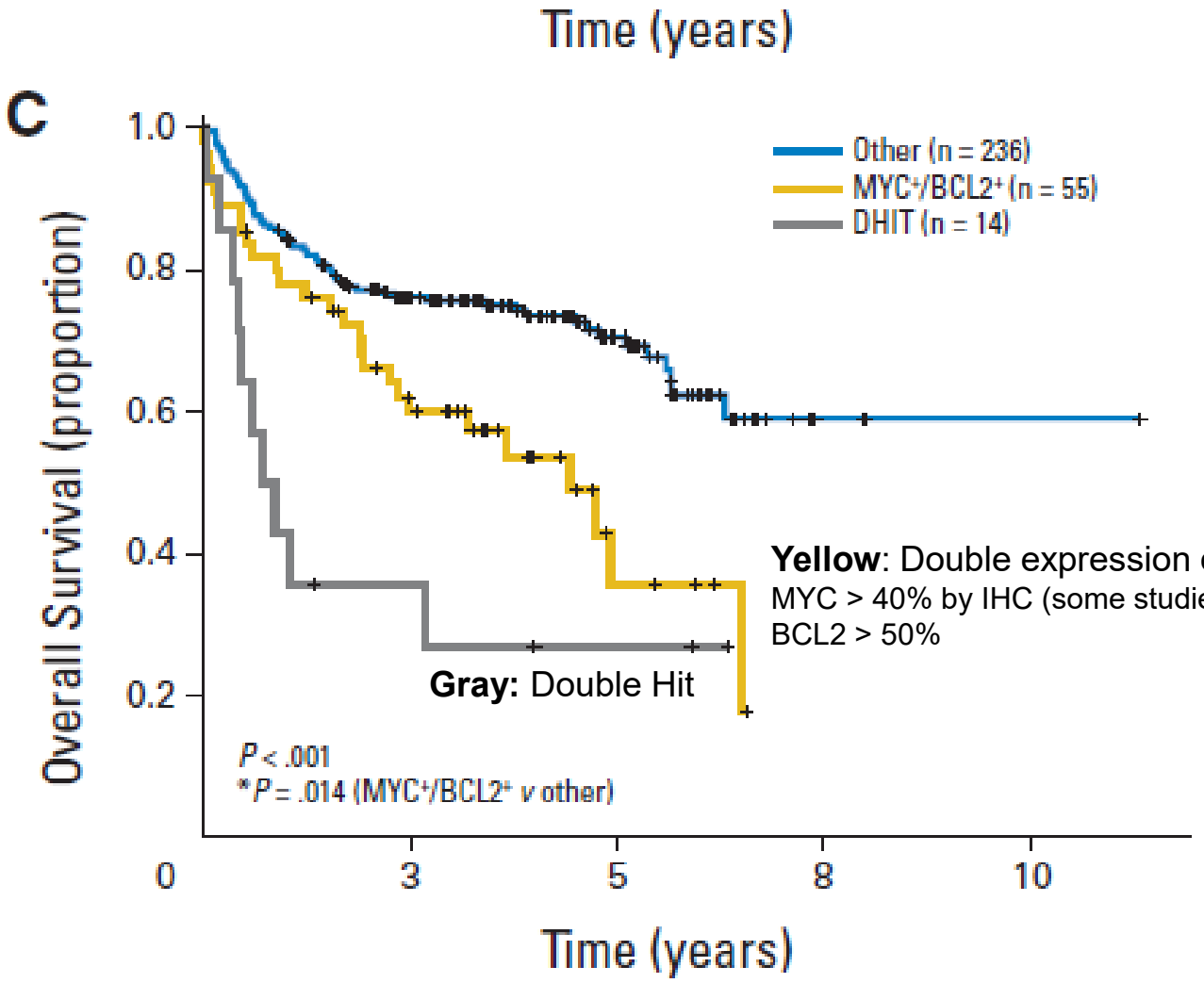
DLBCL and Cell of Origin

- **Germinal Center (GCB)**
  - most common
  - *Upregulated genes: BCL6 and EZH2*
- **Activated B-cell (ABC)**
  - < 1/3 of cases
  - *BCR signaling/ NFkB activation*
- **Unclassifiable**
  - < 1/5 cases



Koues Trends Gen 2015, Shaffter Annu Rev Immunol 2012, Shmitz NEJM 2018

MYC/BCL2: Double hit vs Protein Expression



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

Yellow: Double expression of MYC and BCL2
MYC > 40% by IHC (some studies use 50%)
BCL2 > 50%

Gray: Double Hit

Hu Blood 2013

Pretreatment evaluation

- Echo/MUGA
- Fertility evaluation and preference
- Laboratory workup (Hep B, HIV, LDH)
- Venous access
- Staging w/PET CT
  - Detects extranodal sites better than CT: GI, bone, skin/subQ, liver
  - High sensitivity for large B-cell marrow involvement
    - BM Bx still “useful in selected cases (NCCN)- e.g., for
      - Key treatment decisions
      - Baseline cytopenias
      - Uncertain PET result

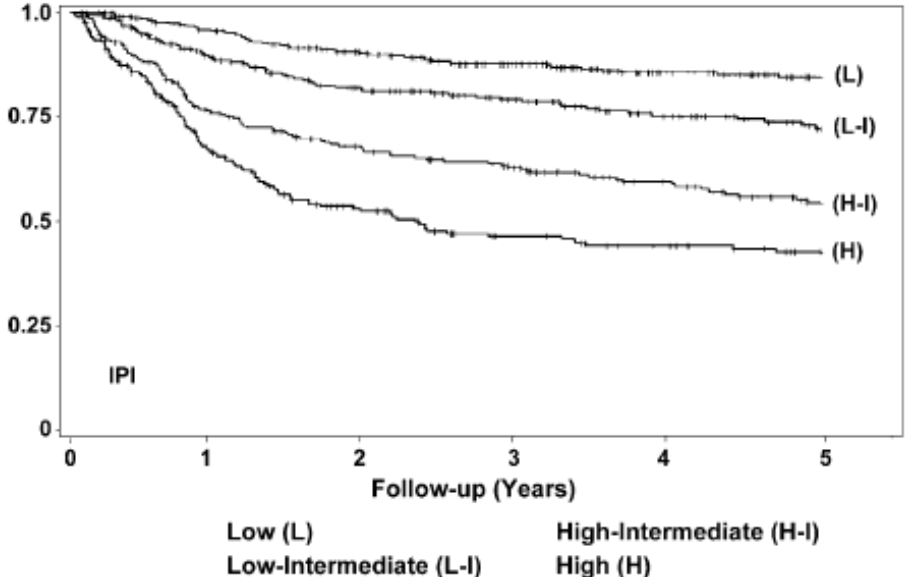
IPI and CNS-IPI: Prognosis and CNS risk

Standard IPI

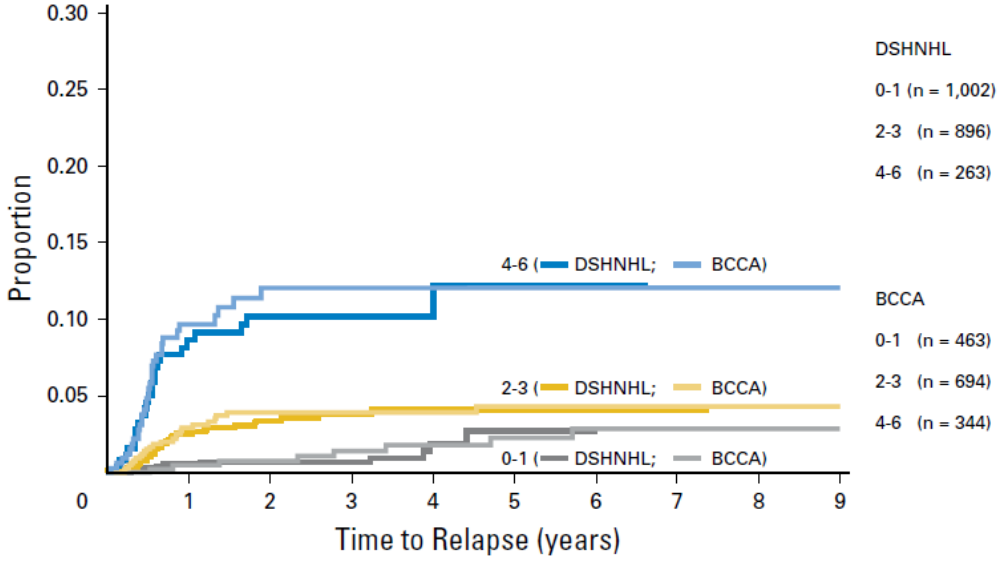
- Age >60
- Stage III/IV
- LDH >ULN
- EN sites >1
- ECOG >1

+ renal or adrenal involvement → CNS IPI

IPI 3-5 "High risk"



CNS IPI 4-6: >10% chance of CNS involvement

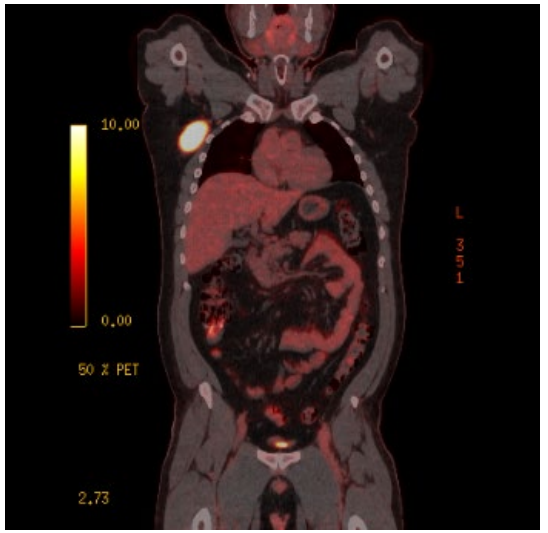


CNS risk with

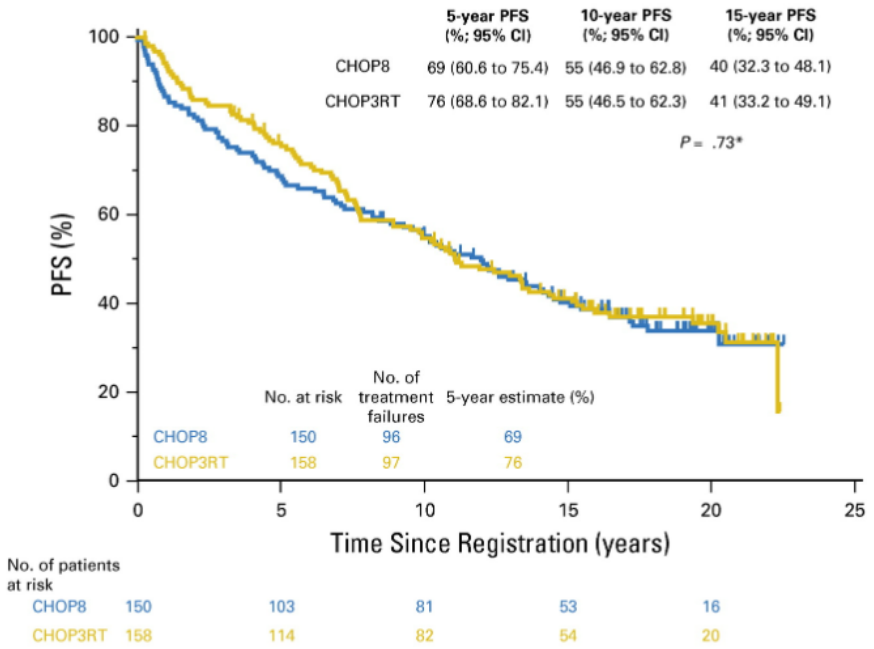
- ***DHL***
- ***Testicular DLBCL***
- ***Breast DLBCL***

Zhou *Blood* 2014. Schmitz JCO 2016.

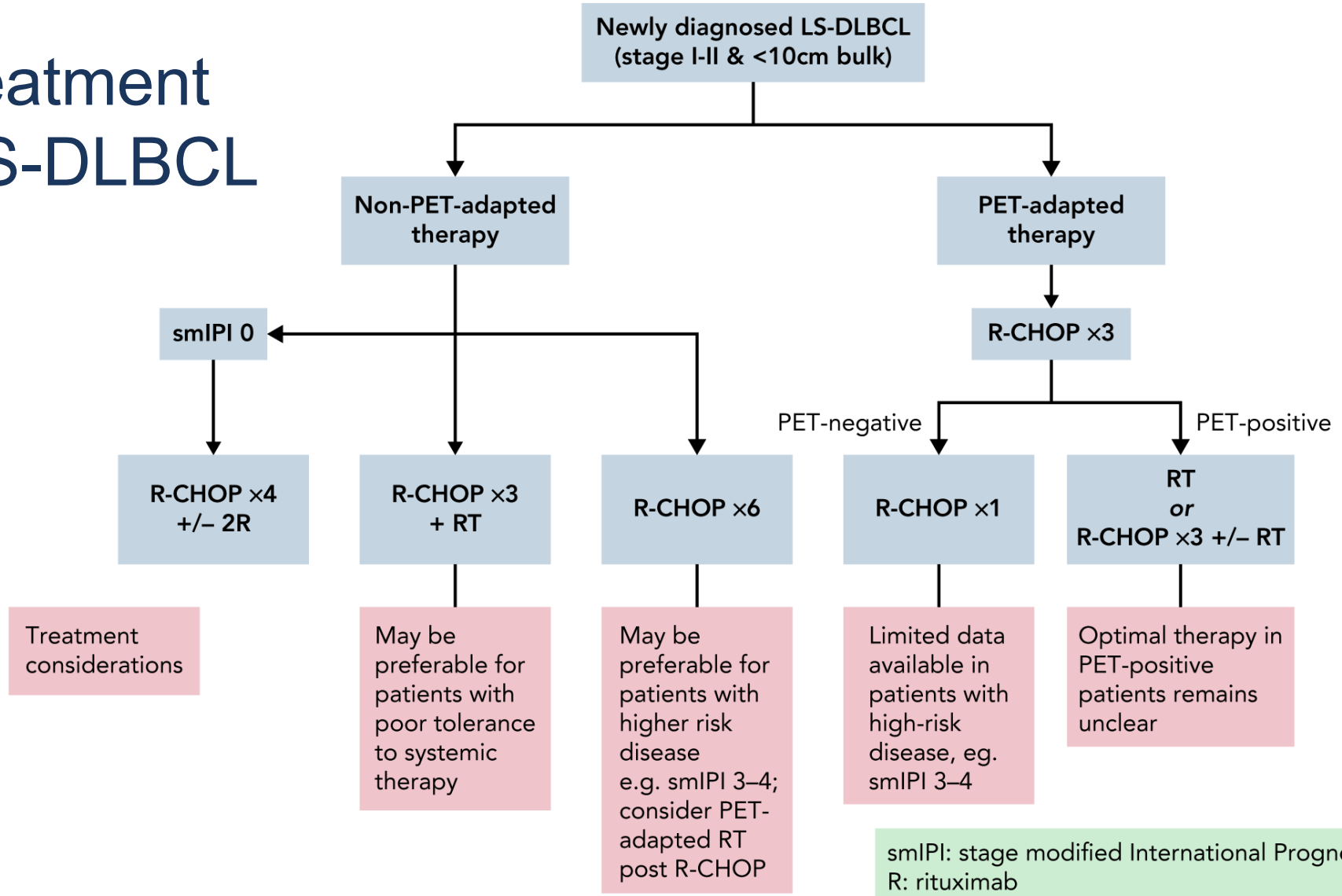
Limited Stage DLBCL



- ≈ 40% of DLBCL cases, high cure rate
- Unique biology
  - continual relapse risk (SWOG- Stephens JCO 2016)
- ? Role of radiation (ISRT, 30 Gy)
  - Not generally needed
    - LYSA/GOELAMS 02-03, SWOG S8736
  - Toxicity and out of field relapses are concerns



Pragmatic treatment options for LS-DLBCL

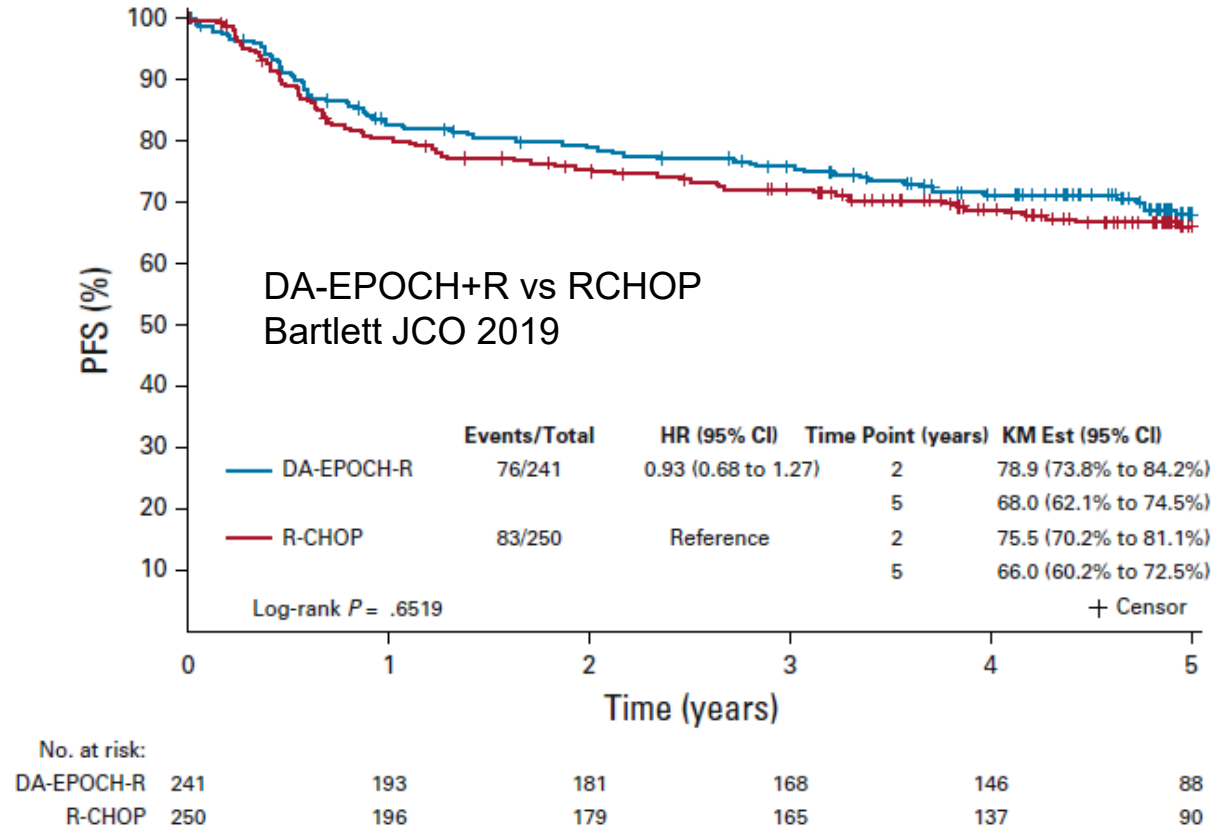


Poeschel Lancet 2019, Lamy Blood 2018, Miller NEJM 1998, Persky JCO 2008, Stephens JCO 2016, Persky JCO 2021: "SWOG S1001", Hawkes Blood 2022

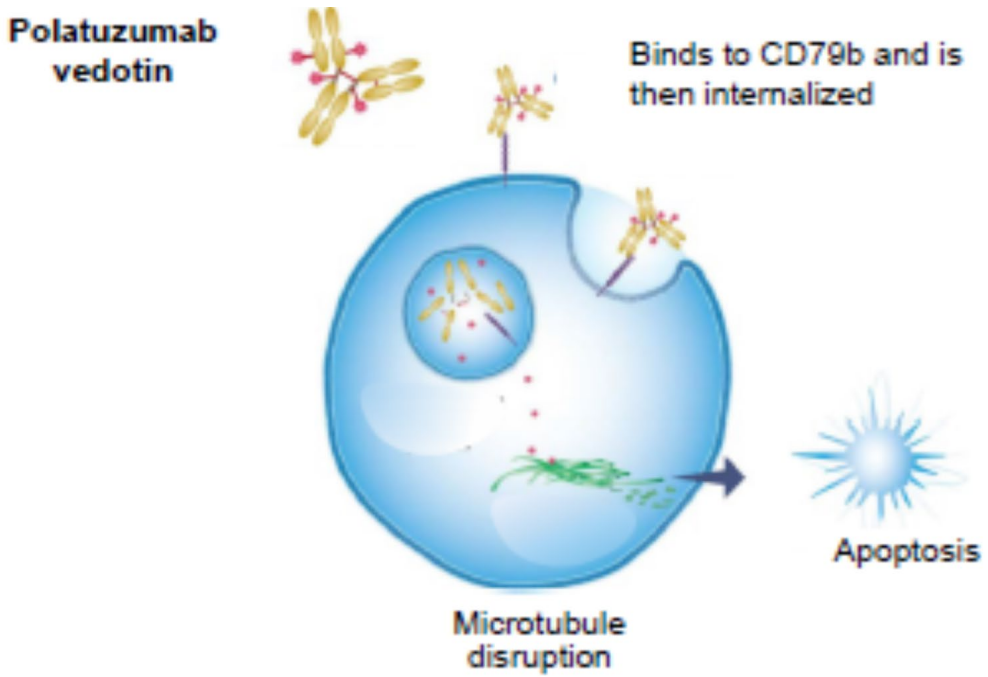
Advanced Stage DLBCL

- RCHOP: 20-year standard
- Cure rate ≈ 70%

Many negative randomized trials vs RCHOP…



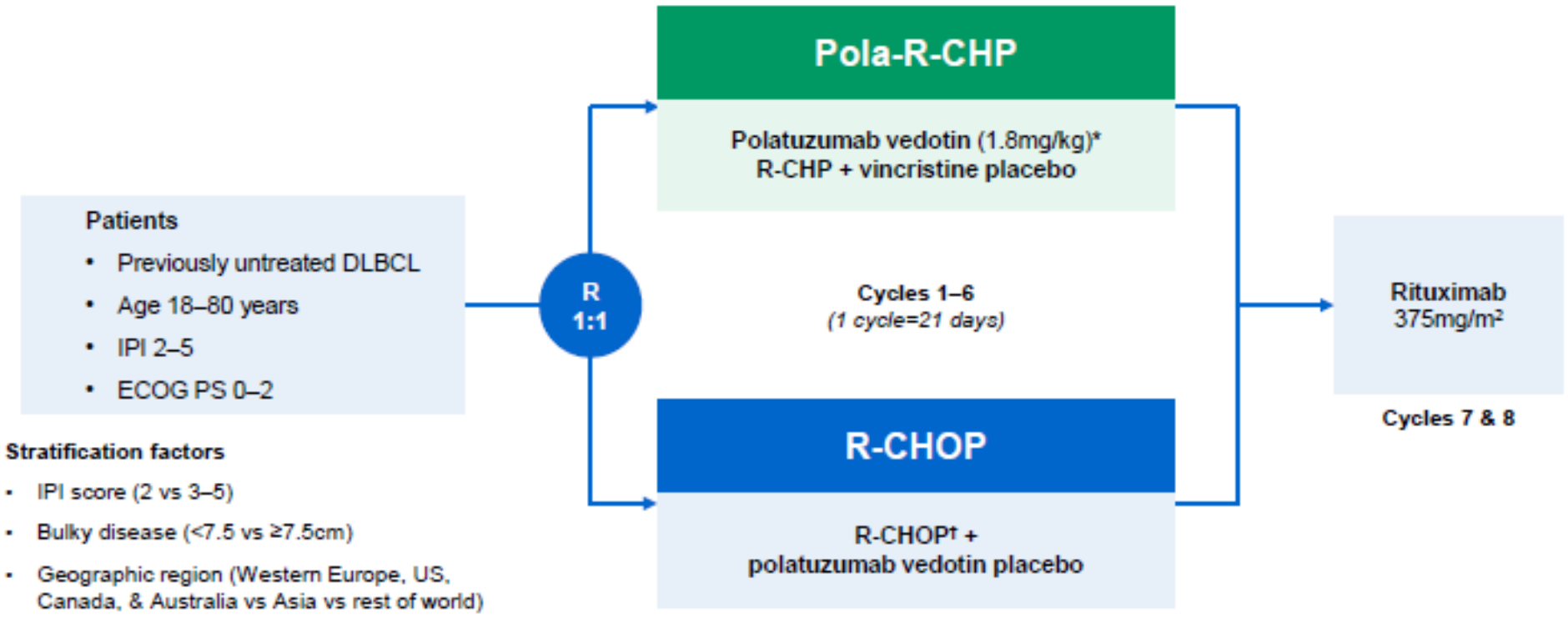
Polatuzumab Vedotin: Basis for POLARIX trial in 1st line DLBCL



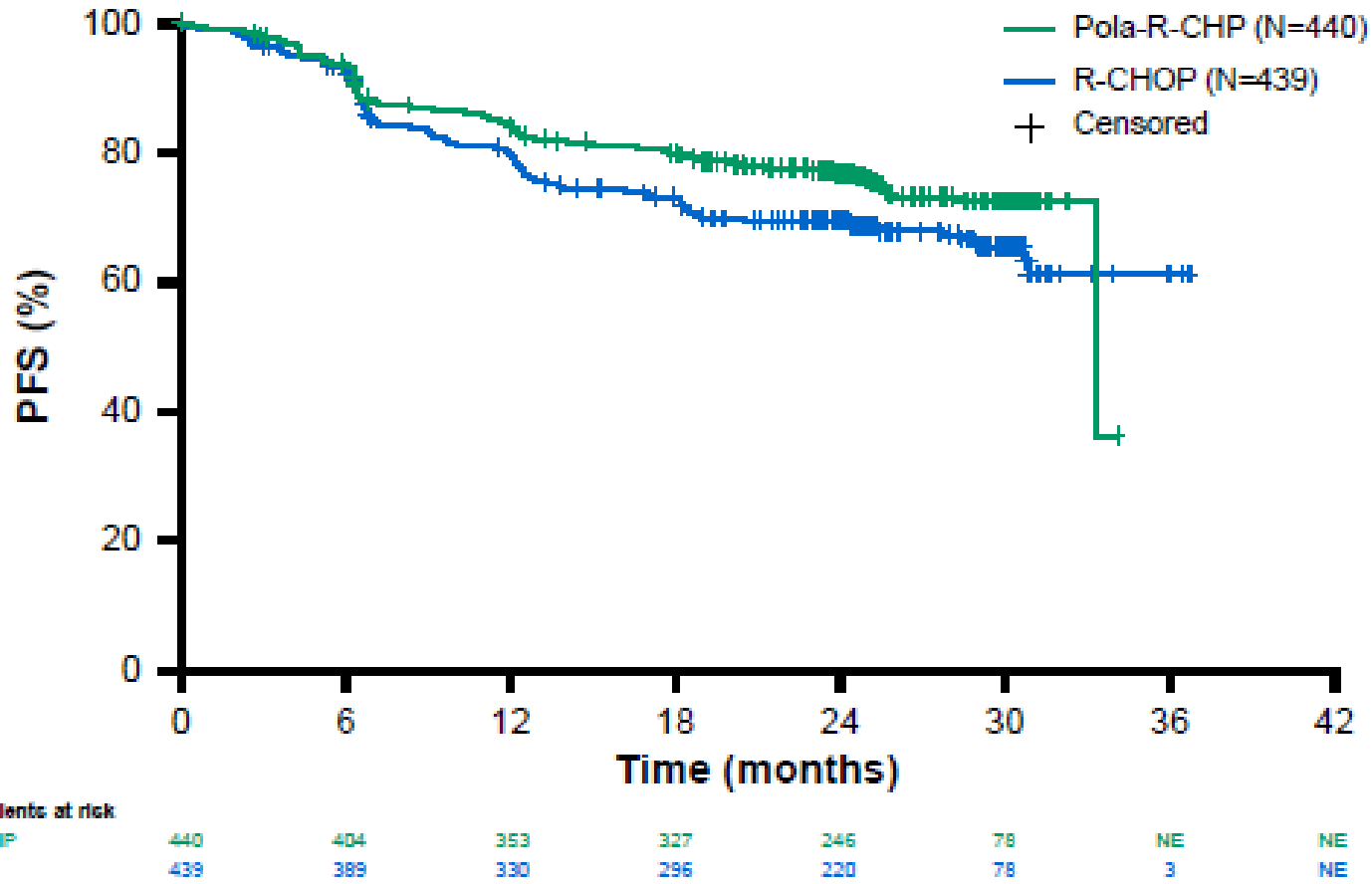
- **Pola monotherapy** in R/R DLBCL: ORR 56%, CR 15%
- **Pola+ BR**: ORR 45%/CR 40%, OS 12.4 months
  - Better in **ABC subtype** HR 0.34 PFS
- **Pola + R**: ORR 54%/ CR 21%

Palanca-Wessels Lancet Oncol 2015, Sehn JCO 2020, Morschauser Lancet Heme 2019

POLARIX: Pola-RCHP vs RCHOP



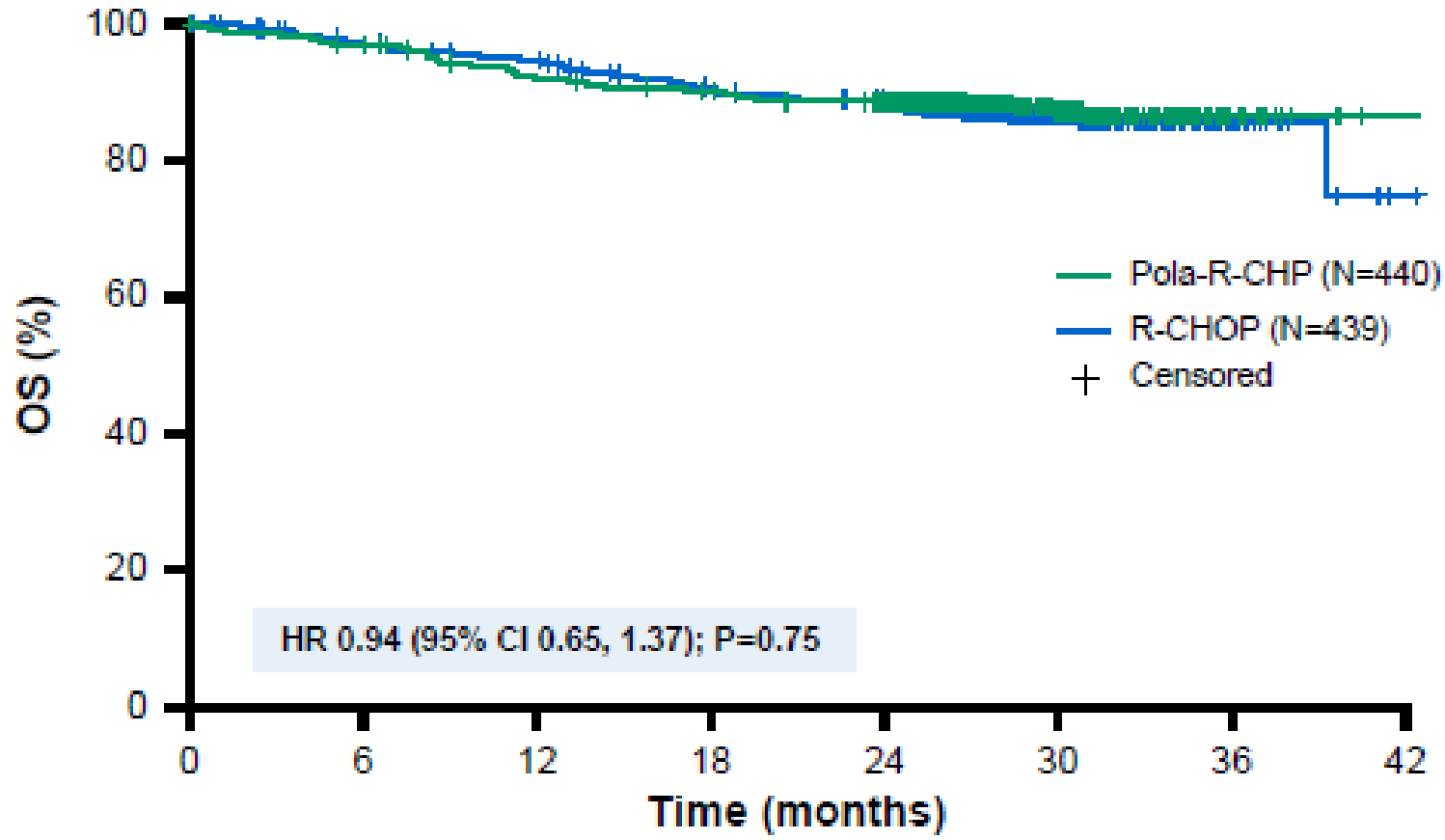
Polarix: Progression-Free Survival



HR 0.73 (P<0.02)
95% CI: 0.57, 0.95

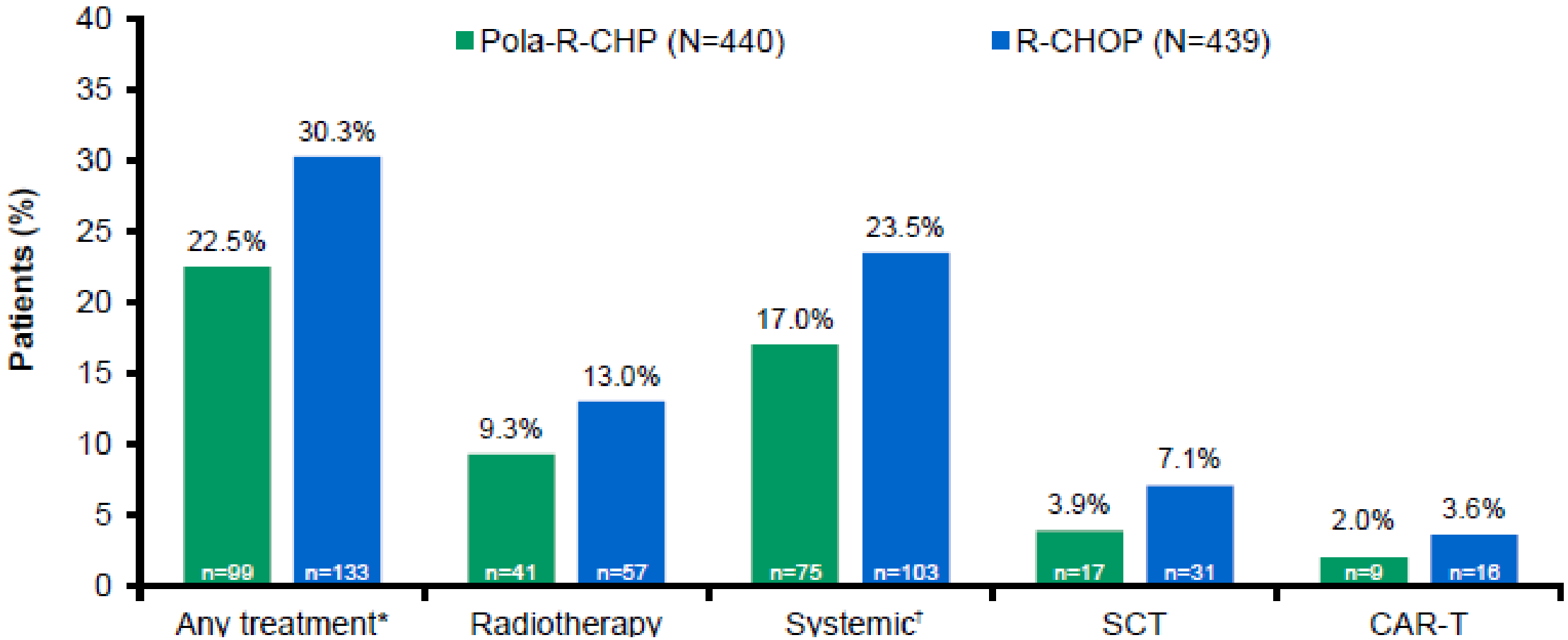
- Pola-R-CHP demonstrated a **27% reduction in the relative risk of disease progression, relapse, or death** versus R-CHOP
- **24-month PFS:**
  76.7% with Pola-R-CHP versus
  70.2% with R-CHOP (Δ=6.5%)

Polarix: Overall Survival

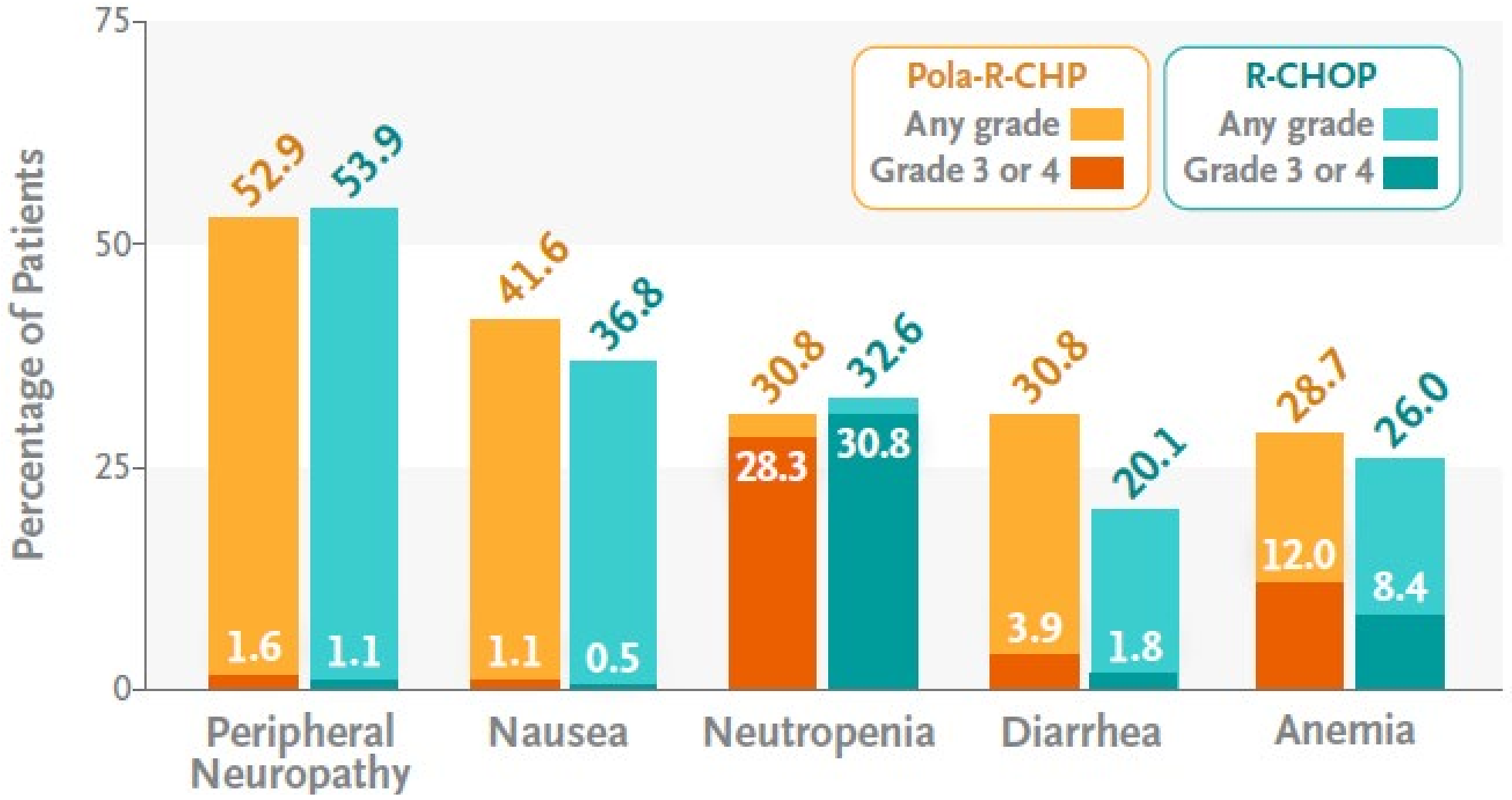


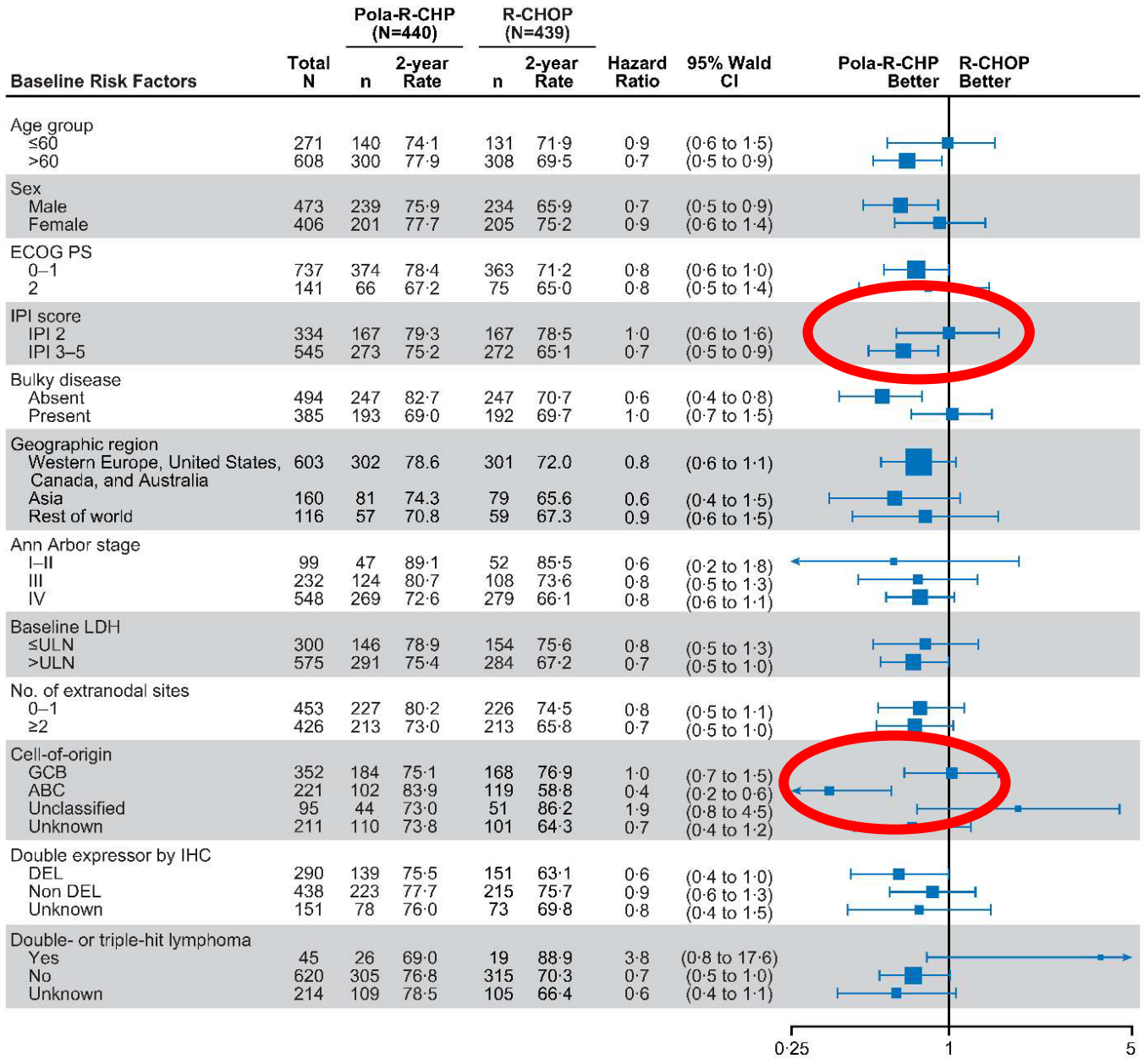
No. of patients at risk								
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	1

Polarix: Subsequent Treatments



Polarix: Toxicity





Baseline Risk Factors	Total N	Pola-R-CHP (N=440) n	Pola-R-CHP (N=440) 2-year Rate	R-CHOP (N=439) n	R-CHOP (N=439) 2-year Rate	Hazard Ratio	95% Wald CI
Age group							
≤60	271	140	74·1	131	71·9	0·9	(0·6 to 1·5)
>60	608	300	77·9	308	69·5	0·7	(0·5 to 0·9)
Sex							
Male	473	239	75·9	234	65·9	0·7	(0·5 to 0·9)
Female	406	201	77·7	205	75·2	0·9	(0·6 to 1·4)
ECOG PS							
0–1	737	374	78·4	363	71·2	0·8	(0·6 to 1·0)
2	141	66	67·2	75	65·0	0·8	(0·5 to 1·4)
IPI score							
IPI 2	334	167	79·3	167	78·5	1·0	(0·6 to 1·6)
IPI 3–5	545	273	75·2	272	65·1	0·7	(0·5 to 0·9)
Bulky disease							
Absent	494	247	82·7	247	70·7	0·6	(0·4 to 0·8)
Present	385	193	69·0	192	69·7	1·0	(0·7 to 1·5)
Geographic region							
Western Europe, United States, Canada, and Australia	603	302	78.6	301	72.0	0.8	(0·6 to 1·1)
Asia	160	81	74.3	79	65.6	0.6	(0·4 to 1·5)
Rest of world	116	57	70.8	59	67.3	0.9	(0·6 to 1·5)
Ann Arbor stage							
I–II	99	47	89·1	52	85·5	0·6	(0·2 to 1·8)
III	232	124	80·7	108	73·6	0·8	(0·5 to 1·3)
IV	548	269	72·6	279	66·1	0·8	(0·6 to 1·1)
Baseline LDH							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
Double expressor by IHC							
DEL	290	139	75·5	151	63·1	0·6	(0·4 to 1·0)
Non DEL	438	223	77·7	215	75·7	0·9	(0·6 to 1·3)
Unknown	151	78	76·0	73	69·8	0·8	(0·4 to 1·5)
Double- or triple-hit lymphoma							
Yes	45	26	69·0	19	88·9	3·8	(0·8 to 17·6)
No	620	305	76·8	315	70·3	0·7	(0·5 to 1·0)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)

Polarix:

Subgroup analyses, PFS (exploratory)

Polarix- Pola + RCHP Conclusions

- **Large, double-blind, placebo-controlled trial**
- **Pola + RCHP: Superior PFS by 6.5%** vs R-CHOP
  - Decreases need for salvage Tx
    - ? benefits high-IPI /non-GCB most
- **Approved** 4/19/23 (IPI 2 or higher DLBCL or HGBCL)
- **Practical considerations**: NCCN “Preferred regimen” alongside R-CHOP, category 1

DLBCL – skeletal and bulky sites: RT consolidation?

Answer is “Maybe”

- *Best use*: Older pts >60 w/PET < CR, limited RT field
- No modern randomized data available
  - retrospective data→ comparable outcomes if EOT PET neg @ known skeletal sites
- Concerns with XRT
  - Efficacy: Out of field relapses
  - Toxicity: Marrow toxicity, 2nd CA risk

Held JCO 2013, Freeman Blood 2021

Take home message for frontline management of DLBCL

- **Limited stage:**
  - RT generally not needed, but may be useful in selected cases
  - Abbreviated chemo can be considered in non-bulky, low-risk disease
  - RCHOP * 6 cycles for bulky or high-risk disease

- **Advanced stage:**
  - Pola-RCHP has become a new standard therapy (possibly more benefit in high IPI score or ABC subtype)
  - Controversial role of consolidative RT for bulky, skeletal sites

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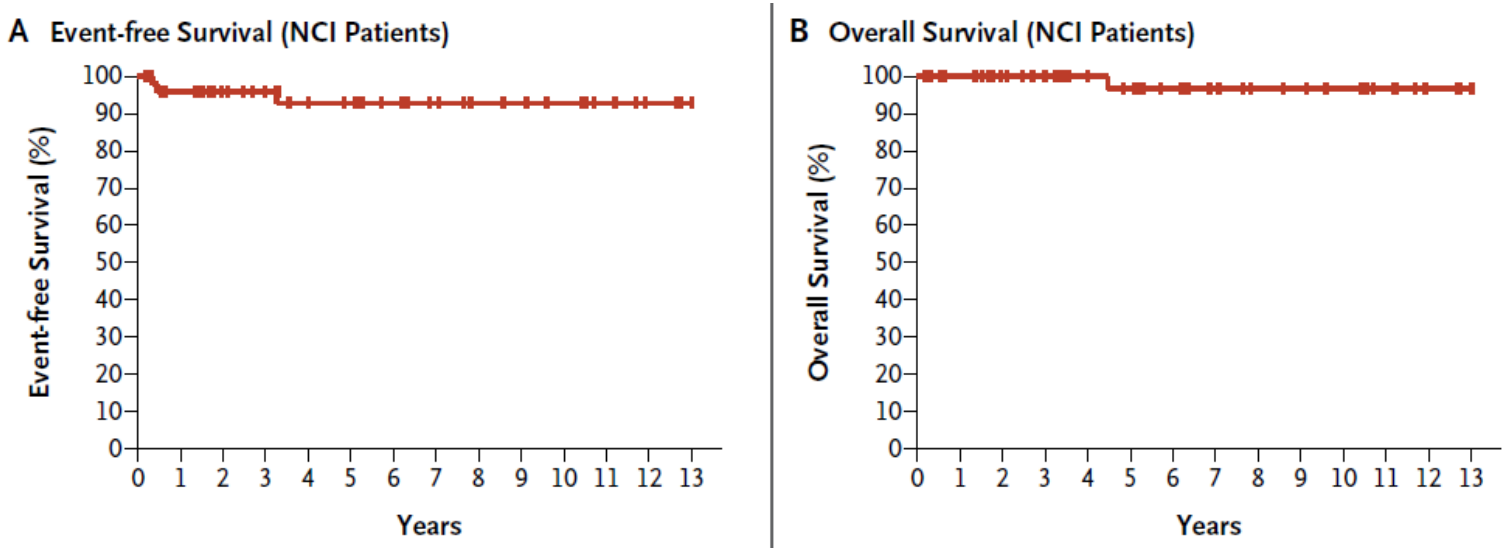
Primary Mediastinal B-Cell Lymphoma

- Thymic B-cell origin
- Biology overlaps cHL
- Younger / female
  - bulky disease, EN relapses
- CD30 generally +, FISH 9p24 common



DA-EPOCH-R outcomes (single arm trial)

Treatments

- RCHOP x 6, historically + ISRT
- DA-EPOCH-R, without planned RT

- ?Need RT if PET negative-- **New trial data: IELSG-37**

Dunleavy, NEJM 2013

Primary Mediastinal Lymphoma: IELSG 37

Design: Induction chemo then PET
- PET neg: randomized RT 30 Gy vs none

Primary endpoint PFS

Interim analysis: median follow-up of 58.8 months

PET negative then…	PFS (%)	OS (%)
Observation (n=132)	96.2	99.2
XRT 30 Gy (N=136)	98.5	99.3
	P=.27	P=.60

Conclusion: XRT may be safely omitted if CR after chemotherapy (DV 1-3)

Martelli EHA June 2023, Zucca ASCO 2023

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High-Grade B-Cell Lymphoma

Double Hit: MYC + BCL2 rearrangements

- Large, intermediate, or blastoid cells
- GCB gene expression profile, overlaps with Burkitt
- **Unique** from single MYC-r; MYC gains; MYC/BCL6-r, double protein expression
  - mostly will fall under DLBCL

Aggressive clinical presentation

- Higher risk of EN and CNS involvement

Notable, related subtype: HGBCL-NOS

- Morphologic definition, poor reproducibility

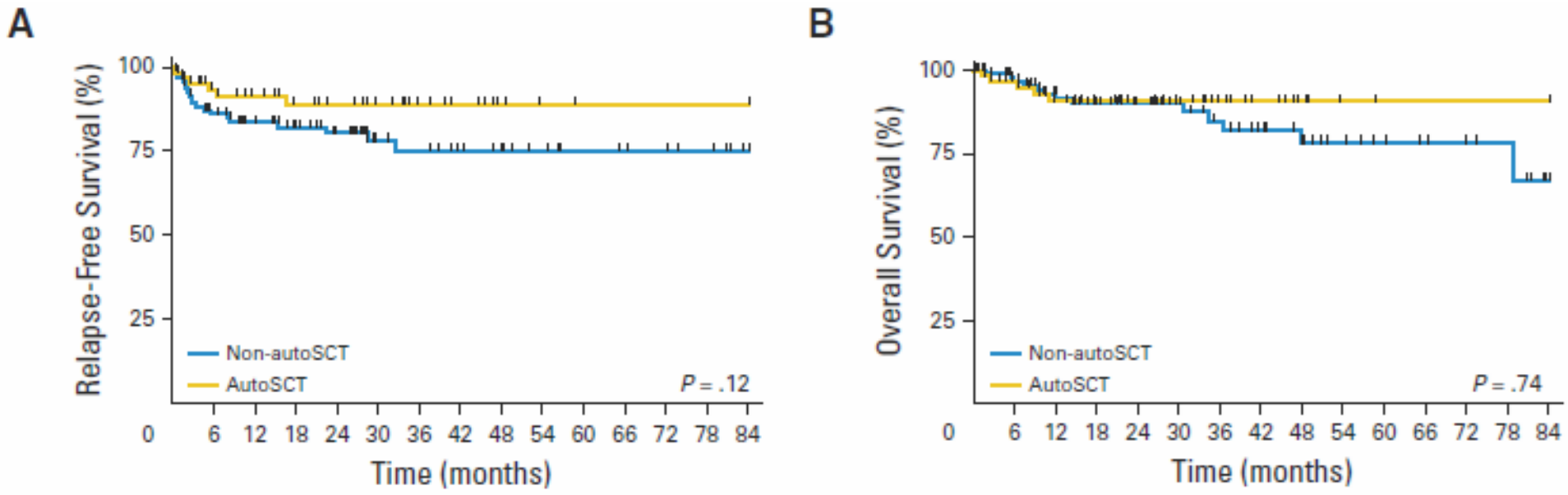
High-Grade B-Cell Lymphoma

- **Optimal 1st line Tx still undefined**
  - Consider intensive regimens, such as DA-EPOCH-R
    - especially for high IPI
  - No randomized data showing benefit to intensive Tx
    - retrospective data variable[1]
  - Pola-RCHP??
    - Small subset (N=45), no obvious signal of PFS benefit in subset analysis
  - Consider adding ISRT for localized disease, bulky PR

*Magnusson EHA 2021 (*Abstract #S224): similar 4 yr OS w/ RCHOP and DA-EPOCH based on Flatiron database (50-55%)

HGBCL in CR1: Role of Auto SCT?

- 159 patients with HGBCL (“double hit”) who achieved CR
- Nonrandomized comparison: ASCT vs observation
- Median f/u = 26.5 months (range, 0.2-114.6)



Landsburg JCO 2017

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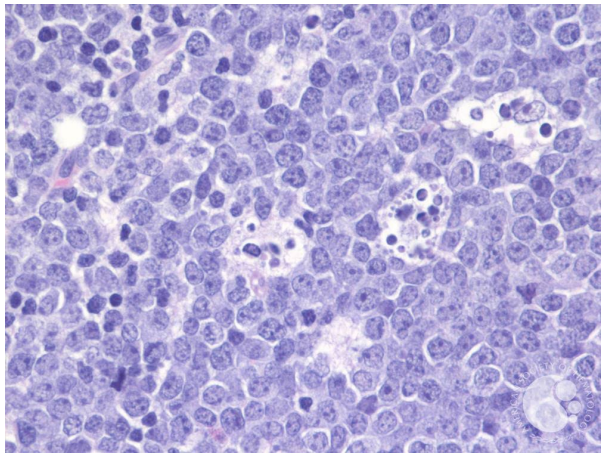
Burkitt Lymphoma

Subtypes

- Endemic (African)
- Sporadic (non-endemic)
- Immunodeficiency-associated

Presentation (Sporadic)

- Rapidly growing /bulky mass, high IDH
- Distal ileum, cecum, other GI sites; EN sites
- Very high Ki67
- FISH: MYC rearrangment



Starry sky pattern

Van Gogh- The Starry Night 1889
ASH image bank: Carll/Venkataraman

Burkitt Lymphoma

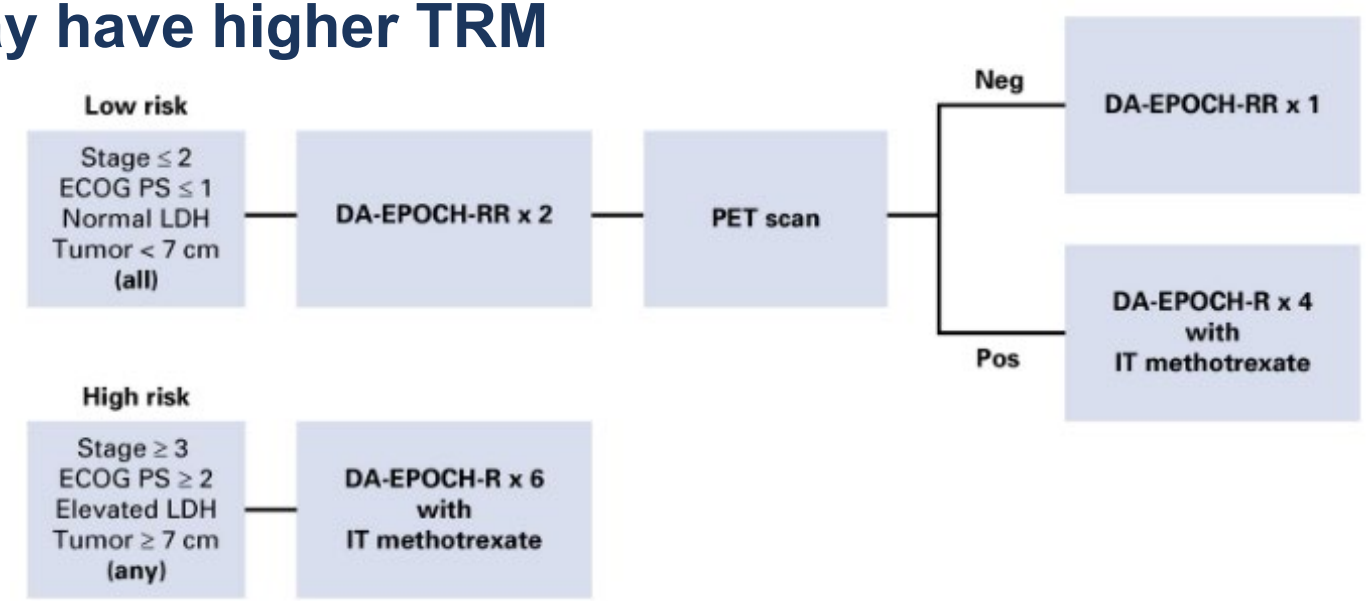
Treatment Standards

- Rituximab +

  Magrath (CODOX-M/IVAC); HyperCVAD+ Mtx/ara-C; da- EPOCH; risk adapted da- EPOCH

  - Similar 2y PFS between CODOX-M/IVAC 2 cycles and da- EPOCH 6 cycles
  - No randomized data for other comparisons

  HyperCVAD+R may have higher TRM



Evens Blood 2021, Chamuleau Lancet Haematol 2023, Roschewski JCO 2020

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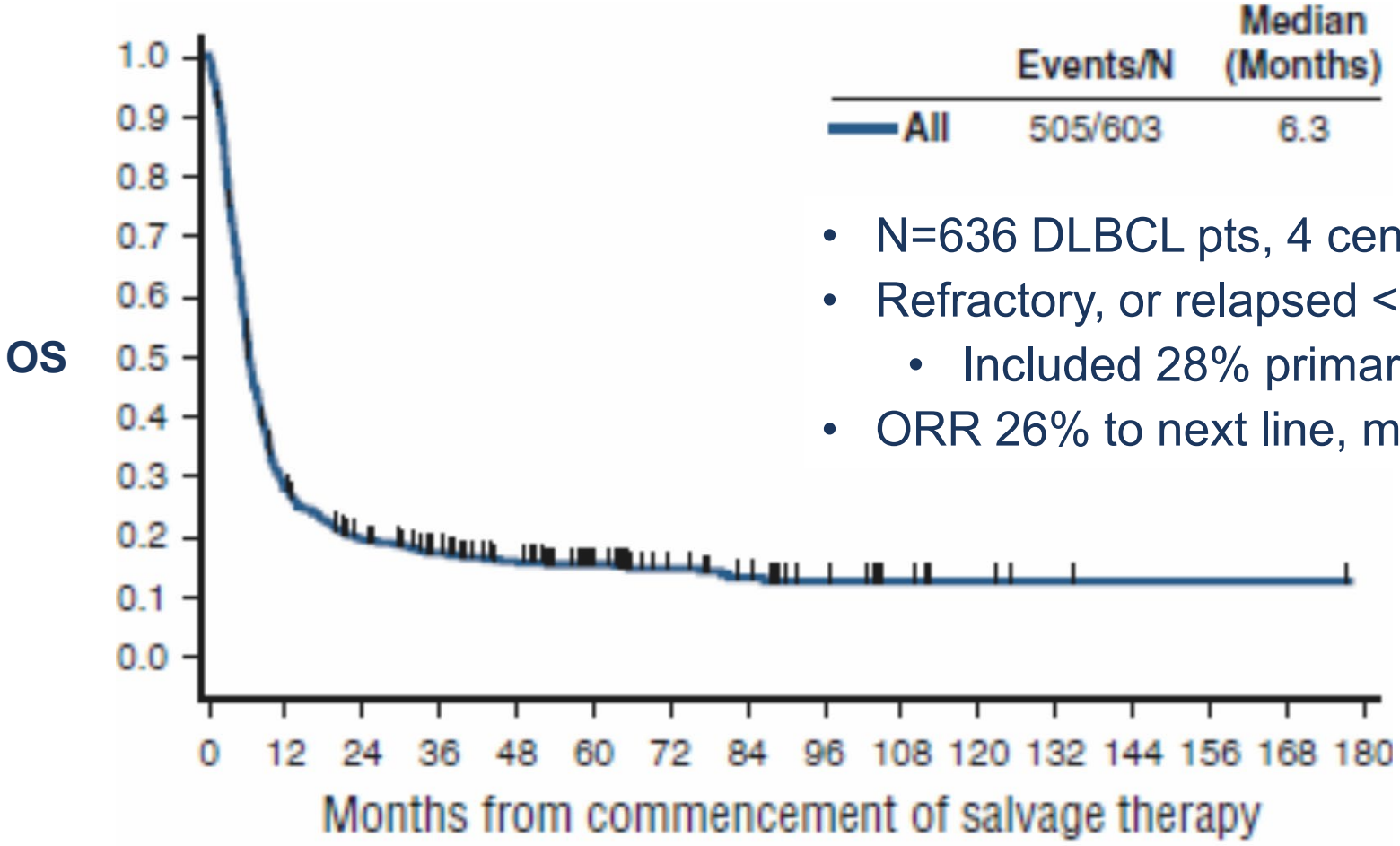
Relapsed/Refractory DLBCL

- **Major recent advances**
  - Cellular immunotherapy- CAR T-cells
  - Bispecific Ab's
  - Novel agents
- **Unmet needs**
  - Post CAR T-relapse (or ineligible); sequencing Tx around CAR T-cells
  - CNS disease: Prophylaxis and tx
  - Managing R/R subtypes (PMBCL, HGBCL/DLBCL with MYC/BCL2, Richter)

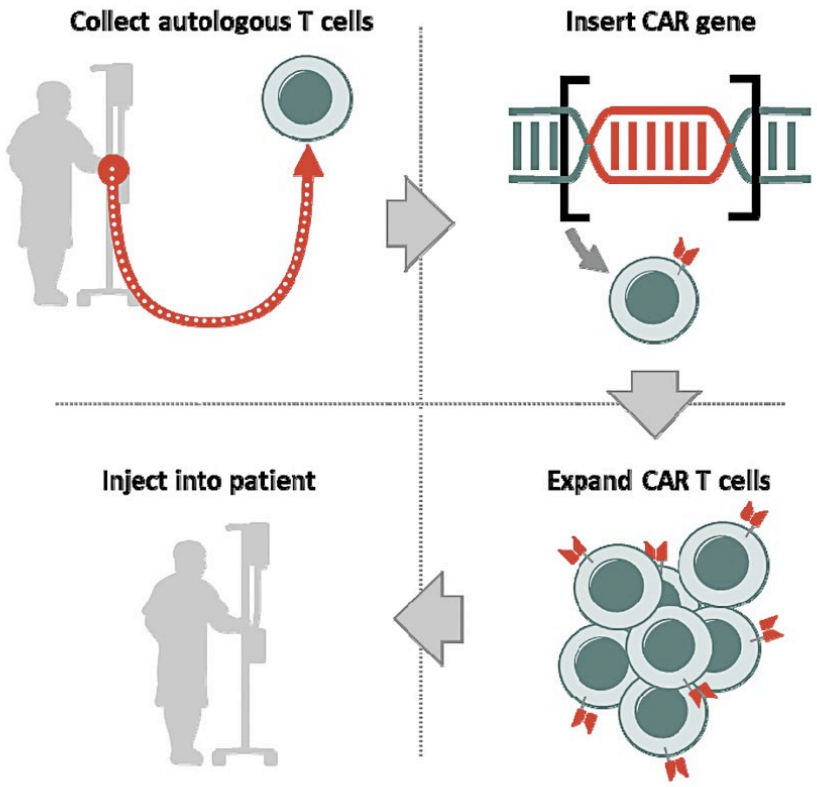
Chemorefractory DLBCL: “Scholar-1” observational study

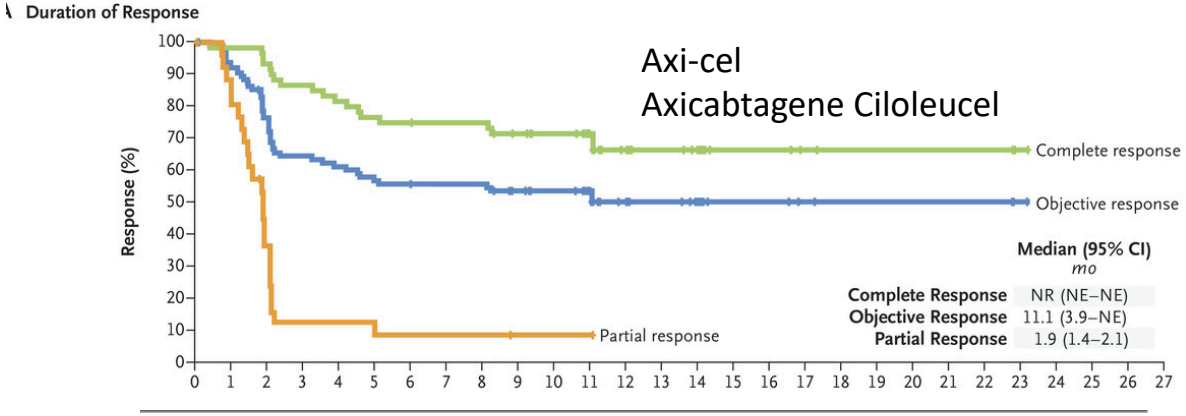


- N=636 DLBCL pts, 4 centers
- Refractory, or relapsed <12 mo from ASCT
  - Included 28% primary refractory
- ORR 26% to next line, median OS 6.3 mo

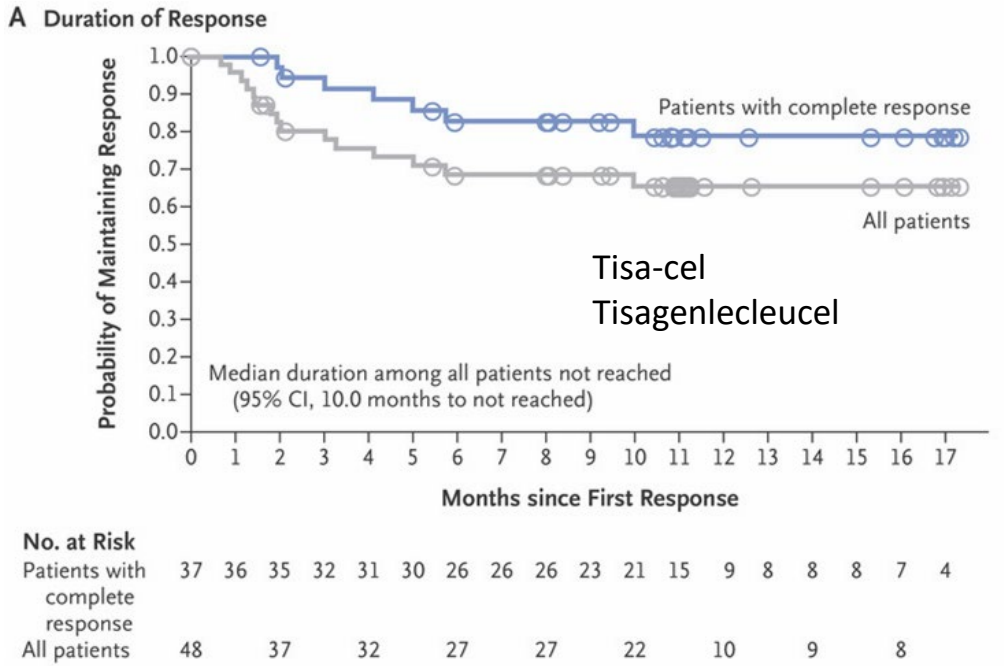
Crump Blood 2017

CD19 CAR T-cells: Durable CR's in pivotal trials





Axi-cel
Axicabtagene Ciloleucel



Tisa-cel
Tisagenlecleucel

Subklewe Trans Med Hemotherapy 2019, Axi-cel: Neelapu SS et al. N Engl J Med 2017;377:2531-2544. Tisa-cel: SJ Schuster et al. N Engl J Med 2019;380:45-56.

CD19 CAR T-cells: Overview of Toxicities

Cytokine release syndrome

- Inflammatory cytokines, immune activation
- 2-3 days post infusion
- Common, mostly mild/moderate in severity

"ICANS"- Immune effector cell-associated neurotoxicity syndrome

- Endothelial activation/BBB disruption
- 3-10 days post infusion
- Uncommon, severe in 10-30% (more w/CD28 costim domain)

Cytopenias, hypogammaglobulinemia

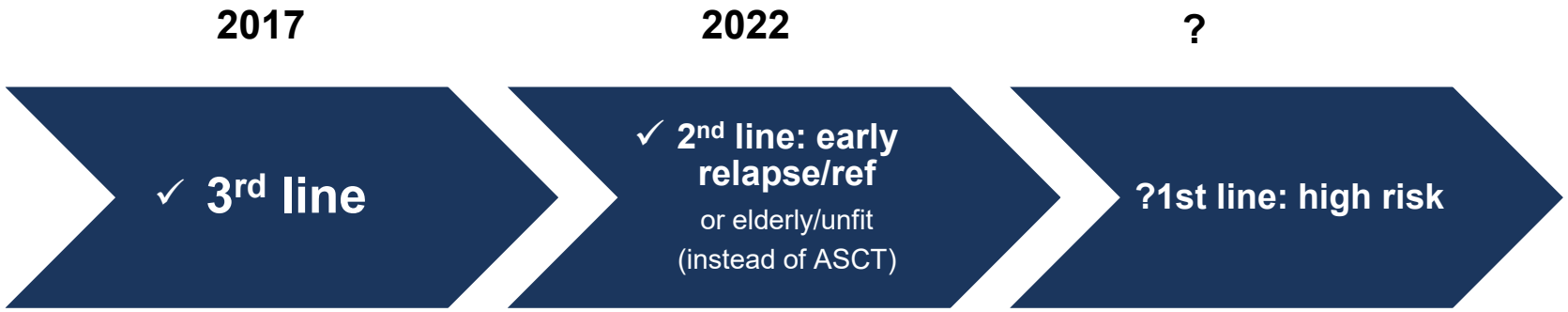
- 30-60% severe cytopenia post CAR T

Panaite/Shadman Leuk Lymp 2022, Sharma Cancers 2022

Patient Selection for CAR T

- **Histology-** primarily DLBCL, tFL, PMBCL, HGBCL
- **Target antigen expression (e.g., CD19+)?**
- **Comorbidities**
- **Plan bridging/disease control: The race against production time**
  - Avoid T-cell depletion, excess myelotox, and CD19 –directed therapies

CD19 CAR T-cells: Shifting to earlier lines in DBLCL



- **Zuma-1 (Axi-cel)**
- **Juliet (Tisa-cel)**
- **Transcend (Liso-cel)**

- **Zuma-7 (axi-cel)**
- **Transform (Liso-cel)**
- **PILOT (Liso-cel) for elderly/unfit**

- **Zuma-12 (axi-cel),** positive iPET phase 2
- **Zuma-23 (axi-cel),** CART vs. RCHOP/REPOCH, phase 3

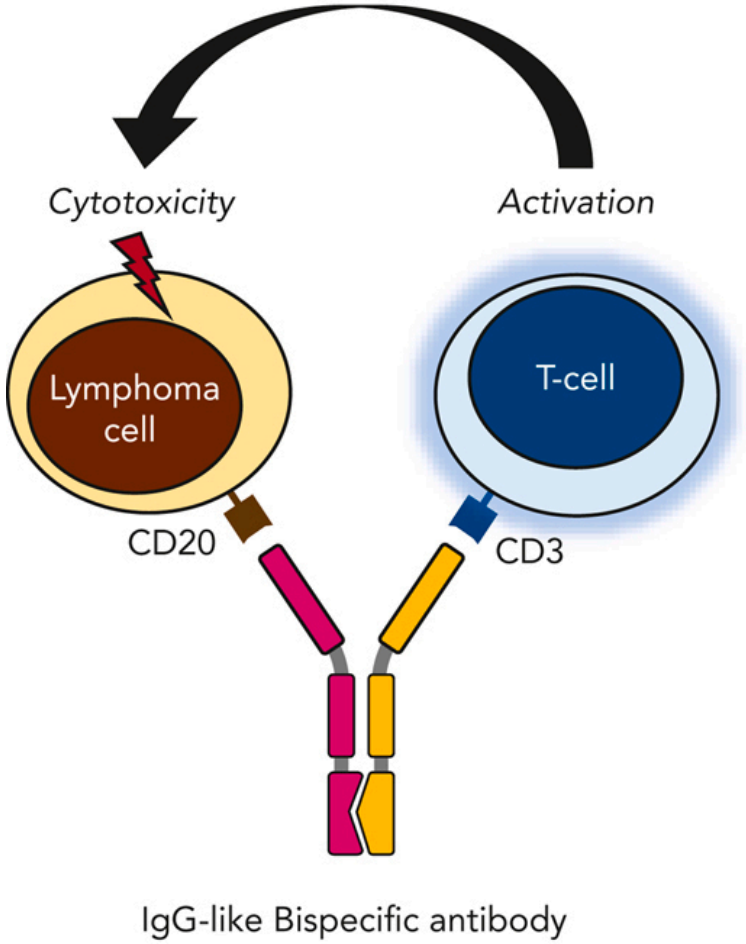
Liso-cel and Axi-cel: Approval, DLBCL Refractory/Relapsing 12 months from 1st line

	TRANSFORM	Zuma-7
Comparison	Liso-cel vs ASCT (N=92 each)	Axi-cel vs ASCT (N=180/179)
CR	66% vs 39% (p<.001)	65% vs 32% (p<.001)
EFS	10.1 vs 2.3 mo (p<.0001)	8.3 vs 2.0 mo (p<.001)
OS	NR vs 29.9 mo, p=.0987 79.1% vs 64.2% at 1 year	**NR vs 31.1 mo, p=.03** **54.6% vs 46% (4-year)**
Notes	• Bridging allowed (1 cycle, chemo) • Stable disease week 9 counted as an event • PFS not reached at 17.5 mo f/u	• No bridging (steroids only) • Stable disease week 21 (day 150) an event • 14.7 mo PFS in Axi-cel (3.7 mo PFS in ASCT)

TRANSFORM: Kamdar Lancet 2022, Abramson Blood 2023

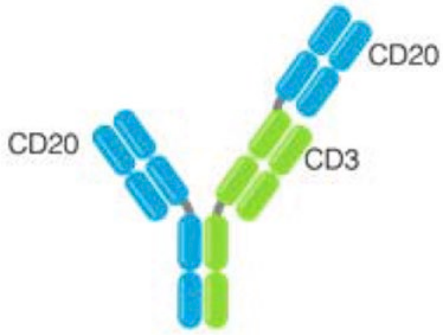
ZUMA-7: Locke NEJM 42022, Westin NEJM 2023

Bispecific Antibodies: New options in 2024

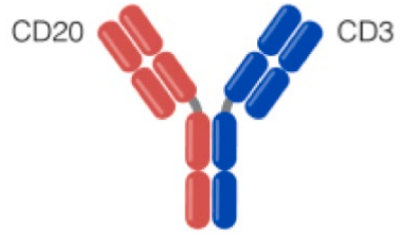


IgG-like Bispecific antibody

Glofitamab: CD20 x CD3, 2:1 tumor- to T-cell binding



Epcoritamab: CD20 x CD3



Odronextamab: CD20 x CD3

Falchi Blood 2023

3rd line Bispecifics in Aggressive BCL : Use and CRS prophylaxis

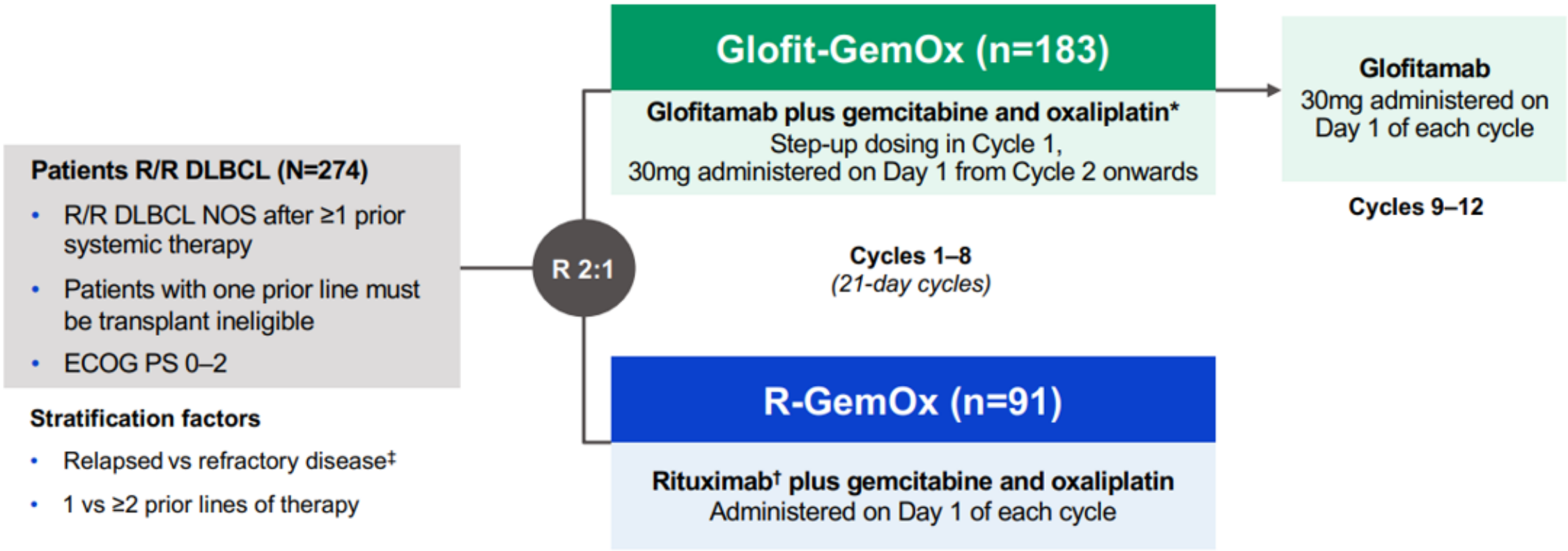
	Epcoritamab	Glofitamab
FDA Approval	DLBCL-NOS, including those arising from indolent lymphoma, HGBCL	DLBCL-NOS, tFL
Population (Required prior therapy)	**2 prior Tx**, including anti-CD20 and prior failure or ineligibility for autoSCT	**2 prior Tx**, including anti-CD20 and prior anthracycline
Route	SC	IV
Duration	**Indefinite therapy**, weekly /twice-monthly/ 28-day cycles	**Fixed duration,** 12 cycles; weekly then 21-day cycles
CRS mitigation	• Step-up dosing • Prednisolone given daily x 4 for each dose with cycle • 24 hr inpatient monitoring for first full dose	• Step-up dosing • Obinutuzumab pre-therapy • IV methylpred for cycles 1 and 2 • Hospitalized for 1st dose, outpatient for subsequent unless ≥ G2 CRS

3rd line Bispecifics in Aggressive BCL: Efficacy and Toxicity Summary

	Epcoritamab	Glofitamab
ORR/CR, %	**63/39**	**52/39**
PFS, mo	4.4	4.9
DOR, mo	**12**	**18.4**
OS, mo	Not reached at median f/u 10.7 mo	11.5
Cytokine release syndrome All grade/ Gr 3+, %	49.7/**2.5**	63/**4**

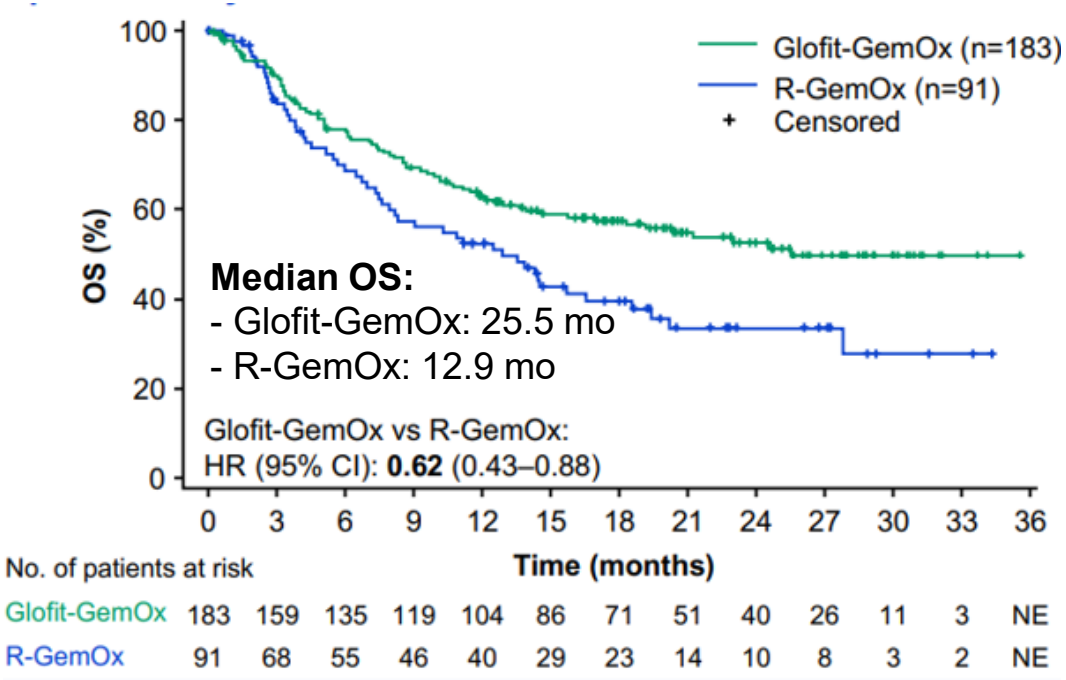
Glofitamab: Dickinson NEJM 2022
Epcoritamab: Thieblemont JCO 2023

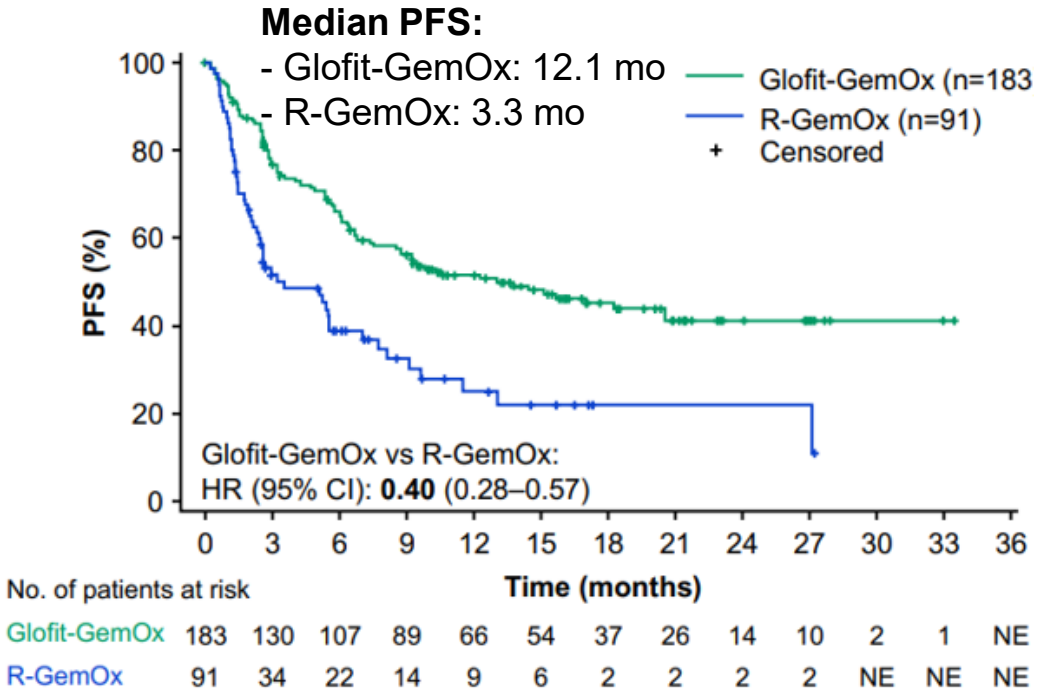
≥2nd line Bispecifics+chemo in Aggressive BCL: STARGLO trial (on-going)



*Gemcitabine 1000mg/m² and oxaliplatin 100mg/m². In C1, Gpt administered on D1, GemOx on D2, followed by glofit 2.5mg on D8 and glofit 10mg on D15; in C2–8, glofit 30mg and GemOx are administered on D1. †Rituximab 375mg/m². ‡Relapsed disease: recurrence following a response that lasted ≥6 months after completion of the last line of therapy; refractory disease: disease that did not respond to, or that progressed <6 months after, completion of the last line of therapy. ASCT, autologous stem cell transplant; C, cycle; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; Gpt, obinutuzumab pre-treatment; NOS, not otherwise specified; R 2:1, patients randomized in a 2:1 ratio.

≥2nd line Bispecifics+chemo in Aggressive BCL: STARGLO trial (on-going)





Response rate:
- Glofit-GemOx: ORR 68.3%, CR rate 58.5%
- R-GemOx: ORR 40.7%, CR rate 25.3%

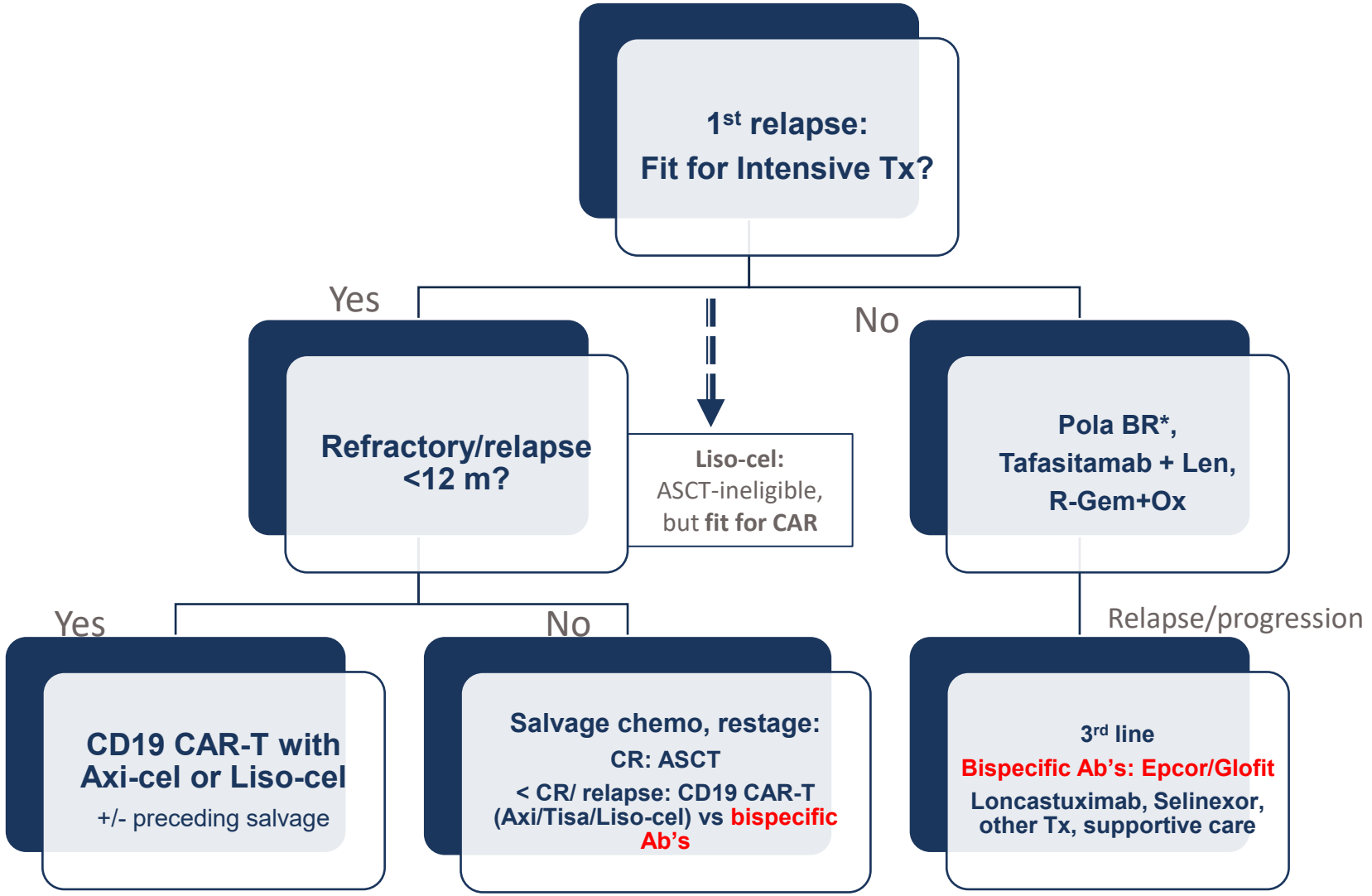
Adverse events:
- Glofit-GemOx: serious 54%, G3-5 78%, G5 8%
- R-GemOx: serious 17%, G3-5 41%, G5 5%

Glofit-GemOx:
- Better efficacy with OS benefit despite increased AEs (observed AEs c/w known risks of the study drug)
- Data support the use for the treatment of R/R DLBCL (not approved yet)

“Recent history”: Aggressive B-Cell Lymphoma Approvals

Regimen	Mechanism	Study population/ efficacy	Notes
Polatuzumab + BR Sehn JCO 2020	Chemo + CD79 ADC: MMAE payload	**Most pt refractory to prior Tx** Pola BR: 40% CR and mPFS 9.5 m PFS (3.7 w/ BR)	Infectious toxicity: 23% severe infections, 33% d/c for AE - Bridging (without benda) - Role if polaRCHP 1st line?
Selinexor Kalakonda Lancet Haem 2020	Small molecule, targeting nuclear export	Excluded *recent* refractory pts, 28% ORR, CR12%; mPFS <3 mo;	- Modest efficacy, restricted population; oral tx - nausea - 2 prior lines
Tafasitamab + Lenalidomide Salles Lancet Onc 2020	CD19 MoAb + immunomodulator	N-80; 50% 1 prior line - excluded primary refractory - 40% CR rate, mPFS 11.6 mo	- IO/non-chemo option. - Complex dosing - *R/R DLBCL + transplant-ineligible* - 1 prior line approval
Loncastuximab Tesirine 4/23/21 FDA approval, LOTIS-2	CD19 ADC: PBD payload	**N-145. 2 prior lines required + mostly refractory.** ORR 48%, CR 24%; PFS 4.9 mo	- Cytopenias, GGT elevation, volume overload - 2 prior lines

Current Treatment of R/R Aggressive B-NHL



*off-label; FDA label is after at least 2 prior tx

Fred Hutch
Cancer Center

Thank you

mydi@fredhutch.org

@DiMengyang