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

- Institutional research funding: Schrodinger, BeOne, Regeneron, Eli Lilly, AbbVie, Dren Bio

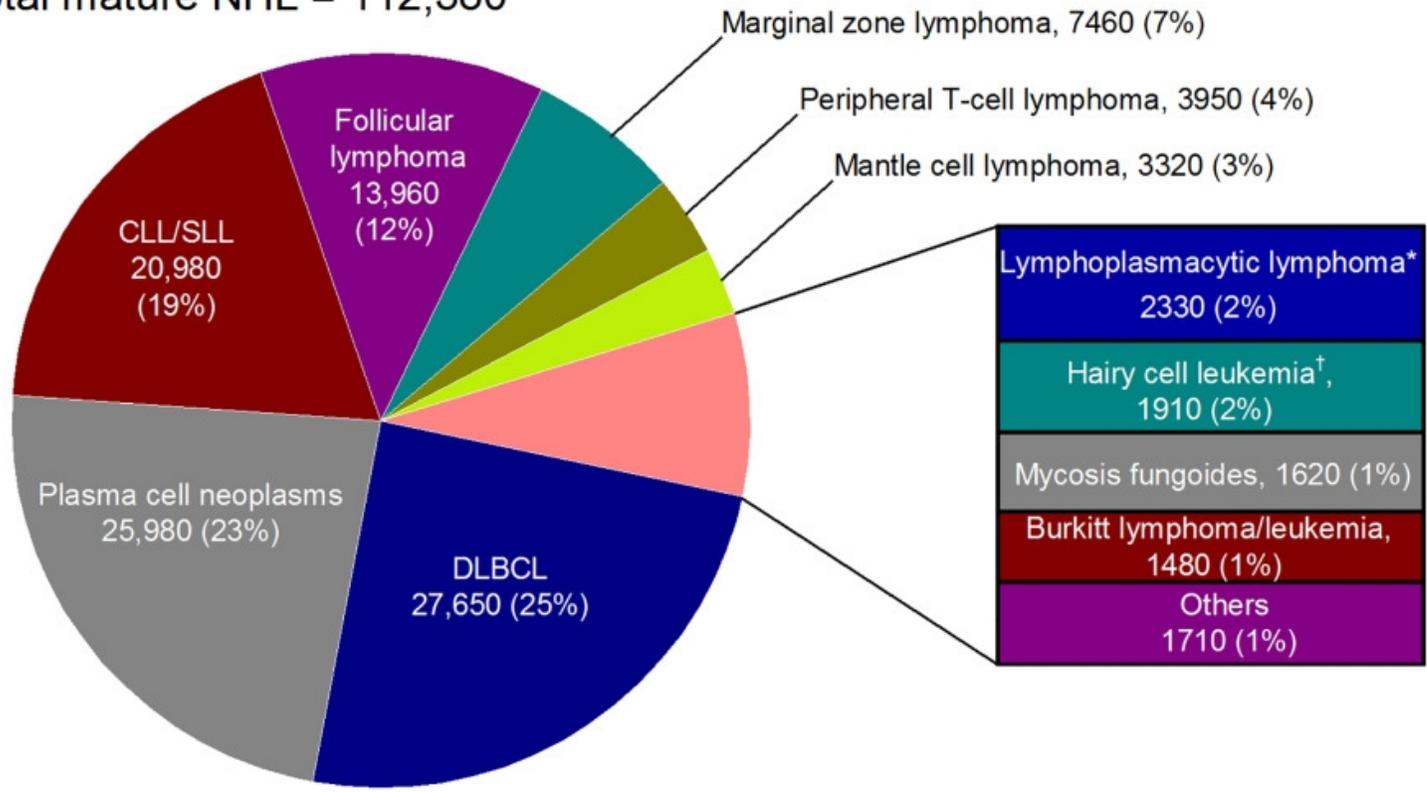- Honorarium/Consultancy: Genetech, BeOne, AbbVie, Incyte, Merck

Topics

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

Topics

- **Diffuse Large B-Cell Lymphoma (DLBCL)**
  - **Primary Mediastinal Large B-Cell Lymphoma (PMBCL)**
- Double hit (MYC/BCL2)
- Burkitt Lymphoma
- Relapsed /refractory Aggressive B-Cell Lymphomas
- Mantle Cell Lymphoma
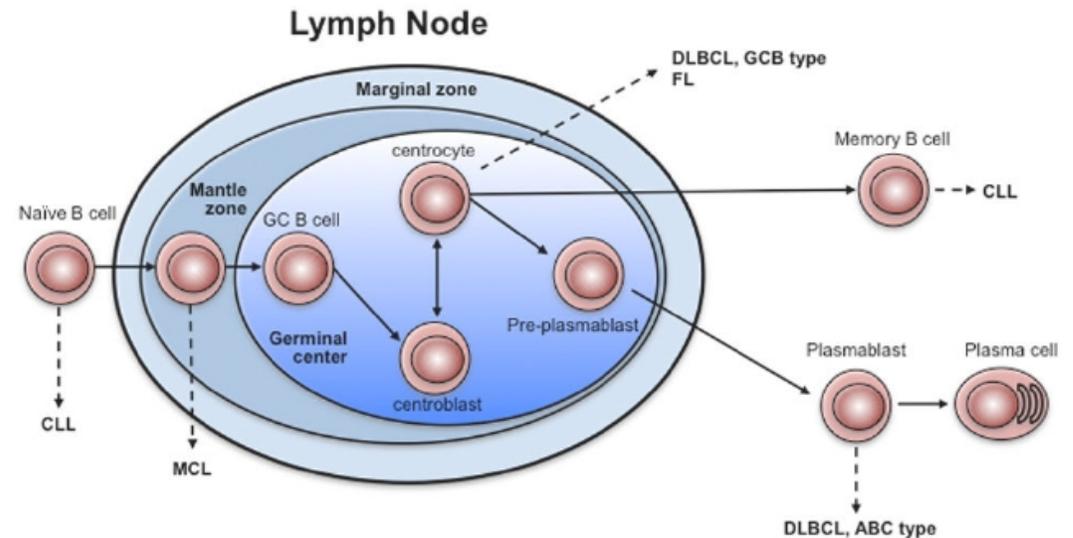
US Lymphoid Malignancy Incidence

Total mature NHL = 112,380

Follicular lymphoma 13,960 (12%)

CLL/SLL 20,980 (19%)

Plasma cell neoplasms 25,980 (23%)

DLBCL 27,650 (25%)

Marginal zone lymphoma, 7460 (7%)

Peripheral T-cell lymphoma, 3950 (4%)

Mantle cell lymphoma, 3320 (3%)

Lymphoplasmacytic lymphoma* 2330 (2%)

Hairy cell leukemia[†], 1910 (2%)

Mycosis fungoides, 1620 (1%)

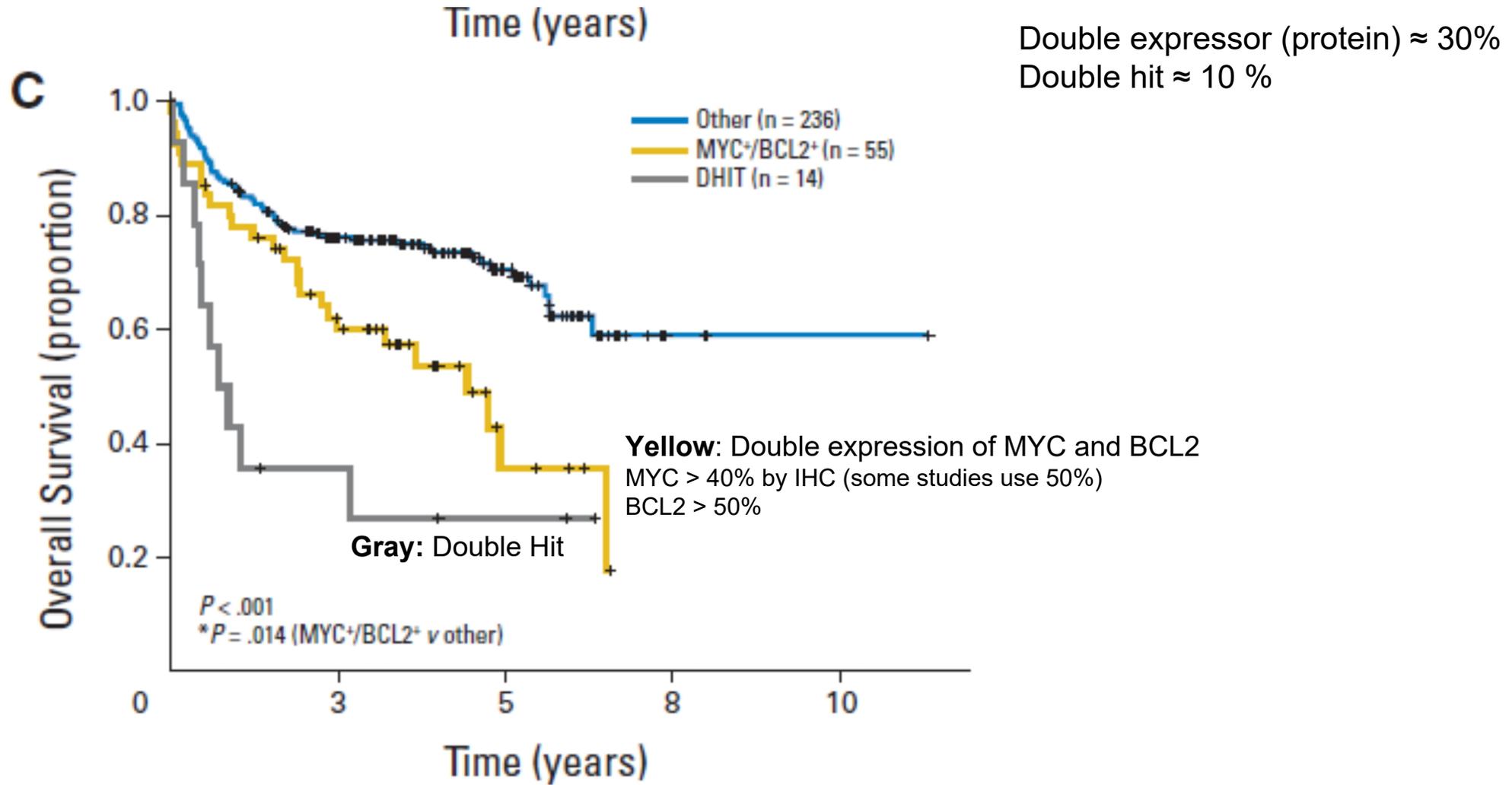Burkitt lymphoma/leukemia, 1480 (1%)

Others 1710 (1%)

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

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

Lymph Node

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
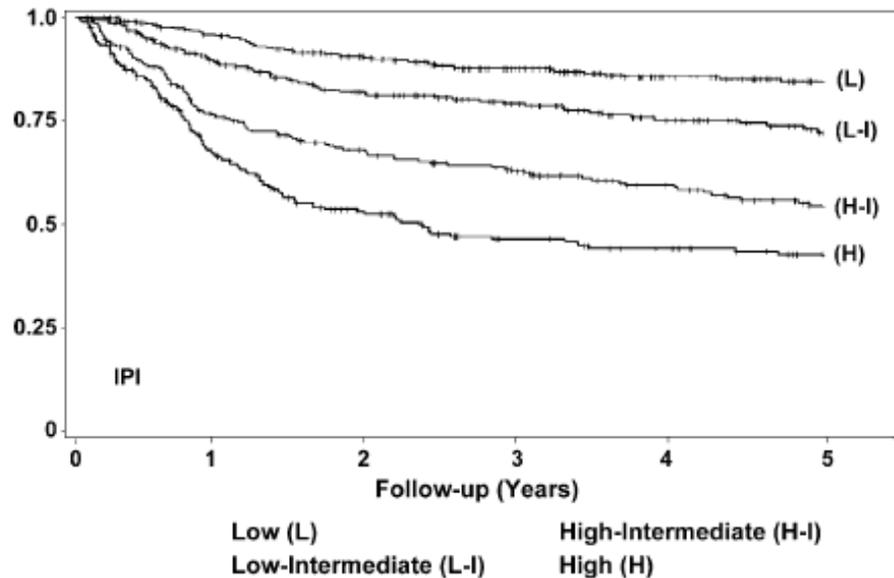   - Uncertain PET result

IPI and CNS-IPI: Prognosis and CNS risk
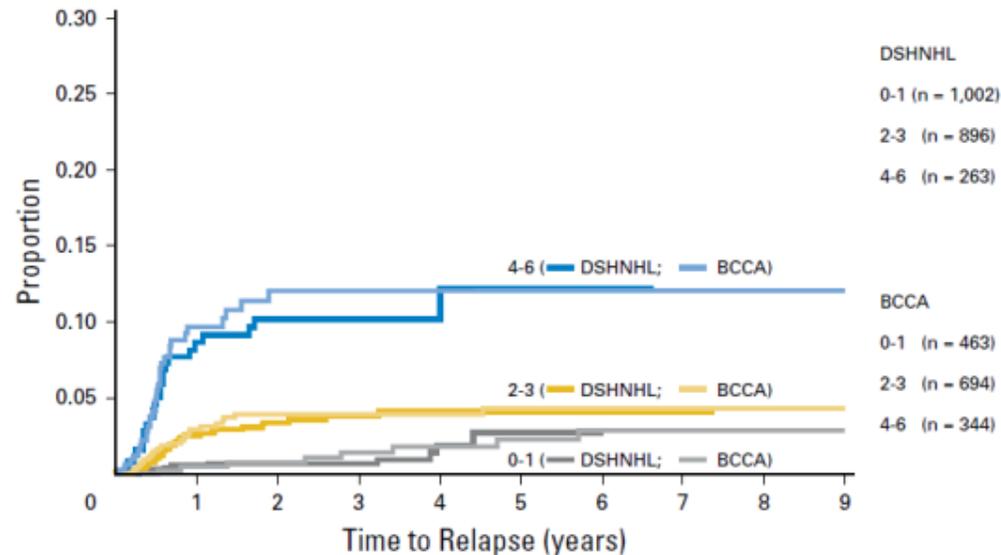
Standard IPI
- Age >60
- Stage III/IV
- LDH >ULN
- EN sites >1
- ECOG >1

+ renal or adrenal involvement→ CNS IPI

IPI 3-5 "High risk"

Low (L)   High-Intermediate (H-I)
Low-Intermediate (L-I)   High (H)

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

DSHNHL
0-1 (n = 1,002)
2-3 (n = 896)
4-6 (n = 263)

BCCA
0-1 (n = 463)
2-3 (n = 694)
4-6 (n = 344)

CNS risk with
- *DHL*
- *Testicular DLBCL*
- *Breast DLBCL*

Zhou *Blood* 2014. Schmitz JCO 2016.
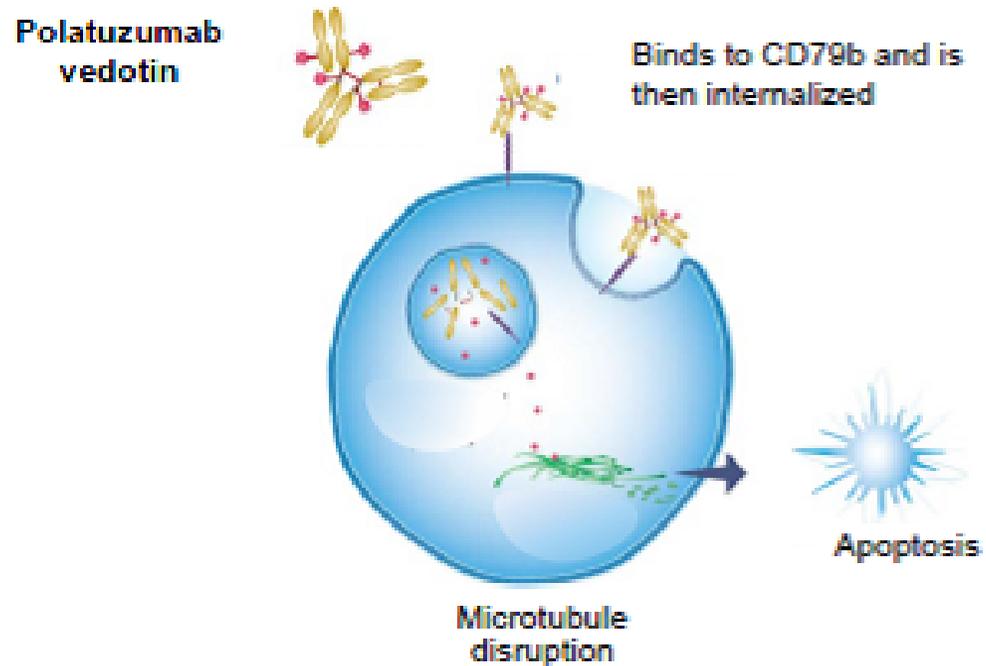
Diffuse large B cell lymphoma

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

Many negative randomized trials vs RCHOP…

DA-EPOCH+R vs RCHOP
Bartlett JCO 2019

	Events/Total	HR (95% CI)	Time Point (years)	KM Est (95% CI)
DA-EPOCH-R	76/241	0.93 (0.68 to 1.27)	2	78.9 (73.8% to 84.2%)
			5	68.0 (62.1% to 74.5%)
R-CHOP	83/250	Reference	2	75.5 (70.2% to 81.1%)
			5	66.0 (60.2% to 72.5%)

Log-rank P = .6519   + Censor

No. at risk:

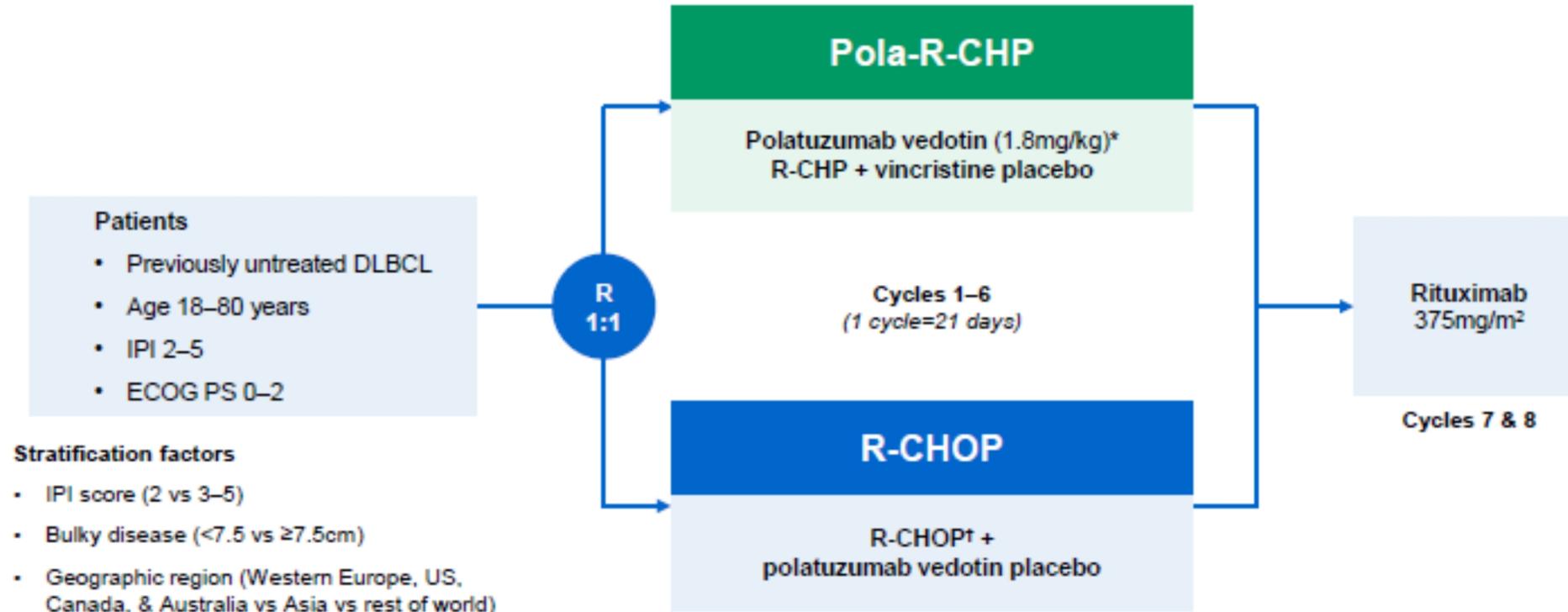|						
DA-EPOCH-R	241	193	181	168	146	88
R-CHOP	250	196	179	165	137	90
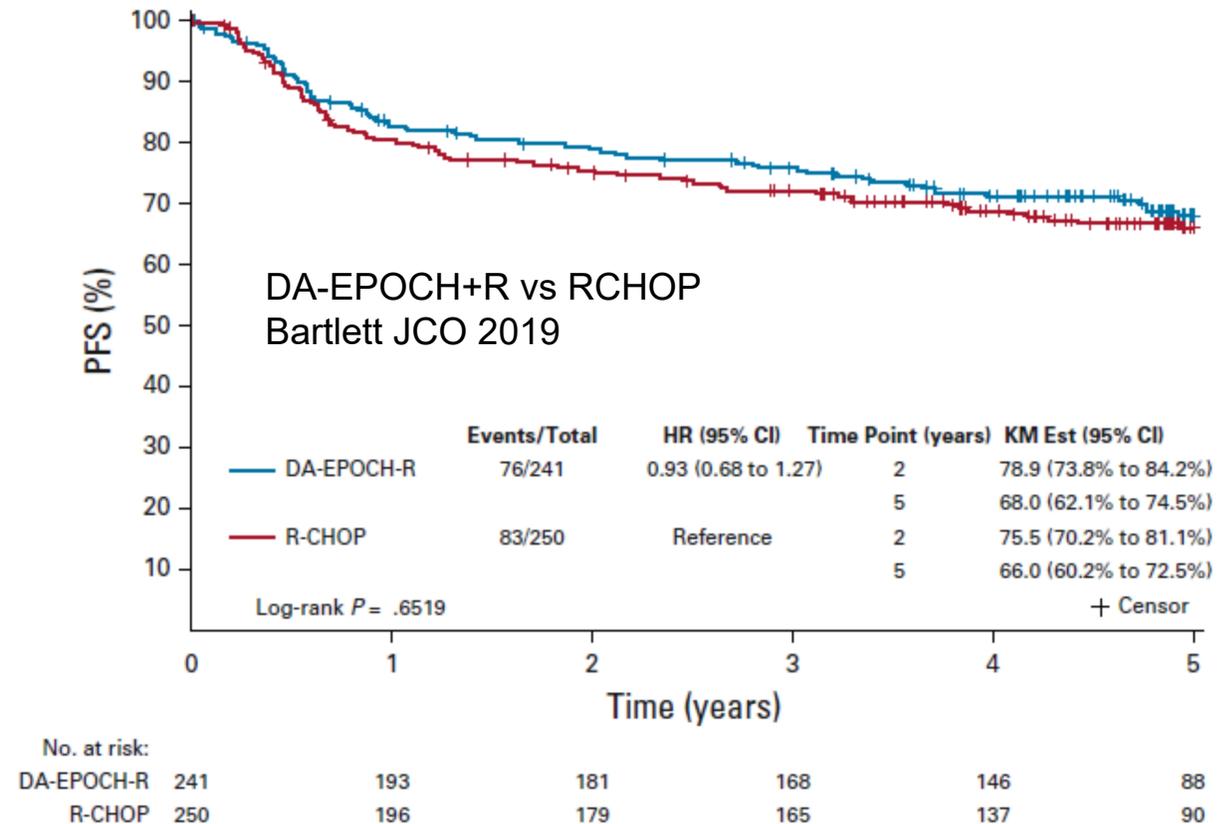
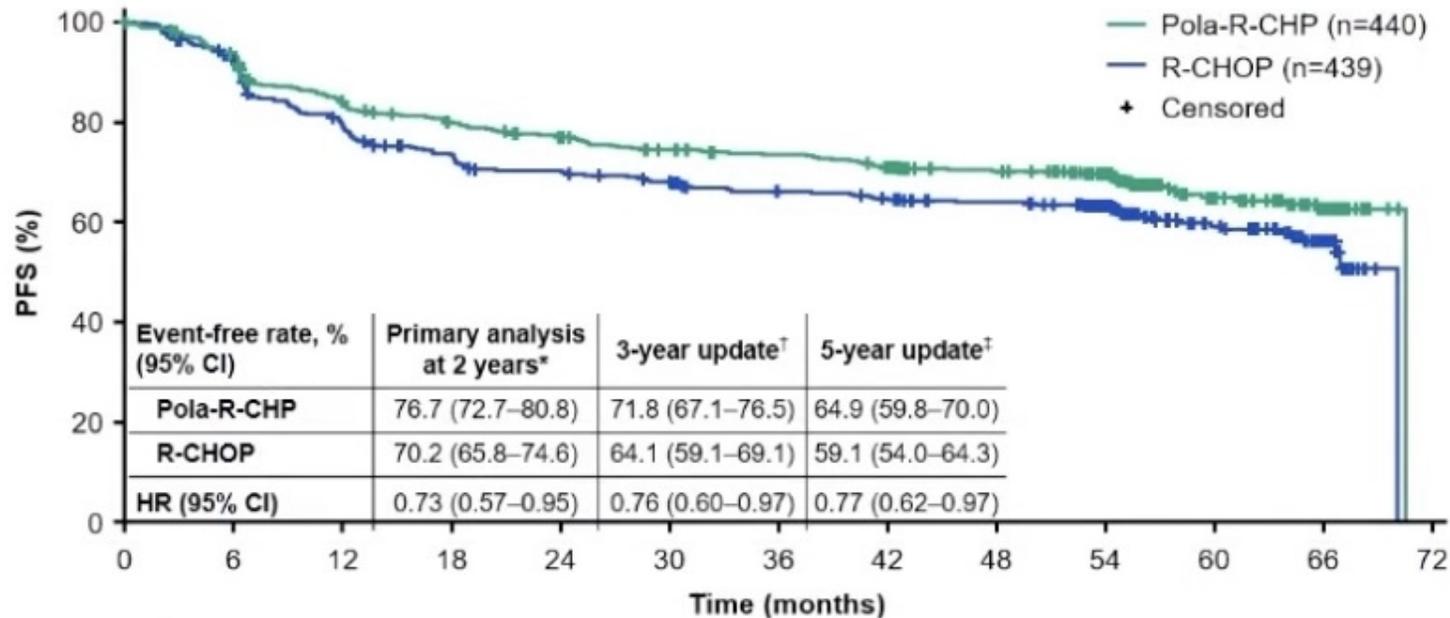# Polatuzumab Vedotin: Basis for POLARIX trial in 1st line DLBCL

- **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

Patients
- Previously untreated DLBCL
- Age 18–80 years
- IPI 2–5
- ECOG PS 0–2

Stratification factors
- IPI score (2 vs 3–5)
- Bulky disease (<7.5 vs ≥7.5cm)
- Geographic region (Western Europe, US, Canada, & Australia vs Asia vs rest of world)

R 1:1

Pola-R-CHP
Polatuzumab vedotin (1.8mg/kg)*
R-CHP + vincristine placebo

Cycles 1–6
(1 cycle=21 days)

R-CHOP
R-CHOP† +
polatuzumab vedotin placebo

Rituximab
375mg/m²

Cycles 7 & 8

Polarix: Progression-Free Survival

Event-free rate, % (95% CI)	Primary analysis at 2 years*	3-year update[†]	5-year update[‡]
Pola-R-CHP	76.7 (72.7–80.8)	71.8 (67.1–76.5)	64.9 (59.8–70.0)
R-CHOP	70.2 (65.8–74.6)	64.1 (59.1–69.1)	59.1 (54.0–64.3)
HR (95% CI)	0.73 (0.57–0.95)	0.76 (0.60–0.97)	0.77 (0.62–0.97)

Patients remaining at risk

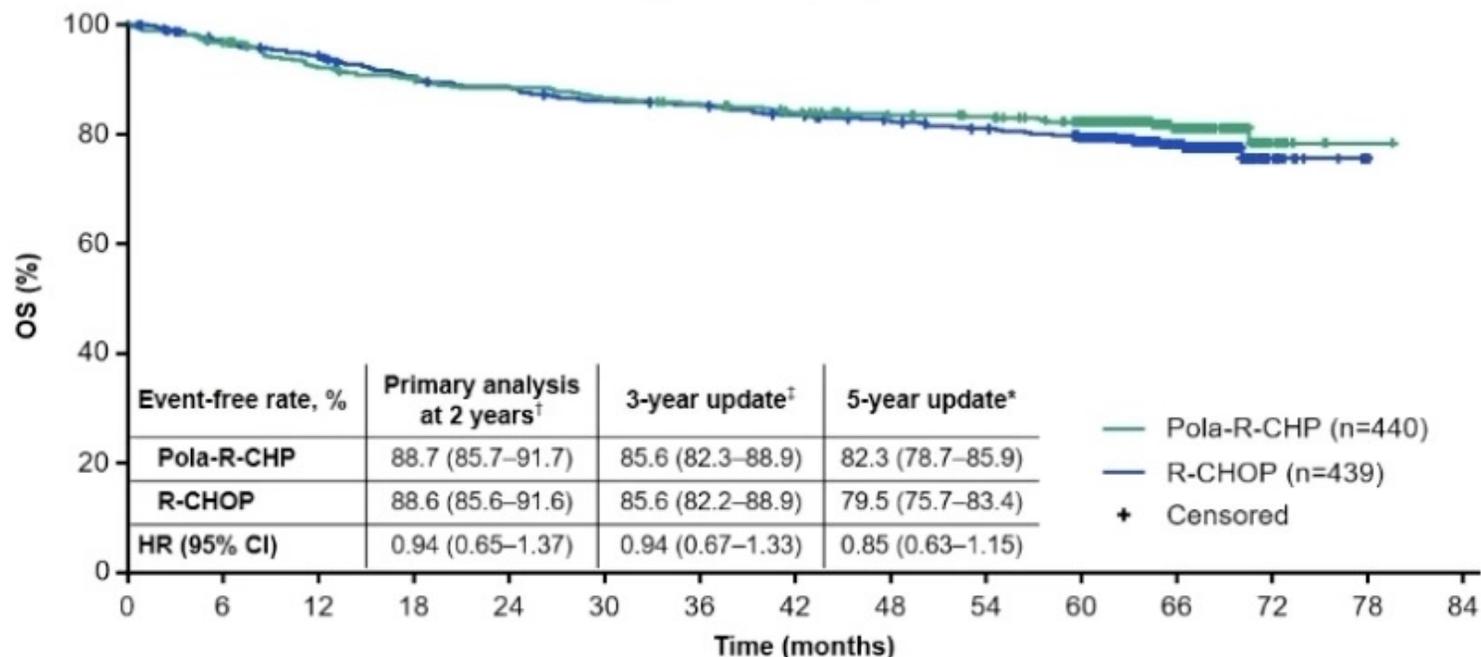|													
Pola-R-CHP	440	407	357	335	318	303	292	280	258	213	100	56	NE
R-CHOP	439	391	332	302	287	274	258	251	240	192	95	54	NE

At the 5-year follow up, Pola-R-CHP had a **sustained and significant PFS benefit**, confirming results from the primary analysis of PFS at 2 years of follow up (HR 0.73).[1]

*Data cut-off: June 28, 2021; [†]Data cut-off: June 15, 2022; [‡]Data cut-off: July 5, 2024.
CI, confidence interval; HR, hazard ratio; NE, not evaluable.

1. Tilly H, et al. N Eng J Med 2022;386:351–63.

Polarix: Overall Survival

OS in the global population*

Event-free rate, %	Primary analysis at 2 years[†]	3-year update[‡]	5-year update*
Pola-R-CHP	88.7 (85.7–91.7)	85.6 (82.3–88.9)	82.3 (78.7–85.9)
R-CHOP	88.6 (85.6–91.6)	85.6 (82.2–88.9)	79.5 (75.7–83.4)
HR (95% CI)	0.94 (0.65–1.37)	0.94 (0.67–1.33)	0.85 (0.63–1.15)

- Pola-R-CHP (n=440)
- R-CHOP (n=439)
- + Censored

Deaths, n[§]	Pola-R-CHP (n=440)	R-CHOP (n=439)
Primary analysis at 2 years[†]	53	57
5-year update*	79	91

Patients remaining at risk

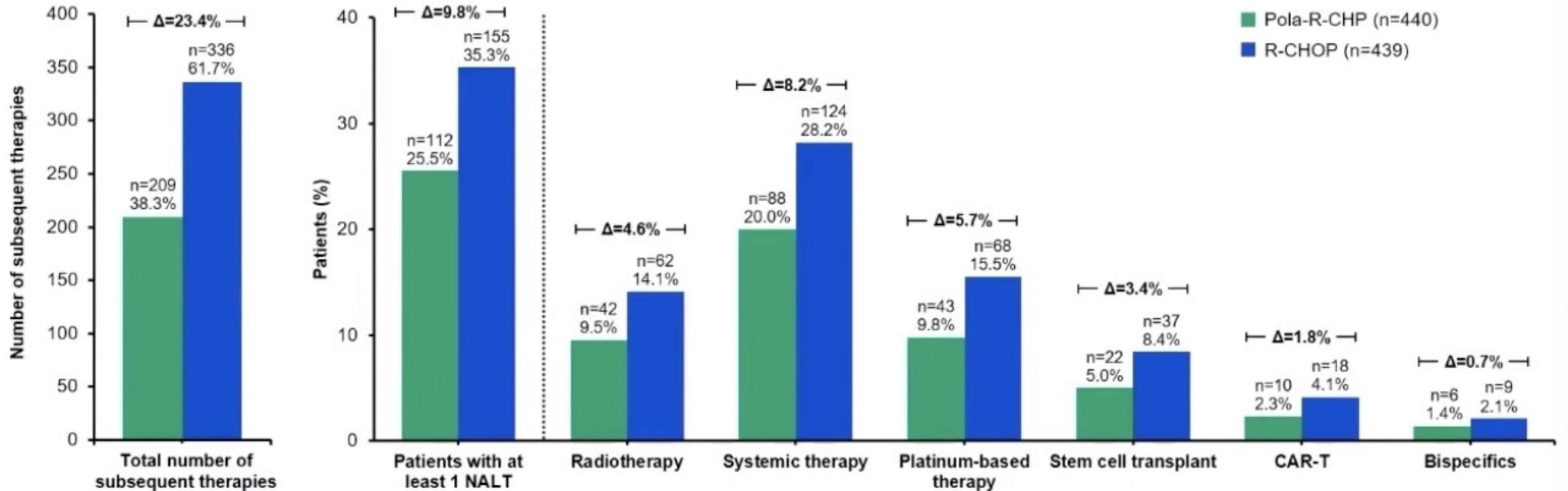|														
Pola-R-CHP	440	424	399	389	381	373	366	355	343	338	319	124	12	1	NE
R-CHOP	439	415	403	382	372	361	357	347	338	329	311	128	13	1	NE

After 5 years of follow-up, numerically fewer deaths were observed in the Pola-R-CHP versus R-CHOP arm, with an associated HR of 0.85 (0.63–1.15).

*Data cut-off: July 5, 2024; [†]Data cut-off: June 28, 2021; [‡]Data cut-off: June 15, 2022; [§]In addition to the known deaths, there were two patients (one in the Pola-R-CHP arm and one in the R-CHOP arm) who died due to an unknown cause and an unknown death date and were not counted as death events in the OS analysis.
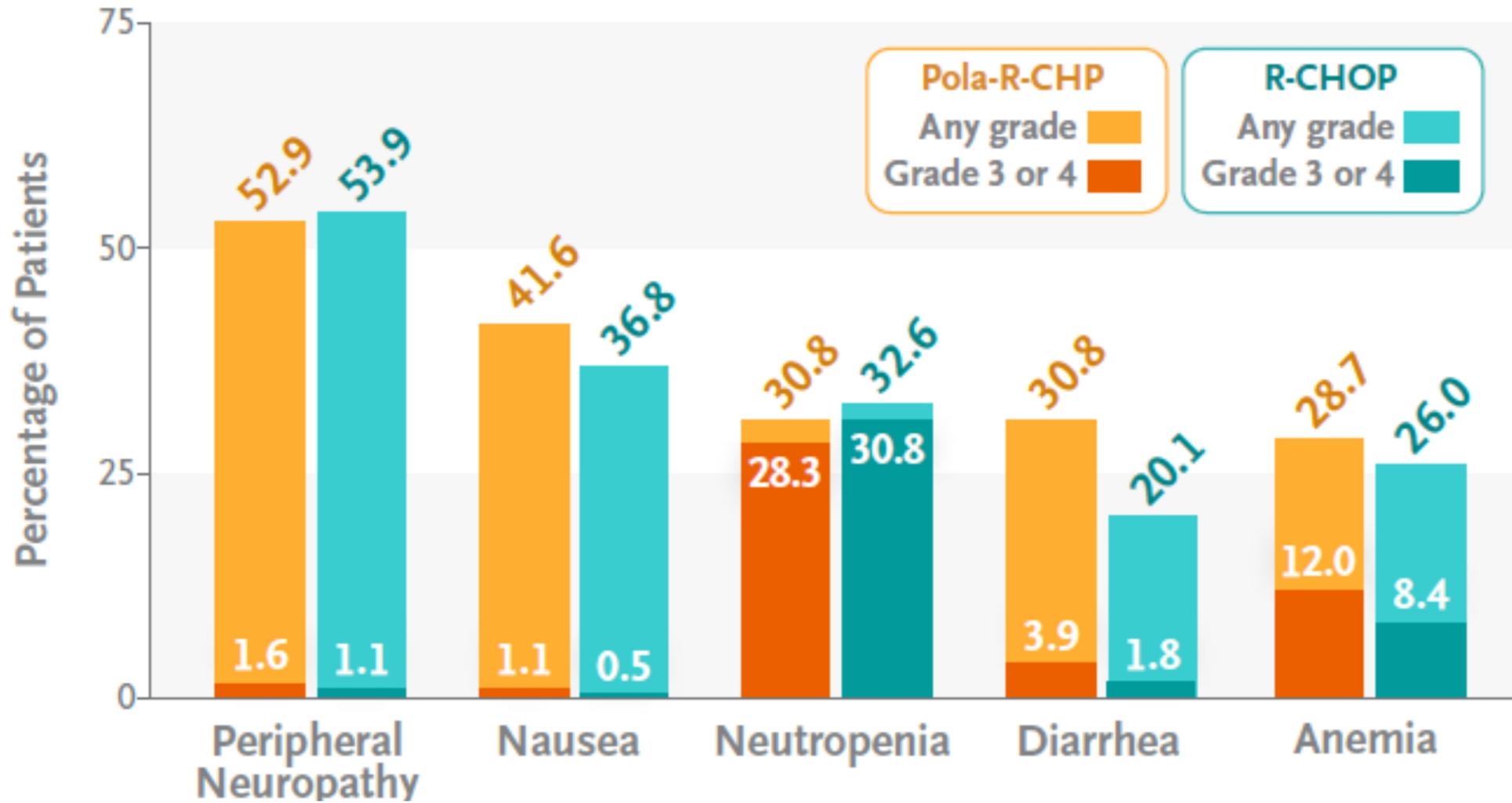
Polarix: Subsequent Treatments

Patients treated with Pola-R-CHP required 23% fewer subsequent therapies versus patients treated with R-CHOP

Subsequent therapies in the global ITT population

Legend:
- Pola-R-CHP (n=440)
- R-CHOP (n=439)

Total number of subsequent therapies (Number of subsequent therapies):
- Δ=23.4%
- Pola-R-CHP: n=209, 38.3%
- R-CHOP: n=336, 61.7%

Patients with at least 1 NALT (Patients %):
- Δ=9.8%
- Pola-R-CHP: n=112, 25.5%
- R-CHOP: n=155, 35.3%

Radiotherapy:
- Δ=4.6%
- Pola-R-CHP: n=42, 9.5%
- R-CHOP: n=62, 14.1%

Systemic therapy:
- Δ=8.2%
- Pola-R-CHP: n=88, 20.0%
- R-CHOP: n=124, 28.2%

Platinum-based therapy:
- Δ=5.7%
- Pola-R-CHP: n=43, 9.8%
- R-CHOP: n=68, 15.5%

Stem cell transplant:
- Δ=3.4%
- Pola-R-CHP: n=22, 5.0%
- R-CHOP: n=37, 8.4%

CAR-T:
- Δ=1.8%
- Pola-R-CHP: n=10, 2.3%
- R-CHOP: n=18, 4.1%

Bispecifics:
- Δ=0.7%
- Pola-R-CHP: n=6, 1.4%
- R-CHOP: n=9, 2.1%

Polarix: Toxicity

5-year PFS and OS outcomes show consistent treatment effect of Pola-R-CHP across subgroups in the global population

Baseline risk factors		PFS Pola-R-CHP (n=440) n	60-month (%)	R-CHOP (n=439) n	60-month (%)	HR	95% Wald CI	OS Pola-R-CHP (n=440) n	60-month (%)	R-CHOP (n=439) n	60-month (%)	HR	95% Wald CI
All patients		440	64.9	439	59.1	0.78	0.62–0.97	440	82.3	439	79.5	0.85	0.63–1.16
Age group	≤65	225	69.6	219	64.3	0.80	0.57–1.11	225	89.1	219	84.7	0.73	0.44–1.21
	>65	215	60.0	220	54.5	0.78	0.58–1.06	215	75.3	220	74.5	0.95	0.65–1.38
Stratification – IPI score	2	167	67.2	167	68.3	0.91	0.61–1.36	167	87.6	167	87.4	0.96	0.53–1.75
	3–5	273	63.2	272	53.5	0.72	0.55–0.94	273	79.2	272	74.7	0.81	0.57–1.15
Stratification – bulky disease (≥ 7cm)	Absent	247	69.9	247	60.0	0.61	0.44–0.83	247	83.9	247	80.9	0.79	0.52–1.20
	Present	193	58.5	192	57.9	1.02	0.73–1.41	193	80.3	192	77.9	0.92	0.60–1.43
Baseline LDH	≤1xULN	146	65.3	154	64.8	0.83	0.55–1.23	146	88.7	154	87.9	0.85	0.45–1.61
	>1xULN	291	64.3	284	55.7	0.77	0.59–1.01	291	79.0	284	74.9	0.85	0.60–1.19
No. of extranodal sites	0–1	227	68.1	226	64.2	0.78	0.56–1.09	227	83.7	226	81.9	0.86	0.56–1.34
	≥2	213	61.2	213	53.8	0.78	0.58–1.06	213	80.9	213	77.1	0.85	0.56–1.28
NHL subtype	DLBCL	373	65.7	367	58.8	0.75	0.59–0.95	373	81.9	367	79.8	0.89	0.64–1.23
	HGBL, DHL/THL	43	66.0	50	57.6	0.67	0.33–1.37	43	85.4	50	72.4	0.46	0.18–1.22
	Other LBCL	24	49.7	22	70.3	1.86	0.69–5.04	24	83.3	22	90.9	1.93	0.35–10.52
NanoString COO	NanoString GCB	187	65.9	170	65.8	1.07	0.74–1.56	187	82.9	170	82.3	0.99	0.60–1.61
	NanoString ABC	106	72.5	129	45.8	0.38	0.24–0.59	106	84.6	129	69.9	0.49	0.28–0.88
	NanoString UNC	44	55.2	53	70.8	1.60	0.79–3.25	44	76.9	53	94.2	4.46	1.23–16.21
	Unknown	103	60.2	87	59.7	0.83	0.51–1.33	103	81.3	87	79.0	0.80	0.42–1.51
Double expressor by IHC	DEL	139	63.1	151	50.0	0.65	0.45–0.94	139	76.4	151	73.0	0.84	0.53–1.33
	Non DEL	223	66.6	215	64.7	0.89	0.64–1.24	223	86.3	215	82.8	0.81	0.51–1.30
	Unknown	78	63.7	73	63.5	0.84	0.48–1.47	78	81.6	73	84.1	1.18	0.53–2.59

- PFS and OS by subgroups, including high-risk subgroups, generally favor Pola-R-CHP; however, subgroup analyses are exploratory and generally underpowered (especially for OS).

- Patient characteristics are multidimensional; therefore, translating univariate subgroup results into patient care should be applied with caution.

DEL, double-expressor lymphoma; IHC, immunohistochemistry; LBCL, large B-cell lymphoma; LDH, lactate dehydrogenase; ULN, upper limit of normal; UNC, unclassified.

Polarix- Pola + RCHP Conclusions

- **Large, double-blind, placebo-controlled trial**

- **Pola + RCHP: Superior PFS by 5.8%** 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

Topics

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

Primary Mediastinal B-Cell Lymphoma

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

A Event-free Survival (NCI Patients)
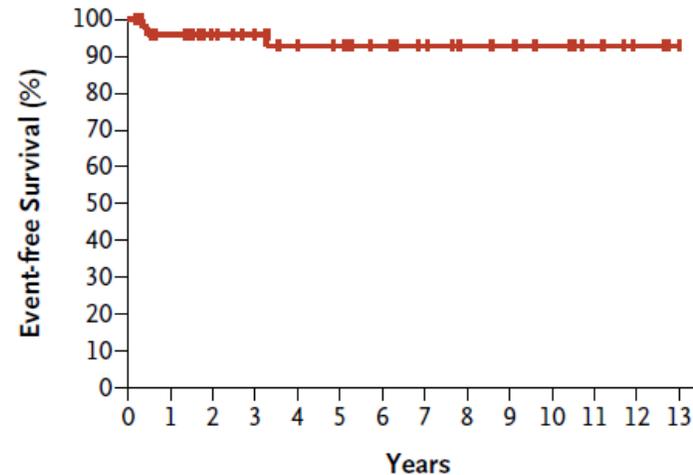
B Overall Survival (NCI Patients)
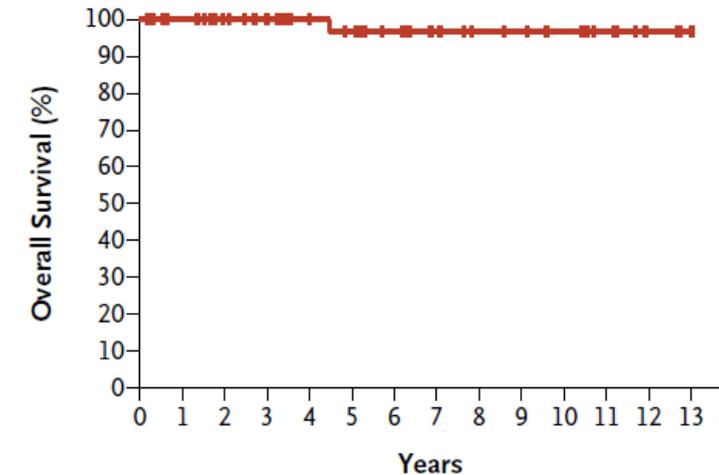
DA-EPOCH-R outcomes (single arm trial)

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)

Topics

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

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

*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)
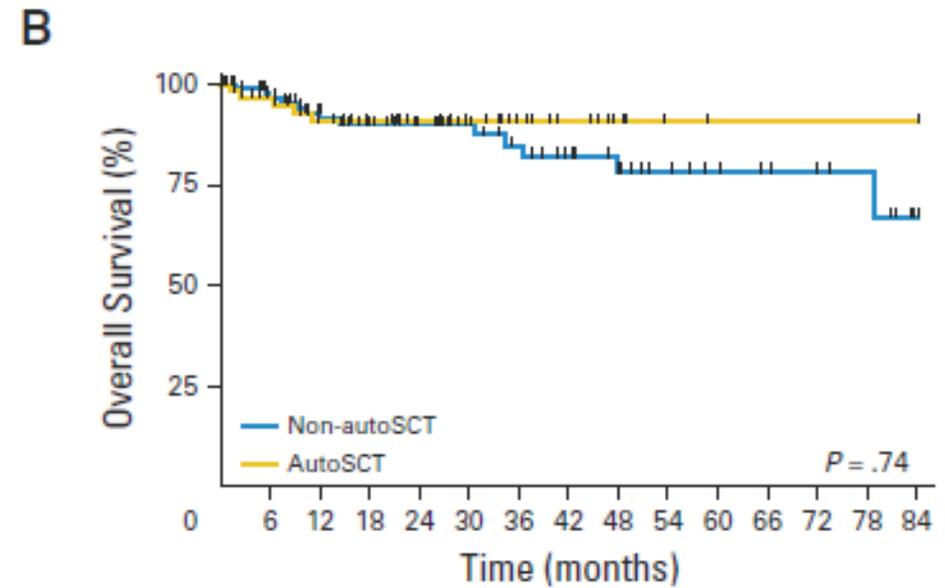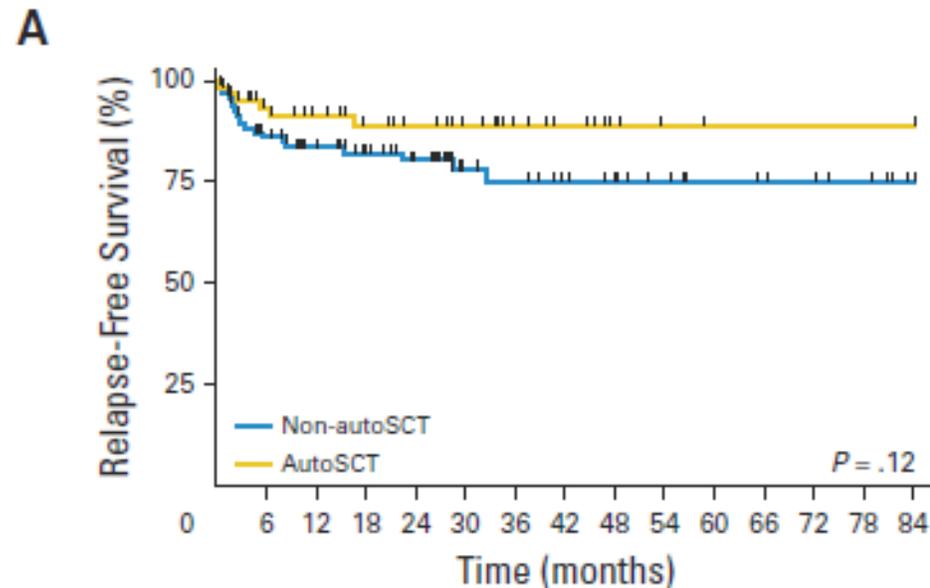
Landsburg JCO 2017

Topics

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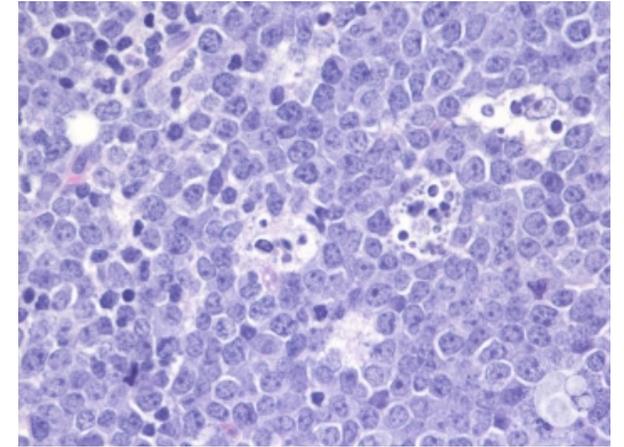- Relapsed /refractory Aggressive B-Cell Lymphomas
- Mantle Cell Lymphoma

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

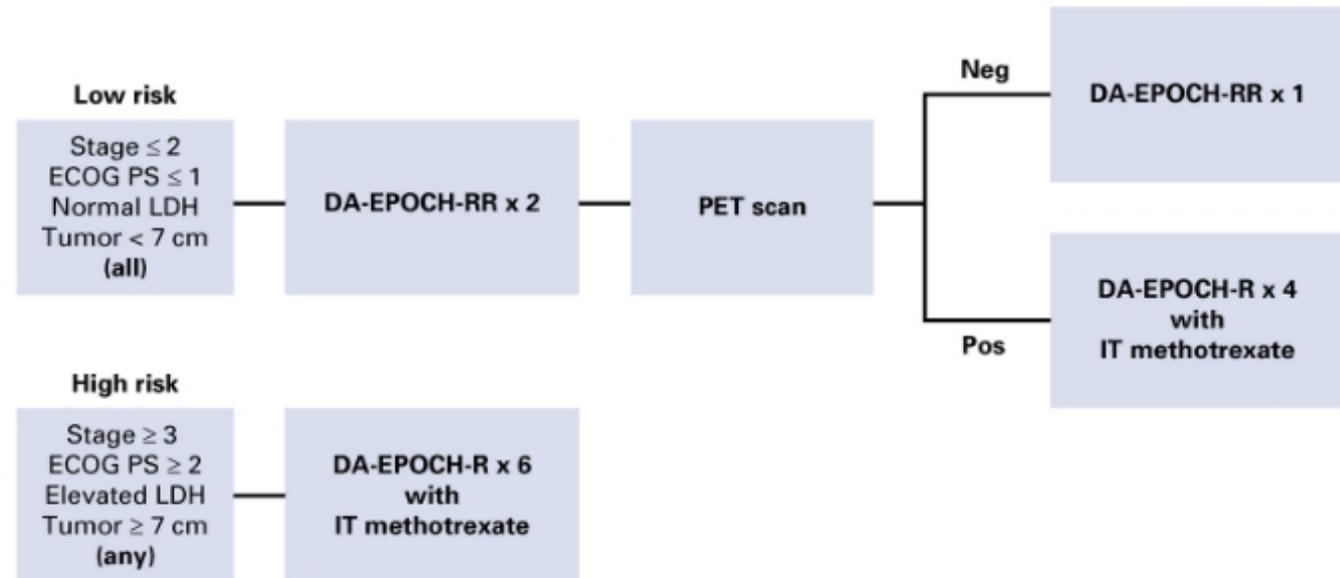- Very high Ki67

- FISH: MYC rearrangment

Starry sky pattern

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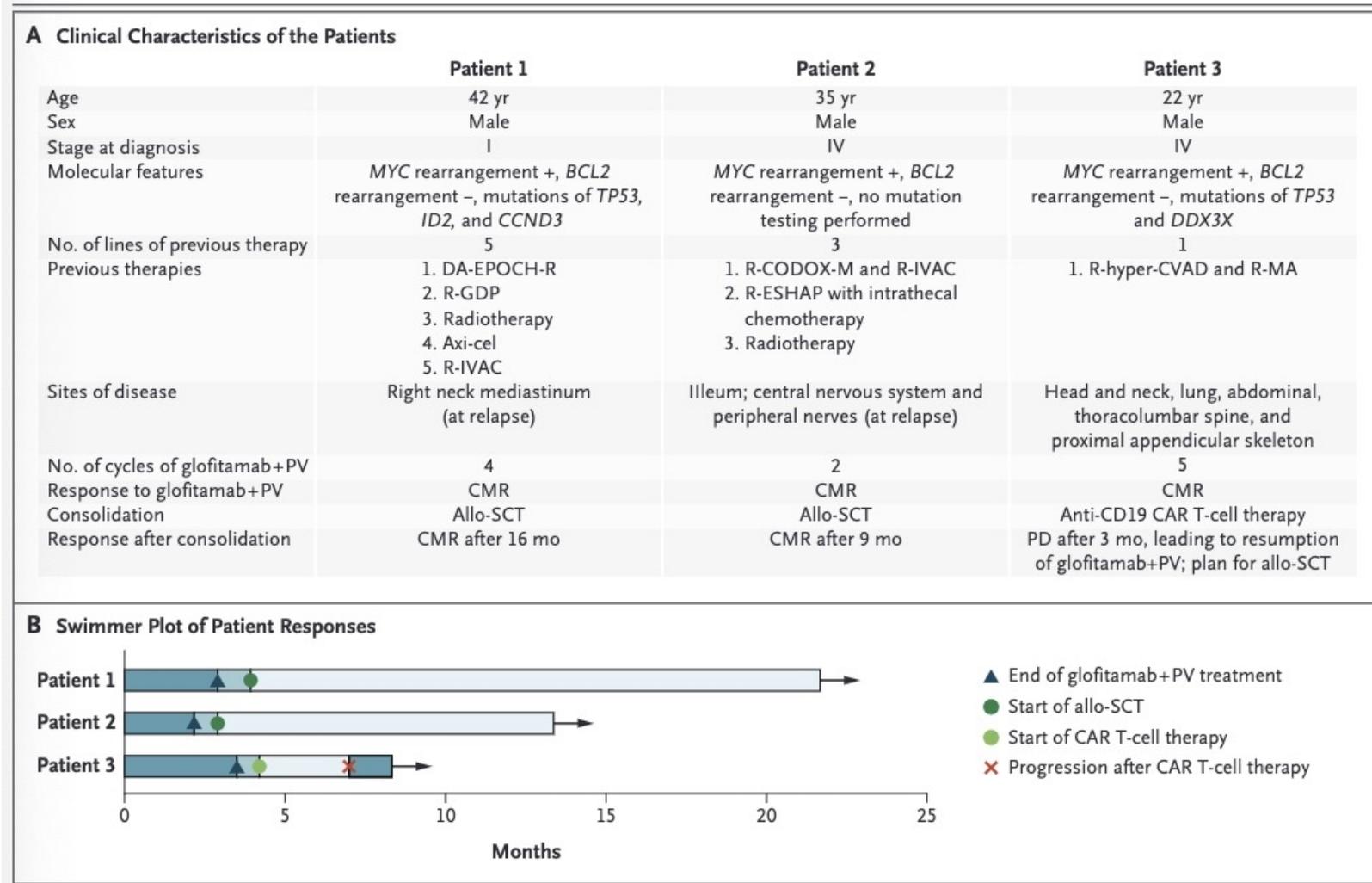
Burkitt Lymphoma

Treatment Standards

- Goal is to cure in the frontline
- Rituximab +

  Magrath (CODOX-M/IVAC); HyperCVAD+ Mtx/ara-C; da- EPOCH; risk adapted da- EPOCH (lack of randomized data for most comparisons) **HyperCVAD+R may have higher TRM**

- Therapy de-escalation?
  - Similar 2y PFS between CODOX-M/IVAC 2 cycles and da- EPOCH 6 cycles
  - Risk-adapted DA-EPOCH

Burkitt Lymphoma

Polatuzumab+glofitamab in r/r setting

A Clinical Characteristics of the Patients

	Patient 1	Patient 2	Patient 3
Age	42 yr	35 yr	22 yr
Sex	Male	Male	Male
Stage at diagnosis	I	IV	IV
Molecular features	MYC rearrangement +, BCL2 rearrangement –, mutations of TP53, ID2, and CCND3	MYC rearrangement +, BCL2 rearrangement –, no mutation testing performed	MYC rearrangement +, BCL2 rearrangement –, mutations of TP53 and DDX3X
No. of lines of previous therapy	5	3	1
Previous therapies	1. DA-EPOCH-R 2. R-GDP 3. Radiotherapy 4. Axi-cel 5. R-IVAC	1. R-CODOX-M and R-IVAC 2. R-ESHAP with intrathecal chemotherapy 3. Radiotherapy	1. R-hyper-CVAD and R-MA
Sites of disease	Right neck mediastinum (at relapse)	Illeum; central nervous system and peripheral nerves (at relapse)	Head and neck, lung, abdominal, thoracolumbar spine, and proximal appendicular skeleton
No. of cycles of glofitamab+PV	4	2	5
Response to glofitamab+PV	CMR	CMR	CMR
Consolidation	Allo-SCT	Allo-SCT	Anti-CD19 CAR T-cell therapy
Response after consolidation	CMR after 16 mo	CMR after 9 mo	PD after 3 mo, leading to resumption of glofitamab+PV; plan for allo-SCT

B Swimmer Plot of Patient Responses

▲ End of glofitamab+PV treatment
● Start of allo-SCT
● Start of CAR T-cell therapy
✕ Progression after CAR T-cell therapy

Topics

- Diffuse Large B-Cell Lymphoma (DLBCL)
  - Primary Mediastinal Large B-Cell Lymphoma (PMBCL)
- Double hit (MYC/BCL2)
- Burkitt Lymphoma
- **Relapsed /refractory Aggressive B-Cell Lymphomas**
- Mantle Cell Lymphoma
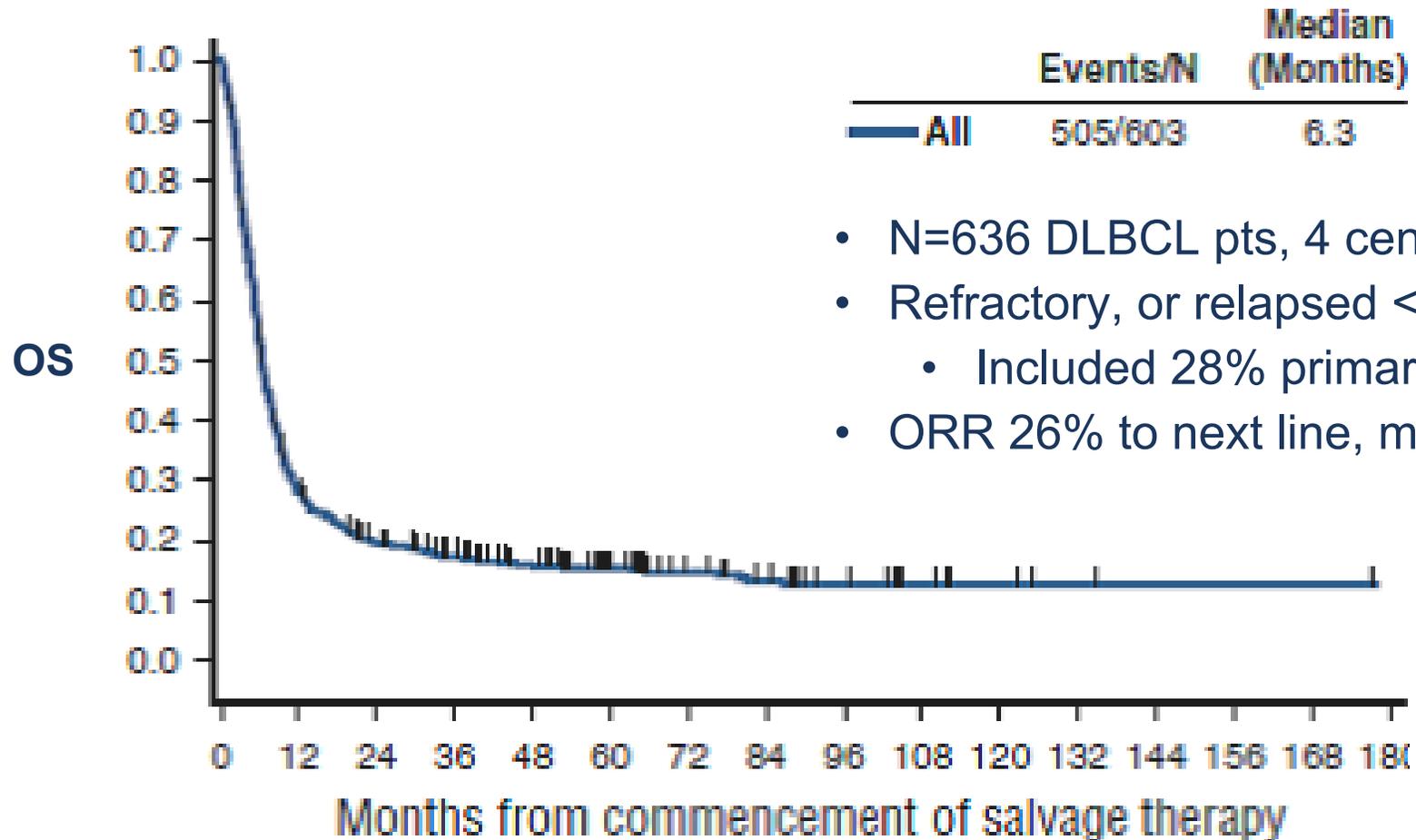
Relapsed/Refractory DLBCL

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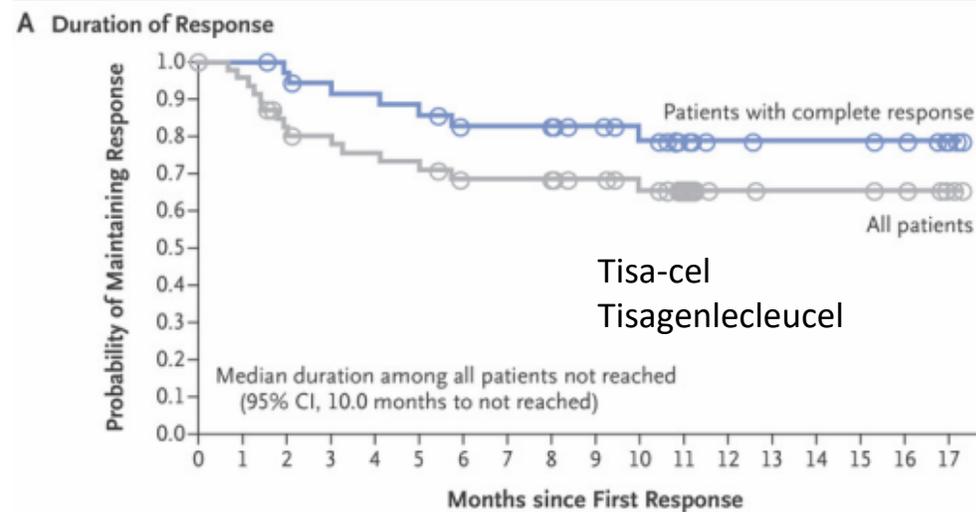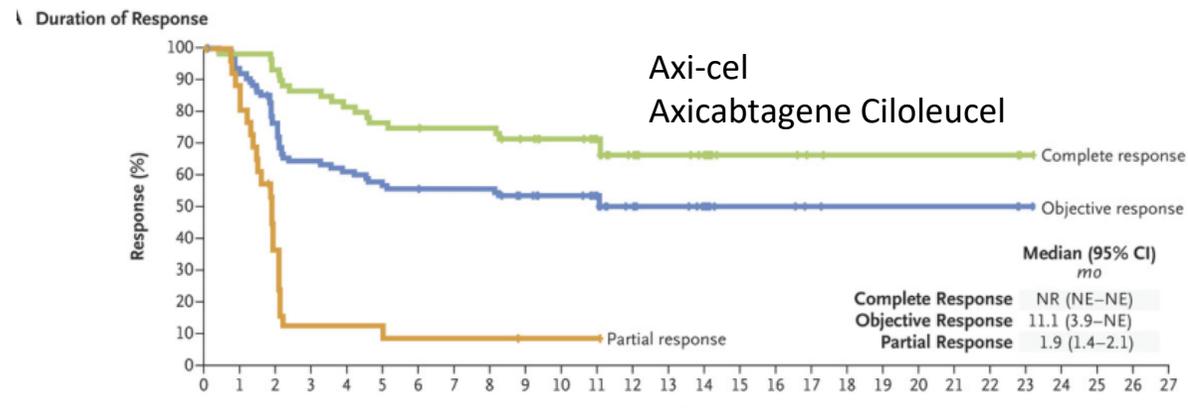 - Novel agents
- **Unmet needs**
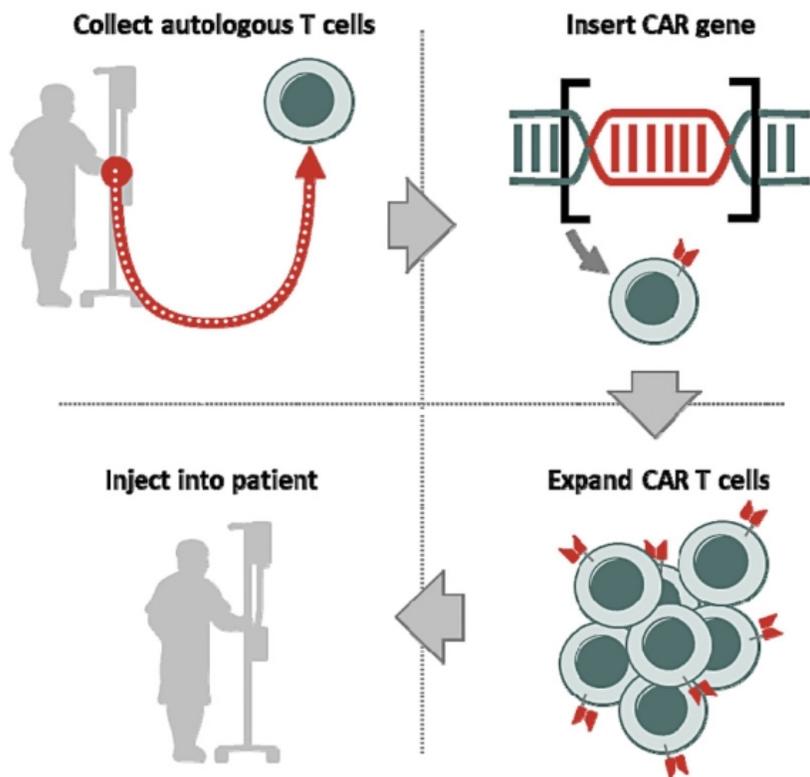 - Post CAR T-relapse (or ineligible); sequencing Tx around CAR T-cells
  - CNS disease: Prophylaxis and tx
  - Managing R/R subtypes (PMBCL, HGBCL/DLBCL with MYC/BCL2, Richter)

Chemorefractory DLBCL: "Scholar-1" observational study

	Events/N	Median (Months)
All	505/603	6.3

- 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

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

2017

2022

?

✓ **3rd line**

✓ **2nd line: early relapse/ref**
or elderly/unfit
(instead of ASCT)

?1st line: high risk

- **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 <u>Refractory/Relapsing 12 months</u> from 1st line

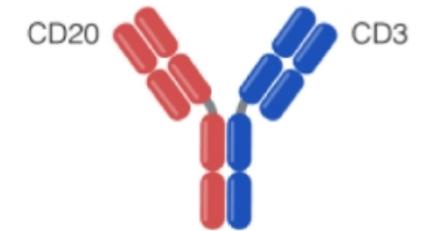|	TRANSFORM	Zuma-7
Comparison	Liso-cel vs ASCT (N=92 each)	Axi-cel vs ASCT (N=180/179)
CR	66% vs 39% (p<.001)	65% vs 32% (p<.001)
EFS	10.1 vs 2.3 mo (p<.0001)	8.3 vs 2.0 mo (p<.001)
OS	NR vs 29.9 mo, p=.0987 79.1% vs 64.2% at 1 year	**NR vs 31.1 mo, p=.03** **54.6% vs 46% (4-year)**
Notes	• Bridging 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)

Bispecific Antibodies: New options in 2024
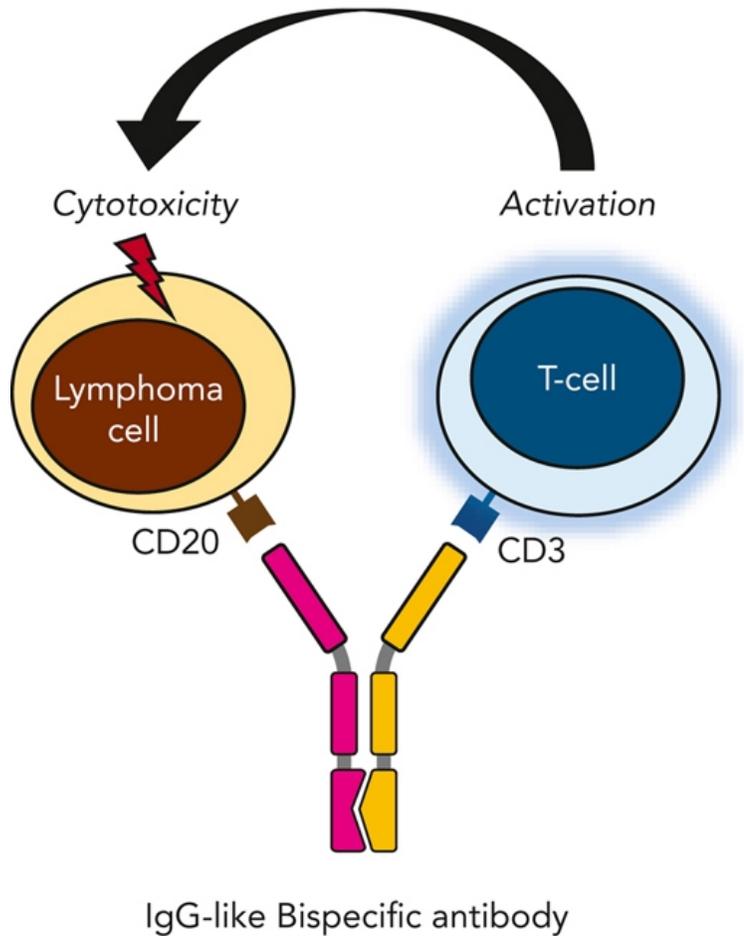
Glofitamab: CD20 x CD3, 2:1 tumor- to T-cell binding
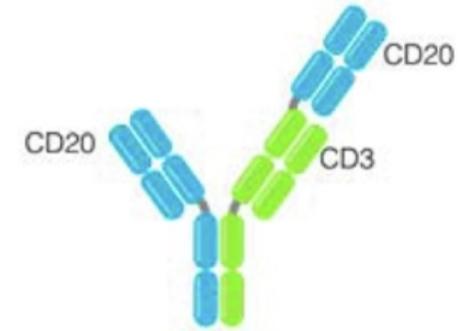
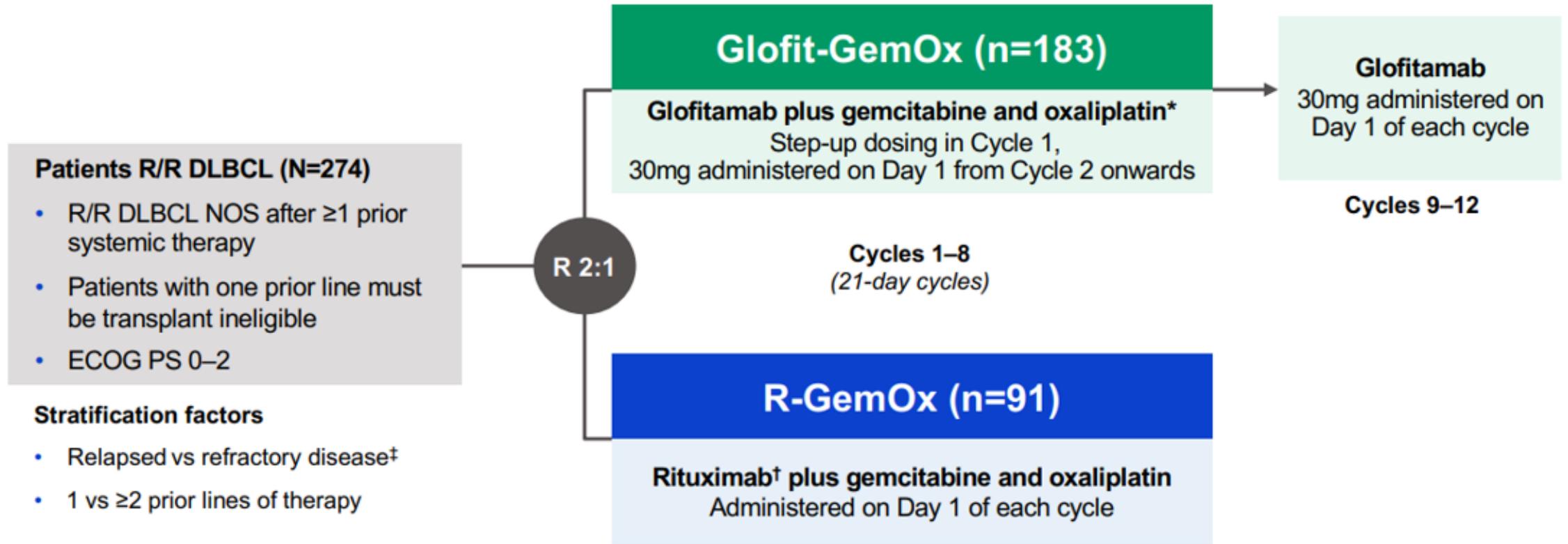**Epcoritamab**: CD20 x CD3

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 $\geq$ G2 CRS

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

	Epcoritamab	Glofitamab
ORR/CR, %	63/39	52/40
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, Blood (2024) 144 (Supplement 1): 865.
Epcoritamab: Thieblemont JCO 2023, Blood (2024) 144 (Supplement 1): 4480.

Patients R/R DLBCL (N=274)

- R/R DLBCL NOS after ≥1 prior systemic therapy
- Patients with one prior line must be transplant ineligible
- ECOG PS 0–2

Stratification factors

- Relapsed vs refractory disease‡
- 1 vs ≥2 prior lines of therapy

R 2:1

Glofit-GemOx (n=183)

Glofitamab plus gemcitabine and oxaliplatin*
Step-up dosing in Cycle 1,
30mg administered on Day 1 from Cycle 2 onwards

Cycles 1–8
(21-day cycles)

Glofitamab
30mg administered on Day 1 of each cycle

Cycles 9–12

R-GemOx (n=91)

Rituximab† plus gemcitabine and oxaliplatin
Administered on Day 1 of each cycle

*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.

Abramson EHA 2024

≥2nd line Bispecifics+chemo in Aggressive BCL: STARGLO trial

Efficacy:

Median OS:
- Glofit-GemOx: 25.5 mo
- R-GemOx: 12.9 mo

Glofit-GemOx vs R-GemOx:
HR (95% CI): **0.62 (0.43–0.88)**

No. of patients at risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Glofit-GemOx	183	159	135	119	104	86	71	51	40	26	11	3	NE
R-GemOx	91	68	55	46	40	29	23	14	10	8	3	2	NE

Median PFS:
- Glofit-GemOx: 12.1 mo
- R-GemOx: 3.3 mo

Glofit-GemOx vs R-GemOx:
HR (95% CI): **0.40 (0.28–0.57)**

No. of patients at risk	0	3	6	9	12	15	18	21	24	27	30	33	36
Glofit-GemOx	183	130	107	89	66	54	37	26	14	10	2	1	NE
R-GemOx	91	34	22	14	9	6	2	2	2	2	NE	NE	NE

Adverse events:

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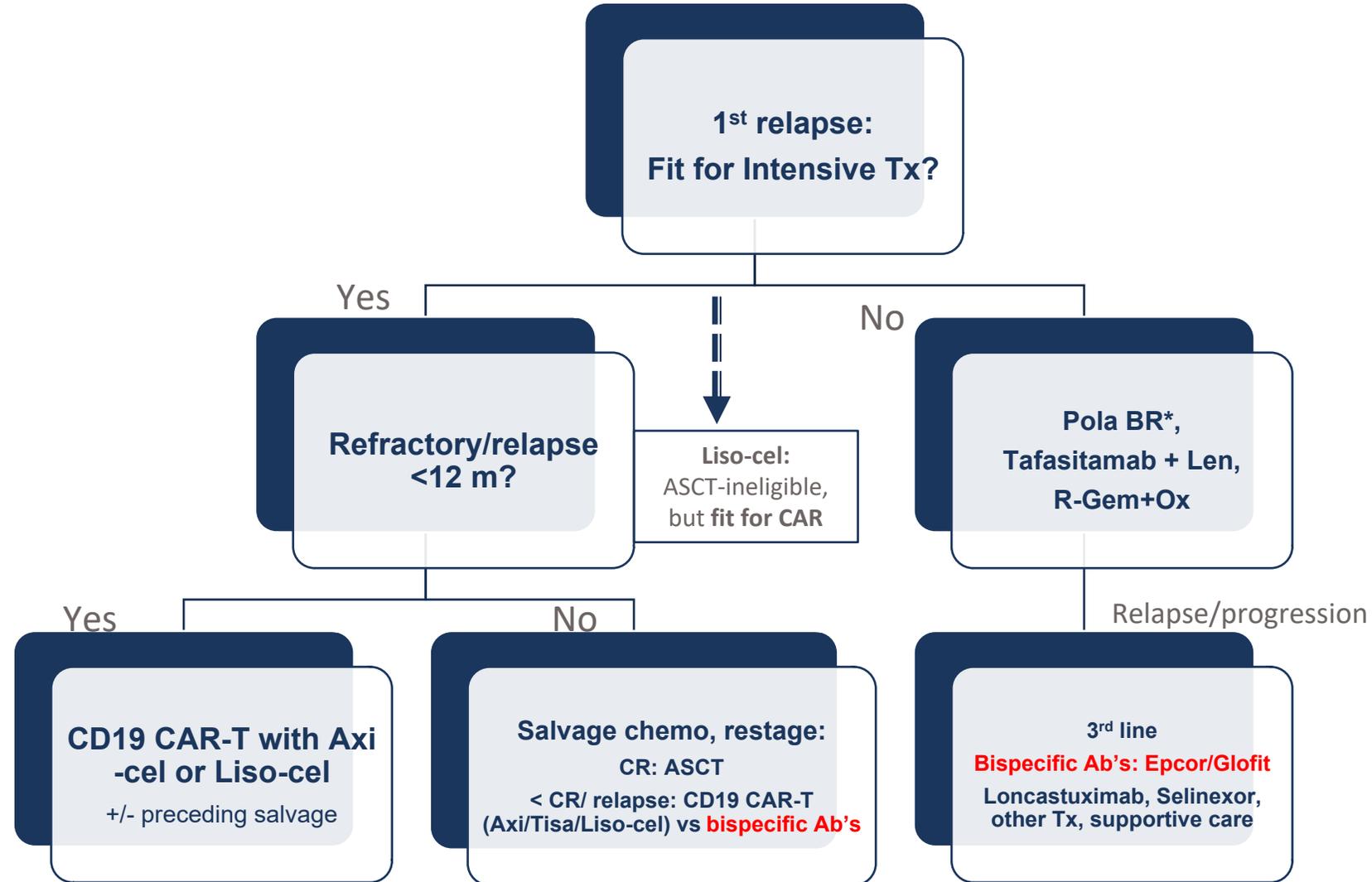- R-GemOx: serious 17%, G3-5 41%, G5 5%

Conclusions:

- **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, ODAC meeting this year)

Abramson EHA 2024

"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

1st relapse:
Fit for Intensive Tx?

Yes → **Refractory/relapse <12 m?**

→ **Liso-cel:** ASCT-ineligible, but **fit for CAR**

No → **Pola BR*, Tafasitamab + Len, R-Gem+Ox**

Yes → **CD19 CAR-T with Axi-cel or Liso-cel** +/- preceding salvage

No → **Salvage chemo, restage:** CR: ASCT; < CR/ relapse: CD19 CAR-T (Axi/Tisa/Liso-cel) vs **bispecific Ab's**

Relapse/progression → **3rd line** **Bispecific Ab's: Epcor/Glofit** Loncastuximab, Selinexor, other Tx, supportive care

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

Topics

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

Mantle cell lymphoma

- Highly heterogeneous disease
  - Indolent disease may only require monitoring
  - Risk stratification: MIPI- score, other high-risk features (high Ki-67, TP53 aberrance, blastoid/pleomorphic morphology)
- Rapidly evolving treatment landscape
  - Treatment naive disease
  - Relapsed/refractory disease

1st line treatment of MCL

Younger/Fit (TP53wt) patients

- **Intensive induction and ASCT** (and R maintenance) if CR
- **CIT +/- BTKi for induction + BTK-i/R for maintenance for 2 years** (TRIANGLE)

The TRIANGLE study: ASCT in 1ˢᵗ line MCL

Is ASCT better than ibrutinib-containing therapy alone?
What's the benefit adding Ibrutinib to 1ˢᵗ line ASCT/intensive therapy?

- 1ˢᵗ line MCL ≤ 65, suitable for ASCT
- **N=870**
  - Accrual 7/2016-12/2020
- **31 months** of follow-up
- **Maintenance R** was added (all arms) during study, 60% received
- **Primary endpoint: Failure-free survival (FFS)**
  - Events= SD after induction, any progression, death

Arm A (control)
R-CHOP/R-DHAP x 3 — ASCT — Observation   *"standard"*

Arm A + I (experimental)
R-CHOP+I/R-DHAP x 3 — ASCT — 2 yrs I-maintenance — Observation   *"kitchen sink"*

Arm I (experimental)
R-CHOP+I/R-DHAP x 3 — 2 yrs I-maintenance — Observation   *"Ibrutinib+Chemo alone"*

1:1:1 R
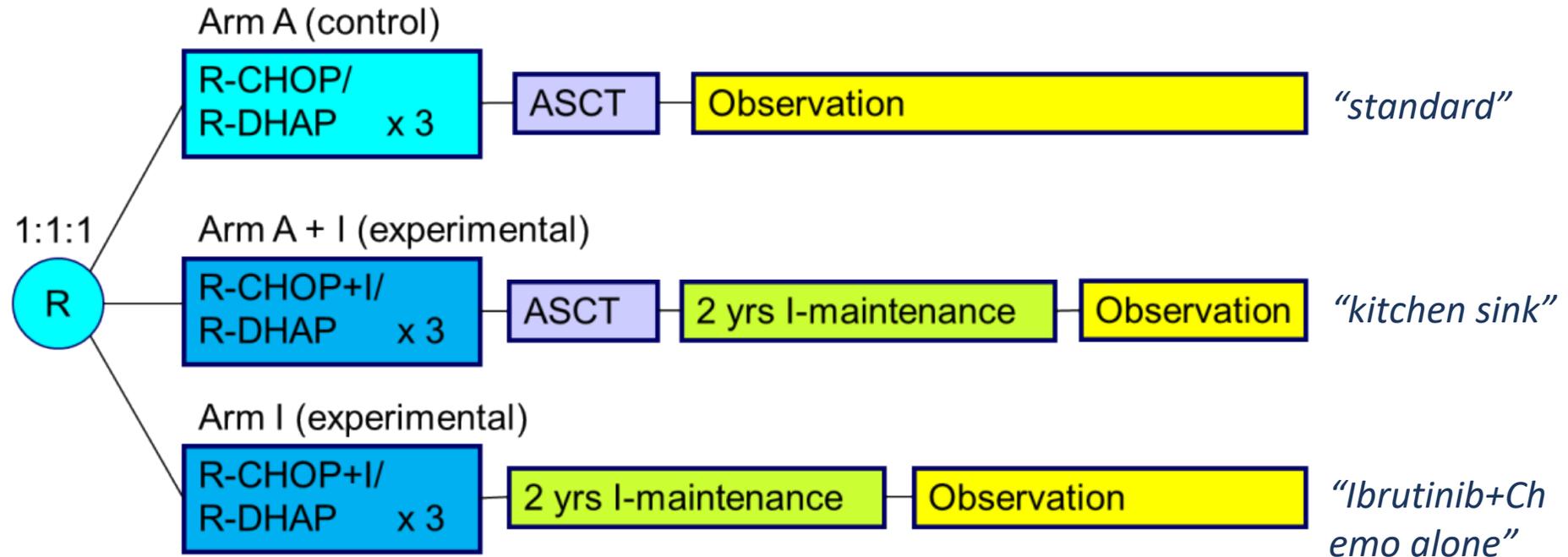
- R maintenance was added during trial conduct in all 3 trial arms, about 60% received

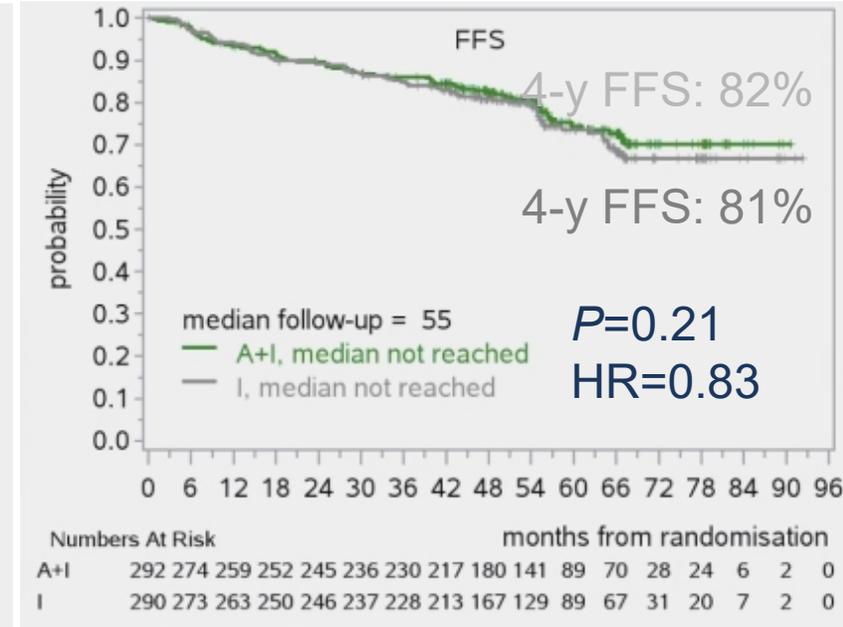Dreyling Lancet 2024.

Ibrutinib given during RCHOP and as 2 years of maintenance

TRIANGLE study: Ibrutinib-containing arms with best FFS
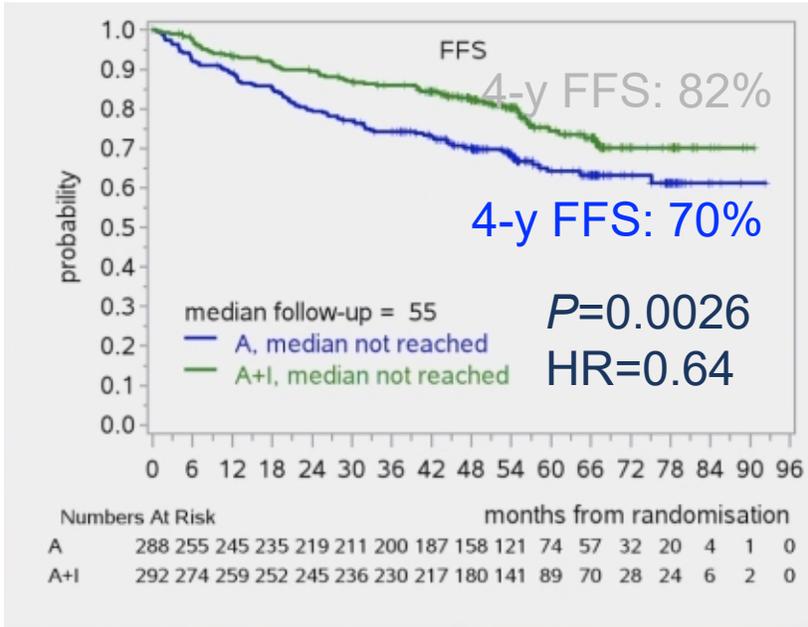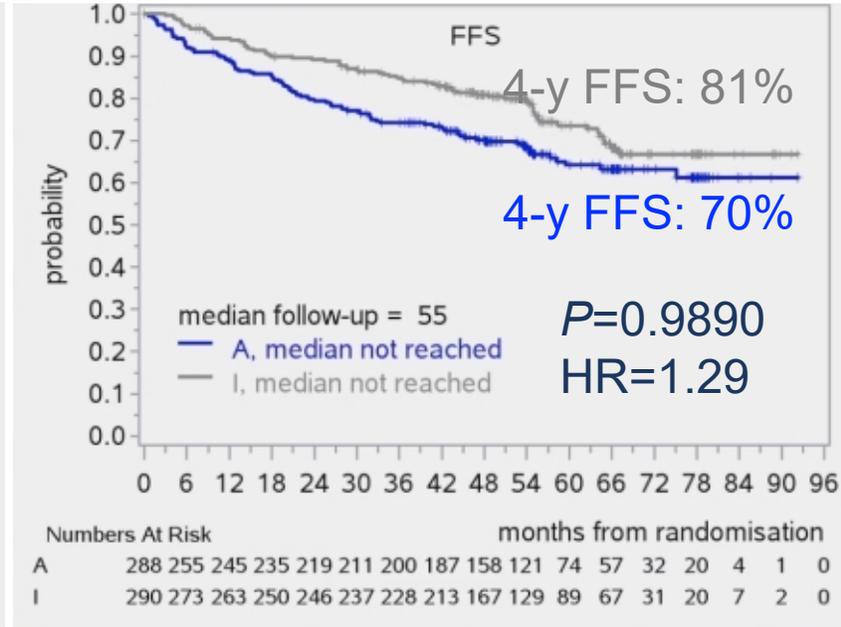
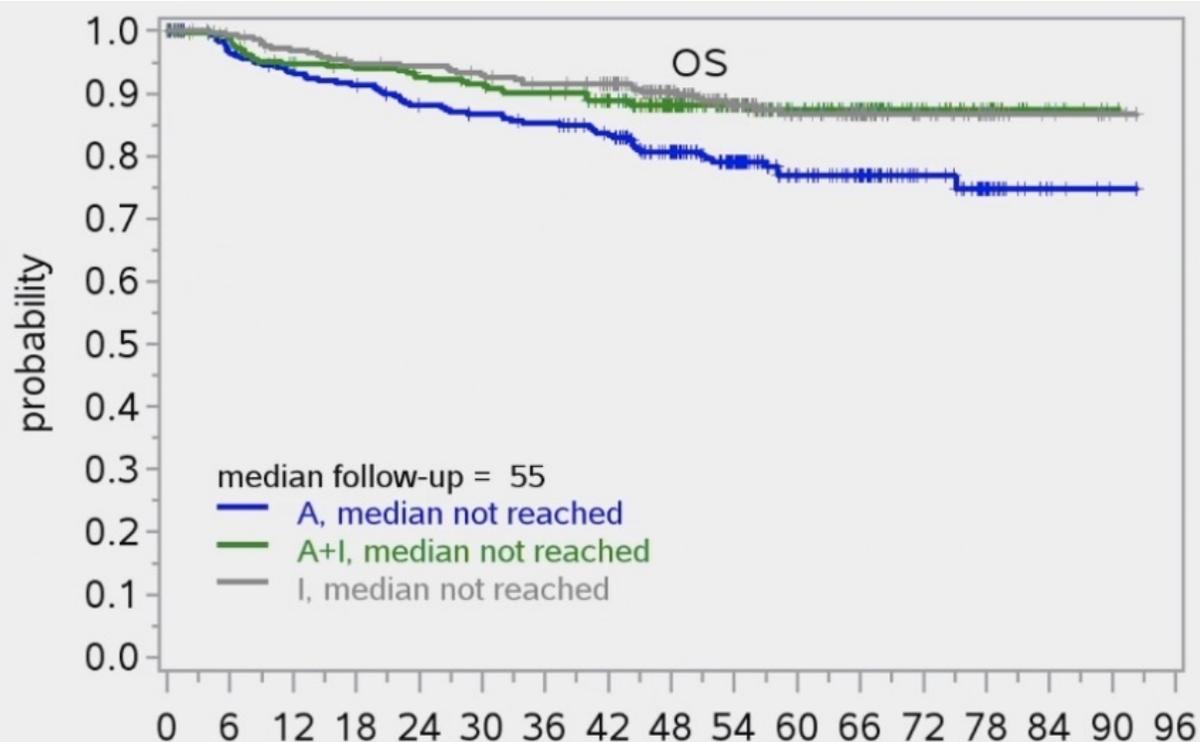A+I superior to A | A not superior to I | A+I not superior to I

Dreyling Lancet 2024.

TRIANGLE study: Ibrutinib-containing arms with best OS

4-year OS:
- A: 81%
  (MCL Younger exp.: 80%)
- A+I: 88%
- I: 90%

two-sided test, (α = 5%):
- A vs. I: p=0.0019, HR: 0.565
- A vs. A+I: p=0.0036, HR I: 0.587
- A+I vs. I: ongoing

A main point: ASCT (A) NOT better than ibrutinib + chemo alone (I)– so not justified based on these results

Dreyling Lancet 2024.
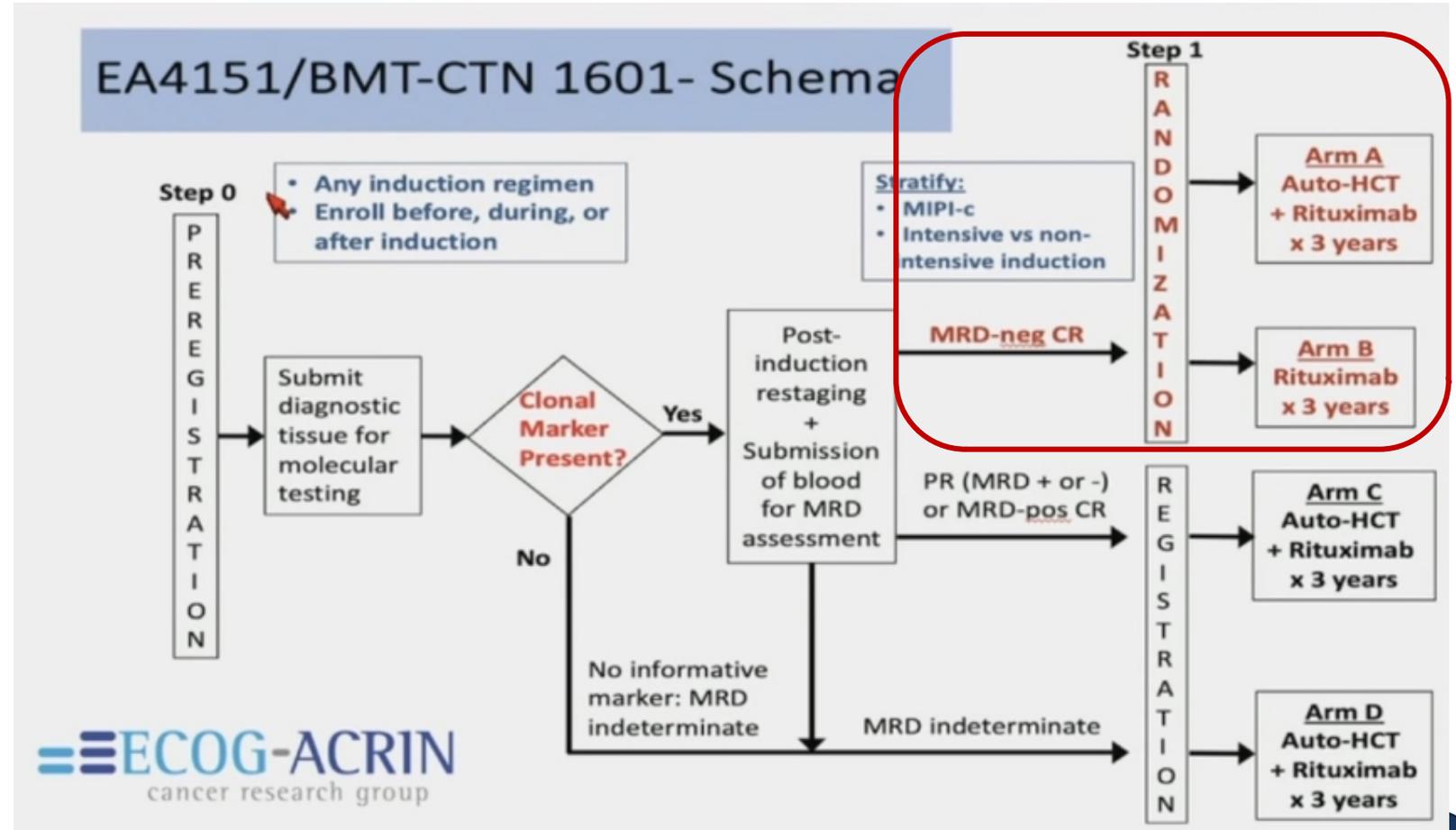
1st line treatment of MCL

Younger/Fit (TP53wt) patients

- **Intensive induction and ASCT** (and R maintenance) if CR ([EA4151 trial](#))
- **CIT +/- BTKi for induction + BTK-i/R for maintenance for 2 years** ([TRIANGLE](#))
  - BTK-I after other (non-TRIANGLE) induction tx
  - Substituting ibrutinib with acalabrutinib/zanubrutinib x 2 years

ECOG-ACRIN EA4151 trial: role of ASCT in deep first remission

- Deep first remission: as measured by an immunoglobulin high throughput sequencing MRD assay (clonoSEQ®) with sensitivity to $1*10^{-6}$
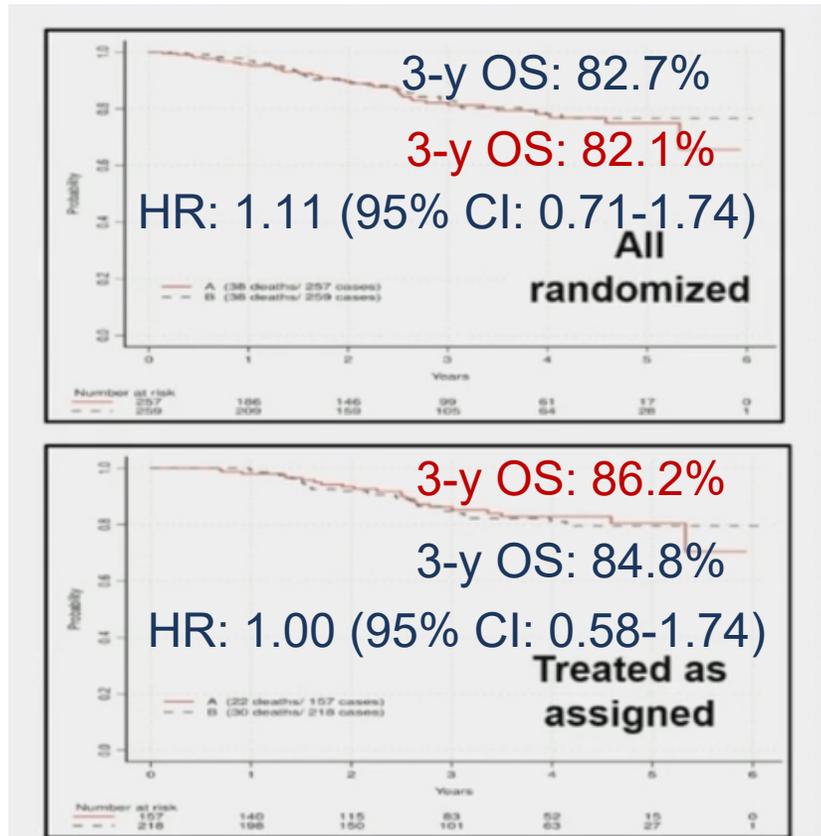
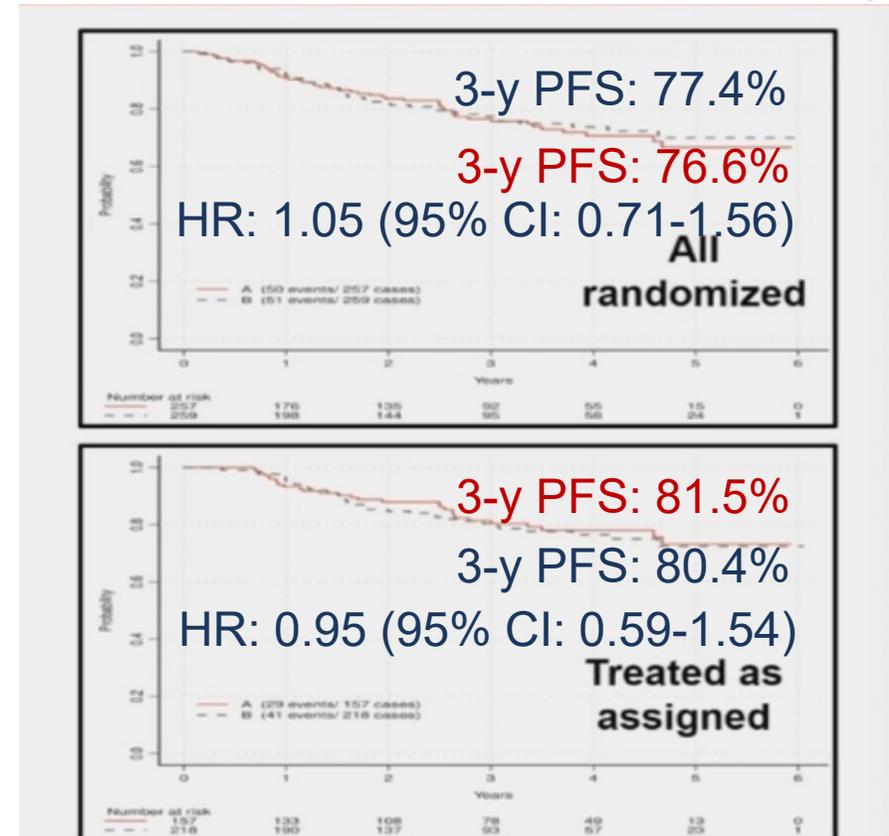N=494 in arms A and B
Median age: 59-61
MIPI high-int: 35%

ASH 2024.

ECOG-ACRIN EA4151 trial: role of ASCT in deep first remission

Median follow-up: 2.7 years

OS

3-y OS: 82.7%

3-y OS: 82.1%

HR: 1.11 (95% CI: 0.71-1.74)

All randomized

A (38 deaths/ 257 cases)
B (38 deaths/ 259 cases)

3-y OS: 86.2%

3-y OS: 84.8%

HR: 1.00 (95% CI: 0.58-1.74)

Treated as assigned

A (22 deaths/ 157 cases)
B (30 deaths/ 218 cases)

PFS

3-y PFS: 77.4%

3-y PFS: 76.6%

HR: 1.05 (95% CI: 0.71-1.56)

All randomized

A (50 events/ 257 cases)
B (51 events/ 259 cases)

3-y PFS: 81.5%

3-y PFS: 80.4%

HR: 0.95 (95% CI: 0.59-1.54)

Treated as assigned

A (29 events/ 157 cases)
B (41 events/ 218 cases)

- HR for OS crossed the futility boarder (0.984 for arm A vs B)
- No difference in OS based on MIPI and intensiveness of therapy
- No difference in PFS

Challenging role of ASCT in patients with MRD-neg CR

Fred Hutchinson Cancer Center

ASH 2024.

1st line treatment of MCL

Younger/Fit (TP53wt) patients

- **Intensive induction and ASCT** (and R maintenance) if CR (EA4151 trial)
- **CIT +/- BTKi for induction + BTK-i/R for maintenance for 2 years** (TRIANGLE)
  - NCCN panel lacks consensus; but can consider:
    - BTK-I after other (non-TRIANGLE) induction tx
    - Substituting ibrutinib with acalabrutinib/zanubrutinib x 2 years

Elderly MCL patients

- **BR or VR-CAP; likely R maintenance.**
- **Adding BTKi in high-risk pts** (SHINE and ECHO trials)

Classical TP53 mutated

- Consider non-chemo approach: zanu/obin/ven (BOVIN trial)

Treatment of R/R MCL

- **Continuous BTK-I** (acalabrutinib, zanubrutinib) if no prior BTKi

- **Pirtobrutinib** if prior covalent BTKi

- **Vigilant restaging and planning for CD19 CAR-T (early referral, BTKi as bridging)**
  - Especially in high MIPI, blastoid variant

- Some role remains for allo SCT, not likely auto SCT

- NCCN-listed regimens (non BTK/CAR-T)
  - **Glofitamab**
  - Len + ritux
  - RBAC500
  - BR (if no prior benda), Gem Ox
  - (Bortezomib, Off-labe venetoclax)

TCE	ORR	CR rate	Median PFS	Median OS
Glofitamab (N=60) [1]	85%, 74% with prior BTKi	78%, 71% with prior BTKi	17 m	30 m
Polatuzumab+ musonetuzumab (N=42) [2]	88%	79%	19 m	21 m

Fred Hutchinson Cancer Center

1. J Clin Oncol. 2025 Jan 20;43(3):318-328.
2. ICML 2025, abstract 050.

Take home messages for MCL

- Heterogeneous disease with need of risk stratification
- Frontline management
  - Moving away from using ASCT
  - Consider non-chemo approach in pts with TP53 mutation
- Management in r/r setting
  - Covalent BTKi, non-covalent BTKi, CART, etc.
  - Vigilant planning for CART
  - Emerging role of TCE

Thank you

mydi@fredhutch.org   @DiMengyang