# Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Diffuse Large B-Cell Lymphoma (Part 2 of a 4-Part Series)

*A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting*

**Friday, December 8, 2023**

**11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)**

## Faculty

**Michael Dickinson, MD**
**Grzegorz S Nowakowski, MD**
**Gilles Salles, MD, PhD**
**Laurie H Sehn, MD, MPH**
**Jason Westin, MD, MS**

## Moderator

**Neil Love, MD**

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# Faculty

**Michael Dickinson, MD**
Hematologist
Lead of Aggressive Lymphoma
CAR-T Specialist
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MD Anderson Cancer Center
Houston, Texas

## Moderator

**Neil Love, MD**
Research To Practice
Miami, Florida

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# Prof Dickinson — Disclosures

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# Dr Salles — Disclosures

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| **Data and Safety Monitoring Board/Committee** | BeiGene Ltd |

# Dr Sehn — Disclosures

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# Dr Westin — Disclosures

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| **Data and Safety Monitoring Board/Committee** | Century Therapeutics |

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# Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Chronic Lymphocytic Leukemia (Part 3 of a 4-Part Series)

*A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting*

**Friday, December 8, 2023**

**3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)**

## Faculty

**Farrukh T Awan, MD**
**Matthew S Davids, MD, MMSc**
**Stephen J Schuster, MD**
**William G Wierda, MD, PhD**
**Jennifer Woyach, MD**

## Moderator

**Neil Love, MD**

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# Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Multiple Myeloma (Part 4 of a 4-Part Series)

*A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting*

**Friday, December 8, 2023**

**7:00 PM – 9:00 PM PT (10:00 PM – 12:00 AM ET)**

## Faculty

**Amrita Krishnan, MD**
**Sagar Lonial, MD**
**Robert Z Orlowski, MD, PhD**
**Noopur Raje, MD**
**Paul G Richardson, MD**

## Moderator

**Neil Love, MD**

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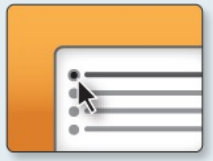
# Clinicians in the Meeting Room

**Networked iPads are available.**

**Review Program Slides: Tap the Program Slides button to review speaker presentations and other program content.**



**Answer Survey Questions: Complete the premeeting survey.**

**Ask a Question: Tap Ask a Question to submit a challenging case or question for discussion. We will aim to address as many questions as possible during the program.**

**Complete Your Evaluation: Tap the CME/NCPD Evaluation button to complete your evaluation electronically to receive credit for your participation.**

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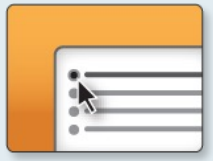
# Clinicians Attending via Zoom

**Review Program Slides: A link to the program slides will be posted in the chat room at the start of the program.**



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# About the Enduring Program

- The live meeting is being video and audio recorded.
- The proceedings from today will be edited and developed into an enduring web-based video/PowerPoint program.
  An email will be sent to all attendees when the activity is available.
- To learn more about our education programs, visit our website, **www.ResearchToPractice.com**

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# Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Diffuse Large B-Cell Lymphoma (Part 2 of a 4-Part Series)

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**Jason Westin, MD, MS**

## Moderator

**Neil Love, MD**

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# Agenda

**Module 1: Up-Front Management of Diffuse Large B-Cell Lymphoma (DLBCL) — Dr Salles**

**Module 2: Promising Investigational Approaches to First-Line Therapy for DLBCL — Dr Nowakowski**

**Module 3: Selection and Sequencing of Novel Therapies for Relapsed/Refractory (R/R) DLBCL — Dr Sehn**

**Module 4: Incorporation of CAR T-Cell Therapy into the Management of R/R DLBCL — Dr Westin**

**Module 5: Role of Bispecific Antibodies in the Treatment of DLBCL — Prof Dickinson**

# DLBCL Survey Respondents

Jeremy S Abramson, MD, MMSc
Stephen M Ansell, MD, PhD
Nancy L Bartlett, MD
Jonathon B Cohen, MD
Michael Dickinson, MD
Andrew M Evens, DO, MA, MSc
Christopher R Flowers, MD, MS
Jonathan W Friedberg, MD, MMSc
Brad S Kahl, MD
Ann S LaCasce, MD, MMSc
Kami Maddocks, MD
Franck Morschhauser, MD, PhD
Grzegorz S Nowakowski, MD
Tycel Phillips, MD
Gilles Salles, MD, PhD
Laurie H Sehn, MD, MPH
Sonali M Smith, MD
Max S Topp, MD
Jason Westin, MD, MS
Andrew D Zelenetz, MD, PhD

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# Consulting Faculty

**Andrew M Evens, DO, MBA, MSc**
Rutgers Cancer Institute of New Jersey
Rutgers Robert Wood Johnson Medical School
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**Tycel Phillips, MD**
City of Hope Comprehensive Cancer Center
Duarte, California

**Kami Maddocks, MD**
The James Cancer Hospital and Solove Research Institute
The Ohio State University Comprehensive Cancer Center
Columbus, Ohio

**Max S Topp, MD**
Universitätsklinikum Würzburg
Würzburg, Bavaria, Germany

**Franck Morschhauser, MD, PhD**
CHU Lille
Lille, France

**Andrew D Zelenetz, MD, PhD**
Memorial Sloan Kettering Cancer Center
Weill Cornell Medical College
New York, New York

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# FDA Investigating 'Serious Risk' of Secondary Cancer After CAR-T Therapy

## Press Release: November 29, 2023

“The FDA has launched an investigation into what it called a ‘serious risk’ of T-cell malignancies in patients treated with autologous chimeric antigen receptor (CAR) T-cell therapies targeting B-cell maturation antigen (BCMA) or CD19.

The agency has received multiple reports of T-cell malignancies, including CAR-positive lymphomas, from clinical trials and postmarketing adverse event data sources, according to a statement posted on the FDA website. Serious outcomes of these secondary malignancies have included hospitalization and death. The notice and investigation pertain to all currently approved BCMA- and CD19-targeted CAR T-cell products.

‘Although the overall benefits of these products continue to outweigh their potential risks for their approved uses, FDA is investigating the identified risk of T-cell malignancy with serious outcomes, including hospitalizations and death, and is evaluating the need for regulatory action,’ agency officials said in the statement. ‘As with all gene therapy products with integrating vectors (lentiviral or retroviral vectors), the potential risk of developing secondary malignancies is labeled as a class warning in the US prescribing information for approved BCMA-directed and CD19-directed genetically modified autologous T-cell immunotherapies.’”

https://www.medpagetoday.com/hematologyoncology/hematology/107569

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# Agenda

**Module 1: Up-Front Management of Diffuse Large B-Cell Lymphoma (DLBCL) — Dr Salles**

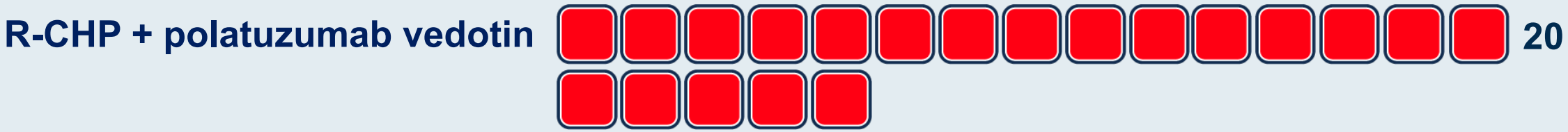
**Module 2: Promising Investigational Approaches to First-Line Therapy for DLBCL — Dr Nowakowski**

**Module 3: Selection and Sequencing of Novel Therapies for Relapsed/Refractory (R/R) DLBCL — Dr Sehn**

**Module 4: Incorporation of CAR T-Cell Therapy into the Management of R/R DLBCL — Dr Westin**

**Module 5: Role of Bispecific Antibodies in the Treatment of DLBCL — Prof Dickinson**

# Which first-line therapy would you generally recommend for an otherwise healthy 65-year-old patient with Stage IV activated B-cell (ABC)-type high-risk DLBCL?




Survey of 20 US-based clinical investigators November 2023

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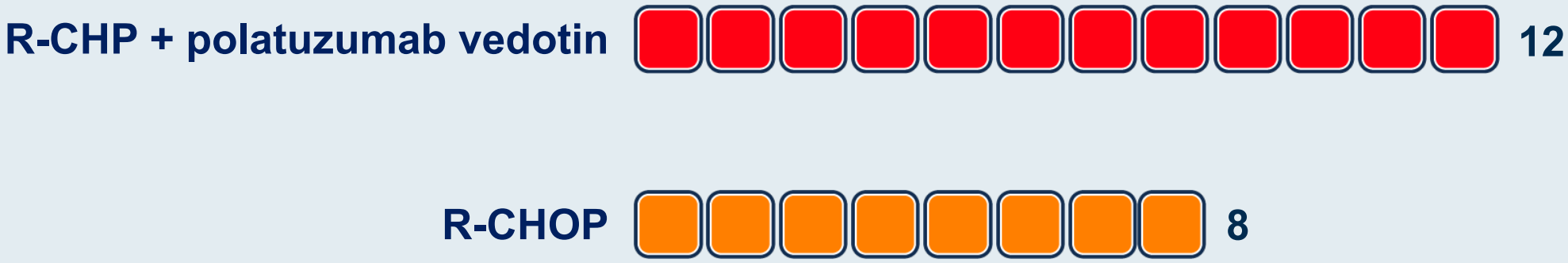
# Which first-line therapy would you generally recommend for an otherwise healthy 65-year-old patient with Stage IV germinal center B-cell (GCB)-type high-risk DLBCL?




Survey of 20 US-based clinical investigators November 2023

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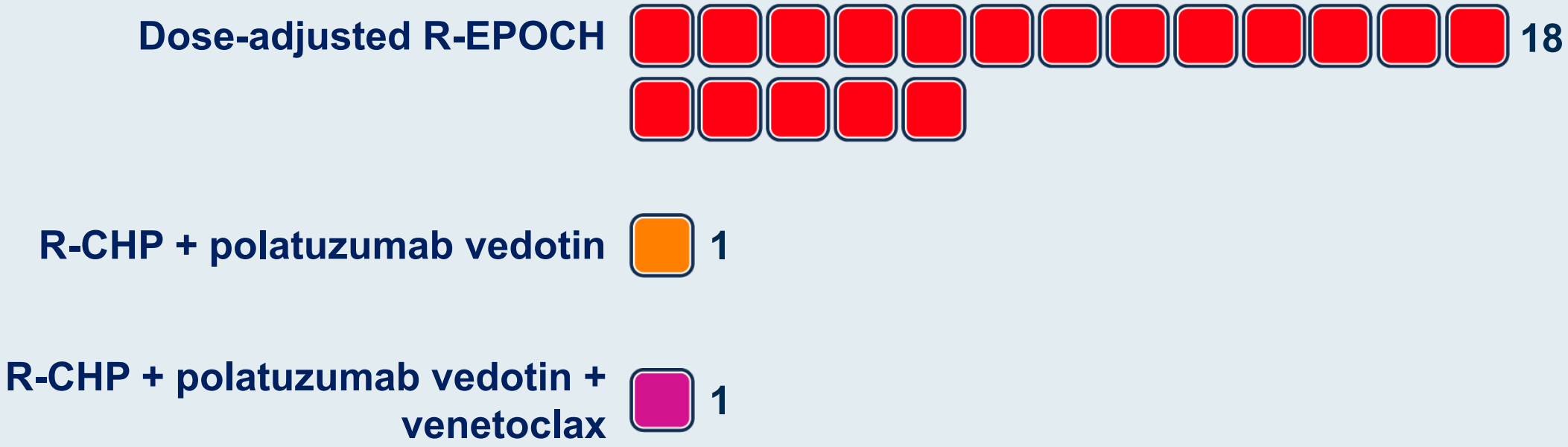
# Which first-line therapy would you generally recommend for an otherwise healthy 65-year-old patient with Stage IV double-hit DLBCL?




R-EPOCH = rituximab/etoposide/prednisone/vincristine/cyclophosphamide/doxorubicin

Survey of 20 US-based clinical investigators November 2023

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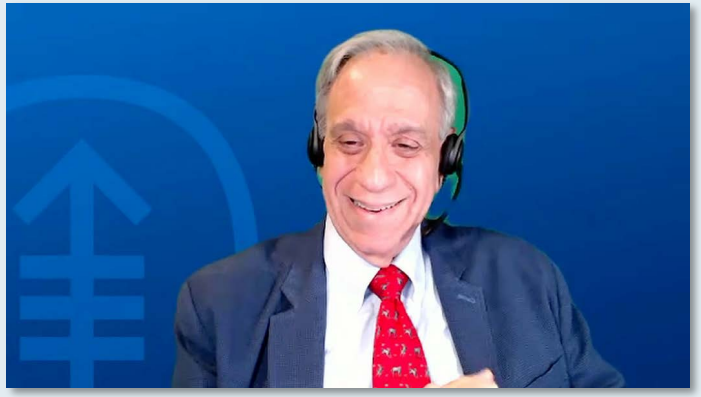
# Incorporation of the POLARIX regimen into clinical practice

Tycel Phillips, MD

Kami Maddocks, MD



Andrew D Zelenetz, MD, PhD

Andrew M Evens, DO, MBA, MSc

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# Selection of up-front therapy for patients with DLBCL

Franck Morschhauser, MD, PhD

Max S Topp, MD

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# Up-Front Management of Diffuse Large B-Cell Lymphoma (DLBCL)

- Key clinical and patient-related factors (eg, age/performance status, comorbidities, cell of origin, molecular profile, extent of disease) influencing the choice of initial therapy for patients with DLBCL
- Published research establishing R-CHOP as the historical standard of care in DLBCL; documented efforts evaluating alternative up-front regimens (eg, dose-adjusted R-EPOCH) or the addition of other systemic therapies (eg, bortezomib, lenalidomide)
- Key efficacy and safety findings from the Phase III POLARIX trial comparing polatuzumab vedotin/R-CHP to R-CHOP for previously untreated DLBCL
- Clinical activity observed with polatuzumab vedotin/R-CHP versus R-CHOP in various patient subsets in POLARIX


## Professor Gilles SALLES

Lymphoma Service
Steven Greenberg Chair
Memorial Sloan Kettering Cancer Center
New York, US

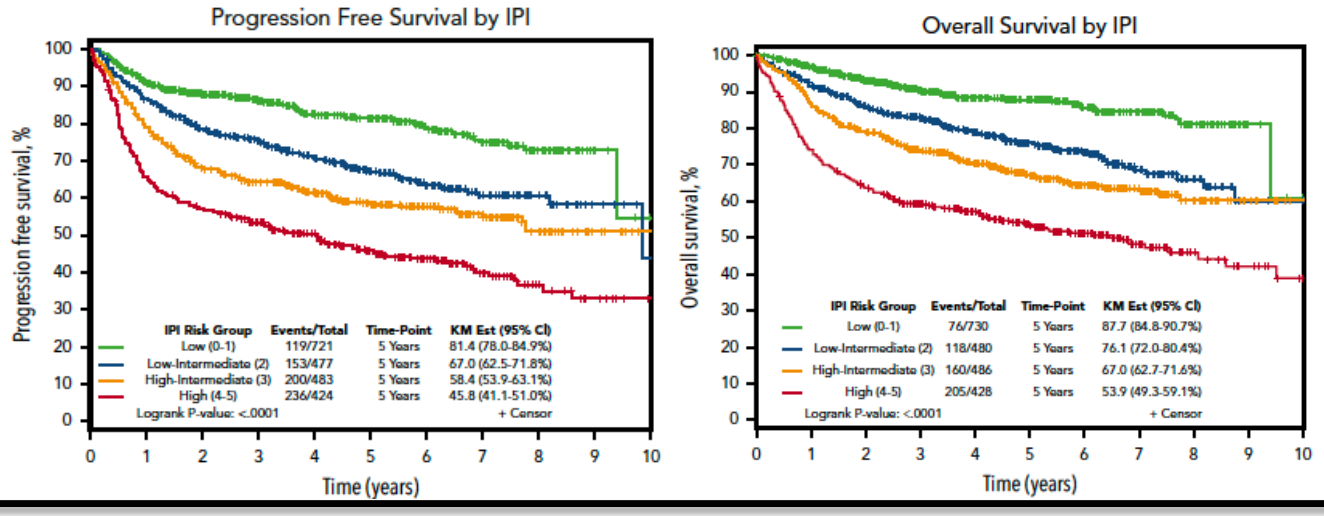
Memorial Sloan Kettering Cancer Center

# International Prognostic Index

## IPI risk factors, 1 point each: a, b

- Age > 60 years
- Serum LDH > normal
- Stage III–IV disease
- ECOG PS 2–4
- Two or more extranodal sites

**L = 0 or 1**
**L–I = 2**
**H–I = 3**
**H = 4 or 5**




**Some variants exist (R-IPI ; NCCN-IPI ; …)**

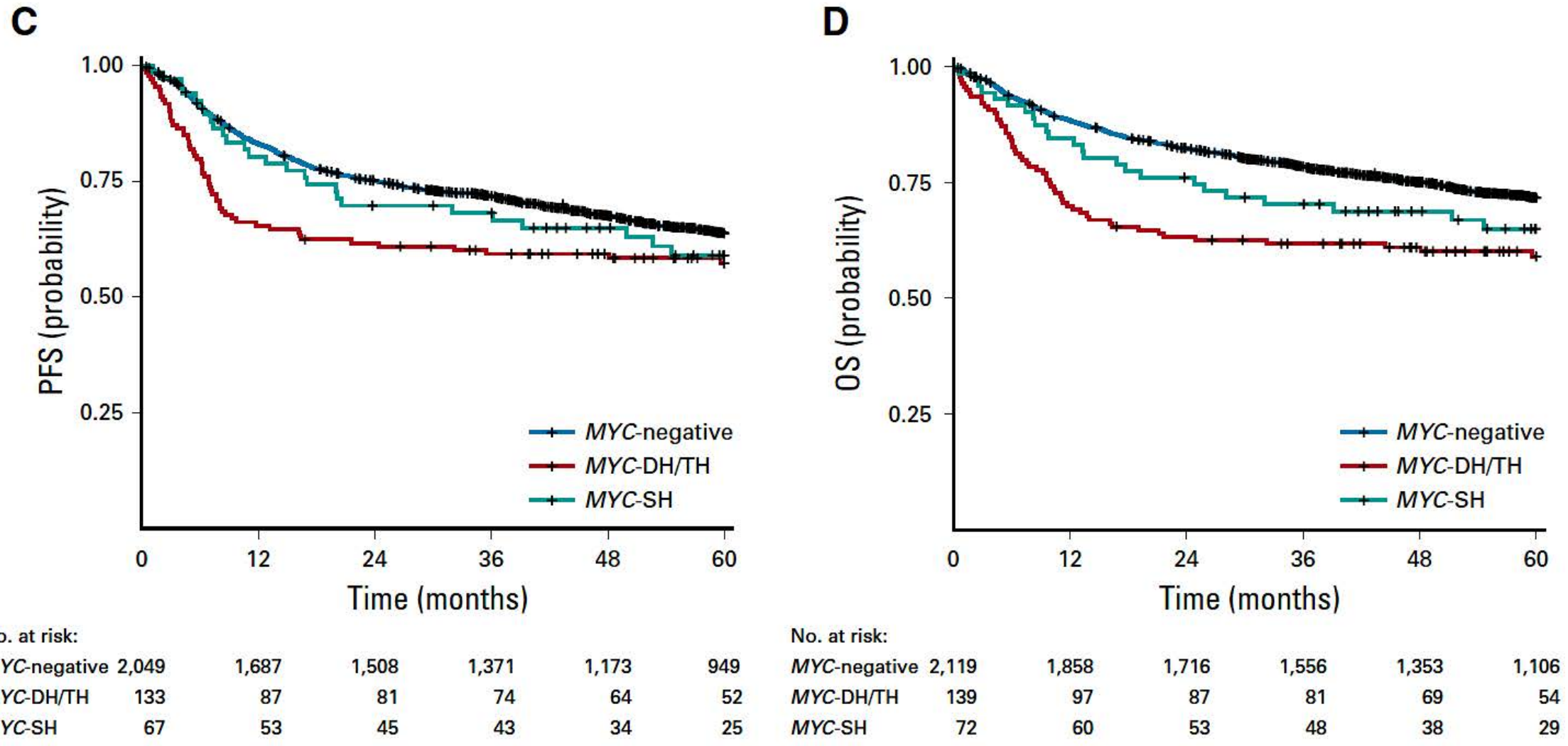
## CNS-IPI risk factors, 1–3 points each c)

- Age > 60 years (1)
- ECOG PS 2–4 (1)
- Serum LDH > normal (1)
- Two or more extranodal sites (1)
- Stage III–IV disease (1)
- Kidney or Adrenal involvement (1)

| | *2-y CNS recurrence risk* |
|---|---|
| L (46%)= 0 or 1 | *0.6% (0% to 1.2%)* |
| I (41%) = 2 or 3 | 3.4% (2.2% to 4.4%) |
| H (12%) = 4 to 6 | *10.2% (6.3% to 14.1%)* |


a) The International NHL Prognostic Factors Project. N Engl J Med. 1993;329:987–94 ; b) Ruppert AS et al. Blood. 2020 Jun 4;135(23):2041-2048 ; c) Schmitz N et al., J Clin Oncol. 2016 Sep 10;34(26):3150-6

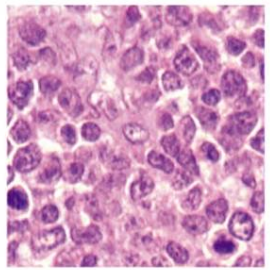
# Double-hit (MYC/BCL2) and triple-hit lymphoma

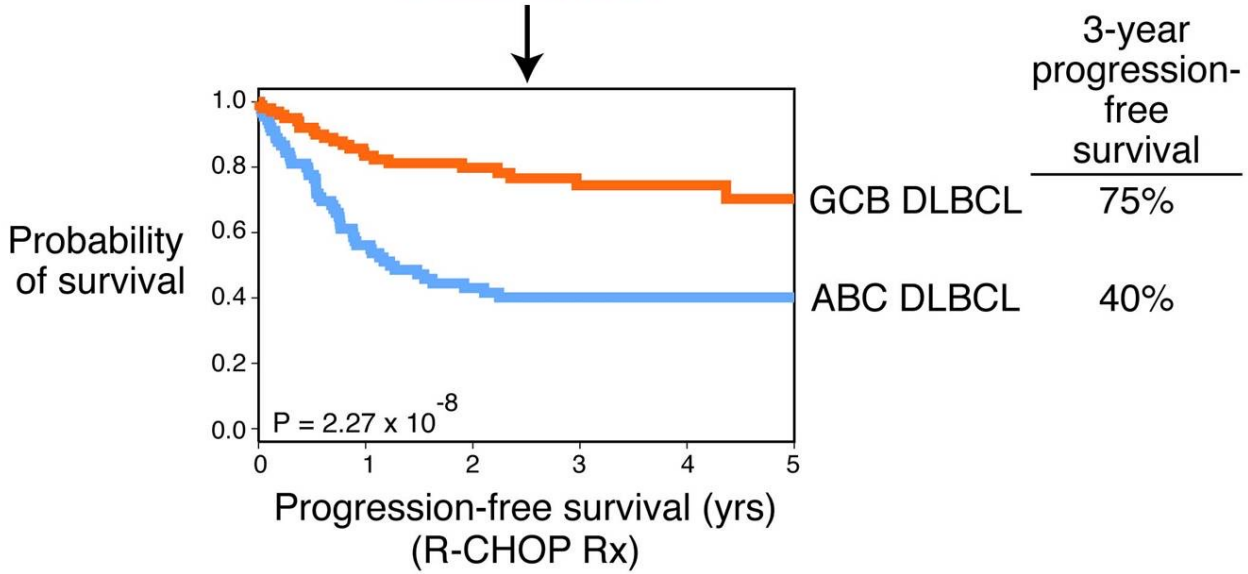



Rosenwald A, et al. J Clin Oncol. 2019 Dec 10;37(35):3359-3368

# Dissecting Cancer Into Molecularly and Clinically Distinct Subtypes by Gene Expression Profiling

Diffuse Large B Cell Lymphoma (DLBCL)



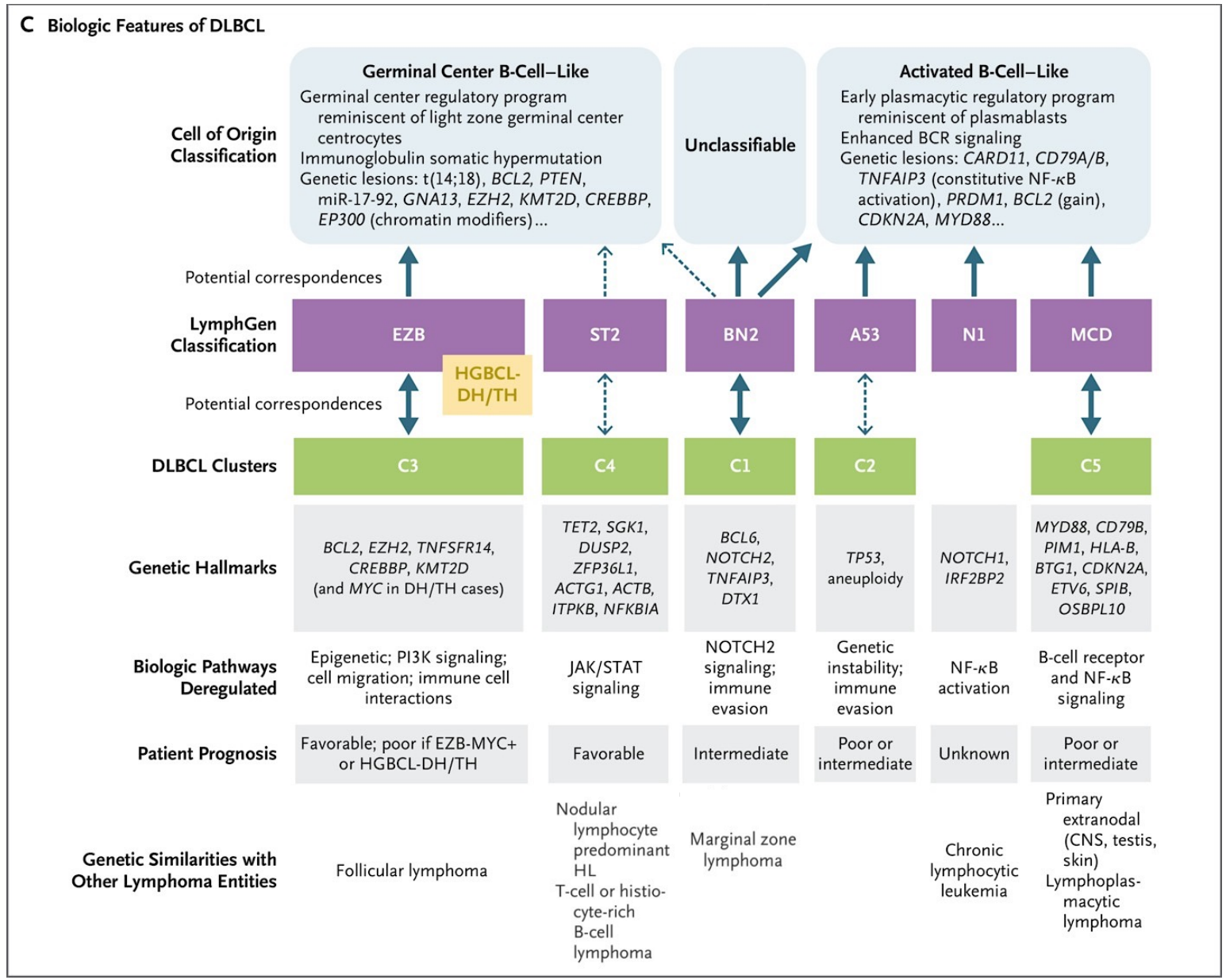



| | 3-year progression-free survival |
|---|---|
| GCB DLBCL | 75% |
| ABC DLBCL | 40% |

Subtype-specific response To chemotherapy

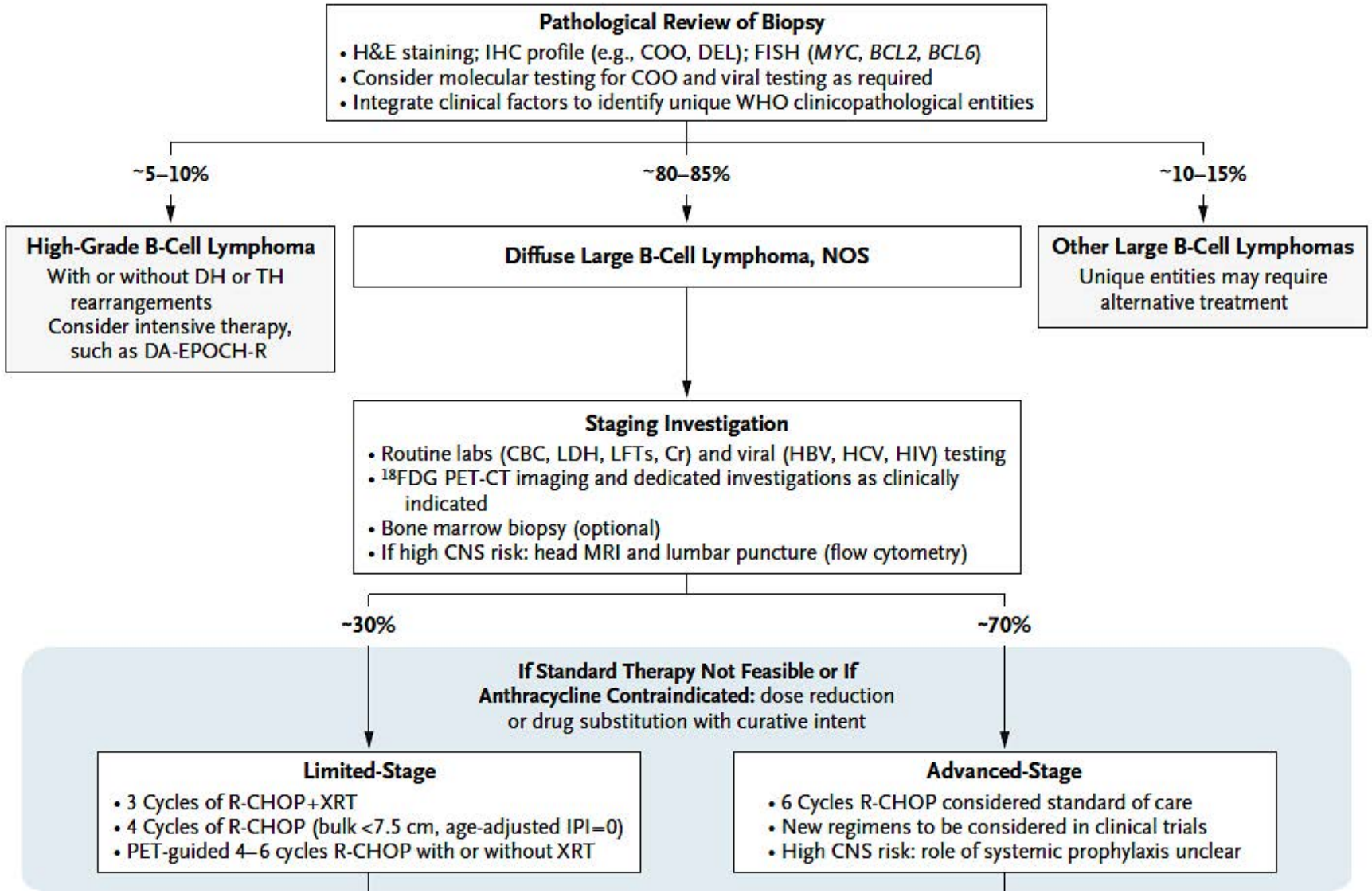
Presented By Louis Staudt at 2016 ASCO Annual Meeting

# Diffuse Large B-Cell Lymphoma (DLBCL): Biologic Features




Sehn LH, Salles G. *N Engl J Med.* 2021;384:842–858.

# Management of newly diagnosed DLBCL




Sehn LH, Salles G. *N Engl J Med.* 2021;384:842–858.

# GELA study: 10-year follow-up
## (patients 60 to 80 years at inclusion)

**Figure 3. Event-free survival**

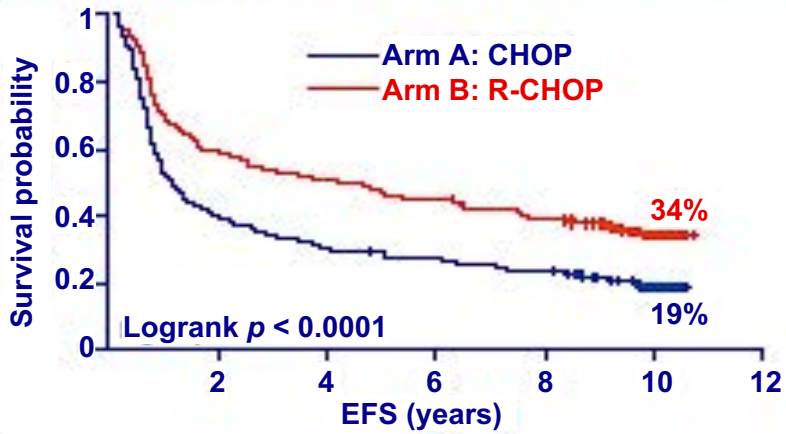



**Figure 4. Progression-free survival**

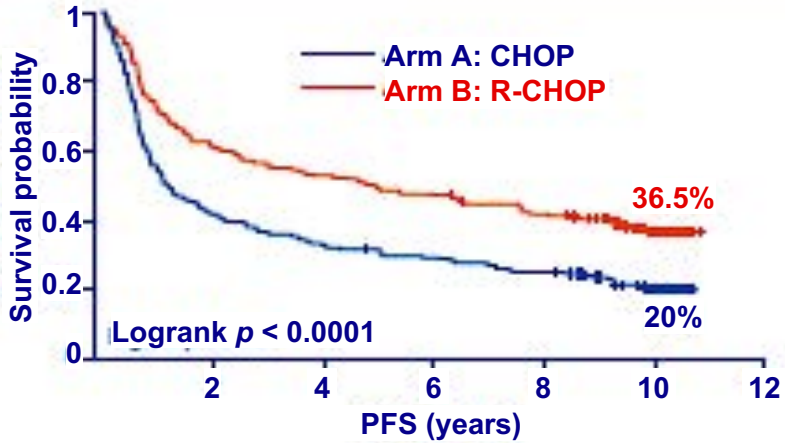



**Figure 5. Disease-free survival for patients in CR**

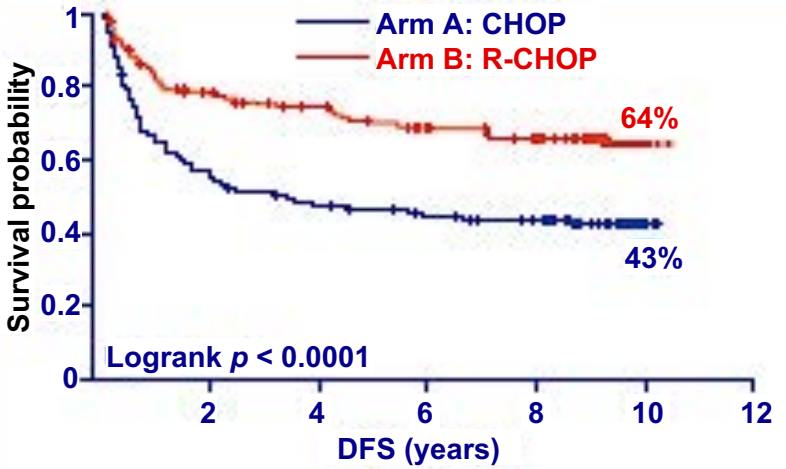
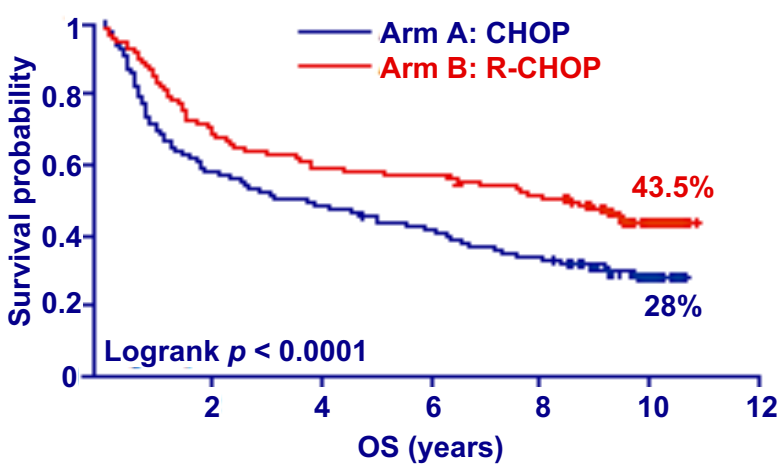


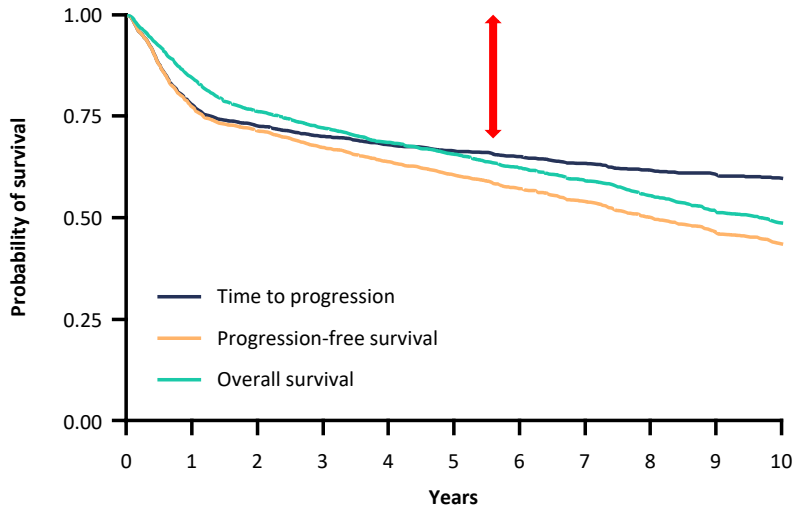

**Figure 6. Overall survival**




*B Coiffier et al., Blood 2010*

# DLBCL: Other attempts to improve R-CHOP

**R-CHOP-21**




**Intensify therapy:**
*ASCT[1], CHOP-14[2], ACVBP[3], DA-R-EPOCH[4]*

**Add a new targeted agent:**
*bortezomib[5], ibrutinib[6] and lenalidomide[7]*

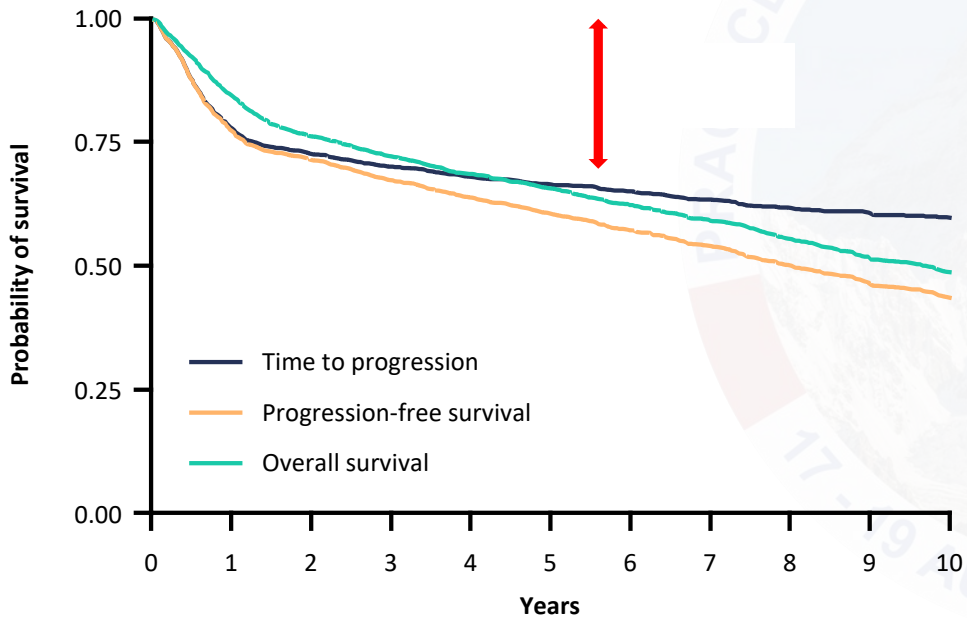
**Consolidate with maintenance**
*rituximab[8], lenalidomide[9], enzastaurin[10], everolimus[11]*

**Replace one component**
*bortezomib[12], obinutuzumab[13]*

*1: Schmitz 2012; Stiff, 2013 ; Chiapella 2017 ; 2: Cunningham, 2013 ; Delarue 2013; 3 Recher 2011; 4: Bartlett, 2019 ; 5: Leonard, 2019 ; Davies, 2019 ; 6: Younes, 2019 ; 7: Nowakowski, 2021 ; 8: Habberman, 2006; Jaeger, 2015 ; 9 :Thieblemont 2017 ; 10: Crump 2018 ; 11: Witzig 208 ; 12: Offner 205 ; 13 : Vitolo, 2017.*

# DLBCL: Other attempts to improve R-CHOP

## R-CHOP-21




**8 cycles R-CHOP= 6 cycles R-CHOP**[14]

**Intensify therapy:**
*ASCT*[1], *CHOP-14*[2], *ACVBP*[3], *DA-R-EPOCH*[4]

**Add a new targeted agent:**
*bortezomib*[5], *ibrutinib*[6]
*and lenalidomide*[7]

**Consolidate with maintenance**
*rituximab*[8], *lenalidomide*[9],
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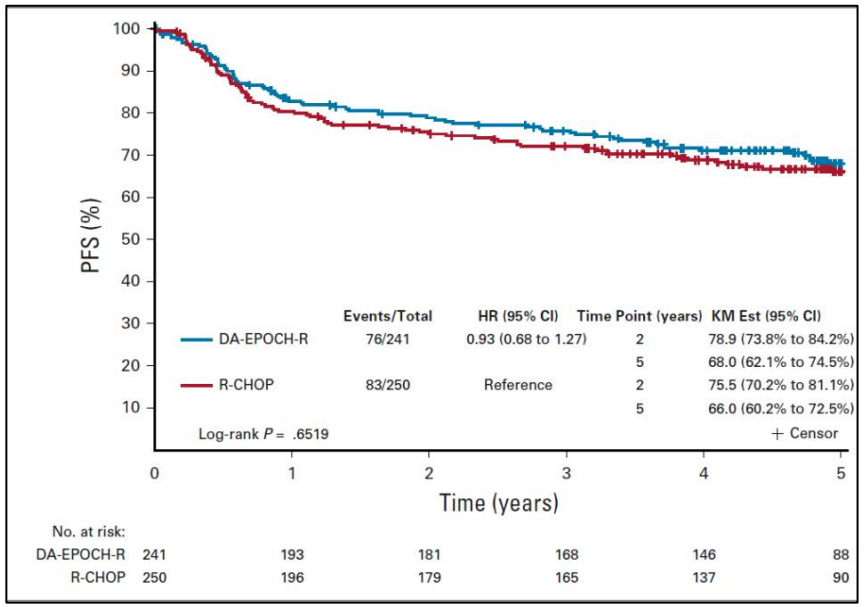
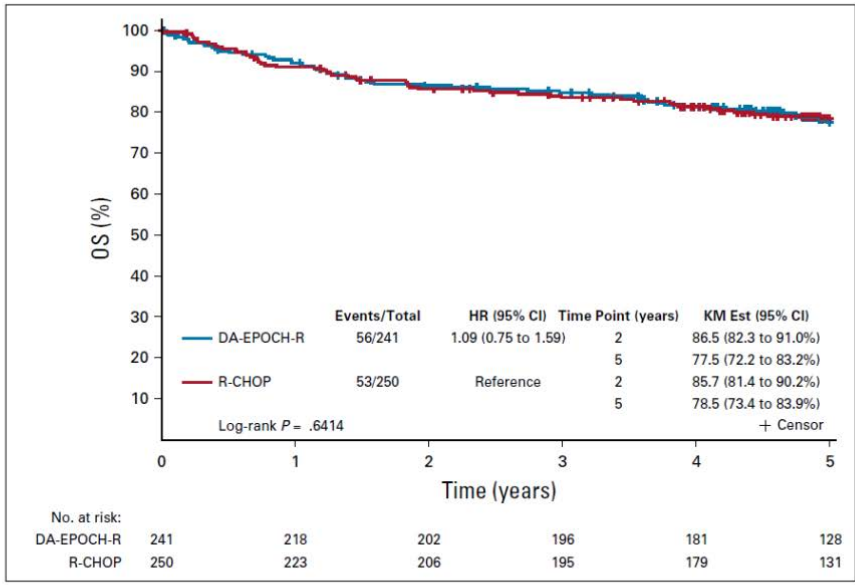
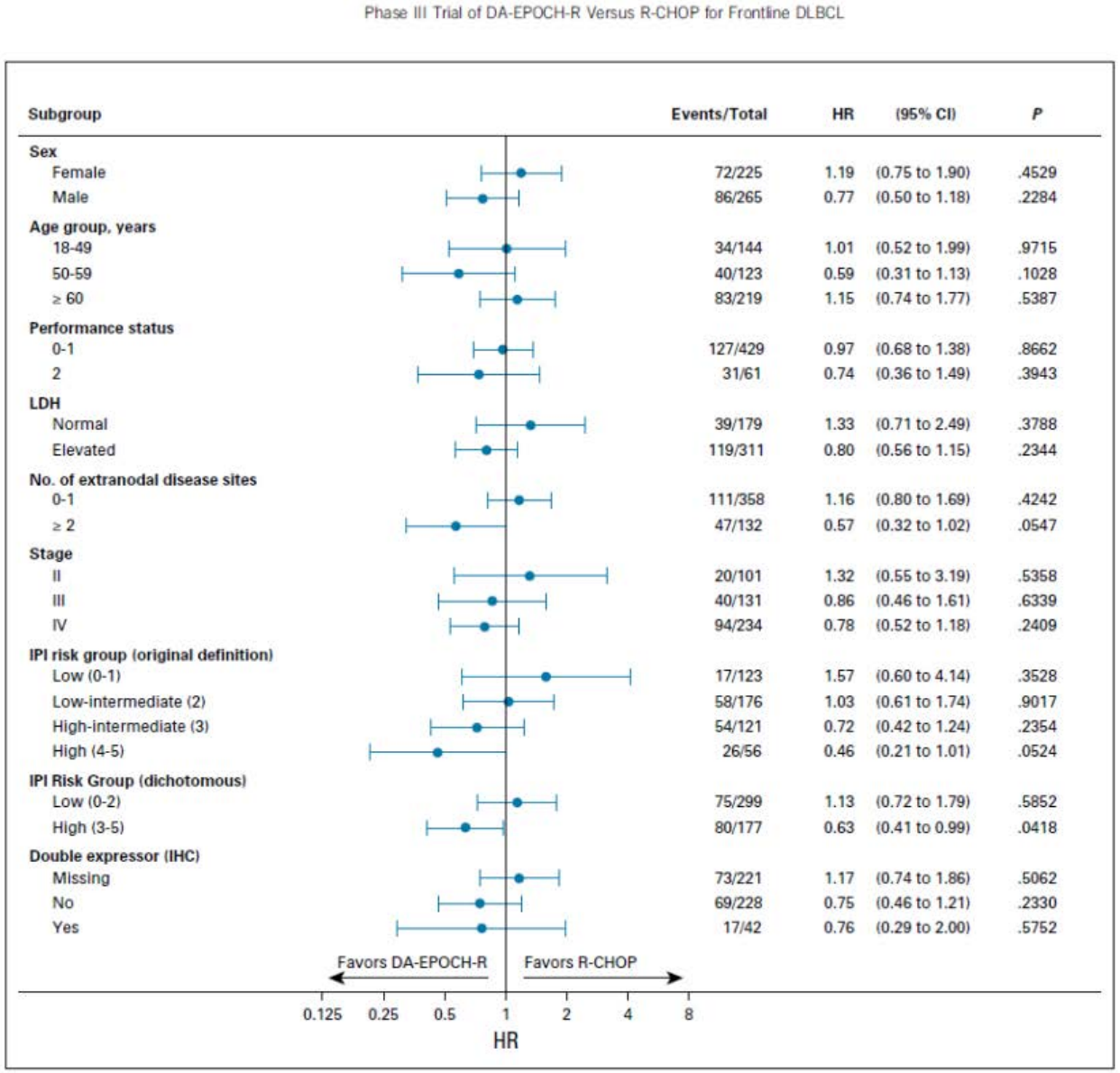
*7: Nowakowski, 2021 ; 8: Habberman, 2006; Jaeger, 2015 ; 9 :Thieblemont 2017 ; 10: Crump 2018 ; 11: Witzig 208 ; 12: Offner 205 ; 13 : Vitolo, 2017; 14: Pfreundschuh 2008; Sehn 2018.*

# DA-EPOCH-R vs R-CHOP: Phase III trial

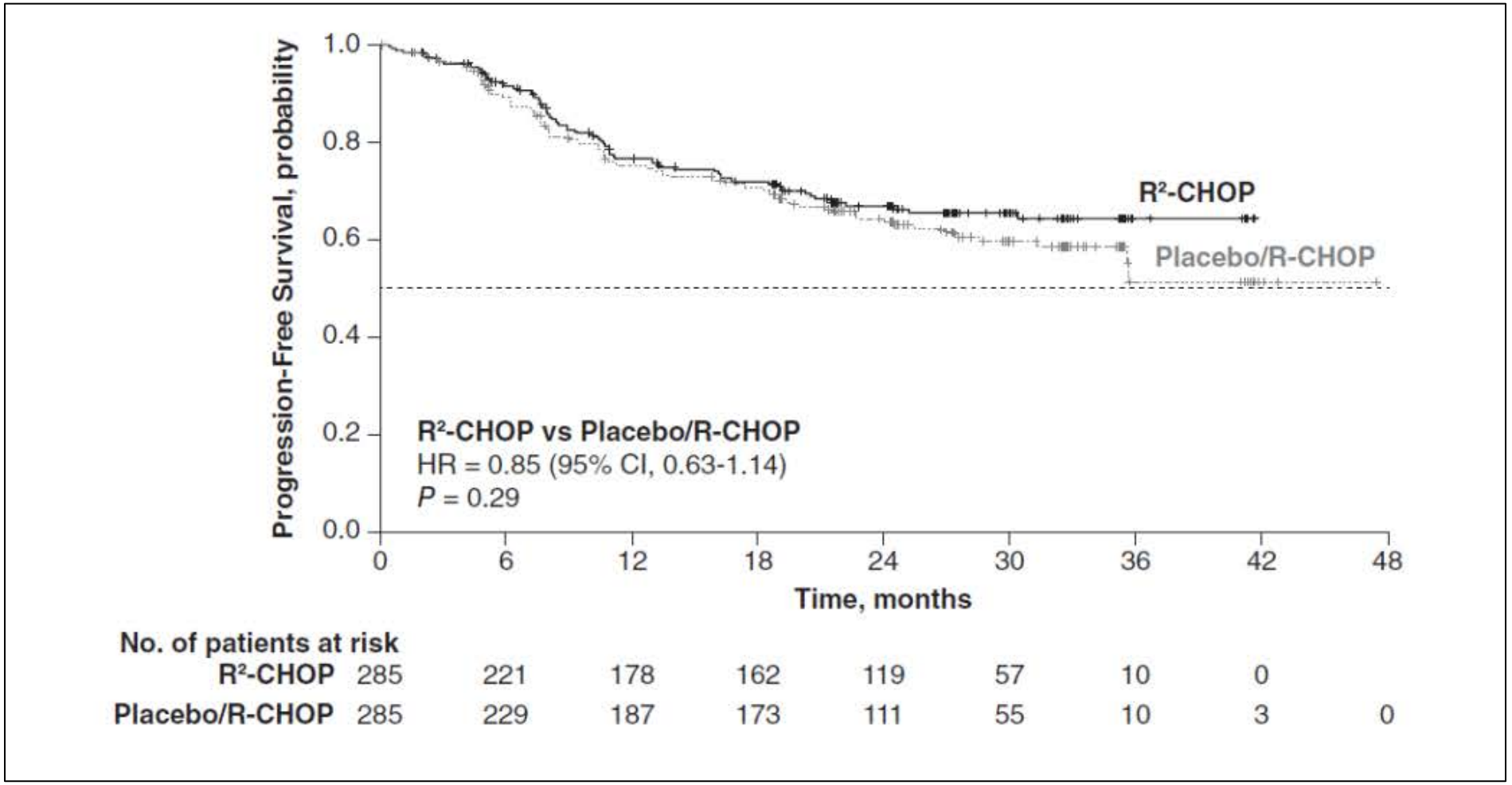


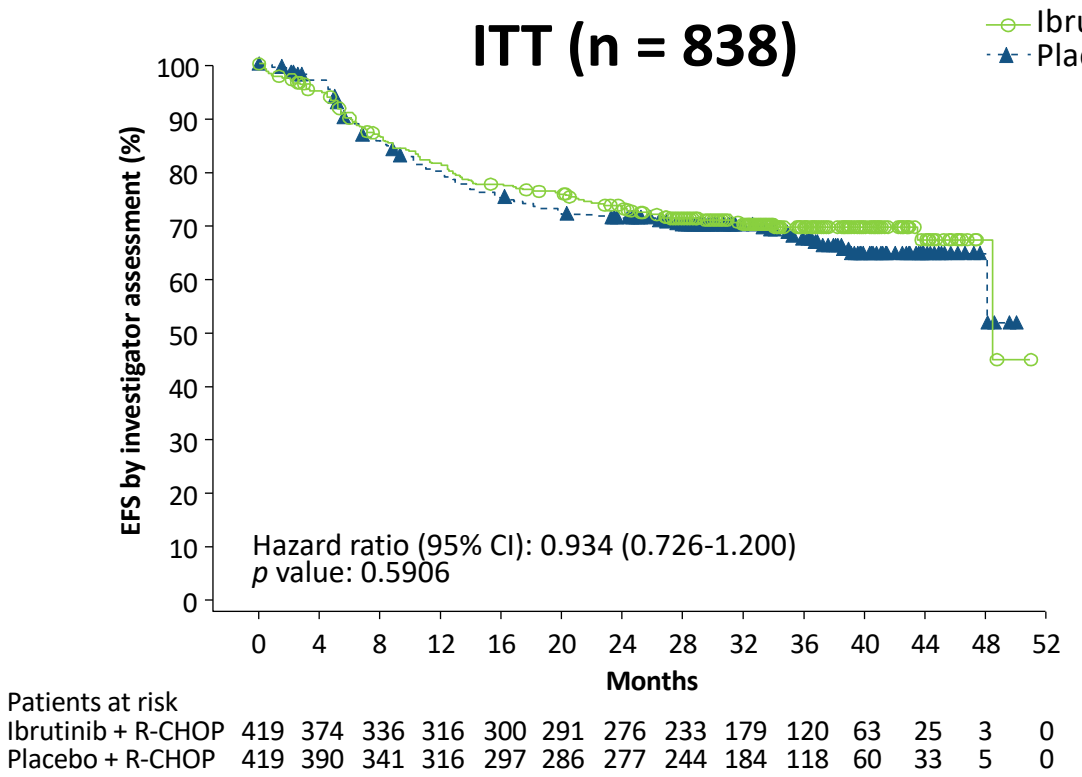

Bartlett NL et al. *J Clin Oncol*. 2019;37(21):1790-1799.

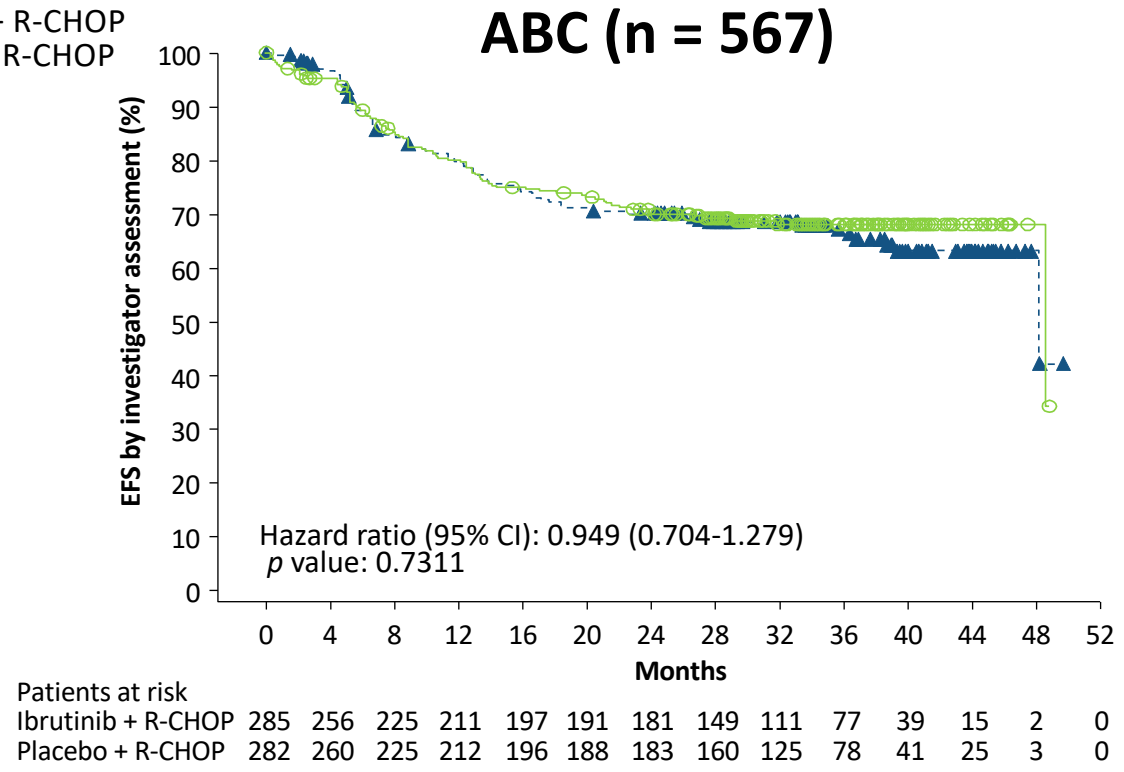
# ROBUST: Phase III randomized study of lenalidomide/R-CHOP ($R^2$-CHOP) vs placebo/R-CHOP in previously untreated ABC-type DLBCL




Vitolo U et al. 2019; Nowakowski GS et al. *J Clin Oncol*. 2021;39(12):1317-1328.

# PHOENIX: R-CHOP +/- Ibrutinib in Newly Diagnosed Non-GCB DLBCL
# Phase 3, double-blind, placebo-controlled



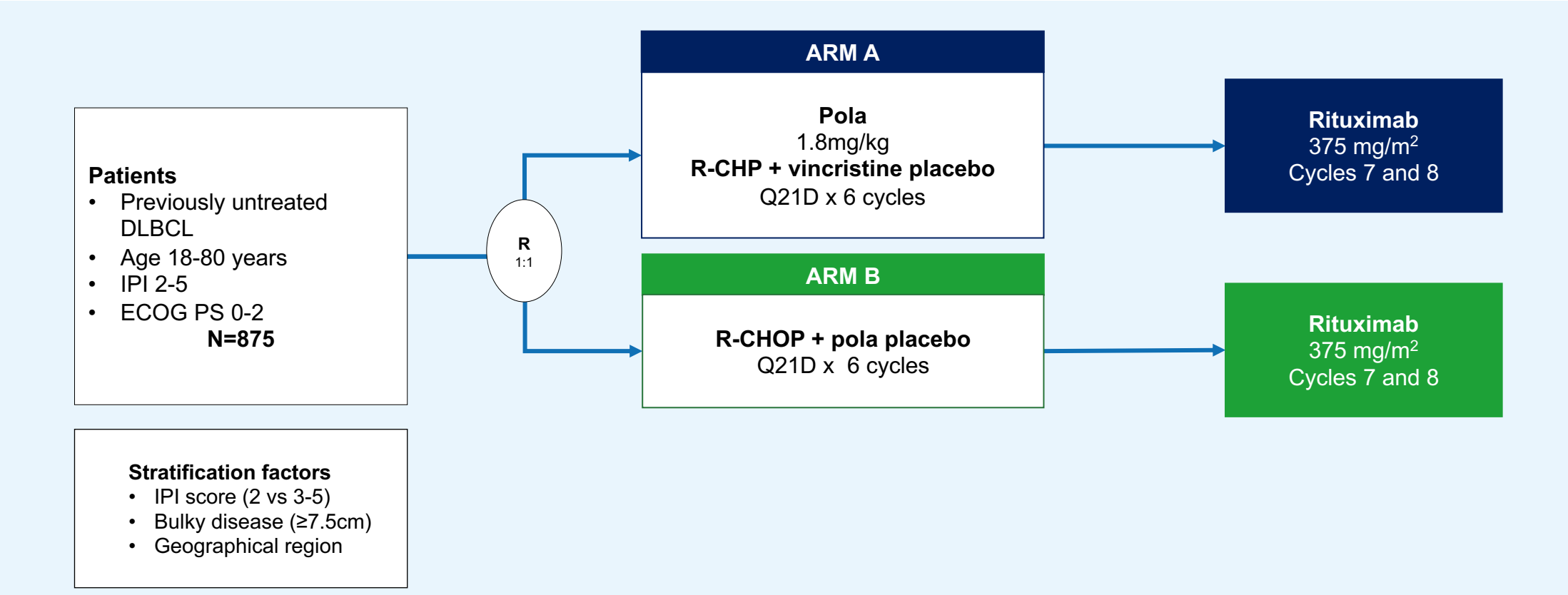




- **Overall response (89.3% vs 93.1%) and CR rates (67.3% vs 68.0%) were similar**

Younes A et al. *J Clin Oncol*. 2019;37(15):1285-1295.

# POLARIX: Study Design

A double-blinded, phase 3, placebo-controlled trial

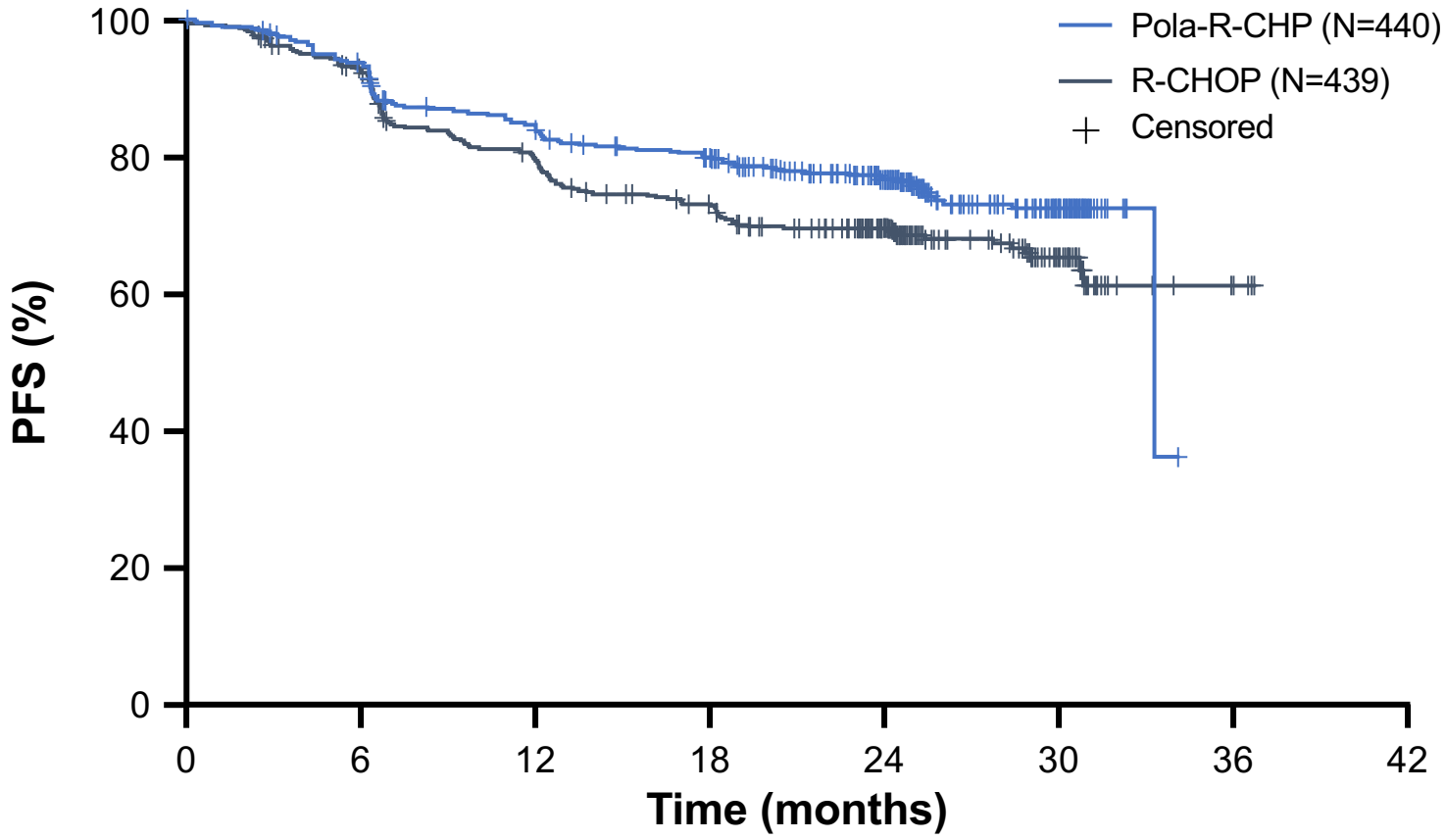



ECOG PS, Eastern Cooperative Oncology Group Performance Status; IPI, international prognostic index; LYSA, Lymphoma Study Association; LYSARC, Lymphoma Academic Research Organisation; Q21D, every 21 days; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; R-CHP, rituximab, cyclophosphamide, doxorubicin, and prednisone.

Collaboration with LYSA and LYSARC

# POLARIX Primary Endpoint: Progression-Free Survival

## Pola-R-CHP Significantly Improved PFS Versus R-CHOP




**No. of patients at risk**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pola-R-CHP | 440 | 404 | 353 | 327 | 246 | 78 | NE | NE |
| R-CHOP | 439 | 389 | 330 | 296 | 220 | 78 | 3 | NE |

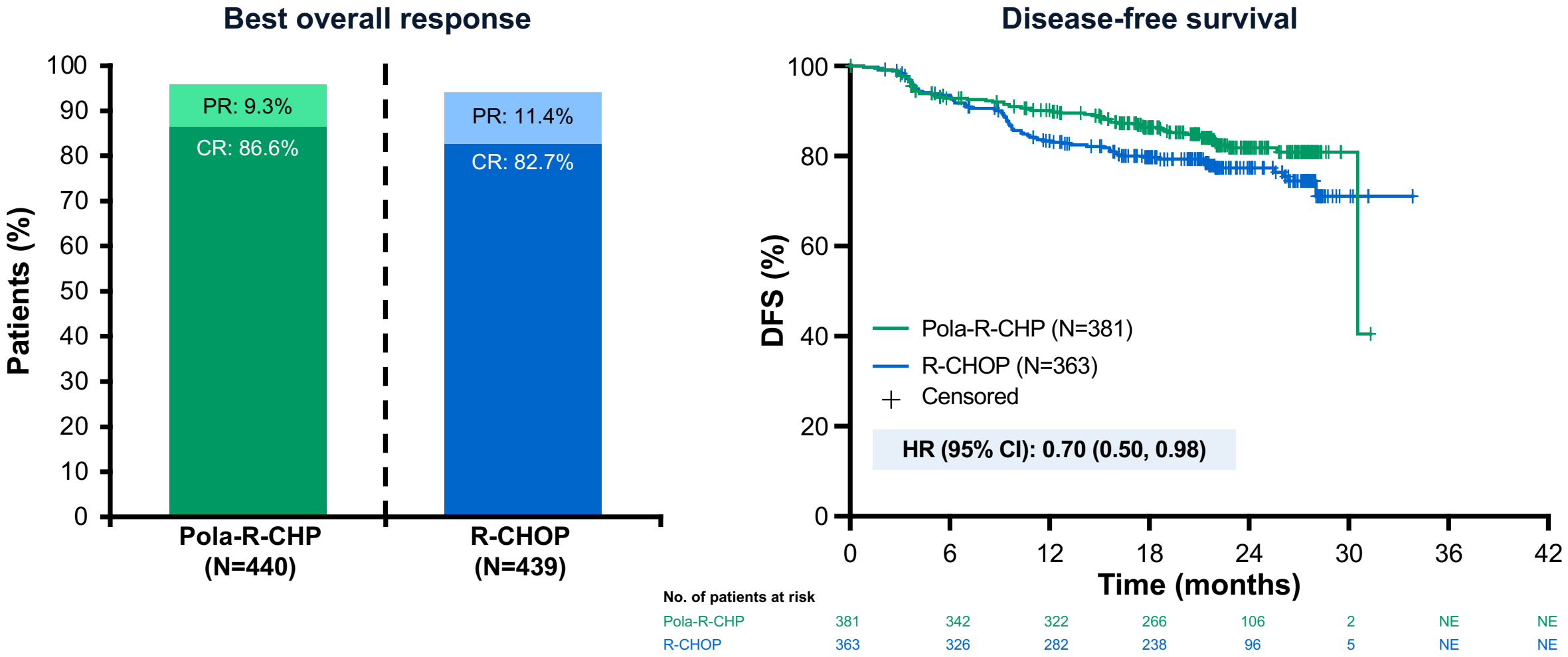
**HR 0.73** **95% CI, 0.57, 0.95**

- 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%**)

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.
NE, not evaluable.

Tilly H et al. *N Engl J Med*. 2022;386(4):351-363.

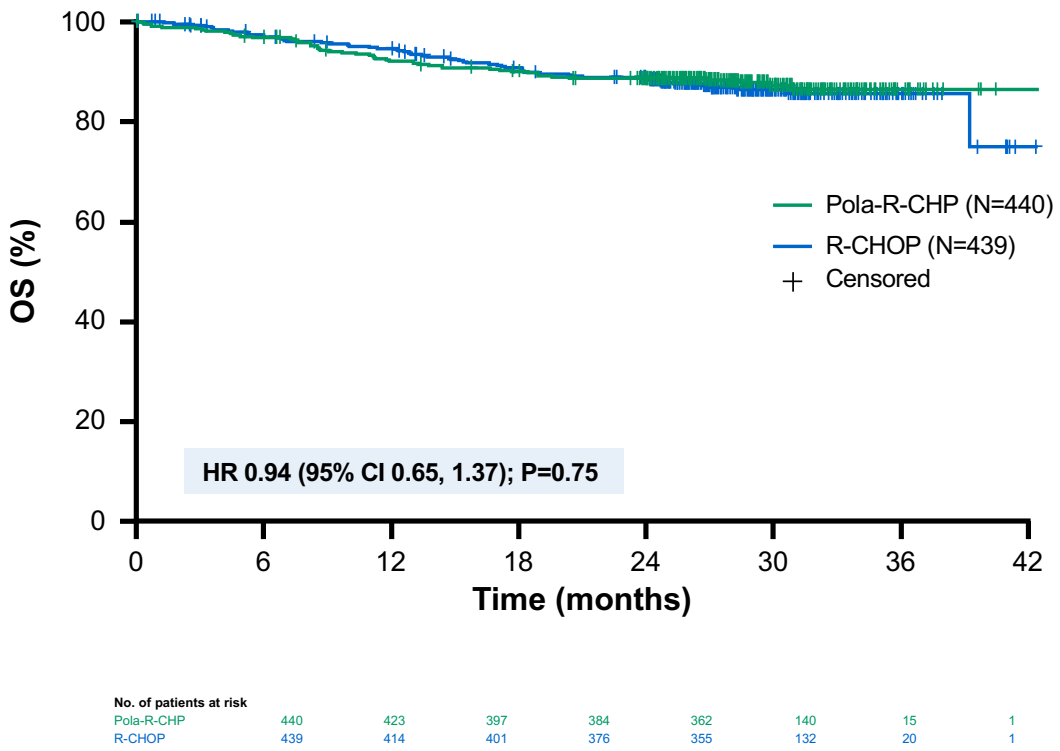
# POLARIX: Response Rates and Disease-Free Survival



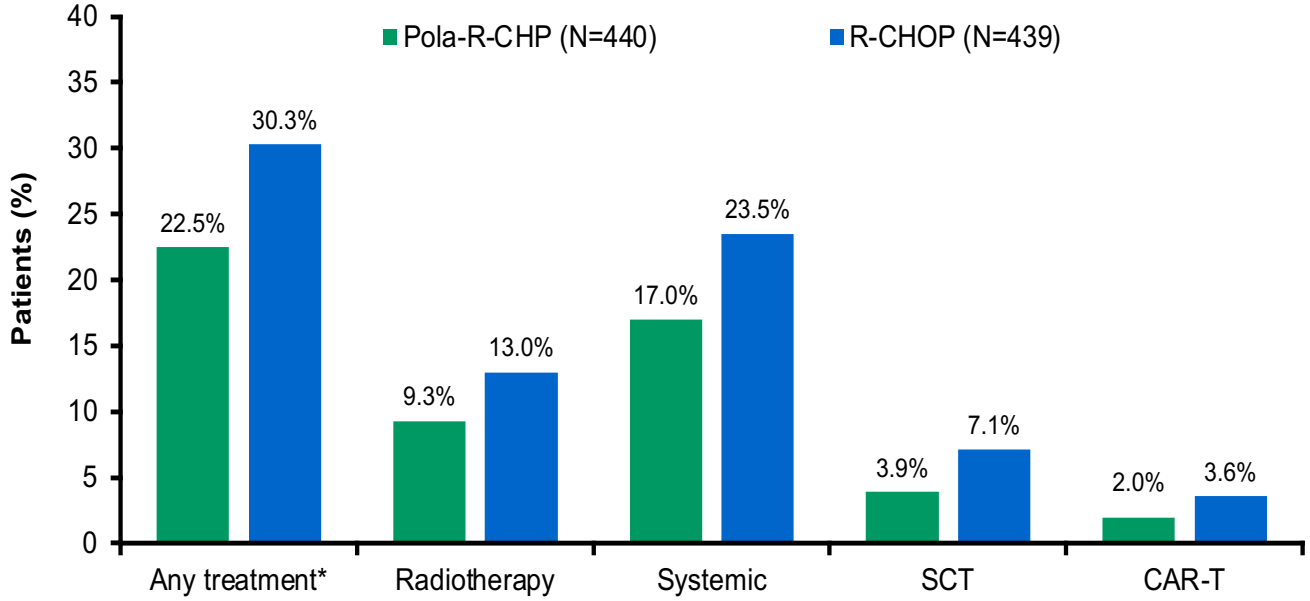

ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up. Disease-free survival (DFS) defined as the time from the date of the first occurrence of a documented complete response to the date of progression, relapse, or death from any cause for the subgroup of patients with a best overall response of CR.

Tilly H et al. *N Engl J Med*. 2022;386(4):351-363.

# POLARIX: Overall Survival

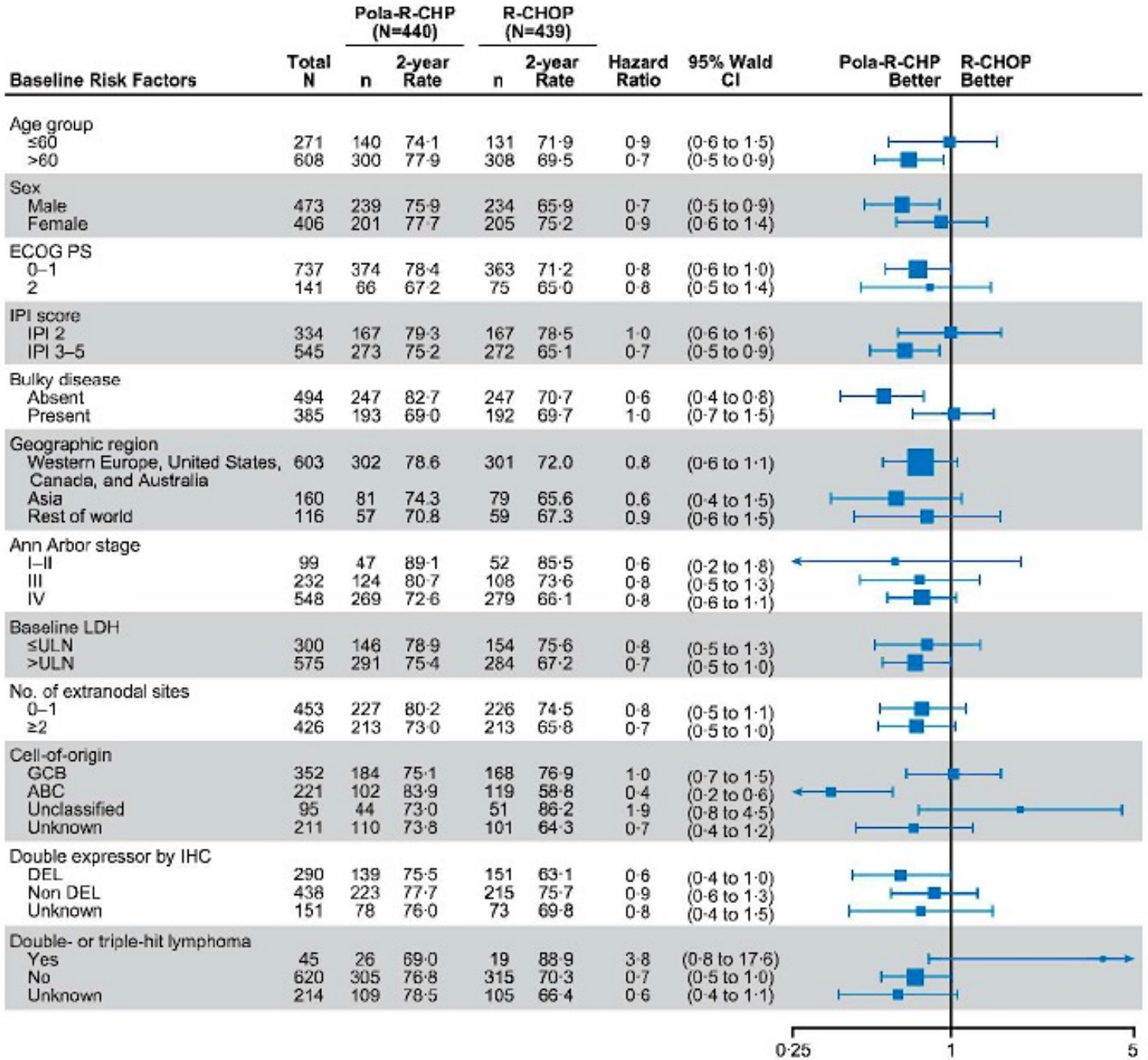



## Patients receiving subsequent treatments

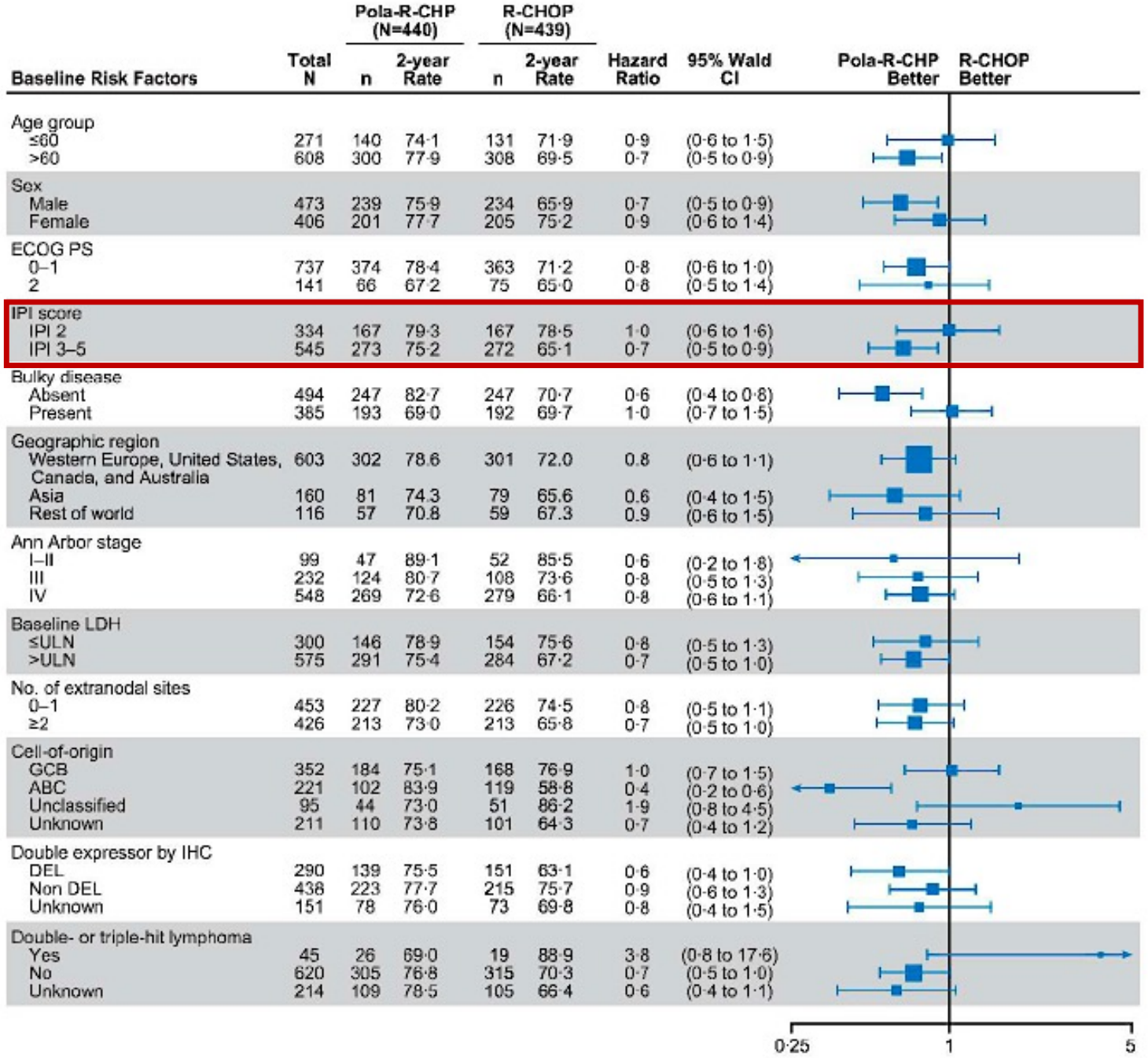



ITT population. Data cut-off: June 28, 2021; median 28.2 months' follow-up.

Tilly H et al. *N Engl J Med*. 2022;386(4):351-363.




Tilly H et al. *N Engl J Med*. 2022;386(4):351-363.



| 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 | | | | | | | |
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| No. of extranodal sites | | | | | | | |
| 0–1 | 453 | 227 | 80·2 | 226 | 74·5 | 0·8 | (0·5 to 1·1) |
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| ABC | 221 | 102 | 83·9 | 119 | 58·8 | 0·4 | (0·2 to 0·6) |
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| 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) |
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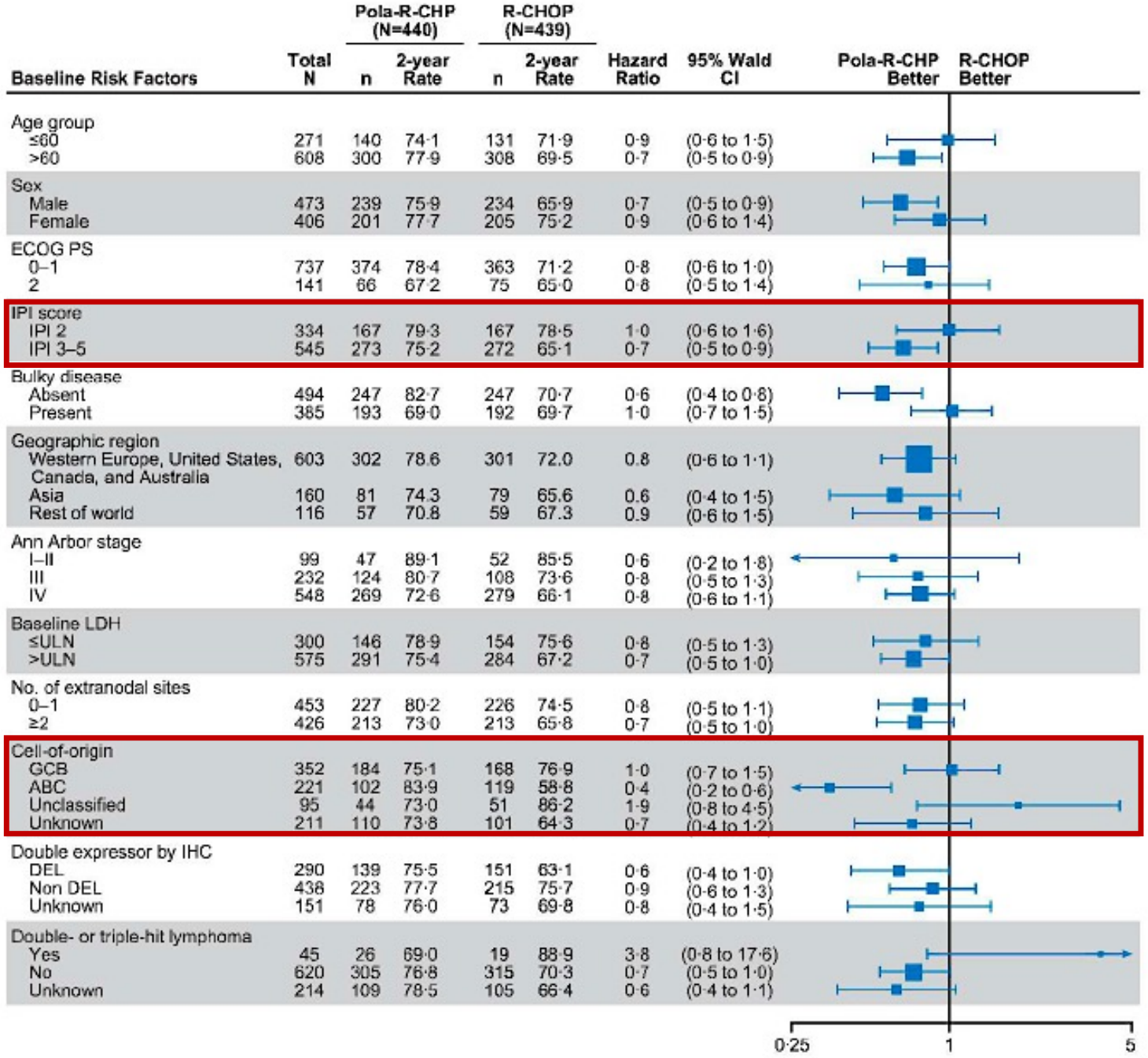
**10% PFS difference in pts with IPI 3-5**

Tilly H et al. *N Engl J Med*. 2022;386(4):351-363.



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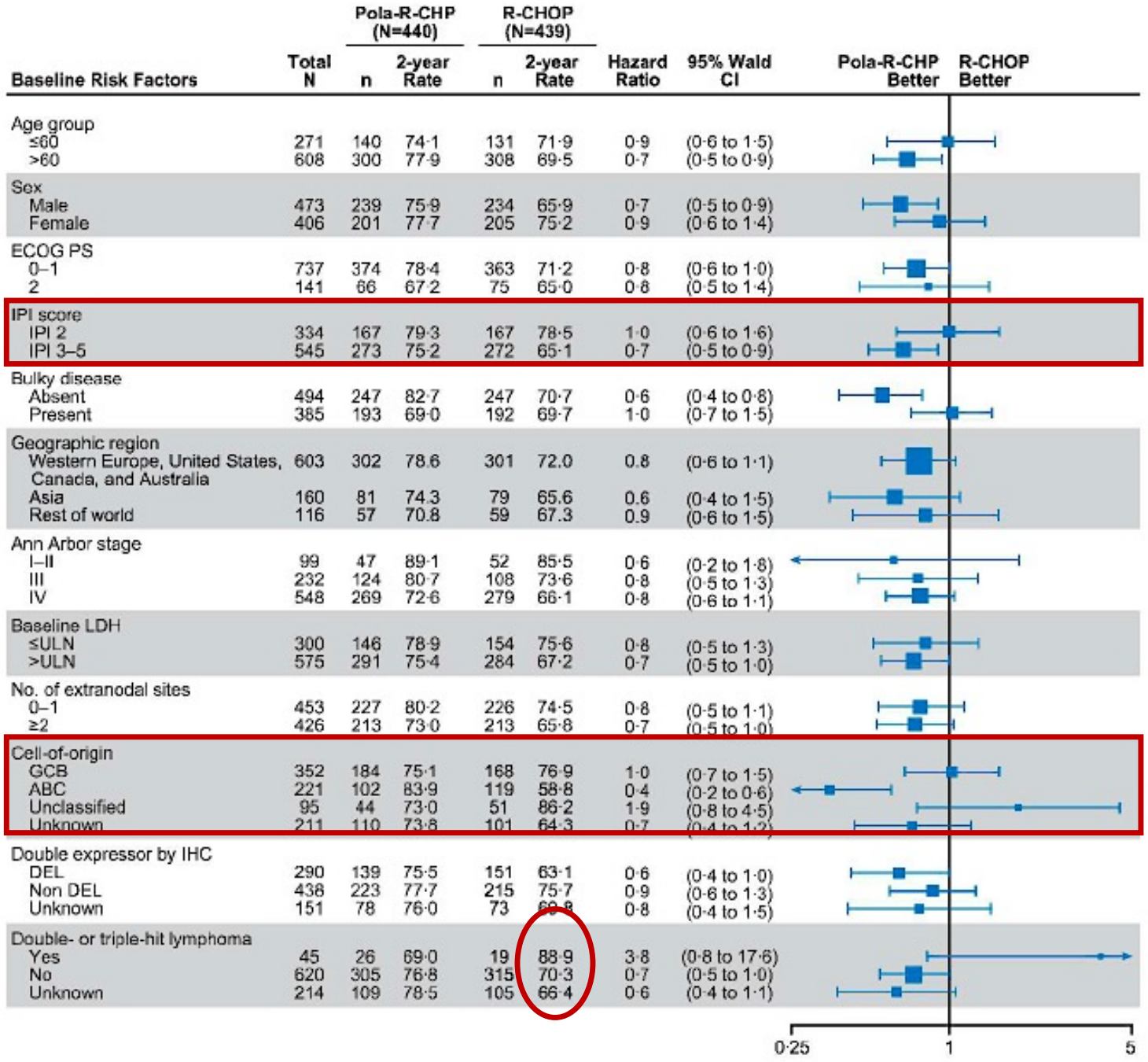
**10% PFS difference in pts with IPI 3-5**

**15% PFS difference in pts with ABC DLBCL**

Tilly H et al. *N Engl J Med*. 2022;386(4):351-363.

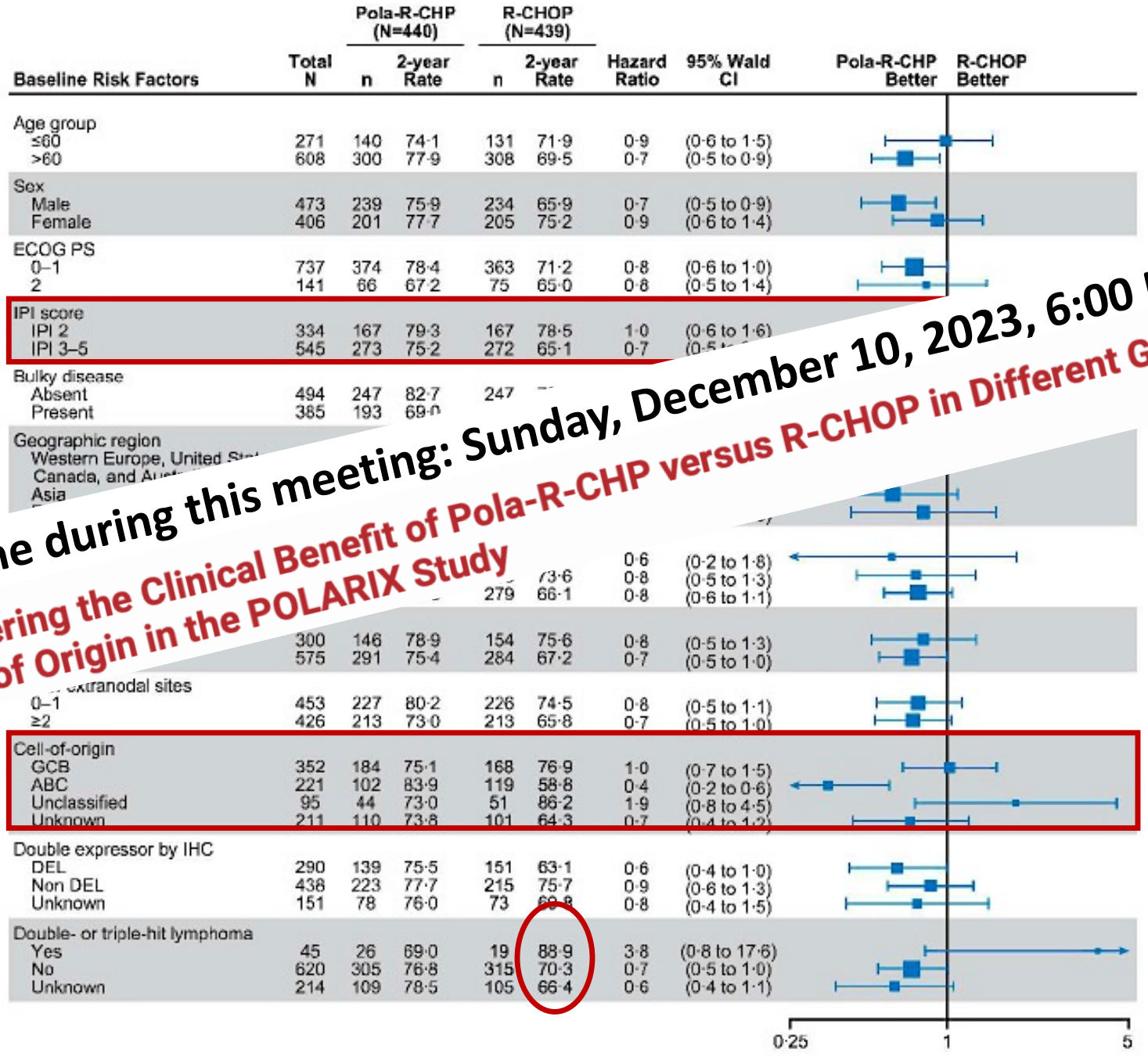



**10% PFS difference in pts with IPI 3-5**

**15% PFS difference in pts with ABC DLBCL**

**Unusual outcome for control arm pts with DH/TH**

Tilly H et al. *N Engl J Med*. 2022;386(4):351-363.




**More to come during this meeting: Sunday, December 10, 2023, 6:00 PM-8:00 PM**

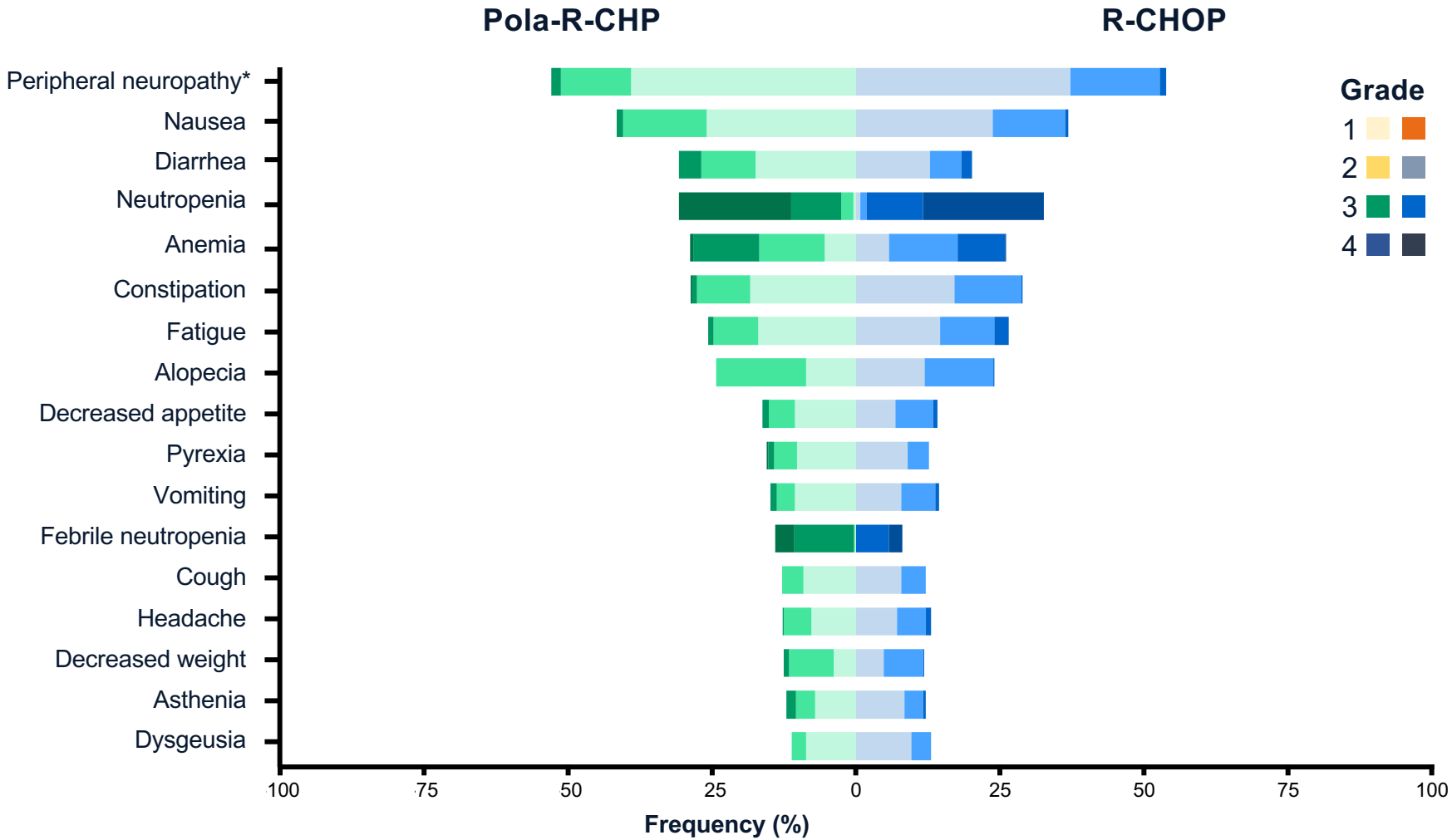
**3000 Deciphering the Clinical Benefit of Pola-R-CHP versus R-CHOP in Different Genetic Subtypes Beyond Cell of Origin in the POLARIX Study**

**15% PFS difference in pts with ABC DLBCL**

**Unusual outcome for control arm pts with DH/TH**

Tilly H et al. *N Engl J Med*. 2022;386(4):351-363.

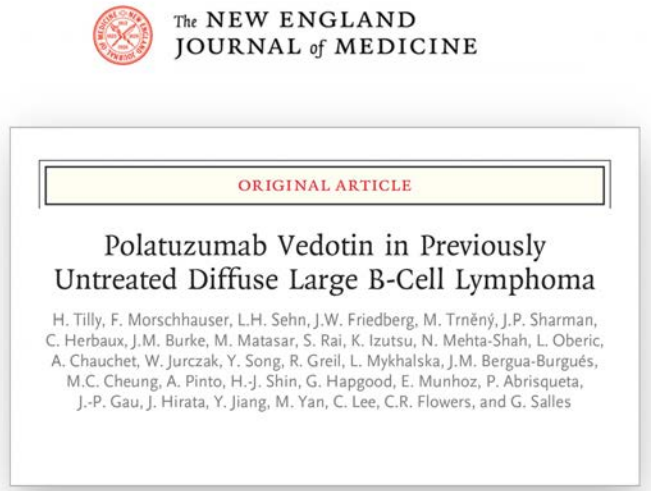
# POLARIX: Common Adverse Events




Data cut-off: June 28, 2021. Adverse events are Medical Dictionary for Regulatory Activities version 24.0 preferred terms; shown are all-grade adverse events occurring in ≥12% of patients in any treatment arm. *Peripheral neuropathy is defined by standard organ class group of preferred terms.

Tilly H et al. *N Engl J Med*. 2022;386(4):351-363.

# POLARIX: Conclusions




**Pola-R-CHP significantly prolongs PFS** compared with R-CHOP (HR 0.73) in patients with intermediate- and high-risk previously untreated DLBCL

The **safety profiles** of Pola-R-CHP and R-CHOP were **comparable**

**Exploratory analyses** are ongoing with regards to various subgroups and other prognostic classification systems

These results **support the use of Pola-R-CHP** in the initial management of patients with DLBCL

Tilly H et al, NEJM 2022

# Agenda

**Module 1: Up-Front Management of Diffuse Large B-Cell Lymphoma (DLBCL) — Dr Salles**

**Module 2: Promising Investigational Approaches to First-Line Therapy for DLBCL — Dr Nowakowski**

**Module 3: Selection and Sequencing of Novel Therapies for Relapsed/Refractory (R/R) DLBCL — Dr Sehn**

**Module 4: Incorporation of CAR T-Cell Therapy into the Management of R/R DLBCL — Dr Westin**

**Module 5: Role of Bispecific Antibodies in the Treatment of DLBCL — Prof Dickinson**

RTP RESEARCH TO PRACTICE

# Which first-line therapy would you generally recommend for an otherwise healthy 80-year-old patient with Stage IV ABC-type high-risk DLBCL?


Survey of 20 US-based clinical investigators November 2023

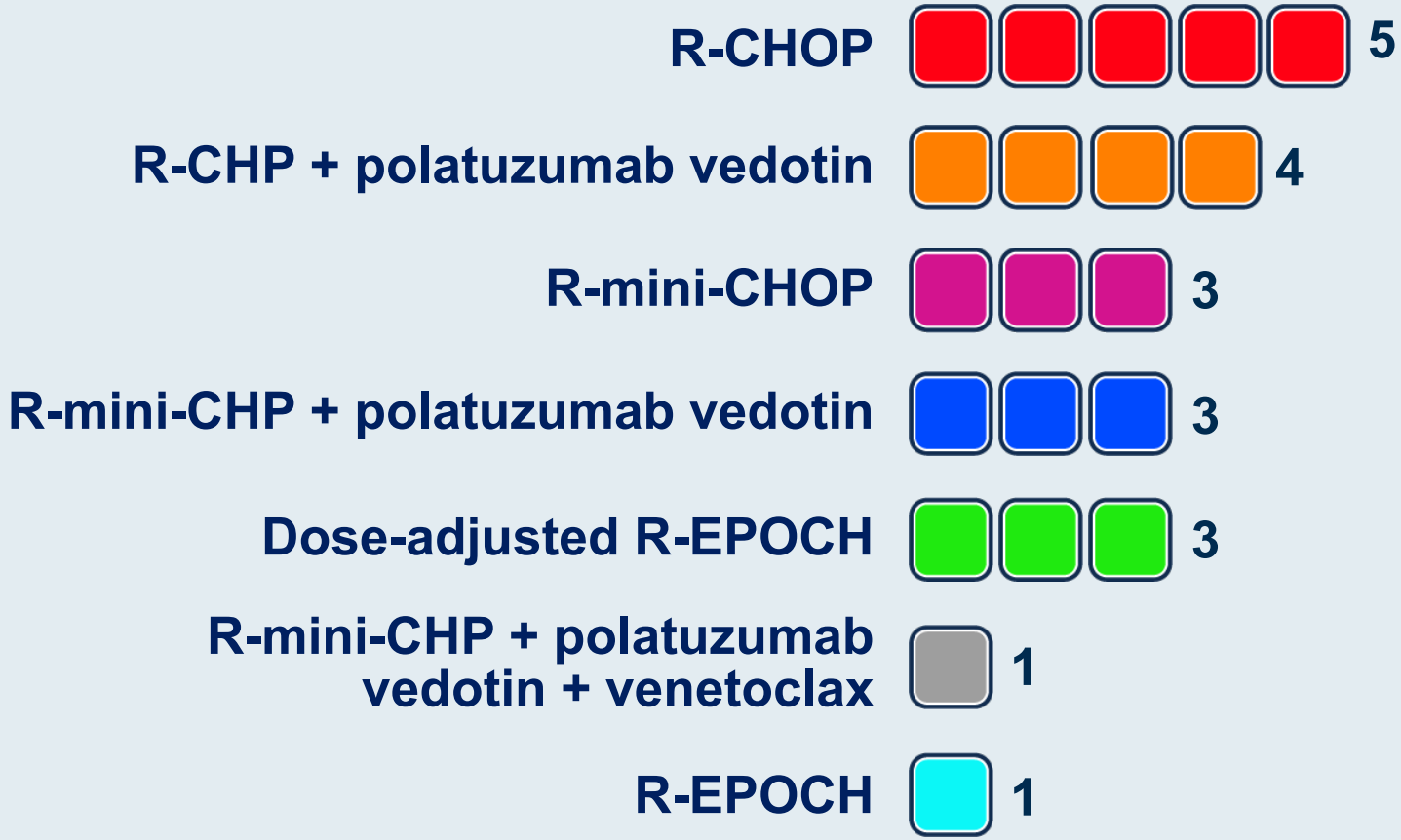
RTP RESEARCH TO PRACTICE

# Which first-line therapy would you generally recommend for an otherwise healthy 80-year-old patient with Stage IV GCB-type high-risk DLBCL?


Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Which first-line therapy would you generally recommend for an otherwise healthy 80-year-old patient with Stage IV double-hit DLBCL?




Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# A 75-year-old woman with a history of congestive heart failure and a LVEF of 45% presents with Stage IV GCB-type high-risk DLBCL. Which initial therapy would you most likely recommend?


R-CEOP = rituximab/cyclophosphamide/etoposide/vincristine/prednisone;
R-GCVP = rituximab/gemcitabine/cyclophosphamide/vincristine/prednisolone

Survey of 19 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# When was the last time you recommended CNS prophylaxis for a patient with DLBCL?

**3 months ago (median; range 1-24)**

## What type of CNS prophylaxis did you employ?


Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Role of CNS prophylaxis in therapy for DLBCL

**Andrew M Evens, DO, MBA, MSc**

RTP
RESEARCH
TO PRACTICE

# Role of tumor-informed circulating tumor DNA assays in the care of patients with non-Hodgkin lymphoma

**Max S Topp, MD**

RTP
RESEARCH
TO PRACTICE

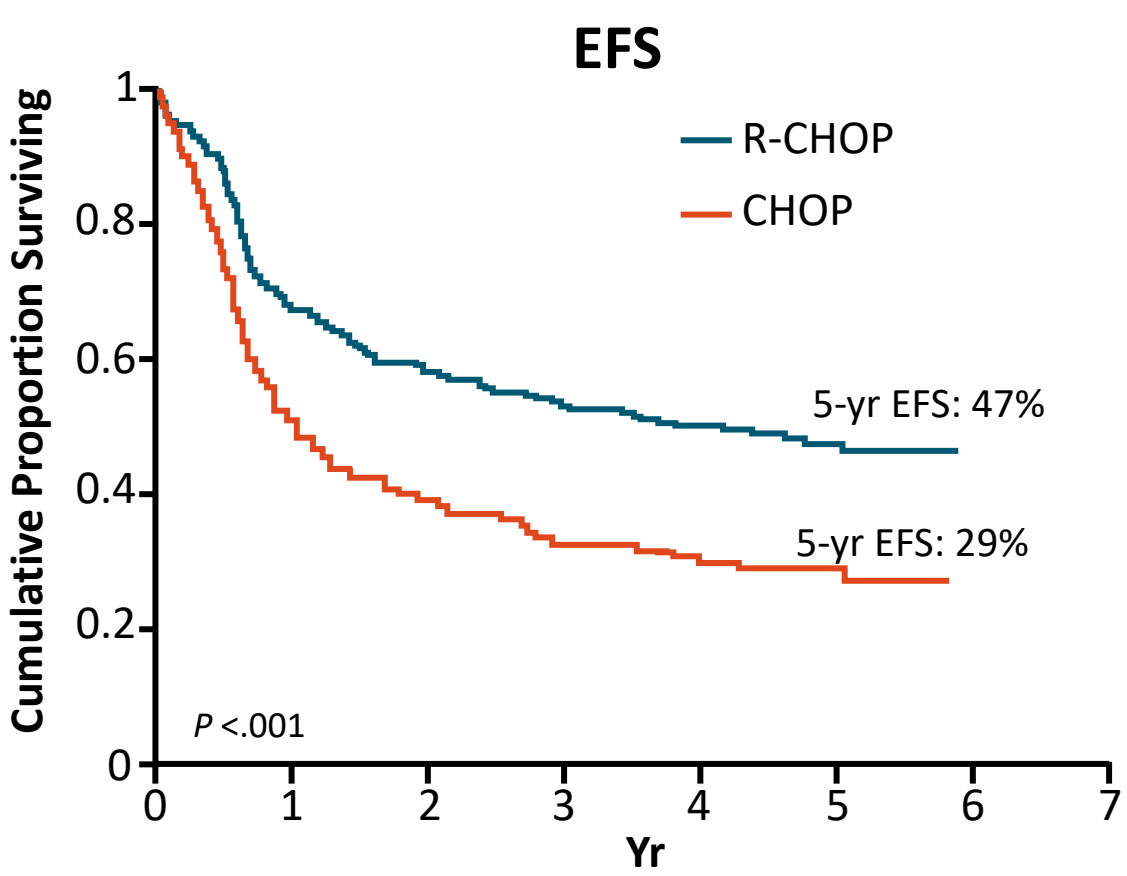
MAYO CLINIC

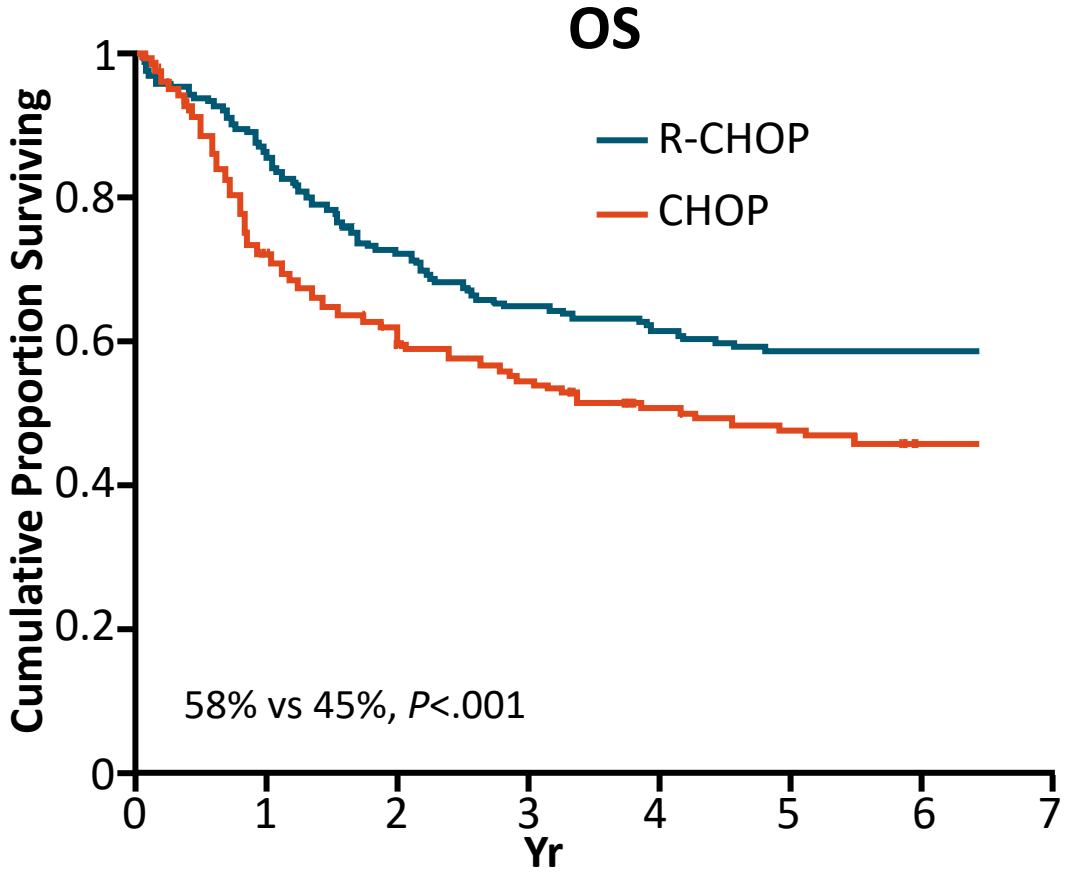
# Promising Investigational Approaches to First-line Therapy for DLBCL

Grzegorz (Greg) S. Nowakowski MD, FASCO
Professor of Medicine and Oncology
Chair, Lymphoid Malignancy Group
Deputy Director Mayo Clinic Comprehensive Cancer Center - Clinical Research
Mayo Clinic

# R-CHOP Has Been the Standard Initial Therapy for DLBCL for >20 Yr

- Long-term outcomes from randomized study of 399 previously untreated patients with DLBCL

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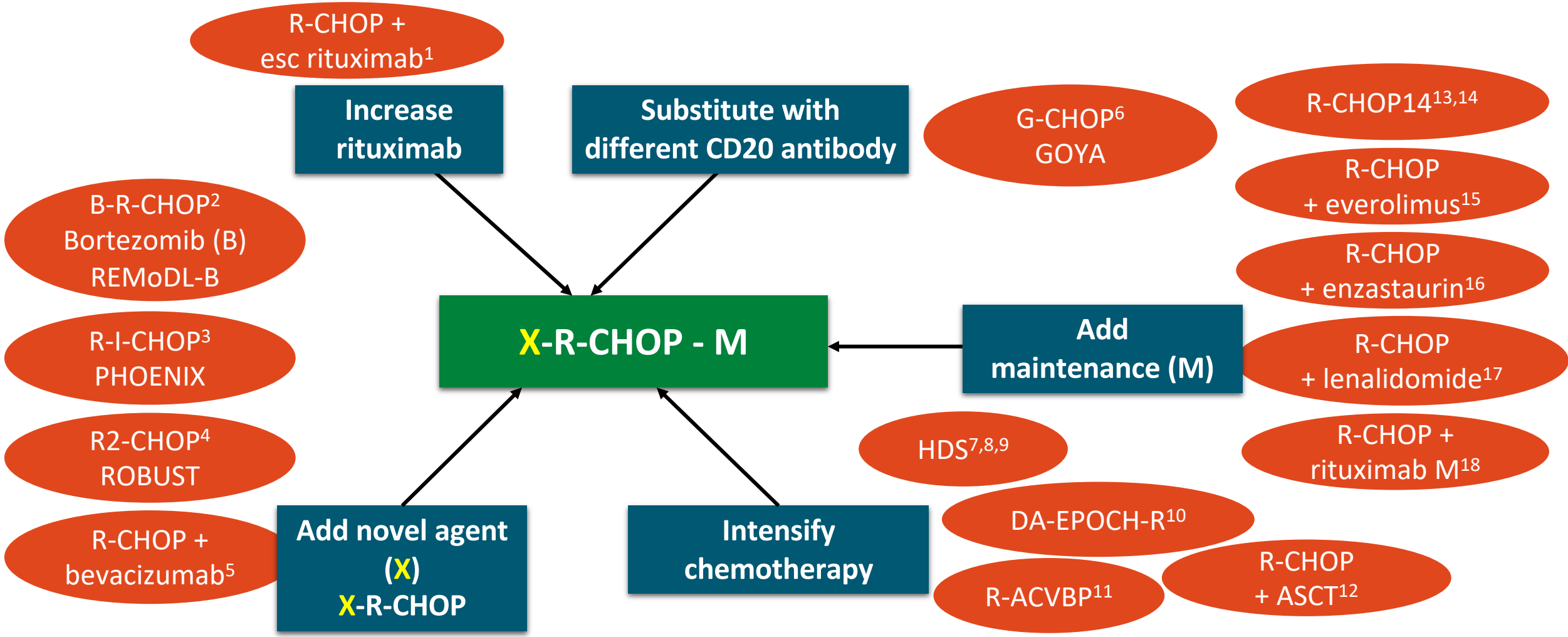
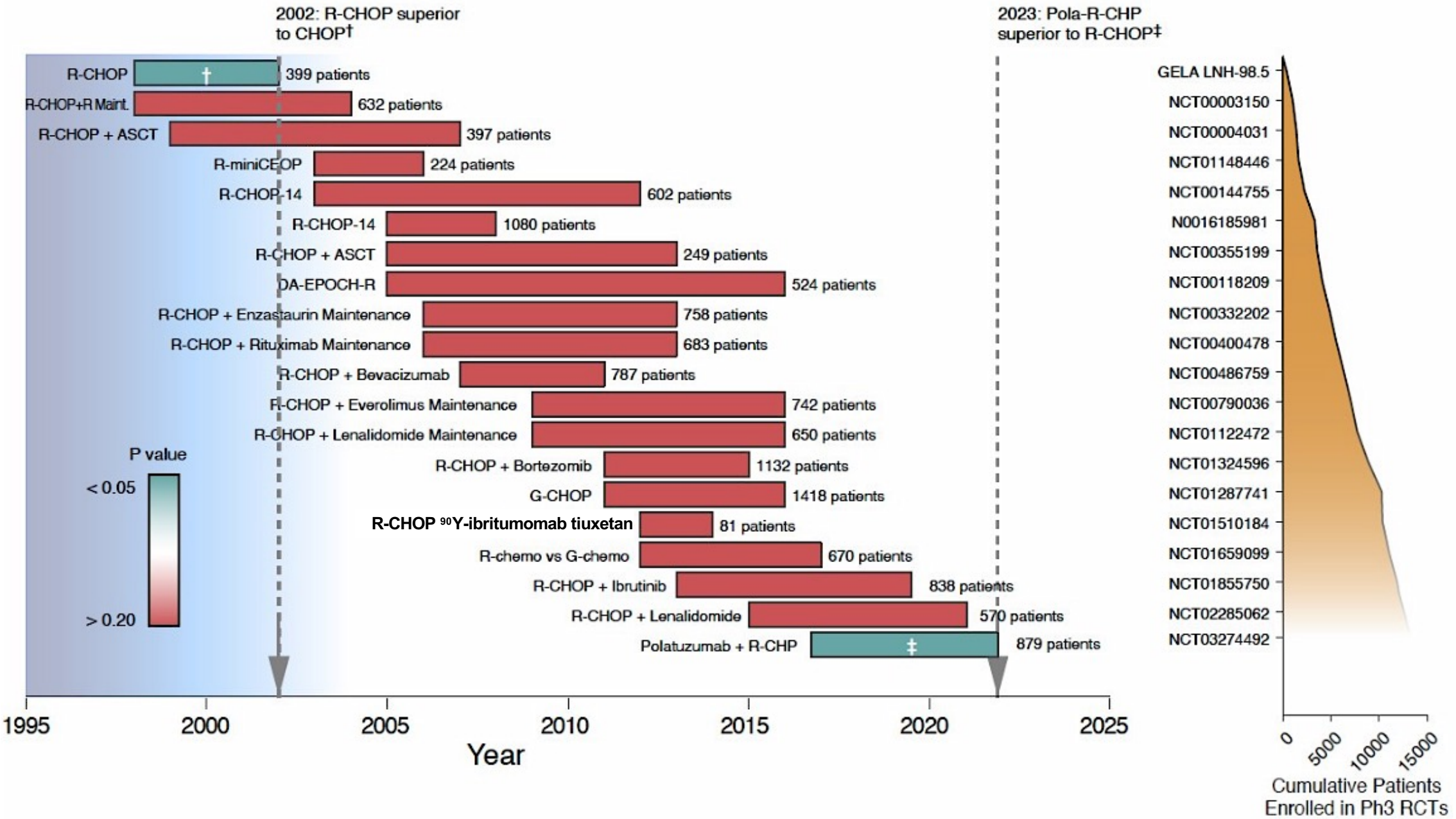
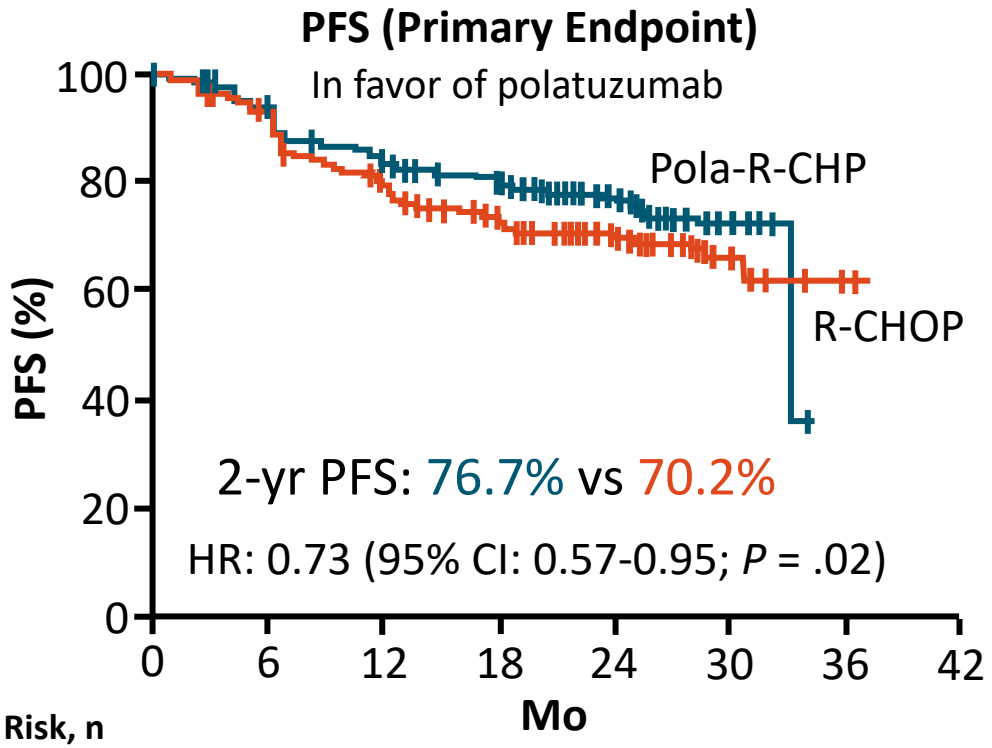
# Improving on R-CHOP in DLBCL




1. He. Cancer Med. 2021;10:7650. 2. Davies. Lancet Oncol. 2019;20:649. 3. Younes. ASH 2018. Abstr 784. 4. Vitolo. ICML 2019. 5. Seymour. Haematologica. 2014;99:1343. 6. Vitolo. JCO. 2017;35:3529. 7. Schmitz. Lancet Oncol. 2012;13:1250. 8. Cortelazzo. JCO. 2016;34:4015. 9. Chiappella. Lancet Oncol. 2017;18:1076. 10. Wilson. Blood. 2016;128:469. 11. Casasnovas. Blood. 2017;130:1315. 12. Stiff. NEJM. 2013;369:1681. 13. Delarue. Lancet Oncol. 2013;14:525. 14. Cunningham. Lancet. 2013;381:1817. 15. Witzig. Ann Oncol. 2018;29:707. 16. Crump. JCO. 2016;34:2484. 17. Thieblemont. JCO. 2017;35:2473. 18. Jaeger. Haematologica 2015;100:955. 19. Palmer. NEJM 2023;389:764-766.

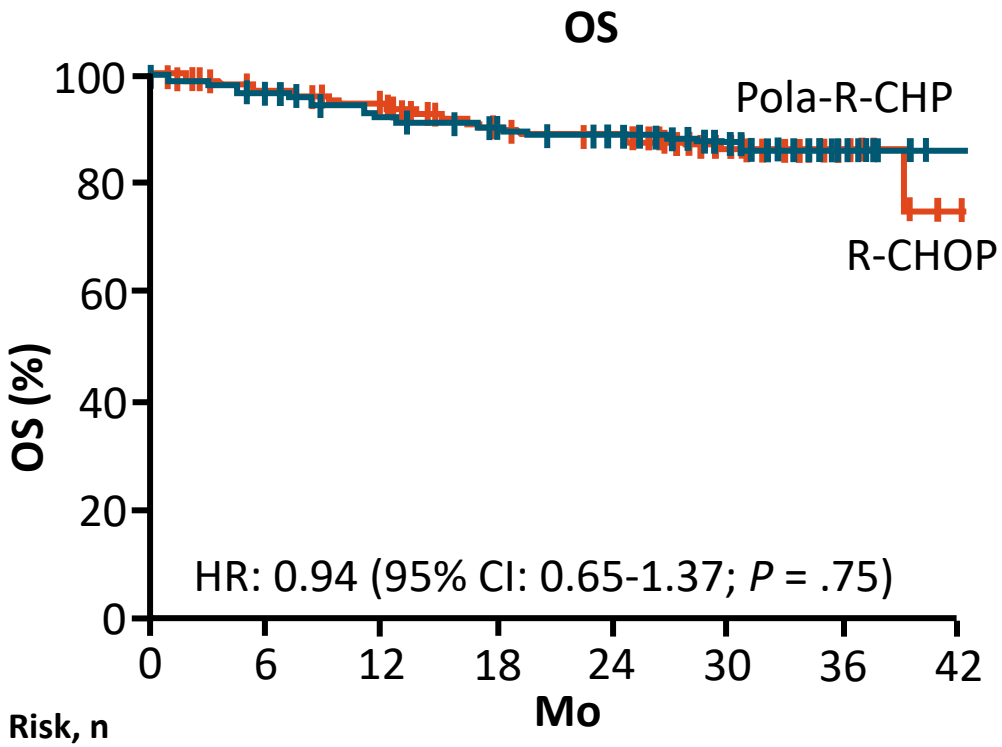

2002: R-CHOP superior to CHOP†
2023: Pola-R-CHP superior to R-CHOP‡
R-CHOP
399 patients
R-CHOP+R Maint.
632 patients
R-CHOP + ASCT
397 patients
R-miniCEOP
224 patients
R-CHOP-14
602 patients
R-CHOP-14
1080 patients
R-CHOP + ASCT
249 patients
DA-EPOCH-R
524 patients
R-CHOP + Enzastaurin Maintenance
758 patients
R-CHOP + Rituximab Maintenance
683 patients
R-CHOP + Bevacizumab
787 patients
R-CHOP + Everolimus Maintenance
742 patients
R-CHOP + Lenalidomide Maintenance
650 patients
R-CHOP + Bortezomib
1132 patients
G-CHOP
1418 patients
R-CHOP 90Y-ibritumomab tiuxetan
81 patients
R-chemo vs G-chemo
670 patients
R-CHOP + Ibrutinib
838 patients
R-CHOP + Lenalidomide
570 patients
Polatuzumab + R-CHP
879 patients
P value
< 0.05
> 0.20
1995
2000
2005
2010
2015
2020
2025
Year
GELA LNH-98.5
NCT00003150
NCT00004031
NCT01148446
NCT00144755
N0016185981
NCT00355199
NCT00118209
NCT00332202
NCT00400478
NCT00486759
NCT00790036
NCT01122472
NCT01324596
NCT01287741
NCT01510184
NCT01659099
NCT01855750
NCT02285062
NCT03274492
0
5000
10000
15000
Cumulative Patients Enrolled in Ph3 RCTs

# POLARIX: Polatuzumab Vedotin + R-CHP vs R-CHOP




**Patients at Risk, n**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pola-R-CHP | 440 | 404 | 353 | 327 | 246 | 78 | NE | NE |
| R-CHOP | 439 | 389 | 330 | 296 | 220 | 78 | 3 | NE |




**Patients at Risk, n**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Pola-R-CHP | 440 | 423 | 397 | 384 | 362 | 140 | 15 | 1 |
| R-CHOP | 439 | 414 | 401 | 376 | 355 | 132 | 20 | 2 |

- Best overall response rate: **95.9 %** vs **94.1%**
  - Complete response rate: **86.6%** vs **82.7%**

Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2022;386:351.

# ODAC on March 9th

For OS the bar is where it was 20 years ago….but benefit in PFS

**Christopher S. Coffey, PhD, MS**
*Professor, Department of Biostatistics; Director, Clinical Trials Statistical & Data Management Center, University of Iowa*

Yes, essentially for the reasons that the prior two stated.

**Grzegorz (Greg) S. Nowakowski MD**
*Professor of medicine and oncology; Deputy director for clinical research, Mayo Clinic Comprehensive Cancer Center*

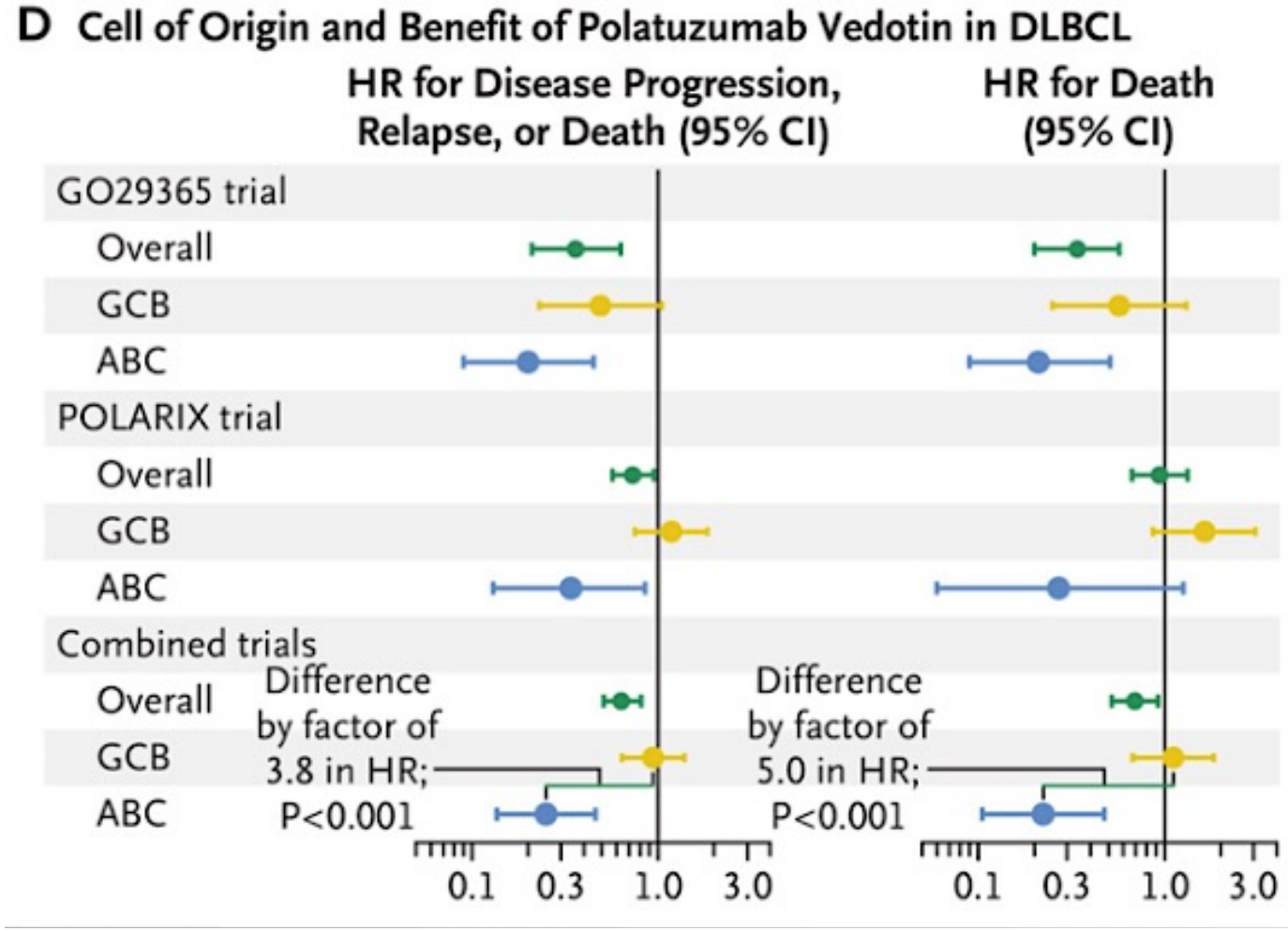
> I would like to note, however, that I would consider this regimen to be an option rather than a standard, in a setting of lack of overall survival difference from R-CHOP. I would consider them equivalent, including in ongoing clinical trials. I would not hesitate to randomize patients still to R-CHOP control, because there's no overall survival difference.
>
> – *Grzegorz S. Nowakowski*

I voted yes, because I do believe that this gain in progression-free survival is clinically meaningful for patients, and also leads to reduction in the need of subsequent therapies, and there was no major toxicity signals, which would be detrimental in this study.

I would like to note, however, that I would consider this regimen to be an option rather than a standard, in a setting of lack of overall survival difference from R-CHOP. I would consider them equivalent, including

FDA Analysis of OS in DLBCL NOS - ODAC March 9th, 2023

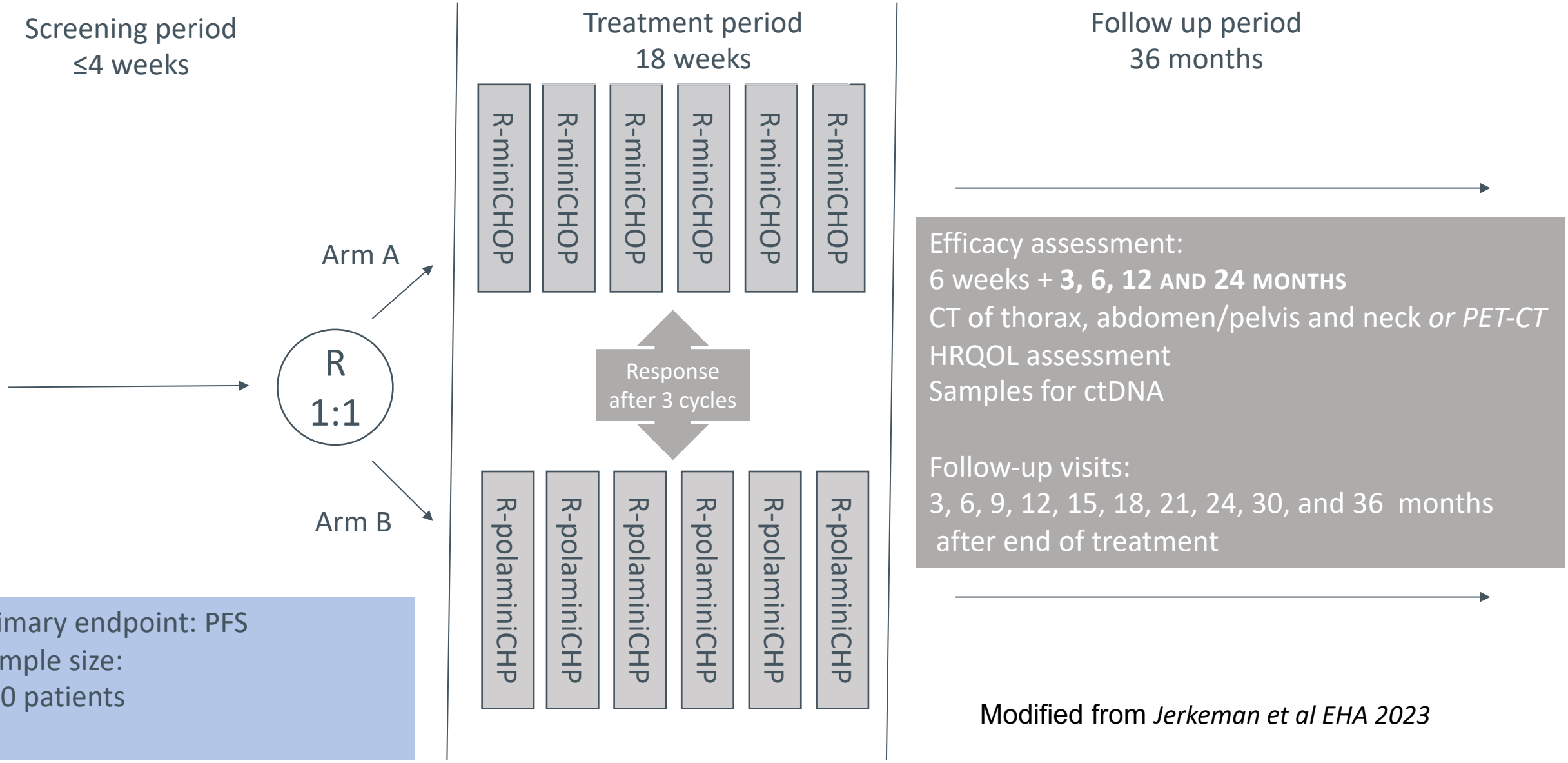
# COO and Benefit of Polatuzumab Vedotin




**How do we interpret subset analysis in trials in regard to (ABC) DLBCL?**

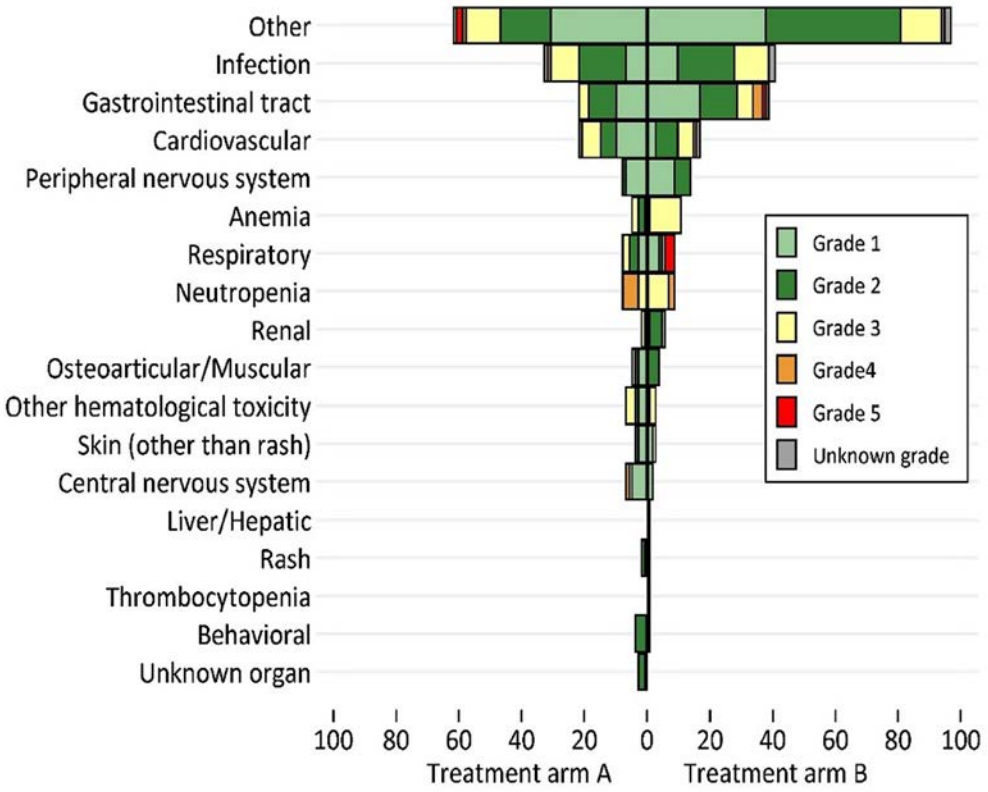
Palmer, A. N Engl J Med 2023; 389:764-766

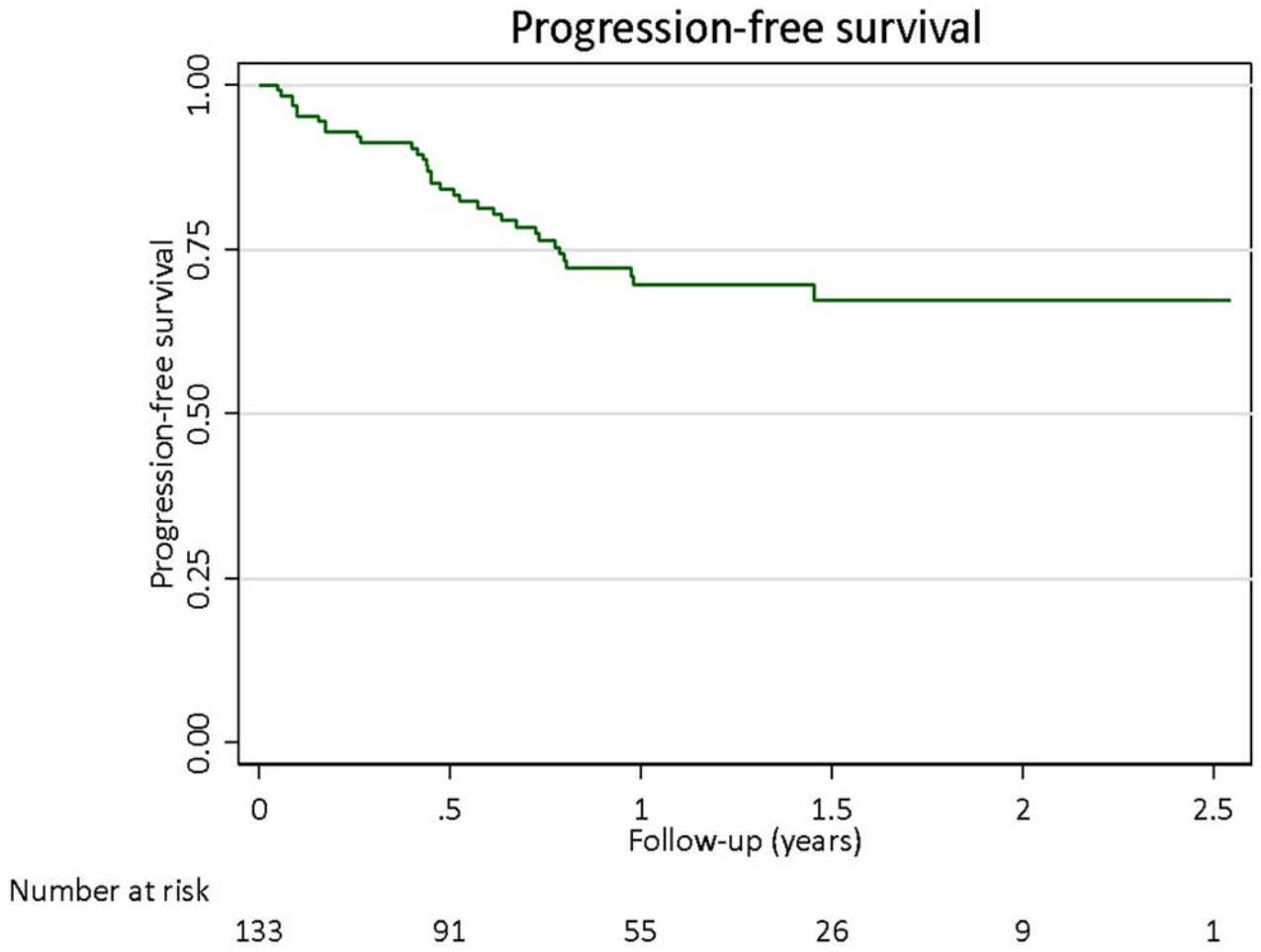
# PHASE 3 POLAR BEAR TRIAL IN ELDERLY OR FRAIL PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA




Modified from *Jerkeman et al EHA 2023*

# POLAR BEAR safety and pooled progression-free survival



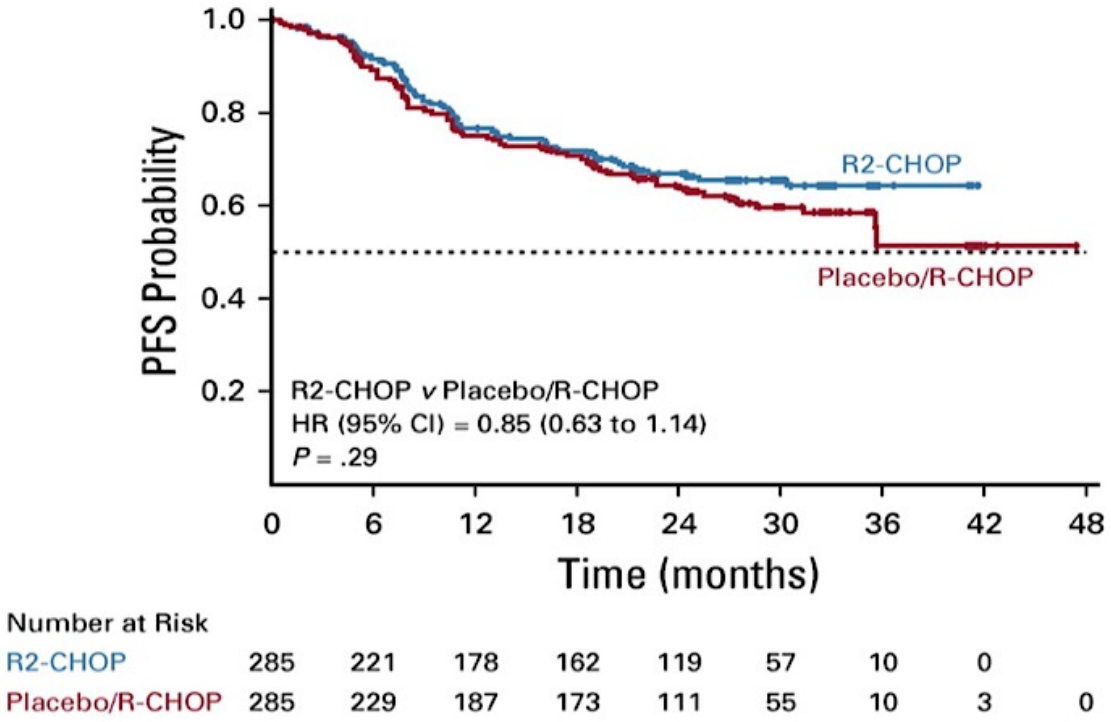




Median follow-up 1.1 years

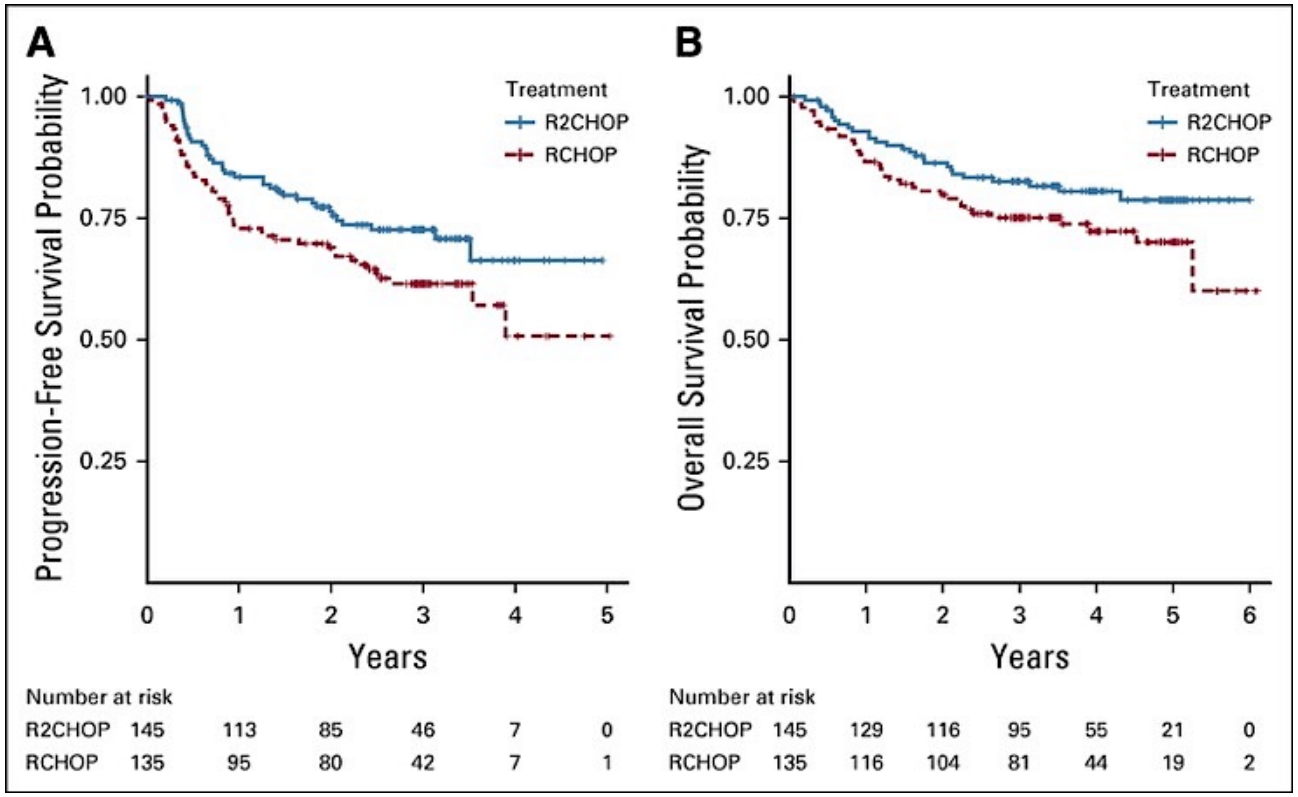
Modified from *Jerkeman et al EHA 2023*

# Results of Randomized Studies of Lenalidomide Plus RCHOP (R2CHOP) vs. RCHOP

**Robust**




**E1412**

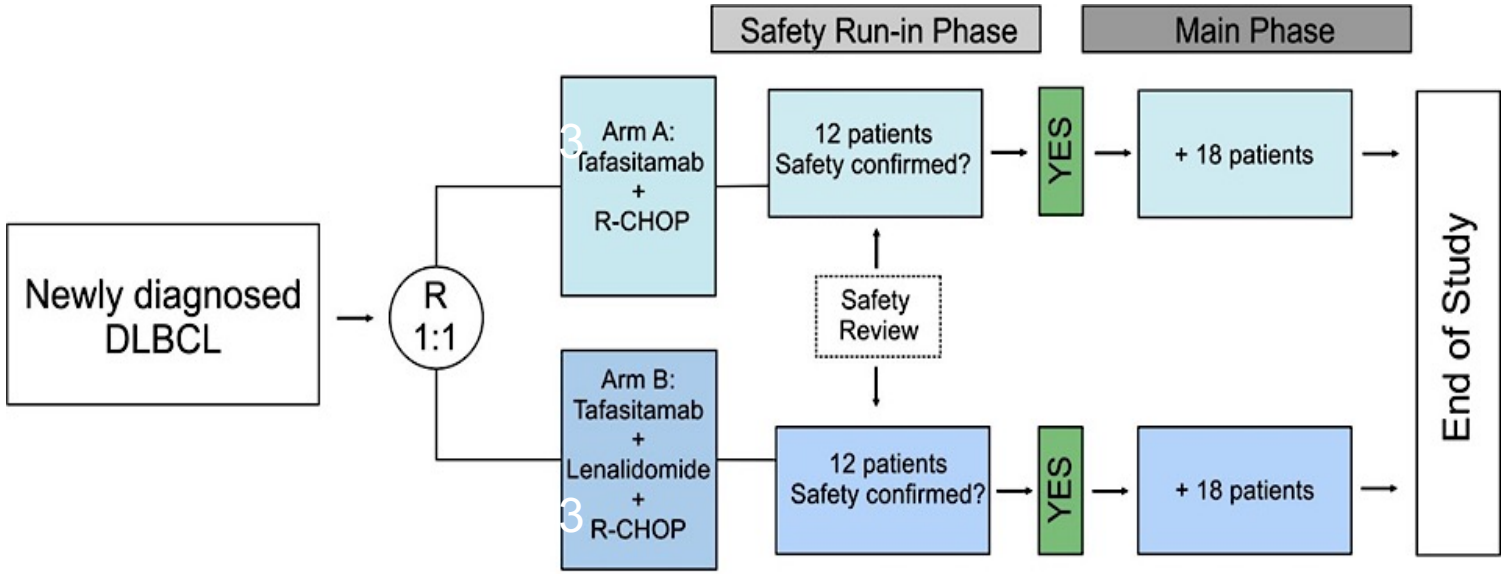


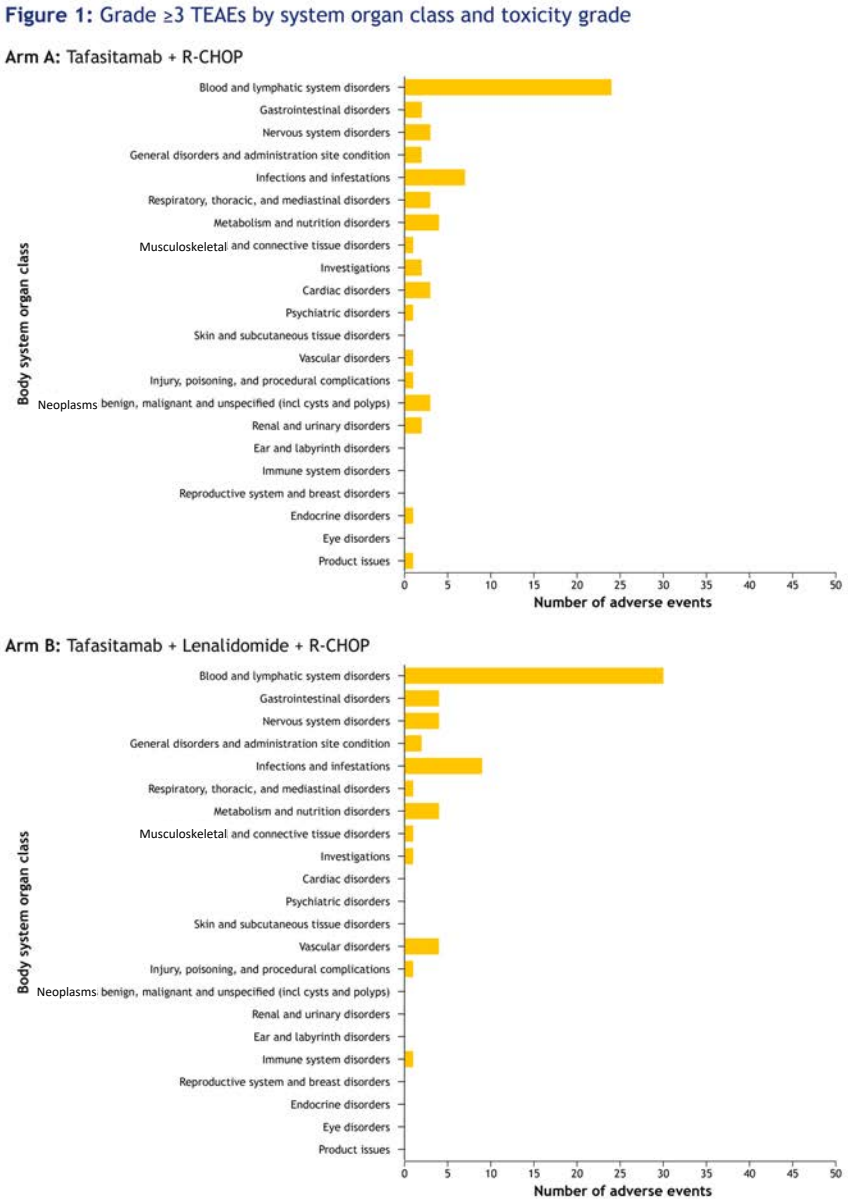


Nowakowski GS et al. *J Clin Oncol.* 2021 Feb 23;JCO2001366.

Nowakowski GS et al. *J Clin Oncol*. 2021 Feb 8;JCO2001375.

# First-MIND Trial – RCHOP/R2CHOP (E1412 dose) Plus Tafasitamab




- Neutropenia and thrombocytopenia more common in arm B but no increase in neutropenic fever/infections
- Discontinuations due to AEs rare and not different average relative dose intensity of RCHOP
- ORR at EOT was 75.8% (arm A) vs 81.8% (arm B)

Nowakowski et al. ASH 2022, Beleda ASH 2021.

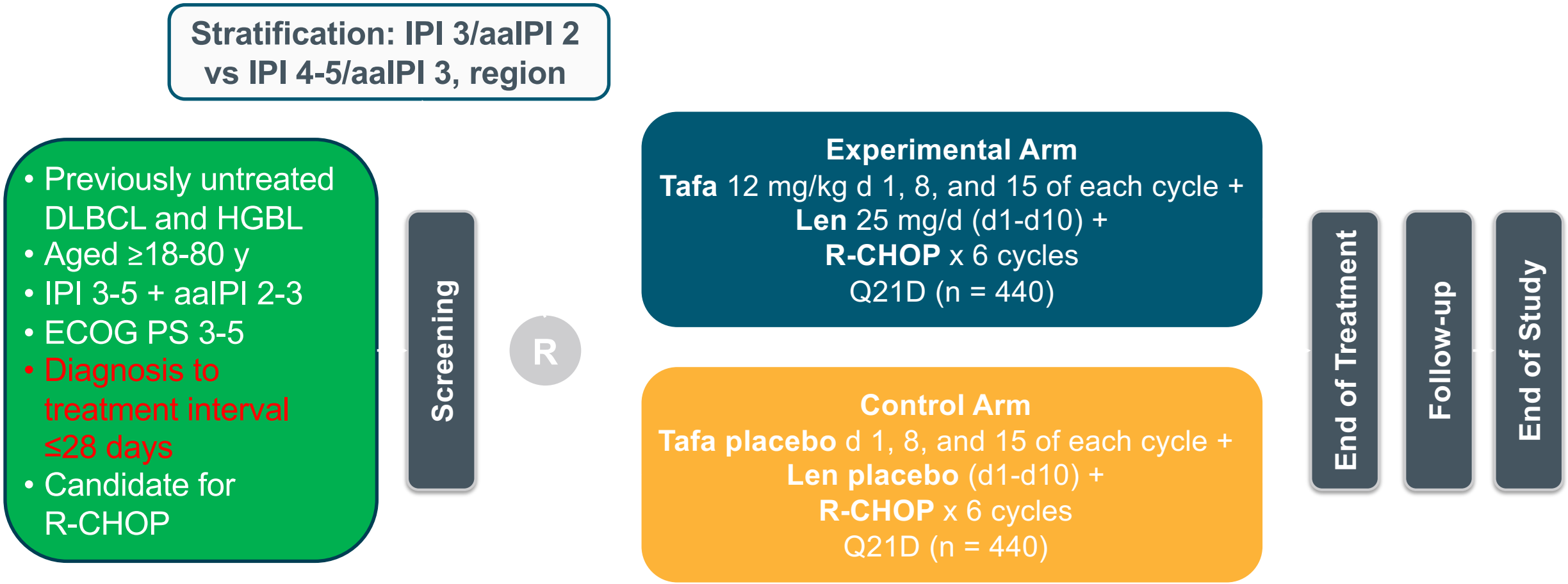
# First-MIND: Efficacy After ≥18 Months' Follow-Up

| Event | T+R-CHOP (n=33) | T/L+R-CHOP (n=33) | T/L+R-CHOP IPI 3–5 (n=22) |
|---|---|---|---|
| ORR, n (%) [95% CI] | | | |
| CR or PR (at EoT) | 25 (75.8) [57.7, 88.9] | 27 (81.8) [64.5, 93.0] | 18 (81.8) [59.7, 94.8] |
| CR or PR (best response across all visits) | 30 (90.9) [75.7, 98.1] | 31 (93.9) [79.8, 99.3] | 20 (90.9) [70.8, 98.9] |
| 18-month DoR rate, % [95% CI] | 72.7 [52.7, 85.3] | 78.7 [58.5, 89.9] | 76.6 [48.8, 90.5] |
| 18-month DoCR rate, % [95% CI] | 74.5 [53.8, 87.0] | 86.5 [63.8, 95.5] | 80.0 [50.0, 93.1] |
| 24-month PFS rate, % [95% CI] | 72.7 [52.7, 85.3] | 76.8 [57.1, 88.3] | 73.6 [47.3, 88.2] |
| 24-month OS rate, % [95% CI] | 90.3 [72.9, 96.8] | 93.8 [77.3, 98.4] | 95.2 [70.7, 99.3] |

CI, confidence interval; CR, complete response; DoCR, duration of complete response; DoR, duration of response; EoT, end of treatment; IPI, International Prognostic Index; L, lenalidomide; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone; T, tafasitamab.

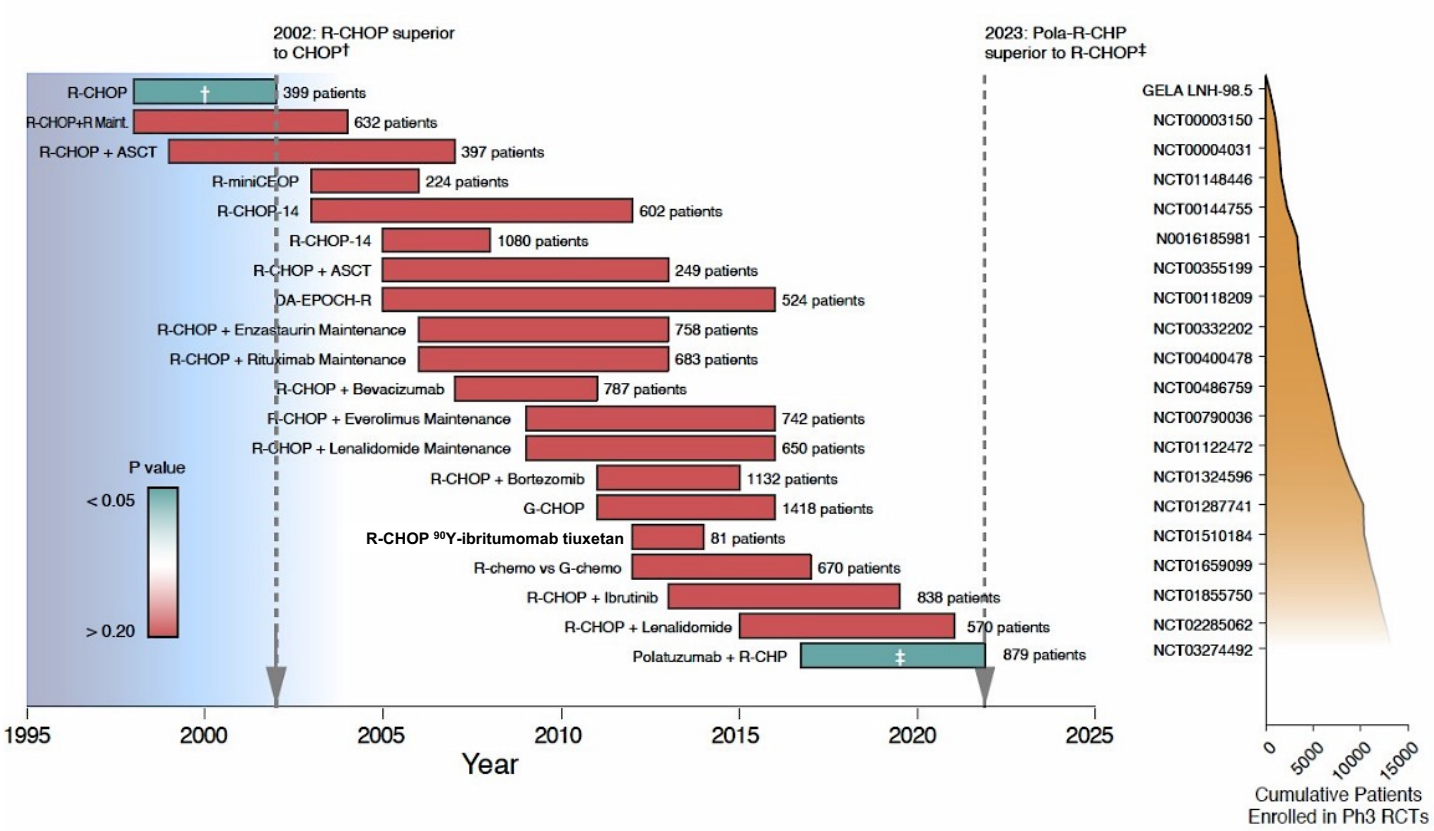
Nowakowski GR et al. ASH 2022;Abstract 1619.

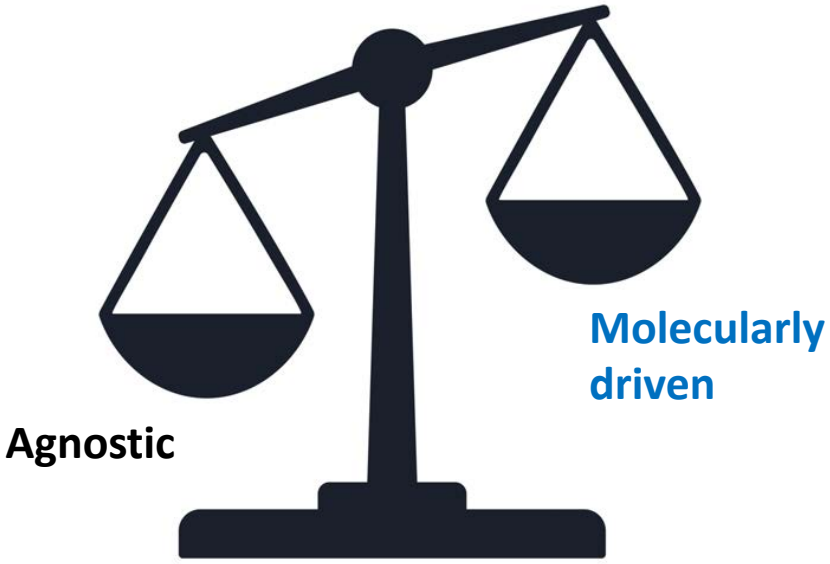
# Front-MIND Newly Diagnosed DLBCL

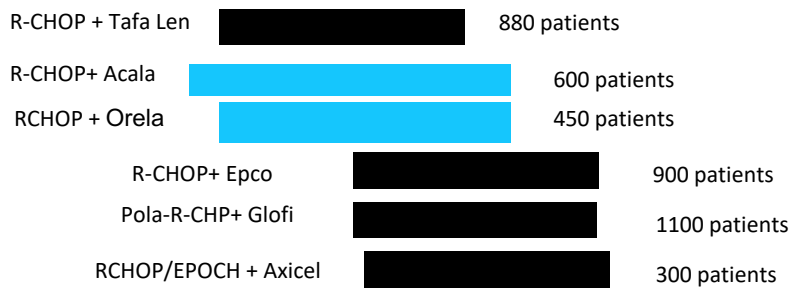


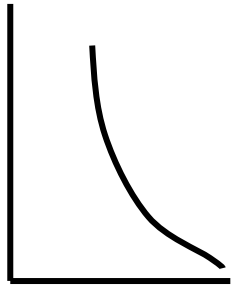

NCT04824092

# Beyond RCHOP – Molecularly Driven or Agnostic?



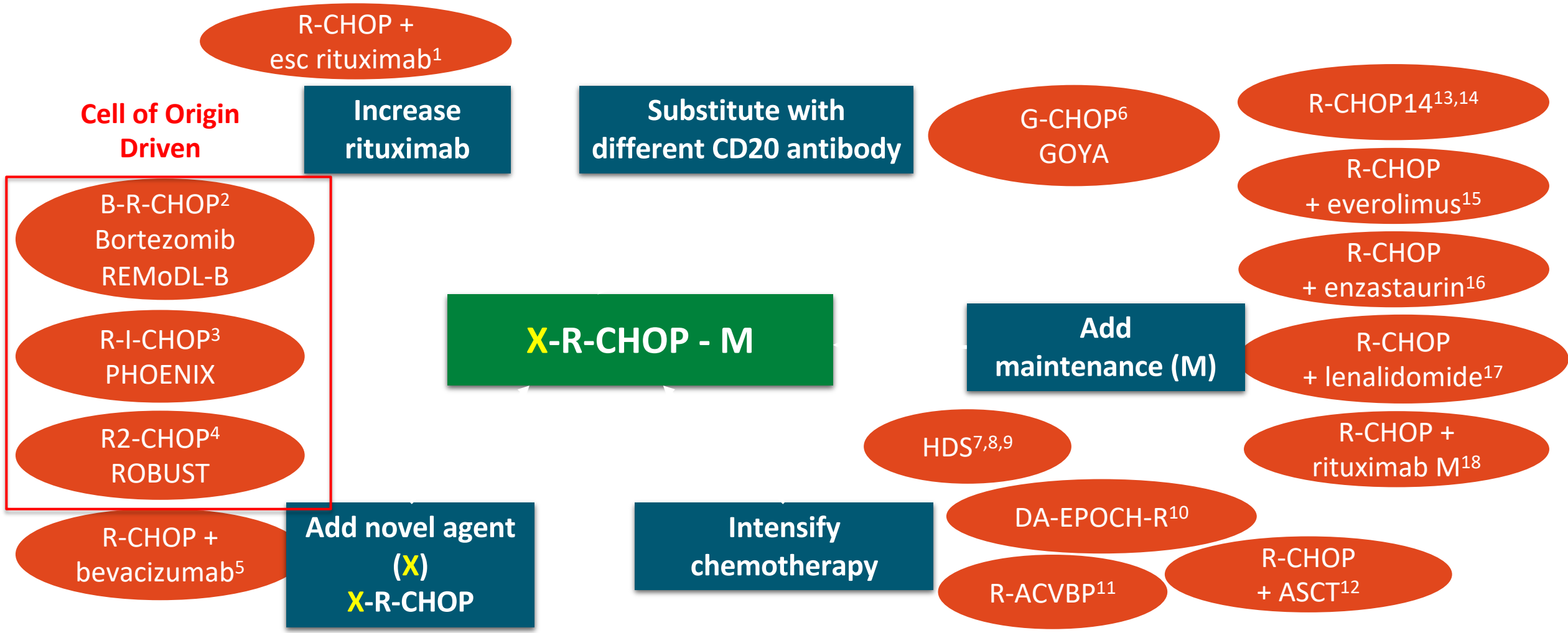



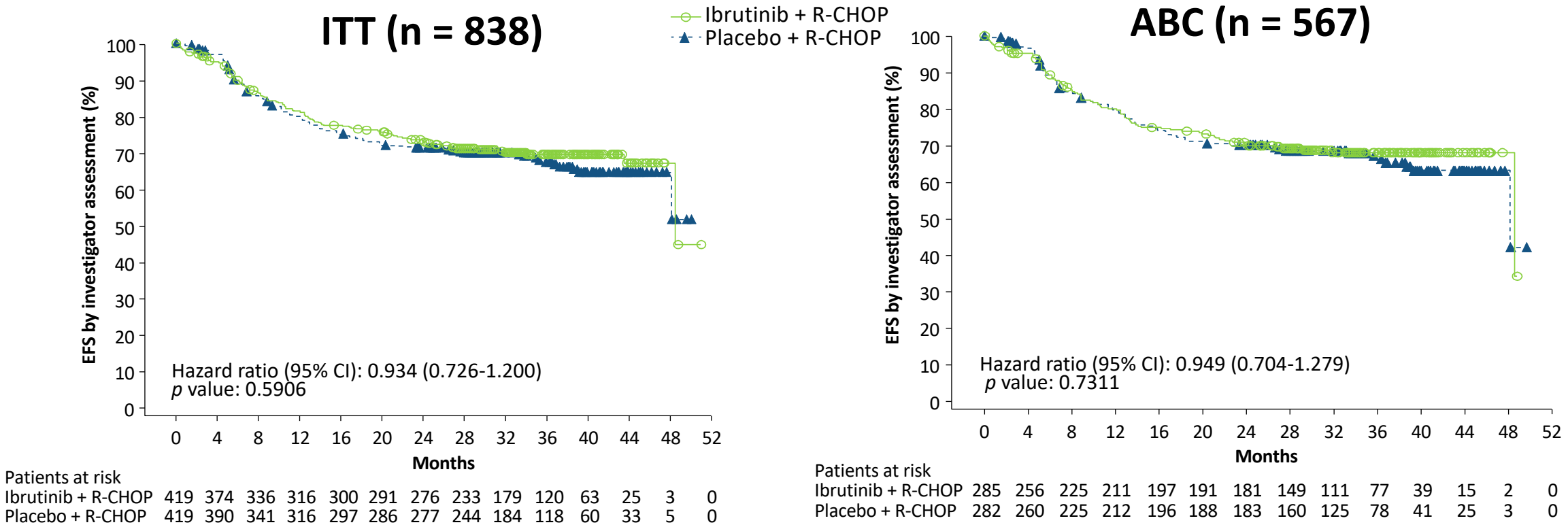
20,000

# Improving on R-CHOP in DLBCL




1. He. Cancer Med. 2021;10:7650. 2. Davies. Lancet Oncol. 2019;20:649. 3. Younes. ASH 2018. Abstr 784. 4. Vitolo. ICML 2019. 5. Seymour. Haematologica. 2014;99:1343. 6. Vitolo. JCO. 2017;35:3529. 7. Schmitz. Lancet Oncol. 2012;13:1250. 8. Cortelazzo. JCO. 2016;34:4015. 9. Chiappella. Lancet Oncol. 2017;18:1076. 10. Wilson. Blood. 2016;128:469. 11. Casasnovas. Blood. 2017;130:1315. 12. Stiff. NEJM. 2013;369:1681. 13. Delarue. Lancet Oncol. 2013;14:525. 14. Cunningham. Lancet. 2013;381:1817. 15. Witzig. Ann Oncol. 2018;29:707. 16. Crump. JCO. 2016;34:2484. 17. Thieblemont. JCO. 2017;35:2473. 18. Jaeger. Haematologica 2015;100:955.

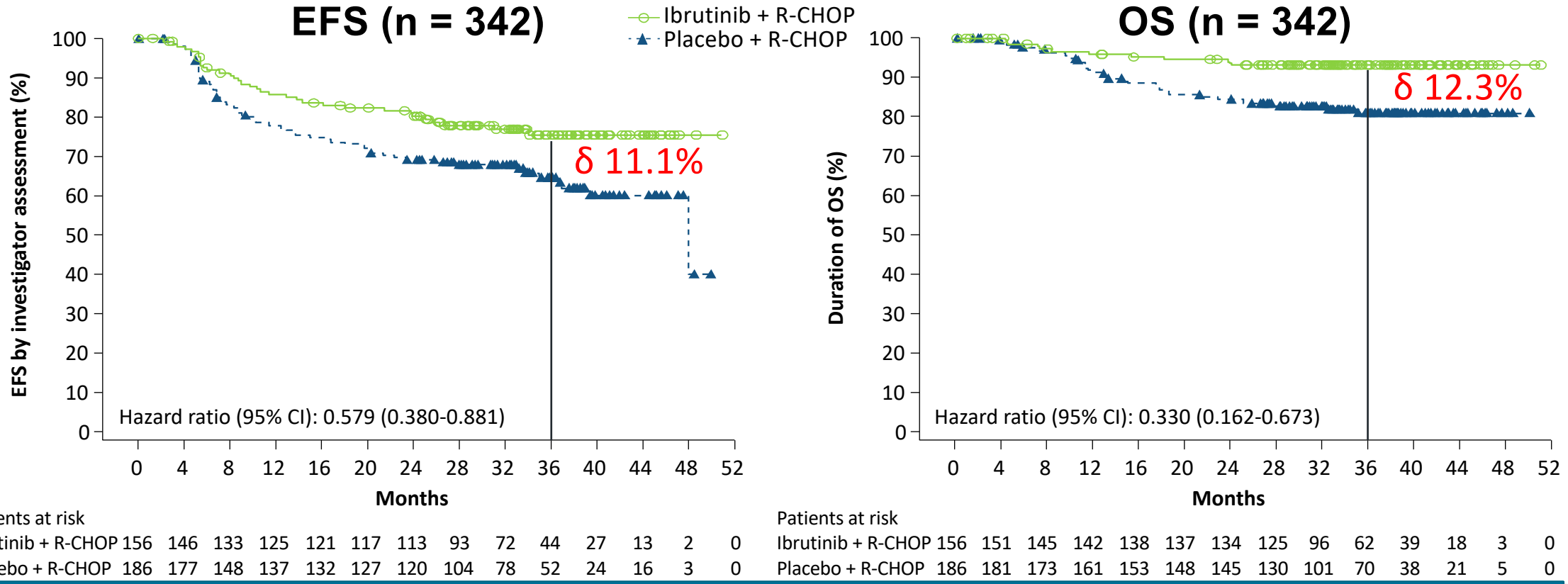
# PHOENIX: R-CHOP +/- Ibrutinib in Newly Diagnosed Non-GCB DLBCL
# Phase 3, double-blind, placebo-controlled




- **Overall response (89.3% vs 93.1%) and CR rates (67.3% vs 68.0%) were similar**

Younes A et al. *J Clin Oncol*. 2019;37(15):1285-1295.

# EFS and OS in Patients < 60 Years

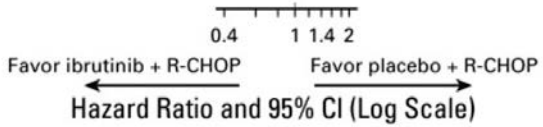



- **Ibrutinib + R-CHOP improved EFS and OS vs placebo + R-CHOP in patients < 60 years of age**
- **Subgroup analyses showed that EFS benefit was consistent across most subgroups for baseline factors**
- **A similar trend with age was seen in patients with the ABC subtype (HR [95% CI]: 0.532 [0.307-0.922] for EFS; HR [95% CI]: 0.345 [0.138-0.862] for OS)**
- **More patients on the placebo + R-CHOP arm received subsequent antilymphoma therapy (25.2% vs 33.5%)**

Younes A et al. *J Clin Oncol*. 2019;37(15):1285-1295.

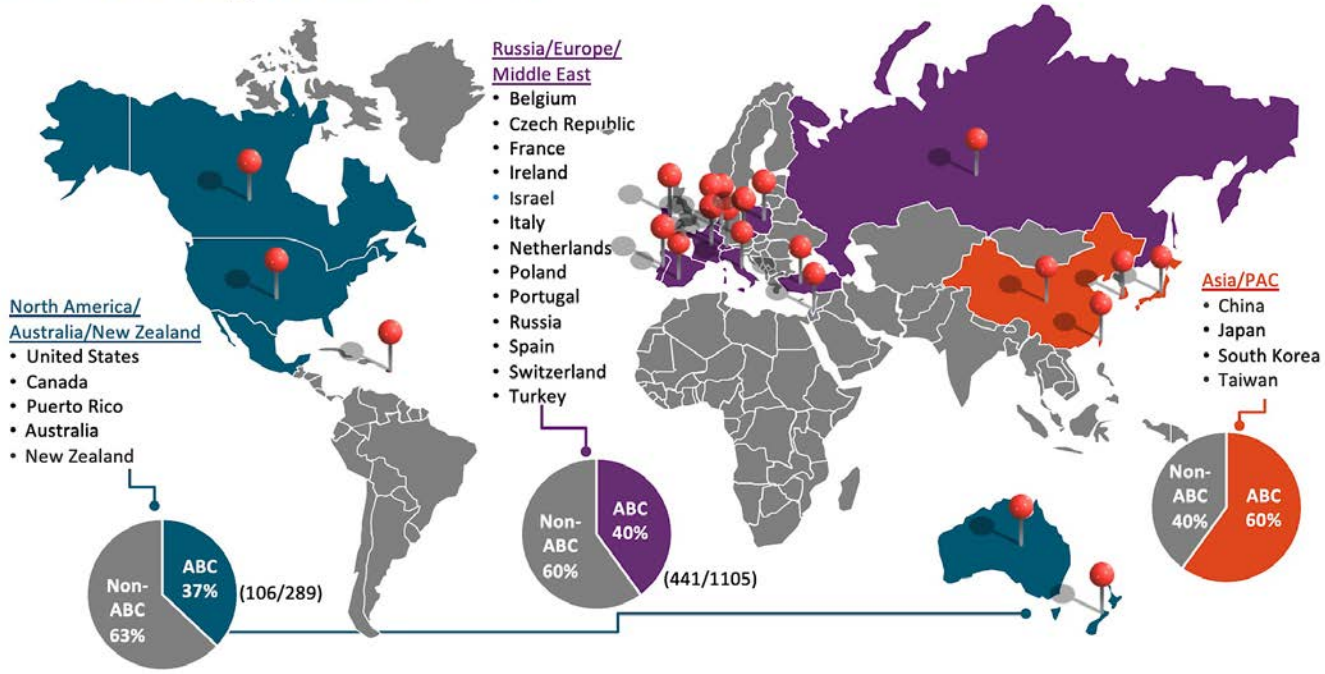
# PHOENIX trial subgroup analysis

| Group | Hazard ratio (95% CI) | Ibrutinib + R-CHOP Event/N | Placebo + R-CHOP Event/N |
|---|---|---|---|
| All patients | 0.93 (0.73 to 1.20) | 118/419 | 129/419 |
| Sex | | | |
| Female | 0.73 (0.50 to 1.07) | 47/198 | 63/193 |
| Male | 1.12 (0.80 to 1.56) | 71/221 | 66/226 |
| Race | | | |
| White | 0.94 (0.68 to 1.31) | 66/237 | 75/250 |
| Nonwhite | 0.91 (0.62 to 1.33) | 52/182 | 54/169 |
| Region | | | |
| US/Western Europe | 1.22 (0.72 to 2.06) | 30/131 | 26/131 |
| Rest of world | 0.85 (0.64 to 1.13) | 88/288 | 103/288 |
| Age, years | | | |
| < 65 | 0.71 (0.51 to 1.01) | 54/231 | 81/259 |
| ≥ 65 | 1.24 (0.85 to 1.80) | 64/188 | 48/160 |
| Baseline ECOG | | | |
| 0 to 1 | 1.01 (0.77 to 1.32) | 109/381 | 106/357 |
| 2 | 0.55 (0.25 to 1.19) | 9/38 | 23/62 |
| R-IPI score | | | |
| Low (1 to 2) | 0.79 (0.53 to 1.17) | 45/236 | 56/238 |
| High (3 to 5) | 1.07 (0.77 to 1.48) | 73/183 | 73/181 |
| Number of treatment cycles | | | |
| 6 | 0.92 (0.66 to 1.28) | 68/246 | 75/246 |
| 8 | 0.92 (0.63 to 1.36) | 50/173 | 54/173 |




Younes A et al. *J Clin Oncol*. 2019;37(15):1285-1295.

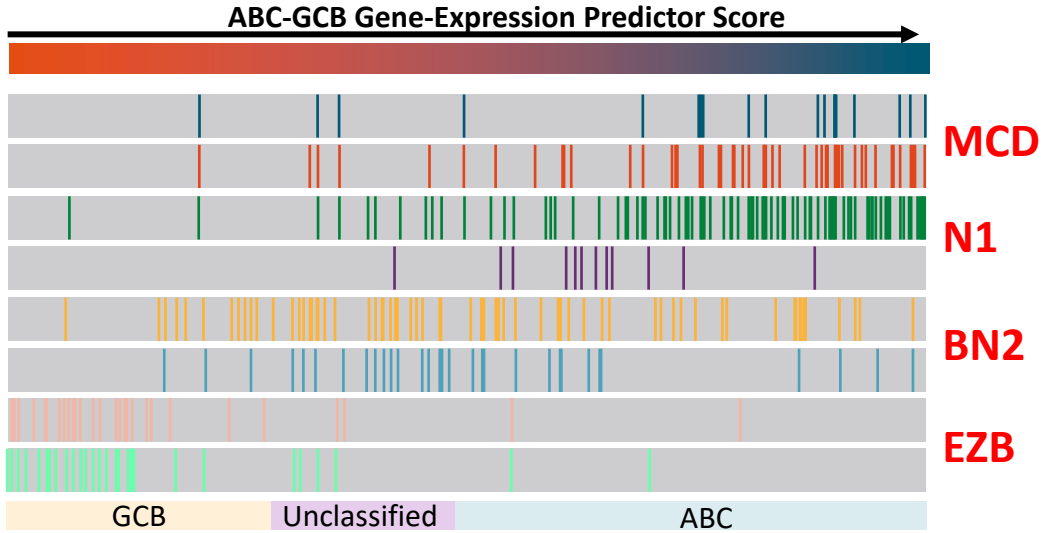
## ROBUST Trial: Geographical Distribution of Cell of Origin in DLBCL

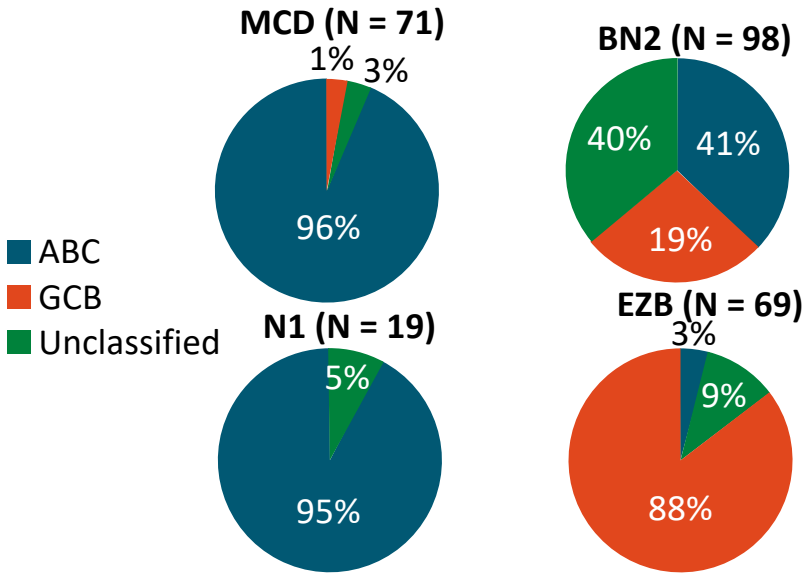


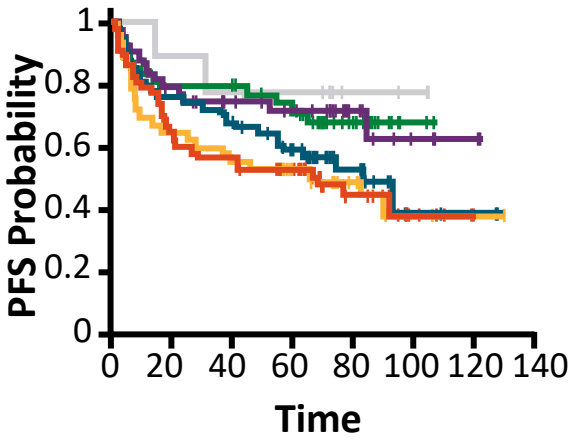

Nowakowski. Haematologica. 2020;105:e72.

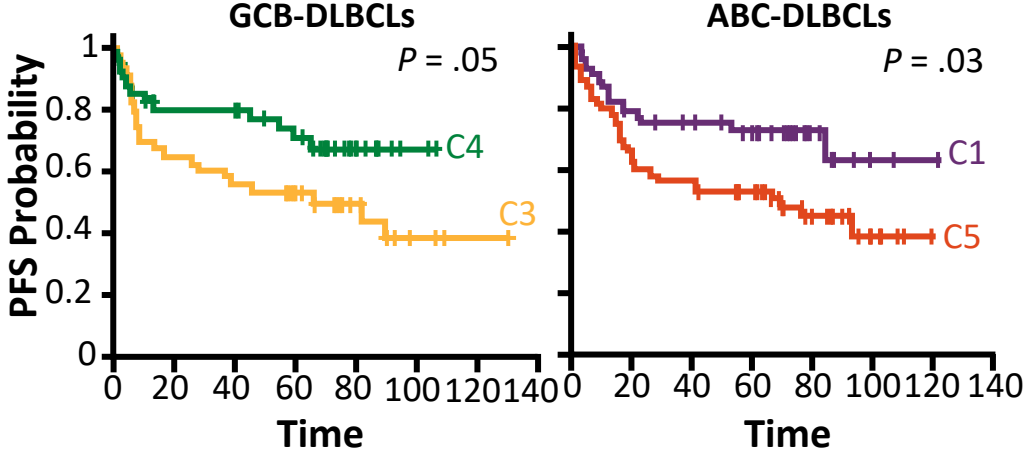
# Integrated Genomic Analyses Identify Subgroups Within and Distinct From Cell of Origin

| Genetic Feature | $Log_{10}$ *P* Value | GCB | Unclass-ified | ABC |
|---|---|---|---|---|
| | | *Prevalence (%)* | | |
| *CD79B+MYD88*$^{L265P}$ Double mutation | -6.4 | 0.6 | 1.7 | 11.5 |
| *CD79B* mutation | -13.8 | 0.6 | 6.1 | 25.4 |
| *MYD88*$^{L265P}$ mutation | -17.0 | 1.2 | 7.8 | 28.8 |
| *NOTCH1* mutation | -3.8 | 0.0 | 0.9 | 6.1 |
| *BCL6* fusion | -4.1 | 11.6 | 33.0 | 18.6 |
| *NOTCH2* mutation | -5.3 | 3.0 | 20.0 | 6.4 |
| *BCL2* translocation | -20.4 | 28.0 | 5.2 | 0.7 |
| *EZH2* mutation | -12.1 | 22.0 | 5.2 | 1.7 |




Chapuy. Nat Med. 2018;24:679. Schmitz. NEJM. 2018;378:1396.

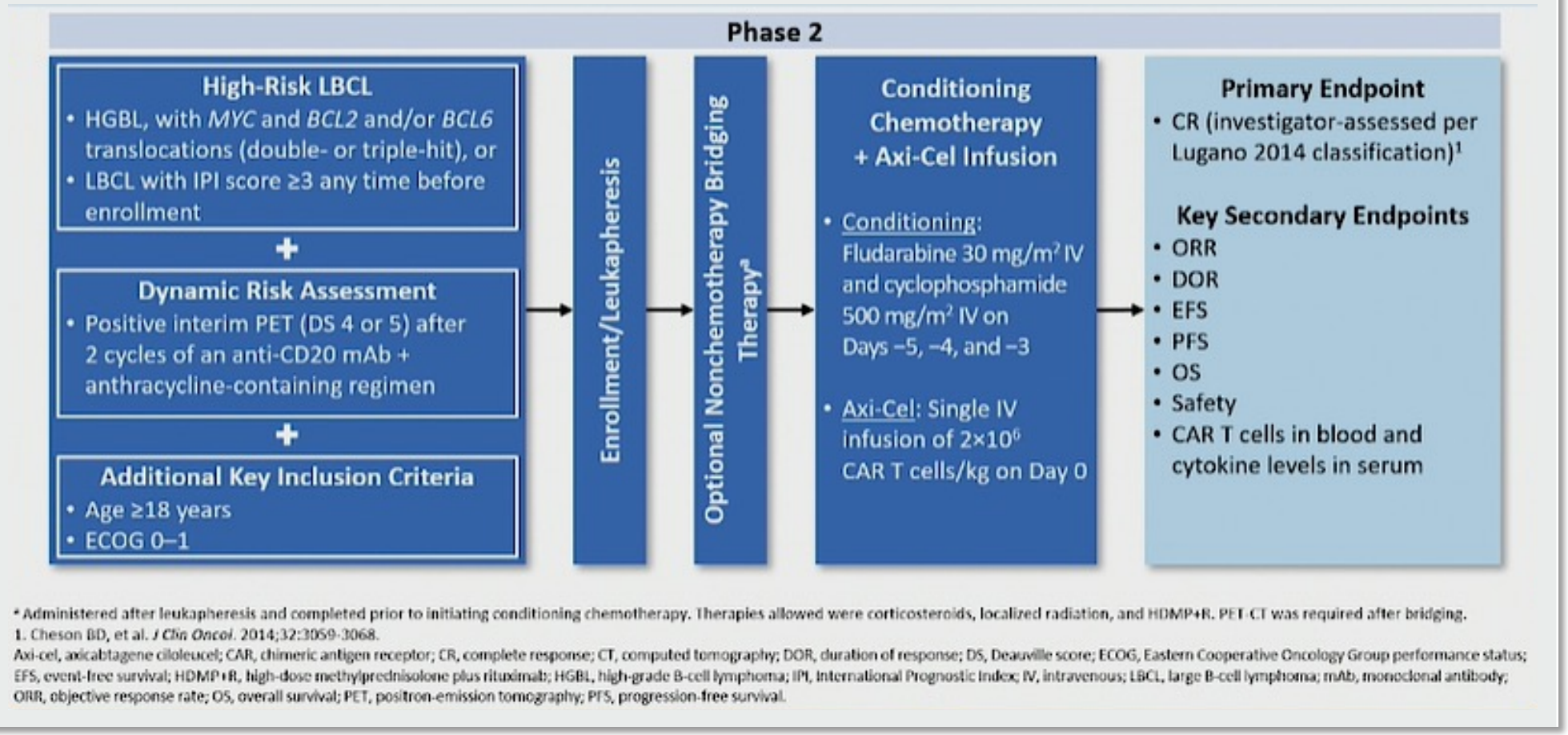
# BTK inhibitors plus RCHOP approaches

- **Younger patients**
  - Phase 3 study**, <65 (now 70) yo, non-GCB**: Acalabrutinib (A) R-CHOP vs RCHOP (Escalade)
- **Molecular profiling**
  - Phase 3 Orelabrutinib plus RCHOP vs RCHOP in **MCD subtype** of DLBCL (BELIEVE-01) (NCT05234684)
- **3rd generation BTKs all comers or non-GCB**
  - Zanubrutinib plus CIT (RCHOP, DAEPOCHR)
  - Orelabrutinib plus CIT (RCHOP, DAEPOCHR)

# ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) As First-Line Therapy in Patients with High-Risk Large B-Cell Lymphoma (LBCL)

| Overview | Primary analysis of ZUMA-12 evaluating axi-cel vs SOC as 1L therapy in patients with high-risk LBCL |
|---|---|

## Study Design




* Administered after leukapheresis and completed prior to initiating conditioning chemotherapy. Therapies allowed were corticosteroids, localized radiation, and HDMP+R. PET-CT was required after bridging.

1. Cheson BD, et al. *J Clin Oncol*. 2014;32:3059-3068.

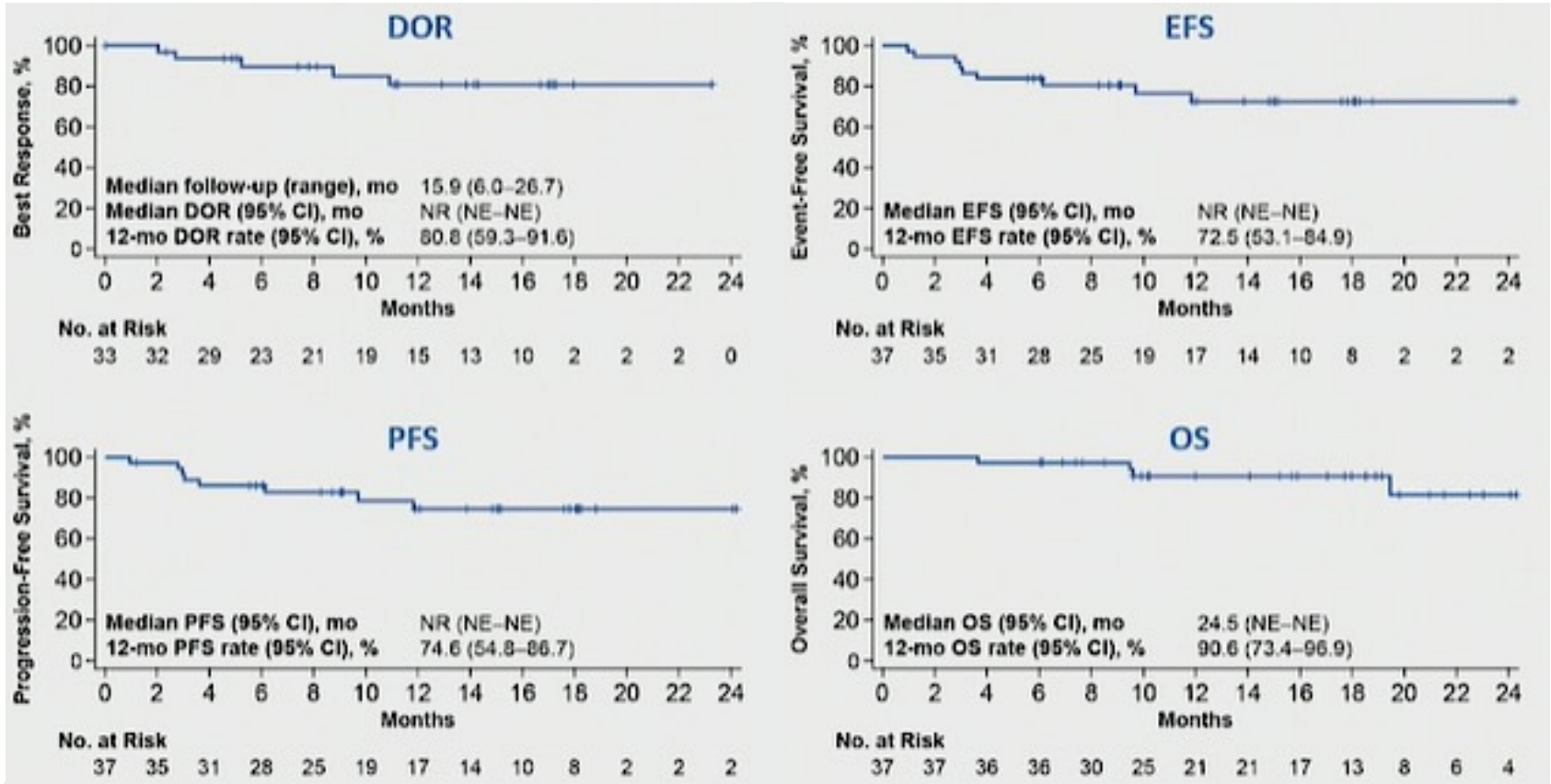
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CT, computed tomography; DOR, duration of response; DS, Deauville score; ECOG, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HDMP+R, high-dose methylprednisolone plus rituximab; HGBL, high-grade B-cell lymphoma; IPI, International Prognostic Index; IV, intravenous; LBCL, large B-cell lymphoma; mAb, monoclonal antibody; ORR, objective response rate; OS, overall survival; PET, positron-emission tomography; PFS, progression-free survival.

Neelapu S, et al. American Society of Hematologists Annual Meeting. December 11-14, 2021. Abstract #739.

# ZUMA-12: A Phase 2 Study of Axicabtagene Ciloleucel (Axi-Cel) As First-Line Therapy in Patients with High-Risk Large B-Cell Lymphoma (LBCL)

## Duration of response/ Progression-free survival

## Event-free survival/ Overall survival

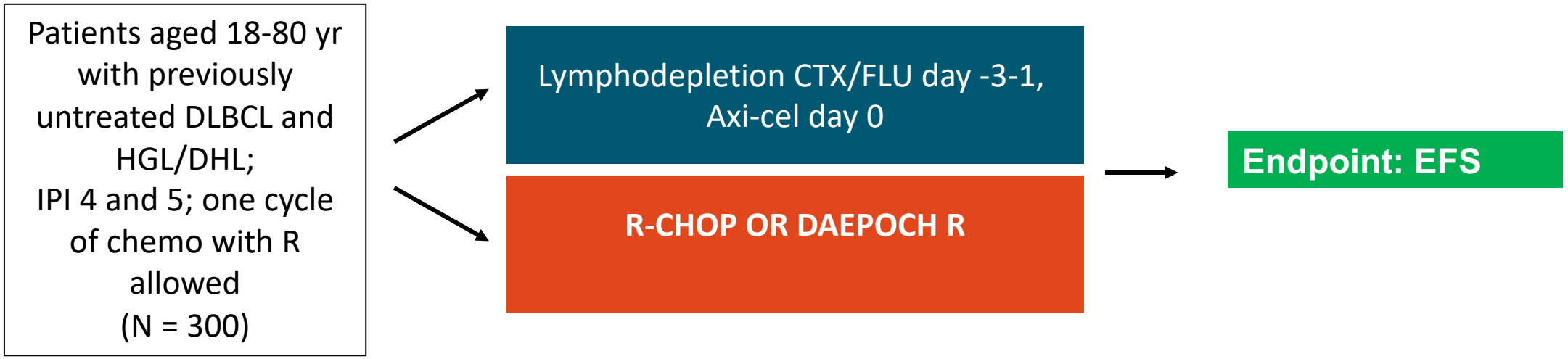



[a] Analyses done in all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10$^6$ CAR T cells/kg.
DOR, duration of response; EFS, event-free survival; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free survival.

- Among efficacy-evaluable patients, axi-cel demonstrated high response rates of ORR (89%) and CR (78%) at a median follow-up of 15.9 months
  - 73% of patients remained in response at data cutoff
- Medians for DoR, PFS, EFS, and OS were not reached
- Manageable safety profile of axi-cel with no new safety signals observed

Neelapu S, et al. American Society of Hematologists Annual Meeting. December 11-14, 2021. Abstract #739. Neelapu SS et al. Nat Med 2022 April;28(4):735-42.

# Axicabtagene Ciloleucel vs CIT as First-line Treatment in Participants With High-risk Large B-cell Lymphoma (ZUMA-23)




NCT05605899

# Conclusions

- RCHOP remains a valid control arm and a valid backbone
  - Possible more benefit in ABC DLBCL
- Pola RCHP alternative
  - Mini RCHP feasible
- Most trails focus on high-risk patients:
  - IPI
  - Short time from dx to rx
  - High molecular risk
- CART and bispecific ab promising in front-line – awaiting phase 3
- BTK inhibitors with RCHOP use several strategies – molecular subtype focus

**Molecularly Agnostic**

- CAR T-cell therapy
- Tafasitamab/ lenalidomide
- Bispecifics
- COO agnostic small molecules

Molecularly selected

- BTK inhibitors
- PI3K inhibitors
- BCL2 inhibitors
- Others

# Agenda

**Module 1: Up-Front Management of Diffuse Large B-Cell Lymphoma (DLBCL) — Dr Salles**

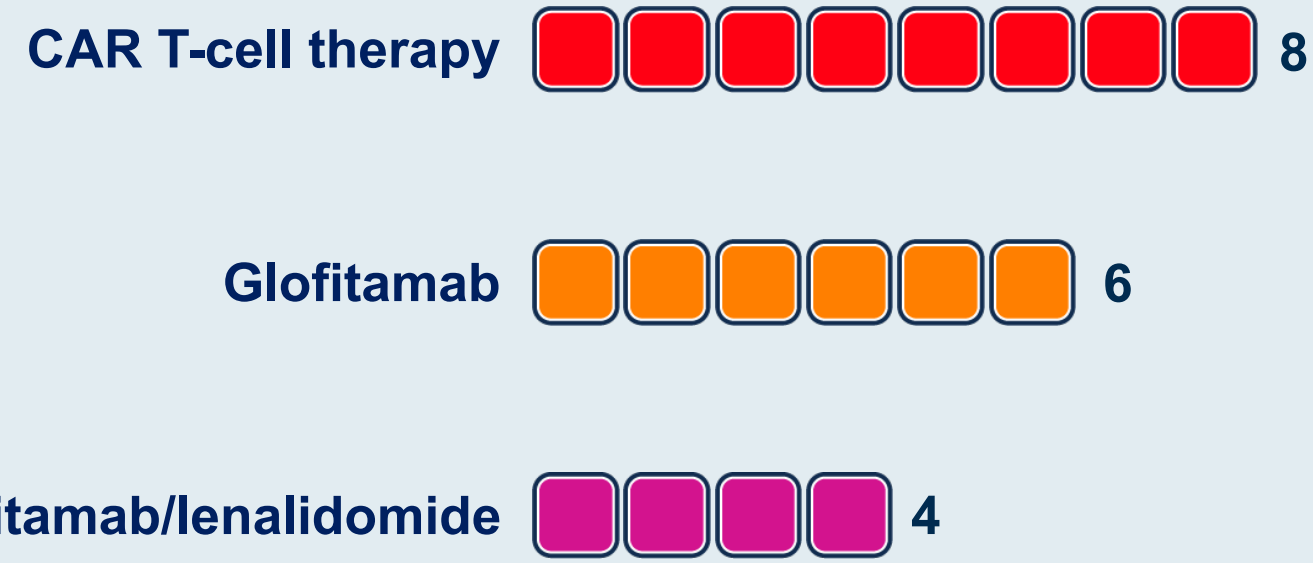
**Module 2: Promising Investigational Approaches to First-Line Therapy for DLBCL — Dr Nowakowski**

**Module 3: Selection and Sequencing of Novel Therapies for Relapsed/Refractory (R/R) DLBCL — Dr Sehn**

**Module 4: Incorporation of CAR T-Cell Therapy into the Management of R/R DLBCL — Dr Westin**

**Module 5: Role of Bispecific Antibodies in the Treatment of DLBCL — Prof Dickinson**

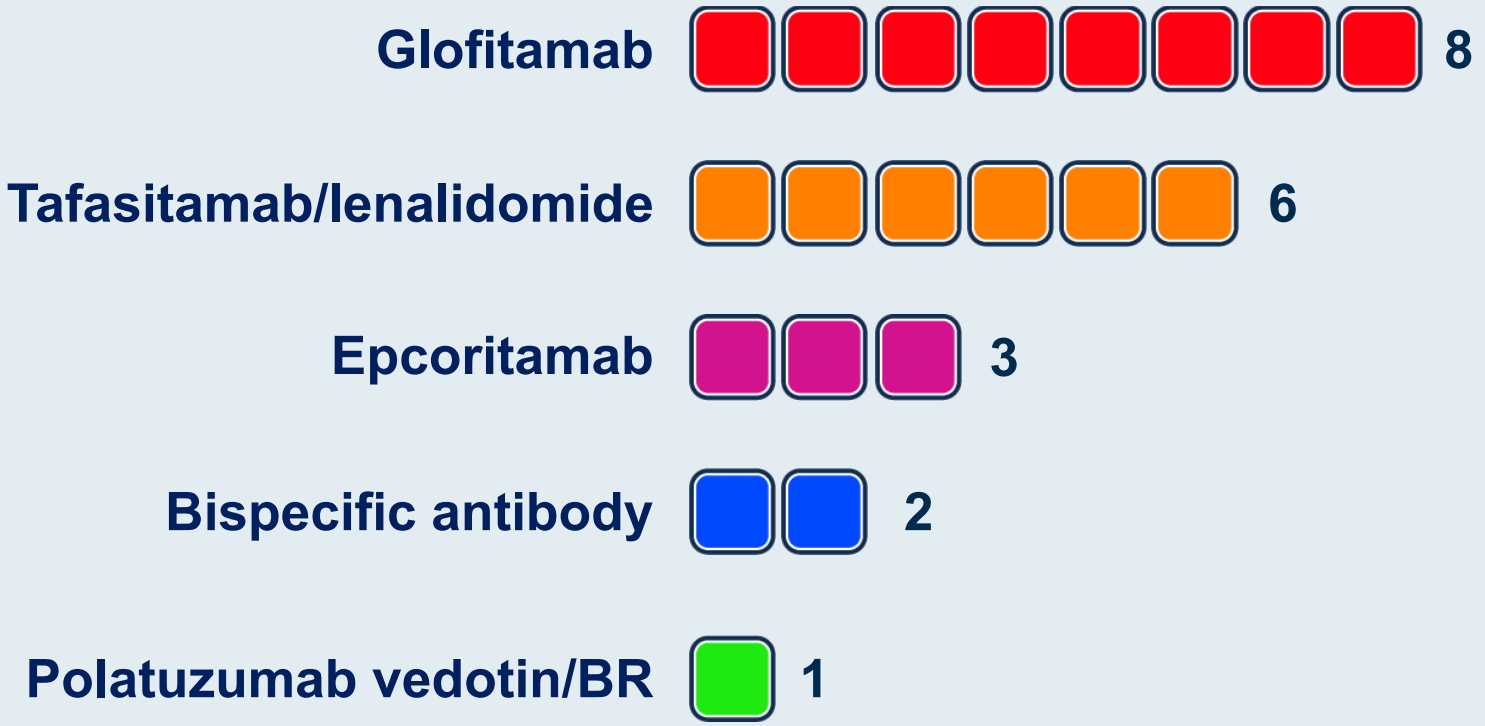
## Regulatory and reimbursement issues aside, which therapy would you generally recommend first for an older (80-year-old) patient with DLBCL who experiences disease progression on front-line R-CHOP and is not eligible for intensive chemotherapy?




Survey of 18 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

## Regulatory and reimbursement issues aside, which therapy would you generally recommend first for a patient with DLBCL who experiences disease progression on front-line R-CHOP and is not eligible for intensive chemotherapy or CAR T-cell therapy?




Survey of 19 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Based on your personal clinical experience and knowledge of available data, for each of the following agents please estimate the chance that a patient with DLBCL will experience toxicity during treatment that will require withholding dosing. What is the primary toxicity patients experience that leads to withholding dosing?

| | Chance of withholding (Median) | Primary toxicity |
|---|---|---|
| Polatuzumab vedotin | 10% | Cytopenias, neuropathy |
| Tafasitamab/lenalidomide | 5% | Cytopenias (lenalidomide) |
| Loncastuximab tesirine | 20% | Cytopenias |

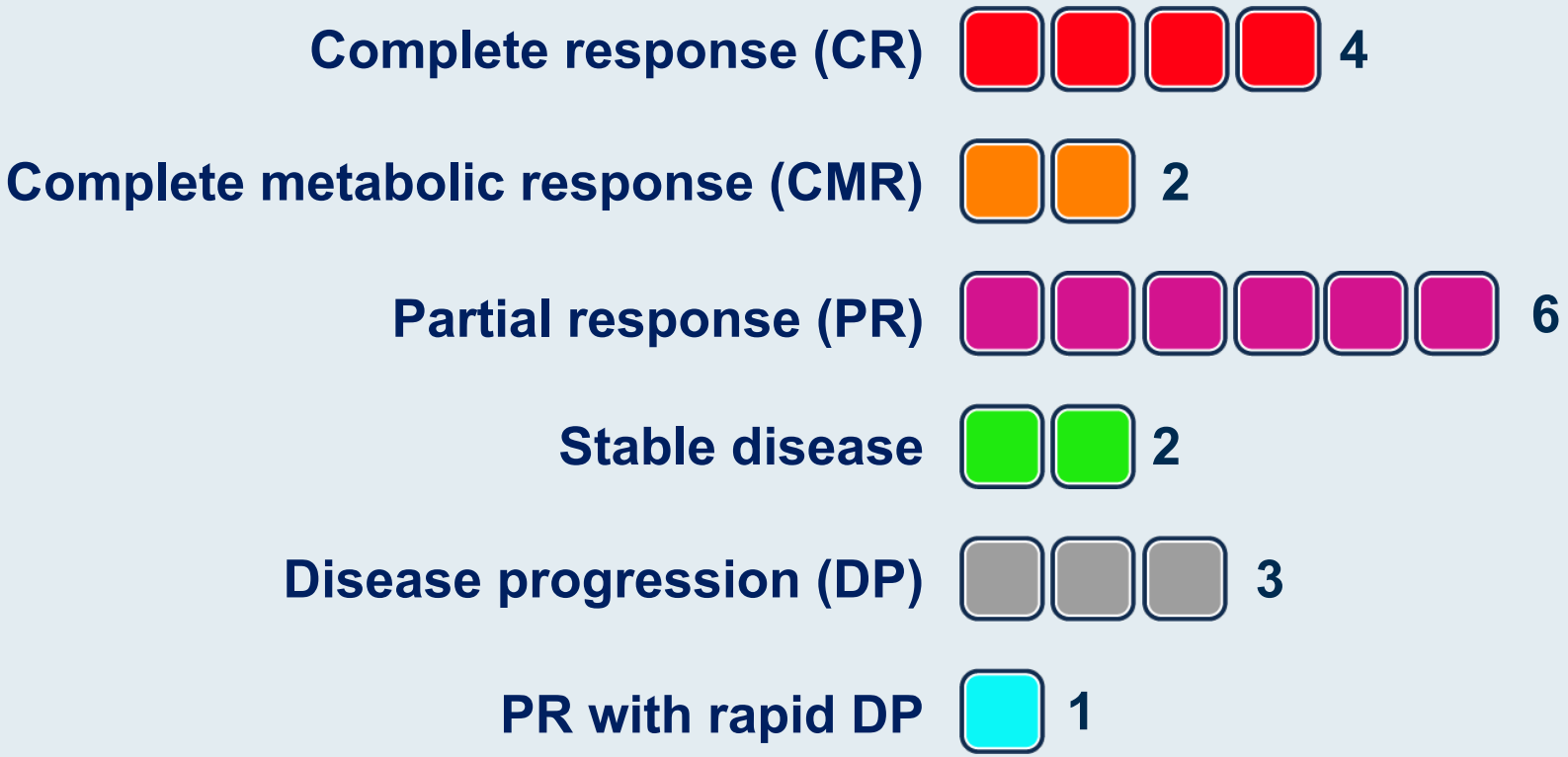
Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Please describe a patient with DLBCL you've cared for this year who received tafasitamab/lenalidomide.

**Patient age:** 80 (median; range 56-82)

**Patient's response to therapy:**

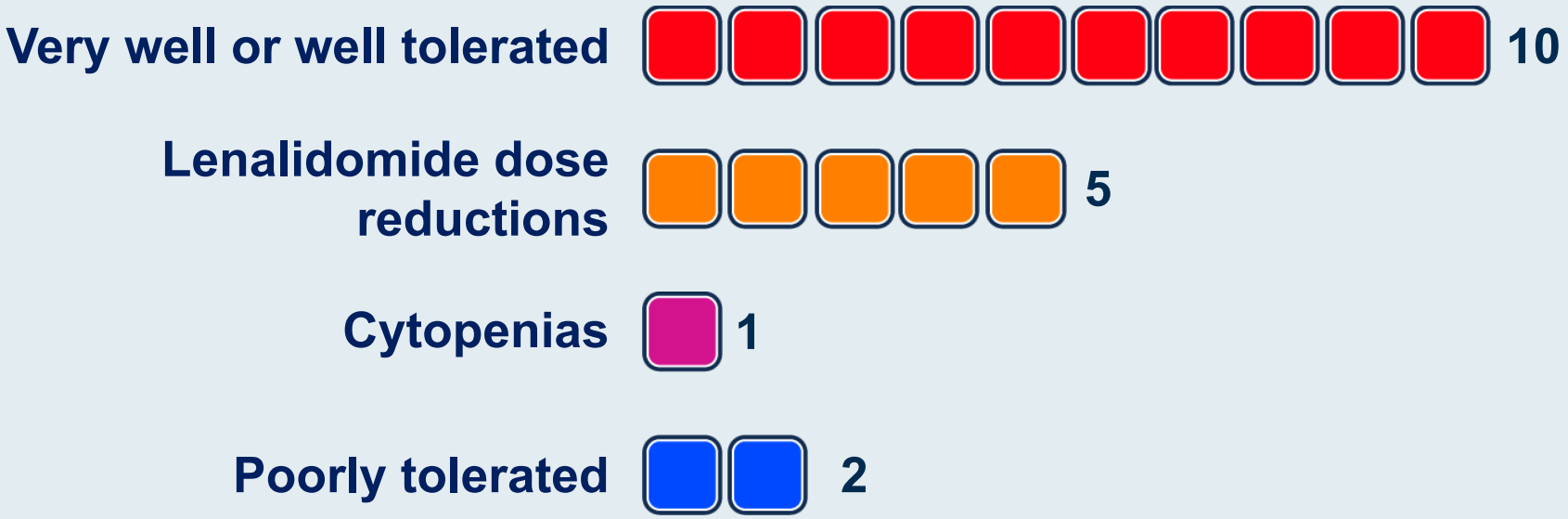



Survey of 18 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Please describe a patient with DLBCL you've cared for this year who received tafasitamab/lenalidomide.

## Patient's tolerance of therapy:



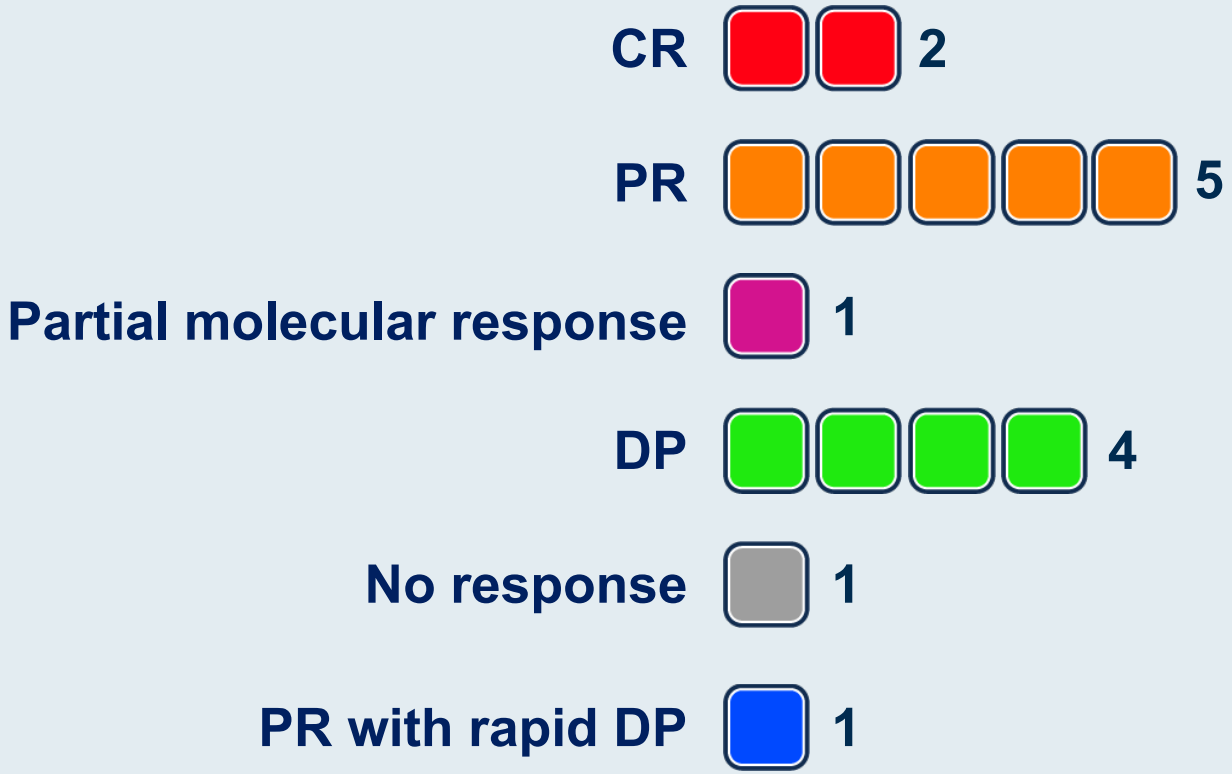

Survey of 18 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Please describe a patient with DLBCL you've cared for this year who received loncastuximab tesirine.

**Patient age:** 68 (median; range 39-80)

**Patient's response to therapy:**

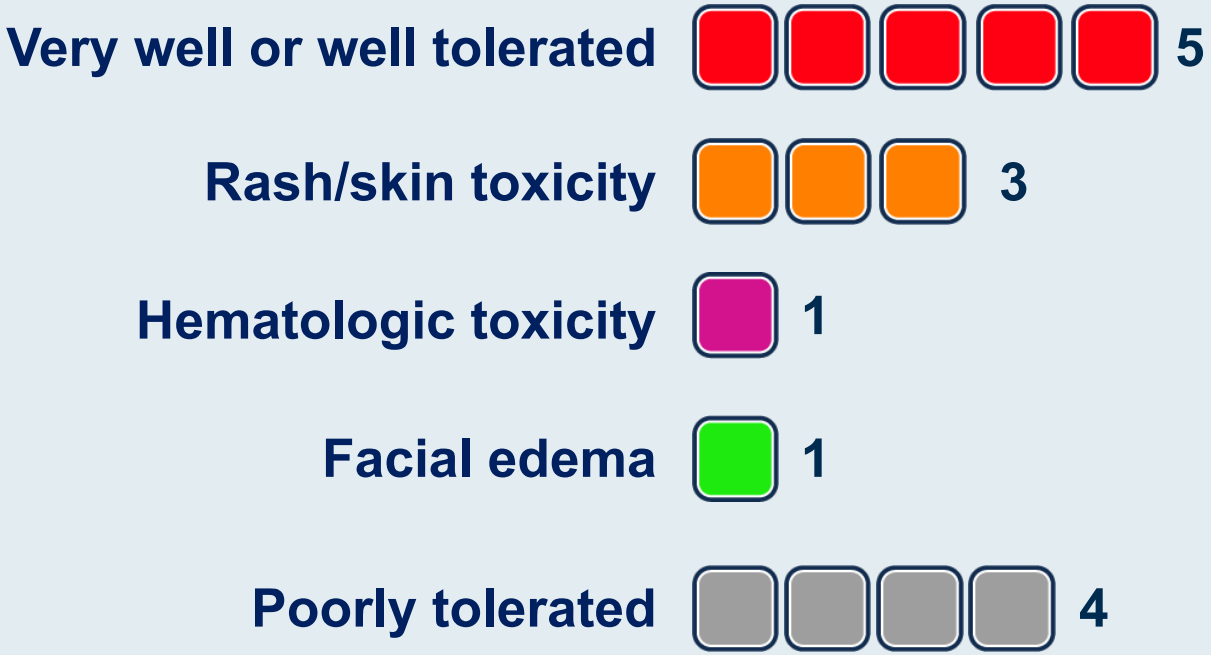



Survey of 14 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Please describe a patient with DLBCL you've cared for this year who received loncastuximab tesirine.

## Patient's tolerance of therapy:




Survey of 14 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Clinical experience with tafasitamab/lenalidomide for R/R DLBCL

Tycel Phillips, MD

Andrew D Zelenetz, MD, PhD

RTP
RESEARCH
TO PRACTICE

# Efficacy and tolerability of tafasitamab in combination with lenalidomide

Max S Topp, MD

Andrew M Evens, DO, MBA, MSc

RTP
RESEARCH
TO PRACTICE

# Clinical experience with loncastuximab tesirine for patients with R/R DLBCL

Max S Topp, MD

Franck Morschhauser, MD, PhD

Kami Maddocks, MD

RTP
RESEARCH
TO PRACTICE

# Activity and safety of the antibody-drug conjugates polatuzumab vedotin and loncastuximab tesirine

Tycel Phillips, MD

Andrew D Zelenetz, MD, PhD

RTP
RESEARCH
TO PRACTICE

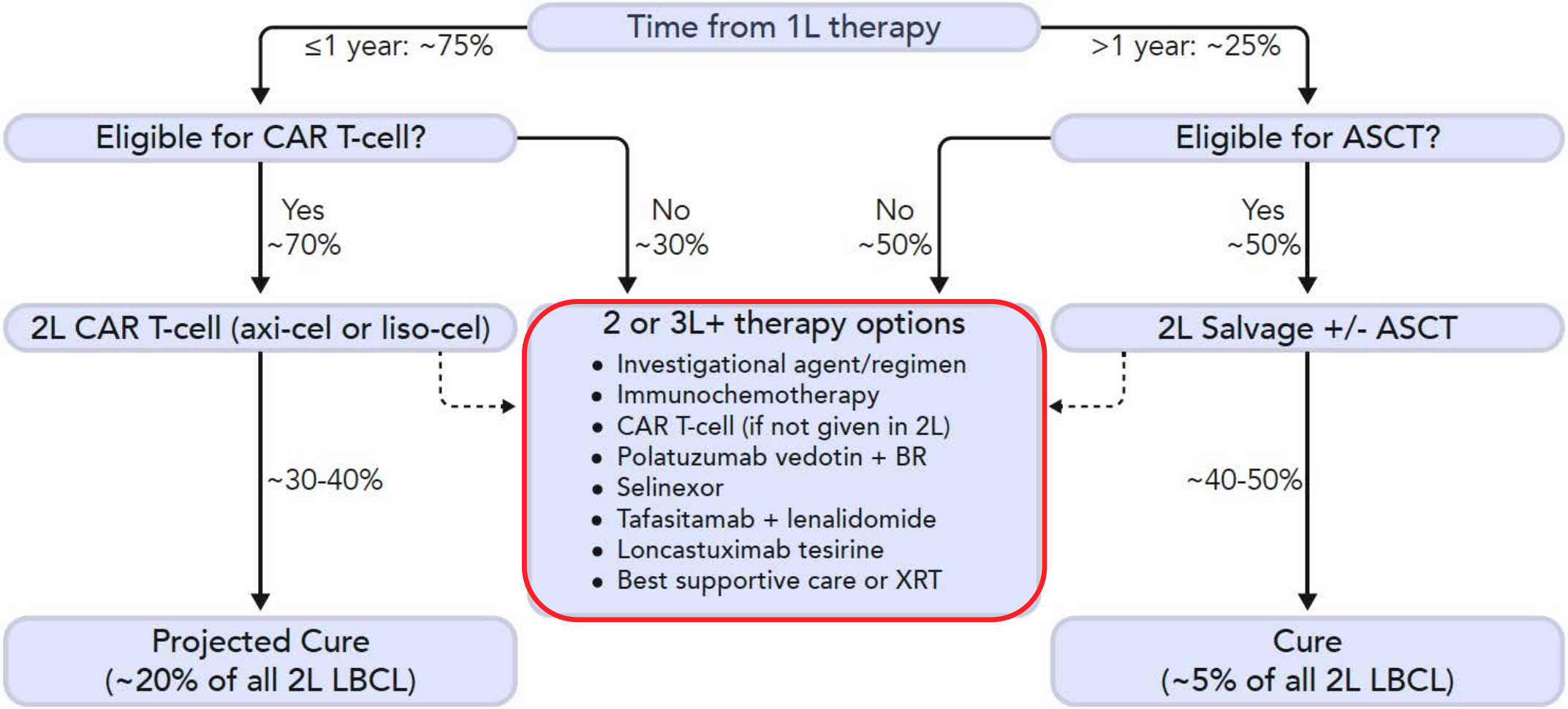
# Sequencing Novel Therapies for R/R DLBCL

**Laurie H. Sehn, MD, MPH**

**Chair, Lymphoma Tumour Group**

***BC Cancer Centre for Lymphoid Cancer***
***Vancouver, Canada***

# New Algorithm for Relapsed/Refractory LBCL




*Westin and Sehn. Blood 2022*

# Novel Agents Recently Approved in R/R DLBCL

| | Pola-BR[1] | Tafasitamab/ Lenalidomide[2] | Loncastuximab Tesirine[3] | Selinexor[4] |
|---|---|---|---|---|
| **MOA** | Anti-CD79b ADC | Anti-CD19 MAb + Immunomodulator | Anti-CD19 ADC | XPO-1 inhibitor |
| **ORR** | 45% | 58% | 48% | 29% |
| **CR rate** | 40% | 40% | 24% | 10% |
| **PFS** | 9.2m | 11.6m | 4.9m | 2.6m |
| **DOR** | 12.6m | 43.9m | 10.3m | 9.3m |
| **OS** | 12.4m | 33.5m | 9.9m | NR |

≥1 prior line

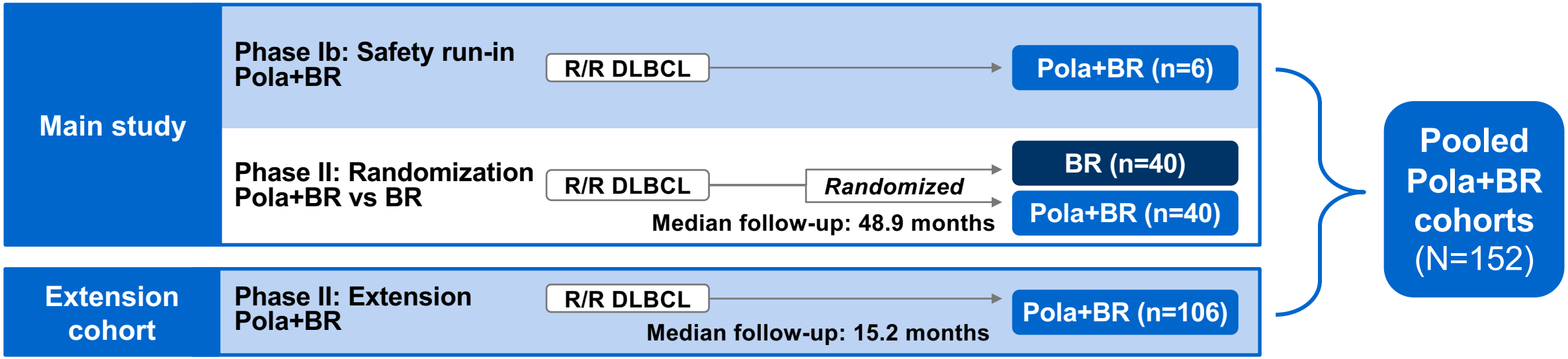
≥2 prior lines

[1]Sehn LH et al. *Blood Adv.* 2022;6(2):533-543. [2]Duell J, et al. *Haematologica*. Published online August 31, 2023. [3]Furqan F, *Ther Adv Hematol*.2022;13:20406207221087511. Published 2022 Mar 22. [4]Maerevoet M, et al. *J Hematol Oncol*. 2021;14(1):111. Published 2021 Jul 16.

# Phase I/IIb: Polatuzumab Vedotin-BR in ASCT-Ineligible DLBCL

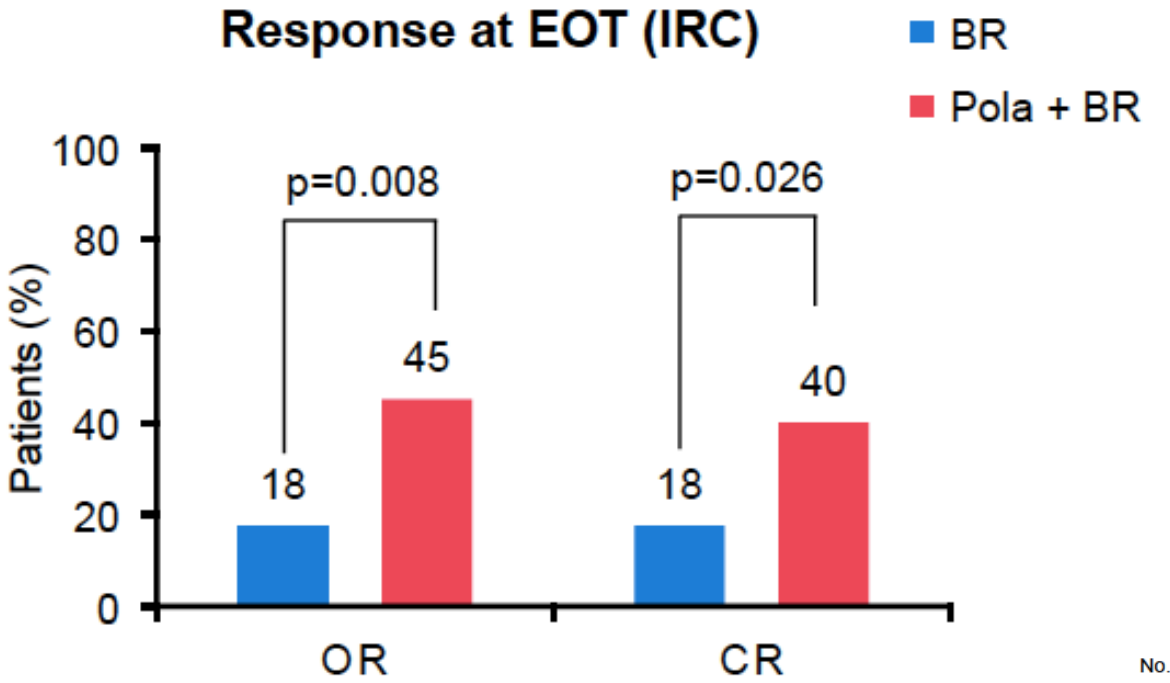
**Inclusion:** transplant-ineligible DLBCL, ≥1 line of therapy

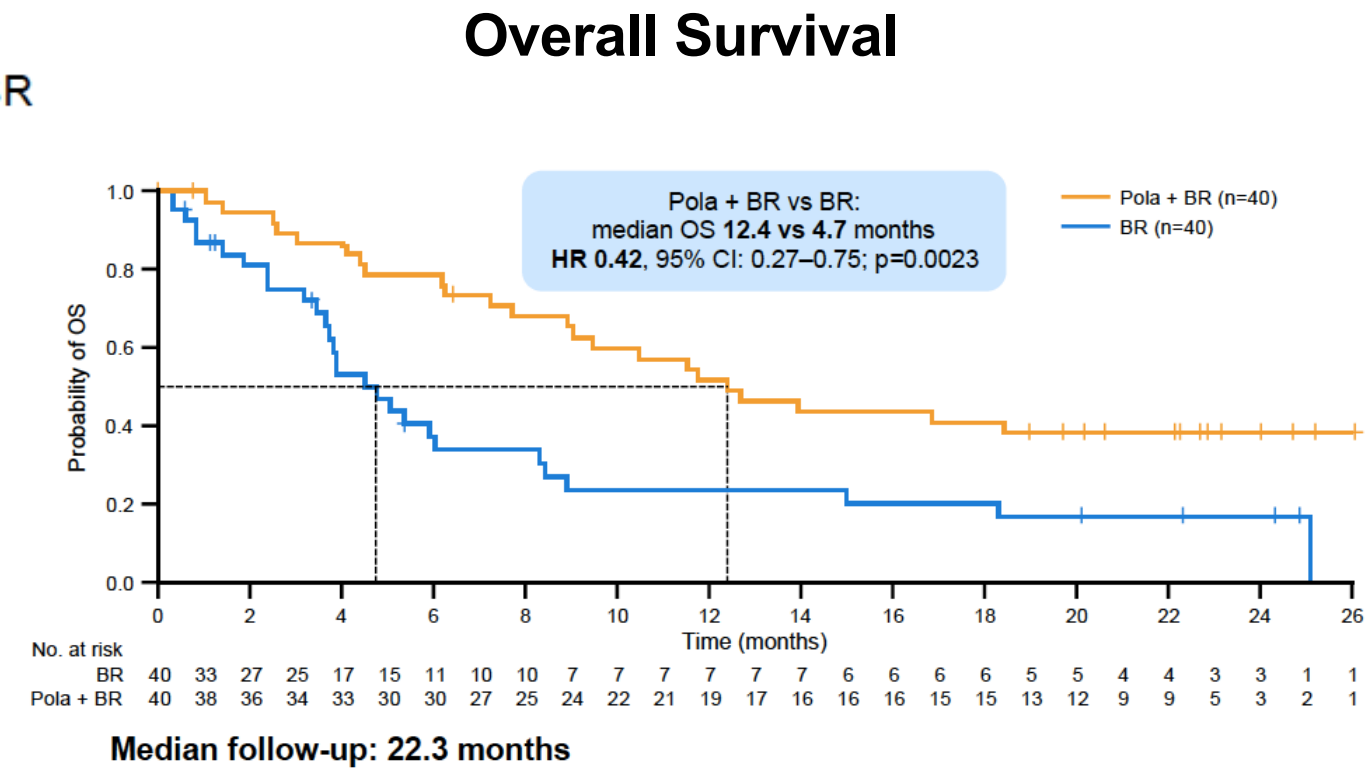
**Exclusion:** prior allo-SCT; history of transformation; current grade >1 PN




*Pola 1.8 mg/kg on D1 of each cycle of BR; up to 6 cycles at 3-weekly interval

# GO29365 Randomized Phase II: Pola-BR vs BR



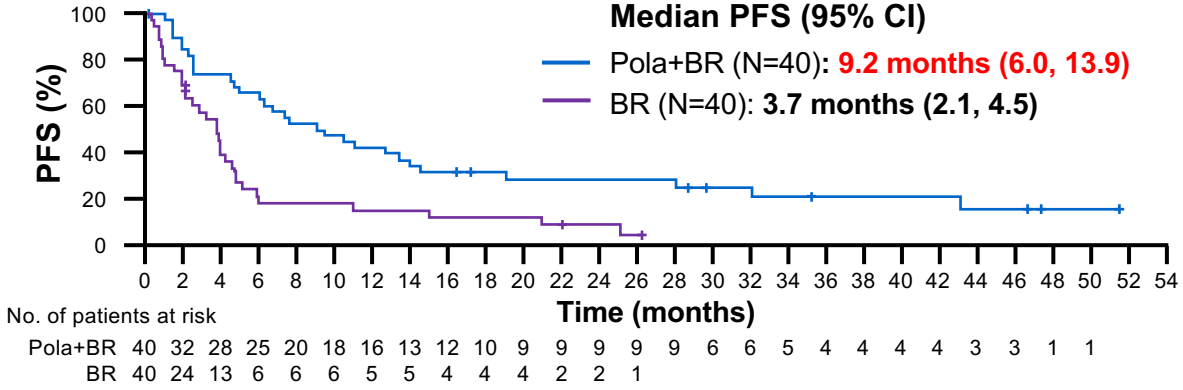



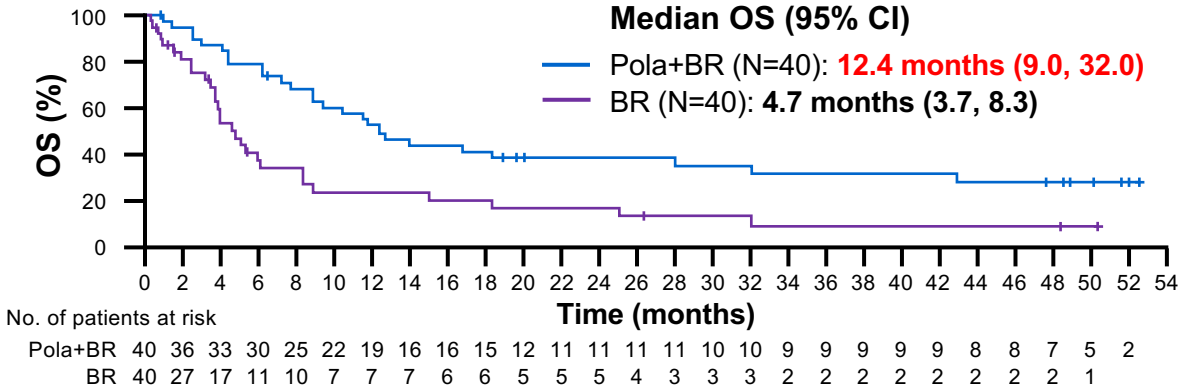

**Median follow-up: 22.3 months**

*Sehn et al, JCO 2020*

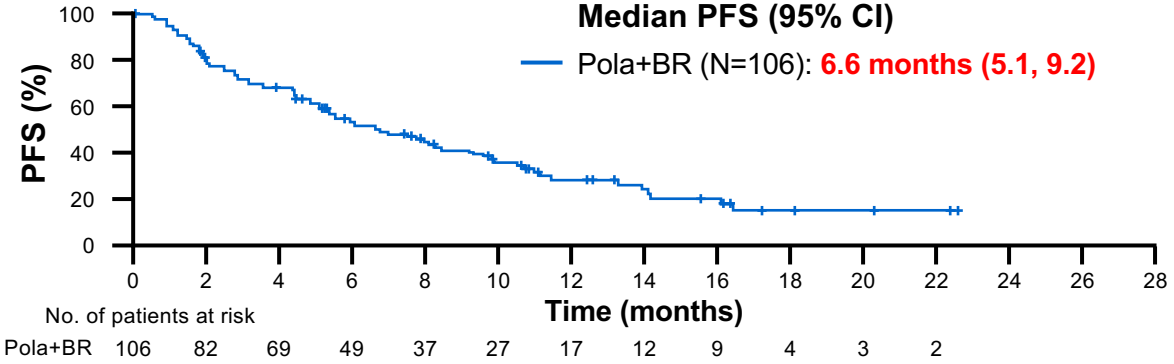
# PFS and OS in Randomized and Extension Cohorts

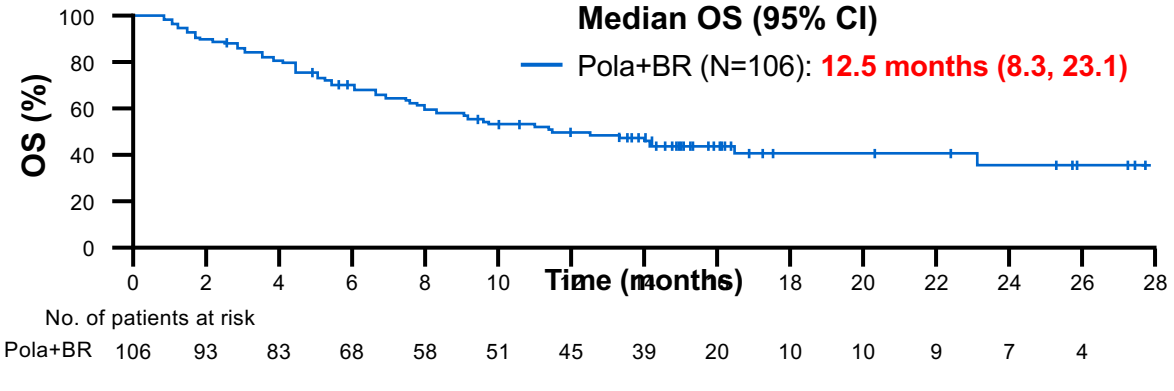
## Randomized




## Extension cohort




**<u>Randomized cohort</u>**:

- Survival benefit persists with longer follow-up
- 2-y PFS: 28.4%, 2-y OS was 38.2%

**<u>Pooled cohort</u>**:

- Non-primary refractory patients:
  Median PFS: 13.4 m, median OS: 32 m

*Sehn et al, Blood Advances 2021*

# Safety Summary in Pooled Pola+BR Cohort

| Common AEs, n (%) | Pooled Pola+BR (N=151) | |
|---|---|---|
| | Any grade | Grade 3–4 |
| **Hematological AEs** | | |
| Neutropenia | **71 (47.0)** | **49 (32.5)** |
| Thrombocytopenia | 49 (32.5) | 31 (20.5) |
| Anemia | 49 (32.5) | 19 (12.6) |
| **Non-hematological AEs** | | |
| Infections and infestations | **74 (49.0)** | **33 (21.9)** |
| Diarrhea | 54 (35.8) | 6 (4.0) |
| Nausea | 50 (33.1) | 1 (0.7) |
| Pyrexia | 44 (29.1) | 2 (1.3) |
| Fatigue | 40 (26.5) | 3 (2.0) |
| Decreased appetite | 39 (25.8) | 4 (2.6) |
| **AEs of special interest** | | |
| Peripheral neuropathy‡ | **47 (31.1)** | **3 (2.0)** |

- **Main side effects**:
  - Neutropenia
  - Infection
  - Peripheral neuropathy

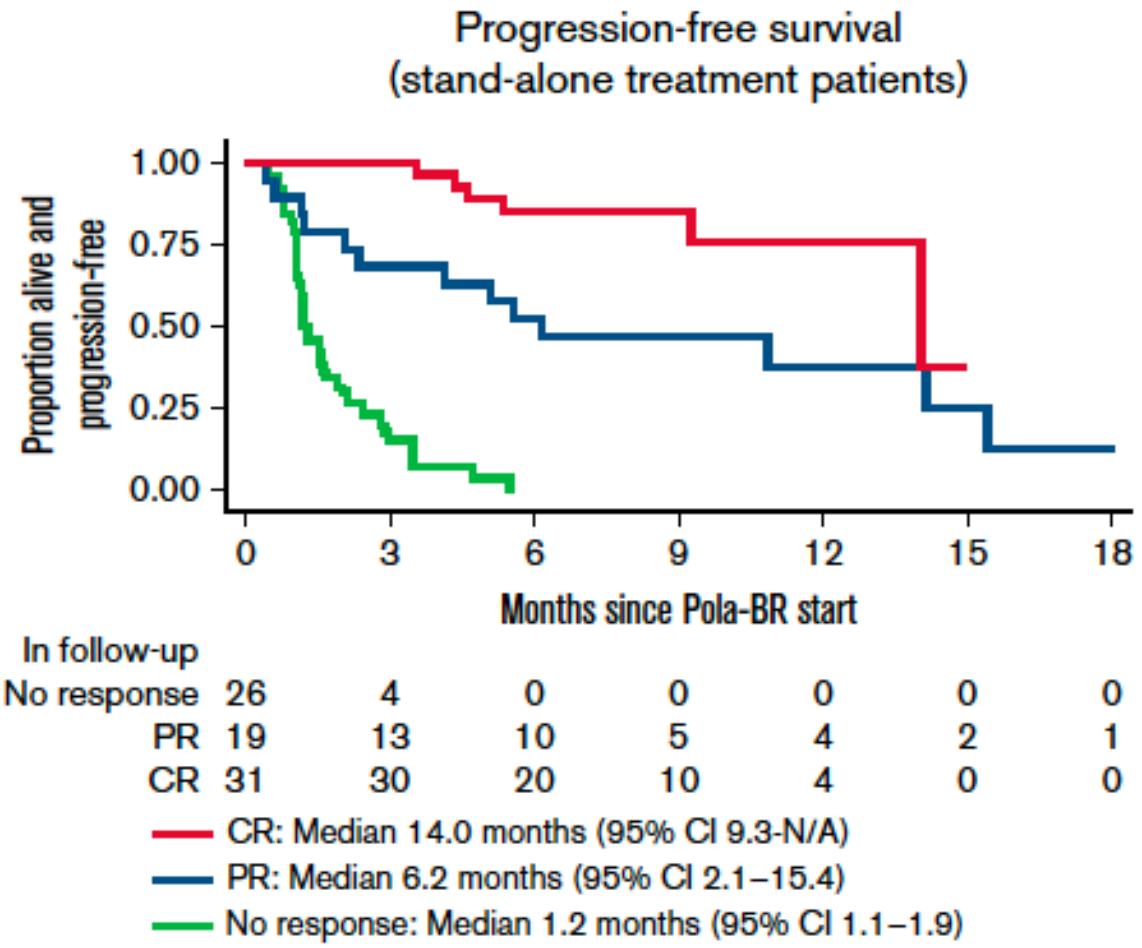
*Sehn et al, Blood Advances 2021*

# Real-World Assessment of Pola-BR in R/R DLBCL

- Retrospective UK cohort, largely treated on early access program
- Median follow-up 7.7 m

- Stand-alone therapy n=78
  - median age 75 y
  - Median cycles: 4
  - ORR 65.8% (39.7%CR, 24.4% PR)
  - Median PFS: 5.4 m (95%CI 3.0-10.8)

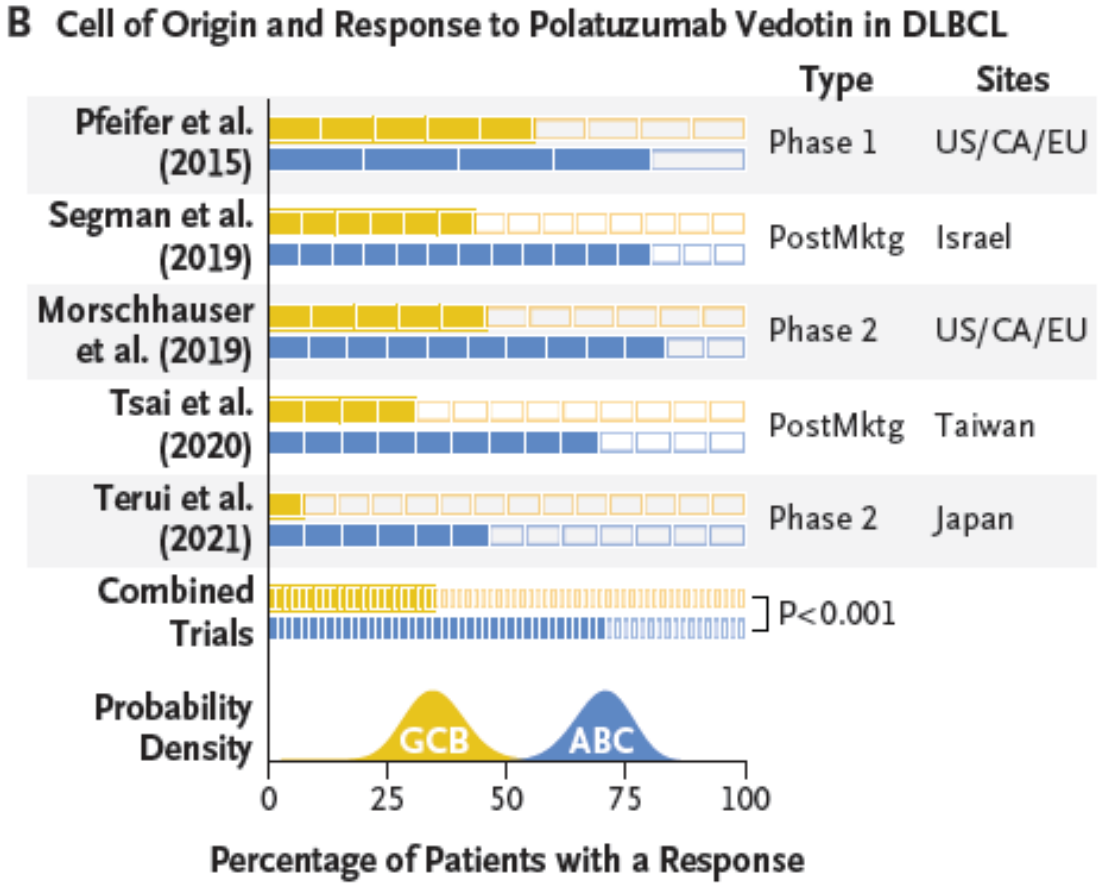
- Bridge to CAR T-cell therapy n=40
  - median age 67 y
  - Median cycles: 1
  - ORR 42.1% (17.5%CR, 22.5% PR)
  - 77.5% received CAR T-cell therapy



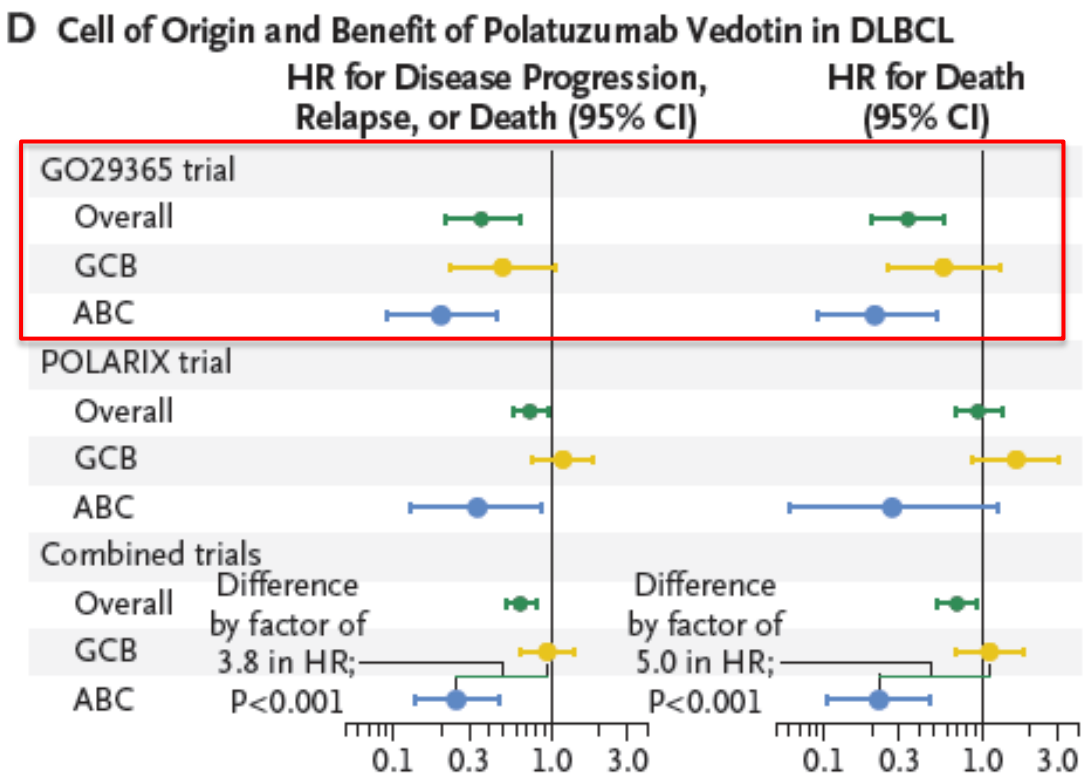

*Northend M et al. Blood Advances 2022*

# Cell-of-Origin and Therapeutic Benefit from Polatuzumab Vedotin

## Single Arm Data

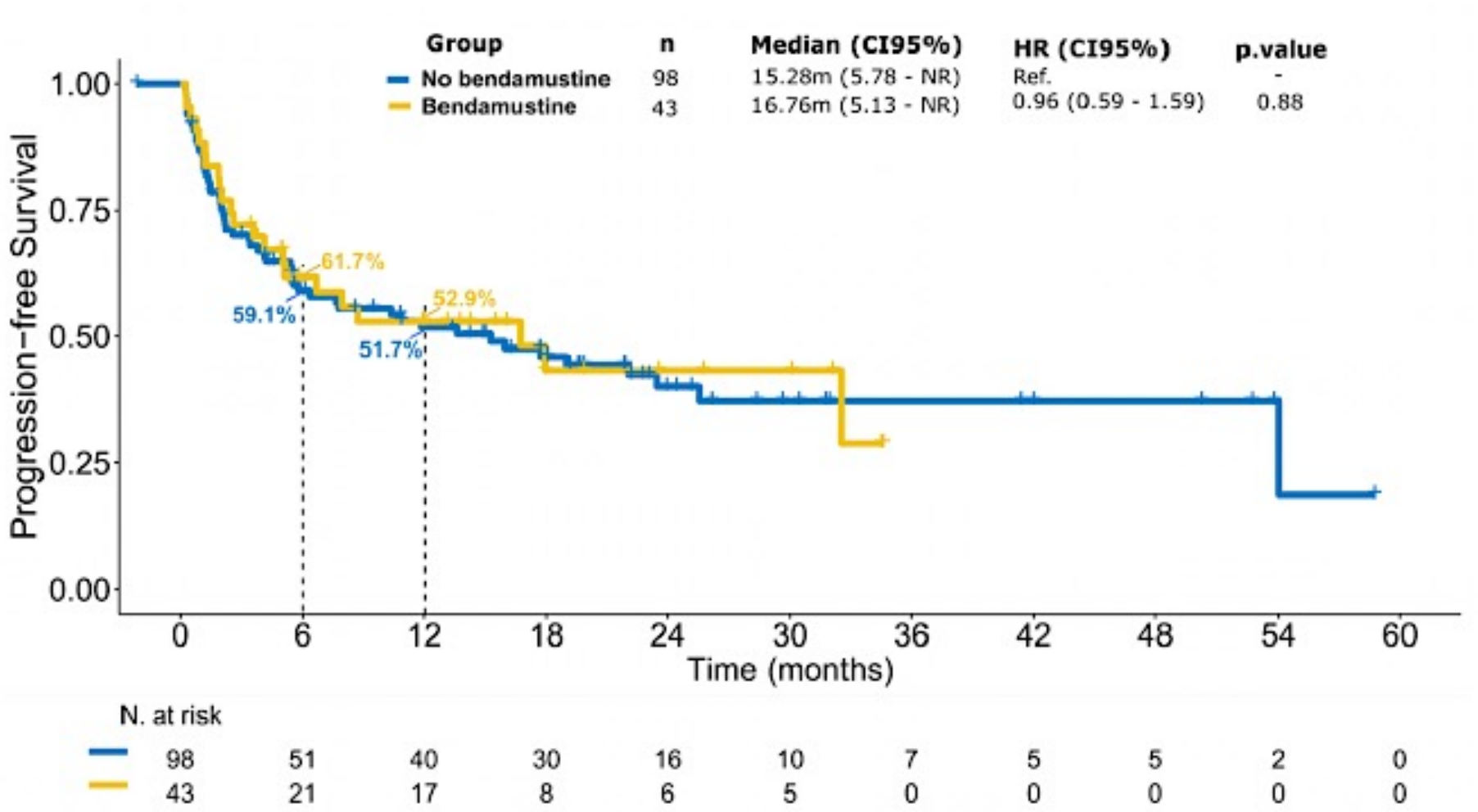



## Randomized Trial Data




*Palmer AC et al. NEJM 2023*

# PFS with Bispecifics Based on Prior Bendamustine




*Iacoboni G et al. ASH 2023 abstract 310; Saturday 4:45*

# Tafasitamab and Lenalidomide: L-MIND Study

Phase 2, single-arm, open-label, multicenter study (NCT02399085)

**R-R DLBCL**
- 1-3 prior regimens
- not eligible for HDCT and ASCT
- primary refractory patients were to be excluded

**Cycle 1-3**
Tafasitamab 12 mg/kg q4w; d 1, 8, 15, 22*
+
Lenalidomide 25 mg/d p.o. d 1-21

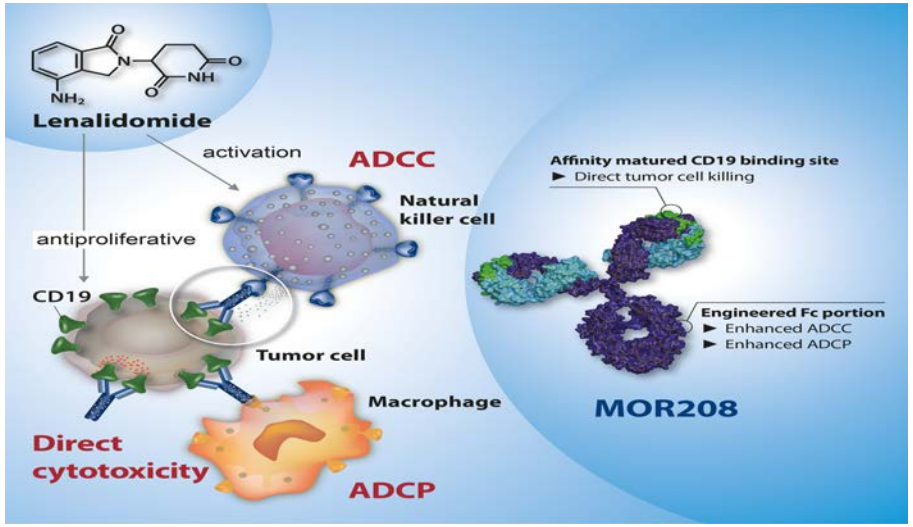
**Cycle 4 -12**
Tafasitamab 12 mg/kg q4w; d 1, 15
+
Lenalidomide 25 mg/d p.o. d 1-21

≥SD

**Cycle 12+**
Tafasitamab 12 mg/kg d 1, 15
+
Lenalidomide 25 mg/d p.o. d 1-21

until progression

* a loading dose of MOR208 was administered on day 4 of cycle 1




**Primary endpoint**
- ORR (Central read)

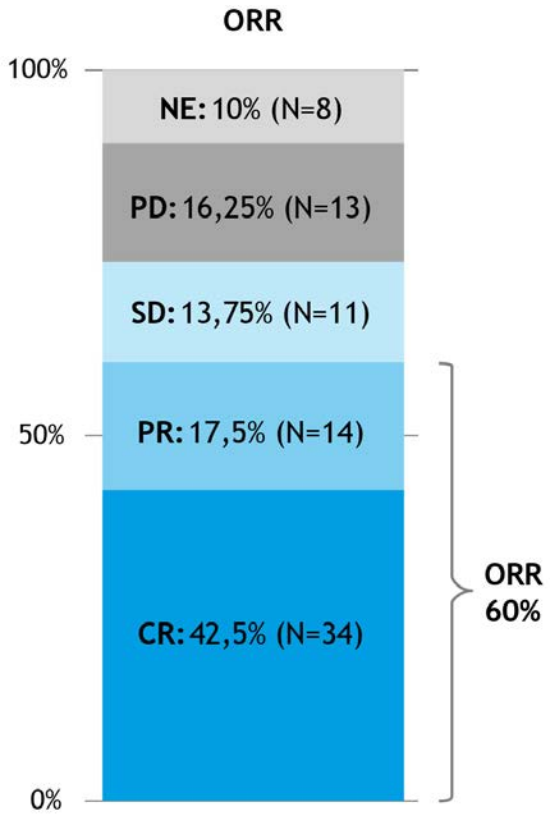
**Secondary endpoints**
- PFS
- DoR
- OS
- Safety of the Tafasitamab + LEN combination
- Exploratory and biomarker-based analyses

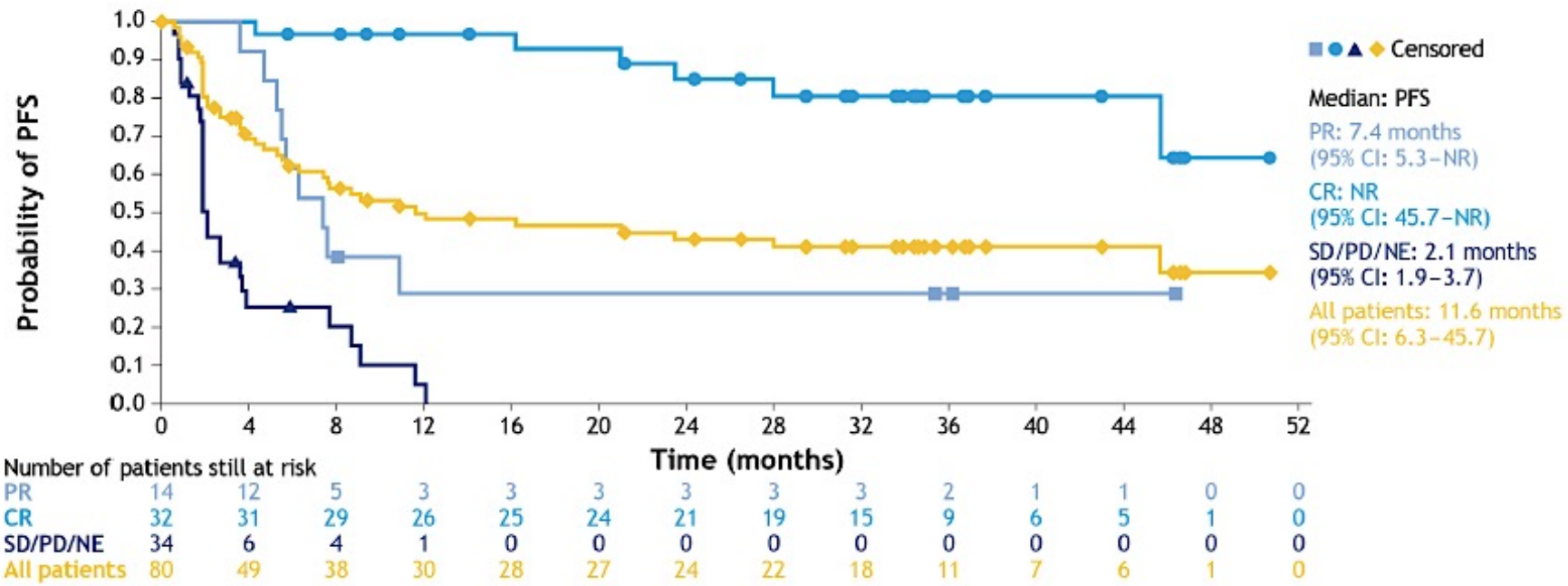
*Salles G et al, Lancet Oncology 2020*

# L-MIND Trial: Efficacy (n=80)

**ORR 60%, CR rate 43% by IRC**

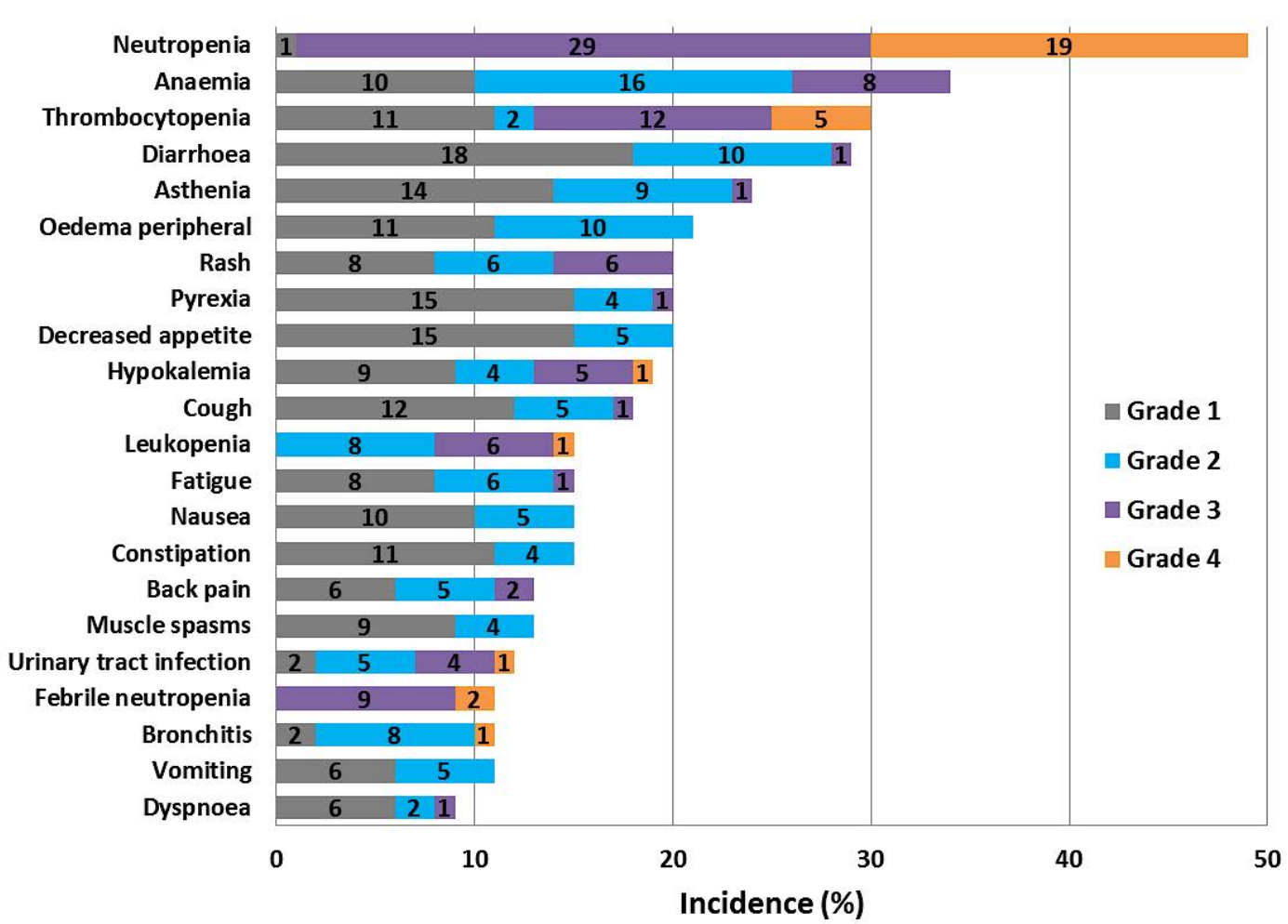
➔ Median follow-up 33.9 months
➔ Median PFS: 11.6 mos (95% CI: 6.3 - 45.7 mos)




*Salles G et al, Lancet Oncology 2020, Duell J et al, Haematologica 2021*

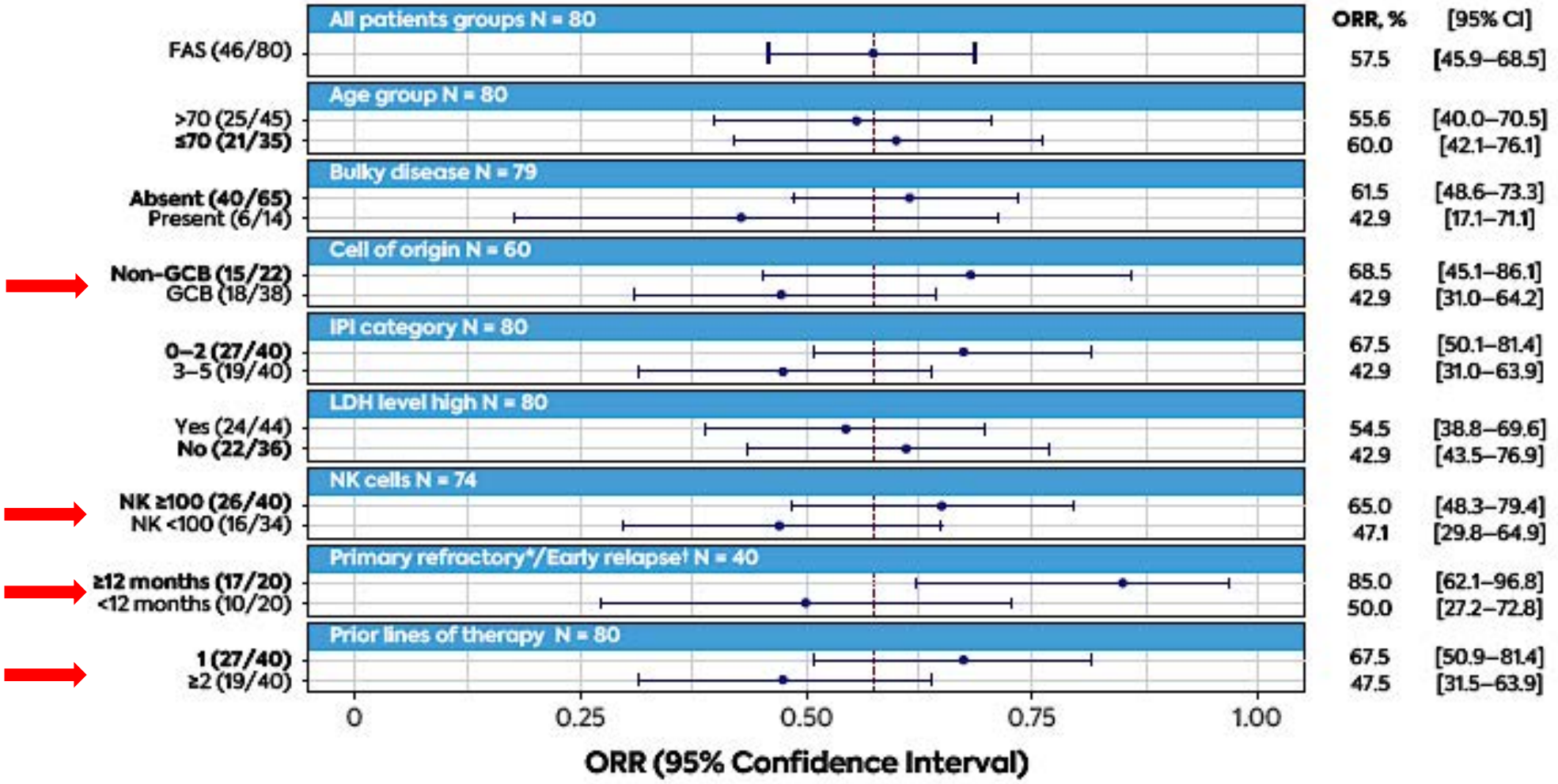
# L-MIND: Safety by Treatment Phase




- **Main side effects** (primarily occur during first year):
  - Cytopenias
  - Diarrhea
  - Peripheral edema
  - Rash
  - Fatigue
  - Infection

***Salles G et al, Lancet Oncol 2020***

# L-MIND: 5-Year Subgroup Analysis of ORR




*Duell J et al, ICML 2023*

# Real-World Assessment of Tafa/Len in R/R DLBCL

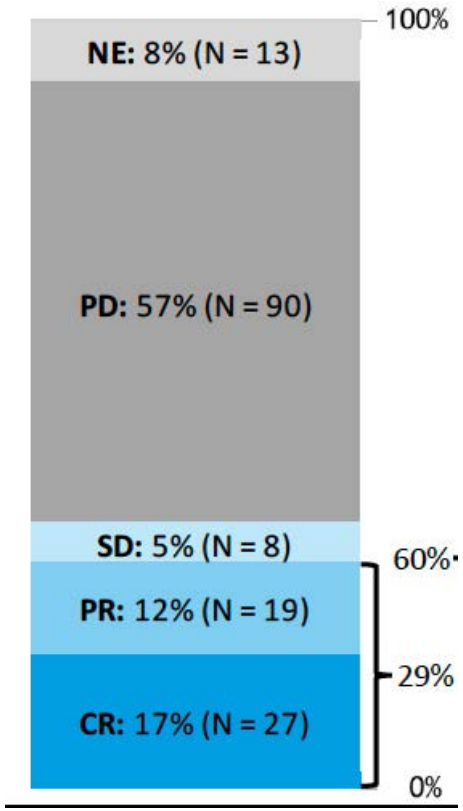
- Retrospective US multi-centre cohort
- Received at least 1 cycle tafasitamab/lenalidomide
- Aug 2020-Aug 2022

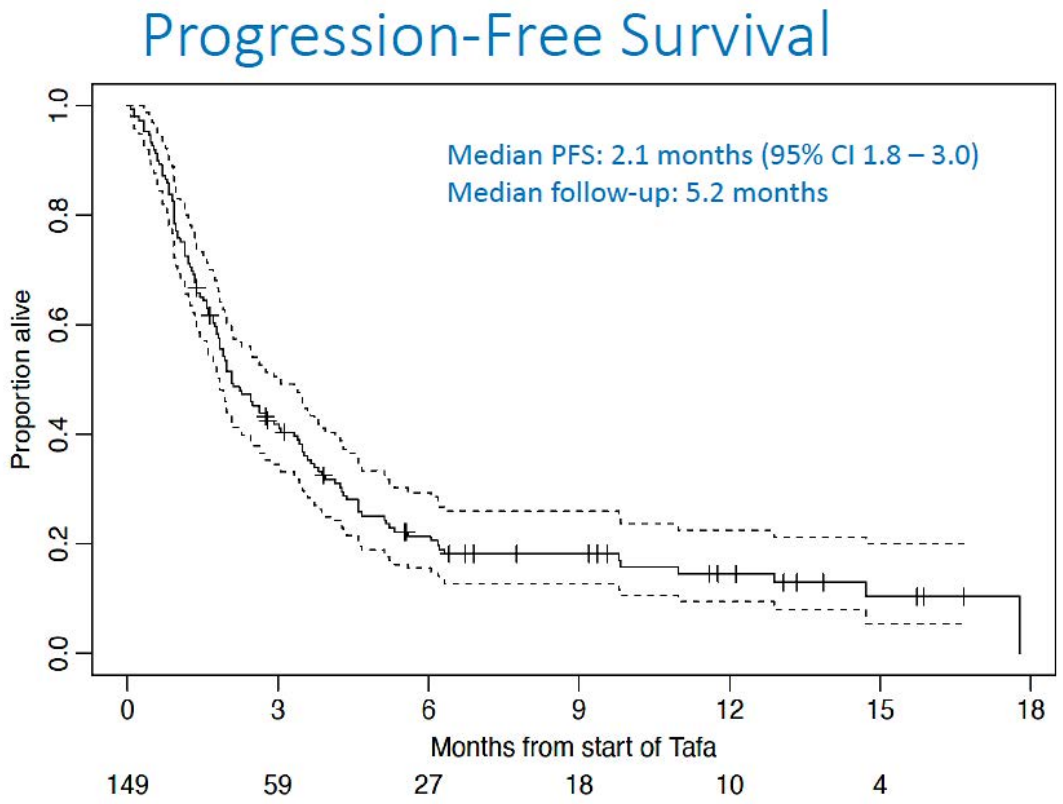
**L-MIND Eligible: 11%**

**Reasons for L-MIND ineligibility:**

| | |
|---|---|
| • EGFR < 60 ml/min | 33% |
| • Prior anti-CD19 therapy | 28% |
| • >3 prior lines of therapy | 23% |
| • ECOG PS 3-4 | 18% |
| • High-grade B cell lymphoma | 15% |

Best Response



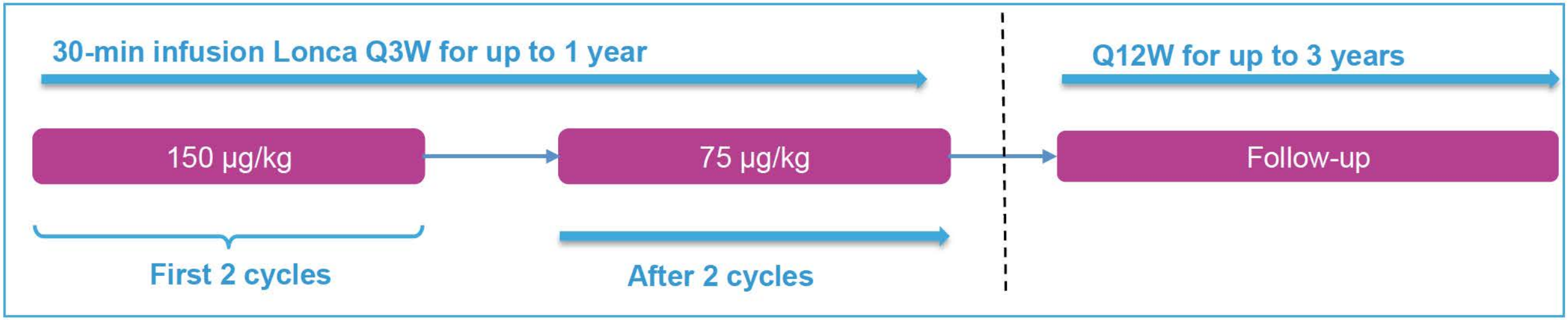




*Qualls D et al. ASH 2022*

# Loncastuximab Tesirine: LOTIS-2 Trial
# Single Arm Open Label Phase 2 Study in DLBCL

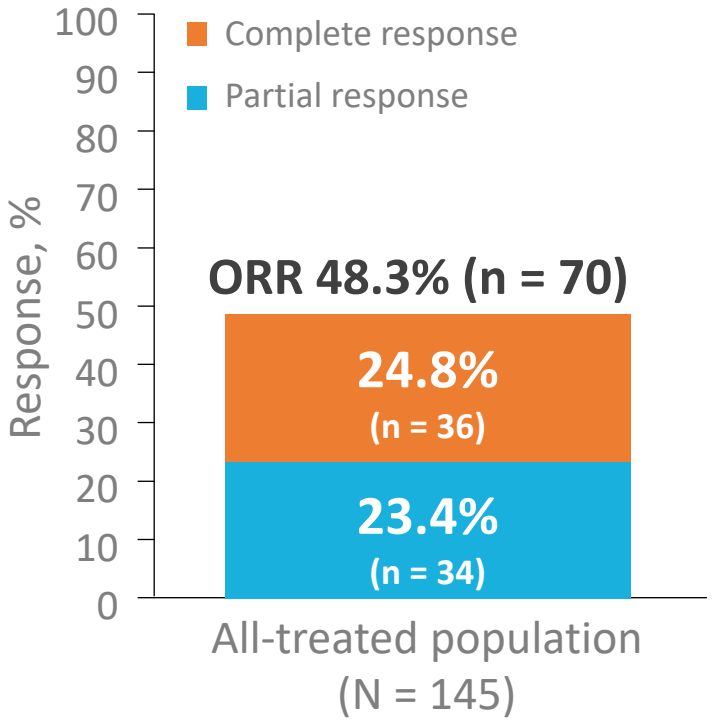
**Patient population:**
**Patients with R/R DLBCL following ≥2 lines of prior systemic therapy**

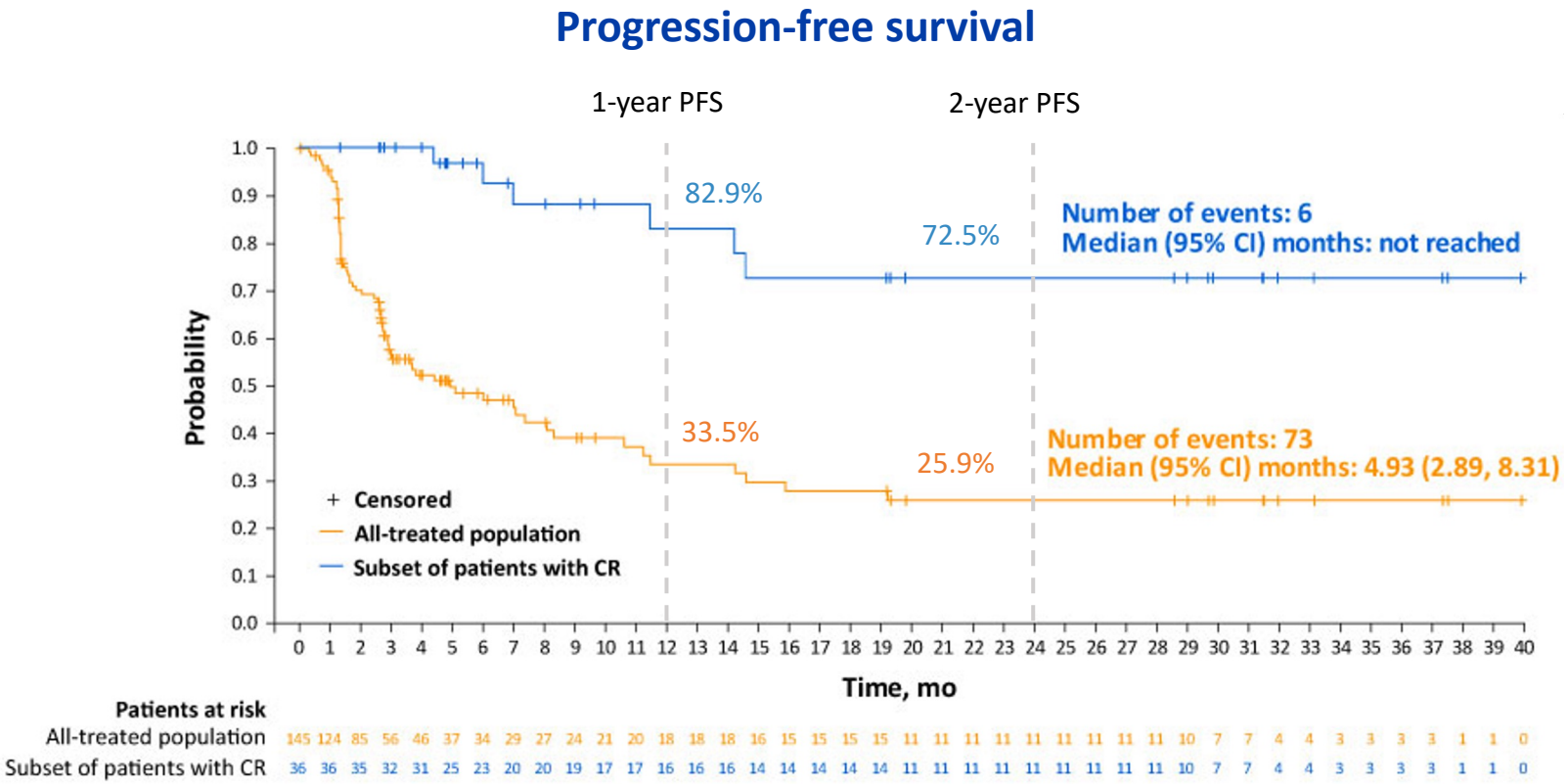
**Primary objective:**
Evaluate efficacy, **using ORR** (central review), and **safety** of the full Phase 2 study population




*Caimi et al, Lancet Oncology 2021*

# Overall Response Rate and Long-term PFS




*Caimi et al, ICML 2023*

# Loncastuximab Tesirine Safety

| TEAEs, any grade in ≥30% of patients | All-treated population, N = 145 |
|---|---|
| Patients with any TEAE | 98.6% |
| Increased GGT | 42% |
| Neutropenia | 40% |
| Thrombocytopenia | 33% |
| Anemia | 26% |
| Peripheral edema | 20% |
| Nausea | 23% |

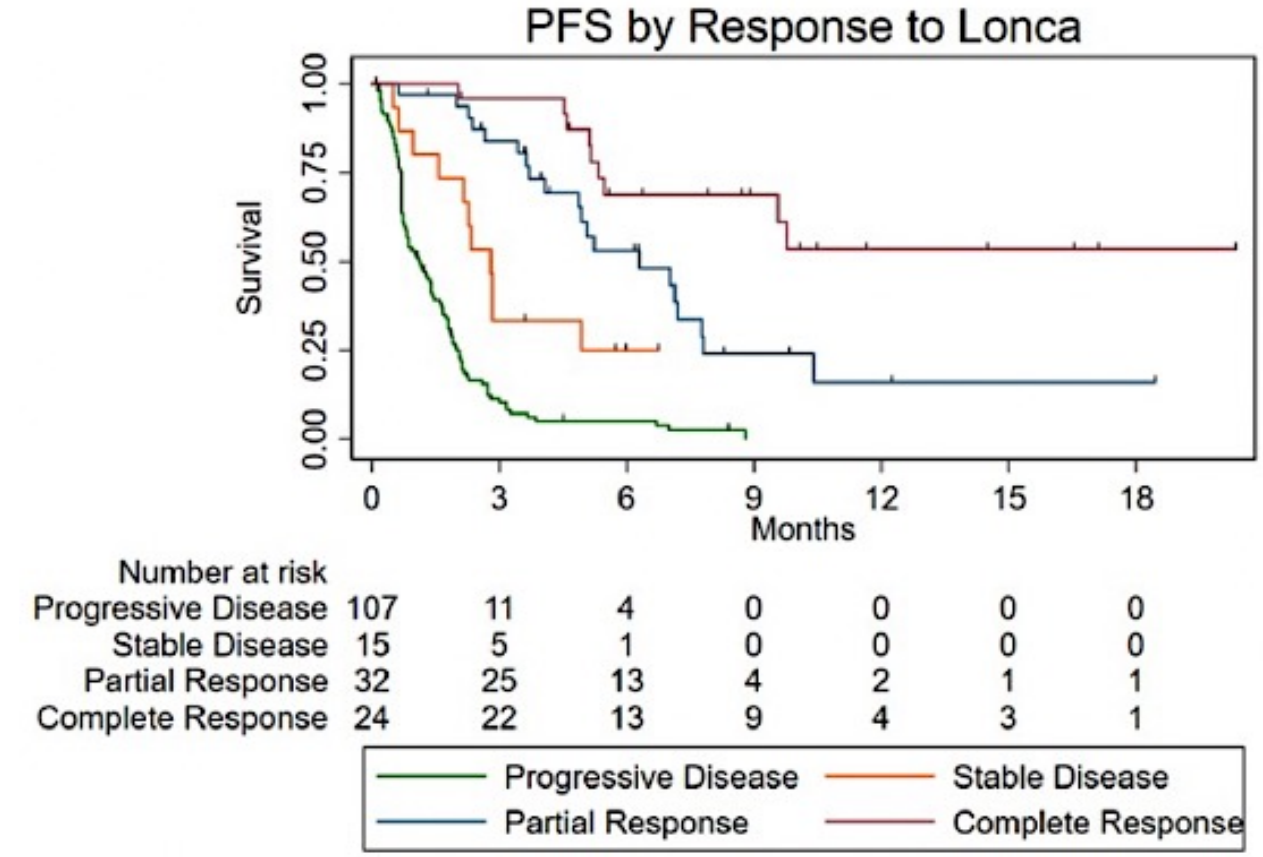
| TEAEs, grade ≥3 in ≥10% of patients | All-treated population, N = 145 |
|---|---|
| Patients with any TEAE | 73.8% |
| Neutropenia | 26% |
| Thrombocytopenia | 18% |
| Increased GGT | 17% |
| Anemia | 10% |
| Leukopenia | 9% |
| Hypophosphatemia | 6% |

- **Main side effects:**
  - Cytopenias
  - Transaminitis
  - Peripheral edema
  - Nausea
  - Hypophosphatemia

***Caimi et al, ICML 2023***

# Loncastuximab Tesirine Real World Analysis

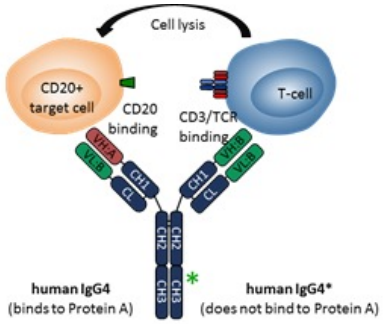
| | | Total N=187 | LOTIS-2 N=145 |
|---|---|---|---|
| Sex | Male | 119 (63.6%) | 85 (59%) |
| Age, years | <65 | 76 (40.6%) | 65 (45%) |
| | 65-75 | 62 (33.2%) | 59 (41%) |
| | >75 | 49 (6.2%) | 21 (14%) |
| Race | Asian | 11 (6.5%) | |
| | African American/Black | 14 (8.3%) | |
| | White | 144 (85.2%) | |
| Histology | *de novo* DLBCL | 102 (54.5%) | 98 (67.6%) |
| | HGBL | 33 (17.6%) | 11 (8%) |
| | Transformed DLBCL | 41 (21.9%) | 29 (20%) |
| | Other | 11 (5.9%) | |
| Stage | I-II | 23 (12.5%) | 33 (23%) |
| | III-IV | 161 (87.5%) | 112 (77%) |
| Cell of Origin | GCB | 61 (32.6%) | 48 (33%) |
| | nonGCB | 96 (51.3%) | 23 (16%) |
| | Missing | 30 (16.0%) | 74 (51%) |
| Double Hit | No | 123 (65.8%) | |
| | Yes | 36 (19.3%) | 15 (10%) |
| | Missing | 28 (15.0%) | |
| ECOG PS | 0-1 | 111 (74.0%) | |
| | 2-4 | 39 (26.0%) | |
| Elevated LDH at Lonca Initiation | No | 47 (25.1%) | |
| | Yes | 139 (74.3%) | |
| | Missing | 1 (0.5%) | |
| Bulky disease >10cm | No | 154 (82.8%) | 137 (94% |
| | Yes | 32 (17.2%) | 8 (6%) |
| CD19+ at Lonca Initiation | No | 19 (10.2%) | |
| | Yes | 109 (58.3%) | |
| | Unknown | 59 (31.6%) | |
| Lonca line of therapy | 2nd or 3rd | 36 (19.3%) | 63 (43%) |
| | 4th | 39 (20.9%) | 35 (24%) |
| | >4th | 112 (59.9%) | 47 (32%) |
| Response to 1st Line Therapy: | Relapsed | 126 (68.1%) | 99 (68%) |
| | Refractory | 59 (31.9%) | 29 (20%) |
| Response to most recent therapy | < CR | 171 (91.4%) | 84 (58%) |
| | CR | 16 (8.6%) | 43 (30%) |
| Previous CAR | No | 75 (40.1%) | 132 (91%) |
| | Yes | 112 (59.9%) | 13 (9%) |



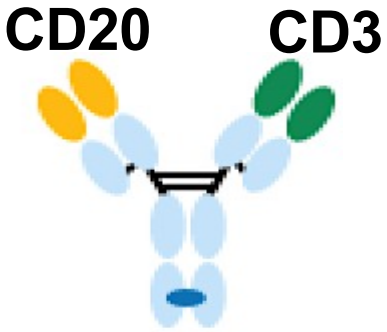

ORR 33%; CRR 14%; median PFS 2.1 m

***Ayers E et al, ASH 2023 abstract 312; Saturday 5:15***

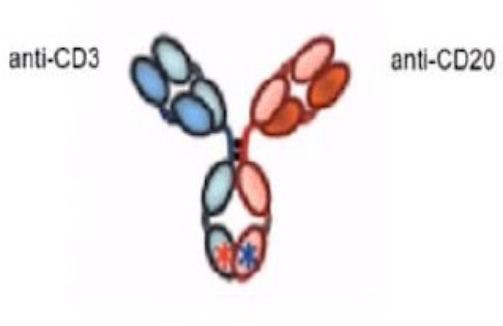
# Where do CD20/CD3 Bispecific Antibodies fit in?



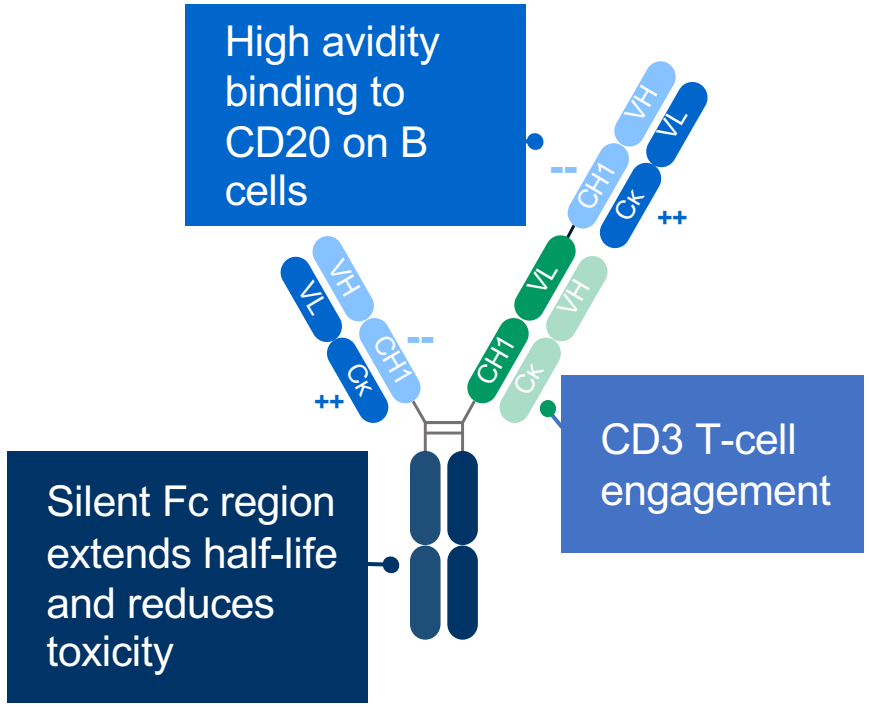

**Odronextamab**
**(IV)**
**(REGN1979)**
**IgG4**




**Mosunetuzumab**
**(IV/SC)**




**Epcoritamab**
**(SC)**
**Duobody**
**GEN3013**




**Glofitamab (IV)**
**CD20-TCB**

# Sequencing Novel Agents

- Novel agents overcoming chemo-resistance in DLBCL have emerged
- Sequencing novel agents in R/R setting should consider
  - Goals of therapy (?curative, palliative, bridging)
  - prior treatment (?frontline pola-R-CHP)
  - Comparative efficacy versus toxicity
  - Patient characteristics and preferences
- Predictive biomarkers will be essential for patient-tailored approach

# Agenda

**Module 1: Up-Front Management of Diffuse Large B-Cell Lymphoma (DLBCL) — Dr Salles**

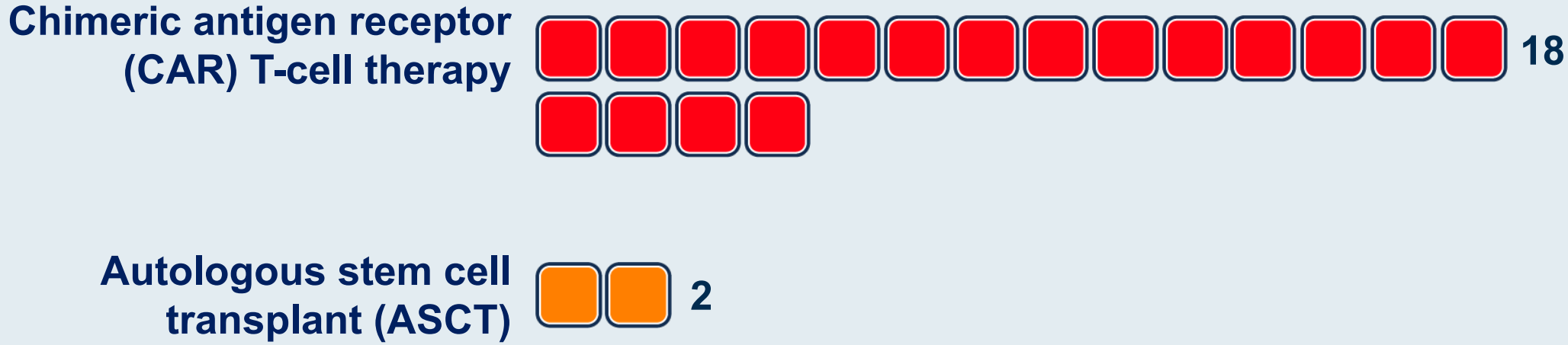
**Module 2: Promising Investigational Approaches to First-Line Therapy for DLBCL — Dr Nowakowski**

**Module 3: Selection and Sequencing of Novel Therapies for Relapsed/Refractory (R/R) DLBCL — Dr Sehn**

**Module 4: Incorporation of CAR T-Cell Therapy into the Management of R/R DLBCL — Dr Westin**

**Module 5: Role of Bispecific Antibodies in the Treatment of DLBCL — Prof Dickinson**

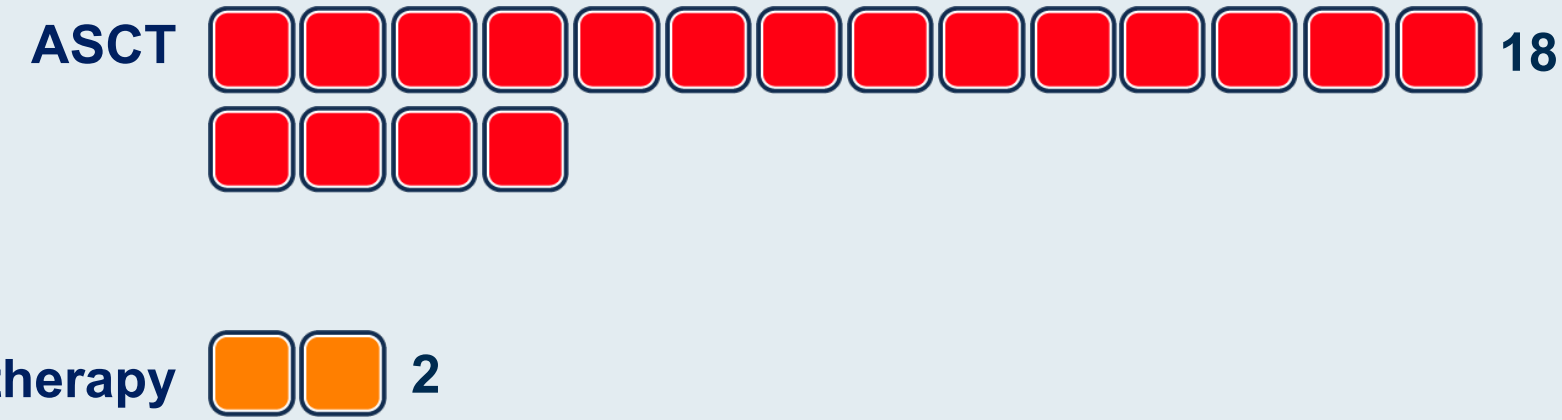
# Regulatory and reimbursement issues aside, which second-line therapy would you recommend for a younger (65-year-old), transplant-eligible patient with DLBCL who experiences disease relapse 12 months after R-CHOP?




Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

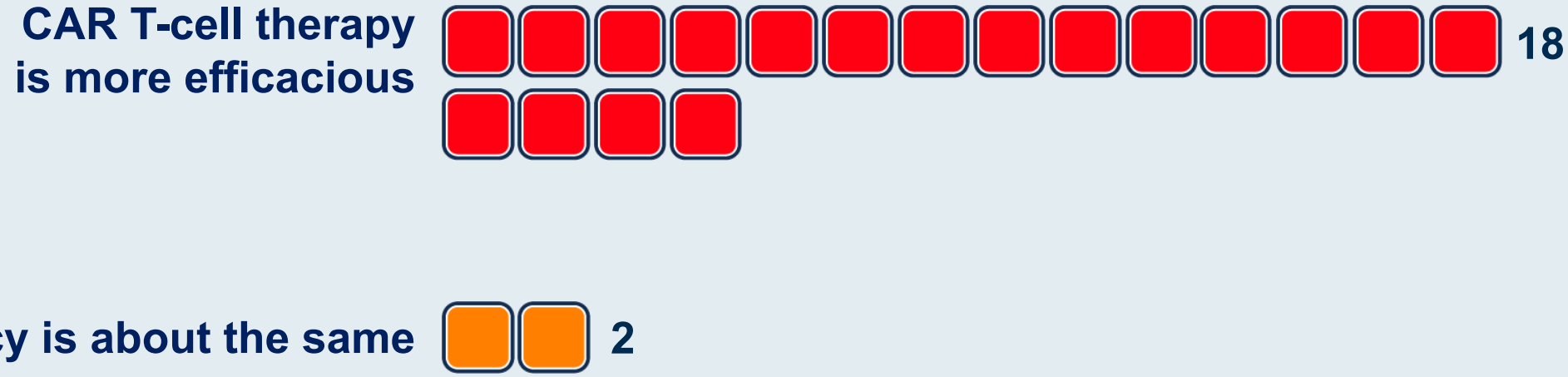
## Regulatory and reimbursement issues aside, which second-line therapy would you recommend for a younger (65-year-old), transplant-eligible patient with DLBCL who experiences disease relapse 30 months after R-CHOP?




Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

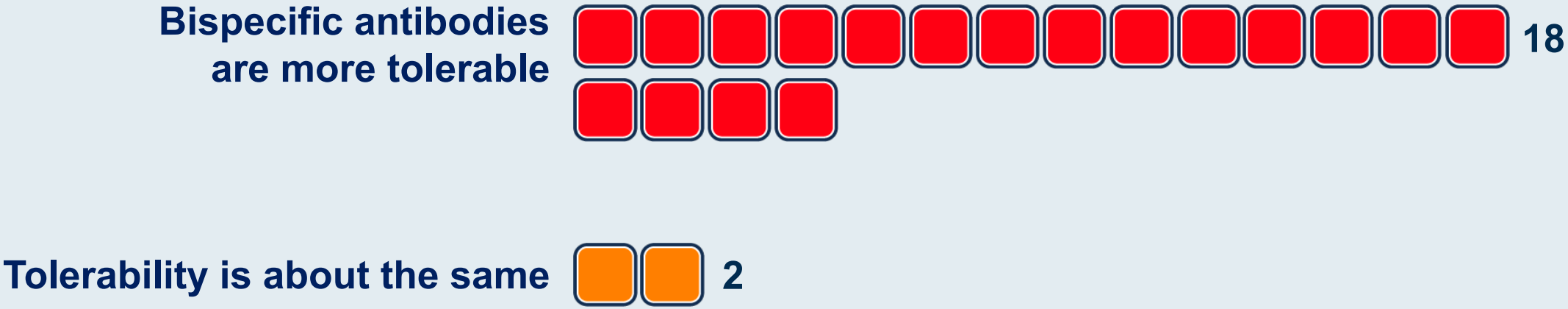
# Based on your personal clinical experience and knowledge of available data, how would you compare the global efficacy of bispecific antibodies to that of CAR T-cell therapy for patients with DLBCL?




Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Based on your personal clinical experience and knowledge of available data, how would you compare the global tolerability of bispecific antibodies to that of CAR T-cell therapy for patients with DLBCL?



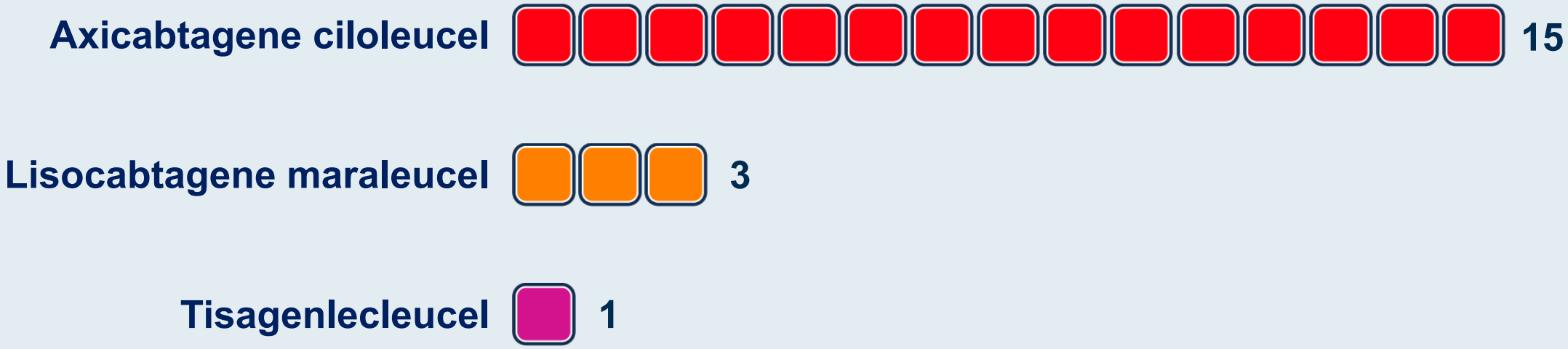

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Please describe a patient with DLBCL you've cared for this year who received CAR T-cell therapy.

**Patient age:** 62 (median; range 31-80)

## CAR T-cell platform the patient received:

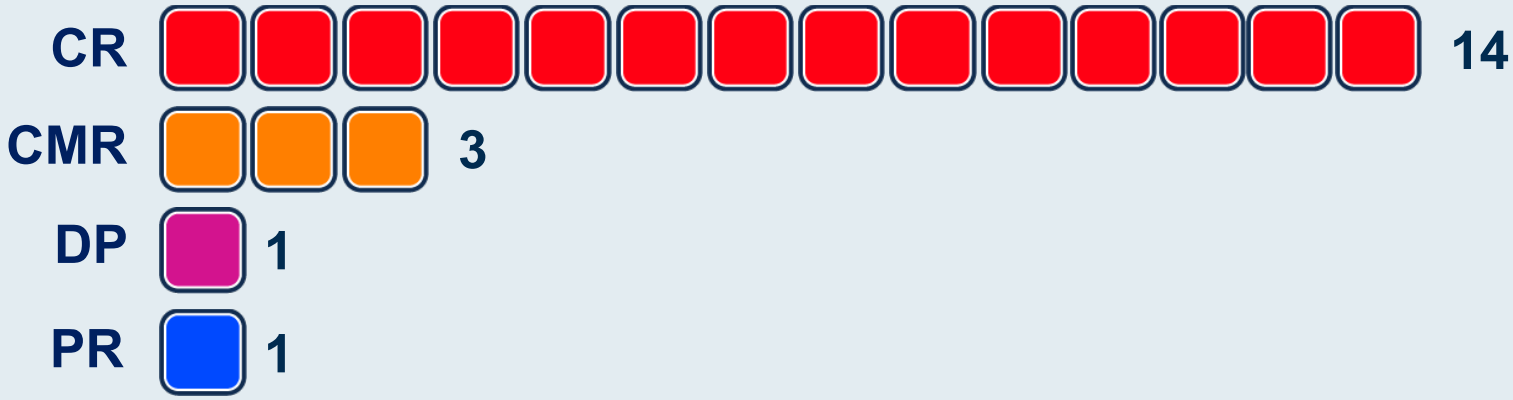



Survey of 19 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Please describe a patient with DLBCL you've cared for this year who received CAR T-cell therapy.

## Patient's response to therapy:

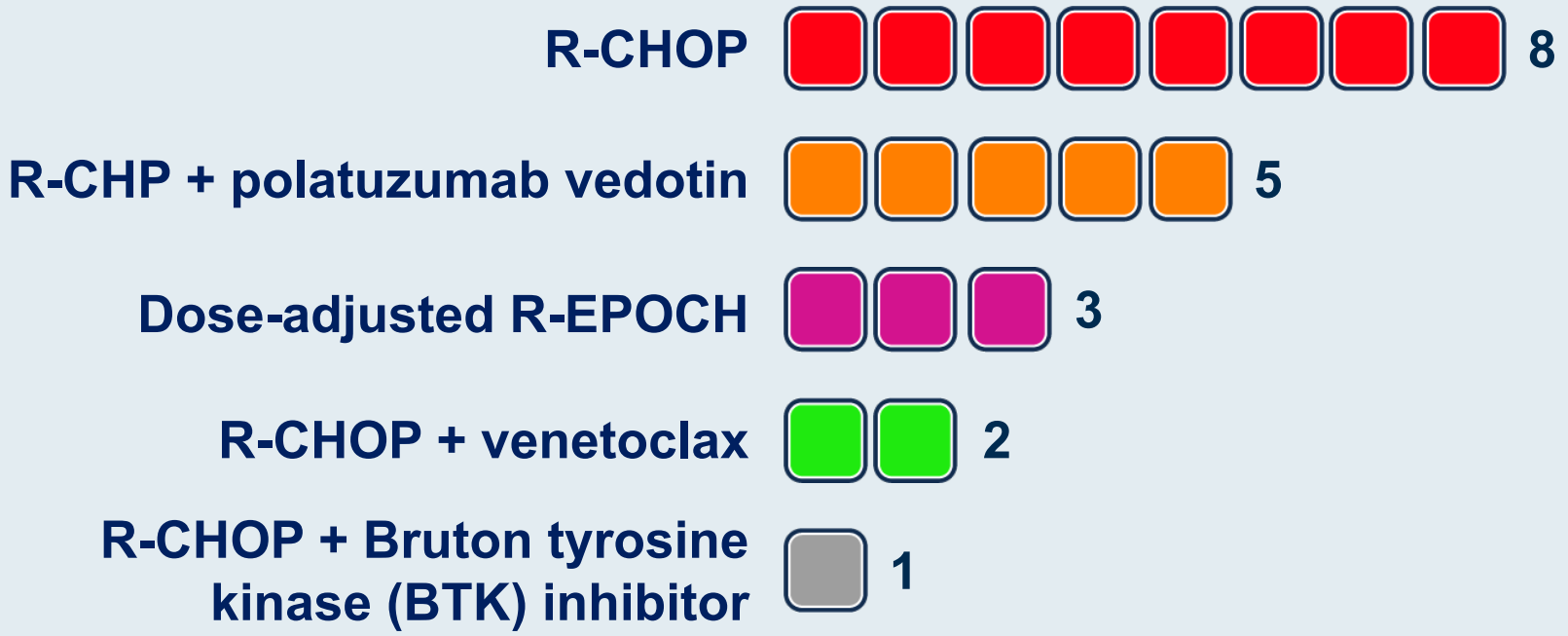



## Patient's tolerance of therapy:


Survey of 19 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

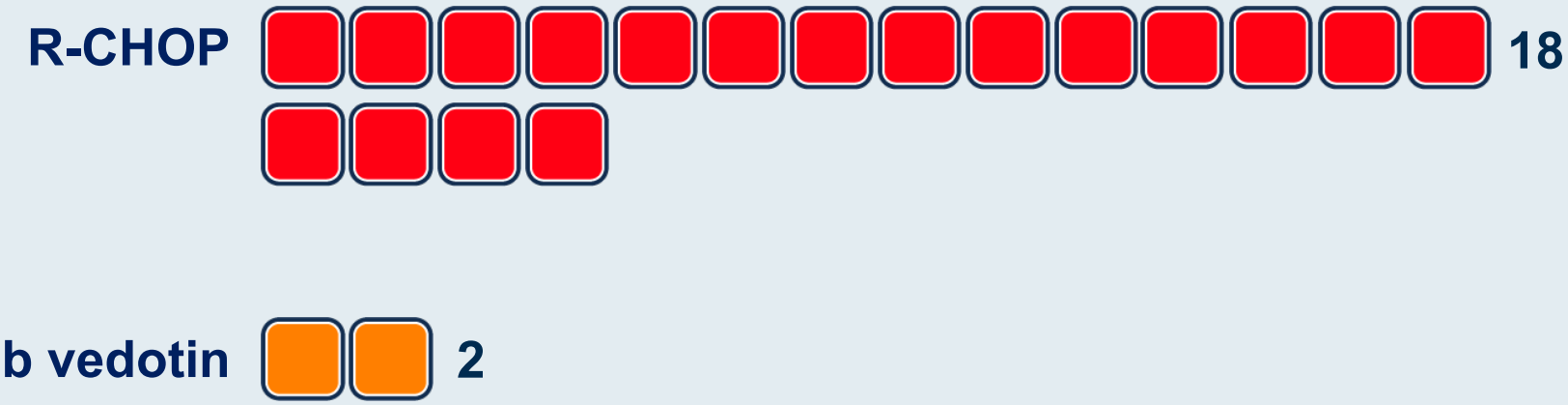
# A 65-year-old otherwise healthy patient with a history of chronic lymphocytic leukemia treated with ibrutinib presents with Richter's transformation. What would you recommend?




Survey of 19 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# A 65-year-old otherwise healthy patient with a history of follicular lymphoma treated with first-line bendamustine/rituximab presents with histologic transformation to DLBCL. What would you recommend?




Survey of 20 US-based clinical investigators November 2023

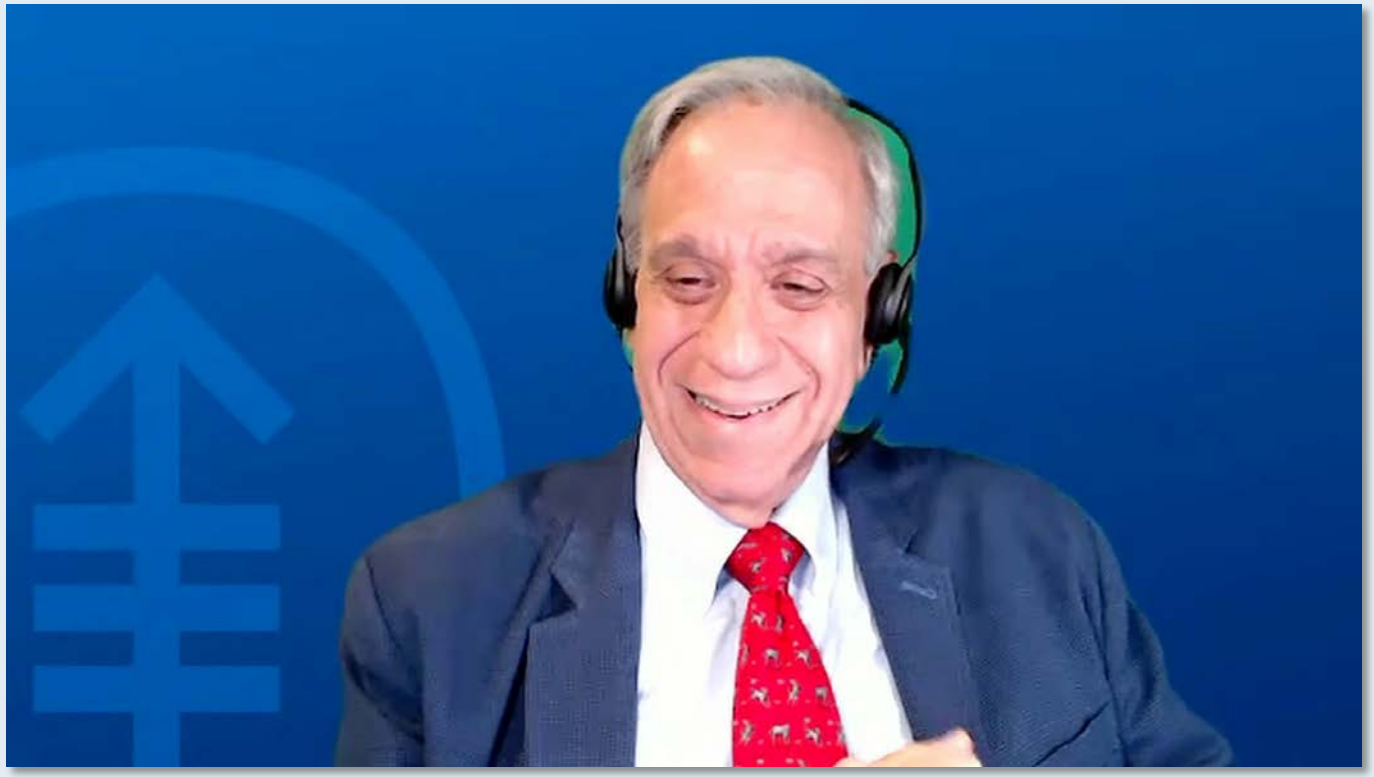
RTP RESEARCH TO PRACTICE

# Approach for patients with DLBCL and disease relapse after initial therapy

**Tycel Phillips, MD**

RTP
RESEARCH
TO PRACTICE

# Cost and accessibility of CAR T-cell therapies



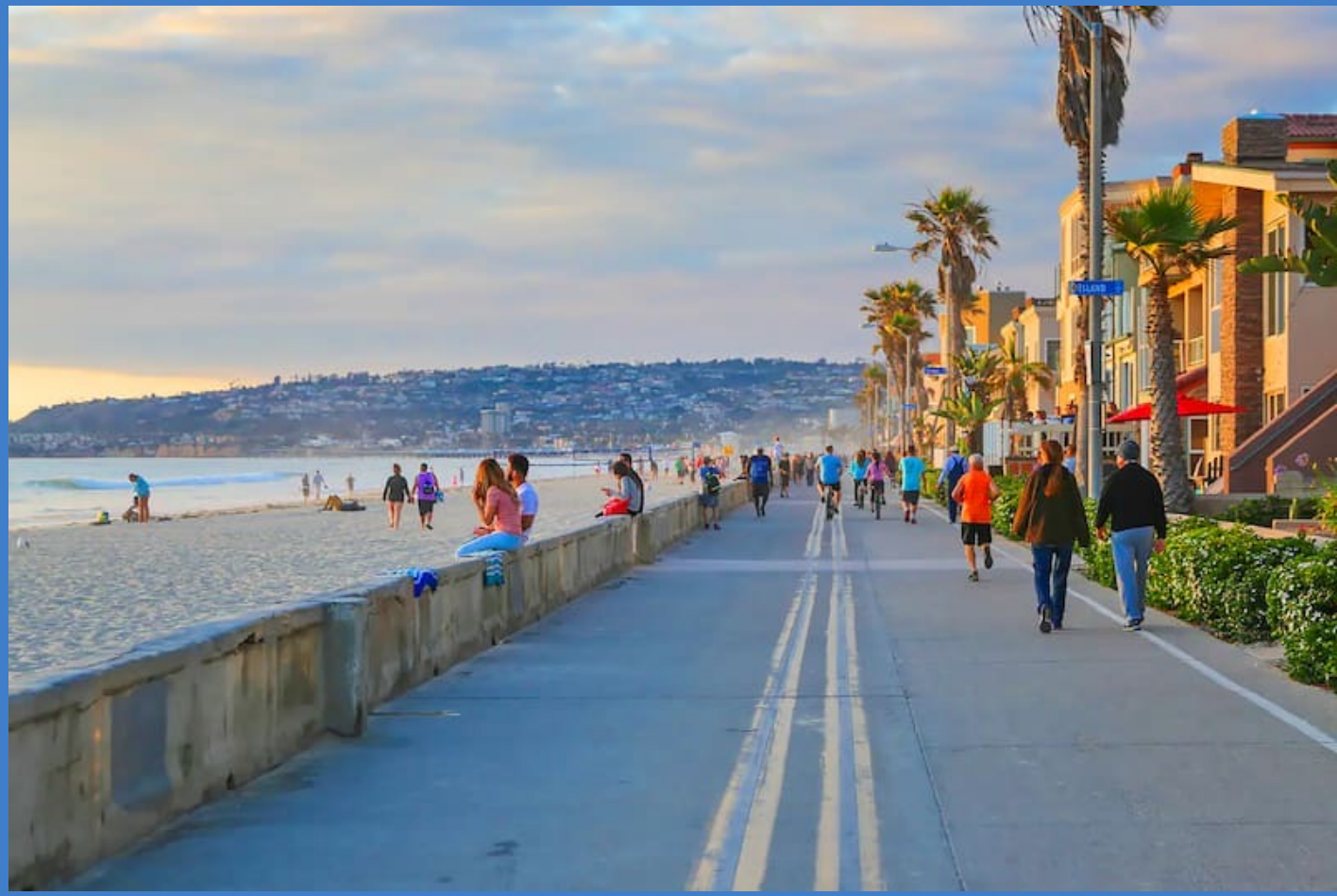
Andrew D Zelenetz, MD, PhD

RTP
RESEARCH
TO PRACTICE

Making Cancer History®

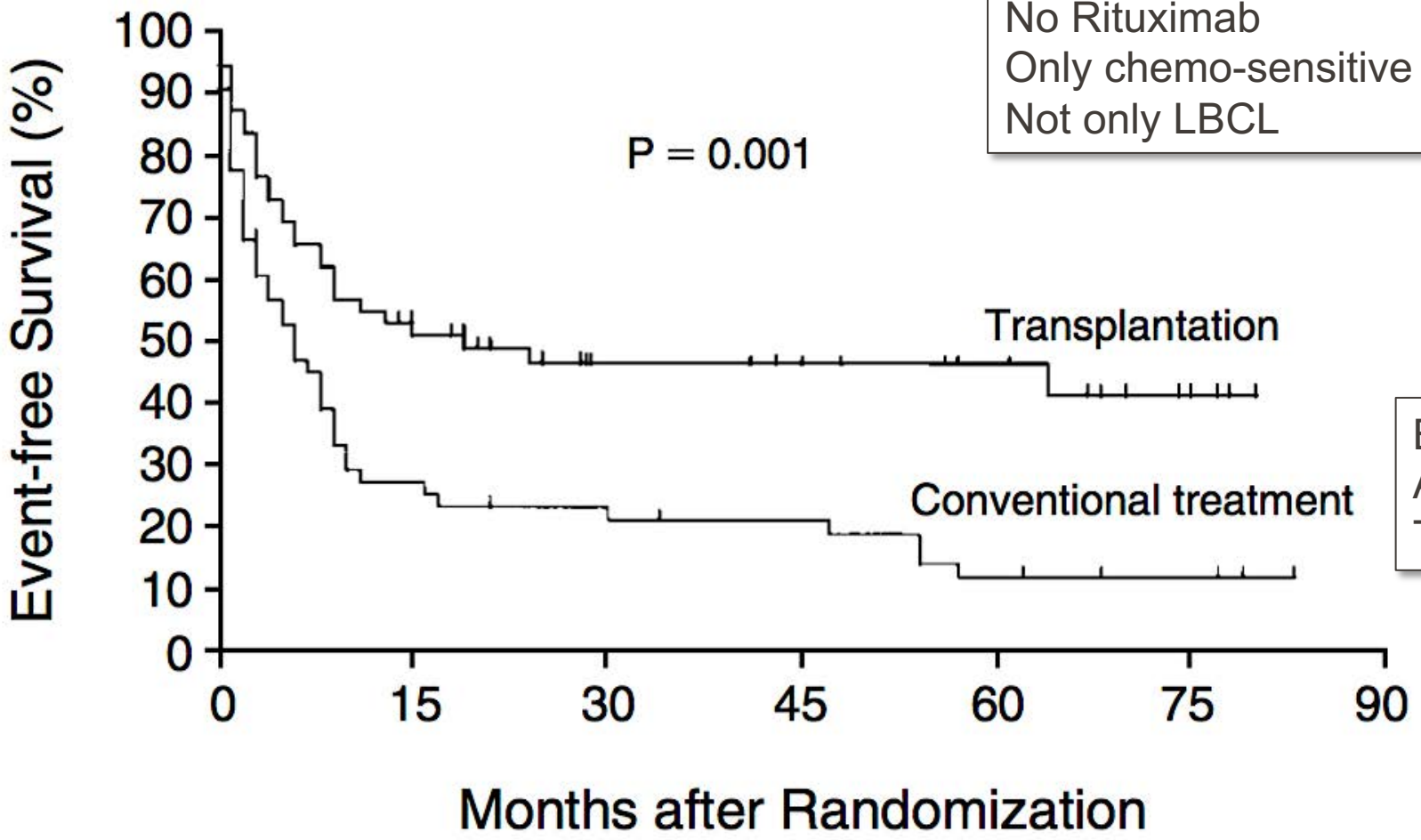
THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

# Incorporation of CAR T-Cell Therapy into the Management of DLBCL



**Jason Westin, MD MS FACP**
**Director, Lymphoma Clinical Research**
**Section Chief, Aggressive Lymphoma**
**Professor, Department of Lymphoma & Myeloma**
**MD Anderson Cancer Center, Houston TX**

# Auto Stem Cell Transplant in relapsed NHL Parma Trial




No Rituximab
Only chemo-sensitive
Not only LBCL

Based on these data, AutoSCT was THE 2L Therapy for nearly 30y

Philip NEJM 1995

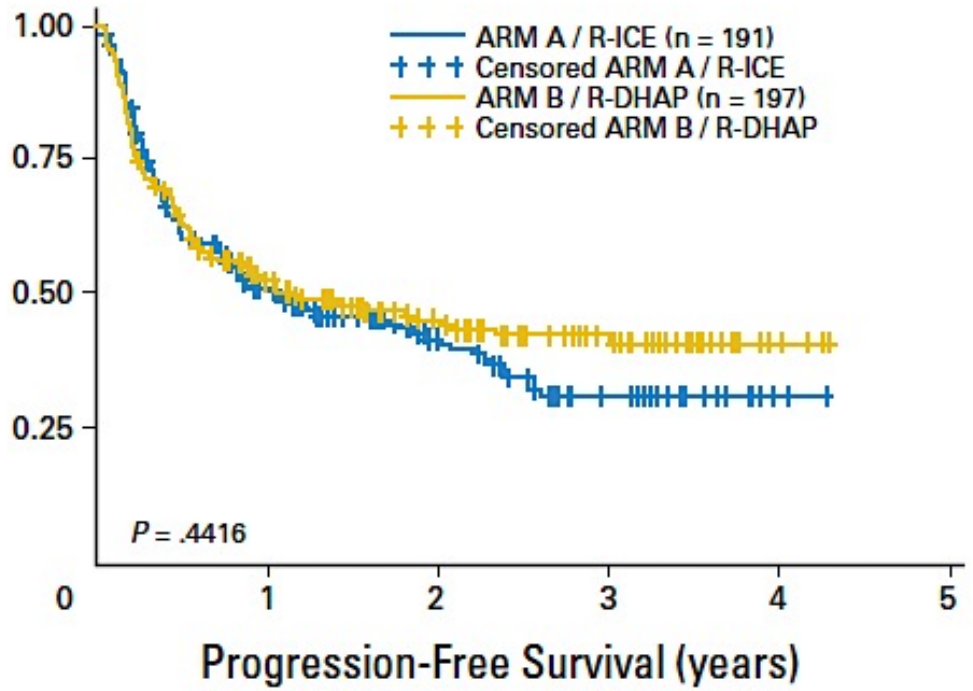
VOLUME 28 · NUMBER 27 · SEPTEMBER 20 2010

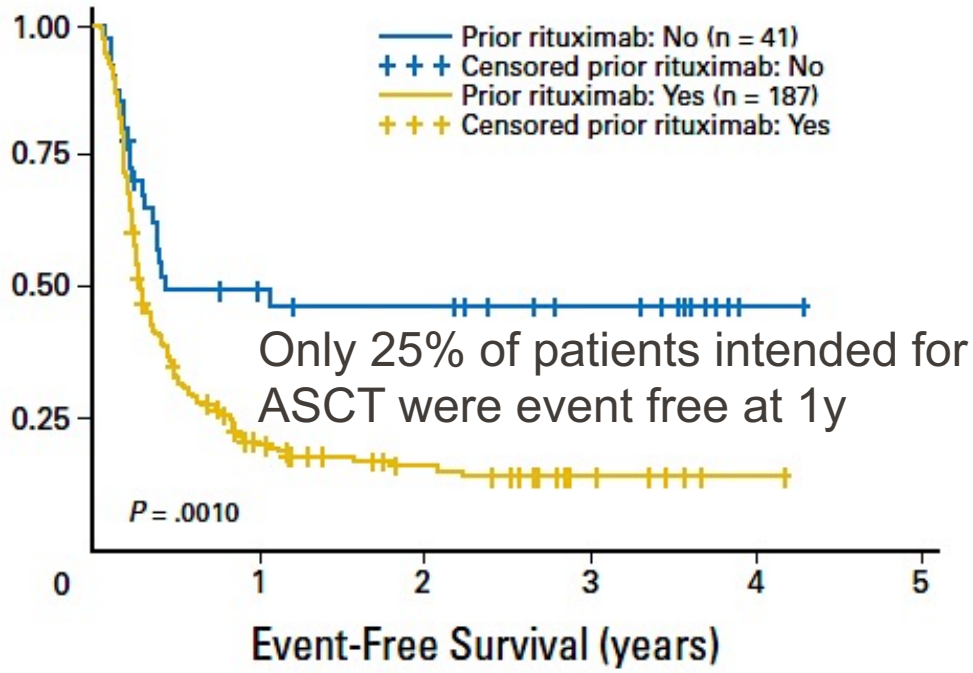
JOURNAL OF CLINICAL ONCOLOGY | ORIGINAL REPORT

# Salvage Regimens With Autologous Transplantation for Relapsed Large B-Cell Lymphoma in the Rituximab Era

*Christian Gisselbrecht, Bertram Glass, Nicolas Mounier, Devinder Singh Gill, David C. Linch, Marek Trneny, Andre Bosly, Nicolas Ketterer, Ofer Shpilberg, Hans Hagberg, David Ma, Josette Brière, Craig H. Moskowitz, and Norbert Schmitz*

Relapse <12 months from 1L therapy

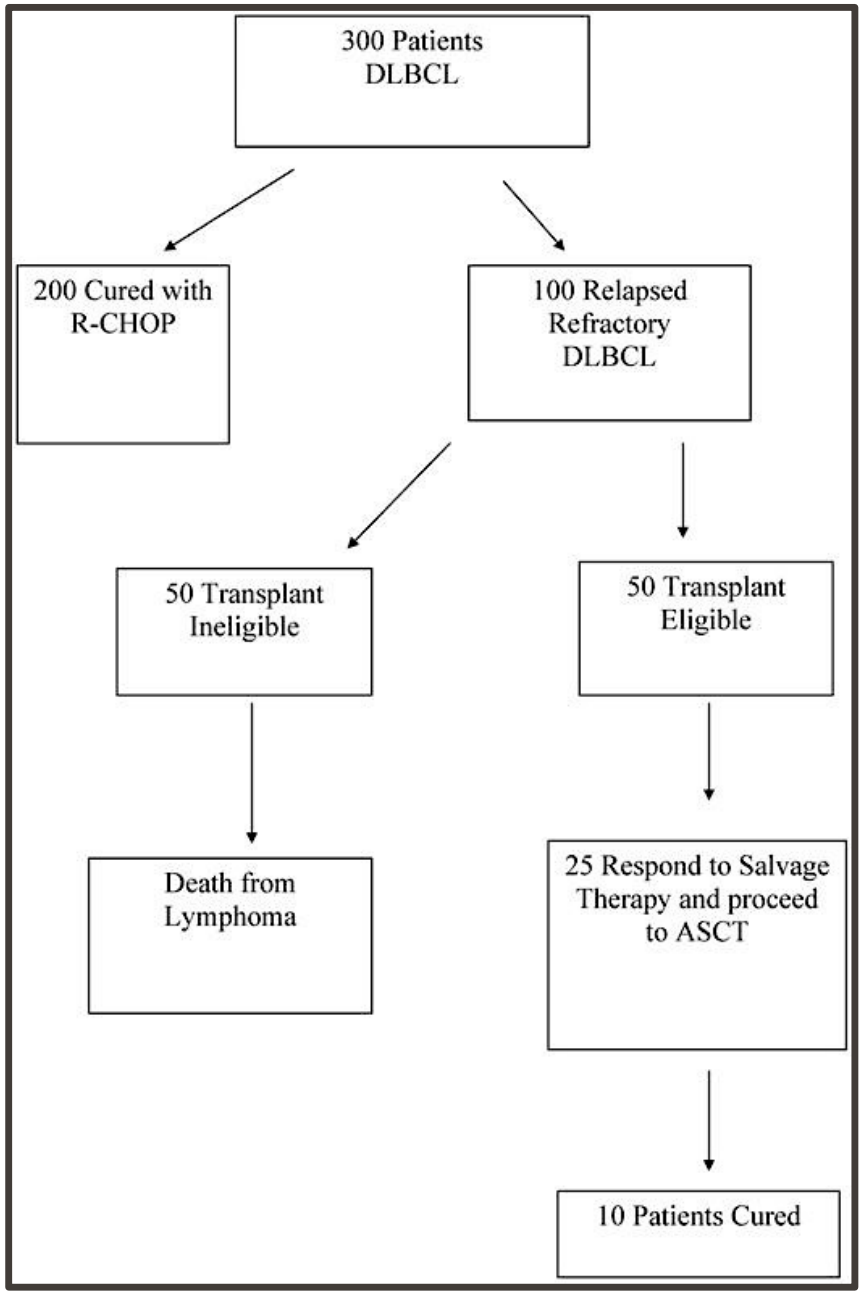



Only 25% of patients intended for ASCT were event free at 1y

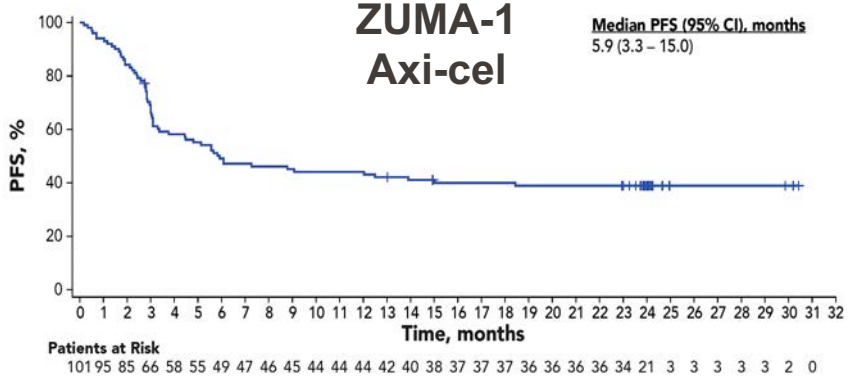
Gisselbrecht et al, JCO 2010

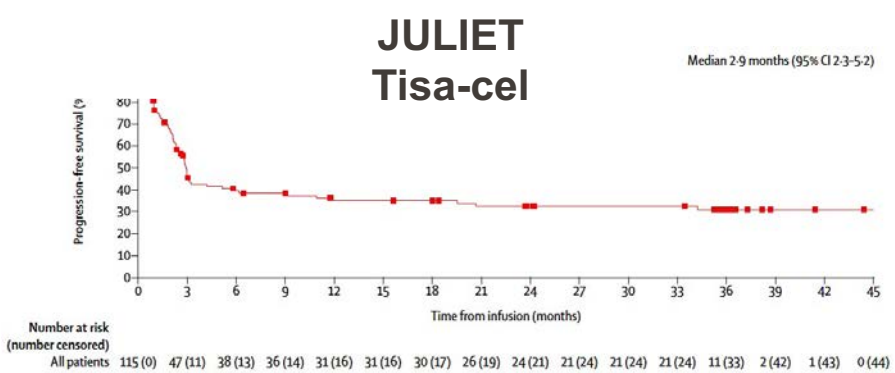
# The 2L algorithm

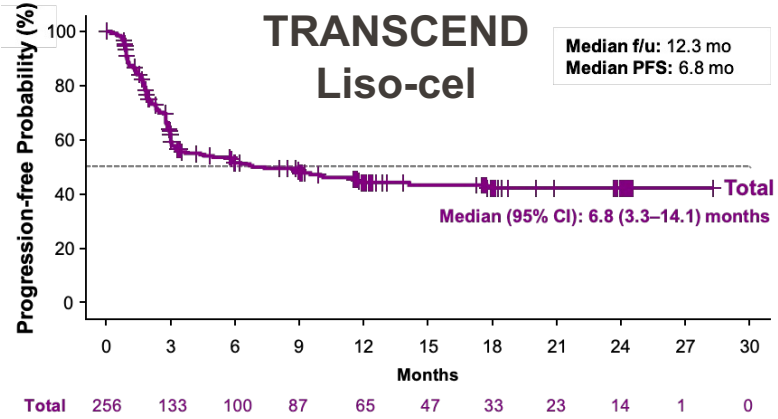



Friedberg ASH Ed Program 2011

# CAR T-cells in ≥3L for LBCL: PFS



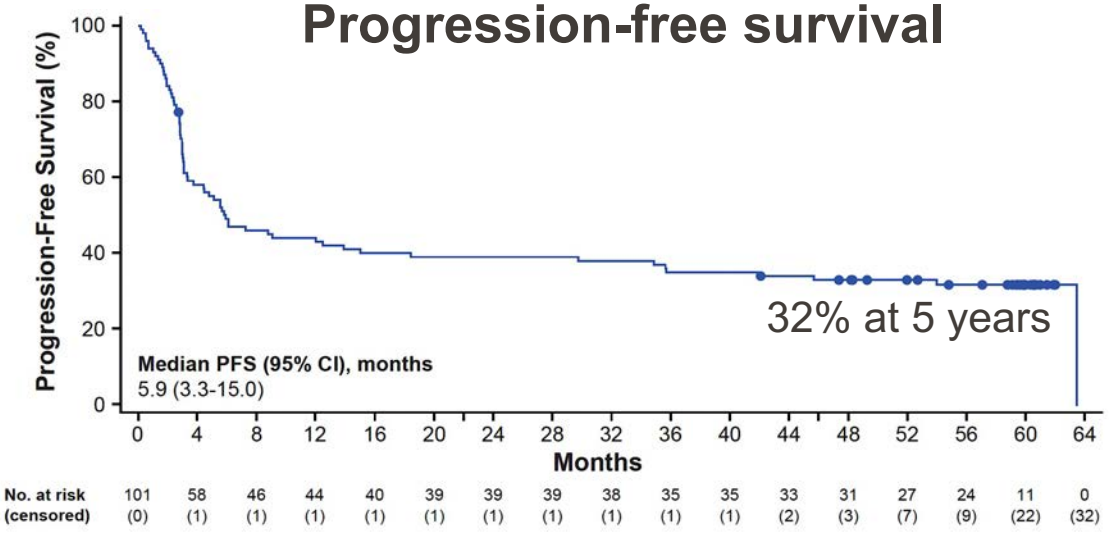

**Approval**

**Axi-cel, tisa-cel, and liso-cel for adult patients with r/r LBCL after 2 or more lines of systemic therapy**

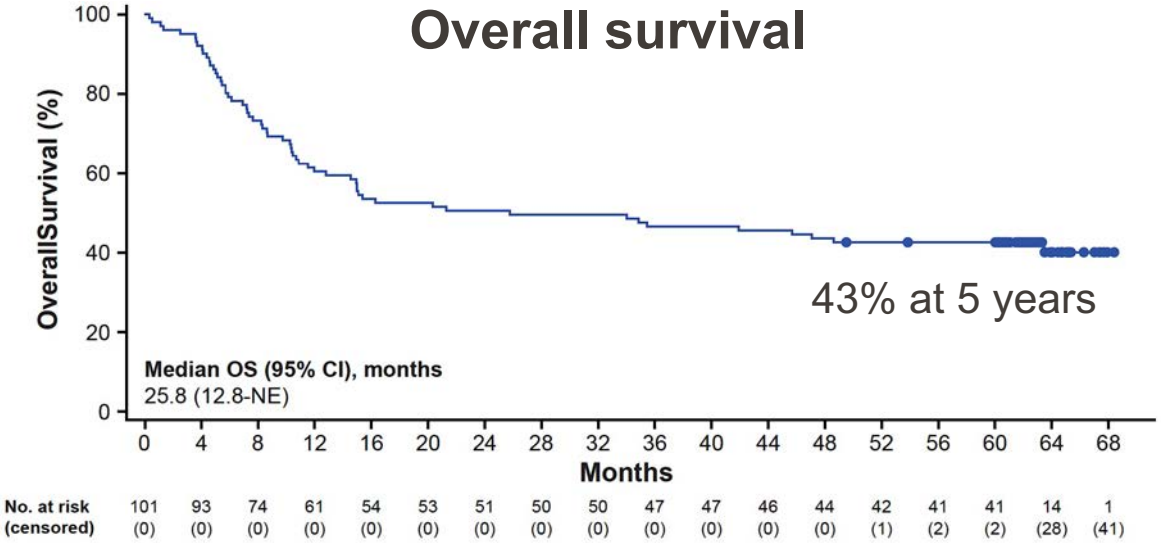
Neelapu SS et al. *N Engl J Med.* 2017;377:2531-2544. Locke FL et al. *Lancet Oncol.* 2019;20(1):31-42.
Schuster SJ et al. *N Engl J Med.* 2019;380:45-56. Schuster SJ et al. *Lancet Oncol.* 2021;22(10):1403-1415.
Abramson JS et al. *Lancet.* 2020;396(10254):839-852.

# ZUMA-1 with 5 year follow up – axicabtagene ciloleucel

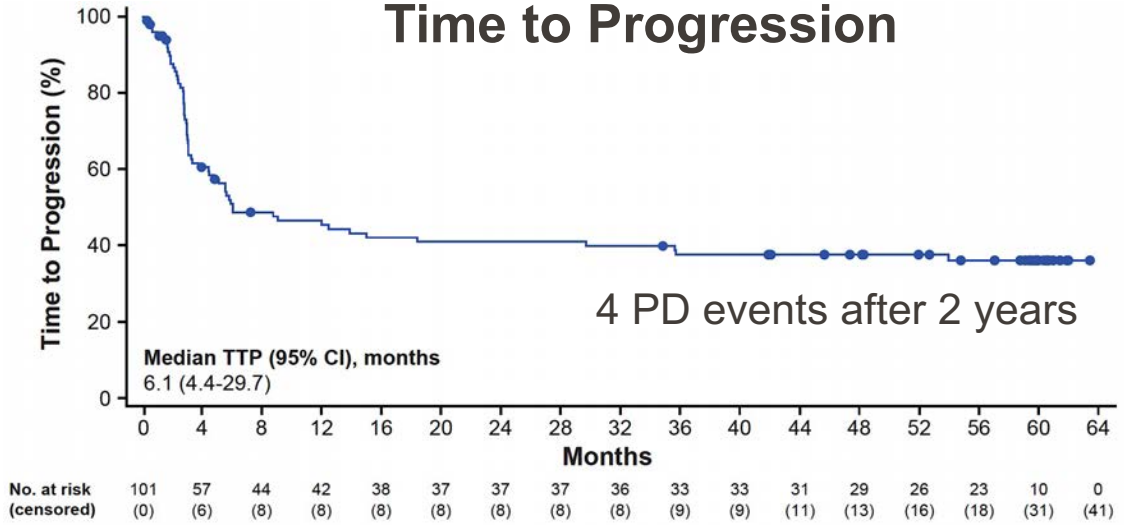
## Progression-free survival



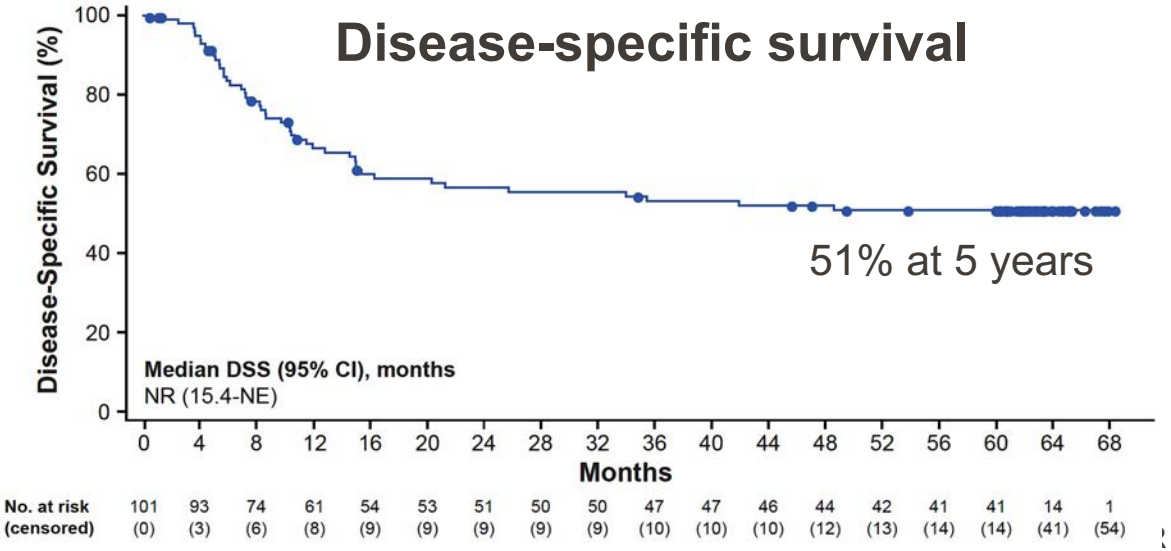

## Overall survival




## Time to Progression



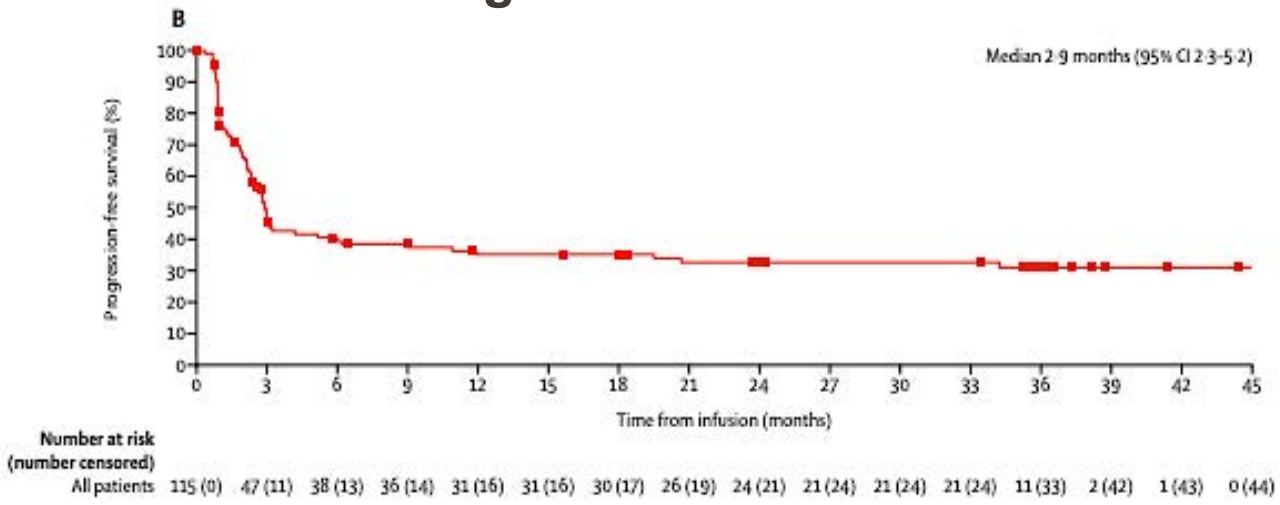

## Disease-specific survival



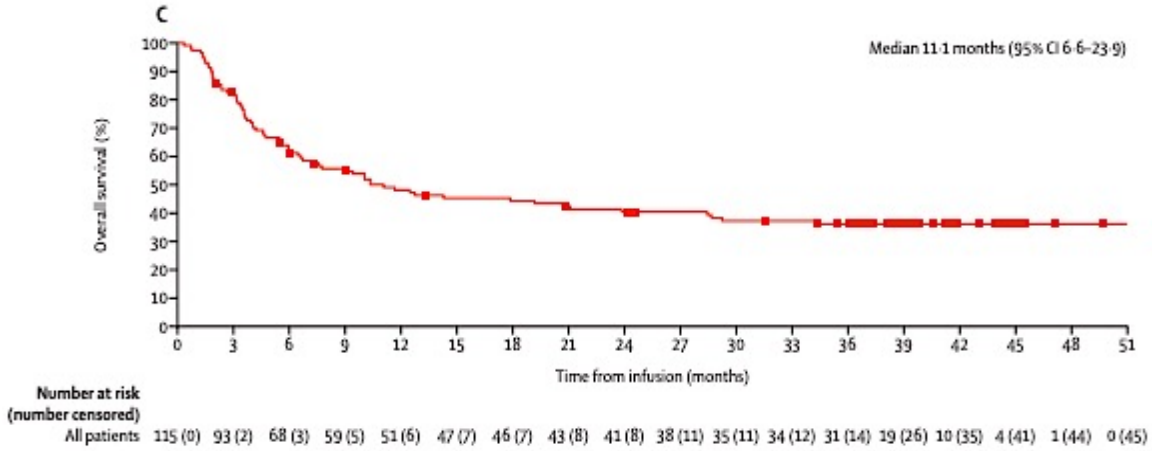

Neelapu et al. *Blood,* 2023 May 11;141(19):2307-2315

# JULIET with 40 month follow up - tisagenlecleucel

## Progression-free survival




## Overall survival

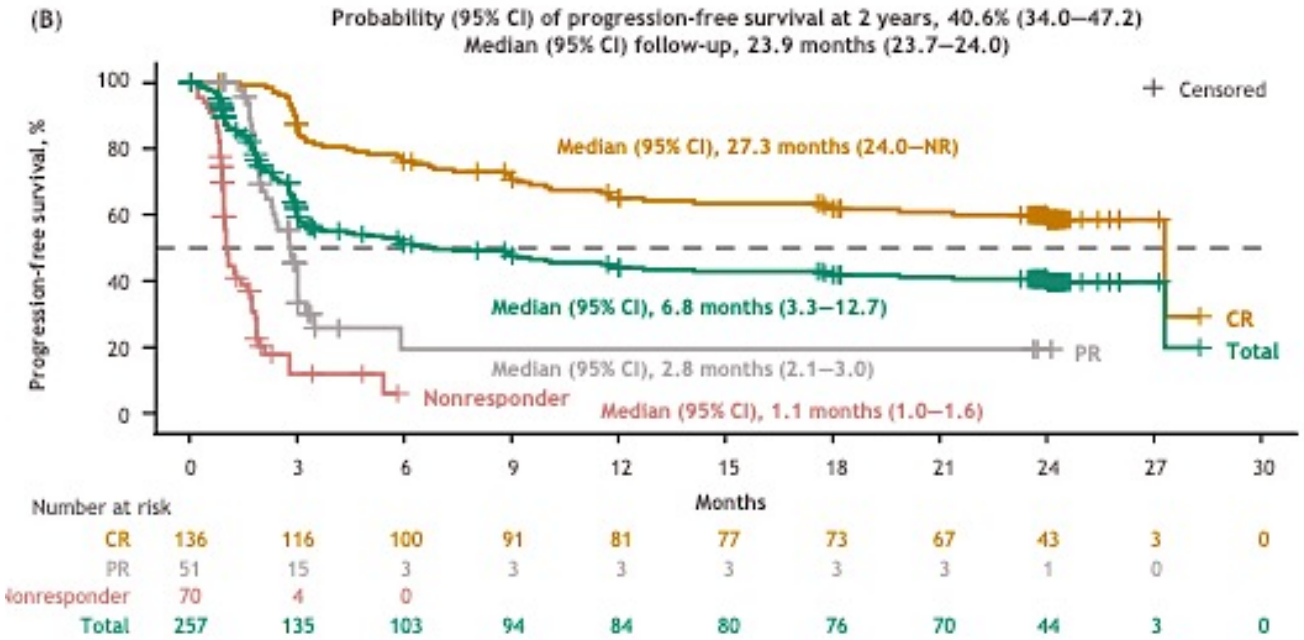




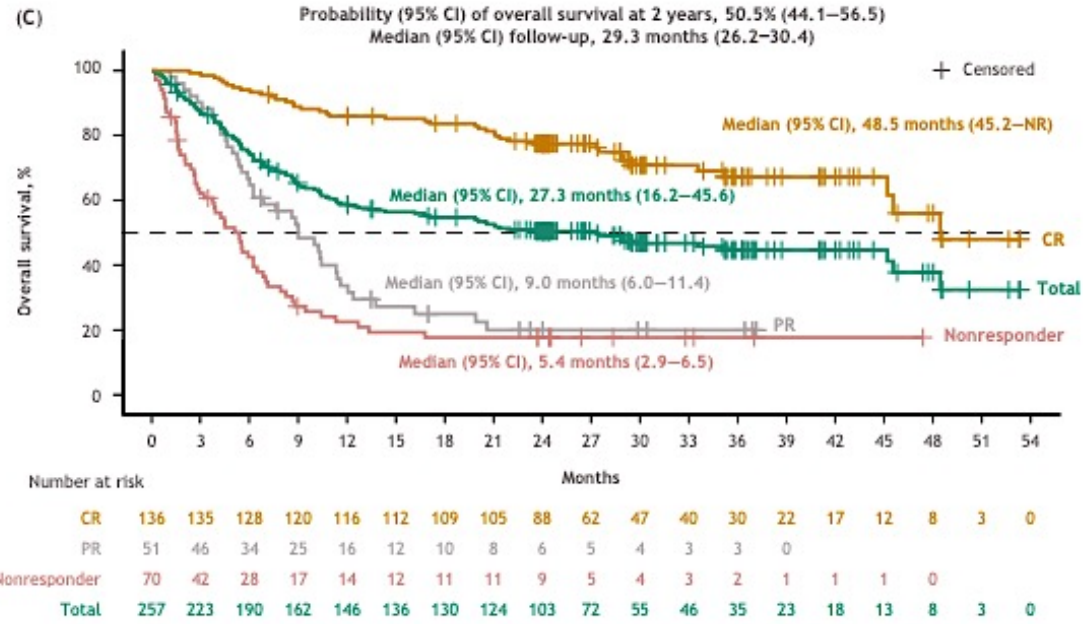

Schuster et al, Lancet Oncol, 2021 Oct; 22 (10) 1403-1415

# TRANSCEND with 24 month follow up – lisocabtagene maraleucel

## Progression-free survival



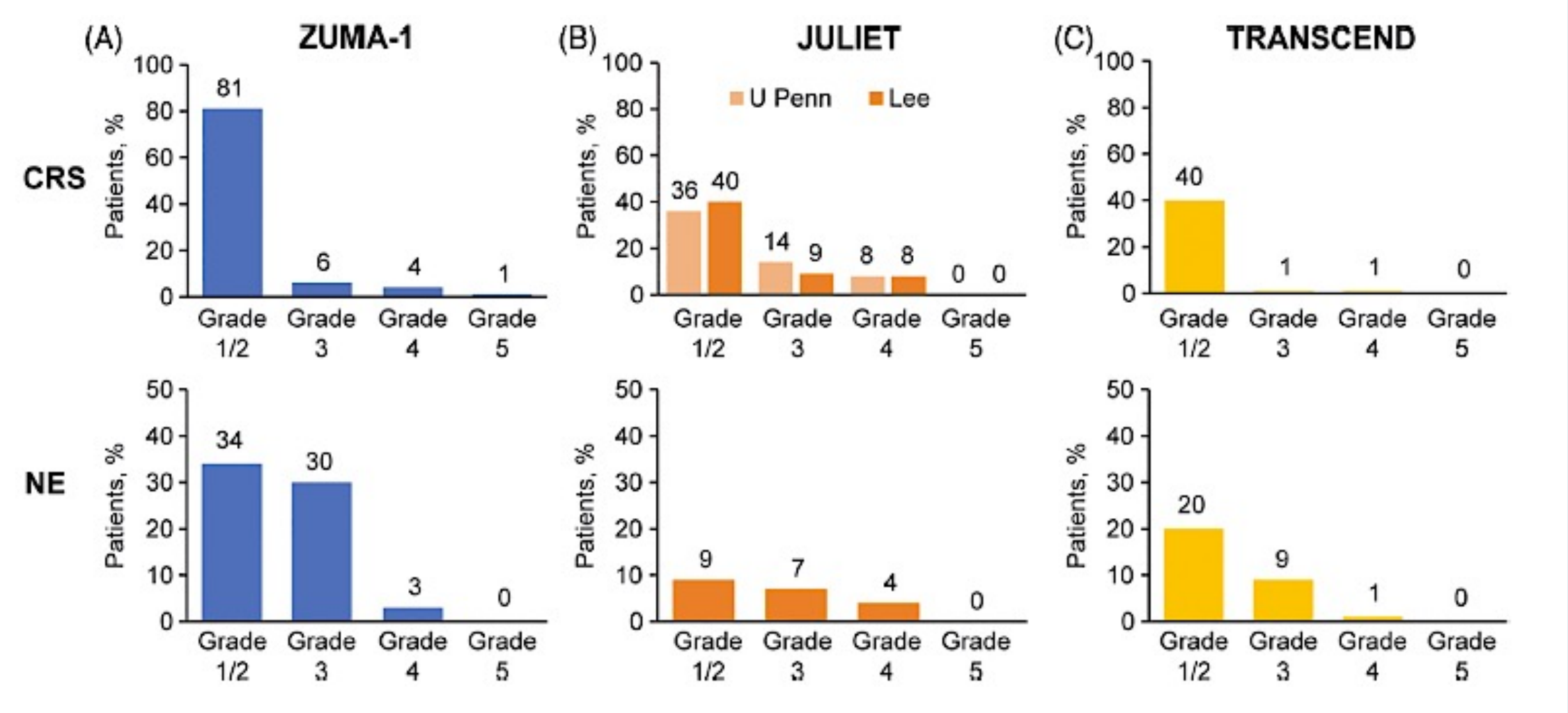

## Overall survival






Abramson et al, Blood 2023 Oct 27 online

# Rates of Cytokine Release Syndrome (CRS) and Neurological Adverse Events (AEs) in CAR T-Cell Therapy Trials for Multiregimen-Relapsed DLBCL



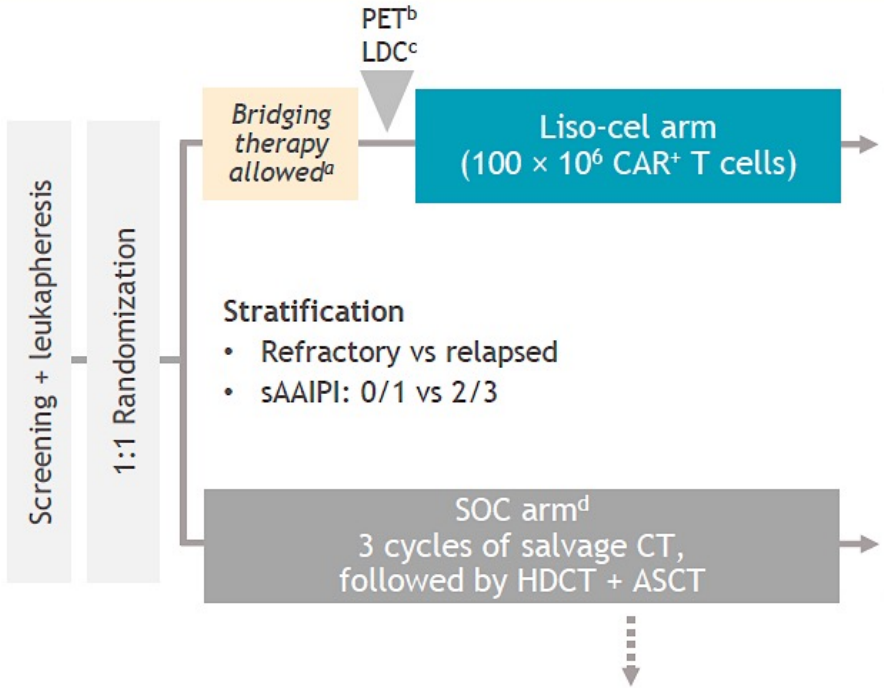

Westin JR et al. *Am J Hematol* 2021;96:1295-312.

# If CAR T-cell is great in 3L, what about 2L?

# TRANSFORM study design

**Key eligibility**

- Age 18–75 years
- Aggressive NHL
  - DLBCL NOS (de novo or transformed from indolent NHL), HGBCL (double/triple hit) with DLBCL histology, FL3B, PMBCL, THRBCL
- Refractory or relapsed ≤ 12 months after 1L treatment containing an anthracycline and a CD20-targeted agent
- ECOG PS ≤ 1
- Eligible for HSCT
- Secondary CNS lymphoma allowed
- LVEF > 40% for inclusion
- No minimum absolute lymphocyte count




***Primary endpoint***

- EFS (per IRC)

***Key secondary endpoints***

- CR rate, PFS, OS

***Other secondary endpoints***

- Duration of response, ORR, PFS on next line of treatment
- Safety, PROs

***Exploratory endpoints***

- Cellular kinetics
- B-cell aplasia

TRANSFORM PRO data
Poster (Abs 3845)
Abramson et al.
Dec 13, 2021, 6:00 pm (EST)

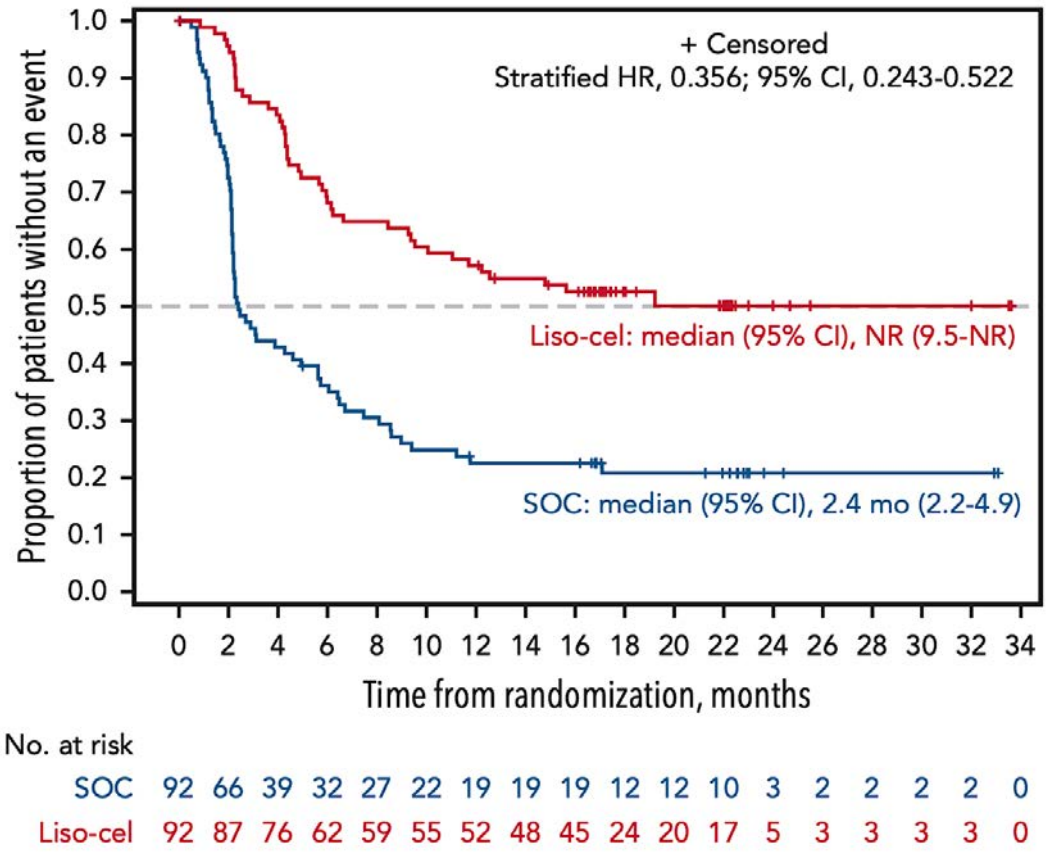
- **EFS is defined as time from randomization to death due to any cause, progressive disease, failure to achieve CR or PR by 9 weeks post-randomization, or start of a new antineoplastic therapy, whichever occurs first**

[a]Patients may have received a protocol-defined SOC regimen to stabilize their disease during liso-cel manufacturing; [b]Only for patients who received bridging therapy; [c]Lymphodepletion with fludarabine 30 mg/m² and cyclophosphamide 300 mg/m² for 3 days; [d]SOC was defined as physician's choice of R-DHAP, R-ICE, or R-GDP.
DLBCL, diffuse large-B cell lymphoma; FL3B, follicular lymphoma grade 3B; HGBCL, high-grade B-cell lymphoma; IRC, independent review committee; LDC, lymphodepleting chemotherapy; NOS, not otherwise specified; PD, progressive disease; PMBCL, primary mediastinal large B-cell lymphoma; PRO, patient-reported outcome; sAAIPI, secondary age-adjusted International Prognostic Index; THRBCL, T-cell/histiocyte-rich large B-cell lymphoma.

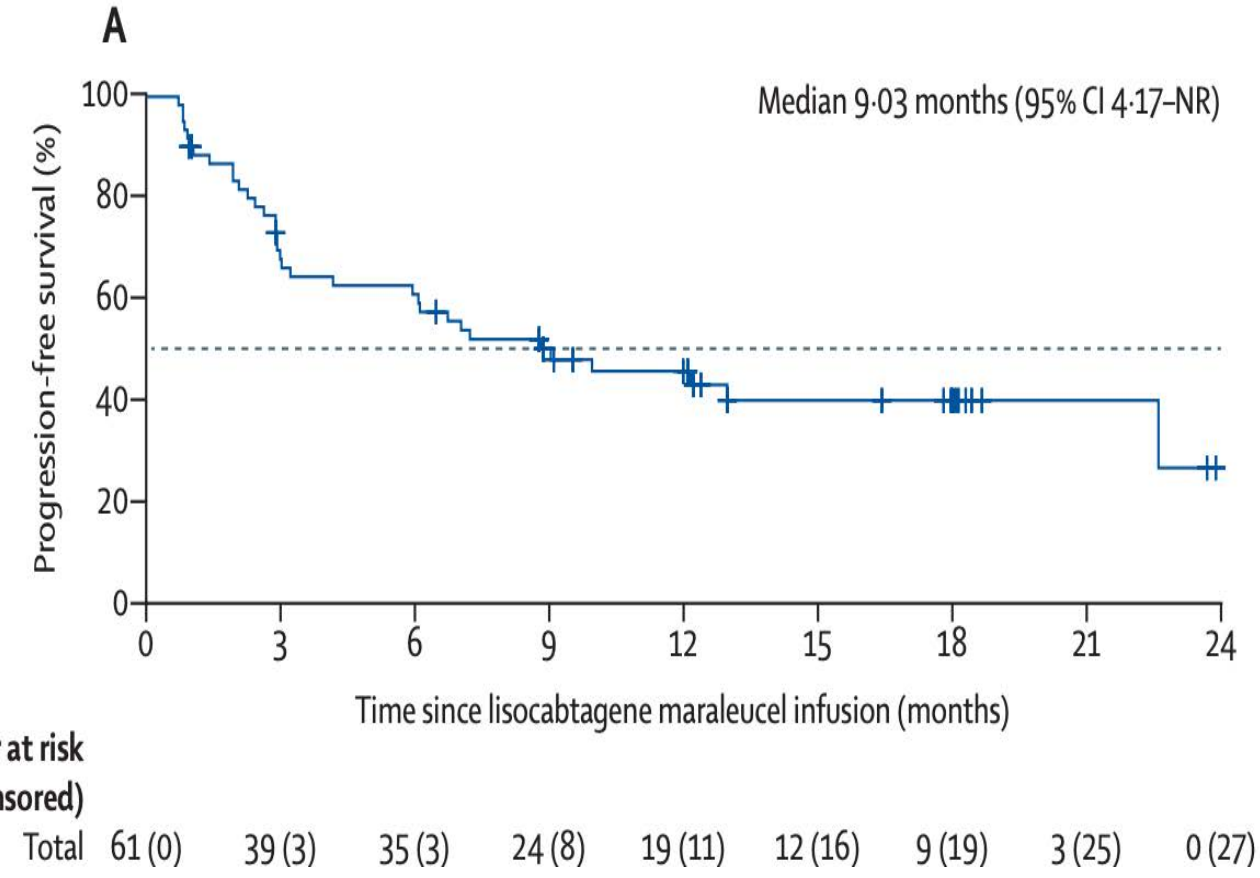
Kamdar M, et al. ASH 2021 [Abstract #91]

# TRANSFORM: Liso-cel is superior to SOC

## PFS




## PFS PILOT




Abramson et al, Blood 2023, Seghal et al, Lancet Oncology 2023

# TRANSFORM: Treatment-Emergent Adverse Events (AEs) of Special Interest – Cytokine Release Syndrome (CRS) and Neurological Events (NEs) with Lisocabtagene Maraleucel

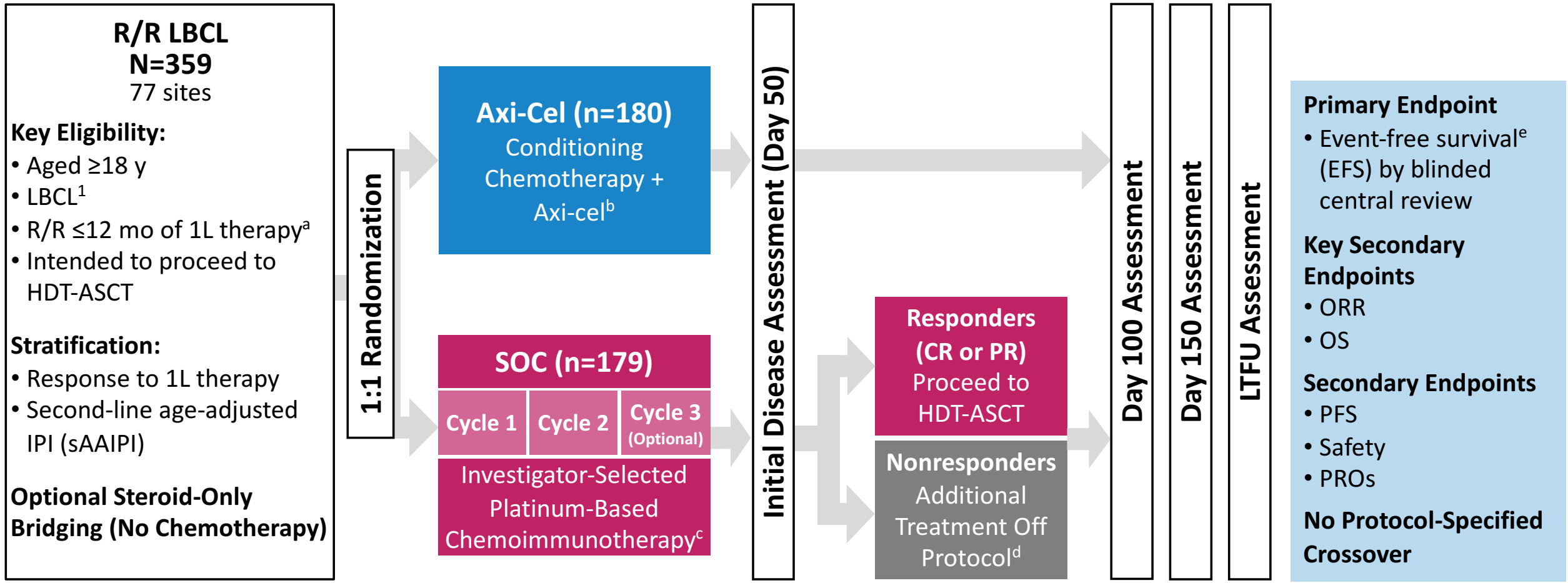
| AEs of special interest of CRS or NEs | Liso-cel (n = 92) |
|---|---|
| **CRS, n (%)*** | |
| Any grade | 45 (49) |
| Grade 1 | 34 (37) |
| Grade 2 | 10 (11) |
| Grade 3 | 1 (1) |
| Grade 4/5 | 0 |
| Median (range) time to onset, d | 5.0 (1-63) |
| Median (range) time to resolution, d | 4.0 (1-16) |
| **NEs, n (%)†** | |
| Any grade | 10 (11) |
| Grade 1 | 4 (4) |
| Grade 2 | 2 (2) |
| Grade 3 | 4 (4) |
| Grade 4/5 | 0 |
| Median (range) time to onset, d | 11.0 (7-17) |
| Median (range) time to resolution, d | 4.5 (1-30) |

*Graded per the Lee 2014 criteria.[11]

†Defined as investigator-identified neurological AEs related to liso-cel and graded using the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.

Abramson JS et al. *Blood* 2023;141(14):1675-84.

# ZUMA-7 Study Schema and Endpoints: Axi-Cel Versus SOC as Second-Line Therapy in Patients With R/R LBCL

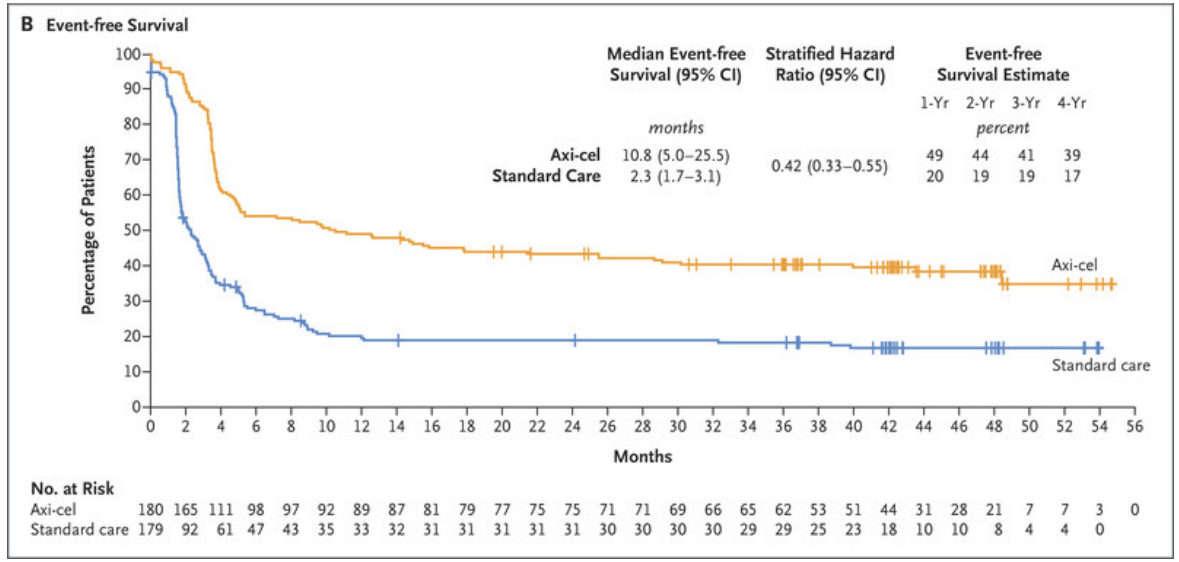



[a] Refractory disease was defined as no CR to 1L therapy; relapsed disease was defined as CR followed by biopsy-proven disease relapse ≤12 months from completion of 1L therapy. [b] Axi-cel patients underwent leukapheresis followed by conditioning chemotherapy with cyclophosphamide (500 mg/m$^2$/day) and fludarabine (30 mg/m$^2$/day) 5, 4, and 3 days before receiving a single axi-cel infusion (target intravenous dose, 2×10$^6$ CAR T cells/kg). [c] Protocol-defined SOC regimens included R-GDP, R-DHAP, R-ICE, or R-ESHAP. [d] 56% of patients received subsequent cellular immunotherapy. [e] EFS was defined as time from randomization to the earliest date of disease progression per Lugano Classification,[2] commencement of new lymphoma therapy, or death from any cause.

1. Swerdlow SH, et al. *Blood.* 2016;127:2375-2390. 2. Cheson BD, et al. *J Clin Oncol.* 2014;32:3059-3068.

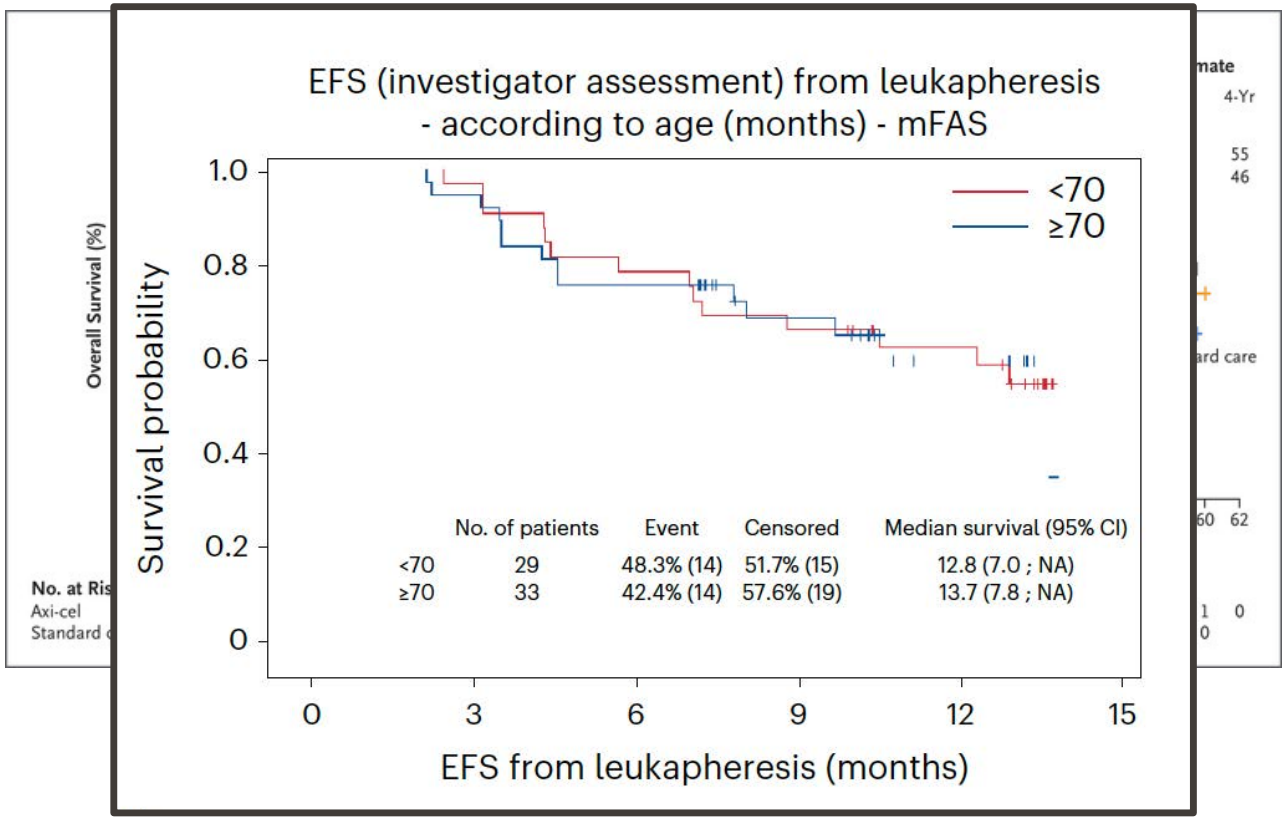
# ZUMA-7: Axi-cel is superior to SOC

## EFS




## ALYCANTE

## EFS




Westin et al, NEJM 2023

Houot et al, Nat Med 2023

# ZUMA-7: Key Safety Data with Axicabtagene Ciloleucel at OS Primary Analysis

| AEs of Interest, % | Axi-Cel n=170 | | SOC n=168 | |
|---|---|---|---|---|
| | Any Grade | Grade ≥3 | Any Grade | Grade ≥3 |
| CRS | 92% | 6% | – | – |
| Neurologic event | 61% | 21% | 20% | 1% |
| Hypogammaglobulinemia | 11% | 0% | 1% | 0% |
| Cytopenia | 80% | 75% | 80% | 75% |
| Infections | 45% | 16% | 32% | 12% |

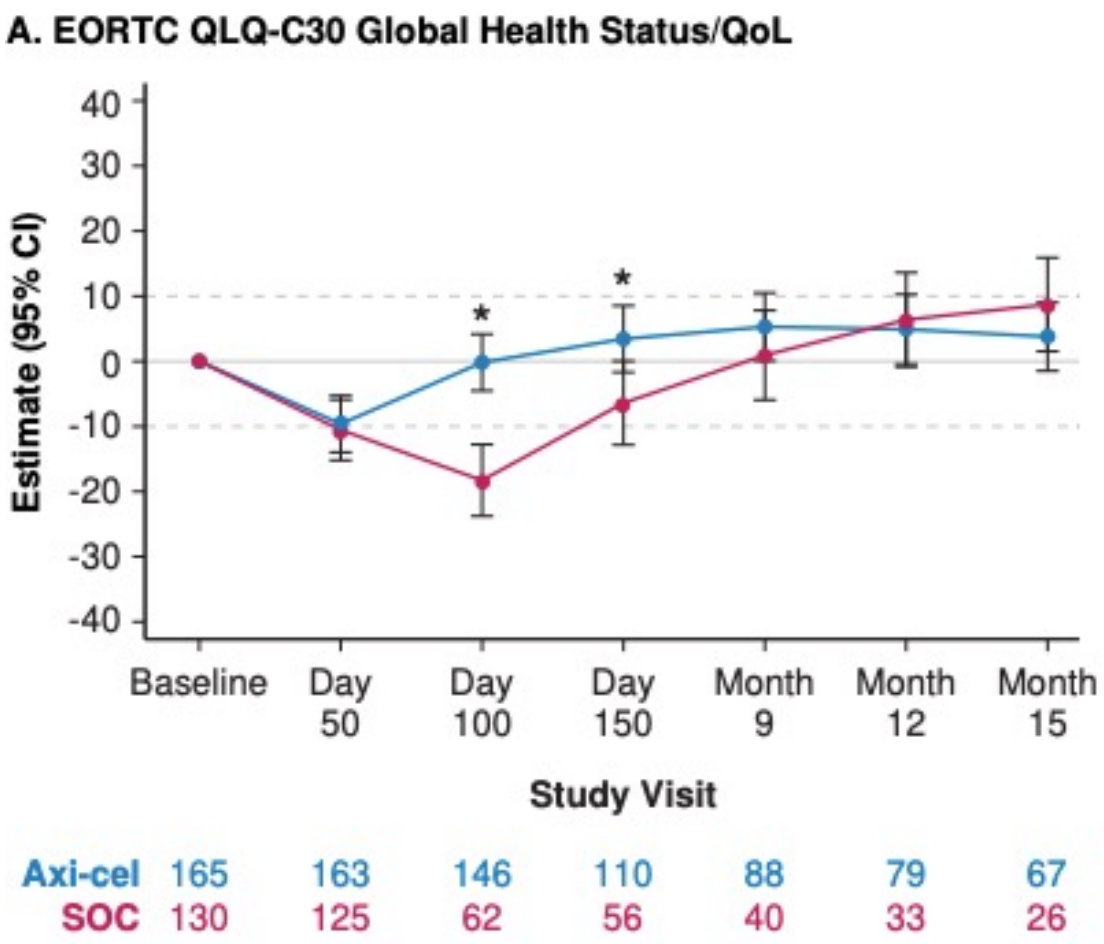
| Reason for Death | Axi-Cel n=170 | SOC n=168 |
|---|---|---|
| Progressive disease, n (%) | 51 (30) | 71 (42) |
| Grade 5 AE during protocol-specific reporting period, n (%) | 8 (5)[a] | 2 (1)[b] |
| New or secondary malignancy, n (%) | 2 (1)[c] | 0 |
| Other reason for death,[d] n (%) | 13 (8) | 18 (11) |
| Definitive therapy-related mortality,[e] n/N (%) | 1/170 (1)[f] | 2/64 (3)[g] |

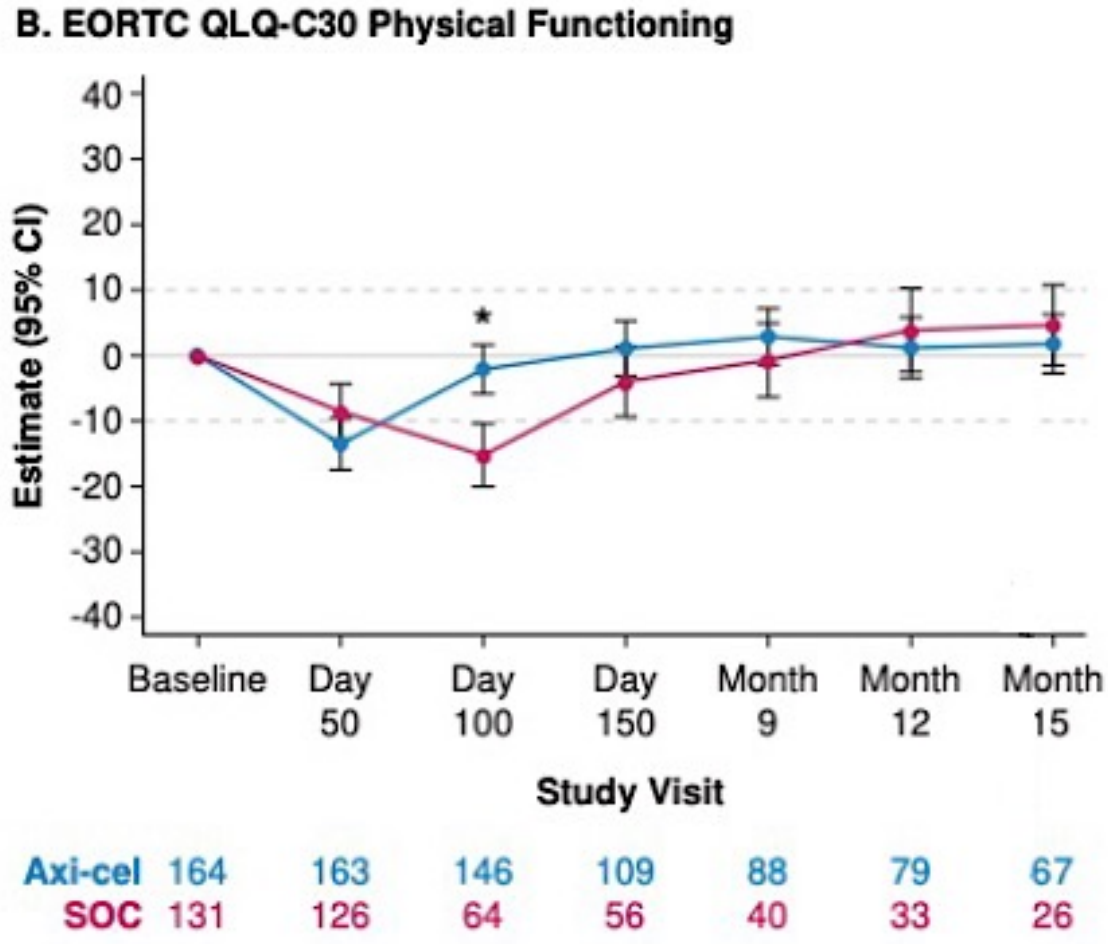
- No changes in cumulative treatment-related serious or fatal AEs occurred since the primary EFS analysis

Data here are presented for the safety analysis set. Fewer SOC patients remained in the AE reporting period post-progression or start of new lymphoma therapy; thus, cross-arm comparisons of AE rates warrant cautious interpretation. [a] COVID-19 (n=2), sepsis (n=2), hepatitis B reactivation, myocardial infarction, pneumonia, and progressive multifocal leukoencephalopathy (n=1 each). [b] Acute respiratory distress syndrome and cardiac arrest (n=1 each). [c] One patient died of acute myeloid leukemia and one died of lung adenocarcinoma, both deemed unrelated to study treatment per investigator assessment. [d] Includes fatal AEs that occurred outside of the protocol-specified AE reporting window. COVID-19 (n=4), other infection/inflammation (n=3), neurologic organ failure (n=2), respiratory organ failure, cardiac organ failure, progressive disease, and unknown (n=1 each) in the axi-cel arm. Other infection/inflammation (n=7), unknown (n=5), COVID-19 (n=4), respiratory organ failure, and cardiopulmonary/neurologic organ failure (n=1 each) in the SOC arm. [e] Related to axi-cel or high-dose therapy with autologous stem cell transplantation. [f] Hepatitis B reactivation. [g] Cardiac arrest and acute respiratory distress syndrome (n=1 each).
AE, adverse event; axi-cel, axicabtagene ciloleucel; CRS, cytokine release syndrome; EFS, event-free survival; SOC, standard of care.

Westin JR et al. ASCO 2023;Abstract LBA107.

# Quality of Life – ZUMA-7

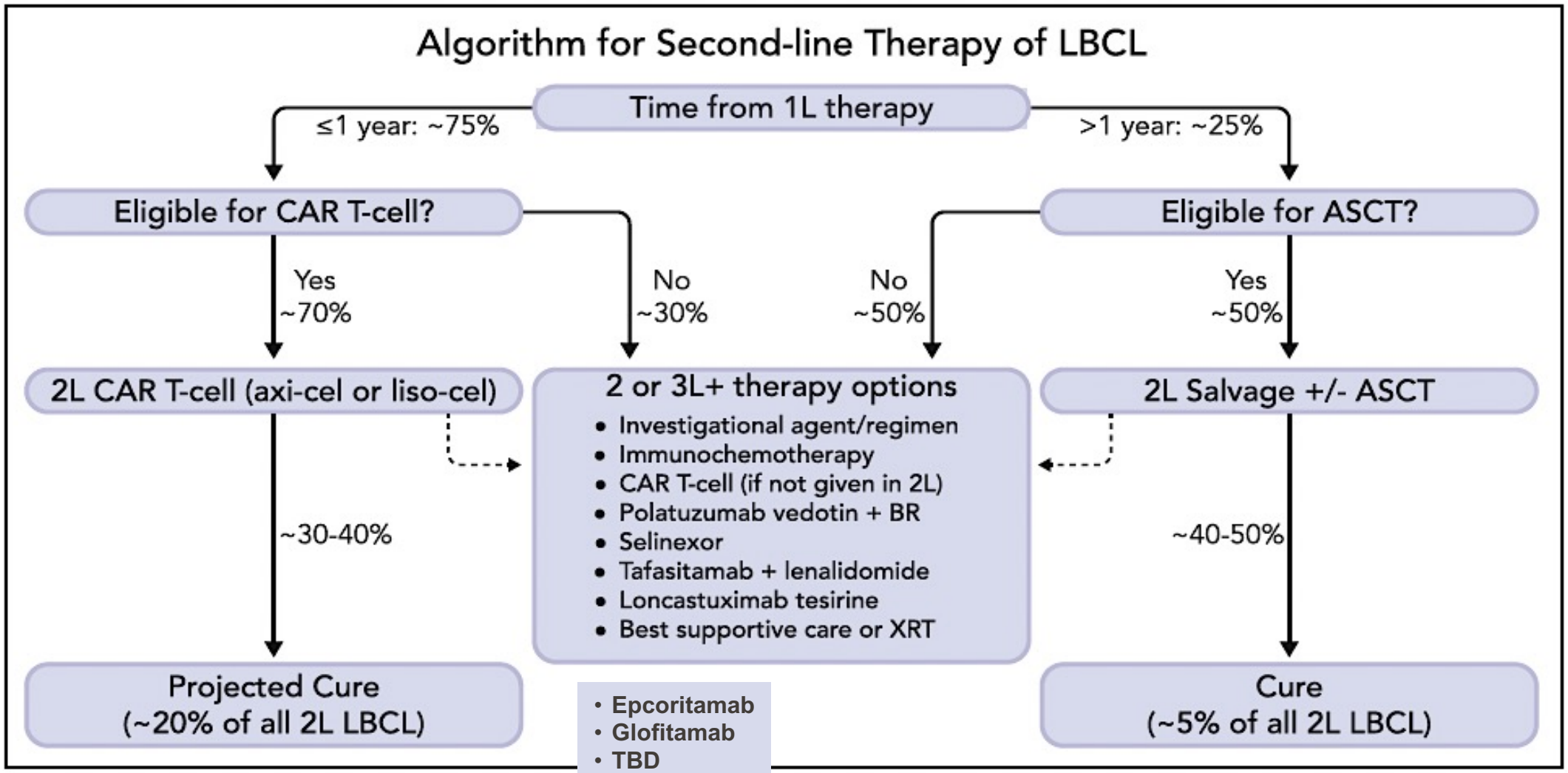



Elsawy Blood 2022

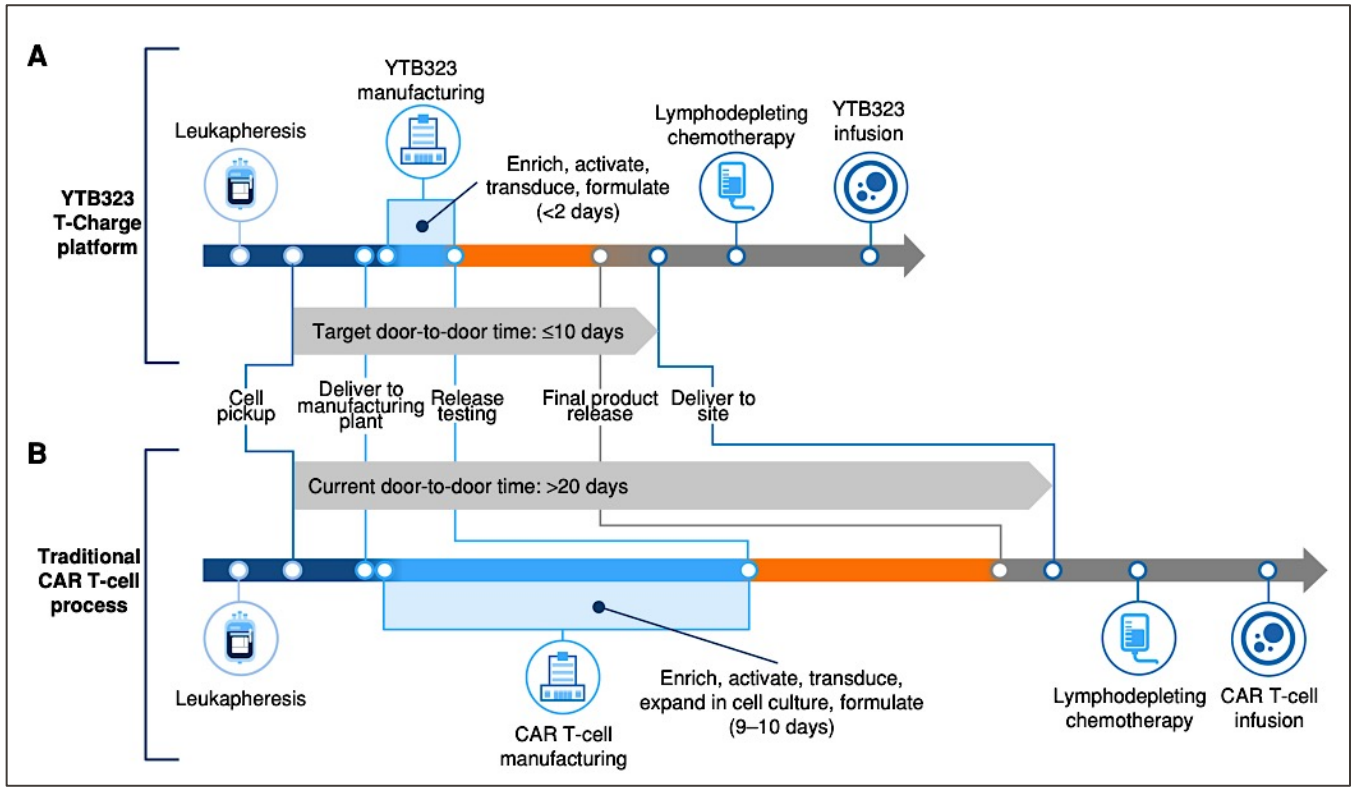
Similar findings with liso-cel, Abramson et al, Blood Advances 2022

# New 2L algorithm

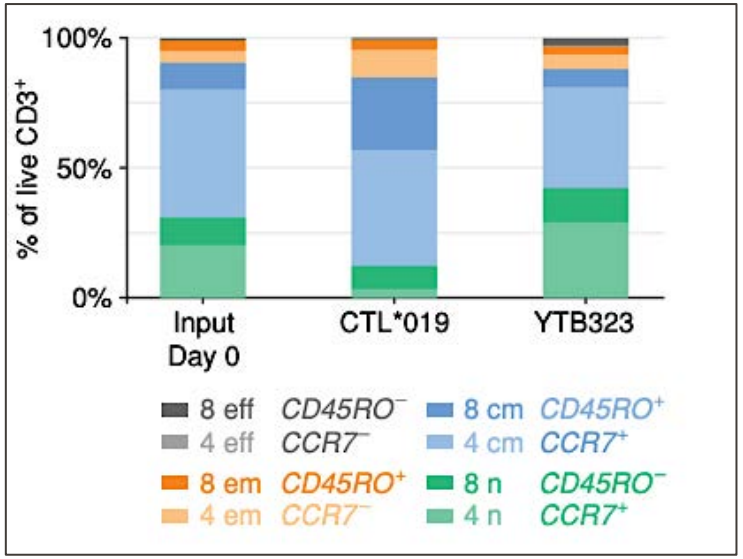



Westin & Sehn, Blood 2022

# On the horizon: YTB323 (rapcabtagene autoleucel)

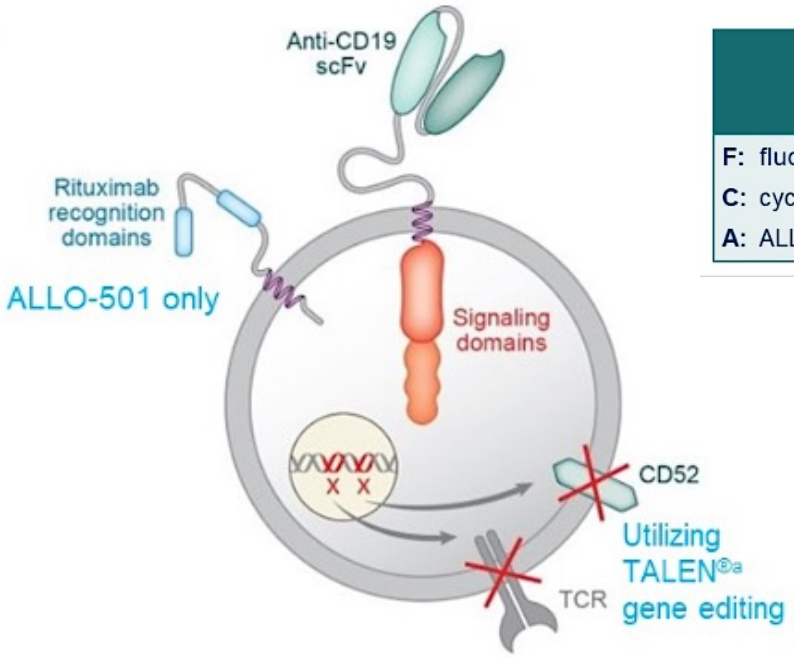



| | Patients evaluable for efficacy at month 3 ($N$ = 19) | |
|---|---|---|
| | DL1 ($n$ = 4) | DL2 ($n$ = 15) |
| CR at month 3, $n$ (%) | 1 (25) | 11 (73) |
| CR at last assessment before YTB323,[a] $n$ (%) | 1 (25) | 2 (13) |
| PR, $n$ (%) | 0 | 0 |
| SD, $n$ (%) | 0 | 0 |
| PD, $n$ (%) | 3 (75) | 2 (13) |
| Unknown | 0 | 2 (13) |




144 Dickinson et al, Cancer Discovery 2023

# On the horizon: ALLO-501A




**Selected Phase 2 Treatment Regimen**

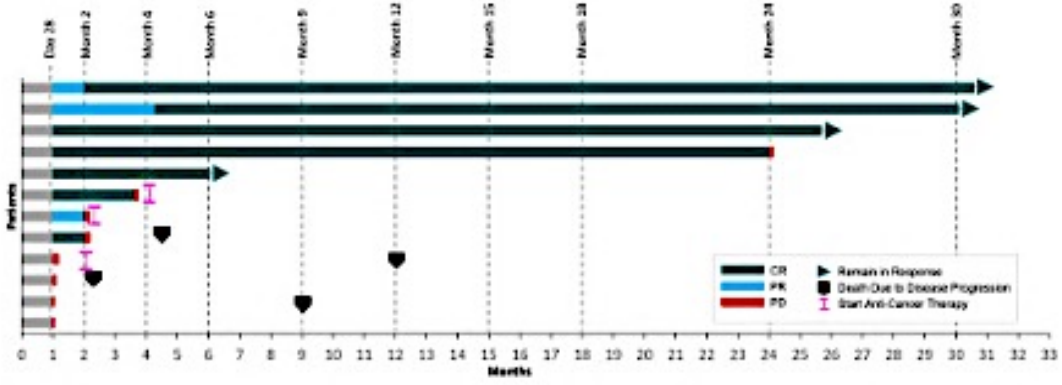
| 3-day lymphodepletion with FCA90 | Single-dose of ALLO-501A or ALLO-501 | Follow-up (ongoing) |
|---|---|---|
| **F:** fludarabine 30 mg/m$^2$/day<br>**C:** cyclophosphamide 300 mg/m$^2$/day<br>**A:** ALLO-647 30 mg/day (total dose: 90 mg) | 120-360 x $10^6$ viable CAR+ cells | |

**Response Rates**

| | N=12 |
|---|---|
| ORR, n (%) | 8 (67) |
| CR, n (%) | 7 (58) |
| 6 months CR[a], n (%) | 5 (42) |

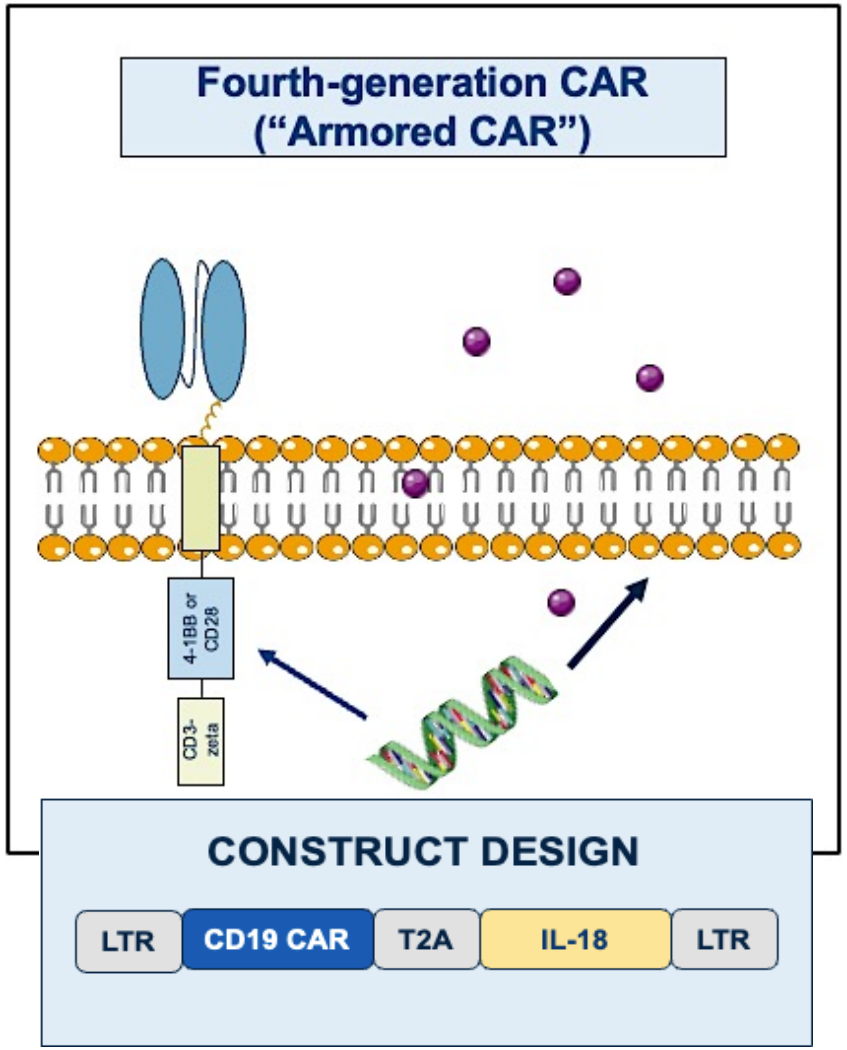
[a] Analysis of patients who had the opportunity to be followed through Month 6 or experienced disease progression prior to Month 6

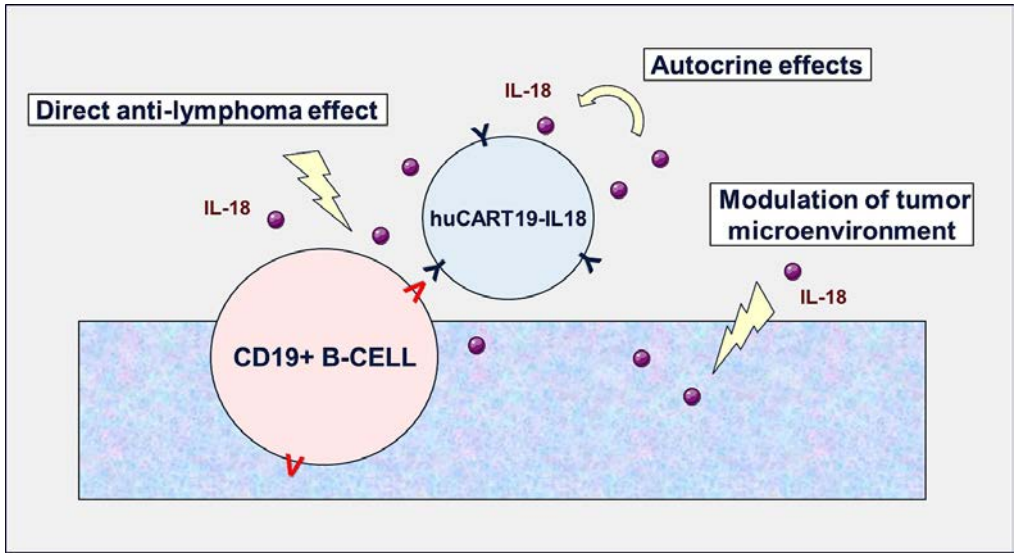
**Swimmer Plot of Tumor Response**

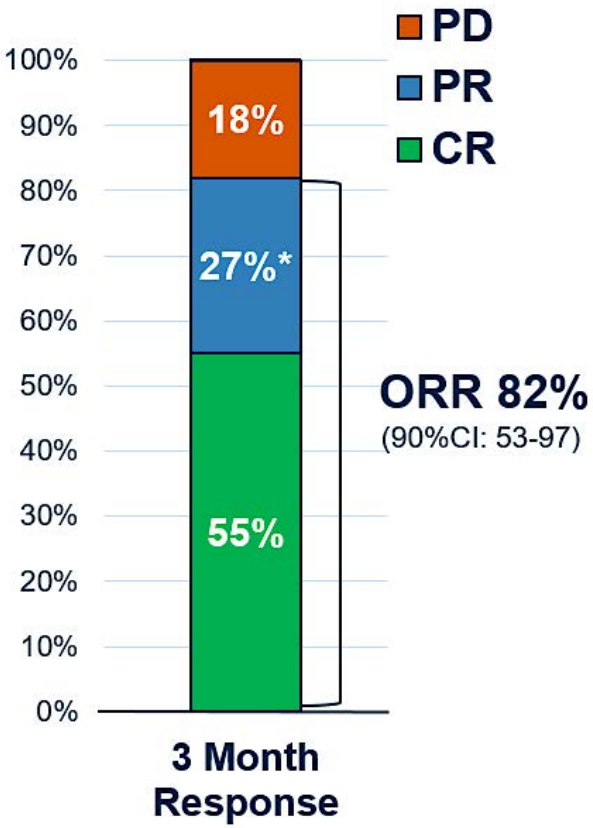



Locke et al, J Clin Oncol 41, 2023 (suppl 16; abstr 2517)

# On the horizon: huCART19-IL18




Svoboda et al, ICML 2023

# Agenda

**Module 1: Up-Front Management of Diffuse Large B-Cell Lymphoma (DLBCL) — Dr Salles**

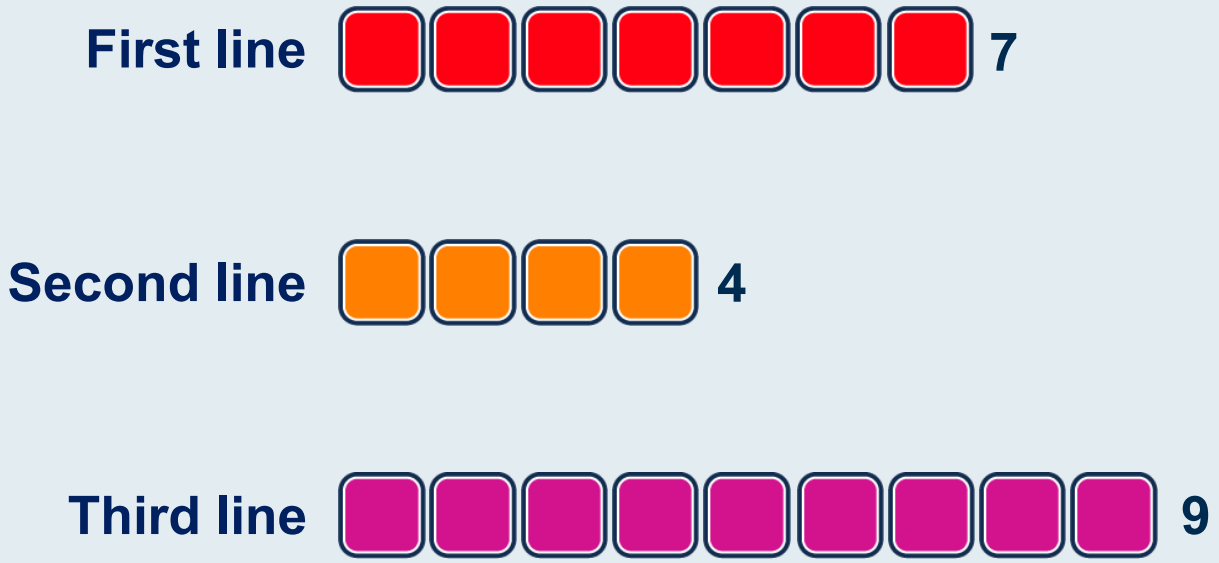
**Module 2: Promising Investigational Approaches to First-Line Therapy for DLBCL — Dr Nowakowski**

**Module 3: Selection and Sequencing of Novel Therapies for Relapsed/Refractory (R/R) DLBCL — Dr Sehn**

**Module 4: Incorporation of CAR T-Cell Therapy into the Management of R/R DLBCL — Dr Westin**

**Module 5: Role of Bispecific Antibodies in the Treatment of DLBCL — Prof Dickinson**

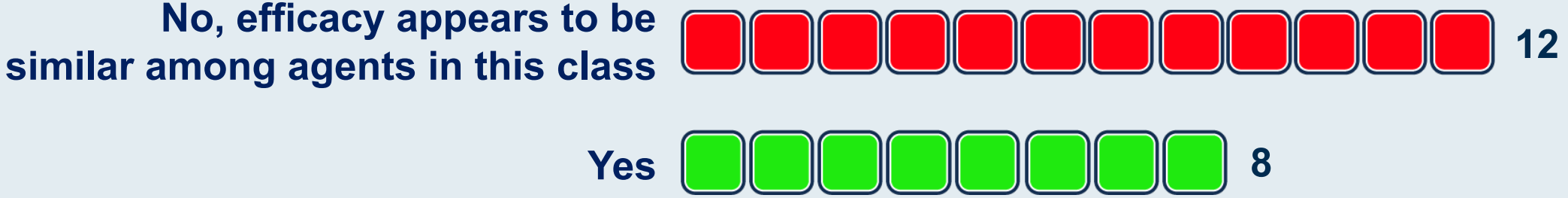
# Regulatory and reimbursement issues aside, at what point would you like to use a bispecific antibody for a patient with Stage IV DLBCL?



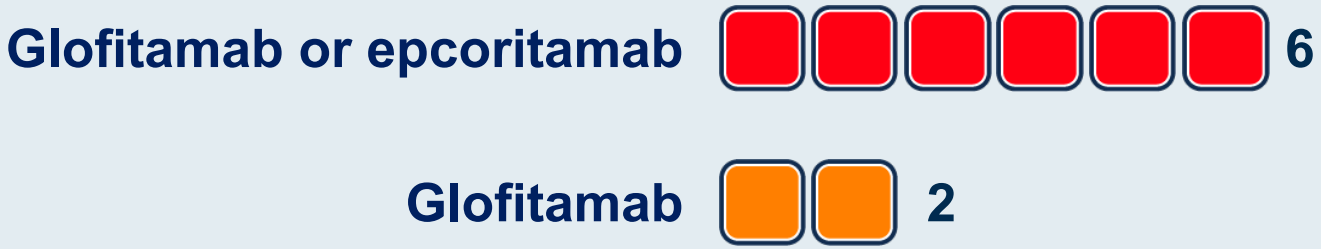

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

## Based on your personal clinical experience and knowledge of available data, do you believe 1 or more bispecific antibodies are more efficacious than others when used in the management of DLBCL?




## Which bispecific antibody is more efficacious?




Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Based on your personal clinical experience and knowledge of available data, for each of the following agents please estimate the chance that a patient with DLBCL will experience toxicity during treatment that will require withholding dosing. What is the primary toxicity patients experience that leads to withholding dosing?

| | Chance of withholding (Median) | Primary toxicity |
|---|---|---|
| Epcoritamab | 10% | Cytopenias, CRS |
| Glofitamab | 13% | Cytopenias, CRS |
| Odronextamab | 13% | Cytopenias, CRS |

CRS = cytokine release syndrome

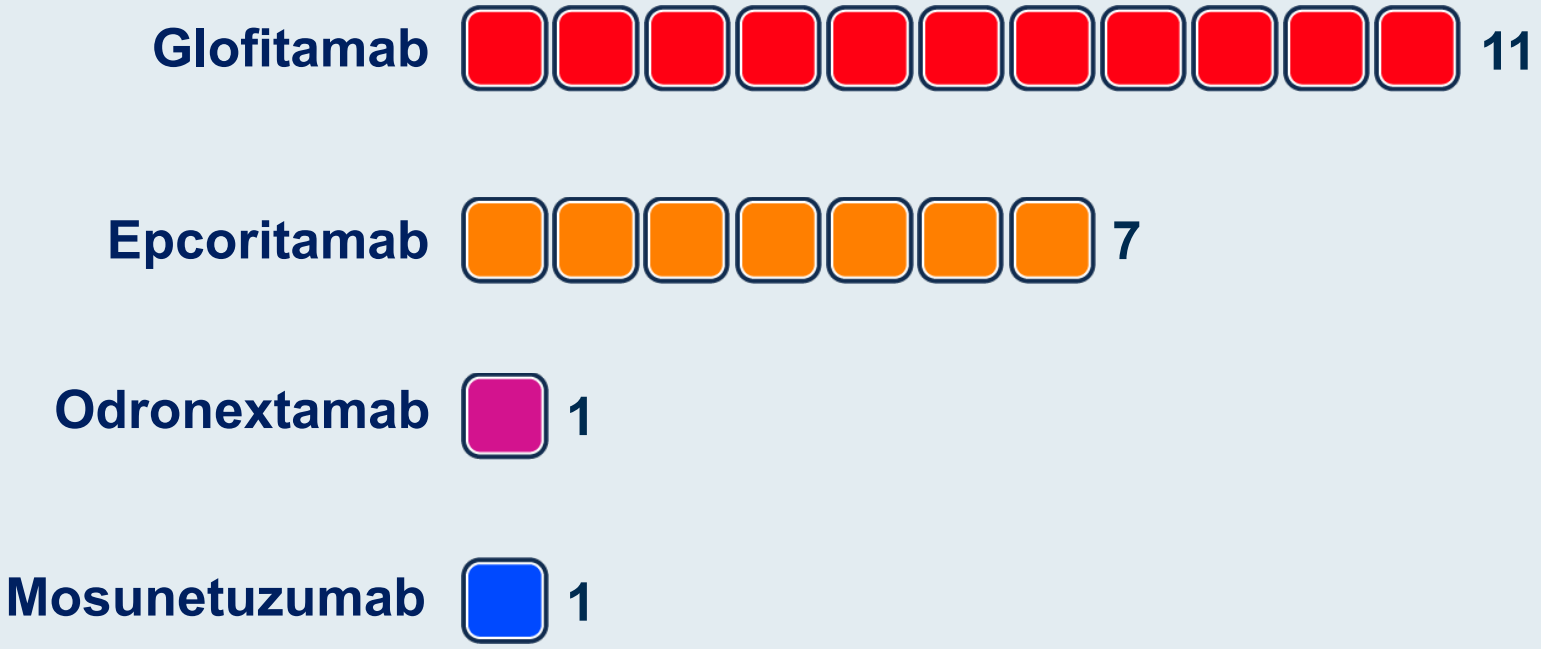
Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Please describe a patient with DLBCL you've cared for this year who received a bispecific antibody.

**Patient age:** 67 (median; range 19-81)

## Bispecific antibody the patient received:



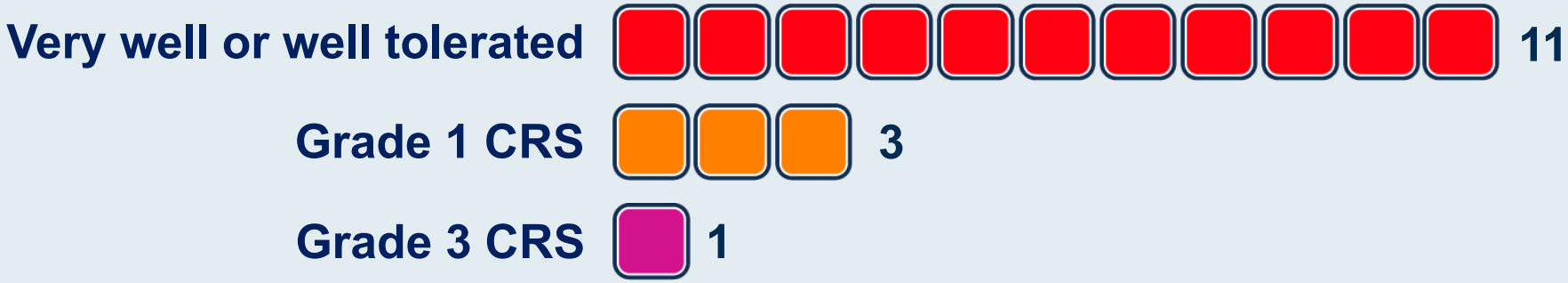

Survey of 20 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Please describe a patient with DLBCL you've cared for this year who received a bispecific antibody.

## Patient's response to therapy:


## Patient's tolerance of therapy:




Survey of 19 US-based clinical investigators November 2023

RTP RESEARCH TO PRACTICE

# Key similarities and differences between the bispecific antibodies epcoritamab and glofitamab

**Andrew M Evens, DO, MBA, MSc**

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TO PRACTICE

# Selection and sequencing of CAR T-cell therapy and bispecific antibodies for patients with R/R DLBCL

**Tycel Phillips, MD**

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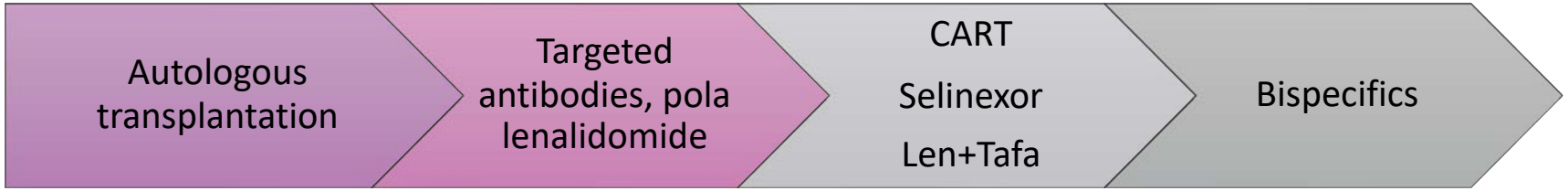
TO PRACTICE

# CD20 x 3 Bispecific antibodies for diffuse large B-cell Lymphoma: Data from Phase 2 trials Research To Practice: ASH San Diego

A/Prof Michael Dickinson
Lead, Aggressive Lymphoma
Peter MacCallum Cancer Centre
and Royal Melbourne Hospital

Peter Mac
Peter MacCallum Cancer Centre
Victoria Australia

# Evolving landscape in DLBCL



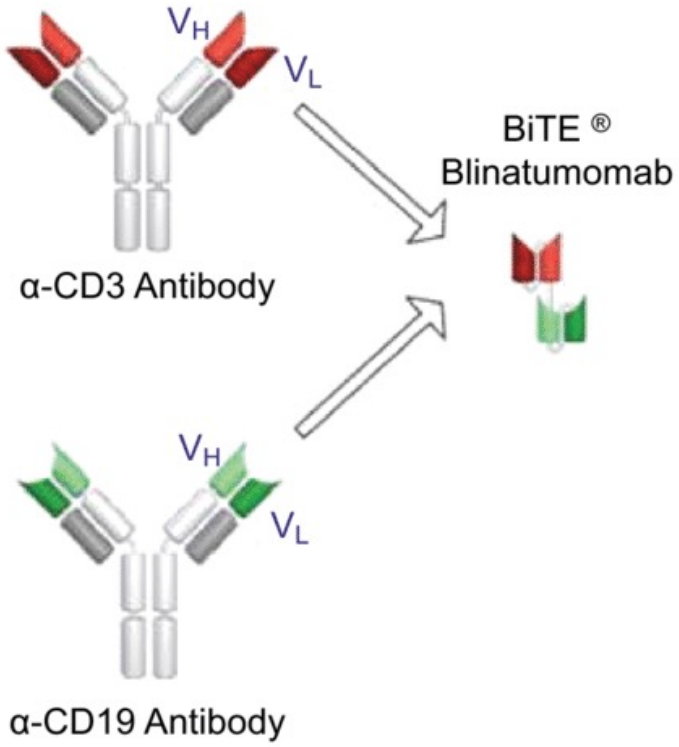

Cure is hard to achieve without a transplant

We should chase cure whether the patient is transplant eligible or not

*…. And it might be possible without CAR-T*

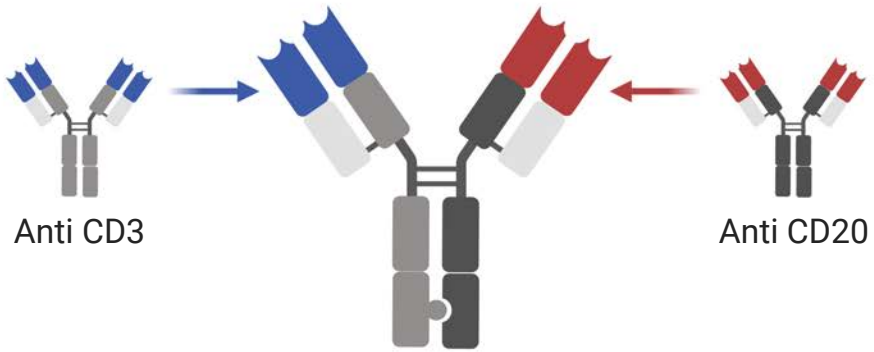
# “BiTEs” ® – small molecules, short half-life, given as an infusion

## Blinatumomab: CD19



# Structural Features of the CD20x3 Bispecific Antibodies

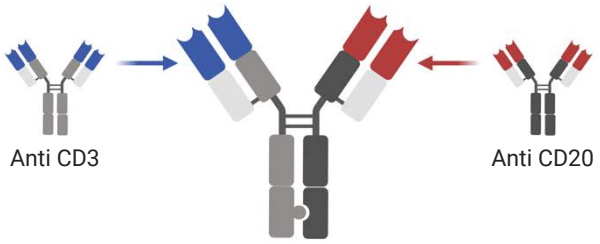
*T-cell, binding,  activation, expansion, T-cell mediated target cell death at low receptor occupancy*




1:1 format bispecific
(eg mosunetuzumab,
ondronextamab,
epcoritamab)

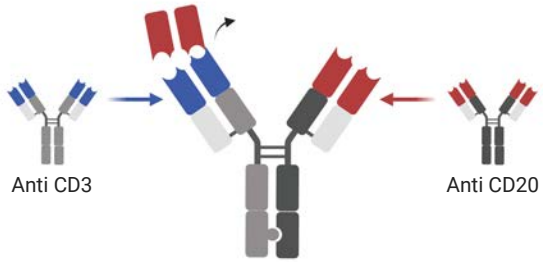
- CD3 on T-cells
- *CD20* on B-cells (normal and malignant)
- Full length antibody
- FC modifications and silencing
- Long half life

# Features of the CD20x3 Bispecific Antibodies



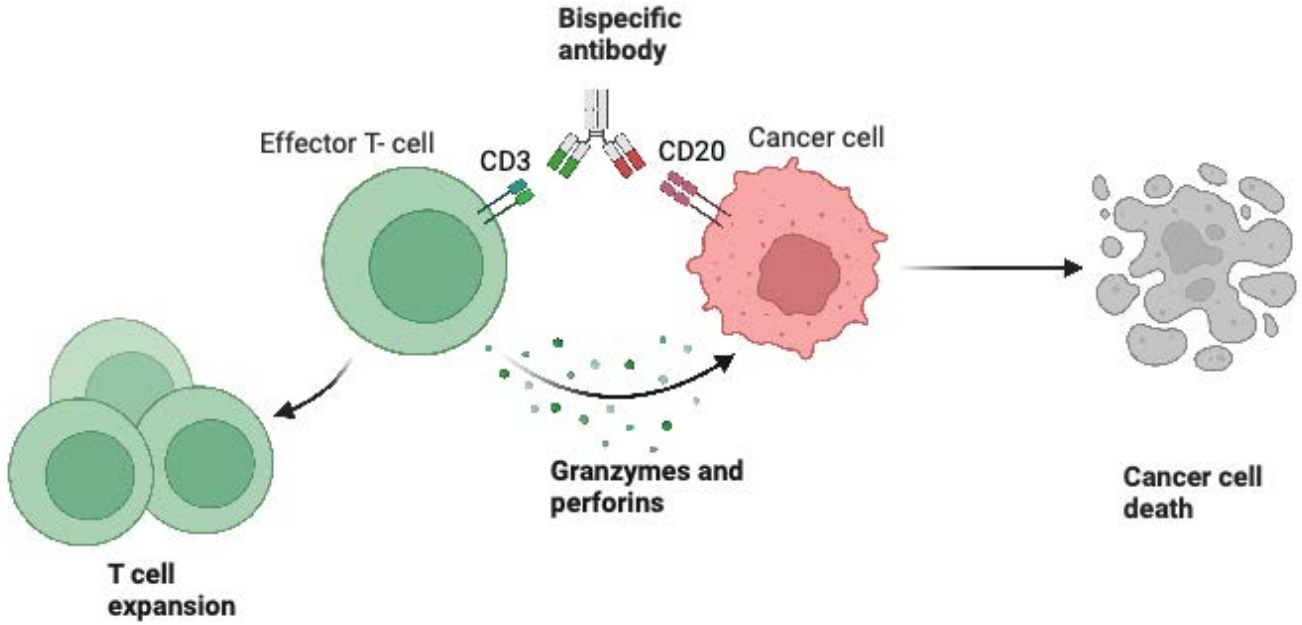

1:1 format bispecific (eg mosunetuzumab, ondronextamab, epcoritamab)

1:1




2:1 format bispecific (glofitamab)

2:1




*T-cell, binding, activation, expansion, T-cell mediated target cell death at low receptor occupancy*

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# Common and differentiating design elements of the Glofitamab, Epcoritamab and Odronextamab trials in DLCBL

- All 3 trials included patients with R/R DLBCL and at least two prior treatment lines; However prior CAR-T exposure was excluded in odronextamab trial.
- All trials allowed transformed lymphoma, but Richter's syndrome was only allowed in expansion arm of odronextamab trial.
- The primary endpoint was CR in the glofitamab trial, ORR for epco and ondronextamab.
- 2 dosing strategies were evaluated in ELM 2 (Odronextamab)-
- All trials use steroid prophylaxis prior to bispecifics
- All use step up strategies to mitigate CRS
- Only the glofitamab trial also uses the anti-CD20 antibody Obinutuzumab

# Delivery and scheduling- Comparing the Bispecifics

| Treatment | Route/ $T^{1/2}$ | Cycles | Duration | CRS mitigation | No. visits in 24w | No. visits in 52 weeks |
|---|---|---|---|---|---|---|
| **Glofitamab** | IV<br><br>8d post single dose | Q21d:<br>2 (weekly) steps to target then q3w to C12 | Fixed | Obinutuzumab<br>Step up<br>Steroids<br>**One dose dex** | 10 | 14 |
| **Epcoritamab** | SC<br><br>22d (post ramp) | Q28d<br>Weekly C1-3<br>Q2w 4-9<br>Q4w 10 onwards | Until PD | Step Up<br>Steroids<br>**4 days /dose**<br>**- new mitigation abstract at ASH23** | 18 | ~27 |
| Odronextamab | IV | Q21d<br>6 doses C1, 3 doses C2-4<br>Then q14d until m9 then q4 weekly if in CR | Until PD | Step Up<br>Split dosing<br>Steroids<br>**Dex pre each dose** | 21 | ~32 |

*Data from Dickinson et al, NEJM 2022, Thieblemont et al. JCO 2023, and Ayyappan et al. ASH 2023 Abstract + Kim et al ASH 2022 Presentation*

*Note: the clinical profile, dosing and risk mitigation strategies of these drugs are still in evolution.*
*For odro: Total doses estimated based on available publications/presentations.*

# *Patient Characteristics across the trials*

| Characteristic | Glofitamab (n=155) NEJM | Epcoritamab (n=157) JCO | Odronextamab (n=127) (ASH23) |
|---|---|---|---|
| Age | 66 (21-90) | 64 (20-83) | 66 |
| Prior Rx (median, range) | 3 (2-7) | 3 (2-11) | 2 (2-8) |
| Primary refractory | 58.4% | 61% | 57% |
| Refractory to last Rx | 85.7% | 83% | 86.4% |
| HGBL | 7.1% | 6% | 13.6% |
| Transformed lymphoma | 17.5% | 25% | 17% *5% Richter's |
| PMBCL | 4% | 3% | |
| Prior CART | 33% | 39% | Excluded in ELM-2 |
| Prior ASCT | 18.2% | 20% | 15.7% |

*Data from Dickinson et al, NEJM 2022, Thieblemont et al. JCO 2023, and Ayyappan et al. ASH 2023 Abstract + Kim et al ASH 2022 Presentation*

# Bispecifics lead to impressive complete remission rates in DLBCL

| | Pivotal | Pivotal | |
|---|---|---|---|
| **Characteristic** | **Glofitamab (n=154)** | **Epcoritamab (n=157)** | **Odronextamab (n=127)*** |
| ORR (%) | 51.6 | 63 | 52% |
| CRR(%) | **39.4** | **39** | **31%** |

Primary endpoint: CR rate for Glofitamab and ORR for Epcoritamab

*data from ASH Abstracts and conference presentations

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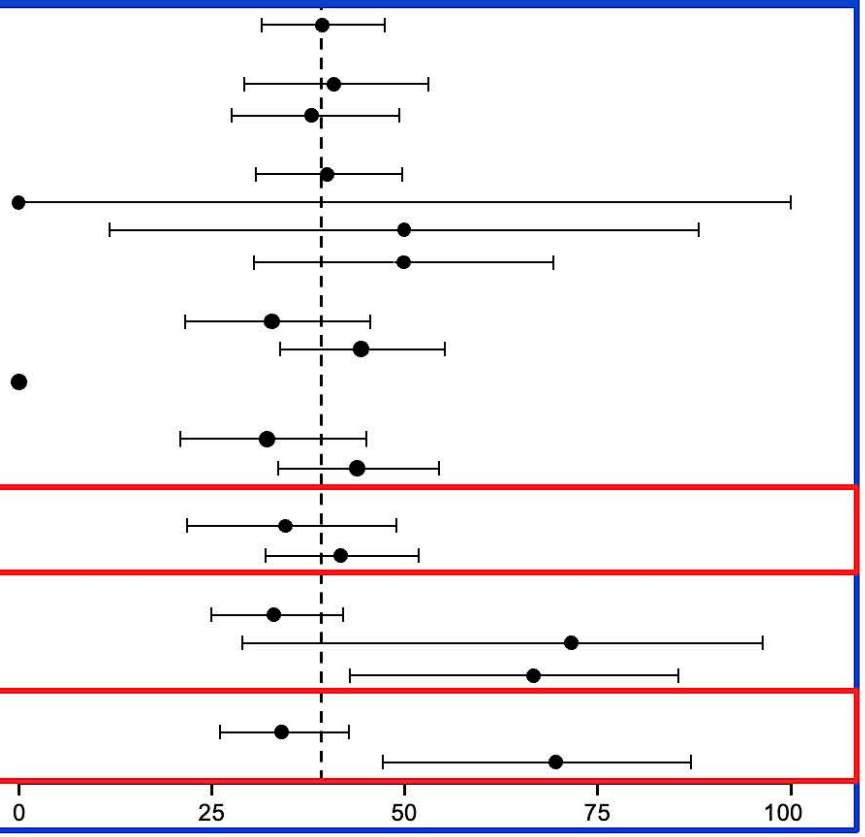
*Data from Dickinson et al, NEJM 2022, Thieblemont et al. JCO 2023, and Ayyappan et al. ASH 2023 Abstract + Kim et al ASH 2022 Presentation*

# Complete Responses consistent across high-risk subgroups: Glofitamab

| Subgroups | No. of patients | CR (95% CI) by IRC |
|---|---|---|
| **Overall** | 155 (100%) | 39% (32%, 48%) |
| **Age group** | | |
| <65 | 71 (46%) | 41% (29%, 53%) |
| ≥65 | 84 (54%) | 38% (28%, 49%) |
| **NHL subtype at study entry** | | |
| DLBCL | 110 (71%) | 40% (31%, 50%) |
| HGBCL | 11 (7%) | 0% |
| PMBCL | 6 (4%) | 50% (12%, 88%) |
| trFL | 28 (18%) | 50% (31%, 69%) |
| **Bulky disease >6cm** | | |
| Yes | 64 (41%) | 33% (22%, 46%) |
| No | 90 (58%) | 44% (34%, 55%) |
| Unknown/Missing | 1 (1%) | 0% |
| **Number of prior line of therapies** | | |
| 2 | 62 (40%) | 32% (21%, 45%) |
| ≥3 | 93 (60%) | 44% (34%, 55%) |
| **Prior CAR-T therapy** | | |
| Yes | 52 (34%) | 35% (22%, 49%) |
| No | 103 (66%) | 42% (32%, 52%) |
| **Post ASCT** | | |
| No | 127 (82%) | 33% (25%, 42%) |
| Refractory | 7 (5%) | 71% (29%, 96%) |
| Relapsed | 21 (14%) | 67% (43%, 85%) |
| **R/R to last prior therapy** | | |
| Refractory | 132 (85%) | 34% (26%, 43%) |
| Relapsed | 23 (15%) | 70% (47%, 87%) |




*Similar observations with epcoritamab and odronextamab (excl. CART in ph2)*

Data from Dickinson et al, NEJM 2022

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# PRIOR CAR-T – Complete remissions

| Epcoritamab | Glofitamab | Odronextamab (Caution not from same cohort) |
|---|---|---|
| • CAR-T naïve: 42%<br>• Exposed: 34% | • CAR-T naive: 42<br>• Exposed: 35% | • Unexposed (Ph2:<br>• Exposed: 32.3% |

*Data from Dickinson et al, NEJM 2022, Thieblemont et al. JCO 2023, Kim et al ASH 2022 Presentation*

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# How durable are the complete remissions?

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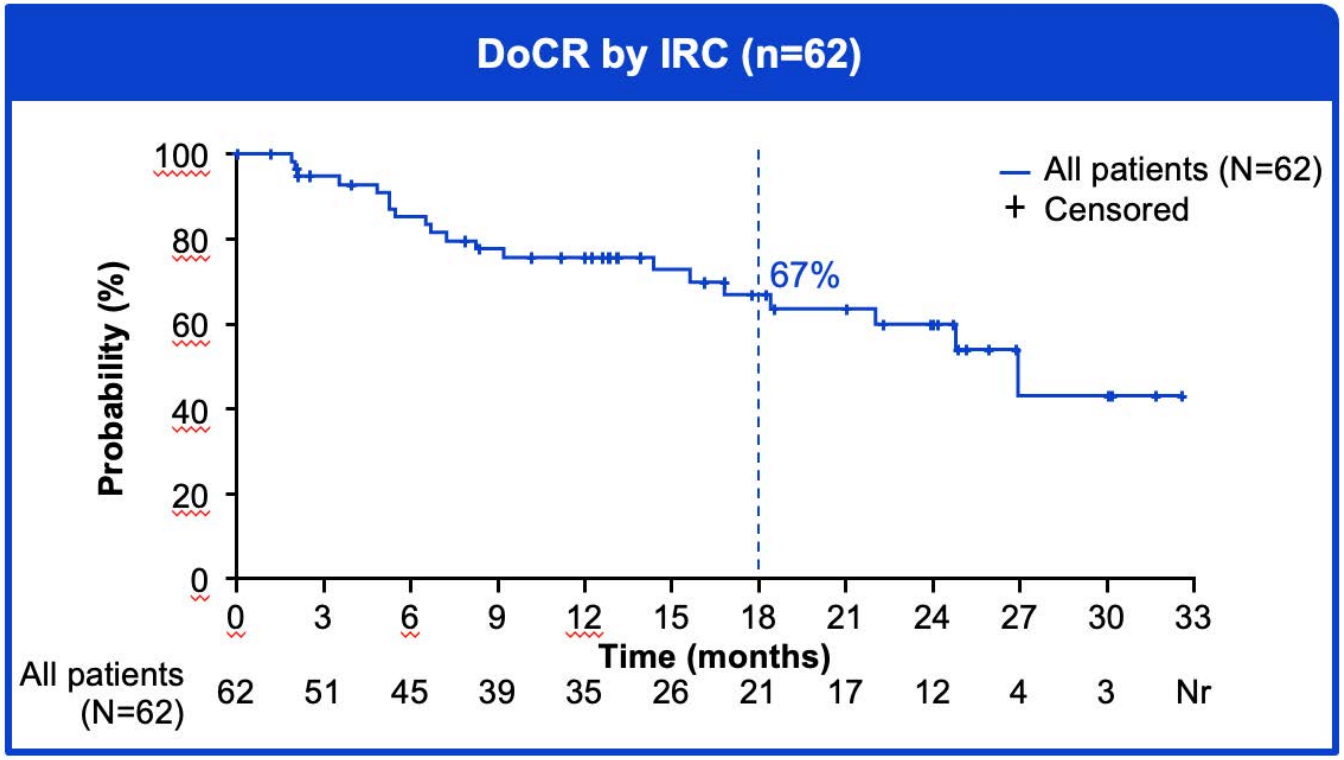
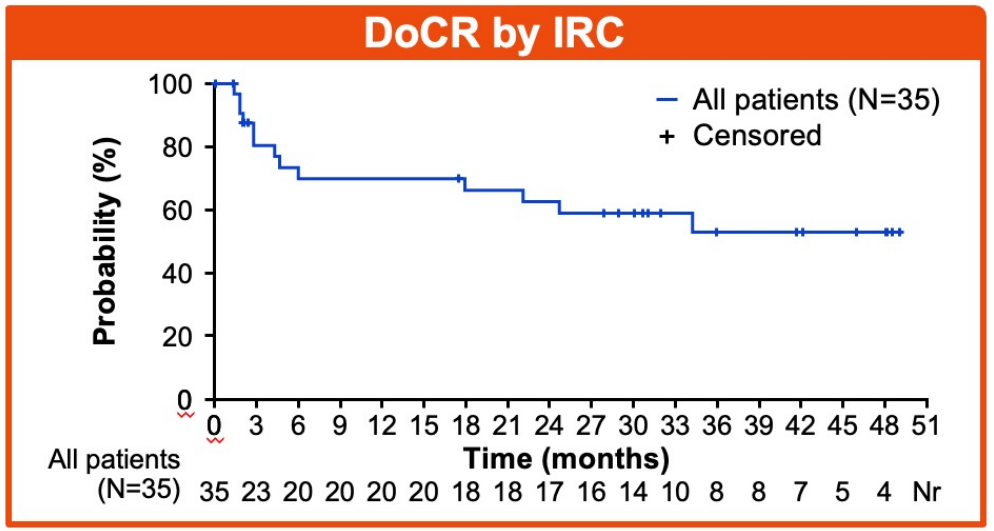
# Durability of CR:Glofitamab




*Phase 2 at RP2D*




| | N=35 |
|---|---|
| **Median CR follow-up, months (range)** | **32** (0–49) |
| 24-months DoCR, % (95% CI) | **62.6** (45.0–80.3) |

*Long Follow up of Phase 1 <RP2D*

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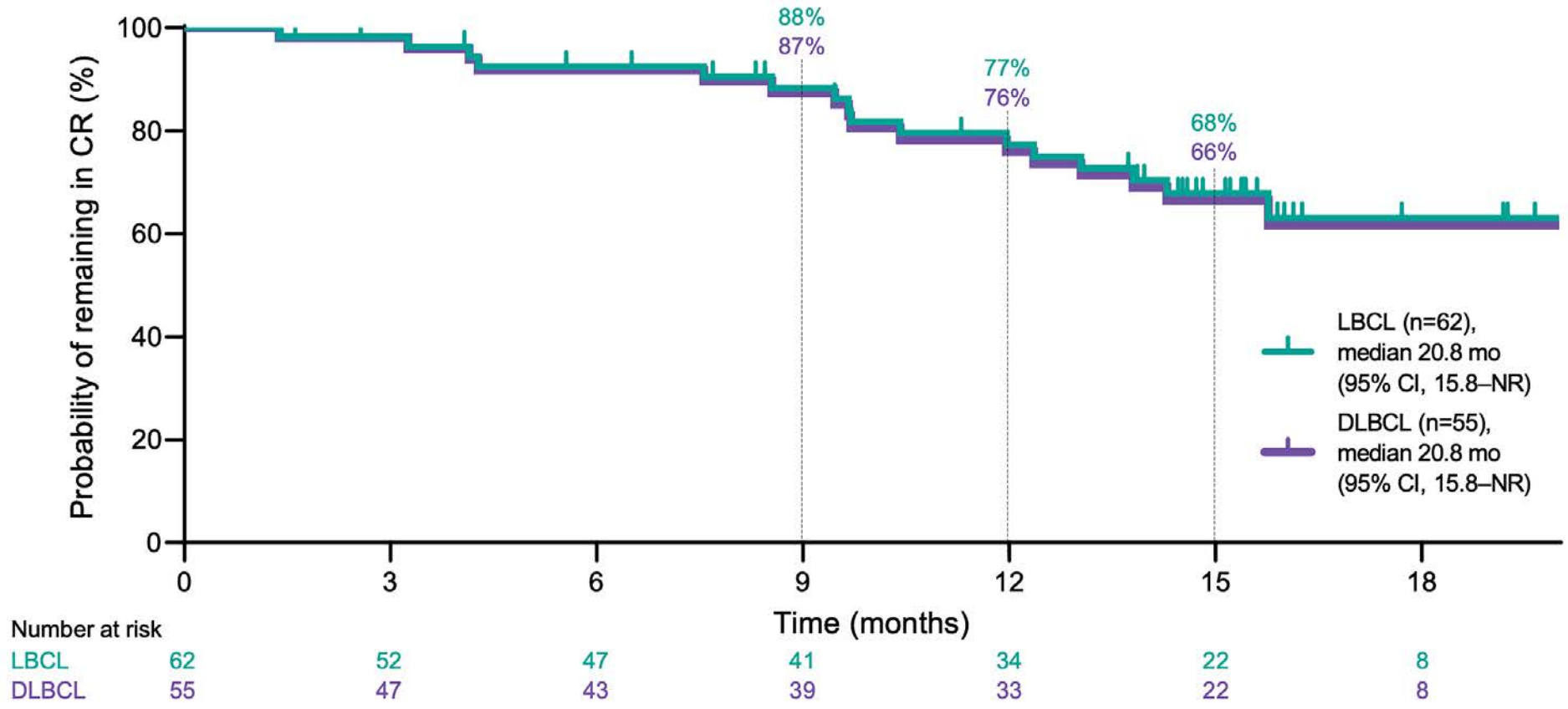
*Data from Dickinson et al, ICML 2023.*

# Durability of CR Epcoritamab

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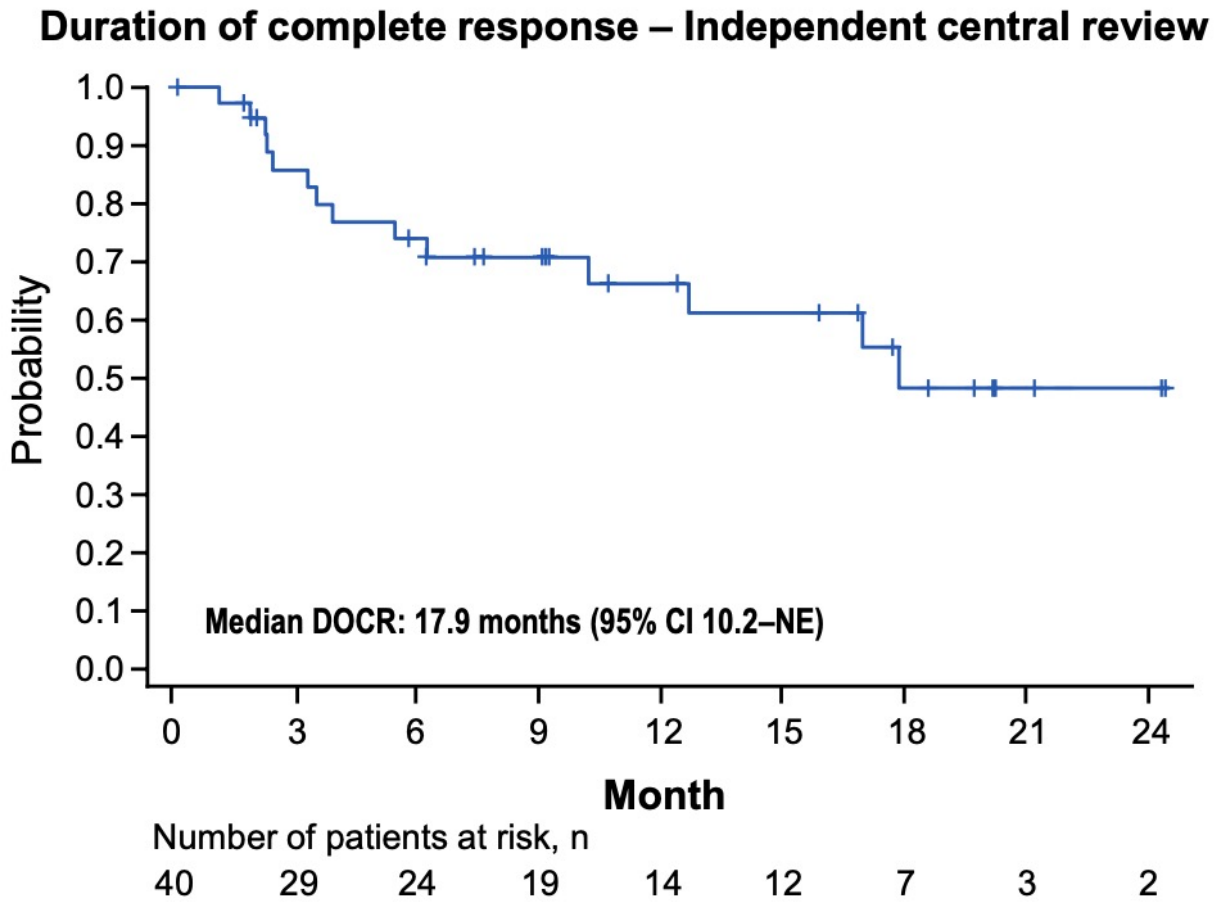
*Thieblemont et al. ICML 2023*

# Durability of CR Odronextamab




- 12-month DOCR: 66.4% (95% CI: 47.1–80.1)
- 18-month DOCR: 48.3% (95% CI: 26.1–67.4)

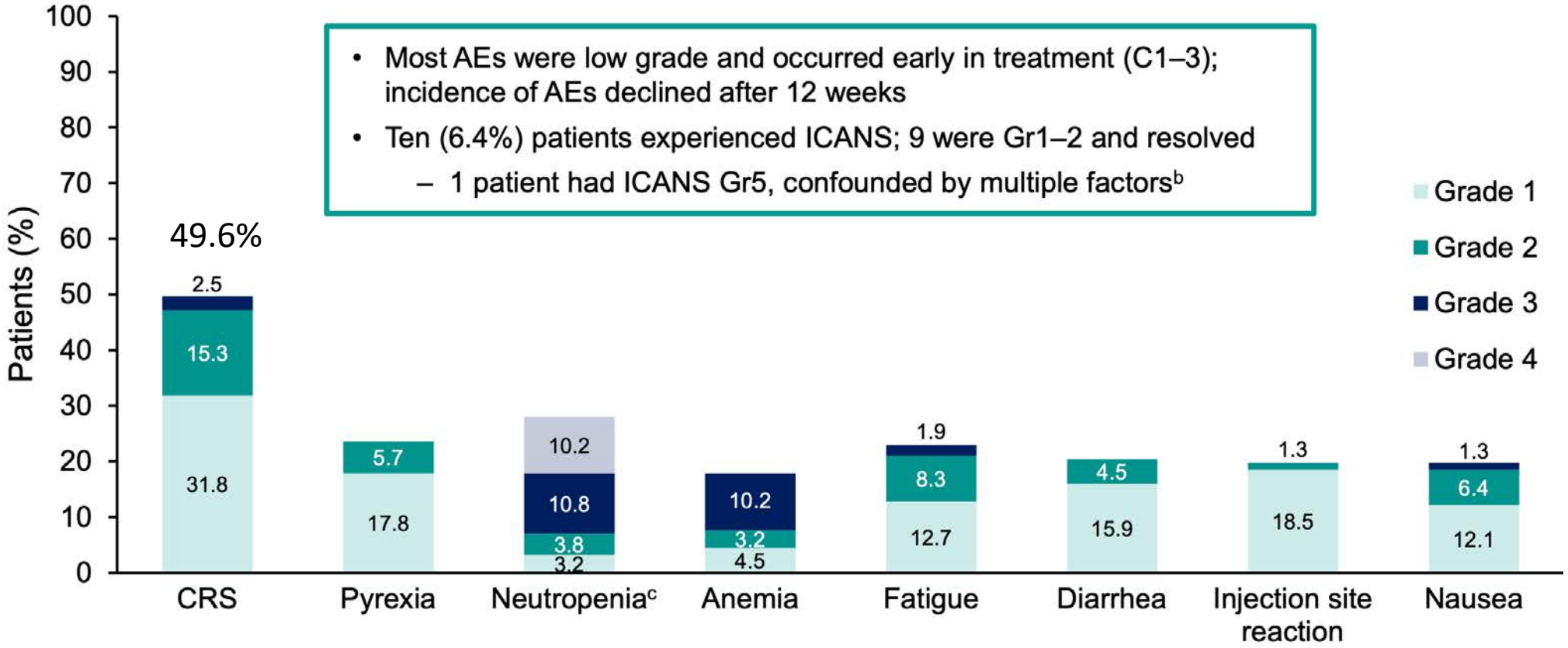
*Data from Kim et al ASH 2022 Presentation*

# Toxicity of bispecifics – Top tips

- Key toxicities:
  - Cytokine release syndrome:
    - Fever; signs like sepsis (hypotension and hypoxia)
    - Relates to burden of disease, distribution of antigen (blood, extranodal)
    - Dose –related: but prior successful dosing at lower doses reduces risk (first dose effect)
    - Always consider if infusion reaction: Is this CRS?
- Neutropenia
- Steroid -related effects
- Not-well-quantified later effects of B-cell depletion (infection, potential for hypogammaglobulinaemia and its complications)

# Epcoritamab - safety

**Treatment-Emergent Adverse Events[a] (≥15%) by Grade**




[a]COVID incidence 4.5%. [b]Patient experienced ICANS after intermediate dose with multiple confounders, including extensive opioid use for Gr3 pancreatitis, hyperammonemia, multifocal cerebral infarcts in setting of possible microangiopathy, and tocilizumab administration. [c]Combined term includes neutropenia and decreased neutrophil count.

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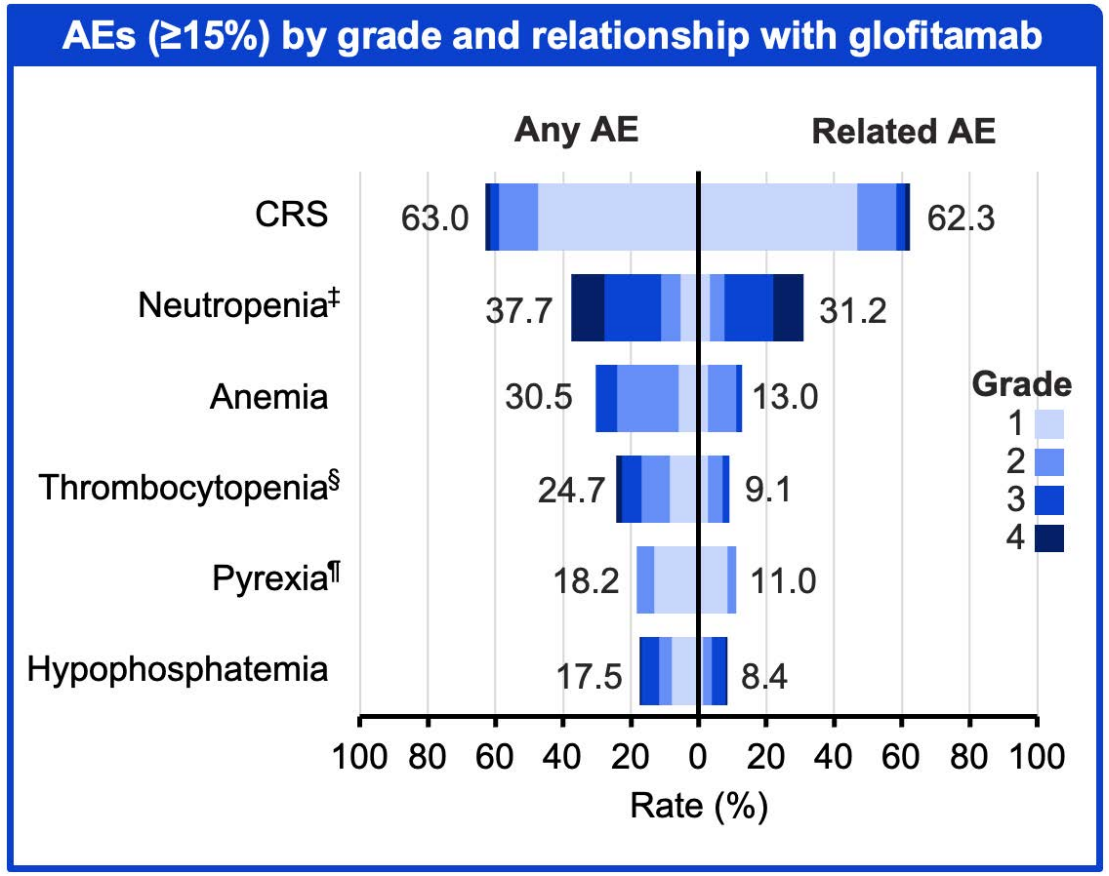
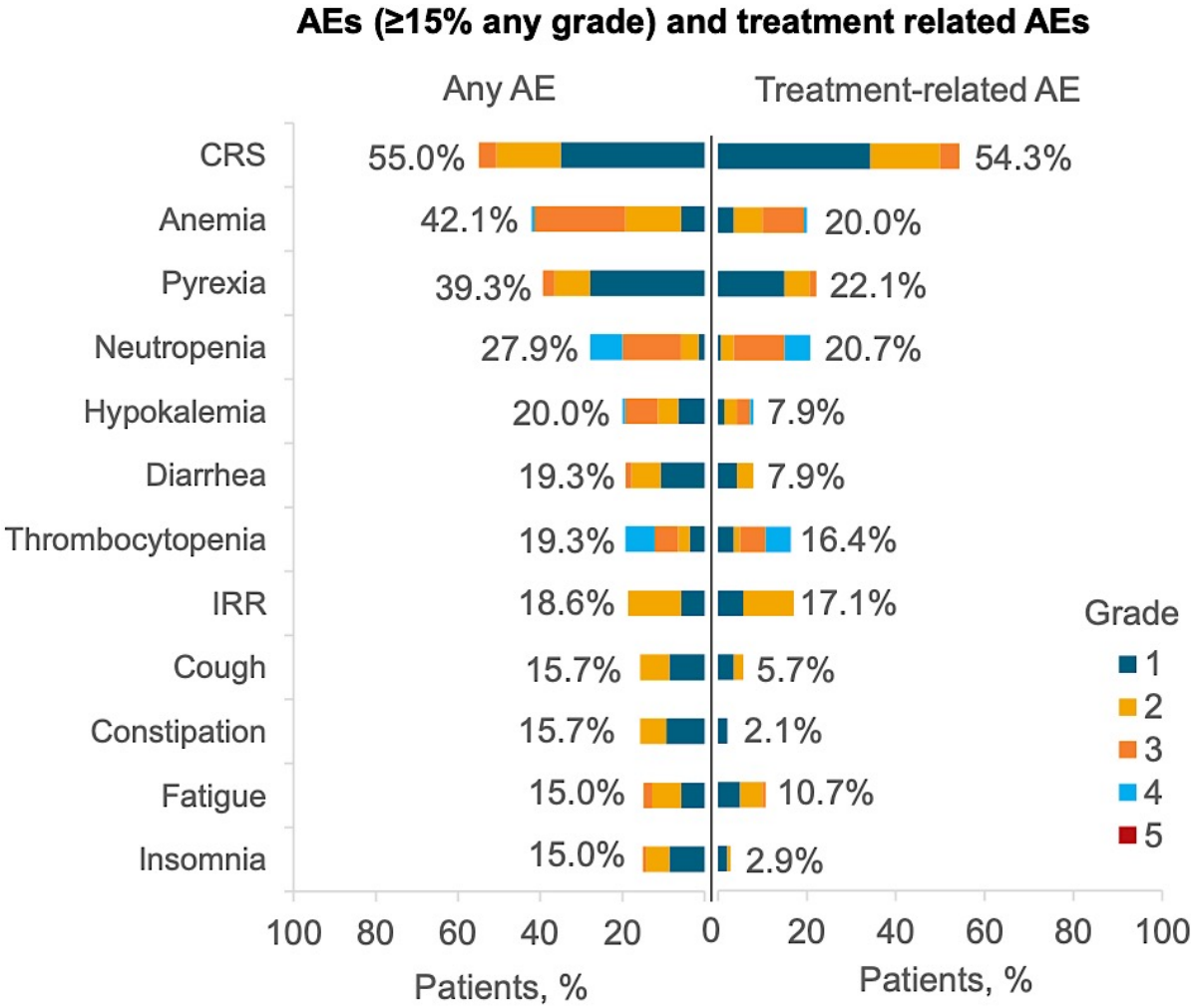
*Thieblemont et al. JCO 2023*

# Glofitamab toxicity

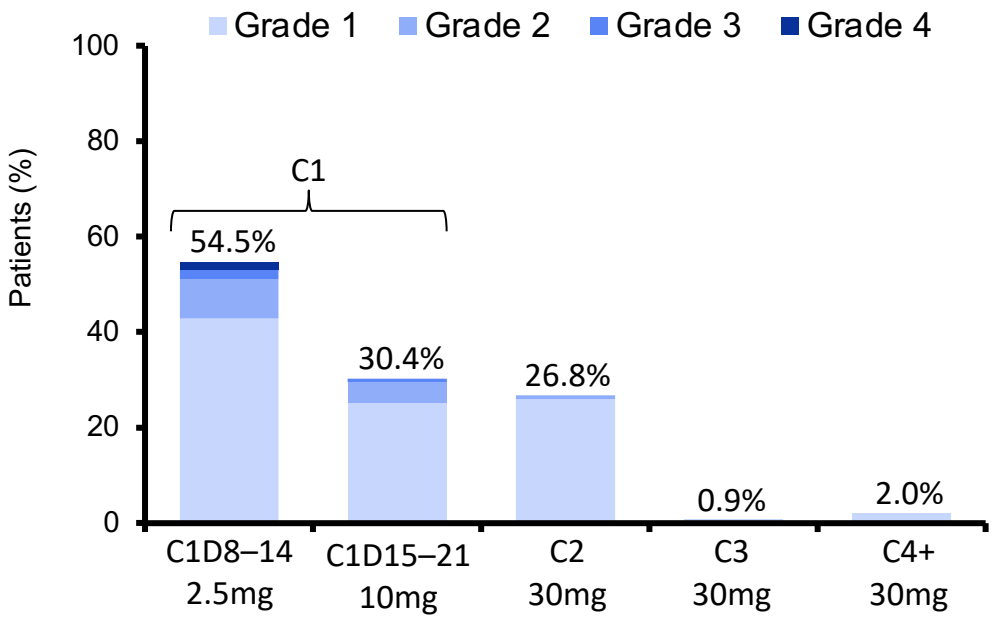



# Odronextamab (ELM2, ASH22)

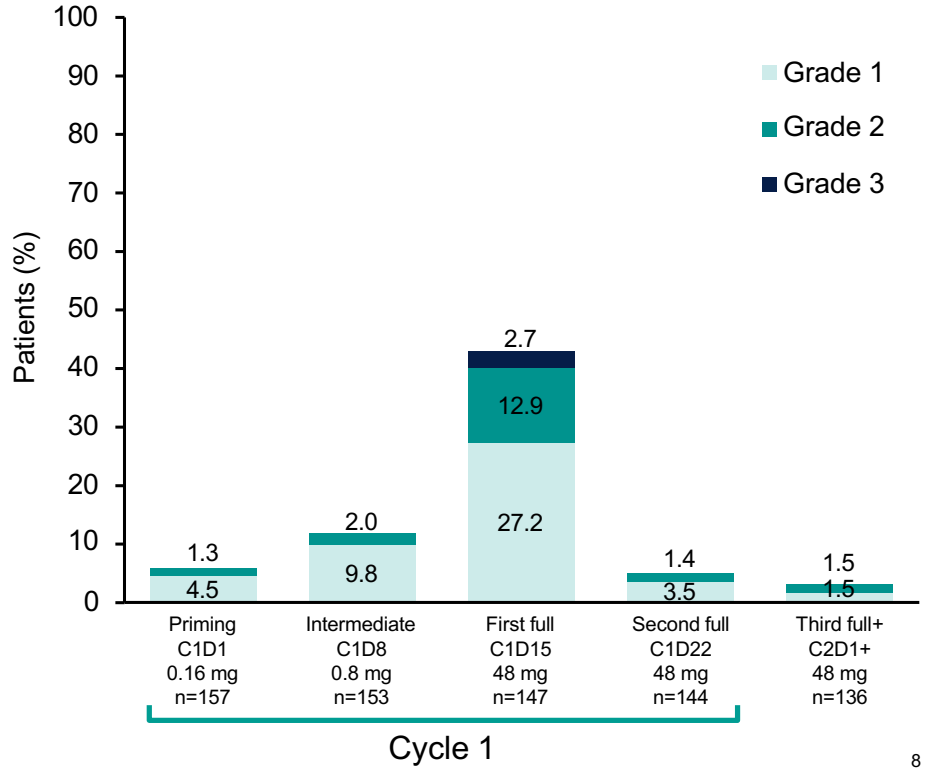



*Data from Dickinson et al, ICML 2023.*

# CRS rates and grades over time: Glofit vs Epco- Monotherapy Pivotal data




*CRS: Glofitamab ASCO/EHA 2022*

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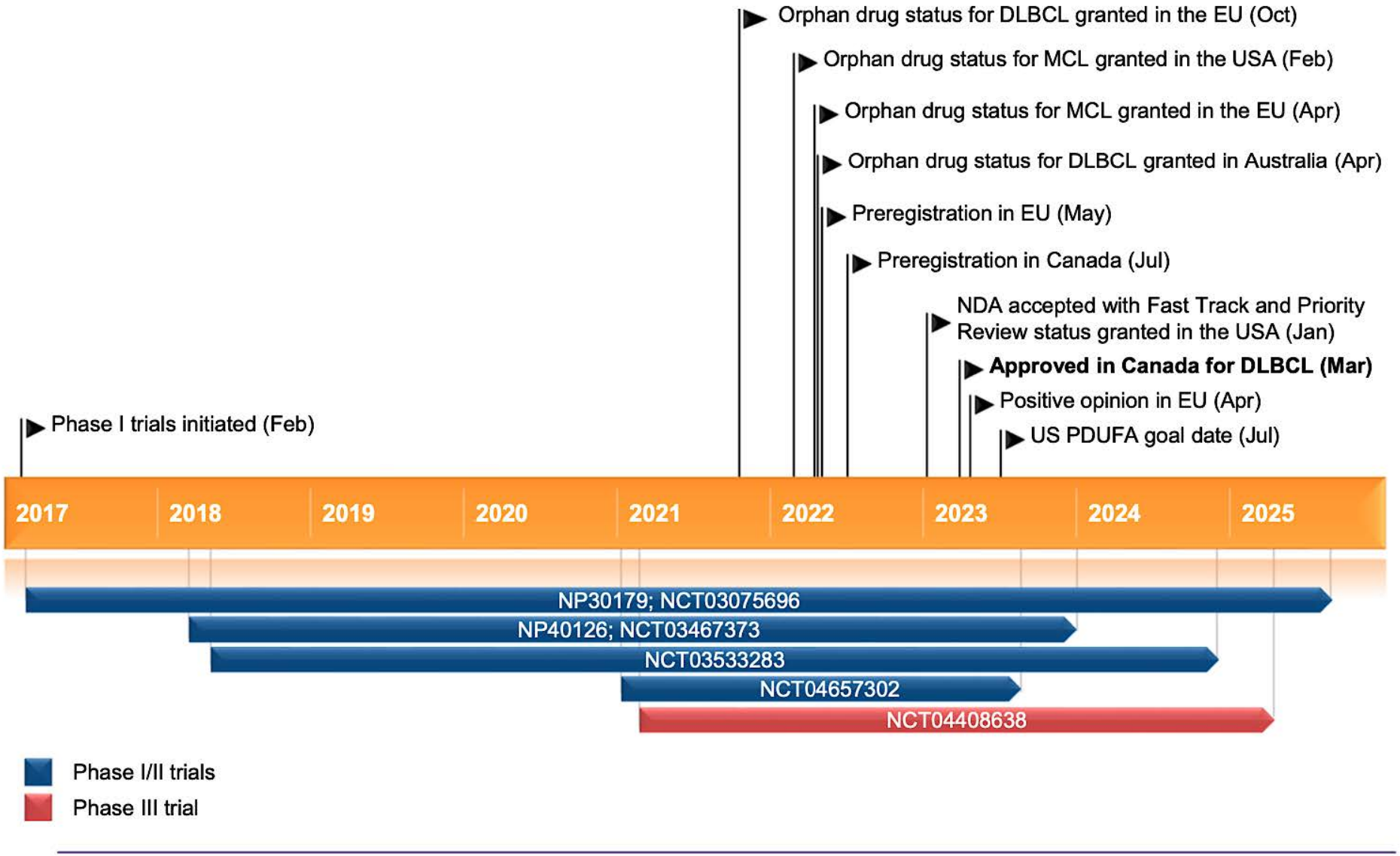
*CRS: Epcoritamab EHA 2022*

Dickinson M, Carlo-Stella C, Morschhauser F, et al. Glofitamab in patients with relapsed/refractory (R/R) diffuse large B-cell lymphoma (DLBCL) and ≥ 2 prior therapies: Pivotal phase II expansion results. *Journal of Clinical Oncology*. 2022;40(16_suppl):7500-7500. doi:10.1200/JCO.2022.40.16_suppl.7500; and EHA 2022 Thieblemont C, Phillips T, al. e. SUBCUTANEOUS EPCORITAMAB IN PATIENTS WITH RELAPSED OR REFRACTORY LARGE B-CELL LYMPHOMA (EPCORE NHL-1): PIVOTAL RESULTS FROM A PHASE 2 STUDY. presented at: European Haematology Association; 2022; Vienna.

# *Features of CAR-T and bispecifics*

| | Auto CAR-T | Glofitamab / Epcoritamab |
|---|---|---|
| 3L Approval | Y | Y |
| 2L Approval | Y | N |
| Off the shelf | N | Y |
| Mandatory lymphodepletion | Y | N |
| CRS | >> | Lower grade |
| Neurotoxicity | Higher | Lower/ nearly absent |
| Randomised trial evidence | Y (2L) | Not yet |
| Haematological Toxicity | Y | Limited -Y – febrile neutropenia uncommon. |
| Registry data | Y | No |

# Glofitamab approvals




Shirley, M., *Glofitamab: First Approval.* Drugs, 2023. **83**(10): p. 935-941.

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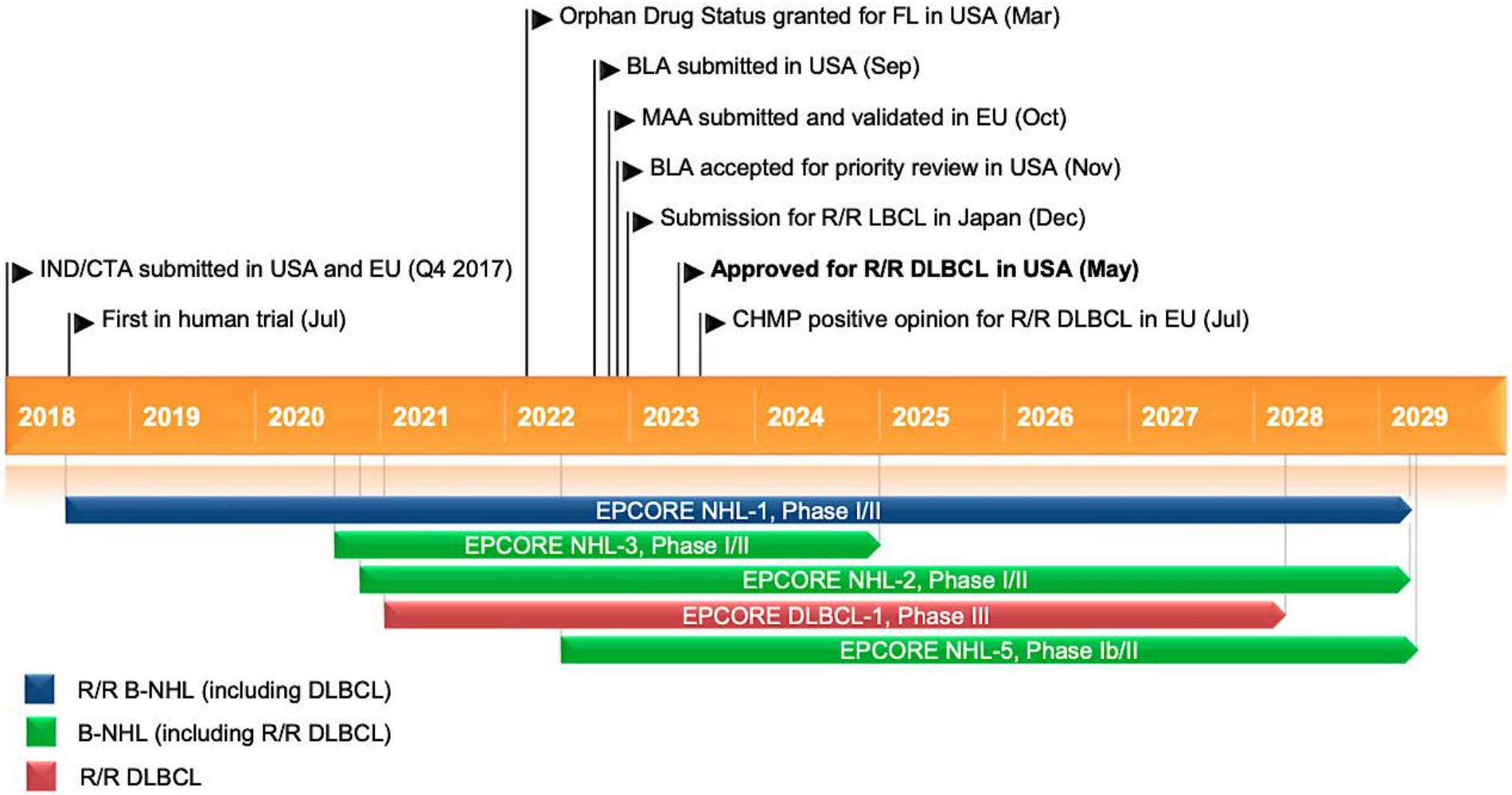
# Epcoritamab Approvals




Frampton, J.E., *Epcoritamab: First Approval.* Drugs, 2023. **83**(14): p. 1331-1340.

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# Conclusions

- 2 available agents in DLBCL following 2 prior lines of therapy. Promising data for a third.
- In class-toxicities that are best managed if well-anticipated.
- Developed as outpatient treatment.
- Effective (generally) in post-CAR-T setting
- Substantial differences in the practicalities of treatment

# Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Diffuse Large B-Cell Lymphoma (Part 2 of a 4-Part Series)

*A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting*

**Friday, December 8, 2023**

**11:30 AM – 1:30 PM PT (2:30 PM – 4:30 PM ET)**

## Faculty

**Michael Dickinson, MD**
**Grzegorz S Nowakowski, MD**
**Gilles Salles, MD, PhD**
**Laurie H Sehn, MD, MPH**
**Jason Westin, MD, MS**

## Moderator

**Neil Love, MD**

RTP RESEARCH TO PRACTICE

# Beyond the Guidelines: Clinical Investigator Perspectives on the Management of Chronic Lymphocytic Leukemia (Part 3 of a 4-Part Series)

*A CME Friday Satellite Symposium and Virtual Event Preceding the 65th ASH Annual Meeting*

**Friday, December 8, 2023**

**3:15 PM – 5:15 PM PT (6:15 PM – 8:15 PM ET)**

## Faculty

**Farrukh T Awan, MD**
**Matthew S Davids, MD, MMSc**
**Stephen J Schuster, MD**
**William G Wierda, MD, PhD**
**Jennifer Woyach, MD**

## Moderator

**Neil Love, MD**

RTP RESEARCH TO PRACTICE

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