7th POSTGRADUATE

Lymphoma Conference

# Frontline treatments in DLBCL: the actual scenario and the ongoing trials

Greg Nowakowski
Mayo Clinic

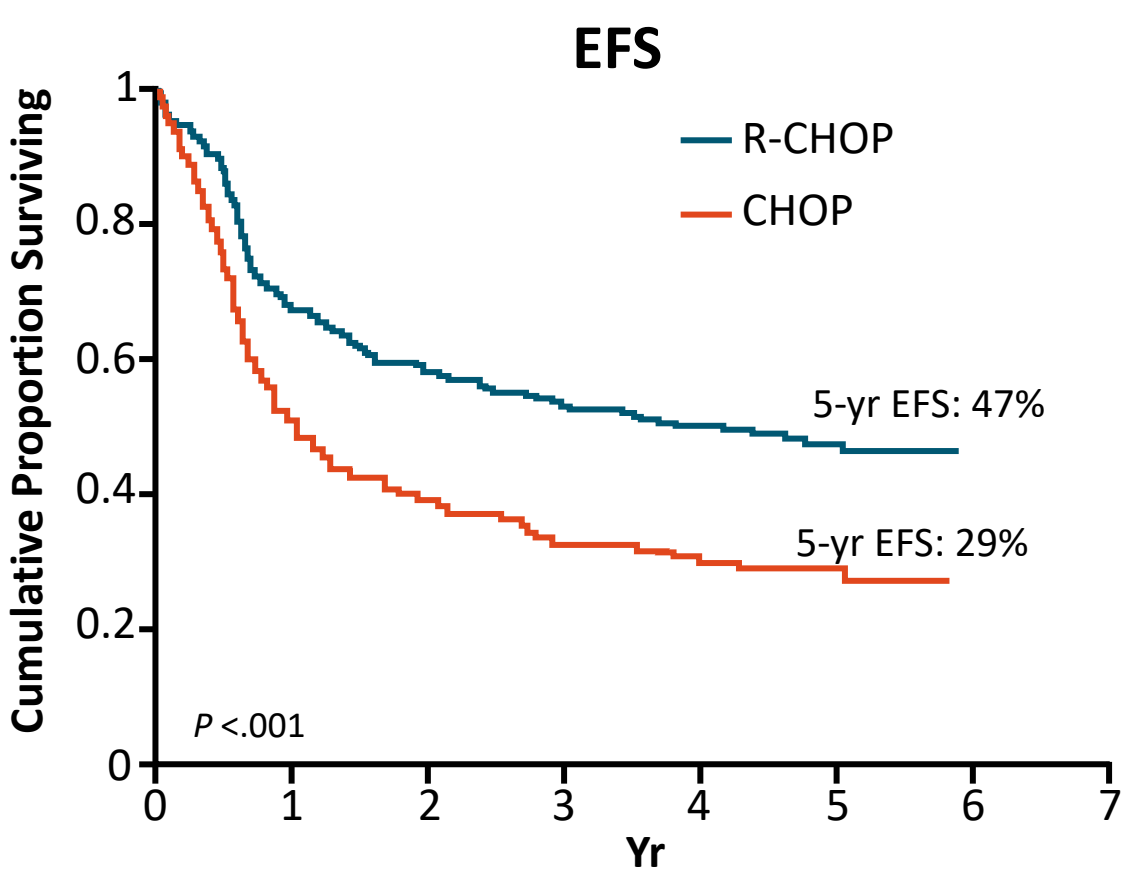
Rome,
March 16-17 -2023

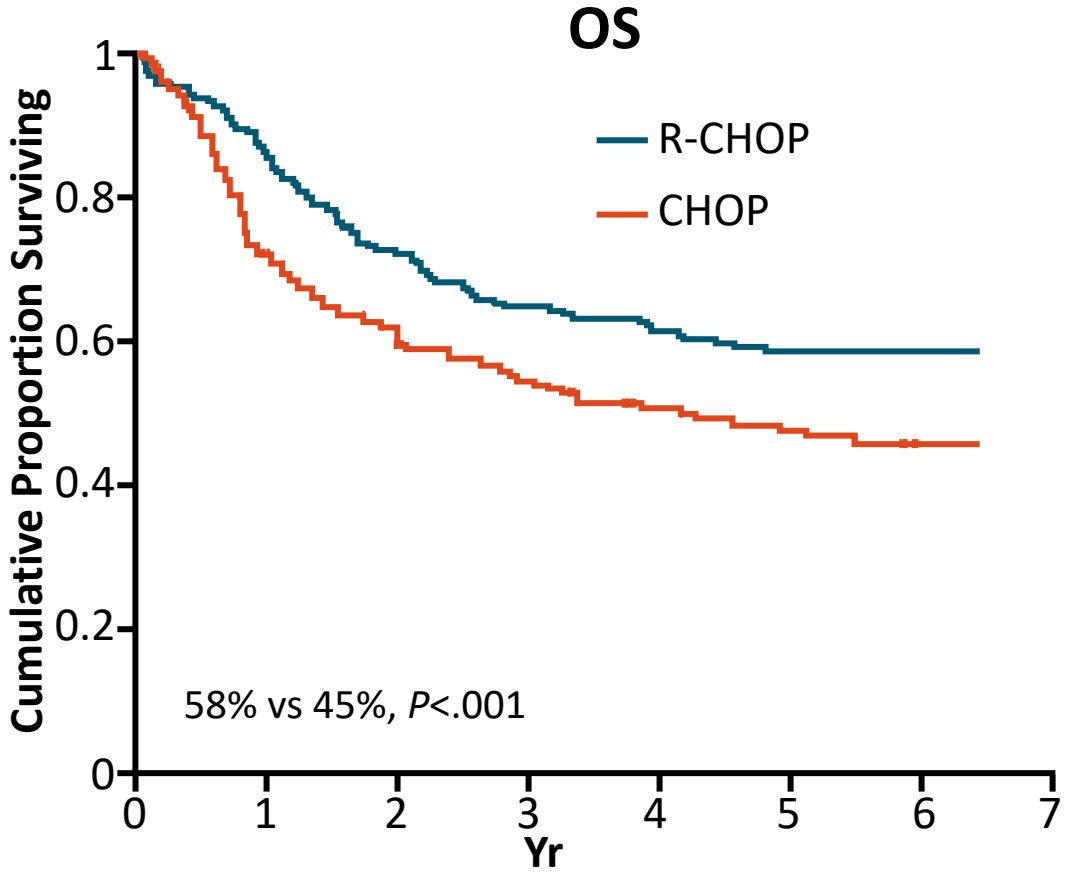
Donna Camilla Savelli Hotel

President:
P.L. Zinzani

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

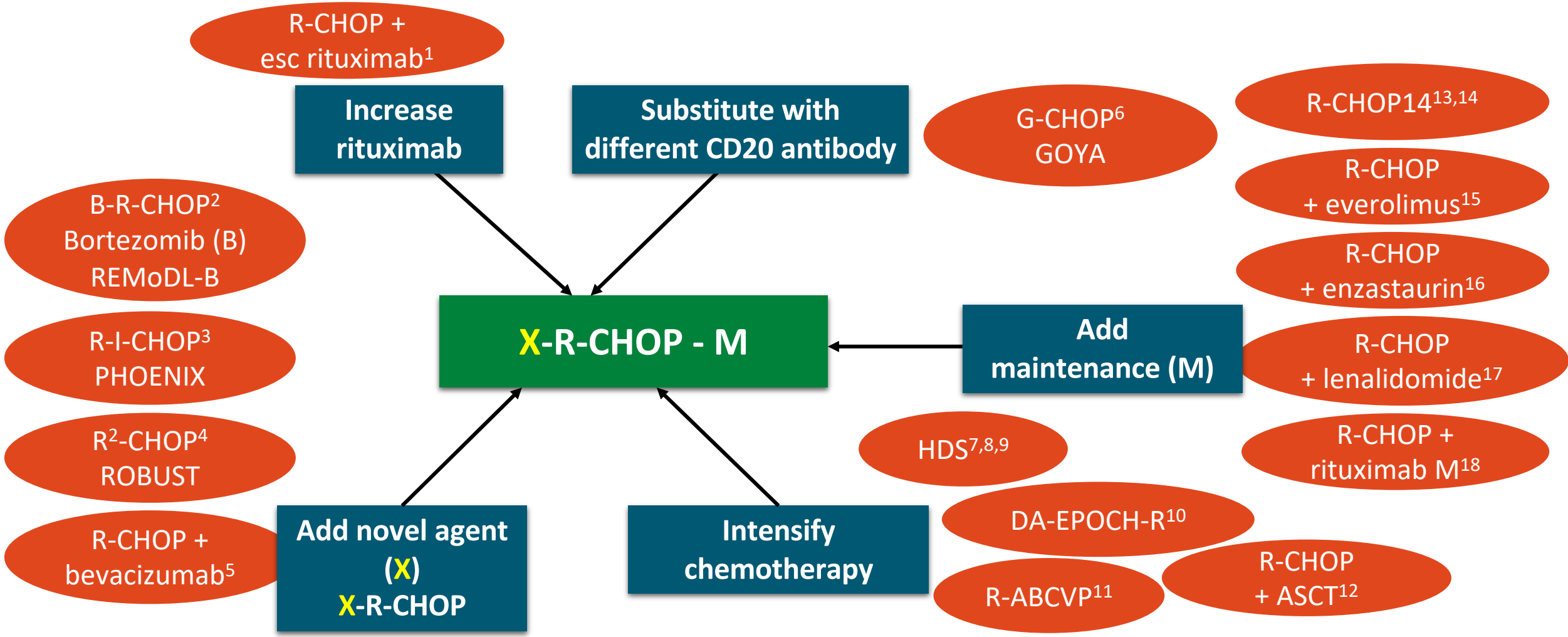
- Long-term outcomes from randomized study of 399 previously untreated patients with DLBCL




Coiffier. NEJM. 2002;346:235. Feugier. JCO. 2005;23:4117.

# Improving on R-CHOP in DLBCL

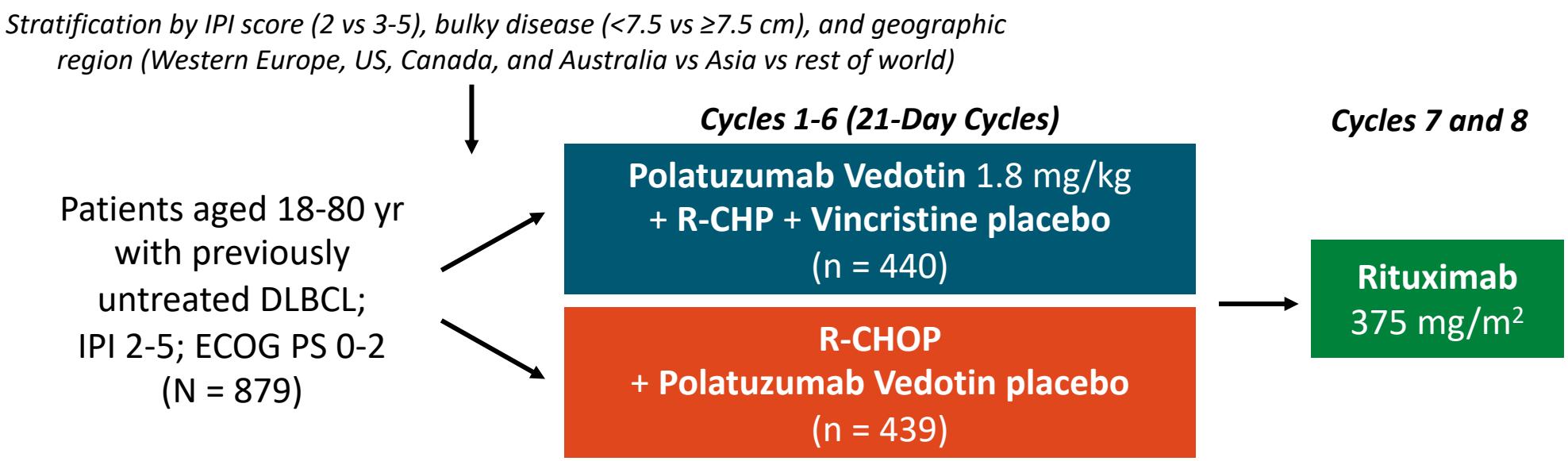



1. He. Cancer Med. 2021;10:7650. 2. Davies. Lancet Oncol. 2019;20:649. 3. Younes. ASH 2018. Abstr 784. 4. Vitolo. ICML 2019. 5. Seymour. Haematologica. 2014;99:1343. 6. Vitolo. JCO. 2017;35:3529. 7. Schmitz. Lancet Oncol. 2012;13:1250. 8. Cortelazzo. JCO. 2016;34:4015. 9. Chiappella. Lancet Oncol. 2017;18:1076. 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.

# Is RCHOP still a standard and a reasonable control arm and backbone ?

# POLARIX: Polatuzumab + R-CHP vs R-CHOP in Previously Untreated DLBCL

- Multicenter, double-blind, placebo-controlled phase III trial

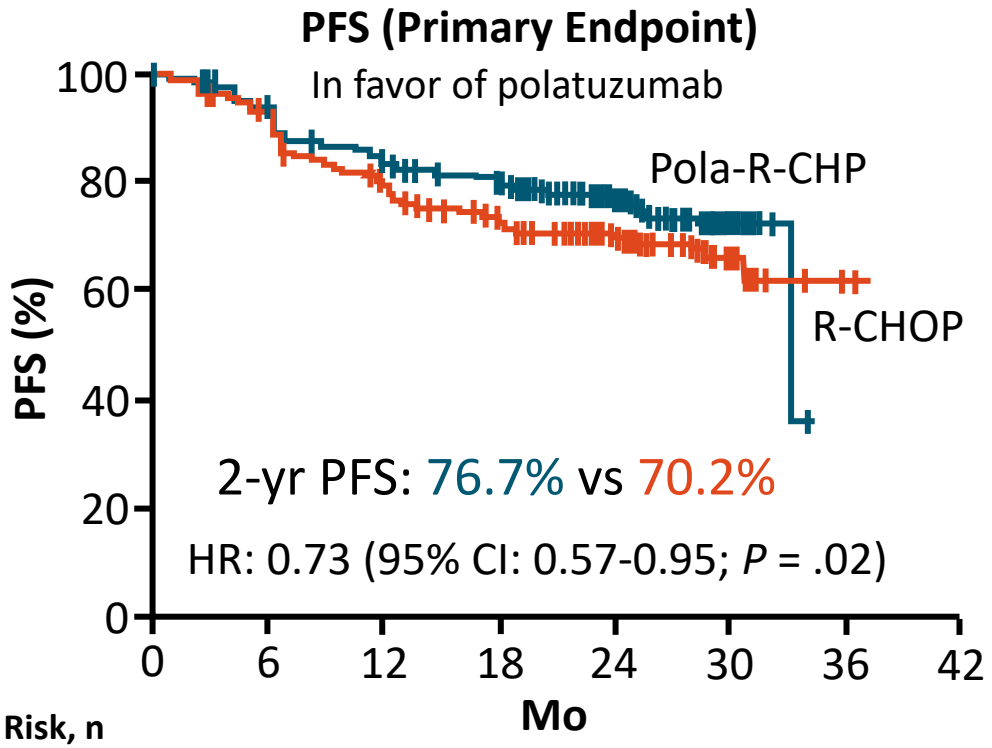



R-CHOP: IV rituximab 375 mg/m², cyclophosphamide 750 mg/m², doxorubicin 50 mg/m², and vincristine 1.4 mg/m² administered on Day 1 + oral prednisone 100 mg QD Days 1-5.

- **Primary endpoint:** investigator-assessed PFS
- **Secondary endpoints:** EFS, CRR at end of treatment, DFS, OS, safety

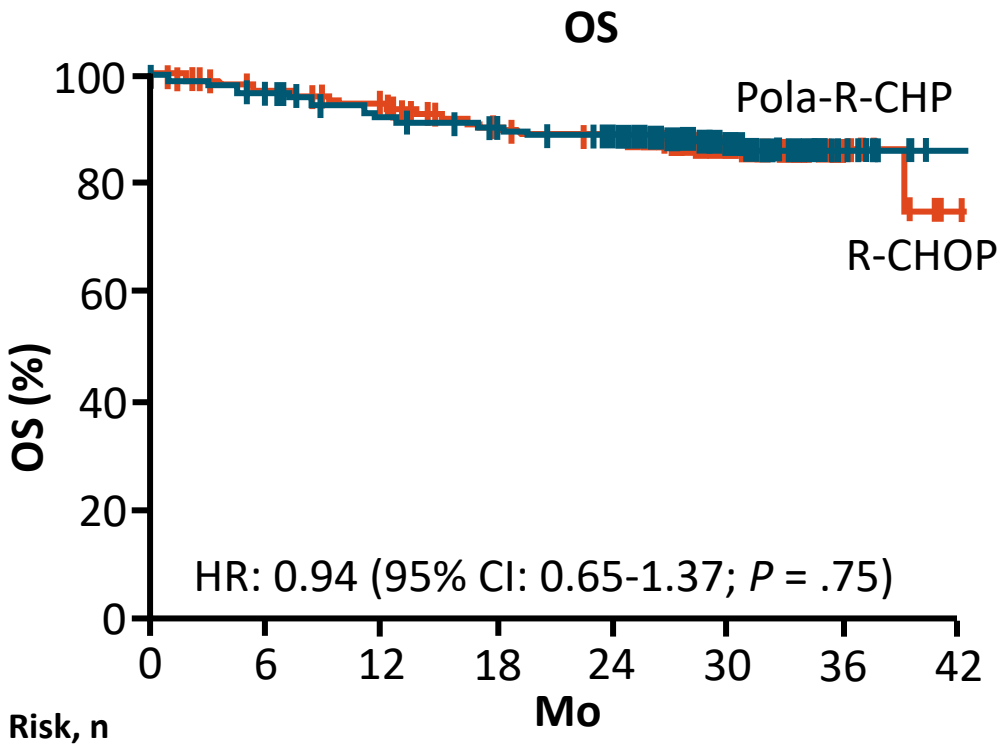
Tilly. ASH 2021. Abstr LBA1. Tilly. NEJM. 2022;386:351.

# 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.

# FDA ODAC March 9°, 2023 – Polatuzumab vedotin in front line DLBCL

1. Modest PFS benefit of pola+R-CHP
2. OS results
3. Other efficacy endpoints
4. Heterogeneity of study population

# Other secondary endpoints: modest differences

**Modified EFS**

HR 0.75 (95% CI: 0.58, 0.96); p = 0.0244*

2-year difference: 6.2%

* alpha allocation = 0.05

**Duration of response**

| | Pola+R-CHP (N=422) | R-CHOP (N=413) |
|---|---|---|
| **2-year DOR rate (95% CI)** | 75.7% (71.0, 80.3) | 71.7% (67.1, 76.2) |
| **Difference (95% CI)** | 4.0% (-2.5, 10.5) | |

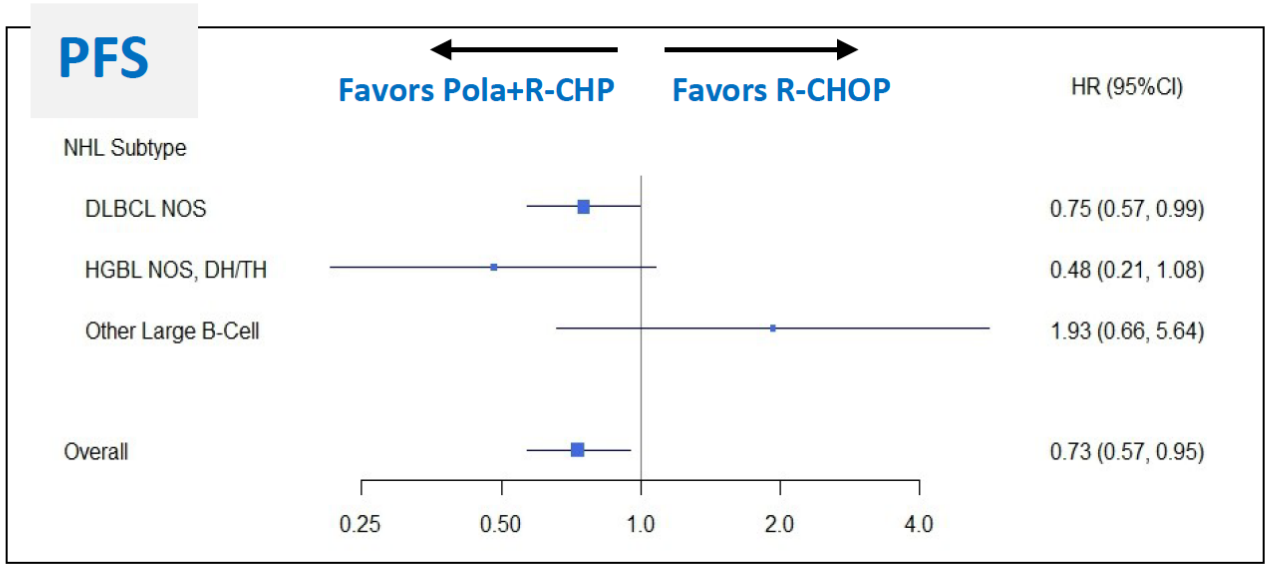
**Disease-free survival**

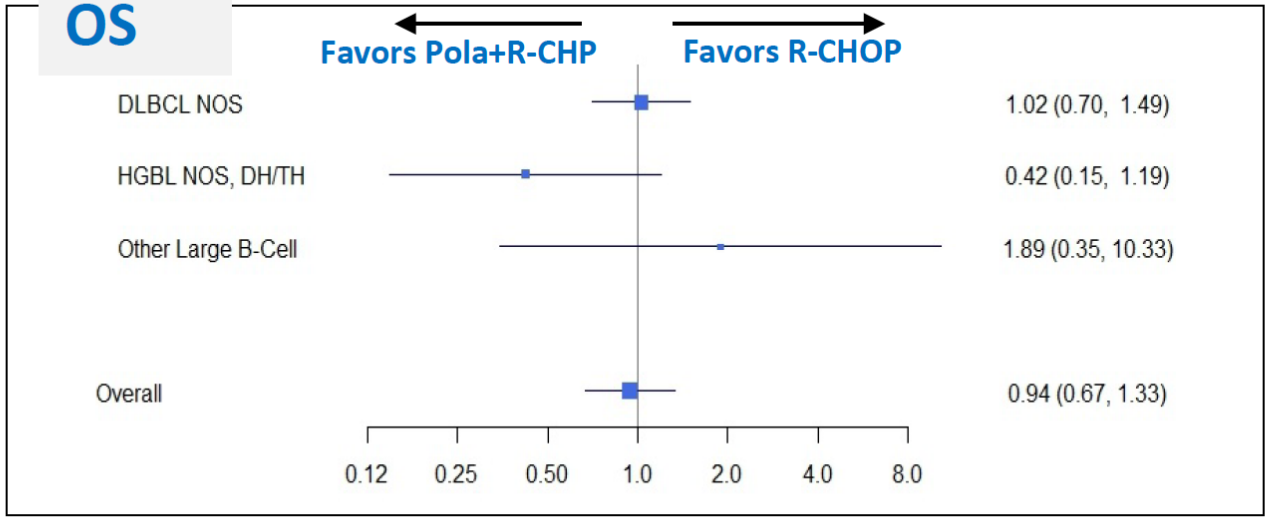
| | Pola+R-CHP (N=381) | R-CHOP (N=363) |
|---|---|---|
| **2-year DFS rate (95% CI)** | 81.8% (77.4, 86.2) | 77.4% (72.7, 82.0) |
| **Difference (95% CI)** | 4.4% (-1.9, 10.8) | |



DOR, disease-free survival; DFS, disease-free survival

# Heterogenous population and outcomes

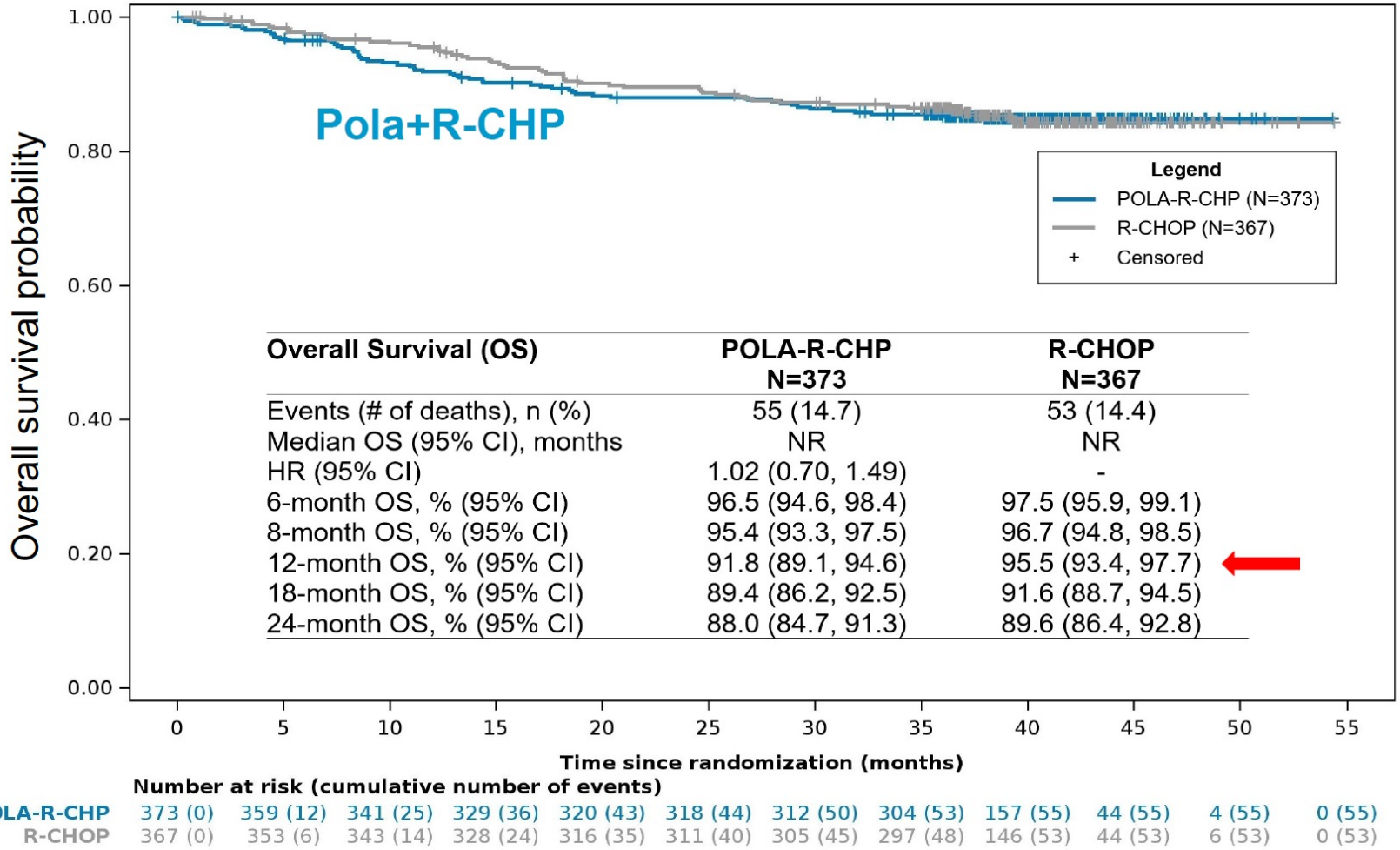



| | Pola+R-CHP | R-CHOP |
|---|---|---|
| **DLBCL NOS** (n=740) | | |
| CR rate | 76.7% | 74.9% |
| Difference | **1.7%** | |
| **HGBL** (n=93) | | |
| CR rate | 88.4% | 64.0% |
| Difference | **24.4%** | |
| **Other large B-cell lymphomas** (n=46) | | |
| CR rate | 79.2% | 81.8% |
| Difference | **-2.7%** | |

NHL, non-Hodgkin lymphoma; DH/TH, double-hit/triple-hit
Source: FDA review

# Heterogenous outcomes: Overall survival in DLBCL NOS




| Overall Survival (OS) | POLA-R-CHP N=373 | R-CHOP N=367 |
|---|---|---|
| Events (# of deaths), n (%) | 55 (14.7) | 53 (14.4) |
| Median OS (95% CI), months | NR | NR |
| HR (95% CI) | 1.02 (0.70, 1.49) | - |
| 6-month OS, % (95% CI) | 96.5 (94.6, 98.4) | 97.5 (95.9, 99.1) |
| 8-month OS, % (95% CI) | 95.4 (93.3, 97.5) | 96.7 (94.8, 98.5) |
| 12-month OS, % (95% CI) | 91.8 (89.1, 94.6) | 95.5 (93.4, 97.7) |
| 18-month OS, % (95% CI) | 89.4 (86.2, 92.5) | 91.6 (88.7, 94.5) |
| 24-month OS, % (95% CI) | 88.0 (84.7, 91.3) | 89.6 (86.4, 92.8) |

NR, not reached
Source: FDA review

# ODAC on March 9th

So the bar is where it was 20 years ago….

**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

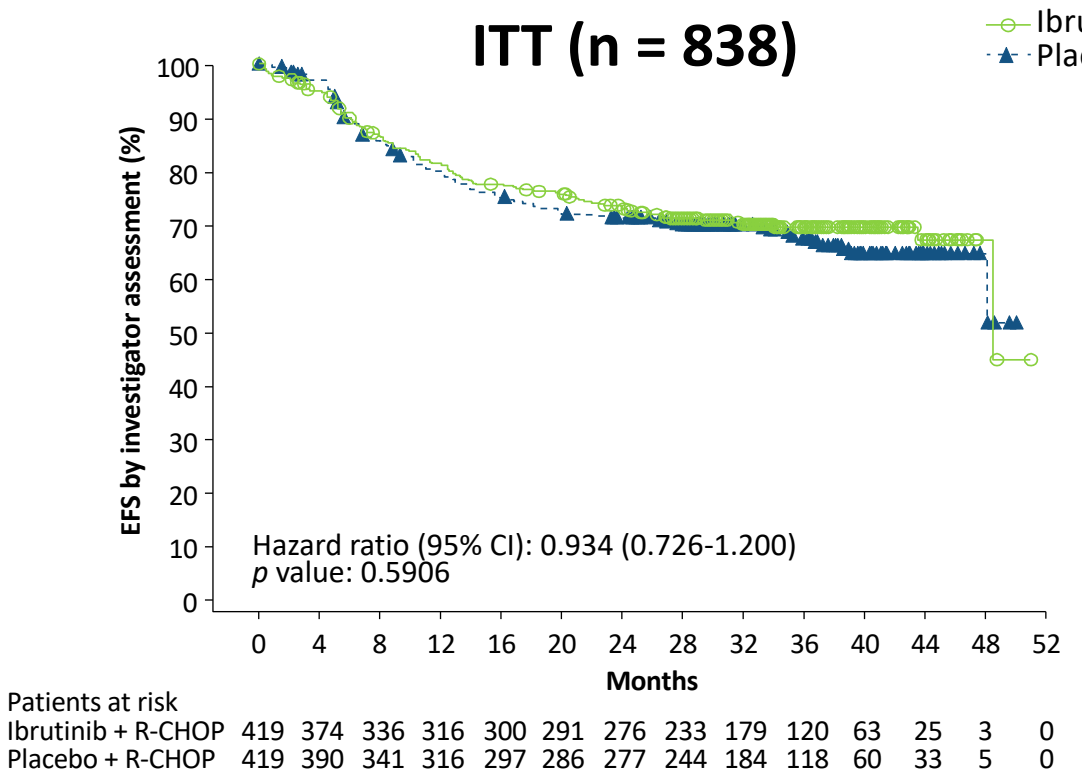
FDA Analysis of OS in DLBCL NOS - ODAC March 9th, 2023

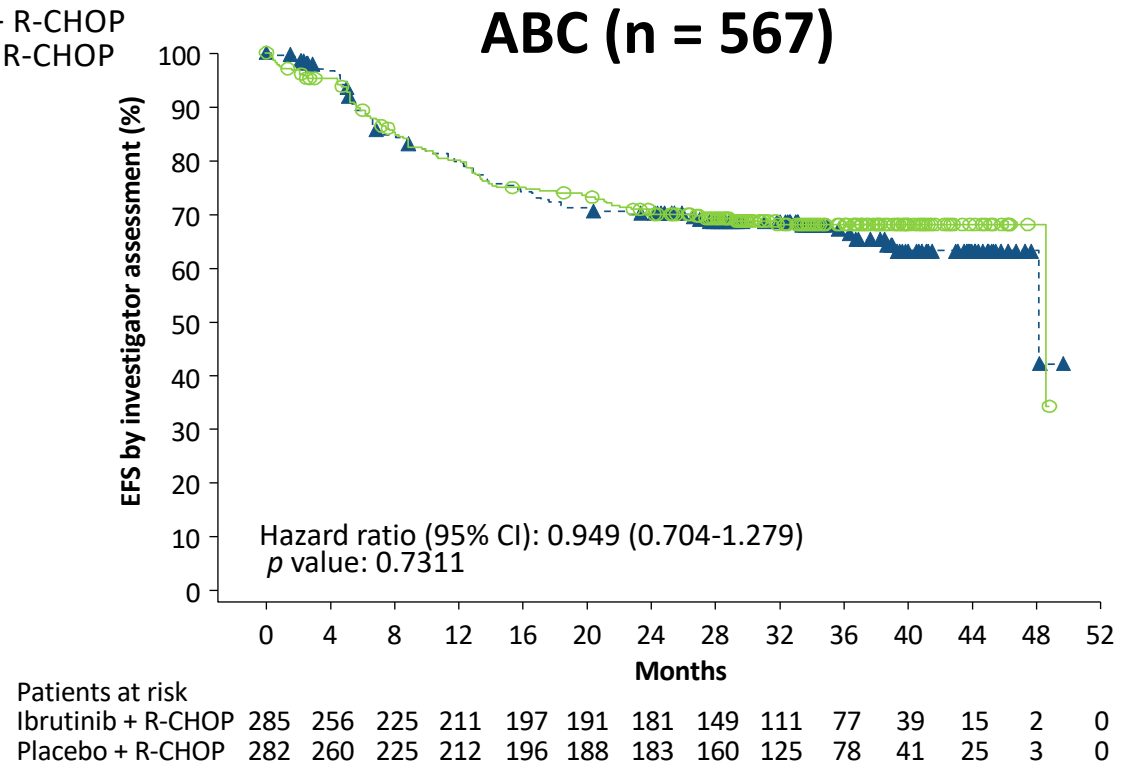
# Ongoing trials

- Circa 116 active trials in front line DLBCL, > 40 in China, >16 with BTK inhibitors
- Most X+RCHOP
- Several chemo free in elderly (non-chemo candidates) patients
- 14 randomized phase 2/3 studies
  - 4 BTK inhibitors
  - 6 in China
- Other small molecules: PI3KI, Epigenetic agents
- Novel antibodies and antibody drug conjugates
- Bispecific antibodies
- CART

# Learning from past - small molecules: Example of BTK inhibitors

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

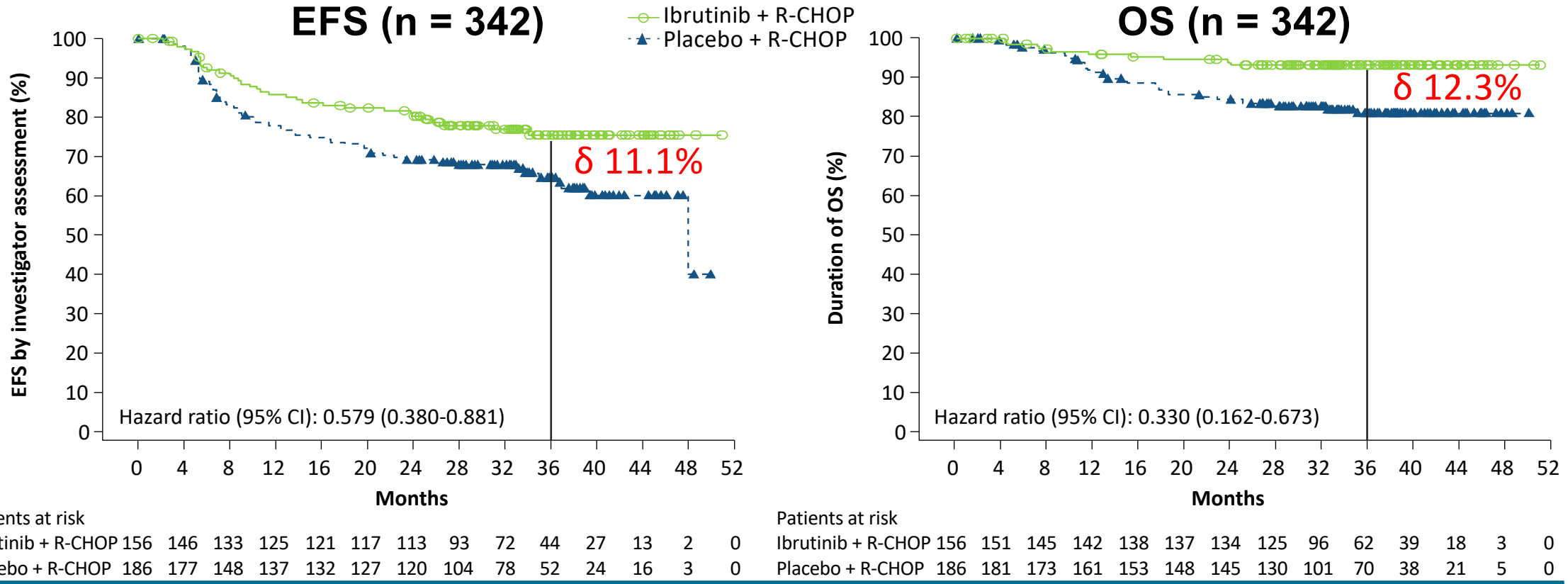



- **Overall response (89.3% vs 93.1%) and CR rates (67.3% vs 68.0%) were similar**

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

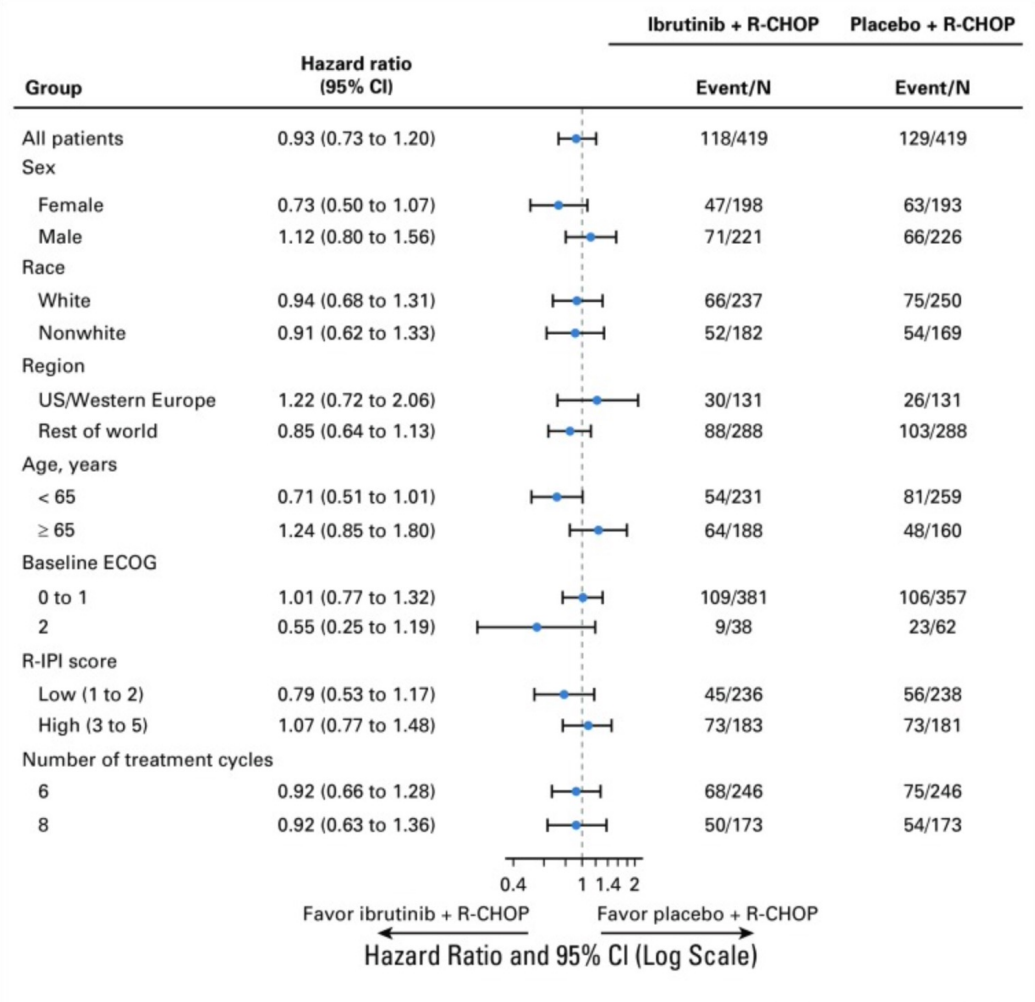
# EFS and OS in Patients < 60 Years




- **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

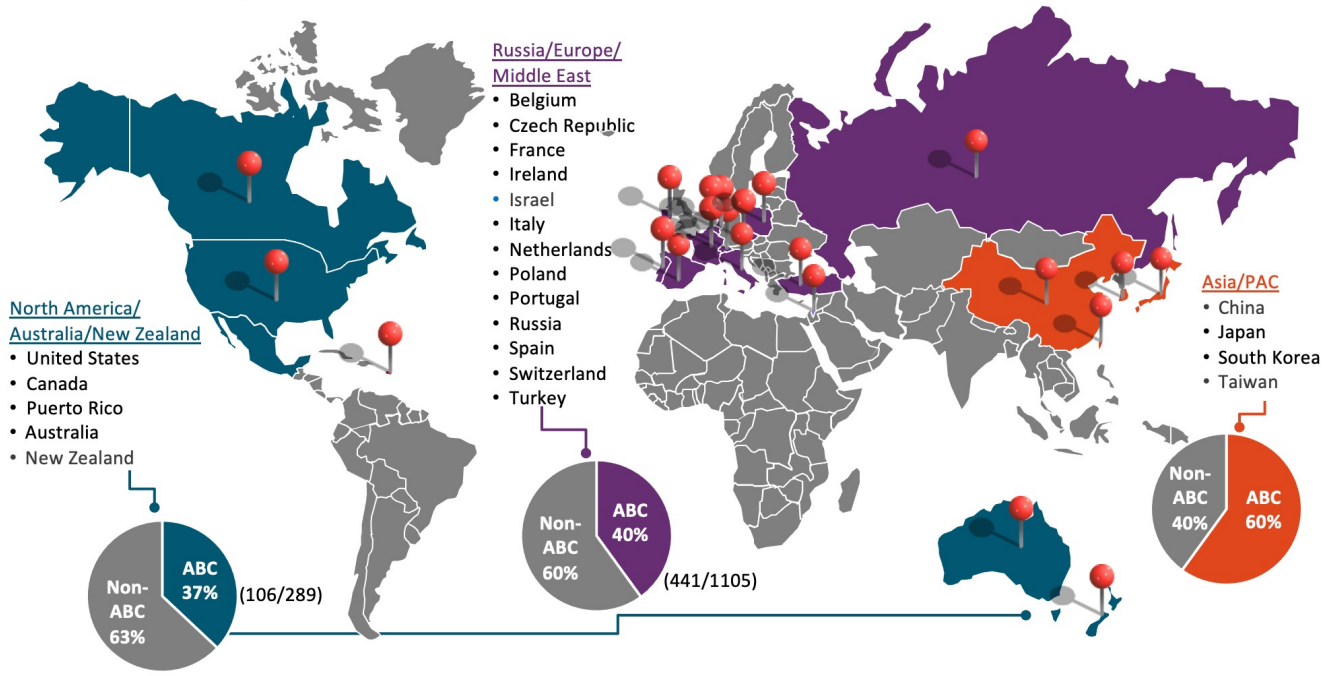


| Group | Hazard ratio (95% CI) | Ibrutinib + R-CHOP Event/N | Placebo + R-CHOP Event/N |
|---|---|---|---|
| All patients | 0.93 (0.73 to 1.20) | 118/419 | 129/419 |
| Sex | | | |
| Female | 0.73 (0.50 to 1.07) | 47/198 | 63/193 |
| Male | 1.12 (0.80 to 1.56) | 71/221 | 66/226 |
| Race | | | |
| White | 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

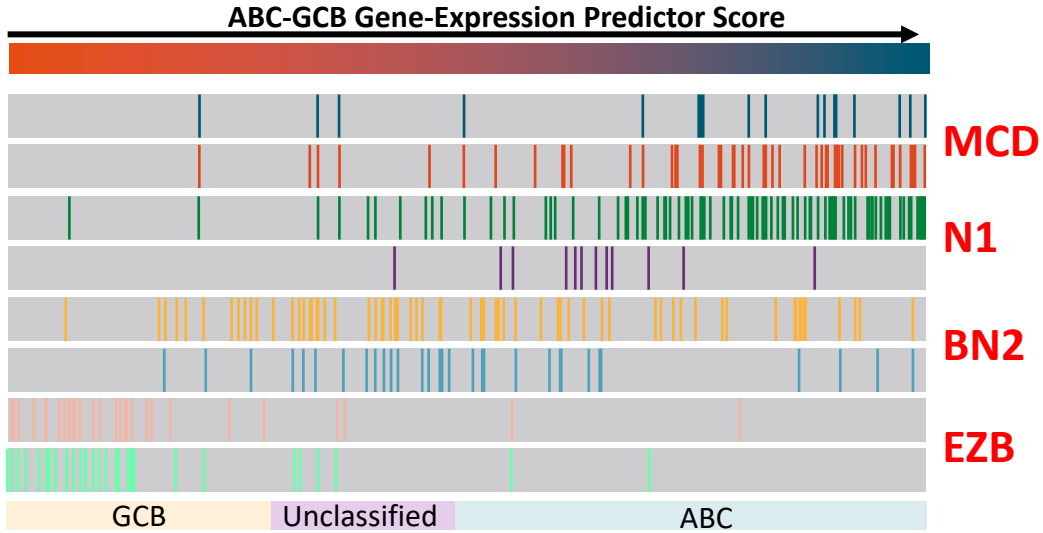


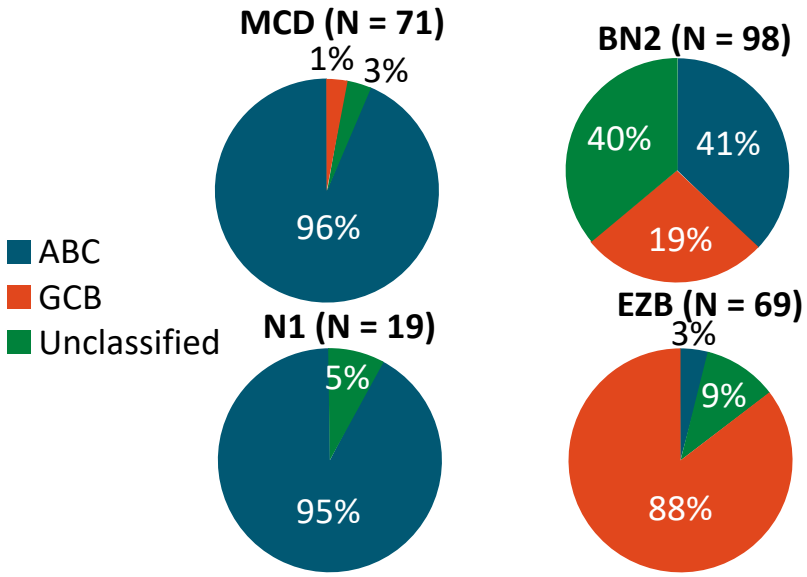


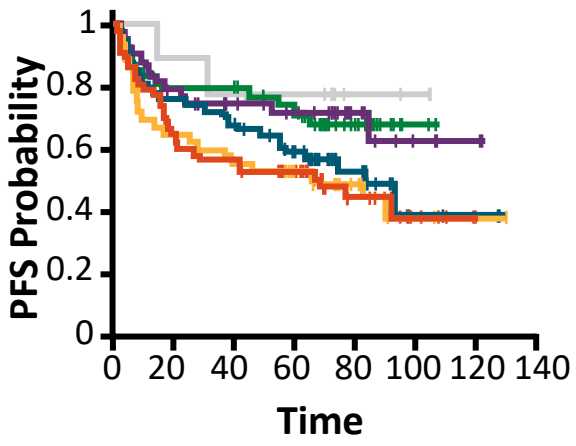
Nowakowski. Haematologica. 2020;105:e72.

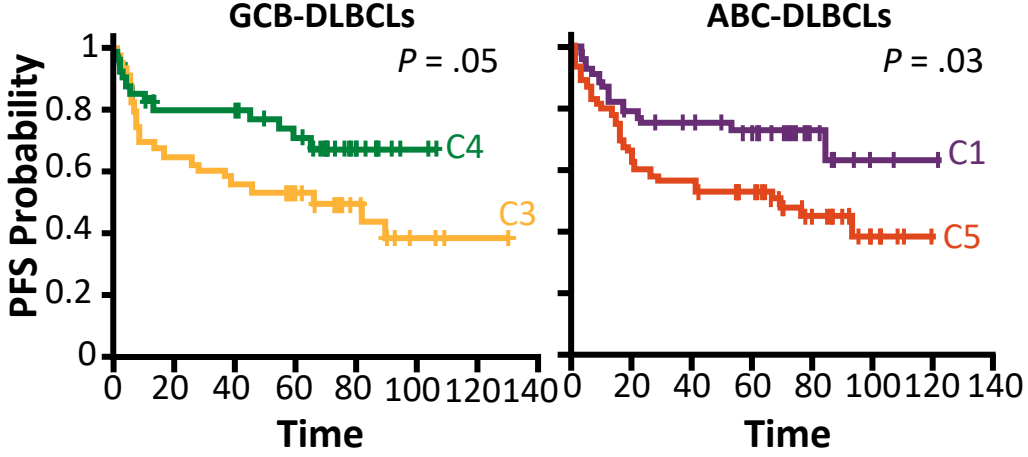
# Integrated Genomic Analyses Identify Subgroups Within and Distinct From Cell of Origin

| 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)
- **Deeper molecular profiling**
  - Phase 3 Orlelabrutinib plus RCHOP vs RCHOP in **MCD subtype** of DLBCL (Belive 01) (NCT05234684)
- **3rd generation BTKs all commers or non-GCB**
  - Zanubrutinib plus CIT (RCHOP, DAEPOCHR)
  - Orlelabutinib plus CIT (RCHOP, DAEPOCHR)
  - ECOG is planning multi arm molecularly driven study one of them BTK inh

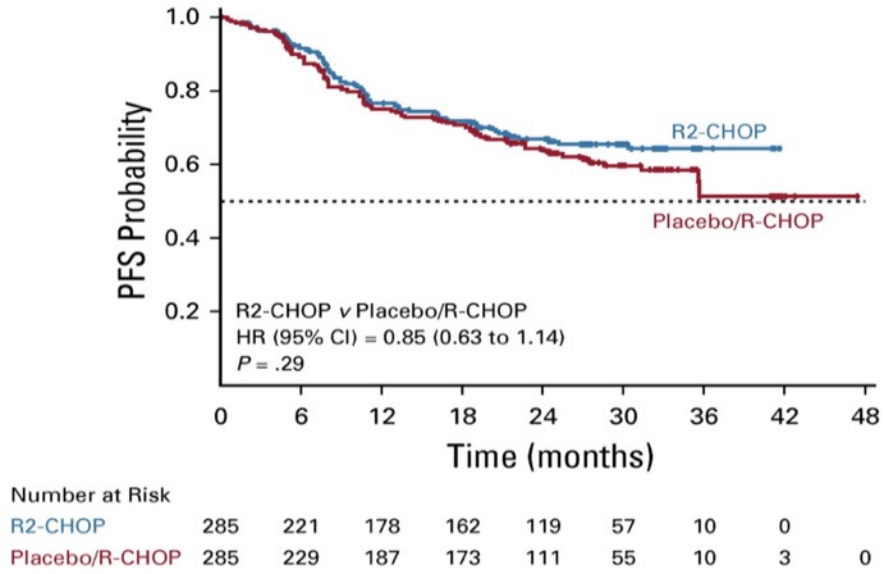
# Learning from the past and adding new agent example of: XY+RCHOP

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

original reports

## ROBUST: A Phase III Study of Lenalidomide Plu R-CHOP Versus Placebo Plus R-CHOP in Previously Untreated Patients With ABC-Type Diffuse Large B-Cell Lymphoma

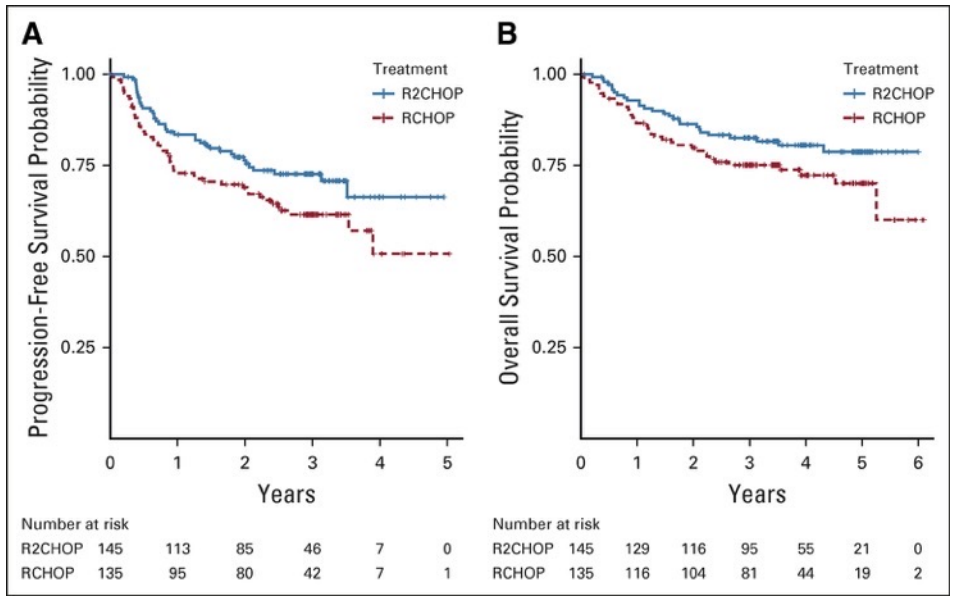
Grzegorz S. Nowakowski, MD[1]; Annalisa Chiappella, MD[2]; Randy D. Gascoyne, MD[3]; David W. Scott, MBChB, PhD[3]; Qingyuan Zhang, MD[4]; Wojciech Jurczak, MD, PhD[5]; Muhit Özcan, MD, PhD[6]; Xiaonan Hong, MD[7]; Jun Zhu, MD[8]; Jie Jin, MD[9]; David Belada, MD[10]; Juan Miguel Bergua, MD[11]; Francesco Piazza, MD[12]; Heidi Mócikova, MD[13]; Anna Lia Molinari, MD[14]; Dok Hyun Yoon, MD[15]; Federica Cavallo, MD[16]; Monica Tani, MD[17]; Kazuhito Yamamoto, MD, PhD[18]; Koji Izutsu, MD[19]; Koji Kato, MD[20]; Myron Czuczman, MD[21]; Sarah Hersey, MS, MBA, RAC[22]; Adrian Kilcoyne, MD[21]; Jacqueline Russo, BS[21]; Krista Hudak, PharmD[21]; Jingshan Zhang, PhD[21]; Steve Wade, BS[23]; Thomas E. Witzig, MD[1]; and Umberto Vitolo, MD[2]; on behalf of the ROBUST Trial Investigators




original reports

## Addition of Lenalidomide to R-CHOP Improves Outcomes in Newly Diagnosed Diffuse Large B-Cell Lymphoma in a Randomized Phase II US Intergroup Study ECOG-ACRIN E1412

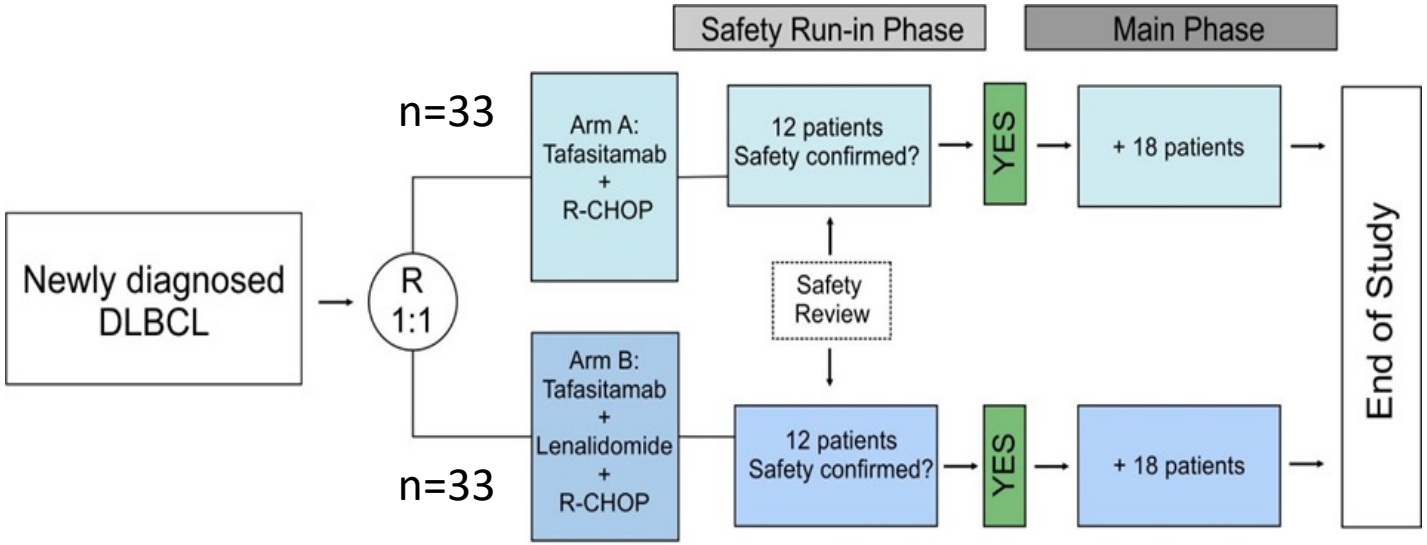
Grzegorz S. Nowakowski, MD[1]; Fangxin Hong, PhD[2]; David W. Scott, MD[3]; William R. Macon, MD[4]; Rebecca L. King, MD[4]; Thomas M. Habermann, MD[1]; Nina Wagner-Johnston, MD[5]; Carla Casulo, MD[6]; James L. Wade, MD[7]; Gauri G. Nagargoje, MD[8]; C. M. Reynolds, MD[9]; Jonathon B. Cohen, MD, MS[10]; Nadia Khan, MD[11]; Jennifer E. Amengual, MD[12]; Kristy L. Richards, MD, PHD[13†]; R. F. Little, MD[14]; John P. Leonard, MD[13]; Jonathan W. Friedberg, MD, MMSc[6]; Lale Kostakoglu, MD, MPH[15]; Brad S. Kahl, MD[16]; and Thomas E. Witzig, MD[1]




Nowakowski GS et al. *J Clin Oncol.* 2021Feb23;JCO2001366.

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

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

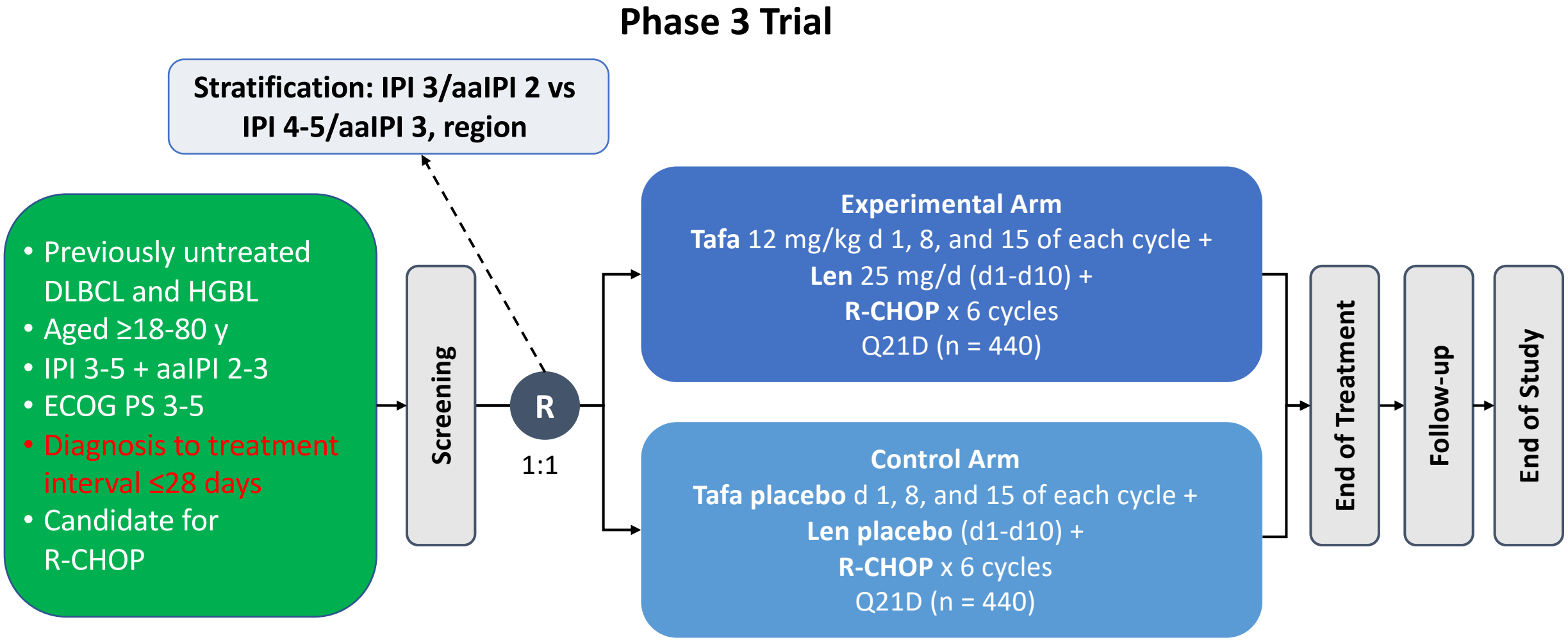



- Neutropenia and thrombocytopenia more common in arm B but no increase in neutropenic fever/infections
- Discontinuations due to AEs rare and not different average relative dose intensity of R-CHOP
- ORR at EOT was 75.8% (arm a) vs 81.8% (arm B)

**Figure 1:** Grade ≥3 TEAEs by system organ class and toxicity grade


Nowakowski et al. ASH 2022, Beleda ASH 2021.

# Front-MIND Newly Diagnosed DLBCL




NCT04824092

# Escaping forward - example of bispecific antibodies + R-CHOP

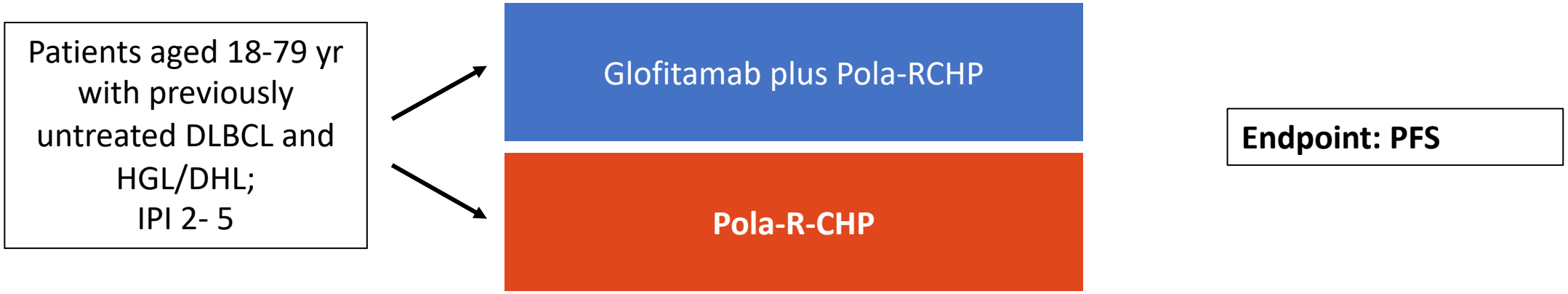
# Epcoritamab in Combination With R-CHOP vs R-CHOP in Newly Diagnosed DLBCL

Patients aged 18-79 yr with previously untreated DLBCL and HGL/DHL;
IPI 2- 5 (**IPI2 capped at 30%)**
(N = 900)


**Endpoint: PFS**

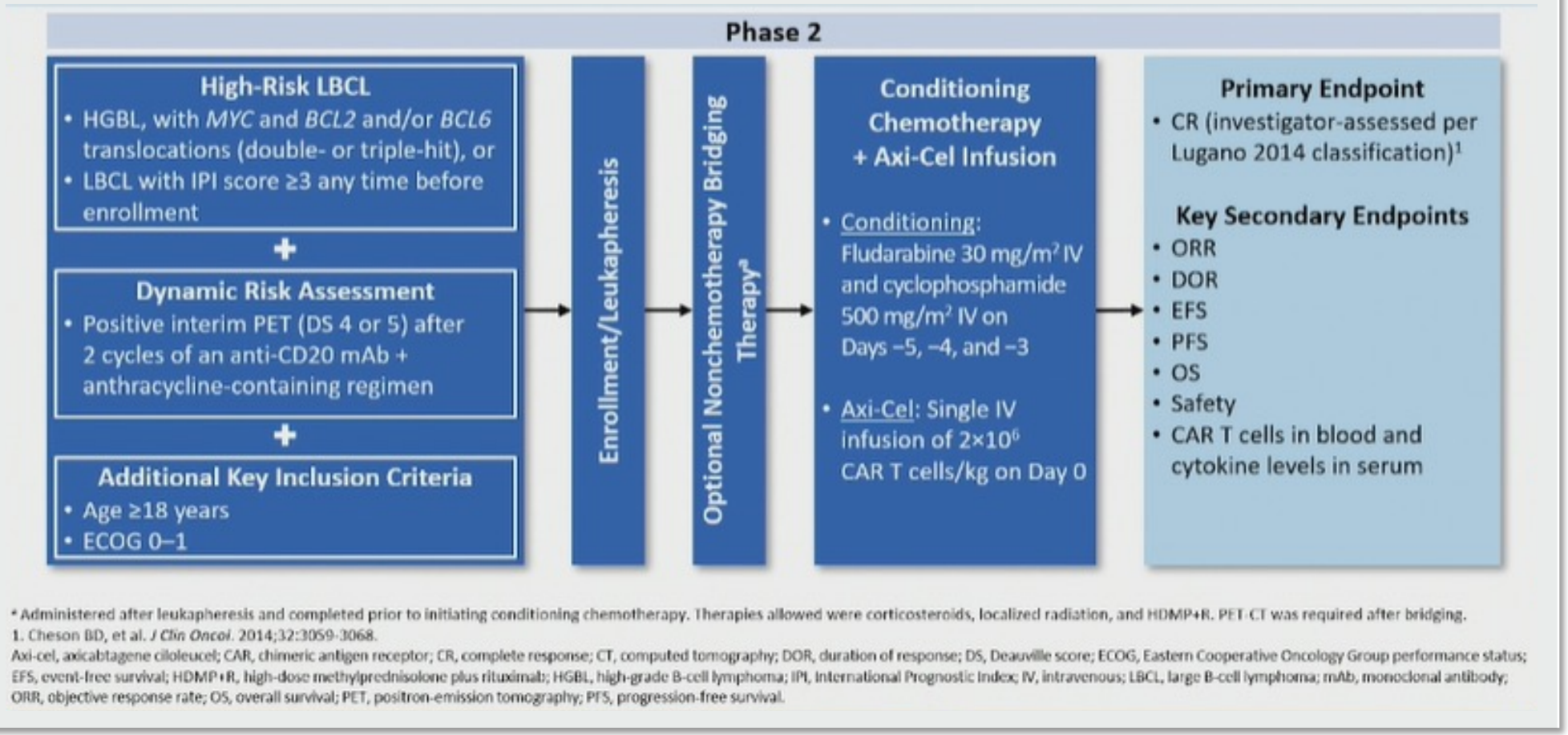
NCT05578976

# Glofitamab in Combination With R-CHP vs R-CHOP in Newly Diagnosed DLBCL



# Jumping ahead - example of CART in front line

# 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.

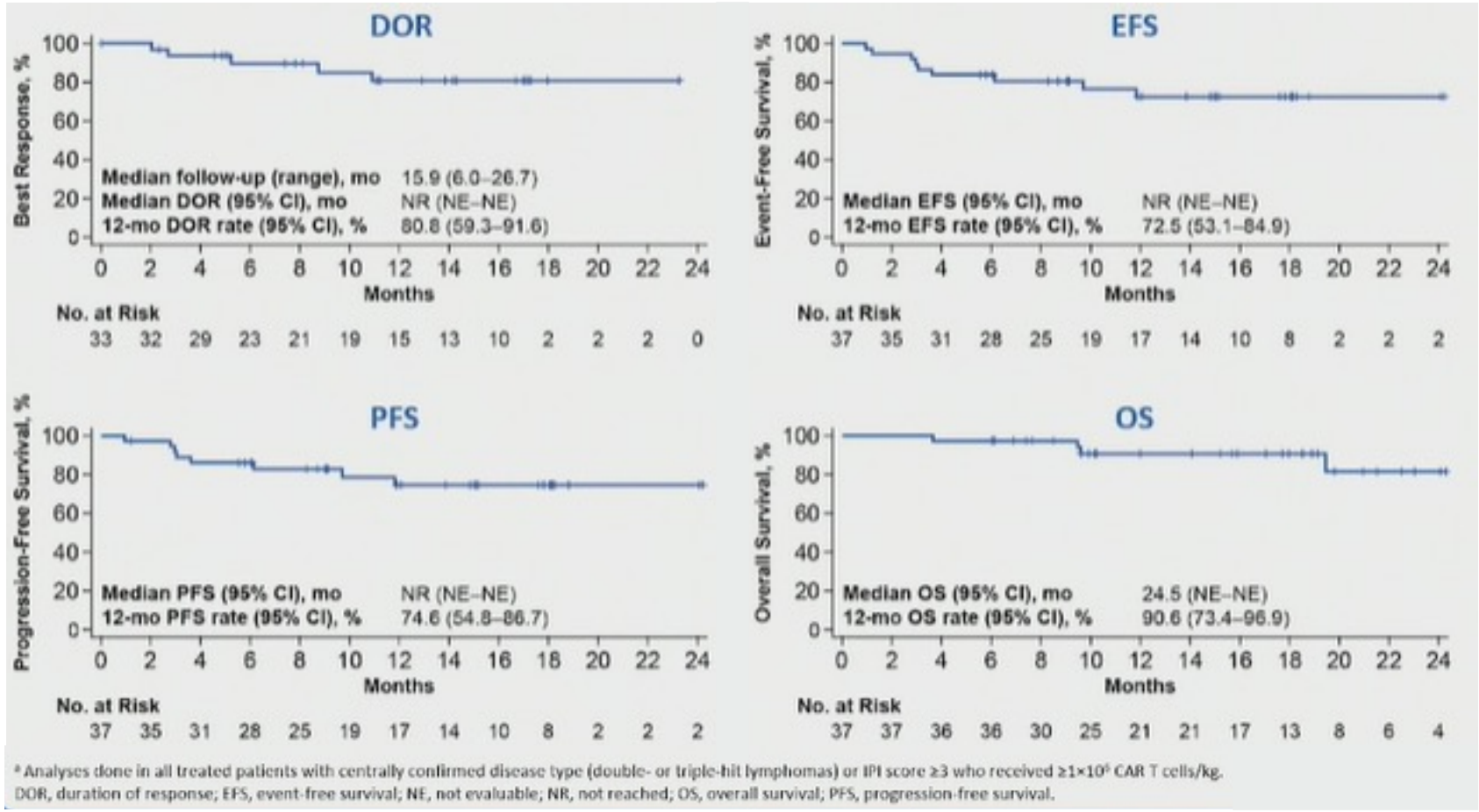
Axi-cel, axicabtagene ciloleucel; CAR, chimeric antigen receptor; CR, complete response; CT, computed tomography; DOR, duration of response; DS, Deauville score; ECOG, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HDMP+R, high-dose methylprednisolone plus rituximab; 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

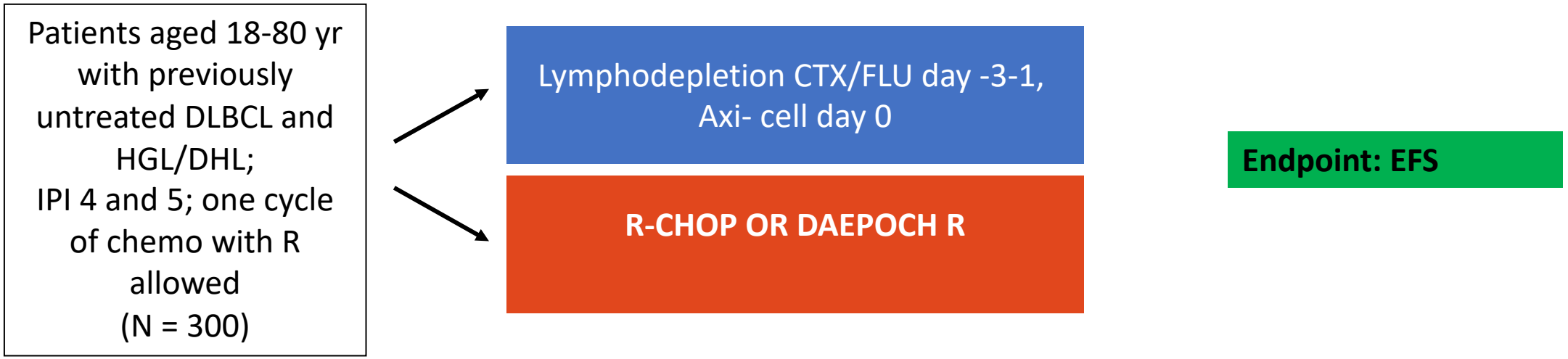



[a] Analyses done in all treated patients with centrally confirmed disease type (double- or triple-hit lymphomas) or IPI score ≥3 who received ≥1×10$^6$ CAR T cells/kg.
DOR, duration of response; EFS, event-free survival; NE, not evaluable; NR, not reached; OS, overall survival; PFS, progression-free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

# 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
- Pola RCHP alternative
- Most trails focus on high-risk patients:
  - IPI
  - Short time from dx to rx
  - High molecular risk
- Molecularly driven or MRD driven trials difficult – lack of companion diagnostics; prolongs time to rx

# Conclusions

- RCHOP remains a valid control arm and a valid backbone
- Pola RCHP alternative
- Most trails focus on high-risk patients:
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- Molecularly driven or MRD driven trials difficult – lack of companion diagnostics; prolongs time to rx

Molecularly selected

- BTK inhibitors
- PI3K inhibitors
- BCL2 inhibitors
- Others

**Molecularly Agnostic**

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


# Thank You

nowakowski.grzegorz@mayo.edu