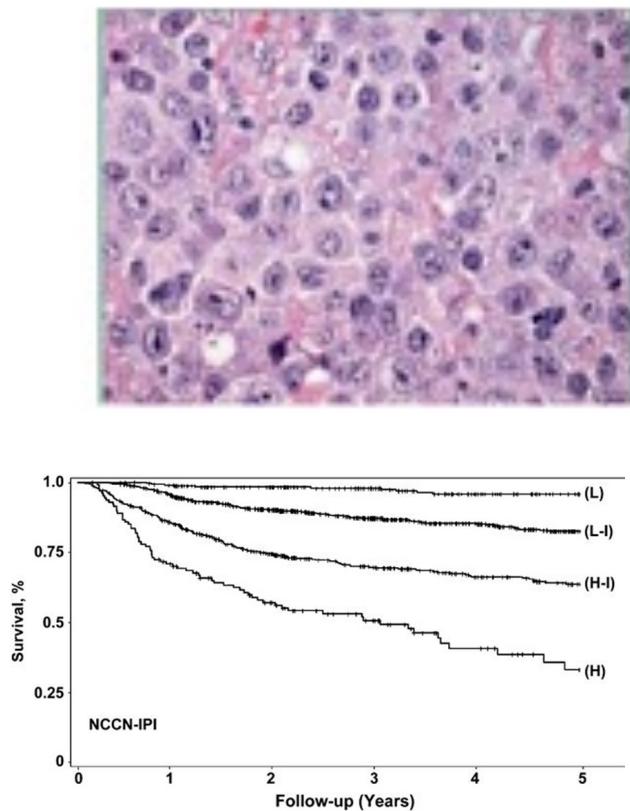


Therapy of Diffuse Large B-cell Lymphoma (DLBCL)

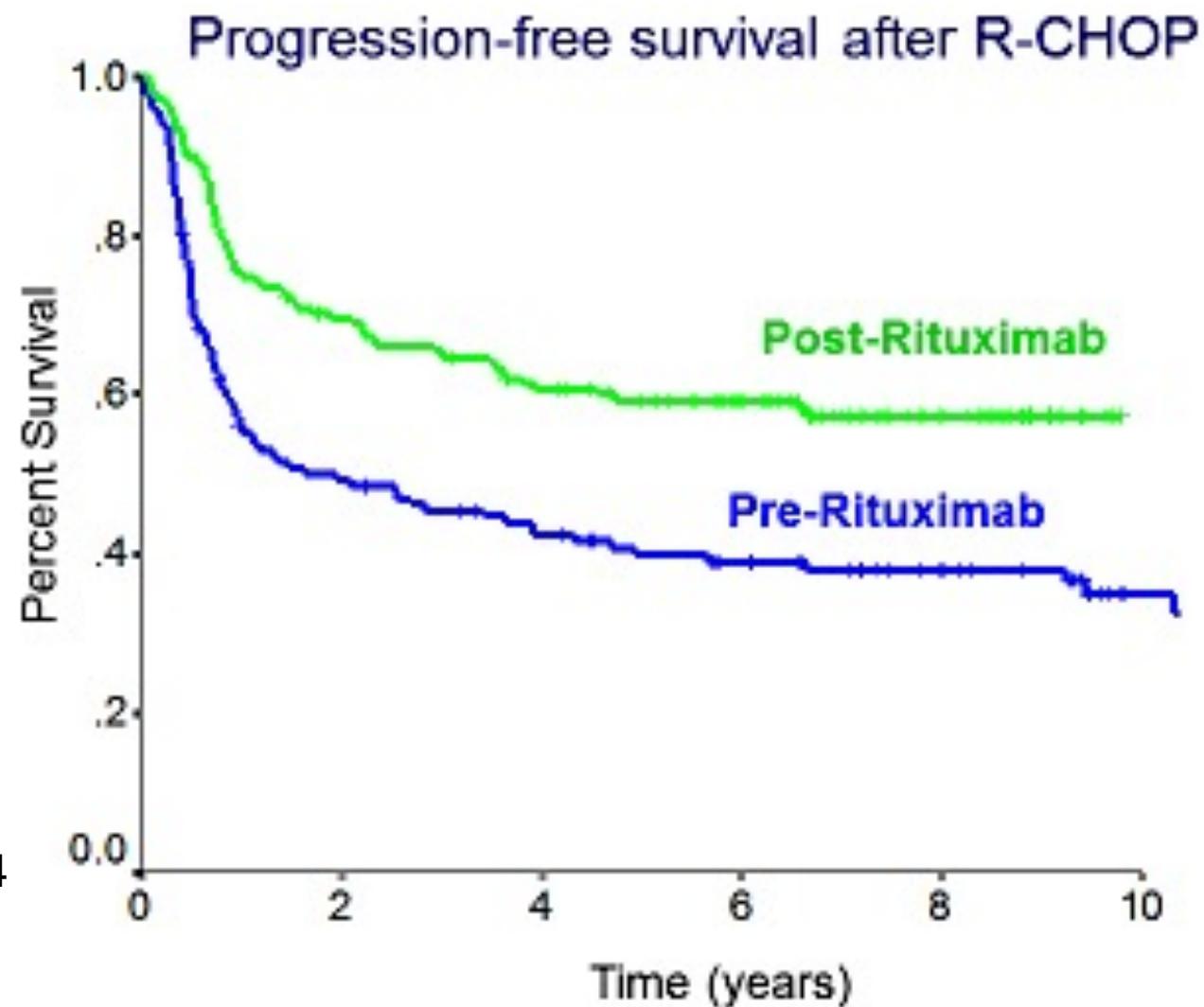
Jonathan W. Friedberg M.D.



RCHOP has been the “standard” therapy of DLBCL



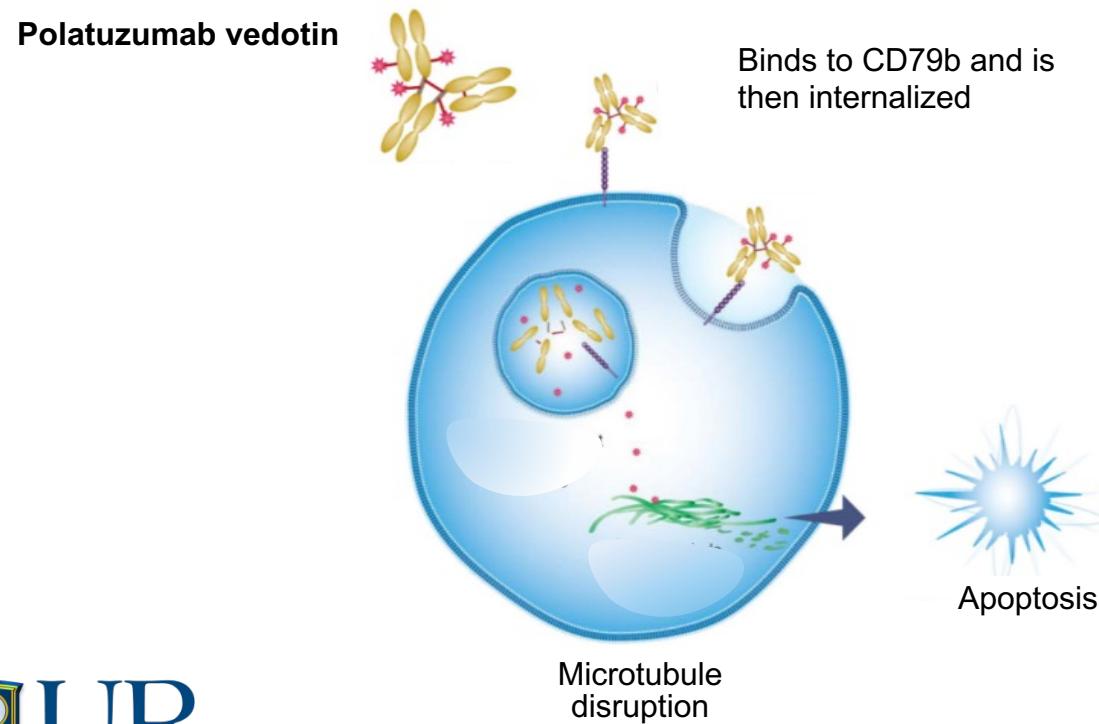
Zhou et al, *Blood* 123: 837, 2014



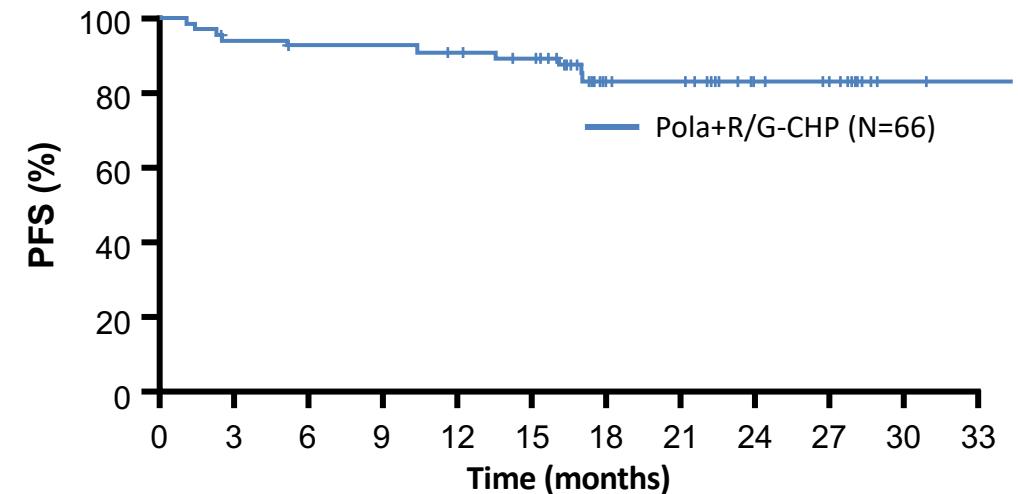
Updated from Sehn, L et al, *J Clin Oncol* 23:5027, 2005

Polatuzumab vedotin is an ADC targeting CD79b

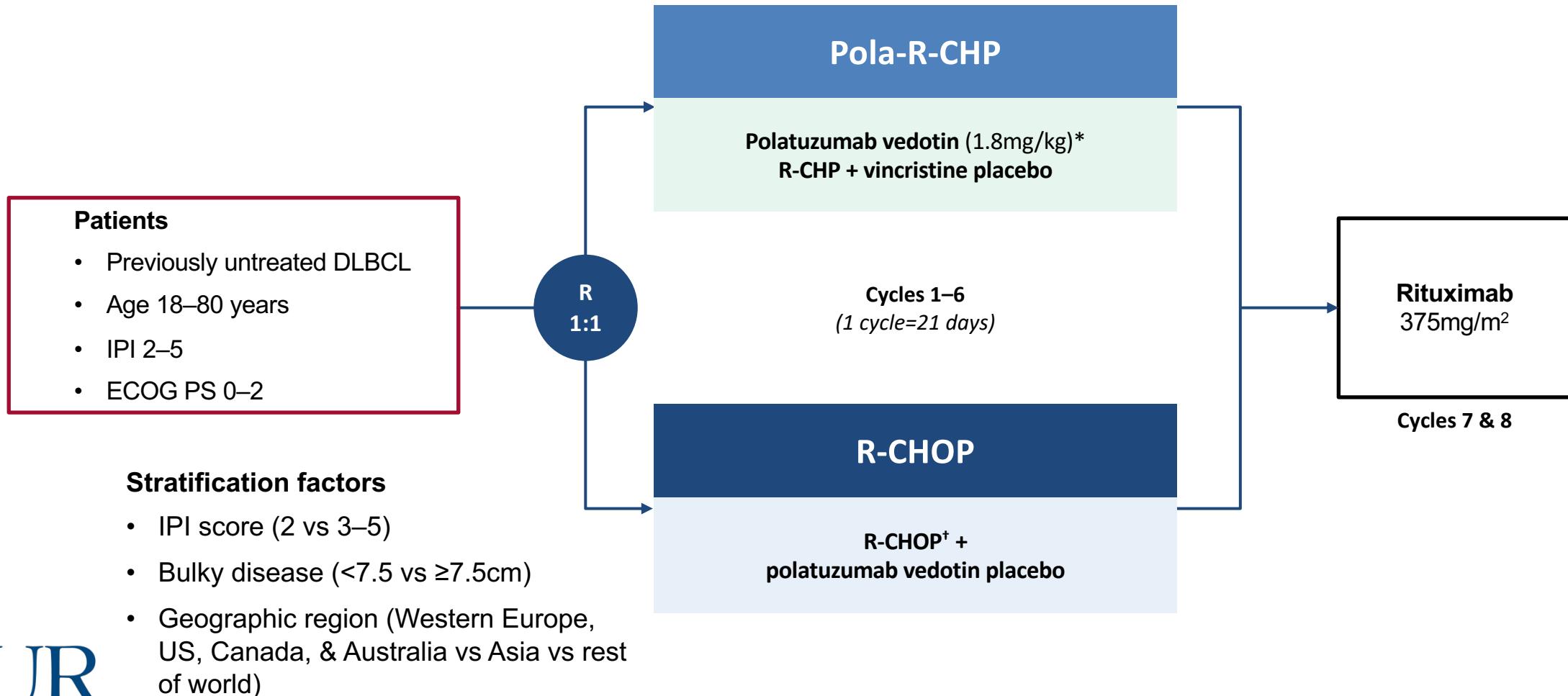
CD79b is ubiquitously expressed on DLBCL cells



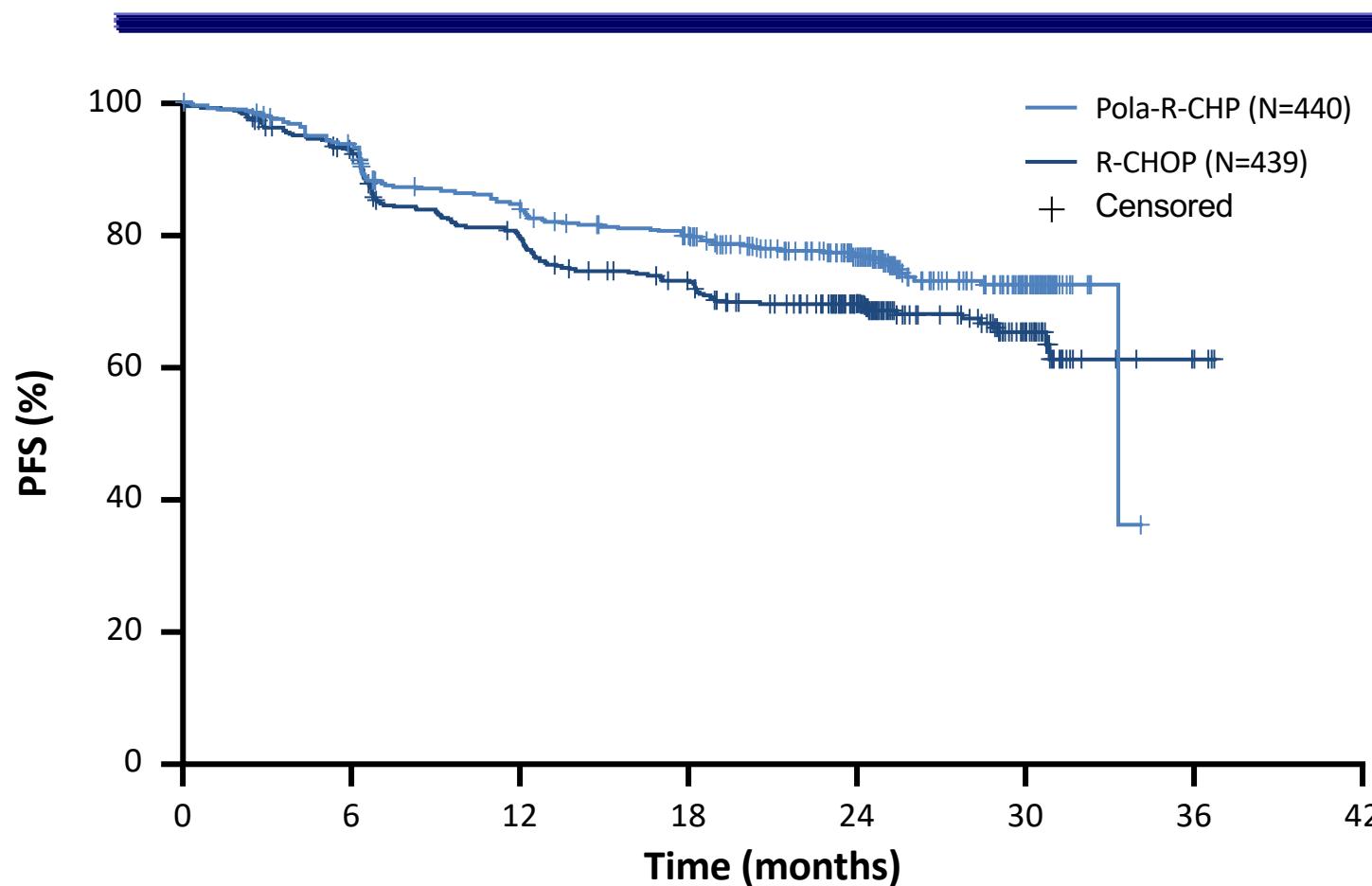
PFS after Pola+R/G-CHP in first-line DLBCL



POLARIX: A randomized double-blinded study



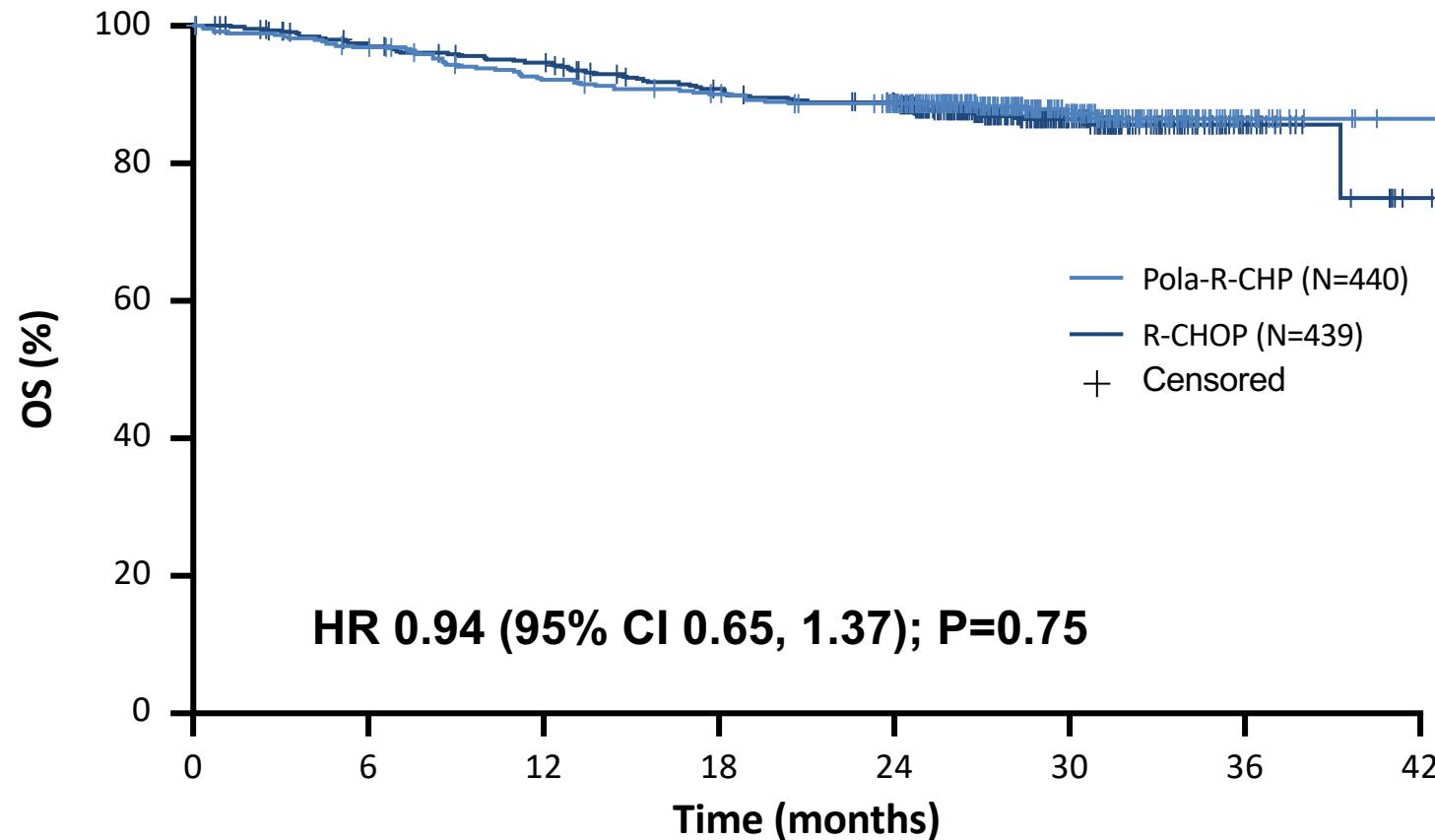
POLARIX Primary endpoint: Progression-free survival



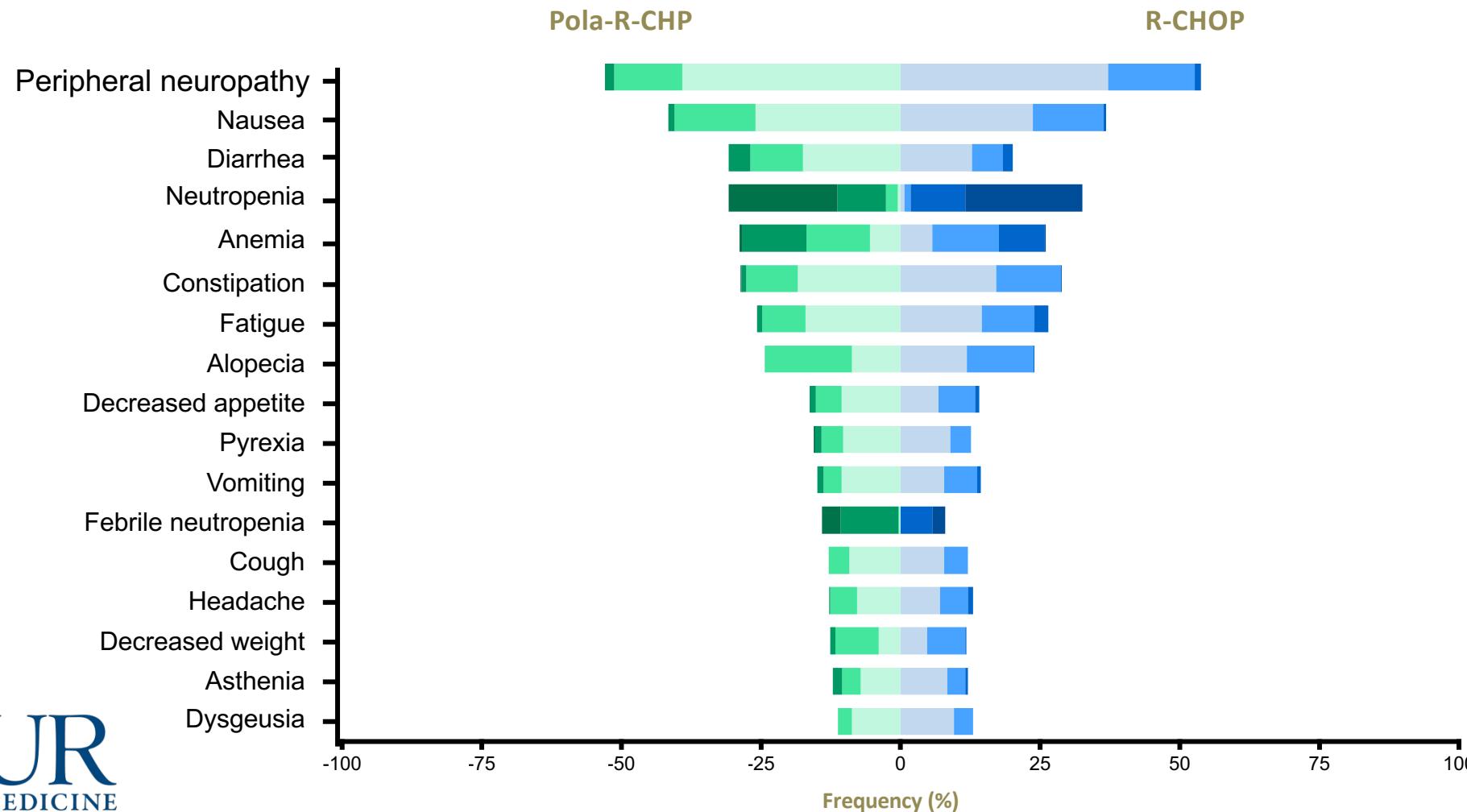
HR 0.73 (P<0.02)

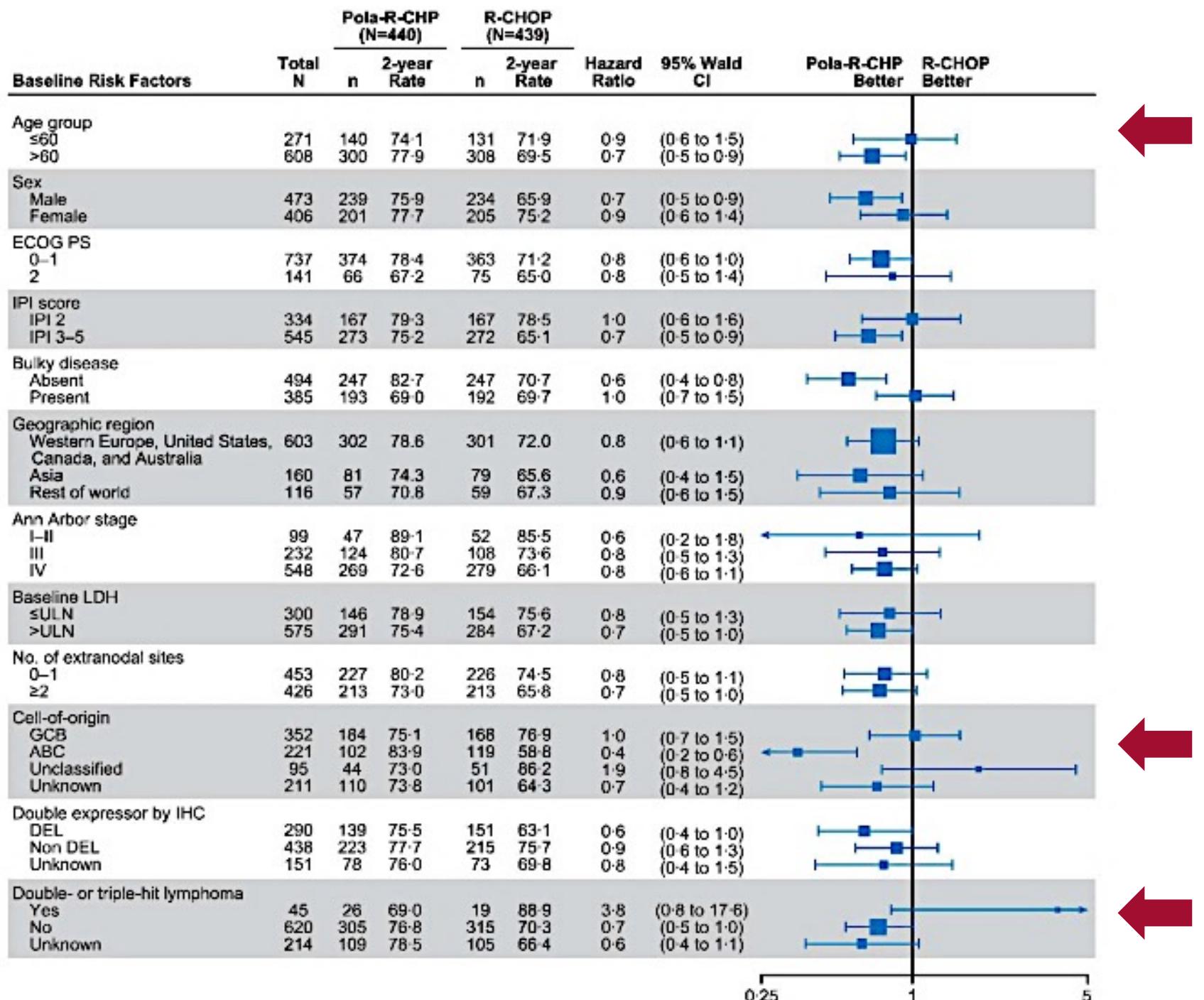
- **24-month PFS:**
76.7% with Pola-R-CHP
70.2% with R-CHOP
($\Delta=6.5\%$)

Overall survival: POLARIX trial



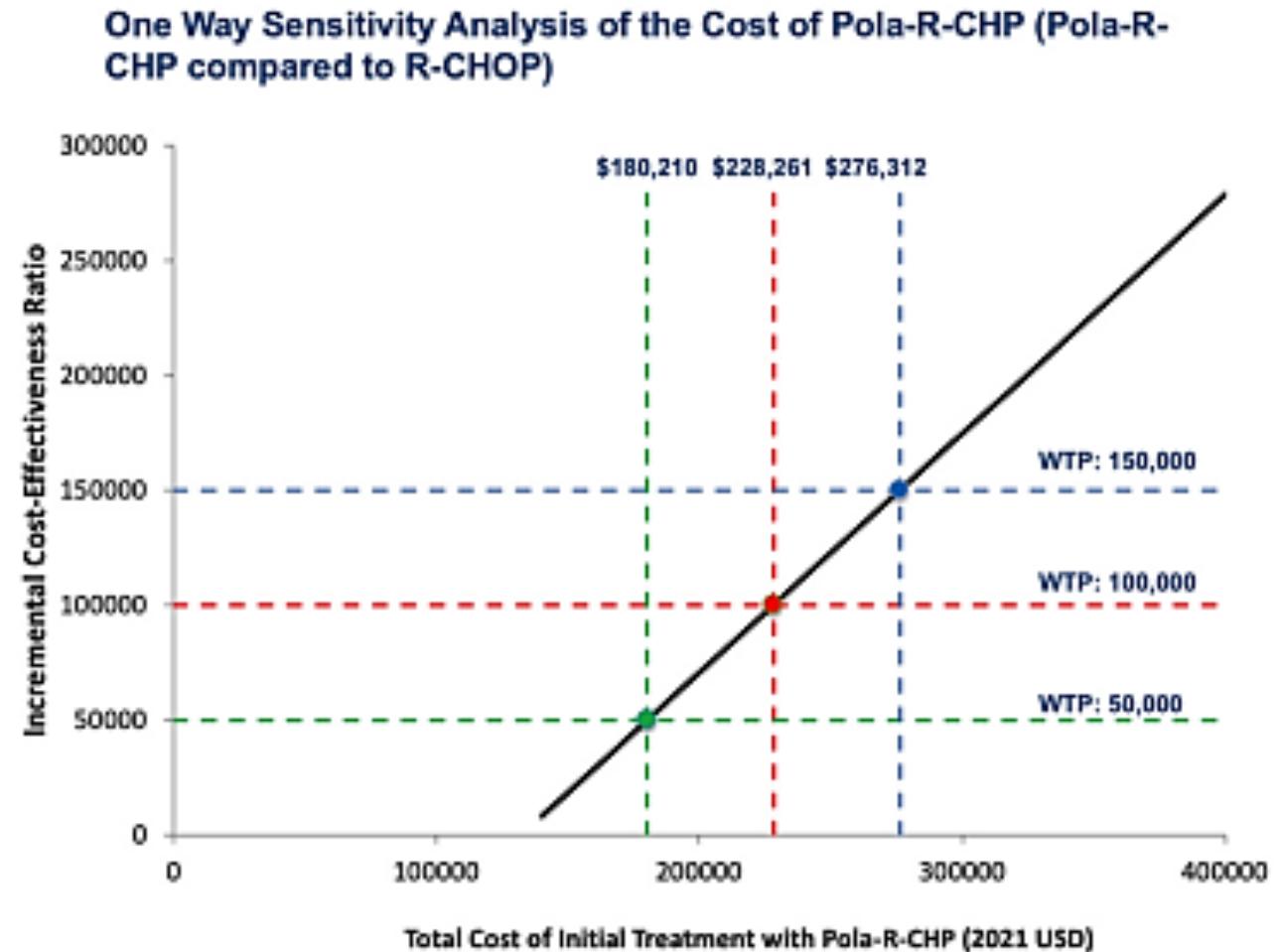
Common adverse events: POLARIX trial





Cost effectiveness of R-Pola-CHP depends upon long-term outcomes

- Routine use of R-Pola-CHP will add significantly to health expenditures.
- Markov Model
 - Threshold 150K/QALY
 - If 5 year PFS > 66%, then cost-effective
- Identifications of subgroups that have maximal benefit would improve cost-effectiveness.



Should R-Pola-CHP replace RCHOP?

Strengths:

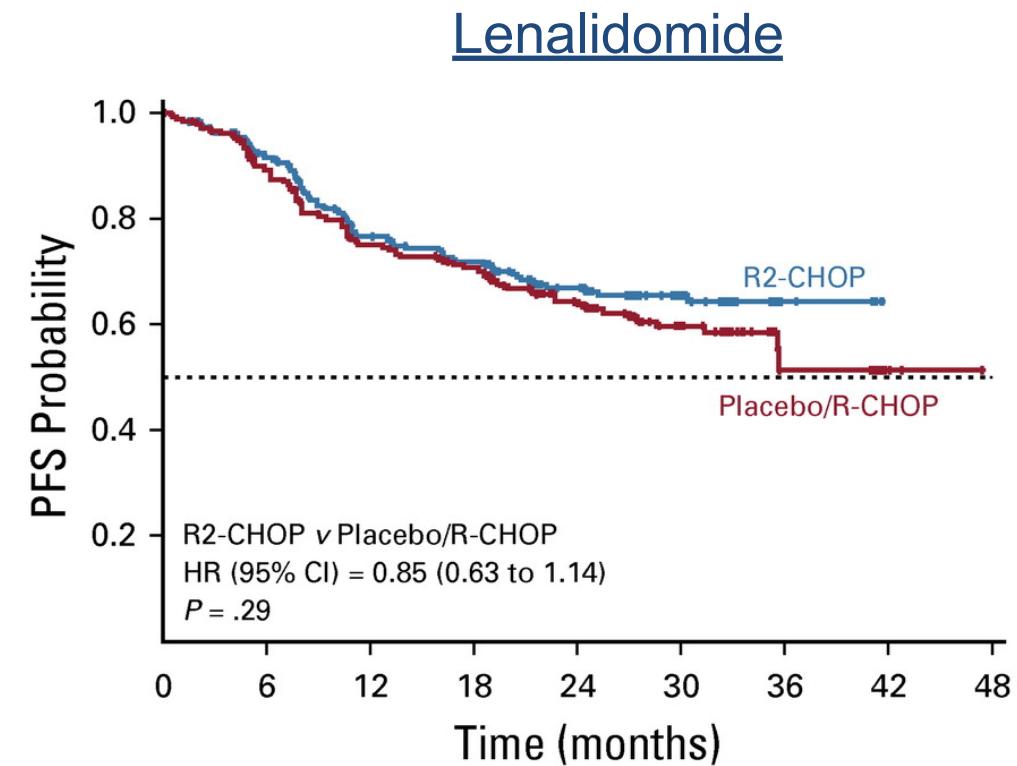
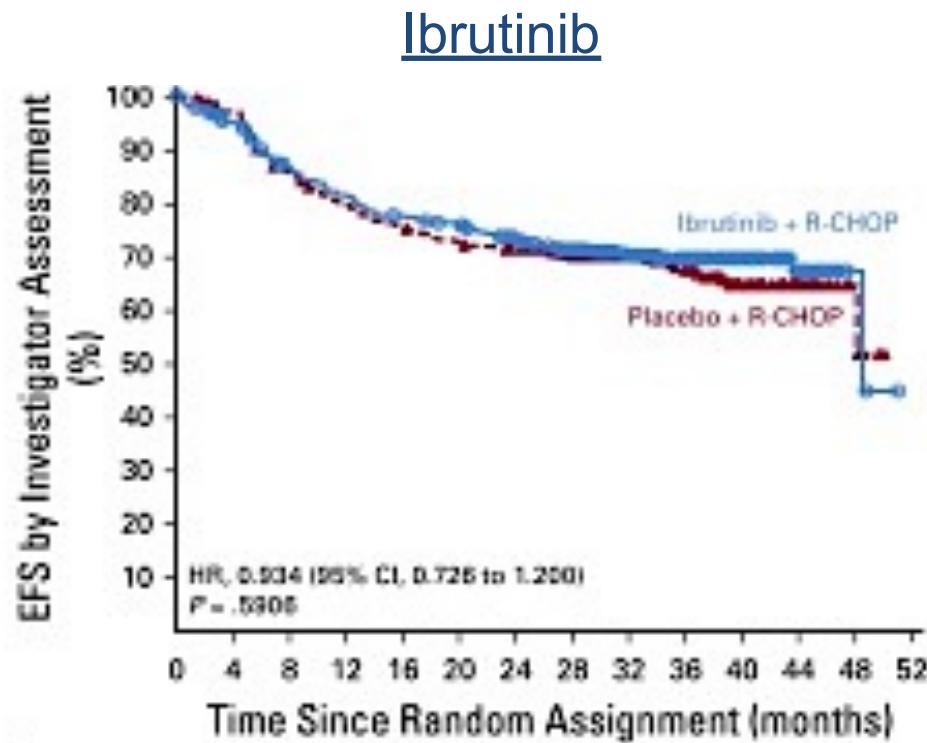
- Enhanced PFS with median follow-up of more than two years: likely cures.
- No toxicity differences; double-blind design
- Higher risk patients appeared to disproportionately benefit
- Borderline cost-effective when considering costs (financial and physical) of salvage therapy

Concerns:

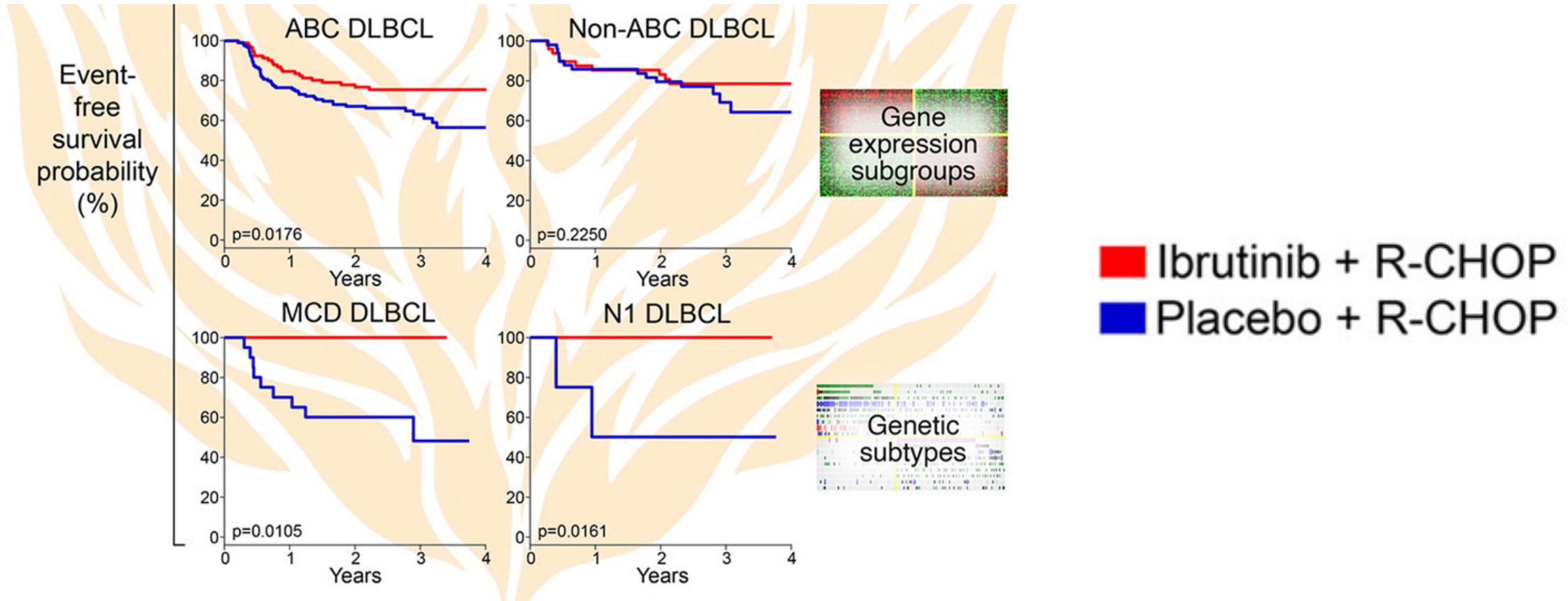
- Relatively small (6%) PFS difference at two year benchmark
- Certain subsets (GCB, double hit) appear to not benefit
- Expensive
- Uncertain impact on outcome of salvage treatments
- No overall survival benefit (yet)



Rational agents targeting ABC DLBCL have single agent activity, but do not improve outcome when added to RCHOP



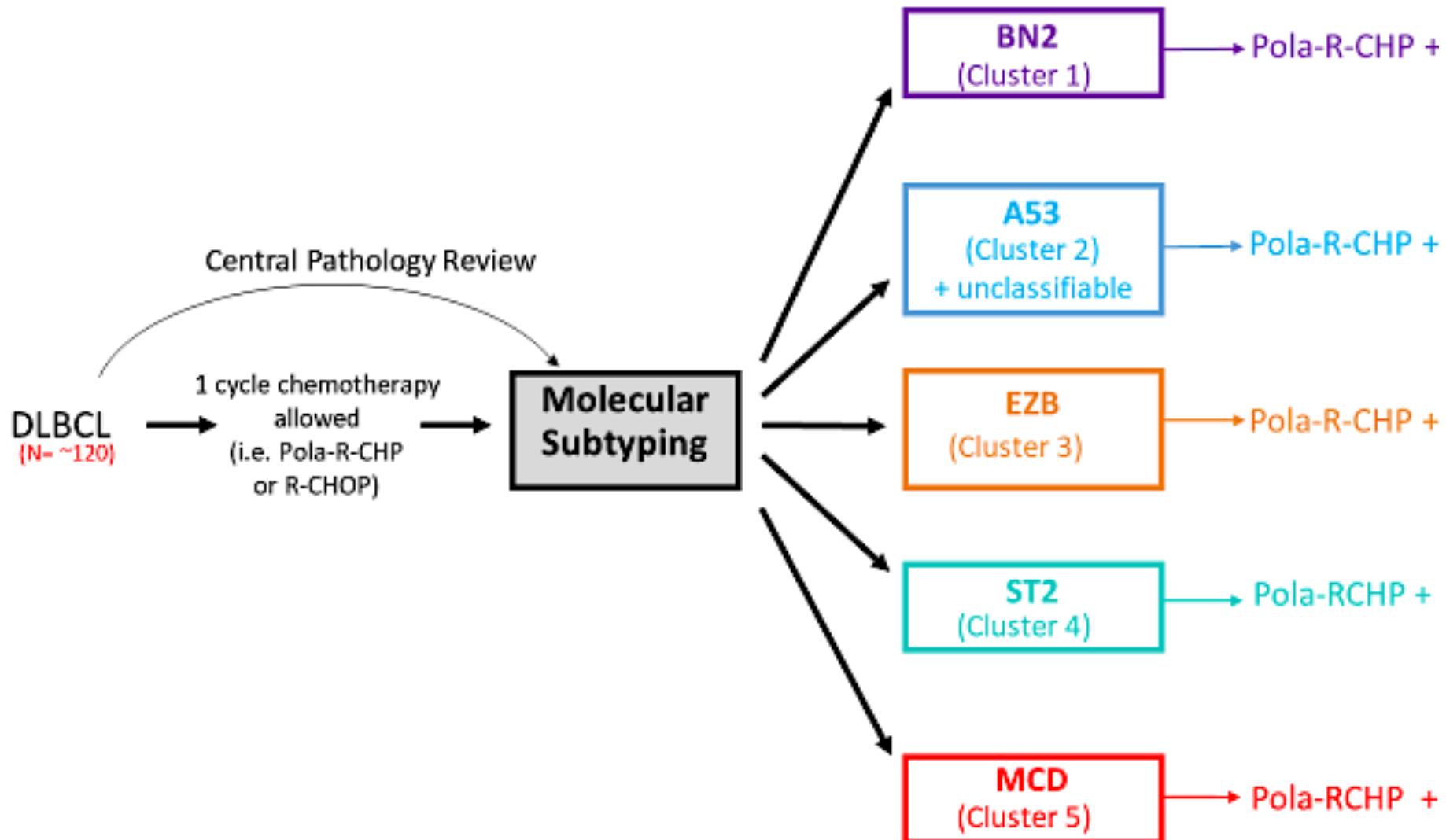
Sequencing reveals further heterogeneity of DLBCL: Analysis of phase III PHOENIX trial



Ongoing trials

- Tafasitamab/Lenalidomide + RCHOP vs. RCHOP (high int and high risk)
- Acalabrutinib + RCHOP vs. RCHOP (nonGCB; < age 70)
- Epcoritamab + RCHOP vs. RCHOP (pending; IPI 2-5)
- Elderly studies:
 - Azacitidine + RminiCHOP vs. RminiCHOP (SWOG S1918; > age 75)
 - Mosunetuzumab +/- polatuzumab
 - Loncastuximab + rituximab

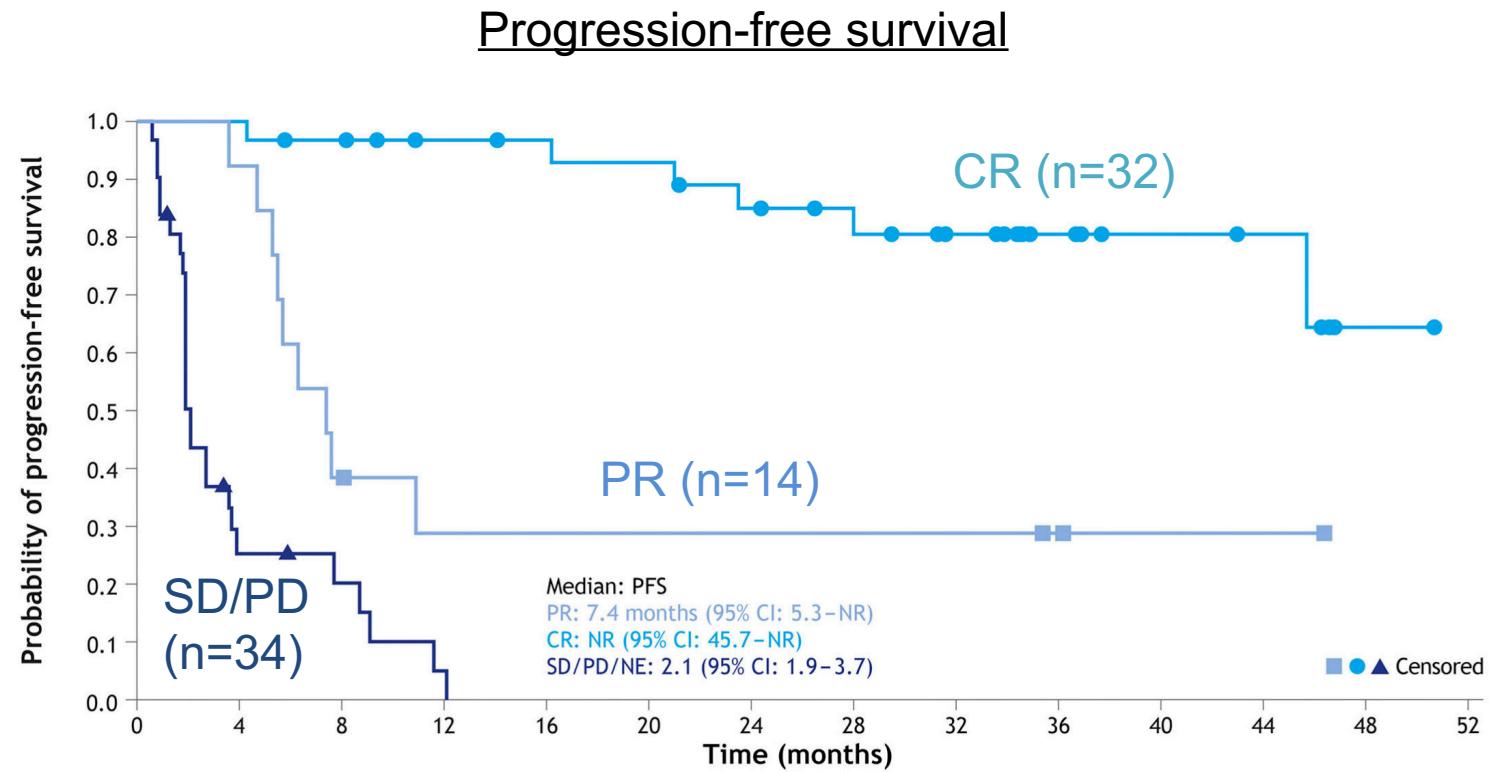
The future: ECOG trial concept



Relapsed/Refractory Diffuse Large B-cell Lymphoma (DLBCL)

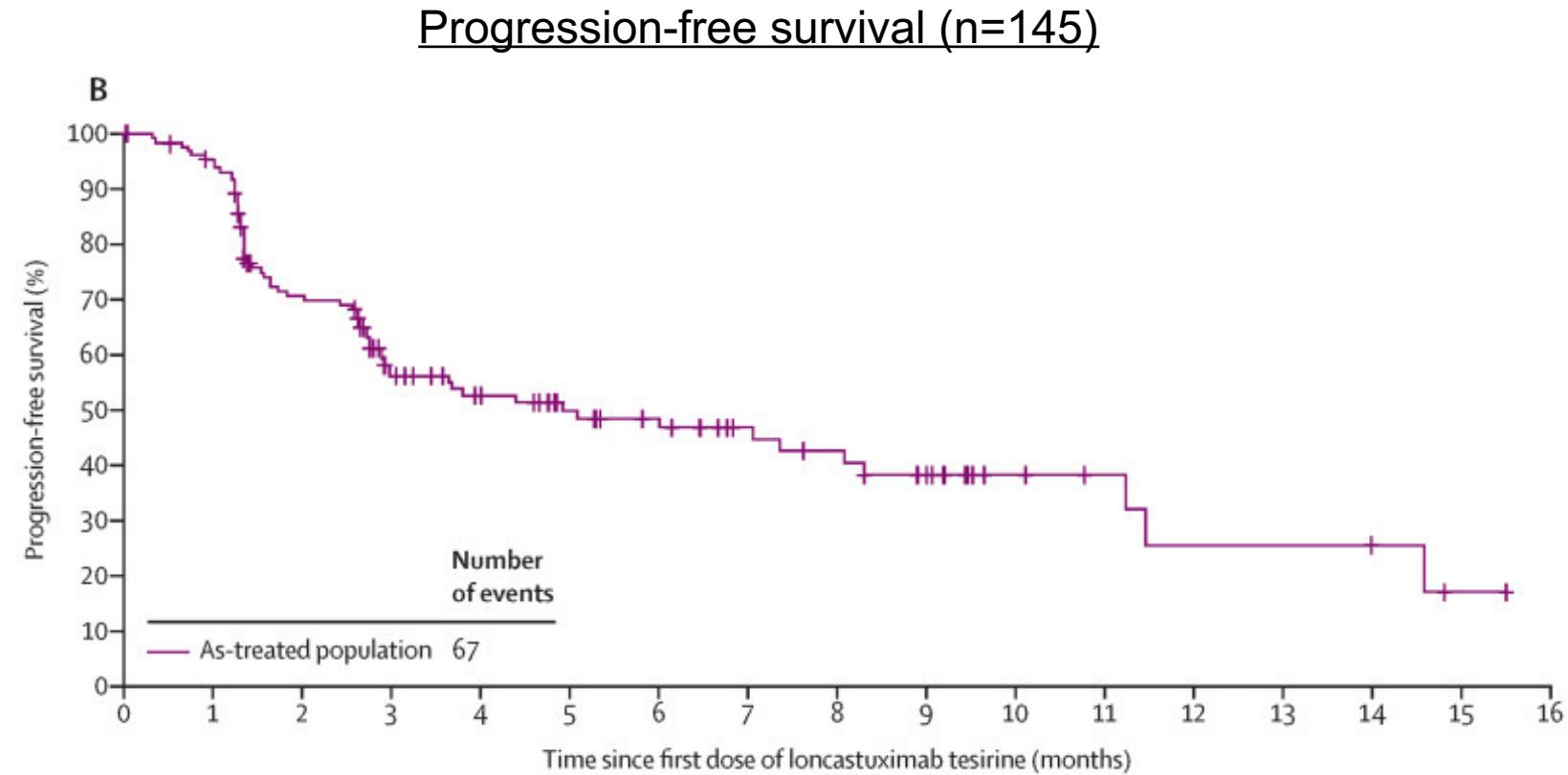
Tafasitamab (anti-CD19) + Lenalidomide pivotal trial

- 12 months combined therapy, then tafasitamab alone q 2 weeks
- ORR 57%; CR 40%
- Median OS 33 months
- Key adverse events
 - Neutropenia, infections
 - 42 deaths; 31 from PD



Loncastuximab (CD19 ADC) pivotal trial

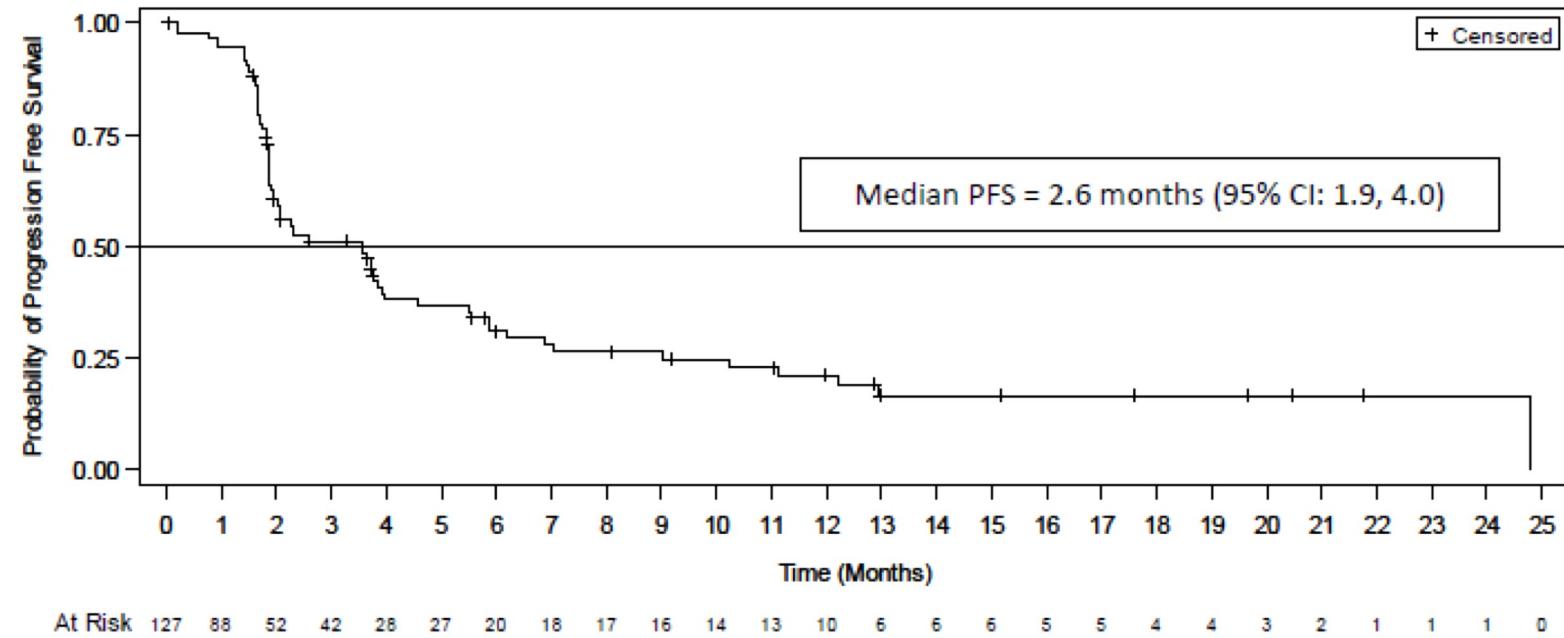
- 12 months q 3 weeks
- ORR 46%; CR 19%
- Key adverse events
 - Neutropenia, infections
 - Increased GGT
 - Edema/effusions
 - Dose delays common



Selinexor (exportin-1) pivotal trial

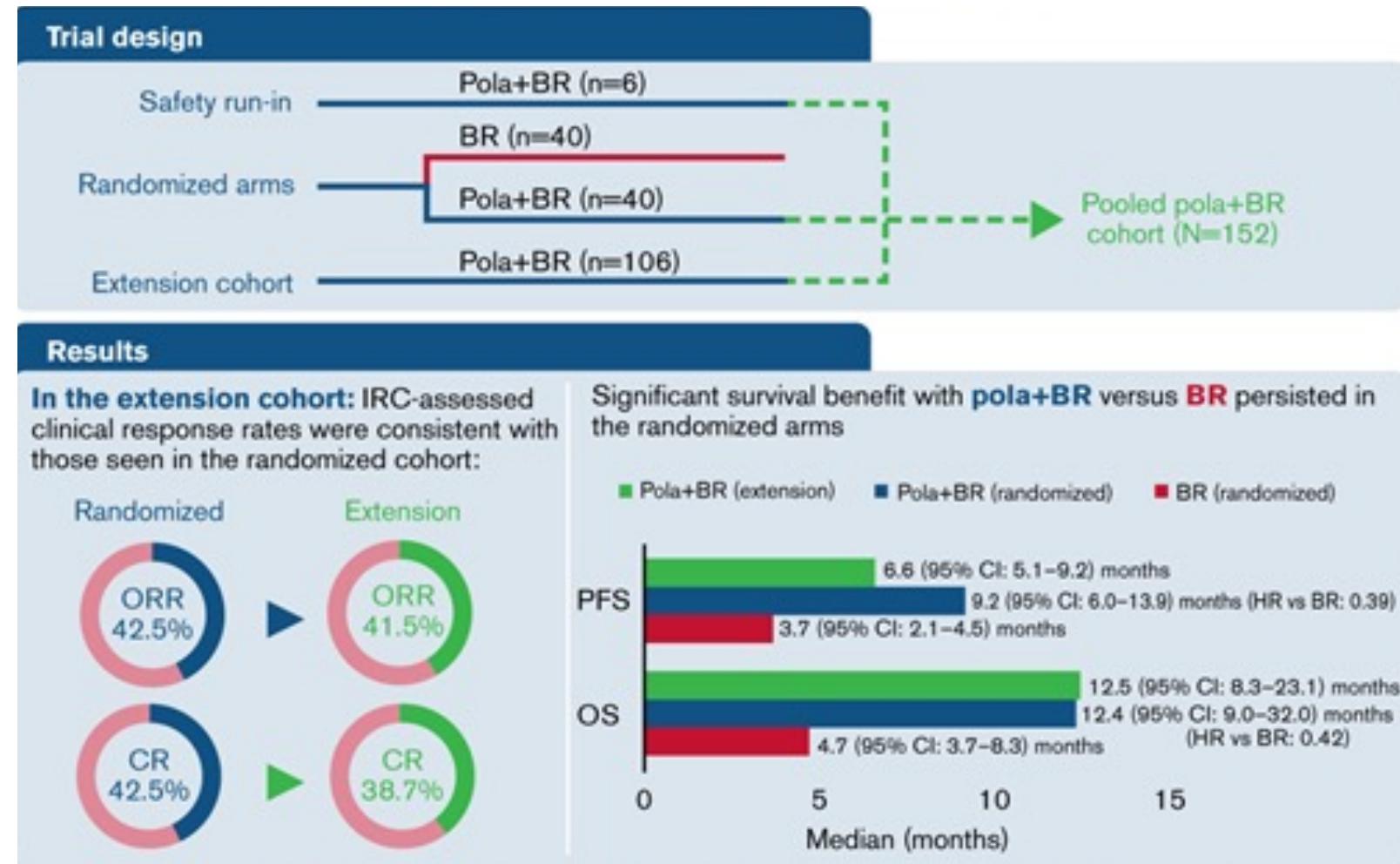
- Oral therapy twice weekly
- ORR 28%; CR 12%
- Key adverse events
 - Neutropenia, thrombocytopenia
 - Fatigue
 - Nausea
 - Dose delays common

Progression-free survival (n=127)

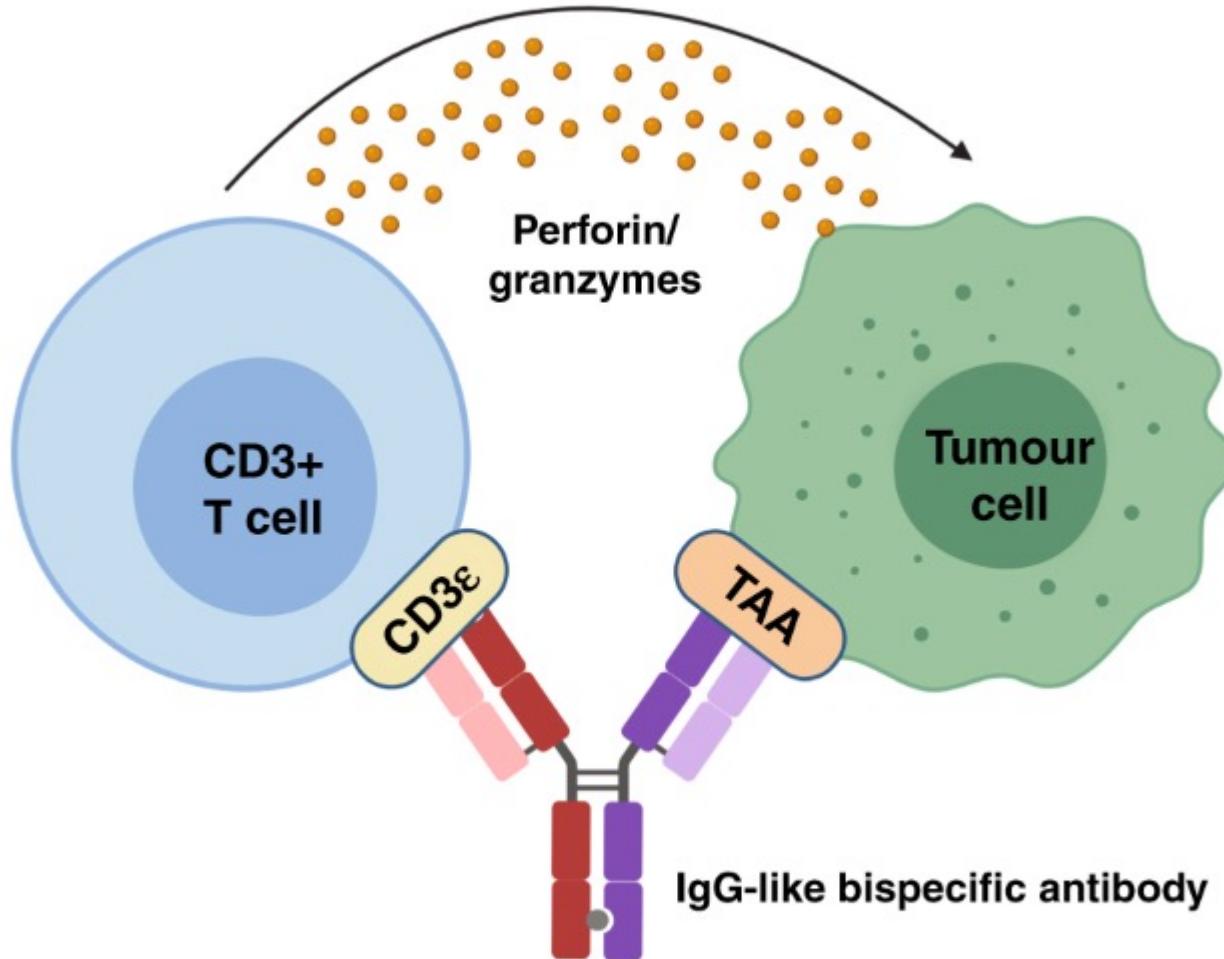


Bendamustine/rituximab +/- polatuzumab (CD79b ADC)

- 6 cycles of therapy
- ORR and CRs
 - BR: 18%;
 - BR/pola: 42%
- Key adverse events
 - Neutropenia, anemia, thrombocytopenia
 - Increased GGT



Redirected tumour lysis

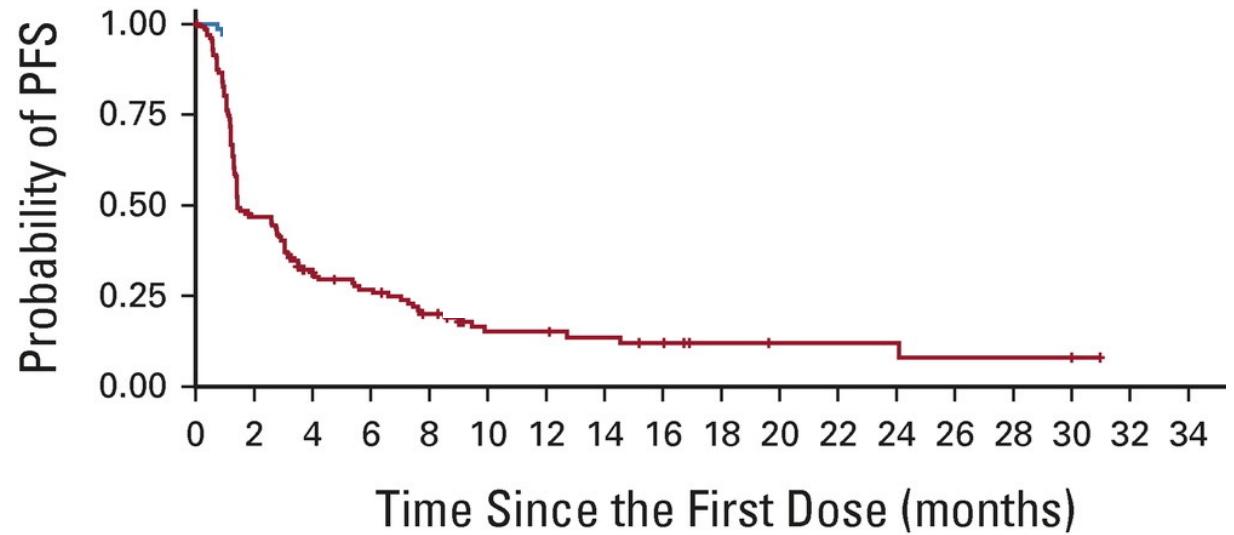


**CD3 bispecific T-cell redirection mechanism
of action in cancer immunotherapy**

Mosunetuzumab experience

- 82 patients with DLBCL; additional patients with transformed and mantle cell lymphoma.
- ORR 35%; CR 19%
- Key adverse events
 - Neutropenia
 - CRS (low grade; cycle 1)
 - Diarrhea

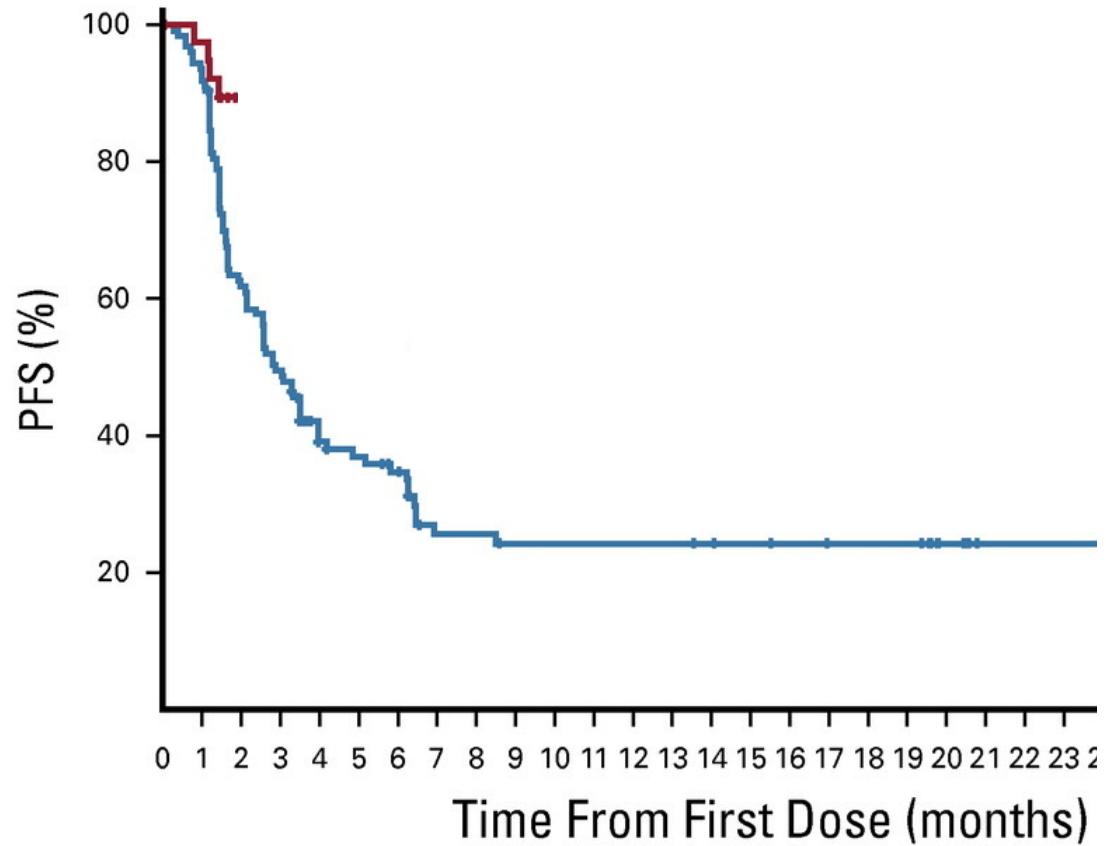
Progression-free survival (n=129)



Glofitamab experience

- 73 patients with DLBCL; additional patients with transformed and mantle cell lymphoma.
- ORR 48%; CR 39%
- Key adverse events
 - Neutropenia
 - CRS (low grade; cycle 1)
 - 2 cases of neurotoxicity

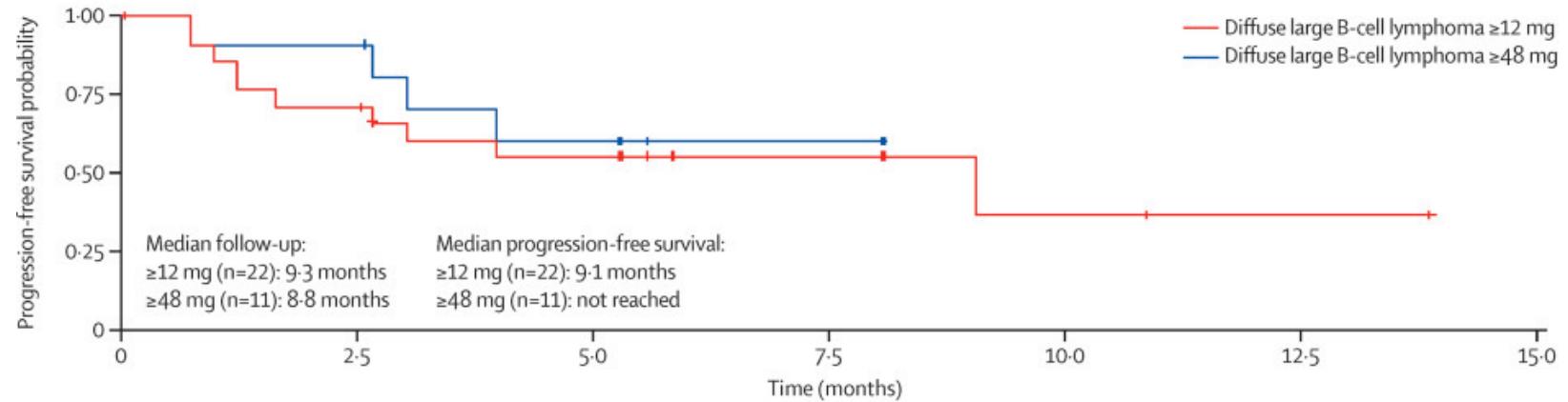
Progression-free survival (n=127)



Epcoritamab experience

Progression-free survival (n=22)

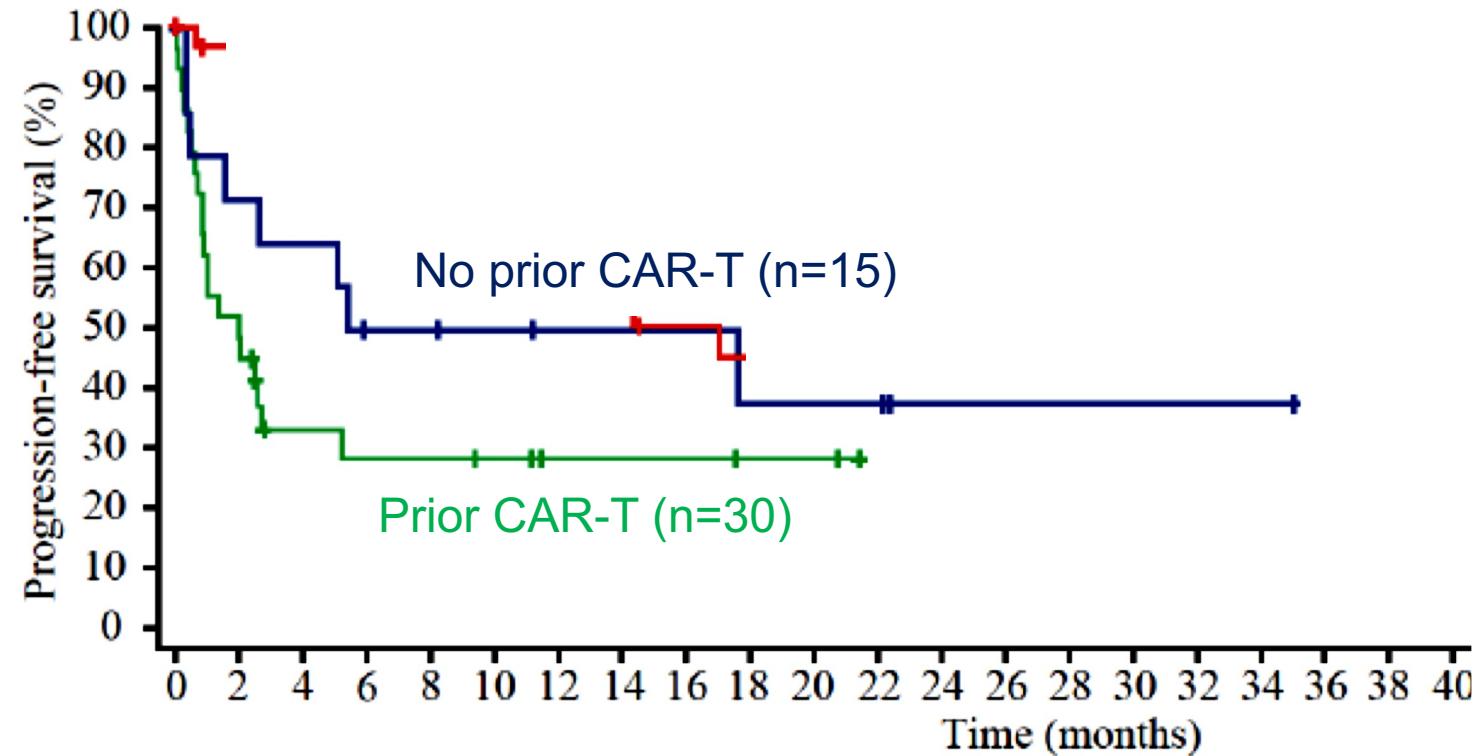
- Subcutaneous administration
- ORR 68%; CR 45%
- Key adverse events
 - Fever
 - CRS
 - Injection site reactions



Odronextamab experience

- ORR: 53% no CAR-T; 33% post CAR-T
- Key adverse events
 - Anemia
 - Fever, CRS
 - Infections

Progression-free survival (n=45)



Some key ASH abstracts on bispecifics in DLBCL

- 737 Golfitamab + RCHOP
- 441 Golfitamab relapses rare after CR
- 443 Epcoritamab + RDAX/C as salvage therapy
- 444 Odronextamab in relapsed/refractory DLBCL
- 738 Mosunetuzumab monotherapy for elderly patients with DLBCL



UR
MEDICINE

WILMOT
CANCER INSTITUTE

APPENDIX

Frontmind: A Phase III, Multicenter, Randomized, Double-Blind Study of Tafasitamab + Lenalidomide + R- CHOP Versus R-CHOP Alone for Newly Diagnosed High- Intermediate and High-Risk Diffuse Large B-Cell Lymphoma

Vitolo U et. al.

ASH 2022; Poster Abstract 2947.

Sunday, December 11, 2022, 6:00 PM-8:00 PM