Polatuzumab vedotin (POLIVY®)

Presentation to the Oncologic Drugs Advisory Committee

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Agenda

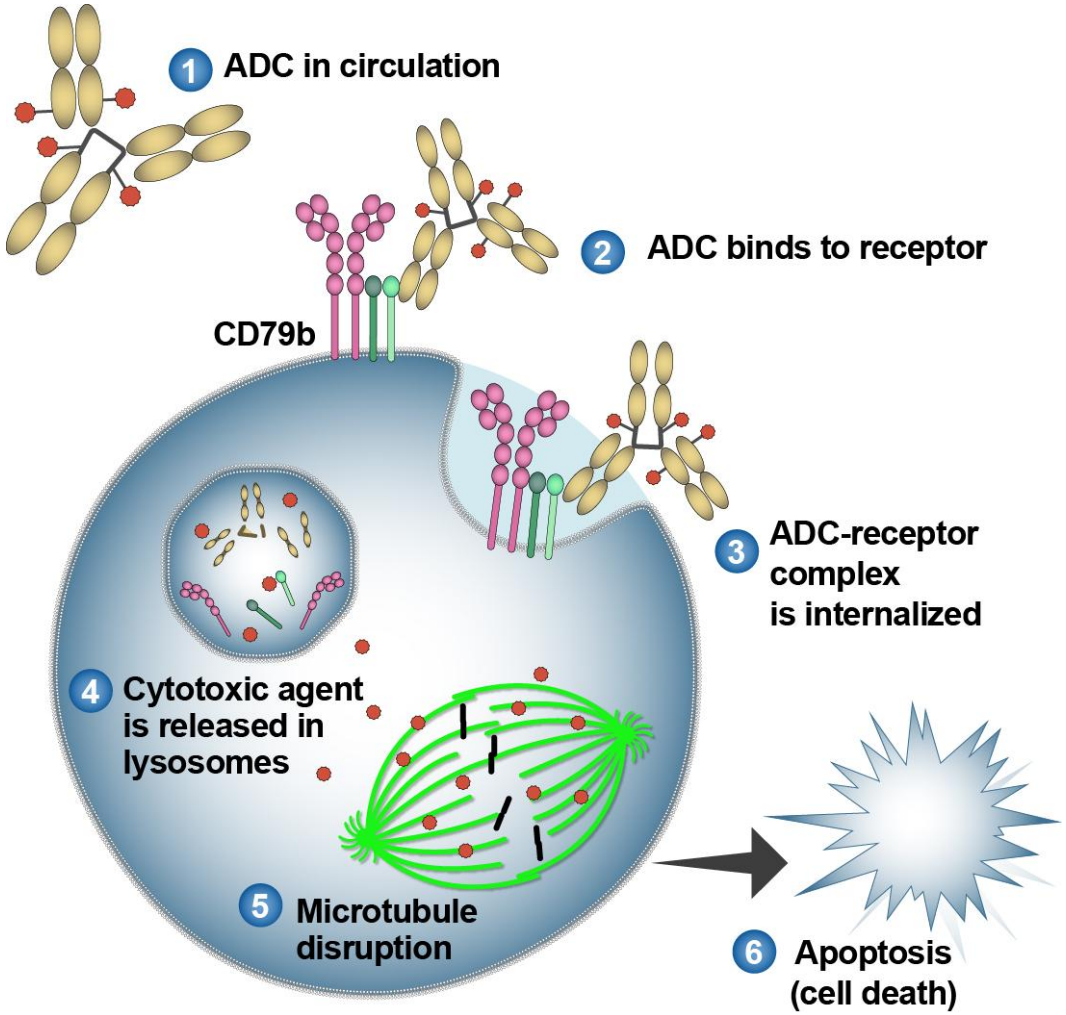
Introduction	**Charles Fuchs, MD** *Genentech*
DLBCL Background & Unmet Need	**Christopher Flowers, MD, MS, FASCO** *M.D. Anderson Cancer Center, Houston*
POLARIX Efficacy & Safety	**Jamie Hirata, PharmD** *Genentech*
Clinical Perspective	**Jonathan W. Friedberg, MD, MMSc** *Wilmot Cancer Institute, University of Rochester*
Closing Remarks	**Charles Fuchs, MD** *Genentech*

Sponsor's Position on Polatuzumab Vedotin for 1L Diffuse Large B-cell Lymphoma (DLBCL)

- R-CHOP cures approximately 60% of patients, but up to 40% are refractory or relapse to R-CHOP.
- POLARIX designed to decrease relapse to increase chance for cure.
  - Double blinded, placebo-controlled Phase III trial evaluating Pola+R-CHP vs. R-CHOP, with PFS as primary endpoint.
- POLARIX is 1st study in 20 years to demonstrate positive benefit/risk in 1L.
- **Polatuzumab Vedotin + R-CHP offers a clinically meaningful benefit and offers the best chance of cure for 1L patients.**

Polatuzumab vedotin:

A first-in-class antibody drug conjugate that targets CD79b[1,2]



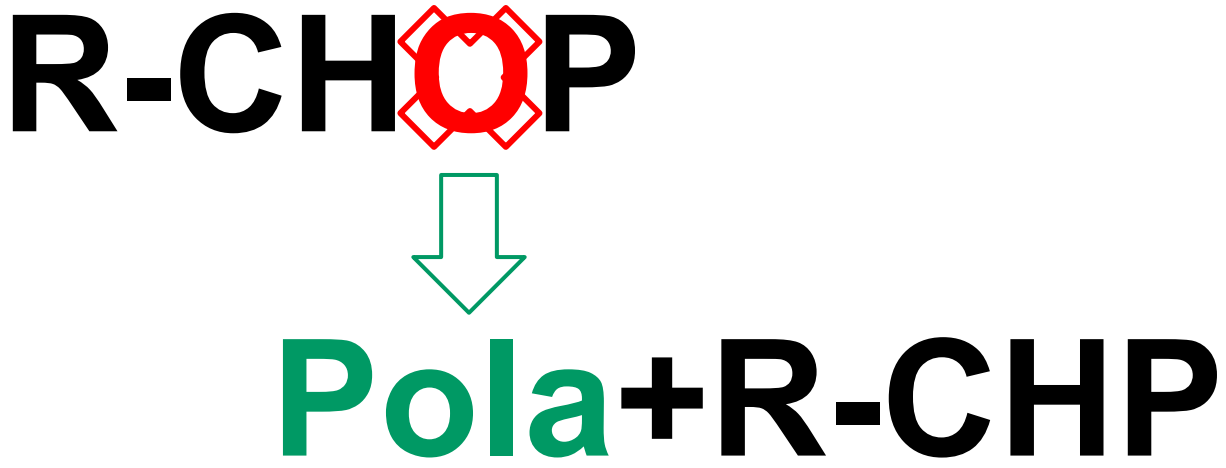
- CD79b is a signaling component of the B-cell antigen receptor complex that is ubiquitously expressed in DLBCL.
- Polatuzumab vedotin consists of a potent microtubule inhibitor (MMAE) conjugated to a CD79b monoclonal antibody via a protease-cleavable peptide linker.
- This linker and MMAE technology have been used in other FDA-approved products such as ADCETRIS® (brentuximab vedotin), PADCEV® (enfortumab vedotin-ejfv), and TIVDAK® (tisotumab vedotin-tftv).

[1] Dornan D, et al. Blood 2009;114:2721–29.
[2] Polson AG, et al. Blood 2007;110:616–23.
ADC, antibody–drug conjugate; MMAE, monomethyl auristatin E.

Regulatory Status of Polatuzumab Vedotin in DLBCL

Orphan Drug Designation Dec 2016	Polatuzumab vedotin for the treatment of DLBCL.
Breakthrough Therapy Designation Sep 2017 **Accelerated Approval Jun 2019**	**GO29365 (Phase 2)**: Polatuzumab vedotin + BR in **3L+ DLBCL** *"POLIVY is a CD79b-directed antibody-drug conjugate indicated in combination with bendamustine and a rituximab product for the treatment of adult patients with relapsed or refractory diffuse large B-cell lymphoma, not otherwise specified, after at least two prior therapies.* *Accelerated approval was granted for this indication based on complete response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial".*
Confirmation of Clinical Benefit	**POLARIX (Phase 3)**: Polatuzumab vedotin + R-CHP in **1L DLBCL** • Met primary endpoint of PFS (June 2021). ***OR*** **POLARGO (Phase 3)**: Polatuzumab vedotin + R-GemOx in **R/R DLBCL** • Study is ongoing.

POLARIX Scientific Hypothesis



Replacing vincristine in R-CHOP with polatuzumab vedotin increases efficacy without significantly increasing toxicity for 1L DLBCL patients.

- MMAE is ~10x more potent than vincristine (Oncovin®).
- Antibody-drug-conjugate technology delivers a high level of MMAE to the tumor while limiting the systemic release of unconjugated MMAE.

Points for Consideration

- Areas of alignment
  - Statistically significant improvement in PFS.
  - Safety profile comparable between Pola+R-CHP and R-CHOP.
- Clinical relevance of PFS and secondary endpoints.
- Heterogeneity across histologic and biologic subtypes.

Disease Background & Unmet Need in DLBCL

Christopher Flowers, MD, MS, FASCO
Chair, Professor
Department of Lymphoma/Myeloma
M.D. Anderson Cancer Center, Houston

Diffuse Large B-cell Lymphoma

Most common aggressive lymphoma[1]

- In the United States, approximately **27,360** people diagnosed with DLBCL each year.[2]
- Routine diagnosis of DLBCL/LBCL can be made by a hematopathologist.
- Patients typically present with **advanced stage** disease and **require therapy.**
  - Clinical course can be debilitating due to[3]:
    - Constitutional symptoms
    - Local symptoms of lymphadenopathy
    - End-organ damage from disease involvement
    - Bone marrow failure that may lead to infections, anemia, and thrombocytopenia

[1] Sehn LH, Salles G. N Engl J Med 2021;384(9):842-858.
[2] Teras LR, et al. CA Cancer J Clin 2016; 66:443-459.
[3] Flowers CR, et al. CA Cancer J Clin 2010;60:393-408.

First Line (1L) Therapy for DLBCL and Subtypes

R-CHOP is standard 1L therapy

- DLBCL is heterogeneous and comprises numerous subtypes
  - Molecular and genomic: activated B-cell, germinal-center B-cell.
  - Clinical location: primary mediastinal, primary cutaneous, primary CNS.
  - Histologic staining: expression of MYC, BCL2, ALK, staining for EBV.
  - Cytogenetic: rearrangements of MYC and BCL2 and/or BCL6.
  - Morphologic: immunoblastic, centroblastic, blastoid.

No evidence for benefit over R-CHOP in any subtype from previous randomized control trials, including more intensive regimens.[1]

[1]National Comprehensive Cancer Network. Clinical practice guidelines in oncology (NCCN Guidelines®) B-cell lymphomas (Version 1 2023). Available at: http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

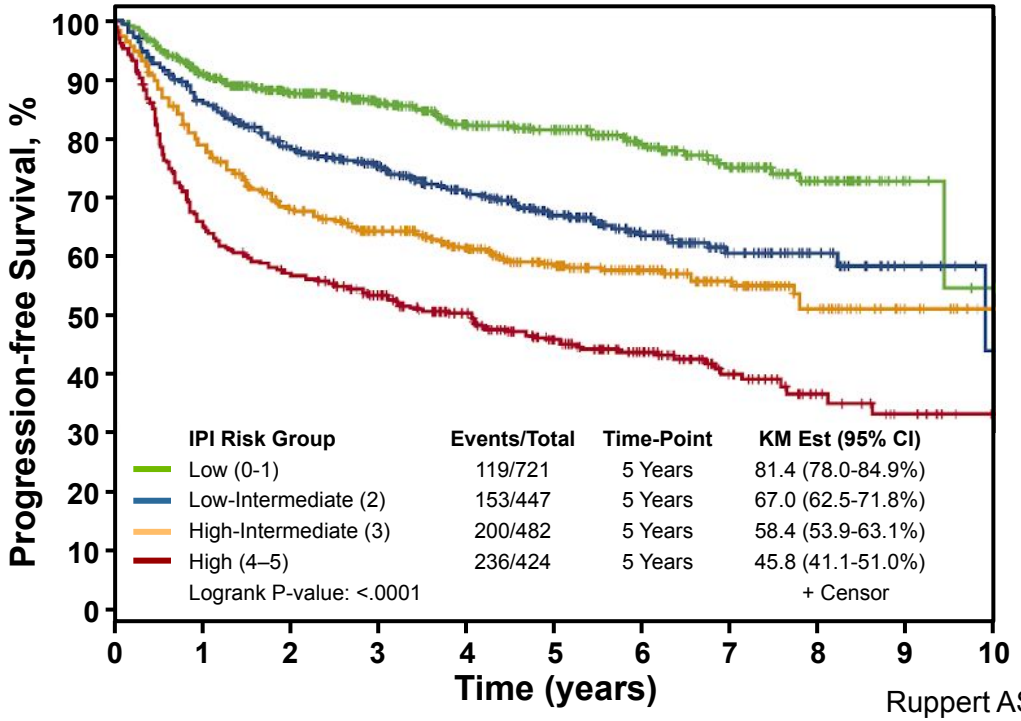
R-CHOP Outcomes by International Prognostic Index (IPI)

Clinical factors identify 1L DLBCL patients that have poor outcomes

Factor	Risk Factor if:
Age	>60 years
ECOG Performance Status	≥ 2
LDH	> normal
Extranodal sites	≥ 2
Ann Arbor Stage	III-IV

N Engl J Med. 1993;329(143):987-994.

Progression-free Survival by IPI with R-CHOP



Ruppert AS, et al. Blood 2020;135:2041-8.

ECOG, Eastern Cooperative Oncology Group; LDH, Lactate dehydrogenase.

R-CHOP is a Familiar Outpatient Regimen

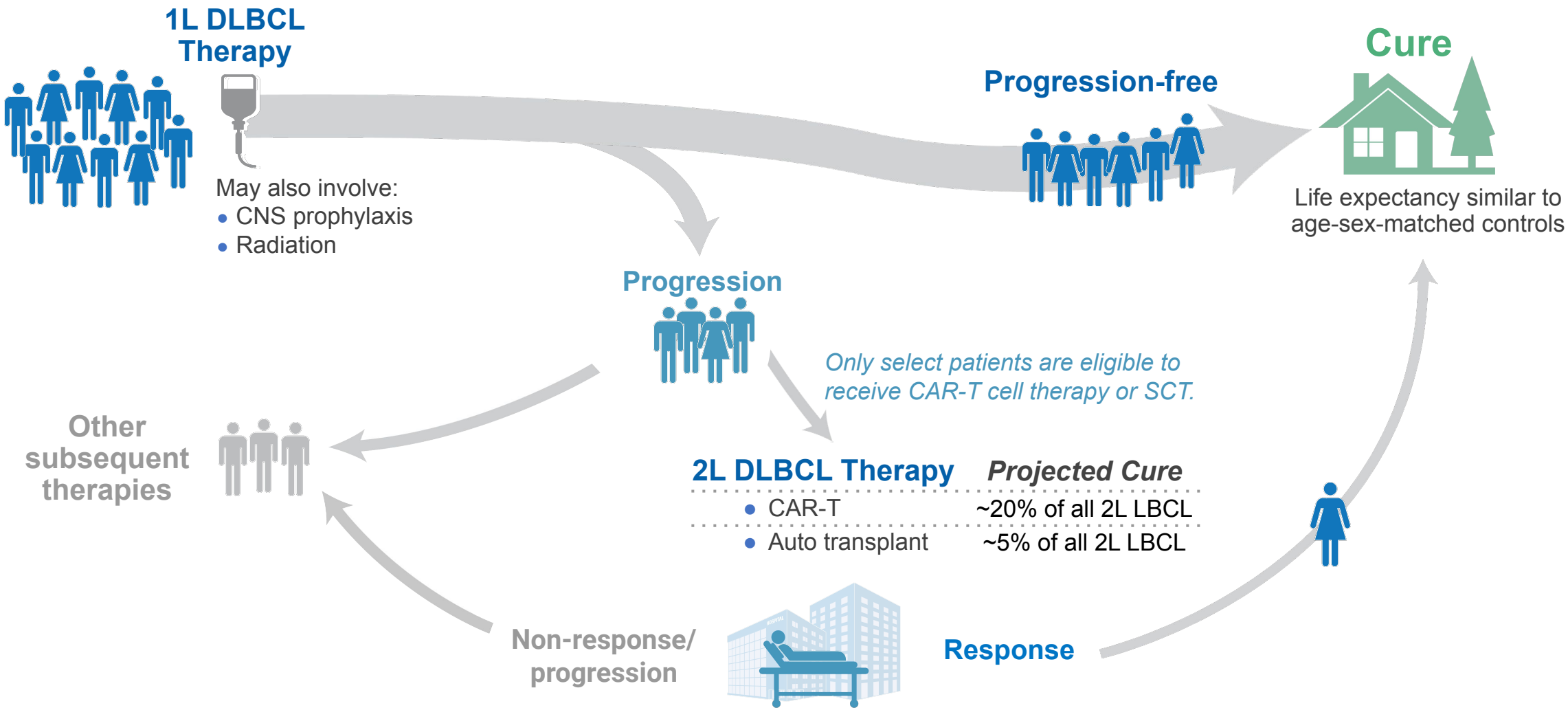
Health care providers are comfortable with management of risks

- Safety profile is manageable.
  - Common Grade 3-4 adverse events include:[1-4]
    - Neutropenia: **38%-58%**
    - Febrile neutropenia: **9%-15%**
    - High grade Infectious complications are expected and manageable
      - Pneumonia: **2.6%-6%**
- Supportive care with G-CSF and dose modifications are used in clinical practice and clinical trials.

[1] Vitolo U, et al. J Clin Oncol 2017;35:3529-3537; [2] Davies A, et al. 2019;20:649-62; [3] Younes A, et al. J Clin Oncol 2019;37:1285-1295; [4] Nowakowski GS, et al J Clin Oncol 2021;39:1317-1328.

DLBCL Patient Journey

Likelihood of cure is highest with treatment in 1L setting



Westin J and Sehn LH. Blood 2022;139 (18): 2737–2746.
CAR-T, chimeric antigen receptor T-cell; SCT, stem cell transplantation.

Identifying a Meaningful Endpoint in DLBCL

- **Overall survival**
  - Important and is the most reliable endpoint for cancer.[1]
  - Statistical models with >7500 patients established OS as an endpoint that requires very long follow-up for 1L DLBCL (> 10 years).[2]

[1] Food and Drug Administration (FDA) Guidance. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. December 2018. https://www.fda.gov/media/71195/download. Accessed: 18 November 2022.
[2] Shi Q, et al. J Clin Oncol 2018;36:2593-2602.

Progression-free Survival is a Meaningful Endpoint in 1L DLBCL

PFS measures what is most meaningful to patients

- **Progression-free survival** - time from randomization to relapse, progression or death.[1, 2]
  - 10 randomized trials for 1L DLBCL have used PFS/EFS as primary endpoint, and targeted a clinically meaningful HRs of at least 0.75.[3-7]

Clinically meaningful PFS target:
25% reduction in the risk of progression, relapse, or death,
translating into an absolute improvement of **5-7% in PFS at 24 months.**

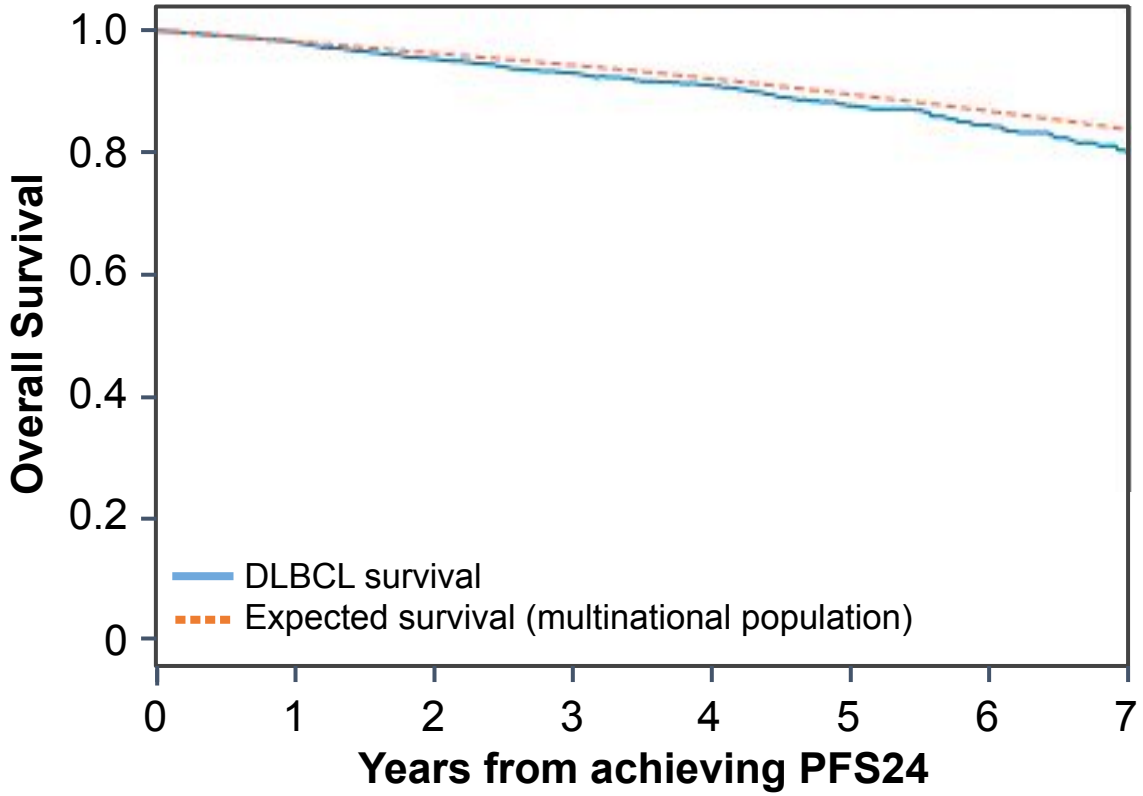
[1] Food and Drug Administration (FDA) Guidance. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. December 2018. https://www.fda.gov/media/71195/download. Accessed: 18 November 2022.
[2] Shi Q, et al. J Clin Oncol 2018;36:2593-2602. [3] Bartlett NL, et al. J Clin Oncol 2019;37(21):1790-1799. [4]Thieblemont C, et al. J Clin Oncol 2017;35:2473-2481.
[5] Vitolo U et al. J Clin Oncol 2017;35:3529-3537. [6]Davies et al. Lancet Oncol 2019;20:649-662. [7]Nowakowski et al. J Clin Oncol 2021;39:1317-1328.

PFS24 is a Meaningful Milestone in 1L DLBCL

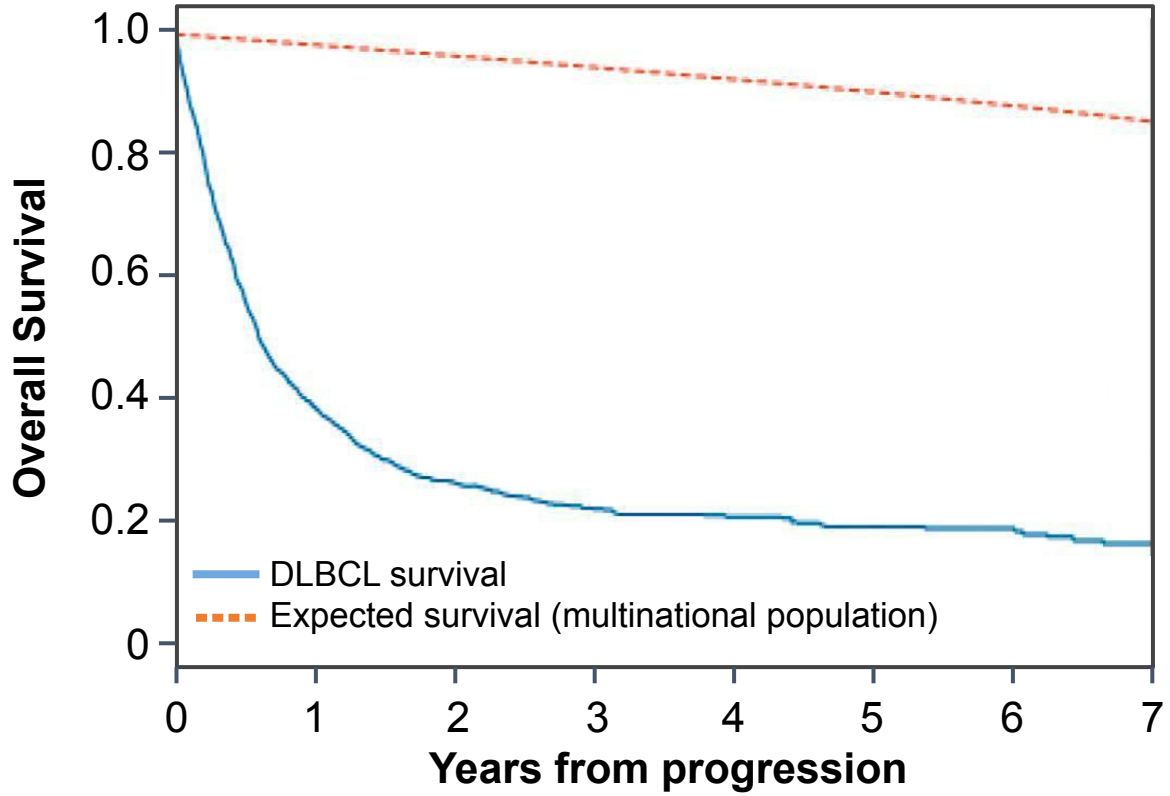
Life Expectancy is Highly Likely to Match General Population = Cure in 1L DLBCL

- Patients who are progression-free at 24 months are highly likely to have similar life expectancy as that of a sex- and age-matched general population.[1]

Overall survival from achieving PFS24



Overall survival from progression within 24 months



[1] Maurer MJ, et al. Ann Oncol 2018;29:1822-1827.

How Patients Experience DLBCL Relapse and Progression

DLBCL Symptoms:	B-symptoms (fever, night sweats, weight loss), pain, organ impairment.
Salvage treatments:	Lower cure rates, hospitalization, higher morbidity profile, access to curative therapy.
Late effects of salvage treatment:	Second malignancies, organ dysfunction, immunodeficiency.
Increased non-relapse mortality:	Due to therapies and their late effects.
Psychosocial distress:	Loss of productivity, Quality of Life.

DLBCL: A Lymphoma Clinician's Perspective

- 1L therapy is best chance of cure.
- Unmet need to reduce relapse/progression in 1L.
  - Significant toxicity is associated with therapy at relapse.
- PFS in clinical trials translate to clinical benefit for patients.
  - HR of 0.75 translates to improvement of 5-7% at 2 years.
- PFS improvement is clinically meaningful to patients in 1L DLBCL.

POLARIX

Jamie Hirata, PharmD

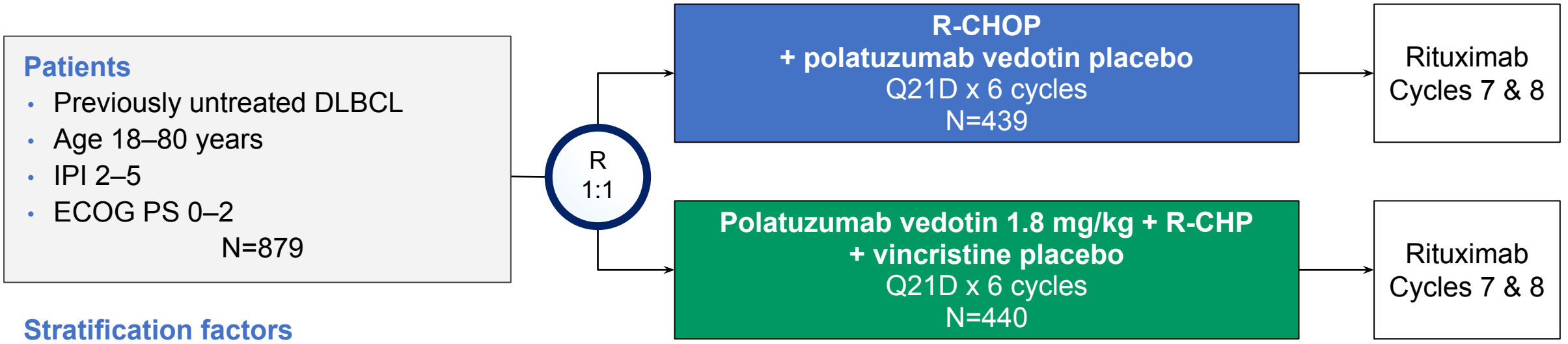
Global Development Leader, Polatuzumab Vedotin

Genentech

POLARIX is a Phase III Study Evaluating Pola+R-CHP vs R-CHOP

Multiregional, randomized, double-blind, active and placebo controlled trial

- Collaboration with the Lymphoma Study Association (LYSA) and Steering Committee.



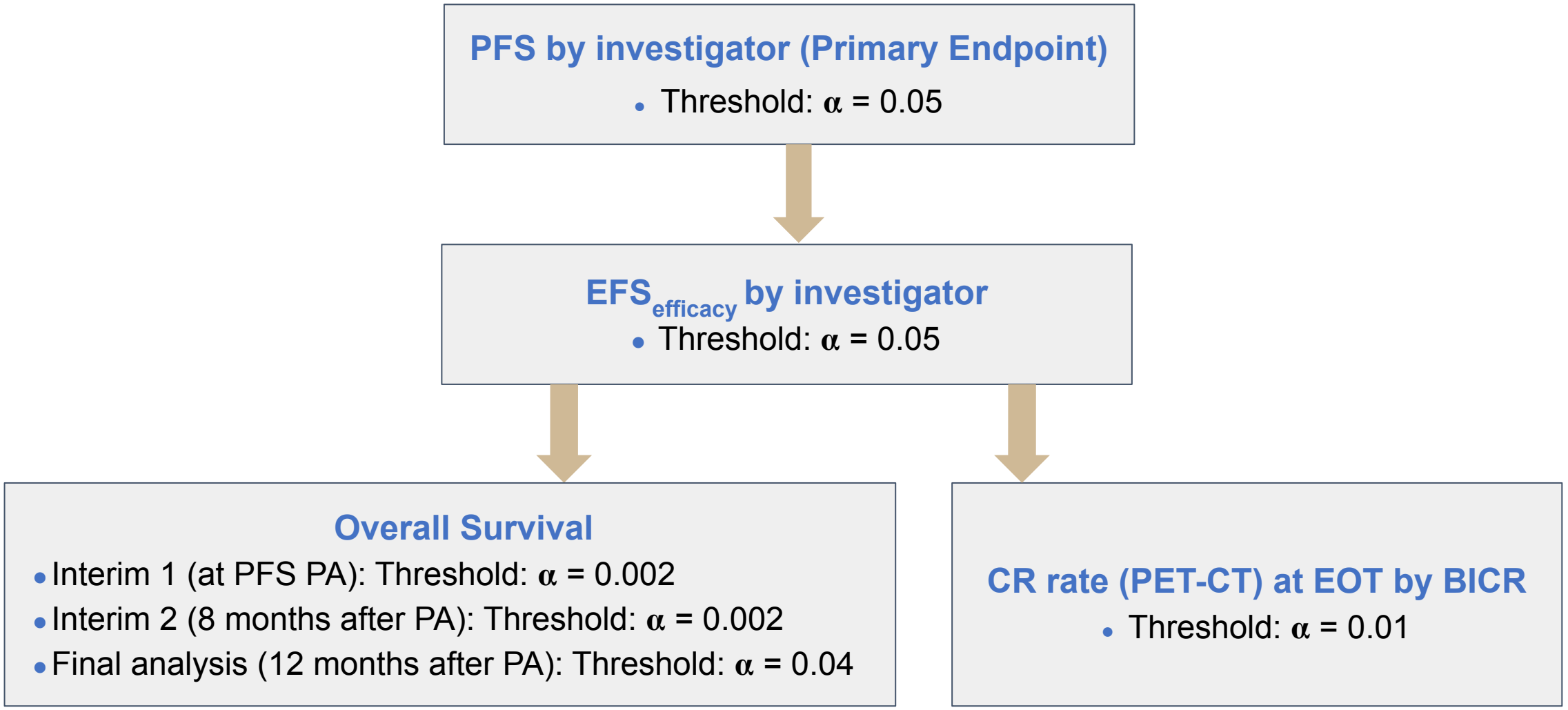
Stratification factors

- IPI score (2 vs 3–5)
- Bulky disease (≥7.5 cm vs absence)
- Geographic region*

- 27% of patients were recruited in the United States

*Western Europe, United States, Canada and Australia versus Asia versus Rest of World.
IPI, International Prognostic Index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; Q21D, every 21 days.

Study Endpoints and Hierarchical Testing



All α levels are two-sided.
BICR, blinded independent central review; CR, complete response; $EFS_{efficacy}$, event-free survival efficacy; EOT, end of treatment; PA, primary analysis; PFS, progression-free survival.

Statistical Analysis Plan

- Primary analysis was planned on the ITT population after:
  - Approximately 228 PFS events were observed.[1]
  - All patients were followed for at least 24 months.[2]
- Primary analysis was conducted after 241 PFS events were observed.
  - Minimum follow up: 24 months.
  - Median follow up: 28.2 months.
- FDA feedback was incorporated in the statistical analysis plan.
  - Analysis methodologies and all censoring rules for PFS were reviewed.

[1] With the target PFS HR of 0.69 and a two-sided alpha of 0.05, it required 228 PFS events to ensure that the power for the PFS analysis is at least 80%.

[2] A minimum follow-up of 24 months was aligned with the FDA to ensure sufficient follow-up at the primary analysis.
Clinical cut-off date: June 28, 2021

Patient Demographics and Baseline Characteristics

Balanced between the 2 arms and representative of patients with 1L DLBCL

Intention-to-Treat population		R-CHOP (N=439)	Pola+R-CHP (N=440)
Age	Median (range), years	66 (19–80)	65 (19–80)
Sex, n (%)	Male	234 (53)	239 (54)
ECOG Performance Status, n (%)	0–1 2	363 (83) 75 (17)	374 (85) 66 (15)
Bulky disease (≥7.5cm), n (%)	Present	192 (44)	193 (44)
Elevated LDH, n (%)	Yes	284 (65)	291 (66)
Time from diagnosis to treatment initiation	Median, days	27	26
Ann Arbor Stage, n (%)	III–IV	387 (88)	393 (89)
Extranodal sites, n (%)	≥2	213 (49)	213 (48)
IPI score, n (%)	2 3–5	167 (38) 272 (62)	167 (38) 273 (62)
Cell-of-origin, n (%)*	ABC GCB Unclassified	119 (35) 168 (50) 51 (15)	102 (31) 184 (56) 44 (13)
MYC/BCL2 expression, n (%)*	Double expression	151 (41)	139 (38)
MYC/BCL2/BCL6 rearrangement, n (%)*	Double-/triple-hit	19 (6)	26 (8)

*In the Pola+R-CHP and R-CHOP groups, respectively, the numbers of patients evaluable for cell-of-origin were 330 and 338, with IHC for MYC/BCL2 expression were 362 and 366, and with FISH for *MYC/BCL2/BCL6* rearrangements were 331 and 334.

ABC, activated B-cell; ECOG, Eastern Cooperative Oncology Group; GCB, germinal center B-cell; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

EFFICACY

POLARIX Met Primary Endpoint of PFS

Pola+R-CHP demonstrated a 27% reduction in the relative risk of disease progression, relapse or death versus R-CHOP

Clinical Benefit	POLARIX demonstrated a statistically significant and clinically meaningful improvement in PFS in 1L DLBCL.

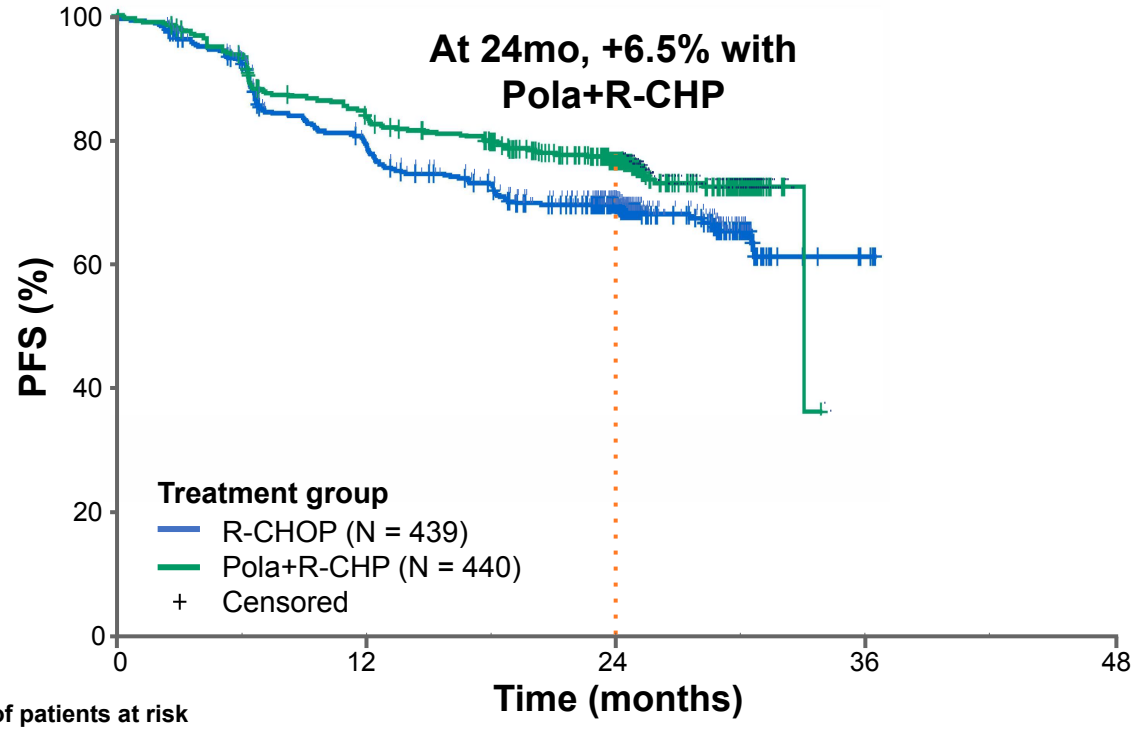
		R-CHOP N=439	Pola+R-CHP N=440
PFS	Pt with events	134 (30.5%)	107 (24.3%)
	HR [95% CI]	**0.73** [0.57, 0.95]	
	Stratified log-rank p-value	0.0177	
	2 year rate [95% CI]	70.2% [65.8%, 74.6%]	76.7% [72.7%, 80.8%]
	Difference in event free rate [95% CI]	6.5% [0.5%, 12.5%]	

Clinical cut-off date: June 28, 2021

PFS Remains Consistent with an Additional 1 Year of Follow-up

Primary PFS Analysis (CCOD: June 28, 2021)

Median follow-up: 28.2 months

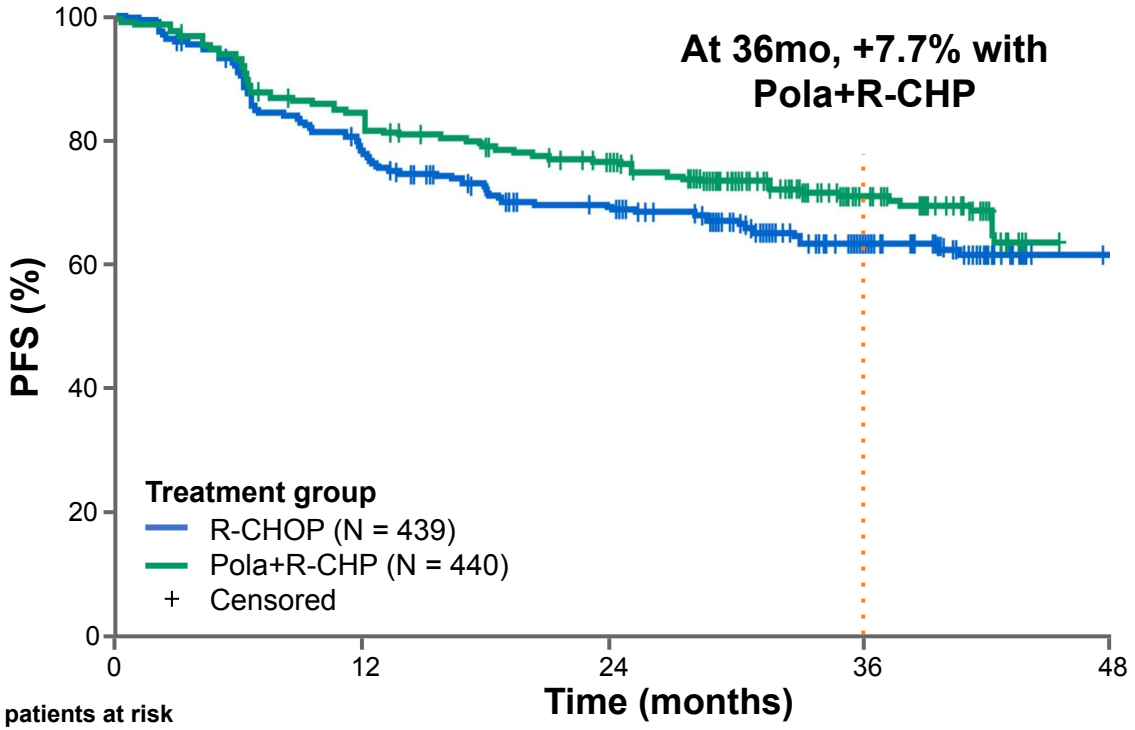


No. of patients at risk

R-CHOP	439	330	220	3	NE
Pola+R-CHP	440	353	246	NE	NE

PFS with Additional Follow-Up (CCOD: June 15, 2022)

Median follow-up: 39.7 months



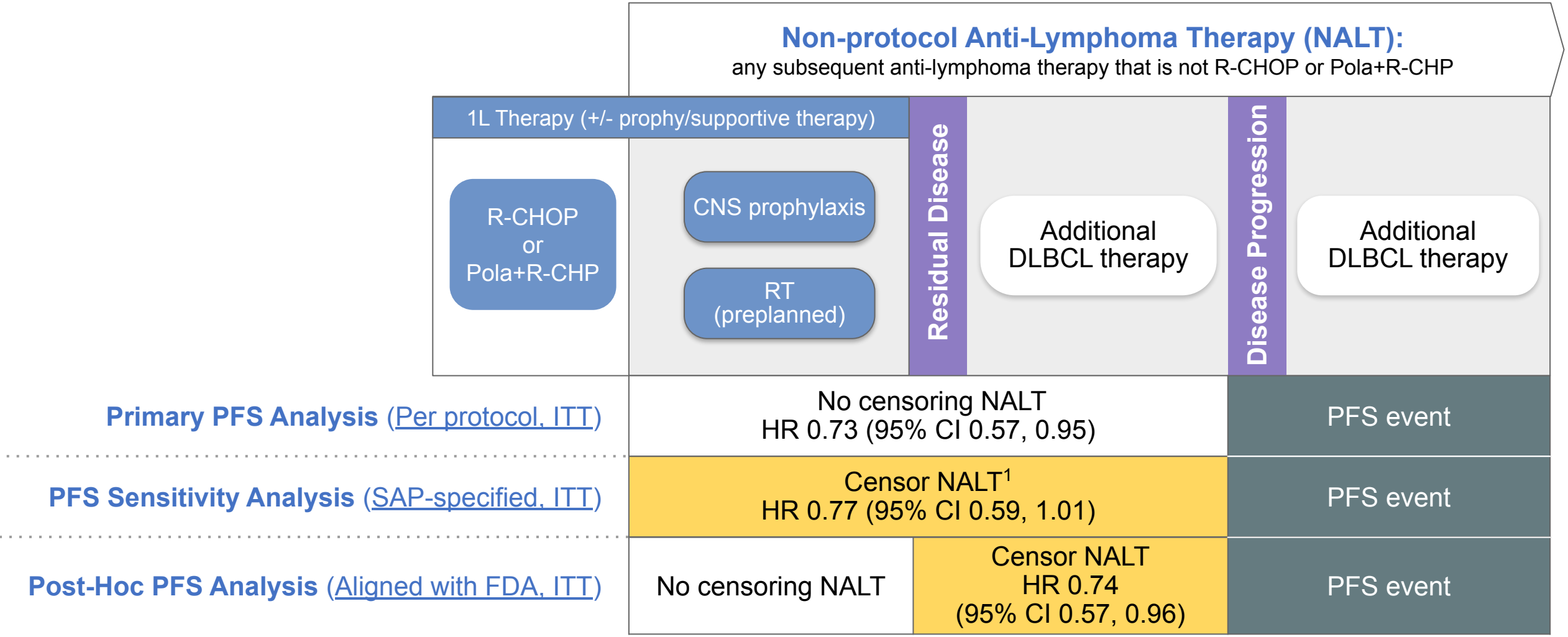
No. of patients at risk

R-CHOP	439	331	284	94	2
Pola+R-CHP	440	354	313	103	NE

CCOD = Clinical Cut-off Date

How do Subsequent Therapies Impact PFS Results?

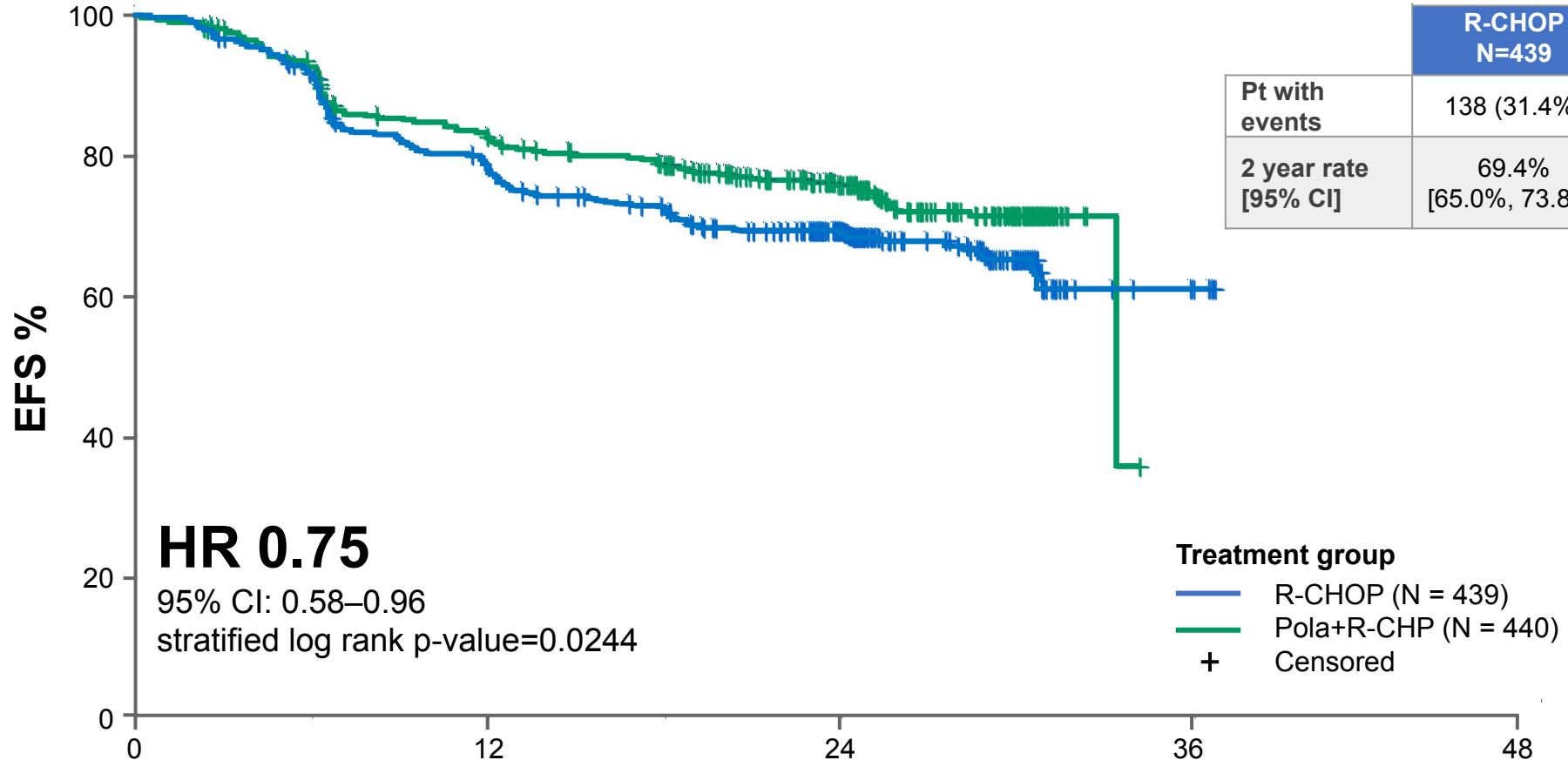
Censoring for therapy beyond 1L SOC is consistent with primary PFS analysis



[1]Excluding pre-planned radiotherapy.
Clinical cut-off date: June 28, 2021

$EFS_{efficacy}$ was Statistically Significant and Consistent with PFS

Events also include NALT given for efficacy and residual disease



	R-CHOP N=439	Pola+R-CHP N=440
Pt with events	138 (31.4%)	112 (25.5%)
2 year rate [95% CI]	69.4% [65.0%, 73.8%]	75.6% [71.5%, 79.7%]

No. of patients at risk

R-CHOP	439	327	218	3	NE
Pola+R-CHP	440	348	243	NE	NE

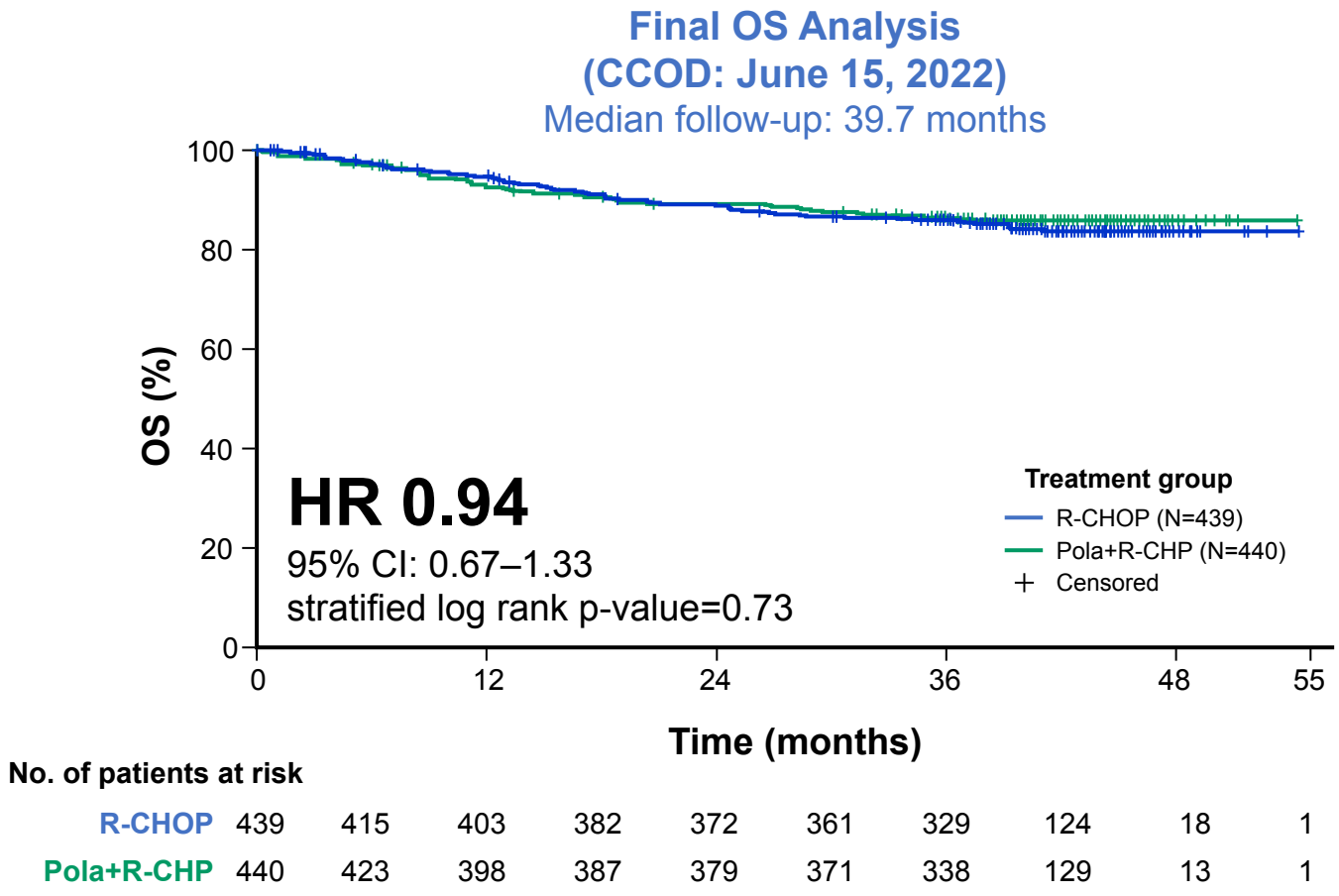
Clinical cut-off date: June 28, 2021

Overall Survival Analyses

Most patients are alive to date

Pre-planned OS analyses	R-CHOP (N=439)	Pola+R-CHP (N=440)
1st Interim Analysis (28.1 months†)		
Patient w/ event, n (%)	57 (13.0)	53 (12.0)
HR [95% CI]	0.94 (0.65, 1.37)	
2nd Interim Analysis (36.1 months†)		
Patient w/ event, n (%)	64 (14.6)	61 (13.9)
HR [95% CI]	0.95 (0.67, 1.35)	
Final Analysis (39.7 months†)		
Patient w/ event, n (%)	67 (15.3)	64 (14.5)
HR [95% CI]	0.94 (0.67, 1.33)	

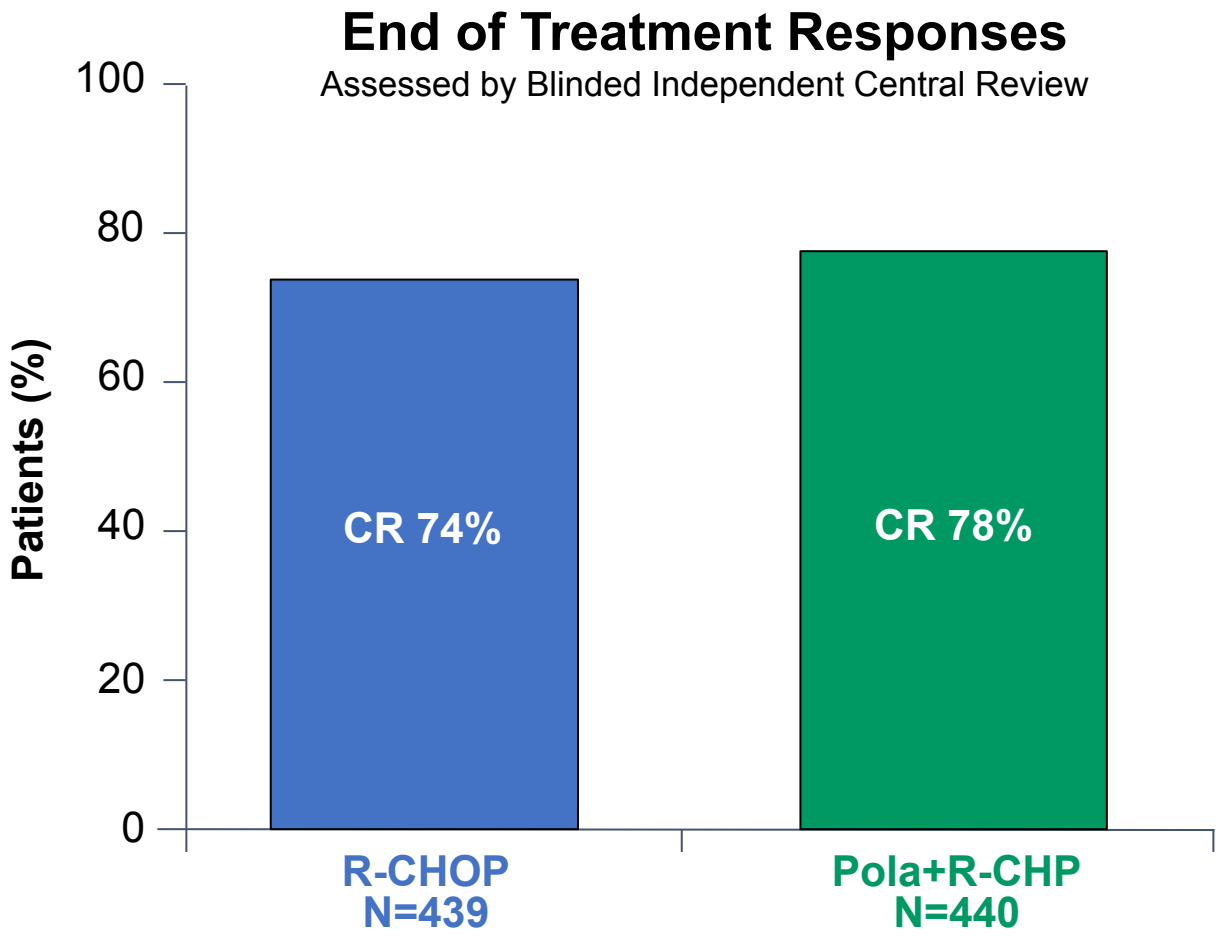
† Median follow up



Clinical cut-off date: 1st Interim, June 28, 2021; 2nd Interim, February 25, 2022; Final Analysis, June 15, 2022.

End of Treatment Complete Response by PET

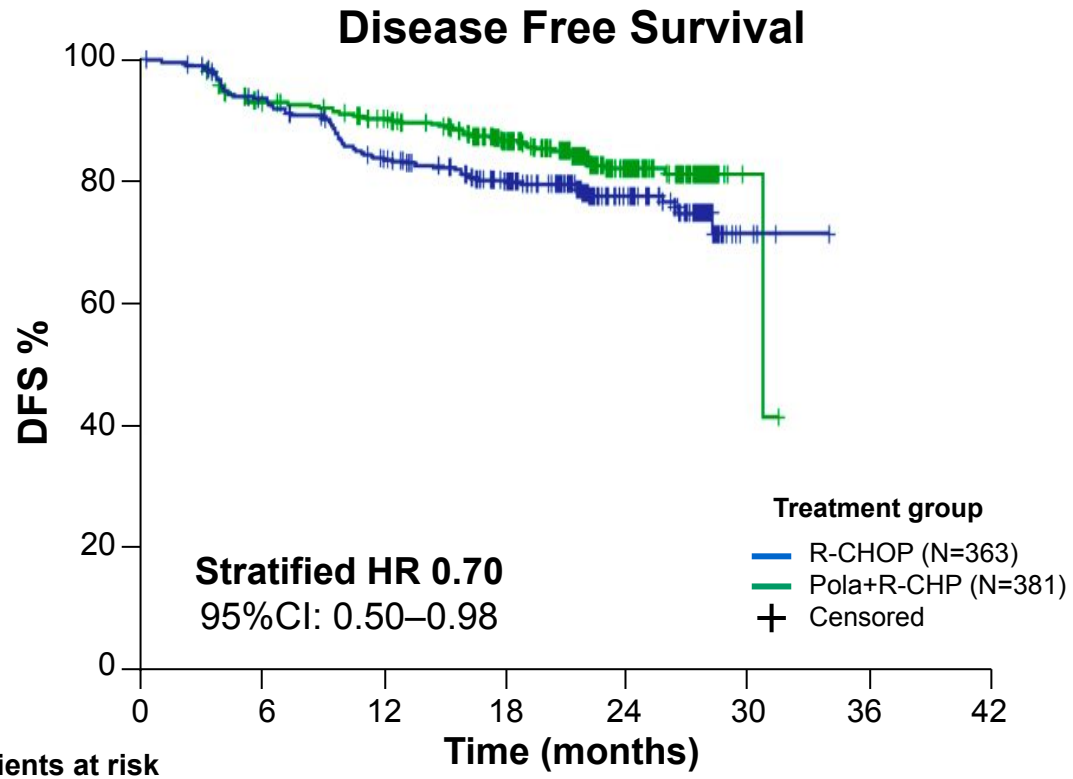
Numerically higher with Pola+R-CHP, not statistically significant



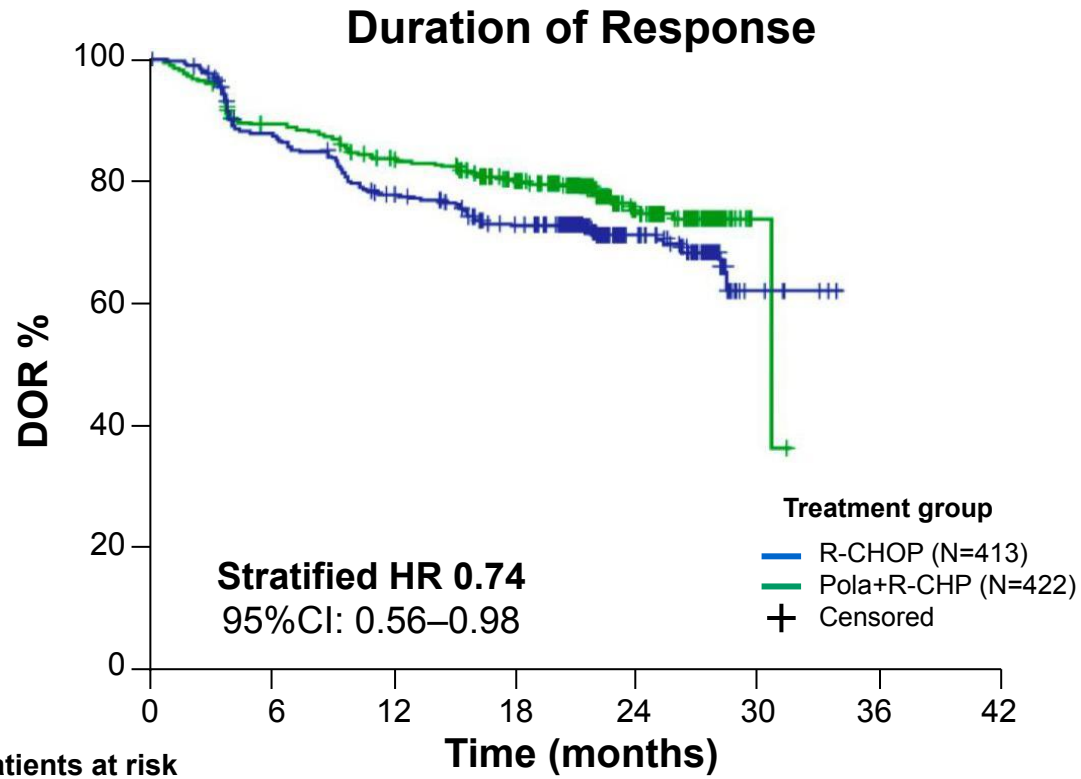
	R-CHOP N=439	Pola+R-CHP N=440
Patient with CR, n (%) [95% CI]	325 (74.0%) [69.7%, 78.1%]	343 (78.0%) [73.8%, 81.7%]
Difference in CR rate [95% CI]	3.9% [-1.9%, 9.7%]	
p-value	0.1557	

Clinical cut-off date: June 28, 2021

Responses are More Durable with Pola+R-CHP



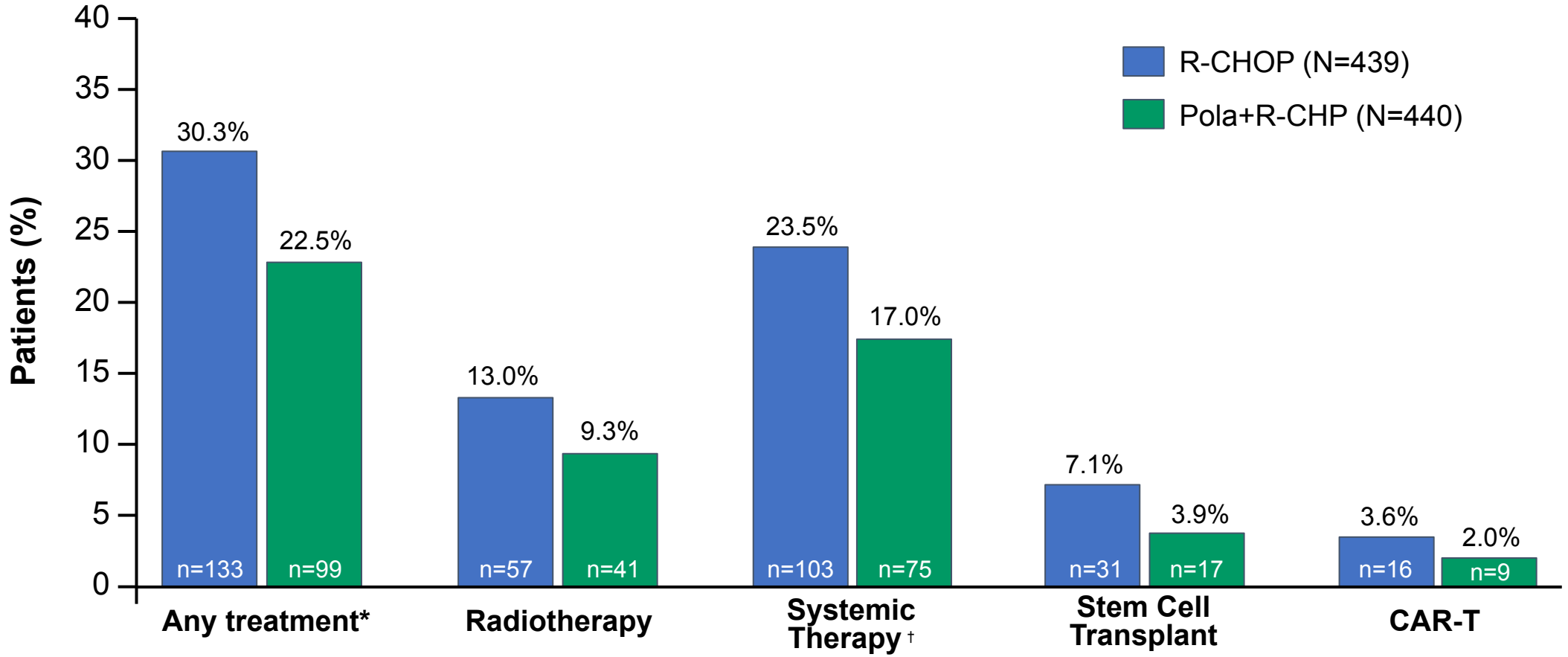
No. of patients at risk								
R-CHOP	363	326	282	238	96	5	NE	NE
Pola+R-CHP	381	342	322	266	106	2	NE	NE



No. of patients at risk								
R-CHOP	413	350	306	272	112	7	NE	NE
Pola+R-CHP	422	367	337	301	119	2	NE	NE

Clinical cut-off date: June 28, 2021

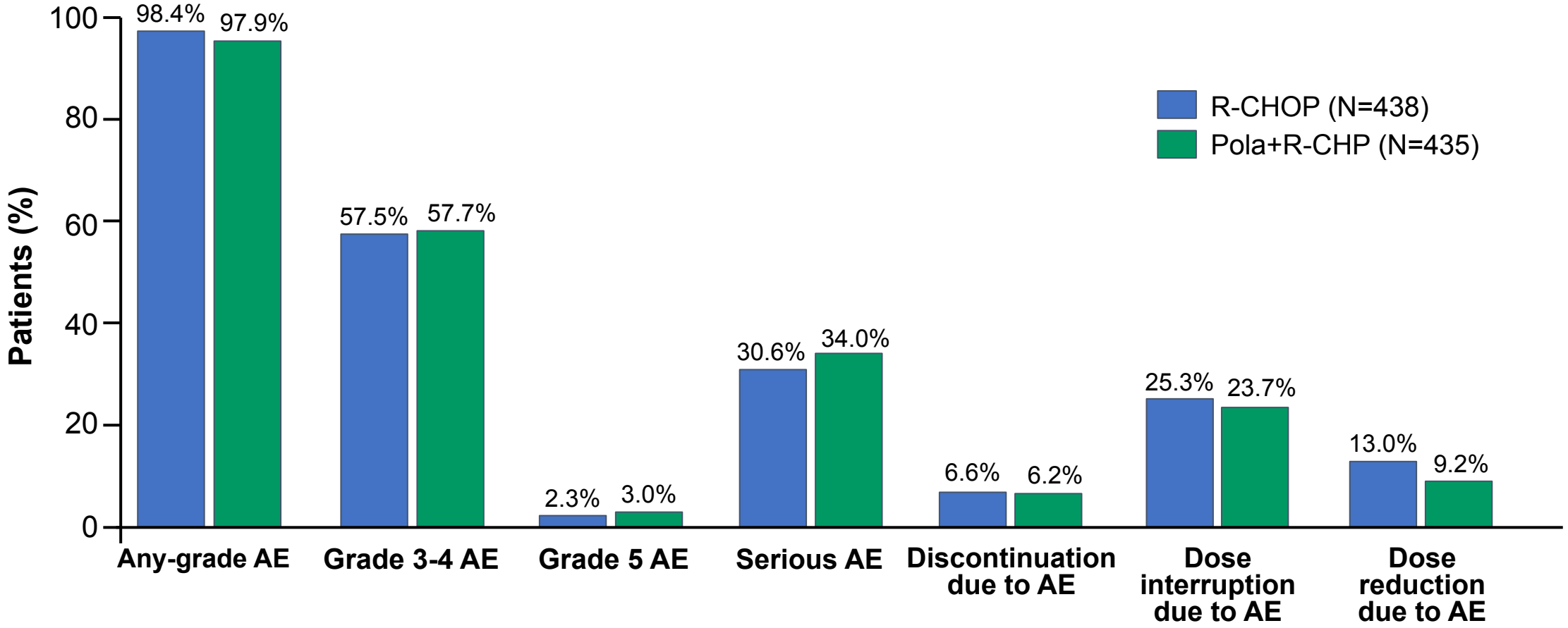
Patients in Pola+R-CHP Arm Required Less Subsequent Lymphoma Therapies



Clinical cut-off date: June 28, 2021. *Subsequent lymphoma treatment was defined as non-protocol anti-lymphoma therapy; †Includes any monotherapy, multi-drug, or cell-based regimen. CAR-T, chimeric antigen receptor T-cell therapy.

SAFETY

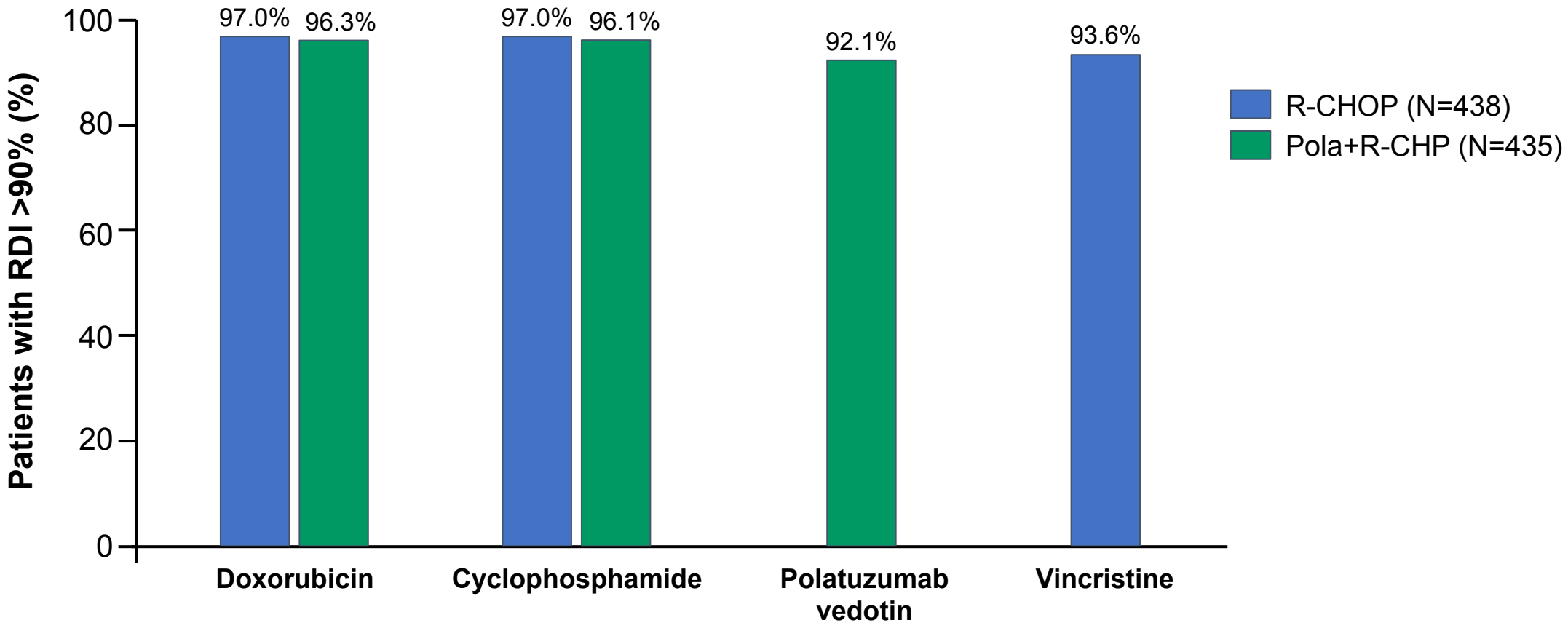
Overall Safety Profile of Pola+R-CHP is Comparable to R-CHOP



Clinical cut-off date: June 28, 2021

Relative Dose Intensity was Maintained with Pola+R-CHP

- Better efficacy outcomes in 1L DLBCL are associated with higher relative dose intensity.[1, 2]



[1] Bataillard EJ, et al. Blood Adv 2021;5(9):2426-2437.
[2] Yamaguchi H, et al. J Clin Exp Hematop 2011;51:1-5.
Clinical cut-off date: June 28, 2021

Most Common Adverse Events are Consistent with R-CHOP

Grade 3-4 AEs were generally comparable between arms and most were associated with myelosuppression

AE, n (%)	R-CHOP (N=438)		Pola+R-CHP (N=435)	
	Any grade	Grade 3–4	Any grade	Grade 3–4
Blood and lymphatic system disorders				
Neutropenia	143 (32.6)	135 (30.8)	134 (30.8)	123 (28.3)
Febrile neutropenia	35 (8.0)	35 (8.0)	62 (14.3)	60 (13.8)
Anemia	114 (26.0)	37 (8.4)	125 (28.7)	52 (12.0)
Nervous system disorders				
Peripheral neuropathy†	236 (53.9)	5 (1.1)	230 (52.9)	7 (1.6)
Gastrointestinal disorders				
Nausea	161 (36.8)	2 (0.5)	181 (41.6)	5 (1.1)
Vomiting	63 (14.4)	3 (0.7)	65 (14.9)	5 (1.1)
Diarrhea	88 (20.1)	8 (1.8)	134 (30.8)	17 (3.9)
Constipation	127 (29.0)	1 (0.2)	125 (28.7)	5 (1.1)
Other				
Fatigue	116 (26.5)	11 (2.5)	112 (25.7)	4 (0.9)
Alopecia	105 (24.0)	1 (0.2)	106 (24.4)	0
Pyrexia	55 (12.6)	0	68 (15.6)	6 (1.4)
Decreased appetite	62 (14.2)	3 (0.7)	71 (16.3)	5 (1.1)

†Data presented here refer to grouped term peripheral neuropathy, which included preferred terms: neuropathy peripheral, peripheral sensory neuropathy, paresthesia, hypoesthesia, polyneuropathy, peripheral motor neuropathy, dysesthesia, neuralgia, peripheral sensorimotor neuropathy, hypotonia, hyporeflexia, neuromyopathy, paresthesia ear, peroneal nerve palsy, skin burning sensation.

Clinical cut-off date: June 28, 2021

Neutropenia and Febrile Neutropenia did not Impact the Delivery of the Treatment

99.1% of all events of neutropenia, including febrile neutropenia, had resolved

- G-CSF prophylaxis was high (93.2% in R-CHOP and 90.1% in Pola+R-CHP).
- No febrile neutropenia was observed after completion of chemotherapy with Cycle 6 in both arms.

	R-CHOP N=438	Pola+R-CHP N=435
Neutropenia (all grade),* n (%)	187 (42.7)	200 (46)
Grade 3/4	176 (40.2)	182 (41.8)
Grade 5	0	0
Serious	37 (8.4)	50 (11.5)
Febrile neutropenia	35 (8.0)	62 (14.3)
Serious	28 (6.4)	43 (9.9)
AE leading to any study treatment:		
Discontinuation	0	2 (0.5)
Dose reduction	7 (1.6)	7 (1.6)
Dose interruption	28 (6.4)	23 (5.3)

* Includes the following preferred terms: neutropenia, febrile neutropenia, neutrophil count decreased, neutropenic sepsis, agranulocytosis, and neutropenic colitis.

Clinical cut-off date: June 28, 2021

Fatal Infections were Similar Between Treatment Arms

- Most infections were low grade; no fatal opportunistic infections were reported.

	R-CHOP N=438	Pola+R-CHP N=435
Infections (all grade), n (%)	187 (42.7)	216 (49.7)
Grade 3/4	49 (11.2)	61 (14.0)
Grade 5	6 (1.4)	5 (1.1)
Serious	45 (10.3)	61 (14.0)
AE leading to any study treatment:		
Discontinuation	10 (2.3)	7 (1.6)
Dose reduction	4 (0.9)	1 (0.2)
Dose interruption	22 (5.0)	27 (6.2)

Clinical cut-off date: June 28, 2021

Peripheral Neuropathy Profile is Similar Between Treatment Arms

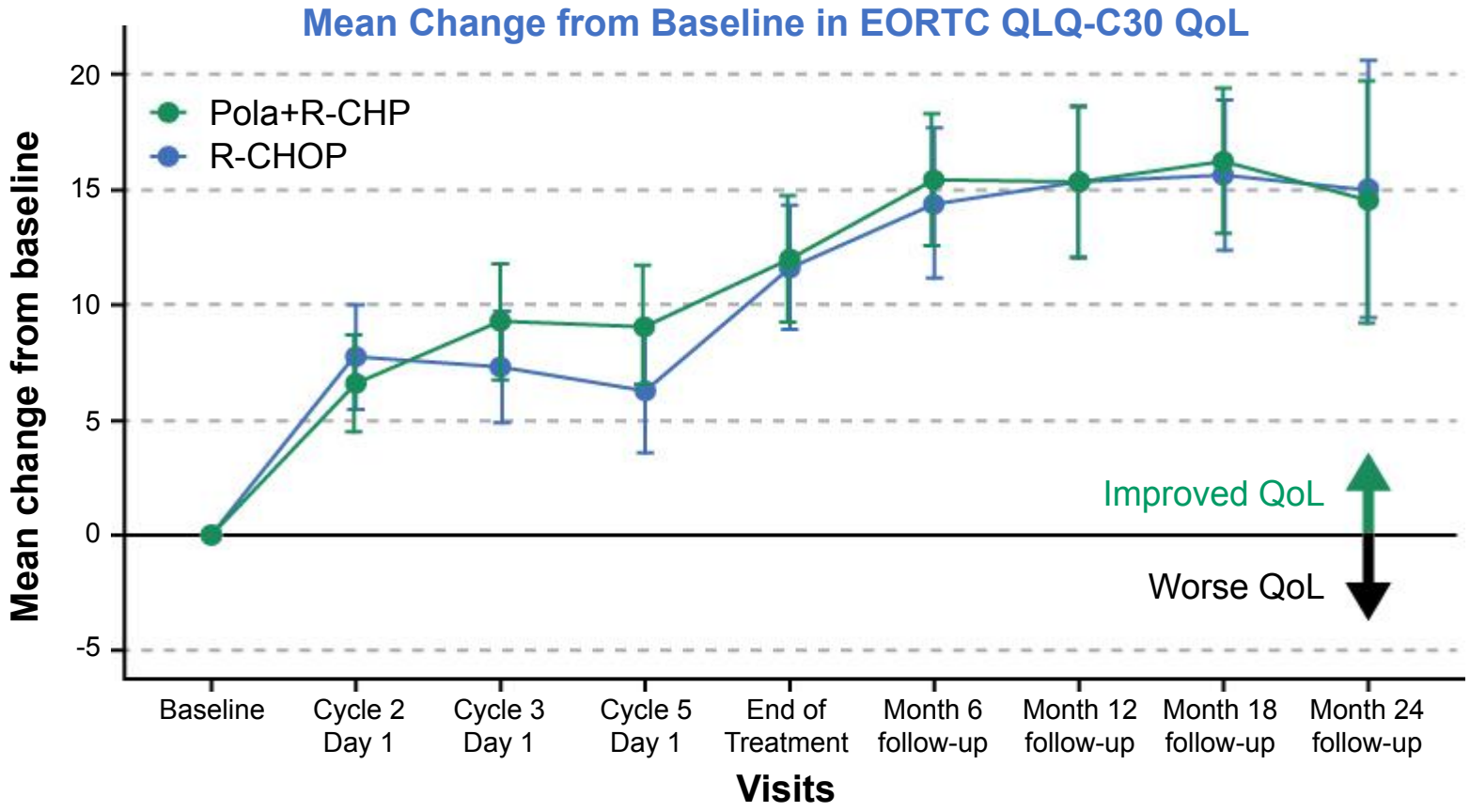
	R-CHOP N=438	Pola+R-CHP N=435
Any-grade peripheral neuropathy,* n (%)	236 (53.9)	230 (52.9)
Grade 1	163 (37.2)	170 (39.1)
Grade 2	68 (15.5)	53 (12.2)
Grade 3	5 (1.1)	7 (1.6)
Grade 4/5	0	0
AE leading to vincristine or polatuzumab vedotin:		
Discontinuation	9 (2.1)	3 (0.7)
Dose reduction	35 (8)	17 (3.9)
Dose interruption	3 (0.7)	3 (0.7)

*Peripheral neuropathy included preferred terms: neuropathy peripheral, peripheral sensory neuropathy, paraesthesia, hypoaesthesia, polyneuropathy, peripheral motor neuropathy, dysaesthesia, neuralgia, peripheral sensorimotor neuropathy, hypotonia, hyporeflexia, neuromyopathy, paraesthesia ear, peroneal nerve palsy, skin burning sensation.

Clinical cut-off date: June 28, 2021

Global Quality of Life was Similar Between Treatment Arms

- Scales only collected before disease progression or relapse.
- Quality of life improves while on treatment, and more so after treatment completion.
  - Patients have similar quality of life, consistent with similar safety and tolerability of regimens.



Clinical cut-off date: June 28, 2021
EORTC QLQ-C30, European Organisation For Research And Treatment Of Cancer Quality of Life Questionnaire Core 30
Mean QoL scores at baseline: Pola+R-CHP (59.8) and R-CHOP (62.1). Higher scores represent better quality of life; Error bars represent 95% confidence interval.

Conclusion of Benefit/Risk of Polatuzumab Vedotin + R-CHP for the Treatment of Previously Untreated DLBCL

- POLARIX met its primary endpoint showing superior PFS.
- A more durable PFS and higher proportion without disease progression at 2-years with Pola+R-CHP is meaningful for patients.
  - Avoidance relapse and progression.
  - Less subsequent anti-lymphoma treatment was required in the Pola+R-CHP arm.
- Pola+R-CHP and R-CHOP have a comparable safety profile.
- Totality of data demonstrates a clinically meaningful benefit with Pola+R-CHP.

DLBCL Clinical Perspective

Jonathan W. Friedberg, MD, MMSc

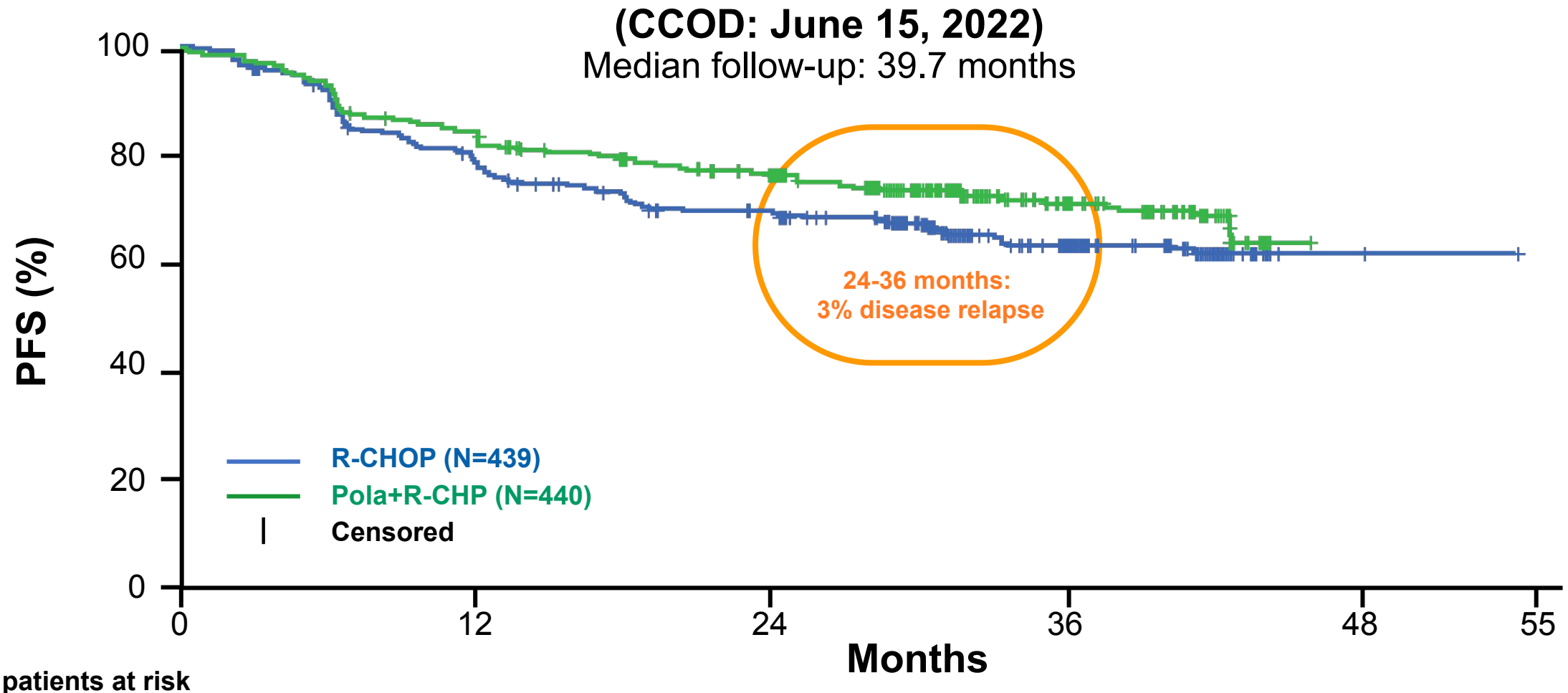
Samuel Durand Professor and Director

Wilmot Cancer Institute, University of Rochester

What to Make of POLARIX Data?

- Diffuse large B-cell lymphoma is curable with medical therapy.
- R-CHOP has been the standard treatment for more than 20 years.
- POLARIX is the first large randomized positive trial demonstrating PFS benefit.

PFS from POLARIX



No. of patients at risk

R-CHOP	439	331	284	94	2	1
Pola+R-CHP	440	354	313	103	NE	NE

Conclusions

- Ultimate goal of treating DLBCL is to maximize cure rate, and avoid toxic, costly salvage therapy.

- Pola+R-CHP accomplishes this, and should be approved for upfront therapy of DLBCL.

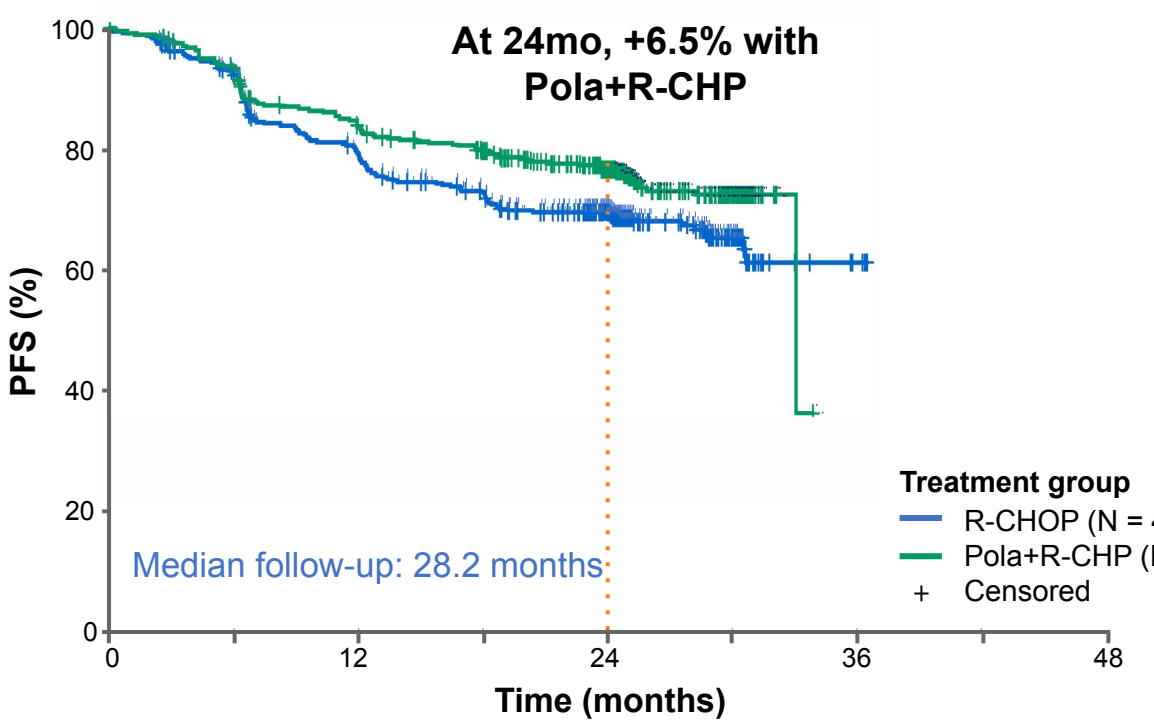
Sponsor's Position on Polatuzumab Vedotin for 1L DLBCL

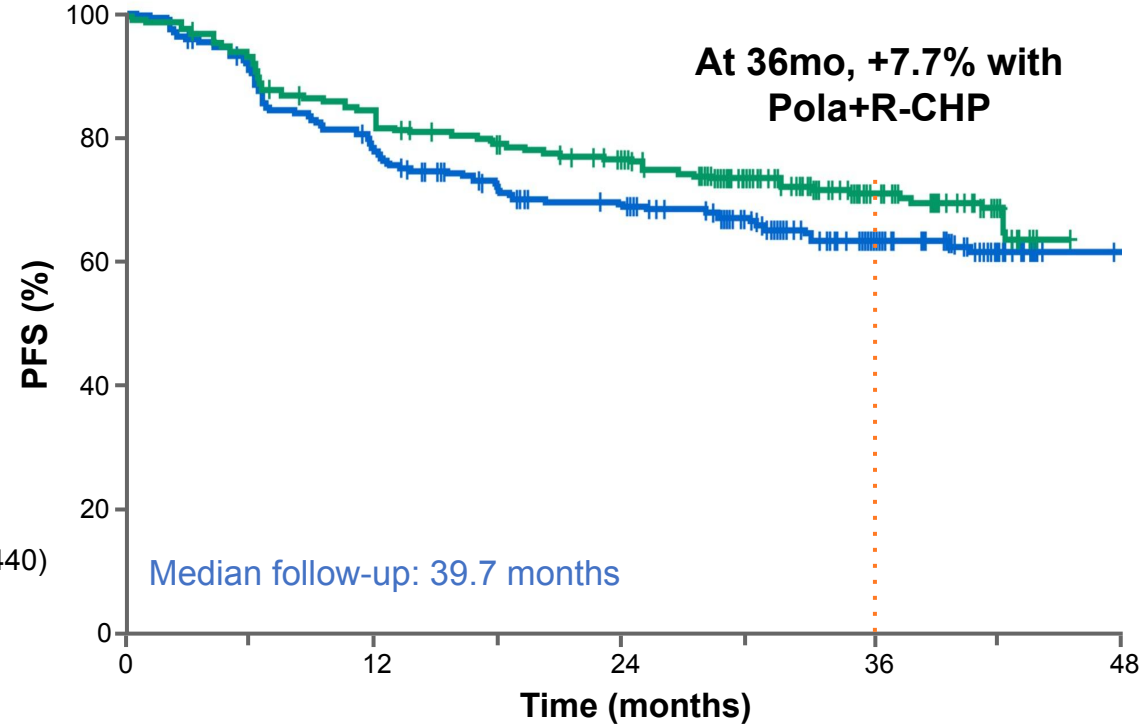
Charles Fuchs, MD
Senior Vice President
Global Head of Oncology & Hematology Drug Development
Genentech

The Evolving Nature of Overall Survival in DLBCL Trials

- Following 1L, second and later line therapies allow patients to live much longer with relapsed disease.
- OS as an endpoint requires very long follow-up for 1L DLBCL.
- POLARIX consistently shows no evidence of a detriment to OS.

PFS Remains Consistent with an Additional 1 Year of Follow-up

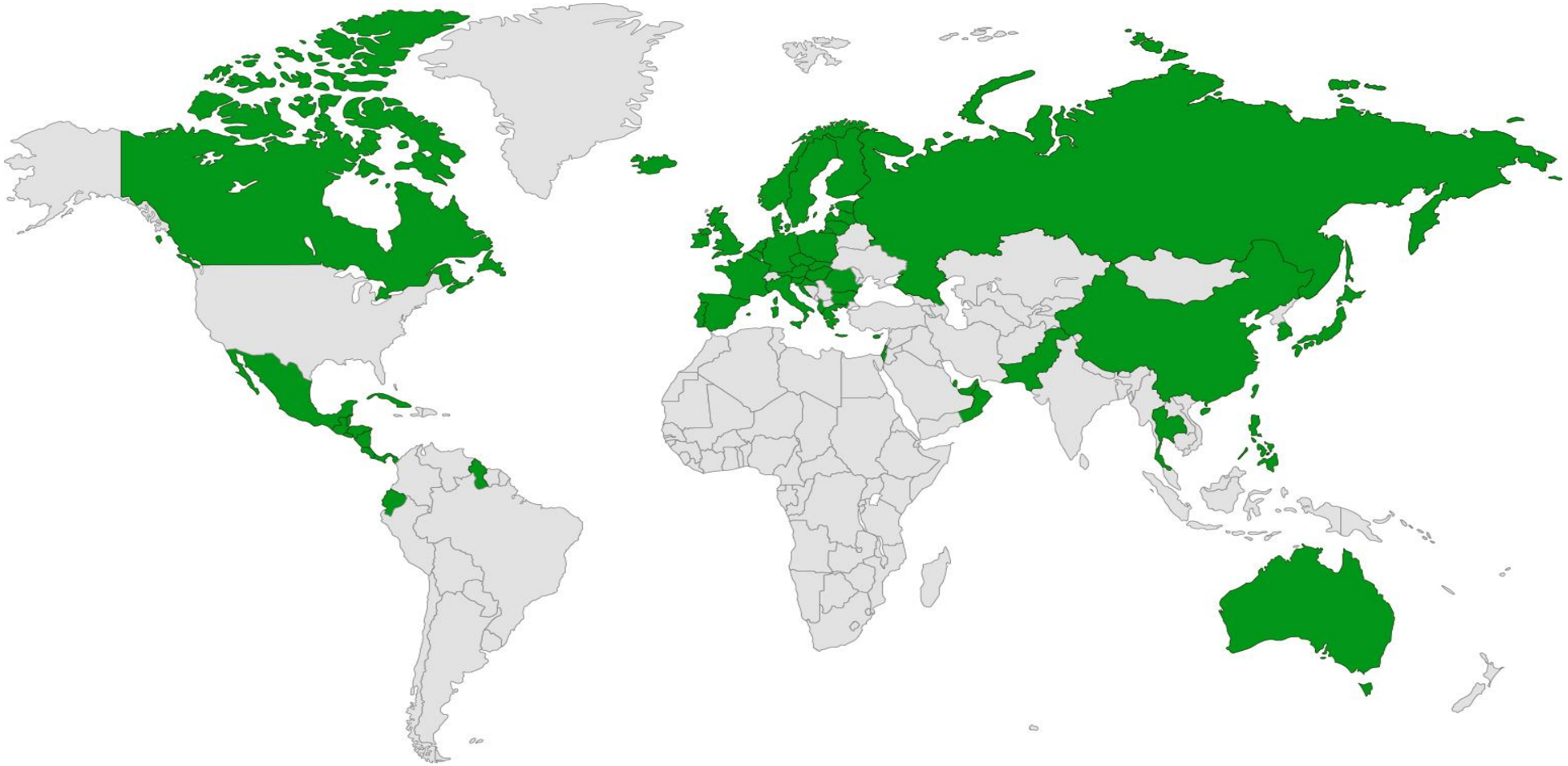




Assuming 27,360 1L DLBCL patients in the U.S., a 6.5% improvement in 2-year PFS could prevent progression or relapse in over 1,700 patients annually.

Global Regulatory Approvals for 1L DLBCL

Polatuzumab vedotin in combination with R-CHP is currently approved for the treatment of 1L DLBCL in >60 countries including in the European Union, United Kingdom, Canada, Japan, and China.



Sponsor's Position on Polatuzumab Vedotin for 1L DLBCL

- **Polatuzumab Vedotin + R-CHP offers the best chance of cure for 1L patients.**
- The magnitude of benefit in PFS as documented by the POLARIX trial is clinically meaningful.
- The safety of the Pola+R-CHP regimen is manageable and comparable to R-CHOP.
- **The favorable benefit/risk profile of Pola+R-CHP supports approval for patients with 1L DLBCL in the US.**

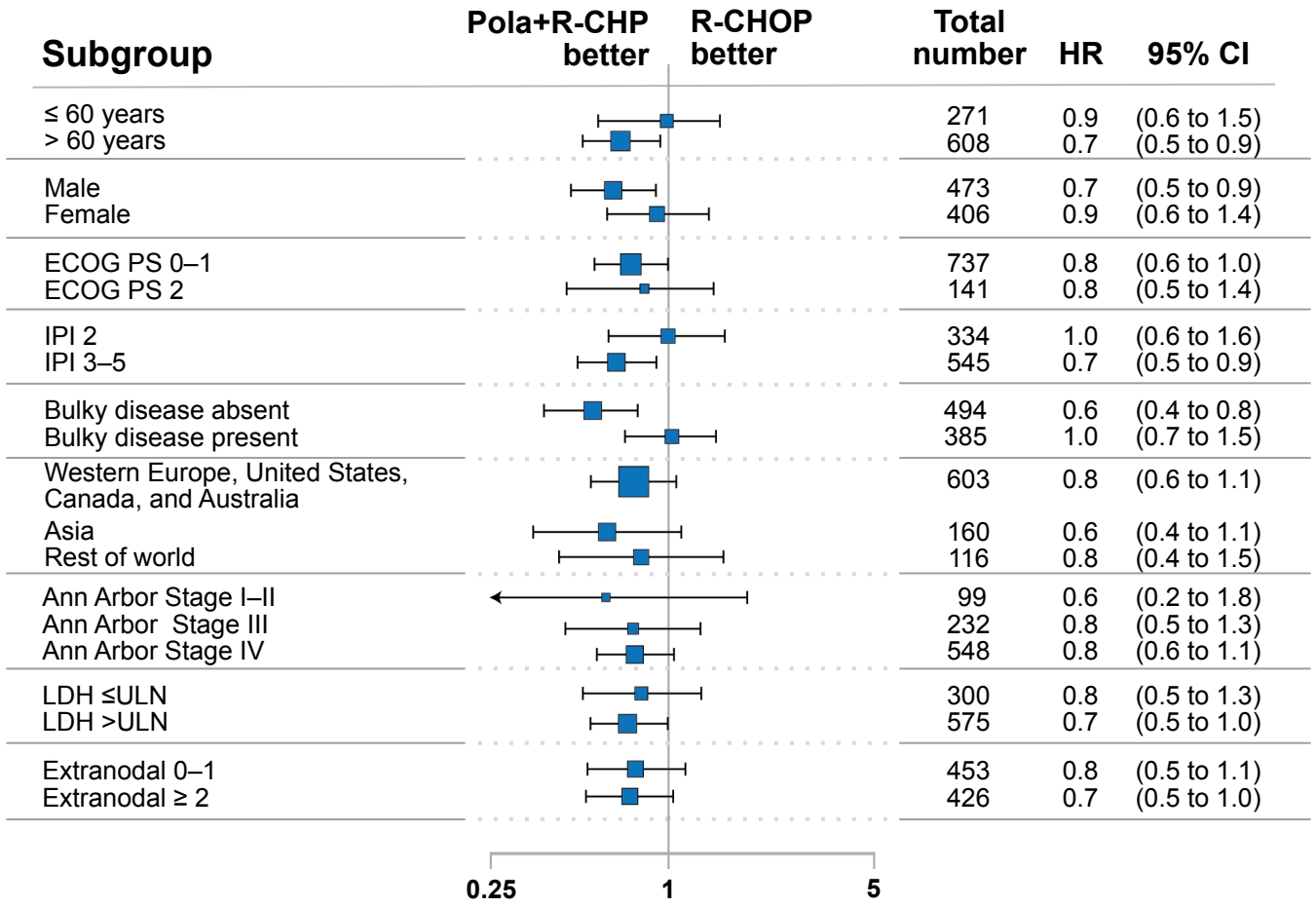
Polatuzumab vedotin (POLIVY®)

Presentation to the Oncologic Drugs Advisory Committee

BLA 761121/S-008

Genentech, Inc.

PFS: Subgroup Analysis Largely Favors Pola+R-CHP



- Majority of evaluated subgroups in univariate analysis favored Pola+R-CHP (HR estimate < 1).
- All subgroups are underpowered, resulting in wide confidence intervals.

Clinical cut-off date: June 28, 2021

Deaths During 8 to 18 Months

No clear trends among reasons for death during 8 to 18 months

	R-CHOP N=439	Pola+R-CHP N=440
Number of deaths, n	22	25
Median age (range), yr	70.5 (46-78)	67 (37-80)
Reason for Death, n		
Progressive disease	14	16
Adverse Event	0	0
Other*	8	9

*Other = Death not due to AE from study treatment or disease progression

Deaths due to ‘Other’, 8 to 18 Months

Deaths not known to be due to study treatment, or due to disease progression

R-CHOP (n=8)		
Age	Study Day	Cause of Death
64	276	Death (no further details)
61	304	Death (no further details)
73	413	Stroke
70	413	COVID-19 infection
76	461	Septic shock
76	500	Cardiac arrest
73	515	Second cancer
59	528	Acute interstitial pneumonia

Pola+R-CHP (n=9)		
Age	Study Day	Cause of Death
65	250	Death (no further details)
78	251	Death (no further details)
77	294	Sepsis
68	340	No additional details
58	341	Colitis, lymphoma, hepatic insufficiency
66	386	Pulmonary sepsis
75	506	COVID-19
45	518	Sepsis
52	536	Death (no further details)

POLARIX: Evaluation of Body Weight on Safety

Adverse Event	Incidence: n (%)	
	≤ 100 kg (N=397)	>100 kg (N=43)
Fatal AEs	11 (2.8)	2 (4.7)
SAEs	136 (34.3)	14 (32.6)
Grade 3+ AEs	245 (61.7)	22 (51.2)

Analysis of Pola + R-CHP arm only.
Cut off date: June 28, 2021.

Similar incidence of AEs for patients > 100 kg compared to patients ≤ 100 kg.

Neuropathy Symptoms are More Common with Vincristine

- Between Cycles 2 and Cycle 6, higher neuropathy rates (between 8% and 12.4%) observed with vincristine; dose modifications were similarly higher in R-CHOP compared to Pola+R-CHP.