POLATUZUMAB-RCHP FOR NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA

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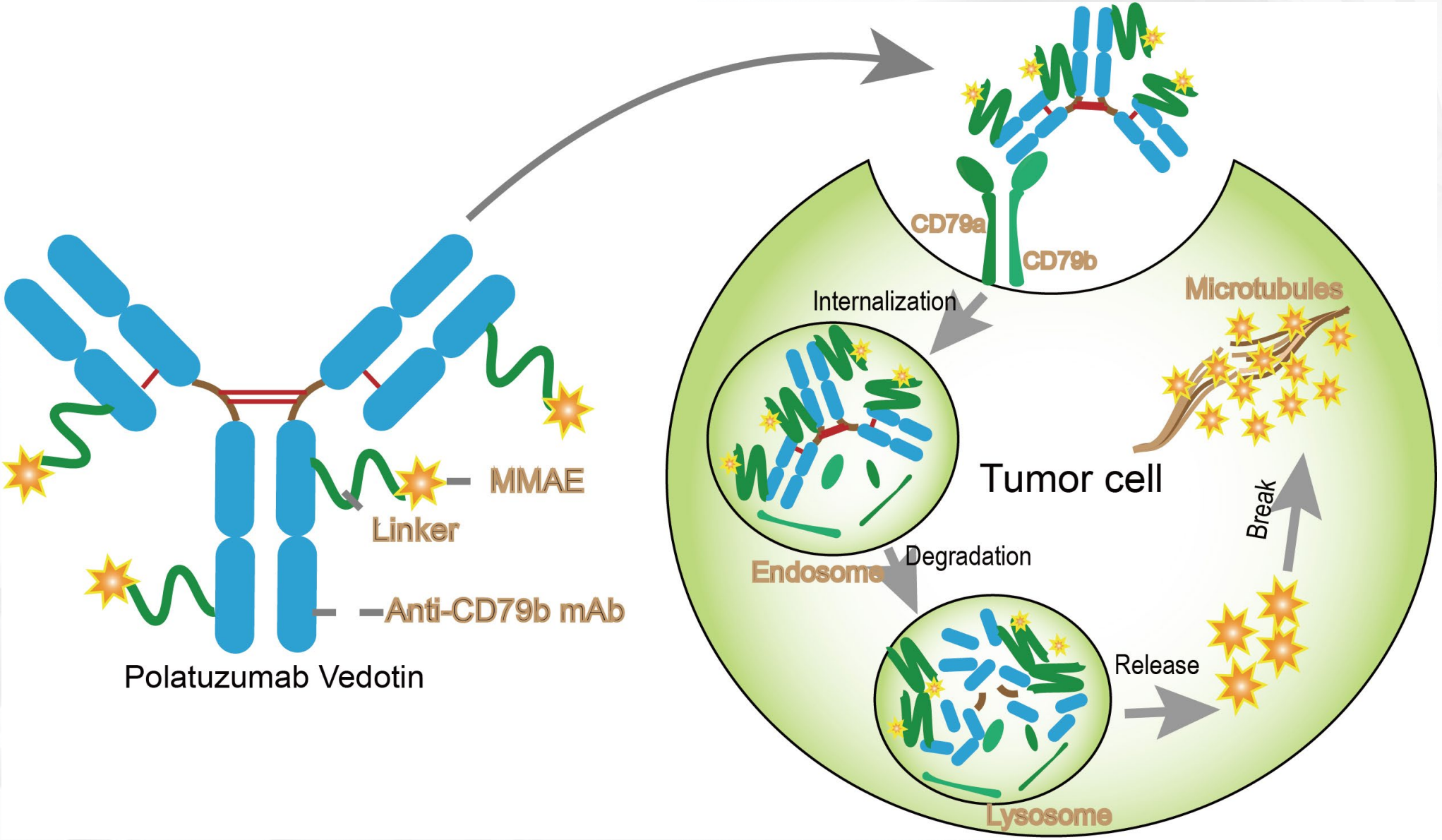
POLATUZUMAB : ANTIBODY DRUG CONJUGATE TARGETING CD79B



POLARIX: RANDOMIZED, DOUBLE BLIND PHASE 3 TRIAL OF RCHOP VS. POLATUZUMAB-RCHP

ELIGIBILITY CRITERIA

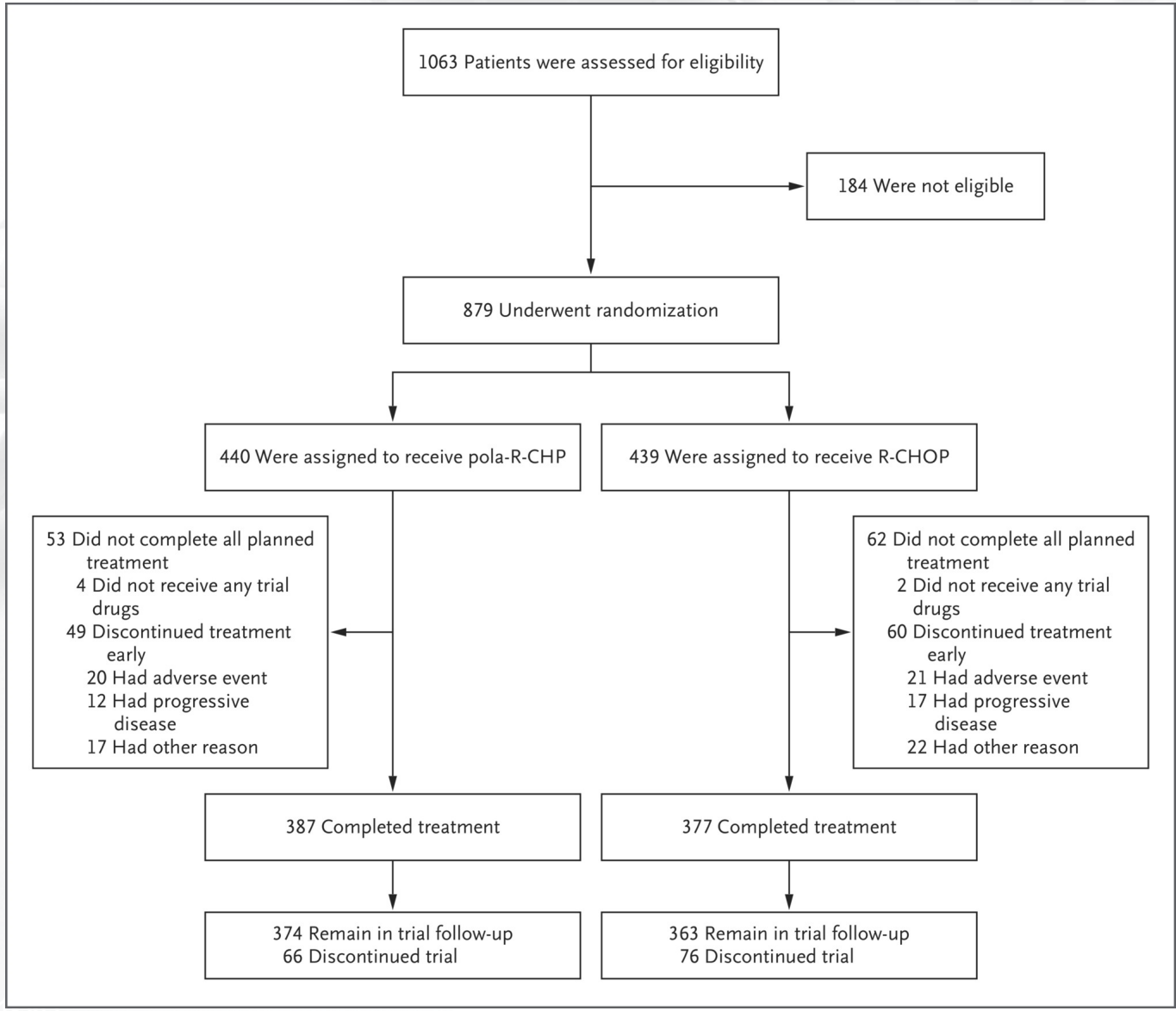
- 18-80 years
- EGOG PS 0-2
- IPI score 2-5
- Untreated DLBCL (GCB & non-GCB), HGBCL including double hit/expressor, T-cell rich B-cell
- No prior indolent NHL; no PMBCL, grey zone, primary cutaneous
- No CNS involvement, no hep C

RCHP-POLATUZUMB Q21 D x 6 cycles + 2 R alone cycles

- Polatuzumab 1.8 mg/kg D1
- Rituximab 375 mg/m2 D1
- Cyclophosphamide 750 mg/m2 D1
- Doxorubicin 50 mg/m2 D1
- Placebo 1.4 mg/m2 D1
- Prednisone 100 mg D1-5
- GCSF
- *IT prophylaxis and consolidative XRT to bulky sites per physician*

RCHOP x 6 cycles + 2 R alone cycles

- Placebo 1.8 mg/kg D1
- Rituximab 375 mg/m2 D1
- Cyclophosphamide 750 mg/m2 D1
- Doxorubicin 50 mg/m2 D1
- Vincristine 1.4 mg/m2 D1 (Capped 2 mg)
- Prednisone 100 mg D1-5
- GCSF
- *IT prophylaxis and consolidative XRT to bulky sites per physician*



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PATIENT DEMOGRAPHICS & ENDPOINTS

- **Primary Endpoint**
  - Investigator assessed PFS
    - Investigator determined progression, relapse or death counted as events
    - AIM to detect 23% lower risk of PD, relapse or death with Pola-RCHP (HR 0.77)
- **Secondary Endpoints**
  - Investigator assessed EFS
    - Events defined as PD, relapse, death, initiation of any treatment, or biopsy confirmed residual disease at end of treatment.
  - PET-based CR at end of treatment determined by central review
  - OS

Demographics	Pola-RCHP (n=440)	RCHOP (n=439)
Median age	65 (19-80)	66 (19-80)
> 60	300 (68.2)	308 (70.2)
Female	201 (45.7%)	205 (46.7%)
Stage I-II	47 (10.7)	52 (11.8)
Stage III-IV	393 (89.3)	387 (88.2)
EN sites ≥ 2	213 (48.4)	213 (48.5)
Bulky ≥ 7.5 cm	193 (43.9)	192 (43.7)
Elevated LDH	291 (66.1)	284 (64.7)
IPI 2	167 (38)	167 (38)
IPI 3-5	273 (62)	272 (62)
COO: GCB ABC Unclassified	184/330 (55.8) 102/330 (30.9) 44/330 (33.3)	168/338 (49.7) 119/338 (35.2) 51/338 (15.1)
Double expressor	139/362 (38.4)	151/366 (41.3)
Double Hit	26/331 (7.9)	19/334 (5.7)

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TREATMENT EXPOSURE

Pola-RCHP	RCHOP
97.1% completed 6 cycles	88.5% completed 6 cycles
88% completed 6 cycles + 2 additional Rituximab	85.9% completed 6 cycles + 2 additional Rituximab
Median dose intensity of Rituximab, doxorubicin, & cyclophosphamide > 99%	Median dose intensity of Rituximab, doxorubicin, & cyclophosphamide > 99%
6.2% discontinued one Pola-RCHP drug 9.2% required dose reductions	6.6% discontinued one RCHOP drug 13% required dose reductions
19 (4.4%) discontinued polatuzumab	22 (5.0%) discontinued vincristine
GCSF utilized in 90.1%	GCSF utilized in 93.2%
11 (2.5%) patients received pre-planned XRT	18 (4.1%) patients received pre-planned XRT
72 (16.4%) received IT prophylaxis	86 (19.6%) received IT prophylaxis

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EFFICACY

Median F/up: 28.2 mos (1-43)

2-year PFS:
Pola-RCHP: 76.7% (95% CI 72.7-80.8)

RCHOP: 70.2% (95% CI 65.8-74.6)

27% lower risk of PD, relapse or death with Pola-RCHP compared to RCHOP (HR 0.73, 95% CI 0.57 to 0.95, p=0.02)

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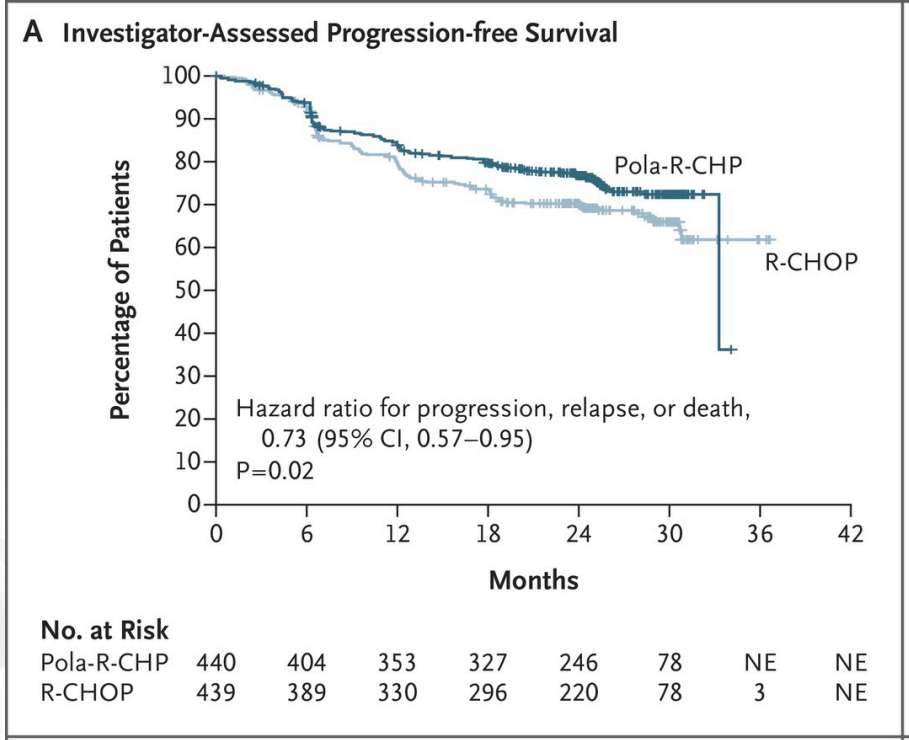

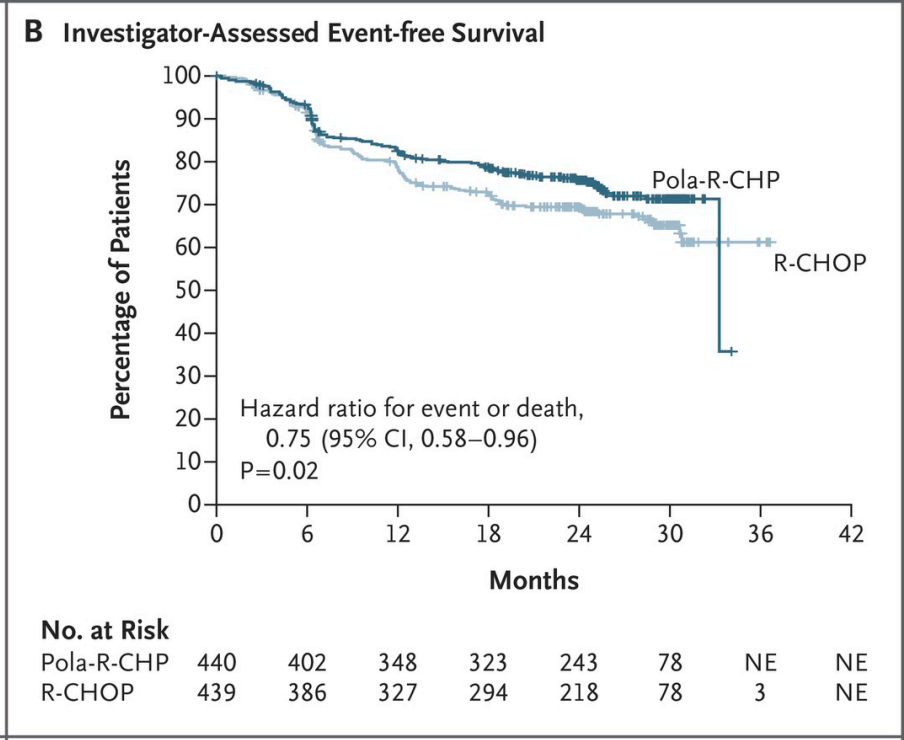

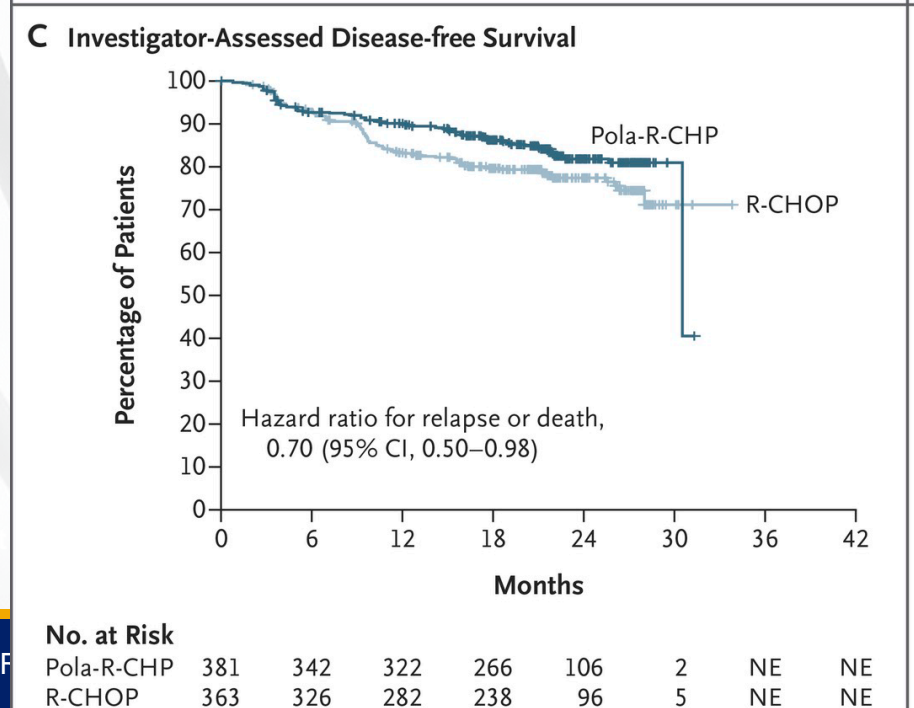

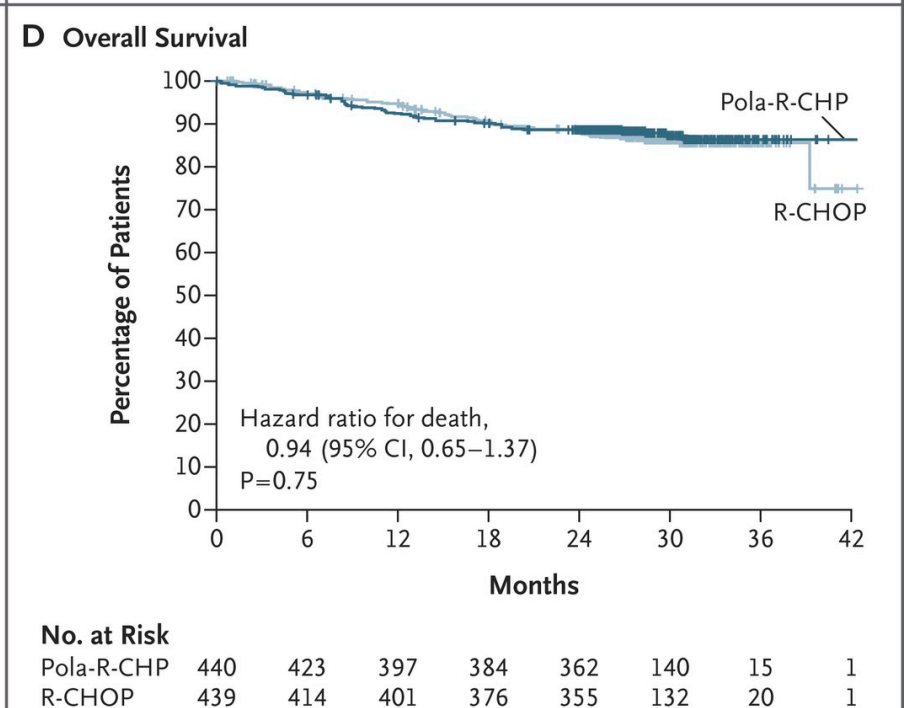

EFFICACY

Pola-RCHP	RCHOP
3% CNS RELAPSE	2.7% CNS RELAPSE
99 (22.5%) subsequent therapy for PD or relapse	133 (30.3%) subsequent therapy for PD or relapse
3.9% AutoSCT 2.0% CART	7.1% AutoSCT 3.6% CART

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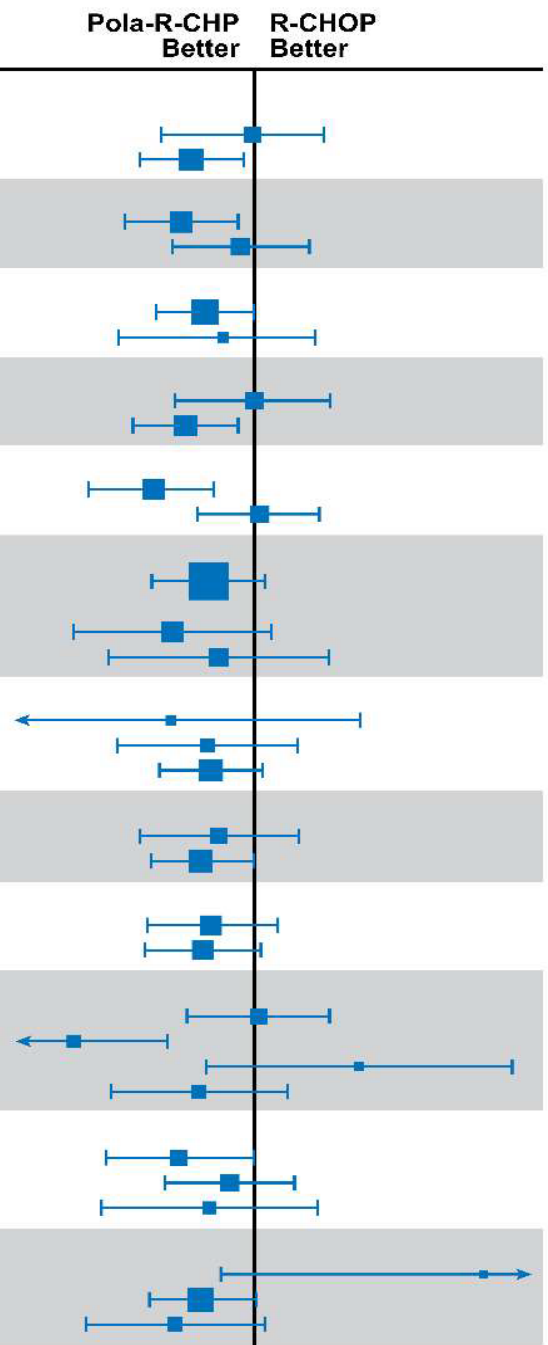
Table 2. Efficacy (Intention-to-Treat Population).

Variable	Pola-R-CHP (N=440)	R-CHOP (N=439)	Hazard Ratio (95% CI)	P Value
Progression-free survival*				
Patients who died or had progression or relapse — no. (%)	107 (24.3)	134 (30.5)	0.73 (0.57–0.95)	0.02
Earliest event — no.				
Death	19	20		
Progression or relapse	88	114		
Estimate at 1 year (95% CI) — %	83.9 (80.4–87.4)	79.8 (75.9–83.6)		
Estimate at 2 years (95% CI) — %	76.7 (72.7–80.8)	70.2 (65.8–74.6)		
Event-free survival*				
Patients who died, had progression or relapse, or had other events — no. (%)†	112 (25.5)	138 (31.4)	0.75 (0.58–0.96)	0.02
Earliest event — no.				
Death	18	20		
Progression or relapse	86	106		
Other†	8	12		
Estimate at 2 years (95% CI) — %	75.6 (71.5–79.7)	69.4 (65.0–73.8)		
Response status at treatment completion‡				
Overall response — no. (%)	376 (85.5)	368 (83.8)		
Complete response	343 (78.0)	325 (74.0)		
Partial response	33 (7.5)	43 (9.8)		
Stable disease — no. (%)	8 (1.8)	6 (1.4)		
Progressive disease — no. (%)	22 (5.0)	28 (6.4)		
Not evaluated or data missing — no. (%)	34 (7.7)	37 (8.4)		
Overall survival				
Patients who died — no. (%)	53 (12.0)	57 (13.0)	0.94 (0.65–1.37)	0.75
Estimate at 2 years (95% CI) — %	88.7 (85.7–91.6)	88.6 (85.6–91.6)		
Disease-free survival§				
No. of patients who could be evaluated¶	381	363		
Patients who died or had relapse — no. (%)	62 (16.3)	79 (21.8)	0.70 (0.50–0.98)	
Earliest event — no.				
Death	8	13		
Relapse	54	66		

* Events of progression or relapse were assessed by the investigator.
† Other events are subsequent therapy for lymphoma or biopsy-confirmed residual disease after treatment.

SUBGROUP ANALYSIS

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							
≤ULN	300	146	78·9	154	75·6	0·8	(0·5 to 1·3)
>ULN	575	291	75·4	284	67·2	0·7	(0·5 to 1·0)
No. of extranodal sites							
0–1	453	227	80·2	226	74·5	0·8	(0·5 to 1·1)
≥2	426	213	73·0	213	65·8	0·7	(0·5 to 1·0)
Cell-of-origin							
GCB	352	184	75·1	168	76·9	1·0	(0·7 to 1·5)
ABC	221	102	83·9	119	58·8	0·4	(0·2 to 0·6)
Unclassified	95	44	73·0	51	86·2	1·9	(0·8 to 4·5)
Unknown	211	110	73·8	101	64·3	0·7	(0·4 to 1·2)
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)
Unknown	214	109	78·5	105	66·4	0·6	(0·4 to 1·1)



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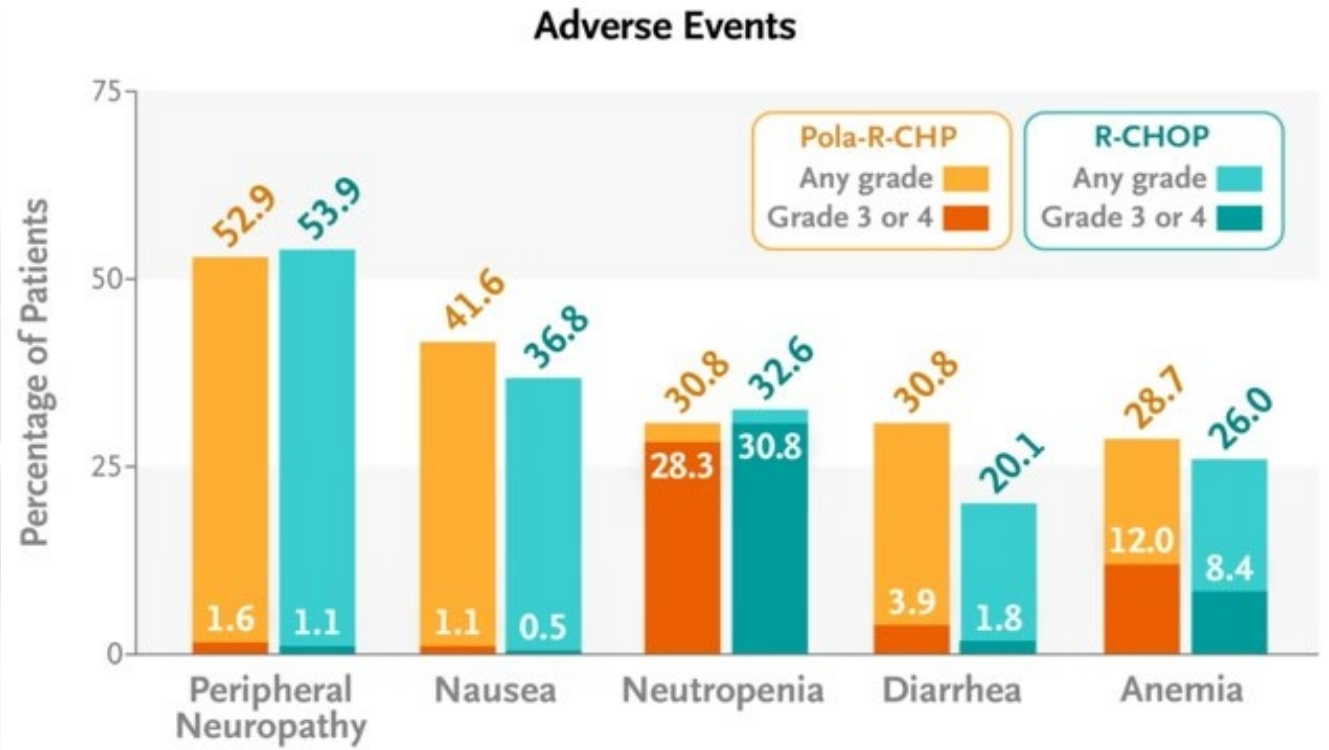
SAFETY

Table 3. Adverse Events during the Treatment Period (Safety Population).*

Adverse Event	Pola-R-CHP (N=435)		R-CHOP (N=438)	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
	number of patients (percent)			
Peripheral neuropathy†	230 (52.9)	7 (1.6)	236 (53.9)	5 (1.1)
Nausea	181 (41.6)	5 (1.1)	161 (36.8)	2 (0.5)
Neutropenia	134 (30.8)	123 (28.3)	143 (32.6)	135 (30.8)
Diarrhea	134 (30.8)	17 (3.9)	88 (20.1)	8 (1.8)
Anemia	125 (28.7)	52 (12.0)	114 (26.0)	37 (8.4)
Constipation	125 (28.7)	5 (1.1)	127 (29.0)	1 (0.2)
Fatigue	112 (25.7)	4 (0.9)	116 (26.5)	11 (2.5)
Alopecia	106 (24.4)	0	105 (24.0)	1 (0.2)
Decreased appetite	71 (16.3)	5 (1.1)	62 (14.2)	3 (0.7)
Pyrexia	68 (15.6)	6 (1.4)	55 (12.6)	0
Vomiting	65 (14.9)	5 (1.1)	63 (14.4)	3 (0.7)
Febrile neutropenia	62 (14.3)	60 (13.8)	35 (8.0)	35 (8.0)
Headache	56 (12.9)	1 (0.2)	57 (13.0)	4 (0.9)
Cough	56 (12.9)	0	53 (12.1)	0
Decreased weight	55 (12.6)	4 (0.9)	52 (11.9)	1 (0.2)
Asthenia	53 (12.2)	7 (1.6)	53 (12.1)	2 (0.5)
Dysgeusia	49 (11.3)	0	57 (13.0)	0

* Shown are the most common adverse events, which were defined as adverse events of any grade that occurred in at least 12% of the patients in either treatment group. These adverse events are *Medical Dictionary for Regulatory Activities*, version 24.0, preferred terms. Adverse events of any grade were reported in 426 patients (97.9%) in the pola-R-CHP group and in 431 patients (98.4%) in the R-CHOP group; adverse events of grade 3 or higher in 264 (60.7%) and 262 (59.8%), respectively; serious adverse events in 148 (34.0%) and 134 (30.6%), respectively; and adverse events of grade 5 in 13 (3.0%) and 10 (2.3%), respectively.

† Peripheral neuropathy includes the following preferred terms from the system organ class of peripheral neuropathy: peripheral neuropathy, peripheral sensory neuropathy, paresthesia, hypoesthesia, polyneuropathy, peripheral motor neuropathy, dysesthesia, neuralgia, peripheral sensorimotor neuropathy, hypotonia, hyporeflexia, neuromyopathy, ear paresthesia, peroneal nerve palsy, and skin burning sensation.



Median time to onset of neuropathy: 2.3 mos Pola-RCHP
1.9 mos RCHOP

Median time to resolution of neuropathy: 4.0 mos Pola-RCHP
4.5 mos RCHOP

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COMPARISON

	Pola-RCHP	RCHOP
EFFICACY (PFS)	**2YR PFS 76.7%** ***27% LOWER RISK OF PD, RELAPSE, or DEATH (HR 0.73, 95% CI: 0.57-0.95, p=0.02)***	**2YR PFS 70.2%**
EFFICACY (OS)	**2YR 88.7% (95% CI 85.7-91.6)** *F/up of 28 months is too short to see OS benefit, and 2-year PFS is a recognized surrogate for OS in DLBCL*	**2YR 88.6% (85.6-91.6)**
SUBGROUPS (NOT ADEQUATELY POWERED)**	MORE FAVORABLE IN HIGHER RISK PATIENTS (> 60, IPI 3-5, stage III-IV, ABC) **NO DATA IN IPI 0,1** **NOT RECOMMENDED DOUBLE HIT (?Pola-REPCH – Lynch, ASCO 2022, abstr 7546)**	CONSIDER IN LOWER RISK PATIENTS (≤ 60, IPI 2, Stage I-II, GCB) **FAVORED FOR IPI 0,1** **NOT RECOMMENDED DOUBLE HIT**
DOSE INTENSITY	> 99% R, doxorubicin, cyclophosphamide 91.7% planned Polatuzumab doses administered	> 99% R, doxorubicin, cyclophosphamide 88.5% planned vincristine doses administered
TOXICITY	Neuropathy 52.9% (Grade 3-4: 1.6%) FN 14.3% (Grade 3-4: 13.8%) Diarrhea 30.8% (Grade 3-4: 3.9%)	Neuropathy 53.9% (Grade 3-4 1.1%) FN 8% (Grade 3-4: 8%) Diarrhea 20.1% (Grade 3-4: 1.8%)

POLA-RCHP VS RCHOP

NUMBER NEEDED TO TREAT	**15 patients** receive Pola-RCHOP for 1 patient to have improved PFS
EXPENSE	**Not known** ($105 per mg = $13,230 per 1.8 mg/kg dose in 70 kg patient) Adds $79,920 to RCHP costs for 6 cycles 1 cost-effectiveness analyses concluded that Pola-RCHP is cost effective with a gain of 0.81 QALYs with increased cost of $66,218 added to standard RCHOP (*Kambhampati, et al. ASCO Annual Meeting, 2022, abstract 7568)*
FDA APPROVAL	**?** Some insurance companies are approving Pola-RCHP

RECOMMEND POLA-RCHP FOR ALL NEWLY DIAGNOSED DLBCL (INCLUDING DOUBLE EXPRESSOR), AGE 18-80 (DEFINITELY > 60), STAGE III-IV or IPI 2-5