ABCL-073

Polatuzumab Vedotin plus Rituximab, Cyclophosphamide, Doxorubicin, and Prednisone (Pola-R-CHP) Versus Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone (R-CHOP) Therapy in Patients with Previously Untreated Diffuse Large B-cell Lymphoma (DLBCL): Results from the Phase III POLARIX Study

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Summary

R-CHOP is the current standard of care for patients with newly diagnosed DLBCL; however, approximately 40% of patients are not cured and an unmet need remains for patients with previously untreated disease.

POLARIX is a Phase III study of Pola-R-CHP vs R-CHOP in patients with previously untreated DLBCL.

The proportion of patients surviving at 2 years was significantly higher with Pola-R-CHP (76.7%) compared with R-CHOP (70.2%); an absolute difference of 6.5%.

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

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

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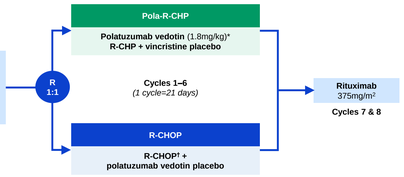
Background

- The current standard of care for patients with newly diagnosed diffuse large B-cell lymphoma (DLBCL) is R-CHOP; however, approximately 40% of patients are not cured,[1,2] and an unmet need remains for patients with previously untreated disease.
- Polatuzumab vedotin, a CD79b-targeting antibody–drug conjugate, is approved in relapsed/refractory DLBCL in combination with bendamustine and rituximab, and has also demonstrated promising first-line activity when combined with rituximab, cyclophosphamide, doxorubicin, and prednisone (Pola-R-CHP) in a Phase Ib/II study.[3]
- Here we report the efficacy and safety analysis from the Phase III POLARIX study (NCT03274492),[4] which compared Pola-R-CHP vs R-CHOP in patients with previously untreated DLBCL.

Study design

- Double-blind, placebo-controlled, international study of patients with previously untreated DLBCL and an International Prognostic Index (IPI) of 2–5.
- Patients were randomised 1:1 to receive six cycles of Pola-R-CHP (with a vincristine placebo) or R-CHOP (with a polatuzumab vedotin placebo); all patients also received two additional cycles of rituximab (**Figure 1**).
- The primary efficacy endpoint was investigator-assessed progression-free survival (PFS).
- Key secondary endpoints included investigator-assessed event-free survival (EFS), independent review committee-assessed complete response (CR) rate at end-of-treatment by positron emission tomography-computed tomography (PET-CT), disease-free survival (DFS), overall survival (OS) and safety.

Figure 1. Study design.



*IV on Day 1; †R-CHOP: IV rituximab 375mg/m², cyclophosphamide 750mg/m², doxorubicin 50mg/m², and vincristine 1.4mg/m² (max. 2mg) on Day 1, plus oral prednisone 100mg once daily on Days 1–5.
DLBCL, diffuse large B-cell lymphoma; IPI, International prognostic index; IV, intravenous; ECOG PS, Eastern Cooperative Oncology Group performance status; Pola-R-CHP, polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and prednisone; R, randomised; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.
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Patient population

- Overall, 879 patients were randomised, 440 to Pola-R-CHP and 439 to R-CHOP (**Table 1**).
- Median age was 65 (range 19–80) years, and the majority of patients had an IPI 3–5 (62.0%).

Table 1. Baseline characteristics.

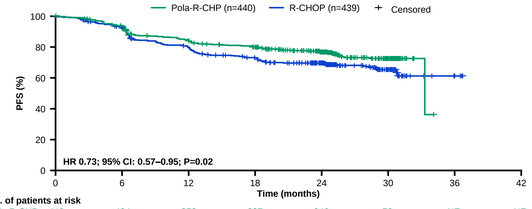
ITT population	Pola-R-CHP (n=440)	R-CHOP (n=439)
Age in years, median (range)	65 (19–80)	66 (19–80)
Sex, n (%)		
Male	239 (54)	234 (53)
ECOG PS, n (%)		
0–1	374 (85)	363 (83)
2	66 (15)	75 (17)
Presence of bulky disease (≥7.5cm), n (%)	193 (44)	192 (44)
Elevated LDH, n (%)	291 (66)	284 (65)
Time from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

*In the Pola-R-CHP and R-CHOP groups, respectively, the numbers of patients evaluable for COO 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; †MYC-rearrangement with BCL2 and/or BCL6 rearrangement.
ABC, activated B-cell; COO, cell-of-origin; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in situ hybridization; GCB, germinal centre B-cell; IHC, immunohistochemistry; IPI, International prognostic index; ITT, intent-to-treat; LDH, lactate dehydrogenase; Pola-R-CHP, polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.
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Pola-R-CHP significantly improved PFS vs R-CHOP

- The 2-year PFS rate was 76.7% (95% confidence interval [CI]: 72.7–80.8) with Pola-R-CHP vs 70.2% (95% CI: 65.8–74.6) with R-CHOP (Δ=6.5%).
- Pola-R-CHP demonstrated a 27.0% reduction in the relative risk of disease progression, relapse or death vs R-CHOP (hazard ratio [HR] 0.73; 95% CI: 0.57–0.95; P=0.02; **Figure 2**).

Figure 2. Investigator-assessed progression-free survival.



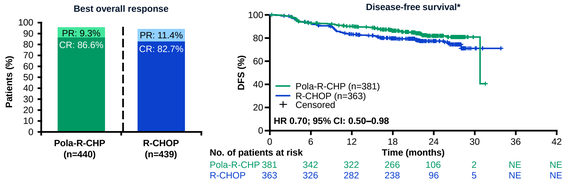
No. of patients at risk								
Pola-R-CHP	440	404	353	327	246	78	NE	NE
R-CHOP	439	389	330	296	220	78	3	NE

ITT population. Data cut-off: 28 June 2021; median 28.2 months' follow-up.
CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; NE, not evaluable; PFS, progression-free survival; Pola-R-CHP, polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.
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Key secondary endpoints

- EFS favored Pola-R-CHP compared with R-CHOP (HR 0.75; 95% CI: 0.58–0.96; P=0.02).
- The end-of-treatment PET-CT CR rate was not significantly different with Pola-R-CHP vs R-CHOP (78.0% vs 74.0%; P=0.16); however, DFS suggested responses were more durable with Pola-R-CHP than with R-CHOP (HR 0.70; 95% CI: 0.50–0.98; **Figure 3**).
- There was no difference in OS between treatment arms (HR 0.94; 95% CI: 0.65–1.37; P=0.75; **Figure 4**).

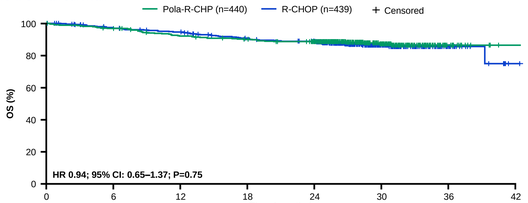
Figure 3. Response rates and disease-free survival.



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

ITT population. Data cut-off: 28 June 2021; median 28.2 months' follow-up. *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.
CI, confidence interval; CR, complete response; DFS, disease-free survival; HR, hazard ratio; ITT, intent-to-treat; NE, not evaluable; Pola-R-CHP, polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and prednisone; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.
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Figure 4. Overall survival.



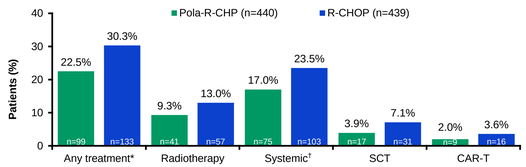
No. of patients at risk								
Pola-R-CHP	440	423	397	384	362	140	15	1
R-CHOP	439	414	401	376	355	132	20	1

ITT population. Data cut-off: 28 June 2021; median 28.2 months' follow-up. CI, confidence interval; HR, hazard ratio; ITT, intent-to-treat; OS, overall survival; Pola-R-CHP, polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and prednisone; PR, partial response; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.
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Subsequent treatment for lymphoma

- At the time of data cut-off, 99 (23%) and 133 (30%) patients in the Pola-R-CHP and R-CHOP arms, respectively, had received at least one subsequent anti-lymphoma therapy.
- Fewer patients in the Pola-R-CHP than the R-CHOP arm received subsequent anti-lymphoma therapies across various treatment modalities (**Figure 5**).

Figure 5. Proportion of patients receiving subsequent therapies.



Data cut-off: 28 June 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; Pola-R-CHP, polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone; SCT, stem cell transplant.

Safety summary

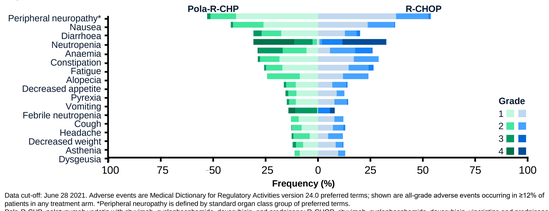
- Safety profiles were similar with Pola-R-CHP and R-CHOP (**Table 2**).
- The most common grade 3 or 4 adverse events were neutropenia (28.3% in the Pola-R-CHP group and 30.8% in the R-CHOP group), febrile neutropenia (13.8% and 8.0%, respectively), and anemia (12.0% and 8.4%, respectively, **Figure 6**).
- The frequency and severity of peripheral neuropathy were similar for Pola-R-CHP vs R-CHOP (any grade, 52.9% vs 53.9%; grade 2–3, 13.8% vs 16.7%).

Table 2. Adverse events during treatment period.

n, (%)	Pola-R-CHP (n=435)	R-CHOP (n=438)
Any grade AEs	426 (97.9)	431 (98.4)
Grade 3–4	251 (57.7)	252 (57.5)
Grade 5	13 (3.0)	10 (2.3)
Serious AEs	148 (34.0)	134 (30.6)
AEs leading to:		
Discontinuation of any study drug	27 (6.2)	29 (6.6)
Polatuzumab vedotin / vincristine	19 (4.4)	22 (5.0)
Dose reduction of any study drug	40 (9.2)	57 (13.0)

Safety population. Data cut-off: 28 June 2021.
AE, adverse event; Pola-R-CHP, polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

Figure 6. 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.
Pola-R-CHP, polatuzumab vedotin with rituximab, cyclophosphamide, doxorubicin, and prednisone; R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone.

Conclusions

- Pola-R-CHP significantly prolongs PFS compared with R-CHOP (HR 0.73) in patients with intermediate- or high-risk previously untreated DLBCL.
- The proportion of patients surviving at 2 years was significantly higher with Pola-R-CHP compared with R-CHOP (76.7% vs 70.2%, respectively); an absolute difference of 6.5%.
- The safety profiles of Pola-R-CHP and R-CHOP were comparable.
- These results support the use of Pola-R-CHP in the initial management of patients with DLBCL.

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Disclosures

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Mehta-Shah:** Advisory Committee/Consultancy: Bristol-Myers Squibb: Consultancy; Celgene: Consultancy; Genentech, Inc.: Consultancy; Gilead: Consultancy; Janssen: Consultancy; Kite: Consultancy; Merck: Consultancy; Novartis: Consultancy; Pharmacyclics: Consultancy; Seattle Genetics: Consultancy; Takeda: Consultancy; Verastem: Consultancy; Xencor: Consultancy; Research Funding; AbbVie: Consultancy; Acerta: Consultancy; Adaptive: Consultancy; Bristol-Myers Squibb: Consultancy; Celgene: Consultancy; Epizyme: Consultancy; Genentech, Inc.: Consultancy; Gilead: Consultancy; Janssen: Consultancy; Karyopharm: Consultancy; Kite: Consultancy; Merck: Consultancy; Morphosys: Consultancy; Novartis: Consultancy; Pharmacyclics: Consultancy; Seattle Genetics: Consultancy; Takeda: Consultancy; Verastem: Consultancy; Xencor: Consultancy; **L. Oberic:** Advisory Committee/Consultancy: Abbvie: Consultancy; Honoraria; Celgene: Consultancy; Honoraria; Gilead: Consultancy; Honoraria; Janssen: Consultancy; Honoraria; Roche: Consultancy; Honoraria; Speakers Bureau; Abbvie: Consultancy; Honoraria; Celgene: Consultancy; Honoraria; Gilead: Consultancy; Honoraria; Janssen: Consultancy; Honoraria; Roche: Consultancy; Honoraria; **A. Chauchet:** Advisory Committee/Consultancy: Abbvie: Consultancy; Honoraria; Gilead: Consultancy; Honoraria; Janssen: Consultancy; Honoraria; Roche: Consultancy; Honoraria; Speakers Bureau; Abbvie: Consultancy; Honoraria; Gilead: Consultancy; Honoraria; Janssen: Consultancy; Honoraria; Roche: Consultancy; Honoraria; **W. Jurczak:** Advisory Committee/Consultancy: Abbvie: Consultancy; Honoraria; Astellas: Consultancy; Honoraria; AstraZeneca: Consultancy; Honoraria; Beigene: Consultancy; Honoraria; Bristol-Myers Squibb: Consultancy; Honoraria; Celgene: Consultancy; Honoraria; Gilead: Consultancy; Honoraria; Janssen: Consultancy; Honoraria; Merck: Consultancy; Honoraria; Novartis: Consultancy; Honoraria; Roche: Consultancy; Honoraria; Takeda: Consultancy; Honoraria; Speakers Bureau; Abbvie: Consultancy; Honoraria; Astellas: Consultancy; Honoraria; AstraZeneca: Consultancy; Honoraria; Beigene: Consultancy; Honoraria; Bristol-Myers Squibb: Consultancy; Honoraria; Celgene: Consultancy; Honoraria; Gilead: Consultancy; Honoraria; Janssen: Consultancy; Honoraria; Merck: Consultancy; Honoraria; Novartis: Consultancy; Honoraria; Roche: Consultancy; Honoraria; Takeda: Consultancy; Honoraria; **Y. Song:** Advisory Committee/Consultancy: Abbvie: Consultancy; Honoraria; Astellas: Consultancy; Honoraria; AstraZeneca: Consultancy; Honoraria; Beigene: Consultancy; Honoraria; Bristol-Myers Squibb: Consultancy; Honoraria; Celgene: Consultancy; Honoraria; Gilead: Consultancy; Honoraria; Janssen: Consultancy; Honoraria; Merck: Consultancy; Honoraria; Novartis: Consultancy; Honoraria; Roche: Consultancy; Honoraria; Takeda: Consultancy; Honoraria; Speakers Bureau; Abbvie: Consultancy; Honoraria; Astellas: Consultancy; Honoraria; AstraZeneca: Consultancy; Honoraria; Beigene: Consultancy; Honoraria; Bristol-Myers Squibb: Consultancy; Honoraria; Celgene: Consultancy; Honoraria; Gilead: Consultancy; Honoraria; Janssen: Consultancy; Honoraria; Merck: Consultancy; Honoraria; Novartis: Consultancy; Honoraria; Roche: Consultancy; Honoraria; Takeda: Consultancy; Honoraria; **R. Greil:** Advisory Committee/Consultancy: Abbvie: Consultancy; Honoraria; Amgen: Consultancy; Honoraria; Astellas: Consultancy; Honoraria; AstraZeneca: Consultancy; Honoraria; Beigene: Consultancy; Honoraria; Bristol-Myers Squibb: Consultancy; Honoraria; Celgene: Consultancy; Honoraria; Gilead: Consultancy; Honoraria; Janssen: Consultancy; Honoraria; Merck: Consultancy; Honoraria; Novartis: Consultancy; Honoraria; Roche: Consultancy; Honoraria; Takeda: Consultancy; Honoraria; Speakers Bureau; Abbvie: Consultancy; Honoraria; Amgen: Consultancy; Honoraria; Astellas: Consultancy; Honoraria; AstraZeneca: Consultancy; Honoraria; Beigene: Consultancy; Honoraria; Bristol-Myers Squibb: Consultancy; Honoraria; Celgene: Consultancy; Honoraria; Gilead: Consultancy; Honoraria; Janssen: Consultancy; Honoraria; Merck: Consultancy; Honoraria; Novartis: Consultancy; Honoraria; Roche: Consultancy; Honoraria; Takeda: Consultancy; Honoraria; **L. Mykhalska:** Advisory Committee/Consultancy: Abbvie: Consultancy; Honoraria; Gilead: Consultancy; Honoraria; Janssen: Consultancy; Honoraria; Roche: Consultancy; Honoraria; Speakers Bureau; Abbvie: Consultancy; Honoraria; Gilead: Consultancy; Honoraria; Janssen: Consultancy; Honoraria; Roche: Consultancy; Honoraria; **J. Bergua Burgués:** Advisory Committee/Consultancy: Abbvie: Consultancy; Honoraria; Gilead: Consultancy; Honoraria; Janssen: Consultancy; Honoraria; Roche: Consultancy; Honoraria; Speakers Bureau; Abbvie: Consultancy; Honoraria; Gilead: Consultancy; Honoraria; Janssen: Consultancy; Honoraria; Roche: Consultancy; Honoraria; **M. Cheung:** Advisory Committee/Consultancy: Abbvie: Consultancy; Honoraria; Astellas: Consultancy; Honoraria; AstraZeneca: Consultancy; Honoraria; Beigene: Consultancy; Honoraria; Bristol-Myers Squibb: Consultancy; Honoraria;