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Updated results of a Phase Ib/II randomised study: Polatuzumab vedotin (Pola) plus bendamustine (B) with rituximab (R) in relapsed/refractory diffuse large B-cell lymphoma (R/R DLBCL)

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INTRODUCTION

- Patients with transplant-ineligible R/R DLBCL have poor outcomes and limited treatment options.[1]
- Pola is an antibody-drug conjugate targeting CD79b, a component of the B-cell receptor ubiquitously expressed in DLBCL.[2]
- Pola in combination with B and R (pola-BR) was recently approved by the US Food and Drug Administration (FDA) for the treatment of third-line or later R/R DLBCL.[3]
- Results from the Phase (Ph) Ib safety run-in (pola-BR) and Ph II randomised DLBCL arms (pola-BR vs BR) of GO29365 have been previously reported.[4] With an additional year of follow-up (f/up), we report updated outcomes of this DLBCL cohort (ClinicalTrials.gov: NCT02257567).

METHODS

- Key eligibility criteria: transplant-ineligible DLBCL with ≥1 prior therapy (excludes grade 3b follicular lymphoma, transformed indolent non-Hodgkin lymphoma and central nervous system lymphoma). Prior autologous stem cell transplant (SCT) was allowed. Exclusion criteria: SCT-eligible, prior allogeneic SCT.
- Study endpoints and methods were previously reported.[4]
- Exploratory analysis: for patients treated with pola-BR in the randomised Ph II cohort, associations between baseline characteristics and response durations >12 months by investigator assessment (INV) were examined using Fisher's exact test.

CONCLUSIONS

- With an additional year of follow-up, PFS (INV) and OS remain significantly better for patients receiving pola-BR than BR.
- Seventeen (38%) patients treated with pola-BR had response durations (INV) ≥12 months and 13 (29%) patients had long-term durable responses lasting ≥24 months.
- No new safety signals were identified.
- The addition of pola to BR did not appear to increase the risk of second malignancy or infection (including VZV and PJP) compared with BR alone.
- The majority of PN observed was low grade, manageable, and mostly reversible.
- Pola in combination with BR was recently approved by the FDA[3] and represents an effective treatment option for patients with R/R DLBCL.

RESULTS

- As of 15 March 2019, median f/up for the Ph Ib pola-BR and Ph II randomised (pola-BR vs BR) cohorts was 46 and 30 months, respectively.

Patients

- Baseline characteristics for patients in the Ph II randomised cohort were previously described.[3,4] The median number of prior lines of therapy was 2, with 75% of pola-BR and 85% of BR patients refractory to their last prior therapy.
- Ph Ib pola-BR (n=6): 4 remain alive in f/up and 2 discontinued the study (both died from progressive disease [PD]).
- Ph II pola-BR (n=40): 9 patients remain alive in f/up and 31 discontinued the study (15 died from PD, 10 died from an adverse event (AE), 5 withdrew consent, 1 other reason).
- Ph II BR (n=40): 2 alive remain in f/up and 38 discontinued the study (19 died from PD, 10 died from an AE, 6 withdrew consent, 3 other reasons).

Safety

- The overall safety profile has been previously described.[3,4] The safety-evaluable population includes all patients in the Ph Ib/II randomised arms that received at least one dose of any study drug (pola-BR, n=45).
- Peripheral neuropathy [PN] events (per Standardised MedDRA Query) occurred in 40% (18/45) of patients treated with pola-BR (all grade 1–2). Median time to resolution was approximately 8 days (range: 0–69) with 56% (10/18) experiencing complete resolution. Eight patients had ongoing PN at cutoff: 4 discontinued the study due to death from PD/AE, 3 had unresolved grade 1, and 1 had improving PN (maximum grade 1).
- Second malignancies occurred in 4% (2/45) and 5% (2/39) of patients treated with pola-BR and BR, respectively (**Table 1**).
- No new viral or *Pneumocystis jirovecii* pneumonia (PJP) infections were observed with additional f/up. Five patients treated with pola-BR had infections (2 herpes zoster [VZV], 2 cytomegalovirus [CMV] infection, 1 PJP) and 3 patients treated with BR had infections (2 VZV, 1 CMV) on study.

Table 1. Second malignancies (safety evaluable)

Treatment	Second malignancy	Age (years)/ gender	Cycles received	Study day of onset	Prior lines
Pola-BR	Prostate cancer	75/M	6	766	R-CHOP R-GemOx
	Squamous cell carcinoma	73/M	5	219	R-CHOP
	Myelodysplastic syndrome			263	
BR	Papillary thyroid cancer	77/F	6	160	R-CHOP
	Epiglottic carcinoma	74/M	6	215	R-CHOP
	Myelodysplastic syndrome			444	

BR, bendamustine and rituximab; F, female; M, male; Pola, polatuzumab vedotin; R-CHOP, rituximab-cyclophosphamide, doxorubicin, vincristine, and prednisone; R-GemOx, rituximab-gemcitabine, oxaliplatin.

Efficacy

- Ph Ib: all 3 responders remain in remission without further therapy. Median duration of response (DOR) by INV was 44.6 months (95% confidence interval [CI]: not estimable [NE]–NE; range: 28.9–44.6 months). Median progression-free survival (PFS) by INV and overall survival (OS) were 24.3 months (95% CI: 1.8–46.7) and NE (95% CI: 5.6–NE), respectively.
- Randomised Ph II: 9 (23%) patients in the pola-BR arm and 2 (5%) in the BR arm had an ongoing response as of last f/up. Time to first response corresponded with the interim response assessment time point, with a median of 2.0 months in both arms.
- Updated DOR, PFS, and OS for the Ph II randomised arms (intent-to-treat [ITT]) are shown in **Table 2**, **Figure 1**, and **Figure 2**. A swimlane plot of DOR (INV) for these patients is shown in **Figure 3**. One patient in the pola-BR arm (allogeneic SCT) and 2 patients in the BR arm (1 allogeneic SCT; 1 radiation) received consolidative therapy.

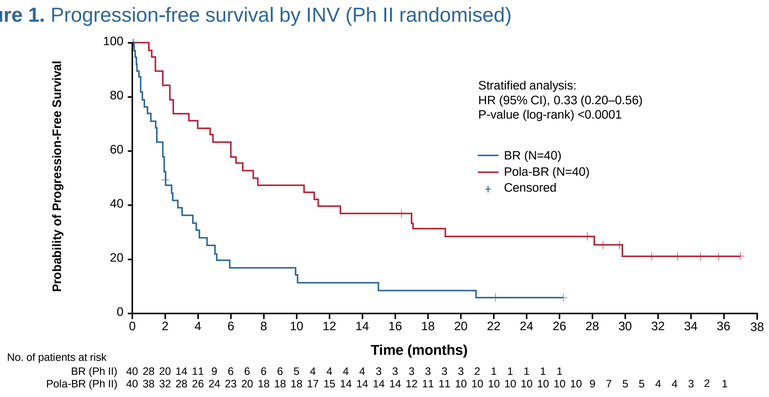
Table 2. Updated efficacy outcomes (Ph II randomised)

INV-assessed	Pola-BR (n=40)	BR (n=40)
Median DOR, months (95% CI)*†	12.7 (5.8–27.9)	4.1 (2.6–12.7)
HR (95% CI)	0.42 (0.19–0.91); p=0.0245	
Median PFS, months (95% CI)	7.5 (4.9–17.0)	2.0 (1.5–3.7)
HR (95% CI)	0.33 (0.20–0.56); p<0.0001	
Median OS, months (95% CI)	12.4 (9.0–32.0)	4.7 (3.7–8.3)
HR (95% CI)	0.41 (0.24–0.71); p=0.0011	

HR (hazard ratio) and p-values based on stratified analysis. *All responding patients: pola-BR n=28; BR n=13.
†Median DOR (95% CI) by INV after censoring for consolidative therapy: pola-BR 10.3 months (5.8–NE); BR 3.3 months (2.6–18.9).
BR, bendamustine and rituximab; CI, confidence interval; DOR, duration of response; INV, investigator assessment; NE, not estimable; OS, overall survival; PFS, progression-free survival; Ph, phase; pola, polatuzumab vedotin.

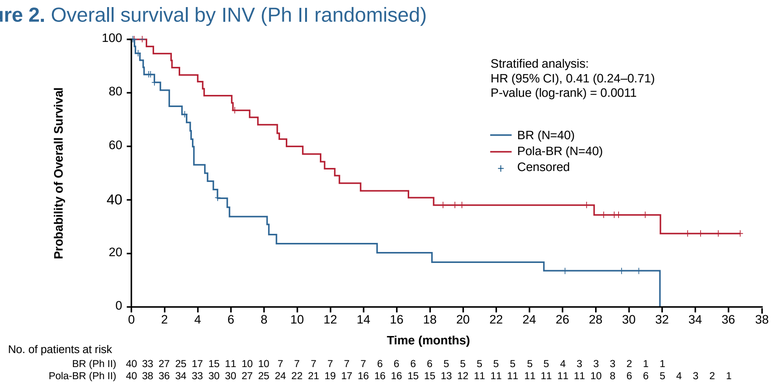
- Ph Ib/II pola-BR: 38% (17/45) patients had response durations ≥12 months (INV) and 29% (13/45) patients had long-term durable responses lasting ≥24 months (INV). One patient underwent consolidative allogeneic SCT and remains in remission as of data cutoff (response duration ≥27.7 months).
- Randomised Ph II: 48% (19/40) patients in the pola-BR arm and 18% (7/40) patients in the BR arm had documented persistent responses (defined as having two consecutive responses of complete response [CR] or partial response [PR] per INV). Median OS for these patients was NE (32.0–NE) in the pola-BR arm and 25.0 months (14.9–32.0) in the BR arm.
- Randomised Ph II pola-BR: no baseline characteristics, including lines of prior therapy or refractory status, were significantly associated with responses lasting >12 months (INV) for all responding patients treated with pola-BR. Results from the Fisher's exact test are shown in **Table 3**.

Figure 1. Progression-free survival by INV (Ph II randomised)



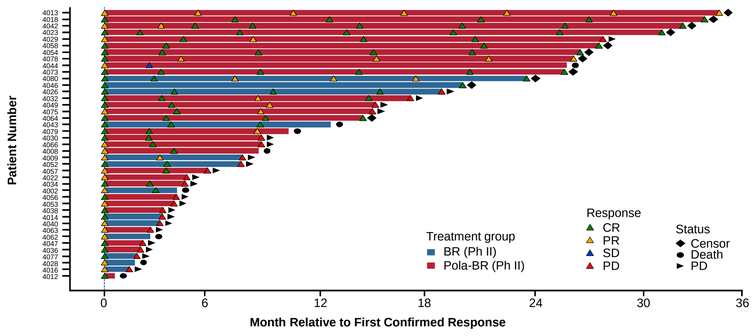
BR, bendamustine and rituximab; CI, confidence interval; HR, hazard ratio; INV, investigator assessment; Ph, phase; Pola, polatuzumab vedotin.

Figure 2. Overall survival by INV (Ph II randomised)



BR, bendamustine and rituximab; CI, confidence interval; HR, hazard ratio; INV, investigator assessment; Ph, phase; Pola, polatuzumab vedotin.

Figure 3. Progression-free survival by INV (Ph II randomised)



BR, bendamustine and rituximab; CR, complete response; INV, investigator assessment; PD, progressive disease; Ph, phase; pola, polatuzumab vedotin; PR, partial response; SD, stable disease.

Table 3. Baseline characteristics according to DOR >12 months by INV (Ph II randomised; pola-BR)

Baseline factor, n (%)	DOR ≤12 months (n=14)	DOR >12 months (n=14)	Fisher's exact test
Age, years			
≥65	10 (71.4)	8 (57.1)	0.695
<65	4 (28.6)	6 (42.9)	
Ann Arbor stage at study entry			
I/II	1 (7.1)	4 (28.6)	0.326
III/IV	13 (92.9)	10 (71.4)	
IPI at study entry			
0–2	4 (28.6)	9 (64.3)	0.128
3–5	10 (71.4)	5 (35.7)	
Prior lines of treatment			
1	4 (28.6)	5 (35.7)	>0.999
2 or more	10 (71.4)	9 (64.3)	
Refractory to the last prior treatment			
Yes	10 (71.4)	8 (57.1)	0.695
No	4 (28.6)	6 (42.9)	
Primary refractory			
Yes	6 (42.9)	4 (28.6)	0.695
No	8 (57.1)	10 (71.4)	
Prior stem cell transplant			
Yes	5 (35.7)	3 (21.4)	0.678
No	9 (64.3)	11 (78.6)	
DOR to prior last treatment			
≤12 months	10 (71.4)	10 (71.4)	>0.999
>12 months	4 (28.6)	4 (28.6)	
Double expressor			
Yes	4 (28.6)	6 (42.9)	0.695
No	10 (71.4)	8 (57.1)	
Cell of origin	(n=14)	(n=9)	
ABC	9 (64.3)	6 (66.7)	>0.999
GCB	5 (35.7)	3 (33.3)	

ABC, activated B-cell-like; BR, bendamustine and rituximab; DOR, duration of response; GCB, germinal center B-cell-like; INV, investigator assessment; IPI, International Prognostic Index; Ph, phase; pola, polatuzumab vedotin.

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