ABCL-568

Subcutaneous (SC) mosunetuzumab in combination with polatuzumab vedotin shows a sustained progression-free survival (PFS) benefit compared with rituximab plus polatuzumab vedotin in patients with relapsed or refractory (R/R) large B-cell lymphoma after long-term follow-up

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Background

- NCT03671018 is an ongoing Phase Ib/II study evaluating SC mosunetuzumab (Mosun) plus polatuzumab vedotin (Pola) in patients with R/R large B-cell lymphoma (LBCL).[1–4]
- In an earlier analysis of the randomized Phase II part of the study, Mosun (SC)-Pola demonstrated improved efficacy versus rituximab (R)-Pola after a median follow-up of 18 months
  - Objective response and complete response (CR) rates were 77.5% and 57.5% with Mosun-Pola versus 50.0% and 35.0% with R-Pola
  - Median duration of CR (DOCR) and PFS were not reached in the Mosun-Pola arm versus not reached and 6.4 months in the R-Pola arm
  - Mosun-Pola also had a manageable safety profile, including a low rate of cytokine release syndrome (CRS; 10%; all events Grade 1–2).[4]
- Mosun (SC)-Pola has shown consistent results in patients with R/R LBCL in the global Phase III SUNMO study (NCT05171647).[5,6]
- We present an updated analysis of the randomized Phase II part of the NCT03671018 study in patients with R/R LBCL after a median follow-up of >2 years.

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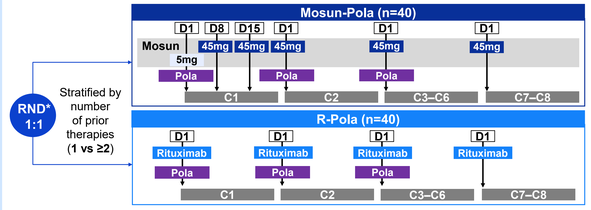
Patients with R/R LBCL and ≥1 previous line of treatment were randomized 1:1 to receive Mosun-Pola or R-Pola (Figure 1)

- The primary endpoint was best objective response rate (ORR) by independent review committee (IRC) using Lugano 2014 criteria.[7]
- Secondary endpoints included duration of response (DOR), PFS, overall survival (OS), and safety

Figure 1. Study design (NCT03671018)[1]

Key inclusion criteria
- LBCL (DLBCL, HGBCL, or FL Grade 3b; trFL included)
- ≥1 prior line of therapy, including an anti-CD20-directed therapy
- Transplant ineligible

Dosing regimens
- **Mosun:** SC with step-up dosing in C1; total of 8 cycles
- **Pola:** 1.8mg/kg IV on D1 of C1–6
- **Rituximab:** 375mg/m^2 IV on D1 of C1–8
- **No mandatory hospitalization**



- **CRS premedication:** Mandatory corticosteroids at C1; not required for C2 and beyond.†
- **Retreatment:** Permitted in cases of PD following completion of therapy in patients who achieved a CR on Mosun SC-Pola.
- **Potential crossover:** Patients on R-Pola with PD during treatment or at EOT, or with SD at EOT, could cross over to Mosun-Pola (up to 8 cumulative Pola cycles).

*It was estimated that ~80–160 patients with R/R LBCL would be enrolled in the randomized Phase II part of the study. The margin of error for 95% exact Clopper–Pearson CIs for estimation of the true ORR would not exceed ±16.7% and ±11.6% with 40 and 80 patients in each arm, respectively. †For patients receiving Mosun SC, corticosteroid premedication consisting of 20mg dexamethasone (preferred) or 80mg methylprednisolone (IV/oral) was administered prior to the administration of each Mosun dose in C1. The administration of corticosteroid premedication was optional for patients who did not experience CRS in the previous cycle. C, cycle; CI, confidence interval; D, day; DLBCL, diffuse large B-cell lymphoma; EOT, end of treatment; FL, follicular lymphoma; HGBCL, high-grade B-cell lymphoma; PD, disease progression; RND, randomized; SD, stable disease; trFL, transformed follicular lymphoma.

As of November 15, 2024, 80 patients had been enrolled, including 54 in the United States (US) (Table 1)

- Median number of cycles received (range): Mosun, 8 (1–8), Pola, 6 (1–6); rituximab, 4 (1–8), Pola, 4 (1–6).
- Median follow-up was 25.7 months (range: 1–35) for Mosun-Pola and 27.2 months (range: 0–34) for R-Pola.

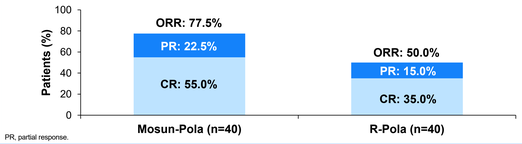
Table 1. Baseline patient characteristics

n (%) unless stated	Mosun-Pola (n=40)	R-Pola (n=40)
Median age, years (range)	71.5 (36–87)	67.5 (24–92)
Male	25 (62.5)	24 (60.0)
Region of enrolment		
US	30 (75.0)	24 (60.0)
Canada	5 (12.5)	6 (15.0)
Europe	5 (12.5)	10 (25.0)
Race		
Asian	1 (2.5)	0
Native Hawaiian or other Pacific Islander	0	1 (2.5)
White	39 (97.5)	39 (97.5)
Ethnicity		
Hispanic or Latino	5 (12.5)	11 (27.5)
Not Hispanic or Latino	35 (87.5)	25 (62.5)
Not stated/unknown	0	4 (10.0)
IPI score		
0–1	9 (22.5)	8 (20.0)
2–3	22 (55.0)	24 (60.0)
4–5	9 (22.5)	8 (20.0)
Histology		
DLBCL	27 (67.5)	33 (82.5)
HGBCL	10 (25.0)	6 (15.0)
FL Grade 3b	3 (7.5)	1 (2.5)
trFL	5 (12.5)*	9 (22.5)†
ECOG PS‡		
0–1	40 (100)	36 (90.0)
2	0	3 (7.5)
Ann Arbor stage III–IV	31 (77.5)	34 (85.0)
Cell-of-origin	n=37	n=39
GCB	22 (59.5)	25 (64.1)
Non-GCB (by GEP or IHC)	14 (37.8)	11 (28.2)
Unknown	1 (2.7)	3 (7.7)
Double/triple-hit	8/37 (21.6)	3/39 (7.7)
Bulky disease >7.5cm	8 (20.0)	10 (25.0)
Extranodal involvement	24 (60.0)	29 (72.5)
Number of prior lines of therapy, median (range)	2 (1–5)	3 (1–9)
1	13 (32.5)	12 (30.0)
≥2	27 (67.5)	28 (70.0)
Prior ASCT	6 (15.0)	9 (22.5)
Prior CAR T-cell therapy	14 (35.0)	15 (37.5)
Refractory to CAR T-cell therapy§	10/14 (71.4)	12/15 (80.0)
Primary refractory/ early relapse¶	25 (62.5)	28 (70.0)
Elevated LDH**	22 (55.0)	25 (62.5)

*Four patients with DLBCL and one patient with HGBCL had trFL. †Eight patients with DLBCL and one patient with HGBCL had trFL. ‡One patient (R-Pola arm) who did not receive study treatment had no baseline ECOG PS recorded as baseline ECOG PS was defined as the last record before treatment start date. §Relapse <6 months after CAR T-cell therapy. ¶Primary refractory: relapse <6 months after first-line therapy; early relapse: relapse 6–12 months after first-line therapy. **>1 × upper limit of normal. ASCT, autologous stem cell transplant; CAR, chimeric antigen receptor; GCB, germinal centre-derived B cell; GEP, gene expression profiling; IHC, immunohistochemistry; IPI, International Prognostic Index; LDH, lactate dehydrogenase.

Mosun-Pola demonstrated higher ORR and CR rates versus R-Pola (Figure 2)

Figure 2. IRC-assessed response rates in the efficacy-evaluable population



PR, partial response.

Mosun-Pola was associated with more durable responses than R-Pola (Table 2; Figure 3)

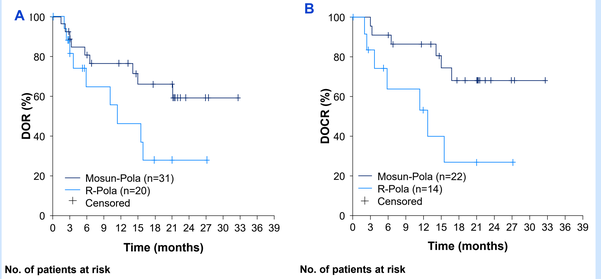
Table 2. IRC-assessed DOR and DOCR

	Mosun-Pola (n=31)	R-Pola (n=20)
mDOR, months (95% CI)	NR (15.0–NE)	11.3 (5.8–NE)
18-month rate, % (95% CI)	65.8 (46.1–85.6)	27.8 (1.6–54.0)
24-month rate, % (95% CI)	59.3 (37.7–80.8)	27.8 (1.6–54.0)

	Mosun-Pola (n=22)	R-Pola (n=14)
mDOCR, months (95% CI)	NR (16.8–NE)	12.7 (3.6–NE)
18-month rate, % (95% CI)	68.0 (46.4–89.6)	26.5 (0.0–56.6)
24-month rate, % (95% CI)	68.0 (46.4–89.6)	26.5 (0.0–56.6)

mDOCR, median DOCR; mDOR, median DOR; NE, not estimable; NR, not reached.

Figure 3. IRC-assessed A) DOR and B) DOCR



Mosun-Pola prolonged median PFS by four times versus R-Pola (Table 3; Figure 4)

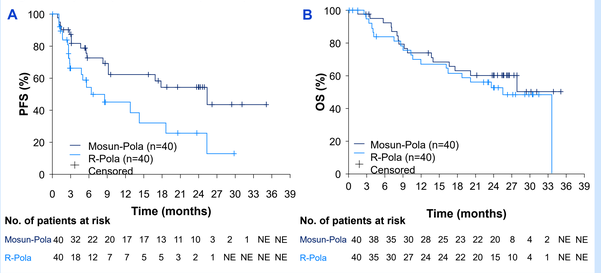
Table 3. PFS (IRC assessed) and OS

	Mosun-Pola (n=40)	R-Pola (n=40)
mPFS, months (95% CI)	25.4 (9.2–NE)	6.4 (4.7–18.6)
HR (95% CI)	0.47 (0.24–0.94)	
p-value*	0.0287	
18-month rate, % (95% CI)	54.2 (36.4–72.0)	32.0 (11.8–52.2)
24-month rate, % (95% CI)	54.2 (36.4–72.0)	25.6 (5.9–45.2)

	Mosun-Pola (n=40)	R-Pola (n=40)
mOS, months (95% CI)	NR (17.6–NE)	25.5 (16.2–NE)
HR (95% CI)	0.78 (0.40–1.53)	
p-value*	0.4749	
18-month rate, % (95% CI)	62.9 (47.4–78.3)	61.4 (45.6–77.3)
24-month rate, % (95% CI)	60.1 (44.4–75.8)	52.6 (36.1–69.1)

*Descriptive only. HR, hazard ratio; mPFS, median PFS; mOS, median OS.

Figure 4. A) PFS (IRC-assessed) and B) OS



Mosun-Pola demonstrated improved efficacy versus R-Pola in patients with early relapse or who were refractory to first-line therapy (Table 4)

Table 4. IRC-assessed efficacy in patients with early relapse or primary refractory disease

Efficacy endpoint	Mosun-Pola (n=25)	R-Pola (n=28)
ORR, n (%)	17 (68.0)	11 (39.3)
CR, n (%)	10 (40.0)	7 (25.0)
mDOR, months (95% CI)	NR (3.3–NE)	5.8 (3.0–NE)
mDOCR, months (95% CI)	NR (NE–NE)	5.8 (2.4–NE)
mPFS, months (95% CI)	9.2 (4.6–NE)	5.6 (2.7–NE)
mOS, months (95% CI)	27.9 (13.7–NE)	18.8 (9.0–NE)

No new safety signals were observed with >2 years of follow-up (Table 5)

- CRS events were low-grade and limited to C1D1 (**Table 6**; **Figure 5**).

Table 5. Adverse event (AE) summary

n (%) unless stated	Mosun-Pola (n=40)	R-Pola (n=40)
Any AE	40 (100)	39 (100)
Serious AE	13 (32.5)	10 (25.6)
Grade 3–4 AE	22 (55.0)	20 (51.3)
Grade 5 (fatal) AE*	2 (5.0)	1 (2.6)
Mosun related	1 (2.5)	0
Pola related	1 (2.5)	0
AE leading to treatment discontinuation†	3 (7.5)	3 (7.7)
Treatment-related AE leading to treatment discontinuation	2 (5.0)	2 (5.1)
Mosun related	0	0
Pola related	2 (5.0)	2 (5.1)

AEs of interest, n (%)		Mosun-Pola (n=40)	R-Pola (n=39)
ICANS	Any	0	0
Febrile neutropenia	Any	1 (2.5)	0
	Grade 3	1 (2.5)	0
Peripheral neuropathy	Any	4 (10.0)	2 (5.1)
	Grade 1	3 (7.5)	2 (5.1)
	Grade 2	1 (2.5)	0
Infections	Any	18 (45.0)	13 (33.3)
	Grade 1–2	10 (25.0)	7 (17.9)
	Grade 3	5 (12.5)	4 (10.3)
	Grade 4	1 (2.5)	2 (5.1)
	Grade 5	2 (5.0)	0
Neutrophil count decreased/neutropenia	Any	16 (40)	9 (23.1)
	Grade 2	3 (7.5)	0
	Grade 3	7 (17.5)	4 (10.3)
	Grade 4	6 (15.0)	5 (12.8)

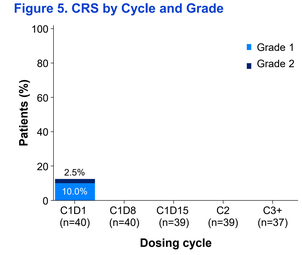
*Mosun-Pola: COVID-19 (n=1), COVID-19 pneumonia (n=1); R-Pola: hepatic failure (n=1). †Mosun-Pola: COVID-19 pneumonia (n=1), peripheral motor neuropathy (n=1), peripheral sensory neuropathy (n=1); R-Pola: peripheral neuropathy (n=1), neutrophil count decreased (n=1), pain in extremity (n=1). ICANS, immune effector cell-associated neurotoxicity syndrome.

Table 6. CRS by ASTCT criteria[8]

	Mosun-Pola (n=40)
Any Grade, n (%)	5 (12.5)
Grade 1	4 (10.0)
Grade 2	1 (2.5)
Median CRS duration, days (range)	2 (1–5)
Median time to first onset,* days (range)	2 (1–3)
CRS management, n (%)	
Steroids	1 (2.5)
Steroids + tocilizumab	1 (2.5)
Tocilizumab	1 (2.5)
Low-flow oxygen	1 (2.5)
ICU admissions	0
Events resolved, %	100

*From the most recent dose. ASTCT, American Society for Transplantation and Cellular Therapy criteria; ICU, intensive care unit.

Figure 5. CRS by Cycle and Grade



B-cell recovery was observed 12–15 months after treatment completion.

Figure 6. Subset profiling in B cells*

- B-cell depletion occurred by C2 and was sustained throughout treatment (**Figure 6**).
- B-cell recovery was subsequently observed in most patients (58% [11/19] recovered to ≥70 cells/µl) by 12–15 months after treatment completion.

*Performed centrally as part of a panel that measures T, B, and NK cells via quantitative flow cytometry. Blue line: 70-cell lower end of normal cut-off. NK, natural killer.

Mosun-Pola showed promising efficacy after crossover from R-Pola (Figure 7)

Figure 7. DOR* for crossover patients

*Investigator-assessed. †Unexplained death.

Median follow-up of 18.7 months
- ORR: 50.0% (n=10; 95% CI, 27.2–72.8).
- CR rate: 20.0% (n=4; 95% CI, 5.7–43.7).
- DOR: 15.7 months (95% CI, 2.8–NE).
- DOCR: NE (95% CI, 15.7–NE).

- The safety profile was consistent with initial Mosun-Pola treatment.
- Serious AEs occurred in 25.0% (n=5)
- Grade 5 AEs occurred in 5.0% (n=1†)

Conclusions

- Fixed-duration, outpatient Mosun-Pola continues to demonstrate clinically meaningful and sustained improvements in DOR and PFS compared with R-Pola.
- Mosun-Pola also demonstrated improved efficacy versus R-Pola in patients with early relapse or who were refractory to first-line therapy.
- With Mosun-Pola, CRS events were low-grade and limited to C1D1 and no new safety signals were observed since the previous analysis, underscoring its tolerability and suitability for outpatient administration.
- Although this cohort enrolled primarily in the US, consistent results were observed in the global Phase III SUNMO study evaluating Mosun SC-Pola in R/R LBCL.

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