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Mosunetuzumab monotherapy is an effective and well-tolerated treatment option for patients with relapsed/refractory follicular lymphoma who have received ≥2 prior lines of therapy: Pivotal results from a Phase I/II study

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Summary

Mosunetuzumab is a CD20xCD3 T-cell engaging bispecific monoclonal antibody that has shown encouraging efficacy and manageable safety in a Phase I dose-escalation study of patients with relapsed/refractory (R/R) follicular lymphoma (FL)

Here we report results from a pivotal Phase II expansion cohort of patients with R/R FL and ≥2 prior therapies (NCT02500407)

Mosunetuzumab had a manageable safety profile and was administered using cycle (C) 1 step-up dosing without mandatory hospitalization

Mosunetuzumab induced high rates of complete remission (60%), with responses achieved in heavily pre-treated/high-risk patients

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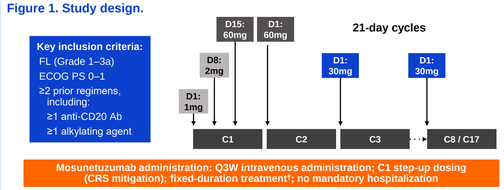
Background

- FL is characterized by recurrent relapses; response rate and duration decrease with successive treatment lines with conventional agents.[1] Progression of disease within two years (POD24) and refractory disease are associated with poor prognosis.[2,3]
- Mosunetuzumab is a CD20xCD3 T-cell engaging bispecific monoclonal antibody that redirects T cells to eliminate B cells, including those that cause malignant disease.[4] It is an off-the-shelf, fixed-duration treatment and can be administered as an outpatient regimen.
- In a Phase I/II study (NCT02500407),[5,6] escalating doses of mosunetuzumab were active and well tolerated in patients with R/R FL and ≥2 prior therapies, including patients with POD24 and double-refractory disease.[7] Pivotal Phase II expansion results are presented here.

Study design: Single-arm, pivotal, Phase II expansion

- All patients had R/R FL (Grade 1–3a) and ≥2 prior therapies (**Figure 1**).
- The primary endpoint was complete response (CR as the best response) rate evaluated by an independent review facility (IRF)* assessed vs 14% historical control CR rate.[8]
- Secondary endpoints included objective response rate (ORR), duration of response (DoR), progression-free survival (PFS), and safety and tolerability.

Figure 1. Study design.



*Assessed by CT and PET-CT using Cheson 2007 criteria;[9] †8 cycles if CR after C8, 17 cycles if PR/SD after C8.
Ab, antibody; CR, complete response; CRS, cytokine release syndrome; CT, computed tomography; D, Day; ECOG PS, Eastern Cooperative Oncology Group performance status; PET, positron emission tomography; PR, partial response; SD, stable disease; Q3W, once every 3 weeks.

As of August 27, 2021, 90 patients were enrolled and more than half had double-refractory disease or POD24

- The median age of patients was 60 years and the median number of prior therapy lines was 3 (range: 2–10; **Table 1**).
- Overall, 78.9% of patients were refractory to any prior anti-CD20 therapy, 53.3% were refractory to any prior anti-CD20 therapy and alkylating agent (double refractory), and 52.2% had POD24.
- The median duration of follow-up was 18.3 months and 82.2% of patients received up to eight cycles of treatment.

Table 1. Baseline characteristics.

	N=90
Median age, years (range)	60 (29–90)
Male, n (%)	55 (61.1)
ECOG PS, n (%)	
0	53 (58.9)
1	37 (41.1)
Ann Arbor stage, n (%)	
I–II	21 (23.3)
III–IV	69 (76.7)
Median number of prior therapy lines, n (range)	3 (2–10)
Refractory to last prior therapy, n (%)	62 (68.9)
Refractory to any prior anti-CD20 therapy, n (%)	71 (78.9)
Refractory to any prior anti-CD20 therapy and alkylator therapy (double refractory), n (%)	48 (53.3)
POD24, n (%)	47 (52.2)

Cut-off date: August 27, 2021.

Primary endpoint met: CR rate greater than historical control

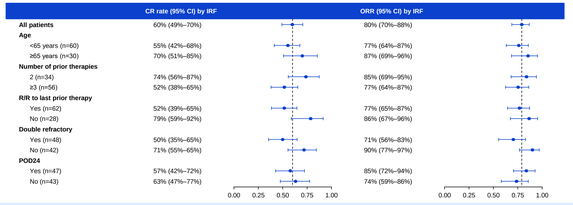
- ORR (CR/PR) and CR rate in all patients were 80% and 60%, respectively (**Table 2**); 60% CR rate significantly greater (p<0.0001)* than 14% historical control CR rate.
- Response rates were comparable in high-risk sub-groups, including patients with double-refractory disease and POD24 (**Figure 2**).

Table 2. Response rates.

	IRF N (%) [95% CI]	Investigator N (%) [95% CI]	Concordance IRF vs investigator
CR	54 (60) [49–70]	54 (60) [49–70]	93%
ORR	72 (80) [70–88]	70 (78) [68–86]	96%

*Exact binomial test with two-sided alpha level of 5%; CI, confidence interval.

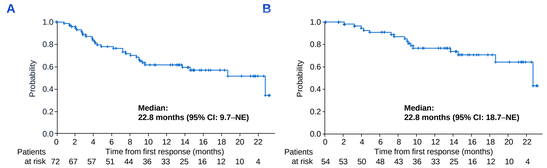
Figure 2. Response rates in high-risk sub-groups.



Responses were durable and maintained in many patients after treatment completion (Figure 3)

- Median PFS was 17.9 months (**Figure 4**).

Figure 3. DoR in overall responders (A) and in complete responders (B).

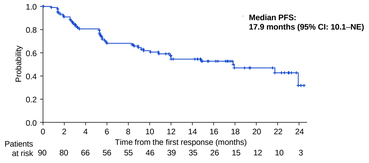


Median time to first response, months (range)	1.4 (1.1–8.9)
12-month event-free rate, % (95% CI)	62 (50–74)
18-month event-free rate, % (95% CI)	57 (44–70)

Median time to first response, months (range)	3.0 (1.1–18.9)
12-month event-free rate, % (95% CI)	76 (65–88)
18-month event-free rate, % (95% CI)	70 (57–84)

NE, not estimable.

Figure 4. PFS (N=90).



Mosunetuzumab had a manageable safety profile

- Common adverse events (AEs) by Grade (≥15%), included CRS, fatigue, headache, pyrexia, and hypophosphatemia (**Figure 5**).
- AEs leading to mosunetuzumab discontinuation occurred in four patients (**Table 3**).

Figure 5. AEs (≥15%) by Grade and relationship with mosunetuzumab.

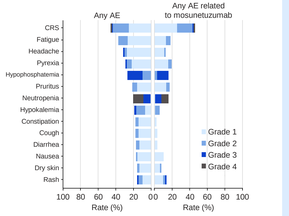


Table 3. Safety summary.

N (%)	N=90
AE	90 (100)
Mosunetuzumab related*	83 (92.2)
Grade 3/4 AE	63 (70.0)
Mosunetuzumab related*	46 (51.1)
Serious AE	42 (46.7)
Mosunetuzumab related*	30 (33.3)
Grade 5 (fatal) AE	2 (2.2)†
Mosunetuzumab related*	0
AE leading to treatment discontinuation	4 (4.4)‡
Mosunetuzumab related*	2 (2.2)‡

*AE considered related to treatment by the investigator; †mosunetuzumab unrelated: malignant neoplasm progression and unexplained death (one patient each); ‡mosunetuzumab related: CRS (two patients); mosunetuzumab unrelated: Epstein-Barr viremia and Hodgkin's disease (one patient each).

CRS was predominantly low grade and occurred during C1

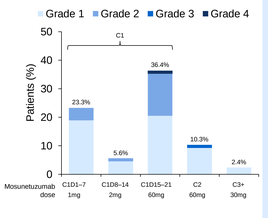
- CRS events of any grade were reported in 44.4% of patients, 95% of which were Grade 1/2 (**Table 4**).
- CRS primarily occurred during C1 and was mostly associated with C1D1 step-up (23.3%) and C1D15 target doses (36.4%; **Figure 6**). All events resolved.

Table 4. CRS summary.

	N=90
Any grade CRS, n (%)*	40 (44.4)
Grade 1	23 (25.6)
Grade 2	15 (16.7)
Grade 3	1 (1.1)
Grade 4	1 (1.1)†
Median time to CRS onset, hours (range)	
C1D1	5.2 (1.2–23.7)
C1D15	26.6 (0.1–390.9)
Median CRS duration, days (range)	3 (1–29)
Corticosteroids for CRS management, n (%)	10 (11.1)
Tocilizumab for CRS management, n (%)	7 (7.8)

*Assessed using American Society for Transplantation and Cellular Therapy (ASTCT) criteria;[10] †patient with leukemic-phase FL.

Figure 6. CRS by Cycle and Grade.



ICANS events were infrequent and all Grade 1–2

- Potential immune effector cell-associated neurotoxicity syndrome (ICANS)-like events of any grade were reported in 4.4% of patients. All ICANS events resolved.
- Neutropenia and Grade 3/4 neutropenia were reported in 28.9% and 26.7% of patients, respectively; no febrile neutropenia events were reported.
- Serious AEs of infection (any Grade) occurred in 20% of patients; 14.4% were Grade 3/4.

Conclusions

- The pivotal Phase II study with mosunetuzumab met its primary efficacy endpoint (CR rate: 60%, p<0.001; ORR: 80%).
- Deep and durable responses were achieved in patients with heavily pre-treated/high-risk R/R FL, with fixed-duration treatment.
- A manageable tolerability profile was observed, with most CRS confined to C1 and low Grade; no mosunetuzumab-related fatal events occurred.
- Mosunetuzumab is the first T-cell-engaging bispecific antibody to demonstrate clinically meaningful outcomes for patients with R/R FL in a pivotal Phase II setting and is a potentially promising off-the-shelf, outpatient therapy.

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