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Mosunetuzumab Monotherapy Continues to Demonstrate Durable Responses in Patients With Relapsed and/or Refractory Follicular Lymphoma After ≥2 Prior Therapies: 3-Year Follow-up From a Pivotal Phase II Study

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Summary

Mosunetuzumab is a CD20×CD3 T-cell-engaging bispecific antibody that redirects T cells to engage and eliminate B cells, including those that cause malignant disease

We present updated results from the pivotal Phase II study of mosunetuzumab in heavily pre-treated patients with relapsed and/or refractory (R/R) follicular lymphoma (FL)

Fixed-duration mosunetuzumab achieved long-lasting remissions: responses were durable with >3 years of follow-up and 3-year progression-free and overall survival rates were robust and stable

After the end of treatment, the median time for B-cell recovery to quantitative levels is 18.4 months

Deep molecular responses occurred early and all patients who achieved a complete response (CR) had undetectable MRD (uMRD) at Cycle (C) 8

Background

- Mosunetuzumab is a CD20×CD3 T-cell-engaging bispecific antibody that redirects T cells to engage and eliminate B cells, including those that cause malignant disease[1,2]
- Mosunetuzumab has been granted conditional marketing authorization by the European Medicines Agency and accelerated approval by the US Food and Drug Administration for the treatment of R/R FL after ≥2 prior systemic therapies[3,4]
- Previous analysis of the pivotal Phase II study at a median follow-up of 18.3 months demonstrated (data cut-off: Aug 27, 2021):
  - High response rates with durable responses in heavily pre-treated patients with R/R FL[5]
  - Off-the-shelf, fixed-duration treatment that can be administered in the outpatient setting[5]
- We present updated results from the Phase II study after a median time on study of 37.4 months (data cut-off: May 2, 2023)

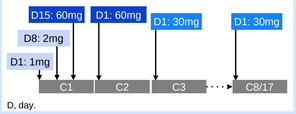
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Phase II study design

- NCT02500407 is a pivotal, single-arm, Phase II expansion study of mosunetuzumab in patients with R/R FL and ≥2 prior therapies
- Key inclusion criteria included: FL Grade 1–3a, Eastern Cooperative Oncology Group performance status (ECOG PS) 0–1, and ≥2 prior therapies (including an anti-CD20 antibody and an alkylator)
- Intravenous mosunetuzumab administered in 21-day cycles with step-up dosing in C1 (**Figure 1**)
  - Mosunetuzumab was administered for 8 cycles if a complete response (CR) was achieved after C8, or for 17 cycles if a partial response (PR) or stable disease (SD) was achieved after C8
- Retreatment with mosunetuzumab was permitted at relapse for patients who achieved a CR
- Mandatory hospitalization was not required.
- The study previously met its primary endpoint: 60% CR rate versus 14% historic control (p<0.0001)[5,6]

Figure 1. Mosunetuzumab dosing schedule



D, day.

As of May 2, 2023, the median time on study was 37.4 months

- Baseline patient characteristics are shown in **Table 1**

Table 1. Baseline characteristics.

	N=90
Median age, years (range)	**60** (29–90)
Male, n (%)	**55** (61)
ECOG PS, n (%)	
0	**53** (59)
1	**37** (41)
Ann Arbor stage, n (%)	
I/II	**21** (23)
III/IV	**69** (77)
Median lines of prior therapy, (range)	**3** (2–10)
Prior autologous stem cell transplant, n (%)	**28** (31)*
Refractory to last prior therapy, n (%)	**62** (69)
Refractory to any prior anti-CD20 therapy, n (%)	**71** (79)
POD24, n (%)	**47** (52)
Double refractory to prior anti-CD20 and alkylator therapy, n (%)	**48** (53)

*Data updated based on subsequent snapshot. POD24, progression of disease within 24 months from the first systemic therapy.

Mosunetuzumab provided durable responses with >3 years of follow-up

- At the previous data cut-off (Aug 27, 2021), mosunetuzumab demonstrated high response rates (**Table 2**) and the median duration of response (DOR) was not reached (NR)[5]
- At the current data cut-off, mosunetuzumab demonstrated durable responses (**Table 2**)
  - Most patients (72.7%, 95% confidence interval [CI]: 60.8–86.8) with a CR are estimated to remain alive and progression-free 30 months after their first response
- With a median follow-up of >36 months, progression-free and overall survival rates at 3 years were robust and stable (**Table 2**)

Table 2. Efficacy analyses.

CCOD	Efficacy endpoint	N=90
Aug 27, 2021[5]	**ORR** by independent committee review, %	**80** (95% CI: 70–88)
	CR rate by independent committee review, %	**60** (95% CI: 49–70)
	ORR by investigator, %	**78** (95% CI: 68–86)
	CR rate by investigator, %	**60** (95% CI: 49–70)
May 2, 2023	**Median DOR,** months; *n=70** 30-month rate, %†	**35.9** (95% CI: 20.7–NE) **56.6** (95% CI: 44.2–68.9)†
	Median DOR in patients with CR, months; *n=54**	**35.9** (95% CI: NE–NE)
	Median DOR in patients with PR, months; *n=16**	**4.0** (95% CI: 2.5–6.7)
	Median PFS, months 36-month rate, %	**24.0** (95% CI: 12.0–NE) **43.2** (95% CI: 31.3–55.2)
	Median OS, months 36-month rate, %	**NR** (95% CI: NE–NE) **82.4** (95% CI: 73.8–91.0)

*Responders per investigator assessment. †36-month DOR data are not available as this analysis was conducted from the first response assessment, therefore the landmark analysis is shorter for the duration outputs.
CCOD, clinical cut-off date; NE, not estimable; ORR, overall response rate; OS overall survival; PFS, progression-free survival.

Retreatment efficacy data are encouraging with mosunetuzumab

- Details of patients' subsequent anti-lymphoma therapy are in **Table 3**
- Five patients received mosunetuzumab retreatment, three of these patients had a CR and two had SD

Table 3. New anti-lymphoma therapy.

	N=90
Median time to next therapy or death, months (95% CI)	**37.3** (18.0–NE)
Any new anti-lymphoma therapy, n (%)	**36** (40)
New systemic treatments, n (%)	
Chemotherapy ± immunotherapy	**35** (39)
Phosphoinositide 3-kinase inhibitors ± immunotherapy	**20** (22)
Chimeric antigen receptor T-cell therapy	**10** (11)
Bruton tyrosine kinase inhibitors ± venetoclax	**9** (10)
Lenalidomide ± immunotherapy	**5** (6)
	4 (4)
Radiotherapy, n (%)	**9** (10)
Excision of tumor, n (%)	**2** (2)
Allogeneic stem cell transplant, n (%)	**2** (2)
Autologous stem cell transplant, n (%)	**2** (2)

Mosunetuzumab has a manageable safety profile with outpatient administration

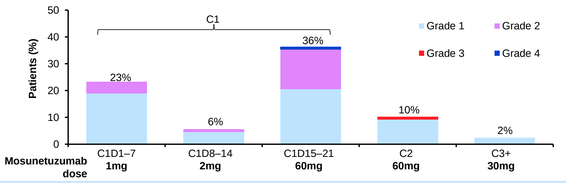
- No new adverse events (AEs) were reported since the previous data cut-off[5]
- The incidence of AEs and serious AEs remains unchanged with this extended follow-up (**Table 4**)
- The most common AEs and mosunetuzumab-related AEs with an incidence of ≥15% were cytokine release syndrome (CRS), fatigue and headache; these were mostly Grade 1/2
- CRS was predominantly low-grade and occurred during C1 (**Table 4**, **Figure 2**)
  - All CRS events were resolved and no new events were reported in this extended follow-up

Table 4. Safety outcomes.

	N=90
Safety summary, n (%)	
Any grade AE / Mosunetuzumab related	**90** (100) / **83** (92)
Grade 3/4 AE / Mosunetuzumab related	**63** (70) / **46** (51)
Serious AE / Mosunetuzumab related	**42** (47) / **30** (33)
Grade 5 AE / Mosunetuzumab related	**2** (2)* / **0**
AE leading to treatment discontinuation / Mosunetuzumab related	**4** (4)† / **2** (2)
CRS summary by the American Society for Transplantation and Cellular Therapy criteria[7]‡	
CRS (any grade), n (%)	**40** (44)
Grade 1 / 2	**23** (26) / **15** (17)
Grade 3 / 4	**1** (1) / **1** (1)
Median time to CRS onset, hours (range)	
C1D1 / C1D15	**5** (1–24) / **27** (0–391)
Median CRS duration, days (range)	**3** (1–29)
Corticosteroids for CRS management, n (%)	**10** (11%)§
Tocilizumab for CRS management, n (%)	**7** (8)§
Events resolved, %	100

*Malignant neoplasm progression (n=1, onset study D94) and unexplained death (n=1, onset study D60). †Mosunetuzumab related: CRS (n=2, onset study D15 and D22 [both recovered]); mosunetuzumab unrelated: Epstein-Barr viremia (n=1, onset study D11, recovered) and Hodgkin's disease (n=1, onset study D193, not recovered); ‡Data cut-off: August 27, 2021, as no new CRS events occurred subsequently; §Four patients received both corticosteroids and tocilizumab for CRS management.

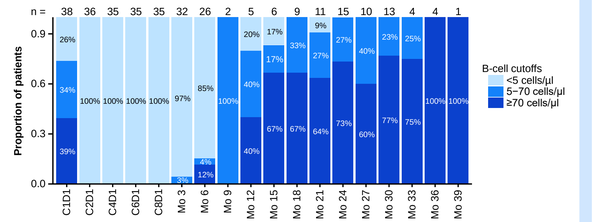
Figure 2. CRS by cycle and grade.



B-cell recovery is detectable at a median of 18.4 months after the end of mosunetuzumab treatment

- Peripheral blood B-cell depletion following treatment with mosunetuzumab occurred rapidly by the initiation of C2 dosing in all patients (n=74, **Figure 3**)
- An exploratory analysis was performed to assess B-cell recovery in patients with available samples from end of treatment (C8) and various follow-up timepoints (n=38)
  - Median time to recovery to quantitative levels was 18.4 months (95% CI: 12.8–25.0)
  - Median time to recover to the lower level of normal was 25.1 months (95% CI: 19.0–NE)

Figure 3. CD19+ B cells.*

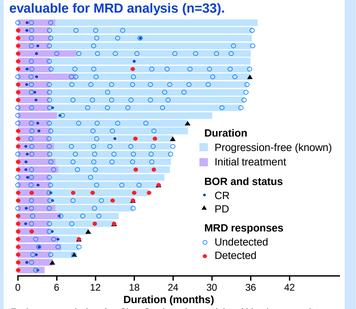


*CD19+ B cells were monitored by flow cytometry at C1, C2, C4, and C8, and every 3 months during follow-up or until progression or next lymphoma treatment. The lower limit of quantitation was 5 cells/µl and the lower limit of normal was 70 cells/µl. Depletion was analyzed in all patients with a pre-dose and at least one on-treatment sample. Recovery was analyzed in patients with a CR and at least one follow-up sample. Mo, month.

uMRD is achieved with fixed-duration dosing of mosunetuzumab

- Thirty-three patients who achieved a CR had samples available for minimal residual disease (MRD) analysis; of these, 73% (n=24/33) had detectable MRD prior to mosunetuzumab dosing (detection threshold: 1×10^{-6})
  - uMRD was achieved by C4 in most patients (93%, n=28/30) who achieved a CR
  - All evaluable patients that achieved a CR had uMRD at the end of treatment (n=28/28)
- MRD kinetics are consistent with observed durable responses (**Figure 4**)

Figure 4. Swimlane plot of patients with a CR evaluable for MRD analysis (n=33).



Exploratory analysis using ClonoSeq in patient peripheral blood mononuclear cells collected longitudinally during and post mosunetuzumab treatment.
BOR, best overall response.

Conclusions

- In heavily pre-treated patients with R/R FL, fixed-duration mosunetuzumab is well-tolerated and achieved long-lasting remissions
  - Durable responses were observed with >3 years of follow-up: the estimated 30-month DOR rate was 72.7% in patients with a CR
  - The 3-year OS rate with mosunetuzumab was 82.4%
- Mosunetuzumab has a manageable safety profile with outpatient administration
  - No new AEs were reported in this extended follow-up
- Retreatment efficacy data are encouraging with mosunetuzumab
- Pharmacodynamic evaluation supports fixed-duration treatment
  - B-cell recovery is detectable at a median of 18.4 months after the end of treatment
  - Deep molecular responses occurred early; all patients who achieved a CR had uMRD at C8

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