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Fixed-duration Subcutaneous Mosunetuzumab (Mosun SC) Leads to High Rates of Durable Responses, Low Rates of Cytokine Release Syndrome (CRS), and Non-Inferior Exposure Compared with Intravenous Administration in Patients with Relapsed/Refractory (R/R) Follicular Lymphoma (FL): Primary Analysis of a Pivotal Phase II Study

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Summary

An ongoing Phase I/II study is evaluating the pharmacokinetics (PK), efficacy and safety of subcutaneous (SC) mosunetuzumab (Mosun) with Cycle (C) 1 step-up dosing in patients with relapsed/refractory (R/R) follicular lymphoma (FL)

In the pivotal Phase II Mosun SC single-arm cohort, co-primary PK endpoints were met, with Mosun SC demonstrating non-inferior exposure versus intravenously (IV) administered Mosun (within-study comparator cohort)

Mosun SC had a manageable safety profile with a low incidence and severity of cytokine release syndrome (CRS) events

Mosun SC achieved high rates of complete and durable remissions in a heavily pretreated and high-risk patient population with R/R FL who have received ≥2 prior therapies

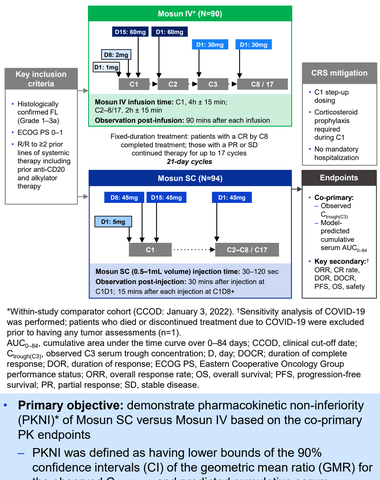
Background

- Mosun is a CD20xCD3 T-cell engaging bispecific antibody that redirects T-cells to eliminate malignant B-cells[1]
  - Mosun IV is approved by the US FDA and EMA for the treatment of patients with R/R FL after ≥2 prior lines of therapy.[2,3]
- In a Phase II study (NCT02500407), fixed-duration Mosun IV demonstrated a manageable safety profile and induced a high complete response (CR) rate (60%) in patients with R/R FL.[4]
- A Mosun SC formulation that aims to further improve patient safety and convenience is under evaluation.[5–7]
- In the Phase I/II portion of the study, Mosun SC demonstrated encouraging efficacy, similar to Mosun IV, with a manageable safety profile in heavily pre-treated patients with R/R B-cell non-Hodgkin lymphoma.[6,7]
- We present PK, safety, and efficacy data from the primary analysis of Mosun SC at the recommended Phase II dose, using a within-study comparison of Mosun IV in patients with R/R FL who have received ≥2 prior therapies.

NCT02500407 is an open-label, multicenter Phase I/II study of Mosun in patients with R/R B-cell hematologic malignancies

- Data reported herein are from the Phase II dose-expansion part of the study alongside a within-study comparison of Mosun IV (**Figure 1**).

Figure 1. Study overview.



*Within-study comparator cohort (CCOD: January 3, 2022). †Sensitivity analysis of COVID-19 was performed; patients who died or discontinued treatment due to COVID-19 were excluded prior to having any tumor assessments (n=1).
$AUC_{0–84}$, cumulative area under the time curve over 0–84 days; CCOD, clinical cut-off date; $C_{trough(C3)}$, observed C3 serum trough concentration; D, day; DOCR; duration of complete response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

- **Primary objective:** demonstrate pharmacokinetic non-inferiority (PKNI)* of Mosun SC versus Mosun IV based on the co-primary PK endpoints
  - PKNI was defined as having lower bounds of the 90% confidence intervals (CI) of the geometric mean ratio (GMR) for the observed $C_{trough(C3)}$ and predicted cumulative serum $AUC_{0–84}$ being above the predefined margin of 0.8.

*PKNI analysis included patients treated with Mosun SC produced from an updated drug development process.

As of data cut-off (July 24, 2024), 94 patients were enrolled in the Mosun SC cohort

- Patients treated with Mosun SC were enrolled during the COVID-19 pandemic (Apr 2021–Feb 2023); the majority of patients from the within-study comparator Mosun IV cohort were enrolled prior to the COVID-19 pandemic (May 2019–Sept 2020).
- In the Mosun SC cohort, the median time on study was 26.1 (range: 1–40) months
  - Median number of prior lines of therapy was 3 (range: 2–8; **Table 1**).

Table 1. Baseline characteristics.

n (%) unless stated		Mosun IV* 1/2/60/30mg (N=90)	Mosun SC 5/45/45mg (N=94)
Median age, years (range)		60 (29–90)	65 (35–84)
Female		35 (38.9)	41 (43.6)
Race	American Indian or Alaska Native	1 (1.1)	0
	Asian	8 (8.9)	10 (10.6)
	Black or African American	4 (4.4)	2 (2.1)
	White	74 (82.2)	80 (85.1)
	Native Hawaiian or other Pacific Islander	0	1 (1.1)
	Unknown	3 (3.3)	1 (1.1)
Ethnicity	Hispanic or Latino	7 (7.8)	2 (2.1)
	Not Hispanic or Latino	77 (85.6)	88 (93.6)
	Not stated or unknown	6 (6.7)	4 (4.3)
Ann Arbor stage	III or IV	69 (76.7)	82 (87.2)
FLIPI score	≥3	40 (44.4)	53 (56.4)
Median no. of prior lines, n (range)		3 (2–10)	3 (2–8)
Prior cancer therapies	BTKi	6 (6.7)	6 (6.4)
	CAR T cell	3 (3.3)	4 (4.3)
	IMiD	13 (14.4)	25 (26.6)
	PI3K inhibitor	17 (18.9)	11 (11.7)
Refractory to last prior therapy		62 (68.9)	59 (62.8)
Refractory to any prior anti-CD20		71 (78.9)	62 (66.0)
Double refractory to prior anti-CD20 and alkylator		48 (53.3)	44 (46.8)
POD24		47 (52.2)	41 (43.6)

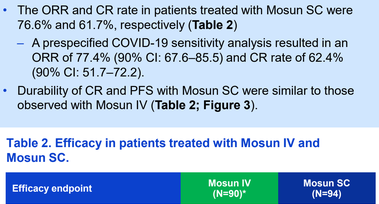
*Within-study comparison cohort (CCOD: January 3, 2022).
BTKi, Bruton's kinase inhibitor; CAR, chimeric antigen receptor; FLIPI, Follicular Lymphoma International Prognostic Index; IMiD, immunomodulatory imide drugs; PI3K, phosphoinositide 3-kinase; POD24, disease progression (PD) within 24 months from start of first line therapy.

- In the Mosun SC cohort, the median duration of treatment and safety follow-up was 7.9 (range: 1–21) months
  - For both cohorts, the median number of cycles was 8 (range: 1–17).
- As of the CCOD, no patient remained on active initial treatment, 60 (63.8%) had completed initial treatment and 34 (36.2%) had discontinued (death, n=4; PD, n=22; adverse events [AEs], n=4; physician decision, n=1; withdrawal, n=2 and lost to follow-up, n=1).

Mosun SC exposure was non-inferior compared with Mosun IV

- PKNI analysis for patients receiving Mosun SC (68/94) or Mosun IV (90/90) demonstrated that the co-primary endpoints were met
  - 90% CI lower bounds of GMR values were ≥0.8:
    - The $C_{trough(C3)}$ was 1.39 (90% CI: 1.18–1.63) and the $AUC_{0–84}$ was 1.06 (90% CI: 0.92–1.21)
  - Predicted Mosun SC and IV concentrations are presented in **Figure 2**.

Figure 2. Predicted Mosun IV* and Mosun SC concentration over time.



*Within-study comparison cohort (CCOD: January 03, 2022).

Mosun SC achieved high rates of complete and durable responses

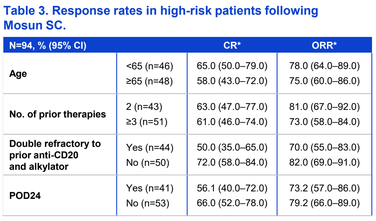
- The ORR and CR rate in patients treated with Mosun SC were 76.6% and 61.7%, respectively (**Table 2**)
  - A prespecified COVID-19 sensitivity analysis resulted in an ORR of 77.4% (90% CI: 67.6–85.5) and CR rate of 62.4% (90% CI: 51.7–72.2).
- Durability of CR and PFS with Mosun SC were similar to those observed with Mosun IV (**Table 2; Figure 3**).

Table 2. Efficacy in patients treated with Mosun IV and Mosun SC.

Efficacy endpoint	Mosun IV (N=90)*	Mosun SC (N=94)
Median time on study, months (range)	22.5 (2–32)	26.1 (1–40)
ORR,† n (%)	73 (81.1)	72 (76.6)
CR,† n (%)	54 (60.0)	58 (61.7)
Median time to first response,†‡ months (range)	1.5 (1–15)	2.8 (1–21)
Median DOR,† months (95% CI)	22.8 (22.4–NE)	22.8 (18.8–NE)
18-month DOR, % (95% CI)	58.5 (46.4–70.7)	64.1 (52.1–76.1)
Median DOCR,† months (95% CI)	NR (18.7–NE)	34.6 (20.7–NE)
18-month DOCR, % (95% CI)	67.6 (53.7–81.5)	69.7 (57.1–82.3)
Median PFS,† months (95% CI)	17.9 (10.9–NE)	23.7 (14.6–NE)
18-month PFS, % (95% CI)	49.7 (38.1–61.2)	56.8 (46.4–67.2)
Median OS, months (95% CI)	NR (NE–NE)	NR (NE–NE)
18-month OS, % (95% CI)	88.0 (80.9–95.0)	88.0 (81.3–94.6)

*Within-study comparison cohort (CCOD: January 3, 2022). †By IRF assessment. ‡Tumor assessment computed tomography and positron emission tomography scans were performed at screening, 6 weeks (optional), 3 months, and once every 3 months thereafter during therapy. IRF, independent review faculty; NE, not estimable; NR, not reached.

Figure 3. Kaplan–Meier estimates of (A) DOCR and (B) PFS with Mosun IV and Mosun SC in patients with R/R FL.



*Within-study comparison cohort (CCOD: January 3, 2022).

- In patients treated with Mosun SC, response rates in high-risk subgroups were generally consistent with the overall population (**Table 3**).

Table 3. Response rates in high-risk patients following Mosun SC.

N=94, % (95% CI)		CR*	ORR*
Age	<65 (n=46)	65.0 (50.0–79.0)	78.0 (64.0–89.0)
	≥65 (n=48)	58.0 (43.0–72.0)	75.0 (60.0–86.0)
No. of prior therapies	2 (n=43)	63.0 (47.0–77.0)	81.0 (67.0–92.0)
	≥3 (n=51)	61.0 (46.0–74.0)	73.0 (58.0–84.0)
Double refractory to prior anti-CD20 and alkylator	Yes (n=44)	50.0 (35.0–65.0)	70.0 (55.0–83.0)
	No (n=50)	72.0 (58.0–84.0)	82.0 (69.0–91.0)
POD24	Yes (n=41)	56.1 (40.0–72.0)	73.2 (57.0–86.0)
	No (n=53)	66.0 (52.0–78.0)	79.2 (66.0–89.0)

*By IRF assessment.

Mosun SC had a manageable safety profile

- In the Mosun SC cohort, the most common AEs of any grade were injection-site reactions (60.6%), fatigue (35.1%), CRS (29.8%), and diarrhea (20.2%)
  - Lower rates of Grade 3–4 AEs and serious AEs were observed in the Mosun SC cohort; higher rates of Grade 5 (fatal) AEs and AEs leading to discontinuation were attributed to patient enrollment during the COVID-19 pandemic (**Table 4**).

Table 4. Summary of safety profile.

n (%)	Mosun IV* (N=90)	Mosun SC (N=94)
AE	90 (100)	93 (98.9)
Grade 3–4 AE	63 (70.0)	46 (48.9)
Serious AE	42 (46.7)	37 (39.4)
Grade 5 (fatal) AE	1 (1.1)†	5 (5.3)‡
AE leading to Mosun discontinuation	4 (4.4)	7 (7.4)

*Within-study comparison cohort (CCOD: January 3, 2022). †One fatal AE of death (unknown cause).‡COVID-19 pneumonia (n=2), COVID-19 (n=1), general health deterioration (n=1), and hemophagocytic lymphohistiocytosis (n=1).

- In the Mosun SC cohort, three suspected all-grade immune effector cell-associated neurotoxicity syndrome events occurred: lethargy (Grade 1, n=2) and memory impairment (Grade 1, n=1).
- Infections were reported in 51 (54.3%) patients; 15 (16.0%) were Grade 3–4 and 3 (3.2%) were Grade 5 (fatal).
- Neutropenia occurred in 20 (21.3%) patients; most events were Grade 3–4 (18.0%).
- Febrile neutropenia was reported in two patients (both Grade 3) and both resolved.
- CRS was reported in 29.8% of patients in the Mosun SC cohort compared with 44.4% in the Mosun IV cohort (**Table 5**).
- In the Mosun SC cohort, CRS events were predominantly low grade and all events occurred during C1 (C1D1–7: 19%; C1D8–14: 13%; C1D15–21: 2%).

Table 5. CRS summary.

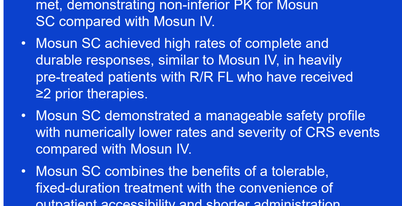
CRS by ASTCT* n (%), unless stated	Mosun IV (N=90)†	Mosun SC (N=94)
Any grade CRS	40 (44.4)	28 (29.8)
Grade 1	23 (25.6)	19 (20.2)
Grade 2	15 (16.7)	7 (7.4)
Grade 3–4	2 (2.2)	2 (2.1)
Serious AE	21 (23.3)	15 (16.0)
Median CRS duration, days (range)	2 (1–6)	2 (1–15)
CRS management		
Corticosteroids	11 (12.2)	6 (6.4)
Tocilizumab	7 (7.8)	8 (8.5)
CRS resolved	40 (100)	32 (100)

*By ASTCT consensus grading.8 †Within-study comparison cohort (CCOD: January 3, 2022). ASTCT, American Society for Transplantation and Cellular Therapy.

Cytokine levels were lower after Mosun SC step-up-dosing compared with Mosun IV

- Interleukin-6 (IL-6) levels increased after initial C1D1 administration with Mosun IV and decreased following subsequent dosing, despite an increase in drug concentration (**Figure 4**).
- Mosun SC elicited a lower cytokine response than Mosun IV.
- A similar trend was observed in interferon-γ levels (data not shown).

Figure 4. IL-6 levels after Mosun IV and SC administration.



Conclusions

- The co-primary PK endpoints ($C_{trough(C3)}$ and $AUC_{0–84}$) were met, demonstrating non-inferior PK for Mosun SC compared with Mosun IV.
- Mosun SC achieved high rates of complete and durable responses, similar to Mosun IV, in heavily pre-treated patients with R/R FL who have received ≥2 prior therapies.
- Mosun SC demonstrated a manageable safety profile with numerically lower rates and severity of CRS events compared with Mosun IV.
- Mosun SC combines the benefits of a tolerable, fixed-duration treatment with the convenience of outpatient accessibility and shorter administration times than Mosun IV.

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