Subcutaneous mosunetuzumab leads to high rates of durable responses, low rates of cytokine release syndrome, and non-inferior exposure compared with intravenous administration in patients with relapsed/refractory follicular lymphoma: primary analysis of a pivotal Phase II study

Nancy L. Bartlett,[1] Laurie H. Sehn,[2] Sarit Assouline,[3] Pratyush Giri,[4] John Kuruvilla,[5] Stephen J. Schuster,[6] Sung-Soo Yoon,[7] Keith Fay,[8] Georg Hess,[9] Martin Dreyling,[10] Norma C. Gutierrez,[11] Eva Cybulski,[12] Antonia Kwan,[12] Elicia Penuel,[12] Samuel Tracy,[12] Denison Kuruvilla,[12] Joseph Chen,[12] Volker Wiebking,[12] Michael C. Wei,[12] L. Elizabeth Budde[13]

Presented by Brannon Flores on behalf of the authors

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

Previously presented at the 66th American Society of Hematology (ASH) Annual Meeting December 7–10, 2024

Background

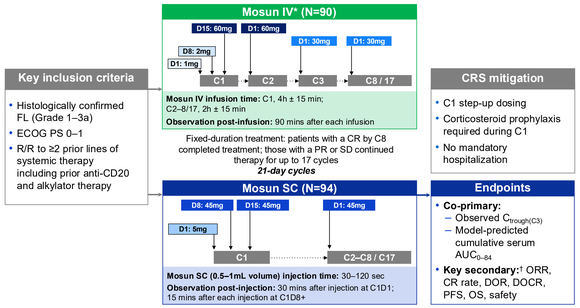
- Mosun is a CD20xCD3 T-cell engaging bispecific antibody that redirects T-cells to eliminate malignant B-cells[1]
  - Mosun IV is approved by the US FDA and EMA for the treatment of patients with R/R FL after ≥2 prior lines of therapy.[2,3]
- In a Phase II study (NCT02500407), fixed-duration Mosun IV 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.

[1]Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO, USA; [2]BC Cancer Centre for Lymphoid Cancer and the University of British Columbia, Vancouver, BC, Canada; [3]Jewish General Hospital, Montreal, QC, Canada; [4]Royal Adelaide Hospital, Adelaide, Australia; [5]Princess Margaret Cancer Centre, Toronto, ON, Canada; [6]Lymphoma Program, Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [7]Seoul National University Hospital, Seoul, South Korea; [8]St Vincent's Hospital and Royal North Shore Hospital, Sydney, Australia; [9]University Cancer Center Mainz, University Medical School of the Johannes Gutenberg-University, Mainz, Germany; [10]Ludwig-Maximilians-University Hospital Munich, Munich, Germany; [11]Institute of Biomedical Research of Salamanca (IBSAL), University Hospital, Salamanca, Spain; [12]Genentech, Inc., South San Francisco, CA, USA; [13]City of Hope National Medical Center, Duarte, CA, USA.

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)

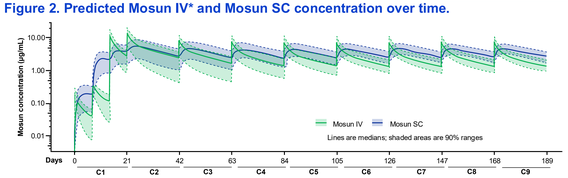
*Within-study comparison cohort (CCOD: January 3, 2022). BTKi, Bruton's kinase inhibitor; CAR, chimeric antigen receptor; FLIPI, Follicular Lymphoma International Prognostic Index; IMiD, immunomodulatory imide drugs; PI3K, phosphoinositide 3-kinase; POD24, disease progression (PD) within 24 months from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

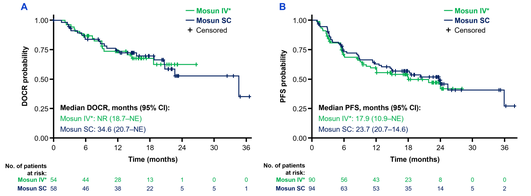
Table 2. Efficacy in patients treated with Mosun IV and Mosun SC.

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.

- Durability of CR and PFS with Mosun SC were similar to those observed with Mosun IV (**Table 2; Figure 3**).

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.

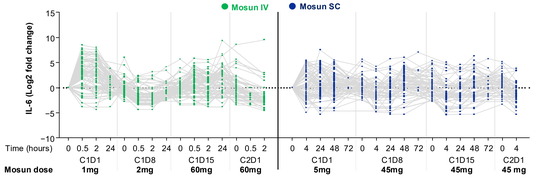
CRS by ASTCT* n (%), unless stated	Mosun IV (N=90)†	Mosun SC (N=94)
Any grade CRS	40 (44.4)	28 (29.8)
Grade 1	23 (25.6)	19 (20.2)
Grade 2	15 (16.7)	7 (7.4)
Grade 3–4	2 (2.2)	2 (2.1)
Serious AE	21 (23.3)	15 (16.0)
Median CRS duration, days (range)	2 (1–6)	2 (1–15)
CRS management		
Corticosteroids	11 (12.2)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

Presented at the 2025 Network for Collaborative Oncology Development & Advancement (NCODA) International Fall Summit | October 15–17, 2025

References

1. Sun LL, et al. Sci Transl Med 2015;7:287ra70.
2. LUNSUMIO™ US PI. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761263s000lbl.pdf [Accessed October 2024].
3. LUNSUMIO SmPC. https://www.medicines.org.uk/emc/product/14121/smpc#gref [Accessed October 2024].
4. Budde LE, et al. Lancet Oncol 2022;23:1055–65.
5. Bartlett NL, et al. ASH 2021;Poster P3573.
6. Matasar MJ, et al. ASH 2020;Abstract P2096.
7. Budde LE, et al. ASH 2022;Poster 1628.
8. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.

Acknowledgments

The authors would like to thank the patients and their families, the study investigators, the study coordinators and nurses, and the study sponsor. NCT02500407 is sponsored by Genentech, Inc. Safety analyses were provided by Fidelis Sabalvaro, MD, of Genentech, Inc. Third party medical writing assistance, under the direction of all authors, was provided by Deirdre Kelly, PhD, of Ashfield MedComms, an Inizio company, and was funded by F. Hoffmann-La Roche Ltd.

Disclosures

NLB: employment (Washington University School of Medicine), research funding (ADC Therapeutics, Autolus, BMS, Celgene, F. Hoffmann-La Roche Ltd, Forty Seven, Genentech, Inc., Janssen, Kite Pharma, Merck, Millennium, Pharmacyclics, Seattle Genetics), membership on an entity's board of directors or advisory committees (ADC Therapeutics, F. Hoffmann-La Roche Ltd, Genentech, Inc., Seattle Genetics), **LHS:** consultancy and honoraria (AbbVie, Acerta, Amgen, Apobiologix, AstraZeneca, BMS/Celgene, F. Hoffmann-La Roche Ltd, Genentech, Inc., Gilead, Incyte, Janssen, Kite, Karyopharm, Lundbeck, Merck, MorphoSys, Sandoz, Seattle Genetics, Servier, Teva, Takeda, TG Therapeutics, Verastem), **PG:** employment (Royal Adelaide Hospital), honoraria (F. Hoffmann-La Roche Ltd education session 2021), membership on an entity's board of directors or advisory committees (F. Hoffmann La-Roche Ltd 2019), **JK:** consultancy (AbbVie, BMS, F. Hoffmann-La Roche Ltd, Gilead, Merck, Seattle Genetics), research funding (AstraZeneca, F. Hoffmann-La Roche Ltd, Merck, Novartis), honoraria (AbbVie, Amgen, AstraZeneca, BMS, F. Hoffmann-La Roche Ltd, Genmab, Gilead, Incyte, Janssen, Merck, Novartis, Pfizer, Seattle Genetics), other (DSMB Karyopharm), **SJS:** consultancy (AbbVie, AstraZeneca, BeiGene, BioNTech; Caribou Biosciences, Celgene/Juno Therapeutics, F. Hoffmann-La Roche Ltd, Genentech, Inc., Genmab, Janssen, Kite Pharmaceuticals, Legend Biotech, Novartis, viTToria biotherapeutics), research funding (Celgene/Juno Therapeutics, F. Hoffmann-La Roche Ltd, Genentech, Inc., Merck, Novartis), honoraria (AstraZeneca, BeiGene, Celgene/Juno Therapeutics, F. Hoffmann-La Roche Ltd, Genentech, Inc., Janssen, Legend Biotech, Nordic Nanovector, Novartis), membership on an entity's board of directors or advisory committees (Caribou Biosciences, Nordic Nanovector, Novartis) **SA:** consultancy and honoraria (AbbVie, Amgen, AstraZeneca, BMS, BeiGene, F. Hoffmann-La Roche Ltd, Genentech, Inc., Gilead, Jazz, Novartis, Paladin), research funding (Novartis), **S-SY:** consultancy (Amgen, Antengene, Astellas, Celgene, Chugai, Janssen, Novartis, Takeda), research funding (F. Hoffmann-La Roche Ltd, Genentech, Inc., Kyowa Kirin, Yuhan), **KF:** employment (St. Vincent's Hospital), **NCG:** employment (University Hospital of Salamanca), honoraria (Amgen, Janssen), **MD:** research funding (AbbVie, Bayer, BMS/Celgene, F. Hoffmann-La Roche Ltd, Gilead/Kite, Janssen), honoraria (Amgen, AstraZeneca, F. Hoffmann-La Roche Ltd, Gilead/Kite, Janssen, Lilly/Loxo, Novartis), **GH:** consultancy (AbbVie, ADC Therapeutics, AstraZeneca, Genmab, Gilead/Kite, Incyte, Janssen, MorphoSys, Miltenyi, Novartis, F. Hoffmann-La Roche Ltd, Takeda), research funding (Celgene, F. Hoffmann-La Roche Ltd, Gilead/Kite, Incyte, Janssen, MorphoSys, Pfizer), honoraria (AbbVie, AstraZeneca, BeiGene, BMS, F. Hoffmann-La Roche Ltd, Genmab, Gilead, Incyte, Janssen), other (Gilead/Kite, Janssen), **VW, EC, AK, EP, ST, DK, JC:** employment (Genentech, Inc.), equity (F. Hoffmann-La Roche Ltd), **MCW:** employment (Genentech, Inc.), stockholder, stock options, and patents and royalties (F. Hoffmann-La Roche Ltd), **LEB:** employment (City of Hope National Medical Center), consultancy (ADC Therapeutics, AstraZeneca, AbbVie, F. Hoffmann-La Roche Ltd, Genentech, Inc., Genmab, Janssen, Regeneron), research funding (AstraZeneca, Merck, Mustang Therapeutics).