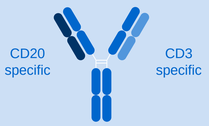
Updated experience from mosunetuzumab in multiply relapsed follicular lymphoma: promising efficacy from a Phase I trial

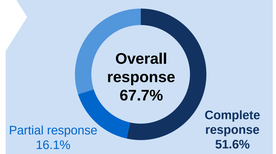
Sarit Assouline,[1] Won Seog Kim,[2] Laurie H. Sehn,[3] Stephen J. Schuster,[4] Chan Yoon Cheah,[5] Loretta J. Nastoupil,[6] **Mazyar Shadman**,[7] Sung-Soo Yoon,[8] Matthew J. Matasar,[9] Catherine Diefenbach,[10] Gareth P. Gregory,[11] Nancy L. Bartlett,[12] Michael C. Wei,[13] Michelle Y. Doral,[13] Shen Yin,[13] Raluca Negricea,[14] Chi-Chung Li,[13] Elicia Penuel,[13] Huang Huang,[14] L. Elizabeth Budde[15]

Summary

Mosunetuzumab is a novel T-cell engaging bispecific antibody.



Mosunetuzumab showed high response rates in participants with R/R FL.



A Phase III clinical trial will investigate mosunetuzumab in combination with lenalidomide in patients with R/R FL.

Mosunetuzumab induces pharmacodynamic changes in T-cell margination and activation.

[1]Jewish General Hospital, Montreal, QC, Canada; [2]Sungkyunkwan University School of Medicine, Samsung Medical Center, Seoul, Republic of Korea; [3]BC Cancer Centre for Lymphoid Cancer and University of British Columbia, Vancouver, BC, Canada; [4]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [5]Linear Clinical Research and Sir Charles Gairdner Hospital, Nedlands, WA, Australia; [6]MD Anderson Cancer Center, Houston, TX, USA; [7]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [8]Seoul National University Hospital, Seoul, Republic of Korea; [9]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [10]Perlmutter Cancer Center at NYU Langone Health, New York, NY, USA; [11]School of Clinical Sciences at Monash Health, Monash University, Clayton, VIC, Australia; [12]Washington University School of Medicine, St. Louis, MO, USA; [13]Genentech, Inc., South San Francisco, CA, USA; [14]F. Hoffmann-La Roche Limited, Mississauga, ON, Canada; [15]City of Hope National Medical Center, Duarte, CA, USA.

Background

- Follicular lymphoma (FL) is characterized by recurrent relapses. Despite available therapies FL remains an incurable disease.
- Treatment options for patients with FL having received ≥2 prior systemic therapies is limited, and patients typically have a poor prognosis.[1]
- High-risk subgroups include patients who have progression of disease within 24 months after the initiation of frontline treatment (POD24)[2] or are refractory to both a prior anti-CD20 antibody and an alkylating agent (double refractory).
- Mosunetuzumab is a full-length, fully humanized immunoglobulin G1 CD20xCD3 bispecific antibody that redirects T cells to engage and eliminate malignant B cells.[3]
- We present the updated safety, efficacy and pharmacokinetics of mosunetuzumab in patients with relapsed/refractory (R/R) B-cell lymphoma from an ongoing open-label, multicenter, Phase I/Ib, dose-escalation and expansion trial (GO29781; NCT02500407).

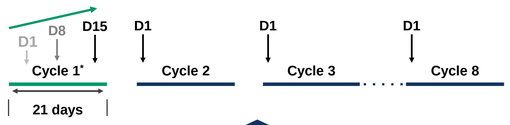
GO29781 is an ongoing Phase I/Ib study of mosunetuzumab in R/R FL

- Patients with R/R FL (Grades 1–3a) who were ≥18 years old, had ≥2 prior systemic therapies, expected to express CD20 and had an Eastern Cooperative Oncology Group (ECOG) performance status ≤1 were eligible for inclusion.
- Participants received intravenous mosunetuzumab as step-doses in Cycle 1 days 1 and 8 and then target doses on Day 15 and Day 1 of each subsequent 21-day cycle (**Figure 1**).
- Primary objectives included efficacy of mosunetuzumab including recommended Phase II dose and best objective response and safety and tolerability of mosunetuzumab inclusive of dose-limiting toxicities and maximum tolerated dose.

Figure 1. Mosunetuzumab dosing schedule

Cycle 1 D1/D8/D15 dose: 0.4/1.0/2.8–1/2/13.5mg

Cycles 2–8 (D1) dose: Cycle 1 D15 dose



Patients who achieve CR by Cycle 8 discontinue therapy; for patients with PR or SD, treatment may continue up to 17 cycles until PD or unacceptable toxicity
Retreatment was permitted for patients with a complete response who relapsed

*Premedication with steroids (20mg IV dexamethasone or 80mg IV methylprednisolone) required C1–2 and optional C3+.
C, cycle; CR, complete response; D, day; IV, intravenous; PD, progressive disease; PR, partial response; SD, stable disease

62 patients with R/R FL were treated with mosunetuzumab after ≥2 prior systemic therapies

- At data cut-off on August 07, 2020, 62 participants were included (**Table 1**).
- Participants had a median age (range) of 59 (27–85) years and received a median (range) of 3 (2–11) prior therapies. Thirty-eight participants (61.3%) were double refractory (refractory to both a prior anti-CD20 antibody and an alkylating agent), 29 (46.8%) had POD24 after first systemic therapy, and four (6.5%) received prior chimeric antigen receptor T-cell (CAR-T) therapy.

Table 1. Demographics and baseline characteristics

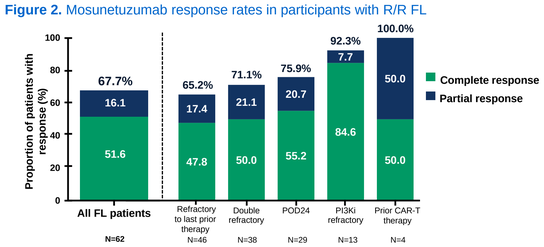
Characteristics		R/R FL (N=62)
Median age, years (range)		59 (27–85)
Sex, n (%)		
	Female	22 (35.5)
	Male	40 (64.5)
ECOG performance status at baseline, n (%)		
	0	37 (59.7)
	1	25 (40.3)
High-risk subgroups, n (%)		
	Double refractory	38 (61.3)
	POD24	29 (46.8)
Prior therapies		**R/R FL (N=62)**
Median prior systemic therapies, n (range)		3 (2–11)
Prior therapies, n (%)		
	Anti-CD20	62 (100)
	Alkylator therapy	62 (100)
	PI3Ki	13 (21.0)
	Autologous stem cell transplant	12 (19.4)
	Immunomodulatory imide drugs	5 (8.1)
	CAR-T	4 (6.5)
Refractory* to last prior therapy, n (%)		46 (74.2)
Refractory* to prior anti-CD20 therapy, n (%)		54 (87.1)

*Refractory defined as no response (PR or CR) or PD within ≤6 months of treatment.
CAR-T, chimeric antigen receptor T-cell; CR, complete response; ECOG, Eastern Cooperative Oncology Group; FL, follicular lymphoma; PD, progressive disease; PI3Ki, phosphoinositide 3-kinase inhibitor; POD24, progression of disease within 24 months after systemic therapy; PR, partial response; R/R, relapsed/refractory.

High and consistent complete response rates were observed in high-risk populations

- The overall response rate (ORR) and complete response (CR) rate were 67.7% (42/62) and 51.6% (32/62), respectively (**Figure 2**).

Figure 2. Mosunetuzumab response rates in participants with R/R FL

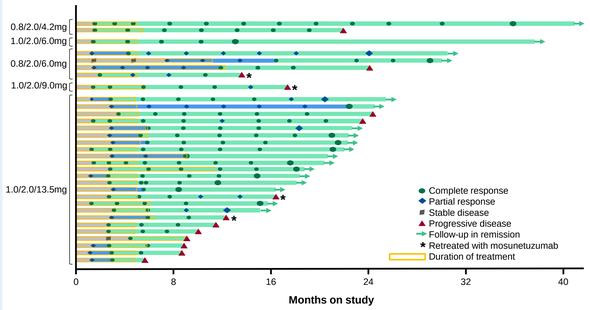


CAR-T, chimeric antigen receptor T-cell; FL, follicular lymphoma; PI3Ki, phosphoinositide 3-kinase inhibitor; POD24, progression of disease within 24 months; R/R, relapsed/refractory.

Durable responses were achieved with mosunetuzumab

- Time to median follow-up after first response was 18.4 months (range 2–34; **Figure 3**).
- Time to median duration of response (DOR) was 20.4 months (95% confidence interval [CI]: 9.4–22.7), and in participants achieving CR was 21.0 months (95% CI: 16.0–22.7).
- In total 4 participants (6.5%) were retreated (2 CR and 2 partial response [PR]).

Figure 3. Duration of response in participants who achieved complete response (efficacy population)



Mosunetuzumab has an acceptable safety profile

- Adverse events (AEs) and serious adverse events (SAE) were reported in 60 (96.8%) and 22 participants (35.5%), respectively (**Table 2**).

Table 2. Summary of adverse events (safety evaluable population)

Adverse event (AE), n (%)	Participants (N=62)
Any AE	**60 (96.8)**
Treatment related	45 (72.6)
Serious AE	**22 (35.5)**
Treatment related	9 (14.5)
Grade ≥3 AE	**42 (67.7)**
Treatment related	22 (35.5)
Grade 5 AE (excluding disease progression)	**1* (1.6)**
AE leading to treatment discontinuation	**5** (8.1)**
Treatment related	4 (6.5)

*Grade 5 AE: pneumonia (n=1; onset Day 73). **AEs leading to treatment discontinuation: pneumonia, atrial flutter (unrelated to treatment), neutropenia, arthritis, alanine aminotransferase increased (n=1 each).

- The most common (>5% of participants) Grade 3–4 AE was neutropenia (22.6%), of which 15.1% were deemed related to mosunetuzumab (**Table 3**).
- Out of 23 any grade neutropenia, 21 (91.3%) resolved by the data cut-off; febrile neutropenia (any Grade): 2 (3.2%)

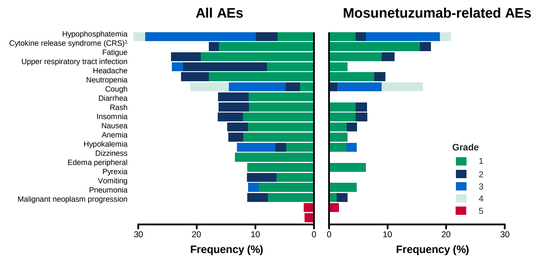
Table 3. Summary of Grade 3–4 adverse events (safety evaluable population)

Common Grade 3–4 adverse events (>5% of participants)*	Participants (N=62)
Neutropenia	**14 (22.6%)**
Treatment related	10 (15.1%)
Hypophosphatemia	**13 (21.0%)**
Treatment related	13 (21.0%)
Anemia	**4 (6.5%)**
Treatment related	1 (1.6%)
Serious infections	**12 (19.5%)**

*At least one adverse event.

- The most common (>10% of participants) grade ≥3 AEs included hypophosphatemia and neutropenia (**Figure 4**).

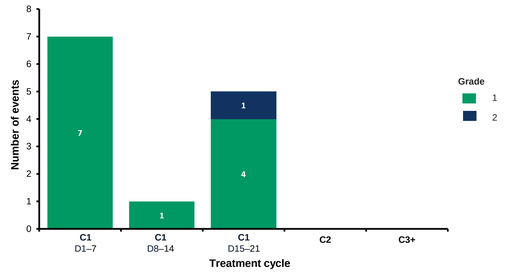
Figure 4. Grade 1–4 AEs with an incidence of ≥10% or Grade 5



1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25:625–38.
AE, adverse event.

Cytokine release syndrome (CRS) events all occurred during Cycle 1 step-up dosing

Figure 5. CRS events by treatment cycle and ASTCT Grade[1]



1. Lee DW, et al. Biol Blood Marrow Transplant 2019;25(4):625–38
ASTCT, American Society of Transplantation and Cellular Therapy; C, cycle; D, day.

CRS events were all Grade 1 or 2

- All CRS events resolved without tocilizumab, intensive care unit admission, or vasopressors.
- CRS signs and symptoms included: pyrexia (17.7%, n=11), headache (4.8%, n=3) and tachycardia (3.2%, n=2).
- Similar CR rates were observed between participants who experienced CRS (45% [5/11]) and those who did not (52.9% [27/51]).

Table 4. Summary of CRS (safety evaluable population)

n (%) with ≥1 AE	Safety evaluable patients (N=62)
Any grade CRS (ASTCT grading)	**11 (17.7%)**
Grade 1	10 (16.1%)
Grade 2	1 (1.6%)
Grade ≥3	0
Serious CRS events*	**4 (6.5%)**
Median onset of first CRS event	1 day (range: 1.0–24.0)
Median duration	2 days (range: 1.0–8.0)

*Serious CRS events: Grade 1 (n=3), Grade 2 (n=1). All were serious die to monitoring of CRS.
AE, adverse event; ASTCT, American Society of Transplantation and Cellular Therapy; CRS, cytokine release syndrome.

Conclusions and future directions

Fixed duration of mosunetuzumab induces high and consistent response rates across multiple high-risk FL subsets, with durable responses. Assessment of higher dose levels is ongoing to maximize efficacy.

Mosunetuzumab monotherapy has an acceptable safety profile, with low Grade 2 and no Grade ≥3 CRS in patients with previously treated FL.

A Phase III clinical trial will investigate mosunetuzumab in combination with lenalidomide in patients with R/R FL.

References

1. Batlevi CL, et al. Blood Cancer J 2020;10:74.
2. Casulo C, et al. Blood 2017;133:1540–7.
3. Sun LL, et al. Sci Transl Med 2015;7(282):287ra70.

Acknowledgments

The authors would like to thank the study participants and their families, as well as the study investigators, research coordinators and nurses. This study was sponsored by Genentech, Inc. Medical writing support for the development of this poster, under the direction of the authors, was provided by Georgia Pangratiou, PhD, of Ashfield MedComms, an Ashfield Health company, and funded by F. Hoffmann-La Roche Ltd.

Disclosures

SA: consultancy and honoraria (Pfizer, Janssen, AbbVie, AstraZeneca, F. Hoffmann-La Roche Ltd, BeiGene); speakers bureau (Janssen, AbbVie, AstraZeneca); research funding (F. Hoffmann-La Roche Ltd, BeiGene, Takeda). **WSK**: research funding (F. Hoffmann-La Roche Ltd, Pfizer, JJ, Celltrion, Kyowa Kirn, Donga, Mundipharma). **LHS**: consultancy and honoraria (Amgen, AbbVie, Apobiologix, AstraZeneca, Genentech, Inc., Acerta, Celgene, Janssen, Kite, Gilead, Karyopharm, Lundbeck, Merck Sharp & Dohme, MorphoSys, F. Hoffmann-La Roche Ltd, Seattle Genetics, Teva, Takeda, Servier, Chugai, TG Therapeutics, Verastem Oncology); research funding (Genentech, Inc., F. Hoffmann-La Roche Ltd, Teva). **SJS**: consultancy and honoraria (AlloGene, AstraZeneca, BeiGene, Genentech, Inc./ F. Hoffmann-La Roche Ltd, Juno/Celgene, Loxo Oncology, Nordic Nanovector, Novartis, Tessa Therapeutics); research funding (Novartis, Genentech, Inc./ F. Hoffmann-La Roche Ltd). **CYC**: honoraria (Celgene, F. Hoffmann-La Roche Ltd, Merck Sharp & Dohme, Janssen, Gilead, Ascentage Pharma, Acerta, Loxo Oncology, TG therapeutics); research funding (Celgene, F. Hoffmann-La Roche Ltd, AbbVie, Merck Sharp & Dohme). **LJN**: honoraria (Celgene, Genentech, Inc., Bayer, Garnida, Gilead/Kite, Novartis, TG Therapeutics, Janssen, Pfizer); research funding (Karus Therapeutics, Celgene, Genentech, Inc., Novartis, Merck Sharp & Dohme, TG Therapeutics, LAM Therapeutics, Janssen, Pfizer). **MS**: current employment (Fred Hutchinson/University of Washington); consultancy (AbbVie, Genentech, Inc., AstraZeneca, Sound Biologics, Pharmacyclics, Verastem, ADC Therapeutics, BeiGene, Cellectar, Bristol-Myers Squibb, Mophosys, Atara Biotherapeutics); research funding (Mustang Bio, Celgene, Pharmacyclics, Gilead, Genentech, Inc., AbbVie, TG Therapeutics, BeiGene, AstraZeneca, Sunesis). **S-SY**: consultancy (Amgen, Novartis, Janssen); honoraria (Amgen, Novartis); research funding (Kyowahako Kirin, F. Hoffmann-La Roche Ltd, YuhanPharma). **MJM**: current employment (Memorial Sloan Kettering Cancer Center); consultancy (Genentech, Inc., Merck Sharp & Dohme, Bayer, Juno Therapeutics, F. Hoffmann-La Roche Ltd, Teva, Rocket Medical, Seattle Genetics, Daiichi Sankyo, Takeda); honoraria (Genentech, Inc., Bayer, F. Hoffmann-La Roche Ltd, Seattle Genetics, Takeda, GlaxoSmithKline, Janssen, Pharmacyclics, Immunovaccine Technologies); research funding (Genentech, Inc., Bayer, F. Hoffmann-La Roche Ltd, Rocket Medical, Seattle Genetics, GlaxoSmithKline, IGM Biosciences, Janssen, Pharmacyclics, Immunovaccine Technologies); current equity holder in publicly-traded company (Merck Sharp & Dohme). **CD**: consultancy (Bristol-Myers Squibb, Genentech, Inc., Merck Sharp & Dohme, Seattle Genetics); research funding (Bristol-Myers Squibb, Denovo, Genentech, Inc., Incyte, LAM Therapeutics, MEI, Merck Sharp & Dohme, Seattle Genetics, Millenium/Takeda, Trillium). **GPG**: consultancy (Janssen); honoraria (F. Hoffmann-La Roche Ltd, Novartis, Sandoz, Gilead, AbbVie, Merck Sharp & Dohme); speakers bureau (F. Hoffmann-La Roche Ltd, Novartis, AbbVie); membership on an entity's Board of Directors or advisory committees (F. Hoffmann-La Roche Ltd, Novartis, Sandoz, Gilead). **NLB**: consultancy (Kite Pharma, Pfizer, Seattle Genetics); research funding (ADC Therapeutics, Autolus, Bristol-Myers Squibb, Celgene, Forty Seven, Genentech, Inc., Immune Design, Janssen, Kite Pharma, Merck Sharp & Dohme, Millennium, Pfizer, Pharmacyclics, Seattle Genetics, Affimed Therapeutics, Dynavax, Gilead, MedImmune, Novartis); membership on an entity's Board of Directors or advisory committees (Kite Pharma, Pfizer, ADC Therapeutics, Genentech, Inc./F. Hoffmann-La Roche Ltd, Seattle Genetics, BTG, Acerta). **MCW and MYD**: current employment (Genentech, Inc.); current equity holder in a publicly-traded company (F. Hoffmann-La Roche Ltd). **SY**: current employment and current equity holder in publicly-traded company (Genentech, Inc.). **RN**: current employment (Genentech, Inc.). **C-CL and EP**: current employment (Genentech, Inc./F. Hoffmann-La Roche Ltd); current equity holder in a publicly-traded company (F. Hoffmann-La Roche Ltd). **HH**: current employment (F. Hoffmann-La Roche Ltd). **LEB**: consultancy (F. Hoffmann-La Roche Ltd, Kite Pharma); speakers bureau (AstraZeneca); research funding (Merck Sharp & Dohme, Amgen, AstraZeneca, Mustang Therapeutics).