Patterns of response to 200 mg linvoseltamab in patients with relapsed/refractory multiple myeloma: Longer follow-up of the LINKER-MM1 study

Sundar Jagannath[1], Joshua Richter[1], Madhav V. Dhodapkar[2], James E. Hoffman[3], Hans C. Lee[4], Attaya Suvannasankha[5], Mansi R. Shah[6], Suzanne Lentzsch[7], Jeffrey A. Zonder[8], Rachid Baz[9], Joseph J. Maly[10], Swathi Namburi[11], Ka Lung Wu[12], Matthew Pianko[13], Jing Christine Ye[13], Rebecca Silbermann[14], Chang-Ki Min[15], Marie-Christiane Vekemans[16], Markus Munder[17], Ja Min Byun[18], Joaquín Martínez Lopez[19], Michelle DeVeaux[20], Dhruti Chokshi[20], Anita Boyapati[20], Anasuya Hazra[20], Karen Rodriguez Lorenc[20], Glenn S. Kroog[20], Yariv Houvras[20], Naresh Bumma[21]

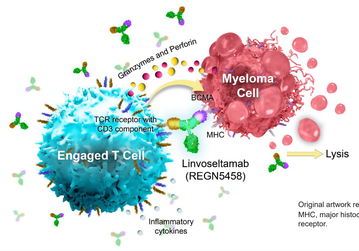
[1]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [2]Emory University School of Medicine, Atlanta, GA, USA; [3]University of Miami Health System, Miami, FL, USA; [4]The University of Texas MD Anderson Cancer Centre, Houston, TX, USA; [5]Indiana University Simon Cancer Center and Roudebush VAMC, Indianapolis, IN, USA; [6]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [7]Columbia University Medical Center, New York, NY, USA; [8]Karmanos Cancer Institute, Detroit, MI, USA; [9]Department of Malignant Hematology, H. Lee Moffitt Cancer Center, Tampa, FL, USA; [10]Norton Cancer Institute, Louisville, KY, USA; [11]Swedish Cancer Institute Seattle, WA, USA; [12]Ziekenhuis Netwerk Antwerpen Stuivenberg, Antwerp, Belgium; [13]Rogel Cancer Center, University of Michigan Medical School, Ann Arbor, MI, USA; [14]Knight Cancer Institute, Oregon Health & Science University, Portland, OR, USA; [15]Department of Hematology, College of Medicine, Catholic Hematology Hospital and Leukemia Research Institute, Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, South Korea; [16]Department of Hematology, Cliniques Universitaires Saint-Luc, Université Catholique de Louvain (UCLouvain), Brussels, Belgium; [17]Department of Internal Medicine III, University Medical Center Mainz, Mainz, Germany; [18]Department of Internal Medicine, Seoul National University College of Medicine, Seoul National University Hospital, Seoul, Korea; [19]Hospital Universitario 12 de octubre, Universidad Complutense, CNIO, Madrid, Spain; [20]Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA; [21]The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA.

Background

- Linvoseltamab, REGN5458, is a human BCMA×CD3 bispecific antibody that effectively induces T-cell-mediated cytotoxicity of malignant MM plasma cells
- In the ongoing LINKER-MM1 (NCT03761108) study, linvoseltamab demonstrated encouraging efficacy and a generally manageable safety profile in patients with R/R MM[1]
- Here we report the results at 8.1 months median duration of follow-up from all patients treated with the 200 mg dose that includes 12 Phase 1 patients and 105 Phase 2 patients

Data cut-off date of June 7, 2023.
[1]Lee HC, et al. American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, USA, 2–6 June 2023 Oral Presentation.
BCMA, B-cell maturation antigen; CD, cluster of differentiation; MM multiple myeloma; R/R MM relapses/refractory MM.

Figure 1. Linvoseltamab mechanism of action



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MHC, major histocompatibility complex; TCR, T-cell receptor.

LINKER-MM1 study: Phase 2 design

Figure 2. Linvoseltamab IV dosing schedule for 200 mg phase 2 expansion cohort

- The first full dose was given at week 3 of the study
- For patients who achieved VGPR or better by week 24, dosing frequency decreased from 2 to 4 weeks

Key eligibility criteria for phase 2:
- Active MM per IMWG criteria
- Prior ≥three lines of therapy and triple-exposed disease (exposed to at least one IMiD + one PI + one anti-CD38 Ab); or triple-refractory disease (refractory to at least one IMiD + one PI + one anti-CD38 Ab)

Key phase 2 objectives:
- Primary: ORR as determined by a blinded independent review committee (IRC; per IMWG criteria)
- Secondary: ORR by investigator assessment, DOR, PFS, MRD status, and OS

Ab, antibody; DOR, duration of response; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; IV, intravenous; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; PI, proteasome inhibitor; PFS, progression-free survival; VGPR, very good partial response.

Baseline Characteristics

Table 1. Patient and disease characteristics

n (%), unless otherwise stated	200 mg (n=117)
Age	
Median (range)	70 (37–91)
≥75	31 (26.5)
Male	64 (54.7)
Race	
White	83 (70.9)
Black or African American	20 (17.1)
Asian	10 (8.5)
Eastern Cooperative Oncology Group (ECOG) performance status	
0	33 (28.2)
1	84 (71.8)
ISS Stage	
I	49 (41.9)
II	41 (35.0)
III	21 (17.9)
Missing	6 (5.1)
Extramedullary plasmacytomas (EMP)	17 (14.5)
High risk cytogenetics*	46 (39.3)
Bone marrow plasma cells (BMPC) percentage	
<50%	64 (54.7)
≥50%	27 (23.1)
Missing	26 (22.2)
Soluble B-cell maturation antigen (BCMA), median (range) ng/mL	365.5 (18.7–4,430.0)

*Presence of del(17p) and/or translocation t(4;14) and/or translocation t(14;16).

Table 2. Prior treatments

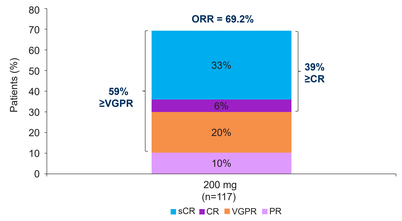
n (%)	200 mg (n=117)
Prior autologous transplant	75 (64.1)
Median prior lines of therapy, n (range)	5 (2–16)
Exposure status	
At least triple-exposed	117 (100)
At least quad-exposed	112 (95.7)
At least penta-exposed	89 (76.1)
Refractory status	
At least triple-refractory	94 (80.3)
At least quad-refractory	74 (63.2)
At least penta-refractory	30 (25.6)
Refractory to last line of therapy§	98 (83.8)

§Includes patients with a lack of response or relapse within 60 days of last line of therapy. Triple-exposed/refractory: ≥1 PI, ≥1 IMiD, and ≥1 anti-CD38 Ab. Quad-exposed/refractory: ≥2 PI, ≥1 IMiD, and ≥1 anti-CD38 Ab or ≥1 PI, ≥2 IMiD, and ≥1 anti-CD38 Ab. Penta-exposed/refractory: ≥2 PI, ≥2 IMiD, and 1 anti-CD38 Ab; BMPC, bone marrow plasma cells; IMiD, immunomodulatory drug; PI, proteasome inhibitor.

- Median age was 70 years old, with 37.6% of the population <65, 35.9% 65-74, and 26.5% ≥75 years of age
- EMP were ≥2 cm and excluded patients with only paramedullary plasmacytomas

Efficacy per IRC assessment

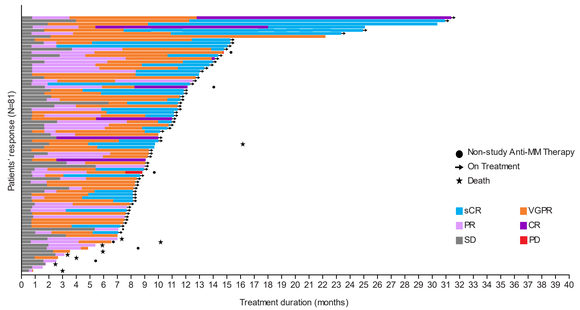
Figure 3. Objective response rate



- ORR was 69.2% with 59% of patients achieving ≥ VGPR and 39% achieving ≥CR
- Median time to ≥PR was 1 month, to ≥VGPR was 2.6 months, and to ≥CR, 7.6 months
- In patients who had prior exposure to the anti-BCMA antibody-drug conjugate belantamab mafodotin (n=10), ORR was 70%
- Among patients with CR or sCR with available MRD data (N=37), 50%‡ were MRD-negative at 10^{-5}

Data cut-off date of June 7, 2023. Median duration of follow-up: 8.1 months (range 0.2–31.5)
‡MRD data include clonoSEQ and Euroflow. Eight patients had missing data due to missing specimens or specimen quality.
CR, complete response; PR, partial response; sCR, stringent complete response.

Figure 4. Responses per IRC are early, durable, and deepen over time*

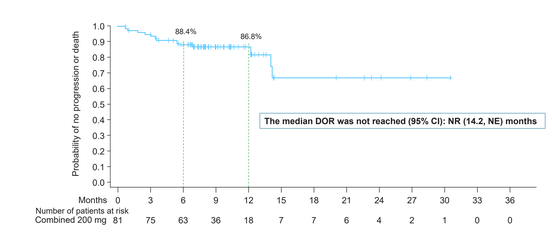


- At 8.1 months median duration of follow-up, 50% of patients are still ongoing core treatment

*Estimated Kaplan–Meier method. Data cut-off date of June 7, 2023. Median duration of follow-up: 8.1 months (range 0.2–31.5)
MR, minimal response; NE, not evaluable; PD, progressive disease; PR, partial response; SD, stable disease.

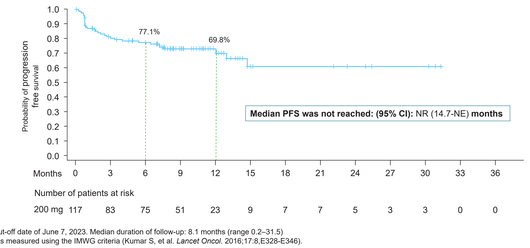
Duration of Response Per IRC Assessment

Figure 5. Kaplan–Meier curve of DOR per IRC assessment



Data cut-off date of June 7, 2023. Median duration of follow-up: 8.1 months (range 0.2–31.5)
Percentages are based on number of patients with PR; * Initial dose.
CI, confidence interval; NE, not evaluable.

Figure 6. Kaplan–Meier curve of PFS† per IRC assessment



Data cut-off date of June 7, 2023. Median duration of follow-up: 8.1 months (range 0.2–31.5)
†PFS as measured using the IMWG criteria (Kumar S, et al. *Lancet Oncol*. 2016;17:8,E328-E346).

Safety

Table 3. Treatment–emergent adverse events

	200 mg cohort – (n=117)	
Treatment exposure, median (range), weeks	35.0 (1 – 137)	
TEAEs‡, n (%)	Any grade	Grade 3–4
Hematologic TEAEs		
Neutropenia†	38.5	37.6
Anemia†	38.5	30.8
Thrombocytopenia†	17.9	14.5
Lymphopenia†	12.0	11.1
Non-hematologic TEAEs		
CRS	46.2	0.9
Diarrhea	35.0	1.7
Cough	34.2	0
Fatigue	32.5	0
Arthralgia	29.1	0
Hypokalaemia	22.2	2.6
Headache†	21.4	0.9
Nausea	21.4	0
Dyspnea	19.7	0.9
Back pain	17.9	1.7
Vomiting	17.9	0
Constipation	16.2	0
Pyrexia	16.2	0

- The most common Grade 3/4 TEAEs were hematologic events
- Common non-hematologic events were mainly Grade 1/2
- CRS was the most reported TEAE and was mostly mild to moderate (0.9%, Grade 3)
- Adjudicated ICANS* (any grade) occurred in nine patients (7.7%); mostly after the initial dose and all concurrently with CRS; Grade 3 ICANS occurred in 3 patients, no Grade 4-5 cases
- TEAEs leading to death on treatment or within 30 days following the last dose were reported in 13 patients, with the majority due to infections (10 patients). Two events (one *pneumocystis jirovecii* pneumonia, one pseudomonal sepsis) were considered treatment drug-related, as per the treating physician.

Data cut-off date of June 7, 2023. Median duration of follow-up: 8.1 months (range 0.2–31.5)
AEs per NCI-CTCAE v5.0. CRS per ASTCT (Lee DW, et al. Biol Blood Marrow Transplant. 2019;25:625-638). *Neurologic events consistent with ICANS were reviewed by the sponsor and evaluated according to guidelines in Lee., 2019. ‡Table includes TEAEs of any grade reported in ≥15% of patients; †Composite terms. ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; ICANS, immune effector cell-associated neurotoxicity syndrome; NCI, National Cancer Institute; TEAE, treatment-emergent adverse event.

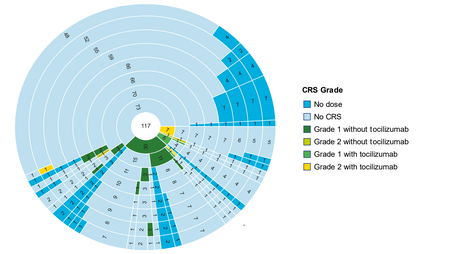
Table 4. TEAE of interest: Infections

	200 mg cohort (n=117)	
TEAEs, n (%)	Any grade	Grade 3–4
Infections	81 (69.2)	43 (36.8)
Pneumonia	18 (15.4)	16 (13.7)
COVID-19	17 (14.5)	6 (5.1)
Upper respiratory tract	15 (12.8)	2 (1.7)
Opportunistic infections*	10 (8.5)	7 (6.0)
PJP	5 (4.3)	3 (2.6)
CMV infections	2 (1.7)	2 (1.7)
CMV reactivation	3 (2.6)	2 (1.7)

*One case of progressive multifocal leukoencephalopathy (PML) occurred after the data cutoff date;
AEs per NCI-CTCAE v5.0. CMV, cytomegalovirus; COVID-19, coronavirus disease 2019; CTCAE, Common Terminology Criteria for Adverse Events; NCI, National Cancer Institute; PJP, *Pneumocystis jirovecii* pneumonia; TEAE, treatment-emergent adverse event.

- All cases of PJP occurred prior to the institution of mandatory prophylaxis

Figure 7. A temporal analysis of CRS onset, severity and anti IL-6R use



Data cut-off date of June 7, 2023. Median duration of follow-up: 8.1 months (range 0.2–31.5).
The sunburst plot presents the incidence and severity of CRS and use of tocilizumab by patient with each of the first 8 treatment weeks as a separate ring starting with week 1 in the innermost ring. Within each ring the number of patients with each combination of CRS grade and use/no use of tocilizumab is shown by a different color.

- CRS was reported in 46.3% of patients; Grade 1 in 35.9%, Grade 2 in 9.4% of patients, and Grade 3 in 0.9% (one patient)
- Most CRS occurred in the step-up dosing period (most commonly after the first dose) and before the first full dose on week 3
- No Grade 3 or higher CRS occurred after the step-up dosing period
- No Grade 4 or Grade 5 CRS reported
- CRS onset usually occurred on the day of dosing, with resolution within 1 day
- 22 (19%) patients experienced recurrent CRS
- Tocilizumab was administered to 24 (20.5%) patients
- Recurrent CRS after tocilizumab was rare; only one patient experienced CRS after tocilizumab.

Conclusions

- At a median follow up of 8.1 months, **linvoseltamab induced a high rate of responses (per IRC) that deepened further** since the last data cut (median follow-up of 5.6 months[1])
  - At the recommended dose of 200 mg: 69% ORR, 39% ≥CR, and 59% ≥VGPR
  - Among patients with CR or sCR with available MRD data (N=37), **50% had no measurable residual disease**
- **Responses were early and durable**
  - Median time to response was 1 month
  - Median DOR was not reached; **estimated 9-month rate of DOR was 86.8%**
  - Median PFS was not reached; **estimated 9-month rate of PFS was 72.8%**
- The favorable efficacy profile of linvoseltamab is complemented by a **convenient administration schedule**: Q4W from week 24 onwards for patients who reached VGPR or better
- Linvoseltamab showed a generally manageable safety profile with **no new safety signals with longer follow up**
  - The most common TEAEs were CRS, neutropenia (37.6% grade 3/4) and anemia (30.8% grade 3/4)
  - CRS rate was 46.2% (0.9% Grade 3; 0% ≥ Grade 4) and effectively managed with standard of care
- The predictable timing and low rate of CRS allows as per protocol to date an **inpatient monitoring schedule** of 1 day at week 1 and week 2
- **A Phase 3 Trial, LINKER-MM3, is ongoing** in patients with RRMM (NCT05730036)

[1]Lee HC, et al. American Society of Clinical Oncology (ASCO) Annual Meeting, Chicago, IL, USA, 2–6 June 2023 Oral Presentation.

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