Safety and efficacy of linvoseltamab combined with anti-CD38 monoclonal antibodies daratumumab or isatuximab in patients with relapsed/refractory multiple myeloma: Initial results from the multicohort, Phase 1b LINKER-MM2 trial

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Background and objective

- Several novel agents, including bispecific antibodies and CAR T cell therapies, have recently become available for the treatment of patients with heavily pretreated RRMM[1]
- LINVO is a human BCMA×CD3 bispecific antibody approved for the treatment of patients with TCE RRMM after ≥3 prior therapies (EU)[2] or ≥4 prior LoT (US)[3]
  - In the Phase 1/2 LINKER-MM1 trial (NCT03761108) in patients with RRMM, LINVO demonstrated high efficacy and generally manageable safety with an ORR of 71% (≥CR 52%); infections were reported in 75% of patients and the most common TEAE was CRS (46%)[4]
- LINVO in combination with several established and investigational anti-cancer therapies is under evaluation in the multicohort Phase 1b LINKER-MM2 trial (NCT05137054)[5]
  - Combination therapy with an anti-CD38 mAb, such as DARA or ISA, may provide additional benefit to patients with RRMM[6,7]
- Here, we report the pooled safety and efficacy data of the combination therapies LINVO + DARA or ISA across three linvoseltamab dose cohorts, from the dose-finding portion of the LINKER-MM2 trial, at a median overall follow-up of 11.6 months

Key takeaways

- **Combining LINVO with anti-CD38 mAbs DARA or ISA was feasible in patients with heavily pretreated RRMM, including patients exposed (50%) or refractory (33%) to anti-CD38 mAbs**
- **Safety profile of LINVO + DARA or ISA combination therapy was consistent with the expectations for these combinations based on the known profiles of each treatment as monotherapy**
- **The two DLTs, and the three TEAEs leading to death, were due to infections, despite SoC anti-microbial prophylaxis**
- **At a median follow-up of 11.6 months, treatment with LINVO + DARA or ISA combination therapy resulted in a high rate of durable responses in a patient population with heavily pretreated RRMM**
  - **ORR: 87%; ≥CR rate: 53%**
  - **12-month DOR rate: 77%; 12-month PFS rate: 74%**
- **These results support the ongoing evaluation of combination therapy of LINVO plus an anti-CD38 mAb and further evaluation in earlier LoT**

Abbreviations

AE, adverse event; BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cells; C, Cycle; CAR, chimeric antigen receptor; CD, cluster of differentiation; CI, confidence interval; CMV, cytomegalovirus; CR, complete response; CRS, cytokine release syndrome; D, Day; DARA, daratumumab; DCR, double-class refractory; DL, dose level; DLT, dose-limiting toxicity; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EU, European Union; ICANS, immune effector cell-associated neurotoxicity syndrome; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; ISA, isatuximab; ISS, International Staging System; IV, intravenous; LINVO, linvoseltamab; LoT, line(s) of therapy; mAb, monoclonal antibody; MRD, minimal residual disease; ORR, objective response rate; PD, progressive disease; PFS, progression-free survival; PI, proteasome inhibitor; PR, partial response; QXW, once every X weeks; QW, once weekly; R-ISS, Revised International Staging System; RRMM, relapsed/refractory multiple myeloma; sBCMA, soluble B-cell maturation antigen; SC, subcutaneous; sCR, stringent complete response; SD, stable disease; SoC, standard of care; StD, standard deviation; TCE, triple-class exposed; TEAE, treatment-emergent adverse event; US, United States of America; VGPR, very good partial response.

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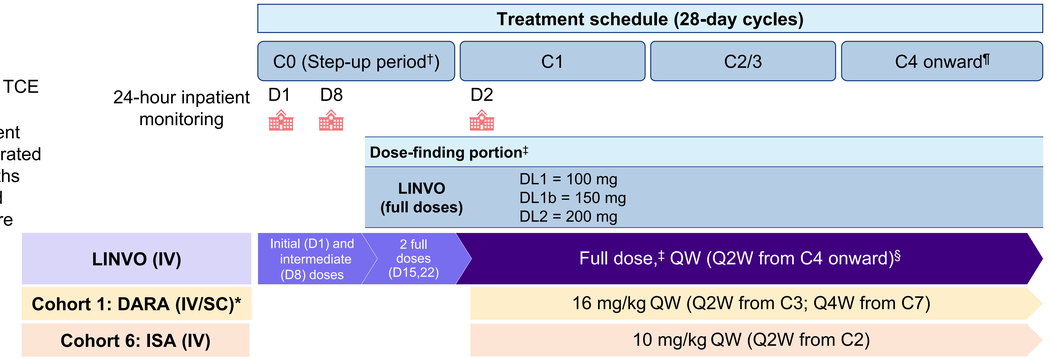
Study design schematic of the multicohort, open-label Phase 1b LINKER-MM2 trial (NCT05137054), conducted across 42 sites in the USA, France, Greece, Israel, and Spain

Key eligibility criteria

- Age ≥18 years
- Diagnosis of RRMM
- ≥3 LoT, or ≥2 LoT if either TCE or DCR (IMiD + PI)
- Prior DARA or ISA treatment permitted if previously tolerated and ≥6 months or ≥3 months washout, respectively, had elapsed since last exposure



Primary endpoints:

- DLTs
- Incidence/severity of TEAEs

Key secondary endpoints:

- ORR, DOR, and PFS
- Rate of MRD negativity**

Dexamethasone IV prophylaxis premedication was administered 1–3 hours before LINVO infusion in C0 and C1, and 1–3 hours before DARA and ISA infusion in C1–7+ and C1–4+, respectively. Throughout the study duration, SoC anti-microbial prophylaxis could be considered as clinically indicated to manage infections (including opportunistic); acyclovir or equivalent medication is recommended for all patients to prevent herpes simplex virus and varicella zoster virus reactivation. *At the start of C3, the DARA route of administration/formulation may be changed from IV to SC for patient convenience. †LINVO was administered with a regimen that used step-up dosing (5 mg C0D1, 25 mg C0D8) to help mitigate the risk of CRS; a step-up dose could be repeated if not adequately tolerated before advancing to the next incremental dose. ‡Dose finding was planned for 100 mg and 200 mg, with an option for intermediate DLs or de-escalation to 50 mg if required due to toxicity. §For patients receiving ≥100 mg of LINVO with a confirmed response of ≥VGPR, LINVO dosing frequency was decreased to Q4W following C6 of treatment. ¶LINVO + DARA and LINVO + ISA treatments were continued after C4 until disease progression or any other discontinuation criterion was met. **Defined as the proportion of patients who have reached MRD negativity (at 10^{-5} test sensitivity by clonoSEQ or EuroFlow).

Patient baseline characteristics and prior therapy

Characteristic, n (%) unless specified	DL1 LINVO 100 mg + DARA/ISA* (n=18)	DL1b LINVO 150 mg + DARA/ISA* (n=16)	DL2 LINVO 200 mg + DARA only* (n=8)	Total (N=42)*
Median follow-up, months (range)	17.4 (0–30)	10.1 (2–19)	8.8 (3–13)	11.6 (0–30)
Age				
Median (range), years	67 (52–86)	71 (42–78)	72 (50–78)	68 (42–86)
≥75 years	5 (27.8)	5 (31.3)	3 (37.5)	13 (31.0)
Male	10 (55.6)	11 (68.8)	3 (37.5)	24 (57.1)
Race				
White	16 (88.9)	14 (87.5)	6 (75.0)	36 (85.7)
Black or African American	0	1 (6.3)	1 (12.5)	2 (4.8)
Not reported	2 (11.1)	1 (6.3)	1 (12.5)	4 (9.5)
ECOG performance status				
0	9 (50.0)	10 (62.5)	3 (37.5)	22 (52.4)
1	8 (44.4)	6 (37.5)	5 (62.5)	19 (45.2)
2	1 (5.6)	0	0	1 (2.4)
ISS stage at study entry				
I	10 (55.6)	9 (56.3)	4 (50.0)	23 (54.8)
II	5 (27.8)	5 (31.3)	3 (37.5)	13 (31.0)
III	3 (16.7)	1 (6.3)	1 (12.5)	5 (11.9)
Missing	0	1 (6.3)	0	1 (2.4)
sBCMA				
Median (range), ng/mL	332.5 (108.0–1910.0)	262.00 (137.0–652.0)	296.0 (168.0–1770.0)	301.5 (108.0–1910.0)
≥400 ng/mL	6 (33.3)	1 (6.3)	2 (25.0)	9 (21.4)
BMPC ≥50%	5 (27.8)	5 (31.3)	1 (12.5)	11 (26.2)
Baseline plasmacytomas status	9 (50.0)	2 (12.5)	2 (25.0)	13 (31.0)†
High-risk cytogenetics by R-ISS	7 (38.9)	4 (25.0)	3 (37.5)	14 (33.3)
Gain of 1q	6 (33.3)	6 (37.5)	3 (37.5)	15 (35.7)
Number of prior LoT, median (range)	3 (2–6)	3 (2–6)	4 (2–8)	3 (2–8)
Exposure to ≥1 anti-CD38 mAb	8 (44.4)	8 (50.0)	5 (62.5)	21 (50.0)
Exposure to ≥1 IMiD/PI	18 (100)/ 18 (100)	16 (100)/ 16 (100)	8 (100)/ 8 (100)	42 (100)/ 42 (100)
Refractory to ≥1 anti-CD38 mAb	6 (33.3)	6 (37.5)	2 (25.0)	14 (33.3)
Refractory to ≥1 IMiD/PI	17 (94.4)/ 14 (77.8)	15 (93.8)/ 13 (81.3)	4 (50.0)/ 5 (62.5)	36 (85.7)/ 32 (76.2)
Prior LoT				
3	8 (44.4)	8 (50.0)	5 (62.5)	21 (50.0)
4	7 (38.9)	7 (43.8)	5 (62.5)	19 (45.2)
5	2 (11.1)	4 (25.0)	1 (12.5)	7 (16.7)
Refractory to prior LoT				
3	3 (16.7)	5 (31.3)	1 (12.5)	9 (21.4)
4	2 (11.1)	4 (25.0)	1 (12.5)	7 (16.7)
5	0	3 (18.8)	1 (12.5)	4 (9.5)
Refractory to last LoT	17 (94.4)	15 (93.8)	3 (37.5)	35 (83.3)

*All patients who started treatment on or before May 07, 2025, were included in the safety analysis set: DL1 (DARA, n=12; ISA, n=6), DL1b (DARA, n=6; ISA, n=10), or DL2 (DARA, n=8; ISA, n=0); 38 patients were included in the efficacy analysis set: DL1 (DARA, n=11; ISA, n=5), DL1b (DARA, n=5; ISA, n=10), or DL2 (DARA, n=7; ISA, n=0). †Includes paramedullary or paraskeletal plasmacytomas (n=10, 23.8%) and extramedullary plasmacytomas (n=4, 9.5%); one patient (DL1) had both paramedullary and extramedullary plasmacytomas.

Primary endpoints: DLTs and safety summary

DLTs

- One DLT was observed at DL1b in the ISA cohort (Grade 3 Epstein–Barr virus pharyngitis)
- One DLT was observed at DL2 in the DARA cohort (Grade 5 CMV pneumonia)

Safety summary	DL1 LINVO 100 mg + DARA/ISA (n=18)	DL1b LINVO 150 mg + DARA/ISA (n=16)	DL2 LINVO 200 mg + DARA only (n=8)	Total (N=42)
Exposure to LINVO,* mean (StD), months	14.1 (10.6)	6.8 (5.1)	6.5 (4.3)	9.9 (8.5)
Exposure to DARA/ISA, mean (StD), months	14.5 (10.0)	6.1 (5.1)	6.1 (4.5)	9.6 (8.5)
Any TEAE,† n (%)	18 (100)	16 (100)	8 (100)	42 (100)
Grade ≥3	16 (88.9)	14 (87.5)	8 (100)	38 (90.5)
Serious	14 (77.8)	7 (43.8)	6 (75.0)	27 (64.3)
Leading to discontinuation of LINVO	0	2 (12.5)	0	2 (4.8)
Leading to discontinuation of DARA or ISA	0	3 (18.8)	0	3 (7.1)
Leading to death	2 (11.1)	1 (6.3)	1 (12.5)	4 (9.5)‡

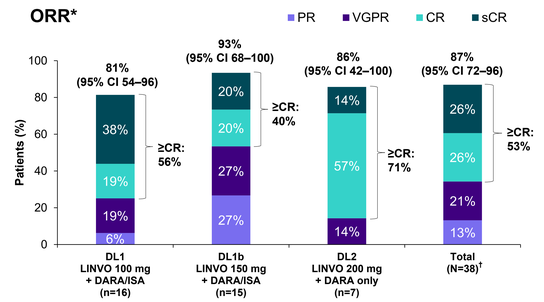
*Exposures measured at data cut-off date irrespective of LINVO doses. †Onset or worsening after the first dose of study treatment to within 30 days of last dose. ‡Sudden death (DL1, n=1), septic shock (DL1, n=1), lower respiratory tract infection leading to respiratory failure (DL1b, n=1), and CMV pneumonia (DL2, n=1).

TEAE* summary

n (%)	Total (N=42) All Grade	Total (N=42) Grade 3/4
Number of patients with any TEAEs	42 (100)	34 (81.0)
Any TEAEs		
Infections	33 (78.6)†	15 (35.7)
CMV infection/viremia‡	8 (19.0)	2 (4.8)
Anemia‡	24 (57.1)	13 (31.0)
Neutropenia‡	19 (45.2)	19 (45.2)
Thrombocytopenia‡	18 (42.9)	8 (19.0)
Diarrhea	16 (38.1)	1 (2.4)
CRS	14 (33.3)	1 (2.4)§
Fatigue	13 (31.0)	2 (4.8)
Cough	9 (21.4)	0
Headache‡	9 (21.4)	0

*Onset or worsening after the first dose of study treatment to within 30 days of last dose. †There were three Grade 5 infections (n=3): CMV pneumonia, lower respiratory tract infection leading to respiratory failure, and septic shock. ‡Composite term. §This Grade 3 CRS event occurred during the step-up period and fully resolved.

Key secondary endpoints

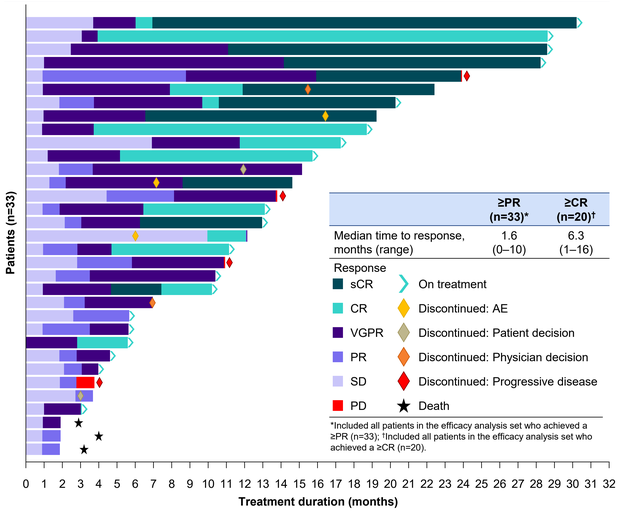


DOR	n=33
6-month rate, % (95% CI)	86.5 (67.8–94.7)
12-month rate, % (95% CI)	77.3 (55.7–89.3)
PFS	**n=38**
6-month rate, % (95% CI)	78.1 (60.9–88.4)
12-month rate, % (95% CI)	74.0 (55.5–85.7)

Of 15 MRD-evaluable patients who achieved CR, 14 (93.3%) were MRD negative (10^{-5} by clonoSEQ or EuroFlow)

Individual response rates may not sum to the ORR and ≥CR due to rounding. *ORR determined by investigator using IMWG criteria. †The efficacy analysis set (N=38) included all patients who received ≥1 dose of LINVO + DARA or ISA and underwent ≥1 post-baseline response assessment after C1D1: 16 patients in DL1 (DARA, n=11; ISA, n=5), 15 patients in DL1b (DARA, n=5; ISA, n=10), and 7 patients in DL2 (DARA, n=7; ISA, n=0).

Responses over time*†



*Included all patients in the efficacy analysis set who achieved a ≥PR (n=33); †Included all patients in the efficacy analysis set who achieved a ≥CR (n=20).

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