MM-364

Elranatamab, a B-Cell Maturation Antigen (BCMA)-CD3 Bispecific Antibody, for Patients With Relapsed/Refractory Multiple Myeloma (RRMM): Extended Follow-up and Biweekly Administration From the MagnetisMM-3 Study

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Objective

- Results from the MagnetisMM-3 trial in patients naïve to BCMA-directed therapies (Cohort A) after ~15 mo of follow-up, including patients who switched from QW to Q2W elranatamab administration, are presented

Conclusions

- Elranatamab remains efficacious in patients with RRMM after ~15 mo of follow-up
  - High response rate (ORR, 61.0%) with early, deep, and durable responses observed (15-mo DOR rate, 71.5%)
  - With a median follow-up of 14.7 mo, median PFS and OS have not been reached (rates at 15 mo: PFS, 50.9%; OS, 56.7%)
- Deepened and/or sustained responses were observed in the majority of responders who switched from QW to Q2W elranatamab dosing ≥6 mo before the data cut-off
- The safety profile of elranatamab is manageable
  - 12/32 mg step-up priming regimen with premedication successfully mitigated the rate and severity of CRS and ICANS
  - Most common grade 3/4 TEAEs were hematologic
  - Infections were reported in 69.9% of patients. Infection monitoring, prophylaxis, and education are recommended for patients with MM receiving T-cell redirecting therapies
- Among patients who switched to Q2W dosing, the incidence of grade 3/4 TEAEs decreased by >10% after the switch
- These results support the continued development of elranatamab both as a monotherapy and in combination with standard or novel therapies for patients with MM

References: **1.** Shah N, et al. Leukemia 2020;34:985-1005. **2.** Bahlis NJ, et al. J Clin Oncol 2021;39(15 suppl):8006. **3.** Sebag M, et al. Blood 2021;138(suppl 1):895. **4.** Jakubowiak A, et al. J Clin Oncol 2022;40(16 suppl):8014. **5.** Raje N, et al. Blood 2022;140(suppl 1):388.

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Background

- B-cell maturation antigen (BCMA) is a member of the tumor necrosis factor receptor superfamily universally expressed on multiple myeloma (MM) cells[1]
- Elranatamab is a humanized bispecific antibody that targets both BCMA-expressing MM cells and CD3-expressing T cells[1]
- Data from the ongoing phase 1 MagnetisMM-1 study (NCT03269136) demonstrated the safety and efficacy of elranatamab in patients with relapsed/refractory MM (RRMM)[2-5]
  - After a median follow-up of 12.0 mo, among responders (objective response rate [ORR]=64%) the median duration of response (DOR) was 17.1 mo (95% CI, 10.6—not evaluable [NE])[5]
  - These results support further development of elranatamab both as a monotherapy and in combination with other agents

Methods

- MagnetisMM-3 (NCT04649359) is an open-label, multicenter, non-randomized, phase 2 study designed to evaluate the efficacy and safety of elranatamab monotherapy in patients with RRMM
  - Enrolled patients were refractory to at least 1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody
- Patients were enrolled to 1 of 2 independent, parallel cohorts:
  - Those naïve to BCMA-directed therapies (Cohort A), and
  - Those with previous exposure to BCMA-directed antibody–drug conjugates or CAR-T cells (Cohort B)
- Patients received subcutaneous elranatamab 76 mg one weekly (QW) on a 28-day cycle (days 1, 8, 15, and 22) with a step-up priming regimen of 12 mg on day 1 and 32 mg on day 4 during the first week
  - Hospitalization was required for ~48 h following the first step-up dose, and for ~24 h after the second step-up dose
  - Premedication was required before the first 3 doses
- Patients who received QW dosing for ≥6 cycles and achieved a partial response (PR) or better for ≥2 mo had their dosing interval changed to once every 2 wk (Q2W)
- Dose modifications were permitted for toxicity
- Minimal residual disease (MRD)-negativity was assessed by next-generation sequencing
  - Evaluable patients included those who achieved complete response (CR)/ stringent CR (sCR) with an evaluable sample and an identified baseline clone
- This analysis reports efficacy and safety results in BCMA-naïve patients (Cohort A)
  - Data cut-off was March 14, 2023 (~15 mo after the last patients first dose), except for cytokine release syndrome (CRS) and immune-effector cell-associated neurotoxicity syndrome (ICANS) which was January 12, 2023
- Post-hoc analyses included efficacy and safety in patients who switched from QW to Q2W dosing
  - Treatment-emergent adverse events (TEAEs) were evaluated within the 3-mo window before vs after the switch

Results

PATIENTS AND TREATMENT

- Patient demographics and characteristics are shown in **Table 1**
- Median duration of treatment was 5.6 (range, 0.03–24.4) mo
  - 48.0% of patients had been treated for >6 mo and 35.8% of patients had been treated for >12 mo
- At the data cut-off, 33.3% of patients were still receiving elranatamab
- Most common primary reasons for permanent treatment discontinuation were progressive disease (39.0%) and adverse events (13.8%)

Table 1: Demographics and baseline characteristics

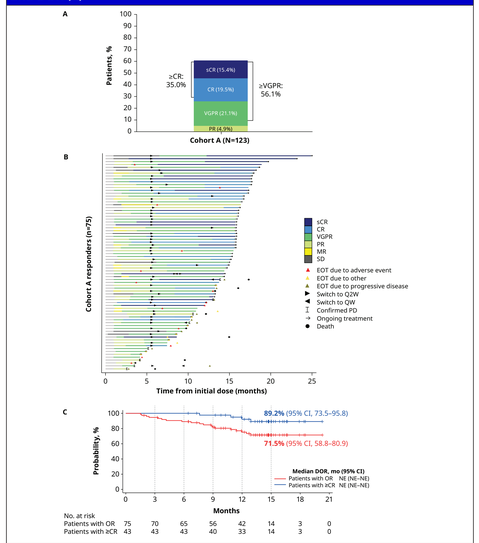
	Cohort A (N=123)[a]
Age, median (range), y	68 (36–89)
Male, n (%)	68 (55.3)
Race	
White	72 (58.5)
Asian	16 (13.0)
Black or African American[b]	9 (7.3)
Not reported/unknown[c]	26 (21.1)
ECOG performance status, n (%)	
0	45 (36.6)
1	71 (57.7)
2	7 (5.7)
R-ISS disease stage, n (%)	
I	28 (22.8)
II	68 (55.3)
III	19 (15.4)
Unknown	8 (6.5)
Cytogenetic risk, n (%)	
Standard	83 (67.5)
High[d]	31 (25.2)
Missing	9 (7.3)
Extramedullary disease by BICR, n (%)[e]	39 (31.7)
Bone marrow plasma cells, n (%)	
<50%	89 (72.4)
≥50%	26 (21.1)
Missing	8 (6.5)
≥1 poor prognosis feature[f]	81 (65.9)
Prior lines of therapy, median (range)	5 (2–22)
Prior stem cell transplant, n (%)	87 (70.7)
Exposure status, n (%)	
Triple-class[g]	123 (100)
Penta-drug[h]	87 (70.7)
Refractory status, n (%)	
Triple-class[g]	119 (96.7)
Penta-drug[h]	52 (42.3)
Refractory to last line of therapy, n (%)	118 (95.9)

[a] Includes 4 patients who received 1 step-up priming dose of 44 mg in Wk 1; [b] 17% (n=8/47) of patients enrolled in the United States were Black or African American; [c] Includes patients recruited in countries where the collection of race is prohibited; [d] Includes t(4;14), t(14;16), del(17p) chromosomal abnormalities; [e] Extramedullary disease was defined as presence of any plasmacytoma (extramedullary and/or paramedullary) with a soft-tissue component; [f] Poor prognosis feature refers to ≥1 of the following: ECOG performance status of 2, R-ISS disease stage of 3, extramedullary disease at baseline, high cytogenetic risk, or bone marrow plasma cell involvement ≥50%; [g] Triple-class refers to ≥1 proteasome inhibitor, 1 immunomodulatory drug, and 1 anti-CD38 antibody; [h] Penta-drug refers to ≥2 proteasome inhibitors, 2 immunomodulatory drugs, and 1 anti-CD38 antibody
BICR=blinded independent central review; ECOG=Eastern Cooperative Oncology Group; R-ISS=Revised Multiple Myeloma International Staging System

EFFICACY

- After a median follow-up of 14.7 (range, 0.2–25.1) mo, confirmed ORR per blinded independent central review (BICR) was 61.0% (95% CI, 51.8–69.6) (**Figure 1A**)
- MRD-negativity (sensitivity threshold 10–5) was achieved in 89.7% of evaluable patients who achieved CR/sCR (n=29)
- Among patients who achieved an objective response (n=75), median time to response was 1.2 (range, 0.9–7.4) mo
- At the time of data cut-off, 66.7% (n=50/75) of objective responses were ongoing (**Figure 1B**)
- The median DOR was not reached (95% CI, NE–NE), and the Kaplan–Meier (KM) probability of maintaining the response at 15 mo was 71.5% (95% CI, 58.8–80.9) (**Figure 1C**)

Figure 1: Best overall response per BICR (A), durability of response (B), and DOR (C)



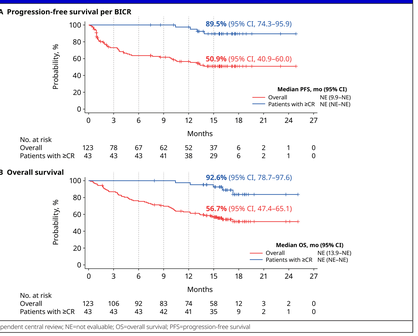
Panel b: Responses per BICR. Reason to switch from QW to Q2W treatment determined by investigator
BICR=blinded independent central review; CR=complete response; DOR=duration of response; EOT=end of treatment; MR=minimal response; ORR=objective response rate; PD=progressive disease; PR=partial response; sCR=stringent complete response; SD=stable disease; VGPR=very good partial response; QW=once weekly; Q2W=every 2 weeks

- Median progression-free survival (PFS) and overall survival (OS) had not been reached at the time of data cut-off, with KM rates of 50.9% (95% CI, 40.9–60.0) and 56.7% (95% CI, 47.4–65.1) at 15 mo (**Figure 2**)

SAFETY

- TEAEs were reported in all 123 patients treated with elranatamab, with grade 3/4 events reported in 70.7% of patients
  - Most commonly reported TEAEs are shown in **Table 2**
- Among patients who received the 2 step-up priming regimen (n=119), CRS and ICANS, respectively, were reported in 56.3% (grade 3/4, 0%) and 3.4% (grade 3/4, 0%) of patients
  - No patients permanently discontinued treatment due to CRS or ICANS

Figure 2: Outcomes in patients with RRMM receiving elranatamab



BICR=blinded independent central review; NE=not evaluable; OS=overall survival; PFS=progression-free survival

Table 2: Most common TEAEs (any grade ≥20%)

	Cohort A (N=123)[a]	
Patients, n (%)	Any grade	Grade 3/4
Hematologic		
Anemia	60 (48.8)	46 (37.4)
Neutropenia	60 (48.8)	60 (48.8)
Thrombocytopenia	38 (30.9)	29 (23.6)
Lymphopenia	33 (26.8)	31 (25.2)
Non-hematologic		
CRS	71 (57.7)	0
Diarrhea	52 (42.3)	2 (1.6)
Fatigue	45 (36.6)	4 (3.3)
Decreased appetite	41 (33.3)	1 (0.8)
Pyrexia	37 (30.1)	5 (4.1)
COVID-19–related[b]	36 (29.3)	19 (15.4)
Injection site reaction	33 (26.8)	0
Nausea	33 (26.8)	0
Hypokalemia	32 (26.0)	13 (10.6)
Cough	31 (25.2)	0
Headache	29 (23.6)	0

[a] Includes 4 patients who received 1 step-up priming dose of 44 mg in Wk 1; [b] Includes preferred terms in COVID-19 (narrow) standardized MedDRA queries
AEs were graded by Common Terminology Criteria for Adverse Events v5.0, except for CRS and ICANS which were graded by American Society for Transplant and Cellular Therapy criteria (Lee DW, et al. Biol Blood Marrow Trans. 2019;25:625). TEAEs were defined as any new event that occurred from the start of elranatamab treatment through 90 d or the last dose or start of new anticancer therapy, whichever occurs first
AE=adverse event; CRS=cytokine release syndrome; MedDRA=Medical Dictionary for Regulatory Activities; TEAE=treatment-emergent adverse event

Table 3: AEs of special interest: Infections

	Cohort A (N=123)		
Patients, n (%)	Any grade	Grade 3/4	Grade 5
Infection TEAEs in ≥5% of patients			
COVID-19–related[a]	36 (29.3)	19 (15.4)	2 (1.6)
Upper respiratory tract infection	20 (16.3)	0	0
Pneumonia	20 (16.3)	10 (8.1)	0
Sinusitis	13 (10.6)	2 (1.6)	0
Urinary tract infection	12 (9.8)	4 (3.3)	0
Sepsis	8 (6.5)	8 (6.5)	0
Bacteremia	7 (5.7)	2 (1.6)	0
CMV infection reactivation	7 (5.7)	2 (1.6)	0
Key infection TEAEs occurring in <5% of patients[b]			
Pneumocystis jirovecii pneumonia	6 (4.9)	5 (4.1)	0
CMV infection	4 (3.3)	0	0
Adenoviral hepatitis	1 (0.8)	0	1 (0.8)
Adenovirus infection	1 (0.8)[c]	0	1 (0.8)[c]
Hepatitis B reactivation	1 (0.8)	0	0
Pneumonia adenoviral	1 (0.8)[c]	0	1 (0.8)[c]
Pneumonia cytomegaloviral	1 (0.8)	1 (0.8)	0
Pneumonia pseudomonal	1 (0.8)	0	1 (0.8)

[a] Includes preferred terms in COVID-19 (narrow) standardized MedDRA queries; [b] Key infection TEAEs includes preferred terms: CMV infection reactivation, Pneumocystis jirovecii pneumonia, CMV infection, Adenoviral hepatitis, Adenovirus infection, Hepatitis B reactivation, Pneumonia adenoviral, Pneumonia CMV, Pneumonia pseudomonal. [c] Preferred Terms both reported in 1 patient
Administration of antibacterial and/or antiviral agents for infection prophylaxis was permitted for patients at increased risk of infection in accordance with local standard of care practice and/or institutional guidelines
AE=adverse event; CMV=cytomegalovirus; MedDRA=Medical Dictionary for Regulatory Activities Terminology; TEAE=treatment-emergent adverse event

- Infections were reported in 69.9% (grade 3/4, 39.8%; grade 5, 6.5%) of patients (**Table 3**)
  - Most frequently reported were COVID-19–related TEAEs (29.3%)
- Among patients with quantitative immunoglobulin (Ig) data (n=72), 98.6% had immune paresis (defined as ≥2 uninvolved Ig <lower limit of normal) at baseline
- Overall, 43.1% of patients received IgG replacement during the study
- Peripheral neuropathy was reported in 20.3% (grade 3/4, 1.6%) of patients
  - Most common (≥5% of patients) event reported was peripheral sensory neuropathy (7.3%)
  - All events were grade 1/2, except for 1 patient with grade 3 Guillain-Barré syndrome and 1 patient with grade 3 muscle atrophy
  - No Grade 5 peripheral neuropathy events were observed
  - Permanent treatment discontinuation due to peripheral neuropathy events was reported in 2.4% of patients
  - A medical history of peripheral neuropathy at baseline was reported in:
    - 56.0% of patients who developed peripheral neuropathy TEAEs
    - 40.8% of patients who did not develop peripheral neuropathy TEAEs
- TEAEs led to death in 25 patients (11 due to progressive disease) of which 4 were considered treatment-related by investigator
  - 1 patient with adenovirus infection and pneumonia adenoviral
  - 1 patient with adenoviral hepatitis
  - 1 patient with pneumonia pseudomonal
  - 1 patient with failure to thrive

EFFICACY AND SAFETY WITH Q2W DOSING

- There were 50 responders by BICR who switched to Q2W dosing ≥6 mo prior to the data cut-off; among these patients, 80.0% of patients maintained or improved their response ≥6 mo after the switch (**Figure 1B**)
- Among all 58 patients who switched to Q2W dosing, the incidence of any grade TEAEs was 94.8% (grade 3/4, 58.6%) within the 3 mo before switching and 89.7% (grade 3/4, 46.6%) in the 3 mo after