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Safety and Efficacy of Elranatamab + Nirogacestat in Patients With Relapsed or Refractory Multiple Myeloma: Results From the Phase 1b MagnetisMM-4 Study

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Objective

To evaluate the safety, tolerability, and optimal dosing of ELRA in combination with NIRO in patients with RRMM

Conclusions

- Across 5 evaluated DLs, the combination of ELRA plus NIRO yielded response rates of 50.0% to 70.0%
  - The optimal DL for the combination with no DLT was identified as ELRA 32 mg QW + NIRO 100 mg QD
- These initial results suggest that careful evaluation is warranted when combining BCMA-targeted BsAbs with a GSI

Supplementary Materials

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References: 1. Lesokhin AM, et al. Nature Med 2023;29:2259-2267. **2.** Pont MJ, et al. Blood. 2019;134:1585-1597.

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Background

- Elranatamab (ELRA) is a bispecific antibody (BsAb) targeting B-cell maturation antigen (BCMA) on myeloma cells and CD3 on T cells
  - In the phase 2 MagnetisMM-3 study (NCT04649359), ELRA monotherapy demonstrated deep, durable responses (objective response rate [ORR], 61.0%; ≥complete response [CR], 35.0%) with manageable safety in patients with relapsed or refractory multiple myeloma (RRMM) and no prior BCMA-directed therapy[1]
- MagnetisMM-4 (NCT05090566) is a phase 1b/2 umbrella trial evaluating ELRA in combination with other anti-cancer treatments for patients with MM
  - The MagnetisMM-4 sub-study A is evaluating ELRA plus the gamma-secretase inhibitor (GSI) nirogacestat (NIRO) in patients with RRMM
  - GSIs block BCMA cleavage, potentially enhancing the efficacy of BCMA-directed therapy[2]

Methods

- Eligible patients (age ≥18 years) for sub-study A had:
  - ≥3 prior lines of therapy
  - RRMM refractory to ≥1 immunomodulatory drug, ≥1 proteasome inhibitor, and ≥1 anti-CD38 antibody
  - Eastern Cooperative Oncology Group performance status ≤1
  - Adequate liver, renal, and bone marrow function
  - No prior BCMA-BsAb treatment
- Dose escalation followed a Bayesian logistic regression model
- At each dose level (DL), patients received subcutaneous ELRA with oral NIRO in 28-day cycles starting on cycle (C) 1, day (D) 1
  - **DL1:** 1 step-up priming dose of ELRA 4 mg on C0D1, then ELRA 4 mg weekly (QW) + NIRO 100 mg twice daily (BID)
  - **DL2:** 2 step-up priming doses of ELRA 4 and 8 mg on C0D1 and C0D4, respectively, then ELRA 12 mg QW + NIRO 100 mg BID
  - **DL3:** 2 step-up priming doses of ELRA 12 and 32 mg on C0D1 and C0D4, respectively, then ELRA 32 mg QW + NIRO 100 mg BID
  - **DL3A:** 2 step-up priming doses of ELRA 12 and 32 mg on C0D1 and C0D4, respectively, then ELRA 32 mg QW + NIRO 100 mg once daily (QD)
  - **DL4A:** 2 step-up priming doses of ELRA 12 and 32 mg on C0D1 and C0D4, respectively, then ELRA 76 mg QW + NIRO 100 mg QD
- The primary endpoint was dose-limiting toxicity (DLT) during the DLT observation period, which is approximately 35 days from C0D1 through the end of C1
- Secondary endpoints included safety and efficacy measures including ORR and CR rate (CRR) per International Myeloma Working Group criteria by investigator
- Data cutoff was March 14, 2025

Results

PATIENTS AND TREATMENT

- 34 patients received ELRA and NIRO in 5 DLs (**Table 1**)
- Study treatment exposure is shown in **Table 2**

Table 1. Baseline demographics and disease characteristics

	DL1 n=2	DL2 n-=6	DL3 n=10	DL3A n=10	DL4A n=6	Total N=34
Age, median (range), years	61.0 (59-63)	55.0 (42-67)	68.0 (44-78)	69.5 (59-80)	67.5 (57-79	64.5 (42-80)
Male, n (%)	1 (50.0)	4 (66.7)	6 (60.0)	9 (90.0)	3 (50.0)	23 (67.6)
Race, n (%)						
Black or African American	0	1 (16.7)	0	1 (10.0)	2 (33.3)	4 (11.8)
White	2 (100)	5 (83.3)	9 (90.0)	9 (90.0)	4 (66.7)	29 (85.3)
Not reported	0	0	1 (10.0)	0	0	1 (2.9)
ECOG PS, n (%)						
0	0	4 (66.7)	5 (50.0)	4 (40.0)	2 (33.3)	15 (44.1)
1	2 (100)	2 (33.3)	5 (50.0)	6 (60.0)	4 (66.7)	19 (55.9)
R-ISS disease stage, n (%)						
I	0	1 (16.7)	3 (30.0)	2 (20.0)	2 (33.3)	8 (23.5)
II	2 (100)	4 (66.7)	4 (40.0)	3 (30.0)	3 (50.0)	16 (47.1)
III	0	1 (16.7)	2 (20.0)	2 (20.0)	0	5 (14.7)
Unknown	0	0	1 (10.0)	3 (30.0)	1 (16.7)	5 (14.7)
Cytogenetic risk, n (%)						
Standard	2 (100)	4 (66.7)	5 (50.0)	7 (70.0)	3 (50.0)	21 (61.8)
High[a]	0	2 (33.3)	5 (50.0)	3 (30.0)	3 (50.0)	13 (38.2)
Extramedullary disease, n (%)	0	0	5 (50.0)	2 (20.0)	0	7 (20.6)
Prior LOTs, median (range)	5.5 (5-6)	3.5 (3-5)	5.0 (4-12)	5.0 (3-11)	5.0 (4-8)	5.0 (3-12)
Prior stem cell transplant, n (%)	2 (100)	3 (50.0)	7 (70.0)	8 (80.0)	6 (100)	26 (76.5)
Exposure status, n (%)						
Triple-class[b]	2 (100)	6 (100)	10 (100)	10 (100)	6 (100)	34 (100)
Penta-drug[c]	2 (100)	3 (50.0)	8 (80.0)	7 (70.0)	6 (100)	26 (76.5)
Refractory status, n (%)						
Triple-class[b]	2 (100)	6 (100)	10 (100)	9 (90.0)	6 (100)	33 (97.1)
Penta-drug[c]	0	3 (50.0)	4 (40.0)	5 (50.0)	3 (50.0)	15 (44.1)
Refractory to last line of therapy, n (%)	2 (100)	6 (100)	10 (100)	8 (80.0)	5 (83.3)	31 (91.2)

[a]Includes t(4;14), t(14;16), del(17p) chromosomal abnormalities; [b] Triple-class refers to ≥1 proteasome inhibitor, ≥1 immunomodulatory drug, and ≥1 anti-CD38 antibody; [c] Penta-drug refers to ≥2 proteasome inhibitors, ≥2 immunomodulatory drugs, and ≥1 anti-CD38 antibody
DL=dose level; ECOG PS=Eastern Cooperative Oncology Group performance status; LOT=line of therapy; R-ISS=Revised Multiple Myeloma International Staging System

Table 2. Study treatment exposure at cutoff date[a]

	DL1 n=2	DL2 n-=6	DL3 n=10	DL3A n=10	DL4A n=6
Median duration of treatment (range), weeks	11.1 (11.1-11.1)	19.1 (1.9-161.3)	34.4 (3.7-115.4)	20.4 (5.0-39.3)	12.8 (5.0-19.0)
Treatment ongoing, n (%)	0	2 (33.3)	2 (20.0)	4 (40.0)	4 (66.7)

[a]March 14, 2025
DL=dose level

DLTs

- 6 DLTs were reported in 2 DLs (**Table 3**)
- The optimal DL for the combination with no DLT was identified as DL3A (ELRA 32 mg QW + NIRO 100 mg QD)

Table 3. DLTs in evaluable patients per DL

	DL1 n=2	DL2 n=6	DL3 n=10	DL3A n=10	DL4A n=6
Patients evaluable for DLT, n (%)	2 (100)	4 (66.7)	8 (80.0)	7 (70.0)	5 (83.3)
Patients with DLT, n (%)[a]	0	0	4 (50.0)	0	2 (40.0)
DLTs observed			• 2 pts with G3 diarrhea • 1 pt with G3 pneumonia • 1 pt with G3 fatigue and G4 neutropenia		• 1 pt with G3 diarrhea • 1 pt with G3 decreased appetite and G3 dehydration

[a]Percent of evaluable patients.
DLT=dose-limiting toxicity; G=grade; pt=patient

EFFICACY

- The median follow-up overall was 8.5 (95% CI, 3.8-20.4) months, estimated by reverse Kaplan-Meier (**Figure 1)**
- ORR (95% CI) was 61.8% (43.6-77.8) overall

SAFETY

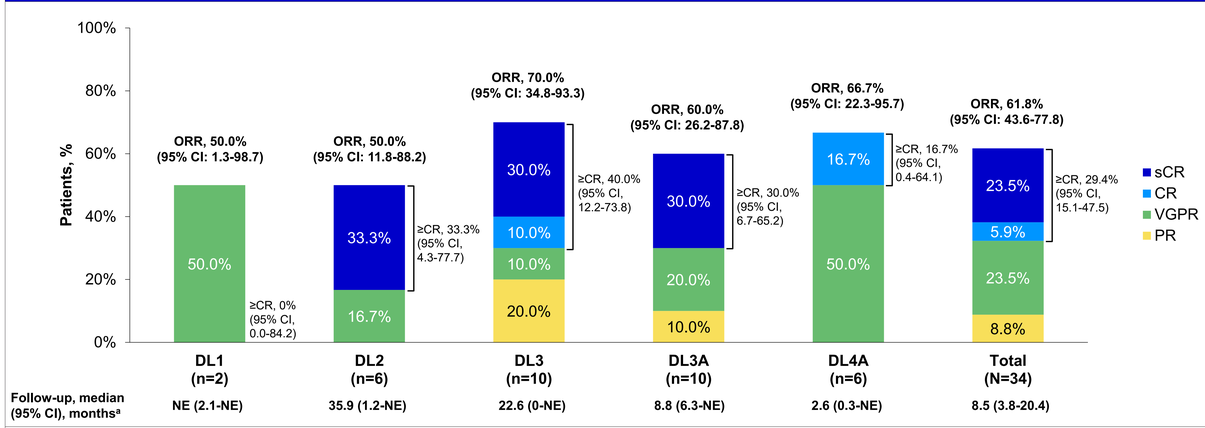
- Diarrhea, neutropenia, and infections were the most common (any grade >30%) treatment-emergent adverse events (TEAEs; **Table 4**)
- Immune effector cell–associated neurotoxicity syndrome occurred in 5.9% of patients, all Grade 1

Table 4. TEAEs occurring in ≥30% of patients

	Total N=34	
TEAE, n (%)	**Any grade**	**Grade 3/4**
Any	34 (100)	25 (73.5)
Hematologic TEAEs		
Neutropenia	20 (58.8)	18 (52.9)
Anemia	16 (47.1)	10 (29.4)
Thrombocytopenia	14 (41.2)	10 (29.4)
Nonhematologic TEAEs		
Diarrhea	22 (64.7)	8 (23.5)
Infections[a]	19 (55.9)	5 (14.7)
Cytokine release syndrome	16 (47.1)	0
Hypokalemia	14 (41.2)	8 (23.5)
Nausea	14 (41.2)	4 (11.8)
Cough	12 (35.3)	0
Fatigue	11 (32.4)	3 (8.8)
Decreased appetite	11 (32.4)	3 (8.8)
Hypophosphatemia	11 (32.4)	2 (5.9)

[a]Infections include all preferred terms under the system organ class Infections and infestations
TEAE=treatment-emergent adverse event

Figure 1. Response rates per DL



[a]By reverse Kaplan-Meier
CR=complete response; DL=dose level; NE=not estimable; ORR=objective response rate; PR=partial response; sCR=stringent complete response; VGPR=very good partial response