4056

# Quantitative Clinical Pharmacology Analysis to Support the Dose Escalation of Elranatamab + Nirogacestat in the MagnetisMM-4 Study

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## Objective

To inform further dose escalation (≥DL 4) in MagnetisMM-4

## Conclusions

The PK, PD, dose-response analysis, and QSP modeling support NIRO 100 mg QD to improve safety and further dose escalation of ELRA to 76 mg QW to maximize efficacy in patients with high baseline disease burden/sBCMA

## 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
  - 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 efficacy of BCMA-directed therapy[2]

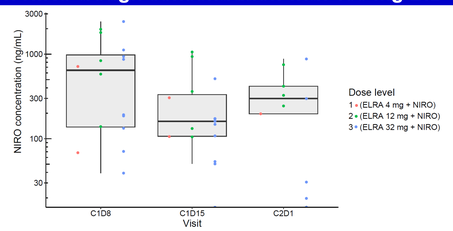
## Methods

- At the time of this analysis, 3 dose level (DL) cohorts had been completed as follows:
  - **DL1 (n=2):** 1 step-up priming dose of ELRA 4 mg on Cycle (C) 0 Day (D) 1, then ELRA 4 mg weekly (QW) + NIRO 100 mg twice daily (BID)
  - **DL2 (n=6):** 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 (n=10):** 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
  - However, NIRO dose reductions were observed in the majority of the patients
- Pharmacokinetic (PK) data of ELRA plus NIRO were analyzed in comparison with their monotherapy profiles to explore potential drug-drug interaction (DDI)
- Soluble BCMA (sBCMA) levels were assessed to explore the pharmacological activity of NIRO and ELRA
- Dose-response analysis for safety was performed to inform the selection of further NIRO doses to mitigate gastrointestinal (GI) toxicity
- A quantitative systems pharmacology (QSP) model[3] was adapted and fitted to literature data on BCMA BsAb plus GSI combinations leveraging data using the following literature and clinical data
  - PK-pharmacodynamic (PD) model in healthy individuals[3] to quantify the effect of NIRO using fold changes in BCMA density
  - Adjust sBCMA shedding rates by leveraging competitor clinical data to simulate reliable response rate improvements from drug combinations
- This updated QSP model was used to predict the efficacy of the following dose combinations of ELRA plus NIRO
  - ELRA 32 mg, ELRA 32 mg NIRO 50 mg, ELRA 32 mg + NIRO 100 mg once daily (QD) (DL3A)
  - ELRA 76 mg, ELRA 76 mg NIRO 50 mg, ELRA 76 mg + NIRO 100 mg QD (DL4)

## Results

- The median exposure of NIRO (C1D8, C1D15, C2D1: 648,154, 220 ng/mL) with NIRO 100 mg BID generally appeared comparable to their monotherapy profile (232 ng/mL) at early cycles (**Figure 1**). However, NIRO PK showed high variability (CV≥100%) across patients

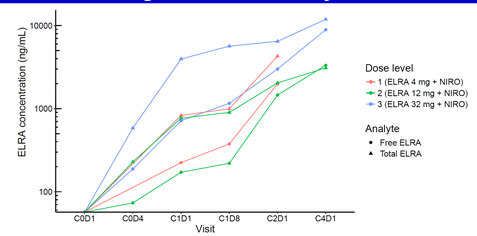
### Figure 1. NIRO trough concentration with 100 mg BID




C=cycle; D=day; ELRA=elranatamab; NIRO=nirogacestat

- The median exposure of ELRA 32 mg (DL3) appeared comparable to monotherapy and showed dose-proportional increase compared with lower doses (**Figure 2**)

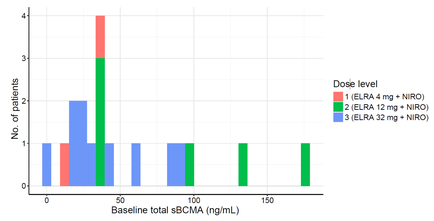
### Figure 2. ELRA trough concentration by visit




C=cycle; D=day; ELRA=elranatamab; NIRO=nirogacestat

- The majority of patients (89%, 16/18) had baseline sBCMA below 100 ng/mL (**Figure 3**)

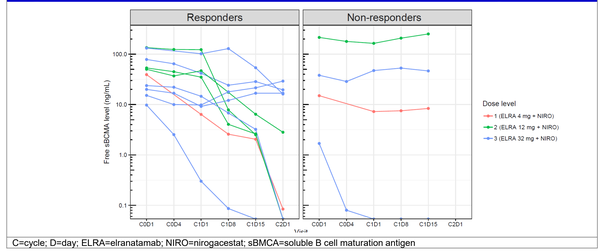
### Figure 3. Distribution of baseline sBCMA level




ELRA=elranatamab; NIRO=nirogacestat; sBCMA=soluble B cell maturation antigen

- In responders, the free sBCMA level generally dropped rapidly following ELRA administration (**Figure 4**)

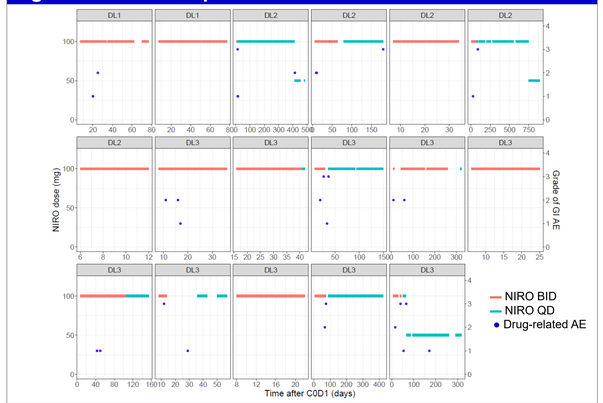
### Figure 4. Free sBCMA concentration-time profile by visit




C=cycle; D=day; ELRA=elranatamab; NIRO=nirogacestat; sBMCA=soluble B cell maturation antigen

- NIRO 100 mg BID is associated with more GI adverse events (AEs); NIRO dose reduction improved tolerability (**Figure 5** and **Table 1**)

### Figure 5. Individual profile of NIRO dose and related GI AE




N=17. Accurate dosing record is not available for 1 patient in DL2
AE=adverse event; BID=twice daily; C=cycle; D=day; GI=gastrointestinal; NIRO=nirogacestat; QD=once daily

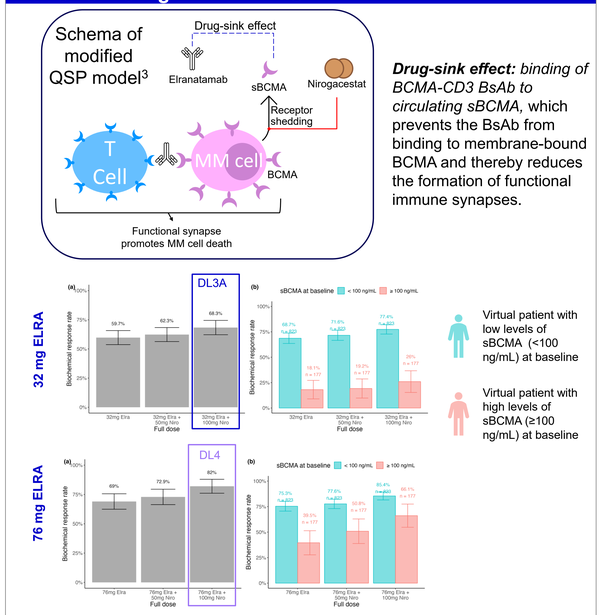
### Table 1. Dose reduction of NIRO and associated GI AEs

| | NIRO 100 mg BID | NIRO 100 mg QD |
|---|---|---|
| Patients with dose reduction, % (n/N) | 55.6% (10/18) | 16.7% (3/18) |
| Grade ≥2 AE (no. of events/treatment duration in month, All/related AE only) | 0.133/0.124 | 0.018/0.018 |
| Grade ≥3 AE (no. of events/ treatment duration day, All/related AE only) | 0.050/0.041 | 0.013/0.013 |

AE=adverse event; BID=twice dailyGI=gastrointestinal; NIRO=nirogacestat; QD=once daily

- QSP simulation demonstrated superior efficacy with ELRA 76 mg QW + NIRO 100 mg QD vs ELRA 32 mg QW + NIRO 100 mg QD (**Figure 6**)

### Figure 6. QSP simulations of 1,000 virtual patients treated with 32 or 76 mg ELRA + NIRO




***Drug-sink effect:*** *binding of BCMA-CD3 BsAb to circulating sBCMA,* which prevents the BsAb from binding to membrane-bound BCMA and thereby reduces the formation of functional immune synapses.

BsAb=bispecific antibody; ELRA=elranatamab; MM=multiple myeloma; NIRO=nirogacestat; QSP=quantitative systems pharmacology; sBCMA=soluble B cell maturation antigen;

## Discussion

- Both NIRO and ELRA achieved exposure comparable to that of the monotherapy, suggesting absence of DDI. The NIRO dose-response relationship for GI AEs was evaluated as sparse NIRO exposure data limited typical exposure-response analysis
- NIRO 100 mg QD was recommended for the next DL due to poor tolerability of NIRO 100 mg BID
- Both the ELRA PK profile and QSP simulation support further dose escalation of ELRA to 76 mg
- The following clinical results of DL ≥3 were reported in a separate poster, "Safety and Efficacy of Elranatamab + Nirogacestat in Patients With Relapsed or Refractory Multiple Myeloma: Results From the Phase 1b MagnetisMM-4 Study", presented at ASH 2025 (Poster no. 4058)

**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. **3.** Shearer T, et al. Cancer Res Commun 2024;4:3114-3123. **4.** Poels KE, et al. NPJ Syst Biol Appl. 2025;11:102.

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