

# Elranatamab Exposure-Safety Analysis in Patients With Relapse or Refractory Multiple Myeloma: Insights From MagnetisMM Studies

Pooneh Soltantabar,<sup>1</sup> Jennifer Hibma,<sup>2</sup> Diane Wang,<sup>1</sup> Akos Czibere,<sup>1</sup> Anne Hickman,<sup>1</sup> Mohamed Elmeliegy<sup>1</sup>

<sup>1</sup> Oncology Research and Development, Pfizer Inc, USA  
<sup>2</sup> Research and Development, Pfizer Inc, USA

## Objectives



- To assess the relationship between elranatamab exposure and grade  $\geq 3$  neutropenia/infection and adverse events (AEs) leading to dose modifications via time-varying Cox proportional hazards (PH) analysis
- To identify potential significant covariates affecting the elranatamab (ELRA) exposure-response (ER) relationship for grade  $\geq 3$  neutropenia/infection and AEs leading to dose modifications

## Background

- ELRA is a heterodimeric humanized bispecific antibody approved for treatment of relapsed/refractory multiple myeloma (RRMM). ELRA is comprised of one arm that binds to B-cell maturation antigen (BCMA) and another arm that binds to CD3
- The phase 2 MagnetisMM-3 trial (NCT04649359) supported the effectiveness of ELRA in RRMM with a manageable safety profile
- The recommended dosing regimen of ELRA is 12/32-mg step-up doses, followed by a full dose of 76 mg once weekly (QW) and reduction of the dosing intensity after  $\geq 24$  weeks to once every 2 weeks (Q2W) in patients who achieve a response
- Higher ELRA exposure was shown to be associated with incidence of any-grade and grade  $\geq 2$  cytokine release syndrome (CRS). The 2 step-up priming dose regimen is the optimal regimen for CRS mitigation<sup>1</sup>
- The relationship between ELRA exposure and selected AEs was previously reported using logistic regression analysis. ELRA AEs are managed via dose modifications, which motivated the use of concentration at time of the event,  $C_{avg,event}$  for the logistic regression analysis. This analysis showed a relatively flat relationship between ELRA exposure and the selected safety endpoints.<sup>2</sup> The potential bias introduced by the causal dependence of  $C_{avg,event}$  on the event time<sup>3</sup> and the bias introduced by using static metrics (eg,  $C_{avg,d28}$ ), which does not account for dose modifications, motivated conducting the ER analysis using a time-varying Cox PH analysis

## Methods

- The ER-safety analysis of ELRA monotherapy was performed using pooled data from 4 studies: MagnetisMM-1 (first in human phase 1, NCT03269136), MagnetisMM-2 (Japan phase 1, NCT04798586), MagnetisMM-3 (phase 2), and MagnetisMM-9 (phase 1/2, NCT05014412). These studies included a dose range of 0.1 to 50  $\mu\text{g}/\text{kg}$  intravenously (IV) and 80 to 1000  $\mu\text{g}/\text{kg}$  (6-76 mg) QW subcutaneously (SC) allowing for characterization of the ELRA exposure-safety profile across a wide dosing range
- Selected safety endpoints (namely grade  $\geq 3$  infections, grade  $\geq 3$  neutropenia, and AEs leading to dose modifications) were analyzed via time-varying Cox PH analysis

- To account for the difference in time to incidence of AEs and for potential ELRA dosing delays, time-varying average ELRA concentration ( $C_{avg,t}$ ) was used as the pharmacokinetic (PK) metric in this analysis<sup>4</sup>
- First, visual examination was conducted via comparisons of  $C_{avg,t}$  values in patients with or without the specified event at each time point when the events occurred
- Univariable Cox PH model was used to quantify the effects of ELRA  $C_{avg,t}$  and other baseline covariates on safety endpoints ( $P=.05$ )
- The significant covariates identified from the univariable analysis were simultaneously included in the multivariable Cox PH analysis. ELRA exposure measure,  $C_{avg,t}$ , was carried forward to the multivariable analyses regardless of significance
- Lastly, final model was developed by Cox PH analysis of significant covariates/exposure metric identified in the multivariable step ( $P=.01$ ). PH assumption was tested using Schoenfeld residuals

## Results

### INCIDENCE SUMMARY

- The ER analysis was conducted on 324 participants treated with ELRA monotherapy. A summary of selected safety endpoints are presented in **Table 1**
- The incidence data across different dose levels for each cohort/study and the total incidence clearly showed that the incidence rates are consistent across both low- and high-dose cohorts, indicating a flat ER-safety profile concerning these safety events

**Table 1. Selected safety events in the exposure-safety analysis**

Safety event	MM-1				MM-2	MM-3	MM-9	Total
	Part 1 IV	Part 1 SC	Part 1.1 QW + part 2	Part 1.1 Q2W				
N	23	30	22	13	4	187	45	324
Infection grade $\geq 3$ , n (%)	3 (13.0)	10 (33.3)	9 (40.9)	3 (23.1)	2 (50.0)	84 (44.9)	24 (53.3)	135 (41.7)
Neutropenia grade $\geq 3$ , n (%)	4 (17.4)	16 (53.3)	15 (68.2)	10 (76.9)	3 (75.0)	82 (43.9)	26 (57.8)	156 (48.1)
Dose modifications, n (%)	9 (39.1)	20 (66.7)	15 (68.2)	8 (61.5)	3 (75.0)	142 (75.9)	38 (84.4)	235 (72.5)

ELRA dosing per cohort/study:

- MM-1/part 1 IV: 0.1-50 mg/kg QW
- MM-1/part 1 SC: 80-100  $\mu\text{g}/\text{kg}$  QW
- MM-1/part 1.1 QW, part 2: 44/76 mg QW, 600/1000  $\mu\text{g}/\text{kg}$  QW
- MM-1/part 1.1 Q2W: 600/1000  $\mu\text{g}/\text{kg}$  Q2W
- MM-2: 600/1000  $\mu\text{g}/\text{kg}$  QW
- MM-3: 12/32/76 mg QW
- MM-9: 4/20/76/76 or 116 mg

ELRA=elranatamab, MM-1=MagnetisMM-1, MM-2=MagnetisMM-2, MM-3=MagnetisMM-3, MM-9=MagnetisMM-9; Q2W=every 2 weeks; QW=once weekly; SC=subcutaneous

### GRAPHICAL EXPLORATION

- The potential ER relationship for grade  $\geq 3$  infections, grade  $\geq 3$  neutropenia, and AEs leading to dose modifications was analyzed by comparing  $C_{avg,t}$  between patients with and without these events on each event occurrence day (**Figure 1**)
- The mostly overlapping LOWESS lines for patients with events and with events suggest no relationship between these safety events and exposure

### COX PH ANALYSIS

#### Grade $\geq 3$ infection

- In the univariable analysis, higher baseline alanine aminotransferase (ALT) levels were significantly associated with grade  $\geq 3$  infection ( $P \leq .05$ ) in univariable analysis. Both baseline ALT and  $C_{avg,t}$  (not significant in univariable analysis) were included in the multivariable analysis. Baseline ALT levels were no longer significant in the multivariable analysis ( $P \geq .01$ ), and exposure remained insignificant
- Final Cox PH model indicated that none of the covariates or exposure metrics were significant predictors of grade  $\geq 3$  infection

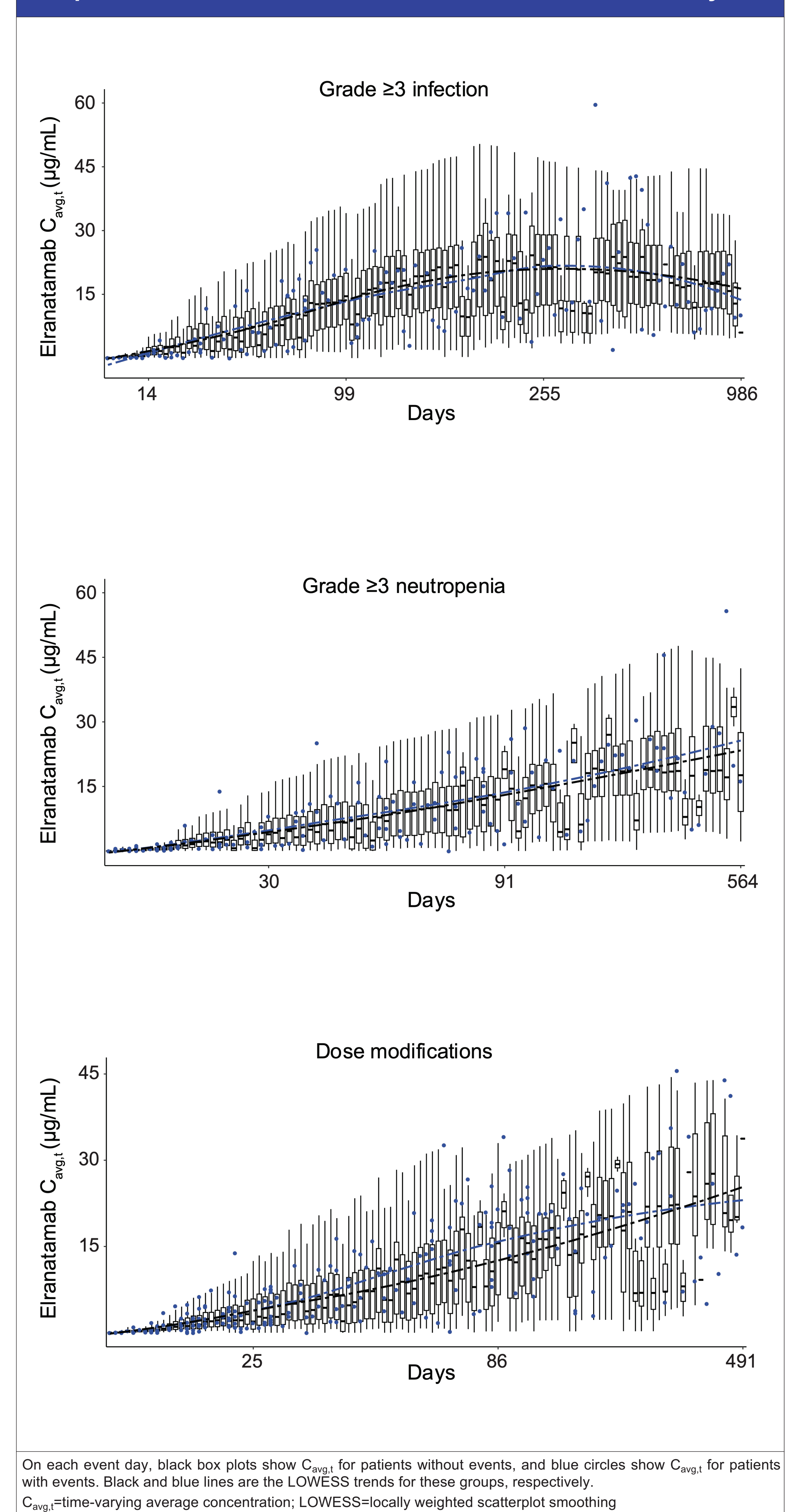
#### Grade $\geq 3$ neutropenia

- In the univariable analysis, higher baseline bilirubin and higher  $C_{avg,t}$  were significantly associated with grade  $\geq 3$  neutropenia
- Both baseline bilirubin levels and  $C_{avg,t}$  were included in the multivariable analysis. Baseline bilirubin remained significant ( $P \leq .01$ )
- Final model suggested higher baseline bilirubin levels were associated with a higher risk of grade  $\geq 3$  neutropenia with  $P = .005$  (**Table 2**). Higher baseline bilirubin levels were reported to be associated with neutropenia<sup>5-7</sup>

#### AEs leading to dose modifications

- In univariable analysis, higher  $C_{avg,t}$ , race (Asian), lower body weight, and higher baseline albumin levels were significantly associated with dose modifications ( $P \leq .05$ ), which were later included in the multivariable analysis
- Final Cox PH model suggested that none of the covariates or exposure metrics were significant predictors of dose modifications

**Figure 1. Comparison of  $C_{avg,t}$  in patients with safety events and patients without events on each event occurrence day**



**Table 2. Final analysis of Cox PH model**

Safety event	Variable	Coefficient	HR (95% CI)	P value
Infection grade $\geq 3$	No significant covariates in the final model			
Neutropenia grade $\geq 3$	Baseline bilirubin (mg/dL)	0.47	1.6 (1.151-2.226)	.005
Dose modifications	No significant covariates in the final model			

HR=hazard ratio; PH=proportional hazards

## Conclusions

- No statistically significant relationship was observed between ELRA exposure, the incidence of grade  $\geq 3$  AEs of neutropenia/infection, and AEs leading to dose modifications, as assessed by the graphical diagnostic and Cox PH analysis.
- ELRA demonstrated a flat exposure-safety profile. This finding, together with the positive exposure-efficacy relationship for ELRA, collectively support a meaningful clinical benefit and a favorable benefit-risk ratio observed for the recommended dosing regimen of ELRA 76 mg QW



### Electronic Poster

Please scan this quick response (QR) code with your smartphone app to view this poster. If you do not have a smartphone, access the poster via the internet at: <https://scienflic.com/congressposter.com/p/80b1sp3f1a369vkm>

**References:** 1. Elmeliegy M, et al. Blood 2022;140(suppl 1):7174-7175. 2. Soltantabar P, et al. Clin Lymphoma Myeloma Leuk 2023;23:S211-S212. Abstract P-313. 3. Wiens MR, et al. CPT: Pharmacometrics Syst Pharmacol 2024;13:187-191. 4. Hibma J, et al. ACP 2022. Abstract PMX-421. 5. Tsai WN, et al. Ann Clin Biochem 2015;52:251-258. 6. Yamada Y, et al. Med Oncol 2019;36:63. 7. Fujiwara Y, et al. Jpn J Clin Oncol 2007;37:358-364.

**Acknowledgments:** We thank the MagnetisMM trial patients and their families, as well as the study investigators, nurses, and site staff. This study was sponsored by Pfizer.

**Disclosures:** All authors report employment with Pfizer. ME also reports stock and other ownership interests with Pfizer.

**Contact:** Pooneh Soltantabar, Pooneh.Soltantabar@pfizer.com

Copyright © 2024