

Matching-Adjusted Indirect Comparison of Elranatamab versus Teclistamab in Patients with Triple-Class Exposed/Refractory Multiple Myeloma: Updated Results

Isha Mol¹, Yannan Hu¹, Thomas W LeBlanc², Joseph C Cappelleri³, Haitao Chu⁴, Guido Nador⁵, Didem Aydin⁶, Isabel Perez Cruz⁷, Patrick Hlavacek⁸

¹EVA Health Economics, Cytel, Inc., Rotterdam, the Netherlands; ²Division of Hematologic Malignancies and Cellular Therapy, Duke University School of Medicine, Durham, NC, USA; ³Statistics, Pfizer Inc., Groton, CT, USA; ⁴Statistics, Pfizer Inc., New York, NY, USA; ⁵Medical Affairs, Pfizer Inc., Tadworth, UK; ⁶Medical Affairs, Pfizer Inc., Istanbul, Turkey; ⁷Medical Affairs, Pfizer Inc., New York, NY, USA; ⁸Value & Evidence, Pfizer Inc., New York, NY, USA

Correspondence: Isha Mol, Email isha.mol@cytel.com

Background: Due to the absence of a head-to-head trial directly comparing elranatamab and teclistamab in triple-class exposed/refractory multiple myeloma (TCE/R MM), a matching-adjusted indirect treatment comparison (MAIC) was previously conducted. The aim of the current study was to update this prior MAIC with more mature clinical data from both trials.

Methods: The approach of the MAIC remained consistent with the previous study, with the exception of more mature data (28.4 months and 30.4 months of follow-up for elranatamab from MagnetisMM-3 (NCT04649359) and teclistamab from MajesTEC-1 (NCT03145181, NCT04557098), respectively). Individual patient-level data from MagnetisMM-3 (N = 116) were reweighted to match published aggregated data from MajesTEC-1. Variables included for adjustment were age (≥ 75 years), sex (for OS only), median time since diagnosis, International Staging System disease stage, high-risk cytogenetics, extramedullary disease, number of prior lines of therapy, Eastern Cooperative Oncology Group performance status, and penta-exposed/refractory status. An unanchored MAIC was conducted based on the National Institute for Health and Care Excellence Decision Support Unit 18 example code. A sensitivity analysis was conducted in which missing baseline characteristics data were imputed for elranatamab.

Results: In the base-case analysis, elranatamab was associated with significantly longer PFS (hazard ratio [HR] 0.55 [95% confidence intervals (CI): 0.37, 0.81], $p < 0.05$), OS (HR [95% CI]: 0.60 [0.40, 0.91], $p < 0.05$, and DoR 0.56 [0.31, 0.99] $p < 0.05$) compared with teclistamab. Results were largely consistent in the sensitivity analysis, except that the differences in OS were non-significant. A subgroup analysis of patients with a complete response or better was consistent with the base case.

Conclusion: The results of this updated MAIC of elranatamab and teclistamab in TCE/R MM support the findings of the previous MAIC over a longer-term follow-up, now indicating significantly improved PFS, OS, and DoR with elranatamab versus teclistamab.

Keywords: triple-class exposed/refractory multiple myeloma, TCE/R MM, elranatamab, teclistamab, matching-adjusted indirect comparison, MAIC, MagnetisMM-3, MajesTEC-1

Triple-class exposed/refractory multiple myeloma (TCE/R MM; ie, patients who have been exposed to/become refractory to a proteasome inhibitor, an immunomodulatory drug, and a monoclonal antibody) remains an incurable disease with a poor prognosis and an estimated median survival of up to 12 months based on real-world United States (US) and European data.¹⁻³ In recent years, novel therapy options have been developed for TCE/R MM, such as chimeric antigen receptor-T cell therapies, nuclear export inhibitors, and bispecific antibodies targeting B-cell maturation antigen (BCMA) and CD3, such as elranatamab and teclistamab.

Results from clinical trials of two BCMA-CD3 bispecific antibodies, MagnetisMM-3 (elranatamab, NCT04649359) and MajesTEC-1 (teclistamab, NCT03145181, NCT04557098), demonstrated favorable efficacy and safety in patients with TCE/R MM.^{4,5} Based on the results of these trials, both treatments received US Food and Drug Administration (FDA) and European Medicines Agency (EMA) approval for the treatment of adult patients with TCE/R MM.⁶⁻⁹

Given the absence of head-to-head trials comparing elranatamab and teclistamab, prior comparative evidence has been limited to unanchored matching-adjusted indirect treatment comparisons (MAICs).¹⁰ The prior MAIC demonstrated significantly higher objective response rate (ORR) and progression-free survival (PFS) with elranatamab versus teclistamab (odds ratio [95% confidence intervals (CI)] 1.79 [1.01, 3.19] and hazard ratio [HR; 95% CI] 0.59 [0.39, 0.89] respectively). However, only numerically (ie, non-significant) complete response rate (CRR), longer duration of response (DoR), and overall survival (OS) were observed with elranatamab versus teclistamab.

The previous MAIC study was based on data from the 14.7-month follow-up of MagnetisMM-3 (for all efficacy outcomes) and 14.1-month follow-up of MajesTEC-1 for ORR, CRR, and DoR (~23 months for PFS and OS).¹⁰ As the data from both trials have matured over time, the objective of this study was to conduct an updated MAIC based on a median follow-up of 28.4 months for MagnetisMM-3 (data-cut-off date: March 2024) and 30.4 months for MajesTEC-1 (data-cutoff date: August 2023).^{11,12}

Eligibility criteria were similar between the trials, with the exception of the enrollment of patients with TCR MM in MagnetisMM-3 versus TCE MM in MajesTEC-1. Specifically, there were 97% of patients with TCR MM in MagnetisMM-3 (Cohort A) and 78% of patients with TCR MM in MajesTEC-1. Furthermore, patients with Eastern Cooperative Oncology Group performance status (ECOG PS) >1 were excluded in MajesTEC-1. Accordingly, patients with ECOG PS 2 were removed from the MagnetisMM-3 population in this analysis (n = 7), decreasing the trial population of MagnetisMM-3 to 116 patients. Also, as patients with prior BCMA exposure were excluded from MajesTEC-1, the main analysis was performed with Cohort A (BCMA naïve) from MagnetisMM-3.

Individual patient data (IPD) from MagnetisMM-3 (N = 116) were reweighed to match published aggregated data from MajesTEC-1 (N = 165). As described in more detail in Mol et al 2024, baseline characteristics for MajesTEC-1 were sourced from Moreau et al 2022.¹³ Patient characteristics from MagnetisMM-3 and MajesTEC-1 are shown in Table 1. Adjustment of baseline characteristics, identified through univariate Cox regressions using MagnetisMM-3 IPD

Table 1 Patient Demographics and Baseline Characteristics

	MagnetisMM-3 (Cohort A; N = 116)	MajesTEC-1 (N = 165)
Age, median, years	68	64
≥75 years	18%	15%
Sex, male	55%	58%
Median time since diagnosis, years	6.2	6.0
High-risk cytogenetics	27%	23%
ISS Risk Stage		
Stage I	30%	52%
Stage II	37%	35%
Stage III	20%	12%

(Continued)

Table 1 (Continued).

	MagnetisMM-3 (Cohort A; N = 116)	MajesTEC-1 (N = 165)
ECOG status		
0	39%	33%
I	61%	67%
Extramedullary disease	28%	17%
Number of prior lines, median	5	5
>3 lines of therapy	79%	74%
Refractory/exposure status		
Triple-class refractory ^a	97%	78%
Penta-drug refractory	41%	30%
Penta-drug exposed	71%	70%

Notes: ^aTriple-class refractory status was not possible to adjust for in the MAIC due to the small size of the resulting ESS.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IMiD, immunomodulatory drug; ISS, International Staging System.

and a systematic literature review, with validation by clinical experts, was carried out to account for differences between the trials. The identified variables included age (≥ 75 years), sex (for OS only), median time since diagnosis, International Staging System disease stage, high-risk cytogenetics, extramedullary disease, number of prior lines of therapy, ECOG PS, and penta-exposed/refractory status. In a sensitivity analysis, certain missing values in baseline characteristics reported in the MagnetisMM-3 were imputed by randomly assigning a data point from the observed values to patients with missing data.

Following the National Institute for Health and Care Excellence Decision Support Unit 18 example code, we conducted an unanchored MAIC analysis in R Studio to estimate HRs (with 95% CIs) on PFS, OS, and DoR for elranatamab versus teclistamab.^{14,15} Only time-to-event endpoints were considered for these analyses, as response outcomes remained unchanged between data-cut updates of MagnetisMM-3 and MajesTEC-1. Outcomes were assessed in the overall population and the subset of patients who achieved a CR or higher (\geq CR).

Distributions of the identified key baseline characteristics were matched following adjustment, resulting in an elranatamab effective sample size (ESS) of 76 for PFS and DoR and 74 for OS in the base case. The ESS was 91 for PFS and DoR and 87 in the sensitivity analysis.

Elranatamab was associated with a significantly longer PFS, OS, and DoR than teclistamab in the base-case analysis of all patients (Table 2). The results were largely consistent in the sensitivity analysis, with elranatamab associated with significantly longer PFS (Figure 1) and DoR (Figure 2), but only numerically (not significantly) longer for OS (Figure 3).

Similarly, PFS, OS, and DoR were all significantly longer with elranatamab versus teclistamab among patients who achieved \geq CR in both the base-case and sensitivity analyses, except for the sensitivity analysis of OS (as observed in the overall population).

The limitations of the previously published MAIC should be considered alongside these updated results. The main limitation of this MAIC study lies in its ability to adjust only for baseline variables reported in both MagnetisMM-3 and MajesTEC-1, leaving unmeasurable differences unaddressed. Due to the large impact on ESS, we could not adjust for the difference in the proportion of patients with TCR MM between the two studies, ie, 97% in MagnetisMM-3 compared to 78% in MajesTEC-1.

Table 2 Efficacy Outcomes: Elranatamab (Cohort A) versus Teclistamab

Outcome and Analysis	ESS ^a	HR (95% CI)	p-value
All patients			
PFS			
Naïve comparison	116	0.77 (0.55, 1.06)	0.11
Base case	76	0.55 (0.37, 0.81)	<0.05
Sensitivity analysis (imputation with base case)	91	0.56 (0.39, 0.82)	<0.05
OS			
Naïve comparison	116	0.96 (0.70, 1.34)	0.83
Base case	74	0.60 (0.40, 0.91)	<0.05
Sensitivity analysis (imputation with base case)	87	0.69 (0.47, 1.01)	0.06
DoR^b			
Naïve comparison	116	0.63 (0.39, 1.03)	0.07
Base case	76	0.56 (0.31, 0.99)	<0.05
Sensitivity analysis (imputation with base case)	91	0.58 (0.33, 0.99)	<0.05
Patients with ≥CR^c			
PFS			
Naïve comparison	45	0.33 (0.14, 0.80)	<0.05
Base case	31	0.28 (0.11, 0.74)	<0.05
Sensitivity analysis (imputation with base case)	38	0.24 (0.09, 0.60)	<0.05
OS			
Naïve comparison	45	0.67 (0.28, 1.62)	0.38
Base case	31	0.35 (0.13, 0.96)	<0.05
Sensitivity analysis (imputation with base case)	36	0.43 (0.17, 1.09)	0.07
DoR^b			
Naïve comparison	45	0.34 (0.14, 0.81)	<0.05
Base case	31	0.28 (0.11, 0.75)	<0.05
Sensitivity analysis (imputation with base case)	38	0.24 (0.09, 0.61)	<0.05

Notes: Bold font indicates statistical significance (ie, $p < 0.05$). ^aESS represents the number of independent unweighted individuals required to achieve the same precision as the weighted sample estimate. It was calculated as the square of the sum of weights divided by the sum of the squared weights. In the sensitivity analysis, the ESS increased compared to the base case due to the imputation of missing values. ^bWhile DoR is only captured among patients with a response, the MAIC weighs all patients, regardless of response. ^cThe ESS reported for the patients who achieved CR was calculated as the sum of weights among patients with ≥CR squared, divided by the sum of the squared weight among the same group of patients.

Abbreviations: CI, confidence interval; CR, complete response; DoR, duration of response; ESS, effective sample size; HR, hazard ratio; PFS, progression-free survival.

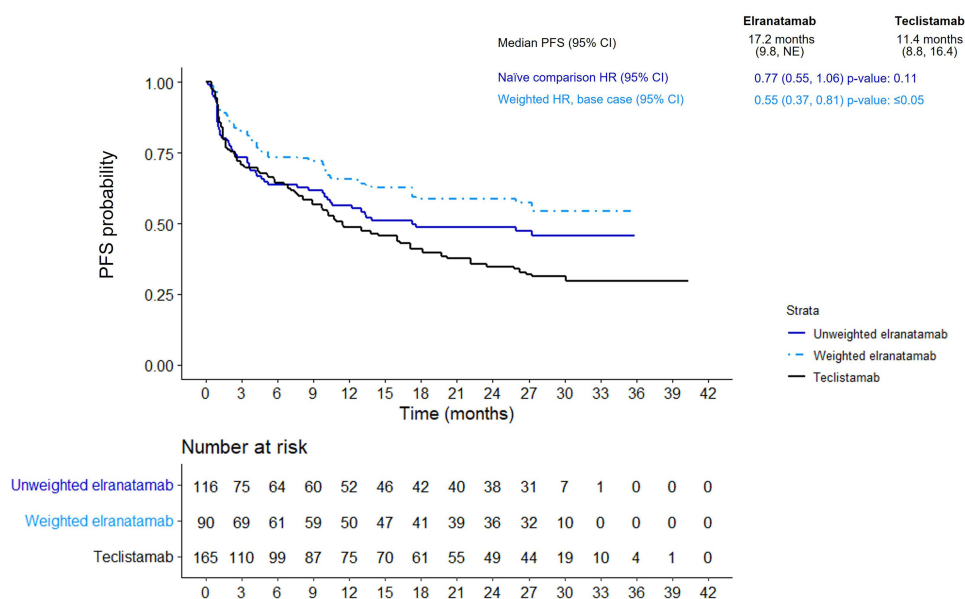


Figure 1 Results of PFS for elranatamab (cohort A) versus teclistamab.

Note: The number at risk shown for “Weighted elranatamab” was the weighted number of patients at risk over time, based on the weights directly derived from the MAIC.
Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NE, not evaluable; PFS, progression-free survival.

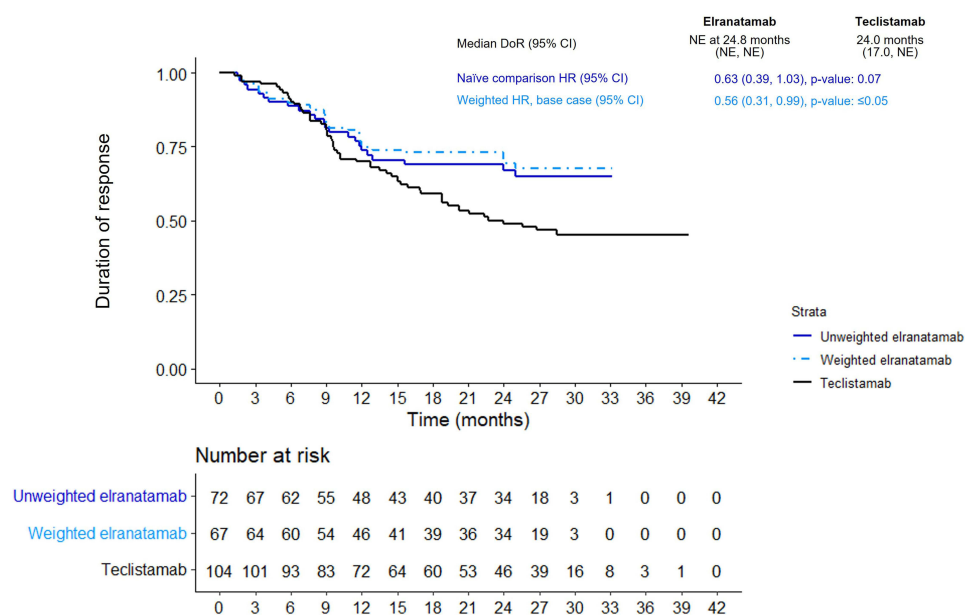


Figure 2 Results of DoR for elranatamab (cohort A) versus teclistamab.

Note: The number at risk shown for “Weighted elranatamab” was the weighted number of patients at risk over time, based on the weights directly derived from the MAIC.
Abbreviations: CI, confidence interval; DoR, duration of response; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NE, not evaluable.

In this updated MAIC of elranatamab and teclistamab with a long-term follow-up of over 28 months for both treatments, a significantly longer PFS, OS, and DoR were demonstrated in favor of elranatamab in the base-case analysis as well as among patients who achieved \geq CR.

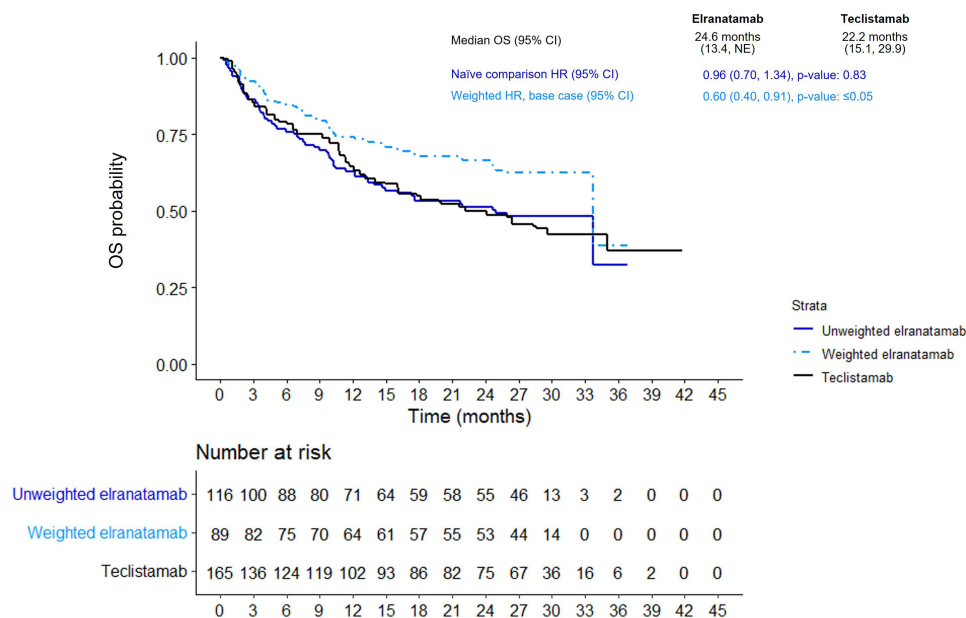


Figure 3 Results of OS for elranatamab (cohort A) versus teclistamab.

Note: The number at risk shown for “Weighted elranatamab” was the weighted number of patients at risk over time, based on the weights directly derived from the MAIC.

Abbreviations: CI, confidence interval; ESS, effective sample size; HR, hazard ratio; MAIC, matching-adjusted indirect comparison; NE, not evaluated, OS, overall survival.

These results add confidence to the conclusions of the previous MAIC that elranatamab is an effective option for treating patients with TCE/R MM based on more mature efficacy data. Importantly, this analysis demonstrated significantly improved DoR and OS with elranatamab versus teclistamab, which were only numerically longer with elranatamab versus teclistamab in the original analysis.¹⁰

Data Sharing Statement

Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

Ethical Statement

Ethical approval is not required for this updated analysis as per federal regulations 45 CFR 46.104(d), since it utilized data from two published Phase II trials, ie, MagnetisMM-3 and MajesTEC-1. Please refer to the respective trial publications for the ethical standards the trials followed.

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