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SHORT REPORT

An Updated Indirect Comparison of Elranatamab Versus a Real-World External Control Arm in Triple-Class Refractory Multiple Myeloma

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Purpose: Elranatamab is a BCMAxCD3 bispecific antibody approved for the treatment of relapsed/refractory multiple myeloma (RRMM). The registrational Phase 2 MagnetisMM-3 (NCT04649359) trial was single-armed; the aim of this indirect comparison was to contextualize the efficacy of the most recent 28.4-month follow-up data cut from this trial, allowing for more mature data, with real-world data serving as an external control.

Patients and Methods: We conducted a retrospective cohort study to indirectly compare the efficacy observed in the elranatamab arm of MagnetisMM-3 Cohort A (BCMA-naïve; N=123) from the March 26, 2024 data cut with COTA, a US-based oncology electronic health record database, as an external control. All MM patients with triple-class refractory disease who initiated a new line of therapy (representing real-world physician's choice) between November 2015 and August 2023 in the COTA database were included. MagnetisMM-3 inclusion (eg, ≥18 years, measurable disease within 90 days of the index, Eastern Cooperative Oncology Group [ECOG] ≤ 2) and exclusion criteria (eg, plasma cell leukemia, smoldering MM) were applied to obtain comparable patient populations across sources. The elranatamab cohort was compared with the physician's choice cohort on progression-free survival (PFS), overall survival (OS), and duration of response (DOR) using Cox proportional hazard models implementing inverse probability of treatment weighting to adjust for any remaining imbalances on confounding variables.

Results: N=123 patients treated with elranatamab were compared with 577 patients treated with real-world physicians' choice of therapy. Compared with physician's choice, elranatamab significantly improved PFS (HR = 0.38 [0.22, 0.65], p<0.05), OS (HR = 0.58 [0.35, 0.96], p<0.05), and DOR (HR = 0.16 [0.07, 0.34], p<0.05).

Conclusion: In this comparison of patients from the MagnetisMM-3 trial and real-world patients who resemble those from the trial, patients treated with elranatamab exhibited significantly better clinical outcomes compared with treatments currently used in real-world clinical practice.

Keywords: hematology, bispecific antibody, efficacy, clinical trial, electronic health record

Introduction

Multiple myeloma (MM) is a hematological malignancy that is characterized by the rapid accumulation of monoclonal plasma cells in the bone marrow.[1] The clinical prognosis for patients with MM is often quite poor, with less than 60% of patients surviving five years.[2–4]

The core treatment classes used in MM include immunomodulator (IMiD), proteasome inhibitor (PI), and anti-CD38 therapies.[5] For patients with MM who have relapsed or become refractory to these treatment classes, several additional options have recently become available, including chimeric antigen receptor T-cell therapies and bispecific antibodies.[6–11] As the bone marrow microenvironment can foster tumor survival and immune evasion, contributing to therapeutic resistance, such novel

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therapeutic approaches have the potential to overcome these resistance mechanisms.[12] One of these therapies, elranatamab, is a humanized bispecific antibody targeting B-cell maturation antigen (BCMA) on myeloma cells and CD3 on T cells which has been approved for the treatment of patients with relapsed/refractory MM (RRMM) in the United States, Europe, Japan, and several other countries.[10,11]

The registrational trial for elranatamab was the single-armed phase 2 MagnetisMM-3 (NCT04649359) study in patients with triple-class refractory (TCR) MM.[13,14] Due to the absence of a control arm within the MagnetisMM-3 trial, contextualizing elranatamab's clinical profile can be challenging. To do so, prior studies have relied upon both matching-adjusted indirect comparisons[15,16] as well as indirect comparisons using real-world data to compare elranatamab's clinical efficacy with existing treatment options.[17] However, these studies relied upon approximately 15 months of follow-up data from MagnetisMM-3; at this length of follow-up, the core endpoints of overall survival (OS) and duration of response (DOR) were both immature in the MagnetisMM-3 trial. The aim of this indirect comparison was to update our prior analysis versus real-world data by leveraging more mature clinical data from MagnetisMM-3 to contextualize the profile of elranatamab.

Materials and Methods

Data Sources

This retrospective cohort study compared an elranatamab cohort from the MagnetisMM-3 trial with a cohort of real-world patients with TCR MM disease from the COTA US-based oncology electronic health record database. Details on each of these data sources are described below. The study protocol was submitted and reviewed by Pearl IRB (Indianapolis, IN, USA), which determined the study met exempt status based on federal regulations (45 CFR 46.104).

MagnetisMM-3

MagnetisMM-3 (NCT04649359) is an open label, multicenter, non-randomized, phase 2 study of elranatamab among patients with TCR MM.[13,14] The study enrolled two independent and parallel cohorts: 1) Cohort A, which included participants who are naïve to BCMA-directed therapies (N = 123) and 2) Cohort B, which included participants who have received a prior BCMA-directed therapy (N = 64). The March 26, 2024, data cut from MagnetisMM-3, which included a median follow-up time of 28.4 months, was used for the analyses. The clinical data from this data cut has been previously reported, with a median progression-free survival (PFS) and OS of 17.2 and 24.6 months, respectively, for Cohort A; a median DOR was not reached.[14] Given insufficient numbers of patients who have received prior BCMA-directed therapies in real-world data sources, the focus of the present analysis was to contextualize Cohort A.

COTA

The COTA database is derived from the electronic health records of healthcare provider sites including academic institutions, community centers, and hospital systems representing 500,000 patients from over 200 sites of care in the US. This source was selected based on its data completeness and representativeness as established in prior research.[17] Patients with TCR MM who initiated a subsequent new line of therapy (LOT) between November 2015 and August 2023 were identified for inclusion, with the full observation period concluding December 2023.

Sample

All participants from Cohort A (ie, BCMA-therapy naïve) in the MagnetisMM-3 trial were included to represent the elranatamab arm in this study (N = 123). The inclusion and exclusion criteria from the MagnetisMM-3 trial were imposed on the COTA database to identify a similar population of patients with TCR MM who were using physician's choice of therapy, as described in previous research (Figure 1).[17]

Measures

Outcomes

The outcomes for this study included PFS, OS, and DOR, which represent the key efficacy endpoints in MM trials. PFS was defined as the time from the date of the initiation (ie, index date) of either elranatamab (in MagnetisMM-3) or the physician's choice of treatment regimen (in COTA) until progression, as confirmed through the International Myeloma Working Group

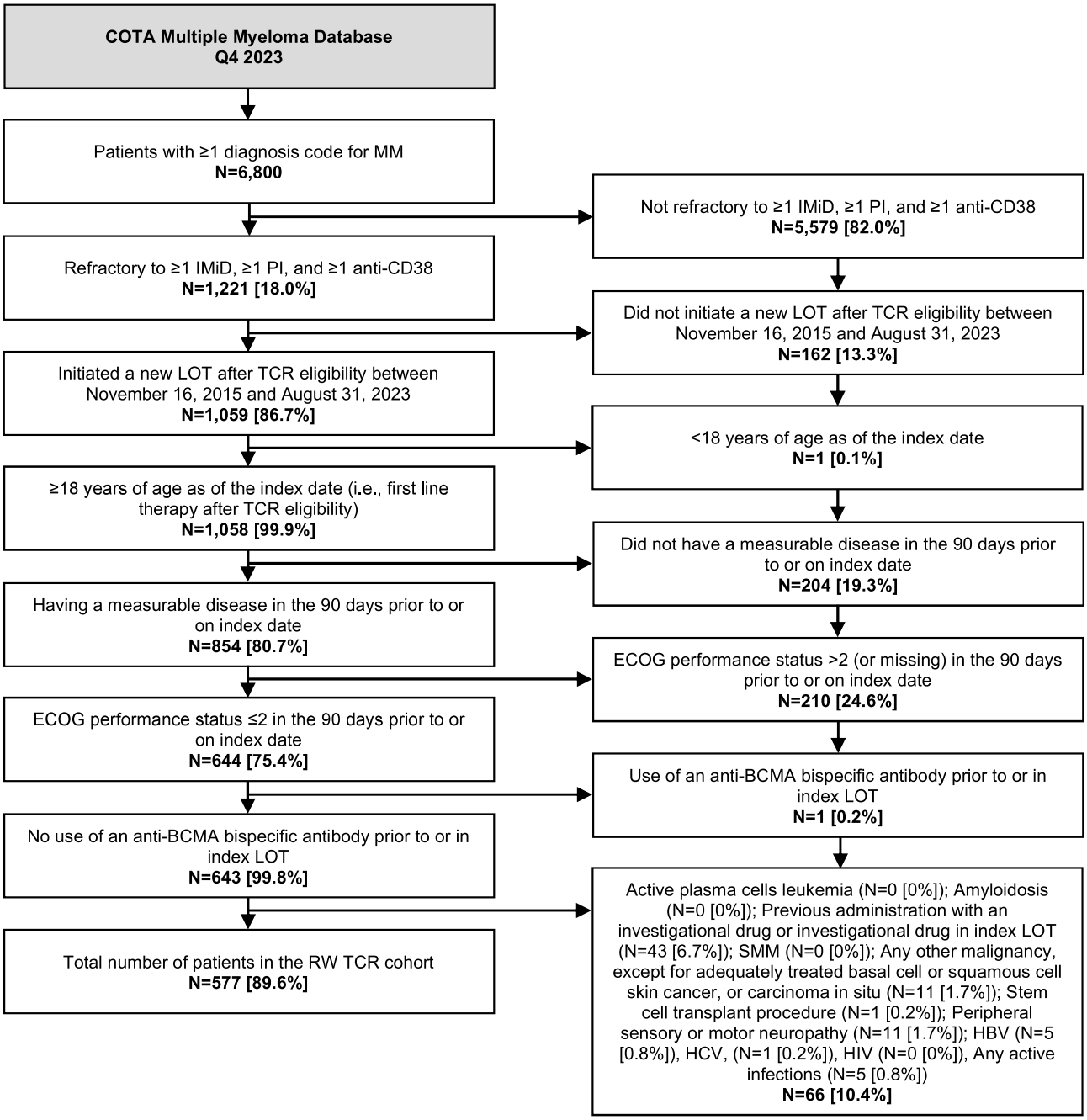

Figure 1 Sample flowchart.

Abbreviations: BCMA, B-cell maturation antigen; ECOG, Eastern Cooperative Oncology Group IMiD, immunomodulator drug; HBV, hepatitis B virus; HCV, hepatitis C virus; LOT, line of therapy; MM, multiple myeloma; PI, proteasome inhibitor; RW, real world; SMM, smoldering multiple myeloma; TCR, triple-class refractory.

criteria or HCP-reported progression, or death due to any cause, whichever occurred first. OS was defined as the time from the index date until the date of death due to any cause. DOR was only calculated for patients who had achieved a response on elranatamab or physician's choice and was defined as the time from the first documentation of an objective response until progression or death due to any cause, whichever occurred first.

Confounding Variables

Ensuring that baseline factors related to treatment assignment and outcomes are captured is critical to ensure the validity of an analysis with an external control arm. As described in more detail in previous research,[17] a systematic literature review was conducted to identify variables most strongly and consistently correlated with outcomes in real-world data studies conducted

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among RRMM patients, which were then validated with clinical input and supplemented with additional variables to further enhance the balance across the two arms. These variables were age, sex, race, cytogenetic risk (ie, t(4:14), t(14:16), or del17p), number of prior lines of therapy, ECOG performance status, time since initial MM diagnosis, penta-refractory status, international staging system (ISS), presence of bone lesions, extramedullary disease (EMD), stem cell transplant prior to index, comorbid conditions (assessed using the Charlson comorbidity index [CCI]), and levels of serum albumin, calcium, hemoglobin, serum creatine, bilirubin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT).

Statistical Analyses

The statistical approach is described in more detail elsewhere.[17] Briefly, inverse probability of treatment (IPT) weighting, which is a well-established method for causal inference in nonrandomized studies, was used to: 1) diminish the effect of confounding by observed baseline patient characteristics, 2) improve covariate balance, and 3) obtain unbiased estimates of treatment effects. IPT weights were calculated by using the propensity scores from a logistic regression model predicting treatment arm (elranatamab vs physician's choice) from the identified confounding variables noted above. Comparisons between treatment groups (elranatamab vs physician's choice) on PFS, OS, and DOR were conducted using Cox proportional hazard models both before (ie, "unweighted analyses") and after applying the IPT weights ("weighted analyses"). Missing data, which were only present for laboratory variables, were addressed using multiple imputations using chained equations (MICE) using the fully conditional specification method.[18] Specifically, the confounding variables noted above along with other variables (ie, those correlated with missingness or the laboratory value with missing data), were used in the imputation models to estimate the missing values. Results across the different datasets (each with different imputed results) were then pooled.

Additional sensitivity analyses were also performed which relied upon a doubly robust estimation method, which simultaneously modeled both exposure status along with the outcome. This allowed for unbiased estimates even if there were remaining imbalances across cohorts post-IPT weighting, provided the outcome model is correctly specified.[19] Finally, we also performed a quantitative bias assessment using e-values to determine how large the effect size must be for an unmeasured confounder to nullify our results.[20]

Results

Baseline Characteristics

The 123 patients from Cohort A in MagnetisMM-3 represented the elranatamab arm (mean age 67.1 years, 55.3% male) and 577 patients from COTA represented the physician's choice arm (mean age 67.2 years, 53.9% male). Over 180 unique physician's choice regimens were observed among these latter patients with daratumumab + pomalidomide + dexamethasone (DPd; 7.3%) and elotuzumab + pomalidomide + dexamethasone (EPd; 5.4%) as the most common. Baseline characteristics before and after statistical adjustment are shown in Table 1. Prior to weighting, the

Table 1 Baseline Demographics and Patient Characteristics for the Elranatamab and Physician's Choice Arms Before and After Inverse Probability of Treatment Weighting

	Before Imputing Missing Data				After Imputing Missing Data	
	Unweighted				Unweighted	IPT-Weighted
	Elranatamab Arm (N=123)	Physician's Choice Arm (N=577)	SMD	p-value	SMD	SMD
Age at index, mean (SD)	67.1 (9.4)	67.2 (10.0)	0.011	0.907	0.011	0.218
Female, n (%)	55 (44.7)	266 (46.1)	0.028	0.780	0.028	0.041
White, n (%)	72 (58.5)	415 (71.9)	0.284	0.003	0.284	0.047
ISS stage, n (%)			1.350	0.000	1.350	0.115
Stage I	36 (29.3)	58 (10.1)				
Stage II	46 (37.4)	70 (12.1)				
Stage III	24 (19.5)	51 (8.8)				
Unknown or not assessed	17 (13.8)	398 (69.0)				

(*Continued*)

Table 1 (Continued).

	Before Imputing Missing Data				After Imputing Missing Data	
	Unweighted				Unweighted	IPT-Weighted
	Elranatamab Arm (N=123)	Physician's Choice Arm (N=577)	SMD	p-value	SMD	SMD
ECOG, n (%)			0.290	0.095	0.290	0.128
0	45 (36.6)	181 (31.4)				
1	71 (57.7)	326 (56.5)				
2	7 (5.7)	70 (12.1)				
Time from initial MM diagnosis to index date (years), mean (SD)	6.6 (3.8)	5.6 (4.0)	0.247	0.013	0.247	0.100
Bone lesions during the baseline period or on the index date, n (%)	35 (28.5)	267 (46.3)	0.375	0.000	0.375	0.077
Extramedullary disease, n (%)	38 (30.9)	97 (16.8)	0.335	0.000	0.335	0.391
High-risk cytogenetics [t(4;14), t(14;16) or del(17p)], n (%)	31 (25.2)	165 (28.6)	0.077	0.447	0.077	0.224
Charlson Comorbidity Index Score, n (%)			0.221	0.328	0.221	0.289
2	83 (67.5)	432 (74.9)				
3	21 (17.1)	83 (14.4)				
4	11 (8.9)	44 (7.6)				
5	6 (4.9)	13 (2.3)				
6+	2 (1.6)	5 (0.9)				
Number of prior LOTs, mean (SD)	5.2 (2.6)	4.8 (2.3)	0.175	0.090	0.175	0.049
Penta-refractory, n (%)	51 (41.5)	99 (17.2)	0.554	0.000	0.554	0.247
SCT during the baseline period, n (%)	87 (70.7)	369 (64.0)	0.145	0.152	0.145	0.021
Aspartate aminotransferase (AST) (microkat/L)			0.077	0.380	0.085	0.075
Mean (SD)	0.4 (0.2)	0.4 (0.3)				
Median (IQR)	0.4 (0.3–0.5)	0.3 (0.2–0.4)				
Alanine aminotransferase (ALT) (microkat/L)			0.234	0.008	0.228	0.058
Mean (SD)	0.3 (0.2)	0.4 (0.4)				
Median (IQR)	0.3 (0.2–0.4)	0.3 (0.3–0.5)				
Hemoglobin (g/L)			0.195	0.047	0.199	0.040
Mean (SD)	110.3 (18.6)	106.5 (20.3)				
Median (IQR)	109.0 (98.0–124.0)	110.0 (90.0–120.0)				
Creatinine clearance (mL/min)			0.214	0.042	0.222	0.043
Mean (SD)	75.3 (29.9)	68.7 (32.0)				
Median (IQR)	67.2 (57.0–90.8)	68.0 (45.9–88.7)				
Calcium in serum or plasma (mmol/L)			0.237	0.007	0.222	0.148
Mean (SD)	2.3 (0.2)	2.3 (0.2)				
Median (IQR)	2.3 (2.3–2.4)	2.2 (2.2–2.5)				
Bilirubin (mmol/L)			0.058	0.451	0.053	0.135
Mean (SD)	9.5 (5.0)	9.0 (10.7)				
Median (IQR)	8.6 (6.8–12.0)	0.0 (0.0–17.1)				
Serum albumin (g/L)			0.647	0.000	0.597	0.211
Mean (SD)	3.8 (0.6)	3.4 (0.6)				
Median (IQR)	3.9 (3.5–4.2)	3.0 (3.0–4.0)				

Notes: Unweighted results before imputing missing data represent the data from the two arms only after applying inclusion/exclusion criteria. Unweighted results after imputing missing data (using multiple imputation through chained equations) represents the data after applying inclusions/exclusion criteria and imputing missing data, which only affected lab values (ie, the unweighted SMD values are nearly identical before and after MICE). The IPT weighted results represent the results after imputing missing data and applying the weights to balance the cohorts on the identified confounding variables.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; IPT, inverse probability of treatment; IQR, interquartile range; ISS, International Staging System; LOT, line of therapy; MICE, multiple imputation by chained equations; SCT, stem cell transplant; SD, standard deviation; SMD, standardized mean difference.

cohorts were generally comparable, though patients in the elranatamab arm were more likely to be non-White (41.5% vs 28.1%), have extramedullary disease (30.9% vs 16.8%), be penta-refractory (41.5% vs 17.2%), and have been diagnosed longer ago (6.6 vs 5.6 years) compared with the physician's choice arm. Applying MICE to address

missing data among laboratory variables and IPT weights improved the balance in the distribution of baseline demographic and disease characteristics considerably between the elranatamab and the physician's choice arms (Table 1). However, it should be noted that missing data were uncommon outside of laboratory values. Even in these cases, only creatinine clearance (11.4% and 21.1% in elranatamab and physician's choice arms, respectively) and serum albumin (17.1% in the elranatamab arm) had more than 4.5% missing data. The overall weighted standardized mean difference (SMD) was 0.133, below the threshold of 0.20 indicating sufficient balance across cohorts.[21,22]

Comparative Effectiveness

Prior to applying the IPT weights, elranatamab exhibited a significantly longer PFS (hazard ratio [HR] = 0.49 [95% confidence interval: 0.37, 0.65], $p < 0.05$) and OS (HR = 0.64 [0.49, 0.83], $p < 0.05$), and, among responders, longer DOR (HR = 0.17 [0.11, 0.26], $p < 0.05$). Post-weighting the results were similar though the HR effects were strengthened. Patients treated with elranatamab exhibited a significantly longer PFS (HR = 0.38 [0.22, 0.65], $p < 0.05$), longer OS (HR = 0.58 [0.35, 0.96], $p < 0.05$), and DOR among responders (HR = 0.16 [0.07, 0.34], $p < 0.05$). Kaplan–Meier curves are shown in Figures 2–4. Our sensitivity analysis using the doubly robust estimator closely aligned with our primary estimates (PFS: HR = 0.57 [0.42, 0.77], $p < 0.05$; OS: HR = 0.62 [0.45, 0.84], $p < 0.05$; DOR: HR = 0.20 [0.11, 0.39], $p < 0.05$). Furthermore, e-values estimated that an unmeasured confounder would need to have a risk ratio of ≥2.0 with both the treatment group and the outcome to fully explain the observed effects. The existence of such an unmeasured confounder would be highly unlikely given our analysis already included all established prognostic factors based on the literature and clinical opinion.

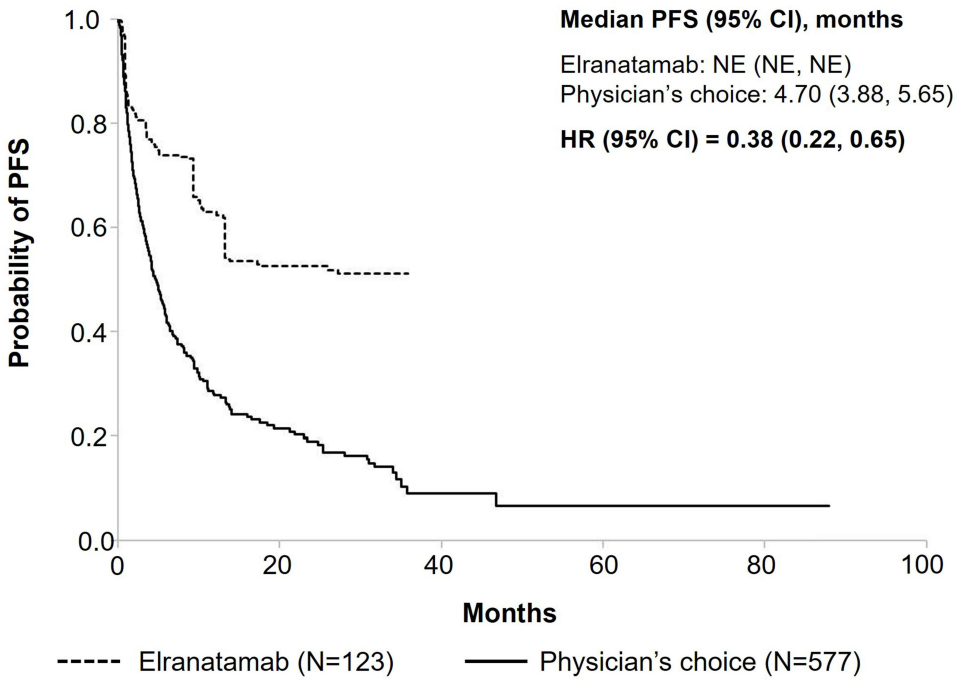

Figure 2 Progression-free survival differences between elranatamab in MagnetisMM-3 and real-world physician's choice in the COTA database, after applying multiple imputation and IPT weighting.
Abbreviations: NE, not estimable; PFS, progression-free survival.

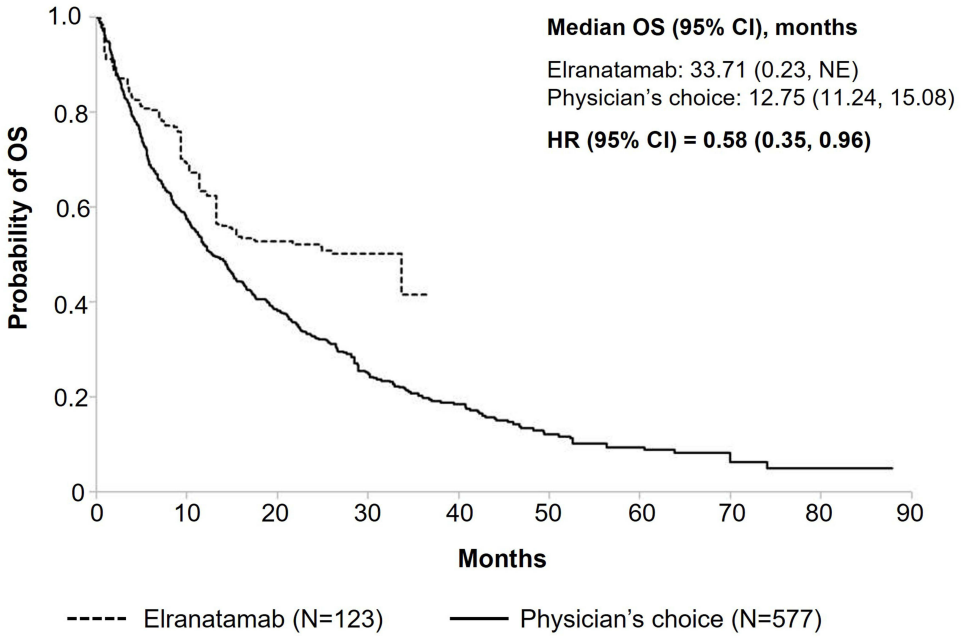

Figure 3 Overall survival differences between elranatamab in MagnetisMM-3 and real-world physician's choice in the COTA database, after applying multiple imputation and IPT weighting.
Abbreviations: NE, not estimable; OS, overall survival.

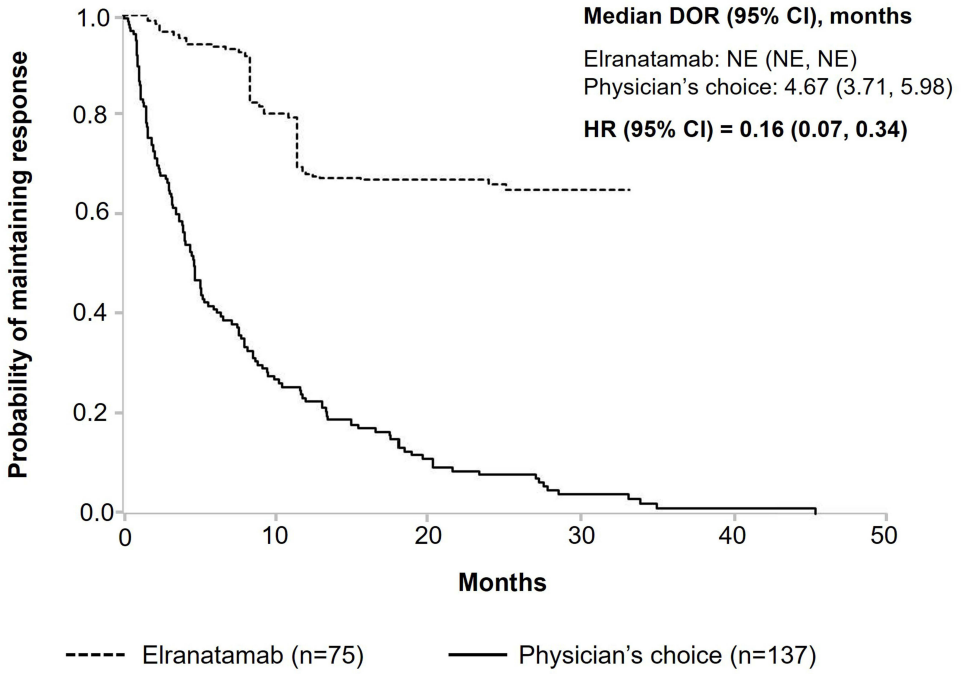

Figure 4 Duration of response differences between elranatamab in MagnetisMM-3 and real-world physician's choice in the COTA database, after applying multiple imputation and IPT weighting.
Abbreviations: DOR, duration of response; NE, not estimable.

Discussion

The number of available therapies to treat patients with RRMM continues to expand, providing increasing options for patients. However, with the lack of comparative trial designs in later line settings, it can be challenging to put the clinical profile of any one individual therapy for RRMM within the context of what presently exists. The aim of this study was to

update prior indirect comparisons to provide a more robust assessment of how the clinical efficacy of patients treated with elranatamab would compare to a similar cohort of patients using a different set of therapies in the real world. Such studies can provide useful context, which could support regulatory submissions, inform treatment sequencing and decision making, and influence future trial designs.

Because the average SMD across baseline characteristics between the elranatamab and physician's choice cohorts was small (0.133), we believe the groups were similar post-weighting. Consistent with the conclusions from prior analyses relying on less mature data,[15–17] the results from this indirect comparison indicated that BCMA-therapy naïve participants treated with elranatamab in MagnetisMM-3 demonstrated improved clinical outcomes and had significantly longer PFS, OS, and DOR compared with patients treated with physician's choice therapies from real-world clinical practice. This provides additional evidence for the role of BCMA-directed therapy in MM treatment. Indeed, ongoing trials are exploring the earlier use of such therapies (eg, NCT05020236, NCT06152575, NCT05623020, NCT06183489).

Limitations

The comparison of trial data with an external control arm has several limitations. First, applying inclusion and exclusion criteria from a clinical trial to real-world data sources requires adjustments due to data availability and differences in assessment which may have impacted the comparability between the treatment arms. Differential availability of information and the imprecision of the data capture may have resulted in residual confounding. Although the observation periods for the two cohorts partially overlap, there are patients from the external control arm who were included at an earlier point of time than the trial. The physician's choice cohort is also exclusively from the US; it is unclear how the findings compare with those from the trial population's geographic footprint. Also, unlike clinical trial settings with specific definitions of study outcomes and scheduled assessments described in the protocol, assessments in real-world clinical practice settings may not be made consistently across patients and physicians. This bias could favor the external control arm (ie, longer time to events) considering that patients are monitored less frequently for response and progression in clinical practice. Finally, the DOR endpoint remains immature even after >28 months of follow-up; further analyses with even longer follow-up would be necessary to confirm the durability of response.

Although the scope of this particular analysis was limited to efficacy (due to the lack of comparability in safety assessment methodology across real-world and trial sources), future research should consider including safety-related comparisons as well. Similarly, future directions may consider exploring specific subgroups of clinical relevance (eg, cytogenetic risk, line of therapy).

Conclusion

Overall, the results suggest that in the comparison between patients enrolled in the MagnetisMM-3 trial and patients in the real world who resemble those from the trial, patients treated with elranatamab exhibited significantly and clinically meaningfully longer PFS, OS, and DOR compared with physician's choice of treatment in the real world.

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.

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Disclosure

LJC has received honoraria from Amgen, Bristol Myers Squibb, Celgene, Janssen, Karyopharm Therapeutics, and Sanofi; has been in a consulting or advisory role with AbbVie, Adaptive Biotechnologies, AstraZeneca, Bristol Myers Squibb, Caribou, Celgene, Genentech, Janssen, and Karyopharm Therapeutics; has received research funding from Amgen, Bristol Myers Squibb, Celgene, Janssen and Juno; and has been in a Speakers' Bureau role for Amgen and Sanofi. TWL has received honoraria from Agilix Health and Lilly; has been in a consulting or advisory role with AbbVie/Genentech, Agios/Servier, Apellis, Astellas Pharma, BeiGene, Blue Note Therapeutics, Bristol Myers Squibb/Celgene, Deverra Therapeutics/Coeptis, Flatiron Health, Geron, Gilead, GSK, Incyte, Lilly, Menarini/Stemline, Rigel, Syndax, Novartis, and Pfizer; reports institutional funding from Bristol Myers Squibb and Jazz Pharmaceuticals; and has received fees for travel, accommodations, and expenses from AbbVie/Genentech, Agios, Bristol Myers Squibb/Celgene, and Incyte. HT has received honoraria from Amgen, AstraZeneca, Lilly, Novartis, Pfizer, Roche Pharma AG, and Vifor Pharma; has been in a consulting or advisory role with AstraZeneca, Daiichi Sankyo Pharmaceutical, Eickler, Exact Sciences, Gilead, GSK, Lilly, MSD, Novartis, Pfizer, Roche Pharma AG, and Seagen. PS has been in a consulting or advisory role with Amgen, CARsgen Therapeutics, Celgene, Janssen, Regeneron, MMRF, and Karyopharm Therapeutics; and reports institutional funding from Amgen, Bristol Myers Squibb, Janssen, and Skyline Diagnostics. FV and SMAJ are employees of STATLOG, which was a paid consultant to Pfizer in connection with the development of this manuscript. PH, AM, CHK, PC, DMH, GN, and MD are employees at and hold stock ownership in Pfizer. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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