Comparative Efficacy of Talquetamab vs. Current Treatments in the LocoMMotion and MoMMent Studies in Patients with Triple-Class-Exposed Relapsed/Refractory Multiple Myeloma

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ABSTRACT

Introduction: Talquetamab, a bispecific antibody targeting GPRC5D × CD3, is approved for the treatment of patients with triple-class -exposed (TCE) relapsed/refractory multiple myeloma (RRMM) on the basis of the results from the phase I/II MonumenTAL-1 trial. The relative effectiveness of talquetamab vs. real-world physician's choice of therapy (RWPC) was assessed using adjusted comparisons.

Methods: An external control arm for MonumenTAL-1 (subcutaneously administered talquetamab 0.4 mg/kg weekly [QW] and 0.8 mg/kg every other week [Q2W]) was created from two observational real-world studies: LocoMMotion and MoMMent. Imbalances in baseline covariates were adjusted using inverse probability weighting. The relative effectiveness of talquetamab vs. RWPC was estimated for overall response rate (ORR), ≥ very good partial response (VGPR), and ≥ complete response

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(CR); odds ratios and relative response ratios (RRs) were derived from weighted logistic regression. Hazard ratios (HRs) for duration of response (DOR), progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS) were estimated using a weighted Cox proportional hazards model.

Results: After reweighting, baseline characteristics were balanced across cohorts. In adjusted comparisons, patients treated with talquetamab QW ($n = 143$) had significantly improved outcomes vs. RWPC; RRs were ORR 2.67, $p < 0.0001$; $\geq$ VGPR 4.70, $p < 0.0001$; $\geq$ CR 78.05, $p = 0.0002$; and HRs were PFS 0.52, $p < 0.0001$; TTNT 0.48, $p < 0.0001$; OS 0.36, $p < 0.0001$. Patients treated with talquetamab Q2W ($n = 145$) also had significantly improved outcomes vs. RWPC; RRs were ORR 2.62, $p < 0.0001$; $\geq$ VGPR 5.04, $p < 0.0001$; $\geq$ CR 101.14, $p = 0.0002$; and HRs were PFS 0.40, $p < 0.0001$; TTNT 0.39, $p < 0.0001$; OS 0.37, $p < 0.0001$.

Conclusion: Effectiveness of talquetamab for both schedules was significantly better than RWPC for ORR, $\geq$ VGPR, $\geq$ CR, PFS, OS, and TTNT, highlighting its clinical benefit for patients with TCE RRMM.

Trial Registration: MonumenTAL-1, ClinicalTrials.gov identifier NCT03399799/NCT04634552; LocoMMotion, ClinicalTrials.gov identifier NCT04035226; MoMMent, ClinicalTrials.gov identifier NCT05160584.

Keywords: LocoMMotion; MoMMent; MonumenTAL-1; Talquetamab; Triple-class-exposed relapsed/refractory multiple myeloma

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Key Summary Points

Why carry out this study?

Patients with relapsed/refractory multiple myeloma (RRMM) have a poor prognosis, indicating a need for new, efficacious, and well-tolerated treatment options to improve outcomes.

The ongoing, single-arm MonumenTAL-1 (NCT03399799, NCT04636552) study is investigating the efficacy and safety of talquetamab, a T cell-redirecting bispecific antibody targeting GPRC5D × CD3, which was recently approved in patients with RRMM who are triple-class-exposed (TCE; i.e., prior treatment with an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody).

The objective of this study was to compare outcomes in patients with TCE RRMM who were treated with either of two doses of talquetamab (0.4 mg/kg weekly or 0.8 mg/kg every other week) in MonumenTAL-1 vs. patients treated with TCE RRMM who were treated with real-world physician's choice of therapy from the prospective, observational LocoMMotion and MoMMent studies.

What was learned from the study?

Patients treated with either dose of talquetamab in MonumenTAL-1 had significant improvements in most efficacy outcomes compared with an eligibility-matched patient cohort treated with real-world physician's choice of therapy.

The results indicate that talquetamab may provide a highly effective treatment option for patients with TCE RRMM, who have historically limited options.

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INTRODUCTION

The past decade has seen the introduction of new agents for the treatment of multiple myeloma (MM), including immunomodulatory agents (IMiDs), proteasome inhibitors (PIs), and anti-CD38 monoclonal antibodies (mAbs), that have improved survival in patients with MM [1]. Although the use of these agents has improved outcomes for patients overall, most patients experience cycles of relapse and remission that require further treatment [2–7]. With each subsequent line of therapy (LOT), the remission period typically becomes shorter than the previous one, and the disease becomes harder to treat [6]. There is no well-established standard of care for patients with MM who are triple-class-exposed (TCE; i.e., have received IMiDs, PIs, and anti-CD38 mAbs). These patients often have a poor prognosis and limited treatment options [8, 9]. Therefore, there is an unmet medical need to improve patient outcomes using therapies that have new targets or mechanisms of action.

Talquetamab is a first-in-class, off-the-shelf, T cell-redirecting bispecific antibody that targets G protein-coupled receptor class C group 5 member D (GPRC5D)-expressing malignant plasma cells and CD3 on T cells [10, 11]. The safety and efficacy results from the MonumenTAL-1 study, a single-arm, open-label, multicenter, phase I/II study in patients with TCE relapsed/refractory MM (RRMM) who previously received at least three prior LOTs (phase II inclusion criteria), have led to the approval of talquetamab for the treatment of patients with RRMM [12]. Two recommended phase II doses (RP2Ds) of subcutaneously administered talquetamab (0.4 mg/kg weekly [QW] or 0.8 mg/kg every other week [Q2W]) were selected on the basis of the results of the phase I portion of the MonumenTAL-1 study [13, 14]. In the phase I analysis with 30 patients in the 0.4 mg/kg QW cohort and 44 patients in the 0.8 mg/kg Q2W cohort, overall response rates (ORRs) were 70.0% and 63.6%, respectively; the median times to first confirmed responses were 0.9 and 1.2 months,

respectively, and a clinically manageable safety profile was observed [13].

For studies that do not include a control arm, such as MonumenTAL-1, adjusted treatment comparisons to an external control arm may be used to assess the benefits of a treatment relative to regimens used in clinical practice [15]. LocoMMotion is a prospective, observational study of real-world physician's choice of therapy (RWPC) in patients with TCE RRMM who were enrolled between August 2019 and October 2020 [9]. MoMMent is a prospective, observational study designed in a similar manner as LocoMMotion to continue the investigation of current RWPC and associated outcomes in patients with TCE RRMM who received at least three prior LOTs; patients in MoMMent were enrolled between November 2021 and July 2022 [16]. Both LocoMMotion and MoMMent studies were specifically designed as external control arms mimicking the ongoing single-arm trials (e.g., MonumenTAL-1) to serve as the benchmark for comparison with novel therapies. In the study reported here, individual patient data (IPD) of patients from MonumenTAL-1 were compared with a similar population of patients from LocoMMotion and MoMMent who met MonumenTAL-1 eligibility criteria and further adjusted for any imbalances in baseline prognostic factors to assess the comparative effectiveness of the two RP2Ds of subcutaneous (SC) talquetamab vs. therapies currently available for RWPC in patients with TCE RRMM. More specifically, the study sought to evaluate the comparative effectiveness of SC talquetamab vs. RWPC with respect to the ORR, depth of response (very good partial response or better [$\geq$ VGPR] and complete response or better [$\geq$ CR] rates), duration of response (DOR), progression-free survival (PFS), time to next treatment (TTNT), and overall survival (OS).

METHODS

Patient Populations

IPD from MonumenTAL-1 (NCT03399799, NCT04634552), LocoMMotion (NCT04035226), and MoMMent (NCT05160584) were used to conduct adjusted comparisons between talquetamab and RWPC. IPD from MonumenTAL-1 included all patients treated with talquetamab 0.4 mg/kg QW ($n = 143$) or 0.8 mg/kg Q2W ($n = 145$), and IPD from LocoMMotion and MoMMent included 177 patients who met MonumenTAL-1 eligibility criteria. All patients included in the comparative effectiveness analyses were aligned with key inclusion and exclusion criteria from the MonumenTAL-1 phase II portion of the study that included patients with measurable disease as defined by International Myeloma Working Group (IMWG) consensus criteria, had received at least three prior LOTs (IMiDs, PIs, and anti-CD38 mAbs), had progressive disease $\leq$ 12 months since last LOT, had an Eastern Cooperative Oncology Group performance status (ECOG PS) of 0–2, had adequate bone marrow reserve (defined as hemoglobin $\geq$ 8 g/dL) and renal function (defined as creatinine clearance $\geq$ 40 mL/min/1.73 m^2), and had not received prior T cell redirection therapy, including chimeric antigen receptor (CAR)-T cell therapy or bispecific antibodies. The index date for all studies was the date of treatment initiation. Detailed descriptions regarding data sources and study designs are presented in Supplementary Materials Appendix S1.

MonumenTAL-1 was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent. An independent ethics committee or institutional review board at each study center approved the study protocol (Supplementary Materials Tables S1–S3). The LocoMMotion and MoMMent studies were conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. An independent ethics committee/institutional review board at each center approved the study protocol.

Efficacy Endpoints

The ORR, $\geq$ VGPR rate, $\geq$ CR rate, and PFS were assessed on the basis of IMWG consensus

criteria [17] by an independent review committee in MonumenTAL-1 and a response review committee in LocoMMotion and MoM-Ment as described previously [9, 13]; LocoM-Motion and MoMMent utilized the same response review committee to ensure consistency across studies. Additional efficacy endpoints assessed were DOR, TTNT, and OS. All endpoints were compared between both RP2Ds of talquetamab and RWPC. Outcomes were assessed from the date of treatment initiation in MonumenTAL-1, LocoMMotion, and MoMMent.

Statistical Analyses

The inverse probability of treatment weighting (IPTW) method, using the average treatment effect in the treated (ATT) approach [18], was implemented to balance the RWPC population with the talquetamab cohorts with respect to baseline patient characteristics identified as important prognostic factors (details on covariate selection provided below). The IPTW-ATT approach involved two steps. First, a multivariable logistic regression propensity score model was fit by regressing treatment (receipt of talquetamab vs. RWPC) on a set of baseline patient characteristics identified as important prognostic factors. The propensity scores were transformed into ATT weights assigned to the RWPC cohort so that they would resemble the talquetamab cohorts with respect to baseline patient characteristics. The degree of imbalance in baseline characteristics between groups was assessed using standardized mean differences (SMDs): values closer to 0 reflect better balance, and values > 0.2 reflect important differences. In the second step, weighted logistic regression was used to estimate odds ratios (ORs) and response ratios (RRs) with corresponding 95% confidence intervals (CIs) for response outcomes [19]. Weighted Cox proportional hazards regression was used to estimate hazard ratios (HRs) with corresponding 95% CIs for time-to-event endpoints. Kaplan–Meier median duration estimates and plots (unweighted and ATT-weighted) were also generated for the time-to-

event endpoints. Data are presented in the results as RR (95% CI) and HR (95% CI).

The selection of prognostic baseline characteristics for adjustment in the base case analyses was based on consultations with clinical experts; the chosen characteristics were age, sex, type of MM, years since MM diagnosis, ECOG PS, International Staging System (ISS) stage, extramedullary disease, previous hematopoietic stem cell transplant, number of previous LOTs, average duration of previous LOTs, time to progression on previous LOT, refractory status, hemoglobin levels, lactate dehydrogenase levels, and creatinine clearance. Cytogenetic risk was not included in the main adjusted analyses because of a high rate of missingness (44.1% in the RWPC cohort, 7.7% in the talquetamab 0.4 mg/kg QW cohort, and 11.7% in the talquetamab 0.8 mg/kg Q2W cohort). Race was also not included in the main adjusted analyses because the high weights assigned to the small number of non-white patients enrolled in LocoMMotion to account for the higher proportion of non-white patients in MonumenTAL-1 increased the imbalance of other factors; however, a sensitivity analysis was conducted that included both cytogenetic risk and race in the adjustment models, and missing cytogenetic risk was defined as a separate category.

Average treatment effect (ATE) and average treatment effect in the overlap (ATO) weights were used as sensitivity analyses. Multivariable regressions were also conducted as a sensitivity analysis, including a binary treatment indicator and baseline prognostic variables for adjustment in the model, along with propensity score matching using an optimal matching algorithm. Propensity score matching was implemented via optimal matching where matches were formed by minimizing the total within-pair difference in the logit of propensity scores [20]. Each patient treated with talquetamab was matched to a RWPC patient without replacement, and only the matches with differences within a caliper of 0.20 of the standard deviation of the logit of the propensity score were retained [21].

Quantitative bias analysis of unmeasured confounding was used to assess the robustness

of the study by estimating the *E*-value [22–24]. The *E*-value represents the minimum association that an unmeasured confounder would need to have with both the treatment and the outcome, conditional on the measured covariates, to fully explain a treatment–outcome association; a large *E*-value indicates that considerable unmeasured confounding would be needed to explain a treatment effect estimate. Additionally, all combinations of values for associations of a potential unmeasured confounder with both the treatment and the outcomes of interest required to alter the conclusion on the treatment effect (of which the *E*-value is the specific combination with both values being equal) are presented graphically using bias plots.

Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA) and R version 3.6.1 and 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient Characteristics

The median follow-up was 16.3 months in MonumenTAL-1 for both cohorts (18.8 months for 0.4 mg/kg QW and 12.7 months for 0.8 mg/kg Q2W; data cutoff of January 17, 2023), 26.4 months in LocoMMotion (data cutoff of October 27, 2022), and 9.3 months in MoMMent (data cutoff of March 13, 2023). Before reweighting, substantial differences (SMDs > 0.2) were observed in many of the base case variables: the talquetamab 0.4 mg/kg QW cohort had a higher proportion of patients with immunoglobulin G (IgG) subtype (53.1% vs. 39.0%), extramedullary plasmacytomas (23.1% vs. 10.7%), prior stem cell transplant (79.0% vs. 66.7%), age < 65 years (45.5% vs. 30.5%), penta-drug refractory (29.4% vs. 18.1%), > 4 prior LOTs (55.2% vs. 41.2%), and progression on their last regimen in < 3 months (30.8% vs. 16.4%) compared with the RWPC cohort (Table 1). The RWPC cohort had a greater proportion of patients who were triple-class refractory only (excluding patients who were quad- or penta-class-refractory; 23.7% vs.

11.2%) compared with the talquetamab 0.4 mg/kg QW cohort. Before reweighting, the talquetamab 0.8 mg/kg Q2W cohort had a higher proportion of patients with IgG subtype (53.1% vs. 39.0%), extramedullary plasmacytomas (25.5% vs. 10.7%), prior stem cell transplant (78.6% vs. 66.7%), age < 65 years (43.4% vs. 30.5%), > 4 prior LOTs (52.4% vs. 41.2%), progression on their last regimen in < 3 months (28.3% vs. 16.4%), an average duration of prior LOTs of < 10 months (25.5% vs. 15.3%), and an ECOG PS of 0 (38.6% vs. 23.7%) compared with the RWPC cohort (Table 1). The RWPC cohort had a greater proportion of patients who were triple-class refractory (23.7% vs. 16.6%) and had an average duration of prior LOTs of ≥ 15 months (59.9% vs. 50.3%) compared with the talquetamab 0.8 mg/kg Q2W cohort. After reweighting, baseline characteristics were well balanced between the RWPC cohort (*n* = 177) and both the talquetamab 0.4 mg/kg QW (*n* = 143) and 0.8 mg/kg Q2W (*n* = 145) cohorts. Most SMD values were < 0.10, and the maximum values were 0.15 and 0.21 for the QW and Q2W cohorts, respectively (Table 1, Supplementary Materials Fig. S1).

Treatment Regimens Received in Real-World Clinical Practice

In the RWPC cohort, 74 treatment combinations were used; however, only three regimens were prescribed to > 10% of patients (pomalidomide plus cyclophosphamide plus dexamethasone [16.4%]; pomalidomide plus dexamethasone [11.9%]; carfilzomib plus dexamethasone [10.2%]; Supplementary Materials Table S4). The LocoMMotion study period occurred earlier than the MoMMent study period; therefore, only a limited number of patients received belantamab mafodotin (*n* = 13) or selinexor (*n* = 1) because these agents only became available at the end of the LocoMMotion recruitment period. The MoMMent study was initiated to reflect the most recent antimyeloma treatments (patients enrolled from November 2021 to July 2022); however, the majority of patients received the same regimens as those used in LocoMMotion,

Table 1 Group demographic balance before and after IPTW-ATT weighting for the comparison of talquetamab 0.4 mg/kg QW and 0.8 mg/kg Q2W with RWPC cohorts

Covariate	Observed RWPC cohort, n (%) (n = 177)	Talquetamab 0.4 mg/kg QW, n (%) (n = 143)	ATT-adjusted RWPC cohort, n (%) (n = 177)	SMD	Talquetamab 0.8 mg/kg Q2W, n (%) (n = 145)	ATT-adjusted RWPC cohort, n (%) (n = 177)	SMD
Refractory status[a]				0.099			0.115
≤ Double[b]	50 (28.2)	37 (25.9)	41 (23.0)		45 (31.0)	60 (33.8)	
Triple[c]	42 (23.7)	16 (11.2)	17 (9.7)		24 (16.6)	26 (14.6)	
Quadruple[d]	53 (29.9)	48 (33.6)	61 (34.4)		41 (28.3)	44 (24.6)	
Penta[e]	32 (18.1)	42 (29.4)	58 (32.9)		35 (24.1)	48 (26.9)	
ISS stage at study entry				0.115			0.089
I	70 (39.5)	62 (43.4)	69 (38.8)		65 (44.8)	76 (42.9)	
II	71 (40.1)	53 (37.1)	66 (37.5)		45 (31.0)	51 (29.1)	
III	36 (20.3)	28 (19.6)	42 (23.7)		35 (24.1)	50 (28.0)	
Time to progression in previous line				0.139			0.095
< 3 months	29 (16.4)	44 (30.8)	66 (37.4)		41 (28.3)	58 (32.6)	
≥ 3 months	148 (83.6)	99 (69.2)	111 (62.6)		104 (71.7)	119 (67.4)	
Extramedullary disease[f]				0.097			0.122
Yes	19 (10.7)	33 (23.1)	48 (27.3)		37 (25.5)	55 (31.0)	
No	158 (89.3)	110 (76.9)	129 (72.7)		108 (74.5)	122 (69.0)	
Number of previous LOTs				0.032			0.102
≤ 4	104 (58.8)	64 (44.8)	76 (43.1)		69 (47.6)	75 (42.5)	
> 4	73 (41.2)	79 (55.2)	101 (56.9)		76 (52.4)	102 (57.5)	
Years since diagnosis				0.039			0.133
< 6	77 (43.5)	64 (44.8)	76 (42.8)		67 (46.2)	70 (39.6)	
≥ 6	100 (56.5)	79 (55.2)	101 (57.2)		78 (53.8)	107 (60.4)	
Average duration of prior lines				0.046			0.098
< 10 months	27 (15.3)	25 (17.5)	33 (18.6)		37 (25.5)	45 (25.5)	
10–14 months	44 (24.9)	41 (28.7)	53 (29.7)		35 (24.1)	36 (20.3)	

Table 1 continued

Covariate	Observed RWPC cohort, *n* (%) (*n* = 177)	Talquetamab 0.4 mg/kg QW, *n* (%) (*n* = 143)	ATT-adjusted RWPC cohort, *n* (%) (*n* = 177)	SMD	Talquetamab 0.8 mg/kg Q2W, *n* (%) (*n* = 145)	ATT-adjusted RWPC cohort, *n* (%) (*n* = 177)	SMD
≥ 15 months	106 (59.9)	77 (53.8)	91 (51.6)		73 (50.3)	96 (54.3)	
Age				0.080			0.095
< 65 years	54 (30.5)	65 (45.5)	73 (41.5)		63 (43.4)	69 (38.8)	
≥ 65 years	123 (69.5)	78 (54.5)	104 (58.5)		82 (56.6)	108 (61.2)	
Hemoglobin (g/ dL)				0.144			0.026
< 12	122 (68.9)	110 (76.9)	146 (82.7)		113 (77.9)	140 (79.0)	
≥ 12	55 (31.1)	33 (23.1)	31 (17.3)		32 (22.1)	37 (21.0)	
LDH (units/L)				0.008			0.091
< 280	122 (68.9)	108 (75.5)	133 (75.2)		111 (76.6)	142 (80.3)	
≥ 280	55 (31.1)	35 (24.5)	44 (24.8)		34 (23.4)	35 (19.7)	
Creatinine clearance (mL/ min)				0.145			0.210
< 60	43 (24.3)	40 (28.0)	43 (24.3)		45 (31.0)	40 (22.5)	
60 to < 90	84 (47.5)	72 (50.3)	85 (48.0)		68 (46.9)	87 (49.2)	
≥ 90	50 (28.2)	31 (21.7)	49 (27.7)		32 (22.1)	50 (28.3)	
ECOG PS				0.005			0.043
0	42 (23.7)	44 (30.8)	55 (31.0)		56 (38.6)	72 (40.7)	
1–2	135 (76.3)	99 (69.2)	122 (69.0)		89 (61.4)	105 (59.3)	
Sex				0.123			0.096
Male	96 (54.2)	78 (54.5)	86 (48.4)		83 (57.2)	93 (52.5)	
Female	81 (45.8)	65 (45.5)	91 (51.6)		62 (42.8)	84 (47.5)	
MM type				0.095			0.101
IgG	69 (39.0)	76 (53.1)	102 (57.8)		77 (53.1)	103 (58.1)	
Non-IgG	108 (61.0)	67 (46.9)	75 (42.2)		68 (46.9)	74 (41.9)	
Previous hematopoietic stem cell transplant				0.037			0.083
Yes	118 (66.7)	113 (79.0)	142 (80.5)		114 (78.6)	145 (81.9)	

Table 1 continued

Covariate	Observed	Talquetamab 0.4 mg/kg QW, n (%) (n = 143)	ATT-adjusted		Talquetamab 0.8 mg/kg Q2W, n (%) (n = 145)	ATT-adjusted	
	RWPC cohort, n (%) (n = 177)		RWPC cohort, n (%) (n = 177)	SMD		RWPC cohort, n (%) (n = 177)	SMD
No	59 (33.3)	30 (21.0)	35 (19.5)		31 (21.4)	32 (18.1)	

The pre-weighting and post-weighting distributions of baseline prognostic factors by intervention group are shown. ATT-weighted patient frequencies are rounded to the nearest integer. SMDs > 0.2 are considered to indicate important imbalances between groups. Results were adjusted for refractory status, ISS stage, time to progression on last regimen, extramedullary plasmacytomas, number of previous LOTs, years since MM diagnosis, average duration of previous lines, age, hemoglobin levels, LDH levels, creatinine clearance, ECOG PS, sex, type of MM, and previous hematopoietic stem cell transplant

ATT average treatment effect in the treated population, *ECOG PS* Eastern Cooperative Oncology Group performance status, *IgG* immunoglobulin G, *IMiD* immunomodulatory agent, *IPTW* inverse probability treatment weighting, *ISS* International Staging System, *LDH* lactate dehydrogenase, *LOT* line of therapy, *MM* multiple myeloma, *mAb* monoclonal antibody, *PI* proteasome inhibitor, *Q2W* every other week, *QW* weekly, *RWPC* real-world physician's choice of therapy, *SMD* standardized mean difference

[a]Refractoriness was defined as progressive disease/relapse (physician's choice cohort) and by International Myeloma Working Group consensus criteria (MonumenTAL-1)

[b]Refractory status less than triple refractory

[c]Refractory to one IMiD, one PI, and one anti-CD38 mAb

[d]Refractory to at least two IMiDs, one PI, and one anti-CD38 mAb or at least two PIs, one IMiD, and one anti-CD38 mAb

[e]Refractory to at least two IMiDs, at least two PIs, and one anti-CD38 mAb

[f]Refers to soft-tissue mass that is not in contact with bone; does not include bone-based plasmacytomas. In the RWPC cohort, this includes patients with extramedullary disease at baseline and a small proportion who developed it during follow-up

with the exception of three patients treated with idecabtagene vicleucel (ide-cel); these data highlight the lack of a well-established standard of care and accessibility of CAR-T cell treatment for these patients. At the time of data cutoff, 107 patients received subsequent antimyeloma therapy, of which 54 patients (51%) received at least one novel agent, mainly belantamab mafodotin (n = 32) and selinexor (n = 13) but also bispecific antibodies (n = 12) and CAR-T (n = 4).

## Comparative Analysis of Efficacy Outcomes

The observed ORR for talquetamab 0.4 mg/kg QW was 74.1% vs. 37.3% in the RWPC cohort, and responders on talquetamab 0.4 mg/kg QW reached deeper levels of response than RWPC responders (Fig. 1). After IPTW-ATT adjustment, talquetamab 0.4 mg/kg QW showed significantly improved response vs. RWPC: ORR, 74.1% vs. 27.8% (RR 2.67 [1.90–3.74]; $p < 0.0001$); ≥ VGPR, 59.4% vs. 12.7% (RR 4.70 [2.95–7.48]; $p < 0.0001$); and ≥ CR, 33.6% vs. 0.4% (RR 78.05 [8.11–751.03]; $p = 0.0002$) (Figs. 1 and 2). These data indicate that patients treated with talquetamab 0.4 mg/kg QW were 2.7-, 4.7-, and 78.1-fold more likely to reach ORR, ≥ VGPR, and ≥ CR, respectively. In addition, ATT-adjusted PFS (median 7.5 vs. 4.1 months; HR 0.52 [0.39–0.71]; $p < 0.0001$), TTNT (median 9.1 vs. 4.6 months; HR 0.48 [0.36–0.64]; $p < 0.0001$), and OS (median not reached vs. 9.2 months; HR 0.36 [0.25–0.53]; $p < 0.0001$) were significantly longer with talquetamab 0.4 mg/kg QW vs. RWPC. DOR was numerically longer with talquetamab 0.4 mg/kg
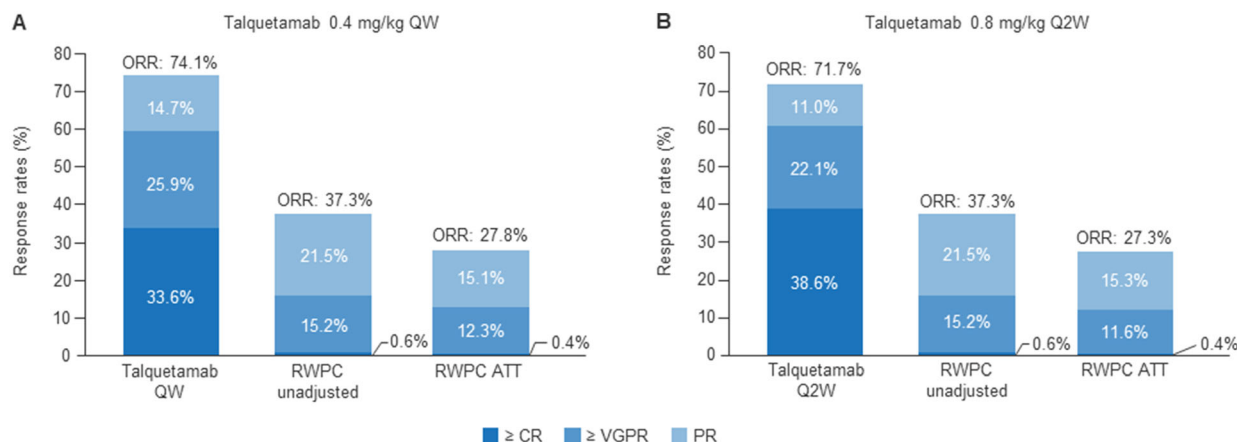
Fig. 1 Observed and ATT-adjusted response rates for talquetamab vs. RWPC. ≥ *CR* complete response or better, ≥ *VGPR* very good partial response or better, *ATT* average treatment effect in the treated, *ORR* overall response rate, *PR* partial response, *Q2W* every other week, *QW* weekly, *RR* response rate ratio, *RWPC* real-world physician's choice of therapy
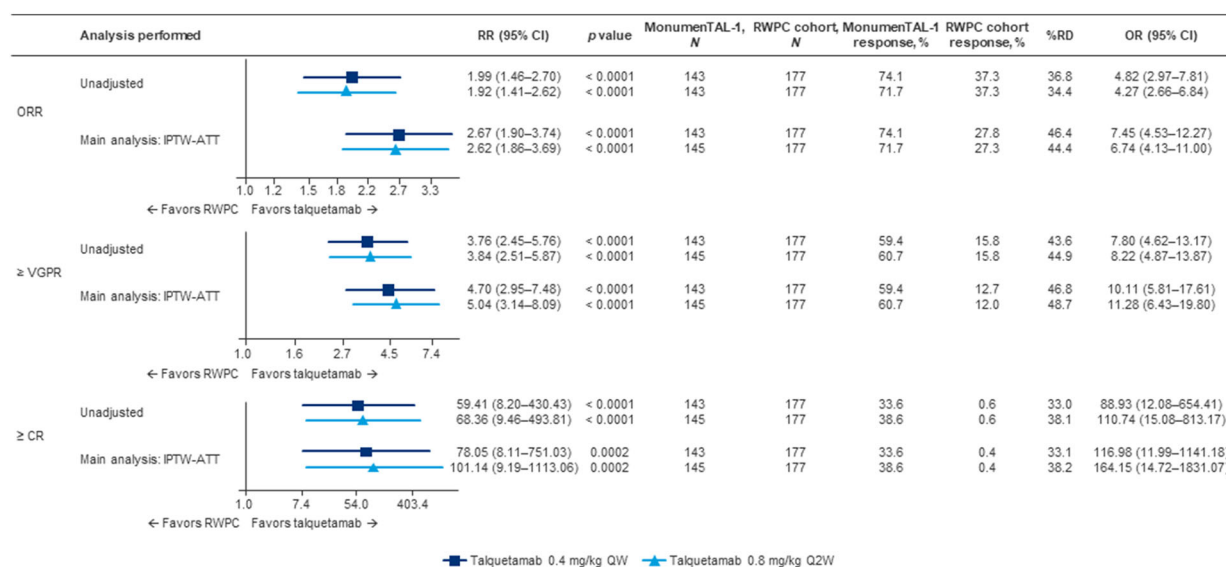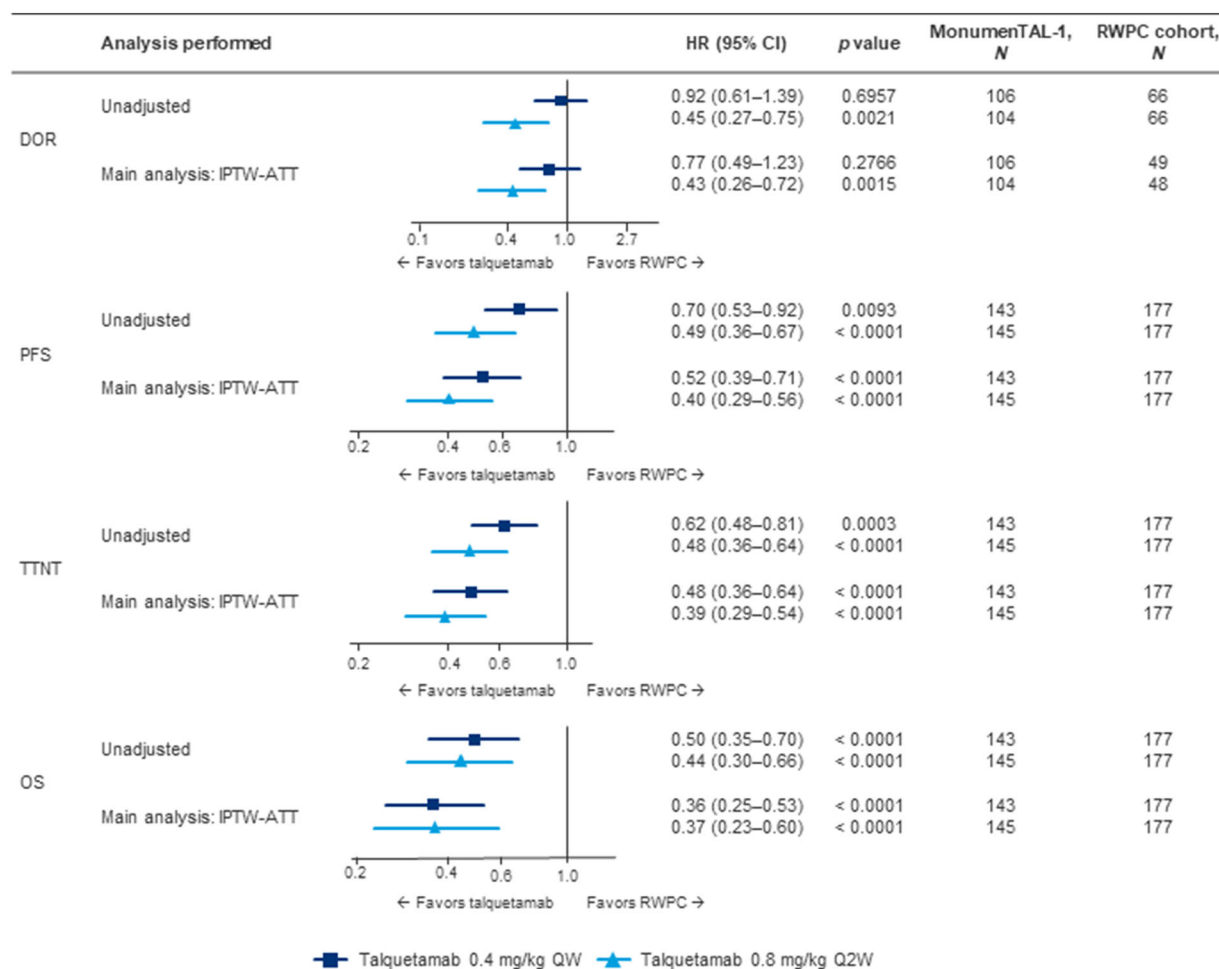

Fig. 2 Summary of unadjusted and adjusted results for clinical response for talquetamab 0.4 mg/kg QW and talquetamab 0.8 mg/kg Q2W vs. RWPC. ≥ *CR* complete response or better, ≥ *VGPR* very good partial response or better, *ATT* average treatment effect in the treated, *CI* confidence interval, *IPTW* inverse probability of treatment weighting, *OR* odds ratio, *ORR* overall response rate, *Q2W* every other week, *QW* weekly, *RD* rate difference, *RR* response rate ratio, *RWPC* real-world physician's choice of therapy

QW vs. RWPC (median 9.5 vs. 7.7 months; HR 0.77 [0.49–1.23]; $p = 0.2766$) (Figs. 3 and 4).

After IPTW-ATT adjustment, patients treated with talquetamab 0.8 mg/kg Q2W also had significantly improved outcomes vs. RWPC: ORR, 71.7% vs. 27.3% (RR 2.62 [1.86–3.69]; $p < 0.0001$); ≥ VGPR, 60.7% vs. 12.0% (RR 5.04 [3.14–8.09]; $p < 0.0001$); and ≥ CR, 38.6% vs. 0.4% (RR 101.14 [9.19–1113.06]; $p = 0.0002$). Median DOR was not reached vs. 9.0 months

Fig. 3 Summary of unadjusted and adjusted results for time-to-event outcomes for talquetamab 0.4 mg/kg QW and talquetamab 0.8 mg/kg Q2W vs. RWPC. *ATT* average treatment effect in the treated, *CI* confidence interval, *DO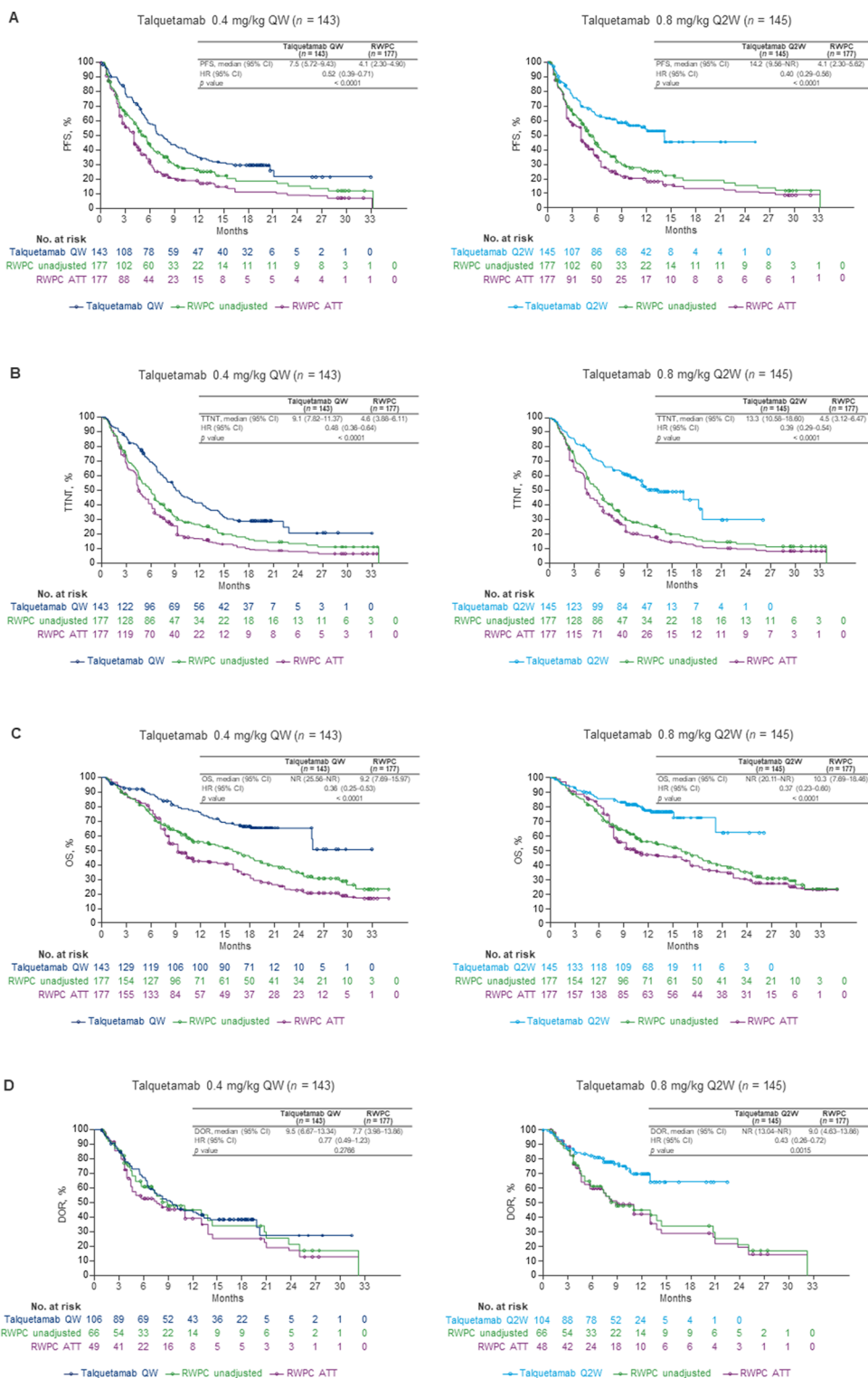R* duration of response, *HR* hazard ratio, *IPTW* inverse probability of treatment weighting, *OS* overall survival, *PFS* progression-free survival, *Q2W* every other week, *QW* weekly, *TTNT* time to next treatment, *RWPC* real-world physician's choice of therapy

(HR 0.43 [0.26–0.72]; $p = 0.0015$); median PFS was 14.2 vs. 4.1 months (HR 0.40 [0.29–0.56]; $p < 0.0001$); median TTNT was 13.3 vs. 4.5 months (HR 0.39 [0.29–0.54]; $p < 0.0001$); and median OS was not reached vs. 10.3 months (HR 0.37 [0.23–0.60]; $p < 0.0001$) (Figs. 1, 2, 3, 4).

Figure 4a, b and c present the observed Kaplan–Meier survival curves for talquetamab RP2Ds and the observed and ATT-adjusted Kaplan–Meier survival curves for the RWPC cohort, further illustrating the improved outcomes for talquetamab on PFS, TTNT, and OS. The main findings from the ATT-adjusted analyses were consistent with those from sensitivity analyses conducted to assess the effect of varying the statistical methods, including alternate weighting schemes (ATE) and overlap (ATO), multivariable regression, propensity matching, and covariates used (Supplementary Materials Appendix S2 and S3).

Results for the quantitative bias analyses are provided in Supplementary Materials Fig. S2. In the 0.4 mg/kg QW cohort, estimated E-values vary between 2.50 (PFS comparison) and 4.78 (ORR comparison), indicating that a binary unmeasured confounder requires a minimum association with both treatment and outcome

◀**Fig. 4** Unadjusted and adjusted Kaplan–Meier curves for **a** PFS, **b** TTNT, **c** OS, and **d** DOR. *ATT* average treatment effect in the treated, *CI* confidence interval, *DOR* duration of response, *HR* hazard ratio, *OS* overall survival, *PFS* progression-free survival, *Q2W* every other week, *QW* weekly, *RWPC* real-world physician's choice of therapy, *TTNT* time to next treatment

between 2.50 to 4.78 to explain the observed treatment effect for PFS and ORR, respectively, independent of all adjusted prognostic factors. The bias plots visualize, by endpoint, all combinations of confounder-exposure and confounder-outcome associations required in the same way as the *E*-value (presents a special case of all these combinations, where both associations are identical, and is indicated by a large dot on every bias curve). To illustrate, in the case of talquetamab 0.4 mg/kg QW vs RWPC for OS, the bias curve is indicated by the blue curve in Supplementary Materials Fig. S2A with an *E*-value of 3.40 and includes the point (4.00; 3.00) indicated by the triangle. This means that, if there existed a non-observed prognostic variable for which the mortality in the high-risk subgroup was three times higher compared with the low-risk subgroup, then this high-risk subgroup should be at least four times more prevalent in the RWPC cohort compared with the talquetamab 0.4 mg/kg QW cohort in order to change the OS HR to 1.00 when additionally adjusting for this theoretical variable, and thus could explain or reverse the conclusion of improved OS in favor of talquetamab. This same reasoning holds for any other point on the curve, representing a combination of prognostic value and imbalance between cohorts. Additionally, this potential missing confounder should be independent of any of the prognostic factors already adjusted for, otherwise the prognostic value and imbalance should be even more extreme.

DISCUSSION

There is an unmet medical need to improve outcomes in patients with TCE RRMM using therapies that have new targets or mechanisms of action, as demonstrated by the lack of a clear standard of care illustrated by the many different treatment regimens and poor outcomes observed with most available treatments. Newly approved B cell maturation antigen-targeting agents, including the CAR-T cell therapies ide-cel and cilta-cel and the bispecific antibody teclistamab, have shown ORRs of 67%, 83%, and 63%, respectively, in patients with TCE RRMM [25–27]. However, the accessibility of CAR-T cell therapies in real-world practice remains limited because of manufacturing delays and limited access in a majority of European countries. Talquetamab, a first-in-class, off-the-shelf, readily manufactured GPRC5D × CD3 bispecific antibody, received approval in both the USA and Europe in August 2023, demonstrating high efficacy, with responses that continue to deepen over time, and clinically manageable safety in patients with heavily pre-treated RRMM in the MonumenTAL-1 study [10, 11, 13]. MonumenTAL-1 was designed as a single-arm study because there is no established standard of care for TCE RRMM and therefore a randomized controlled trial was not feasible or ethical. The lack of a well-established and effective treatment regimen for patients with TCE RRMM is highlighted by the 74 different treatment regimens identified in LocoMMotion and MoMMent among the 177 patients included in this analysis, and the most frequent regimen (pomalidomide plus cyclophosphamide plus dexamethasone) represented only 16.4% of patients. In the absence of randomized comparisons, adjusted treatment comparisons can be performed between different treatment regimens using statistical methods that control for differences in patients' baseline characteristics [28]. The comparative analyses presented here represent high-quality evidence of the comparative effectiveness of talquetamab vs. RWPC.

Data for the RWPC cohort were obtained from LocoMMotion and MoMMent, which included patients from across Europe and the USA and are representative of RWPC across different settings. A key advantage of using the LocoMMotion and MoMMent studies was the availability of a wide range of clinically relevant baseline risk factors and outcomes assessed by

IMWG criteria that are consistent with those captured in MonumenTAL-1. This allowed for the generation of robust comparative analyses on all relevant endpoints, including response and survival outcomes, and proper adjustment for confounding bias due to imbalances in prognostic baseline characteristics. The LocoM-Motion and MoMMent studies remain the only prospective studies designed specifically to collect data on RWPC in patients with heavily pretreated TCE RRMM and can be considered benchmarks for comparative analyses for novel therapies.

Our analyses demonstrated clinically and statistically significant advantages in response and survival outcomes with both R2PDs of talquetamab compared with RWPC in patients with TCE RRMM who had received at least three previous LOTs. When adjustments for differences in patient populations were made, patients treated with talquetamab 0.4 mg/kg QW were 2.7-, 4.7-, and 78.1-fold more likely to achieve response (ORR), $\geq$ VGPR, and $\geq$ CR, respectively, vs. patients receiving RWPC. Similarly, patients treated with talquetamab 0.8 mg/kg Q2W were 2.6-, 5.0-, and 101.1-fold more likely to achieve response (ORR), $\geq$ VGPR, and $\geq$ CR, respectively, vs. patients receiving RWPC. The significantly higher rate of $\geq$ CR with talquetamab is particularly notable given that $\geq$ CR rate is an important measure of depth of response and is associated with prolonged remission and greater improvement in quality of life [29, 30]. These data are also supported by the longer DOR with talquetamab, with reductions in the risk of progression or death of 23% (QW) and 57% (Q2W) for patients who responded to talquetamab compared with responders in the RWPC cohort. Patients receiving either of the RP2Ds of talquetamab also had significantly better PFS and OS outcomes, with significant reduction of the risk of progression or death of 48% and 60% and of the risk of death of 64% and 63% for talquetamab 0.4 mg/kg QW and 0.8 mg/kg Q2W, respectively. Results for TTNT were similar to PFS. These results further demonstrate the long-term benefits of talquetamab.

As in any non-randomized study, residual and unmeasured confounding variables cannot

be excluded; however, the prospective nature of the LocoMMotion and MoMMent studies allowed the collection of a wide range of clinically important prognostic factors that were assessed in the same way as in the MonumenTAL-1 study. The list of clinically important prognostic factors for adjustment was identified a priori on the basis of a review of the literature and consultations with clinical experts and was further validated by the prognostic strength of these factors in the MonumenTAL-1 and RWPC cohorts. Imbalances between cohorts on all these risk factors were minimal after ATT weighting, strengthening the validity of the adjusted comparisons. Cytogenetic risk was identified a priori as a prognostic factor but was not included in the main analyses because of high missingness, which indicates that cytogenetic risk is not routinely assessed in real-world practice. However, in sensitivity analyses that included cytogenetic risk, efficacy estimates across all endpoints were similar, despite the limitation of imbalance on missingness between treatment cohorts. Although baseline characteristics are well balanced across a wide range of clinically relevant prognostic factors, we acknowledge there may still be potential sources of residual confounding bias in this comparison, including baseline patient comorbidities and fitness level that were not captured in the observational studies. However, a quantitative bias analysis, performed for all treatment comparisons across all endpoints, illustrated the robustness of the treatment effect estimate against potential unmeasured confounders. These analyses indicate that the level of prognostic value and imbalance of potential residual confounders should be implausibly high to explain the observed treatment effects.

Physicians were allowed to prescribe on the basis of clinical judgment, as there were no restrictions on treatment types used in LocoM-Motion and MoMMent, resulting in a comparator cohort representative of regimens that are widely available in clinical practice. The highly varied and individualized therapies, reflecting the lack of standard of care in real-world clinical practice and resulting in low patient numbers for specific treatment

combinations, did not allow for comparisons vs. individual therapies.

Although patients in MoMMent initiated treatment between November 2021 and July 2022, when CAR-T cell treatments were already approved, only a few patients received this therapy. Teclistamab was approved in Europe in August 2022 and in the USA in October 2022, both of which occurred after completion of enrollment in the MoMMent study [31, 32]. However, of all patients included in the RWPC cohort who received subsequent treatment after the treatment line initiated at baseline, 51% were treated with at least one novel agent, indicating that OS observed in the RWPC cohort may reflect the benefit of other novel agents. Further evaluation of novel immunotherapies and the benefit of innovative drugs when given earlier in the disease course in the real-world setting will be important in the future to better define the optimal use of available treatments in RRMM.

CONCLUSION

Although new therapies have been recently approved for patients with TCE RRMM, their accessibility is limited, and a clear standard of care is still not established. Robust comparative evidence for talquetamab in the single-arm MonumenTAL-1 study was generated using a RWPC cohort from the prospective LocoMMotion and MoMMent studies. Results from adjusted treatment comparisons demonstrated clinically and statistically significant improvements with both RP2Ds of talquetamab compared with RWPC in patients with TCE RRMM. Results of sensitivity analyses were consistent with those of the main analysis. On the basis of these data, the GPRC5D-targeting bispecific antibody talquetamab, at either dosing schedule, 0.4 mg/kg QW or 0.8 mg/kg Q2W, offers a substantial clinical benefit for patients with TCE RRMM and is a highly effective therapy to address unmet treatment needs in this patient population.

Declarations

Conflict of Interest. Hermann Einsele has received honoraria from Amgen, BMS, EUSA Pharma, Genesis, GSK, Janssen, Novartis, Sanofi, and Takeda, travel expenses from Amgen, EUSA Pharma, and Takeda and research funding from Amgen, Genesis, GSK, Janssen, Sanofi, and Takeda. Philippe Moreau has served in a consulting or advisory role and received honoraria from AbbVie, Amgen, Celgene, GSK, Janssen, Oncopeptides, and Sanofi. Nizar Bahlis has a consulting or advisory role with AbbVie, Amgen, BMS, Forus, GSK, Janssen, Pfizer, Sanofi, and Takeda, received honoraria from AbbVie, Amgen, BMS, Forus, Janssen, and Sanofi, has been a member of the steering committee at AbbVie, GSK, and Janssen and has received research funding from Janssen and Pfizer. Manisha Bhutani has received funding from Adaptive Biotechnologies, Amgen, Bluebird Bio, Bristol Myers Squibb/Celgene, Celularity Inc., Cerecor, Janssen, Legend Biotech, MedImmune, and Takeda. Laure Vincent has received funding from Janssen, honoraria from BMS and Janssen, travel expenses from Amgen, BMS, GSK, Janssen, Sanofi, and Takeda, and has participated on an advisory board for BMS, Janssen, and Takeda. Lionel Karlin has served in a consulting or advisory role and received honoraria from Amgen, BMS/Celgene, GSK, Janssen, Sanofi, Stemline, and Takeda, has received travel expenses from Amgen, BMS/Celgene, Janssen, Sanofi, and Takeda, and has an immediate family member employed by Laoratoira Aguettant. Aurore Perrot has received honoraria or served a consulting role with AbbVie, Amgen, BMS, Janssen, Pfizer, Sanofi, and Takeda. Hartmut Goldschmidt has served in a consulting or advisory role for Adaptive Biotechnologies, Amgen, BMS, Celgene, Janssen-Cilag, Sanofi, and Takeda, received travel funding from Janssen-Cilag and Sanofi, honoraria from Amgen, BMS, Celgene, Chugai Pharma, GSK, Janssen-Cilag, Novartis, and Sanofi, research funding from Amgen, BMS, Celgene, Chugai Pharma Europe, Incyte, Janssen, Molecular Partners, MSD, Mundipharma, Novartis, and Takeda, and discloses other relationships with Amgen, Celgene/BMS, Chugai Pharma Europe, Janssen, and Sanofi. Niels WCJ van de Donk has received research support from Amgen, Bristol Myers Squibb, Celgene, Cellectis, Janssen Pharmaceuticals, and Novartis, and serves on advisory boards for AbbVie, Adaptive, Amgen, Bayer, Bristol Myers Squibb, Celgene, Janssen Pharmaceuticals, Novartis, Pfizer, Roche, Servier, and Takeda (all paid to their institution). Enrique M Ocio, Joaquin Martinez Lopez, Paula Rodríguez-Otero, Dominik Dytfeld, Joris Diels, Vadim Strulev, Imene Haddad, Thomas Renaud, Eric Ammann, Jedelyn Cabrieto, Nolen Perualila, Ryan Gan, Youyi Zhang, Trilok Parekh, and Claire Albrecht are employees of Janssen and may own stock in Johnson & Johnson/Janssen. Katja Weisel has served in a consulting or advisory role for Adaptive Biotechnologies, Amgen, BMS, Celgene, GSK, Janssen-Cilag, Karyopharm Therapeutics, Oncopeptides, Roche, Sanofi, and Takeda, received travel, accommodations, and/or expenses from Amgen, BMS, Celgene, GSK, Janssen-Cilag, and Takeda, honoraria from AbbVie, Adaptive Biotechnologies, Amgen, BMS, Celgene, GSK, Janssen-Cilag, Karyopharm Therapeutics, Novartis, Oncopeptides, Pfizer, Roche/Genentech, Sanofi, and Takeda, and research funding from Amgen, BMS, Celgene, GSK, Janssen-Cilag, and Sanofi. Maria-Victoria Mateos has served in a consulting or advisory role for AbbVie, Amgen, Celgene, GSK, Janssen-Cilag, Pfizer, Regeneron, Roche/Genentech, and Takeda, and

received honoraria from AbbVie/Genentech, Amgen, Celgene, GSK, Janssen-Cilag, Sanofi, and Takeda.

Ethical Approval. Data analyzed in this study were received from the MonumenTAL-1, LocoMMotion, and MoMMent studies. MonumenTAL-1 was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guidelines for Good Clinical Practice. All patients provided written informed consent. An independent ethics committee or institutional review board at each study center approved the study protocol (Supplementary Materials Tables S1–S3). The LocoMMotion and MoMMent studies were conducted in accordance with the Declaration of Helsinki. All patients provided written informed consent. An independent ethics committee/institutional review board at each center approved the study protocol.

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