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Linvoseltamab versus real-world International Myeloma Working Group standard-of-care in triple-class exposed relapsed/refractory multiple myeloma

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LINKER-MM1 (NCT03761108) is a Phase 1/2 study of linvoseltamab, a human BCMA×CD3 bispecific antibody for patients with relapsed/refractory multiple myeloma (RRMM) who are triple-class exposed (TCE) with ≥ 3 prior lines of therapy (3L+), or triple-class refractory (TCR). To contextualize efficacy data from LINKER-MM1, the Phase 2 linvoseltamab 200 mg cohort ($N = 105$) was compared with an international external control arm (ECA) comprising 203 patients from participating International Myeloma Working Group sites who met LINKER-MM1 eligibility criteria based on chart reviews. The ECA reflected real-world standard-of-care (RW SOC). An independent data review committee assessed data relevance, quality, and cohort comparability, while a separate independent central review committee evaluated response data. Inverse probability of treatment weighting was used to balance baseline characteristics between the linvoseltamab arm and the ECA. Linvoseltamab had a higher objective response rate (weighted odds ratio 3.0 [95% confidence interval (CI): 1.9–4.1]) and longer median progression-free survival (weighted hazard ratio [wHR] 0.33 [95% CI: 0.28–0.40]), time to next treatment (wHR 0.34 [95% CI: 0.29–0.44]), and overall survival (wHR 0.72 [95% CI: 0.58–0.98]) than RW SOC. These findings highlight linvoseltamab's potential as an effective treatment for 3L+ and TCE/TCR RRMM.

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INTRODUCTION

Multiple myeloma (MM) is a highly heterogeneous and mostly incurable malignancy that accounts for approximately 10% of all hematologic cancers [1, 2]. Until recently, treatment options for relapsed and/or refractory MM (RRMM) included conventional chemotherapy, salvage autologous stem cell transplant, and combinations of proteasome inhibitors, immunomodulatory drugs, anti-cluster of differentiation 38 (CD38) monoclonal antibodies, and corticosteroids [3–5]. Patients who become triple-class exposed (TCE) or triple-class refractory (TCR) after treatment with a proteasome inhibitor, immunomodulatory drug, and anti-CD38 monoclonal antibody have poor clinical outcomes. However, since 2020, several new treatment options, including B-cell maturation antigen (BCMA)-directed chimeric antigen

receptor T cell (CAR T) therapies, BCMA×cluster of differentiation 3 (CD3) and GPR5D×CD3 bispecific antibodies, and anti-BCMA antibody–drug conjugates (ADC), have been widely approved based on high objective response rates (ORR) and improved progression-free survival (PFS) [6–14].

Linvoseltamab is a BCMA×CD3 bispecific antibody that functions by simultaneously binding T cells and plasma cells, effecting tumor cell lysis [15], and was approved in April 2025 in Europe and July 2025 in the US for the treatment of RRMM [16–18]. Efficacy and safety of linvoseltamab are being evaluated in the global Phase 1/2 LINKER-MM1 clinical trial (NCT03761108) in patients with TCE/TCR RRMM who progressed on their most recent treatment. Linvoseltamab has demonstrated deep and durable responses with an acceptable safety profile [19, 20]. The ongoing

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Phase 2 portion of LINKER-MM1 includes 105 patients receiving the 200 mg linvoseltamab registrational dose [21].

The primary objective of this study was to assess the distribution of real-world (RW) treatment regimens for RRMM patients with ≥ 3 prior lines of therapy and TCE (3L+/TCE) or TCR status meeting similar eligibility criteria to the LINKER-MM1 trial. Secondly, it was intended to contextualize findings from the Phase 2 200 mg cohort from the LINKER-MM1 trial by comparing ORR, PFS, time to next treatment (TTNT), and overall survival (OS) outcomes between LINKER-MM1 and the RW-derived external control arm (ECA).

This is the primary analysis of a two-part study (NCT05673967) in which LINKER-MM1 was compared separately against two distinct ECAs. Elsewhere, LINKER-MM1 was compared with the secondary ECA cohort including patients identified in two US electronic health record data sources, COTA and Guardian Research Network (GRN), and predominantly reflected standard-of-care (SOC) at US community oncology sites [22, 23]. The primary ECA cohort described herein included patients who received treatment at International Myeloma Foundation (IMF) International Myeloma Working Group (IMWG) sites. For each comparison, LINKER-MM1 eligibility criteria were applied to RW data to construct the ECA, and the populations were aligned through inverse probability of treatment weighting (IPTW).

METHODS

Study Design and Patients

This study applied the target trial emulation framework to de-identified patient-level data from LINKER-MM1 and an ECA comprising patients from IMWG sites to emulate a randomized trial [24]. IMWG data were collected from the same geographic regions as in LINKER-MM1 (US, Europe, and Asia) through chart reviews using electronic case record forms. Patients initiating RRMM treatment who were 3L+/TCE or TCR and met other eligibility criteria similar to those of the LINKER-MM1 trial (Supplementary Table 1) were included in the IMF IMWG RW SOC cohort.

This analysis was determined to be exempt from institutional review board (IRB) approval by the Mayo Clinic IRB.

Data Sources

LINKER-MM1 Trial. The linvoseltamab cohort included 105 Phase 2 patients from LINKER-MM1 who received the 200 mg registrational dose at 22 global sites, with 81.0% from the US, 10.5% from Europe, and 8.6% from Asia (data cutoff: July 23, 2024). Additional details on the LINKER-MM1 trial have been published elsewhere [21, 25]. The study was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study protocol and all amendments were approved by the IRB or independent ethics committee at each participating site and are available online. All patients provided written informed consent prior to participation.

Participating IMF IMWG Sites. The IMWG conducts collaborative basic, clinical, and translational myeloma research in 41 countries worldwide, and participating sites in this study reflected SOC at leading academic sites in the US, Europe, and Asia, with high levels of access to and expertise with the newest highly effective therapies. Patient data were obtained by chart review through an electronic case record form completed at 15 participating IMWG sites. Data collected included demographic and clinical information, anti-myeloma treatment history, laboratory results, and outcomes.

Patients were eligible for the RW SOC cohort if, after becoming 3L+/TCE or TCR, at least one subsequent line of therapy (LOT) was initiated between November 16, 2015, and June 30, 2022, and they met other key LINKER-MM1 eligibility criteria. Patients were eligible for inclusion on the start date of the first eligible LOT after 3L+/TCE or TCR status was achieved. RW patients could have multiple eligible LOTs, but only one LOT per patient was included in the analysis, chosen by weighted random sampling based on the distribution of TCR status and prior LOTs in the LINKER-MM1 cohort. Index dates were defined as the start date of each eligible LOT after entry into the cohort; the pre-index period was defined as the time from MM

diagnosis until the day before the index date; and the post-index period was defined as the time after the index date to the earliest of death, last visit, or end of the study period. A visual representation of the study schema can be found in Supplementary Fig. 1.

Eligibility Criteria

LINKER-MM1 eligibility criteria were applied to the ECA. Although not all criteria were applicable to RW clinical practice data, most of the LINKER-MM1 criteria were either fully applied or adapted if needed.

Five of 11 inclusion criteria for the linvoseltamab cohort were applied to the RW SOC cohort, including: age ≥ 18 years; Eastern Cooperative Oncology Group performance status (ECOG PS) ≤ 1 at baseline; confirmed MM diagnosis prior to the index date; measurable disease (defined by ≥ 1 of: serum M-protein ≥ 1 g/dL, urine M-protein ≥ 200 mg/24 hours, or free light chains ≥ 10 mg/dL); and 3L+/TCE or TCR before the index date. Additionally, a recorded response to the index therapy (one of stringent complete response, complete response, very good partial response [VGPR], partial response [PR], minimal response, stable disease, progressive disease [PD], or death) was required to avoid missing RW data, as all responses were recorded and evaluable in the LINKER-MM1 data. Eighteen of 24 exclusion criteria for the linvoseltamab cohort were applied to the RW SOC cohort, including exclusion for prior treatment with BCMA-directed immunotherapies (anti-BCMA ADCs were not excluded). Supplementary Table 1 provides further details on the application and modification of eligibility criteria.

Endpoints

Clinical endpoints were assessed as described in Supplementary Table 2 along with the LINKER-MM1 endpoint definitions. ORR was the primary endpoint in the Phase 2 portion of the LINKER-MM1 trial and a primary endpoint for the ECA comparison. ORR was defined as the proportion of patients achieving a best overall response of PR or better; assessment included all LINKER-MM1 patients, but RW SOC patients with non-evaluable or missing responses were excluded from the primary analysis. For response evaluations, the LINKER-MM1 trial and RW SOC cohort used separate, blinded independent central review committees (BICRC). The BICRC for the RW SOC cohort (distinct from the IDRC discussed previously) was responsible for standardizing response assessment across IMWG sites based on the 2016 IMWG response criteria [26], and consisted of three MM experts from the IMF who were blinded to the treating physicians' response assessments. Response assessments were based on laboratory data extracted from IMWG sites (i.e., M-protein tracked by either serum protein electrophoresis, urine protein electrophoresis, or serum free light chain levels; serum and urine immunofixation; and, where available, bone marrow cell percentage, information on bone lesions, and plasmacytoma changes).

PFS, TTNT, and OS were measured from the start of study treatment until the date of first PD or death, date of death, or date of subsequent LOT initiation, respectively. Duration of response (DOR) was measured from the date of first documented response (per IMWG criteria) until the date of PD or death. Data were censored if outcomes were not observed at the cutoff date (June 30, 2022) as described in Supplementary Table 2.

Statistical Analysis

In a previous study, five hematology experts had ranked the importance of RRMM prognostic factors identified by a systematic literature review [27]. These were used in this study. Of 25 variables identified, 12 were candidates for use in the model to construct stabilized IPTW [28] designed to estimate the average treatment effect on the treated in the linvoseltamab-treated population, with weights truncated at 4 [29, 30]. This included age at index, TCR status, ECOG PS, extramedullary plasmacytomas, creatinine clearance, platelet count, lactate dehydrogenase, number of prior LOTs, albumin, prior hematopoietic stem cell transplant, time since initial diagnosis, and hemoglobin. Four variables were not available in both the trial and IMF data (Supplementary Table 3) and nine variables had missingness above the prespecified threshold of 30%. Missing data were otherwise imputed via multiple imputation by chained equations [31].

Prognostic factors for the IPTW were selected based on two predefined criteria: effective sample size (ESS) ≥ 100 and ESS per degree of freedom ≥ 10 . To assess these criteria, the initial model adjusted for the top five ranked covariates and then additional covariates were added sequentially based on their rank until the ESS criteria were no longer met. Imbalance

between the two cohorts was assessed using standardized mean differences (SMDs), which were calculated before and after applying the weights. Absolute SMDs (aSMDs) ≤ 0.1 indicate good balance; those > 0.1 and ≤ 0.2 indicate moderate balance; and those > 0.2 indicate imbalance [32].

Unweighted and weighted odds ratios (ORs) were estimated for ORR using logistic regression. Time-to-event outcomes, including PFS, TTNT, and OS, were assessed using weighted Kaplan–Meier estimators and Cox proportional hazards models. All 95% confidence intervals (CIs) were calculated using the bias-corrected and accelerated bootstrap (BCa) with 500 replications. DOR was analyzed descriptively using Kaplan–Meier methods, with medians and 95% CIs reported. *P*-values were obtained using the ratio of the point estimate to standard error derived from the 95% CI limits [33]. As multiple endpoints underwent hypothesis testing, a fixed-sequence procedure (starting with ORR, followed by PFS, TTNT, and OS, respectively) was conducted to address multiplicity in testing the primary and secondary endpoints ($\alpha = 0.05$). All analyses were conducted in R (version 4.3.2).

Sensitivity Analyses

Several sensitivity analyses were conducted to explore alternate definitions of outcomes, which were assessed differently in the LINKER-MM1 trial and ECA, and to address missing RW data. The primary analysis of ORR was repeated with a more stringent definition of best overall response $\geq$ VGPR rather than $\geq$ PR as in the primary analysis. Next, ORR was assessed including non-evaluable responses as non-response as opposed to being excluded from the primary analysis. In addition, time-to-event outcomes used alternative definitions: PFS was analyzed treating the start of a new LOT after index as a PD event rather than a censoring criterion, and TTNT was analyzed treating death as an event rather than a censoring criterion. All outcomes were also re-assessed excluding RW SOC patients with life expectancies < 6 months based on a prediction model [34], to align with LINKER-MM1 eligibility criteria, which excluded patients with physician-assessed life expectancies < 6 months at baseline. Propensity score matching, as an alternative to IPTW, was also used. *E*-values, which indicate the strength of the relationship an unmeasured confounder would need to have with both the treatment and outcome to nullify any observed effect estimates [35], were estimated for each comparative endpoint. Finally, to address potential temporal confounding, a sensitivity analysis was conducted in which the RW SOC cohort was stratified by calendar period of index therapy initiation relative to the LINKER-MM1 accrual window. The linvoseltamab cohort was then compared with RW SOC patients initiating treatment during the LINKER-MM1 accrual period (“overlap period”) and those initiating outside that period (“non-overlap period”).

Post-hoc Analyses

A post hoc analysis calculated ORR for the linvoseltamab 200 mg cohort compared to RW SOC sub-cohorts defined by receipt of CAR T and/or anti-BCMA ADC directed therapy at the index date using an intention-to-treat (ITT) approach. Time-to-event endpoints were not examined because follow-up in the CAR T and anti-BCMA ADC directed therapy subgroups was substantially shorter (e.g., median 8.4 months for 44 patients who received CAR T or anti-BCMA ADC directed therapies), limiting data maturity.

Subgroup Analyses

Analyses of ORR, PFS, TTNT, and OS were performed within levels of top-ranked prognostic factors (age, ethnicity, ECOG PS, cytogenetic risk, International Staging System [ISS], extramedullary plasmacytomas, and refractory status) with a minimum weighted sample size ≥ 10 .

Independent Data Review Committee

A five-member independent data review committee (IDRC) was responsible for assessing data collected from the IMWG sites and ensuring the comparison between the LINKER-MM1 trial and RW ECA data was valid. The IDRC included two MM experts, two clinical epidemiologists, and one health decision scientist who assessed data relevance, quality, and completeness. Relevance was evaluated by assessing the generalizability of study populations based on the geographic distribution of patients, endpoint definitions, and distribution of SOC treatments. Proposed analysis methods and sensitivity analyses were reviewed by the IDRC to promote data quality. The feasibility of valid comparisons was determined

by reviewing baseline characteristics and statistics regarding cohort balance after IPTW. Lastly, the IDRC recommended specific analyses to evaluate the robustness and validity of the results while being blinded to endpoint assessments and endorsed the comparative analyses once these recommendations had been implemented [36].

RESULTS

Population

The linvoseltamab cohort included 105 patients, each contributing one LOT. In the IMF IMWG RW SOC cohort, 203 patients from 15 IMWG sites contributed a total of 309 LOTs (Supplementary Table 4). After applying weighted random sampling, the RW SOC cohort consisted of 91 patients from the US, 87 from Europe, and 25 from Asia, each contributing one LOT.

Baseline Characteristics

Baseline characteristics are presented in Table 1 for both the linvoseltamab and RW SOC cohorts. Prior to weighting, the aSMD was ≤ 0.10 for age at index, TCR status, extramedullary plasmacytomas, prior hematopoietic stem cell transplant, lactate dehydrogenase, time from initial diagnosis, and sex. After imputation and weighting, the aSMD was ≤ 0.10 for all prognostic factors adjusted for in the IPTW (age at index, TCR status, ECOG PS, extramedullary plasmacytomas, creatinine clearance, platelet count, lactate dehydrogenase, number of prior LOTs, albumin, prior hematopoietic stem cell transplant, time since initial diagnosis, and hemoglobin). Additionally, although not adjusted for in the IPTW, the cohorts were moderately balanced (aSMD > 0.10 and ≤ 0.20) in terms of sex and MM subtypes. However, the two cohorts were imbalanced (aSMD > 0.20) for ISS at index, revised ISS (R-ISS) at index, best response to prior therapy, $\beta 2$ microglobulin, and calcium before or after IPTW, as these were not included in the model used to construct the IPTW. The SMD distribution before and after IPTW for covariates with less than 30% missing information is shown in Supplementary Fig. 2.

Distribution of Treatment Regimens in the RW SOC Cohort

There was a total of 66 unique treatment regimens across the 203 LOTs, with corticosteroids representing the most common drug class used as part of a treatment regimen ($> 75\%$; Supplementary Table 5, Supplementary Table 6). The most common treatment regimens at index (Table 2) were CAR T (11.3%); anti-BCMA ADC (10.3%); carfilzomib, pomalidomide, dexamethasone (7.9%); any anti-CD38 monoclonal antibody, pomalidomide, dexamethasone (5.4%); and cyclophosphamide, pomalidomide, dexamethasone (4.9%). Of note, 87 patients (42.9%) received a subsequent LOT after the index LOT (Supplementary Table 7).

Objective Response Rate

The primary analysis of ORR included 194 patients from the RW SOC (Table 3), after removing nine patients with non-evaluable responses. The ORR was higher among patients in the linvoseltamab cohort (69.5%) compared with the weighted RW SOC cohort (43.4%). The resulting comparative analyses showed a statistically significant relative treatment effect favoring linvoseltamab, with a weighted OR of 3.0 (95% CI: 1.9–4.1; $p < 0.001$). The *E*-value for this OR was 2.9 with a CI lower bound of 2.1, indicating that any unmeasured cofounder would need to have an association with both ORR and treatment of at least 2.1 (expressed as a risk ratio) to potentially negate the observed effect for ORR (Supplementary Table 8). Similarly, in a sensitivity analysis that considered best overall response of $\geq$ VGPR, patients treated with linvoseltamab had deeper response compared with the weighted RW SOC cohort (62.9% vs. 20.8%; Table 3), yielding a weighted OR of 6.4 (95% CI: 4.3–8.9; $p < 0.001$). Similar trends were observed in sensitivity analyses where RW patients with non-evaluable responses were considered as either non-responders

Table 1. Baseline demographics and disease characteristics of patients in the linvoseltamab (LINKER-MM1 trial) and RW SOC cohorts.

Covariate ^a	Linvoseltamab <i>n</i> = 105	RW SOC			aSMD	
		Unimputed ^b <i>n</i> = 203	Imputed ^c <i>n</i> = 203	Weighted ^d <i>n</i> = 198.1 ^h	Unweighted ^e ---	Weighted ^{f,g} ---
Top prognostic factors included in IPTW meeting ESS ≥ 100 and ESS/df > 10						
Age (years) at index date						
Mean (StD)	67.6 (10.4)	67.1 (9.1)	67.1 (9.1)	67.6 (8.7)	0.046	0.002
Refractory status						
Any PI, <i>n</i> (%)	98 (93.3)	178 (87.7)	178.0 (87.7)	175.4 (88.6)	0.192	0.164
Any IMiD, <i>n</i> (%)	97 (92.4)	192 (94.6)	192.0 (94.6)	186.5 (94.1)	0.089	0.068
Any anti-CD38 mAb, <i>n</i> (%)	90 (85.7)	192 (94.6)	192.0 (94.6)	184.3 (93.1)	0.302	0.242
TCR, <i>n</i> (%)	85 (81.0)	165 (81.3)	165.0 (81.3)	163 (82.1)	0.008	0.028
Penta-drug refractory, <i>n</i> (%)	29 (27.6)	49 (24.1)	49.0 (24.1)	51.8 (26.2)	0.080	0.032
Refractory to last therapy, <i>n</i> (%)	89 (84.8)	181 (89.2)	181.0 (89.2)	171.6 (86.7)	0.131	0.054
ECOG PS within 60 days prior to index date						
0, <i>n</i> (%)	28 (26.7)	66 (33.3)	67.2 (33.1)	52.3 (26.4)		
1, <i>n</i> (%)	77 (73.3)	132 (66.7)	136.0 (67.0)	145.7 (73.6)	0.138	0.009
Missing, <i>n</i>	0	5	0	0		
Extramedullary plasmacytomas status within 90 days prior to index date						
Present, <i>n</i> (%)	17 (16.2)	22 (12.1)	28.4 (14.0)	30.5 (15.4)		
Absent, <i>n</i> (%)	88 (83.8)	160 (87.9)	174.6 (86.0)	167.6 (84.6)	0.063	0.019
Missing, <i>n</i>	0	21	0	0		
Creatinine clearance (mg/dL) within 60 days prior to index date						
Mean (StD)	78.0 (30.1)	89.0 (38.6)	89.8 (38.3)	77.8 (33.7)	0.320	0.021
Missing, <i>n</i>	1	7	0	0		
Platelet count (10 ³ /μl) within 60 days prior to index date						
Mean (StD)	178.4 (73.3)	163.2 (68.3)	163.2 (68.1)	175.7 (71.5)	0.217	0.037
Missing, <i>n</i>	0	1	0	0		
LDH grouped within 60 days prior to index date						
< 280 units/L, <i>n</i> (%)	80 (83.3)	129 (83.8)	170.5 (84.0)	156.6 (83.6)	0.014	0.027
≥ 280 units/L, <i>n</i> (%)	16 (16.7)	25 (16.2)	32.5 (16.0)	32.5 (16.4)		
Missing, <i>n</i>	9	49	0	0		
Number of prior lines of therapy						
Mean (StD)	5.0 (2.0)	4.3 (2.3)	4.3 (2.3)	5.3 (3.0)	0.353	0.081
Serum albumin (g/dL) within 60 days prior to index date						
Mean (StD)	3.7 (0.59)	3.8 (0.54)	3.8 (0.53)	3.7 (0.56)	0.117	0.034
Missing, <i>n</i>	0	12	0	0		
Prior HSCT						
Yes, <i>n</i> (%)	69 (65.7)	128 (63.7)	129.5 (63.8)	122.6 (61.9)		
No, <i>n</i> (%)	36 (34.3)	73 (36.3)	73.5 (36.2)	75.5 (38.1)	0.040	0.077
Missing, <i>n</i>	0	2	0	0		
Time (years) from initial diagnosis to start of index treatment						
Mean (StD)	6.3 (3.9)	6.3 (4.4)	6.3 (4.4)	6.4 (3.7)	0.017	0.014
Hemoglobin (g/dL) within 60 days prior to index date						
Mean (StD)	10.5 (1.7)	11.3 (1.8)	11.3 (1.7)	10.6 (1.6)	0.408	0.014
Missing, <i>n</i>	0	1	0	0		
Other prognostic factors not included in IPTW						
Cytogenetic risk						
Standard, <i>n</i> (%)	65 (61.9)	98 (88.3)	141.9 (69.9)	126.2 (63.7)	0.170	0.038
High, <i>n</i> (%)	40 (38.1)	13 (11.7)	61.1 (30.1)	71.9 (36.3)		
Missing, <i>n</i>	0	92	0	0		
ISS at index						
I, <i>n</i> (%)	45 (45.5)	44 (44.4)	77.0 (37.9)	61.6 (31.1)	0.151	0.299
II, <i>n</i> (%)	37 (37.4)	35 (35.4)	65.6 (32.3)	69.3 (35.0)	0.106	0.048
III, <i>n</i> (%)	17 (17.2)	20 (20.2)	60.4 (29.8)	67.2 (33.9)	0.285	0.370
Missing, <i>n</i>	6	104	0	0		

Table 1. continued

Covariate ^a	Linvoseltamab <i>n</i> = 105	RW SOC			aSMD	
		Unimputed ^b <i>n</i> = 203	Imputed ^c <i>n</i> = 203	Weighted ^d <i>n</i> = 198.1 ^h	Unweighted ^e ---	Weighted ^{f,g} ---
R-ISS at index						
I, <i>n</i> (%)	25 (25.5)	22 (28.9)	57.4 (28.3)	49.7 (25.1)	0.039	0.033
II, <i>n</i> (%)	59 (60.2)	44 (57.9)	92.0 (45.3)	91.7 (46.3)	0.277	0.260
III, <i>n</i> (%)	14 (14.3)	10 (13.2)	53.6 (26.4)	56.9 (28.7)	0.291	0.339
Missing, <i>n</i>	7	127	0	0		
Time (months) to relapse from upfront HSCT						
Mean (StD)	20.8 (15.4)	66.7 (53.5)	66.0 (44.8)	64.8 (39.2)	0.985	1.044
Missing, <i>n</i>	78	114	0	0		
Best response to last prior therapy						
sCR, <i>n</i> (%)	1 (1.0)	0 (0)	0 (0)	0 (0)	0.167	0.166
CR, <i>n</i> (%)	5 (4.8)	3 (4.6)	15.3 (7.5)	11.3 (5.7)	0.113	0.043
VGPR, <i>n</i> (%)	10 (9.5)	5 (7.7)	26.3 (13.0)	22.6 (11.4)	0.107	0.061
PR, <i>n</i> (%)	21 (20.0)	12 (18.5)	36.5 (18.0)	29.5 (14.9)	0.052	0.140
MR, <i>n</i> (%)	1 (1.0)	4 (6.2)	19.9 (9.8)	25.0 (12.6)	0.353	0.418
SD, <i>n</i> (%)	19 (18.1)	10 (15.4)	33.2 (16.4)	37.6 (19.0)	0.046	0.025
PD, <i>n</i> (%)	23 (21.9)	26 (40.0)	56.7 (27.9)	51.7 (26.1)	0.137	0.097
Not evaluable, <i>n</i> (%)	23 (21.9)	5 (7.7)	15.1 (7.4)	20.3 (10.3)	0.440	0.332
Not applicable, <i>n</i> (%)	2 (1.9)	0 (0)	0 (0)	0 (0)	0.237	0.235
Missing, <i>n</i>	0	138	0	0		
β2 microglobulin (mg/L)						
Mean (StD)	4.2 (2.8)	4.4 (3.1)	4.7 (2.5)	5.3 (2.9)	0.170	0.334
Missing, <i>n</i>	6	109	0	0		
Calcium (mg/dL) within 60 days prior to index date						
Mean (StD)	9.4 (0.89)	9.0 (0.95)	9.0 (0.91)	9.1 (0.93)	0.417	0.384
Missing, <i>n</i>	0	21	0	0		
Multiple myeloma subtype						
IgA, <i>n</i> (%)	22 (21.0)	38 (18.7)	38.0 (18.7)	30.9 (15.6)	0.056	0.141
IgG, <i>n</i> (%)	57 (54.3)	117 (57.6)	116.9 (57.6)	120 (60.6)	0.067	0.127
Light chain, <i>n</i> (%)	23 (21.9)	43 (21.2)	43.0 (21.2)	42.6 (21.5)	0.018	0.010
Other heavy chain, <i>n</i> (%)	3 (2.9)	3 (1.5)	3.0 (1.5)	3.2 (1.6)	0.100	0.088
Non-secretory, <i>n</i> (%)	0 (0)	2 (1.0)	2.0 (1.0)	1.4 (0.7)	0.122	0.105
Missing, <i>n</i>	0	0	0	0		
Sex						
Female, <i>n</i> (%)	44 (41.9)	95 (46.8)	95 (46.8)	99.5 (50.2)		
Male, <i>n</i> (%)	61 (58.1)	108 (53.2)	108 (53.2)	98.6 (49.8)	0.098	0.167

^aThis table reports covariates (prognostic factors) available in both the linvoseltamab and RW SOC cohorts, regardless of the percentage of missingness.

^bPercentages for categorical variables are calculated without missing categories. Only absolute *n* values are reported for missing data.

^cUnweighted *n* values are averages from multiple imputation datasets and then rounded.

^dWeighted *n* values were obtained after pooling covariates and weights following multiple imputation.

^eComparing linvoseltamab with RW SOC cohort after multiple imputation but before IPTW.

^fComparing linvoseltamab with RW SOC cohort after multiple imputation and after IPTW.

^gCovariates included in IPTW were age at index, TCR status, ECOG PS, EMP, creatinine clearance, platelet count, LDH, number of prior LOTs, albumin, prior HSCT, time since initial diagnosis, and hemoglobin. Only these covariates achieved ESS of at least 100 and ESS per df of at least 10. SMDs for other covariates are reported even though they were not included in IPTW.

^hESS = 128.

aSMD absolute standardized mean difference, CR complete response, df degrees of freedom, ECOG PS Eastern Cooperative Oncology Group performance status, ESS effective sample size, HSCT hematopoietic stem cell transplant, Ig immunoglobulin, IMiD immunomodulatory drug, IPTW inverse probability of treatment weighting, ISS International Staging System, LDH lactate dehydrogenase, LOT line of therapy, mAb monoclonal antibody, MR marginal response, PD progressive disease, PI proteasome inhibitor, PR partial response, R-ISS revised International Staging System, RW real-world, sCR stringent complete response, SD stable disease, SOC standard-of-care, StD standard deviation, TCR triple-class refractory, VGPR very good partial response.

(OR 3.2, 95% CI: 2.1–4.4; *p* < 0.001) or responders (OR 2.7, 95% CI: 1.7–3.6; *p* < 0.001) (Supplementary Table 9), when the primary analysis was repeated after excluding seven patients with predicted life expectancy of < 6 months (Supplementary Table

10; OR 3.0, 95% CI: 2.2–4.7; *p* < 0.001), when using propensity score matching instead of IPTW (Supplementary Table 11; OR 4.1, 95% CI: 3.7–6.4; *p* < 0.001), and when linvoseltamab was compared with RW SOC in the overlap (OR 2.5, 95% CI: 1.4–4.7) and non-

Table 2. Most common treatment regimens (in five or more LOTs) received across all eligible LOTs in the RW SOC cohort.

Treatment regimens, <i>n</i> (%)	RW SOC (unweighted) <i>n</i> = 203	RW SOC (weighted) <i>n</i> = 198.1 ^a
CAR T	23 (11.3)	19.3 (9.7)
Anti-BCMA ADC	21 (10.3)	33.8 (17.0)
Carfilzomib, pomalidomide, dexamethasone	16 (7.9)	10.4 (5.3)
Anti-CD38 mAb (daratumumab or isatuximab), pomalidomide, dexamethasone	11 (5.4)	7.6 (3.8)
Cyclophosphamide, dexamethasone, pomalidomide	10 (4.9)	7.5 (3.8)

^aEffective sample size = 128.

ADC antibody–drug conjugate, BCMA B-cell maturation antigen, CAR T chimeric antigen receptor T cell, CD cluster of differentiation, LOT line of therapy, mAb monoclonal antibody, RW real-world, SOC standard-of-care.

Table 3. Comparative analysis of ORR estimates in the linvoseltamab and RW SOC cohorts.

Outcome	Linvoseltamab <i>n</i> = 105	RW SOC (unweighted) ^a <i>n</i> = 194	RW SOC (weighted) ^a <i>n</i> = 189.6 ^b
Objective response (excluding non-evaluable responses)^c			
Yes, <i>n</i> (%)	73 (69.5)	95 (49.0)	82.2 (43.4)
No, <i>n</i> (%)	32 (30.5)	99 (51.0)	107 (56.6)
OR (95% BCa CI) ^d for linvoseltamab vs. RW SOC	---	2.4 (1.8–3.3)	3.0 (1.9–4.1)
<i>p</i> -value	---	< 0.001	< 0.001
≥ VGPR			
Yes, <i>n</i> (%)	66 (62.9)	49 (25.3)	39.4 (20.8)
No, <i>n</i> (%)	39 (37.1)	145 (74.7)	150.2 (79.2)
OR (95% BCa CI) ^d for linvoseltamab vs. RW SOC	---	5.0 (3.6–6.8)	6.4 (4.3–8.9)
<i>p</i> -value	---	< 0.001	< 0.001

^aNine non-evaluable LOTs were removed from the primary analysis.^bEffective sample size = 122.^cDefined as percentage of patients who achieved a best overall response of partial response or better, excluding non-evaluable or missing responses.^d95% CIs were computed via BCa across 500 iterations.

BCa bias-corrected and accelerated bootstrap, CI confidence interval, LOT line of therapy, OR odds ratio, ORR objective response rate, RW real-world, SOC standard-of-care, VGPR very good partial response.

overlap (OR 3.4, 95% CI: 1.9–6.0) time periods (Supplementary Table 12). In a post-hoc analysis, ORR in the linvoseltamab 200 mg cohort (69.5%) was compared with RW SOC cohorts based on CAR T or anti-BCMA ADC directed therapies at index date, with ORR 48.0% for patients who received CAR T or anti-BCMA ADC directed therapies at index date and 41.7% for those who did not (details in Supplementary Table 13).

Progression-Free Survival

The median PFS was not reached in the linvoseltamab cohort versus 6.0 months in the weighted RW SOC cohort, resulting in a statistically significant weighted hazard ratio (wHR) of 0.33 (95% CI: 0.28–0.40; $p < 0.001$) favoring linvoseltamab (Table 4, Fig. 1A). For this hazard ratio (HR), the E-value and its CI upper bound were 3.7 and 3.2, respectively (Supplementary Table 8). Consistent results were observed across sensitivity analyses where the start of a new LOT was defined as a progression event rather than a censoring criterion (Supplementary Table 14; HR 0.31, 95% CI: 0.27–0.37; $p < 0.001$), after application of a life expectancy model that removed seven patients with a predicted life expectancy of < 6 months (Supplementary Table 15; HR 0.34, 95% CI: 0.27–0.41; $p < 0.001$), when using propensity score matching instead of IPTW (Supplementary Table 16; HR 0.30, 95% CI: 0.22–0.33; $p < 0.001$), and when linvoseltamab was compared with RW SOC in the overlap (HR 0.37, 95% CI: 0.23–0.60) and non-overlap (HR 0.32, 95% CI: 0.22–0.48) time periods (Supplementary Table 12).

Time to Next Treatment

The median TTNT was not reached in the linvoseltamab cohort versus 12.0 months in the weighted RW SOC cohort, resulting in a statistically significant wHR of 0.34 (95% CI: 0.29–0.44; $p < 0.001$) favoring linvoseltamab (Table 4, Fig. 1B). For this HR, the E-value and its CI upper bound were 3.6 and 2.9, respectively (Supplementary Table 8). Consistent results were observed across sensitivity analyses including when death was treated as an event rather than a censoring criterion (Supplementary Table 14; HR 0.24, 95% CI: 0.21–0.29; $p < 0.001$), after removing patients with life expectancy < 6 months (Supplementary Table 15; HR 0.34, 95% CI: 0.28–0.44; $p < 0.001$), when using propensity score matching instead of IPTW (Supplementary Table 16; HR 0.28, 95% CI: 0.17–0.32; $p < 0.001$), and when linvoseltamab was compared with RW SOC in the overlap (HR 0.34, 95% CI: 0.18–0.61) and non-overlap (HR 0.36, 95% CI: 0.23–0.57) time periods (Supplementary Table 12).

Overall Survival

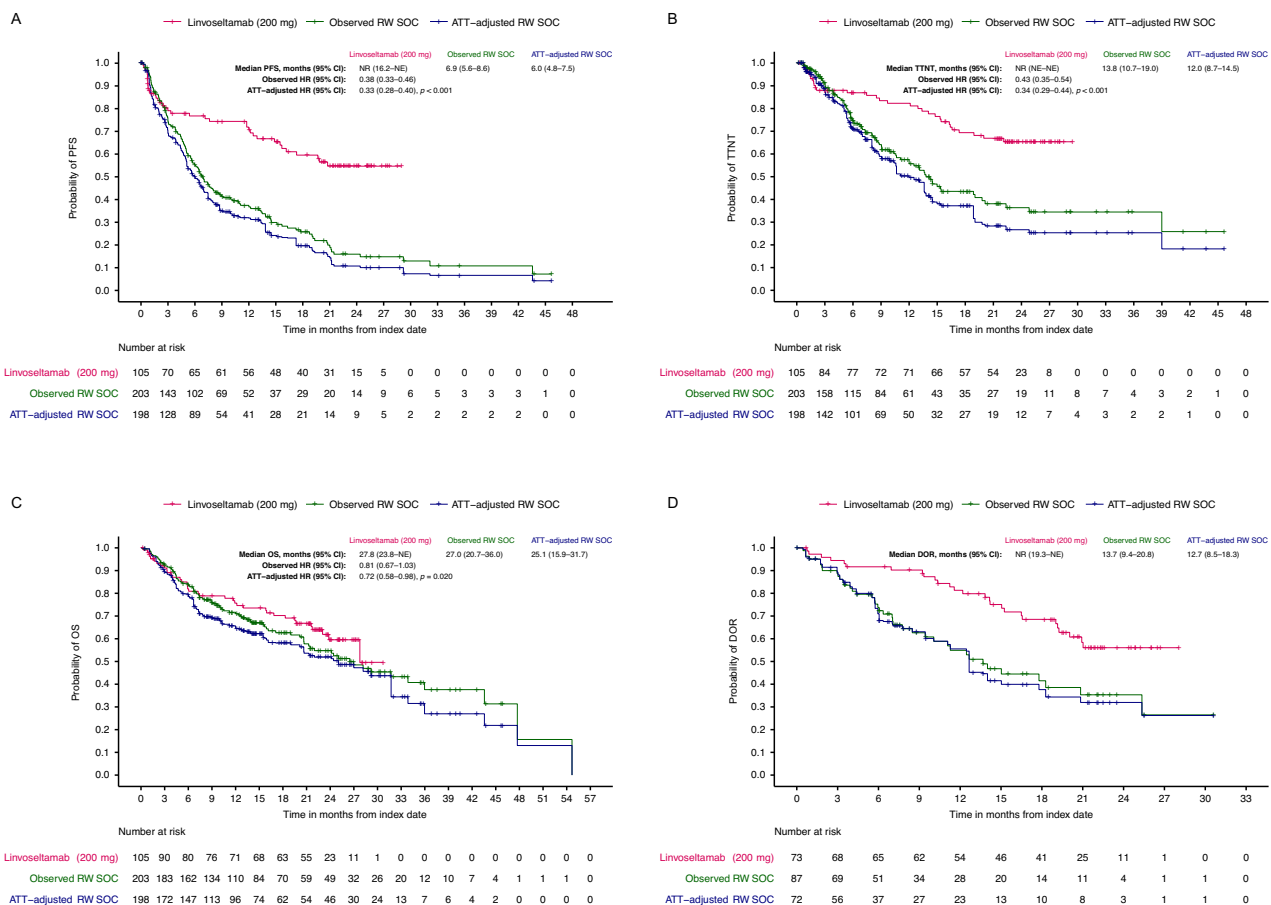
The median OS for the linvoseltamab cohort was 27.8 months versus 25.1 months in the weighted RW SOC cohort, resulting in a wHR of 0.72 (95% CI: 0.58–0.98; $p = 0.020$) favoring linvoseltamab (Table 4, Fig. 1C). For this HR, the E-value and its CI upper bound were 1.8 and 1.1, respectively (Supplementary Table 8). In a sensitivity analysis where patients with a life expectancy of < 6 months were removed, the results remained consistent (Supplementary Table 15; HR 0.70, 95% CI: 0.51–0.94; $p = 0.044$).

Table 4. Analysis of time-to-event endpoints using Cox proportional hazards model in the linvoseltamab and RW SOC cohorts.

Outcome	Linvoseltamab <i>n</i> = 105	RW SOC (unweighted) <i>n</i> = 203	RW SOC (weighted) ^a <i>n</i> = 198.1 ^b
PFS			
Months, median (95% CI)	NR (16.2–NE)	6.9 (5.6–8.6)	6.0 (4.8–7.5)
HR (95% BCa CI) ^a for linvoseltamab vs. RW SOC	---	0.38 (0.33–0.46)	0.33 (0.28–0.40)
<i>p</i> -value	---	< 0.001	< 0.001
TTNT			
Months, median (95% CI)	NR (NE–NE)	13.8 (10.7–19.0)	12.0 (8.7–14.5)
HR (95% BCa CI) ^a for linvoseltamab vs. RW SOC	---	0.43 (0.35–0.54)	0.34 (0.29–0.44)
<i>p</i> -value	---	< 0.001	< 0.001
OS			
Months, median (95% CI)	27.8 (23.8–NE)	27.0 (20.7–36.0)	25.1 (15.9–31.7)
HR (95% BCa CI) ^a for linvoseltamab vs. RW SOC	---	0.81 (0.67–1.03)	0.72 (0.58–0.98)
<i>p</i> -value	---	0.060	0.020
DOR^c			
Months, median (95% CI)	NR (19.3–NE)	13.7 (9.4–20.8)	12.7 (8.5–18.3)

^a95% CIs were computed via BCa across 500 iterations.^bEffective sample size = 128.^cDOR was a descriptive analysis only and no HR was calculated per the study protocol.

BCa bias-corrected and accelerated bootstrap, CI confidence interval, DOR duration of response, HR hazard ratio, NE not estimable, NR not reached, OS overall survival, PFS progression-free survival, RW real-world, SOC standard-of-care, TTNT time to next treatment.

**Fig. 1** Kaplan–Meier plots for time-to-event endpoints in the linvoseltamab 200 mg (LINKER-MM1 trial) and RW SOC cohorts. **A** PFS. **B** TTNT. **C** OS. **D** DOR. ATT average treatment effect on the treated, DOR duration of response, HR hazard ratio, NE not estimable, NR not reached, OS overall survival, PFS progression-free survival, RW real-world, SOC standard-of-care, TTNT time to next treatment.

Results were also consistent when using propensity score matching instead of IPTW (Supplementary Table 16; HR 0.60, 95% CI: 0.43–0.74; $p < 0.001$). OS comparisons were directionally consistent but not statistically significant in either time period (overlap: HR 0.78, 95% CI: 0.43–1.40; non-overlap: HR 0.68, 95% CI: 0.43–1.10; Supplementary Table 12).

Duration of Response

The median DOR was not reached for the linvoseltamab cohort versus 12.7 months in the weighted RW SOC cohort (Table 4, Fig. 1D). For the RW SOC cohort, the median DOR was consistent across sensitivity analyses: 10.1 months when excluding patients with life expectancy < 6 months (Supplementary Table 15), 11.1 months when applying propensity score matching instead of IPTW (Supplementary Table 16), and 10.1 and 12.7 months, respectively, when stratifying the RW SOC cohort into overlap and non-overlap time periods (Supplementary Table 12).

Subgroup Analyses

Results of predefined subgroup analyses were generally consistent with the primary analyses, favoring linvoseltamab with the exception of the high cytogenetic risk subgroups for ORR and OS; both of these were small ($n < 15$ in the ECA) with wide 95% CIs (Supplementary Fig. 3).

DISCUSSION

Linvoseltamab was associated with a significantly higher ORR and prolonged PFS, TTNT, and OS compared with IMF IMWG RW SOC therapy, with consistent results across multiple outcomes and both sensitivity and subgroup analyses.

The RW SOC cohort reflected evolving treatments, with patients at IMWG sites more likely to receive newer index therapies, such as CAR T, compared with patients in historical ECAs (IMWG sites: 11.3% of patients received index CAR T therapy, LocoMMotion and MoMMent: 1.3% [37]; LocoMMotion: 1.7% [38]; Flatiron and COTA: 0% [39]). Of the 66 unique regimens reported in the RW SOC cohort, the two most common were CAR T therapies and anti-BCMA ADCs, reflecting greater uptake of newer, more effective therapies at the academic sites included in this analysis than at community oncology sites [23]. This may also apply to post-index therapies, which included CAR T for 13.8% of patients receiving subsequent treatments at IMWG sites, although subsequent treatment in other historical ECAs was not reported. Understanding subsequent treatment is particularly important in the evaluation of OS findings, since OS is not censored at the end of the index LOT, and subsequent treatment, including CAR T and other newer therapies, may impact OS findings attributed to the index therapy. Indeed, although linvoseltamab showed significant benefit in OS compared with RW SOC, the magnitude of the improvement was smaller than that observed for PFS and TTNT. This smaller difference is likely attributable to the fact that only 29.9% of patients in LINKER-MM1 received any subsequent therapy after linvoseltamab treatment—and none received CAR T therapy—compared with the 42.9% of RW SOC patients who received subsequent therapy, with 13.8% receiving CAR T therapy. Nevertheless, linvoseltamab still produced longer OS than RW SOC.

Even though the present ECA included more patients treated in the index LOT with the latest highly effective treatments (including anti-BCMA therapies) than in prior ECAs, the linvoseltamab cohort still demonstrated statistically significantly better outcomes compared with RW SOC. Additionally, the results remained generally consistent across a range of sensitivity and subgroup analyses designed to evaluate the robustness of outcomes and suitability of populations. Further, in the primary analysis of ORR, LINKER-MM1 imputed non-response to those patients who were not evaluable, whereas nine comparable non-evaluable patients

were excluded from the RW SOC, biasing results toward the RW SOC. Despite this, linvoseltamab was still more effective than RW SOC, with similar results seen in the sensitivity analysis in which non-evaluable patients were treated equally as non-responders in both cohorts.

Importantly, results reported for the IMF IMWG RW SOC cohort in this study showed greater effectiveness for the SOC regimens than those found in historical ECA studies in TCE/TCR RRMM patients, including KarMMa-RW (ORR 32.2%; median PFS 3.5 months; median OS 14.7 months) [40], LocoMMotion (ORR 31.9%; median PFS 4.6 months; median OS 13.8 months) [41] and two studies conducted using a combined LocoMMotion + MoMMent dataset by Moreau et al. (ORR 26.2%; median PFS 4.1 months; median OS 13.3 months; median DOR 8.1 months) [37] and Einsele et al. (ORR 27.8%; median PFS 4.1 months; median TTNT 4.6 months; median OS 9.2 months; median DOR 7.7 months) [38]. Similar historical ECA findings were also observed in other RW cohorts derived from US electronic health records such as COTA (ORR 31.8%; median PFS 4.7 months; median OS 12.8 months) [39, 42], COTA-GRN combined (ORR 40.7%; median PFS 4.4 months; median TTNT 6.7 months; median OS 12.9 months) [23], and Flatiron (ORR 30.5%; median PFS 3.7 months; median TTNT 4.9 months; median OS 14.5 months) (details in Supplementary Table 17) [39, 43].

This difference may potentially be reflective of key differences in the IMWG study population compared with historical ECAs. These differences include the larger percentage of academic sites, geographic representation, and the application of inclusion/exclusion criteria. This IMF IMWG RW SOC cohort consists entirely of academic sites covering patients who are receiving care from MM specialists. In comparison, historical ECAs consist of a mix of academic and community centers. Furthermore, whereas historical ECAs tend to have limited geographic representation (LocoMMotion: patient population 91% EU, 9% US; MoMMent: 100% EU; Costa et al., 2023 and Krishnan et al., 2023: 100% US), the IMF cohort represents a more global SOC experience with 45% of patients coming from the US, 43% from the EU, and 12% from Asia.

An additional explanation for the greater effectiveness observed in the IMF IMWG RW SOC cohort versus historical ECAs is the extensive effort made to apply all relevant inclusion/exclusion criteria that could be implemented from the LINKER-MM1 trial to the RW SOC cohort, to allow robust comparisons. This differed from historical ECAs where only some of the key inclusion/exclusion criteria were applied [37, 38]. On the other hand, the IMF IMWG RW SOC cohort excluded patients if they had inadequate hepatic function, evidence of significant cardiovascular disease, and/or pulmonary disease, criteria not commonly applied in other ECAs. These more stringent criteria have the potential to impact treatment outcomes by selecting for healthier patients and were applied to emulate the framework of the LINKER-MM1 trial. The trial emulation framework also included a systematic literature review for prognostic factors and subsequent objective rankings by MM experts [44, 45]; a BICRC to assess response objectively in the same manner as the clinical trial; and a separate IDRC to assess the methods, data quality, and comparability, who recommended proceeding with a comparative analysis on the strength of the RW data. Notably, even with the particularly strong performance of the SOC treatments in this ECA compared with historical examples, linvoseltamab still showed significantly greater effectiveness across all key outcomes. Another sensitivity analysis stratified the RW SOC cohort into overlapping and non-overlapping timeframes relative to the LINKER-MM1 accrual period, yielding results consistent with the primary findings.

Despite these strengths, RW-derived ECAs have inherent limitations, including challenges related to data availability and risk of bias. Several baseline covariates with $< 30\%$ missing data

were imputed under the assumption that data were missing at random and two of the top five prognostic variables (cytogenetic risk, R-ISS/ISS) could not be adjusted for due to significant missingness ($\geq 30\%$). Furthermore, like other observational studies, unmeasured confounding is a concern due to an absence of randomization, but this was partially addressed using E-values to demonstrate the minimum size of any meaningful unmeasured confounders. Finally, response assessments were more frequent in LINKER-MM1 than in RW data, occurring at 4-week intervals in the former and at variable intervals in the latter (commonly of multiple months), potentially underestimating the effectiveness of linvoseltamab.

In conclusion, findings from this study demonstrated significantly improved efficacy of linvoseltamab compared with the RW SOC from IMWG sites with access to newer and effective therapies. The results from linvoseltamab are particularly notable as the ECA used in this study showed better RW SOC outcomes relative to previously published ECAs. Overall, these results suggest that linvoseltamab provides an effective and promising treatment option for patients with RRMM.

DATA AVAILABILITY

Qualified researchers may request access to study documents (including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan) that support the methods and findings reported in this manuscript. Individual anonymized participant data will be considered for sharing (1) once the product and indication has been approved by major health authorities (e.g., FDA, EMA, PMDA, etc.) or development of the product has been discontinued globally for all indications on or after April 2020 and there are no plans for future development (2) if there is legal authority to share the data and (3) there is not a reasonable likelihood of participant re-identification. Submit requests to <https://vivli.org/>.

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AUTHOR CONTRIBUTIONS

SK, SJ, KCW, LR, XL, CH, JG, OH, AB, JH, WG, RES, JJJ, GSK, KRL, QM, and BGMD designed and directed the research. SK, SJ, KCW, LR, XL, MAD, EK, DSS, JM, JD, JdIR, PAC, JHL, MVM, BP, AG, DD, EMO, JB, SO, MB, FE, MN, and RH provided data and clinical expertise. NB, PS, MSH, MSi, DW, KH, and MEDW analyzed the data and drafted the initial manuscript. All authors critically reviewed the manuscript and approved the final version.

COMPETING INTERESTS

CH, JG, OH, AB, JH, WG, RES, JJJ, GSK, KRL, and QM are employees and shareholders of Regeneron Pharmaceuticals, Inc. JH and RES hold shares in Pfizer Inc. NB, PS, MSH, MSi, DW, KH, and MEDW are employees of EVERSANA. EVERSANA consults for various pharmaceutical and medical device companies. SK has received consulting/advisory role fees from Takeda, Janssen Oncology, Genentech/Roche, AbbVie, Bristol Myers Squibb/Celgene, Pfizer, Regeneron, Sanofi, and K36, travel/accommodation/expenses from AbbVie and Pfizer, and research funding from Takeda, AbbVie, Novartis, Sanofi, Janssen Oncology, MedImmune, Roche/Genentech, CARsgen Therapeutics, Allogene Therapeutics, GSK, Regeneron, and Bristol Myers Squibb. SJ has received consulting fees from Bristol Myers Squibb, Poseida, Caribou, Genmab, Grail, GSK, Janssen, Legend Biotech, Regeneron, Sanofi, and Takeda, and travel/accommodation/expenses from Regeneron, IMS, Legend Biotech, and Poseida. KCW has received research grants, honoraria, and/or consulting fees from AbbVie, Amgen, Adaptive Biotech, AstraZeneca, Beigene, Bristol Myers Squibb, Cellcentric, Janssen, GSK, Karyopharm, Novartis, Oncopeptides, Pfizer, Regeneron, Roche Pharma, Sanofi,

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ADDITIONAL INFORMATION

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