Adjusted comparison of outcomes between patients from CARTITUDE-1 *versus* multiple myeloma patients with prior exposure to proteasome inhibitors, immunomodulatory drugs and anti-CD38 antibody from the prospective, multinational LocoMMotion study of real-world clinical practice

Maria-Victoria Mateos,[1*] Katja Weisel,[2*] Thomas Martin,[3] Jesús G. Berdeja,[4] Andrzej Jakubowiak,[5] A. Keith Stewart,[6] Sundar Jagannath,[7] Yi Lin,[8] Joris Diels,[9] Francesca Ghilotti,[10] Pushpike Thilakarathne,[9] Nolen J. Perualila,[9] Jedelyn Cabrieto,[9] Benjamin Haefliger,[11] Nichola Erler-Yates,[12] Clare Hague,[13] Carolyn C. Jackson,[14] Jordan M. Schecter,[14] Vadim Strulev,[15] Tonia Nesheiwat,[16] Lida Pacaud,[16] Hermann Einsele[17] and Philippe Moreau[18]

[1]University Hospital of Salamanca/IBSAL, CIC, Salamanca, Spain; [2]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [3]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [4]Sarah Cannon Research Institute, Nashville, TN, USA; [5]University of Chicago, Chicago, IL, USA; [6]University Health Network and the Princess Margaret Cancer Centre, Toronto, Ontario, Canada; [7]Mount Sinai Medical Center, New York, NY, USA; [8]Mayo Clinic, Rochester, MN, USA; [9]Janssen Pharmaceutica NV, Beerse, Belgium; [10]Janssen-Cilag SpA, Cologno Monzese, Italy; [11]Cilag GmbH International, Zug, Switzerland; [12]Janssen-Cilag GmbH, Neuss, Germany; [13]Janssen-Cilag N.V., High Wycombe, UK; [14]Janssen R&D, Raritan, NJ, USA; [15]EMEA Medical Affairs, Janssen Pharmaceutica NV, Beerse, Belgium; [16]Legend Biotech USA Inc., Piscataway, NJ, USA; [17]Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany and [18]Clinical Hematology, University Hospital Hotel-Dieu, Nantes, France

**M-VM and KW contributed equally as first authors.*

Correspondence: M.V. Mateos
mvmateos@usal.es

Received: December 14, 2021.
Accepted: December 13, 2022.
Early view: December 22, 2022.

https://doi.org/10.3324/haematol.2022.280482

Abstract

Ciltacabtagene autoleucel (cilta-cel) is a chimeric antigen receptor T-cell therapy studied in patients with multiple myeloma exposed to three classes of treatment in the single-arm CARTITUDE-1 study. To assess the effectiveness of cilta-cel compared to real-world clinical practice (RWCP), we performed adjusted comparisons using individual patients' data from CARTITUDE-1 and LocoMMotion, a prospective, multinational study of patients with multiple myeloma triple-class exposed of treatment. Comparisons were performed using inverse probability weighting. In CARTITUDE-1, 113 patients were enrolled, and 97 patients were infused with cilta-cel. In LocoMMotion, 248 patients were enrolled, and 170 patients were included in the comparisons *versus* infused patients. Ninety-two unique regimens were used in LocoMMotion, most frequently carfilzomib-dexamethasone (13.7%), pomalidomide-cyclophosphamide-dexamethasone (13.3%) and pomalidomide-dexamethasone (11.3%). Adjusted comparisons showed that patients treated with cilta-cel were 3.12-fold more likely to respond to treatment than those managed by RWCP (response rate, 3.12, 95% confidence interval [95% CI]: 2.24-4.00), had their risk of progression or death reduced to by 85% (progression-free survival hazard ratio=0.15, 95% CI: 0.08-0.29), and a risk of death lowered by 80% (overall survival hazard ratio HR=0.20, 95% CI: 0.09-0.41). The incremental improvement in health-related quality of life from baseline for cilta-cel *versus* RWCP at week 52, as measured by EORTC QLQ-C30 Global Health Status, was 13.4 (95% CI: 3.5-23.6) and increased to 30.8 (95% CI: 21.8-39.8) when including death as additional information regarding patients' health status. Patients treated with cilta-cel experienced more adverse events than those managed with RWCP (any grade: 100% *vs*. 83.5%). The results from this study demonstrate improved efficacy outcomes of cilta-cel *versus* RWCP and highlight its potential as a novel and effective treatment option for patients with multiple myeloma triple-class exposed of antimyeloma treatment. CARTITUDE-1 is registered with *clinicaltrials gov. Identifier: NCT03548207*. LocoMMotion is registered with *clinicaltrials gov. Identifier: NCT04035226*.

Introduction

Multiple myeloma (MM) is a hematologic cancer in which clonal proliferation of malignant plasma cells occurs along with overproduction of myeloma protein (M-protein).[1] MM is a highly heterogeneous cancer associated with a variable clinical course and significant clinical burden whose severity progresses over time.[2-4] MM represents 1% of all cancers worldwide and nearly 10% of hematologic neoplasms.[1] Approximately 50,000 patients in the European Union and USA are diagnosed with MM each year, while nearly 30,000 die during this same time frame.[5]

Therapies such as immunomodulatory agents, proteasome inhibitors and monoclonal antibodies have contributed to meaningful improvements in patients' outcomes over the past decade.[6-11] However, despite these therapeutic advances, MM remains an incurable disease.[2,12] For MM patients previously exposed to proteasome inhibitors, immunomodulatory agents and anti-CD38 antibodies ("triple-class exposed"), there is currently no standard of care; patients' outcomes are very poor, and include a median overall survival of 9.3 months.[4,13] New, more efficacious treatment options are needed for these patients to extend their survival, halt disease progression and improve their quality of life.[13-15]

Chimeric antigen receptor T-cell (CAR-T) therapy is a novel approach to treatment that offers potential for long-term disease control in some hematologic cancers.[16] Ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) is an experimental CAR-T therapy that targets B-cell maturation antigen (BCMA).[17] CARTITUDE-1 (*clinicaltrials gov. Identifier: NCT03548207*), an open-label, single-arm, clinical trial, investigated the safety and efficacy of cilta-cel in patients with triple-class exposed relapsed/refractory MM (RRMM).[18, 19]

CARTITUDE-1 was designed as a single-arm study because of the lack of clinical equipoise and the absence of an established standard-of-care therapy for patients with triple-class exposed RRMM, which precluded the performance of a traditional randomized trial. In such situations, adjusted comparisons of trial outcomes compared to those observed in an external cohort of similar patients may provide valuable information on the benefits of cilta-cel relative to treatments used in clinical practice, thereby creating an external control arm. LocoMMotion (*clinicaltrials gov. Identifier: NCT04035226*) was designed to be the first prospective, non-interventional, multinational study of therapies used in real-world clinical practice (RWCP) in triple-class exposed patients and was designed such that clinical outcome measures and eligibility criteria were matched to those of CARTITUDE-1.[20,21] In this study, individual patients' data from CARTITUDE-1 and LocoMMotion were analyzed to compare the effectiveness of cilta-cel *versus* currently available real-world clinical practice (RWCP), therapies in patients with triple-class exposed RRMM.

Methods

A synopsis of the study methods is provided below. Detailed descriptions regarding data sources, design, outcomes and approach to analysis are provided in the *Online Supplementary Appendix S1*.

Individual patients' data from the CARTITUDE-1 trial (*clinicaltrials gov. Identifier: NCT03548207*, data cut July 2021) and the LocoMMotion prospective, multinational, non-interventional cohort study (*clinicaltrials gov. Identifier: NCT04035226,* data cut May 2021) were used to conduct adjusted comparisons between the effects of cilta-cel and RWCP. In CARTITUDE-1, 113 patients were enrolled and underwent apheresis. Sixteen patients discontinued the study between apheresis and infusion with cilta-cel. Data

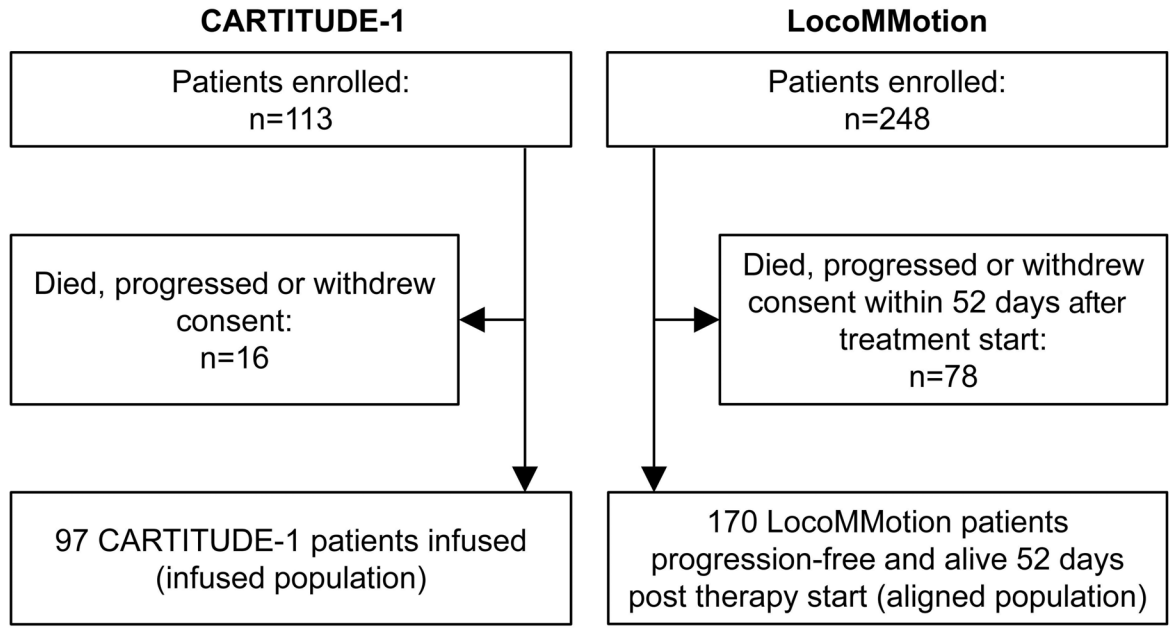


Figure 1. Selection of patients for the CARTITUDE-1 and LocoMMotion populations. Patients in CARTITUDE-1 were treated with ciltacabtagene autoleucel, patients in the LocoMMotion study were treated with real-world clinical practice.

from the set of 97 patients infused with cilta-cel in CARTITUDE-1 were compared with the data from the set of 170 patients from LocoMMotion, who were progression-free 52 days after treatment initiation (*Online Supplementary Appendix S2*). These groups are referred to as the infused/aligned populations. Second, analyses were also performed involving the 113 patients enrolled in CARTITUDE-1, along with all 248 patients enrolled in LocoMMotion, referred to as the enrolled populations.

In CARTITUDE-1, the index date was the date of apheresis for the enrolled population and the date of infusion for the infused population. The index date for the enrolled population from LocoMMotion was the date of treatment initiation, while the date of treatment initiation plus 52 days was used for the aligned population.

Overall response rate (ORR), very good partial response or better (≥VGPR), complete response or better (≥CR), progression-free survival (PFS) and overall survival (OS) were compared between cilta-cel and RWCP. Two patient-related outcomes, the EuroQoL Group's EQ visual analog scale (EQ VAS) and the European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) global health status (GHS) were measured over time and were compared without adjustment. The frequency and severity of adverse events were also compared.

Adjusted comparisons between cilta-cel and RWCP were performed using inverse probability weighting methods to estimate the average treatment effect in the treated population (IPW-ATT). The prognostic baseline characteristics to be adjusted for in the statistical analyses were based upon a review of the literature and consultations with clinical experts. The degree of imbalance between groups was assessed using standardized mean differences, with values >0.2 considered to reflect importance differences. Weighted logistic regression was used for response outcomes to estimate odds ratios (OR) with 95% confidence intervals (95% CI), transformed to response-rate ratios (RR). Weighted Cox proportional hazards regression was used to estimate hazard ratios (HR) with corresponding 95% CI. Sensitivity analyses using overlap weighting[22] (ATO) and multivariable regression analyses including the same prognostic variables as covariates in the models to estimate the relative treatment effects were performed. Given the wide range of treatment regimens used in RWCP, two sensitivity analyses were performed to explore the impact of this on the relative treatment effect. Subgroups of patients treated with novel therapies (immunomodulatory agents, proteasome inhibitors, monoclonal antibodies, selinexor and belantamab) and patients treated with a combination of three or more therapies were explored.

The sponsor together with the investigators designed the comparative study, were involved in the data analysis and interpretation and the writing of the manuscript. CARTITUDE-1 and LocoMMotion, funded and conducted by the sponsor, were performed in accordance with the Declaration of Helsinki and International Conference on Harmonisation guidelines for Good Clinical Practice. An independent ethics committee/institutional review board at each study center approved the protocols.

Results

Patient populations

Two populations of patients were analyzed: the infused/aligned and enrolled cohorts. The infused cohort for CARTITUDE-1 consisted of 97 patients[18] and its aligned population from LocoMMotion contained 170 patients. The enrolled cohort contained 113 patients from CARTITUDE-1 and 248 patients from LocoMMotion (Figure 1).

Treatment regimens received in real-world clinical practice

In total, 92 unique regimens were used in LocoMMotion. A full list of the treatments received at baseline is provided in *Online Supplementary Appendix S3*. Treatment regimens most commonly received at baseline by patients in the RWCP cohort were carfilzomib-dexamethasone (12.9%), pomalidomide-cyclophosphamide-dexamethasone (10.9%) and pomalidomide-dexamethasone (9.7%). The ten most frequently used regimens at baseline were given to 54.7% of all patients, and 43 patients (17.3%) received a regimen that was not received by any other patient in the sample. Selinexor, available only in the USA during study recruitment for LocoMMotion, was used twice. Belantamab mafodotin was approved in the USA and European Union for 3 months during the LocoMMotion recruitment period and was received by seven patients in their line of treatment of interest (in 5 cases as monotherapy, in 2 cases in combination regimens).

Prognostic value of baseline characteristics

The following baseline characteristics were considered *a priori* to be prognostic and adjusted for in the comparative analyses: refractory status, International Staging System (ISS), time to progression on last prior line of treatment, presence of extramedullary disease, number of prior lines of treatment, years since MM diagnosis, average duration of prior lines of treatment, age, sex, hemoglobin, lactate dehydrogenase level, creatinine clearance, Eastern Cooperative Oncology Group performance status (ECOG PS), MM type, history of stem cell transplant, race and cytogenetic risk. The prognostic value of these baseline characteristics was explored first in the LocoMMotion cohort (*Online Supplementary Appendix S6*). Refractory status, ISS stage, time to progression on last prior line of treatment, hemoglobin concentration, and ECOG PS were shown to be signifi-

cantly associated with outcomes. However, in a combined analysis of CARTITUDE-1 and LocoMMotion using a multivariable model, only ISS stage and ECOG PS retained a statistically significant influence on survival, as there are associations between baseline characteristics (*Online Supplementary Appendix S6*). The prognostic value of the baseline characteristics for response rates and PFS were generally similar (*Online Supplementary Appendix S6*).

Comparative analysis of efficacy endpoints

Infused/aligned populations

Table 1 shows the baseline characteristics before and

Table 1. Demographic balance between groups before and after inverse probability weighting for the infused/aligned population.

Covariate	Categories	Cilta-cel (CARTITUDE-1) (N=97), %	Pre-IPW ATT		Post-IPW ATT	
			RWCP cohort (N=170), %	SMD	RWCP cohort (N=108), %	SMD
Refractory status	≤ Double Triple Quadruple Penta	12.4 8.2 37.1 42.3	28.2 27.6 27.1 17.1	0.85	9.3 7.6 32.0 51.1	0.17
ISS stage at study entry	I II III	62.9 22.7 14.4	35.9 28.2 35.9	0.62	65.4 23.0 11.5	0.06
Time to progression on prior LOT, months	<3 ≥3	37.1 62.9	22.4 77.6	-0.33	40.4 59.6	0.07
Extramedullary disease	Yes No	13.4 86.6	12.4 87.6	-0.03	21.9 78.1	0.23
N of prior LOT	≤4 5+	34.0 66.0	51.2 48.8	0.35	31.6 68.4	-0.05
Years since diagnosis	<6 6+	46.4 53.6	41.8 58.2	-0.09	42.5 57.5	-0.08
Average duration of prior LOT, months	<8.14 8.14 to <11.76 11.76+	20.6 22.7 56.7	9.4 17.6 72.9	0.40	24.5 22.8 52.7	0.10
Age, years	<65 years 65+ years	63.9 36.1	35.9 64.1	-0.58	70.5 29.5	0.14
Hemoglobin, g/dL	<12 12+	92.8 7.2	71.2 28.8	-0.59	95.9 4.1	0.14
LDH, units/L	<280 280+	87.6 12.4	74.7 25.3	-0.34	88.8 11.2	0.04
Creatinine clearance, mL/min	<60 60 - <90 90+	17.5 30.9 51.5	40.6 31.8 27.6	0.60	14.3 27.2 58.5	0.17
ECOG PS	0 1	40.2 59.8	27.1 72.9	-0.50	33.4 66.6	-0.14
Sex	Male Female	58.8 41.2	52.9 47.1	-0.12	62.8 37.2	0.08
MM type	IgG Non-IgG	58.8 41.2	42.4 57.6	-0.33	61.2 38.8	0.05
Summary diagnostics						
SMD with absolute value >0.2, N (%)		11/14 (78.6)			1/14 (7.1)	
Mean absolute SMD		0.41			0.11	

The pre-weighting and post-weighting distributions of demographics by intervention group are shown. Standardized mean differences >0.2 were considered to indicate differences between groups. Cilta-cel: ciltacabtagene autoleucel; IPW: inverse probability weighting; ATT: average treatment effect in the treated population; RWCP: real-world clinical practice; SMD: standardized mean difference; ISS: International Staging System; LOT: lines of therapy; LDH: lactate dehydrogenase; ECOG PS: Eastern Cooperative Oncology Group Performance Status; MM: multiple myeloma; IgG: immunoglobulin G.

after weighting for the base case including refractory status, ISS stage, time to progression on last prior line of treatment, presence of extramedullary disease, number of prior lines of treatment, years since MM diagnosis, average duration of prior lines of treatment, age, sex, hemoglobin concentration, lactate dehydrogenase level, creatinine clearance, ECOG PS and MM type. The models including the extended variables are shown in sensitivity analyses (*Online Supplementary Appendix S4*, section 3.4.3 sensitivity analyses, *Online Supplementary Appendix S7*). Prior to reweighting of the infused/aligned populations, examination of standardized mean differences found imbalances

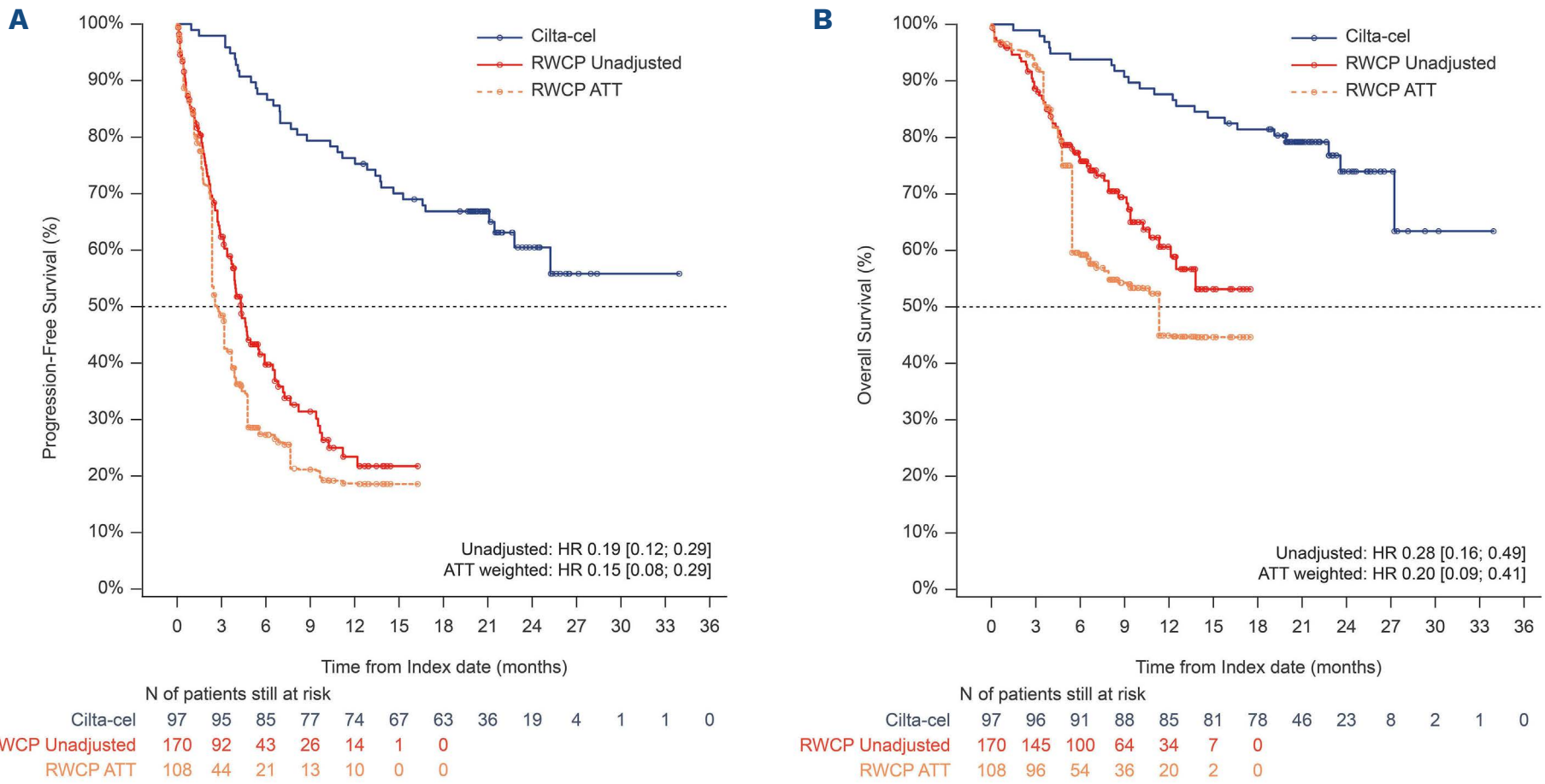


Figure 2. Unadjusted and adjusted Kaplan-Meier survival curves for the infused/aligned population. (A) Progression-free survival. (B) Overall survival. Blue lines represent the survival of patients treated with ciltacabtagene autoleucel, the solid red lines represent the unadjusted survival of patients treated with real-world clinical practice (RMCP) and the dotted orange lines are adjusted Kaplan-Meier curves following inverse probability weighting. Cilta-cel: ciltacabtagene autoleucel; ATT: average treatment effect in the treated population; HR: hazard ratio.

Table 2. Summary of observed and adjusted rates of clinical response in the infused/aligned population.

Outcome	Observed response %		Adjusted RWCP response % (95% CI)	Observed OR (95% CI)	IPW-ATT adjusted OR (95% CI)	IPW-ATT adjusted response-rate ratio (95% CI)
	Cilta-cel (N=97)	RWCP (N=170)				
ORR	97.9	42.9	31 (23-41)	63.12 (15.06-264.53)	103.87 (24.17-446.37)	3.12 (2.24-4.00)
≥VGPR	94.8	17.6	17 (11-25)	85.87 (32.14-229.39)	91.55 (32.63-256.89)	5.67 (3.25-8.08)
≥CR	82.5	0.6	0 (0-93)	795.29 (104.01-6081.21)	NE	NE

Observed and adjusted data comparing rates of clinical response in the infused/aligned population between patients treated with ciltacabtagene autoleucel or real-world clinical practice (RWCP). Adjusted comparisons account for the effects of refractory status, International Staging System stage, time to progression on prior line of treatment, presence of extramedullary disease, number of prior lines of treatment, years since diagnosis of multiple myeloma, average duration of prior lines of treatment, patients' age and sex, hemoglobin at index date, lactate dehydrogenase at index date, creatinine clearance at index date, Eastern Cooperative Oncology Group Performance Status, and type of multiple myeloma. All comparisons favored ciltacabtagene autoleucel (Cilta-cell). 95% CI: 95% confidence interval; OR: odds ratio; IPW: inverse probability weighting; ATT: average treatment effect in the treated population; ORR: overall response rate; VGPR: very good partial response; CR: complete response; NE: not estimable.

in most of the baseline characteristics. Imbalances can bias an unadjusted comparison both in favor of and against the intervention. Here, we found imbalances in both directions, however, the most important differences were observed for refractory status, time to progress on prior line of treatment, and average duration of prior lines of treatment, which suggest that the CARTITUDE-1 population had more aggressive myeloma. After IPW-ATT weighting, imbalances between the cilta-cel and RWCP cohorts were greatly reduced with all standardized mean differences <0.2, except for extramedullary disease (standardized mean difference =0.23) (Table 1; *Online Supplementary Appendix S5*). *Online Supplementary Appendix S5* further illustrates that propensity score distributions were different before reweighting and became very similar after reweighting.

Response endpoints

Table 2 summarizes the observed rates and adjusted treatment comparisons for ORR, ≥VGPR and ≥CR. The ORR for cilta-cel was 97.9% *versus* 42.9% for RWCP. Rates of ≥VGPR and ≥CR were 94.8% and 82.5%, respectively, with cilta-cel, compared to 17.6% and 0.6%, respectively, with RWCP. IPW-ATT adjusted comparisons favored cilta-cel for ORR (RR=3.12, 95% CI: 2.24-4.00; *P*<0.0001) and ≥VGPR (RR=5.67, 95% CI: 3.25-8.08; *P*<0.0001). As only one patient (0.6%) in the RWCP group achieved ≥CR compared to 80 (82.5%) with cilta-cel, an IPW-ATT adjusted comparison could not be estimated; however, the extreme difference in observed ≥CR rates between the cilta-cel and RWCP groups reflects the significantly higher efficacy of cilta-cel.

Progression-free survival

The median PFS in the cilta-cel group was not reached, while the median PFS for patients in RWCP was 4.34 months (95% CI: 3.65-5.55). Figure 2A presents the observed and adjusted Kaplan-Meier curves for PFS for both groups; the IPW-ATT adjusted HR for cilta-cel *versus* RWCP was 0.15 (95% CI: 0.08-0.29; *P*<0.0001). The proportional hazards assumption was met for all analyses.

Overall survival

In both the cilta-cel and RWCP populations, median OS was not reached when unadjusted. The median OS for the adjusted RWCP population was 11.33 months. Figure 2B presents Kaplan-Meier curves for OS in both groups. Following IPW-ATT-based adjustment, the HR comparing groups was 0.20 (95% CI: 0.09-0.41; *P*<0.0001), favoring cilta-cel. The proportional hazards assumption was met for all analyses.

Enrolled populations

Prior to reweighting of the enrolled population, examination of standardized mean differences found imbalances in nine baseline characteristics; however, after IPW-ATT weighting had been performed, imbalances between the cilta-cel and RWCP cohorts were greatly reduced, with all standardized mean differences below 0.20 (*Online Supplementary Appendix S4* and *S5*).

Response endpoints

Table 3 summarizes the observed rates and adjusted treatment comparisons for ORR, ≥VGPR and ≥CR. The ORR for cilta-cel was 84.1% *versus* 29.8% for RWCP. Rates of ≥VGPR and ≥CR were 81.4% and 70.8%, respectively, with cilta-cel, compared to 12.5% and 0.4%, respectively, with RWCP. After IPW-ATT adjustment, comparisons favored cilta-cel for each of ORR (RR=4.34, 95% CI: 2.69-6.00; *P*<0.0001) and ≥VGPR (RR=8.08, 95% CI: 3.63-12.53; *P*<0.0001). As only one patient in LocoMMotion achieved

Table 3. Summary of observed and adjusted rates of clinical response in the enrolled population.

Outcome	Observed response %		Adjusted RWCP response % (95% CI)	Observed OR (95% CI)	IPW-ATT adjusted OR (95% CI)	IPW-ATT adjusted response-rate ratio (95% CI)
	Cilta-cel (N=113)	RWCP (N=248)				
ORR	84.1	29.8	19.0 (13-27)	12.41 (7.00-22.00)	22.00 (11.14-43.35)	4.34 (2.69-6.00)
≥VGPR	81.4	12.5	10.0 (6-17)	30.67 (16.74-56.17)	39.08 (18.19-83.98)	8.08 (3.63-12.53)
≥CR	70.8	0.4	0 (0-100)	598.79 (80.60-4,448.22)	NE	NE

Observed and adjusted data comparing rates of clinical response in the enrolled population between patients treated with ciltacabtagene autoleucel or real-world clinical practice (RWCP). Adjusted comparisons account for the effects of refractory status, International Staging System stage, time to progression on prior line of treatment, presence of extramedullary disease, number of prior lines of treatment, years since MM diagnosis, average duration of prior lines of treatment, patients' age and sex, hemoglobin at index date, lactate dehydrogenase at index date, creatinine clearance at index date, Eastern Cooperative Oncology Group Performance Status, and type of multiple myeloma. All comparisons favored ciltacabtagene autoleucel (Cilta-cel). RWCP: real-world clinical practice; 95% CI: 95% confidence interval; OR: odds ratio; IPW: inverse probability weighting; ATT: average treatment effect in the treated population; ORR: overall response rate; VGPR: very good partial response; CR: complete response; NE: not estimable.

≥CR, IPW-ATT adjusted comparison could not be derived; however, the extreme difference in observed CR rates between the cilta-cel and RWCP groups reflects a significant difference between therapies.

Progression-free survival and overall survival

Results of the unadjusted comparison produced an estimate of effect for PFS that favored cilta-cel (HR=0.23, 95% CI: 0.16-0.33; *P*<0.0001). After IPW-ATT reweighting, the PFS HR was 0.19 (95% CI: 0.11-0.32; *P*<0.0001). The unadjusted comparison for OS between cilta-cel and RWCP favored cilta-cel (HR=0.32, 95% CI: 0.20-0.50; *P*<0.0001). Following IPW-ATT based adjustment, the OS HR was 0.32 (95% CI: 0.17-0.58; *P*<0.0001), again supporting the unadjusted results (Figure 3B). The proportional hazards assumption was met for all analyses.

Sensitivity analyses

To assess the robustness of the findings, sensitivity analyses were performed by using overlap weighting and multivariable regression (*Online Supplementary Appendix S1*) and by including additional baseline characteristics (race, history of stem cell transplant and cytogenetic risk; see *Online Supplementary Appendix S1* for details regarding these variables) for the adjusted analyses. Figure 3 shows consistent results for IPW-ATO and multivariable regression with the main analyses (IPW-ATT), for both response (Figure 3A) and survival endpoints (Figure 3B). The impact of additionally including race, history of stem cell transplantation and cytogenetic risk on results was minimal (*Online Supplementary Appendix S7*), which can be explained by their low prognostic value. However, including these additional covariates caused imbalances in the baseline characteristics in the ATT-based results, which were balanced in the main analyses. *Online Supplementary Appendix S7* shows results of relative treatment comparisons related to use of the extended model including all available baseline characteristics.

Results from the sensitivity analyses excluding patients who were not treated with a regimen that included a novel therapy and excluding patients treated with a single or combination of two therapies were less stable, but generally consistent with the overall results (*Online Supplementary Appendix S7*).

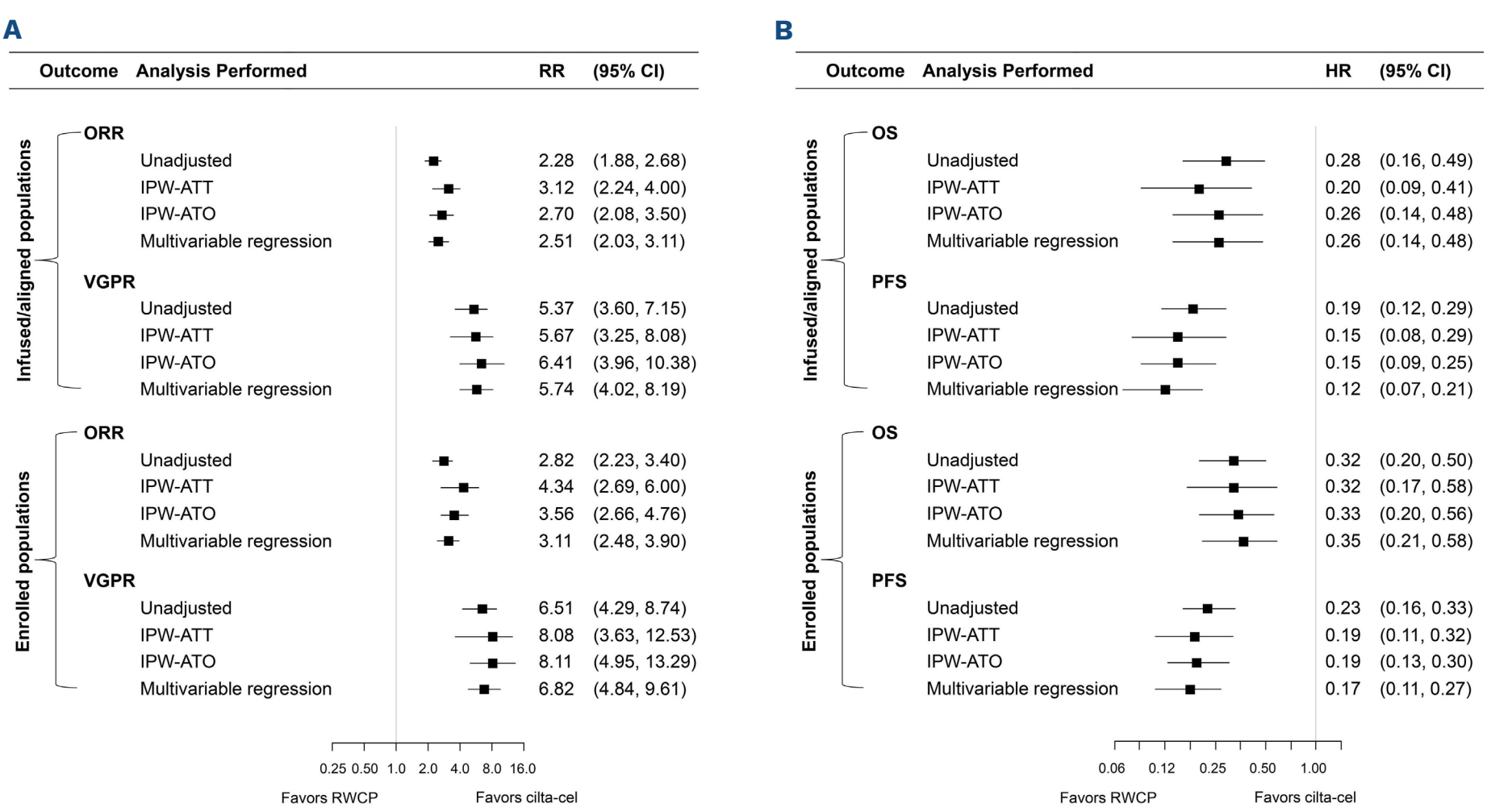
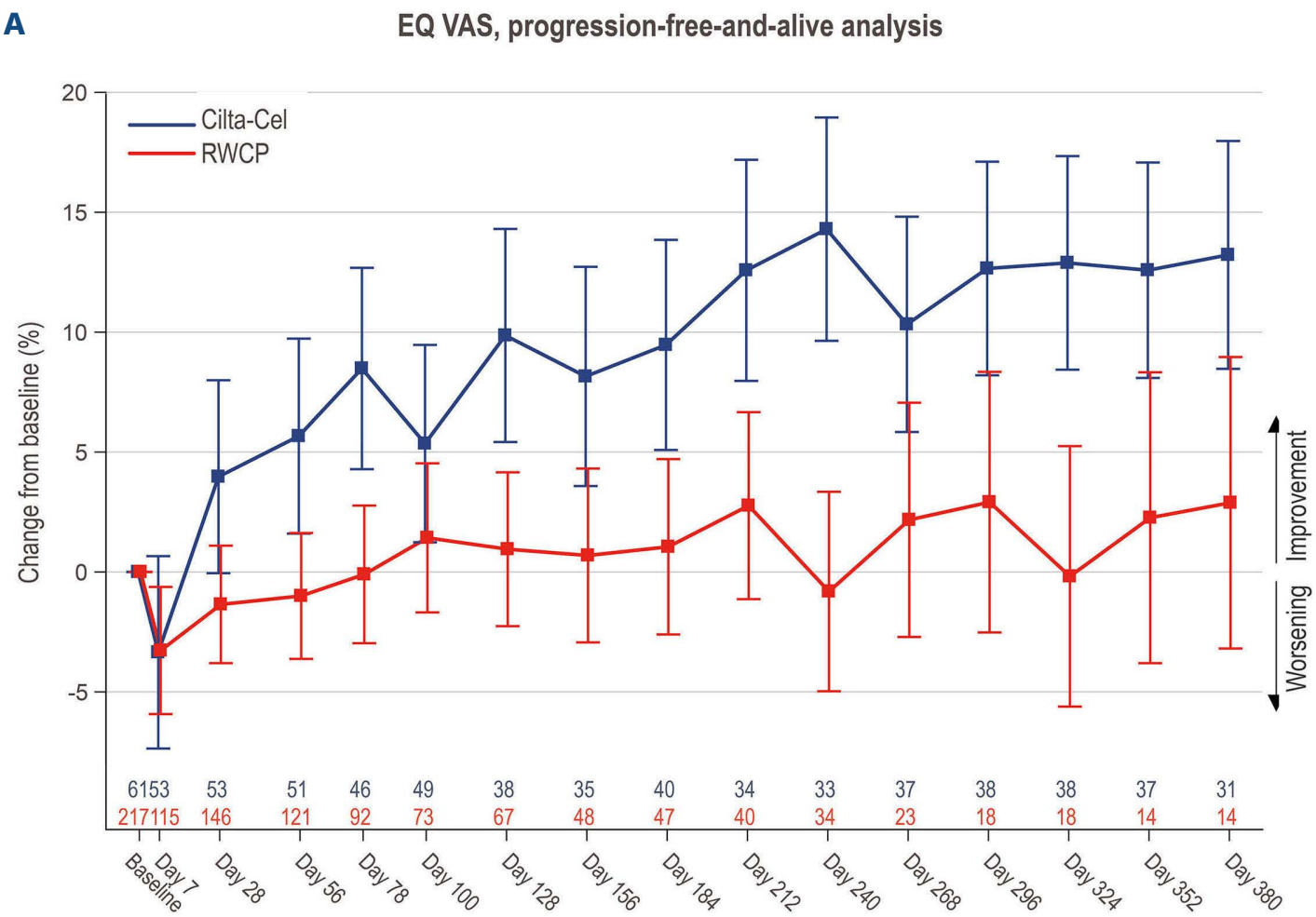


Figure 3. Summary of unadjusted and adjusted comparisons for response and survival outcomes. (A) Forest plots of response outcomes showing response ratios with corresponding 95% confidence intervals (95% CI) comparing ciltacabtagene autoleucel (cilta-cel) *versus* real-world clinical practice (RWCP) with different analytical methods and for the infused/aligned and enrolled patient populations. Values >1 favor cilta-cel, values <1 favor RWCP. (B) Forest plots of survival outcomes showing hazard ratios (HR) with corresponding 95% confidence intervals comparing cilta-cel *versus* RWCP with different analytical methods and for the infused/aligned and enrolled patient populations. Values <1 favor cilta-cel, values >1 favor RWCP. RR: response rate ratio; ORR: overall response rate; IPW: inverse probability weighting; ATT: average treatment effect in the treated population; ATO: average treatment effect in the overlap population; VGPR: very good partial response; RWCP: real-world clinical practice; OS: overall survival; PFS: progression-free survival.

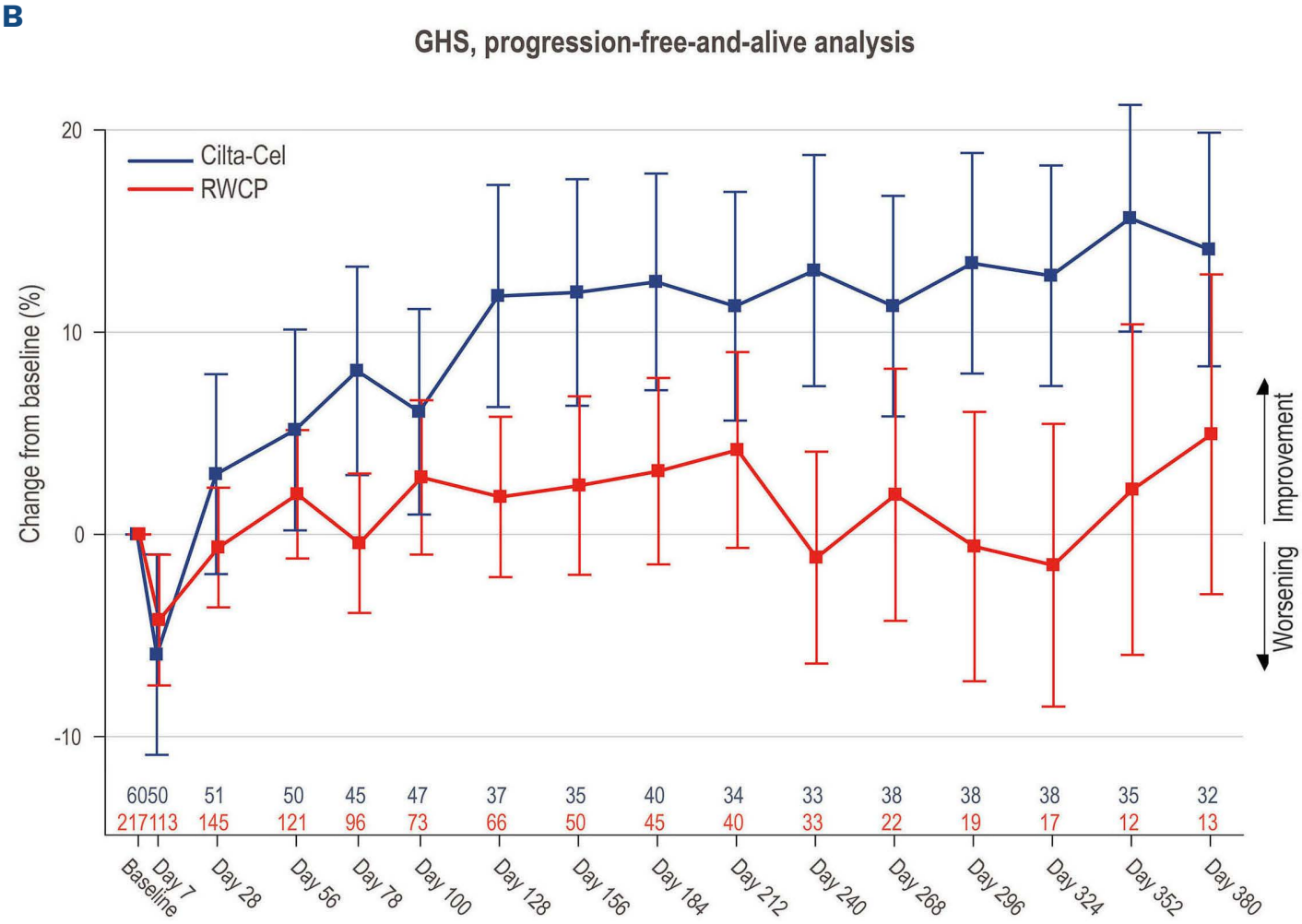
Comparative analyses of patient-reported outcomes

Figure 4A and B shows the evolution of EQ VAS and GHS, respectively, compared to baseline over time for patients alive and progression-free. After an initial reduction in quality of life at day 7, patients in both the cilta-cel[23] and RWCP groups demonstrated improved outcomes over time. Patients treated with cilta-cel experienced continuously improving quality of life over time, as measured by absolute differences *versus* baseline on a 0-100 standardized scale for EQ VAS and GHS, which increased from 4.0

A

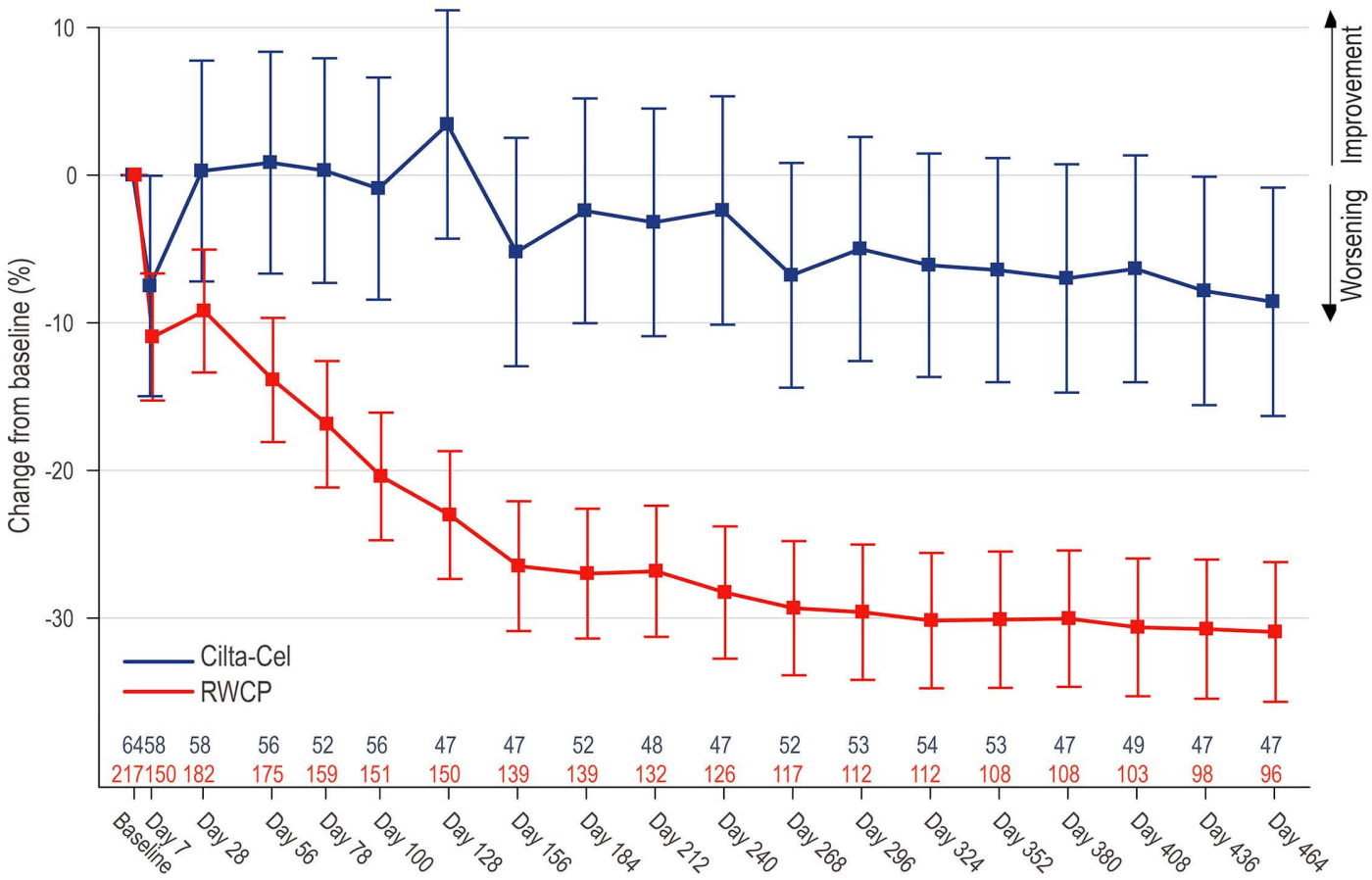


B



Continued on following page.

C



D

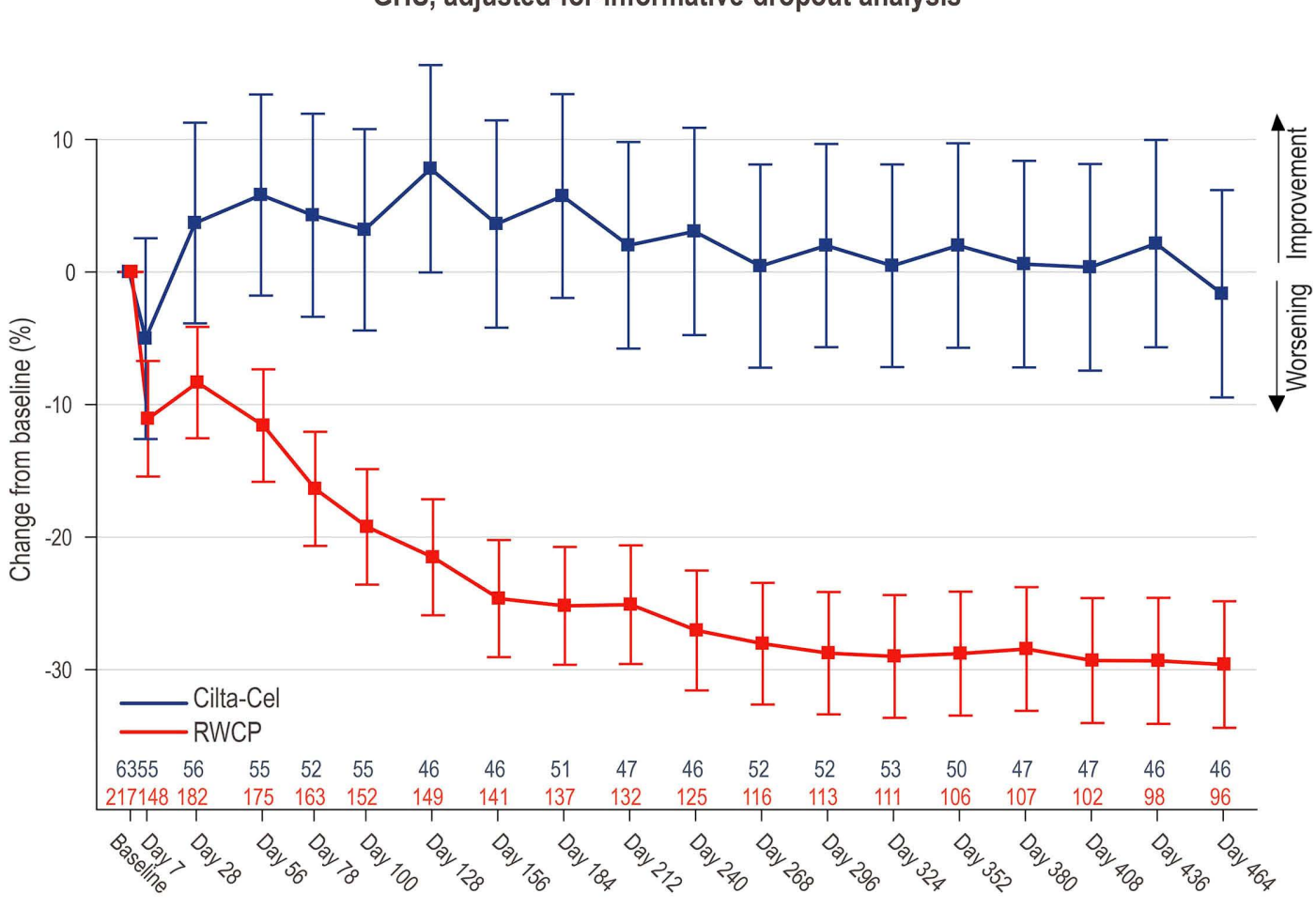


Figure 4. Comparisons of patient-reported outcomes. (A) Comparison of EuroQoL Group's EQ visual analog scale (EQ VAS) of patients who were alive and did not initiate subsequent therapy. (B) Comparison of EORTC QLQ-C30 global health status (GHS) of patients who were alive and did not initiate subsequent therapy. (C) Comparison of EQ VAS of patients who were alive and did not initiate subsequent therapy or died, i.e., adjusted for informative dropout analysis. (D) Comparison of EORTC QLQ-C30 GHS of patients who were alive and did not initiate subsequent therapy or died, i.e., adjusted for informative dropout analysis; cilta-cel: ciltacabtagene autoleucel; RWCP: real-world clinical practice.

and 3.0 at week 4 to 12.6 and 15.6 at week 52, respectively. Improvements with RWCP were considerably smaller (from -1.4 and -0.7 at week 4 to 2.3 and 2.2 at week 52). The differences in improvement *versus* baseline between cilta-cel and RWCP increased up to 10.3 (P=0.0076) for EQ VAS and 13.4 (P=0.0081) for GHS at week 52. The "adjusted-for-informative-dropout" analysis, which included death as additional information regarding patients' health status,[24] showed thatimprovements for cilta-cel *versus* RWCP were 23.7 (P<0.0001) and 30.8 (P<0.0001) for the EQ VAS and GHS, respectively (Figure 4C, D), illustrating the conservative nature of the main analysis.

Comparison of safety outcomes

Detailed safety findings for CARTITUDE-1 [18] and LocoMMotion[20,21] have been previously reported elsewhere. Unadjusted comparison of all adverse events showed higher rates of adverse events for cilta-cel *versus* RWCP across organ classes. All patients treated with cilta-cel experienced at least one adverse event, while 83.5% of patients treated with RWCP had at least one adverse event. This was also the case for grade 3/4 events (93.8% *vs*. 49.2%) (Table 4). Mateos *et al*.[21] indicated that adverse events had been underreported for RWCP in LocoMMotion because of the observational nature of this study. Six (6.2%) patients treated with cilta-cel and 19 (7.7%) patients with RWCP experienced an adverse event with an outcome of death. Cytokine release syndrome and CAR-T therapy-related neurotoxicites occurred in 95% and 21% of patients in CARTITUDE-1, respectively, and were manageable.

Discussion

Despite improvements in treatments for patients with MM in recent years, there is still a pressing need for novel therapies to address unmet treatment needs for patients with triple-class exposed RRMM. Patients treated with cilta-cel have demonstrated early, deep and durable clinical responses and the therapy had a manageable safety profile within the recent CARTITUDE-1 trial. Due to a lack of an established standard of care and clinical equipoise, CARTITUDE-1 was designed as a single-arm trial. Hence, the

Table 4. Summary of adverse events observed with an incidence >25% and of special interest.

Hematologic AE occurring in ≥25%	Cilta-cel, %		RWCP[a], %	
	Any grade	Grade 3/4	Any grade	Grade 3/4
Neutropenia	95.9	94.8	15.7	13.3
Anemia	81.4	68.0	25.8	10.9
Thrombocytopenia	79.4	59.8	23.0	17.7
Leukopenia	61.9	60.8	7.3	4.8
Lymphopenia	53.6	50.5	6.5	5.6
Non-hematologic AE occurring in ≥25% and AE of special interest				
Cytokine release syndrome	94.8	4.1	NA[c]	NA[c]
Total CAR T-cell neurotoxicities	20.6	9.3	NA[c]	NA[c]
ICANS	16.5	2.1	NA[c]	NA[c]
Other CAR T-cell neurotoxicities[b]	12.4	8.2	NA[c]	NA[c]
Metabolism and nutrition disorders				
Hypocalcemia	32.0	3.1	1.2	0.4
Hypophosphatemia	30.9	7.2	0.4	0.0
Decreased appetite	28.9	1.0	2.4	0.4
Hypoalbuminemia	27.8	1.0	0.4	0.0
Gastrointestinal disorders				
Diarrhea	29.9	1.0	15.3	0.8
Nausea	27.8	1.0	9.3	1.2
Other				
Fatigue	37.1	5.2	12.1	0.8
Cough	35.1	0.0	3.2	0.0
AST increased	28.9	5.2	1.2	0.4
ALT increased	24.7	3.1	1.6	1.2

[a]Adverse events underreported for real-world clinical practice (RWCP). [b]Events not reported as immune effector cell-associated neurotoxicity syndrome (ICANS) in CARTITUDE-1 (i.e., onset after a period of recovery from cytokine release syndrome [CRS] and/or ICANS); [c]No chimeric antigen receptor (CAR) T-cell treatments used in LocoMMotion. Adverse events (AE) ≥25% and of special interest (CRS, CAR-T cell neurotoxicities) are reported for ciltacabtagene autoleucel (cilta-cel) and RWCP for any grade and for grade 3/4 adverse events. NA: not applicable; ICANS: immune effector cell-associated neurotoxicity syndrome; AST: aspartate aminotransferase; ALT: alanine aminotransferase.

benefits of cilta-cel need to be compared to those of the group of therapies used in the context of current clinical practice. In such situations, adjusted comparisons *versus* data from the real world are needed, and this approach has become highly relevant for health technology assessment.[25,26] Such adjusted comparisons use statistical methods to overcome the lack of randomization and the related potential for confounding bias. The LocoMMotion study was designed as the first prospective, multinational study of RWCP interventions in patients with advanced MM. The LocoMMotion cohort can be considered highly representative of the clinical population of interest as it includes patients from nine European countries and the USA, reflecting RWCP across different settings. The prospective design and alignment with CARTITUDE-1 guaranteed that eligibility criteria and definitions of all clinically important baseline characteristics and endpoints were identical in both studies, which allowed the most robust comparisons between cilta-cel and current RWCP on all relevant endpoints, including response, PFS, OS, patient-related outcomes and safety. Given these strengths along with the rigorous analytical approaches, the findings of this study represent the highest quality comparative evidence on the benefits of cilta-cel for patients with triple-class exposed RRMM.

Based upon the analyses performed, clinically and statistically significant advantages with cilta-cel *versus* outcomes of RWCP were found for ORR, ≥VGPR, ≥CR, PFS, OS and patient-reported outcomes. Patients treated with cilta-cel were 3.1 times more likely to achieve a response (ORR) compared to RWCP patients and 5.7 times more likely to achieve ≥VGPR. Hazard ratios for OS demonstrated a reduced risk of death by 80% and an improvement in PFS of 85%. Gains in quality of life over 52 weeks were significantly better for cilta-cel than for RWCP, ranging between 10.3% and 30.8%, depending on the endpoint and the analytical approach. Unadjusted safety comparisons indicate higher rates of hematologic adverse events and CAR-T therapy-specific adverse events for cilta-cel.

Additional strength is conferred to the findings in this study, both by the internal consistency of results, as well as by the consistency with comparison to similar analyses of cilta-cel *versus* other external cohorts.[27-29]

While randomized controlled trials remain the gold-standard design when evaluating the benefits and safety of new medical interventions, such trials may not be feasible and/or ethical when clinical equipoise is lacking, and no established standard-of-care therapy exists. For these reasons, CARTITUDE-1 was performed as a single-arm study, and adjusted comparisons as presented here represent high quality evidence on the comparative effectiveness of cilta-cel relative to RWCP.

As with any non-randomized study, the potential for residual confounding for unobserved patients' characteristics cannot be ruled out. However, in the current study the prospective collection of patients' characteristics at baseline in LocoMMotion was broad, which allowed data analyses to adjust for clinically important factors. Accounting for these characteristics was a key step in addressing differences between the two cohorts to avoid confounding bias in the comparative analyses, and represents an important strength of this study as opposed to naïve treatment comparisons or comparisons with existing data sources, which do not include all clinically relevant prognostic baseline variables. While three baseline characteristics (race, history of stem cell transplantation, cytogenetic risk) were not adjusted for in the main analysis, they were included in sensitivity analyses that showed consistent results. Although cytogenetic risk at baseline was previously shown to be a relevant predictive factor,[30] missingness in LocoMMotion was high (37.9%), which reflects that cytogenetic testing is not routinely performed in clinical practice. As cytogenetic testing cannot be mandated in a non-interventional study, missingness could not be reduced. However, in the case of LocoMMotion, no association of outcomes with cytogenetic risk was observed in patients for whom data were available. Similar missingness in cytogenetic risk was observed in other real-world evidence sources and even in clinical trials.[31,32] Similar challenges for LocoMMotion were also observed for CR rates and adverse events.

The LocoMMotion study was performed with no restrictions on the types of treatments that could be received by patients, thereby allowing treating physicians to prescribe patients with the therapy they deemed most appropriate. The wide variety of treatment regimens used in the LocoMMotion cohort illustrates the absence of an established standard-of-care therapy for patients with triple-class exposed RRMM, and is representative of current clinical practice.

Although new therapies for the population of triple-class exposed RRMM patients have recently emerged, the RWCP group in the current study included only limited numbers of patients receiving selinexor or belantamab mafodotin, as these treatments only became available following their approvals in the USA and European Union toward the end of the recruitment period in LocoMMotion. Given the rapidly changing treatment landscape of MM and the heterogeneity of patients, further clinical and real-world studies are needed to better compare cilta-cel against these and other emerging therapies.

Comparisons of cilta-cel to individual therapies were not possible because of the highly varied treatments selected by physicians for their patients. However, two sensitivity analyses, excluding patients from the LocoMMotion cohort who received a regimen without a novel component and who received one or two treatments in combination, were performed. Due to the smaller sample sizes, results from these analyses were less stable, but generally consistent with the overall results illustrating that the comparative efficacy estimates for cilta-cel *versus* RWCP were consistent across treatment combinations, and were not being driven

by the heterogeneity in the LocoMMotion study or by patients receiving a particular therapy/combination.
The comparison of CARTITUDE-1 to the prospective LocoMMotion study on RWCP designed to match CARTITUDE-1 provides the highest quality possible comparative evidence for a single-arm trial. Findings from the adjusted treatment comparisons showed clinically and statistically significant improvements with cilta-cel compared to RWCP in MM patients exposed to three classes of treatment (proteasome inhibitors, immunomodulatory agents, anti-CD38 antibodies) and highlight cilta-cel's potential as a novel and highly effective therapy to address unmet treatment needs in patients with triple-class exposed RRMM.

Disclosures

MVM has received honoraria from and is a member on boards of directors/advisory committees for Janssen, Celgene, Takeda, and Amgen; has received honoraria from Adaptive; and is a member on boards of directors/advisory committees for GSK, AbbVie, EDO, and Pharmamar. KW is a member on boards of directors/advisory committees for Amgen, Celgene, Janssen, and Sanofi; is a consultant for and receives honoraria from BMS and Takeda); has provided consultancy for Adaptive Biotech and Juno. TM has received research funding from Janssen, Amgen, and Sanofi and acts as a consultant for Oncopeptides and GSK. JGB has received research funding from AbbVie, Amgen, Acetylon, Bluebird, Bristol Myers Squibb, Celgene, Cellularity, Constellation, CRISPR, Therapeutics, CURIS, EMD Serono, Genentech, Glenmark, Janssen, Kesios, Lilly, Novartis, Poseida, Teva, Takeda Pharmaceuticals, and Vivolux; and has acted as a consultant for Amgen, Bioclinica, Bristol Myers Squibb, Celgene, CRISPR Therapeutics, Janssen, Karyopharm, Kite Pharma, Legend, Prothena, Servier, Takeda Pharmaceuticals, and SecuraBio. AJ has received consulting fees and honoraria from AbbVie, Adaptive, Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Juno, Karyopharm, and Sanofi; and is a member of a board of directors or advisory committee for AbbVie, Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen, Karyopharm, and Sanofi. AKS has received honoraria from Aventis, Janssen, Amgen, Oncopeptides, Bristol Myers Squibb, GlaxoSmithKline, and Sanofi; and is a member of a board of directors or advisory committee for Genomics England and Tempus. SJ is a consultant for Bristol Myers Squibb, Janssen, Karyopharm Therapeutics, Merck, Sanofi, Legend Biotech, and Takeda Pharmaceuticals. YL has provided consultancy services for Bluebird Bio, Celgene, Gamida Cells, Janssen, Huno, Kite, Novartis, Sorrento, Legend BioTech, and Vineti; and has received research funding from Bluebird Bio, Celgene, Janssen, Kite, Merck, and Takeda Pharmaceuticals. JD, FG, PT, NJP, JC, NEY, CH, JMS, and VS are employees of Janssen. BH was a previous employee of Janssen. CCJ is employed with Janssen; and is a consultant physician at the Memorial Sloan Kettering Cancer Center (New York, NY, USA). TN and LP are employees of Legend Biotech. HE has no conflicts of interest to disclose. PM has received consultancy fees and/or honoraria from Celgene, Janssen, Amgen, Takeda, and AbbVie.

Contributions

MVM, KW, JD, BH, NEY, CH, and VS conceived the study. JD, FG, PT, BH, and NEY were responsible for the methodology. JD, FG, PT, NJP, and JC were responsible for software and formal analysis. MVM, KW, TM, JGB, AJ, AKS, SJ, YL, CCJ, JMS, VS, HE, and PM conducted the investigation. MVM, KW, TM, JGB, AJ, AKS, SJ, YL, JD, CH, CCJ, JMS, VS, HE, and PM organized resources. MVM, KW, JD, FG, PT, NJP, JC, CCJ, JMS, VS, and PM curated the data. JD, FG, PT, and BH wrote and prepared the original draft of the manuscript. MVM, KW, TM, JGB, AJ, AKS, SJ, YL, JD, FG, PT, NJP, JC, BH, NEY, CH, CCJ, JMS, VS, TN, LP, HE, and PM wrote, reviewed and/or edited the manuscript. JD, FG, PT, and BH contributed to the visualization. MVM, KW, JD, CH, JMS, and PM supervised the study. The project administrators were BH and NEY. All authors read and agreed to the published version of the manuscript.

Acknowledgments

We thank all patients who participated in the CARTITUDE-1 and LocoMMotion studies, their families and caregivers, the physicians and nurses who cared for patients and supported the studies, as well as staff members of CARTITUDE-1 and LocoMMotion sites, and staff members involved in data collection, data analysis and interpretation. We also thank staff from Eversana Inc. for their support in the development of this work.

Funding

This study was funded by Janssen Pharmaceutica NV and Legend Biotech Inc.

Data-sharing statement

Data used for this study were derived from the CARTITUDE-1 and LocoMMotion studies. CARTITUDE-1 data-sharing is governed by the Janssen Pharmaceutical Companies of Johnson & Johnson's data-sharing policy that is available online. As noted in the policy, requests for access to the study data can be submitted through Yale Open Data.

References

1. Kyle RA, Rajkumar SV. Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma. Leukemia. 2009;23(1):3-9.
2. Raab MS, Cavo M, Delforge M, et al. Multiple myeloma: practice patterns across Europe. Br J Haematol. 2016;175(1):66-76.
3. Benyamini N, Adir S, Gatt ME, et al. Real-life data on the

outcome of daratumomab-refractory myeloma patients: multi-center experience. Blood. 2018;132(Suppl_1):3259.
4. Haefliger B, Diels J, Ghilotti F, et al. Baseline characteristics and survival outcomes of patients with tri-exposed multiple myeloma in a German registry. Proceedings of the EHA2021-European Hematology Association Conference. https://oncologyinformationservice.com/wpcontent/uploads/pdf/Publikationen%20PDFs/Haefliger_et_al_EBMT_EHA_Poster_OIs.pdf Accessed 15 April 2023
5. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J, et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer. 2013;49(6):1374-1403.
6. Usmani SZ, Nahi H, Plesner T, et al. Daratumumab monotherapy in patients with heavily pretreated relapsed or refractory multiple myeloma: final results from the phase 2 GEN501 and SIRIUS trials. Lancet Haematol. 2020;7(6):e447-e455.
7. Miguel JS, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. Lancet Oncol. 2013;14(11):1055-1066.
8. San-Miguel JF, Hungria VT, Yoon SS, et al. Panobinostat plus bortezomib and dexamethasone versus placebo plus bortezomib and dexamethasone in patients with relapsed or relapsed and refractory multiple myeloma: a multicentre, randomised, double-blind phase 3 trial. Lancet Oncol. 2014;15(11):1195-1206.
9. Orlowski RZ, Nagler A, Sonneveld P, et al. Randomized phase III study of pegylated liposomal doxorubicin plus bortezomib compared with bortezomib alone in relapsed or refractory multiple myeloma: combination therapy improves time to progression. J Clin Oncol. 2007;25(25):3892-3901.
10. Dimopoulos MA, Moreau P, Palumbo A, et al. Carfilzomib and dexamethasone versus bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma (ENDEAVOR): a randomised, phase 3, open-label, multicentre study. Lancet Oncol. 2016;17(1):27-38.
11. Dimopoulos MA, Chen C, Spencer A, et al. Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma. Leukemia. 2009;23(11):2147-2152.
12. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32(3):309-322.
13. Gandhi UH, Cornell RF, Lakshman A, et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia. 2019;33(9):2266-2275.
14. Robak P, Drozdz I, Szemraj J, Robak T. Drug resistance in multiple myeloma. Cancer Treat Rev. 2018;70:199-208.
15. Kumar V, Ailawadhi M, Dutta N, et al. Trends in early mortality from multiple myeloma: a population-based analysis. Clin Lymphoma Myeloma Leuk. 2021;21(5):e449-e455.
16. Majzner RG, Mackall CL. Clinical lessons learned from the first leg of the CAR T cell journey. Nat Med. 2019;25(9):1341-1355.
17. Madduri D, Berdeja JG, Usmani SZ, et al. CARTITUDE-1: phase 1b/2 study of ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T cell therapy, in relapsed/refractory multiple myeloma. Blood. 2020;136(Suppl 1):22-25.
18. Berdeja JG, Madduri D, Usmani SZ, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021;398(10297):314-324.
19. A study of JNJ-68284528, a chimeric antigen receptor T cell (CAR-T) therapy directed against B-cell maturation antigen (BCMA) in participants with relapsed or refractory multiple myeloma (CARTITUDE-1). 2020. https://www.clinicaltrials.gov/ct2/show/NCT03548207 Accessed 14 December 2021
20. Mateos M-V, Weisel K, Stefano VD, et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed/refractory multiple myeloma (RRMM) receiving ≥3 prior lines of therapy. J Clin Oncol. 2021;39(Suppl 15):S8041.
21. Mateos MV, Weisel K, De Stefano V, et al. LocoMMotion: a prospective, non-interventional, multinational study of real-life current standards of care in patients with relapsed and/or refractory multiple myeloma. Leukemia. 2022;36(5):1371-1376.
22. Li F, Thomas LE, Li F. Addressing extreme propensity scores via the overlap weights. Am J Epidemiol. 2019;188(1):250-257.
23. Martin T, Lin Y, Agha M, et al. Health-related quality of life in the CARTITUDE-1 study of ciltacabtagene autoleucel for relapsed/refractory multiple myeloma. Blood. 2020;136(Suppl_1):41-42.
24. Ratcliffe J, Young T, Longworth L, Buxton M. An assessment of the impact of informative dropout and nonresponse in measuring health-related quality of life using the EuroQol (EQ-5D) descriptive system. Value Health. 2005;8(1):53-58.
25. Patel D, Grimson F, Mihaylova E, et al. Use of external comparators for Health Technology Assessment submissions based on single-arm trials. Value Health. 2021;24(8):1118-1125.
26. Goring S, Taylor A, Müller K, et al. Characteristics of non-randomised studies using comparisons with external controls submitted for regulatory approval in the USA and Europe: a systematic review. BMJ Open. 2019;9(2):e024895.
27. Costa LJ, Lin Y, Martin TG, et al. Cilta-cel versus conventional treatment in patients with relapse/refractory multiple myeloma. J Clin Oncol. 2021;39(15_suppl):8030.
28. Weisel K, Martin T, Krishnan A, et al. Comparison of ciltacabtagene autoleucel (cilta-cel) in CARTITUDE-1 versus standard of care in triple-class exposed multiple myeloma patients in clinical trials of daratumumab. Proceedings of the EHA2021-European Hematology Association Conference. Abstract EP977.
29. Martin TG, Krishnan AY, Yong K, et al. Comparison of outcomes with ciltacabtagene autoleucel (cilta-cel) in CARTITUDE-1 versus real-world standard of care (RW SOC) for patients (pts) with triple-class exposed relapsed/refractory multiple myeloma (RRMM). J Clin Oncol. 2021;39(Suppl 15):S8045.
30. Perrot A, Lauwers-Cances V, Tournay E, et al. Development and validation of a cytogenetic prognostic index predicting survival in multiple myeloma. J Clin Oncol. 2019;37(19):1657-1665.
31. Dimopoulos MA, Terpos E, Boccadoro M, et al. Daratumumab plus pomalidomide and dexamethasone versus pomalidomide and dexamethasone alone in previously treated multiple myeloma (APOLLO): an open-label, randomised, phase 3 trial. Lancet Oncol. 2021;22(6):801-812.
32. Merz M, Goldschmidt H, Hari P, et al. Adjusted comparison of outcomes between patients from CARTITUDE-1 versus multiple myeloma patients with prior exposure to PI, IMiD and anti-CD-38 from a German Registry. Cancers (Basel). 2021;13(23):5996.