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ORIGINAL RESEARCH

Comparative Effectiveness of Ciltacabtagene Autoleucel in CARTITUDE-4 Versus Real-World Physician's Choice of Therapy from the Flatiron Registry in Lenalidomide-Refractory Multiple Myeloma

Cyrille Touzeau · Brea Lipe · Abdullah M. Khan · Binod Dhakal · Sandhya Nair · Jianming He · João Mendes · Seina Lee · Carolina Lonardi · Ana Slaughter · Nikoletta Lendvai · Jordan M. Schecter · Diana Chen · Man Zhao · Tzu-min Yeh · Xavier Leleu · Noemí Puig · Dominik Dytfeld · Elena Zamagni · Katja Weisel · Lionel Karlin · Michel Delforge · Paolo Corradini · Roberto Mina · Wilfried Roeloffzen · Surbhi Sidana

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ABSTRACT

Introduction: Ciltacabtagene autoleucel (cilta-cel) is approved for relapsed or refractory multiple myeloma (RRMM). In the CARTITUDE-4 study (NCT04181827), cilta-cel demonstrated superior efficacy versus pomalidomide, bortezomib, and dexamethasone or daratumumab, pomalidomide, and dexamethasone in patients with RRMM after 1–3 prior lines of therapy (LOT). We conducted an indirect treatment comparison to understand the comparative efficacy of cilta-cel versus real-world (RW) physician's choice of treatment for lenalidomide-refractory MM.

Methods: De-identified data from the Flatiron Health MM cohort registry (January 2020 to May 2024) were compared with data from CARTITUDE-4 (data cutoff May 1, 2024). Key eligibility criteria for CARTITUDE-4 were used to match patients from the Flatiron database. Baseline covariates of prognostic significance were adjusted using inverse probability of treatment weighting. Outcomes for comparative effectiveness included progression-free survival (PFS), RW PFS, time to next treatment (TTNT),

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C. Touzeau (✉)
Service d'Hématologie, Centre Hospitalier Universitaire de Nantes, Nantes Université, 5 All. de l'Île Gloriette, 44000 Nantes, France
e-mail: Cyrille.TOUZEAU@chu-nantes.fr

C. Touzeau
Centre de Recherche en Cancérologie et Immunologie Intégrée Nantes Angers, INSERM, Centre National de la Recherche Scientifique, Université d'Angers, Université de Nantes, Nantes, France

C. Touzeau
Site de Recherche Intégrée sur le Cancer, Imaging and Longitudinal Investigations to Ameliorate Decision-Making (ILIAD), French National Cancer Institute–French Ministry of Health–INSERM, 12558, Nantes, France

B. Lipe
University of Rochester Medical Center, Rochester, NY, USA

and overall survival (OS). Sensitivity analyses were conducted.

***Results*:** The CARTITUDE-4 cohort included data from 208 patients who received cilta-cel; the median follow-up was 33.6 months. The real-world cohort included 932 patients (1445 eligible LOT) from the Flatiron database; the median follow-up was 23.6 months. In base case analyses, compared with the Flatiron cohort, patients treated with cilta-cel had improved PFS (hazard ratio [HR] 0.29 [95% confidence interval (CI)] 0.22–0.36; $p<0.001$), RW-PFS (HR 0.29 [95% CI 0.23–0.37]; $p<0.001$), TTNT (HR 0.32 [95% CI 0.25–0.41]; $p<0.001$), and OS (HR 0.59 [95% CI 0.41–0.84]; $p=0.003$). These findings were consistent across all sensitivity analyses.

***Conclusion*:** Cilta-cel lengthened TTNT and demonstrated meaningful prolongation in PFS and OS compared with real-world physician's choice for lenalidomide-refractory MM. These data highlight the value of cilta-cel as an effective therapy in earlier-line patients with relapsed, lenalidomide-refractory MM exposed to proteasome inhibitors and immunomodulatory drugs.

***Trial registration*:** CARTITUDE-4: ClinicalTrials.gov ID NCT04181827.

Keywords: Ciltacabtagene autoleucel; Flatiron health database; Relapsed or refractory multiple myeloma; CARTITUDE-4; Real-world data; Indirect treatment comparison; CAR-T

A. M. Khan
The Ohio State University Comprehensive Cancer Center, Columbus, OH, USA

B. Dhakal
Medical College of Wisconsin, Milwaukee, WI, USA

S. Nair
Johnson & Johnson, Beerse, Belgium

J. He · J. Mendes · S. Lee · N. Lendvai · J. M. Schecter · T. Yeh
Johnson & Johnson, Raritan, NJ, USA

C. Lonardi
Johnson & Johnson, Buenos Aires, Argentina

A. Slaughter
Johnson & Johnson, Zug, Switzerland

D. Chen
Johnson & Johnson, Shanghai, China

M. Zhao
IQVIA, Shanghai, China

X. Leleu
CHU Poitiers, Poitiers, France

N. Puig
Centro de Investigación del Cancer, Hospital Universitario de Salamanca, Instituto de Investigacion Biomedica de Salamanca, Salamanca, Spain

D. Dytfeld
Poznan University of Medical Sciences, Poznań, Poland

E. Zamagni
University of Bologna, Bologna, Italy

K. Weisel
University Medical Center Hamburg-Eppendorf, Hamburg, Germany

L. Karlin
Hôpital Lyon Sud, Hospices Civils de Lyon, Pierre-Bénite, France

M. Delforge
University of Leuven, Leuven, Belgium

P. Corradini
Divisione di Ematologia, Fondazione IRCCS Istituto Nazionale dei Tumori, Università di Milano, Milan, Italy

R. Mina
The Division of Hematology, AOU Citt. della Salute e della Scienza di Torino, and the Department of Molecular Biotechnology and Health Sciences, University of Turin, Turin, Italy

W. Roeloffzen
University Medical Center Groningen, Groningen, Netherlands

S. Sidana
Stanford University School of Medicine, Stanford, CA, USA

Key Summary Points

Why carry out this study?

Indirect treatment comparisons (ITCs) can be used to assess the benefits of treatments used in clinical trials relative to those used in clinical practice in the absence of head-to-head comparisons.

Data from head-to-head comparisons for ciltacabtagene autoleucel (cilta-cel) versus established standard of care regimens used in real-world clinical practice for the treatment of lenalidomide-refractory multiple myeloma (MM) after 1–3 prior lines of therapy are lacking.

This ITC evaluated the relative efficacy of cilta-cel using data from the CARTITUDE-4 data versus standard-of-care real-world physician's choice of therapies from the Flatiron registry.

What was learned from this study?

Cilta-cel prolonged the time to next anti-myeloma treatment and reduced the risk of disease progression or death compared with real-world physician's choice for lenalidomide-refractory MM.

These data demonstrate that cilta-cel is an effective therapy in patients with relapsed or refractory MM who have received at least one prior line of therapy and are lenalidomide-refractory.

INTRODUCTION

Therapeutic advances including proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies have improved patient outcomes. However, multiple myeloma (MM) remains incurable [1–7]. Additionally, most patients with MM will relapse on these standard therapies and have worse outcomes with each subsequent line of therapy (LOT) [8–12]. Lenalidomide, an IMiD, is recommended across all lines of MM therapy, including newly diagnosed and relapsed or refractory MM (RRMM) [13], but resistance has been reported [12, 14, 15], highlighting the need for additional effective therapies.

Currently, combination therapies of daratumumab, an anti-CD38 monoclonal antibody, with pomalidomide (IMiD) plus dexamethasone (DPd), and daratumumab with carfilzomib (PI) plus dexamethasone (DKd), as well as pomalidomide with bortezomib (PV) plus dexamethasone (PVd) are preferred regimens for the treatment of lenalidomide-refractory MM after 1–3 prior LOT, based on National Comprehensive Cancer Network (NCCN), International Myeloma Working Group (IMWG), and European Society for Medical Oncology (ESMO) guidelines [10, 16, 17].

Ciltacabtagene autoleucel (cilta-cel), a chimeric antigen receptor T cell (CAR-T) therapy directed against B cell maturation antigen, demonstrated superior efficacy and a manageable safety profile versus physician's choice of standard care (PVd or DPd) in patients with lenalidomide-refractory MM after 1–3 prior LOT in the randomized, phase 3 CARTITUDE-4 study (NCT04181827) [18, 19]. At 33.6-month median follow-up, overall survival (OS) significantly improved in the cilta-cel group versus the standard-care group. Median OS was not reached in the cilta-cel group (95% confidence interval [CI] not estimable) or standard-care group (95% CI 37.75 months to not estimable; hazard ratio [HR], 0.55 [95% CI 0.39–0.79]; $p = 0.0009$); 30-month OS rates were 76.4% and 63.8%, respectively. Additionally, median progression-free survival (PFS) was not reached (95% CI 34.50 months to not estimable) in the cilta-cel group and was 11.79 months (95% CI 9.66–14.00) in the standard-care group (HR for progression or death, 0.29 [95% CI 0.22–0.39], protocol-specified weighted analysis); 30-month PFS rates were 59.4% and 25.7%, respectively. Adverse events (AEs) were consistent with the known safety profile of cilta-cel [20]. No new safety signals, including movement and neurocognitive AEs or cranial nerve palsy, were observed after an additional 17.7 months of follow-up [18, 19].

Although DPd and PVd are established regimens for the treatment of

lenalidomide-refractory MM after 1–3 prior LOT, the treatment choices are not exclusively restricted to these regimens [21]. Additionally, availability and access to these therapies varies worldwide; therefore, it is important to generate results comparing cilta-cel with standard-care regimens used in real-world (RW) clinical practice settings. Indirect treatment comparisons (ITCs) can be used to assess the benefits of treatments used in clinical trials relative to those used in clinical practice in the absence of head-to-head comparisons [22–24]. ITC methods allow for creation of an external, RW control arm representing patients who would have been randomized to physician's choice of treatment. This RW cohort can be compared with the cilta-cel cohort in CARTITUDE-4.

In this study, we performed an ITC to evaluate the comparative effectiveness of cilta-cel in CARTITUDE-4 and RW physician's choice of treatment from the Flatiron Health database in patients with lenalidomide-refractory MM after 1–3 prior LOT.

METHODS

Data Source

CARTITUDE-4 (NCT04181827) is a phase 3, randomized, open-label trial assessing the efficacy and safety of cilta-cel versus RW physician's choice of effective standard care in patients with lenalidomide-refractory MM after 1–3 LOT, including a PI and an IMiD [18, 19]. Patient recruitment included 81 sites in the USA, Europe, Asia, and Australia. No information was available whether a patient enrolled was also included in the Flatiron database. The primary endpoint was PFS, which was defined as the time from randomization to the first documentation of disease progression or death. Secondary endpoints included rate of complete response or better, overall response rates, minimal residual disease negativity, OS, AEs, pharmacokinetics and worsening of patient-reported symptoms as assessed by the Multiple Myeloma Symptom and Impact Questionnaire. Treatment responses and disease progression were determined according to the International Myeloma Working Group (IMWG) criteria. Time to next treatment (TTNT) was also assessed.

CARTITUDE-4 was conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation guidelines for Good Clinical Practice. The independent ethics committee or institutional review board at each site approved the protocol (Supplemental Table S1). All patients provided written informed consent.

Flatiron Health's longitudinal database consists of de-identified patient-level electronic health record (EHR) data primarily from US community-based oncology clinics but also academic centers. The database includes an MM cohort registry from over 280 cancer clinics [25]. Flatiron Health leverages this database to develop RW data offerings on a tumor-by-tumor type basis. The Flatiron Health MM dataset includes diagnostic and treatment details captured during routine clinical care, either as structured data (e.g., International Classification of Diseases, 9th and 10th Revisions codes, laboratory values [e.g., M-protein level], medication orders, and medication administrations) or unstructured data (e.g., abstracted data obtained from EHR documents, including confirmed diagnosis, fluorescence in situ hybridization cytogenetics and karyotyping at diagnosis, and stem cell transplant). Additional derived variables include LOT and International Staging System (ISS) stage at time of diagnosis.

Patient Population

Individual patient data from CARTITUDE-4 (enrollment 10 July 2020 through 17 November 2021; data cutoff for this analysis was May 1, 2024) and de-identified EHR data derived from the Flatiron Health MM cohort registry between January 2020 and May 2024 were used to conduct adjusted comparisons between cilta-cel and RW treatment. The timeframe of the RW cohort was chosen to align with enrollment in CARTITUDE-4 and to better represent the current treatment landscape in MM.

Data from patients in the cilta-cel cohort from the CARTITUDE-4 study were compared

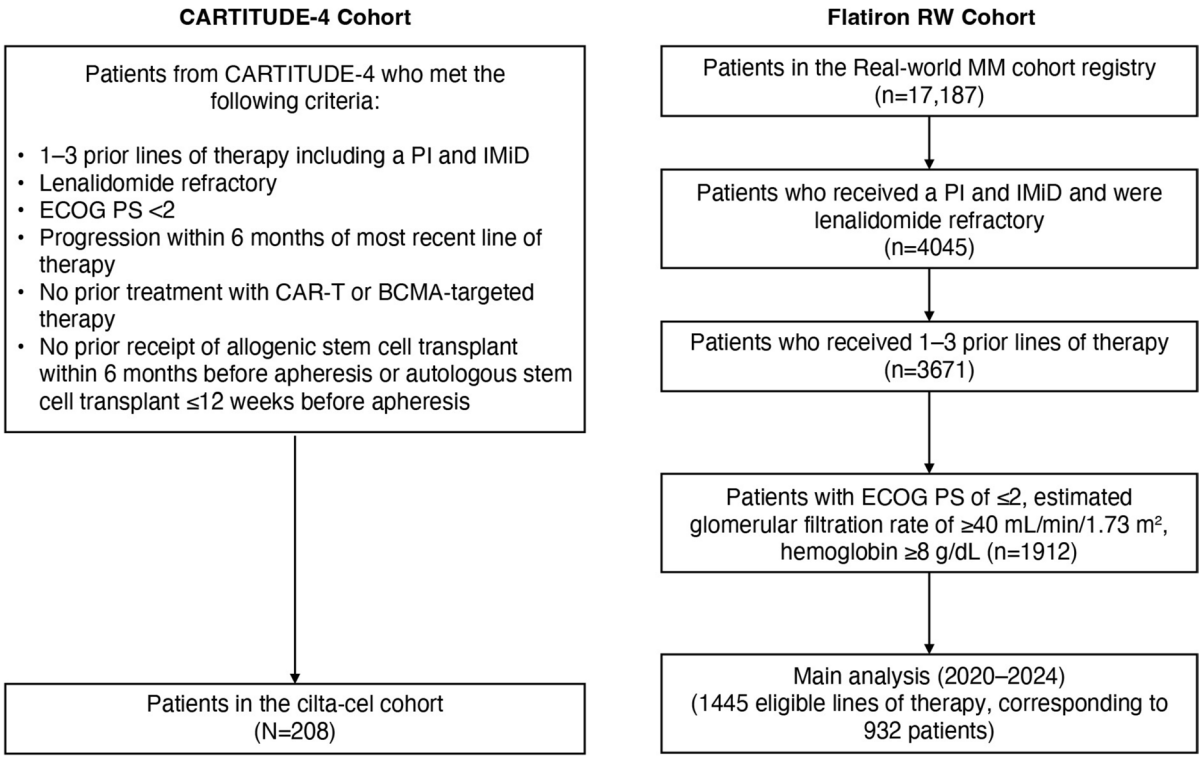

Fig. 1 Patient selection procedure. *BCMA* B cell maturation antigen, *CAR-T* chimeric antigen receptor T cell, *ECOG PS*, Eastern Cooperative Oncology Group performance score, *IMiD* immunomodulatory drug, *MM* multiple myeloma, *PI* proteasome inhibitor, *RW* real-world

with patients from the de-identified Flatiron database who met key CARTITUDE-4 eligibility criteria (Fig. 1). All patients had lenalidomide-refractory MM after 1–3 LOT, including a PI and an IMiD [18, 21]. Refractory MM was defined as nonresponsive disease (i.e., not achieving minimal response or disease progression on therapy) with primary or salvage therapy, or disease progression within 60 days of last therapy [26, 27].

Outcomes

Comparative effectiveness analyses included the intent-to-treat population from the CARTITUDE-4 cilta-cel cohort and all eligible patients from the RW physician's choice of treatment cohort.

Comparative effectiveness of cilta-cel versus RW treatment was assessed by PFS, real-world PFS (RW-PFS), TTNT, and OS. Safety was not in the scope of this analysis. PFS was defined as the duration from the index date to the date of disease progression or death due to any cause, whichever occurred first. Disease progression was evaluated per IMWG criteria. For patients who had not progressed and were alive at the time of the data cutoff, data were censored at the last disease evaluation before the start of any subsequent antimyeloma therapy. PFS in the RW cohort may be underestimated as disease progression was measured by M-protein and serum-free light chain only; other measurements such as bone marrow or bone lesion assessments were lacking. Therefore, RW-PFS was assessed for both cohorts in this study. RW-PFS was defined as the duration from the index date to the date of next antimyeloma treatment, disease progression, or death, whichever comes first. For patients who had not developed any of these events, data were censored at the last disease evaluation. TTNT was defined as the time from index date to the initiation date of next antimyeloma treatment or death, whichever occurred first. Patients

who were still alive and did not initiate a new LOT at the data cutoff were censored at the last date known to be alive. OS was defined as the time from the index date to the date of death. Patients who were still alive at the data cutoff were censored at the last date known to be alive. The index date (time 0) in CARTITUDE-4 for all outcomes was the date of randomization; the index date in the RW cohort was defined as the date when patients met inclusion criteria.

Statistical Analyses

To account for imbalances in baseline patient characteristics between the CARTITUDE-4 and RW cohorts, inverse probability of treatment weighting (IPTW) with average treatment effects in the treated derived from propensity scores was performed to ensure that patients in the RW cohort resembled patients in CARTITUDE-4. IPTW uses a balancing score to derive weights for the desired target population, which minimizes confounding and removes potential effect modifiers. To identify and rank prognostic factors that might influence effectiveness estimates, a clinician-driven process was used. A list of potential factors was identified a priori by consulting studies from a literature review conducted to identify clinical outcomes in patients with triple-class-exposed RRMM and was presented to a panel of clinical experts [24]. Among 15 prognostic factors, the panel prioritized five: refractory status, cytogenetic profile, ISS stage, time to progression on last regimen, and total plasmacytoma (extramedullary plasmacytomas and soft-tissue components of bone-based plasmacytomas [24]). Total plasmacytoma was not available from the Flatiron Health database and therefore was not included. Additional prognostic variables identified by the panel that were considered key covariates for the IPTW analyses were number of prior LOT, years since MM diagnosis, age, hemoglobin, and lactate dehydrogenase (LDH) levels. LDH levels were also excluded because of missingness in the Flatiron Health database, resulting in eight top-ranked variables utilized in the base case analysis: refractory status, time to progression on the last regimen, cytogenetic profile, ISS stage, number of prior LOT, years since MM diagnosis, age, and hemoglobin. Prior stem cell transplant, Eastern Cooperative Oncology Group performance status (ECOG PS), race, sex, and type of MM were also identified by the panel as key factors and, in addition to the eight variables in the base case analysis, were adjusted for in a sensitivity analysis ("fully adjusted analysis"). Population differences between CARTITUDE-4 and the RW cohort were assessed using standardized mean differences (SMDs) (small, 0 to 0.1; moderate, >0.1 to ≤ 0.2; substantial, >0.2) [28]. For both the CARTITUDE-4 and RW cohorts, no imputation was conducted for the missing cytogenetic data and was thus treated as a separate category; however, the actual distribution of high versus standard cytogenetic risk in each database may differ. For the RW cohort, variables with missing values (ISS stage, hemoglobin, and ECOG PS) were imputed using the last observation prior to the index date.

Estimates of comparative effectiveness were derived for both the unadjusted (cilta-cel vs RW physician's choice of treatment prior to IPTW) and the adjusted comparison (IPTW). Treatment effect estimates, effective sample size, and covariate balance are reported for both scenarios. Sensitivity analyses evaluated the impact of alternative statistical methods and variable adjustment and were conducted using the multivariate regression and doubly robust methods [29]. First patient case weighting (i.e., the first LOT satisfying the inclusion criteria and not including patients with multiple eligible LOT) was also conducted as a sensitivity analysis. Transformations and interaction terms were not included.

For time-to-event outcomes, a weighted Cox proportional hazards model was used to derive a HR and its respective 95% CI. A weighted Kaplan–Meier method was used to derive the median time to event, each with its respective 95% CI. To account for patients with multiple index dates, the variance was estimated using a robust sandwich variance estimator specifying the patient identifier.

A significance level of 0.05 was used for all comparisons, without adjustment for multiplicity. All statistical analyses were performed with R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Selection of Patients

The CARTITUDE-4 cohort included data from 208 patients randomized to the cilta-cel arm, with a median follow-up of 33.6 months (data cutoff May 1, 2024). The RW cohort included 932 patients from the de-identified Flatiron database, contributing 1445 eligible LOT between January 2020 and May 2024. Median follow-up was 23.6 months.

Overall and RW cohort weight distributions are shown in Supplementary Table S2. Before reweighting, substantial differences (SMD > 0.20) between the CARTITUDE-4 and RW cohorts were observed for several of the baseline characteristic variables. More patients in the CARTITUDE-4 cohort had high-risk cytogenetics (59.4% vs 37.8%), defined as del17p, t[4;14], t[14;16], or gain/amp[1q] for both cohorts [18, 21]), progressed on their last LOT > 16 months before the index treatment (51.0% vs 24.5%), had an MM diagnosis ≥ 3 years before the index treatment (50.0% vs 34.3%), and had a prior stem cell transplant (82.2% vs 30.2%). In contrast, the RW cohort had a greater proportion of patients with ISS Stage III disease (5.8% vs 16.8%), who were ≥ 65 years of age (39.4% vs 66.0%), and were refractory to a PI (49.5% vs 71.6%) (Table 1).

After reweighting, baseline characteristics were balanced between the two cohorts (Table 1). Most SMD values were < 0.10, with the maximum value of 0.10 in the base case analysis and 0.13 in the fully adjusted analysis (Table 1; Supplemental Fig. S1).

Treatment Regimens Received in RW Clinical Practice

In the RW cohort from the Flatiron database, across all eligible LOT, more than 50 treatment regimens were prescribed (Table 2). The most commonly prescribed treatment regimens were anti-CD38-based regimens, including DPd (16.0%), daratumumab monotherapy (8.2%), DKd (7.5%), DVd (daratumumab, bortezomib, and dexamethasone; 6.8%), DRd (daratumumab, lenalidomide, and dexamethasone; 1.8%), and Isa-Kd (isatuximab, carfilzomib, and dexamethasone; 1.5%). Of the 1445 eligible LOT, 17.7% were other drug combinations (i.e., all drugs not recommended as regimens for the treatment of MM by the NCCN, which may include any PI, IMiD, anti-CD38 monoclonal antibody, melphalan, cyclophosphamide, or selinexor).

Comparative Analysis of Efficacy Outcomes

In unadjusted analysis, patients in the cilta-cel cohort from CARTITUDE-4 showed significantly longer PFS (median not reached [NR] vs 8.1 months; HR 0.32 [95% CI 0.25–0.40), RW-PFS (median NR vs 8.1 months; HR 0.32 [95% CI 0.26–0.40]), TTNT (median NR vs 9.9 months; HR 0.35 [95% CI 0.28–0.43]), and OS (median NR vs 45.3 months; HR 0.60 [95% CI 0.43–0.82]) compared with the RW cohort (IPTW, $p \le 0.001$ for all) (Table 3). For the cilta-cel cohort, the estimated 24- and 30-month OS rates were 79% and 76%; for the RW cohort, the unweighted 24- and 30-month OS rates were 70% and 66%, and weighted 24- and 30-month OS rates were 70% and 65%, respectively.

The base case analysis showed similar results, i.e., significantly improved outcomes were found in the cilta-cel cohort compared with the RW cohort (Table 3, Figs. 2, 3, 4, Supplemental Fig. S2). After adjustment, for patients in the cilta-cel cohort from CARTITUDE-4 compared with patients in the RW cohort, PFS (median NR vs 8.2 months; HR 0.29 [95% CI 0.22–0.36]; $p < 0.001$) (Supplemental Fig. S2), RW-PFS (median NR vs 8.2 months; HR 0.29 [95% CI 0.23–0.37]; $p < 0.001$) (Fig. 2a), TTNT (median NR vs 9.4 months; HR 0.32 [95% CI 0.25–0.41]; $p < 0.001$) (Fig. 3a), and OS were significantly longer (median NR vs 45.4 months; HR 0.59 [95% CI 0.41–0.84]; $p = 0.003$) (Fig. 4a). All p values were based on IPTW.

Overall, results in the fully adjusted analysis were consistent with the base case analysis (Table 3, Figs. 2, 3, 4, Supplemental Fig. S2). After adjustment, in patients in the cilta-cel cohort from CARTITUDE-4 compared with patients in the RW cohort, PFS (median NR

Table 1 Group demographic balance before and after IPTW weighting for the comparison of the CARTITUDE-4 cilta-cel and RW cohorts

Variables	CARTITUDE-4 cilta-cel cohort ($n = 208$)	Observed (before weighting)		Base case (weighted)		Base case fully adjusted (weighted)	
		RW cohort ($n = 1445$[a])	SMD	RW cohort ESS ($n = 463$[b])	SMD	RW cohort ESS ($n = 249$[b])	SMD
Refractory to PI, *n* (%)	103 (49.5)	1035 (71.6)	− 0.46	108 (54.6)	− 0.11	108 (55.8)	− 0.13
Refractory to anti-CD38, *n* (%)	50 (24.0)	371 (25.7)	− 0.04	54 (27.0)	− 0.07	53 (27.5)	− 0.08
Progression on the last LOT > 16 months before the index treatment, *n* (%)	106 (51.0)	354 (24.5)	0.57	94 (47.3)	0.08	87 (44.9)	0.13
Cytogenetic risk category, *n* (%)							
High-risk[c]	123 (59.1)	546 (37.8)	0.44	114 (57.3)	0.04	109 (56.5)	0.05
Standard-risk	69 (33.2)	616 (42.6)	− 0.20	68 (34.3)	− 0.02	68 (35.3)	− 0.04
Unknown	16 (7.7)	283 (19.6)	− 0.35	17 (8.4)	− 0.02	16 (8.2)	− 0.01
ISS stage, *n* (%)							
I	136 (65.4)	843 (58.3)	0.15	131 (65.7)	− 0.01	124 (64.3)	0.02
II	60 (28.8)	359 (24.8)	0.09	56 (28.1)	0.02	57 (29.4)	− 0.01
III	12 (5.8)	243 (16.8)	− 0.35	12 (6.2)	− 0.01	12 (6.3)	− 0.02
Prior lines of treatments, *n* (%)							
1	68 (32.7)	390 (27.0)	0.12	56 (28.3)	0.10	51 (26.7)	0.13
2	83 (39.9)	538 (37.2)	0.05	84 (42.3)	− 0.05	88 (45.8)	− 0.12
3	57 (27.4)	517 (35.8)	− 0.18	58 (29.4)	− 0.04	53 (27.5)	− 0.00
Time from MM diagnosis to index treatment ≥ 3 years, *n* (%)	104 (50.0)	495 (34.3)	0.32	105 (52.7)	− 0.06	97 (50.1)	− 0.00
Age ≥ 65 years, *n* (%)	82 (39.4)	954 (66.0)	− 0.55	82 (41.1)	− 0.03	78 (40.7)	− 0.03
Hemoglobin category ≥ 12, *n* (%)	78 (37.5)	664 (46.0)	− 0.17	74 (37.2)	0.01	72 (37.4)	0.00
Prior transplant, *n* (%)	171 (82.2)	437 (30.2)	1.23	83 (41.7)	0.96	155 (80.3)	0.05
ECOG PS score 1, *n* (%)	94 (45.2)	854 (59.1)	− 0.28	105 (52.8)	− 0.15	88 (45.8)	− 0.01
Race category, *n* (%)							
Black or African American	6 (2.9)	241 (16.7)	− 0.48	38 (19.1)	− 0.56	6 (2.8)	0.00
Not reported/other	45 (21.6)	269 (18.6)	0.08	38 (19.1)	0.06	42 (21.7)	− 0.00
White	157 (75.5)	935 (64.7)	0.24	123 (61.8)	0.30	145 (75.5)	0.00

Table 1 continued

Variables	CARTITUDE-4 cilta-cel cohort ($n = 208$)	Observed (before weighting)		Base case (weighted)		Base case fully adjusted (weighted)	
		RW cohort ($n = 1445$[a])	SMD	RW cohort ESS ($n = 463$[b])	SMD	RW cohort ESS ($n = 249$[b])	SMD
Male, *n* (%)	116 (55.8)	786 (54.4)	0.03	105 (52.7)	0.06	108 (55.8)	0.00
Female, *n* (%)	92 (44.2)	659 (45.6)	− 0.03	94 (47.3)	− 0.06	85 (44.2)	− 0.00
Type of MM, *n* (%)							
IgG	113 (54.3)	870 (60.2)	− 0.12	125 (62.7)	− 0.17	106 (55.2)	− 0.02
Light chain	47 (22.6)	228 (15.8)	0.17	24 (11.9)	0.27	39 (20.2)	0.06
Other	48 (23.1)	347 (24.0)	− 0.02	50 (25.4)	− 0.05	47 (24.6)	− 0.04

The base case analysis adjusted for refractory status, time to progression on last regimen, cytogenetic risk, ISS stage, number of prior LOT, years since MM diagnosis, age, and hemoglobin. The fully adjusted analysis adjusted for all variables in the base case, plus prior stem cell transplant, ECOG PS, race, sex, and type of MM

Cilta-cel ciltacabtagene autoleucel, *ECOG PS* Eastern Cooperative Oncology Group performance status, *ESS* effective sample size, *IgG* immunoglobulin G, *IPTW* inverse probability of treatment weighting, *ISS* International Staging System, *LOT* line of therapy, *MM* multiple myeloma, *PI* proteasome inhibitor, *RW* real-world, *SMD* standardized mean difference

[a]1445 eligible LOT corresponding to 932 patients

[b]Weighted patient numbers were rounded to whole numbers

[c]In the RW cohort, high-risk cytogenetics included any of the following: del17p, t(4;14), or t(14;16). In the CARTITUDE-4 cilta-cel cohort, high-risk cytogenetics included any of the following: del17p, t(4;14), t(14;16), or gain/amp(1q)

vs 8.3 months; HR 0.28 [95% CI 0.22–0.38]; $p < 0.001$) (Supplemental Fig. S2), RW-PFS (median NR vs 8.3 months; HR 0.29 [95% CI 0.22–0.38]; $p < 0.001$) (Fig. 2b), and TTNT were significantly longer (median NR vs 9.9 months; HR 0.31 [95% CI 0.23–0.40]; $p < 0.001$) (Fig. 3b). The OS was similar in patients in the cilta-cel cohort compared with patients in the RW cohort after adjustment (median NR in both cohorts; HR 0.78 [95% CI 0.52–1.16]; $p = 0.222$) (Fig. 4b). All *p* values were based on IPTW.

Sensitivity analyses using doubly robust and multivariable regression, as well as first patient case weighting, yielded similar results (Supplemental Table S3 and S4).

DISCUSSION

This ITC study compared cilta-cel from the CARTITUDE-4 study with RW physician's choice of treatment from the Flatiron Health MM cohort, using propensity scores to align patient populations. Cilta-cel demonstrated superiority over the RW cohort for all outcomes, with similar favorable results in the fully adjusted analysis. Results from the base case analysis showed that cilta-cel reduced the risk of progression or death by 71%, reduced the risk of progression, initiating next treatment, or death by 71%, reduced the risk of initiation of the next LOT or death by 68%, and reduced the risk of death by 41% compared with the RW cohort. Results were consistent with the base case and fully adjusted analyses when doubly robust or multivariable regression were used in place of IPTW. Overall, the robustness and consistency of these findings across all analyses suggest that cilta-cel represents a promising treatment option for patients with MM in earlier LOT who are refractory to lenalidomide.

The strength of the control arm used in the present ITC study provided additional confidence in the findings. It captured the most

Table 2 Treatment regimens in the RW cohort in ≥ 1% of patients

Treatment regimen, *n* (%)	*N* = 1445
Other drug combination[a]	256 (17.7)
DPd	231 (16.0)
Others	120 (8.3)
Daratumumab monotherapy	118 (8.2)
DKd	108 (7.5)
DVd	98 (6.8)
KPd	64 (4.4)
Pd	57 (3.9)
Kd	43 (3.0)
Clinical trial[b]	39 (2.7)
CyKd	39 (2.7)
Rd	34 (2.4)
EloPd	31 (2.1)
Vd	27 (1.9)
DRd	26 (1.8)
PVd	22 (1.5)
CyVd	21 (1.5)
IsaKd	21 (1.5)

Percentages are calculated with the number of eligible lines of therapy in the all-treated analysis set as denominator ($N = 1445$). Patients can be counted in more than 1 regimen or combination if they have received more than 1 combination in their treatment before progression or death

Cy cyclophosphamide, *d* dexamethasone, *D* daratumumab, *Elo* elotuzumab, *IMiD* immunomodulatory drug, *Isa* isatuximab, *K* carfilzomib, *MM* multiple myeloma, *NCCN* National Comprehensive Cancer Network, *P* pomalidomide, *PI* proteasome inhibitor, *R* lenalidomide, *V* bortezomib

[a]Included all drugs not recommended as regimens for the treatment of MM by NCCN, which may include any PI, IMiD, anti-CD38 monoclonal antibody, melphalan, cyclophosphamide, or selinexor

[b]Details on the specific drug(s) being used in the context of a clinical trial were unavailable in the Flatiron Health database

recent innovative regimens available in clinical practice, as this analysis included patients treated from 2020 to 2024. In the unadjusted RW cohort, the median PFS, RW-PFS, TTNT, and OS were 8.1, 8.1, 9.9, and 45.3 months, respectively. Compared with the present analysis, similar results for median PFS (10.7 months) but not median OS (23.8 months) were observed in a RW, retrospective study in patients who were lenalidomide refractory [30]. In another RW cohort [31], median OS (21.5 months) was also lower than that observed in our RW cohort in lenalidomide-refractory patients with 1–3 prior LOT. However, considering that CARTITUDE-4 is an international study with study centers in the USA, Europe, Asia, and Australia, whereas the Flatiron data are from the USA only, the comparison with the other regions of the world may be different.

The current analysis was conducted in patients with lenalidomide-refractory MM. In CARTITUDE-4, the refractory status was defined prospectively using trial criteria, whereas in the RW cohort, it relied on retrospective EHR-based proxies, which might lead to overestimated refractoriness. Further, over 50 distinct treatment regimens were included in the RW cohort and patient numbers in various treatment groups (e.g., anti-CD38-based regimens or non-CD38-based therapies) were limited, resulting in insufficient data to carry out meaningful subgroup or stratified analysis. Limitations of the present analysis included the potential for residual confounding, which is not uncommon in a nonrandomized study. However, the availability of individual patient-level data from both cohorts enabled adjustment for imbalances in important prognostic factors. Although the process ensured key clinical factors were balanced between the two patient populations (i.e., one included participants in the international trial CARTITUDE-4 who received cilta-cel, the other included patients who received care from US academic and community cancer centers), total plasmacytomas and LDH levels were unavailable a priori in the de-identified database for the RW cohort. In addition, the missingness in the cytogenetic risk between the two data sources may present different risk mixes, and the actual distributions of the high-risk and

Table 3 IPTW base case analysis and fully adjusted analysis results

Outcome/Analysis	CARTITUDE-4 vs RW cohort		
	Median, months	HR (95% CI)	*P* value
PFS			
Unadjusted	NR vs 8.1	0.32 (0.25–0.40)	< 0.001
Base case analysis	NR vs 8.2	0.29 (0.22–0.36)	< 0.001
Fully adjusted analysis	NR vs 8.3	0.28 (0.22–0.38)	< 0.001
RW-PFS			
Unadjusted	NR vs 8.1	0.32 (0.26–0.40)	< 0.001
Base case analysis	NR vs 8.2	0.29 (0.23–0.37)	< 0.001
Fully adjusted analysis	NR vs 8.3	0.29 (0.22–0.38)	< 0.001
TTNT			
Unadjusted	NR vs 9.9	0.35 (0.28–0.43)	< 0.001
Base case analysis	NR vs 9.4	0.32 (0.25–0.41)	< 0.001
Fully adjusted analysis	NR vs 9.9	0.31 (0.23–0.40)	< 0.001
OS			
Unadjusted	NR vs 45.3	0.60 (0.43–0.82)	0.001
Base case analysis	NR vs 45.4	0.59 (0.41–0.84)	0.003
Fully adjusted analysis	NR vs NR	0.78 (0.52–1.16)	0.222

CI confidence interval, *HR* hazard ratio, *IPTW* inverse probability of treatment weighting, *NR* not reached, *OS* overall survival, *PFS* progression-free survival, *RW* real-world, *TTNT* time to next treatment

standard-risk cytogenetics in each cohort were unknown. Matching on missing cytogenetic data was incomplete, albeit the same definition of high-risk cytogenetics was applied to both the cilta-cel and the RW cohorts. An external control arm from a RW data source such as the Flatiron Health database can be used to estimate the relative therapeutic effects of cilta-cel versus RW physician's choice of treatment in clinical practice; however, estimates may be biased if there are significant differences in baseline characteristics between the patient populations. These variations in baseline characteristics can be mitigated by indirect, well-balanced analyses of nonrandomized populations across all variables potentially prognostic of outcomes. ITCs using IPTW methods are used to assess the benefits of a treatment relative to regimens used in clinical practice and ensure unbiased comparative effectiveness data that can assist physicians and payers in making decisions. IPTW methods are a robust and feasible approach due to the access of patient-level data. Another limitation is that information on response outcomes, such as overall and complete response rates, were unavailable for the RW cohort, which prevented comparative effectiveness analyses of these outcomes. Furthermore, monitoring of patients in RW databases is less rigorous and subject to greater variation than in clinical trials, where patients are regularly monitored. Lastly, PFS data quality may also be a limitation, as progression data such as bone marrow plasma cells, bone lesions, and the size of soft-tissue plasmacytomas were more likely to be missing for patients in the RW cohort than in CARTITUDE-4. To avoid underestimating progression in the RW cohort, we assessed RW-PFS, which accounts

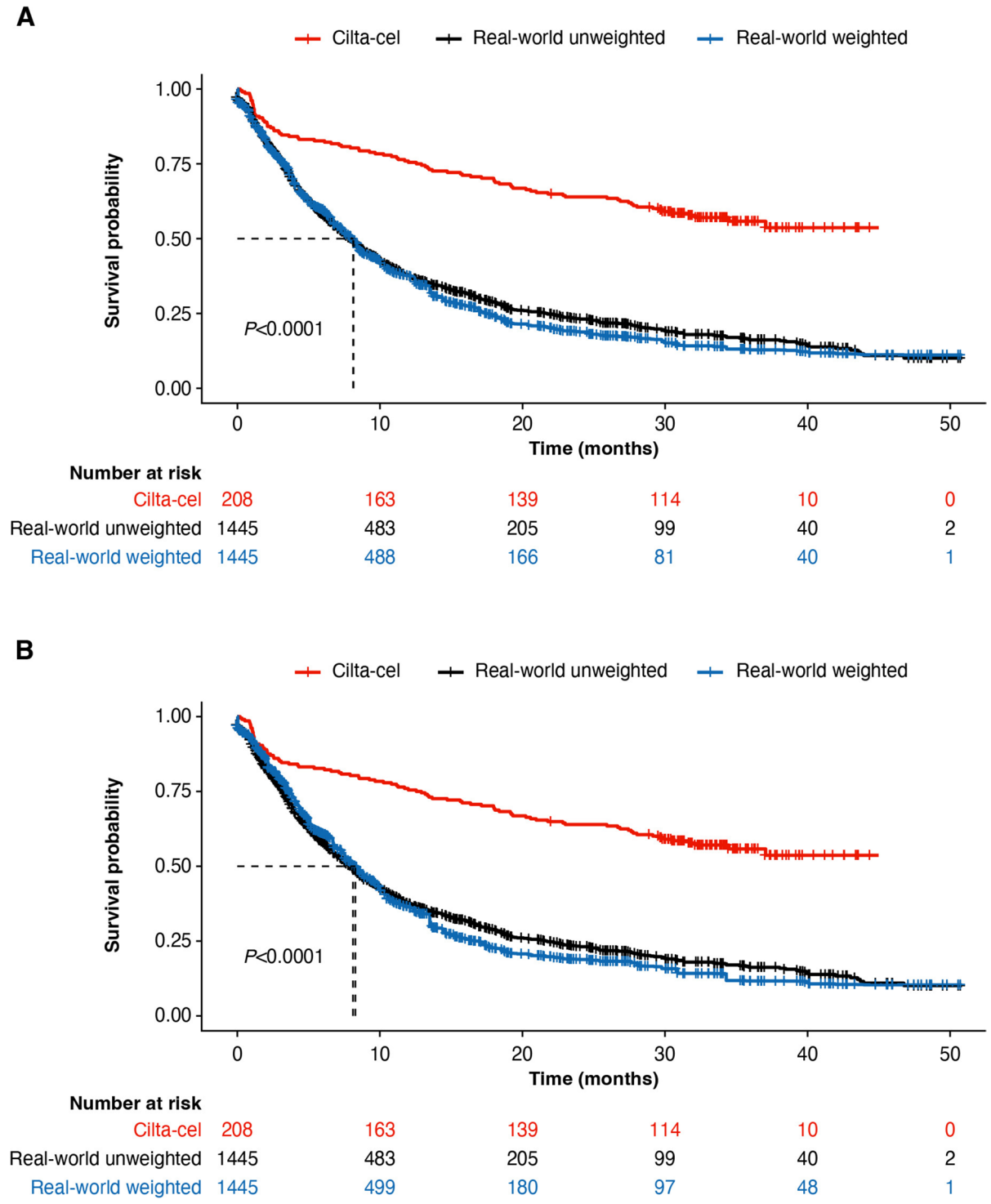

Fig. 2 Adjusted (ATT-weighted) Kaplan–Meier plots of real-world progression-free survival for **a** base case analysis and **b** fully adjusted analysis. *ATT* average treatment effect in the treated, *cilta-cel* ciltacabtagene autoleucel

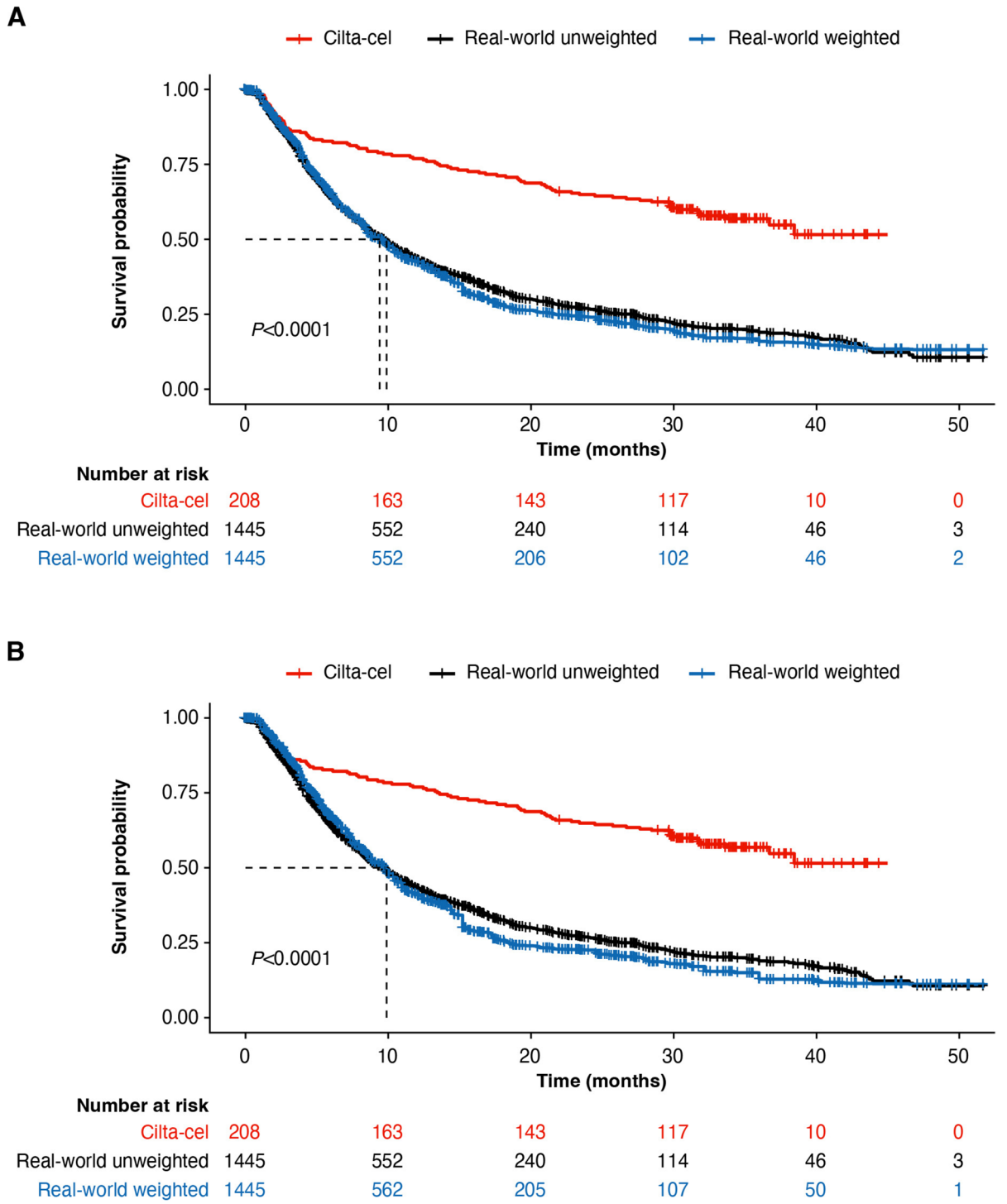

Fig. 3 Adjusted (ATT-weighted) Kaplan–Meier plots of time to next treatment for **a** base case analysis and **b** fully adjusted analysis. *ATT* average treatment effect in the treated, *cilta-cel* ciltacabtagene autoleucel

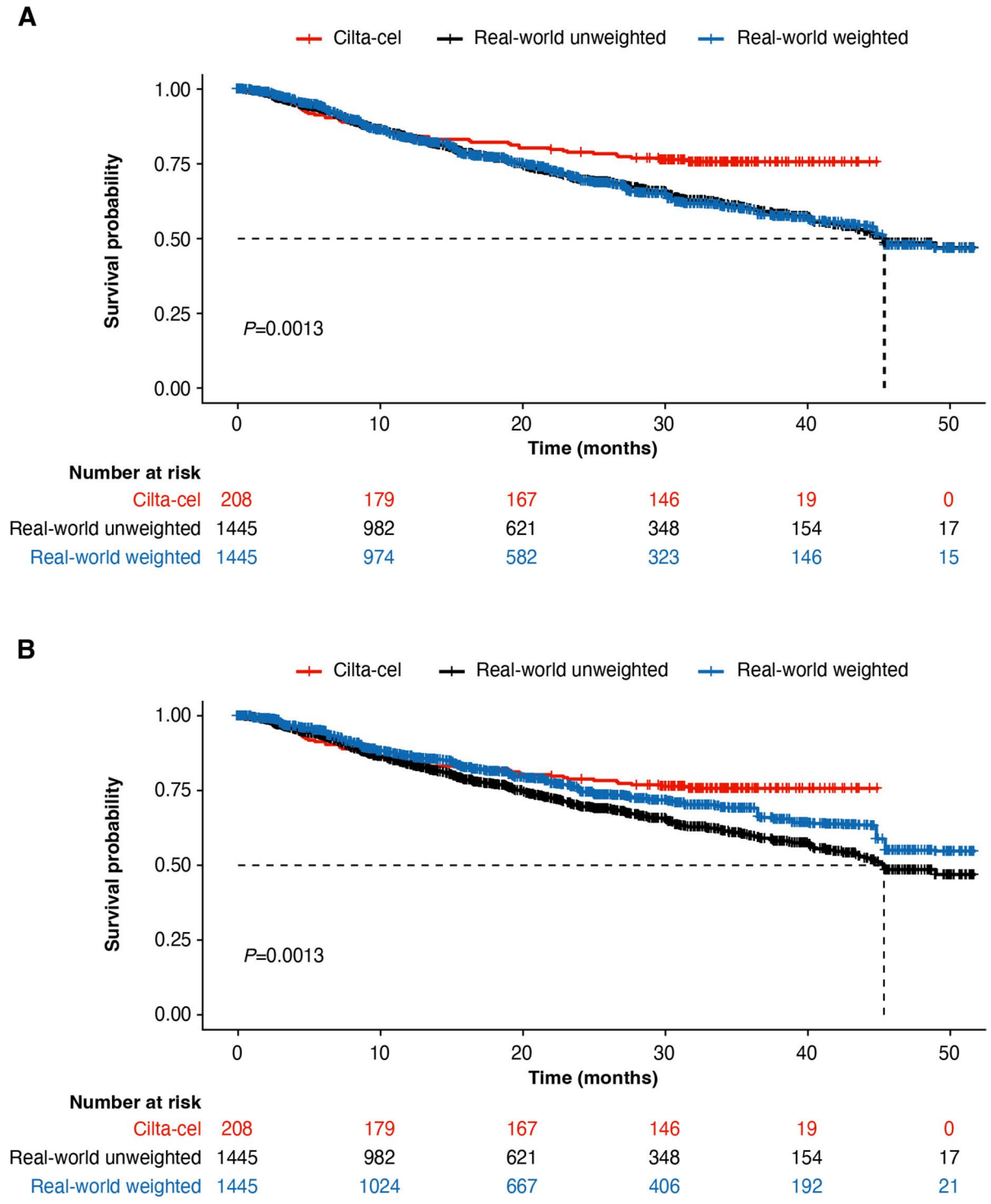

Fig. 4 Adjusted (ATT-weighted) Kaplan–Meier plots of overall survival for **a** base case analysis and **b** fully adjusted analysis. *ATT* average treatment effect in the treated, *cilta-cel* ciltacabtagene autoleucel

for TTNT. Results were consistent with the PFS comparison. OS data quality is not expected to be affected, as methods to assess OS have been validated for the de-identified database [32].

CONCLUSION

In our analyses, ITC methods were used to compare patient-level data from the CARTITUDE-4 clinical study with an external control arm created from eligible patients with lenalidomide-refractory MM after 1–3 prior LOT who received RW treatment in a de-identified database. After adjusting for baseline characteristics, cilta-cel showed statistically significant superiority for PFS, RW-PFS, TTNT, and OS versus RW treatment. Sensitivity analyses supported the results of the base case analyses. On the basis of these results, cilta-cel provides superior clinical benefit compared with RW physician's choice of conventional regimens, highlighting the value of cilta-cel as an effective therapy in patients with lenalidomide-refractory MM as early as first relapse.

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Author Contributions. Cyrille Touzeau, Brea Lipe, Abdullah M Khan, Binod Dhakal, Sandhya Nair, Jianming He, João Mendes, Seina Lee, Carolina Lonardi, Ana Slaughter, Nikoletta Lendvai, Jordan M Schecter, Diana Chen, Man Zhao, Tzu-min Yeh, Xavier Leleu, Noemí Puig, Dominik Dytfeld, Elena Zamagni, Katja Weisel, Lionel Karlin, Michel Delforge, Paolo Corradini, Roberto Mina, Wilfried Roeloffzen, and Surbhi Sidana contributed to the study conception and design, material preparation, and data collection. Cyrille Touzeau, Brea Lipe, Abdullah M Khan, Binod Dhakal, Sandhya Nair, Jianming He, João Mendes, Seina Lee, Carolina Lonardi, Ana Slaughter, Nikoletta Lendvai, Jordan M Schecter, Diana Chen, Man Zhao, Tzu-min Yeh, Xavier Leleu, Noemí Puig, Dominik Dytfeld, Elena Zamagni, Katja Weisel, Lionel Karlin, Michel Delforge, Paolo Corradini, Roberto Mina, Wilfried Roeloffzen, and Surbhi Sidana performed the analysis and contributed to the development of the first and subsequent drafts of the manuscript. Cyrille Touzeau, Brea Lipe, Abdullah M Khan, Binod Dhakal, Sandhya Nair, Jianming He, João Mendes, Seina Lee, Carolina Lonardi, Ana Slaughter, Nikoletta Lendvai, Jordan M Schecter, Diana Chen, Man Zhao, Tzu-min Yeh, Xavier Leleu, Noemí Puig, Dominik Dytfeld, Elena Zamagni, Katja Weisel, Lionel Karlin, Michel Delforge, Paolo Corradini, Roberto Mina, Wilfried Roeloffzen, and Surbhi Sidana read and approved the final manuscript. Cyrille Touzeau, Brea Lipe, Abdullah M Khan, Binod Dhakal, Sandhya Nair, Jianming He, João Mendes, Seina Lee, Carolina Lonardi, Ana Slaughter, Nikoletta Lendvai, Jordan M Schecter, Diana Chen, Man Zhao, Tzu-min Yeh, Xavier Leleu, Noemí Puig, Dominik Dytfeld, Elena Zamagni, Katja Weisel, Lionel Karlin, Michel Delforge, Paolo Corradini, Roberto Mina, Wilfried Roeloffzen, and Surbhi Sidana meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Declarations

Conflict of Interest. Cyrille Touzeau: Honoraria – AbbVie, Amgen, Bristol Myers Squibb/Celgene, Janssen, Pfizer, Sanofi, Takeda; consulting or advisory role – AbbVie, Amgen, Bristol Myers Squibb/Celgene, Janssen, Pfizer, Takeda; research funding – Sanofi (Inst); travel, accommodations, expenses – Johnson & Johnson/Janssen, Pfizer, Sanofi. Brea Lipe: Consulting or advisory role – AbbVie, GlaxoSmithKline, Janssen, Karyopharm Therapeutics, Pfizer, Sanofi; research funding – Amgen. Abdullah M Khan: Speakers' bureau – Amgen, Sanofi; research funding – Bristol Myers Squibb, Sanofi; travel, accommodations, expenses – Bristol Myers Squibb. Binod Dhakal: Consulting or advisory role – Amgen, Arcellx, Genentech/Roche, GlaxoSmithKline, Janssen Oncology, Natera, Pfizer, Sanofi, Pfizer, Takeda; speakers bureau – Janssen Oncology; honoraria – Celgene, GlaxoSmithKline, Karyopharm Therapeutics, Sanofi; research funding – Amgen (Inst), Arcellx (Inst), CARsgen Therapeutics (Inst), Bristol Myers Squibb/Celgene (Inst), GlaxoSmithKline, Janssen Oncology (Inst), Sanofi (Inst). Man Zhao: Employment – Haisco Pharmaceutical (I), IQVIA, Janssen; research funding – Haisco Pharmaceutical (I); patents, royalties, other intellectual property – Haisco Pharmaceutical (I). Xavier Leleu: Honoraria – Bristol Myers Squibb, Takeda. Noemí Puig: Honoraria – Amgen, Celgene, Janssen, Pfizer, Sanofi, Takeda, The Binding Site; consulting or advisory role – Amgen, Celgene, Janssen, Pfizer, Sanofi, Takeda, The Binding Site; speakers bureau – Celgene; research funding – Amgen, Celgene, Janssen, Pfizer, Takeda; travel, accommodations, expenses – Amgen, Celgene, Janssen, Pfizer, Takeda, The Binding Site. Dominik Dytfeld: Honoraria – Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Pfizer; consulting or advisory role – Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Pfizer; research funding – Bristol Myers Squibb, Janssen; travel, accommodations, expenses – Amgen, Janssen, Bristol Myers Squibb, Pfizer. Elena Zamagni: Honoraria and advisory role – Amgen, Bristol Myers Squibb, GlaxoSmithKline, Janssen, Menarini-Stemline, Oncopeptides, Pfizer, Sanofi. Katja Weisel: Honoraria – AbbVie, Adaptive Biotechnologies, Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen (Inst), Janssen-Cilag, Karyopharm Therapeutics, Menarini, Novartis, Oncopeptides, Pfizer, Roche, Sanofi, Stemline Therapeutics, Takeda; consulting or advisory role – Adaptive Biotechnologies, Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen-Cilag, Karyopharm Therapeutics, Menarini, Oncopeptides, Roche, Sanofi, Takeda; research funding – AbbVie (Inst), Amgen (Inst), Bristol Myers Squibb/Celgene (Inst), Celgene (Inst), GlaxoSmithKline (Inst), Janssen-Cilag (Inst), Sanofi (Inst); travel, accommodations, expenses – Amgen, Bristol Myers Squibb, Celgene, GlaxoSmithKline, Janssen-Cilag, Menarini, Takeda. Lionel Karlin: Honoraria – AbbVie, Amgen, Celgene, Johnson & Johnson, Takeda; consulting or advisory role – Amgen, Celgene, Johnson & Johnson, Takeda; travel, accommodations, expenses – Amgen, Johnson & Johnson. Michel Delforge: Honoraria – Amgen, Bristol Myers Squibb, GlaxoSmithKline, Johnson & Johnson; consulting or advisory role – Johnson & Johnson. Paolo Corradini: Honoraria – AbbVie, Amgen, Celgene, Gilead/Kite, Janssen, Novartis, Roche, Sanofi, Takeda; consulting or advisory role – AbbVie, ADC Therapeutics, Amgen, BeiGene, Celgene, Daiichi Sankyo, Gilead/Kite, GlaxoSmithKline, Incyte, Janssen, Kyowa Kirin, Nerviano Medical Science, Novartis, Roche, Sanofi, Takeda. Roberto Mina: Honoraria – AbbVie, Amgen, Bristol Myers Squibb, Janssen Pharmaceuticals, Sanofi; consulting or advisory role – Bristol Myers Squibb, GlaxoSmithKline, Janssen-Cilag EMEA, Janssen Pharmaceuticals, Pfizer, Takeda. Wilfried Roeloffzen: Honoraria – Amgen (Inst), Fondation Sanofi Espoir (Inst), Janssen Biotech (Inst); consulting or advisory role – Bristol Myers Squibb (Inst); travel, accommodations, expenses – AbbVie. Surbhi Sidana: Consulting or advisory role – AbbVie, BiolineRx, Bristol Myers Squibb/

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