ORIGINAL ARTICLE

Cilta-cel or Standard Care in Lenalidomide-Refractory Multiple Myeloma

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ABSTRACT

BACKGROUND

Ciltacabtagene autoleucel (cilta-cel), a B-cell maturation antigen (BCMA)–directed CAR T-cell therapy, is effective in heavily pretreated patients with relapsed or refractory multiple myeloma. We investigated cilta-cel in earlier treatment lines in patients with lenalidomide-refractory disease.

METHODS

In this phase 3, randomized, open-label trial, we assigned patients with lenalidomide-refractory multiple myeloma to receive cilta-cel or the physician's choice of effective standard care. All the patients had received one to three previous lines of treatment. The primary outcome was progression-free survival.

RESULTS

A total of 419 patients underwent randomization (208 to receive cilta-cel and 211 to receive standard care). At a median follow-up of 15.9 months (range, 0.1 to 27.3), the median progression-free survival was not reached in the cilta-cel group and was 11.8 months in the standard-care group (hazard ratio, 0.26; 95% confidence interval [CI], 0.18 to 0.38; P<0.001). Progression-free survival at 12 months was 75.9% (95% CI, 69.4 to 81.1) in the cilta-cel group and 48.6% (95% CI, 41.5 to 55.3) in the standard-care group. More patients in the cilta-cel group than in the standard-care group had an overall response (84.6% vs. 67.3%), a complete response or better (73.1% vs. 21.8%), and an absence of minimal residual disease (60.6% vs. 15.6%). Death from any cause was reported in 39 patients and 46 patients, respectively (hazard ratio, 0.78; 95% CI, 0.5 to 1.2). Most patients reported grade 3 or 4 adverse events during treatment. Among the 176 patients who received cilta-cel in the as-treated population, 134 (76.1%) had cytokine release syndrome (grade 3 or 4, 1.1%; no grade 5), 8 (4.5%) had immune effector cell–associated neurotoxicity syndrome (all grade 1 or 2), 1 had movement and neurocognitive symptoms (grade 1), 16 (9.1%) had cranial nerve palsy (grade 2, 8.0%; grade 3, 1.1%), and 5 (2.8%) had CAR-T–related peripheral neuropathy (grade 1 or 2, 2.3%; grade 3, 0.6%).

CONCLUSIONS

A single cilta-cel infusion resulted in a lower risk of disease progression or death than standard care in lenalidomide-refractory patients with multiple myeloma who had received one to three previous therapies. (Funded by Janssen and Legend Biotech; CARTITUDE-4 ClinicalTrials.gov number, NCT04181827.)

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A Quick Take is available at NEJM.org

Most patients with multiple myeloma have a relapse after standard treatment,[1,2] and outcomes worsen with each subsequent line of therapy.[3-5] Lenalidomide is an immunomodulator that is recommended[6,7] for newly diagnosed and relapsed or refractory multiple myeloma. The use of lenalidomide has become widespread as early-line treatment, including as maintenance therapy.[1,8] The frequency of lenalidomide resistance early in the treatment journey is increasing,[1,8] which has led to a growing need for new, effective therapies for lenalidomide-refractory disease.[8] High treatment attrition — only 13 to 35% of patients receive four or more lines of therapy — also highlights the need to use effective therapies early.[9]

In early trials, ciltacabtagene autoleucel (cilta-cel), a chimeric antigen receptor T-cell (CAR-T) therapy directed against B-cell maturation antigen (BCMA), led to early, deep, and durable responses in patients with relapsed or refractory multiple myeloma. In the phase 1b–2 CARTITUDE-1 trial involving patients who had received at least three lines of therapy, the median progression-free survival was 34.9 months.[10-12] The phase 2 CARTITUDE-2 trial showed the efficacy of cilta-cel in small groups (cohorts A and B) at earlier disease stages, with response rates of 95 to 100% and an estimated duration of response of at least 12 months in 79 to 89% of patients who had a response. After approximately 1.5 years of follow-up, 75 to 90% of patients remained progression-free.[13,14] In a phase 3 trial of another CAR-T therapy, idecabtagene vicleucel, involving patients who had received two to four lines of therapy for multiple myeloma, investigators found a median progression-free survival of 13.3 months (hazard ratio, 0.49 as compared with standard treatments).[15]

We conducted the phase 3 CARTITUDE-4 trial to compare cilta-cel with the physician's choice of either of two highly effective standard-of-care therapies in patients with lenalidomide-refractory multiple myeloma after one to three lines of therapy. Here, we report the efficacy and safety results from the interim analysis.

Methods

Trial Design and Patients

We conducted this open-label, randomized trial at 81 sites in the United States, Europe, Asia, and Australia. Eligible patients had lenalidomide resistance[16] and had received one to three lines of therapy, including a proteasome inhibitor and an immunomodulatory drug. All the patients had an Eastern Cooperative Oncology Group performance-status score of 1 or less (on a scale ranging from 0 to 5, with higher scores indicating greater disability). In addition, none of the patients had received CAR-T therapy or BCMA-targeted treatment. Full eligibility criteria are provided in the protocol, available with the full text of this article at NEJM.org.

Randomization and Treatments

Patients were assigned in a 1:1 ratio by means of computer-generated randomization to receive standard care (physician's choice of pomalidomide, bortezomib, and dexamethasone [PVd][17] or daratumumab, pomalidomide, and dexamethasone [DPd])[18] or a single cilta-cel infusion, administered after the physician's choice of bridging therapy (PVd or DPd). Randomization was stratified according to the selection of PVd or DPd, disease severity according to the International Staging System (ISS) at screening (I, II, or III), and the number of previous lines of therapy (1 or 2 to 3).

In the standard-care group, DPd was administered in 28-day cycles and PVd in 21-day cycles until disease progression (see the Supplementary Appendix, available at NEJM.org). According to the protocol, if patients had disease progression after standard treatment, crossover from the standard-care group to the cilta-cel group was not permitted. Patients in the cilta-cel group underwent apheresis, followed by at least one bridging therapy cycle (with the number of cycles based on clinical status and cilta-cel manufacturing time) and lymphodepletion (300 mg of cyclophosphamide per square meter of body-surface area and 30 mg of fludarabine per square meter daily for 3 days). Five to seven days after the initiation of lymphodepletion, a single cilta-cel infusion (target dose, 0.75×10^6 CAR+ viable T cells per kilogram of body weight) was administered. Patients in the cilta-cel group who had confirmed disease progression during bridging therapy or lymphodepletion were assessed as having a progression event and could receive cilta-cel as subsequent therapy at the investigator's discretion.

OUTCOMES AND ASSESSMENTS

The primary outcome was progression-free survival, which was defined as the time from randomization to the first documentation of disease progression or death. The key secondary outcomes were sequentially tested in order at each prespecified significance level and included complete response or better, overall response, minimal residual disease (MRD) negativity, overall survival, and worsening of patient-reported symptoms as assessed by the Multiple Myeloma Symptom and Impact Questionnaire. Additional secondary outcomes included adverse events and cilta-cel pharmacokinetics.

Treatment responses and disease progression were determined according to the International Myeloma Working Group criteria[16] with the use of a validated computer algorithm.[19] Blood and 24-hour urine samples were analyzed at a central laboratory until the confirmation of disease progression. The presence of MRD was assessed centrally by next-generation sequencing (clonoSEQ, version 2.0, Adaptive Biotechnologies) on bone marrow samples at a sensitivity of 1.0×10^{-5}.

Cytokine release syndrome and immune effector cell–associated neurotoxicity syndrome (ICANS) were graded according to consensus criteria of the American Society for Transplantation and Cellular Therapy.[20] Other adverse events, including investigator-assessed non-ICANS neurotoxicity, were graded according to the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 5.0.[21]

OVERSIGHT

The trial was funded by Janssen and Legend Biotech, and representatives of the companies were involved in the collection, analysis, and interpretation of the data. The trial was conducted in accordance with the Declaration of Helsinki and International Council for Harmonisation guidelines for Good Clinical Practice. All patients provided written informed consent. The independent ethics committee or institutional review board at each site approved the trial protocol. A data and safety monitoring committee monitored all safety data collected in the clinical program and evaluated the interim safety and efficacy data (see the Supplementary Appendix).

All the authors contributed to trial conduct, data analyses, and drafting of the manuscript and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Medical writing assistance was funded by Janssen Global Services; all drafts were critically reviewed, revised, and approved by the authors.

STATISTICAL ANALYSIS

We estimated that the enrollment of 400 patients and the occurrence of 250 events of disease progression or death would provide the trial with 90% power to detect a relative reduction of 35% in the risk of disease progression or death. This calculation was based on the results of a log-rank test at an overall two-sided alpha level of 0.05, under a group sequential design with one interim analysis to evaluate the primary outcome, a prespecified analysis to be conducted after the occurrence of approximately 188 primary-outcome events. The significance level that was required to establish superiority was determined on the basis of the number of events that were observed, with the use of O'Brien–Fleming boundaries and implemented by the Lan–DeMets alpha-spending method. Details are provided in the Supplementary Appendix.

Efficacy was evaluated in the intention-to-treat population, which included all the patients who had undergone randomization. Adverse events were evaluated in the safety population, which included all the patients who had received any portion of a trial treatment. Adverse events that were specific to CAR-T therapy were evaluated in the as-treated population (patients who had received cilta-cel as the trial treatment).

Progression-free survival was estimated by means of the Kaplan–Meier method. We used a stratified constant piecewise weighted log-rank test (in which a weight of 0 was assigned for the log-rank statistic for weeks 0 to 8 after randomization and a weight of 1 after that period)[22,23] to compare the trial groups, because both groups received the same treatments during the bridging period. The hazard ratio and its two-sided 95% confidence intervals were estimated with the use of a stratified Cox regression model with treatment as the sole explanatory variable. We used the Kaplan–Meier method and stratified log-rank tests to analyze other time-to-event outcomes. Binary outcomes were analyzed with the use of stratified Cochran–Mantel–Haenszel tests. The worsening of symptoms was defined as a meaningful increase (estimated by distribution-

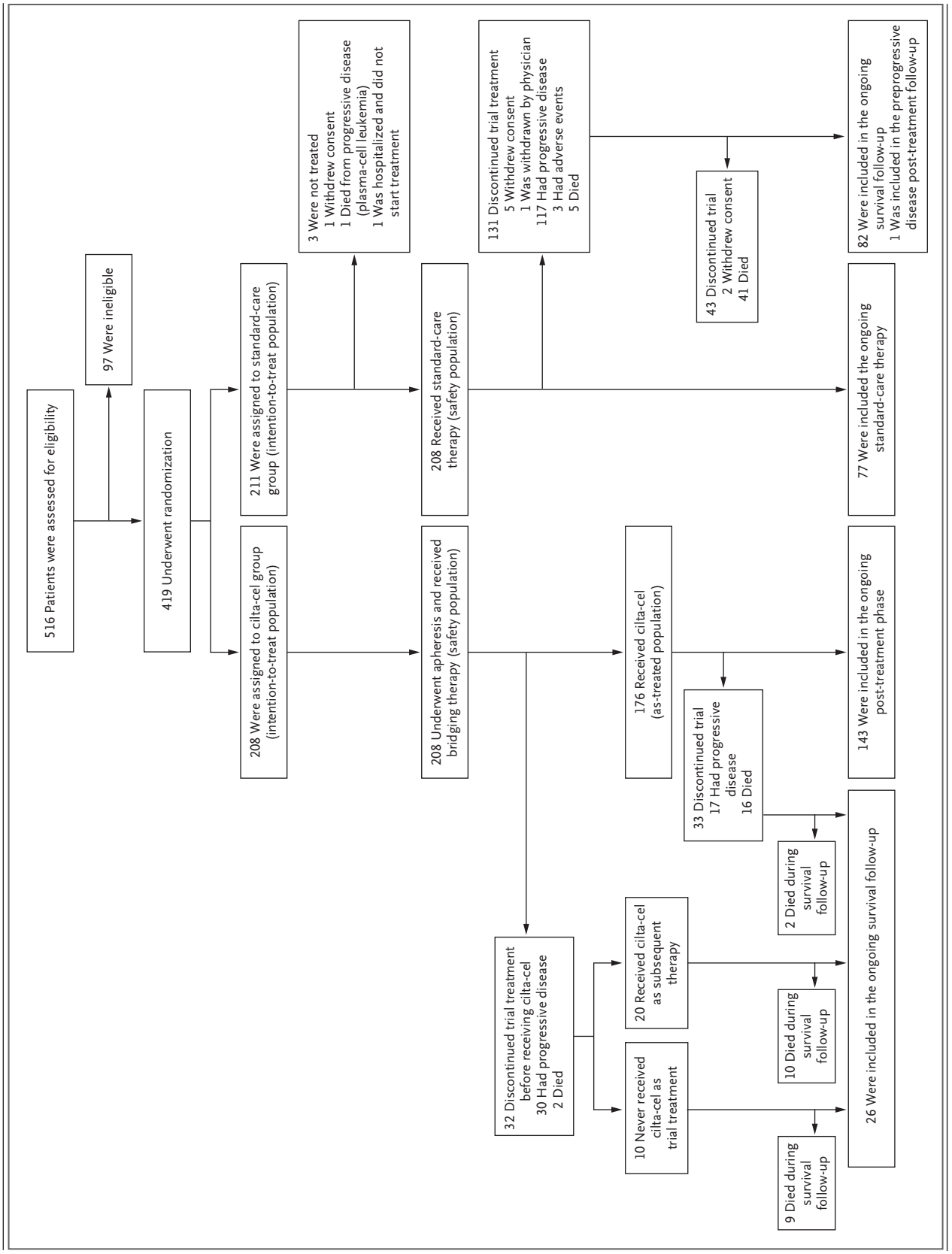

Figure 1 (facing page). Enrollment and Outcomes.
Of the 208 patients who were assigned to receive cilta-cel, 176 (84.6%) actually received the treatment (as-treated population). The remaining 32 patients discontinued trial participation before receiving cilta-cel, mainly because of disease progression during bridging therapy or lymphodepletion. Of these 32 patients, 20 received cilta-cel as a subsequent therapy. Of the 211 patients who were assigned to received standard care, 208 (98.6%) received it; of these patients, 131 (63.0%) discontinued treatment, primarily because of disease progression. A total of 21 deaths occurred in the cilta-cel group during follow-up after a progression event. The 26 patients in the ongoing survival follow-up after progression included 1 patient who never received cilta-cel as a trial treatment, 10 who received cilta-cel as subsequent therapy, and 15 who discontinued the trial in the as-treated population.

based methods of at least half a standard deviation of pooled baseline values) without a subsequent reduction in myeloma symptoms.

RESULTS

PATIENTS

From July 10, 2020, through November 17, 2021, a total of 419 patients were randomly assigned to receive cilta-cel (208 patients) or standard care (211 patients). Of the patients in the standard-care group, 183 received DPd and 28 received PVd. All the patients in the cilta-cel group received bridging therapy (DPd in 182 or PVd in 26).

Of the patients in the cilta-cel group, 176 (84.6%) actually received cilta-cel (as-treated population). The remaining 32 patients discontinued trial participation before receiving cilta-cel, predominantly because of disease progression during bridging therapy or lymphodepletion. Of these patients, 20 received cilta-cel as a subsequent therapy. No patients discontinued a trial treatment because of drug-manufacturing failure. The median time from the receipt of apheresis material to product release was 44 days (range, 25 to 127) (see the Supplementary Appendix). In the standard-care group, 208 patients (98.6%) received the assigned drug; of these patients, 131 (63.0%) discontinued treatment, primarily because of disease progression (in 56.3%) (Fig. 1). By the data-cutoff date (November 1, 2022), the median follow-up was 15.9 months (range, 0.1 to 27.3).

The characteristics of the patients were well balanced in the two groups (Table 1). The demographic characteristics largely reflected real-world patients with myeloma (Table S1 in the Supplementary Appendix). High-risk cytogenetic features — del17p, t(4;14), t(14;16), or gain/amp(1q) — were identified in 59.4% of the patients in the cilta-cel group and in 62.9% of those in the standard-care group; at least two high-risk cytogenetic abnormalities were identified in 20.7% and 23.2%, respectively. Soft-tissue plasmacytomas were identified at baseline in 21.2% of the patients in the cilta-cel group and in 16.6% in the standard-care group. In the cilta-cel group, 30 patients (14.4%) had triple-class drug resistance; 50 (24.0%) had resistance to anti-CD38 antibody. The median cilta-cel dose was 0.71×10^6 cells per kilogram. In the standard-care group, patients received a median of 12 treatment cycles (range, 1 to 28).

EFFICACY

Cilta-cel resulted in a significantly lower risk of disease progression or death than standard care (hazard ratio, 0.26; 95% confidence interval [CI], 0.18 to 0.38; P<0.001). The median duration of progression-free survival was not reached in the cilta-cel group and was 11.8 months (95% CI, 9.7 to 13.8) in the standard-care group (Fig. 2). At 12 months in the intention-to-treat population, progression-free survival was 75.9% (95% CI, 69.4 to 81.1) in the cilta-cel group and 48.6% (95% CI, 41.5 to 55.3) in the standard-care group. An unweighted sensitivity analysis showed results that were similar to those in the primary analysis (Table S2). Similar effects were seen in all subgroups of patients, including those with high-risk cytogenetic features, soft-tissue plasmacytomas, triple-class–refractory disease, and other high-risk disease factors, as well as across different numbers of previous lines of therapy (Fig. S1).

During the first 8 weeks after randomization, disease progression or death occurred in 22 patients in the cilta-cel group and in 8 patients in the standard-care group. All these events occurred before the infusion of cilta-cel while patients were receiving the same therapy in the two groups. During the bridging period, patients in the cilta-cel group received doses of pomalidomide and bortezomib that were approximately 14% lower than those in the standard-care group, which could have affected the primary outcome.

More patients in the cilta-cel group than in

Table 1. Demographic and Disease Characteristics of the Patients at Baseline.*

Characteristic	Cilta-cel (N=208)	Standard Care (N=211)
Demographic features		
Median age (range) — yr	61.5 (27–78)	61.0 (35–80)
Male sex — no. (%)	116 (55.8)	124 (58.8)
Race or ethnic group — no. (%)†		
Asian	16 (7.7)	20 (9.5)
Black	6 (2.9)	7 (3.3)
White	157 (75.5)	157 (74.4)
Other	1 (0.5)	1 (0.5)
Missing data	28 (13.5)	26 (12.3)
Hispanic or Latino ethnic group — no. (%)†		
Yes	18 (8.7)	10 (4.7)
No	152 (73.1)	165 (78.2)
Missing data	38 (18.3)	36 (17.1)
Geographic region — no. (%)		
Europe	128 (61.5)	129 (61.1)
North America	32 (15.4)	32 (15.2)
Asia	27 (13.0)	25 (11.8)
Australia	21 (10.1)	25 (11.8)
Clinical history		
ECOG performance-status score — no. (%)‡		
0	114 (54.8)	121 (57.3)
1	93 (44.7)	89 (42.2)
2	1 (0.5)	1 (0.5)
International Staging System stage — no. (%)		
I	136 (65.4)	132 (62.6)
II	60 (28.8)	65 (30.8)
III	12 (5.8)	14 (6.6)
Median time since diagnosis (range) — yr	3.0 (0.3–18.1)	3.4 (0.4–22.1)
Presence of soft-tissue plasmacytomas — no. (%)§	44 (21.2)	35 (16.6)
Bone marrow plasma cells ≥60% — no./total no. (%)¶	42/206 (20.4)	43/208 (20.7)
Cytogenetic risk — no./total no. (%)		
Standard	69/207 (33.3)	70/210 (33.3)
High	123/207 (59.4)	132/210 (62.9)
Gain/amp(1q)	89/207 (43.0)	107/210 (51.0)
del(17p)	49/207 (23.7)	43/210 (20.5)
t(4;14)	30/207 (14.5)	30/210 (14.3)
t(14;16)	3/207 (1.4)	7/210 (3.3)
With ≥2 high-risk abnormalities	43/207 (20.8)	49/210 (23.3)
With del(17p), t(4;14), or t(14;16)	73/207 (35.3)	69/210 (32.9)
Missing data	15/207 (7.2)	8/210 (3.8)
Tumor BCMA expression ≥50% — no. (%)	141 (67.8)	138 (65.4)

Table 1. (Continued.)

Characteristic	Cilta-cel (N=208)	Standard Care (N=211)
Previous lines of therapy — no. (%)		
1	68 (32.7)	68 (32.2)
2	83 (39.9)	87 (41.2)
3	57 (27.4)	56 (26.5)
Previous immunomodulatory drug — no. (%)	208 (100.0)	211 (100.0)
Lenalidomide	208 (100.0)	211 (100.0)
Pomalidomide	8 (3.8)	10 (4.7)
Previous anti-CD38 antibody	53 (25.5)	55 (26.1)
Daratumumab	51 (24.5)	54 (25.6)
Isatuximab	2 (1.0)	2 (0.9)
Previous proteasome inhibitor — no. (%)	208 (100.0)	211 (100.0)
Bortezomib	203 (97.6)	205 (97.2)
Carfilzomib	77 (37.0)	66 (31.3)
Ixazomib	21 (10.1)	21 (10.0)
Triple-class exposure — no. (%)‖	53 (25.5)	55 (26.1)
Penta-drug exposure — no. (%)**	14 (6.7)	10 (4.7)
Refractory status — no. (%)		
Lenalidomide	208 (100.0)	211 (100.0)
Bortezomib	55 (26.4)	48 (22.7)
Carfilzomib	51 (24.5)	45 (21.3)
Any anti-CD38 antibody	50 (24.0)	46 (21.8)
Daratumumab	48 (23.1)	45 (21.3)
Ixazomib	15 (7.2)	17 (8.1)
Pomalidomide	8 (3.8)	9 (4.3)
Triple-class‖	30 (14.4)	33 (15.6)
Penta-drug**	2 (1.0)	1 (0.5)

* BCMA denotes B-cell maturation antigen.
† Race or ethnic group was reported by the patients. Among the patients who were enrolled in the United States, 9 (14.1%) were Black. The designation of "Other" includes American Indian and Alaska Native ethnic groups.
‡ Listed is the latest available performance-status score on the Eastern Cooperative Oncology Group (ECOG) scale that was recorded on or before the initiation of apheresis or cycle 1. All the patients met the inclusion criteria of an ECOG performance-status score of 0 or 1 before randomization.
§ Soft-tissue plasmacytomas include extramedullary and bone-based plasmacytomas with a measurable soft-tissue component.
¶ In the measurement of bone marrow plasma cells, the maximum value from bone marrow biopsy and bone marrow aspirate was selected if both results were available.
‖ Triple-class therapy includes one proteasome inhibitor, one immunomodulatory drug, and one anti-CD38 monoclonal antibody.
** Penta-drug therapy includes at least two proteasome inhibitors, at least two immunomodulatory drugs, and one anti-CD38 monoclonal antibody.

the standard-care group had a complete response or better (73.1% vs. 21.8%), for a risk ratio of 2.9 (95% CI, 2.3 to 3.7; P<0.001) and an odds ratio of 10.3 (95% CI, 6.5 to 16.4) (Table 2 and the Supplementary Appendix). The overall response (partial response or better) was 84.6% and 67.3%, respectively, for a risk ratio of 2.2 (95% CI, 1.5 to 3.1; P<0.001) and an odds ratio of 3.0 (95% CI, 1.8 to 5.0). Among the patients who had a response, an estimated 84.7% in the cilta-cel group

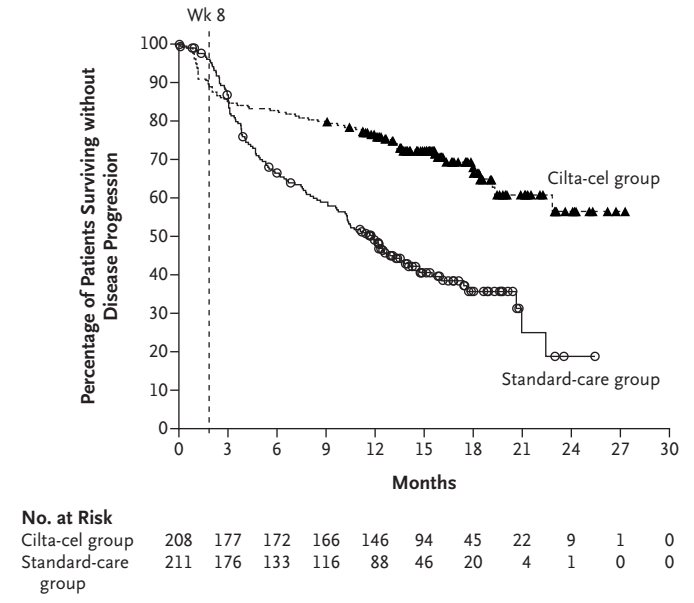

Figure 2. Kaplan–Meier Analysis of Progression-free Survival (Intention-to-Treat Population).

At a median follow-up of 15.9 months (range, 0.1 to 27.3), the median progression-free survival was not reached in the cilta-cel group and was 11.8 months in the standard-care group (hazard ratio, 0.26; 95% confidence interval [CI], 0.18 to 0.38; P<0.001). During the first 8 weeks after randomization (indicated by the vertical dashed line), disease progression or death occurred in 22 patients in the cilta-cel group and in 8 patients in the standard-care group. All these events occurred before the infusion of cilta-cel while patients were receiving the same therapy in the two groups.

as compared with 63.0% in the standard-care group continued to have a response for at least 12 months.

MRD negativity at any time during the trial occurred in 60.6% of the patients in the cilta-cel group and in 15.6% of those in the standard-care group, for a risk ratio of 2.2 (95% CI, 1.8 to 2.6; P<0.001) and an odds ratio of 8.7 (95% CI, 5.4 to 13.9). Among the patients who had evaluable samples (144 in the cilta-cel group and 101 in the standard-care group), MRD negativity occurred in 126 (87.5%) and 33 (32.7%), respectively.

Overall survival data were immature at the time of this report (hazard ratio, 0.78; 95% CI, 0.5 to 1.2; P=0.26). At 12 months, an estimated 84.1% of patients in the cilta-cel group were alive, as compared with 83.6% in the standard-care group.

The median time until symptom worsening was 23.7 months (95% CI, 22.1 to not estimable) in the cilta-cel group and 18.9 months (95% CI, 16.8 to not estimable) in the standard-care group (hazard ratio, 0.42; 95% CI, 0.26 to 0.68). Efficacy results for the 176 patients who received cilta-cel in the as-treated population are provided in Figure S2 and Table S3.

SAFETY

In the safety population (208 patients in each of the two groups), grade 3 or 4 adverse events occurred in 201 patients (96.6%) in the cilta-cel group and in 196 (94.2%) in the standard-care group (Table 3). The most common grade 3 or 4 adverse events in both groups were hematologic; most high-grade cytopenias in patients who received cilta-cel recovered to grade 2 or less by day 60 (Table S4). Serious adverse events were reported in 92 patients (44.2%) in the cilta-cel group and in 81 (38.9%) in the standard-care group (Table S5). In the standard-care group, 3 patients (1.4%) discontinued treatment and 115 (55.3%) had cycle delays because of adverse events.

Second primary cancers were diagnosed in 9 patients (4.3%) in the cilta-cel group and in 14 (6.7%) in the standard-care group; hematologic and cutaneous or noninvasive cancers were the most common (Table S6).

During treatment, infections occurred in 129 patients (62.0%) in the cilta-cel group and in 148 (71.2%) in the standard-care group; of these infections, 26.9% and 24.5%, respectively, were of grade 3 or 4. Coronavirus disease 2019 (Covid-19) that was considered to have occurred during treatment was diagnosed in 29 patients (13.9%) in the cilta-cel group and in 55 (26.4%) in the standard-care group (Table 3). On the basis of adverse-event reporting and laboratory results, the incidence of hypogammaglobulinemia was 90.9% in the cilta-cel group and 71.6% in the standard-care group; on the basis of adverse-event reporting alone, the corresponding incidence was 42.3% and 6.2%, respectively. A total of 65.9% and 12.5% of patients, respectively, received intravenous immune globulin.

Death from any cause was reported in 39 patients in the cilta-cel group and in 46 in the standard-care group; 1 patient in the standard-care group died before the initiation of treatment. Death from disease progression was reported in 14 patients in the cilta-cel group (8 of whom did not receive cilta-cel) and in 30 in the standard-care group; 10 and 5 deaths, respec-

Table 2. Treatment Response and Minimal Residual Disease (Intention-to-Treat Population).

Variable	Cilta-cel (N=208)	Standard Care (N=211)	Odds Ratio (95% CI)*
Overall response — no. (%)†	176 (84.6)	142 (67.3)	3.0 (1.8–5.0)
Type of response — no. (%)			
Stringent complete response	121 (58.2)	32 (15.2)	
Complete response	31 (14.9)	14 (6.6)	
Very good partial response	17 (8.2)	50 (23.7)	
Partial response	7 (3.4)	46 (21.8)	
Minimal response	1 (0.5)	11 (5.2)	
Stable disease	13 (6.2)	47 (22.3)	
Progressive disease	17 (8.2)	6 (2.8)	
Not evaluable	1 (0.5)	5 (2.4)	
Complete response or better	152 (73.1)	46 (21.8)	10.3 (6.5–16.4)
Very good partial response or better	169 (81.2)	96 (45.5)	5.9 (3.7–9.4)
12-month duration of response — % (95% CI)	84.7 (78.1–89.4)	63.0 (54.2–70.6)	
Median time to first response (range) — mo	2.1 (0.9–11.1)	1.2 (0.6–10.7)	
Median time to best response (range) — mo	6.4 (1.1–18.6)	3.1 (0.8–20.6)	
No minimal residual disease — no. (%)‡	126 (60.6)	33 (15.6)	8.7 (5.4–13.9)
12-month progression-free survival — % (95% CI)	75.9 (69.4–81.1)	48.6 (41.5–55.3)	

* Listed are Mantel–Haenszel estimates of the common odds ratio for stratified values. An odds ratio of more than 1 indicates an advantage for cilta-cel.
† Overall response was defined as a partial response or better.
‡ Data regarding minimal residual disease (which was assessed at a threshold of 1×10^{-5} by next-generation sequencing) were available for 126 of 144 patients (87.5%) in the cilta-cel group and for 33 of 101 patients (32.7%) in the standard-care group.

tively, were caused by adverse events during treatment (associated with Covid-19 in 7 patients and 1 patient, respectively). A total of 15 deaths in the cilta-cel group and 11 deaths in the standard-care group were due to adverse events that were not considered by the investigator to be related to a trial treatment. These deaths occurred after the start of subsequent therapy or more than 112 days after the cilta-cel infusion or more than 30 days after the last dose of a standard-care treatment (Table S7).

Of the 176 patients who received cilta-cel in the as-treated population, 134 (76.1%) had cytokine release syndrome (grade 1 or 2 in 132 and grade 3 in 2). The median time until the onset was 8 days (range, 1 to 23), and the duration was 3 days (range, 1 to 17) (Table S8). CAR-T–related neurotoxic events occurred in 36 patients (20.5%), with grade 1 or 2 in 31 and grade 3 or 4 in 5. All 8 cases of ICANS (4.5%) were of grade 1 or 2, with a median of 9.5 days (range, 6 to 15) until onset and a median duration of 2 days (range, 1 to 6) (Table S9). One episode of movement and neurocognitive adverse events (grade 1) was reported in a male patient with previous grade 2 cytokine release syndrome whose disease was resistant to bridging therapy (Table S10). Onset was on day 85 after infusion and was ongoing at the time of data cutoff. Cranial nerve palsies, which most commonly affected cranial nerve VII, were reported in 16 patients (9.1%) (grade 1 or 2 in 14 and grade 3 in 2), and median onset was 21 days (range, 17 to 60) after infusion; 14 patients had recovered by the time of data cutoff. CAR-T–related peripheral neuropathies were reported in 5 patients (2.8%); 3 had recovered by data cutoff (Table S10).

CILTA-CEL PHARMACOKINETICS

Among the 176 patients in the as-treated population who received cilta-cel, CD3+CAR+ cells in blood peaked at a median of 13 days after

Table 3. Adverse Events (Safety Population).*

Adverse Event	Cilta-cel (N=208)		Standard Care (N=208)	
	All	Grade 3 or 4	All	Grade 3 or 4
Any adverse event — no. (%)	208 (100.0)	201 (96.6)	208 (100.0)	196 (94.2)
Hematologic event — no. (%)	197 (94.7)	196 (94.2)	185 (88.9)	179 (86.1)
Neutropenia	187 (89.9)	187 (89.9)	177 (85.1)	171 (82.2)
Thrombocytopenia	113 (54.3)	86 (41.3)	65 (31.2)	39 (18.8)
Anemia	113 (54.3)	74 (35.6)	54 (26.0)	30 (14.4)
Lymphopenia	46 (22.1)	43 (20.7)	29 (13.9)	25 (12.0)
Infection — no. (%)	129 (62.0)	56 (26.9)	148 (71.2)	51 (24.5)
Upper respiratory tract†	39 (18.8)	4 (1.9)	54 (26.0)	4 (1.9)
Covid-19‡	29 (13.9)	6 (2.9)	55 (26.4)	12 (5.8)
Lower respiratory tract or lung§	19 (9.1)	9 (4.3)	36 (17.3)	8 (3.8)
Other — no. (%)				
Nausea	101 (48.6)	0	38 (18.3)	2 (1.0)
Hypogammaglobulinemia	88 (42.3)	15 (7.2)	13 (6.2)	1 (0.5)
Diarrhea	70 (33.7)	8 (3.8)	56 (26.9)	5 (2.4)
Fatigue	60 (28.8)	4 (1.9)	68 (32.7)	2 (1.0)
Headache	55 (26.4)	0	27 (13.0)	0
Constipation	49 (23.6)	1 (0.5)	44 (21.2)	2 (1.0)
Hypokalemia	39 (18.8)	8 (3.8)	14 (6.7)	3 (1.4)
Asthenia	36 (17.3)	1 (0.5)	34 (16.3)	5 (2.4)
Peripheral edema	35 (16.8)	0	24 (11.5)	2 (1.0)
Decreased appetite	34 (16.3)	2 (1.0)	11 (5.3)	0
Peripheral sensory neuropathy	33 (15.9)	0	38 (18.3)	1 (0.5)
Back pain	33 (15.9)	2 (1.0)	39 (18.8)	2 (1.0)
Arthralgia	32 (15.4)	2 (1.0)	25 (12.0)	1 (0.5)
Pyrexia	32 (15.4)	0	32 (15.4)	2 (1.0)
Dyspnea	28 (13.5)	1 (0.5)	41 (19.7)	1 (0.5)
Insomnia	23 (11.1)	2 (1.0)	52 (25.0)	6 (2.9)
CAR-T–associated adverse event — no./total no.¶				
Cytokine release syndrome	134/176 (76.1)	2/176 (1.1)	—	—
Neurotoxicity‖	36/176 (20.5)	5/176 (2.8)	—	—
Immune effector cell–associated neurotoxicity syndrome and associated symptoms	8/176 (4.5)	1/176 (0.1)	—	—
Other	30/176 (17.0)	4/176 (2.3)	—	—
Movement or neurocognitive	1/176 (0.6)	0	—	—

* Listed are adverse events that occurred in at least 15% of the patients in either group and were considered by the investigator to be related to a trial treatment or occurred after the initiation of treatment (apheresis in the cilta-cel group and day 1 in the standard-care group) up to 30 days after the last dose of a trial treatment, before the initiation of subsequent therapy, or within 112 days after the cilta-cel infusion (cilta-cel group only). CAR-T denotes chimeric antigen receptor T-cell, and Covid-19 coronavirus disease 2019.

† Upper respiratory tract infections included preferred terms nasopharyngitis, sinusitis, rhinitis, tonsillitis, pharyngitis, laryngitis, and pharyngotonsillitis.

‡ Covid-19 includes preferred terms Covid-19 pneumonia and asymptomatic Covid-19. In addition to 6 (cilta-cel) and 12 (standard-care) grade 3 or 4 events, grade 5 events occurred in 7 patients and 1 patient, respectively (Table S7).

§ Lower respiratory tract infections included pneumonia and bronchitis.

¶ CAR-T–associated adverse events were evaluated in the 176 patients who received cilta-cel in the as-treated population.

‖ There were no fatal neurotoxic events. One case of grade 3 syncope was reported as a symptom of grade 2 immune effector cell–associated neurotoxicity syndrome. Included in the category of "other" CAR-T–associated events were those that were not classified as immune effector cell–associated neurotoxicity syndrome or its associated symptoms. Other neurotoxic events included (but were not limited to) movement and neurocognitive adverse events, cranial nerve palsy, and peripheral neuropathy.

infusion; the mean (±SD) number of cells was 1523±5987 per cubic millimeter. These cells remained detectable for a median of 57 days (range, 13 to 631). During the first 28 days after the administration of cilta-cel, the mean area under the curve was 12,504±55,281 CD3+CAR+ cells.

DISCUSSION

In patients with lenalidomide-refractory multiple myeloma after one to three previous lines of therapy, a single cilta-cel infusion resulted in a lower risk of disease progression or death (the primary outcome) than highly effective standard-care treatments (mostly DPd) at a median follow-up of 15.9 months. At 12 months, progression-free survival was 75.9% as compared with 48.6% with standard care. Similar effects were seen in all subgroups that were evaluated, including patients with high-risk cytogenetic abnormalities, soft-tissue plasmacytomas, triple-class–refractory disease, ISS stage III status, and other high-risk features. Moreover, cilta-cel had higher response rates, deeper and more durable responses, and a higher frequency of MRD negativity than standard care; the time until patient-reported worsening of symptoms was complementary to clinical outcomes. These results indicate that cilta-cel is an effective treatment for patients with lenalidomide-refractory disease as early as the first relapse. The results also add to the consistently strong efficacy that cilta-cel has shown throughout its clinical development, including in similar, early lines of therapy populations in CARTITUDE-2,[13,14] and confirm the efficacy observed in heavily pretreated patients who received cilta-cel in CARTITUDE-1.[10,11]

The protocol did not mandate the physician's choice of standard-care (or bridging) therapy on the basis of previous exposure or resistance to the previous receipt of proteasome inhibitors or daratumumab. However, most patients received DPd, and the standard-care treatments in CARTITUDE-4 performed as expected according to the findings of the APOLLO and OPTIMISMM trials involving patients with multiple myeloma.[17,18]

A potential limitation of the trial design was that two highly efficacious triplet regimens — daratumumab, carfilzomib, and dexamethasone and isatuximab, carfilzomib, and dexamethasone — were not approved at the time of trial initiation and could not be included as standard-care options. These two regimens have since entered clinical practice as treatment options.[24-27] However, the populations in these trials differed from our trial population, and lenalidomide resistance was not a criterion for inclusion.

Patients in our two trial groups received the same medications that were administered during the period of bridging therapy in the cilta-cel group. Thus, a prespecified weighting method was used in the two groups to focus outcomes on events after the cilta-cel infusion. The numbers of progression events or deaths that were reported during trial weeks 0 to 8 — all of which preceded the cilta-cel infusion — were higher in the cilta-cel group than in the standard-care group. This difference may have been due to lower doses of DPd and PVd that were used in the cilta-cel group. The occurrence of these early events meant that the benefit of cilta-cel did not become apparent in the Kaplan–Meier curve for the primary analysis until 3 months.

Understanding the mechanisms of drug resistance is an area of interest that will ultimately assist in the sequencing of myeloma therapies. These analyses are in progress. The median duration of progression-free survival in CARTITUDE-4 extended beyond the median duration of detectability in CAR T cells, a result that was similar to observations in CARTITUDE-1.

Before the clinical cutoff date, 7 deaths related to Covid-19 were documented in the cilta-cel group, of which 6 infections were diagnosed within 4 months after the cilta-cel infusion, when patients were most immunocompromised. Furthermore, the time period coincided with the emergence of the omicron variant and the relaxing of Covid-19–related restrictions in some regions. These deaths contributed to the higher number of fatal events observed in the cilta-cel group than in the standard-care group in the first year after randomization and highlight the need for strict prevention measures and aggressive treatment of Covid-19 in patients receiving CAR-T therapies. After safety measures that were consistent with international guidelines were introduced, no deaths related to Covid-19 occurred in the cilta-cel group (see the Supplementary Appendix). The incidence of Covid-19 infection that was considered to have occurred during a trial treatment was lower in the cilta-cel group than in the standard-care group (13.9% vs. 26.4%). Furthermore, the incidence of all infec-

tions during the trial period was similar with cilta-cel and standard care (62.0% vs. 71.2%), which suggested that with appropriate prophylaxis and treatment, infection risk is generally treatable in patients receiving cilta-cel.

Overall, CAR-T–specific adverse events were manageable with appropriate supportive care. Lower rates of cytopenias, cytokine release syndrome, and CAR-T–related neurotoxicity were seen in CARTITUDE-4 than in CARTITUDE-1, which suggests that cilta-cel may have a better side-effect profile when used earlier in treatment.[10,11] Effective bridging therapy enables better control of tumor burden before CAR-T infusion. The incidence of movement and neurocognitive adverse events was also lower in CARTITUDE-4 (0.6%) than in CARTITUDE-1 (6.0%),[10,11] a difference that may be related to management strategies that were implemented to mitigate this risk.[28] Cranial nerve palsies are a recognized side effect of CAR-T therapies,[10,29] and such events that were observed in our trial were mild to moderate; most cases had resolved by the data-cutoff date. No clear risk factors for cranial nerve palsies have been identified, and the mechanism is not understood.

In this trial, we found a favorable risk–benefit profile for a single infusion of cilta-cel as compared with standard care. As with other myeloma treatments, real-world translation of clinical trial results will be influenced by a variety of factors, including patient selection and fitness, patient heterogeneity, treatment accessibility and setting, and patient or physician preference.[30] Nonetheless, the strong progression-free survival benefit and rapid and deep response with cilta-cel highlight the potential for cilta-cel to become a therapeutic option for patients with myeloma after the first relapse.

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APPENDIX

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REFERENCES

1. van de Donk NWCJ. Sequencing multiple myeloma therapies with and after antibody therapies. Hematology Am Soc Hematol Educ Program 2020;2020:248-58.
2. Rodríguez-Lobato LG, Pereira A, Fernández de Larrea C, et al. Real-world data on survival improvement in patients with multiple myeloma treated at a single institution over a 45-year period. Br J Haematol 2022;196:649-59.
3. Yong K, Delforge M, Driessen C, et al. Multiple myeloma: patient outcomes in real-world practice. Br J Haematol 2016;175:252-64.
4. Dhakal B, Einsele H, Potluri R, et al. P-240: Real-world assessment of treatment patterns and outcomes in patients with lenalidomide-refractory relapsed multiple myeloma from the SEER-Medicare database. Clin Lymphoma Myeloma Leuk 2022;22:S167.
5. Dhakal B, Einsele H, Potluri R, et al. P899: Real-world assessment of treatment patterns and outcomes in patients with lenalidomide-refractory relapsed/refractory multiple myeloma from the optum database. HemaSphere 2022;6:790-1.
6. Dimopoulos MA, Moreau P, Terpos E, et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up. HemaSphere 2021;5(2):e528.
7. NCCN guidelines: multiple myeloma. Version 3.2023. National Comprehensive Cancer Network, 2023.
8. de Arriba de la Fuente F, Montes Gaisán C, de la Rubia Comos J. How to manage patients with lenalidomide-refractory multiple myeloma. Cancers (Basel) 2022;15:155.
9. Fonseca R, Usmani SZ, Mehra M, et al. Frontline treatment patterns and attrition rates by subsequent lines of therapy in patients with newly diagnosed multiple myeloma. BMC Cancer 2020;20:1087.
10. 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;398:314-24.
11. Martin T, Usmani SZ, Berdeja JG, et al. Ciltacabtagene autoleucel, an anti-B-cell maturation antigen chimeric antigen receptor T-cell therapy, for relapsed/refractory multiple myeloma: CARTITUDE-1 2-year follow-up. J Clin Oncol 2023;41:1265-74.
12. Lin Y, Martin TG, Usmani SZ, et al. CARTITUDE-1 final results: phase 1b/2 study of ciltacabtagene autoleucel in heavily pretreated patients with relapsed/refractory multiple myeloma. J Clin Oncol 2023;41:Suppl:8009. abstract.
13. van de Donk NWCJ, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel (ciltacel), a BCMA-directed CAR-T cell therapy, in patients with multiple myeloma (MM) and early relapse after initial therapy: CARTITUDE-2 cohort B 18-month follow-up. Blood 2022;140:7536-7.
14. Einsele H, Cohen AD, Delforge M, et al. Biological correlative analyses and updated clinical data of ciltacabtagene autoleucel, a BCMA-directed CAR-T cell therapy, in lenalidomide-refractory patients with progressive multiple myeloma after 1–3 prior lines of therapy: CARTITUDE-2, cohort A. Presented at the American Society of Clinical Oncology Annual Meeting, Chicago, June 3–7, 2022. abstract.
15. Rodriguez-Otero P, Ailawadhi S, Arnulf B, et al. Ide-cel or standard regimens in relapsed and refractory multiple myeloma. N Engl J Med 2023;388:1002-14.
16. Rajkumar SV, Harousseau J-L, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood 2011;117:4691-5.
17. Richardson PG, Oriol A, Beksac M, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed or refractory multiple myeloma previously treated with lenalidomide (OPTIMISMM): a randomised, open-label, phase 3 trial. Lancet Oncol 2019;20:781-94.
18. 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;22:801-12.
19. Palumbo A, Chanan-Khan A, Weisel K, et al. Daratumumab, bortezomib, and dexamethasone for multiple myeloma. N Engl J Med 2016;375:754-66.
20. Lee DW, Santomasso BD, Locke FL, et al. ASTCT consensus grading for cytokine release syndrome and neurologic toxicity associated with immune effector cells. Biol Blood Marrow Transplant 2019;25:625-38.
21. Common terminology criteria for adverse events (CTCAE) version 5.0. Department of Health and Human Services, November 27, 2017 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_5x7.pdf).
22. Xu Z, Zhen B, Park Y, Zhu B. Designing therapeutic cancer vaccine trials with delayed treatment effect. Stat Med 2017;36:592-605.
23. Zucker DM, Lakatos E. Weighted log rank type statistics for comparing survival curves when there is a time lag in the effectiveness of treatment. Biometrika 1990;77:853-64.
24. Usmani SZ, Quach H, Mateos M-V, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): updated outcomes from a randomised, multicentre, open-label, phase 3 study. Lancet Oncol 2022;23:65-76.
25. Dimopoulos M, Quach H, Mateos M-V, et al. Carfilzomib, dexamethasone, and daratumumab versus carfilzomib and dexamethasone for patients with relapsed or refractory multiple myeloma (CANDOR): results from a randomised, multicentre, open-label, phase 3 study. Lancet 2020;396:186-97.
26. Moreau P, Dimopoulos M-A, Mikhael J, et al. Isatuximab, carfilzomib, and dexamethasone in relapsed multiple myeloma (IKEMA): a multicentre, open-label, randomised phase 3 trial. Lancet 2021;397:2361-71.
27. Moreau P, Dimopoulos MAC, Mikhael J, et al. VP5-2022: Updated progression-free survival (PFS) and depth of response in IKEMA, a randomized phase III trial of isatuximab, carfilzomib and dexamethasone (Isa-Kd) vs Kd in relapsed multiple myeloma (MM). Ann Oncol 2022;33:664-5.
28. Cohen AD, Parekh S, Santomasso BD, et al. Incidence and management of CAR-T neurotoxicity in patients with multiple myeloma treated with ciltacabtagene autoleucel in CARTITUDE studies. Blood Cancer J 2022;12:32.
29. Highlights of prescribing information: ABECMA (idecabtagene vicleucel). Summit, NJ: Celgene Corporation, a Bristol-Myers Squibb Company, 2021 (https://www.fda.gov/media/147055/download).
30. Richardson PG, San Miguel JF, Moreau P, et al. Interpreting clinical trial data in multiple myeloma: translating findings to the real-world setting. Blood Cancer J 2018;8:109.