original reports

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

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abstract

PURPOSE CARTITUDE-1, a phase Ib/II study evaluating the safety and efficacy of ciltacabtagene autoleucel (cilta-cel) in heavily pretreated patients with relapsed/refractory multiple myeloma, yielded early, deep, and durable responses at 12 months. Here, we present updated results 2 years after last patient in (median follow-up [MFU] approximately 28 months), including analyses of high-risk patient subgroups.

METHODS Eligible patients had relapsed/refractory multiple myeloma, had received ≥ 3 prior lines of therapy or were double refractory to a proteasome inhibitor and immunomodulatory drug and had received prior proteasome inhibitor, immunomodulatory drug, and anti-CD38 therapy. Patients received a single cilta-cel infusion 5-7 days after lymphodepletion. Responses were assessed by an independent review committee.

RESULTS At a MFU of 27.7 months (N = 97), the overall response rate was 97.9% (95% CI, 92.7 to 99.7); 82.5% (95% CI, 73.4 to 89.4) of patients achieved a stringent complete response. Median duration of response was not estimable. Median progression-free survival (PFS) and overall survival (OS) were not reached; 27-month PFS and OS rates were 54.9% (95% CI, 44.0 to 64.6) and 70.4% (95% CI, 60.1 to 78.6), respectively. Overall response rates were high across all subgroups (95.1%-100%). Duration of response, PFS, and/or OS were shorter in patients with high-risk cytogenetics, International Staging System stage III, high tumor burden, or plasmacytomas. The safety profile was manageable with no new cilta-cel–related cytokine release syndrome and one new case of parkinsonism (day 914 after cilta-cel) since the last report.

CONCLUSION At approximately 28 months MFU, patients treated with cilta-cel maintained deep and durable responses, observed in both standard and high-risk subgroups. The risk/benefit profile of cilta-cel remained favorable with longer follow-up.

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ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

The standard of care (SOC) for relapsed multiple myeloma (MM) involves a multidrug regimen that may include a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), a monoclonal antibody, and a corticosteroid.[1] However, patients may eventually become resistant to these treatments.[2,3] Lower depth and durability of response have been reported with each successive line of therapy (LOT),[4] and patients who are refractory to multiple drug classes have suboptimal outcomes. The median overall survival (OS) with SOC is 11.2 months for patients who are refractory to < 3 prior LOT and 5.6 months for penta-refractory patients (refractory to anti-CD38 antibody, two PIs, and two IMiDs).[2]

There is an unmet medical need to extend survival and delay progression in heavily pretreated patients with refractory MM. Two novel agents with different mechanisms of action, selinexor[5] and belantamab mafodotin,[6] were recently approved for patients with relapsed or refractory MM (RRMM) who received ≥ 4 prior LOT but had overall response rates (ORRs) of only 21% to 34% in clinical trials.[7-9]

Personalized immunotherapy using a chimeric antigen receptor (CAR) involves genetically modifying a patient's own T cells so that they can identify and kill malignant plasma cells.[10] The first B-cell maturation antigen (BCMA)–directed CAR-T cell immunotherapy, idecabtagene vicleucel (ide-cel), was approved in the

CONTEXT

Key Objective

To determine if the efficacy and safety profile of ciltacabtagene autoleucel (cilta-cel) previously seen at 12-month median follow-up in patients with heavily pretreated multiple myeloma was maintained at 28 months in the overall and high-risk patient populations.

Knowledge Generated

Deep and durable responses to cilta-cel are demonstrated at 28 months with a positive risk/benefit profile. Median progression-free survival and overall survival have not been reached. All high-risk patient subgroups had high response rates, suggesting that cilta-cel offers greater efficacy than what is observed with other available treatment options in these patients. Long-term monitoring for late-onset toxicities is important, and cilta-cel safety has been shown to be manageable.

Relevance

Cilta-cel is a valuable new treatment option for heavily pretreated patients, including high-risk patients who may be difficult to treat.

United States for patients with RRMM after exposure to ≥ 4 prior LOT[11] and was granted conditional approval in 2021 in the European Union for patients with RRMM who received ≥ 3 therapies and progressed on their last therapy.[12] Approval was based on the results from the phase II KarMMa trial, which demonstrated an ORR of 73% and a median progression-free survival (PFS) of 8.8 months across all dose cohorts in heavily pretreated patients (median six prior LOT).[13]

Ciltacabtagene autoleucel (cilta-cel, JNJ-68284528) is a differentiated CAR-T therapy with two BCMA-targeting single-domain antibodies to confer avidity.[14] It was recently approved by the US Food and Drug Administration for the treatment of adult patients with RRMM after ≥ 4 prior LOT, including a PI, an IMiD, and an anti-CD38 monoclonal antibody.[15] In March 2022, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a positive opinion of cilta-cel, for an indication in patients with ≥ 3 prior LOT.[16] Initial results from the phase Ib/II, single-arm CARTITUDE-1 trial demonstrated that cilta-cel led to early, deep, and durable responses among 97 patients with RRMM exposed to a median of six prior therapies.[14] At a median follow-up (MFU) of 12 months, ORR was 97% with 67% of patients reaching stringent complete response (sCR). The median duration of response (DOR) and median PFS were not estimable (NE).[14] Here, we present a prespecified analysis of the CARTITUDE-1 study, which was completed in early 2022, with a MFU of 28 months.

METHODS

Study Design and Treatment

CARTITUDE-1 was a single-arm, open-label, multicenter, phase Ib/II study conducted in patients with RRMM to characterize the safety of cilta-cel and confirm the recommended phase II dose (phase Ib) and evaluate clinical efficacy (phase II; ClinicalTrials.gov identifier: NCT03548207). The study design and primary results have been previously reported.[14] Patients were required to have received ≥ 3 prior LOT, including a PI, IMiD, and an anti-CD38 antibody, or to be double refractory to PI and IMiD and have received an anti-CD38 antibody, with evidence of progressive disease (PD) within 12 months of the last LOT. Patients received a single cilta-cel infusion (target dose 0.75×10^6 CAR-positive viable T cells/kg; range, $0.5\text{-}1.0 \times 10^6$) 5-7 days after lymphodepletion (300 mg/m^2 cyclophosphamide, 30 mg/m^2 fludarabine once daily for 3 days). Retreatment with cilta-cel was permitted within the same dose range in patients with documented PD ≥ 6 months after cilta-cel infusion with best response of at least minimal response who had no ongoing hematologic (grade ≥ 3) or nonhematologic (grade ≥ 2) toxicities.

An independent ethics committee or institutional review board at each study center approved the study protocol, and all patients provided written informed consent. The study Protocol (online only) was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization guidelines for Good Clinical Practice.

End Points and Assessments

The primary efficacy end point of phase II was ORR; secondary end points were rates of sCR, complete response (CR), and very good partial response; minimal residual disease (MRD) negativity; DOR; PFS; and OS.[14] Response was assessed by an independent review committee and adjudicated per International Myeloma Working Group (IMWG) criteria.[17-19]

MRD was assessed at baseline; day 28; and 6, 12, 18, and 24 months using next-generation sequencing (clonoSEQ v2.0; Adaptive Biotechnologies, Seattle, WA) regardless of disease status. An additional sample was collected and

assessed at the time of suspected CR and every 12 months until PD for patients who remained on study. MRD negativity was assessed in samples that passed calibration or quality control and included sufficient cells for evaluation at the testing threshold of 10^{-5}.

Extramedullary (EM) plasmacytomas were assessed for patients with a history of plasmacytomas or if clinically indicated at screening, by clinical examination or radiologic imaging, with continuing follow-up using the same method of evaluation at regular assessments post-treatment.

Adverse events (AEs) were graded using National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0. Cytokine release syndrome (CRS) was graded according to Lee criteria[20] in phase Ib and American Society for Transplantation and Cellular Therapy (ASTCT) criteria[21] in phase II. Neurotoxicity was graded using NCI-CTCAE v5.0 in phase Ib, and immune-effector cell-associated neurotoxicity syndrome (ICANS) was graded by ASTCT criteria[21] in phase II.[14] Other neurotoxicities (events not reported as ICANS) were graded by NCI-CTCAE version 5.0.

Statistical Analysis

Statistical analyses and sample size calculations have been described previously.[14] The primary efficacy analysis set included all patients who received cilta-cel at the target dose range. Safety was assessed in all cilta-cel–treated patients.

ORR and two-sided 95% CIs were calculated on the basis of the exact binomial distribution. Time-to-event efficacy end points were estimated using the Kaplan-Meier method. Durability of MRD-negative status was characterized by quantifying MRD-negative status rates (10^{-5}) sustained for at least 6 or 12 months.

Subgroup analyses were conducted in the following patient subgroups: age $\geq$ 65 years, Black/African American, 3 and $\geq$ 4 prior LOT, triple-class refractory, penta-drug refractory, standard- and high-risk cytogenetic status, International Staging System (ISS) stage III, bone marrow plasma cell percentage at baseline ($\leq$ 30%, $>$ 30% to $<$ 60%, and $\geq$ 60%), tumor BCMA expression at baseline ($<$ 80%, $\geq$ 80%), and presence of plasmacytomas (bone-based and EM).

RESULTS

Patients and Treatment

As of the January 11, 2022, data cutoff, 66 of the 97 patients who received cilta-cel infusion remained on study (Fig 1). As previously reported, the median time from receipt of the apheresis material to release of cilta-cel was 29 days

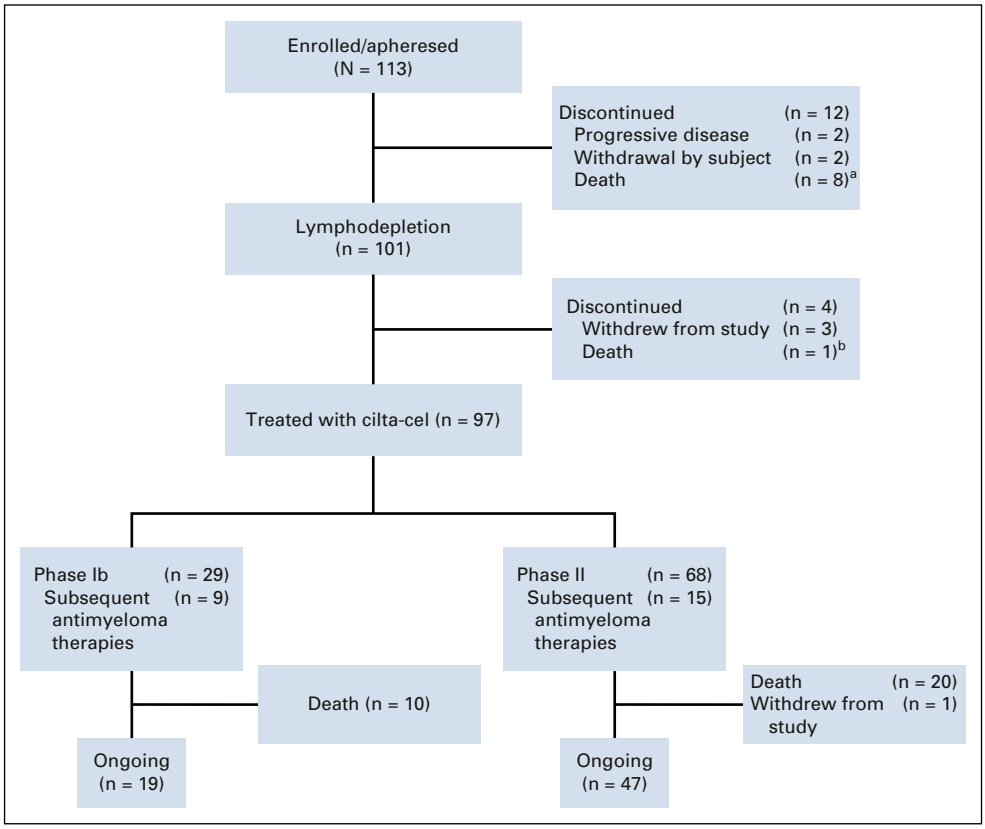

FIG 1. Patient disposition. [a]Because of progressive disease (5), acute cardiorespiratory arrest (1), sepsis (1), and subdural hematoma (1). [b]Because of acute respiratory failure. cilta-cel, ciltacabtagene autoleucel.

(interquartile range 28-33); no patient discontinued the study because of manufacturing failure.[14] All patients treated with cilta-cel received a dose within the target range (median, 0.71 × 10^6 cells/kg; range, 0.51-0.95 × 10^6). At baseline, patients had received a median of six (range, 3-18) prior LOT. Of 96 patients with evaluable bone marrow biopsy and/or aspirate samples, 21.9% had high disease burden (≥ 60% plasma cells). Plasmacytomas were detected at screening in 19 (19.6%) patients (13 [13.4%] EM, and six [6.2%] bone-based [Appendix Table A1, online only]).

Efficacy

All patients who received cilta-cel were included in the efficacy analyses (N = 97). At a MFU of 27.7 months, ORR was 97.9%, sCR rate was 82.5% (no patient was CR only), very good partial response rate was 12.4%, and PR rate was 3.1% (Table 1). The median time to first response was 1 month, the median time to best response was 2.6 months, and the median time to CR or better was 2.9 months. Median DOR and median PFS were not reached (Fig 2A); the time point at which 75% of patients were progression-free (75th percentile) was 12.9 months (95% CI, 6.97 to 18.04). At the 27-month time point, PFS rates were 54.9% in the overall population and 64.2% in patients with sCR. Median OS was not reached, and the 75th percentile was 24.1 months (95% CI, 14.62 to not estimable). The 27-month OS rate in the overall population was 70.4% (Fig 2B). As of the data cutoff, three patients have been retreated with cilta-cel (same dose as the initial treatment; Table 2).

TABLE 1. Response to Ciltacabtagene Autoleucel[a]

Variable	Total (N = 97)
Overall response	
Patients with a response, No.[b]	95
Rate, % (95% CI)	97.9 (92.7 to 99.7)
Best overall response rate, % (95% CI)	
sCR	82.5 (73.4 to 89.4)
MRD-negative sCR[c]	44.3 (34.2 to 54.8)
CR	0 (NE to NE)
VGPR	12.4 (6.6 to 20.6)
PR	3.1 (0.6 to 8.8)
Minimal response	0 (NE to NE)
SD	0 (NE to NE)
PD	1.0 (0 to 5.6)
Not evaluable	1.0 (0 to 5.6)
Median duration of response, months (95% CI)	NE (23.3 to NE)
Median time to first response, months (range)	1.0 (0.9 to 10.7)
Median time to best response, months (range)	2.6 (0.9 to 17.8)
Median time to CR or better, months (range)	2.9 (0.9 to 17.8)
MRD negativity, No. (%)	
No. of patients evaluable for MRD at 10^{-5}	61
Rate, No. (%)	56 (91.8)
No. of patients evaluable for MRD at 10^{-6}	52
Rate, No. (%)	39 (75.0)

Abbreviations: CR, complete response; ITT, intent-to-treat; MRD, minimal residual disease; NE, not estimable; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

[a]Assessed by independent review committee.

[b]Sum of sCR, CR, VGPR, and PR.

[c]ITT population.

Sixty-one patients had samples evaluable for MRD status, defined as those that passed calibration and quality control and had sufficient cells for evaluation. At the 10^{-5} threshold, 56 (91.8%) patients achieved MRD negativity, which was sustained for ≥ 6 months in 68% (34 of 50 with sufficient follow-up) and ≥ 12 months in 55% (24 of 44 with sufficient follow-up). PFS rates in patients who achieved sustained MRD negativity for ≥ 6 and ≥ 12 months were 73.0% (95% CI, 52.1 to 85.9) and 78.8% (95% CI, 51.5 to 91.8), respectively (Fig 2C), and OS rates were 93.5% (95% CI, 76.1 to 98.3) and 90.8% (95% CI, 67.7 to 97.6), respectively. Of 52 patients with a sample evaluable for MRD status at the 10^{-6} threshold, 39 (75.0%) achieved MRD negativity.

Efficacy in Patient Subgroups

Most patients in high-risk subgroups responded to cilta-cel (ORR range, 95.1%-100%), including those treated with three prior LOT (100%), and those with a high-risk cytogenetic profile (100%), high tumor burden (≥ 60% bone marrow plasma cells; 95.2%), or plasmacytomas (100%; Appendix Table A2, online only). MRD negativity rates in evaluable patients (at 10^{-5}) were 80%-100% across all subgroups. Compared with the overall cilta-cel population, patients with ISS stage III disease, high cytogenetic risk, plasmacytomas, or high tumor burden had shorter DOR (Fig 3) and lower PFS and OS rates. Patients with 30%-60% bone marrow plasma cells also had shorter DOR and a lower PFS rate than the overall population, and Black/African American patients had a reduced OS rate.

Safety

Hematologic adverse events. The most common (≥ 25%) grade 3/4 treatment-emergent AEs (TEAEs) were hematologic (Table 3). On the basis of laboratory results, grade 3/4 thrombocytopenia occurred in 60 patients; 20 (33.3%) had recovered to grade ≤ 2 by day 30, and 35 (58.3%) recovered by day 60. Grade 3/4 neutropenia was reported in 95 patients; 66 (69.5%) had recovered to grade ≤ 2 by day 30 and 85 (89.5%) by day 60. Grade 3/4 lymphopenia occurred in 96 patients; 84 (87.5%) had recovered to grade ≤ 2 by day 30 and 88 (91.7%) by day 60.

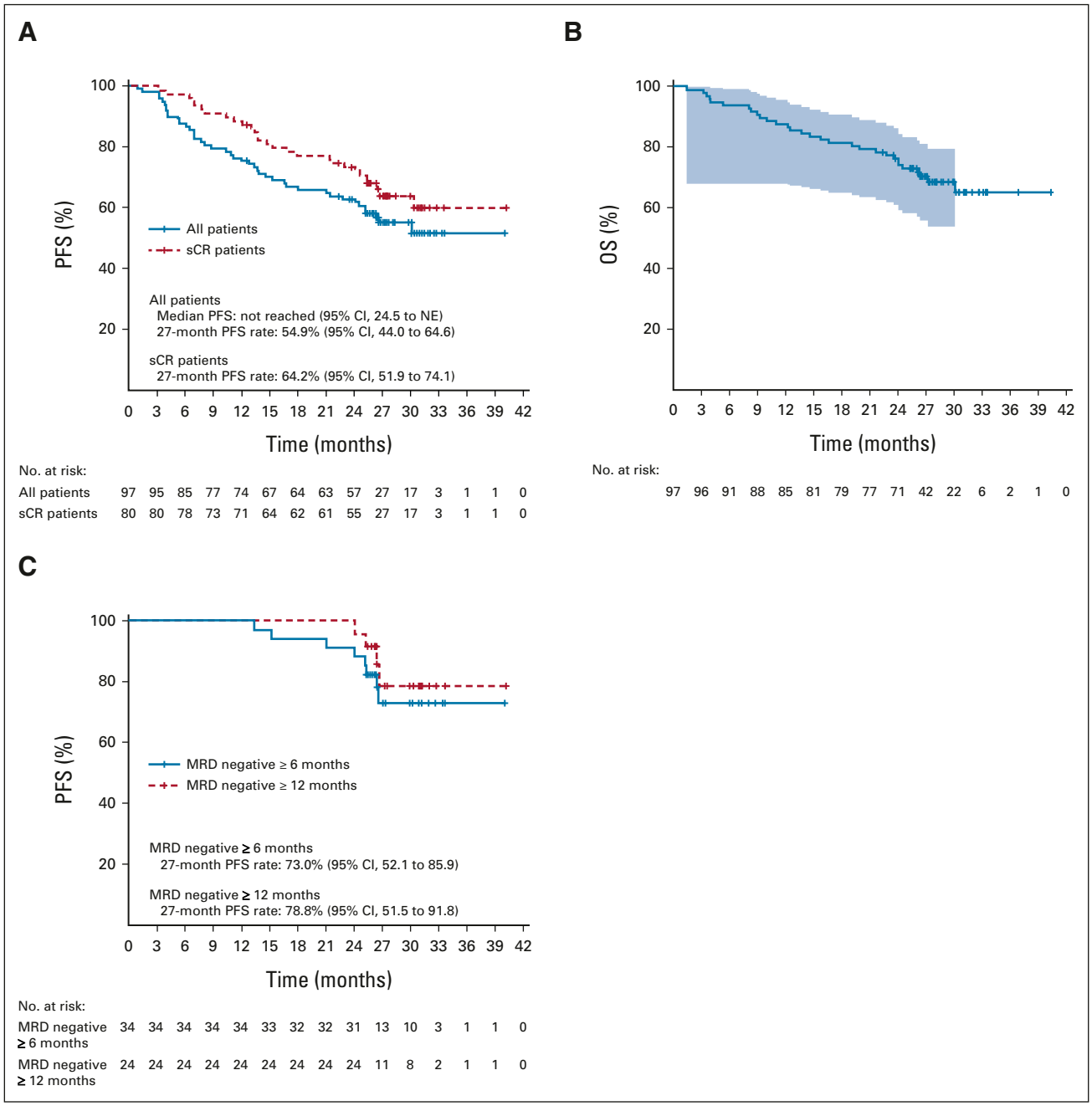

FIG 2. (A) PFS for the overall population and patients with sCR. (B) OS. Shading shows 95% confidence bands. (C) PFS in patients with sustained MRD negativity (10^{-5}) for ≥ 6 months or ≥ 12 months. MRD, minimal residual disease; NE, not estimable; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response.

Nonhematologic AEs. The most common grade 3/4 nonhematologic TEAEs (≥ 5%) were pneumonia (10.3%), hypophosphatemia (7.2%), increased gamma-glutamyl transferase (6.2%), hypertension (6.2%), fatigue (5.2%), and increased AST (5.2%).

Cytokine release syndrome and neurotoxicity. Since the primary 12-month publication, no new events of CRS (no changes in the incidence, time to onset, or duration) occurred. One new case of signs and symptoms of parkinsonism (previously termed movement and neurocognitive TEAEs) occurred, for a total of six in the CARTITUDE-1 study.[14] This patient had seven prior LOT, a history of ongoing peripheral sensory neuropathy at study entry, and grade 2 CRS and grade 3 ICANS after cilta-cel infusion. On day 914, the patient experienced cognitive slowing, gait instability, and neuropathy (all grade 1), and tremor (grade 3). Subsequent lumbar puncture was negative for CAR-T cells. The symptoms did not improve on a short course of levodopa. Without further

TABLE 2. Response, CAR-T Expansion, and Antidrug Antibody Status in Patients Retreated With Ciltacabtagene Autoleucel

Variable	Patient 1	Patient 2	Patient 3
Best response			
Initial treatment	sCR	sCR	VGPR
After retreatment	PD	SD	SD
CAR-T cell expansion after retreatment	None	None	None
Antidrug antibody status			
Before retreatment	Positive	Negative	Negative
After retreatment	Data not available[a]	Negative	Negative

Abbreviations: CAR, chimeric antigen receptor; PD, progressive disease; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

[a]One patient who was antidrug antibody–positive after the initial treatment was pending additional data to confirm antidrug antibody status after retreatment.

treatment, the patient is stable and functioning (able to work), with slight improvement in his gait instability, and remains in sCR.[14] Three of the six total patients with parkinsonism have died (two from other underlying causes [sepsis and lung abscess] and one related to parkinsonism). Of the other two who are living, one has recovered and one is recovering (ongoing grade 2 symptoms) at the time of the data cut.

Secondary primary malignancies. In total, 20 secondary primary malignancies (SPMs) were reported in 16 patients; all were unrelated to cilta-cel. Nine patients had hematologic SPM, including one case of low-grade B-cell lymphoma, six cases of myelodysplastic syndrome, and three cases of fatal acute myeloid leukemia (AML; one patient had both myelodysplastic syndrome and fatal AML). Four patients had squamous cell carcinoma; one of these also had basal cell carcinoma. One patient had basal cell

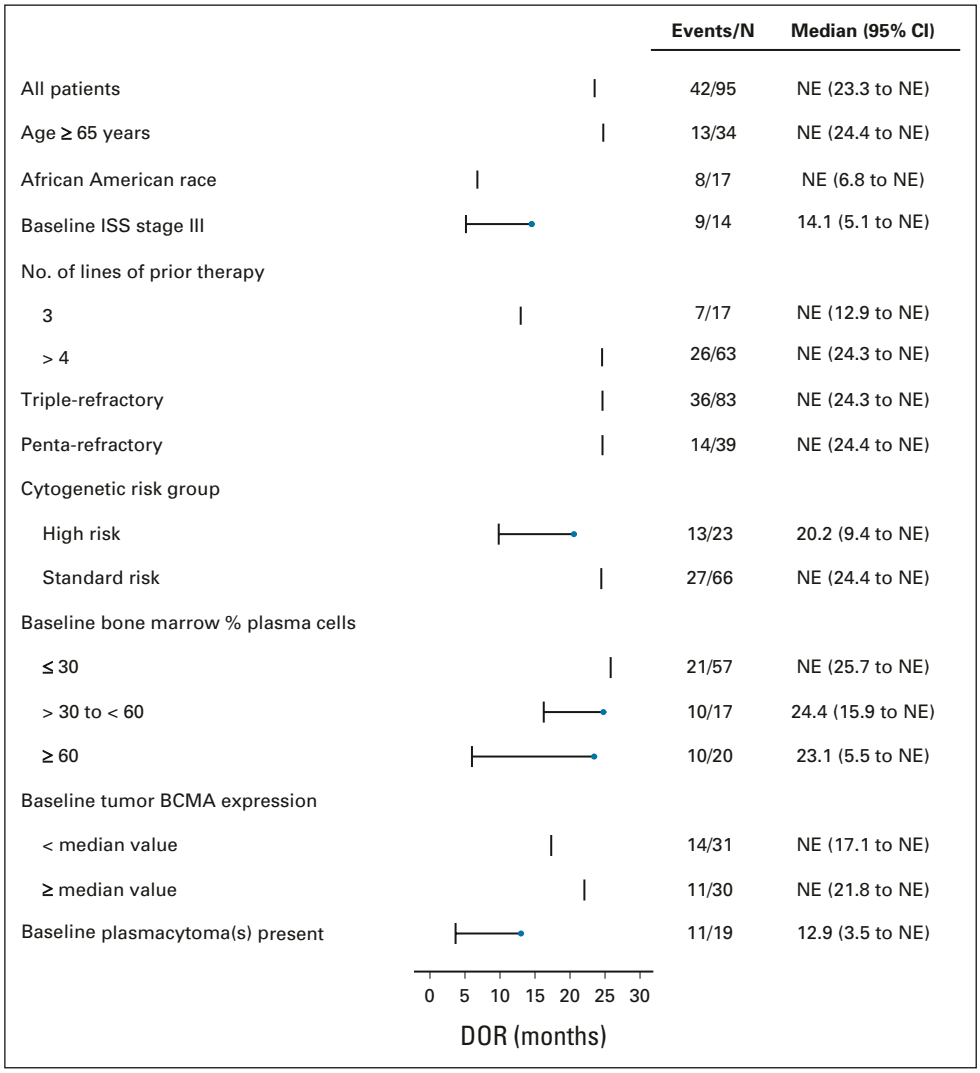

FIG 3. Forest plot of DOR in patient subgroups. BCMA, B-cell maturation antigen; DOR, duration of response; ISS, International Staging System; NE, not estimable.

TABLE 3. Treatment-Emergent AEs in ≥ 20% of Patients

	Total (N = 97), No. (%)		
AE	**Any Grade**	**Grade 3/4**	**Grade 5**
Any AE	97 (100)	91 (94)	6 (6.2)
Hematologic			
Neutropenia	93 (95.9)	92 (94.8)	0
Anemia	79 (81.4)	66 (68.0)	0
Thrombocytopenia	77 (79.4)	58 (59.8)	0
Leukopenia	60 (61.9)	59 (60.8)	0
Lymphopenia	52 (53.6)	49 (50.5)	0
Metabolism and nutrition disorders			
Hypocalcemia	31 (32.0)	3 (3.1)	0
Hypophosphatemia	30 (30.9)	7 (7.2)	0
Decreased appetite	28 (28.9)	1 (1.0)	0
Hypoalbuminemia	27 (27.8)	1 (1.0)	0
Hyponatremia	22 (22.7)	4 (4.1)	0
Hypokalemia	20 (20.6)	2 (2.1)	0
GI			
Diarrhea	29 (29.9)	1 (1.0)	0
Nausea	27 (27.8)	1 (1.0)	0
Constipation	22 (22.7)	0	0
Others			
Fatigue	36 (37.1)	5 (5.2)	0
Cough	34 (35.1)	0	0
AST increased	28 (28.9)	5 (5.2)	0
ALT increased	24 (24.7)	3 (3.1)	0
Pyrexia	20 (20.6)	0	0
Chills	20 (20.6)	0	0
Cytokine release syndrome	92 (94.8)	4 (4.1)	1 (1.0)
Neurotoxicity[a]	21 (21.6)	11 (11.3)	1 (1.0)

Abbreviation: AE, adverse event.

[a]Includes immune effector cell–associated neurotoxicity syndrome and other neurotoxicities.

carcinoma that was present before cilta-cel infusion. One patient each had malignant melanoma, adenocarcinoma, or myxofibrosarcoma, and one patient had prostate cancer in addition to his squamous cell carcinoma and AML reported above.

Deaths. A total of 30 deaths occurred during the study after cilta-cel infusion (Fig 1 and Appendix Table A3, online only). No deaths occurred within the first 30 days, two occurred within 100 days, and 28 occurred > 100 days post infusion. Fourteen patients died because of PD. Six deaths were treatment related (investigator assessed) and occurred within the first 12 months; details have been published previously.[14] The remaining 10 deaths were due to AEs not related to study treatment (Appendix Table A3).

DISCUSSION

This prespecified analysis of the CARTITUDE-1 trial at 28 months MFU demonstrates the sustained clinical benefit of cilta-cel in patients with RRMM who had received a median of six prior LOT. As median PFS has not yet been reached, clinical benefit continues for many patients. Responses to a single infusion of cilta-cel deepened from 67% with sCR at 12-month MFU to 82.5% at 28 months.[14] Response depth and durability were related, as illustrated by the higher rates of PFS in patients with sCR and/or sustained MRD negativity.[22]

All patient subgroups had high rates of response to cilta-cel, including those with plasmacytomas, high-risk cytogenetics, and ISS stage III. In some high-risk subgroups, DOR, PFS, and/or OS were lower than the overall population, which is expected in these difficult-to-treat groups. Cilta-cel efficacy in these populations was more favorable than other available or recently approved therapies for patients with heavily pretreated RRMM.[13,23,24] The subgroup analysis was limited by small sample size of some groups. Furthermore, EM plasmacytomas were not assessed in all patients, but rather evaluated either clinically or radiologically only in those with a history of EM disease. Although the efficacy of cilta-cel in heavily pretreated patients is encouraging, shifting its use to earlier LOTs may improve long-term outcomes for patients. This approach is currently under evaluation in the CARTITUDE-2 (ClinicalTrials.gov identifier: NCT04133636), CARTITUDE-4 (ClinicalTrials.gov identifier: NCT04181827), CARTITUDE-5 (ClinicalTrials.gov identifier: NCT04923893), and *E*magine/CARTITUDE-6 (EMN28; ClinicalTrials.gov identifier: NCT05257083) trials.

The depth and durability of responses achieved with cilta-cel highlight the potential of the CAR-T approach to transform the current treatment paradigm for RRMM. Because of the lack of established SOC and clinical equipoise, CARTITUDE-1 was necessarily limited by its design as a single-arm trial. Indirect treatment comparisons between the CARTITUDE-1 results and real-world SOC, in data sets comprising European and/or US patients (MAMMOTH study and the prospective LocoMMotion study), found that cilta-cel significantly improved outcomes versus real-world therapies in triple-class exposed patients with RRMM.[3,25] In a matching-adjusted indirect treatment comparison using data from the similarly designed CARTITUDE-1[14] and KarMMa[13] trials, cilta-cel appeared to have higher response rates and longer DOR and PFS than ide-cel.[26] After a MFU of 13.3 months, the ORR in the KarMMa trial was 73% across all dose cohorts (33% CR or better) and 81% with the highest dose evaluated (450×10^6 cells; 39% CR or better). The median PFS was 8.8 months across all doses and 12.1 months at the highest dose, with ide-cel demonstrating durable CAR T-cell persistence.[13] In contrast, the efficacy results for cilta-cel in CARTITUDE-1 were achieved despite a lack of detectable

CAR T-cell persistence in peripheral blood after infusion; most patients did not have detectable cilta-cel CAR transgene levels in peripheral blood at 6-month follow-up.[14,27]

The unique structural makeup of cilta-cel may contribute to its differentiated efficacy compared with ide-cel. The cilta-cel CAR features two BCMA-targeting, single-domain antibodies comprising two variable regions of heavy chains designed to confer avidity[14] while ide-cel comprises an extracellular single-chain variable fragment with one heavy and one light chain targeting a single epitope of BCMA.[28-30]

Other recently approved agents for treating triple-class refractory RRMM, selinexor[5] and belantamab mafodotin,[6] have demonstrated limited clinical benefit in heavily pretreated patients with RRMM. ORR with selinexor was 26%, and the median PFS was 3.7 months.[7] Similarly, treatment with the recommended dosage of belantamab mafodotin resulted in an ORR of 31% and a median PFS of 2.9 months.[8]

The safety profile of cilta-cel remained manageable at 28-month MFU, with a risk/benefit profile that remains favorable. TEAEs were consistent with the 1-year MFU.[14] Of the SPM observed, none were classified as related to cilta-cel and six were nonmelanoma skin cancers. This patient population was heavily pretreated, including with IMiDs (100%), alkylating agents (melphalan 83%; cyclophosphamide 65%), and/or autologous stem-cell transplantation (90%), all of which are associated with increased risk of SPM.[31,32] Furthermore, these heavily treated patients have survived longer with cilta-cel than with other available treatments, and, therefore, continued follow-up is warranted.[32]

One new case of parkinsonism (day 914 after cilta-cel) was observed since the last report and is manageable as the patient is stable to improving with no CAR-T cell–directed treatments. This patient had grade 2 CRS and grade 3 ICANS, two risk factors that have been associated with parkinsonism after cilta-cel.[33,34] Implementation of patient management strategies after CARTITUDE-1 have reduced the incidence of parkinsonism from 6% in CARTITUDE-1 to $< 0.5\%$ across the other studies of the cilta-cel program. Parkinsonism events appear to be a class effect of BCMA CAR-T therapies,[11] and the delayed onset of this case underscores the need for continued patient monitoring. As cilta-cel is extending the lifespan of heavily pretreated RRMM patients, late-onset side effects may be observed with long-term follow-up.

Patients from the CARTITUDE-1 trial will continue to be followed for up to 15 years after infusion in a separate study (CARTinue, MMY4002) to further evaluate long-term efficacy and safety.

In conclusion, these longer-term data from CARTITUDE-1 in triple-class exposed patients with RRMM demonstrate deep and durable responses to cilta-cel over time, including in high-risk subgroups. The safety profile continues to be manageable. The recent approval of cilta-cel (CARVYKTI; Janssen Biotech, Inc, Horsham, PA) in the US and positive CHMP opinion by the EMA will help fill an unmet medical need in this difficult-to-treat population.

AFFILIATIONS

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APPENDIX

TABLE A1. Patient Demographics and Baseline Characteristics

Characteristic	Phase 1b (n = 29)	Phase 2 (n = 68)	Total (N = 97)
Median age, years	60.0 (57-67)	62.0 (55-70)	61.0 (56-68)
Sex			
Male	14 (48%)	43 (63%)	57 (59%)
Female	15 (52%)	25 (37%)	40 (41%)
Race			
White	20 (69%)	49 (72%)	69 (71%)
Black	5 (17%)	12 (18%)	17 (18%)
Asian	1 (3%)	0	1 (1%)
American Indian/ Alaska native	1 (3%)	0	1 (1%)
Native Hawaiian/other Pacific islander	0	1 (1%)	1 (1%)
Not reported	2 (7%)	6 (9%)	8 (8%)
Ethnicity			
Hispanic or Latino	2 (7%)	4 (6%)	6 (6%)
Not Hispanic or Latino	25 (86%)	60 (88%)	85 (88%)
Not reported	2 (7%)	4 (6%)	6 (6%)
Median time since diagnosis, years	5.1 (3.5-7.8)	6.7 (4.6-8.5)	5.9 (4.4-8.4)
Type of myeloma by immunofixation			
Light chain	8 (28%)	16 (24%)	24 (25%)
Kappa	5 (17%)	10 (15%)	15 (16%)
Lambda	3 (10%)	6 (9%)	9 (9%)
Extramedullary plasmacytomas ≥1	4 (14%)	9 (13%)	13 (13%)
Bone marrow plasma cells ≥60%	7 (24%)	14 (21%)	21 (22%)
ECOG performance-status score			
0	12 (41%)	27 (40%)	39 (40%)
1	14 (48%)	40 (59%)	54 (56%)
2	3 (10%)	1 (2%)	4 (4%)
ISS stage			
I	20 (69%)	41 (60%)	61 (63%)
II	9 (31%)	13 (19%)	22 (23%)
III	0	14 (21%)	14 (14%)
High-risk cytogenetic profile	7 (24%)	16 (24%)	23 (24%)
del17p	4 (14%)	15 (22%)	19 (20%)
t(14;16)	2 (7%)	0	2 (2%)
t(4;14)	1 (3%)	2 (3%)	3 (3%)
Tumor BCMA expression			
≥50%	18/20 (90%)	39/42 (93%)	57/62 (92%)
Median previous therapies for multiple myeloma	5.0 (4.0-8.0)	6.0 (4.0-8.0)	6.0 (4.0-8.0)
Previous stem-cell transplantation			
Autologous	26 (90%)	61 (90%)	87 (90%)
Allogeneic	0	8 (12%)	8 (8%)
Prior proteasome inhibitors			
Carfilzomib			
Exposed	26 (90%)	57 (84%)	83 (86%)
Refractory	21 (72%)	42 (62%)	63 (65%)
Bortezomib			
Exposed	25 (86%)	67 (99%)	92 (95%)
Refractory	15 (52%)	51 (75%)	66 (68%)
Ixazomib			
Exposed	9 (31%)	20 (29%)	29 (30%)
Refractory	7 (24%)	20 (29%)	27 (28%)
Prior immunomodulatory drugs			
Lenalidomide			
Exposed	29 (100%)	67 (99%)	96 (99%)
Refractory	22 (76%)	57 (84%)	79 (81%)
Pomalidomide			
Exposed	26 (90%)	63 (93%)	89 (92%)
Refractory	22 (76%)	59 (87%)	81 (84%)
Prior anti-CD38 monoclonal antibodies			
Daratumumab			
Exposed	27 (93%)	67 (99%)	94 (97%)
Refractory	27 (93%)	67 (99%)	94 (97%)[a]
Penta-drug exposed[b]	22 (76%)	59 (87%)	81 (84%)
Triple-class refractory[c]	25 (86%)	60 (88%)	85 (88%)
Penta-drug refractory[b]	9 (31%)	32 (47%)	41 (42%)
Refractory to last line of therapy	28 (97%)	68 (100%)	96 (99%)

NOTE. Data are median (IQR) or No. (%). Reprinted from The Lancet, Vol 398, Issue 10297, Jesus G. Berdeja, Deepu Madduri, Saad Z. Usmani, Andrzej Jakubowiak, Mounzer Agha, Adam D. Cohen, A. Keith Stewart, Parameswaran Hari, Myo Htut, Alexander Lesokhin, Abhinav Deol, Nikhil C. Munshi, Elizabeth O'Donnell, David Avigan, Indrajeet Singh, Enrique Zudaire, 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," pages 4-5, Copyright (2021), with permission from Elsevier.[14]

Abbreviations: BCMA, B-cell maturation antigen; ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System.

[a]Two additional patients were refractory to other anti-CD38 antibodies.

[b]Two or more proteasome inhibitors, two or more immunomodulatory drugs, and one anti-CD38 antibody.

[c]One or more proteasome inhibitors, one or more immunomodulatory drug, and one anti-CD38 antibody.

TABLE A2. Efficacy Outcomes in Patient Subgroups

Subgroup	Patients, No. (%)	ORR, % (95% CI)	Median DOR, Months (95% CI)	MRD 10^{-5} Negativity,[a] No. (%)	Median PFS, (95% CI)	27-Month PFS, % (95% CI)	27-Month OS, % (95% CI)
Overall	97 (100)	97.9 (92.7 to 99.7)	NE (23.3 to NE)	56/61 (91.8)	NE (24.5 to NE)	54.9 (44.0 to 64.6)	70.4 (60.1 to 78.6)
≥ 65 years[b]	35 (36)	97.1 (85.1 to 99.9)	NE (24.4 to NE)	21 (91.3)	NE (25.2 to NE)	55.9 (36.2 to 71.7)	70.9 (52.6 to 83.2)
Black/African American	17 (18)	100.0 (80.5 to 100)	NE (6.8 to NE)	10 (83.3)	NE (7.7 to NE)	51.8 (26.2 to 72.4)	58.8 (32.5 to 77.8)
3 prior LOT	17 (18)	100.0 (80.5 to 100)	NE (12.9 to NE)	8 (80.0)	NE (13.8 to NE)	56.7 (30.0 to 76.6)	76.5 (48.8 to 90.4)
≥ 4 prior LOT	80 (82)	97.5 (91.3 to 99.7)	28.3 (23.3 to NE)	48 (94.1)	30.1 (24.5 to NE)	54.0 (41.7 to 64.8)	69.0 (57.3 to 78.1)
Triple-class refractory	85 (88)	97.6 (91.8 to 99.7)	NE (24.3 to NE)	50 (92.6)	NE (25.2 to NE)	55.6 (43.8 to 65.9)	69.7 (58.4 to 78.5)
Penta-drug refractory	41 (42)	95.1 (83.5 to 99.4)	NE (24.4 to NE)	17 (85.0)	NE (25.3 to NE)	61.6 (44.0 to 75.1)	66.8 (49.3 to 79.4)
Cytogenetic risk							
Standard risk	68 (70)	97.1 (89.8 to 99.6)	NE (24.4 to NE)	40 (95.2)	NE (25.3 to NE)	57.8 (44.3 to 69.1)	72.9 (60.4 to 82.0)
High risk	23 (24)	100.0 (85.2 to 100)	20.2 (9.4 to NE)	14 (82.4)	21.1 (10.8 to NE)	43.5 (23.3 to 62.1)	64.6 (41.4 to 80.5)
ISS stage III	14 (14)	100.0 (76.8 to 100)	14.1 (5.1 to NE)	6 (100.0)	15.0 (6.1 to NE)	34.3 (11.6 to 58.7)	50.0 (22.9 to 72.2)
Bone marrow plasma cells							
≤ 30%	58 (60)	98.3 (90.8 to 100)	NE (25.7 to NE)	28 (96.6)	NE (30.1 to NE)	64.3 (50.0 to 75.5)	75.7 (62.4 to 84.8)
> 30% to < 60%	17 (18)	100.0 (80.5 to 100)	24.4 (15.9 to NE)	14 (87.5)	25.3 (16.8 to NE)	35.3 (11.6 to 60.5)	86.3 (54.7 to 96.5)
≥ 60%	21 (22)	95.2 (76.2 to 99.9)	23.1 (5.5 to NE)	14 (87.5)	24.1 (6.5 to NE)	45.9 (23.6 to 65.6)	45.9 (23.6 to 65.6)
Baseline tumor BCMA expression							
≥ median (80%)	31 (32)	96.8 (83.3 to 99.9)	NE (21.8 to NE)	16 (94.1)	NE (26.4 to NE)	65.8 (45.1 to 80.2)	75.9 (55.6 to 87.9)
< median (80%)	31 (32)	100.0 (88.8 to 100)	NE (17.1 to NE)	22 (95.7)	NE (18.0 to NE)	54.8 (36.0 to 70.3)	71.0 (51.6 to 83.7)
Presence of baseline plasmacytomas[c]	19 (20)	100.0 (82.4 to 100)	12.9 (3.5 to NE)	10 (90.9)	13.8 (5.3 to NE)	47.4 (24.4 to 67.3)	52.1 (28.0 to 71.6)

Abbreviations: BCMA, B-cell maturation antigen; CR, complete response; DOR, duration of response; ISS, International Staging System; LOT, lines of therapy; MRD, minimal residual disease; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response.

[a]In MRD-evaluable patients; MRD was assessed in evaluable samples at 10^{-5} threshold by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) in all treated patients at day 28 and at 6, 12, 18, and 24 months regardless of the status of disease measured in blood or urine. Only MRD assessments within 3 months of achieving CR/sCR until death/progression/subsequent therapy (exclusive) are considered.

[b]There were eight patients age > 75 years. No difference was observed in ORR between these patients and other age subgroups.

[c]Includes bone-based and extramedullary plasmacytomas.

TABLE A3. Study Deaths

Deaths	Total (N = 97)	Time of Death After Cilta-Cel Infusion, Days
Total deaths during the study, No.	30	45-917
Due to progressive disease	14	253-746
Due to AEs unrelated to treatment	10	
Pneumonia	1	109
Acute myelogenous leukemia[a]	3	418, 582, 718
Ascites[b]	1	445
MDS	1	803
Respiratory failure	3	733, 793, 829
Septic shock	1	917
Due to AEs related to treatment, No.	6	
Sepsis and/or septic shock	2	45, 162
CRS/HLH	1	99
Lung abscess	1	119
Respiratory failure	1	121
Neurotoxicity	1	247

Abbreviations: AEs, adverse events; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; MDS, myelodysplastic syndrome.

[a]One patient with acute myelogenous leukemia also had MDS and a cytogenetic profile consistent with MDS (del20q [present before cilta-cel infusion], loss of 5q); another patient who died from acute myelogenous leukemia had both prostate cancer and squamous cell carcinoma of the scalp.

[b]Patient died from ascites unrelated to cilta-cel as assessed by the investigator because of noncirrhotic portal fibrosis and nonalcoholic steatosis that was present for many years preceding the study.