# Cilta-cel in lenalidomide-refractory multiple myeloma (CARTITUDE-4): an updated analysis including overall survival from an open-label, multicentre, randomised, phase 3 trial

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## Summary

**Background** In CARTITUDE-4, a single infusion of ciltacabtagene autoleucel (cilta-cel) significantly prolonged progression-free survival in patients with lenalidomide-refractory multiple myeloma. We report updated overall survival and longer-term efficacy and safety outcomes.

**Methods** CARTITUDE-4 is an open-label, multicentre, randomised, phase 3 trial at 81 hospital sites in the USA, Europe, Asia, and Australia. Eligible patients were adults (aged >18 years) with lenalidomide-refractory multiple myeloma, with one to three previous treatment lines, including a proteasome inhibitor and an immunomodulatory drug, and an Eastern Cooperative Oncology Group performance status of 0 or 1. After the trial started, the threshold defining measurable disease was lowered to 0·5 g/dL from 1·0 g/dL serum monoclonal paraprotein on July 2, 2021, to increase trial access. Patients were randomly assigned (1:1) via a computerised algorithm and balanced with permuted blocks, with stratification by physician's choice of pomalidomide–bortezomib–dexamethasone versus daratumumab–pomalidomide–dexamethasone, International Staging System stage, and number of previous treatment lines. Patients were assigned to cilta-cel (apheresis, bridging therapy [at least one pomalidomide–bortezomib–dexamethasone or daratumumab–pomalidomide–dexamethasone cycle], lymphodepletion, then cilta-cel infusion [$0·75 \times 10^6$ CAR T cells per kg]) or standard of care (pomalidomide–bortezomib–dexamethasone [21-day cycles: 4 mg/day oral pomalidomide on days 1–14; 1·3 mg/m² subcutaneous bortezomib twice a week for 2 weeks for eight cycles, then once a week for 2 weeks per cycle; 20 mg or, if aged >75 years, 10 mg oral dexamethasone on days 1, 2, 4, 5, 8, 9, 11, and 12 for eight cycles, then days 1, 2, 8, and 9 per cycle] or daratumumab–pomalidomide–dexamethasone [28-day cycles: 1800 mg subcutaneous daratumumab weekly for 2 cycles, every 2 weeks for four cycles, then every 4 weeks; 4 mg/day oral pomalidomide on days 1–21; 40 mg/week or, if aged >75 years, 20 mg/week oral or intravenous dexamethasone]). The primary endpoint was progression-free survival, previously published. In this Article, we report a prespecified second interim analysis of overall survival and an updated analysis of progression-free survival in the intention-to-treat population. This trial was registered at ClinicalTrials.gov (NCT04181827) and is ongoing.

**Findings** Patients were randomly assigned between July 10, 2020, and Nov 17, 2021, to receive cilta-cel (n=208) or standard of care (n=211). At a median follow-up of 33·6 months (IQR 20·3–35·0), median progression-free survival was not reached (95% CI 34·5 months–not evaluable) in the cilta-cel group versus 11·8 months (9·7–14·0) in the standard-of-care group (HR 0·29 [95% CI 0·22–0·39]). Median overall survival was not reached (95% CI not evaluable) with cilta-cel versus not reached (37·7 months–not evaluable) with standard of care (HR 0·55 [95% CI 0·39–0·79]; p=0·0009). 30 (14%) of 208 patients in the cilta-cel group and 77 (37%) of 208 in the standard-of-care group had maximum grade 3 treatment-emergent adverse events, most commonly anaemia (72 [35%]) in the cilta-cel group and neutropenia (59 [28%]) in the standard-of-care group. Rates of maximum grade 4 treatment-emergent adverse events were 156 (75%) with cilta-cel and 116 (56%) with standard of care, most commonly neutropenia (152 [73%] with cilta-cel and 112 [54%] with standard of care). Serious treatment-emergent adverse events occurred in 98 (47%) patients in each group. Deaths in the safety population occurred in 50 (24%) in the cilta-cel group and 82 (39%) in the standard-of-care group, including due to treatment-related adverse events in six (3%; four due to infection) in the cilta-cel group and five (2%; all due to infection) in the standard-of-care group.

**Interpretation** The significantly improved overall survival and patient-reported measures in CARTITUDE-4 reinforce the use of cilta-cel in treating relapsed or refractory multiple myeloma as early as after first relapse.

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## Introduction

In patients with multiple myeloma, lenalidomide-refractory disease is increasingly common, occurring as early as the first relapse, and is associated with poor prognosis.[1–5] Ciltacabtagene autoleucel (cilta-cel) is a B-cell maturation antigen (BCMA)-directed chimeric antigen receptor (CAR) T-cell therapy approved by the US Food and Drug Administration and the European Commission to treat lenalidomide-refractory relapsed multiple myeloma after one or more previous treatment lines, including a proteasome inhibitor and an immunomodulatory agent. Approval was based on the CARTITUDE-4 trial, which compared a single cilta-cel infusion with physician's choice of continuously administered pomalidomide–bortezomib–dexamethasone or daratumumab–pomalidomide–dexamethasone, two standard-of-care regimens available at the time of study design.[5] At the primary analysis (median follow-up 15·9 months [IQR 12·4–17·8]), significant and clinically meaningful improvement in progression-free survival was observed in the cilta-cel group (median not reached for cilta-cel *vs* 11·8 months [95% CI 9·7–13·8] for standard of care; hazard ratio [HR] 0·26 [95% CI 0·18–0·38] for the protocol-specified weighted analysis, p<0·001; 0·40 [0·29–0·55] for the protocol-specified unweighted sensitivity analysis, p<0·001).[5] In this Article, we report protocol-specified overall survival and updated efficacy and safety outcomes in CARTITUDE-4 at the second interim analysis.

## Methods

### Study design and participants

CARTITUDE-4 is an ongoing, randomised, open-label, multicentre, phase 3 trial conducted at 81 hospital sites across the USA, Europe, Asia, and Australia (appendix pp 3–15); the full design and eligibility criteria are available

### Research in context

#### Evidence before this study

We searched PubMed records between Oct 1, 2019, and May 31, 2024, using the terms "multiple myeloma", "lenalidomide-refractory", "relapsed", and "refractory" with no language restrictions. At the time of study design, there were no randomised studies published for chimeric antigen receptor (CAR) T-cell therapy in the treatment of relapsed or lenalidomide-refractory multiple myeloma. At the time of the data cutoff, the primary analysis for CARTITUDE-4 was the only published randomised study of CAR T-cell therapy for the treatment of patients with lenalidomide-refractory multiple myeloma with one to three previous lines of therapy. CARTITUDE-4 evaluated a single ciltacabtagene autoleucel (cilta-cel) infusion in patients with lenalidomide-refractory multiple myeloma and one to three previous lines of therapy, including a proteasome inhibitor and immunomodulatory drug, compared with standard of care (daratumumab–pomalidomide–dexamethasone and pomalidomide–bortezomib–dexamethasone). At a median follow-up of 15·9 months (primary analysis), cilta-cel significantly improved progression-free survival (primary endpoint) compared with standard of care in patients with lenalidomide-refractory multiple myeloma after one to three previous lines of therapy. Additionally, significant and clinically meaningful improvements in key secondary endpoints including complete response or better, overall response, and minimal residual disease negativity were observed. At the time of the primary analysis, overall survival was immature. An updated study of idecabtagene vicleucel (ide-cel) in KarMMa-3 was published after this search timeframe and in a different population of patients with relapsed refractory multiple myeloma who had two to four previous lines of therapy. At a median follow-up of 30·9 months, median overall survival was 41·4 months for ide-cel versus 37·9 months for standard regimens (hazard ratio 1·01 [95% CI 0·73–1·40]). However, this study allowed crossover from standard regimens upon progressive disease, which confounded the overall survival interpretation.

#### Added value of this study

The results of this analysis report updated overall survival at a median follow-up of 33·6 months. With an additional 18 months of follow-up, patients given a single cilta-cel infusion had a significant improvement in overall survival compared with standard of care. Additionally, a single dose of cilta-cel also positively affected health-related quality of life by extending the time to worsening of symptoms compared with standard of care, as measured by the Multiple Myeloma Symptom and Impact Questionnaire total symptom score, an endpoint prespecified in the testing hierarchy. Key secondary endpoints remained generally unchanged from the primary study results. The safety profile of cilta-cel was consistent with previous analysis, and the overall benefit-to-risk profile of cilta-cel remains favourable in patients with lenalidomide-refractory multiple myeloma after one to three previous lines of therapy.

#### Implications of all the available evidence

CARTITUDE-4 is the first phase 3 study to show a significant overall survival benefit with a CAR T-cell therapy in relapsed or refractory multiple myeloma. Cilta-cel significantly reduced the risk of death and improved quality of life compared with standard of care in patients with lenalidomide-refractory disease as early as after first relapse with longer-term follow-up. These data will help to inform treatment decisions in patients with lenalidomide-refractory multiple myeloma as early as after one previous line of therapy.

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See Online for appendix

in the protocol previously published with the primary analysis.[5] Briefly, eligible adult patients (aged >18 years) had a documented diagnosis of multiple myeloma per International Myeloma Working Group (IMWG) criteria[6] and measurable disease, defined as a serum monoclonal paraprotein (M-protein) concentration of at least 0·5 g/dL (amended on July 2, 2021, from 1·0 g/dL to enable access to more patients) or urine M-protein concentration of at least 200 mg/24 h; or light-chain multiple myeloma without measurable M-protein in serum or urine (serum free light chain ≥10 mg/dL and abnormal serum free light-chain ratio). Patients were lenalidomide refractory (per IMWG consensus guidelines[7]); had received one to three previous treatment lines, including a proteasome inhibitor and an immunomodulatory agent; had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1; had documented evidence of disease progression per IMWG criteria based on investigator discretion on or within 6 months or their last regimen; and had no previous CAR T-cell or BCMA-targeted treatment. Sex was reported based on patients' medical records in the database. Other eligibility criteria are reported in the appendix (p 16).

The protocol was approved by each site's independent ethics committee or institutional review board (appendix pp 3–15). The study was conducted in accordance with the International Council for Harmonisation Good Clinical Practice guidelines and the principles of the Declaration of Helsinki. All patients provided written informed consent.[5] An Independent Data Monitoring Committee had access to aggregated data summaries by treatment group. The study was registered with ClinicalTrials.gov (NCT04181827).

### Randomisation and masking

Patients were randomly assigned 1:1 to receive standard of care (ie, pomalidomide–bortezomib–dexamethasone or daratumumab–pomalidomide–dexamethasone) or cilta-cel via a computer-generated randomisation sequence. We balanced randomisation using permuted blocks and stratified by standard of care (pomalidomide–bortezomib–dexamethasone *vs* daratumumab–pomalidomide–dexamethasone), International Staging System stage (I *vs* II *vs* III), and number of previous treatment lines (one *vs* two or three). Patients and site staff were not masked due to differences in dosing and administration.

### Procedures

Patients randomly assigned to standard of care received either pomalidomide–bortezomib–dexamethasone in 21-day cycles (pomalidomide 4 mg/day orally on days 1–14 of each cycle; bortezomib 1·3 mg/m² subcutaneously twice a week for 2 weeks for the first eight cycles, then once a week for 2 weeks thereafter; and dexamethasone 20 mg/day [for patients aged ≤75 years] or 10 mg/day [for patients aged >75 years] orally on days 1, 2, 4, 5, 8, 9, 11, and 12 from cycles 1–8, then on days 1, 2, 8, and 9 of each cycle) or daratumumab–pomalidomide–dexamethasone in 28-day cycles (daratumumab 1800 mg subcutaneously once a week for cycles 1 and 2, then once every 2 weeks for cycles 3–6, then once every 4 weeks starting at cycle 7; pomalidomide 4 mg/day orally on days 1–21 of each cycle; and dexamethasone 40 mg/week [for patients aged ≤75 years] or 20 mg/week [for patients aged >75 years] orally or intravenously) until disease progression, death, intolerable toxicity, the withdrawal of consent, or the end of the study. Crossover from the standard-of-care to the cilta-cel group was not permitted.

Patients randomly assigned to cilta-cel underwent apheresis, one or more cycles of bridging therapy (pomalidomide–bortezomib–dexamethasone or daratumumab–pomalidomide–dexamethasone), lymphodepletion (intravenous cyclophosphamide 300 mg/m² and fludarabine 30 mg/m² daily for 3 days), and a single cilta-cel infusion (target dose of $0{\cdot}75\times10^6$ CAR-positive viable T cells per kg 5–7 days after the start of lymphodepletion). Patients were monitored for efficacy until confirmed disease progression, the withdrawal of consent, or the end of the study. Patients with confirmed disease progression during bridging therapy or lymphodepletion in the cilta-cel group could receive cilta-cel as subsequent therapy. Dose modifications for daratumumab–pomalidomide–dexamethasone and pomalidomide–bortezomib–dexamethasone due to adverse events were permitted per investigator discretion, except for daratumumab dose reductions.

IMWG criteria[7] and a validated computerised algorithm[8] were used to identify treatment responses and disease progression (appendix p 16). Patients unevaluable for response were listed as not evaluable. Minimal residual disease (MRD) negativity was assessed in bone marrow ($10^{-5}$ and $10^{-6}$ thresholds) in a central laboratory by next-generation sequencing (clonoSEQ, version 2.0; Adaptive Biotechnologies, Seattle, WA, USA). Radiographic assessments, including CT scans, were conducted locally as clinically indicated to document disease progression. Timing of MRD assessments is described in the appendix (p 16). Time to symptom worsening, a patient-reported outcome, was assessed with the Multiple Myeloma Symptom and Impact Questionnaire (MySIm-Q); the timing of assessments, previously reported, is described in the appendix (p 16).[5] Briefly, MySIm-Q data after baseline were collected in the standard-of-care group every 3–4 weeks during the first 3 study months, then every 3 months until disease progression. In the cilta-cel group, MySIm-Q data after baseline were collected on day 1 of bridging therapy; day 1 of lymphodepletion; day 28 after cilta-cel infusion (approximate study month 3); approximate study months 6, 9, and 12; and then every 6 months until disease progression. Patients were monitored continuously for adverse events. Details on genetic testing for patients who developed myelodysplastic syndrome, acute myeloid leukaemia, or

both are described in the appendix (p 16). Cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome (ICANS) were graded by the investigator using the American Society for Transplantation and Cellular Therapy consensus criteria.[9] Other adverse events, including investigator-assessed non-ICANS neurotoxicity, were graded by the investigator using the Common Terminology Criteria for Adverse Events of the National Cancer Institute, version 5.0.[10]

### Outcomes

The primary endpoint was progression-free survival (defined as the duration from the date of randomisation to either progressive disease [according to the IMWG criteria, assessed at a central laboratory] or death, whichever comes first); the primary endpoint was previously reported in the first interim analysis, in which progression-free survival reached significance and was therefore met.[5] The secondary endpoints were the rate of complete response (defined as the proportion of patients with a complete response or better according to IMWG response criteria, assessed at a central laboratory), overall MRD negativity rate ($10^{-5}$ threshold; defined as the proportion of patients who had MRD negativity at any time after the date of randomisation before initiation of subsequent therapy), sustained MRD negativity rate (defined as the proportion of patients who had MRD negativity, confirmed a minimum of 1 year apart and without any examination showing an MRD-positive status in between), rate of MRD negativity in patients with complete response or stringent complete response at 12 months (±3 months), overall survival (measured from the date of randomisation to the date of death due to any cause), progression-free survival on next-line therapy (defined as the interval between the date of randomisation and the date of event, defined as progressive disease as assessed by the investigator that starts after the next line of therapy, or death from any cause, whichever occurs first), time to worsening of symptoms (defined as the interval from the date of randomisation to the start date of worsening as measured by the MySIm-Q total symptom score[11]), overall response rate (defined as the proportion of patients who had partial response or better), the safety profile of cilta-cel by incidence and severity of adverse events, and immunogenicity of cilta-cel by presence of anti-cilta-cel antibodies.

Key secondary endpoints included the rates of complete response or better, overall response, and overall MRD negativity, which were also previously reported and reached significance in the first interim analysis.[5] The other key secondary endpoints, overall survival and time to worsening of symptoms on the MySlm-Q, were sequentially tested in this second interim overall survival analysis by use of a hierarchical procedure.[11] In this Article, we report a prespecified second interim analysis of overall survival and an updated analysis of progression-free survival in the intention-to-treat population. We also report secondary endpoints MRD negativity rate, rate of complete response or better, progression-free survival on next-line therapy, and time to symptom worsening on the MySIm-Q. We also present a safety analysis via assessment of the number of adverse events.

### Statistical analysis

Detailed statistical methodology was previously published (appendix pp 17–18).[5] The primary endpoint (progression-free survival) was assessed and previously published in the first interim analysis. This second interim overall survival analysis was prespecified to occur at the same time as this final progression-free survival analysis, when approximately 250 progression-free survival events had accumulated.

Efficacy was evaluated in the intention-to-treat population, defined as all patients who were randomly assigned to a treatment group. Patients were evaluable for the analysis of MRD negativity if the MRD sample passed calibration and quality control, including having sufficient cells for evaluation at the respective testing threshold, and if a postbaseline sample was available for testing. Adverse events were evaluated in all patients who received any portion of study treatment (safety population). Efficacy and adverse events specific to CAR T-cell therapy were evaluated in patients who received cilta-cel as study treatment.

Progression-free survival, overall survival, and MySIm-Q time to symptom worsening were estimated by the Kaplan–Meier method and were compared between treatment groups by a stratified log-rank test. As previously reported, the primary endpoint of progression-free survival was a stratified constant piecewise weighted test, and an unweighted test as a sensitivity analysis.[5] Overall survival data were censored at the patients' last date known to be alive; progression-free survival and MySIm-Q data were censored at date of the last disease assessment before the start of any subsequent antimyeloma therapy, and at randomisation for patients with no disease assessment after baseline. MySIm-Q data were censored at date of last assessment for those who did not have symptom worsening. MySIm-Q worsening was defined as a meaningful increase (estimated by distribution-based methods of at least half a standard deviation from pooled baseline values) without a subsequent reduction in myeloma symptoms; death due to disease progression was considered as worsening. MySIm-Q event-free rates were estimated with the Kaplan–Meier method. Treatment effects were estimated with stratified Cox proportional hazards models with treatment as the sole explanatory variable. As prespecified, the proportional hazards assumption was tested for progression-free survival, but not overall survival, and was not met (appendix pp 17–18). Treatment effects in complete response or better, overall response,

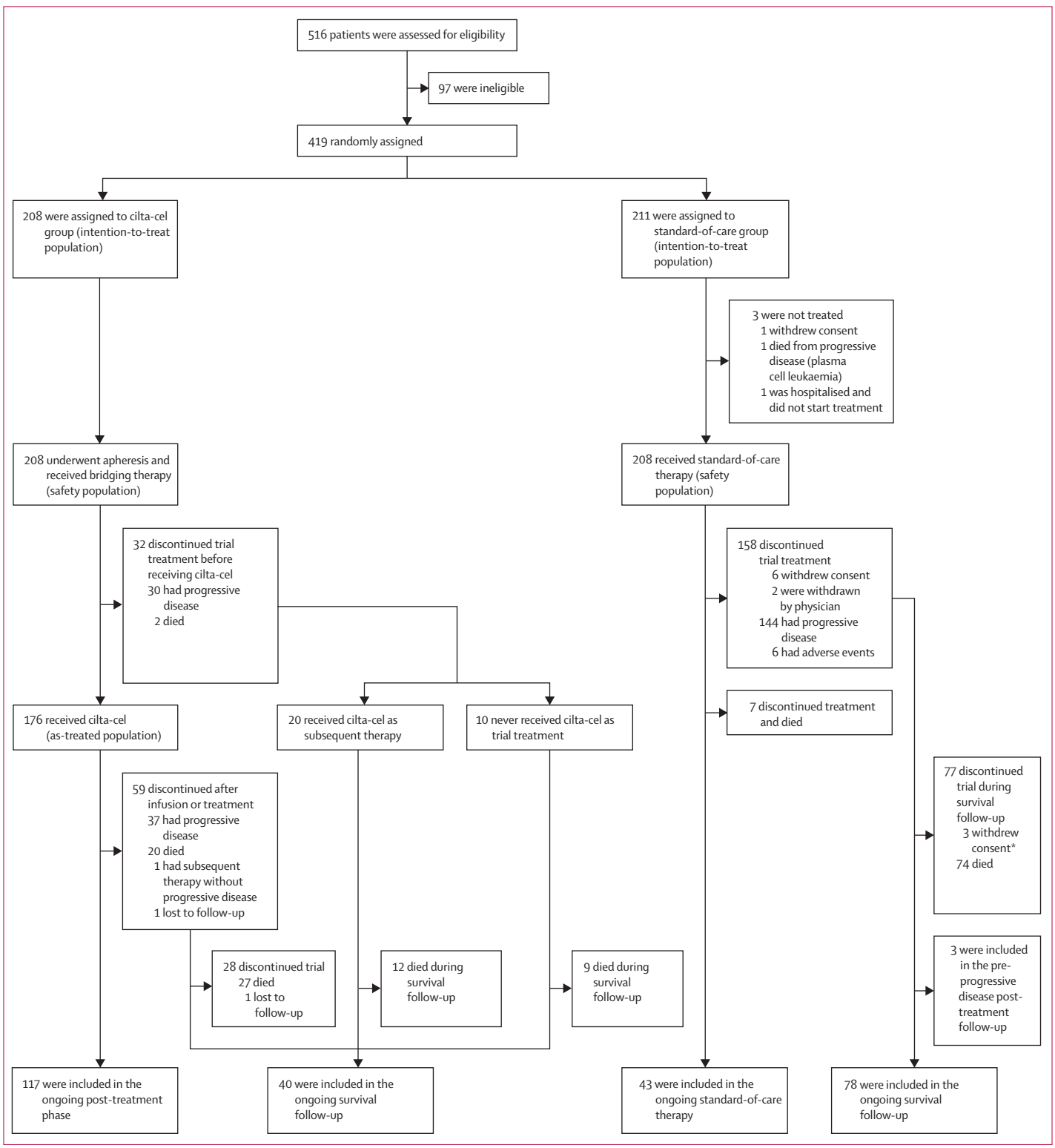



***Figure 1:*** **Trial profile**
*Includes one death.

and overall MRD negativity were estimated with Cochran–Mantel–Haenszel odds ratios. Progression-free survival, complete response or better, overall response, and overall MRD negativity reached significance in the primary analysis,[5] and were therefore not formally tested in the current analysis, and p values are not reported. The significance level required to establish superiority of overall survival at this prespecified second interim analysis, 0·0108, was established based on the observed number of deaths by use of the power (Kim-DeMets) spending function with a parameter of 2. The key secondary endpoint of MySIm-Q time to symptom worsening was sequentially tested after overall survival according to the prespecified hierarchical testing procedure.

Progression-free survival and overall survival were assessed in prespecified subgroups in protocol-defined exploratory analyses, and post hoc for other subgroups (ie, patients with cytogenetic high risk with at least two of four markers that are abnormal and excluding gain/amp (1q), and patients who were daratumumab naive). Antimyeloma treatment-free survival (defined as the time from the date of the last study treatment to subsequent therapy or death due to progressive disease, whichever occurred first), efficacy in patients who received cilta-cel as the study treatment (ie, the as-treated population), overall MRD in MRD-evaluable patients, sustained MRD negativity rate (defined as the proportion of patients who had MRD negativity, confirmed a minimum of 1 year apart and without any examination showing an MRD-positive status in between) with complete response or better, overall survival in patients in CARTITUDE-4 and CARTITUDE-1 who received cilta-cel as study treatment (including stratified by the number of previous lines of therapy), and genetics of patients with myelodysplastic syndrome and/or acute myeloid leukaemia were assessed post hoc. The estimated 30-month rates of progression-free survival, overall survival, and MySIm-Q in the intention-to-treat population were analysed in a prespecified analysis using the Kaplan–Meier method. Estimated 30-month rates of treatment-free survival and of overall survival and progression-free survival in the as-treated group were analysed post hoc using the Kaplan–Maier method. We chose 30 months as the timepoint for analysis because it occurred before the median follow-up duration. Statistical analyses were conducted with SAS (version 9.4).


### Role of the funding source

The funders of the study had roles in study design, data collection, data analyses, data interpretation, and the writing of this article.

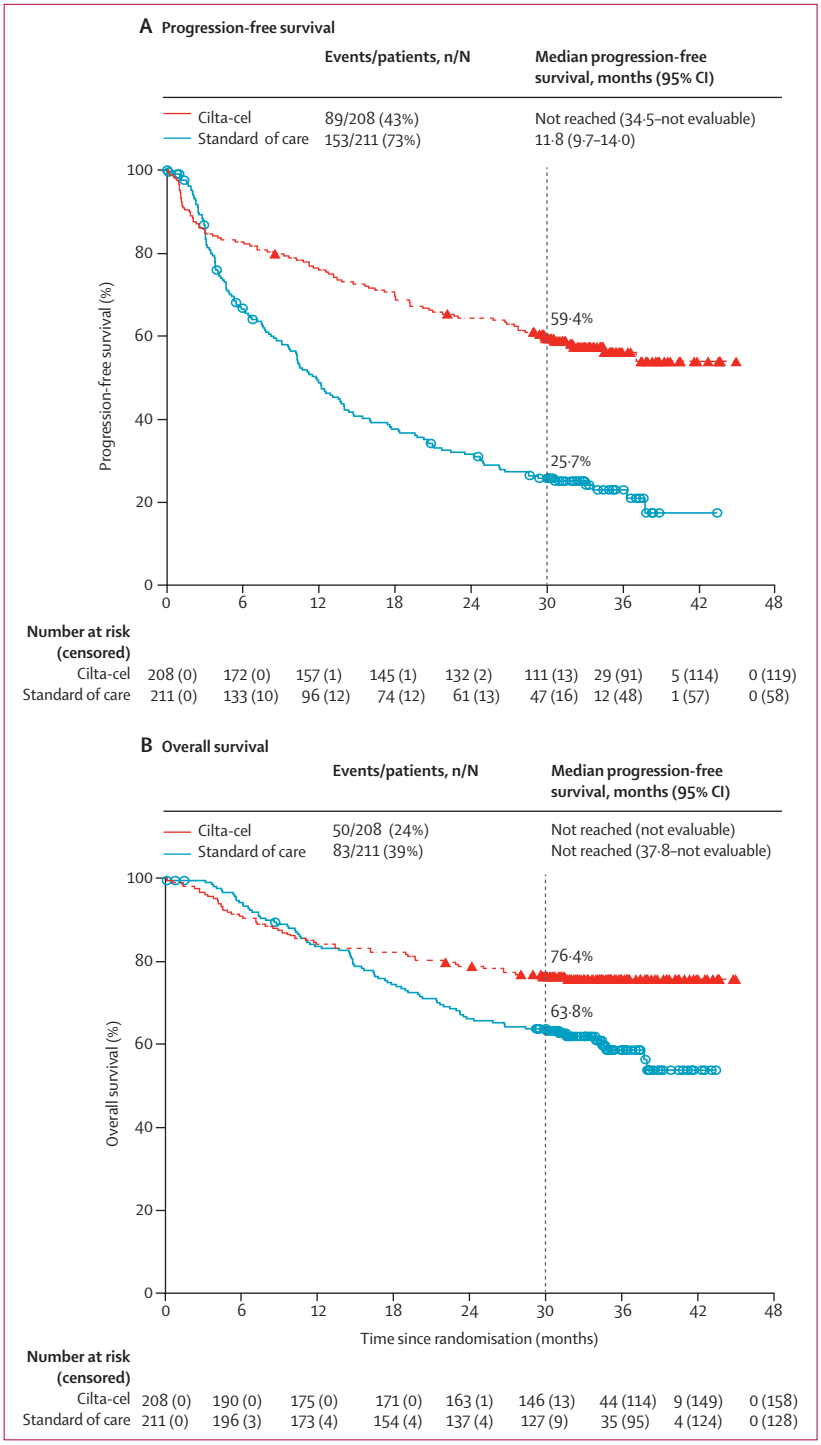




*Figure 2:* **Kaplan–Meier estimates of overall survival and progression-free survival (intention-to-treat population)**
(A) Progression-free survival. (B) Overall survival. The dashed lines indicate these outcomes at 30 months.

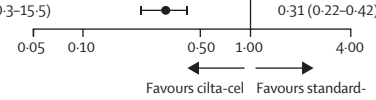
## Results

Between July 10, 2020, and Nov 17, 2021, 516 patients were assessed for eligibility, of whom 419 patients were enrolled and randomly assigned to the cilta-cel (208 patients) or standard-of-care group (211 patients; 28 treated with pomalidomide–bortezomib–dexamethasone and 183 treated with daratumumab–pomalidomide–dexamethasone).[5] Three patients in the standard-of-care

group did not receive study treatment (figure 1). At the data cutoff on May 1, 2024, median follow-up duration was 33·6 months (IQR 20·3–35·0). Reasons patients were censored from time-to-event analyses are summarised in the appendix (p 19). The status of patients in the study is shown in figure 1. Baseline characteristics of both treatment groups were generally well balanced (appendix pp 20–21).[5] The median cilta-cel dose was $0·71\times10^6$ cells/kg (IQR 0·62–0·78) and the median number of treatment cycles in the standard-of-care group was 12 (IQR 5–31).

**A**

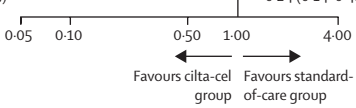
| | Cilta-cel events/patients | Cilta-cel median (95% CI) | Standard of care events/patients | Standard of care median (95% CI) | HR*† (95% CI) |
|---|---|---|---|---|---|
| **Overall population** | 89/208 | NE (34·5–NE) | 153/211 | 11·8 (9·7–14·0) | 0·29 (0·22–0·39) |
| **Sex** | | | | | |
| Male | 48/116 | NE (31·7–NE) | 90/124 | 10·3 (5·7–12·5) | 0·29 (0·20–0·43) |
| Female | 41/92 | NE (23·0–NE) | 63/87 | 14·0 (10·5–21·7) | 0·31 (0·20–0·49) |
| **Age** | | | | | |
| <65 years | 55/126 | NE (29·9–NE) | 101/131 | 10·7 (7·8–13·1) | 0·27 (0·19–0·39) |
| 65–75 years | 34/78 | NE (27·6–NE) | 50/76 | 13·7 (8·4–21·0) | 0·38 (0·23–0·61) |
| **Race** | | | | | |
| White | 72/157 | 37·1 (29·8–NE) | 118/157 | 10·7 (8·4–13·8) | 0·32 (0·23–0·44) |
| Other | 16/45 | NE (26·7–NE) | 28/47 | 17·4 (10·3–25·1) | 0·28 (0·13–0·61) |
| **Region** | | | | | |
| Europe | 60/128 | 37·1 (23·0–NE) | 100/129 | 10·5 (8·4–14·0) | 0·32 (0·22–0·45) |
| North America | 14/32 | NE (20·2–NE) | 21/32 | 11·2 (4·1–18·3) | 0·28 (0·13–0·61) |
| Other | 15/48 | NE (NE–NE) | 32/50 | 13·6 (7·6–26·7) | 0·27 (0·14–0·53) |
| **Baseline ECOG performance score** | | | | | |
| 0 | 40/114 | NE (37·1–NE) | 84/121 | 13·6 (10·3–18·4) | 0·27 (0·18–0·41) |
| ≥1 | 49/94 | 28·8 (18·1–NE) | 69/90 | 10·3 (5·5–12·2) | 0·33 (0·21–0·49) |
| **Investigator's choice of standard-of-care treatment‡** | | | | | |
| Pomalidomide–bortezomib–dexamethasone | 19/26 | 15·4 (2·1–29·1) | 26/28 | 5·0 (3·4–10·5) | 0·25 (0·11–0·53) |
| Daratumumab–pomalidomide–dexamethasone | 70/182 | NE (37·1–NE) | 127/183 | 12·6 (10·3–16·0) | 0·29 (0·21–0·41) |
| **Number of lines of prior therapy** | | | | | |
| One | 28/68 | NE (27·8–NE) | 45/68 | 17·4 (11·1–26·7) | 0·41 (0·25–0·67) |
| Two or three | 61/140 | NE (29·9–NE) | 108/143 | 10·2 (6·2–12·2) | 0·26 (0·18–0·37) |
| **ISS staging§** | | | | | |
| I | 47/136 | NE (NE–NE) | 91/132 | 14·7 (11·2–20·6) | 0·28 (0·19–0·41) |
| II | 34/60 | 30·2 (18·4–NE) | 50/65 | 6·2 (4·1–11·8) | 0·30 (0·18–0·51) |
| III | 8/12 | 17·3 (2·9–NE) | 12/14 | 3·4 (2·5–11·5) | 0·41 (0·16–1·08) |
| **Presence of soft tissue plasmacytomas** | | | | | |
| Yes | 26/44 | 16·9 (3·6–NE) | 30/35 | 4·7 (3·1–8·4) | 0·36 (0·20–0·66) |
| No | 63/164 | NE (37·1–NE) | 123/176 | 13·1 (10·5–16·1) | 0·28 (0·20–0·39) |
| **Tumour burden¶** | | | | | |
| Low | 42/126 | NE (NE–NE) | 85/129 | 14·0 (10·5–20·6) | 0·27 (0·18–0·41) |
| Intermediate | 26/52 | 30·6 (21·0–NE) | 40/52 | 11·8 (4·7–21·1) | 0·34 (0·19–0·60) |
| High | 21/30 | 12·3 (6·1–32·1) | 28/30 | 4·7 (3·1–7·6) | 0·21 (0·10–0·44) |
| **Type of multiple myeloma‖** | | | | | |
| IgG | 40/100 | NE (32·1–NE) | 72/98 | 12·2 (9·1–18·4) | 0·29 (0·19–0·44) |
| Non-IgG | 20/31 | 18·0 (3·6–NE) | 24/36 | 12·2 (7·1–17·4) | 0·57 (0·29–1·14) |
| **Cytogenetic risk at study entry** | | | | | |
| High risk** | | | | | |
| Any of four markers abnormal | 60/123 | 37·1 (26·7–NE) | 102/132 | 10·3 (7·6–12·6) | 0·29 (0·20–0·41) |
| At least two of four markers abnormal | 23/43 | 29·8 (10·8–NE) | 40/49 | 6·7 (4·7–10·3) | 0·30 (0·17–0·54) |
| Excluding gain/amp(1q) | 38/73 | 29·9 (18·0–NE) | 56/69 | 9·1 (5·1–11·8) | 0·26 (0·16–0·42) |
| Standard risk | 22/69 | NE (NE–NE) | 43/70 | 20·6 (11·2–33·6) | 0·32 (0·18–0·59) |
| **Bone marrow plasma cells** | | | | | |
| ≤30% | 49/133 | NE (37·1–NE) | 79/121 | 13·1 (10·4–19·6) | 0·31 (0·21–0·46) |
| >30% to <60% | 16/31 | 30·6 (18·0–NE) | 36/44 | 10·2 (5·5–21·0) | 0·30 (0·16–0·57) |
| ≥60% | 22/42 | 30·6 (11·3–NE) | 35/43 | 9·1 (3·9–12·2) | 0·28 (0·15–0·52) |
| **Baseline renal function††** | | | | | |
| <60 mL/min per 1·73 m² | 15/27 | 27·6 (10·8–NE) | 35/43 | 7·1 (4·3–11·5) | 0·31 (0·15–0·62) |
| ≥60 mL/min per 1·73 m² | 74/181 | NE (34·5–NE) | 118/168 | 12·6 (10·3–15·5) | 0·31 (0·22–0·42) |




(Figure 3 continues on next page)

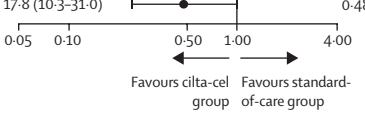
**A**

| | Cilta-cel events/patients | Cilta-cel median (95% CI) | Standard of care events/patients | Standard of care median (95% CI) | HR*† (95% CI) |
|---|---|---|---|---|---|
| **Baseline hepatic function (based on NCI criteria)** | | | | | |
| Normal | 78/184 | NE (34·5–NE) | 122/171 | 12·0 (10·2–15·5) | 0·30 (0·22–0·42) |
| Impaired (mild, moderate, and severe liver dysfunction) | 11/24 | NE (6·6–NE) | 31/40 | 6·1 (3·4–14·0) | 0·30 (0·14–0·67) |
| **Refractory to** | | | | | |
| Proteasome inhibitor + immunomodulatory drug | 49/103 | 37·1 (23·0–NE) | 75/96 | 7·8 (4·7–11·5) | 0·25 (0·17–0·38) |
| Anti-CD38+ immunomodulatory drug | 31/50 | 19·2 (9·3–34·5) | 41/46 | 4·3 (3·4–5·7) | 0·25 (0·14–0·44) |
| Proteasome inhibitor + anti-CD38+ immunomodulatory drug | 17/30 | 22·9 (2·6–NE) | 29/33 | 4·1 (3·1–7·8) | 0·17 (0·08–0·38) |
| Last line of previous therapy | 86/205 | NE (34·5–NE) | 151/208 | 11·9 (9·7–14·0) | 0·30 (0·22–0·40) |
| **Previous exposure to** | | | | | |
| Daratumumab | 30/51 | 19·3 (9·7–NE) | 47/54 | 4·5 (3·6–7·5) | 0·24 (0·14–0·42) |
| Bortezomib | 85/203 | NE (34·5–NE) | 147/205 | 11·9 (9·8–14·0) | 0·30 (0·22–0·40) |
| Bortezomib and daratumumab | 27/48 | 22·3 (9·7–NE) | 43/50 | 4·7 (3·6–7·5) | 0·24 (0·13–0·43) |
| **Daratumumab naive** | | | | | |
| Yes | 59/157 | NE (37·1–NE) | 106/157 | 14·0 (11·8–19·8) | 0·31 (0·22–0·44) |
| No | 30/51 | 19·3 (9·7–NE) | 47/54 | 4·5 (3·6–7·5) | 0·24 (0·14–0·42) |




**B**

| | | | | | |
|---|---|---|---|---|---|
| **Overall population** | 50/208 | NE (NE–NE) | 83/211 | NE (37·7–NE) | 0·55 (0·39–0·79) |
| **Sex** | | | | | |
| Male | 27/116 | NE (NE–NE) | 54/124 | 38·0 (31·6–NE) | 0·48 (0·30–0·76) |
| Female | 23/92 | NE (NE–NE) | 29/87 | NE (NE–NE) | 0·75 (0·43–1·29) |
| **Age** | | | | | |
| <65 years | 30/126 | NE (NE–NE) | 50/131 | NE (34·7–NE) | 0·58 (0·37–0·92) |
| 65–75 years | 20/78 | NE (NE–NE) | 32/76 | 37·7 (30·1–NE) | 0·58 (0·33–1·01) |
| **Race** | | | | | |
| White | 37/157 | NE (NE–NE) | 62/157 | NE (34·7–NE) | 0·56 (0·37–0·84) |
| Other | 13/45 | NE (NE–NE) | 15/47 | NE (38·0–NE) | 0·90 (0·43–1·90) |
| **Region** | | | | | |
| Europe | 33/128 | NE (NE–NE) | 47/129 | NE (37·7–NE) | 0·70 (0·45–1·09) |
| North America | 6/32 | NE (NE–NE) | 12/32 | NE (19·2–NE) | 0·44 (0·16–1·17) |
| Other | 11/48 | NE (NE–NE) | 24/50 | 38·0 (21·7–NE) | 0·40 (0·19–0·81) |
| **Baseline ECOG performance score** | | | | | |
| 0 | 17/114 | NE (NE–NE) | 45/121 | NE (37·7–NE) | 0·35 (0·20–0·62) |
| ≥1 | 33/94 | NE (NE–NE) | 38/90 | NE (22·0–NE) | 0·83 (0·52–1·32) |
| **Investigator's choice of standard-of-care treatment‡** | | | | | |
| Pomalidomide–bortezomib–dexamethasone | 12/26 | NE (11·7–NE) | 14/28 | 34·0 (15·5–NE) | 0·86 (0·40–1·87) |
| Daratumumab–pomalidomide–dexamethasone | 38/182 | NE (NE–NE) | 69/183 | NE (37·7–NE) | 0·52 (0·35–0·77) |
| **Number of lines of prior therapy** | | | | | |
| One | 13/68 | NE (NE–NE) | 23/68 | NE (37·7–NE) | 0·56 (0·28–1·11) |
| Two or three | 37/140 | NE (NE–NE) | 60/143 | NE (31·0–NE) | 0·57 (0·38–0·86) |
| **ISS staging§** | | | | | |
| I | 25/136 | NE (NE–NE) | 39/132 | NE (NE–NE) | 0·61 (0·37–1·00) |
| II | 18/60 | NE (NE–NE) | 37/65 | 26·8 (18·6–38·0) | 0·44 (0·25–0·78) |
| III | 7/12 | 21·3 (3·8–NE) | 7/14 | 30·2 (5·6–NE) | 1·14 (0·40–3·26) |
| **Presence of soft tissue plasmacytomas** | | | | | |
| Yes | 16/44 | NE (19·7–NE) | 19/35 | 19·5 (11·4–NE) | 0·62 (0·32–1·21) |
| No | 34/164 | NE (NE–NE) | 64/176 | NE (37·7–NE) | 0·53 (0·35–0·81) |
| **Tumour burden¶** | | | | | |
| Low | 23/126 | NE (NE–NE) | 40/129 | NE (NE–NE) | 0·56 (0·34–0·94) |
| Intermediate | 15/52 | NE (NE–NE) | 23/52 | 37·7 (23·5–NE) | 0·59 (0·31–1·13) |
| High | 12/30 | NE (13·4–NE) | 20/30 | 17·8 (10·3–31·0) | 0·48 (0·23–0·99) |




(Figure 3 continues on next page)

**B**

| | Cilta-cel events/patients | Cilta-cel median (95% CI) | Standard of care events/patients | Standard of care median (95% CI) | HR*† (95% CI) |
|---|---|---|---|---|---|
| **Type of multiple myeloma‖** | | | | | |
| IgG | 22/100 | NE (NE–NE) | 38/98 | NE (34·5–NE) | 0·55 (0·33–0·94) |
| Non-IgG | 13/31 | NE (19·7–NE) | 16/36 | 37·7 (23·0–NE) | 1·00 (0·48–2·08) |
| **Cytogenetic risk at study entry** | | | | | |
| High risk** | | | | | |
| Any of four markers abnormal | 30/123 | NE (NE–NE) | 54/132 | 38·0 (34·0–NE) | 0·54 (0·35–0·85) |
| At least two of four markers abnormal | 15/43 | NE (29·8–NE) | 28/49 | 23·0 (17·3–NE) | 0·57 (0·30–1·07) |
| Excluding gain/amp(1q) | 21/73 | NE (NE–NE) | 33/69 | NE (21·4–NE) | 0·56 (0·32–0·96) |
| Standard risk | 15/69 | NE (NE–NE) | 24/70 | NE (34·7–NE) | 0·62 (0·33–1·19) |
| **Bone marrow plasma cells** | | | | | |
| ≤30% | 28/133 | NE (NE–NE) | 40/121 | NE (NE–NE) | 0·62 (0·38–1·00) |
| >30% to <60% | 7/31 | NE (NE–NE) | 21/44 | 37·7 (19·2–NE) | 0·40 (0·17–0·94) |
| ≥60% | 15/42 | NE (27·6–NE) | 21/43 | 34·5 (14·8–NE) | 0·67 (0·35–1·30) |
| **Baseline renal function††** | | | | | |
| <60 mL/min per 1·73 m² | 11/27 | NE (19·7–NE) | 25/43 | 30·1 (11·8–NE) | 0·59 (0·29–1·20) |
| ≥60 mL/min per 1·73 m² | 39/181 | NE (NE–NE) | 58/168 | NE (38·0–NE) | 0·60 (0·40–0·90) |
| **Baseline hepatic function (based on NCI criteria)** | | | | | |
| Normal | 43/184 | NE (NE–NE) | 64/171 | NE (38·0–NE) | 0·59 (0·40–0·87) |
| Impaired (mild, moderate, and severe liver dysfunction) | 7/24 | NE (31·7–NE) | 19/40 | 37·7 (19·9–NE) | 0·57 (0·24–1·36) |
| **Refractory to** | | | | | |
| Proteasome inhibitor + immunomodulatory drug | 28/103 | NE (NE–NE) | 45/96 | 34·7 (21·4–NE) | 0·51 (0·32–0·82) |
| Anti-CD38+ immunomodulatory drug | 18/50 | NE (23·1–NE) | 22/46 | 34·0 (16·5–NE) | 0·70 (0·37–1·30) |
| Proteasome inhibitor + anti-CD38+ immunomodulatory drug | 9/30 | NE (NE–NE) | 17/33 | 34·0 (14·9–NE) | 0·53 (0·24–1·20) |
| Last line of previous therapy | 48/205 | NE (NE–NE) | 82/208 | NE (37·7–NE) | 0·55 (0·39–0·79) |
| **Previous exposure to** | | | | | |
| Daratumumab | 17/51 | NE (NE–NE) | 27/54 | 34·0 (16·4–NE) | 0·61 (0·33–1·12) |
| Bortezomib | 47/203 | NE (NE–NE) | 81/205 | NE (37·7–NE) | 0·55 (0·38–0·78) |
| Bortezomib and daratumumab | 15/48 | NE (NE–NE) | 26/50 | 26·7 (16·4–NE) | 0·53 (0·28–1·00) |
| **Daratumumab naive** | | | | | |
| Yes | 33/157 | NE (NE–NE) | 56/157 | NE (37·7–NE) | 0·56 (0·36–0·86) |
| No | 17/51 | NE (NE–NE) | 27/54 | 34·0 (16·4–NE) | 0·61 (0·33–1·12) |

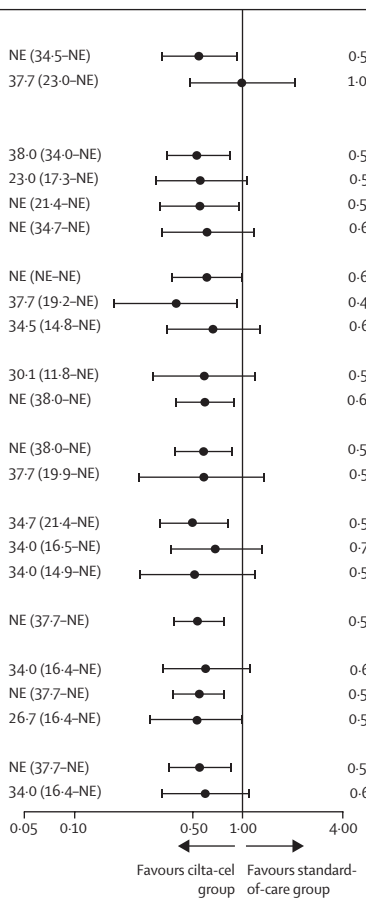



***Figure 3:*** **Forest plot of subgroup analysis on progression-free survival and overall survival (intention-to-treat population)**
(A) Progression-free survival. (B) Overall survival. ECOG=Eastern Cooperative Oncology Group. HR=hazard ratio. ISS=International Staging System. NCI=National Cancer Institute. NE=not evaluable. *For the overall population row, HR and 95% CI were calculated from a Cox proportional hazards model with treatment as the sole explanatory variable and stratified with investigator's choice (pomalidomide–bortezomib–dexamethasone or daratumumab–pomalidomide–dexamethasone), ISS staging (I, II, or III) and number of previous lines (one *vs* two or three) as randomised. For the subgroups, HR and 95% CI were calculated from a Cox proportional hazards model with treatment as the sole explanatory variable. †Only progression-free survival events that occurred more than 8 weeks after randomisation were included. ‡Based on the Interactive Web Response System randomisation strata. §ISS staging is derived based on serum β2-microglobulin and albumin. ¶Low tumour burden is defined as meeting all following parameters (as applicable): bone marrow plasma cell <50%, serum M-protein <3 g/dL, and serum free light chain <3000 mg/L; high tumour burden is defined as meeting any of the following parameters: bone marrow plasma cell ≥80%, serum M-protein ≥5 g/dL, serum free light chain ≥5000 mg/L; intermediate tumour burden did not fit either criteria of high or low tumour burden. ‖Analysis is based on patients with measurable disease in serum. **Includes the patients who are positive for any of del(17p), t(14;16), t(4;14), or gain/amp(1q) by fluorescence in situ hybridisation testing. ††Based on the Modification of Diet in Renal Disease formula.

A total of 242 progression-free survival events (89 [43%] in 208 patients in the cilta-cel group and 153 [73%] in 211 patients the standard of care group) had occurred. Median progression-free survival was not reached (95% CI 34·5 months–not evaluable) in the cilta-cel group and 11·8 months (9·7–14·0) in the standard-of-care group (HR 0·29 [95% CI 0·22–0·39]; protocol-specified weighted analysis; figure 2A); estimated 30-month progression-free survival rates were 59·4% (95% CI 52·3–65·7) in the cilta-cel group and 25·7% (19·8–31·9) in the standard-of-care group (appendix p 22). A protocol-specified unweighted sensitivity analysis also showed progression-free survival benefit in the cilta-cel group compared with standard-of-care (HR 0·39 [95% CI 0·30–0·51]). Progression-free survival benefit was consistent across prespecified subgroups based on demographic and disease characteristics in the cilta-cel versus standard-of-care groups (figure 3A).

At data cutoff, 133 overall survival events had occurred (50 in the cilta-cel group and 83 in the standard-of-care group). Median overall survival was not reached in either

the cilta-cel group (95% CI not evaluable) or the standard-of-care group (95% CI 37·7–not evaluable; HR 0·55 [95% CI 0·39–0·79]; p=0·0009; figure 2B), showing a significant difference in overall survival in favour of cilta-cel. Estimated 30-month overall survival rates were 76·4% (95% CI 70·0–81·6) in the cilta-cel group and 63·8% (56·9–69·9) in the standard-of-care group (appendix p 22). Overall survival benefit was consistent across almost all the prespecified subgroups based on demographic and disease characteristics in the cilta-cel versus standard-of-care groups (figure 3B).

At data cutoff, 65 (31%) of 208 patients in the cilta-cel group and 146 (69%) of 211 patients in the standard-of-care group (intention-to-treat populations) received one or more subsequent antimyeloma therapies (CAR T-cell, bispecific, or anti-BCMA antibody-drug conjugate therapy: 44 [21%] in the cilta-cel group and 124 [59%] in the standard-of-care group; appendix p 23). Of the 65 patients in the cilta-cel group who received subsequent therapy, 20 (31%) received cilta-cel after progression on bridging therapy, nine (14%) progressed on bridging therapy but never received cilta-cel, and 36 (55%) had progressed after receiving cilta-cel as study treatment. Of the 146 patients in the standard-of-care group who received subsequent therapy, 36 (25%) received CAR T-cell therapy, including eight (5%) who received cilta-cel therapy.

At data cutoff, overall MRD negativity at a $10^{-5}$ threshold at any time during the study occurred in 129 (62%) of 208 patients in the cilta-cel group and 39 (18%) of 211 in the standard-of-care group; overall MRD negativity at a $10^{-6}$ threshold occurred in 119 (57%) in the cilta-cel group and 19 (9%) in the standard-of-care group (appendix p 24). 63 (30%) patients in the cilta-cel group and 108 (51%) in the standard-of-care group were unevaluable for MRD, with the most frequent reasons being calibration failure (cilta-cel n=33, standard of care n=30) and having no sample after baseline (cilta-cel n=27, standard of care n=76; appendix p 25). Some additional patients also had indeterminate assay results at the $10^{-6}$ threshold. In a post-hoc analysis among only the patients who were MRD evaluable, overall MRD negativity at a $10^{-5}$ threshold occurred in 129 (89%) of 145 patients in the cilta-cel group and 39 (38%) of 103 in the standard-of-care group and; at a $10^{-6}$ threshold, overall MRD negativity occurred in 119 (86%) of 139 in the cilta-cel group and 19 (19%) of 102 in the standard-of-care group (appendix p 24).

A complete response or better occurred in 160 (77%) of 208 patients in the cilta-cel group and 51 (24%) of 211 patients in the standard-of-care group (appendix p 22). A total of 176 (85%) patients in the cilta-cel group and 142 (67%) in the standard-of-care group had a treatment response. Of patients evaluable for MRD at a $10^{-5}$ threshold, 75 (52%) of 145 in the cilta-cel group and ten (10%) of 103 in the standard-of-care group had a sustained (ie, ≥12 months) MRD-negative complete response or better.

Median progression-free survival on next-line therapy was not reached for the cilta-cel group (95% CI not evaluable) and was 25·3 months (21·6–32·9) for the standard-of-care group (HR 0·46 [95% CI 0·34–0·63]).

At data cutoff, a total of 79 MySIm-Q symptom worsening events had occurred (cilta-cel n=30, standard of care n=49). Median time to symptom worsening was not reached (95% CI not evaluable) in the cilta-cel group and was 34·3 months (32·2–not evaluable) in the standard-of-care group (HR 0·38 [95% CI 0·24–0·61]; p<0·0001; figure 4). Estimated 30-month MySIm-Q event-free rates were 76·8% (95% CI 67·6–83·8) in the cilta-cel group and 63·1% (52·7–71·8) in the standard-of-care group.

In a post-hoc assessment of treatment-free survival in the cilta-cel group, median treatment-free survival was not reached (95% CI 36·6–not evaluable); the 30-month estimated treatment-free rate was 66·0% (58·6–72·4; appendix p 26). Among the 176 patients who received cilta-cel in the as-treated population and were assessed post hoc, the estimated 30-month rate for overall survival was 85·2% (95% CI 79·0–89·7) and for progression-free survival was 70·2% (62·8–76·4; appendix pp 27–28). Additional post-hoc efficacy results for this population are in the appendix (p 29). Post-hoc analysis of overall survival based on the number of previous lines of therapy combining data from CARTITUDE-4 and CARTITUDE-1, given that both studies included patients with three previous lines of therapy, showed that cilta-cel use in earlier treatment lines resulted in higher overall survival rates compared with later-line use (appendix p 30).

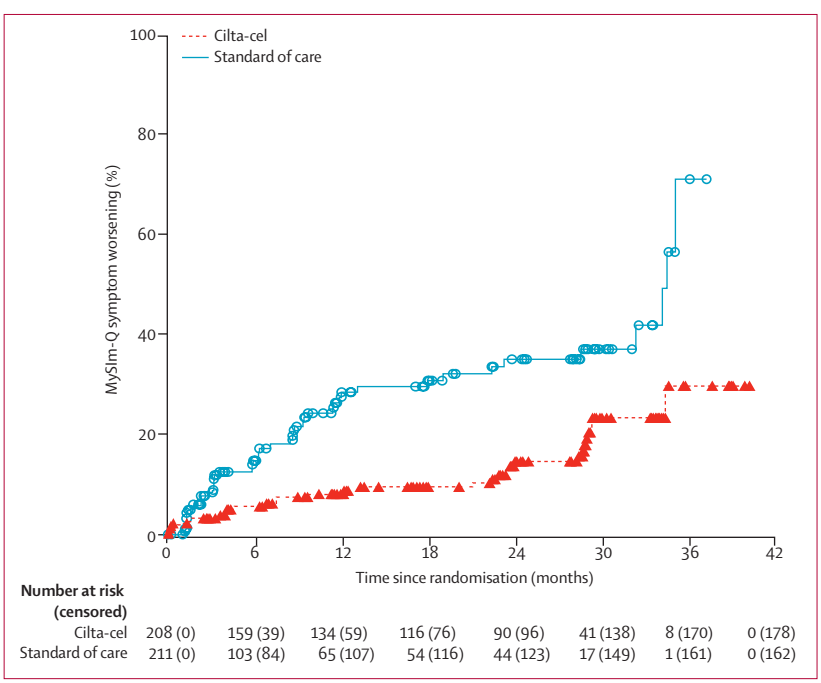



*Figure 4:* **Kaplan–Meier estimates of time to worsening in MySIm-Q total symptom scale**
MySIm-Q=Multiple Myeloma Symptom and Impact Questionnaire.

In the safety population, treatment-emergent adverse events at a maximum grade of 3 or 4 occurred in 186 (89%) of 208 patients in the cilta-cel group and 193 (93%) of 208 patients in the standard-of-care group: 30 (14%) in the cilta-cel group and 77 (37%) in the standard-of-care group had maximum grade 3 treatment-emergent adverse events, and 156 (75%) in the cilta-cel group and 116 (56%) in the standard-of-care group had maximum grade 4 adverse events (table; appendix pp 31–35). Grade 3–4 cytopenias were the most frequent treatment-emergent adverse events in both groups, with the most common grade 3 event being anaemia in the cilta-cel group (72 [35%]) and neutropenia in the standard-of-care group (59 [28%]), and neutropenia being the most common grade 4 event in both (cilta-cel: 152 [73%]; standard of care: 112 [54%]). Serious treatment-emergent adverse events occurred in 98 (47%) patients in each group (appendix p 36). Serious treatment-related adverse events occurred in 67 (32%) patients in the cilta-cel group and 54 (26%) in the standard-of-care group (appendix p 37). In the cilta-cel group, maximum grade 3 treatment-emergent infections occurred in 49 (24%) patients and maximum grade 4 in one (<1%); in the standard-of-care group, the respective incidences were 54 (26%) patients and two (1%; appendix pp 31–35). Grade 5 infections in the safety population occurred in

| | Cilta-cel (n=208) | | | | Standard of care (n=208) | | | |
|---|---|---|---|---|---|---|---|---|
| | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 | Grade 1–2 | Grade 3 | Grade 4 | Grade 5 |
| Any treatment-emergent adverse event | 7 (3%) | 30 (14%) | 156 (75%) | 15 (7%) | 6 (3%) | 77 (37%) | 116 (56%) | 9 (4%) |
| Haematological events | 1 (<1%) | 31 (15%) | 165 (79%) | 0 | 6 (3%) | 63 (30%) | 116 (56%) | 0 |
| Anaemia | 39 (19%) | 72 (35%) | 2 (1%) | 0 | 26 (13%) | 31 (15%) | 0 | 0 |
| Thrombocytopenia | 26 (13%) | 39 (19%) | 48 (23%) | 0 | 26 (13%) | 30 (14%) | 11 (5%) | 0 |
| Lymphopenia | 3 (1%) | 8 (4%) | 36 (17%) | 0 | 4 (2%) | 22 (11%) | 3 (1%) | 0 |
| Leukopenia | 2 (1%) | 7 (3%) | 18 (9%) | 0 | 6 (3%) | 7 (3%) | 3 (1%) | 0 |
| Neutropenia | 0 | 35 (17%) | 152 (73%) | 0 | 7 (3%) | 59 (28%) | 112 (54%) | 0 |
| Infections and infestations | 73 (35%) | 49 (24%) | 1 (<1%) | 9 (4%) | 96 (46%) | 54 (26%) | 2 (1%) | 7 (3%) |
| Upper respiratory tract infections | 19 (9%) | 4 (2%) | 0 | 0 | 48 (23%) | 4 (2%) | 0 | 0 |
| COVID-19 | 17 (8%) | 3 (1%) | 0 | 0 | 57 (27%) | 6 (3%) | 0 | 0 |
| Pneumonia | 6 (3%) | 8 (4%) | 0 | 1 (<1%) | 12 (6%) | 11 (5%) | 1 (<1%) | 0 |
| COVID-19 pneumonia | 2 (1%) | 3 (1%) | 0 | 7 (3%) | 0 | 12 (6%) | 0 | 2 (1%) |
| Other events | | | | | | | | |
| Cytokine release syndrome | 132 (63%) | 2 (1%) | 0 | 0 | 1 (<1%) | 0 | 0 | 0 |
| Nausea | 101 (49%) | 0 | 0 | 0 | 41 (20%) | 2 (1%) | 0 | 0 |
| Hypogammaglobulinaemia | 78 (38%) | 16 (8%) | 0 | 0 | 16 (8%) | 2 (1%) | 0 | 0 |
| Diarrhoea | 62 (30%) | 8 (4%) | 0 | 0 | 59 (28%) | 6 (3%) | 0 | 0 |
| Fatigue | 56 (27%) | 4 (2%) | 0 | 0 | 66 (32%) | 4 (2%) | 0 | 0 |
| Headache | 55 (26%) | 0 | 0 | 0 | 27 (13%) | 0 | 0 | 0 |
| Constipation | 48 (23%) | 1 (<1%) | 0 | 0 | 45 (22%) | 2 (1%) | 0 | 0 |
| Peripheral sensory neuropathy | 33 (16%) | 0 | 0 | 0 | 42 (20%) | 1 (<1%) | 0 | 0 |
| Back pain | 30 (14%) | 2 (1%) | 0 | 0 | 43 (21%) | 3 (1%) | 0 | 0 |
| Dyspnoea | 27 (13%) | 1 (<1%) | 0 | 0 | 42 (20%) | 1 (<1%) | 0 | 0 |
| Insomnia | 21 (10%) | 2 (1%) | 0 | 0 | 48 (23%) | 7 (3%) | 0 | 0 |
| CAR T-associated adverse events† | | | | | | | | |
| Cytokine release syndrome | 132 (75%) | 2 (1%) | 0 | 0 | NA | NA | NA | NA |
| Neurotoxicity‡ | 31 (18%) | 5 (3%) | | | NA | NA | NA | NA |
| Immune effector cell-associated neurotoxicity syndrome | 8/176 (5%) | 0 | 0 | 0 | NA | NA | NA | NA |
| Other§ | 26 (15%) | 4 (2%) | | | NA | NA | NA | NA |
| Parkinsonism | 1 (1%) | 0 | 0 | 0 | NA | NA | NA | NA |

Data are n (%). Listed are treatment-emergent adverse events of maximum grade 1 or 2 that occurred in at least 20% of either treatment group, and any treatment-emergent adverse event of maximum grade 3, 4, or 5 that occurred in at least 5% of either treatment group, considered by the investigator to be related to a study treatment or occurred after the initiation of treatment (apheresis in the cilta-cel group and day 1 in the standard-of-care group) up to 30 days after the last dose of a study treatment, before the initiation of subsequent therapy, or within 112 days after the cilta-cel infusion (cilta-cel group only). CAR=chimeric antigen receptor. NA=not applicable. †Analysed in the patients who received cilta-cel as study treatment (n=176). ‡There were no fatal neurotoxicities. §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) parkinsonism, cranial nerve palsy, and peripheral neuropathy. Appendix (pp 31–35) shows maximum grade 1–2 treatment-emergent adverse events that occurred in 10% or more of patients in either treatment group and all maximum grade 3, 4, and 5 treatment-emergent adverse events.

***Table:*** **Treatment-emergent adverse events in the safety population**

16 (8%) in the cilta-cel group and 19 (9%) in the standard-of-care group, of whom 13 (6%) and eight (4%) died during the first year from the start of study treatment, and two (1%) and eight (4%) died during the second year, respectively. Intravenous immunoglobulin was administered to 147 (71%) in the cilta-cel group and 42 (20%) in the standard-of-care group.

Second primary malignancies occurred in 27 (13%) in the cilta-cel group and 24 (12%) in the standard-of-care group; of these, haematological malignancies were reported in seven (3%) in the cilta-cel group (myelodysplastic syndrome in four patients [2%; two progressed to acute myeloid leukaemia], acute myeloid leukaemia in one patient [<1%], and CAR-positive peripheral T-cell lymphoma in two patients [1%]) and in one (<1%) patient in the standard-of-care group (Epstein–Barr virus-associated lymphoma; appendix p 38). The median time to onset of myelodysplastic syndrome, acute myeloid leukaemia, or both from cilta-cel infusion was 385 days (IQR 302–715; range 56–758). Post-hoc analyses showed that all five patients who developed myelodysplastic syndrome and/or acute myeloid leukaemia in the cilta-cel group carried pre-existing mutations at baseline before cilta-cel infusion in one or more major driver genes for myelodysplastic syndrome and/or acute myeloid leukaemia, including *TP53* and *DNMT3A* (appendix p 39); no CAR transgene and/or protein was detected in the three patients with evaluable samples. The two patients with CAR-positive T-cell lymphoma had pre-existing loss-of-function *TET2* variants (details published elsewhere[12]).

Death from any cause was reported in 50 (24%) patients in the cilta-cel safety population and 82 (39%) in the standard-of-care safety population (appendix p 40). Death from disease progression was reported in 21 (10%) patients in the cilta-cel group (eight of whom did not receive cilta-cel) and 51 (25%) in the standard-of-care group. A total of 17 (8%) patients in the cilta-cel group and 23 (11%) in the standard-of-care group died due to treatment-related adverse events that were not considered to be treatment-emergent per the investigator. Treatment-related grade 5 adverse events occurred in six (3%) patients in the cilta-cel group, most commonly due to infections (in four patients; three due to COVID-19 pneumonia and one due to neutropenic sepsis), and in five (2%) patients in the standard-of-care group, all due to infections (one each due to COVID-19 pneumonia, neutropenic sepsis, *Pneumocystis jirovecii* pneumonia, progressive multifocal leukoencephalopathy, and septic shock; appendix p 41).

In the cilta-cel group, 33 (16%) patients died within the first year of random assignment: 11 (5%) never received cilta-cel, nine (4%) progressed during bridging therapy and received cilta-cel as subsequent therapy, and 13 (6%) received cilta-cel as the study treatment, of whom nearly half (n=7) died due to COVID-19 pneumonia (appendix p 42). Non-relapse deaths in the 176 patients who received cilta-cel as study treatment were primarily due to infections in the first year (appendix p 43).

No new cases of movement and neurocognitive treatment-emergent adverse events (hereafter referred to as parkinsonism) or cranial nerve palsy occurred with additional follow-up. In the 176 patients who received cilta-cel as study treatment, one (1%) patient had ongoing grade 1 parkinsonism at the time of data cutoff. At the time of the previous report, 14 of the 16 (9%) patients who developed cranial nerve palsy had recovered;[5] the two remaining patients improved to grade 1 by the current data cutoff. The median time to recovery for the 14 patients who developed cranial nerve palsy was 61·0 days (IQR 34·0–95·0) and the median time to improvement from the maximum grade was 24·5 days (14·5–47·0).

In the cilta-cel group, two (8%) of the 26 patients who received bortezomib had dose reductions of the drug, 73 (35%) of 207 had dose reductions of pomalidomide, and 22 (11%) of 208 had dose reductions of dexamethasone (appendix p 44). In the standard-of-care group, cycle delays occurred in 149 (72%) of 208 patients (131 [63%] due to adverse events); four (15%) of 26 had dose reductions of bortezomib, 120 (45%) of 208 had dose reductions of pomalidomide, and 93 (45%) of 208 had dose reductions of dexamethasone. In the standard-of-care group, drug-related treatment-emergent adverse events led to the discontinuation of the associated drug in four (2%) of 182 patients for daratumumab, one (4%) of 26 for bortezomib, seven (3%) of 208 for pomalidomide, and 31 (15%) of 208 patients for dexamethasone. In the cilta-cel group, drug-related events leading to discontinuation of the associated drug occurred in four (2%) of 207 patients for pomalidomide and zero patients for daratumumab, bortezomib, and dexamethasone.

## Discussion

At a median follow-up of 33·6 months, a significant benefit in overall survival was observed with cilta-cel versus standard of care (HR 0·55 [95% CI 0·39–0·79]) in patients with lenalidomide-refractory multiple myeloma after one to three previous lines of therapy. To our knowledge, we present the first phase 3 study to show significant overall survival benefit with CAR T-cell therapy in multiple myeloma and the second time any CAR T-cell therapy has shown significant overall survival benefit in the oncology setting.[13] Analysis of overall survival in multiple prespecified subgroups showed a consistent benefit with cilta-cel versus standard of care; furthermore, cilta-cel use in earlier treatment lines showed higher proportions of patients alive compared with use in later lines. More than twice as many patients were estimated to be progression free and alive in the cilta-cel versus standard-of-care group at 30 months (59·4% *vs* 25·7%). Cilta-cel led to deep and durable disease control in a greater proportion of patients than standard of care, as evidenced by higher rates of sustained

MRD negativity in the cilta-cel group. A single cilta-cel infusion provided antimyeloma treatment-free survival to an estimated 66·0% (95% CI 58·6–72·4) of patients at 30 months. Furthermore, despite a greater proportion of patients in the standard-of-care group versus the cilta-cel group receiving CAR T-cell, bispecific, or BCMA-directed antibody-drug conjugate therapies as subsequent therapy after progression, the overall survival advantage observed with cilta-cel was significant.

Adverse events were consistent with the known safety profile of cilta-cel and the previous analysis.[5] The most common grade 3 or 4 adverse events in both treatment groups were cytopenias, with some (eg, neutropenia) occurring at a higher rate in the cilta-cel group than the standard-of-care group. However, although cytopenias are known to be associated with lymphodepletion before CAR T-cell treatment,[14] we have previously shown that most patients have immune reconstitution after cilta-cel infusion.[15] Four new cases of haematological second primary malignancies (including one T-cell lymphoma) in the cilta-cel group and one new case in the standard-of-care group were observed since the previous analysis. The overall incidences of haematological, second primary malignancies are consistent with rates reported for other CAR T-cell therapies.[16] Preliminary molecular analysis of patients who developed myelodysplastic syndrome, acute myeloid leukaemia, or both showed pre-existing, potentially pathogenic mutations at baseline; however, further research is needed to fully understand the risk factors and aetiology of haematological second primary malignancies after CAR T-cell therapy. Analysis of two CAR-positive T-cell lymphomas after cilta-cel in CARTITUDE-4 has been previously described.[12] Additionally, T-cell malignancies are recognised as a class effect after CAR T-cell immunotherapy.[17]

Effective bridging therapy before cilta-cel is important and more easily accomplished in earlier lines of therapy, which might in part underlie the improved safety profile in CARTITUDE-4 versus CARTITUDE-1, such as the lower rates of cytopenias, cytokine release syndrome, ICANS, and parkinsonism.[18] The incidence of treatment-emergent parkinsonism was lower in patients who received cilta-cel as study treatment in CARTITUDE-4 (one [1%]) compared with CARTITUDE-1 (six [6%]).[18] Most cranial nerve palsies in CARTITUDE-4 were mild to moderate and resolved by the data cutoff. No new cases of parkinsonism or cranial nerve palsy were observed with additional follow-up. There are case reports of parkinsonism that resolved with early intervention,[19,20] highlighting the importance of early diagnosis. Parkinsonism has been seen with anti-BCMA CAR T-cell therapies other than cilta-cel.[21] Although the aetiology is not fully understood, it appears to be associated with high CAR T-cell expansion.[22] Absolute lymphocyte count at and around peak expansion has been suggested as a potential surrogate for CAR T-cell expansion.[23,24] Considering this, absolute lymphocyte count can potentially be monitored closely in the first days to weeks after infusion and some centres have initiated the administration of a short course of low-dose steroids to patients who might be at risk of neurotoxicities (ie, parkinsonism) based on their absolute lymphocyte count in an attempt to reduce the incidence and severity of parkinsonism.[25] However, the evidence is limited and more data are needed.

Deaths in the intention-to-treat cilta-cel group within the first year from randomisation were primarily in patients who progressed before receiving cilta-cel, and half of the deaths in patients who received cilta-cel as study treatment were due to COVID-19. An initial crossing of the progression-free survival and overall survival curves is seen, with more early events in the cilta-cel group than the standard-of-care group. Based on an intention-to-treat analysis, starting from randomisation, this finding was unexpected as both groups received the same therapies and underwent the same assessment schedule during the CAR T-cell manufacturing period. The early progression-free survival events in the cilta-cel group were primarily due to patients who progressed on bridging therapy and occurred before receiving cilta-cel. 20 patients who progressed during bridging therapy received cilta-cel as subsequent therapy; however, deaths in this group also contributed to the early crossing of the overall survival curve. These data emphasise the importance of adequate bridging therapy and disease control before cilta-cel infusion.

In CARTITUDE-4, pomalidomide–bortezomib–dexamethasone and daratumumab–pomalidomide–dexamethasone were used as comparators based on their approvals and contemporaneous treatment guidelines, and the rapidly evolving therapeutic landscape includes newer, efficacious regimens that have since been approved for the CARTITUDE-4 patient population.[5] Nevertheless, the results seen with cilta-cel in CARTITUDE-4 compare favourably with trials of newer regimens in early line treatment of relapsed multiple myeloma. Carfilzomib-based regimens, assessed in IKEMA and CANDOR,[26,27] and belantamab mafodotin-based regimens, assessed in DREAMM-7 and DREAMM-8,[28,29] report MRD-negative complete response rates of 22–26% compared with 57% for cilta-cel in our current report. Cross-trial comparisons are limited by the differences in study design and patient populations between the trials, and longer-term follow-up is required to support the effect of deep responses on survival outcomes as assessed by MRD negativity. Cilta-cel also showed significant overall survival improvement compared with idecabtagene vicleucel in patients who had two to four previous treatment lines based on a matching-adjusted indirect comparison analysis.[30]

A limitation of our analysis is that patient-reported outcomes questionnaires, including the MySIm-Q, were administered less frequently during the first 3 study months in the cilta-cel group than the standard-of-care

group. Due to the patient-reported outcomes assessment schedule for the cilta-cel group, transient declines in quality of life, including those potentially related to CAR T-cell-associated adverse events, might not have been detected. However, in the prespecified analysis, if a decline was followed by improvement, the decline was not considered to be symptom worsening.

In conclusion, a one-time infusion of cilta-cel in CARTITUDE-4 showed significant survival and quality-of-life benefits. These data show that cilta-cel can improve clinical outcomes for patients with lenalidomide-refractory multiple myeloma as early as first relapse.

#### Contributors

Conception and design: HE, JS-M, BD, CT, XL, NWCJvdD, SS, AO, YCC, SJH, M-VM, JM-L, PC, LK, DC, QL, T-mY, JMS, PJH, and RP. Provision of study materials or patients: HE, JS-M, BD, CT, XL, NWCJvdD, SS, AO, YCC, SJH, M-VM, JM-L, PC, LK, PJH, and RP. Collection and assembly of data: all authors. Data analysis and interpretation: all authors. Manuscript writing: all authors. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication. HE, DC, QL, T-mY, KL, VP, AS, CL, NB, AG, MV, JMS, NL, MK, NP, and EF verified the underlying data. All authors directly accessed the underlying data reported in the manuscript.

#### Declaration of interests

HE has participated in a consulting or advisory role for Amgen, BMS, Celgene, GSK, Johnson & Johnson, Novartis, Sanofi, and Takeda; has received travel accommodations from Amgen, BMS, Celgene, Novartis, Sanofi, and Takeda; has received honoraria from Amgen, BMS, Celgene, GSK, Johnson & Johnson, Novartis, Sanofi, and Takeda; and has received research funding from Amgen, BMS, Celgene, GSK, Johnson & Johnson, Sanofi. JS-M has participated in a consulting or advisory role for AbbVie, Amgen, BMS, Celgene, GSK, Haemalogix, Johnson & Johnson, Karyopharm Therapeutics, MSD, Novartis, Regeneron, Roche, Sanofi, Secura Bio, and Takeda. BD has participated in a consulting or advisory role for Amgen, Arcellx, Genentech/Roche, GSK, Johnson & Johnson, Natera, Pfizer, Sanofi, and Takeda, and has participated in speakers' bureau for Johnson & Johnson. CT has participated in a consulting or advisory role for Johnson & Johnson, has received travel accommodations from Johnson & Johnson, and has received honoraria from Johnson & Johnson. XL has participated in a consulting or advisory role for Johnson & Johnson. NWCJvdD has participated in an advisory role for AbbVie, Adaptive, Amgen, Bayer, Celgene, BMS, Galapagos, Johnson & Johnson, Kite Pharma, Merck, Novartis, Oncopeptides, Pfizer, Roche, Sanofi, Servier, and Takeda; and has received research support from Amgen, BMS, Celgene, Cellectis, Johnson & Johnson, and Novartis, all paid to institution. SS has participated in a consulting or advisory role for AbbVie, BiolineRx, BMS, Genentech, Johnson & Johnson, Kite/Arcellx, Legend, Magenta Therapeutics, Oncopeptides, Pfizer, Regeneron, Sanofi, and Takeda; and has received research funding from AbbVie, Allogene, BMS, Johnson & Johnson, Magenta Therapeutics, and Novartis. AO has participated in a consulting role for Celgene/BMS, Johnson & Johnson, and Sanofi; and has participated in speakers' bureau for Celgene/BMS, GSK, and Sanofi. YCC has participated in a consulting or advisory role for Johnson & Johnson; has received travel grant from Johnson & Johnson; has received honoraria from Amgen, GSK, and Takeda; and has received research funding from Amgen and Takeda. SJH has participated in a consulting or advisory role for AbbVie, Amgen, Celgene/BMS, GSK, Haemalogix, Johnson & Johnson, Novartis, Roche/Genentech, Sanofi, and Takeda; has participated in speakers' bureau for AbbVie, Amgen, Celgene/BMS, GSK, Johnson & Johnson, Novartis, Roche/Genentech, Takeda, and TERUMO; has given expert testimony for EUSA Pharma and TERUMO; has received honoraria from AbbVie, Amgen, Celgene/BMS, GSK, Haemalogix, Johnson & Johnson, Novartis, Roche/Genentech, Sanofi, and Takeda; and has received research funding from Haemalogix and Johnson & Johnson. M-VM has participated in an advisory role for AbbVie, Amgen, BMS, GSK, Johnson & Johnson, Kite, Oncopeptides, Pfizer, Regeneron, Roche, Sanofi, Stemline, and Takeda; and has received honoraria from AbbVie, Amgen, BMS, GSK, Johnson & Johnson, Pfizer, Regeneron, Sanofi, and Stemline. JM-L has participated in a consulting or advisory role for Astellas Pharma, BMS, Johnson & Johnson, Novartis, Roche, and Sanofi, and has received research funding from BMS. PC has participated in an advisory role for AbbVie, ADC Therapeutics, Amgen, BeiGene, Celgene, Daiichi Sankyo, Eli Lilly, Gilead/Kite, GSK, Incyte, Johnson & Johnson, Jazz Pharma, Novartis, Pfizer, Roche, Sanofi, SOBI, and Takeda. LK has participated in a consulting or advisory role for AbbVie, Amgen, Celgene/BMS, Johnson & Johnson, GSK, Sanofi, Stemline, and Takeda; has received travel accommodations from AbbVie, Amgen, Celgene/BMS, Johnson & Johnson, Sanofi, and Takeda; and has received honoraria from Amgen, Celgene/BMS, Johnson & Johnson, GSK, Sanofi, Stemline, and Takeda. PJH has participated in an advisory role for Antengene, Gilead, GSK, Johnson & Johnson, and Pfizer; has received research funding from Novartis; and has received travel support from Johnson & Johnson. RP has participated in a consulting or advisory role for Celgene/BMS, GSK, Johnson & Johnson, and Roche; has received travel accommodations from Johnson & Johnson and GSK; has received honoraria from AbbVie, Celgene, GSK, Janssen, and Sanofi; has received research funding from GSK and Pfizer; and is supported by the National Institute for Health and Care Research University College London Hospitals Biomedical Research Centre. DC, QL, VP, AS, CL, NB, and AG are employees of Johnson & Johnson. T-mY, KL, MV, JMS, and NL are employees of and hold stock from Johnson & Johnson. MK was an employee of Legend Biotech USA at the time of this study. NP and EF are employees of and hold stock from Legend Biotech USA. All other authors declare no competing interests.

#### Data sharing

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. De-identified aggregate and/or individual patient data can be made available after publication. A proposal to access the study data including details of how they would be used can be submitted through the Yale Open Data Access Project site at http://yoda.yale.edu.

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