ORIGINAL ARTICLE

Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma

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ABSTRACT

BACKGROUND

Idecabtagene vicleucel (ide-cel, also called bb2121), a B-cell maturation antigen–directed chimeric antigen receptor (CAR) T-cell therapy, has shown clinical activity with expected CAR T-cell toxic effects in patients with relapsed and refractory multiple myeloma.

METHODS

In this phase 2 study, we sought to confirm the efficacy and safety of ide-cel in patients with relapsed and refractory myeloma. Patients with disease after at least three previous regimens including a proteasome inhibitor, an immunomodulatory agent, and an anti-CD38 antibody were enrolled. Patients received ide-cel target doses of 150×10^6 to 450×10^6 CAR-positive (CAR+) T cells. The primary end point was an overall response (partial response or better); a key secondary end point was a complete response or better (comprising complete and stringent complete responses).

RESULTS

Of 140 patients enrolled, 128 received ide-cel. At a median follow-up of 13.3 months, 94 of 128 patients (73%) had a response, and 42 of 128 (33%) had a complete response or better. Minimal residual disease (MRD)–negative status ($<10^{-5}$ nucleated cells) was confirmed in 33 patients, representing 26% of all 128 patients who were treated and 79% of the 42 patients who had a complete response or better. The median progression-free survival was 8.8 months (95% confidence interval, 5.6 to 11.6). Common toxic effects among the 128 treated patients included neutropenia in 117 patients (91%), anemia in 89 (70%), and thrombocytopenia in 81 (63%). Cytokine release syndrome was reported in 107 patients (84%), including 7 (5%) who had events of grade 3 or higher. Neurotoxic effects developed in 23 patients (18%) and were of grade 3 in 4 patients (3%); no neurotoxic effects higher than grade 3 occurred. Cellular kinetic analysis confirmed CAR+ T cells in 29 of 49 patients (59%) at 6 months and 4 of 11 patients (36%) at 12 months after infusion.

CONCLUSIONS

Ide-cel induced responses in a majority of heavily pretreated patients with refractory and relapsed myeloma; MRD-negative status was achieved in 26% of treated patients. Almost all patients had grade 3 or 4 toxic effects, most commonly hematologic toxic effects and cytokine release syndrome. (Funded by bluebird bio and Celgene, a Bristol-Myers Squibb company; KarMMa ClinicalTrials.gov number, NCT03361748.)

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Despite treatment advances in multiple myeloma, relapses are common.[1-4] No standard of care has been established for patients who have disease progression despite receiving the three main classes of myeloma therapy (immunomodulatory agents, proteasome inhibitors, and anti-CD38 antibodies), and outcomes are poor, with infrequent complete responses, a median progression-free survival of 3 to 4 months, and a median overall survival of 8 to 9 months.[5-8] Chimeric antigen receptor (CAR)–modified T cells are a promising new treatment, and CD19-directed CAR T cells are approved for B-cell cancers.[9,10] The B-cell maturation antigen (BCMA)–directed CAR T cell idecabtagene vicleucel (ide-cel, also called bb2121) showed promising efficacy in a phase 1 study involving patients with relapsed or refractory myeloma.[11] These results prompted a pivotal study (KarMMa) to assess the efficacy and safety of ide-cel in patients with triple-class-exposed relapsed and refractory myeloma and to evaluate pharmacokinetics, immunogenicity, and potential biomarkers for response and progression.

Methods

Study Design and Patients

In this single-group, phase 2 study, eligible patients were 18 years of age or older; had received at least three previous regimens for multiple myeloma, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody; had disease that was refractory to their last regimen (progression within 60 days after the last dose) according to International Myeloma Working Group (IMWG) criteria[12] (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org); had measurable disease; and had adequate organ function. A complete description of the study design and eligibility criteria are provided in the protocol (available at NEJM.org).

Ide-cel was manufactured as described previously.[11,13] The actual doses delivered were within 20% of the target doses. Bridging therapy was allowed during manufacturing but was stopped at least 14 days before lymphodepletion and was restricted to certain drug classes and to drugs previously received.

Lymphodepletion with fludarabine (30 mg per square meter of body-surface area per day) and cyclophosphamide (300 mg per square meter per day) occurred on 3 consecutive days followed by 2 days of rest before ide-cel infusion. Patients received target doses of 150×10^6, 300×10^6, or 450×10^6 CAR-positive (CAR+) T cells. Patients were followed for at least 24 months and then asked to participate in a separate long-term follow-up study (GC-LTFU-001; ClinicalTrials.gov number, NCT03435796).

Study Oversight

The study was designed by the authors in conjunction with the sponsors and conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. The study protocol was approved by local or independent institutional review boards or ethics committees at participating sites. All the patients provided written informed consent. The authors affirm the accuracy and completeness of reported data and adherence of the study to the protocol. Medical writing assistance was funded by Bristol Myers Squibb. All drafts were critically reviewed and revised by the authors.

End Points and Assessments

The primary end point was an overall response (partial response or better), defined according to IMWG Uniform Response Criteria for Multiple Myeloma[12] as assessed by an independent review committee. The key secondary end point was a complete response or better (comprising complete and stringent complete responses). Additional secondary end points included time to response and duration of response, progression-free and overall survival, minimal residual disease (MRD), safety, pharmacokinetics, and immunogenicity.

Adverse events were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03. Cytokine release syndrome was graded according to published criteria (Table S2).[14] Neurotoxic effects were identified by investigators as defined events and graded according to the NCI CTCAE on the basis of the highest individual symptom grade. Tumor response and disease progression were assessed according to IMWG criteria.[12] MRD negativity was evaluated in bone marrow aspirates by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) with a minimum cutoff of 10^{-5} nucleated cells. Exploratory end points included levels of cytokines and soluble BCMA (sBCMA) as well as tumor BCMA expression.

Additional information is provided in the Methods section in the Supplementary Appendix.

STATISTICAL ANALYSIS

The primary efficacy analysis was performed in the population of patients treated with ide-cel (128 patients). The sample size for the primary end point (overall response) was based on a one-sample binomial test with normal approximation, under the assumption of 15% dropout between the time of enrollment and ide-cel treatment. The null hypothesis to be tested was that the percentage of patients receiving ide-cel with a best overall response of partial response or better would be 50% or less. If the null hypothesis was rejected, a null hypothesis that no more than 10% of patients receiving ide-cel would have a best overall response of complete or stringent complete response was to be tested. Time-to-event analyses and associated 95% confidence intervals were estimated with the use of Kaplan–Meier methods. Censoring of data for progression-free survival and response duration was based on Food and Drug Administration censoring rules.[15] All statistical analyses were performed with the use of SAS software, version 9.4 or higher. Statistical tests were not performed on subgroup analyses.

RESULTS

PATIENTS

Between December 13, 2017, and November 13, 2018, a total of 140 patients were enrolled and underwent leukapheresis, of whom 128 received ide-cel infusions. Twelve patients discontinued the study before ide-cel infusion (including 1 patient who discontinued after unsuccessful manufacture of the CAR T-cell product) (Fig. S1). At the time of data cutoff for this report (January 14, 2020), 62 patients remained in the primary study. Among the 128 treated patients, the median age was 61 years (range, 33 to 78), and the median time since diagnosis was 6 years (range, 1 to 18) (Table 1). A total of 65 patients (51%) had a high tumor burden (≥50% bone marrow plasma cells), 50 (39%) had extramedullary disease, 21 (16%) had stage III disease at screening according to the revised International Staging System, and 45 (35%) had a high-risk cytogenetic abnormality, defined as del(17p), t(4;14), or t(14;16).

The 128 treated patients had received a median of 6 previous antimyeloma regimens (range, 3 to 16), and 120 (94%) had received previous autologous hematopoietic stem-cell transplants (Table 1). A total of 108 patients (84%) had disease that was triple refractory (to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody), 77 (60%) had disease that was penta-exposed (to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab), and 33 (26%) had disease that was penta-refractory, according to IMWG criteria and on the basis of the most recent exposure to individual agents. A total of 112 patients (88%) received bridging therapy during the manufacturing period (Table S3), with a median duration of 15 days (range, 1 to 33). Baseline evaluations, including myeloma restaging, were performed after completion of bridging therapy. Responses to bridging therapy were observed in 5 of 112 patients (4%); additional details are reported in the Supplementary Appendix.

EFFICACY

Of 128 patients who received ide-cel, 4, 70, and 54 were treated at target doses of 150×10^6, 300×10^6, and 450×10^6 CAR+ T cells, respectively. Tumor response in treated patients is presented in Figure 1A; efficacy results in the 140 enrolled patients are summarized in Table S4. At a median follow-up of 13.3 months (range, 0.2 to 21.2), 94 of 128 patients (73%; 95% confidence interval [CI], 66 to 81) had a response ($P<0.001$), and 42 of 128 patients (33%) had a complete or stringent complete response. A total of 67 patients (52%) had a very good partial response or better. At the target doses of 150×10^6, 300×10^6, and 450×10^6 CAR+ T cells, a response was observed in 2 of 4 patients (50%), in 48 of 70 patients (69%), and in 44 of 54 patients (81%), respectively, and a complete response or better was observed in 1 of 4 patients (25%), in 20 of 70 patients (29%), and in 21 of 54 patients (39%). Of the 42 patients with a complete or stringent complete response, 33 (79%) also had MRD-negative status at a sensitivity level of 10^{-5}, corresponding to 26% (95% CI, 19 to 34) of the treated population; the remaining 9 patients (21%) could not be evaluated for MRD (Fig. 1A and Table S5). High incidences of response (overall response in ≥50% of patients and complete or stringent complete response in ≥10% of patients) were consistently observed in most subgroups examined, including older patients, those who received bridging therapy, and those with more aggressive disease features, including high-

Table 1. Baseline Characteristics of the Patients Who Received Idecabtagene Vicleucel (Ide-cel).*

Characteristic	Ide-cel Target Dose of CAR+ T Cells			Total (N=128)
	150×10^6 (N=4)	300×10^6 (N=70)	450×10^6 (N=54)	
Median age (range) — yr	54 (49–69)	61 (33–76)	62 (43–78)	61 (33–78)
Male sex — no. (%)	4 (100)	38 (54)	34 (63)	76 (59)
Median time from initial diagnosis to screening (range) — yr	10 (6–12)	7 (2–18)	6 (1–17)	6 (1–18)
Extramedullary disease — no. (%)†	0	34 (49)	16 (30)	50 (39)
High tumor burden — no. (%)‡	3 (75)	34 (49)	28 (52)	65 (51)
Tumor BCMA expression ≥50% at screening — no. (%)	4 (100)	60 (86)	45 (83)	109 (85)
ECOG performance-status score — no. (%)§				
0	3 (75)	31 (44)	23 (43)	57 (45)
1	1 (25)	38 (54)	29 (54)	68 (53)
2	0	1 (1)	2 (4)	3 (2)
R-ISS disease stage — no. (%)¶				
I	0	12 (17)	2 (4)	14 (11)
II	3 (75)	43 (61)	44 (81)	90 (70)
III	1 (25)	12 (17)	8 (15)	21 (16)
Unknown	0	3 (4)	0	3 (2)
Cytogenetic abnormality — no. (%)				
High-risk‖	1 (25)	20 (29)	24 (44)	45 (35)
del(17p)	1 (25)	10 (14)	12 (22)	23 (18)
t(4;14)	0	12 (17)	11 (20)	23 (18)
t(14;16)	0	2 (3)	4 (7)	6 (5)
Other				
1q amp	2 (50)	17 (24)	26 (48)	45 (35)
13q34 monosomy	2 (50)	16 (23)	16 (30)	34 (27)
13q14 del	2 (50)	6 (9)	10 (19)	18 (14)
1p del	0	4 (6)	4 (7)	8 (6)
Bridging therapy — no. (%)**	4 (100)	61 (87)	47 (87)	112 (88)
Median no. of previous antimyeloma regimens (range) — no. (%)	9 (4–12)	6 (3–16)	5 (3–13)	6 (3–16)
>1 Previous antimyeloma regimen per year — no. (%)	2 (50)	36 (51)	22 (41)	60 (47)
Previous autologous HSCT — no. (%)	4 (100)	67 (96)	49 (91)	120 (94)
>1 transplantation	3 (75)	23 (33)	18 (33)	44 (34)
Refractory status — no. (%)††				
Immunomodulatory agent	4 (100)	70 (100)	52 (96)	126 (98)
Proteasome inhibitor	4 (100)	63 (90)	49 (91)	116 (91)
Anti-CD38 monoclonal antibody	4 (100)	66 (94)	50 (93)	120 (94)
Daratumumab	3 (75)	61 (87)	45 (83)	109 (85)
Double-refractory disease‡‡	4 (100)	63 (90)	47 (87)	114 (89)
Triple-refractory disease§§	4 (100)	60 (86)	44 (81)	108 (84)
Penta-refractory disease¶¶	1 (25)	24 (34)	8 (15)	33 (26)

Table 1. (Continued.)

* Percentages may not total 100 because of rounding. BCMA denotes B-cell maturation antigen, and HSCT hematopoietic stem-cell transplantation.
† Extramedullary disease was defined as paraskeletal soft-tissue masses, soft-tissue masses spreading outside the bone marrow, or both.
‡ A high tumor burden was defined as at least 50% CD138-positive plasma cells in bone marrow.
§ Eastern Cooperative Oncology Group (ECOG) performance-status scores range from 0 to 5, with higher scores indicating greater disability.
¶ The revised International Staging System (R-ISS) disease stage was derived from the ISS stage at enrollment, cytogenetic abnormality (yes vs. no), and serum lactate dehydrogenase concentration.
‖ High-risk cytogenetic abnormalities included the following: del(17p), t(4;14), and t(14;16).
** Therapy was used as a bridge from leukapheresis to lymphodepletion.
†† Refractory was defined as disease progression on or within 60 days after the last dose of the most recent drug given in each drug class.
‡‡ Double-refractory disease was refractory to an immunomodulatory agent and a proteasome inhibitor.
§§ Triple-refractory disease was refractory to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody.
¶¶ Penta-refractory disease was refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab.

risk cytogenetic abnormalities, triple- or penta-refractory disease, a high tumor burden, and extramedullary disease (Fig. 1B and Fig. S2).

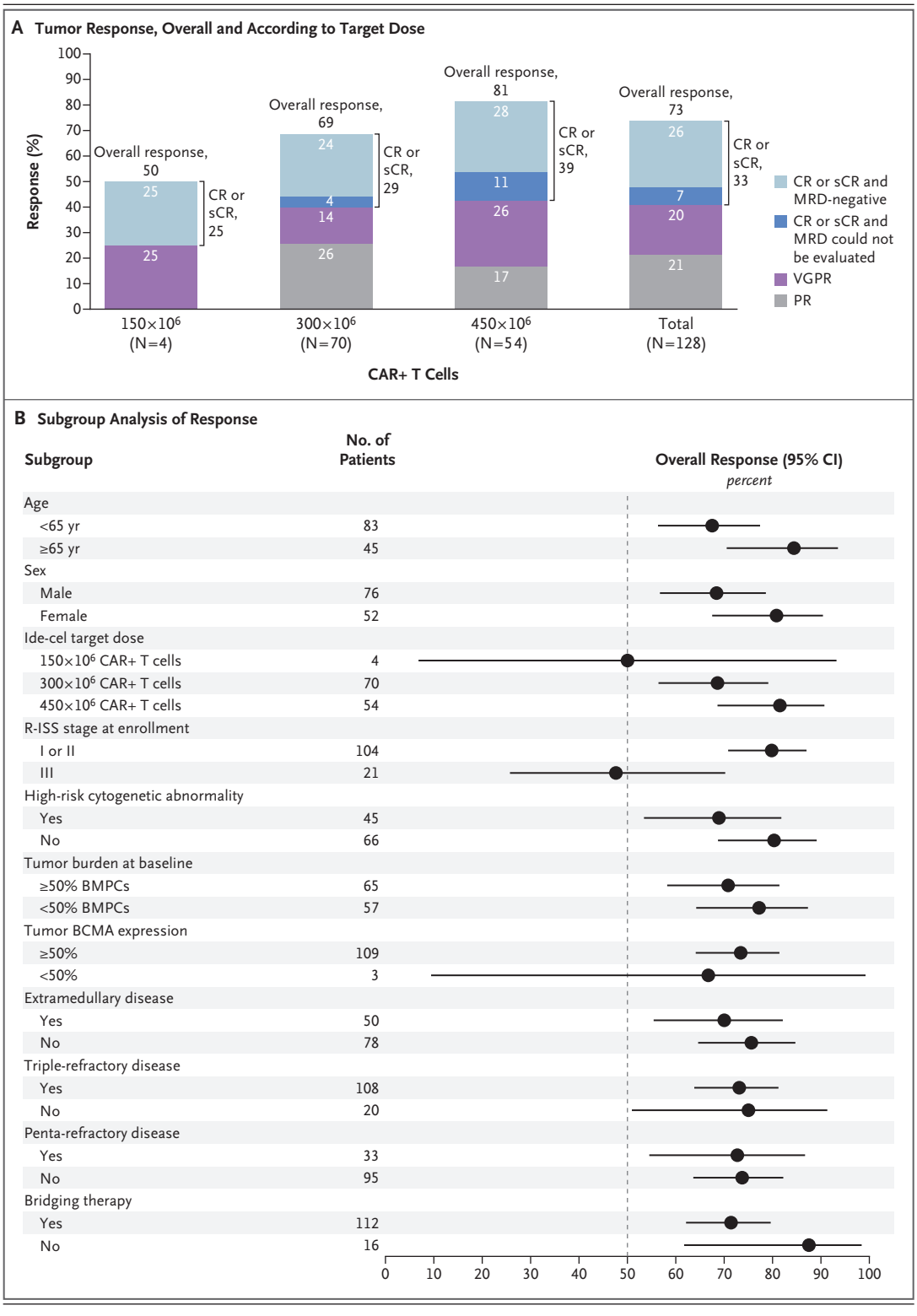
The median time to first response was 1.0 month (range, 0.5 to 8.8); the median time to a complete response or better was 2.8 months (range, 1.0 to 11.8). The Kaplan–Meier estimate for median duration of response was 10.7 months (95% CI, 9.0 to 11.3) overall and 11.3 months (95% CI, 10.3 to 11.4) at the 450×10^6 dose (Fig. 2A). The response duration increased with the depth of response; the median response duration was 4.5 months (95% CI, 2.9 to 6.7), 10.4 months (95% CI, 5.1 to 11.3), and 19.0 months (95% CI, 11.3 to could not be estimated) in patients having a best response of partial response (27 patients), very good partial response (25 patients), and complete or stringent complete response (42 patients), respectively (Fig. 2B).

The Kaplan–Meier estimated median progression-free survival was 8.8 months overall (95% CI, 5.6 to 11.6), 12.1 months (95% CI, 8.8 to 12.3) at the 450×10^6 dose, and 20.2 months (95% CI, 12.3 to could not be estimated) in patients having a complete or stringent complete response (Fig. 2C and Fig. S3). The Kaplan–Meier estimated median overall survival was 19.4 months (95% CI, 18.2 to could not be estimated), with an overall survival of 78% at 12 months (Fig. 2D). Data on overall survival are immature, with data for 84 patients (66%) censored, including 39 of 54 patients (72%) at the 450×10^6 dose.

After disease progression, 28 patients were retreated with ide-cel (Table S4). Six patients (21%) had a second response, with durations of response ranging from 1.9 to 6.8 months; all the patients who had a response were retreated at a dose higher than their initial dose.

SAFETY

Adverse events were reported in all 128 patients treated with ide-cel, with grade 3 or 4 events occurring in 127 patients (99%) (Table 2). Most adverse events, with the exception of hypogammaglobulinemia and infections, occurred within the first 8 weeks after infusion (Table S6). Most grade 3 or 4 events were hematologic toxic effects, including neutropenia in 114 patients (89%), anemia in 77 (60%), and thrombocytopenia in 67 (52%), and were at least partially related to the lymphodepleting chemotherapy administered before ide-cel infusion. Among patients with persistent grade 3 or 4 neutropenia (52 patients) or thrombocytopenia (62 patients) 1 month after infusion, the median time to recovery to grade 2 or lower was 1.9 months (range, 1.2 to 5.6) and 2.1 months (range, 1.2 to 13.8), respectively (Table S7 and Fig. S4). Four bleeding events of grade 3 or 4 were observed, including cerebral, gastrointestinal, conjunctival, and postprocedural hemorrhage events; the cerebral hemorrhage event occurred after myeloma progression. Infections occurred in 88 patients (69%) and were of grade 3 or 4 in 28 (22%). Use of antimicrobial agents, growth factors, and immune globulin was common (Table S8). The incidence and severity of cytopenias and infections did not differ substantially according to dose (Table S9).



Cytokine release syndrome occurred in 107 patients (84%) and was mostly of grade 1 or 2 (Table 2 and Table S10). Five patients (4%) had grade 3 cytokine release syndrome, 1 (<1%) had grade 4, and 1 (<1%) had grade 5 (300×10^6 dose level). The median time to the onset of cytokine release syndrome was 1 day (range, 1 to 12), with a median duration of 5 days (range, 1 to 63).

Figure 1 (facing page). Tumor Response and Subgroup Analysis of Response.

Panel A shows tumor response according to the idecabtagene vicleucel (ide-cel) target dose of chimeric antigen receptor–positive (CAR+) T cells and among all treated patients, and Panel B shows the incidence of response according to patient characteristics. All responses were confirmed and assessed on the basis of the International Myeloma Working Group Uniform (IMWG) Response Criteria for Multiple Myeloma (details on the criteria for disease response are provided in the Supplementary Appendix). An overall response was defined as a partial response (PR) or better. The 450×10^6 dose group included 2 patients who did not have any response-assessment data or whose only assessment could not be evaluated. Negativity for minimal residual disease (MRD) was assessed in bone marrow aspirate and determined at a sensitivity level of at least 10^{-5} nucleated cells by means of a next-generation sequencing assay (clonoSEQ, Adaptive Biotechnologies) in patients who had a complete response (CR) or stringent complete response (sCR) and who could be evaluated for MRD. Of 42 patients with a CR or sCR, 33 were MRD-negative at 10^{-5} within a 3-month window before first having a CR or sCR, 8 could not be evaluated for MRD because of technical deficiencies, and 1 did not have values within the 3-month window before a CR or sCR. The revised International Staging System (R-ISS) criteria were as follows: stage I, serum $beta_2$-microglobulin level of less than 3.5 mg per liter, serum albumin level of at least 3.5 g per deciliter, standard-risk chromosomal abnormalities, and normal lactic acid dehydrogenase level; stage II, not stage I or III; and stage III, serum $beta_2$-microglobulin level of at least 5.5 mg per liter and either high-risk chromosomal abnormalities on fluorescence in situ hybridization or high lactic acid dehydrogenase level. High-risk cytogenetic abnormalities were defined as del(17p), t(4;14), and t(14;16). Triple-refractory disease was refractory to an immunomodulatory drug, a proteasome inhibitor, and an anti-CD38 antibody. Penta-refractory disease was refractory to two immunomodulatory drugs (lenalidomide and pomalidomide), two proteasome inhibitors (bortezomib and carfilzomib), and one anti-CD38 antibody (daratumumab). BCMA denotes B-cell maturation antigen, BMPC bone marrow plasma cell, and VGPR very good partial response.

Management of cytokine release syndrome included tocilizumab in 67 patients (52%) and glucocorticoids in 19 (15%). At doses of 150×10^6, 300×10^6, and 450×10^6 CAR+ T cells, cytokine release syndrome of any grade was observed in 2 of 4 patients (50%), 53 of 70 patients (76%), and 52 of 54 patients (96%), respectively, with cytokine release syndrome of grade 3 or higher observed in 0 patients, 4 patients (6%), and 3 patients (6%). Investigator-identified neurotoxic effects were reported in 23 patients (18%), of whom 4 (3%) had grade 3 events; no grade 4 or 5 neurotoxic effects were observed (Table 2 and Table S11). The median time to any neurotoxic effect was 2 days (range, 1 to 10), and the median duration was 3 days (range, 1 to 26). At doses of 150×10^6, 300×10^6, and 450×10^6 CAR+ T cells, neurotoxic effects of any grade were reported in 0 of 4 patients, 12 of 70 patients (17%), and 11 of 54 patients (20%), respectively, with grade 3 events in 0 patients, 1 patient (1%), and 3 patients (6%). Use of glucocorticoids, tocilizumab, or both for management of cytokine release syndrome and neurotoxic effects increased with increasing dose of CAR+ T cells.

A total of 44 treated patients (34%) died during the study, with most deaths (27) attributed by the investigator to complications of myeloma progression (Table S12). Three patients (2%) died within 8 weeks after ide-cel infusion from ide-cel–related adverse events (bronchopulmonary aspergillosis, gastrointestinal hemorrhage, and cytokine release syndrome). One patient (1%) died between 8 weeks and 6 months from an ide-cel–related adverse event (cytomegaloviral pneumonia). Five patients (4%) died after 6 months from unrelated adverse events, and an additional 8 patients (6%) died after disease progression.

CELLULAR PHARMACOKINETIC PROFILE AND IMMUNOGENICITY

Pharmacokinetic analysis was based on a data cutoff date of April 19, 2019, which provided 3 months of follow-up after the last ide-cel infusion. Among patients in whom pharmacokinetics could be evaluated (127 patients), maximum CAR+ T-cell expansion (C_{max}) occurred at a median of 11 days (Fig. 3A and Table S13). Although high interpatient variability was observed at all doses, upper quartiles of exposure (area under the curve of the transgene level from time of dose to 28 days [$AUC_{0–28\ days}$]) were observed more frequently at the 450×10^6 dose (Fig. 3B). Exposures were higher in patients who had a response than in those who did not (Fig. S5A), and higher exposure was associated with deeper response and longer progression-free survival (Fig. 3C and 3D). CAR+ T cells were detected in 29 of 49 patients (59%) at 6 months and in 4 of 11 patients (36%) at 12 months after infusion (Table S14).

Among treated patients, 5 were positive for antidrug antibodies before infusion. After infusion, antidrug antibodies were not detected earlier than 3 months; thereafter, the percentage of

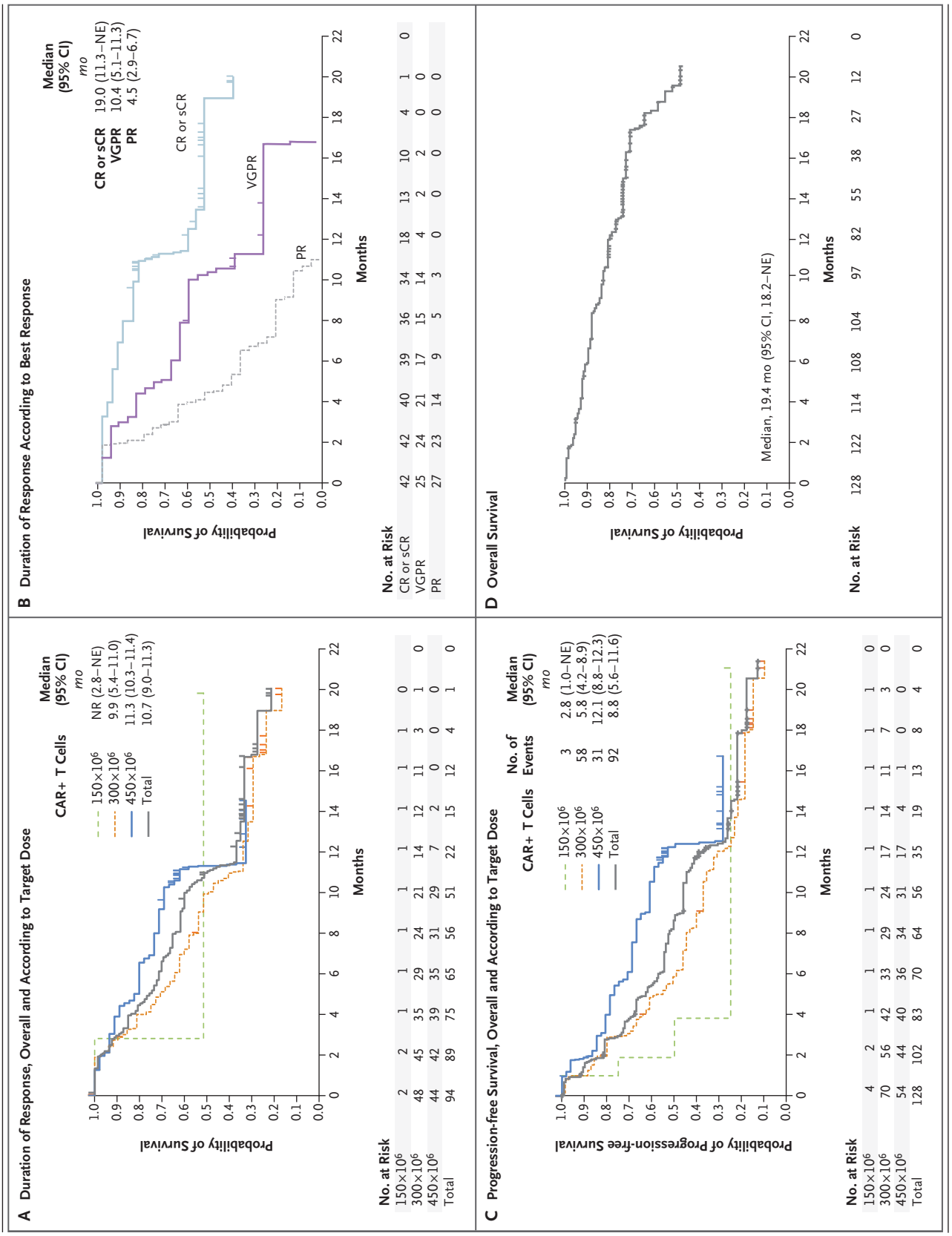


Figure 2 (facing page). Progression-free Survival, Duration of Response, and Overall Survival.

Panel A shows Kaplan–Meier curves of duration of response, overall and according to target dose, in the treated population, and Panel B Kaplan–Meier curves of best response in the same population; response was determined on the basis of a review by the independent response committee. Panel C shows a Kaplan–Meier curve of progression-free survival overall and according to target dose in the treated population. Events are the first documented disease progression or death from any cause during the study, whichever occurred earlier, after ide-cel infusion. Progression-free survival among patients with disease progression or death after two or more consecutive missed scheduled assessments or after subsequent antimyeloma therapy (SAMT) was censored at the last efficacy assessment that could be evaluated before those missed scheduled assessments or before the start of SAMT. Panel D shows a Kaplan–Meier curve of overall survival in the treated population on the basis of a review by the independent response committee according to IMWG criteria with the application of Food and Drug Administration (FDA) censoring rules.[15] Duration of response was defined as the time from the date of the first documented response (PR or better) to the first documentation of disease progression or death, whichever occurred first. Patients with a PR or better according to IMWG criteria with the application of FDA censoring rules were included. Tick marks indicate censored data. NE denotes could not be estimated, and NR not reached.

Table 2. Adverse Events, Cytokine Release Syndrome, and Neurotoxic Effects in the 128 Patients Who Received Ide-Cel.

Variable	Any Grade	Grade 3 or 4
	no. of patients (%)	
Adverse event*		
Any	128 (100)	127 (99)
Hematologic		
Neutropenia	117 (91)	114 (89)
Anemia	89 (70)	77 (60)
Thrombocytopenia	81 (63)	67 (52)
Leukopenia	54 (42)	50 (39)
Lymphopenia	35 (27)	34 (27)
Febrile neutropenia	21 (16)	20 (16)
Gastrointestinal		
Diarrhea	45 (35)	2 (2)
Nausea	37 (29)	0
Constipation	20 (16)	0
Other		
Hypokalemia	45 (35)	3 (2)
Fatigue	43 (34)	2 (2)
Hypophosphatemia	38 (30)	20 (16)
Hypocalcemia	34 (27)	10 (8)
Pyrexia	32 (25)	3 (2)
Hypomagnesemia	30 (23)	0
Decreased appetite	27 (21)	1 (<1)
Headache	27 (21)	1 (<1)
Hypogammaglobulinemia	27 (21)	1 (<1)
Cough	26 (20)	0
Hyponatremia	24 (19)	7 (5)
Hypoalbuminemia	22 (17)	4 (3)
Aspartate aminotransferase level increased	21 (16)	2 (2)
Hypotension	21 (16)	1 (<1)
Cytokine release syndrome†	107 (84)	7 (5)
Neurotoxic effect‡	23 (18)	4 (3)

* Shown are adverse events that occurred in 15% or more of the patients who received ide-cel.
† The clustered term includes the preferred term; events were uniformly graded according to Lee et al.[14] Included is one patient who had progression to a grade 5 event.
‡ Investigator-identified neurotoxicity was the preferred term.

antidrug antibody–positive patients increased over time, from 21% (21 of 102) at month 3 to 65% (34 of 52) at month 12 (Fig. 3A and Table S15). Exposure variables ($AUC_{0–28\ days}$ and C_{max}) were not affected by positivity for antidrug antibodies before or after infusion. Antidrug antibodies had no effect on the incidence of response or of complete response or better and had no noticeable effect on progression-free survival. All 6 patients who had a response to retreatment were antidrug antibody–negative (Table S16).

BIOMARKERS

Levels of proinflammatory markers, including cytokines, ferritin, and C-reactive protein, increased early after ide-cel infusion and decreased by month 1, with peak levels higher in patients having cytokine release syndrome of grade 3 or higher (Fig. S6). Baseline cytokine levels were not associated with higher-grade cytokine release syndrome or neurotoxic effects. Soluble BCMA was assessed as a serum-based universal marker of myeloma burden. Baseline sBCMA levels were elevated in treated patients and decreased rapidly after infusion in patients who had a response, with nadir values achieved within 3 months (Fig. 3A and Fig. S5B and S5C). Achievement of undetectable sBCMA levels increased with depth of response (17 of 27 pa-

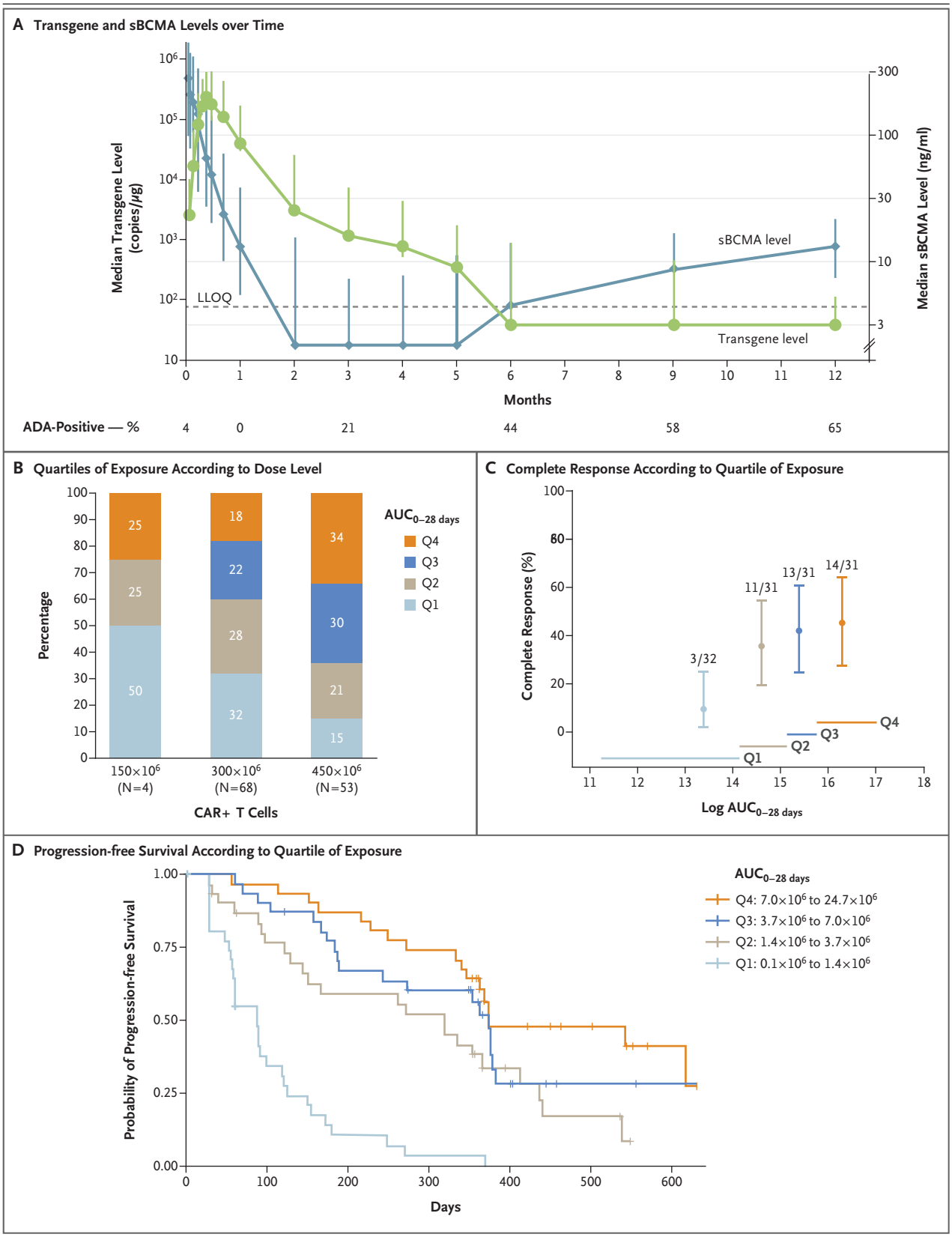


Figure 3 (facing page). Cellular Pharmacokinetics.
Panel A shows transgene levels, soluble BCMA (sBCMA) levels, and the percentage of patients who were antidrug antibody (ADA)–positive over time. I bars indicate interquartile ranges. Panel B shows the quartiles of exposure at each dose level. Panels C and D show complete response (including stringent complete response) and progression-free survival, respectively, according to quartile of exposure. $AUC_{0–28\ days}$ denotes area under the curve of the transgene level from time of dose to 28 days, C_{max} maximum concentration, LLOQ lower limit of quantification, and Q quartile.

tients [63%] with a partial response, 21 of 26 [81%] with a very good partial response, and 36 of 38 [95%] with a complete or stringent complete response). Higher CAR+ T-cell expansion (C_{max}) was associated with increased depth of sBCMA reduction. Time to rebound of sBCMA from undetectable levels was longest at the 450×10^6 dose (Fig. S5D). Duration of undetectable sBCMA correlated with response duration, and clearance of sBCMA at month 2 was associated with longer progression-free survival (Fig. S5E and S5F).

At baseline, 110 of 112 tumor samples (98%) expressed BCMA, with 109 having at least 50% BCMA-positive plasma cells, and all the patients had detectable levels of sBCMA. At disease progression, 69 of 71 patients (97%) had rising sBCMA levels (>40 ng per milliliter) consistent with progression of BCMA-expressing myeloma (Table S17), and 15 of 16 evaluated patients who had a response (94%) retained BCMA-expressing tumor cells in bone marrow. Loss of tumor BCMA expression was suspected in 3 of 71 patients (4%) who could be evaluated at progression (Table S18). In one of these patients, biallelic genomic loss of BCMA on chromosome 16p was subsequently confirmed.[16]

DISCUSSION

Treatment with ide-cel resulted in frequent and deep responses in patients with triple-class-exposed relapsed and refractory myeloma in the pivotal phase 2 KarMMa study. A response was observed in 73% of the treated patients, and a complete response or better was observed in 33%; a somewhat higher frequency and somewhat greater depth of response were observed at the 450×10^6 dose (response in 81% of the patients and complete response or better in 39%). The patients were heavily pretreated (median, six previous regimens) and had disease that was refractory to most available therapies (84% triple refractory, with an incidence of response to bridging therapy of 4%) with multiple high-risk features, including many with a high tumor burden, high-risk cytogenetic abnormalities, and extramedullary disease. Nevertheless, antitumor activity was observed in all these subgroups. Nearly all tumors expressed BCMA, a finding that supports the use of ide-cel in relapsed and refractory myeloma without restriction based on tumor BCMA expression. The fact that MRD-negative responses occurred in approximately a quarter of the patients highlights the depth of response induced by ide-cel.

Efficacy after a single ide-cel infusion was encouraging, with a median response duration of 10.7 months, progression-free survival of 8.8 months, and overall survival of 19.4 months across treated patients. The median response duration and progression-free survival were numerically longer at the 450×10^6 dose (11.3 months and 12.1 months, respectively). Increased depth of response was also associated with improved response durability; patients with a complete or stringent complete response had a longer median response duration at 19.0 months. Median CAR+ T-cell expansion increased at higher target doses and was associated with longer progression-free survival. Ide-cel showed durable persistence in blood, with 36% of patients who could be evaluated having detectable CAR+ T cells at 12 months. The presence of these cells did not guard against recurrence; it is unclear whether the myeloma cells became resistant to the CAR T cells or the T cells became functionally compromised in some way. These efficacy results compare favorably with results in similarly heavily pretreated patients with relapsed or refractory myeloma treated with two recently approved regimens, selinexor plus dexamethasone and belantamab mafodotin (median progression-free survival, 3.7 months and 2.9 months, respectively).[5,17]

Reductions in sBCMA levels after infusion paralleled tumor response, and a longer time to sBCMA rebound was associated with a longer duration of response. Nearly all patients who could be evaluated had elevated sBCMA values (97%) and still had detectable levels of tumor BCMA (93%) at the time of myeloma progres-

sion, findings that suggest that BCMA antigen loss is an uncommon mechanism of escape from ide-cel. In contrast, CD19 epitope loss is reported to be a relatively common escape mechanism after treatment with CD19-directed CAR T-cell therapy, especially in patients with acute leukemia.[18,19] Determination of long-term disease-free survival with ide-cel requires additional follow-up of these heavily pretreated patients with myeloma.

Observed toxic effects were consistent with those in previous reports.[11] Cytokine release syndrome of grade 3 or higher and neurotoxic effects were observed in no more than 6% of patients at all doses of CAR+ T cells. High-grade hematologic toxic effects were common but transient. A small number of adverse events were fatal.

Results of the KarMMa study support substantial antitumor activity for ide-cel across a target dose range of 150×10^6 to 450×10^6 CAR+ T cells. The 450×10^6 dose appeared to be somewhat more effective than the other doses.

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APPENDIX

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