Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Munshi NC, Anderson LD Jr, Shah N, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med 2021;384:705-16. DOI: 10.1056/NEJMoa2024850

Supplementary Appendix

Supplement to: Munshi N., Anderson Jr., L.D., Shah, N., et al. Idecabtagene Vicleucel in Relapsed and Refractory Multiple Myeloma.

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METHODS

Study Design

The study consisted of three periods: pretreatment (screening, leukapheresis, and bridging therapy [if needed]), treatment (lymphodepleting chemotherapy [LDC] and infusion with idecabtagene vicleucel [ide-cel, bb2121]), and post-treatment (after ide-cel infusion). If necessary, per investigator discretion, patients could have received bridging therapy for myeloma disease control following leukapheresis while ide-cel was being manufactured, provided the last dose of bridging therapy was administered ≥14 days prior to the initiation of LDC. Bridging therapies could include glucocorticoids, alkylating agents, immunomodulatory agents, proteasome inhibitors, and/or anti-CD38 antibodies as single agents or in combination. During the treatment period, patients received one 3-day cycle of LDC with fludarabine and cyclophosphamide starting 5 days before ide-cel infusion. Prior to proceeding with ide-cel infusion, the patient's clinical status must not have significantly worsened compared with initial eligibility criteria such that, in the opinion of the treating physician, the patient would have an increased risk of toxicities associated with ide-cel infusion. Starting with protocol amendment 3.0, patients who met at least one of the following criteria on the day of scheduled ide-cel infusion had their infusion delayed:

- Suspected or active systemic infection
- Onset of fever ≥38 °C/100.4 °F, not related to underlying disease
- Requirement for supplemental oxygen to keep saturation >91%
- Cardiac arrhythmia not controlled with medical management
- Hypotension requiring vasopressor support
- New onset or worsening of other nonhematologic organ dysfunction grade ≥3
- Taking any of the prohibited medications

Ide-cel was administered at a target dose range of 150 to 450 (±20%) × 10^6 CAR+ T cells per infusion. The original target doses were 150 and 300 × 10^6 CAR+ T cells based on the original protocol specified target dose range of 150 to 300 × 10^6 CAR+ T cells. The initial 4 patients were

dosed at 150 × 10^6 CAR+ T cells and, thereafter, patients were treated at the target dose of 300. Based on evolving safety data from the ongoing phase 1 trial, CRB-401, supporting the tolerability of the 450 × 10^6 CAR+ T cells, an amendment to the study was written to expand the allowable target dose range to 150 to 450 × 10^6 CAR+ T cells. After implementation of this protocol amendment (2.0) at participating clinical sites, nearly all newly enrolled patients received a target dose of 450 (±20%) × 10^6 CAR+ T cells within an allowed dose range of 150 to 540 × 10^6 CAR+ T cells. As a result, patients treated at the target dose of 450 × 10^6 CAR+ T cells were enrolled in the latter part of the study. Patients were required to be hospitalized the day of infusion through 14 days after infusion. All patients had an Eastern Cooperative Oncology Group performance status of 0 or 1. Measurable disease was defined by serum (≥1.0 g/dL) or urine (≥200 mg/24 hours) monoclonal protein or serum free light chains (FLCs; involved FLCs ≥10 mg/dL with abnormal ratio). The full study protocol is available with the full text of this article at NEJM.org.

End Points and Assessments

Efficacy assessments included serum and urine protein electrophoresis and immunofixation, serum immune globulins, serum FLC assay, clinical and/or radiological extramedullary plasmacytoma assessments (if applicable; included contiguous bone lesions as well as organ and nodal involvement), radiographic assessment for bone lesions, minimal residual disease (MRD), and bone marrow aspirate and bone marrow biopsy. Response based on results from central laboratories was assessed according to the International Myeloma Working Group (IMWG) response criteria.[1] If progressive disease occurred after month 24, assessments were performed every 12 months for up to 5 years or until documented progression.

MRD assessments were performed at screening, at baseline (after bridging therapy), and at all bone marrow assessment timepoints through month 12 independent of IMWG response. After month 12, MRD assessments were performed in patients with a very good partial response (VGPR) or better and in patients with MRD-negative status at their last prior assessment. MRD in the bone

marrow was measured centrally using both 8-color flow cytometry (standardized EuroFlow™) and next-generation sequencing (NGS). The primary analysis of MRD status was the proportion of patients who achieved at least a complete response and MRD-negative status at any timepoint within 3 months prior to achieving a complete response until the time of disease progression or death based on NGS using a sensitivity level of 10^{-5} nucleated cells. A secondary analysis was performed based on a sensitivity level of 10^{-6} nucleated cells and is provided in the supplementary appendix (Table S5).

Progression-free survival was defined as the time from first ide-cel infusion to the first documentation of progressive disease or death due to any cause, whichever occurred first. Time to response was defined as the time from first ide-cel infusion to first documentation of a partial response or better. Duration of response was defined as the time from first documentation of a partial response or better to disease progression or death due to any cause, whichever occurred first.

Safety assessments included complete physical examination including neurologic examination and vital signs, Mini Mental State Examination, clinical laboratory and replication competent lentivirus evaluations, pregnancy testing, concomitant medications and procedures, and adverse events. Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). Neurologic events the investigators considered to be CAR T-associated were reported as “neurotoxicity” and classified as investigator-identified neurotoxicity. Similarly, any events the investigators attributed to cytokine release syndrome were reported as “cytokine release syndrome” and graded according to the Lee criteria.[2] Individual signs and symptoms characterizing the investigator-identified neurotoxicity and cytokine release syndrome events were captured separately and graded according to the NCI CTCAE v4.03.

Expansion and persistence of CAR+ T cells were analyzed to determine the cellular pharmacokinetic profile of ide-cel. CD3+ cells were purified from whole blood and their DNA purified as previously described.[3] The time course of vector transgene copies per microgram genomic DNA, as measured by quantitative PCR (qPCR), was assessed. Using the pharmacokinetic data, noncompartmental analysis was performed to calculate parameters, such as time of maximum observed transgene level (T_{max}), maximum transgene level occurring at T_{max} (C_{max}), time of last measurable transgene level (T_{last}), and area under the curve (AUC) using software program Phoenix WinNonlin version 8.1.

Potential immune response to ide-cel was evaluated for humoral and cell-mediated responses. Serum samples collected postinfusion were evaluated for the formation of antidrug antibodies using an immunoassay designed and validated to detect antibodies to the extracellular CAR domain. Cell-mediated immune responses were evaluated using an Interferon-gamma ELISpot assay performed on peripheral blood mononuclear cells (PBMCs). PBMC samples were stimulated *ex vivo* using peptides spanning the extracellular domain of the CAR construct. Antigen-specific immune responses and the resulting production of interferon gamma was then detected by ELISpot.

Biomarker Analyses

Baseline and postinfusion levels of 27 immune-related soluble factors (on days 1−28) were evaluated by Luminex immunoassay in the plasma. MRD status was evaluated in bone marrow aspirate by next-generation sequencing (ClonoSEQ®, Adaptive Biotechnologies) at baseline and at months 1, 3, 6, 12, 18, and 24 agnostic of response. Correlations between each biomarker and key safety and efficacy endpoints were explored.

Tumor-associated BCMA expression was assessed from bone marrow biopsies by immunohistochemistry using a monoclonal antibody directed against an intracellular B-cell maturation antigen (BCMA) epitope. Biopsies with any CD138+ cells (≥1%) were evaluated for BCMA expression. To confirm negative BCMA expression (<5% of CD138+ cells), a threshold of 3% CD138+

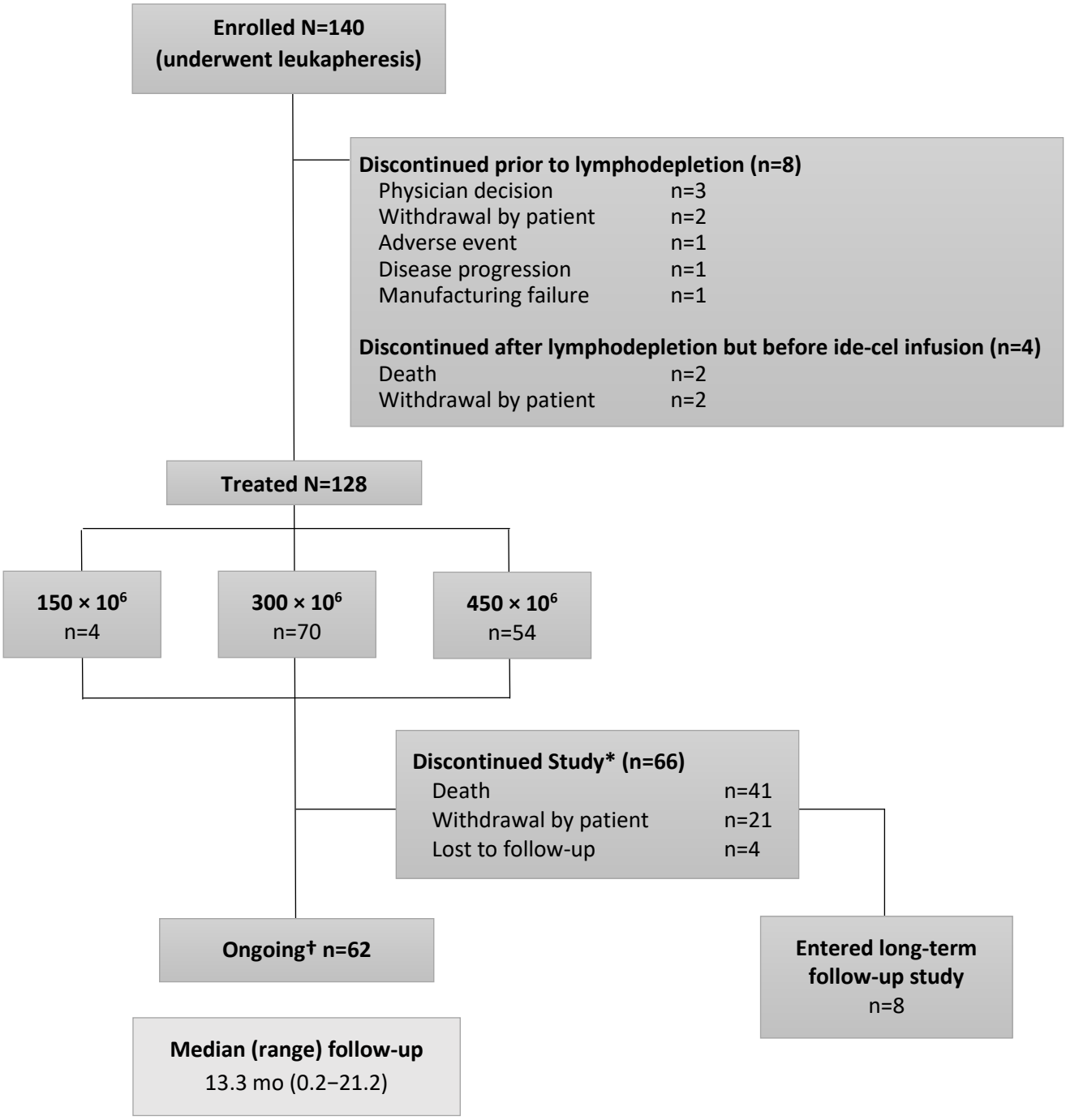
cells in the biopsy was required to provide a sufficient number of cells for evaluation; tumor cell surface BCMA expression was quantified on fresh bone marrow aspirates by flow cytometry using Quantibrite™ beads. Soluble BCMA was assessed in serum longitudinally (day 1 through disease progression) using Luminex immunoassay to monitor anti-tumor responses and infer tumor BCMA expression at disease progression in patients with no available bone marrow biopsies.

RESULTS

Response to Bridging Therapy

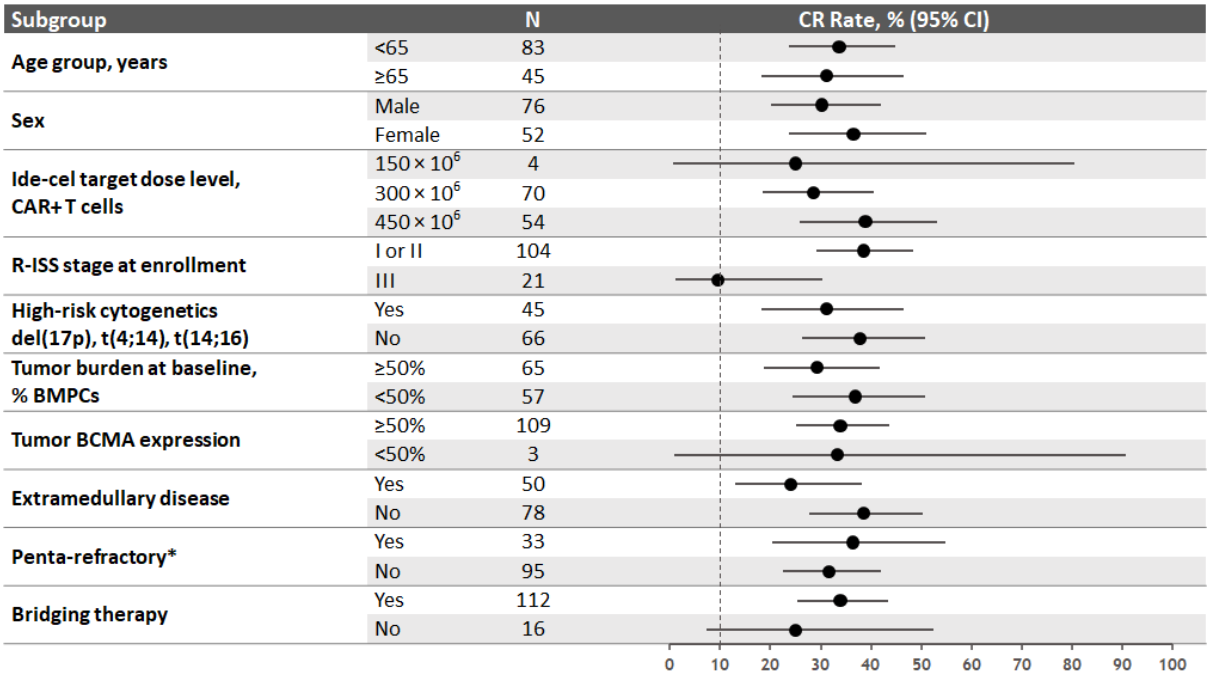
Overall, 88% of patients received bridging therapy for disease control during the manufacturing period, most commonly dexamethasone (70%), cyclophosphamide (37%), daratumumab (28%), carfilzomib (23%), bortezomib (20%), and pomalidomide (19%) (Table S3). Following completion of bridging therapy, baseline evaluations and restaging revealed five patients had responded to bridging therapy per investigator assessment, including four with a partial response and one with a VGPR; there were no complete responses to bridging therapy.

Figure S1. CONSORT Diagram



*Includes 48 patients who discontinued after initial ide-cel infusion without entering the retreatment period and 18 patients who discontinued during the retreatment period. Of the 25 patients who discontinued due to withdrawal by patient or loss to follow-up, 23 discontinued following disease progression, 1 following a lack of response but without confirmed disease progression, and 1 while in an ongoing response.
†Includes 50 patients ongoing after initial ide-cel infusion without retreatment and 12 patients ongoing after entering retreatment period (regardless of whether the patient has yet received ide-cel retreatment).

Figure S2. Complete Response Rate by Baseline Characteristics. BMPC denotes bone marrow plasma cell, CR complete response, R-ISS revised International Staging System.



*Refractory to two immunomodulatory drugs (lenalidomide and pomalidomide), two proteasome inhibitors (bortezomib and carfilzomib), and one anti-CD38 antibody (daratumumab).

Figure S3. Progression-Free Survival by Best Response. Kaplan-Meier curve of progression-free survival by best overall response based on Independent Response Committee review according to International Myeloma Working Group criteria applying FDA censoring rules.[1,4]

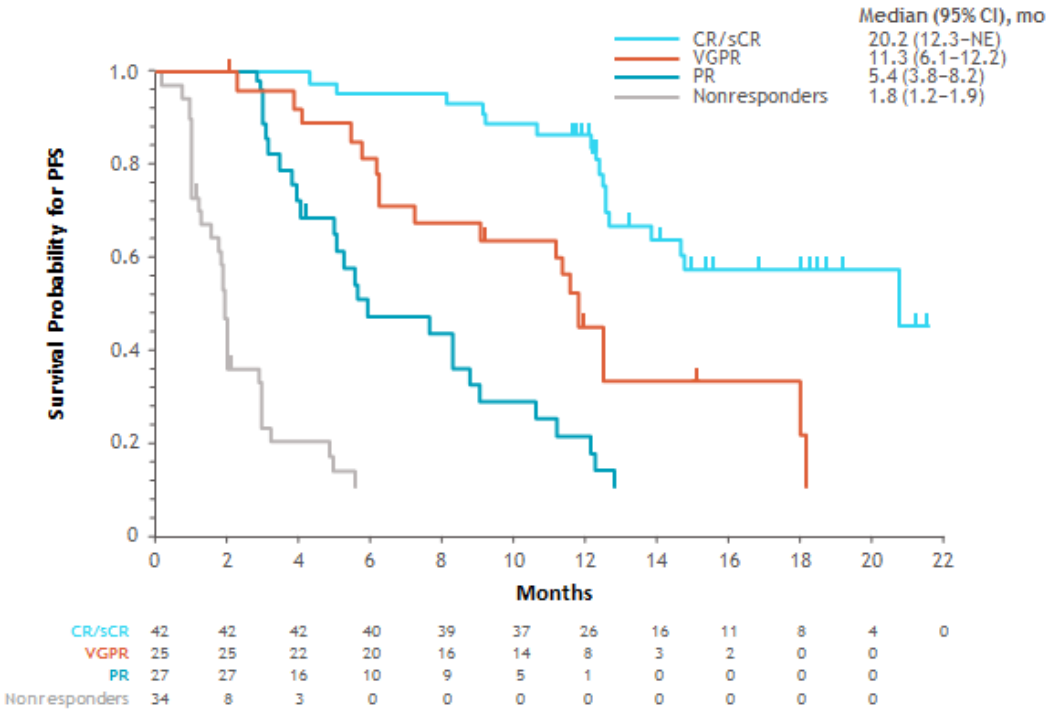


Figure S4. Time to Recovery of Grade 3/4 Cytopenias in Patients Without Recovery by Month 1. Patients with grade 3/4 cytopenias (absolute neutrophil counts <1000 cells/µL (N = 9) or platelets <50,000/µL (N = 20) based on laboratory values) on or before month 1 are included. Recovery is defined as absolute neutrophil counts ≥1000 cells/µL and platelets ≥50,000 cells/µL. Time to recovery is defined as the time from infusion to the first time when recovery criteria were met. The median follow-up of the 20 patients without documented recovery from grade 3/4 thrombocytopenia was 4.0 months and the median follow-up of the 9 patients without documented recovery from grade 3/4 neutropenia was 1.8 months. Patients who withdrew consent (typically following disease progression) or were lost to follow-up prior to cytopenia recovery were censored at their last assessment. Patients who died before cytopenia recovery were censored at the data cutoff date (accounting for all except one tick mark beyond month 12).

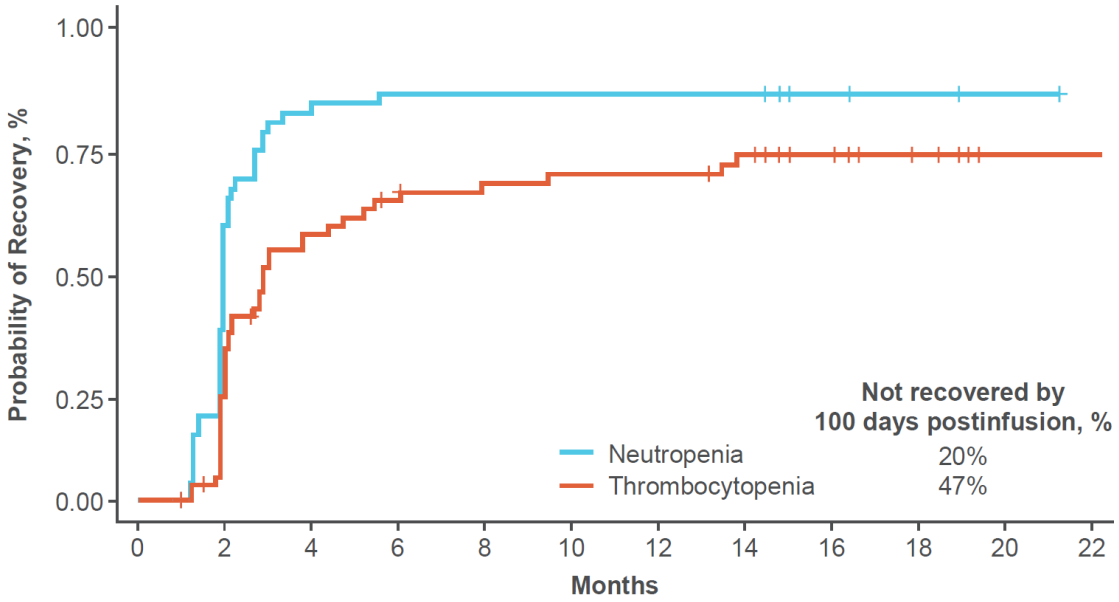
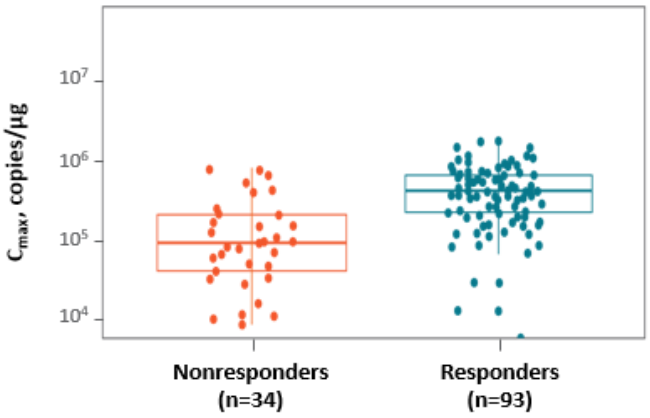
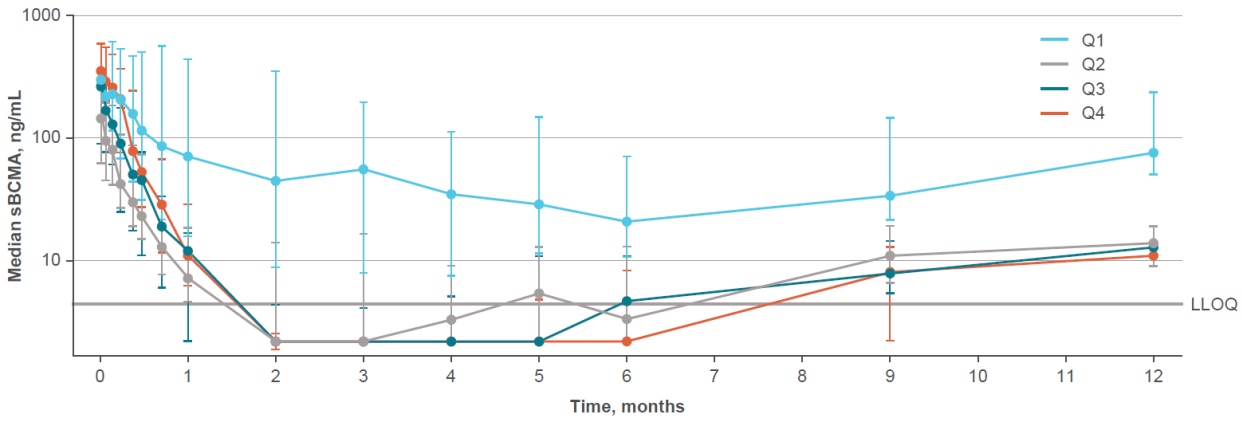


Figure S5. Ide-cel Peak Exposure in Responders and Nonresponders (A), sBCMA Levels Over Time by Quartiles of Exposure (B) and Best Response (C), Time to sBCMA Rebound by Target Dose (D) and Duration of Response (E), and Median PFS by sBCMA Clearance at Month 2 (F). Error bars represent interquartile range. Data cutoff date for panel C was October 16, 2019. $AUC_{0–28days}$ denotes area under the curve (AUC) of the transgene level from time of dose to 28 days, CR complete response, DOR duration of response, LLOQ lower limit of quantitation, NR no response, PR partial response, Q quartile, sBCMA soluble B-cell maturation antigen, VGPR very good partial response.

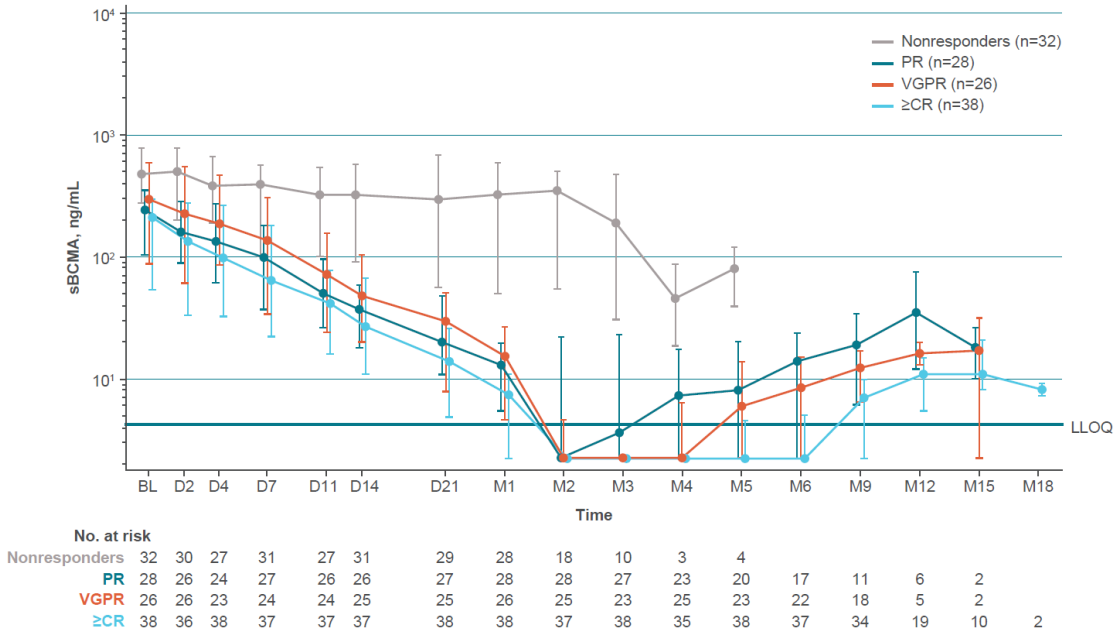
A. Ide-cel Peak Exposure in Responders Versus Nonresponders



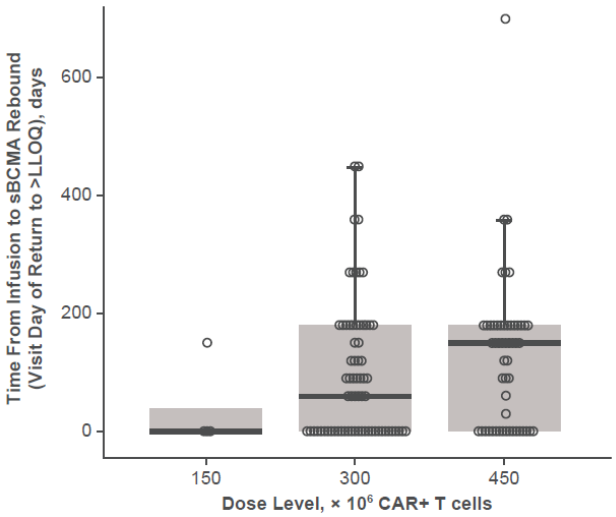
B. sBCMA Concentration Over Time by $AUC_{0–28days}$ Quartiles



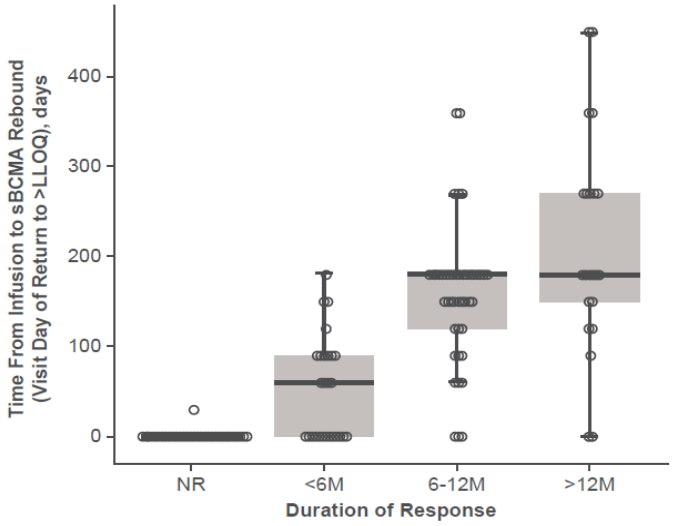
C. sBCMA Concentration Over Time by Best Response



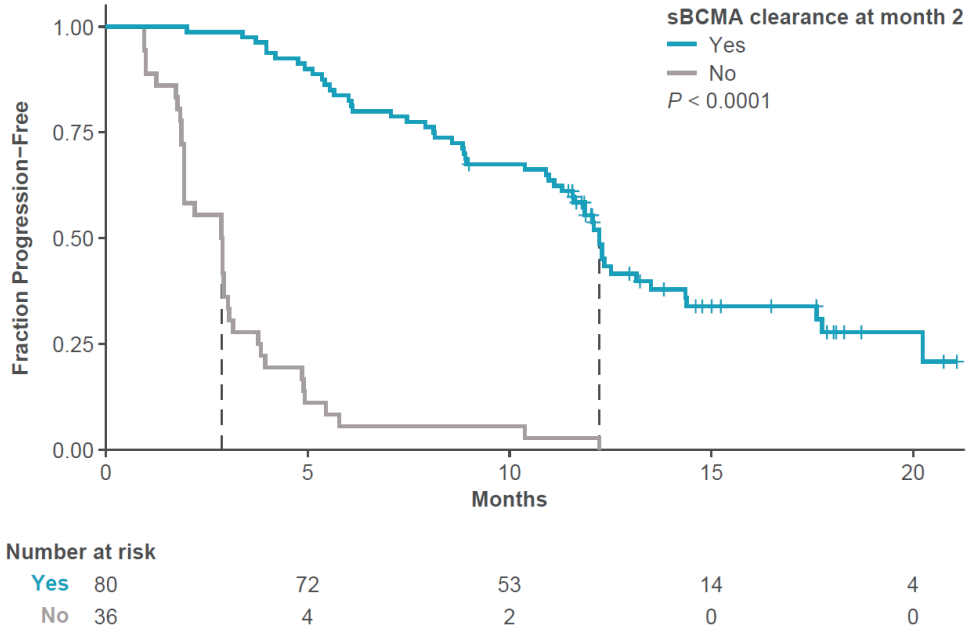
D. Time to sBCMA Rebound Above the LLOQ by Target Dose



E. Time to sBCMA Rebound Above the LLOQ by Duration of Response



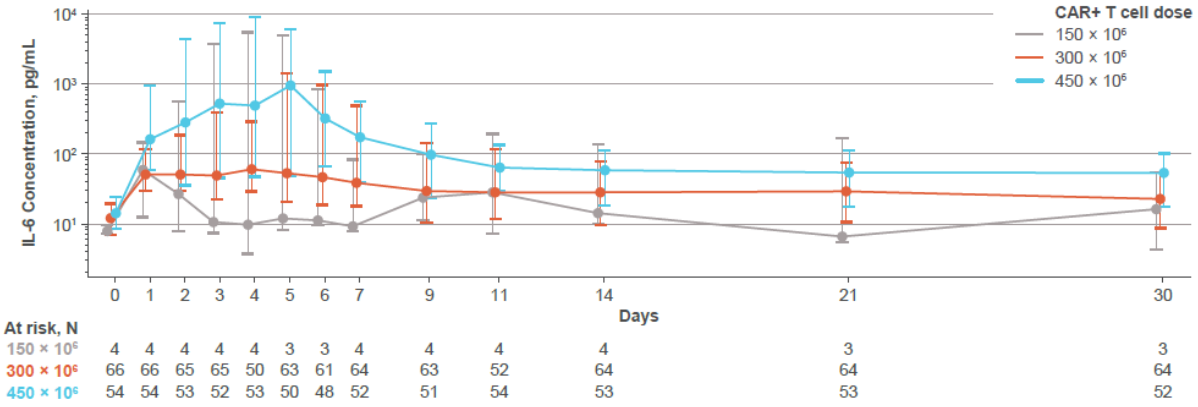
F. Median PFS by sBCMA Clearance at Month 2



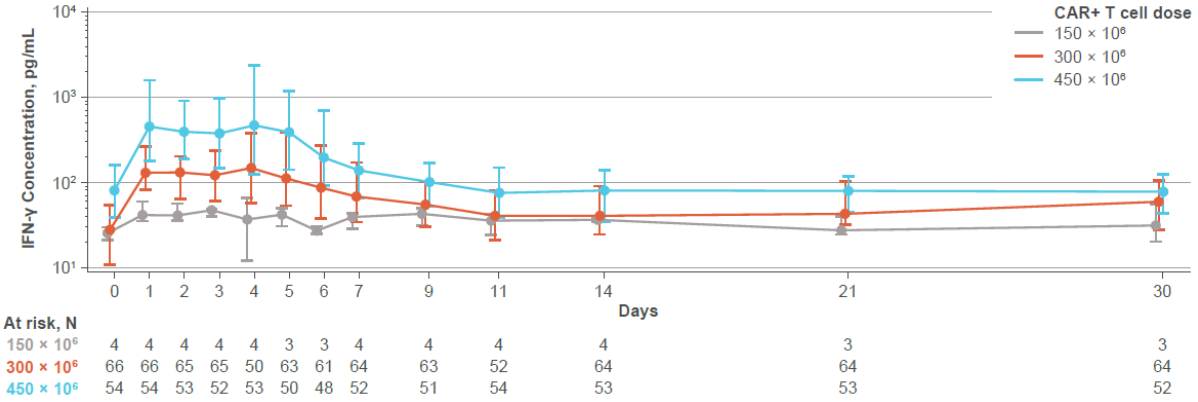
Number at risk					
Yes	80	72	53	14	4
No	36	4	2	0	0

Figure S6. Median Cytokine Levels Over Time by Target Dose (A, B) and CRS Grade (C, D). Error bars represent interquartile range. Data cutoff date for panels A and B was October 16, 2019. CRS denotes cytokine release syndrome, IFN-γ interferon gamma, IL-6 interleukin 6.

A. IL-6 Concentration by Dose



B. IFN-γ Concentration by Dose



C. IL-6 Concentration by CRS Grade

D. IFN-γ Concentration by CRS Grade

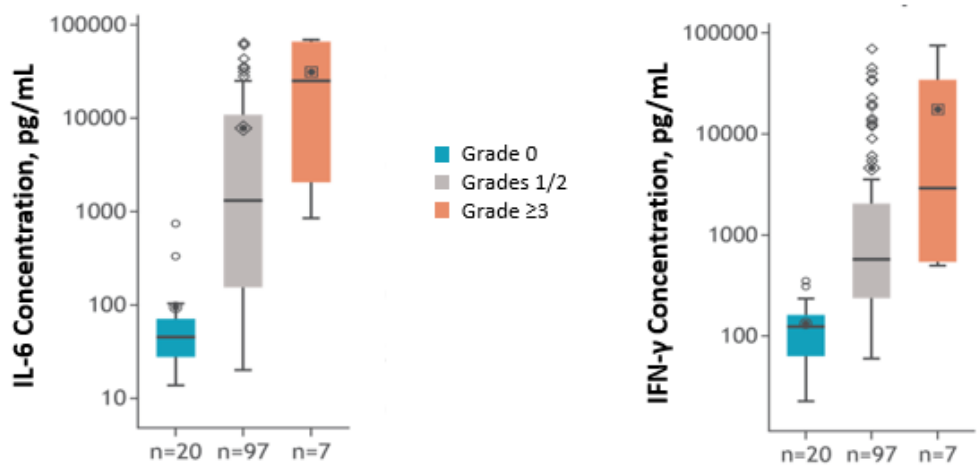


Table S1. International Myeloma Working Group (IMWG) Uniform Response Criteria.[1]

Response	IMWG Criteria
sCR	CR, as defined below, plus normal FLC ratio, and absence of clonal plasma cells* by immunohistochemistry or flow cytometry
CR	Negative immunofixation of serum and urine, and disappearance of any soft tissue plasmacytomas, and <5% plasma cells in bone marrow* In patients in whom the only measurable disease is by serum FLC levels: a normal FLC ratio of 0.26 to 1.65
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or ≥90% reduction in serum M-component plus urine M-component level <100 mg/24 hours In patients in whom the only measurable disease is by serum FLC levels: a >90% decrease in the difference between involved and uninvolved FLC levels
PR	≥50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to <200 mg/24 hours If the serum and urine M-protein are unmeasurable,† a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light chain assay is also not measurable, ≥50% reduction in bone marrow plasma cells is required in place of M-protein, provided baseline percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
MR	≥25% but ≤49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50%–89% In addition to the above criteria, if present at baseline, 25%–49% reduction in the size of soft tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
No Change / Stable Disease	Not meeting criteria for CR, VGPR, PR, MR or progressive disease
Progressive Disease†	Increase of ≥25% from lowest response value in any one or more of the following: Serum M-component (the absolute increase must be ≥0.5 g/dL)‡ and/or Urine M-component (the absolute increase must be ≥200 mg/24 hour) and/or Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (the absolute increase must be >10 mg/dL) Only in subjects without measurable serum and urine M-protein levels and without measurable disease by FLC levels: bone marrow plasma cell percentage (the absolute percentage must be ≥10%) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder
Relapse	Clinical relapse requires one or more of the following direct indicators of increasing disease and/or end organ dysfunction that are considered related to the underlying plasma cell proliferative disorder.‡ 1. Development of new soft tissue plasmacytomas or bone lesions

Response	IMWG Criteria
	2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.5 mg/dL) [2.875 mmol/L] 4. Decrease in hemoglobin of >2 g/dL [1.25 mmol/L] or to <10g/dL 5. Rise in serum creatinine by 2 mg/dL or more [177 µmol/L or more] 6. Hyperviscosity

CR, complete response; CRAB, calcium, renal insufficiency, anemia or bone lesions; DFS, disease-free survival; FLC, free light chain; MR, minor response; PR, partial response; sCR, stringent complete remission; VGPR, very good partial response.

*Confirmation with repeat bone marrow biopsy not needed.

†All response categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy. In the IMWG criteria, CR subjects must also meet the criteria for progressive disease shown here to be classified as progressive disease for the purposes of calculating time to progression and progression-free survival. The definitions of relapse, clinical relapse and relapse from CR are not to be used in calculation of time to progression or progression-free survival.

‡For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define relapse if starting M-component is ≥5 g/dL.

Table S2. Cytokine Release Syndrome (CRS) Revised Grading System.[2]

Grade	Toxicity
1	Symptoms are not life threatening and require symptomatic treatment only, eg, fever, nausea, fatigue, headache, myalgias, malaise
2	Symptoms require and respond to moderate intervention: Oxygen requirement <40%, hypotension responsive to fluids or low dose of one vasopressor, or grade 2 organ toxicity
3	Symptoms require and respond to aggressive intervention: Oxygen requirement ≥40%, hypotension requiring high dose or multiple vasopressors, or grade 3 organ toxicity or grade 4 transaminitis
4	Life-threatening symptoms: Requirement for ventilator support or grade 4 toxicity (excluding transaminitis)
5	Death

Grades 2-4 refer to CTCAE v4.0 grading.

Table S3. Antimyeloma Bridging Therapies Received by ≥10% of Patients.

	Total (N=128) *number of patients (percent)*
≥1 bridging therapy*	112 (88)
Glucocorticoids	94 (73)
Dexamethasone	90 (70)
Proteasome inhibitors	54 (42)
Carfilzomib	30 (23)
Bortezomib	25 (20)
Alkylating agents	52 (41)
Cyclophosphamide	47 (37)
Monoclonal antibodies	38 (30)
Daratumumab	36 (28)
Immunomodulatory agents	29 (23)
Pomalidomide	24 (19)

*Patients who received at least one drug as bridging therapy.

Table S4. Tumor Response and Progression-Free Survival in All Enrolled Patients and Retreated Patients.

	Total Enrolled (N=140)	Total Retreated (N=28)
Best overall response—no. (%)	94 (67)	6 (21)
Stringent complete response	41 (29)	0
Complete response	1 (1)	0
Very good partial response	25 (18)	1 (4)
Partial response	27 (19)	5 (18)
Stable disease	22 (16)	5 (18)
Progressive disease	8 (6)	15 (54)
Not evaluable*	14 (10)	2 (7)
Median progression-free survival (95% CI)—mo	9.5 (6.9–12.5)	1.0 (1.0–2.1)

Progression-free survival is measured from time of enrollment in the total enrolled population and from time of ide-cel re-infusion in the retreated population.

*Patients who did not have response assessment data or whose only assessment was not evaluable for response.

Table S5. MRD Negativity in Patients With at Least a Complete Response.

	Total (N=128)	Patients With ≥ CR (N=42)
MRD status at 10^{-5} nucleated cells and ≥ CR —no. (%)		
MRD-negative	33 (26)	33 (79)
MRD-positive	0	0
Not evaluable*	9 (7)	9 (21)
Indeterminate	0	0
MRD status at 10^{-6} nucleated cells and ≥ CR —no. (%)		
MRD-negative	20 (16)	20 (48)
MRD-positive	7 (5)	7 (17)
Not evaluable*	9 (7)	9 (21)
Indeterminate	6 (5)	6 (14)

MRD examined by next-generation sequencing assay (clonoSEQ; Adaptive Biotechnologies). Only MRD values within 3 months of achieving CR/sCR until progression or death (exclusive) were considered. Values may not add up due to rounding.
CR denotes complete response, MRD minimal residual disease, sCR stringent complete response.
*Of the 9 patients who achieved ≥ CR who were not evaluable for MRD, 7 did not have a malignant clone identified at baseline, 1 was missing the baseline sample, and 1 did not have an MRD assessment performed within 3 months of achieving CR/sCR.

Table S6. Adverse Events of Any Grade by Period.

	≤8 Wk (N=128)	>8 Wk to ≤6 Mo (N=122)	>6 Mo to ≤24 mo† (N=101)
	number of patients (percent)		
Adverse event*			
Any	128 (100)	109 (89)	62 (61)
Hematologic			
Neutropenia	116 (91)	34 (28)	11 (11)
Anemia	87 (68)	25 (20)	12 (12)
Thrombocytopenia	76 (59)	33 (27)	12 (12)
Leukopenia	54 (42)	16 (13)	4 (4)
Lymphopenia	32 (25)	12 (10)	6 (6)
Febrile neutropenia	14 (11)	4 (3)	4 (4)
Immune system disorder			
Cytokine release syndrome	107 (84)	0	0
Hypogammaglobulinemia	6 (5)	19 (16)	2 (2)
Gastrointestinal			
Diarrhea	31 (24)	17 (14)	1 (1)
Nausea	31 (24)	5 (4)	2 (2)
Constipation	17 (13)	3 (2)	3 (3)
Infections			
Pathogen unspecified	25 (20)	40 (33)	17 (17)
Viral	15 (12)	21 (17)	5 (5)
Bacterial	16 (13)	3 (2)	4 (4)
Fungal	7 (5)	3 (2)	1 (1)
Other			
Hypokalemia	43 (34)	2 (2)	1 (1)
Fatigue	38 (30)	6 (5)	2 (2)
Hypophosphatemia	37 (29)	3 (2)	1 (1)
Hypocalcemia	33 (26)	3 (2)	2 (2)
Hypomagnesemia	29 (23)	1 (<1)	2 (2)
Hyponatremia	24 (19)	1 (<1)	1 (1)
Headache	23 (18)	3 (2)	4 (4)
Hypoalbuminemia	22 (17)	1 (<1)	0
Pyrexia	20 (16)	12 (10)	4 (4)
Aspartate aminotransferase increased	18 (14)	5 (4)	1 (1)
Decreased appetite	16 (13)	10 (8)	2 (2)
Cough	17 (13)	10 (8)	1 (1)
Hypotension	17 (13)	3 (2)	2 (2)

*Adverse events occurring in at least 15% of the population and infections are reported.
†Only events that were grade ≥3, serious, or of special interest were collected after month 6 per protocol.

Table S7. Time to Recovery From Persistent Grade 3 or 4 Neutropenia or Thrombocytopenia.

Parameter	Ide-cel Target Dose, CAR+ T Cells			Total (N=128)
	150×10^6 (N=4)	300×10^6 (N=70)	450×10^6 (N=54)	
Patients with grade 3 or 4 neutropenia—no.*	4	67	54	125
Patients with persistent grade 3 or 4 neutropenia at month 1—no.†	2	24	26	52
Recovered—no.	1	21	21	43
Median (range) time to recovery—months	2.9 (2.9–2.9)	1.9 (1.3–5.6)	1.9 (1.2–4.0)	1.9 (1.2–5.6)
Not recovered—no. (%)	1	3	5	9
Death	0	3 (100)	4 (80)	7 (78)
Lost to follow-up	1 (100)	0	1 (20)	2 (22)
Patients with grade 3 or 4 thrombocytopenia—no.*	3	43	37	83
Patients with persistent grade 3 or 4 thrombocytopenia at month 1—no.†	2	33	27	62
Recovered—no.	0	24	18	42
Median (range) time to recovery—months	NA	2.4 (1.9–9.5)	2.1 (1.2–13.8)	2.1 (1.2–13.8)
Not recovered—no. (%)	2	9	9	20
Death	1 (50)	6 (67)	6 (67)	13 (65)
Ongoing thrombocytopenia	0	1 (11)	2 (22)	3 (15)
Lost to follow-up	1 (50)	2 (22)	1 (11)	4 (20)

NA, not applicable.
*Events occurring within month one of ide-cel infusion.
†Events at last value within one month of ide-cel infusion.

Table S8. Concomitant Medications of Interest.

	Total (N=128) *number of patients (percent)*
Antibiotics	122 (95)
Antivirals	121 (95)
Myeloid colony stimulating factors	112 (88)
Antimycotics	79 (62)
Intravenous immune globulins	79 (62)
Anticytokine drugs	70 (55)
Antiprotozoal*	32 (25)
Erythropoietin stimulating agents	8 (6)
Antimycobacterials*	6 (5)
Thrombopoietic agents	4 (3)

*Included drugs used for anti-pneumocystis prophylaxis.

Table S9. Cytopenias and Infections by Dose Level.

	150×10^6 (N=4)	**300×10^6 (N=70)**	**450×10^6 (N=54)**
	number of patients (percent)		
Adverse event			
Cytopenia	4 (100)	67 (96)	53 (98)
Neutropenia	4 (100)	66 (94)	51 (94)
Anemia	4 (100)	51 (73)	34 (63)
Thrombocytopenia	4 (100)	45 (64)	35 (65)
Lymphopenia	2 (50)	20 (29)	16 (30)
Pancytopenia	0	2 (3)	0
Infections	3 (75)	47 (67)	38 (70)
Pathogen unspecified	2 (50)	35 (50)	26 (48)
Viral	3 (75)	17 (24)	15 (28)
Bacterial	0	6 (9)	13 (24)
Fungal	0	6 (9)	4 (7)

Table S10. Characteristics and Management of CRS.

Parameter	Ide-cel Target Dose, CAR+ T Cells			Total (N=128)
	150×10^6 (N=4)	300×10^6 (N=70)	450×10^6 (N=54)	
Patients with a CRS event—no. (%)*	2 (50)	53 (76)	52 (96)	107 (84)
Grade 1	1 (25)	33 (47)	27 (50)	61 (48)
Grade 2	1 (25)	16 (23)	22 (41)	39 (30)
Grade 3	0	2 (3)	3 (6)	5 (4)
Grade 4	0	1 (1)	0	1 (<1)
Grade 5	0	1 (1)	0	1 (<1)
Median (range) time to onset—days	7 (2–12)	2 (1–12)	1 (1–10)	1 (1–12)
Median (range) duration—days	5 (3–7)	4 (2–28)	7 (1–63)	5 (1–63)
Tocilizumab use—no. (%)†	1 (25)	30 (43)	36 (67)	67 (52)
1 dose	1 (25)	21 (30)	22 (41)	44 (34)
>1 dose	0	9 (13)	14 (26)	23 (18)
Glucocorticoid use—no. (%)	0	7 (10)	12 (22)	19 (15)
Siltuximab use—no. (%)	0	1 (1)	0	1 (<1)
Anakinra use—no. (%)	0	1 (1)	1 (2)	2 (2)

CRS denotes cytokine release syndrome.

*Uniformly graded per Lee DW, et al.[2]

†The decision to give tocilizumab was at the treating physician's discretion based on protocol-specified toxicity management guidelines.

Table S11. Characteristics and Management of Investigator-Identified Neurologic Toxicity Events.

Parameter	Ide-cel Target Dose, CAR+ T Cells			Total (N=128)
	150×10^6 (N=4)	300×10^6 (N=70)	450×10^6 (N=54)	
Patients with a neurotoxicity event—no. (%)*	0	12 (17)	11 (20)	23 (18)
Grade 1	0	7 (10)	5 (9)	12 (9)
Grade 2	0	4 (6)	3 (6)	7 (5)
Grade 3	0	1 (1)	3 (6)	4 (3)
Median (range) time to onset—days	NA	3 (1–10)	2 (1–5)	2 (1–10)
Median (range) duration—days†	NA	3 (2–26)	5 (1–22)	3 (1–26)
Glucocorticoid use—no. (%)	0	2 (3)	8 (15)	10 (8)
Tocilizumab use—no. (%)	0	0	3 (6)	3 (2)
Anakinra use—no. (%)	0	0	1 (2)	1 (<1)

NA denotes not applicable.
*Investigator-identified neurologic toxicity events were captured using a single preferred term and graded according to the NCI CTCAE v4.03 on the basis of highest individual symptom grade.
†One ongoing event was excluded from the calculation.

Table S12. Deaths by Dose and Period.

	≤8 Wk	>8 Wk to ≤6 Mo	>6 Mo to ≤24 mo	Total
		number of patients (percent)		
150 × 10^6 CAR+ T cells (N=4)				
Overall deaths	0	0	2 (50)	2 (50)
Disease progression	0	0	2 (50)	2 (50)
Adverse event	0	0	0	0
Other causes	0	0	0	0
Missing	0	0	0	0
300 × 10^6 CAR+ T cells (N=70)				
Overall deaths	2 (3)	5 (7)	20 (29)	27 (39)
Disease progression	1 (1)	4 (6)	13 (19)	18 (26)
Adverse event	1 (1)	1 (1)	3 (4)	5 (7)
Other causes	0	0	3 (4)	3 (4)
Missing	0	0	1 (1)	1 (1)
450 × 10^6 CAR+ T cells (N=54)				
Overall deaths	3 (6)	4 (7)	8 (15)	15 (28)
Disease progression	1 (2)	4 (7)	2 (4)	7 (13)
Adverse event	2 (4)	0	2 (4)	4 (7)
Other causes	0	0	4 (7)	4 (7)
Missing	0	0	0	0
All ide-cel treated (N=128)				
Overall deaths	5 (4)	9 (7)	30 (23)	44 (34)
Disease progression	2 (2)	8 (6)	17 (13)	27 (21)
Adverse event	3 (2)	1 (<1)	5 (4)	9 (7)
Other causes	0	0	7 (5)	7 (5)
Missing	0	0	1 (<1)	1 (<1)

Primary causes of death are shown.

Table S13. Summary of Ide-cel Pharmacokinetic Parameters.

Parameter	Ide-cel Target Dose, CAR+ T Cells			
	150×10^6 (N=4)	**300×10^6 (N=69)**	**450×10^6 (N=54)**	**Total (N=127)**
C_{max} (copies/μg)	204,229 (169) N=4	180,185 (210) N=69	321,117 (126) N=54	231,278 (178) N=127
T_{max} (days)	14 (11–14) N=4	11 (7–30) N=69	11 (7–28) N=54	11 (7–30) N=127
T_{last} (days)	58 (29–142) N=4	119 (21–365) N=69	115 (22–184) N=54	119 (21–365) N=127
$AUC_{0–28days}$ (days*copies/μg)	1,942,929 (154) N=4	2,138,414 (215) N=68	4,277,327 (152) N=53	2,860,340 (197) N=125

$AUC_{0–28days}$ denotes area under the curve of the transgene level from time of dose to 28 days, C_{max} the maximum transgene level occurring at T_{max}, CV coefficient of variation, T_{max} the time of maximum observed transgene level, T_{last} time of last measurable transgene level.
Pharmacokinetic analysis population excludes one patient who died on day 4 and had no evaluable pharmacokinetic samples available. Data are presented as geometric mean (% geometric CV) except T_{max} and T_{last} shows the median (min–max).
Data cutoff date: April 19, 2019.

Table S14. Ide-cel Persistence Over Time.

	Month 1	Month 3	Month 6	Month 9	Month 12
No. at risk	118	100	49	27	11
No. (%) with detectable CAR+ T cells	117 (99)	75 (75)	29 (59)	10 (37)	4 (36)

Persistence is measured by detectable transgene levels.
Data cutoff date was April 19, 2019.

Table S15. Antidrug Antibody Titer Over Time.

	Month 1	Month 3	Month 6	Month 9	Month 12
No. with available ADA results	123	102	80	67	52
No. (%) ADA-positive	0*	21 (21)	35 (44)	39 (58)	34 (65)
Titer					
Median (Q1, Q3)	NA	480 (60, 3840)	960 (120, 7680)	3840 (480, 7680)	3840 (960, 30720)
Minimum−maximum	NA	15−61440	15−61440	15−122880	15−122880

ADA denotes antidrug antibody, NA not applicable, Q, quartile.
*Includes the 5 patients who tested ADA positive preinfusion.

Table S16. Antidrug Antibody Status by Response to Retreatment.

Retreatment response	ADA-Positive (N=16)	ADA-Negative (N=12)
	number of patients (percent)	
Yes	0	6 (50)
No	16 (100)	6 (50)

ADA denotes antidrug antibody.
Two-sided *P* = 0.0025 using Fisher's exact test.

Table S17. Status of Tumor BCMA Expression and sBCMA Levels Before Ide-cel Infusion and at Disease Progression.

	Nonresponders	Responders	Total
Tumor BCMA			
Pre-infusion			
No. at risk	30	82	112
BCMA positivity <5%—no.	1*	1*	2*
Disease progression			
No. at risk	11	16	27
BCMA positivity <5%—no. (%)	1 (9)	1 (6)	2 (7)
BCMA positivity >5%—no. (%)	10 (91)	15 (94)	25 (93)
sBCMA			
Pre-infusion			
No. at risk	33	90	123
sBCMA <LLOQ—no.	0	0	0
Disease progression			
No. at risk	27	44	71
sBCMA <LLOQ—no. (%)	0	2 (5)	2 (3)
sBCMA >LLOQ—no. (%)	27 (100)	42 (95)	69 (97)

sBCMA denotes soluble B-cell maturation antigen.
Pre-infusion is last non-missing value before ide-cel infusion (screening or baseline evaluation); percent BCMA positivity is evaluated on CD138+ cells.
*Two patients with <5% baseline BCMA expression had 1% CD138+ plasma cells on bone marrow biopsies for evaluation and were reported as 0% and 1% BCMA-positive.
Data cutoff date was October 16, 2019.

Table S18. Summary of BCMA Expression and sBCMA Levels at Disease Progression for Patients with Evidence of Antigen Escape.

		BCMA+ and CD138+ Expression by IHC at Disease Progression		Peripheral sBCMA Level at Disease Progression
	BOR	**% CD138+**	**% BCMA+**	**Serum sBCMA, ng/mL**
Patient A	PR	60	1	2.2*
Patient B	SD	25	0	5.3
Patient C	VGPR	NA†	NA†	2.2*

BCMA denotes B-cell maturation antigen, BOR best overall response, IHC immunohistochemistry, PR partial response, sBCMA soluble B-cell maturation antigen, SD stable disease, VGPR very good partial response.
*For biomarker-based assays where lower limit of quantification (LLOQ) values are available, all concentrations below the LLOQ were imputed to LLOQ/2; sBCMA LLOQ is 4.4 ng/mL, imputed as 2.2 ng/mL.
†Progressive disease bone marrow biopsy not collected for evaluation.
Note: % BCMA is the % of CD138+ tumor cells that express any level of BCMA.
Data cutoff date was October 16, 2019.

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