Supplementary Appendix

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

Supplementary Appendix

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METHODS

Study Design

The study consisted of a dose escalation and expansion phase. A minimum of 3 patients were enrolled in each dose escalation cohort (50, 150, 450, and 800 × 10^6 CAR+ T cells) with expansion to a minimum of 6 patients in the event of a dose-limiting toxicity. At the discretion of the Safety Review Committee, dose escalation cohorts were expanded or divided into independent groups based on low vs high tumor burden (< vs ≥50% bone marrow plasma cells). The expansion phase evaluated a dose range of 150 to 450 × 10^6 CAR+ T cells and explored activity in patients with low tumor B-cell maturation antigen (BCMA) expression (<50% BCMA expression in CD138+ cells). The full protocol is available with the full text of this article at NEJM.org

End Points and Assessments

Primary outcome measures were incidence of adverse events 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), abnormal laboratory test results, and dose-limiting toxicities as defined below. Secondary outcome measures include disease-specific response criteria (including complete response, very good partial response, and partial response according to the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma) and measurement of tumor BCMA expression by immunohistochemistry performed locally as previously described.[28] The exploratory end point progression-free survival was defined as the time from bb2121 infusion to the date of either the first observation of progressive disease or occurrence of death due to any cause, whichever occurred first. Duration of response was defined as the time, in months, from when response criteria were first met for a partial response or better to the first date the criteria for disease progression were met or the patient died due to any cause, whichever occurred first. Time

to recovery of grade 3/4 cytopenia was defined as the time, in weeks, from first occurrence of a grade 3/4 event to the first date when recovery criteria were met.

Dose-Limiting Toxicities

Dose-limiting toxicities are defined as any bb2121-related grade ≥3 toxicity occurring within the 21 days after infusion, with the following exceptions:

- Grade ≤3 cytokine release syndrome that responds to appropriate medical intervention within 3 days and recovers to grade ≤2
- Grade ≤3 neurotoxicity lasting <3 days that recovers to grade ≤2
- Grade ≤4 tumor lysis syndrome lasting <7 days
- Grade ≤3 neutropenia of any duration or grade 4 neutropenia lasting <28 days
- Grade ≤3 anemia of any duration or grade 4 anemia lasting <28 days
- Grade ≤3 thrombocytopenia of any duration or grade 4 thrombocytopenia lasting <28 days
- All cytopenias except neutropenia, anemia, and thrombocytopenia as described above
- Fever of any grade, including febrile neutropenia
- Grade ≤3 diarrhea lasting <72 hours
- Grade ≤3 nausea and/or vomiting lasting <72 hours
- Grade ≤3 fatigue lasting <7 days
- Grade ≤4 transaminase, bilirubin, creatinine kinase, blood urea nitrogen, or creatinine elevation lasting <7 days
- Asymptomatic lipase elevation in the absence of any clinical signs or symptoms of pancreatitis
- Any nonhematologic grade 3 clinical laboratory AE that is asymptomatic and rapidly reversible (returns to baseline or to grade ≤2 within 7 days).

Grade 3/4 adverse events related to bb2121 occurring after the first 21 days after infusion will be assessed by the Safety Review Committee and considered in decisions regarding the maximum tolerated dose and recommended part two dose. Dosing of another subject or escalation to a higher dose level will be delayed if qualification of an ongoing toxicity as a dose-limiting toxicity is pending.

Cellular Kinetics Assay

Copies of vector transgene per micrograms genomic DNA was determined by quantitative PCR (qPCR). Briefly, CD3+ cells were isolated to high purity from whole blood collected in a K2-EDTA tube, using Miltenyi whole blood CD3 human microbeads (Miltenyi Biotec). CD3+ cell purity was determined after analysis by flow cytometry using hCD3-BV510 (Biolegend®). Genomic DNA from the purified CD3+ cell pellet was extracted using a Nucleospin Blood QuickPure® kit (Takara Bio USA), and DNA concentration was determined by a Qubit™ double-stranded DNA Broad Range Assay kit and Qubit™ 3.0 Fluorometer (Life Technologies). One hundred ng of purified CD3+ DNA was included in the qPCR reaction for specific quantification of the bb2121 transgene (*Psi-gag*), and a reference housekeeping gene (*RNaseP*). Detection and quantification of the *Psi-Gag* sequence and *RNaseP* was achieved using target-specific oligonucleotide primers and dual-labeled oligonucleotide hydrolysis probes as previously described.[28] The amplified targets were detected in real time by the Stratagene Mx3005P instrument using TaqMan® Universal PCR Master Mix, no UNG (Thermo Fisher Scientific), and quantified using a standard curve. Quantified copies of vector transgene per reaction is reported as copies per standardized input DNA (100 ng). Fluorescence data was analyzed using MxPro software.

Primer probe sequences:

- *Psi-Gag* forward primer (Sigma or Integrated DNA Technologies) custom synthesis, Sequence 5’ to 3’: GGA GCT AGA ACG ATT CGC AGT TA
- *Psi-Gag* reverse primer (Sigma or Integrated DNA Technologies) custom synthesis, Sequence 5’ to 3’: GGT TGT AGC TGT CCC AGT ATT TGT C

- *Psi-Gag* dual-labeled oligonucleotide [robe (5'-FAM, 3'-BHQ-1) (Biosearch Technologies or Integrated DNA Technologies) custom synthesis, Sequence 5' to 3': FAM/ACA GCC TTC TGA TGT CTC TAA AAG GCC AGG/BHQ-1
- TaqMan RNaseP Copy Number Reference Assay (Thermo Fisher Scientific)

Pharmacokinetics Flow Assay

The presence of anti-BCMA CAR+ CD4 and CD8 T cells was determined in anti-coagulated peripheral whole blood containing EDTA. Briefly, 100 µL of whole blood was added to TruCOUNT™ tubes (BD Biosciences) and incubated with anti-CD3-APC, anti-CD4-BV510, anti-CD8-BV421, and anti-CD45-FITC antibodies (Biolegend) as well as the anti-CAR reagent, recombinant human BCMA (rhBCMA), conjugated to phycoerythrin (PE)-labeled immunoglobulin Fc (rhBCMA-Ig Fc-PE) for 30 to 35 minutes at 2–8 °C. During the last 5 to 10 minutes of antibody incubation, 7-AAD (Biolegend) was added. Red blood cells were then lysed using 1× FACS lysing solution (BD Biosciences) for 10 to 15 minutes at room temperature. Samples were acquired on a BD FACSCanto II™ cell analyzer (BD Biosciences) and analyzed using BD FACSDIVA™ software (BD Biosciences). Fluorescence Minus One controls were used for placement of gates. The percent of CD4+ and CD8+ cells of live CD45+CD3+CAR+ cells is reported.

Characterization of the bb2121 Drug Product

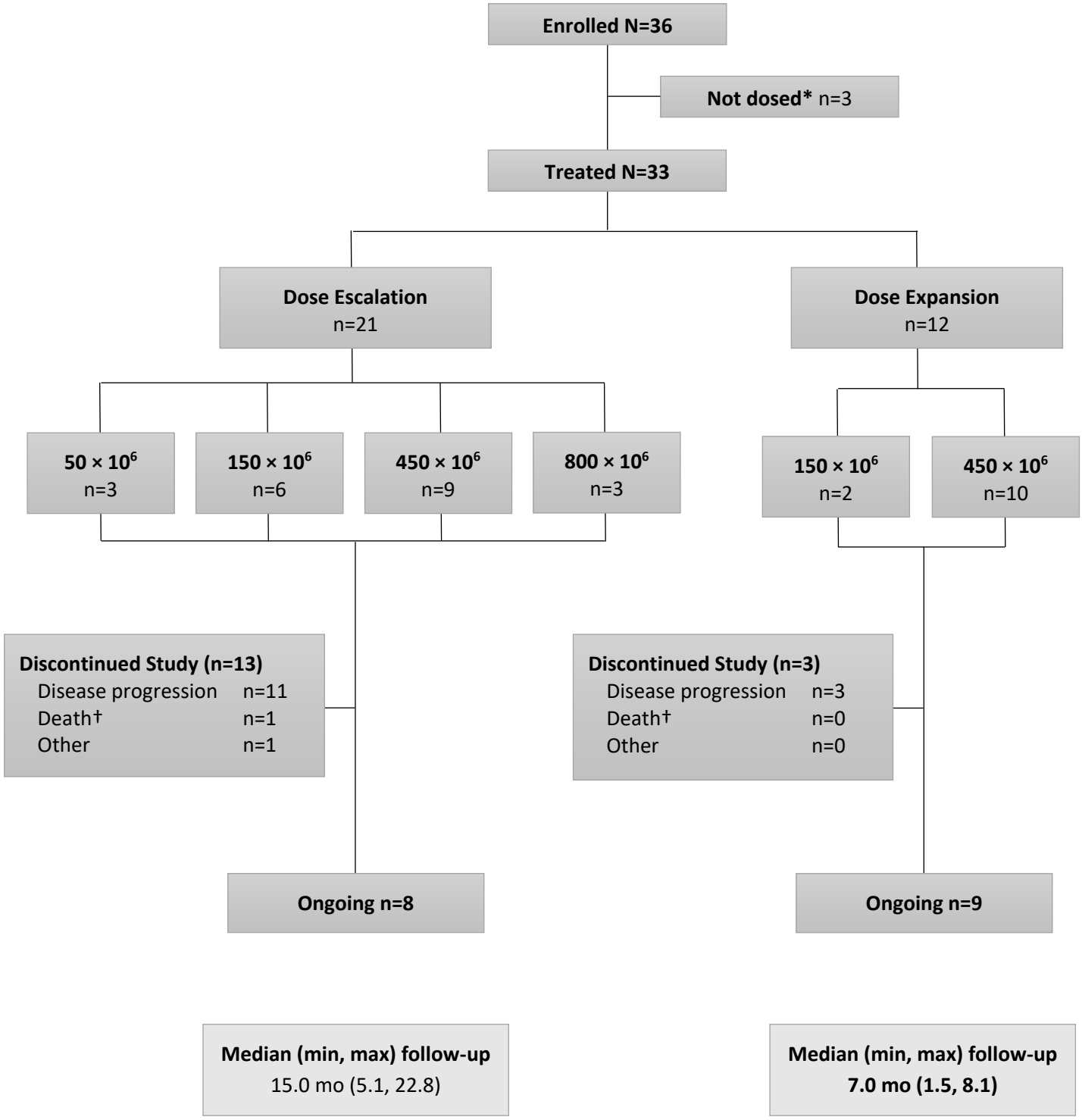
The bb2121 drug product was characterized for the proportion of CAR+ CD4 and CD8 T cells by flow cytometry as part of the quality control release criteria. Briefly, samples were thawed and washed. The cells were then incubated with anti-CD8 fluorescein isothiocyanate, anti-CD45 PerCP-Cy5.5, anti-CD4 PE-Cy7, and anti-CD3-APC antibodies (BD Biosciences) as well as rhBCMA-Ig Fc-PE for 20 to 40 minutes at 2–8 °C. Following a wash step, cells were labeled with the LIVE/DEAD® Fixable Near-IR Dead Cell Stain Kit (Molecular Probes) for 20 to 40 minutes at 2–8 °C according to the manufacturer's instructions to exclude dead cells. Fluorescence Minus One controls were used for

placement of gates. Samples were acquired on a BD FACSCanto II™ cell analyzer (BD Biosciences) and analyzed using FlowJo™ Single Cell Analysis Software v9.0 (FlowJo, LLC). The percent of CD4+ and CD8+ cells of CD45+CD3+ CAR+ cells is reported.

RESULTS

Patients were to receive lymphodepletion with fludarabine 30 mg/m^2/day and cyclophosphamide 300 mg/m^2/day before infusion of bb2121 on day 0. However, 7 patients had protocol-specified dose reduction of fludarabine to 24 mg/ m^2/day based on renal function and 1 patient received no fludarabine as a planned deviation based on creatinine clearance <30 mL/min for which approval of the Food and Drug Administration was received ahead of time.

Figure S1. CONSORT Diagram



*Three patients underwent leukapheresis but discontinued before initial bb2121 infusion.
†Six additional patients died during the long-term follow-up study owing to disease progression.

Figure S2. Time to Recovery of Grade 3/4 Cytopenias. Patients with grade 3/4 cytopenias (absolute neutrophil counts <1000 cells/µL or platelets <50,000/µL 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. Median and 95% CI are from Kaplan-Meier estimates.

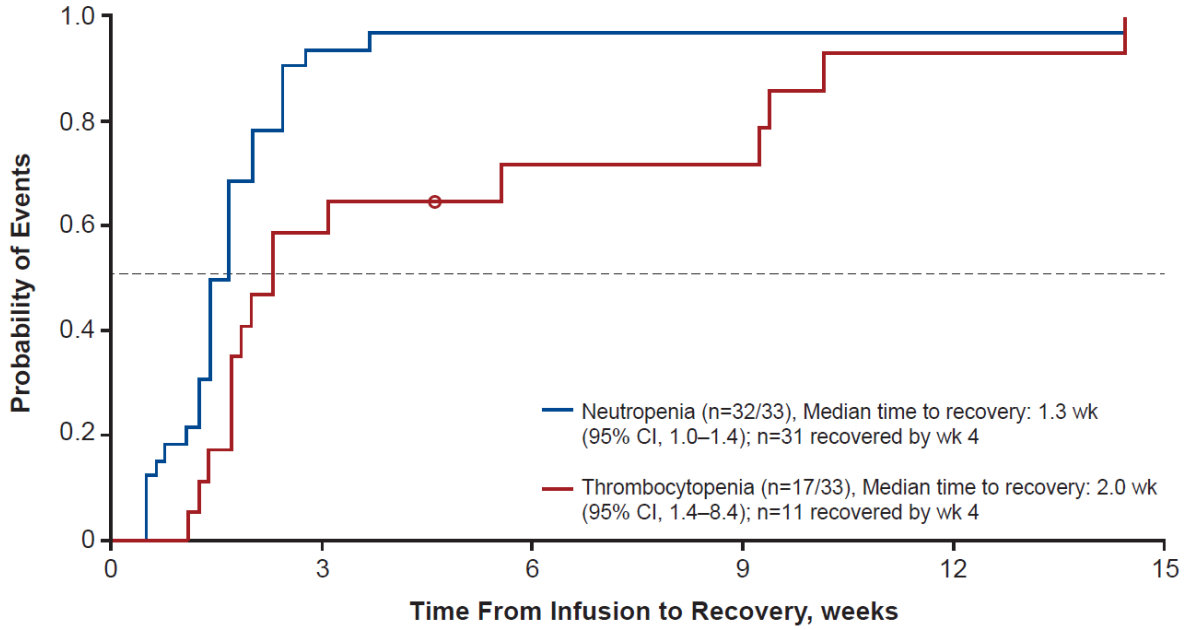


Figure S3. Subgroup Analysis of Cytokine Release Syndrome. $AUC_{0\text{-}28d}$ denotes area under the curve during the first 28 days after infusion, BCMA B-cell maturation antigen, C_{max} maximum concentration, CRP C-reactive protein, CRS cytokine release syndrome, FLC, free light chain, IFN interferon, M monoclonal, TNF tumor necrosis factor. *One patient dosed at 205 × 10^6 CAR T cells is included in the 450 × 10^6 dose group. †Bridging therapy between leukapheresis and lymphodepletion. ‡High tumor burden was defined as ≥50% CD138-positive cells by central laboratory analysis (first preference) or by local analysis of bone marrow plasma cells (second preference). In the absence of both, tumor burden was determined by the Safety Review Committee.. §Involved free light chain (FLC) was defined as the higher value between κ-FLC and λ-FLC at baseline if the ratio was abnormal or by immunofixation if the ratio was normal. For results below detection limits, κ-FLC and λ-FLC values were set to 1.3 mg/L and 1.7 mg/L, respectively.

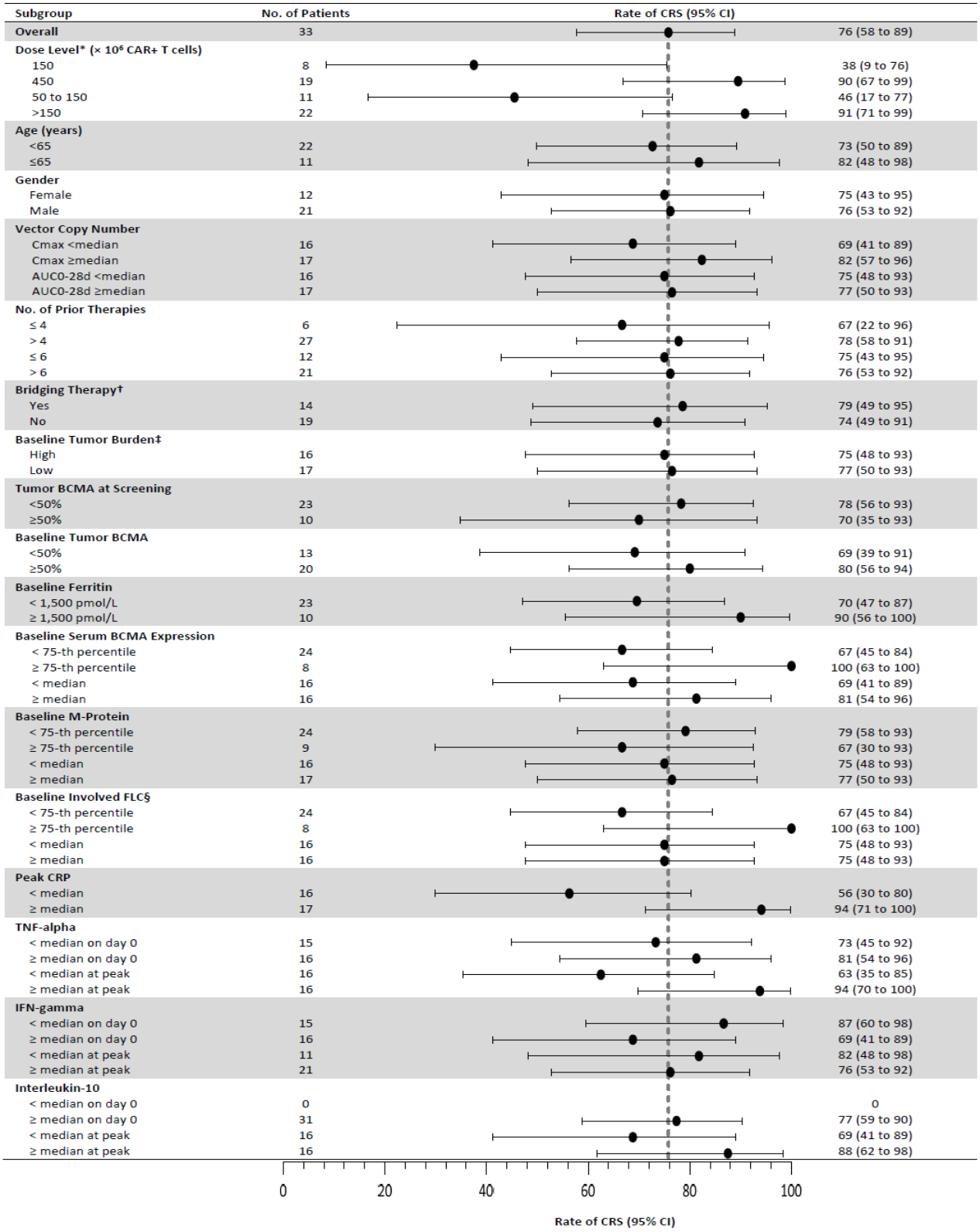
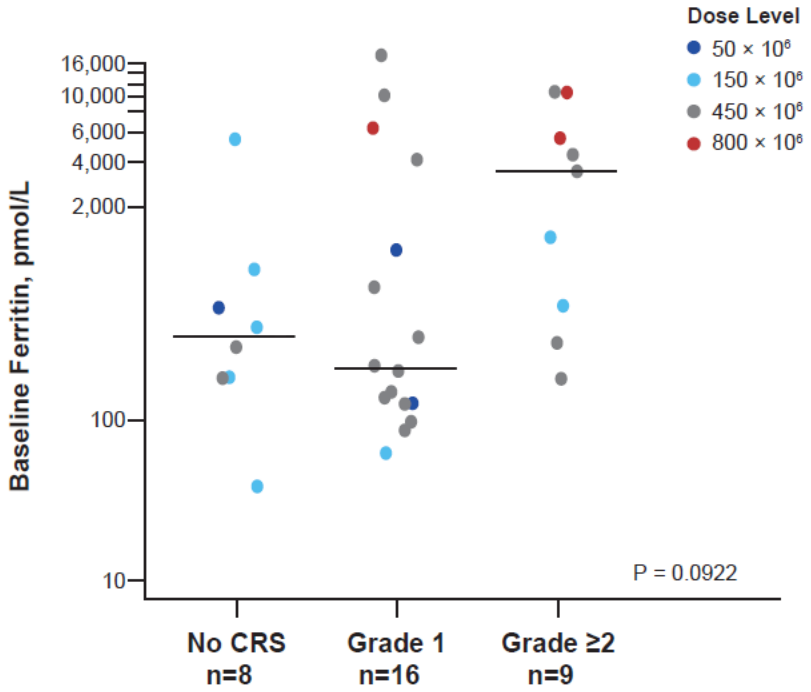


Figure S4. Median Ferritin (A) and C-Reactive Protein (B) Levels by Cytokine Release Syndrome Severity. Data are presented in patients without any CRS events (no CRS), patients with grade 1 CRS (Grade 1), and patients with grade 2 or higher CRS (grade ≥2). P values by the Kruskal-Wallis test. CRS denotes cytokine release syndrome.

A) Ferritin Levels



B) C-Reactive Protein

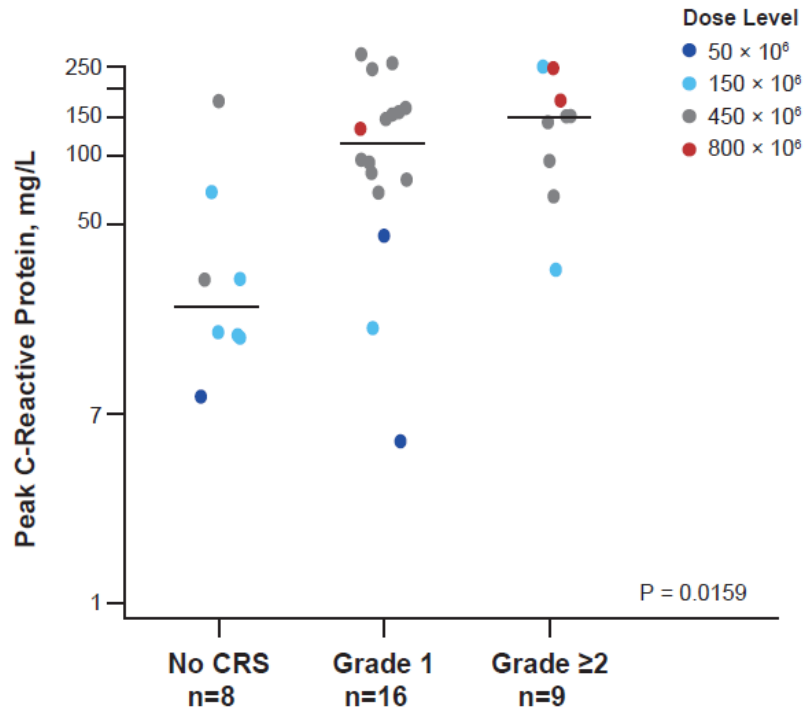
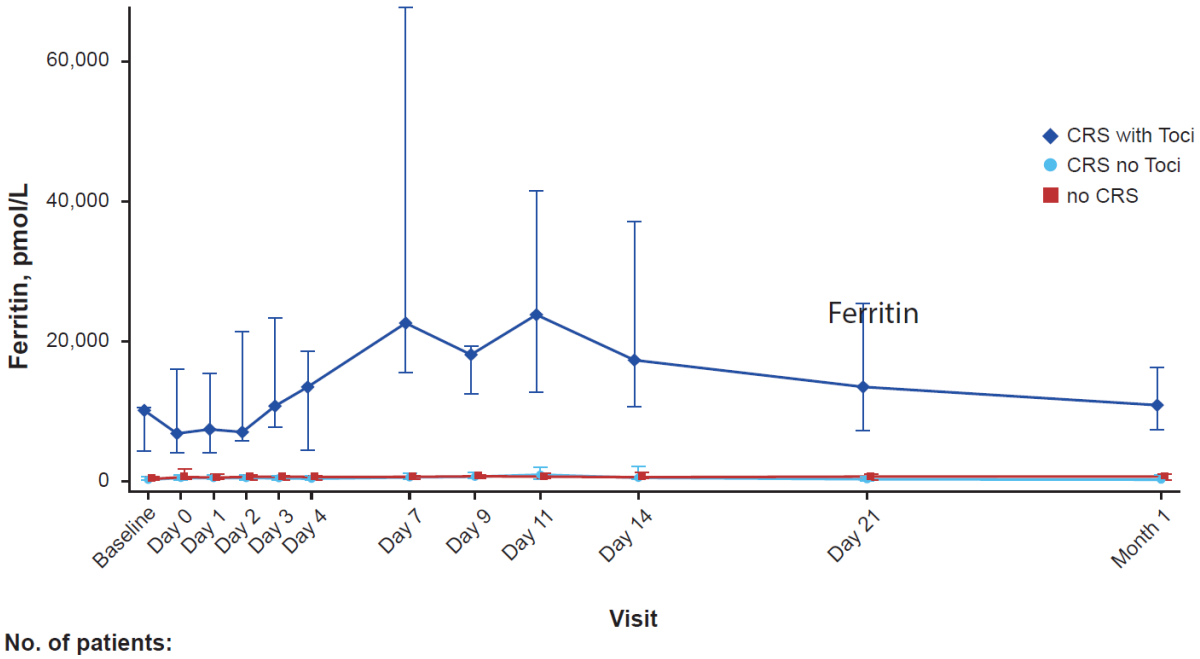


Figure S5. Post-Infusion Values of Ferritin (A) and C-Reactive Protein (B). Points represent median values and error bars represent interquartile ranges (Q1 and Q3). CRS denotes cytokine release syndrome, Toci tocilizumab.

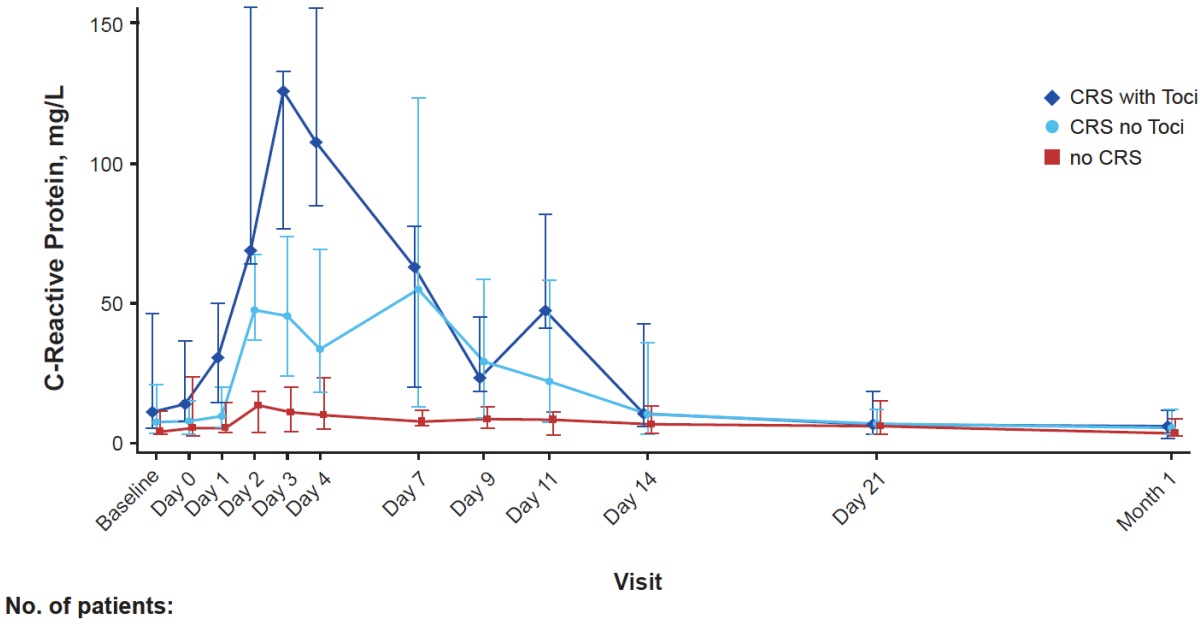
A. Ferritin



No. of patients:

CRS with Toci	7	6	7	6	6	7	6	4	5	7	6	6
CRS no Toci	18	17	17	18	18	17	18	18	16	18	16	17
No CRS	8	8	8	7	7	7	7	7	7	7	7	7

B. C-Reactive Protein

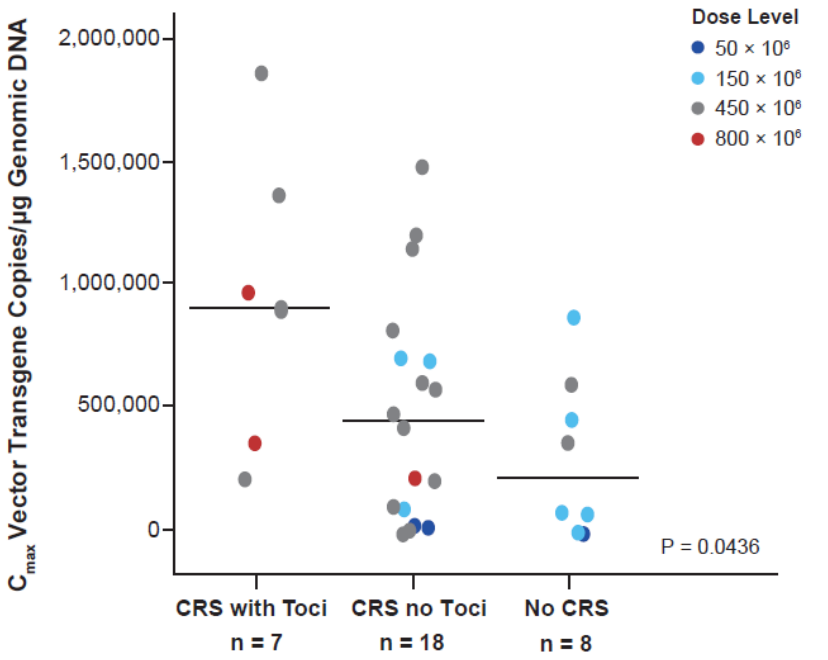


No. of patients:

CRS with Toci	7	7	6	7	7	7	7	6	5	3	6	6
CRS no Toci	18	18	17	18	18	18	18	18	18	18	17	18
No CRS	8	8	8	8	8	8	8	8	8	8	8	8

Figure S6. Peak Vector Transgene Copies in Patients With and Without CRS Treated with Tocilizumab (A) or Steroids (B). Peak vector transgene copies per microgram genomic DNA in CD3-enriched peripheral blood from patients with cytokine release syndrome (CRS) managed with tocilizumab (CRS with Toci) or steroids (CRS with Steroids), CRS that did not prompt tocilizumab treatment (CRS no Toci) or steroid treatment (CRS no Steroids), and patients without any CRS events (no CRS). Bars indicate medians. P values are by the Kruskal-Wallis test.

A)



B)

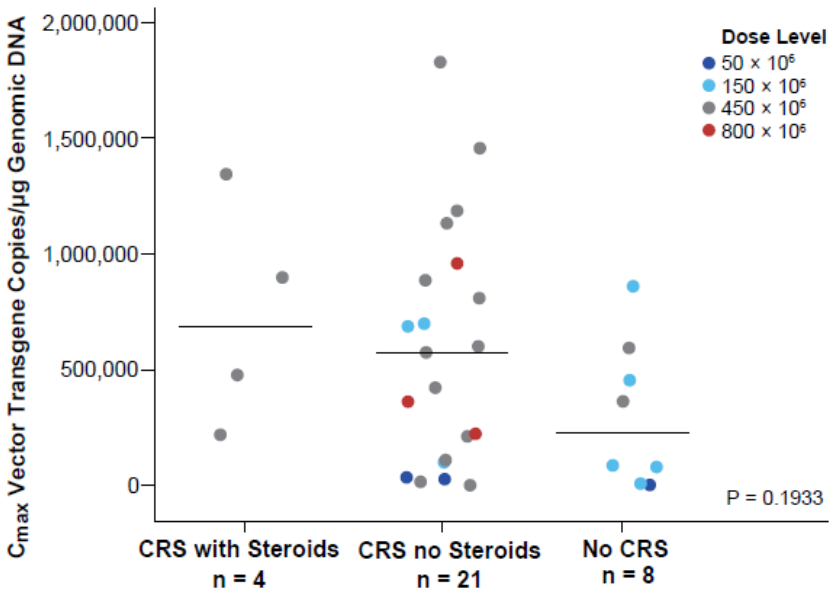
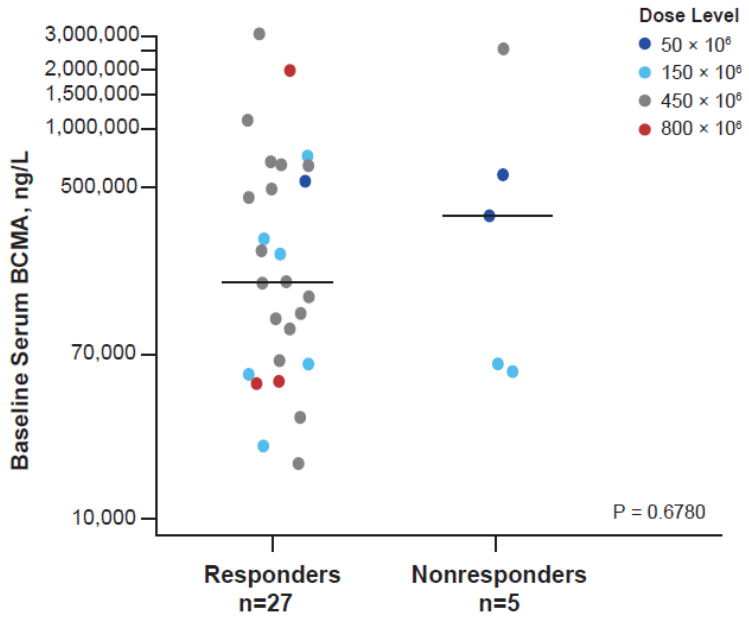


Figure S7. Effect of Baseline Serum (A) and Tumor (B) B-Cell Maturation Antigen Levels on Response. Responder is defined as having a best reponse of partial response or better. Others include those who did not achieve a partial response and those without a post-baseline response assessment. Lines indicate medians. P values are based on 2-sided Wilcoxon rank sum test. BCMA denotes B-cell maturation antigen. Baseline is defined as the last value before start of lymphodepletion.

A. Baseline Serum BCMA



B. Baseline Tumor BCMA Expression

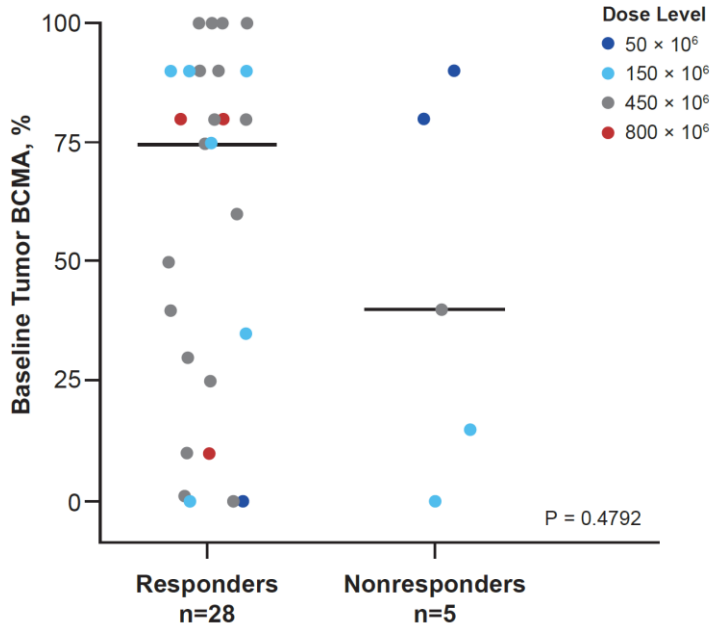
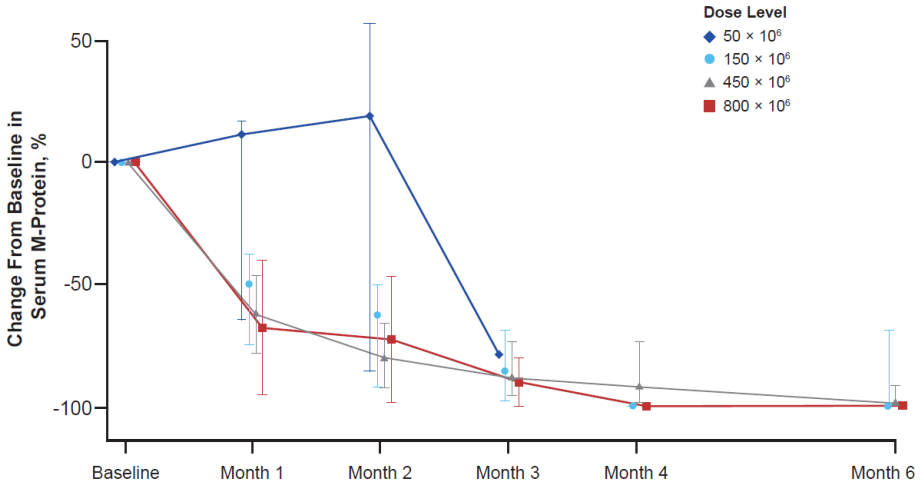


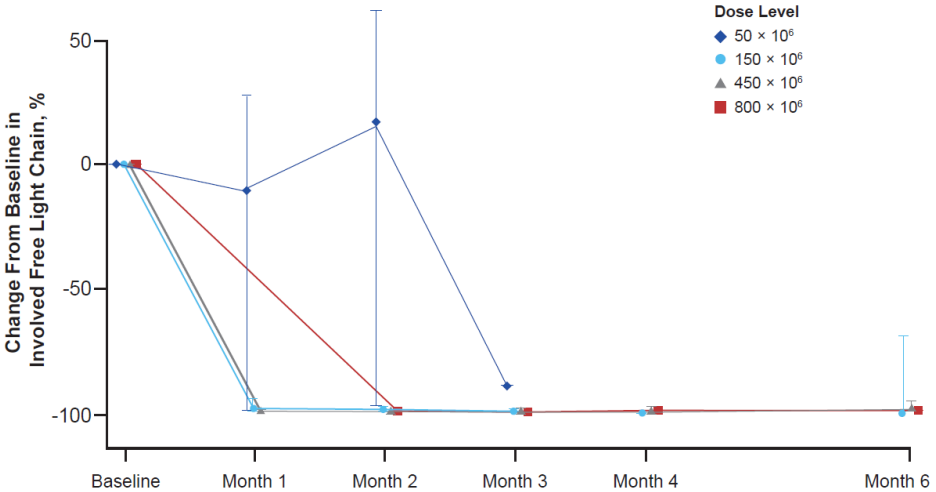
Figure S8. Changes From Baseline in Serum Monoclonal Protein (A), Free Light Chains (B), and B-Cell Maturation Antigen (C). Points represent median values and error bars represent interquartile ranges (Q1 and Q3). Involved free light chain (FLC) was analyzed in patients with baseline FLC ≥10 mg/dL and was defined as the higher value between κ-FLC and λ-FLC at baseline if the ratio was abnormal or by immunofixation if the ratio was normal. For results below detection limits, κ-FLC and λ-FLC were set to 1.3 mg/L and 1.7 mg/L, respectively. Baseline is defined as the last value before start of lymphodepletion. BCMA denotes B-cell maturation antigen.

A) Serum Monoclonal Protein



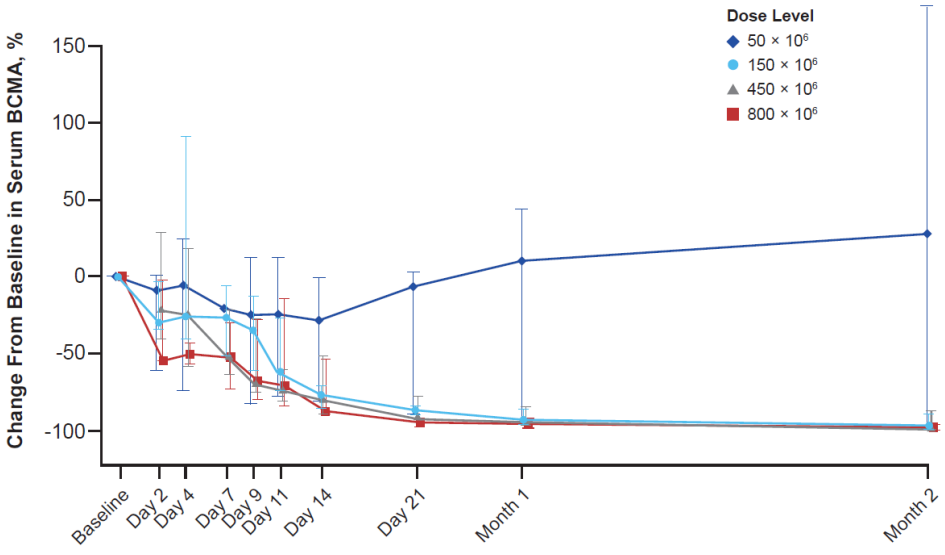
No. of patients:						
50 × 10⁶	3	3	3	1	0	0
150 × 10⁶	5	5	5	4	4	4
450 × 10⁶	10	10	10	10	10	10
800 × 10⁶	2	2	2	2	1	2

B) Serum Free Light Chain



No. of patients:						
50 × 10⁶	3	3	3	1	0	0
150 × 10⁶	6	6	5	5	5	5
450 × 10⁶	13	13	12	12	12	10
800 × 10⁶	1	0	1	1	1	1

C) Serum B-Cell Maturation Antigen

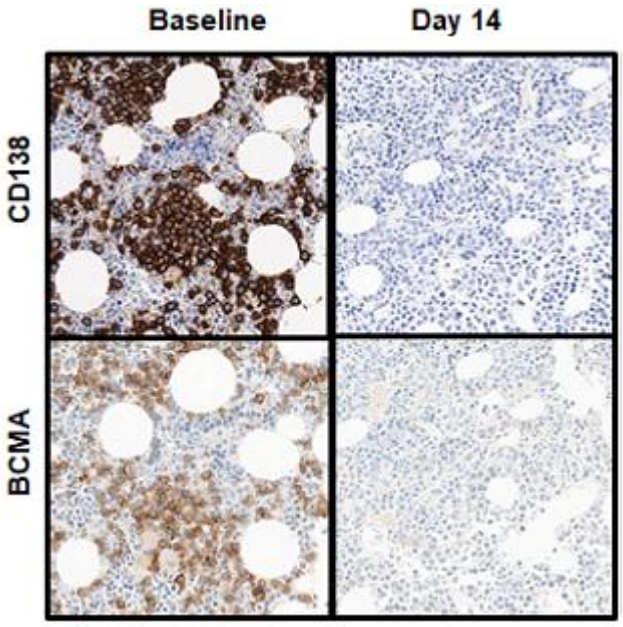


No. of patients:

50 × 10^6	3	3	3	3	3	3	3	3	3	3
150 × 10^6	8	7	7	7	7	7	6	7	7	6
450 × 10^6	18	18	18	18	17	17	18	17	18	17
800 × 10^6	3	3	2	3	3	3	3	2	3	3

Figure S9. Clearance in Bone Marrow by Immunohistochemistry (A) and Tumor Burden Reduction by PET Imaging (B) in Individual Patients. BCMA denotes B-cell maturation antigen, PET positron emission tomography

A) Bone Marrow Clearance



B) PET Imaging of Patient With Extramedullary Disease

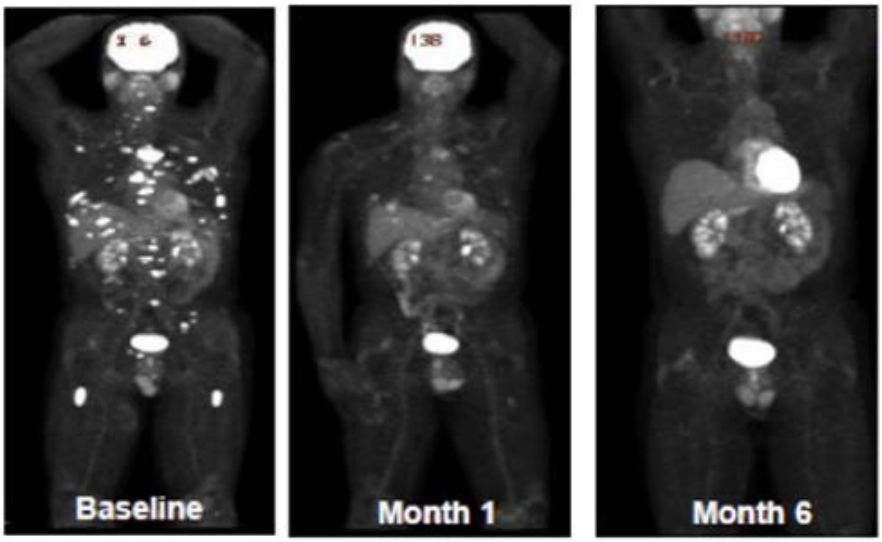


Figure S10. Correlation Between CAR+ CD4/CD8 T Cell Ratio in the Final Product and at Peak Expansion. Circles indicate individual patients; 6 patients with a peak CD3+ CAR+ value below the lower limit of quantification (10 cells/uL) were excluded from the analysis. R denotes the Spearman-rank correlation coefficient. The 2-sided P value assesses if the Spearman-rank correlation coefficient is significantly different from 0.

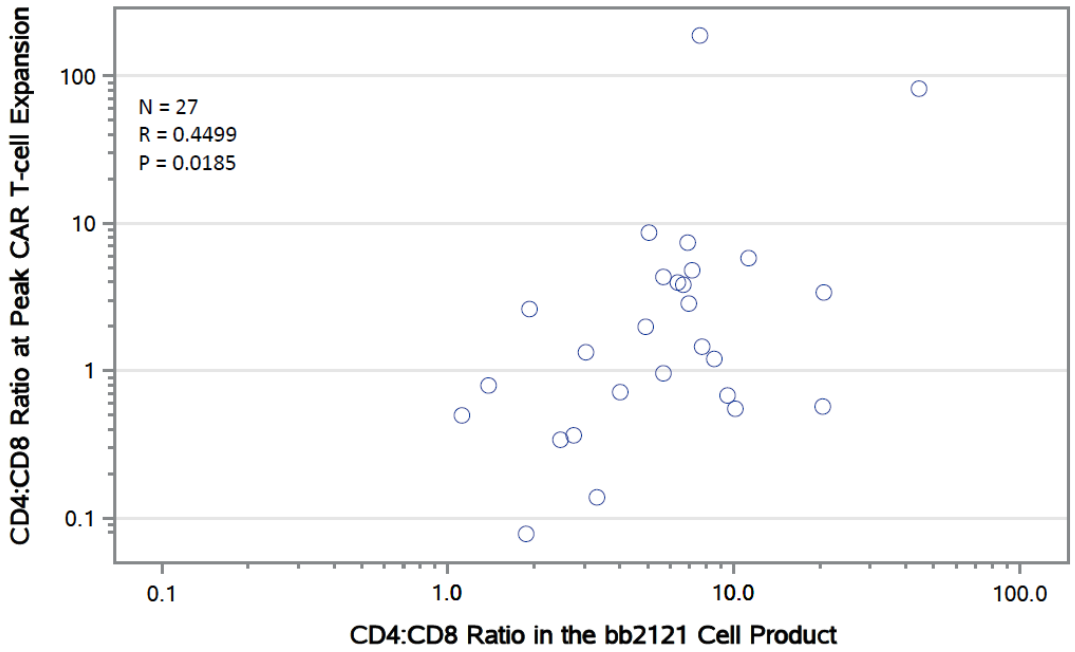


Figure S11. Vector Transgene Copy $AUC_{0\text{-}28d}$ in Patients With and Without a Response. All patients (N=33) had ≥1 month of cellular kinetics data. Horizontal lines indicate the medians. Circles indicate individual patients by dose. P value based on a 2-sided Wilcoxon rank sum test. $AUC_{0\text{-}28d}$ denotes area under the curve during the first 28 days after infusion.

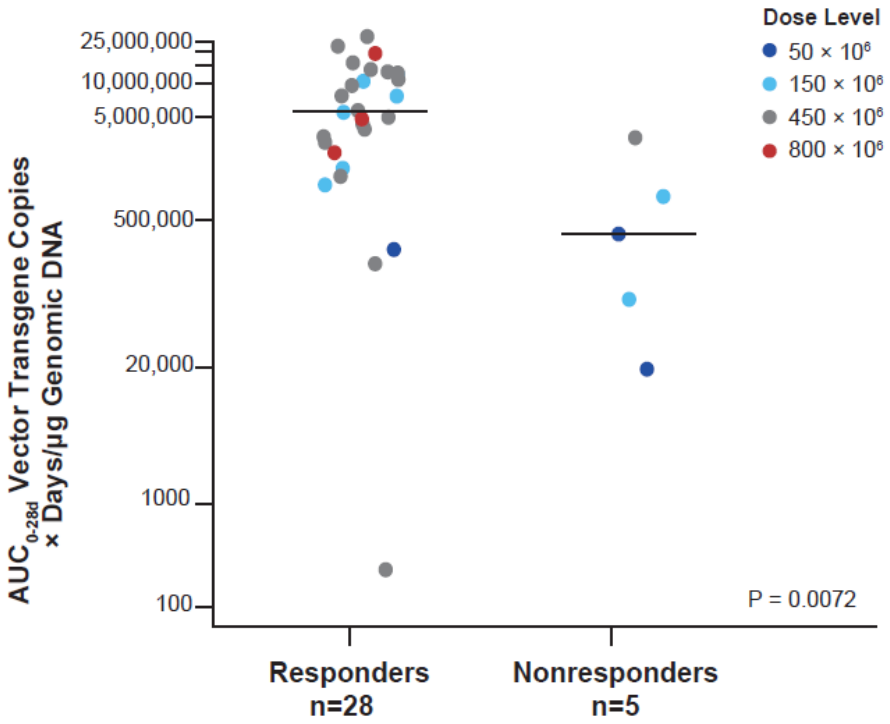


Table S1. International Myeloma Working Group (IMWG) Uniform Response Criteria[2]

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 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 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

Response	IMWG Criteria
	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. Bridging Therapies Received From Leukapheresis to Lymphodepletion.

	Total (N=33) *number of patients (percent)*
≥1 bridging therapy*	14 (42)
Corticosteroids	
Dexamethasone	12 (36)
Alkylating agents	
Bendamustine	3 (9)
Cyclophosphamide	2 (6)
Melphalan	1 (3)
Immunomodulatory agents	
Lenalidomide	1 (3)
Pomalidomide	2 (6)
Thalidomide	2 (6)
Proteasome inhibitors	
Bortezomib	3 (9)
Carfilzomib	2 (6)
Monoclonal antibodies	
Daratumumab	3 (9)
Other/not classified	
Bendamustine hydrochloride	1 (3)
Nelfinavir mesylate	1 (3)
Etoposide	1 (3)
Cisplatin	1 (3)

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

Table S3. Additional Baseline Characteristics of the Safety Population.

Characteristic	Dose Escalation (N=21)	Expansion (N=12)	Total (N=33)
Age			
Median (min–max)—yr	57 (37–74)	64 (46–75)	60 (37–75)
Age ≥65 yr—no. (%)	5 (24)	6 (50)	11 (33)
Male sex—no. (%)	13 (62)	8 (67)	21 (64)
Median (min–max) time since diagnosis—yr*	4 (1–16)	6 (1–36)	5 (1–36)
High tumor burden—no. (%)†	11 (52)	5 (42)	16 (49)
Extramedullary disease—no. (%)	4 (19)	5 (42)	9 (27)
Tumor BCMA expression ≥50%—no. (%)‡	21 (100)	2 (17)	23 (70)
Disease stage—no. (%)§			
I	6 (29)	1 (8)	7 (21)
II	11 (52)	3 (25)	14 (42)
III	4 (19)	4 (33)	8 (24)
Unknown	0	4 (33)	4 (12)
ECOG performance-status score—no. (%)			
0	8 (38)	2 (17)	10 (30)
1	11 (52)	10 (83)	21 (64)
2	2 (10)	0	2 (6)
High-risk cytogenetics—no. (%)‖	8 (38)	7 (58)	15 (46)
Bridging therapy—no. (%)¶	7 (33)	7 (58)	14 (42)
Median (min, max) vein-to-vein time—d	34 (33–68)	34 (33–62)	34 (33–68)
Progression on last line of therapy—no. (%)	11 (52)	10 (83)	21 (64)
No. of prior anti-myeloma regimens—no. (%)			
Median (min, max)	7 (3–14)	8 (3–23)	7 (3–23)
3–6	9 (43)	3 (25)	12 (36)
7–10	9 (43)	5 (42)	14 (42)
>10	3 (14)	4 (33)	7 (21)

Prior autologous SCT—no. (%)						
0	0		1 (8)		1 (3)	
1	15 (71)		8 (67)		23 (70)	
≥2	6 (29)		3 (25)		9 (27)	
Prior therapies—no. (%)	**Exposed**	**Refractory**	**Exposed**	**Refractory**	**Exposed**	**Refractory**
Bortezomib	21 (100)	13 (62)	12 (100)	7 (58)	33 (100)	20 (61)
Carfilzomib	19 (91)	12 (57)	11 (92)	7 (58)	30 (91)	19 (58)
Lenalidomide	21 (100)	17 (81)	12 (100)	7 (58)	33 (100)	24 (73)
Pomalidomide	19 (91)	14 (67)	12 (100)	12 (100)	31 (94)	26 (79)
Daratumumab	15 (71)	9 (43)	12 (100)	9 (75)	27 (82)	18 (55)
Bort/Len	21 (100)	12 (57)	12 (100)	5 (42)	33 (100)	17 (52)
Bort/Len/Car/Pom/Dara	15 (71)	3 (14)	11 (92)	3 (25)	26 (79)	6 (18)

BCMA denotes B-cell maturation antigen, Bort bortezomib, Car carfilzomib, Dara daratumumab, ECOG Eastern Cooperative Oncology Group, Len lenalidomide, Pom pomalidomide, SCT stem cell transplant.

*Time since initial diagnosis to screening.

†Tumor burden was determined by the investigator with high burden defined as ≥50% CD138-positive cells by central laboratory analysis (first preference) or by local analysis of bone marrow plasma cells (second preference). In the absence of both, tumor burden was determined by the Safety Review Committee.

‡Tumor BCMA expression at screening.

§Based on the International Staging System at screening. Four patients in the expansion phase were not available.

‖As reported by investigators based on local assessment of screening bone marrow. High-risk includes the following abnormalities: del(17p), t(4;14), or t(14;16).

¶From leukapheresis to lymphodepletion.

Table S4. Adverse Events Including Symptoms of Cytokine Release Syndrome.

	Total (N=33)		
	Any Grade	**Grade 3**	**Grade 4**
	number of patients (percent)		
Adverse event*			
Any	33 (100)	3 (9)	28 (85)
Hematologic			
Neutropenia	30 (91)	1 (3)	28 (85)
Leukopenia	21 (64)	6 (18)	14 (42)
Thrombocytopenia	21 (64)	6 (18)	12 (36)
Anemia	20 (61)	16 (49)	0
Lymphopenia	7 (21)	4 (12)	3 (9)
Gastrointestinal			
Nausea	14 (42)	1 (3)	0
Vomiting	12 (36)	1 (3)	0
Diarrhea	10 (30)	1 (3)	0
Constipation	9 (27)	0	0
Respiratory			
Cough	11 (33)	0	0
Nasal congestion	8 (24)	0	0
Dyspnea	6 (18)	0	0
Epistaxis	6 (18)	1 (3)	0
Productive cough	6 (18)	0	0
Other			
Cytokine release syndrome NOS	25 (76)	2 (6)	0
Pyrexia	25 (76)	2 (6)	0
Fatigue	17 (52)	2 (6)	0
Upper respiratory tract infection	14 (42)	3 (9)	0
Headache	13 (39)	1 (3)	0
Hypotension	13 (39)	3 (9)	0
Chills	12 (36)	0	0
Hypocalcemia	11 (33)	1 (3)	0
Peripheral edema	10 (30)	1 (3)	0
Sinus tachycardia	8 (24)	2 (6)	0
Tachycardia	8 (24)	0	0
Hypokalemia	8 (24)	0	0
Hypophosphatemia	8 (24)	3 (9)	0
Dizziness	8 (24)	1 (3)	0
Arthralgia	7 (21)	0	0
Hypoalbuminemia	7 (21)	0	0
Decreased appetite	6 (18)	0	0
Hyperglycemia	6 (18)	1 (3)	0
Back pain	6 (18)	0	0
Confusional state	5 (15)	0	0
Pain in extremity	5 (15)	0	0
Hyponatremia	5 (15)	3 (9)	0

NOS denotes not otherwise specified.

*Adverse events, including those designated as symptoms of cytokine release syndrome, that occurred in 15% or more of the safety population. One grade 5 event was reported (cardio-respiratory arrest).

Table S5. Adverse Events and Cytokine Release Syndrome From Week 8 Through Month 6.

	Total (N=31)		
	Any Grade	**Grade 3**	**Grade 4**
	number of patients (percent)		
Adverse event*			
Any	28 (90)	13 (42)	9 (29)
Hematologic			
Neutropenia	17 (55)	8 (26)	8 (26)
Leukopenia	12 (39)	5 (16)	3 (10)
Thrombocytopenia	12 (39)	2 (7)	3 (10)
Anemia	5 (16)	1 (3)	0
Gastrointestinal			
Nausea	7 (23)	1 (3)	0
Diarrhea	4 (13)	1 (3)	0
Vomiting	4 (13)	1 (3)	0
Other			
Upper respiratory tract infection	8 (26)	2 (7)	0
Cough	6 (19)	0	0
Fatigue	4 (13)	0	0
Pyrexia	4 (13)	0	0
Cytokine release syndrome†	0	0	0

*Adverse events not designated as symptoms of cytokine release syndrome that occurred in 10% or more of the safety population from week 8 through 6 months after infusion. One grade 5 event was reported (cardio-respiratory arrest).
†Clustered term including the preferred term; uniformly graded per Lee DW, et al.[30]

Table S6. Characteristics and Management of Cytokine Release Syndrome (Safety Population).

Parameter	Total (N=33)
Patients with a CRS event—no. (%)	
Any-grade	25 (76)
Grade ≥3	2 (6)
Median (min–max) time to onset, days	
Any-grade	2 (1–25)
First grade ≥3	5 (4–6)
Median (min–max) duration, days	
Any-grade	5 (1–32)
Grade ≥3	2 (2–2)
Tocilizumab use—no. (%)†	7 (21)
Corticosteroid use—no. (%)‡	4 (12)

CRS denotes cytokine release syndrome.
*Uniformly graded per Lee DW, et al.[30]
†The decision to give tocilizumab was at the treating physician's discretion based on protocol-specified toxicity management guidelines.
‡Steroid doses administered for treatment of CRS included dexamethasone 10 to 20 mg, hydrocortisone 40 mg and methylprednisolone 100 mg.

Table S7. Adverse Events Considered Symptoms of Cytokine Release Syndrome.

	Total (N=33)		
	Any Grade	**Grade 3**	**Grade 4**
Adverse event*	*number of patients (percent)*		
Any	25 (76)	4 (12)	1 (3)
Constitutional			
Pyrexia	19 (58)	1 (3)	0
Chills	5 (15)	0	0
Fatigue	3 (9)	1 (3)	0
Lethargy	1 (3)	1 (3)	0
Weight increased	1 (3)	1 (3)	0
Pelvic pain	1 (3)	0	0
Noncardiac chest pain	1 (3)	0	0
Peripheral edema	1 (3)	0	0
Cardiovascular			
Hypotension	7 (21)	0	0
Tachycardia	5 (15)	0	0
Sinus tachycardia	1 (3)	0	0
Capillary leak syndrome	1 (3)	0	0
Orthostatic hypotension	1 (3)	0	0
Neurologic			
Headache	5 (15)	1 (3)	0
Confusional state	3 (9)	0	0
Brain edema	1 (3)	0	0
Somnolence	1 (3)	0	0
Tremor	1 (3)	0	0
Bradyphrenia	1 (3)	0	0
Respiratory			
Hypoxia	3 (9)	2 (6)	0
Tachypnea	1 (3)	0	0
Gastrointestinal			
Nausea	2 (6)	0	0
Vomiting	1 (3)	0	0
Abdominal discomfort	1 (3)	0	0
Coagulation			
Fibrin D dimer increased	1 (3)	0	0
Hepatic			
Aspartate aminotransferase increased	2 (6)	1 (3)	0
Alanine aminotransferase increased	2 (6)	0	0
Renal			
Hypocalcemia	1 (3)	1 (3)	0
Hyponatremia	1 (3)	1 (3)	0
Hypophosphatemia	1 (3)	0	0
Acute kidney injury	1 (3)	0	0
Blood creatinine increased	1 (3)	0	0
Hematologic			
Anemia	1 (3)	1 (3)	0
Febrile neutropenia	1 (3)	1 (3)	0
Thrombocytopenia	1 (3)	0	1 (3)
Other			
C-reactive protein increased	3 (9)	0	0

Photophobia	1 (3)	0	0
Cytokine release syndrome NOS	3 (9)	0	0

NOS, not otherwise specified.

*Adverse events designated as symptoms of cytokine release syndrome in the case report form; symptoms were not available for 2 patients. All events occurred during the first 8 weeks; no patients experienced symptoms of cytokine release syndrome during the second reporting period (week 8 through month 6).

Table S8. Characteristics and Management of Neurotoxicity (Safety Population).

Parameter	Total (N=33)
Patients with an event—no. (%)*	
Any-grade	14 (42)
Grade ≥3	1 (3)
Median (min–max) time to onset, days	
Any-grade	5 (3–11)
First grade ≥3†	11 (11–11)
Median (min–max) duration, days	
Any-grade	8 (1–251)
Grade ≥3	22 (12–32)
Corticosteroid use—no. (%)‡	2 (6)

*Events occurring in the first 90 days and including the following preferred terms: bradyphrenia, brain edema, confusional state, dizziness, hallucination, insomnia, lethargy, memory impairment, neurotoxicity, nystagmus, somnolence, and tremor.
†Only one patient reported grade ≥3 neurotoxicity with onset at day 11.
‡Steroid doses used included dexamethasone 10 mg for treatment of grade 1 neurotoxicity and methylprednisolone 1000 mg daily for 3 days followed by a rapid taper to 250, 125 and 60 mg for treatment of the one case of grade 4 neurotoxicity.

Table S9. Tumor Response by Baseline Characteristics.*

	Dara-Exposed		Dara Last Line†		Penta-Exposed		Serum BCMA‡		Cytogenetic Risk§		Tumor Burden‖		Bridging Therapy		EMD		PD on Last Regimen	
Outcome	Yes (N=27)	No (N=6)	Yes (N=21)	No (N=12)	Yes (N=26)	No (N=7)	<Median (N=16)	≥Median (N=16)	High (N=15)	Not High/ Unknown (N=18)	High (N=16)	Low (N=17)	Yes (N=14)	No (N=19)	Yes (N=9)	No (N=24)	Yes (N=21)	No (N=12)
Objective response¶																		
No. with response	23	5	19	9	22	6	14	13	11	17	12	16	14	14	8**	20	19	9
Rate—% (95% CI)	85 (66.3 to 95.8)	83 (35.9 to 99.6)	91 (69.6 to 98.8)	75 (42.8 to 94.5)	85 (65.1 to 95.6)	86 (42.1 to 99.6)	88 (61.7 to 98.4)	81 (54.4 to 96.0)	73 (44.9 to 92.2)	94 (72.7 to 99.9)	75 (47.6 to 92.7)	94 (71.3 to 99.9)	100 (76.8 to 100)	74 (48.8 to 90.9)	89 (51.8 to 99.7)	83 (62.6 to 95.3)	91 (69.6 to 98.8)	75 (42.8 to 94.5)
Best overall response—no. (%)																		
Stringent complete response	11 (41)	1 (17)	10 (48)	2 (17)	11 (42)	1 (14)	6 (38)	5 (31)	6 (40)	6 (33)	7 (44)	5 (29)	7 (50)	5 (26)	3 (33)	9 (38)	10 (48)	2 (17)
Complete response	2 (7)	1 (17)	0	3 (25)	2 (8)	1 (14)	2 (13)	1 (6)	1 (7)	2 (11)	0	3 (18)	2 (14)	1 (5)	1 (11)	2 (8)	1 (5)	2 (17)
Very good partial response	7 (26)	2 (33)	6 (29)	3 (25)	7 (27)	2 (29)	4 (25)	5 (31)	3 (20)	6 (33)	4 (25)	5 (29)	4 (29)	5 (26)	2 (22)	7 (29)	6 (29)	3 (25)
Partial response	3 (11)	1 (17)	3 (14)	1 (8)	2 (8)	2 (29)	2 (13)	2 (13)	1 (7)	3 (17)	1 (6)	3 (18)	1 (7)	3 (16)	2 (22)	2 (8)	2 (10)	2 (17)
Stable disease	3 (11)	1 (17)	1 (5)	3 (25)	3 (12)	1 (14)	1 (6)	3 (19)	3 (20)	1 (6)	4 (25)	0	0	4 (21)	1 (11)	3 (13)	2 (10)	2 (17)
Progressive disease	1 (4)	0	1 (5)	0	1 (4)	0	1 (6)	0	1 (7)	0	0	1 (6)	0	1 (5)	0	1 (4)	0	1 (8)

BCMA denotes B-cell maturation antigen, Dara daratumumab, EMD extramedullary disease, PD progressive disease.

*Includes confirmed responses assessed based on the International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma (details on the criteria for disease response are provided in the Supplementary Appendix).

†Includes use of daratumumab as part of the last line of myeloma therapy or as bridging therapy.

‡Based on median BCMA levels among all infused patients.

§As reported by investigators based on local assessment of screening bone marrow. High risk is defined as having del(17p), t(4;14), or t(14;16).

‖Tumor burden was determined by the investigator with high burden defined as ≥50% CD138-positive cells by central laboratory analysis (first preference) or by local analysis of bone marrow plasma cells (second preference). In the absence of both, tumor burden was determined by the Safety Review Committee.
¶Objective response is defined as attaining a partial response or better.
**Of 9 patients with EMD at baseline, 5 have progressed and 3 of the 5 had progression, at least in part, in sites of EMD.

Table S10. CAR T Cell Persistence Over Time.

	Month 1	Month 3	Month 6	Month 12
No. at risk	24	22	23	10
No. (%) with detectable vector	23 (96)	19 (86)	13 (57)	2 (20)

All 33 patients were included in the analysis. Data from samples with <50 ng total DNA input were excluded.

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