Cytopenias and infections following ciltacabtagene autoleucel in heavily pretreated relapsed or refractory multiple myeloma

Danai Dima,[1*] Jennifer M. Logue,[2*] Syed Hamza Bin Waqar,[2*] Lauren C. Peres,[2] Christelle M. Colin-Leitzinger,[2] Gabriel De Avila,[2] Eric C. Smith,[2] Lawrence Skelson,[2] Kristy L. Matte,[2] Brandon Blue,[2] Vanna N. Hovanky,[3] Mahmoud Gaballa,[4] Oren Pasvolsky,[4] Laura B. Oswald,[2] Gliceida M. Galarza Fortuna,[5] Charlotte B. Wagner,[5] Shaun DeJarnette,[6] Christen Dillard,[4] Fabiana Perna,[2] Lekha Mikkilineni,[3] Hitomi Hosoya,[3] Ciara L. Freeman,[2] Kenneth H. Shain,[2] Rachid C. Baz,[2] Ariel Grajales-Cruz,[2] Omar Castaneda Puglianini,[2] Melissa Alsina,[2] Frederick L. Locke,[2] Leyla O. Shune,[6] Douglas W. Sborov,[5] Krina K. Patel,[4#] Surbhi Sidana,[3#] and Doris K. Hansen[2#]

[1]University of Washington, Fred Hutch Cancer Center, Seattle, WA; [2]H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL; [3]Stanford University School of Medicine, Stanford, CA; [4]MD Anderson Cancer Center, Houston, TX; [5]University of Utah School of Medicine, Salt Lake City, UT and [6]University of Kansas Medical Center, Kansas City, KS, USA

DD, JML and SHBW contributed equally as first authors.

#KKP, SS and DKH contributed equally as senior authors.

Correspondence: D.K. Hansen
Doris.Hansen@moffitt.org

S. Sidana
surbhi.sidana@stanford.edu

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SUPPLEMENT

DETAILS OF ANTIBIOTIC PROPHYLAXIS

A. Moffitt Cancer Center	
Antiviral prophylaxis:	Acyclovir 800mg PO BID
Start	Day -1 or when ANC < 500/uL (whichever occurs first)
Stop	Day 360 (12 months)
PJP prophylaxis:	Bactrim SS 1 tablet PO daily or alternative (pentamidine, atovaquone)
Start	Day 30
Stop	Day 180 (6 months) or when CD4 count > 200 cells/microliter
Antifungal prophylaxis:	Fluconazole 400mg PO daily
Start	When ANC < 500/uL
Stop	When ANC > 500/uL
Other considerations	Voriconazole 200mg PO BID for history of invasive fungal infection, neutropenia >14 days on admission, anticipated steroid duration >14 days, or patients with ANC < 500/uL for > 14 days post-CAR T infusion with long-term cytopenias anticipated.
Antibacterial prophylaxis:	Levofloxacin 500 mg PO daily
Start	When ANC < 500/uL
Stop	When ANC > 500/uL

B. Stanford University	
Antiviral prophylaxis:	Acyclovir 800 mg PO BID. Can decrease to 400 mg BID after 1 month
Start	Day +1
Stop	Minimum 12 months, stop when CD4 > 200 cells/microliter
PJP prophylaxis:	Bactrim SS 1 tablet PO daily or alternative (atovaquone)
Start	Day +14 or sooner if on high dose steroids for ≥4 days
Stop	Minimum 12 months, stop when CD4 >200 cells/microliter
Antifungal prophylaxis:	Posaconazole 300 mg PO daily
Start	For prolonged severe neutropenia (ANC < 500/uL) >7 days OR prolonged steroid use for ≥4 days OR if methylprednisolone 1g is given OR persistent neutropenia at Day +28 OR consider for late onset severe neutropenia
Stop	Per provider discretion when off steroids or resolution of neutropenia. Typically stop Day +30
Antibacterial prophylaxis:	Levaquin 750 mg PO daily
Start	When ANC < 500/uL, if neutropenia occurs after Day +30 or lasts >14 days and is not responsive to G-CSF. Case by case in other situations when on prolonged steroids for CAR-T related AEs and neutropenic.
Stop	When ANC > 500/uL

C. University of Kansas Medical Center	
Antiviral prophylaxis:	Acyclovir 800 mg PO BID
Start	Day of cell infusion
Stop	Continue until CD4 >200 cells/microliter
PJP prophylaxis:	Bactrim DS 1 tablet PO BID twice/week or alternative (pentamidine, dapsone, atovaquone)
Start	Day 20
Stop	Continue until CD4 >200 cells/microliter
Antifungal prophylaxis:	Fluconazole 400 mg PO daily
Start	Day -2 of HDC
Stop	Post-nadir ANC >500/uL x1
Other considerations	
Antibacterial prophylaxis:	Levofloxacin 750 mg PO daily
Start	Day -2 of HDC
Stop	When ANC > 500/uL

D. University of Utah, Huntsman Cancer Institute	
Antiviral prophylaxis:	Acyclovir 800mg PO BID
Start	Day 0
Stop	6 months or until CD4 is >200 cells/microliter, whichever is longer
PJP prophylaxis:	Bactrim SS 1 tablet once daily is the preferred agent (alternatives: pentamidine, atovaquone, dapsone)
Start	Day 30
Stop	Day 180 or when CD4 is > 200 cells/microliter, whichever is longer
Other considerations	If patients receive >1 dose of tocilizumab, >3 days of corticosteroids (e.g., ≥10 mg dexamethasone per day) or one dose ≥1g methylprednisolone IV) or second-line agents for CRS management (eg, anakinra, siltuximab), begin PJP prophylaxis with IV pentamidine until standard PJP prophylaxis is started at day +30
Antifungal prophylaxis:	Fluconazole 400 mg PO daily (alternative = caspofungin)
Start	When ANC < 500/uL
Stop	When ANC > 500/uL
Other considerations	Patients with the following criteria are started on Posaconazole rather than fluconazole: 1. History of allogeneic transplant within 6 months prior to CAR-T 2. History of invasive mold infection on active therapy within 6 months of CAR-T 3. Patients who are neutropenic prior to day 0 4. Severe neutropenia (ANC <500/uL) for > 2 weeks. Posaconazole should be continued until neutropenia resolution. 5. If patients receive >1 dose of tocilizumab, >3 days of corticosteroids (eg, ≥10 mg dexamethasone per day) or one dose ≥1g methylprednisolone IV), or second-line agents for management of CRS (eg, anakinra, siltuximab), switch patients from fluconazole to anti-mold active prophylaxis with Posaconazole 300 mg PO or IV daily. a. Continue Posaconazole for 30 days after discontinuation of immunosuppression (corticosteroid, tocilizumab, anakinra, etc.) or longer at the discretion of the infectious disease team. 6. Voriconazole or isavuconazole are alternatives to posaconazole on hospital discharge.
Antibacterial prophylaxis:	Levofloxacin 500 mg PO daily (alternatives: ciprofloxacin, cefpodoxime)
Start	When ANC < 500/uL
Stop	When ANC > 500/uL

E. MD Anderson Cancer Center	
Antiviral prophylaxis:	Valacyclovir 500 mg PO daily
Start	Day 0
Stop	Day 360 at least (At least 1 year post CAR-T infusion; may stop after 1 year if CD4 count > 200 cells/microliter)
PJP prophylaxis:	Pentamidine inhaled or IV once weekly, before or after, CAR-T infusion, and then: Bactrim 1 DS tablet PO every Monday, Wednesday, Friday or 1 SS tablet PO daily
Start	For Bactrim: 3-4 weeks after infusion
Stop	For Bactrim: At least 1 year post-infusion; may stop after 1 year if CD4 count > 200 cells/microliter
Antifungal prophylaxis:	Fluconazole 200-400 mg PO daily
Start	CAR-T infusion day or when ANC < 500/uL
Stop	Continue until ANC > 500/uL for 3 consecutive days without growth factor support
Other considerations	For high-risk patients: Posaconazole 300 mg PO or IV daily
Antibacterial prophylaxis:	Levofloxacin 500 mg PO daily
Start	ANC ≤ 500/uL
Stop	ANC > 500/uL for 3 consecutive days without growth factor support

SUPPLEMENTARY TABLES

Table S1. Apheresis and product characteristics

Characteristic	N = 105
Collection goal (TBV), Median (Range)	4.6 (2.0 – 6.7)
Whole blood processed (L), Median (Range)	14.886 (6.268 – 30.542)
Final collection volume (mL), Median (Range)	247 (93 – 460)
Access type, n (%)	
Central venous catheter	70 (67%)
Peripheral	35 (33%)
Run time (min), Median (Range)	243 (102 – 614)
Time from apheresis to CAR-T infusion (days), Median (Range)	69.5 (49 – 134)
Total bags infused, Median (Range)	1 (1 – 2)
Total dose volume (mL), n (%)	
140	2 (1.9%)
70	94 (90%)
30	8 (7.7%)
Total cell dose (million cells), Median (Range)	0.6 (0.1 – 0.9)

Description of apheresis data and cilta-cel product characteristics. TBV: Total blood volume.

Table S2. Clinical outcomes following cilta-cel therapy

Characteristic	N = 105
CRS maximum grade – n (%)	
0	25 (24%)
1	57 (54%)
2	20 (19%)
3	1 (1%)
4	1 (1%)
5	1 (1%)
Time to CRS onset (days) – median (range)	7 (0 – 13)
Time to maximum severity CRS (days) – median (range)	7 (0 – 13)
Duration of CRS (days) – median (range)	2 (1 – 11)
ICANS maximum grade – n (%)	
0	91 (87%)
1	6 (5.7%)
2	5 (4.8%)
3	1 (1%)
4	2 (1.9%)
5	0 (0%)
Time to ICANS onset (days) – median (range)	8 (1 – 51)
Time to maximum severity ICANS (days) – median (range)	8.5 (1 – 53)
Duration of ICANS (days) – median (range)	2 (1 – 42)
Delayed Neurotoxicity – n (%)	14 (13%)
Parkinsonian	3 (2.9%)
Bell's palsy	6 (5.7%)
Polyneuropathy	3 (2.9%)
PRES	2 (1.9%)
Treatment for toxicity – n (%)	
Steroid use	42 (40%)
Tocilizumab use	59 (56%)
Anakinra use	7 (6.7%)
IEC-HS	3 (3%)
Day 30 response – n (%)	
ORR	82 (83%)
CR or sCR	27 (27%)
MRD negative	16/18 (89%)
VGPR	15 (15%)
PR	40 (40%)
MRD negative	61 (87%)
Day 90 response – n (%)	
ORR	85 (89%)
CR or sCR	45 (47%)
MRD negative	27 (90%)
VGPR	24 (25%)
PR	16 (17%)
MRD negative	58 (87%)
Best response in first 90 days – n (%)	
ORR	94 (92%)
CR or sCR	64 (63%)
MRD negative	41 (64%)
MRD unknown	23 (36%)
VGPR	15 (15%)
PR	15 (15%)

CRS: Cytokine release syndrome. ICANS: Immune effector cell-associated neurotoxicity syndrome. IEC-HS: Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome ORR: Overall response rate, calculated as patients with at least partial response (PR). CR: Complete response. sCR: Stringent complete response. MRD: Minimal residual disease. VGPR: Very good partial response.

Table S3. Patient characteristics by grade ≥ 3 cytopenia by CTCAE at day 30

	Grade ≥ 3 cytopenia at day 30		
Characteristic	**No**, N = 49	**Yes**, N = 54	**p-value**
Age (years), Median (Range)	63 (30 – 76)	63 (33 – 76)	0.8
≥ 70 years, n (%)	10 (20%)	12 (22%)	0.8
Male Sex, n (%)	27 (55%)	29 (54%)	0.9
Extramedullary disease, n (%)	9 (19%)	22 (41%)	**0.016**
Unknown	1	0	
High marrow burden (≥50%), n (%)	6 (13%)	10 (19%)	0.4
Unknown	1	2	
Circulating Plasma Cells at pre-LD, n (%)	0 (0%)	1 (3.7%)	0.5
Unknown	17	27	
ECOG status at LD, n (%)			>0.9
0-1	45 (96%)	51 (94%)	
≥ 2	2 (4.3%)	3 (5.6%)	
Unknown	2	0	
R-ISS at CAR-T infusion, n (%)			0.2
I	13 (31%)	8 (17%)	
II	17 (40%)	27 (57%)	
III	12 (29%)	12 (26%)	
Unknown	7	7	
High risk cytogenetics (not including gain 1q), n (%)	14 (35%)	27 (59%)	**0.028**
Unknown	9	8	
High risk cytogenetics (including gain 1q), n (%)	25 (61%)	37 (80%)	**0.045**
Unknown	8	8	
Number of prior lines of therapy, Median (Range)	5 (3 – 15)	5 (3 – 12)	0.13
> 4, n (%)	27 (55%)	41 (76%)	**0.026**
Bridging Therapy, n (%)	43 (88%)	46 (85%)	0.7
Prior autoSCT, n (%)	42 (86%)	45 (83%)	0.7
Prior BCMA-directed therapy, n (%)	5 (10%)	4 (7.4%)	0.7
Refractory to Immunomodulatory agent, n (%)	42 (86%)	47 (87%)	0.8
Refractory to Proteasome Inhibitor, n (%)	41 (84%)	48 (89%)	0.4
Refractory to Daratumumab or Isatuximab, n (%)	46 (94%)	48 (89%)	0.5
Double-refractory, n (%)	38 (78%)	42 (78%)	>0.9
Triple-refractory, n (%)	37 (76%)	38 (70%)	0.6
Penta-refractory, n (%)	12 (24%)	15 (28%)	0.7
Eligible for CARTITUDE trial, n (%)	22 (45%)	24 (44%)	>0.9
Marrow Cellularity (%) at Day 30, Median (Range)	30 (0.3 – 80)	30 (0.3 - 80)	>0.9
Unknown	16	20	
Any grade cytopenia at apheresis, n (%)	36 (73%)	50 (93%)	0.009
Neutropenia at apheresis	14 (29%)	16 (30%)	>0.9
Anemia at apheresis	18 (37%)	39 (72%)	**<0.001**
Thrombocytopenia at apheresis	12 (24%)	30 (56%)	**0.001**
Any grade cytopenia at day -5, n (%)	36 (73%)	49 (91%)	**0.021**
Neutropenia at day -5	9 (18%)	23 (43%)	**0.008**
Anemia at day -5	24 (49%)	42 (78%)	**0.002**
Thrombocytopenia at day -5	13 (27%)	27 (50%)	**0.015**
CAR-HEMATOTOX score, n (%)			**0.006**
Low	33 (80%)	24 (52%)	
High	8 (20%)	22 (48%)	
Unknown	8	8	

Distribution of patient characteristics by grade ≥ 3 cytopenia by CTCAE grading at day 30 using Wilcoxon rank sum test, Pearson's Chi-squared test, and Fisher's exact test for univariate analysis. P values ≤ 0.05 are represented in bold. LD: lymphodepletion chemotherapy. ECOG: Eastern Cooperative Oncology Group. R-ISS: Revised International Staging System. Double-refractory disease: Refractory to an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI). Triple-refractory disease: Refractory to an IMiD, PI and daratumumab. Penta-refractory disease: Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab.

Table S4. Association of clinical outcomes with grade ≥ 3 cytopenia by CTCAE at day 30 post cilta-cel.

	Grade ≥ 3 cytopenia at day 30		
Characteristic	**No**, N = 49	**Yes**, N = 54	**p-value**
Total cell dose (million cells), Median (Range)	0.6 (0.4 – 0.8)	0.6 (0.1 – 0.9)	0.3
CRS Maximum Grade, n (%)			0.2
No CRS	15 (31%)	10 (19%)	
Grade 1 or 2	34 (69%)	43 (80%)	
Grade ≥ 3	0 (0%)	1 (1.9%)	
Day of onset of CRS relative to infusion, Median (Range)	7 (3 – 11)	6.5 (0 – 13)	>0.9
Day of Max CRS (relative to infusion), Median (Range)	7 (3 – 11)	7 (0 – 13)	>0.9
Duration of CRS (days), Median (Range)	3 (1 – 5)	2 (1 – 8)	0.4
ICANS Maximum Grade, n (%)			0.3
No ICANS	46 (94%)	45 (83%)	
Grade 1 or 2	2 (4.1%)	7 (13%)	
Grade ≥ 3	1 (2.0%)	2 (3.7%)	
Day of onset of ICANS relative to infusion, Median (Range)	8 (6 – 14)	8 (1 – 51)	0.9
Day of Max ICANS (relative to infusion), Median (Range)	8 (7 – 14)	8 (1 – 53)	0.9
Duration of ICANS (days), Median (Range)	2 (1 – 2)	1 (1 – 42)	>0.9
Delayed Neurotoxicity, n (%)	7 (14%)	7 (13%)	0.8
Treatment for toxicity, n (%)			
Steroid Use	17 (35%)	23 (43%)	0.4
Tocilizumab Use	19 (39%)	38 (70%)	**0.001**
Anakinra Use	2 (4.1%)	4 (7.4%)	0.7
Day 30 response, n (%)			
ORR	35 (78%)	47 (90%)	0.087
sCR or CR	12 (27%)	15 (29%)	0.8
Day 90 response, n (%)			
ORR	42 (98%)	43 (86%)	0.065
sCR or CR	22 (51%)	23 (46%)	0.6
Best ORR at ≤ 12 months, n (%)			0.7
< PR	2 (4.3%)	4 (7.5%)	
PR or better	45 (96%)	49 (92%)	

Distribution of clinical outcomes by grade ≥ 3 cytopenia by CTCAE grading at day 30 using Wilcoxon rank sum test, Pearson's Chi-squared test, and Fisher's exact test for univariate analysis. P values ≤ 0.05 are represented in bold. CRS: Cytokine release syndrome. ICANS: Immune effector cell-associated neurotoxicity syndrome. ORR: Overall response rate, calculated as patients with at least partial response (PR). CR: Complete response. sCR: Stringent complete response.

Table S5. Patient characteristics by any grade early ICAHT

	Any Grade Early ICAHT		
Characteristic	**No**, N = 50	**Yes**, N = 55	**p-value**
Age (years), Median (Range)	65 (30 – 76)	61 (33 – 76)	0.2
≥ 70 years, n (%)	11 (22%)	12 (22%)	>0.9
Male Sex, n (%)	31 (62%)	27 (49%)	0.2
Extramedullary disease, n (%)	13 (27%)	18 (33%)	0.5
Unknown	1	0	
High marrow burden (≥50%), n (%)	7 (15%)	11 (20%)	0.4
Unknown	2	1	
Circulating Plasma Cells at pre-LD, n (%)	0 (0%)	2 (6.3%)	0.5
Unknown	21	23	
ECOG status at LD, n (%)			0.2
0-1	48 (98%)	49 (91%)	
≥ 2	1 (2.0%)	5 (9.3%)	
Unknown	1	1	
R-ISS at CAR-T infusion, n (%)			0.6
I	9 (22%)	12 (24%)	
II	22 (54%)	22 (44%)	
III	10 (24%)	16 (32%)	
Unknown	9	5	
High risk cytogenetics (not including gain 1q), n (%)	21 (55%)	22 (44%)	0.3
Unknown	12	5	
High risk cytogenetics (including gain 1q), n (%)	29 (74%)	35 (70%)	0.6
Unknown	11	5	
Number of prior lines of therapy, Median (Range)	5 (3 – 15)	5 (4 – 12)	0.2
> 4, n (%)	29 (58%)	41 (75%)	0.072
Bridging Therapy, n (%)	45 (90%)	46 (84%)	0.3
Prior autoSCT, n (%)	41 (82%)	47 (85%)	0.6
Prior BCMA-directed therapy, n (%)	6 (12%)	3 (5.5%)	0.3
Refractory to Immunomodulatory agent, n (%)	44 (88%)	47 (85%)	0.7
Refractory to Proteasome Inhibitor, n (%)	43 (86%)	48 (87%)	0.8
Refractory to Daratumumab or Isatuximab, n (%)	44 (88%)	52 (95%)	0.3
Double-refractory, n (%)	40 (80%)	42 (76%)	0.7
Triple-refractory, n (%)	37 (74%)	40 (73%)	0.9
Penta-refractory, n (%)	15 (30%)	13 (24%)	0.5
Eligible for CARTITUDE trial, n (%)	23 (46%)	24 (44%)	0.8
Marrow Cellularity (%) at Day 30, Median (Range)	30 (0.3 - 70)	30 (0.3 – 80)	0.5
Unknown	15	23	
Any cytopenia at apheresis, n (%)	36 (72%)	52 (95%)	**0.002**
Neutropenia at apheresis	9 (18%)	22 (40%)	**0.014**
Anemia at apheresis	22 (44%)	37 (67%)	**0.016**
Thrombocytopenia at apheresis	15 (30%)	27 (49%)	**0.046**
Any cytopenia at day -5, n (%)	38 (76%)	49 (89%)	0.075
Neutropenia at day -5	11 (22%)	22 (40%)	**0.047**
Anemia at day -5	28 (56%)	40 (73%)	0.073
Thrombocytopenia at day -5	15 (30%)	27 (49%)	**0.046**
CAR-HEMATOTOX score, n (%)			0.10
Low	30 (73%)	27 (56%)	
High	11 (27%)	21 (44%)	
Unknown	9	7	

Distribution of patient characteristics by any grade early ICAHT between days 0-30 using Wilcoxon rank sum test, Pearson's Chi-squared test, and Fisher's exact test for univariate analysis. P values ≤ 0.05 are represented in bold. LD: lymphodepletion chemotherapy. ECOG: Eastern Cooperative Oncology Group. R-ISS: Revised International Staging System. Double-refractory disease: Refractory to an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI). Triple-refractory disease: Refractory to an IMiD, PI and daratumumab. Penta-refractory disease: Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab.

Table S6. Association of clinical outcomes with any grade early ICAHT at day 30 post cilta-cel

	Any Grade Early ICAHT		
Characteristic	**No**, N = 50	**Yes**, N = 55	**p-value**
Total cell dose (million cells), Median (Range)	0.6 (0.3 – 0.8)	0.6 (0.1 – 0.9)	0.4
CRS Maximum Grade, n (%)			0.11
No CRS	15 (30%)	10 (18%)	
Grade 1 or 2	35 (70%)	42 (76%)	
Grade ≥ 3	0 (0%)	3 (5.5%)	
Day of onset of CRS relative to infusion, Median (Range)	7 (3 – 12)	6 (0 – 13)	**<0.001**
Day of Max CRS (relative to infusion), Median (Range)	8 (3 – 12)	6 (0 – 13)	**0.004**
Duration of CRS (days), Median (Range)	2 (1 – 5)	3 (1 – 11)	**0.003**
ICANS Maximum Grade, n (%)			0.3
No ICANS	45 (90%)	46 (84%)	
Grade 1 or 2	5 (10%)	6 (11%)	
Grade ≥ 3	0 (0%)	3 (5.5%)	
Day of onset of ICANS relative to infusion, Median (Range)	8 (8 – 9)	6.0 (1.0, 51.0)	0.7
Day of Max ICANS (relative to infusion), Median (Range)	8.0 (8.0, 12.0)	9.0 (1.0, 53.0)	>0.9
Duration of ICANS (days), Median (Range)	1.0 (1.0, 3.0)	4.0 (1.0, 42.0)	0.2
Delayed Neurotoxicity, n (%)	7 (14%)	7 (13%)	0.8
Treatment for toxicity, n (%)			
Steroid Use	16 (32%)	26 (47%)	0.11
Tocilizumab Use	21 (42%)	38 (69%)	**0.005**
Anakinra Use	3 (6.0%)	4 (7.3%)	>0.9
Day 30 response, n (%)			
ORR	36 (82%)	46 (84%)	0.8
sCR or CR	11 (25%)	16 (29%)	0.6
Day 90 response, n (%)			
ORR	41 (98%)	44 (83%)	**0.039**
sCR or CR	22 (52%)	23 (43%)	0.4
Best ORR at ≤ 12 months, n (%)			0.3
< PR	2 (4.3%)	6 (11%)	
PR or better	45 (96%)	49 (89%)	

Distribution of clinical outcomes by any grade early ICAHT between days 0-30 using Wilcoxon rank sum test, Pearson's Chi-squared test, and Fisher's exact test for univariate analysis. P values ≤ 0.05 are represented in bold. CRS: Cytokine release syndrome. ICANS: Immune effector cell-associated neurotoxicity syndrome. ORR: Overall response rate, calculated as patients with at least partial response (PR). CR: Complete response. sCR: Stringent complete response.

Table S7. Patient characteristics by grade ≥ 3 cytopenia by CTCAE at day 90

	Grade ≥ 3 cytopenia at day 90		
Characteristic	**No**, N = 69	**Yes** N = 22	**p-value**
Age (years), Median (Range)	63 (30 - 76)	64.5 (47 - 73)	0.8
≥ 70 years, n (%)	17 (25%)	3 (14%)	0.4
Male Sex, n (%)	37 (54%)	10 (45%)	0.5
Extramedullary disease, n (%)	21 (31%)	6 (27%)	0.7
Unknown	1	0	
High marrow burden (≥50%), n (%)	11 (16%)	4 (19%)	0.7
Unknown	2	1	
Circulating Plasma Cells at pre-LD, n (%)	1 (2.3%)	0 (0%)	>0.9
Unknown	25	14	
ECOG status at LD, n (%)			>0.9
0-1	64 (94%)	21 (95%)	
≥ 2	4 (5.9%)	1 (4.5%)	
Unknown	1	0	
R-ISS at CAR-T infusion, n (%)			0.2
I	17 (28%)	3 (17%)	
II	31 (51%)	7 (39%)	
III	13 (21%)	8 (44%)	
Unknown	8	4	
High risk cytogenetics (not including gain 1q), n (%)	24 (42%)	12 (63%)	0.11
Unknown	12	3	
High risk cytogenetics (including gain 1q), n (%)	41 (71%)	14 (74%)	0.8
Unknown	11	3	
Number of prior lines of therapy, Median (Range)	5 (3 - 15)	5 (4 - 11)	0.3
> 4	41 (59%)	17 (77%)	0.13
Bridging Therapy, n (%)	59 (86%)	19 (86%)	>0.9
Prior autoSCT, n (%)	57 (83%)	19 (86%)	>0.9
Prior BCMA-directed therapy, n (%)	4 (5.8%)	1 (4.5%)	>0.9
Refractory to Immunomodulatory agent, n (%)	61 (88%)	17 (77%)	0.3
Refractory to Proteasome Inhibitor, n (%)	62 (90%)	16 (73%)	0.075
Refractory to Daratumumab or Isatuximab, n (%)	64 (93%)	19 (86%)	0.4
Double-refractory, n (%)	57 (83%)	13 (59%)	**0.023**
Triple-refractory, n (%)	54 (78%)	12 (55%)	**0.030**
Penta-refractory, n (%)	18 (26%)	3 (14%)	0.2
Eligible for CARTITUDE trial, n (%)	32 (46%)	12 (55%)	0.5
Marrow Cellularity (%) at Day 90, Median (Range)	30 (0 – 85)	25 (0 – 62.5)	0.2
Unknown	15	5	
Any cytopenia at apheresis, n (%)	56 (81%)	20 (91%)	0.3
Neutropenia at apheresis	20 (29%)	6 (27%)	0.9
Anemia at apheresis	36 (52%)	14 (64%)	0.3
Thrombocytopenia at apheresis	22 (32%)	13 (59%)	**0.022**
Any cytopenia at day -5, n (%)	57 (83%)	19 (86%)	>0.9
Neutropenia at day -5	20 (29%)	6 (27%)	0.9
Anemia at day -5	46 (67%)	14 (64%)	0.8
Thrombocytopenia at day -5	25 (36%)	10 (45%)	0.4
CAR-HEMATOTOX score, n (%)			0.4
Low	38 (66%)	15 (75%)	
High	20 (34%)	5 (25%)	
Unknown	11	2	

Distribution of patient characteristics by grade ≥ 3 cytopenia by CTCAE grading at day 90 using Wilcoxon rank sum test, Pearson's Chi-squared test, and Fisher's exact test for univariate analysis. P values ≤ 0.05 are represented in bold. LD: lymphodepletion chemotherapy. ECOG: Eastern Cooperative Oncology Group. R-ISS: Revised International Staging System. Double-refractory disease: Refractory to an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI). Triple-refractory disease: Refractory to an IMiD, PI and daratumumab. Penta-refractory disease: Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab.

Table S8. Patient characteristics by any grade late ICAHT (beyond day 30)

	Any Grade Late ICAHT		
Characteristic	**No**, N = 65	**Yes**, N = 26	**p-value**
Age (years), Median (Range)	64 (30 – 76)	62 (46 – 73)	0.6
≥ 70 years, n (%)	17 (26%)	3 (12%)	0.13
Male Sex, n (%)	36 (55%)	11 (42%)	0.3
Extramedullary disease, n (%)	20 (31%)	7 (27%)	0.7
Unknown	1	0	
High marrow burden (≥50%), n (%)	9 (14%)	6 (24%)	0.3
Unknown	2	1	
Circulating Plasma Cells at pre-LD, n (%)	1 (2.4%)	0 (0%)	>0.9
Unknown	23	16	
ECOG status at LD, n (%)			0.3
0-1	59 (92%)	26 (100%)	
≥ 2	5 (7.8%)	0 (0%)	
Unknown	1	0	
R-ISS at cart infusion, n (%)			0.12
I	18 (31%)	2 (10%)	
II	28 (47%)	10 (50%)	
III	13 (22%)	8 (40%)	
Unknown	6	6	
High risk cytogenetics (not including gain 1q), n (%)	21 (39%)	15 (68%)	**0.020**
Unknown	11	4	
High risk cytogenetics (including gain 1q), n (%)	37 (67%)	18 (82%)	0.2
Unknown	10	4	
Number of prior lines of therapy, Median (Range)	5 (4 – 15)	5.5 (3 – 11)	0.4
> 4	39 (60%)	19 (73%)	0.2
Bridging Therapy, n (%)	54 (83%)	24 (92%)	0.3
Prior autoSCT, n (%)	53 (82%)	23 (88%)	0.5
Prior BCMA-directed therapy, n (%)	5 (7.7%)	0 (0%)	0.3
Refractory to Immunomodulatory agent, n (%)	58 (89%)	20 (77%)	0.2
Refractory to Proteasome Inhibitor, n (%)	59 (91%)	19 (73%)	**0.045**
Refractory to Daratumumab or Isatuximab, n (%)	61 (94%)	22 (85%)	0.2
Double-refractory, n (%)	54 (83%)	16 (62%)	**0.028**
Triple-refractory, n (%)	51 (78%)	15 (58%)	**0.045**
Penta-refractory, n (%)	16 (25%)	5 (19%)	0.6
Eligible for CARTITUDE trial, n (%)	26 (40%)	18 (69%)	**0.012**
Marrow Cellularity (%) at Day 90, Median (Range)	30 (0 – 85)	30 (10 – 62.5)	0.9
Unknown	13	7	
Any cytopenia at apheresis, n (%)	53 (82%)	23 (88%)	0.5
Neutropenia at apheresis	15 (23%)	11 (42%)	0.067
Anemia at apheresis	34 (52%)	16 (62%)	0.4
Thrombocytopenia at apheresis	24 (37%)	11 (42%)	0.6
Any cytopenia at day -5, n (%)	54 (83%)	22 (85%)	>0.9
Neutropenia at day -5	16 (25%)	10 (38%)	0.2
Anemia at day -5	42 (65%)	18 (69%)	0.7
Thrombocytopenia at day -5	25 (38%)	10 (38%)	>0.9
CAR-HEMATOTOX score, n (%)			0.7
Low	38 (69%)	15 (65%)	
High	17 (31%)	8 (35%)	
Unknown	10	3	

Distribution of patient characteristics by any grade late ICAHT after day 30 using Wilcoxon rank sum test, Pearson's Chi-squared test, and Fisher's exact test for univariate analysis. P values ≤ 0.05 are represented in bold. LD: lymphodepletion chemotherapy. ECOG: Eastern Cooperative Oncology Group. R-ISS: Revised International Staging System. Double-refractory disease: Refractory to an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI). Triple-refractory disease: Refractory to an IMiD, PI and daratumumab. Penta-refractory disease: Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab.

Table S9. Multivariable analysis of risk factors associated with grade ≥ 3 cytopenia by CTCAE at day 90

Characteristic	N	Event N	OR[1]	95% CI[1]	p-value
(Intercept)	79	21	0.38	0.09, 1.67	0.2
High marrow burden (≥50%)	14	4	1.10	0.26, 3.92	0.9
Grade ≥ 3 cytopenia at day -5	14	4	1.11	0.27, 3.88	0.9
Number of prior lines of therapy	79	21	0.99	0.78, 1.22	>0.9

Exploratory multivariable logistic regression analysis of risk factors associated with grade ≥ 3 cytopenia at day 90, by CTCAE grading. Odds ratio (OR) and 95% confidence interval (CI) are shown for the association of each selected patient. No statistically significant risk factor was identified.

Table S10. Details of infections after cilta-cel

A. Infections in the first 30 days

Infection Type	Incidence, N = 31
Bacterial, n (%)	13 (42%)
Unspecified bacterial abscess	1
Unspecified bacterial pneumonia	2
Burkholderia species (*mycetohabitans rhizoxinica*) bacteremia	1
Clostridioides difficile colitis	2
Enterocolitis with pneumatosis	1
Klebsiella oxytoca bacteremia	1
Klebsiella pneumonia	1
MRSA bacteremia	1
MRSA pneumonia	1
Staphylococcus epidermidis central line associated bacteremia	1
VRE bacteremia	1
Fungal, n (%)	5 (16%)
Unspecified fungemia	1
Mold/rhizopus pneumonia	1
Thrush	3
Viral, n (%)	13 (42%)
Astrovirus gastroenteritis	1
Cytomegalovirus viremia	3
COVID-19	1
Parainfluenza virus	3
Rhinovirus +/- enterovirus	4
Respiratory syncytial virus	1

B. Infections day 31 – 100

Infection Type	Incidence, N = 32
Bacterial, n (%)	13 (41%)
Unspecified bacterial bronchitis	2
Unspecified bacterial folliculitis	1
Unspecified bacterial upper respiratory infection	3
Unspecified bacterial perirectal abscess	1
Unspecified bacterial pneumonia	1
Clostridioides difficile colitis	1
Pseudomonas aeruginosa bacteremia due to myositis	1
Pseudomonas aeruginosa bacteremia secondary to pneumonia/bronchiectasis	1
Streptococcus mitis bacteremia	1
Shiga-like toxin-producing e. coli colitis	1
Viral, n (%)	19 (59%)
Adenovirus	2
Cytomegalovirus viremia	1
COVID-19	2
Influenza A	1
Norovirus gastroenteritis	1
Progressive multifocal leukoencephalopathy due to JC virus	1
Rhinovirus +/- enterovirus	8
Respiratory syncytial virus	2
Varicella zoster virus (shingles)	1

C. Infections after day 100

Infection Type	Incidence, N = 25
Bacterial, n (%)	10 (40%)
Unspecified bacterial cellulitis	1
Unspecified bacterial cystitis	1
Unspecified bacterial pneumonia	3
Unspecified bacterial sinusitis	1
Unspecified periodontitis	1
Unspecified otitis	1
Haemophilus influenzae pneumonia	2
Viral	15 (60%)
COVID-19	4
Metapneumovirus	2
Parainfluenza	4
Rhinovirus +/- enterovirus	2
Respiratory syncytial virus	2
Unspecified viral upper respiratory infection	1

88 total infections occurred in 51 (49%) patients. There were 28 total severe infections in 15 patients. 6 patients experienced infection in the first 30 days then had another infection between days 31 - 100. A) In the first 30 days after cilta-cel, 31 infections occurred in 23 patients; 15 severe infections occurred in 9 patients. B) Between days 31 and 100, 32 infections occurred in 24 patients, with 10 severe infections occurred in 7 patients. C) After day 100, 25 infections occurred in 17 patients, 3 severe infections occurred in 3 patients.

Table S11. Association of severe infections with patient characteristics and clinical outcomes

Characteristic	Patients with severe Infection		
	No N = 85	Yes N = 20	p-value
Age (years), Median (Range)	63 (30 – 76)	64 (33, 75)	0.8
≥ 70 years	19 (22%)	4 (20%)	>0.9
Male Sex, n (%)	42 (49%)	16 (80%)	**0.013**
Extramedullary disease, n (%)	24 (29%)	7 (35%)	0.6
Unknown	1	0	
High marrow burden (≥50%), n (%)	14 (17%)	4 (20%)	0.7
Unknown	3	0	
ECOG status at LD, n (%)			**0.012**
0-1	81 (98%)	16 (80%)	
≥ 2	2 (2.4%)	4 (20%)	
Unknown	2	0	
R-ISS at CAR-T infusion, n (%)			0.2
I	19 (26%)	2 (11%)	
II	36 (49%)	8 (44%)	
III	18 (25%)	8 (44%)	
Unknown	12	2	
High risk cytogenetics (not including gain 1q), n (%)	34 (49%)	9 (50%)	>0.9
Unknown	15	2	
High risk cytogenetics (including gain 1q), n (%)	52 (73%)	12 (67%)	0.6
Unknown	14	2	
Number of prior lines of therapy, Median (Range)	5 (3 – 15)	5.5 (4 – 10)	0.6
> 4, n (%)	55 (65%)	15 (75%)	0.4
Bridging Therapy, n (%)	73 (86%)	18 (90%)	>0.9
Prior autoSCT, n (%)	73 (86%)	15 (75%)	0.3
Prior BCMA-directed therapy, n (%)	8 (9.4%)	1 (5.0%)	>0.9
Refractory to Immunomodulatory agent, n (%)	75 (88%)	16 (80%)	0.5
Refractory to Proteasome Inhibitor, n (%)	74 (87%)	17 (85%)	0.7
Refractory to Daratumumab or Isatuximab, n (%)	77 (91%)	19 (95%)	>0.9
Double-refractory, n (%)	67 (79%)	15 (75%)	0.8
Triple-refractory, n (%)	62 (73%)	15 (75%)	0.9
Penta-refractory, n (%)	21 (25%)	7 (35%)	0.3
Eligible for CARTITUDE trial, n (%)	38 (45%)	9 (45%)	>0.9
Total cell dose (million cells), Median (Range)	0.6 (0.1 – 0.9)	0.6 (0.42 – 0.7)	0.6
Granulocyte colony stimulating factor (G-CSF), n (%)	54 (64%)	14 (70%)	0.6
CD34 stem cell boost, n (%)	7 (8.2%)	3 (15%)	0.4
Intravenous immunoglobulin (IVIG), n (%)	43 (51%)	12 (60%)	0.4
CRS Maximum Grade, n (%)			**0.036**
No CRS	24 (28%)	1 (5.0%)	
Grade 1 or 2	59 (69%)	18 (90%)	
Grade ≥3	2 (2.4%)	1 (5.0%)	
ICANS Maximum Grade, n (%)			0.072
No ICANS	76 (89%)	15 (75%)	
Grade 1 or 2	8 (9.4%)	3 (15%)	
Grade ≥3	1 (1.2%)	2 (10%)	
Delayed Neurotoxicity, n (%)	8 (9.4%)	6 (30%)	**0.025**
Treatment for toxicity, n (%)			
Steroid Use	30 (35%)	12 (60%)	**0.042**
Tocilizumab Use	45 (53%)	14 (70%)	0.2
Anakinra Use	3 (3.5%)	4 (20%)	**0.024**

Distribution of severe infections by patient baseline characteristics and clinical outcomes using Wilcoxon rank sum test, Pearson's Chi-squared test, and Fisher's exact test for univariate analysis. P values ≤ 0.05 are represented in bold. LD: lymphodepletion chemotherapy. ECOG: Eastern Cooperative Oncology Group. R-ISS: Revised International Staging System. Double-refractory disease: Refractory to an immunomodulatory agent (IMiD) and a proteasome inhibitor (PI). Triple-refractory disease: Refractory to an IMiD, PI and daratumumab. Penta-refractory disease: Refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib and daratumumab. CRS: Cytokine release syndrome. ICANS: Immune effector cell-associated neurotoxicity syndrome.

Table S12. Association of severe infections with cell counts and immunoglobulin levels

Characteristic	Patients with severe Infection		p-value
	No N = 85	**Yes** N = 20	
CD4 count at apheresis, Median (Range)	270 (79 – 843)	241 (73 – 465)	0.3
Unknown	48	8	
CD8 count at apheresis, Median (Range)	304 (75 – 1,295)	470 (30 – 1,608)	0.7
Unknown	48	8	
CD19 count at apheresis, Median (Range)	14 (1 – 303)	9.5 (1 – 193)	0.7
Unknown	48	8	
IgG at day -5, Median (Range)	590 (109 – 9,976)	296 (109 – 4,020)	0.2
Unknown	40	7	
IgA at day -5, Median (Range)	9 (2 – 1,216)	14 (2 – 2,526)	0.5
Unknown	41	7	
IgM at day -5, Median (Range)	7 (5 – 84)	5 (5 – 27)	0.6
Unknown	41	7	
WBC at day -5, Median (Range)	4.0 (0.7 – 8.9)	4.8 (1.7 – 10.2)	0.15
ANC at day -5, Median (Range)	2.4 (0.0 – 6.9)	2.9 (0.6 – 7.7)	0.3
CAR-HEMATOTOX score, n (%)			0.052
Low	49 (69%)	8 (44%)	
High	22 (31%)	10 (56%)	
Unknown	14	2	
IgG at day 90, Median (Range)	368 (101 – 1,243)	347 (123 – 459)	0.5
Unknown	13	10	
IgA at day 90, Median (Range)	1 (1 – 64)	1 (1 – 16)	**0.014**
Unknown	14	10	
IgM at day 90, Median (Range)	2 (2 – 27)	2 (2 – 16)	>0.9
Unknown	14	10	
WBC at day 90, Median (Range)	3.6 (1.0 – 9.2)	3.6 (1.1 – 8.2)	0.8
Unknown	9	5	
ANC at day 90, Median (Range)	2.0 (0.1 – 7.1)	1.8 (1.0 – 5.1)	0.9
Unknown	9	5	
CD4 count at day 90, Median (Range)	176 (50 – 479)	146 (75 – 932)	0.7
Unknown	38	13	
CD8 count at day 90, Median (Range)	325.5 (50 – 1,992)	211 (47 – 516)	0.11
Unknown	39	13	
CD19 count at day 90, Median (Range)	6 (0 – 152)	0 (0 – 99)	0.10
Unknown	14	2	

Distribution of severe infections by cell counts and immunoglobulin levels using Wilcoxon rank sum test, Pearson's Chi-squared test, and Fisher's exact test for univariate analysis. P values ≤ 0.05 are represented in bold. WBC: White blood cell. ANC: Absolute neutrophil count.

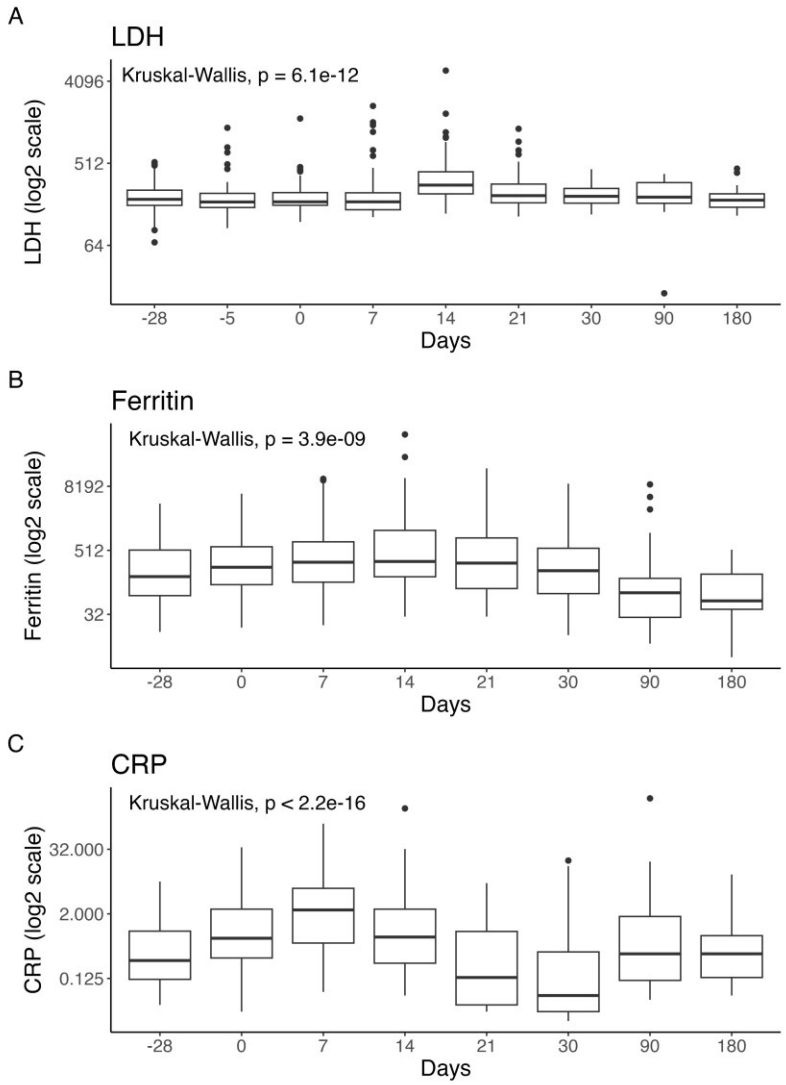
Table S13: Causes of Death

Cause of Death	Total Deaths, N = 16 (100%)
Myeloma Progression	6 (38%)
Infection	5 (31%)
Non-ICANS delayed Neurotoxicity	3 (19%)
Cytokine Release Syndrome	1 (6%)
IEC-HS	1 (6%)

IEC-HS, Immune Effector Cell-Associated Hemophagocytic Lymphohistiocytosis-Like Syndrome; ICANS, Immune effector cell-associated neurotoxicity syndrome

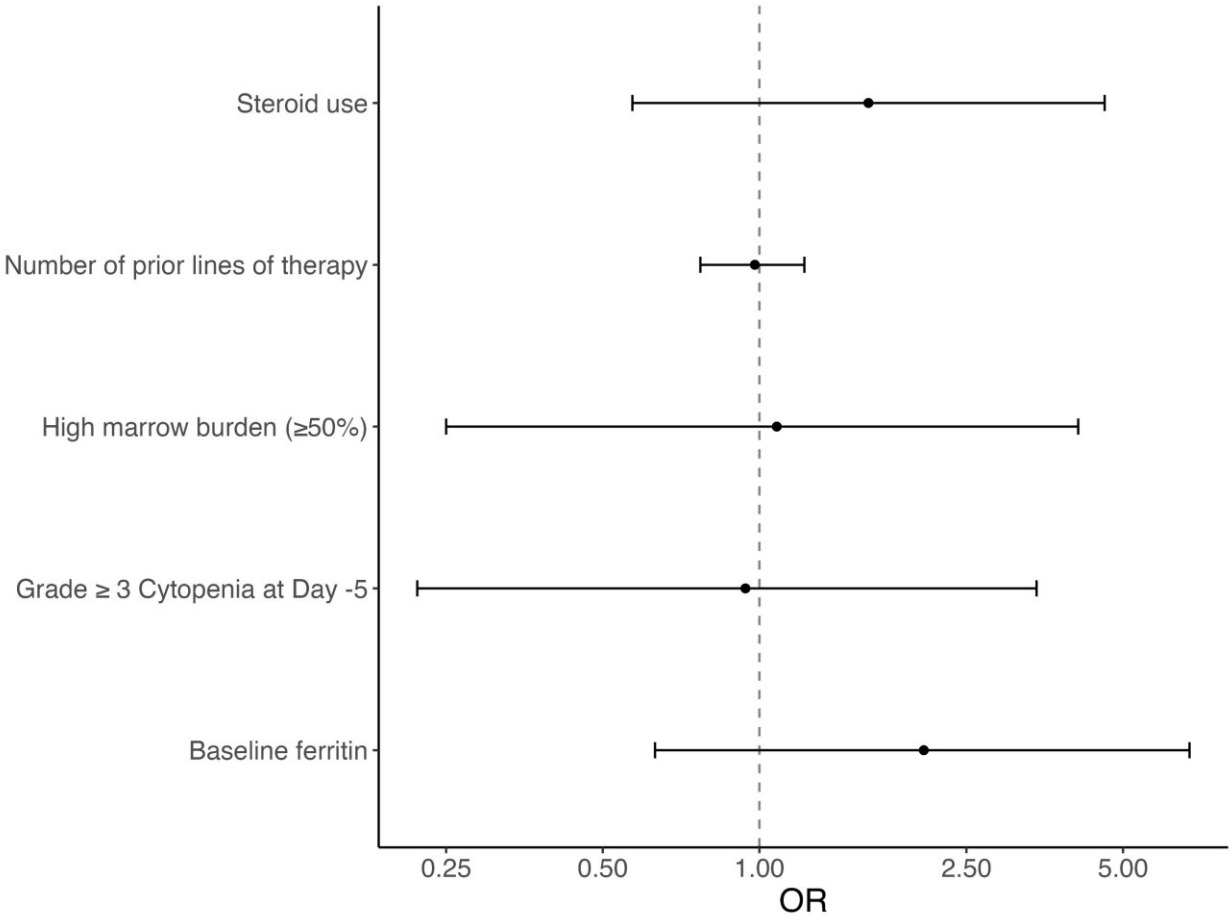
SUPPLEMENTARY FIGURES

Figure S1. Inflammatory markers after cilta-cel



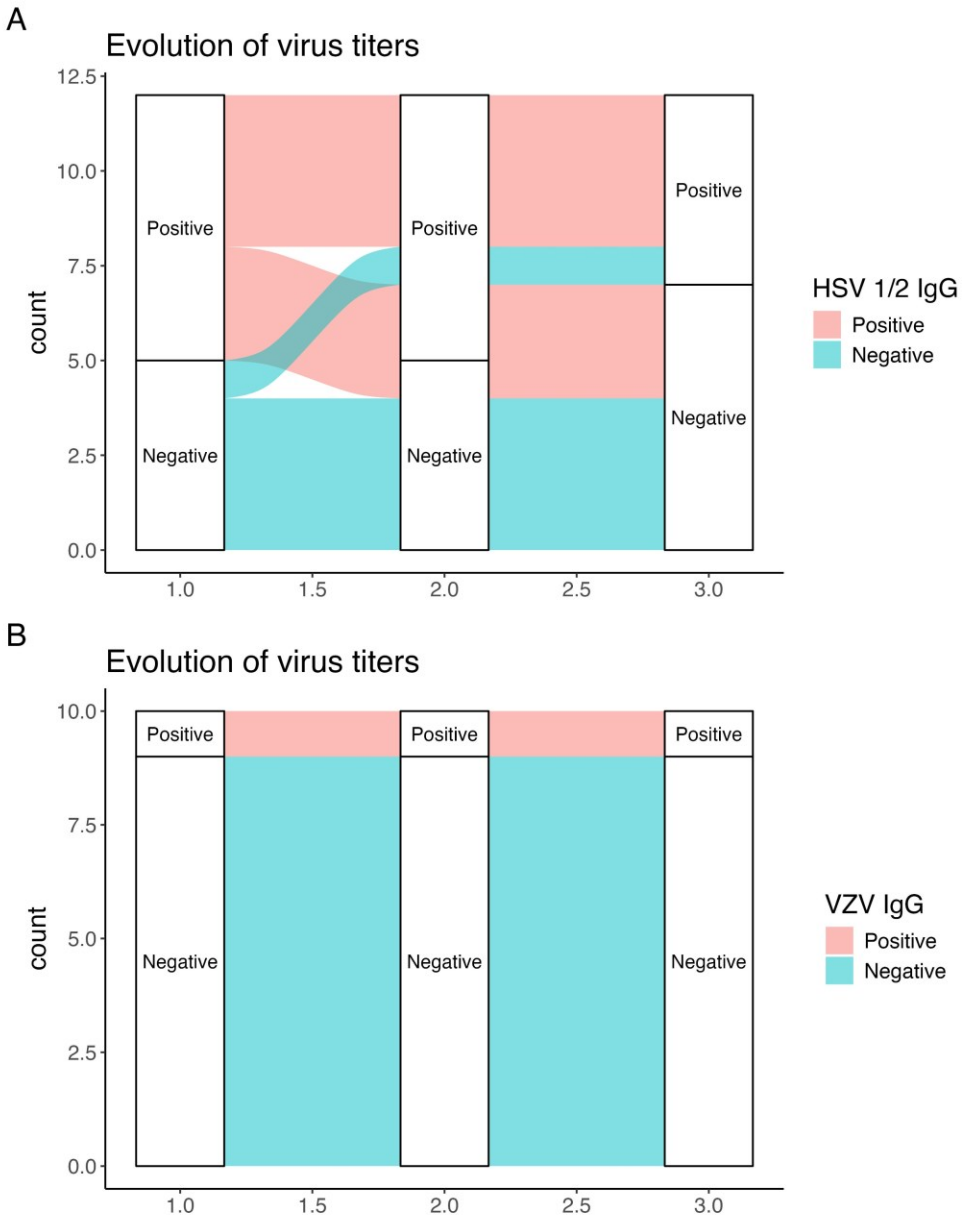
Box and whisker plots for inflammatory markers with Kruskal-Wallis rank sum tests for P-values. Trends from apheresis to day 180, represented with a $\log_2$ scale, for: A) Lactate dehydrogenase (LDH); B) Ferritin; and C) C-reactive protein (CRP). All were clinically significant with $P < 0.001$.

Figure S2. Forest plot for multivariable analysis of grade ≥ 3 cytopenia by CTCAE at day 90



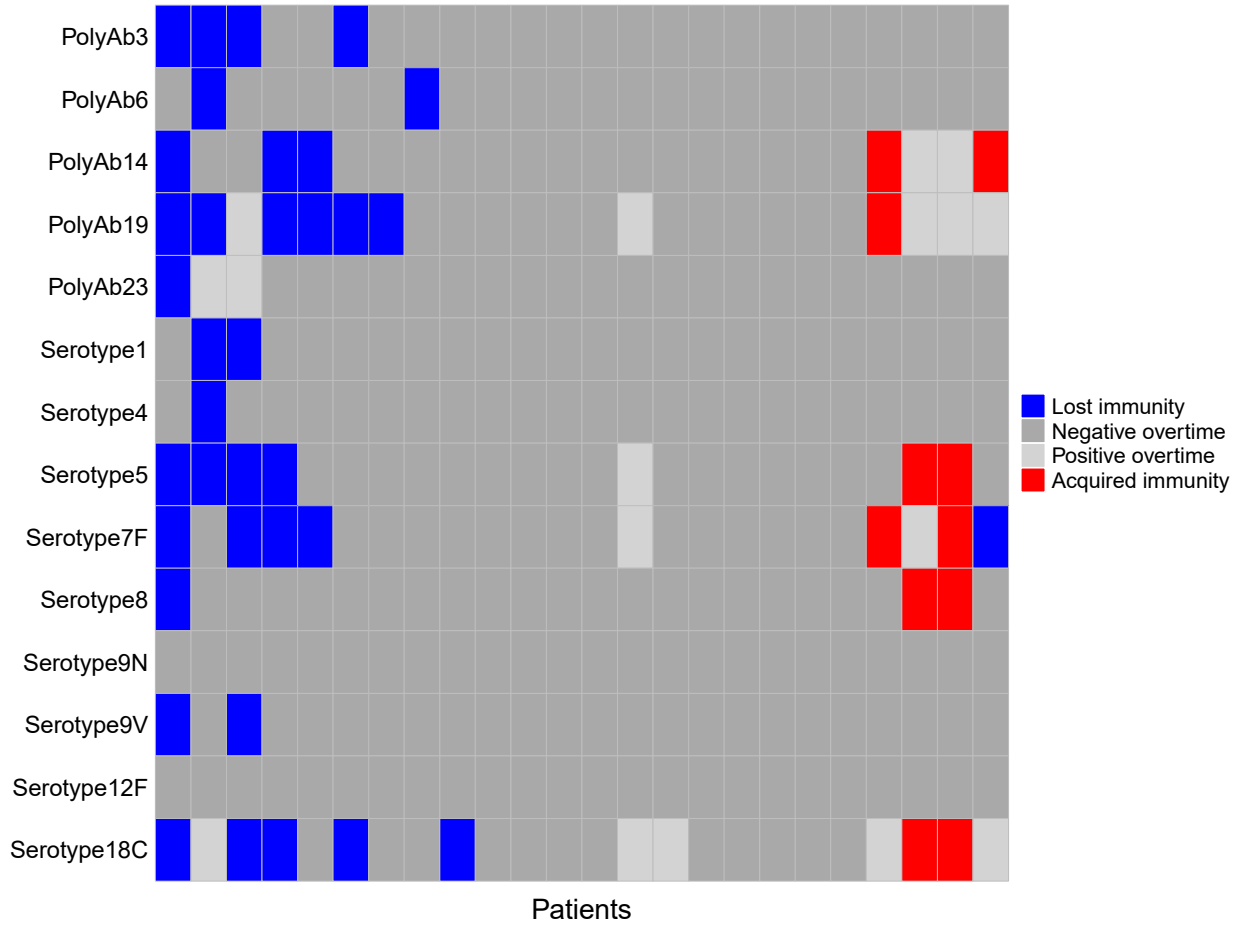
Forest plot of the association of selected patient characteristics with grade ≥ 3 cytopenia at day 90, by CTCAE grading. Actual values for odds ratio (OR) and 95% confidence interval (CI) for each characteristic are provided in Table S9.

Figure S3. Evolution of viral immunity after cilta-cel



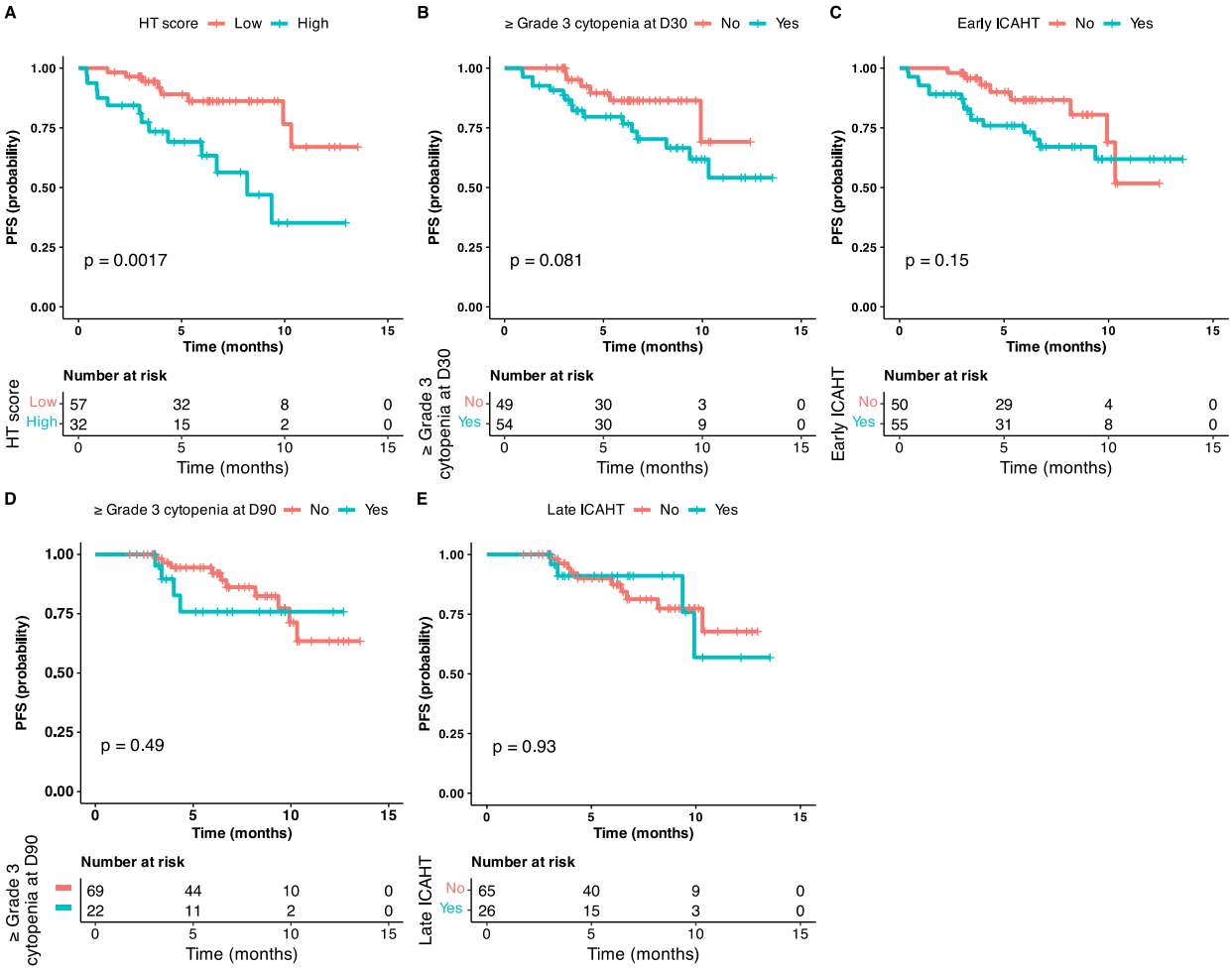
Alluvial plots for evolution of viral immunity. A) Comparison of paired HSV 1/2 IgG antibodies from apheresis, day 90, and day 180, N = 24. Per clinical lab definitions a titer ≤ 0.89 was considered negative and ≥ 1.10 was considered positive. While titers ≥ 0.90 and ≤ 1.09 would have been considered indeterminate, there were no patients with indeterminate values. 12 patients did not have data at day 180. B) Comparison of paired VZV IgG antibodies from apheresis, day 90, and day 180, N = 24. Results were reported as positive, negative, or equivocal. Due to inability to categorize equivocal as truly positive or negative, 3 patients with equivocal results at apheresis and/or day 90 were excluded from this analysis. 11 patients did not have data at day 180.

Figure S4. Evolution of pneumococcal immunity after cilta-cel



Heat map for evolution of pneumococcal immunity. Comparison of 14 separate paired pneumococcal IgG antibody titers from apheresis and day 90, N = 24. Each column represents a patient. Per the clinical lab definition an antibody concentration > 1.0 ug/mL was considered long-term protection (immunity).

Figure S5. Survival analysis by cytopenia grading



Progression free survival (PFS) by the different grading systems for hematologic toxicity. Kaplan-Meier PFS curves depict differences in survival of the patients by (A) CAR-HEMATOTOX score (low versus (vs) high); (B) CTCAE grade ≥ 3 cytopenia at day 30 (no vs yes); (C) Early immune effector cell-associated hematotoxicity (ICAHT) (no vs yes); (D) CTCAE grade ≥ 3 cytopenia at day 90 (no vs yes); and (E) Late ICAHT (no vs yes). Only the CAR-HEMATOTOX score showed a statistically significant difference in PFS (P=0.0017).

Figure S6. Non-relapse mortality