MELVIN AND BREN SIMON
CANCER CENTER

INDIANA UNIVERSITY

Managing Side Effects of CART and Bispecific therapies

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CAR T cells are genetically modified to bind to tumor-associated antigens on target cells to induce cell death[1,2]

CARs are **fusion proteins** that have **a tumor-associated antigen-targeted recognition region** and a **co-stimulation domain**[1,2]

BCMA-directed CAR T cells are genetically modified T cells that express a CAR with an anti-BCMA recognition region[1,2]

CAR T cells **recognize** tumor-associated antigens in an **MHC-independent manner**[2]

Upon CAR T cell binding to the antigen, T-cell activation is initiated, resulting in multiple myeloma cell lysis and death[1]

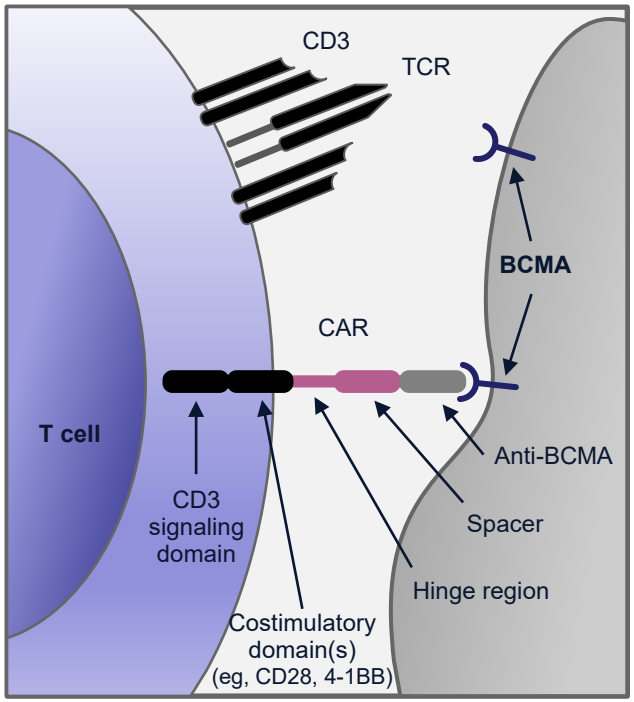


Figure adapted from Shah N, et al. *Leukemia*. 2020;34:985-1005.

BCMA=B-cell maturation antigen; CAR=chimeric antigen receptor; CD=cluster of differentiation; MHC=major histocompatibility complex; **TCR=T-cell receptor.**

1. Shah N, et al. *Leukemia.* 2020;34:985-1005. 2. Cho SF, et al. *Front Immunol.* 2018;9:1821.

Clinical aspects of tumor antigen-directed CAR T-cell therapy[1-3]

Key mechanistic feature

Combines **target specificity of mAbs** with the **cytotoxicity of T cells**[1]

Production

Autologous T cells are collected from the patient, modified to express the CAR, and expanded ex vivo. May take **1 to 2 months** before patient receives therapy[1-5]

Administration

Currently administered as a **one-time intravenous dose**[1,6]

BCMA=B-cell maturation antigen; CAR=chimeric antigen receptor; mAb=monoclonal antibody.

1. Kleber M, et al. *J Clin Med.* 2021;10(18):4088. 2. Shah N, et al. *Leukemia.* 2020;34(4):985-1005. 3. Penn Medicine News. https://www.pennmedicine.org/news/news-releases/2022/march/penn-researchers-shorten-manufacturing-time-for-car-t-cell-therapy. Published March 29, 2022. Accessed December 1, 2022. **4.** Advisory Board Daily Briefing. https://www.advisory.com/daily-briefing/2022/06/03/car-t-therapy Published June 3, 2022. Accessed December 2, 2022. **5.** Tully S, et al. *JCO Clinical Cancer Informatics.* 2019;3:1-9. **6. Institute for Clinical and Economic Review. https://icer.org/wp-content/uploads/2020/10/ICER_Multiple-Myeloma_Final-Report_Unredacted_112222.pdf. Accessed November 29, 2022.**

Bispecific antibodies (BsAbs) drive interaction between malignant cells and immune effector cells[1-3]

BsAbs **engage BCMA on MM cells and CD3 on T cells,** bringing T cells into close proximity to MM cells[1,2]

Recruitment of cytotoxic T cells to MM cells **leads to formation of a cytolytic synapse**[3]

Cytolytic enzymes are released with the **ability to induce tumor cell lysis**[1,3]

BsAbs act independently of the MHC, generating a robust T-cell response, activating cytotoxic CD8+ T cells as well as regulatory and helper CD4+ T cells, **without the need for co-stimulatory molecules**[1,3]

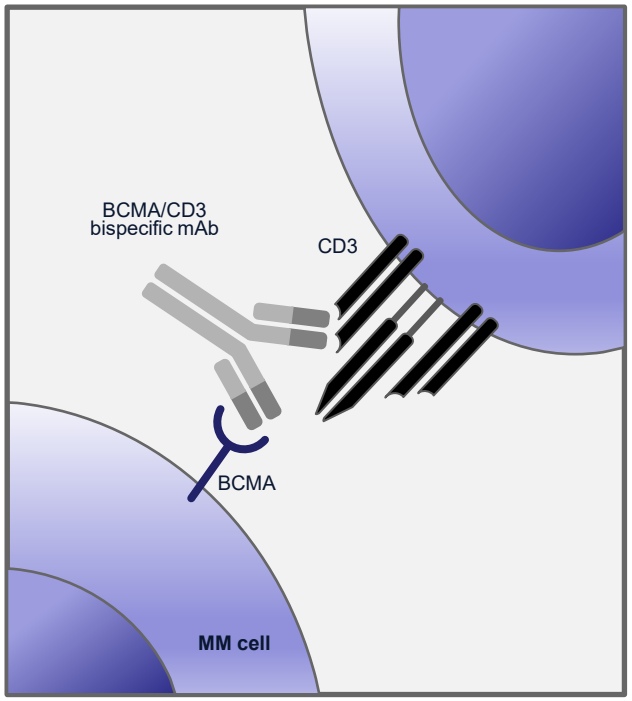


Figure adapted from Shah N, et al. *Leukemia*. 2020;34:985-1005.

BCMA=B-cell maturation antigen; CD=cluster of differentiation; mAb=monoclonal antibody; MHC=major histocompatibility complex; MM=multiple myeloma.

1. Caraccio C, et al. *Front Immunol*. 2020;11:501. 2. Nadeem O, et al. *Immunotargets Ther*. 2020;9:201-215. 3. Abramson HN. *Int J Mol Sci*. 2020;21:5192.

Updated Results From CARTITUDE-1: Phase 1b/2 Study of Ciltacabtagene Autoleucel, a B-cell Maturation Antigen–Directed Chimeric Antigen Receptor T Cell Therapy, in Patients With Relapsed/Refractory Multiple Myeloma

Thomas Martin[1*], Saad Z Usmani[2], Jesus G Berdeja[3], Andrzej Jakubowiak[4], Mounzer Agha[5], Adam D Cohen[6], Parameswaran Hari[7], David Avigan[8], Abhinav Deol[9], Myo Htut[10], Alexander Lesokhin[11], Nikhil C Munshi[12], Elizabeth O'Donnell[13], A Keith Stewart[14], Jordan M Schecter[15], Jenna D Goldberg[15], Carolyn C Jackson[15], Tzu-Min Yeh[15], Arnob Banerjee[16], Alicia Allred[16], Enrique Zudaire[16], William Deraedt[17], Deepu Madduri[15], Yunsi Olyslager[17], Changwei Zhou[18], Lida Pacaud[18], Yi Lin[19], Sundar Jagannath[20]

[1]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [2]Levine Cancer Institute, Charlotte, NC, USA; [3]Sarah Cannon Research Institute, Nashville, TN, USA; [4]University of Chicago, Chicago, IL, USA; [5]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [6]Abramson Cancer Center, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA; [7]Medical College of Wisconsin, Milwaukee, WI, USA; [8]Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA; [9]Karmanos Cancer Institute, Wayne State University, Detroit, MI, USA; [10]City of Hope Comprehensive Cancer Center, Duarte, CA, USA; [11]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [12]Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [13]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [14]University Health Network and the Princess Margaret Cancer Centre, Toronto, ON, Canada; [15]Janssen R&D, Raritan, NJ, USA; [16]Janssen R&D, Spring House, PA, USA; [17]Janssen R&D, Beerse, Belgium; [18]Legend Biotech USA, Piscataway, NJ, USA; [19]Mayo Clinic, Rochester, MN, USA; [20]Mount Sinai Medical Center, New York, NY, USA

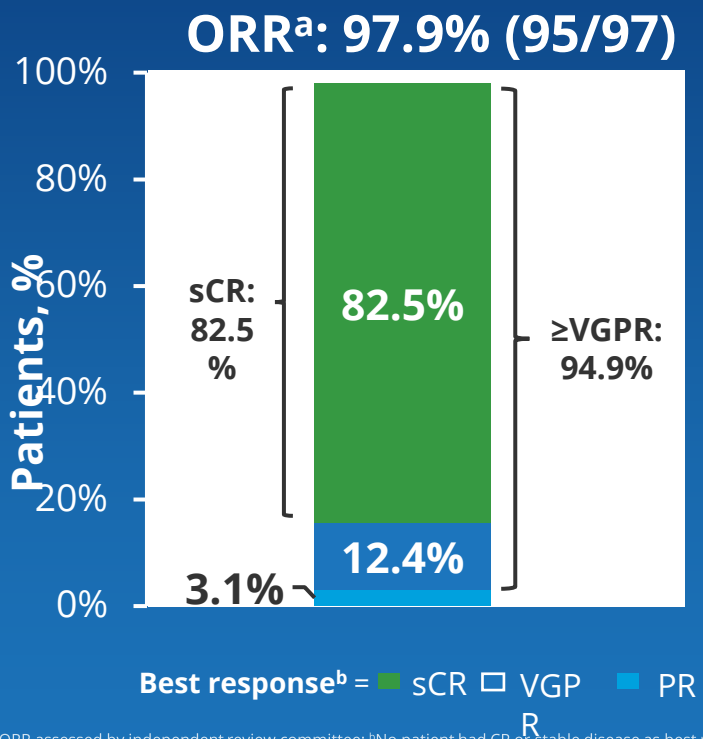
*Presenting author.

Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

Additional information can be viewed by scanning the QR code or accessing this link: https://www.oncologysciencehub.com/ASH2021/Cilta-cel/ThomasMartin

CARTITUDE-1: Efficacy Response

- Med prior lines =6
- No new safety signals; MNT incidence has decreased to 0.5% in CARTITUDE program



Responses deepened over time from the 1-year follow-up

Best response at any time	Median–1 year follow-up	Median–2 years follow-up
sCR, %	67	83

- Median time to first response was 1 month (range, 0.9–10.7)
- Median time to best response was 2.6 months (range, 0.9–17.8)
- Median time to CR or better was 2.9 months (range, 0.9–17.8)
- Median duration of response was not estimable (21.8 months–NE)

[a]ORR assessed by independent review committee; [b]No patient had CR or stable disease as best response.
CR, complete response; NE, not estimable; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

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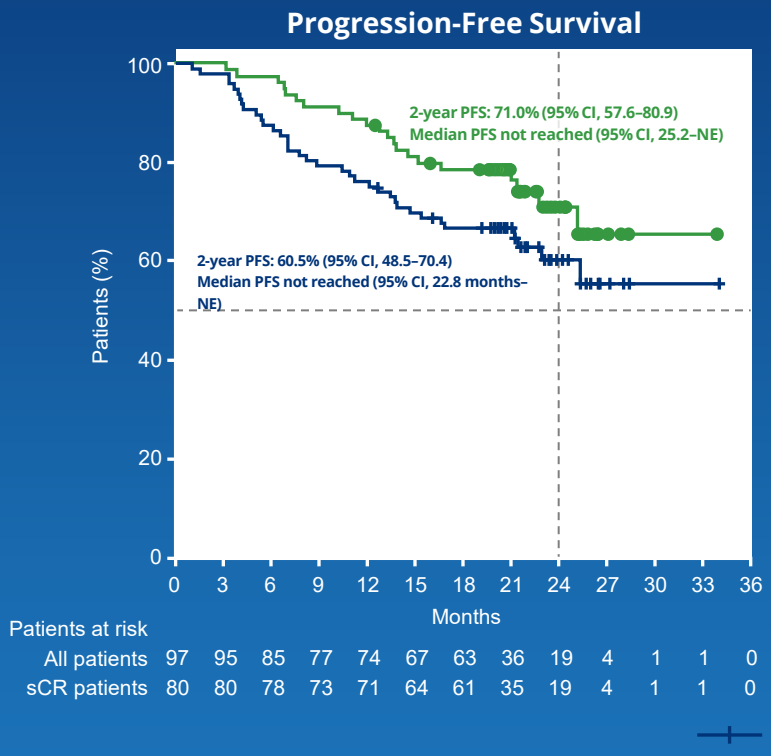
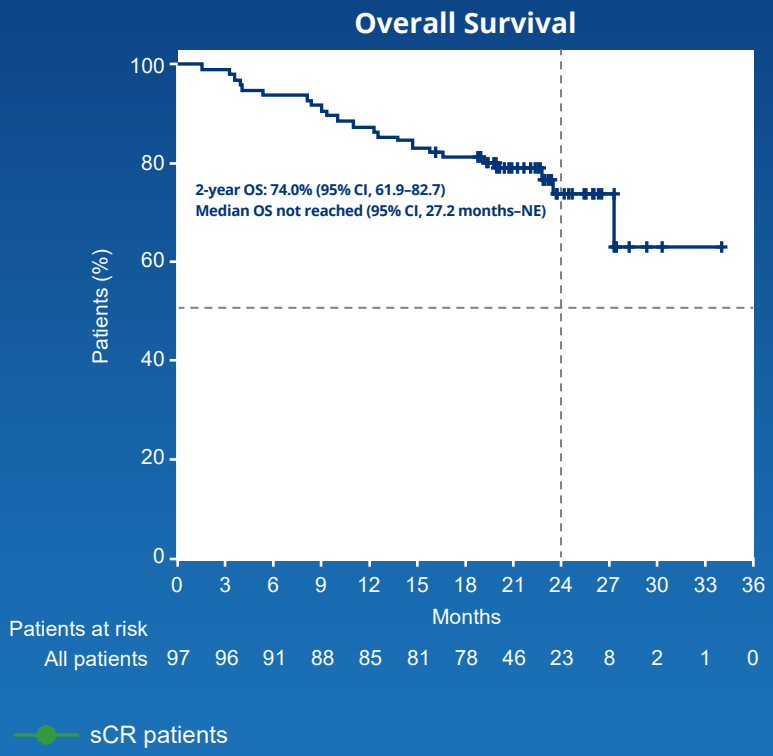
CARTITUDE-1: Progression-Free Survival and Overall Survival





All patients sCR patients

MRD, minimal residual disease; NE, not estimable; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response

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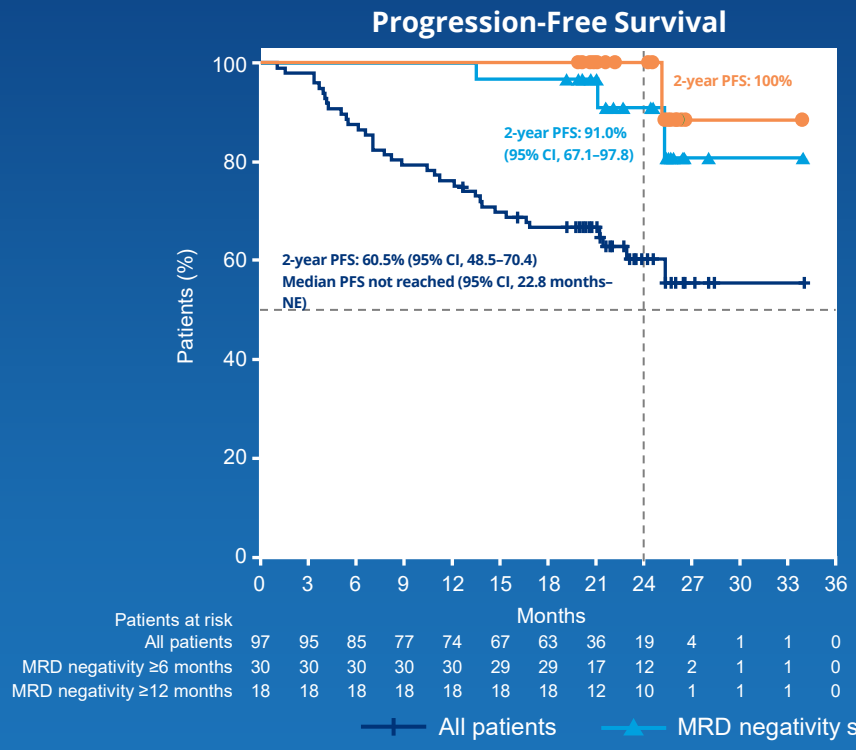
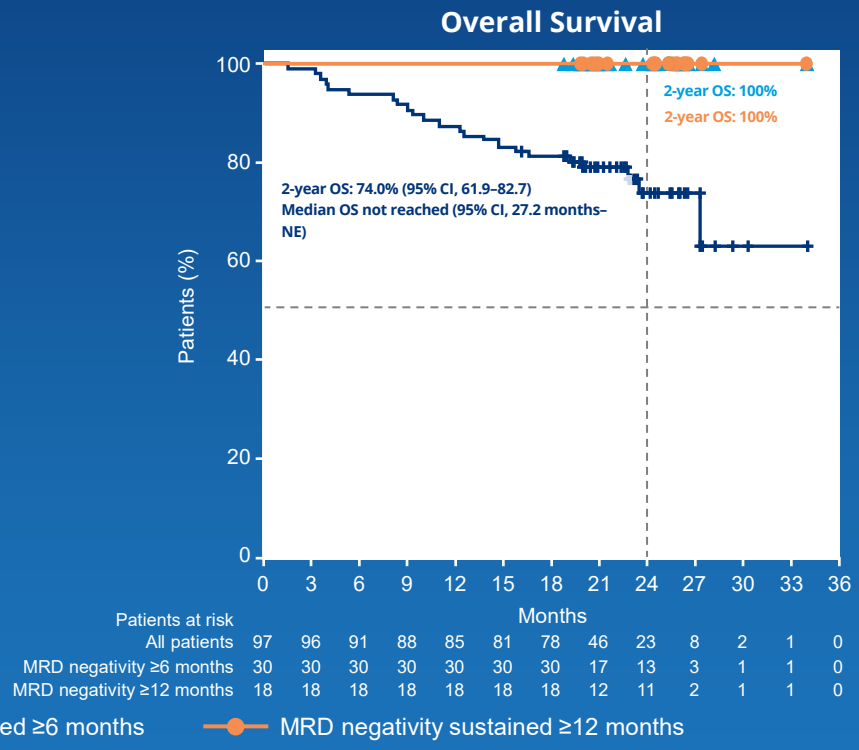
CARTITUDE-1: Progression-Free Survival and Overall Survival by MRD Negativity (10^{-5}) sustained for ≥ 6 and 12 months

- Of the 61 patients evaluable for MRD, 92% were MRD-negative (at 10^{-5})





All patients | MRD negativity sustained ≥6 months | MRD negativity sustained ≥12 months

MRD, minimal residual disease; OS, overall survival; PFS, progression-free survival

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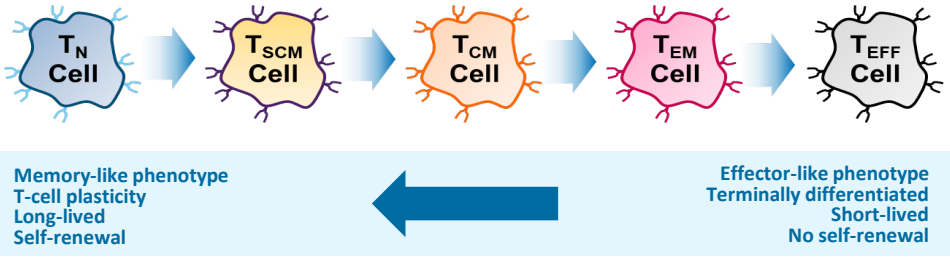
Updated clinical and correlative results from the Phase I CRB-402 study of the BCMA-targeted CAR T cell therapy bb21217 in patients with relapsed and refractory multiple myeloma

Noopur Raje, MD[1], Nina Shah, MD[2], Sundar Jagannath, MD[3], Jonathan L. Kaufman, MD[4], David S. Siegel, MD PhD[5], Nikhil Munshi, MD[6], Jacalyn Rosenblatt, MD[7], Yi Lin, MD, PhD[8], Andrzej Jakubowiak, MD, PhD[9], Alison Timm, MA[10], Ashish Yeri, PhD[10], Nathan Martin, PhD[11], Timothy B. Campbell, MD PhD[11], Olivia Finney, PhD[10], Anna Truppel-Hartmann, MD[10], Fabio Petrocca, MD[10] Jesus G Berdeja, MD[12] and Melissa Alsina, MD[13]

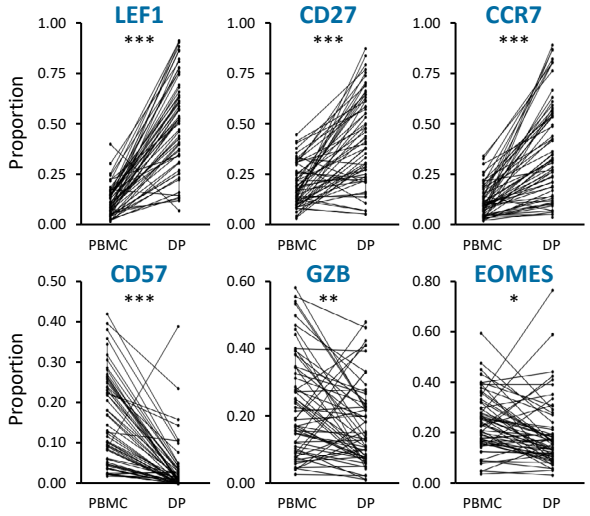
[1]Cancer Center, Massachusetts General Hospital, Boston, MA [2]University of California San Francisco, San Francisco, CA; TN [3]Mount Sinai Hospital, New York, NY; [4]Winship Cancer Institute / Department of Hematology and Medical Oncology, Emory University School of Medicine, Atlanta, GA [5]Myeloma Division, John Theurer Cancer Center, Hackensack University Medical Center, Hackensack, NJ; [6] Dana-Farber Cancer Institute, Boston, MA; [7]Beth Israel Deaconess Medical Center, Boston, MA; [8]Division of Hematology, Mayo Clinic, Rochester, MN; [9]University of Chicago Medicine, Chicago, IL; [10]2seventy bio Inc, Cambridge MA; [11] Bristol Myers Squibb Company, Princeton, NJ; [12]Sarah Cannon Research Institute, Nashville, [13] Department of Blood and Marrow Transplantation and Cellular Immunotherapy, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

bb21217: Anti-BCMA CAR T Cell Therapy Product for Multiple Myeloma

- bb21217 uses the same CAR molecule as bb2121,[1] but is cultured with the PI3K inhibitor, bb007, to enrich for T cells displaying a memory-like phenotype
- CAR T cells enriched for this phenotype may persist and function for longer than non-enriched CAR T cells[2]
- Hypothesized that persistence of functional CAR T cells after infusion may be one determinant of duration of response



bb21217 Process Enriches Drug Product for T Cells Displaying Memory-Like Phenotype[3]



N=59

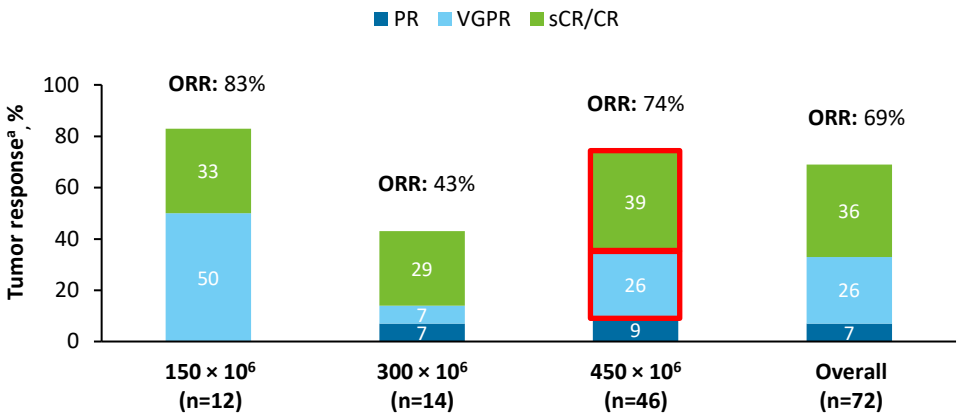
*** $P<0.001$; ** $0.001 < P < 0.01$; * $0.01 < P < 0.05$

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CCR7, C-C chemokine receptor type 7; DP, drug product; EOMES, eomesodermin; GZB granzyme B; LEF, Lymphoid enhancer binding factor; PI3K, phosphoinositide 3 kinase; $T_{CM}/T_{EFF}/T_{EM}/T_N/T_{SCM}$, central memory/effector/effector memory/naïve/stem cell memory T cell; PBMC, peripheral blood mononuclear cell

1. Friedman KM, et al. *Hum Gene Ther.* 2018;29:585–601; 2. Fraietta JA, et al. *Nat Med*. 2018;24:563–571; 3. Alsina M, et al. Presented at ASH 2020; Abstract #130.

Tumor Response and MRD Status

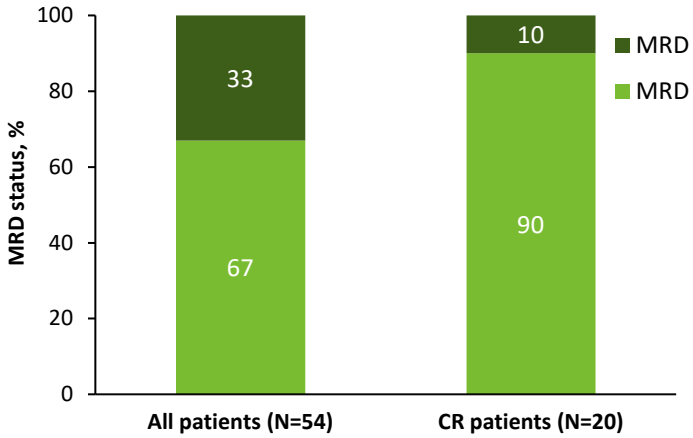
prior lines = 6
CRS = 75%, neurotox = 15%



	150 × 10⁶ (n=12)	300 × 10⁶ (n=14)	450 × 10⁶ (n=46)	Overall (n=72)
Median follow-up (min, max), mo	24.6 (4, 41)	11.9 (3, 30)	10.9 (<1, 28)	12.1 (<1, 41)
Median time to first response (min, max), mo				
≥PR	1.0 (1, 2)	1.0 (1, 1)	1.0 (1, 2)	1.0 (1, 2)
≥CR	4.4 (1, 10)	13.0 (3, 28)	3.1 (1, 15)	3.6 (1, 28)

Patients in the 450 group treated with bb21217 produced using an updated manufacturing process (n=32) had similar ORR (**81%**) and CR (**41%**) to that of the 450 group as a whole.

MRD status at 10^{-5} sensitivity[b]



47% of MRD negative patients sustained MRD negativity at mo 9

72% of MRD negative patients with CR sustained MRD negativity at mo 9

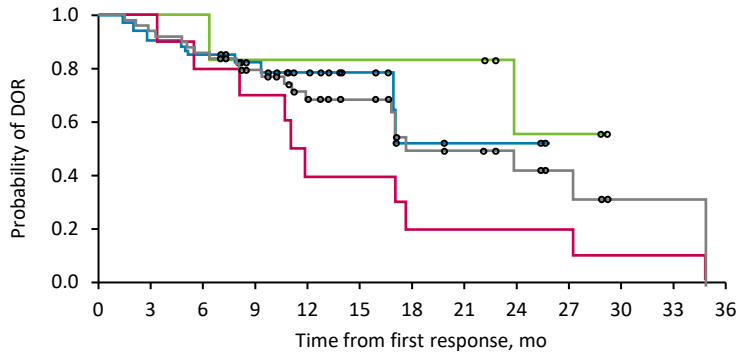
CAR, chimeric antigen receptor; CR, complete response; mo, month; MRD, minimal residual disease; ORR, objective response rate; PD, progressive disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
[a]Response confirmed by a consecutive response of the same category or better. Includes subjects whose response is recorded as "inevaluable" or "not done"; [b]Among evaluable patients. MRD assessment by Adaptive next-generation sequencing;

Data cut-off: 16JUL2021

Duration of Response

Duration of Response by Dose

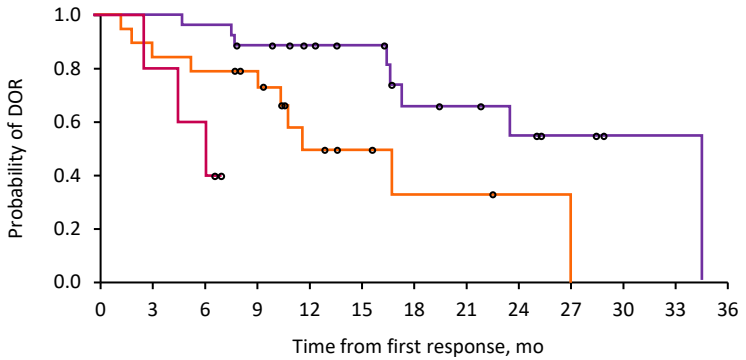
Dose	N	Events	Median DOR (95% CI), mo
150 × 10^6	10	10	11.5 (3.3–17.6)
300 × 10^6	6	2	NE (6.4–NE)
450 × 10^6	34	9	NE (16.8–NE)
Overall	50	21	23.8 (16.8–NE)



At risk:													
150 × 10^6	10	10	8	7	4	4	2	2	2	2	1	1	0
300 × 10^6	6	6	6	5	5	5	5	5	2	2	0	0	0
450 × 10^6	34	31	29	21	13	8	3	2	2	0	0	0	0
Overall	50	47	43	33	22	17	10	9	6	4	1	1	0

Duration of Response by Best Response

Dose	N	Events	Median DOR (95% CI), mo
sCR/CR	26	8	34.8 (17.0–NE)
VGPR	19	10	11.9 (9.4–NE)
PR	5	3	6.4 (2.9–NE)



At risk:													
sCR/CR	26	26	25	20	16	13	8	7	5	3	1	1	0
VGPR	19	17	15	13	6	4	2	2	1	1	0	0	0
PR	5	4	3	0	0	0	0	0	0	0	0	0	0

Median PFS (Overall): 12.8 months (95% CI 7.3–18.6); **Recommended P2 dose (450 x 10^6 CAR+ T cells):** 18.0 months (95% CI 6.0–NE)

CI, confidence interval; DOR, duration of response; mo, month; NE, not estimable; PFS progression free survival.

Data cut-off: 16JUL2021

Beyond BCMA??

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Phase I First-in-Class Trial of MCARH109, a G Protein Coupled Receptor Class C Group 5 Member D (GPRC5D) Targeted CAR T Cell Therapy in Patients with Relapsed or Refractory Multiple Myeloma

Sham Mailankody, Claudia Diamonte, Lisa Fitzgerald, Peter Kane, Xiuyan Wang, Devanjan Sikder, Brigitte Sénéchal, Vladimir Bermudez, Diana Frias, Justina Morgan, Patrick Grant, Terence Purdon, Kinga Hosszu, Sean Devlin, Urvi Shah, Jonathan Landa, Alexander Lesokhin, Neha Korde, Hani Hassoun, Carlyn Tan, Malin Hultcrantz, Gunjan Shah, Heather Landau, David Chung, Michael Scordo, Mikhail Roshal, Ola Landgren, Ahmet Dogan, Sergio Giralt, Jae Park, Isabelle Rivière, Renier Brentjens, Eric L. Smith

ASH Annual Meeting 2021; Abstract 827

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Baseline Characteristics (n=17)

	25 X10^6 CAR+ T cells (n=3)	50 X10^6 CAR+ T cells (n=3)	150 X10^6 CAR+ T cells (n=6)	450 X10^6 CAR+ T cells (n=5)	Total (N=17)
Median (range) age, years (range)	60 (38-76)	50 (39-56)	59 (40-74)	65 (63-73)	60 (38-76)
Male, n (%)	2 (67)	3 (100)	4 (67)	4 (80)	13 (77)
High-risk cytogenetics, n (%)*	3 (100)	2 (67)	3 (60)	5 (100)	13 (77)
Extramedullary plasmacytoma, n (%)	3 (100)	1 (33)	3 (50)	0 (0)	7 (41)
Non-secretory myeloma	2 (67)	0 (0)	1 (20)	0 (0)	3 (18)
Prior Lines of Therapy, median (range)	6 (6-8)	7 (4-8)	7 (5-14)	6 (5-12)	6 (4-14)
Refractory to last line, n (%)	3 (100)	3 (100)	5 (83)	3 (60)	14 (82)
Penta-exposed, n (%)	3 (100)	3 (100)	6 (100)	5 (100)	17 (100)
Triple-refractory, n (%)	3 (100)	3 (100)	6 (100)	4 (80)	16 (94)
Prior Autologous Transplant, n (%)	3 (100)	3 (100)	6 (100)	5 (100)	17 (100)
Prior Allogeneic Transplant, n (%)	0 (0)	2 (67)	1 (0)	0 (0)	3 (18)
Prior BCMA therapy, n (%)**	1 (33)	1 (33)	4 (67)	4 (80)	10 (59)
Prior CART therapy, n (%)	0 (0)	1 (33)	3 (50)	4 (80)	8 (47)
Bridging therapy, n (%) **Refractory to bridging, n (%)**	3 (100) 3 (100)	3 (100) 3 (100)	6 (100) 5 (83)	4 (80) 4 (80)	16 (94) 15 (88)

*includes t (4;14), 1q amplification, del 17p, t (14;16)
**includes any BCMA bispecific antibody, antibody drug conjugate, or CART therapy

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Clinical Responses (n=16)

CRS= 93%, neurotox = 6%
Nail changes = 56%
Rash= 19%
Dysgeusia = 6%

Response	25 X10^6 CAR+ T cells (n=3)	50 X10^6 CAR+ T cells (n=3)	150 X10^6 CAR+ T cells (n=5)	450 X10^6 CAR+ T cells (n=5)	Total (N=16)
Minimal Response or better, n (%)	2 (67)	3 (100)	3 (60)	5 (100)	13 (81)
Partial Response or better, n (%)	1 (33)	3 (100)	2 (40)	5 (100)	11 (69)
Very Good Partial Response or better, n (%)	1 (33)	2 (67)	0 (0)	4 (80)	7 (44)
Complete Response or better, n (%)	0 (0)	1 (33)	0 (0)	3 (60)	4 (25)
BM MRD negativity*, n (%)	2 (67)	2 (67)	2 (40)	2 (50)	8 (50)

Response	Prior BCMA therapy (n=10)	Prior CAR T therapy (n=8)
Partial Response or better, n (%)	8 (80)	6 (75)
Complete Response or better	3 (30)	3 (38)
BM MRD negativity*, n (%)	5 (50)	2 (25)

* MRD assessment by multicolor flow cytometry (sensitivity: 1 in 10^5)

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Adverse events associated with CART and Bispecific therapies

Hematologic toxicities

Similar to other anti-myeloma therapies, BCMA-directed therapies are associated with hematologic toxicities, specifically **cytopenias**[1-3]

Immune-related adverse events

Immune-related adverse events, such as **CRS, ICANS, and infection,** have been observed with CAR T-cell and BsAb therapies[1-3]

BCMA=B-cell maturation antigen; BsAb=bispecific antibody; CAR=chimeric antigen receptor; CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome.

1. Kleber M, et al. *J Clin Med.* 2021;10(18):4088. 2. Mohan M, et al. *Blood Adv*. Published online December 21, 2021. 3. Zhou X, et al. *Front Immunol.* 2020;11:620312.

CAR T-cell Toxicities

- Cytokine Release Syndrome (CRS)
- Neurological toxicities
    - CAR T-cell associated Encephalopaty Syndrome (CRES)
    - Immune Effector Cell Associated Neurotoxicity Syndrome (ICANS)
- Prolonged cytopenias
- B-cell aplasia
- Hypogammaglobulinaemia
- Toxicities are usually manageable and reverisible

CRS can present as a variety of symptoms, potentially impacting multiple organs

Clinical presentation of CRS

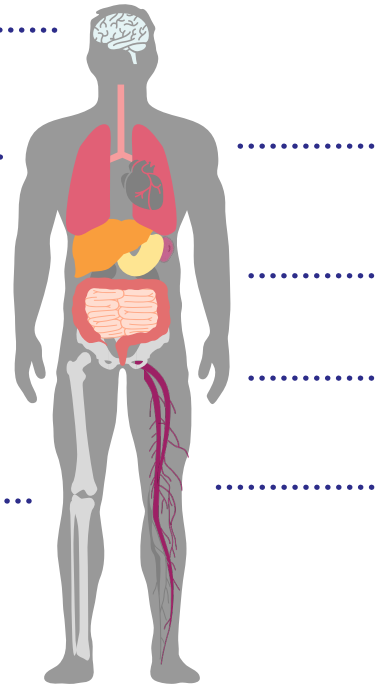
Brain
Headache, confusion, hallucination, delirium, aphasia, paresis, seizures

Lung
Tachypnea, hypoxia, pulmonary edema, respiratory failure

Live
Hepatomegaly, elevated liver enzymes, hypofibrinogenemia, liver failure

Gastrointestinal tract
Diarrhea, nausea, vomiting

Musculoskeletal and skin
Myalgia, arthralgia, rigor, rash, edema



Unspecific symptoms
Fever, fatigue, anorexia

Cardiovascular system
Tachycardia, hypotension, troponin elevation, arrhythmia, QT prolongation, stress, cardiomyopathy, acute heart failure

Spleen
Splenomegaly

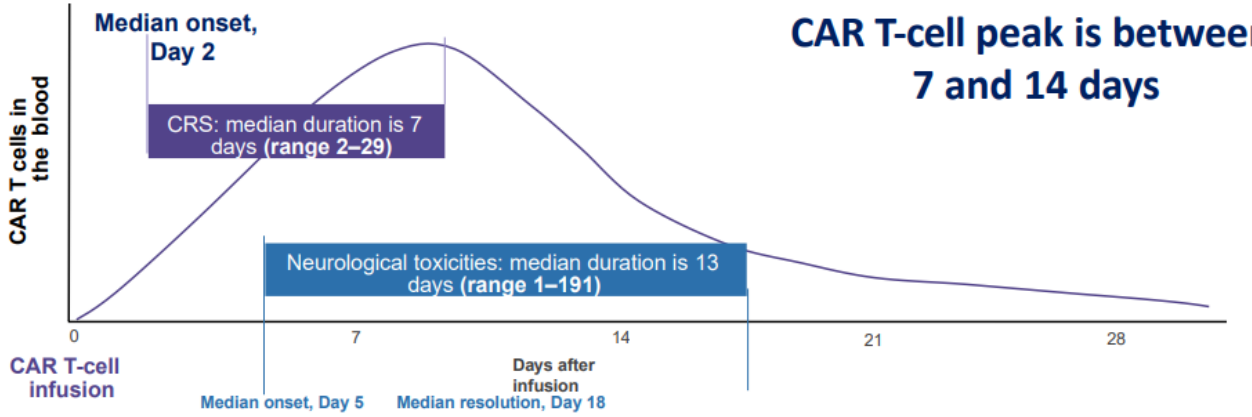
Kidneys
Acute kidney injury, renal failure

Blood and lymphatic
Cytopenias, coagulopathy (PTT↑, INR↓), febrile neutropenia, DIC

CRS=cytokine release syndrome; DIC=disseminated intravascular coagulation; INR=international normalized ratio; PTT=partial thromboplastin time.
Shimabukuro-Vomhagen A, et al. *J Immunother Cancer*. 2018;6(1):56.

Clinical trials have established the timing and duration of acute adverse events

CRS coincides with maximal T-cell expansion[1]
CRS may occur within minutes but more typically within days[1,2]



CAR T-cell peak is between 7 and 14 days

While CRS and NEs are acute adverse events, NEs may be present later (>Day 30 post infusion).

Cytopenias are common and can be long-lasting.

AE: adverse event; CAR: chimeric antigen receptor; CRS: cytokine release syndrome; SmPC: Summary of Product Characteristics; NE: neurological event; RMM: risk minimisation measure 1. Lee DW, *et al. Blood* 2014; 124:188–195. 2. Yescarta SmPC (May 2019; available at www.ema.europa.eu)

Management of CRS depends on the grade of severity

ASTCT CRS consensus grading†

CRS parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38° C			
			With	
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor ± vasopressin	Requiring multiple vasopressors (excluding vasopressin)
			And/or†	
Hypoxia	None	Requiring low-flow nasal cannula‡	Requiring high-flow nasal cannula,‡ face mask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Organ toxicities associated with CRS may be graded according to CTCAE v5.0 but they do not influence CRS grading.
*Fever is defined as temperature ≥38° C (100.4° F) not attributable to any other cause in patients who have CRS then receive antipyretic or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.
†CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5° C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.
‡Low-flow nasal cannula is defined as oxygen delivered at <6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.
ASTCT=American Society for Transplantation and Cellular Therapy; BiPAP=bilevel positive airway pressure; CPAP=continuous positive airway pressure; CRS=cytokine release syndrome; CTCAE=Common Terminology Criteria for Adverse Events.
Lee DW, et al. *Biol Blood Marrow Transplant.* 2019;25(4):625-638.

ASTCT Management Recommendations of CRS includes symptom control and prophylactic treatment

Management strategies for CRS[1-7]

Prophylactic treatment*	• IL-1 inhibition, antipyretics, or tocilizumab (an IL-6R–blocking antibody) may be used prior to T-cell directed therapies
Mild CRS	• Symptom management with antihistamines, antipyretics, and fluids • May require low-flow nasal cannula†
Moderate to severe CRS	• Symptom management with – Tocilizumab with or without immunosuppression with corticosteroids – Intensive supportive care, including fluid resuscitation and vasopressors for hypotension and supplemental oxygen delivery as needed for hypoxia

- **There is no consensus regarding CRS resolution[1]**
  - **After therapies are used, patients are still considered to have CRS until all signs and symptoms leading to initial diagnosis have been resolved**
  - **Cases of severe CRS may be considered resolved when fever, oxygen, and pressor requirements are resolved**

*Preclinical data have demonstrated potential value of CRS prophylaxis. The decision to utilize prophylactic strategies can be considered at clinician's discretion.[3]
†Low-flow nasal cannula is defined as oxygen delivered at <6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/min.
ASTCT=American Society for Transplantation and Cellular Therapy; CRS=cytokine release syndrome; IL-1=interleukin 1; IL-6R=interleukin 6 receptor.
1. Lee DW, et al. *Biol Blood Marrow Transplant*. 2019;25(4):625-638. **2.** Morris EC, et al. *Nat Rev Immunol*. 2022;22(2):85-96. **3.** Shi X, Wu H. *Eur J Inflamm*. 2022;20:1-10. **4.** Dave P, et al. *Cureus*. 2021;13(9):e17709. **5.** Yanez L, et al. *Hemasphere*. 2019;3:(2):e186. **6.** Shah N, et al. *J Immunother Cancer*. 2020;8(2):e000734. **7.** Neelapu SS, et al. *Nat Rev Clin Oncol*. 2018;15(1):47-62.

Infections are assessed according to CTCAE criteria

CTCAE AE grading

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Severity	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only	Moderate; limiting age-appropriate instrumental ADL*	Severe or medically significant but not immediately life-threatening; disabling; limiting self-care ADL†	Life-threatening consequences	Death
Intervention	Intervention not indicated	Minimal, local, or noninvasive intervention indicated	Hospitalization or prolongation of hospitalization indicated	Urgent intervention indicated	

*Instrumental ADL refers to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
†Self-care ADL refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.
ADL=activities of daily living; AE=adverse event; CTCAE=Common Terminology Criteria for Adverse Events.
National Cancer Institute. Common terminology criteria for adverse events (CTCAE). Version 5.0.
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf. Accessed December 6, 2022.

IMWG infection management strategies

Patients with MM should be under surveillance for potential infections; fever should always be considered as a marker of infections for patients

	Management strategies for infections
Prophylactic treatment	• Antibacterial prophylaxis with levofloxacin or consider trimethoprim sulfamethoxazole for patients at risk of *Pneumocystis jirovecii* pneumonia (patients with RRMM, treatment with high-dose dexamethasone) • Antiviral prophylaxis with acyclovir for patients who are seropositive for herpes simplex virus and varicella-zoster virus or for patients receiving a PI or targeted monoclonal antibodies
Vaccinations	• Inactivated influenza vaccine, inactivated *Streptococcus pneumoniae* vaccine, varicella zoster, and extension of the recombinant zoster vaccine
Exposure to hepatitis A, varicella-zoster virus, or measles	• Passive immunizations
Febrile neutropenia	• Broad-spectrum antibiotics • Reserve IVIG for specific situations, such as life-threatening infections and an IgG concentration below 400 mg/dL with recurrent infections

IgG=immunoglobulin G; IMWG=International Myeloma Working Group; IVIG=intravenous immunoglobulin; MM=multiple myeloma; PI=proteasome inhibitor; RRMM=relapsed/refractory multiple myeloma.

Raje NS, et al. *Lancet Haematol*. 2022;9(2):e143-e161.

CRS and Neurotoxicity of Major Clinical trials

	B-ALL		DLBCL			MCL	MM
	ELIANA[1]	ZUMA-3[2]	JULIET[3]	ZUMA-1[4]	TRANSCEND[5]	ZUMA-2[6]	CRB-401[7]
CAR T-cell agent	Tisagenlecleucel	Brex. autoleucel	Tisagenlecleucel	Axicabtagene ciloleucel	Lisocabtagene maraleucel	Brex. autoleucel	Idecabtagene Vicleucel
Construct	Anti–CD19-41BB-CD3z	Anti–CD19-CD28-CD3z	Anti–CD19-41BB-CD3z	Anti–CD19-CD28-CD3z	Anti–CD19-41BB-CD3z	Anti–CD19-CD28-CD3z	Anti-BCMA
N treated	75	45	111	101	269	68	33
CRS, %	77*	93†	58*	93†	42†	91†	76
Grade ≥ 3 CRS, %	46*	29†	22*	13†	2†	15†	6
NT, %	40	78	21	64	30	63	42
Grade ≥ 3 NT, %	13	38	12	28	10	31	3

*Per Penn scale. †Per Lee Scale.

1. Maude. NEJM. 2018;378:439. 2. Shah. ASCO 2019. Abstr 7006. 3. Schuster. NEJM. 2019;380:45.
4. Neelapu. NEJM. 2017;377:2531. 5. Abramson. ASH 2019. Abstr 241. 6. Wang. NEJM. 2020;382:1331. 7. Raje. NEJM. 2019;380:1726.

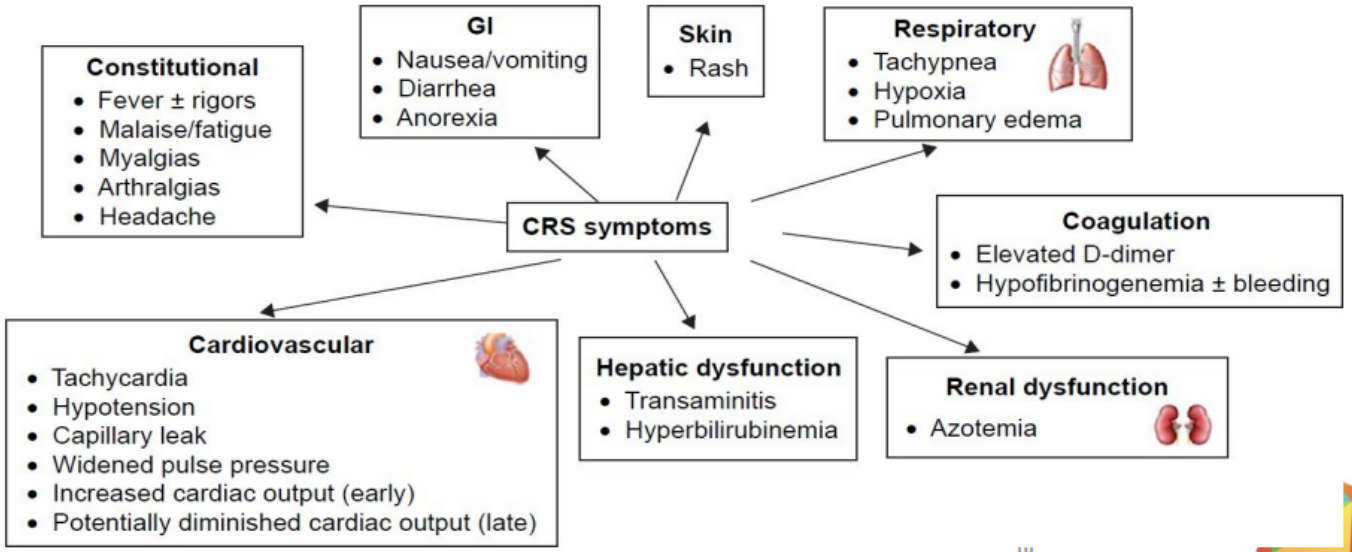
Cytokine release syndrome (CRS)

CLINICAL SYMPTOMS

- fever
- hypotension
- widespread organ dysfunction

From mild flu-like symptoms → Severe inflammatory syndrome

CLINICAL EFFECTS



Riegler and al., Therapeutics and clinical risk managment, 2019

Cytokine release syndrome (CRS)

RISK FACTORS

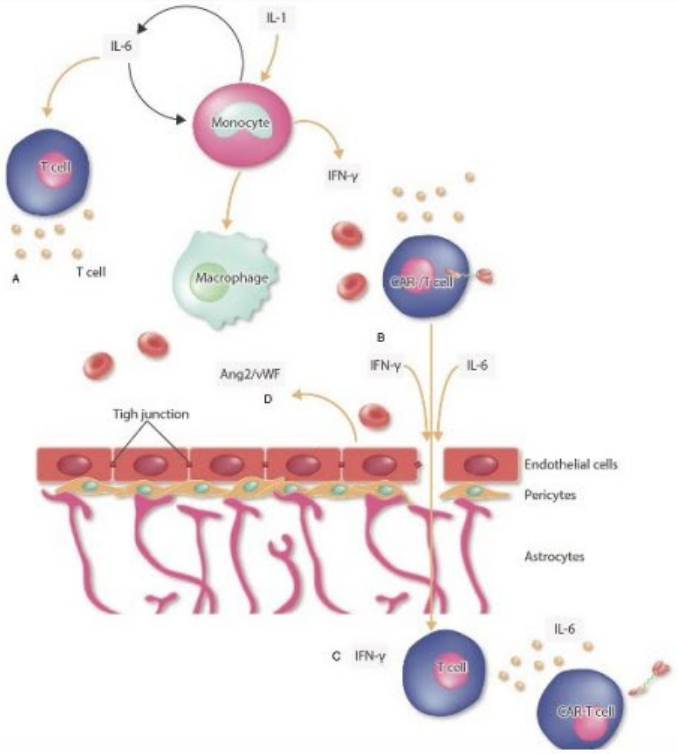
- higher peak in vivo proliferation of CAR T cells
- higher burden disease
- Baseline thrombocytopenia and baseline elevated LDH
- higher cell doses
- ALL rather than NHL

INCIDENCE RATE

- From 35 to 93% depending on the product infused and disease treated
- Severe CRS: 12-47% patients after CD19 CAR T cell therapy

Lee et *al.*, 2014; Hay et *al.*, Blood, 2017; Park *et al*. 2018, Hay *et al*., BJH, 2018

Immune effector cell-associated neurotoxicity syndrome (ICANS)



- Neurologic symptoms may include altered mental status, aphasia, altered level of consciousness, and seizures or seizure-like activity.
- The start of neurologic symptoms has been noted between 3 to 23 days (median 10 days)
- The symptoms are variable and generally occur as CRS is resolving or after CRS resolution.
- Seizure prophylaxis with Keppra (500 mg BID) in high risk patients for those treated with CNS irradiation or other intensive CNS directed therapy.

Borrega JG et al journal. HemaSphere (2019) 3:2(e191)

ASTCT Guidelines for Grading of ICANS

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (pt is unarousable)
Depressed level of consciousness	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (> 5 mins) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

*See next slide; an ICE score of 0 may be classified as grade 3 ICANS if patient is awake with global aphasia; otherwise classified as grade 4 ICANS if unarousable.

Lee. Biol Blood Marrow Transplant. 2019;25:625.

Immune Effector Cell Associated Encephalopathy (ICE) Score

Parameter	Score (Points)
Orientation: year, month, city, hospital	4
Naming: ability to name 3 objects (eg, point to clock, pen, button)	3
Following commands: ability to follow simple commands (eg, "show me 2 fingers" or "close your eyes and stick out your tongue")	1
Writing: ability to write a standard sentence (eg, "our national bird is the bald eagle")	1
Attention: ability to count backwards from 100 by 10	1

Scoring:

10, no impairment
7-9, grade 1 ICANS
3-6, grade 2 ICANS
0-2, grade 3 ICANS
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS

Lee. Biol Blood Marrow Transplant. 2019;25:625.

Principles of Toxicity Management

- Appropriate screening per institutional standards
- Baseline labs
  - CRP, ferritin
  - CBC, CMP, coagulopathy
  - Tumor lysis syndrome labs
- Initiation of antiepileptic drugs
- Appropriate bacterial/fungal/viral prophylaxis per institutional standards
- Pre-infusion/LD chemo
- Monitor CBC, CMP, and coagulopathy
- Monitor for tumor lysis syndrome
- Monitor CRP and ferritin
- Daily assessments for at least 7 days
  - FDA requirement for axicabtagene ciloleucel
  - Fevers? Hypotension? Hypoxia?
  - Mental status

Axicabtagene ciloleucel PI. Tisagenlecleucel PI. Neelapu. Nat Rev Clin Oncol. 2018;15:47. MD Anderson. CAR cell therapy toxicity assessment and management. 2017.

Management of CRS and ICANS

CRS

- Supportive care
- **Tocilizumab**
- Steroids (dexamethasone)
- More steroids (methylprednisolone)
- Other: cyclophosphamide

ICANS

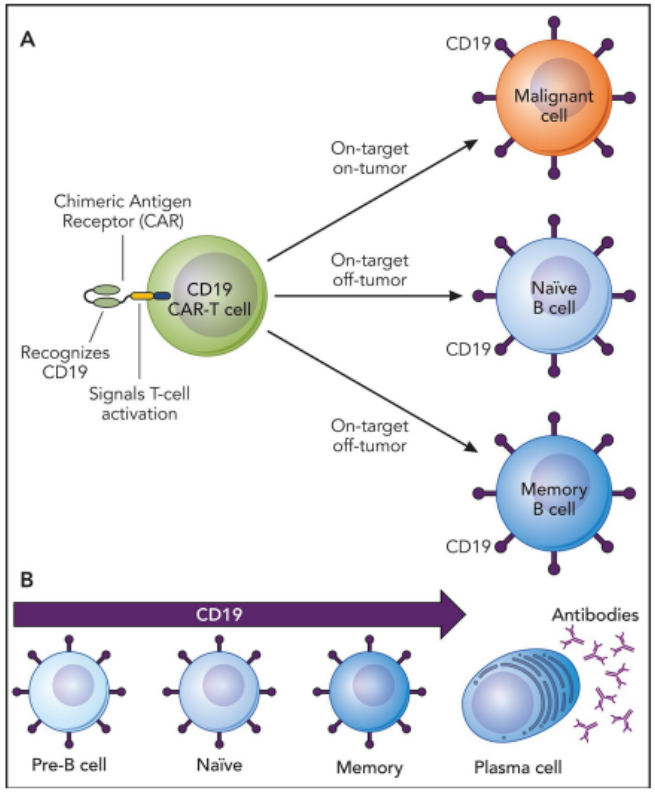
ICANS

- Seizure prophylaxis
- **Steroids (dexamethasone)**
- Increase steroids
- Change steroids (methylprednisolone)
- Other: consider cyclophosphamide

Axicabtagene ciloleucel PI. Tisagenlecleucel PI. Neelapu. Nat Rev Clin Oncol. 2018;15:47.
MD Anderson. CAR cell therapy toxicity assessment and management. 2017.

Long term toxicity

- Highly immunosuppressed patients: extensive past trteatment +/- transplant
- Lymphodepletion chemotherapy prior CAR-T cell infusion
- Cytokine release syndrome and neurotoxicity
- Depletion of malignant and normal/healty B cell subsets



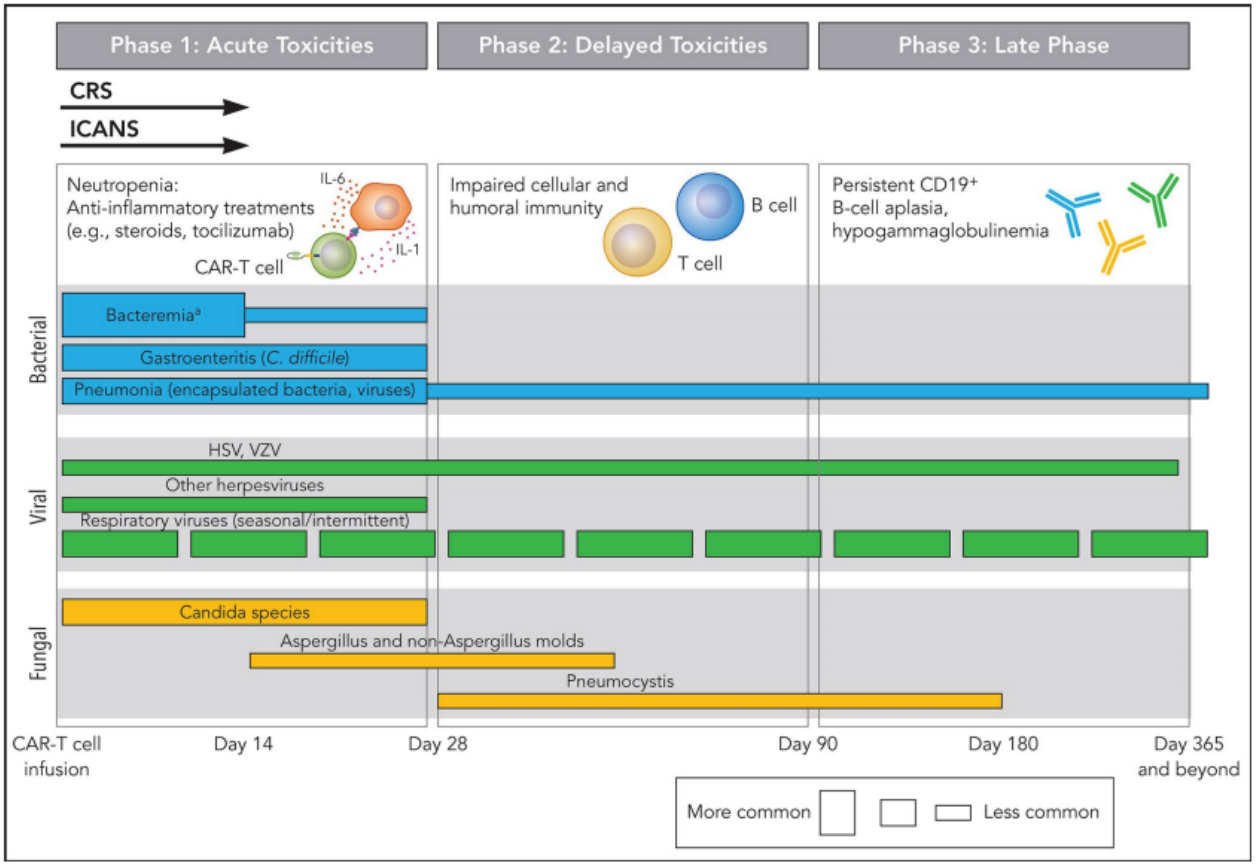
Hill et al. Blood 2020

Long term toxicity: Prolonged Cytopenia

- Occurs after the period expected to be related to Lymphodepleting chemotherapy and after resolution of CRS
- ELIANA study: 37%; JULIET study 34%; ZUMA-1: 40%
- Biphasic pattern: 2 through levels with intermediate recovery
  - BM aspiration: normal cellularity without paucity of progenitors, (except patient with poor hematopoietic reserves or MDS)
  - Rapid response to G-CSF: is suggestive of an alternative modality of bone marrow inhibition distinct from CT-induced cytotoxicity

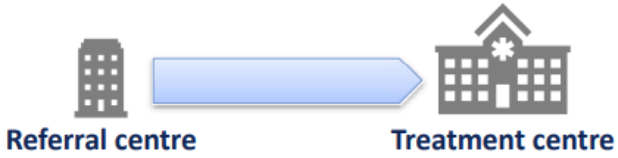
Fried et al. BMT 2019

Infections

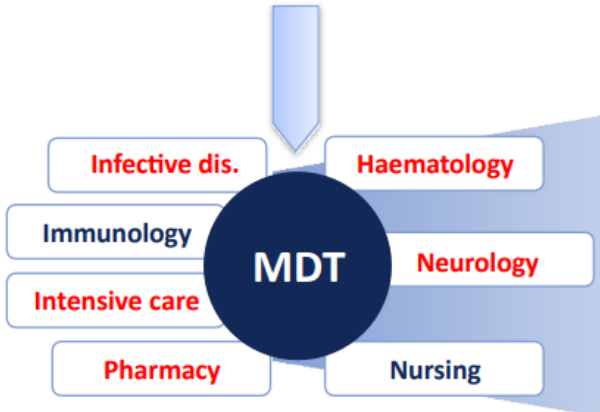


Hill et al. Blood 2020

Role of a multidisciplinary team in the decision to treat and management of patients



The decision to treat a patient with CAR-T therapy is made by a MDT at a designated treatment centre[1–3]



- Evaluation of risks
- Clinical decision making
- Expert advice for complex cases
- Advice and review of informed consent
- Management of treatment, post-treatment and follow-up

CAR-T, chimeric antigen receptor T-cell; MDT, multidisciplinary team.

1. Chomienne C, et al. *HemaSphere.* 2019;03:04. 2. NHS England. CAR-T therapy. Service specification nos. 170100S and 170099S. Available at: www.england.nhs.uk/wp-content/uploads/2018/12/Tisagenlecleucel-Chimeric-Antigen-Receptor-T-Cell-CAR-T-Therapy-for-ALL-and-DLBCL.pdf and www.england.nhs.uk/wp-content/uploads/2018/12/Axicabtagene-Ciloleucel-Chimeric-Antigen-Receptor-T-Cell-CAR-T-Therapy-for-the-treatment-of-adult-patients-wit.pdf, respectively (accessed 3 July 2020). 3. Yakoub-Agha I, et al. *Haematologica.* 2020;105:297–316.

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