What are the latest approaches for using CAR T cell therapy in Multiple Myeloma?

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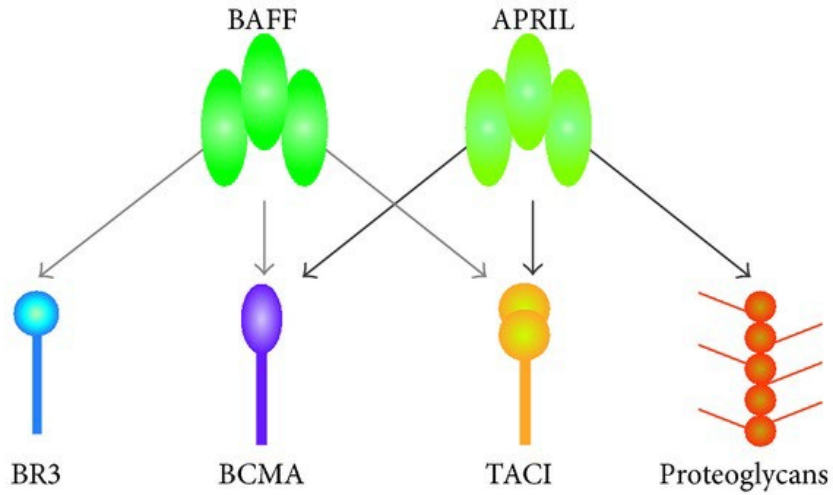
BCMA: B cell maturation antigen

- Member of TNFR (TNFRS17)
- Regulate B cell proliferation and survival, maturation to plasma cells
- Expression/ activation associated with myeloma cell growth/ survival
- Exclusively expressed on the surface of plasmablasts and differentiated PCs



Cho et al, *Frontiers in Immunol,* 2018
Tobon et al, *Autoimm Dis,* 2013

UCSF

Idecabtagene vicleucel (ide-cel, bb2121), a BCMA-targeted CAR T cell therapy, in patients with relapsed and refractory multiple myeloma (RRMM): initial KarMMa results

Nikhil C. Munshi, MD[1]; Larry D. Anderson, Jr, MD, PhD[2]; Nina Shah, MD[3]; Sundar Jagannath, MD[4]; Jesus Berdeja, MD[5]; Sagar Lonial, MD[6]; Noopur Raje, MD[7]; David S. Siegel, MD, PhD[8]; Yi Lin, MD, PhD[9]; Albert Oriol, MD[10]; Philippe Moreau, MD[11]; Ibrahim Yakoub-Agha, MD, PhD[12]; Michel Delforge, MD[13]; Fabio Petrocca, MD[14]; Jamie N. Connarn, PhD[15]; Payal Patel[15]; Liping Huang, PhD[15]; Timothy B. Campbell, MD, PhD[15]; Kristen Hege, MD[15]; and Jesus San Miguel, MD, PhD[16] *on behalf of the KarMMa study investigators*

[1]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; [3]University of California San Francisco, San Francisco, CA, USA; [4]Mount Sinai Hospital, New York, NY, USA; [5]Sarah Cannon Research Institute and Tennessee Oncology, Nashville, TN, USA; [6]Emory School of Medicine, Atlanta, GA, USA; [7]Massachusetts General Hospital, Boston, MA, USA; [8]Hackensack University Medical Center, Hackensack, NJ, USA; [9]Mayo Clinic, Rochester, MN, USA; [10]Institut Josep Carreras and Institut Catala d'Oncologia, Hospital Germans Trias i Pujol, Badalona, Spain; [11]Centre Hospitalier Universitaire de Nantes, Nantes, France; [12]Centre Hospitalier Regional Universitaire de Lille, Lille, France; [13]University Hospital Leuven, Leuven, Belgium; [14]bluebird bio, Cambridge, MA, USA; [15]Bristol Myers Squibb, Princeton, NJ, USA; and [16]Clinical Universidad de Navarra, Navarra, Spain

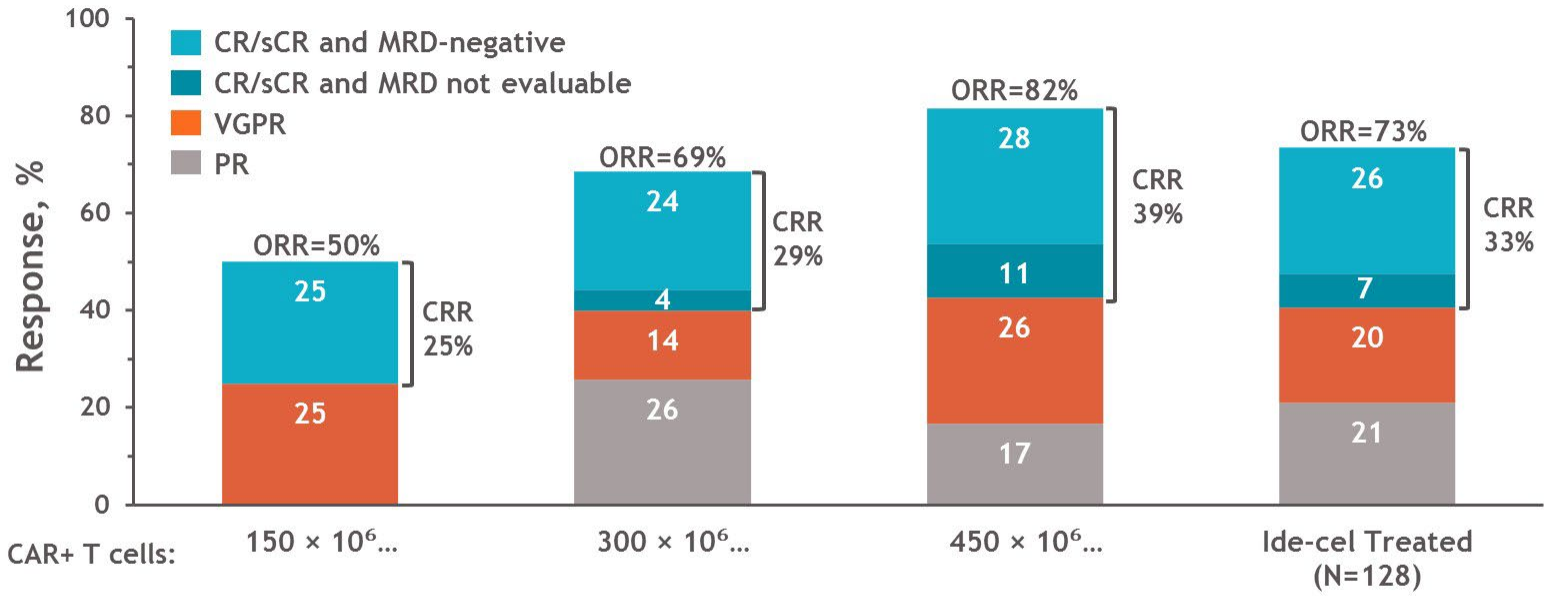
Presentation Number 8503

Presented By Nikhil Munshi at ASCO 2020

Best Overall Response

Median # prior regimens: 6

CRS: 84%
Neurotox: 18%

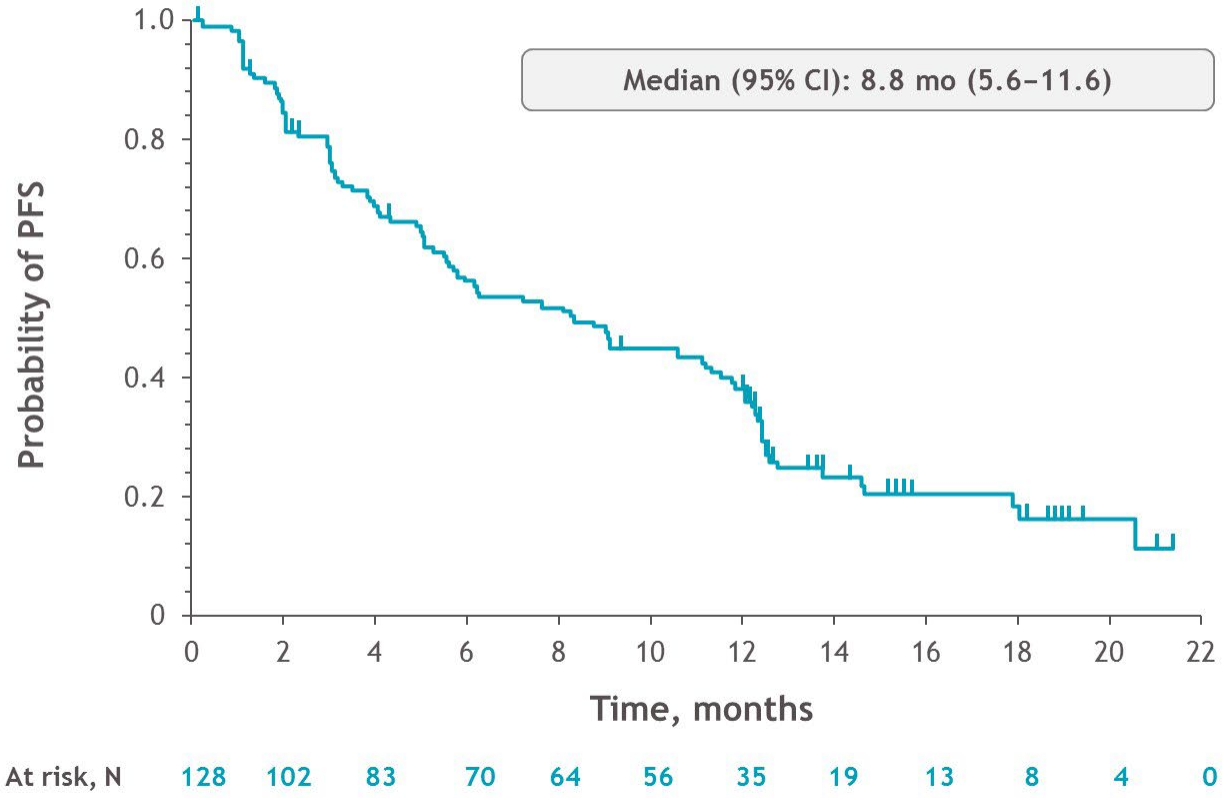


- Primary (ORR >50%) and key secondary (CRR >10%) endpoints met in the ide-cel treated population
  - *ORR of 73% (95% CI, 65.8–81.1; P<0.0001*)*
  - *CRR (CR/sCR) of 33% (95% CI, 24.7–40.9; P<0.0001)*
- Median time to first response of 1.0 mo (range, 0.5–8.8); median time to CR of 2.8 mo (range, 1.0–11.8)
- Median follow-up of 13.3 mo across target dose levels

Data cutoff: 14 Jan 2020. MRD-negative defined as $<10^{-5}$ nucleated cells by next generation sequencing. Only MRD values within 3 mo of achieving CR/sCR until progression/death (exclusive) were considered.
Values may not add up due to rounding.
CR/sCR, complete response/stringent CR; CRR, CR rate; MRD, minimal residual disease; ORR, overall response rate (≥PR); PR, partial response; VGPR, very good PR. **P* value at the primary data cutoff with same ORR and 95% CI.

Munshi et al, ASCO 2020

Progression-Free Survival

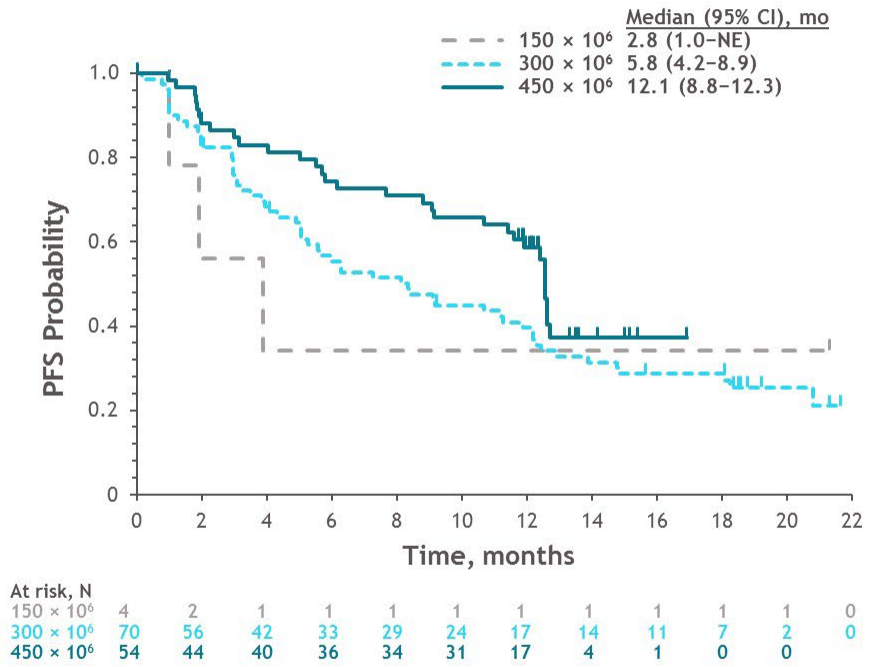


Data cutoff: 14 Jan 2020. PFS, progression-free survival.

Munshi et al, ASCO 2020

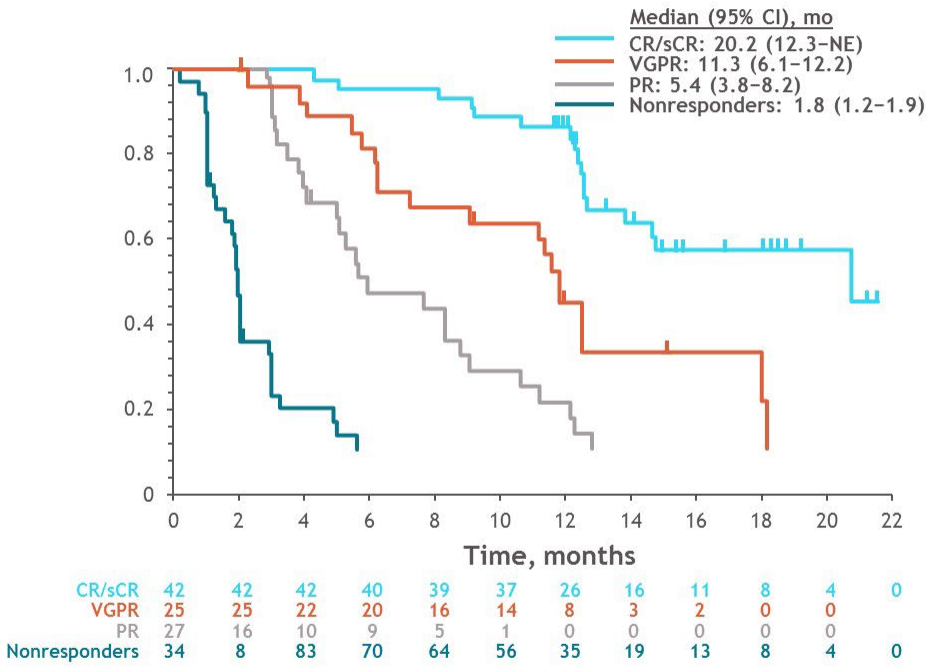
Progression-Free Survival

PFS by Target Dose



- PFS increased with higher target dose; median PFS was 12 mo at 450 × 10^6 CAR+ T cells

PFS by Best Response

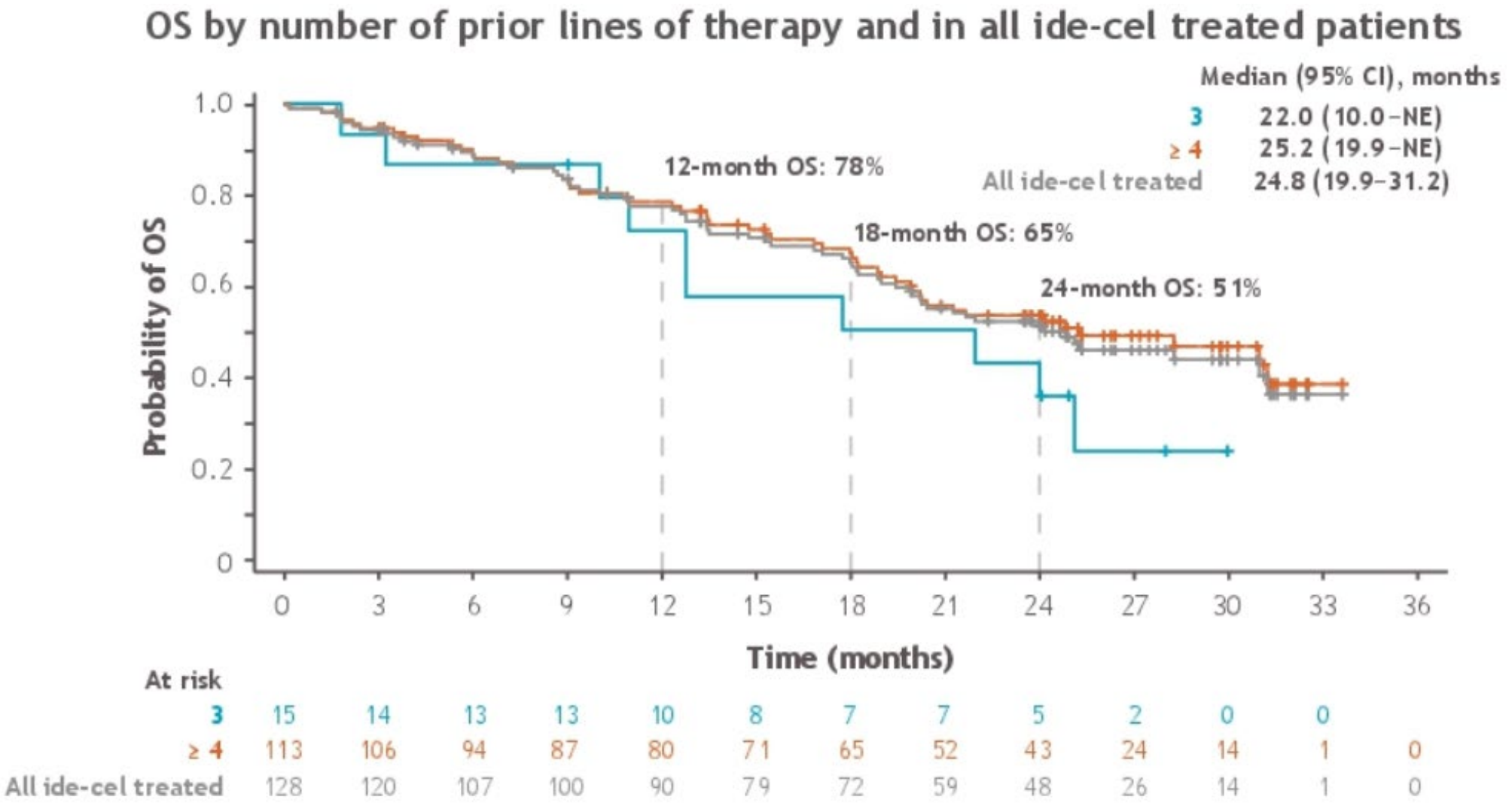


- PFS increased by depth of response; median PFS was 20 mo in patients with CR/sCR

Data cutoff: 14 Jan 2020. NE, not estimable; PFS, progression-free survival.

Munshi et al, ASCO 2020

KarMMa: Updated OS[1]



1. Anderson LD, et al. ASCO 2021. Abstract 8016.

Ide-cel package

- Safety ✓
- Efficacy ✓
- PFS ✓
- Likely improvement of PFS over conventional care ✓
- QOL improvement ✓

FDA NEWS RELEASE

FDA Approves First Cell-Based Gene Therapy for Adult Patients with Multiple Myeloma

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

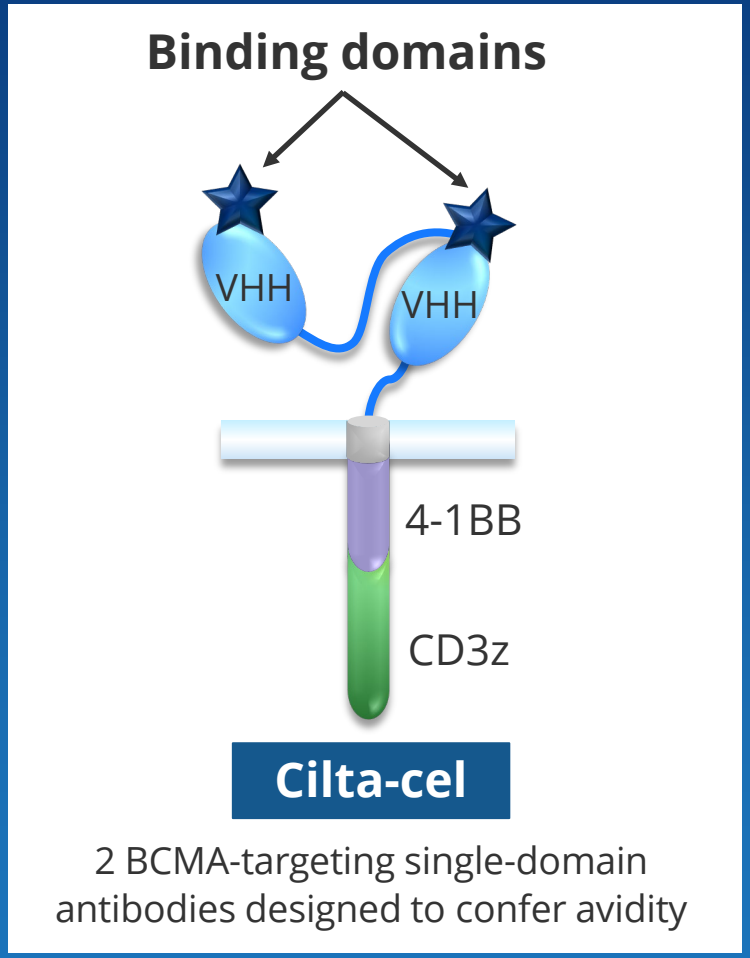
Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

*Presenting author.

CARTITUDE-1: Introduction

Ciltacabtagene autoleucel (cilta-cel; JNJ-68284528) is a chimeric antigen receptor T-cell therapy for the treatment of patients with RRMM[1]

- In the phase 1b/2 CARTITUDE-1 study, early, deep, and durable responses were observed with a single cilta-cel infusion in heavily pretreated patients with RRMM[1]
  - At a median follow-up of 12.4 months
    - Cilta-cel had a manageable safety profile
    - ORR and sCR were 97% and 67%, respectively
    - Overall 12-month PFS and OS rates were 77% and 89%, respectively
    - Median PFS and duration of response were not reached (95% CI, 16.8–not estimable and 15.9–not estimable, respectively)
- **Here, we report updated results from the CARTITUDE-1 study with a longer duration of follow-up (median ~2 years)[a]**



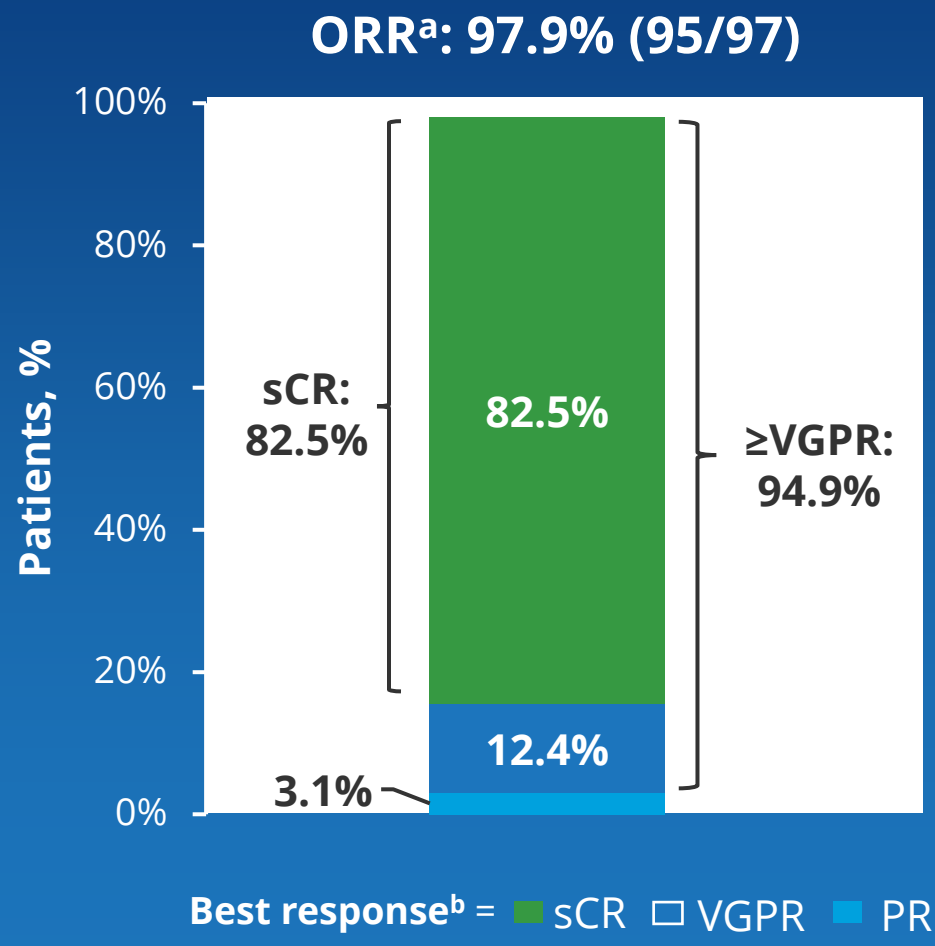
[a]Median 21.7 months, data cut-off July 22,2021

BCMA, B-cell maturation antigen; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; sCR, stringent complete response; VHH, single variable domain on a heavy chain

1. Berdeja JG, et al. *Lancet* 2021; 398:314-24.

CARTITUDE-1: Efficacy Response

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



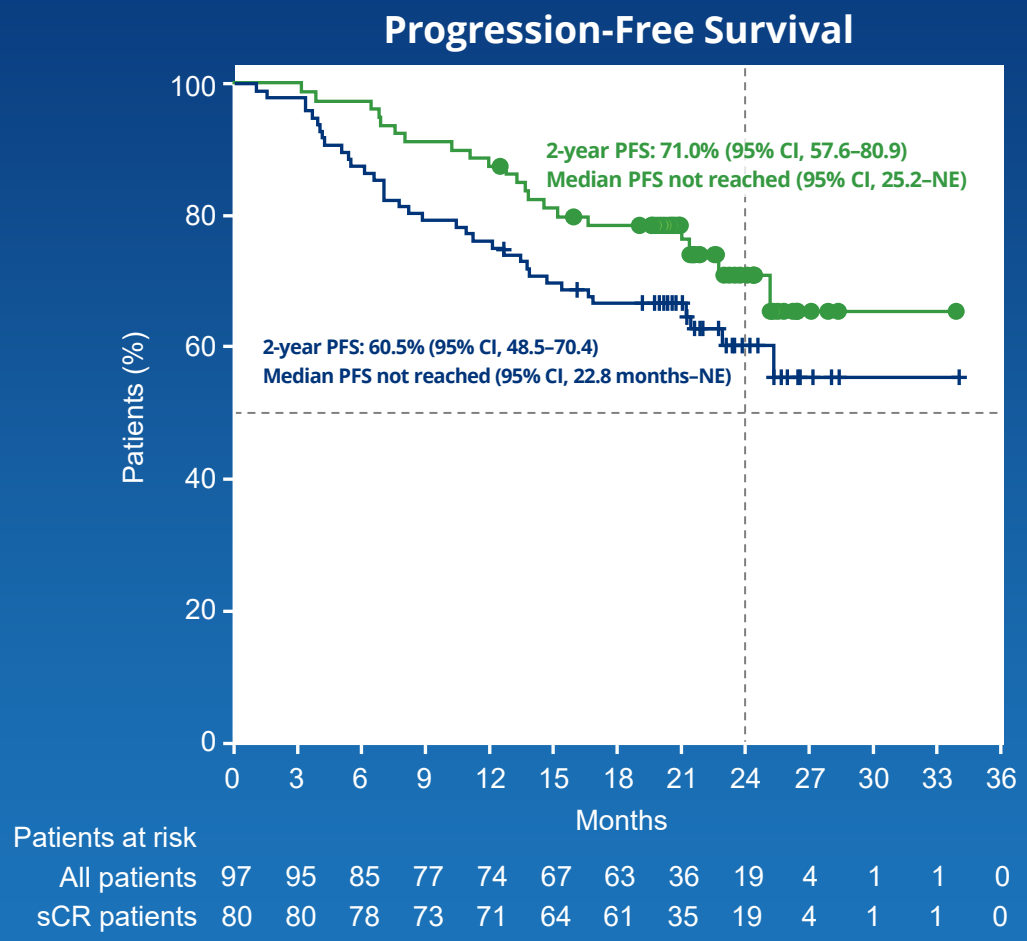
Responses deepened over time from the 1-year follow-up

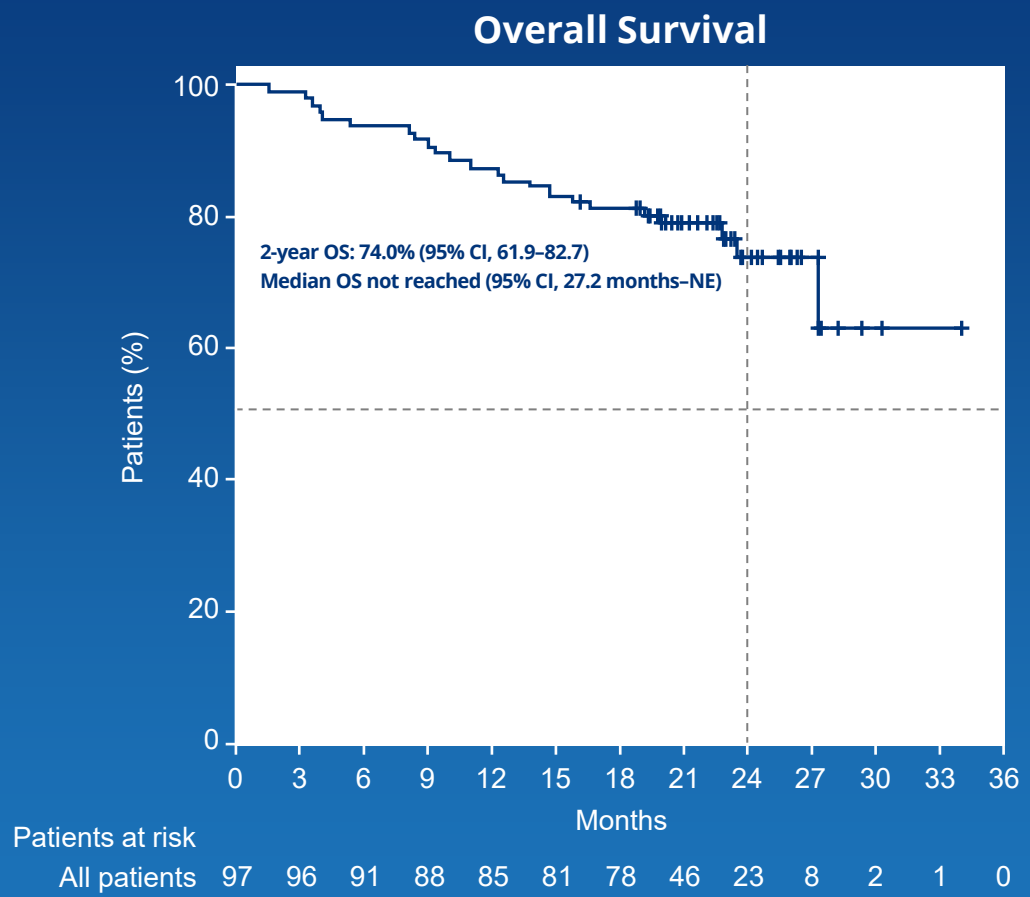
Best response at any time	Median–1 year follow-up	Median–2 years follow-up
sCR, %	67	83

- 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

CARTITUDE-1: Progression-Free Survival and Overall Survival





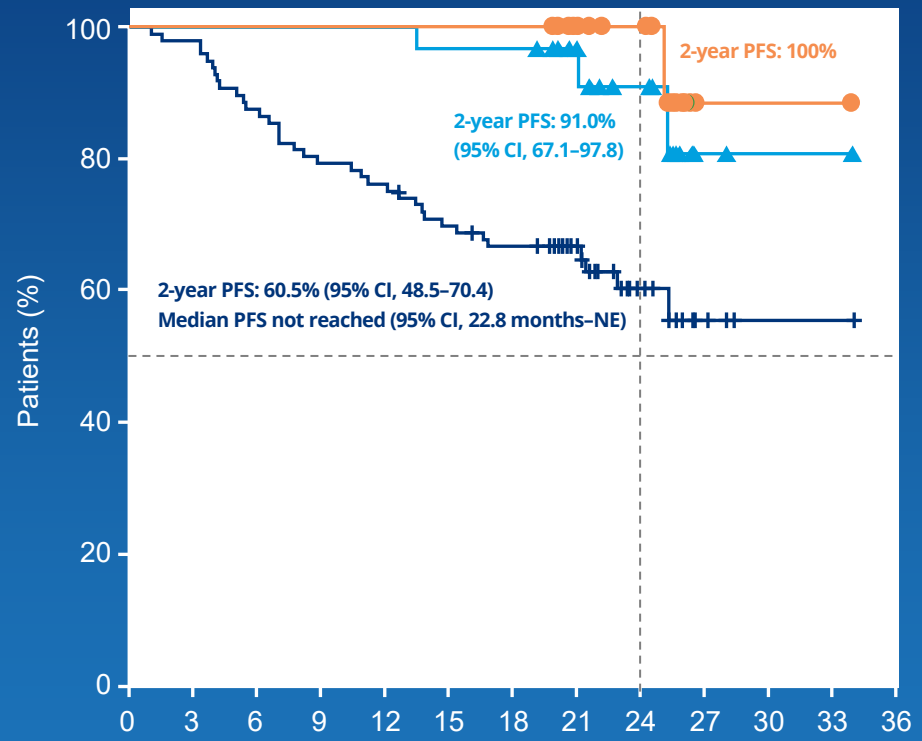
All patients sCR patients

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

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

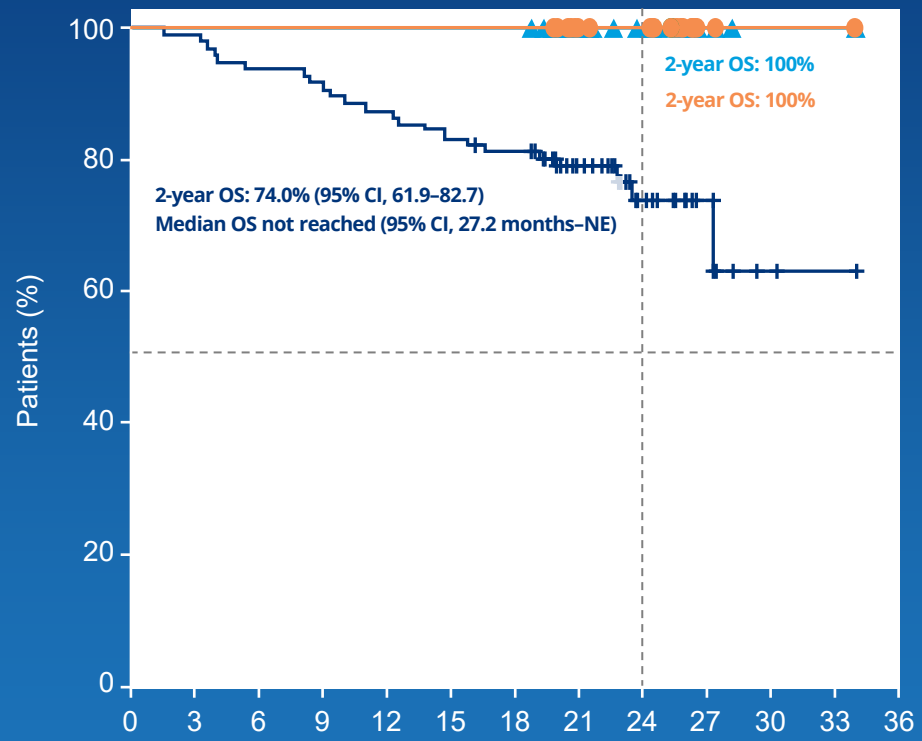
- Of the 61 patients evaluable for MRD, 92% were MRD-negative (at 10^{-5})

Progression-Free Survival



Patients at risk													
All patients	97	95	85	77	74	67	63	36	19	4	1	1	0
MRD negativity ≥6 months	30	30	30	30	30	29	29	17	12	2	1	1	0
MRD negativity ≥12 months	18	18	18	18	18	18	18	12	10	1	1	1	0

Overall Survival



Patients at risk													
All patients	97	96	91	88	85	81	78	46	23	8	2	1	0
MRD negativity ≥6 months	30	30	30	30	30	30	30	17	13	3	1	1	0
MRD negativity ≥12 months	18	18	18	18	18	18	18	12	11	2	1	1	0

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

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

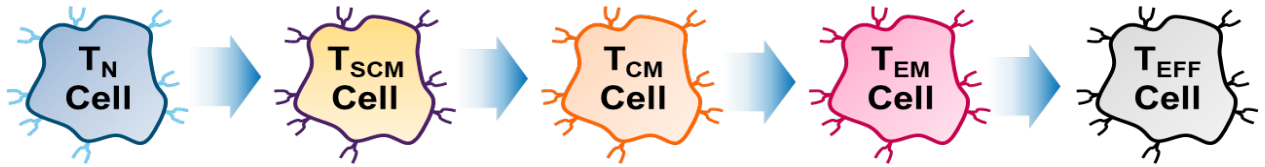
Updated clinical and correlative results from the Phase I CRB-402 study of the BCMA-targeted CAR T cell therapy bb21217 in patients with relapsed and refractory multiple myeloma

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

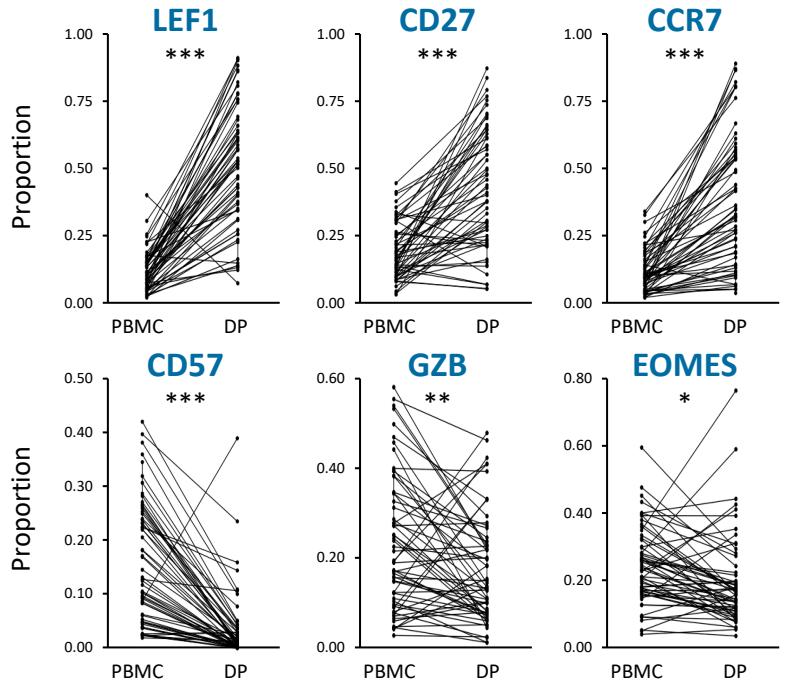
- bb21217 uses the same CAR molecule as bb2121,[1] but is cultured with the PI3K inhibitor, bb007, to enrich for T cells displaying a memory-like phenotype
- CAR T cells enriched for this phenotype may persist and function for longer than non-enriched CAR T cells[2]
- Hypothesized that persistence of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



Memory-like phenotype
T-cell plasticity
Long-lived
Self-renewal

Effector-like phenotype
Terminally differentiated
Short-lived
No self-renewal

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



N=59

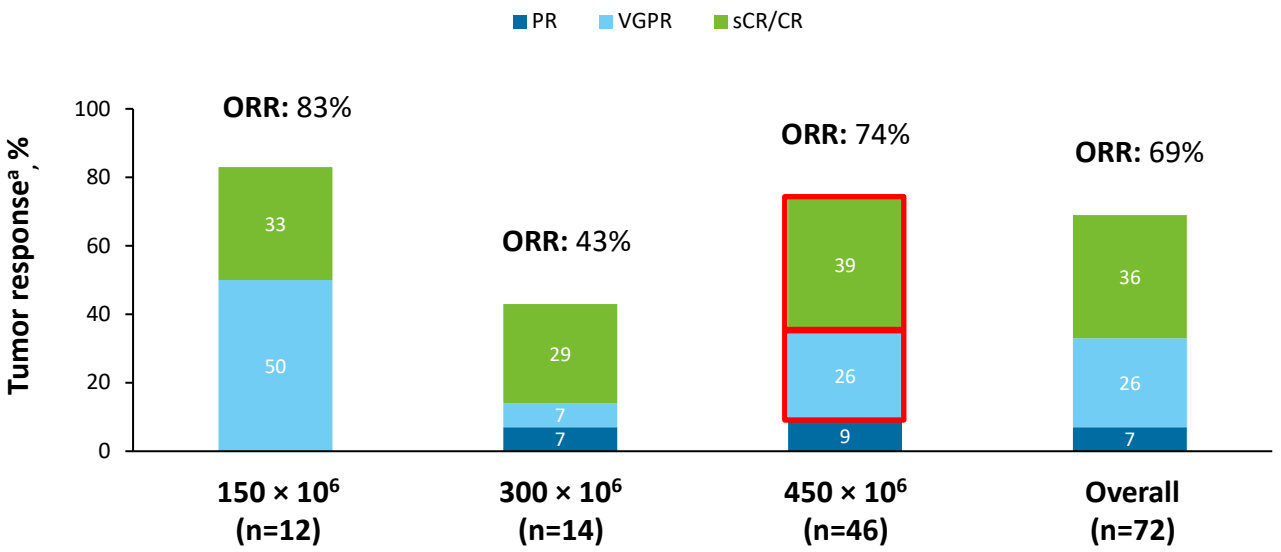
*** P<0.001; ** 0.001 < P < 0.01; * 0.01 < P < 0.05

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

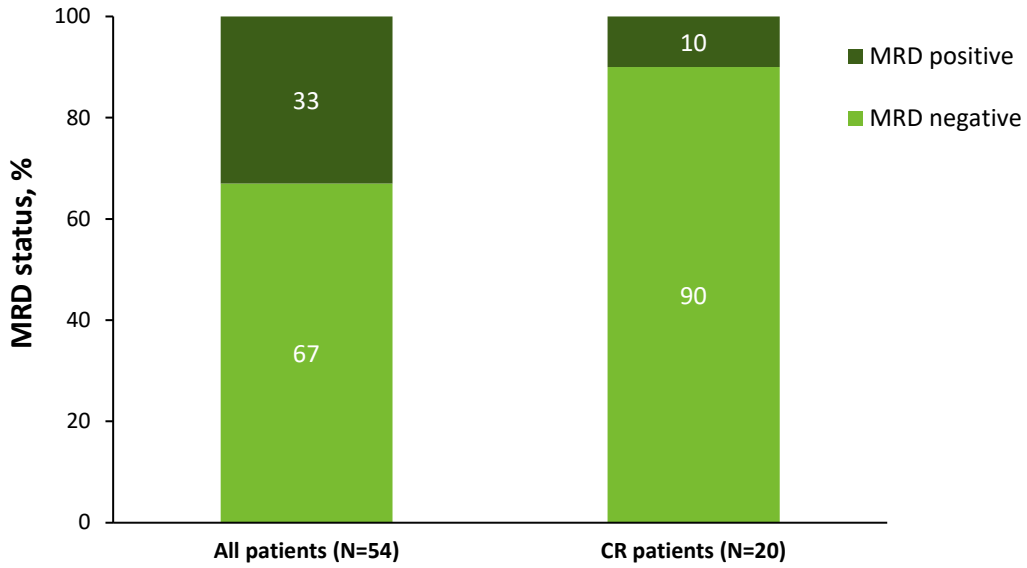
Med prior lines = 6
CRS = 75%, neurotox = 15%



	150 × 10^6 (n=12)	300 × 10^6 (n=14)	450 × 10^6 (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

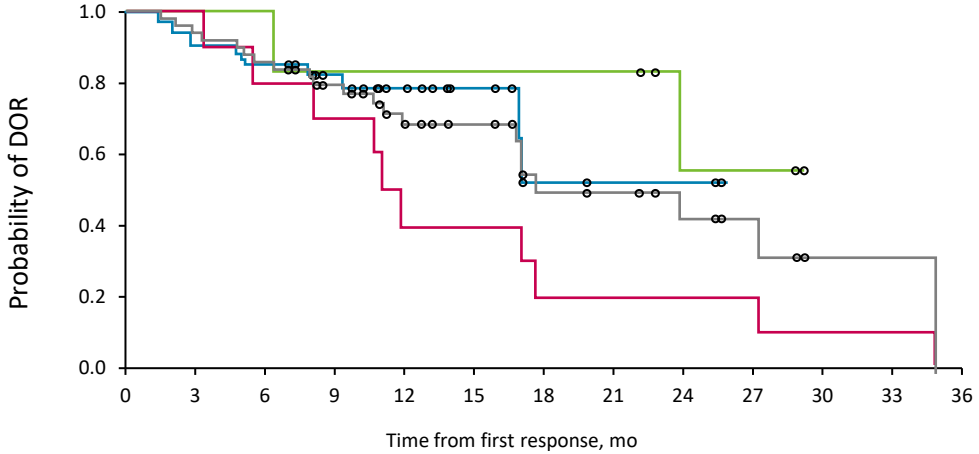
72% of MRD negative patients with CR sustained MRD negativity at mo 9

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;

Duration of Response

Duration of Response by Dose

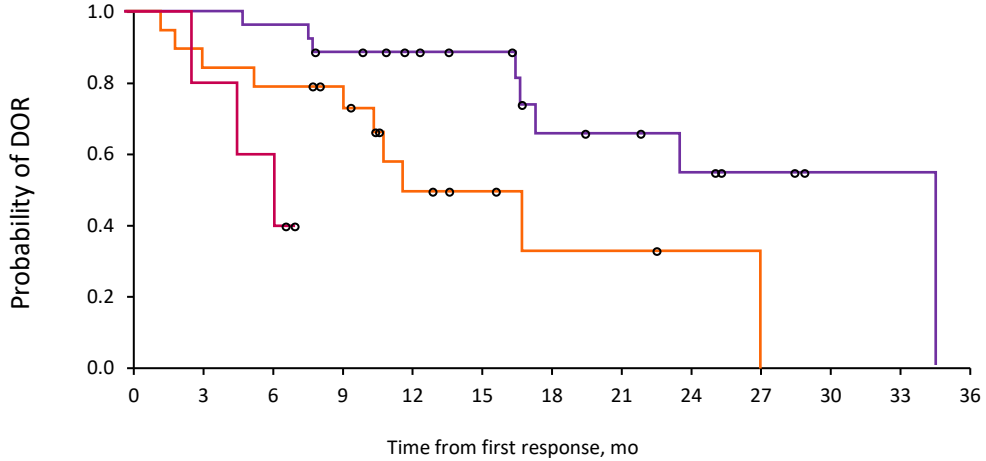
Dose	N	Events	Median DOR (95% CI), mo
150 × 10^6	10	10	11.5 (3.3–17.6)
300 × 10^6	6	2	NE (6.4–NE)
450 × 10^6	34	9	NE (16.8–NE)
Overall	50	21	23.8 (16.8–NE)



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[I]	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)



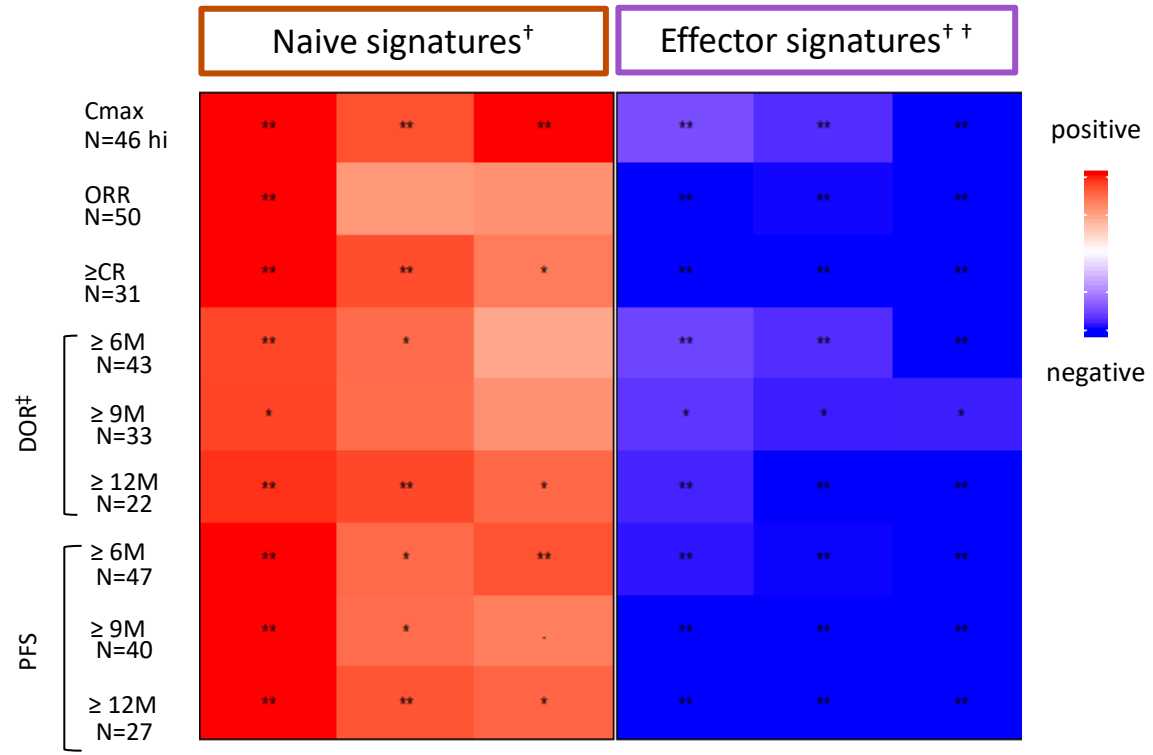
At risk:													
sCR/CR	26	26	25	20	16	13	8	7	5	3	1	1	0
VGPR	19	17	15	13	6	4	2	2	1	1	0	0	0
PR	5	4	3	0	0	0	0	0	0	0	0	0	0

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.

Memory like phenotype is positively associated with better clinical outcomes including response and duration or response

Drug Product: T Cell Phenotype (N=72)

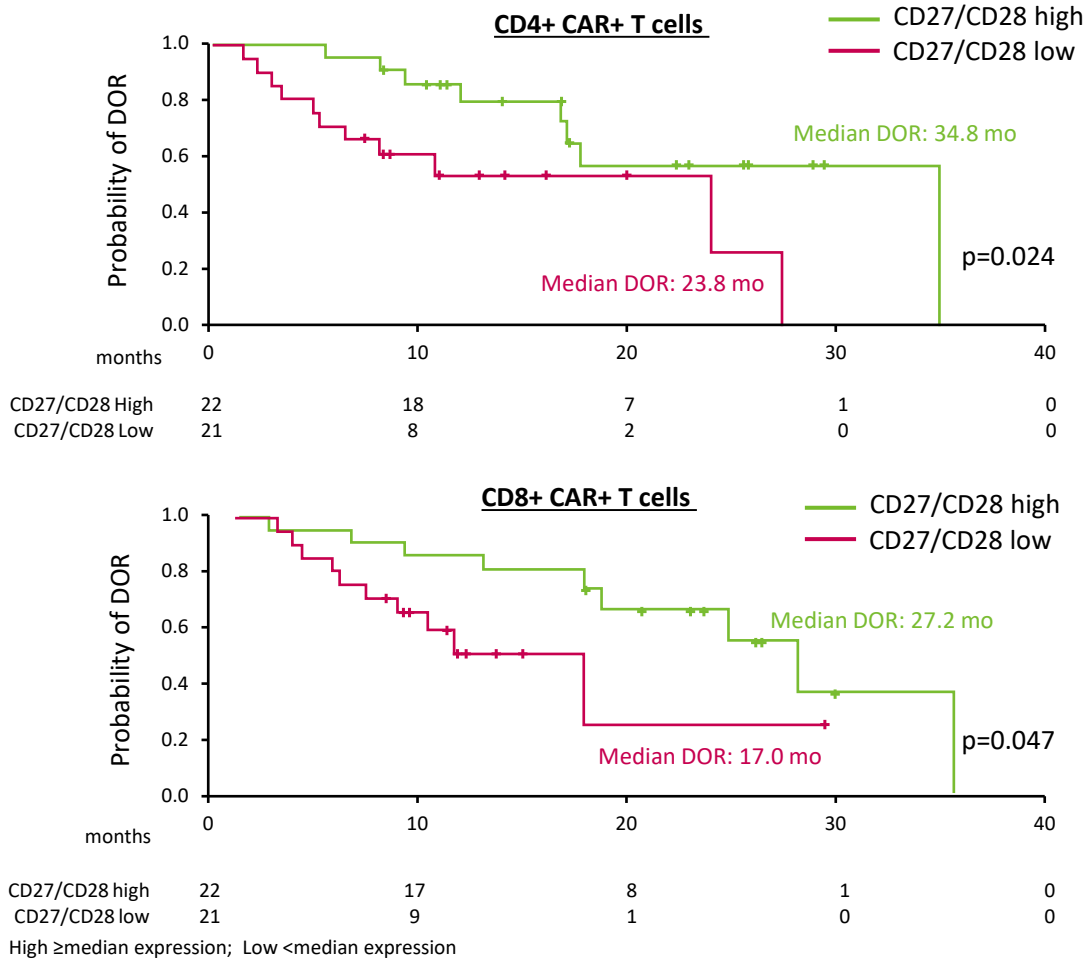


† Goldrath_Naive_vs_eff_CD8_Tcell_up; GSE11057_naive_Vs_eff_meory_CD4_Tcell_up; GSE9650_naive_vs_eff_CD8_Tcell_up

†† Kaech_Naive_vs_day8_eff_CD8_TCELL_DN; GSE9650_Naive_vs_Eff_CD8_Tcell_Dn; GSE11057_Naive_vs_eff_Memory_CD4_Tcell_Dn

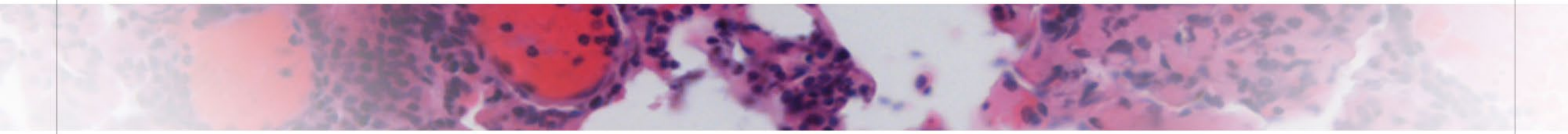
**0.001 < P < 0.01; * 0.01 < P < 0.05; • 0.05<P<0.1 ‡ N=50

Peak Expansion: T Cell Phenotype (N=43)



High ≥median expression; Low <median expression

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide



UNIVERSAL Updated Phase 1 Data Validates the Feasibility of Allogeneic Anti-BCMA ALLO-715 Therapy for Relapsed/Refractory Multiple Myeloma

Sham Mailankody, MBBS[1], Michaela Liedtke, MD[2], Surbhi Sidana, MD[3], Jeffrey V. Matous, MD[4], Saurabh Chhabra, MD, MS[5], Olalekan O. Oluwole, MBBS, MPH[6], Shahbaz A. Malik, MD[7], Shaji Kumar, MD[8], Rajneesh Nath, MD[9], Faiz Anwer, MD[10], Jose Carlos Cruz, MD[11], Sundar Jagannath, MD[12], Myo Htut[13], Noopur S. Raje, MD[14], David S. Siegel, MD, PhD[15], Erin E. Karski, MD[16], Wade Lovelace[16], Afrodite Lourbakos, PhD[16], Arun Balakumaran, MD, PhD[16], and Parameswaran Hari[5]

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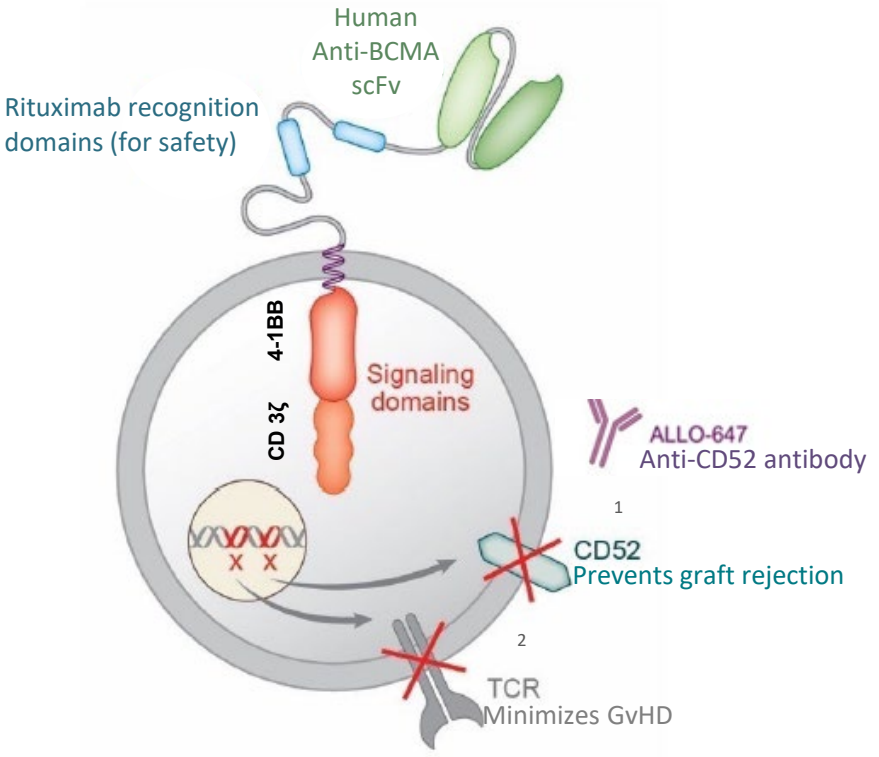
Srinand Ponnathapura Nandakumar, PhD, formally of Allogene Therapeutics, provided additional support.

Presented by Sham Mailankody, MBBS

NCT04093596

The First Allogeneic anti-BCMA CAR T Study for R/R Multiple Myeloma

- BCMA cell therapy has demonstrated unprecedented efficacy, but is not readily available to all patients
- Allogeneic chimeric antigen receptor (CAR) T cell therapy has the potential for all eligible patients to receive therapy on demand and supports re-dosing
- ALLO-715 (anti-BCMA) is an allogeneic CAR T cell product utilizing TALEN®* gene editing specifically designed to
  - Disrupt TCRα constant gene – to reduce the risk graft-versus-host disease (GvHD)
  - Edit CD52 gene – permits use of ALLO-647 (a humanized anti-CD52 mAb) to selectively deplete host T cells while protecting donor cells



1. TALEN-mediated CD52 KO allows selective lymphodepletion with ALLO-647
2. TALEN-mediated TRAC KO eliminates TCRα expression to minimize risk of GvHD

Patient Flow

Median Time from Enrollment to Start of Treatment for All Patients: 5 Days

Part A Enrolled (N=48)

5 patients became ineligible due to organ failures from rapidly progressing disease

Part A Safety Population (N=43)

Part A Efficacy Population (N=43)

CAR+ T Cell Dose	Lymphodepletion Regimen			
	FCA39	FCA60	FCA90	CA39
40 x 10^6 Cells (DL1)	3	–	–	–
160 x 10^6 Cells (DL2)	4	–	–	3
320 x 10^6 Cells (DL3)	11	10	3	3
480 x 10^6 Cells (DL4)	3	3	–	–

*Overall median follow-up time = **4 Months***

- Patient flow includes patients enrolled in Part A of study
  - Part A was a single dose of ALLO-715 cells in dose escalation which was previously presented
  - Multiple LD regimens were evaluated at DL3 and DL4
- This presentation focuses on the results from the expansion of DL3

Encouraging Efficacy Seen with Additional Patients at DL3

Med prior lines = 5
CRS= 56%, neurotox = 14%

Cell Dose & LD Regimen	DL3 (320M CAR+ T Cells)*				DL4 (480M CAR+ T Cells)	
	FCA39 N=11	FCA60 N=10	FCA90 N=3	FCA ALL N=24	FCA39 N=3	FCA60 N=3
ORR†, n (%) (95% CI)	**7 (64)** (31, 89)	**8 (80)** (44, 98)	**2 (67)** (9, 99)	**17 (71)** (49, 87)	**1 (33)** (0.8, 91)	**2 (67)** (9, 99)
VGPR+ Rate, n (%)	5 (46)	5 (50)	1 (33)	11 (46)	0	2 (67)
CR/sCR Rate, n (%)	3 (27)	3 (30)	0	6 (25)	0	0
mDOR, months (95% CI)	8.3 (3.4, 11.3)	NE (5.6, NE)	3.1 (2.4, 3.1)	8.3 (3.4, 11.3)	1.4 (NE, NE)	NE (1.5, NE)
Median follow-up, months (range)**	3.3 (0.5, 3.8)	3.8 (3.1, 11.2)	--	3.8 (0.5, 11.2)	--	7.4 (7.4, 7.4)

- In the FCA 320M CAR+ cell dose group, 17 patients **(71%) achieved an overall response rate (ORR)**
  - 11 (46%) were VGPR+, of those 6 (25%) were CR/sCR

* Three patients treated with 320M CAR+ cells and the CA LD regimen are not included above. Two of those responded with one pt achieving a CR
† Clinical response evaluation was based on IMWG response criteria, Kumar et al, 2016
** Median follow-up is for censored pts

Beyond BCMA??

Memorial Sloan Kettering Cancer Center™

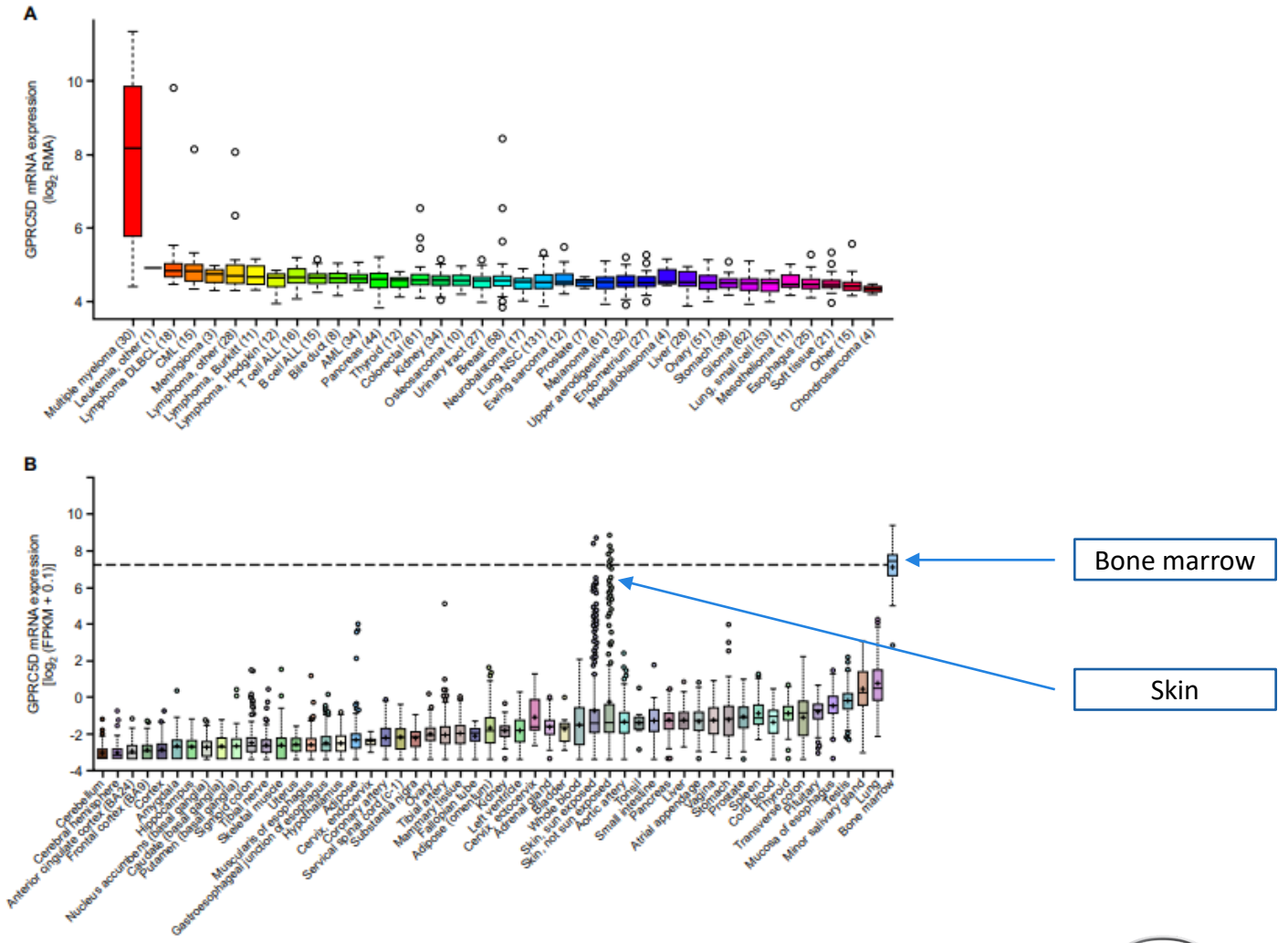
Phase I First-in-Class Trial of MCARH109, a G Protein Coupled Receptor Class C Group 5 Member D (GPRC5D) Targeted CAR T Cell Therapy in Patients with Relapsed or Refractory Multiple Myeloma

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

Memorial Sloan Kettering Cancer Center™

GPRC5D: Highly expressed in myeloma; limited normal tissue expression



Smith EL. et al. Science Translational Medicine 2019

Memorial Sloan Kettering Cancer Center

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 (%)	3 (100)	3 (100)	6 (100)	4 (80)	16 (94)
Refractory to bridging, n (%)	3 (100)	3 (100)	5 (83)	4 (80)	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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UCARTCS1A, an allogeneic CAR T-cell therapy targeting CS1 in patients with relapsed/refractory multiple myeloma (RRMM): Preliminary translational results from a first-in-human phase I trial (MELANI-01)

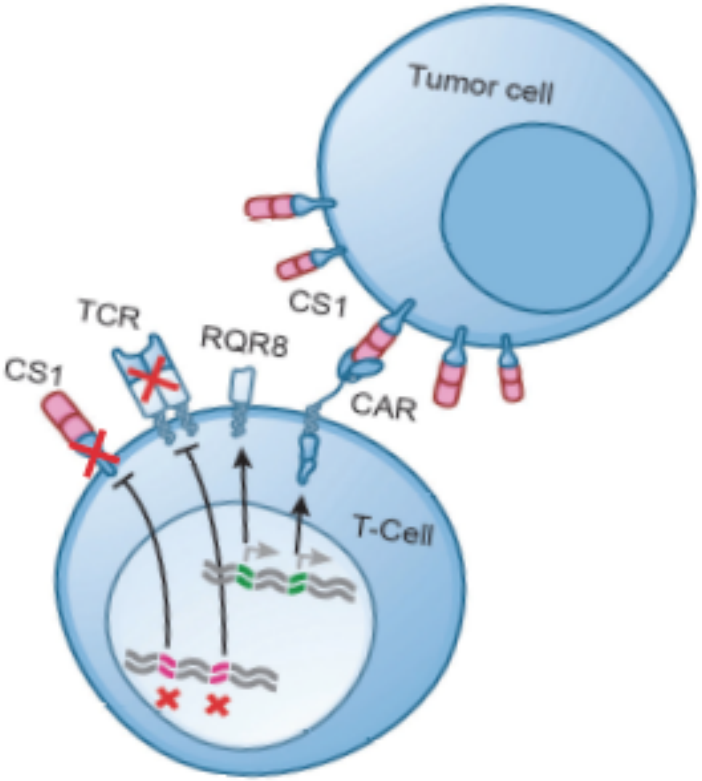
Krina K Patel[1], Mini Bharathan[2], David Siegel[3], Adriana Rossi[4], Mark G. Frattini[2], Julianne Smith[5], Carrie Brownstein[2]

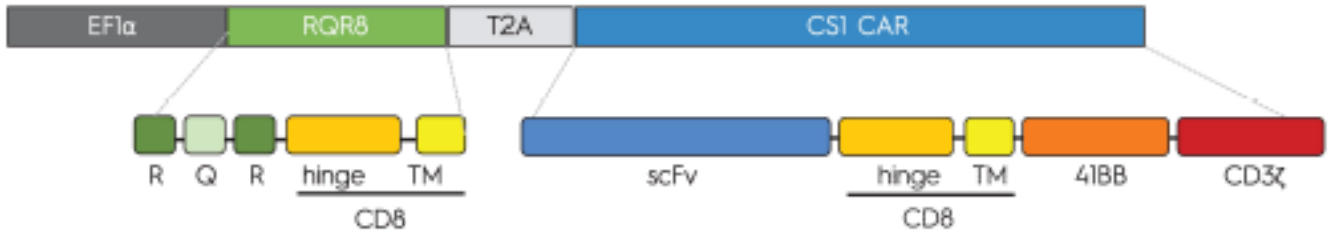
[1]The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Cellectis, Inc., New York, NY, [3]John Theurer Cancer Center, Hackensack, NJ, [4]Weill Cornell Medical College, New York, NY, [5]Cellectis, S.A., Paris

UCARTCS1A: First Allogeneic CAR-T Cell Therapy To Target CS1/SLAMF7

UCARTCS1A Product Attributes

- **Anti-CS1 CAR:** Targets CS1/SLAMF7+ tumor cells-highly and consistently expressed in MM
- **TRAC gene KO**: Avoid GvHD by disrupting TCR assembly
- **CS1 KO:** Facilitate robust UCARTCS1A expansion and yield by avoiding fratricide
- **RQR8 safety switch**: CD20 mimotope in RQR8 could be engaged by rituximab



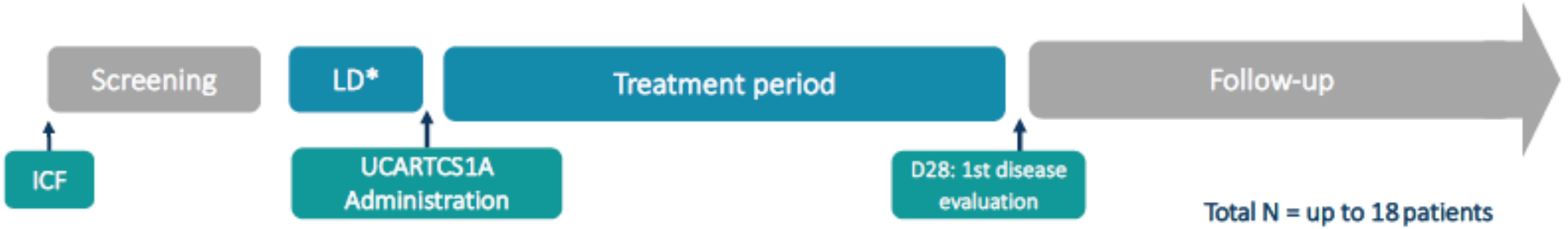


R= CD20 mimotope (rituximab)
Q= CD34 epitope (QBEnd10)

CAR, chimeric antigen receptor; CS1, CD2 subset-1 (also CD319/SLAMF7); GvHD, graft-versus-host disease; KO, knock-out; LD, lymphodepletion; TCR, T cell receptor; TRAC, T-cell receptor

MELANI-01: Study Schema

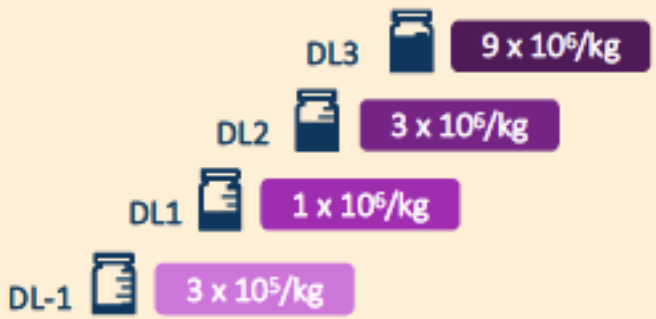
Patient flow



Key Eligibility

- Patients with confirmed MM (IMWG criteria) relapsed after prior MM therapy
- ECOG PS <2
- No prior investigational drug or cell/gene therapy targeting CS1
- Adequate organ function

Dose escalation



Key Objectives

Primary and Secondary

- Safety and tolerability
- MTD and Efficacy

Exploratory Objectives

- CS1 expression on MM cells
- UCARTCS1A expansion and persistence
- Changes in serum biomarkers; immune cell reconstitution

(NCT04142619)

*Lymphodepletion: Fludarabine 30mg/m2/day, Day -5 to -2; Cyclophosphamide 1g/m^2/day, Day -4 to -2.

CS1, CD2 subset-1 (also CD319/SLAMF7); D, day; DL, dose level; ECOG PS, Eastern Cooperative Oncology Group performance status; ICF, informed consent form; IMWG, International Myeloma Working Group; LD, lymphodepletion; LTFU, long-term follow-up; MM, multiple myeloma; MTD, maximum tolerated dose; RRMM, relapsed/refractory multiple myeloma; Y, year.

All Treated Patients: Baseline Characteristics and Clinical Response

Patient ID Dose level	Light chain disease	Prior lines of therapy	Cytogenetics	Tumor Burden (Screen)-Local lab analysis*	CAR T cell detection	Clinical Response
102-101 DL-1	kappa	• 1st treatment in 2009 • 15 lines of therapy including auto-transplant (twice), BCMA CAR T, daratumumab, elotuzumab + pom	del(17p), t(4;14)	BM aspirate + biopsy: 5% plasma cells	Detection at D9 and D11 (<LLOQ)	PD
102-109 DL-1	kappa	• 1st treatment in 2015 • 12 prior lines including 1 auto-transplant, BCMA ADC	Normal	No detectable plasma cells (measurable plasmacytoma)	Not detected	SD
102-107 DL-1	kappa	• 1st treatment in 2015 • 11 prior lines including 2 auto-transplant and daratumumab	del(17p), t(4;14), 1q21 (CKS1B) t(11;14)	BM biopsy: 60% plasma cells	Not detected	Patient withdrew at D24
102-111 DL1	lambda	• 1st treatment in 2016 • 4 prior lines including auto-transplant, daratumumab, elotuzumab	+1q21 (CKS1B)	BM aspirate & biopsy: 90% plasma cells	Initial detection at D9 **Peak** levels at D28	PR with MRD negativity by D28 VGPR at M3
102-113 DL2	kappa	• 1st treatment in 2015 • 13 lines including auto-transplant, venetoclax, elotuzumab, daratumumab, 2x BCMA CAR T	t(11;14) & monosomy 13 as per history	BM aspirate & biopsy: 1% plasma cells (aspirate quality poor)	Initial detection at D7 **Peak** levels D7-D11	PR on D14

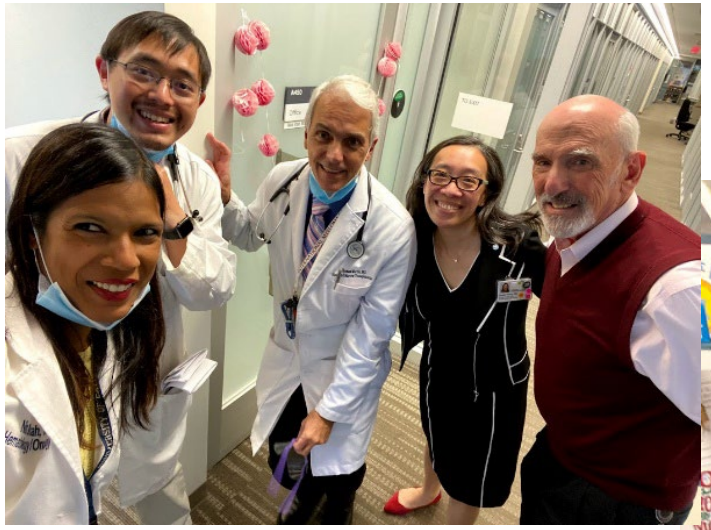
***Exploratory analysis: 97-100 % of detected plasma cells expressed CS1 with high intensity in all patients**

CAR T has arrived…now what??

- Label: 4 lines of treatment
- Hypothetical patient:
  1. VRD→ ASCT→ len maintenance
  2. DPD/ DKD/ IKD
  3. KCD/ PCD
  4. ???
- But what about the #myelennial patients??
- KRD, D-VRD may make this a little more challenging
- → but no one ever said single agent dex couldn't be a line…
- How will we decide between CAR and T cell engager?

Conclusions

- Autologous BCMA CAR T cells
- Exciting therapies on the horizon
- But no cures yet!
- The future is immunotherapy bright
  - I suspect 2nd line by 2023
  - No worries – always room for new CELMoDs, alkylating agents and Selinexor
  - Room for personalization
- Now have to consider: cost, quality of life, accessibility, referral patterns, logistics



THANK YOU!

@ninashah33

#myelennial

UCSF