CAR T-Cell Therapy for Relapsed/Refractory Multiple Myeloma

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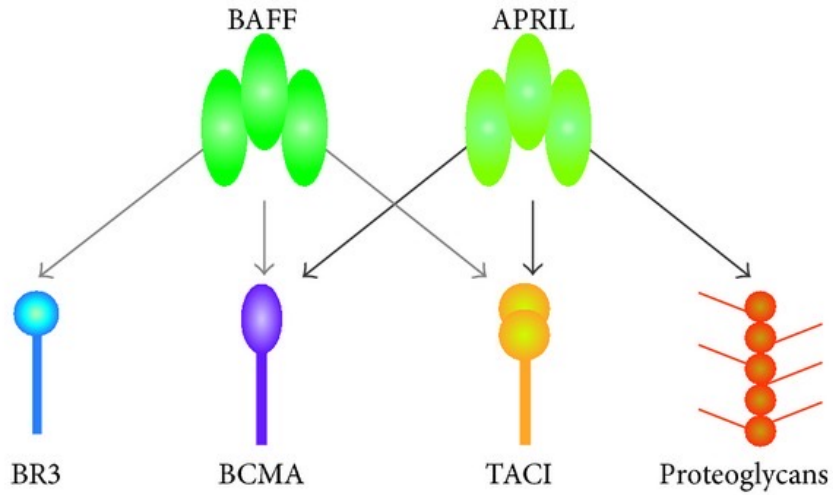
BCMA: B-cell maturation antigen

- 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

2020 ASCO ANNUAL MEETING
UNITE AND CONQUER: ACCELERATING PROGRESS TOGETHER

KarMMa™

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*

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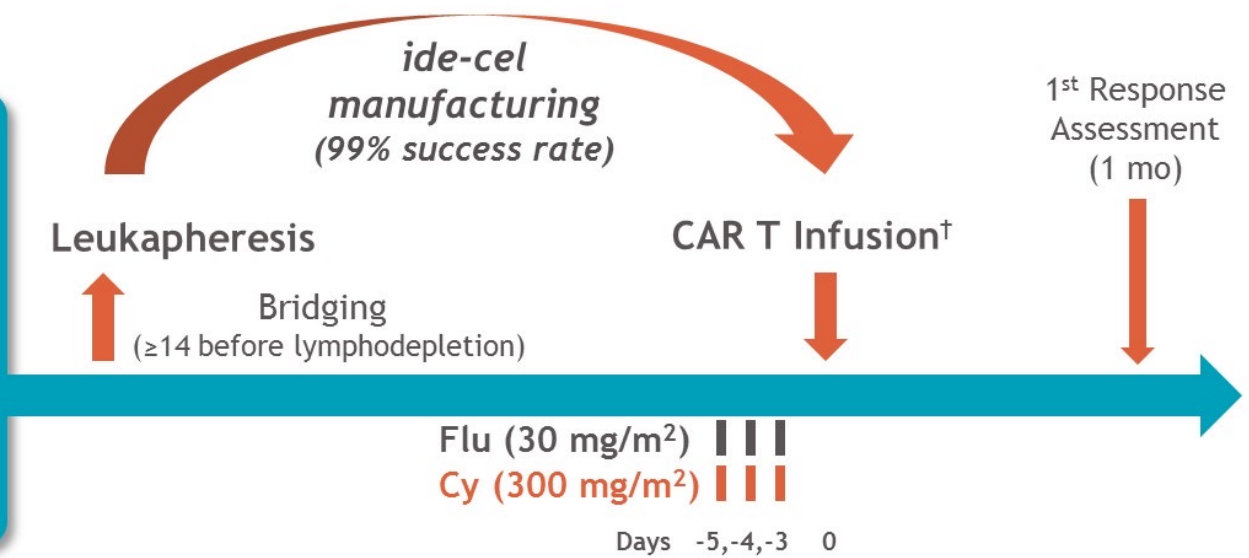
Presentation Number 8503

Phase II Pivotal KarMMa Study

- RRMM
- ≥3 prior regimens with ≥2 consecutive cycles each (or best response of PD)
- Previously exposed to:
  - IMiD agent
  - Proteasome inhibitor
  - Anti-CD38 antibody
- Refractory to last prior therapy per IMWG*



Study Status as of Jan 14, 2020

Screened N=158

Leukapheresed N=140

Treated N=128 (Target Dose CAR+ T cells)

150 × 10⁶	n=4
300 × 10⁶	n=70
450 × 10⁶	n=54

Median Follow-up (mo)

150 × 10⁶	18.0
300 × 10⁶	15.8
450 × 10⁶	12.4
Total	13.3

Endpoints

- **Primary**: ORR (null hypothesis ≤50%)
- **Secondary:** CRR (key secondary; null hypothesis ≤10%), Safety, DOR, PFS, OS, PK, MRD‡, QOL, HEOR
- **Exploratory:** Immunogenicity, BCMA expression/loss, cytokines, T cell immunophenotype, GEP in BM

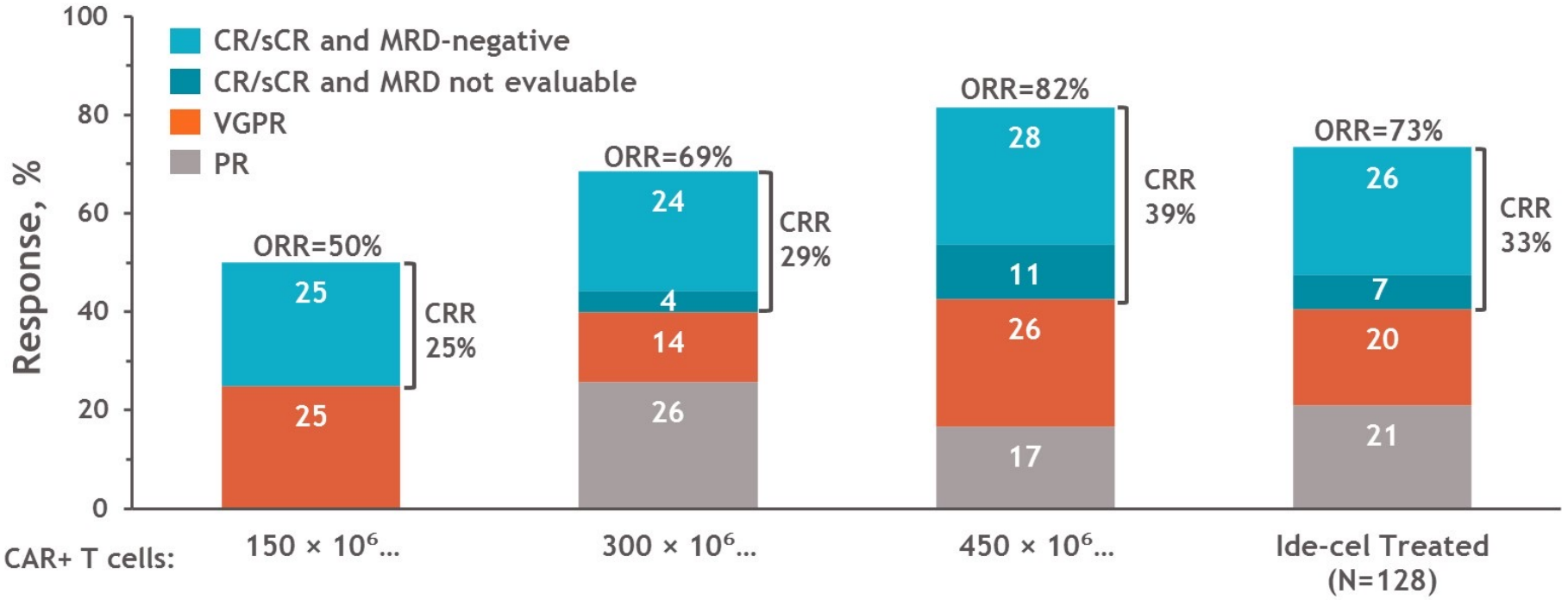
CRR, complete response rate; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; GEP in BM, gene expression profile in bone marrow; HEOR, health economics and outcomes research; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; QOL, quality of life.
*Defined as documented disease progression during or within 60 d from last dose of prior antimyeloma regimen. †Patients were required to be hospitalized for 14 d post-infusion. Ide-cel retreatment was allowed at disease progression for best response of at least stable disease. ‡By next-generation sequencing.

EudraCT: 2017-002245-29
ClinicalTrials.gov: NCT03361748

Best Overall Response

Median # prior regimens: 6

CRS: 84%
Neurotox: 18%

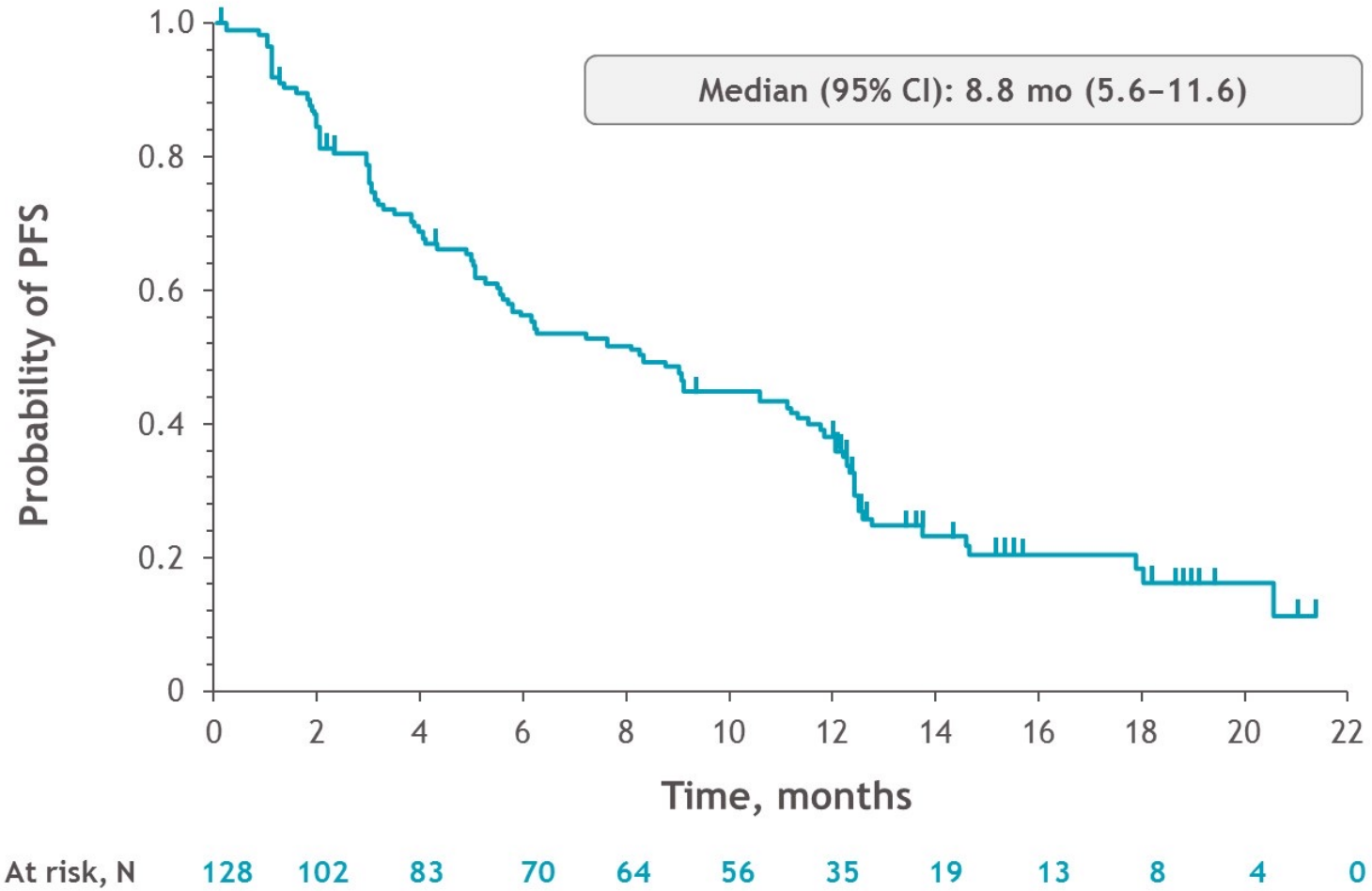


- Primary (ORR >50%) and key secondary (CRR >10%) endpoints met in the ide-cel treated population
  - *ORR of 73% (95% CI, 65.8–81.1; P<0.0001*)*
  - *CRR (CR/sCR) of 33% (95% CI, 24.7–40.9; P<0.0001)*
- Median time to first response of 1.0 mo (range, 0.5–8.8); median time to CR of 2.8 mo (range, 1.0–11.8)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

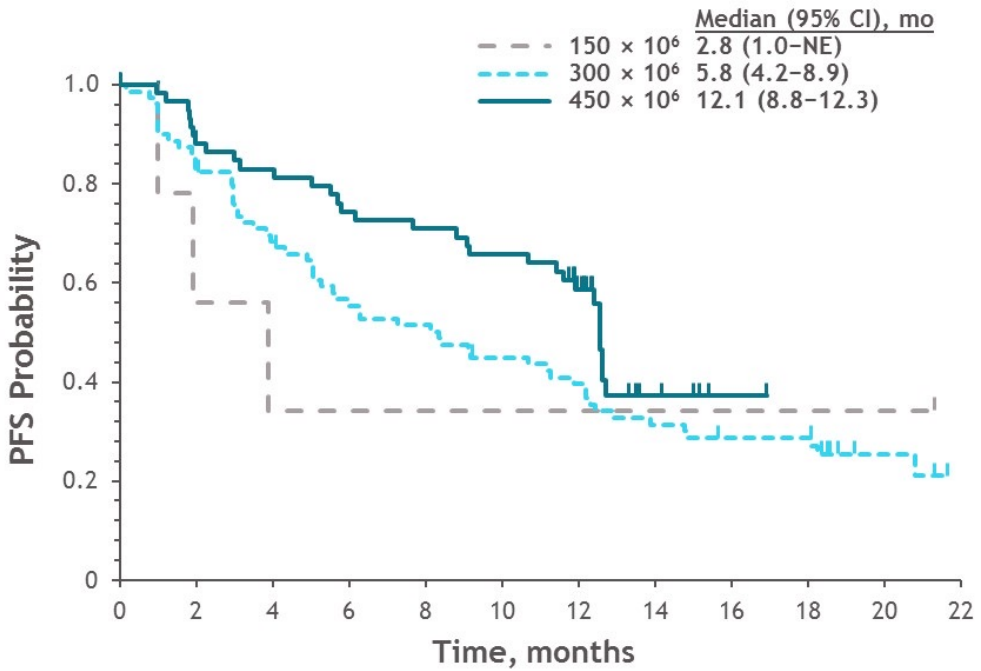


Data cutoff: 14 Jan 2020. PFS, progression-free survival.

Munshi et al, ASCO 2020

Progression-Free Survival

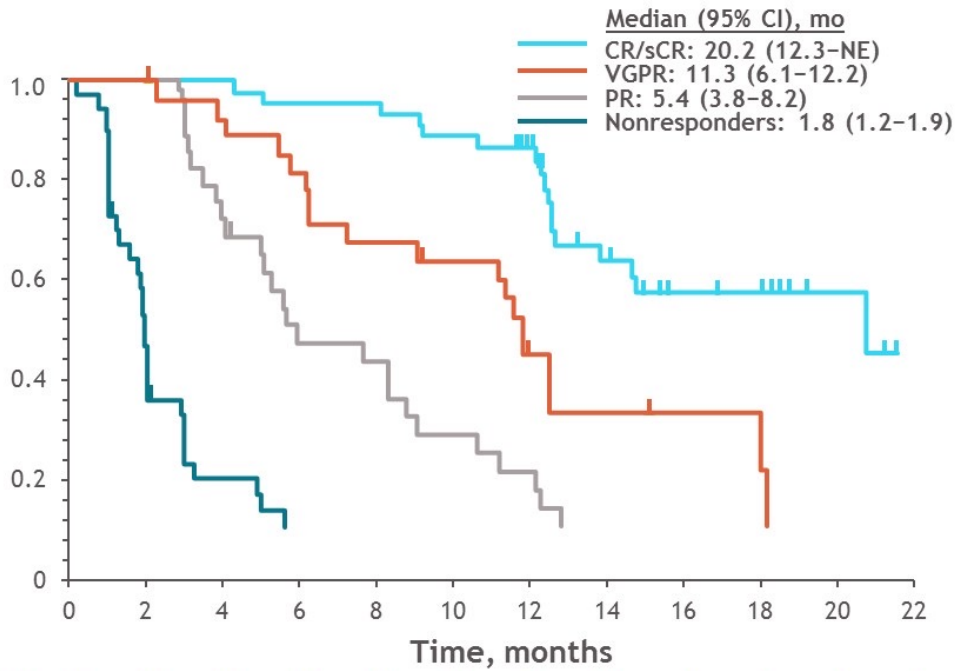
PFS by Target Dose



At risk, N												
150 × 10⁶	4	2	1	1	1	1	1	1	1	1	1	0
300 × 10⁶	70	56	42	33	29	24	17	14	11	7	2	0
450 × 10⁶	54	44	40	36	34	31	17	4	1	0	0	

- PFS increased with higher target dose; median PFS was 12 mo at 450 × 10⁶ CAR+ T cells

PFS by Best Response



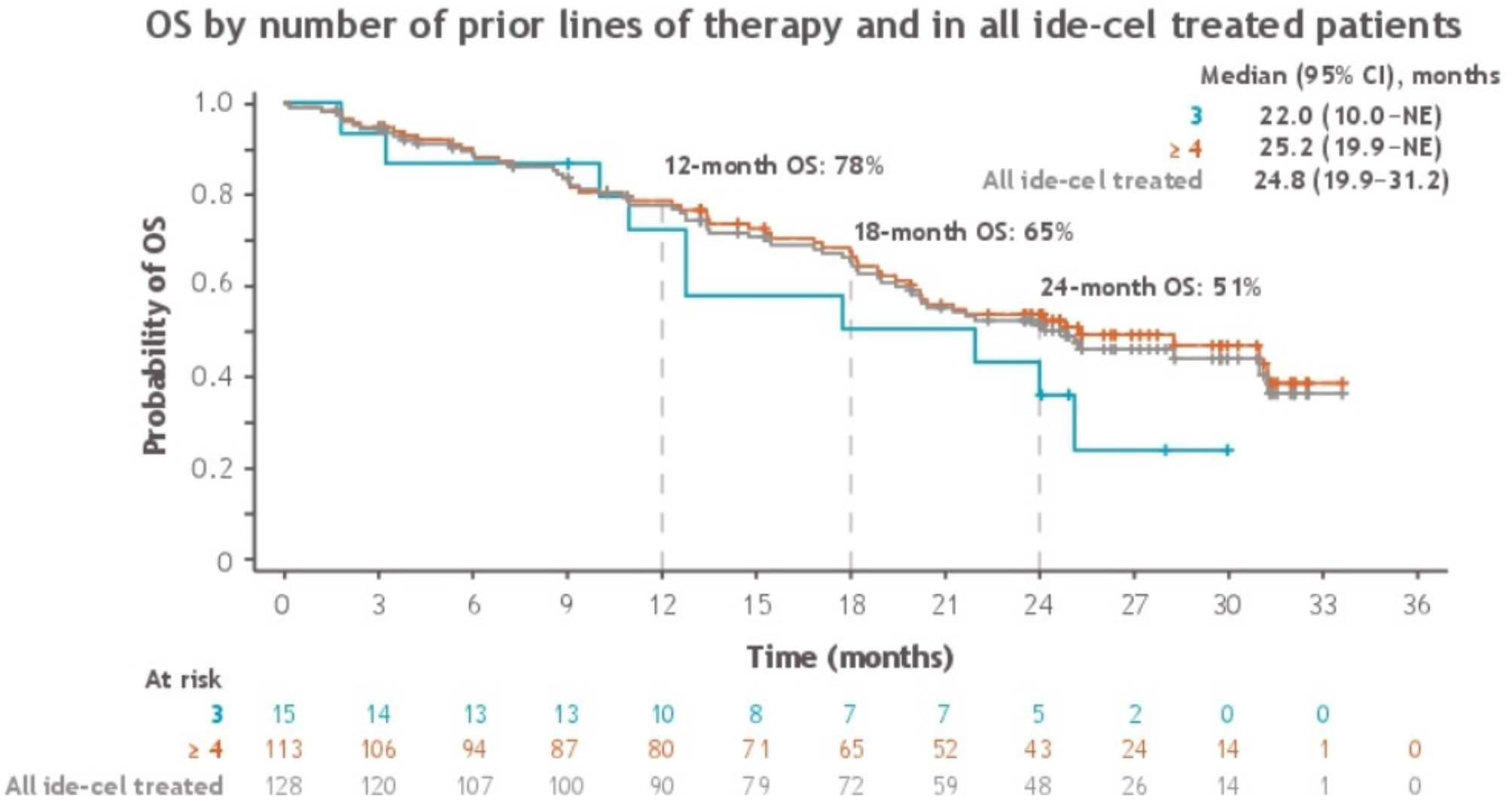
CR/sCR	42	42	42	40	39	37	26	16	11	8	4	0
VGPR	25	25	22	20	16	14	8	3	2	0	0	
PR	27	16	10	9	5	1	0	0	0	0	0	
Nonresponders	34	8	83	70	64	56	35	19	13	8	4	0

- 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

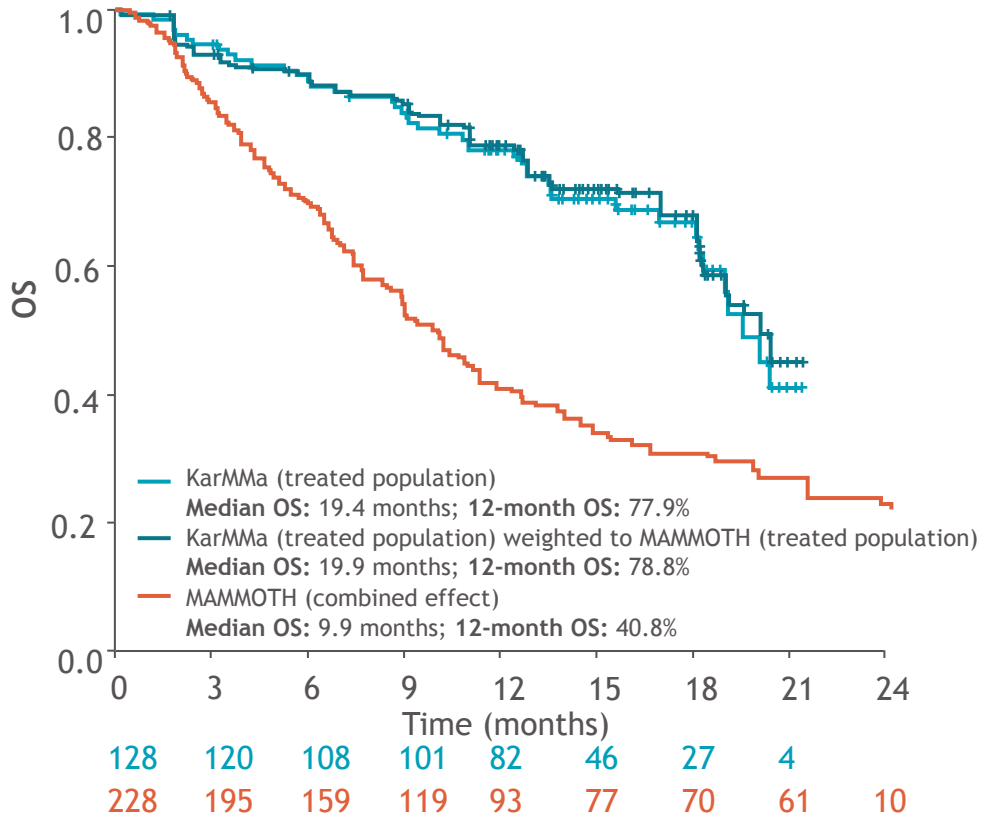
KarMMa: Updated OS[1]



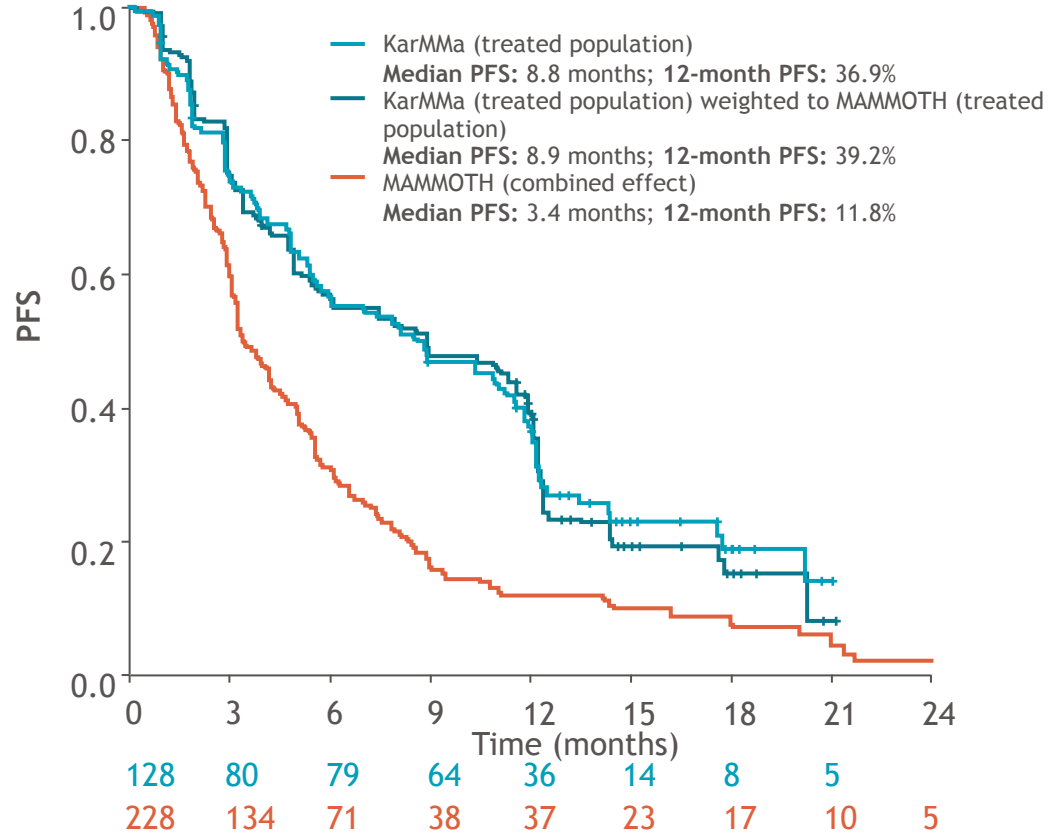
1. Anderson LD, et al. ASCO 2021. Abstract 8016.

OS and PFS: ide-cel versus conventional care

OS: Ide-cel (KarMMa treated population) versus conventional care (MAMMOTH treated population)



PFS: Ide-cel (KarMMa treated population) versus conventional care (MAMMOTH treated population)

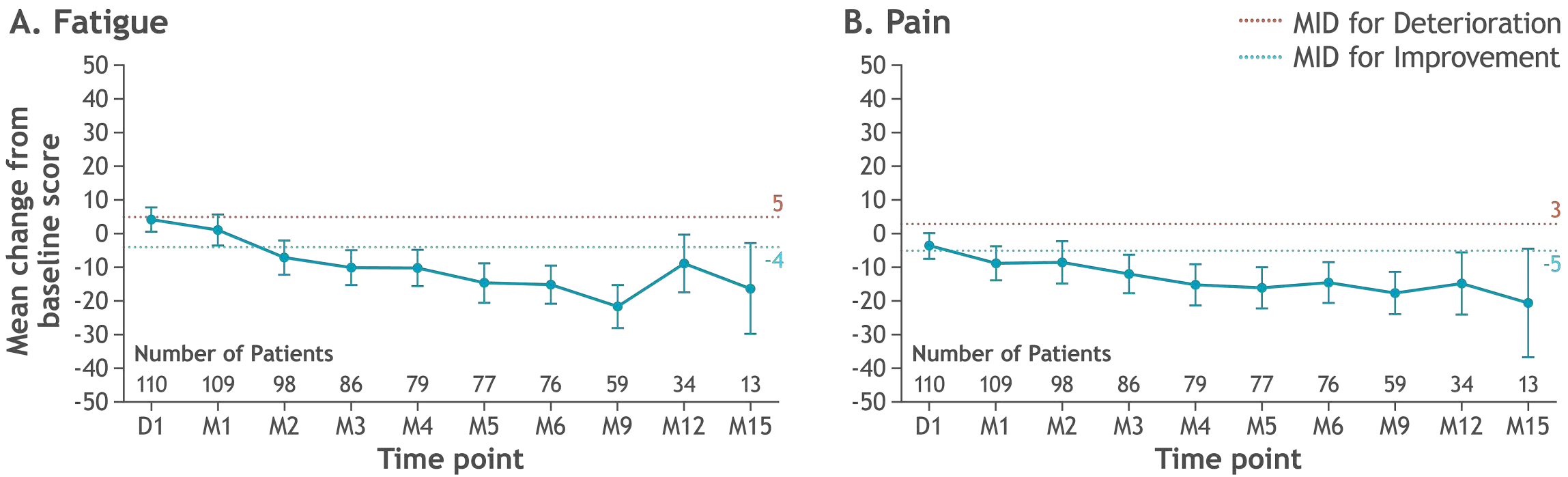


- Median OS and median PFS were significantly longer for the ide-cel-treated population (weight-matched) compared with the conventional care population in MAMMOTH in the base case

OS, overall survival; PFS, progression-free survival.

Shah N, et al. ASH 2020 [abstract #1653]

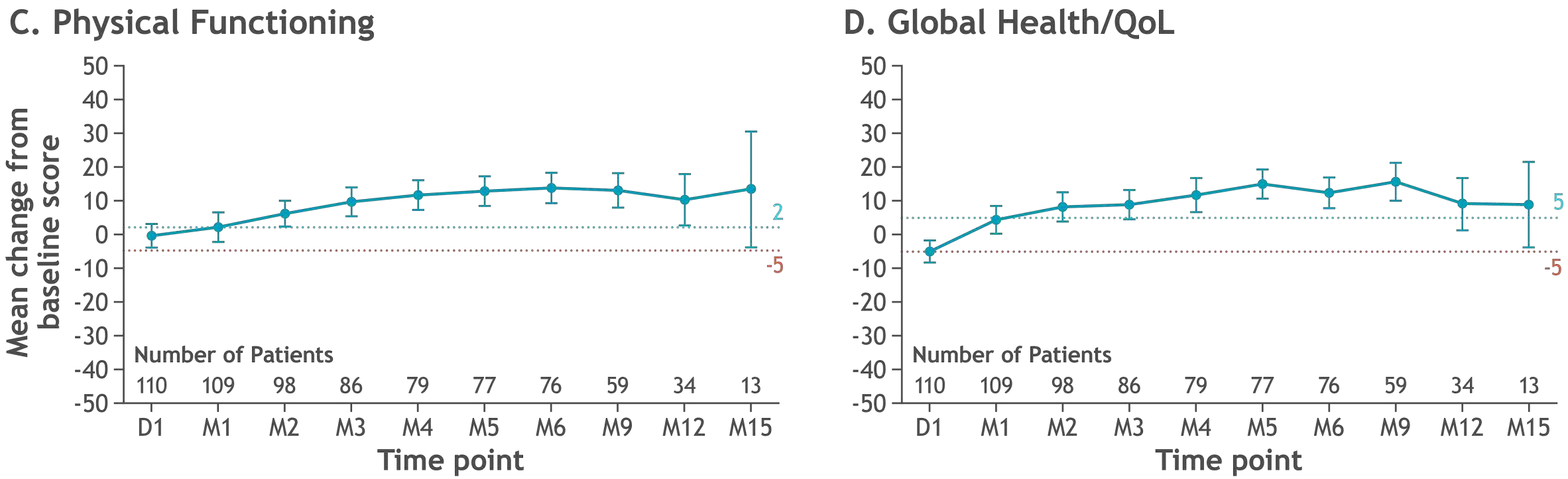
Figure 3. Mean change from baseline in EORTC QLQ-C30 subscale scores



D, day; M, month; MID, Minimal Important Difference.
Baseline defined as last non-missing assessment on/prior to day of lymphodepleting chemotherapy.
Error bars represent 95% confidence intervals.

Delforge M et al; EHA 2020 #EP1000]

Figure 3. Mean change from baseline in EORTC QLQ-C30 subscale scores (Cont.)

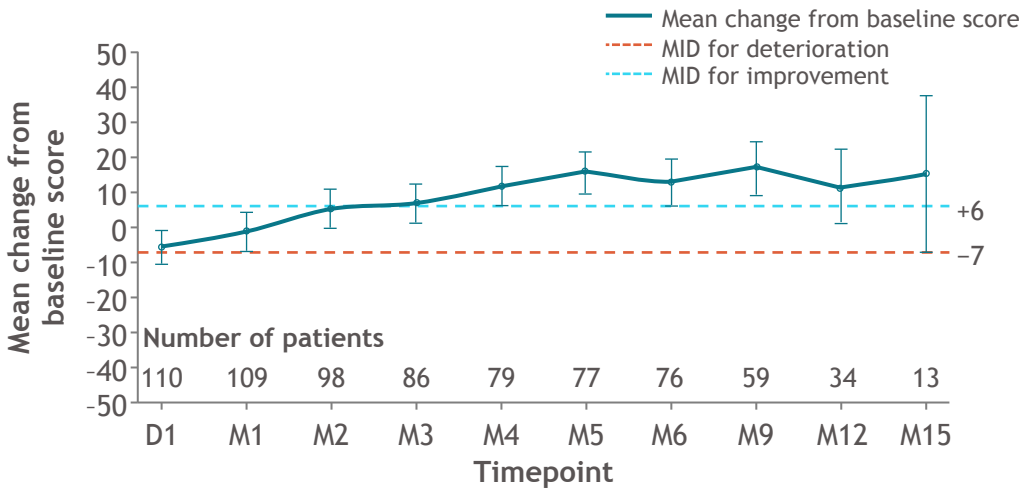


D, day; M, month; MID, Minimal Important Difference.
Baseline defined as last non-missing assessment on/prior to day of lymphodepleting chemotherapy.
Error bars represent 95% confidence intervals.

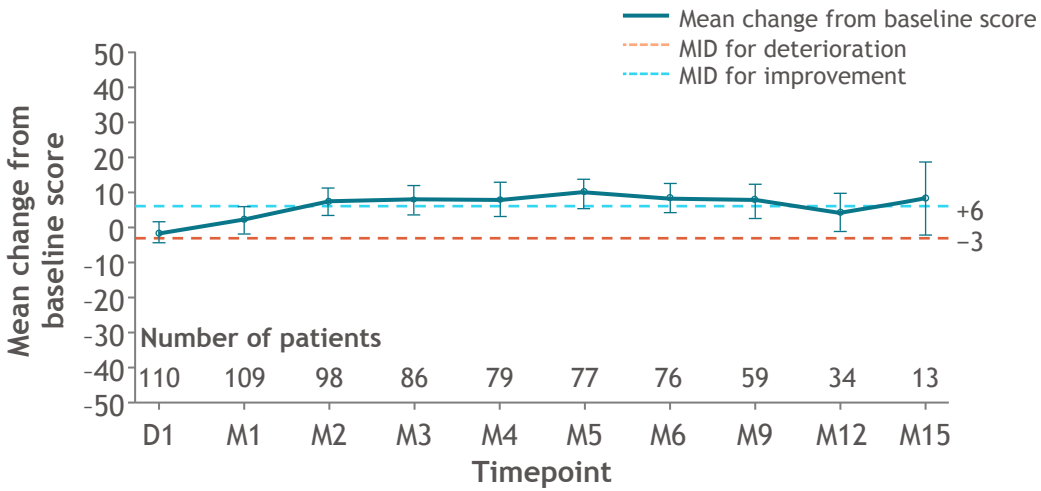
Delforge M et al; EHA 2020 #EP1000]

KarMMa: Clinically meaningful improvements were observed on all functioning EORTC QLQ-C30 secondary subscales

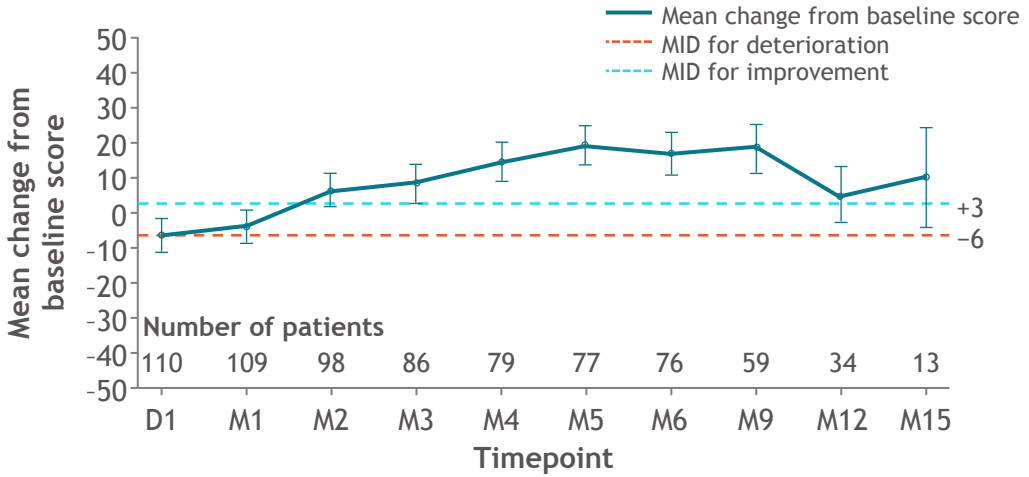
Role Functioning



Emotional Functioning



Social Functioning



These improvements were statistically significant for the Role Functioning and Social Functioning subscales at multiple time points

Day 1 is day of infusion. Error bars denote 95% confidence intervals.
D1, Day 1; M, month; MID, minimal important difference.

Shah N, et al. ASH 2020 [abstract #437]

Ide-cel total 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

2021 ASCO® ANNUAL MEETING

CILTACABTAGENE AUTOLEUCEL, A B-CELL MATURATION ANTIGEN–DIRECTED CHIMERIC ANTIGEN RECEPTOR T-CELL THERAPY, IN RELAPSED/REFRACTORY MULTIPLE MYELOMA: UPDATED RESULTS FROM CARTITUDE-1

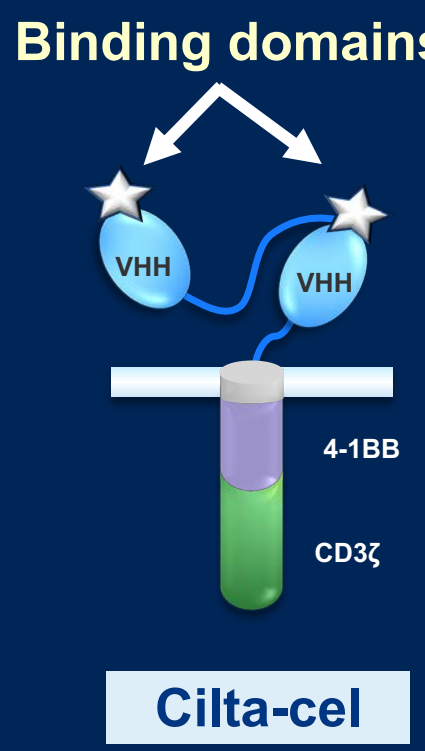
Saad Z Usmani[1], Jesus G Berdeja[2], Deepu Madduri[3], Andrzej Jakubowiak[4], Mounzer Agha[5], Adam D Cohen[6], Parameswaran Hari[7], Tzu-Min Yeh[8], Yunsi Olyslager[9], Arnob Banerjee[10], Carolyn C Jackson[8], Alicia Allred[10], Enrique Zudaire[10], William Deraedt[9], Xiaoling Wu[11], Marlene J Carrasco-Alfonso[11], Muhammad Akram[11], Yi Lin[12], Thomas Martin[13], Sundar Jagannath[3]

[1]Levine Cancer Institute-Atrium Health, Charlotte, NC, USA; [2]Sarah Cannon Research Institute, Nashville, TN, USA; [3]Mount Sinai Medical Center, New York, NY, USA; [4]University of Chicago, Chicago, IL, USA; [5]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [6]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [7]Medical College of Wisconsin, Milwaukee, WI, USA; [8]Janssen R&D, Raritan, NJ, USA; [9]Janssen R&D, Beerse, Belgium; [10]Janssen R&D, Spring House, PA, USA; [11]Legend Biotech USA, Inc, Piscataway, NJ, USA; [12]Mayo Clinic, Rochester, MN, USA; [13]UCSF Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA

June 8, 2021

CARTITUDE-1: Introduction

- CARTITUDE-1 (NCT03548207) is a phase 1b/2 study evaluating cilta-cel, a CAR T-cell therapy with two BCMA–targeting single-domain antibodies, in patients with R/R MM who have been heavily pretreated[1]
  - At a median follow-up of 12.4 months after cilta-cel treatment, the overall response rate was 97% with an sCR rate of 67%; overall 12-month PFS and OS rates were 77% and 89%, respectively
- Here, we present updated results from CARTITUDE-1 in patients with a longer follow-up (median: 18 months)



BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; OS, overall survival; PFS, progression-free survival; R/R MM, relapsed refractory multiple myeloma; sCR, stringent complete response; VHH, variable heavy chain.

1. Madduri D, et al. *Blood* 2020;136(Suppl 1):22–25.

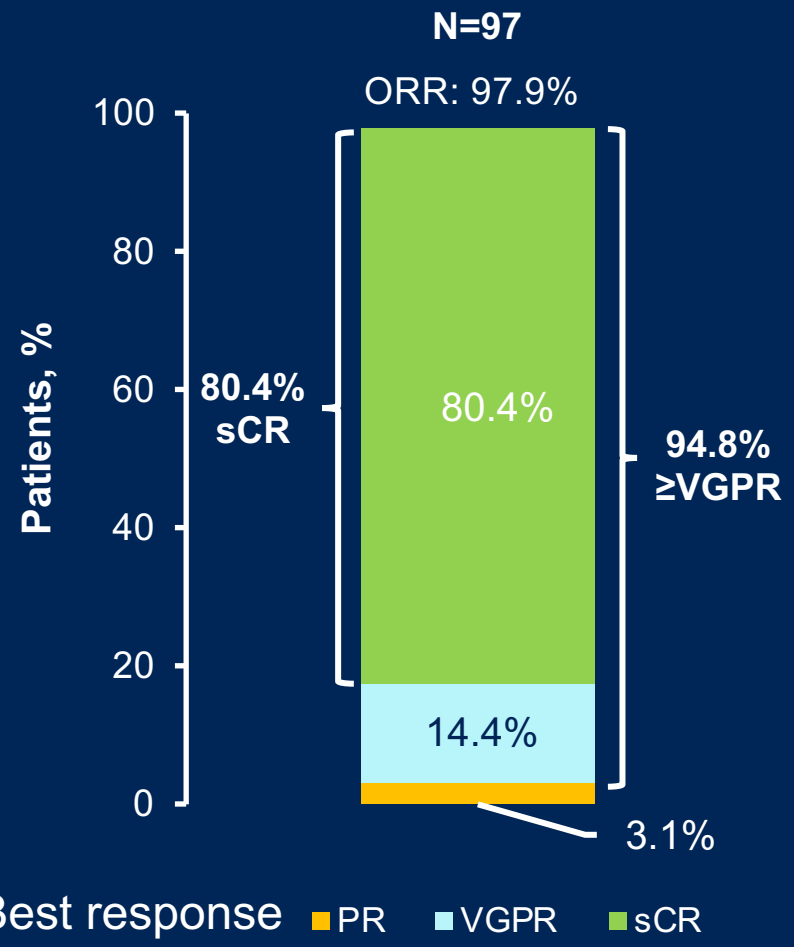
CARTITUDE-1: Baseline Characteristics

Characteristic	
Age, median (range) years	61.0 (43–78)
Male, n (%)	57 (58.8)
Black/African American, n (%)	17 (17.5)
All plasmacytomas,[a] n (%)	19 (19.6)
Extramedullary plasmacytomas, n (%)	13 (13.4)
Bone-based plasmacytomas, n (%)	6 (6.2)
Bone-marrow plasma cells ≥60%, n (%)	21 (21.9)
Years since diagnosis, median (range)	5.9 (1.6–18.2)
High-risk cytogenetic profile, n (%)	23 (23.7)
del17p	19 (19.6)
t(14;16)	2 (2.1)
t(4;14)	3 (3.1)
Tumor BCMA expression ≥50%, n (%)	57 (91.9)[b]

Characteristic	
Prior lines of therapy, median (range)	6.0 (3–18)
Prior lines of therapy, n (%)	
3	17 (17.5)
4	16 (16.5)
≥5	64 (66.0)
Previous stem-cell transplantation, n (%)	
Autologous	87 (89.7)
Allogeneic	8 (8.2)
Triple-class exposed,[c] n (%)	97 (100)
Penta-drug exposed,[d] n (%)	81 (83.5)
Triple-class refractory[c]	85 (87.6)
Penta-drug refractory[d]	41 (42.3)
Refractory status, n (%)	
Carfilzomib	63 (64.9)
Pomalidomide	81 (83.5)
Anti-CD38 antibody	96 (99.0)
Refractory to last line of therapy, n (%)	96 (99.0)

BCMA, B-cell maturation antigen; IMiD, immunomodulatory drug; PI, proteasome inhibitor.
[a]All plasmacytomas include extramedullary and bone-based plasmacytomas. [b]Denominator n=62, the number of evaluable samples; BCMA expression detected in all evaluable samples. [c]At least 1 PI, at least 1 IMiD, and 1 anti-CD38 antibody. [d]At least 2 PIs, at least 2 IMiDs, and 1 anti-CD38 antibody.

CARTITUDE-1: Overall Response Rate

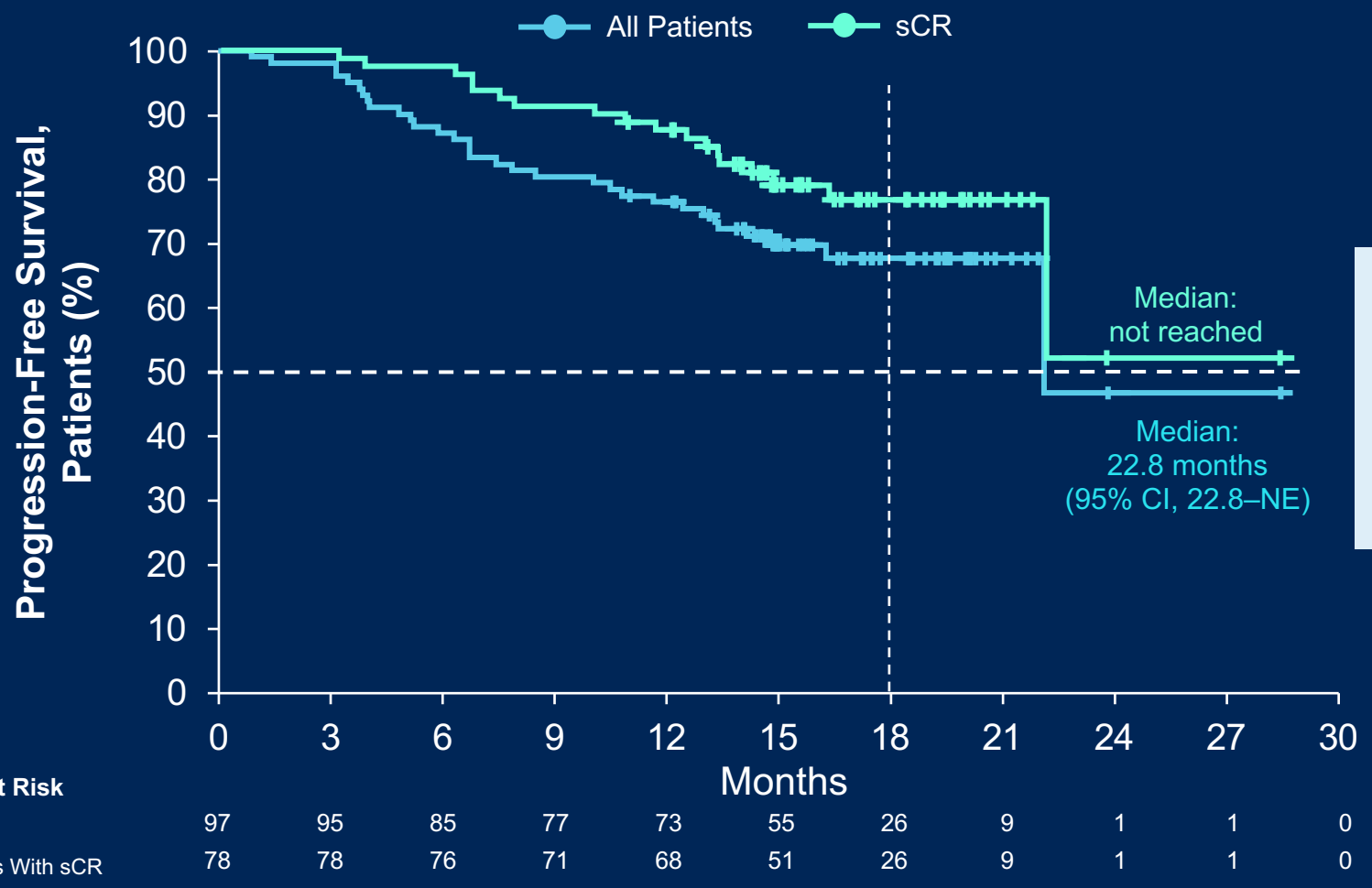


With longer follow-up, responses deepened with increasing rate of sCR

- Median time to first response: 1 month (range, 0.9–10.7)
- Median time to best response: 2.6 months (range, 0.9–15.2)
- Median time to ≥CR: 2.6 months (range, 0.9–15.2)
- Median duration of response: 21.8 months (95% CI, 21.8–NE)
  - Estimated 73% of responders have not progressed or died at 12 months
  - Median duration of response not reached in patients with sCR
- Response rates were comparable (range, 95–100%) across different subgroups (eg, number of prior lines of therapy, refractoriness, extramedullary plasmacytomas, and cytogenetic risk)[a]

CR, complete response; ORR, overall response rate; sCR, stringent complete response; VGPR, very good partial response. ORR assessed by independent review committee. [a]Subgroups by number of prior lines of therapy (≤4, >4), refractoriness (triple-class, penta-drug), cytogenetic risk (high risk, standard risk), baseline bone marrow plasma cells (≤30%, >30 to <60%, ≥60%), baseline tumor BCMA expression (≥median, <median), and baseline plasmacytomas (including extramedullary and bone-based).

CARTITUDE-1: Progression-Free Survival



Number at Risk

All Patients	97	95	85	77	73	55	26	9	1	1	0
Responders With sCR	78	78	76	71	68	51	26	9	1	1	0

18-month PFS
All Patients: 66.0% (95% CI, 54.9–75.0)
sCR: 75.9% (95% CI, 63.6–84.5)

18-month OS
All patients: 80.9% (95% CI, 71.4–87.6)

Median duration of follow-up: 18 months (range, 1.5–30.5)

NE, not estimable; PFS, progression-free survival; OS, overall survival; sCR, stringent complete response.

CARTITUDE-1: Safety

No new safety signals with longer follow-up

	N=97	
	Any grade	**Grade 3/4**
Hematologic AEs ≥25%, n (%)		
Neutropenia	93 (95.9)	92 (94.8)
Anemia	79 (81.4)	66 (68.0)
Thrombocytopenia	77 (79.4)	58 (59.8)
Leukopenia	60 (61.9)	59 (60.8)
Lymphopenia	51 (52.6)	48 (49.5)
Nonhematologic AEs ≥25%, n (%)		
Metabolism and nutrition disorders		
Hypocalcemia	31 (32.0)	3 (3.1)
Hypophosphatemia	30 (30.9)	7 (7.2)
Decreased appetite	28 (28.9)	1 (1.0)
Hypoalbuminemia	27 (27.8)	1 (1.0)
Gastrointestinal		
Diarrhea	29 (29.9)	1 (1.0)
Nausea	27 (27.8)	1 (1.0)
Other		
Fatigue	36 (37.1)	5 (5.2)
Cough	34 (35.1)	0
AST increased	28 (28.9)	5 (5.2)
ALT increased	24 (24.7)	3 (3.1)

CRS	**N=97**
Patients with a CRS event,[a] n (%)	92 (94.8)
Time to onset, median (range) days	7 (1–12)
Duration, median (range) days	4 (1–97)[b]

Of 92 patients with CRS, majority (94.6%) were grades 1/2
CRS resolved in 91 (98.9%) patients within 14 days of onset

	N=97
Total CAR T-cell neurotoxicities, n (%)	
Any Grade	20 (20.6)
Grade ≥3	10 (10.3)
ICANS, n (%)	
Any Grade	16 (16.5)
Grade ≥3	2 (2.1)
Other neurotoxicities,[c] n (%)	
Any Grade	12 (12.4)
Grade ≥3	9 (9.3)

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ASTCT, American Society for Transplantation and Cellular Therapy; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis.
[a]CRS was graded using Lee et al. (*Blood* 2014) in the phase 1b portion of the study and ASTCT in phase 2; in this combined analysis, Lee et al. criteria were mapped to ASTCT criteria for patients in the phase 1b portion.
[b]The patient with 97-day duration died due to CRS/HLH. [c]Events not reported as ICANS (ie, onset after a period of recovery from CRS and/or ICANS).

EFFICACY AND SAFETY OF THE BCMA-DIRECTED CAR T-CELL THERAPY, CILTACABTAGENE AUTOLEUCEL, IN PATIENTS WITH PROGRESSIVE MULTIPLE MYELOMA AFTER 1–3 PRIOR LINES OF THERAPY: INITIAL RESULTS FROM CARTITUDE-2

Mounzer Agha[1,*], Adam Cohen[2], Deepu Madduri[3], Yael C Cohen[4], Michel Delforge[5], Jens Hillengass[6], Hartmut Goldschmidt[7], Katja Weisel[8], Marc-Steffen Raab[9,10], Christoph Scheid[11], Jordan M Schecter[12], Kevin C De Braganca[12], Helen Varsos[12], Liwei Wang[12], Martin Vogel[13], Marlene J Carrasco-Alfonso[14], Muhammad Akram[14], Xiaoling Wu[14], Tonia Nesheiwat[14], Hermann Einsele[15]

[1]UPMC Hillman Cancer Center, Pittsburgh, PA, USA; [2]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA; [3]Mount Sinai Medical Center, New York, NY, USA; [4]Tel-Aviv Sourasky (Ichilov) Medical Center, and Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [5]Universitaire Ziekenhuizen Leuven, Leuven, Belgium; [6]Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA; [7]University Hospital Heidelberg, Internal Medicine V and National Center for Tumor Diseases (NCT), Heidelberg, Germany; [8]University Medical Center Hamburg-Eppendorf, Hamburg, Germany; [9]University Hospital Heidelberg, Heidelberg, Germany; [10]Clinical Cooperation Unit Molecular Hematology/Oncology, German Cancer Research Center, Heidelberg, Germany; [11]University of Cologne, Cologne, Germany; [12]Janssen R&D, Raritan, NJ, USA; [13]Janssen Global Services, LLC, Raritan, NJ, USA; [14]Legend Biotech USA, Inc, Piscataway, NJ, USA; [15]Universitätsklinikum Würzburg, Medizinische Klinik und Poliklinik II, Würzburg, Germany

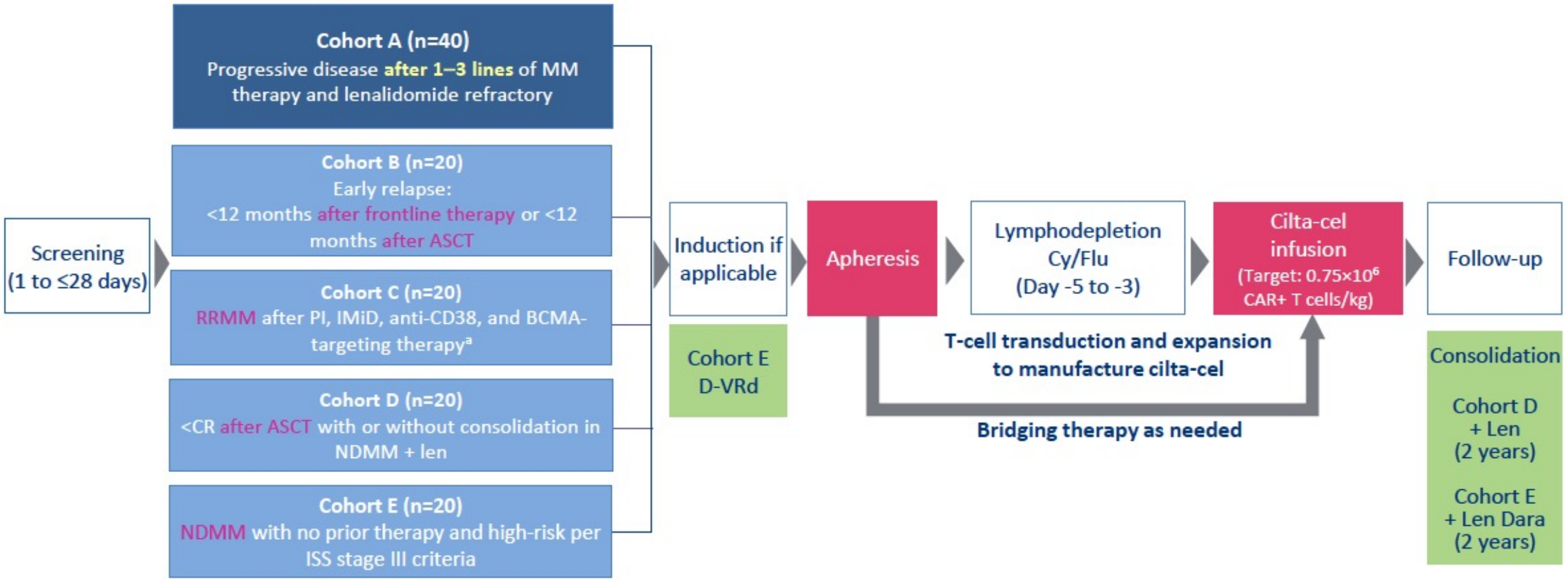
UCSF

House of CARs

Trial	CAR T product	Med prior lines	Special Sauce	ORR	CRS %	Neurotox %	Survival data	Notes
KarMMa-1 (phase II, n=128)	bb2121 (Ide-cel)	6		73% (82% @450 dose)	84%	18%	mPFS 8.8mo, 12.1 mo @450 dose OS 24.8	CAR-T Par-T in 2021!!
CARTITUDE-1 (phase Ib/II, n-97)	JNJ-4528 (Cilta-cel)	6	Bi-epitope binding to BCMA	97%	92%	20.1% (16.5% ICANS)	@ 18 mo: 66% prog-free; DOR 21.8 m	Google to the yahoo?
LUMMICAR-2 (phase Ib/II, n=18-20)	CT053	5	Fully human	94% (n=18)	77-83%	15-17%	NA	
PRIME (phase I/II, n=55)	P-BCMA-101	8	Piggy-bac system, centyrin technology	67% w/ nanoplasmid (n=6); 44-75% w/OG mfg (n=30)	17%	3.8%	NA	
CRB-402 (phase I, n-69)	bb21217	6	PI3Ki culture to increase Tscm cells	68% (73% at 450 dose, 84% w/ new mfg)	70%	16%	mDOR 17 mo (all doses)	Memory cell phenotype in DP may correlate w/ response
UNIVERSAL (phase I, n=26-31)	Allo-715	5	Allo CART	60-67% at 320 dose	45%	0	NA	Variability in LD, tx within 5 days of enrollment!! No GVH
FasT CART	GCO12F	5	CD19 BCMA dual CAR T, ON manufact	95%	95%	0	NA	

UCSF

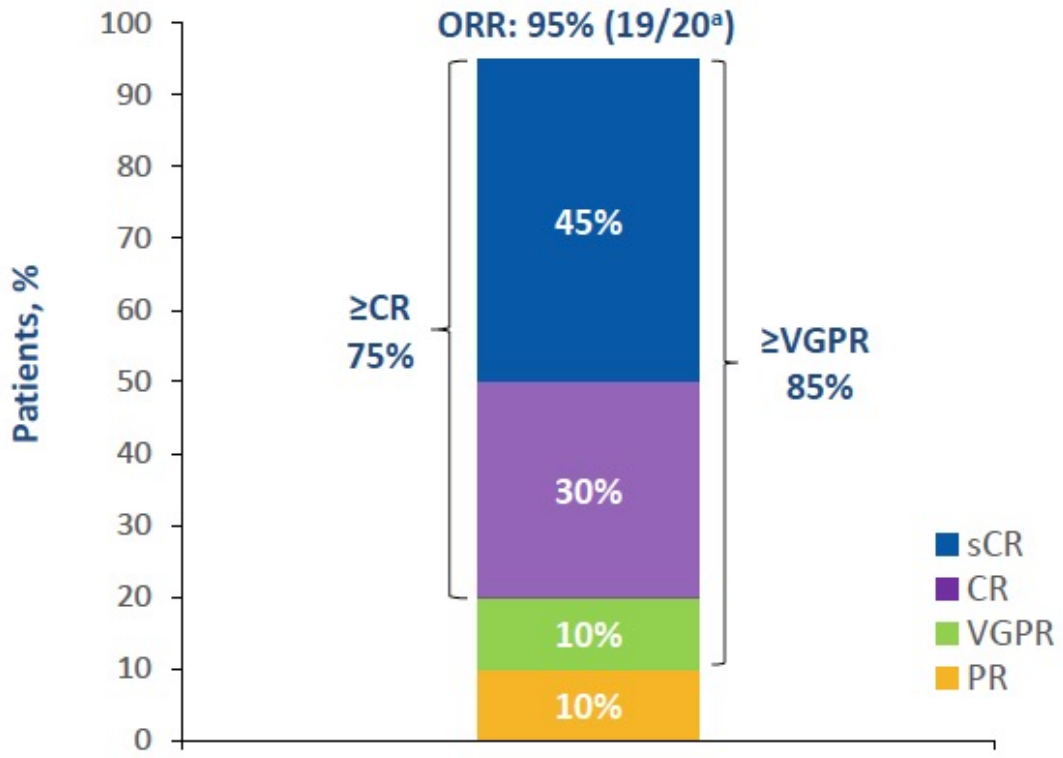
CARTITUDE-2: Phase 2 Multi-Cohort Study in Various MM Settings



[a]Excluding prior BCMA-targeting cellular therapy.

ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CR, complete response; Cy, cyclophosphamide; Dara, daratumumab; D-VRd, daratumumab, bortezomib, lenalidomide, and dexamethasone; Flu, fludarabine; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; ISS, International Staging System; Len, lenalidomide; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma.

CARTITUDE-2: Overall Response Rate and MRD Negativity



- Median time to first response: 1.0 month (range, 0.7–3.3)
- Median time to CR or better: 1.9 months (range, 0.9–5.1)
- All patients (n=4) with MRD-evaluable[b] samples at the 10^{-5} threshold were MRD negative at data cut-off

Data cut-off date: Jan 2021. [a]Patient who did not respond had stable disease. [b]MRD was assessed in evaluable samples (ie, patients with identifiable clone at baseline and sufficient cells for testing at 10^{-5} threshold in post treatment samples) by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) in all treated patients.
CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

Ide-cel has arrived…now what??

- Label: 4 lines of treatment
- Our patients
  1. VRD→ ASCT→ len maintenance
  2. DPD
  3. KCD
  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?

Case 2: 68 y/o F receives BCMA CAR T cells for RRMM

- 24 h after infusion of T cells she has fever to 38.5, BP 106/66
- Feels fatigued
- CRP = 3.6→ 72.8
- Receives acetaminophen→ fever recurs, BP now 89/56
- Received tocilizumab → defervesces, BP better
- 2 days later fever recurs but with newly elevated ferritin, decreasing fibrinogen
- Receives anakinra → afebrile after 24 hours