VCC VIRTUAL Challenging Case Clinic

Multiple Myeloma SERIES

CAR T-cell Therapy: For Whom and When?

May 25, 2022

University of Nebraska Medical Center

Bio Ascend™

Introductions

Course Director

Sagar Lonial, MD, FACP

Chief Medical Officer
Professor and Chair, Department of Hematology and Medical Oncology
Anne and Bernard Gray Family Chair in Cancer
Winship Cancer Institute of Emory University
Atlanta, Georgia

Presenter

Nina Shah, MD

Professor of Clinical Medicine
Multiple Myeloma Translational Initiative
Division of Hematology-Oncology
University of California San Francisco

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Disclosures

Sagar Lonial, MD, FACP

Consulting Fees: Amgen Inc., Bristol-Myers Squibb Company, Celgene Corporation, GlaxoSmithKline LLC, Janssen Oncology, Karyopharm Therapeutics, Merck & Co., Novartis

Nina Shah, MD

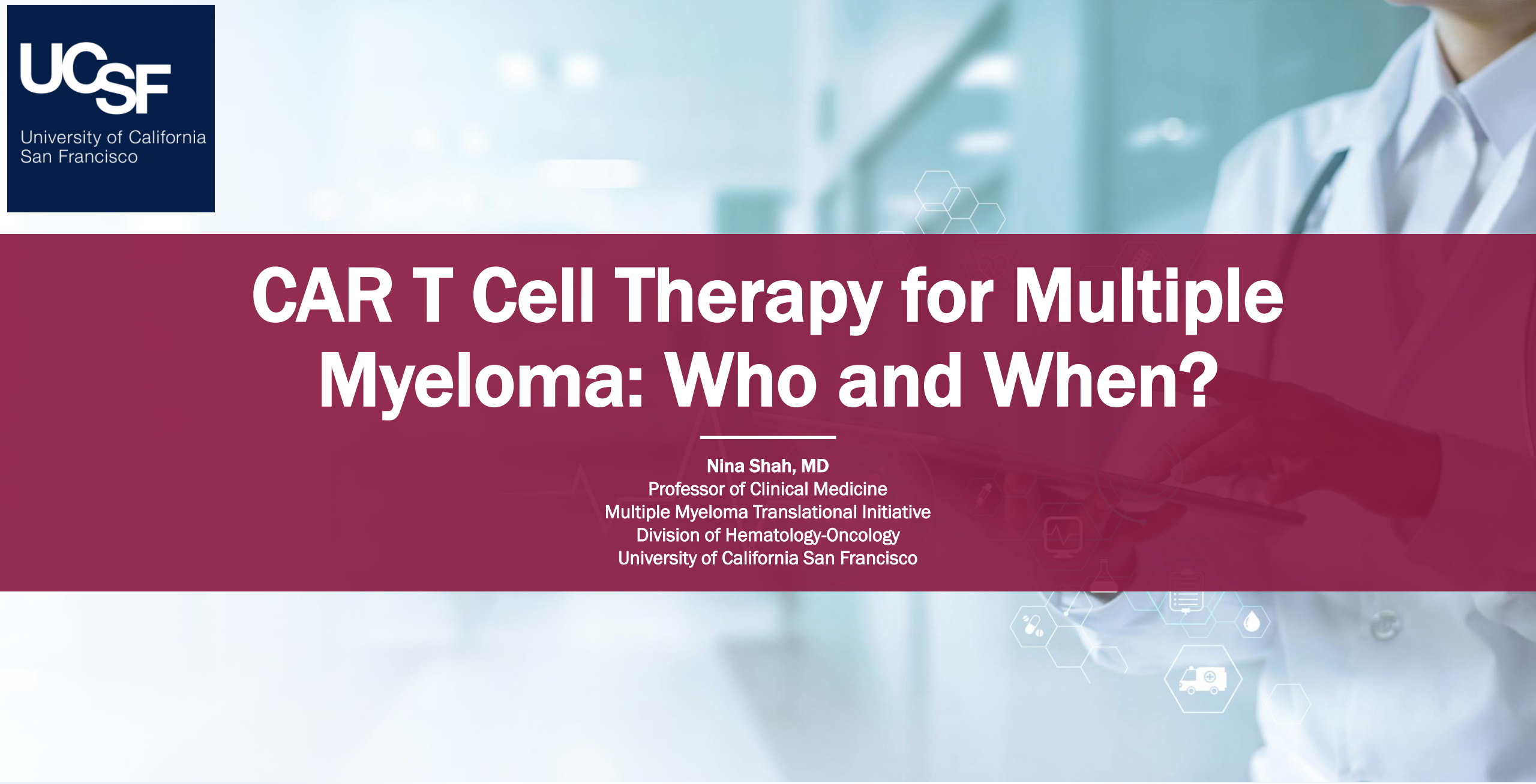
Consulting Fees: GSK, Amgen, Indapta Therapeutics, Sanofi, BMS, CareDx, Kite, Karyopharm
Contracted Research: Celgene/BMS, Janssen, Bluebird Bio, Sutro Biopharma, Teneobio, Poseida, Nektar
I will be discussing non-FDA approved indications during my presentation

Planning Committee

The following planning committee members have nothing to disclose:
UNMC: Brenda Ram, CMP, CHCP
Bio Ascend: Chloe Dunnam; Tisheeka Graham-Steed, PhD; Danielle Kashou, MBA; Kraig Steubing

Learning Objectives

- ✓ Evaluate best available evidence regarding the treatment of newly diagnosed and relapsed/refractory MM
- ✓ Assess the implications of emerging clinical trial data regarding therapeutic approaches for patients with MM
- ✓ Develop strategies to optimize the outcomes of complicated MM cases



CAR T Cell Therapy for Multiple Myeloma: Who and When?

Nina Shah, MD
Professor of Clinical Medicine
Multiple Myeloma Translational Initiative
Division of Hematology-Oncology
University of California San Francisco

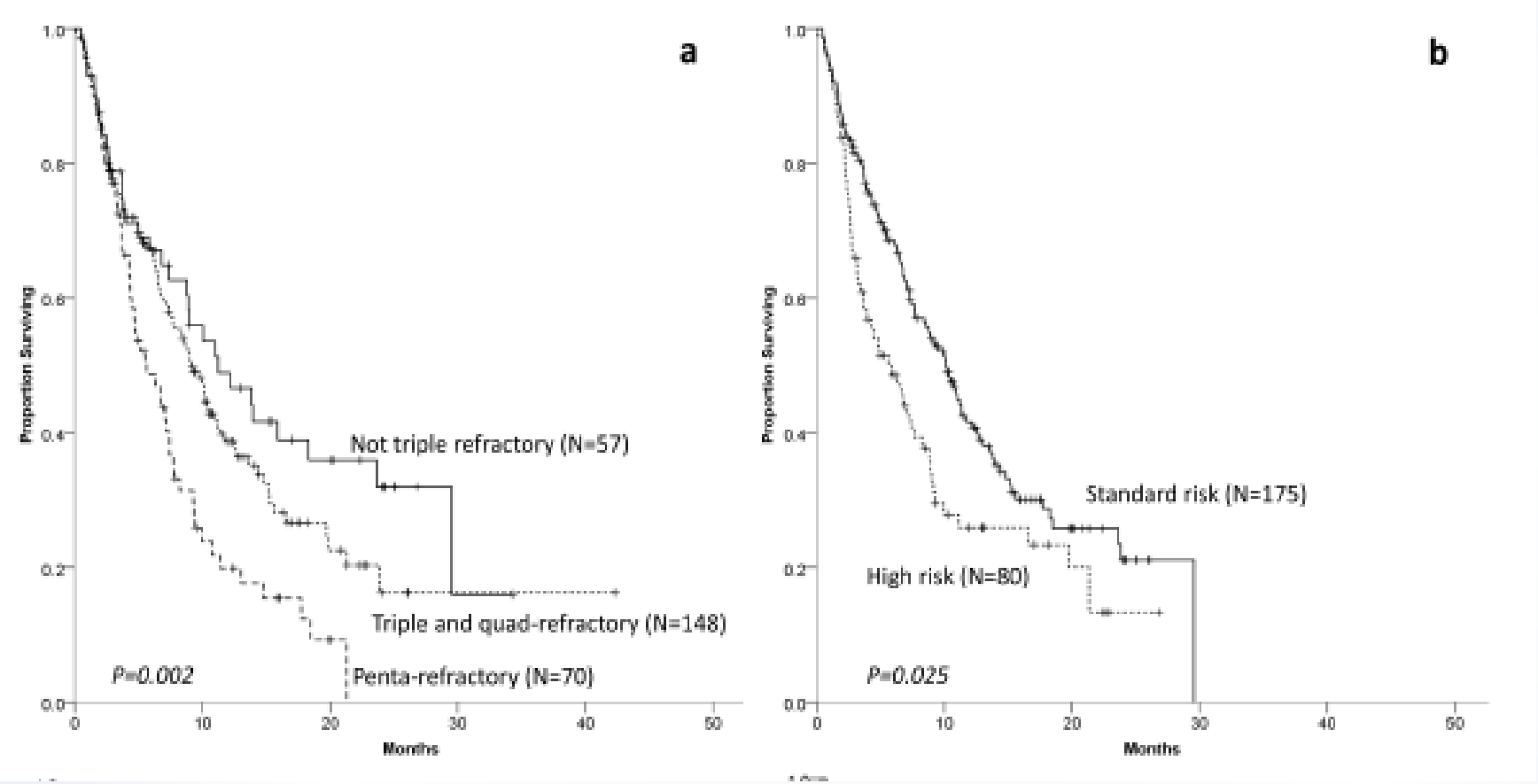
Patient Case

- ✓ 62-year-old male with R-ISS stage I MM (standard risk)
- ✓ Treatment: RVd induction → ASCT → R maintenance: CR
- ✓ 3.5 years: PD → DPd: VGPR
- ✓ 1 year: new L2 plasmacytoma (RT) and rising M protein → KCd
- ✓ 7 months: PD → XVd: SD → PD
- ✓ Patient retains a relatively good functional status (PS of 1)

Is this patient triple-class refractory? If so, what are the current options?

A. Selinexor
B. Belantamab mafodotin
C. CAR T
D. Bispecifics

Relapsed/refractory multiple myeloma: An unmet need

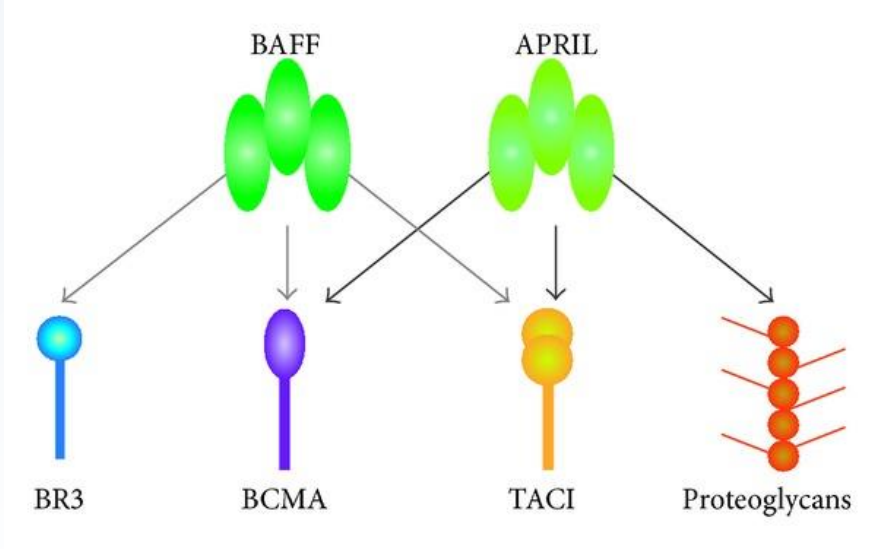


The unexpected stars of MM therapy

- Antibody-drug conjugates
- CAR T cells
- Bispecific T cell engagers

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

2017

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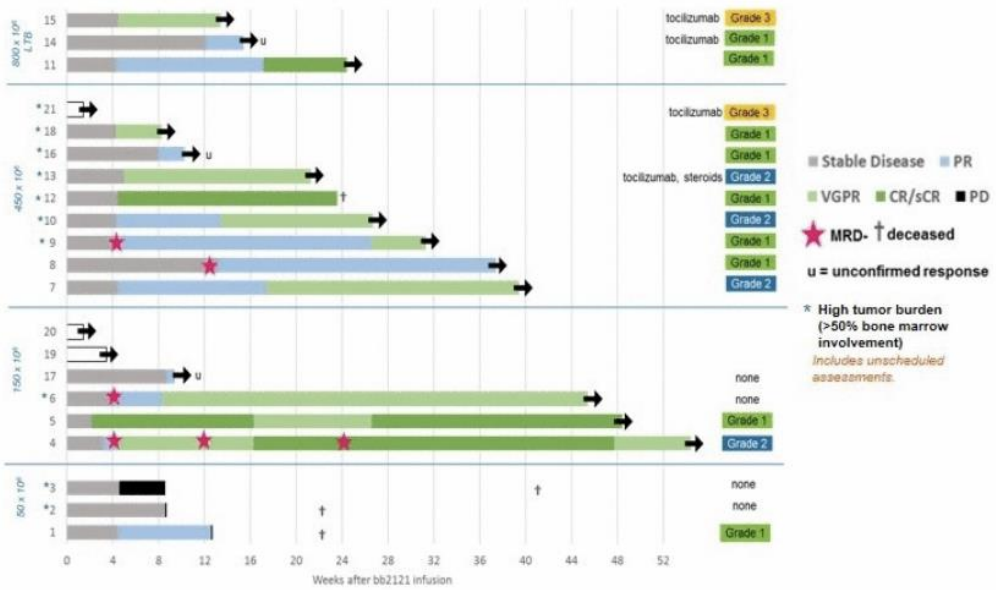
First bb2121 Results!!

CRB-401: All bb2121 Patients in Active Dose Cohorts Achieved an Objective Response, Duration up to 54 Weeks



bb2121 has induced durable and deepening responses in a heavily pre-treated population (median 7 prior therapies) with relapsed/refractory multiple myeloma, including:

- 100% ORR, 73% VGPR or better, 27% CR (at doses > 50 x 10^6)
- MRD negative results in all evaluable patients (N=4)
- No disease progression in patients treated with doses > 50 x 10^6, with 1 patient past 1 year and 8 patients past 6 months

To date, the safety profile of bb2121 has been manageable at all tested doses

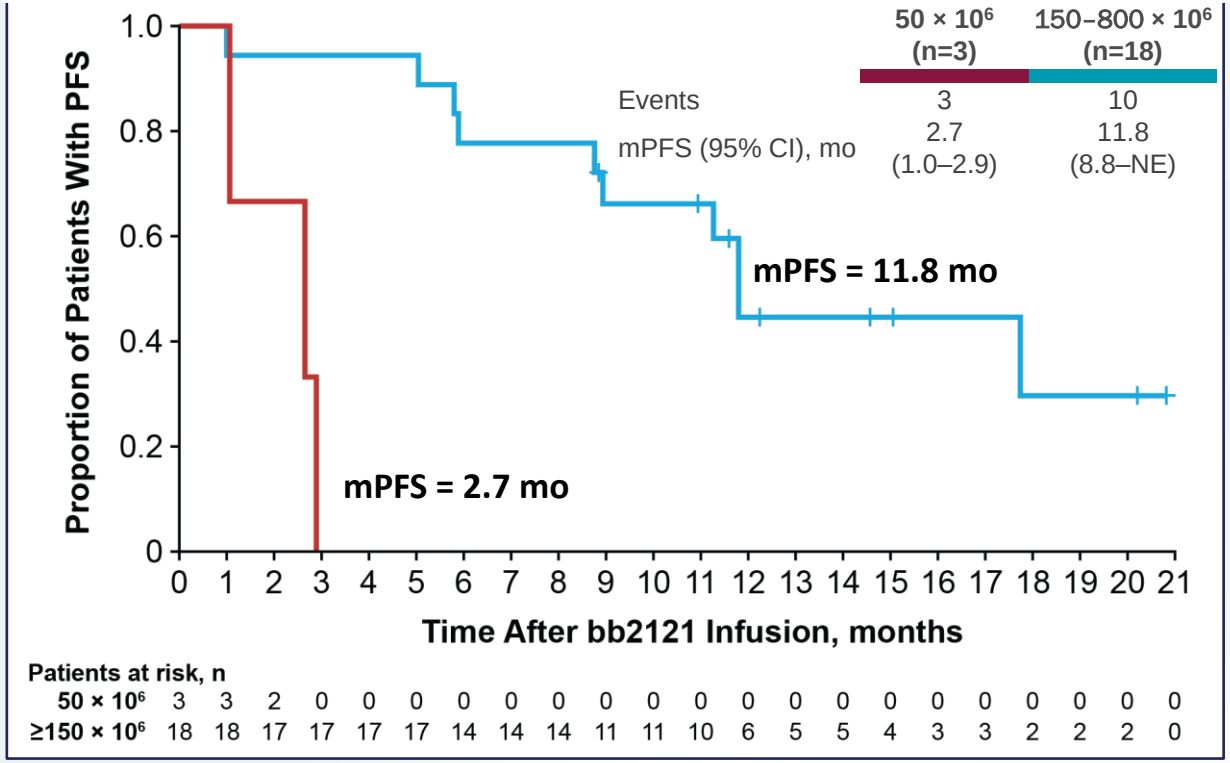
- No DLTs
- The 2 reported events of grade 3 CRS resolved within 24 hours
- No grade 3/4 neurotoxicity reported

Data Presented at ASCO 2017; Data Cutoff of May 4, 2017

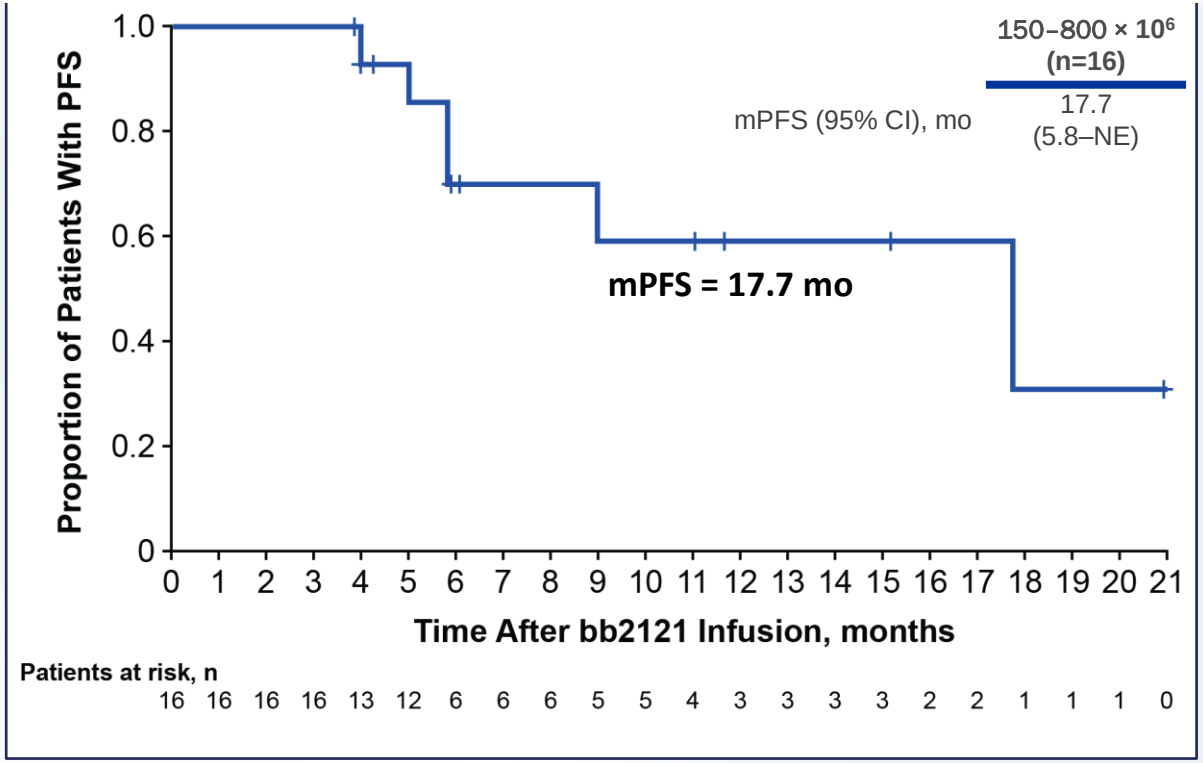
Progression-Free Survival

- mPFS of 11.8 months at active doses (≥150 × 106 CAR+ T cells) in 18 subjects in dose escalation phase
- mPFS of 17.7 months in 16 responding subjects who are MRD-negative

PFS at Inactive (50 × 10^6) and Active (150–800 × 10^6) Dose Levels[a]



PFS in MRD-Negative Patients



Data cutoff: March 29, 2018. Median and 95% CI from Kaplan-Meier estimate. NE, not estimable. [a]PFS in dose escalation cohort.

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

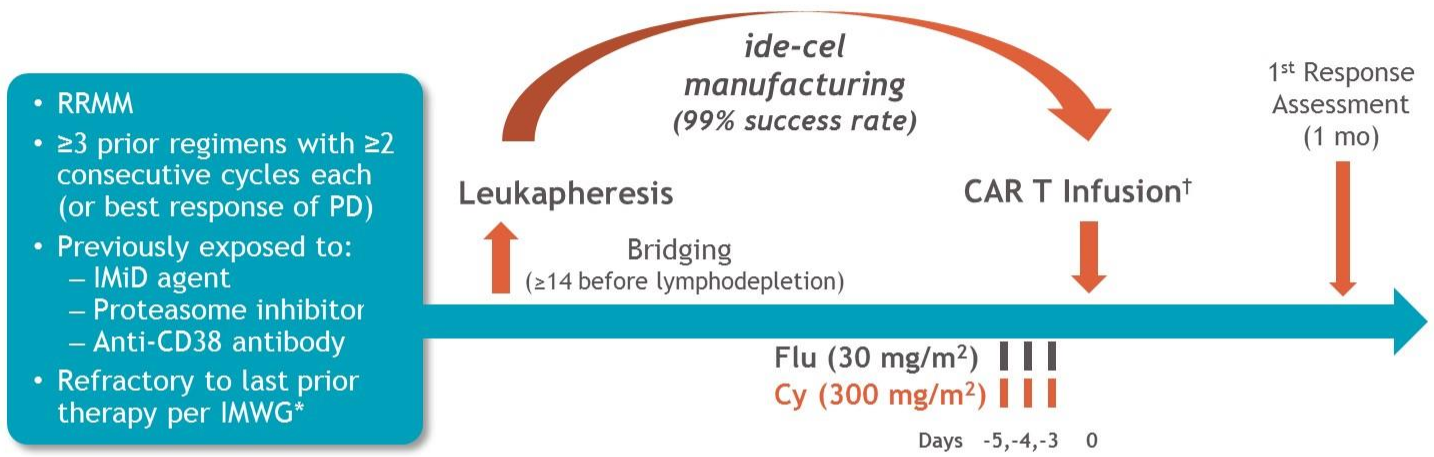
Nikhil C. Munshi, MD[1]; Larry D. Anderson, Jr, MD, PhD[2]; Nina Shah, MD[3]; Sundar Jagannath, MD[4]; Jesus Berdeja, MD[5]; Sagar Lonial, MD[6]; Noopur Raje, MD[7]; David S. Siegel, MD, PhD[8]; Yi Lin, MD, PhD[9]; Albert Oriol, MD[10]; Philippe Moreau, MD[11]; Ibrahim Yakoub-Agha, MD, PhD[12]; Michel 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*

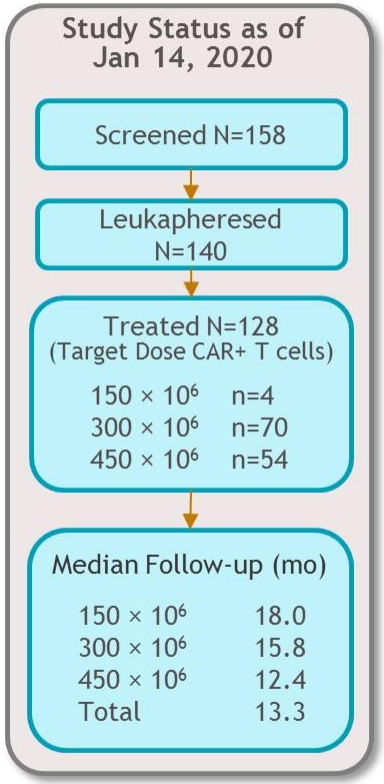
[1]The LeBow Institute for Myeloma Therapeutics and Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA; [2]Simmons Comprehensive Cancer Center, UT Southwestern Medical Center, Dallas, TX, USA; [3]University of California San Francisco, San Francisco, 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

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*





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

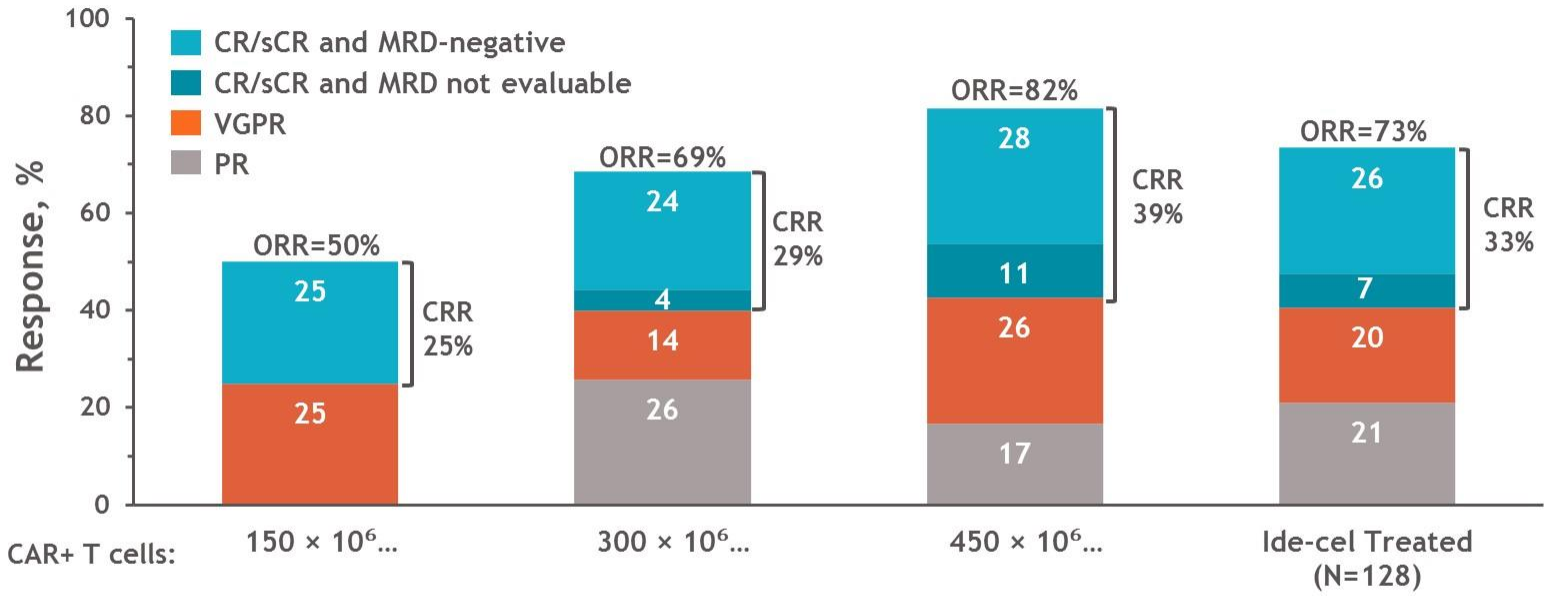
CRR, complete response rate; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; GEP in BM, gene expression profile in bone marrow; HEOR, health economics and outcomes research; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR, 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.

Incidence and Management of CRS

Target Dose, × 10^6 CAR+ T cells	150 (n=4)	300 (n=70)	450 (n=54)	Ide-cel Treated (N=128)
≥1 CRS event, n (%)	2 (50)	53 (76)	52 (96)	107 (84)
Max. grade (Lee Criteria)*				
1/2	2 (50)	49 (70)	49 (91)	100 (78)
3	0	2 (3)	3 (6)	5 (4)
4	0	1 (1)	0	1 (<1)
5	0	1 (1)	0	1 (<1)
Median onset, d (range)	7 (2–12)	2 (1–12)	1 (1–10)	1 (1–12)
Median duration, d (range)	5 (3–7)	4 (2–28)	7 (1–63)	5 (1–63)
Tocilizumab, n (%)	1 (25)	30 (43)	36 (67)	67 (52)
Corticosteroids, n (%)	0	7 (10)	12 (22)	19 (15)

- CRS frequency increased with dose, but mostly low grade
- ≤6% grade 3 or higher CRS events at all target doses, including one grade 5 event
- CRS treated with corticosteroids was infrequent (≤22%) at all target doses

Data cutoff: 14 Jan 2020. Siltuximab was used to manage CRS in 1 patient who was treated with 300 x 10^6 CAR+ T cells. Anakinra was used to manage CRS in 1 patient who was treated with 300 x 10^6 CAR+ T cells.
*CRS graded according to Lee criteria [Lee et al., *Blood* 2014;10;124(2):188-195].
CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; NCI, National Cancer Institute.

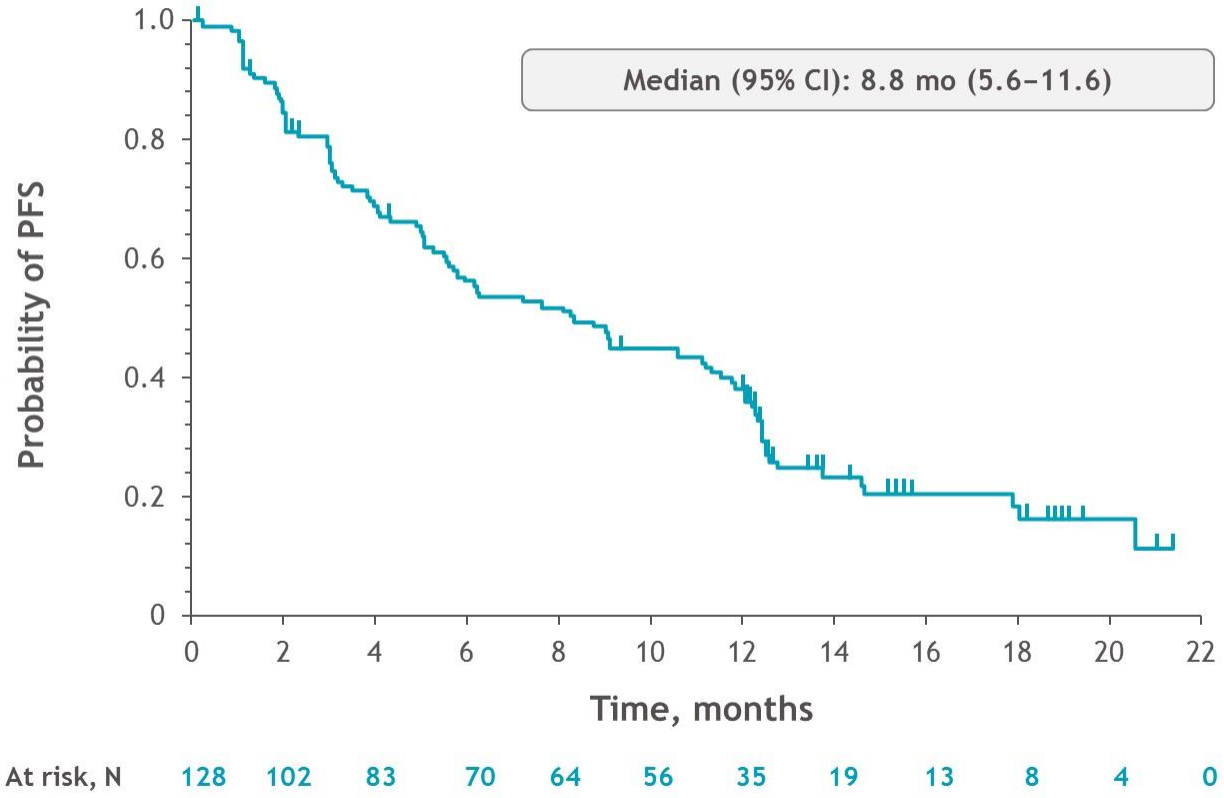
Incidence and Management of Neurotoxicity

Target Dose, × 10^6 CAR+ T cells	150 (n=4)	300 (n=70)	450 (n=54)	Ide-cel Treated (N=128)
≥1 NT event, n (%)	0	12 (17)	11 (20)	23 (18)
Max. grade (CTCAE)*				
1	0	7 (10)	5 (9)	12 (9)
2	0	4 (6)	3 (6)	7 (5)
3	0	1 (1)	3 (6)	4 (3)
Median onset, d (range)	NA	3 (1–10)	2 (1–5)	2 (1–10)
Median duration, d (range)	NA	3 (2–26)	5 (1–22)	3 (1–26)
Tocilizumab, n (%)	NA	0	3 (6)	3 (2)
Corticosteroids, n (%)	NA	2 (3)	8 (15)	10 (8)

- NT mostly low grade and was similar across target doses
- Incidence of grade 3 NT events was uncommon (≤6%) at all target doses; no grade 4 or 5 events
- NT managed with corticosteroids was infrequent (≤15%) at all target doses

Data cutoff: 14 Jan 2020. CTCAE, Common Terminology Criteria for Adverse Events; NA, not applicable; NCI, National Cancer Institute; NT, neurotoxicity (investigator-identified).
*Investigator-identified NT events were graded according to the NCI CTCAE v4.03.

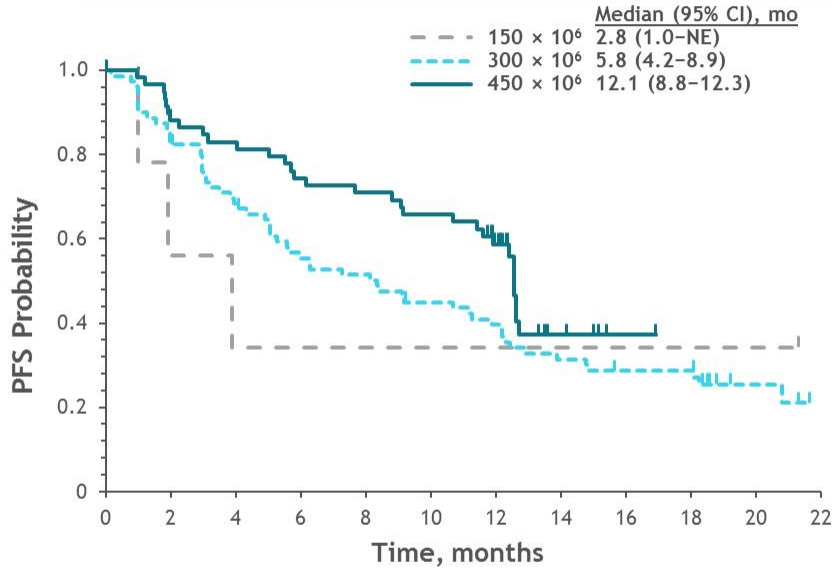
Progression-Free Survival



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

Progression-Free Survival

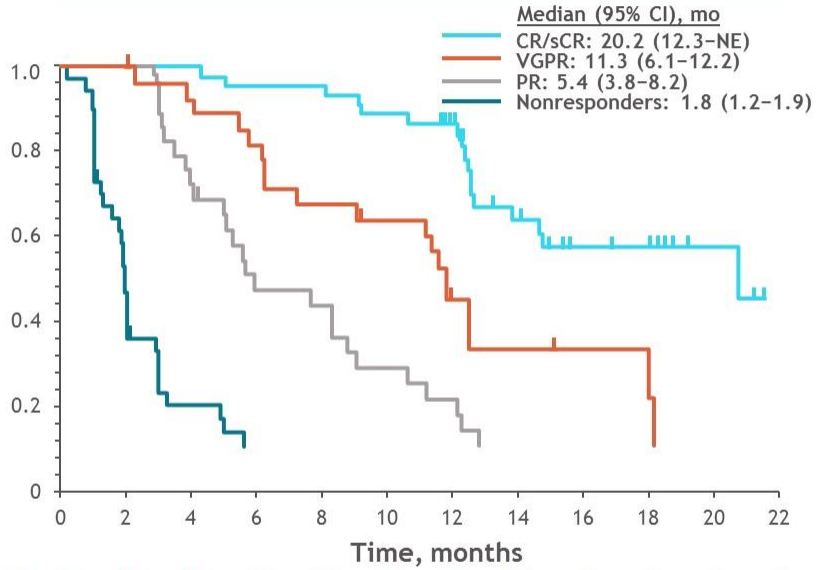
PFS by Target Dose



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 × 10^6 CAR+ T cells

PFS by Best Response

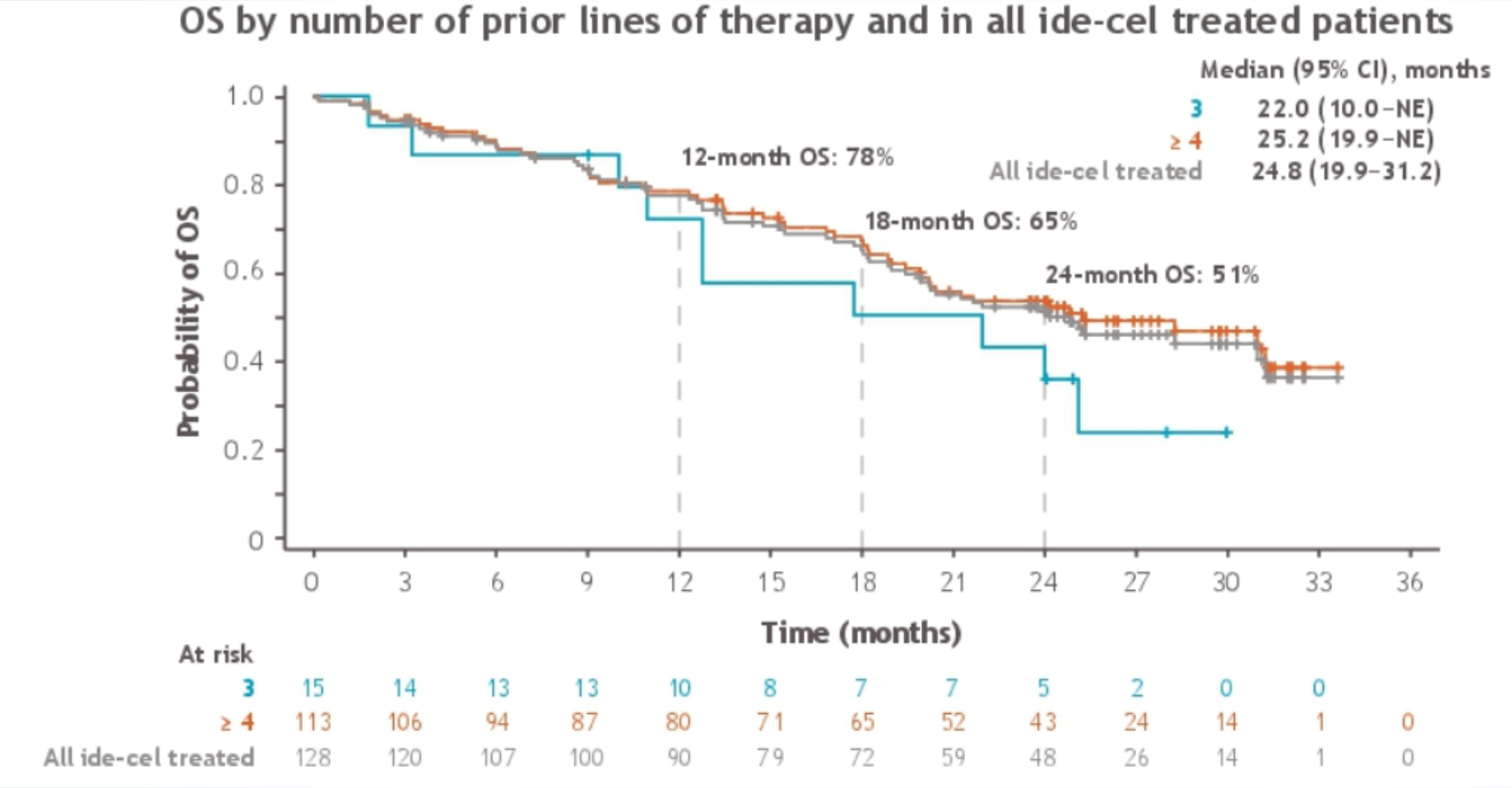


CR/sCR	42	42	42	40	39	37	26	16	11	8	4	0
VGPR	25	25	22	20	16	14	8	3	2	0	0	
PR	27	16	10	9	5	1	0	0	0	0	0	
Nonresponders	34	8	83	70	64	56	35	19	13	8	4	0

- 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.

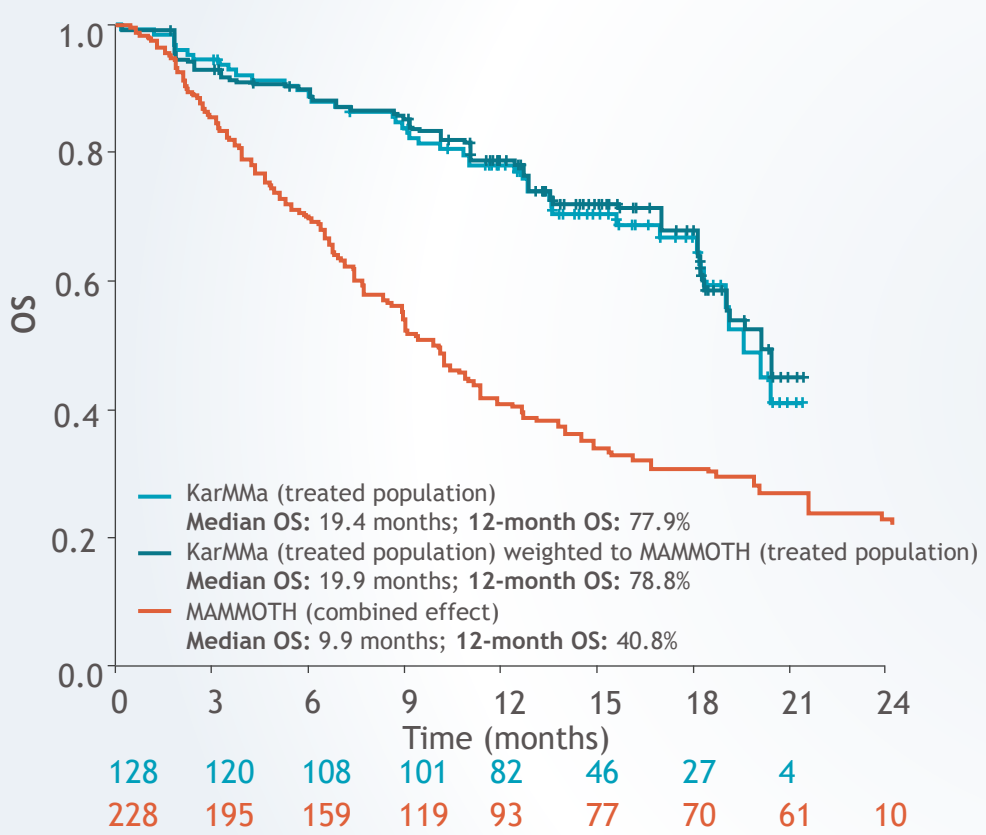
KarMMa: Updated OS[1]



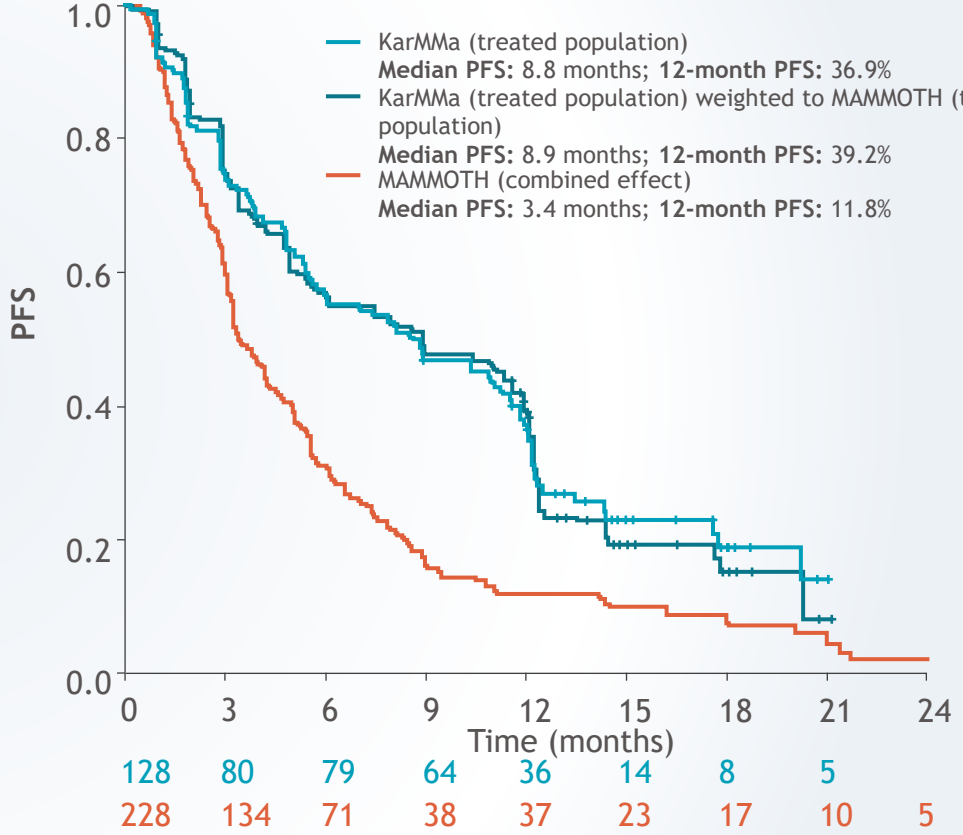
1. Anderson LD, et al. ASCO 2021. Abstract 8016.

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)

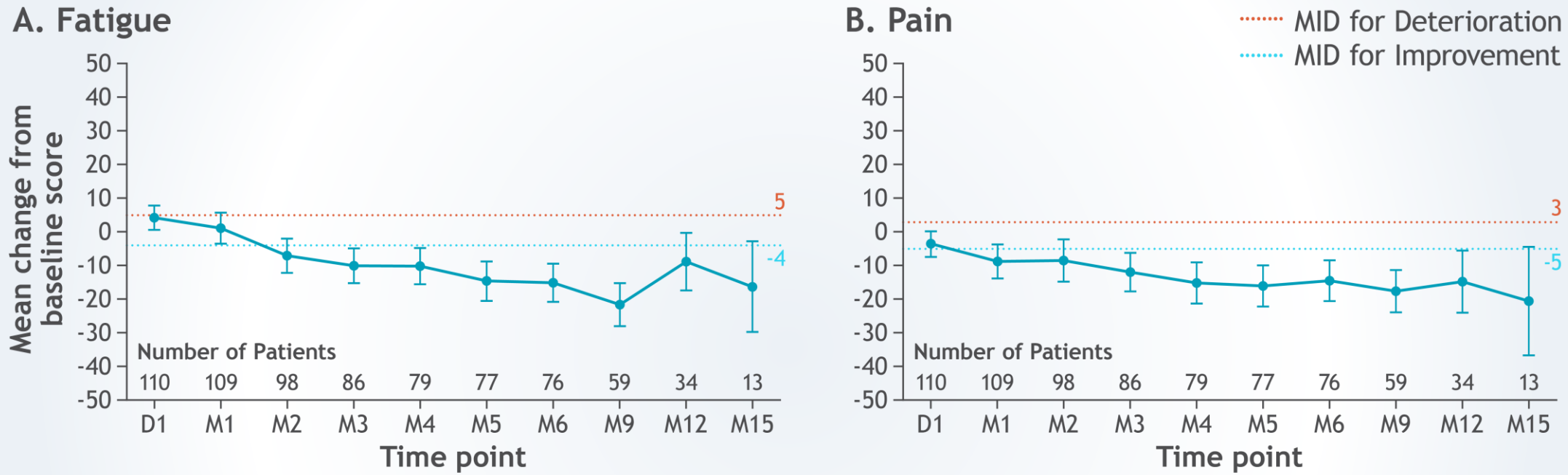


- Median OS and median PFS were significantly longer for the ide-cel-treated population (weight-matched) compared with the conventional care population in MAMMOTH in the base case

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

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

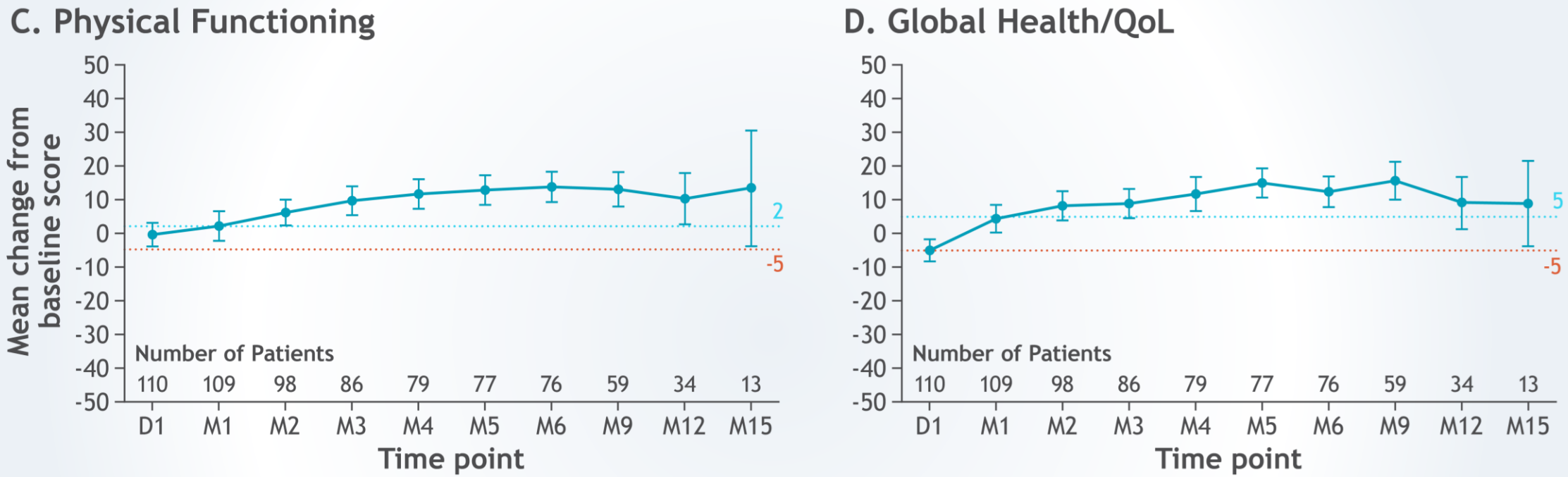
Mean change from baseline in EORTC QLQ-C30 subscale scores



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]

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

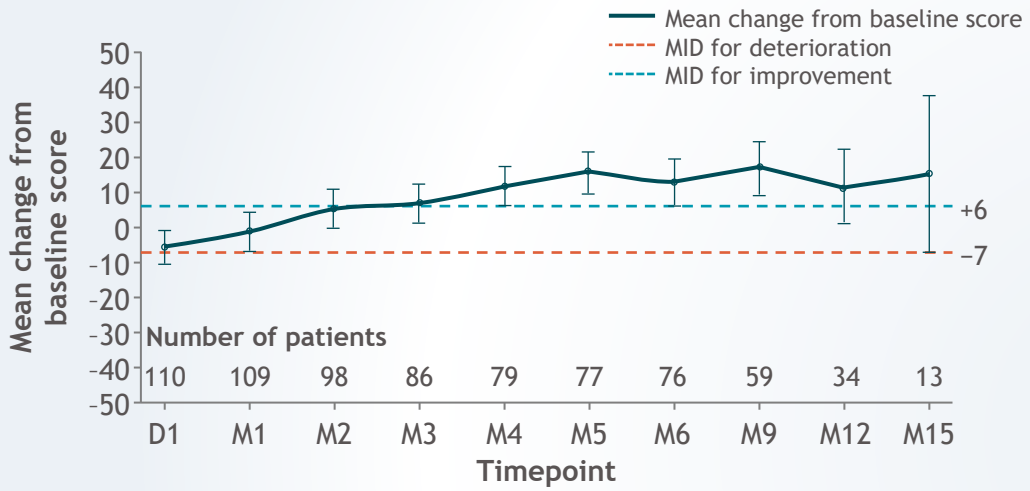


D, day; M, month; MID, Minimal Important Difference.
Baseline defined as last non-missing assessment on/prior to day of lymphodepleting chemotherapy.
Error bars represent 95% confidence intervals.

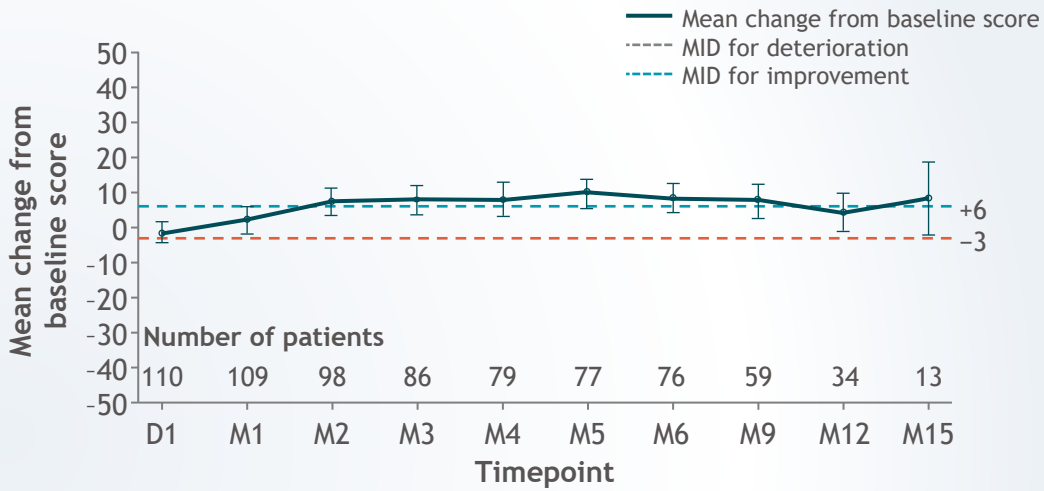
Delforge M et al; EHA 2020 #EP1000]

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

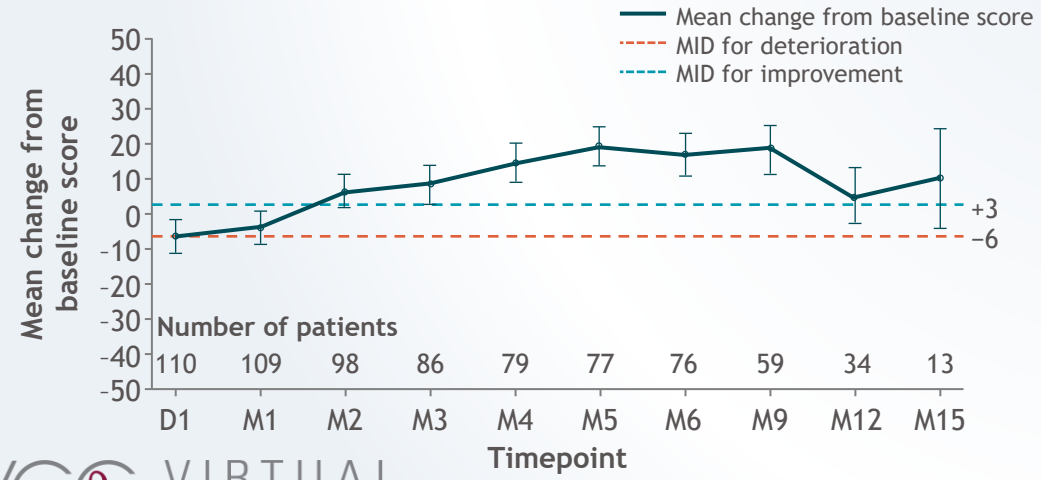
Role Functioning



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 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

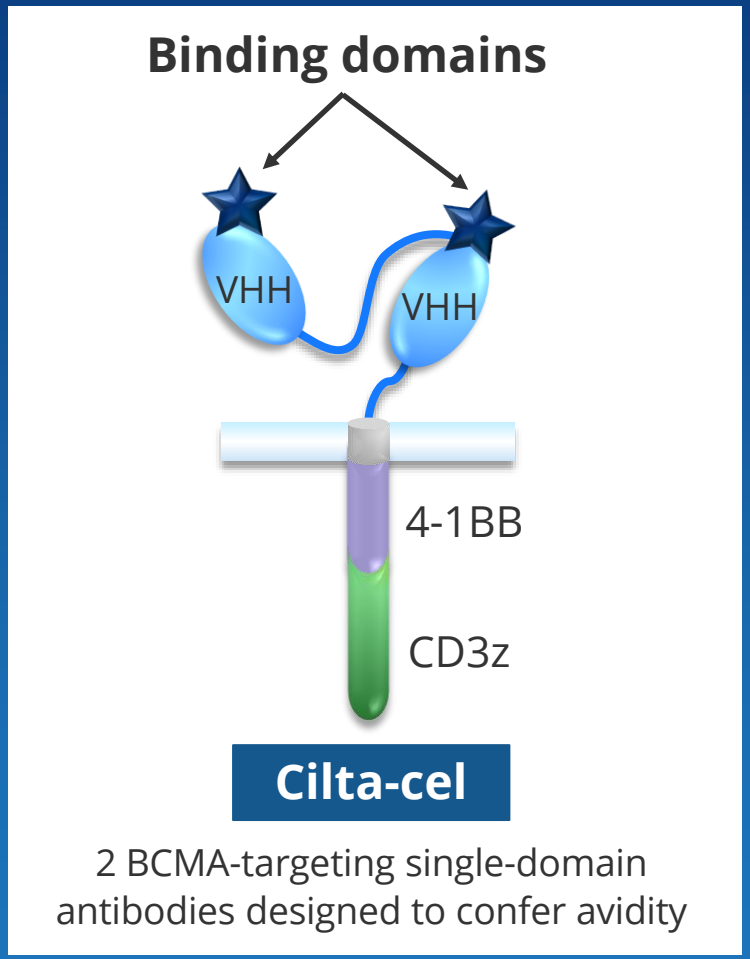
Presented at the 63rd American Society of Hematology (ASH) Annual Meeting & Exposition; December 11-14, 2021; Atlanta, GA/Virtual.

*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]**



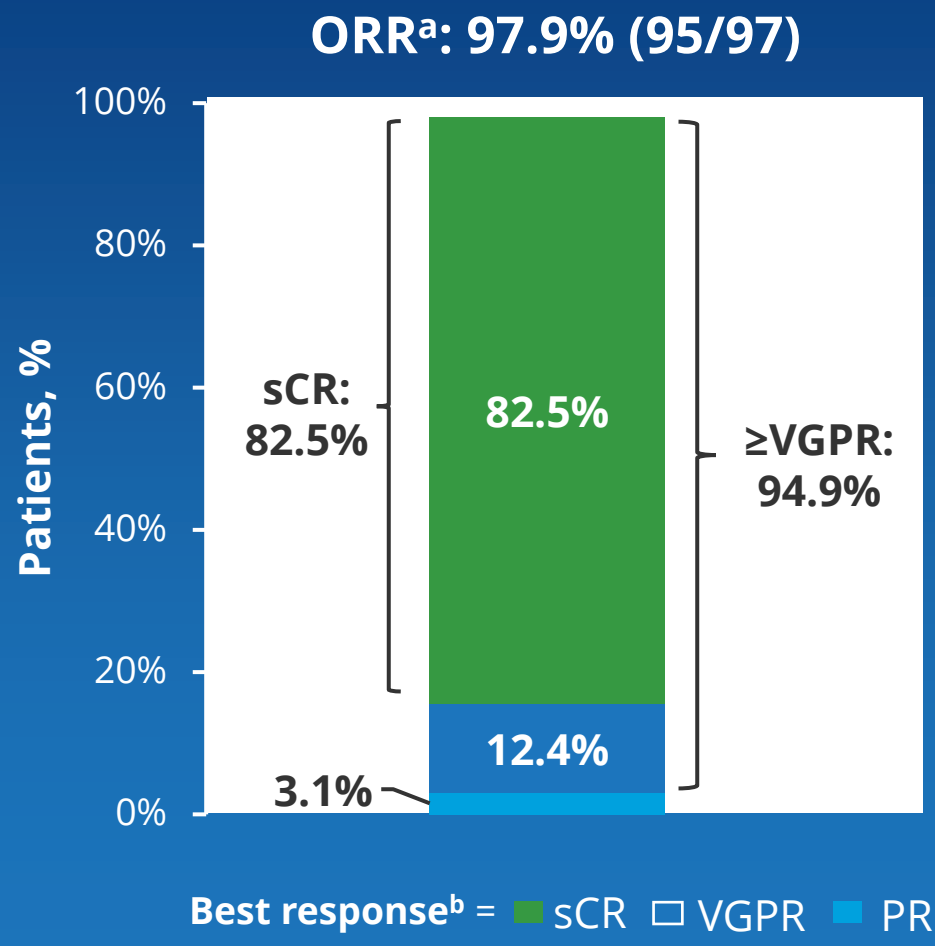
[a]Median 21.7 months, data cut-off July 22,2021

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



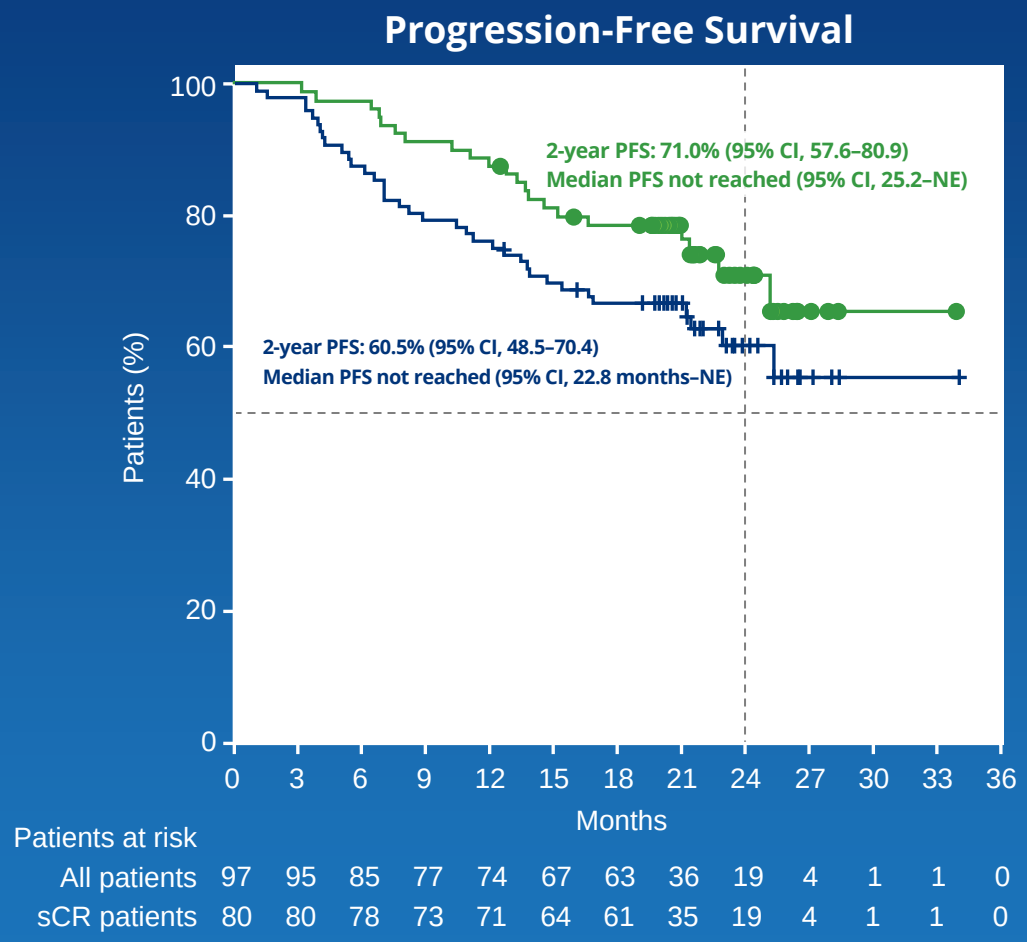
Responses deepened over time from the 1-year follow-up

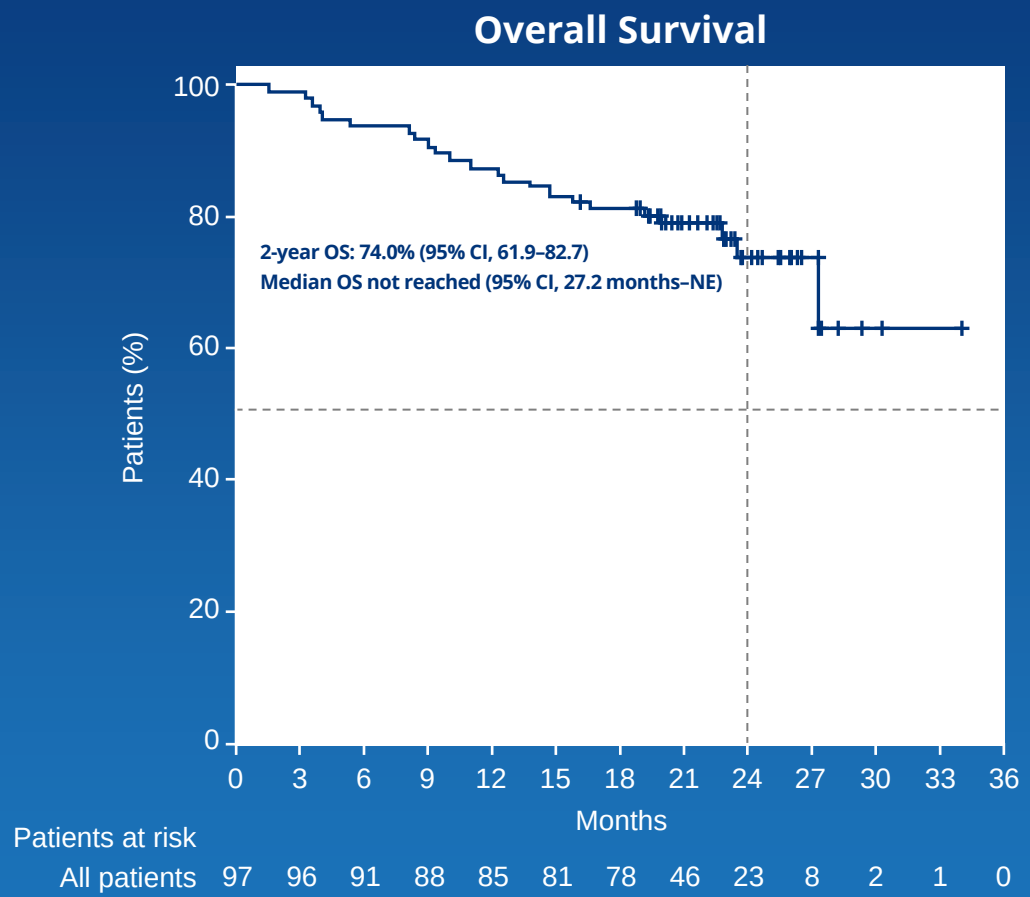
Best response at any time	Median–1 year follow-up	Median–2 years follow-up
sCR, %	67	83

- 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





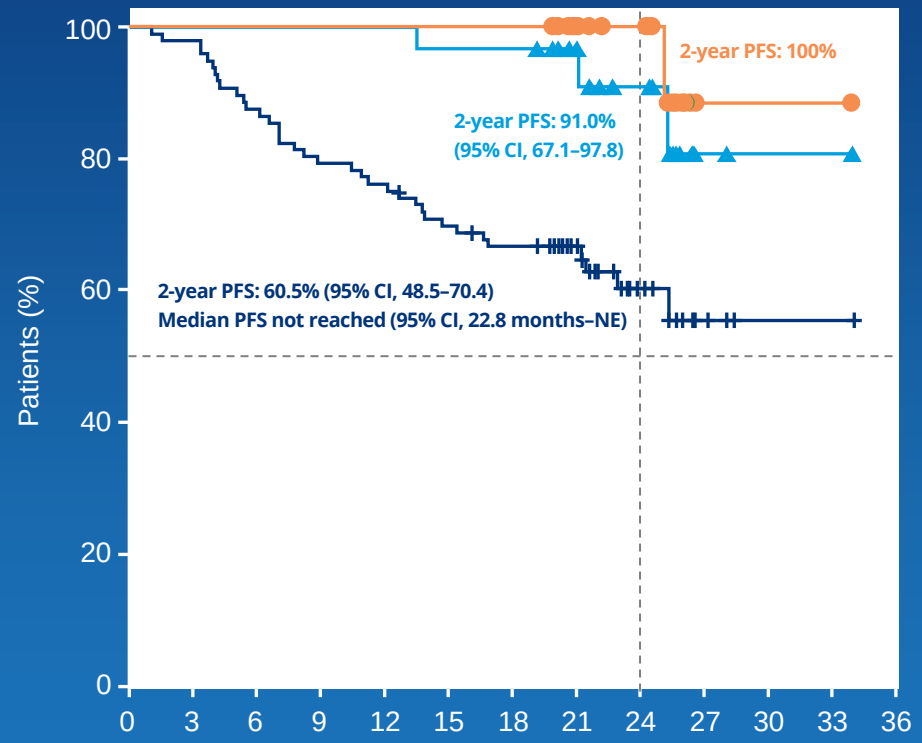
All patients sCR patients

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

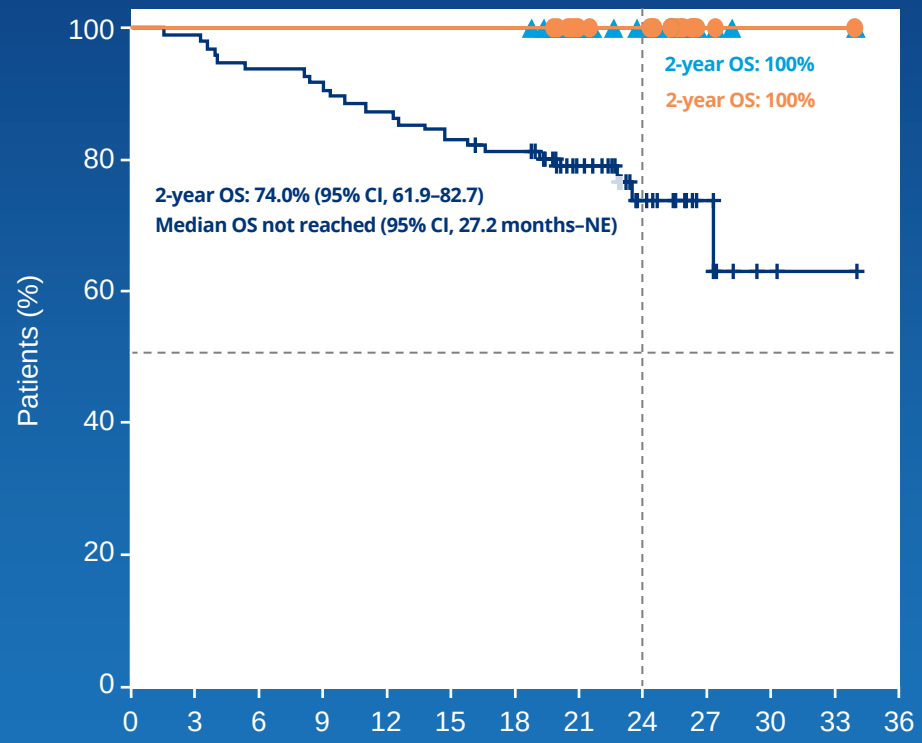
- Of the 61 patients evaluable for MRD, 92% were MRD-negative (at 10^{-5})

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

INNOVATION

U.S. FDA Approves Ciltacabtagene Autoleucel, Janssen's First Cell Therapy, a BCMA-Directed CAR-T Immunotherapy for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma

Practical aspects of CAR T therapy

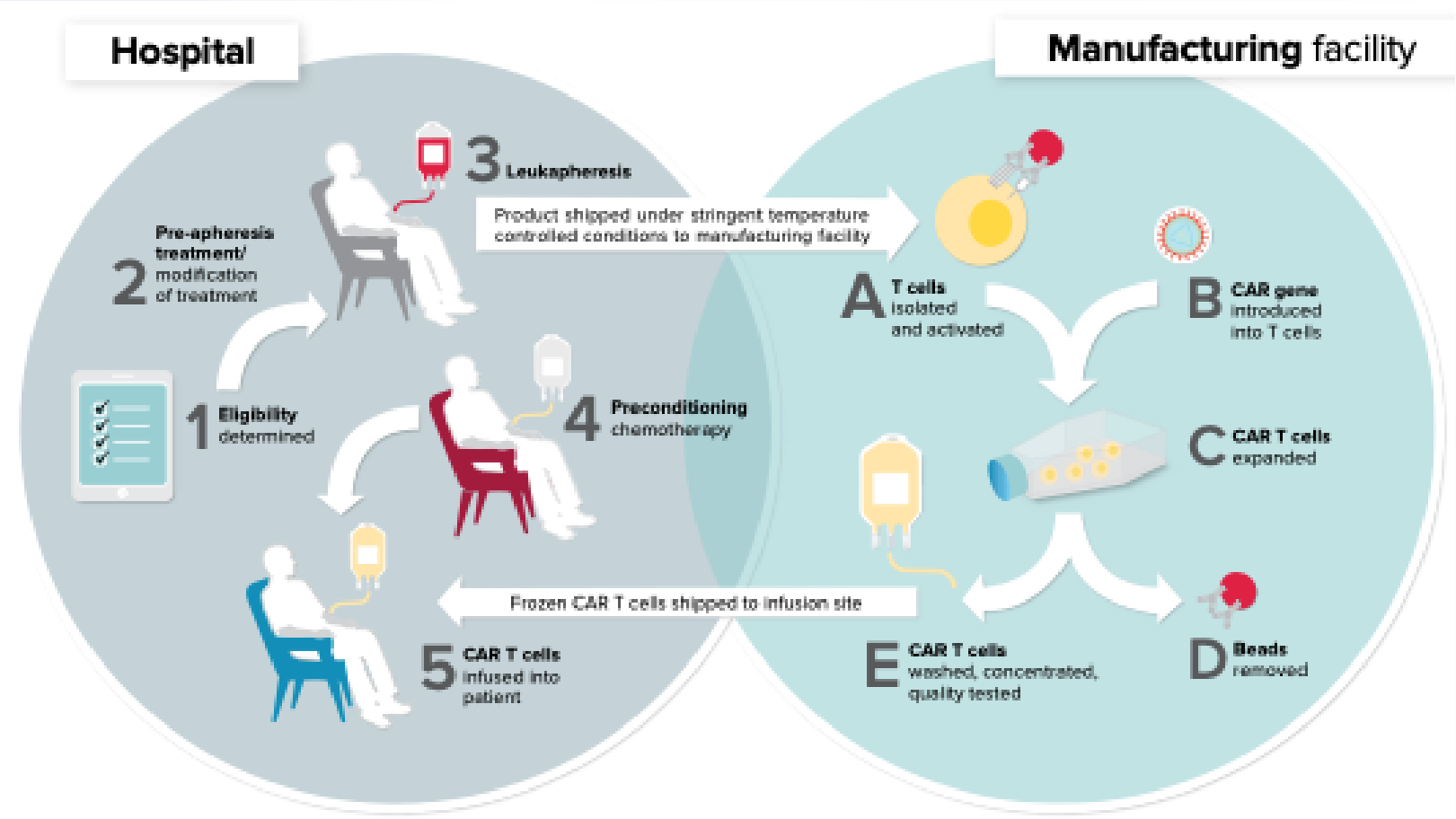
Patient selection

- >4 lines (TBA for bispecifics)
- No significant co-morbidities
- Have to time appropriately between apheresis slot and eventual cell infusion

Logistics

- CRS likely
- Cell infusion or 1st dose in-patient at specialty center
- Co-monitoring limited thereafter with local MD

How Are CAR T Cells Manufactured/Engineered?



- Production of CAR T cells takes approximately 10 to 14 days
- The time from endogenous T-cell collection to CAR T-cell infusion varies, but typically ranges from
1 to 5 weeks

Leukemia & Lymphoma Society. Facts about chimeric antigen receptor (CAR) T-cell therapy. https://www.lls.org/sites/default/files/National/USA/Pdf/Publications/FSHP1_CART_Factsheet_June2018_FINAL.pdf. Accessed July 3, 2019.

Practical aspects of CAR T therapy

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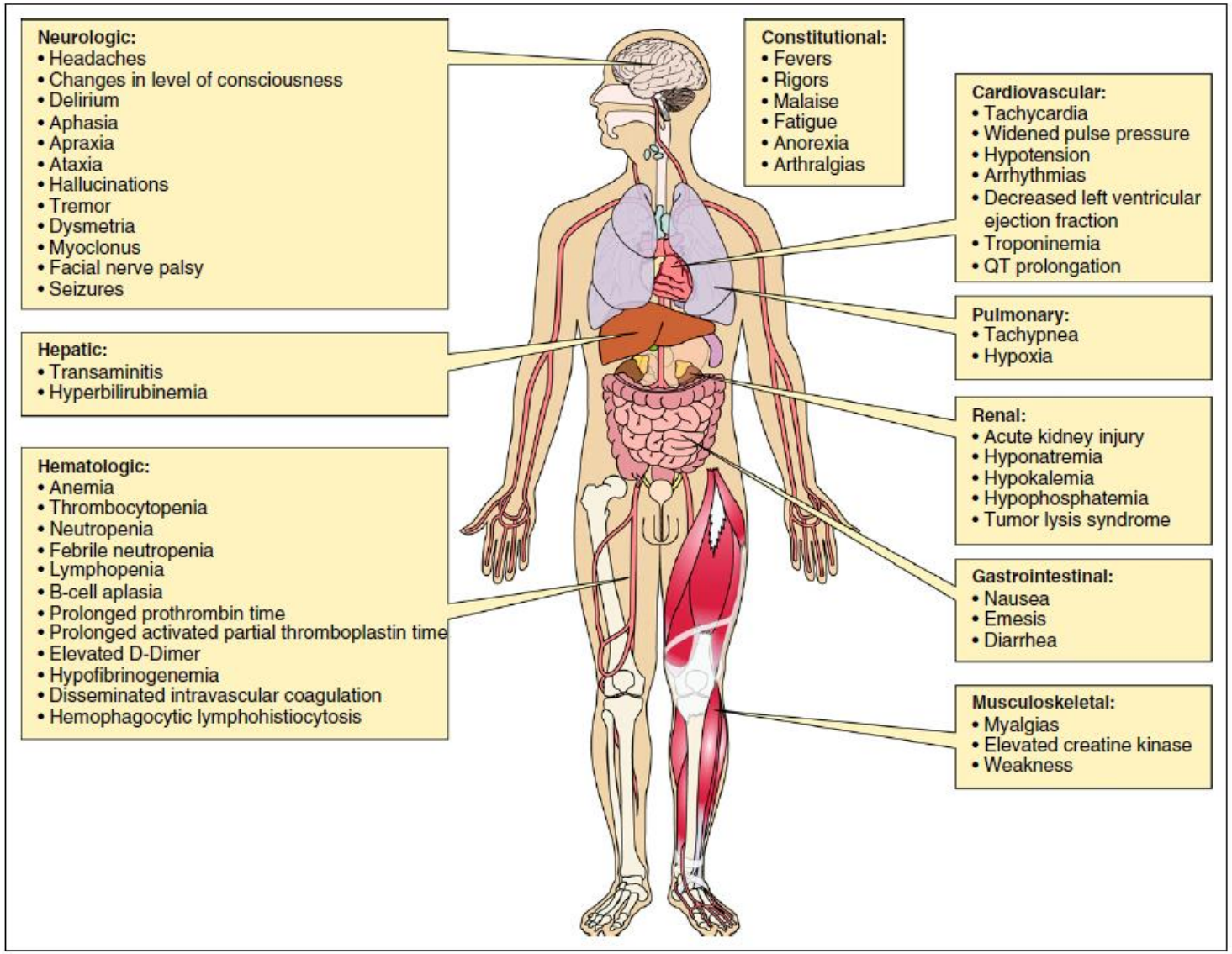
Cytokine Release Syndrome (CRS)

- Systemic inflammatory response that occurs as CAR T cells activate and expand
- High levels of CRP, ferritin, IL-6, IL-10
- Typically 1-14 days after infusion
- Flu-like symptoms with fever
- Can progress to life threatening hypotension, hypoxia, and death
- High disease burden associated with more severe CRS

CRS



Brudno, *Blood* 2016

Grading System	Grade 1	Grade 2	Grade 3	Grade 4
CTCAE version 4.03	Mild reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (antihistamines, NSAIDs, narcotics, IV fluids); prophylactic Medications indicated for ≥24 h	Prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae (eg, renal impairment, pulmonary infiltrate)	Life-threatening consequences; pressor or ventilatory support indicated
CTCAE version 5.0	Fever, with or without constitutional symptoms	Hypotension responding to fluids. Hypoxia responding to <40% FiO2	Hypotension managed with one pressor. Hypoxia requiring ≥40% FiO2	Life-threatening consequences; urgent intervention needed
Lee criteria	Symptoms are not life-threatening and require symptomatic treatment only (fever, nausea, fatigue, headache, myalgias, malaise)	Symptoms require and respond to moderate intervention: • Oxygen requirement <40% FiO2 OR • Hypotension responsive to IV fluids or low dose of one vasopressor OR • Grade 2 organ toxicity	Symptoms require and respond to aggressive intervention: • Oxygen requirement ≥40% FiO2 OR • Hypotension requiring high-dose or multiple vasopressors OR • Grade 3 organ toxicity* or grade 4 transaminitis	Life-threatening symptoms: • Requirement for ventilator support OR • Grade 4 organ toxicity* (excluding transaminitis)
Penn criteria	Mild reaction: Treated with supportive care, such as antipyretics, antiemetics	Moderate reaction: Some signs of organ dysfunction (grade 2 creatinine or grade 3 LFTs) related to CRS and not attributable to any other condition. Hospitalization for management of CRS-related symptoms, including neutropenic fever and need for IV therapies (not including fluid resuscitation for hypotension)	More severe reaction: Hospitalization required for management of symptoms related to organ dysfunction, including grade 4 LFTs or grade 3 creatinine, related to CRS and not attributable to any other condition Hypotension treated with multiple fluid boluses or low-dose vasopressors Coagulopathy requiring fresh frozen plasma, cryoprecipitate, or fibrinogen concentrate Hypoxia requiring supplemental oxygen (nasal cannula oxygen, high flow oxygen, CPAP, or BiPAP)	Life-threatening complications such as hypotension requiring high-dose vasopressors Hypoxia requiring mechanical ventilation
MSKCC criteria	Mild symptoms requiring observation or supportive care only (eg, antipyretics, antiemetics, pain medication)	Hypotension requiring any vasopressors <24 h Hypoxia or dyspnea requiring supplemental oxygen <40%	Hypotension requiring any vasopressors ≥24 h Hypoxia or dyspnea requiring supplemental oxygen ≥40%	Life-threatening symptoms Hypotension refractory to high dose vasopressors Hypoxia or dyspnea requiring mechanical ventilation
CARTOX criteria	Temperature ≥38°C Grade 1 organ toxicity	Hypotension responds to IV fluids or low-dose vasopressor Hypoxia requiring FiO2 <40% Grade 2 organ toxicity	Hypotension needing high-dose or multiple vasopressors Hypoxia requiring FiO2 ≥40% Grade 3 organ toxicity or grade 4 transaminitis	Life-threatening hypotension Needing ventilator support Grade 4 organ toxicity except grade 4 transaminitis

Adapted from Lee et al, *BBMT;* 2019

Revised ASTCT Grading System

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C	Temperature ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, 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 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/minute. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at >6 L/minute.

Lee et al, *BBMT;* 2019

Case Continued

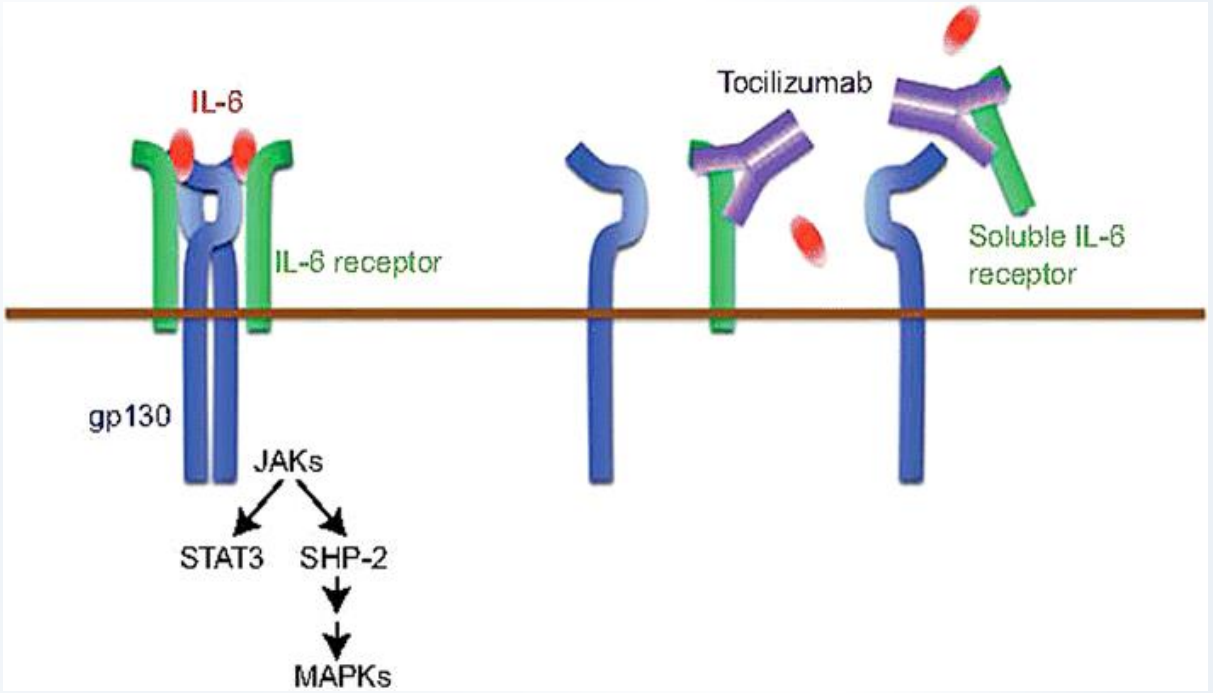
- Our patient receives ide-cel
- Night of infusion: fever to 38.9, BP 104/72, HR 110, O2 Sat 98% on RA

What grade is this CRS?

A. 1
B. 2
C. 3
D. 4

CRS management

- Supportive care
- Tocilizumab
- Steroids (dexamethasone)
- More steroids (methylprednisolone)
- Other
  - Cyclophosphamide



CAR-T related neurotoxicity, aka ICANS: Immune effector cell-associated neurotoxicity syndrome

- Delirium
- Encephalopathy
- Aphasia
- Lethargy
- Difficulty concentrating
- Agitation
- Tremor
- Seizures
- Cerebral edema
- (Headache)
- Usually after CRS

- CAR T cells
- Fever
- Hospitalization
- Dexamethasone
- Fludarabine

"…an awake patient who is mute and does not respond verbally or physically to an examiner"

Lee et al, *BBMT* 2019

Pathophysiology of ICANS

- Endothelial activation →blood-brain barrier disruption
- Elevated levels of the excitatory NMDA receptor agonists?
- Proinflammatory cytokines
- Activated T and myeloid cells

Assessment tools

CARTOX-10 [12]	ICE
• **Orientation:** orientation to year, month, city, hospital, president/prime minister of country of residence: 5 points • **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points • **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point • **Attention:** ability to count backwards from 100 by 10: 1 point	• **Orientation:** orientation to year, month, city, hospital: 4 points • **Naming:** ability to name 3 objects (eg, point to clock, pen, button): 3 points • **Following commands:** ability to follow simple commands (eg, "Show me 2 fingers" or "Close your eyes and stick out your tongue"): 1 point • **Writing:** ability to write a standard sentence (eg, "Our national bird is the bald eagle"): 1 point • **Attention:** ability to count backwards from 100 by 10: 1 point

CARTOX-10 (left column) has been updated to the ICE tool (right column). ICE adds a command-following assessment in place of 1 of the CARTOX-10 orientation questions. The scoring system remains the same.
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 et al, *BBMT* 2019

Table 6
ASTCT ICANS Consensus Grading for Adults

Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
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 min); 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

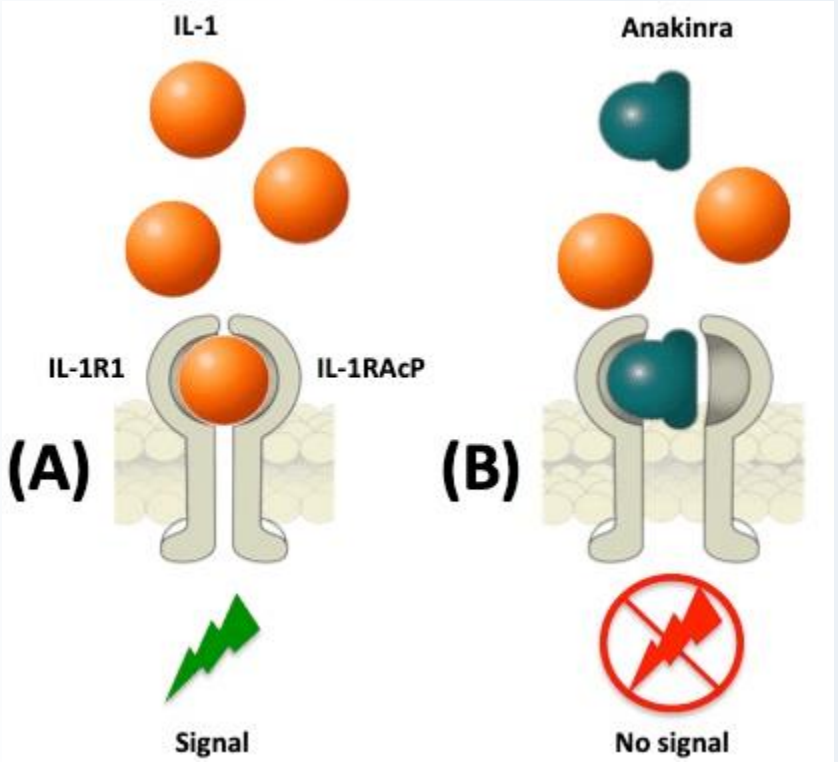
Lee et al, *BBMT* 2019

ICANS Management

- Seizure prophylaxis
- Steroids (dexamethasone)
- Increase steroids
- Change steroids (methylprednisolone)
- Other
  - Consider cyclophosphamide

Other CAR-T toxicities

- Cytopenias
  - Supportive care
  - Growth factors
- Macrophage activation-like syndrome
  - Measure ferritin, IL-2R, NK cell activation, coags
  - Anakinra
- Immunosuppression
  - IVIg
  - Antimicrobial prophylaxis



CAR T cells have 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
- Logistical challenges: vein to vein time
- **How can we pick the right patients to optimize outcome??**
- How will we decide between CAR and T cell engager?

Baseline correlates of complete response to idecabtagene vicleucel (ide-cel, bb2121), a BCMA-directed CAR T cell therapy in patients with relapsed and refractory multiple myeloma: subanalysis of the KarMMa trial

Nina Shah,[1] Nikhil Munshi,[2] Jesús G. Berdeja,[3] Sundar Jagannath,[4] Olivia Finney,[5] Nathan Martin,[6] Amit Agarwal,[6,*] Everton Rowe,[6] Timothy B. Campbell,[6] Jesús San-Miguel[7]

[1]UCSF Medical Center, San Francisco, CA, USA; [2]Dana-Farber Cancer Institute, Boston, MA, USA; [3]Sarah Cannon Cancer Center and Tennessee Oncology, Nashville, TN, USA; [4]Mount Sinai Medical Center, New York, NY, USA; [5]2seventy bio, Cambridge, MA, USA; [6]Bristol Myers Squibb, Princeton, NJ, USA; [7]Clínica Universidad de Navarra, CIMA, CIBERONC, IDISNA, Pamplona, Spain

*Affiliation at the time of the study; current affiliation: Arch Oncology, Brisbane, CA, USA

ASH 2021, Poster 1739

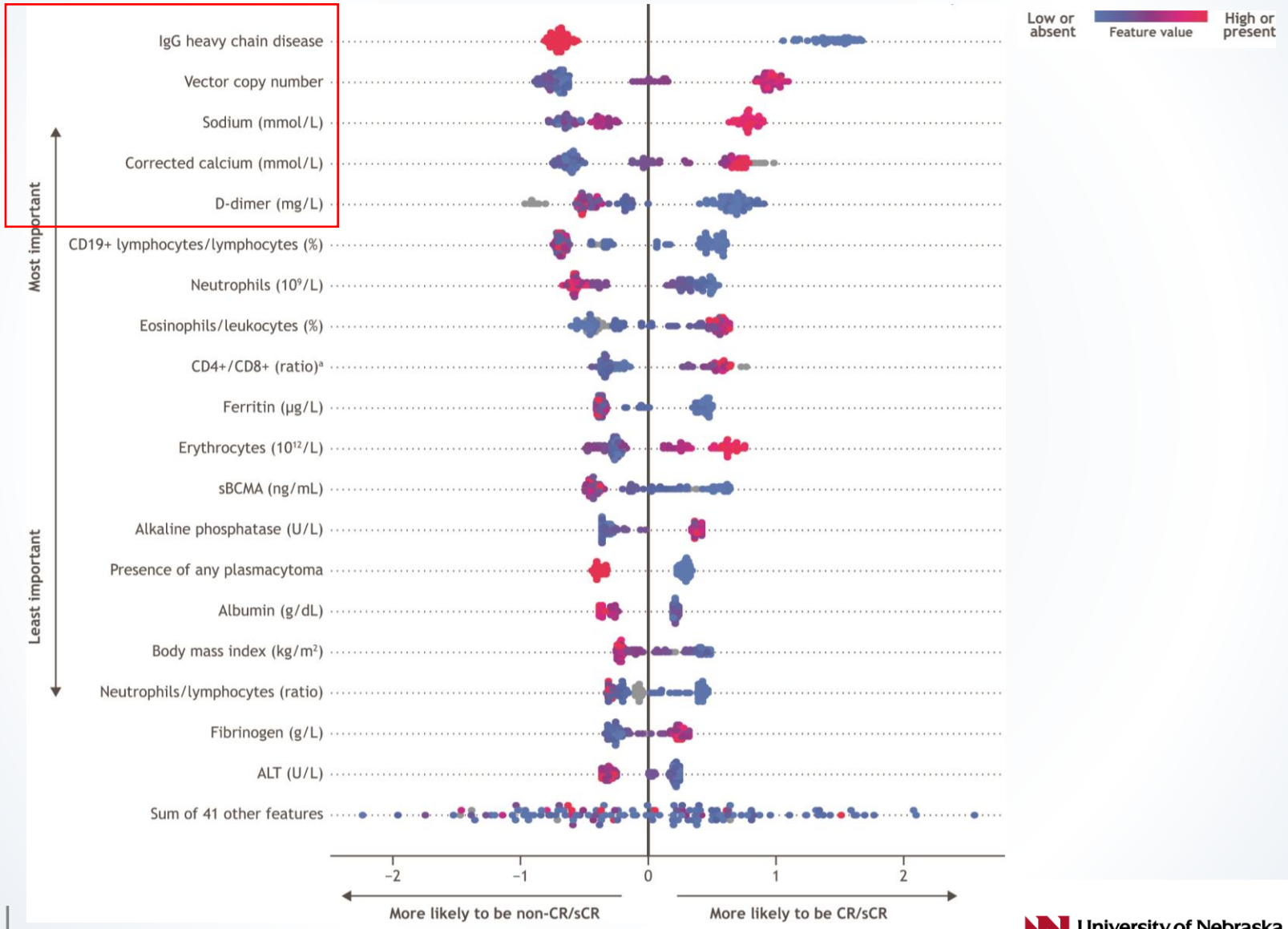
Correlates of CR/sCR versus non-CR/sCR based on univariate and multivariate logistic regression

Baseline or drug product characteristic	Odds ratio	*P* value	Positive or negative correlate of CR/sCR[a]
Univariate correlates of CR/sCR vs non-CR/sCR			
Presence of IgG heavy chain disease	0.162	< 0.0001	Negative
sBCMA (ng/mL)[b]	0.646	0.0007	Negative
D-dimer (mg/L)	0.559	0.0015	Negative
β2 microglobulin ≥ 5.5 mg/L (vs < 3.5 mg/L)	0.201	0.0072	Negative
Ferritin (µg/L)	0.802	0.0155	Negative
Revised ISS stage III (vs I/II)	0.168	0.0207	Negative
Presence of extramedullary disease	0.428	0.0394	Negative
Hemoglobin (g/L)	1.025	0.0255	Positive
Vector copy number in drug product	1.290	0.0287	Positive
Multivariate correlates of CR/sCR vs non-CR/sCR			
Presence of IgG heavy chain disease	0.100	< 0.0001	Negative
sBCMA (ng/mL)[b]	0.637	0.0110	Negative
PT-INR[c]	0.005	0.0365	Negative
Vector copy number in drug product	1.486	0.0168	Positive

[a]For continuous variables, positive correlates of CR/sCR indicate that higher values increased the probability of CR/sCR; negative correlates indicate that higher values decreased the probability of CR/sCR; [b]sBCMA values were reported as integers; [c]PT-INR was reported in increments of 0.1.
PT-INR, prothrombin time-international normalized ratio.

Shah N, et al. ASH 2021 [Poster 1739]

Baseline patient and drug product correlates of CR/sCR based on the multivariate XGBoost model



Each dot represents an individual patient. Gray dots indicate missing values for that particular feature.
[a]From patient laboratory measurements.

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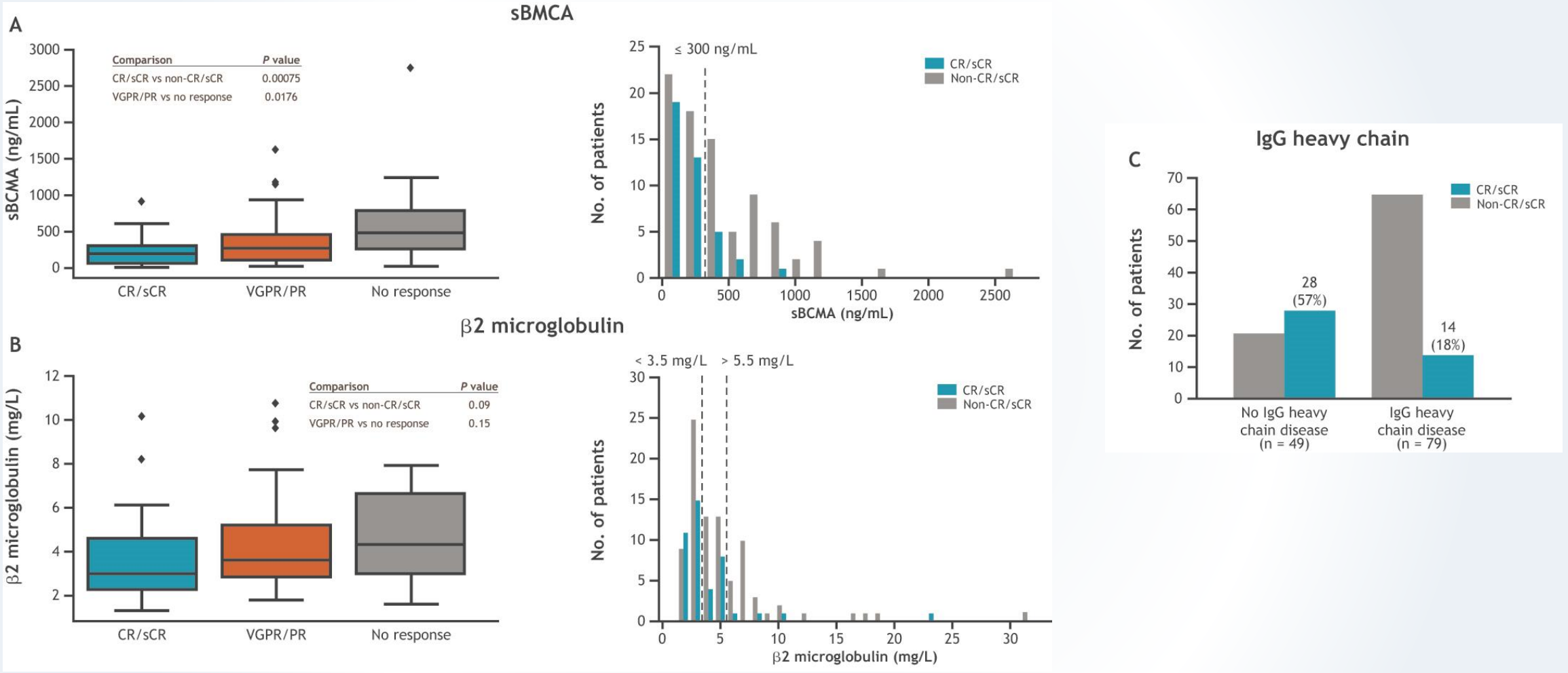
Baseline tumor characteristics as correlates of response



In panels A and B, each box represents Q1, Q3, and median. Whiskers represent the lowest value greater than Q1 − 1.5*IQR and the highest value less than Q3 + 1.5*IQR. Some outliers have not been shown to visualize the difference in medians, but all data were included in statistical tests.
IQR, interquartile range; Q1, quartile 1; Q3, quartile 3.

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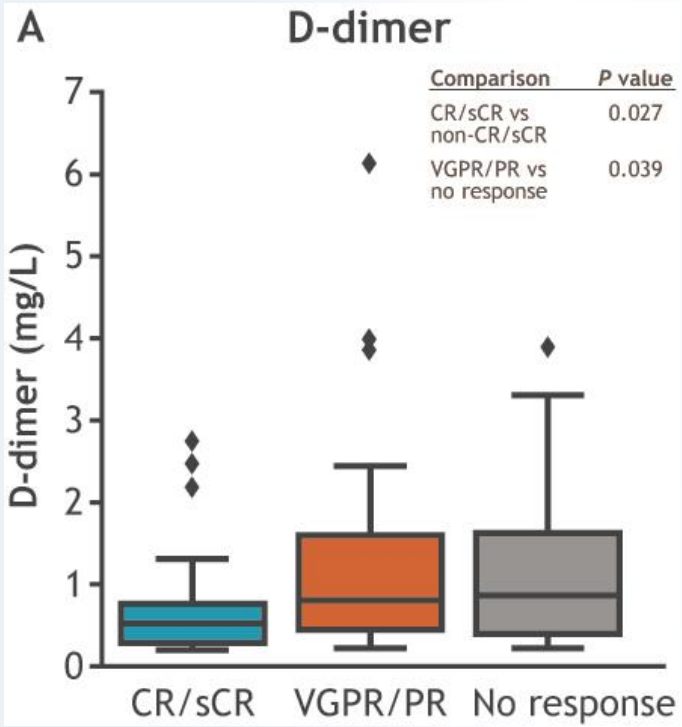
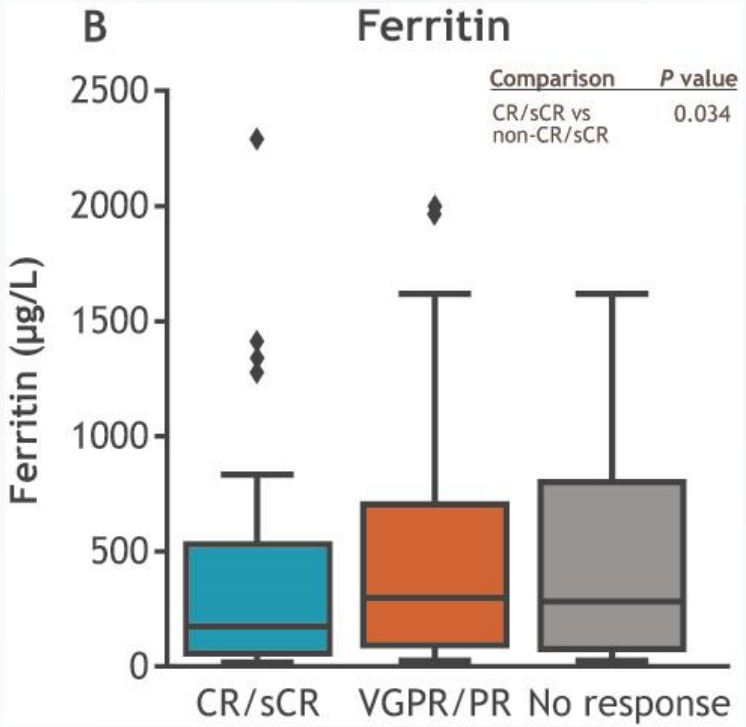
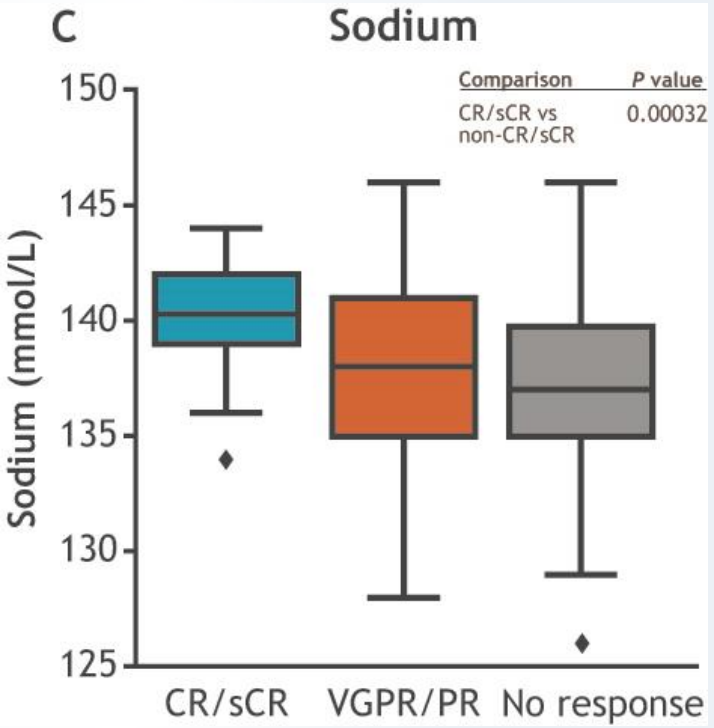
Baseline clinical laboratory measurements and inflammation indicators as correlates of response







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Shah N, et al. ASH 2021 [Poster 1739]

Conclusions- correlates of CR

- In this subanalysis of the pivotal KarMMa trial, 76% of patients with CR/sCR were MRD negative; more than half of them maintained MRD negativity at 12 months
- Multivariate analyses identified IgG heavy chain disease, sBCMA, and PT-INR as negative correlates of CR/sCR and vector copy number in drug product levels as a positive correlate of CR/sCR
- The XGBoost model identified the tumor-related factors sBCMA and IgG heavy chain disease as indicators of response
- Ferritin, D-dimer, and sodium levels were also identified as correlates of response, suggesting that improved patient health characteristics and lower inflammation could impact outcomes
- The correlates identified in this analysis are generally consistent with those previously reported with CD19-directed CAR T cell therapies and may help clinicians to decide which patients have the best chance of a deep clinical response to ide-cel in real-world practice
- These preliminary findings will be validated in larger future ide-cel clinical datasets
- Selecting for patients with a low tumor burden or controlling sBCMA levels during manufacturing with bridging therapy may aid in attaining CR/sCR with ide-cel

Shah N, et al. ASH 2021 [Poster 1739]

CARTITUDE-1 subgroup analysis: Efficacy outcomes in subgroups of patients defined by baseline characteristics

		Patients, n (%)	ORR, % (95% CI)	Median DOR, Months (95% CI)	MRD 10^{-5} negativity,[b] % (95% CI)	2-year PFS, % (95% CI)	2-year OS, % (95% CI)
Overall		97 (100)	97.9 (92.7–99.7)	NE (21.8–NE)	91.8 (81.9–97.3)	60.5 (48.5–70.4)	74.0 (61.9–82.7)
≥65 years[a]		35 (36)	97.1 (85.1–99.9)	NE (24.3–NE)	91.3 (72.0–98.9)	74.0 (55.9–85.5)	70.9 (45.4–86.1)
Black/African American		17 (18)	100.0 (80.5–100)	NE (6.8–NE)	83.3 (51.6–97.9)	58.2 (31.7–77.5)	57.0 (18.0–83.2)
3 prior LOT		17 (18)	100.0 (80.5–100)	NE (12.9–NE)	80.0 (44.4–97.5)	66.2 (35.5–84.8)	81.4 (52.6–93.6)
≥4 prior LOT		80 (82)	97.5 (91.3–99.7)	NE (20.2–NE)	94.1 (83.8–98.8)	60.2 (47.7–70.7)	71.9 (57.7–82.1)
Triple-class refractory		85 (88)	97.6 (91.8–99.7)	NE (24.3–NE)	92.6 (82.1–97.9)	63.5 (51.8–73.1)	72.7 (59.4–82.2)
Penta-drug refractory		41 (42)	95.1 (83.5–99.4)	NE (NE–NE)	85.0 (62.1–96.8)	68.3 (51.7–80.2)	68.0 (45.9–82.6)
Cytogenetic risk	Standard risk High risk	68 (70) 23 (24)	97.1 (89.8–99.6) 100.0 (85.2–100)	NE (21.8–NE) 20.2 (9.4–NE)	95.2 (83.8–99.4) 82.4 (56.6–96.2)	64.1 (49.5–75.5) 48.4 (25.1–68.4)	73.6 (58.2–84.0) 73.7 (50.5–87.2)
ISS Stage III at baseline		14 (14)	100.0 (76.8–100)	13.8 (5.1–NE)	100.0 (54.1–100)	NE (NE–NE)	NE (NE–NE)
Baseline bone marrow plasma cells	≤30% >30 to <60% ≥60%	58 (60) 17 (18) 21 (22)	98.3 (90.8–100) 100.0 (80.5–100) 95.2 (76.2–99.9)	NE (21.8–NE) NE (15.9–NE) NE (5.5–NE)	96.6 (82.2–99.9) 87.5 (61.7–98.4) 87.5 (61.7–98.4)	66.5 (51.1–78.1) 54.6 (23.0–78.0) 51.6 (28.7–70.4)	75.9 (59.1–86.5) 94.1 (65.0–99.1) 52.4 (22.4–75.6)
Baseline tumor BCMA expression	≥median (80%) <median (80%)	31 (32) 31 (32)	96.8 (83.3–99.9) 100.0 (88.8–100)	NE (21.8–NE) NE (20.5–NE)	94.1 (71.3–99.9) 95.7 (78.1–99.9)	67.3 (44.8–82.3) 63.9 (41.2–79.7)	80.9 (58.2–92.0) 67.6 (40.8–84.3)
Presence of baseline plasmacytomas[c]		19 (20)	100.0 (82.4–100)	12.9 (4.0–NE)	90.9 (58.7–99.8)	47.4 (24.4–67.3)	46.4 (15.8–72.6)

[a]There were 8 patients aged ≥75 years. No difference was observed in ORR between these patients and other age subgroup; [b]In MRD-evaluable patients; MRD was assessed in evaluable samples at 10-5 threshold by next-generation sequencing (clonoSEQ, Adaptive Biotechnologies) in all treated patients at day 28, and at 6, 12, 18, and 24 months regardless of the status of disease measured in blood or urine. Only MRD assessments (10-5 testing threshold) within 3 months of achieving CR/sCR until death/progression/subsequent therapy (exclusive) are considered; [c]Includes bone-based and extramedullary plasmacytomas.

BCMA, B-cell maturation antigen; CR, complete response; DOR, duration of response; ISS, International Staging System; LOT, lines of therapy; MRD, minimal residual disease; NE, not estimable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; sCR, stringent complete response

CARTITUDE-1 subgroup analysis: Conclusions

- ORR was high across all subgroups, including patients with high-risk disease and those who are difficult to treat (with EMD)
- Despite shorter DOR, PFS, and OS in patients with high-risk cytogenetics, baseline ISS stage III MM, and baseline plasmacytomas, cilta-cel efficacy was still favorable when compared to approved MM therapies[1-3]
  - High-risk patients are being further evaluated in the CARTITUDE-2 trial (NCT04133636)

Responses to cilta-cel were durable up to 2 years in most subgroups of patients with heavily pretreated RRMM, with consistent safety across subgroups

Responses were still favorable in high-risk populations compared to recently approved MM therapies

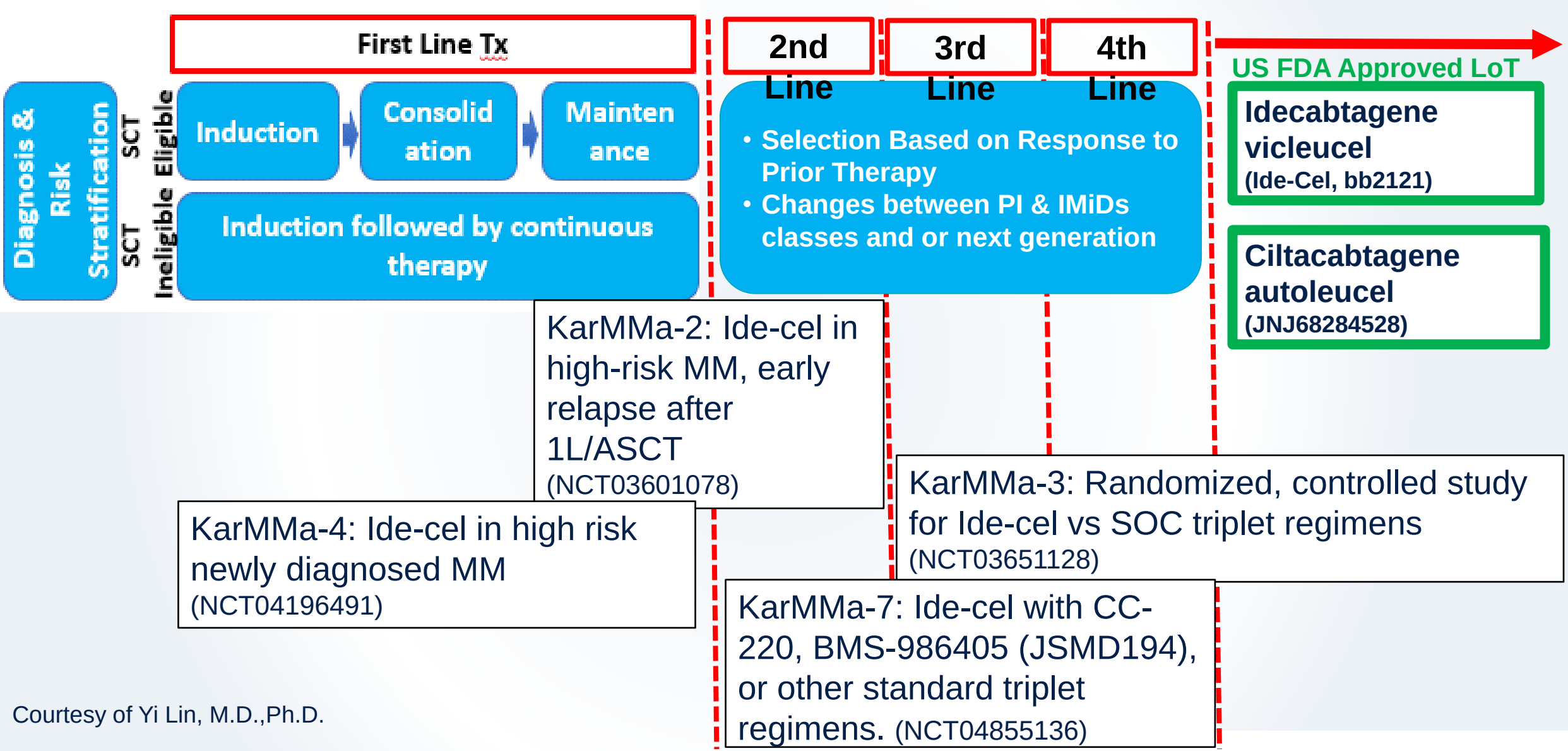
Cilta-cel, ciltacabtagene autoleucel; DOR, duration of response; EMD, extramedullary disease; MM, multiple myeloma; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma

1. Munshi NC, et al. *N Engl J Med* 2021; 384:705-716. 2. Richardson PG, et al. *Blood Cancer J* 2020; 10:106. 3. Richter J, et al. *Ther Adv Hematol* 2020; 11:2040620720930629.

BCMA Therapeutics: Advantages/Disadvantages

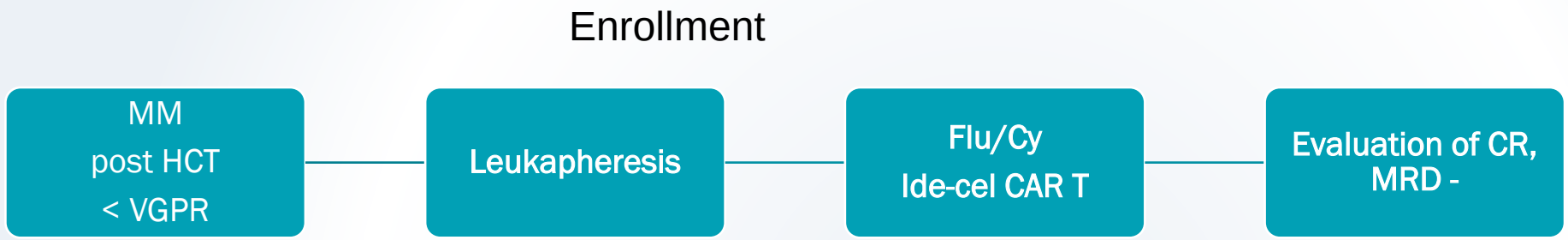
	Antibody–Drug Conjugate	CAR T-Cells	Bispecific Antibody
Advantages	Off the shelf	Personalized	Off the shelf
	Targeted cytotoxicity Not dependent on T-cell health	Targeted immuno-cytotoxicity	Targeted immuno-cytotoxicity
	No lymphodepletion No steroids	Single infusion (“one and done”)	No lymphodepletion Minimal steroids
	Available to any infusion center Outpatient administration	Potentially persistent	
Disadvantages		FACT-accredited center required (hospitalization likely required)	Initial hospitalization required
	Currently requires REMS/ophtho	CRS and neurotoxicity; requires ICU and neurology services	CRS and neurotoxicity possible
	Single agent activity low in CD38-refractory patients	Dependent on T-cell health (manufacturing failures)	Dependent on T-cell health (T-cell exhaustion)
	Requires continuous administration	Requires significant social support – caregiver required	Requires continuous administration
	$$$	$$$$	$$$

CAR-T investigations in earlier lines of therapy



Courtesy of Yi Lin, M.D.,Ph.D.

BMT CTN 1902 Study Schema



~9 mo post auto HCT
No prior disease Progression

- Population: Patients with suboptimal response (<VGPR) after an autoHCT and 6 mo of maintenance
- Intervention: CAR T cells and continuation of maintenance
- Primary endpoint: CR and MRD negative
  - Aim to improve 6mo CR from <10% to 30%

House of CARs

Trial	Company	CAR T product	Med prior lines	Special Sauce	ORR	CRS %	Neurotox %	Survival data	Notes
Karmma-1 (phase II, n=128)	Celgene/ BMS	Bb2121 (Ide-cel)	6		73% (82% @450 dose)	84%	18%	mPFS 8.8mo, @450 dose: 12.1 mo OS 24.8	FDA approved 2021, ≥4L
CARTITUDE-1 (phase Ib/II, n-97)	Janssen	JNJ-4528 (Cilta-cel)	6	Bi-epitope binding to BCMA	98%	92%	20.1% (16.5% ICANS)	@ 24 mo: 60% prog-free;	FDA approved 2022, ≥4L
LUMMICAR-2 (phase Ib/II, n=18-20)	CARSgen	CT053	5	Fully human	94% (n=18)	77-83%	15-17%	NA	
PRIME (phase I/II, n=55)	Poseida	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)	Bluebird	bb21217	6	PI3Ki culture to increase Tscm cells	69% (74% at 450 dose, 81% w/ new mfg)	75%	15%	PFS 12.8 mo, 18 mo @450; mDOR 23.8 mo (all doses)	Memory cell phenotype in DP may correlate w/ response
UNIVERSAL (phase I, n=43, 24 in 320 dose)	Allogene	Allo-715	5	Allo CART	71% at 320 dose	56%	14%	NA	Variability in LD, tx within 5 days of enrollment!! No GVH
FasT CART	Gracell	GC012F	5	CD19 BCMA dual CAR T, ON manufact	95%	95%	0	NA	
MCARH109, ph 1 n=17 (59% prior BCMA exposed)	MSKCC	MCARH109	6	**GPRC5D-CAR**	69%	93%	6%	NA	Nail changes = 56% Rash= 19% Dysgeusia = 6%

Conclusions

- CAR T cell therapy for myeloma yields impressive ORR, PFS data, better than conventional care
- But no cures yet! #plateauenvy
- How do we optimize patient experience and patient selection?
  - Clinical factors relating to tumor burden, disease risk
  - Production factors (VCN)
- Will we follow the lymphoma evolution?
- Have to consider cost, quality of life, accessibility, referral patterns, logistics

THANK YOU!

@ninashah33

#myelennial