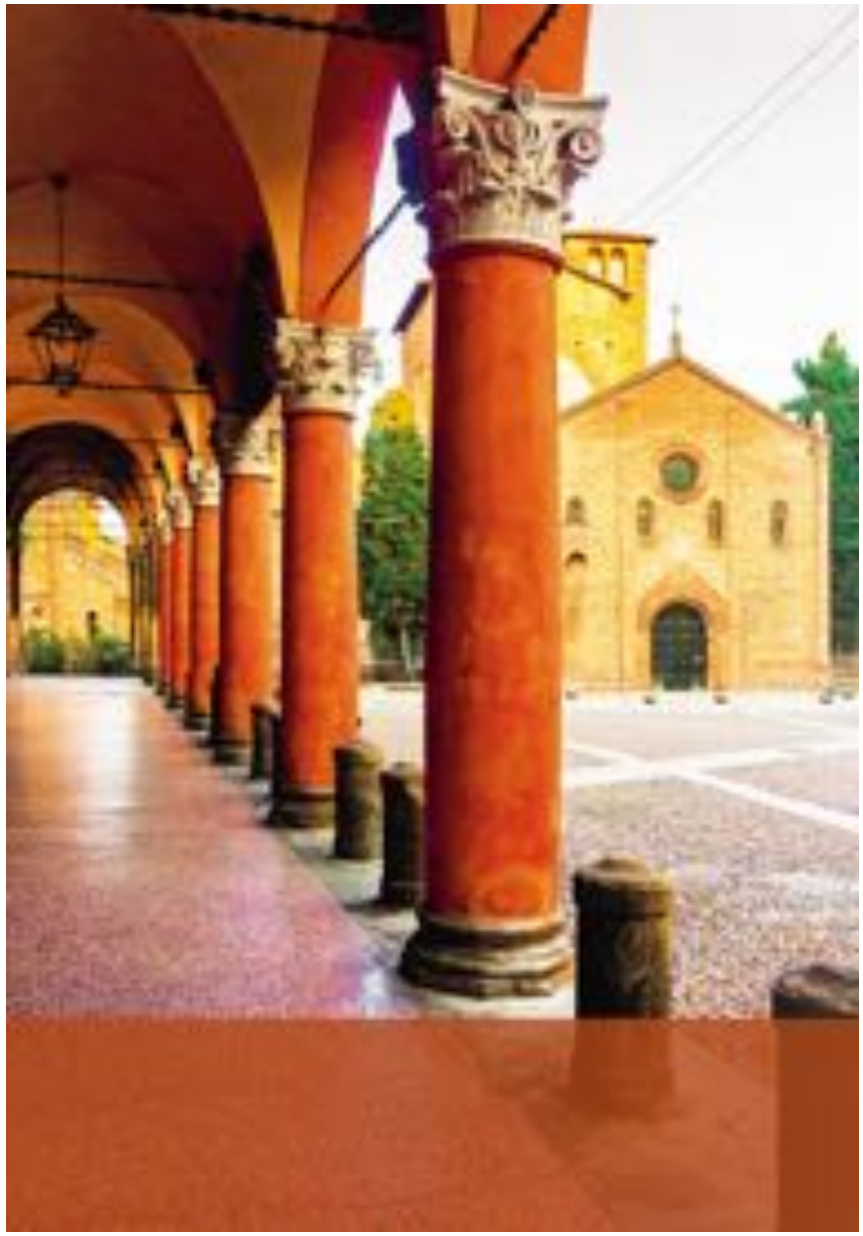

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

L'immunoterapia nel mieloma multiplo ricaduto/refrattario: dagli anticorpi monoclonali alle cellule CAR-T

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Caso clinico 3: Con immunoterapia cellulare adottiva (CAR-T)

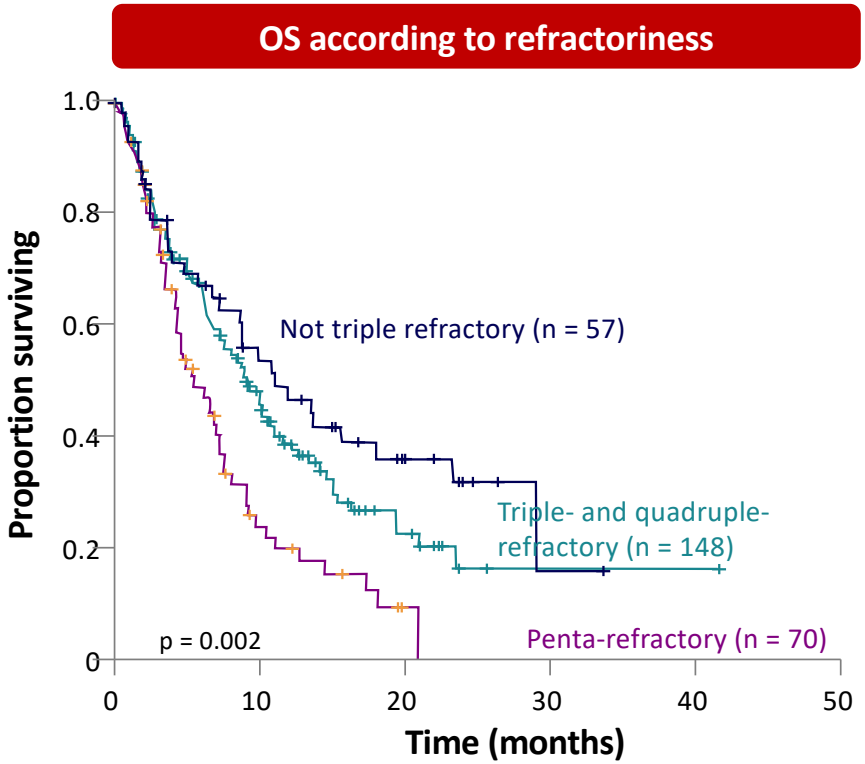
Bologna, 3-4 Novembre 2021 - Starhotel Excelsior

Disclosures of Michele Cavo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Glaxo Smith Kline			X			X	Honoraria
Janssen			X		X	X	Honoraria
Sanofi			X		X	X	Honoraria
Roche			X			X	Honoraria
Amgen			X			X	Honoraria
Takeda			X			X	Honoraria
AbbVie			X			X	Honoraria
Bristol Myers Squibb			X		X	X	Honoraria
Celgene			X		X	X	Honoraria

Poor outcomes in triple- and penta-refractory MM patients

- 275 MM patients refractory to anti-CD38 mAbs
- mOS from refractoriness to CD38:
  - all patients: 8.6 months
  - "non-triple-refractory": 11.2 months
  - "triple- and quad-refractory": 9.2 months
  - "penta-refractory": 5.6 months
- 249 patients received further treatment:
  - mPFS: 3.4 months
  - mOS: 9.3 months



- Non-triple-refractory: refractory to 1 CD38 mAb, and not both PI and IMiD compound
- Triple- and quad-refractory: refractory to 1 CD38 mAb + 1 IMiD compound + 1 PI; or 1 CD38 mAb + 1 PI + 1 or 2 IMiD compounds; or 1 CD38 mAb + 1 or 2 PIs + 1 IMiD compound
- Penta-refractory: refractory to 1 CD38 mAb + 2 PIs + 2 IMiD compounds

mOS, median overall survival; mPFS, median progression-free survival.

Gandhi UH, et al. Leukemia. 2019;Mar 11 [Epub ahead of print].

Clinical Case

G.C. (male, 57 years old)

Comorbidities: right nephrectomy due to ureteral tubercolosis (1997)

Diagnosis of **IgG/lambda MM** in January 2017

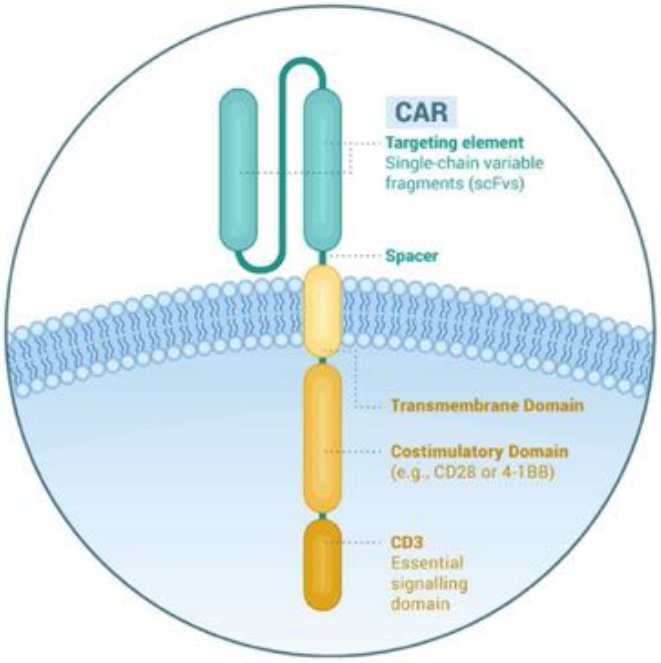
- ISS 2, R-ISS 3
- bone marrow biopsy: **80-90% of PCs**
- FISH: amp(1q21) and t(4:14) positivity
- 18-FDG PET-CT: negative for bone lesions
- MRI: **3 focal lesions** (D1, D9, L1)
- **Hb 9.1 g/dl**, creatinine 0,80 mg/dl, calcemia 9,0 mg/dl, serum MC 4.1 g/dl, sFLC lambda 350 mg/L (ratio 0.01), urine MC (620 mg/d)

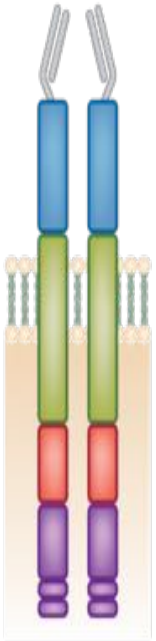
Clinical Case

- **first line therapy**: KRD x 4 (FORTE study) → PD → VTD-PACE x 3 + double ASCT + VTD x 2 (consolidation), and then Bort maintenance → VGPR
- October 2019: PD
- **second line therapy**: PCd x 6 → SD/PD
- **third line therapy**: Dara-Rd x 2→ PD

- enrollment into **KarMMa-3 study** → randomization to the CAR-T cell arm → **apheresis (04 Jan 2021)**

CAR-T (chimeric antigen receptor-T cells): structure and functions





-**Extracellular domain** that binds specifically to a target molecule expressed on the tumor cell surface:
-**Single-chain variable fragment** (scFv)
-Recognize tumor-associated antigens in a non-MHC-specific manner

-**Transmembrane hinge region** derived from CD8 provides flexibility to allow reorientation to bind antigen

-**Intracellular costimulatory domain (II and III-IV generation CAR-T)**: CD28 or 4-1BB (more robust cytokine production and enhanced cytolytic activity of CAR-Ts)

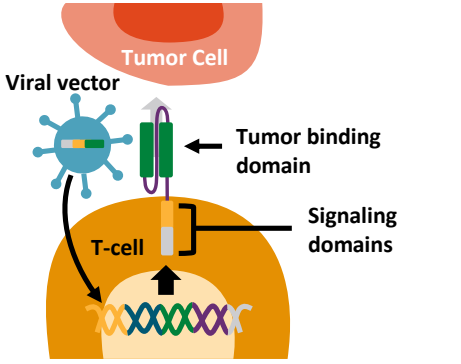
-**Intracellular T-cell activation domain**: CD3ζ

- **Antigen recognition** via extracellular domain and **HLA-independent activation of T cells** with powerful cytotoxic and memory functions via intracellular domain
- **Remodelling of tumor suppressive microenvironment**

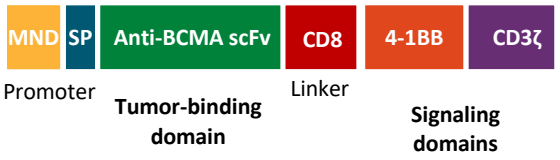
CAR, chimeric antigen receptor; MHC, major histocompatibility complex; MM, multiple myeloma; NK, natural killer.

Adapted from Kershaw MH et al. Nat rev Cancer 2013

Idecabtagene Vicleucel (ide-cel; bb2121): anti-BCMA CAR T-Cell Construct Design

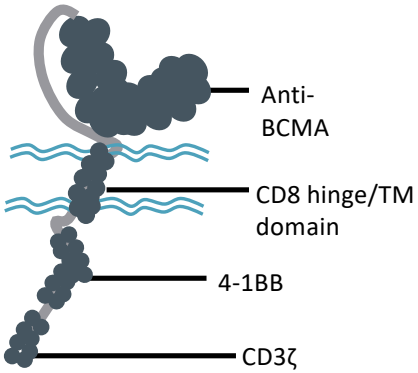


Idecabtagene CAR design



Extracellular domain
Targeting domain
Hinge/TM domain

Intracellular domain
Costimulatory domain
T-cell activation domain



Idecabtagene: second-generation CAR construct

- **Autologous** T-cells transduced with a lentiviral vector encoding CAR specific for BCMA
- Targeting domain: **Anti-BCMA**
- Costimulatory domain: **4-1BB**
- T-cell activation domain: **CD3ζ**

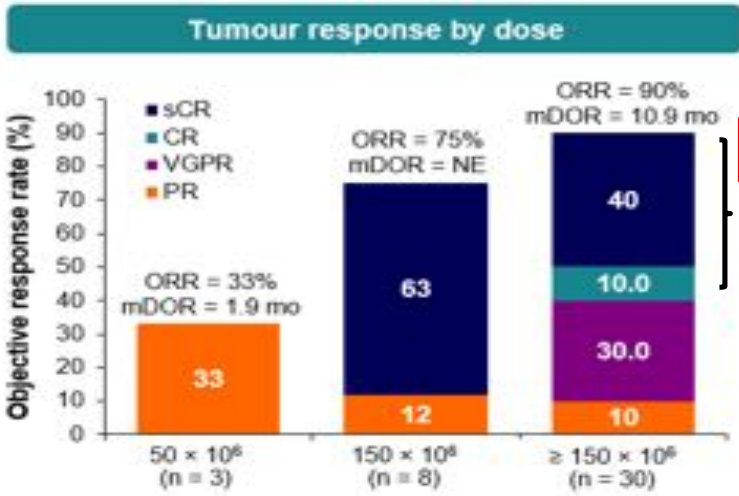
4-1BB associated with less toxicity and more durable CAR T-cell persistence than CD28 costimulatory domain

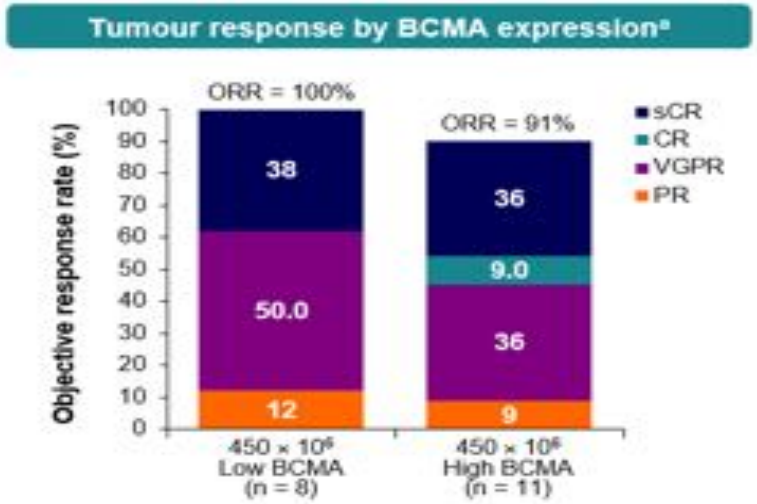
BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CD, cluster of differentiation; MND, dl587 rev primer-binding site substituted; scFv, short chain variable fragment; SP, signaling peptide; TM, transmembrane domain.

1. Raje N et al, *N Engl J Med* 2019;380:1726–37. **2.** Raje N, et al. ASCO 2018. Abstract. 8007.

First-in-class anti-BCMA CAR-T cell construct approved by FDA and EMA

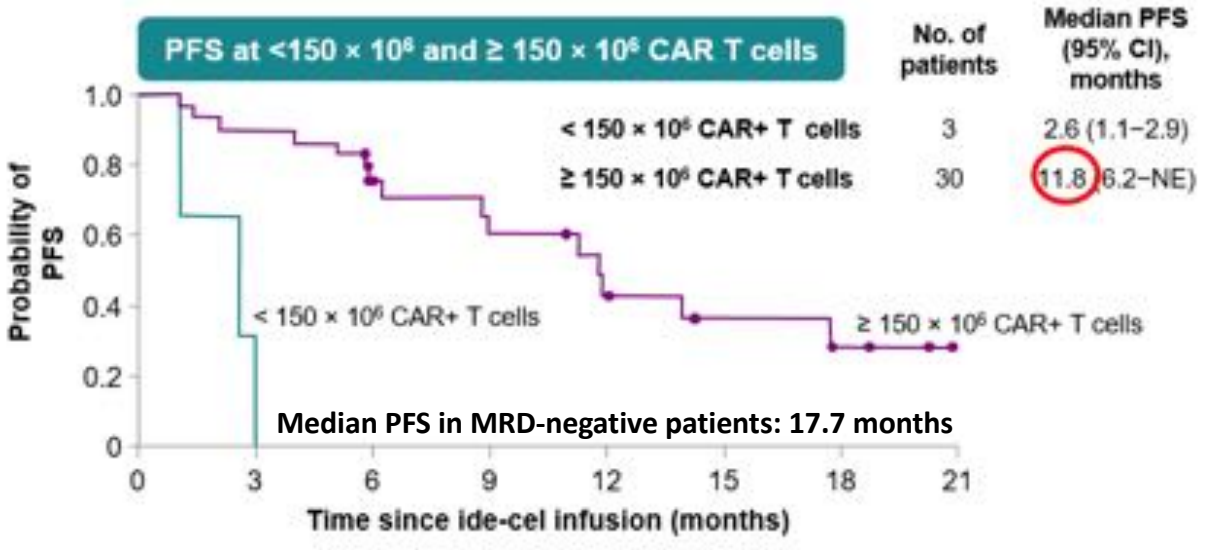
Ide-cel (bb2121) phase 1 study: efficacy outcomes





15/16 responders who were assessed for MRD had undetectable MRD

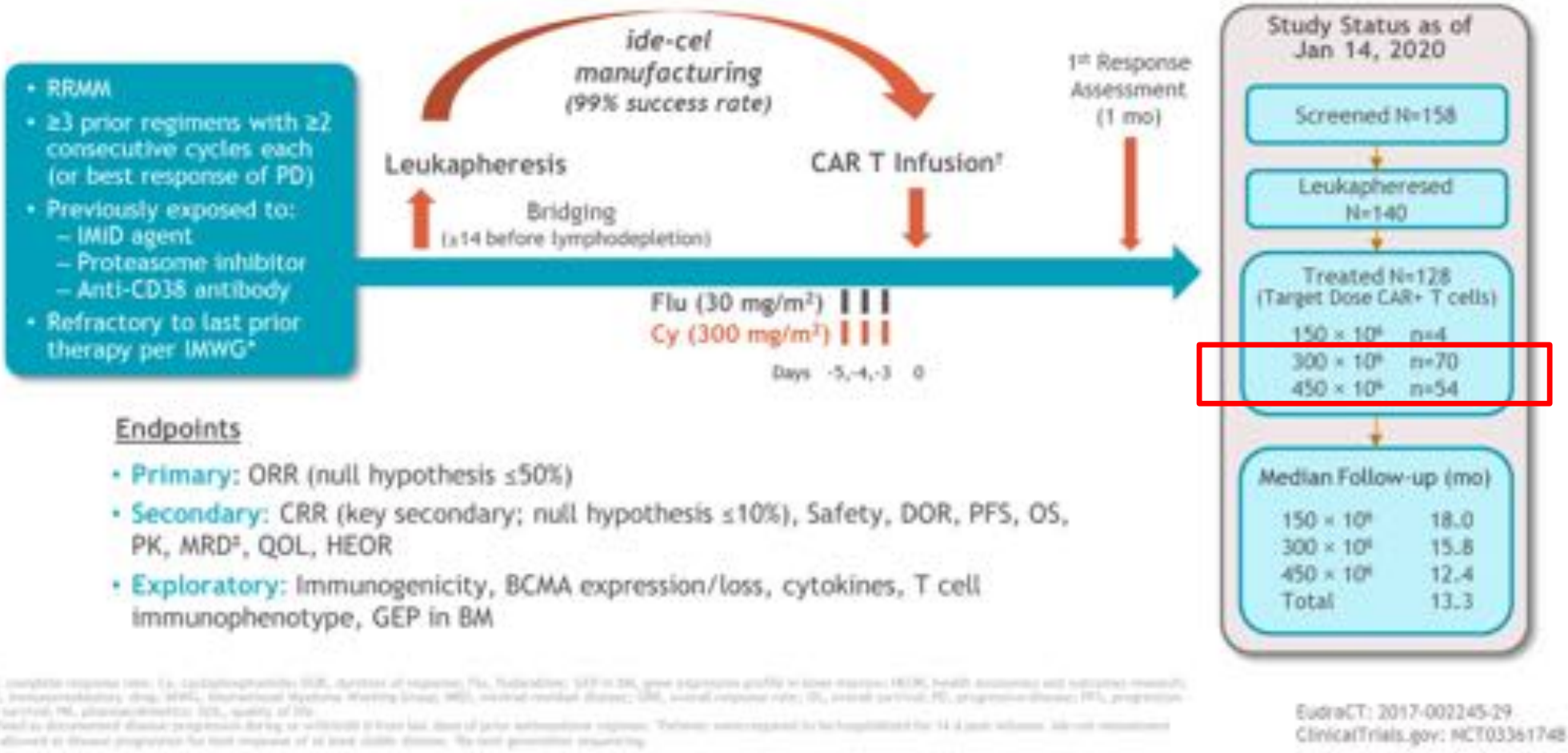
≥ CR: 50%



Median CAR-T persistence: 6 months

Raje N, et al. N Engl Med. 2019;380:1726-37.

Phase II Pivotal KarMMa Study



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

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

Munshi N, et al. N Engl Med. 2021;384:705-16.

KarMMa: Baseline Characteristics

Characteristic	Ide-cel Treated (N = 128)
Median age, years (range)	61 (33–78)
Male, %	59
ECOG PS, % ▪ 0 ▪ 1 ▪ 2	 45 53 2
R-ISS stage, % ▪ I ▪ II ▪ III	 11 70 16
High-risk cytogenetics (del[17p], t[4;14], t[14;16]), %	35
High tumor burden (≥ 50% BMPCs), %	51

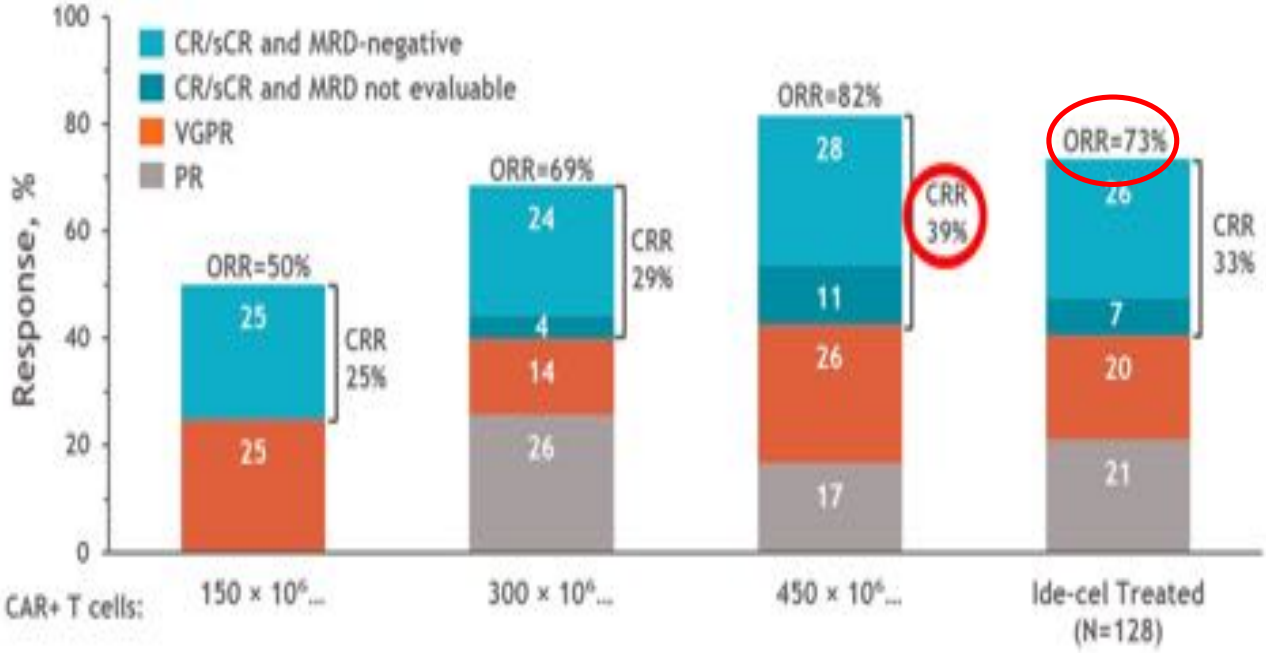
Characteristic	Ide-cel Treated (N = 128)
Tumor BCMA expression (≥ 50% BCMA positive), %	85
Extramedullary disease, %	39
Median time since initial diagnosis, years (range)	6 (1–18)
Median no. of prior anti-MM regimens (range)	6 (3–16)
Prior autologous SCT, % ▪ 1 ▪ >1	 94 34
Any bridging therapies for MM, %	88
Refractory status, % ▪ Anti-CD38 mAb refractory ▪ Triple refractory	 94 84

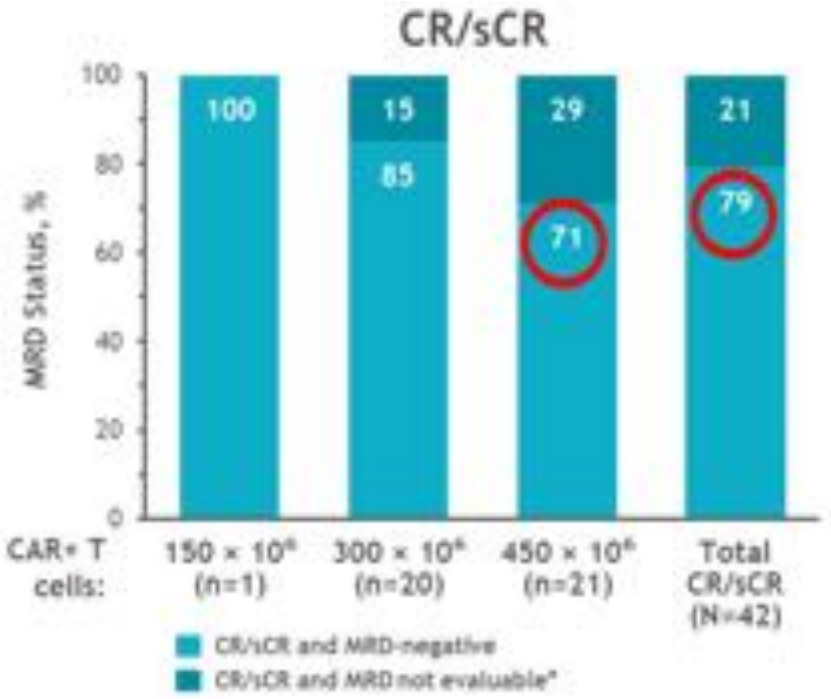
88% of patients received bridging therapy; only 4% responded

BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cell; ECOG PS, Eastern Cooperative Oncology Group performance score; ida-cel, idecabtagene vicleucel; mAb, monoclonal antibody; MM, multiple myeloma; SCT, stem cell transplant.

Munshi N, et al. N Engl Med. 2021;384:705-16.

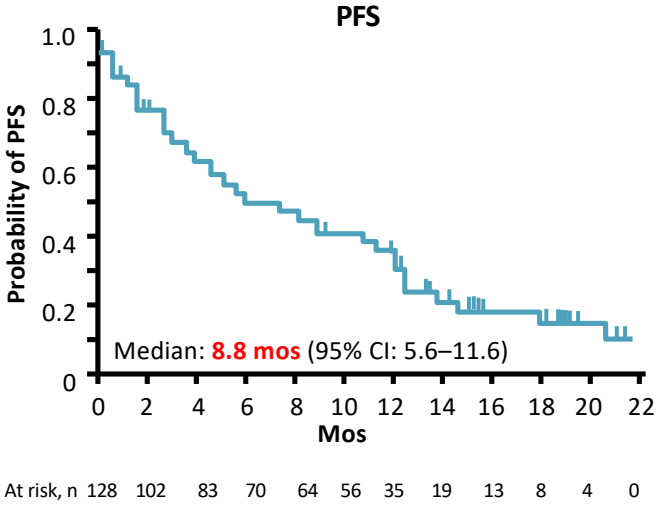
Phase 2 KarMMa study: best ORR and MRD neg rates

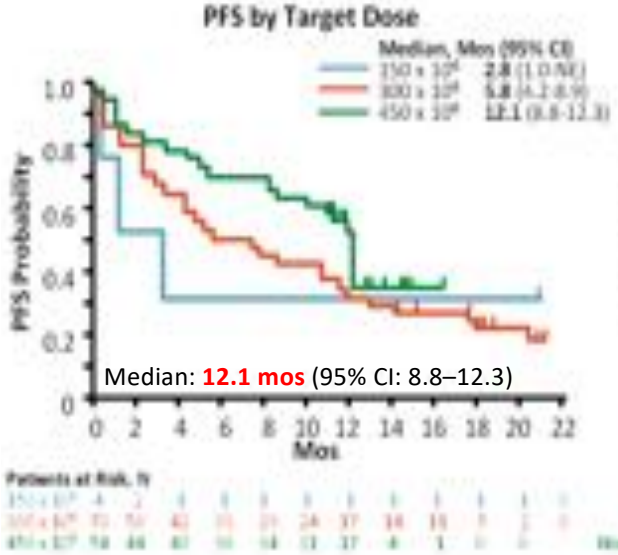


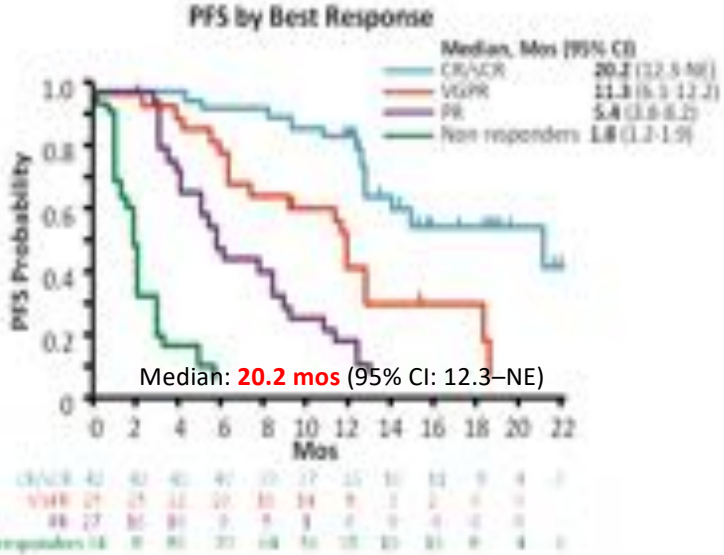


Munshi N, et al. N Engl Med. 2021;384:705-16.

KarMMa: PFS

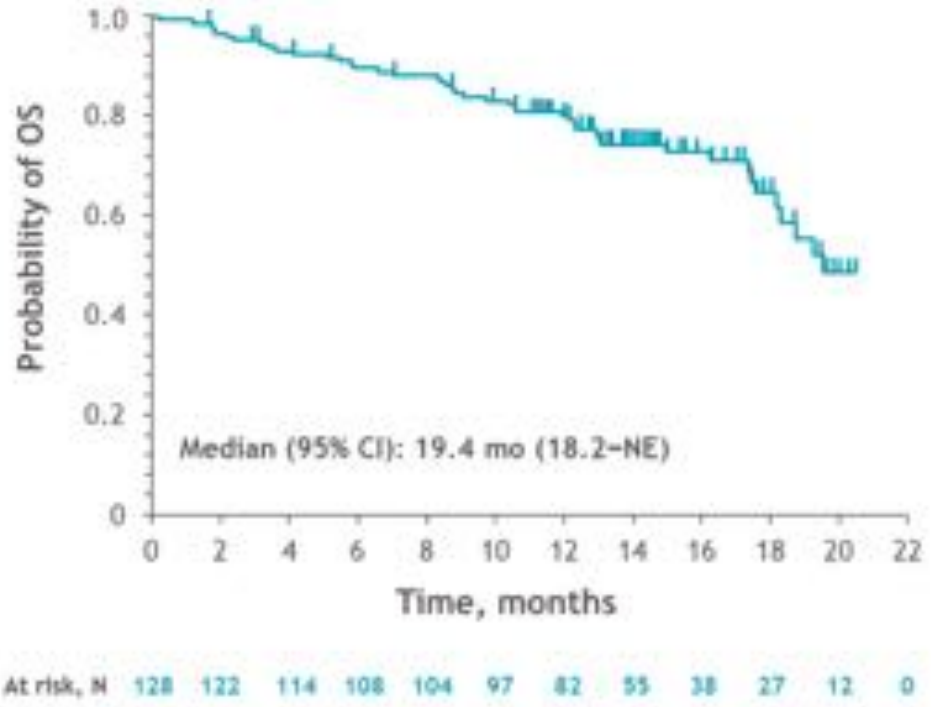






Munshi N, et al. N Engl Med. 2021;384:705-16.

KarMMa: OS

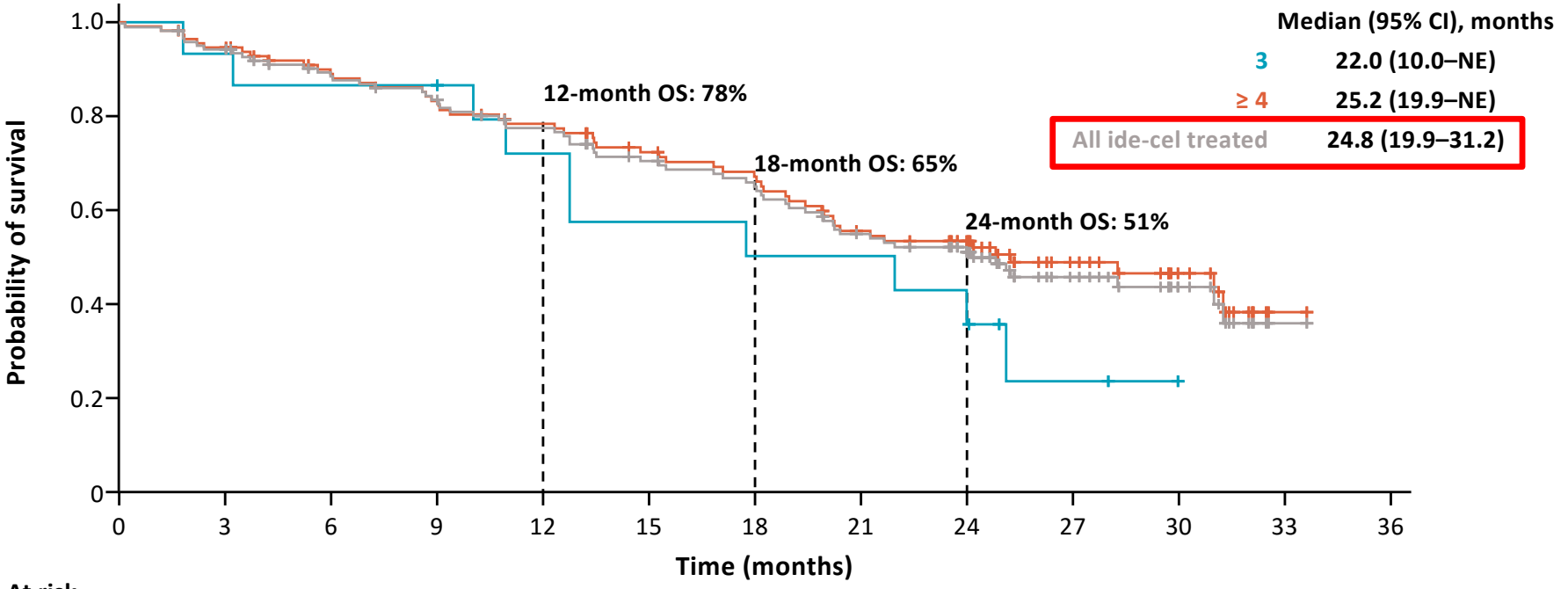


- 78% of all ide-cel treated patients were event-free at 12 mo
- Survival data are immature with 66% of patients censored overall; 72% at target dose of 450 × 10^6 CAR+ T cells

EMA approval for pts **who have received at least three prior therapies including an IMiD, PI, and anti-CD38 moAb**

Munshi N, et al. N Engl Med. 2021;384:705-16.

OS in the ITT population and by number of prior lines of therapy



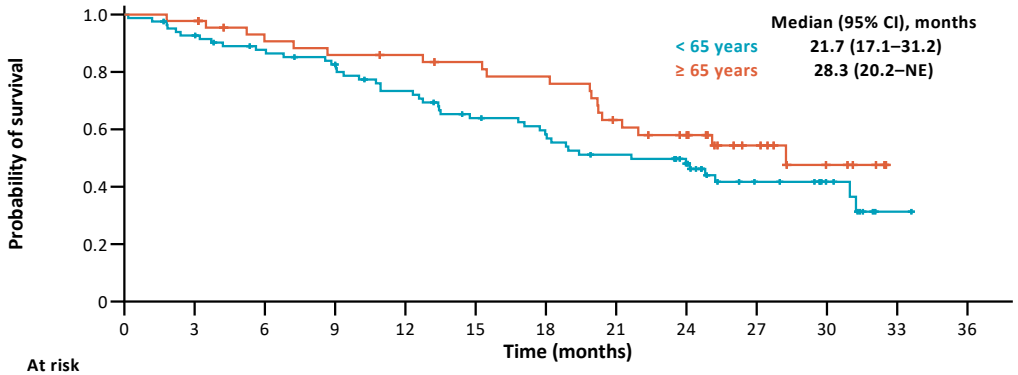
At risk

3	15	14	13	13	10	8	7	7	5	2	0	0	0
≥ 4	113	106	94	87	80	71	65	52	43	24	14	1	0
All ide-cel treated	128	120	107	100	90	79	72	59	48	26	14	1	0

- Median OS was 24.8 months among all ide-cel treated patients
- Median OS was 22.0 and 25.2 months in patients with 3 and ≥ 4 prior lines of therapy, respectively

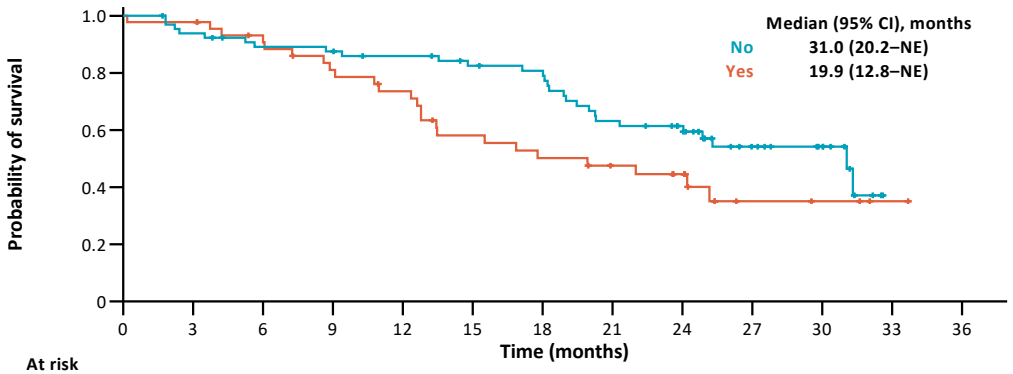
OS in high-risk patient subgroups

Age



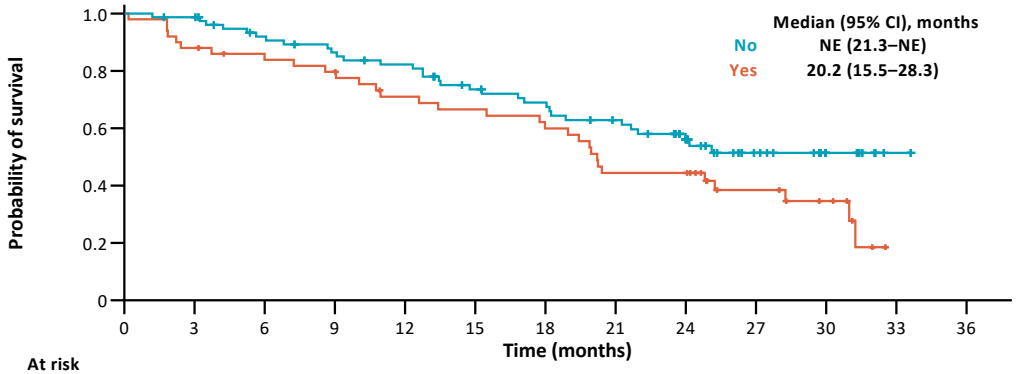
At risk													
< 65 years	83	76	69	64	55	46	41	35	28	15	9	1	0
≥ 65 years	45	44	38	36	35	33	31	24	20	11	5	0	0

High-risk cytogenetics



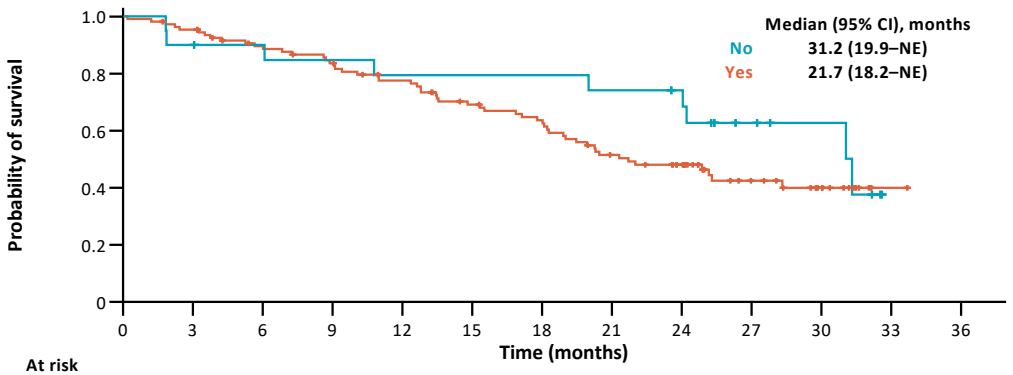
At risk													
No	66	61	56	55	52	48	45	36	29	16	9	0	0
Yes	45	44	38	33	29	22	19	16	13	4	3	1	0

Extramedullary disease



At risk													
No	78	76	67	62	58	49	45	39	28	15	7	1	0
Yes	50	44	40	38	32	30	27	20	20	11	7	0	0

Triple refractory



At risk													
No	20	18	17	16	15	15	15	14	12	7	5	0	0
Yes	108	102	90	84	75	64	57	45	36	19	9	1	0

- Median OS was > 20 months in several key high-risk subgroups, including age (≥ 65 years), extramedullary disease, and triple-refractory status

Clinical Case

Bridging therapy: DaraPd x 1 → PD

Pre Car-T cells: serum MC 2821 mg/dL, sFLC lambda 360 mg/l (ratio 257), urine MC 198 mg/die.

21-23 Feb 2021: lymphodepleting chemoterapy
- Fludarabine 30 mg/mq (day -5 to day -3)
- **Cyclophosphamide 300 mg/mq** (day -5 to day -3)

26 Feb 2021: **ide-cell reinfusion**

Complications:
- **grade II CRS** → Tocilizumab 8 mg/kg (3 doses) → progressive resolution
- **DIC** (INR 1.45, aPTT 1.45, low fibrinogen, D-dimer increase, ATIII reduction) → plasma support

Most Commons Adverse Events

AE,* n (%)	Ide-cel Treated (N=128)	
	Any Grade	Grade ≥3
Hematologic		
Neutropenia	117 (91)	114 (89)
Anemia	89 (70)	77 (60)
Thrombocytopenia	81 (63)	67 (52)
Leukopenia	54 (42)	50 (39)
Lymphopenia	35 (27)	34 (27)
Gastrointestinal		
Diarrhea	45 (35)	2 (2)
Nausea	37 (29)	0
Other		
Hypokalemia	45 (35)	3 (2)
Fatigue	43 (34)	2 (2)
Hypophosphatemia	38 (30)	20 (16)
Hypocalcemia	34 (27)	10 (8)
Pyrexia	32 (25)	3 (2)
Hypomagnesemia	30 (23)	0
Decreased appetite	27 (21)	1 (<1)
Headache	27 (21)	1 (<1)
Hypogammaglobulinemia	27 (21)	1 (<1)
Cough	26 (20)	0
CRS†	107 (84)	7 (5)

- Cytopenias were common; not dose related
- Median time to recovery of grade ≥3 neutropenia and thrombocytopenia was 2 mo (95% CI, 1.9–2.1) and 3 mo (95% CI, 2.1–5.5), respectively
- Delayed recovery (>1 mo) of grade ≥3 neutropenia in 41% of patients and thrombocytopenia in 48%‡
- Infections (including bacterial, viral, fungal) were common (69%); not dose-related
- 5 deaths (4%) within 8 wk of ide-cel infusion
  - 2 following MM progression
  - 3 from AEs (CRS, aspergillus pneumonia, GI hemorrhage)
- 1 additional death from AE (CMV pneumonia) within 6 mo, in the absence of MM progression

Data cutoff: 14 Jan 2020. AE, adverse event; CMV, cytomegalovirus; CRS, cytokine release syndrome; GI, gastrointestinal.
*Events reported in 20% or more patients. †Clustered term including the preferred terms confirmed graded per Lee DW, et al. Includes 1 patient with grade 5 CRS event was observed.
‡Includes patients with grade 3-4 cytopenia at 1 mo post-infusion.

Munshi N, et al. N Engl Med. 2021;384:705-16.

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

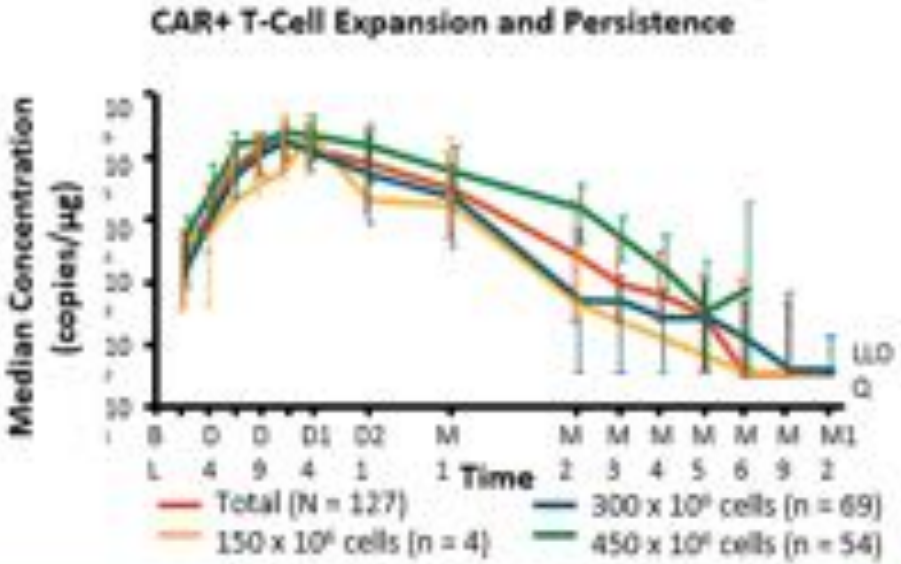
Incidence and management of neurotoxicity

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)

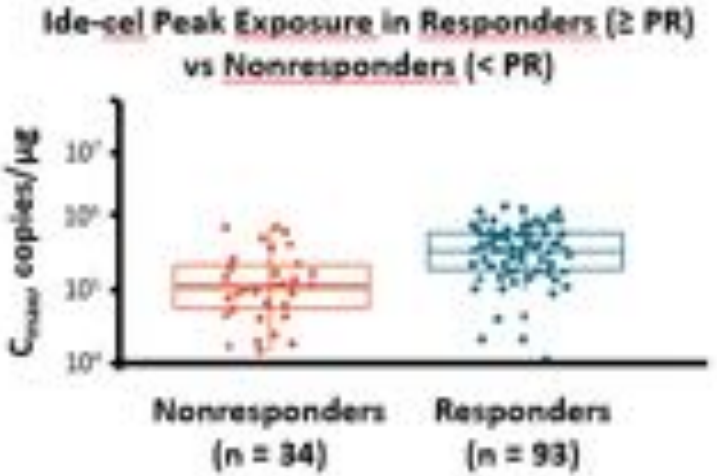
- NT mostly low grade and was similar across target doses
- Incidence of grade 3 NT events was uncommon (≤6%) at all target doses; no grade 4 or 5 events
- NT managed with corticosteroids was infrequent (≤15%) at all target doses

Munshi N, et al. N Engl Med. 2021;384:705-16.

KarMMa: CAR T-Cell Parameters



	Mo 1	Mo 3	Mo 6	Mo 9	Mo 12
Evaluable patients, n	118	100	49	27	11
Patients with detectable vector, n (%)	117 (99)	75 (75)	29 (59)	10 (37)	4 (36)



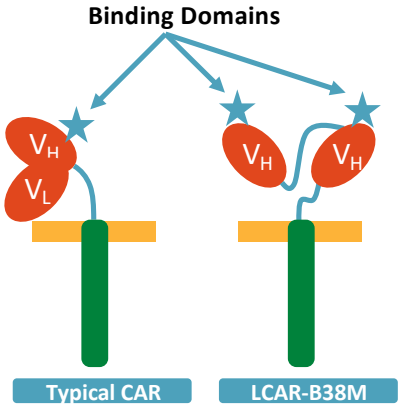
- Median peak CAR+ T-cell expansion: 11 days
- **At higher target doses, median expansion increased**
- Higher peak exposure in responders vs nonresponders
- **Durable persistence noted up to 1 yr**

CAR, chimeric antigen receptor; ida-cel, idecabtagene vicleucel; MRD, measurable residual disease; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

Munshi N, et al. N Engl Med. 2021;384:705-16.

Ciltacabtagene Autoleucel (cilta-cel; JNJ-4528; LCAR-B38M)

- Lentiviral vector-based + 4-1BB costimulatory domain; BCMA-catching domain **targets 2 different epitopes** simultaneously



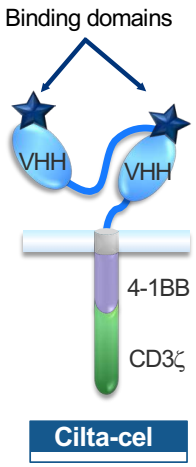
- **LEGEND-2:** single-arm, open-label phase I trial in which patients with RRMM (resistant to ≥ 3 prior tx lines) treated with increasing doses of LCAR-B38M (N = 57)[1,2]
- **CARTITUDE-1:** single-arm, open-label phase Ib/II trial in which patients with R/R MM (resistant to ≥ 3 prior tx lines) treated with increasing doses of JNJ-4528 (N = 97)[3,4]

License application accepted by FDA and granted priority review in May 2021

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; RRMM, relapsed/refractory multiple myeloma; tx, treatment; VH, variable heavy chain; VL, variable light chain.

1. Zhao WH, et al. Blood. 2018;132(Suppl 1):955. 2. Wang BY, et al. Blood. 2019;134(Suppl 1):579. 3. Berdeja JG, et al. J Clin Oncol. 2020;38(15_suppl):Abstract 8505. 4. Madduri D, et al. ASH 2020. Presentation 177.

Phase 1b/2 CARTITUDE-1 study



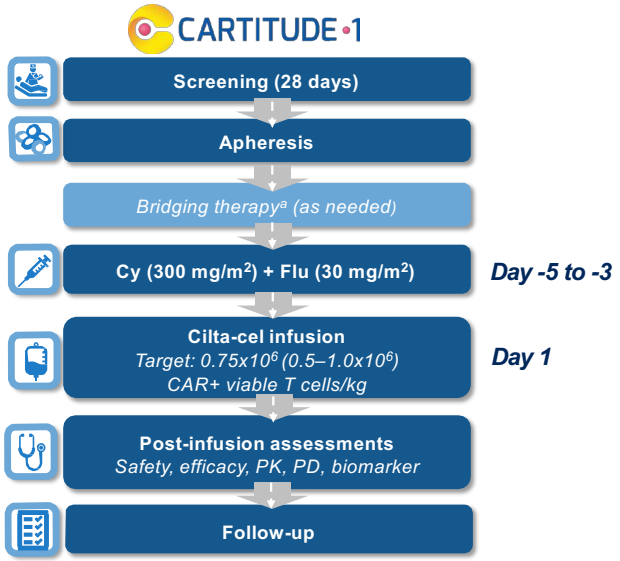
Primary objectives

- Phase 1b: Characterize the safety of cilta-cel and confirm the recommended phase 2 dose
- Phase 2: Evaluate the efficacy of cilta-cel by ORR

Key eligibility criteria

- Progressive MM per IMWG criteria
- ECOG PS ≤1
- Measurable disease
- **At least 3 prior lines of therapy, including PI, IMiD, and anti-CD38 or double-refractory**

- **Median administered dose: 0.71x10^6 (0.51–0.95x10^6) CAR+ viable T cells/kg**



CAR, chimeric antigen receptor; clita-cel, ciltacabtagene autoleucel; CD, cluster of differentiation; Cy, cyclophosphamide; ECOG PS, Eastern Cooperative Oncology Group performance score; Flu, fludarabine; IMiD, immunomodulatory imide drug; IMWG, International Myeloma Working Group; MM, multiple myeloma; ORR, overall survival rate; PD, pharmacodynamics; PI, proteasome inhibitor; PK, pharmacokinetics.

1. Madduri D, et al. ASH 2020. Presentation 177.

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]

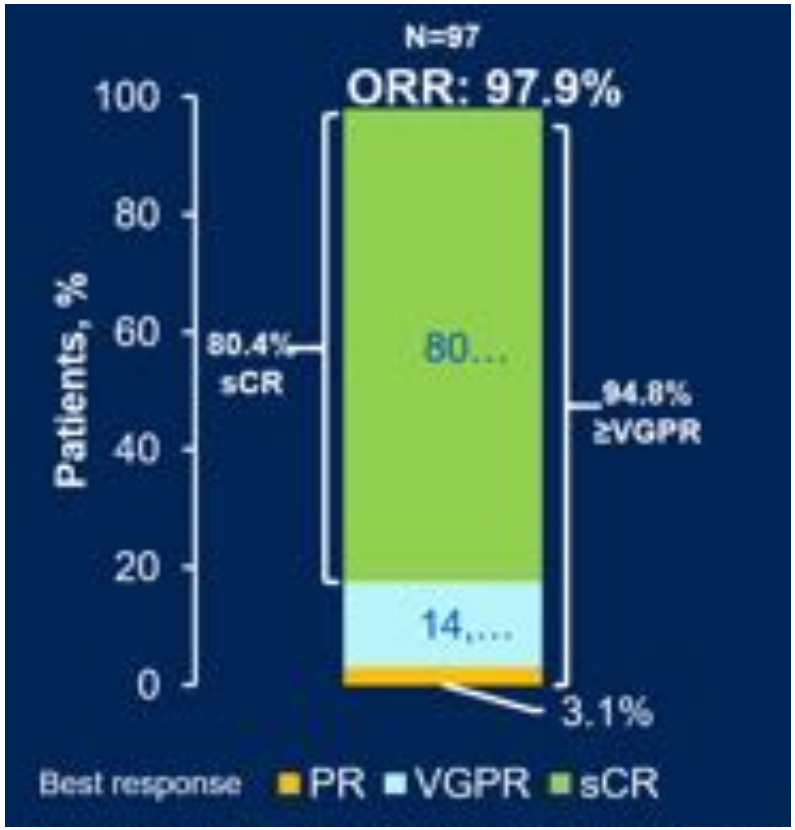
Characteristic	
Prior lines of therapy, median (range)	6.0 (3–18)
Prior lines of therapy, n (%)	
3	17 (17.5)
4	16 (16.5)
≥5	64 (66.0)
Previous stem-cell transplantation, n (%)	
Autologous	87 (89.7)
Allogeneic	8 (8.2)
Triple-class exposed,[c] n (%)	97 (100)
Penta-drug exposed,[d] n (%)	81 (83.5)
Triple-class 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.

Berdeja JG et al, Lancet 2021; 398: 314-24; Usmani SA et al., oral presentation ASCO 2021

CARTITUDE-1: Overall Response Rate

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



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).

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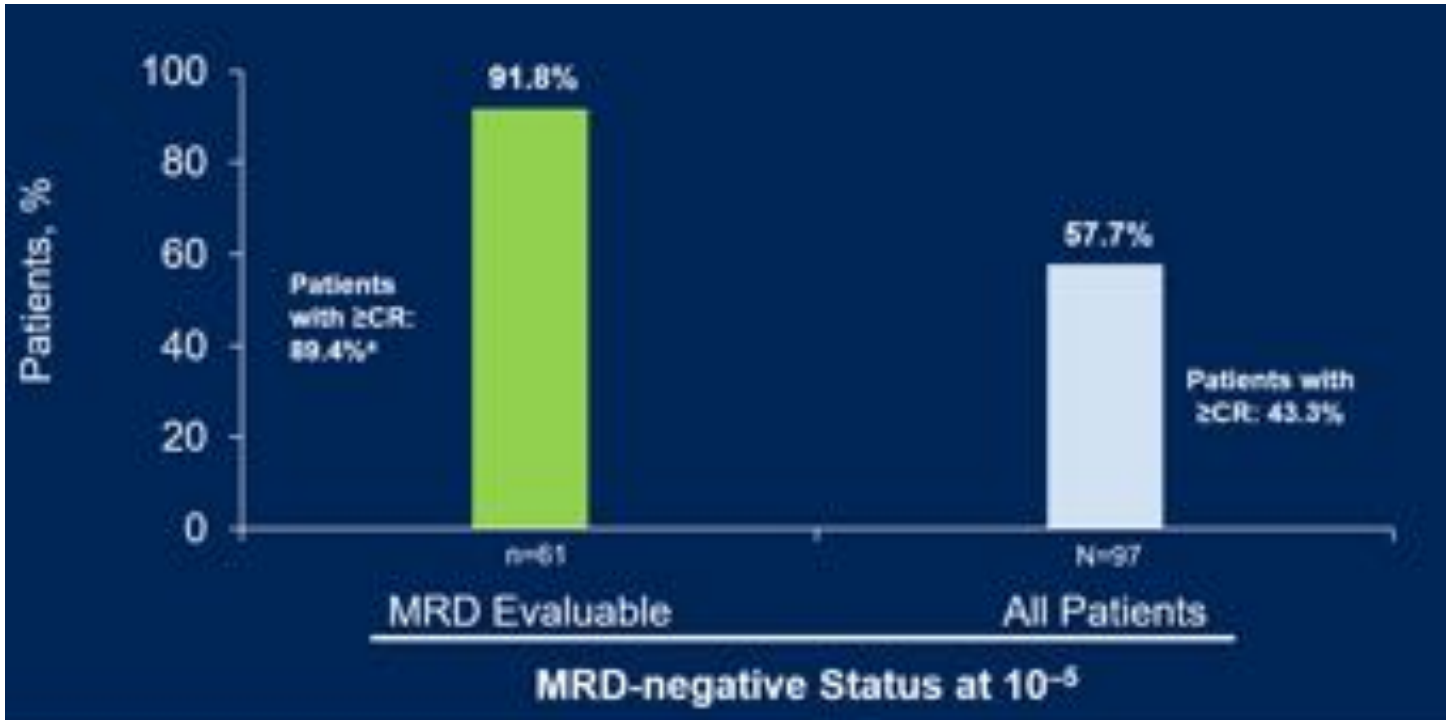
CARTITUDE-1: Minimal Residual Disease 10^{-5}



Almost all (91.8%) evaluable patients were MRD negative

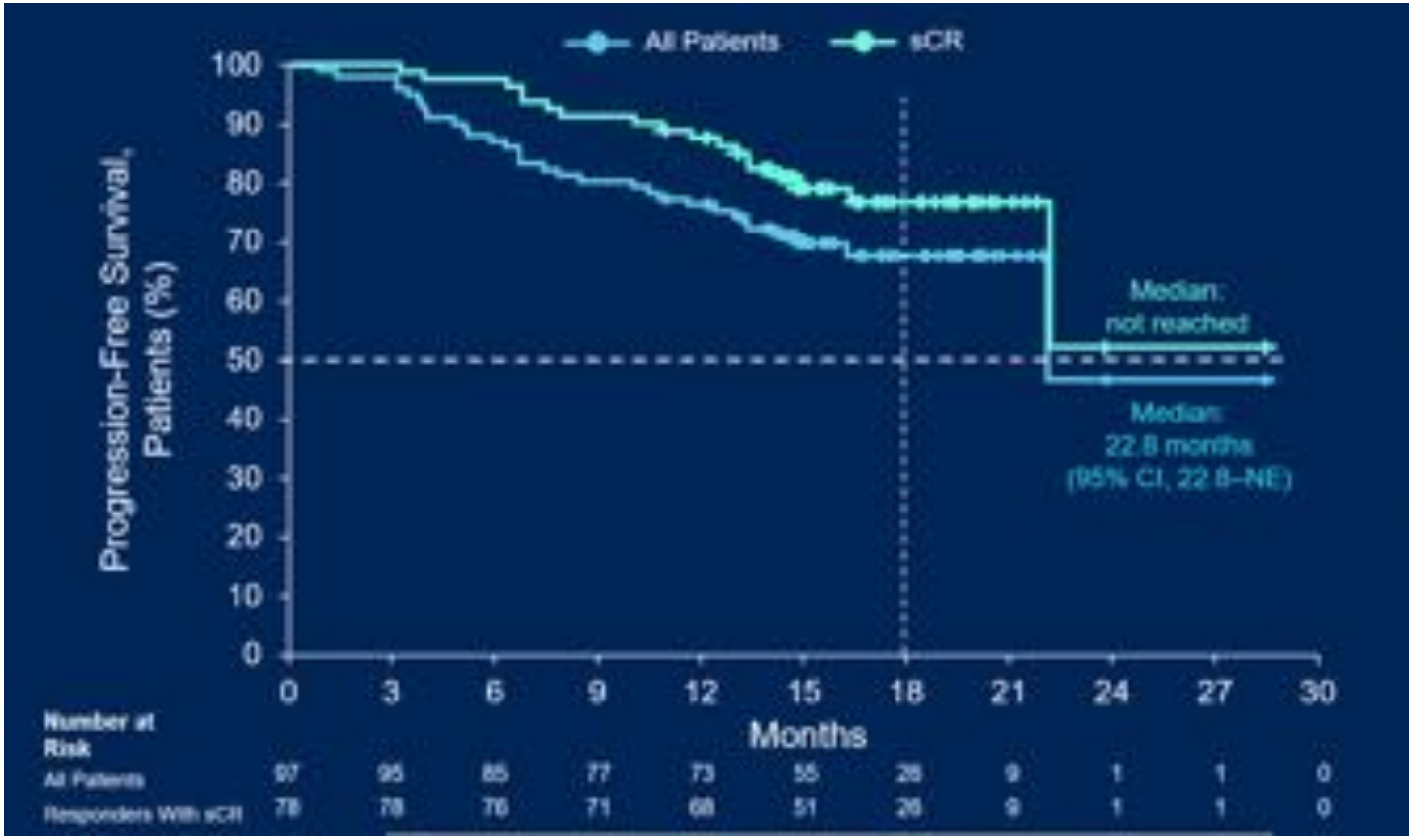
Median time to MRD 10^{-5} negativity: 1 month (range, 0.8–7.7)

MRD, minimal residual disease; sCR, stringent complete response.
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 at Day 28, and at 6, 12, 18, and 24 months regardless of the status of disease measured in blood or urine. [a]Denominator n=47; evaluable MRD sample within 3 months of achieving CR/sCR until death/progression/subsequent therapy.

Usmani SA et al., oral presentation ASCO 2021

CARTITUDE-1: Progression-Free Survival

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



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)

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

Usmani SA et al., oral presentation ASCO 2021

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 (time to onset: 8 days, median)	**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 **(time to onset: 27 days, median)**	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).

Usmani SA et al., oral presentation ASCO 2021

CARTITUDE-1: Safety

No new incidence of neurotoxicity
No additional movement and neurocognitive TEAEs[a]

Movement and Neurocognitive TEAEs

Occurred in 5 of 97 patients

Risk factors (2 or more)

- High tumor burden[b]
- Grade ≥2 CRS
- ICANS
- High CAR T-cell expansion and persistence

Patient Management Strategies[c]

- Enhanced bridging therapy to reduce tumor burden
- Early and aggressive treatment of CRS and ICANS
- Handwriting assessments and extended monitoring

CARTITUDE Program Level
Over 100 Additional Patients[d] Have Been Dosed

- Patient management strategies to prevent or reduce these AEs have been successfully implemented in new and ongoing cilta-cel studies
- This is reliant on effective implementation of these patient management strategies

Saad Z Usmani et al., oral presentation ASCO 2021

Safety Across Anti-BCMA CAR T Trials in R/R MM

	KarMMa: Idecabtagene Vicleucel (ide-cel; bb2121) N = 128	CARTITUDE-1: Ciltacabtagene Autoleucel (clita-cel; JNJ-4528) N = 97
Decreased ANC grade ≥3, %	89	95
Decreased platelets grade ≥ 3, %	52	60
CRS: all/grade ≥3, %	84/6	95/4
Median time to CRS, days (range)	1 (1–12)	7 (1–12)
Median duration CRS, days (range)	5 (1–63)	4 (1–97)
ICANS: all/grade ≥3, %	18/3	16.5/2
HLH/MAS, %	–	7
Infections: all/grade ≥3, %	69/–	58/20
Toci/steroid/anakinra use, %	52/15/0	69/22/19
AEs related deaths	4	6

AE, adverse event; ANC, absolute neutrophil count; BCMA, B-cell maturation antigen; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; MAS, macrophage activation syndrome.

1. *Munshi N, et al. ASCO 2020. Abstract 8503.* ***2.*** *Madduri D, et al. ASH 2020. Presentation 177.*

Conclusions

- There is **an unmet medical need of novel treatments** to improve long-term outcomes **for patients with triple-class refractory MM**
- Results from KarMMa and CARTITUDE-1 studies have established a positive risk-benefit profile for a single infusion of **BCMA-targeting CAR-T cells**, yielding unprecedented high CR and MRD-neg rates in end-stage and heavily pretreated MM patients. However,
- Although both PFS and OS curves look promising, **no plateau** has yet been reported and we should **aim at curing a fraction of patients**.
- How can we do that?
- Better understanding of the mechanisms underlying (**suboptimal**) **persistence of CAR-T cells,** and **treatment resistance** (antigen escape, loss or modulation of the antigen)
- **Improvements in the quality of T cells** (collected in earlier lines of treatment, “off-the-shelf” cellular therapies, including allo CAR-T), **CAR design** (dual targets), and **manufacturing process** (purified CD4+ and CD8+ cells enriched for central memory phenotype)
- **Earlier use**, eventually **combined with novel agents** targeting the BM microenvironment (IMiDs, CELMoDs)