ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

CAR-T per il trattamento del MMRR: ide-cel & cilta-cel”

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“Le nuove frontiere dell’immunoterapia per la cura del mieloma multiplo: dalla teoria alla pratica”

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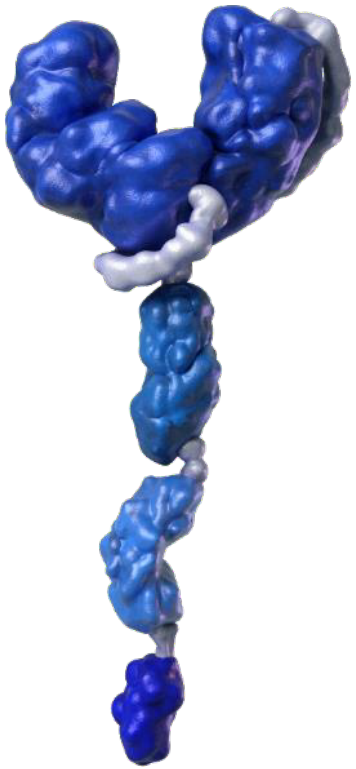
Disclosures: Michele Cavo

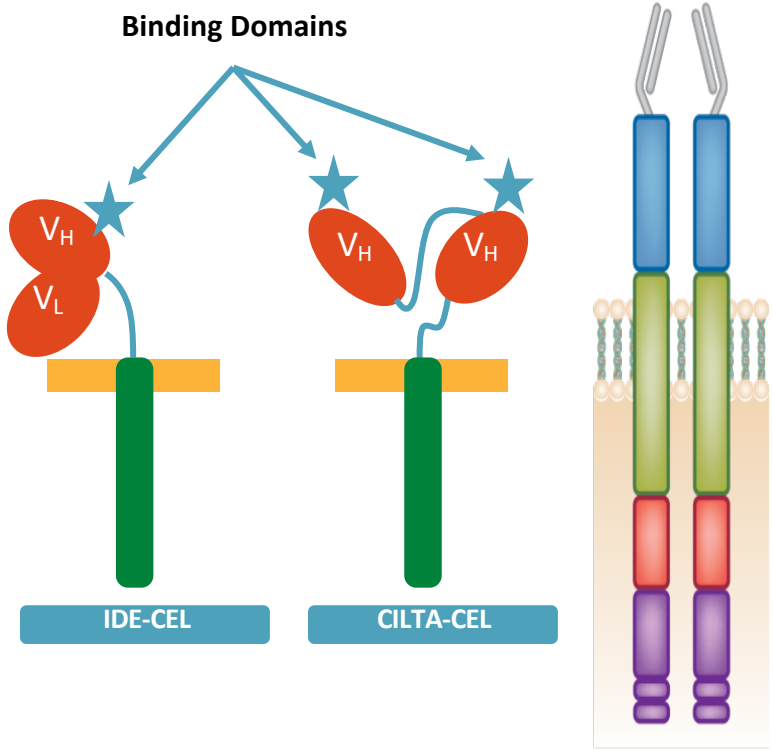
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
GlaxoSmithKline			×			×	Honoraria
Janssen			×		×	×	Honoraria
Sanofi			×		×	×	Honoraria
Roche			×			×	Honoraria
Amgen			×			×	Honoraria
Takeda			×			×	Honoraria
AbbVie			×			×	Honoraria
Bristol Myers Squibb			×		×	×	Honoraria
Celgene			×		×	×	Honoraria

CAR-T: structure and functions

Ide-cel



Cilta-cel



-**Extracellular domain** that binds specifically to a target molecule expressed on the tumor cell surface:

-**Single-chain variable fragment** (scFv) **consisting of a heavy and light chain variable region derived fom an anti-BCMA mAb**

-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 generation CAR-T)**: CD28 or 4-1BB (more robust cytokine production and enhanced cytolytic activity of CAR-Ts)

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

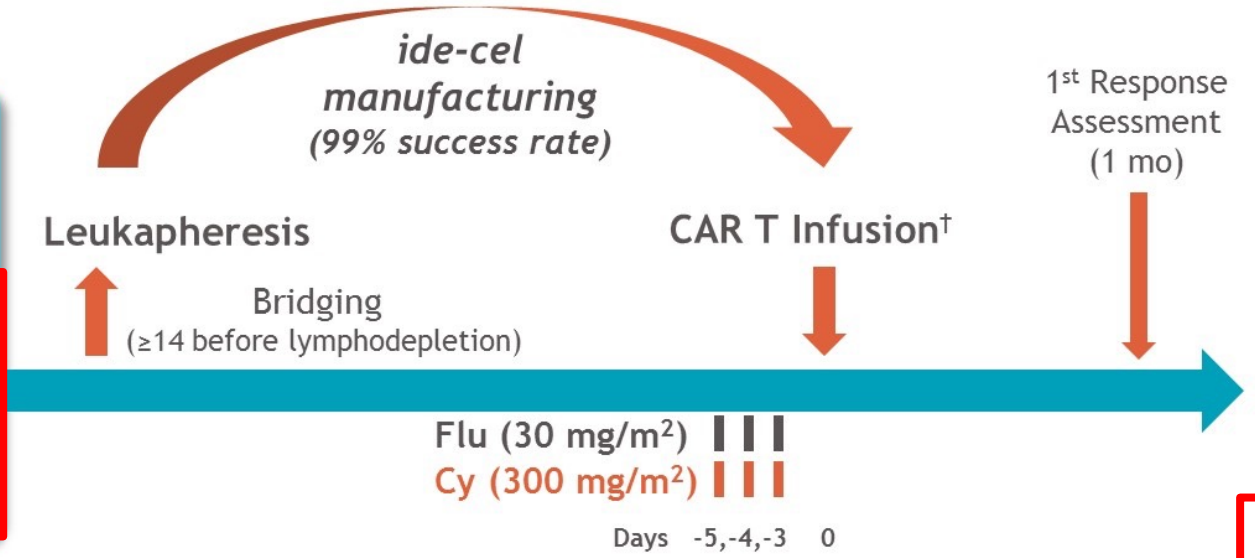
- **Antigen recognition** via extracellular domain and **HLA-independent activation of T cells** with powerful cytotoxic and memory functions via intracellular domain
- **Remodelling of tumor suppressive microenvironment**

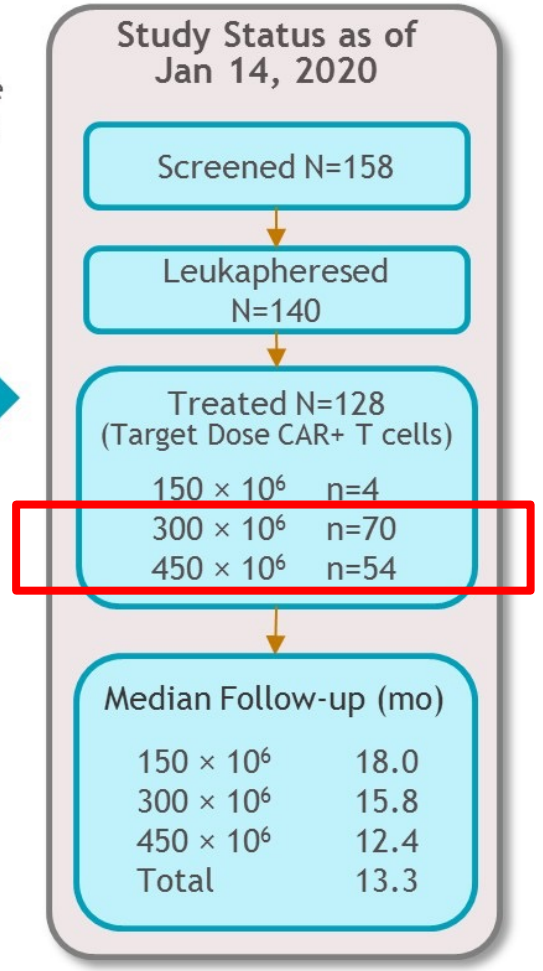
Adapted from Kershaw MH et al. Nat rev Cancer 2013

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

Phase 2 KarMMa study of bb2121 (ide-cel)

- 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

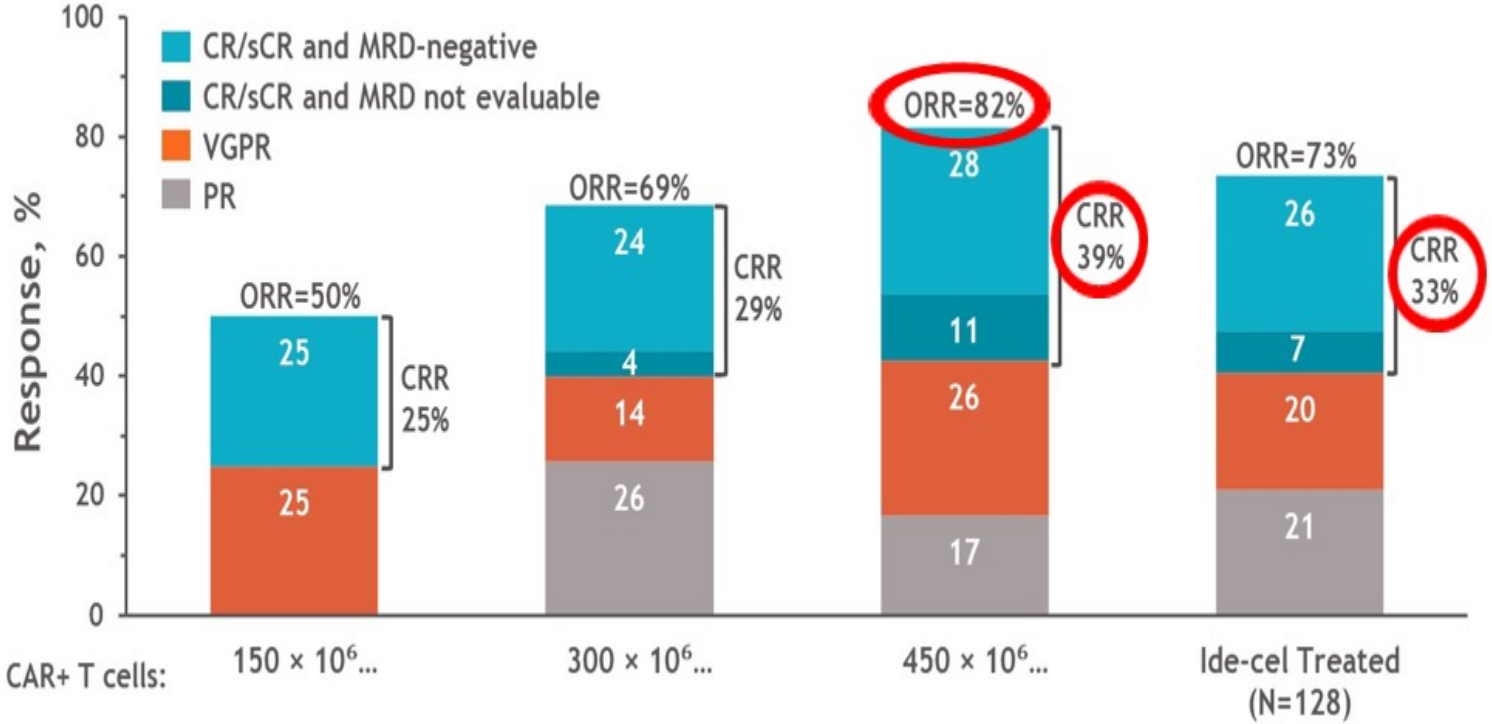
- **Primary**: ORR (null hypothesis ≤50%)
- **Secondary**: CRR (key secondary; null hypothesis ≤10%), Safety, DOR, PFS, OS, PK, MRD‡, QOL, HEOR
- **Exploratory**: Immunogenicity, BCMA expression/loss, cytokines, T cell immunophenotype, GEP in BM

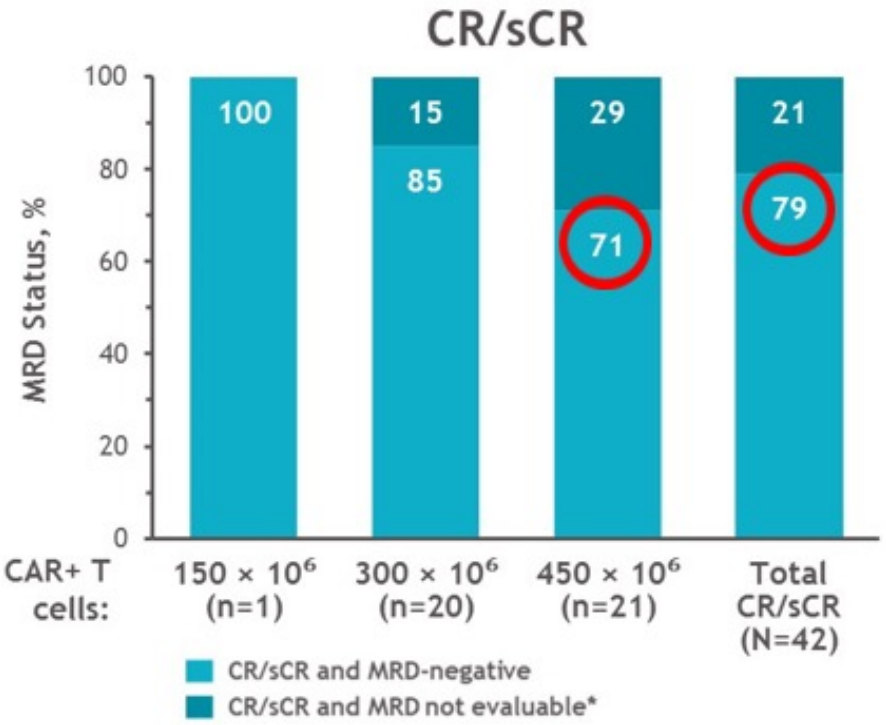
CRR, complete response rate; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; GEP in BM, gene expression profile in bone marrow; HEOR, health economics and outcomes research; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MRD, minimal residual disease; ORR,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

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

KarMMa: response and MRD negativity by target dose





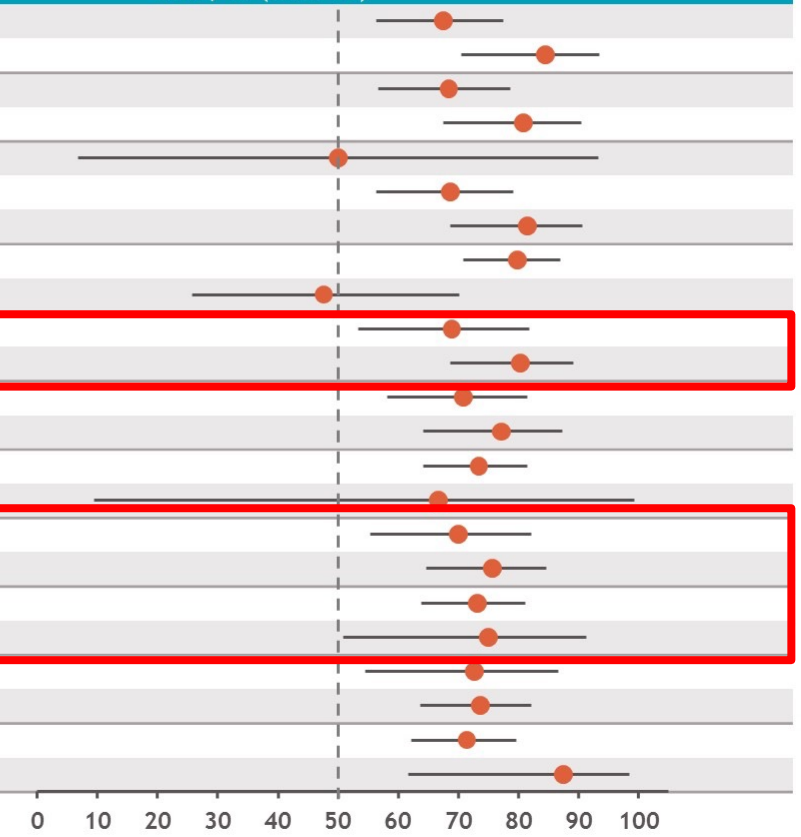
Munshi N, et al. N Engl Med. 2021;384:705-16.

Response rates by prespecified subgroups

Clinically Meaningful Efficacy (ORR) Observed Across Subgroups

KarMMa™

Subgroup		N	ORR, % (95% CI)
Age group, years	<65	83	
	≥65	45	
Sex	Male	76	
	Female	52	
Ide-cel target dose level, CAR+ T cells	150 × 10^6	4	
	300 × 10^6	70	
	450 × 10^6	54	
R-ISS stage at enrollment	I or II	104	
	III	21	
High-risk cytogenetics del(17p), t(4;14), t(14;16)	Yes	45	
	No	66	
Tumor burden at baseline, % BMPCs	≥50%	65	
	<50%	57	
Tumor BCMA expression	≥50%	109	
	<50%	3	
Extramedullary disease	Yes	50	
	No	78	
Triple-refractory*	Yes	108	
	No	20	
Penta-refractory†	Yes	33	
	No	95	
Bridging therapy	Yes	112	
	No	16	



Data cutoff: 14 Jan 2020. *Defined as refractory to an IMiD agent, PI, and CD-38 antibody. †Defined as refractory to 2 IMiD agents, 2 PIs, and 1 anti-CD38 antibody. BCMA, B-cell maturation antigen; BMPC, bone marrow plasma cell; R-ISS, revised International Staging System.

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

Undetectable MRD by NGS

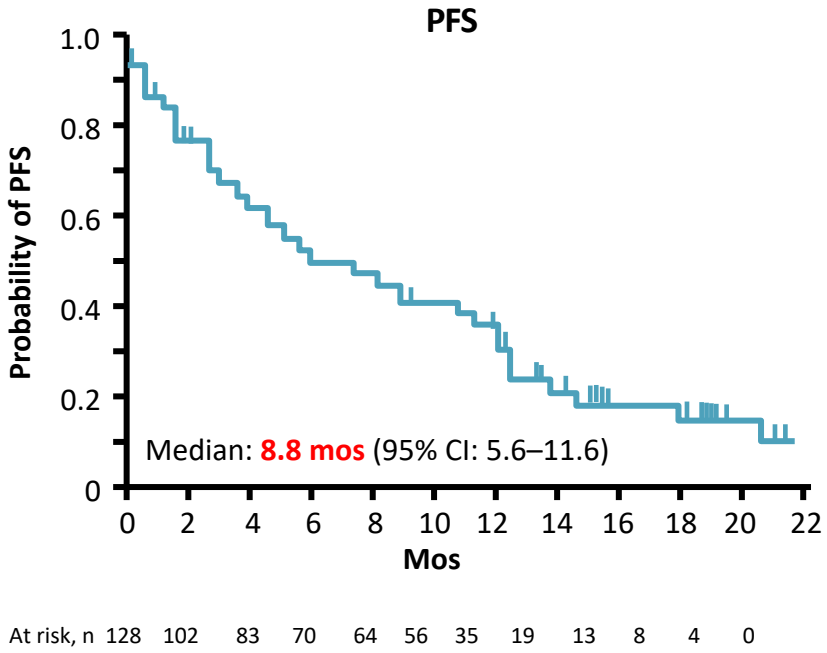
MRD[c] negativity in patients with at least a CR

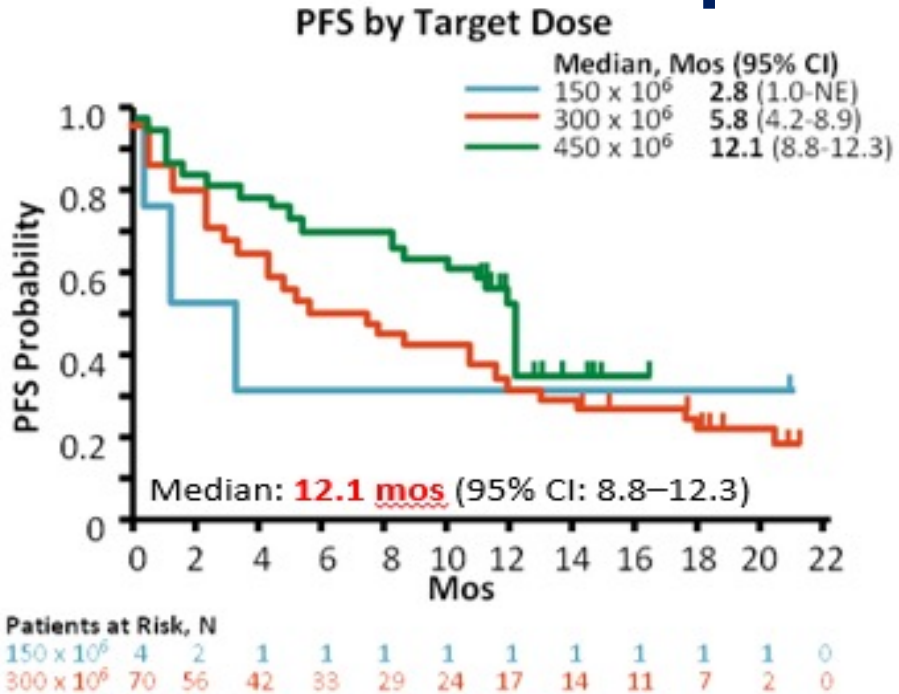
	Total (n = 128)	Patients with ≥ CR (n = 42)
MRD status at 10^{-5} nucleated cells and ≥ CR, n (%)		
MRD negative	33 (26)	33 (79)
MRD positive	0	0
NE[d]	9 (7)	9 (21)
Indeterminate	0	0
MRD status at 10^{-6} nucleated cells and ≥ CR, n (%)		
MRD negative	20 (16)	20 (48)
MRD positive	7 (5)	7 (17)
NE[d]	9 (7)	9 (21)
Indeterminate	6 (5)	6 (14)

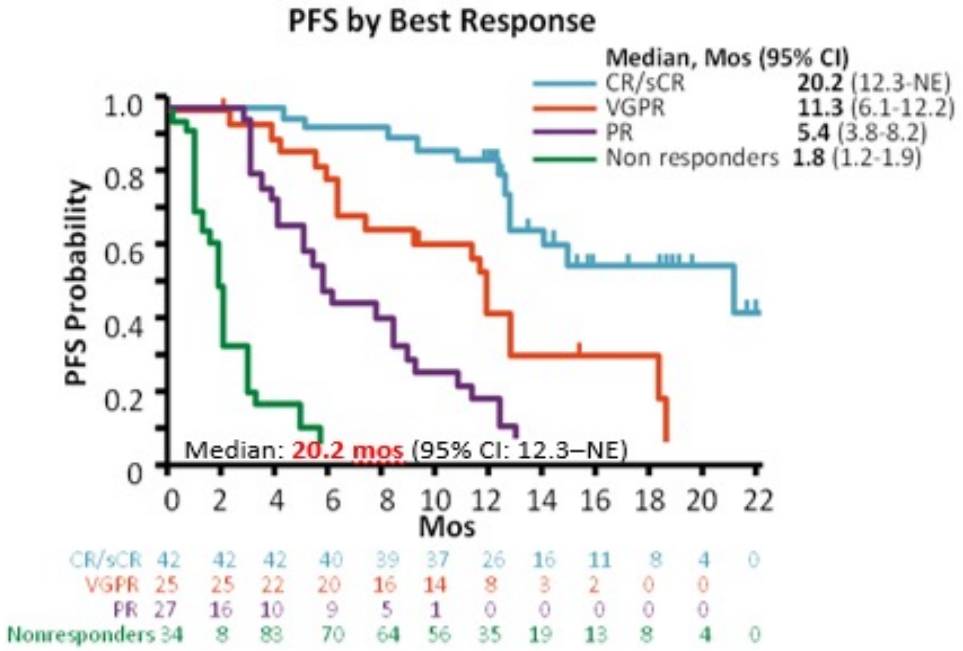
[c]MRD examined by next-generation sequencing assay (clonoSEQ; Adaptive Biotechnologies). Only MRD values within 3 months of achieving CR/sCR until progression or death (exclusive) were considered. Values may not add up due to rounding. [d]Of the 9 patients who achieved ≥ CR who were not evaluable for MRD, 7 did not have a malignant clone identified at baseline, 1 was missing the baseline sample, and 1 did not have an MRD assessment performed within 3 months of achieving CR/sCR.

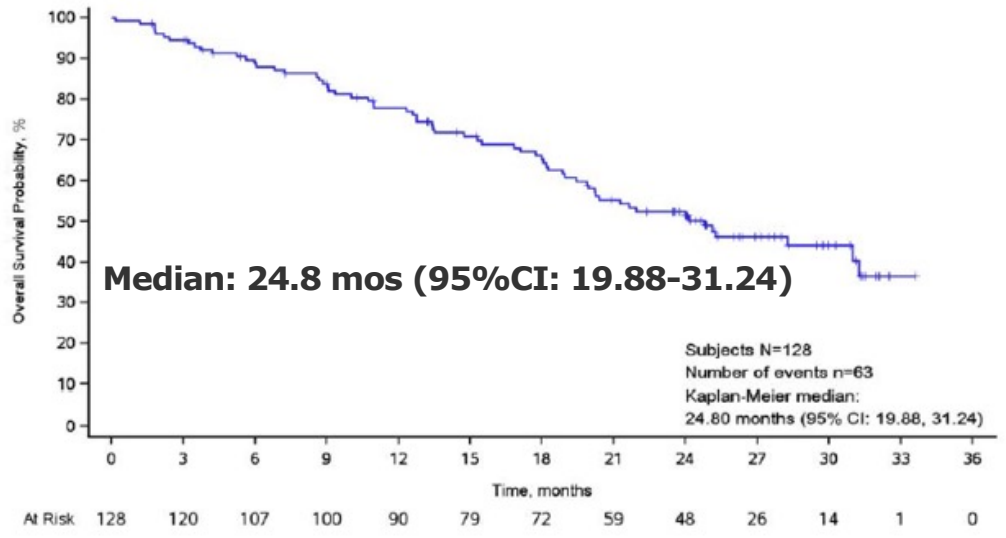
Munshi N et al., N Engl J Med. 2021;384:705-16.

KarMMa: outcomes by target dose and best response



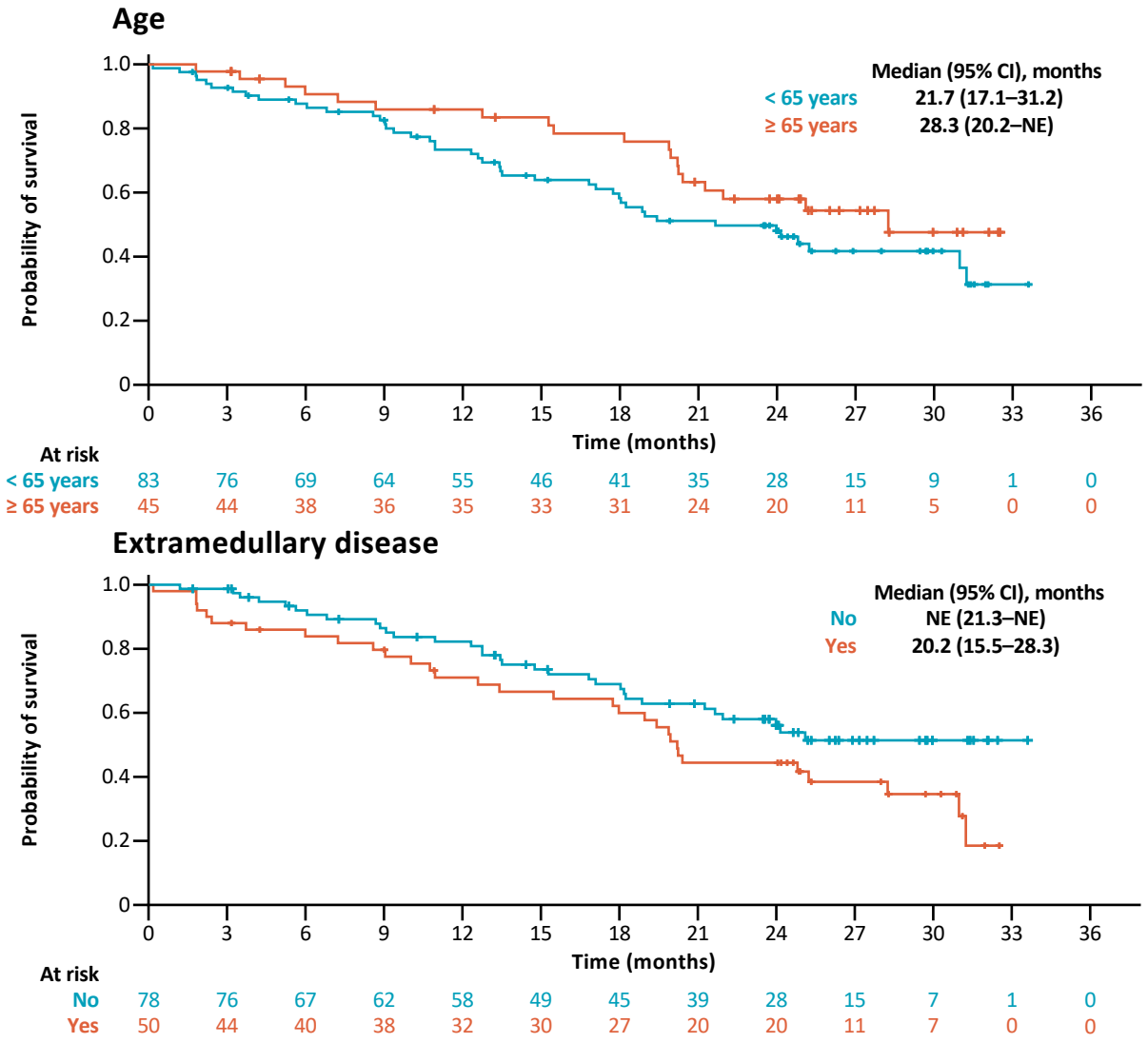


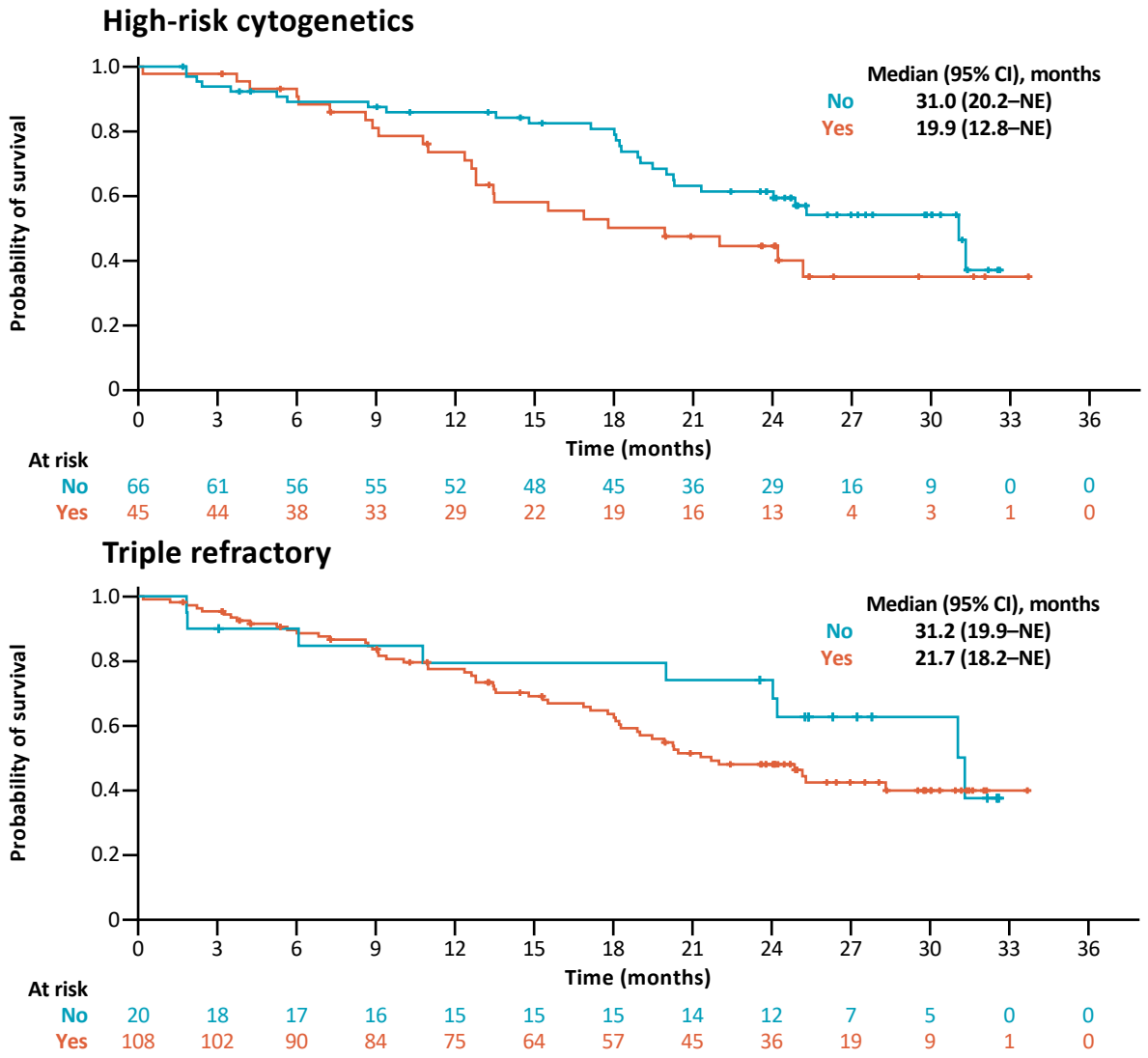




Munshi N, et al. N Engl Med. 2021;384:705-16.

OS in high-risk subgroups

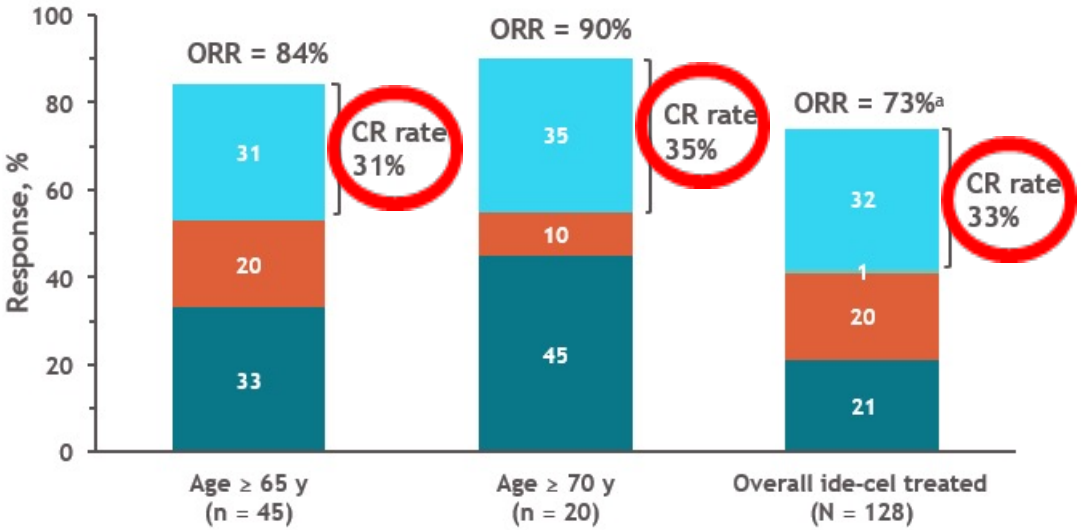


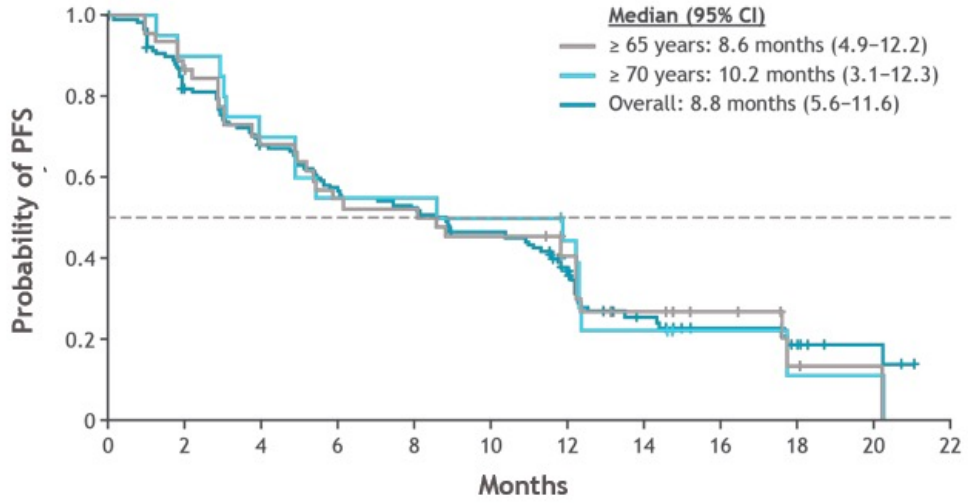


- Median OS was > 20 months in several key high-risk subgroups, including age (≥ 65 years), extramedullary disease, and triple-refractory status

Cavo M et al., 48° Congresso Nazionale SIE 2021 (Oral abstract)

Outcomes in patients aged ≥65 (n=45) and ≥70 yrs (n=20)

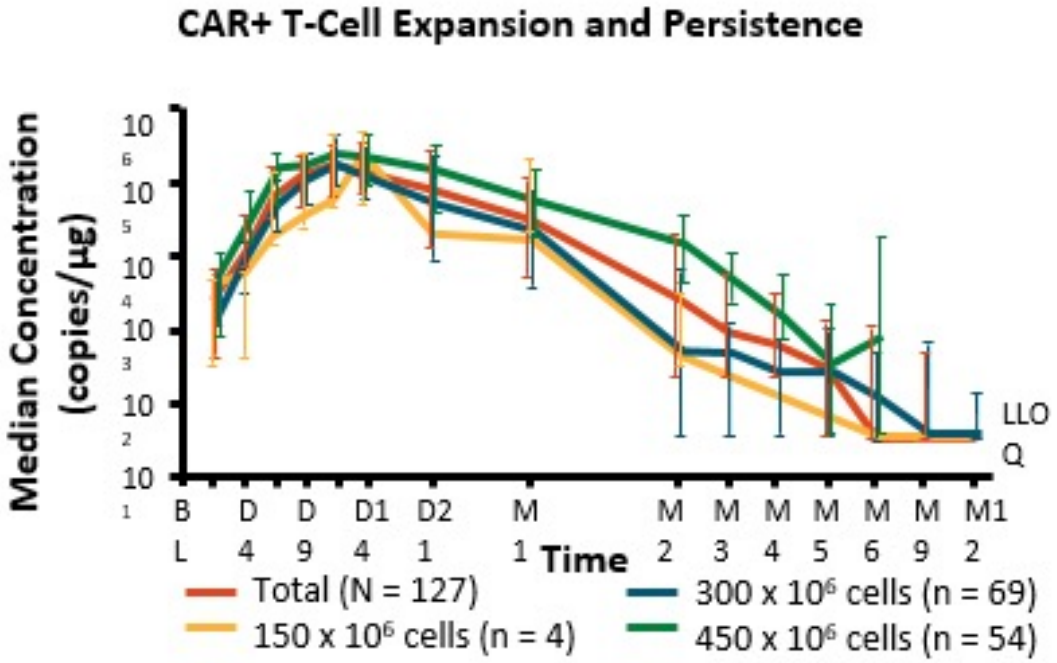




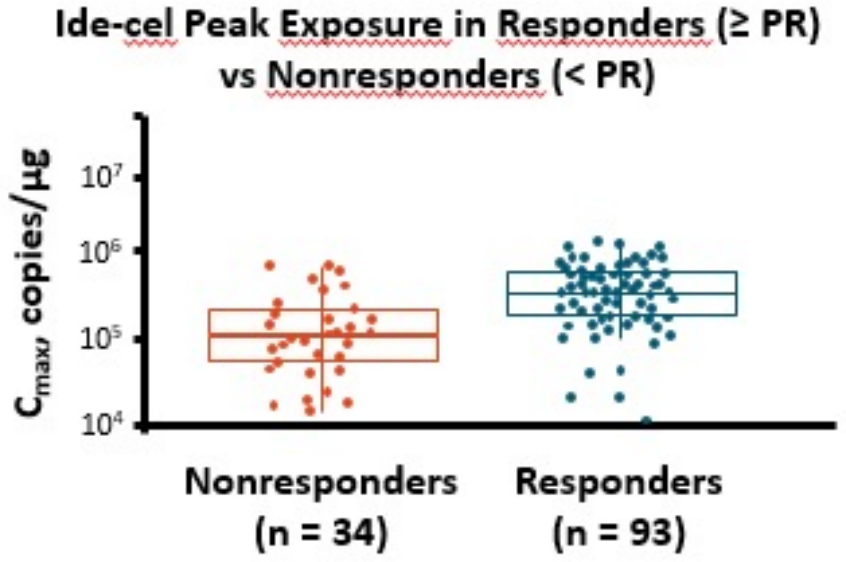
	Age ≥ 65 y	Age ≥ 70 y	Overall ide-cel treated
	(n = 45)	(n = 20)	(N = 128)
≥ 1 CRS event, n (%)	40 (89)	20 (100)	107 (84)
Max. grade (Lee criteria),[a] n (%)	23 (51)	10 (50)	61 (48)
1			
2	15 (33)	8 (40)	39 (31)
≥ 3	2 (4)	2 (10)	7 (5)
Time to onset, median (range), d	1 (1–12)	1 (1–12)	1 (1–12)
≥ 1 NT event, n (%)	11 (24)	6 (30)	23 (18)
Max. grade (CTCAE),[b] n (%)	6 (13)	5 (25)	12 (9)
1			
2	1 (2)	0	7 (5)
3	4 (9)	1 (5)	4 (3)
Time to onset, median (range), d	2 (1–6)	2 (1–6)	2 (1–10)

Berdeja J et al. ASH Meeting 2020 (Abstract 1367)

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)

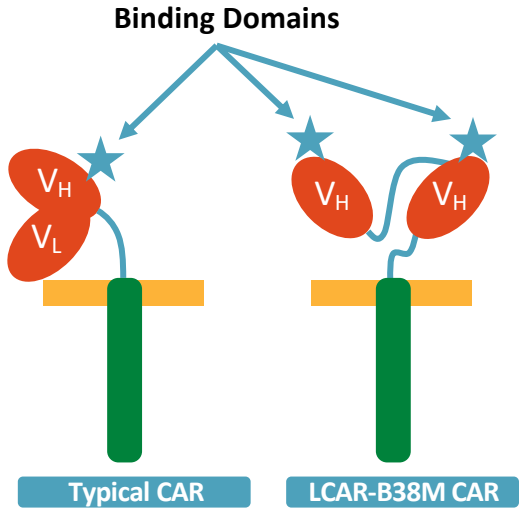


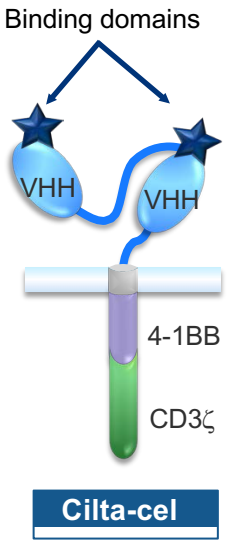
- Median peak CAR+ T-cell expansion: 11 days
- **At higher target doses, median expansion increased**
- Higher peak exposure in responders vs nonresponders
- **Durable persistence noted up to 1 yr**

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

Phase 1b/2 CARTITUDE-1 study of cilta-cel

Two BCMA-catching single-domain antibodies designed to confer avidity by targeting two different epitopes simultaneously



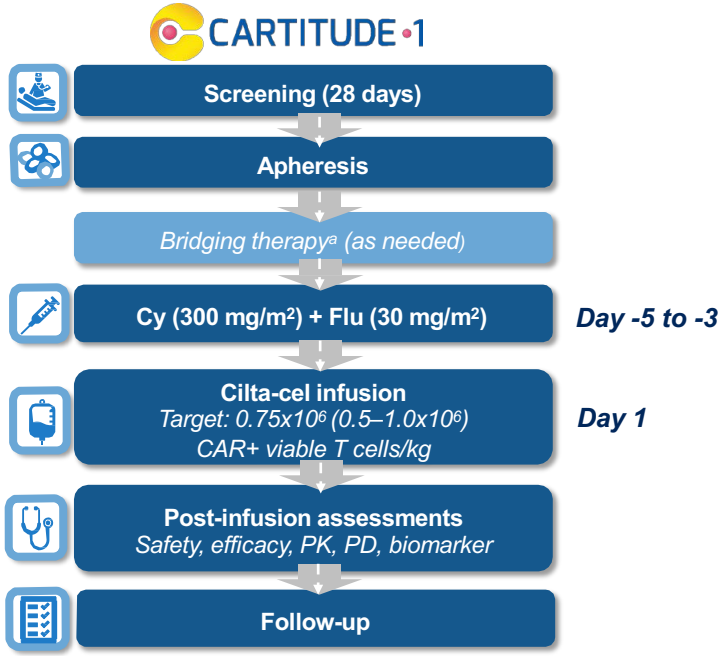


Primary objectives

- 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

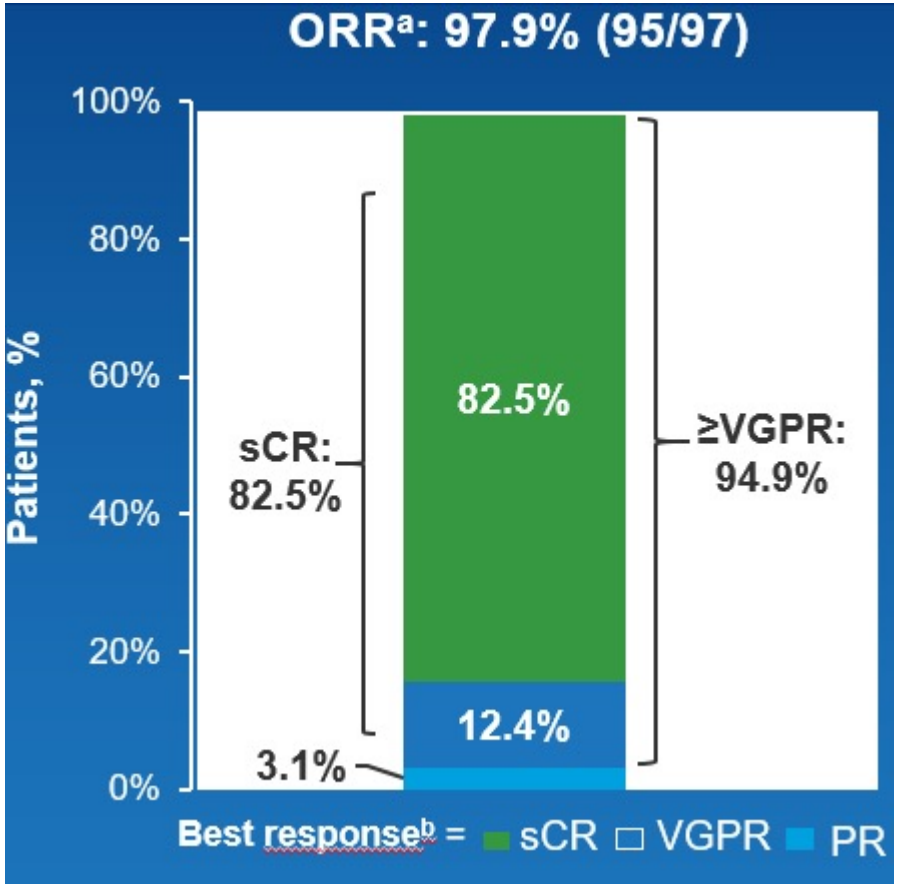
- Progressive MM per IMWG criteria
- ECOG PS ≤1
- Measurable disease
- **At least 3 prior lines of therapy, including PI, IMiD, and anti-CD38 or double-refractory**



Median administered dose:
0.71x10⁶ (range 0.51–0.95x10⁶) CAR+ T cells/kg

Berdeja JG, et al. Lancet July 24;398: 314-24.

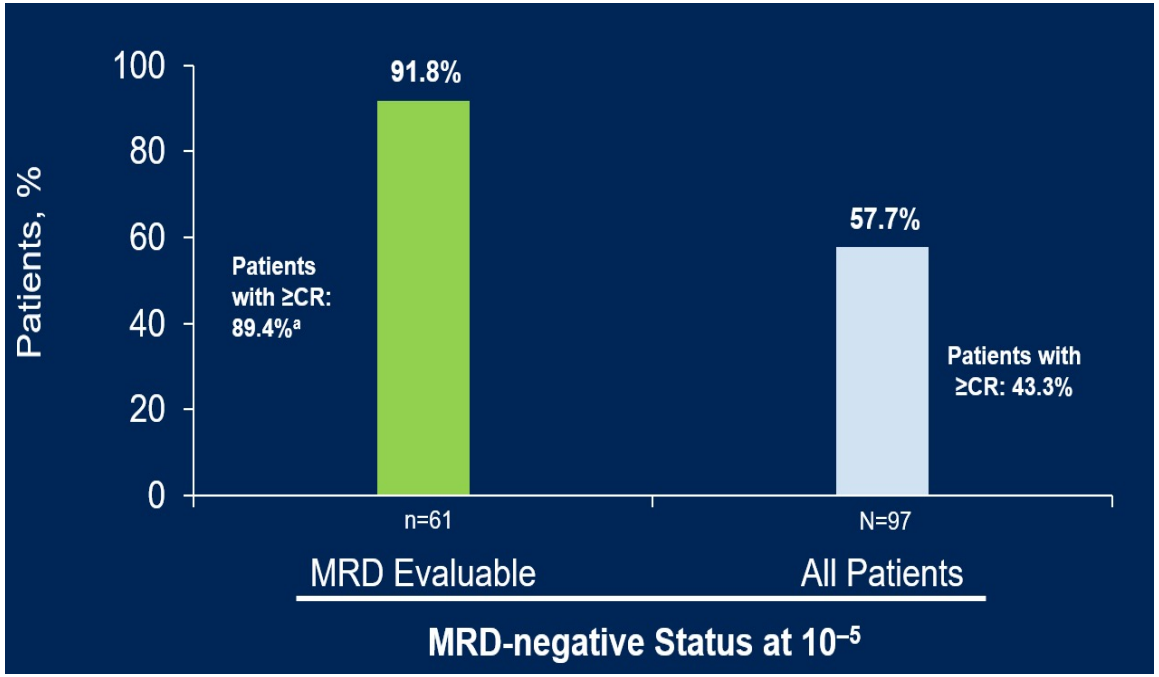
CARTITUDE-1: response and MRD negativity



- Median time to first response was 1 month (range, 0.9–10.7)
- 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)

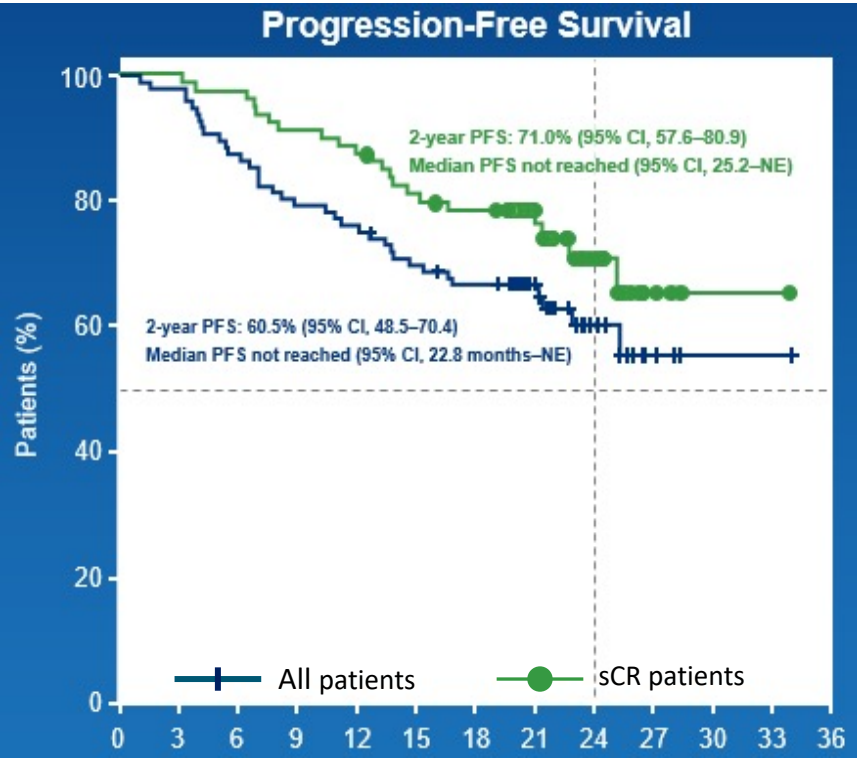
Median follow-up: ~2 years

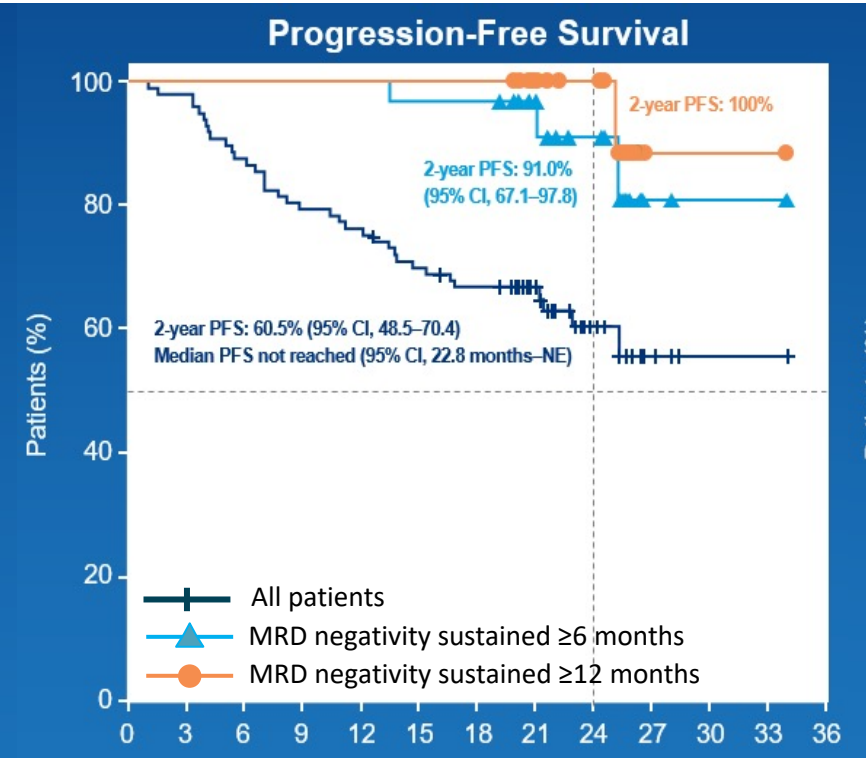
Best response at any time	Median–1 year follow-up	Median–2 years follow-up
sCR, %	67	83

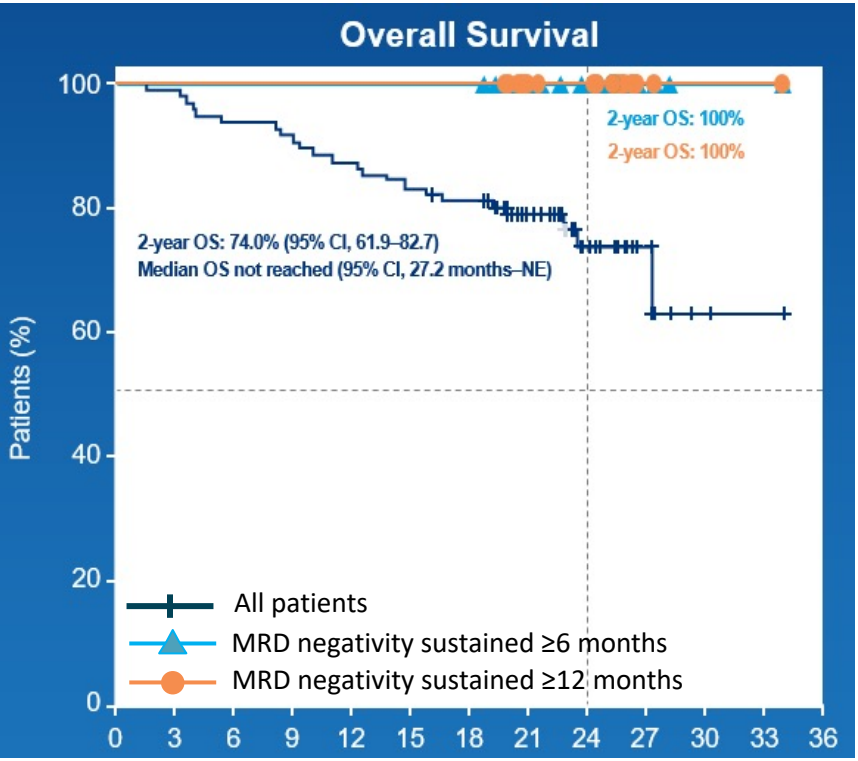


Martin T, et al. Blood 2021;138 (Suppl 1):549 (oral presentation);

CARTITUDE-1: PFS and OS for all pts and by depth of response







Martin T, et al. Blood 2021;138 (Suppl 1):549 (oral presentation);

CARTITUDE-1:efficacy outcomes in subgroups of patients

		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	68 (70)	97.1 (89.8–99.6)	NE (21.8–NE)	95.2 (83.8–99.4)	64.1 (49.5–75.5)	73.6 (58.2–84.0)
	High risk	23 (24)	100.0 (85.2–100)	20.2 (9.4–NE)	82.4 (56.6–96.2)	48.4 (25.1–68.4)	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%	58 (60)	98.3 (90.8–100)	NE (21.8–NE)	96.6 (82.2–99.9)	66.5 (51.1–78.1)	75.9 (59.1–86.5)
	>30 to <60%	17 (18)	100.0 (80.5–100)	NE (15.9–NE)	87.5 (61.7–98.4)	54.6 (23.0–78.0)	94.1 (65.0–99.1)
	≥60%	21 (22)	95.2 (76.2–99.9)	NE (5.5–NE)	87.5 (61.7–98.4)	51.6 (28.7–70.4)	52.4 (22.4–75.6)
Baseline tumor BCMA expression	≥median (80%)	31 (32)	96.8 (83.3–99.9)	NE (21.8–NE)	94.1 (71.3–99.9)	67.3 (44.8–82.3)	80.9 (58.2–92.0)
	<median (80%)	31 (32)	100.0 (88.8–100)	NE (20.5–NE)	95.7 (78.1–99.9)	63.9 (41.2–79.7)	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

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

CARTITUDE-1: sustained MRD

- Patients with sustained MRD negativity were defined as those who had **2 MRD-negative results after cilta-cel infusion** and prior to progression or subsequent therapy that were ≥6 months apart, without any MRD-positive results in between
- Landmark analyses were conducted at 6 and 12 months to address immortal time bias

MRD negativity in CARTITUDE-1

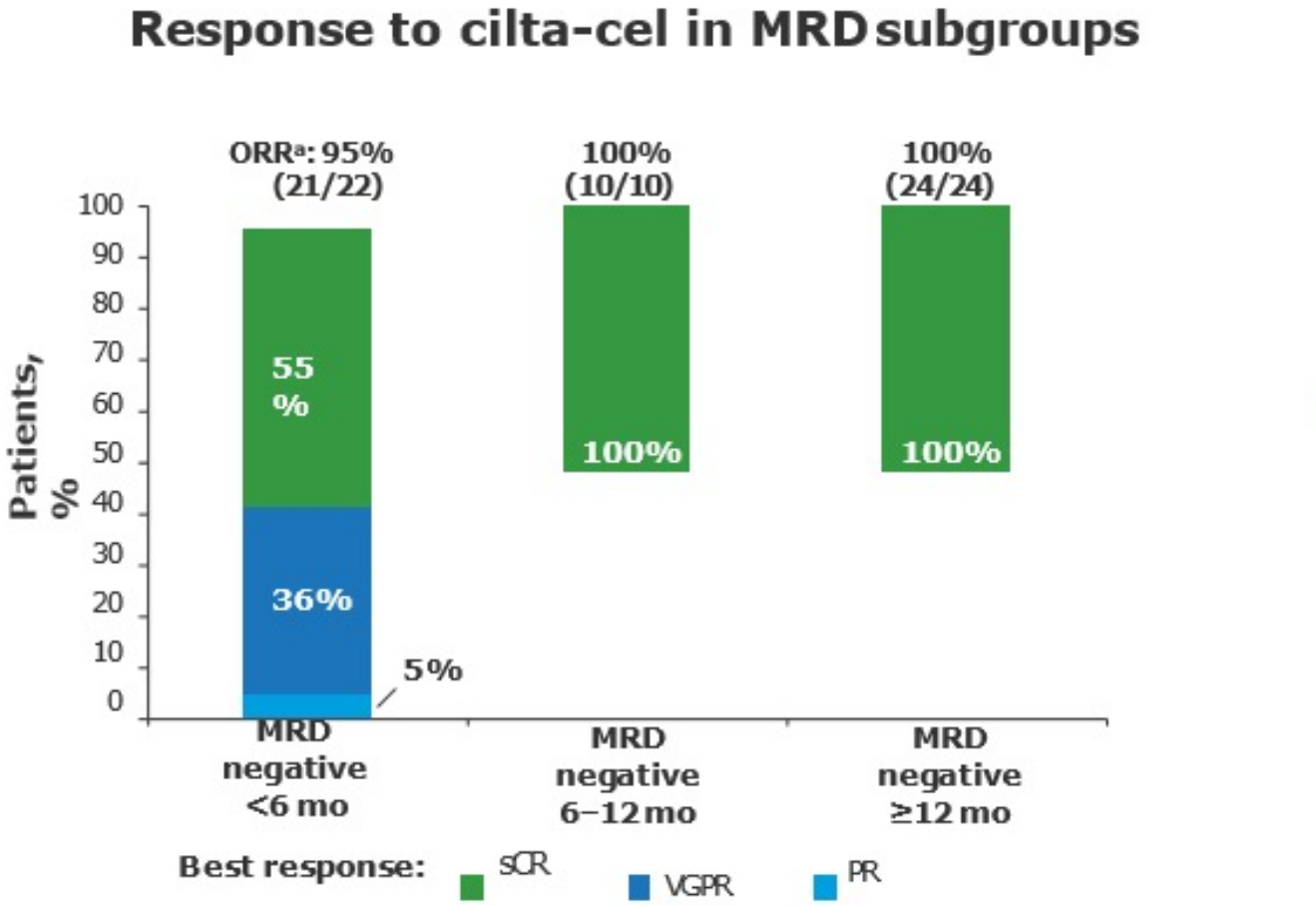
- Of the 61 patients evaluable for MRD, 56 (91.8%) patients achieved MRD negativity
- MRD negativity was sustained:
  - <6 months in 22 patients
  - 6–12 months in 10 patients
  - ≥12 months in 24 patients

Baseline characteristic	MRD negative <6 months (n=22)	Sustained MRD negative (n=34)	
		6–12 months (n=10)	≥12 months (n=24)
Age, median (range), y	59.5 (51–75)	66.0 (54–77)	63.0 (43–78)
Female, n (%)	8 (36.4)	6 (60.0)	13 (54.2)
Race, n (%)			
White	17 (77.3)	7 (70.0)	14 (58.3)
Black	4 (18.2)	2 (20.0)	4 (16.7)
Time since diagnosis, median (range), y	4.8 (1.6–16.3)	5.0 (1.6–8.1)	7.0 (2.5–18.2)
Plasmacytomas, n (%)	6 (27.3)	2 (20)	2 (8.3)
Extramedullary	4 (18.2)	2 (20)	1 (4.2)
Bone-based	2 (9.1)	0	1 (4.2)
High-risk cytogenetic profile, n (%)	6 (27.3)	2 (20)	6 (25.0)
ECOG performance status at screening, n (%)			
0	10 (45.5)	4 (40.0)	12 (50.0)
1	10 (45.5)	6 (60.0)	12 (50.0)
2	2 (9.1)	0	0
International Staging System stage, n (%)			
I	15 (68.2)	5 (50.0)	18 (75.0)
II	6 (27.3)	2 (20.0)	4 (16.7)
III	1 (4.5)	3 (30.0)	2 (8.3)
Tumor BCMA expression ≥50%, n/N (%)	14/14 (100)	4/6 (66.7)	16/18 (88.9)
Previous stem cell transplant, n (%)			
Autologous	19 (86.4)	6 (60.0)	22 (91.7)
Allogeneic	1 (4.5)	0	2 (8.3)
No. of prior LOT for MM, median (range)	5.0 (3–18)	4.5 (3–12)	5.5 (3–11)
Triple-class refractory,[a] n (%)	21 (95.5)	8 (80.0)	21 (87.5)
Penta-drug exposed,[b] n (%)	18 (81.8)	7 (70.0)	19 (79.2)
Penta-drug refractory,[b] n (%)	6 (27.3)	4 (40.0)	7 (29.2)
Refractory to last LOT, n (%)	22 (100)	10 (100)	24 (100)

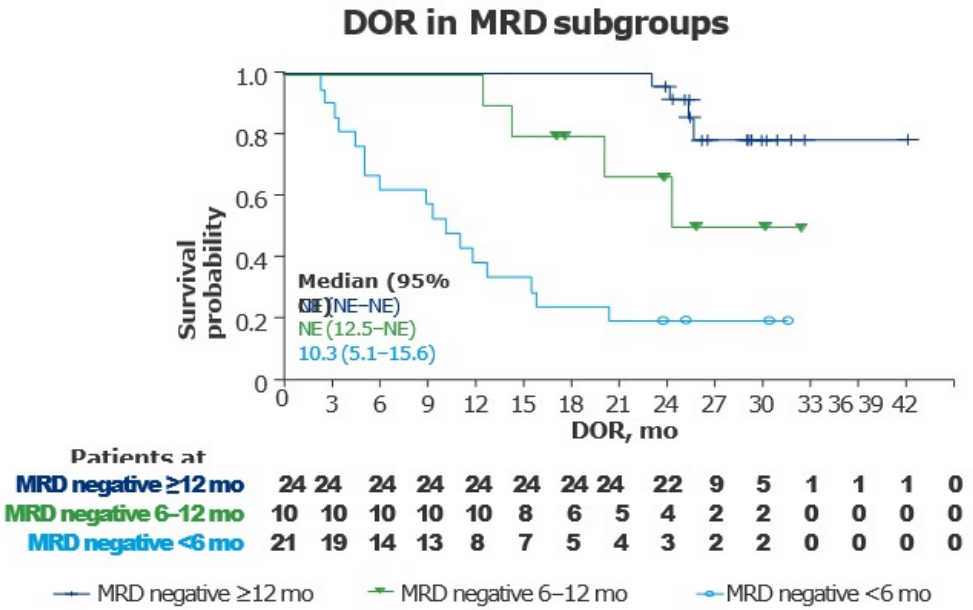
[a]≥1 PI, ≥1 IMiD, and 1 anti-CD38 antibody. [b]≥2 PIs, ≥2 IMiDs, and 1 anti-CD38 antibody.
BCMA, B-cell maturation antigen; ECOG, Eastern Cooperative Oncology Group; LOT, line of therapy; MM, multiple myeloma; MRD, minimal residual disease.

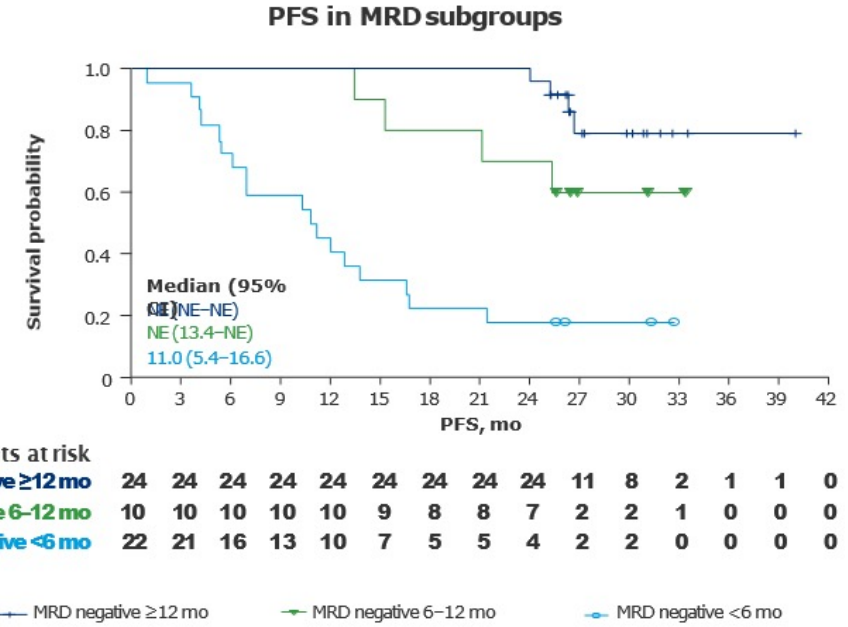
1. Martin T, et al. *J Clin Oncol* Published online June 4, 2022. doi: 10.1200/JCO.22.00842.

CARTITUDE-1 sustained MRD: efficacy



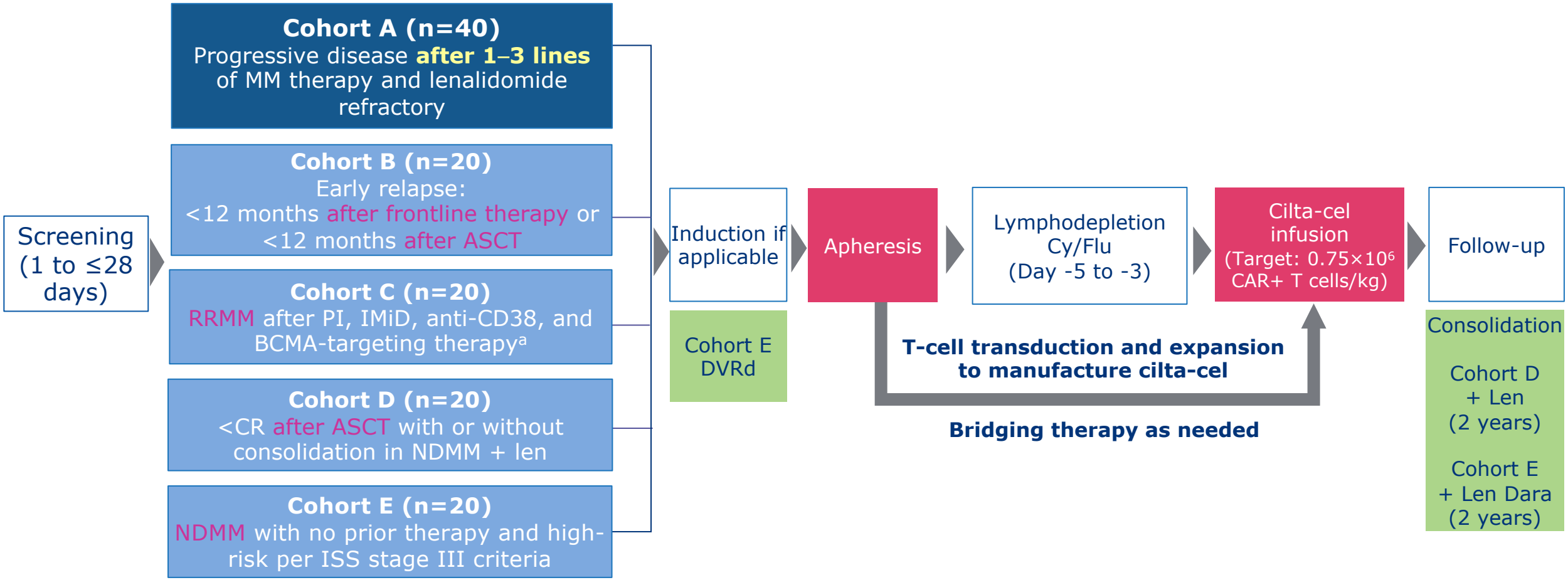
Response: All patients with sustained MRD negativity for ≥6 months achieved sCR





Munshi et al. - Poster 2030 ASH 2022

CARTITUDE-2: phase 2 multi-cohort study



[a]Excluding prior BCMA-targeting cellular therapy.

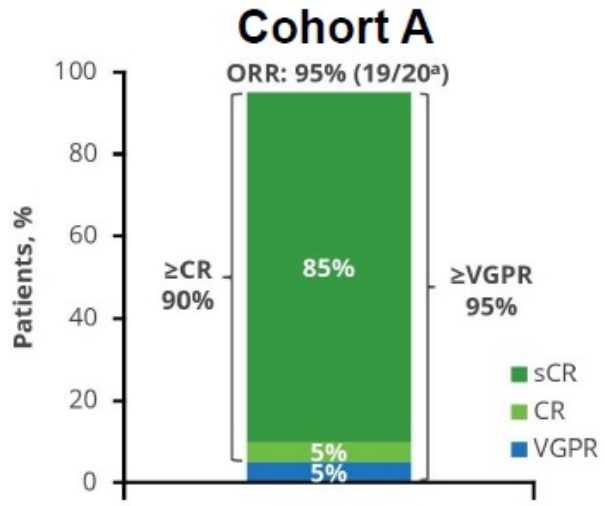
ASCT, autologous stem cell transplant; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; CR, complete response; Cy, cyclophosphamide; Dara, daratumumab; DVRd, daratumumab, bortezomib, lenalidomide and dexamethasone; Flu, fludarabine; IMiD, immunomodulatory drug; ISS, international staging system; Len, lenalidomide; MM, multiple myeloma; NDMM, newly diagnosed multiple myeloma; PI, proteasome inhibitor.

Mounzer Agha et al., ASCO 2021

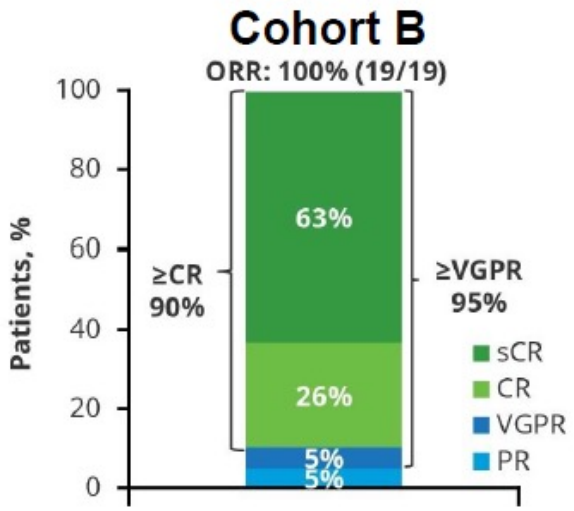
CARTITUDE-2 cohort A: 1-3 prior tx, len-refractory

CARTITUDE-2

- Cohort A: Patients with progressive MM after 1–3 prior lines of therapy, lenalidomide refractory
- Cohort B: Patients with progressive MM following early relapse after initial therapy that included a PI and IMiD
- Screening (1 to ≤28 days)
- Apheresis
- *Bridging therapy (as needed)*
- Cy (300 mg/m²) + Flu (30 mg/m²) (day -5 to -3)
- Cilta-cel infusion
  Target: 0.75×10⁶ (0.5–1.0×10⁶) CAR+ viable T cells/kg (day 1)
- Postinfusion assessments (day 1 to 100)
  Safety, efficacy, PK, PD, biomarker
- Posttreatment assessments (day 101 up to end of cohort)
  Safety, efficacy, PK, PD, biomarker
- Follow-up



[a]One patient demonstrated a minimal response.
sCR, stringent CR



AEs ≥20%, n (%)	N=20	
	Any Grade	Grade 3/4
Hematologic		
Neutropenia	19 (95)	19 (95)
Thrombocytopenia	16 (80)	7 (35)
Anemia	15 (75)	9 (45)
Lymphopenia	14 (70)	14 (70)
Leukopenia	11 (55)	11 (55)
CAR-T–related AEs		
CRS	19 (95)	2 (10)
Neurotoxicity	6 (30)	1 (5)
ICANS	3 (15)	0
Other	3 (15)[a]	1 (5)

[a]One patient had peripheral sensorimotor neuropathy, one had anosmia and dysgeusia, and one had facial paralysis.

AEs ≥20%, n (%)	N=19	
	Any Grade	Grade 3/4
Hematologic		
Neutropenia	18 (95)	17 (90)
Anemia	11 (58)	9 (47)
Thrombocytopenia	11 (58)	5 (26)
Lymphopenia	6 (32)	6 (32)
Leukopenia	5 (26)	5 (26)
CAR-T–related AEs		
CRS	16 (84)	1 (5)
Neurotoxicity	5 (26)	1 (5)
ICANS	1 (5)	0
Other	4 (21)	1 (5)
Parkinsonism	1 (5)	1 (5)

Mounzer E. Agha et al., EHA 2022 oral presentation S185

CARTITUDE-2: cohort B

- CARTITUDE-2 cohort B consists of patients with **early relapse after initial therapy with a PI and IMiD**, defined as **progression within 12 months** after ASCT or from the start of anti-MM therapy for patients who have not had ASCT

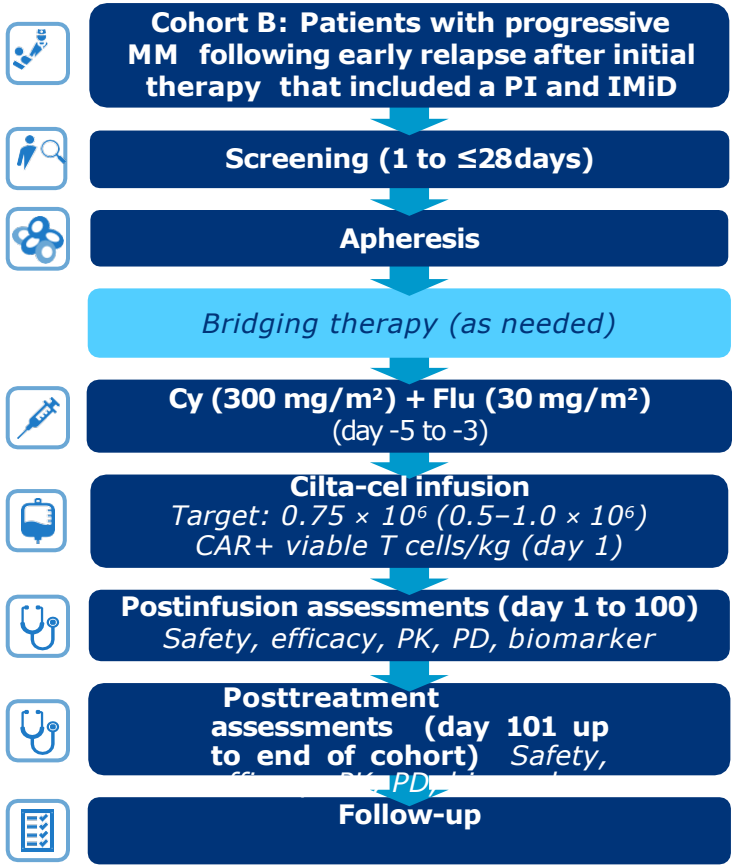
Primary endpoint

- MRD negativity (10^{-5} threshold)
  - Assessed by next-generation sequencing or next-generation flow

Secondary endpoints

- ORR per IMWG response criteria
- DOR
- Time to response
- Incidence and severity of AEs
  - Assessed per CTCAE version 5.0
  - CRS and ICANS graded per ASTCT criteria

CARTITUDE-2 cohort B study design

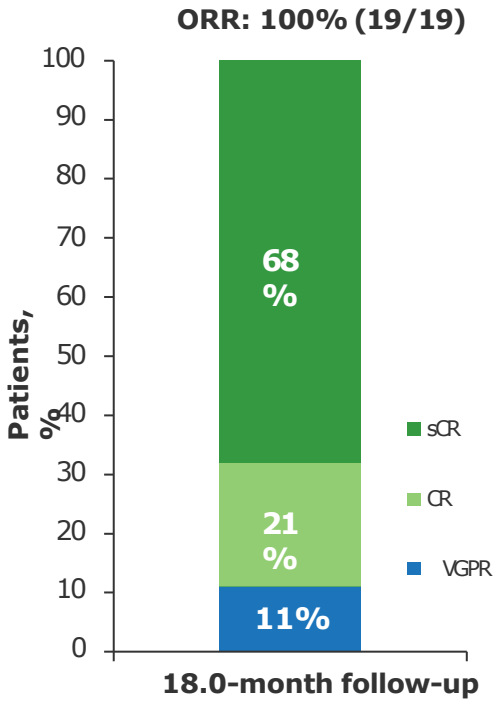


AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; CTCAE; Common Terminology Criteria for Adverse Events; CRS, cytokine release syndrome; Cy, cyclophosphamide;
DOR; duration of response; Flu, fludarabine; ICANS, immune effector cell–associated neurotoxicity syndrome; IMWG, International Myeloma Working Group; MRD, minimal residual disease;
ORR, overall response rate; PD, pharmacodynamics; PK, pharmacokinetics.

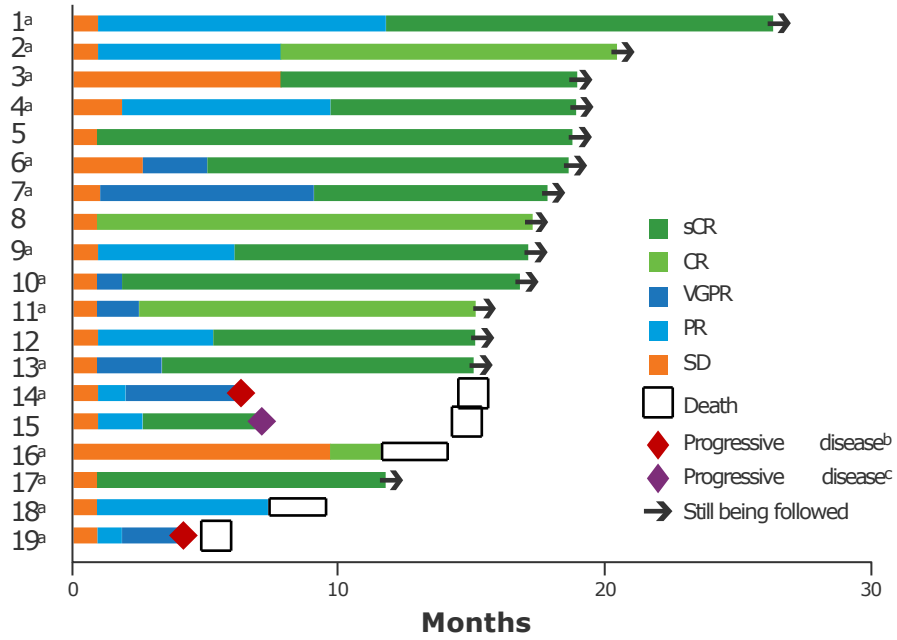
CARTITUDE-2 cohort B: efficacy

- ORR was 100% (95% CI, 82.4–100.0) and responses deepened at this longer follow-up
  - **90% (95% CI, 66.9–98.7) achieved ≥CR**
  - **100% (95% CI, 82.4–100.0) achieved ≥VGPR**
- Median time to first response: 0.95 months (range, 0.9–9.7)
- Median time to best response: 5.09 months (range, 0.9–11.8)
- Median DOR was not reached
- Median PFS and OS at 18-month median follow-up were not reached
  - **18-month PFS rate was 83% (95% CI, 55.9–94.3)**
  - **18-month OS rate was 83% (95% CI, 55.7–94.2)**
- Of 15 patients with MRD-evaluable samples at 10^{-5} threshold, 14 (93.3%) were MRD negative
  - Of 3 patients with high-risk cytogenetics, 2 (66.7%) were MRD negative at 10^{-5} threshold

Overall response rate



Response and DOR in responders



[a]Patients who received autologous stem cell transplant. [b]PD per International Myeloma Working Group criteria. [c]PD per investigator assessment based on a light chain escape.
CR, complete response; DOR, duration of response; MRD, minimal residual disease; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; sCR, stringent CR; SD, stable disease; VGPR, very good partial response.

CARTITUDE-2: cohort C

(18-Month Median Follow-up)

- CARTITUDE-2 cohort B consists of patients with **prior exposure to a PI, IMiD, anti-CD38 mAb, and non-cellular BCMA-targeting therapy**

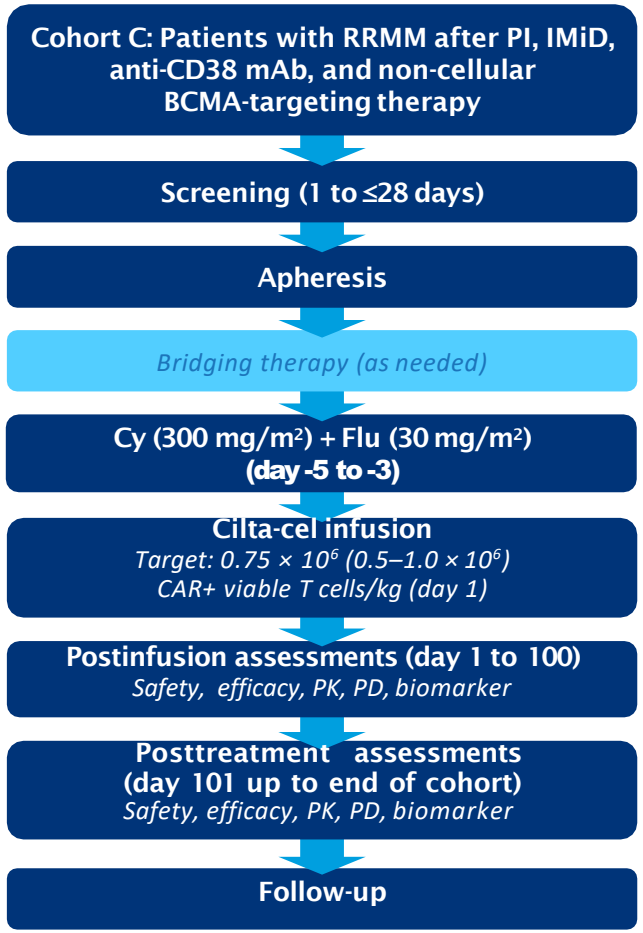
Primary endpoint

- MRD negativity (10^{-5} threshold) assessed by next-generation sequencing or next-generation flow

Secondary endpoints

- ORR
- DOR
- Time to response and duration of MRD negativity
- Incidence and severity of AEs
  - Assessed per CTCAE v5.0
  - CRS and ICANS graded per ASTCT criteria

CARTITUDE-2 study design



AE, adverse event; ASTCT, American Society for Transplantation and Cellular Therapy; BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; cilta-cel, ciltacabtagene autoleucel; CRS, cytokine release syndrome; CTCAE, Common Terminology Criteria for AEs; Cy, cyclophosphamide; DOR, duration of response; Flu, fludarabine; ICANS, immune effector cell–associated neurotoxicity syndrome; IMiD, immunomodulatory drug; mAb, monoclonal antibody; MRD, minimal residual disease; ORR, overall response rate; PD, pharmacodynamics; PI, proteasome inhibitor; PK, pharmacokinetics; RRMM, relapsed/refractory multiple myeloma.

CARTITUDE-2 cohort C: study population

(18-Month Median Follow-up)

- As of June 2022, patients from cohort C (N=20) had a median follow-up of 18 months (range, 0.6–22.7)
  - 90% of patients were anti-BCMA refractory
  - Patients received a median of 8 (range, 4–13) prior LOT
    - **13 patients with prior ADC therapy**
    - **7 with prior BsAb therapy**
- Median time from last anti-BCMA agent to cilta-cel infusion was 6.4 months (range, 2.0–24.6)
- Best responses to prior anti-BCMA treatment
  - sCR: ADC (n=1)
  - CR: BsAb (n=1)
  - VGPR: ADC (n=2); BsAb (n=1)
  - **Stable/progressive disease: Full cohort (n=15)**

Baseline characteristic	Full cohort (N=20)
Age, median (range), y	62.5 (44–81)
Male, n (%)	12 (60)
Race, n (%)	
White	19 (95)
Black	1 (5)
Bone marrow plasma cells[a] ≥60%, n (%)	6 (32)
Extramedullary plasmacytomas, n (%)	5 (25)
High-risk cytogenetic profile,[b] n (%)	3 (15)
Time from initial MM diagnosis, median (range), y	6.3 (2.5–16.3)
ISS stage at study entry, n (%)	
I	8 (40)
II	4 (20)
III	8 (40)
Number of prior LOT, median (range)	8 (4–13)
Anti-BCMA in last LOT, n (%)	6 (30)
Refractory status, n (%)	
Triple-class[c]	18 (90)
Penta-drug[d]	11 (55)
Anti-BCMA	18 (90)
To last LOT	19 (95)

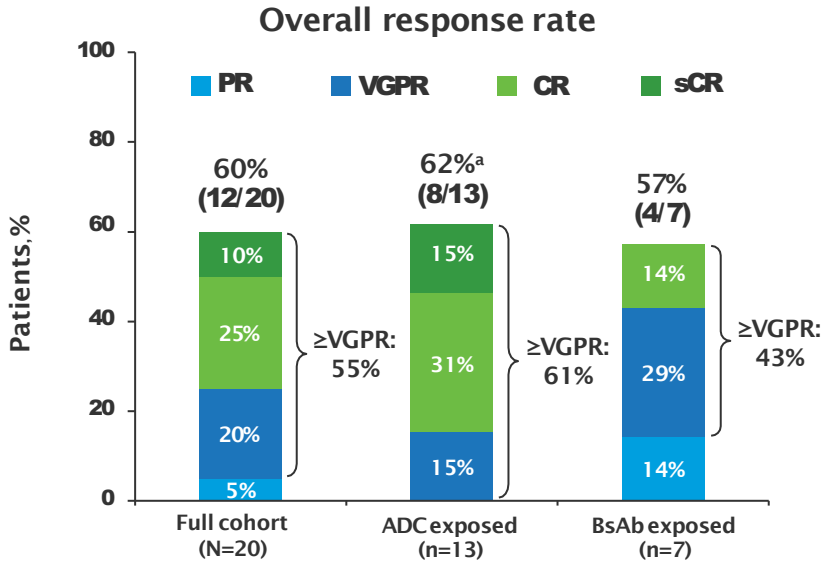
[a]Maximum value from bone marrow biopsy and bone marrow aspirate is selected if both results are available; n=19 . [b]All del17p; missing data in 8 (40%) patients. [c]≥1 PI, ≥1 IMiD, and 1 anti-CD38 antibody. [d]≥2 PIs, ≥2 IMiDs, and 1 anti-CD38 antibody.

ADC, antibody-drug conjugate; BCMA, B-cell maturation antigen; BsAb, bispecific antibody; cilta-cel, ciltacabtagene autoleucel; CR, complete response; IMiD, immunomodulatory drug; ISS, International Staging System; LOT, line of therapy; MM, multiple myeloma; PI, proteasome inhibitor; sCR, stringent complete response; VGPR, very good partial response.

CARTITUDE-2 cohort C: efficacy

(18-Month Median Follow-up)

- Of the 10 patients with MRD-evaluable samples at 10^{-5} threshold, 7 (70%) were MRD negative
  - 5 of 7 patients in the ADC-exposed group
  - 2 of 3 patients in the BsAb-exposed group
- ORR was 60% (95% CI, 36.1–80.9) in the full cohort and was similar in patients exposed to prior ADC vs prior BsAb
  - Median DOR was 12.3 months
  - Median PFS was 9.1 months
- Response to cilta-cel was associated with shorter duration of exposure to last anti-BCMA agent and longer time from last anti-BCMA treatment to apheresis



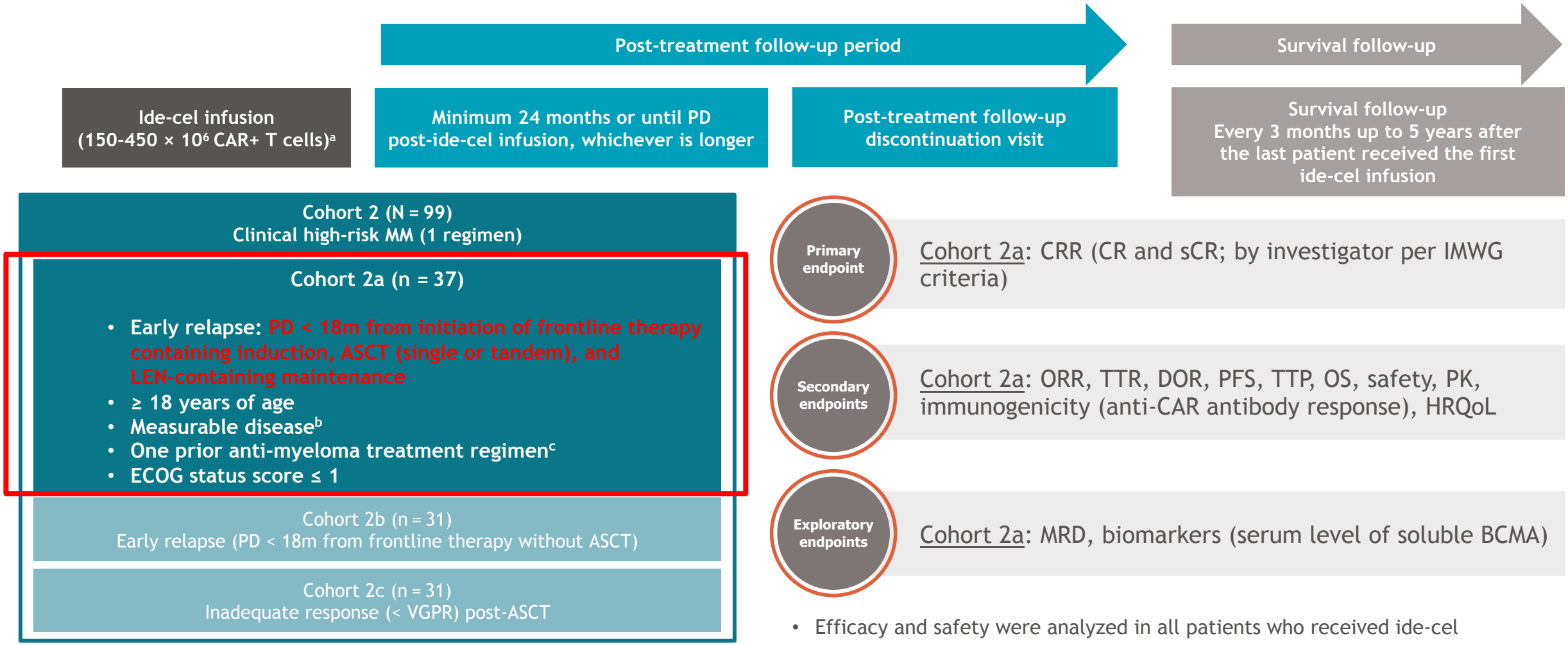
[a]Percentages may not sum appropriately due to rounding.

Median DOR and PFS

Estimate, months (95% CI)	Full cohort (N=20)	ADC exposed (n=13)	BsAb exposed (n=7)
DOR	12.3 (7.2–NE)	13.3 (7.2–NE)	8.2 (4.4–NE)
PFS	9.1 (1.5–13.2)	9.5 (1.0–15.2)	5.3 (0.6–NE)

ADC, antibody-drug conjugate; BsAb, bispecific antibody; BCMA, B-cell maturation antigen; cilta-cel, ciltacabtagene autoleucel; CR, complete response; DOR, duration of response; MRD, minimal residual disease; NE, not evaluable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

KarMMa-2 cohort 2a: study design

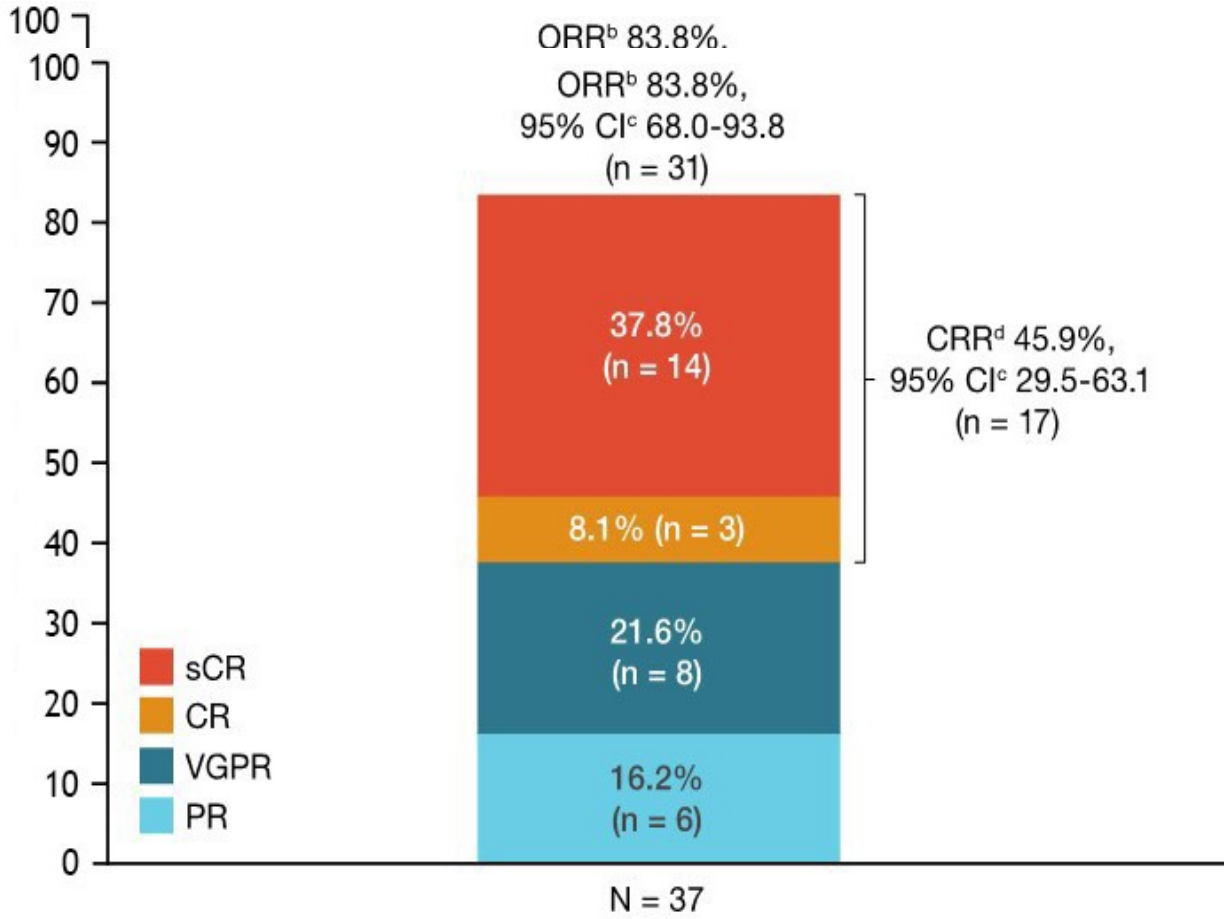


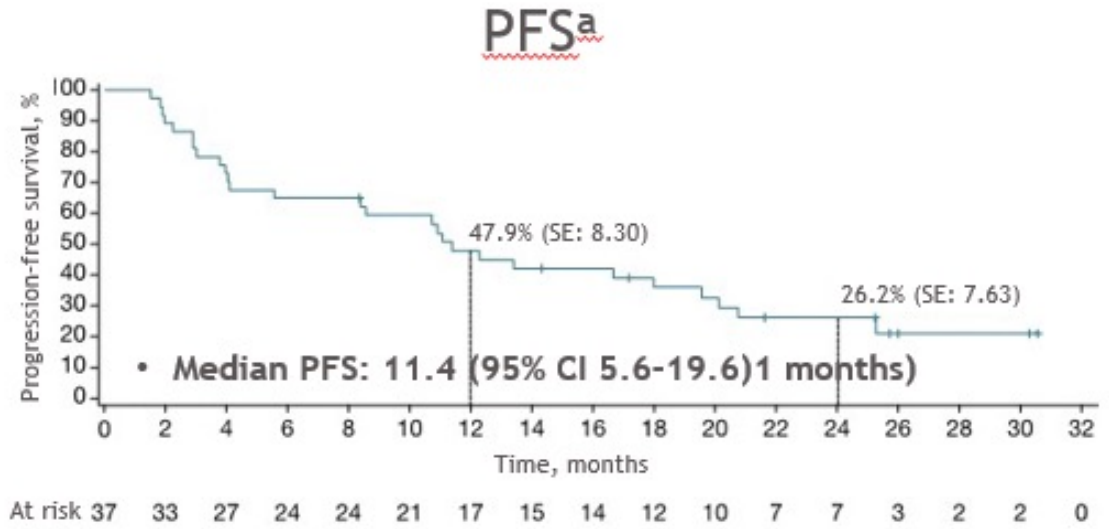
- Efficacy and safety were analyzed in all patients who received ide-cel

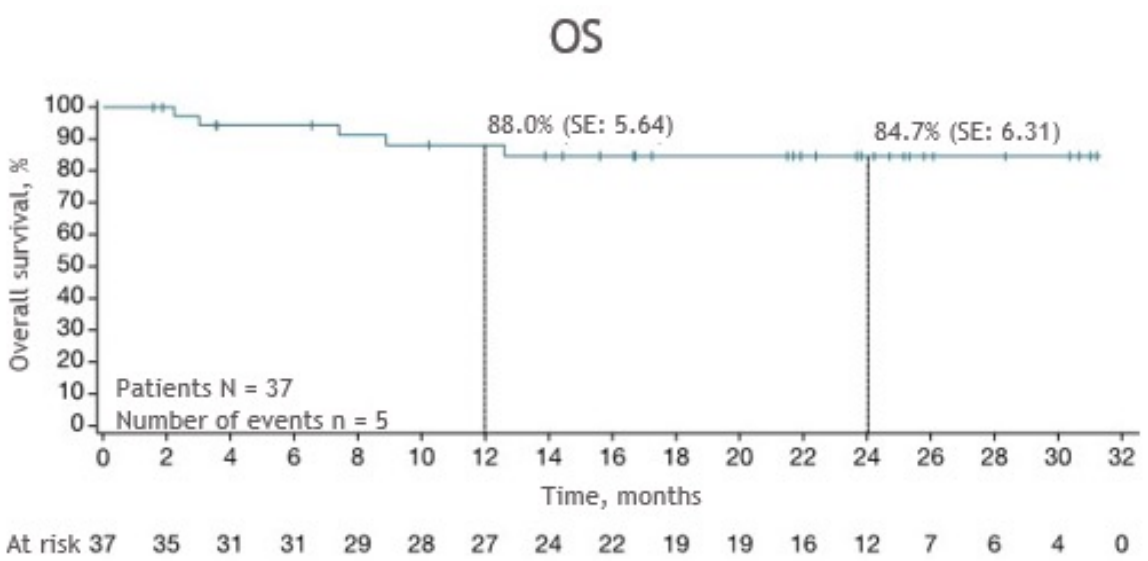
ClinicalTrials.gov Identifier: NCT03651128. CR, complete response; CRR, complete response rate; DOR, duration of response; ECOG, Eastern Cooperative Oncology Group; HRQoL, health-related quality of life; HSCT, hematopoietic stem cell transplant; LEN, lenalidomide; MRD, minimal residual disease; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PK, pharmacokinetics; sBCMA, soluble BCMA; sCR, stringent complete response; TTP, time to progression; TTR, time to response; VGPR, very good partial response.
[a]After lymphodepletion (cyclophosphamide 300 mg/m^2 + fludarabine 30 mg/m^2 × 3), patients received a single infusion of ide-cel at a range of 150-450 × 10^6 CAR+ T cells (up to an additional 20%; ≥ 20% considered over the protocol-specified doses). [b]Measurable disease determined by M-protein (serum protein electrophoresis ≥ 0.5 g/dL or urine protein electrophoresis ≥ 200 mg/24 hours) and/or light chain MM without measurable disease in serum or urine (serum immunoglobulin free light chain ≥ 10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio).[c]Induction with or without HSCT and with or without maintenance therapy is considered a single regimen.

KarMMa-2 cohort 2a: efficacy outcomes

Best overall response

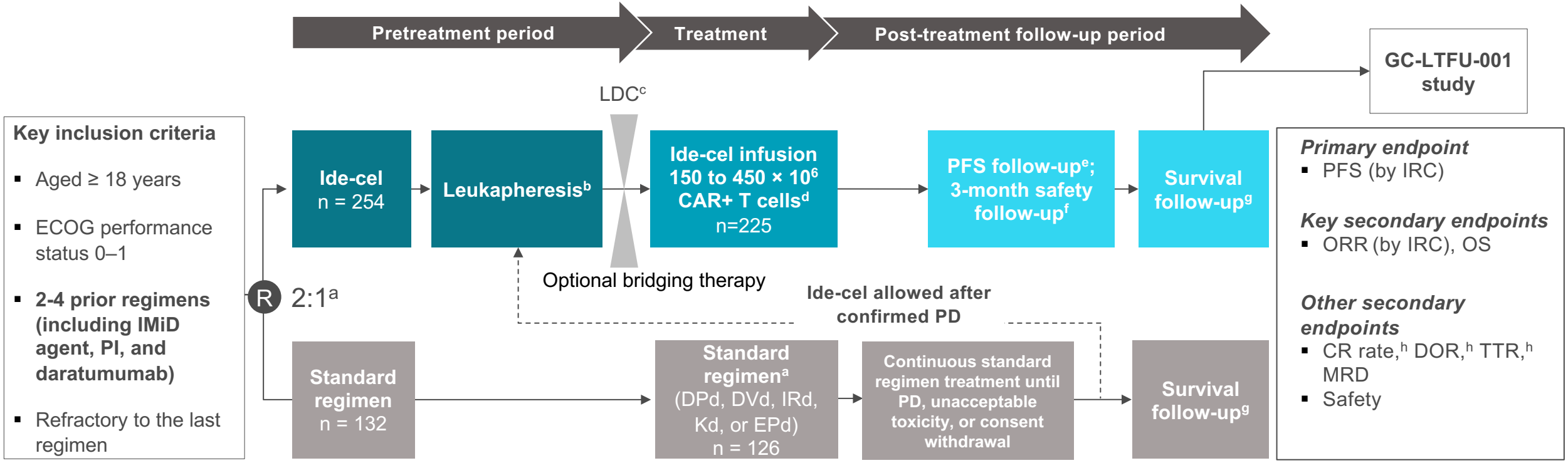






[a]Patients with PR or better (2 patients had minimal response; 2 had stable disease and 0 had PD). [b]Clopper-Pearson CI. [c]Patients with sCR or CR. [d]Patients with sCR, CR, or VGPR.
CI, confidence interval; CR, complete response; CRR, complete response rate; ORR, overall response rate; PR, partial response; sCR, stringent CR; VGPR, very good partial response.

KarMMa-3: study design



Stratification factors

- Age (< 65 vs ≥ 65 years)
- Number of prior regimens (2 vs 3 or 4)
- High-risk cytogenetics (t[4;14], t[14;16], or del[17p]; yes vs absent/unknown)

Data cutoff: April 18, 2022

Median (range) duration of follow-up: 18.6 (0.4–35.4) months

Rodriguez-Otero P et al, N Engl J Med 2023 Feb 10. doi: 10.1056/NEJMoa2213614. Online ahead of print

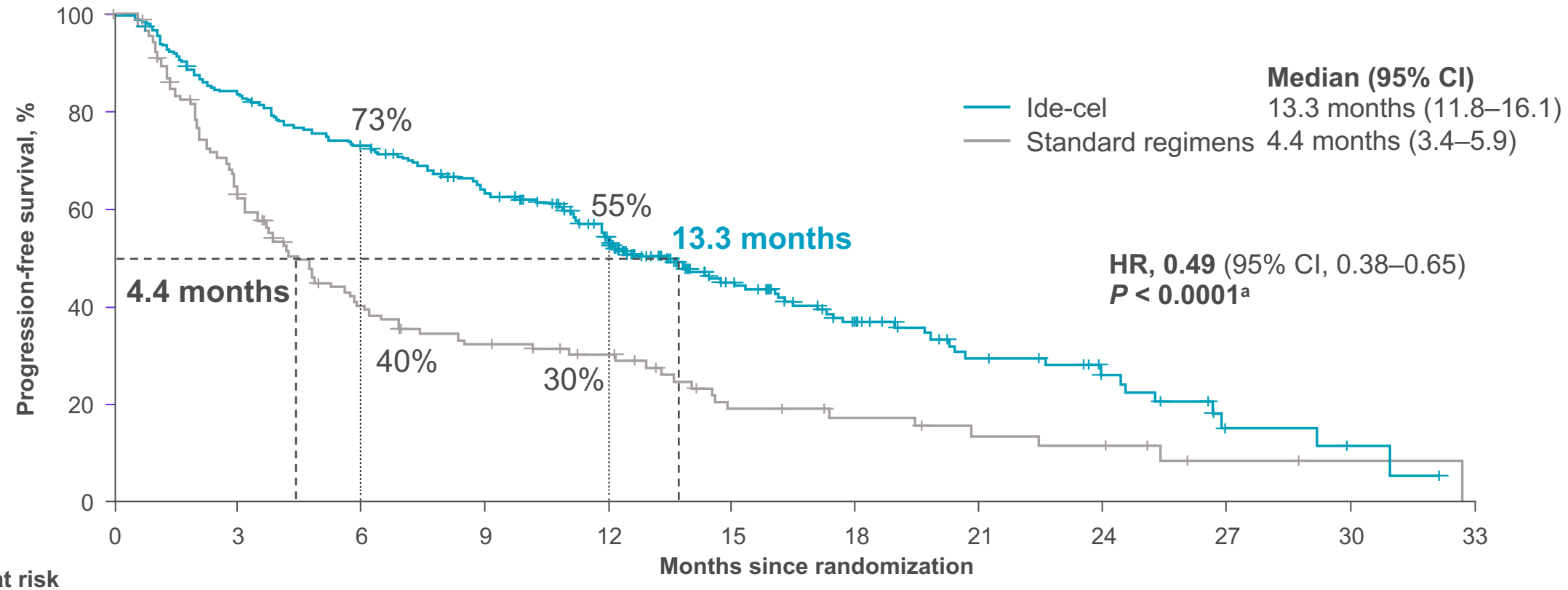
Prior treatment

Treatment	Ide-cel (n = 254)	Standard regimens (n = 132)
Median (range) number of prior regimens	3 (2–4)	3 (2–4)
Median (range) time to progression on last prior antimyeloma therapy, months	7.1 (0.7–67.7)	6.9 (0.4–66.0)
Refractory status, n (%)		
IMiD agent refractory	224 (88)	124 (94)
PI refractory	189 (74)	95 (72)
Daratumumab[a]	242 (95)	123 (93)
Double-class refractory[b]	169 (67)	91 (69)
Triple-class refractory[c]	164 (65)	89 (67)

[a]1 patient in each arm was refractory to isatuximab; [b]Refractory to ≥1 IMiD agent and 1 PI; [c]Refractory to ≥1 IMiD agent, 1 PI, and 1 anti-CD38 antibody.

Rodriguez-Otero P et al, N Engl J Med 2023 Feb 10. doi: 10.1056/NEJMoa2213614. Online ahead of print

Progression-free survival (ITT population)



Patients at risk

Ide-cel	254	206	178	149	110	62	40	22	14	4	2	0
Standard regimens	132	75	42	32	25	13	10	7	6	2	1	0

PFS based on IMWG criteria per IRC. [a]Based on stratified log-rank test.
IMWG, International Myeloma Working Group.

Rodriguez-Otero P et al, N Engl J Med 2023 Feb 10. doi: 10.1056/NEJMoa2213614. Online ahead of print

CAR-T cell therapy in MM

	Approved CAR-T cells		Academic	Alternative manufacturing	Human scFv		Allo-CAR	GPRC5D
	Ide-cel KarMMa[1] (n = 128)	Cilta-cel CARTITUDE-1[2] (n = 97)	ARI0002h[3] (n = 30)	P-BCMA-101 PRIME[5] (n = 53)	CT053[6] LUMMICAR (n = 20)	CT103A[7] (n= 79)	ALLO-715 UNIVERSAL[8] (n = 43)	MCARH10[9] (n= 17)
Phase	II	Ib/II	I/II	I/II	I	I/II	I	I
Target	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	BCMA	GPRC5D
scFv	Chimeric mouse	Chimeric llama	Humanized	Chimeric mouse	Human	Human	Human	Human
Co-stim	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB	4-1BB
Specificity	Autologous	Autologous	Autologous	Autologous - piggyBac	Autologous	Autologous	Allogenic CD52 & TCR KO	Autologous
Age, (range)	61 (33-78)	61 (56-68)	61 (36-74)	60 (42-74)	62 (33-76)	56 (39-70)	64 (46-77)	60 (38-76)
# of lines	6	6	4	8	NA	5	5	6
HR cytog, %	35	24	36	NA	NA	35	48	77
EMD, %	39	13	20	NA	NA	NA	21	41
Triple-R, %	84	88	61	60	NA	17	91	94

*There are no head-to-head comparisons of these data and naïve comparison should be conducted with caution

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; EMD, extramedullary disease; HR cytog, high-risk cytogenetics; NA, not available; ScFv, single-chain variable fragment; TCR, T-cell receptor; triple-R, triple-class refractory

1. Munshi N et al. N Eng J Med 2021;384:705-16; 2. Berdeja J et al. Lancet 2021;398;314-24; 3. Fernández de Larrea C, et al. ASH 2021;abstract 2837; 4. Raje N et al. ASH 2021 abstract 548; 5. Costello C, et al. ASH 2020;abstract 134; 6. Kumar S, et al. ASH 2020; 7. Li C, et al. ASH 2021;abstract 143; 8. Mailankody S, et al. ASH 2021;abstract 615; 9. Mailankody S, et al. ASH 2021;abstract 827

Tailoring and sequencing immunotherapies for MM

Selection of immunotherapy

Bispecific
CAR

New CARs/dual CAR
NK or T or both
Better constructs
New manufacturing (rapid)

Selection of targets
BCMA
GPRC5D
FcRH5
Other antigen targets

Optimal selection of patients

Who will benefit the most from each of these strategies? **Earlier treatment lines? (upfront?)**, lower tumor burden?, which cytogenetic risk?

Combined with each other?
Administered sequentially?

Rodríguez-Lobato LG et al. Front Oncol. 2020;10:1243

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; NK, natural killer; ScFv, single-chain variable fragment