



# SINTOMA'24

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# When to consider bispecific and CAR T therapy in multiple myeloma?

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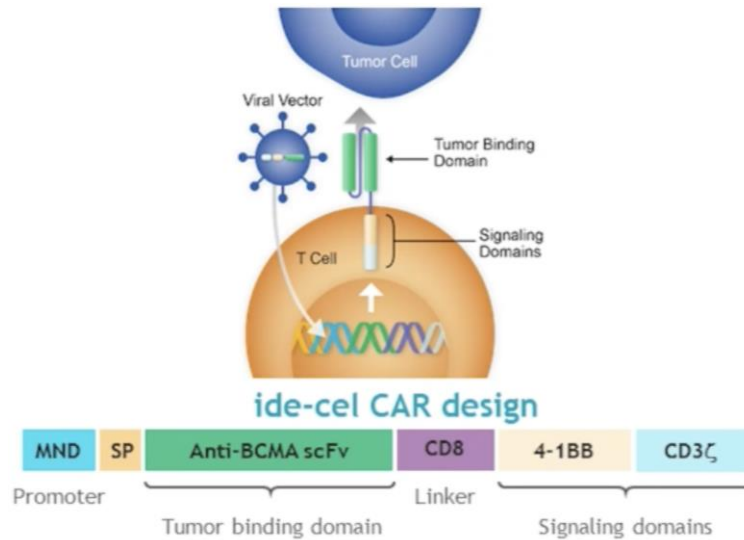
# Disclosures

- Consultancy: Amgen, Janssen, GSK, BMS, Abbvie, Astrazeneca, Pfizer, K-36 Therapeutics, Genentech
- Research Funding: 2Seventy bio, Pfizer
- Membership on an entity's Board of Directors or advisory committees: Immuneel, Caribou biosciences



# Idecabtagene-Vicleucel (ide-cel, Abecma): Approved March 2021

- Autologous CAR T-cell
- Anti-BCMA scFv
- 4-1BB costimulatory domain
- CD3z intracellular signaling domain

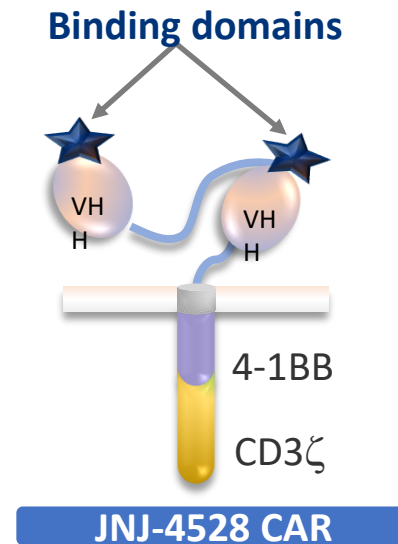


## \*\*FDA Label:

- 2-4 Prior Lines of Therapy for Idecel and Rev refractory > 1L for ciltacel

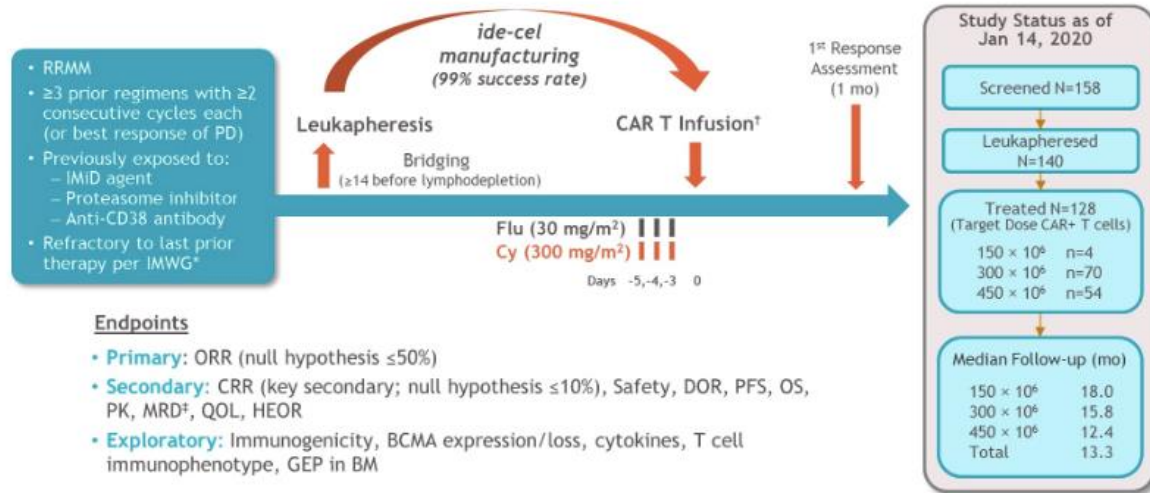
# Ciltacabtagene Autoleucel (JNJ-4528): Approved Feb 2022

- Autologous CAR T-cell
- **Two BCMA-targeting sites (increased avidity)**
- 4-1BB signaling domain
- CD3z intracellular signaling domain

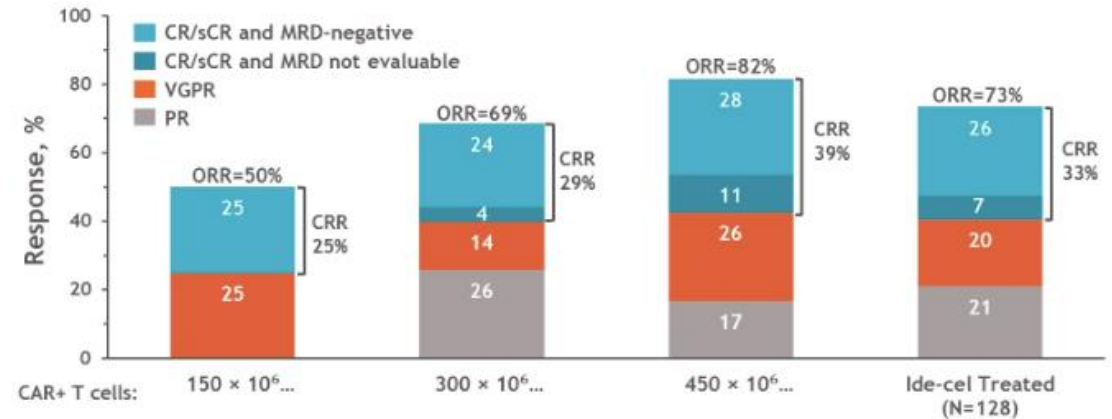


# KarMMa: Ide-cel Registration Study

## Trial design



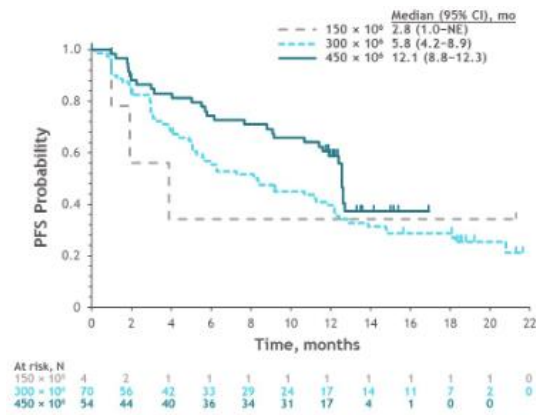
## Response



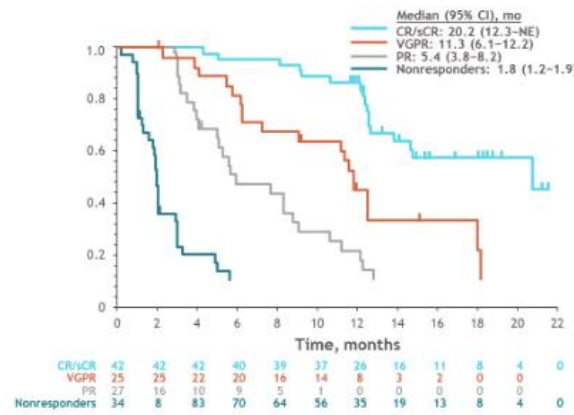
- Primary (ORR > 50%) and key secondary (CRR >10%) endpoints met in the Ide-cel treated population
  - ORR of 73% (95% CI, 65.8-81.1; P<0.0001)
  - CRR (CR/sCR) of 33% (95% CI, 24.7-40.9; P<0.0001)
- Median time to first response of 1.0 mo (range, 0.5-8.8); median time to CR of 2.8 mo (range, 1.0-11.8)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

# KarMMa: PFS and MRD-negativity

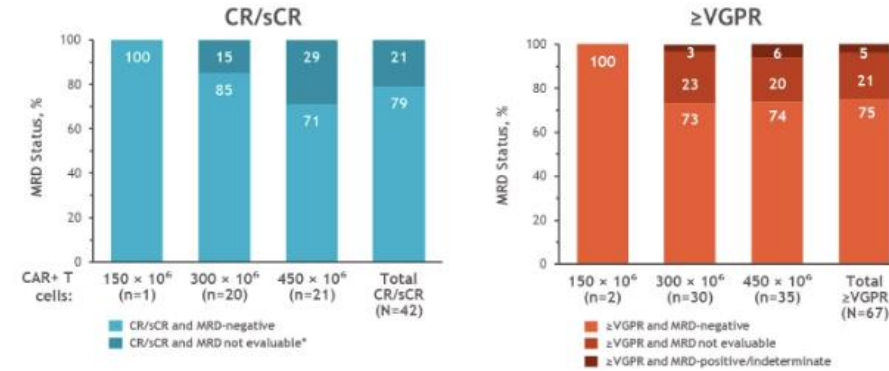
PFS by Target Dose



PFS by Best Response



MRD-negativity by target dose



- PFS increased with higher target dose
- Median PFS was 12 mo at 450 x 10<sup>6</sup> CAR+ T cells
- mOS 24.8 months (95% CI: 19.9-31.2) among all treated patients
- PFS increased by depth of response
- Median PFS was 20 mo in patients with CR/sCR

Target Dose, CAR+ T cells	150 x 10 <sup>6</sup>	300 x 10 <sup>6</sup>	450 x 10 <sup>6</sup>	Total
All ide-cel treated	N=4	N=70	N=54	N=128
MRD-negative and >CR, n(%) [95% CI]	1 (25) [0.6-80.6]	17 (24) [14.8-36.0]	15 (28) [16.5-41.6]	33 (26) [18.5-34.3]
MRD-negative and ≥VGPR, n(%) [95% CI]	2 (50) [6.8-93.2]	22 (31) [20.9-43.6]	26 (48) [34.4-62.2]	50 (39) [30.6-48.1]

## Trial design

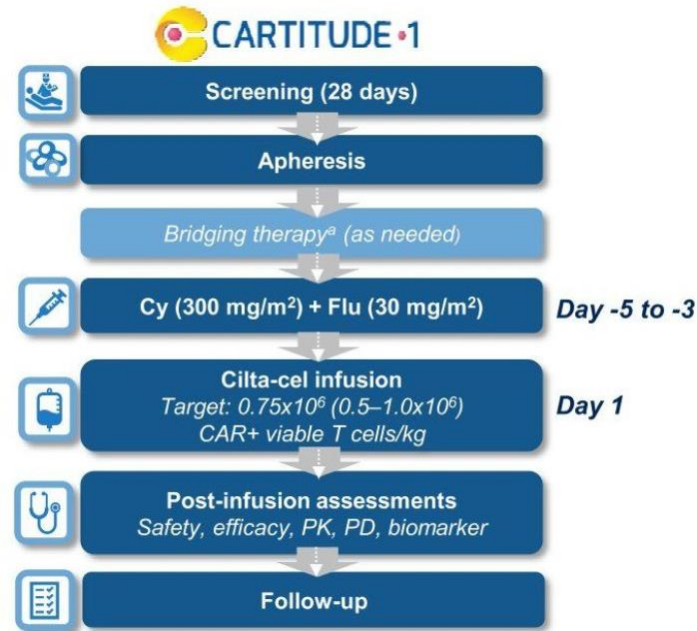
### Primary objectives

- 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

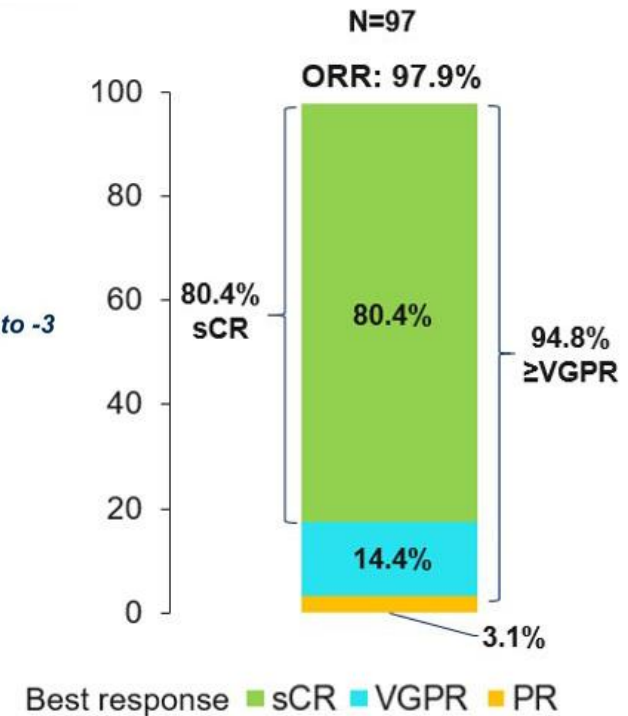
### Key eligibility criteria

- Progressive MM per IMWG criteria
- ECOG PS  $\leq 1$
- Measurable disease
- $\geq 3$  prior therapies or double refractory
- Prior PI, IMiD, anti-CD38 therapy

- Median administered dose:  $0.71 \times 10^6$  ( $0.51$ – $0.95 \times 10^6$ ) CAR+ viable T cells/kg

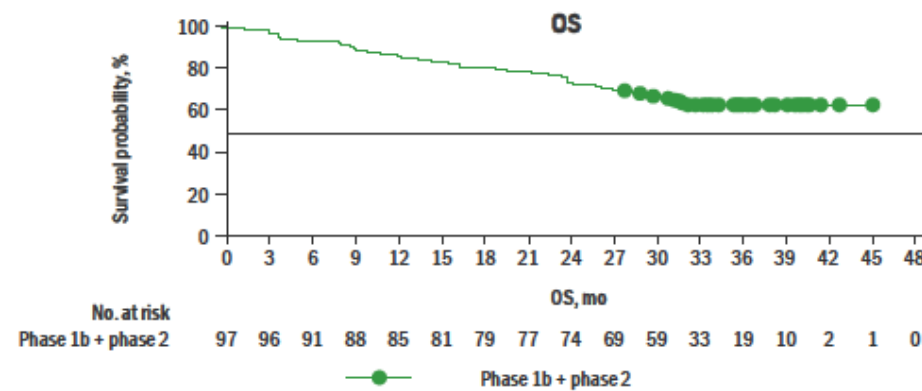
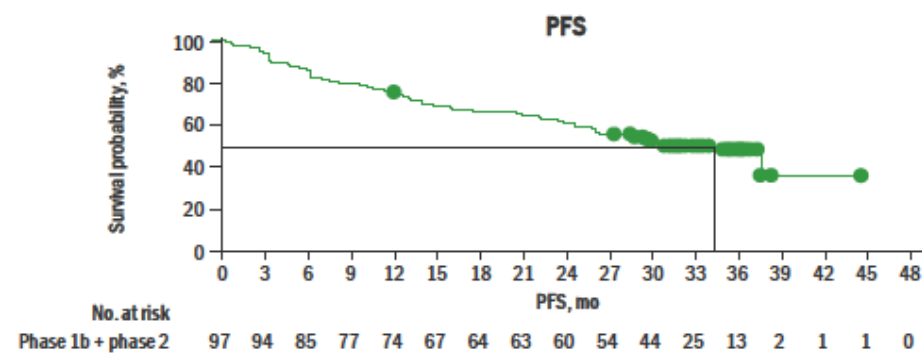
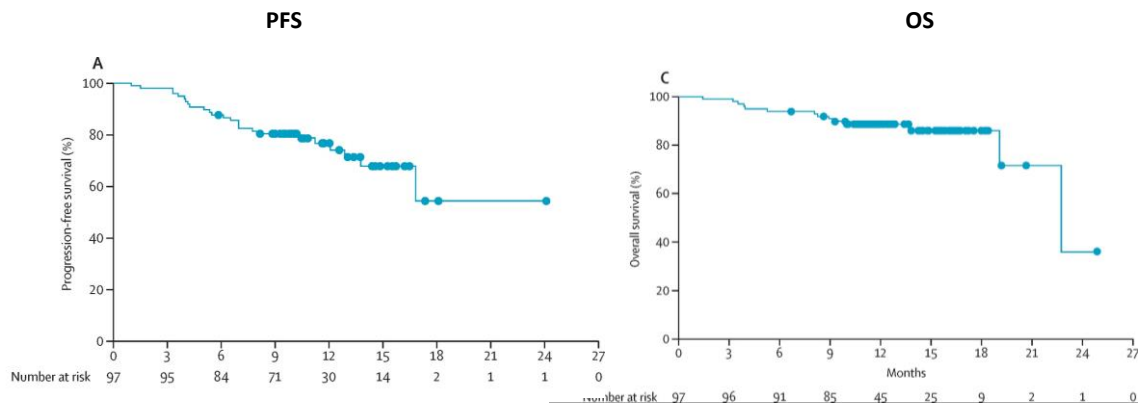


## Response



~27 months

~3 years



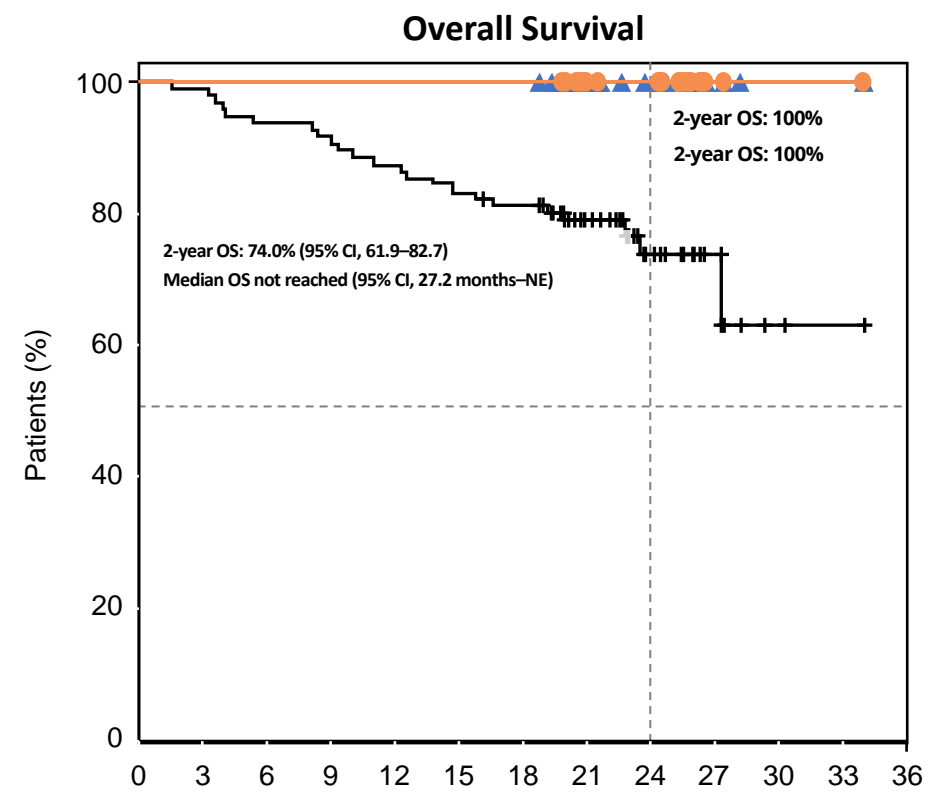
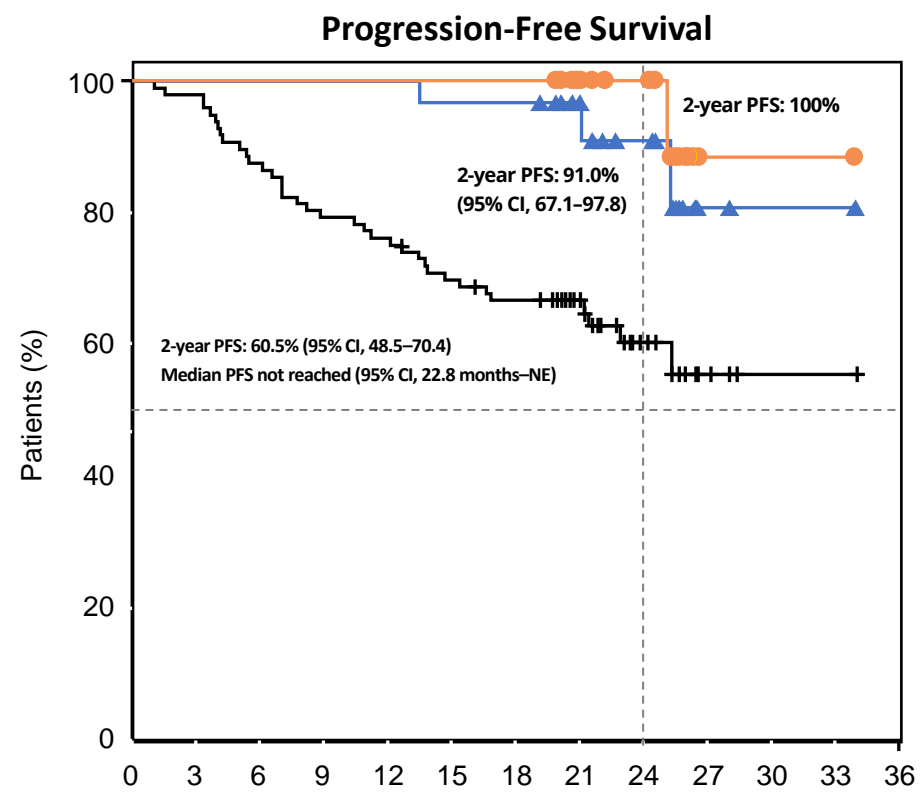
**PFS by CR and sustained MRD negativity**

Subgroups	mPFS (95% CI), mo	30-mo PFS rate	36-mo PFS rate
All patients	34.9 (25.2–NE)	54.2%	47.5%
≥CR <sup>a</sup>	38.2 (34.9–NE)	66.8%	59.8%
12-mo sustained MRD negativity <sup>b</sup>	NR (NE–NE)	74.9%	NE
12-mo sustained MRD-negative ≥CR <sup>b</sup>	NR (NE–NE)	78.5%	NE



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

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



Patients at risk	Months												
	0	3	6	9	12	15	18	21	24	27	30	33	36
All patients	97	95	85	77	74	67	63	36	19	4	1	1	0
MRD negativity $\geq 6$ months	30	30	30	30	30	29	29	17	12	2	1	1	0
MRD negativity $\geq 12$ months	18	18	18	18	18	18	18	12	10	1	1	1	0

Patients at risk	Months												
	0	3	6	9	12	15	18	21	24	27	30	33	36
All patients	97	96	91	88	85	81	78	46	23	8	2	1	0
MRD negativity $\geq 6$ months	30	30	30	30	30	30	30	17	13	3	1	1	0
MRD negativity $\geq 12$ months	18	18	18	18	18	18	18	12	11	2	1	1	0

All patients    
  MRD negativity sustained  $\geq 6$  months    
  MRD negativity sustained  $\geq 12$  months

# KarMMa and CARTITUDE-1

## CRS and NT

	Ide-cel	Cilta-cel
<b>FDA approval</b> Trial, Reference Publication	KarMMa (n=124) Munshi NEJM 2021	CARTITUDE-1 (n=97) Berdeja Lancet 2021
<b>Safety</b>		
CRS (all; grades 3–4)	84% (5%)	95% (5%)
Median onset of CRS	1 day	7 days
ICANS (all; grades 3–4)	18% (3%)	17% (2%)
<b>Delayed neurotoxicity (all; grades 3-4)</b>	<b>None</b>	<b>12% (9%)</b>
Infections (all; grades 3–4)	69% (22%)	58% (20%)
Grades 3–4 neutropenia > 1 month	41%	10%
Grades 3–4 thrombocytopenia > 1 month	48%	25%

# CARTITUDE-1: Safety

- **No new treatment-related deaths**
- **A total of 20 SPMs were reported in 16 patients**
  - Nine patients with hematologic malignancies (1 low-grade B-cell lymphoma, 6 MDS, 3 fatal AML[one patient had both MDS and fatal AML])
  - One patient each with malignant melanoma, adenocarcinoma, myxofibrosarcoma, and prostate cancer
  - Six non-melanoma skin cancers
- **One new case of signs and symptoms of parkinsonism (previously termed movement and neurocognitive TEAEs) (total n=6)**
  - On day 914, patient experienced cognitive slowing, gait instability, and neuropathy (all grade 1), and tremor (grade 3); he is currently stable and functioning, and remains in sCR with no steroids or anticytokine therapies given
  - Work-up is ongoing, including a differential diagnosis as post-encephalitis syndrome
  - Had 2 risk factors for parkinsonism (grade 2 CRS and grade 3 ICANS) after cilta-cel<sup>5,6</sup>
- **Outcomes in the previously reported 5 patients with parkinsonism<sup>1,2</sup>**
  - 3 have died (two from other underlying causes [sepsis and lung abscess] and one related to parkinsonism)
  - One patient has recovered, and one is recovering (ongoing grade 2 symptoms) at the time of the data cut
- **Following implementation of patient management strategies, the incidence of parkinsonism has decreased from 6% in CARTITUDE-1 to <0.5% across the CARTITUDE program**

## Deaths

	Total (N=97)	Time of death post cilta-cel infusion (days)
Total deaths during the study	30	45–917
Due to progressive disease	14	253–746
AEs unrelated to treatment (n=9)		
Pneumonia	1	109
Acute myeloid leukemia <sup>a</sup>	3	418, 582, 718
Ascites <sup>b</sup>	1	445
Myelodysplastic syndrome	1	803
Respiratory failure	3	733, 793, 829
Septic shock	1	917
AEs related to treatment (n=6)		
Sepsis and/or septic shock	2	45, 162
CRS/HLH	1	99
Lung abscess	1	119
Respiratory failure	1	121
Neurotoxicity	1	247

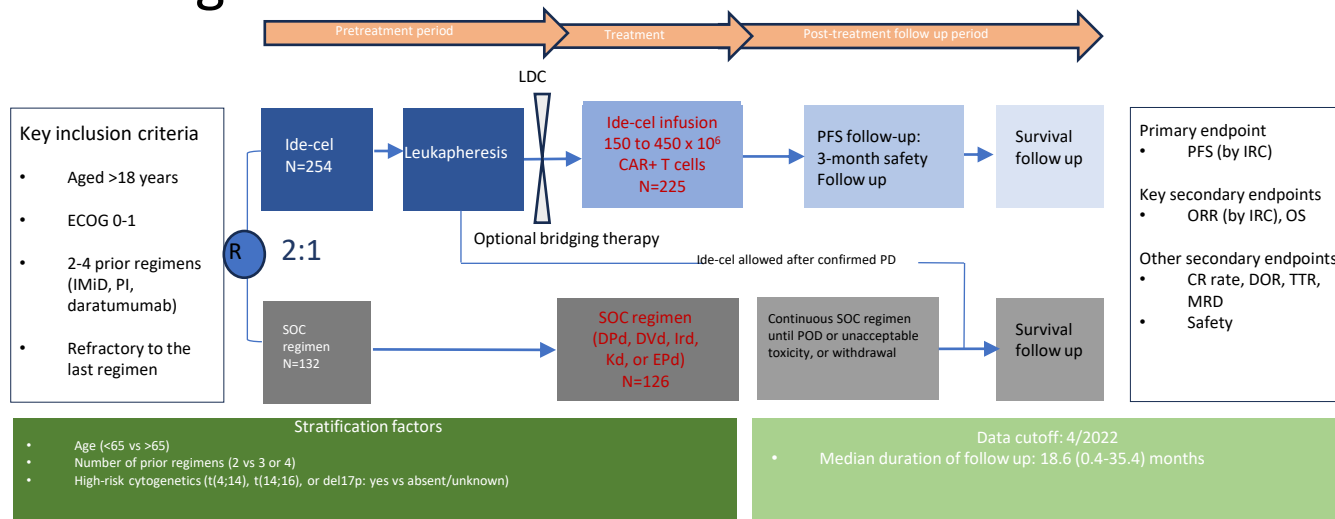
<sup>a</sup>One patient with AML also had MDS and a cytogenetic profile consistent with MDS (del120q [present before cilta-cel infusion], loss of 5q); another patient who died from AML had both prostate cancer and squamous cell carcinoma of the scalp. <sup>b</sup>Patient died from ascites unrelated to cilta-cel as assessed by the investigator due to noncirrhotic portal fibrosis and nonalcoholic steatosis that was present for many years preceding the study. AML, acute myelogenous leukemia; AEs, adverse events; CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; ICANS, immune effector cell-associated neurotoxicity syndrome; MDS, myelodysplastic syndrome; sCR, stringent complete response; SPM, secondary primary malignancies; TEAE, treatment-emergent AE

1. Berdeja JG, et al. *Lancet* 2021; 398:314-24. 2. Cohen AD, et al. *Blood Cancer J* 2022; 12:32.

CAR T-cell therapy  
in earlier lines



# Trial design

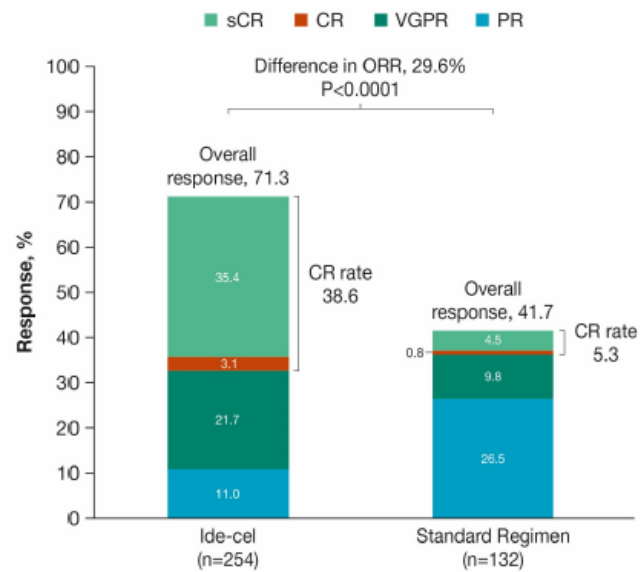


# Baseline characteristics

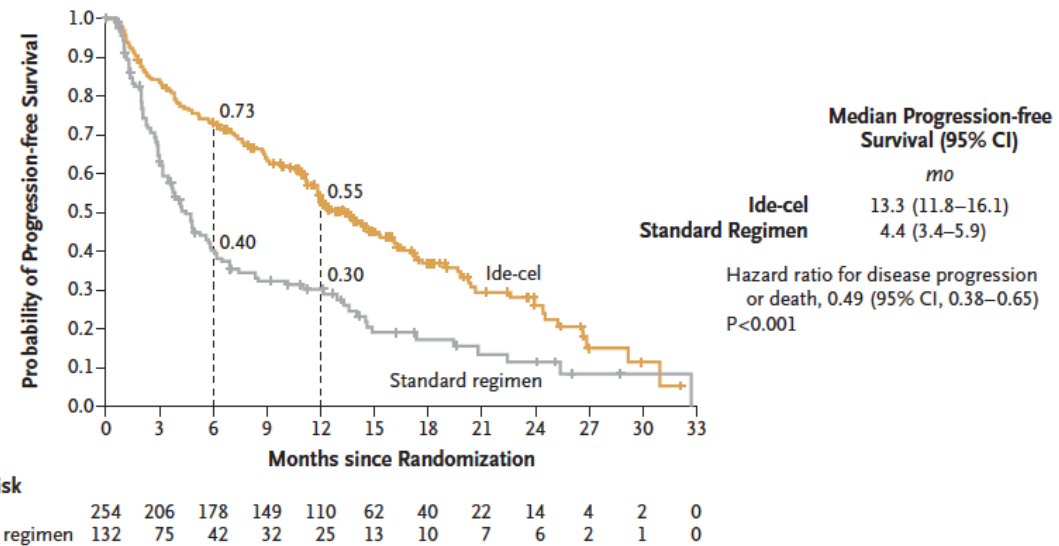
Median age	63 yrs
Median time since diagnosis	4.1 yrs
Median prior therapies	N=3
Triple-class refractoriness	66%
Daratumumab refractoriness	95%
High-risk cytogenetics	44%

Phase 3 KarMMa-3 study compared ide-cel vs SOC in R/R patients MM after 2-4 prior lines

# Response



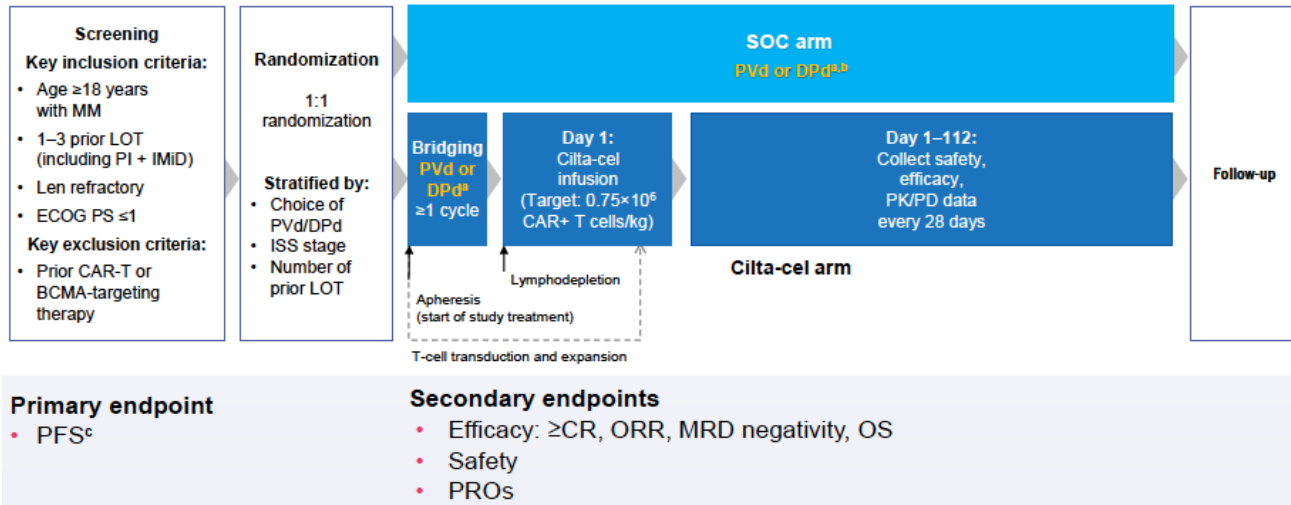
# PFS



Phase 3 KarMMa-3 study compared ide-cel vs SOC in R/R patients MM after 2-4 prior lines

# CARTITUDE-4: Cilta-cel vs DPd/PVd After 1-3 Lines

## Trial design

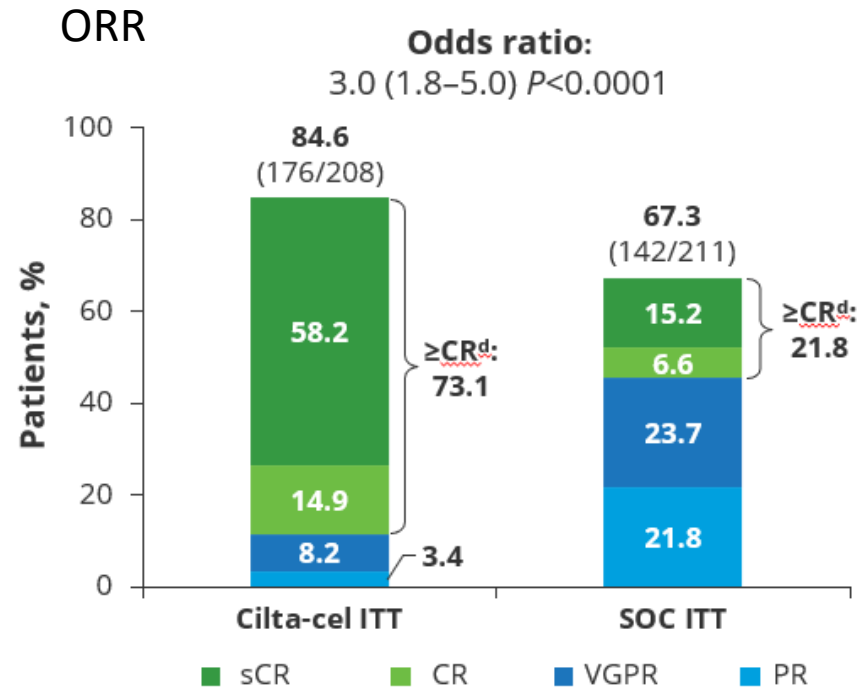


## Baseline characteristics

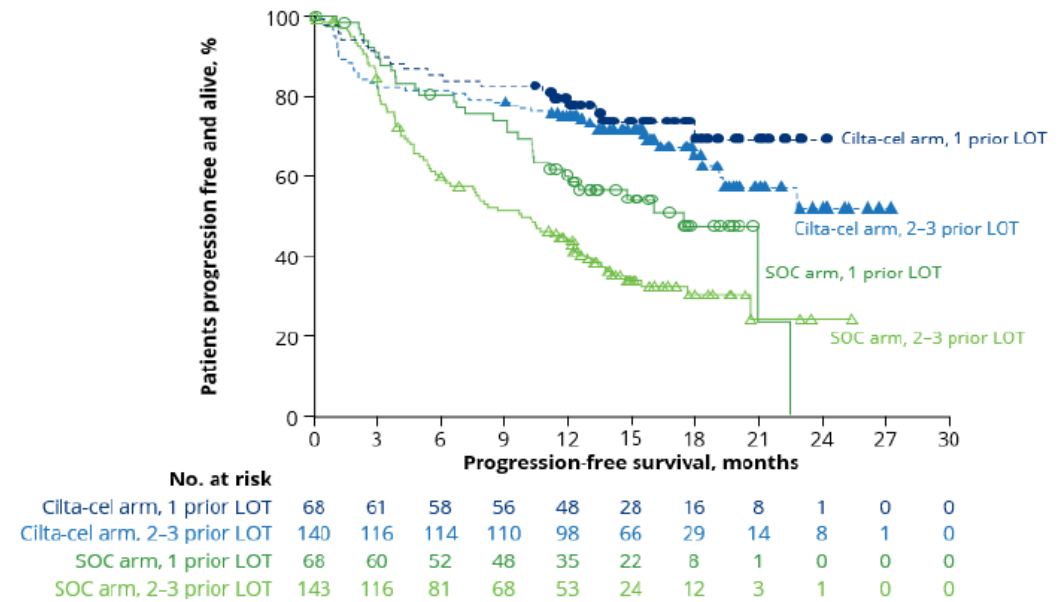
Median age	61.5 yrs
Median time since diagnosis	3 yrs
Median prior therapies	N=2
Triple-class refractoriness	14.4%
Daratumumab refractoriness	23.1%
High-risk cytogenetics	59.4%

Phase 3 CARTITUDE-4 compared cilta-cel vs SOC in R/R patients MM after 1-3 prior lines

# CARTITUDE-4: Response and PFS



**PFS by treatment and number of prior lines**



Phase 3 CARTITUDE-4 compared cilta-cel vs SOC in R/R patients MM after 1-3 prior lines



# KarMMa-3 / CARTITUDE-4: CRS and NT

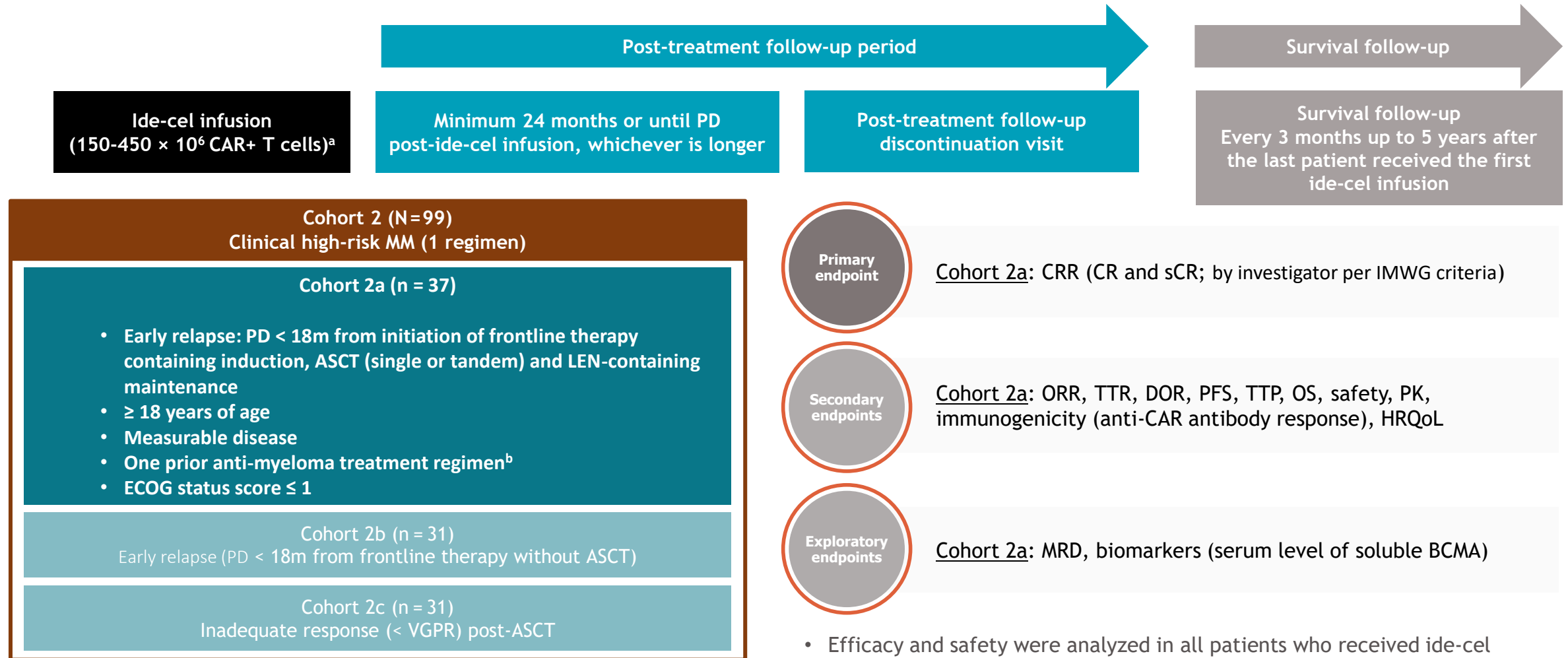
## KarmMMa-3

	Ide-cel (n = 225)
<b>CRS,<sup>a</sup> n (%)</b>	
Any grade	197 (88)
Grade 3/4	9 (4)
Grade 5	2 (1)
<b>Median (range) time to first onset, days<sup>b</sup></b>	1.0 (1.0–14.0)
<b>Median (range) duration, days</b>	3.5 (1.0–51.0)
<b>iiNT,<sup>c</sup> n (%)</b>	
Any grade	34 (15)
Grade 3/4	7 (3)
Grade 5	0
<b>Median (range) time to first onset, days<sup>b</sup></b>	3.0 (1.0–317.0)
<b>Median (range) duration, days</b>	2.0 (1.0–37.0)

## CARTITUDE-4

AEs, n (%)	As-treated patients (n=176)				
	Any grade	Grade 3/4	Median time to onset, days	Median duration, days	Resolved, n
CRS	134 (76.1)	2 (1.1)	8	3	134
Neurotoxicity <sup>a</sup>	36 (20.5)	5 (2.8)			
ICANS	8 (4.5)	0 <sup>b</sup>	10	2	8
Other <sup>c</sup>	30 (17.0)	4 (2.3)			
Cranial nerve palsy <sup>d</sup>	16 (9.1)	2 (1.1)	21	77	14
Peripheral neuropathy	5 (2.8)	1 (0.6)	63	201	3
MNT	1 (0.6)	0	85	–	0

# KarMMa-2 cohort 2 study design



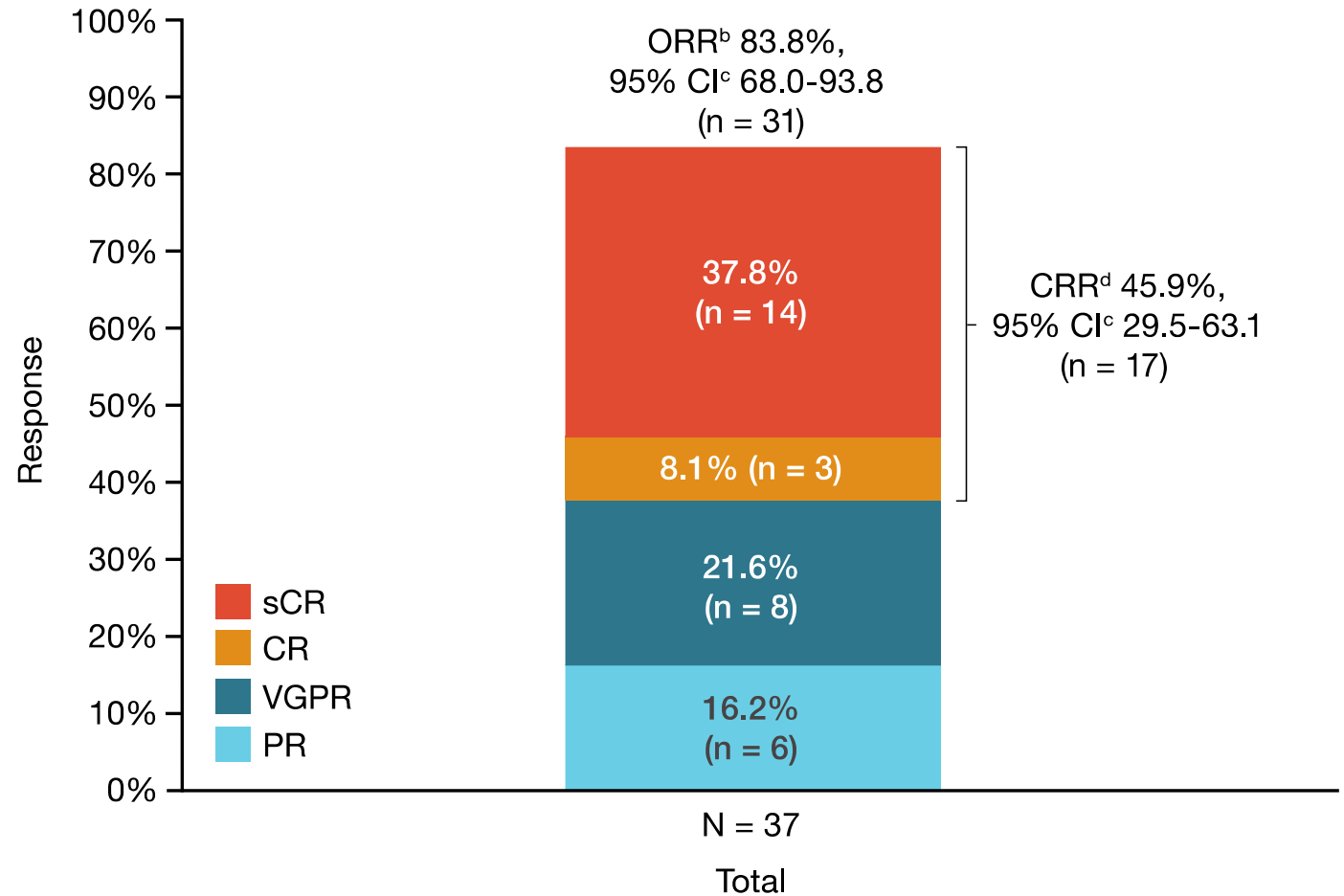
ClinicalTrials.gov Identifier: NCT03651128

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.

<sup>a</sup>After lymphodepletion (cyclophosphamide 300 mg/m<sup>2</sup> + fludarabine 30 mg/m<sup>2</sup> × 3), patients received a single infusion of ide-cel at a range of 150-450 × 10<sup>6</sup> CAR+ T cells (up to an additional 20%; ≥ 20% considered over the protocol-specified doses). <sup>b</sup>Induction with or without HSCT and with or without maintenance therapy is considered a single regimen

# Best overall response

- Primary endpoint was met, with 45.9% achieving  $\geq$  CR ( $P < 0.0001$ )
- ORR was 83.8% (95% CI 68.0-93.8)
- Median time to first response<sup>a</sup> was 1.0 month (range 0.9-2.9 months)

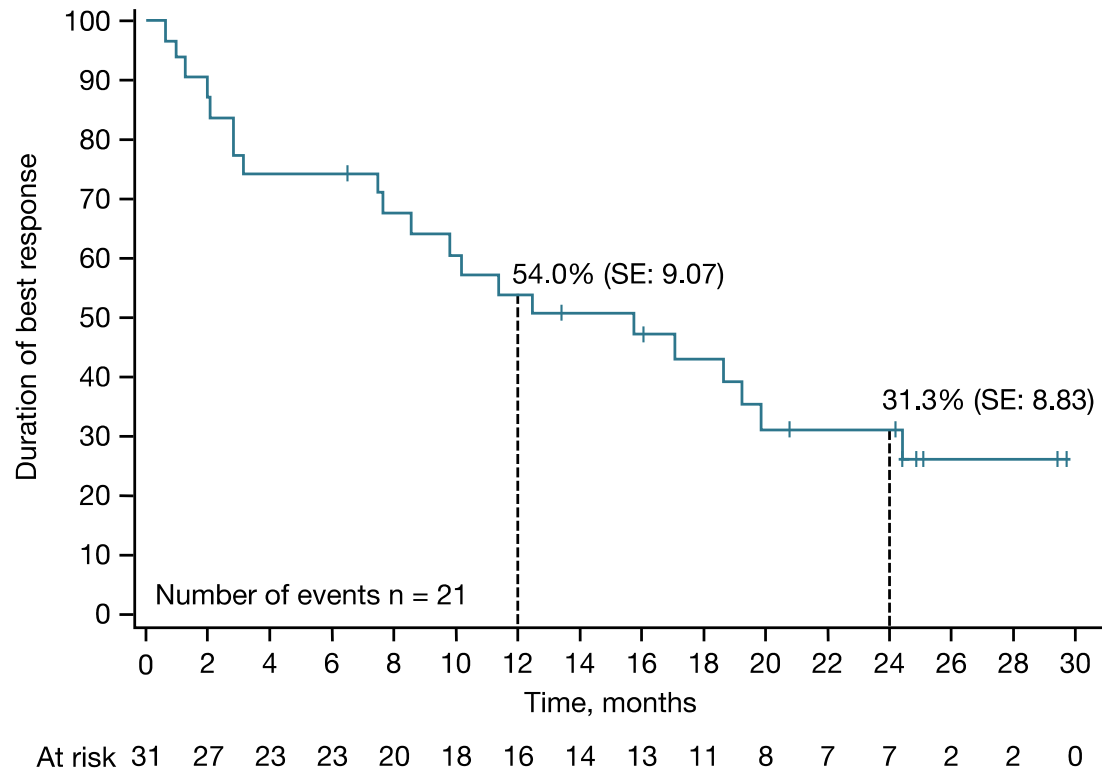


The primary efficacy endpoint was the complete response (CR) rate (proportion of patients who achieved CR or sCR); the primary analysis was planned for at least 6 months after the last patient received ide-cel infusion.

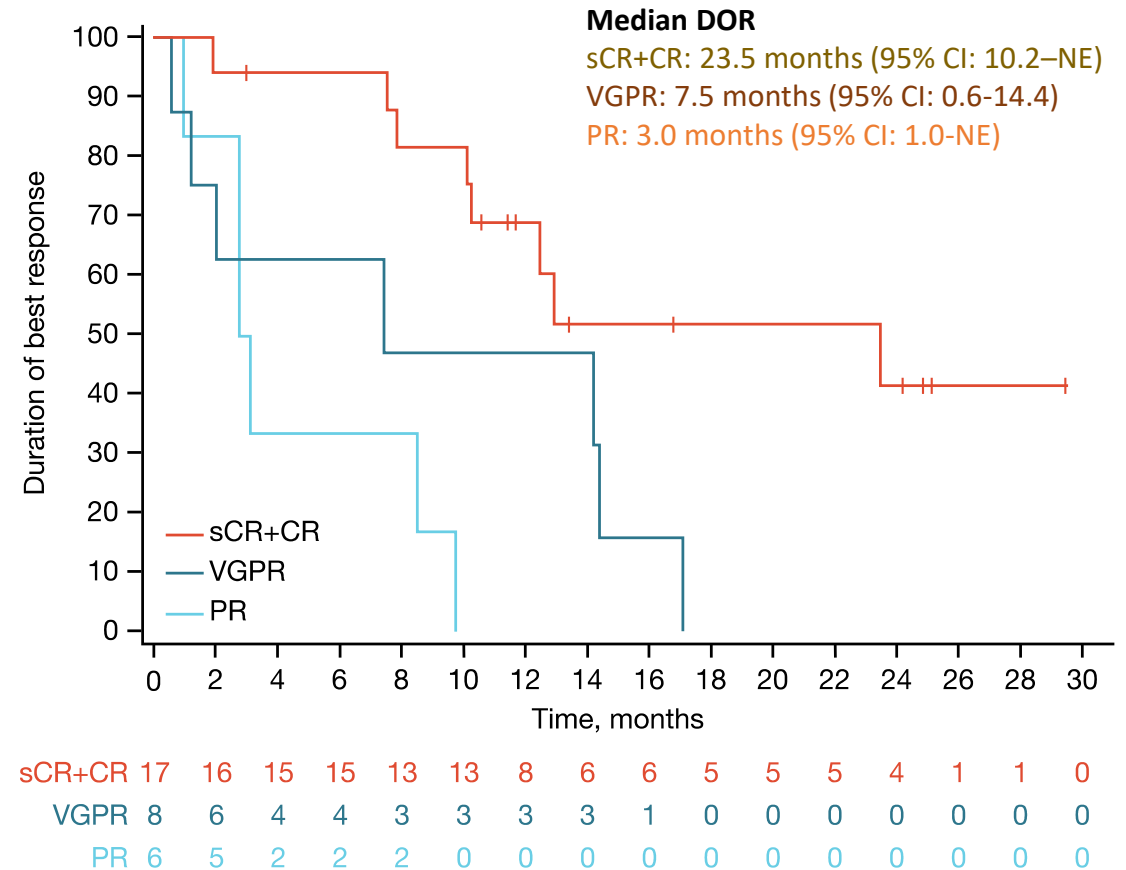
<sup>a</sup>Response defined as PR or better based on IMWG Criteria by investigator assessment; measured from infusion. <sup>b</sup>Patients with PR or better (2 patients had minimal response; 4 had stable disease and 0 had PD). <sup>c</sup>Clopper-Pearson CI. <sup>d</sup>Patients with sCR or CR.

# Duration of best response<sup>a</sup>

- Median duration of best response in all patients who responded was 15.7 months (95% CI: 7.6–19.8)



- Median duration of best response in patients who achieved  $\geq$  CR was 23.5 months (95% CI: 10.2–NE)

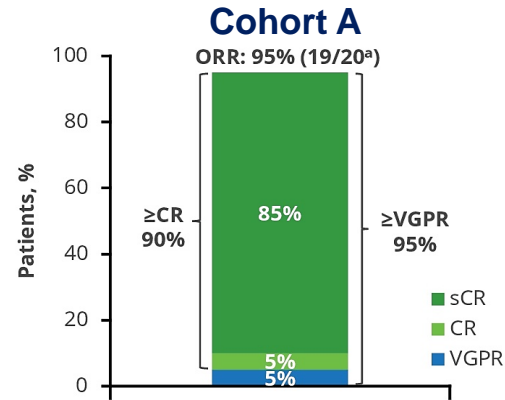
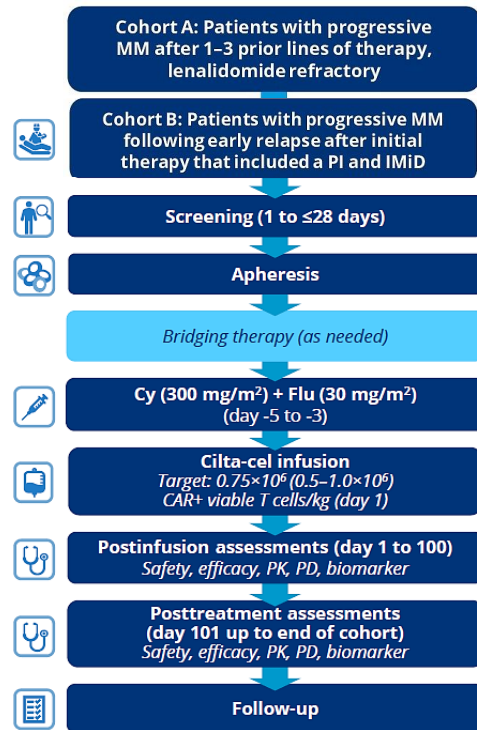


NE, not evaluable; SE, standard deviation.

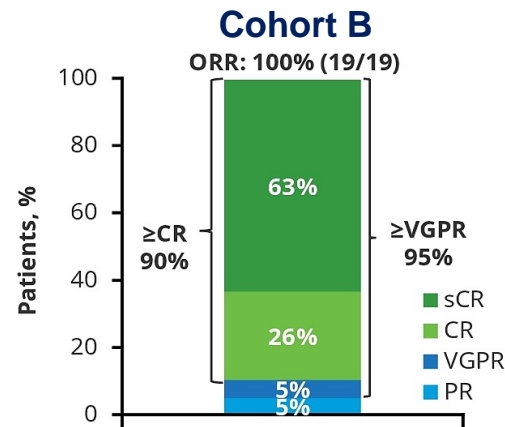
<sup>a</sup>Responders only, based on IMWG criteria: investigator assessment



# Using CAR T-cell therapy at earlier lines of therapy: CARTITUDE-2



<sup>a</sup>One patient demonstrated a minimal response.  
sCR, stringent CR



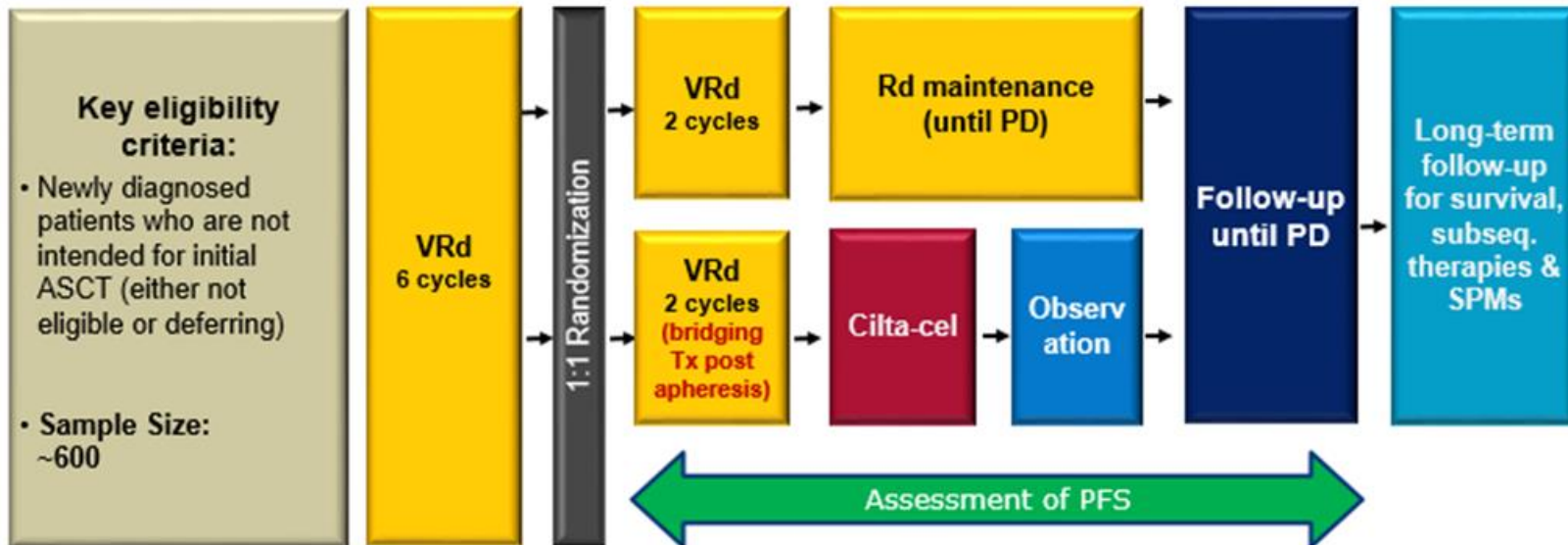
CR, complete response; CRS, cytokine release syndrome; Cy, cytarabine; Flu, fludarabine; ORR, overall response rate; PD, pharmacodynamics; PK, pharmacokinetics; PR, partial response; sCR, stringent CR; VGPR, very good partial response

AEs ≥20%, n (%)	N=20	
	Any Grade	Grade 3/4
<b>Hematologic</b>		
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)
<b>CAR-T-related AEs</b>		
CRS	19 (95)	2 (10)
Neurotoxicity	6 (30)	1 (5)
ICANS	3 (15)	0
Other	3 (15) <sup>a</sup>	1 (5)

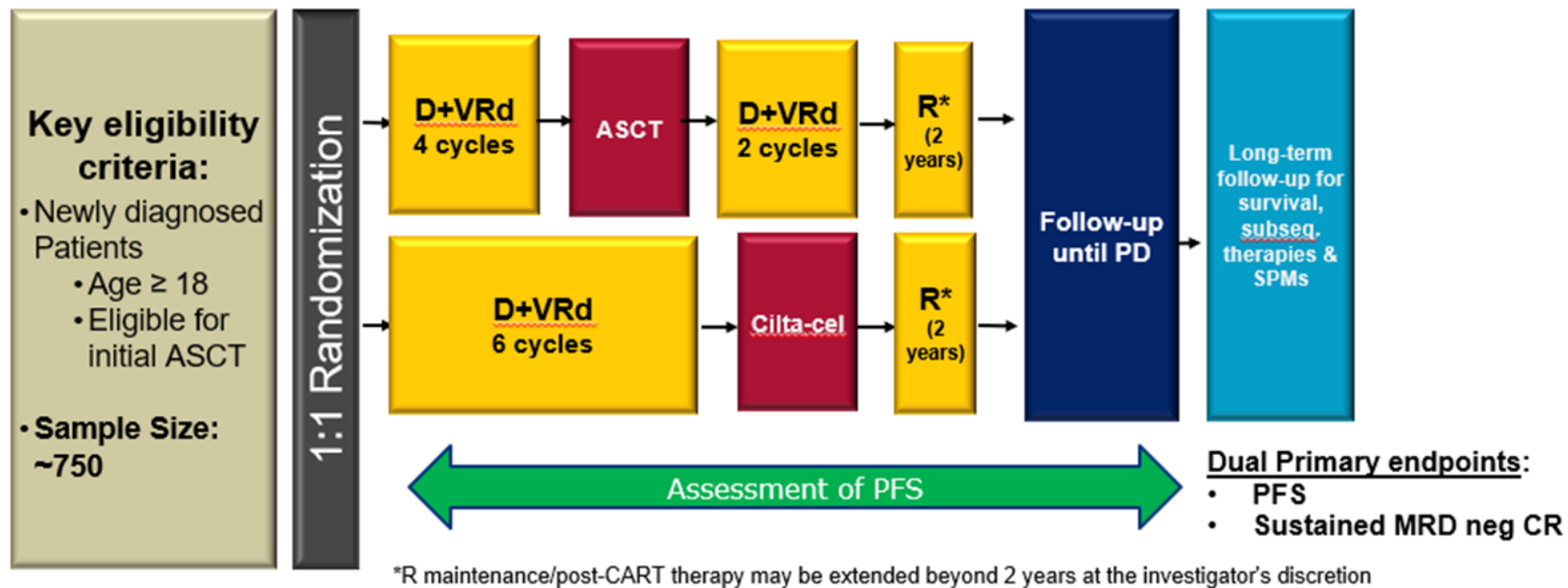
<sup>a</sup>One patient had peripheral sensorimotor neuropathy, one had anosmia and dysgeusia, and one had facial paralysis.

AEs ≥20%, n (%)	N=19	
	Any Grade	Grade 3/4
<b>Hematologic</b>		
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)
<b>CAR-T-related AEs</b>		
CRS	16 (84)	1 (5)
Neurotoxicity	5 (26)	1 (5)
ICANS	1 (5)	0
Other	4 (21)	1 (5)
Parkinsonism	1 (5)	1 (5)

# CARTITUDE-5: Randomized, phase 3 in NDMM, not intended for transplant



# CARTITUDE-6: Randomized, phase 3 in NDMM, transplant eligible

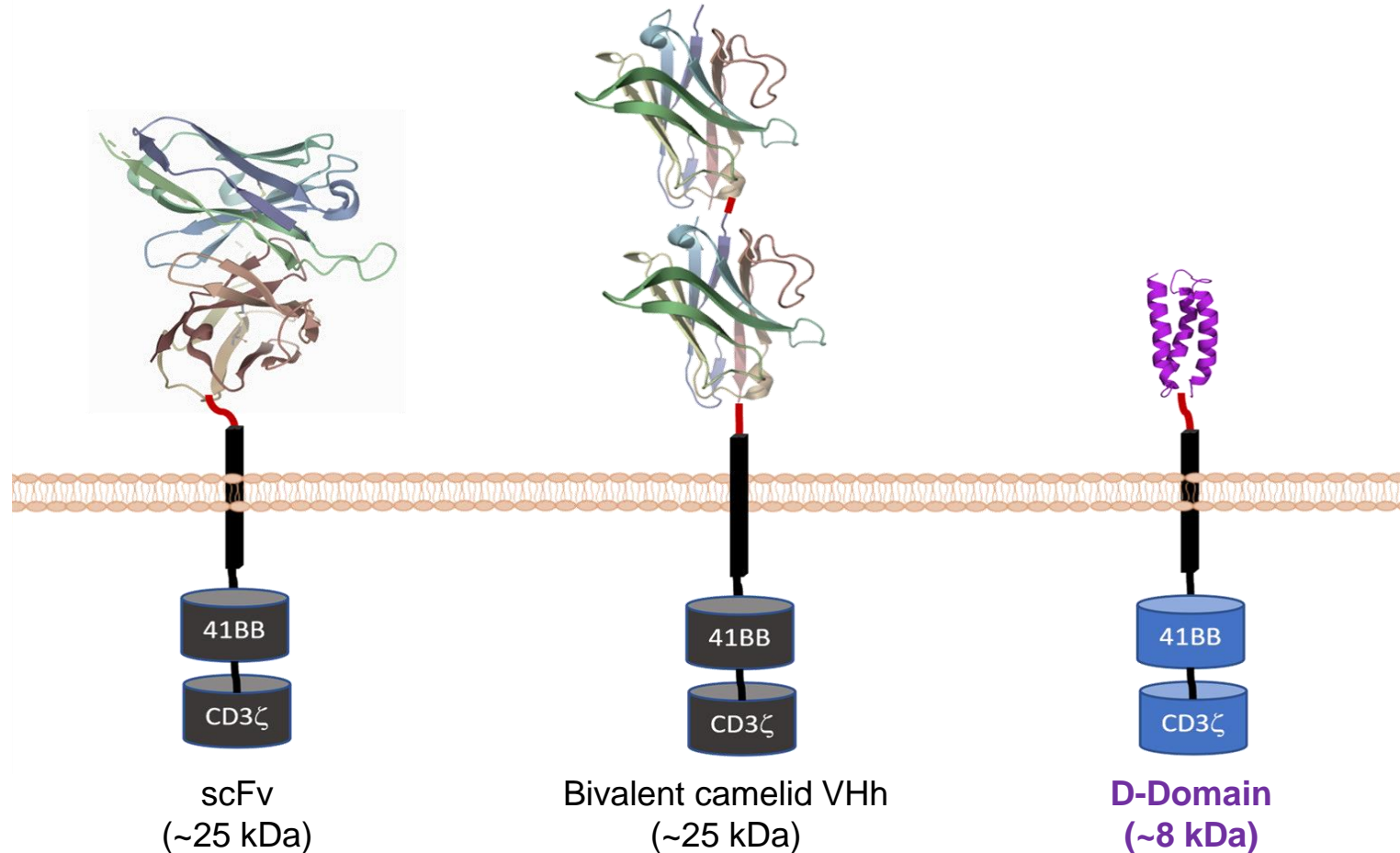


# Emerging CAR-T therapies in R/R myeloma



# Anitocabtagene autoleucl (anito-cel/CART-ddBCMA)

Autologous BCMA-directed CAR T-cell therapy using a novel, D-Domain binder<sup>1</sup>



## D-Domain Attributes: Non-Antibody Derived Synthetic Protein<sup>1,2</sup>

Size

Small D-Domain construct facilitates high transduction efficiency, CAR positivity, and CAR density on the T-cell surface<sup>2-4</sup>

Stability

Rapid D-Domain folding, lack of disulfide bonds, and a hydrophobic core enables stability at and beyond physiologic conditions<sup>5,6</sup>

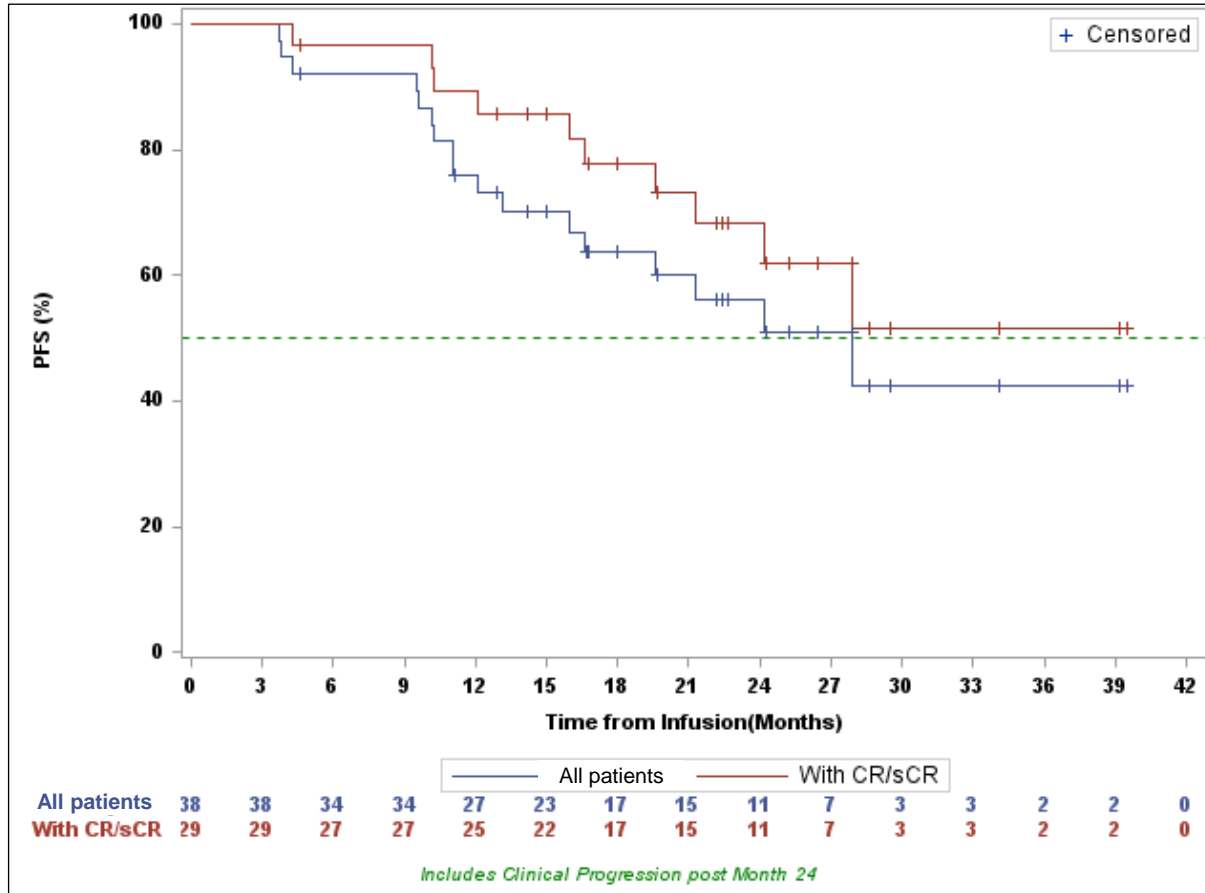
Structure

Due to small size and compact structure, D-Domain CARs have a low risk of tonic signaling<sup>6</sup>

<sup>1</sup>Rotte, et al. *Immuno-Oncology Insights* 2022; 3(1), 13–24; <sup>2</sup>Frigault, et al. *Blood Adv.* 2023; 7(5):768-777; <sup>3</sup>Cante-Barrett, et al. *BMC Res. Notes* 2016; 9:13; <sup>4</sup>Buonato, et al. *Mol. Cancer Ther.* 2022; 21(7):1171-1183; <sup>5</sup>Zhu, et al. *Proc. Nat. Acad. Sci.* 2003; 100(26): 15486-15491; <sup>6</sup>Qin, et al. *Mol. Ther.* 2019; 27(7): 1262-1274.

# Anito-cel Phase 1 Results: All Patients, CR/sCR Patients

Median Follow-Up: All Patients 26.5-mo. [14-44]; CR/sCR Patients 26.5-mo. [15-44]



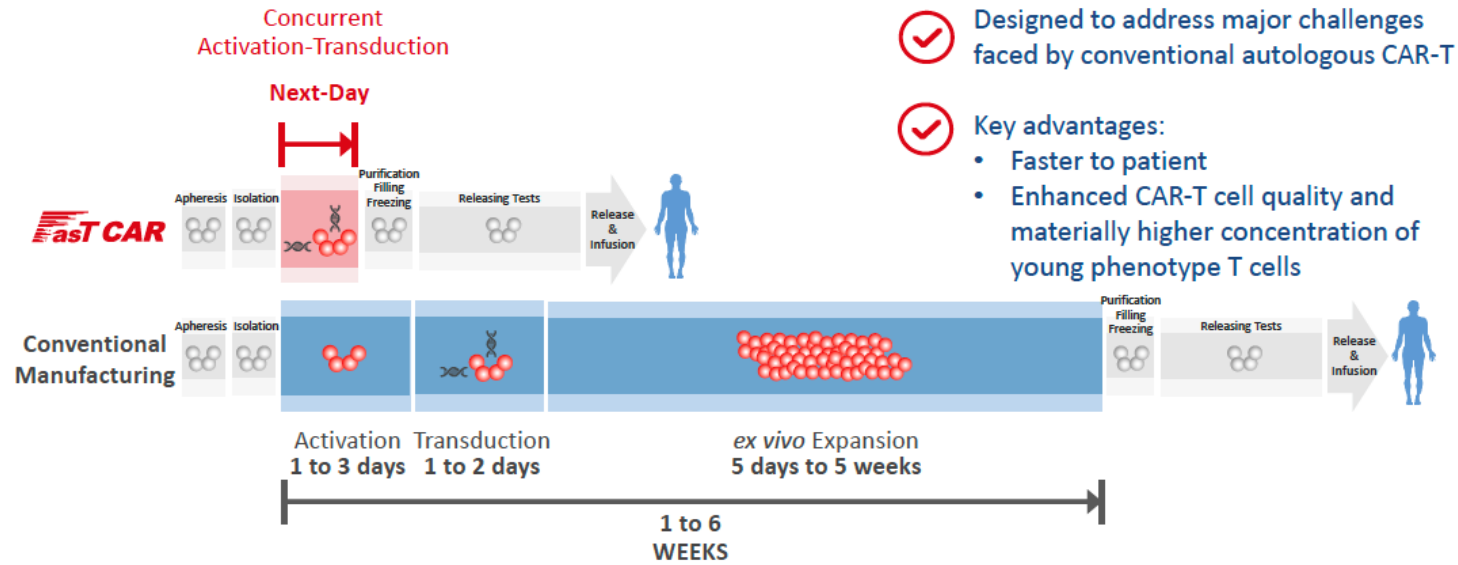
	Time (months)	PFS Estimate (%)	95% Confidence Interval (%)
All Patients (n = 38)	6	92.1	77.5, 97.4
	12	75.9	58.7, 86.6
	18	63.7	45.7, 77.2
	24	56.0	37.3, 71.1

- Median PFS not reached for all patients (n=38)
- Median PFS not reached for CR/sCR patients (n=29, 76%)
- 89% (n=25/28) of evaluable\* patients MRD negative at minimum of 10<sup>-5</sup> sensitivity

Note: Data cut-off October 15, 2023; \* Evaluable patients had identifiable malignant clone in the baseline bone marrow aspirate

# GC012F: FasTCAR Cuts Manufacturing Time to Next-Day

Combines Activation & Transduction Steps, and Eliminates Need for *ex vivo* Expansion



## GC012F: Study Design

Single-center, open label, single-arm IIT<sup>1</sup> study (N=22)

FPI August 2021

Patients continue to be assessed for response

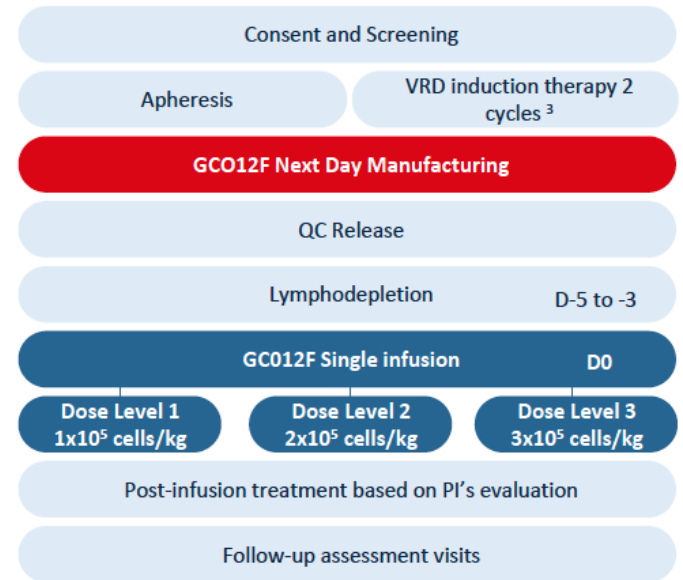
Data cut-off Oct 1<sup>st</sup> 2023

### Endpoints

- Primary: Adverse Events
- Secondary: ORR, BOR, DOR, MRD; PK/PD

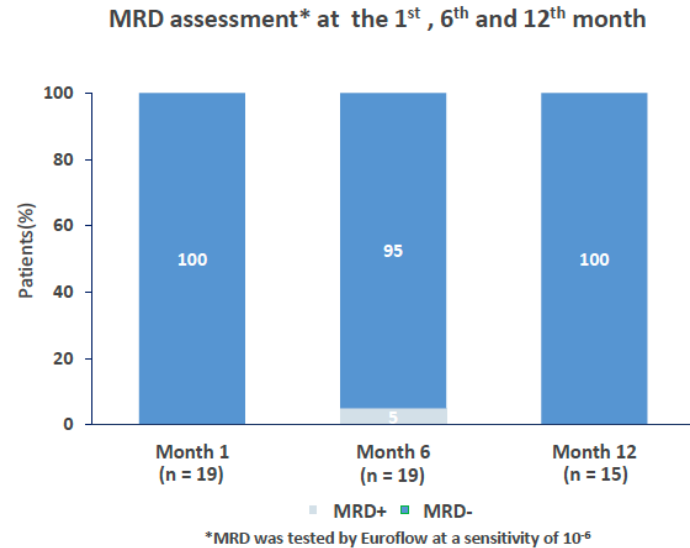
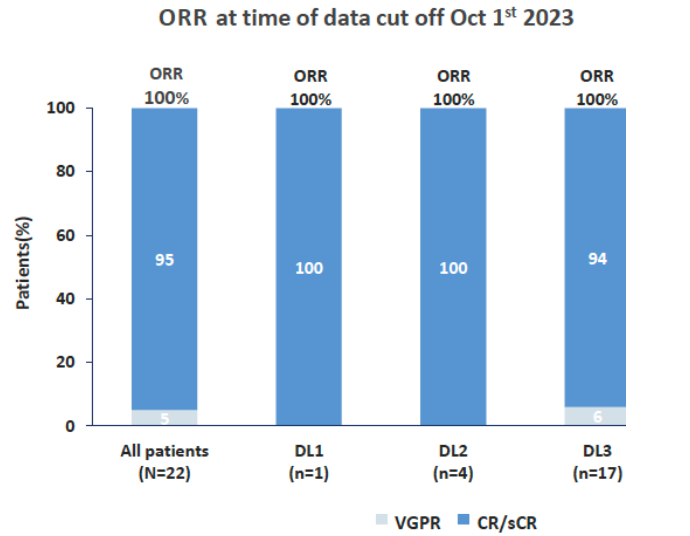
### Key eligibility criteria

- High-risk<sup>2</sup>, transplant eligible, newly-diagnosed multiple myeloma (NDMM)
- Measurable disease
- 18-70 years old
- ECOG 0-2
- Expected survival  $\geq 3$  months

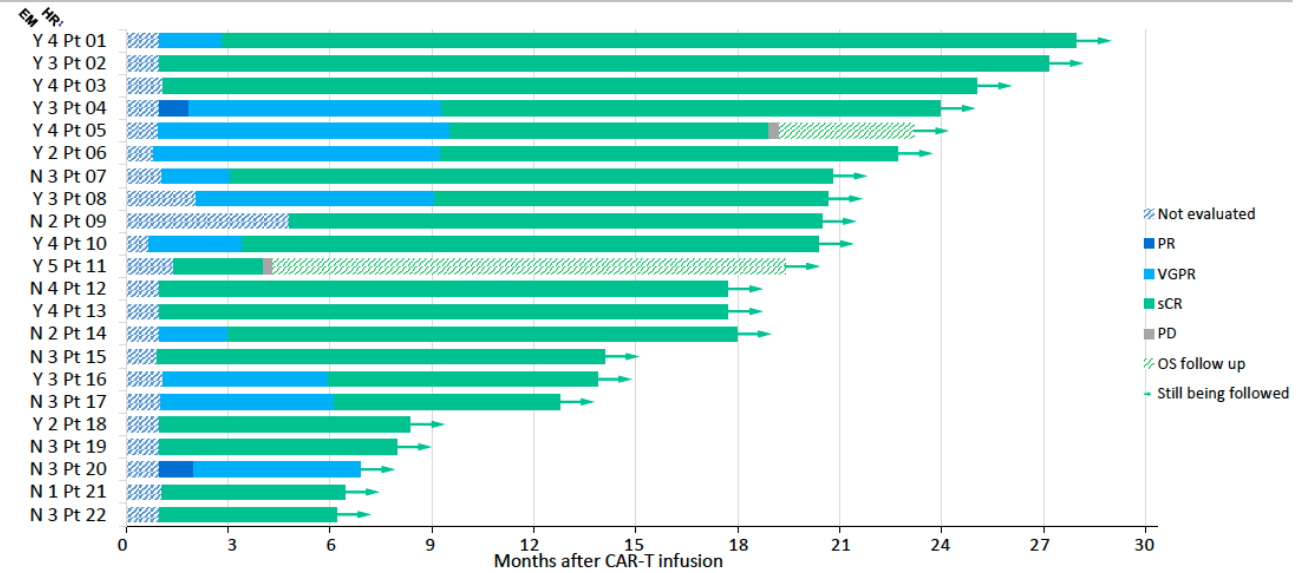


# Efficacy of GC012F

## GC012F: Efficacy Assessment -



## GC012F: Efficacy Assessment – Swimmer plot



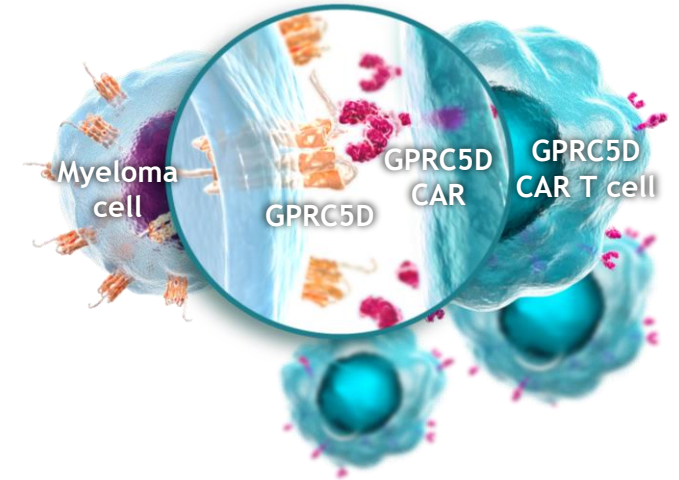
<sup>†</sup>HR: High-risk factors include: a) R-ISS stage II or III; b) High-risk cytogenetics: del17p, t(4;14), t(14;16), or 1q21 ≥4 copies; c) Extramedullary disease; d) IgD or IgE subtype; e) High-risk definition according to mSMART3.0; f) LDH > the upper limit of normal.

What's next?

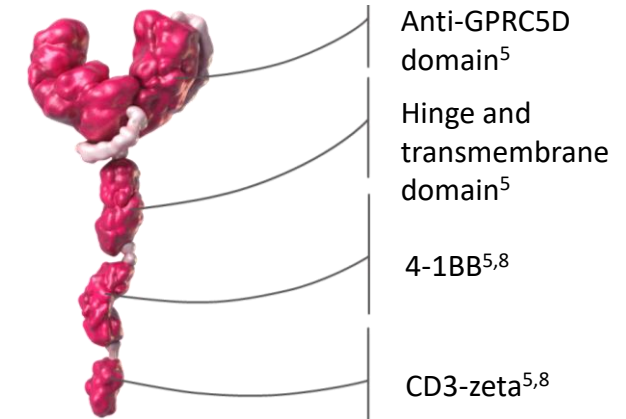
# BMS-986393: a GPRC5D autologous CAR T-cell therapy

- GPRC5D is an emerging and validated target in MM, beyond IMiDs<sup>®</sup>, PIs, anti-CD38 antibodies, and BCMA-targeted therapies<sup>1-5</sup>
- BMS-986393 (CC-95266) is a potential first-in-class autologous CAR T-cell therapy targeting GPRC5D<sup>5</sup> that has been granted FDA RMAT designation for RRMM
- In the phase 1 CC-95266-MM-001 study of BMS-986393 in patients with RRMM (NCT04674813):
  - 150 × 10<sup>6</sup> CAR T cells has been selected as the BMS-986393 RP2D based on the totality of data<sup>6,7</sup>
  - High overall response rates, deepening of responses, and encouraging duration of response continue to be demonstrated in updated data

## BMS-986393 mechanism of action



## GPRC5D-targeted CAR construct



BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor; GPRC5D, G protein-coupled receptor class C group 5 member D; IMiD, immunomodulatory drug; MM, multiple myeloma; PI, proteasome inhibitor; RMAT, regenerative medicine advanced therapy; RP2D, recommended phase 2 dose; RRMM, relapsed and/or refractory multiple myeloma.

1. Berdeja JG, et al. *Lancet* 2021;398:314-324. 2. Munshi NC, et al. *N Engl J Med* 2021;384:705-716. 3. Rodriguez-Otero P, et al. *N Engl J Med* 2023;388:1002-1014.

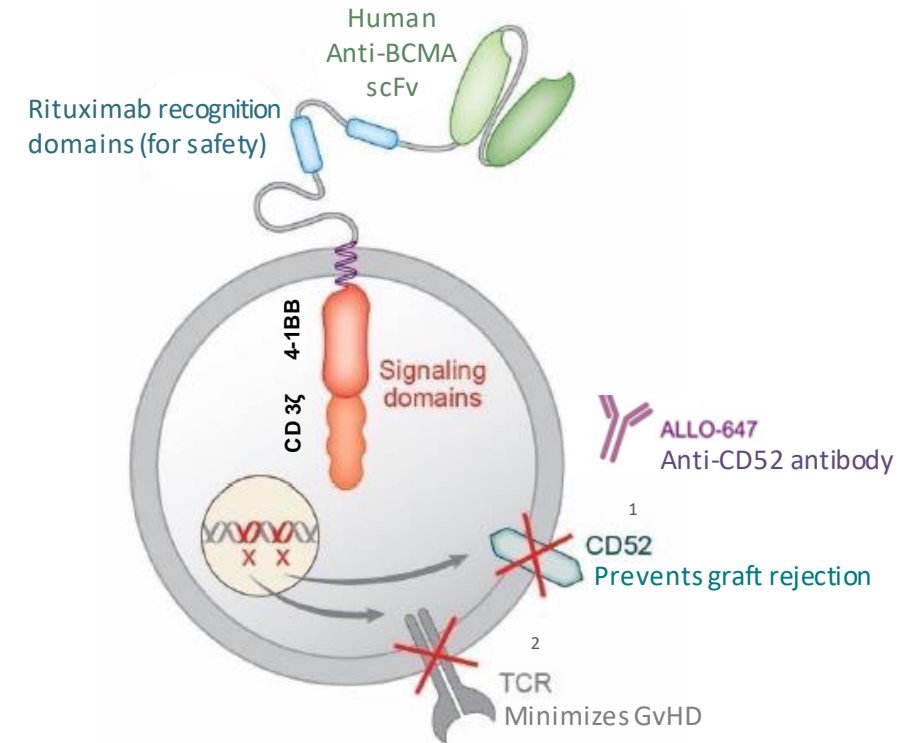
4. Mailankody S, et al. *N Engl J Med* 2022;387:1196-1206. 5. Smith EL, et al. *Sci Transl Med* 2019;11:eaau7746. 6. Bal S, et al. *Blood* 2022;140(suppl 1):883.

7. Bal S, et al. *Hemasphere* 2023;7(suppl):e9863287. 8. Song D-G, et al. *Cancer Res* 2011;71:4617-4627.

Bal S, et al. ASH 2023 [Presentation 219]

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

- BCMA cell therapy has demonstrated unprecedented efficacy, but is not readily available to all patients
- Allogeneic chimeric antigen receptor (CAR) T cell therapy has the potential for all eligible patients to receive therapy on demand and supports re-dosing
- ALLO-715 (anti-BCMA) is an allogeneic CAR T cell product utilizing TALEN®\* gene editing specifically designed to
  - Disrupt TCR $\alpha$  constant gene – to reduce the risk graft-versus-host disease (GvHD)
  - Edit CD52 gene – permits use of ALLO-647 (a humanized anti-CD5 mAb) to selectively deplete host T cells while protecting donor cel



\*TALEN® gene editing is a technology pioneered and controlled by Cellectis.

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





# FDA warns of secondary cancer risk tied to CAR-T therapies that treat cancer



By [Jacqueline Howard](#), CNN

🕒 5 minute read · Updated 4:36 PM EST, Wed January 24, 2024



## MORE FROM CNN



Global cancer cases will jump 77% by 2050, WHO reports

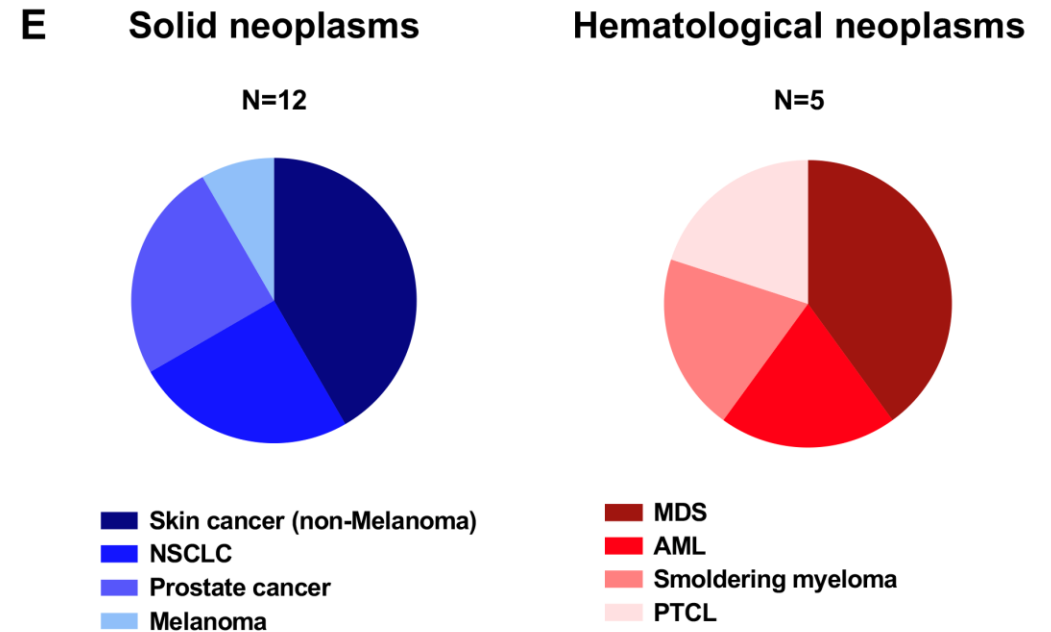
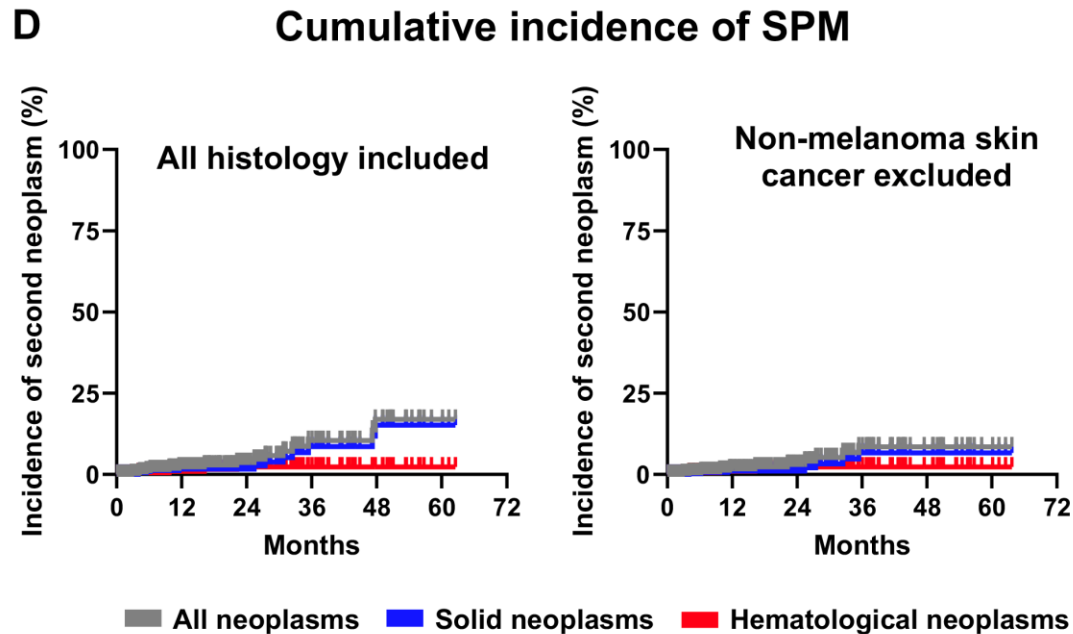


FDA looking into reports of hair loss, suicidal thoughts



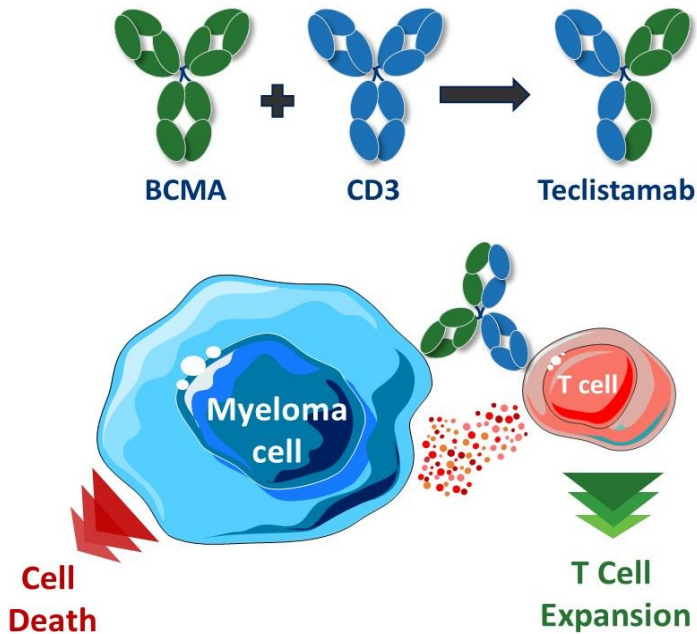
FDA urges consumers not to buy tianep

# Second Primary Cancers after CAR T Cells



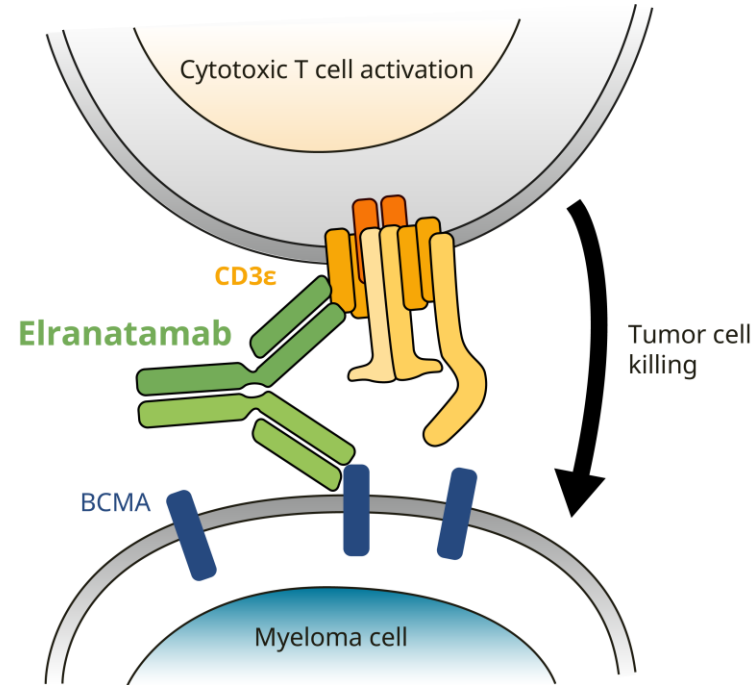
# Teclistamab

Oct 2022



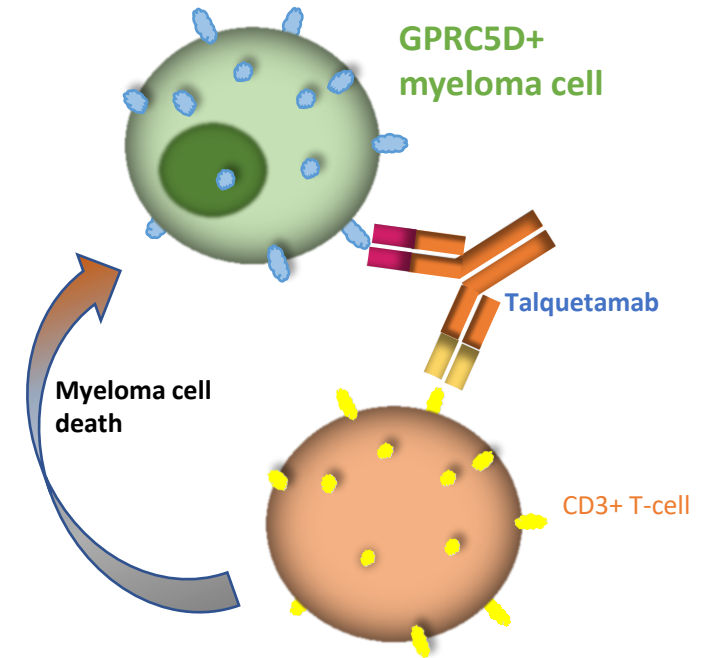
# Elranatamab

Aug 2023



# Talquetamab

Aug 2023



## \*\*FDA Label:

- Four Prior Lines of Therapy
- Previously treated with IMiD, PI and anti-CD38 monoclonal antibody

# Teclistamab: MajesTEC-1 in relapsed/refractory myeloma

## Eligibility

≥3 prior lines

Prior PI, IMiD, and anti-CD38 therapy

No prior BCMA therapy

## Treatment

Step-up doses, subcutaneous: 0.06 and 0.3 mg/kg in week 1

1.5 mg/kg sc weekly

48 hour hospitalization after step up doses and first full dose to monitor for CRS

Step up dosing to mitigate risk of severe CRS

CRS generally observed during step up and first full doses of teclistamab

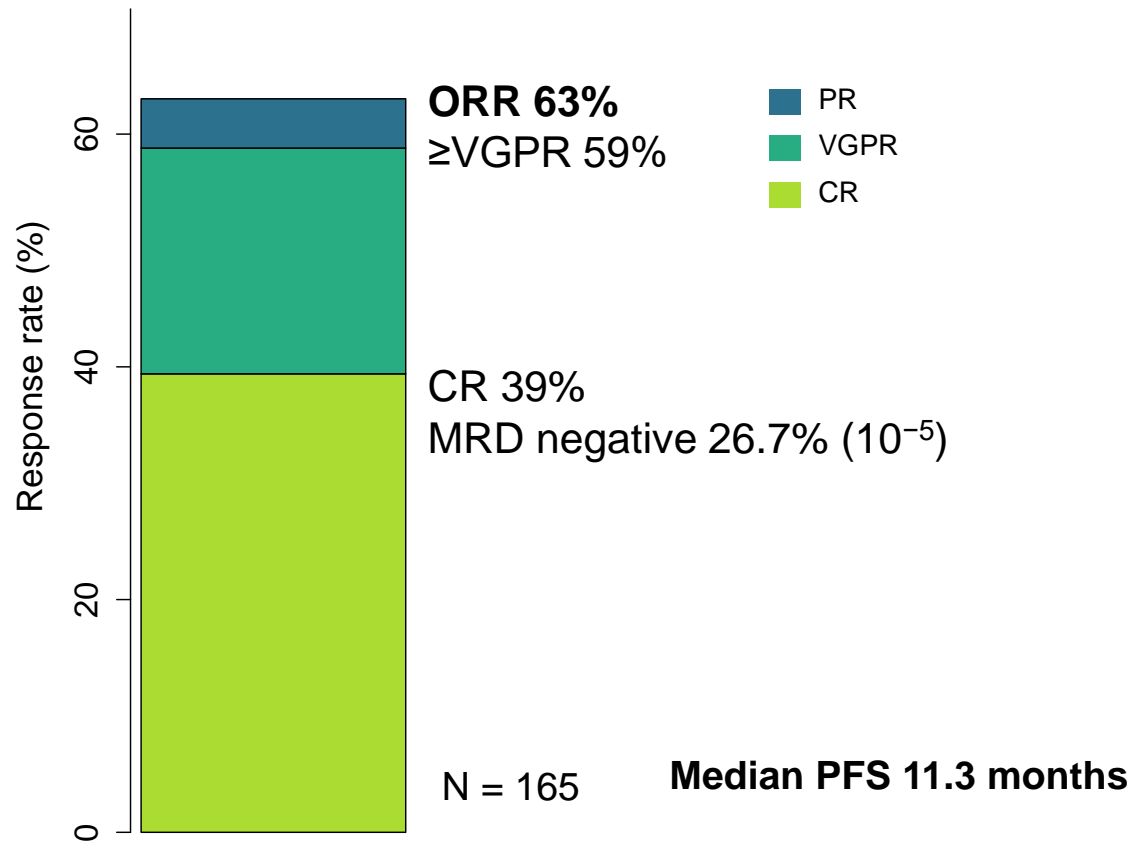
Subcutaneous injection: greater convenience and may delay CRS due to more gradual absorption (trial initially used iv route before moving to sc route)

## Patient demographics

Treatment history	N = 165
Prior lines of therapy, median (range)	5 (2-14)
Triple-class exposed   refractory	100%   77.6%
Penta-drug exposed   refractory	70.3%   30.3%
Refractory to last line of therapy	89.7%



# Teclistamab continued



Belantamab mafodotin, ORR 31%, median PFS 2.9 months  
Lonial S et al., *Lancet Oncol* 2019

Promising ORR 63% and median PFS 11.3 months in triple-class treated patients in an off-the-shelf treatment, requiring monitoring for CRS (72.1% of patients)

Parameter	N = 165
<b>Cytokine release syndrome</b>	
Any CRS	72.1%
Grade 1	50.3%
Grade 2	21.2%
Grade 3	0.6%
≥2 CRS events	32.7%
Time to onset, median (range)	2 (1-6)
Tocilizumab	36.4%
Supplemental oxygen	12.7%
Corticosteroids	8.5%
Single vasopressor	0.6%
<b>Neurotoxicity</b>	
Headache	8.5%
ICANS	3%

CRS in cycle 2+ 3.6%

Among patients with CRS and times recorded (N = 59), median time to CRS was 29 hours (range 4-72) after step up dose 1 and 31 hours (range 9-72) after step up dose 2

## Adverse events related to infection

Grade 3-4 infections, 44.8%

123 patients, 74.5% had hypogammaglobulinemia

65 of these patients received IVIG at physician discretion

PCP pneumonia: 6 patients

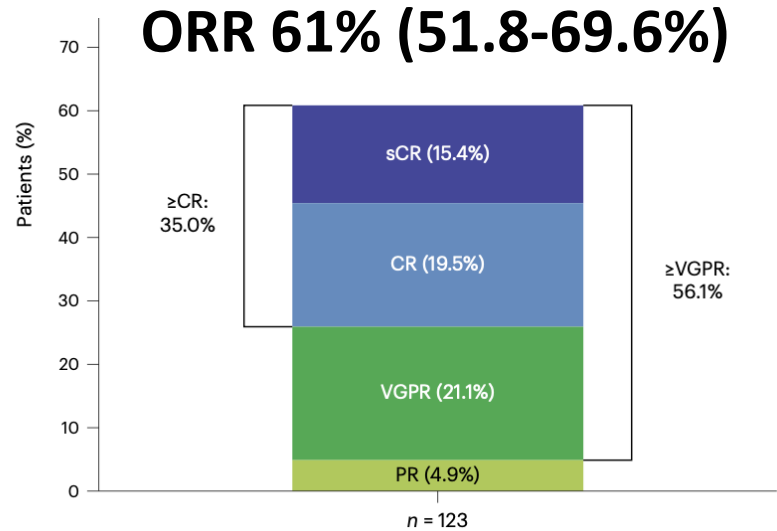
COVID19 infections: 24 patients (includes 12 deaths)

*Trial enrolled patients between March 2020 and August 2021*

# Elranatamab, 2<sup>nd</sup> anti-BCMA bispecific antibody approved (Aug 2023)

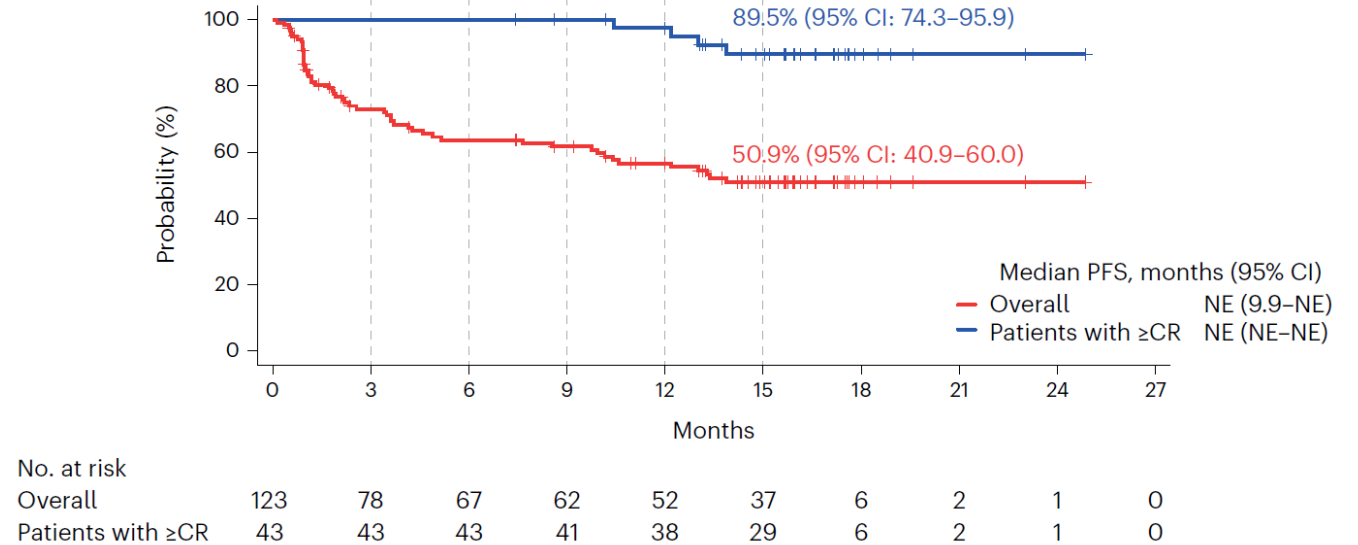
## MagnetisMM-3

Phase 2 study in triple class refractory patients  
Cohort A (N = 123), BCMA naive



## PFS at 15 months, 50.9%

**b**



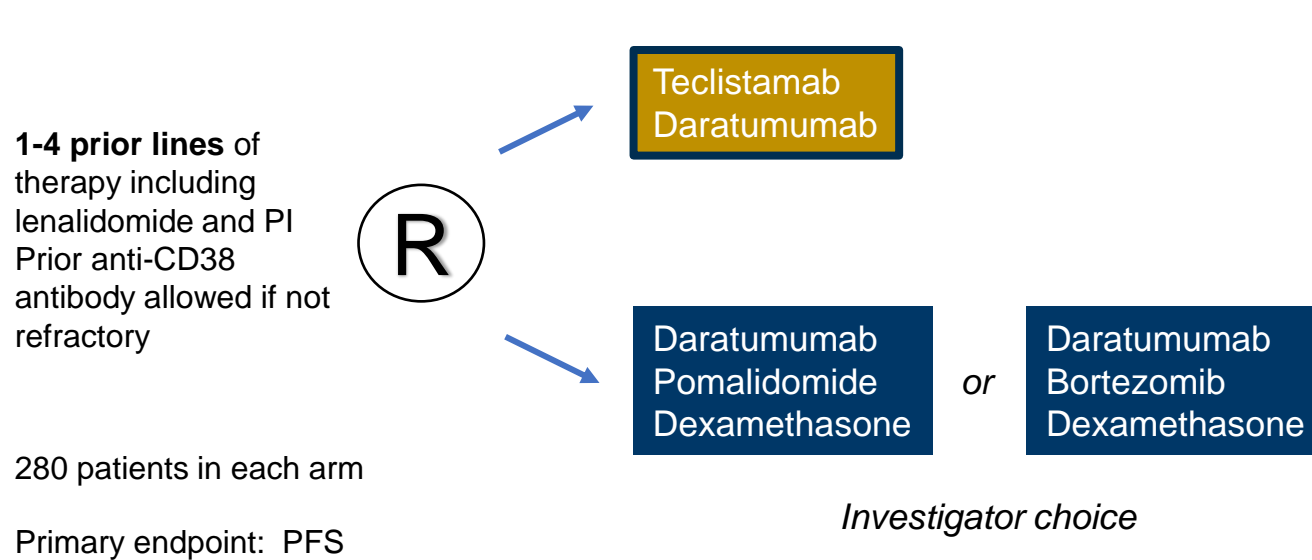
Lesokhin AM et al., *Nat Med* 2023

# Randomized phase III anti-BCMA bispecific antibody trials, in progress

## 1-4 prior lines of therapy

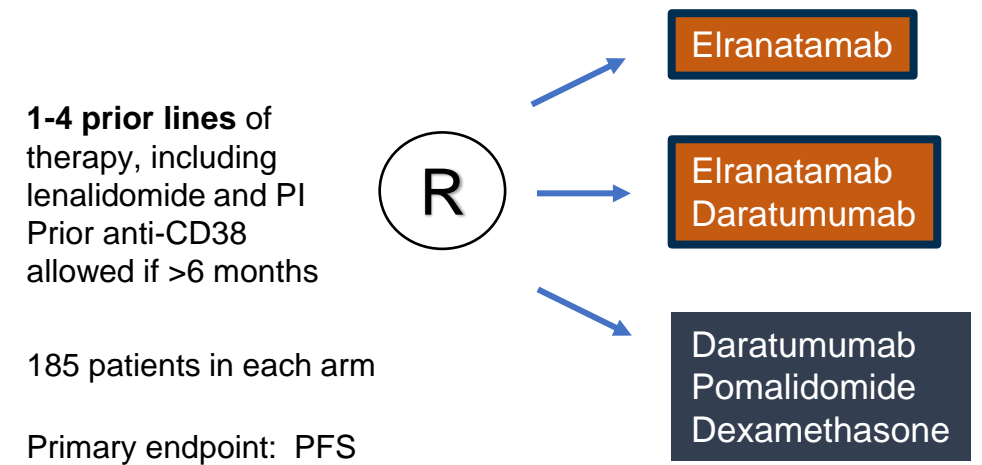
### MajesTEC-3. Teclistamab

Adapted from Mateos M-V et al., ASCO 2022



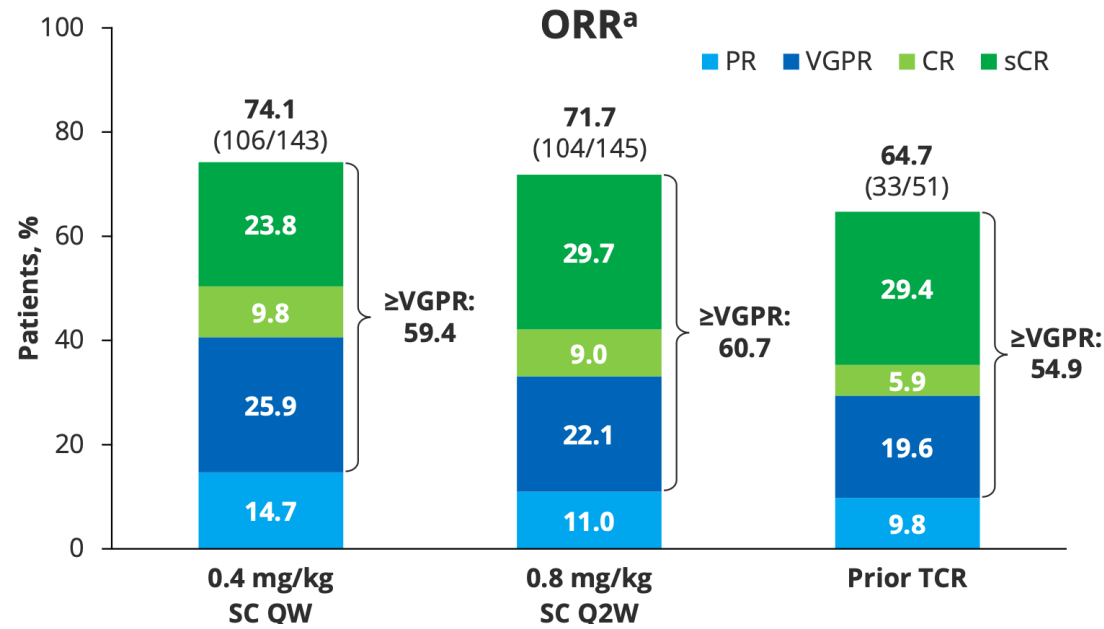
### MagnetisMM-5. Elranatamab

Adapted from Grosicki S et al., ASCO 2022





# Talquetamab: MonumenTAL-1



	0.4 mg/kg SC qW N = 143	0.8 mg/kg SC q2W N = 145	Prior TCR N = 151
Triple class exp   refractory	100%   74%	100%   69%	100   84%
BCMA	0%	0%	100%
ORR	74%	72%	65%
12 m PFS	34.9%	54.4%	38.1%
12 m OS	76.4%	77.4%	62.9%

Prior TCR = CAR T-cells (N = 36) and prior bispecific antibody (N = 18); patients were on either dosing schedule

## Dysgeusia, skin, and nail changes are notable adverse events with anti-GPRC5D therapy

MonumenTAL-1

Less infections than with  
e.g. teclistamab



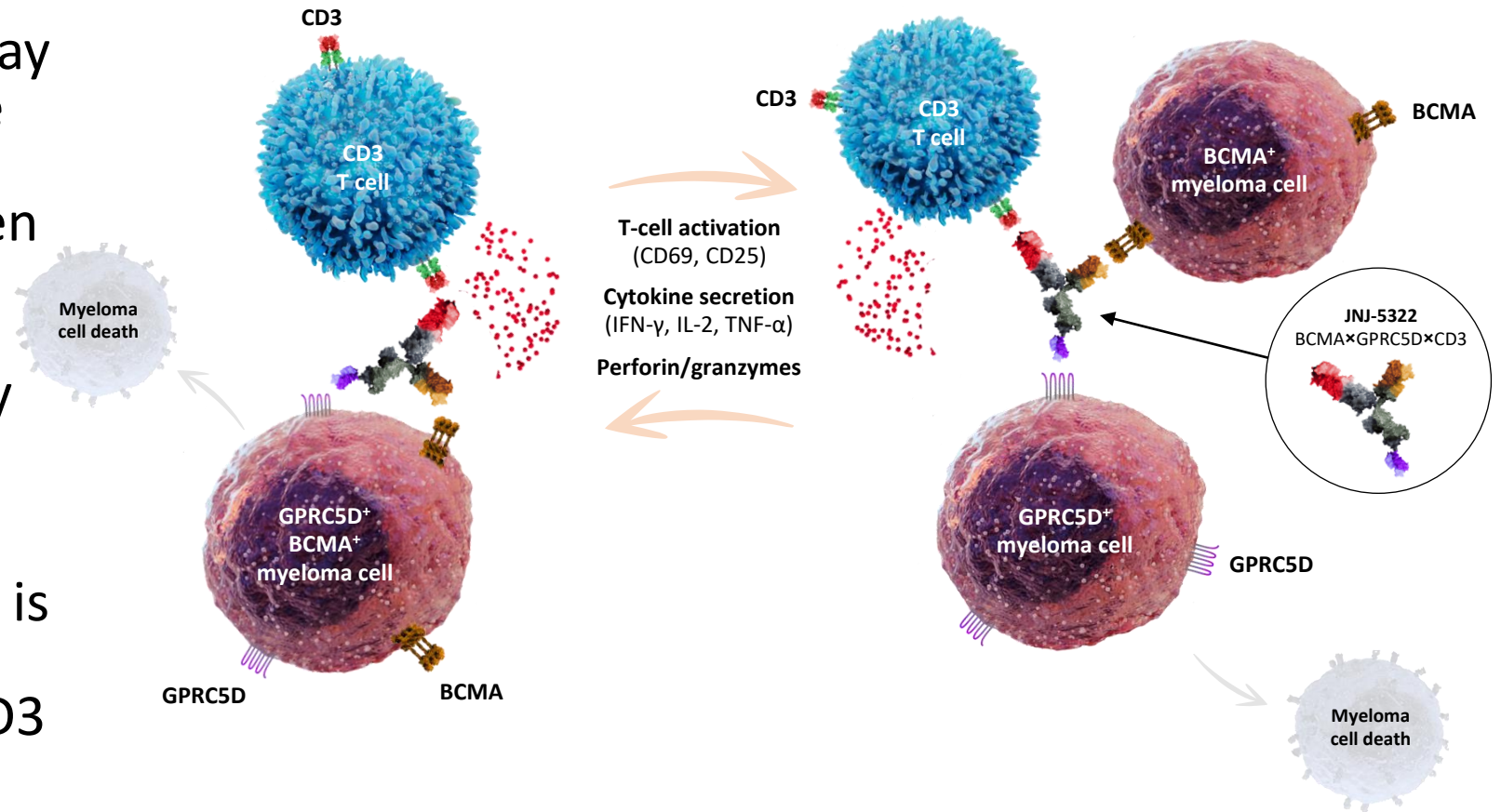
AEs (≥30% in any cohort), n (%)	0.4 mg/kg SC QW (n=143)		0.8 mg/kg SC Q2W (n=145)		Prior TCR (n=51)	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4	Any Grade	Grade 3/4
<b>Nonhematologic AEs</b>						
CRS <sup>b</sup>	113 (79.0)	3 (2.1)	108 (74.5)	1 (0.7)	39 (76.5)	1 (2.0)
Dysgeusia <sup>c</sup>	103 (72.0)	NA	103 (71.0)	NA	39 (76.5)	NA
Infections <sup>d</sup>	84 (58.7)	28 (19.6)	96 (66.2)	21 (14.5)	37 (72.5)	14 (27.5)
Skin related <sup>e</sup>	80 (55.9)	0	106 (73.1)	1 (0.7)	35 (68.6)	0
Nail related <sup>f</sup>	78 (54.5)	0	78 (53.8)	0	32 (62.7)	0
Weight decreased	59 (41.3)	3 (2.1)	60 (41.4)	8 (5.5)	15 (29.4)	0
Rash related <sup>g</sup>	57 (39.9)	2 (1.4)	43 (29.7)	8 (5.5)	18 (35.3)	2 (3.9)
Pyrexia	56 (39.2)	4 (2.8)	40 (27.6)	2 (1.4)	16 (31.4)	0
Dry mouth	38 (26.6)	0	58 (40.0)	0	26 (51.0)	0
Fatigue	35 (24.5)	5 (3.5)	40 (27.6)	1 (0.7)	23 (45.1)	1 (2.0)

Schinke C et al., ASCO 2023

# JNJ-79635322 Is a Potential First-in-Class Trispecific Antibody Targeting BCMA, GPRC5D, and CD3

- Dual antigen targeting may enhance tumor response by circumventing tumor heterogeneity and antigen loss and improving potency due to antigen binding avidity

- JNJ-79635322 (JNJ-5322) is an IgG1 trispecific antibody that binds to CD3 on T cells and BCMA and GPRC5D on MM cells

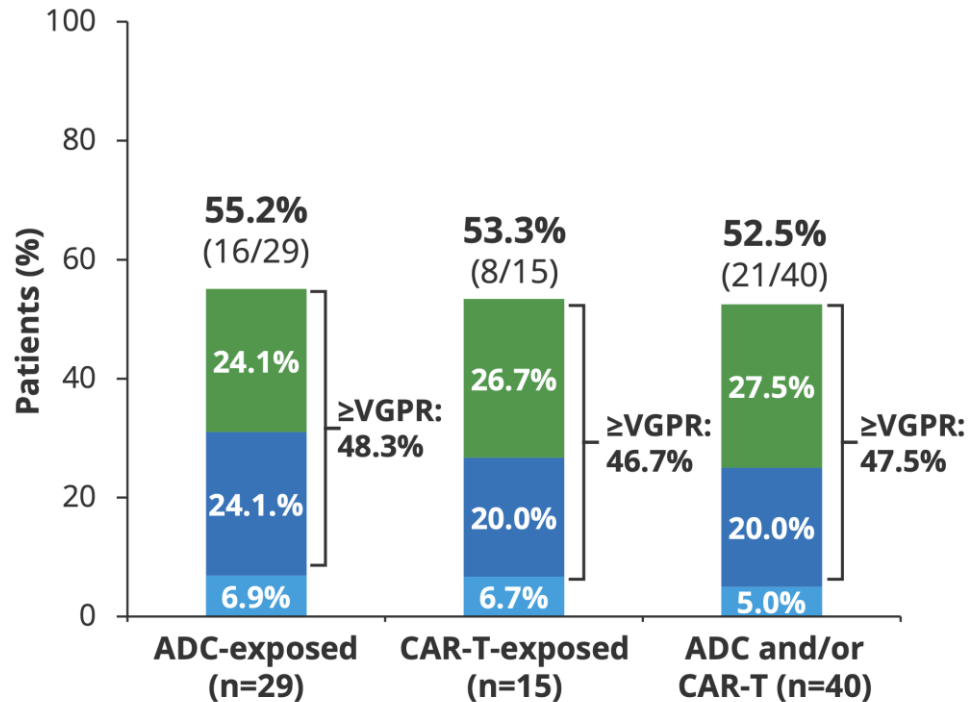


# Questions and Challenges

- Moving therapies early can impact later therapies
- Sequencing
- Duration
- Combinations

# Efficacy of anti-BCMA bispecific antibody *after* prior BCMA therapy

## Cohort C of MajesTEC-1, patients with prior BCMA-targeted therapy



## Elranatamab

ORR 54% (7/13) in prior BCMA therapy  
(9/13 had prior CAR T-cell therapy)

Raje N et al., ASH 2022

Efficacy of anti-BCMA bispecific antibody *after* prior BCMA therapy comparable to BCMA-naïve patients

# CAR T-cell efficacy after prior BCMA bispecific antibody

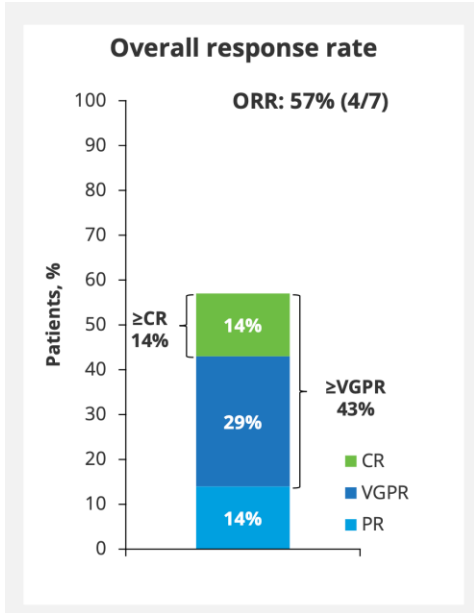
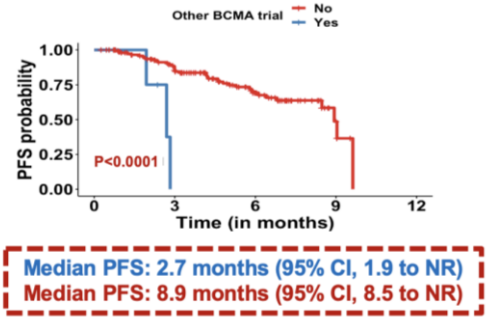
Real world ide-cel  
Median PFS **2.7 months**

CARTITUDE-2 cohort C, prior bispecific antibody (N = 7)  
Median PFS **5.3 months (95% CI, 0.6-NE)**

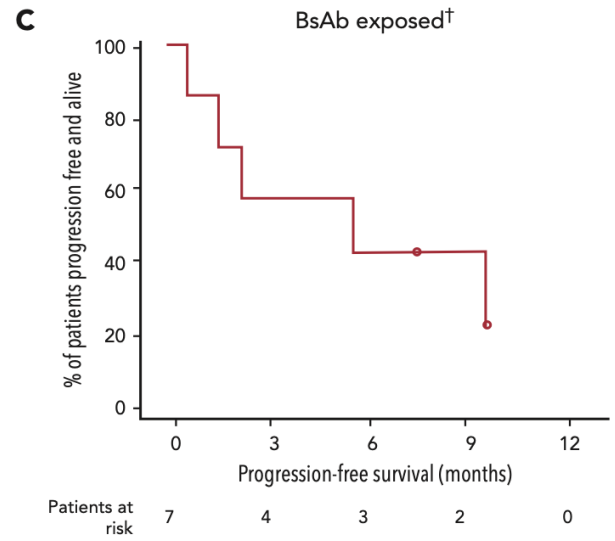
Timing of BCMA-targeting BsAb treatment

Treatments	Responders (n=4)	Nonresponders (n=3)
<b>Duration of last anti-BCMA BsAb treatment, days</b>		
Median	53.5	130.0
Range	23-127	15-260
<b>Time from last anti-BCMA BsAb treatment to apheresis, days</b>		
Median	220.5	84.0
Range	28-281	77-251
<b>Time from last anti-BCMA BsAb treatment to cilta-cel infusion, days</b>		
Median	276.0	124.0
Range	84-329	119-307

BCMA bispecific antibody on trial, N = 4



Median PFS **5.3 months (95% CI, 0.6-NE)**



No prior bispecific N=155

Hansen D et al., IMS 2022

3 of 4 cilta-cel responders did not respond to prior bispecific antibody

Cohen A et al., IMS 2022; Cohen A et al., *Blood* 2023

PFS with CAR T after prior anti-BCMA bispecific antibody significantly lower than in anti-BCMA naïve patients. This may motivate prioritization of CAR T-cell therapy over anti-BCMA bispecific antibody, where feasible.

# When do you consider Cars Versus Bispecifics?

- Patient Considerations: rapid disease progression, renal function, CNS disease
- Vein to vein time
- Slot availability
- Sequence may not matter so much once we go to fixed duration of bispecifics



# Acknowledgements



Our Patients

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@NoopurRajeMD





# Thank you!

**Noopur Raje**

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