POST-NEW ORLEANS 2022
Novità dal Meeting della Società Americana di Ematologia

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Milano
Teatro Dal Verme
2-3-4 Febbraio 2023

COORDINATORI
Angelo Michele Carella
Pier Luigi Zinzani

BOARD SCIENTIFICO
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Mauro Krampera
Fabrizio Pane
Adriano Venditti

DICHIARAZIONE

ELENA ZAMAGNI

Come da nuova regolamentazione della Commissione Nazionale per la Formazione Continua del Ministero della Salute, è richiesta la trasparenza delle fonti di finanziamento e dei rapporti con soggetti portatori di interessi commerciali in campo sanitario.

- Posizione di dipendente in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Consulenza ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Fondi per la ricerca da aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazione ad Advisory Board/HONORARIA **(JANSSEN, AMGEN, SANOFI, BMS, ROCHE, PFIZER, MENARINI-STEMLINE, GSK**
- Titolarietà di brevetti in compartecipazione ad aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Partecipazioni azionarie in aziende con interessi commerciali in campo sanitario **(NIENTE DA DICHIARARE)**
- Altro

Terapie di salvataggio con anticorpi monoclonali e CART

Elena Zamagni

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EMN Trialist Group

Seràgnoli Institute of Hematology
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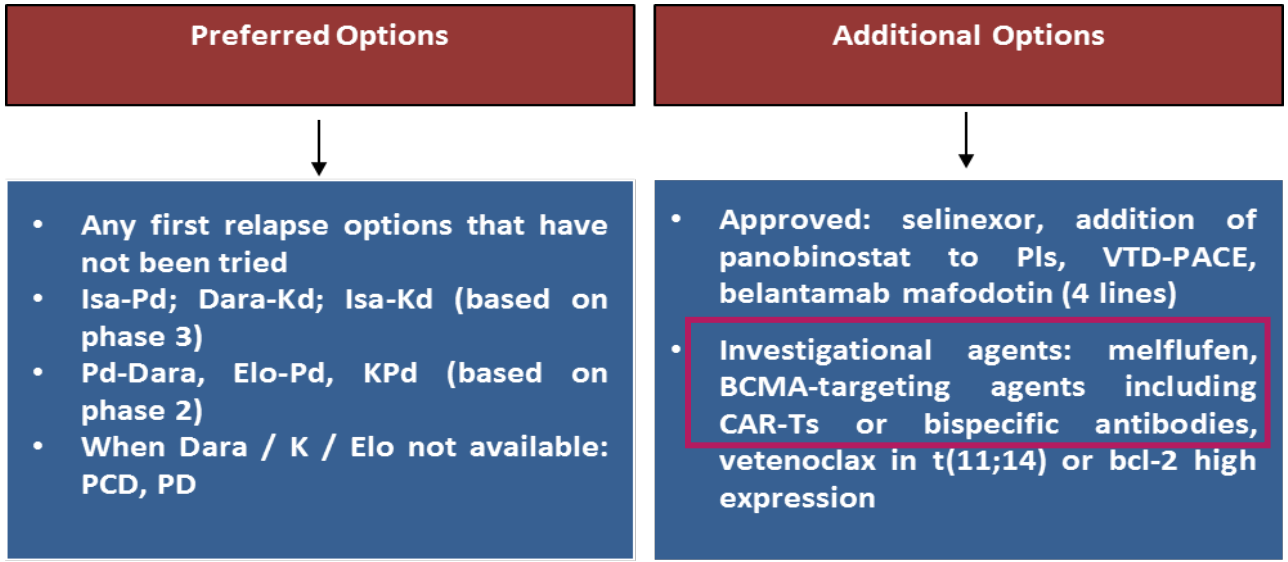
Guidelines 2021: relapsed disease

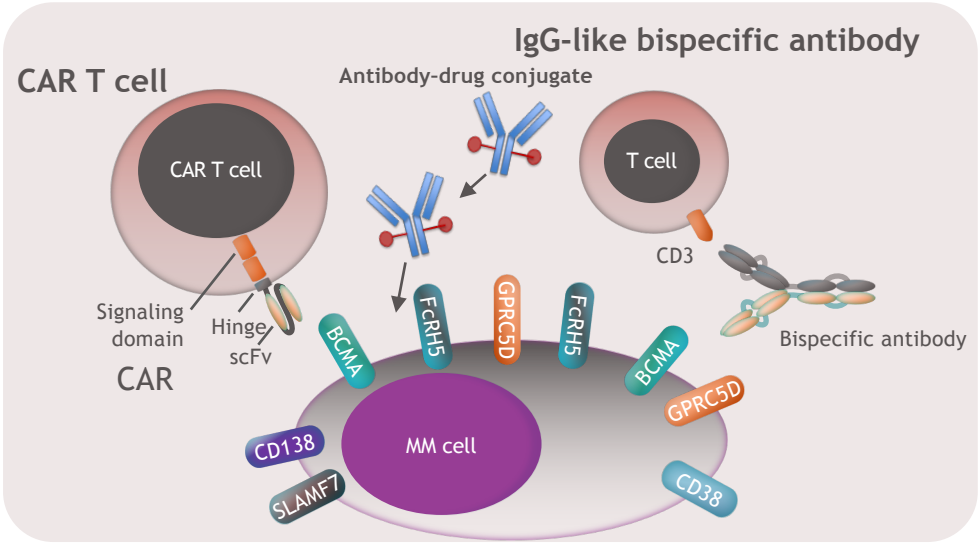
IMWG guidelines 2021

Second or subsequent relapse



Moreau P et al, Lancet Oncol 2021

New modalities to target MM cells and new targets: CAR-T and T-cell engagers



BCMA

- **BCMA is a member of the TNF receptor superfamily**
- APRIL and BAFF are known ligands, leading to activation of the NF-κB pathway
- **BCMA promotes plasma cell survival, growth, resistance to apoptosis, adhesion, and angiogenesis**
- γ-secretase cleaving causes shedding of soluble BCMA
- BCMA is expressed on malignant PCs, at low levels on normal PCs and is absent in non-hematological tissues

FcRH5

- FcRH5 is a **surface protein in the Ig superfamily**
- It is expressed **only in B cells**, with increasing expression in mature B cells and plasma cells
- FcRH5 is involved in **proliferation and isotype expression**

GPRC5D

- GPRC5D is a member of the **G protein-coupled receptor family** with an **unknown function**
- It is highly expressed on malignant PCs, as well as hard keratinized structures (hair shaft, nail, and central region of the tongue)

Image adapted from Verkleij CPM, et al. Curr Opin Oncol. 2020;32:664-71 and Bruins WSC, et al. Front Immunol. 2020;11:1155.
APRIL, a proliferation-inducing ligand; BAFF, B-cell activating factor; BCMA, B-cell maturation antigen; CD, cluster of differentiation; FcRH5, Fc receptor-like 5; GPRC5D, G-protein coupled receptor family C group 5 member D; Ig, immunoglobulin; MM, multiple myeloma; NF-κB, nuclear factor Bs; PC, plasma cell; SLAMF7, signaling lymphocytic activation molecule family member 7; TNF, tumor necrosis factor.

1. Rodríguez-Lobato LG, et al. Front Oncol. 2020;10:1243. 2. Pillarisetti K, et al. Blood Adv. 2020;4:4538-49. 3. Yu B, et al. J Hematol Oncol. 2020;13:125. 4. Verkleij CPM, et al. Blood Adv. 2020;5;2196-215. 5. Smith EL, et al. Sci Transl Med. 2019;11:eaau7746. 6. Li J, et al. Cancer Cell. 2017;31;383-95. 7. Bruins WSC, et al. Front Immunol. 2020;11:1155. 8. Lancman G, et al. Blood Cancer Discov. 2021;2:423-33.

ASH 2022 oral abstracts

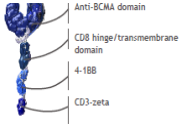
- **New generation CAR-Ts** (Costa LJ et al, abs 566, Bal S et al, abs 364)
- **Talquetamab Monumental-1** adjourned results with extended follow-up (Chari A et al, abs 157)
- **New/further anti-BCMA and anti-GPRC5D Bispecific Antibodies** (**Elranatamab**: Nizar B et al, abs 159, **Alnuctamab**: Wong SW et al, abs 162 , **Forimtamig**: Carlo-Stella C et al, abs 163)
- **New safety management of CRS** with Cevostamab (Trudel S et al, abs 168)
- Snapshot on **sequencing**

CARTs in MM

2 FDA (from fifth line)/EMA (from fourth line) approved anti-BCMA CART (ide-cel, cilta-cel)

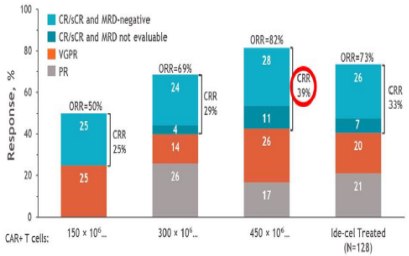
Ide-cel: KarMMa phase 2 trial

Efficacy Results in patients ≥ 3 prior LOT, triple-exposed

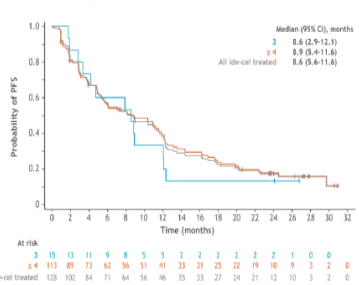


2nd generation CAR construct

Response by CART dose and in all Ide-cel treated patients



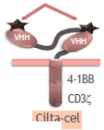
PFS by number of prior lines of therapy and in all Ide-cel treated patients



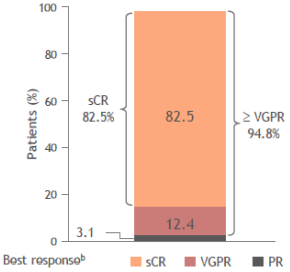
Ide-cel is approved for RRMM patients after ≥4 (FDA) or ≥3 (EMA) prior therapies including an IMiD™, a PI, and an anti-CD38 MoAb.
Data cut-off date: December 21, 2020. Median follow-up was 24.8 months (range, 1.7-33.6 mo).
CI, confidence interval; CR, complete response; ORR, objective response rate; PFS, progression-free survival; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.
1. Munshi NC, et al. N Engl J Med. 2021;384:705-16. 2. Oriol et al. EHA 2021; Poster 1009

Cilta-cel: CARTITUDE-1 phase1b/2

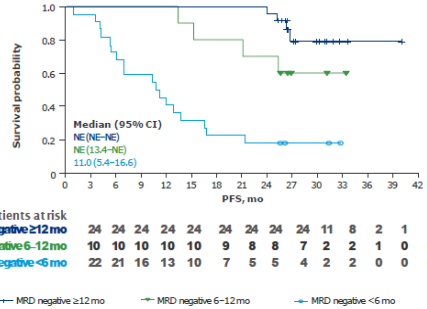
Efficacy Results in patients ≥ 3 prior LOT, triple-exposed



ORR[a] 97.9% (95/97)



PFS in MRD subgroups



MRD negativity rate (10^{-5}) in evaluable pts: 91.8
Median time to MRD: 1 month (0.8-7.7)

Munshi N et al. - Poster 2030 ASH 2022

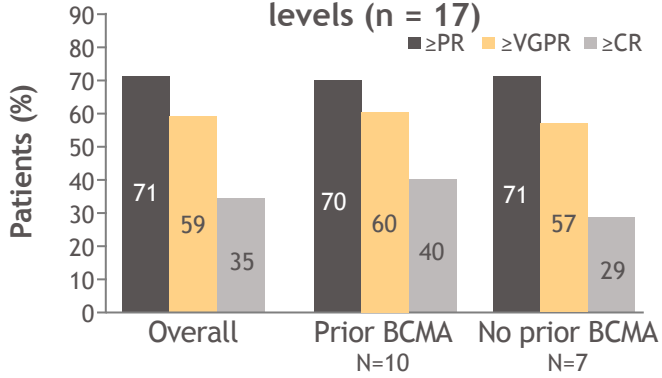
Cilta-cel is approved for patients with RRMM after after ≥4 (FDA) or ≥3 (EMA) prior therapies including an IMiD™, a PI, and an anti-CD38 MoAb.
Data cut-off date: January 11, 2022. Median follow-up of 27.7 months (range, not reported). [a]ORR assessed by independent review committee; [b]No patient had CR or stable disease as best response; [c]27-month PFS rate.
Usmani SZ, et al. Poster presentation at ASCO 2022. J Clin Oncol. 2022;40:abstract 8054.

MCARH109 (GPRC5D-targeted CAR T cell therapy)

Phase 1 first-in-class trial in RRMM

Key inclusion criteria: RRMM ≥3 prior lines, prior IMiD™ agent, prior PI and anti-CD38 mAb.
Key baseline characteristics: median age: 60y (38-76); high-risk cytogenetics: 76%; EMD, 41%, median prior lines: 6 (4-14); prior BCMA: 59%; prior BCMA-targeting CAR T cells: 47%; triple-class refractory 94%

Response rates across all dose levels (n = 17)

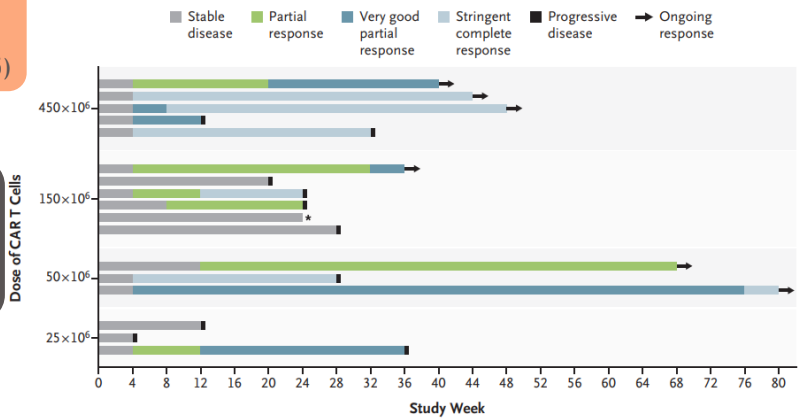


50% of patients were MRD negative

Schedule: dose escalation:
25×10⁶ (n = 3); 50 ×10⁶ (n = 3);
150×10⁶ (n = 6); 450 ×10⁶ (n = 5)

mDoR	7.8 months (95% CI, 5.7 to not reached)
mF/U	10.1

Response over time



AEs any grade (grade ≥ 3) (n = 17):

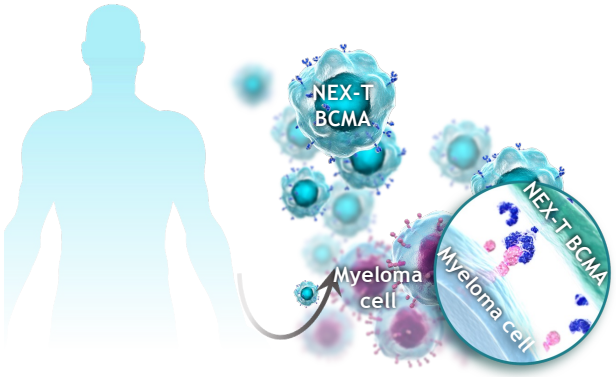
- CRS 88% (6%)
- Neurological complications 6% (6%)
- MAS 6% (6%)
- Infections 18% (12%)
- Maculopapular rash (grade 1) 18%
- Neutropenia (grade ≥ 3) 100%
- Thrombocytopenia (grade ≥ 3) 65%
- **Dysgeusia (grade 1) 12%**
- **Nail changes (grade 1) 65%**

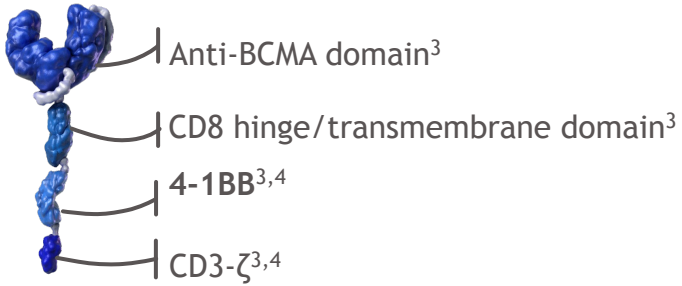
MCARH109 is an investigational product and has not been approved by any regulatory agency
EMD, extramedullary disease; MAS, macrophage activation syndrome.
Mailankody S, et al. N Engl J Med, 2022;387:1196-206

«Next generation» CART

CC-98633/BMS-986354 is a **BCMA CAR T-cell** drug product that contains a fully **human CAR construct** and is **manufactured** using the **NEX-T™ process** (shorten manufacturing and improved potency)

- enriched in **less-differentiated** memory subtypes, composed primarily of **naive-like** and **central memory CAR T** cells, and fewer effector and terminally differentiated CAR T cells
- has ~10-fold **increased proliferative capacity**
- has **superior tumor control** at equivalent CAR T cell dose

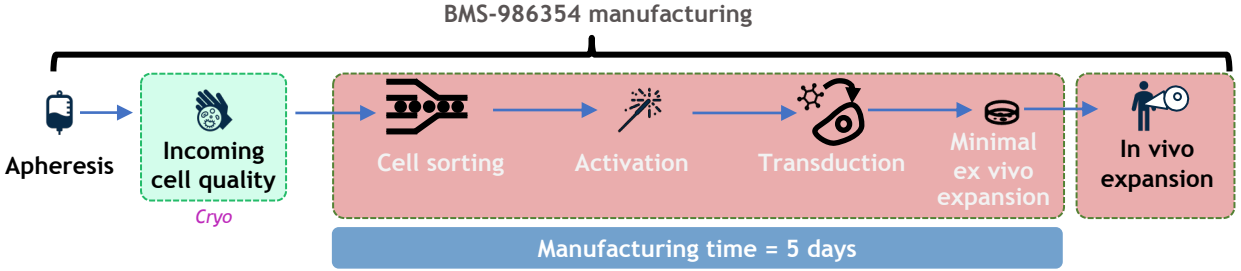




Costa LJ et al. – Abs 566 ASH 2022

Study design

CC-98633/BMS-986354 phase 1 study

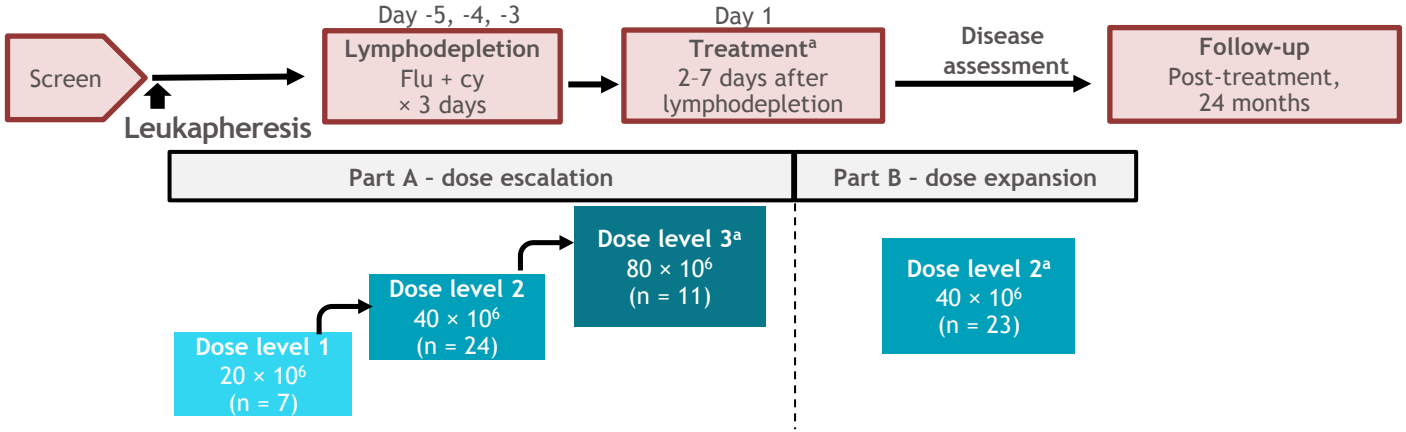


Analysis on **65 pts, 5 median prior LOT**, 6 years from diagnosis.
Median follow-up: 9 months

- **91% triple-refractory**
- **48% penta-refractory**

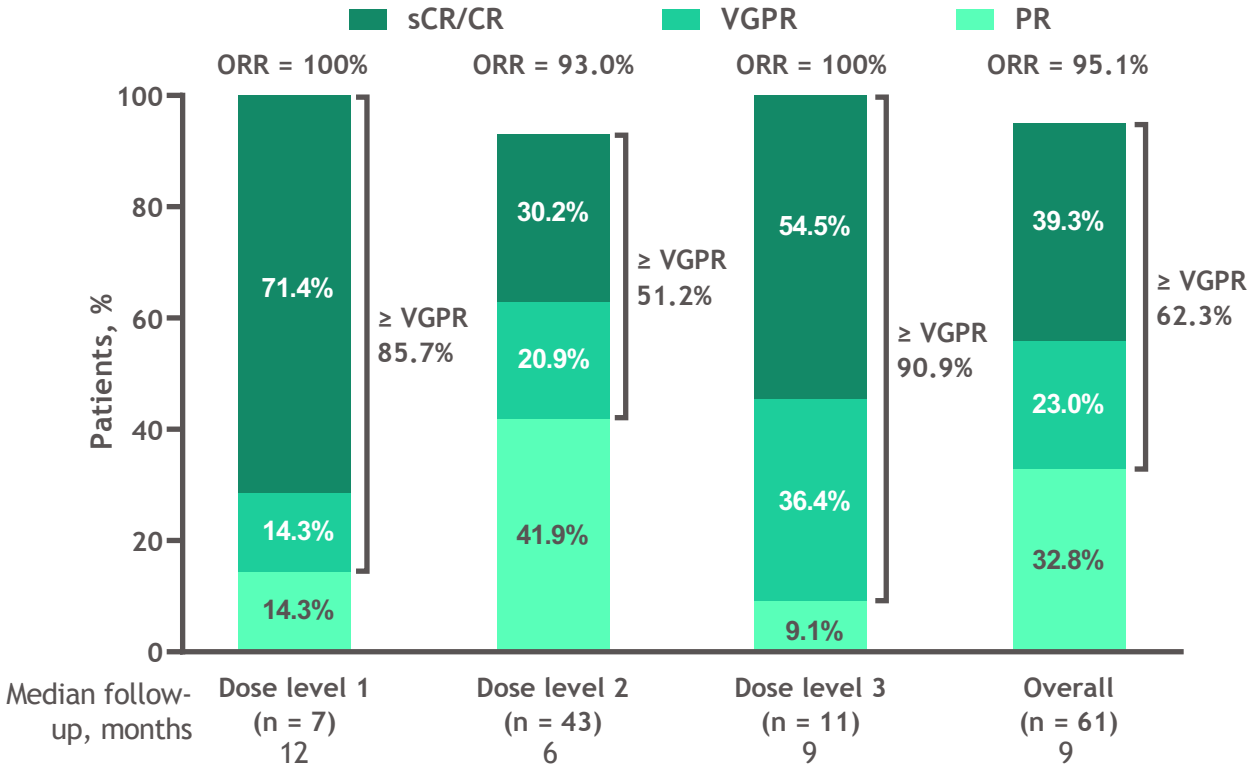
Key eligibility criteria

- **Received ≥ 3 prior regimens**, including autologous stem cell transplant, proteasome inhibitor, immunomodulatory drugs, and an anti-CD38 agent



[a]As of August 19, 2022, 14 patients have been enrolled into dose level 3, of whom 11 have received treatment and 29 patients have been enrolled into Part B, of whom 23 have received treatment.
Flu + cy, fludarabine (30 mg/m²) + cyclophosphamide (300 mg/m²); PS, performance status.

Efficacy outcomes: best overall response and MRD



MRD at 3 months post-infusion

	Overall (n = 61)
MRD evaluable, n	38
MRD negative[a], n	25
Not evaluable, n	23
No trackable clone	15
Missing sample	8

[a]MRD < 1 in 10^{-5} cells

Data cut-off: August 19, 2022. MRD was assessed in bone marrow using a next-generation sequencing assay from Adaptive Biotechnologies in treated patients regardless of response.
CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

Costa LJ, et al. ASH 2022

Safety outcomes: TEAEs

TEAEs occurring in ≥ 30% of patients, n (%)	Overall (n = 65)	
	Any grade	Grade 3/4
Any TEAE	65 (100.0)	54 (83.1)
Hematologic		
Neutropenia	47 (72.3)	33 (50.8)
Anemia	30 (46.2)	19 (29.2)
Thrombocytopenia	30 (46.2)	24 (36.9)
TEAEs of interest		
CRS	53 (81.5)	1 (1.5)
ICANS-type NT	6 (9.2)	1 (1.5)

CRS and NT by dose level	Dose level 1 (n = 7)		Dose level 2 (n = 47)		Dose level 3 (n =11)	
	CRS	NT	CRS	NT	CRS	NT
Any grade, n (%)	5 (71.4)	1 (14.3)	39 (83.0)	3 (6.4)	9 (81.8)	2 (18.2)
Grade 1	2 (28.6)	1 (14.3)	30 (63.8)	2 (4.3)	9 (81.8)	2 (18.2)
Grade 2	3 (42.9)	0 (0.0)	8 (17.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Grade 4	0 (0.0)	0 (0.0)	1 (2.1)	1 (2.1)	0 (0.0)	0 (0.0)
Median onset, days (range)	4.0 (1-8)	8.0 (8-8)	4.0 (2-6)	5.0 (5-9)	4.0 (2-6)	6.5 (5-9)
Median duration, days (range)	2.0 (2-9)	2.0 (2-2)	4.0 (1-7)	3.0 (1-12)	4.0 (2-8)	3.5 (2-5)
Common treatments, n (%)						
Tocilizumab	5 (71.4)	0 (0.0)	36 (76.6)	0 (0.0)	7 (63.6)	0 (0.0)
Steroids	4 (57.1)	1 (14.3)	25 (53.2)	2 (4.3)	4 (36.4)	1 (9.1)
Anakinra	3 (42.9)	1 (14.3)	6 (12.8)	1 (2.1)	1 (9.1)	0 (0.0)

CRS and NT were low-grade, brief, and reversible with treatment

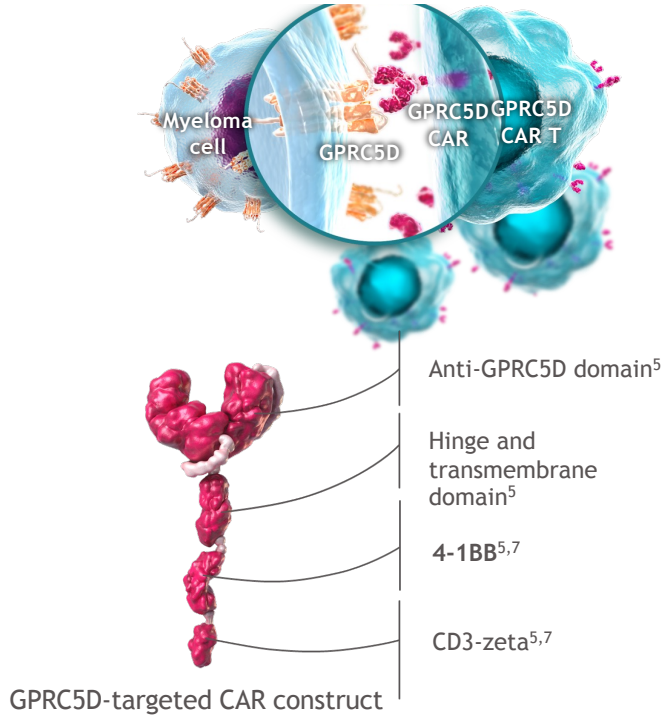
Costa LJ, et al. ASH 2022

«Next generation» CART

BMS-986393 (CC-95266), a **GPRC5D-targeted** autologous CAR T-cell therapy, in patients with R/R MM

Interim results from the dose-escalation (Part A) of study CC-95266-MM-001 (NCT04674813); analysis on the first **33 treated** patients

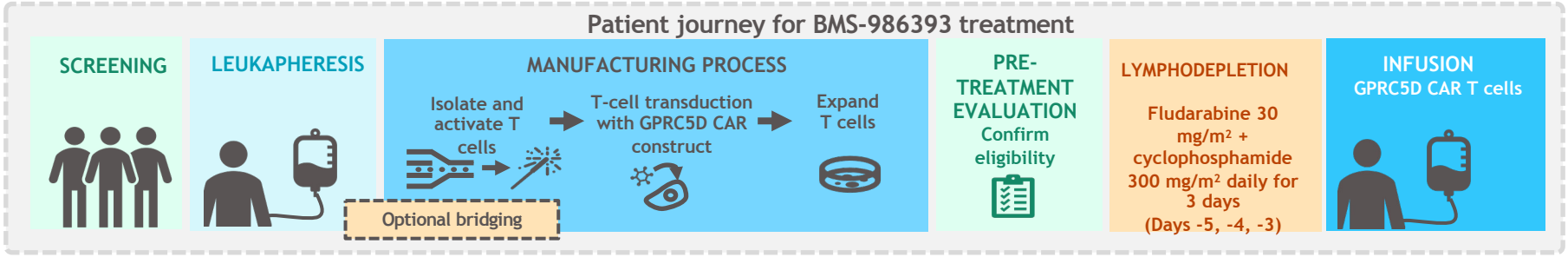
BMS-986393 mechanism of action



Bal S et al. – Abs 364 ASH 2022

Study design and dose schedule

CC-95266-MM-001 (NCT04674813) is a phase 1, multicenter, open-label, dose-escalation and -expansion study[a]



Key eligibility criteria

- R/R MM
- **≥ 3 prior regimens**, including ASCT (unless ineligible), a PI, an IMiD, and an anti-CD38 antibody
- **Progressed within 12 months** of last treatment regimen (unless last therapy was CAR T-cell therapy, which can be ≥ 12 months prior)
- **Prior BCMA-directed therapies allowed**, including CAR T cells

Part A dose-escalation | **Part B dose-expansion[b]**

Modified toxicity probability interval (mTPI-2) design with ≥ 3 patients per dose level

25 x 10^6 CAR T cells → 75 x 10^6 CAR T cells → 150 x 10^6 CAR T cells → 300 x 10^6 CAR T cells → 450 x 10^6 CAR T cells

BMS-986393 at the expansion dose(s)

Dose-escalation is ongoing; MTD has not been exceeded

Primary objectives

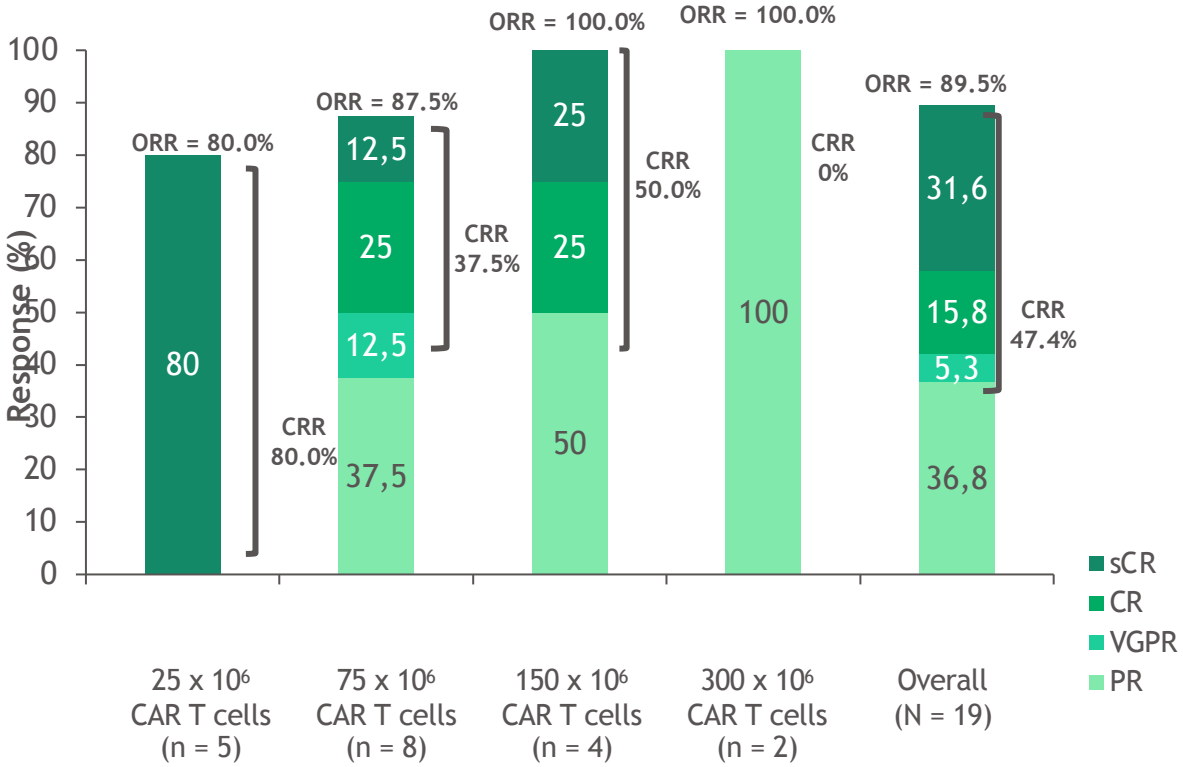
- Assess safety and tolerability
- Determine MTD/RP2D

33 pts, 4 median prior LOT, median follow-up: 3 months

- **54% any prior anti-BCMA** therapy (39% CAR-T)

Bal S, et al. ASH 2022

Best overall response (efficacy-evaluable analysis set[a])



	Median follow-up, months (range)
25 x 10⁶ CAR T cells	12.3 (8.2–15.5)
75 x 10⁶ CAR T cells	5.9 (3.1–8.9)
150 x 10⁶ CAR T cells	4.1 (1.0–4.5)
300 x 10⁶ CAR T cells	2.1 (2.1–2.1)
Overall	5.8 (1.0–15.5)

At the time of analysis, 15/19 (78.9%) patients remained in follow-up

ORR = 77.8% (45% CR) in pts with prior anti-BCMA

Bal S, et al. ASH 2022

TEAEs – overall, hematologic, and non-hematologic

	All treated patients (N = 33)
TEAEs, n (%)	29 (87.9)
TRAEs, n (%)	24 (72.7)
Grade 3/4 TEAEs, n (%)	24 (72.7)
Grade 3/4 TRAEs, n (%)	19 (57.6)

	All treated patients(N = 33)	
	Any grade	Grade 3/4
Neurotoxicities		
ICANS, n (%)	**2 (6.0)**	**0 (0)**
Cerebellar[a], n (%)	0 (0)	0 (0)
On-target/off-tumor AEs		
Skin[b]	10 (30.3)	0 (0)
Dysgeusia/taste disorder	5 (15.2)	0 (0)
Nails[c]	3 (9.1)	0 (0)
Dysphagia	1 (3.0)	0 (0)

	All treated patients (N = 33)	
Hematologic TEAEs (≥ 20% in any dose group), n (%)	Any grade	Grade 3/4
Neutropenia	22 (66.7)	20 (60.6)
Thrombocytopenia	13 (39.4)	7 (21.2)
Anemia	12 (36.4)	7 (21.2)
Leukopenia	7 (21.2)	6 (18.2)
Non-hematologic TEAEs (≥ 20% in overall population), n (%)	Any grade	Grade 3/4
CRS	**21 (63.6)**	**2 (6.1)**
Pyrexia	10 (30.3)	0 (0)
Hypokalemia	10 (30.3)	1 (3.0)
Headache	10 (30.3)	0 (0)
Nausea	9 (27.3)	0 (0)
Hypocalcemia	8 (24.2)	0 (0)
Hypophosphatemia	8 (24.2)	0 (0)
Fatigue	7 (21.2)	0 (0)

Bal S, et al. ASH 2022

TALQUETAMAB
MonumenTAL-1: Phase 1/2 Study Design (NCT03399799/NCT04634552)

Key objectives

- Describe the efficacy and safety at the RP2Ds

Key eligibility criteria

- Adults with measurable MM
- Phase 1: Progression on or intolerance to all established therapies, ECOG PS 0–1
- Phase 2: ≥3 prior lines of therapy that included a PI, an IMiD, and an anti-CD38 antibody

143+145 pts, 5 median prior LOT, median follow-up: **14 months**

- **70% triple-class refractory**
- **25% penta-refractory**

RP2D 0.4 mg/kg QW SC
Prior anti-BCMA ADC treatment allowed
T-cell redirection therapy naive

(Phase 1 [n=21] + Phase 2 [n=122]: N=**143**)

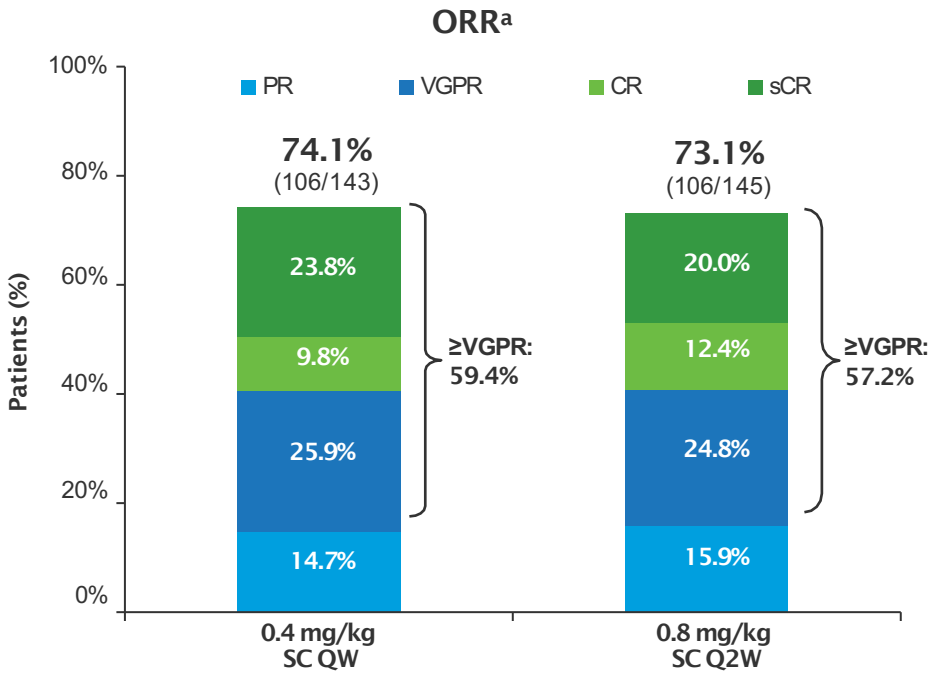
RP2D 0.8 mg/kg Q2W SC
Prior anti-BCMA ADC treatment allowed
T-cell redirection therapy naive

(Phase 1 [n=36] + Phase 2 [n=109]: N=**145**)

Prior T-cell redirection (QW and Q2W)
Previously exposed to T-cell redirection therapies
Dosed with either 0.4 mg/kg weekly SC or 0.8 mg/kg Q2W SC

(Phase 1 [n=17] + Phase 2 [n=34]: N=51)

MonumenTAL-1: Overall Response Rate



- ORR was similar for QW and Q2W schedules
  - **Triple-class refractory: 72.6%** (95% CI, 63.1–80.9) and **71.0%** (95% CI, 61.1–79.6)
  - **Penta-drug refractory: 71.4%** (95% CI, 55.4–84.3) and **70.6%** (95% CI, 52.5–84.9)
  - ORR was consistent across subgroups including number of prior therapies, refractoriness to prior therapy, belantamab exposure, and baseline cytogenetic risk, **except among patients with baseline plasmacytomas**

- **mDOR was ≥9 months** in all groups, with longer DOR in those achieving ≥CR
- **mPFS** at 0.4 mg/kg QW: **7.5 months**
- **mPFS** at 0.8 mg/kg Q2W: **11.9 months**

- 51 pts treated post anti-BCMA agents (71% CAR-T, 35% bispecific Abs), median 6 prior LOT:
  - **72% ORR in the CAR-T** subgroup
  - **44% ORR in the bispecific Abs** subgroup

MonumenTAL-1: Safety

Hematologic adverse events

AEs (≥20% of any RP2D cohort), n(%)	0.4 mg/kg SC QW		0.8 mg/kg SC Q2W	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
Anemia	64 (44.8)	45 (31.5)	57 (39.3)	36 (24.8)
Neutropenia	**49 (34.3)**	**44 (30.8)**	**41 (28.3)**	**32 (22.1)**
Lymphopenia	40 (28.0)	37 (25.9)	38 (26.2)	37 (25.5)
Thrombocytopenia	39 (27.3)	29 (20.3)	39 (26.9)	24 (16.6)

- Most high-grade AEs were cytopenias
- Cytopenias were generally limited to the first few cycles
- Infections occurred in 57% and 50% at the 2 doses (16.8 and 11.7%, respectively, grade 3/4

Non-hematologic adverse events

AEs (≥20% of any RP2D), n(%)	0.4 mg/kg SC QW		0.8 mg/kg SC Q2W	
	Any Grade	Grade 3/4	Any Grade	Grade 3/4
CRS	113 (79.0)	3 (2.1)	105 (72.4)	1 (0.7)
Skin-related AEs[d]	80 (55.9)	0	98 (67.6)	1 (0.7)
Nail-related AEs[e]	74 (51.7)	0	63 (43.4)	0
Dysgeusia[f]	69 (48.3)	NA	67 (46.2)	NA
Rash-related AEs[g]	56 (39.2)	2 (1.4)	39 (26.9)	8 (5.5)
Weight decreased	57 (39.9)	3 (2.1)	47 (32.4)	2 (1.4)
Pyrexia	53 (37.1)	4 (2.8)	35 (24.1)	1 (0.7)
Asthenia	37 (25.9)	3 (2.1)	13 (9.0)	2 (1.4)
Dry mouth	36 (25.2)	0	53 (36.6)	0
Diarrhea	34 (23.8)	3 (2.1)	32 (22.1)	0
Dysphagia	34 (23.8)	0	33 (22.8)	3 (2.1)
Fatigue	32 (22.4)	5 (3.5)	29 (20.0)	1 (0.7)
Decreased appetite	25 (17.5)	2 (1.4)	29 (20.0)	2 (1.4)

- Most **CRS events were grade 1/2** and largely confined to the step-up doses and first full dose (only 10% after full dose)
- **ICANS occurred in 10–11%** of patients across RP2D groups
- Most ICANS events were **grade 1 or 2**
- 7–8% of patients received supportive measures for ICANS across RP2D groups, including tocilizumab and corticosteroids

Forimtamig

Humanized, bispecific anti-GPRC5D Ab Phase 1/2 study

Key inclusion criteria

- RRMM with prior IMiD and PI
- **No established therapy available**
- ECOG performance status 0–1
- **Prior CAR T-cells, ADCs, and bispecific Abs allowed**

Forimtamig dosing

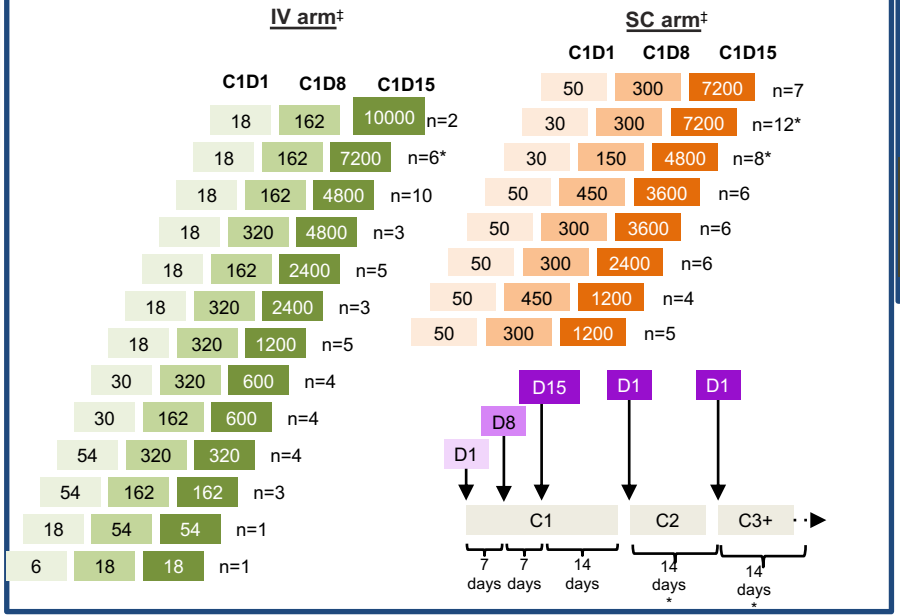
- **Q2W dosing* for 1 year†**
- CRS mitigation measures
  - C1 step dosing
  - C1 corticosteroid premedication
  - Hospitalization for C1 doses only

Objectives

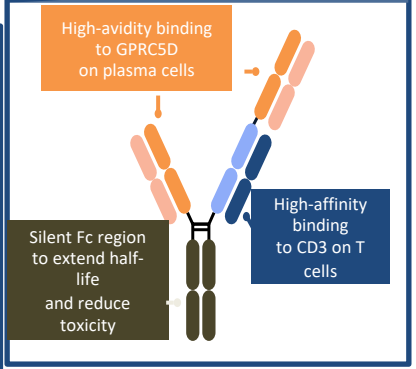
- **Primary:** safety and tolerability, MTD, RP2D
- **Secondary:** PK/PD, immunogenicity, clinical activity

IV and SC dose-escalation overview

Dose-escalation cohorts and dosing regimens (Q2W)



Forimtamig: 2:1 (GPRC5D:CD3) configuration



51 (iv) an 57 (sc) pts, 5 median prior LOT

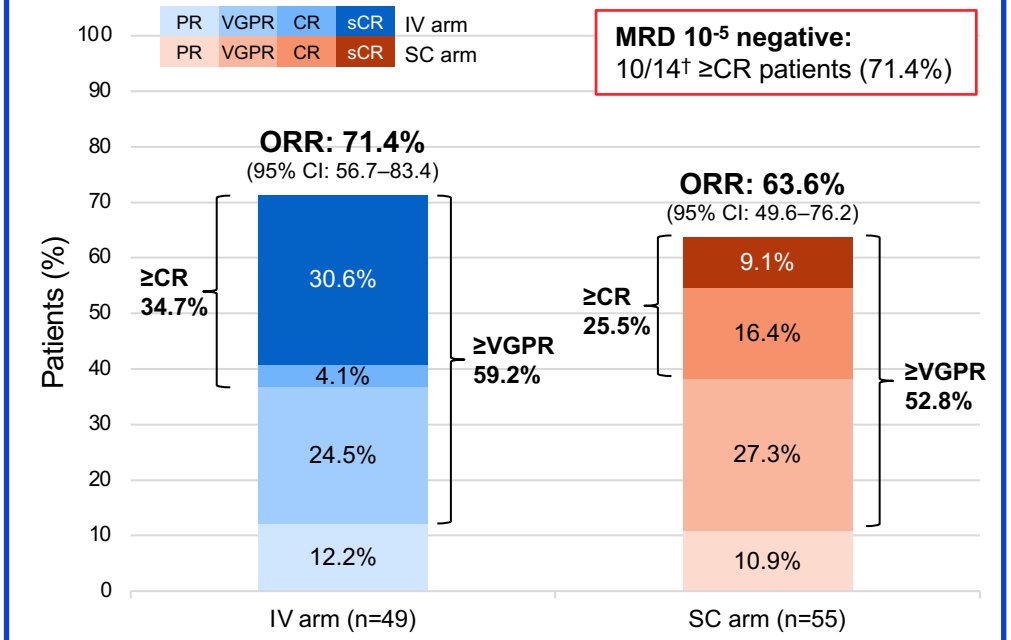
- **62/72% triple-refractory**
- **36/42% penta-refractory**
- **20% prior anti-BCMA**
- 30% EMD

Bacac et al. Clin Cancer Res 2018;24:4785–97

Forimtamig clinical efficacy

	IV arm (n=49)	SC arm (n=55)
Median follow-up, months (range)	11.6 (0.5–20.6)	8.0 (1.1–15.0)
Median time to first response, months (95% CI)	1.4 (1.2–1.8)	1.6 (1.2–2.1)
Median duration of response, months (range)	10.8 (0.0–17.6)	12.5 (1.2–12.5)
Patients with ongoing response at data cut-off, n/N (%)	23/35 (65.7)	25/35 (71.4)
Patients with prior anti-BCMA and response, n/N (%)	5/10 (50.0)	6/11 (54.5)

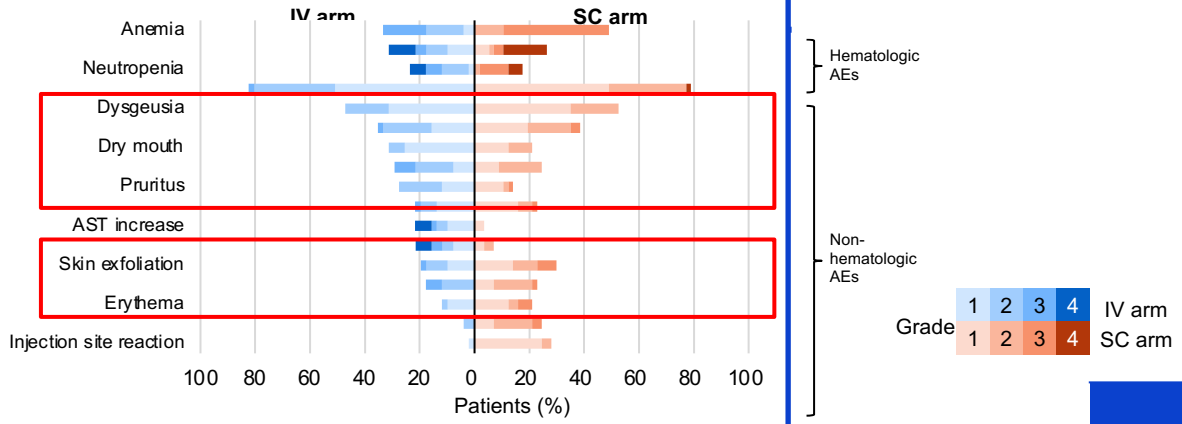
Response rate across all tested target doses (IV: 18–10,000µg; SC 30–7200µg) in efficacy-evaluable patients*



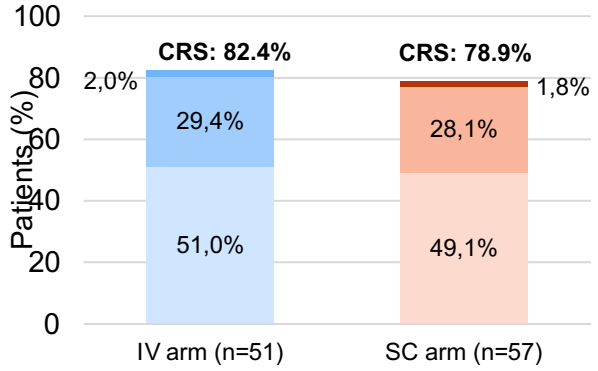
Data cut-off: October 21, 2022; *patients who received ≥1 target dose of forimtamig and had at least one baseline and one on-treatment tumor assessment or discontinued due to clinical progression; †of 14 evaluable patients with available BMA at the time of response across all IV and SC doses so far, 10 had MRD-negative CR at 10^{-5}. BMA, bone marrow aspirate; CI, confidence interval; CR, complete response; MRD, minimal residual disease; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response

Forimtamig adverse event summary

Common (≥20%) hematologic and non-hematologic AEs by Grade



Patients (%) with CRS across all tested target doses (IV: 18–10,000µg; SC 30–7200µg)



- **CRS primarily observed in C1**
- Median time to CRS onset was 5 hours (IV) and 24 hours (SC)
- Median duration of CRS was 2 days (in both IV and SC)
- **ICANS:** 10% both arms, grade ≥ 3 3%

	IV arm (n=51)		SC arm (n=57)	
n (%)	Any Gr	Gr ≥3	Any Gr	Gr ≥3
Skin†	**40 (78.4)**	**6 (11.8)**	**49 (86.0)**	**13 (22.8)**
Mucosal toxicity‡	**37 (72.5)**	**0**	**44 (77.2)**	**3 (5.3)**
Hair and nail changes§	**12 (23.5)**	**0**	**16 (28.1)**	**0**
Hematologic	22 (43.1)	14 (27.5)	33 (57.9)	27 (47.4)
Anemia¶	17 (33.3)	8 (15.7)	28 (49.1)	22 (38.6)
Thrombocytopenia¶	16 (31.4)	7 (13.7)	15 (26.3)	11 (19.3)
Neutropenia¶	12 (23.5)	6 (11.8)	10 (17.5)	9 (15.8)
Infections	31 (60.8)	11 (21.5)	26 (45.6)	15 (26.4)
COVID-19¶	11 (21.6)	1 (2.0)	14 (24.6)	2 (3.6)

Forimtamig AEs were consistent with the target class (GPRC5D) and MoA class

Carlo-Stella C et al. – Abs 163 ASH 2022

Elranatamab

Humanized, bispecific anti-BCMA Ab

MagnetisMM-3 Study

- MagnetisMM-3 is an open-label, multicenter, non-randomized, phase 2 study

Patients with RRMM

Key inclusion criteria:
- Refractory to ≥1 each of the following: proteasome inhibitor, immunomodulatory drug, and anti-CD38 antibody[a]
- ECOG performance status ≤2
- Creatinine clearance ≥30 mL/min
- Platelets ≥25 × 10^9/L
- ANC ≥1.0 × 10^9/L
- Hemoglobin ≥8 g/dL

Cohort A (n=123)
No prior BCMA-directed treatment

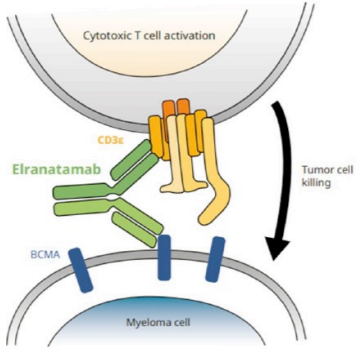
Cohort B (n=64)
Prior BCMA-directed ADC or CAR-T

- Patients will be followed for ~2 y from enrollment

Elranatamab 76 mg SC QW on a 28-d cycle

Primary endpoint
- ORR by BICR[b]

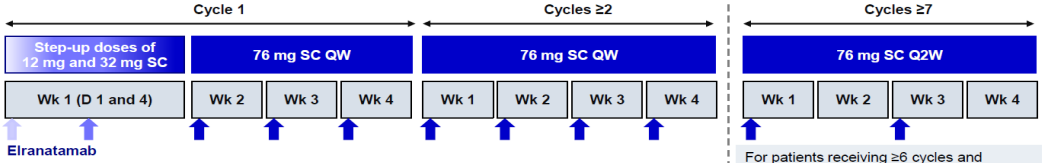
Secondary endpoints
- Duration of response[b,c]
- CR rate[b,c]
- ORR[c]
- ORR by baseline extramedullary disease status[b]
- Duration of CR[b,c]
- Time-to-response[b,c]
- PFS[b,c]
- MRD-negativity rate
- OS
- Safety
- Pharmacokinetics



[a] Refractory was defined as having disease progression while on therapy or within 60 d of last dose in any line, regardless of response
[b] By BICR assessment per IMWG response criteria (Kumar S, et al. Lancet Oncol 2016;17:e328-46)
[c] By investigator assessment per IMWG response criteria
ADC=antibody drug conjugate; ANC=absolute neutrophil count; BCMA=B-cell maturation antigen; BICR=blinded independent central review; CAR-T=chimeric antigen receptor T-cell; CR=complete response; ECOG=Eastern Cooperative Oncology Group; IMWG=International Myeloma Working Group; MRD=minimal residual disease; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; QW=once weekly; SC=subcutaneous

123 pts, 5 median prior LOT, median follow-up: **10.4 months**

- **97% triple-refractory**
- **42% penta-refractory**
- **32% EMD**



For patients receiving ≥6 cycles and achieving partial response or better with responses persisting for ≥2 mo, the dosing interval will be changed to Q2W

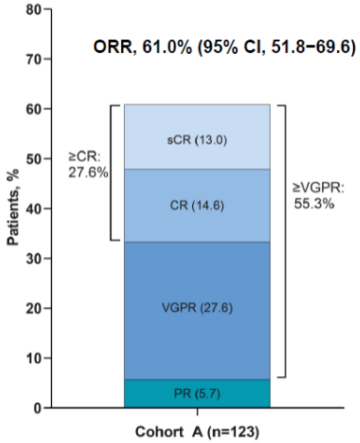
Premedication:
60 min (±15 min) prior to the first 3 doses of elranatamab
- Acetaminophen 650 mg (or paracetamol 500 mg)
- Diphenhydramine 25 mg (or equivalent), oral or IV
- Dexamethasone 20 mg (or equivalent), oral or IV

Elranatamab

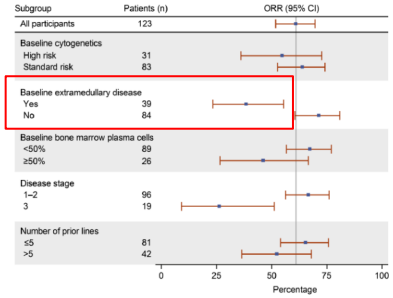
Efficacy

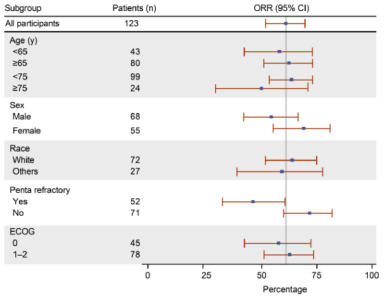
Objective Response Rate per BICR

- Confirmed ORR per BICR was 61.0% (95% CI, 51.8–69.6)
- Among patients who achieved an objective response (n=75), median time to response was 1.2 (range, 0.9–7.4) mo
- MRD-negativity at the threshold of 10^{-5} was achieved by 90.9% of evaluable patients (n=22)

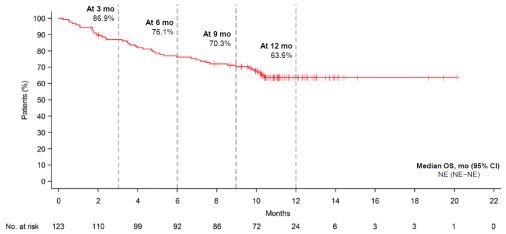


Objective Response Rate per BICR Across Subgroups



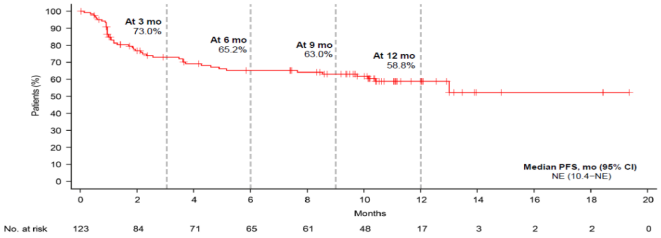


Overall Survival



CI=confidence interval; NE=not evaluable; OS=overall survival

Progression-Free Survival per BICR



Elranatamab

Safety outcomes: TEAEs

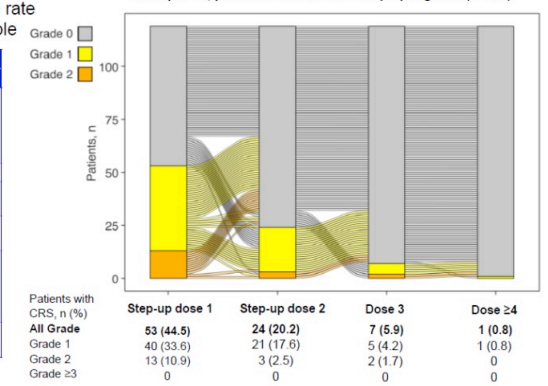
TEAEs in ≥20% of patients, n (%)	Cohort A (N=123) Any grade	Grade 3/4
Hematologic		
Anemia	59 (48.0)	45 (36.6)
Neutropenia	59 (48.0)	59 (48.0)
Thrombocytopenia	37 (30.1)	27 (22.0)
Lymphopenia	32 (26.0)	30 (24.4)
Non-hematologic		
CRS	71 (57.7)	0
Diarrhea	48 (39.0)	2 (1.6)
Fatigue	42 (34.1)	4 (3.3)
Decreased appetite	40 (32.5)	1 (0.8)
Injection site reaction	32 (26.0)	0
Nausea	32 (26.0)	0
COVID-19 related[a]	31 (25.2)	14 (11.4)
Hypokalemia	29 (23.6)	12 (9.8)
Pyrexia	29 (23.6)	4 (3.3)
Cough	27 (22.0)	0
Headache	27 (22.0)	0

AEs of Special Interest: CRS and ICANS

- The step-up priming regimen successfully mitigated the rate and severity of CRS, and the CRS profile was predictable

TEAE of special interest	12/32 mg step-up regimen (n=119)[a] CRS	ICANS
Patients with TEAE, n (%)	67 (56.3)	4 (3.4)
Maximum Grade 1	50 (42.0)	1 (0.8)
Maximum Grade 2	17 (14.3)	3 (2.5)
Maximum Grade ≥3	0	0
Patients with >1 TEAE, n (%)	18 (15.1)	1 (0.8)
Median time to onset of TEAE, d (range)	2.0 (1.0–9.0)	2.5 (1.0–4.0)
Median time to resolution of TEAE, d (range)	2.0 (1.0–19.0)	2.0 (1.0–6.0)
Patients who received tocilizumab[b] or steroids, n (%)		
Tocilizumab	27 (22.7)	2 (1.7)
Steroids	10 (8.4)	2 (1.7)
Permanent discontinuation due to AE, n (%)	0	0

CRS profile, patients received 12/32 step-up regimen (n=119)



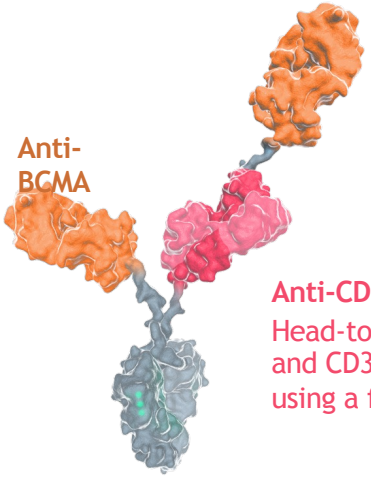
[a] Patients who received 1 step-up priming dose of 44 mg in Wk 1 were excluded from this CRS and ICANS analysis (n=4); [b] Includes tocilizumab and siltuximab
CRS and ICANS which were graded by American Society for Transplant and Cellular Therapy criteria (Lee DW, et al. Biol Blood Marrow Trans 2019;25:62)
AE=adverse event; CRS=cytokine release syndrome; ICANS=immune effector cell-associated neurotoxicity syndrome; TEAE=treatment-emergent adverse event

14

- Most high-grade AEs were cytopenias
- Infections occurred in 67% (grade 3/4 35%), at a median of 45 days
- 41% received IVIG

IV and sc Alnuctamab: Phase 1 study

Alnuctamab: 2+1 BCMA x CD3 TCE[1-4]



Anti-BCMA

Bivalent binding to BCMA in a 2+1 format for superior potency and tumor targeting

Anti-CD3ε

Head-to-tail geometry of BCMA- and CD3ε-binding Fab domains using a flexible linker

FcγR-silent Fc

No binding to FcγR and C1q to minimize infusion-related reactions

- Alnuctamab (BMS-986349; CC-93269) is a **humanized 2+1** IgG1-based TCE that binds to BCMA on myeloma cells and to CD3ε on T cells, enabling specific as well as high affinity and avidity BCMA binding[1,2]
- **In the first-in-human, phase 1, open-label,** dose-finding study (NCT03486067), alnuctamab demonstrated preliminary clinical activity as an IV formulation in patients with RRMM treated with **≥ 3 prior lines of therapy**[3]
- To help manage cytokine release syndrome (CRS) and improve dosing convenience, the phase 1 study pivoted to subcutaneous (SC) administration of alnuctamab
- Here, we present initial results in patients treated with SC alnuctamab and long-term follow-up results in patients treated with IV alnuctamab

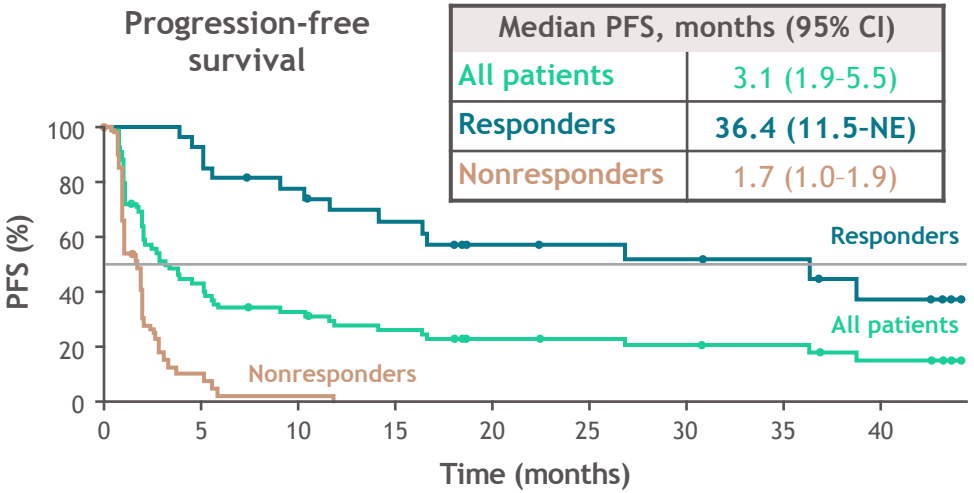
BCMA, B-cell maturation antigen; CD3, cluster of differentiation 3; Fab, antigen-binding fragment; FcγR, Fc gamma receptor, Ig, immunoglobulin; RRMM, relapsed/refractory multiple myeloma; TCE, T-cell engager.

1. Seckinger A, et al. *Cancer Cell* 2017;31:396–410; 2. van der Vuurst de Vries A-R, et al. *HemaSphere* 2020;4(S1). Abstract S198; 3. Costa LJ, et al. *Blood* 2019;134(suppl 1):143; 4. Klein C, et al. *Cancer Res* 2017;77(13_Supplement):3629.

Long-term outcomes of IV alnuctamab in patients with RRMM

- IV alnuctamab was administered in fixed doses (0.15–10 mg) or in step-up doses (single or double) to a **maximum 10-mg target dose**[1]
- 94% and 64% of patients experienced a treatment-related TEAE of any grade and grade 3/4, respectively[a]
- **76% of patients had a CRS** event,[b] including **4** patients with **grade 3** events and **1** patient with a **grade 5** event

	IV alnuctamab (n = 70)
Median follow-up, months (range)	8.0 (0.3–45.8)
ORR, n/N (%)	27/70 (39)
Median DOR, months (95% CI)	**33.6 (10.6-NE)**
Responses ongoing, n/N (%)	13/27 (48)



Database cut-off: September 28, 2022. Data are shown for the safety population.
[a]Two grade 5 AEs (CRS and pneumonia) occurred that were suspected to be treatment related. [b]Seventeen patients had ≥ 2 CRS events.
AEs, adverse events; DOR, duration of response; NE, not evaluable; ORR, overall response rate; PFS, progression-free survival; TEAE, treatment-emergent adverse event.
1. Costa LJ, et al. Oral presentation at the American Society of Hematology (ASH) Annual Meeting; December 7–10, 2019; Orlando, FL, USA. Abstract 143.

Phase 1 study design in patients with RRMM who received SC alnuctamab

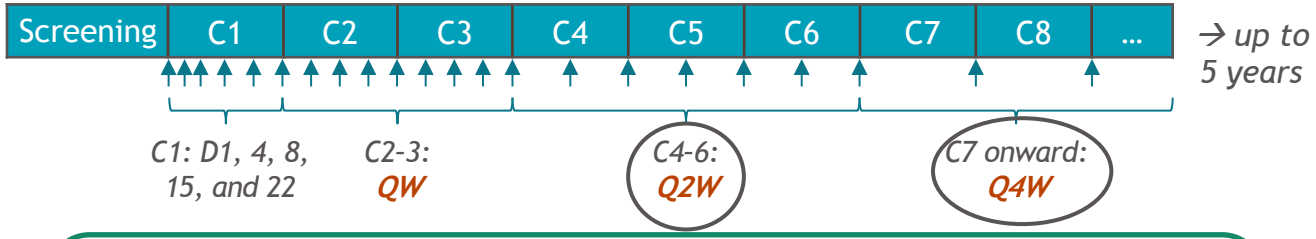
Key eligibility criteria

- RRMM after ≥ **3 prior regimens**, including an immunomodulatory drug (IMiD®), PI, and anti-CD38 therapy
- Progressive disease within 60 days of last regimen
- No prior BCMA-directed therapy

68 pts, at 3 doses, 4 median prior LOT, median follow-up: **4.1 months**

- **63% triple-refractory**
- **28% penta-refractory**

SC alnuctamab dose schedule (28-day cycles)



SC dose escalation

- All cohorts: 2 step-up doses (3 mg on C1D1 and 6 mg on C1D4)
- Target dose (10 mg, 15 mg, 30 mg, or 60 mg) on C1D8 and thereafter

SC cohort expansion – multiple cohorts

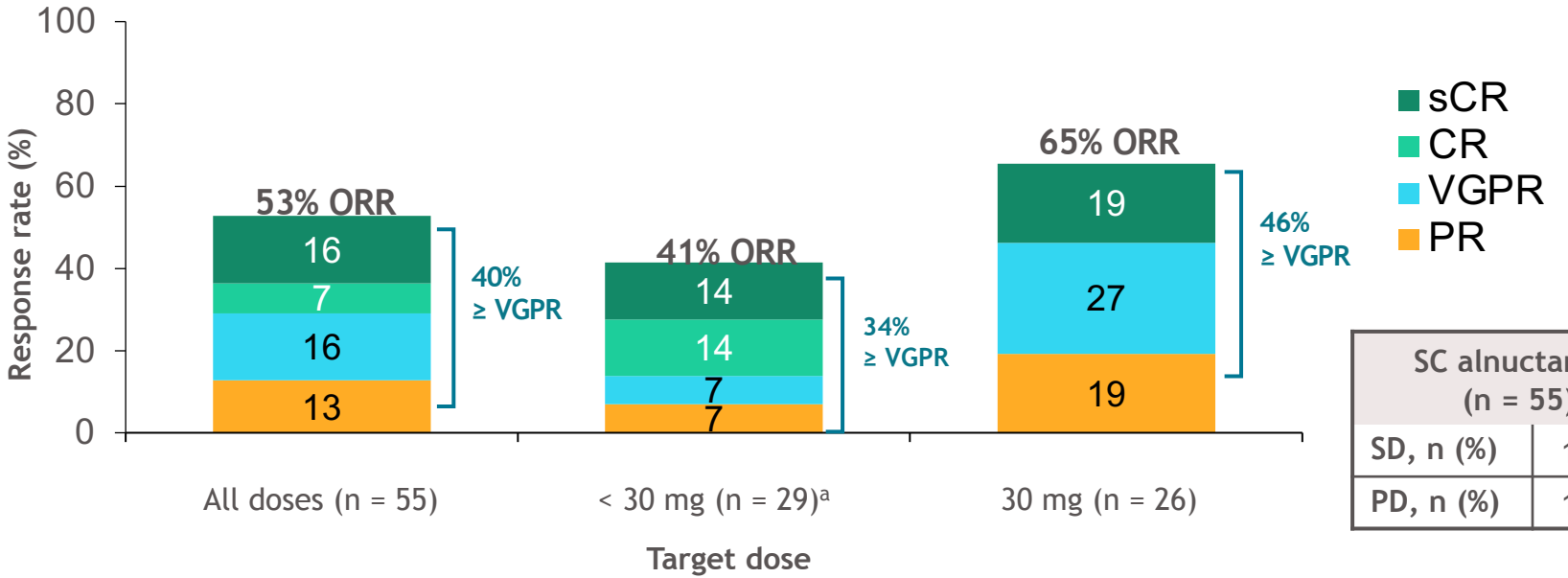
Endpoints

Primary:	Safety and tolerability, NTD, MTD, and RP2D
Secondary:	Preliminary efficacy and PK
Exploratory:	MRD negativity, PD parameters

Premedication with dexamethasone was required prior to administration of the step-up doses and first target dose.
C, cycle; D, day; MRD, minimal residual disease; MTD, maximum tolerated dose; NTD, non-tolerated dose; PD, pharmacodynamic; PI, proteasome inhibitor; PK, pharmacokinetics; RP2D, recommended phase 2 dose; SC, subcutaneous.

Wong SW, et al. ASH 2022

SC alnuctamab: overall response rate



SC alnuctamab (n = 55)	
SD, n (%)	13 (24)
PD, n (%)	11 (20)

- Among 29 patients who achieved a response, 16 of 20 patients with evaluable[b] MRD samples (80%) were MRD negative at C2D1 or C4D1 (≥ 10^{-5} sensitivity)
- MTD not reached

Database cut-off: November 1, 2022. Data are shown for the efficacy-evaluable population, defined as patients who met eligibility criteria, received ≥ 1 dose, and had ≥ 1 post-baseline efficacy assessment or discontinued treatment for lack of efficacy. Patients receiving the 60-mg target dose were excluded due to limited follow-up.
[a]Patients who received 10- or 15-mg target doses. [b]Excludes patients (n=9) who did not have an evaluable MRD sample at either C2D1 or C4D1 because of inadequate sample quality or missing samples. CR, complete response; PD, progressive disease; PR, partial response; sCR, stringent complete response; SD, stable disease; VGPR, very good partial response.

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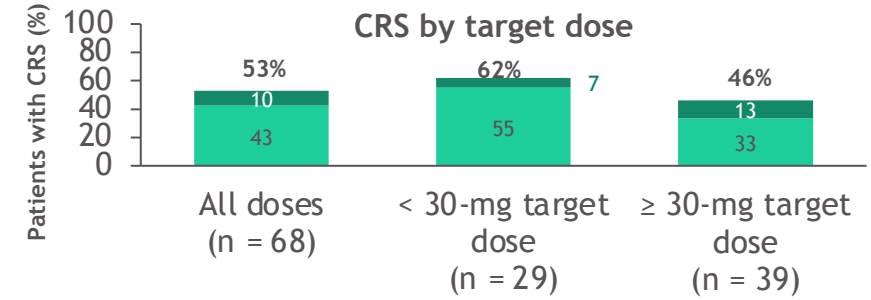
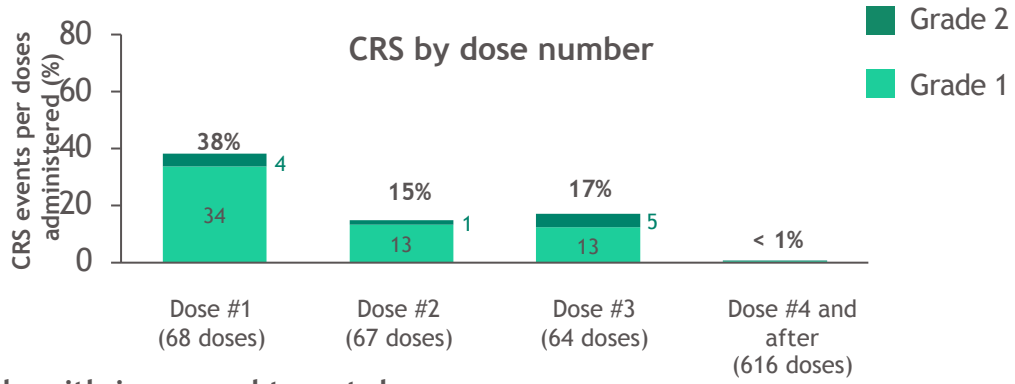
SC alnuctamab: cytokine release syndrome

	Safety population (n = 68)
Patients with a CRS event, n (%)	36 (53)
Grade 1	29 (43)
Grade 2	7 (10)
Grade ≥ 3	0
Patients with ≥ 2 CRS events, n (%)	14 (21)
Median time to onset, days (range)	3 (1–20)
Median duration of CRS, days (range)	2 (1–11)

CRS medication, n (%)	Patients with CRS (n = 36)	Safety population (n = 68)
Tocilizumab	19 (53)	19 (28)
Corticosteroids[a]	10 (28)	10 (15)





- **No significant increase in CRS frequency or grade with increased target dose**
- CRS was most common with the first step-up dose and was less frequent with subsequent doses

Database cut-off: September 28, 2022. Data are shown for safety population.
[a]In addition to premedication with dexamethasone prior to administration of the step-up doses and first target dose.

Wong SW, et al. ASH 2022

New strategies to mitigate CRS/ICANS

Tocilizumab pre-treatment prior to Cevostamab FcRH5 × CD3 bispecific antibody to mitigate CRS

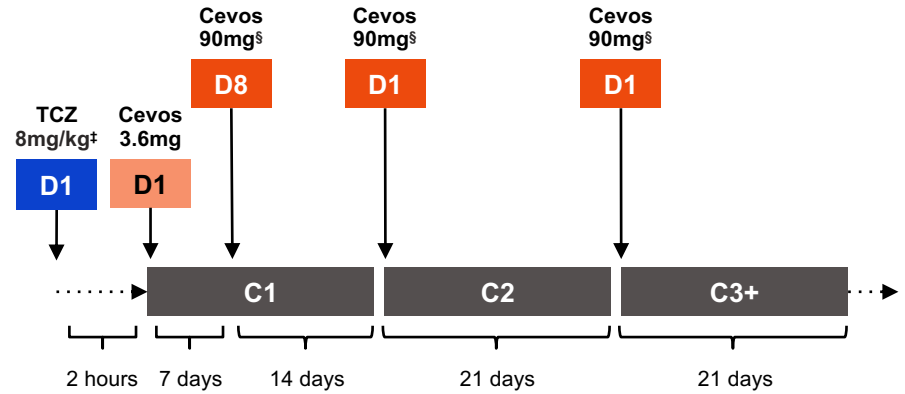
Key inclusion criteria

- RRMM for which no established therapy is available, appropriate or tolerable
- **Prior CAR T-cells, ADCs, and bispecific antibodies allowed**

Cevostamab dosing in all patients

- **Q3W IV infusions for up to 17 cycles***
- C1 single step dosing
- Premedication with acetaminophen, diphenhydramine, and corticosteroid

Single step dosing regimen†



Treatment cohorts in this analysis

- Patients in the TCZ pre-treatment (PT) group received a single 8mg/kg dose of TCZ
- Patient data from the previously enrolled non-TCZ PT 3.6/90mg group served as a retrospective comparator
- Patients in the TCZ PT and non-TCZ PT groups were enrolled at different times, and were not randomized to treatment
- TCZ and/or corticosteroids were allowed in both groups for CRS treatment

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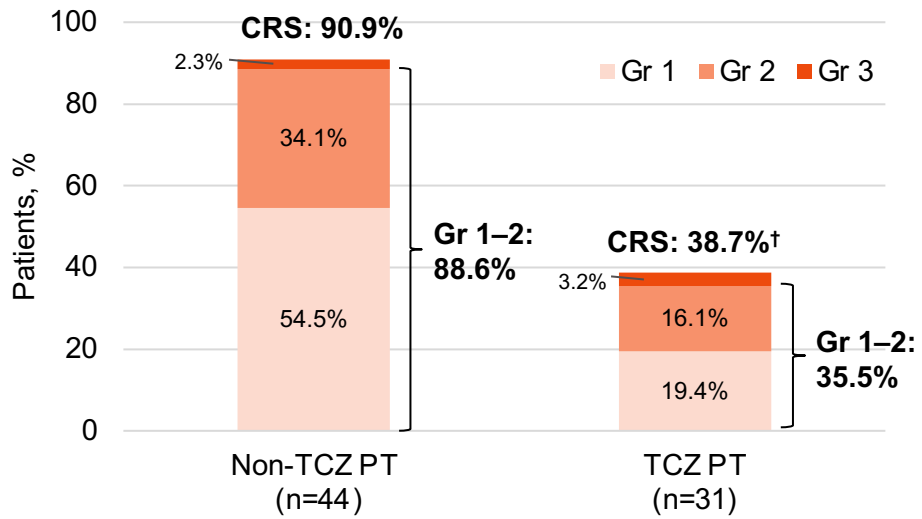
New strategies to mitigate CRS/ICANS

CRS rate and management

Patients (%) with CRS in the non-TCZ PT and TCZ PT groups*



- Median time to CRS onset from infusion of cevostamab was 1 day in both groups (range: non-TCZ PT, 0–3 days; TCZ PT, 1–3 days)
- In the non-TCZ PT group, 16 patients (36.4%) received TCZ treatment
- In the TCZ PT group, 6 patients (19.3%) received TCZ treatment

The overall rate of CRS was significantly lower in the TCZ PT group than in the non-TCZ PT group
No impact of TCZ on response rate and quality

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1. Lee et al. Biol Blood Marrow Transpl 2019;25:625–38

Open questions and future directions:
How to tailor targeted immunotherapy?

	Bispecific antibody	"New generation"CAR T
Response	**ORR: 43-79%** **CR: 19-43%**	**ORR: 73-100%** **CR: 33-83%**
Safety	**CRS** all grade/grade ¾: 38-80%/ **0-3%** **ICANS** all grade/grade ¾: 5-14%/**< 1%** **cytopenia and infections (up to 45% grade ¾)**	**CRS** all grade/grade ¾: 60-80%/ **0-15%** **ICANS** all grade/grade ¾: 6-18%/ **0-6%** **cytopenia, and infections**
Dosing	Q1W/Q2W/Q4W, IV/SC until PD **(starting fixed duration)**	Single dose
Accessibility	Off the shelf	Turnaround time, reducing
Administration	Inpatient for first doses/outpatient Available in community setting	Inpatient Available in community setting

The intention of the graph is not comparative and is provided for ease of viewing information from various products. Direct comparison between products is not intended and should not be inferred.

1. Lonial S, et al. Cancer. 2021;127:4198-212. 2. Becnel MR, et al. Ther Adv Hematol. 2020;11:2040620720979813. 3. Mailankody, S. N Engl J Med. 2022;387:558-61. 4. Minnema MC, et al. Oral presentation at EHA 2022; EHA Library;357046;abstract S182. 5. Munshi NC, et al. N Engl J Med. 2021;384:705-16. 6. Berdeja JG, et al. Lancet. 2021;398:314-24. 7. Mina R, personal opinion on the future direction therapy.

Open questions and future directions
Can we plan sequential ADC, TCE and CAR T?

Ide-cel in pts with prior anti-BCMA

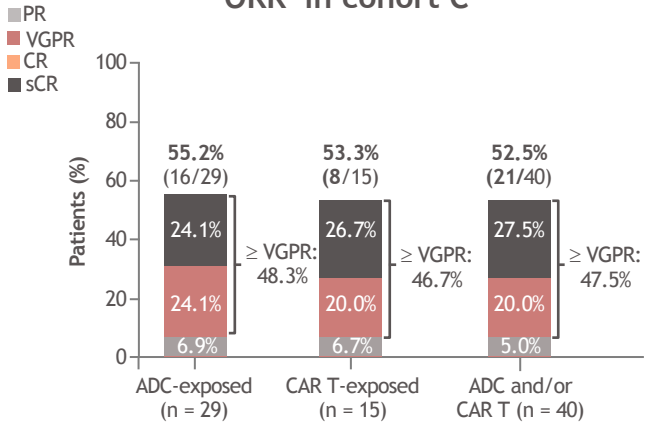
Ide-cel: ≥4 prior lines – real world data[1]

Characteristic	Best response of ≥ CR			PFS		
	OR	95% CI	p	HR	95% CI	p
Prior anti-BCMA	0.30	0.10, 0.79	0.02	2.51	1.21, 5.24	0.014
High-risk cytogenetics	0.79	0.35, 1.75	0.6	2.39	1.18, 4.85	0.016
Extramedullary disease	1.66	0.77, 3.66	0. 2	1.39	0.70, 2.78	0.3
ECOG PS ≥ 2	0.54	0.18, 1.51	0.3	1.91	0.79, 4.58	0.15
Penta-refractory	1.43	0.66, 3.16	0.4	0.93	0.46, 1.87	0.8
Cell dose ≥400 ×10⁶ CAR T-cells	0.90	0.41, 1.97	0.8	0.55	0.27, 1.10	0.09
Patient age, years	0.99	0.95, 1.04	0.7	1.00	0.97, 1.04	0.8

Teclistamab with prior anti-BCMA

MAJESTEC-1, Cohort C

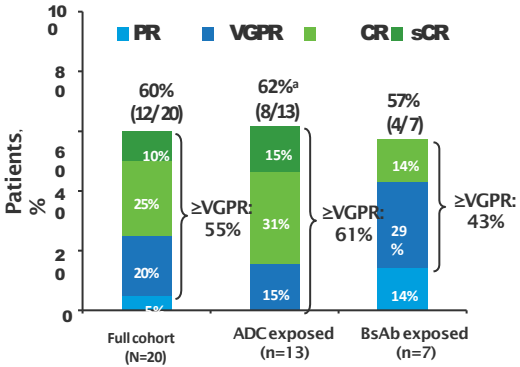
ORR[a] in cohort C



Cilta-cel with prior anti-BCMA

Cartitude-2, Cohort C
18 months follow-up

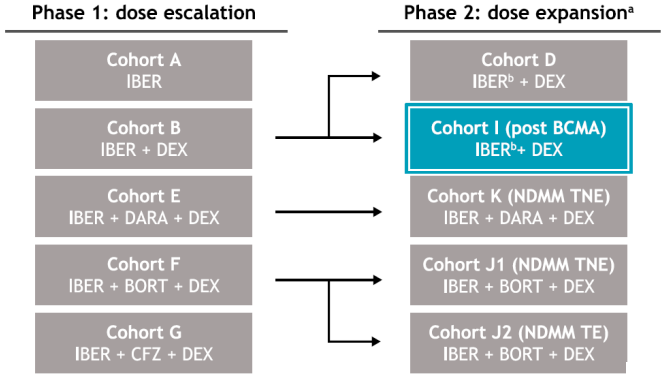
Overall response rate



- Median DOR: 12.3 months (8.2 after BsAb)
- Median PFS: 9.1 months (5.3 after BsAb)

Hansen DK, et al. JCO 2022; Touzeau C, et al. Poster presented at ASCO 2022; J Clin Oncol. 2022;40;abstract 8013; Cohen AD et al, ASH 2022 poster presentation

CelMods after T-cell redirecting therapies: Iberdomide



Key eligibility criteria

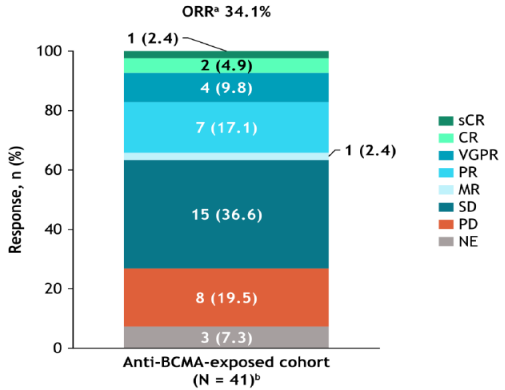
- RRMM
- ≥ 3 prior therapies including an anti-BCMA therapy[c]
- PD on or within 60 days of last antimyeloma therapy (or documented PD at any time if CAR T cell therapy was the last therapy)

Treatments

IBER + DEX
IBER (oral): 1.6 mg on days 1-21
DEX (oral): 40 mg[d] on days 1, 8, 15, 22
28-day cycles

Endpoints

- **Primary:** efficacy (ORR)
- **Secondary:** safety and additional efficacy parameters (such as DOR and PFS)
- **Exploratory:** pharmacodynamics assessments

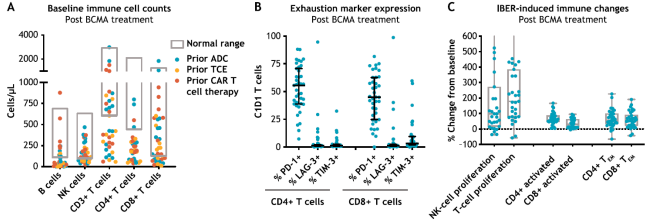


41 pts, 7 median prior LOT, median follow-up: 8.5 months

- **41% post CART**
- **32% post belamaf**
- **22% post bispecific Abs**

- **ORR independent from type of anti-BCMA therapy**
- **mDOR 7.5 mos**

Figure 4. IBER is immune-stimulatory post-BCMA therapy



CONCLUSION

- **T-cell redirecting therapy** (CART and T-cell engagers) is set to become the **first choice** in the treatment of MM patients beyond the third line
- **New generation CARTs** present better acute toxicity profile and show an ORR up to 100%; long-term results currently not available
- **Numerous anti-BCMA and anti-different targets Bispecific Antibodies** are crowding the scene, exploring **SC** administration and **different schedules**; the widespread use of **step-up dose** mitigates the rate of grade 3/4 CRS and ICANS as compared to CART. Specific **off tumor/on target** side effects should be aknowledge
- (Long-term) **infection risk is trasversal** to all T cell redirecting therapies and deserve special attention
- The **«sequencing issue»** of these newer treatment modalities is currently under investigation