WHAT IS THE BETTER TARGET IN RRMM? GPRC5D

Nisha S. Joseph, MD

Associate Professor

Department of Hematology and Medical Oncology

Winship Cancer Institute, Emory University

EMORY WINSHIP CANCER INSTITUTE
National Cancer Institute-Designated Comprehensive Cancer Center

NCI Designated Comprehensive Cancer Center

OBJECTIVES

- To crush Dr. Nooka

WHAT IS GPRC5D

Greatest

Possible

Receptor

Created

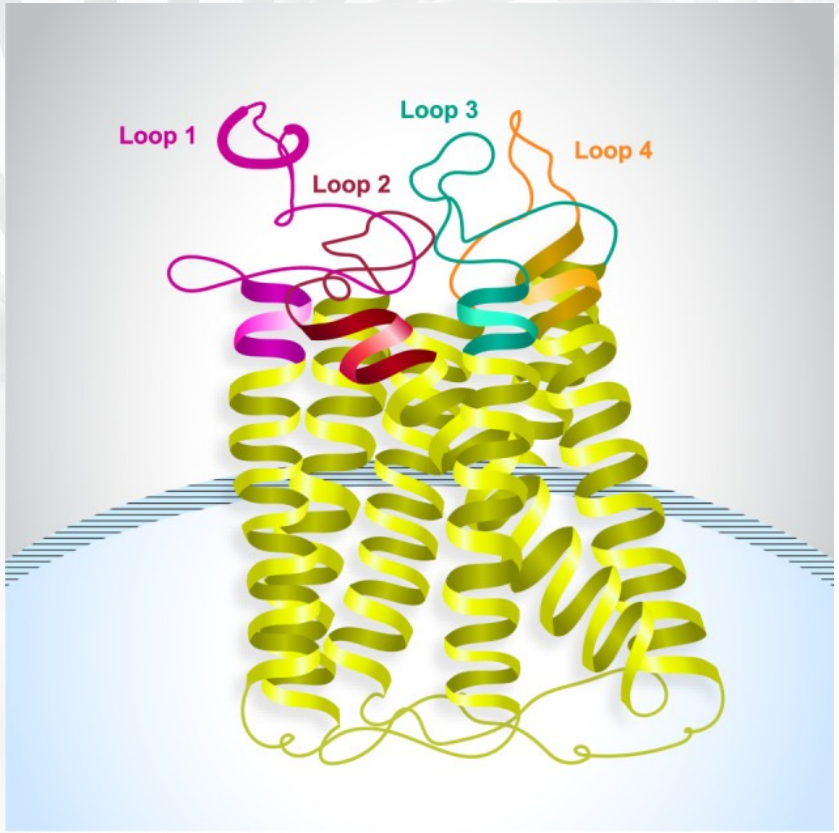
Expression: Malignant plasma cells, hair follicles, oral mucosa/tongue, skin, nail beds

*** Little to no expression in normal B cells, T cells, NK cells unlike BCMA*

*** BCMA- independent expression*

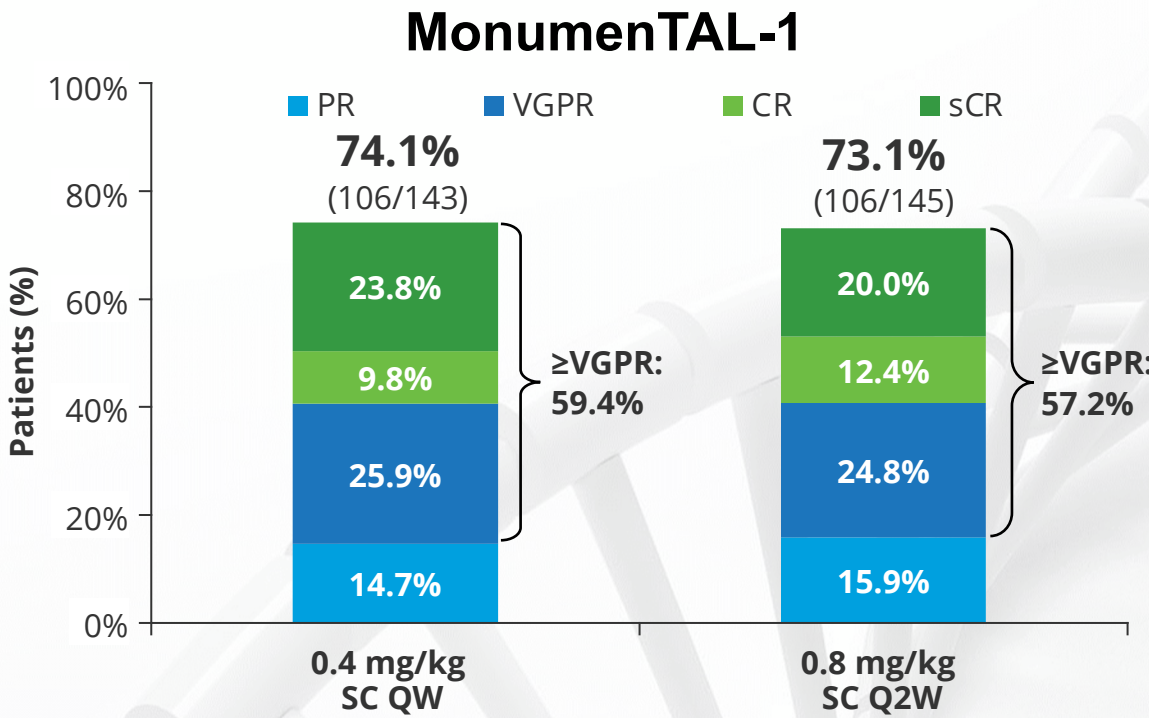
GPRC5D-specific AEs:

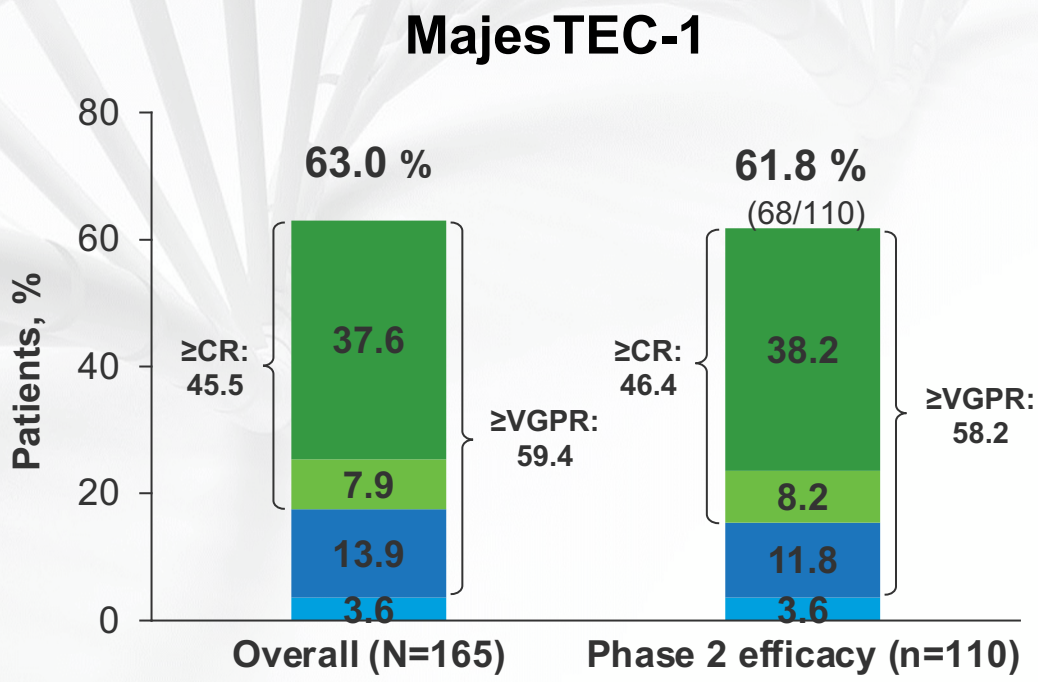
- Dysguesia
- Weight loss
- Skin and nail changes
- Rash



1. Tighter binding → increased cytotoxicity
2. Decreased likelihood of receptor shedding

REALITY BITES: EFFICACY



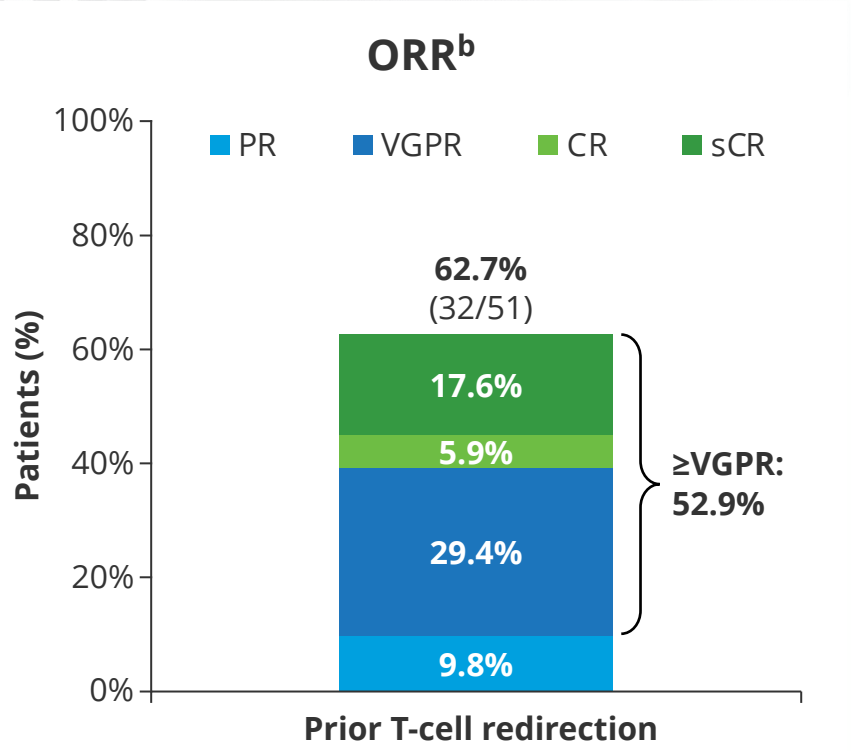


ORR was consistent across subgroups including baseline ISS stage III disease, baseline cytogenetic risk, number of prior therapies, and belantamab exposure

Subgroup analyses in MajesTEC-1/MagnetisMM-1 and -3 demonstrated **lower responses** in RISS 3, EMD, and increased bone marrow plasma cells of ≥60%.

TALQUETAMAB ORR IN PATIENTS WITH PRIOR T-CELL REDIRECTION

- **Patients enrolled in cohort of prior T-cell redirection therapy:**
  - **Were younger** and had a **higher prevalence of high-risk cytogenetics**
  - 71% with prior CAR-T (almost all with anti-BCMA)
  - Remainder with mostly prior BsAb (majority anti-BCMA)
- **ORR was 62.7%**
  - **72.2% ORR** (26/36) in patients with **prior CAR-T therapy**
  - **Prior BsAb:, ORR was 62.5%** (5/8) in pts who had ≥9 mo interval, 50% (3/6) in those who had ≥6 to <9 mo interval, and 45.5% (5/11) in those who had <6 mo interval.
- Median DOR was 12.7 months (range, 3.7–NE) at a median follow-up of 11.8 months (range, 1.0[a]–25.4)



Jakubowiak ASH 2023

INFECTIONS ARE WORSE THAN NAIL CHANGES

MajesTEC-1

AEs of Interest[a], N (%)	N = 165 Any Grade	N = 165 Grade ≥ 3
Hematologic		
Neutropenia	118 (71.5)	108 (65.5)
Anemia	90 (54.5)	62 (37.6)
Thrombocytopenia	70 (42.4)	37 (22.4)
Lymphopenia	60 (36.4)	57 (34.5)
Leukopenia	33 (20.0)	15 (9.1)
Non-Hematologic		
Infection	132 (80.0)	91 (55.2)
COVID-19	48 (29.1)	35 (21.2)
Hypogammaglobulinemia	34 (20.6)	3 (1.8)

Rates of CRS and ICANS similar

MonumenTAL-1

G3-4 infections: 16.8% and 11.7% (0.4 mg/kg qw; 0.8 mg/kg q2w)

AEs (≥20% of any RP2D cohort), n (%)	0.4 mg/kg SC QW[a] (n=143) mFU, 11.0 months[b]		0.8 mg/kg SC Q2W[a] (n=145) mFU, 5.1 months[c]	
	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)
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)

- **Low rates of discontinuation due to Aes** were observed with QW (4.9%) and Q2W (6.2%) schedules

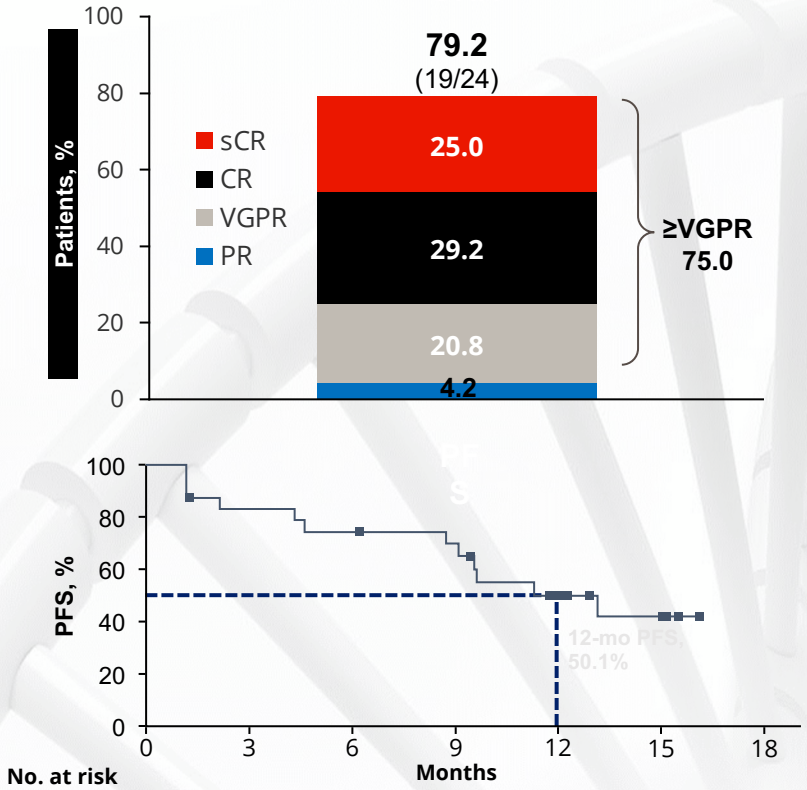
MAJESTEC-1: CLINICALLY RELEVANT INFECTIONS

Clinically relevant infections, n (%)	N=165		
	Any grade	Grade 3/4	Grade 5
Any infection	132 (80.0)	91 (55.2)	21 (12.7)
Respiratory infections	95 (57.6)	32 (19.4)	2 (1.2)
COVID-19 infection	48 (29.1)	35 (21.2)	18 (10.9)
Key viral infections[a]	20 (12.1)	7 (4.2)	1 (0.6)
GI infections	15 (9.1)	2 (2.1)	0
Fungal infections[b]	9 (5.5)	0	0
PJP[c]	7 (4.2)	7 (4.2)	0
HBV reactivation	1 (0.6)	1 (0.6)	0

- Infections were selected based on categories of clinically relevant infections typically occurring in patients with relapsed/refractory multiple myeloma using MedDRA version 24.0. Patients were counted once for any given event, regardless of the number of times they experienced the event. If the toxicity grade was missing for a specific infection, the patient was only counted in the total percentage for that infection. [a]Excluding COVID-19. [b]Excluding PJP. [c]Four of the 7 patients with PJP had no PJP prophylaxis. GI, gastrointestinal; HBV, hepatitis B virus; PJP, *Pneumocystis jirovecii* pneumonia.

MONUMENTAL-1: PROSPECTIVE DOSE INTENSITY REDUCTION COHORTS – RESPONSE MAINTAINED AFTER SWITCH

- Patients with dose reductions had to be in response (n=19); dose reduction occurred at a median of 3.1 mo (range, 2.3–4.2) relative to treatment start



	Prospective (n=19)
Median follow-up, mo (range)[a]	13.2 (4.0+–16.1)
Median PFS, mo (95% CI)[a]	13.2 (8.8–NE)
12-mo PFS rate, % (95% CI)[a]	50.1 (27.9–68.7)
Median DOR, mo (95% CI)	NE (8.3–NE)

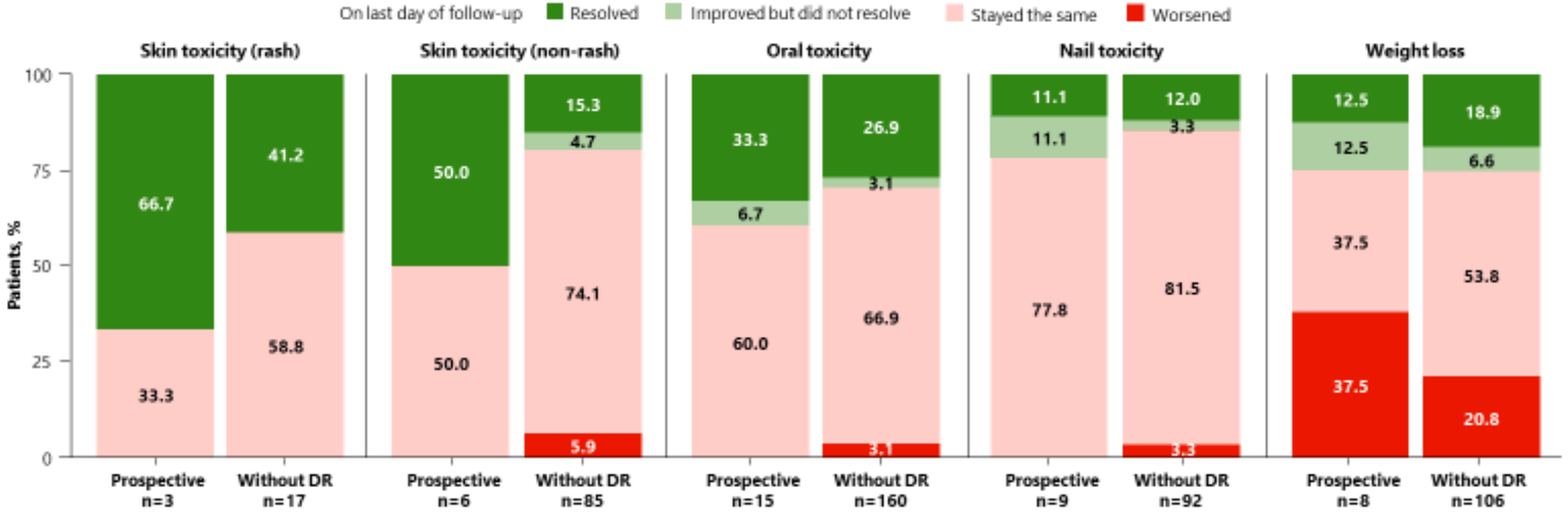
- In the 0.8 mg/kg Q2W registrational cohort (n=145)[1,b]
  - ORR: 71.7%
  - Median PFS: 14.2 mo (95% CI, 9.6–NE)
    - 12-mo PFS rate: 54.4%
  - Median DOR: NE (95% CI, 13.0–NE)

Data cut-off date: October 2, 2023. [a]Based on all patients included in the cohorts (N=24). [b]Data cut-off date: January 17, 2023. CR, complete response; DOR, duration of response; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; PR, partial response; Q2W, every other week; sCR, stringent complete response; VGPR, very good partial response.

1. Touzeau C, et al. Presented at EHA; June 8–11, 2023; Frankfurt, Germany.

MonumenTAL-1: Prospective Dose Intensity Reduction Cohorts – Resolution of GPRC5D-Related AEs vs Matched Cohort

Prospective cohorts with change in AE status after switch vs matched cohort without dose reduction[a]

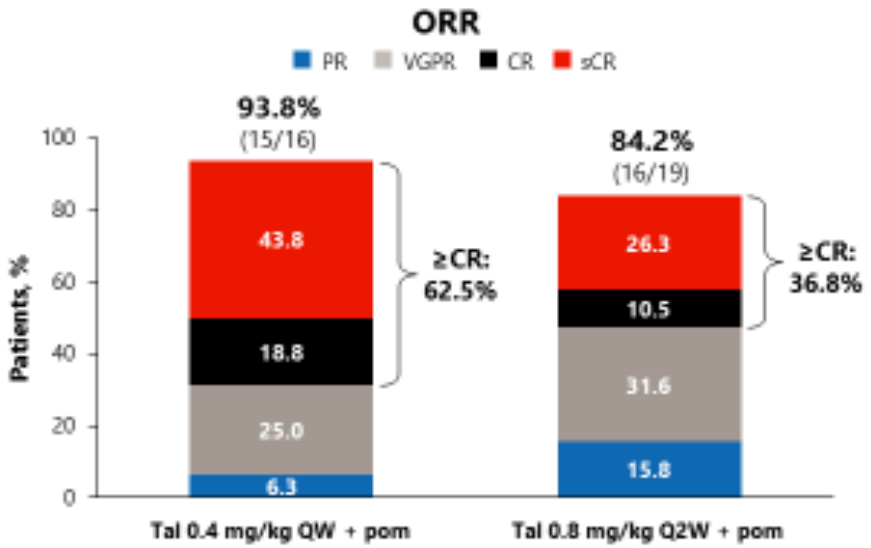


- Trend toward improved resolution of GPRC5D-related AEs, except weight loss

Data cut-off date: October 2, 2023. [a]Patients included had ≥PR before day 200 from the prospective dose intensity reduction cohorts (n=18) and from the MonumenTAL-1 cohort who did not dose reduce (n=206). Each category shows only patients who had a respective AE on day 100. Color signifies how that respective AE grade changed from day 100 to last day of follow-up (within 30 days of last treatment; capped at 500 days).
AE, adverse event; DR, dose reduction; GPRC5D, G protein–coupled receptor family C group 5 member D; PR, partial response.

Presented by A Chari at the 65th American Society of Hematology (ASH) Annual Meeting; December 9–12, 2023; San Diego, CA, USA

MonumenTAL-2 (Tal+Pom): High ORR With Rapid and Deep Responses



	Tal 0.4 mg/kg QW + pom (n=16)	Tal 0.8 mg/kg Q2W + pom (n=19)
Median follow-up, months (range)	15.0 (1.2–19.0)	11.1 (1.2–14.8)
Median time to first response, months (range)	1.7 (0.9–3.3)	1.2 (0–4.8)

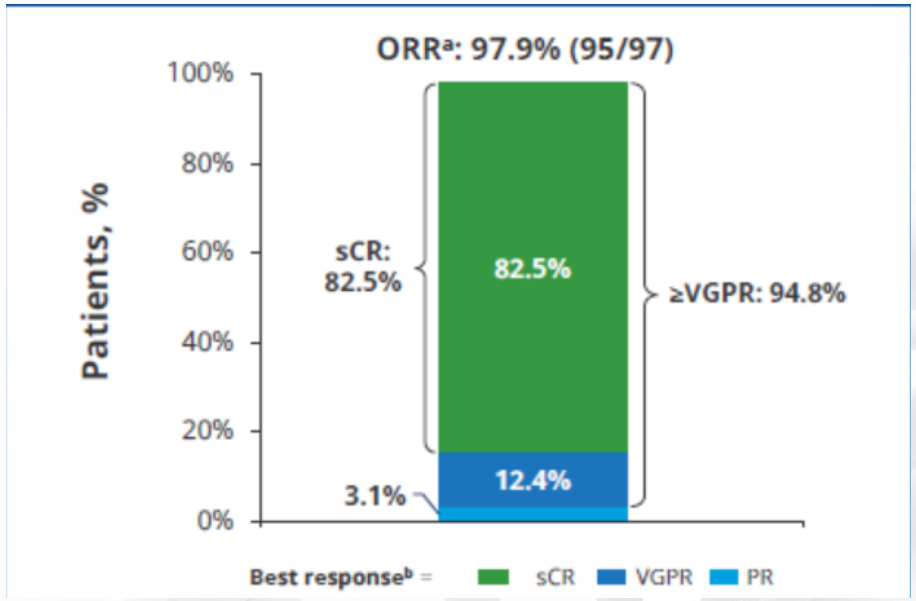
- ORRs were consistent across patient subgroups
  - 100% (3/3) in CAR-T–exposed patients in the QW cohort (no patients had CAR-T exposure in Q2W)
  - 100% (5/5 in QW, 3/3 in Q2W) in pomalidomide-exposed patients in both cohorts
  - 50% (1/2 in QW) and 67% (2/3 in Q2W) in patients with EMD
  - 80% (4/5 in QW) and 75% (3/4 in Q2W) in patients with high-risk cytogenetics

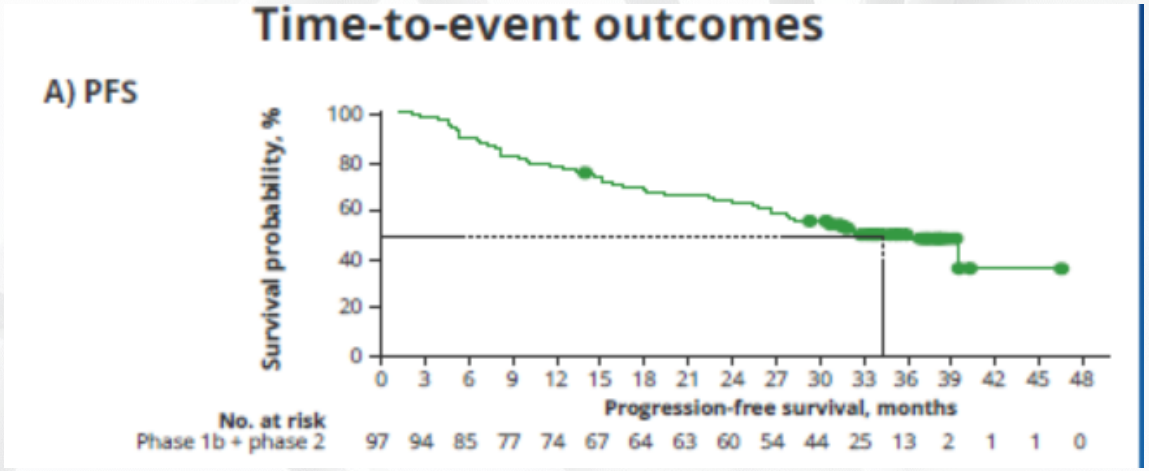
Data cut-off date: October 11, 2023.
CAR, chimeric antigen receptor; CR, complete response; EMD, extramedullary disease; ORR, overall response rate; pom, pomalidomide; PR, partial response; Q2W, every other week; QW, weekly; sCR, stringent complete response; tal, talquetamab; VGPR, very good partial response.

Presented by J Matous at the 65th American Society of Hematology (ASH) Annual Meeting; December 9–12, 2023; San Diego, CA, USA

BCMA CAR-T: CILTACEL

CARTITUDE-1: Ciltacel



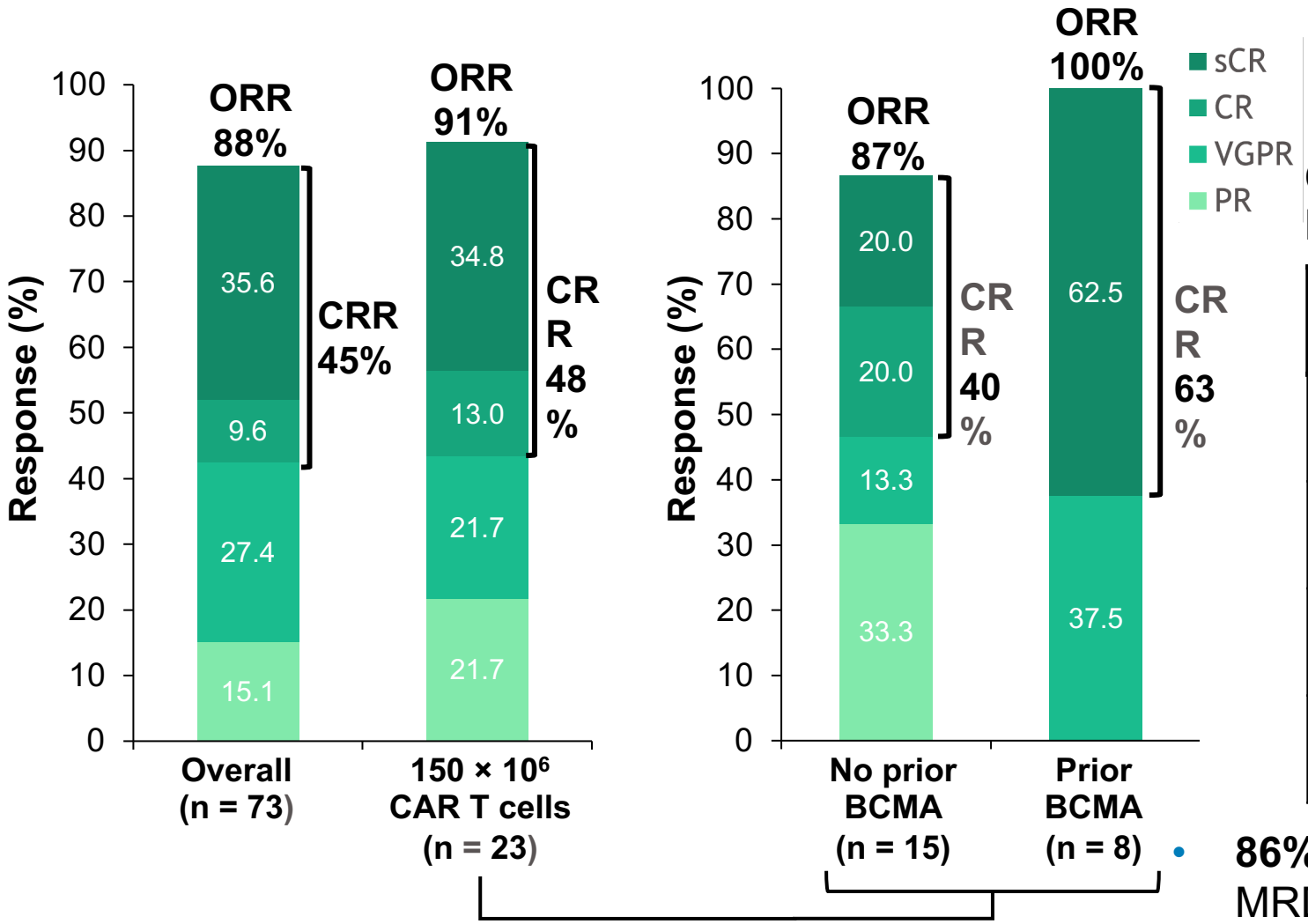


Study deaths

	Patients (N=97)	Time of death post cilta-cel infusion, days
Total deaths during the study	35	45–980
Due to progressive disease	17	253–980
AEs unrelated to treatment	**12**	
Pneumonia	2	109; 887
AML[a]	3	418; 582; 718
Ascites[b]	1	445
MDS	1	803
Respiratory failure	3	733; 793; 829
Septic shock and/or sepsis	2	917; 945
AEs related to treatment	**6**	
Septic shock and/or sepsis	2	45; 162
CRS/HLH	1	99
Lung abscess	1	119
Respiratory failure	1	121
Neurotoxicity	1	247

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[a]	36 (20.5)	5 (2.8)			
ICANS	8 (4.5)	0[b]	10	2	8
Other[c]	30 (17.0)	4 (2.3)			
Cranial nerve palsy[d]	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

BMS-986393 IN RRMM: HIGH RESPONSE RATES IRRESPECTIVE OF PRIOR BCMA-TARGETED THERAPY OR HIGH-RISK FEATURES[A]



ORR in subgroups of interest (all dose levels)

Disease characteristic, % (n/N)	Present	Absent
Prior BCMA treatment	78% 25/32	95% 39/41
Extramedullary disease	84% 26/31	91% 38/42
High-risk cytogenetics[b]	83% 24/29	91% 40/44
Triple-class refractory	88% 50/57	88% 14/16

- **86%** of MRD-evaluable patients with ≥CR achieved MRD negativity

Data cutoff: September 11, 2023. [a]The efficacy-evaluable analysis set includes all patients who received conforming BMS-986393 cell product, had measurable disease at the last disease assessment prior to BMS-986393 infusion, and had ≥ 1 post-infusion disease response assessment. Responses were assessed per International Myeloma Working Group criteria.
[b]del(17p), t(4;14), and/or t(14;16).
CR, complete response; CRR, complete response rate; ORR, overall response rate; PR, partial response; sCR, stringent complete response; VGPR, very good partial response.

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

BMS-986393 IN RRMM: SAFETY PROFILE

	All treated patients (n = 84)		150 × 10^6 CAR T cells (n = 26)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
TEAE, n (%)	77 (91.7)	69 (82.1)	26 (100)	24 (92.3)
Hematologic TEAEs (≥ 30% of all treated patients), n (%)				
Neutropenia	54 (64.3)	52 (61.9)	20 (76.9)	18 (69.2)
Anemia	40 (47.6)	25 (29.8)	13 (50.0)	11 (42.3)
Thrombocytopenia	36 (42.9)	22 (26.2)	10 (38.5)	5 (19.2)
Non-hematologic TEAEs (≥ 30% of all treated patients), n (%)				
CRS	64 (76.2)	3 (3.6)	23 (88.5)	0 (0)
Infections and infestations	34 (40.5)	11 (13.1)	9 (34.6)	3 (11.5)
Hypokalemia	31 (36.9)	4 (4.8)	12 (46.2)	2 (7.7)
Hypocalcemia	28 (33.3)	2 (2.4)	7 (26.9)	0 (0)
Headache	27 (32.1)	1 (1.2)	8 (30.8)	0 (0)
Hypophosphatemia	26 (31.0)	2 (2.4)	11 (42.3)	1 (3.8)

No grade ≥ 3 CRS or MAS/HLH events were observed among the 26 patients at the 150 × 10^6 CAR T-cell dose

TEAEs related to BMS-986393	All treated patients (n = 84)		150 × 10^6 CAR T cells (n = 26)	
On-target/off-tumor, n (%)	Any grade	Grade 3/4	Any grade	Grade 3/4
Dysgeusia/taste disorder	21 (25.0)	0	8 (30.8)	0
Skin[a]	17 (20.2)	0	4 (15.4)	0
Nails[b]	11 (13.1)	0	3 (11.5)	0
Dysphagia	3 (3.6)	0	1 (3.8)	0

86% of on-target/off-tumor skin, nail, and oral AEs did not require treatment; events were transient with a median 25-day duration (range, 2–355)

Low-grade[e] weight loss occurred in 7% of patients

Data cutoff: September 11, 2023. CRS, cytokine release syndrome; HLH, hemophagocytic lymphohistiocytosis; MAS, macrophage activation syndrome; TEAE, treatment-emergent adverse event.

1. Bal S, et al. *Hemasphere* 2023;7(suppl):e9863287.

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

SUMMARY

- Targeting GPRC5D has resulted in higher efficacy to date with less toxicity
- Specific AEs (dysgeusia, nail/skin changes) though majority low grade and manageable; decreased incidence with optimized dosing schedule
- Significantly lower rates of Grade 3-4 infections (receptor biology)
- Promising future directions
  - GPRC5D CAR-T cells
  - GPRC5D BiTEs (Forimtamig)
  - GPRC5D ADCs
  - Tri-specific Abs
  - In combination with MM agents