Prioritizing the target: BCMA vs GPRC5D

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Conflict of Interest Disclosure

Consultancy and Honoraria: AstraZeneca, Blue Earth Diagnostics, Cellectar biosciences, GlaxoSmithKline, Janssen, KITE therapeutics, ONK therapeutics, OPNA, Pfizer, Perceptive informatics LLC, Premier Research Sanofi and Sebia

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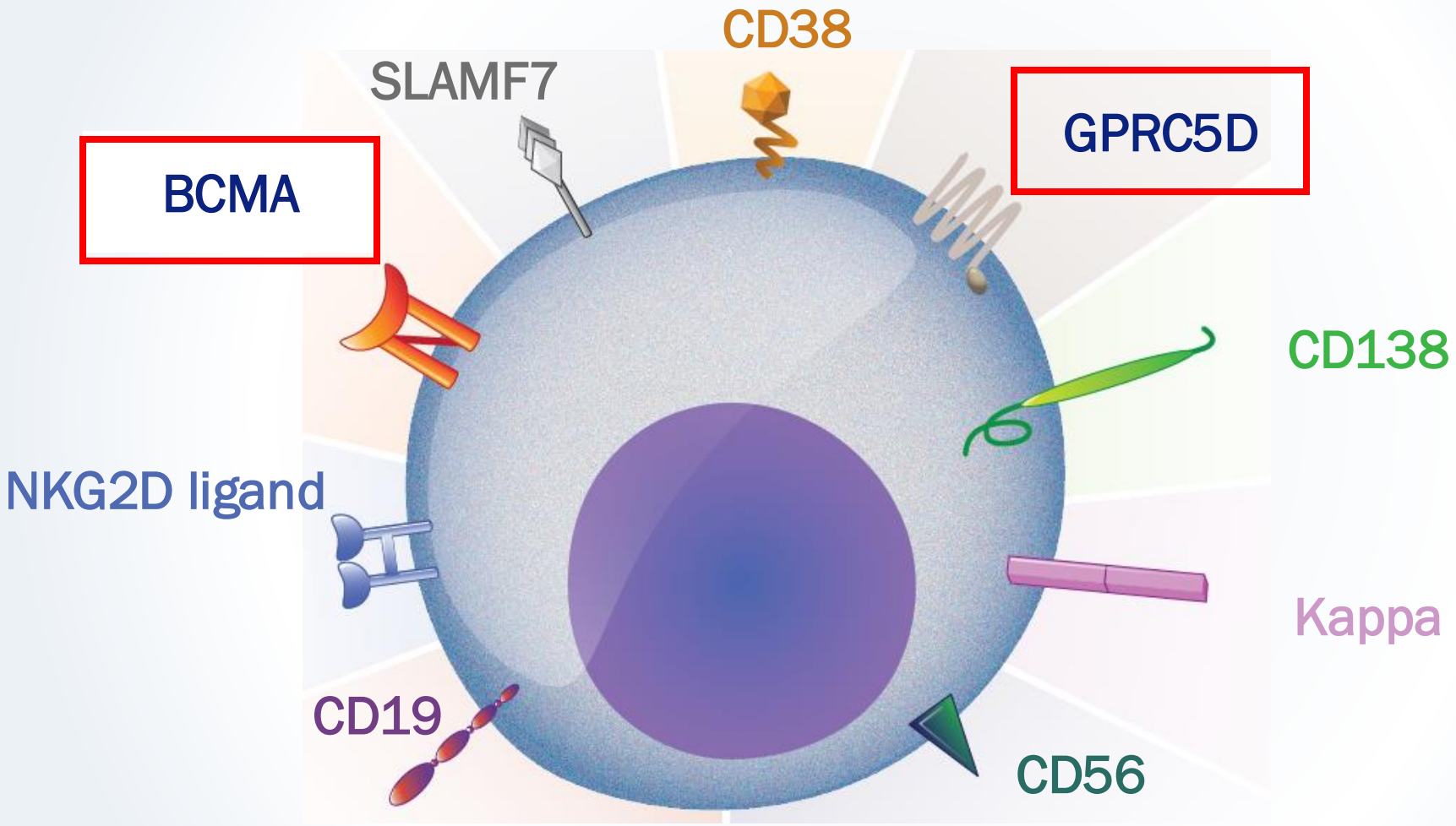
Discussion of off-label drug use: None

Available Multiple Myeloma Therapies and Targets in 2026

IMIDs (cereblon)	PIs (proteasome)	Novel mechanisms	Naked antibodies	ADC	CART	Bispecific antibodies
Thalidomide	Bortezomib	Selinexor (XPO1)	Daratumumab (CD38)	Belantamab (BCMA*MMAF)	Ide-cel (BCMA)	Teclistimab (BCMA*CD3)
Lenalidomide	Carfilzomib	Venetoclax (BCL2)	Isatuximab (CD38)		Cilta-cel (BCMA)	Elranatamab (BCMA*CD3)
Pomalidomide	Ixazomib		Elotuzumab (CS1/SLAMF7)		Anito-cel (BCMA)	Linvoseltamab (BCMA*CD3)
Iberdomide					Arlo-cel (GPRC5D)	Etentamig (BCMA*CD3)
Mezigdomide						Talquetamab (GPRC5D*CD3)
						Cevostamab (FcRH5*CD3)

Belantamab: Continued EU approval since 2020, US withdrawal in 2022, Approval for BVD in 2025
Ide-Cel: US and EU approval in 2021
Cilta-cel: US and EU approval in 2022
Teclistimab: US and EU approval in 2022, Tec + Dara in 2026
Elranatamab and Talquetamab: US and EU approval in 2023
Linvoseltamab: US and EU approval in 2025

Immunotherapy Targets

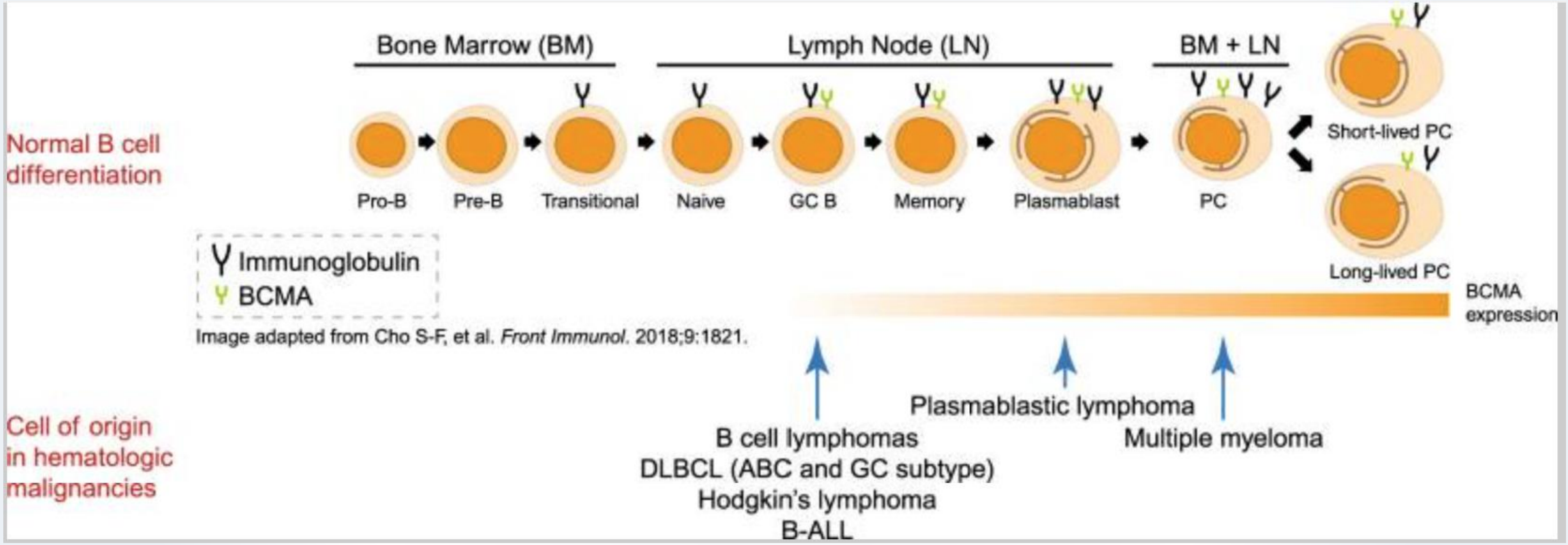


Shah and Mailankody. Best Practice & Research: Clinical Hematology 2019

Progress with new targets/products 2026

Target	Construct	Modality	RRMM	Early relapse	NDMM
CD38	CD38 mab	Naked Ab			
SLAMF7	SLAMF7 mab	Naked Ab			
	SLAMF7*CART	CART			
BCMA	BCMA*MMAF	ADC			
	BCMA*CART	CART			
	BCMA*CD3	BsAb			
	BCMA*CD38*CD3	Trispecifics			
GPRC5D	GPRC5D*CD3	BsAb			
	GPRC5D*CART	CART			
	GPRC5D*MMAE	ADC			
	GPRC5D*BCMA*CD3	Trispecifics			
FCRH5	FcRH5*CD3	BsAb			
	FcRH5*CART	CART			
CD138	CD138*MMAF/MMAE	ADC			
	CD138*CART	CART			

BCMA expression in B-cell development

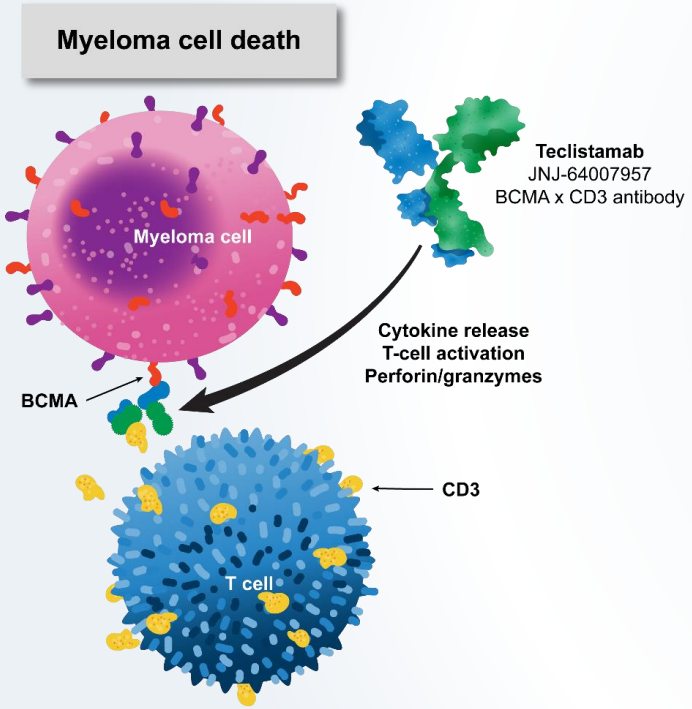


Dogan et al. Blood Cancer Journal. 2020 Jun 30;10(6):73.

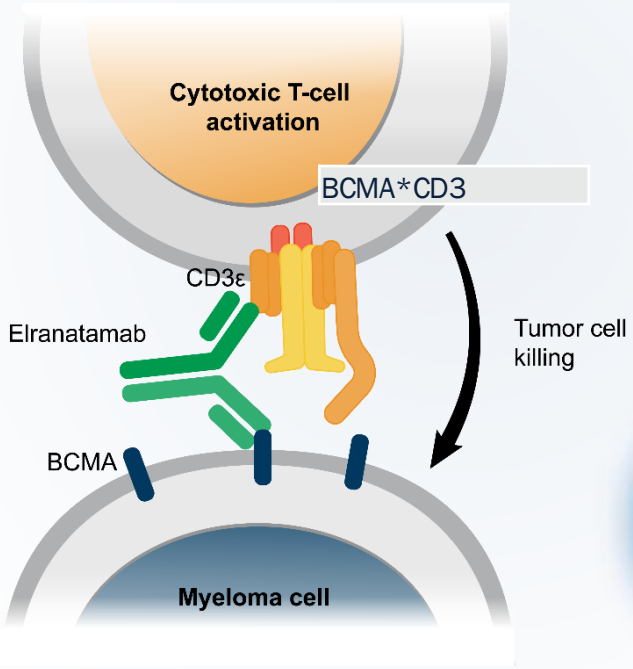
In Myeloma, Bispecific Antibodies Bind to CD3 T Cells and BCMA on the Myeloma Cell[1-3]

BCMA*CD3

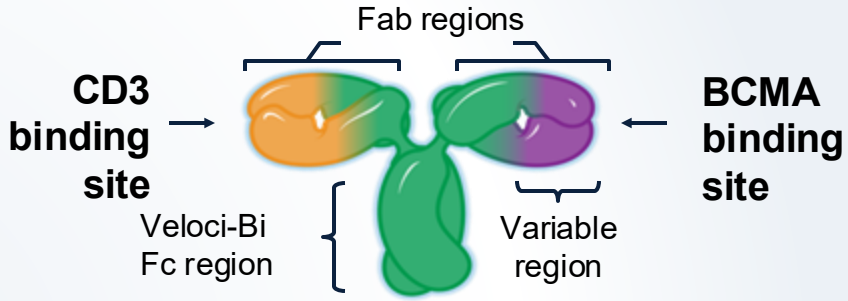
Teclistamab binds to CD3 on T cells and BCMA on plasma cells



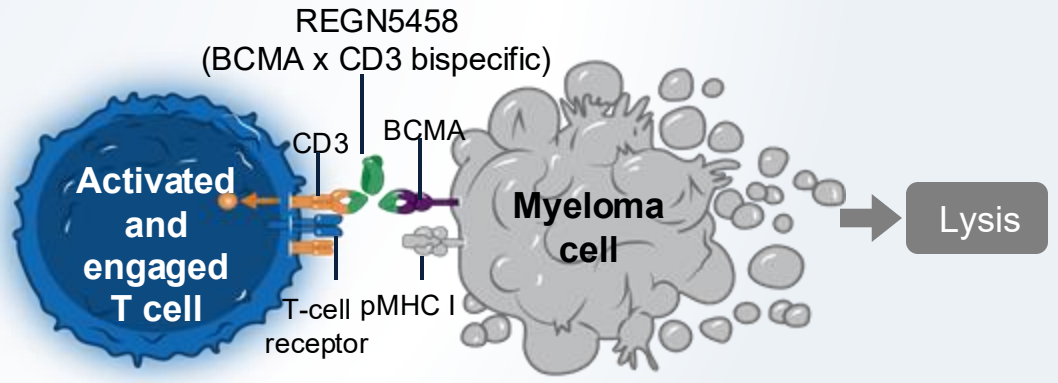
Elranatamab: a humanized bispecific targeting BCMA and CD3



Linvoseltamab Molecular Structure and MOA[1]



Targets T-cell effector function
Induces cytotoxicity of BCMA-expressing MM cells

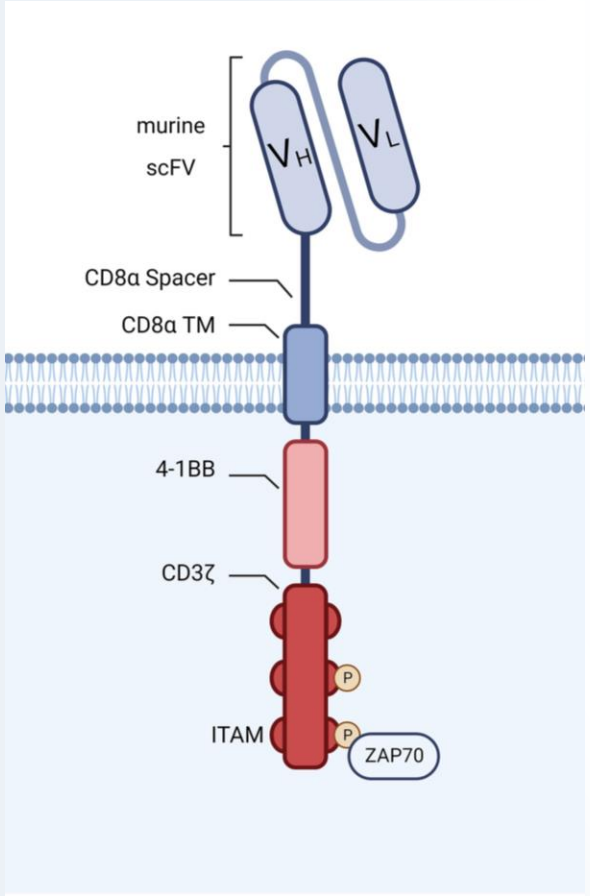


1. Nooka A et al. ASCO 2022. Abstract 8007. 2. Jakubowiak AJ et al. ASCO 2022. Abstract 8014. 3. 1. Zonder JA et al. EHA 2022. Abstract S189

BCMA*CART

BCMA-Directed CAR-T in Multiple Myeloma

Ide-cel (ABECMA)



FDA Approved: Mar 26, 2021

KarMMa Trial

Phase II (n=128)

ORR: 72%

95% CI, 63.2 – 80.8

ORR = sCR + VGPR + PR

mDOR: 22.6 months

95% CI, 14.39 – NE

mPFS: 11.3 months

95% CI, 10.3 – 15.3

mOS: 24.0 months

95% CI, 18.96 – NE

Cilta-cel (CARVYKTI)

FDA Approved: Feb 28, 2022

CARTITUDE-1 Trial

Phase Ib/II (n=97)

ORR: 98%

- 95% CI 92.7–99.7
- ORR = sCR + VGPR + PR

mDOR: 33.9 months

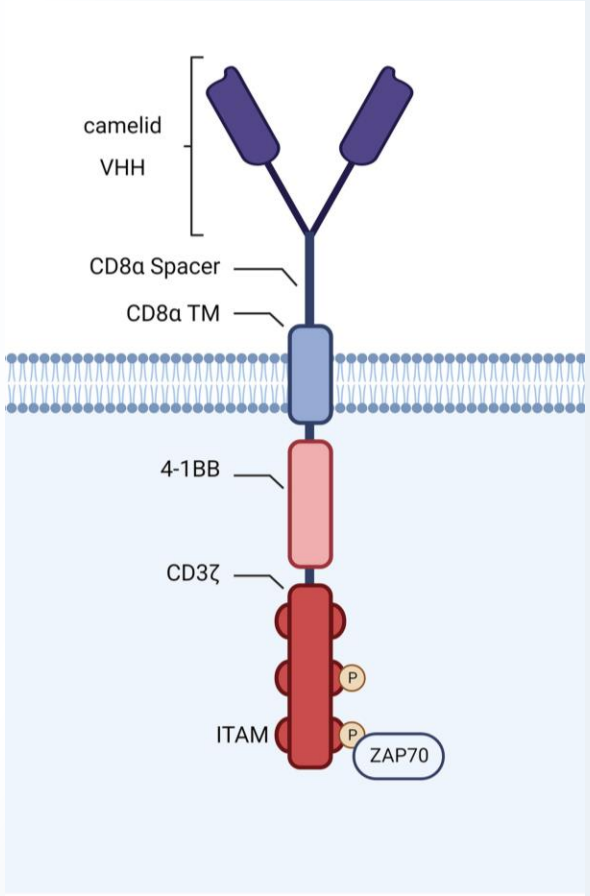
- 95% CI: 25.5 – NE

mPFS: 34.9 months

- 95% CI: 25.2 – NE

mOS: NR

- 62.9% OS at 36 months



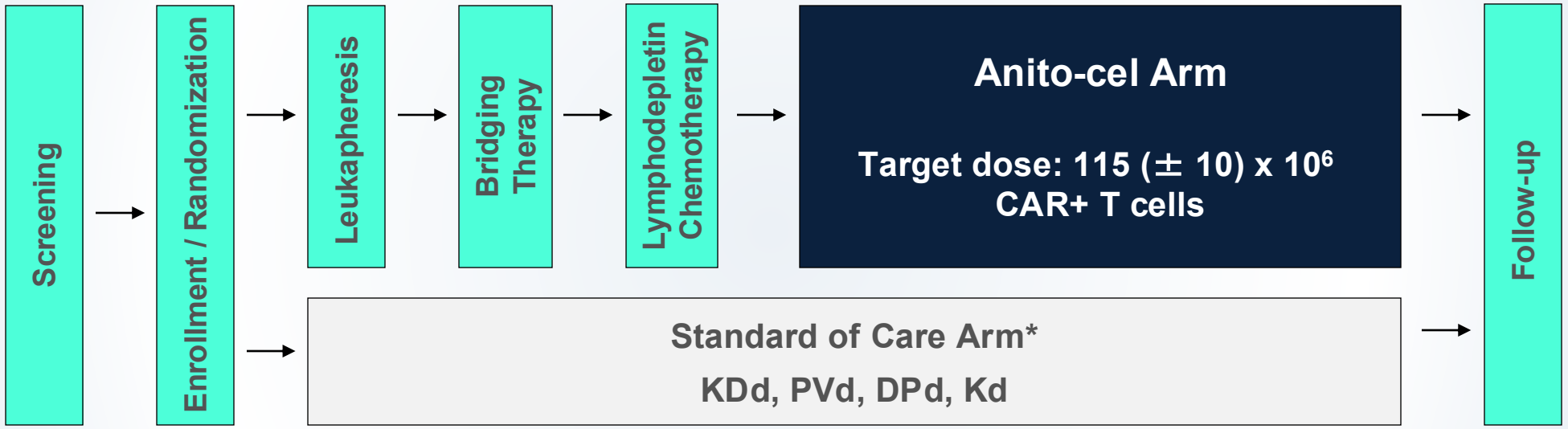
https://www.abecmahcp.com/ (Accessed Feb 15, 2024); Yi Lin et al. *JCO* 41, 8009-8009 (2023).

iMMagine-3 Design, Global Phase 3 Study – completed Enrollment

BCMA*CART

iMMagine-3 (NCT06413498) is a global, Phase 3 trial comparing anito-cel to standard of care therapy in patients with RRMM after 1-3 prior LoT, including an anti-CD38 monoclonal antibody and an iMiD

Anito-cel is being co-developed by Arcellx and Kite, and is being manufactured by Kite for iMMagine-3



Study Design

- 1:1 Randomization
- n = Approximately 450, ~130 sites globally

Patel et al, American Society of Hematology 2025, Abstract 256

Study Endpoints

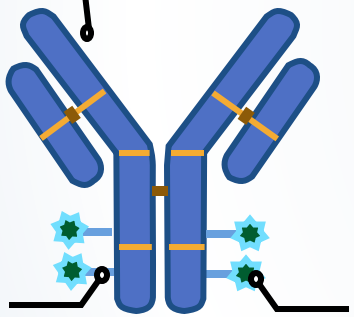
- Primary Endpoints:
  - PFS
  - MRD-negative CR rate at 9 months
- Key Secondary Endpoints: CR rate, MRD, OS, safety

Belantamab Mafodotin: Mechanism of Action

BCMA*ADC

Belantamab mafodotin:
a BCMA-directed antibody and microtubule inhibitor conjugate, comprising 3 components

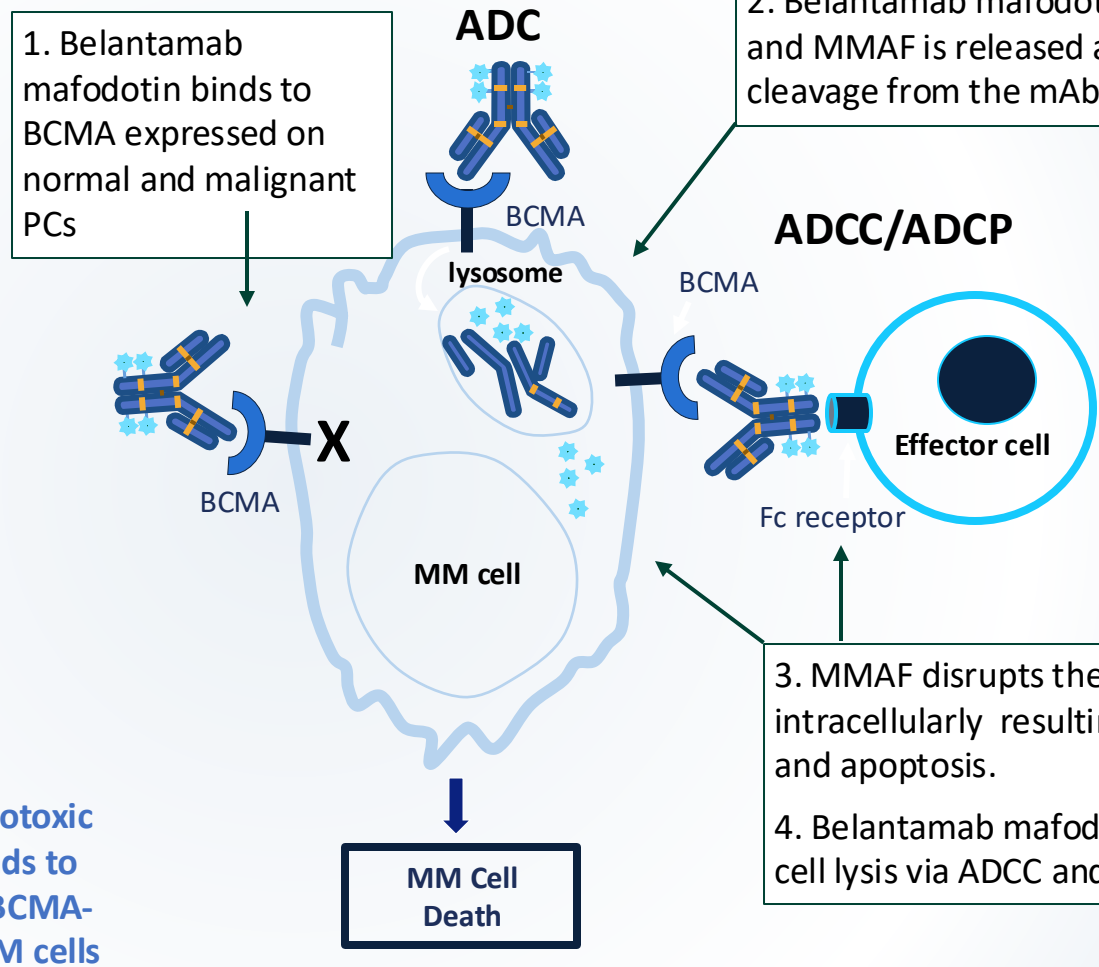
1 **Humanized anti-BCMA IgG1 mAb that binds to BCMA-expressing MM cells**



Protease-resistant maleimidocaproyl linker that joins MMAF to mAb and releases payload only in target cell

3

2 **MMAF: microtubule-disrupting cytotoxic agent that leads to apoptosis of BCMA-expressing MM cells**

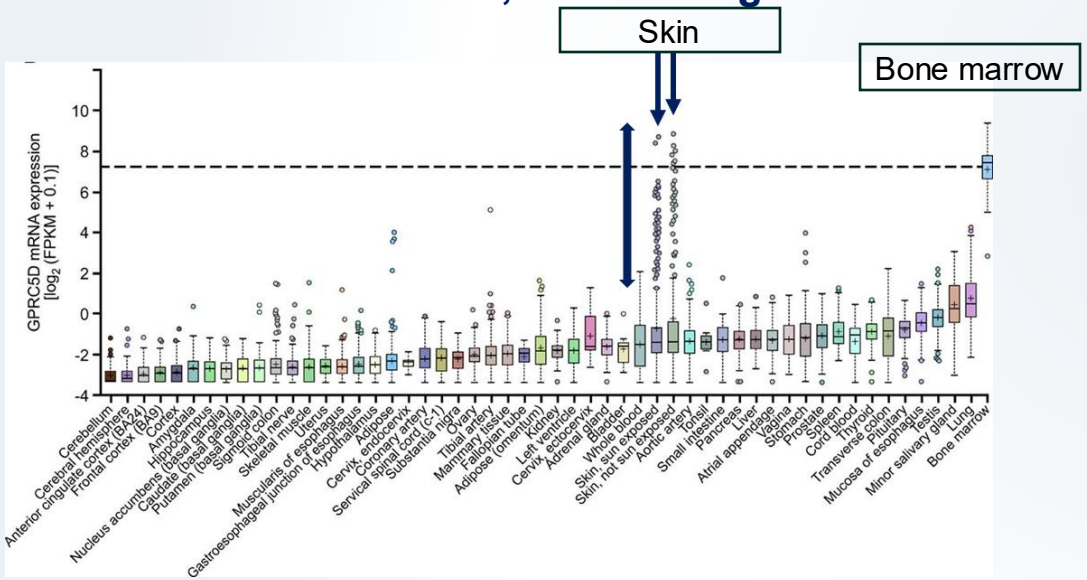


Tai. Blood. 2014;123:3128. Farooq. Ophthalmol Ther. 2020;9:889.

Safety with Talquetamab Reflects On-Target/Off-Tumor Toxicity

GPRC5D*CD3

Variable expression in hair follicle, keratinizing tissue



Oral AEs

Dysgeusia[a]
Incidence: 72.3%
Grade 3/4: N/A
Time to onset: 13-20 days
Resolved: 38.3%
Discontinuation: 0.6%

Dysphagia
Incidence: 24.2%
Grade 3/4: 0.9%
Time to onset: 21-29 days
Resolved: 65.9%
Discontinuation: 0%

Dry mouth
Incidence: 36.0%
Grade 3/4: 0%
Time to onset: 19-26 days
Resolved: 39.0%
Discontinuation: 0%

Skin-related AEs (rash and nonrash)

Weight decrease
Incidence: 39.5%[b]
Grade 3/4: 3.2%
Time to onset: 87-91 days[c]
Resolved: 38.7%
Discontinuation: 0.9%

Rash[d]
Incidence: 34.8%
Grade 3/4: 3.5%
Time to onset: 20-27 days
Resolved: 78.9%
Discontinuation: 0%

Nail-related AEs[e]
Incidence: 55.5%
Grade 3/4: 0%
Time to onset: 64-69 days
Resolved: 29.5%
Discontinuation: 0%

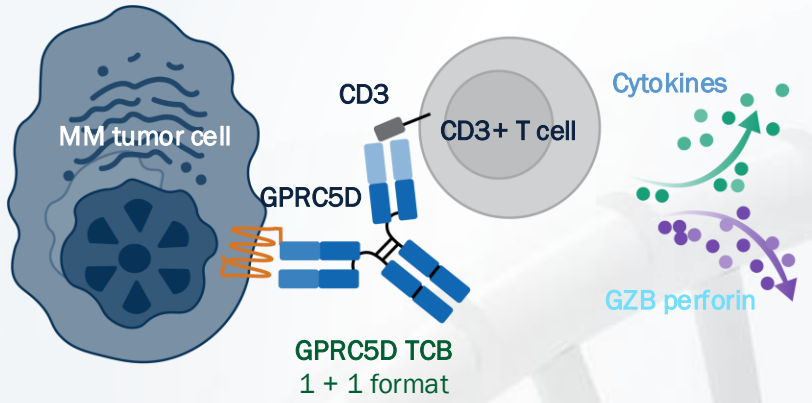
Nonrash[f]
Incidence: 65.2%
Grade 3/4: 0.3%
Time to onset: 26-30 days
Resolved: 59.4%
Discontinuation: 0.9%

Smith et al., Sci Transl 2019; Chari A, CLML 2024

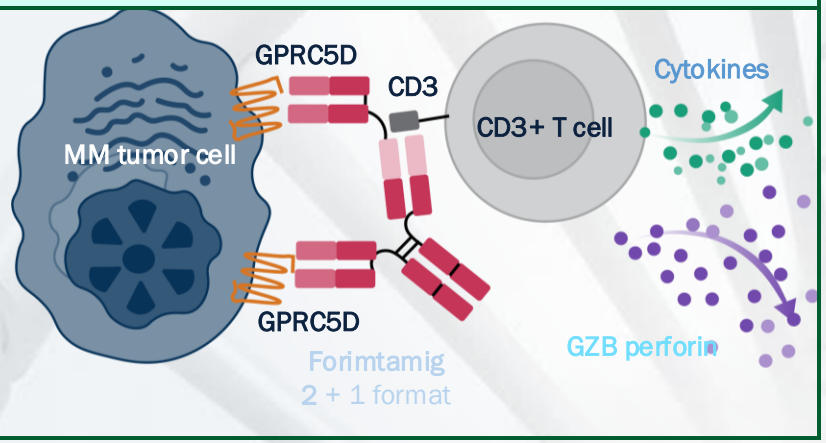
Newer GPRC5D Bispecific Antibodies Are Also Emerging in RRMM[1,2]

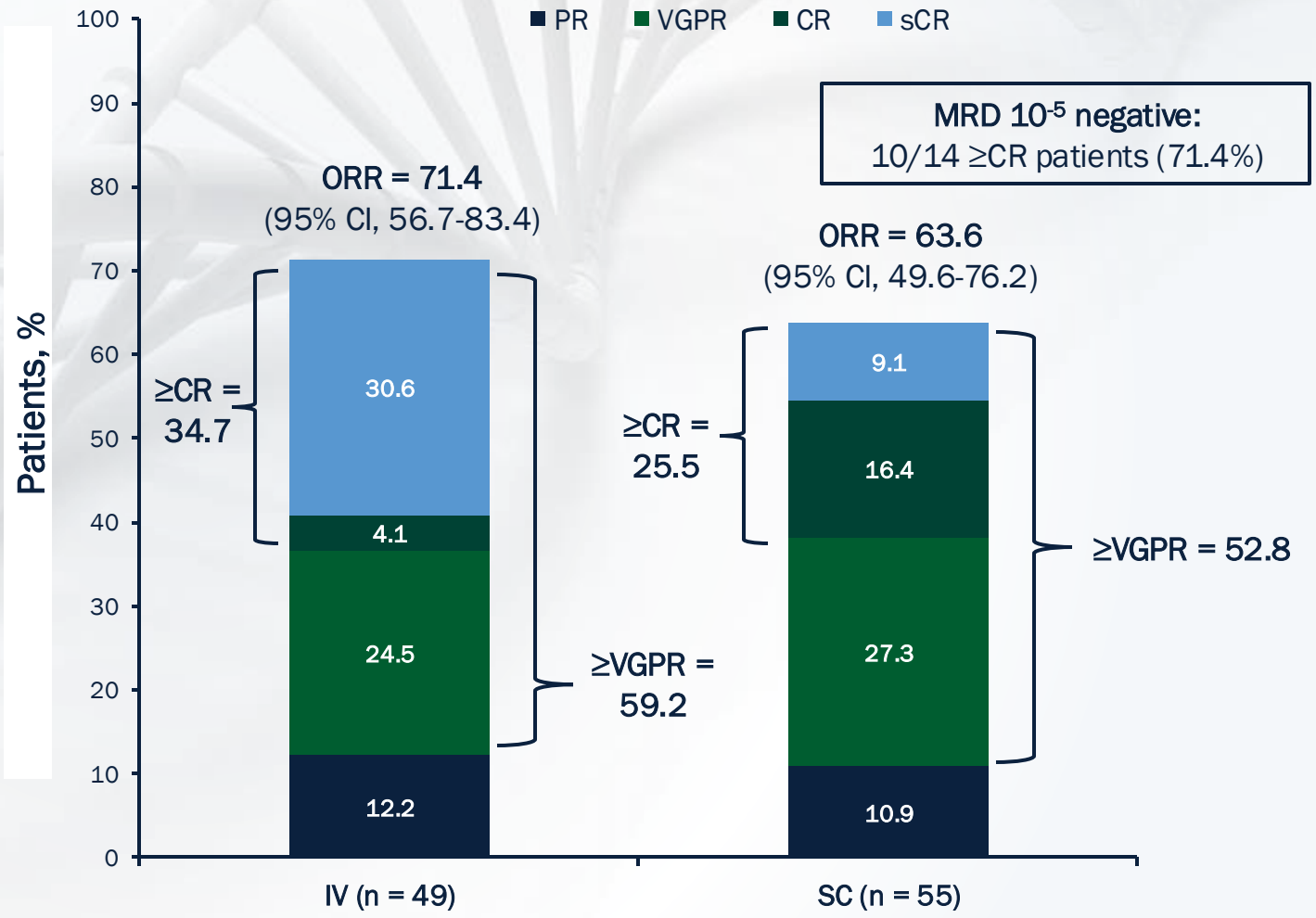
GPRC5D*CD3

1 + 1 GPRC5D TCB exhibits monovalent binding to GPRC5D on myeloma cells



Forimtamig exhibits bivalent binding to GPRC5D on myeloma cells



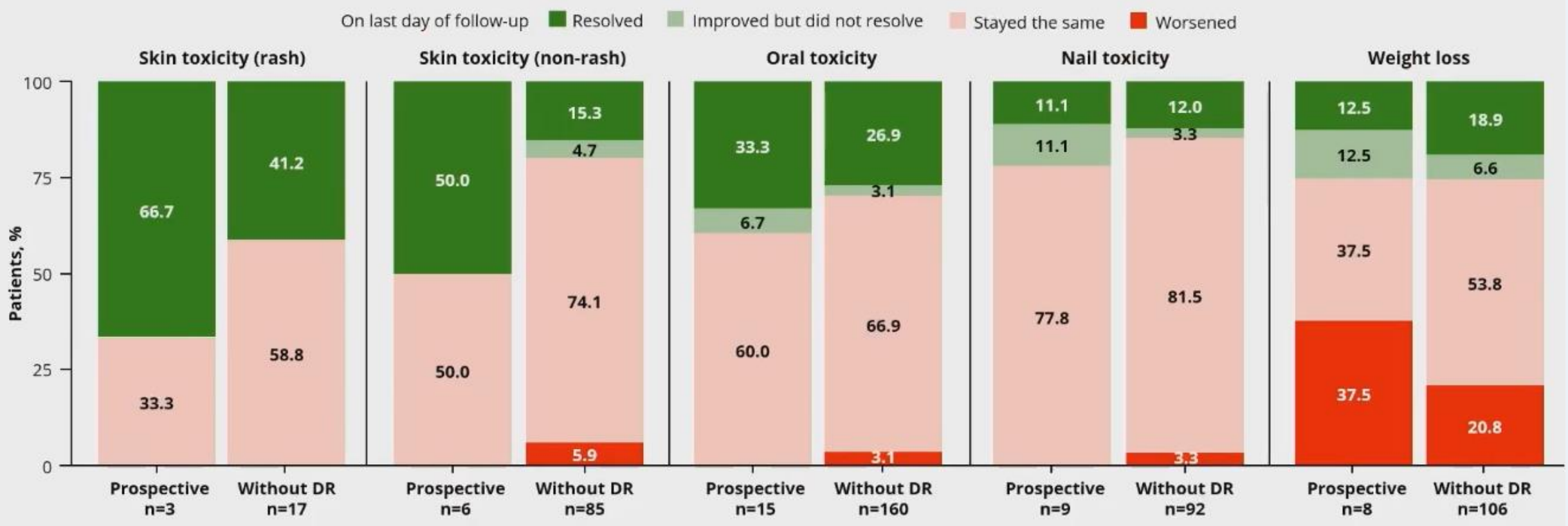


1. Eckmann J et al. *Blood.* 2025;145:202-219. 2. Carlo-Stella C et al. ASH 2022. Abstract 161.

GPRC5D*CD3

Most GPRC5D-Related AEs Improve with Dose Reduction

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

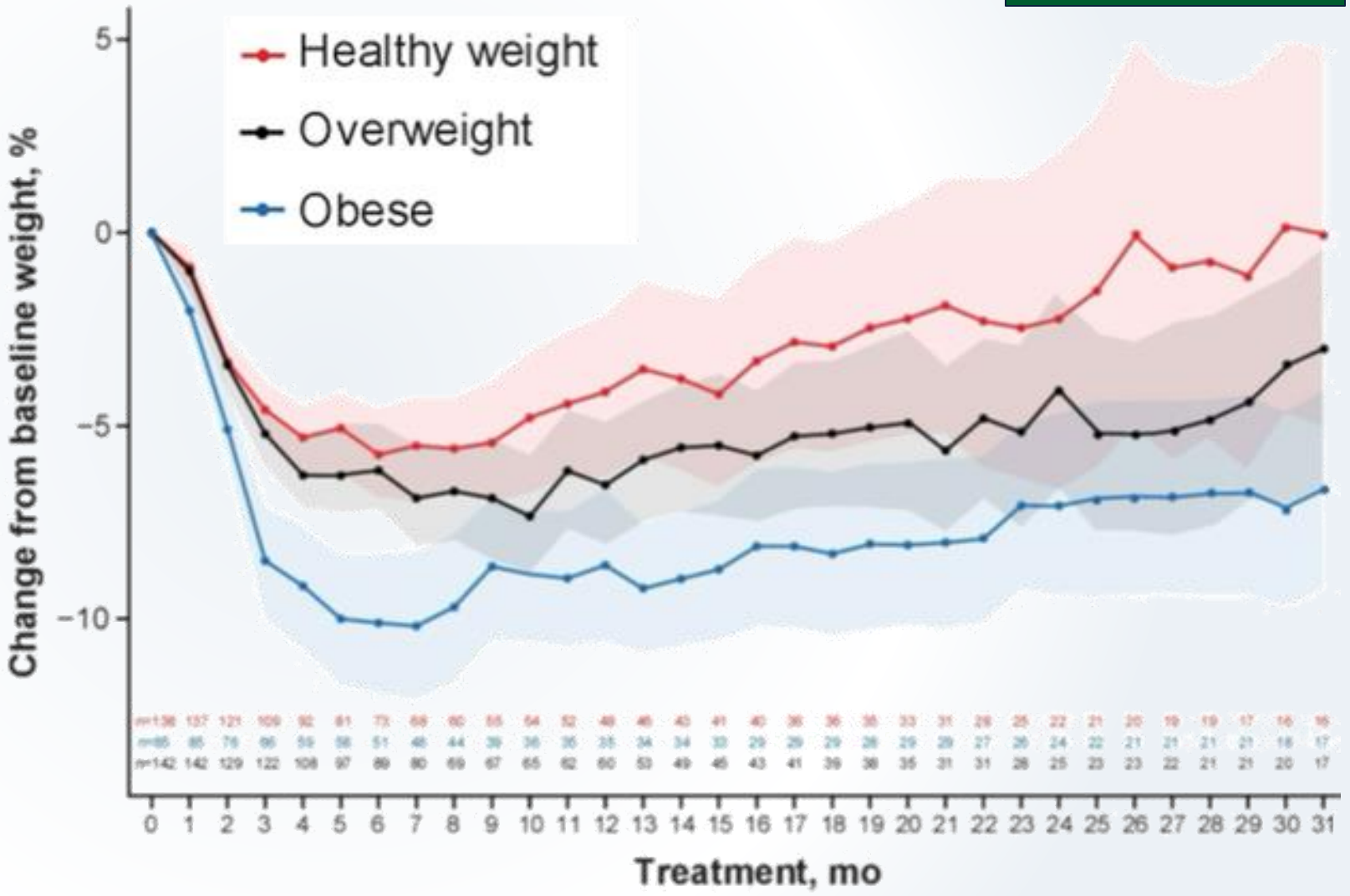


Chari et al. ASH 2023.

Weight Loss with Talquetamab Improves Over Time

GPRC5D*CD3

- Initial mean weight loss was observed in patients before stabilizing and improving
- Patients with a baseline “healthy weight” BMI who remained on treatment returned to their baseline weight over time



Leo Rasche, ASCO 2025

GPRC5D*CD3

Management of Dysgeusia

Dysgeusia is a common adverse effect of talquetamab that is very challenging for patients to tolerate. Diet and recipe modifications are beneficial.

Pearls for management:

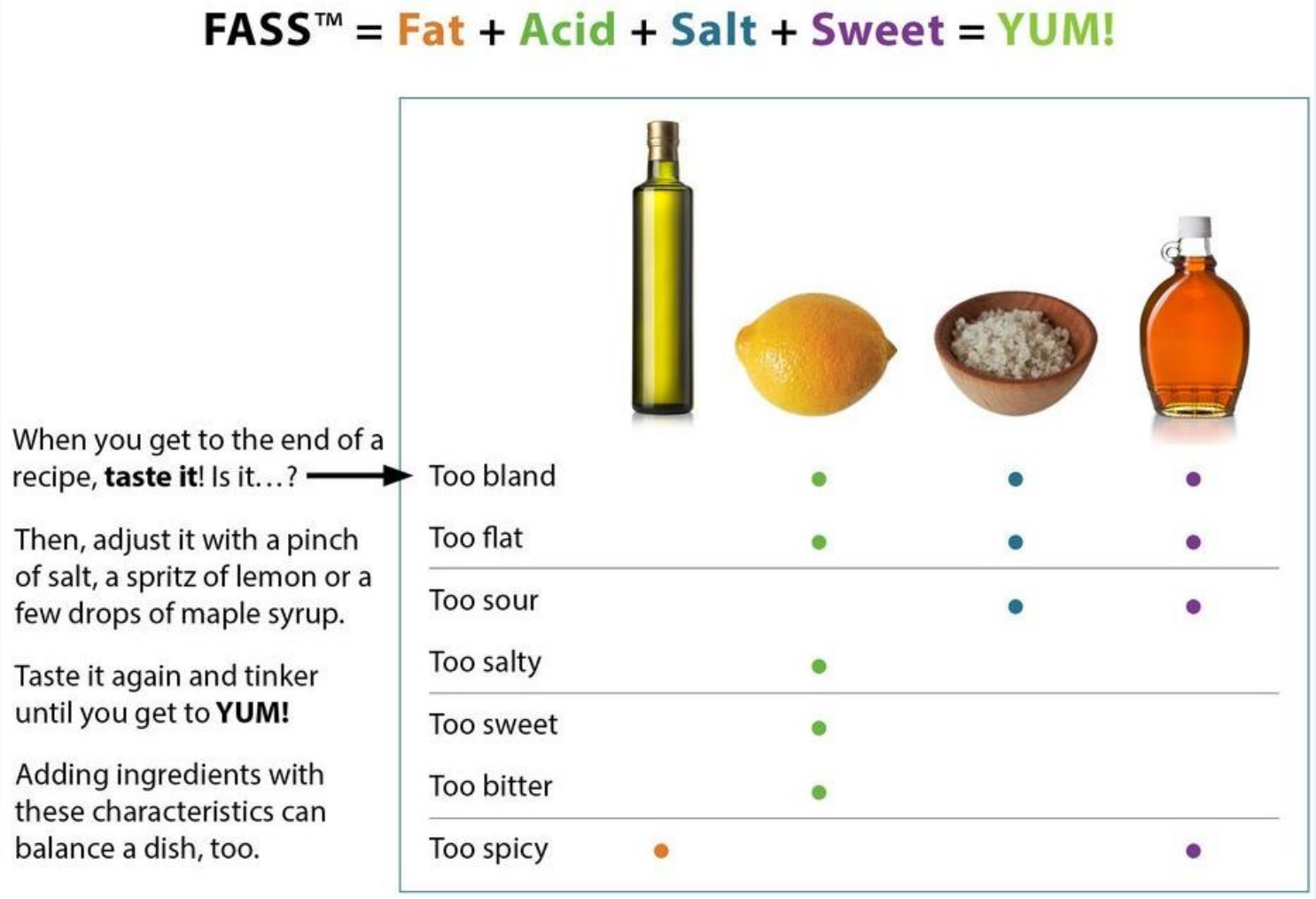
Liberalize diet to identify palatable foods

Add flavors to enhance taste

FASS method helps patients identify flavor additives to combat specific unpalatable tastes

Some providers report success with MSG added to foods

Consider referral to a nutritionist for both dysgeusia and weight loss



Slide Courtesy: Tom Martin, DAVA Whistler Heme 2025

Management of Skin Toxicity

GPRC5D*CD3

Skin peeling is common during the initial treatment with talquetamab and improves over time. Proactive management of skin toxicity can limit progression of skin toxicity and improve the patient experience.

Pearls for management:

Emollients (Cera-Ve, Vanicream, Cetaphil) within minutes of getting out of shower

Topical steroids, e.g. Triamcinolone or Fluocinonide or Clobetasol

Amlactin (Ammonium lactate 12%) for skin exfoliation (OTC)

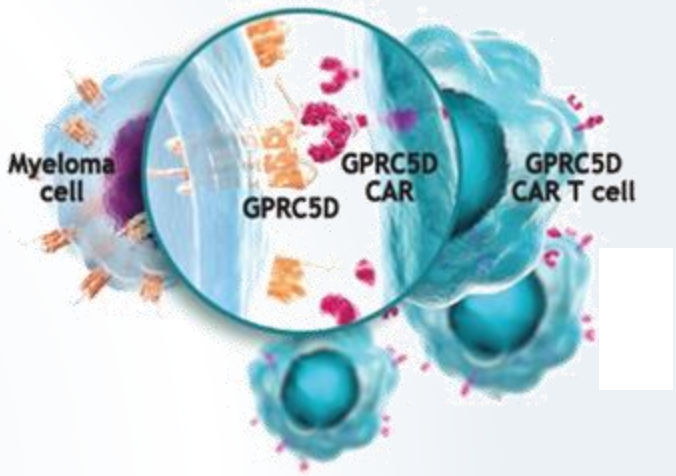
Aquaphor/Vaseline to hands, feet or areas with significant dryness

Wear cotton gloves/socks at least 15-30 minutes to maximize absorption (overnight is best)

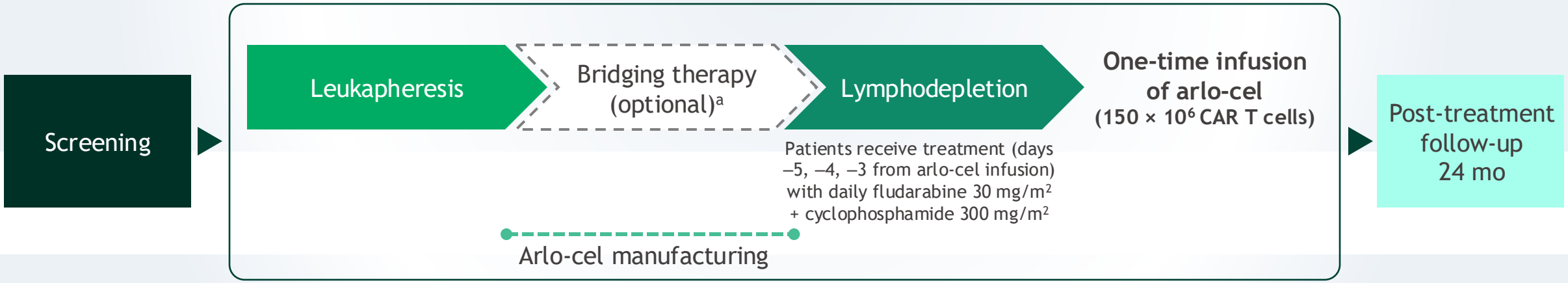
Arlo-cel (GPRC5D*CART)

GPRC5D*CART

- G protein–coupled receptor class C group 5 member D (GPRC5D), a validated therapeutic target in MM, exhibits a restricted expression profile with high expression on malignant plasma cells[5,6]
- Arlo-cel is a potential first-in-class CAR T cell therapy targeting GPRC5D that has demonstrated deep and durable responses with a tolerable safety profile across early- and late-line patients with RRMM[7,8]
- Here we report the final analysis from the first-in-human phase 1 study Cohort C in early-line patients (1–3 pLoT) with RRMM



Multicohort, dose-escalation/expansion study of arlo-cel



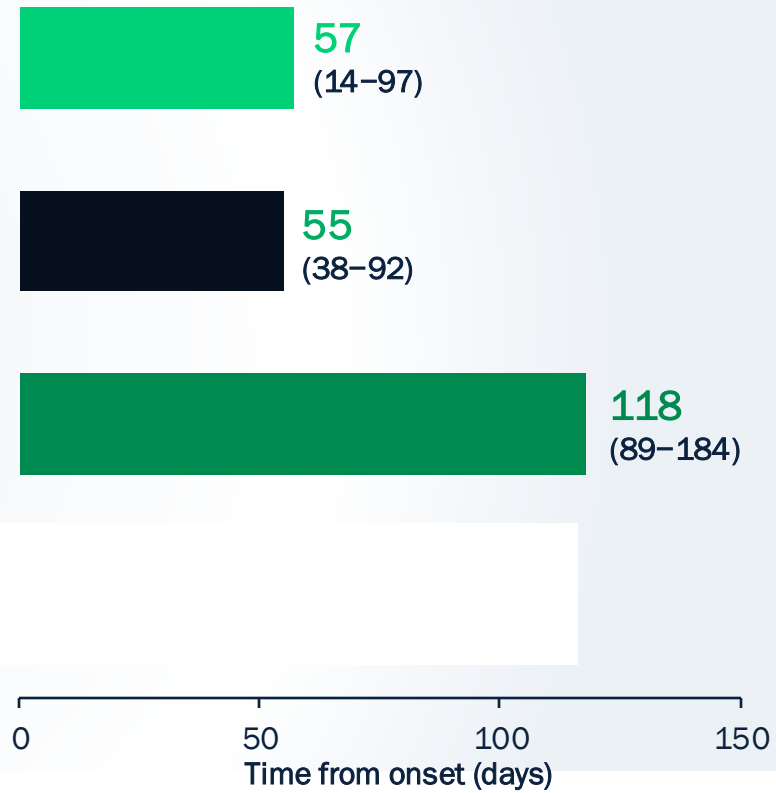
BCMA, B-cell maturation antigen; GPRC5D, G protein–coupled receptor class C group 5 member D; IMiD, immunomodulatory drug; mAb, monoclonal antibody; MM, multiple myeloma; PI, proteasome inhibitor; RRMM, relapsed/refractory multiple myeloma.

1. Malard F, et al. *Nat Rev Dis Primers*. 2024;10:45. **2.** Goel U et al. *Blood Cancer J*. 2023;13:11. **3.** Rajkumar SV. *Am J Hematol*. 2024;99(9):1802-1824. **4.** Bal S, et al. *Leukemia*. 2022;36(3):877-880. **5.**Rodriguez-Otero P, et al. *Blood Cancer J*. 2024;14(1):24. **6.** Chari A et al. *Lancet Haematol*. 2025;12(4):e269-e281. 7. Bal S, et al. Presented at COMy 2026. **8.** Bal S, et al. Presented at IMS 2025. Abstract PA-080.

Select on-target off-tumor events

GPRC5D*CART

	Patients, n (%)	N=31	Resolved, %[a]	Time to resolution (days) median (IQR)
			OVERALL	
Skin	With event	8 (25.8)	88%	38% without intervention	57 (14–97)
	Grade 1	6 (19.4)		
	Grade 2	2 (6.5)		
Oral	With event	13 (41.9)	77%	69% without intervention	55 (38–92)
	Grade 1	10 (32.3)		
	Grade 2	3 (9.7)		
Nail	With event	12 (38.7)	92%	92% without intervention	118 (89–184)
	Grade 1	10 (32.3)		
	Grade 2	2 (6.5)		
Weight loss	With event	1 (3.2)	100%	without intervention	
	Grade 1	1 (3.2)		
	Grade 2	0		



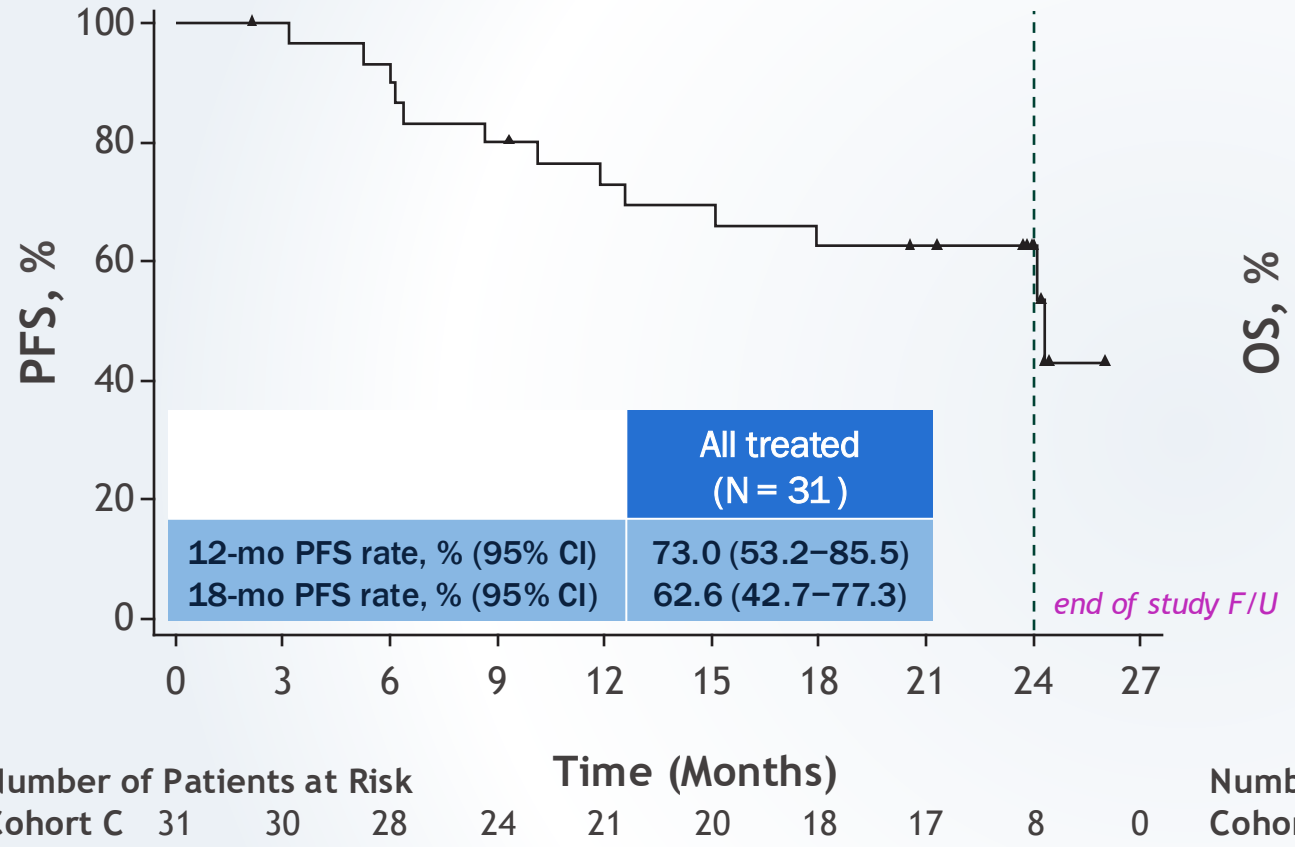
OTOT events and weight loss were all low-grade (grade 1/2); most events resolved

Data cutoff: February 17, 2026. All-treated population. Time to resolution was calculated per episode; only resolved episodes are considered. Multiple events occurring within 1 day from each other are considered as 1 episode.
Medical Dictionary for Regulatory Activities (MedDRA) version 28.1. Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. [a]Percent resolved calculated based on patients with an event.
IQR, interquartile range; OTOT, on-target/off-tumor.

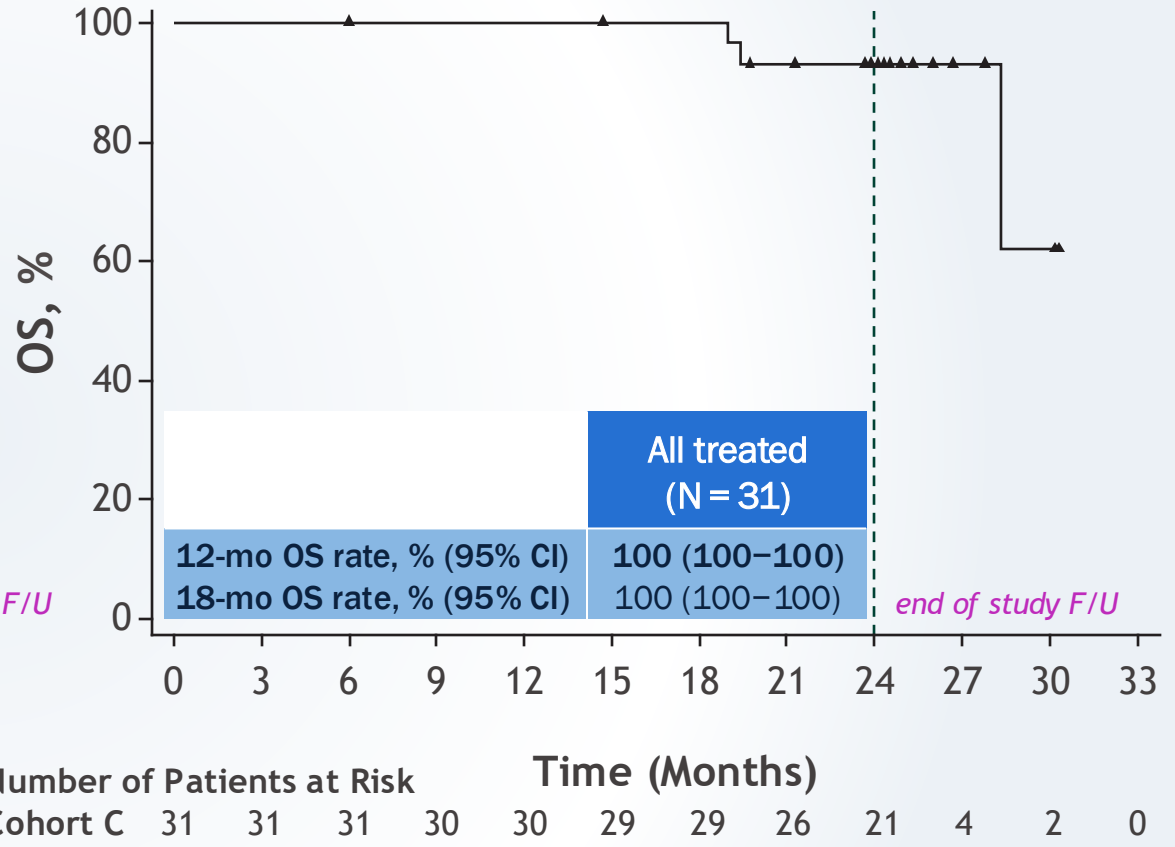
PFS and OS

GPRC5D*CART

PFS



OS

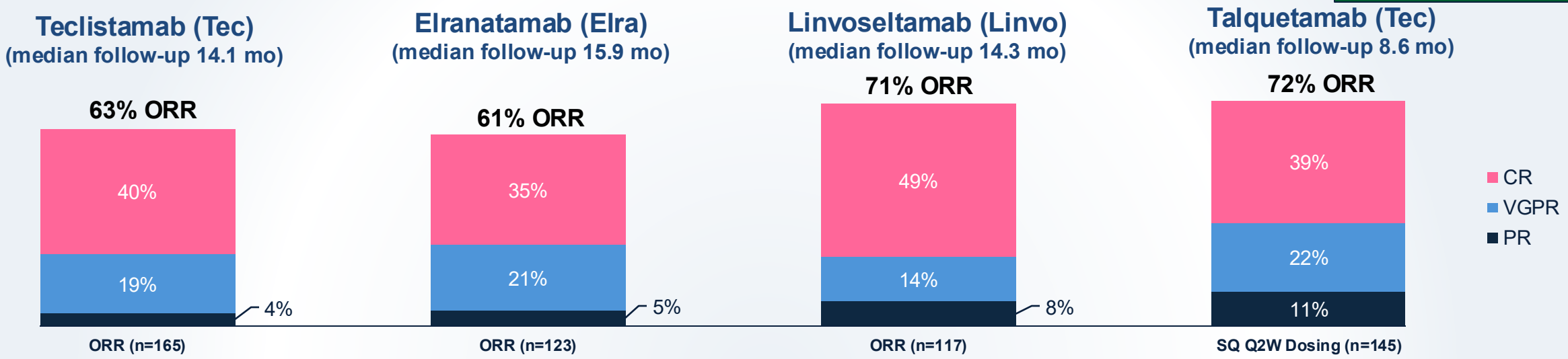


18-month PFS rate was 62.6%

Data cutoff: February 17, 2026. All-treated population. PFS and OS were estimated by Kaplan-Meier methods. Symbols show censored patients. CI, confidence interval; F/U, follow-up; NA, not available; OS, overall survival; PFS, progression-free survival.

BsAbs: Efficacy and Safety

BCMA*CD3
GPRC5D*CD3



Toxicity	Teclistamab	Elranatamab	Linvoseltamab	Talquetamab
Safety				
CRS, any grade/grade ≥3, (%)	72; 1	56; 0	46; 1	76; 2
Median onset/duration, days (range)	2 (1-6)/2 (1-9)	2 (1-9)/2 (1-19)	0 (0-8)/1 (0-4)	2 (1-7)/1(1-26)
NT, any grade/grade ≥3, (%)	15; 0	3; 0	8; 3	5; 0
Median onset/duration, days (range)	2 (1-6)/2 (1-9)	2.5 (1-4)/2 (1-6)	1 (1-4)/2 (1-11)	2.5 (1-16)/2(1-22)

RWE with BsAbs resulted in a high ORR with rapid and durable responses with a comparable toxicity profile to that seen in pivotal trials

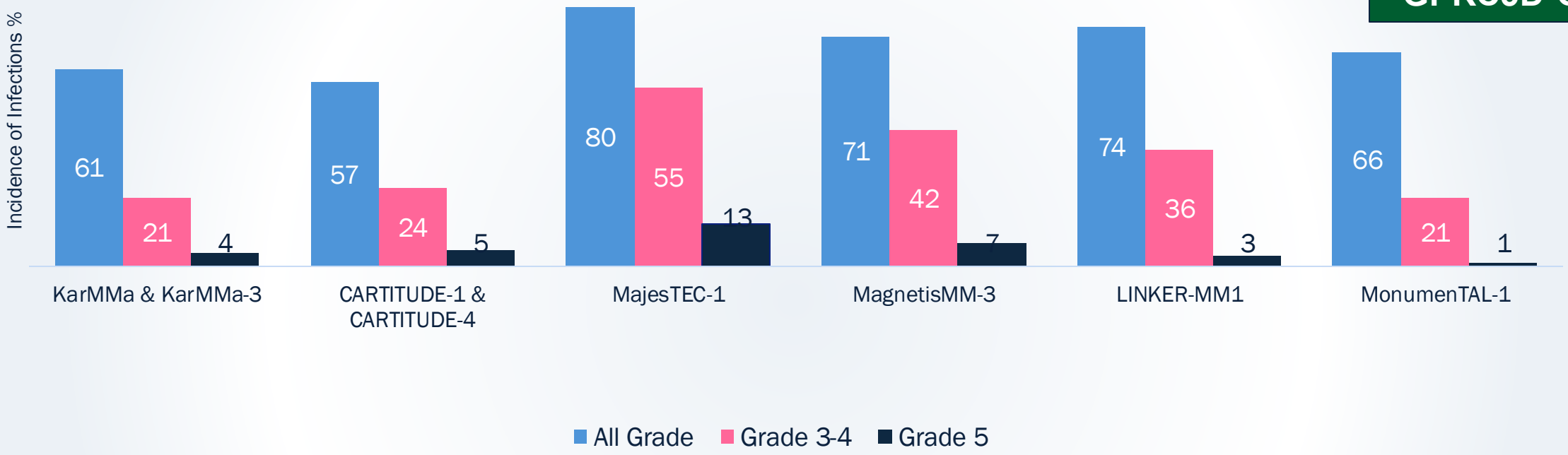
SQ: subcutaneous, Q2W: every 2 weeks

Initial approval: patients with RRMM after ≥ 4 prior LOT, including an IMiD, PI, and an anti-CD38 mAb

Moureau P, et al. *N Engl J Med.* 2022;387(6):495-505; Lesokhin AM, et al. *Nat Med*. 2023;29(9):2259-2267, Tomasson M, et al. *Blood*. 2023;142 (Supplement 1):3385; Chari A, et al. *N Engl J Med*. 2022;387(24):2232-2244; Schinke C, et al. *JCO*. 2024;41:8036-8036

Incidence of Infectious Complications with T-cell Redirecting Therapies

BCMA*CD3
BCMA*CART
GPRC5D*CD3



Significant ↑ of serious infection with BCMA-directed BsAb therapy vs. CAR-T

- Additionally associated with higher risk of infections vs. GPRC5D-directed therapy

Reynolds G, et al. *Blood Adv*. 2023;7(19):5898-5903; Bahlis N, et al. *Nat Med*. 2023;29:2570-2576; Chari A, et al. *N Engl J Med*. 2022;387(24):2232-2244; Moreau P, et al. *N Engl J Med*. 2022;387(6):495-505; Jelinek T, et al. ASH 2024. Abstract 1934; Bumma N, et al. *J Clin Oncol.* 2024;42(22):2702-2712

#1: PFS and OS with Bispecific Antibodies

BCMA*CD3
GPRC5D*CD3

Bispecific Antibody	PFS (months)	OS (months)
Teclistamab	11.4	22.2
Elranatamab	17.2	24.6
Linvoseltamab	NR	31.4
Talquetamab	7.5	34/NR

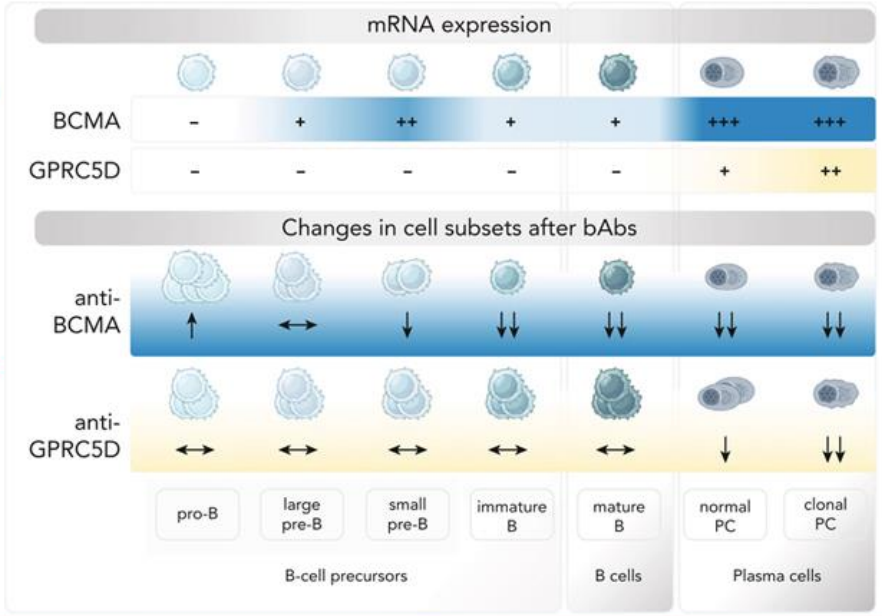
Slide courtesy: Sham Mailankodi

#2: Infection Risk with Bispecific Antibodies

BCMA*CD3
GPRC5D*CD3

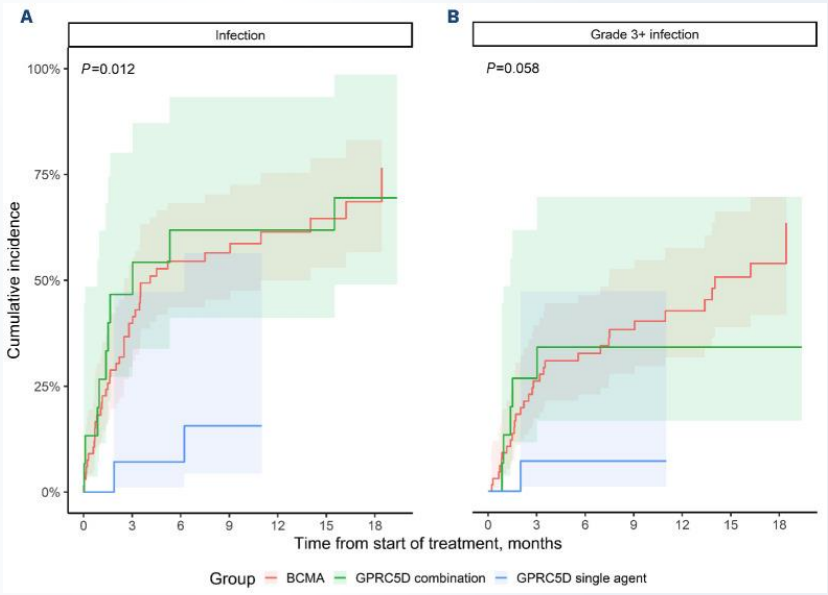
Single cell gene expression of BCMA and GPRC5D

Changes in the proportion of B-cell subsets and plasma cells due to anti-BCMA or anti-GPRC5D bsAbs treatment



Unlike GPRC5D, BCMA is expressed on mature B cells and B-cell precursors

Longitudinal monitoring revealed rapid and persistent depletion of B-cell subsets in patients treated with anti-BCMA bsAbs

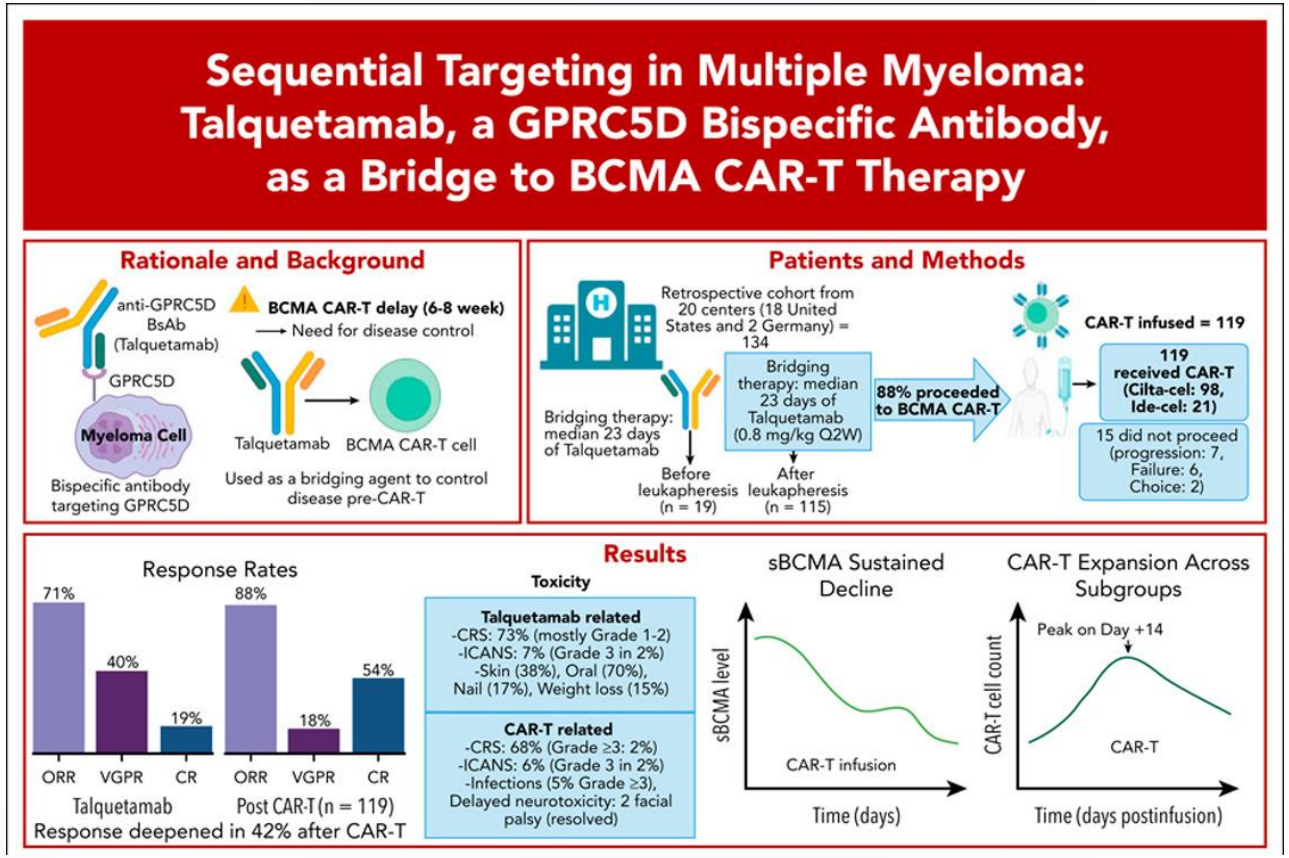


Jelinek et al. Blood 2025; Hammons et al. Haematologica 2023

Slide courtesy: Sham Mailankodi

#3: Talquetamab as an effective bridge to BCMA CAR T cell therapy

BCMA*CD3
GPRC5D*CD3



Dhakal et al. Blood 2025

Slide courtesy: Sham Mailankodi

To target B or G, a Pragmatic Study Design

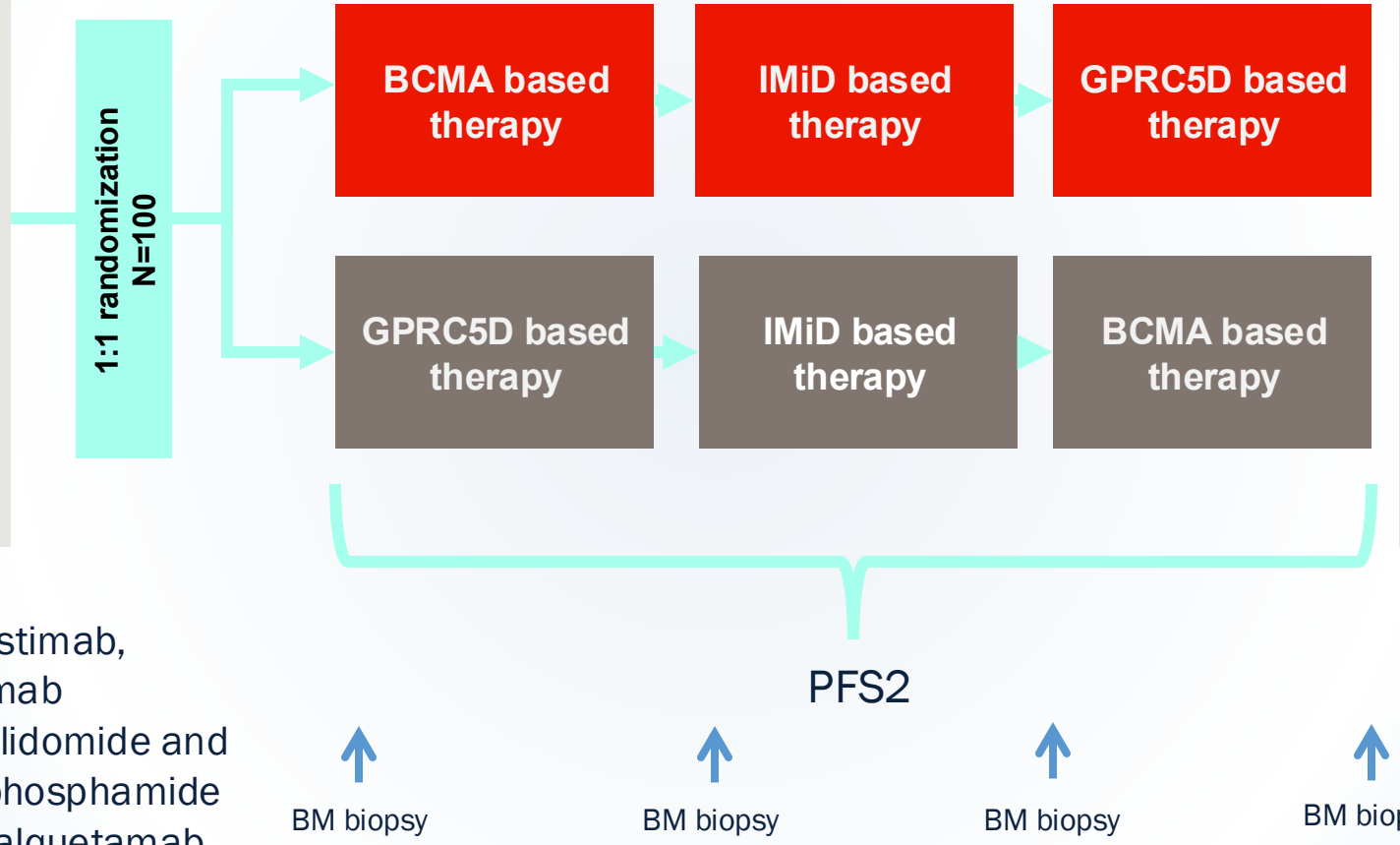
BCMA*CD3
GPRC5D*CD3

Key inclusion criteria

- RRMM
- >3 prior LOTs including a PI, IMID and CD38 monoclonal antibody
- ECOG PS score of 0–2

Key exclusion criteria

- Prior BCMA-directed therapy
- Prior GPRC5D-directed therapy



Primary endpoint

- PFS2 after 2nd bispecific antibody

Key secondary endpoints

- ≥CR and ORR
- MRD negativity (10^{-5})
- PFS
- OS

Other secondary endpoints

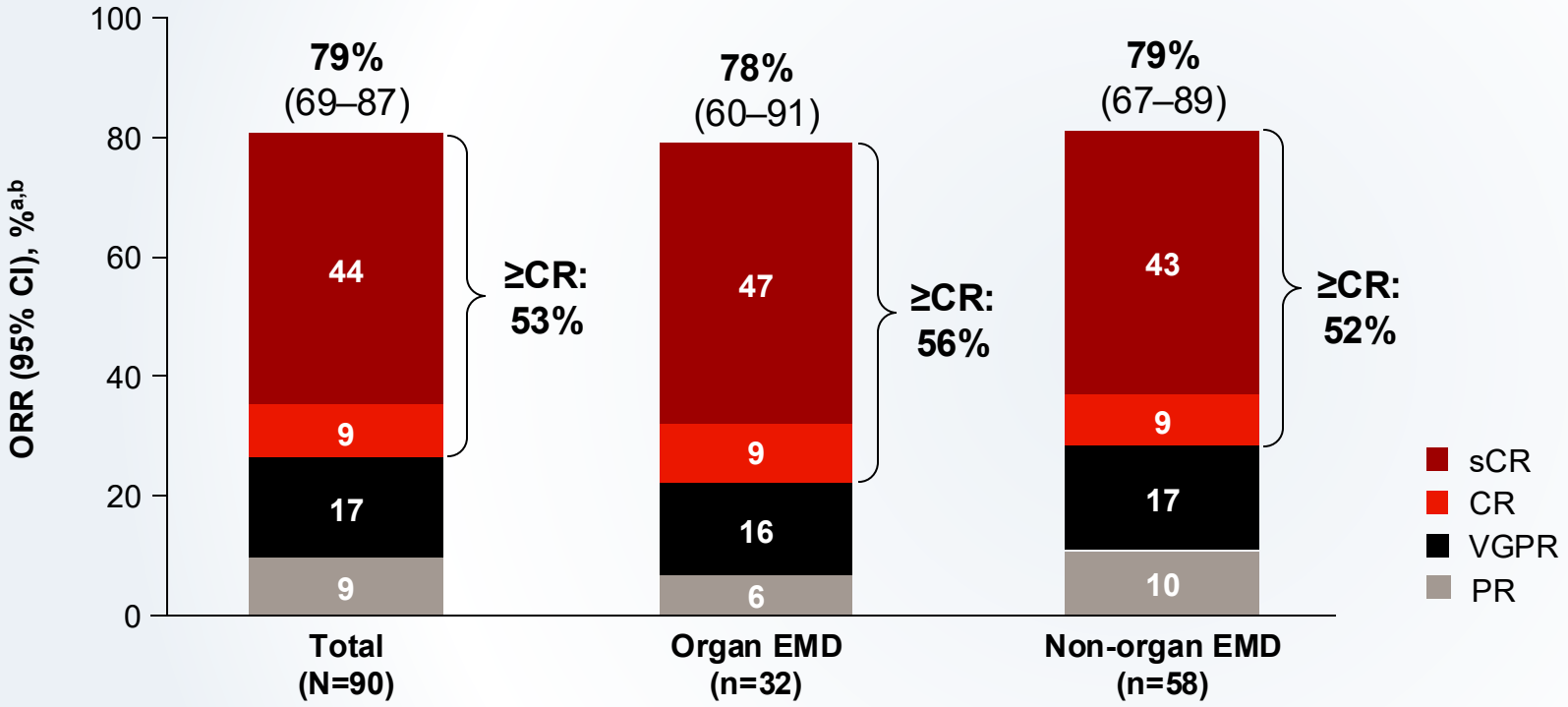
- Hospitalization rate
- Rates of discontinuation

BCMA based therapy: teclistimab, elranatamab or linvoseltamab
IMiD based therapy: pomalidomide and dexamethasone +/- cyclophosphamide
GPRC5D based therapy: talquetamab

Teclistamab and Talquetamab are dosed using established FDA approved schedule

Efficacy and Safety of Talquetamab + Teclistamab in Patients With Relapsed/Refractory Multiple Myeloma and Extramedullary Disease: Updated Phase 2 Results From the RedirecTT-1 Study With Extended Follow-Up

BCMA*CD3
GPRC5D*CD3



- At an overall median follow-up of 16.8 months, median DOR was not reached in organ EMD and 15.4 months in non-organ EMD
  - Organ EMD[c]: kidney, liver, lung, and others
  - Non-organ EMD[d]: lymph node and soft tissue

Patients with true EMD achieved deep responses with dual-antigen targeting Tal and Tec

Mateos et al Presented at the 67thASH Annual Meeting

MonumenTAL-6

BCMA*CD3
GPRC5D*CD3

MonumenTAL-6 Study Design[1]

Key Inclusion Criteria

- ≥18 years with RRMM[a]
- ECOG PS of 0-2
- 1-4 prior LOT[b]

Key Exclusion Criteria

- Prior exposure to Pom, Tec, or GPRC5D-directed therapies

R[c] 1:1:1 N=795[d]

- **Arm A** Tal-Pom (n=265)
- **Arm B** Tal-Tec (n=265)
- Investigator's choice
- **Arm C** EPd or PVd (n=265)

Post treatment follow-up

Primary Endpoints

- Progression-free survival

Secondary Endpoints

Efficacy[e]

- Overall response rate
- Very good partial response or better rate
- Complete response or better rate
- Rate of minimal residual disease–negative (10^{-5}) complete response
- Overall survival
- Progression-free survival on next-line therapy
- Time to next treatment

Pharmacokinetics

- Serum concentrations of Tal and Tec

Immunogenicity

- Presence of antidrug antibodies to Tal and Tec

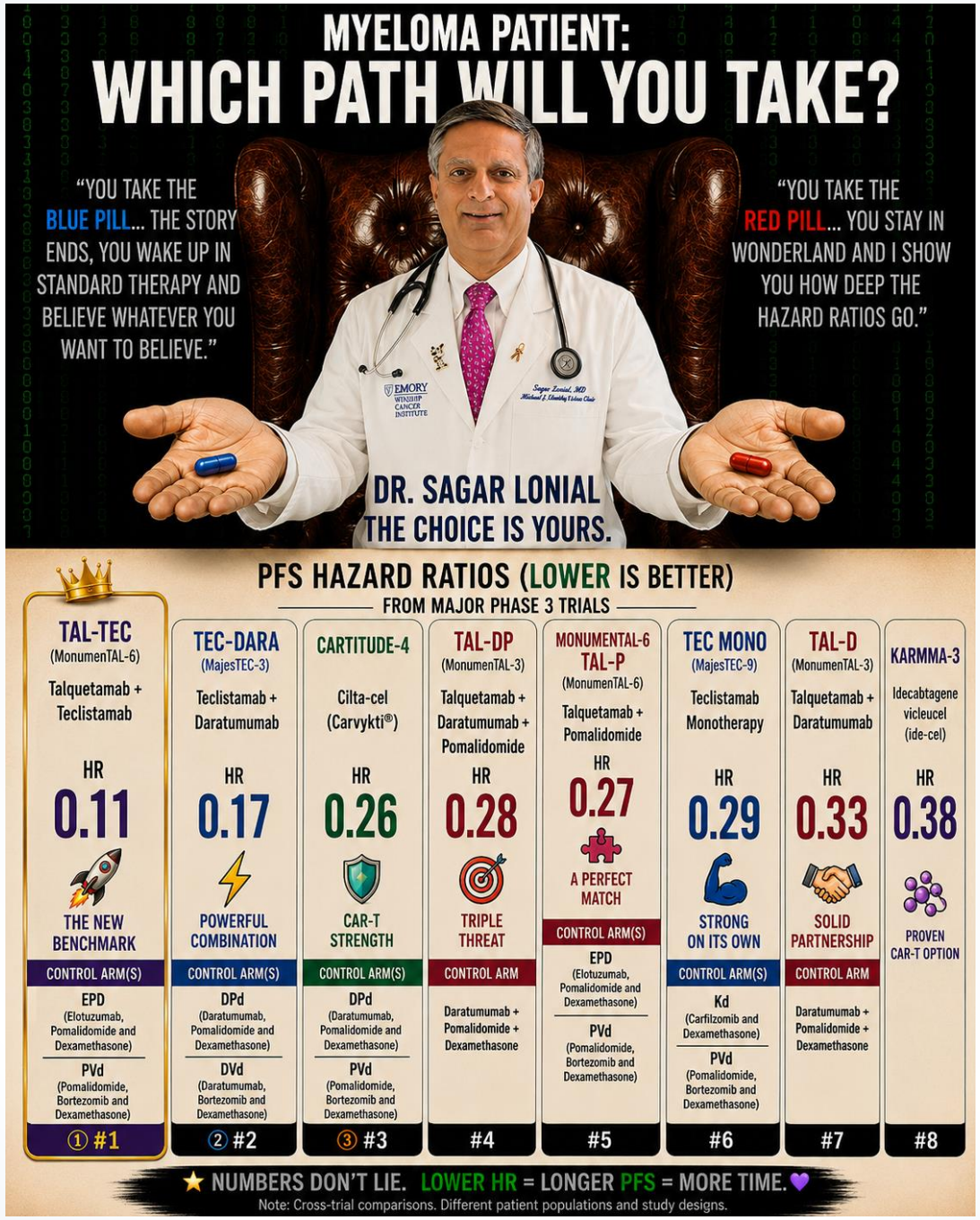
PROs[f]

- Change from baseline and time to worsening in health-related quality-of-life assessments, including MySIm-Q, EORTC QLQ-C30, EQ-5D-5L, Patient Global Impression of Severity, and Epstein Taste Survey
- Meaningful improvement in health-related quality of life

Topline results showed that the Tec-Tal combination reduced the risk of disease progression or death by 89% versus standard of care (hazard ratio [HR] 0.11; 95% confidence interval [CI] 0.08–0.16; p<0.0001). The combination also reduced the risk of death by 62% (HR 0.38).

The Tal-P regimen reduced the risk of disease progression or death by 73% (HR 0.27; 95% CI 0.20–0.35). Both investigational regimens demonstrated statistically significant improvements in overall survival compared with standard treatment. The company disclosed the overall survival hazard ratio only for the Tec-Tal arm.

The company stated that the hazard ratio of 0.11 observed with Tec-Tal is the lowest reported in a Phase 3 study evaluating bispecific therapies in RRMM.



Slide courtesy: Deepu Madduri and Saad Usmani

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MM RF MULTIPLE MYELOMA Research Foundation

International Myeloma Society

International Myeloma Foundation

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