2025 CELL COAST CONFERENCE
OCTOBER 17-18, 2025 | HOTEL FLOR

Bispecific antibodies for relapsed/refractory multiple myeloma

Setting the stage

Oct 17th, 2025

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Pentecost Family Myeloma Research Center

MOFFITT CANCER CENTER

Disclosures

Honoraria:

- Celgene/BMS, Amgen, Takeda, Janssen/Johnson & Johnson, Karyopharm, Sanofi, Adaptive, Regeneron, GSK & Karyopharm, Sebia

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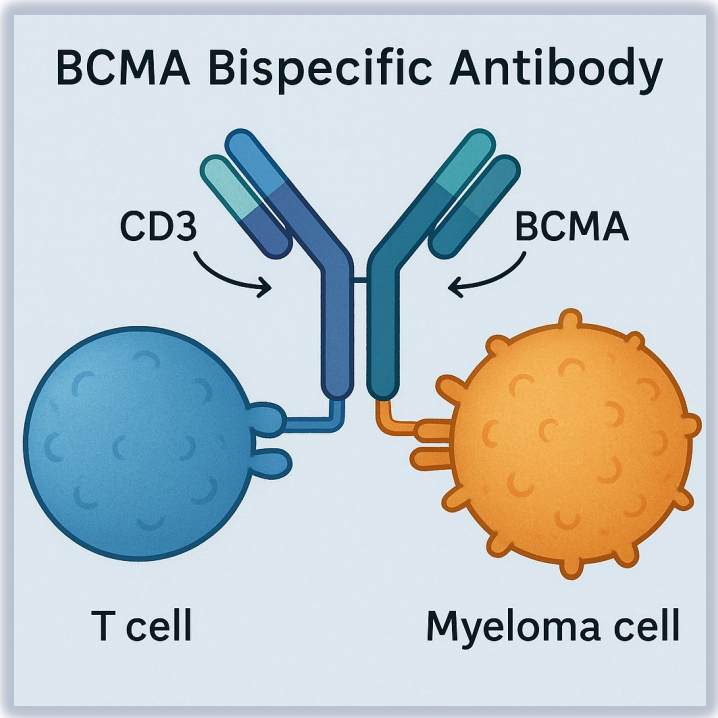
Learning objectives for today's discussion

Bispecific T-cell Engager (BiTE) therapy is emerging as a promising treatment approach for multiple myeloma (MM), especially for patients with relapsed or refractory disease. The future of BiTE therapy in myeloma looks promising due to several key advancements:

1. BCMA Targeting TCEs
2. GPRC5D Targeting TCE
3. CRS and ICANS
4. Combination Therapies
5. Overcoming HR phenotypes



-ChatGPT

We are now in the era of BCMA direct therapy(s)

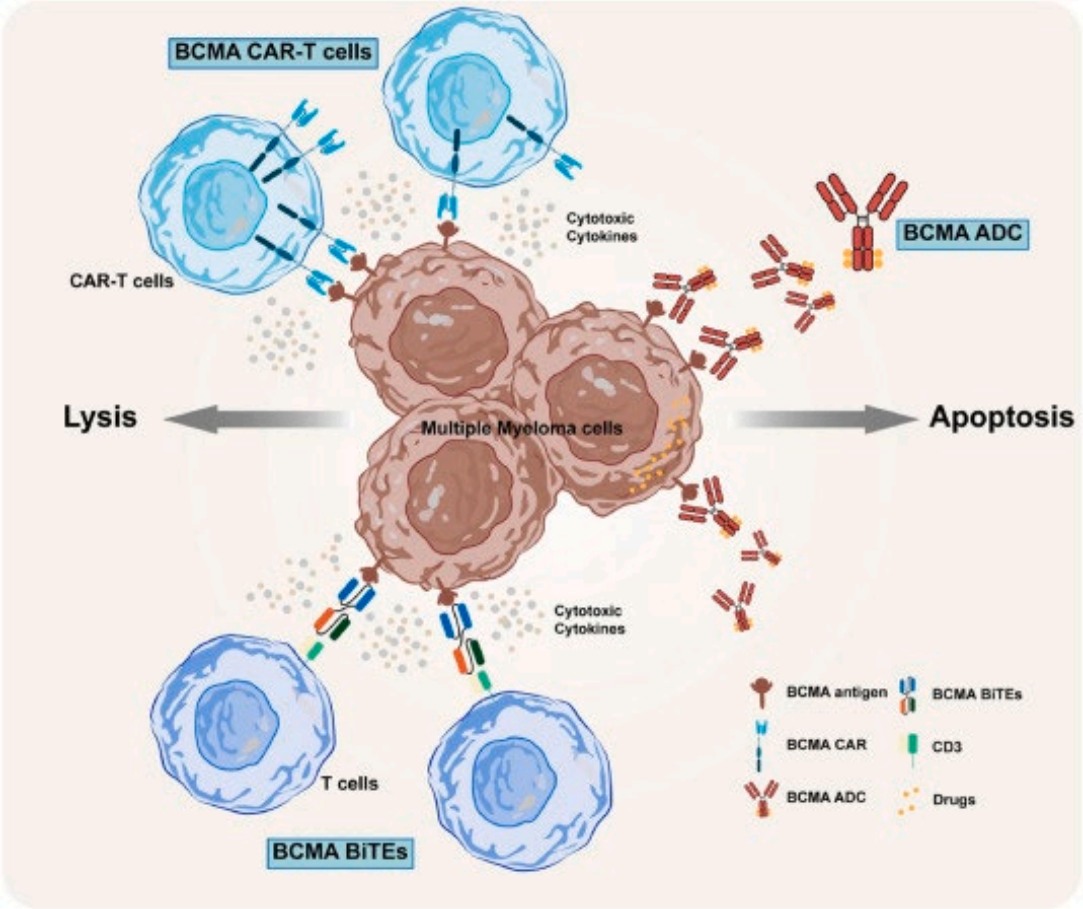
BCMA* targeting agents in RRMM.

Chimeric Antigen Receptor T Cells (CAR-T)

T Cell Engagers (TCE)/Bispecific Antibodies

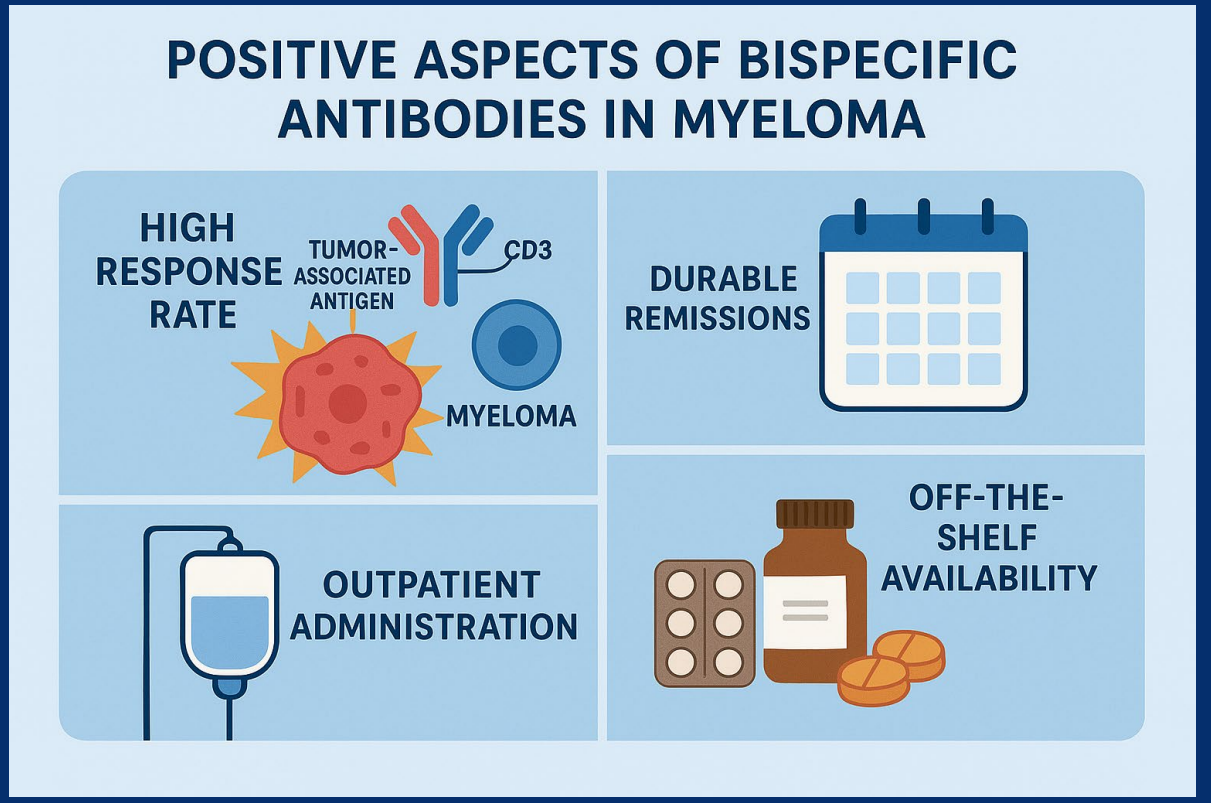
Antibody Drug Conjugates (ADCs)

*GPRC5D too



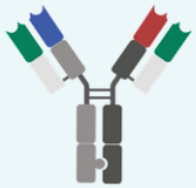
Yang et al Cancer Letter 2023
https://www.sciencedirect.com/science/article/pii/S0304383522004360

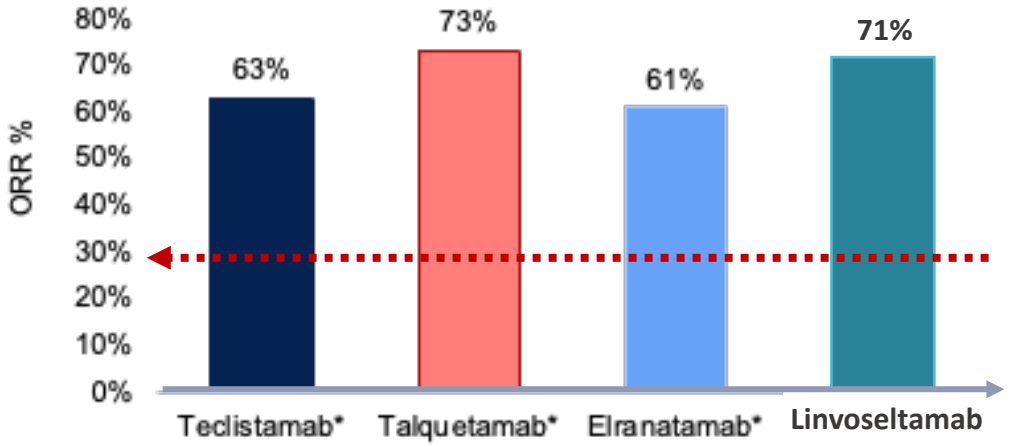
BiTEs are highly effective agents today



Effectiveness → FDA Approved TCE/Bispecific antibodies

Triple-class-exposed:
-Exposed to an immunomodulatory drug, proteasome inhibitor, and CD38 monoclonal antibody

Teclistamab (anti-BCMA)	Talquetamab (anti-GPRC5D)	Elranatamab (anti-BCMA)	Linvoseltamab (anti-BCMA)
IgG1 Fc	IgG1 Fc	IgG2a Fc	Fc region Fab arms
			
10/25/2022	8/9/2023	8/14/2023	7/2/2025



Teclistamab*	Talquetamab*	Elranatamab*	Linvoseltamab
PFS 11.3mo	**PFS** 11.2mo	**PFS** 17.2 mo	**PFS** NR
DoR 18.4mo	**DoR** 17.5mo	**DoR** Not reached	**DoR** 29.4mo

ORR, overall response rate; PFS, progression free survival; DoR, duration of response

Moreau P, et al. *N Engl J Med*. 2022;387:495-505. Touzeau C, et al. *J Clin Oncol.* 2022;40(16 suppl); Abstract 8013. FDA news release 10/25/2022 (www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-teclistamab-cqyv-relapsed-or-refractory-multiple-myeloma). Accessed 11/4/2023. Teclistamab [Package Insert]. Bahlis NJ, et al. ASH 2022; Abstract 159. Lesokhin AM, et al. *Nat Med*. 2023;29(9):2259-2267.

…. Other targets, dosing strategies, binding affinity…

New Bispecific antibodies, different target affinity, new targets, multiple targets, combinations…

Etentamig

		TNB-383B (anti-BCMA)	Cevostamab (anti-FcRL5/FcRH5)	
Fc region Fab arms	IgG1 Fc	IgG4 Fc	IgG1 Fc	Silent Fc region
		αCD3 Bivalent αBCMA IgG4 Fc		
ORR 67%	**ORR** 65%	**ORR** 75%	**ORR** 55%	**ORR** 71%

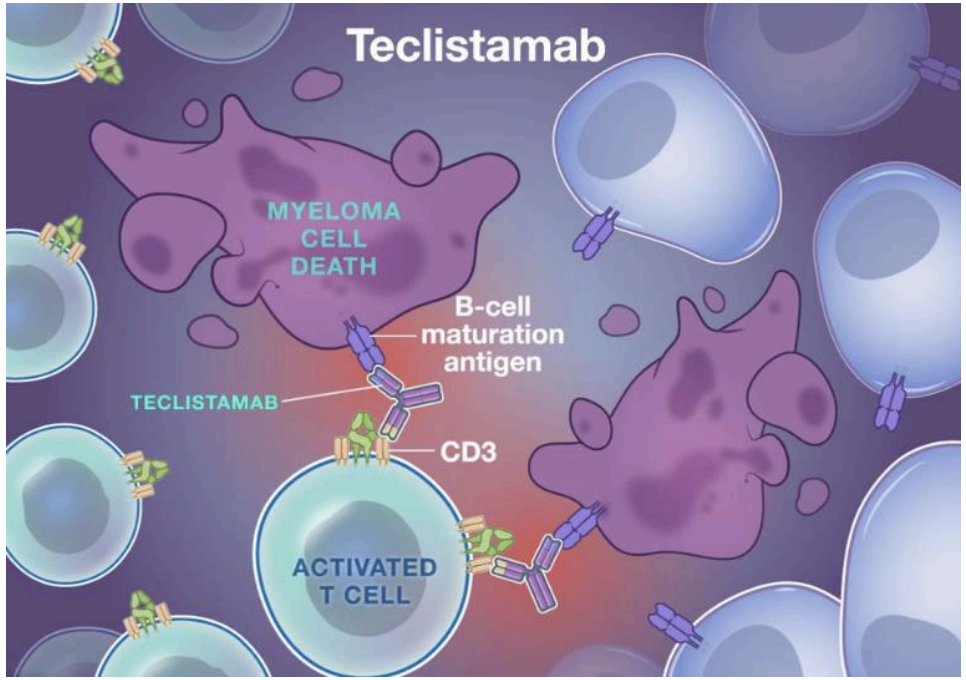
Cho SF, et al. *Front Oncol*. 2022;12:1032775. Hosny M, et al. *J Clin Med*. 2021;10(19):4593. Hasselbalch Riley AC. European Hematology Association (EHA) 2022; Abstract 1580. Richter J, et al. International Myeloma Society (IMS) 2023; Poster P-044; Suvannasankha A, et al. American Association for Cancer Research (AACR) 2023; Wong SW, et al. *Hemasphere*. 2023;7(suppl):e1220745; Voorhees PM, et al. *Blood.* 2022;140(suppl 1):4401-4404; Trudel, et al. abstract #157. 63rd American Society of Hematology Annual Meeting and Exposition; Dec 11, 2021

Teclistamab- BCMA- bispecific antibodies

Overview of Teclistamab bispecific antibody

Teclistamab is a BCMA-directed CD3 T-cell engager approved in October 2022 for patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including:

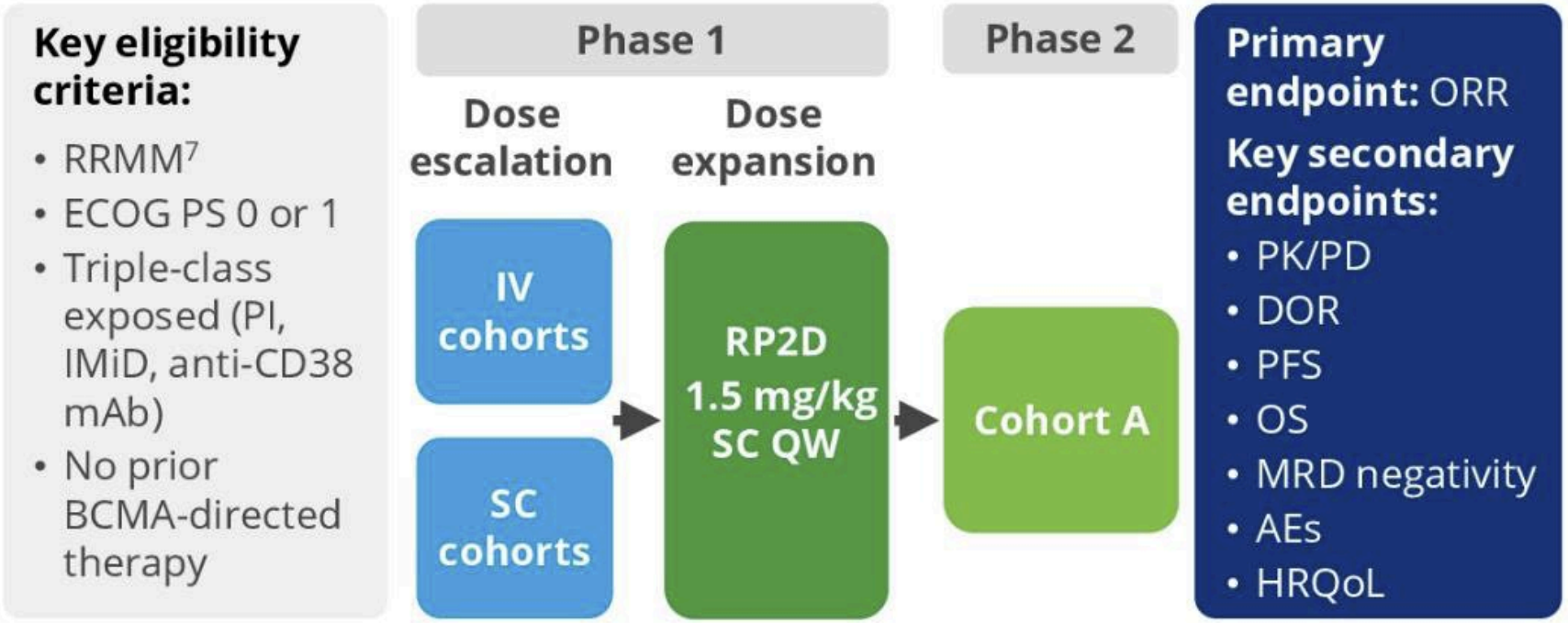
- Proteasome inhibitor
- Immunomodulatory agent
- Anti-CD38 monoclonal antibody



https://www.nejm.org/do/10.1056/NEJMdo006628/full/

Teclistamab- BCMA- bispecific antibodies

MajecTEC-1: Trial Design

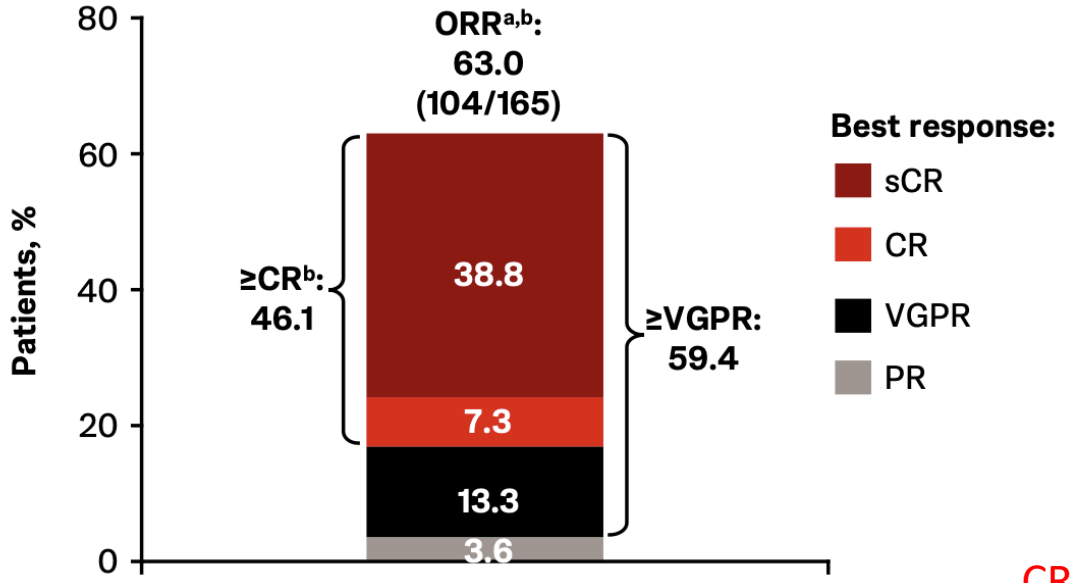


Triple class exposed **100%**
Triple class refractory **77.6%**

Usmani S et al., ASCO 2023; Van de Donk J et al., ASCO 2023

Teclistamab- BCMA- bispecific antibodies

MajecTEC-1: ORR and DOR



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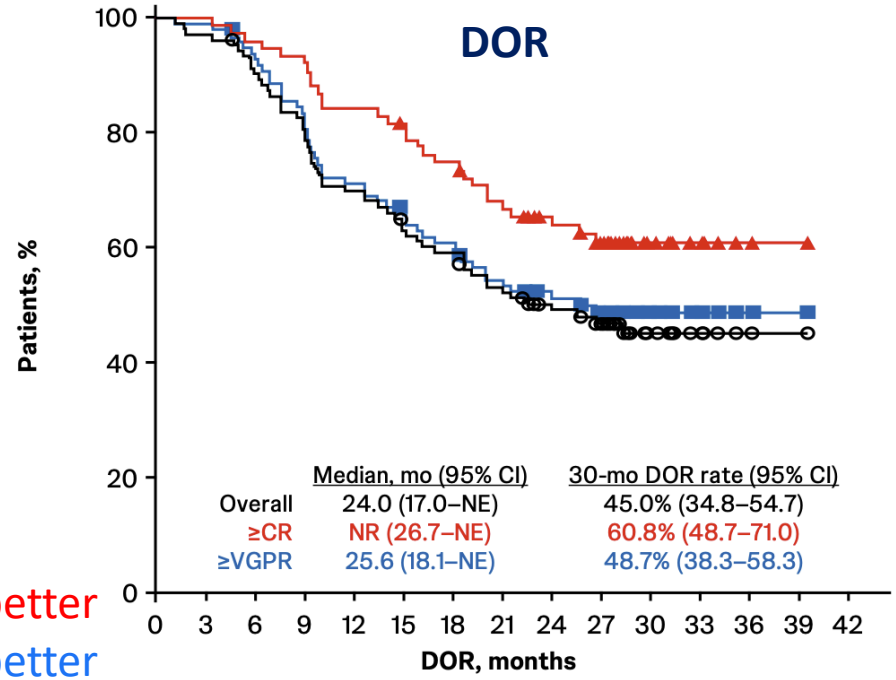
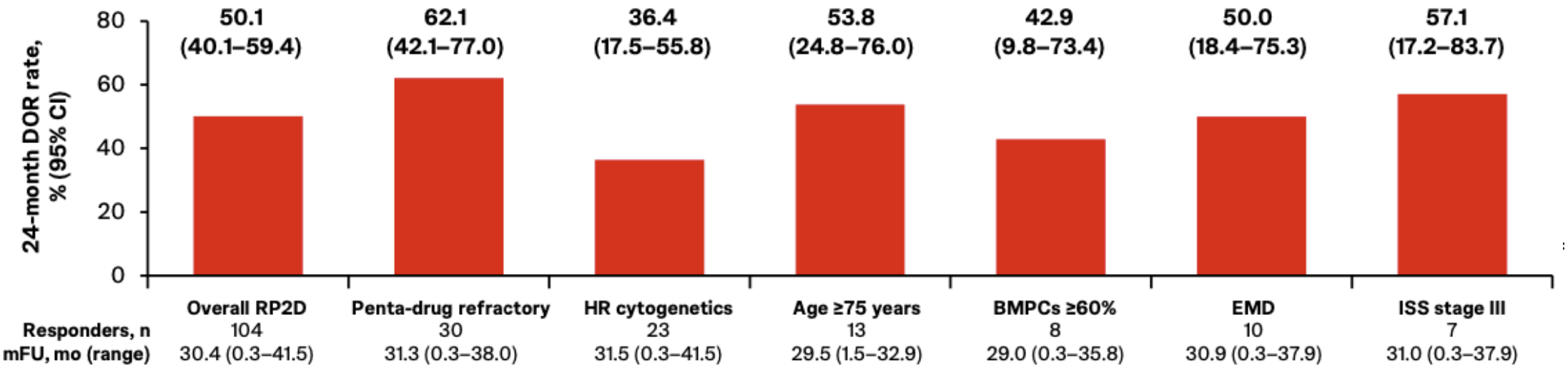


CR or better
VGPR or better
Overall

Albert Oriol, EHA 2024, P942
Usmani S et al., ASCO 2023; Van de Donk J et al., ASCO 2023

Teclistamab- BCMA- bispecific antibodies

MajecTEC-1: Response & DOR in patient with HR features



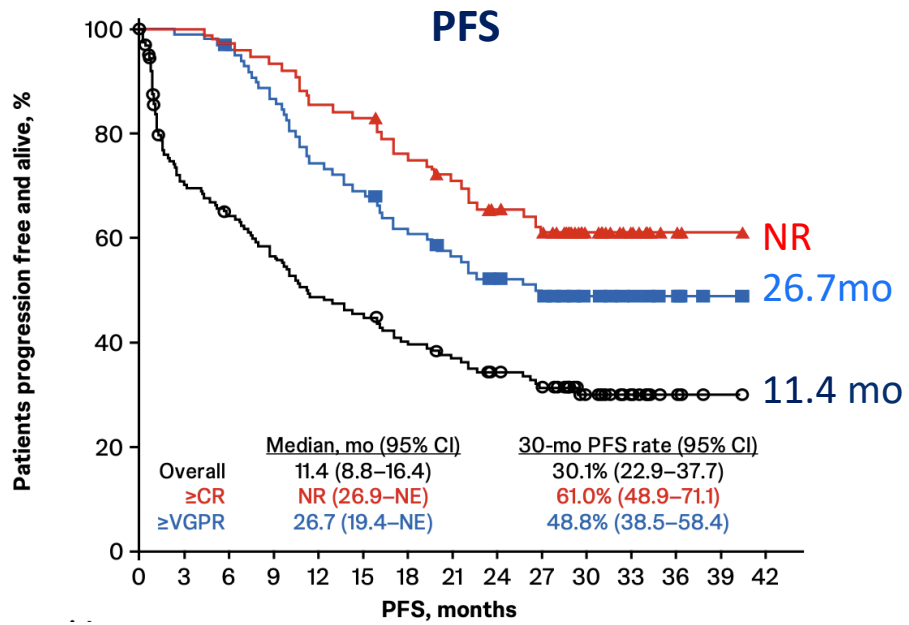
	Overall RP2D	Penta-drug refractory	HR cytogenetics	Age ≥75 years	BMPCs ≥60%	EMD	ISS stage III
Responders, n	104	30	23	13	8	10	7
mFU, mo (range)	30.4 (0.3–41.5)	31.3 (0.3–38.0)	31.5 (0.3–41.5)	29.5 (1.5–32.9)	29.0 (0.3–35.8)	30.9 (0.3–37.9)	31.0 (0.3–37.9)

Results should be interpreted with caution due to small patient numbers. mFU, median follow-up; NE, not estimable; NR, not reached.

Luciano Costa, EHA 2024

Teclistamab- BCMA- bispecific antibodies

MajecTEC-1: PFS & OS by initial response



	mDOR, mo (95% CI)	mPFS, mo (95% CI)	mOS, mo (95% CI)
All RP2D (N=165)[a]	24.0 (17.0–NE)	11.4 (8.8–16.4)	22.2 (15.1–29.9)
≥CR (n=76)[a]	NR (26.7–NE)	NR (26.9–NE)	NR (35.5–NE)
≥VGPR (n=98)[a]	25.6 (18.1–NE)	26.7 (19.4–NE)	NR (31.0–NE)
MRD-neg (n=48)[b]	NR (19.2–NE)	NR (21.0–NE)	NR (29.9–NE)
≤3 pLOT (n=43)	24.0 (14.0–NE)	21.7 (13.8–NE)	NR (18.3–NE)
>3 pLOT (n=122)	22.4 (14.9–NE)	9.7 (6.4–13.1)	17.7 (12.2–29.7)
Phase 2 efficacy (USPI) (n=110)[c]	22.4 (14.9–NE)	10.8 (7.4–16.4)	21.7 (12.7–29.9)
≥CR (n=51)[c]	NR (21.6–NE)	NR (22.8–NE)	NR (NE–NE)

Albert Oriol, EHA 2024, P942

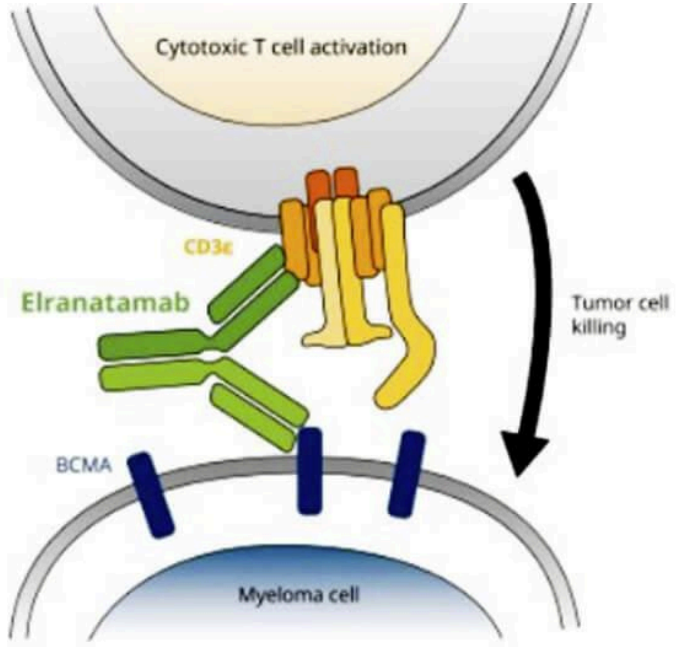
Usmani S et al., ASCO 2023; Van de Donk J et al., ASCO 2023

Elranatamab- BCMA- bispecific antibodies

Overview of Elranatamab bispecific antibody

Elranatamab is a BCMA-directed CD3 T-cell engager approved on August 14th, 2023 for patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including:

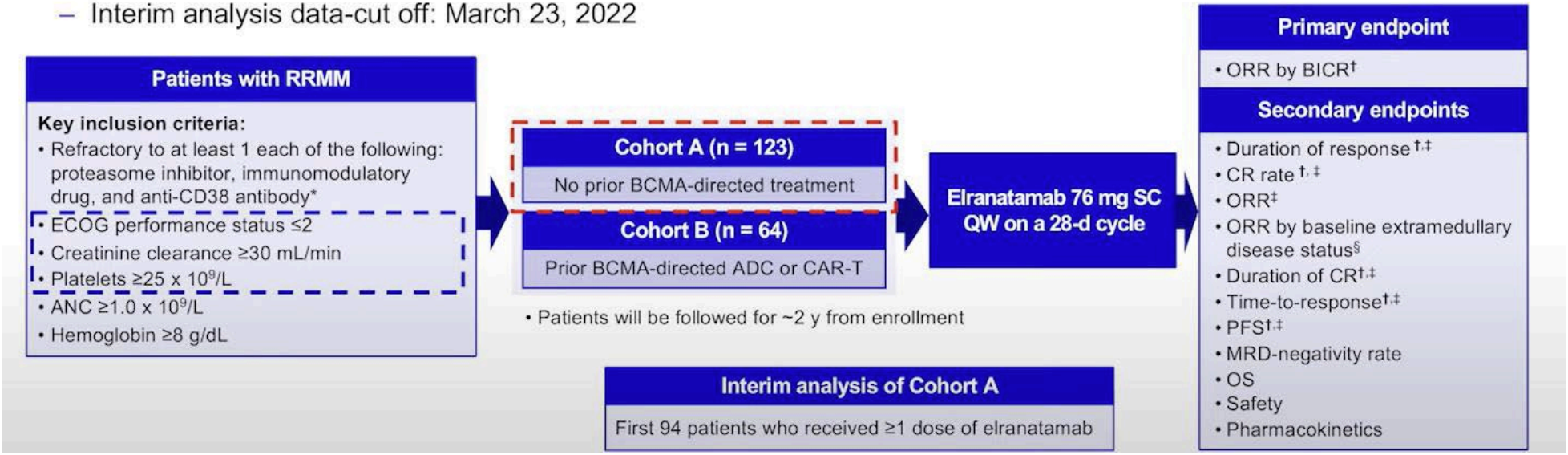
- Proteasome inhibitor
- Immunomodulatory agent
- Anti-CD38 monoclonal antibody



Elranatamab- BCMA- bispecific antibodies

MagnestisMM-3: Trial Design

- MagnetisMM-3 (NCT04649359) is an open-label, multicenter, non-randomized, phase 2 study
  - Interim analysis data-cut off: March 23, 2022

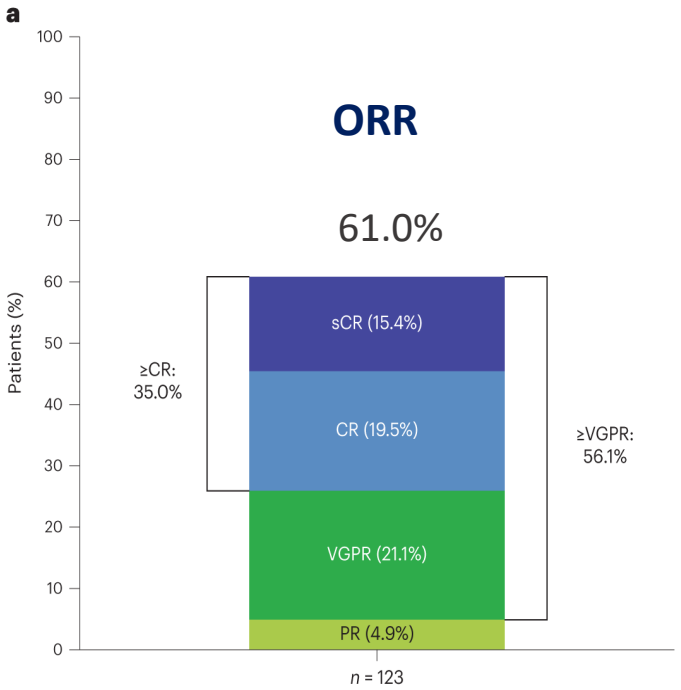


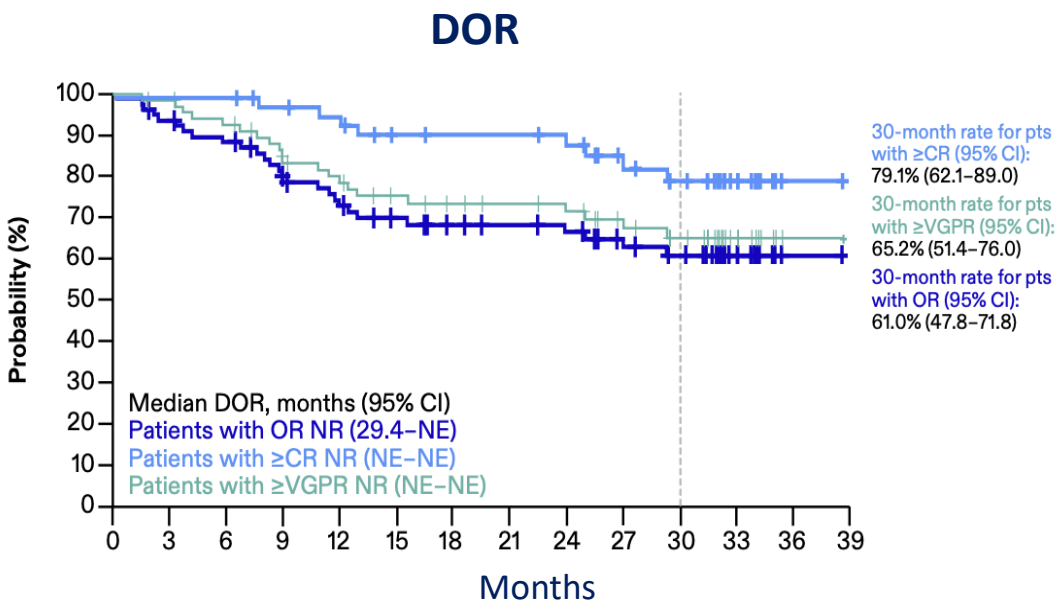
Triple class exposed **100%**
Triple class refractory **96.7%**

Lesokin et al., Nat Med 2023

Elranatamab- BCMA- bispecific antibodies

MagnetisMM-3: ORR and DOR





- ORR per BICR for the overall cohort was 61.0% (95% CI, 51.8-69.6)
- ≥CR was 37.4% and of those patients evaluable for MRD (n=30), the MRD negativity rate was 90.0%

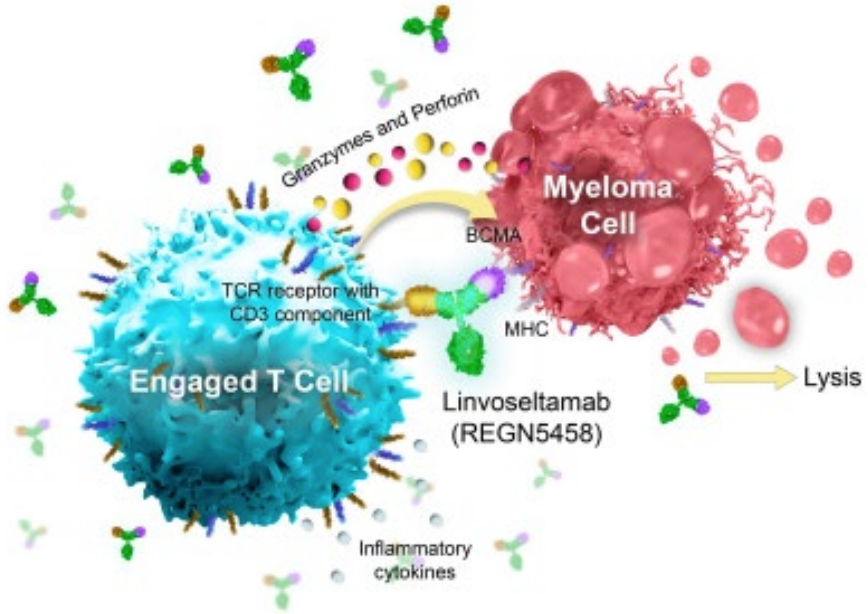
Lesokin et al., Nat Med 2023
H. Miles Prince, ASH 2024

Linvoseltamab- BCMA- bispecific antibodies

Overview of Linvoseltamab bispecific antibody

Linvoseltamab (REGN5458) is a BCMA-directed CD3 T-cell engager approved on ***July 2nd, 2025*** for patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapy including:

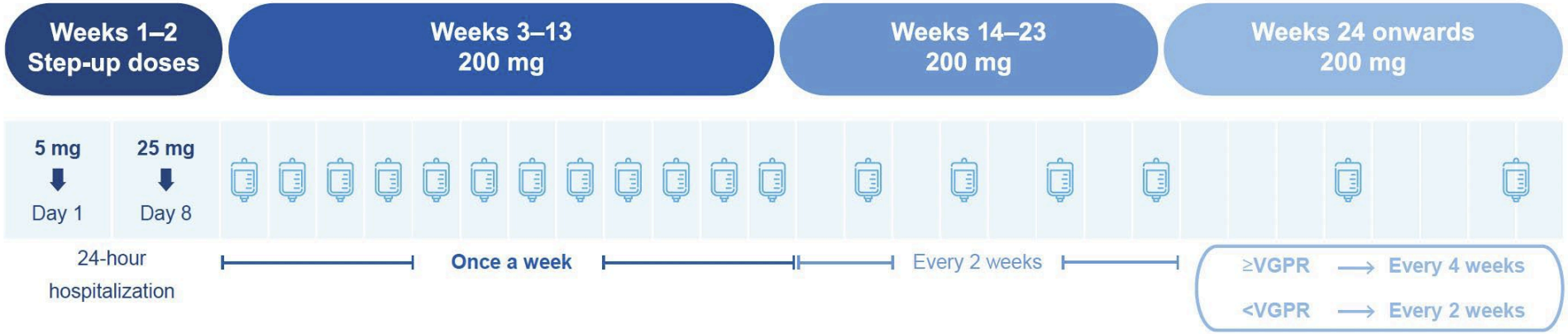
- Proteasome inhibitor
- Immunomodulatory agent
- Anti-CD38 monoclonal antibody



Hans Lee, ASCO 2023

Linvoseltamab- BCMA- bispecific antibodies

LINKER-MM1 phase 2: Trial design



Linvoseltamab required two 1-day hospitalizations and allowed monthly dosing for patients who achieved ≥VGPR (Bumma et al., 2024)

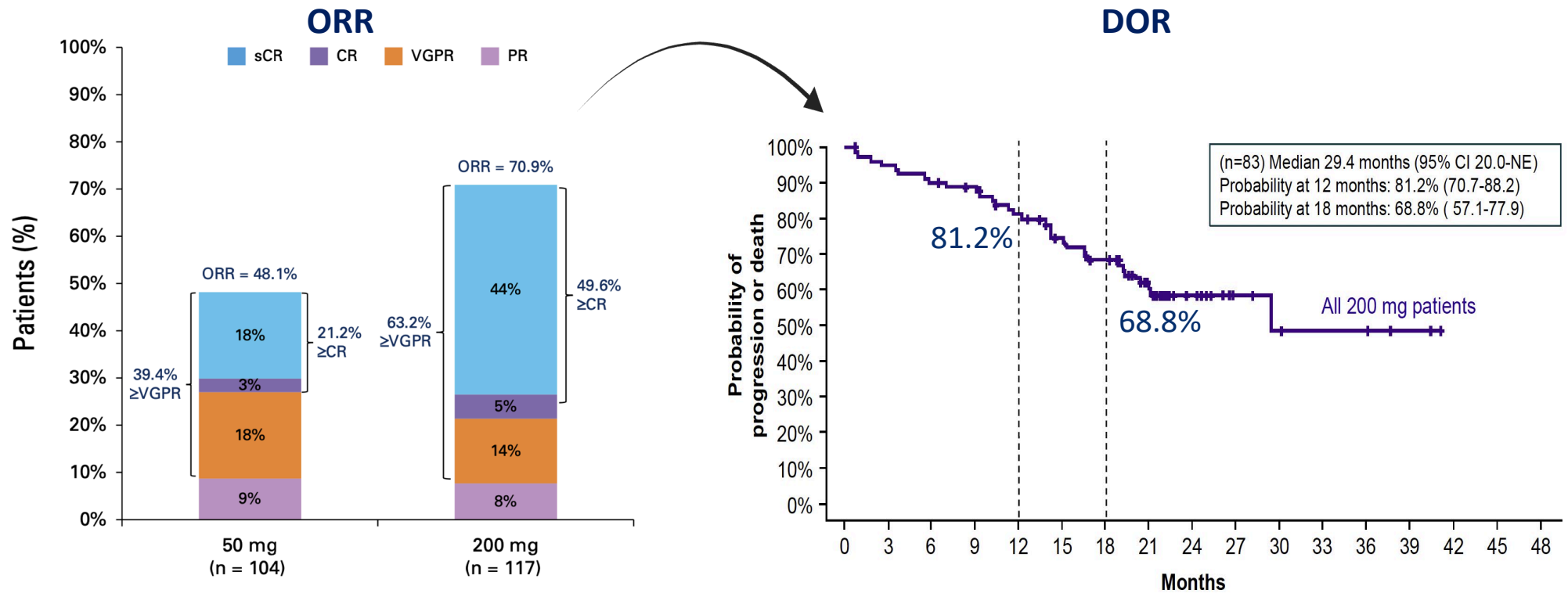
Patient population (Suppl. Table 1) was heavily pretreated with high-risk features:

- Median age of 70 years; 26.5% ≥75 years of age
- Extramedullary plasmacytomas (≥2 cm) per IRC, 14.5%; ISS stage III, 17.9%

Mansi Shah ASH 2024

Linvoseltamab- BCMA- bispecific antibodies

LINKER-MM1: ORR and DOR



Lesokin et al., Nat Med 2023
H. Miles Prince, ASH 2024

Approved BCMA- bispecific antibodies

Summary of key outcomes:

Approved (7/2/2025)

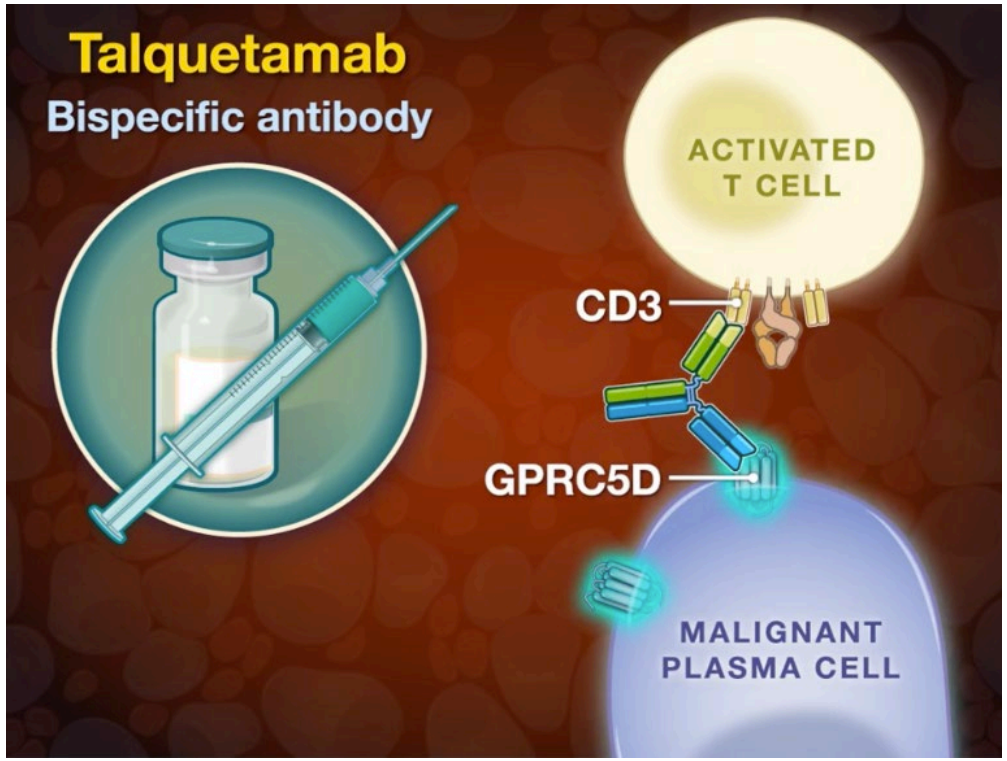
	Approved		~~Emerging~~
	Teclistamab[1,a] (N = 165)	Elranatamab[3] (N = 123)	Linvoseltamab[4] (N = 117)
Median FU, mo	30.4	28.4[b]	14.3
Median prior lines, n	5.0[2]	5.0	5.0
Key outcomes			
ORR, %	63.0	61.0	71.0
mPFS, mo	11.4	17.2	NR[c] (70% at 12 mo)
mOS, mo	22.2	24.6	31.4[c] (75.3% at 12 mo)
mDOR, mo	24.0	NR (66.9% at 24 mo)	29.4[c] (80.9% at 12 mo; n = 83)

Talquetamab- GPRC5D targeting bispecific antibodies

Overview of talquetamab bispecific antibody

Talquetamab is a novel bispecific GPRC5D-directed CD3 T-cell engager that on **August 9, 2023** received FDA approval for patients with relapsed or refractory multiple myeloma who have received at least four prior lines of therapies:

- Proteasome inhibitor
- Immunomodulatory agent
- Anti-CD38 monoclonal antibody

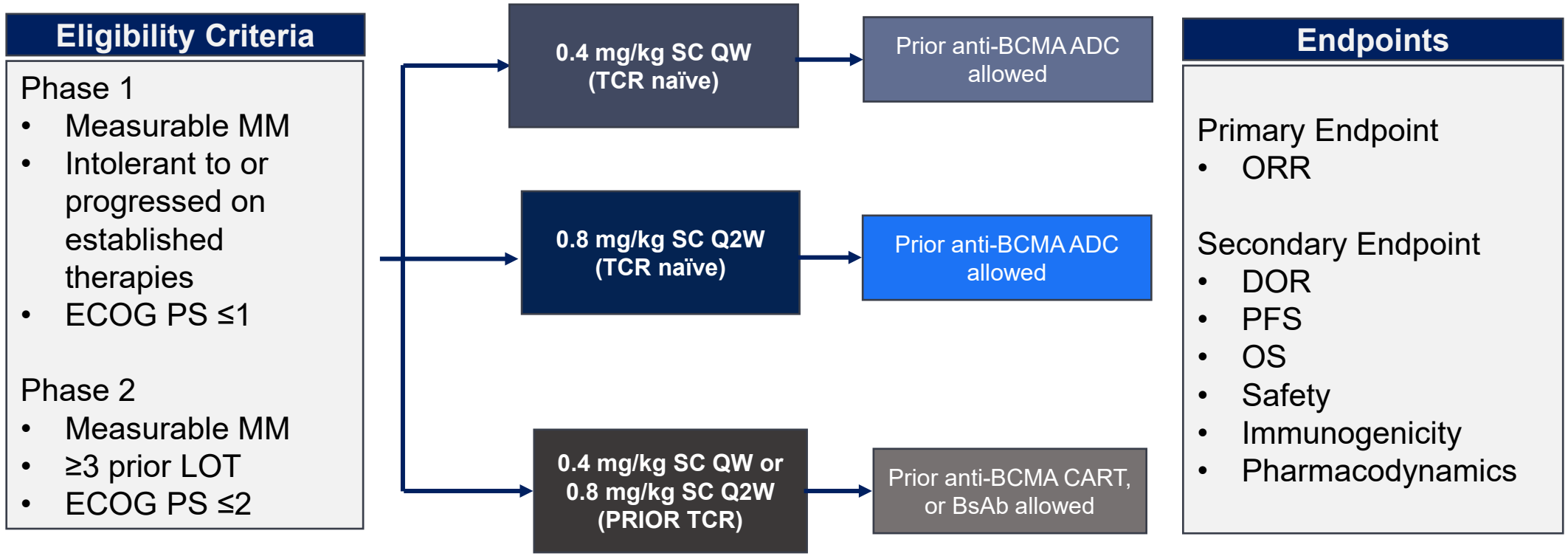


G protein–coupled receptor, family C, group 5, member D (GPRC5D)

Chari et al NEJM 2022
https://www.nejm.org/doi/full/10.1056/NEJMoa2204591

Talq- GPRC5D bispecific antibodies

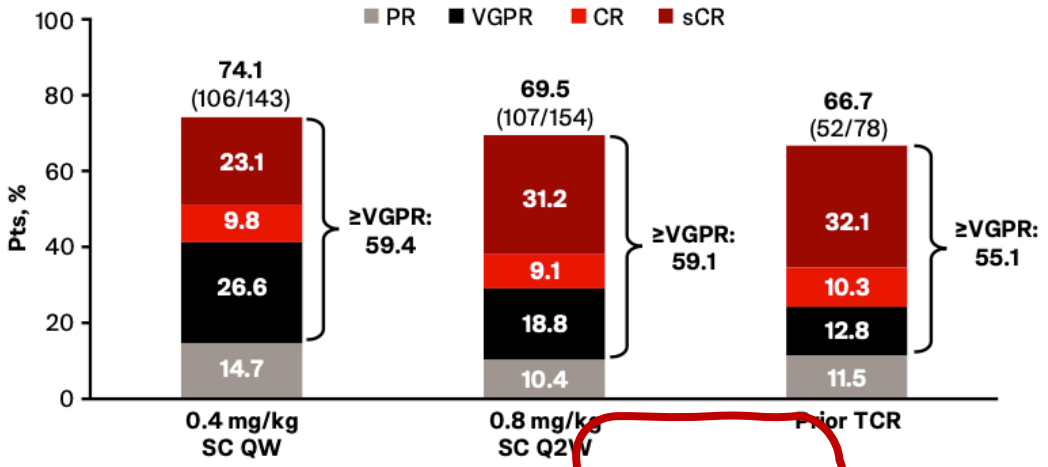
MonumenTAL-1: Trial design



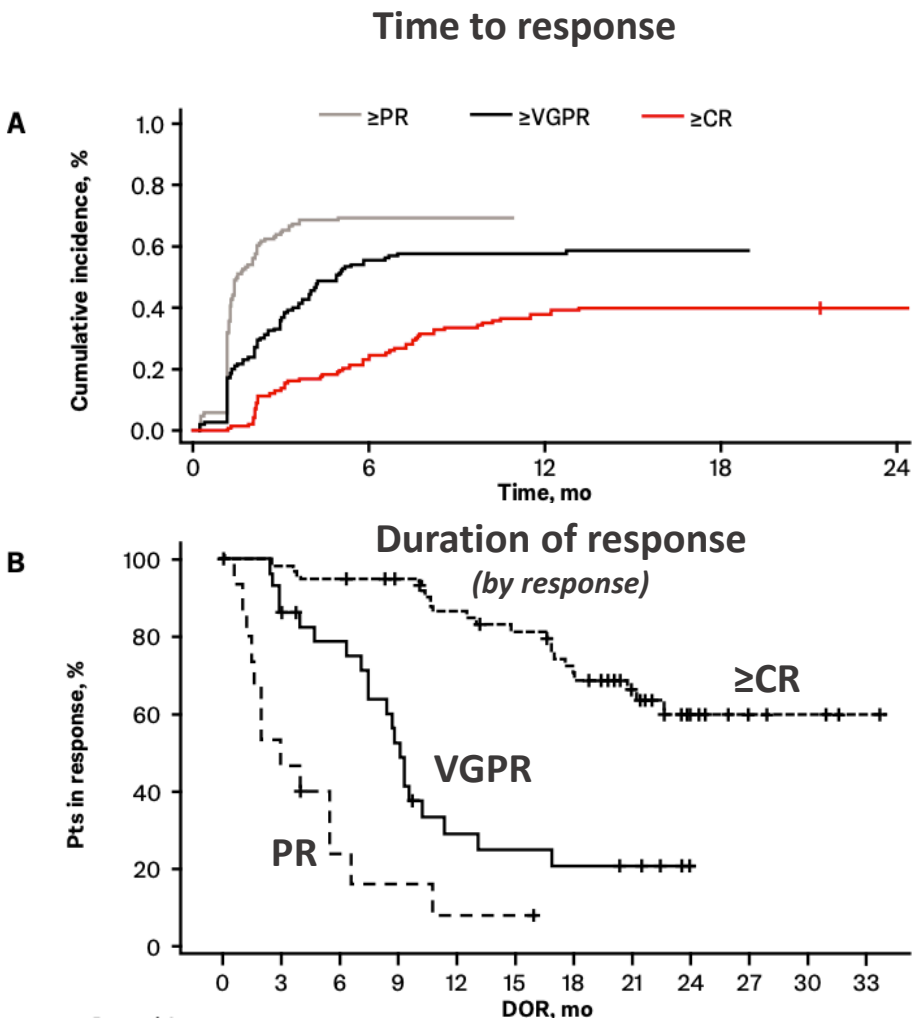
Chari et al NEJM 2022

Talq- GPRC5D bispecific antibodies

MonumenTAL-1: Long-term follow-up



Outcome	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=154)	Prior TCR (n=78)
mFU, mo	29.8	23.4	20.5
mDOR (95% CI),[a] mo	9.5 (6.7–13.4)	17.5 (12.5–NE)	N/A[b]
mDOR in pts with ≥CR (95% CI), mo	28.6 (19.4–NE)	NR (21.2–NE)	N/A[b]
mPFS (95% CI), mo	7.5 (5.7–9.4)	11.2 (8.4–14.6)	7.7 (4.1–14.5)
24-mo OS rate (95% CI), %	60.6 (51.7–68.4)	67.1 (58.3–74.4)	57.3 (43.5–68.9)



Leo Rasche, EHA 2024, P915

Talq- GPRC5D bispecific antibodies

MonumenTAL-1: ORR by HR subgroup

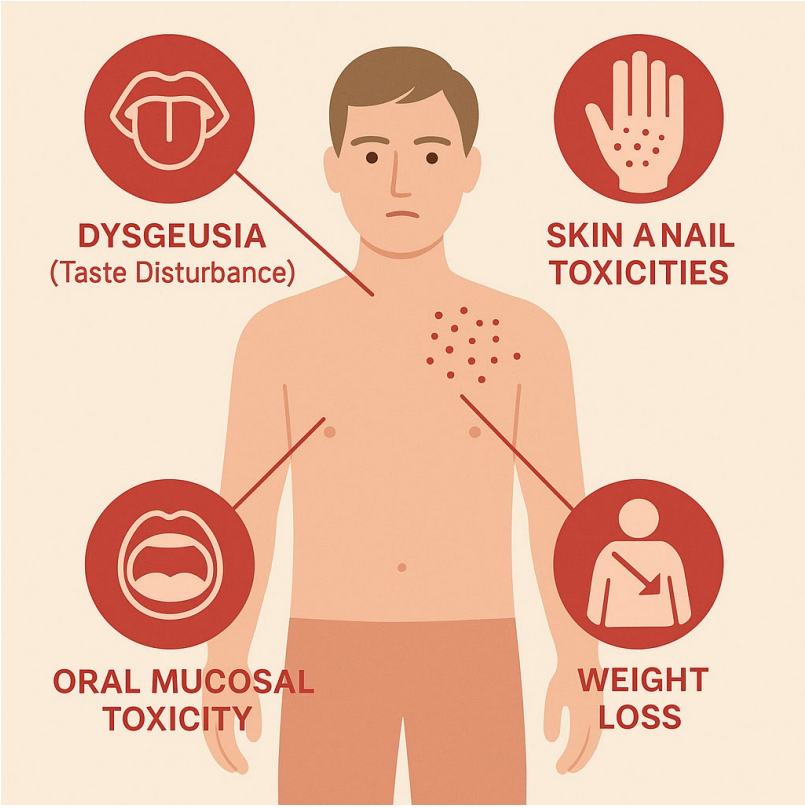
ORR in subgroups, % (95% CI)	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=154)	Prior TCR (n=78)
Age ≥75, years	71.4 (47.8–88.7)	75.8 (57.7–88.9)	80.0 (28.4–99.5)
High-risk cytogenetics[a]	70.7 (54.5–83.9)	75.0 (58.8–87.3)	52.0 (31.3–72.2)
ISS stage III	64.3 (44.1–81.4)	59.5 (42.1–75.2)	76.9 (46.2–95.0)
Baseline renal function, ≤60 mL/min/1.73 m^2	65.0 (48.3–79.4)	65.2 (49.8–78.6)	63.2 (38.4–83.7)
Refractory status			
Triple-class[b]	72.9 (63.4–81.0)	67.3 (57.7–75.9)	65.2 (52.4–76.5)
Penta-drug[c]	71.1 (55.7–83.6)	69.2 (52.4–83.0)	58.8 (40.7–75.4)
≥1 extramedullary plasmacytoma[d]	48.5 (30.8–66.5)	41.5 (26.3–57.9)	44.0 (24.4–65.1)

Leo Rasche, EHA 2024, P915

Talq- GPRC5D bispecific antibodies

MonumenTAL-1: "on target off tumor" Adverse events

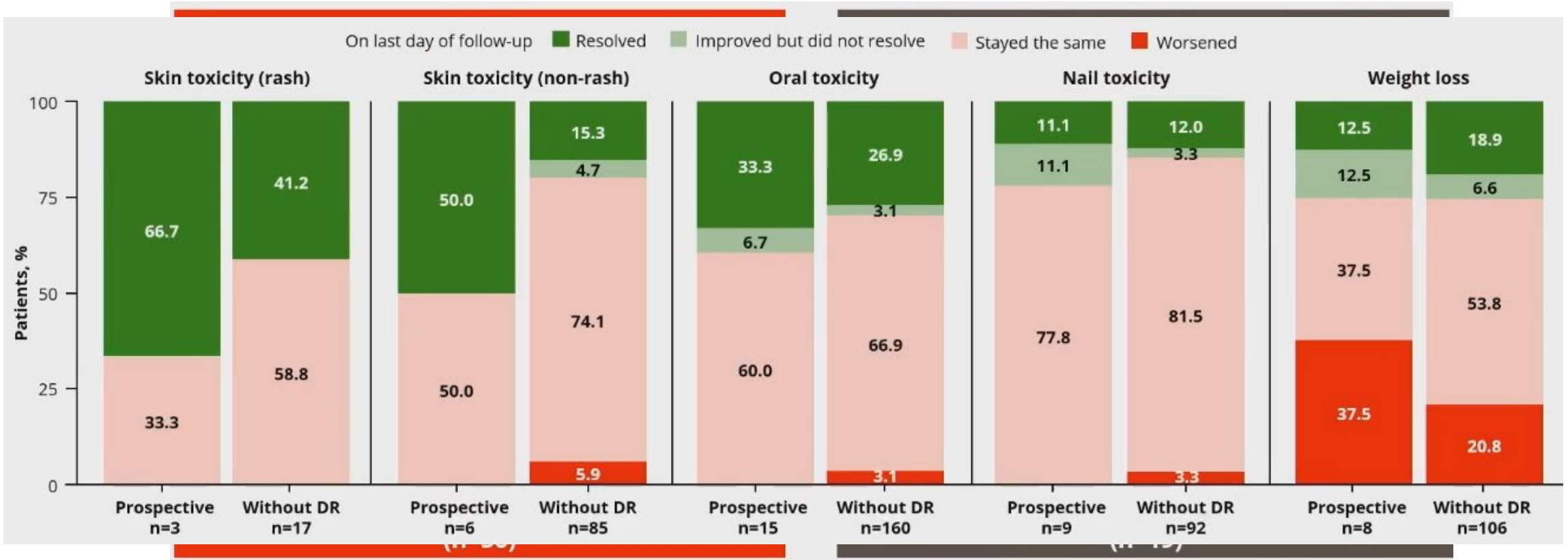
Any-grade AE, n (%)	0.4 mg/kg SC QW (n=143)	0.8 mg/kg SC Q2W (n=154)	Prior TCR (n=78)
Taste-related[a]			
Total	103 (72.0)	110 (71.4)	59 (75.6)
Leading to dose reduction	10 (7.0)	6 (3.9)	4 (5.1)
Leading to discontinuation	0	3 (1.9)	0
Skin-related[b]			
Total	81 (56.6)	113 (73.4)[e]	50 (64.1)
Leading to dose reduction	5 (3.5)	1 (0.6)	2 (2.6)
Leading to discontinuation	2 (1.4)	1 (0.6)	0
Nail-related[c]			
Total	79 (55.2)	82 (53.2)	46 (59.0)
Leading to dose reduction	1 (0.7)	1 (0.6)	1 (1.3)
Leading to discontinuation	0	0	0
Rash-related[d]			
Total	57 (39.9)[f]	46 (29.9)[g]	25 (32.1)[h]
Leading to dose reduction	1 (0.7)	1 (0.6)	0
Leading to discontinuation	0	0	0



Smith et al., Sci Transl 2019; Chari A, CLML 2024; Chari et al NEJM 2022

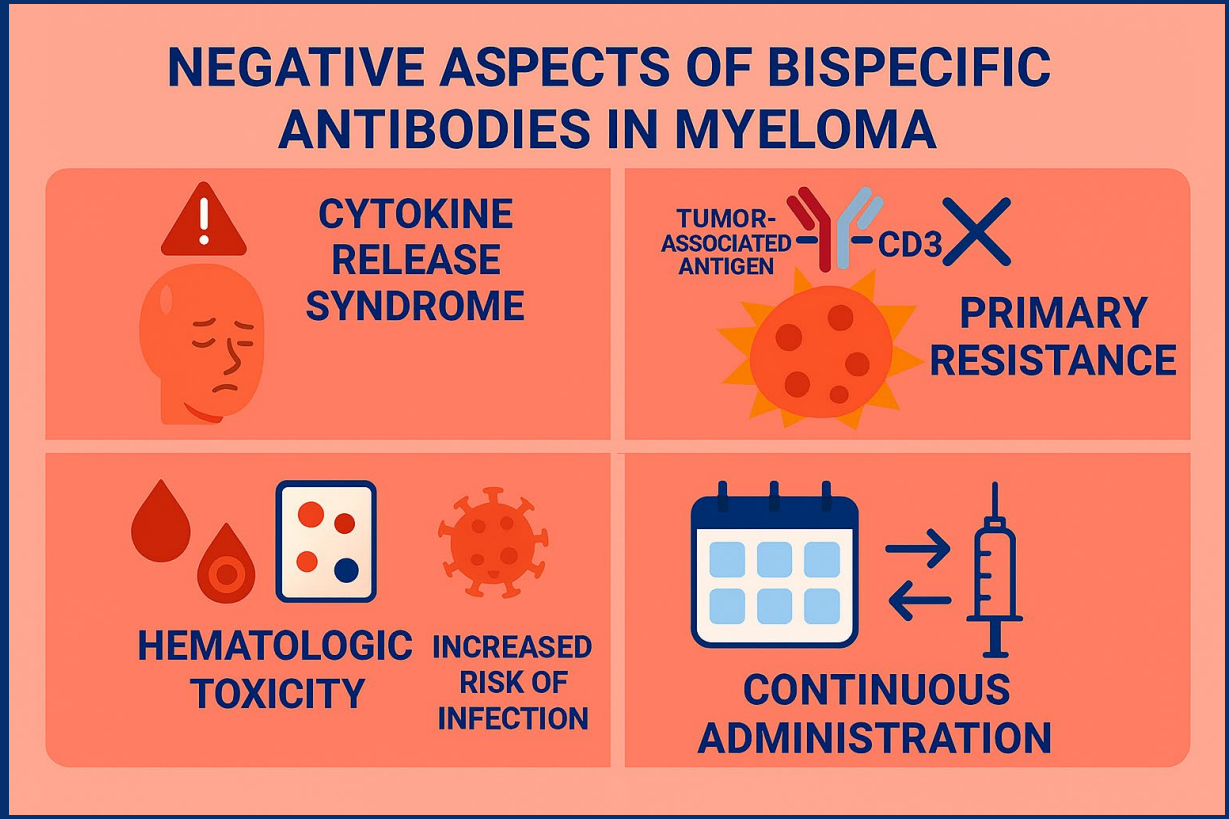
Talq- GPRC5D bispecific antibodies

MonumenTAL-1: "on target off tumor" Adverse events



Chari A et al ASH 2023

It is not perfect.

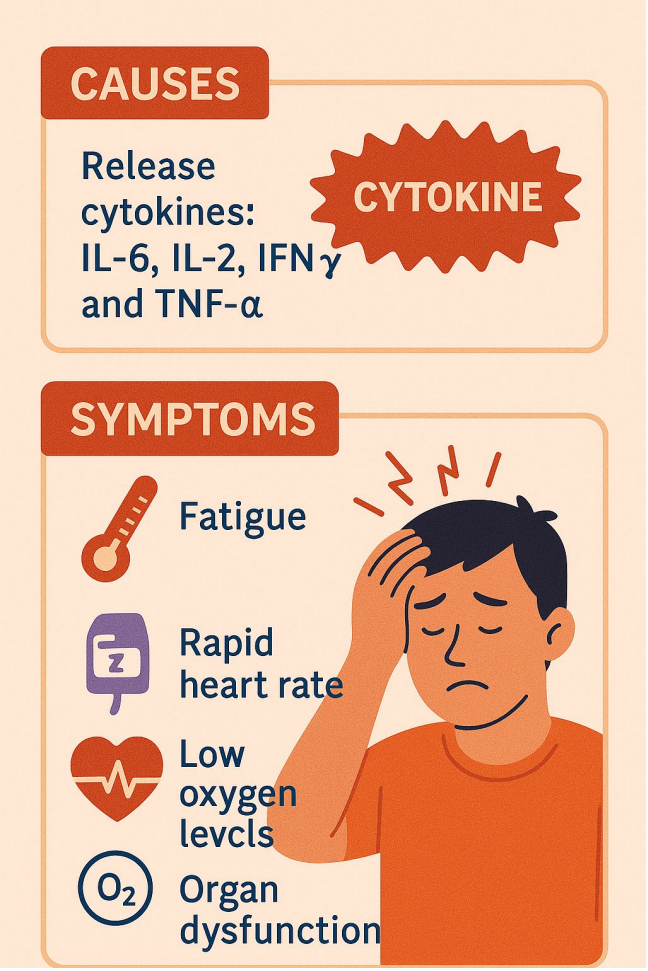


Cytokine release syndrome (CRS) -

Cytokine Release Syndrome (CRS) is a potentially serious systemic inflammatory response that occurs when the immune system is **strongly activated**, leading to a rapid and excessive release of **cytokines**—small proteins that help regulate immune responses.

This activation triggers the release of large amounts of cytokines such as:

- IL-6
- IL-2
- IFN-γ
- TNF-α



CRS & ICANS -

Characteristics by agent:

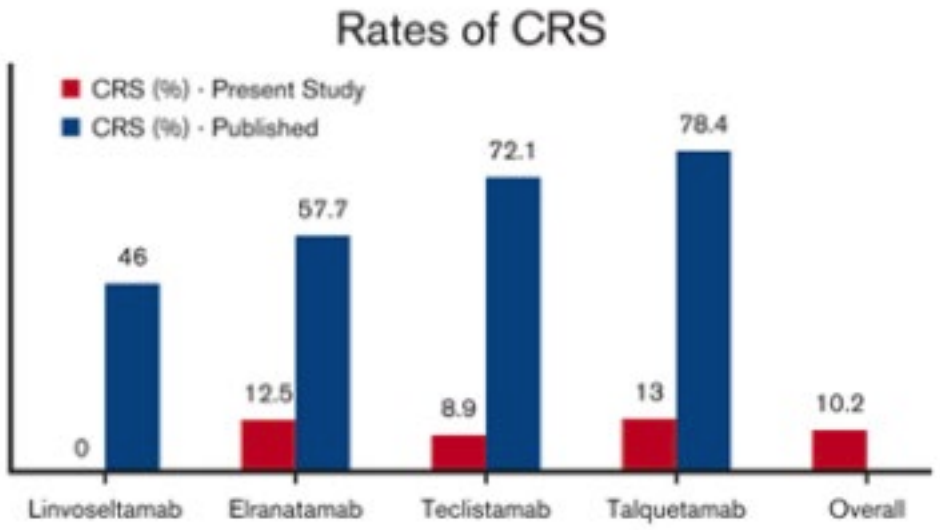
	CRS			ICANS		
	Incidence G1 / G2 / G3+	Time to Onset Median (Range)	Duration Median (Range)	Incidence	Time to Onset Median (Range)	Duration Median (Range)
Teclistamab	50.3% / 21.2% / 0.6%	2 days (1–6)	2 days (1–9)	3%	4 days (2–8)	3 days (1–20)
Elranatamab	42% / 14.3% / 0%	2 days (1–9)	2 days (1–19)	3.4%	2.5 days (1–4)	2 days (1–6)
Talquetamab 0.4 mg/kg QW	62% / 15% / 2%	25.9 hours (17.8–31.9)	14.5 hours (4.0–32.0)	11%	23.6 hours (15.0–53.7)	15.5 hours (2.7–23.9)
Talquetamab 0.8 mg/kg Q2W	57% / 17% / 1%	27.8 hours (21.0–34.6)	17.0 hours (5.6–33.8)	10%	31.9 hours (14.7–52.0)	7.8 hours (3.5–24.9)

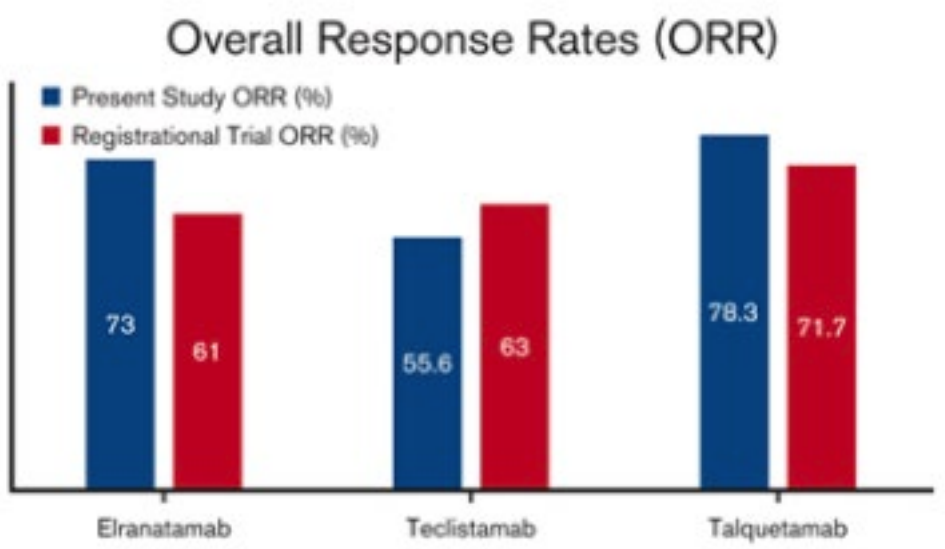
- Tecvayli (teclistamab-cqyv) Prescribing Information.; Moreau P et al. *NEJM*. 2022;387:495-505.;
- Elrexfio (elranatamab-bcmm) Prescribing Information.; Lesokhin AM et al. *Nature Medicine*. 2023;29:2259-2267.;
- Talvey (talquetamab-tgvs) Prescribing Information.; Chari A et al. *Lancet Hematol*. 2025;12:e269-81.

CRS – Prophylaxis

Prophylactic Tocilizumab- “RWE”

- Real-world study of **119** patients conducted at Sylvester Cancer Center at Univ Miami
- Tocilizumab 8 mg/kg IV was administered **1 hour prior** to step up dose 1





Andrew Kowalski et al Blood Adv Oct 2025

CRS – Prophylaxis

Prophylactic *Dexamethasone* on teclistamab

243 patients with RRMM treated with teclistamab at six U.S. academic centers.

133 patients, (55%) developed cytokine-release syndrome (CRS)

- Most cases were mild (grade 1): 1 in 8 were moderate (grade 2); CRS typically lasted ~1 day

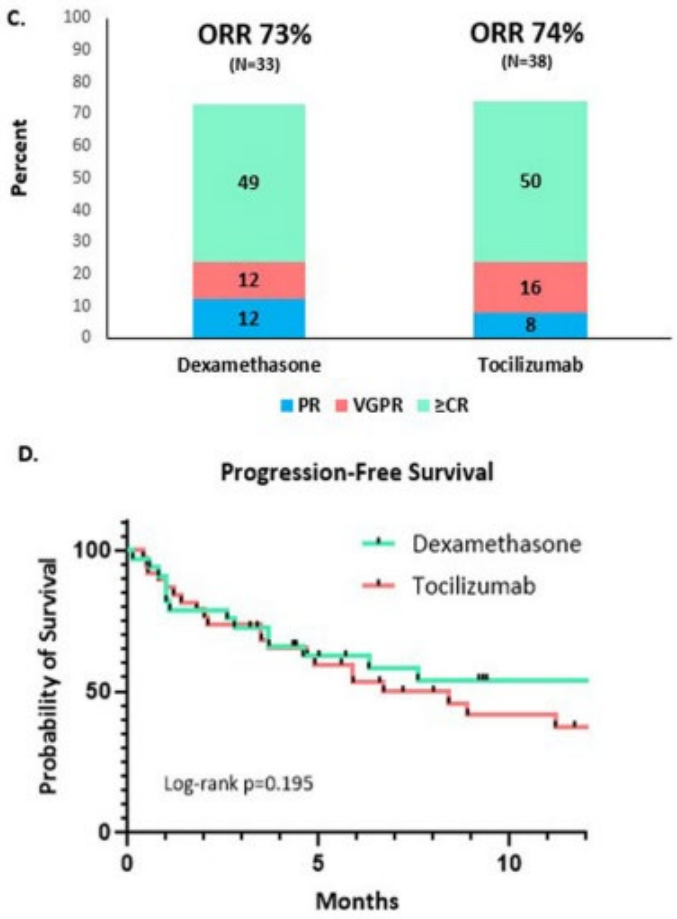
How was CRS handled?

- 23% got only dexamethasone.
- 29% got only tocilizumab.
- 23% received both drugs.
- 25% improved with basic supportive care only (observation, acetaminophen, oxygen, fluids).

Details on dexamethasone use

- Standard dose was 10 mg for nearly three-quarters of events.
- Most patients needed just one dose; 30 % needed a second.

Treatment results looked similar whether CRS was managed with dexamethasone or tocilizumab with an overall response rate ~73-74% and comparable PFS.



- Davis JA, Snyder J, Rice M, Moore DC, Cahoon C, Julian K, Wagner CB, Granger K, Green KM, Atrash S, Hill H, McElwee J, Elsey G, Khouri J, Rudoni J, Mahmoudjafari Z, Nachar VR. Dexamethasone for the management of CRS Related to teclistamab in patients with relapsed/refractory multiple myeloma. Blood Cancer J. 2025 Mar 4;15(1):32

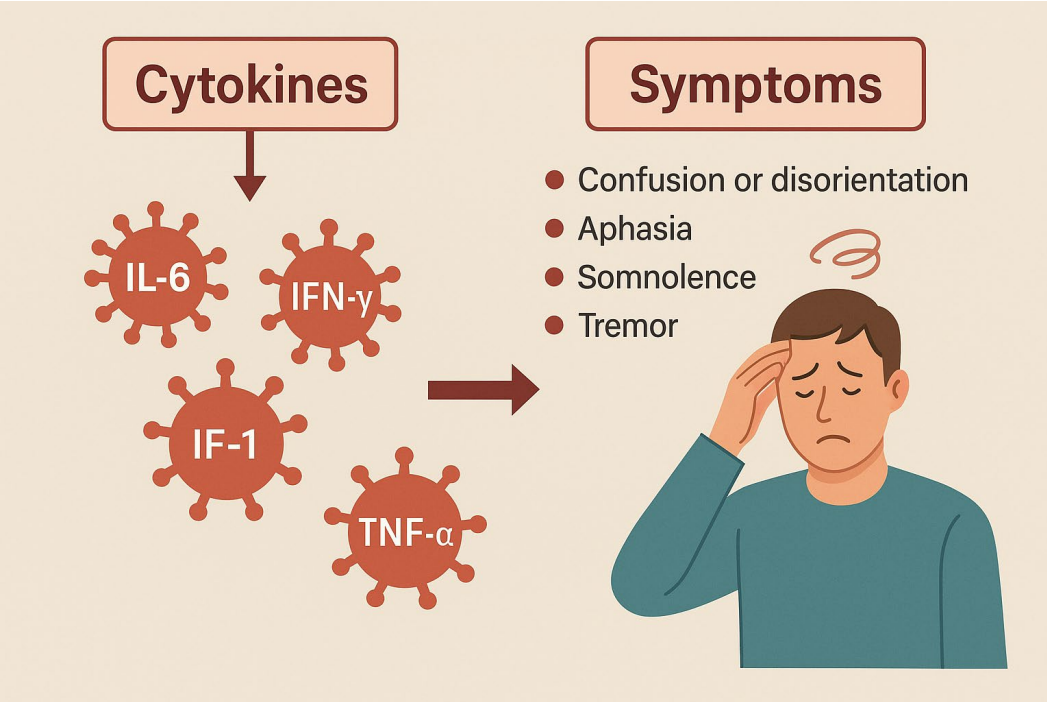
ICANS – Immune Effector Cell-Associated Neurotoxicity Syndrome

ICANS is a type of **neurologic toxicity** that can occur after **immune effector cell therapies**, especially:

- **CAR-T cell therapy**
- **Bispecific T-cell engagers** (e.g., in multiple myeloma)

While not fully understood, ICANS is believed to result from:

- **Cytokine release** and systemic inflammation
- **Blood-brain barrier disruption**
- **Immune cell infiltration** and cytokines (like IL-6, IL-1) affecting the central nervous system



ICANS – Immune Effector Cell-Associated Neurotoxicity Syndrome

Grade	Presenting symptoms	Actions
1	ICE score 7-9	Hold bispecific Consider anti-seizure medication
2	ICE score 3-6	Hold bispecific Administer dex 10 mg q6h until grade 1 Consider anti-seizure medication
3	ICE score 0-2 Seizures Raised ICP (focal edema)	Hold bispecific Administer dex 10 mg q6h until grade 1 Consider anti-seizure medication
4	ICE score 0 Unarousable Repetitive seizures Raised ICP with diffuse edema, etc.	Permanently discontinue bispecific Administer dex 10 mg iv q6h until grade 1 Or methylprednisolone 1000 mg daily x 3 days Consider anti-seizure medication

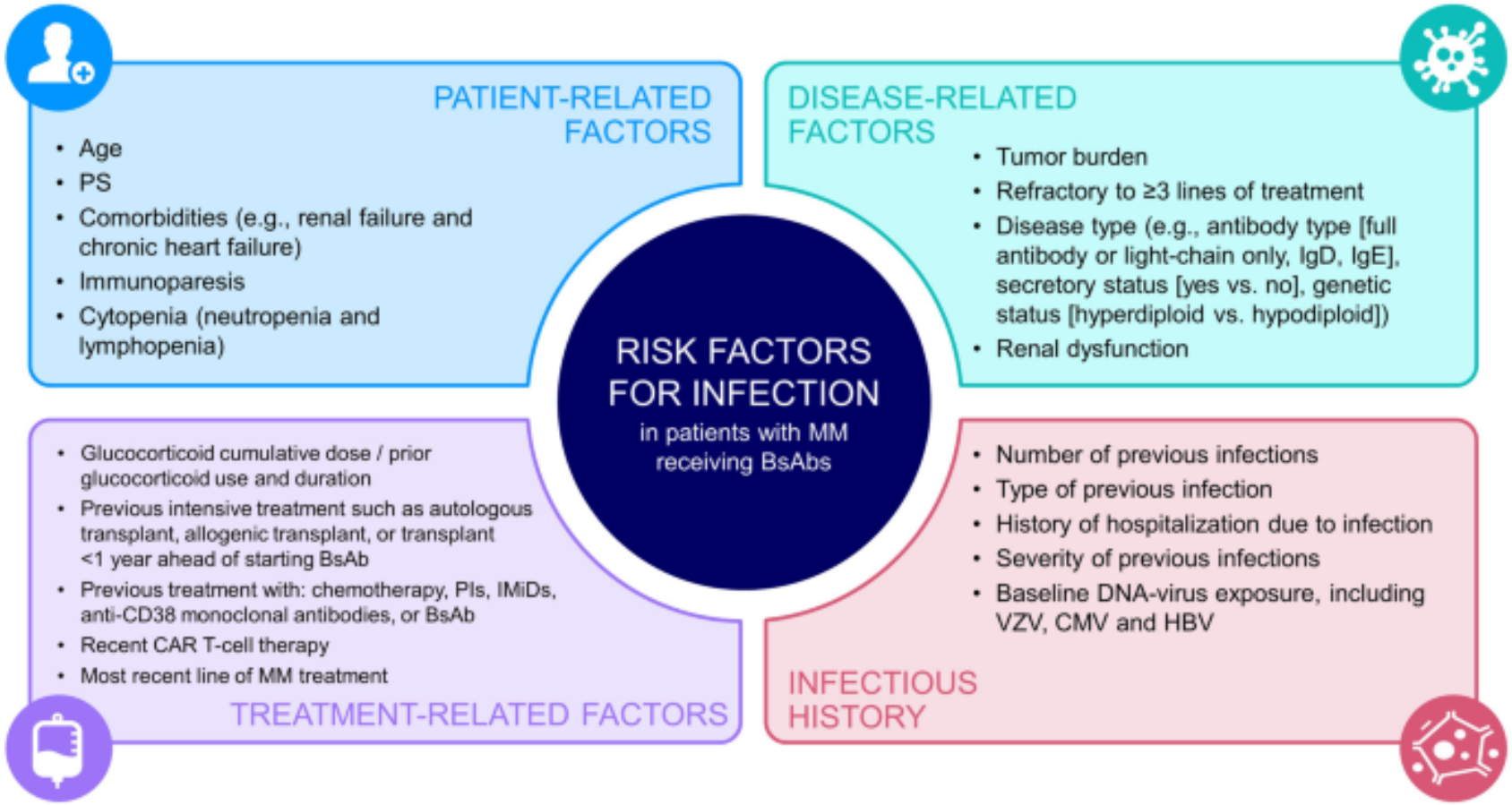
https://tec-talrems.com/

Management of CRS if concurrent CRS as per CRS guidelines
If grade ≥2, patients should be hospitalized following next dose

https://resources.advancedpractitioner.com/multiple-myeloma/focus-on-bsabs/management-of-adverse-effects-in-patients-with-multiple-myeloma-treated-with-bispecific-antibodies/

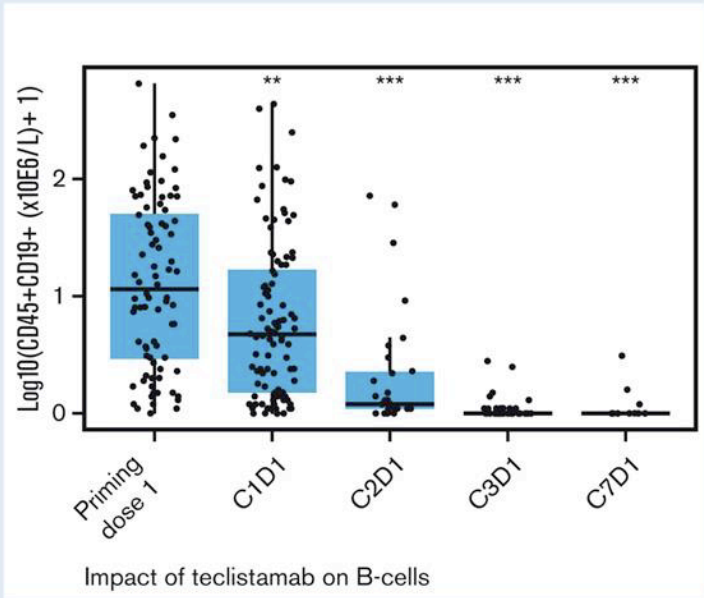
Infection risk.

Infection mitagation strategies are central to improved outcomes with BCMA-BiTEs



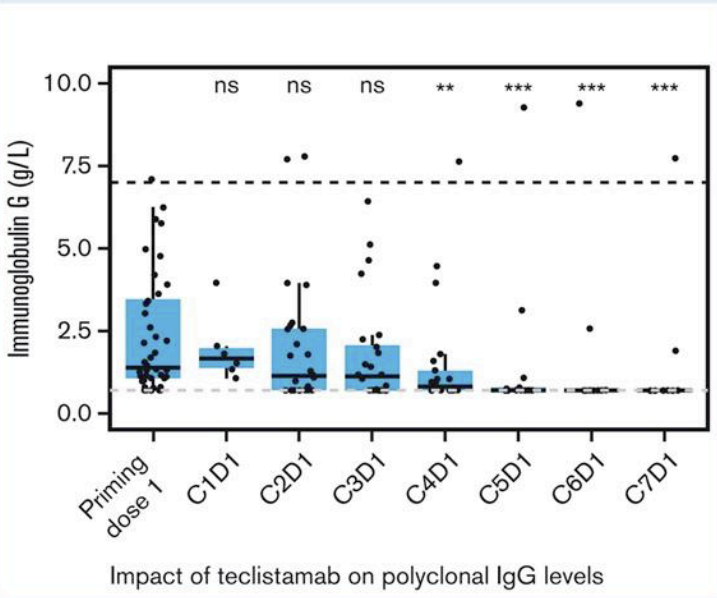
Infection risk.

BCMA TCEs deplete PB B cells & eliminate normal PCs.



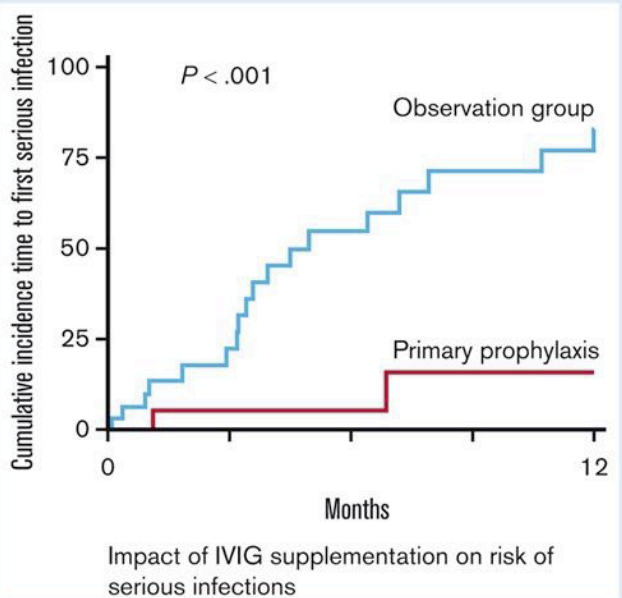
Impact of teclistamab on B-cells

BCMA BsAb treatment results in reduced levels of polyclonal Ig and impaired vaccination response



Impact of teclistamab on polyclonal IgG levels

The negative impact of BCMA BsAbs on humoral immunity can be partially reversed with IVIG supplementation



Impact of IVIG supplementation on risk of serious infections

Making good?

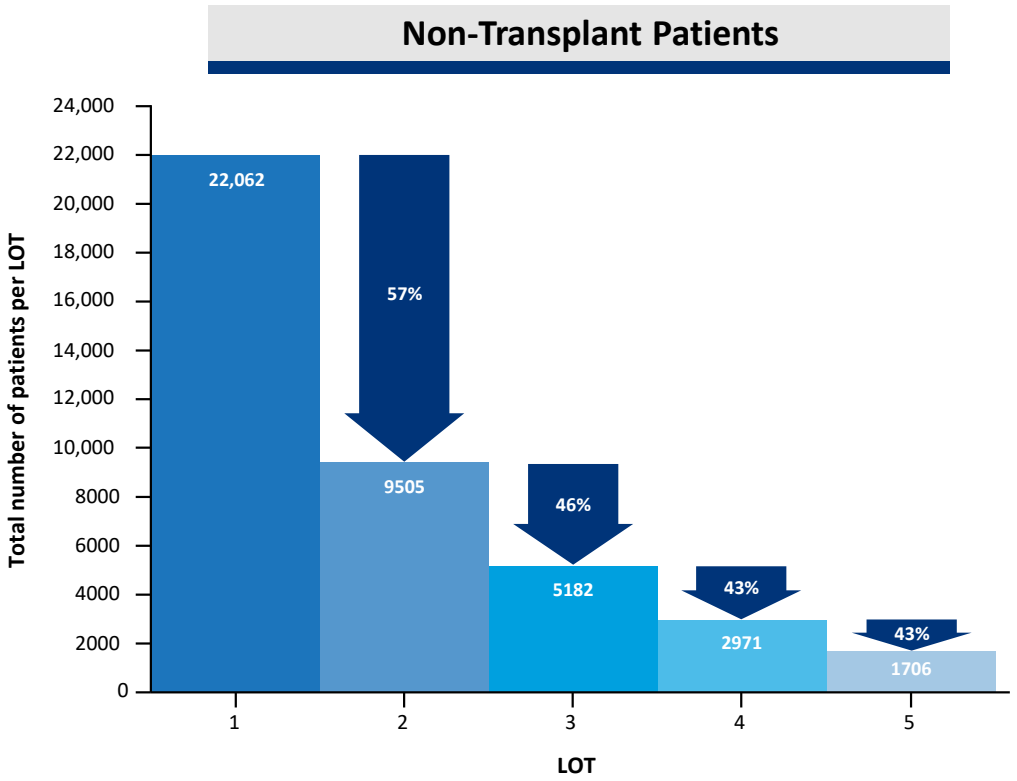
Side by side comparison.

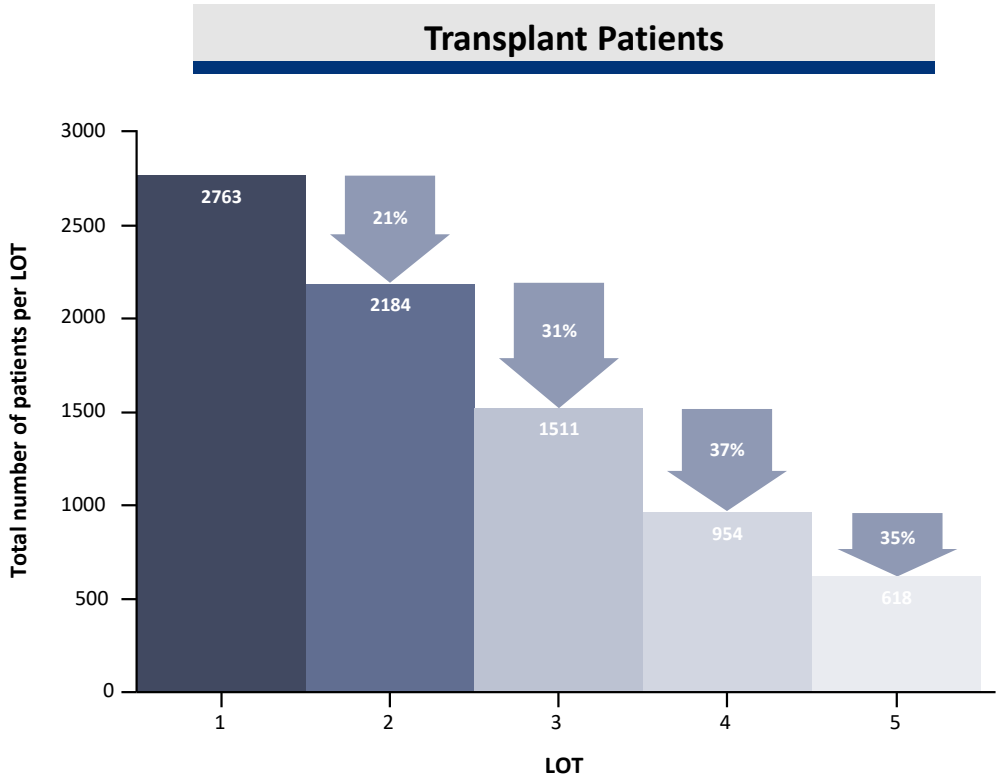
	CAR T Cells	BsAb
Advantages	Personalized	Off the shelf
	Targeted immuno-cytotoxicity	Targeted immuno-cytotoxicity
	Single infusion ("one and done")	No lymphodepletion Minimal steroids
	Potentially persistent	
Disadvantages	FACT-accredited center required (hospitalization likely required)	Initial hospitalization required, *but potential to be given in community.*
	CRS and neurotoxicity; requires ICU and neurology services	CRS and neurotoxicity *possible- some with very little CRS*
	Dependent on T-cell health (manufacturing failures)	Dependent on T-cell health (T-cell exhaustion)
	Requires significant social support; caregiver required	Requires continuous administration
	$$$$	$$$

Shah N. Targeting BCMA in multiple myeloma: evidence-based guidance for current and near future clinical integration. Published April 4, 2022. Accessed October 26, 2022. https://www.clinicaloptions.com/oncology/programs/2022/bcma-in-myeloma/downloadable-slideset/slides-1

Access: We need all therapies accessible to all of our MM patients

High attrition rates →these underscores the need to use the most optimal treatment regimens upfront rather than reserving them for later LOTs in which the clinical benefit may decrease





LOT, line of therapy.

Fonseca R et al. *BMC Cancer.* 2020;20(1):1087.

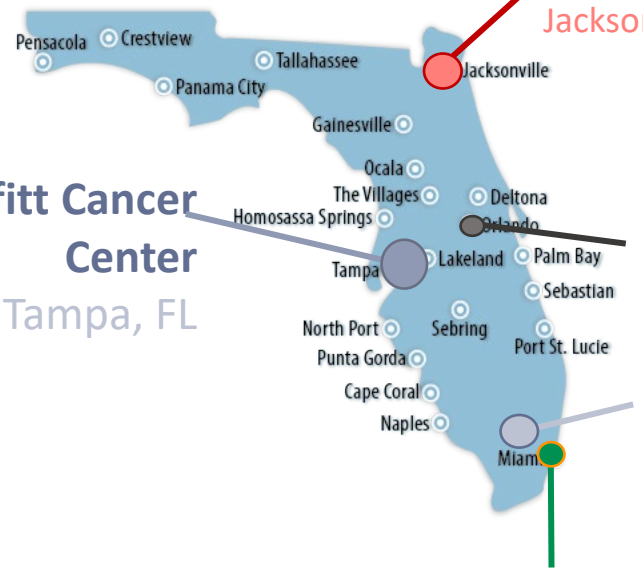
We need all therapies accessible to all of our MM patients

***Florida** as an example* → **22 million people**

MM in Florida-

- 2022 - est **3,490 new** cases of MM (***highest of any state***)
- Incidence **8.2/100,000** (9.6 men & 5.7 woman)

CAR-T



Mayo Clinic Florida
Jacksonville, FL

Moffitt Cancer Center
Tampa, FL

Advent Health Orlando
Orlando, FL

Moffitt at Memorial
Pembroke Pines, FL

Sylvester Comprehensive Cancer Center
Miami, FL

TCEs

- **16** centers and growing in FL (27 sights)
- More community centers every day**
- *Most patients will NEVER come to a MM center **(55.5%)***

https://cancerstatisticscenter.cancer.org/#!/cancer-site/Myeloma

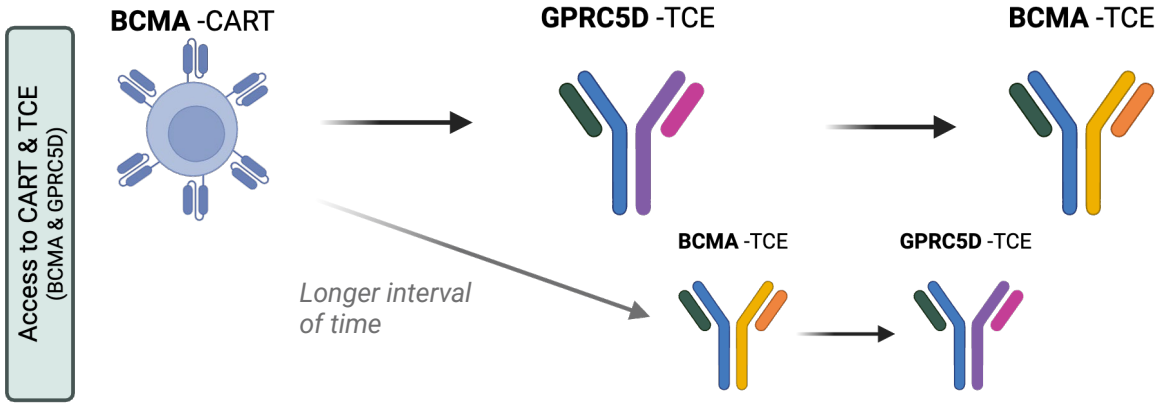
Vardell et al (Sborov) Amer J Hematol 2024

Where do BiTEs fit into MM therapy?

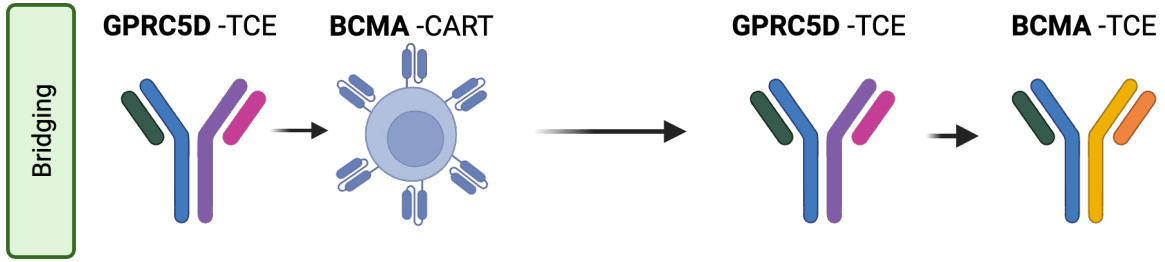
Options

Optimal sequencing of Bispecific antibodies - ”maximize PFSs”

A.



B.

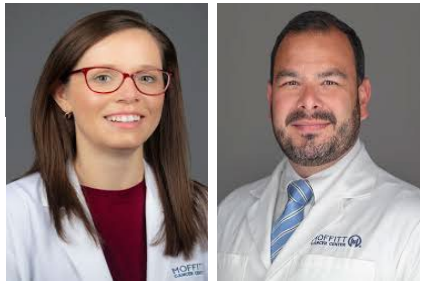


C.

*in patients with high risk for infectious complications/chronic infectious issues consider GPRC5D first

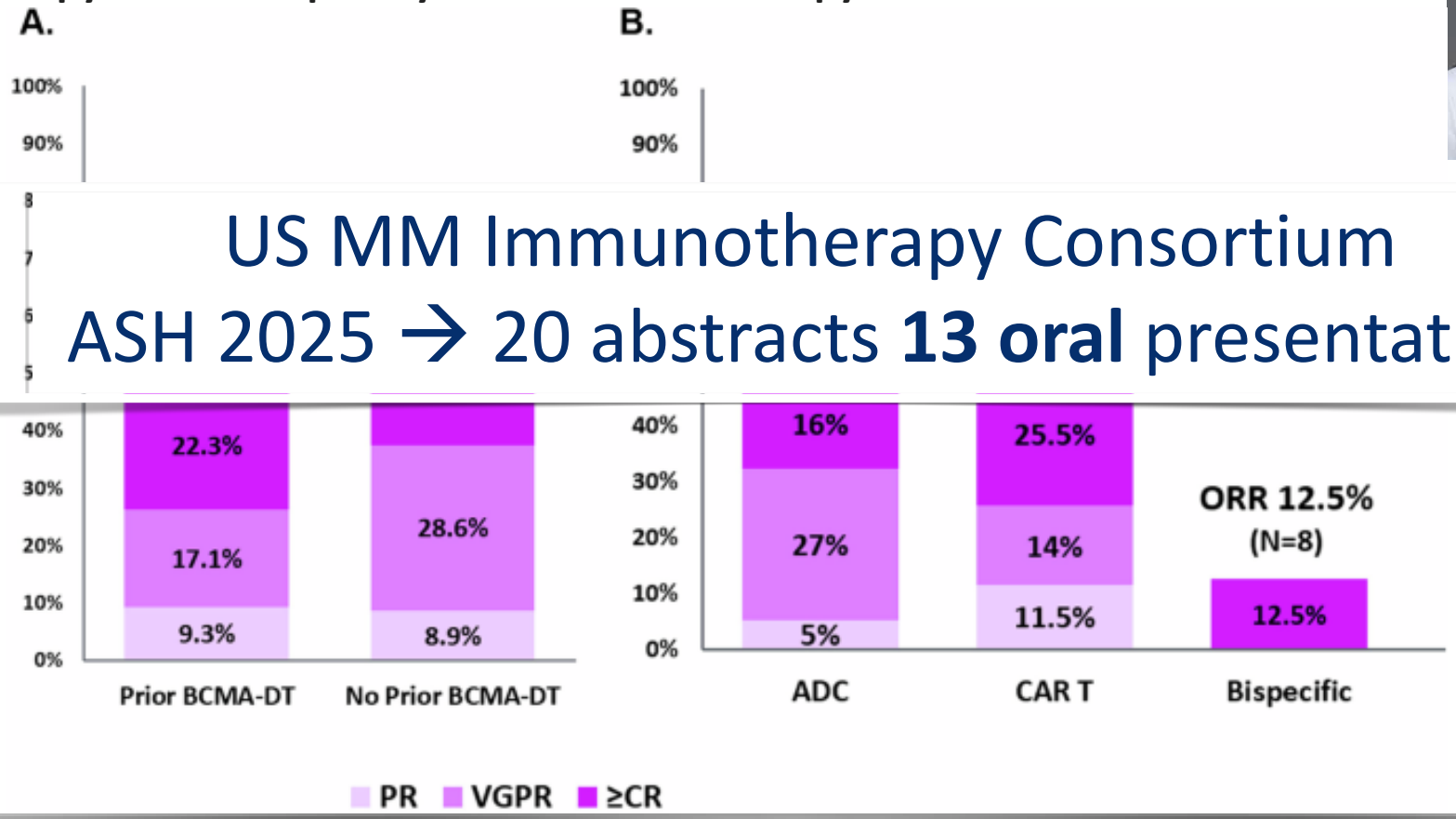
Real world evidence for TCEs

Outcomes of teclistamab in patients with RRMM with prior exposure to BCMA-directed therapy: U.S. Multiple Myeloma Immunotherapy Consortium



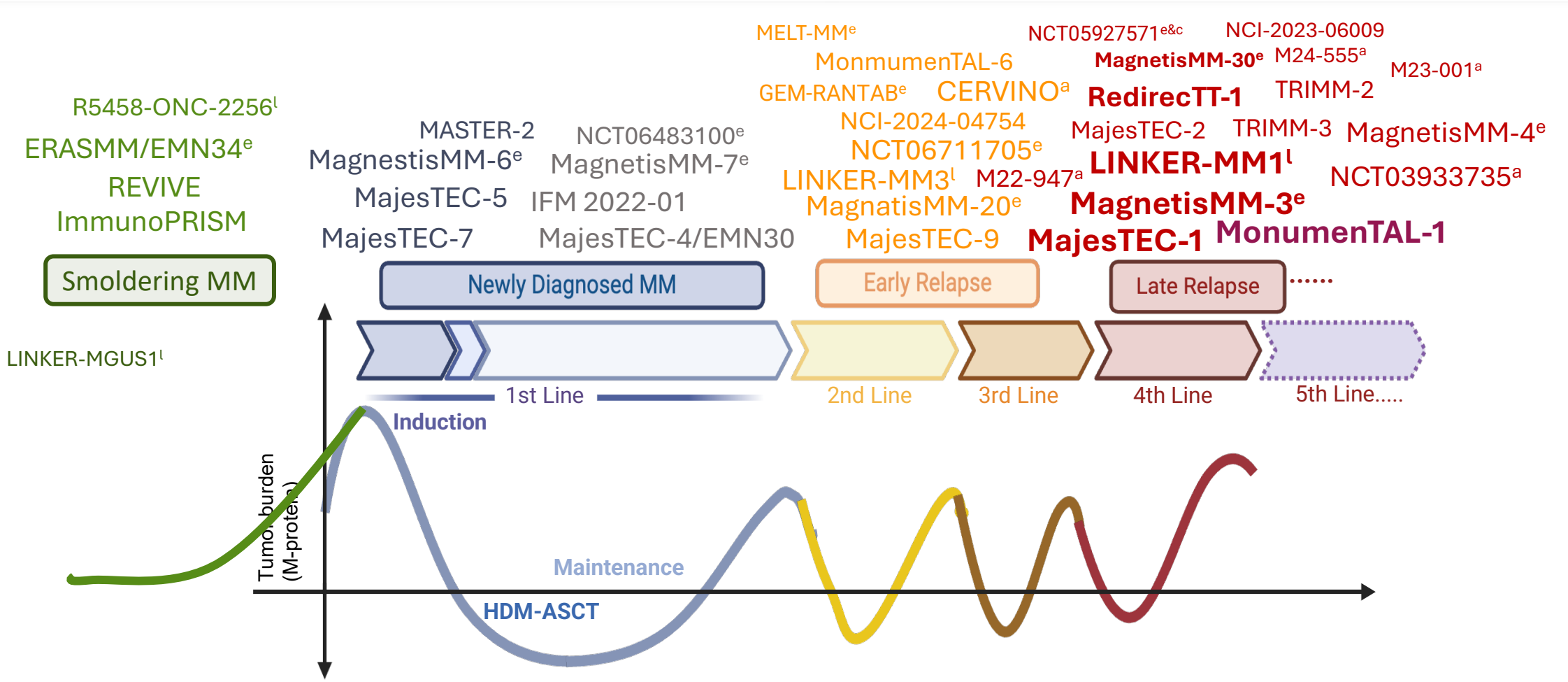
US MM Immunotherapy Consortium

ASH 2025 → 20 abstracts **13 oral** presentation



Dima et al Blood Ca J 2025

When is the best time to give BCMA & GPRC5D BiTEs?

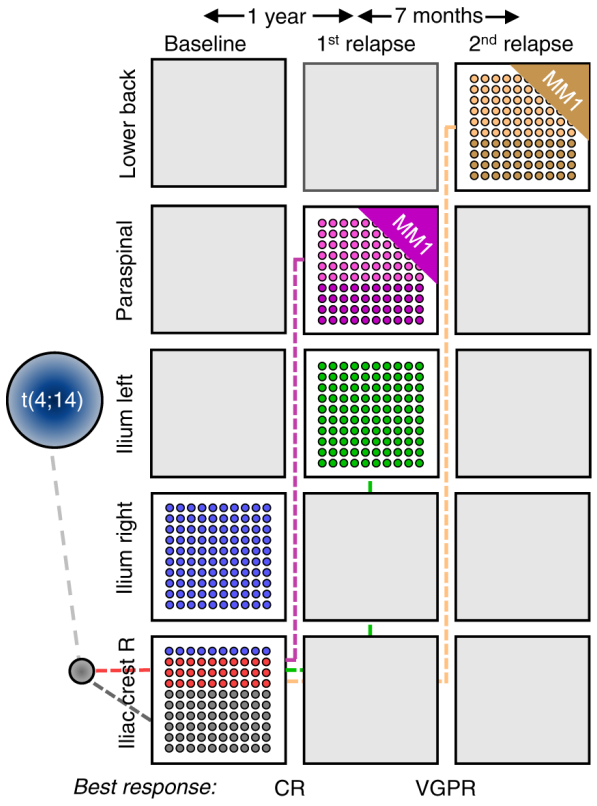


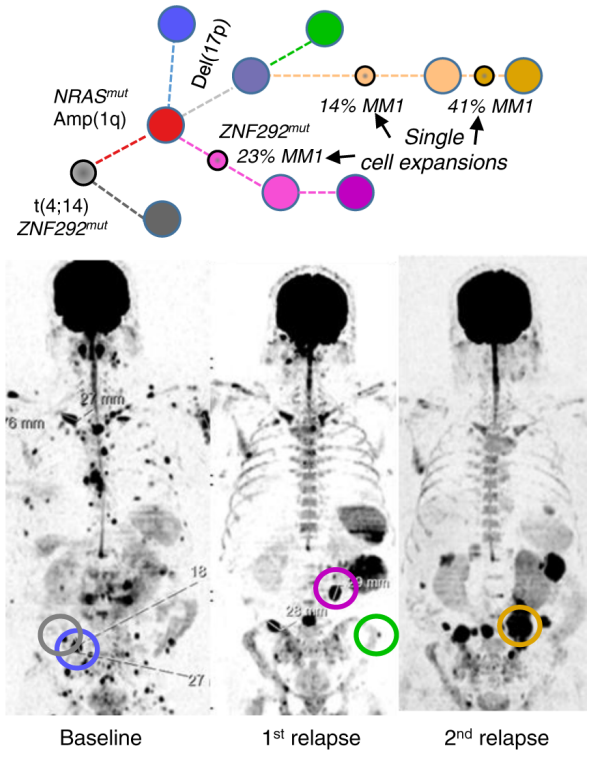
Bumma et al, JCO 2024; Tomasson MH, et al. Blood. 2024;144(Suppl 1): Abstract 1024;
Lesokhin AM et al. *Nat Med*. 2023;29:2259-2267; Moreau et al NEJM 2022; Cohen et al NEJM 2025;
Clinicaltrials.gov

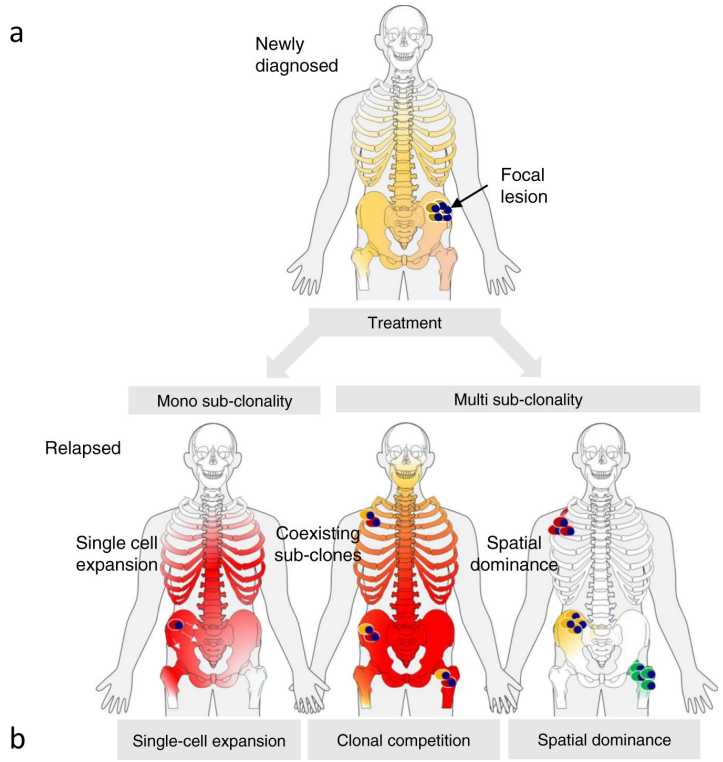
What is next?

We are not done.

Myeloma Is Heterogeneous and Evolves in the Face of Therapy







Rasche et al Nat Comm 2021

Resistance to TCEs

Any anti-BCMA therapy

Any anti-GPRC5D therapy

Non-BCMA/ GPRC5D therapy

Ongoing response (n= 3)

Samur *et al* Nat C

M
Del(16)

arrien *et al* Nat Ca 2023

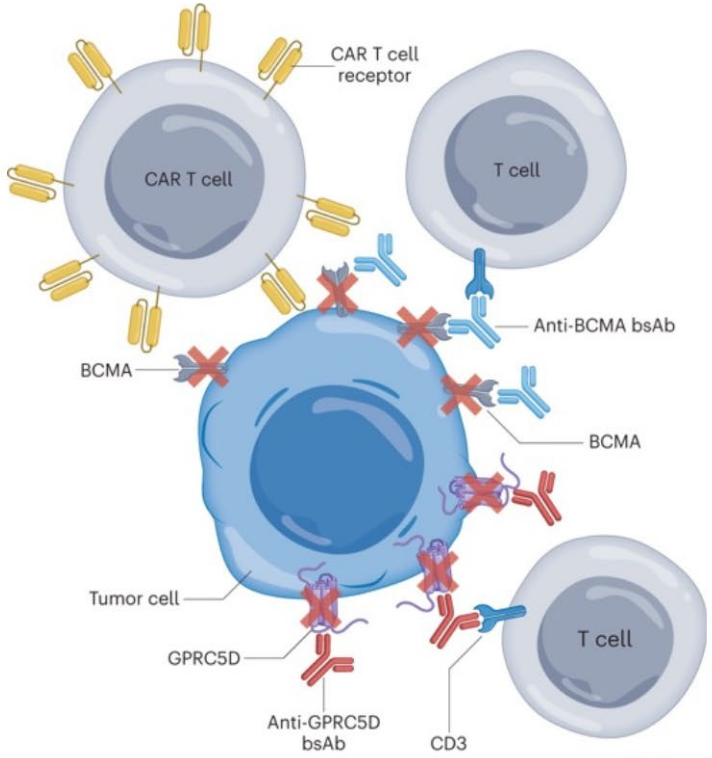
M-01-0288
on1, GPRC5D p.F158fs, G97-
p.W217, p.E27fs, p.S125fs

M-01-0221
- Epigenetic silencing

M-01-0302
- Epigenetic silencing

TNFRSF17 loss
+ p.Ser30del (15%)

Resistance to these TCEs therapies may develop- *we are not done.*

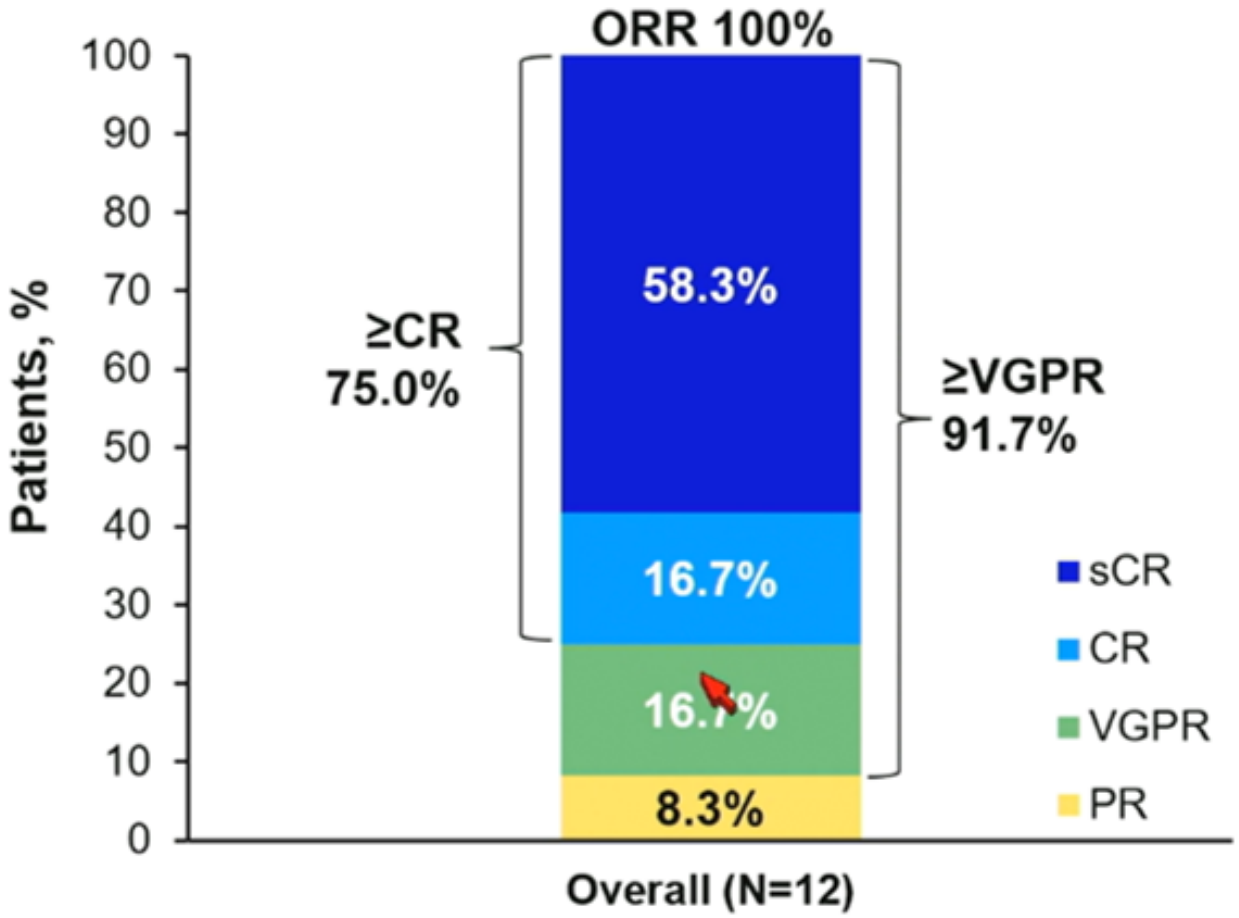


Paiva and San-Miguel Nat Cancer 2023

What about earlier lines & combination therapy?

MAGNITISMM-20

- The confirmed ORR by investigator was 100%
  - ≥CR rate, 75.0% (95% CI, 42.8-94.5)
  - Median time to response was 1.5 months (range, 0.5-3.4)

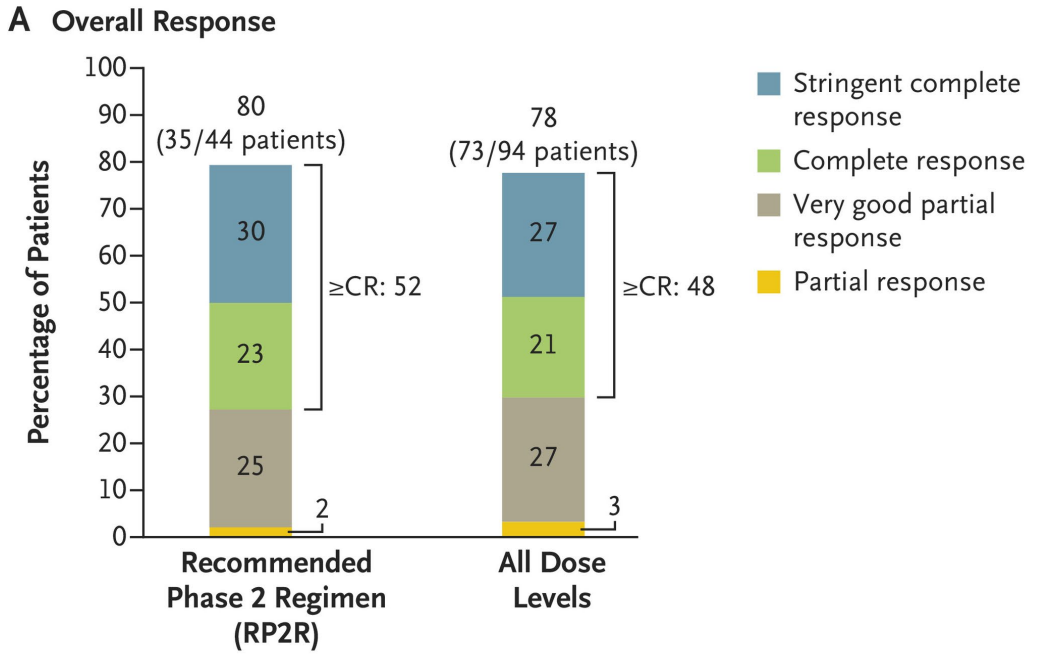


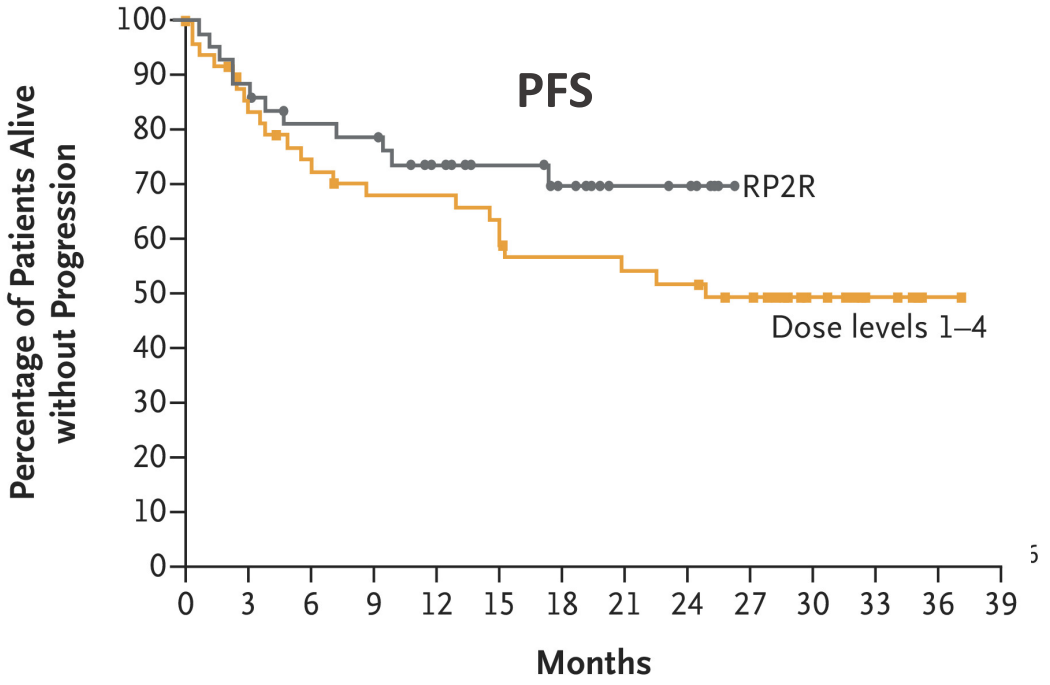
Tomasson MH, et al. Blood. 2024;144(Suppl 1): Abstract 1024.

What about combination TCE therapy?

RedirecTT-1- Phase 1- Talquetamab plus Teclistamab in RRMM

- phase 1b–2 study of talquetamab plus teclistamab in patients with relapsed or refractory multiple myeloma.

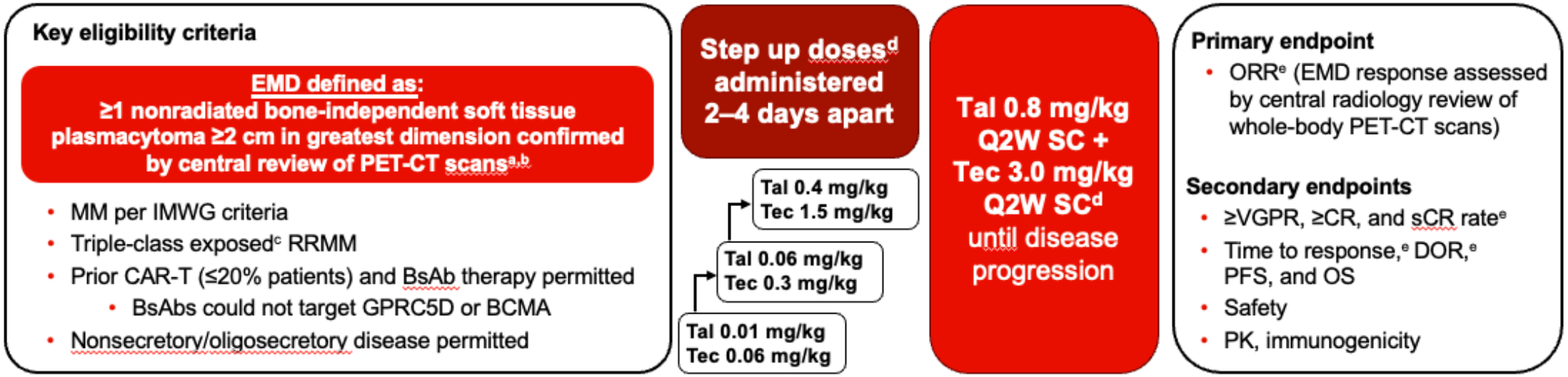




Cohen et al NEJM 2025; https://www.nejm.org/doi/pdf/10.1056/NEJMoa2406536

What about combination therapy in HR subtypes?

RedirecTT-1- Phase 2 of Talq & Tec in RRMM with Extramedullary Disease [EMD].



Option to reduce dosing frequency for both agents to monthly dosing after:

- ≥VGPR and minimum 4 cycles of therapy, *or*
- 6 cycles, per investigator discretion

[a]Patients may have had paraskeletal plasmacytomas in addition to true EMD. [b]Whole body MRI permitted with sponsor approval. [c]Prior PI, IMiD, and anti-CD38 monoclonal antibody. [d]Tal and Tec administered on the same day, 30 (±10) minutes apart, for all step-up and full treatment doses. [e]Response was assessed by independent review committee per IMWG criteria.
CAR, chimeric antigen receptor; DOR, duration of response; IMiD, immunomodulatory drug; IMWG, International Myeloma Working Group; MRI, magnetic resonance imaging; PET-CT, positron emission tomography/computed tomography; PI, proteasome inhibitor; PK, pharmacokinetics; Q2W, every other week; SC, subcutaneous.

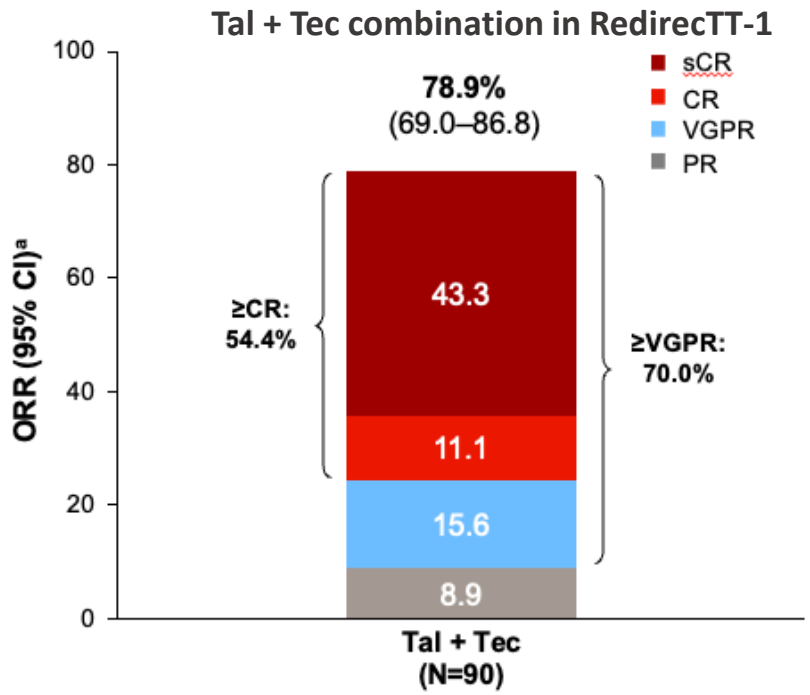
S Kumar et at EHA Congress; June 12–15, 2025; Milan, Italy

What about combination therapy in HR subtypes?

RedirecTT-1- Phase 2 of Talq & Tec in RRMM with Extramedullary Disease [EMD].

Parameter	Tal + Tec (N=90)
Median (range) follow-up, months	12.6 (0.5–19.5)
Median (range) time to first response, months	2.6 (1.0–5.8)
Median (range) time to best response, months	4.7 (1.0–11.9)

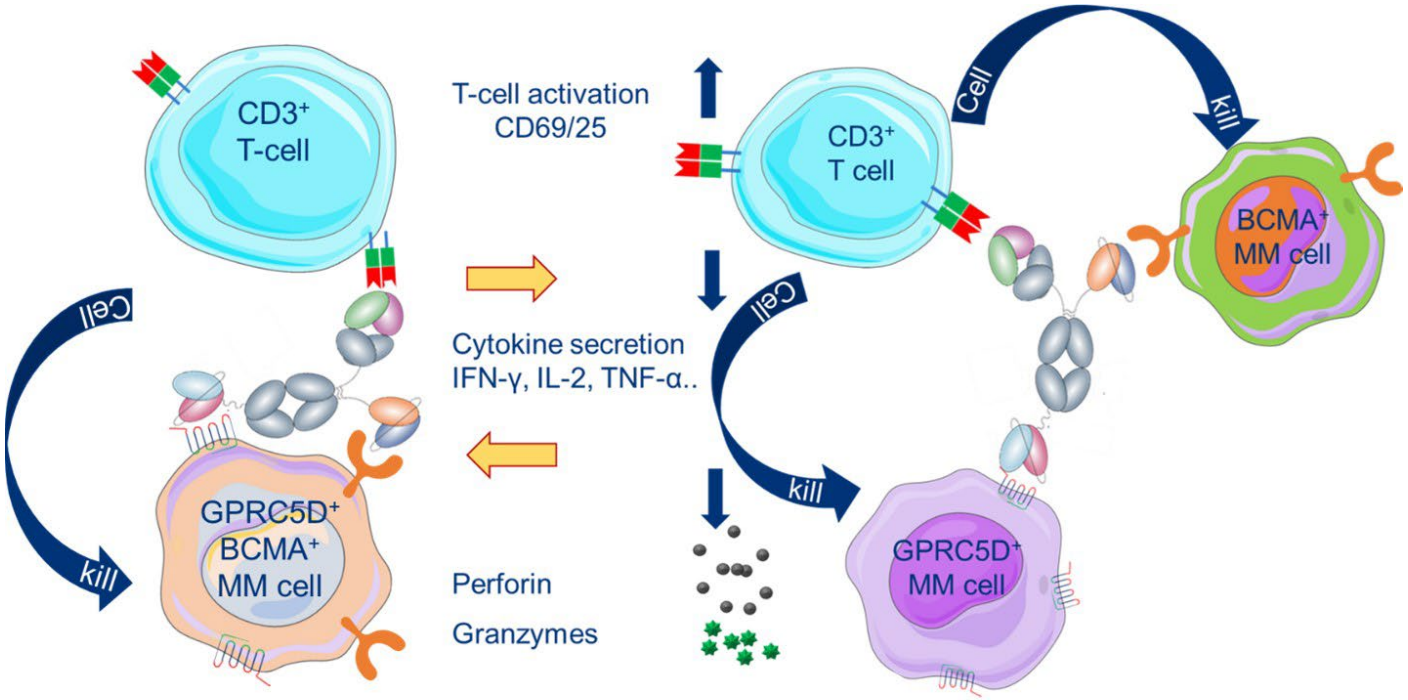
Prior therapy	ORR	95% CI
Anti-BCMA CAR-T, % (n/N)	83.3 (15/18)	58.6–96.4
Anti-FcRH5 BsAb, % (n/N)	75.0 (6/8)	34.9–96.8
Belantamab mafodotin, % (n/N)	90.9 (10/11)	58.7–99.8



S Kumar et at EHA Congress; June 12–15, 2025; Milan, Italy

What about the next generation? Trispecific antibodies

Phase 1 JNJ-79635322, a Novel BCMAxGPRC5DxCD3 T-Cell Redirecting Trispecific Antibody, for the Treatment of Multiple Myeloma (NCT05652335).



Implications

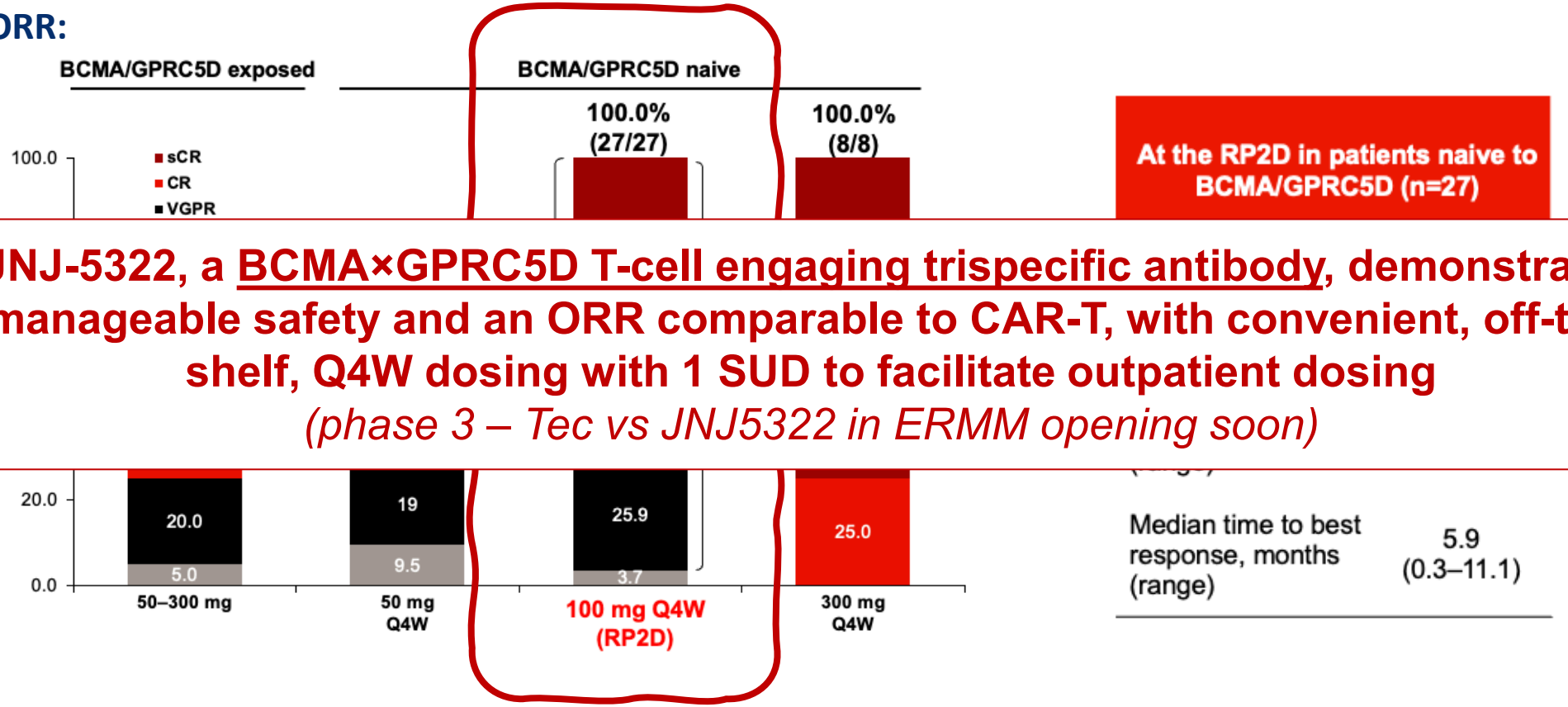
- Enhanced myeloma cell targeting due to **"double lock-down"** effect of binding 2 myeloma antigens
- **More comprehensive targeting of myeloma cells**
  - BCMA-/GPRC5D+,
  - BCMA+/GPRC5D-,
  - Dual BCMA+/GPRC5D+
- Prevention of antigen escape
- Potential to improve GPRC5D-related safety profile
- Manageable CRS profile with only 1 step-up dose needed

Presented by NWCJ van de Donk et al., ASCO Annual Meeting; May 30–June 3, 2025;

What about the next generation? Trispecific antibodies

Phase 1 JNJ-79635322, a Novel BCMAxGPRC5DxCD3 T-Cell Redirecting Trispecific Antibody, for the Treatment of Multiple Myeloma (NCT05652335).

ORR:



At the RP2D in patients naive to BCMA/GPRC5D (n=27)

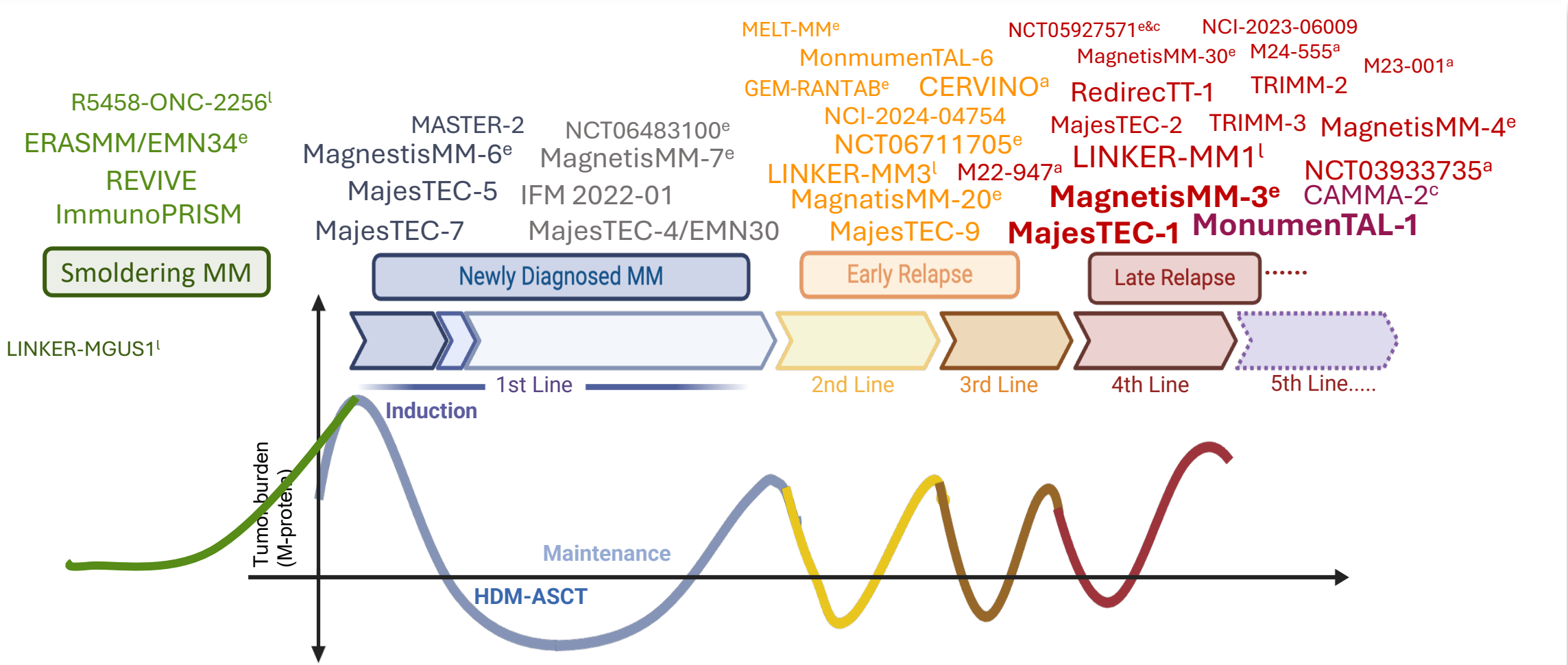
Median time to best response, months (range)	5.9 (0.3–11.1)

JNJ-5322, a BCMA×GPRC5D T-cell engaging trispecific antibody, demonstrated manageable safety and an ORR comparable to CAR-T, with convenient, off-the-shelf, Q4W dosing with 1 SUD to facilitate outpatient dosing

(phase 3 – Tec vs JNJ5322 in ERMM opening soon)

Presented by NWCJ van de Donk et al., ASCO Annual Meeting; May 30–June 3, 2025;

BCMA & GPRC5D BiTEs → we are working to find optimal use



Bumma et al, JCO 2024; Tomasson MH, et al. Blood. 2024;144(Suppl 1): Abstract 1024;
Lesokhin AM et al. *Nat Med*. 2023;29:2259-2267; Moreau et al NEJM 2022; Cohen et al NEJM 2025;
Clinicaltrials.gov

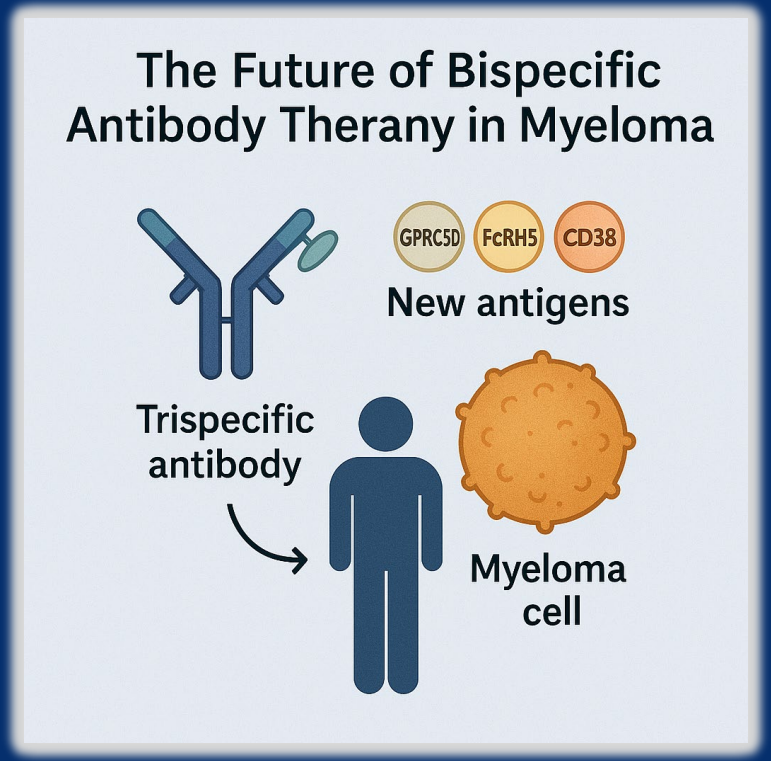
The efficacy of BiTEs is remarkable

We need to continue to better understand the optimal way(s) to give TCEs safely and efficiently in support of our MM patients & community oncologists.
-CRS/ICANS
-Infection risk

Resistance is a reality and we need to continue work to develop new therapies or sequential management strategies

Conclusion

The future of BiTE therapy in myeloma looks bright, with ongoing innovations improving efficacy, safety, and convenience. As new targets and combination strategies emerge, BiTEs could play a central role in the treatment landscape, providing durable responses and expanding treatment options for patients with multiple myeloma.



-ChatGPT

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Our Patients, their families, and care-givers

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Hien Liu M.D.
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John Cleveland Ph.D
Nancy Gillis-Johnson Ph.D.
Lauren Peres Ph.D.
Conor Lynch Ph.D.
Jamie Teer Ph.D.
Sophia Song Ph.D.
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Ethyl Matta
Samantha Seitzler
Buffy Allen
Nina Valetin

Heather Warner
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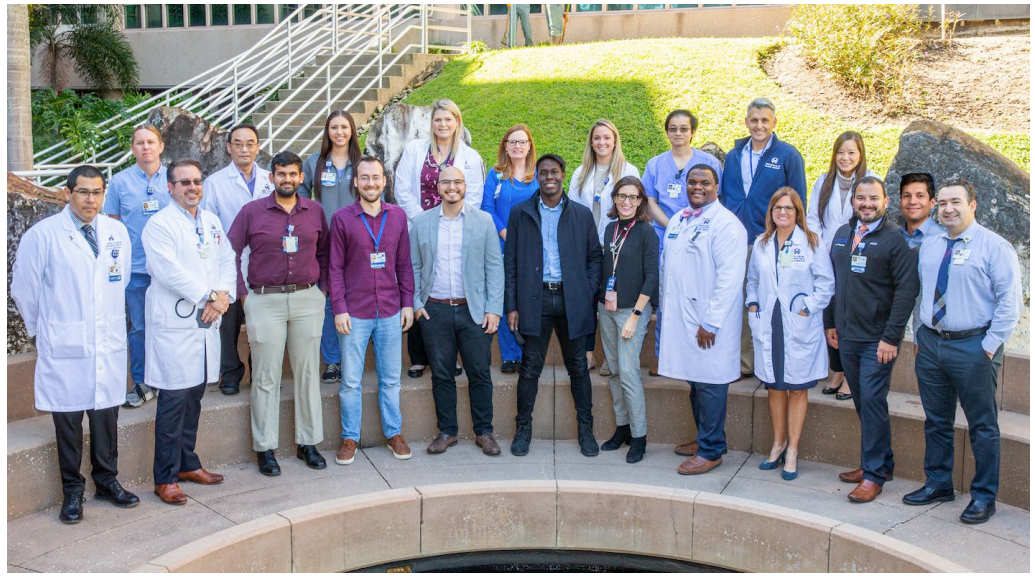

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Questions/Comments -

GPRC5D after BCMA-CART

IMWG Review → T cell directing therapy post BCMA- CART

	Study	N	ORR	CRR	PFS	DOR	Particularities/ unique toxicities
BCMA-targeted CAR T-cells							
Ide-cel	Munshi [3]	28	21%	0%	mPFS 1.0 mo.	n.a.	On trial, second administration of product
Cilta-cel	Martin [76]	3	0%	0%	n.a	n.a	On trial, second administration of product
Ide-cel	Ferreri [65]	5	80%	40%	n.r.	n.r.	RWE, 2 patients had received prior ide-cel
BCMA-targeted TCE							
Teclistamab	Touzeau [78]	15	53%	27%	mPFS 4.4 mo.	n.a	Dedicated MajesTEC-1 cohort
Elranatamab	Nooka [79]	36	53%	20%	mPFS 10 mo.	n.a	Pool from clinical trials
Teclistamab	Riedhammer [80]	21	33%	16%	mPFS 1.8 mo.	n.a	RWE, all prior CAR T-cells were ide-cel
Teclistamab	Dima [73]	43	63%	28%	n/a	n.a	RWE, 38/42 prior CAR T-cells were ide-cel
GPRC5D-targeted CAR T-cells							
MCARH109	Mailankody [20]	8	75%	n.a.	n.a	n.a	Cerebellar toxicity at the highest dose level
BMS-986393	Bal [22]	30	78%(a)	44%(a)	n.a.	n.a	Cerebellar toxicity at the highest dose level
OriCAR-017	Zhang [81]	5	100%	40%%	n.a.	n.a	Skin, nail, taste changes
n.a.	Xia [21]	9	100%	44%	n.a.	n.a	
GPRC5D-targeted TCE							
Talquetamab	Rasche [19]	56	71%	n.a.	n.a.	mDOR 12.3mo.	Subset of MonumenTAL-1 trial
Talquetmab plus daratumumab	Dholaria [82]	11	82%	n.a.	n.a.	n.a.	Subset of TRIMM-2 trial
Talquetamab, daratumumab and pomalidomide	Bhalis [83]	24	83%	71%	74% at 12 mo.	84% at 12 mo.	Subset of TRIMM-2 trial
Forimtamig	Harrison [84]	9	47%(b)	n.a.	n.a.	mDOR 9.0mo. (b)	
Other therapies							
Cevostamab	Kumar [85]	11	73%	27%	n.a	n.a.	Dedicated CAMMA2 trial cohort

Coata et al Leukemia 2025

What about combination therapy?

Other combinations with Tec:

	Tec + Dara[1]			Tec + Dara + Len[2] (MajesTEC-2)		Elra + Dara[3] (MagnetisMM-5)
Treatment	Tec 1.5 mg/kg qw + Dara	Tec 3 mg/kg q2w + Dara	Tec 3 mg/kg qw + Dara	Tec 0.72 mg/kg + Dara + Len	Tec 1.5 mg/kg + Dara + Len	Elra 44 or 76 mg + Dara
N or n	21	39	5	13	19	34
Median prior LOT (range)	5 (1-15)			2 (1-3)	2 (1-3)	4 (2-9)
Triple-class refractory, %	58.5			Not reported		17.6
ORR, %	75	74.1	100	93.5		70.6
PFS	Not reported			Not reported		Not reported
DOR	Not reported			Not reached		Not reached
Median f/u, mo	8.6			8.4		Not reported
Any Gr AE (Gr ≥3) , % **CRS** **Infections** **Neutropenia** **Anemia** **Thrombocytopenia** **ICANS** **Deaths, n** **Hypogamma/IVIG**	67.7 (0) 67.7 (27.7) 49.2 (41.5) 41.5 (27.7) 32.3 (24.6) 2 (0) 4 due to AE Not reported			81.3 (0) 90.6 (37.5) 84.4 (78.1) 21.9 (12.5) 25 (15.6) 0 2 due to AE Not reported		41.7 (0) Not reported; COVID-19: 32.4 (2.9) 47.1 (47.1) 29.4 (26.5) 20.6 (14.7) 0 15 due to AE Not reported

- **1.** Rodriguez-Otero et al. ASCO 2022. Abstract 8032. **2.** Searle et al. ASH 2022. Abstract 160. **3.** Grosicki et al. ASH 2022. Abstract 1921.

What about combination therapy?

Other combinations with Talq

	Tal + Dara TRIMM-2[1]		Tal + Dara + Pom TRIMM-2[2]		Tal + Cet TRIMM-3[3]	Tal + Tec RedirectTT-1[4,5]		Tal + Pom MonumenTAL-2[6,7]	
						RP2R	EMD		
Treatment	Tal 0.4 mg/kg qw + Dara	Tal 0.8 mg/kg q2w + Dara	Tal 0.4 mg/kg qw + Dara + Pom	Tal 0.8 mg/kg q2w + Dara + Pom	**Dose escalation**: Tal 0.4 or 0.8 mg/kg SC q2w + Cet 80, 160 or 240 mg IV q2w **Dose expansion**: Tal 0.8 mg/kg SC q2w + Cet 240 IV q2w	Tec 3.0 mg/kg + Tal 0.8 mg/kg q2w	Tec 3.0 mg/kg + Tal 0.8 mg/kg q2w	Tal 0.4 mg/kg + Pom	Tal 0.8 mg/kg + Pom
N or n	14	51	18	59	44	44	90	16	19
Median prior LOT (range)	5.5 (4-16)	5 (2-14)	6 (3-11)	6 (1-17)	5 (2-11)	4 (2-10)	4 (1-10)	3 (2-12)	3 (2-5)
Triple-class refractory, %	57.1 (35.7 BsAb refractory)	60.8 (19.6 BsAb refractory)	83.3 (38.9 BsAb refractory)	76.3 (37.3 BsAb refractory)	100 (50.0 BsAb refractory)	84.1	100	31.3	21.1
ORR, %	71.4	84.0	100	76.3	70.5	79.5	78.9	88.6	
mPFS, mo	Not reached	19.4	15.4	20.3	6-mo: 61.5%	12-mo: 73.7	15.4	Not reached	
mDOR, mo	Not reached	20.3	13.8	26.4	16.8	12-mo: 91.0	13.8	Not reached	
Median f/u, mo	16.8	15.0	15.8	17.5	11.5	18.2	Not reported	16.8	
Any grade AE (gr ≥3),%									
CRS	71.4 (0)	80.4 (0)	55.6 (0)	79.7 (0)	61.4 (0)	75.0 (0)	77.8 (0)	74.3 (2.9)	
Infections	57.1 (21.4)	72.5 (25.5)	72.2 (16.7)	78.0 (27.3)	81.8 (29.5)	86.4 (47.7)	78.9 (31.1)	80.0 (22.9)	
ICANS	4.6 total (0)	4.6 total (0)	0	5 (not reported)	2 total (0)	3.2 all doses (N=94)	12.2 total	8.6 (0)	
Hypogammaglobulinemia /IVIG, %	33.8% IVIG total	33.8% IVIG total	53.2% IVIG total	53.2% IVIG total	34.1% IVIG total	56.6 all doses (N=94)	86.7% IVIG total	Not reported	
Oral/taste	85.7 (0)	90.2 (3.9)	100 (0)	84.7 (6.8)	81.8 (0)	50.0 (not reported)	78.9 (not reported)	85.7 (0)	
Skin	71.4 (14.3)	84.3 (7.8)	88.9 (0)[a]	67.8 (0)[a]	Non-rash: 70.5 (0) Rash: 31.8 (2.3)	56.8 (0)[a]	68.9 (0)[a]	74.3 (5.7)	
Nail	57.1 (0)	68.6 (2.0)	Nail: 83.3 (0)	55.9 (0)	75.0 (0)	47.7 (0)	55.6 (0	68.6 (0)	

[a] Reported as non-rash AE.

1. Dholaria BR, et al. ASCO 2023. Abstract P911. **2.** Bahlis N, et al. IMS 2024. Abstract OA-01. **3.** Perrot A, et al. EHA 2025. Abstract S200. **4.** Cohen YC, et al. IMS 2024. Abstract OA-03. **5.** Kumar S, et al. EHA 2025. Abstract LB4001. **6.** Matous, et al. ASH 2023. Abstract 1014. **7.** Searle E, et al. EHA 2024. Abstract P911.

D Rate of ICANS by Drug in Present Study and Trial Comparator