When to Use Bispecifics and CAR-Ts in Myeloma?

DDHO 2024

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Disclosures

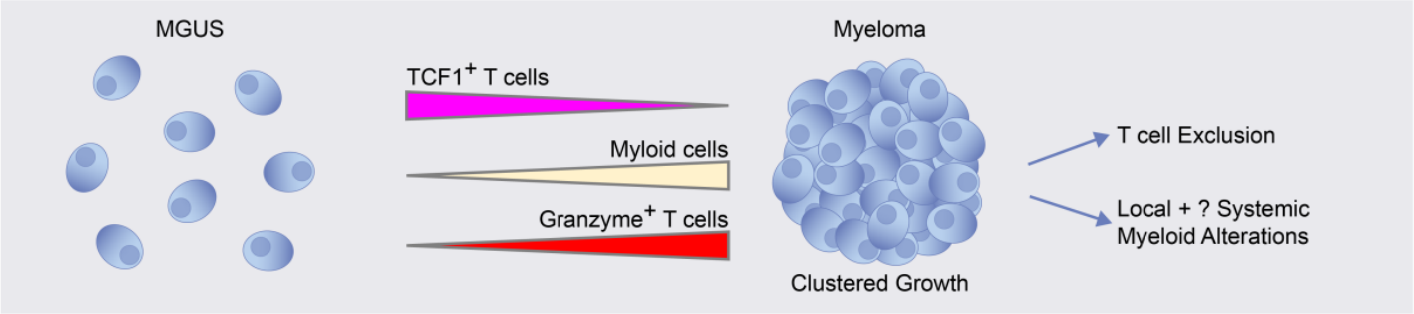
Advisory board: Janssen, Sanofi, Kite, Lava Therapeutics

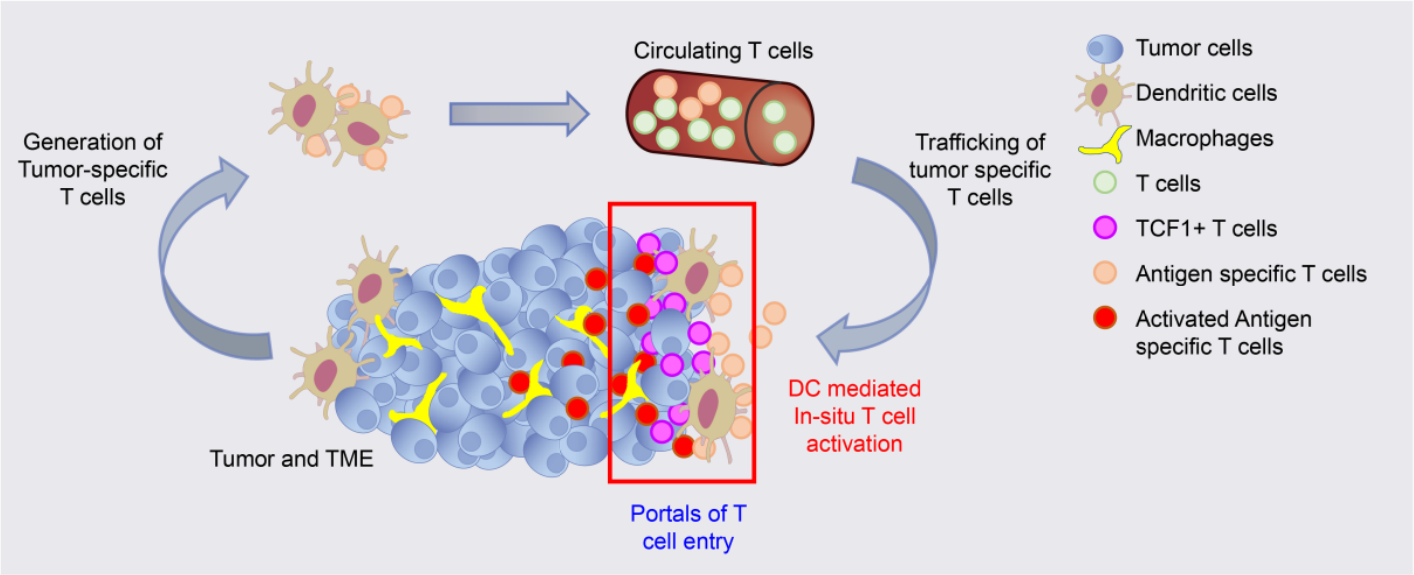
Outline

- A bit of biology
- Key data for T cell redirection in MM
- Clinical considerations for choices*

* My opinions

Key requirements for Regional Immunity in MM





MM but not MGUS tumors grow as clusters that exclude T cells…both in patients and model systems.

<u>Determinants of T cell entry:</u>

Target recognition / specificity

Costimulation

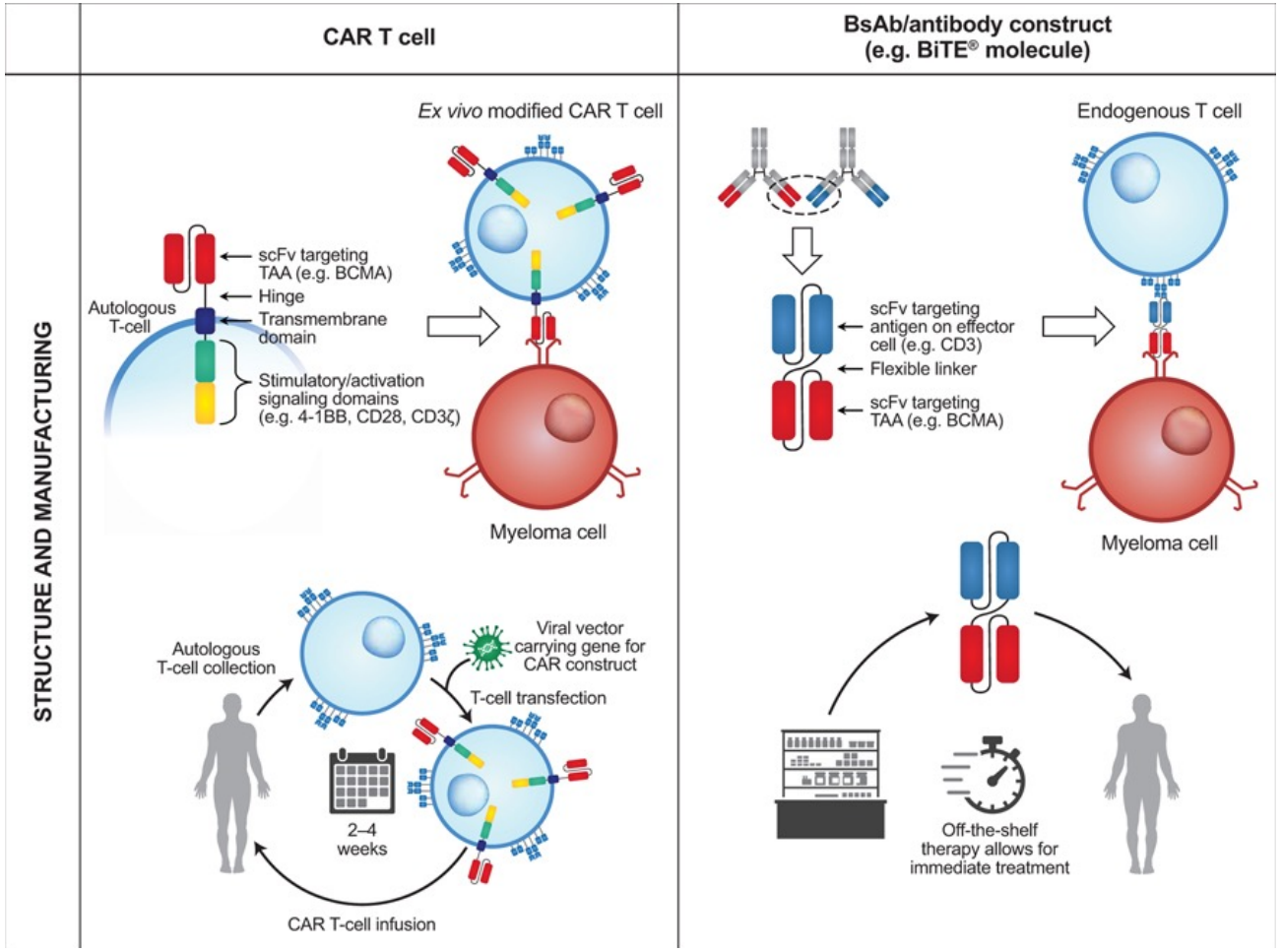
Immune synapse

In situ stimulation / Ag presentation

In-situ regulation of T cell entry provides mechanistic basis for CART and bispecifics in MM.

Robinson et al, J Clin Invest 2023

CAR-Ts and Bispecifics:
Effective but Distinct Approaches for T-cell Redirection



Cohen….Dhodapkar. Clin Cancer Res 2021

Some Biologic Differences In T Cell Redirection Approaches in MM

	Bispecifics	CAR-T cells
Number of Redirected/Engaged T cells	+++	++
Costimulation	+	++
Need for Ongoing Rx for Sustained Redirection	Yes	No
Engagement of endogenous immunity	Yes	Yes
Targets	BCMA, GPRC5D	BCMA

Dhodapkar et al. Blood Cancer Discovery 2022, and unpublished

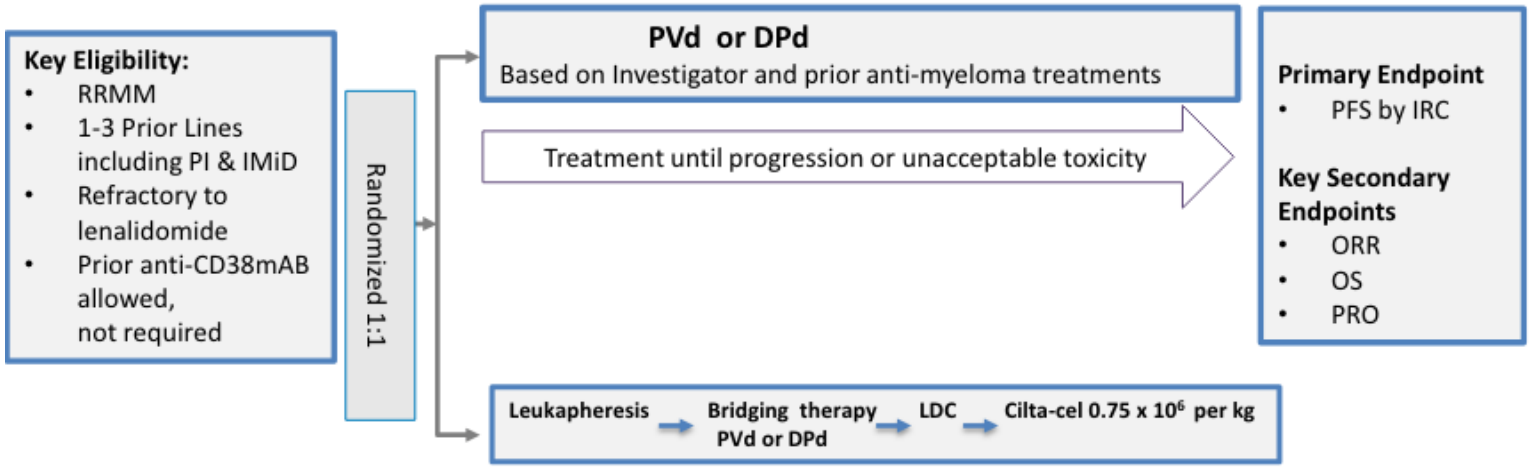
Current Options for T Cell Redirection in MM

BCMA CAR-Ts	Ciltacel	Idecel
Current Label	≥ 1 prior line	≥ 2 prior lines
Prior Rx	PI and IMID	PI, IMID and anti-CD38
Pivotal data	Ph 3 Cartitude-4	Ph 3 KarMMA-3

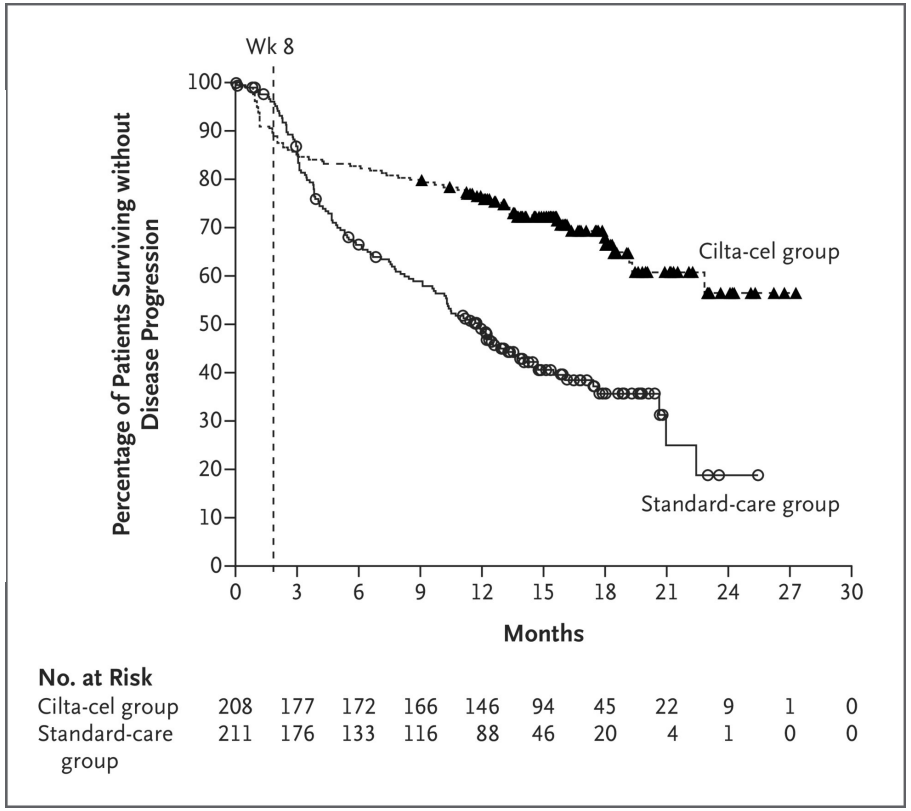
Bispecifics	Teclistamab	Elranatamab	Talquetamab
Current Label	≥ 4 prior lines	≥4 prior lines	≥4 prior lines
Prior Rx	PI, IMID,anti-CD38	PI, IMID, anti-CD38	PI, IMID, anti-CD38
Target	BCMA	BCMA	GPRC5D
Pivotal data	Ph 2 MajesTec	Ph 2 MagnetisMM	Ph 2 MonumenTal

Cilta-Cel v Standard Care in Lenalidomide-Refractory Multiple Myeloma: Cartitude-4

Study Schema



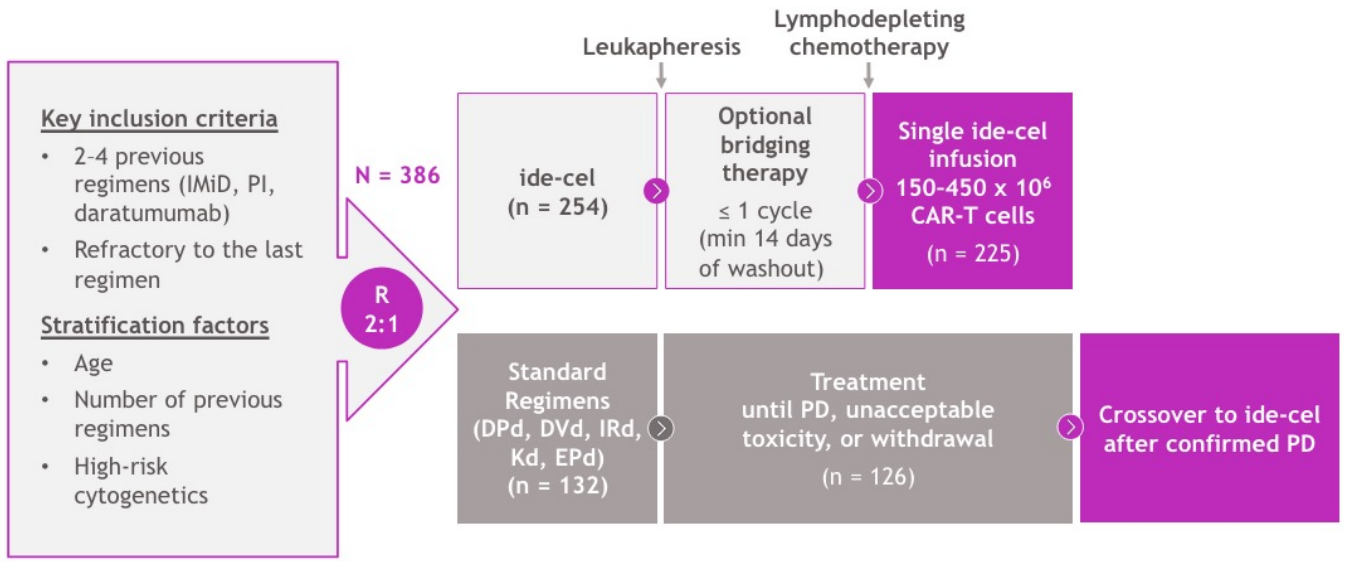
Progression-free Survival (Intention-to-Treat Population).



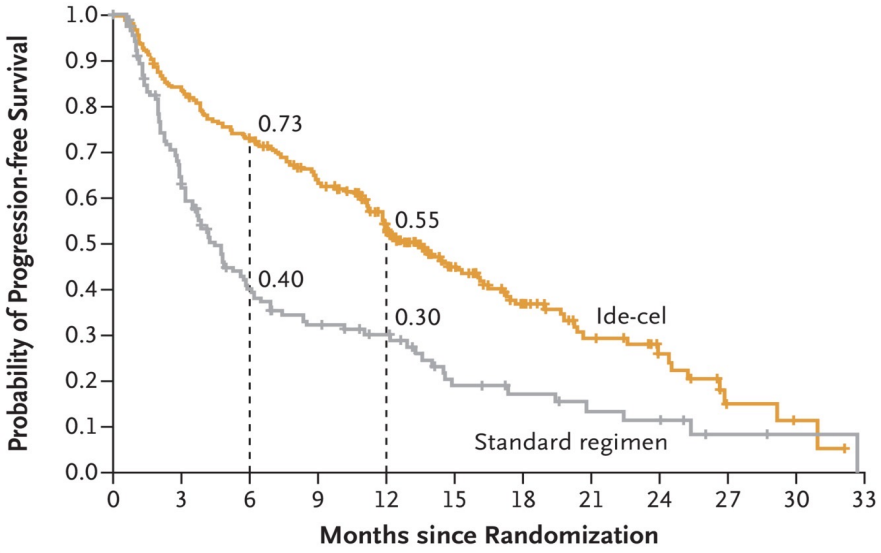
San-Miguel J et al. N Engl J Med 2023;389:335-347

Ide-Cel v Standard Regimens in Relapsed Multiple Myeloma: KarMMa-3

Study Schema



Progression-free Survival



No. at Risk

Ide-cel	254	206	178	149	110	62	40	22	14	4	2	0
Standard regimen	132	75	42	32	25	13	10	7	6	2	1	0

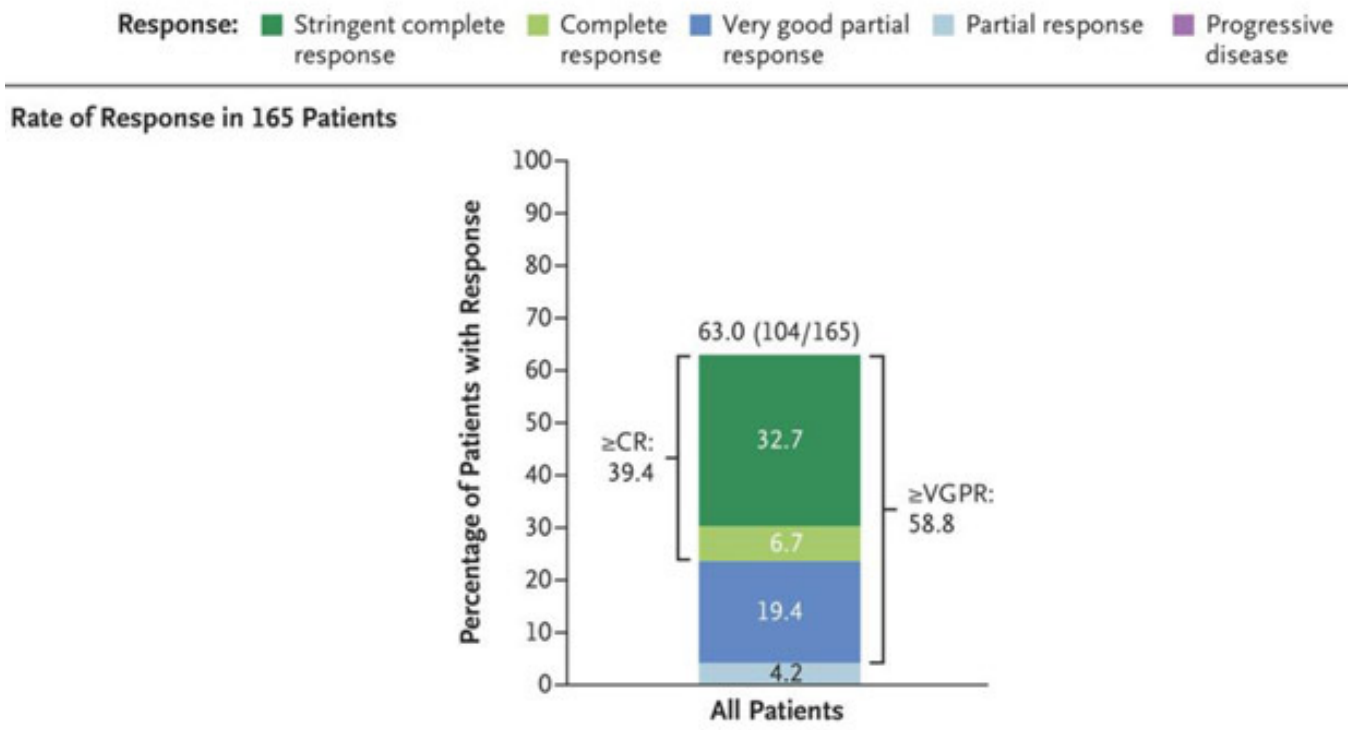
Rodriguez-Otero P et al. N Engl J Med 2023;388:1002-1014

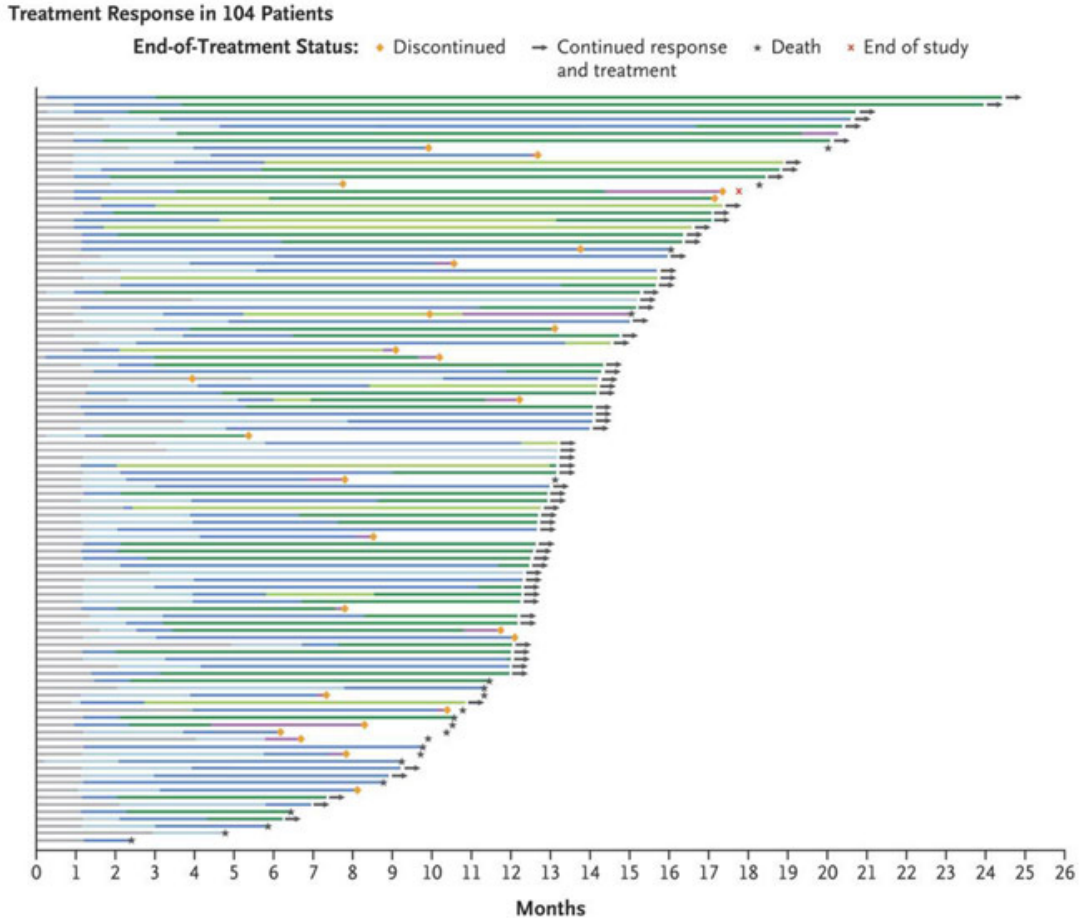
Some Differences Between Karmma3 and Cartitude4

KarMMa-3[1]		CARTITUDE-4[2]
2-4	Prior Lines of Therapy	1-3
Triple-class Exposed (incl CD38)	Prior Treatment Exposure	PI, IMiD exposed, LEN refractory
Not required; only 1 cycle allowed	Bridging Requirement	Required per protocol; 80% received 2 or 3 Cycles
PFS in ITT, including patients who were apheresed but not infused with Ide-cel	Primary Endpoint Analysis Methodology	PFS HR excludes any events within the first 8 weeks of randomization
Allowed; 56% in SR arm went on to receive Ide-cel	cross-over	Not permitted per protocol

1. Rodriguez-Otero P et al. NEJM 2023;389 (11): 1002–1014. 2. San-Miguel J et al. NEJM 2023;389(4): 335–347

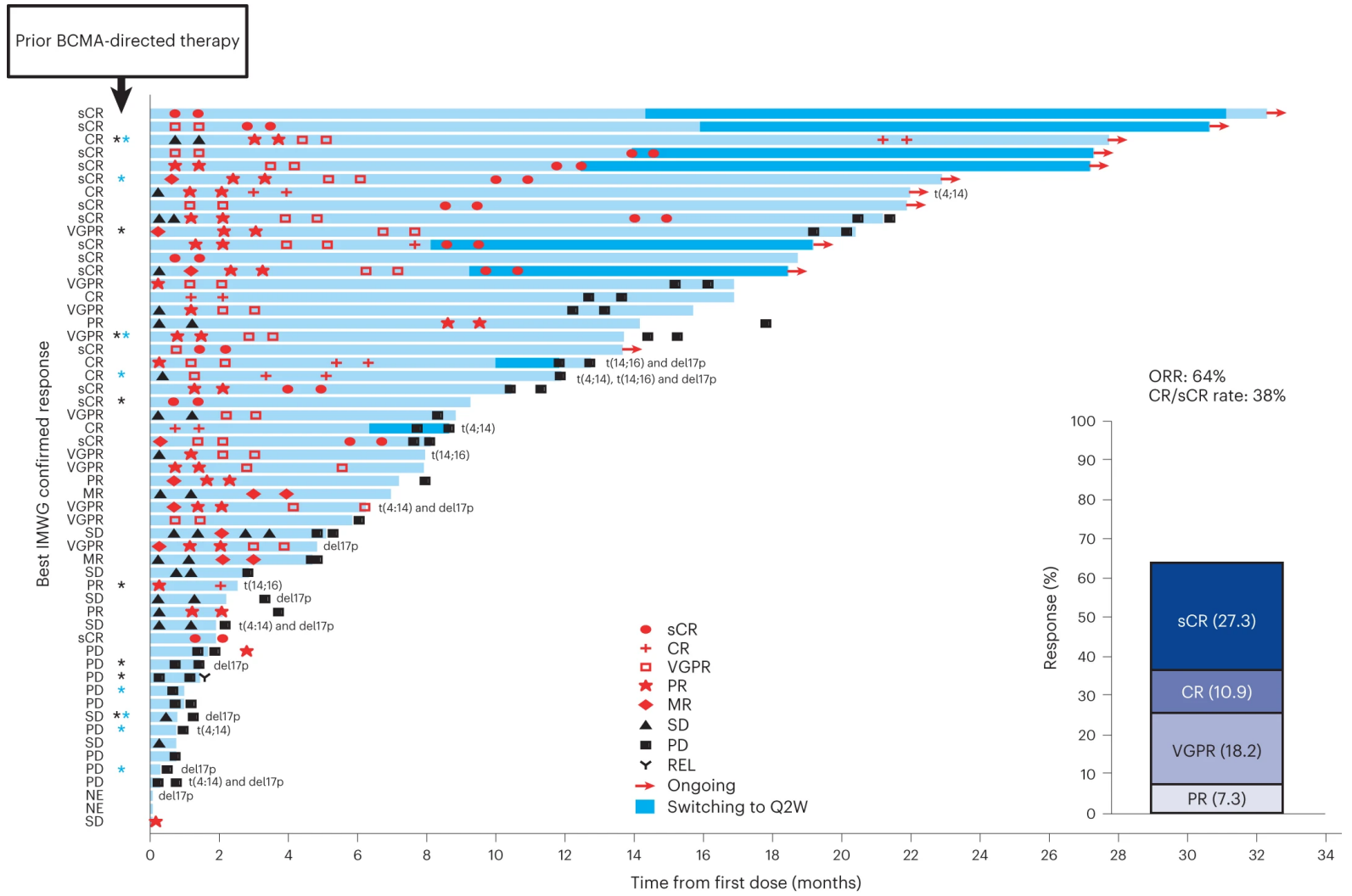
Teclistamab in Relapsed Multiple Myeloma (MajesTEC)





Moreau et al NEJM 2022

Elranatamab in Relapsed Myeloma: MagnetisMM-1 Trial



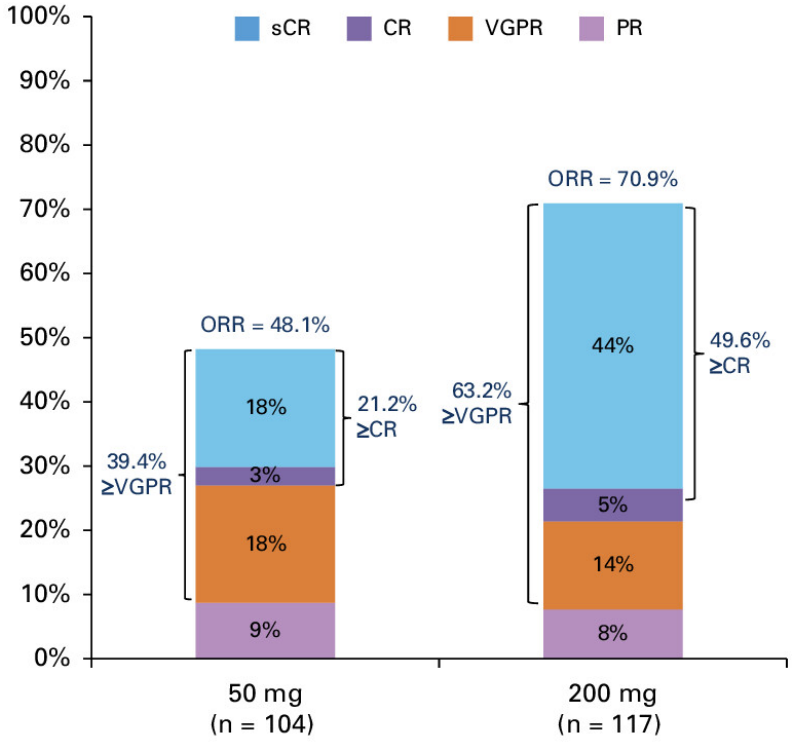
Bahlis et al, Nat Med 2023

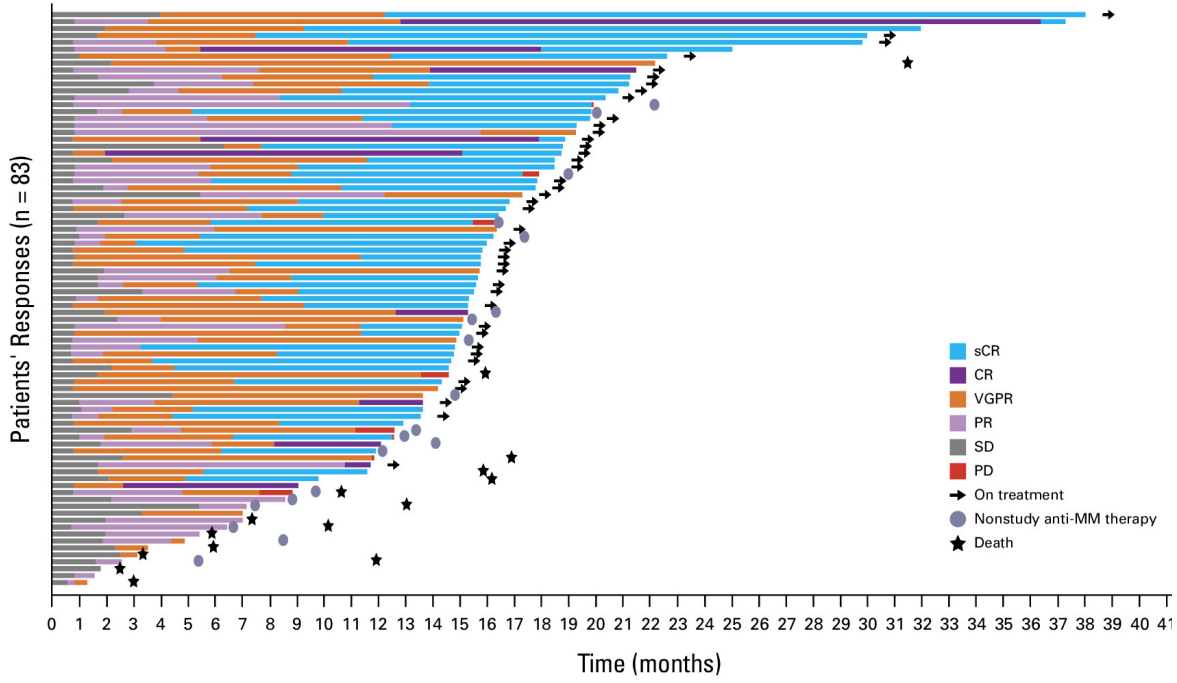
FDA Approved BCMA Bispecifics for MM

	Teclistamab	**Elranantamab**
Mechanism of action	BCMA-directed CD3 T-cell engager	BCMA-directed CD3 T-cell engager
FDA approval	R/R MM after at least 4 LOT including a PI, IMID, and an anti-CD38 mAb	R/R MM after at least 4 LOT including a PI, IMID, and an anti-CD38 mAb
REMS requirement	Yes	Yes
Boxed warning	CRS, ICANS	CRS, ICANS
Recommended admission duration during schedule	For 48 hours after administration of all step-up doses	For 48 hours after administration of first step-up dose and 24 hours after second
Dosing schedule	Day 1: 0.06 mg/kg Day 4: 0.3 mg/kg Day 7: 1.5 mg/kg Weekly dosing starting one week after first treatment dose; may adjust to every other week dosing for patients who achieve and maintain CR or better for at least 6 months	Day 1: 12 mg Day 4: 32 mg Day 8: 76 mg Weekly dosing starting one week after first treatment dose until week 24, then every other week starting at week 25
Treatment duration	Until disease progression or unacceptable toxicity	Until disease progression or unacceptable toxicity

Moore et al, Exp Rev Hem 17: (2024)

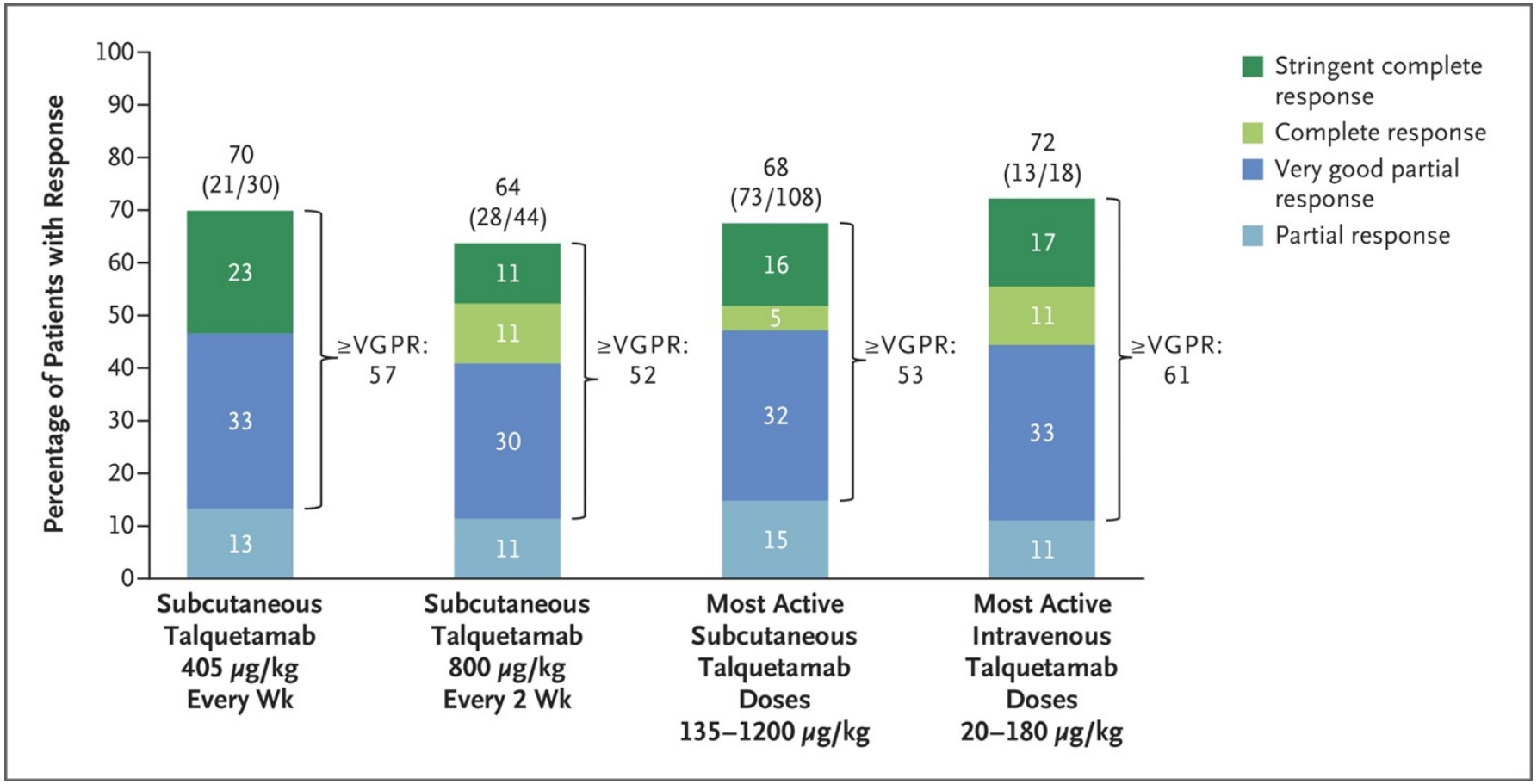
Linvoseltamab in Relapsed Myeloma





Bumma et al, JCO 2024

Talquetamab: GPRC5D-Targeting Bispecific in Relapsed MM

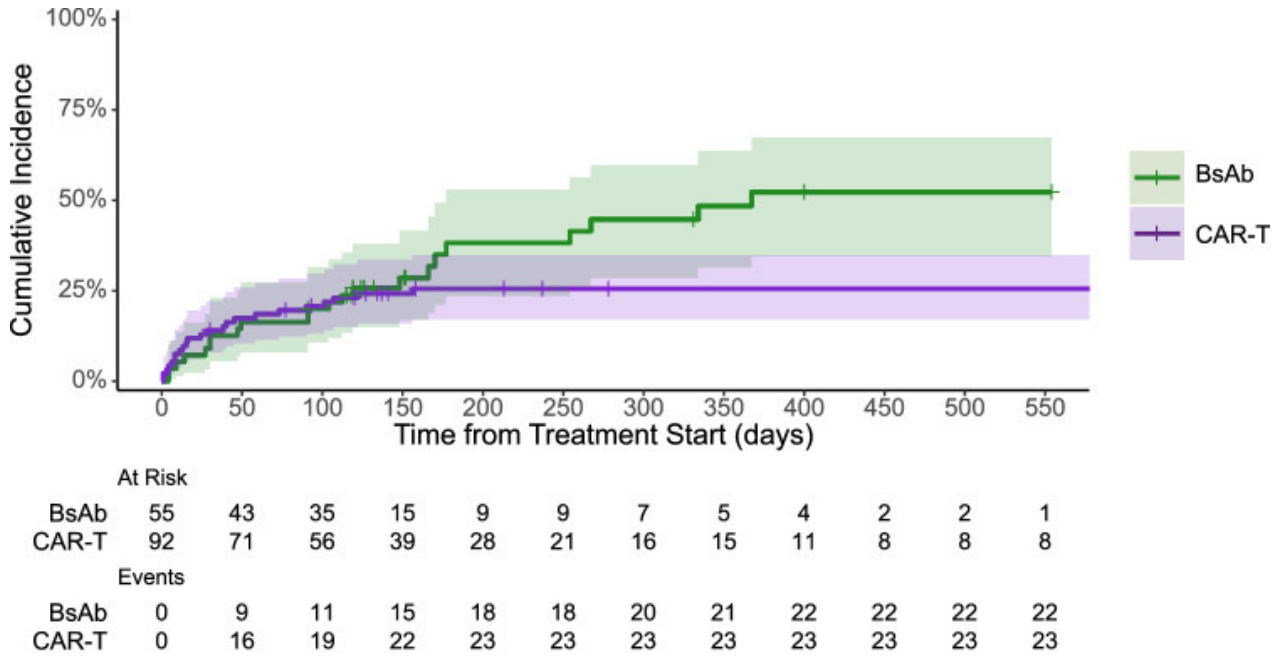


Chari et al. NEJM 2022

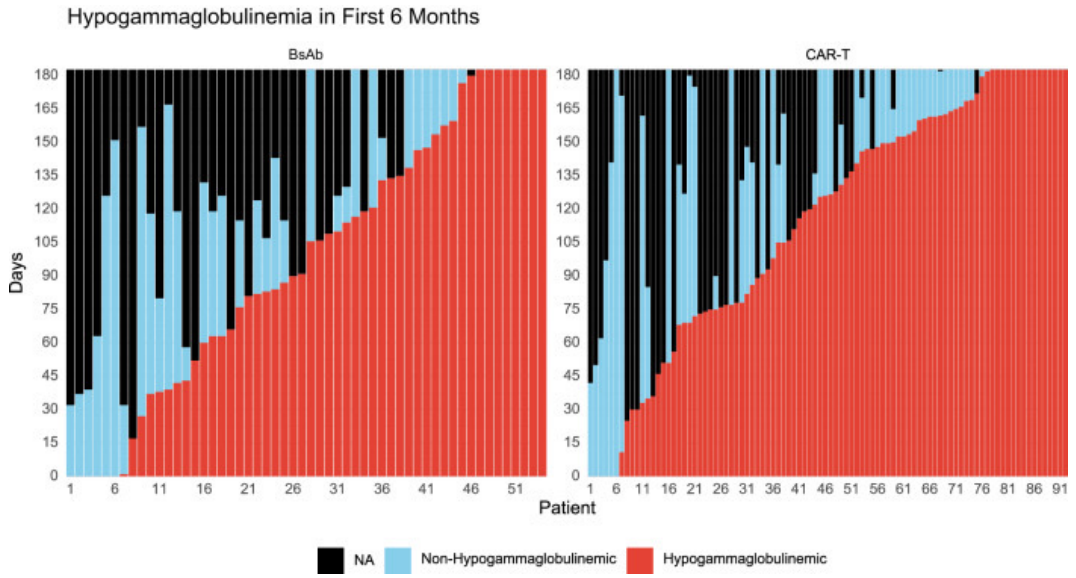
	CAR T-Cell Therapies		Bispecific Therapies	
Feature	Commercial	Investigational	Commercial	Investigational
FDA-approved indication	After four or more previous lines, including an IMiD, PI, and anti-CD38 mAb (ide-cel and cilta-cel)	NA	After four or more previous lines, including an IMiD, PI, and anti-CD38 mAb (teclistamab)	NA
Hospitalization	Yes	Yes	Yes (for step-up dosing during cycle 1)	Generally, yes for initial doses
Treatment frequency	Once	Generally, once	Weekly	Every 1-3 weeks
Lymphodepletion	Yes	Yes	No	No
Manufacturing time	4-6 weeks	None (allogeneic)-approximately 4 weeks	None (off the shelf)	None (off the shelf)
Manufacturing failure	Approximately 10%	Variable	NA	NA
Wait list for commercial manufacturing slots	Yes	NA	NA	NA
Overall response rate, %	73-98	>70	63	Approximately 50-70
Median progression-free survival	8.8-34.9 months	NR	11.3 months	NR
Cytokine release syndrome (grade all/≥3), %	Approximately 85-95/5	Approximately 40-100/<1-7	72/1	Approximately 25-85/0-2
ICANS and/or neurotoxicity (grade all/≥3), %	Approximately 20/3-12	Approximately 2-30/0-3	15/1	Approximately 2-15/0-1
Infections (grade all/≥3), %	Approximately 60-70/~20	Approximately 20-55/12-30 and NR	76/45	Approximately 35-60/ approximately 7-30
Hypogammaglobulinemia (all grade), %	21 and NR	7-24 and often NR	15	14-77 and often NR
Data on minority/underserved populations	Minimal	Minimal	Minimal	Minimal
Data on frail patients	Minimal	Minimal	Minimal	Minimal
Features under development		Novel targets Faster manufacturing Dual-targeting Allogeneic products		Trispecific Novel targets

Holstein et al. JCO 2023

Infectious Complications Following BCMA-directed Therapies

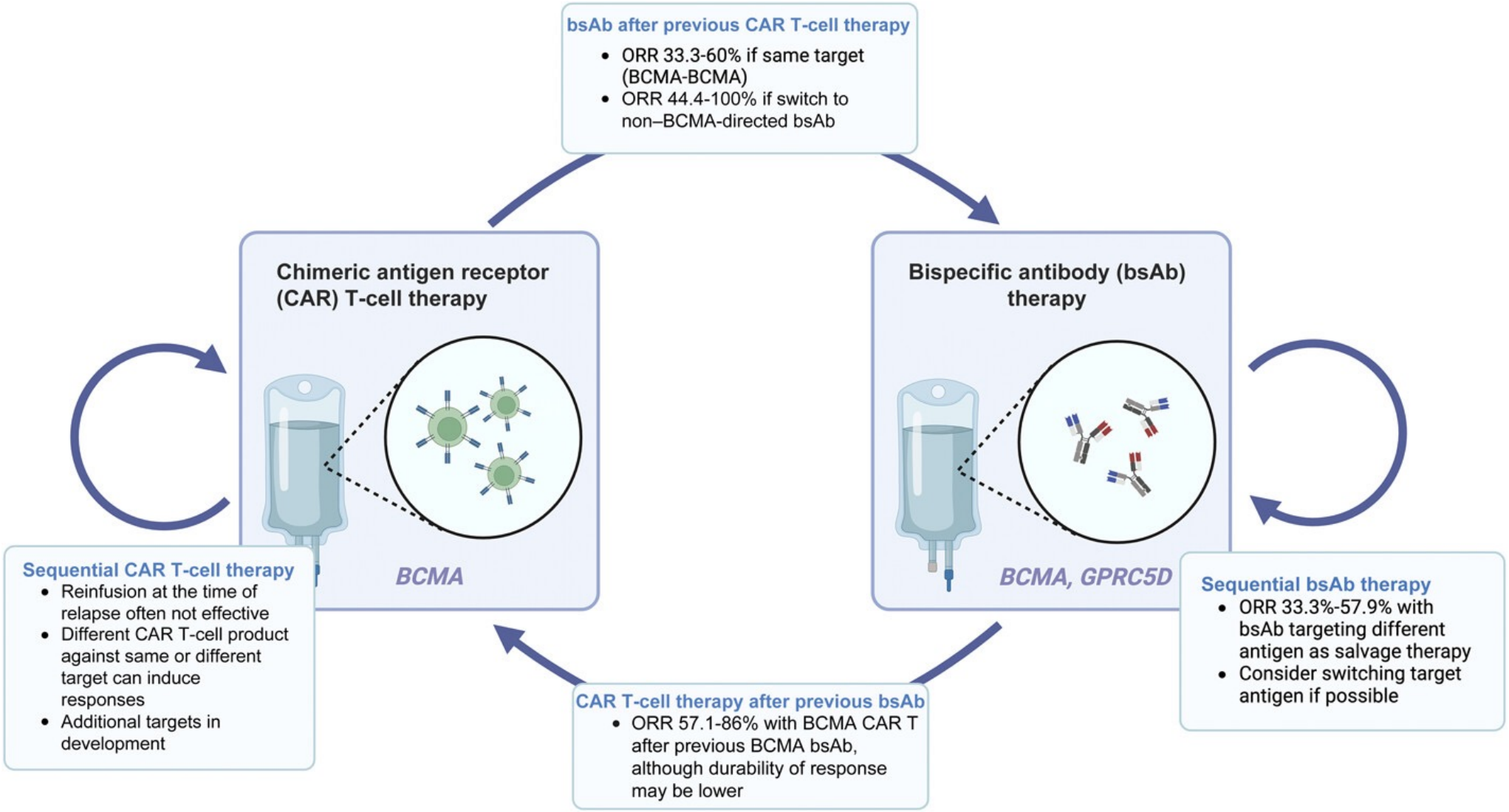


At Risk												
BsAb	55	43	35	15	9	9	7	5	4	2	2	1
CAR-T	92	71	56	39	28	21	16	15	11	8	8	8
Events												
BsAb	0	9	11	15	18	18	20	21	22	22	22	22
CAR-T	0	16	19	22	23	23	23	23	23	23	23	23



Nath et al. Blood Cancer J 2024 14:88

Sequencing T cell Redirection in MM



Mohan et al, ASCO Educational Program 2024

Some Key Considerations For Choosing T Cell Redirection Strategy

General:

Frailty, comorbidities, distance to center, caregiver access, patient preference

Disease:

Prior LOT (linked to current FDA approval), prior target-directed Rx (e.g. bcma), prior bispecific, tempo of dz, availability of effective bridge Rx, cytogenetic risk, EMD, antigen-loss,

Agent:

Target expression pattern/biology and related toxicity considerations

(e.g. dysgeusia, weight loss with GPRC5D; ? Less infections with GPRC5D

Sequencing considerations

Host:

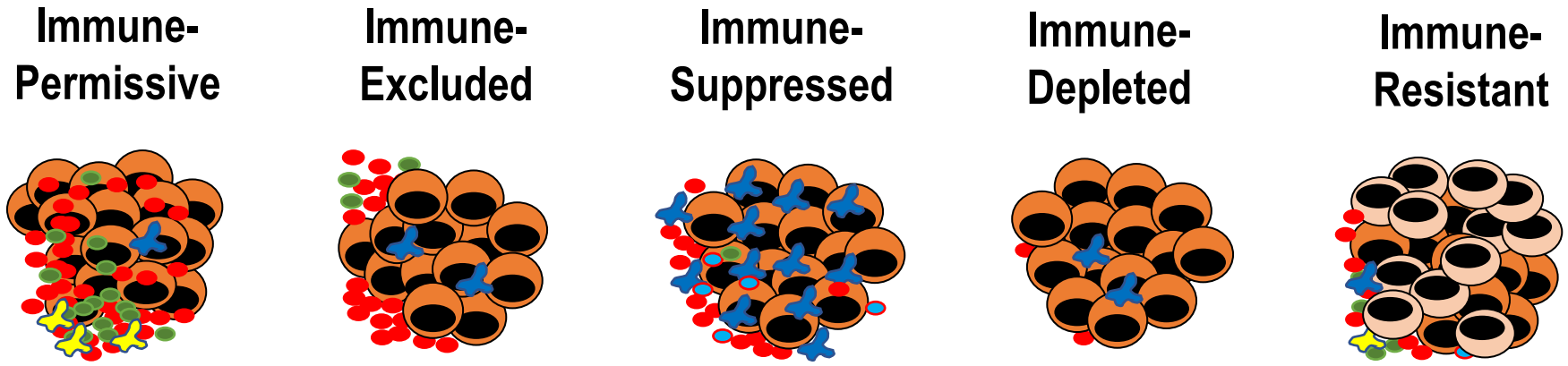
Lymphopenia

Prior / concurrent therapy

Variables that impact choice of CART v bispecific

	Favors CART	Favors bispecific
1-2 prior Lines BCMA naive	✓	Current approval 4+ lines
Sequencing considerations	✓	
Need for urgent Rx		✓
Lack of effective bridge Rx		✓
Too frail for CART		✓
Prefer one and done	✓	
BCMA resistant Dz		✓
High risk and EMD	✓	
Outpatient administration		✓
Rx in community		✓

Integrating MM immunology For Choice of Immune Therapies



	Immune - permissive	Immune-excluded	Immune-suppressed	Immune-deplete	Immune-resistant
Proposed Defining Feature(s)	T cell hotspots with infiltration and Clec9a DCs, lack of terminal diff. T cell clones	T cells at tumor margins without infiltration, lack of Clec9a DCs	Inhibitory myeloid infiltration, immune suppressive cells, T cell exhaustion	Systemic and regional lymphoid depletion	Loss of T cell redirection target, Resistance to immune recognition
Clinical Aspects	Expected favorable course, earlier in disease evolution.	? biology similar to extramedullary plasmacytomas	Potentially diverse mechanisms	Lymphopenia, ? with impaired hematopoiesis, extreme age, frailty, prior extensive chemotherapy	Target-specific loss or mutations in targets for T cell redirection.
Response to T cell redirection	**Yes. Durable responses**	**Yes, but may not be durable**	**Yes, but not durable**	**Unlikely. High risk of CAR-T manufacturing failure.**	**No, but resistance may be limited to specific targets**
Possible solutions / therapeutic goals	Target early eradication of residual disease for possible cures.	Enhance T cell entry, DC recruitment	Combinations to overcome suppression. Optimal combinations may be pathway/mechanism specific.	Direct tumor targeting, restore lympho-hematopoiesis.	Alternate targets or combinatorial targeting. Alternate immune cells (e.g. NK/NK-T)

Dhodapkar M, Blood Adv 2024

Conclusions

- T cell redirection by bispecifics and CART as highly effective therapy for MM.
- Choice of preferred approach is impacted by several factors.
- Early referral to a center with capacity for CAR-T should be considered, preferably one line prior to approved indication.
- Opportunity for collaborative management / care delivery with community, particularly with bispecifics.

Acknowledgments

- Myeloma Team at Emory
  - MDs, Nursing, Pharmacy, Other staff

- Community collaborators

With emerging immune therapies, close collaboration between academia and industry is even more paramount to help improve outcomes.