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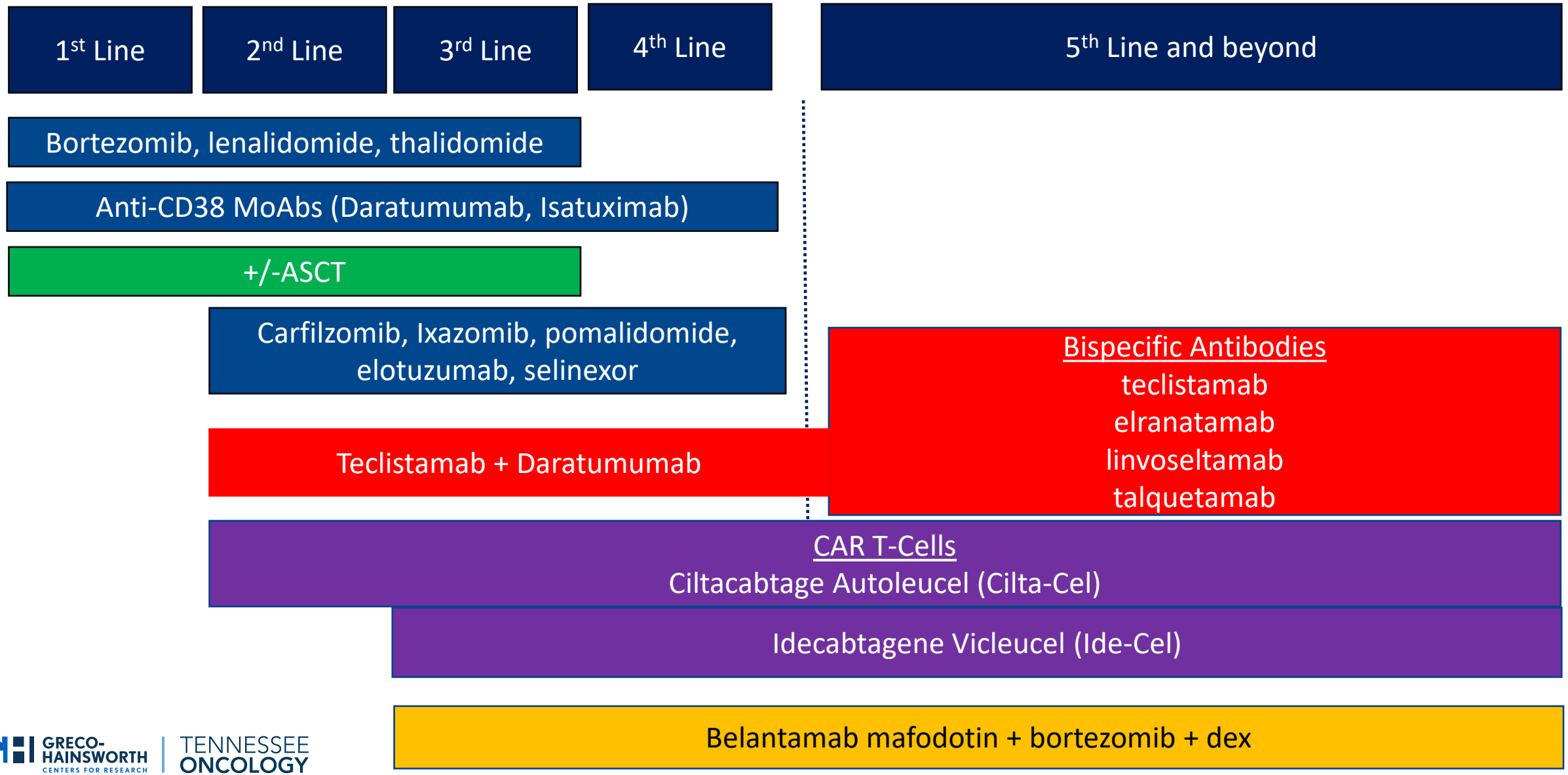
Bispecific Antibodies and T-Cell Engagers: Current and Future Timing and Novel Products

Jesús G. Berdeja, M.D.
Director of Multiple Myeloma Research

Disclosures

- Consultant
  - Astra Zeneca, BMS, Galapagos, J&J, Karyopharm, Kite Pharma, Kyowa Kirin, Pfizer, Regeneron, Roche
- Grant/Research Support
  - Astra Zeneca, BMS, C4 Therapeutics, Caribou Biosciences, Genentech, Gracell, GSK, Ichnos Sciences, J&J, Juno Therapeutics, K36 Therapeutics, Karyopharm, Kite Pharma, Pfizer, Roche, Sanofi

Treatment Landscape for Multiple Myeloma



FDA-Approved Bispecific Therapies

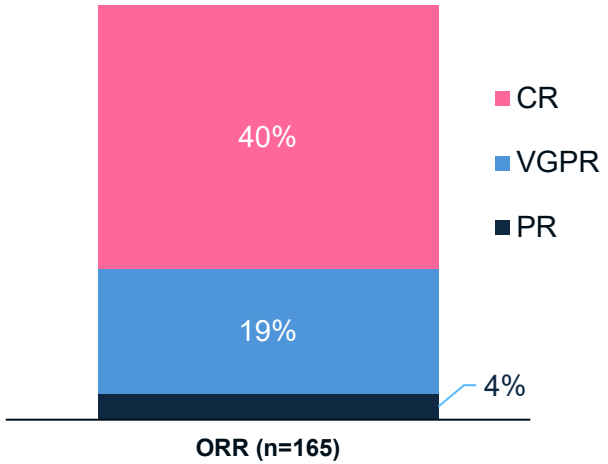
BsAb	Teclistamab (BCMA x CD3) MajesTEC-1 (phase I/II; n=165)	Elranatamab (BCMA x CD3) MagnetisMM-3 (phase I/II; n=123)	Linvoseltamab (BCMA x CD3) LINKER-MM1 (phase I/II; n=117)	Talquetamab (GPRC5D x CD3) MonumenTAL-1 (phase I; n=232)
Trial Population	≥3 LOT, including exposure to 1 PI, 1 IMiD, and 1 anti-CD38 mAb	Cohort A: Refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 mAb	≥3 LOT, including exposure to 1 PI, 1 IMiD, and 1 anti-CD38 mAb	RRMM w/ intolerance to or progressed on established therapies (Data for every 2-week dosing)
ECOG PS > 1, (%)	67	63	85	Excluded PS ≥ 2
Prior BCMA therapy allowed	Not allowed	Cohort A: No	Yes (10)	Yes
Age, median (range) years	64 (33-84)	68 (36-89)	70 (37-91)	64 (39-84)
Age > 65 years, (%)	48	NR	27	30 for > 70
EMD, (%)	17	32	16	32
High-risk cytogenetics, (%)	26	25	39	16
Median LOT, (range)	5	5	5	6
Triple-class refractory, (%)	78	97	82	79
Penta-drug refractory, (%)	30	42	28	30

Moureau P, et al. *N Engl J Med.* 2022;387(6):495-505; Lesokhin AM, et al. *Nat Med*. 2023;29(9):2259-2267; Chari A, et al. N Engl J Med. 2022;387(24):2232-2244

Teclistamab: MajesTEC-1 Trial

Median follow-up 30.4 months

63% ORR



Median PFS, mo	**11.4**
< 3 vs. > 3 prior LOT	21.7 (13.8-NE) vs. 9.7 (6.4-13.1)
Median DOR, mo	**24**
Median OS, mo	**22**

*30-month DOR, PFS and OS rates were ≥ 80% in pts. With sustained MRD [-] for ≥6 months

Selected AEs (≥ 20%), n (%)	(n=165)	
	Any Grade	Grade 3/4
Nonhematologic		
Infections	132 (80)	91 (55.2)
CRS	119 (72.1)	1 (0.6)
Pyrexia	52 (31.5)	1 (0.6)
Fatigue	48 (29.1)	4 (2.4)
Injection site reaction	43 (26.1)	0
Hypogammaglobinemia	34 (20.6)	3 (1.8)

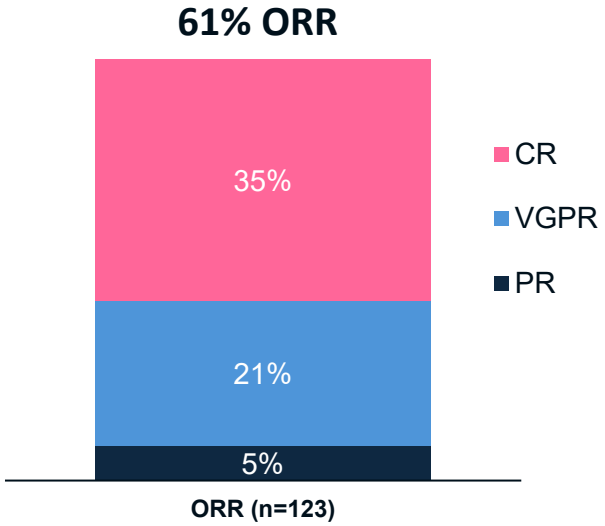
Clinically relevant infections, n (%)	(n=165)		
	Any Grade	Grade 3/4	Grade 5
Respiratory	95 (57.6)	32 (19.4)	2 (1.2)
COVID-19	48 (29.1)	35 (21.2)	18 (10.9)
Key viral	20 (12.1)	7 (4.2)	1 (0.6)
GI	15 (9.1)	2 (2.1)	0
Fungal	9 (5.5)	0	0
PJP	7 (4.2)	7 (4.2)	0

PJP: pneumocystis jirovecii pneumonia

Garfall AL, et al. *JCO* 2024;42:7540-7540; Nooka AK, et al. *JCO* 2022;40, 8007-8007; Moreau P, et al. *N Engl J Med*. 2022;387(6):495-505; Van De Donk NWCJ, et al. *JCO* 2023; 41(16_suppl):801-8011

Elranatamab: Magnetismm-3 Trial

Median follow-up 28.4 months



Median DOR, mo	NR (67% @24 mo)
Median PFS, mo	**17.2** (9.8 – NE)
Median OS, mo	**24.6** (13.4 – NE)

Selected AEs (≥ 20%), n (%)	(n=123)	
	Any Grade	Grade 3/4
Nonhematologic		
Infections	69.9	39.8 (G5: 6.5)
CRS	71 (58)	0
Fatigue	42 (34)	4 (3)
Decreased appetite	40 (33)	1 (1)
Injection side reaction	32 (26)	0
Pyrexia	29 (24)	4 (3)

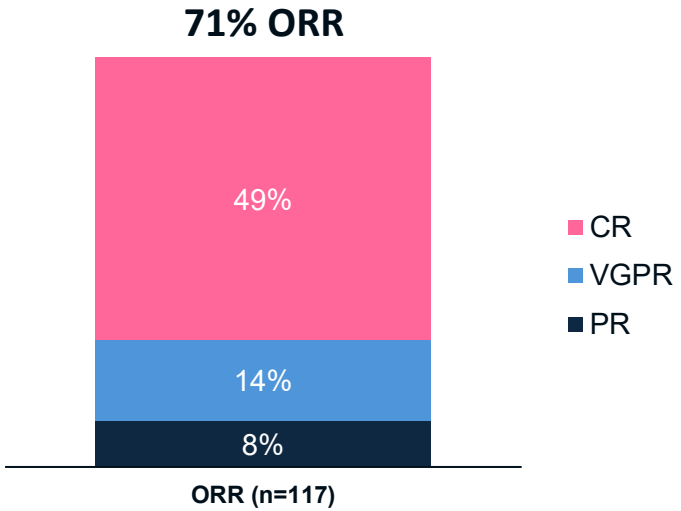
Clinically relevant infections, n (%)	(n=123)		
	Any Grade	Grade 3/4	Grade 5
COVID-19	36 (29)	19 (15)	2 (2)
Respiratory	20 (16)	0	0
PNA	20 (16)	10 (8)	0
Sinusitis	13 (11)	2 (2)	0
UTI	12 (10)	4 (3)	0
Sepsis	8 (7)	8 (7)	0

URTI: upper respiratory tract infection, PNA: pneumonia, UTI: urinary tract infection

Bahlis N, et al. *Nat Med.* 2023;29:2570-2576; Lesokhin AM, et al. *Nat Med.* 2023;29:2259-2267; Tomasson M, et al. *Blood.* 2023;142 (Suppl. 1) :3385; Tomasson, MH, et al. *HemaSphere.* 2024;8:e136; Prince HM, et al. *Blood*. 2024;144 (Suppl. 1):4738

Linvoseltamab: LINKER-MM1

Median follow-up 21.3 months



Median DOR, mo	29.4 (19.2 – NE)
Median PFS, mo	**NR** (17.3 – NE)
12-mo PFS rate, %	70.0 (60.1 – 78.0)
12-mo OS rate, %	75.3 (66.0 – 82.3)
Median OS, mo	**31.4** (21.6 – NE)
Prior BCMA ADC ORR, %	**70**

Selected AEs (≥ 20%), n (%)	(n=117)	
	Any Grade	Grade 3/4
Nonhematologic		
Infections	87 (74)	42 (36)
CRS	54 (46)	2 (2)
ICANS	9 (8)	3 (3)
Pyrexia	20 (17)	0
Fatigue	39 (33)	0
Hypogammaglobinemia	19 (16)	1 (1)

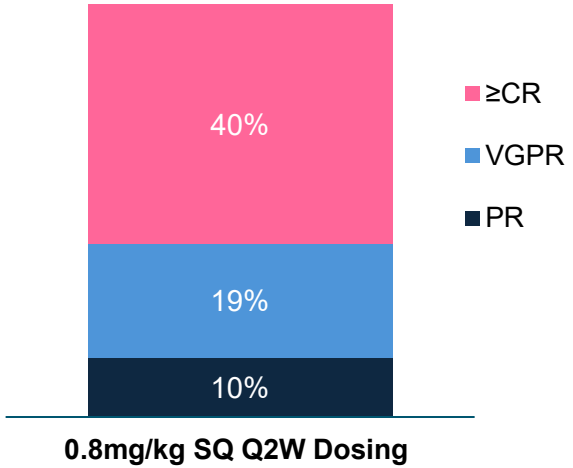
Clinically relevant infections, n (%)	(n=117)		
	Any Grade	Grade 3/4	Grade 5
Respiratory	22 (19)	2 (2)	0
COVID-19	20 (17)	8 (7)	0
Key viral	19 (16)	6 (5)	1 (1)
Fungal	6 (5)	1 (1)	0
PJP	5 (4)	3 (3)	1 (1)
GI	1 (1)	0	0

PJP: pneumocystis jirovecii pneumonia

Lee et al,. Clin Lymphoma Myeloma Leuk. 2026;26(2). Bumma N, et al. *J Clin Oncol*. 2024;42(22):2702-2712

Talquetamab: MonumenTAL-1 Trial

69.5% ORR; (n=107/154)



Durability of responses at mFU 23.4 months (0.8mg/kg SQ Q2W)

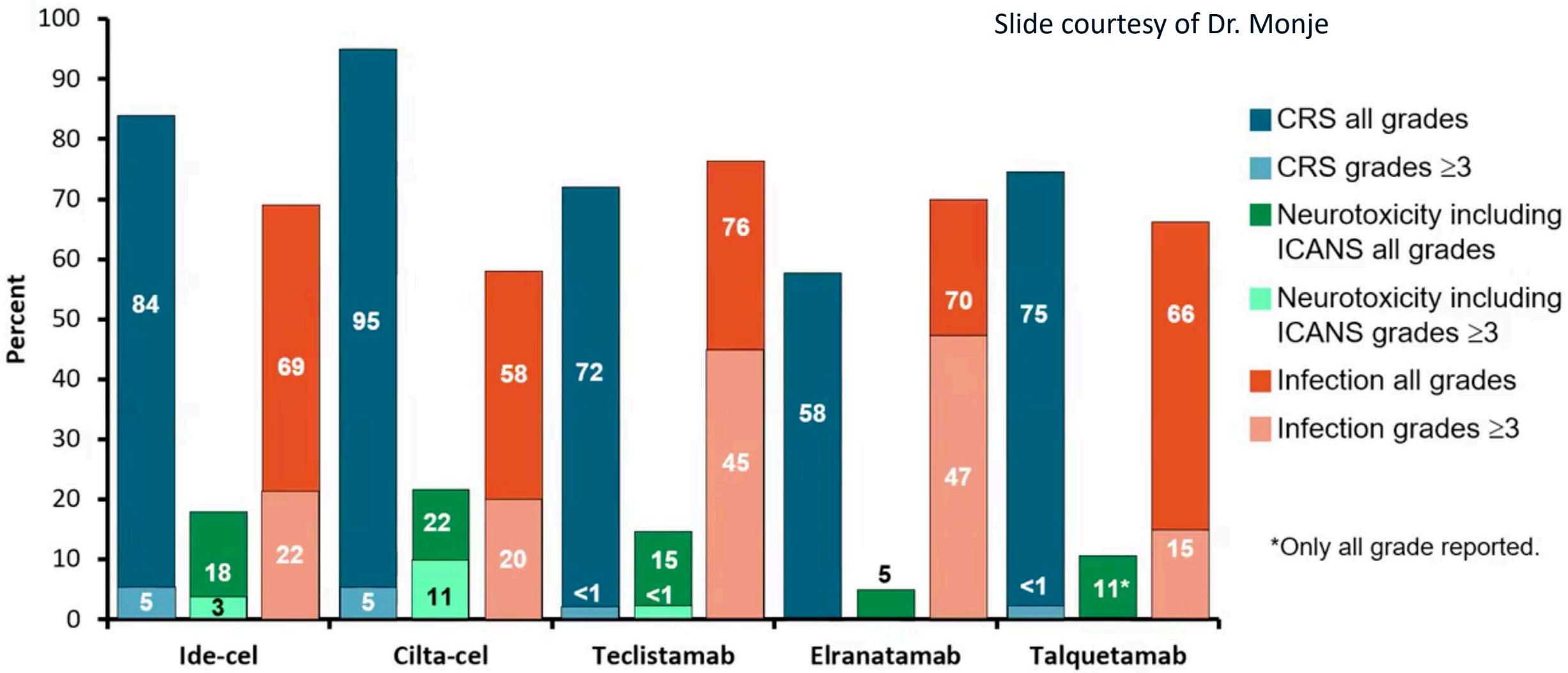
- mDOR = 17.5 months (12.5 - NR)
  - DOR outcomes for CR or better > VGPR > PR
- **mPFS = 11.2 months** (8.4 - 14.6)
- **24-month OS rate 67.1%** (58.3-74.4)
- **Prior BCMA ORR** 67% (78 pts)

AEs (≥ 20% of any RP2D cohort), n (%)	0.8 mg/kg SQ Q2W (n=145) mFU, 5.1 months	
	Any Grade	Grade 3/4
CRS	105 (72.4)	1 (0.7)
Skin-related AEs	98 (67.6)	1 (0.7)
Dysgeusia	67 (46.2)	NA
Nail-related AEs	63 (43.4)	0
Dry mouth	53 (36.6)	0
Weight decreased	47 (32.4)	2 (1.4)
Rash-related AEs	39 (26.9)	8 (5.5)
Pyrexia	35 (24.1)	1 (0.7)
Dysphagia	33 (22.8)	3 (2.1)
Diarrhea	32 (22.1)	0
Fatigue	29 (20.0)	1 (0.7)
Decreased appetite	29 (20.0)	2 (1.4)

Chari et al. Lancet Haematol 2025. Chari A, et al. *N Engl J Med*. 2022;387(24):2232-2244; Schinke CD, et al. *J Clin Oncol*. 2023;41, 8036-8036; Rasche L, et al. *HemaSphere*. 2024;8(S1):1619-1620

Safety Comparison: CRS, ICANS, Infections

Slide courtesy of Dr. Monje



Ludwig, Lancet Oncology 2023; Munshi, NEJM 2021; Berdeja, Lancet 2021; Martin, JCO 2022; Moreau, NEJM 2022; Lesokhin, Nature Medicine 2023; Chari, NEJM 2022; Schinke, ASCO 2023.

Talquetamab: On-target, Off-tumor Toxicities

Dry Mouth
- Hydration, soft/bland foods
- Limit caffeine and alcohol intake
- Gum/hard candy, frozen fruit, ice chips
- Monitor for oral candidiasis
- Routine dental exams

Skin Toxicity
- Hydration, emollients
- Ammonium lactate for pruritus
- Oral antihistamines or topical steroids
- Triamcinolone cream or methylprednisone

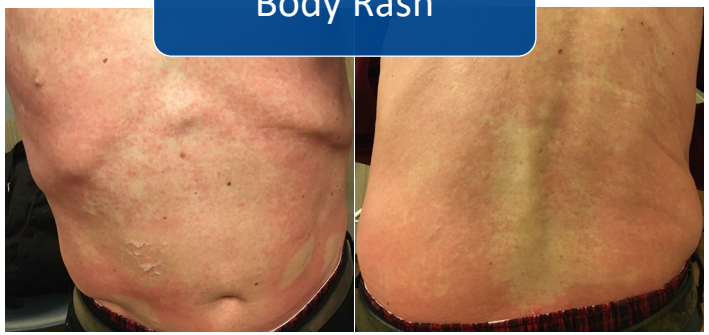
Dysphasia
- Small bites
- Frequent small meals
- Soft or mashed foods

Weight Loss
- Nutrient dense foods
- Oral appetite stimulants
- Small frequent meals, snacks with protein

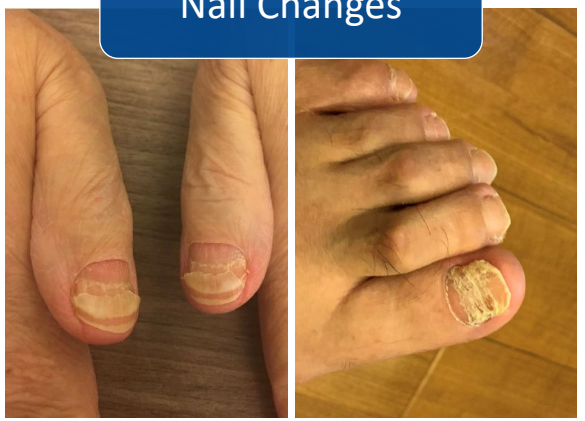
Dysgeusia
- Baking soda/salt water/magic mouth rinse
- Alternative sources of protein

Nail Toxicity
- Nail/finger cots or gloves
- Emollients vitamin E and biotin supplement; nail hardeners

Body Rash



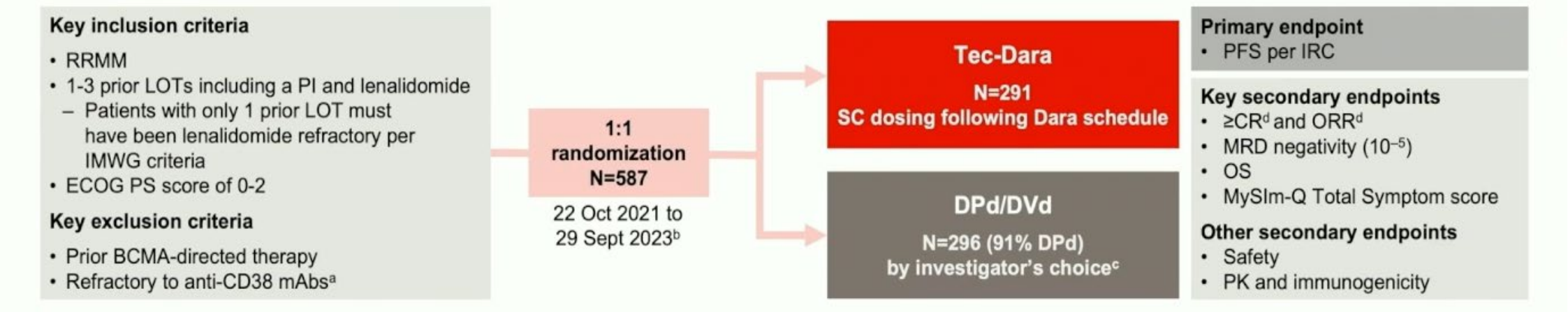
Nail Changes



Palmar/Plantar Desquamation

Catamero D, et al. *Semin Oncol Nurs* 2024;40(5):151712

MajesTEC-3: Phase 3 Study Design and Patient Population



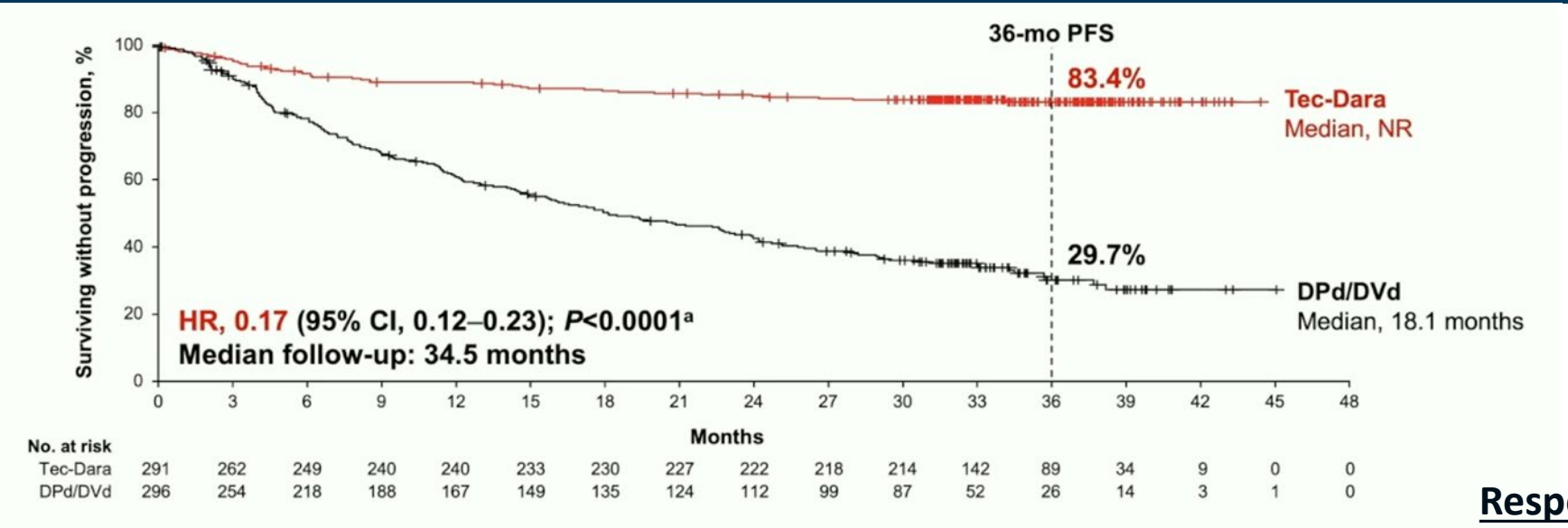
Characteristic	Tec-Dara Arm	SOC Arm
Age: Med (range), yrs	64 (36-88)	63 (25-84)
ISS III, %	8.2	7.8
HR Cytogenetics, %	36.5	35.4
EMD, %	4.8	5.7

Prior Treatments	Tec-Dara Arm	SOC Arm
LOT Med(range), n	2 (1-3)	2 (1-3)
Prior PI, %	99.7	100
Prior IMiD, %	100	100
Prior anti-CD38, %	5.2*	5.4*
Refractory to Len, %	82.5	84.8

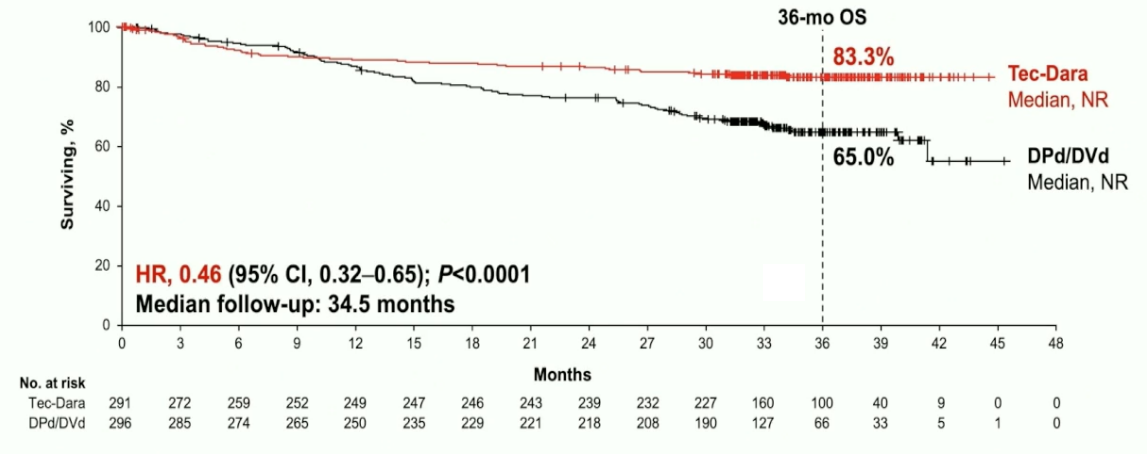
Mateos et al. ASH 2025. Costa et al. NEJM 2025.

MajesTEC-3: Outcomes

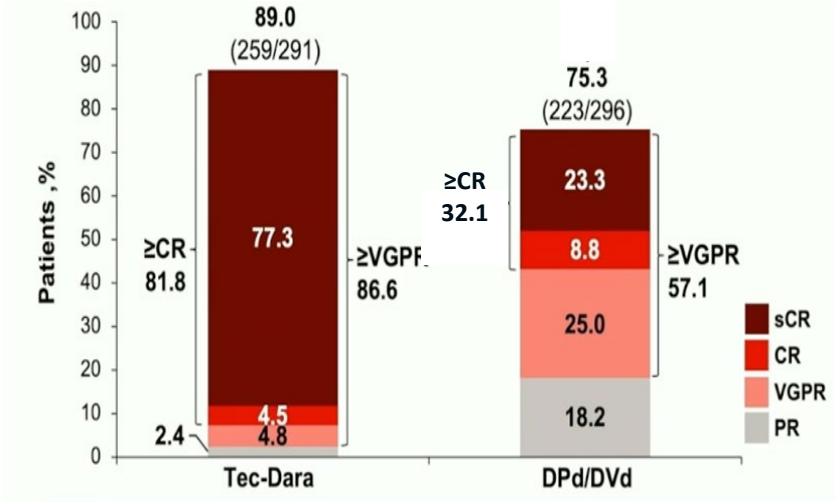
PFS



OS



Response Rate



Mateos et al. ASH 2025. Costa et al. NEJM 2025.

Approved Bispecific Antibody Therapies in Multiple Myeloma

Early Relapse

INDICATION
RRMM after at lest 1 prior LOT, including prior PI and IMiD

- Teclistamab + Daratumumab

Late Relapse

INDICATION
RRMM after at lest 4 prior LOT, including prior PI, IMiD and anti-CD38 ab

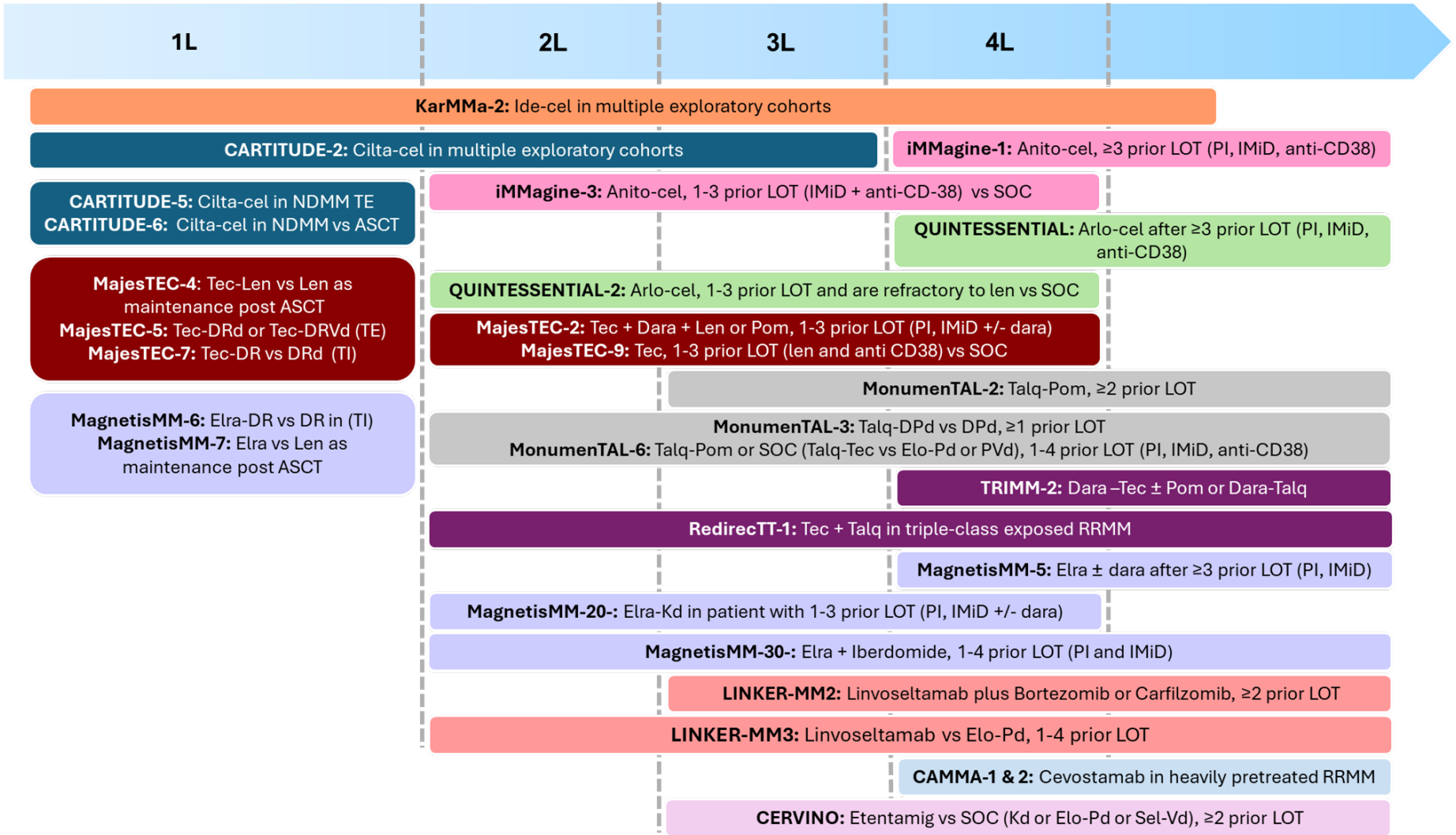
Anti-BCMA bispecific antibodies

- Teclistamab
- Elranatamab
- Linvoseltamab

Anti-GPRC5D bispecific antibodies

- Talquetamab

Sampling of Ongoing Clinical Trials with T-cell Redirecting Therapies in MM



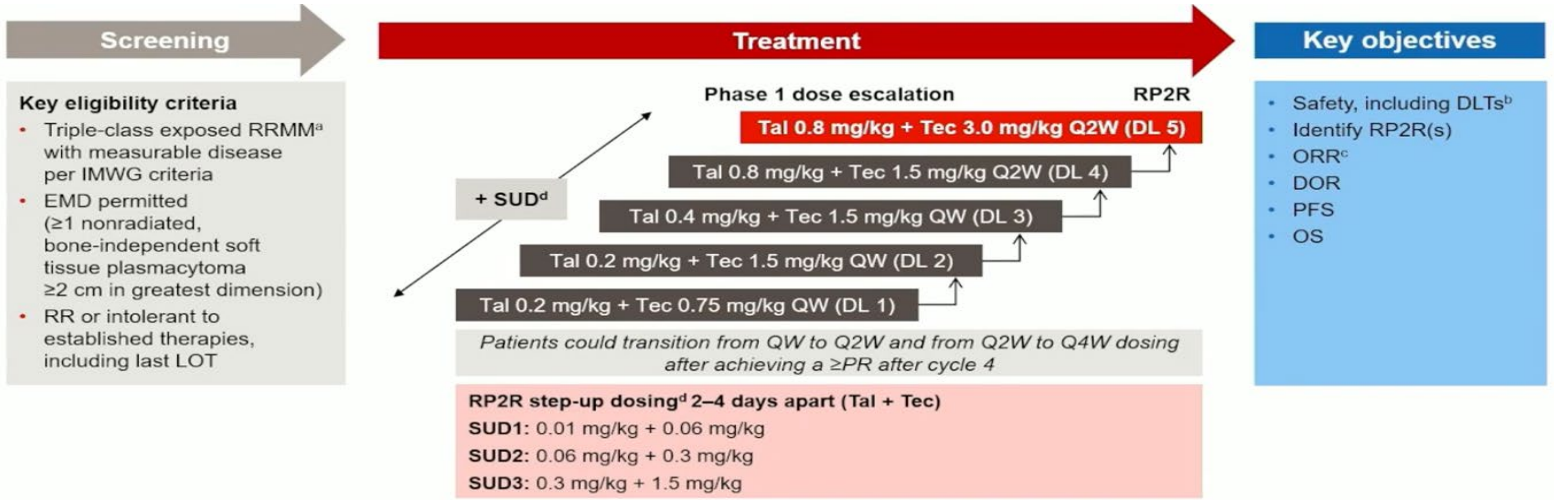
Danai D, Banerjee R, and Hansen DK. *Hematology ASH Education Program* 2025 (in press)

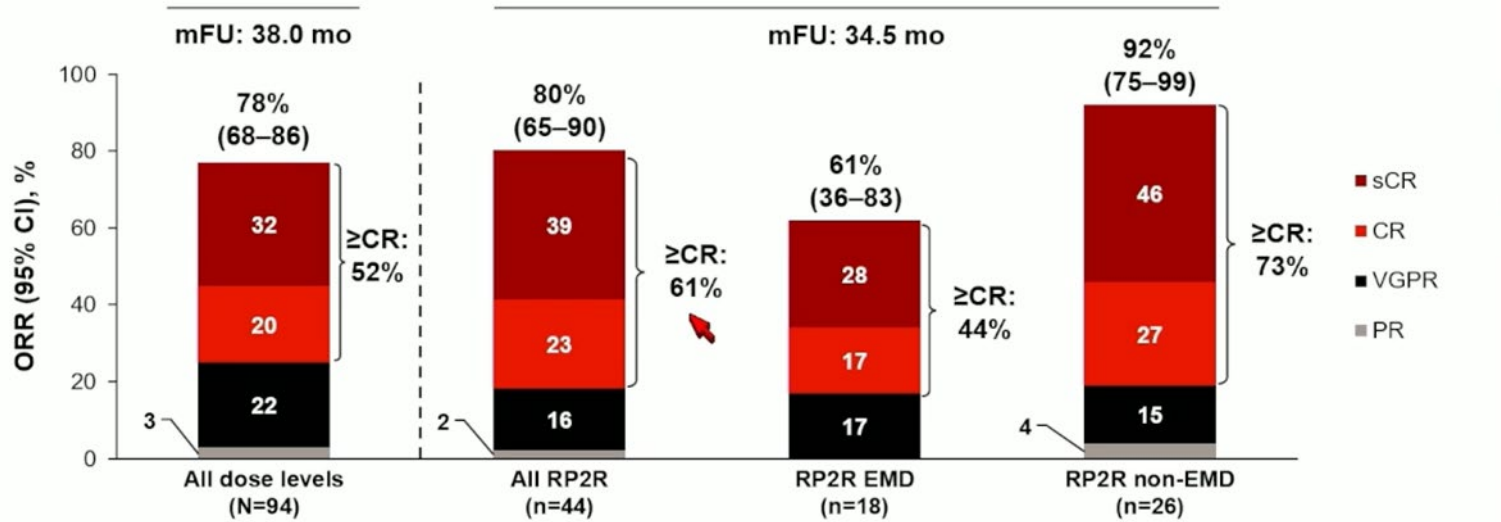
But why stop at 2 targets…

2 Bispecifics together – RedirecTT

Trispecific antibodies

RedirecTT-1: Phase 1b of Tec + Talq in RRMM





Characteristics	
All pts (RP2R), n	94 (44)
LOT Med(range), n	4 (1-11)
TCR, %	87.2
HR Cytogenetics, %	45.1
EMD, %	37.2

Survival	Med FU 38.0 mos
Median PFS, mos	38.6 (21.6-NE)
Median DOR, mos	NR (34.7-NE)
Median OS, mos	NR (39.1-NE)

Adverse Events	All Gr (Gr 3+)
Neutropenia	74.5 (70.2)
Infections	93.6 (53.2)
CRS	80.9 (2.1)
Oral tox	78.2 (1.1)
Nail related	52.1 (0)
Weight Decrease	36.2 (8.5)

Mateos et al: ASH 2025, Abs 701.

RedirecTT-1 Ph2 EMD

Screening

Eligibility criteria
- Triple-class exposed RRMM[a]
- True EMD, defined as ≥1 nonradiated bone-independent soft tissue plasmacytoma ≥2 cm in greatest dimension confirmed by central review of PET-CT scans[b,c]
- Prior CAR-T and non-BCMA/-GPRC5D bispecific antibody therapies were permitted
- Nonsecretory and oligosecretory disease were permitted

Treatment

Tal 0.8 mg/kg Q2W SC[d,e]
+
Tec 3.0 mg/kg Q2W SC[d,e]

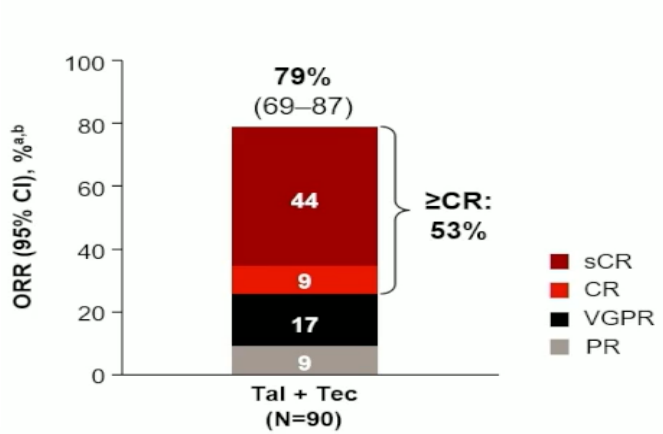
Option to switch to monthly dosing after 4 cycles and ≥VGPR, or after 6 cycles (irrespective of response)

Step-up dosing[d] 2–4 days apart (Tal + Tec)
SUD1: 0.01 mg/kg + 0.06 mg/kg
SUD2: 0.06 mg/kg + 0.3 mg/kg
SUD3: 0.4 mg/kg + 1.5 mg/kg

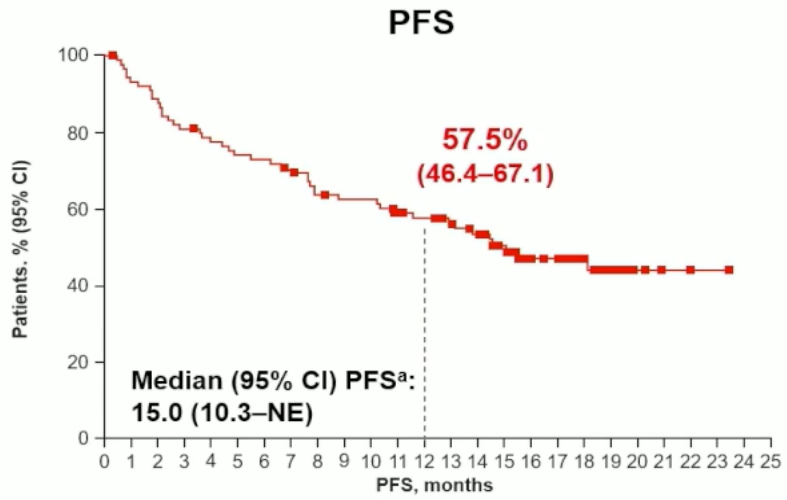
Endpoints

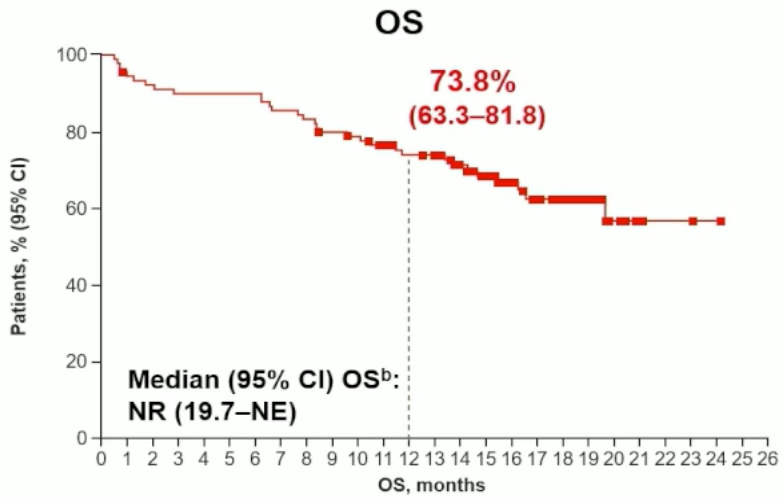
Primary endpoint: ORR[f]

Secondary endpoints:
- DOR[f]
- PFS[f]
- OS
- Safety



Median (range) time to:
- First response, 2.6 (1.0–5.8) months
- Best response, 5.1 (1.0–16.6) months





Usmani et al: ASH 2025, Abs 698. Kumar et al. NEJM epub.

Trispecific Antibodies

ISB 2001 BCMAxCD38xCD3

TRIgnite-1 Ph 1 of ISB 2001 in RRMM

Characteristics	
All pts (≥ 50mc/kg dose), n	35 (33)
LOT Med(range), n	6 (3-11)
TCR, %	49
Anti-CD38 exposed (refractory), %	100 (71)
Prior BCMA, %	46

Efficacy	
All pts	74%
≥ 50mc/kg dose	79%
Prior BCMA	73%
CD38 refractory	72%

Adverse Events, %	All Gr (Gr 3+)
CRS	69 (0)
Infections	74 (29)
Neutropenia	51 (43)

IBI3003 BCMAxGPRC5DxCD3

Ph 1 Study of IBI3003 in RRMM

Characteristics	
All pts (n @≥ 120mc/kg), n	39 (24)
LOT Med(range), n	4 (2-10)
TC Exposed (refractory), %	100 (?)
EMD, %	46.2
Prior BCMA or GPRC5D, %	41

Efficacy	
≥ 120mc/kg dose	83.3%
Prior BCMA/GPRC5D	77.8%
EMD	80%

Adverse Events, %	All Gr (Gr 3+)
CRS	64.1 (0)
Infections	48.7 (28.2)
Oral tox	53.8 (0)
Skin and Nail related	64.1 (5.1)
Weight dec	20.5 (0)

Ramantamig (JNJ-79635322) BCMAxCD38xCD3

Ph 1 Study of JNJ-79635322 in RRMM

Characteristics	
All pts (RP2D), n	147 (36)
LOT Med(range), n	4 (1-11)
TCR, %	53.7
EMD, %	10.9
Prior BCMA or GPRC5D, %	19.7

Efficacy	
BCMA/GPRC5D naïve @RP2D	100%
BCMA/GPRC5D exposed @all doses	55%

Adverse Events, %	All Gr (Gr 3+)
CRS	56.5(0)
Infections	75.5 (28.6)
Oral tox	57.8 (0)
Skin, Nail related	49.7(0.7), 55.1 (0)
Weight dec	12 (0)

Lichtman et al. ASCO 2025, Abs7514. Li et al. ASH 2025, Abs 702. van de Donk et al. ASCO 2025.

So, When Should Bispecific Antibodies Be Given in MM?

In the RR setting: 5th line or higher

In the 1-3 prior LOT space

In 2nd line for all patients

How about special situation/populations…

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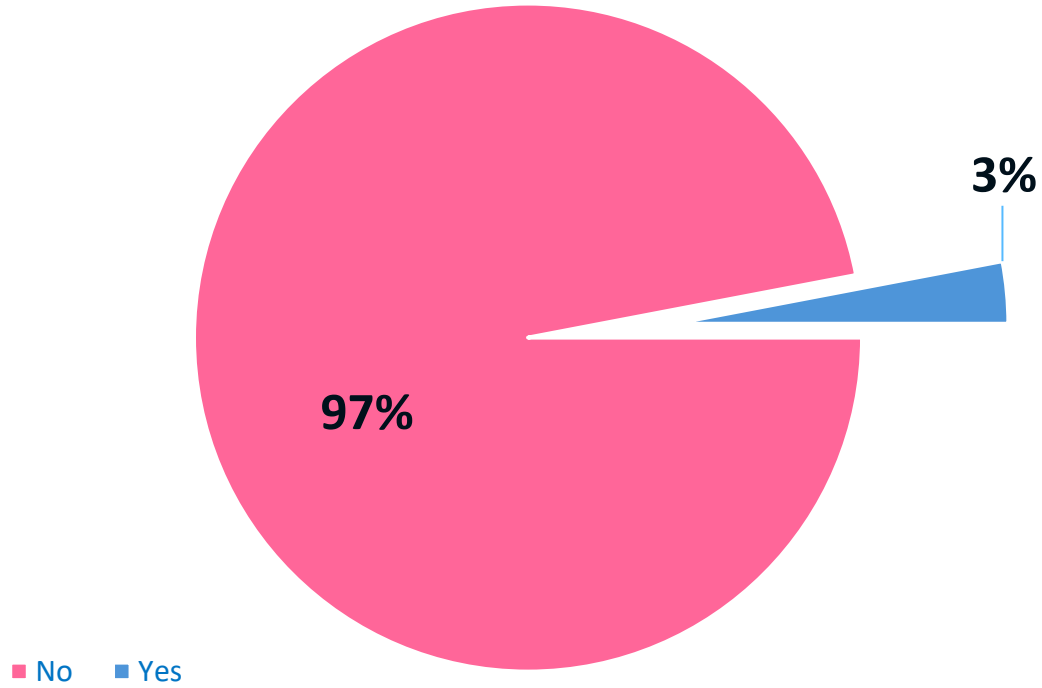
Situations when a BsAb should be chosen over CART

Non-response to bridging w Cilta-cel: 10 x higher risk for parkinsonism

Parkinsonism with SOC cilta-cel: 22 cases of 761 (3%)

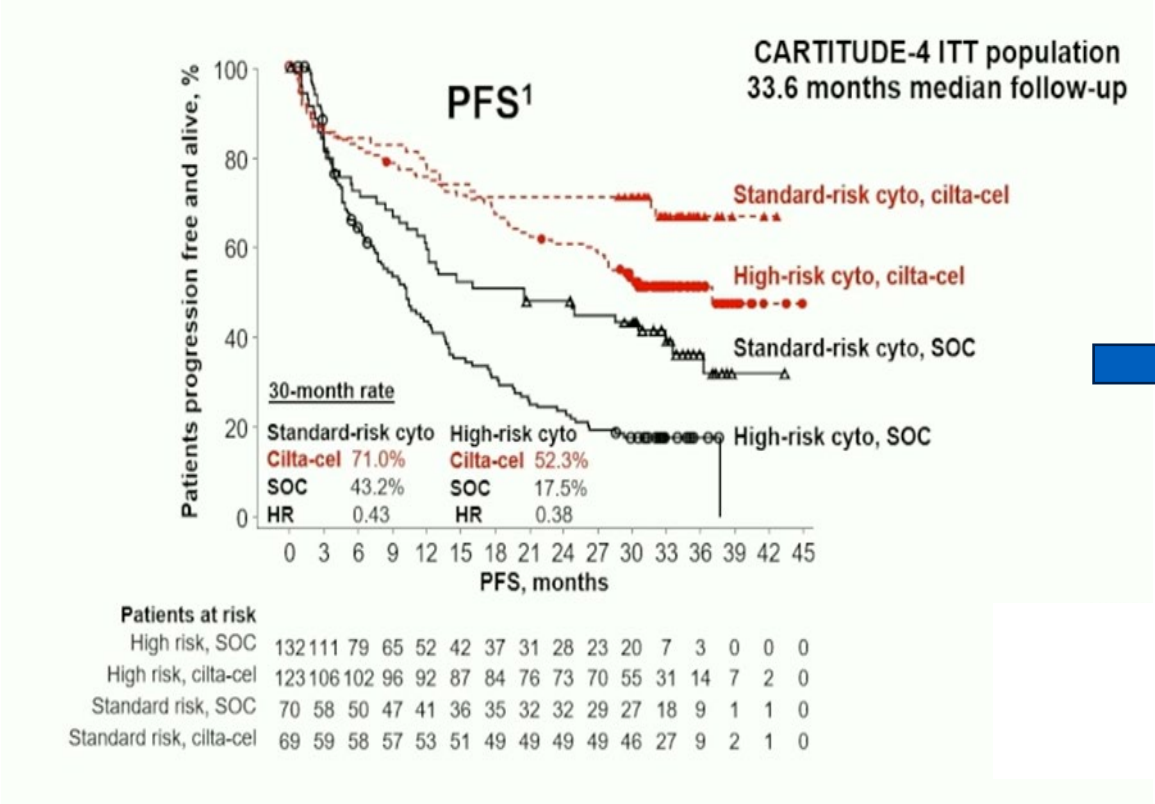


Risk of Parkinsonism in non-responders vs responders to bridging therapy (PR or better):
5% vs 0.5% (p<0.05)

Of 22 cases of Parkinsonism, 21 (95%) patients did not respond to bridging, even though post CAR-T response rate was 91% and CR rate 68%

Sidana S, et al. ASH 2025, abstract 1034

Patients with HR Cytogenetics



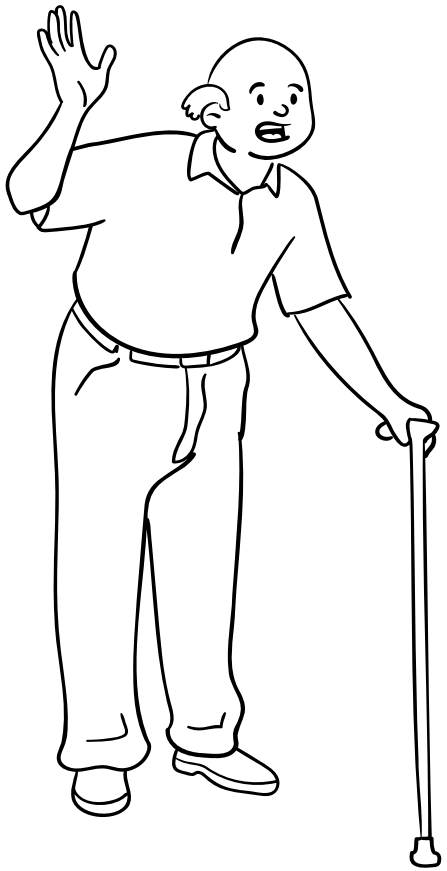
Costa et al. ASH 2025, Abs 94

MajesTEC-3
Tec-Dara vs SOC,
HR 0.17

Subgroup of pts with HR Cytogenetics,
HR 0.15

Costa et al. NEJM 2025

HOW FIT DOES A PATIENT NEED TO BE TO BE ELIGIBLE FOR BsAb THERAPY?



Patients with severe renal impairment… excluded from all clinical trials

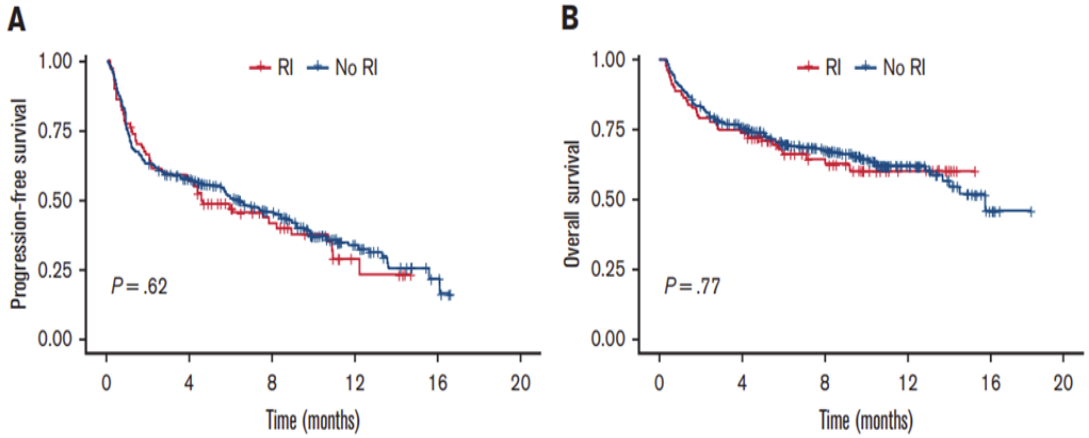
CAR T-cells

- Fludarabine as part of LD chemo needs to be held
- RWD shows feasible but increased toxicity

Sidana et al. Haematologica 2023.

Teclistamab RWE

- 384 pts (81 with RI (inc HD))



Dima et al. Blood Adv 2025.

So, When Should BsAb Be Given in MM?

- Timing of BsAb?
  - All patients should be referred early, and BsAb should be entertained even at 1st relapse
    - Teclistamab-Daratutumab FDA approved

- Which Patients?
  - No age is disqualifying for BsAb consideration
  - Patients who may not be eligible for CART may be eligible for BsAb
  - Patients can proceed with BsAb even with renal insufficiency
  - Proceed with caution in patients with active infection or high risk for infectious complications

- In the RR setting, 3 BCMA BsAb and 1 GPRC5D BsAb are approved
  - Selection between the BCMA-directed therapies is difficult and no true clinic data to differentiate
  - In the setting of a prior BCMA therapy such as CART or ADC
    - BCMA BsAb may still have efficacy but attenuated compared to a BCMA-naïve state
    - GPRC5D-directed therapy is an excellent option in this setting
  - If infection complications are of utmost concern, consideration for GPRC5D-directed therapy instead of BCMA-directed therapy should be considered
- Combinations with SOC, multiple bispecific antibodies and now trispecific antibodies will continue to challenge and define the optimal SOC

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Thank you