Bispecific Antibodies in the Treatment of Multiple Myeloma

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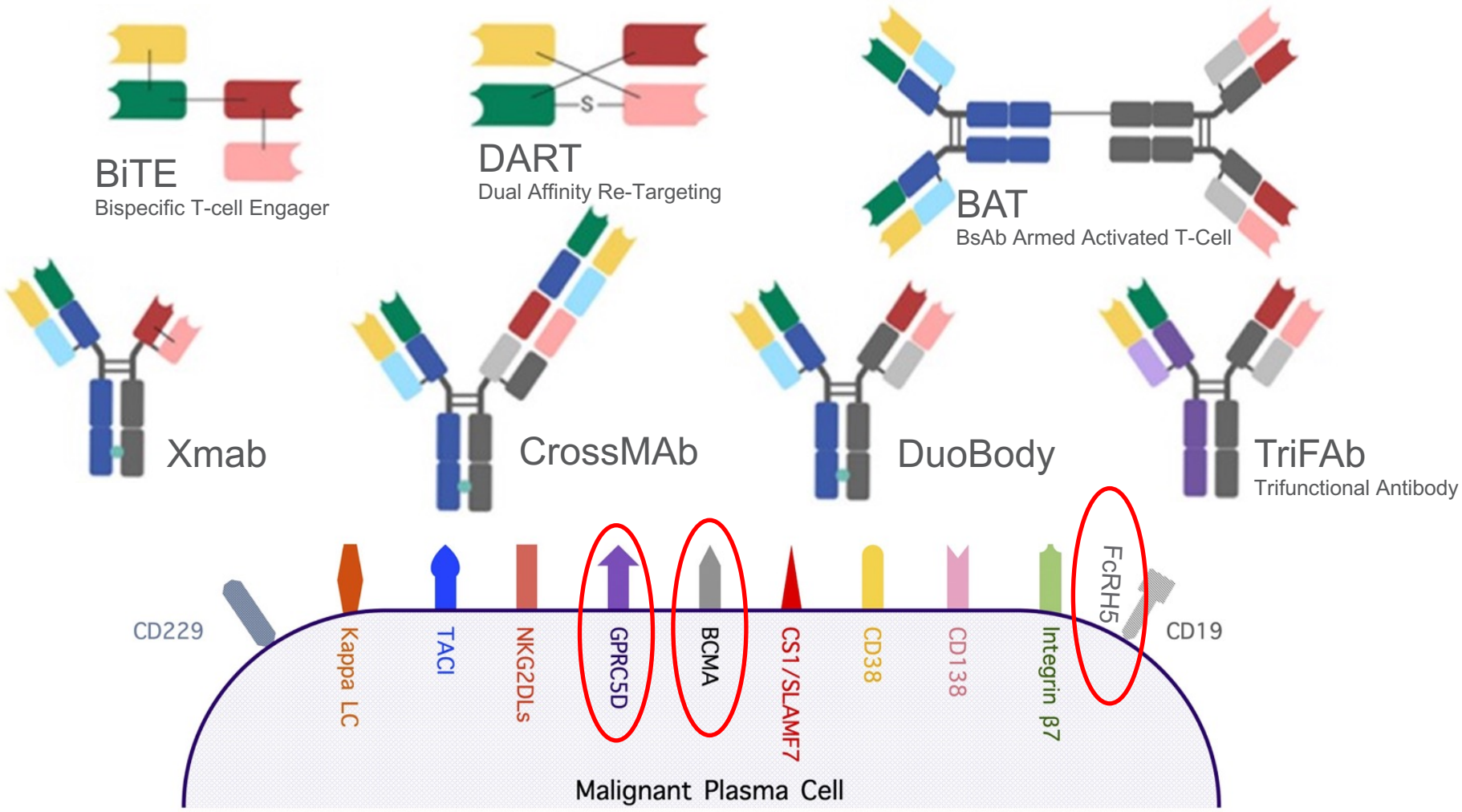
Bispecific antibodies: Many platforms, many targets



Adapted from:
Lejeune. Front. Immunol. 11:762, 2020. Wudhikarn. Hematology Am Soc Hematol Educ Program. 2020;2020:272.

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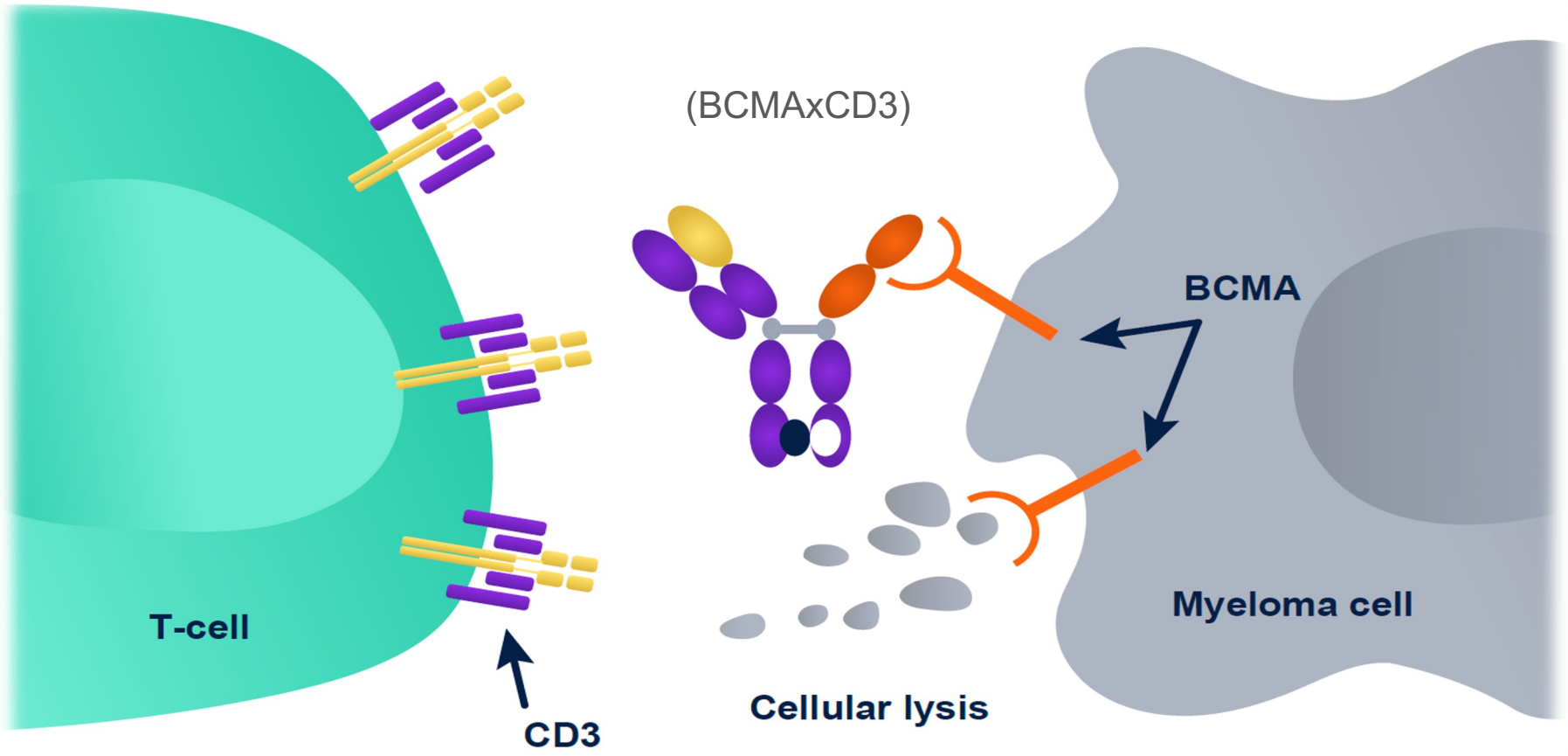
T cell redirecting bispecific antibodies



Shah N, et al. Leukemia. 2020;34:985-1005

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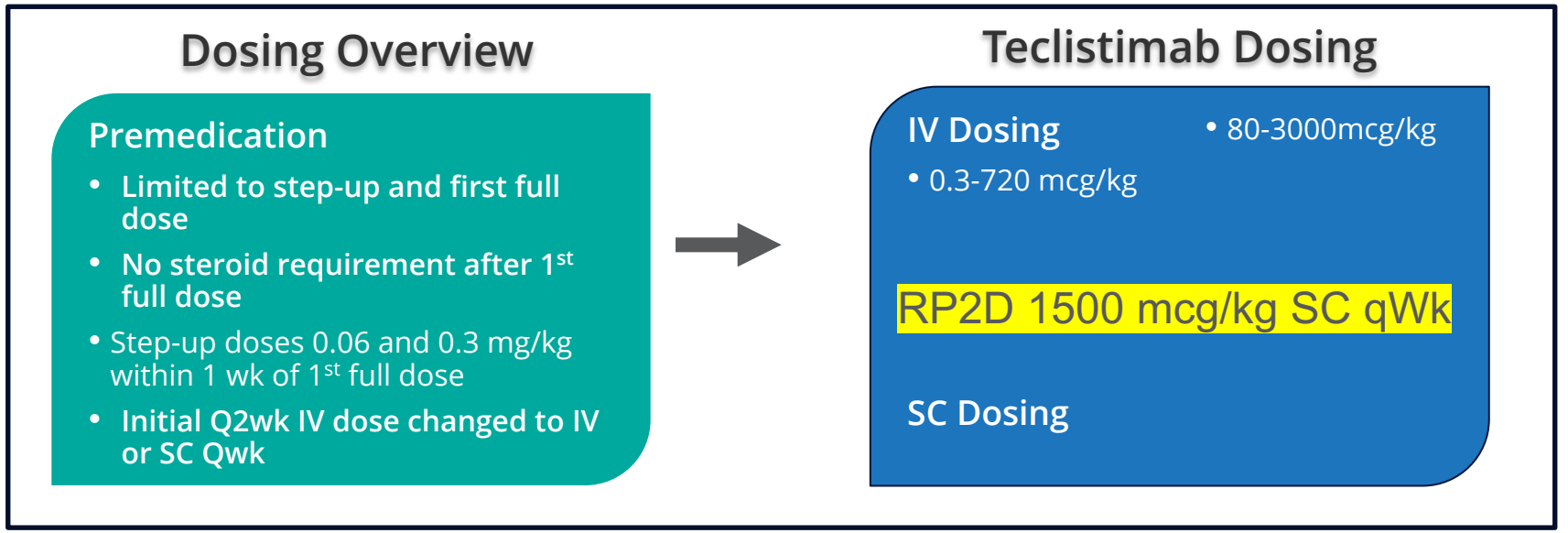
Teclistamab
MajesTEC-1: Study Design

- Phase 1/2, dose escalation study to evaluate teclistamab in patients with RRMM
- ≥3 prior lines of therapy
- No prior BCMA-targeted therapy



Primary endpoints: Phase 1 - safety and determine RP2D. Phase 2 - ORR

Key secondary endpoints: DOR, ≥VGPR, ≥ CR, sCR, TTR, MRD status, PFS, OS, safety, pharmacokinetics, immunogenicity, PRO

Moreau et al. NEJM 2022, 387(6):495-505.

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MajesTEC-1: Patient Baseline Characteristics

Characteristic	Safety Analysis N=165
Age (years), median (range)	64.0 (33–84)
Age ≥75 years, n (%)	24 (14.5)
Male, n (%)	96 (58.2)
Race, n (%)	
White	134 (81.2)
African-American/Black	21 (12.7)
Other[a]	10 (6.1)
Bone marrow plasma cells ≥60%[b], n (%)	18 (11.3)
Extramedullary plasmacytomas ≥1[c], n (%)	28 (17.0)
High-risk cytogenetics[d], n (%)	38 (25.)
ISS stage[e], n (%)	
I	85 (52.5)
II	57 (35.2)
III	20 (12.3)

Characteristic	Safety Analysis N=165
Baseline renal function, n (%)	
<60 mL/min/1.73m^2	44 (26.7)
≥60 mL/min/1.73m^2	121 (73.3)
Time since diagnosis (years), median (range)	6.0 (0.8–22.7)
Prior lines of therapy, median (range)	5.0 (2–14)
Prior stem cell transplantation, n (%)	135 (81.8)
Exposure status, n (%)	
Triple-class exposed[f]	165 (100)
Penta-drug exposed[g]	116 (70.3)
Selinexor	6 (3.6)
Refractory status, n (%)	
Triple-class refractory[f]	128 (77.6)
Penta-drug refractory[g]	50 (30.3)
Refractory to last line of therapy	148 (89.7)

Moreau et al. NEJM 2022, 387(6):495-505.

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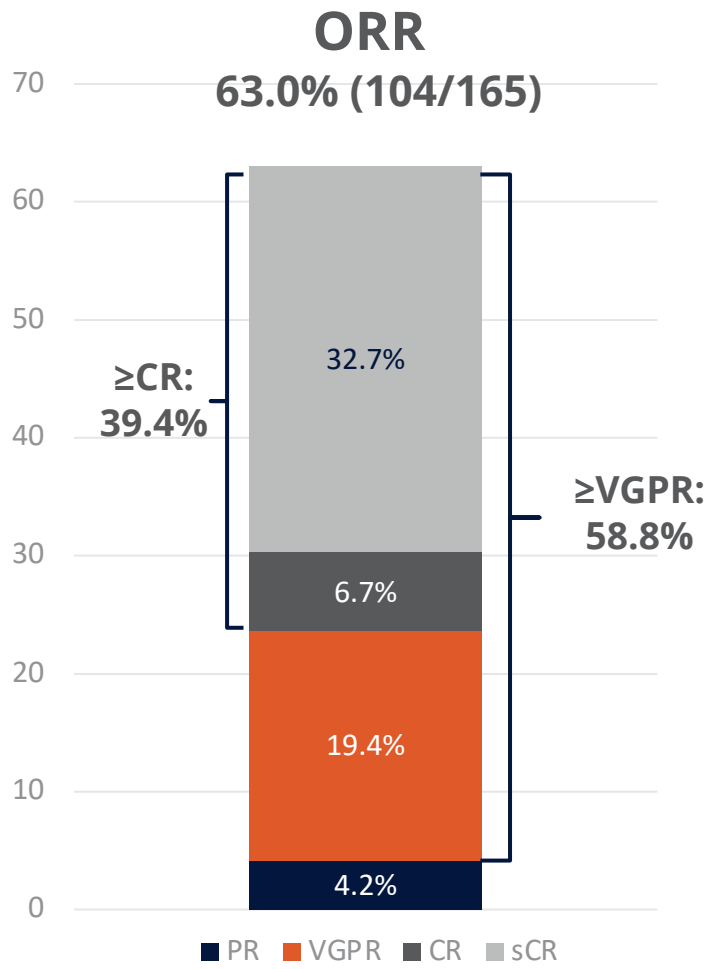
MajesTEC-1: Response



- At a median follow-up of 14.1 months:
  - ORR was 63.0% (95% CI: 55.2–70.4)
  - ≥ VGPR 58.8%
- Median time to first response: 1.2 months
- MRD negativity rate[b]
  - 26.7% at a threshold of 10^{-5}
  - 46% for patients who achieved ≥CR

Moreau et al. NEJM 2022, 387(6):495-505.

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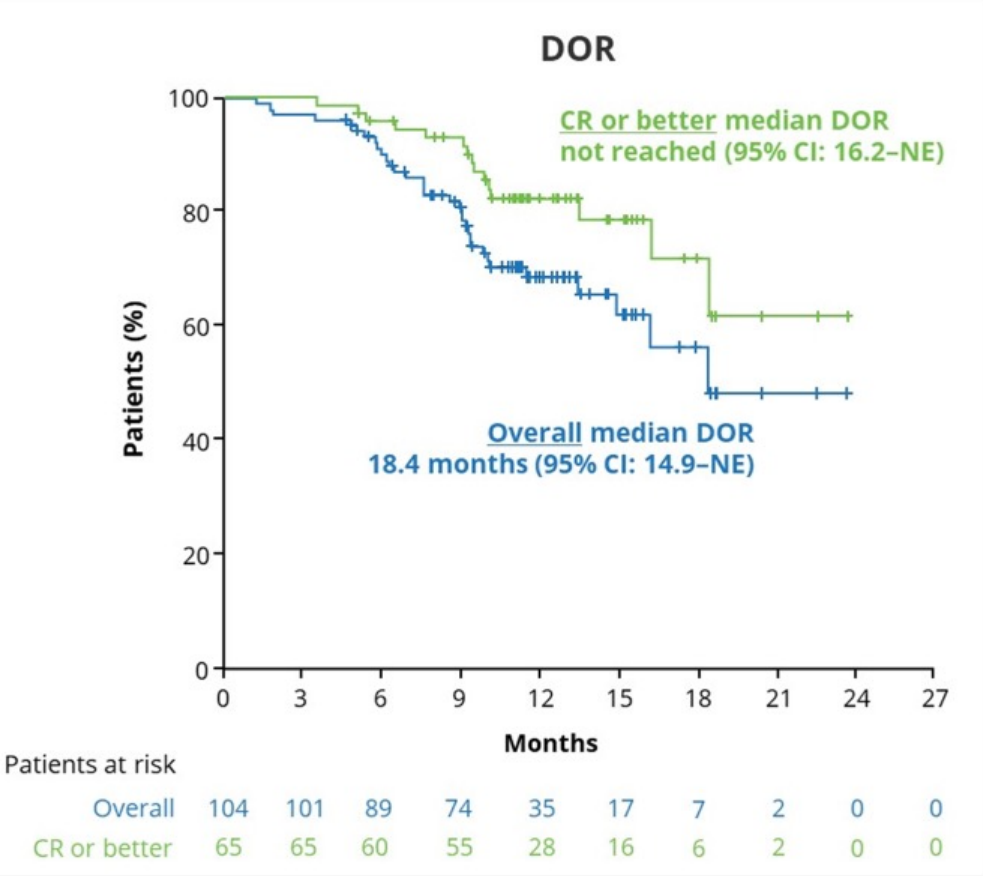
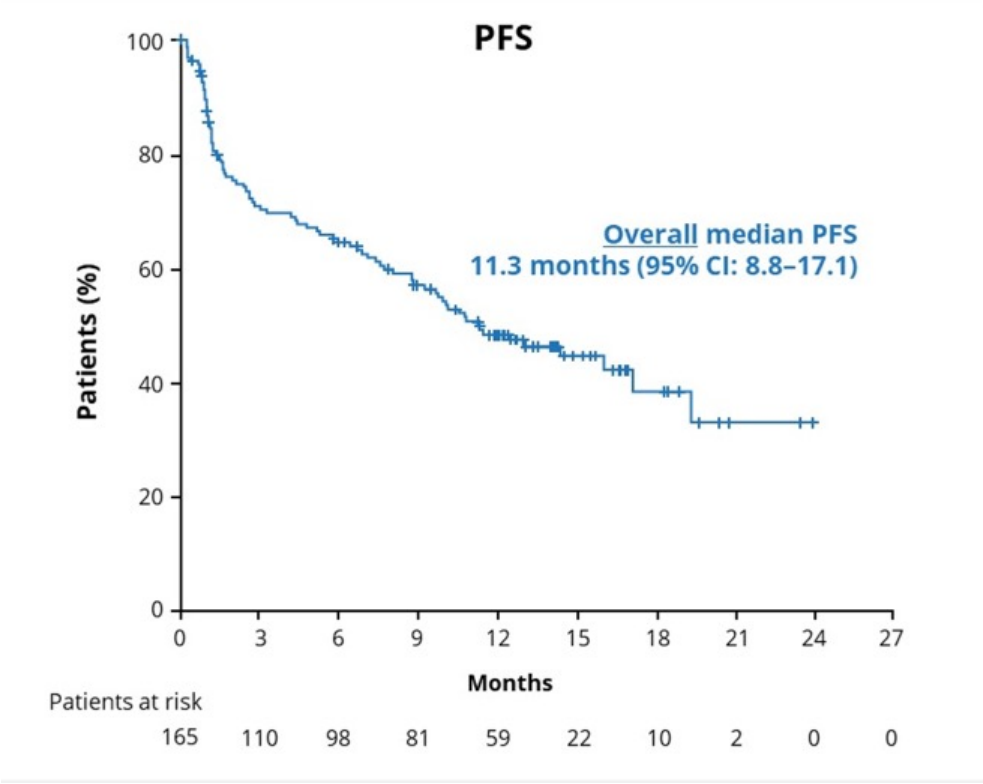
MajesTEC-1: Durability of Response





Median DOR 18.4 mos – Median PFS 11.3 mos – Median OS 18.3 mos

Moreau et al. NEJM 2022, 387(6):495-505.

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MajesTEC-1: Overall Safety Profile

Safety Analysis Set N=165		
AEs ≥20%, n (%)	Any Grade	Grade 3/4
Hematologic		
Neutropenia	117 (71)	106 (64)
Anemia	86 (52)	51 (37)
Thrombocytopenia	66 (40)	35 (21)
Lymphopenia	57 (35)	54 (33)
Nonhematologic		
CRS	119 (72)	1 (0.6)
Diarrhea	47 (29)	6 (4)
Fatigue	46 (28)	4 (2)
Nausea	45 (27)	1 (0.6)
Injection site erythema	43 (26)	0 (0)
Headache	39 (24)	1 (0.6)

- 2 patients discontinued due to AEs (G3 adenoviral pneumonia and G4 PML)
- Infections occurred in 126 (76%) (grade 3/4: 45%)
- 19 deaths due to AEs (5 felt to be related to teclistimab)
  - COVID-19(2); Pneumonia (1), Hepatic failure (1); PML (1)
- CRS occurred in 72%
  - All CRS events were grade 1/2, except for 1 transient-grade 3 CRS event that fully resolved
  - Median time to onset of CRS 2 days
  - 97% of events were confined to step-up and cycle 1
- Neurotoxicity was seen in 14%
  - Most were headaches 8.5%
  - ICANS was seen in 3.0%

Moreau et al. NEJM 2022, 387(6):495-505.

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First FDA-Approved BCMA-Targeted Bispecific Ab

	Indication
Teclistamab	▪ **Adults with R/R multiple myeloma after ≥4 prior lines of therapy**, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal Ab

Teclistamab PI.

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BCMA:CD3 BISPECIFICS IN MULTIPLE MYELOMA

	Teclistamab[1,2,3]	Linvoseltamab[4]	ABBV-383[5]	elranatamab[6]	Alnuctamab[8]
Construct Study	DuoBody MajesTEC-1	Veloci-Bi Fc Phase 1	Triple chain: 2 BCMA Phase 1	DuoBody Magnetissm-3	2+1 CrossMab Phase I
Dose/Sched	IV/SC q1-2wk (Step up) RP2D 1500mcg/kg SC qwk	3-800mg IV (split W1,2) qwk, q2 wks wk16+	0.25-120-mg (no step up) IV Q3wks RP2D 40mg & 60mg IV q3wks	76mg SC QWk (2 step up 12mg and 32mg)	0.005-10mg IV qwk (Step up) 10mg-60mg SC Q1wk C1-3, Q2wx C4-6,Q4wk C6+
Population	165 (Ph1 40, Ph2 125) Median 5 LOT 78% triple refractory	167 Median 6 LOT 90% triple refractory	66* Median 5 LOT 82% triple refractory	123 Median 5 LOT 97% triple refractory 32% EMD	47* Median 4 LOT 62% triple refractory
Safety All Grade (Gr 3+)	CRS 72%(0.6%) Neurotox 14% ICANS 3%(0) Infections 76%(45%)	CRS 48%(0.6%) ICANS 4%(0) Infections ?	CRS 72%(2%) ICANS <1% Infections 43%(22%)	CRS 56%(0) ICANS 3%(0) Infections 62%(32%) PN 17%	CRS 53%(0) ICANS 1 pt, gr 1 Infections ?
Response ORR(VGPR+)	63% (59%)	75% @200-800mg	63%(47%) @40-60mg	61%	51% [77% @ ≥30mg dose]
Durability	DOR 18.4 mos PFS 11.3 mos OS 18.3 mos				
Misc	Cohort A results Excluded prior BCMA Cohort C Prior BCMA[3] ORR(VGPR+) 52.5%(47.5%)	Formerly REGN5458 RP2D 200mg	Formerly TNB-383B *Dose levels 40/60 only	- [7]Magnetissm-1 K-M estimate DOR 17.1m	*SC only - Dose expansion 10mg & 30mg SC

[1]Moreau et al. NEJM 2022, 387(6):495-505. [2]Nooka et al. ASCO 2022, Abs 8007. [3]Touzeau et al. ASCO 2022, Abs 8013.
[4]Bumma et al. ASH 2022, Abs 4555. [5]Voorhees et al. ASH 2022, Abs 1919. [6]Bahlis et al. ASH 2022, Abs 159.
[7]Raje et al. ASH 2022, Abs 158. [8]Wong et al. ASH 2022, Abs 162.

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BCMA Bispecific Ab after prior BCMA Treatments

Teclistamab

- MajesTEC-1: 40 pts enrolled in cohort C, all prior BCMA
  - 29(72.5%) prior ADC
  - 15(37.5%) prior BCMA CART
- ORR(>VGPR)
  - All – 52.5%(47.5%)
  - ADC-exposed 55.2%(48.3%)
  - CART 53.3%(46.7%)
- Med DOR NR
- Safety profile no different than entire population

Touzeau et al. ASCO 2022, Abs 8013

Elranatamab

- MagnetisMM-1: 55 total pts enrolled
  - 13(24%) prior BCMA
    - 8 prior BCMA-ADC
    - 9 prior CAR-T
- ORR(>VGPR)
  - All – 64%(58.2%)
  - Prior BCMA - 54%(46%)
  - Not broken down by type of prior BCMA

Jakubowiak et al. ASCO 2022, Abs 8014

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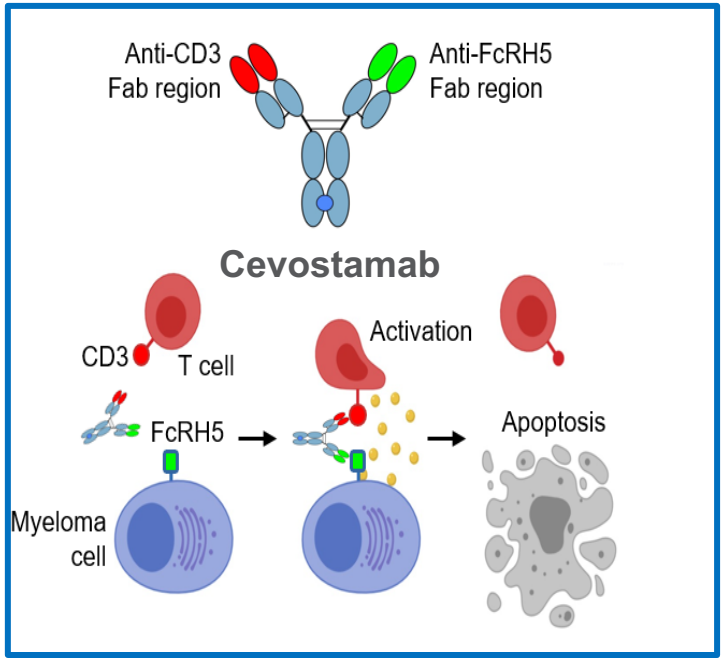
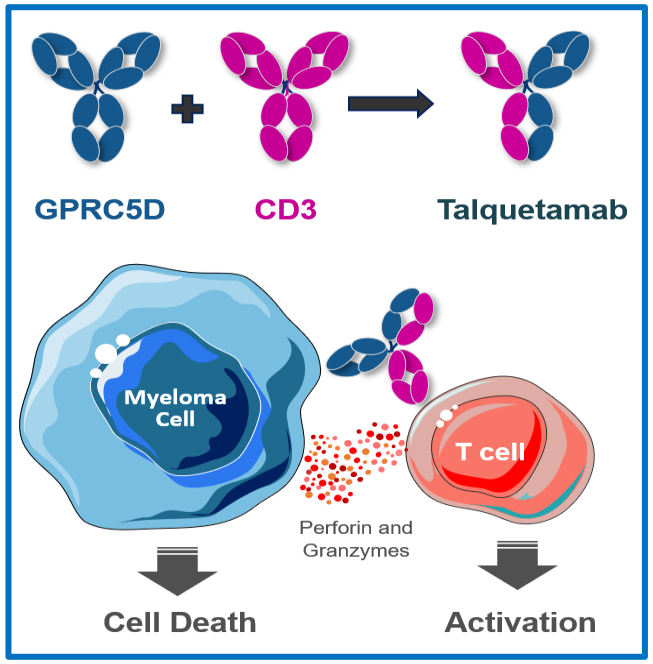
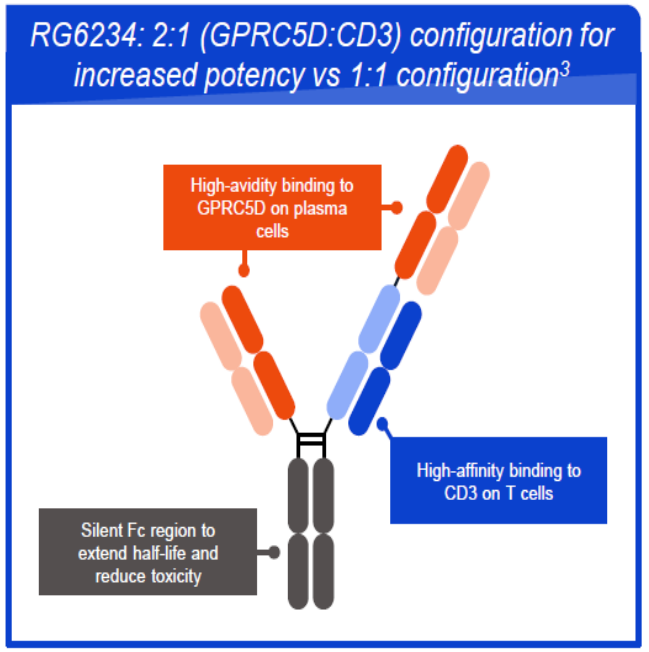
Non-BCMA Targets







FcRH5 – Fc Receptor-homolog 5

- **Expressed exclusively in B cell lineage**
- **Near ubiquitous expression on MM cells**

GPRC5D: G Protein-Coupled Receptor Class C Group 5 Member D

- **Orphan G protein-coupled receptor of unknown function**
- **Limited expression, primarily in plasma cells, skin and salivary glands**
- **Highly expressed in MM cells**

Li et al. Cancer Cell 2017;31:383–95. Sumiyoshi et al. EHA 2021. Smith Sci Transl Med 2019;11(485). Pillarisetti Blood 135(15):1232. Atamaniuk Eur J Clin Invest 42(9):953. Bacac Clin Cancer Res 2018;24:4785-97.

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Non-BCMA Bispecifics in Multiple Myeloma

	Cevostamab[1]	Talquetamab[2]	RG6234[3]
Target Study	FcRH5:CD3	GPRC5D:CD3 MonumenTAL-1	GPRC5D:CD3
Dose/Sched	0.15-198mg (Step up) IV q3wk x 17cycles	405mcg/kg SC qwk (step up)* 800mcg/kg SC q2wkw (step up)	6-10000 mcg IV q2w (Step up) 30-7200mcg SC q2wks
Population	161 (*60) Med LOT 6 85% triple refractory 33.5% prior BCMA	288 (143 + 145) Med LOT 5 74% triple refractory 27% and 16% prior BCMA	51 IV, 54 SC Med LOT 5,4 63%, 73% triple refractory 20%, 21% prior BCMA
Safety All grade (Grade 3+)	CRS 81% (1%) ICANS 14%(1%) Infections 45%(~20%)	CRS 79%(2%), 72%(1%) ICANS NR Infections 57%(19%), 50%(13%)	CRS 82%(2%), 79%(2%) ICANS 9%(2%) Infections 57% (20%), 37%(24%)
Response ORR (VGPR+)	57% (33%) @ 132-198mg* 63% prior BCMA	73%(58%)* Prior BCMA NR	71%(57%), 60%(40%) 56% prior BCMA
Misc	Treatment stops after 1 yr • Lesokhin. Poster 1924, Saturday • Trudel. Oral Abs 567 preemptive tocilizumab	*Response for 400 q wk dosing, 800 q 2wks at ASH - On target toxicity: Dysgeusia 48%, 46% Skin-related 56%,58% Nails 52%/43%	On target toxicity: GI/tongue 71%,74% Skin 72%, 81% Nails 17%, 22%

[1]Trudel et al. ASH 2021, Abs 157. [2]Chari et al. ASH 2022, Abs 157. [3]Carlo-Stella et al. ASH 2022, Abs 161.

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Bispecifics combinations

	MajesTEC-2[1]	MagnetisMM-5[2]	TRIMM-2[3]
Bispecific	teclistamab	elranatamab	talquetamab
Treatment	Tec 0.72 or 1.5mg/kg qwk + Dara + Len 25mg	Elra qwk x 6 cycles then q 2 wks + Dara	Talc 405 SC q1wk and 800 SC q2wk + Dara
Eligibility	1-3 LOT, inc PI/IMiD	≥ 3 LOT, inc PI/IMiD	≥ 3 LOT or double refractory PI/IMiD; prior anti-CD38 allowed
Population	32	28	29
# Prior Tx	2 (31% prior anti-CD38)	5 (18% triple refractory)	6 (79% prior anti-CD38)
ORR	90% (29 evaluable pts)	Will be presented	80%
≥VGPR	immature	Will be presented	67%
CRS All Grades (Grade 3/4)	81%(0) -med TT onset 2 days	50%(0) -med TT onset 2 days	55%(0%) -med TT onset 12-24h
Other Tox	ICANS 0 Neutropenia 75%(69%) Infections* 75%(28%)	ICANS 0 Neutropenia 29% (28%)	Neutropenia 41%(31%) Dysgeusia 48%
Notes	*URI, pneumonia, COVID Phase 3 MajesTEC-7 planned	Part 2: Ph3 randomized - elra mono, elra+dara or elra+dara+pom	-55% prior BCMA Rx

[1]Searle et al. ASH 2022, Abs 160. [2]Grosicki et al. ASH 2022, Abs 1921. [3]Chari et al. ASH 2021, Abs 161.

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Sampling of Future Directions – TIP @ ASH 2022

- Teclistamab
  - MajesTEC-4 (Zamagni. Poster 3242, Sun Dec 11)
    - Phase 3 Tec/Len v Len as maintenance post ASCT
  - MajesTEC-7: (Krishnan. Poster 4558, Mon Dec 12)
    - Phase 3 Tec/Dara/Len vs DRd in NDTIE pts
- Elranatamab
  - MagnetisMM-4: (Landgren. Poster 4567, Mon Dec 12)
    - Phase 1b multicohort study, currently 2 cohorts
    - Cohorts: Elranatamab +nirogacestat or Elranatamab+Len/dex
- Abbv-383
  - Combination (Rodriguez. Poster 3257. Sun, Dec 11)
    - Phase Ib multicohort study, currently 4 planned
    - Cohorts: Abbv-383 + pom/dex or len/dex or dara/dex or nirogacestat
- Linvoseltamab (REGN5458)
  - Phase Ib multcohort study, currently 4 planned (Rodriguez Otero. Poster 1936. Sat, Dec 10)
    - Cohorts: Linvo+Dara; Linvo+Carfilz; Linvo+Len; Linvo+Btz
  - Phase II study of linvoseltamab monotherapy or as induction/consolidation with ASCT (Ferreri. Poster 4551. Mon, Dec 12)
    - Patient population: NDMM both transplant eligible and ineligible
- Talquetamab
  - MonumenTAL-3 (Cohen. Poster 1925, Sat, Dec 10)
    - Phase 3, 3 arm study of Talq+Dara vs talq+Dara+Pom vs DaraPomDex
    - Patient Population: RRMM ≥1 prior LOT, including PI and IMiD

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Take Home Message

- Several BCMA:CD3 bispecifics showing impressive, durable responses
  - Teclistamab is the first to be FDA-approved
- New targets beyond BCMA
  - GPRC5D and FcRH5
- Safety profile appears similar across all studies
  - Nearly all CRS events were grade 1–2 and generally confined to first step-up and full doses
  - Infections are a concern and need to be monitored closely, consider prophylaxis
- Combination studies ongoing
- Unlike autologous CAR T, these are off-the-shelf