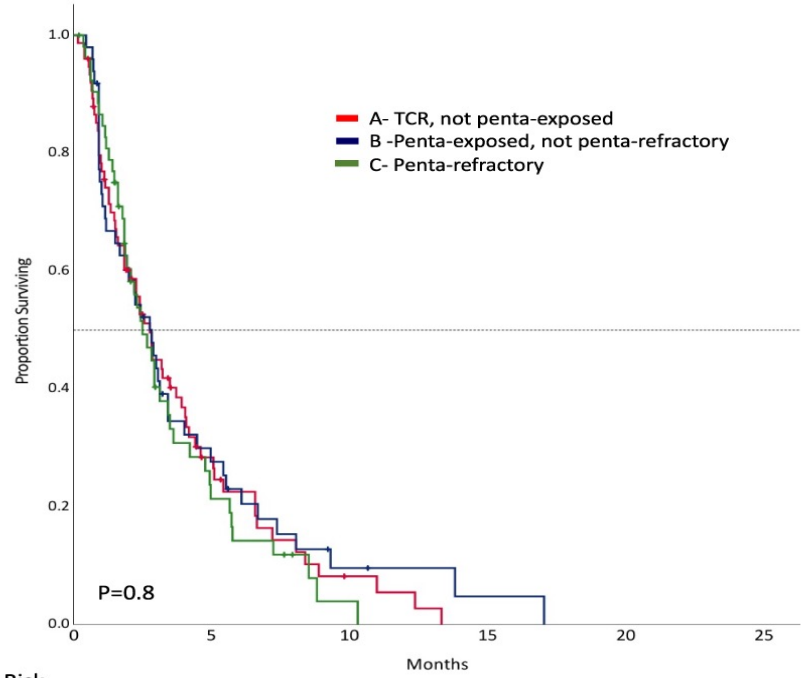
Other Approved and Investigational BCMA-Targeted Strategies for RRMM

Peter Voorhees, M.D.
Professor of Medicine
Levine Cancer Institute, Atrium Health
Charlotte, NC

Triple-Class Refractory Multiple Myeloma

- Retrospective trial of patients with RRMM refractory to a CD38 mAb, a PI and an IMiD
- N = 177
- Median time from diagnosis: 4.8 years
- Median prior lines of therapy: 5 (3 – 17)
- Median PFS: 2.8 months (95% CI 2.3 – 3.2)
- Median OS: 8.6 months (95% CI 6.8 – 10.3)

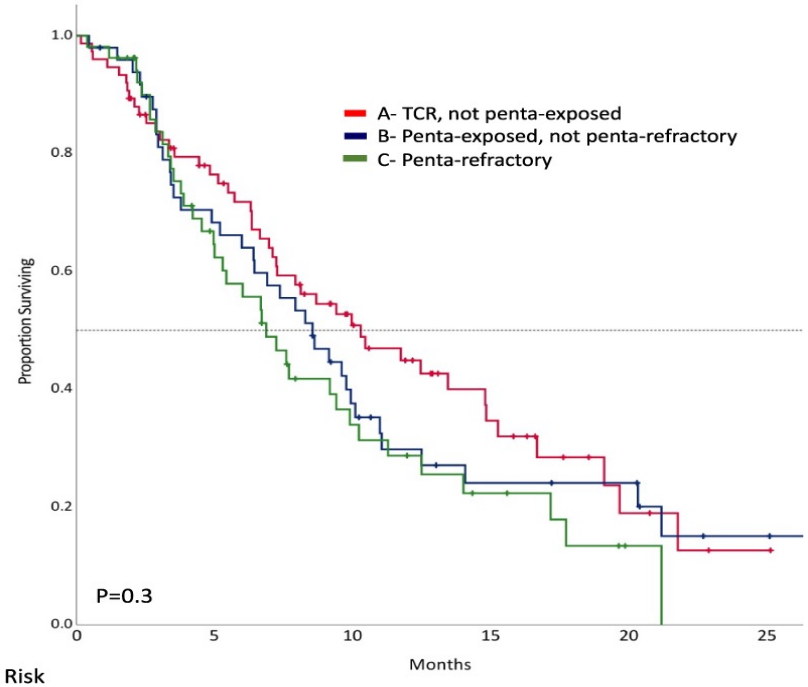
Progression-Free Survival



No. at Risk

A	75	15	3	0	0	0
B	49	12	3	1	0	0
C	53	9	1	0	0	0

Overall Survival

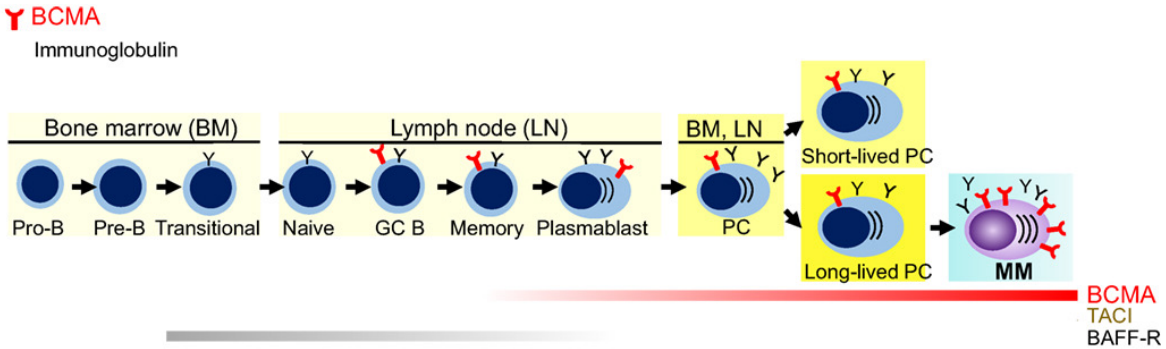


No. at Risk

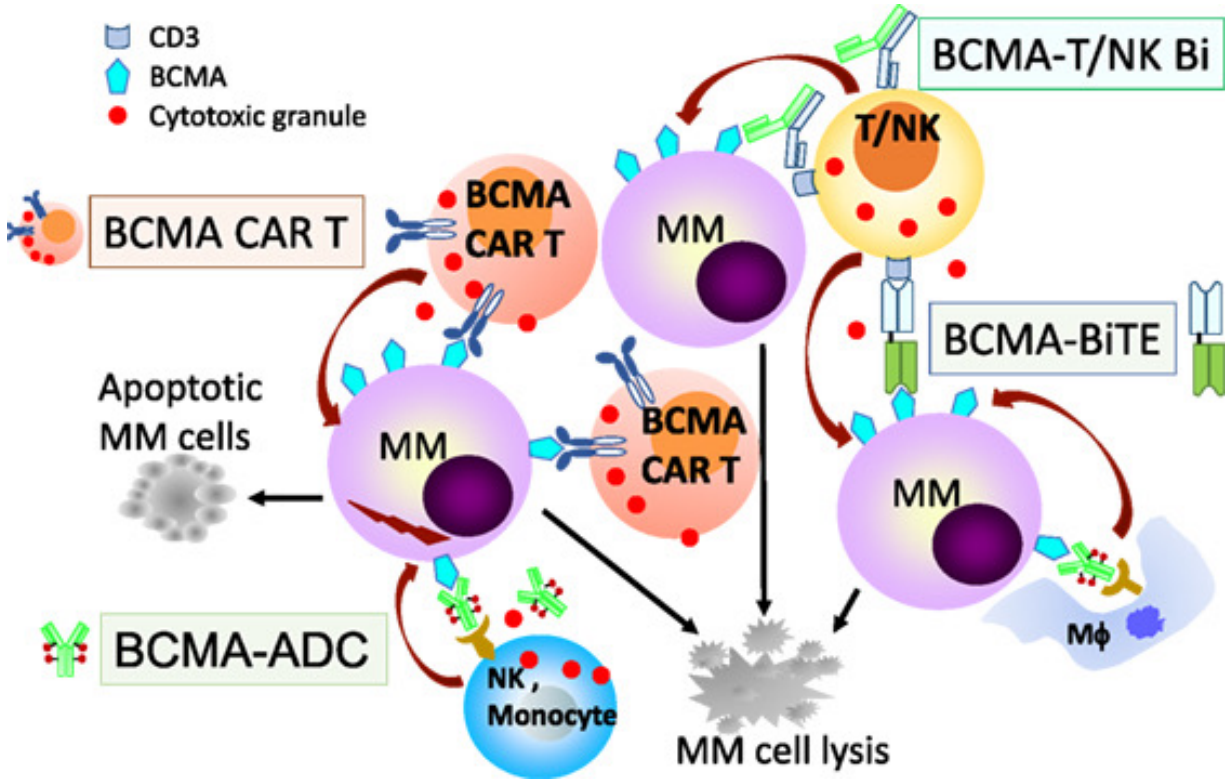
A	75	50	13	4	1	0
B	49	32	8	7	2	1
C	53	29	6	1	0	0

Bal, S et al. Leukemia 2021;Epub ahead of print.

BCMA in Multiple Myeloma



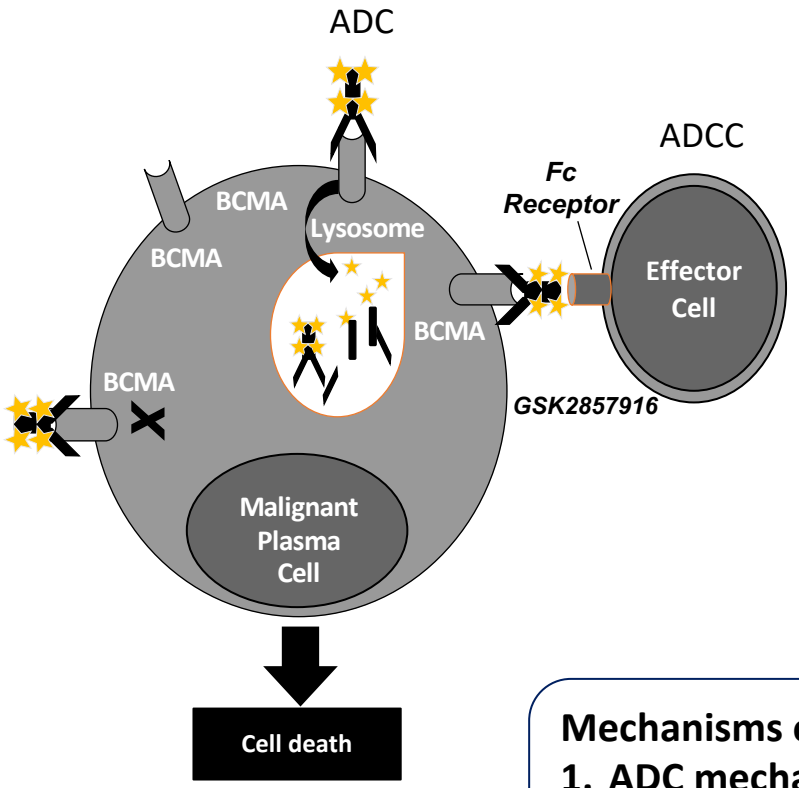
- **Expressed on late memory B cells committed to PC differentiation and PCs**
- **BCMA is critical for survival of long-lived PCs**
- **γ-secretase cleaves BCMA from the cell surface, yielding soluble BCMA**



Cho SF et al. Front Immunol 2018;10:1821

Belantamab Mafodotin (GSK285916): a BCMA-Targeted Antibody Drug Conjugate

- **Belantamab Mafodotin**
  - **Humanized, afucosylated IgG1 anti-BCMA antibody**
  - **Conjugated to the microtubule disrupting agent MMAF via a stable, protease resistant linker**



Fc region of the Antibody	**–Target specific** **–Enhanced ADCC**
Linker	**–Stable in circulation**
Drug	**–MMAF (non cell permeable, highly potent auristatin)**

Mechanisms of Action:
1. **ADC mechanism**
2. **ADCC mechanism**
3. **Immunogenic cell death**

ADC, antibody-drug conjugate; ADCC, antibody-dependent cell-mediated cytotoxicity; BCMA, B-cell maturation antigen; Fc, Fragment crystallizable; IgG, immunoglobulin G; MMAF, monomethyl auristatin-F

Tai YT, et al. Blood 2014;123(20):3128-38.

DREAMM-2: Phase II Trial of Belantamab Mafodotin in Relapsed / Refractory Multiple Myeloma

- **Randomized, phase II trial of 2.5 vs 3.4 mg/kg of belantamab mafodotin q3 wks until PD**
- **Key eligibility criteria: ≥3 prior therapy lines, PI/IMiD refractory, CD38 mAb refractory/intolerant, ECOG PS 0 – 2, CrCl ≥30 mL/min**
- **Baseline characteristics 2.5 mg/kg cohort: 43% ISS stage 3 MM, 42% HRCGs (27% per IMWG criteria), EMD 23%, median therapy lines 7 (3 – 21). 100% triple refractory (65%, 87% and 100% refractory to carfilzomib, pomalidomide and dara, respectively)**

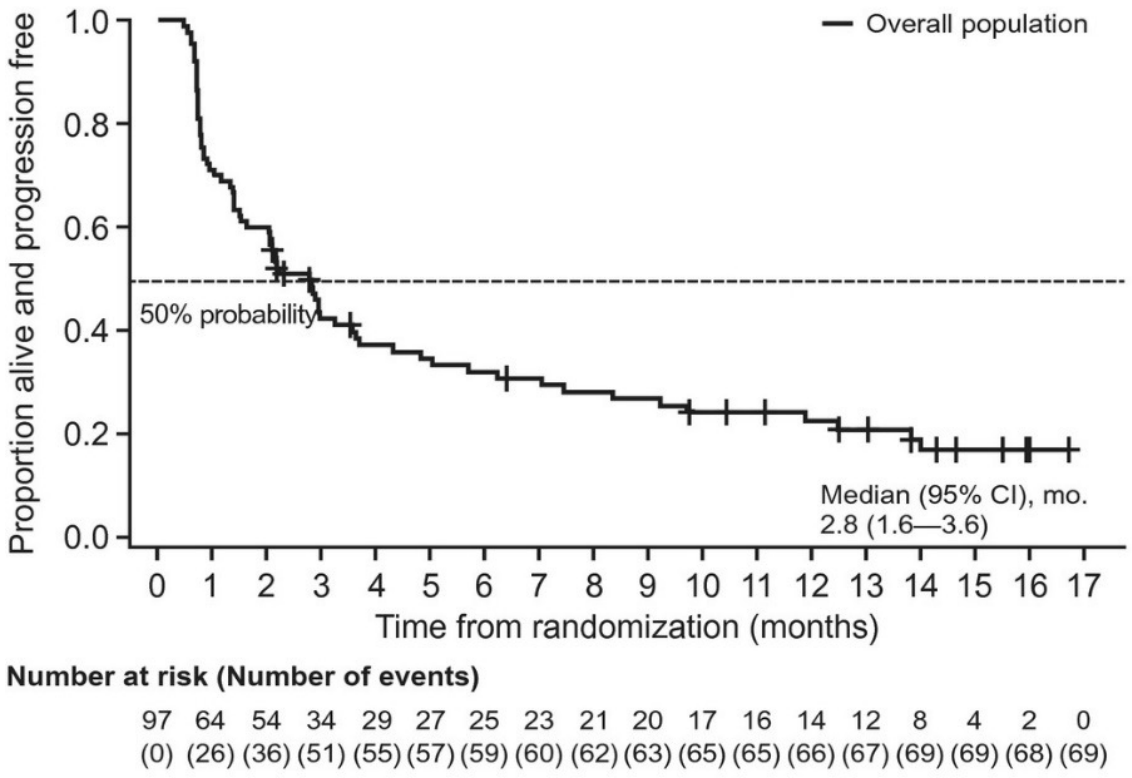
	2.5 mg/kg (N = 97)	3.4 mg/kg (N = 99)
ORR (%)	**31**	**35**
sCR	**2**	**2**
CR	**5**	**3**
VGPR	**11**	**18**
PR	**13**	**12**
MR	**4**	**5**
CBR	**36**	**40**
Median DoR, mos (95% CIs)	**11.0 (4.2 – NR)**	**6.2 (95% CI 4.8 – NR)**

- Responses seen regardless of age, level of renal impairment, presence of high-risk CGs, # of prior lines of therapy or drug class refractoriness
- Patients with EMD did not respond well (2 of 22 pts at 2.5 mg/kg dose)
- Trend towards inferior responses with ISS stage 3 disease at screening

Lonial, S et al. Lancet Oncol 2020;21:207-21

DREAMM-2: Longitudinal Outcomes

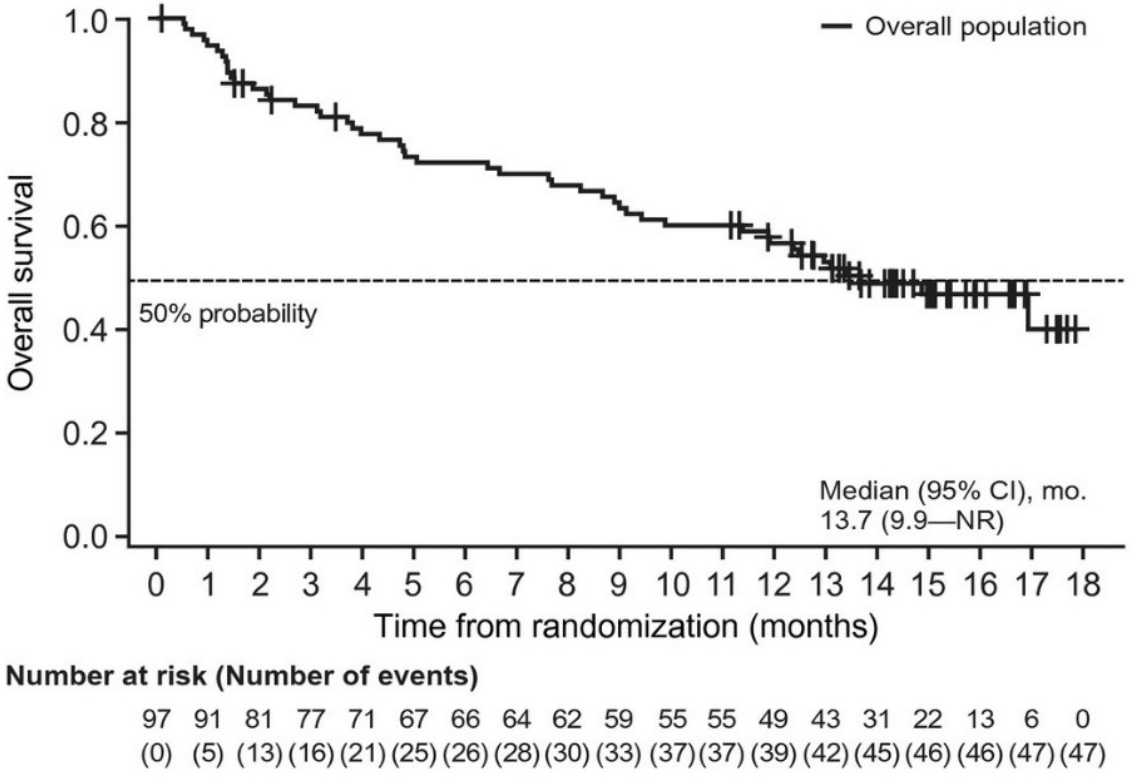
Progression-Free Survival



Number at risk (Number of events)

97	64	54	34	29	27	25	23	21	20	17	16	14	12	8	4	2	0
(0)	(26)	(36)	(51)	(55)	(57)	(59)	(60)	(62)	(63)	(65)	(65)	(66)	(67)	(69)	(69)	(68)	(69)

Overall Survival



Number at risk (Number of events)

97	91	81	77	71	67	66	64	62	59	55	55	49	43	31	22	13	6	0
(0)	(5)	(13)	(16)	(21)	(25)	(26)	(28)	(30)	(33)	(37)	(37)	(39)	(42)	(45)	(46)	(46)	(47)	(47)

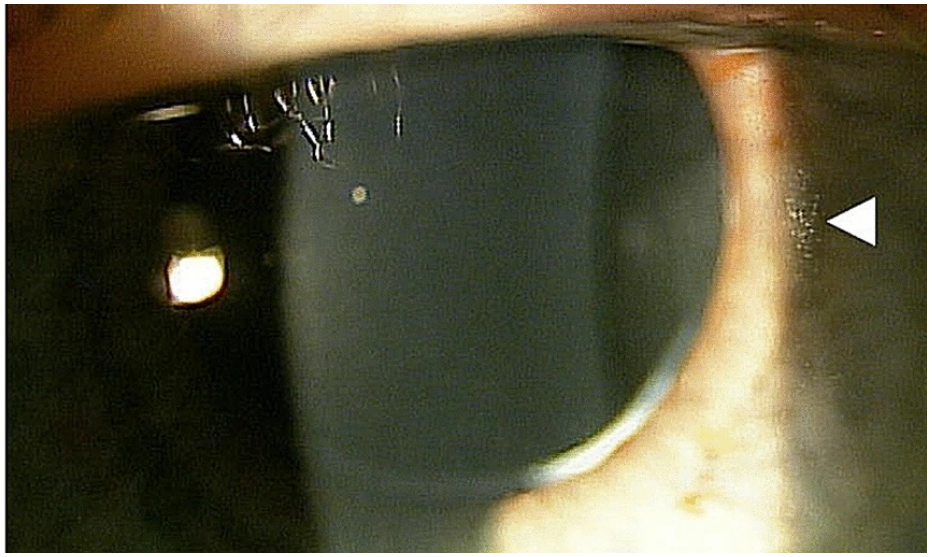
Expected median OS in triple-class refractory myeloma: 8.6 months

Lonial, S et al. Cancer 2021; Online ahead of print.

DREAMM-2: Safety

AE of any grade in ≥15% or ≥Gr3 in ≥5% of pts (%)	All Grades	≥Grade 3
Keratopathy	72	46
Change in BCVA	54	31
Blurred vision	25	4
Dry eyes	15	1
Thrombocytopenia	38	22
Anemia	27	21
Neutropenia	15	11
Nausea	25	0
AST increased	21	2
Fatigue	16	2
IRR	21	3

- 18% had a change of BCVA to 20/50 or worse in their better eye at some point in their treatment course.
- 82% had recovered as of last follow-up



Microcystic epithelial changes on slit lamp examination

Farooq, AV et al. Ophthalmol Ther 2020;9:889-911.
Lonial, S et al. Cancer 2021; Online ahead of print.

Corneal Events: Mitigation Strategy

- Corticosteroid eye drops are not beneficial for prophylaxis or treatment
- Lubricating eye drops ≥4 times per day throughout duration of the treatment period
- No contact lens use during treatment period
- Eye examination with BCVA assessment and slit lamp examination with fluorescein staining prior to each planned dose
- Dose delays and dose reductions per recommendations

Lonial, S et al. Blood Cancer J 2021;11:103.

Belantamab Mafodotin Dose Modifications for Corneal Toxicity

Eye Findings per KVA Scale		Recommended Dose Modifications
Grade 1	Corneal Exam Finding(s)	Continue treatment at the current dose
	• Mild superficial keratopathy	
	Change in BCVA	
	• Decline from baseline of 1 line on the Snellen Visual Acuity	
Grade 2	Corneal Exam Finding(s)	Withhold treatment until improvement in both corneal examination findings and changes in BCVA to Grade 1 or better and resume at same dose
	• Moderate superficial keratopathy	
	Change in BCVA	
	• Decline from baseline of 2 or 3 lines (and Snellen Visual Acuity not worse than 20/200)	
Grade 3	Corneal Exam Finding(s)	Withhold treatment until improvement in both corneal examination findings and changes in BCVA to Grade 1 or better and resume at a reduced dose
	• Severe superficial keratopathy	
	Change in BCVA	
	• Decline from baseline by more than 3 lines (and Snellen Visual Acuity not worse than 20/200)	
Grade 4	Corneal Exam Finding(s)	Consider treatment discontinuation for a Grade 4 event. Based on a benefit:risk assessment, if continuing treatment with belantamab mafodotin is being considered, treatment may be resumed at a reduced dose after the event has improved to Grade 1 or better
	• Corneal epithelial defect	
	Change in BCVA	
	• Snellen Visual Acuity worse than 20/200	

- Mild Keratopathy: Non-confluent MECs, ≥80% involving the cornea periphery
- Moderate Keratopathy: Semi-confluent MECs, ≥80% in the paracentral cornea
- Severe Keratopathy: Confluent MECs, ≥80% in the corneal center

Farooq, AV et al. Ophthalmol Ther 2020;9:889-911. Lonial, S et al. Blood Cancer J 2021;11:103.

Belantamab Mafodotin in Combination with Pomalidomide and Dexamethasone

- **Phase I dose-escalation and dose-expansion trial of belantamab mafodotin + pomalidomide and dexamethasone**
  - Dose levels and schedules for belantamab: 1.92 mg/kg single dose (n = 12), 2.5 mg/kg single dose (n = 7), 2.5 mg/kg loading dose (n = 5), 2.5 mg/kg split dose (n = 6), and 3.4 mg/kg split dose (n = 5)
- **Key eligibility criteria**: ≥2 prior therapy lines, Len/PI-exposed and refractory to last line; ECOG PS 0 – 2, CrCl ≥30 mL/min
- **Baseline characteristics:** median prior regimens: 3; prior ASCT: 68.6%, prior PIs: 100% (80% refractory), prior lenalidomide: 100% (88.6% refractory), and 45.7% prior daratumumab (100% refractory)

Response (%)	Pts (n = 29)
ORR	**25 (86.2)**
• **sCR**	**4 (13.8)**
• **CR**	**0**
• **VGPR**	**15 (51.7)**
• **PR**	**6 (20.7)**

- Median follow-up: 6 months

Additional dosing schedules of belantamab mafodotin being tested in additional dosing schedule cohorts of every 8 and 12-weeks.

Trudel, S et al. ASH 2020.

Belantamab Mafodotin in Combination with Bortezomib and Dexamethasone

- **Phase I dose-escalation and dose-expansion trial of belantamab mafodotin + bortezomib and dexamethasone**
  - Escalation Phase: belantamab: 2.5 mg/kg single dose (n = 6), 3.4 mg/kg single dose (n = 6)
  - Expansion Phase: 2.5 mg/kg single dose, 2.5 mg/kg split dose, and 3.4 mg/kg single dose, 3.4 mg/kg split dose
- **Key eligibility criteria**: ≥1 prior therapy lines, bortezomib naïve / sensitive
- **Baseline characteristics:** median prior regimens: 3 (1 – 11); 33% high-risk cytogenetics

Outcomes at 2.5 mg/kg single dose

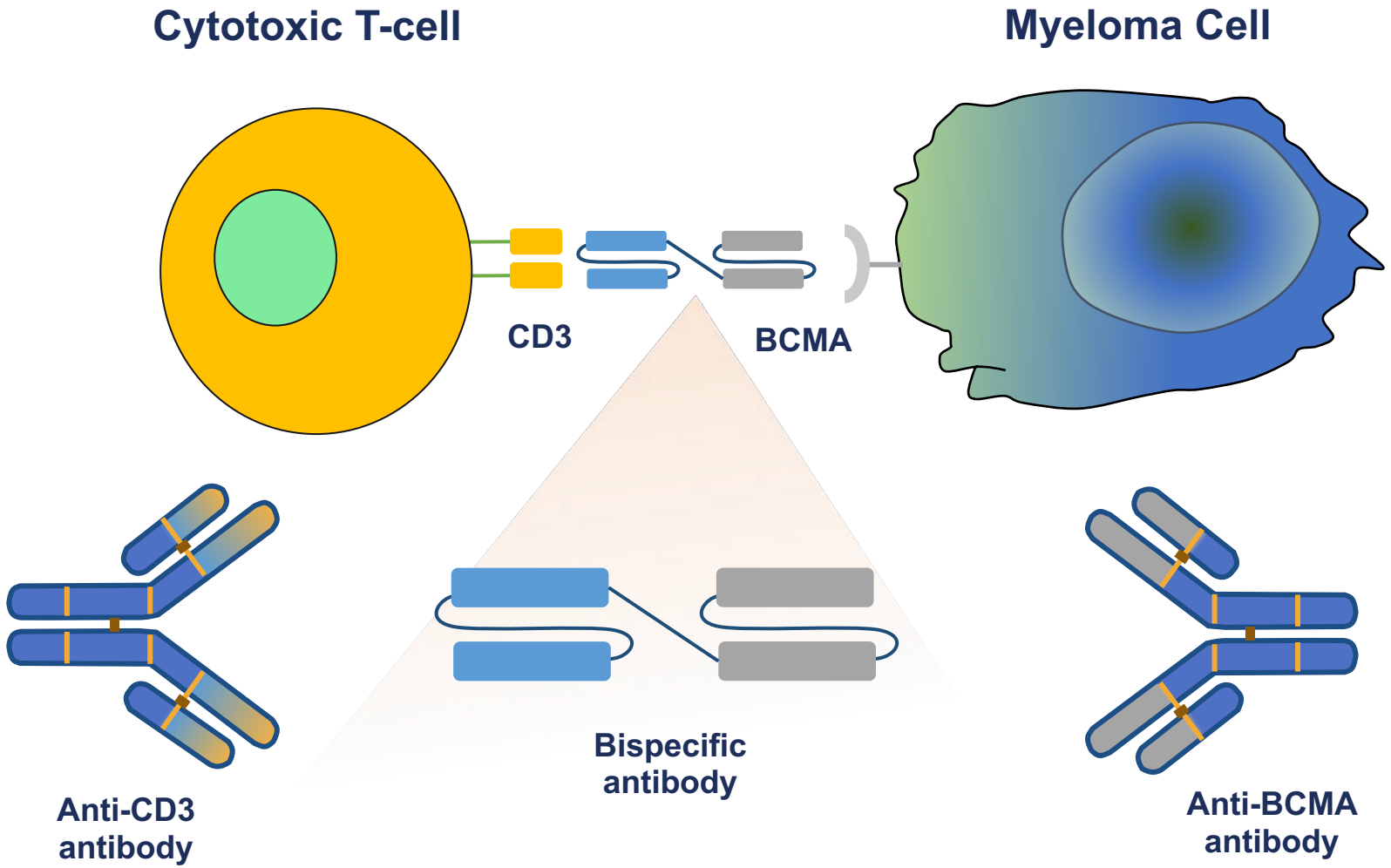
Response (%)	Pts (n = 18)
ORR	**14 (78)**
• **sCR / CR**	**0 (0)**
• **VGPR**	**9 (50)**
• **PR**	**5 (28)**

- Grade 2 and 3 keratopathy seen in 7 and 10 patients
- Grade 3 and 4 thrombocytopenia seen in 3 and 8 patients
- AEs leading to dose reduction: 72%
- AEs leading to dose delay / interruption: 100%

Additional belantamab mafodotin dosing schedules being evaluated

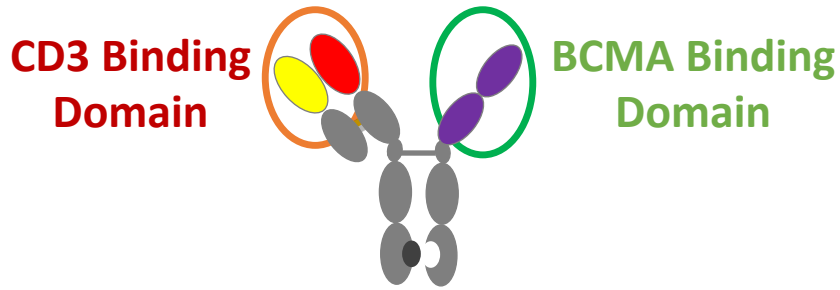
Nooka, A et al. ASCO 2020.

Bispecific Monoclonal Antibodies

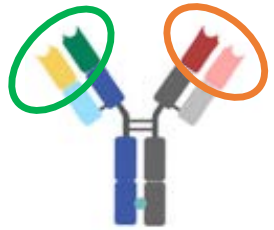


Phase I/II BCMA Bispecific mAb Studies

	TNB-383B	SC Elranatamab	SC Teclistamab
Technology	Novel αCD3 binding moiety		Duobody
BCMA Binding Domains	2	1	1
Dosing	3-Wk cycles 1 – 2-Hr IV infusion every 3 weeks	80 – 1000 mcg/kg SC weekly until PD	1500 mcg/kg SC weekly until PD
Step Up Dosing	No	No	Yes (Priming dosing week -1)
Key Eligibility Criteria	RRMM, ≥3 prior lines, ≥1 PI, ≥1 IMID, ≥1 CD38 mAb, ECOG PS 0 - 2	RRMM, prior PI / IMiD / CD38 mAb, ECOG PS 0 – 1 (PS 2 if MM-related) Prior BCMA-directed therapy allowed	RRMM, refractory or intolerant to available therapy, including ≥1 PI and ≥1 IMID, ECOG PS 0 - 1



NCT03933735



NCT03269136

NCT03145181

BCMA Bispecific mAb Studies: Baseline Characteristics

	TNB-383B	SC Elranatamab	SC Teclistamab 1500 mcg/kg
N Treated	58	30	40
Median Age	66 (37 – 88)	63 (46 – 80)	62.5 (39 – 84)
High Risk CGs	NR	23% (incl del[13q])	37%
EMM	NR	NR	20%
Median Lines of Prior Therapy	6 (3 – 15)	Regimens: 8 (3 – 15)	5 (2 – 11)
Triple Class Refractory	64%	86.7%*	83%

*7 patients treated with prior BCMA-directed therapy: 6 with ADCs, 3 with CAR T

Rodriguez, C et al. ASH 2020

Bahlis, N et al. ASCO 2021 **Krishnan, A et al. ASCO 2021**

BCMA Bispecific mAb Studies: Efficacy

	TNB-383B	SC Elranatamab	SC Teclistamab
Dose	**≥40 mg**	**≥215 mcg/kg**	**1500 mcg/kg**
Sample Size	**15**	**20**	**40**
Response Rate			
ORR	**80%**	**70%***	**65%**
≥CR	**13.3%**	**40%**	**40%**
Duration of Response (DoR)	**22 of 27 ongoing**	**6-mo DoR: 92.3%**	**22 of 26 ongoing**

*3 of 4 BCMA-directed therapy exposed pts responded: 2 VGPRs and 1 sCR

Rodriguez, C et al. ASH 2020

Bahlis, N et al. ASCO 2021 **Krishnan, A et al. ASCO 2021**

BCMA Bispecific mAb Studies: Safety

	TNB-383B ≥40 mg	SC Elranatamab ≥215 mcg/kg	SC Teclistamab 1500 mcg/kg
Cytokine Release Syndrome			
All Grades	80%	90%	70%
Grade 1 / 2	46.7% / 33.3%	70% / 20%	45% / 25%
Grade 3 / 4 / 5	0%	3.3%	0%
Neurotoxicity			
All grades	1 patient with confusion, grade 3	6 patients with ICANS	1 patient
Grade 3 / 4 / 5	--	0%	0%

Rodriguez, C et al. ASH 2020

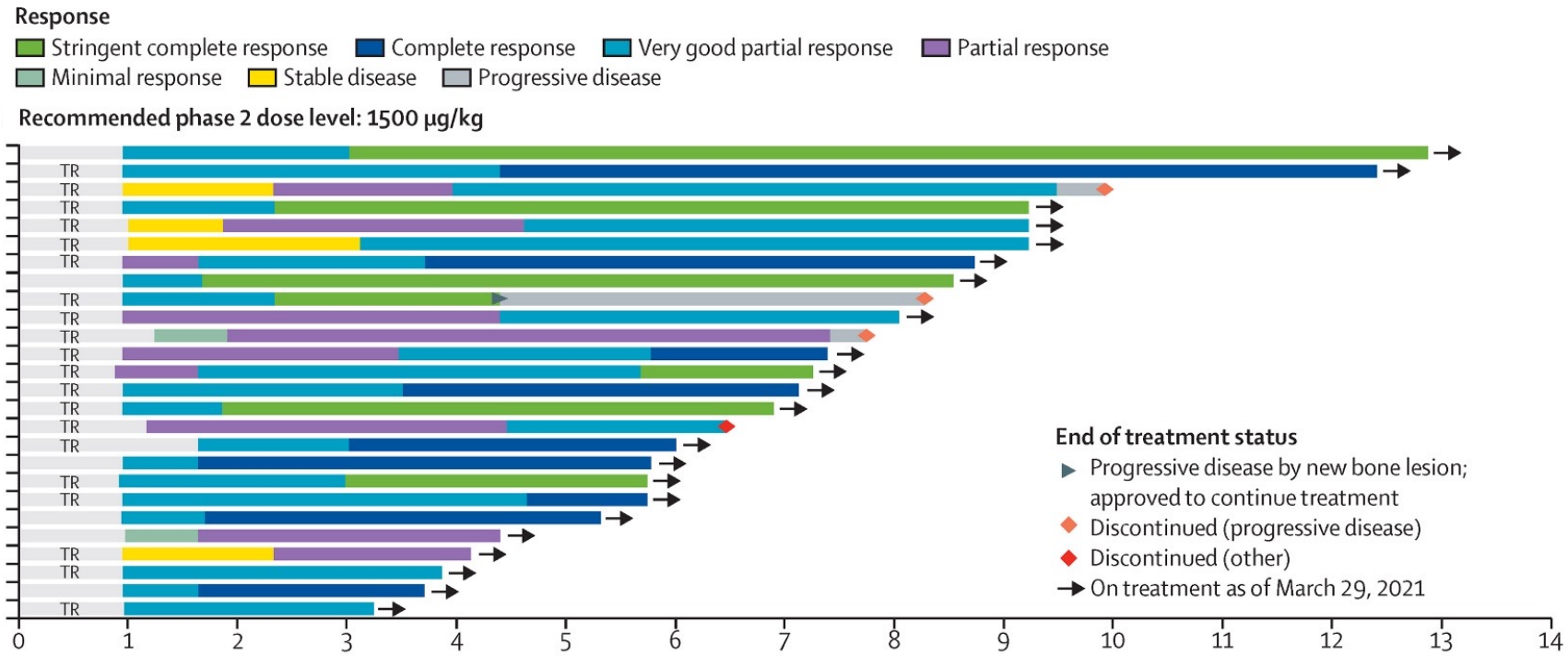
Bahlis, N et al. ASCO 2021 Krishnan, A et al. ASCO 2021

MajesTEC-1: A Phase I Study of Teclistamab in RRMM

Teclistamab: A BCMA-targeted bispecific IgG4 mAb
Baseline characteristics: median prior regimens: 5 (4-6); high-risk cytogenetics: 37%; extramedullary disease: 20%; triple refractory: 83%.

Response at RP2D (%)	N = 40
ORR	65%
sCR	18%
CR	23%
VGPR	18%
PR	8%

69% of CR/sCR patients MRD-



- CRS at RP2D: 70% (0% ≥Grade 3)
- 1 patient with grade 1 neurotoxicity at the RP2D

Usmani S et al. Lancet 2021;398:665-74.

Other Targets for Bispecific mAb Therapy

BCMA BsAbs	Phase of study	NCT#
AMG701	Phase I	NCT03287908
PF-06863135	Phase I	NCT03269136
REGN5458	Phase I/II	NCT03761108
TNB-383B	Phase I	NCT03933735
RO7297089	Phase I	NCT04434469

Novel BsAb	Target	Phase of study	NCT#
Talquetamab	GPRC5D	Phase I	NCT03399799
GBR-1342	CD38	Phase I	NCT03309111
Cevostamab	FcRH5	Phase I	NCT03275103

Conclusions

- Immunotherapy for myeloma is here
- The BCMA-targeted ADC belantamab mafodotin affords access to effective therapy for patients with triple refractory disease
  - Median DoR of 11 months comparable to that seen with idecabtagene vicleucel
  - Requires vigilant management of corneal toxicities
  - Best path forward in combination therapy utilizing less frequent dosing schedules
- BCMA-targeted bispecific mAb therapy demonstrating significant promise
  - ORRs ~60 – 80% with high rates of ≥VGPRs
  - Durability of responses evolving
  - Manageable CRS and neurotoxicity to date
  - As an off-the-shelf product, they represent an attractive alternative to CAR T cell therapy
  - Studies with SoC MM regimens and other I/O agents ongoing and planned

- Thanks to our patients, investigators and other members of the research team at Levine Cancer Institute

Atrium Health
Levine Cancer Institute