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Role of Immunotherapies in Relapsed Multiple Myeloma: When? Which?

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Disclosures

- Research funding: Amgen, Array Biopharma, BMS, Celgene, GSK, Janssen, Merck, Pharmacyclics, Sanofi, Seattle Genetics, SkylineDX, Takeda.
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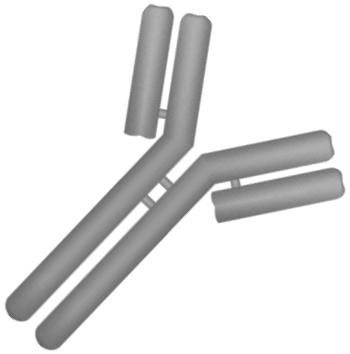
- Speaker: Amgen, BMS, Janssen, Sanofi.

Types of Antibodies

Naked



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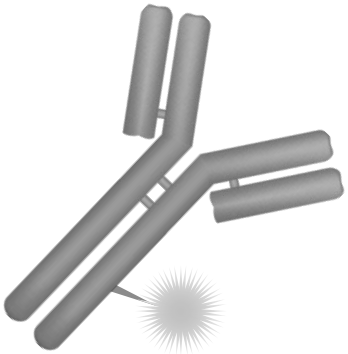
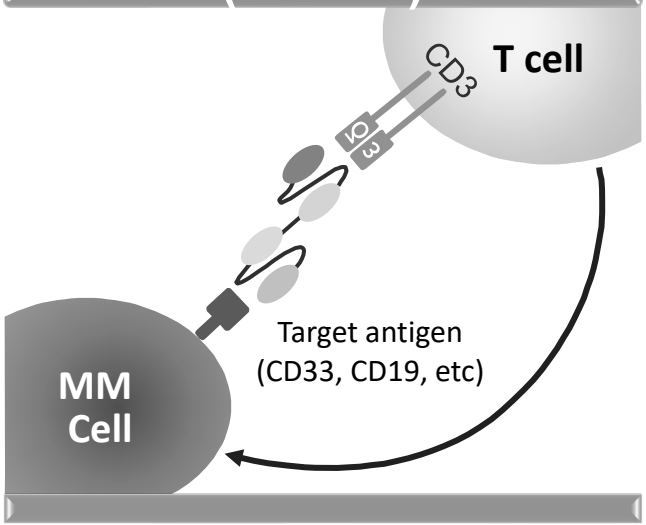
Antibody Drug Conjugates (ADC)



A toxin or radioactive isotope is attached

Bispecific Antibodies (BsAbs)



Engineered so that one end binds to MM cell, the other end binds to T cell

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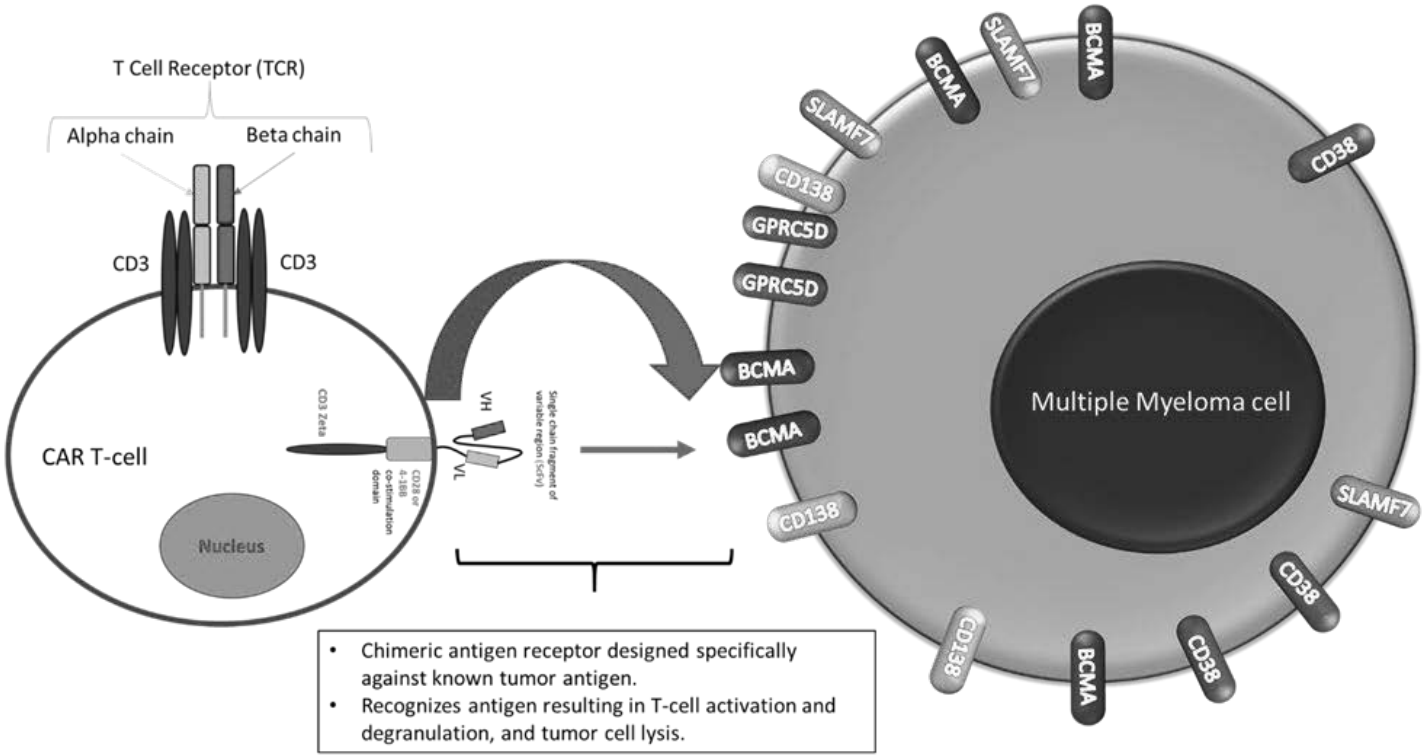
Chimeric Antigen T-Cell Receptor Therapy



- Chimeric antigen receptor designed specifically against known tumor antigen.
- Recognizes antigen resulting in T-cell activation and degranulation, and tumor cell lysis.

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor

Usmani S, personal communication

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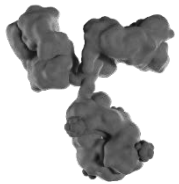
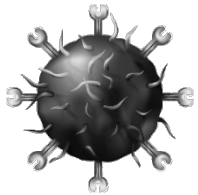
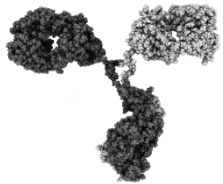
Focus of This Talk

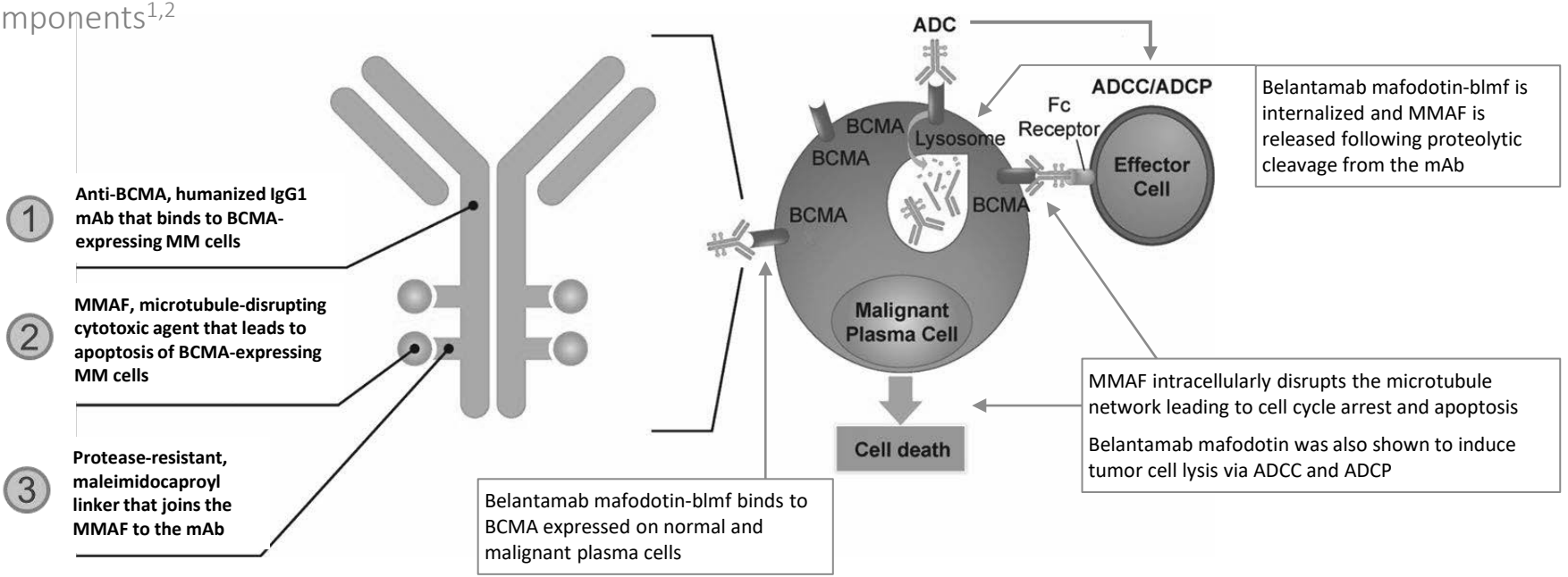
BCMA-targeting modalities

	Antibody-drug conjugate	T-cell activating strategies	
		CAR T-cell therapy	Bispecific antibody
			
Examples:	belantamab mafodotin	Ide-cel (bb2121) Cilta-cel	Teclistamab AMG701

BCMA, B-cell maturation antigen; CAR, chimeric antigen receptor.
Cho SF et al. *Front Immunol.* 2018;9:1821. doi:10.3389/fimmu.2018.01821.

Belantamab Mafodotin (Bela-maf)

Belantamab mafodotin-blmf is a BCMA-directed antibody and microtubule inhibitor conjugate, composed of 3 components[1,2]



1. Tai Y-T, et al. *Blood*. 2014;123(20):3128–3138. 2. Farooq A, et al. *Ophthalmol Ther*. 2020 July 25. doi: 10.1007/s40123-020-00280-8.

ADC, antibody-drug conjugate; ADCC, antibody-dependent cellular cytotoxicity; ADCP, antibody-dependent cellular phagocytosis; BCMA, B-cell maturation antigen; Fc, fragment crystallizable; IgG1, immunoglobulin G1; mAb, monoclonal antibody; MM, multiple myeloma; MMAF, monomethyl auristatin F.

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Bela-maf: Clinical Summary (I)

- Lessons from DREAMM2 Monotherapy Randomized Phase II Trial (Compared 2.5 mg/kg vs 3.4 mg/kg dosing):
  - 2.5 mg/kg: ORR 32%, median PFS 2.8 months, median DOR 11 months, median OS 13.7 months
  - Keratopathy: 71% all grade, 44% grade 3-4
  - Among pts with grade ≥2 keratopathy (N=60) :
    - Median time to onset of first occurrence was 37 days (range, 19-147 days)
    - Median duration of first event was 86.5 days (range, 8-358 days)
    - Most patients (77%) recovered from first occurrence[a,b]
  - Decreased visual acuity: 53% all grade, 28% grade 3-4
  - Best corrected visual acuity (BCVA) change ≥20/50: 18%
  - Among pts with a clinically meaningful change in BCVA of 20/50 or worse in the better-seeing eye (N=17)[c]:
    - Median time to onset of first occurrence was 66 days (range, 20-442 days)
    - Median time to resolution of first occurrence was 22 days (range, 7-64 days)d
    - Most patients (82%) recovered as of last assessment[d]

[a] Represents patients with events that recovered either prior to end of tx or after the end of study tx; recovery was defined as any grade 1 exam finding or no exam finding compared with baseline. [b]Lost to follow-up (n=4), withdrew (n=4), or died (n=9). After follow-up ended for some pts, no more data were available so it is not possible to say if their corneas recovered or not. [c]Better than 20/50 at baseline and 20/50 or worse postbaseline. [d]Recovery was defined as 20/40 or better in the better-seeing eye. After follow-up ended for some pts, no more data were available, so it is not possible to say if their eyesight recovered or not.

1. Farooq AV, et al. *Ophthalmol Ther.* 2020;9(4):889-911. 2. Lonial S, et al. Presented at ASH 2020. Abstract #3224.

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Bela-maf: Clinical Summary (II)

Lessons from DREAMM6 Combination Therapy Phase I Trial (Bela-maf + Bortezomib/Dex):

	Belantamab Mafodotin 2.5 mg/kg SINGLE + Vd (N=18)
Age, median (range), y	67 (47-83)
ISS Stage I/II/III/Unknown, %	22/44/17/17
ECOG PS, n (%) 0-1 2	15 (83) 3 (17)
High-risk cytogenetics, n (%)*	5[†] (28)
Extramedullary disease, n (%)	5 (28)
Prior lines of therapy, median (range)	3 (1-11)
Prior bortezomib therapy, n (%)[‡]	16 (89)
Prior daratumumab therapy, n (%)	9 (50)

[b] t(4;14), t(4, 16) or del17p13, data were not available for 6 pts
[c] Cytogenetics data were not available for 6 patients
[d] Bortezomib refractory status was not collected systematically

Efficacy	Total (n=18)	Prior Bor (n=16)	Prior Dara (n=9)
ORR, % [95% CI]	78 [52.4-93.6]	75 [47.6-92.7]	67 [29.9-92.5]
sCR, %	6	Not reported	Not reported
VGPR, %	61		
PR, %	11		
CBR (≥MR), % [95% CI]	83 [58.6-96.4]	81 [54.4-96.0]	67 [29.9-92.5]
≥VGPR, %	67	63	44

- Part 1 (dose escalation) and Part 2 (dose expansion) of **Arm B** evaluated belantamab mafodotin (2.5 and 3.4 mg/kg IV Q3W) administered as SINGLE (Day 1) or SPLIT dose (divided equally on Days 1 and 8) **+ Vd**[a].
- Combination treatment continued for up to 8 cycles, with single-agent belantamab mafodotin maintenance therapy thereafter

[a] Bortezomib 1.3 mg/m [2] SC and dexamethasone 20 mg IV or orally

AESI, %	Any Grade	Grade ≥3[†]
Keratopathy	100	61
Thrombocytopenia	78	67
Blurred vision	67	28
Peripheral neuropathy	33	0
Dry eye	22	0
IRR	17	0

No patients permanently discontinued belantamab mafodotin treatment, and all keratopathy events were manageable with dose reductions/delays.

Popat R, et al. Presented at ASH 2020. Abstract 1419. AE, adverse event; AESI, adverse event of special interest; IRR, infusion-related reaction; MEC, microcyst-like epithelial change

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Bela-maf: Clinical Summary (III)

Lessons from the ALGONQUIN Phase I Study (Bela-maf + Pomalidomide/Dex):

	N=37
Age, years; median (range)	64 (36-81)
ISS Stage I/II/III, %	46/43/3
High-risk cytogenetics, n/N (%)[b]	9/19 (47%)
Number of prior lines of therapy, median (range)	3 (1-5)
Autologous Stem Cell Transplant	24 (64.9%)
Lenalidomide exposed **Lenalidomide refractory**	37 (100%) 33 (89.2%)
PI exposed Bortezomib Carfilzomib **PI refractory**	37 (100%) 36 (97.3%) 13 (35.1%) 30 (81.1%)
Daratumumab exposed **Daratumumab refractory**	16 (43.2%) 16 (43.2%)
Lenalidomide and PI refractory	27 (73%)
Lenalidomide, PI, and daratumumab refractory	13 (35.1%)

Belantamab mafodotin[a] IV

SINGLE (1.95 or 2.5 mg/kg, day 1) or
SPLIT (2.5 or 3.4 mg/kg, split equally on days 1 and 8) Q4W
+
POM 4 mg D 1-21 and DEX 40 mg (20 mg, age >75 years) weekly

Efficacy	All Evaluable Patients (N=34)
Follow-up (range), mo	7.8 (1.9, 20.3)
Median PFS (95% CI), months	NR (10.8, -)
ORR, % Complete response Very good partial response Partial response	**88** 14.7 52.9 20.6

Corneal Adverse Events	1.92 mg/kg SINGLE (n=12)	2.5 mg/kg Combined[a] (n=20)
Keratopathy[b], n (%)	3 (25)	14 (70)
Visual acuity change[c], n (%)	2 (17)	3 (15)
Median number of patients with dose holds, n (range)	1 (0, 8)	5 (0, 16)

[a] Consists of all patients who received an initial dose of 2.5 mg/kg.
[b] Grade 3/4 keratopathy.
[c] Visual acuity change 20/50 or worse in the better-seeing eye.

Trudel S et al. Poster presented at: American Society of Hematology 2020; Virtual. Poster 725.

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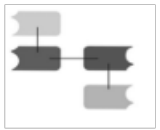
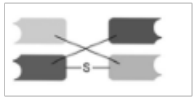
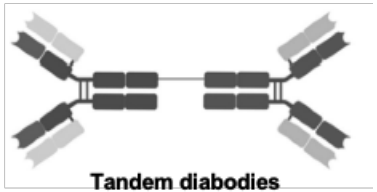
BsAbs – Many Different Platforms



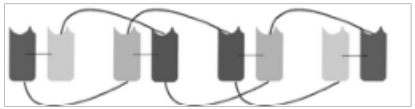
Bispecific T-cell Engager or BiTE (Amgen)



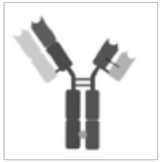
Dual Affinity Re-Targeting or DART (Janssen, Macrogenics)



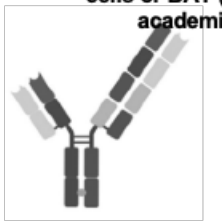
Tandem diabodies or TandAb (Affimed)



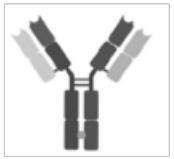
BsAb armed activated T-cells or BAT (mostly academic)



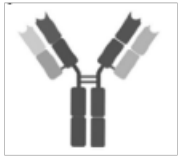
T-cell dependent BsAb Xmab (Xencor, Glenmark, Amgen)



CrossMAb (Celgene, Roche)



Duobody (Genmab)



Trifunctional Antibody or TriFAb

Adapted from Lejeune M et al. Front Immunol 2020 11:762.

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BCMA x CD3 Bispecific Antibodies: Summary

Therapy	Characteristics	N	Population	Safety	Response	DOR/PFS
Teclistamab[1]	▪ Bispecific ▪ IV/SC (RP2D: 1500µg/kg SC) ▪ Weekly and every other week in f/u	157	▪ At SC cohorts: ▪ Median of 5PL ▪ 79% triple refractory ▪ 38% penta refractory	▪ At RP2D: ▪ CRS 70% G1-2 ▪ Neurotox 1% (G1) ▪ Infections 50%	At RP2D, ORR: 65% with 40% sCR/CR	No mature data
AMG701[2]	▪ BiTE modified ▪ IV ▪ Weekly	82	▪ Median of 6PL ▪ 62% triple refractory	▪ CRS 55%, G3-4: 9% ▪ No ICANS ▪ 20% cytopenias	83% ORR at the top dose level and 50% VGPR	No mature data
REGN5458[3]	▪ Bispecific ▪ IV ▪ Weekly and every other week C4->	49	▪ Median of 5PL ▪ 100% triple refractory ▪ 57% penta refractory	▪ CRS 39%, no G3-4 ▪ ICANS 12% ▪ cytopenias 47% and infections 18%	62.5% at 96 mg and 95% of responders were VGPR. Some CR in lower dose levels	Preliminary median DOR: 6m
TNB-383B[4]	▪ Triple chain anti-BCMA bispecific ▪ IV fixed doses ▪ Every 3 weeks	58	▪ Median of 6PL ▪ 64% triple refractory ▪ 34% penta refractory	▪ CRS 45% and no G3-4 ▪ No ICANS ▪ Cytopenias 21% and infections 14%	80% (13% CR) at the dose levels 40-60 mg	No mature data
PF-3135[5]	▪ Bispecific ▪ SC and weekly ▪ RP2D: 1000 µg/kg	30	▪ Median of 8PL ▪ 87% triple refractory ▪ 23% prior BCMA-based therapy	▪ CRS 73% and no G3-4 ▪ ICANS 20% ▪ ISR 50%	83% ORR at RP2D	No mature data

1. Usmani SZ et al. Lancet 2021. 2. Harrison SJ, et al. Presented at ASH 2020. Abstract 181. 3. Madduri D, et al. Presented at ASH 2020. Abstract 291. 4. Rodriguez C, et al. Presented at ASH 2020. Abstract 293.5. Bahlis NJ, et al. Presented at ASCO 2021. Abstract 8006.

Novel Bispecific Antibodies

Therapy	Characteristics	N	Population	Safety	Response	DOR/PFS
Talquetamab[1]	▪ G protein-coupled receptor family C group 5 member D (GPRC5D) x CD3 bispecific antibody ▪ IV or SC admin	184, 30 at RP2D (405 μg/kg))	▪ Median of 6PL (6PL at RP2D) ▪ 76% triple refractory ▪ 28% penta refractory	▪ Infections in 37% of SC and RP2D patients; G3-4 3% at RP2D ▪ Neurotoxicity in 4 SC patients; 2 (7%) at RP2D ▪ CRS 73%, G3-4 2% at RP2D	At RP2D: 70% ORR with ≥ VGPR 60%	No mature data
Cevostamab (BFCR4350A)[2]	▪ FcRH5/CD3 bispecific T-cell engager ▪ Q3W IV infusions	53	▪ Median of 6PL ▪ 72% triple refractory ▪ 45% penta refractory	▪ Thrombocytopenia 32%, G3-4 25% ▪ CRS 76%, G3-4 2% ▪ Neurotoxicity 28%, no G3-4	ORR in ≥3.6/20-mg cohorts: 53% (18/34) in all pts 63% (5/8) in pts with prior anti-BCMA	No mature data

1. Berdeja JG, et al. ASCO 2021. Abstract 8008. 2. Cohen A, et al. ASH 2020. Abstract 292.

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BCMA CARTs: Summary from ASH 2020 and ASH 2021

	CARTITUDE-1[1] Cilta-cel Phase 1	CRB-401[2] Ide-cel Phase 1	CRB-402[3] Bb21217 Phase 1	LUMMICAR-2[4] CT053 Phase 1b	PRIME[5] BCMA-101 Phase 1/2	GC012F[6] Dual CAR-T BCMA+CD19
Patients	97	62	69	20	55	16
Median prior regimens	6	6	6	5	8	NR
Triple refractory, %	87.6%	69.4%	64.0%	85%	60%	NR
CAR-T dose	0.71×10^6 (range 0.5–0.95×10^6)	50, 150, 450 and 800 x 10^6	150, 300, 450 x10^6	1.5-1.8/2.5-3.0 x10^8	0.75-15 x10^6	1.0-3.0 x10^5
ORR	97.9%	75.8%	68.0%/84.0%[a]	94.0%	67%[b]	93.8%
CR/sCR	80.4%	38.7%	28.0%/32.0%[a]	77%/83%[c]	NR	56.3%
CRS, all grades	94.8%	75.8%	NR	15%/17%[c]	17%	100%
CRS, grade 3/4	4%	6.5%	NR	0%	0%	12.5%
Neurotoxicity, all grades	20.6%	35.5%	NR	15%/17%[c]	3.8%	0%
Neurotoxicity, grade 3/4	10.3%	1.6%	NR	8%/0[c]	3.8%	0%

[a]CAR-Ts made using original manufacturing process/updated manufacturing process; [b]0.75x10^6 dose; [c]1.5-1.8/2.5-3.0 x10^8 dose
BCMA, B-cell maturation antigen; CAR-T, chimeric antigen receptor T-cell therapy; CRS, cytokine release syndrome; NR, not reported

1. Usmani et al., ASCO 2021: Abstract 8005; 2. Lin et al., ASH 2020: Abstract 131;
3. Alsina et al., ASH 2020: Abstract 130; 4. Kumar et al., ASH 2020: Abstract 133;
5. Costello et al., ASH 2020: Abstract 134; 6. Jiang et al., ASH 2020: Abstract 178

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CRS/NT Events With BCMA CAR T-Cell Therapies

- CRS and NT events were primarily grade 1/2 and manageable

	KarMMa[1] N = 128	CARTITUDE-1[2] N = 97
≥ 1 CRS event, n (%)	107 (84)	92 (95)
Grade 1/2	100 (78)	87 (95)
≥ Grade 3	7 (5)	5 (5)
Median onset (range), days	1 (1 – 12)	7 (1 – 12)
Median duration (range), days	5 (1 – 63)	4 (1 – 97)
≥ 1 NT event, n (%)	23 (18)	20 (21)
Grade 1/2	18 (12)	10 (10)
≥ Grade 3	5 (4)	10 (10)
ICANS any grade, %	-	17

1. Anderson LD. ASCO 2021. Poster 8016; 2. Usmani S. ASCO 2021. Abstract 8005.

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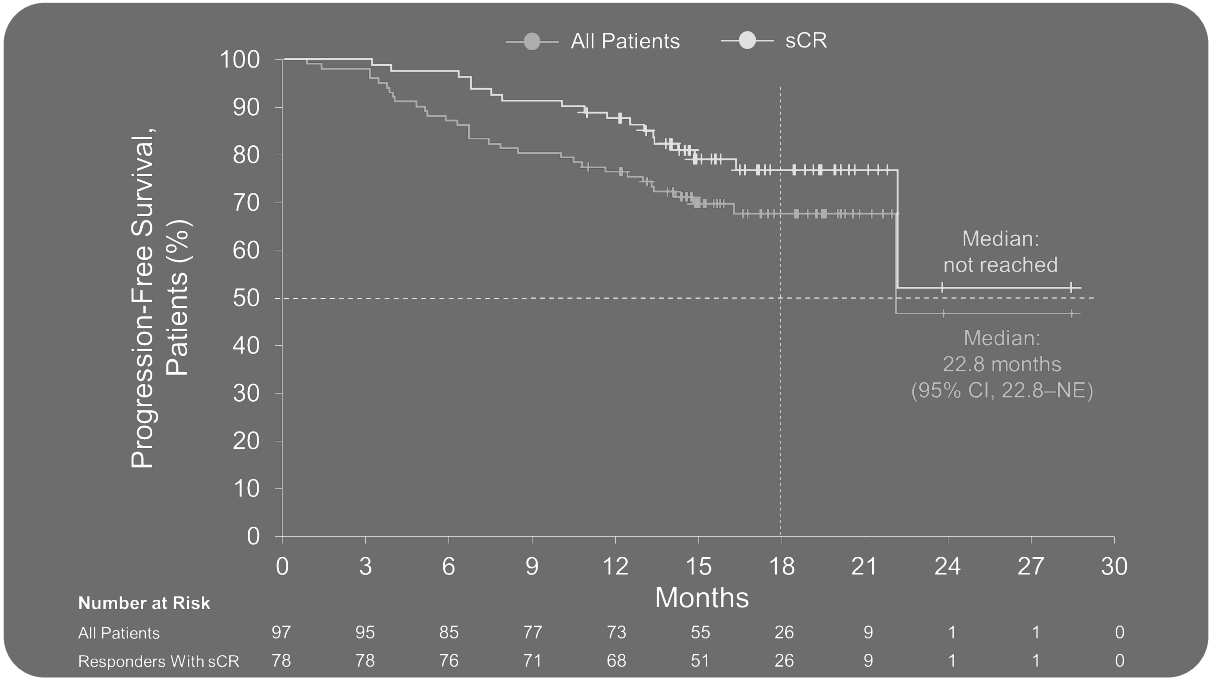
CARTITUDE-1: PFS/OS Updates



18-month PFS
All Patients: 66.0% (95% CI, 54.9–75.0)
sCR: 75.9% (95% CI, 63.6–84.5)

18-month OS
All Patients: 80.9% (95% CI, 71.4–87.6)

Median duration of follow-up 18 months (range, 1.5–30.5)

NE, not estimable; PFS, progression-free survival; OS, overall survival; sCR, stringent complete response.

Usmani et al. ASCO 2021: Abstract 8005.

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Anti-BCMA ALLO-715 and anti-CD52 ALLO-647

Manageable safety profile

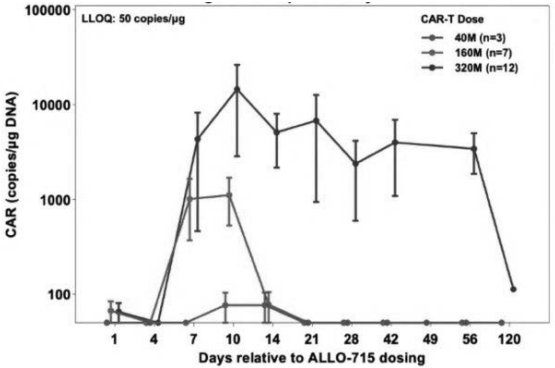
AE of Interest* (N=31)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All Grades
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Cytokine Release Syndrome†	5 (16)	9 (29)	–	–	–	14 (45)
ICANS†	–	–	–	–	–	–
Graft-versus-Host Disease	–	–	–	–	–	–
Infection‡	2 (7)	6 (19)	4 (13)	–	1 (3)	13 (42)
Infusion Reaction to ALLO-647	4 (13)	3 (10)	–	–	–	7 (23)

- Well tolerated across all dose levels
- No GvHD or neurotoxicity
- Manageable grade 1 or 2 CRS
- Infection rate similar to other studies in advanced MM

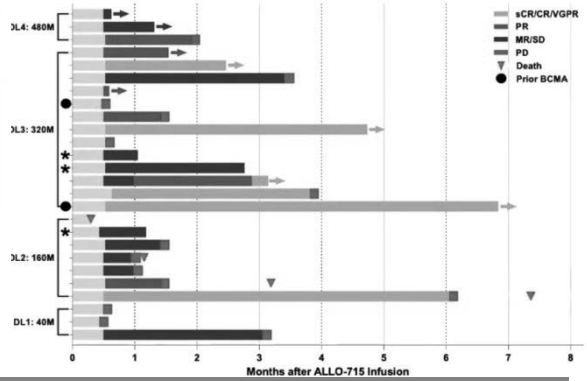
Efficacy outcomes

- 5 of 6 VGPR+ patients were MRD negative
- ORR cell dose dependent
- Improved expansion occurred in patients who received higher cell doses

Average VCN by dose level



Tumor response to treatment



60% (6 patients) achieved ORR, with 40% achieving VGPR+ (sCR, CR or VGPR)

AE, adverse event; BCMA, B-cell maturation antigen; CR, complete response; CRS, cytokine release syndrome; GvHD, graft-versus-host disease; ICANS, Immune effector cell-associated neurotoxicity syndrome; MM, multiple myeloma; MR, minimal response; MRD, minimal residual disease; SD, stable disease; ORR, overall response rate; PD, progressive disease; sCR, stringent complete response; VGPR, very good partial response.

Mailinkody et al., ASH 2020: Abstract 129

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Weighing Efficacy, Safety & Pace of Disease Relapse will be the key..

	Regulatory Approval (Year)	Route & Frequency of Administration	How Quickly Can Patients Get This Modality?	Expected Response (ORR %)	Duration of Response	Safety	Community Setting, Transplant Center or Both	Cost
BCMA-directed Antibody Drug Conjugate	2020	IV q 3 weeks until relapse, progression or intolerance	Off the shelf	32%	~12 months	Keratopathy, Decreased visual acuity (reversible)	Both	++
Bispecific Antibody	TBD	IV or SC, weekly or q 3 weeks until relapse, progression or intolerance	Off the shelf	65-85%	Not reported	Low grade CRS, low NT rate	Both	??
BCMA-directed Auto-CART	2021	IV once	~3-4 weeks between apheresis and infusion.	73-98%	>9 months	CRS/NT	Transplant Center Only	++++
BCMA Directed Allo-CART	TBD	IV once	Off the Shelf	60%	Not reported	CRS/NT	Transplant Center Only	??

Usmani S, personal communication

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Regulatory Approval By Region

- Bela-maf: Approved in US and EU. Submissions to Switzerland, Singapore, South Korea, Hong Kong are under review.
  - US at EU indication: At least 4 prior therapies including PI, IMiD, ani-CD38 mAb

- Ide-cel: Approved in US, EU, Switzerland and Canada. Submission is under review in Japan.
  - US Indication: After 4 or more prior therapies including PI, IMiD, ani-CD38 mAb
  - EU Indication: At least 3 prior therapies including PI, IMiD, ani-CD38 mAb
  - Switzerland Indication:
  - Canada Indication: At least 3 prior therapies including PI, IMiD, ani-CD38 mAb

Usmani S, personal communication

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Summary (I)

- ADCs, bispecific antibodies (BsAb) & CARTs represent a new wave of myeloma treatments that are highly active even in heavily pre-treated patients.
- Toxicities of Belantamab mainly consist of ocular side-effects and low blood counts, all appear reversible.
  - Optimal dosing and schedule are under development.
  - Patients may benefit from combinations, tolerable in older patients.
- Toxicities of BsAb and CARTs mainly consist of cytokine release syndrome (CRS), immune effector cell-associated neurotoxicity syndrome (ICANS), and low blood counts, all of which are treatable.
- There are several BsAb platforms in clinical trials. Compared to CART, they have:
  - Potential advantages: Off the shelf, better safety profile, SC administration
  - Potential disadvantages: Continuous therapy
- BCMA-directed BsAbs and CARTs are showing impressive efficacy in RRMM.
  - Moving to earlier lines of therapies, combinations in the works.
  - Need to incorporate in front-line strategies in high-risk MM (Several concepts are in development)
- Novel targets for BsAbs are in early clinical development, making all IO based MM-therapy strategies realistic in the near future.
  - Treatment targeted at GPRC5D and FcRH5—which are new targets—have shown efficacy.

Usmani S, personal communication

Summary (II)

- How does CAR T-cell therapy differ from the other BCMA-targeted therapies?
  - Advantages: No maintenance, good QoL for patients
  - Disadvantage: Production time, capacity at transplant center

- What are the key aspects to differentiate the emerging CAR T-cell therapies?
  - Vein to vein time
  - Efficacy especially in high risk and EMD
  - Safety
  - Logistics!!

There is place for all these modalities in our armamentarium to help manage multiple myeloma and eventually cure it.

Usmani S, personal communication

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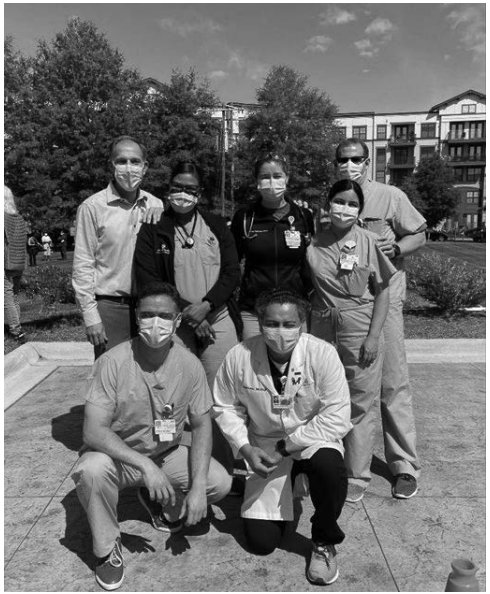
Acknowledgements



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