Managing Myeloma

Taking Aim at an Ideal Therapeutic Target in Relapsed/Refractory Multiple Myeloma

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Disclosures

- **Dr. Sarah Holstein** has received honoraria related to formal advisory activities and as a consultant from Celgene Corporation – A Bristol-Myers Squibb Company, Genentech, Inc., GlaxoSmithKline plc, Oncopeptides, AB, and Sanofi.
- **Dr. Muhamed Baljevic** has received honoraria related to formal advisory activities and as a consultant from Bristol-Myers Squibb Company and Celgene Corporation – A Bristol-Myers Squibb Company. He has received grant support related to research activities from Karyopharm Therapeutics.
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Planning Committee Disclosures

- The individuals listed below from MediCom Worldwide, Inc. reported the following for this activity: Joan Meyer, RN, MHA, Executive Director, Isabelle Vacher, Vice President of Educational Strategy, Wilma Guerra, Program Director, and Andrea Mathis, Project Manager, have no relevant financial relationships.
- The individuals listed below from the University of Nebraska Medical Center, Center for Continuing Education and College of Nursing Continuing Education (UNMC) reported the following for this activity: Brenda Ram, CMP, CHCP, Interim Director, Educational Programs, Heidi Keeler, PhD, RN, Director, UNMC College of Nursing Continuing Nursing Education have no relevant financial relationships.

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Learning Objectives

- Explain the importance of BCMA as a therapeutic target in multiple myeloma, as shown in studies of antibody-drug conjugates, T-cell based therapy, and other approaches
- Integrate BCMA-directed therapy into clinical practice for patients with multiple myeloma
- Develop patient monitoring and management strategies for the toxicities associated with BCMA-targeted therapies

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Managing Myeloma

Targeting BCMA in Myeloma: Where Are We Now and Where Are We Going?

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Current Therapeutic Landscape

- Alkylating agents: cyclophosphamide, melphalan
- Immunomodulatory drugs (IMiDs): thalidomide, lenalidomide, pomalidomide
- Proteasome inhibitors (PIs): bortezomib, ixazomib, carfilzomib
- Anti-CD38 monoclonal antibodies: daratumumab, isatuximab
- Anti-SLAMF7 monoclonal antibody: elotuzumab
- Histone deacetylase inhibitor: panobinostat
- XPO-1 inhibitor: selinexor

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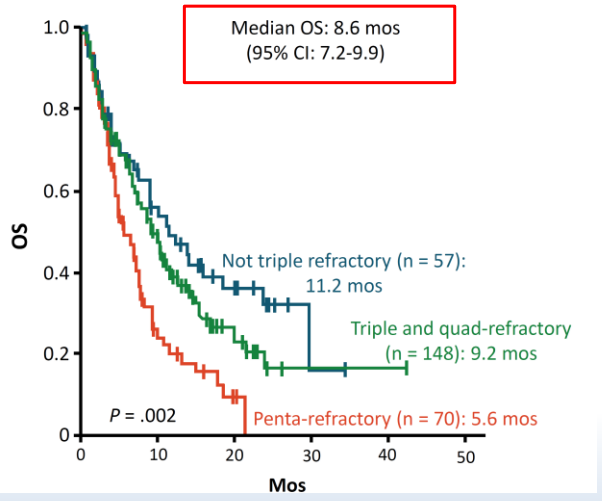
R/R MM in the Modern Era: CD38 Antibody-Refractory Disease in MAMMOTH

- Retrospective study of patients with MM refractory to CD38 antibodies from 14 academic institutions (N = 275)
  - Triple refractory: CD38 antibody + 1 PI + 1 IMiD
  - Quad refractory: CD38 antibody + 1 PI + 2 IMiDs *OR* 2 PIs and 1 IMID
  - Penta-refractory: CD38 antibody + 2 PIs + 2 IMiDs
- 54% triple or quad refractory, 25% penta refractory
- Median prior lines of therapy: 4 (range: 1-16)

Refractory, %	N = 275
Bortezomib	68.4
Carfilzomib	47.3
Lenalidomide	76.7
Pomalidomide	65.1



Gandhi UH, et al. *Leukemia.* 2019;33(9):2266-2275.

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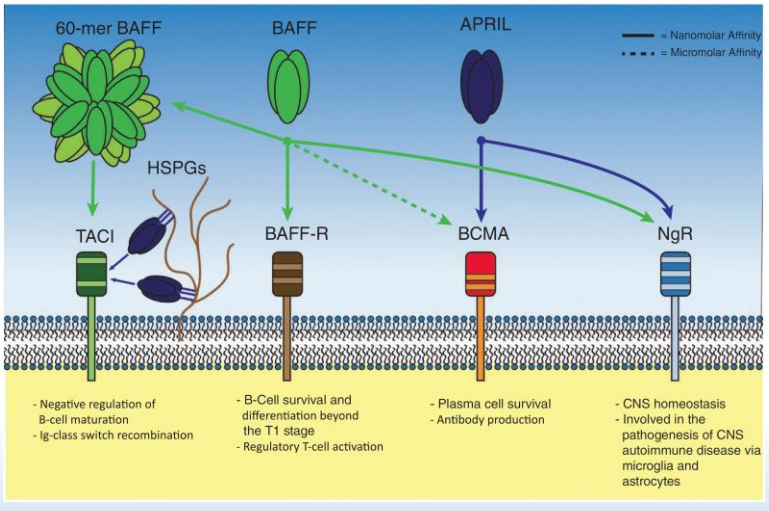
B-cell Maturation Antigen (BCMA)

- Protein found on the cell surface of B cells and plasma cells
- BCMA, TACI, and BAFF-R are the receptors (TNF receptor superfamily members) for BAFF and APRIL, which regulate B-cell survival
  - All three receptors undergo proteolytic shedding
- BCMA-deficient mice have no defects in B-cell homeostasis but have impaired survival of long-lived plasma cells



Hengeveld PJ, Kersten MJ. *Blood Cancer J.* 2015;5(2):e282.

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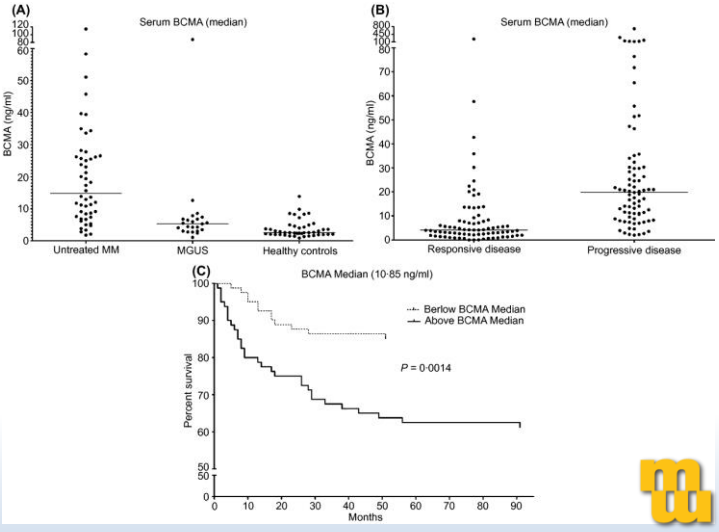
BCMA and Myeloma

- Mouse xenografts with induced overexpression of BCMA grow more rapidly than BCMA-negative controls
- Levels of BCMA are highest in active myeloma patients compared to cells from smoldering myeloma or MGUS patients
- Levels of sBCMA may correlate with prognosis and response to treatment



Sanchez E, et al. *Br Haemtol J.* 2012;158(6):727-738.

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Therapeutic Approaches to Targeting BCMA

- Antibody-drug conjugate therapy: anti-BCMA antibody conjugated to a cytotoxic agent
  - Belantamab mafodotin
- Bispecific T-cell engaging products: dually targeting BCMA on plasma cells and CD3 on T-cells in order to bring the two cell types in close proximity to facilitate T-cell mediated cytolysis
  - Bispecific T-cell engagers
  - Bispecific antibodies
- Chimeric antigen receptor (CAR) T-cells

Belantamab mafodotin received FDA approval on August 5, 2020, as a monotherapy treatment for adult patients with RR/MM who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD.

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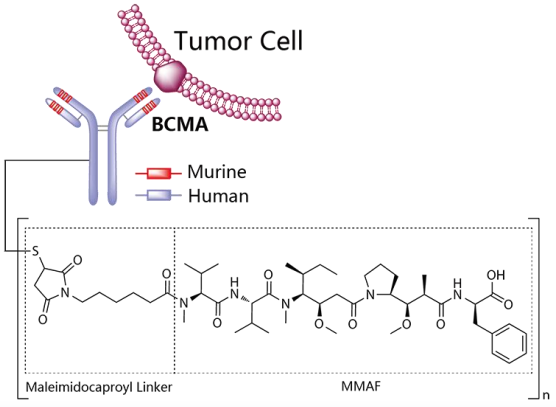
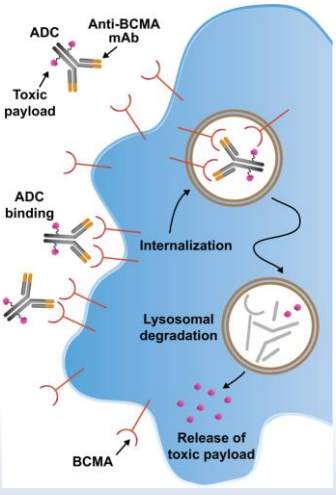
Anti-BCMA-ADC: Belantamab Mafodotin





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Shah N, et al. *Leukemia*. 2020;34(4):985-1000.

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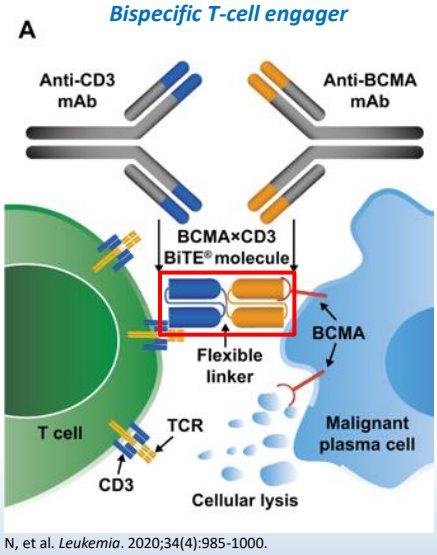
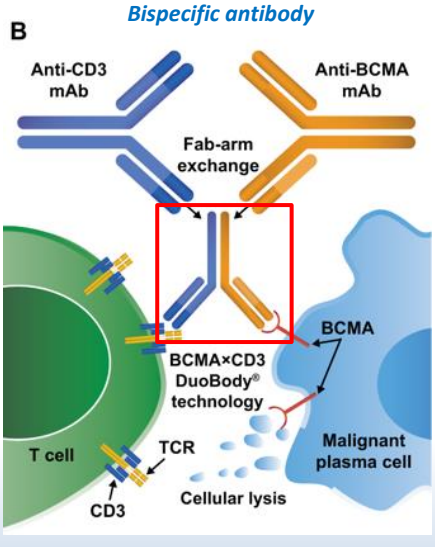
Bispecific Agents





Shah N, et al. *Leukemia*. 2020;34(4):985-1000.

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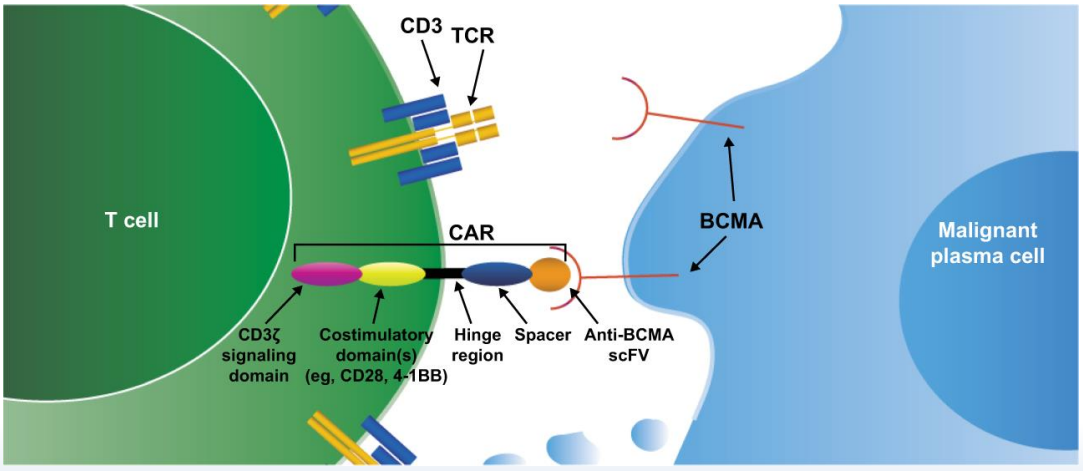
BCMA CAR T-cells



Shah N, et al. *Leukemia*. 2020;34(4):985-1000.

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Future Directions for Anti-BCMA Therapies

- CAR NK cells
- Allogeneic BCMA CAR T-cells
- Multi-targeted CAR T-cells
- γ-secretase inhibitors
- Combination therapies

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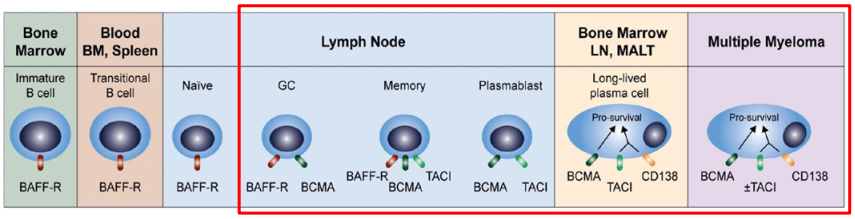
The Efficacy of BCMA-directed Therapy in Myeloma: What Do We Know?



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Seckinger A, et al. *Cancer Cell*. 2017;31:396-410.

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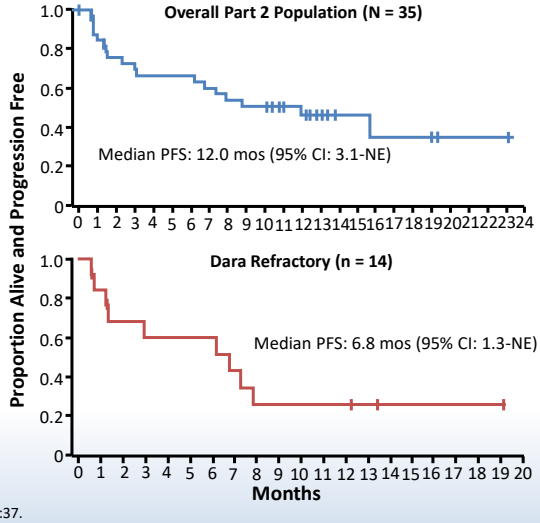
Phase 1 DREAMM-1 Belantamab Mafodotin in R/R MM

- Updated results from Part 2 expansion cohort
  - 97% PI refractory (77% carfilzomib refractory), 95% IMiD refractory (63% pomalidomide refractory), 40% (Dara refractory)
  - Median follow-up: 12.5 mos (range: 0.7-23.2)

Outcome Measure	N = 35
ORR, %	60
▪ sCR	6
▪ CR	9
▪ VGPR	40
▪ PR	6%
Median TTR, mos (95% CI)	1.2 (0.7-1.4)
Median DoR, mos (95% CI)	14.3 (10.6-NE)

- Double (IMiD/PI) refractory ORR: 56.3%
- Triple (IMiD/PI/Dara) refractory ORR: 38.5%



Belantamab mafodotin received FDA approval on August 5, 2020, as a monotherapy treatment for adult patients with RR/MM who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD.
Trudel S, et al. *Lancet Oncol.* 2018;19(12):1641-1653.; Trudel S, et al. *Blood Cancer J.* 2019;9(4):37.

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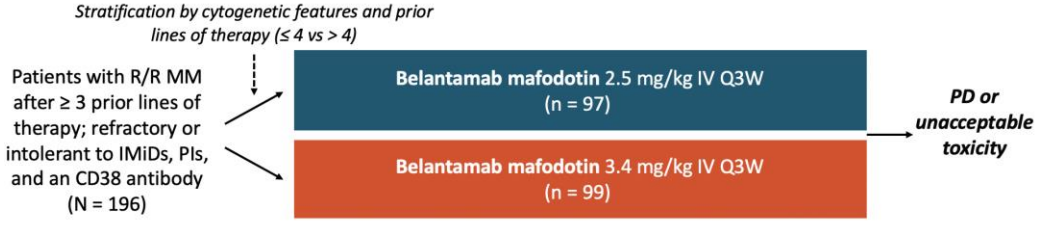
Phase 2 DREAMM-2: Belantamab Mafodotin in R/R MM

- Open-label, randomized phase II trial



- Primary endpoint: ORR
- **Results: ORR in 31% with 2.5 mg/kg vs 34% with 3.4 mg/kg**
- Select grade 3/4 AEs with 2.5 and 3.4 mg/kg: keratopathy (27%, 21%), thrombocytopenia (20%, 33%), anemia (20%, 25%)

Belantamab mafodotin received FDA approval on August 5, 2020, as a monotherapy treatment for adult patients with RR/MM who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD.
Lonial S, et al. *Lancet Oncol.* 2019;21(2):207-221.

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DREAMM-6 in R/R MM: Vd vs B-Vd

- Measurable R/R MM, ≥1 prior therapy; prior AHSCT allowed or AHSCT ineligible; ECOG PS 0-2
- Primary objective: safety, tolerability, ORR
- Secondary objectives: preliminary clinical activity, safety, PK, HRQoL

Part 1: Dose Escalation‡

- Belantamab Mafodotin 3.4 mg/kg single* + Vd† x 21-day cycles (n = 6)
- Belantamab Mafodotin 2.5 mg/kg single* + Vd† x 21-day cycles (n = 6)

Part 2: Dose Expansion (Max 8 Cycles)

- Belantamab Mafodotin 2.5 mg/kg single* + Vd† x 21-day cycles (n = 12)
- Belantamab Mafodotin 2.5 mg/kg split* + Vd† x 21-day cycles (n = 12)
- Belantamab Mafodotin 3.4 mg/kg single* + Vd† x 21-day cycles (n = 9)
- Belantamab Mafodotin 3.4 mg/kg split* + Vd† x 21-day cycles (n = 12)

2.5 mg/kg Q3W B-Vd

- ORR of 78% (14/18 patients): 50% VGPR, 28% PR (95% CI, 52.4–93.6), clinical benefit (≥ MR) 83% (95% CI 58.6–96.4)
- The median DoR has not yet been reached at a median of 18.2 weeks on treatment
- Most frequent AEs: TCP 39%, keratopathy 81%; all patients required dose interruption or delay
- Infusion-related AEs were rare

Belantamab mafodotin received FDA approval on August 5, 2020, as a monotherapy treatment for adult patients with RR/MM who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD.
*Single: Day 1 of 21; Split: 1.25 mg/kg Days 1, 8 of 21. †Bortezomib 1.3 mg/m^2 Days 1, 4, 8, 11 + dex 20 mg Days 1, 2, 4, 5, 8, 9, 11, 12. ‡No DLTs at either dose
Nooka AK, et al. *J Clin Oncol.* 2020:38(suppl):8502.

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AMG 420 in R/R MM

- First-in-human, dose-escalation phase I trial

Patients with R/R MM that progressed after ≥ 2 previous treatment lines (including ≥ 1 each of PI and IMiD); no plasma cell leukemia, extramedullary relapse, CNS involvement, or prior alloSCT (N = 42)

→

AMG 420
Continuous infusion at 0.2-1.6 µg/day in single-patient cohorts, followed by 3.2-800 µg/day in cohorts of 3-6 patients

→

Up to 5 cycles* until PD, toxicity, consent withdrawal, or investigator decision

*6-wk cycles; if benefit perceived by investigator, up to 5 additional cycles allowed

- Primary endpoints: DLT, MTD
- Secondary endpoints: responses, MRD (defined as < 1 tumor cell per 10^4 normal cells in BM using FACS)

Topp MS, et al. *J Clin Oncol.* 2020;38(8):775-783.

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AMG 420 and AMG 701 for RR/MM

AMG 420 Results[1]

- Phase 1 dose escalation (NCT02514239) reported an ORR of 70%, including 5 MRD negative response
- Downsides: 4-week continuous infusion cycle; off for 2 weeks, repeat
- Significant side effects include PN; CRS in 2/3 patients treated at a dose 800 mg/day

AMG 701 Under Investigation[2,3]

- Anti-BCMA-CD3 BiTE molecule with extended half-life
- Weekly dosing possible
- Still need to monitor for CRS
- Large phase 1/2 trial underway

[1]Topp MS, et al. *J Clin Oncol.* 2020;38(8):775-783. [2]Cho S-F, et al. *Blood.* 2019;134(Supplement_1):135. 2. ClinicalTrials.gov Web site. NCT03287908.

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REGN5458: An Anti-BCMA x Anti-CD3 Bispecific Antibody

REGN5458 phase 2 study of SC 3 mg or 6 mg weekly

Study design:

- Inclusion criteria: >3 prior lines of therapy including a PI, IMiD, and anti-CD38 Ab or PD on or after an anti-CD38 Ab and refractory to a PI + IMiD
- Treatment: 16 weekly doses followed by a maintenance phase of 12 doses q2 weeks

Results:

- Median lines prior of therapy: 7
- Response in 4 of 7 patients
- At 6-mg dose (n = 4): ORR in 3 of 4 patients, MRD negative in 2 of 4 patients
- Manageable toxicity profile: lymphopenia, anemia, hypertension

Dose escalation ongoing

Topp MS, et al. *J Clin Oncol.* 2020;38(8):775-783.

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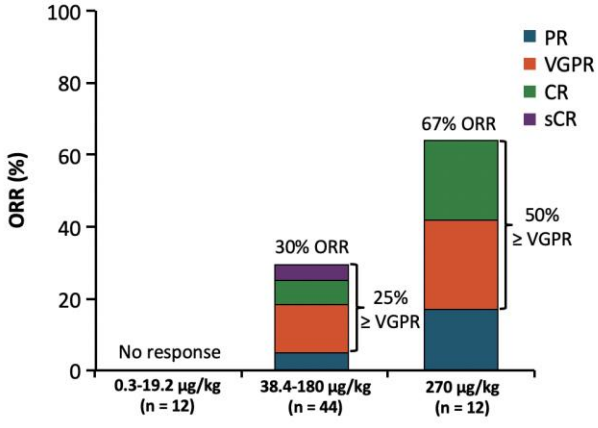
Teclistamab: An Anti-BCMA x Anti-CD3 Bispecific Antibody



- Efficacy data at 720-µg/kg dose are not mature
- At the 270-µg/kg dose, 7/8 responders were triple-class refractory; 5/8 were penta-drug refractory
- 4/5 evaluable patients were MRD negative at 10^{-6}; 2 had MRD-negative CR
- 2/2 evaluable patients maintained MRD negativity for 5 mos (VGPR) and 14 mos (CR)

Most frequent adverse events are CRS, cytopenias

Usmani SZ, et al. *J Clin Oncol.* 2020;38(suppl):100.

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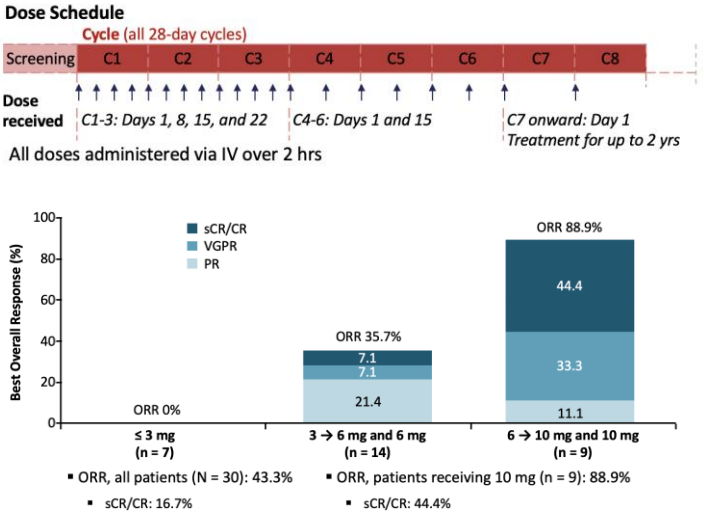
CC-93269: A Humanized Anti-bivalent BCMA x Anti-monovalent CD3ε BiTE

- N = 30 of R/R MM ≥3 regimens; PD within 60 days of last regimen; **no prior BCMA-targeted treatment**
- Part A: dose escalation
  - Stage 1: fixed doses
  - Stage 2: step-up in dose on cycle 1, Day 18
- Part B: cohort expansion
- Primary endpoints: safety (DLTs, AEs, NTD, MTD)
- Secondary endpoints: efficacy (MRD, PK, ADA, PD)

Median time to CRS onset, days (range)	1 (1-9)
Median CRS duration, days (range)	2 (1-6)
Tocilizumab use, n (%)	13 (43.3)
Corticosteroid use, n (%)	22 (73.3)

Costa LI, et al. *Blood*. 2019;134(Supplement_1):143.



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Selected Ongoing or Planned Clinical Trials Exploring anti-BCMA CAR T-cells in Multiple Myeloma

Study name	NCT Identifier	Institution	Study phase	Estimated enrollment *n*	Key inclusion criteria	CAR construct	Treatment arms
CARTIFAN-1	NCT03758417	Multicenter (China)	2	60	≥3 prior lines; PI and IMiDs exposed; PD on last treatment or within 12 months from its end.	LCAR-B38M	Single arm
CARTITUDE-1	NCT03548207	Multicenter (Worldwide)	1–2	110	≥3 prior lines or PI-IMiDs double refractory; PI, IMiD and anti-CD38 mAb exposed; PD on last treatment or within 12 months from its end.	JNJ-68284528 (former LCAR-B38M)	Single arm
EVOLVE	NCT03430011	Multicenter (USA)	1–2	118	≥3 prior lines; PI, IMiD, anti-CD38 mAb and ASCT exposed unless contraindicated; refractory to last line.	JCARH125	Single arm
KarMMa	NCT03361748	Multicenter (Worldwide)	2	150	≥3 prior lines; PI, IMiD, anti-CD38 mAb exposed; refractory to last line.	Bb2121	Single arm
KarMMa-2	NCT03601078	Multicenter (Worldwide)	2	181	Cohort 1: ≥3 prior lines; PI, IMiD, anti-CD38 mAb exposed; refractory to last line. Cohort 2a: 1 prior line; R-ISS 3; PD < 18 months since date of initial therapy (induction, ASCT and lenalidomide containing maintenance required) Cohort 2b: 1 prior line; R-ISS 3; PD < 18 months since date of initial therapy (PI + IMiD + dexamethasone treatment required). Cohort 2c: R-ISS 3; Response < VGPR (excluding PD) after ASCT (Induction with ≥ 3 cycles of PI + IMiD + dexamethasone required).	Bb2121	Single arm
KarMMa-3	NCT03651128	Multicenter (Worldwide)	3	381	2–4 prior lines; PI, IMiD, anti-CD38 mAb exposed; refractory to last line.	Bb2121	Random 2:1 (A:B) Arm A: bb2121 Arm B: standard treatment (DaraPd or DaraVd or IRd per investigator's discretion)

D'Agostino M, Raje N. *Leukemia*. 34:21(1):21-34.

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Efficacy of Selected Anti-BCMA Autologous CAR T-cells in R/R MM

Trial / Agent	Phase	Number of Patients	Median prior N of therapies	Efficacy (ORR, CR)	Response Speed/Duration	Safety
Idecabtagene vicleucel (KarMMa)[1]	2	158	Prior IMiD, PI, anti-CD38, ≥3 prior Rx	ORR: 73% CR: 33% MRD(-): 26%	mTTR: 1 mo PFS 8.8 mos	CRS: 84% (G3: 4% G4: <1% G5: <1%) NT: 18% (G3: 3%)
JNJ-4528 (CARTITUDE-1)[2]	1b/2	29	Prior IMiD, PI, anti-CD38, or double ref. to PI/IMiD, ≥3 prior Rx	ORR: 100% sCR: 86%	mTTR: 1 mo	CRS: 93% (G ≥3: 7%) ICANS: 10% (G ≥3: 3%)
Orvacabtagene autoleucel JCARH125 (EVOLVE)[3]	1b/2	62	Prior IMiD, PI, anti-CD38, AHSCT, ≥3 prior Rx	ORR: 92% sCR/CR: 36% MRD(-): 84%	---	CRS: 3% (G ≥3: 3%) Neur. Ev.: 3% (G ≥3: 3%)
LCAR-B38M (LEGEND-2)[4]	1	57	Must contain prior PI ≥3 prior Rx	ORR: 89% sCR/CR: 74% MRD(-): 68%	mTTR: 1.1 mos PFS 19.9 mos OS 36.1	CRS: 90% (G ≥3: 7%) NT: 2% (G ≥3: 0%)

[1]Munshi N, et al. *J Clin Oncol.* 2020;38(suppl):8503. [2]Bardeja JG, et al. *J Clin Oncol.* 2020;38(suppl):8505. [3]Mailankody S, et al. *J Clin Oncol.* 2020;38(suppl):8504.
[4]Wang B-Y, et al. *Blood.* 2019;134(Supplement_1):579.

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TEAEs Related to BCMA-directed Therapy: What to Expect, and How to Manage Them

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Case Scenarios: CRS

Case 1

- 55-year-old male with R-ISS Stage 3 MM t(4;14)
- RVD, auto PBSCT, VRD maintenance
- Progression: DaraPomDex
- CAR-T transplant
- 12 hours post infusion T 101, HR 110, BP 120/80

Case 2

- 59-year-old male with R-ISS Stage 2 MM
- VD, auto, R; KRd, KPomD, DaraPomD, Erd, Bendamustine
- CAR-T transplant
- 36 hours post transplant T 102, HR 130, BP 78/50, creat 2.1 mg/dL, disoriented, O_2 sat 85%

HOW WOULD YOU MANAGE THESE CASES?

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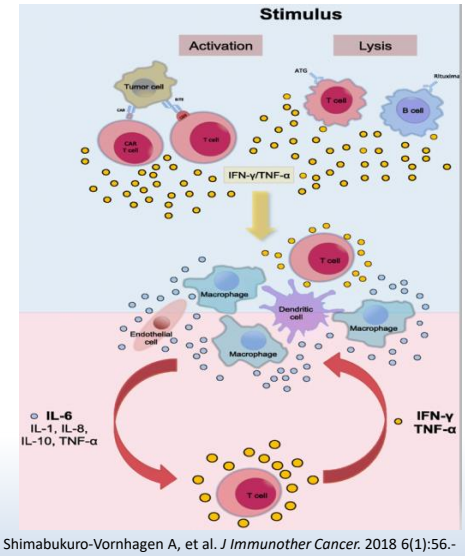
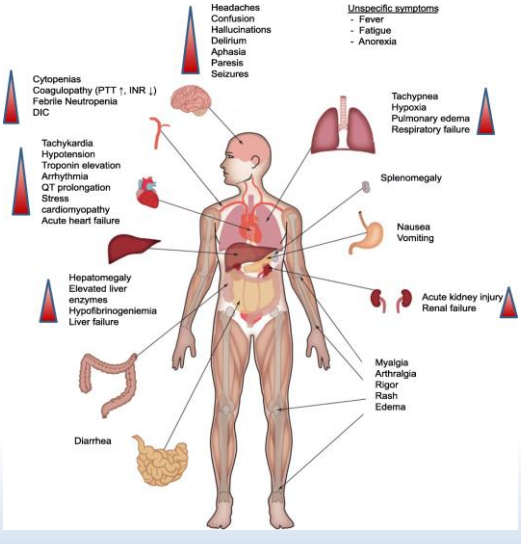
Effector Cells and Targets in CRS



Shimabukuro-Vornhagen A, et al. *J Immunother Cancer.* 2018 6(1):56.-



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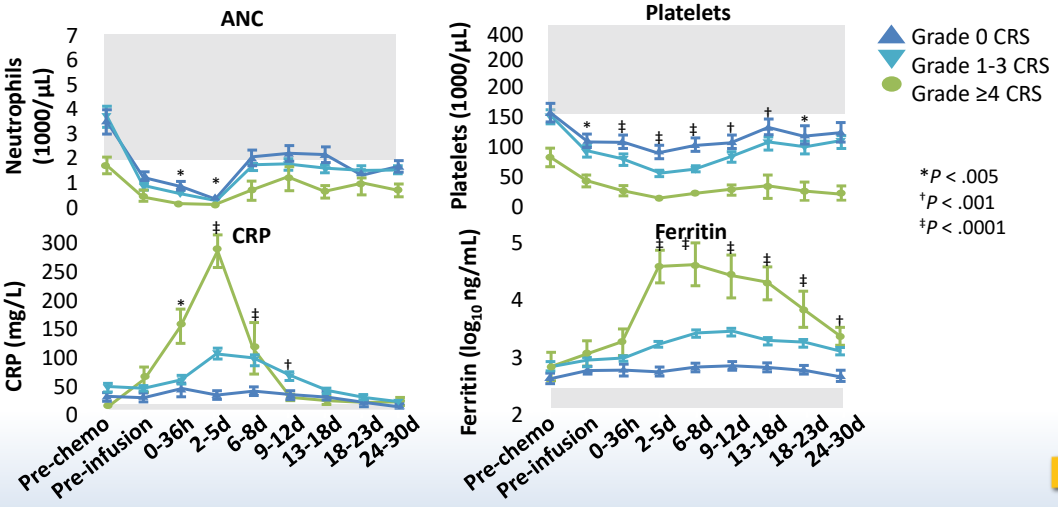
Biomarkers of CRS: Cytopenias and Inflammatory Markers



Hay KA, et al. *Blood*. 2017;130(21):2295-2306.

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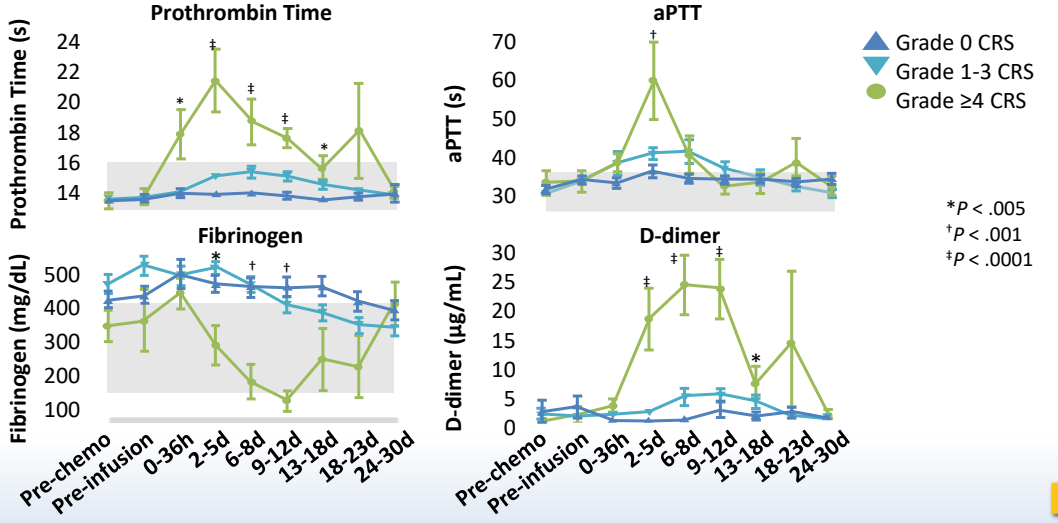
Biomarkers of CRS: Coagulopathy



Hay KA, et al. *Blood*. 2017;130(21):2295-2306.

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ASTCT Guidelines for Grading of CRS: Speaking the Same Language

Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever*	Temp ≥38°C	Temp ≥38°C	Temp ≥38°C	Temp ≥38°C
		With		
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
		And/or†		
Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula,‡ facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

*Fever defined as temperature ≥38°C not attributable to other causes. In patients with CRS who receive antipyretics or anticytokine therapy (eg, tocilizumab, steroids), fever no longer required to grade subsequent CRS severity; CRS grading driven by hypotension and/or hypoxia. †CRS grade determined by more severe event: hypotension or hypoxia not attributable other causes, eg, temperature 39.5°C, hypotension requiring one vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS. ‡Low-flow nasal cannula defined as oxygen delivered at ≤6 L/min. Low flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula defined as oxygen delivered at >6 L/min.

Lee DW, et al. *Blood*. 2019;25(4):625-638.

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New ASTCT Guidelines for Grading of ICANS

(Immune Effector Cell Associated Neurotoxicity Syndrome): ICE Score

Parameter	Score (Points)
Orientation: year, month, city, hospital	4
Naming: ability to name three objects (eg, point to clock, pen, button)	3
Following commands: ability to follow simple commands (eg, "show me two fingers" or "close your eyes and stick out your tongue")	1
Writing: ability to write a standard sentence (eg, "our national bird is the bald eagle")	1
Attention: ability to count backwards from 100 by 10	1

Scoring:
10, no impairment
7-9, grade 1 ICANS
3-6, grade 2 ICANS
0-2, grade 3 ICANS
0 due to patient unarousable and unable to perform ICE assessment, grade 4 ICANS

Lee DW, et al. *Blood*. 2019;25(4):625-638.

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New ASTCT Guidelines for Grading of ICANS

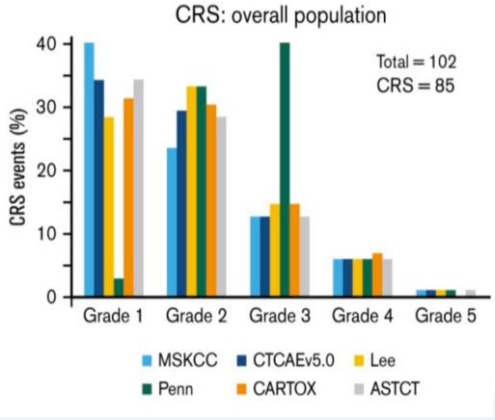
Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse; stupor or coma
Seizure	N/A	N/A	Any clinical seizure focal or generalized that resolves rapidly or nonconvulsive seizures on EEG that resolve with intervention	Life-threatening prolonged seizure (>5 mins) or repetitive clinical or electrical seizures without return to baseline in between
Motor findings‡	N/A	N/A	N/A	Deep focal motor weakness such as hemiparesis or paraparesis
Elevated ICP/cerebral edema	N/A	N/A	Focal/local edema on neuroimaging§	Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilledema; or Cushing's triad

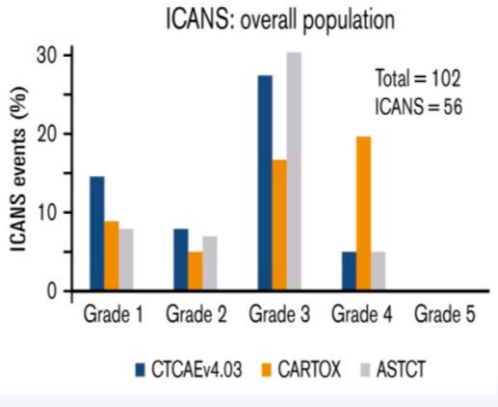
*An ICE score of 0 may be classified as grade 3 ICANS if patient is awake with global aphasia; otherwise classified as grade 4 ICANS if unarousable. †Depressed level of consciousness not attributable to other cause. ‡Tremors and myoclonus associated with immune effector cell therapies may be graded according to CTCAE v5.0, but they do not influence ICANS grading. §Intracranial hemorrhage with or without associated edema is not considered a neurotoxicity feature and is excluded from ICANS grading. It may be graded according to CTCAE v5.0.

Lee DW, et al. *Blood*. 2019;25(4):625-638.

33

Comparison of Grading Systems





Pennisi M, et al. *Blood Adv.* 2020;4(4):676-686.

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Taking Aim at an Ideal Therapeutic Target in Relapsed/Refractory Multiple Myeloma

KarMMa: Common AEs

AEs Occurring in ≥20% Patients , n (%)	All Ide-cel Patients (n = 128)	
	Any Grade	Grade ≥3
Hematologic		
– Neutropenia	117 (91)	114 (89)
– Anemia	89 (70)	77 (60)
– Thrombocytopenia	81 (63)	67 (52)
– Leukopenia	54 (42)	50 (39)
– Lymphopenia	35 (27)	34 (27)
Gastrointestinal		
– Diarrhea	45 (35)	2 (2)
– Nausea	37 (29)	0

AEs Occurring in ≥20% Patients, n (%)	All Ide-cel Patients (n = 128)	
	Any Grade	Grade ≥3
Other		
– Hypokalemia	45 (35)	3 (2)
– Fatigue	43 (34)	2 (2)
– Hypophosphatemia	38 (30)	20 (16)
– Hypocalcemia	34 (27)	10 (8)
– Pyrexia	32 (25)	3 (2)
– Hypomagnesemia	30 (23)	0
– Decreased appetite	27 (21)	1 (<1)
– Headache	27 (21)	1 (<1)
– Hypogammaglobulinemia	27 (21)	1 (<1)
– Cough	26 (20)	0
CRS	**107 (84)**	**7 (5)**

- Cytopenias, infections common but not dose related
- Five (4%) patients died within 8 weeks of ide-cel treatment; 2 due to progression, 3 due to AEs (CRS, aspergillus pneumonia, GI hemorrhage)
  - One additional death within 6 months of treatment due to AE (CMV pneumonia)
- Tocilizumab use: 52%
- Steroid use 15%

Munshi N, et al. *J Clin Oncol*. 2020;38(suppl);abstract 8503.

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CARTITUDE 1 : Similar Pattern of CRS

AEs (≥25% All Grade), n (%)	N = 29	
	All Gr	≥ Gr 3
Hematologic		
Neutropenia	29 (100)	29 (100)
Thrombocytopenia	25 (86)	20 (69)
Anemia	22 (76)	14 (48)
Leukopenia	20 (69)	19 (66)
Lymphopenia	18 (52)	14 (48)
Non-hematologic		
Diarrhea	10 (35)	0
Increased AST	9 (31)	2 (7)
Increased ALT	9 (31)	2 (7)
Headache	8 (28)	0

- CRS
  - All grade: 27 patients (93%)
  - ≥ Grade 3: 2 patients (7%)
- Median time to onset: 7 days (2-12)
- Median duration: 4 days (2-64)
- Treatment:
  - 79% tocilizumab
  - 21% each anakinra or corticosteroids

Madduri D, et al. *Blood*. 2019;134(Supplement_1):577.

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Principles of Toxicity Management: Patient Selection

- Performance status: dictated by protocol, typically ECOG PS ≤2 required
- Many protocols require exposure to three drug classes (IMiD, PI and anti CD 38)
- Require "reasonable" hematologic parameters, ie, platelets >75K, ANC of 1000; no absolute number of peripheral lymphocytes required but >200/uL preferable
- No Hep B, C, HIV or other "active infection"
- EF >45%; CrCl >30 mL/min

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Principles of Toxicity Management

- Appropriate screening per institutional standards
- Baseline labs
  - CRP, ferritin
  - CBC, CMP, coagulopathy
  - Tumor lysis syndrome labs
- Initiation of antiepileptic drugs if not used for prophylaxis
- Appropriate bacterial/fungal/viral prophylaxis per institutional standards
- Pre-infusion/LD chemo
- Monitor CBC, CMP, and coagulopathy
- Monitor for tumor lysis syndrome
- Monitor CRP and ferritin
- Daily assessments for at least 7 days
  - FDA requirement for axicabtagene ciloleucel
  - Fevers? Hypotension? Hypoxia?
  - Mental status

MD Anderson. CAR cell therapy toxicity assessment and management - adult. 2017.; Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62.; Yescarta [package insert]. Santa Monica, CA. Lite Pharma, Inc. 2020.; Kymriah [package insert]. East Hanover, NJ. Novartis Pharmaceuticals Corporation. 2018.

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Principles of Toxicity Management by Grade

Grade	CRS	Neurotoxicity	CRS + Neurotoxicity
1	Supportive care +/- steroids	Supportive care + AEDs	Supportive care + AEDs
2	Tocilizumab	Steroids (dexamethasone* or methylprednisolone†)	Tocilizumab + steroids (dexamethasone*)
3	Tocilizumab + steroids	Steroids (dexamethasone*)	Tocilizumab + steroids (dexamethasone*)
4	Tocilizumab + high-dose steroids ICU/critical care	High-dose steroids (methylprednisolone‡) ICU/critical care	Tocilizumab + high-dose steroids (methylprednisolone‡) ICU/critical care

*Dexamethasone 10-20 mg IV either as a one-time dose or Q6H. †Methylprednisolone 1 mg/kg IV Q12H. ‡High-dose methylprednisolone given at 500 mg IV Q12H for 3 days, then tapered over 2.5 weeks.

- Always rule out/treat alternative causes
- If tocilizumab refractory, consider corticosteroids
- Patients with neurotoxicity should receive AEDs and appropriate CNS imaging, EEG monitoring
- Steroid dosing for neurotoxicity may vary between products
- Patients on steroids should receive appropriate fungal prophylaxis

MD Anderson. CAR cell therapy toxicity assessment and management - adult. 2017.; Neelapu SS, et al. *Nat Rev Clin Oncol.* 2018;15(1):47-62.

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Steroid Use for CRS/CRES: Effect on CAR-T Expansion, Persistence

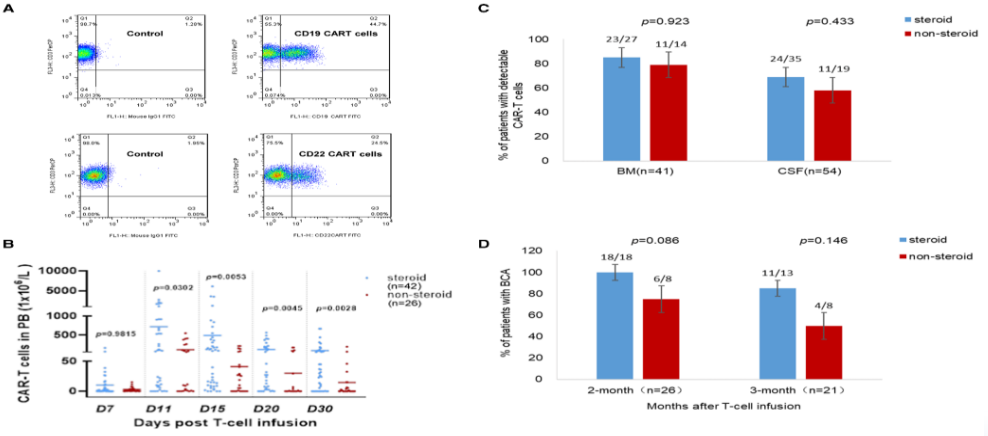

Fig. 1 Kinetics of CAR-T cells in relapsed/refractory B-ALL patients treated or not treated with steroids (detected by flow cytometry). a The representative flow cytometry plots showing CAR-T cells. **b** CAR-T cell numbers in peripheral blood (PB) on day 7, 11, 15, 20 and D30. **c** Percentages of patients with detectable CAR-T cells in bone marrow (BM) and cerebrospinal fluid (CSF), assayed once or twice between day 14 to day 35. **d** Percentages of patients with B-cell aplasia (BCA) at 2 and 3 months. Based on Maude SL et al (N Engl J Med. 2014;371:1507-1517), BCA was defined as less than 3% CD19 or CD22 (4 cases) positive lymphocytes.

Liu S, et al. *Blood Cancer J.* 2020;10(2):15.

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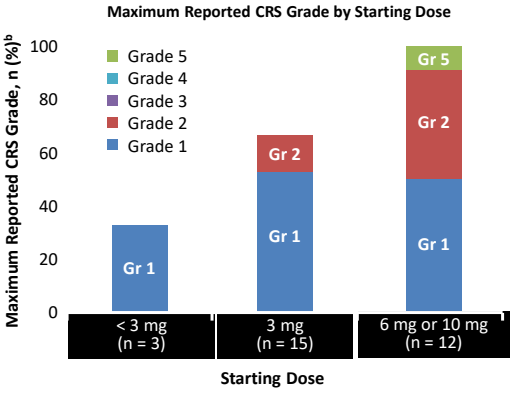
Bi-specific Engagers: CC-93269-MM-001: Cytokine-Release Syndrome Occurs But Is Short Lived

CRS Parameter	N = 30
Patients with a CRS event, n (%)	23 (76.7)
– After first dose	23 (76.7)
– After second dose	7 (23.3)
– After third dose	2 (7.4)*
Maximum CRS grade, n (%)	
– 1	15 (50.0)
– 2	7 (23.3)
– ≥3	1 (3.3)
Median time to onset, days (range)	1 (1-9)
Median duration, days (range)	2 (1-6)
Tocilizumab use, n (%)	13 (43.3)
Corticosteroid use, n (%)	22 (73.3)

*27 patients received a third dose.



- Dexamethasone prophylaxis administered to patients receiving ≥6 mg (cohorts 5-9)
- In cohort 7 (6 → 10 mg), one patient experienced grade 3 CRS at 6 mg followed by grade 5 at 10 mg; contributing factors included progressive disease with extensive extramedullary involvement, and preexisting infection

Costa LJ. *Blood.* 2019;134(Supplement_1):143.

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Phase 2 DREAMM-2: Belantamab Mafodotin in R/R MM

- Open-label, randomized phase 2 trial

Stratification by cytogenetic features and prior lines of therapy (≤4 vs >4)

Patients with R/R MM after ≥3 prior lines of therapy; refractory or intolerant to IMiDs, PIs, and CD38 antibodies (N = 196)

- Primary endpoint: ORR

Belantamab mafodotin 2.5 mg/kg IV Q3W (n = 97)

Belantamab mafodotin 3.4 mg/kg IV Q3W (n = 99)

PD or unacceptable toxicity

- Results: ORR: 30% at 2.5 mg/kg vs 34% at 3.4 mg/kg; PFS: 2.9 mos at 2.5 mg/kg, 4.9 mos in 3.4 mg/kg; OS not yet reached in either group
- Select grade 3/4 AEs with 2.5 and 3.4 mg/kg: keratopathy (27%, 21%), thrombocytopenia (20%, 33%), anemia (20%, 25%)

Belantamab mafodotin received FDA approval on August 5, 2020, as a monotherapy treatment for adult patients with RR/MM who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD.
Lonial S, et al. *Lancet Oncol.* 2019;21:207-221.

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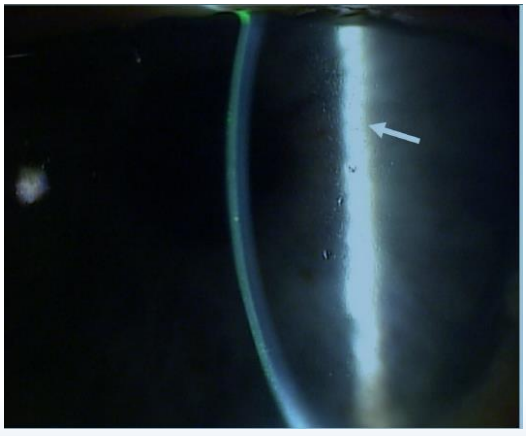
Belantamab-Related Ocular Toxicity

TABLE 3. INCIDENCE, DURATION, AND RESOLUTION OF CORNEAL SYMPTOMS IN PATIENTS RECEIVING BELAMAF (2.5 MG/KG) IN DREAMM-2

	Blurred Vision (n=95)	Subjective Dry Eye (n=95)
Any grade, n (%)	24 (25)	14 (15)
Maximum grade[a]		
Grade 1	11 (12)	9 (9)
Grade 2	9 (9)	4 (4)
Grade 3	4 (4)	1 (1)
Grade 4	0	0
Median time to onset of first occurrence (range), days	51.5 (6–339)	42.0 (12–151)
Median duration of first event (range), days	42.5 (6–441)	39.0 (12–316)
First event outcomes, n/N (%)[b]		
Recovered	16/24 (67)	12/14 (86)
Not recovered	8/24 (33)	2/14 (31)
Dose delays due to event, n (%)	6 (6)[c]	2 (2)
Dose reductions due to event, n (%)	2 (2)[c]	0

CTCAE v4.03, Common Terminology Criteria for Adverse Events version 4.03.
Safety population (n=95) defined as all patients who received ≥1 dose of belamaf.
[a]Event grading per CTCAE v4.03; [b]Recovery was defined as full recovery or return to baseline; [c]Reported as vision blurred.



Epithelial microcyst like epithelial changes on corneal surface

Belantamab mafodotin received FDA approval on August 5, 2020, as a monotherapy treatment for adult patients with RR/MM who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD.
Farooq AV, et al. *Opthalmol Ther*. 2020 Jul 25. doi: 10.1007/s40123-020-00280-8. [Epub ahead of print]

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Conclusion

- CRS is common following BCMA directed CAR-T, bispecific engagers, rare with ADCs
- Life-threatening CRS and CRES is less common
- Early intervention likely important
- Don’t forget “basics”, ie, empiric therapy for neutropenic fevers
- Preparation is very important to prevent poor outcomes
- Steroids may not be detrimental to CAR-T cell survival

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Managing Myeloma

BCMA-directed Therapies: What Do We Know About Resistance Mechanisms and Sequencing?

Sarah Holstein, MD, PhD
Associate Professor of Medicine
Division of Hematology and Oncology
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University of Nebraska Medical Center
Omaha, Nebraska

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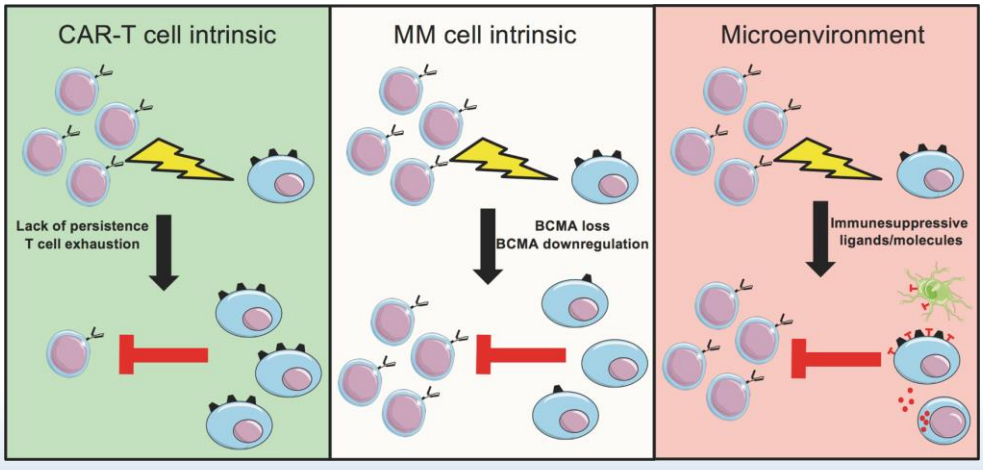
Potential Mechanisms of Resistance to Anti-BCMA CAR T-cell Therapy



D'Agostino M, Raje N. *Leukemia*. 2020;34(1):21-34.

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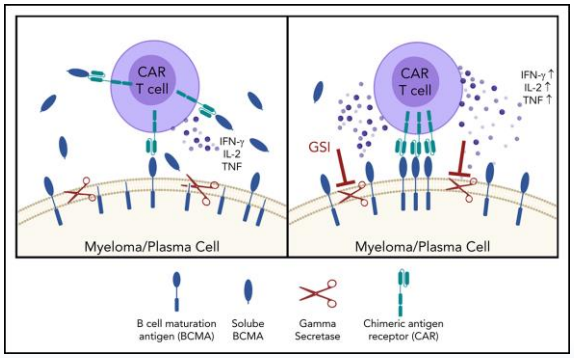
Taking Aim at an Ideal Therapeutic Target in Relapsed/Refractory Multiple Myeloma

Targeting the γ-Secretase



- Phase 1 study of oral g-secretase inhibitor (JSMD194) + BCMA CAR T-cells
  - Seven patients including one who did not respond to prior BCMA CAR T-cells and another who progressed on a BCMA bispecific antibody
  - Initial run-in of 3 doses → ↑BCMA on cell surface and ↓sBCMA
  - 100% ORR in 6 assessable patients (5 VGPR, 1 PR)

Pont M, et al. *Blood.* 2019;134(9):1585-1597.; Cowan AJ, et al. *Blood.* 2020;134(supplement_1):204.

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Sequencing Anti-BCMA Therapies

Majority of clinical trials conducted thus far exclude prior BCMA therapy:

- ADC: Phase 2 DREAMM-2 study
- Bispecifics: AMG 420, teclistamab, CC-93269
- CAR T: bb2121, JNJ-4528

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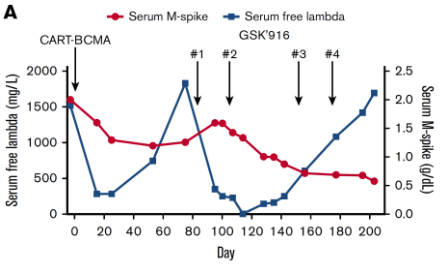
Taking Aim at an Ideal Therapeutic Target in Relapsed/Refractory Multiple Myeloma

Anecdotal Reports

- "Serial treatment of relapsed/refractory multiple myeloma with different BCMA-targeting therapies"[1]
  - Patient #1: penta-refractory, 10 prior lines
    - 1) Phase 1 study of BCMA CAR T-cells → MR
    - 2) Phase 1 study of belantamab mafodotin → MR
  - Patient #2: penta-refractory, 5 prior lines
    - 1) Phase 1 study of belantamab mafodotin (3.4 mg/kg) → PD
    - 2) Pembrolizumab/lenalidomide/dexamethasone → MR
    - 3) Phase 1 study of BCMA CAR T-cells → PR



- Fully human BCMA CAR T-cells[2]
  - 4/16 enrolled patients had previously relapsed on a murine BCMA CAR-T trial
    - All four responded (3 sCR, 1 VGPR)

Belantamab mafodotin received FDA approval on August 5, 2020, as a monotherapy treatment for adult patients with RR/MM who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an IMiD.

[1]Cohen A, et al. *Blood.* 2019;3(16):2487-2490. [2]Li C, et al. *Blood.* 2019;134(supplement_1):929.

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