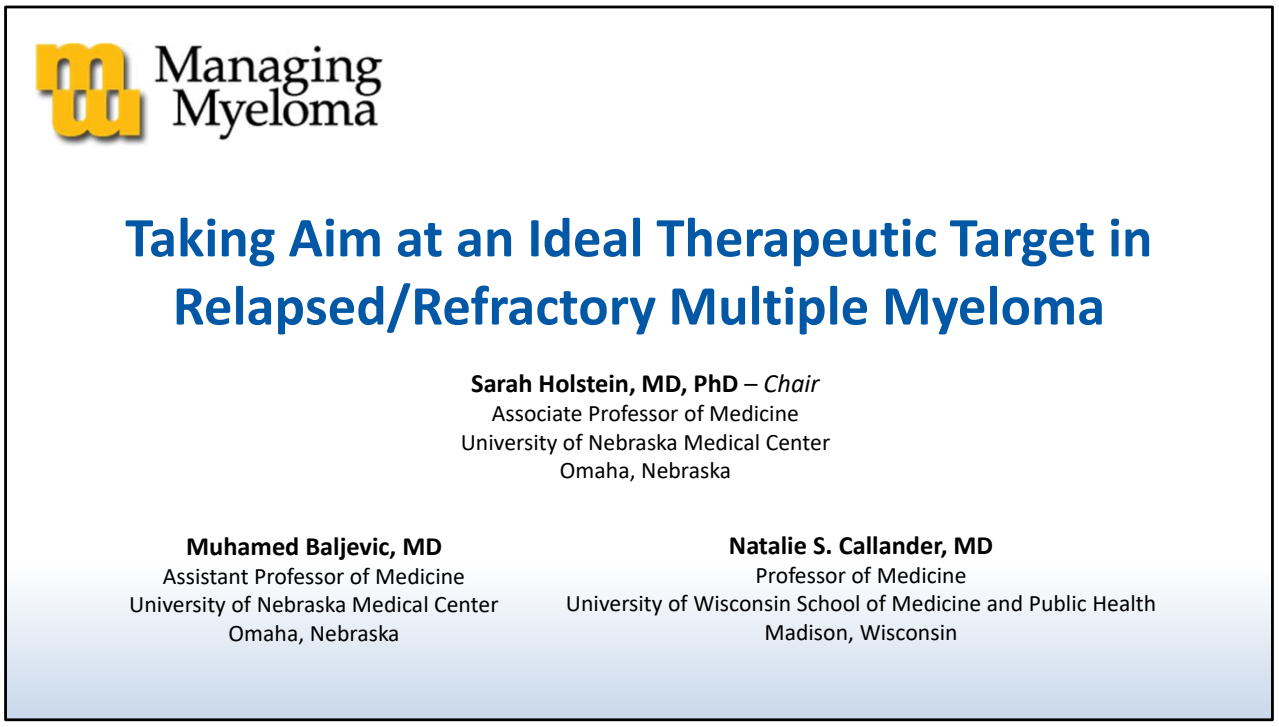
Taking Aim at an Ideal Therapeutic Target in Relapsed/Refractory Multiple Myeloma



Hello, and thank you for joining us. I'm Dr. Sarah Holstein, Associate Professor at the University of Nebraska Medical Center. I'm very pleased to be joined today by two of my colleagues, Dr. Muhamed Baljevic, who is an Assistant Professor at the University of Nebraska Medical Center, and Dr. Natalie Callander, who is a Professor at the University of Wisconsin.

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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.
- **Dr. Natalie Callander** has received honoraria as a consultant from Cellectar Biosciences, Inc.

These are our disclosures.

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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.

These are the disclosures of the planning committee.

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

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

Today, we will be discussing the current status of BCMA-directed therapies and the available data we have to support their use in the relapsed/refractory myeloma setting. We'll start with an overview of BCMA and the three main classes of agents. We will review the efficacy of these agents as well as discuss management strategies for their toxicities. We will conclude with a panel discussion about how to best integrate BCMA-directed therapy into clinical practice.

I'm going to start a discussion today with an overview of the current status of BCMA-directed therapies.

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

First is a brief background. This is the current therapeutic landscape for myeloma. We have our alkylating agents, but really the mainstay these days are the immunomodulatory drugs, which primarily include lenalidomide and pomalidomide; the proteasome inhibitors including bortezomib, ixazomib, carfilzomib; and the anti-CD38 monoclonal antibodies, which include daratumumab and isatuximab. We also have three other agents approved for myeloma including this anti-SLAMF7 monoclonal antibody, a histone deacetylase inhibitor, and an XPO1 inhibitor.

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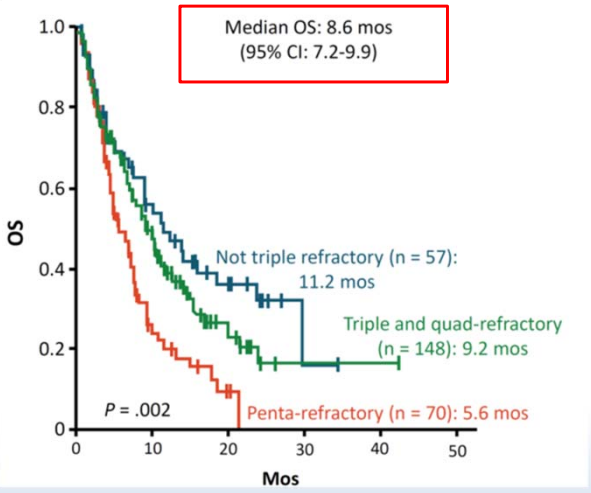
R/R MM in the Modern Era: CD38 Antibody-Refractory Disease in MAMMOTH

- 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.

Once patients become refractory to CD38 antibody therapy, especially in combination with IMiDs or PIs, the management of these patients becomes very difficult. So, I wanted to set the stage by discussing the data from the MAMMOTH study. This was a retrospective study of patients with myeloma that was refractory to CD38 antibodies from 14 different academic institutions. And, overall, on the right-hand side of the slide, you can see that the median overall survival for this patient population is only 8.6 months. And in particular, when you look at the penta-refractory patients, which are refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and an anti-CD38 antibody, you can see that the overall survival is even shorter at a median of 5.6 months. So this patient population represents a very difficult to treat patient population. And it is clear that we need new and improved treatment strategies, including new targets in order to improve outcomes for these patients.

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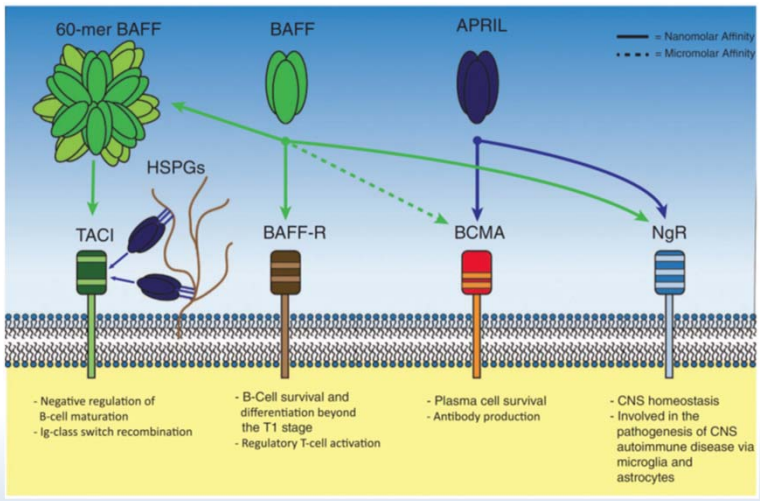
B-cell Maturation Antigen (BCMA)

- 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.

That brings us to BCMA or the B-cell maturation antigen. This is a protein found on the cell surface of B-cells and plasma cells. BCMA, TACI, and BAFF receptor are all receptors belonging to the TNF receptor superfamily, and they bind BAFF and APRIL, which regulate B-cell survival. We'll be discussing this later on, but it's important to note that all three receptors can undergo proteolytic shedding. Notably, BCMA-deficient mice had no defects in B-cell homeostasis, but had impaired survival of long-lived plasma cells showing the importance of BCMA for plasma cell survival.

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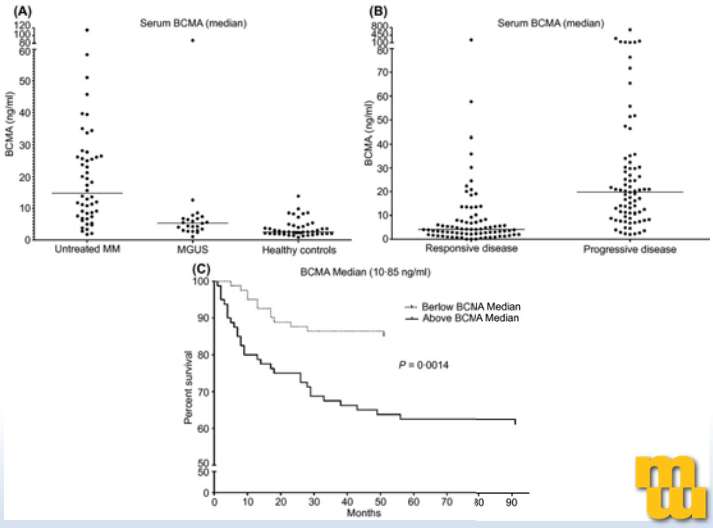
BCMA and Myeloma

- 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.

What do we know about BCMA in myeloma? Well, preclinical studies with mouse xenografts showed that tumor cells that had induced overexpression of BCMA grew more rapidly than BCMA-negative controls. In addition, when patient samples have been evaluated, either the plasma cells or serum BCMA levels, it's been shown that the highest levels of BCMA are found in active myeloma patients compared to samples from MGUS or untreated myeloma patients. Levels of serum soluble BCMA may correlate with prognosis and response to treatment as well, as shown as Figure C on this slide.

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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.

Currently, there are three main approaches to targeting BCMA, and this will be the primary focus of today's talks. The first includes antibody-drug conjugate therapy. This involves an anti-BCMA antibody that's conjugated to a cytotoxic agent. The second class that we'll be discussing are the bispecific T-cell engaging products. These products dually target BCMA on the plasma cell and then CD3 on the T-cells in order to bring the two cell types close together to be able to facilitate T-cell-mediated cytolysis. And then finally, we will also be discussing BCMA-directed chimeric antigen receptor or CAR T-cells.

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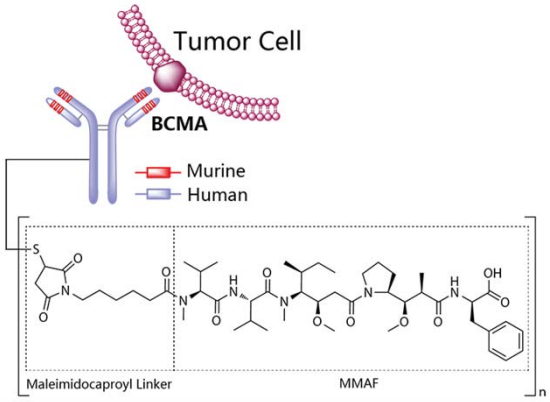
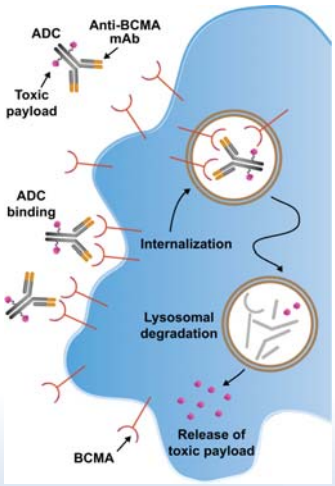
Anti-BCMA-ADC: Belantamab Mafodotin





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

So first, the anti-BCMA-ADC. This is the agent belantamab mafodotin. This agent is an antibody directed against BCMA, which is linked via a cleavable linker to the anti-tubule agent, MMAF. As shown here in this diagram, the antibody carries the toxic payload. The antibody binds to BCMA on the surface of the myeloma cell. The antibody gets internalized and then degraded within the lysosome leading to release of a toxic payload within the myeloma cell.

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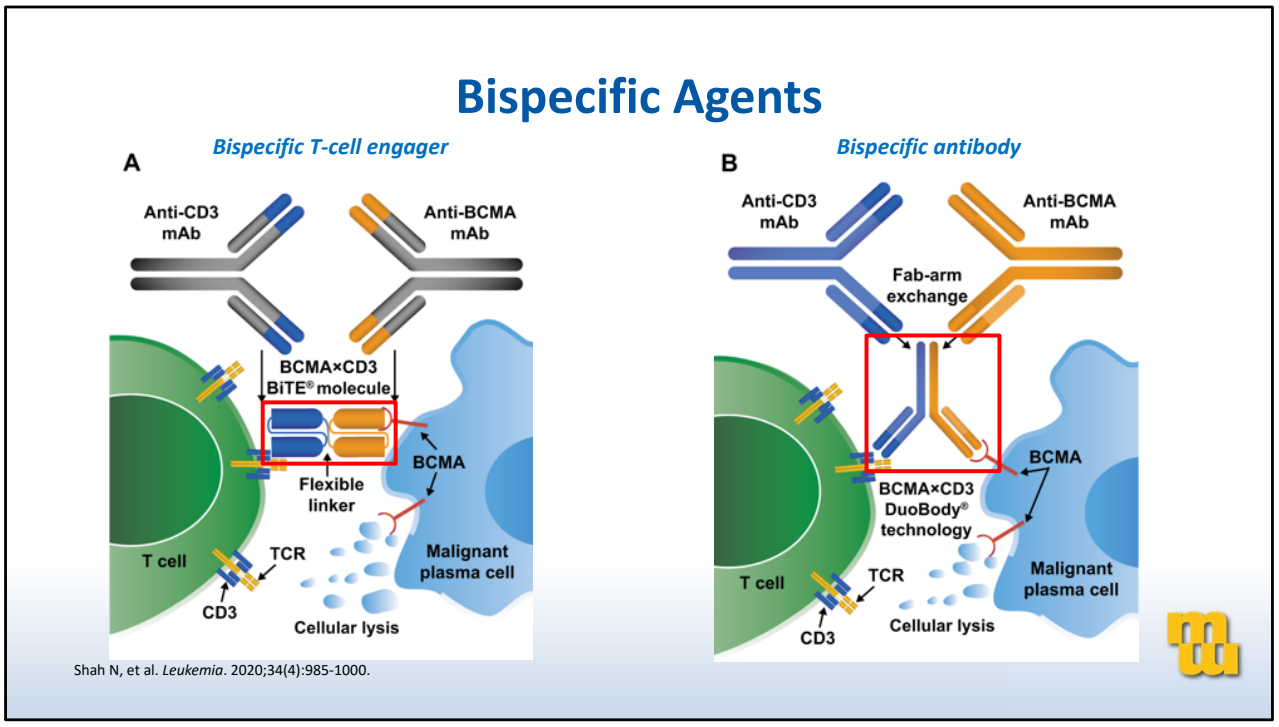

Shah N, et al. *Leukemia*. 2020;34(4):985-1000.

For the bispecific agents, first I'll start with the bispecific T-cell engagers. This involves taking the antigen recognition domains from an anti-CD3 antibody and an anti-BCMA antibody and linking them together with a flexible linker. So, as you can see, this then allows for this agent to bring together in close proximity the T-cell via the CD3 moiety and the plasma cell via the BCMA moiety to enable T-cell-mediated cytolysis. Somewhat related but slightly different is the bispecific antibody approach. Here shown in the red box is a DuoBody approach where you can see that the therapy is a complete antibody. However, half of the antibody has been derived from an anti-CD3 antibody and the other half has been derived from an anti-BCMA antibody. Again, the result is the same. This allows for the T-cell to be brought into close proximity with the BCMA bearing malignant plasma cell.

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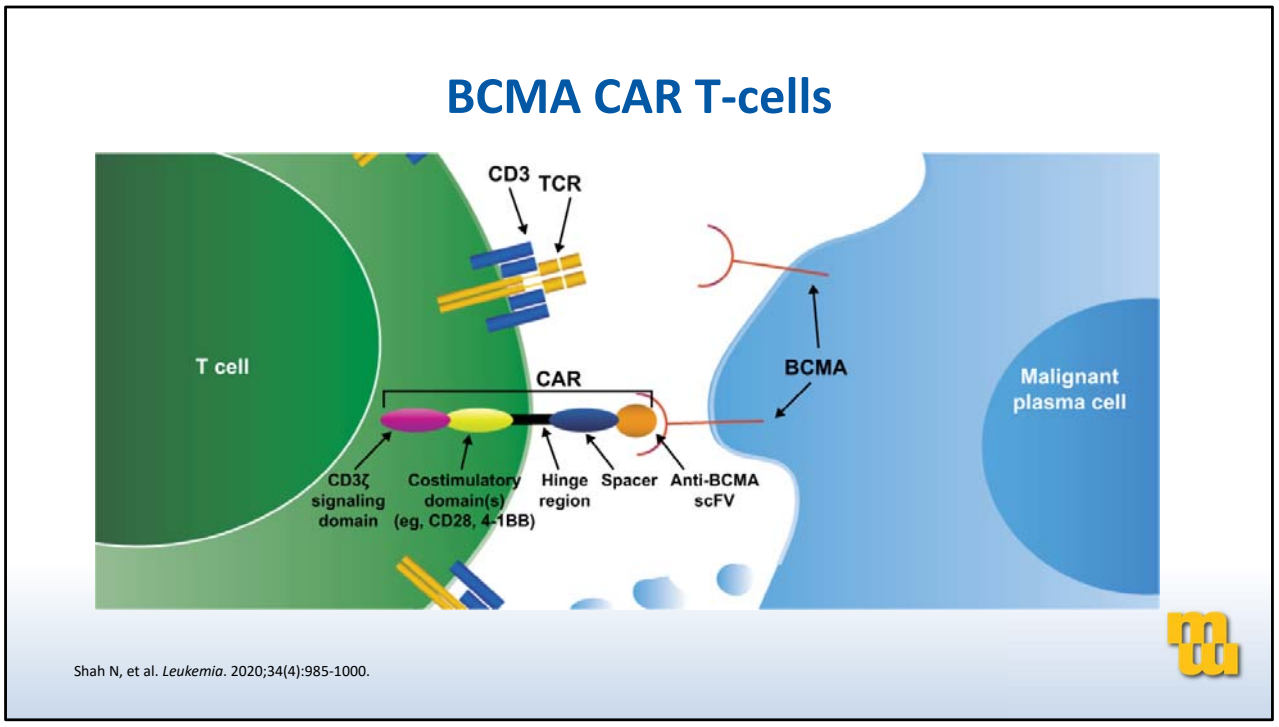

And then finally, we have our BCMA CAR T-cells. The construct for the CAR is very similar to what has been used previously with B-cell lymphomas. Namely, there's a CD3-zeta signaling domain, a costimulatory domain, a hinge region, spacer, but then the antigen recognition part is directed against BCMA. So you have the T-cell with this chimeric antigen receptor on the surface, which then recognizes BCMA on the surface of the malignant plasma cell.

Future Directions for Anti-BCMA Therapies

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

Those three classes represent the current direction of anti-BCMA therapy. But clearly there are many new directions that will lead to our future. Some of these involve the development of CAR-NK cells. There's also interest in the development of allogeneic BCMA CAR T-cells as this might provide an off-the-shelf option. There's also been interest in developing multi-targeted CAR T-cells, for example, there was a recent publication in which the CAR T-cells are directed against both BCMA and GPRC5D. A little bit later on in today's session, we'll be talking about the role of gamma-secretase inhibitors. And then as with everything else we do in myeloma, it is likely that we will move on to using all these BCMA therapies in combination with other myeloma drugs.

So, with that, it's my pleasure to now turn it over to Dr. Baljevic to talk about the efficacy of the BCMA-directed therapies.

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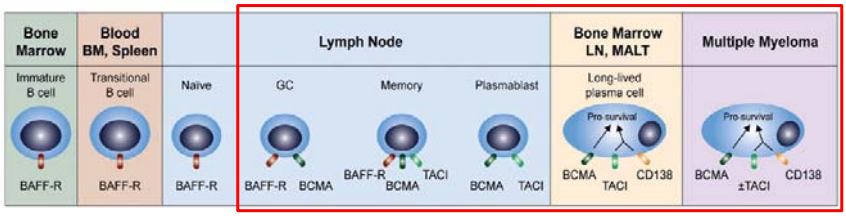
The Efficacy of BCMA-directed Therapy in Myeloma: What Do We Know?



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Department of Internal Medicine
University of Nebraska Medical Center
Omaha, Nebraska

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

Thank you very much Dr. Holstein. It is my pleasure today to address several questions in this evolving field with Dr. Holstein and Dr. Callander, and over the next several slides, I will be talking about the efficacy of BCMA-directed therapy in myeloma and at what point we find ourselves at the moment with the available data.

First, we will start by addressing the anti-BCMA antibody-drug conjugate, belantamab mafodotin. As Dr. Holstein mentioned, this is one of the earlier constructs that became available in targeting BCMA as an antigen. It's important also just to mention at the beginning that because of the breadth of expression of BCMA along the different stages of B-cell development, of course, this became very attractive target for therapeutic purpose in multiple myeloma, but has not been the only target in terms of exploiting therapeutic potentials in relapsed/refractory multiple myeloma.

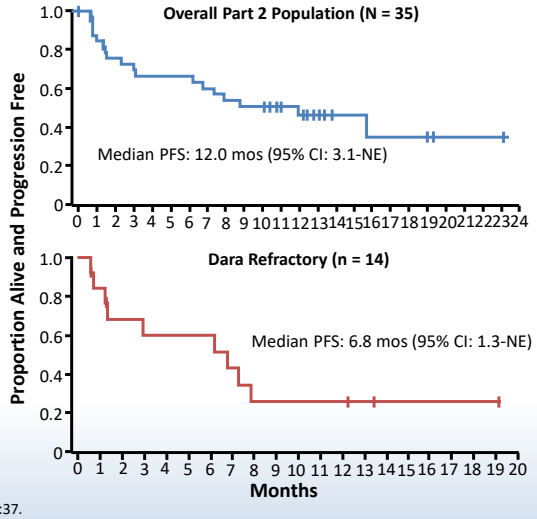
Taking Aim at an Ideal Therapeutic Target in Relapsed/Refractory Multiple Myeloma

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.

Phase I DREAMM-1 belantamab mafodotin study in relapsed/refractory multiple myeloma already reported and this was data that looked at individuals who had relapsed/refractory myeloma where 97% were PR refractory, out of which 77% had Kyprolis resistance or carfilzomib; 95% were IMiD refractory, out of which 63% were exposed and refractory to pomalidomide; and where 40% also were daratumumab anti-CD38 monoclonal antibody refractory. After median follow up of 12.5 months, overall response rates in the cohort of 35 patients was 60% with stringent CR being 6%, complete response or CR 9%, and VGPR or very good partial response of 40%. So, it is quite clear here that overall response rate stretched a significant extent and that median time to response was in fact fairly quick, 1.2 months, and median duration of response in this cohort was just over 14 months. Another piece of data that was available with this study is that double-refractory patients had slightly better overall response rate of 56% than triple-refractory patients with IMiD, PI, and anti-CD38 therapy refractoriness with an overall response rate of 38%.

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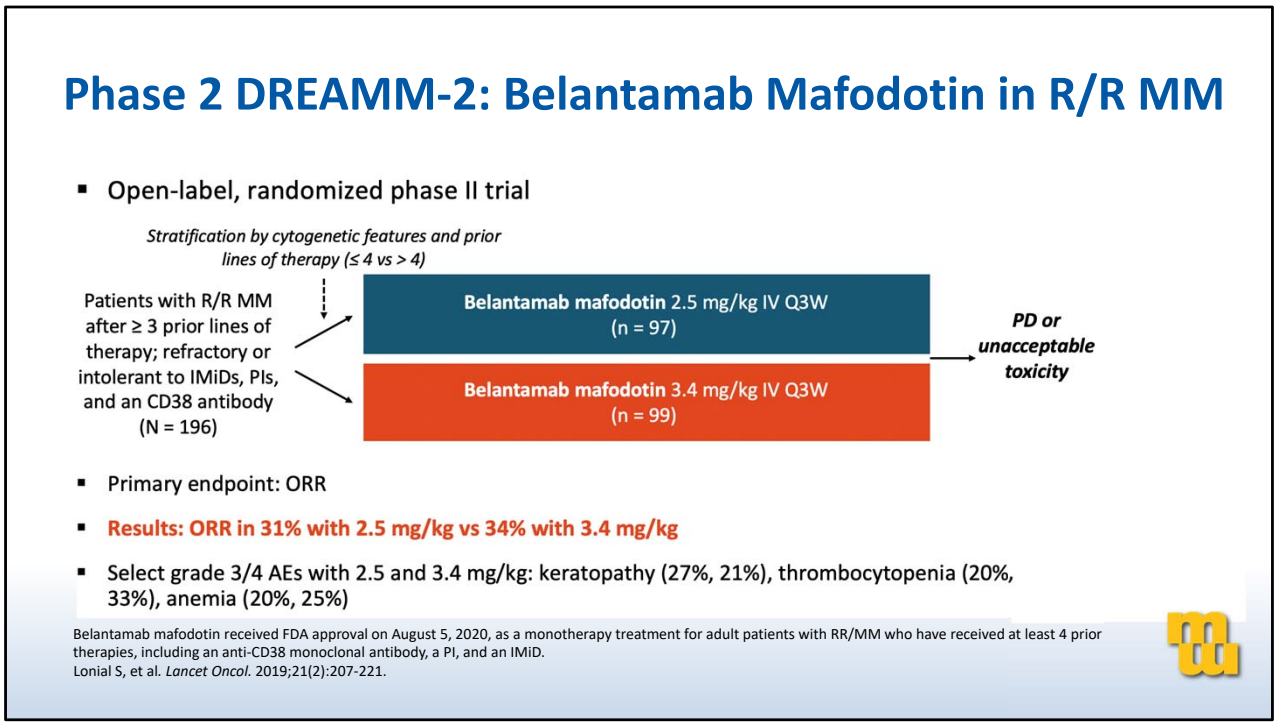

In this trial, two different doses of belantamab mafodotin were explored, 2.5 and 3.4 mg/kg. Primary endpoint was overall response rates. Results showed an overall response rate of 31% with the 2.5 mg dosing versus 34% with the higher 3.4 mg/kg dosing. Dr. Callander will subsequently touch on some of the safety profiles of this and other BCMA therapies, but briefly we can mention that select grade 3/4 adverse events with 2.5 and 3.4 mg dosing included keratopathy and thrombocytopenia, anemia, and notably two deaths that were reported as treatment related at a 2.5 mg dose; one being related to sepsis and the other being related to HLH.

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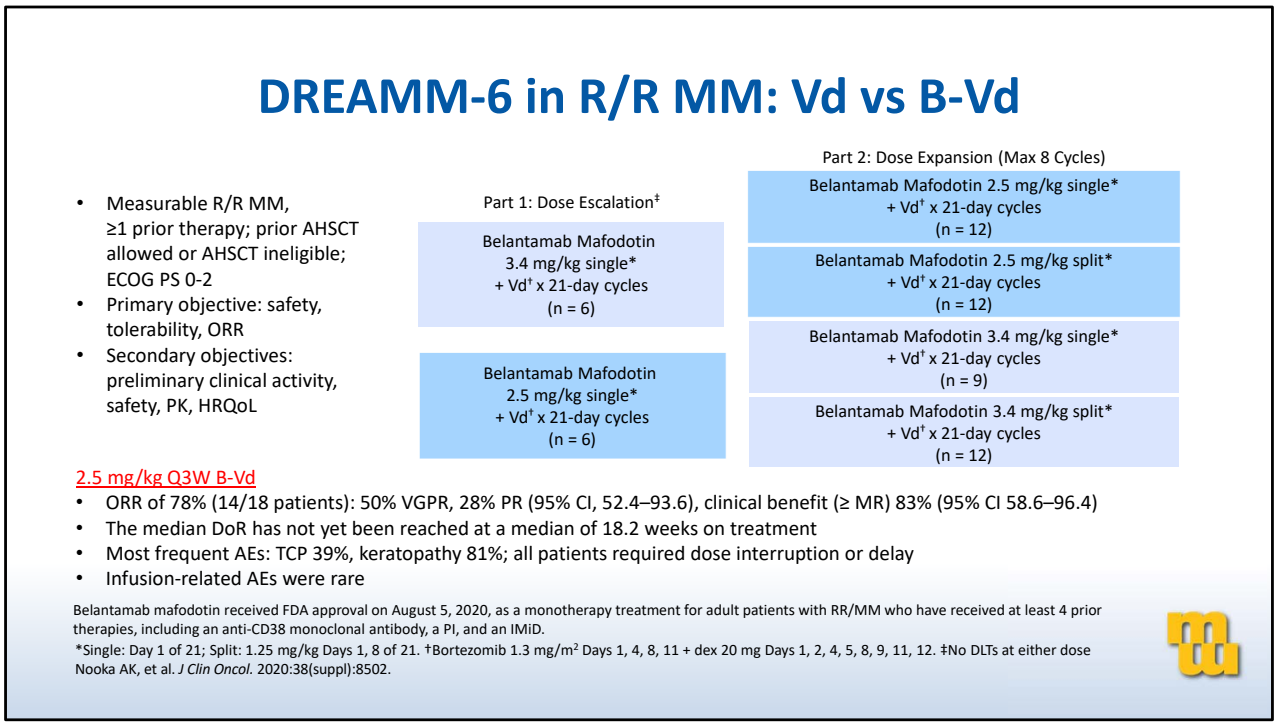

The final study we'll discuss in anti-BCMA ADC subgroup is DREAMM-6 study which was conducted in relapsed/refractory multiple myeloma patients. This is an ongoing two-part, two-arm study evaluating the safety and tolerability and clinical activity of belantamab mafodotin in combination with bortezomib and dexamethasone, and lenalidomide with dexamethasone in patients previously treated with greater than or equal to one prior line of therapy. Here, we're going to present the data of belantamab mafodotin in combination with bortezomib and dexamethasone. Part one, which was dose escalation, and part two, which was dose expansion, evaluated belantamab at 2.5 and 3.4 mg dosing administered a single day one or split dose divided equally on days one and eight in combination with bortezomib and dexamethasone. At the 2.5 mg/kg q.3 weekly dosing in the combination arm with belantamab, bortezomib, and dexamethasone, overall response rate was 78%, out of which 50% achieved very good partial response, and where total clinical benefit, which was defined as response level greater than or equal to minor response and greater, was 83%. The median duration of response has not been reached yet at a median follow up of just over 18 months. Most frequent adverse events were cytopenias and keratopathy. Again, Dr. Callander will be expanding further on.

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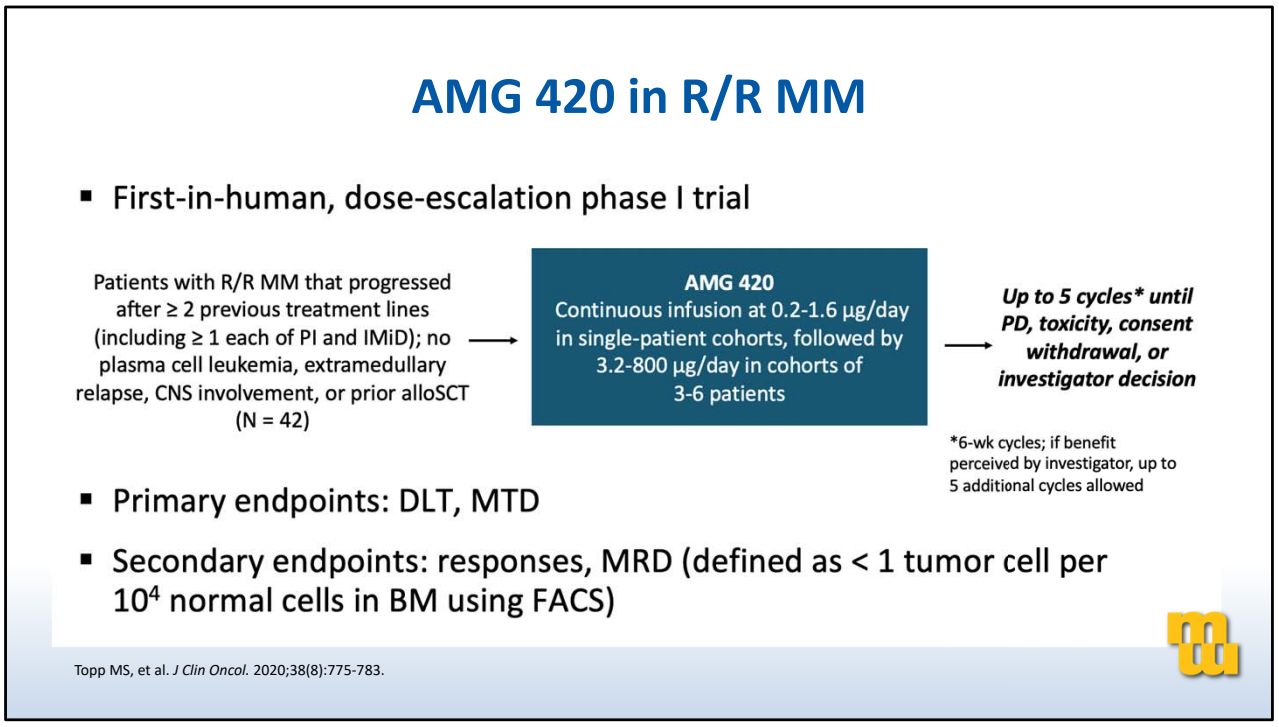

In terms of bispecific T-cell-engager therapies that are targeting BCMA, an early candidate certainly was AMG 420. That was advanced in relapsed/refractory multiple myeloma patients with an early phase trial where therapy was given in patient populations with greater than or equal to two prior lines of therapy including greater than or equal to one each of PI and IMiD. Patients with plasma cell leukemia extramedullary disease CNS involvement in prior allogeneic stem cell transplantation were excluded as is often the case.

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

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.

In the phase I dose escalation study, reported overall response rate was 70%, including five MRD-negative responses. Unfortunately, the downside of this form of therapy was that this was involving a four-week continuous infusion with an off two weeks for a total six weeks cycle. And there were additional significant side effects including peripheral neuropathy and the CRS grades that ultimately were prohibitive for further development of this bispecific antibody. Subsequent to this, AMG 701 entered as a candidate in the anti-BCMA bispecific T-cell engager field. This is a molecule which has an extended half-life where weekly dosing is possible and where certainly side effects are still possible as well. The large phase I and II trial is currently underway and we're expecting to see further data soon.

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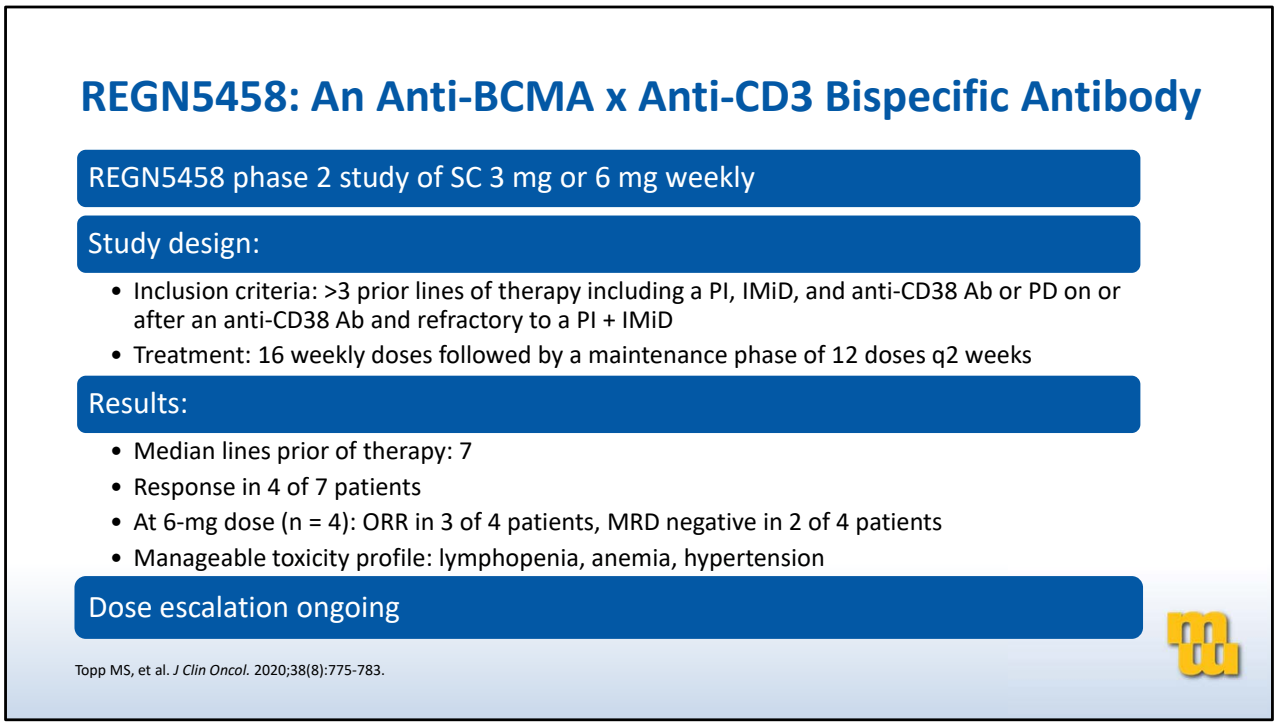

One of the novel agents inside the BCMA bispecific T-cell engager field is REGN5458, anti-BCMA and anti-CD3 bispecific antibody. This data was just recently presented at the ASH 2019 conference. This bispecific antibody has different binding characteristics. And inside the phase I study, it was administered as subcutaneous injection at 3 mg and 6 mg weekly dosing. Responses we're seen in four out of seven patients at a 6 mg dose where four patients were treated, overall response rate was in three out of four patients, with MRD-negative response in two out of four. This bispecific antibody had manageable toxicity profile with lymphopenia, anemia, and hypertension, and at the moment, dose escalation phase is currently ongoing.

It's worth to note that some of these patients, in addition, had extramedullary disease involvement and that the preliminary results actually demonstrated quite efficient resolution of some of the extramedullary and skin sites with plasma cell involvement, so this certainly is one of the promising newer anti-BCMA antibody therapies.

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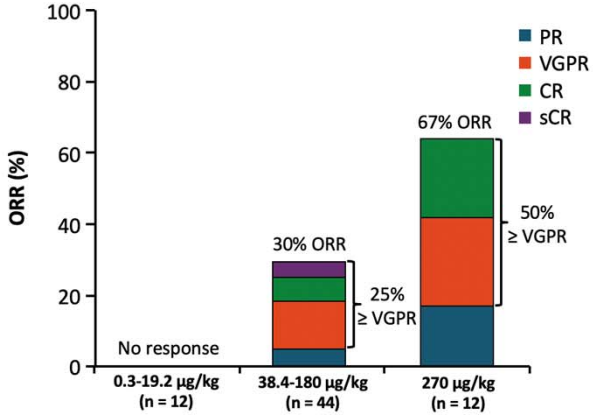
Teclistamab: An Anti-BCMA x Anti-CD3 Bispecific Antibody



- 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.

Another candidate inside the anti-BCMA bispecific antibody is teclistamab, which targets anti-BCMA on myeloma cells as well as anti-CD3 on T-cells. This clinical study in all 78 patients in relapsed/refractory multiple myeloma patients, median age was 64, median number of prior therapy was six, ranging anywhere from 2 to 14, and 72% of participants were triple-class exposed, 62% were triple-class refractory, and 51% were penta-drug refractory. Efficacy data at 720 mcg/kg dose are not mature yet, but at the 270 mcg/kg dosing, seven out of eight responders were triple-class refractory and five out of eight were penta-drug refractory. Overall response rate was 67% with the greater than or equal VGPR rate of 50%. Response deepened over time where 16 out of 21 patients who responded had an ongoing response. BCMA and CD3 bispecific antibodies such as this approach offer off-the-shelf immunity to therapy for patients that will certainly be available at a shorter timeframe than potential CAR T-cell therapies that we'll be touching on in a moment. Adverse events included CRS and cytopenias. CRS was 56%, mainly grade 1 and 2. There was a grade 3 or equal cytopenia rate that was also notable, and Dr. Callander will likely be expanding on some of the specifics in the coming slides.

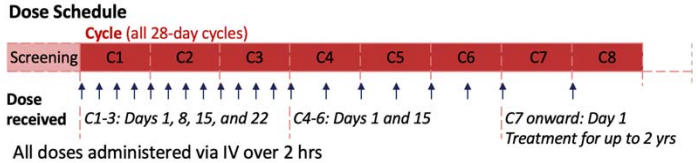
Taking Aim at an Ideal Therapeutic Target in Relapsed/Refractory Multiple Myeloma

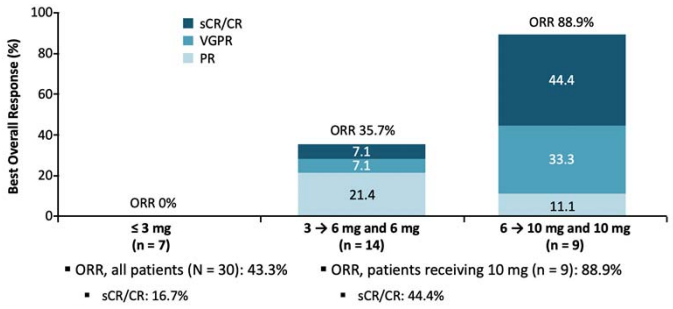
CC-93269: A Humanized Anti-bivalent BCMA x Anti-monovalent CD3ε BiTE

- 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.





An anti-BCMA bispecific antibody of note also includes CC-93269, which is a humanized anti-bivalent BCMA and anti-monovalent CD3 bispecific T-cell engager. This is an asymmetric two-arm humanized IgG T-cell engager that binds bivalently to BCMA and monovalently to CD3 in a two-plus-one format. This early phase clinical trial involved dose escalation in two stages. In stage 1, CC-93269 was given in a fixed dose; and stage 2, patients receive fixed first dose in cycle one, day one followed by intrapatient dose escalation in cycle one, day eight. Overall number of patients exposed in this trial was 30 where patients had to be relapsed/refractory to at least three prior lines of therapy and have progression of disease within 60 days of last regimen. No prior BCMA-targeted treatment was allowed. Median number of prior regiments in this cohort was 6, ranging from 3 to 12. Significant proportion of patients also had prior exposure to autologous stem cell transplants, 73%, allogeneic transplant, 10%, Revlimid or lenalidomide 100%, pomalidomide 84%, bortezomib 100%, carfilzomib 84%, and daratumumab 94%; 88% of patients were refractory to daratumumab, 89% or 17 patients to the last PI, and 84% to the last IMiD. Overall response rate of this bispecific T-cell engager was 88.9% in a higher cohort, which was dosed at 6 mg to 10 mg dosing with VGPR response rate of 33.3%. CR/stringent CR response in the higher cohort of 10 mg included a response rate of 44%, so certainly good quality and deep responses in this early phase clinical trial.

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

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.

Lastly, we will touch base on selected ongoing or planned clinical trials exploring anti-BCMA CAR T-cell therapies in multiple myeloma.

In this space, there's a number of clinical trials that are ongoing that have been completed. But we will pay note to several clinical trials, which have the most mature data, and some of which have already been published. That includes CARTIFAN-1, a multicenter trial from China, which was a phase II trial of the estimated 60 patients; a CARTITUDE-1 multicenter worldwide trial, which was a phase I/phase II with over 100 patients enrolled; EVOLVE trial, which was a multicenter trial in the US, phase I/phase II, with also over 100 patients involved; and a KarMMa trial, which was similarly a multicenter worldwide clinical trial of 150 patients. All these patients, as can be seen, had to have at least three prior lines of therapy involving PIs and IMiDs, had to be exposed to these forms of therapies, some of these trials had to also additionally have anti-CD38 therapy exposure, and they had to be experiencing disease progression in the last treatment within 12 months, for example, like in the CARTITUDE trial.

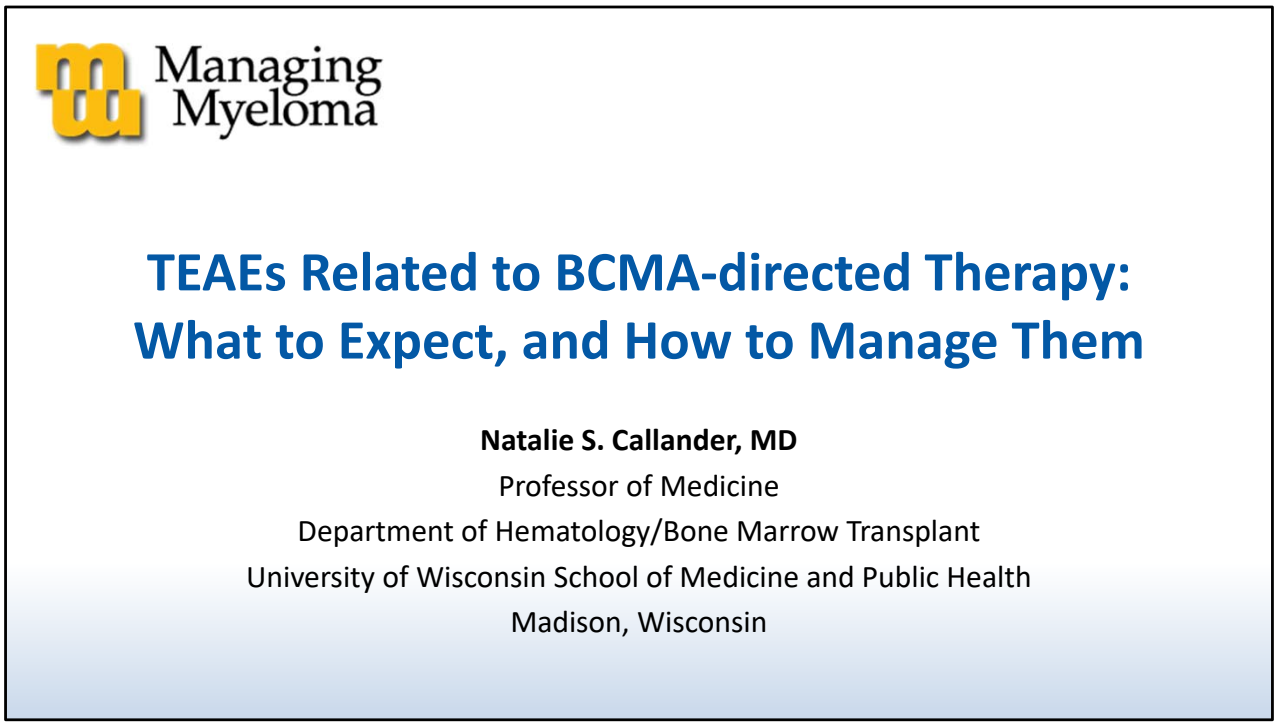
Taking Aim at an Ideal Therapeutic Target in Relapsed/Refractory Multiple Myeloma

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.

Overall responses are as follows: In the KarMMa trial, with 158 patients treated, overall response rate was 73% with complete response of 33% and an MRD-negative response rate of 26%. Median time to response was one month with a PFS reported thus far of 8.8 months. Safety profile included the CRS of 84% with grade 3 CRS of 4% and grade 4 less than 1% with neurotoxicity rate of 18% and a grade 3 neurotoxicity of 3%. CARTITUDE reported on 29 patients with an overall response rate of 100% and a stringent complete response rate of 86%. Median time to respond similarly in this patient cohort was one month or one treatment cycle. CRS rate was 93% with grade 3 CRS of 7% at least, and fusional neurologic side effects included a 10% rate with a grade 3 or equal rate of 3%. EVOLVE JCARH125 trial treated about 62 patients where overall response rate was reported at 92% with stringent complete response plus complete response overall response rate being 36%, and MRD-negative response rate in evaluable patients of 84%. PFS has not been reached yet in this clinical trial at a six-month median follow up. CRS was low at 3% with low rate of grade 3 CRS as well and neurologic symptoms also were very low at 3%. Lastly, the updated results of the LEGEND-2 trial with LCAR-B38M construct that reported on 57 patients reported an overall response rate of 89% with a stringent CR or CR response rate of 74%, and an MRD-negative rate of 68%. It should be noted that in terms of eligibility in this trial, patients required to be exposed to prior therapy which contained the PI and at least three prior lines of therapy. Time to response was similarly short, 1.1 months with a PFS reported at a follow up of 19.9 months and an overall survival of 36.1 months. CRS was 90% with a grade 3 or greater at 7%, and neurotoxicity was low at 2% with no grade 3 or higher neurotoxicity signals. At this point in time, I would like to have Dr. Callander take the next portion of the talk with the toxicity profiles of this therapy.



Alright, thanks very much. So, my portion is going to be talking about treatment emergent adverse events that are related to BCMA therapy, what to expect and how to manage them. So, I wanted to start with a couple of case histories.

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

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

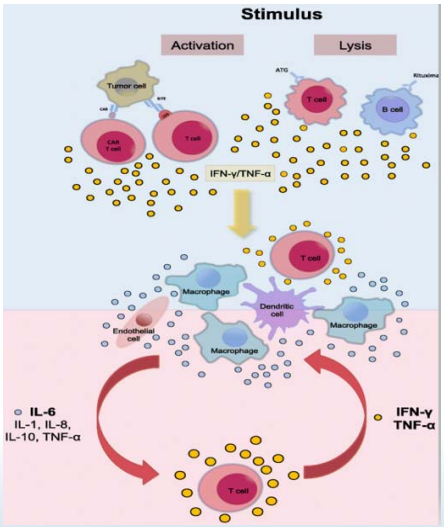
- 59-year-old male with R-ISS Stage 2 MM
- VD, auto, R; KRd, KPomD, DaraPomD, Erd, Bendamustine
- CAR-T transplant
- 36 hours post transplant T 102, HR 130, BP 78/50, creat 2.1 mg/dL, disoriented, O_2 sat 85%

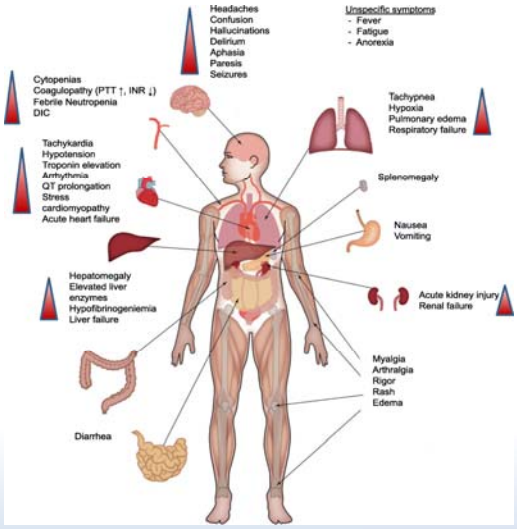
HOW WOULD YOU MANAGE THESE CASES?

These are two patients who both underwent CAR-T transplant. On the left, is a 55-year-old male with revised ISS stage 3 multiple myeloma. Treatment is listed there. This patient underwent a bb2121 CAR-T transplant. In about 12 hours post infusion, spiked a temperature to 101, heart rate of 110, blood pressure of 120/80, but overall the patient is fine and the O2 saturation is normal. On the right, though, is a patient, 59 years old, with revised ISS stage 2 myeloma diagnosis but who has clearly been through many different treatments, also receiving a CAR-T transplant. In 36 hours, this patient post-transplant spikes a temperature of 102, heart rate of 130, blood pressure 78/50; creatinine has bumped to 2.1 mg/dL from normal. The patient is disoriented and O2 saturation on room air is 85%. Now both of these patients actually have cytokine release syndrome but they're obviously in different situations.

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

Effector Cells and Targets in CRS

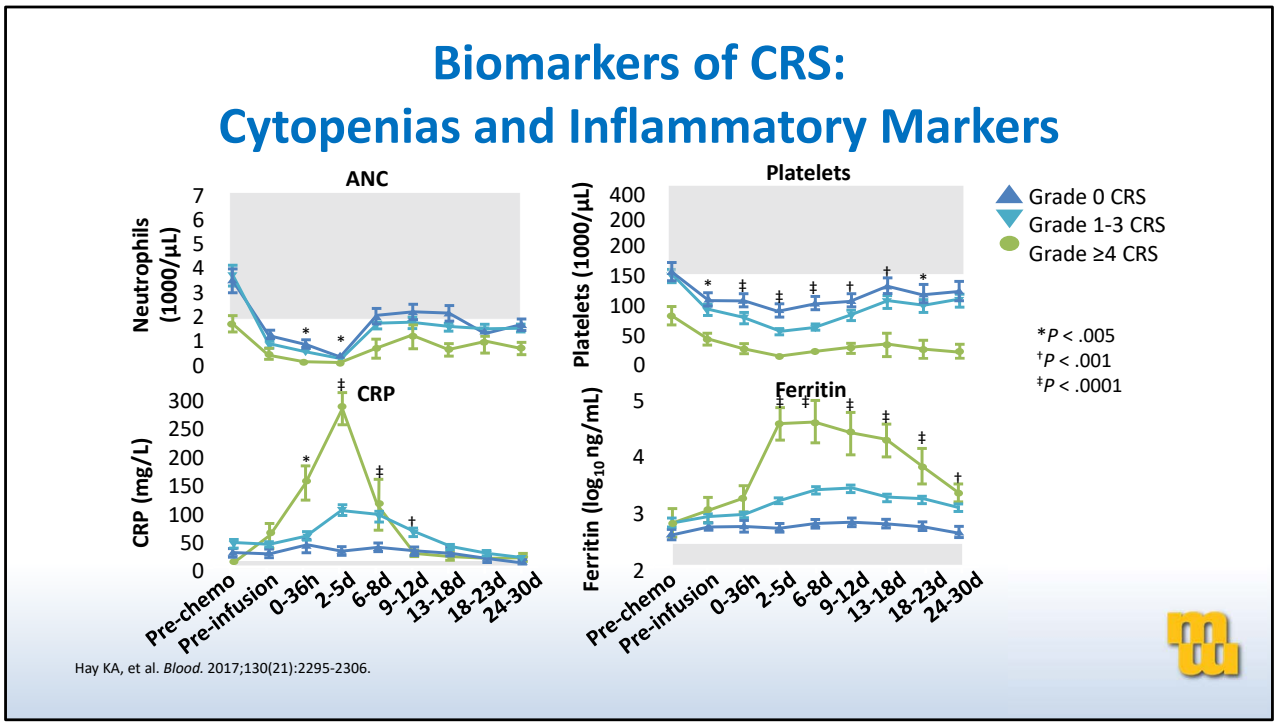




Shimabukuro-Vornhagen A, et al. *J Immunother Cancer.* 2018 6(1):56.-

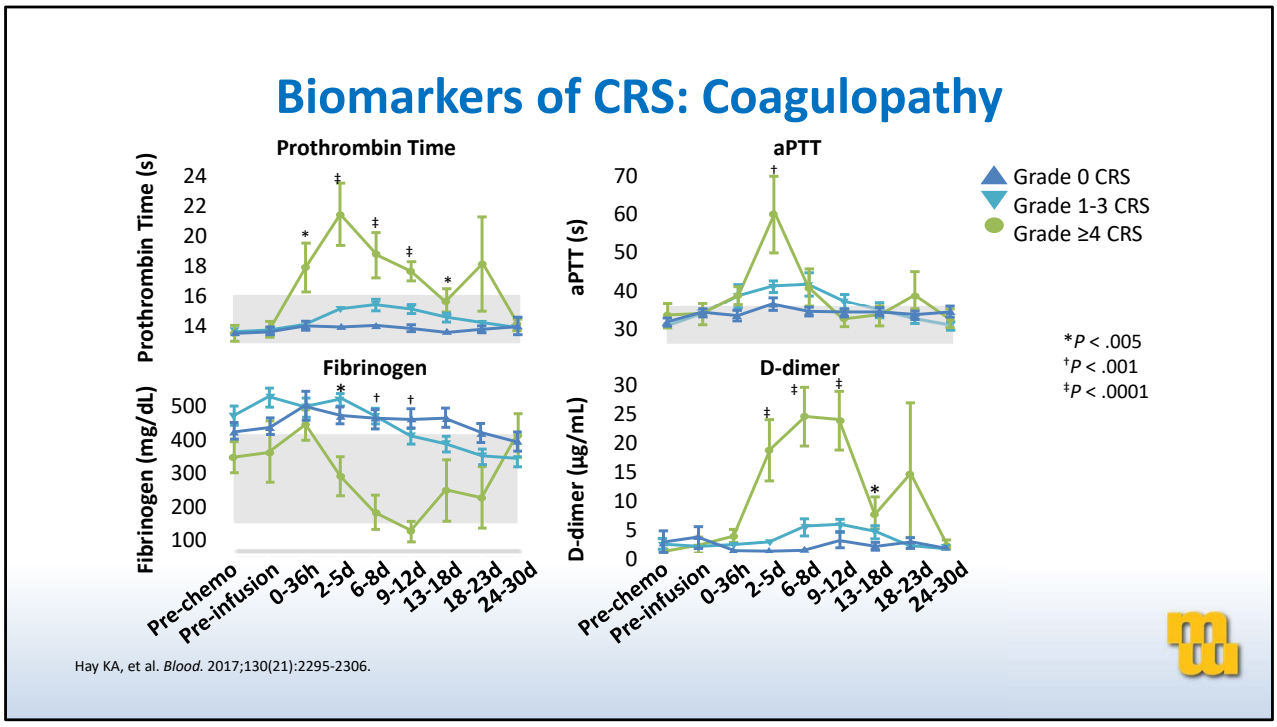
So, cytokine release syndrome is defined as a systemic cytokine-driven inflammatory state that results from the activation and expansion from T-cells that can be part of a CAR-T or other cellular therapies that activate T-cells. And it can range from an extremely mild problem to one where it's really life threatening. And the action does not just involve the T-cells themselves, but also host immune cells are brought into play such as dendritic cells and macrophages, and some of the key cytokines that are involved include IL-6, IL-1, IL-10, TNF-α, and IFN-γ among others. And these cytokines act to have profound effects throughout a number of body systems. So, besides fever, which is really one of the defining symptoms, there can be effects on lungs such as pulmonary edema and hypoxia. The GI tract, you can see diarrhea, nausea and vomiting and anorexia. Patients can have acute kidney injury, not uncommonly. Myopathy is also possible including myositis and actually rhabdomyolysis. Liver failure can be seen. Cardiac events include tachycardia, but also troponin leaks and even carditis as well, and finally cytopenias are extremely common. And in terms of CNS events, patients can present with confusion, like the second patient, but also seizure can happen and then obtundation as well.

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



Now, there are markers that we can follow to decide if somebody is having CRS besides clinical symptoms and very commonly patients who develop CRS have cytopenias including neutropenia and thrombocytopenia. In addition, markers such as C-reactive protein and ferritin are elevated, and if you look at grades of CRS, typically, patients with the highest grade have the most profound deregulation or perturbation of these particular parameters. In one note about ferritin is that patients who start off prior to whatever therapy they're receiving with a ferritin above 1500 seem to be more at risk to develop CRS.

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



Similarly, in terms of coagulation abnormalities, patients often present with prolonged INRs and PTTs. Patients can have profound hypofibrinogenemia if they do have severe CRS grade 4, and also D-dimers can be quite elevated. And as you can see also from the previous graph and this one, these perturbations can actually last quite a bit of time.

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

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.

Now, there have been a number of different grading systems when we talk about CRS. About a year and a half ago, the American Society for Transplant and Cellular Therapy decided to try to consolidate some of these grading systems and come up with something that would provide a common language. And basically what they really did is throw out some of the organ-specific grading parameters and basically left it with fever, hypotension, and hypoxia. And then grades of CRS progress as you develop one after another of these symptoms and findings. So, grade 1 CRS includes fever; grade 2, mild hypoxia; grade 3 requiring a vasopressor plus additional oxygen; and grade 4 requiring unit support including intubation as well as multiple pressors.

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

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.

They also did the same thing for the grading of what is known as cytokine release encephalopathy syndrome and basically developed what's called ICANS, which stands for immune effector cell-associated neurotoxicity syndrome, and this involves first calculating an ICE score. And this is asking the patient several parameters such as their orientation, naming three objects, following some simple commands, writing a sentence, and then counting and, therefore, the patient gets an ICE score between zero and 10.

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

New ASTCT Guidelines for Grading of ICANS

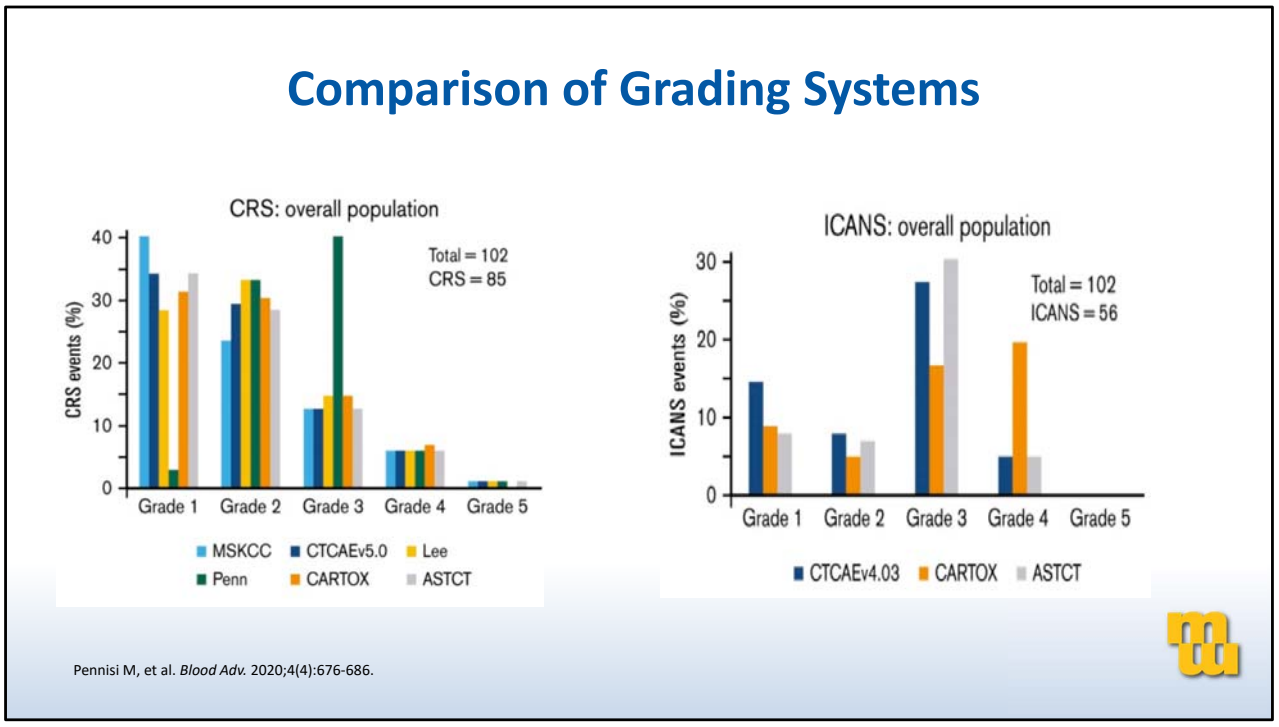
Neurotoxicity Domain	Grade 1	Grade 2	Grade 3	Grade 4
ICE score*	7-9	3-6	0-2	0 (patient is unarousable and unable to perform ICE)
Depressed level of consciousness†	Awakens spontaneously	Awakens to voice	Awakens only to tactile stimulus	Patient is unarousable or requires vigorous or repetitive tactile 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.

Then they go on to be graded. So, based on that ICE score as well as other signs and symptoms including are they awake or not, are they having seizures, are there any motor findings, or is there elevated intracranial pressure or cerebral edema noted. And again, the grading goes from one to four.

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



Now, in comparison with other grading systems, the ASTCT grading system holds up pretty well. The one outlier here in green, on the left bar graph, is from Penn. They relied primarily on some organ system grading. And the CRS, the ICANS also lines up pretty well. So, I think most of the studies are going to try to utilize this ACTCT grading system for clarity.

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

- 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)

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)**

- Tocilizumab use: 52%
- Steroid use 15%

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

Now, let's look at some of the specific incidences of CRS. So, Muhamed mentioned in the previous talk that side effects are quite common in CAR-T trials. But if you look at the table on the left, most of these are actually hematologic problems. So, the majority of patients do develop neutropenia, anemia, and thrombocytopenia; but non-hematologic grade 3/4 toxicity is relatively uncommon as shown on the graph on the right. Now, if we specifically focus on CRS, actually, lots of patients develop CRS, 84% in this KarMMa trial that was updated at ASCO this year, but only about 5% of patients really have grade 3 or higher CRS. So, tocilizumab that is used to block IL-6 was delivered in 52% of patients, and about 15% of patients also received steroids.

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

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

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

- 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

Similarly, in the CARTITUDE-1 trial that Muhamed alluded to, again, same pattern, and this is seen pretty much in all CAR-T trials where the hematologic toxicity is often grade 3 with that neutropenia and thrombocytopenia. But the non-heme toxicity is usually fairly manageable. And in this particular study, CRS of some grade occurred in 93% of patients but, again, only 7% had grade 3. One thing that's demonstrated here is if you look at the KarMMA trial using bb2121, the median time to onset of CRS was about a day. In CARTITUDE, using the JNJ-4528, the median time to onset is seven days with a duration of four days. And in this particular trial, 79% of patients received tocilizumab and 21% received anakinra, the IL-1 blocker, or corticosteroids.

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

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

Now, in terms of toxicity management, one of the principles is patient selection upfront. It's difficult in myeloma because many of the patients, as Dr. Holstein alluded to earlier, these are patients who are often heavily pretreated, and we really are looking for therapies; so, some of them will really have some abnormalities in terms of lab studies at the beginning. We still try to pick people who have reasonable performance statuses, and we also want to try to have some hematologic function. Many of the studies require platelets of at least 50 to 75, and an ANC of 1000. There isn't really a lymphocyte cutoff in most of these studies, but we don't want any signs of active infection and particularly not active viral infections such as hepatitis B, C, or HIV. And then reasonable organ function, so, again, an ejection fraction of about 45%, creatinine clearance at least 30 mL or above.

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

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.

In terms of toxicity should it arise, as shown in the first couple of panels, you want to be looking at CRP and ferritin and hematologic parameters and evidence of coagulopathy, you also have to keep an account that maybe some of the laboratory derangement is actually coming from tumor lysis and so this is something to keep in mind. Most studies asked for either prophylaxis with antiepileptic drugs such as Keppra (levetiracetam), but if they aren't on it and patients look like they're developing CRS, it would be a good time to start them. And most patients are asked to receive bacterial, fungal, and viral prophylaxis. But, again, one thing to remember that particularly as these patients are neutropenic and febrile, they should also be covered for bacterial infections as well. Once a patient has CRS, typically daily labs are required. And depending on the product, some of these patients are going to be inpatients with monitoring happening, and for those receiving outpatient treatment, they will be asked to come into the clinic each day or actually admitted.

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

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.

Now, in terms of treatment, primarily the two drugs that are being used are tocilizumab and steroids and, again, as the grades go up, so does the intervention. Grade 1 CRS typically supportive care only or possibly steroids and then on up with grade 2 tocilizumab and so forth as you can see in this particular table. For neurotoxicity, steroids are really thought to be very important and should be started early. And, again, for patients who might have both, usually the combination is given. You always want to rule out alternative causes and do so on an ongoing basis. And steroid dosing tends to vary from protocol to protocol. One other important thing to keep in mind since these patients are neutropenic, if they are going to be in a prolonged course of steroids, appropriate fungal prophylaxis against an invasive mold should also be considered.

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

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

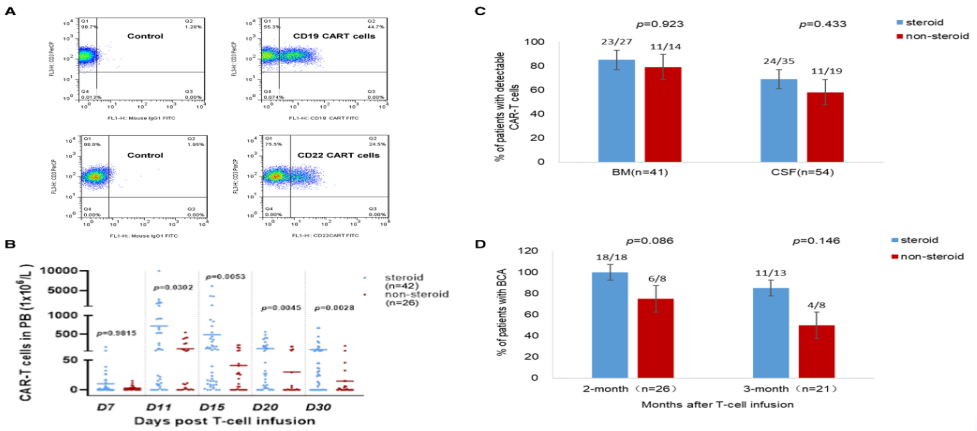


Fig. 1 Kinetics of CAR-T cells in relapsed/refractory B-ALL patients treated or not treated with steroids (detected by flow cytometry). a The representative flow cytometry plots showing CAR-T cells. **b** CAR-T cell numbers in peripheral blood (PB) on day 7, 11, 15, 20 and D30. **c** Percentages of patients 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.

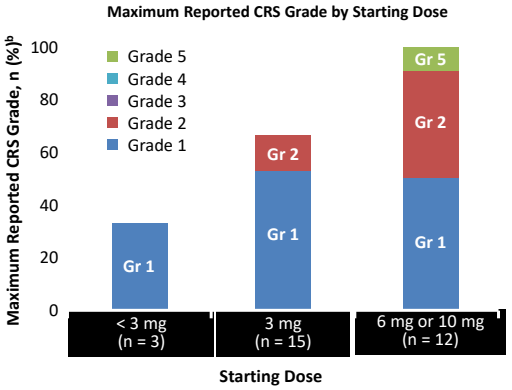
Now, one question that's come up in CAR-T trials and other trials involving T-cell products is, are steroids bad? In other words, are steroids going to make those CAR T-cells or those other T-cells go away? And this is a very interesting study published recently looking at patients with B-cell ALL receiving anti-CD19 CAR-Ts. And what is shown here in the graph, on the bar graph on the right in particular, is if you look at patients who either receive steroids in the blue bars or didn't receive steroids at all in the red, both looking at T-cell numbers immediately at post infusion and then at two and three months, there seems to be no particular detriment in terms of survival of these CAR-Ts leading, I think, many people to conclude that the use of steroids is probably not detrimental and may be a good thing to consider early on.

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

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.

Now, bispecific engagers, as Muhamed mentioned, have the same issue with CRS. The pattern is a little different, though, so I won't repeat some of the data that he showed, high incidence in the CC-93269 product of CRS, but the pattern is that with the first dose, that's where you see most of the CRS, and then with subsequent doses, the incidence goes down so that by the third or fourth dose, you're hardly seeing any CRS at all. And this may be very important once these drugs become commercially available. So, it's possible that there might be a lead in where patients are actually hospitalized for the first couple of doses but as they continue on these products that they can be monitored as an outpatient. Similarly, the grade of CRS is actually fairly mild in this study. Only 3% of patients had grade 3 or higher CRS and this data is very similar to what was presented at ASCO on tocilizumab as well.

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

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)

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

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

PD or unacceptable toxicity

- Primary endpoint: ORR
- 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.

Now, the antibody-drug conjugates, as mentioned, keratopathy has been the side effect of most noteworthiness I guess. The CRS incidents with these antibody-drug conjugates is actually quite low, a couple of percent. But keratopathy seems to occur with belantamab in a fairly high frequency in DREAMM-2 that was 27% of patients.

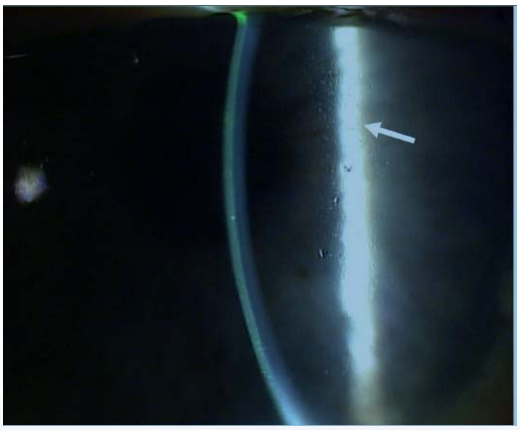
Taking Aim at an Ideal Therapeutic Target in Relapsed/Refractory Multiple Myeloma

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]

And what keratopathy symptomatically is typically dry eyes or blurry eyes, and this is occurring in about at least a quarter of the patients at a grade 3/4 level and requires usually a dose hold. On the right here, is a picture from a cornea showing that these patients get microcyst-like epithelial changes and right now it looks like the best way to manage this is with a dose hold. There was a small study done looking at the effect of steroid eyedrops in preventing this kind of toxicity, and that really seemed to be ineffective.

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

Conclusion

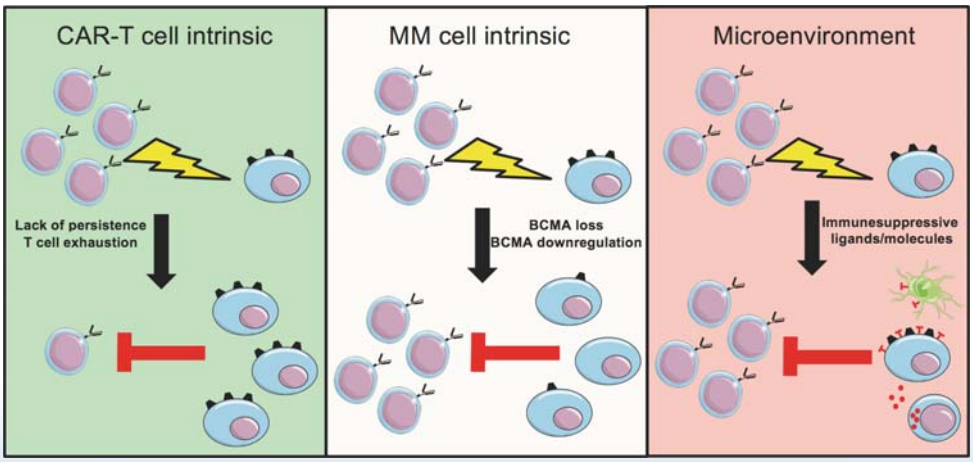
- CRS is common following BCMA directed CAR-T, bispecific engagers, rare with ADCs
- Life-threatening CRS and CRES is less common
- Early intervention likely important
- Don’t forget “basics”, ie, empiric therapy for neutropenic fevers
- Preparation is very important to prevent poor outcomes
- Steroids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

So, in conclusion, CRS is very common following typically CAR-T transplants and it's also quite common following bispecific engager therapy, but it's pretty rare at least it seems so now with antibody-drug conjugates. Life-threatening CRS and CRES or ICANS is fortunately much less common, and early intervention is probably very important in keeping patients from progressing. We should never forget basics of just good oncologic care. So, empiric therapy for neutropenic fevers, steroid-receiving patients should have antifungal coverage. Preparation is really a key here so that most centers who are doing these kinds of T-cell therapies have their tocilizumab on hand, they have their pharmacists working, they have their ICUs ready, their ER is ready to admit these patients if they've come in. And finally, I think that there is now agreement that steroids are probably not detrimental to CAR T-cell survival. And I'm going to turn it back to Dr. Holstein. Thank you.

Thank you, Dr. Callander for that excellent summary. Before we delve into our panel discussion, I just have a few slides talking about what we know about resistance mechanisms and sequencing of these BCMA-directed therapies, and the spoiler is that we don't know a lot.

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

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

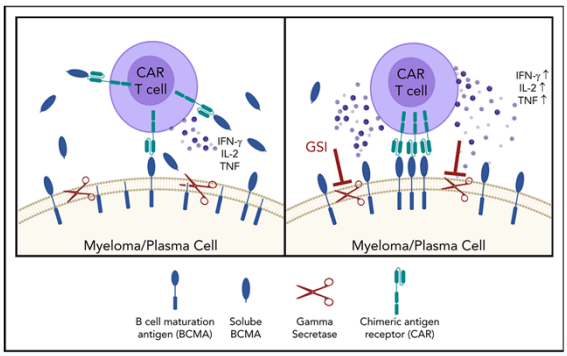


D'Agostino M, Raje N. *Leukemia.* 2020;34(1):21-34.

This is a figure from a CAR T-cell review, but some of this is relevant to other BCMA-directed therapies aside from CAR T-cells. So, here, the authors have broken down potential mechanisms into three classes: One are CAR T-cell intrinsic. So, remember that for many of these studies that have involved BCMA and CAR T-cells, these are very heavily pretreated myeloma patients, so their T-cells might not be as fresh and active as we would like them to be and might have issues with persistence and T-cell exhaustion, especially once inside the body. There are also myeloma cell intrinsic mechanisms of resistance, and one major one appears to be loss of BCMA from the cell surface. Now, this could be occurring through either down regulation of BCMA expression or through cleavage of BCMA leading to the soluble BCMA. And this mechanism of resistance, in particular, would be relevant for all three of the classes that we've discussed as all three of these classes really depend on being able to bind BCMA at the cell surface and not be sucked up in the serum instead. And then there are also microenvironment issues as well. We know that the microenvironment in myeloma is very complex, and that there are variety of immunosuppressant ligands and cells, which might be suppressing either the activity of the CAR T-cells or the patient's native T-cells with respect to the bispecific therapies.

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.

I wanted to touch on just one therapeutic strategy to overcome one of these potential mechanisms of resistance, and that's targeting the gamma secretase. So, if you recall, during my introductory slides, I mentioned that BCMA can be cleaved from the cell surface. And so in this cartoon, the cleavage enzyme is shown by the little scissors icon, and this is the gamma secretase; so, it cleaves the extracellular domain of BCMA leading to the soluble BCMA. And, again, the soluble BCMA can interact with the CAR T-cell or with the ADC or with the bispecific agents, and if those agents are interacting in the serum instead of at the cell surface then they're not going to be effective. So, a potential way to overcome this would be to use an agent which blocks the activity of the gamma secretase and, therefore, leads to a decrease in the soluble levels of BCMA and an increase in the cell surface BCMA levels. So, an interesting proof of concept study was presented at this past year's ASH by Dr. Cohen and colleagues. This was a phase I study where they use an oral gamma-secretase inhibitor in combination with BCMA CAR T-cells. Notably, they had seven patients and they included two patients who had previously received prior BCMA therapy. The study was designed so that patients got an initial three doses of the gamma-secretase inhibitor, and they were able to show that this led to an increase in cell surface BCMA levels and a decrease in soluble BCMA levels. Following the oral administration of the gamma-secretase inhibitor, patients then went on to receive the CAR T-cells and although this is a very small number of patients, it was very encouraging that they saw 100% overall response rate. So, I think this is very intriguing and this therapy could be relevant not only for BCMA CAR T-cells, but certainly could envision using it to try to enhance the activity of bispecific agents and even ADCs as well.

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

Sequencing Anti-BCMA Therapies

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

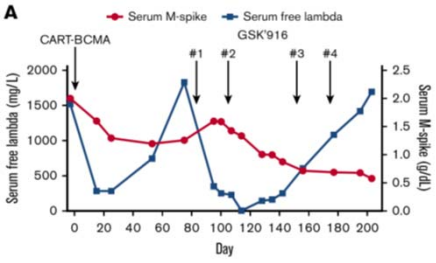
- ADC: Phase 2 DREAMM-2 study
- Bispecifics: AMG 420, teclistamab, CC-93269
- CAR T: bb2121, JNJ-4528

So, what do we know about sequencing anti-BCMA therapies? Truly, we know very, very little. And that's in part because the majority of the clinical trials that have been conducted thus far that you've heard about today have purposely excluded prior BCMA therapies, so this includes a phase II DREAMM-2 study, which is currently being evaluated by the FDA. This includes many of the bispecific antibodies as well as several of the key CAR T-cell players.

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.

So, what we really have at this point are anecdotal reports. We have an interesting report from Dr. Cohen and colleagues published last year showing two patient examples where they received serial treatment of BCMA-directed therapies. The first patient was very heavily treated and initially received phase I study of BCMA CAR T-cells and only achieved a minimal response. Although, if you look over on the right, the red line represents the serum M-spike and the blue line represents the light chain. So, you can see that after CAR T-cell therapy, the lambda light chains decreased very dramatically but then, unfortunately, the patient progressed. Subsequently then, the patient was put on a phase I study of belantamab. And here, again, you can see that there is an initial decrease in the lambda light chains and a minimal response with respect to intact M-protein. The second patient they presented also was very heavily pretreated. Here, they first received belantamab but, unfortunately, progressed. They then received bridging therapy with pembrolizumab, lenalidomide, and dexamethasone, and then were enrolled in a phase I study of BCMA CAR T-cells where they did have a partial response. Some other little bit of data that we have from those past ASH comes from a Chinese CAR T-cell study in which they used a fully human BCMA CAR T-cell construct. Notably, four out of the 16 enrolled patients had previously relapsed on a murine BCMA CAR T-cell trial, and all four of these patients then subsequently responded to this fully human BCMA CAR T-cell construct. So, certainly, there are little glimpses that perhaps there is rationale for using one BCMA therapy after a different one has failed, but clearly we're going to need much more data to understand how to sequence these therapies.

Dr. Holstein: So with that, now, I'd like to turn over to our panelists today to talk about some of these issues, and I think one of the key questions that's on everybody's mind is how we are going to fit in these BCMA-directive therapies into the current treatment paradigm for myeloma. So, I guess more specifically, my first question for my colleagues would be, which patients do you think would be most appropriate for an ADC versus a bispecific versus a CAR T-cell assuming that we are living in a world where all three types of therapies were FDA approved? Dr. Callander, you want to take a stab?

Dr. Natalie Callander: Sure, I mean, I think, one thing that Muhamed alluded to, which is really important, is that both antibody-drug conjugates and bispecific engagers are right there, particularly if patients are relapsed and refractory and quite symptomatic, they often don't have the time, at least with the current technology, for a CAR T-cell to be manufactured and are really looking for a solution right away. So, I think, particularly assuming that belantamab is approved, I think that is going to be a very widely used product right now. I don't know what you all think about that.

Dr. Sarah Holstein: Dr. Baljevic.

Dr. Muhamed Baljevic: I absolutely agree with Dr. Callander regarding this notion. I think one of the things that we have all learned being involved in these trials with some of our patients is that, unfortunately, the time necessary for generation of CAR T-cells can sometimes be just enough for patients to progress. By definition, these trials allowed only bridging forms of therapy that included only therapies that patients have previously already been exposed to, not allowing novel forms of therapy to be used. So, I personally had a patient who lost candidacy and who had a choice of joining a trial with belantamab, for an example. So, I think there's going to have to be some careful and judicious clinical decision making that we don't have to do for our patients to try to determine as best as we can what is the group of patients that might be able to last and wait for the generation time that autologous CAR T-cells will require, and what are those that are probably better off relying on these, sort of, off-the-shelf ready forms of BCMA therapies. One more thing to mention, of course, and I think it's been alluded to in today's talk is that we are potentially heading towards the future where we might even have allogeneic CAR T-cells that are targeting myeloma epitopes available. So, certainly, these levels of considerations will then no longer be an issue, but as you, Dr. Holstein, mentioned, this is really still very much an unexplored area where we're going to start seeing a greater number of patients once these therapies enter market and we no longer just rely on small case studies as you have showed in terms of efficacy of one BCMA therapy after another.

Dr. Sarah Holstein: And assuming that you had a patient whose disease was controllable enough that you could think about CAR T-cell, is there is a reason that you would pick a bispecific over a CAR T-cell or vice versa? Dr. Callander.

Dr. Natalie Callander: Well, we've been fortunate enough to have a couple of the studies

with belantamab open, and some of the patients have had just really outstanding responses. I think it would be lovely to understand exactly who that's going to be if we could figure that out. But, it's obviously a much easier therapy, it's outpatient. When CAR-T transplants go well, it seems like a very reasonable therapy, but there is a lot of morbidity involved with it. I think the results of some of the more upfront studies such as CARTITUDE-4 and, I think KarMMa-3, I think, they're really going to teach us something about whether the effort that is required to have a patient go into a CAR-T program makes sense in comparison with other available therapies.

Dr. Sarah Holstein: Dr. Baljevic, any additional thoughts?

Dr. Muhamed Baljevic: One of the KarMMa trials actually in its design is involving the use of therapies that are available for patients, for example, that have progressed within 18 months following the use of autologous stem cell transplant consolidation or those that were not fit for transplant that have also progressed within that same timeframe or even for individuals who failed to achieve VGPR or greater response depth after induction. So, I think that, particularly data of this type, so here, in this trial, the KarMMa-2 trial here that's shown on the slide with these cohort two subgroups, I think it's going to be particularly valuable once we get more information on these individuals as well because certainly this would involve assessing the efficacy and safety profiles in patients at earlier lines of therapy and surely we also have a number of clinical design that are in planning that will attempt to bring the utility of CAR T-cells at earlier opportunity. So, I think we will learn a lot about what type of patterns of expression and safety profiles we're seeing, and I think that will also raise questions about what in the end we will have to do for these patients who progress, and certainly the mechanisms that you have shown in some of the case reports will be very important as well as other epitopes that are targeted by either bispecific T-cell engagers or CAR T-cell therapies.

Dr. Sarah Holstein: Dr. Callander, are there patients who might have certain comorbidities where you would think, no this patient really should not even be considered for CAR T-cell therapy?

Dr. Natalie Callander: Well, I think you certainly would like to have your patients ambulatory and, you know, again just sort of some baseline ability to do ADLs. The issue comes up is that we all, I think, would agree on this panel that more and more we're seeing patients who have very refractory disease, but still have the performance status that you want to try to give them another therapy. I would certainly say a person with a PS above 3, unless you're completely convinced that it's only related to myeloma and nothing else, I would be nervous about that person but certainly I think most of us would want to have patients who really can perform at least minimal ADLs before considering a CAR-T. But I don't know what you both think.

Dr. Sarah Holstein: Dr. Baljevic?

Dr. Muhamed Baljevic: Dr. Holstein, I would like to hear what you think actually here as well.

Dr. Sarah Holstein: Yes, you know, I think we aren't clear yet. I think the impulses to think about if they were strong enough to be considered for an autotrnasplant then perhaps we should also be able to consider them for a CAR-T, but the two are obviously not equivalent. So, I think we're still learning. With autologous stem cell transplant, all of us have an age threshold where we at least start to get very nervous, and I don't think at this point that we quite understand whether that same age threshold or comorbidity index is the same for CAR-Ts as it is for autologous stem cell transplant or even allogeneic stem cell transplant. So, we're all in the learning phase, I think, at this point. And then I guess for community providers out there, once these agents do become available, do you recommend that before they start any of these agents for their heavily relapsed/refractory patients that they get referred to a myeloma center of excellence or a transplant center of excellence for an opinion first?

Dr. Natalie Callander: I would certainly agree with that, and partly because I'm sure you both have had this experience as well. We've had some patients who had been referred where the local provider, perhaps not understanding what it might take to have a patient go through CAR-T, has sort of been waiting, is kind of like the last thing that we will then refer them in and by the time the patient then shows up, there's too many obstacles, again the hematologic parameters are too low or the patient is now failing. So, of course, we would always encourage people to refer them in early for consideration of clinical trials and cellular therapy.

Dr. Sarah Holstein: Excellent. Any last-minute points that either of you would like to make today?

Dr. Natalie Callander: I would just like to say this is one of the most exciting times, I think, in multiple myeloma treatment that 20 years ago, we were sort of scrounging around for different drugs or different formulations of drugs. We have so many things now we can offer patients, and I think that in it itself is great. I think all of us here have many patients now who are 10 plus years out from their original diagnosis, that used to be amazing, and now it has become sort of routine. I think we're all very excited to learn about these therapies and what we can do to make them work better. So, this has just been a great time, I think.

Dr. Sarah Holstein: I absolutely agree. Dr. Baljevic, any last thoughts?

Dr. Muhamed Baljevic: I will just make two quick points relating to what Dr. Callander alluded to earlier. I think it is very important that there’s going to be a little bit of work left to talk in general about the relevance and importance of CAR T-cell therapy, not just for very high-risk patients. It seems to me that sometimes the reason for delay is that perhaps some providers think that the CAR T-cell is only reserved for very high-risk patients and not standard-risk patients. Certainly by definition, when they're refractory to these grades as these trials are accruing, these are already high-risk patients and it's going to be important,

as was mentioned, to try to refer them as soon as possible so that we can try and appropriately plan and develop strategies that can be timely for these patients and not find ourselves in situations where we lose opportunities to administer and deliver certain form of therapy because of the timing factor.

Dr. Sarah Holstein: So, I want to thank Dr. Baljevic and Dr. Callander for joining me today, and for participating this this panel discussion. Thank you everybody who participated in this activity.