

IMMUNOTHERAPY ADVANCES IN RRMM

Overview

Multiple myeloma has become the most common hematologic malignancy in the United States adult population with over 120,000 people living with the disease. Despite new and more effective treatments, multiple myeloma, unfortunately, remains largely incurable with relapse and disease progression still common.

Dr. Ola Landgren discusses advances in the field of immunotherapy for relapsed refractory multiple myeloma (RRMM). He discusses different treatment modalities and their unique strengths and limitations which have shown high antimyeloma activity that may address a critical unmet need in heavily pretreated and refractory patients. Dr. Landgren indicates that future studies will help identify optimal combinations and sequencing of different immunotherapies.

Target Audience

This activity was developed for community-based hematologists-oncologists, nurse practitioners, nurses, and other healthcare professionals.

Learning Objectives

At the conclusion of this activity, participants should be better able to:

- Assess the factors that determine the choice of therapy for patients with relapsed/refractory multiple myeloma, including disease heterogeneity, risk stratification, prior therapies, patient characteristics and comorbidities, performance status, and treatment goals
- Compare and contrast the current and emerging immunotherapy approaches for patients with RRMM, including the evolving role of immunotherapies targeting BCMA in this setting
- Adequately translate immunotherapy clinical trial findings into the real-world setting for patients with RRMM

- Manage adverse events associated with the use of immunotherapy in the care of patients with RRMM

Faculty

C. Ola Landgren, MD, PhD

Chief, Myeloma Service

Memorial Sloan-Kettering Cancer Center (MSKCC)

New York, NY

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Editor's Note: This is a transcript of a webcast presented on July 20, 2020.

Ola Landgren, MD: Welcome to this presentation entitled, "Immunotherapy Advanced in Relapsed Refractory Multiple Myeloma." This activity is supported by educational grants from Bluebird bio, Sanofi and Legend. My name is Ola Landgren. I'm chief of the Myeloma Service at Memorial Sloan-Kettering Cancer Center in New York City and I'm professor of medicine at Cornell Medical College.

Multiple Myeloma Stats

- The most common hematologic malignancy in the adult population
 - Over 120,000 people living with the disease
 - In the absence of curative therapies, the number of people living with MM will continue to rise rapidly
- US estimates for 2020:
 - 32,270 new cases
 - 12,830 deaths
- Incidence rates:
 - 8.7 per 100,000 men
 - 5.6 per 100,000 women
 - More than twice as high in blacks as in whites
- Median age at the time of diagnosis: 69 years
- 5-year survival rate: 52.2%

Landgren O. *Best Pract Res Clin Haematol*. 2020;13:101155.
Siegel RL, et al. *CA Cancer J Clin*. 2020;70(7):30.
NCI SEER. Available at: seer.cancer.gov/factsheets/multiplemyeloma.html.



As a brief background, multiple myeloma has become the most common hematologic malignancy in the adult population in the United States with over 120,000 people living with the disease. The estimation from the National Cancer Institute and American Cancer Society is that more than 32,000 patients were diagnosed in 2020. This translates into incident rates of 8.7 per 100,000 men and 5.6 per 100,000 women every year. It's twice as common in Blacks compared to Whites. The median age of onset is 69 years and the 5-year survival rate is about 52%.

Multiple Myeloma Complex Genetic and Molecular Landscape

- Historically, two main categories of abnormalities described:
 - Hyperdiploidy, characterized by gains of odd numbered chromosomes
 - Immunoglobulin heavy chain (IGH) translocations, including t(4;14), t(6;14), t(11;14), t(14;16), and t(14;20)
- In addition, recurrent chromosomal gains and losses have been reported, eg, gain 1q, del(13q), and del(17p)
- Some of these aberrations define subgroups of patients associated with poor prognosis, e.g., t(4;14), t(14;16), and del(17p)

Yellapananda V, et al. *Blood Cancer J*. 2019;9(10);
Manser S, et al. *Nat Rev Clin Oncol*. 2017;14:100-113.
Morgan GJ, et al. *Nat Rev Cancer*. 2012;12:335-348.



about 2 main categories of abnormalities. The hyperdiploid cases, about half of patients have gains and losses of odd numbered chromosomes and immunoglobulin heavy chain or IgH translocations involving chromosome 14 in about the other 50%. In addition, there are a lot of other chromosomal gains and losses reported including, for example, 1q gain, 13q deletion and 17p deletion and others. Some of these aberrations have been proposed to confer a high-risk or poor prognosis group but there is much more information coming and more data has been published the past 12 to 24 months.

Multiple Myeloma Complex Genetic and Molecular Landscape (cont.)

- Emerging data suggest that current high-risk definition can be further improved
 - For example, bi-allelic events including TP53 and >3 copies of 1q have been recently associated with poor outcomes
- Current standard-of-care setting:
 - Conventional chromosome analysis, myeloma-targeted FISH panels, and single nucleotide polymorphism (SNP) microarrays to detect translocations and gain/losses
- Neither FISH nor SNP microarray approaches are able to capture somatic point mutations

Yellapananda V, et al. *Blood Cancer J*. 2019;9(10); Maura I, et al. *Nat Commun*. 2019;10:3035; Walker BA, et al. *Leukemia*. 2019;33:1150-1170;
Walker BA, et al. *Blood*. 2018;132:587-597; Lohr JS, et al. *Cancer Cell*. 2014;25:91-101; Blau N, et al. *Nat Commun*. 2014;5:2997.

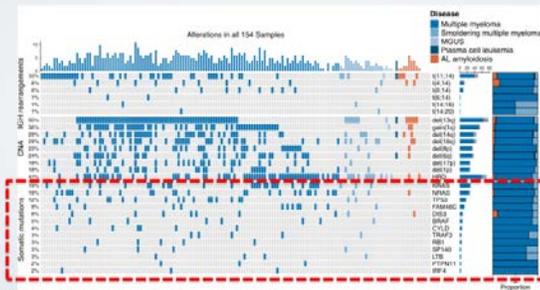


In fact, emerging data suggests that the high-risk definition needs to be further improved. For example, bi-allelic events that include, for example, TP53, seem to be very important and also counting the number of copies of 1q chromosomal aberrations has also been found to be associated with poor prognosis. In the current standard of care setting, people are using conventional chromosome analysis with FISH cytogenetics or SNP array but none of these technologies are able to capture these somatic point mutations that I refer to for the identification of bi-allelic events.

The biology of the disease is complex. When we look with genomic markers, historically, we have talked

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MM-Specific NGS Assay Going Beyond Conventional Cytogenetic Classification



Yellapantula V, et al. Blood Cancer J. 2019;9:101.

Using DNA-based technology, beyond gains and losses and the translocations, it's possible to identify a broad range of somatic mutations. Over 100 frequently recurrent mutations can be found in patients with myeloma. And this would be the way, in the future, to identify patients with true high-risk, merging this information with what you can see with FISH and cytogenetics or you can actually do everything by DNA-based technologies.

Relapsed/Refractory MM Growing Unmet Need

- Despite new and more effective treatments, MM remains incurable.
- Recently, a new subset of patients with triple-refractory disease, ie, refractory to IMiDs, PIs, and mAbs, has emerged.
 - These patients have poor survival outcomes.
 - Thus, there is an urgent and growing unmet clinical need for newer therapeutic strategies for such patients.

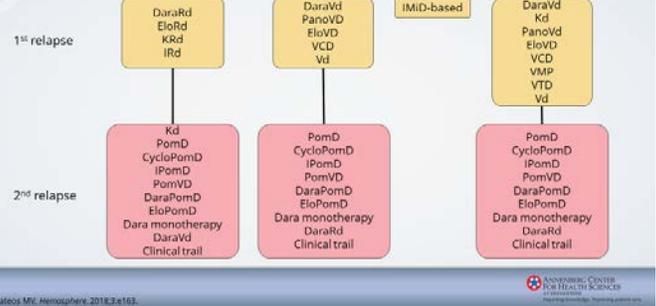
Kumar SK, et al. Leukemia. 2017;31:2443-2448.
Ravi F, et al. Blood Cancer J. 2018;8:26.
Gandhi UA, et al. Leukemia. 2019;33:2256-2275.

Mishael J. Clin Lymphoma Myeloma Leuk. 2020;20:1-7.
Shah N, et al. Leukemia. 2020;34:1085-1005.



Despite new and more effective treatments, multiple myeloma, unfortunately, remains largely incurable. There is not yet any established cure or treatment. Recently, a new subset of patients with triple-refractory disease, ie, refractory to IMiD, PIs and monoclonal antibodies, has emerged. These patients have a particular poor outcome for survival and therefore there is an urgent and growing unmet clinical need for newer therapeutic strategies for these patients. This sets the stage for today's presentation that will cover all the advances in the field of immunotherapy for myeloma.

Relapsed/Refractory MM Current Treatment Options



Mateos M, Hematology. 2018;2:163.

For the relapsed and refractory multiple myeloma patients, there are very many treatment options. This slide summarizes many of those combinations that you also find in the NCCN guideline. In the current guideline, there are almost 40 approved combination therapies for patients with relapsed and refractory disease.

Relapsed/Refractory MM Subsequent Therapy Considerations

- | Patient Factors | Treatment/Disease Factors |
|--|--|
| <ul style="list-style-type: none"> • Age • Comorbidities <ul style="list-style-type: none"> – Renal function – Hepatic function – Neuropathy – Thrombosis – Other • Bone marrow reserve <ul style="list-style-type: none"> – Prior HDT/ASCT – Long-term IMiD therapy – Received alkylating agents • QOL and patient preference | <ul style="list-style-type: none"> • Cytogenetics • R-ISS • Severity and aggressiveness of relapse <ul style="list-style-type: none"> – Progression after therapy – Progression on therapy • Previous therapies <ul style="list-style-type: none"> – Types – Single vs multidrug treatment regimen – Duration • Remission <ul style="list-style-type: none"> – Depth – Duration |

Bazarbachi AH, et al. Leukemia. 2019;33:2343-2357.
Pawlyn C, Davies FE. Blood. 2019;133:660-675.



Which therapies are reasonable to use at the relapse situation? Well, it all depends on both patient factors and of course, treatment and disease factors, age, comorbidities, their reserve of the marrow, quality of life and of course, importantly, patient preference. All those were patient factors. And disease and treatment factors would include biology, if you look at the cytogenetics, stage from initial diagnosis, but I think even more importantly, the severity and the aggressiveness of the relapse, most relapses are biochemical but some of them are symptomatic and they can cause a lot of problems, prior therapies and remission. All these factors we use when we make decisions.

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Relapsed/Refractory MM Current and Emerging Immunotherapy

Targets	Therapeutic Modalities
<ul style="list-style-type: none"> CD38 SLAMF7 (CS1) BCMA Immune checkpoints <ul style="list-style-type: none"> – PD-1/PD-L1, Tim-3, LAG-3, TIGIT FcRH5 GPRC5D NKG2D ligands κ light chain Activated integrin β7 CD19, CD46, CD48, CD56, CD74, CD138, CD229 	<ul style="list-style-type: none"> Naked mAbs ADCs Bispecific mAbs BiTEs CAR T cells CAR NK cells

Coffin AD. Hematology Am Soc Hematol Educ Program. 2019;2019:366-272.
Sidana S, Shah N. Hematology Am Soc Hematol Educ Program. 2019;2019:260-265.
Shah UA, Malankody S. Best Pract Res Clin Haematol. 2020;33:101141.
Ternasca H. J Clin Hematol. 2018;107:279-285. Radhakrishnan SK, et al. J Clin Oncol. 2020;11:798. Hosen N. Cancers. 2018;11:2024.

Targeting CD38 in RRMM Current and Select Emerging Immunotherapy

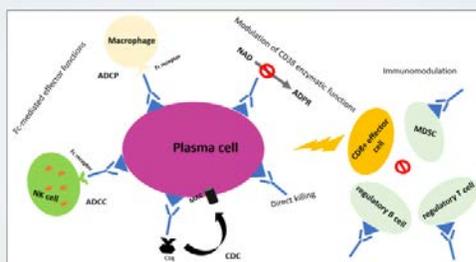
- Daratumumab (naked mAb), FDA approved:
 - In combination with Rd in pts who have received ≥1 prior therapy
 - In combination with Vd in pts who have received ≥1 prior therapy
 - In combination with Pd in pts who have received ≥2 prior therapies including lenalidomide and a PI
 - As monotherapy, in pts who have received ≥3 prior lines of therapy including a PI and an IMiD or who are double-refractory to a PI and an IMiD
- Isatuximab (naked mAb), FDA approved
 - In combination with Pd in pts who have received ≥2 prior therapies including lenalidomide and a PI
- MOR202 (naked mAb, discontinued)
- TAK-079 (naked mAb)
- TAK-573 (naked mAb)
- TAK-169 (naked mAb)
- GBR 1342 (BiTE)
- CD38 CAR T cells

Coffin AD. Hematology Am Soc Hematol Educ Program. 2019;2019:366-272. Washburn K, et al. Best Pract Res Clin Hematol. 2020;33:101141.
Sidana S, Shah N. Hematology Am Soc Hematol Educ Program. 2019;2019:260-265.
Ternasca H. J Clin Hematol. 2018;107:279-285. Radhakrishnan SK, et al. J Clin Oncol. 2020;11:798. Hosen N. Cancers. 2018;11:2024.
DARUMUMAB (daratumumab) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125071Orig1s.001.pdf
ISATUXIMAB (isatuximab) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/125071Orig1s.001.pdf

What type of targets do we have? Now we are moving forward into the presentation with more focus on emerging immunotherapies, both current and emerging ones. CD38, FDA approved since back in 2015, same is true for CS1. BCMA, moving forward, immune checkpoints, FcRH5, in development, GPRC5D, in development, NKG2 ligands, κ or kappa light chain, activated integrin β7 and a whole range of other targets. There are naked antibodies, there are ADCs that carry toxins, we have the bispecific monoclonal antibodies, they have also been labeled as BiTEs, the CAR T cells and also other CARs, focusing on CAR NK cells.

This has led to current and select emerging immunotherapies. Daratumumab was the first FDA-approved antibody targeting CD38 and this is a naked antibody. It's approved for single drug use and also in combination with IMiDs and steroids and proteasome inhibitor and steroids. Isatuximab, naked monoclonal antibody, also FDA approved, the second targeted towards 38 antibody. Approved in combination with pomalidomide/dexamethasone in patients with 2 or more prior lines of therapy. MOR202 is another naked monoclonal antibody going after CD38. And this has been discontinued. And then there are additional naked monoclonal antibodies that also are in development and BiTEs and CAR T cells. So there's a whole range of different strategies to go after CD38.

Targeting CD38 Rationale and Anti-CD38 mAbs MoA



Bonello F, et al. Cancers. 2020;12:15.

Let's start talking about CD38, the rationale and the anti-CD38 monoclonal antibodies. Plasma cells are known to consistently express CD38.

Daratumumab Select Trials in RRMM

Study	Phase	Patients (#)	Previous Therapy (Median #)	Regimen	ORR (%)	Median PFS (Months)	Median OS (Months)
GEN501 + SIRIUS POOLED	2	148	5	Daratumumab monotherapy	31.1	4	20.1
POLLUX	3	569	1	Dara-Rd vs Rd	92.9 vs 76.4	NR vs 17.5	1-year OS 92.1% vs 86.8%
CASTOR	3	498	2	Dara-Vd vs Vd	83.8 vs 63.2	16.7 vs 7.1	NA
EQUULEUS	2	103	4	Dara-Pom-d	60	8.8	17.5
MMY1001	1b	85	2	Dara-Kd	84	1-year PFS 74%	1-year OS 82%

Bonello F, et al. Cancers. 2020;12:15.

Here we have select trials in relapse and refractory. They are phase 2 and phase 3 trials for the most part and then on the bottom you have the 1b which is daratumumab with carfilzomib and dexamethasone. And you see that the overall response rate ranges from 31% to over 90% for these different combinations. The median progression-free survival ranges from single number digits to not reached. And you also see that the

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median overall survival ranges from about 17 months up to much longer. At one year, you have 82% overall survival.

Daratumumab Select Ongoing Trials in RRMM

Study	Setting	Phase	Study Design
EMN14	RRMM (302 pts)	3	Dara-Pom-d vs Pom-d
CANDOR	RRMM (466 pts)	3	Dara-Kd vs Kd

Bonello S, et al. *Cancers*. 2020;12:15.

There were select ongoing trials, daratumumab also for relapsed and refractory with pomalidomide and Dara-Kd in the phase 3 setting. These are large studies.

Isatuximab Select Trials in RRMM

Study	Phase	Patients (#)	Previous Therapy (Median #)	Regimen	ORR (%)	Median PFS (Months)	Median OS (Months)
NCT01749969	1b	57	5	Isa-Rd	56	8.5	NR
NCT02283775	1b	45	3	Isa-Pd	62	17.6	NR
NCT02332850	1b	33	3	Isa-Kd	66	NR	NR
ICARIA-MM	3	307	3	Isa-Pd vs Pd	60 vs 35	11.5 vs 6.5	NA

Bonello S, et al. *Cancers*. 2020;12:15.

Isatuximab has also been published and presented at meetings for the relapsed and refractory setting, phase 1b and phase 3 trials. And here you have combinations with isatuximab with Rev/Dex, isatuximab with Pom/Dex, isatuximab with Kd and isatuximab with Pd vs just Pd in a randomized fashion. And this is what led to the FDA approval, the phase 3 trial. And you have the median PFS in this second right column.

Isatuximab Select Ongoing Trials in RRMM

Study	Patients (#)	Phase	Study Design
IKEMA	302	3	Isa-Kd vs Kd
ICARIA-MM	307	3	Isa-Pom-d vs Pom-d

Bonello S, et al. *Cancers*. 2020;12:15.

There are select trials, large trials in the phase 3 setting.

Daratumumab and Isatuximab Comparison

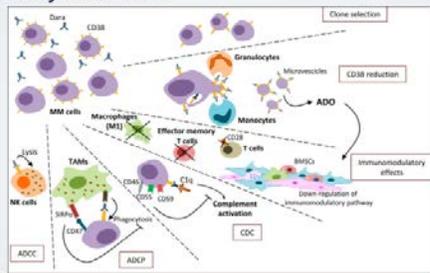
- Bind to distinct CD38 epitopes, which may contribute to the differences in their mode of action.
 - Both induce ADCP and CDC, and both demonstrate ADCC that can be potentiated by other antimyeloma agents.
 - Isatuximab, unlike daratumumab, can also induce direct apoptosis.
 - Isatuximab does not lead to decreased CD38 expression, whereas daratumumab leads to the CD38 clustering and release in microvesicles.
 - Isatuximab, unlike daratumumab, inhibits CD38 ectoenzymatic activity.
- Both are well tolerated, with IRRs being the most common AEs.
 - Mostly grade 1 and 2, seen commonly during the first and second infusions.

Marin TG, et al. *Celr*. 2019;8:1522.
Pfeifer T, Krucka J. *Front Immunol*. 2018;9:1228.
Nooka AK, et al. *J Oncol Pract*. 2018;14:414-422.
van de Donk NWCL, Usmani SZ. *Front Immunol*. 2018;9:2134.

So what's the comparison between daratumumab and isatuximab? They both bind to CD38 epitopes and that may contribute to difference in their mode of action. Both induce so called ADCP and CDC and both demonstrate ADCC that can be potentiated by other antimyeloma agents, particularly the immunomodulatory drugs. Isatuximab, unlike daratumumab, also seems to induce a direct apoptosis or killing the myeloma cells by itself. Isatuximab does not lead to a decrease of CD38 expression, based on some studies, whereas daratumumab seems to lead to CD38 clustering and release in microvesicles. Isatuximab, unlike daratumumab, inhibits CD38 ectoenzymatic activity. Both these drugs are well tolerated with infusion related reactions being the most common adverse events and this of course, refers to the IV use. However, daratumumab is also recently approved as a subcutaneous drug and then you see much less of this. They're mostly grade 1 and 2 and they're commonly seen the first and the second infusions when you give it IV.

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Anti-CD38 mAbs Mechanism of Resistance



Satavaha L, et al. *Cell*, 2020;9:167

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Targeting SLAMF7/CS1 in RRMM Current Immunotherapy

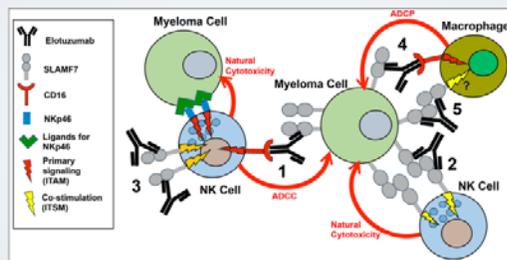
- Elotuzumab (naked mAb), FDA approved:
 - In combination with Rd for the treatment of adult pts with MM who have received 1-3 prior therapies
 - In combination with Pd for the treatment of adult pts with MM who have received ≥ 2 prior therapies including lenalidomide and a PI
- ABBV-838 (ADC, discontinued)

Vil, B, et al. *Clin Cancer Res*, 2020 Jan 22. [Epub ahead of print].
EMPLUCITP (elotuzumab). <http://packageresults.bms.com/gp/campocis.pdf>

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Here you have a summary of the mechanisms of resistance that also probably could be used as a cartoon for mechanism of activity, mechanism of how these drugs actually work. So the cells can figure this out and they can block this in different ways. And there's a lot of research going on trying to find how to go around these mechanisms of resistance.

Targeting SLAMF7/CS1 Rationale and Anti-SLAMF7/CS1 mAb MoA



Campbell KS, et al. *Arrest Immunol*, 2018;9:2551

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Let's move on to SLAMF7 also called CS1 in the more recent literature. This is the elotuzumab monoclonal antibody which is the first CS1 targeted therapy in myeloma, also approved back in 2015. This drug does not have single drug activity but it works well in combination with immunomodulatory drugs and that's how the FDA approval was set up in 2015. This drug is playing together with the macrophages and natural killer cells and those cells are doing the job in terms of killing the myeloma cells.

Elotuzumab is a naked monoclonal antibody. As I mentioned, it was developed in combination with an IMiD, so Revlimid/dexamethasone or lenalidomide/dexamethasone was the first combination and this is for patients with 1 to 3 prior lines of therapy. Recently, the combination with pomalidomide/dexamethasone has been conducted and it's also FDA approved. This is for patients with 2 or more prior lines of therapy, including lenalidomide and a PI. There is another drug called ABBV-838 which is an ADC dragging a conjugate to the tumor cells. That drug binds to CS1 but has been discontinued for development.

Elotuzumab Select Trials in RRMM

Study	Phase	Patients (#)	Previous Therapy (Median #)	Regimen	ORR (%)	Median PFS (Months)	Median OS (Months)
NCT00425347	1	35	5	Elo (0.5–20 mg/kg)	0	NA	NA
ELOQUENT-2	3	321	2	Elo-Rd vs Rd	79 vs 66	19.4 vs 14.9	48 vs 40
ELOQUENT-3	2	117	3	Elo-Pom-d vs Pd	53 vs 26	10.3 vs 4.7	NA
NCT00726869	1	28	2	Elo-V	48	9.5	NA
NCT01478048	2	152	NA	Elo-Vd vs Vd	66 vs 63	9.7 vs 6.9	2-year OS 73% vs 66%

- Ongoing**
- Elotuzumab-PomVd (NCT02718833)

Bonetto F, et al. *Cancers*, 2020;12:15

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Here you have some select trials you in the relapsed and refractory setting using elotuzumab. As you see, for the regimens, we have for the first phase 1 different dosing schedules, doses then you have in combination with lenalidomide/dexamethasone, pomalidomide/dexamethasone, randomized studies with bortezomib and then there is a randomized phase 2 study with bortezomib, dexamethasone plus IMiD, so elotuzumab. And on the right, you see overall response rates and median PFS and OS.

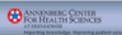
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Anti-CD38 mAbs and Elotuzumab Management of IRRs: Prevention

- Premedication consists of steroids, antihistamines, and acetaminophen, 30-60 min. prior to infusion.*
- For pts treated with CD38-targeting mAbs with higher risk of respiratory complications (eg, FEV1 <80%), post-infusion medication should be considered (eg, antihistamines, β -2 adrenergic receptor agonist by inhalation, or inhalation corticosteroids for pts with asthma and COPD).

*Prophylactic treatment with the oral leukotriene antagonist montelukast 10 mg the day before and again on the morning of infusion is considered by some investigators to be a useful adjunct to the standard premedication with acetaminophen, antihistamine, and corticosteroid to prevent airway reactions following the administration of CD38-targeting antibodies.

van de Donk NW, et al. Blood. 2016;127:581-595.



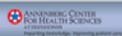
What about the management of infusion-related reactions with the monoclonal antibodies? We all use premedication that typically includes steroids, antihistamines and Tylenol. And it's usually given for half to one hour prior to these infusions and if you give subcutaneous drug, you would also give it about half to one hour before. For patient treated with CD38 targeted monoclonal antibodies with higher risk of respiratory complications, post-infusion medication should also be considered. And that would include antihistamines, β 2 receptor agonist by inhalation or inhalation with steroids for patients with asthma or COPD. All this is in the packet insert.

Anti-CD38 mAbs and Elotuzumab Management of IRRs: Prevention (cont.)

- Because pts who had COPD with a FEV1 <50% of the predicted normal value and moderate or severe persistent asthma within the past 2 years, or who had uncontrolled asthma, were excluded from daratumumab trials, it is recommended to perform FEV1 testing, if there is a suspected COPD; it should be considered to exclude pts from daratumumab treatment, if FEV1 is <50% of predicted normal value.
- FEV1 testing is also recommend for pts who are planned to be treated with isatuximab, given the similar pattern and frequency of IRRs.

*Prophylactic treatment with the oral leukotriene antagonist montelukast 10 mg the day before and again on the morning of infusion is considered by some investigators to be a useful adjunct to the standard premedication with acetaminophen, antihistamine, and corticosteroid to prevent airway reactions following the administration of CD38-targeting antibodies.

van de Donk NW, et al. Blood. 2016;127:581-595.



What about management and prevention continuously with these drugs? Well, because patients who have COPD with an FEV1 less than 50% of the predicted normal value within the past 2 years or patients who have an uncontrolled asthma, they were excluded from daratumumab trials. So therefore, it's recommended to check for FEV1 testing if there is suspected COPD and you have to use your clinical judgment when you administer these drugs for patients like that. FEV1 testing is also recommended for patients who plan to

be treated with isatuximab, given that there's very similar pattern and frequency of infusion-related reactions.

Anti-CD38 mAbs and Elotuzumab Management of IRRs: Treatment

- Interrupt infusion, consider administration of corticosteroids, antihistamines, IV fluid, or β -2 adrenergic receptor agonist by inhalation; after infusion reaction is resolved, restart infusion at lower rate (eg, half of that used before the interruption).
- Pts experiencing respiratory events, which occur more frequently with CD38-targeting mAbs, may benefit from pre- and post-infusion prophylaxis with a bronchodilator or, in case patients have concomitant asthma or COPD, additional medication such as inhalation corticosteroids.

*Prophylactic treatment with the oral leukotriene antagonist montelukast 10 mg the day before and again on the morning of infusion is considered by some investigators to be a useful adjunct to the standard premedication with acetaminophen, antihistamine, and corticosteroid to prevent airway reactions following the administration of CD38-targeting antibodies.

van de Donk NW, et al. Blood. 2016;127:581-595.



If you give these drugs to patients and he or she were to have a reaction, what's the management? The nurses are very skilled and chemo nurses know exactly how to do this. They would certainly interrupt the infusion, they will consider administration of steroids, antihistamines, IV fluid or β 2 adrenergic receptor agonist by inhalation. After the infusion reaction is resolved, then the infusion would be restarted at a lower rate, so that would be typically half of what was used before the drug was stopped. Patients that have symptoms of respiratory events, which occur more frequently with these antibodies, they may benefit from pre- and post-infusion prophylaxis with the bronchodilators. And in case the patients have asthma or COPD, to use additional medication. And again, as I said before, you have to use your clinical judgment in these situations.

Anti-CD38 mAbs and Elotuzumab Management of Other AEs

AE	mAb	Prevention and Management
Any (other than IRR)	CD38-targeting antibodies and elotuzumab	<ul style="list-style-type: none"> • In general, dose-delay is the primary method for the management of side effects (and not dose-reductions)
Infections	CD38-targeting antibodies and elotuzumab	<ul style="list-style-type: none"> • No formal recommendations can be made at the present time. • Herpes zoster prophylaxis should be considered. • It is recommended to screen patients for HIV, HBV, and HCV before start of therapy.

van de Donk NW, et al. Blood. 2016;127:581-595.



Here you have a summary of AEs for antibodies and prevention and management. So in general, dose delay

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is the primary method for management of side effects and not dose reduction. And there is no formal recommendation when it comes to infection at the current time. Herpes zoster prophylaxis, you should certainly consider. It's also recommended to screen patients for HIV, hep B and hep C before starting that.

Anti-CD38 mAbs and Elotuzumab Management of Laboratory Interference

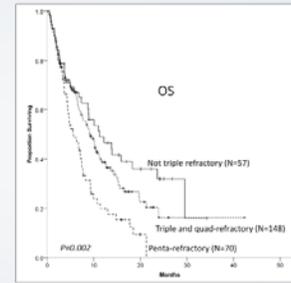
Laboratory test	mAb	Management
Interference with serum protein electrophoresis and immunofixation assays	Several therapeutic mAbs	<ul style="list-style-type: none"> DIRA should be performed when daratumumab-treated patients with IgG-κ M protein have achieved deep response (M-protein <2 g/L) New assays are in development for elotuzumab, isatuximab and MOR202
Interference with multiparametric flow cytometry	Daratumumab, isatuximab, MOR202, and possibly other therapeutic mAbs	<ul style="list-style-type: none"> Use of newly developed Abs for flow cytometry, which bind to different epitopes compared with the therapeutic mAb Application of alternative plasma cell identification markers
Interference with blood compatibility testing	CD38-targeting mAbs (also observed with anti-CD44 mAbs)	<ul style="list-style-type: none"> Denaturation of CD38 from reagent RBCs by dithiothreitol Neutralization of therapeutic mAb with neutralizing Abs or recombinant soluble CD38 Extensive RBC antigen phenotyping before the patient receives the first infusion of the CD38-targeting antibody or RBC antigen genotyping when the patient has already received treatment with an anti-CD38 mAb or a recent blood transfusion (<3 mos) A wallet card that informs physicians and blood banks of the interference with blood compatibility testing should be provided to all patients treated with CD38-binding mAbs

van de Donk NW, et al. *Blood*. 2016;127:681-695.

It's important to mention that there are clinically relevant lab interferences with these drugs. Serum protein electrophoresis and immunofixation assays, they capture monoclonal proteins. And if you give these drugs, the patient will now have an IgG kappa monoclonal band in the blood because you're giving a monoclonal drug. So if a band is seen, you need to use the appropriate lab assays to discern whether it's disease or if it's drug you're seeing. And there are assays for the laboratory, the clinical lab would know how to deal with this. There is also interference with the flow cytometry. The uroflow panel does not work, you have to use other panels. Other antibodies need to be used in order to reliably identify 38 expression. And also clinically very important, there are blood compatibility testing issues. You need to notify the blood bank that the patient has received these antibodies because the type and screen test, the normal test would not work. And you should also make sure the patient has a wallet card to inform physicians and blood banks of interference with blood compatibility testing, that should be done in case they, for example, have to go to the emergency room. So if you're going to give blood or platelets, you do type and screen, you must notify the blood bank. And the patient, as I mentioned, has to be aware, him or herself, to tell other doctors that he or she encounters.

Anti-CD38 mAb-Refractory MM MAMMOTH

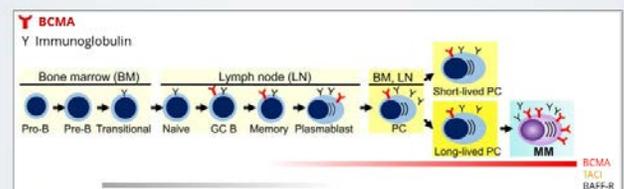
- 275 pts refractory to daratumumab or isatuximab, from 14 US academic centers
 - 57 pts "not triple-refractory" (refractory to 1 CD38 mAb, and not to both a PI and an IMiD); mOS = 11.2 mos
 - 148 pts "triple/quad-refractory" (refractory to 1 CD38 mAb + 1 PI + 1 or 2 IMiDs, or 1 CD38 mAb + 1 or 2 PIs + 1 IMiD); mOS = 9.2 mos
 - 70 pts "penta-refractory" (refractory to 1 CD38 mAb + 2 PIs + 2 IMiDs); mOS = 5.6 mos
- 249 pts (90%) received further therapy



Gandhi LH, et al. *Lancet Oncol*. 2019;33:2266-2275.

Anti-CD38 monoclonal antibody in the relapse setting, this is from the MAMMOTH study. Here you have 275 patients refractory to daratumumab and isatuximab from 14 US academic centers. You see there are 57 patients that are non triple-refractory, they're refractory to one CD38 monoclonal antibody but not to both PI and IMiD. Their median overall survival is less than a year. And then you have 148 patients that are triple or quad-refractory, so they're refractory to a CD38 and a PI and 1 or 2 IMiDs or 1 CD38 monoclonal antibody, 1 or 2 PIs and 1 IMiD. And these patients' median overall survival is only 9.2 months. And then you have the so called penta-refractory patients that are refractory to a CD38 monoclonal antibody, 2 PIs and 2 IMiDs. Their median overall survival is only 5.6 months. So as we have better and better drugs and patients have been through all these different drug combinations in different ways, the patients that we are now meeting who relapse after all these therapies, they have a quite poor outcome. So there is clearly a huge need for new mechanisms of action and I will talk about this shortly. So you see there are 249 patients that have received further therapy.

BCMA as Target in MM Malignant vs Normal PCs Expression

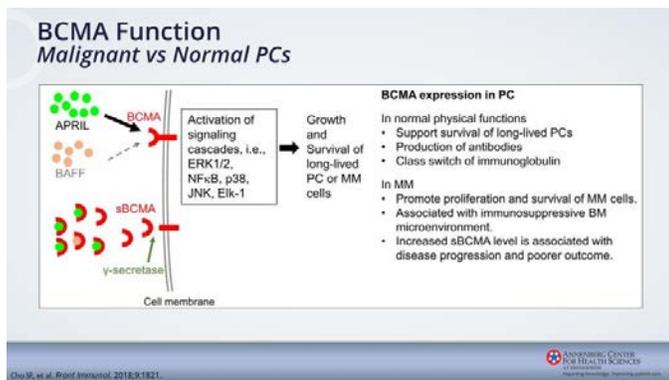


BCMA expression significantly increased on malignant vs normal PCs

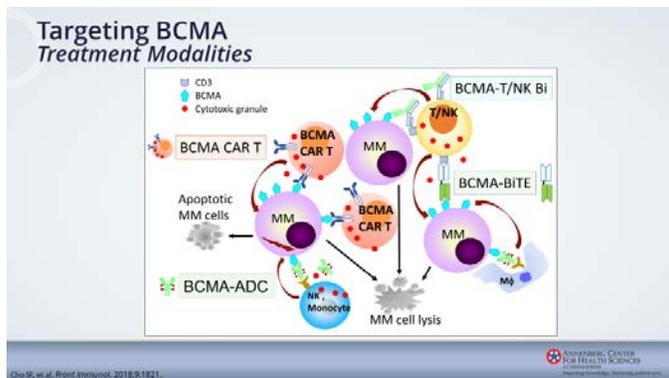
Choi W, et al. *Front Immunol*. 2018;9:1821.

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So that takes us into the next step here, BCMA as a target. I have not talked about BCMA. There is not yet any drug, FDA approved, for BCMA but we hope in 2020 that will change. BCMA is expressed not only in myeloma cells but it's significantly more expressed on the malignant plasma cells compared to normal plasma cells.

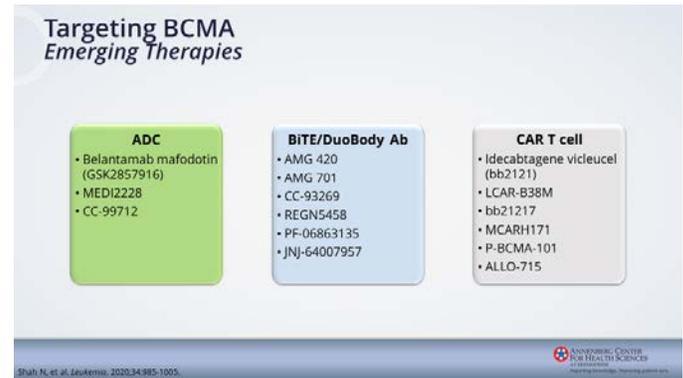


The expression in plasma cells, I mentioned, in normal physiological conditions, it's something that supports survival of the long-lived plasma cells. It's involved in production of antibody and class switch of immunoglobulins. In myeloma, it promotes proliferation and survival of the myeloma cells. It's associated with immunosuppressive marrow microenvironment. And also increased soluble BCMA levels have been associated with disease progression and poor outcome. So the cells can actually shed and get rid of the BCMA and the exact details of this are not entirely clear.

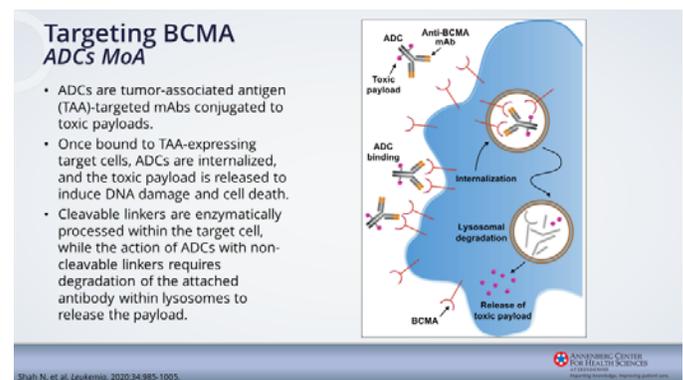


When it comes to targeting BCMA, there are very many strategies in development. I'm sure you have all heard about the CAR T cells that go after BCMA, the ADC, you probably have heard about too and then you have the

bispecific antibodies or BiTEs. And then also the cell therapies that are not only focusing on CAR T cells but you also have NK cells that go after BCMA.



So let's go through this in a little bit more detail. So for the ADC, the first drug in development is belantamab mafodotin, this is also called GSK2857916. So that's a long numeric number. There are the BiTEs, DuoBody antibodies. We have seen publications for AMG 420, there was 701 AMG also and then CC-93269 has been presented, REGN5458, PF-06863135 and JNJ-64007957, these drugs do not yet have names. And then we have the CAR T cells on the right: the bb2121, Ide-cel, we have the LCAR, the bb21217, there is the MCARH, the P-BCMA and then there is also allogeneic CAR T cells, ALLO-715.



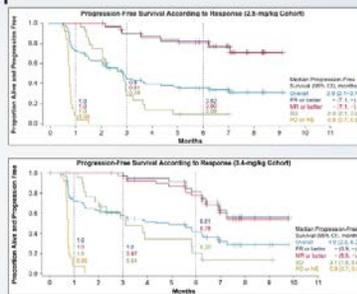
Going after BCMA with ADCs, that means that you have an antibody that binds to the target and then this antibody is conjugated with a toxic payload. So it's basically a way to deliver a drug into the cell. So once bound to the tumor-associated antigen or TAA, the ADC is then internalized, so it goes inside the cell and this toxic payload is then being released like a Trojan horse.

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And once that's released, it induces DNA damage and cell death, so to kill the myeloma cells. These linkers, they are cleavable. And that's an enzymatic process that happens within the target zone. But the action of these ADC with non-cleavable linkers requires a degradation of the attached antibody within lysosomes to release the payload. So again, it's almost like a Trojan horse.

Belantamab Mafodotin DREAMM-2

- 196 pts refractory to prior IMiD, PI, and an anti-CD38 mAb randomized to receive 2 doses of belantamab mafodotin:
 - 2.5 mg/kg IV Q3W (n=97)
 - 3.4 mg/kg IV Q3W (n=99)
- ORR:
 - 31% (2.5 mg/kg cohort)
 - 34% (3.4 mg/kg cohort)
- Median DoR, PFS, and OS: not reached in either cohort
- The most common grade 3-4 AEs were keratopathy (27% and 21%), thrombocytopenia (20% and 33%), and anaemia (20% and 25%) in 2.5 mg/kg and 3.4 mg/kg cohorts, respectively.
- 2 deaths were potentially treatment-related and caused by sepsis (2.5 mg/kg cohort) and hemophagocytic lymphohistiocytosis (3.4 mg/kg cohort).

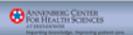


Loriot S, et al. *Lancet Oncol*. 2020;21:207-221



BCMA-Targeted ADCs Select Trials in RRMM

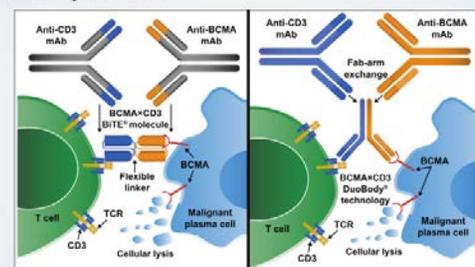
- Belantamab mafodotin vs Pd (DREAMM-3; NCT04162210)
- Belantamab mafodotin + pembrolizumab (DREAMM-4; NCT03848845)
- Belantamab mafodotin ± GSK3174998 or GSK3359609 (DREAMM-5; NCT04126200)
- Belantamab mafodotin + Rd or Vd (DREAMM-6; NCT03544281)
- Belantamab mafodotin + Vd vs Dara-Vd (DREAMM-7; NCT04246047)
- MEDI2228 (NCT03489525)
- CC-99712 (NCT04036461)



This drug has been continued to be tested in combination with other drugs: belantamab mafodotin vs pomalidomide/dexamethasone in the DREAMM-3 study, belantamab mafodotin with pembrolizumab in the DREAMM-4 study, belantamab mafodotin ± GSK3174998 or the other drug called 3359609, this is the DREAMM-5 study. Also belantamab mafodotin with either lenalidomide/dexamethasone or bortezomib/dexamethasone, this is DREAMM-6. And then you have also plus bortezomib/dexamethasone vs daratumumab with bortezomib/dexamethasone, DREAMM-7. And then there is the MEDI2228 and the CC-99712, these are other monoclonal antibodies that are ADCs. So you see there's a whole range of these ADCs in development.

Belantamab mafodotin has been developed in something called the DREAMM program which is part of the GSK development pipeline. And there were several DREAMM studies. This is from the DREAMM-2 study that includes 196 patients with refractory multiple myeloma, they are refractory to prior IMiD, PI and also a CD38 monoclonal antibody. To receive 2 doses of belantamab mafodotin at 2 different dose levels. It's 2.5 mg per kg IV every 3 weeks and 3.4 mg per kg also IV every 3 weeks. These studies show an overall response rate of 31% and 34% respectively. The median duration of response PFS, OS has not been reached in either of these cohorts. The most common grade 3 and 4 adverse events have been reported to be keratopathy, which implies that there are changes in the eye that you can see when you do a careful eye exam, thrombocytopenia in 20% and 33% of patients, anemia in 20%, 25% in the 2.5 per kg dosing and in the 3.4 cohorts respectively. There are 2 deaths that were potentially treatment-related and caused by septicemia and hemophagocytic lymphohistiocytosis in these studies.

Targeting BCMA BiTE/DuoBody Ab MoA



Shah N, et al. *Lancet Oncol*. 2020;21:1005-1015



Let's switch to the bispecific/DuoBody or BiTEs monoclonal antibodies. So this refers to antibodies that can bind to more than one thing. So everything I've showed you so far binds to one particular target, could be CD38 or CS1 or I've showed you previously, binding to BCMA with a toxic payload. Now we're talking about antibodies that can bind to, for example, BCMA but also bind to, in this case, CD3. CD3 is selected because that's

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something that the T cells commonly express. So you can now bind to both the myeloma cell through BCMA and bind to the T cells, so the T cells now end up sitting next to the myeloma cells. And the T cells, they don't like the myeloma cells so they will now kill the myeloma.

AMG 420

First-in-Human Phase 1 Dose Escalation Study

- 42 pts (median 5 prior therapies) received AMG 420 at 0.2-800 mg/d
 - Up to 10 cycles of AMG 420 were given (4-week infusions/6-week cycles)
- 800 mg/d was deemed not tolerable because of 1 grade 3 CRS and 1 grade 3 PN, both of which resolved.
- ORR=31%
 - At the MTD of 400 mg/d, the ORR was 70% (7/10); of these, 5 pts had MRD-negative CR, and 1 had a PR, and 1 had a VGPR; all 7 pts responded during the first cycle, and some responses lasted > 1 year
- Serious AEs (n=20; 48%) included infections (n=14) and PN (n = 2); treatment-related serious AEs included 2 grade 3 PNs and 1 grade 3 edema; there were no grade ≥3 CNS toxicities

Topik MS, et al. J Clin Oncol. 2020;38:775-783.



BCMA-Targeted BiTEs and DuoBody Ab Select Trials in RRMM

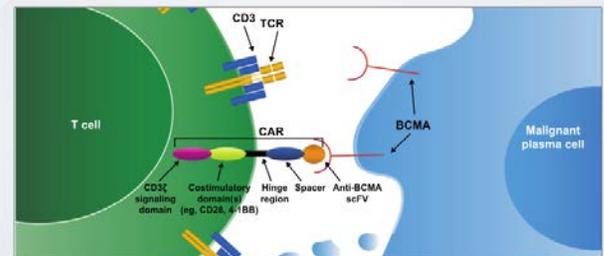
- AMG 420 (NCT04162210)
- AMG 701 (NCT03287908)
- REGN5458 (NCT03761108)
- PF-06863135 (NCT03269136)
- CC-93269 (NCT03486067)
- JNJ-64007957 (DuoBody Ab; NCT03145181)



There are several of these bispecific antibodies in development. I just talked about the AMG 420, you have the next AMG antibody, the 701 and then there's Regeneron's 5458, the PF-06863135, the CC-93269, they're former Celgene, that's now under BMS, and then the JNJ, the DuoBody. So they all have different names: DuoBody, BiTEs, bispecific and other names and they all refer to targeting 2 different antigens, myeloma cells and dragging the T cells there. Different technologies have different names.

AMG 420 first-in-human phase 1 dose escalation study includes 42 patients. This was published in 2020 in *Journal of Clinical Oncology*. I think this is fascinating data. They show 0.2 up to 800 mg dosing, up to 10 cycles of this AMG 420 and the 4-week infusion or 6-week cycles. The 800 mg dosing was deemed not tolerable because there was one grade 3 CRS which is what you have seen for the CAR T cells, I will come back to that in a little bit, and also one grade 3 peripheral neuropathy. Both of these, they were resolved but because they were severe, it was deemed that the maximum tolerated dose would be 400 mg dosing. The overall response rate with this drug is 31% per these reports. With the 400 mg dosing, the overall response rate was reported to be 70%. But I caution you that these are small numbers, so 7 out of 10 patients. Of these, 5 patients were MRD-negative CR, one patient had a PR and one patient had a VGPR, so these are obviously very strong signals. All the 7 patients responded during the first cycle and some of these patients on this study lasted more than one year. The serious adverse events that include about half the patients included infections, peripheral neuropathy, treatment-related serious adverse events including 2 grade 3 peripheral neuropathies and 1 grade 3 edema. There was no grade 3 or higher CNS toxicity.

Targeting BCMA CAR T Cell Therapy MoA



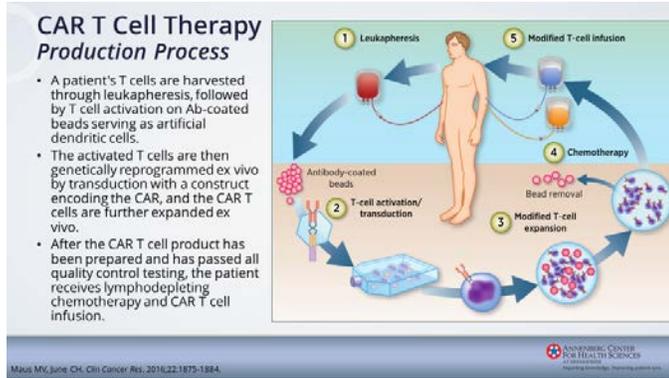
Shah N, et al. Leukemia. 2020;34:985-1005.



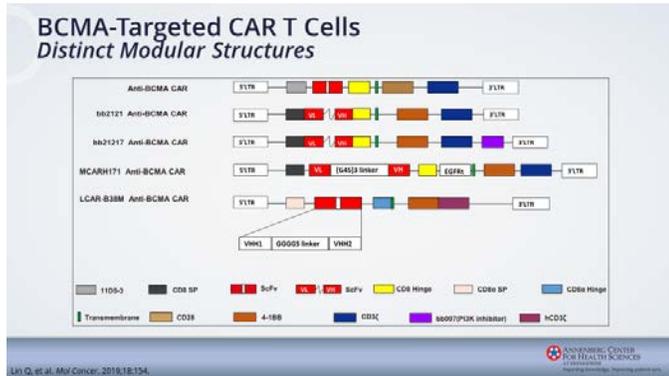
CAR T cells, we have all waited for the CAR T cells to be approved in multiple myeloma and probably we will have the first CAR T cell approved for the treatment, standard of care in myeloma by the end of 2020. So instead of linking the T cells in the body to the plasma cells in myeloma cells, the idea here with the CAR T cells is obviously to take out the person's own T cells and then transduce them with a vector like a virus would attack cells, it's only the vector that would attack T cells and the vector would have to insert code in the genome of these T cells so they do express the receptor that binds to, in this case, BCMA. And then you get back the

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T cells and then now you have T cells that are programmed to bind to BCMA.

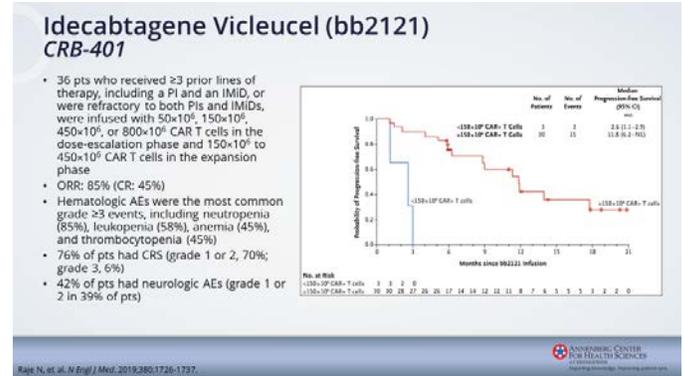


So you make the new system a therapy. So you start off at leukapheresis, you take out these T cells then you transduce them with these vectors. And then you can also expand them and make them happy, you make more and more active. Then you go from 3 to 4, you give some chemotherapy to lower the immune response in the body so the immune system does not kill these cells and then you infuse them back into the patient. And this is how these CAR T cells work.

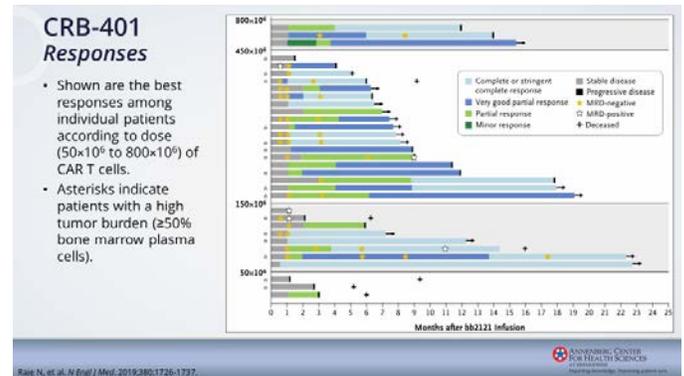


This is referring to the autologous CAR T cells. There are very many different CAR T cells in development, then there are some of them that are no longer being developed. The ones that are furthest along are the bb2121, the JCARH171 and also the JNJ Legend CAR T cell. They are all a little bit different from a manufacturing point of view, the way they are designed, the way these cells are collected and expanded and the whole processing around it. So there are a lot of technical differences, but they all have in common that they are autologous, so they are collected from the person that

will subsequently receive them as the treatment and they are also similar in the sense that they are all targeting BCMA, at least the current versions. There is news of them in development and these other ones we are currently seeing at meetings.



So the bb2121 is the one that's furthest along. This was published in the *New England Journal of Medicine* in 2019. And you can see here on this slide, in red, they have given different dose levels. So if they gave 150 million or more, the median progression-free survival was 11.8 months. So that's a pretty good result given that these patients were very sick, they had received 3 or more prior lines of therapy. The average patient had received 6 or 7 or so prior lines and they were refractory to most other drugs. And we know that those patients if we had treated them with any other FDA-approved therapy, it would typically only last for a few months. So the median progression-free survival of a little bit less than a year is quite encouraging.



There also have been investigations looking at these responses in relation to the depth of the response for individual patients. And there are some patients that

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achieve minimal residual disease negativity and they seem to have maybe even another 6 months or so, on average, median progression-free survival in this patient population.

**LCAR-B38M
LEGEND-2**

- 57 pts who received median 3 prior lines of therapy, including a PI (68%) and an IMiD (86%) or both (60%), were infused with a dual epitope-binding CAR T cell therapy directed against 2 distinct BCMA epitopes (median 0.5×10^6 cells/kg delivered in 3 separate infusions).
- 65% of pts had Grade ≥ 3 AEs (leukopenia, 30%; thrombocytopenia, 23%; and increased AST, 21%).
- 90% of pts had CRS (7% had grade ≥ 3).
- ORR: 88% (CR: 68%; MRD $^-$: 63%)
- At a median follow-up of 8 months, mPFS: 15 months; mOS: not reached.

Zhao WH, et al. *J Hematol Oncol*. 2018;11:141

The LEGEND-2 study is another trial that's going forward and this is the former LEGEND-1 study that has come to the United States and under JNJ's leadership is now developed in the LEGEND-2 study. It has been presented most recently at the ASCO 2020 meeting, showing 100% overall response rate. Still the follow-up is quite short so we have to wait and see. But the overall response rate from the most recent update is very encouraging for this CAR T cell.

**LEGEND-2
Duration of Responses**

- Shown are individual responses and duration of follow-up for patients who achieved at least a PR (n = 50).
- The median time to initial response was 1 month (range, 0.4 to 3.5).

Zhao WH, et al. *J Hematol Oncol*. 2018;11:141

Here you also see from LEGEND-2 presentations, this is from the *Journal Hematologic Oncology* in 2018, individual responses and duration and this is based on 50 patients. But because the field is moving so fast forward, there are some presentations that I referred to at ASCO 2020 that have not yet been published, showing even better results.

BCMA-Targeted CAR T-Cell Therapy Select Trials in RRMM

- Idecabtagene vicleucel (KarMMA, NCT03361748)
- Idecabtagene vicleucel (KarMMA-2, NCT03601078)
- Idecabtagene vicleucel vs DPd, DVd, or IRd (KarMMA-3, NCT03651128)
- LCAR-B38M/JNJ-68284528 (CARTITUDE-1, NCT03548207)
- LCAR-B38M/JNJ-68284528 (CARTIFAN-1, NCT03758417)
- P-BCMA-101 (PRIME, NCT03288493)
- JCARH125 (EVOLVE, NCT03430011)
- bb21217 (CRB402; NCT03274219)
- ALLO-715 (UNIVERSAL, NCT04093596)

The BCMA-targeted CAR T cell therapy select trials for relapsed refractory. The KarMMA trial, you have the KarMMA on the top and KarMMA-2 and then you have KarMMA-3, they all refer to this bb2121 that is furthest along, has been developed in multicenter settings around the world and it's anticipated to get the first FDA approval. And then you have the JNJ, the LCAR, the LEGEND-2 study, the CARTITUDE studies and they are also in development and the most recent, I mentioned, from the ASCO 2020. If I jump further down, the JCARH, this is the Juno CAR. Both the JCARH and the KarMMA are now under the leadership of BMS and they both go after BCMA and they're both autologous. So the evolved study for JCARH was also presented at ASCO and maybe has a slightly better signal than the KarMMA but the follow-up is shorter. So it's hard to know which is going to be the winner. It's going to be KarMMA, it's going to be the JCARH, it's going to be the LCAR, I think the jury is still out.

And then you have the bb21217 where there is a manipulation in the manufacturing of the bb2121 to try to enhance the activity through improved production, but clinical data is not yet available to prove that. And then you have the Allogeneic ALLO-715 which is the first allogeneic BCMA-targeted CAR T cell in myeloma. And that's also interesting, that would be an on-the-shelf product if that were to deliver. The follow-up there is also quite short. So I think overall, it's fair to say that clearly it works, there is already data showing almost one year of progression-free survival on average in heavily pretreated patients and there are multiples of these going forward. We need more follow-up in larger series.

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CAR T Cell Therapy Grading and Management of CRS

ASBMT CRS Grade	Defining Features of Grade	Management
Grade 1	Fever with temperature $\geq 38^{\circ}\text{C}$ but no hypotension or hypoxia	<ul style="list-style-type: none"> Antipyretics and IV hydration Diagnostic work-up to rule out infection Consider growth factors and antibiotics if neutropenic
Grade 2	Fever with hypotension not requiring vasopressors and/or hypoxia requiring low-flow nasal cannula	<ul style="list-style-type: none"> Supportive care as in grade 1 IV fluid boluses and/or supplemental oxygen Tocilizumab +/- dexamethasone or its equivalent of methylprednisolone
Grade 3	Fever with hypotension requiring one vasopressor with or without vasopressin and/or hypoxia requiring high-flow nasal cannula, facemask, nonrebreather mask, or venturi mask	<ul style="list-style-type: none"> Supportive care as in grade 1 Consider monitoring in intensive care unit Vasopressor support and/or supplemental oxygen Tocilizumab + dexamethasone 16-20 mg IV q 6 hrs or its equivalent of methylprednisolone
Grade 4	Fever with hypotension requiring multiple vasopressors (excluding vasopressin) and/or hypoxia requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)	<ul style="list-style-type: none"> Supportive care as in grade 1 Monitoring in intensive care unit Vasopressor support and/or supplemental oxygen via positive pressure ventilation Tocilizumab + methylprednisolone 1000 mg/day

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CAR T Cell Therapy Grading and Management of ICANS (cont.)

ASBMT Grade	Defining Features of Grade	Management
Grade 3	<ul style="list-style-type: none"> ICE score 0-2 and/or depressed level of consciousness but awakens to tactile stimulus Any clinical seizure focal or generalized that resolves rapidly, or nonconvulsive seizures on EEG that resolve with intervention No motor weakness Focal/cortical edema on neuroimaging 	<ul style="list-style-type: none"> Supportive care as in grade 1 Dexamethasone 10-20 mg IV q 6 hours or its equivalent of methylprednisolone Control seizures with benzodiazepines (for short-term control) and levetiracetam +/- phenobarbital and/or lacosamide High-dose methylprednisolone 1000 mg/day for focal/cortical edema
Grade 4	<ul style="list-style-type: none"> ICE score 0 and patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse or stupor or coma Life-threatening prolonged seizure (>5 min); or repetitive clinical or electrical seizures without return to baseline in between Deep focal motor weakness such as hemiparesis or paraparesis Diffuse cerebral edema on neuroimaging; decerebrate or decorticate posturing; or cranial nerve VI palsy; or papilloedema; or Cushing's triad 	<ul style="list-style-type: none"> Supportive care as in grade 1 High-dose methylprednisolone 1000 mg/day Control seizures with benzodiazepines (for short-term control) and levetiracetam +/- phenobarbital and/or lacosamide Imaging of spine for focal motor weakness Lower ICP by hyperventilation, hyperosmolar therapy with mannitol/hypertonic saline, and/or neurosurgery consultation for ventriculoperitoneal shunt in patients with cerebral edema

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When it comes to the CAR T cells, as expected, they induce reactions that involve the immune system. So CRS, obviously, is something that we have seen and we have learned how to manage for those centers that give the CAR T cells. Patient can develop cytokine release syndrome or CRS at different grades. And it can happen either only after a day or so or it can go all the way up to a week depending on which of these CAR T cells that we use. And I would say at this point, this is mainly for specialty centers but it's important to know when talking to patients that this is something that happens.

And here is a continued slide for the same side effects in grade 3 and grade 4.

BCMA-Targeted Treatment Modalities Comparison

	CAR-T	Bispesific Abs	ADC
Off-the-shelf	Not yet	Yes	Yes
Ease of administration	+	+++	+++
Dependent on patient T cell condition	Yes	Yes	No
Results of representative clinical trials			
Protocol	BB2121 (n = 33)	AMG420 (n = 42)	GSK2857916 (n = 35)
Median age, years (range)	58 (37-74)	63	60 (40-75)
Prior treatment lines	Median 7 (range 3-14)	Median 4 (range 2-13)	≥ 5 prior lines
Response	ORR 85% MRD(-) CR 45%	ORR 70% MRD(-) CR 40%	ORR 60%
Median PFS	12 months	9 months	8 months
Major toxicity	Neutropenia 85%, anemia 45%, thrombocytopenia 45%, CRS 76% (grade 3: 6%), neurologic toxic effects 42%	CRS: all grades 38% (severe CRS 2%), serious peripheral neuropathy 5%	Grade 3-4 AEs 80%; corneal AEs (vision blurred, keratitis, photophobia, dry eye, keratopathy, eye pain), thrombocytopenia

Tanaka M, et al. *Cancers*. 2019;11:2009.



CAR T Cell Therapy Grading and Management of ICANS

ASBMT Grade	Defining Features of Grade	Management
Grade 1	<ul style="list-style-type: none"> ICE score 7-9 and/or depressed level of consciousness but awakens spontaneously No seizures, motor weakness, or raised ICP/cerebral edema 	<ul style="list-style-type: none"> Aspiration precautions and IV hydration Seizure prophylaxis with levetiracetam EEG Imaging of brain Consider tocilizumab if there is concurrent CRS
Grade 2	<ul style="list-style-type: none"> ICE score 3-6 and/or depressed level of consciousness but awakens to voice. No seizures, motor weakness, or raised ICP/cerebral edema 	<ul style="list-style-type: none"> Supportive care as in grade 1 Consider dexamethasone or its equivalent of methylprednisolone

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Here we have grading and management of these immune cell adverse events that you see when you use these drugs.

If you look at the CAR T cells, if you look at the bispesific antibodies and then you look at the ADCs, the antibody drug conjugates, if you do some form of a practical summary, compare them head-to-head although they have not been done in one study in a randomized manner, you can just look at individual studies, there are a couple of features that are unique to some of these. So CAR T cells are not yet on the shelf, at least not the autologous ones. The allogeneic or the NK CARs would be off the shelf if that were to move forward clinically in the standard of care setting. For the bispesifics and the ADCs, they are off the shelf. Easy to administer, the CAR T cells would take much more infrastructure, academic institutions, the way it is set up for now dependent on the patient T cell condition. Both the CAR T cells and the bispesifics are dependent on that because they involve the T cells while the ADC is basically drug delivery. And then we have different protocols here, the bb2121, AMG 420 and the GSK2857916 which is the belantamab mafodotin. And you can see how they are different in terms of their

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response rates, the median PFS and their major toxicity. I went over this on the previous slides but here you have some of the data put together side by side. And I caution you, this is just for an overview comparison.

So to summarize, immunotherapies are rapidly expanding and they're likely to provide numerous new treatment options. I've showed you, for the most part, some of the single drug results and many of these strategies are also currently in development in combinations where probably they're going to end up. Different BCMA-targeted treatment modalities including ADCs, BiTEs and CAR T cell therapy, with their unique strength and limitations, have shown high antimyeloma activity that may address a critical unmet need in heavily pretreated and refractory patients. Future studies should help identify optimal combinations and sequencing of different immunotherapies is key to improvement of current and emerging immunotherapies that will be better understanding of the role of the immune system in the pathogenesis in myeloma.