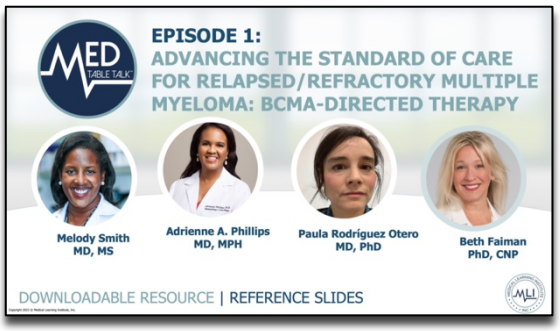
MED TABLE TALK™ EPISODE 1 | ADVANCING THE STANDARD OF CARE FOR RELAPSED/REFRACTORY MULTIPLE MYELOMA: BCMA-DIRECTED THERAPY



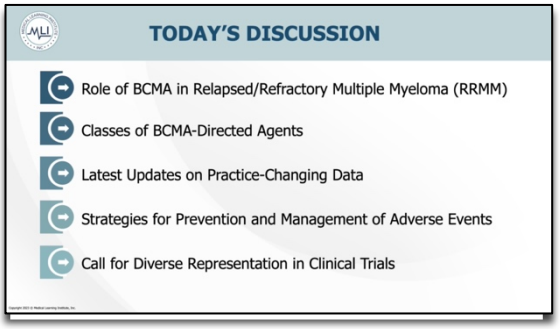
Melody Smith, MD, MS: Hello and welcome to *Med Table Talk*. This is the first of three episodes where we candidly discuss the latest developments of B-cell maturation antigen or BCMA-directed therapies, challenges, and offer practical tips to apply to these novel therapies in relapsed-refractory multiple myeloma.

I'm your host, Melody Smith, and I'm an Assistant Professor and Physician Scientist at the Stanford University School of Medicine. I'm happy to be joined by my esteemed colleagues, Adrienne Phillips and Paula Rodríguez Otero. Adrienne, can you go ahead and introduce yourself?

Adrienne A. Phillips, MD, MPH: Thanks, Melody. My name is Adrienne Phillips, and I'm, I'm an Associate Professor of Clinical Medicine at the Weill Cornell Medicine/New York-Presbyterian Hospital Campus in New York City.

Dr. Smith: Paula, can you introduce yourself to our audience?

Paula Rodríguez Otero, MD, PhD: Sure. Hello everyone. I am Paula Rodríguez Otero. I am Hematologist working at the University of Navarra in Pamplona, Spain, and very happy to be here with you today.



TODAY'S DISCUSSION

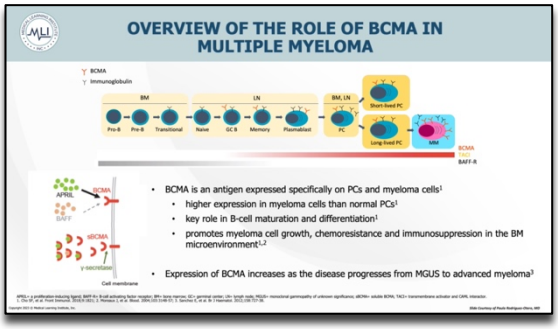
Dr. Smith: Thank you so much. I'm really looking forward to our discussion today. in today's episode, we're going to go through various topics discussing the role of BCMA in relapsed-refractory multiple myeloma, an overview of the classes of BCMA-targeted therapies, the latest updates on practice-changing data, strategies for prevention and management of adverse events, and, also, diverse representation in clinical trials, which is also a very pressing issue.

So, remember this is Episode 1 of 3, so stay tuned to hear what topics in relapsed-refractory multiple myeloma we'll be discussing in future episodes.

So, we've been hearing a lot about BCMA-targeted therapies and new developments related to this therapy. And the big question is why are we investigating BCMA as therapeutic target for patients with relapsed-refractory multiple myeloma?

Dr. Rodríguez Otero: So this is a very important question and BCMA is a very important target, so, first, we know that despite all the advances that we have witnessed in the recent years regarding the treatment of multiple myeloma patients with novel agents and novel combinations that have for sure improved the survival, patients with relapsed my-, patients with myeloma continue to relapse, unfortunately, and they become resistance to more and more classes of drugs and, therefore, there still need novel agents to be rescued with.

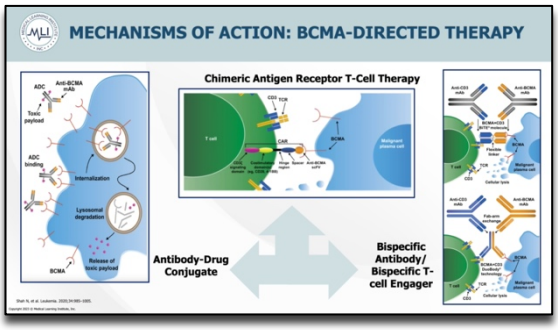
So, so in this regard, patients that fail the classic drug, so immunomodulatory agents, proteasome inhibitors, anti-CD38 monoclonal antibodies still have a dismal outcomes so we do need novel therapies, and BCMA-directed agents have been developed first for the treatment of these highly, highly refractory patients.



OVERVIEW OF THE ROLE OF BCMA IN MULTIPLE MYELOMA

And BCMA is a very relevant target in myeloma for various reasons. First, because it is selectively expressed in the compartment of the plasma cells or the expression outside this tissue is very limited and, therefore, it is a very important or interesting target for drug development and also because BCMA has an important role in the biology of, of the plasma cell. So BCMA is expressed in a higher proportion in tumor cells than normal plasma cells and has a key role in maturation differentiation providing survival advantage for the myeloma cell. So, so blocking this target it really makes a difference in the treatment of myeloma.

Dr. Smith: Yeah. I think those are all, you know, really important points for us to consider that, you know, the myeloma, especially as we think about potential off-target effects, side effects of BCMA, it's really important that it has higher expression in the myeloma compared to the normal plasma cell.



MECHANISMS OF ACTION: BCMA-DIRECTED THERAPY

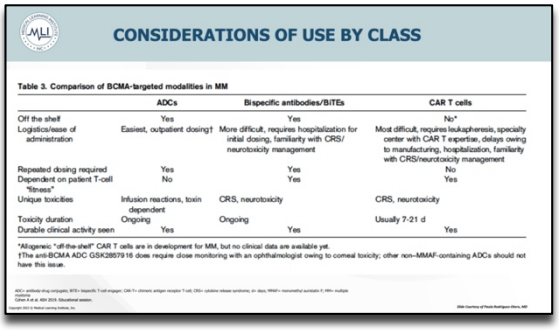
So, you know, as we think about the mechanisms for BCMA targeting in various therapies, there are several different strategies that have been employed. So, one is chimeric antigen receptor T-cell therapy where immune cells, a specific subset of the immune cells which are the T-cells, are engineered to express the BCMA receptor that combine to the BCMA on the myeloma cell and in an MHC-independent manner.

Another approach is bispecific antibodies or bispecific T-cell engagers. This also works through utilizing both CD3 and BCMA to target BCMA on the myeloma cell. And then the final approach is antibody-drug conjugate using this antibody-drug conjugate targeting BCMA on the myeloma cell.

As you think about these therapeutic targets, you know, Paula, your thoughts in terms of, you know, these targets and their potential therapeutic effects. I think it, it'll be important for us to kind of think about based upon the mechanism of action for the way that the BCMA therapy works, we'll have some understanding as to how the patients may respond, the time frame for response, as well as the toxicity, right?

Dr. Rodríguez Otero: Yeah, absolutely. So there are the T-cell regulated therapies that are, as you, as you explained before, the CAR-Ts, the therapies, and the bispecific antibodies on these two modalities do work by redirecting out or enhancing the activity of the T-cells and then we have the antibody-drug conjugates, which is more of a, let's say, a classic drug with an antibody being linked to the tumor cell and then incorporated inside the myeloma cell the cytolytic drug which in, in the case of myeloma with the current development, is a monomethyl auristatin F (MMAF). So really, they are two different, completely different modalities, but they are giving a lot of, of good efficacy data for our patients.

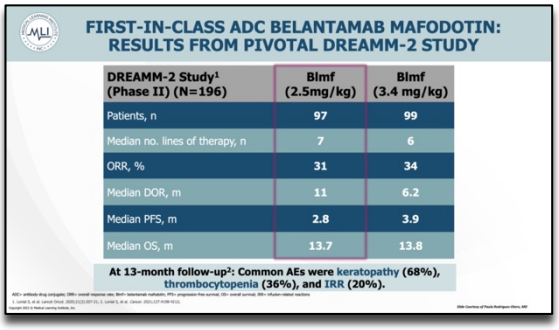
Dr. Phillips: Absolutely. Yeah. So, we have, as you mentioned, a number of BCMA-targeted therapies with multiple mechanisms of actions



CONSIDERATIONS OF USE BY CLASS

So, antibody-drug conjugates and the bispecifics are off-the-shelf therapies that are given at repeated interval dosings. They each have unique side effects, which we'll talk about, but when we compare those therapies to CAR-T therapies, just like they're given in leukemias and lymphomas, are one-time treatments and perhaps the toxicity in that immediate period when they're administered is different, notably the cytokine release and the ICANS. Once you get past that period, you know, the duration of effect is long-lasting and, and you're not administering that therapy anymore.

Other unique toxicities, include with the antibody drug conjugate that's currently available, has a unique ocular toxicity. And both the bispecifics and the CAR-T therapy are immunotherapies and depend on your T-cell function, but patients' T-cell fitness is something that's important to consider with those therapies.



FIRST-IN-CLASS ADC BELANTAMAB MAFODOTIN: RESULTS FROM PIVOTAL DREAMM-2 STUDY

So moving on, belantamab mafodotin, which is the first-in-class antibody-drug conjugate (ADC) which was approved here in the United States I believe back in August of 2020 based on the pivotal results of the DREAMM-2 study, which was a Phase II study enrolling 196 patients and two doses of b-, belantamab were looked at, 2.5 milligrams per kilogram and 3.4 milligrams per kilogram. And these were very heavily pretreated patients, and the overall response rates in both arms were approximately 30%, and the duration of response was ranging between 6 and 11 months, and progression-free survival was approximately 3 months, and median overall survival was approximately 14 months.

The most commonly observed adverse events were keratopathy in two-thirds of patients and then thrombocytopenia in approximately a third and infusion-related reactions in about a fifth of patients.

So despite that being the first-in-class antibody drug conjugate targeting BCMA that was approved, additional studies showed that the drug did not meet its primary endpoint in the DREAMM-3 study, and the FDA, at least here in the United States, had asked the company to withdraw the treatment.

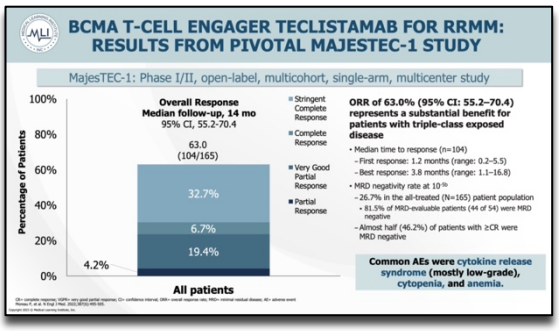
And based on this not meeting the progression-free survival endpoint, the drug has been taken off the market here in the United States.

What's the status of this therapy in Europe, Paula?

Dr. Rodríguez Otero: Yeah. So, in Europe, it's still available so the EMA has not withdrawn the belantamab from the, from the market. In Spain where I live, they, they are wor-, waiting for a new revision of the data that is, I think, expected to take place around the spring, so we do not know how everything will look li-, like after this new revision, but there are also, and I think it is important to, to highlight, that there are other Phase III randomized studies that are ongoing evaluating belantamab in combination with other standard of care agents in myeloma, and there are the DREAMM-3, the 7, 8, then ano-, and a lot of other DREAMM studies

Dr. Smith: Yeah, I agree, Paula. I think that, you know, as we think about belantamab, this may not be the end of the road for it because there are these other studies that are coming. And as we all know, a randomized Phase III study is the gold standard for us to be able to compare new drugs to standard currently FDA-approved therapies. And so it may be that some of these other studies may help to resurrect this drug in the United States

So now I'm going to talk a little bit about another class of a BCMA-targeted therapy and that is one of our BCMA T-cell engagers, teclistamab,



BCMA T-CELL ENGAGER TECLISTAMAB FOR RRMM: RESULTS FROM PIVOTAL MAJESTEC-1 STUDY

So the MajesTEC-1 study evaluated teclistamab and found that the overall response rate for patients with relapsed-re-, refractory multiple myeloma who were treated on an open-label study, a multico-cohort, single-arm study was 63%. And this was a substantial benefit for patients with triple class exposed disease. So that's patients who previously received a three-drug combination for treatment of multiple myeloma.

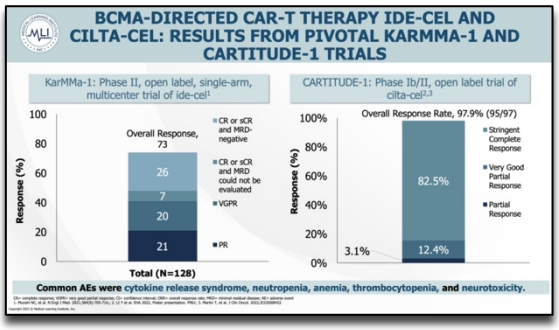
For the patients with their first response, the study noted that the median time to response was 1.2 months, but the best response was 3.8 months. And in terms of MRD negativity, which is the minimal residual disease negativity rate, they found that 26.7% of the patients and all the treat, patients treated in the population had MRD negativity, which is really encouraging data.

So, I mean what are your thoughts in terms of, you know, some of the implications of this teclistamab data for patients, particularly given that you, you know, we are familiar with the side effects for, of teclistamab, but we'll get into that a little bit later, cytokine release syndrome which was mostly low grade, cytopenias and anemia. You know, what do you think about some of this data, Paula?

Dr. Rodríguez Otero: I really think that the data is very impressive. So this is the first of several other BCMA T-cell engagers that are being developed but for sure is a, a great step forward, so we get higher efficacy rate in a very advanced myeloma population with the majority of patients being also refractory to the three main classes of drugs.

More importantly, I will say, the responses are very rapid which in some of these patients, this is critical because the patients are really sick so they need maybe a good and, and, and rapid response, and we do see deep responses with over half of the patients achieving very good partial responses, so really their responses are rapid, are deep, and, and also they are durable because we've seen in this MajesTEC-1 trial that the median progression-free survival was close to one year. So, again, in a population with a, a median of, of four prior lines of therapy, so advanced myeloma patients. And, I think that this is a very i-, important use for patients with myeloma.

Dr. Smith: So, yeah, Paula, you know, you want to talk to us a little bit more about some of the other T-cell-directed therapies



BCMA-DIRECTED CAR-T THERAPY IDE-CEL and CILTA-CEL: RESULTS FROM PIVOTAL KARMMA-1 AND CARTITUDE-1 TRIALS

Dr. Rodríguez Otero: Sure. So, we now have two CAR-T cell treatments that target BCMA that are approved both in the US and also in Europe. So we have idecabtagene vicleucel, ide-cel, which was approved based on the KarMMa-1 trial, which is a Phase II pivotal single-arm study, and with ide-cel alone and in single infusion patients with, again, triple class exposed relapsed-refractory myeloma with a median of, of six prior lines of therapy and had an overall response rate of 73% with one-third of the patients achieving complete response or a stringent complete response.

So in this study, different doses were evaluated. The target do-, dose of ide-cel was established at 450 millions of CAR-Ts, and with this higher dose, the outcomes were slightly improved with a CR rate of 39.8% and a median progression-free survival, again, of one year. So, again, we do see deep responses and durable these responses in, again, a, a population of patients with very advanced myeloma.

And, and the other CAR-T that we have approved and available is ciltacabtagene autoleucel, also know as cilta-cel, and the approval was based on the CARTITUDE, CARTITUDE-1 trial. So in this study, again, similar patient population with very advanced myeloma, and I think the data is really impressive with an overall response rate of 98% and, more importantly, and a stringent complete response rate of 82.5%. So this data has never been seen before in such an advanced myeloma population. And this led to a median progression-free survival that is not yet reached with a median follow-up of that is now over 27 months. So, again, very, very impressive data in very sick patients with very advanced disease.

And, for sure, I mean the, the safety profile is not, is not nothing. I mean we do need to know and to manage the cytokine release syndrome, cytopenia, neurotoxicity, but for sure this is a great novel therapies for, for our patients. —

I'm so impressed by this data. The stringent complete response rate of 80, almost 83% is remarkable.

Dr. Rodríguez Otero: Absolutely.

Dr. Smith: So perhaps now we can talk a little bit about some of the new and emerging BCMA therapies for relapsed-r-, refractory myeloma. Paula, do you want to discuss some of these newer agents?

Dr. Rodríguez Otero: Yeah. So there is a lot going on. You know, in myeloma in the BCMA space, there are several bispecific antibodies that are being developed, so the more advanced in the development is Elranatamab, which is, has now completed the Phase II trial and, and the overall response rate is, is 61%. And the, the survival data is not yet mature, but for sure this is another drug to, to have in mind. And, also, there are other CAR-Ts targeting BCMA that are being developed although the data is still quite preliminary.

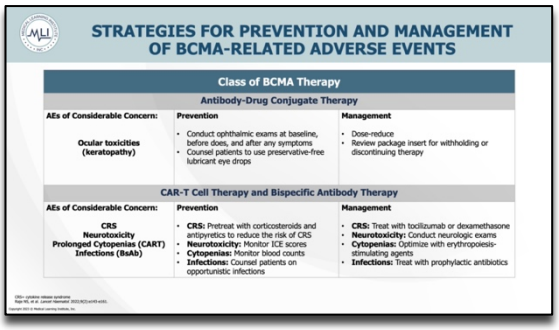
Dr. Smith: Sounds good, and we'll definitely delve more into these new and emerging BCMA therapies in our second episode, so more to come there.

So I would like to now briefly introduce, you know, a guest because we've gone over some of the safety, tolerability of each of these BCMA targeted therapies and how, and, and we know that the toxicity profile of

each of these therapies is distinct and it's important to, in the supportive care of our patients, manage these toxicities.

So today, in order to discuss this further, we'll be joined by Beth Faiman, and I'd like you to go ahead and introduce yourself.

Beth Faiman, PhD, CNP: Thank you so much for the opportunity to speak today. I love hearing this conversation, and I'm so thrilled to be invited to discuss the toxicity. So my name is Beth Faiman. I come to you from the Cleveland Clinic, Department of Hematology and Medical Oncology. And I, on a day-to-day basis, am charged with managing, assessing, and intervening on these side effects.



STRATEGIES FOR PREVENTION AND MANAGEMENT OF BCMA-RELATED ADVERSE EVENTS

So in my mind, the data just that show that there are really two distinct side effect profiles, as you mentioned, Melody, a moment ago. Really the anti-BCMA off-the-shelf A, B, C, belantamab is totally separate. It's convenient once every three weeks dosing. You don't need to premedicate patients. They come in, get the infusion, and go home.

However, there was a high incidence of keratopathy which was mostly microcystic-like changes and decreased best visual acuity which prevents some patients from taking the therapy in the first place. I do still have patient on compassionate use belantamab mafodotin, so it is still perfect option for some patients that had previous treated therapies.

The other bucket is the CAR-T-cell and the bispecific T-cell engagers. These require hospitalization. Cytokine release syndrome we know how to manage – we'll discuss in a moment – but they encompass a lot more discussion. You need to have a caregiver support. It's not just come into the office every three weeks, but it does represent a very effective therapy for patients that have had heavily pretreated relapsed-refractory multiple myeloma.

Dr. Smith: You alluded to the cytokine release syndrome that we see with the bispecific T-cell engagers, you know, in terms of the toxicity and management of that for the CAR-T-cells some distinctions there that you might want to highlight.

Dr. Faiman: The prolonged cytopenias I really am concerned about. We'll discuss strategies in a few moments of what I use, but primarily the cytokine release syndrome tend to be mild or moderate in a majority of patients. Again, this is really related to the CAR-T and the bispecific therapy. One of the things I'm observing is having participated in the clinical trials with people receiving these drugs, we have a nurse, data manager, all these strategies and people that are discussing side effects, planning hospital admission, caregiver support, transportation, all of these things need to be done in standard-of-care therapy that aren't always thought about.

The CRS, although mild to moderate, mild is a mild temperature greater than 100, we give tocilizumab and dexamethasone right away. Not dexamethasone for CAR-T because you don't want to worry about the CAR-T-cell fitness or expansion but definitely for bispecifics.

The other thing with the CRS syndrome that I see is that even moderate can be very, mostly distressing. They're requiring oxygen, they're feeling sick, and the counts drop rather rapidly. So now you're neutropenic so you have to do the infection workup, initiate antibiotics which can sometimes lead to a prolonged hospital stay.

In terms of the neurotoxicity, the immune cell effector neurotoxicity we see, again, we're checking the ICE scores. We have validated tools on the inpatient setting where the nurses or support staff or physicians will regularly check every eight hours for can you go backwards from 100 to 0, you know, mini-mental status type examinations, and really intervene with the same drugs if they have this.

And then, finally, with the prolonged cytopenias, I have had patients that have had CARs like last year and their platelets are still below 50 and they still require intermittent transfusions. We try to optimize that with romiplacin, erythrospoiesis-stimulating agents, and trying to avoid the transfusions unless they're symptomatic s-, 'cause then you worry about iron o-, overload in some of these individuals.

Dr. Smith: I was actually going to ask you, Beth, you know, in your practice, how do you counsel your patients? So we know that for CAR-T-cells, at least for the initial treatment, patients are admitted and observed for an initial you generally about a week to assess for toxicities. But when patients are in the outpatient setting, how do you counsel them to identify and be aware of these toxicities so they know when they need to contact their healthcare provider?

Dr. Faiman: Right. So in my institution, and many institutions in the United States, our model is that the cellular therapies/bone marrow transplant are still under the bone marrow transplant/cellular therapy bucket, so that's a, really a long journey. Patients need to have good enough disease control to be able to harvest their cells and then let that antiviral ve-, vector manufacture the cells and then be reinfused, you know, six, eight weeks later. So this is a process. They need a caregiver, lots of trips to the institution, and we, we really worry about T-cell fitness in these heavily pretreated patients. And that's different than the bispecific antibody. So we counsel them about that method and then the bridging therapy.

But with the bispecific therapy, a lot of patients don't want to be admitted to the hospital nine days, which is what many institutions among the United States, since the FDA approval in October, are doing because a majority will get at least grade 1 CRS and depending on when you administer that drug, it happens at one or two in the morning, so you don't want your patient in the outpatient and struggling with that.

So, again, lots of education about you can get sick, but until it really hits them and they are febrile and in the hospital for a prolonged time, they don't realize how sick they can get. I emphasize the benefits of disease control though and that we know how to manage these side effects.

Dr. Phillips: I just want to get back to this kind of inpatient stay because I've taken care of a lot of CAR-T patients that, you know, have CRS or ICANS at various intervals. So, you know, Melody, I heard you said about a week; Beth, I heard you say nine days. Is any of this standardized? Is there like a period where you can say, "Okay, this, this toxicity is past, the patient can be discharged"?

Dr. Faiman: Right. So in the clinical trials, it was a little bit different, but with the FDA approval and the prescribing information for teclistamab, there's this REMS program that mandates 48 hours observation after the dose. So if you give dose one with the step-up dosing, you might not see it. The very little that I call the baby dose of teclistamab, you might not see a CRS incidence with that dose, but in some patients I have. We've treated about 18 patients since the approval in October outpatient, and I think we've only had about two

people that have been able to be discharged before that nine-day stay 'cause that dose number seven you still need 48 hours observation which is where we came to that nine-day number.

Dr. Smith: Paula, I'd love to hear if in Europe that management in the inpatient setting or outpatient setting is distinct from, from what we've mentioned thus far.

Dr. Rodríguez Otero: So, so, unfortunately, in Europe, we do not have yet any, I mean teclistamab is approved by the EMA but is not yet available in the majority of the country, so we have had access to the expanded access program. And the hospitalization is, as per investigation to this question, something that is not a mandatory hospitalization stay, although I agree with Beth that until you get used to the CRS onset and all of that, maybe it's, it's reasonable to keep the patients in.

I think that something that is important to highlight is that the CRS is rather predictable, so it appears like a median time to two days after the first doses, so is, it's something that you can, you know, expect that it will happen so patients can be reassured that this is something that we are waiting for and it, it for sure it does require all this organization in the hospital.

And just I, I will also take the opportunity to ask Beth what is her experience with infections because the infection problem has also rise as we get more follow-up of all these studies and all these drugs. And what is your opinion, what is your advice to all of us and physician treating patients with the bispecific antibodies particularly?

Dr. Faiman: Right. Thank you for this important question. I, prophylactic antibiotics are used quite regularly. Many of these patients have hypogammaglobulinemia with serum immunoglobulins of maybe less than 400. So we do IVIG. Everybody is on acyclovir prophylaxis and the International Myeloma Working Group, in February of 2022, put forth a paper and consensus guidelines that suggests stratifying your patients into low, intermediate, and high risk and with recommendations as to what antifungal, antiviral, or antibacterial prophylaxis is recommended and that's what I do.

So the future is bright for patients with myeloma. Thank you for allowing me to participate in this rich discussion.

Dr. Smith: Thank you, Beth. We really appreciate your time and your expertise that you've shared with, with us and our audience.

So I think now as we think a little bit more about some of the clinical trials that led to the approval of these drugs, we may want to take some time to think about the enrollment on those clinical trials and understanding how the populations that have enrolled on these clinical trials for the approval of these drugs are they representative of the audiences or the patients who have multiple myeloma that these drugs will ultimately treat? Adrienne, do you want to take some time discuss this a little bit in terms of clinical trial representation and specifically representation of underrepresented minorities in these studies?

Dr. Phillips: Yeah. That's a topic near and dear to my heart because we've made tremendous progress in these BCMA-directed therapies in multiple myeloma, which I don't know if we mentioned at the start is a disease that is twice as common in African Americans compared to Whites, at least here in—

Dr. Smith: Correct.

Dr. Phillips: -the United States.

Dr. Smith: Yes.

Dr. Phillips: So it's amazing that we have these new, novel treatments, we're improving survival; but when you look at the clinical trials, particularly of these BCMA-directed agents and their eligibility and their enrollment, if I could summarize, you know, there weren't that many African Americans enrolled on these trials. And we'll be devoting another episode to disparities in care and the barriers to access to clinical trials, but this is really just to start. We need to make sure that all of these treatments reach the, the target audience that will benefit from them. And we'll all be able to strategize, and we'll have an invited guest to focus specifically on how we can improve access to these novel treatments for all.

Dr. Smith: Thanks for bringing up that point, Adrienne. I think it's really important to think about how these studies, the clinical trials are potentially misrepresenting or underrepresenting the populations that will ultimately benefit, specifically African-American patients who, unfortunately, have such a high incidence of multiple myeloma, as you mentioned

As we wrap up this first episode of *Med Table Talk*, I think we've had a really robust discussion about various BCMA-targeted therapies. And I'd love to end with what we'd like to see in a perfect world given the information based upon our discussion today.

So, Paula, you know, could you give us some of your reflections about what you'd like to see with these therapies in a perfect world?

Dr. Rodríguez Otero: Yeah. So it's always difficult, you know, to, to make these kind of, of conclusions, but I think that I would like to see first these drugs being used in a, in a best way so eventually, as we were discussing in a fixed duration or in combination in earlier disease settings with a good focus on, on, on safety as well as with efficacy. And for sure coming to the last point that we were discussing, I think that it is i-, important to, to expand the access to both clinical trials and to the drugs once, once they are appro-, approved to all patients and all populations to really reflect the needs that we have in the society to, to get a, a, a homogeneous access to the drugs to all patients.

So, so, Adrienne, what, what will you want to, to see in the future?

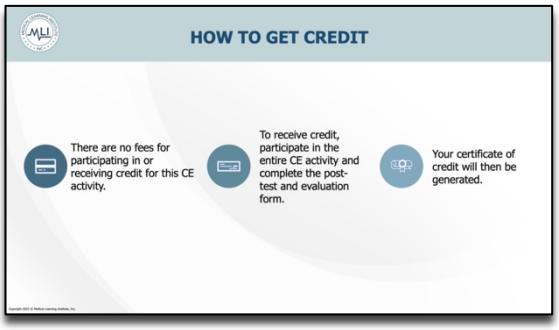
Dr. Phillips: So in a perfect world, I would also like to see these highly efficacious therapies delivered to the patients who most need them and can most benefit from them. And certainly this is very promising initial research, but, again, in the real world if it doesn't reach the patient in the middle of the country who doesn't have access to a cellular therapy center who's going to get it as a tenth line of therapy, then it's really not doing its job. So in my perfect world, I would like all patients to really have access to these great treatments.

Dr. Smith: I definitely echo both of your points. I think in a perfect world, I would like to see a bit more information targeted to providers to help guide their clinical practice as to how to utilize these drugs, particularly what order to utilize them in. I think there's a lot of really exciting data, as we discussed, toxicity profiles that we now know how to manage so much more effectively. But it'll be very important to help guide providers as to the order to use antibody drug conjugates versus T-cell engagers versus CAR-T so that they know, you know, how to use these drugs for their patients with relapsed-refractory multiple myeloma while opening the door that if a patient fails one drug that another future line they can use one of these other agents. So I think that would be what I'd really like to see in the coming years.

I just want to thank both of you, Paula and Adrienne, as well as our guest today, Beth, for participating in today's *Med Table Talk*. There are several resources that you can download from the activity's website.

UPCOMING EPISODES IN THIS SERIES

Dr. Smith: Join us for the next episodes of *Med Table Talk*. Episode 2 entitled, "Navigating the Evidence: Efficacy and Safety of Current and Emerging Agents." And Episode 3, "Creating Patient-Centered Approaches to Care: Best Practices for Utilizing BCMA-Directed Therapy."



HOW TO GET CREDIT

We hope you found this discussion informative and insightful. And now that you've completed this activity, you may get credit by completing the posttest and evaluation. Thank you.