Expanding Therapy Options for the Treatment of Relapsed or Refractory Multiple Myeloma (RRMM): BCMA-Directed Therapies

MED TABLE TALK™ EPISODE 2
NAVIGATING THE EVIDENCE: PATHWAYS FOR NEW AND EMERGING THERAPIES

Melody Smith, MD, MS: Hello, and welcome to the second episode of *Med Table Talk* where we'll be discussing, "Navigating the Evidence: Pathways for New and Emerging BCMA Therapies." I am your host, Melody Smith. I'm an Assistant Professor and Physician Scientist in the Bone Marrow Transplant and Cell Therapy Division at Stanford University School of Medicine, and I'm happy to be joined by my esteemed colleagues, Adrienne Phillips and Paula Rodríguez Otero. Adrienne, can you go ahead and introduce yourself to our audience.

Adrienne Phillips, MD, MPH: Sure, good morning, Melody, and the rest of our audience. My name is Adrienne Phillips. I'm an Associate Professor of Clinical Medicine at Weill Cornell Medicine at New York-Presbyterian Hospital in New York City. I'm also in the Bone Marrow Transplant and Cellular Therapy section.

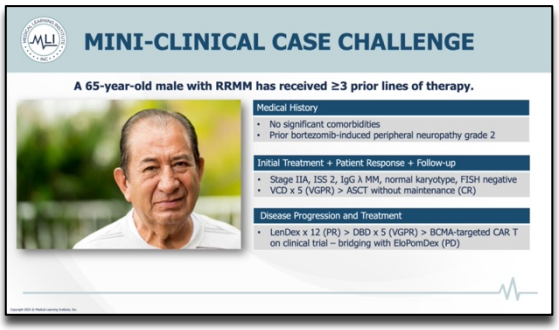
Dr. Smith: And, Paula, can you introduce yourself, please.

Paula Rodríguez Otero, MD, PhD: Hello everyone. Very happy to be here with you again. I am Paula Rodríguez Otero. I am hematologist working at the University of Navarra in Pamplona, Spain.

TODAY'S DISCUSSION

Dr. Smith: So we are really happy in today's episode to pick up where we left off with our first episode and now talk about some drug-resistance mechanisms, efficacy and safety of emerging BCMA-directed therapies, as well as strategies to promote timely initiation of care for underrepresented communities, increase clinical trial enrollment, and advocate for access to care. So, remember, this is Episode 2 of 3, so check out the previous episode and stay tuned to hear what other topics on relapsed/refractory multiple myeloma we'll be discussing in Episode 3.

So, to kick this conversation off, I think it's really important that we first talk about a patient, so we'll have a mini clinical case challenge that we'll discuss to really help to frame our discussion.



MINI-CLINICAL CASE CHALLENGE

So, the patient here is a 65-year-old male with relapsed/refractory multiple myeloma who's received three prior lines of therapy. This gentleman had no significant prior comorbidities, and he did receive prior bortezomib-induced therapy when he got triple therapy; and he developed some Grade 2 peripheral neuropathy.

In terms of his initial treatment response and follow-up, so at diagnosis this patient had Stage IIIA disease, ISS-2, and he had IgG lambda multiple myeloma with a normal karyotype; and it was also FISH-negative.

So, for the first line of therapy, the patient received triple-line therapy, five cycles of VCD which he had a very good partial response. The patient went on to receive an autologous stem cell transplant with maintenance.

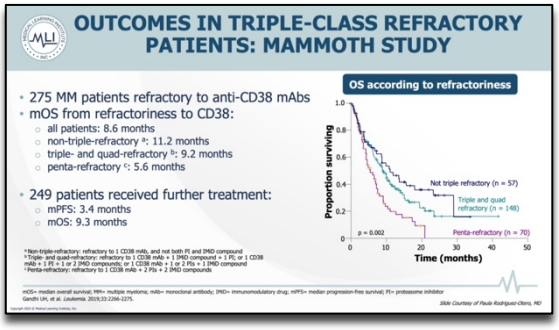
At disease progression, the patient was treated with LenDex for 12 cycles and then received daratumumab-bortezomib-dexamethasone for five cycles with a very good partial response.

And then most recently the patient went on to receive BCMA-targeted CAR T-cell therapies, which we talked about in-depth in in our last episode on a clinical trial. And for the CAR T-cell therapy bridging, he received EloPomDex with a progressive disease after that.

So, you know, I'd like to open it up to my colleagues and talk about how would you classify what's happening with this patient? Paula?

Dr. Rodríguez Otero: Yeah, so I think that this is a classic case of a patient with relapsed myeloma that received subsequent treatments and becomes resistant to each subsequent line because, as you all know very well, the treatment in myeloma is typically given until disease progression.

So now we know this patient has been exposed and is already refractory to proteasome inhibitors, immunomodulatory agents, and also anti-CD38 monoclonal antibodies. So this is what we have called the triple-class refractory, relapsed refractory myeloma patients.

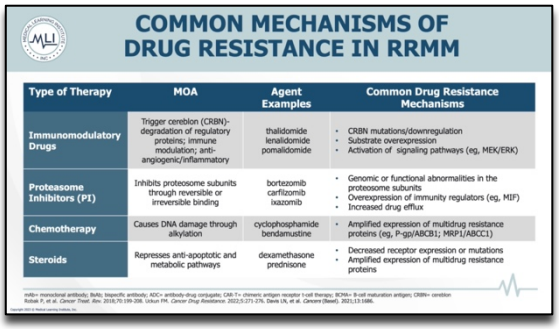


OUTCOMES IN TRIPLE-CLASS REFRACTORY PATIENTS: MAMMOTH STUDY

And we know retrospective data from the MAMMOTH study, and we also have a prospective observational study that is called the LocoMMotion study, and the two studies highlight that these patients that are exposed and become refractory to the three main classes of drug have a disparate outcome with a median progression-free survival that is shorter than 4 months and a median overall survival of less than 10 months. So this is the outcomes that we get in this highly resistant population; and this is why we need to incorporate and operate in as we, we've discussed in the first episode.

So we know that drug, factors contributing to drug resistance are diverse; and, to be honest, when you have a patient in front of you with resistant disease who you do not know exactly what is the mechanism of resistance in that particular patient, so we know that there are genetic alterations that confer resistance to particular drugs. We know that during the therapy, because the patients are continually, continuously exposed, we know that there is clonal selection and there are new clones that emerge that have met resistant mechanisms, whether because of genetic, epigenetic aberrations or other factors, and, for sure, tumor microenvironment, particularly I would say in the era of immunotherapies are also important factors that do contribute to resistance to drugs.

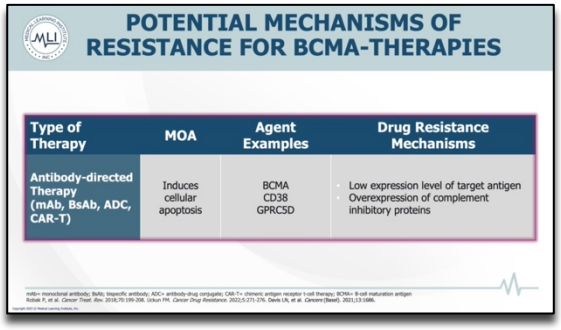
Dr. Smith: Yeah, and I think it was really important, as you mentioned, that with increasing levels of resistance from triple to quad to penta, that the responses are overall worse; and there's different mechanisms for that resistance.



COMMON MECHANISMS OF DRUG RESISTANCE IN RRMM

Dr. Rodríguez Otero: I think that I mean there are several, let's say, well-known mechanisms of resistance. So we know that when patients get exposed to immunomodulatory agents, that that are drugs that are going to bind cereblon to make there, this is the mode of action of these drugs. We know that there are patients that become resistant because of mutations in the cereblon passway, pathways that leads to absence or of action or substrate degradation, and also there are patients that do activate other signaling pathways that at the end of the day confer resistance to both lenalidomide and also to pomalidomide or thalidomide. We know that with proteasome inhibitors, there are also some known mechanisms of resistance like genomic abnormalities of the proteasome subunits that led to impaired binding of the drugs and also some other alterations on multi-drug proteins we know that are responsible of and resistant to some chemotherapies.

But in the eval of the novel immunotherapies, and particularly monoclonal antibodies, and as we discussed previously, CAR Ts and bispecific antibodies, we know that a target, the expression of the target in the tumor cells is also very relevant.



POTENTIAL MECHANISMS OF RESISTANCE FOR BCMA-THERAPIES

And although, let's say with BCMA-targeted drugs, this is probably not the most frequent mechanism of resistance, there has been some reports of patients with a genetic loss of the BCMA locus leading to a onset of BCMA-negative clones, conferring resistance to the drugs, and the same has been also reported to CD38, for example, where we see a downexpression of the target that may also be responsible in part of the resistance to the anti-CD38 monoclonal antibodies.

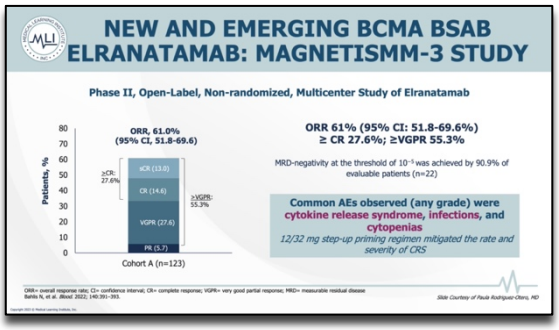
But I think that there is still a lot to know, you know, about the mechanism of resistance to all these drugs and particularly to the novel therapies. And sometimes it's the pa-, in the patient it's very difficult to really dissect what is the real mechanism that is behind that failure of that particular combination.

Dr. Smith: So, I think, you know, it's really important when we're thinking about targeting, using a specific antigen to target therapy, for example, BCMA with multiple myeloma, the presence of the antigen is really relevant for ongoing utilization of that targeted therapy.

Multiple myeloma is still uncurable, and there's an urgent need to develop new therapies for our patients. And recently received a lot of trial updates at the American Society of Hematology's annual meeting in 2022.

Adrienne, how about we discuss some of the most interesting data thus far.

Dr. Phillips: So, yeah, certainly last month in New Orleans, ASH 22 had a number of exciting updates related to BCMA-targeted agents.

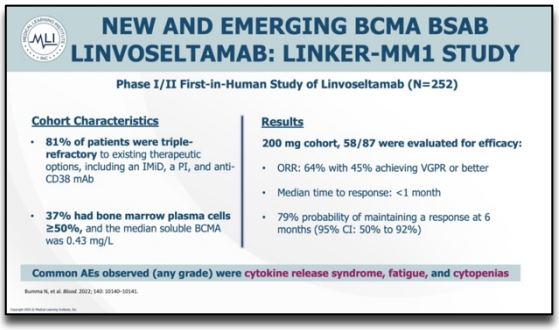


NEW AND EMERGING BCMA BSAB ELRANATAMAB: MAGNETISMM-3 STUDY

So talking about the elranatamab update, this was presented by Bahlis and colleagues, and they specifically focused on the Cohort A of the trial. So this was a Phase II, open label, nonrandomized, multer-, multicenter study of elranatamab. And they found a very impressive overall response rate of 61% with over 25%, a quarter of the patients, having a complete response. They also reported data on an MRD negativity, which was achieved in almost 91% of patients.

And then in terms of toxicities, I think the toxicities were consistent with what we see with these bispecific antibodies. In terms of hematologic toxicities, we saw neutropenia, anemia, thrombocytopenia; and then in terms of nonhematologic toxicities, we saw cytokine release syndrome.

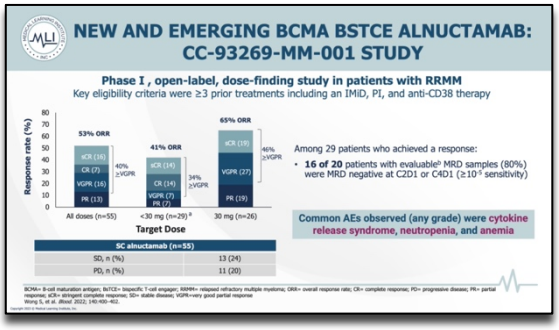
But importantly, they were able to mitigate some of these toxicities, particularly the CRS by the step-up dosing of the elranatamab.



NEW AND EMERGING BCMA BSAB LINVOSELTAMAB: LINKER-MM1 STUDY

Dr. Smith: That's really exciting data, a bispecific antibody therapy that was also presented at ASH for the treatment of patients with relapsed/refractory multiple myeloma. It was a first-in-human study, a Phase I/II study, and the investigators reported on the severity of cytokine release syndrome and noted the various dose levels that were found. And 200 milligram dose was the dose level that's going to be the recommended dose moving forward.

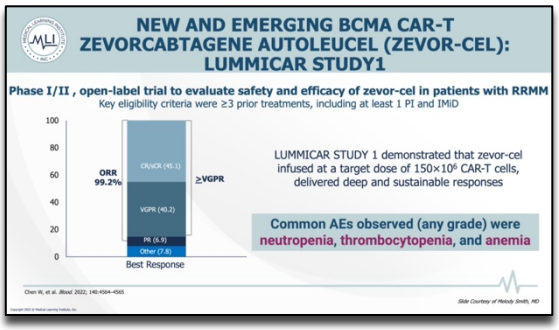
So of the patients who were treated, 252 patients who were treated with this drug on this study, 111 of the patients did experience cytokine release syndrome; and the median duration of that was about 15.4 hours following treatment.



NEW AND EMERGING BCMA BSTCE ALNUCTAMAB: CC-93269-MM-001 STUDY

Alnuctamab, this is results from a Phase I study, a first-in-human study. So for this open-label study, they were doing dose finding and evaluated patients at all doses, as well as patients who received less than 30 milligram dose, as well as those who received 30 milligram dose. They found that in all doses, there was an overall response rate of about 53%; but specifically at the 30 milligram dose, 65% of patients had an overall response rate, and 46% of those patients who had that overall response had a VGPR. So that's really encouraging data to note that among the 29 patients who did achieve a response, 16 of the 20 patients had evaluable MRD samples, and MRD negativity was noted in 80% of those patients.

And so along the same lines in terms of the toxicity that we've previously touched on, some of the toxicity that was noted was cytokine release syndrome, as well as neutropenia, and anemia across various grades.



NEW AND EMERGING BCMA CAR-T ZEVORCABTAGENE AUTOLEUCEL (ZEVOR-CEL): LUMMICAR STUDY 1

So just briefly, Phase II data for our fully human BCMA-targeted CAR T-cell therapy it was presented on zevor-cel. So this was really exciting data. We already have two approved CAR T-cell products that we've mentioned. But this is some exciting data about a target dose level that was infused of 150 million CAR T-cells, and we found that this CAR T-cell product delivered both deep and sustainable responses.

It was well-tolerated, so we look at the duration of response. It was really nice both data in terms of the duration of response, as well as the progression-free survival. So, again, really exciting data, so it'll be interesting to see how that data matures in the future.

So, you know, I think it's a really exciting time in the treatment for relapsed/refractory multiple myeloma. We've reviewed several BCMA-targeted therapies that are new and emerging, and so more data to come, based upon the ASH abstracts that we saw.

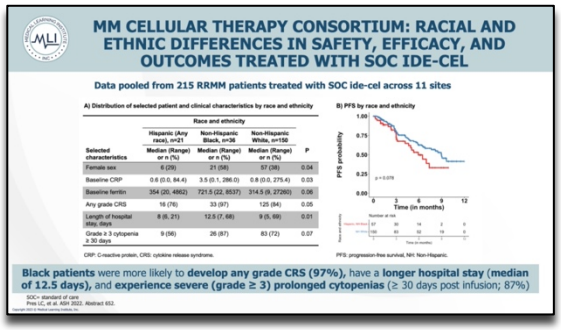
But I do want to talk a little bit more in-depth about the clinical trials that lead to these clinical approvals. So both the NCCN and EDMO, ESMO guidelines support clinical trials for patients who are being treated with new and emerging therapies. And so as we look at the clinical trial participation, it's very important to understand the representation of patients who are enrolled on those clinical trials and some of the underlying disparities that may be a part of those clinical trials.

Particularly as we mentioned in our last episode, African American patients are highly represented or, you know, in the US at least, most commonly diagnosed with multiple myeloma. So it's really important that we think about the representation of the clinical trials and the patients who are being enrolled on these studies for these new and emerging therapeutics.

So in order to delve a little bit more into the data in terms of the clinical trials and clinical trial representation, I'd like to welcome our guest for this episode, Dr. Saad Usmani. Dr. Usmani, can you briefly introduce yourself to our audience?

Saad Usmani, MD, MBA, FACP: Thank you, Dr. Smith, and my esteemed colleagues. I'm Saad Usmani. I'm the Chief of the Myeloma Service at Memorial Sloan Kettering Cancer Center in New York, and, you know, it's a privilege to be here.

Dr. Smith: Thank you. As we begin our sort of discussion about the representation of patients in clinical trials, I would like to touch on this ASH abstract from the Multiple Myeloma Cellular Therapy Consortium that analyzed the racial and ethnic differences in the safety, efficacy, and outcomes of patients treated with standard-of-care ide-cel.



MM CELLULAR THERAPY CONSORTIUM: RACIAL AND ETHNIC DIFFERENCES IN SAFETY, EFFICACY, AND OUTCOMES TREATED WITH SOC IDE-CEL

The investigators looked at 215 patients and looked at the ethnic and racial background, and we do see that there are disparities in terms of the percentage of patients enrolled with the majority of patients that were analyzed, at least in this study, being White. And we can see that there were differences in the progression-free survival of the patients by race and ethnicity, patients who were White versus other.

So, you know, Dr. Usmani, I'd love to understand, you know, a little bit more from your perspective. You know, in our last episode, we just briefly touched on the lack of representation in clinical trials for patients with multiple myeloma, especially underserved populations. And so what is the value of clinical trials, from your perspective, especially for patients with relapsed/refractory multiple myeloma?

Dr. Usmani: Thank you, Dr. Smith. You know, I'll start by saying that, you know, there is a clear recognition now within the myeloma research community that this is an issue; and, you know, there have been several measures to actually address it.

You know, I grew up, you know, as a junior investigator in a program, in a very busy myeloma program where, you know, we were, we had a culture of high clinical trial enrollment. I think more than 60% of the patients coming to see us would go on one or the other clinical trial. But, you know, the minority representation was less than 5%.

So when I had the opportunity of moving and building a program, this is something that, you know, one had to address head on. I think there are several important aspects to it. You know, certainly, both implicit and explicit biases, you know, that one has to overcome. You know, there are perceptions, both on the patients as well as physician side that have to be overcome to improve clinical trial enrollment. But then, you know, systematically, you have to, you know, go a step further and see if you can introduce, you know, certain benchmarks into clinical trials of enrolling minority patients.

For specifically for our Black myeloma patients in the US, you know, they make up, you know, over 20% of patients being diagnosed with myeloma; yet, you know, if you look at historic clinical trial enrollment, you know, on even cooperative group trials, which are seen as supposed to be catered to the community outreach, we see, you know, about 3 odd percent enrollment.

So, I think, you know, a lot of these issues have been, you know, recognized; and we actually have clinical trials that are looking at, you know, increasing enrollments, you know, introducing, you know, champions at each site, or regional site to include clinical trial discussions with patients and then having patient advocates actually improve health literacy and importance of clinical trials out in the communities. I think all of those things are, you know, very important, you know, people going into improving outcomes for our patients.

Dr. Rodríguez Otero: If I may ask, is this because there is a cultural barrier? Is this because there is a financial problem? Or is because the inclusion or exclusion criteria does not fit the same in the different populations because it may be because also that they, you get, I don't know, Hispanic patients; but then you feel at the end of the day that there are some limitations based on the inclusion criteria because I don't know the neutrophil

co-, count is lower and then you- So is it this because there is a cultural financial risk because of the really the design of the trial that make it difficult to the patients to get in?

Dr. Usmani: I would say it's all of the above. There have been studies looking at, you know, socioeconomic status and outcomes in myeloma; and there is certainly a disparity there, you know, towards minorities. So patients get diagnosed with higher burden of disease. You know, they might have more end organ damage. And when you have those kind of presentations, you know, the exclusion criterias like, you know, creatine clearance, you know, or, I mean, you know, degree of anemia or white blood cell count, you know, becomes a problem. And so I think, you know, patients get, you know, excluded from clinical trials because of those reasons as well.

But, you know, one can mitigate by being a little bit more generous in those inclusion and exclusion criterias to include patients. And, you know, that kind of push has to come from us; and, you know, more recently that's what we have been doing as myeloma research community is pushing back on some of those, you know, inclusion/exclusion criteria that do not make intuitive sense, you know, because, you know, when the drugs and regimens get approved, we're using them for all patients, you know, we do.

Dr. Smith: Exactly.

Dr. Usmani: So, you know, I think you raise a very important point. I think all of those things are kind of interlinked as well.

Dr. Phillips: I'd like to comment on that, just looking at it from the provider angle too because certainly there's distrust in the system perhaps amongst some patients with clinical trials. But I think us as providers also have to recognize our implicit bias, and I'm sure there're providers that looking at their patient in their mind think that this would not be a good clinical trial patient; and it's not even offered to them.

So I think the burden is not, you know, on the patient. It's really like what can we as a provider do to bring these trials into the community? We're talking about BCMA-targeted therapies that are such a logistical, you know, it, it's hard to get patients to manufacture T-cells and to monitor for toxicities.

Saad, you and I are across the street in New York City, and we're at these great academic facilities. But how do we get these treatments into Staten Island or Brooklyn or thinking more nationally in the US into the Midwest where maybe they don't have a cellular therapy center or, you know, five cellular therapy centers within five miles and the next available center is 100 miles away? So I think there are a lot of challenges here that we need to address.

Dr. Rodríguez Otero: But also I think you know it's also important because maybe the safety profile it may be different.

Dr. Smith: Right. Yeah, I was just going to touch on that. You know, the ASH abstract that we just briefly mentioned showed differences in progression-free survival based upon ethnicity; but, you know, there could be, one, some underlying differences by ethnic group.

The other thing that could potentially be at play is that patients do their delayed referral, and higher lines of therapy are doing worse because we're just waiting longer for some minority patients to receive the therapy. So I do think that there's, you know, so many factors at play that could be impacting the responses that we're seeing but also that are limiting our ability to really make conclusions about the data that we're seeing from these clinical studies.

And, you know, Saad, you know, have you found any approaches that have been really effective to go out to the community and bring patients to the center in a more rapid clip or to work more closely with community providers to refer them and not wait for patients to come and maybe not benefit as greatly from these newer therapies?

Dr. Usmani: It, you know, boils down to communication and outreach. And, you know, this is something that I was able to do. I mean when I started a new program in North Carolina, you know, I went from a program where, you know, people came to you. Patients came to you, physicians called you up to get patients in. And, you know, in North Carolina, it was the opposite. You know, I had to build that trust with the community. I had to build that trust with, you know, the local oncologists who were providing great care to patients but did not have access to trials or transplant and cellular therapy proc-, you know, procedures.

Dr. Smith: I definitely agree with you because, you know, one thing that comes to mind as we're talking about these new therapies, these novel therapies for patients is that if we as providers, as clinicians, the healthcare system don't work to bridge this divide, whether it's communication or misconceptions with our patients, the disparities are just going to become compounded.

Dr. Usmani: I think the only point that we have not touched upon is actually encouraging, you know, physicians and physician leaders from minorities to take up arms and actually join, you know, the mission in caring for patients with hem malignancies. I think that's something that, you know, many institutions are now recognizing and trying to do. But I think that's a very important, you know, part of how we, you know, break down these barriers and improve, you know, communication with the community at large and improve, you know, outcomes for patients regardless of where they come from.

Dr. Smith: Thank you. Now, thanks for sharing that, and I would like to highlight to our audience that there are resources available for patients and caregivers through organizations such as The Leukemia & Lymphoma Society, as well as the Myeloma Research Foundation as to how we can, you know, help to educate patients and their caregivers to be able to be knowledgeable about these therapies, ask their physicians about these therapies, and identify centers where they can get this treatment if they have myeloma that's relapsed and refractory following multiple prior lines of therapy. So it's really important to know that there are resources out there for you to also educate yourself.

So, Dr. Usmani, thank you so much for your time. I really appreciate that this has been a robust discussion, and we really do appreciate your perspective and insight as to how we can troubleshoot and mitigate some of these disparities that we're currently seeing in clinical trials.

Dr. Usmani: Thank you so much.

Dr. Smith: As we kind of go to sort of recap some of the things that we've discussed, I would like to give us an opportunity to hear from each of our colleagues in terms of some of the take-home messages or really important things that we want you to be left with as we conclude this discussion.

So, Paula, you know, what would you say that you would like to see in a perfect world relating to the new and emerging therapies as well as to representation within clinical trials?

Dr. Rodríguez Otero: In a perfect world, I would like to see novel agents evaluated in all patients, let's say, so, or in the wider populations possible to get a better understanding of the real efficacy and the safety. And more importantly, I want drugs to be available for any patient in need, you know, because this is the beauty of

science that to make, you know, science count for patients and drugs available for patients. And I think that this is the most important part of our work.

And what about you, Adrienne?

Dr. Phillips: So in my perfect world, you know, these are highly specific therapies that right now are benefiting a select few. So as others have said, I would like to have access to all.

And then they are not without their toxicity. So I think in the perfect world, we need to just know how to use these therapies smarter. You know, there was a study that did the step-up dosing, find the correct dose, find the correct mitigation strategy so hopefully these therapies can be given in an outpatient setting, in a rural or community setting. That's also how I think we could deliver these therapies more effectively to patients who need them.

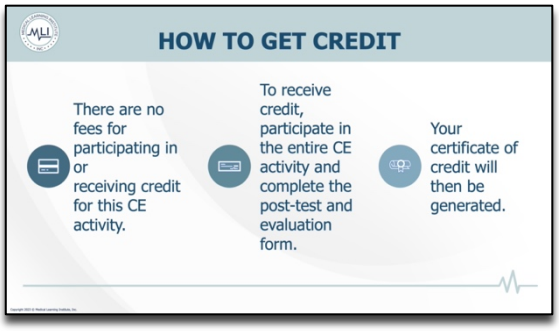
Dr. Smith: And, you know, as I think about a perfect world, all of us as healthcare providers who take care of patients who are receiving these therapies for relapsed/refractory multiple myeloma do have a desire to see less healthcare disparities, particularly as it relates to clinical trials.

I would like to see more guidance from funding and regulatory organizations to help put a little bit more of a framework as to the enrollment on clinical trials because, as was eluded to earlier, sometimes until those guidelines are handed down, the prioritization of representation in clinical trials, although it's at the top of mind, may not be fully actualized. So I think some guidance or maybe even regulations around representation in clinical trials may be beneficial in the future.

I just would like to thank everyone, my colleagues, as well as our guest, Dr. Usmani, for participating in today's *Med Table Talk*. There are several resources that you can download from the activity's website.

JOIN US FOR THE LAST EPISODE OF MED TABLE TALK

Please join us for our final episode, our third episode of the three, where we'll discuss, "Creating Patient-Centered Approaches to Optimal Care: Best Practices for Utilizing BCMA-Targeted Therapy." We hope you learned a lot.



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