CREATING PATIENT-CENTERED APPROACHES TO OPTIMAL CARE: BEST PRACTICES FOR UTILIZING BCMA-DIRECTED THERAPY

Melody Smith, MD, MS: Hello, and welcome to *Med Table Talk*. This is the last of three episodes where we'll discuss, "Creating Patient-centered Approaches to Optimal Care: Best Practices for Utilizing BCMA-directed Therapy." I am your host, Melody Smith. I'm a Physician Scientist at Stanford University in the Division of Bone Marrow Transplant and Cell Therapy. I'm happy to be joined by my esteemed colleagues, Dr. Rodríguez Otero and Dr. Adrienne Phillips. Dr. Rodríguez Otero, could you go ahead and introduce yourself to our audience?

Paula Rodríguez Otero, MD, PhD: Sure, hello everyone. My name is Paula Rodríguez Otero. I am hematologist working at the University of Navarra in Pamplona, Spain.

Dr. Smith: And Dr. Phillips?

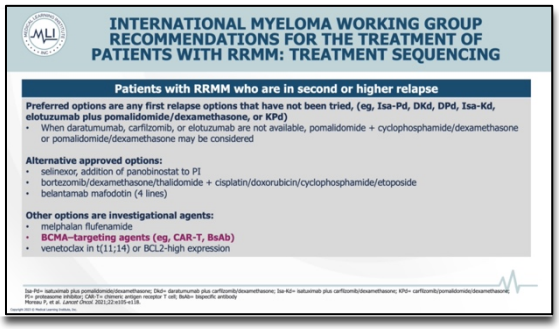
Adrienne Phillips, MD, MPH: I'm Adrienne Phillips. I'm an Associate Professor at Weill Cornell Medicine, New York-Presbyterian Hospital in the Division of Cellular Therapy and Stem Cell Transplant.

TODAY'S DISCUSSION

Dr. Smith: So in today's episode, we're going to be discussing biomarker identification for prognosis and treatment selection for patients with relapsed/refractory multiple myeloma, optimal treatment decision-making, approaches to address health disparities in relapsed/refractory multiple myeloma, and strategies to engage patients in shared decision-making, improved patient outcomes, and advocate for access to care. Remember, this is the final episode of the series; so if you haven't already, check out Episodes 1 and 2 to learn about the evolving treatment landscape using BCMA therapy for relapsed/refractory multiple myeloma.

Picking up where we left off from Episode 2, we had a great discussion in terms of various BCMA targets using antibody-drug conjugates, bispecific therapies, as well as chimeric antigen receptor T-cell therapy. So, Adrienne, you know, regarding treatment sequencing, where do the BCMA therapies, in your perspective, fall in the lineup of therapies that are potentially available for patients with relapsed/refractory multiple myeloma?

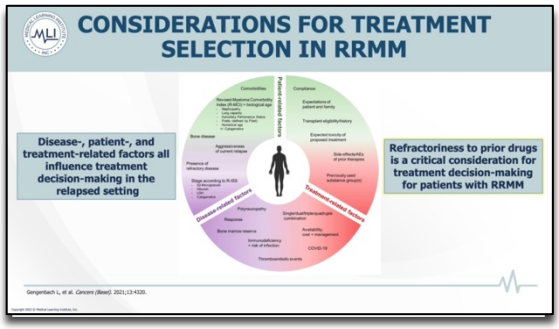
Dr. Phillips: Thanks, Melody. So, the International Myeloma Working Group has recommendations for the treatment of patients with relapsed/refractory multiple myeloma. And the preferred options are really any first relapse options that haven't been tried. And as someone who treats a lot of lymphoma, this is where I feel like there's a gap in knowledge because there's no one size fits all, one direction fits all.



INTERNATIONAL MYELOMA WORKING GROUP RECOMMENDATIONS FOR THE TREATMENT OF PATIENTS WITH RRMM: TREATMENT SEQUENCING

So options, at least in the second line, are higher relapse. You can use daratumumab, carfilzomib, elotuzumab if those haven't been tried. You can use pomalidomide and dexamethasone. You could use selinexor, bortezomib, belantamab; and then BCMA-targeted therapies which are indicated in the third or fourth line could also be used as an investigational agent.

Dr. Smith: So what are some of the top considerations when selecting treatments for your relapsed/refractory multiple myeloma patients with multiple lines of prior therapy? Like when you're making these decisions, Paula, what do you prioritize in determining which patients would be best suited for one of these therapeutics?



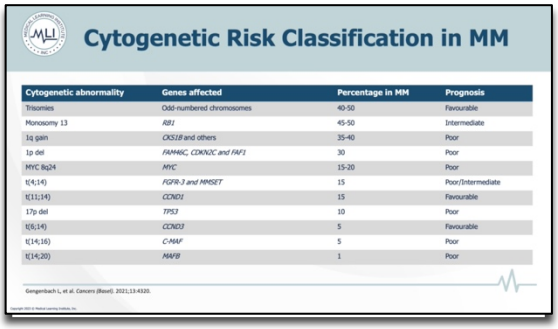
CONSIDERATIONS FOR TREATMENT SELECTION IN RRMM

Dr. Rodríguez Otero: So I think that for sure you need to consider a patient condition, no, so comorbidities, frailty stat tools, age, and also, very importantly, what are the treatments the patient has previously received if there was any, let's say, treatment toxicity that prevents you for using the drug in a new line of therapy. But I think that today one of the most important factors to consider is the refractoriness to prior drugs.

So I think, from a practical perspective, when you face a patient in third- or fourth-line myeloma, probably the treatments the patient has previously received and the drugs to, the disease is refractory to are what is really driven your treatment decisions.

Dr. Smith: And, Adrienne, do you have any other sort of considerations that you keep in mind when you're considering your patients for a BCMA-targeted therapy?

Dr. Phillips: So, yes, I agree with Paula. There are a lot of considerations for treating relapsed/refractory multiple myeloma patients; and they include both disease-related factors, patient-related factors, and treatment-related factors. And all of these will influence your decisions.



CYTOGENETIC RISK CLASSIFICATION IN MM

Speaking specifically about cytogenetic risk classifications in myeloma, we know that about 25% of myeloma patients have a poor risk cytogenetic profile; and the poor risk cytogenetics that we're talking about include the translocation between chromosomes 4 and 14, translocation 14;16, translocation 14;20, the deletion of 17p or a gain of 1q by FISH. So, again, that's about a quarter of myeloma patients; and these mutations and this pattern tells us that these patients are going to have a poor prognosis.

Dr. Rodríguez Otero: Think that also, because we are incorporating a lot of new drugs and we have patients that are now responding better with good responses to the therapies that we have now available, there is a lot of development in the field of prognosis, SMART risk, treatment monitoring, and we have now several

strategies. We can monitor minimal residual disease in the marrow as well in the peripheral blood. We can also evaluate circulating serum BCMA levels, and we have now a lot of knowledge with these techniques.

So we are extremely happy to have Bruno Paiva join us to share his insights on prognostic markers, risk factors, and treatment sequencing for BCMA therapy. Welcome Bruno. Can you please introduce yourself to our audience?

Bruno Paiva, PharmD: Thank you so much, Paula. It is my great pleasure to be here. I'm Bruno Paiva, Director of Flow Cytometry in the University of Navarra, Pamplona, Spain.

Dr. Rodríguez Otero: So recently, the use of minimal or measurable residual disease, MRD status, is being applied in some centers as part of the routine clinical practice and, very importantly, in the context of clinical trials. And we know that achieving MR negativity is one of the most important prognostic factors in myeloma because it is associated with better outcomes. So can you explain as was, what is measurable residual disease and how is it being used as a prognostic marker in myeloma?

Dr. Paiva: Yes, it would be my pleasure. The classical definition of minimal or measurable residual disease, MRD, is the amount of tumor burden that remains after or throughout treatment that is undetectable using conventional methods available in routine diagnostic laboratories, and this residual disease can be detected using more sensitive methods. This being the classical definition, if you wish, I prefer to use other perhaps more dramatic words. That is a fact that providing that nowadays in myeloma there are so many different and highly effective drugs, really monitoring MRD is about the most sensitive and specific evaluation of treatment efficacy.

And I would even say that in this particular disease, myeloma, the methods to evaluate MRD aren't very for-, forefront when compared to other hematological malignancies. Therefore, this is the power of MRD to evaluate to the best of our ability the efficacy of the new and highly effective therapies available to treat patients with multiple myeloma.

But on the other side, and I think this the side that is more important from a clinical point of view, the detection of MRD may help you to resolve the variability, heterogeneity among patients achieving complete remission, those that will not sustain that remission and those that will achieve a longer remission, and usually this is related to detectable or undetectable levels of MRD.

Dr. Phillips: So Bruno, you answered a lot of my questions about how MRD can be used in relapsed/refractory multiple myeloma in terms of treatment selection; but can you comment a little bit more about how MRD can be applied to predict response to BCMA-targeted therapies?

Dr. Paiva: In my opinion, in the relapsed/refractory setting, because of the more aggres-, aggressive nature of myeloma cells at that stage, I think that, generally speaking, perhaps in 90% of the patients, the only way to really achieve a long progression-free survival or time to the next therapy is through the achievement of an undetectable, sustained MRD-negative status.

As we are seeing that in patients that are otherwise in remission but continue to show MRD, after different types of treatment for relapsed/refractory myeloma, time to relapse and eventually a new line of therapy is very, very short. Now, I would not like to overreach what is the value of negative MRD in this setting, that unfortunately, in my opinion, is somehow less than in the newly diagnosed setting. In other words, the progression-free survival may not be as long as we see in the newly diagnosed setting.

This being said, to really achieve long progression-free survival, I do believe that a negative MRD status will be paramount, at least in 85-90% of patients. And, fortunately, there are new regimens that achieve this outcome in a considerable fraction of patients.

Dr. Smith: What would you say are some of the limitations to MRD evaluation in the relapsed/refractory multiple myeloma setting?

Dr. Paiva: In my opinion, the main limitation is the amount of disease spreading at the time of the fourth-, fifth-, sixth-line of therapy. And, therefore, if we consider MRD, this will be informative as a more sensitive tool when compared to the criteria for CR but might be underpowered because of greater disease dissemination.

Dr. Phillips: I wanted to just follow up on a limitation that I think I'm also hearing is that currently is the MRD assessment being done on bone marrow? My patients, you know, don't want to have bone marrow biopsies all the time. So, I would say that could also be a limitation.

Dr. Smith: Um-hmm.

Dr. Rodríguez Otero: So, Bruno, if I may, because I think that one of the limitations of MRD is that it's not widely adopted, let's say.

Dr. Smith: Yes, yes.

Dr. Rodríguez Otero: So like we have heard a lot. Yeah, we have heard a lot. There is a lot of prognostic implications. And I would say that in newly diagnosed, we are all much in favor of waiting to do MRD testing or sequencing, you know, MRD samples to search for sustained MRD. But in the relapsed/refractory setting, with the drugs that we are typically using now, it's of less value because a small proportion of patients do get to these very deep responses.

But for sure, using this new BCMA-targeted therapies, bispecific antibodies, and CAR Ts particularly, that we have seen patients achieving really deep responses, including MRD. And you have also shown data showing that in patients that, for example, after CAR T-cell therapy that are MRD-negative at month three, for example, after CAR T-cell infusion, are the patients that are doing better in compared to patients that remain MRD-positive at one month after infusion. So really, you know, maybe highlighting that these tools may be of greater use in this field, you know, of new therapies where patients have really reached into these deep responses.

Dr. Smith: So just one question, Bruno. What would you say is the knowledge gap or the sensitivity of the assays that needs to be addressed in order for MRD to start helping us guide treatment decisions or be more prognostic, either in the early stage of treatment or in the relapsed/refractory setting?

Dr. Paiva: I will put it this way. A positive result is equally valuable in one setting and the other. But back to your question, the gap, I think that in terms of the robustness of methods, we are there. For sure there will be improvement. And I would say that the gap is more about the time we need to learn from ongoing clinical trials that have used MRD as either a randomization or a stratification factor, prior different duration or intensity of treatment.

Dr. Rodríguez Otero: Yeah, I agree, and I think that also in the setting of BCMA-treatments, and I will say particularly in the setting of bispecifics that are now planned in disease progression, we will keep on learning how to tailor the duration of therapy probably based on patients achieving MRD negativity. And maybe we can

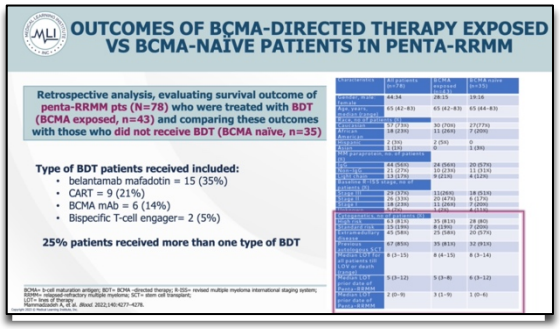
force some long-term toxicities in those patients if we are able to show that they can just stop therapy because the, their responses will be maintained because of the MRD negativity status.

So I think that there is, for sure, a lot of things to learn about how to better incorporate the MRD in our real-world daily clinical basis to fine-tune, as you mentioned, the therapies in our patients.

So I would like to take the opportunity to thank Bruno, Dr. Paiva, for the excellent discussion and thank you very much, Bruno too, for being here with us today.

Dr. Paiva, PhD: Thank you. This was very insightful discussion. I really enjoyed and thank you again for having me.

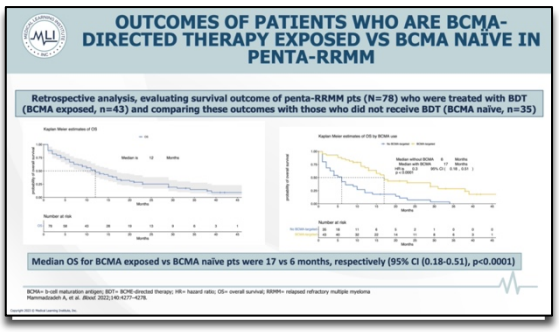
Dr. Rodríguez Otero: So now we wanted to speak a little bit more about sequencing the different BCMA therapies in patients with relapsed/refractory multiple myeloma. So, Adrienne, what is your uptakes of the role of the BCMA therapies and how can we eventually sequence these treatment modalities?



OUTCOMES OF BCMA-DIRECTED THERAPY EXPOSED VS BCMA-NAÏVE PATIENTS IN PENTA-RRMM

Dr. Phillips: Thanks, Paula. There was an interesting abstract presented this past year at ASH by Mammadzadeh and his colleagues who did a retrospective review at the University of Kansas of their penta-refractory myeloma patients. And by penta-refractory, it means they've had two different IMiDs, they've had two different proteasome inhibitors, they've had an anti-CD38 monoclonal, and historically these patients have a poor median overall survival.

So he looked at patients who went on to receive BCMA-directed therapy that could have been belantamab or CAR T or BCMA monoclonal or a bispecific. Of 78 patients, 43 went on to receive BCMA-directed therapy and 35 did not receive BCMA-directed therapy.

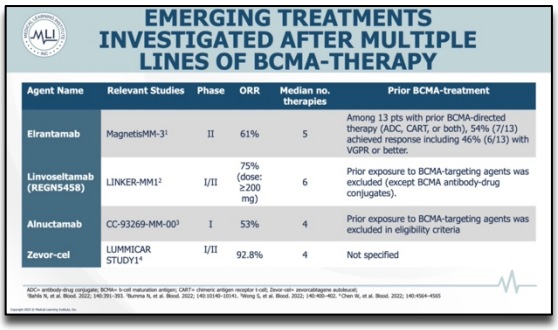


OUCTOMES OF PATIENTS WHO ARE BCMA-DIRECTED THERAPY EXPOSED VS BCMA NAÏVE IN PENTA-RRMM

And in their retrospective analysis, at least their Kaplan-Meier curve showed that the median overall survival for those BCMA exposed, even when they were penta-relapsed/refractory myeloma, was 17 months. And this is compared to just 6 months in those patients who did not receive a BCMA-directed therapy. So, again, retrospective but very interesting; and these patients can continue to be treated and achieve long-term survivals.

Dr. Smith: Adrienne, that was really exciting data that you shared at ASH on the response to BCMA-targeted therapies in penta-refractory multiple myeloma patients.

I do want to just take a moment as well to talk about some of the emerging treatments that are being investigated after either multiple lines of therapy or BCMA-targeted therapy.



EMERGING TREATMENTS INVESTIGATED AFTER MULTIPLE LINES OF BCMA-THERAPY

So a few of those new and emerging therapies that are being investigated include elranatamab, linvoseltamab, alnuctamab, and zevor-cel. It's important to note that the median prior lines of treatment in patients who've been treated with these therapies on trial range from four to six prior lines of therapy. And notably, elrantamab is the only one of these new therapies that has included patients who received BCMA-targeted therapy.

From the reported data among 13 patients with prior BCMA-directed therapy, 54% of those patients who received one of these BCMA-targeted therapies, so 7 out of 13 of those patients achieved a response, including 46% of them with a VGPR or better. So, that's really exciting and encouraging to suggest that patients may be able to receive a BCMA therapy. And then if they relapse, a subsequent one. So, that's really exciting data.

Patients who were treated on the pivotal studies, including CARTITUDE, CARTITUDE-1, KarMMa, and MajesTEC-1 trials, aside from MajesTEC cohort C, none of those patients on those pivotal studies received prior BCMA-directed therapy either.

Now thinking about some of these new and emerging therapies, as well as the patients who were included on the pivotal studies, what are some of the remaining questions regarding the use of BCMA-targeted therapies in treatment sequencing, Paula, and what do you hope to see in the future?

Dr. Rodríguez Otero: So I think that one important aspect to consider when we are thinking about sequencing the different BCMA therapies is that we need to move a little bit away for the classic, you know, patient relapsed, you know, immunomodulatory drugs changing to proteasome inhibitors, and the other way around because these are all drugs targeting the same molecule in the surface of the myeloma cells. So, these are all BCMA-targeting drugs, but the mechanism of action is completely different, so, speaking about this possibility of sequencing between these different agents.

So it is sure that the data that we have today is still scanty, so as you mentioned before, we have some data with teclistamab after prior BCMA antibody-drug conjugates for BCMA CAR Ts. And we have see that 52% of the patients treated with teclistamab after failing BCMA therapies are able to achieve an objective response; and a median duration of response has not yet been reached in this cohort C from the MajesTEC-1 with a median follow-up that is close to one year, so suggesting this sensitivity to other BCMA modalities.

We also have data with cilta-cel, and we do see responses after antibody-drug conjugates or bispecific antibodies. But I will make here a note. I think that if you have a patient that is targeted for a BCMA CAR T, you have the slot available and your patient is in good condition, probably it's interesting to do CAR T-cell first and then using the other drugs eventually later because we have seen responses; but the overall response rate and the progression-free survival is shorter if we use CAR Ts after bispecific antibodies or antibody drug conjugates than probably the other way around. That maybe speaks about a lower target expression or other, you know, T-cell thickness or other issues. But we can take this conclusion, although the data is still preliminary.

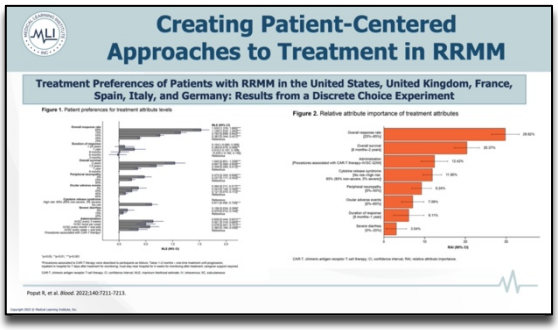
So I think that in the future we need to see more data, more patients treated with different BCMA therapies. I am sure that the real-world use of all these drugs will help us guide in what is the best sequence, and I think that this is very relevant if we want to use these drugs in a better way.

Dr. Smith: Yeah, I think you raised some really important points in terms of the mechanisms of relapse after each of these therapies. These BCMA-targeted therapies may be unique as you touched on antigen density, T-cell fitness, and so ongoing studies will hopefully help to clarify what are those mechanisms of disease relapse or antigen escape for each of these.

You know, also thinking about what are the best practices for sequencing and assessing responses to direct, BCMA-directed therapies, do you have any thoughts about those best practices, Adrienne?

Dr. Phillips: You know, I agree with what's been said, you know, that we need more data. A lot of what we have is preliminary. But I was really fascinated by Bruno's discussion of MRD testing, and I, I'm very hopeful for that in the future to ha-, perhaps be able to guide our treatment selections and hopefully, you know, tell us how to use BCMA-directed therapies in the most ideal way.

Dr. Smith: So perhaps now we can talk about patient-centered approach to how we treat these relapsed/refractory multiple myeloma patients. Do you want to share some of those insights with us, Paula?



CREATING PATIENT-CENTERED APPROACHES TO TREATMENT IN RRMM

Dr. Rodríguez Otero: Yes, so I think that there is a lot of focus now to incorporate the, you know, the patient expectations also in the choice of therapy. And there's been a very interesting paper recently published evaluating treatment preferences of patients with relapsed/refractory multiple myeloma across different countries regarding patients' preferences. For sure, efficacy in terms of overall response rate was one of the first factors that patients consider when deciding about therapy. Overall survival was also very important.

But other aspects such as duration of response, incidence of severe adverse events are all considered by the patients as factors that will influence their decision. So I think that knowing this, I think that we need to educate our patients.

Dr. Phillips: Yeah. I mean I think you have to think of every patient as a individual, and you have to meet them where they are. So, certainly there they have different levels of health literacy, they have different goals and expectations, they have different support to get them through their therapy. So, I think really customizing your decision-making to the individual in front of you is paramount.

Dr. Smith: Yeah, I definitely agree with Adrienne, seeing the whole patient, what their objectives are, what their goals are, and really having a transparent discussion as to the efficacy, but also, like you mentioned, the side effect profile, what's expected of them in terms of the frequency of visits.

Another aspect of patient-centered care and I think in terms of having a healthcare system and treatment of patients with relapsed/refractory multiple myeloma that's representative of the various populations we serve, we touched on in prior episodes about disparities. Adrienne, do you want to speak a little bit to some of the health disparities in vulnerable populations that we encounter as we're treating patients with multiple myeloma?

Dr. Phillips: Sure. I think, you know, first of all, the three of us work at academic centers; so we're seeing patients that can get to us. They have the transportation. They have the referral patterns in place to see, you

know, specialists in myeloma instead of a general hematologist/oncologist that might see all types of malignancies.

So, you know, my goal is to try and reach them, whether it's through networking with community physicians, giving talks or discussions, increasing education and awareness about myeloma, going to churches, going to beauty salons, going to, you know, local social meetings to really just raise awareness about the disease and the different treatment options.

Dr. Rodríguez Otero: Yeah, and I think also, if I may, I think that particularly for older patients or patients with severe comorbidities, we need to wait for, you know, primary care physicians, or, you know, internal medicines, or geriatric doctors to really work along all other things that may happen.

So to good, a good control of hyp-, hypertension, diabetes, if any, other problems, polypharmacy because sometimes, you know, we just care about myeloma, adding the drugs to treat myeloma, and we have little, you know, no, at least myself, you know to control the other drugs that are, that the patient is taking. And I think that this is sometimes one of the problems when we get these old patients with a lot of drugs ongoing already that you add the myeloma drug, you add the dexamethasone, and then you have the infection, you have the hypertension, you have the cardiac dysfunction going on. And then, you know, you need to work with other physicians to really take the patient as a whole, as an individual, as you were mentioning, and to control everything that may happen. And I think that this is also explaining sometime the poor outcome of these very elderly patients.

Dr. Smith: Yeah, I agree. And I think the only other thing I would say about the vulnerable populations is patients with a lower socioeconomic status. I really see this really often that because of the requirement, at least for CAR T-cell therapy, the requirement for a caregiver for that first month after therapy, that we're really impacting our patients who have a lower socioeconomic status because of the impact not only on the patient but that caregiver who needs to have their work interrupted. Not everyone has paid time off of work, so I'm not sure what the solution is; but sitting down and coming up with creative strategies so that we're not limiting access to patients just because they can't afford to have someone take care of them around the clock for that next month is something that we as a field need to work to address.

Dr. Rodríguez Otero: Yeah, I think that you raise a very important point; and I would like to echo that because, you know, in Spain also, you know, there is very, it's very limited number of centers that can provide CAR T that some, a lot of patients need to move from their city to other cities far away, and they will need to bring someone of the family with them, so. And as you mentioned, not everyone can do this; and this is now limiting the access to these very powerful therapies. And I think that, yes, as you mentioned, we need to somehow invent something, you know, to really make these drugs available to the larger majority of patients in need.

Dr. Smith: So, as we start to wrap up, I would like to end on what we'd like to see in a perfect world given the informative conversation that we've had today. We touched on several topics, but, Paula, I'd love to hear what you'd like to see in a perfect world.

Dr. Rodríguez Otero: So in a perfect world, and I will just take one, you know, one of the topics that we have discussed today, I would like to see minimal residual disease tools, whether it's mass spec or flow cytometry, really helping us to guide the treatment of our patients and personalize this treatment to improve the outcomes. It wi-, this will be my hope for that.

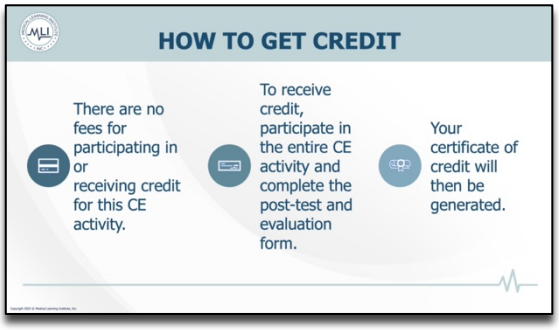
Dr. Phillips: In a perfect world, as someone who works in stem cell transplant and cellular therapy at a highly specialized center, I feel like I'm getting familiarity with how to give these very challenging treatments. And I think in a perfect world, I'd like to continue to get familiarity and experience and be able to extend these highly technical treatments into communities where, perhaps, they don't need to, this is just my opinion, they always need to be given by a specialist in cellular therapy, but perhaps not at my academic center. It can be given closer to the patient.

How about you, Melody? What would you like in a perfect world?

Dr. Smith: Yes, I would go along the lines of what you said, Adrienne. You know, we are representing providers in the US and also in Spain, and I think there're probably similar issues to what we've discussed in terms of the special populations around the world.

And so in a perfect world, I would like to see some type of international initiative that can help to come up with solutions that we may be able to employ to address some of the populations and groups of patients that are not receiving these new BCMA-targeted therapies, ways that we can come up with solutions and potentially even intersect with various pharmaceutical companies to see if there's ways that we can really balance the playing field or the access of care for these therapies for patients.

So on that note, I just want to thank Dr. Rodríguez Otero and Dr. Adrienne Phillips for participating in today's *Med Table Talk* as well as this *Med Table Talk* series for these three episodes along with me. There are several resources that our audience can download from the activity's website. If you have not, please go ahead and check out Episodes 1 and 2 from the series. We hope you learned a lot, and to get credit for this activity, please complete the post-test and evaluation.



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