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BCMA Who and When: Immunotherapies in Patients with RRMM

Announcer:
Welcome to CME on ReachMD. This replay of a live broadcast is titled, “BCMA – Who and When? Immunotherapies in Patients with Relapsed/Refractory Multiple Myeloma,” is provided by Prova Education. Prior to beginning the activity, please be sure to review the faculty and commercial support disclosure statements, as well as the learning objectives.

Dr. Usmani:
Hello and welcome to the Prova Education program titled, “BCMA – Who and When? Immunotherapies in Patients with Relapsed/Refractory Multiple Myeloma.” My name is Saad Usmani. I’m the chief of the myeloma service and I’m joined by my colleagues, Dr. Amrita Krishnan from the City of Hope in Duarte, California and Dr. Sikander Ailawadhi at Mayo Clinic in Jacksonville, Florida. And what we’re going to be focusing on is some of the novel treatment options in the relapsed/refractory multiple myeloma space. And here, you know, we have had a lot of ponderization around class of drug refraction rather than the lines of therapy. And so the three specific classes of drugs that we refer to are the proteasome inhibitors, immunomodulatory drugs, as well as anti-CD38 monoclonal antibodies, and what we found from the MAMMOTH study which looked at this patient population, from roughly a dozen academic centers is the more refractory patients get to classes of therapies as well as drugs within a class of therapy, the dismal the outcome. So if you have someone who is refractory to 2 classes of drugs, the median OS around 11 months. If they are triple-class or triple-drug or quadruple-drug refractory the median OS about 9 months. If patients are penta-refractory, which refers to being refractory to an anti-CD38 monoclonal antibody, 2 MS and 2 PIs then that median OS drops down to about 5.6 months. This highlights the fact that we need novel mechanisms of actions and novel therapies for relapsed/refractory multiple myeloma patients. This is where we’ve seen a lot of news recently about BCMA or B-cell maturation antigen. This particular surface protein is preferentially expressed on mature B-lymphocytes as well as on plasma cells. In fact, its overexpression and activation is associated with progression of multiple myeloma, and that’s what makes it a lucrative target. The good news is we now have 3 BCMA-directed therapies that are FDA-approved. One bispecific antibody, called teclistamab, which was approved in October of 2022, and 2 CAR T-cell therapies that have been approved – one called idecabtagene vicleucel or ide-cel, approved in March of 2021, and ciltacabtagene autoleucel or cilta-cel which was approved in February of 2022. With this being said, I’m going to pass on the baton to Dr. Sikander Ailawadhi, to cover his section of this program. Thank you.

Dr. Ailawadhi:
Hi. I’m Sikander Ailawadhi from Mayo Clinic in Jacksonville, Florida, and today we’ll be talking about leveraging community partnerships to optimize BCMA-directed therapies. Now as these treatments become available, it is extremely important to talk about the logistics and workflow, so that the right treatment can reach the right patient at the right time. So hopefully today we’ll cover some of these factors and topics and be able to come up with a plan of how to get the right treatment to the patients.

We typically talk about some form of this slide or this data, where we say that every time we select a treatment option for a patient, we should take into account patient factors, disease factors and treatment-related factors. And, as our treatment options keep increasing, the number of these factors which have to be taken into account – so whether it’s at home or in the institution, the way of administration, financial implications, caregiver support, comorbidities of the patients, the side effect profile, prior treatments, what worked, what didn’t work, how much did it work for, etc. So I think all of that becomes very, very important and we need to take all of this into consideration

every time we talk to a patient about treatments.

It's important, also, to know that every time a treatment regimen is changed, or a patient needs a new treatment regimen, there is an attrition. This is data from my colleague, Dr. Fonseca in Mayo-Arizona, where it shows that – at least in this particular national data – out of 100 patients who got diagnosed with myeloma, only 1% got to the fifth-line treatment. So you can imagine, we may have these options available, but we have to make an effort to get the patient to the next treatment.

Similarly, it's also important to know that clinical trial population and real-world population is very different. A lot of times, it is very difficult to apply the clinical trial results into the real-world patients, and that's where we also notice that sometimes, once the drugs become approved and start getting utilized, there are so many factors that come into play, and the benefit from a regimen may not exactly be the same as we expected in the clinical trials. So, important to keep that in mind.

So we'll talk briefly about belantamab, as we talked about BCMA-directed options. So belantamab, which is an antibody drug conjugate against BCMA, got approved based on the DREAMM-2 study. Single agent, treatment, single arm study. It had efficacy with a recommended dose of being used every three weeks, and had an overall response rate of about 32%, heavily pretreated patients, median prior lines were 7 – 6-7. But there was a side effect noted, with eye toxicity or keratopathy. So based on that, we started using this drug, but most recently there is data that has come out from the DREAMM-3 trial, which was a randomized, head-to-head between belantamab and pom-dex. And unfortunately, that study did not meet its primary endpoint of progression-free survival improvement. So based on that, as of November 22, this drug has been withdrawn from the market as a single agent, although if patients are on this treatment and are deriving benefit – it's safe – they can continue on it, but new patients will not start on it. There are ongoing combination clinical trials that are clinical trials with kidney dysfunction, etc. Those studies are moving on, and possibly this drug would make a comeback down the road in a combination regimen, but we'll have to wait and watch. So it's important to keep in mind that patients who have been getting it can still continue to get it, if they are deriving benefit.

Other modalities including CAR T-cell therapy and bispecific antibodies have also become available. CAR T's – now we have 2 of them, and recently we have had teclistamab as the bispecific antibody against BCMA that has been FDA-approved. Now there are pros and cons to all these drugs – off the shelf, one-time intervention, continuous therapy, sub-Q, IV manufacturing time, logistics. But whenever we decide that a patient needs a BCMA-directed therapy, we try to take all of these factors into account, to come up with the right treatment for the patient. It's also extremely important to note that, in my opinion, at least personally – in today's day and age, every patient must get a good, fair shot at a BCMA-directed therapy. It's a very, very good treatment modality to go against – go after the BCMA for myeloma patients. We should try our best to get the patient to a legitimate treatment option within this family.

So, as we talk about CAR T-cell therapy, I mentioned that there are now 2 FDA-approved and available in the U.S. – ide-cel, which got approved in March of '21, and cilta-cel, which got approved in February of '22. Structurally different, both go against BCMA, but based on the structural difference and the binding domains, where ide-cel has one binding domain to the tumor, while cilta-cel has two, there are some clinical differences in what we expect out of this. And it's important also to keep in mind that at least currently, the label for these – both of these – is 4 prior lines of therapy, and the patient must have been previously treated with an IMiD, a protease inhibitor, and an anti-CD38 monoclonal antibody.

So when we look at them, this is not head-to-head comparison, but I'm going with the two studies that led to the FDA approval of these agents, and there are some differences in safety. For example, the median onset for CRS – cytokine release syndrome – with cilta-cel is about 7 days. On the other hand, with ide-cel, is about 1 day. So, logistic issues that we have to figure out on our end of – now we're going to, for example, CAR T as an outpatient in a lot of institutions, so how to handle the side effects, for example. Similarly, some amount of delayed neurotoxicity noted with cilta-cel previously, at least as part of the label, but since then we have not necessarily seen too much of an issue there. Also, difference in efficacy – overall response rate, higher, deeper with cilta-cel as compared to ide-cel. Still we're using these both, and we're glad that we have these options available for patients.

CAR T-cell is a slightly complicated process but we have a process figured out in which the patient who is appropriate – it's important to remember, by the way, that these CAR T-cell treatments are the treatment by themselves, as in patients with relapsing/refractory disease, progressing disease, can go into this treatment, unlike transplant which is something we have to clarify to patients all the time, that transplants are given as a consolidative approach. CAR T themselves are the treatment. So when we talk about this treatment patients typically have their T-cells collected, then they are enriched and activated, and then they are transfused with a lengthy virus – CAR construct – basically that's where the CAR is created, which will be against BCMA. These transfused cells are expanded, packaged, sent back to the institution, and we give them to the patient. Before the patient gets it, they get some outpatient lymphodepletion chemotherapy, so that their body is ready to receive the CAR T-cells.

There are several steps that have to happen: patients have to be identified, referred to a specific center, the center identifies eligibility, I

mentioned apheresis, conditioning chemotherapy, infusion, manufacturing, availability of slot, etc., etc. Lots of processes, and we've not had the fair, I would say, luck with CAR T-cells in myeloma because there have been some logistic challenges, but hopefully they are actually improving.

It's also important to realized that the rate of – I'm using a comparison for auto-transplants – our auto-transplant numbers have been increasing over the years in the U.S., but we still know that as for this particular study, only about a third of patients who are eligible for transplant get a transplant. But, I can tell you there's data from other studies showing that only about 20% transplant-eligible patients get transplant in the U.S.

That brings up the important issue that – well, if we're doing that with transplant, which has been there for maybe 25, 30 years, how are we going to fare with CAR T, which is also logistically a bit challenging? There are barriers to optimal care, and these are studies that have shown that a referral center looks for trusted partners – centers that are referral centers that are closer to the patient, closer to the practice, and have experience. So we need to figure out what are the barriers and how to overcome those barriers.

Another study that we've recently done, and this is being presented at this ASH, is surveying healthcare providers in academic and community settings, and we noticed that the centers felt, or the providers felt, that there was insufficient patient information sharing between academics and community. There was a lack of time in clinic to actually discuss all the logistics and issues or processes. Lack of expertise from the referring center – the community center – that they could talk about all of this. So, many barriers that we've identified. So, maybe you can look through the data from the presentation and see what we learned.

There's a lot of coordination of care that is required before, during, and after the CAR T treatment, so again, logistics that can be overcome, but we need to make an effort. I give you a particular workflow that has been discussed. For example, right from intake, consultation, collection, bridging, infusion, early, late care and then regulatory processes. I can say that working in the CAR T space, that a lot of this is done by our centers that are already doing the CAR T treatment. So, community referring group may not have to do much, but that's important for them to know.

And, at the end of it all, I think it's important to remember the study has shown that a lot of times, what we forget are the patients' preferences and what they want. So it's extremely important to always keep in mind what our patient wants, what their goals are. The study had shown that whatever physicians talk was actually quite different from what the patients wanted. So hopefully, we are able to merge those two. And with that, I come to the end of this discussion. Thanks a lot.

Dr. Krishnan:
Hello, everyone. My name is Amrita Krishnan. I am the director of the Judy and Bernard Briskin Center for Myeloma at the City of Hope in Duarte and in Irvine, California. I'm pleased to talk to you today about the nuts and bolts of bispecific antibodies in the treatment of relapsed myeloma.

And why are they important? They're important because as the field moves forward, survival of myeloma has improved, but there are patients who are either initially refractory or become refractory to approved therapies, most notably the major causes – the proteasome inhibitors, the immunomodulatory drugs, and the anti-CD38 antibodies. And those patients who are triple-class refractory have a much shorter median overall survival. Here you see the MAMMOTH study, suggesting the median overall survival for those triple- and quad-refractory patients at 9.2 months. Patients who are penta-refractory have an even poorer overall survival, on the order of about 6 months. So clearly, we still need new agents for patients with relapsed myeloma.

So what are the options that we have? Well, it's exciting that we have many options on the horizon, and in fact, a new option that was recently approved as well. So some of the ones on the horizon that have fairly advanced data are the CELMoDs and also certainly CAR T-cell therapies – we had two approved CAR T-cells for patients with myeloma relapsing after 4 prior lines of therapy, and we're looking at many other novel T-cell constructs in the near future. Today I'm going to talk about bispecific antibodies, and as I mentioned, we are fortunate that in fact this past October, we had a bispecific antibody approved in multiple myeloma. But that's really the tip of the iceberg, and we foresee that many new ones will be soon to follow. I don't want to discount, and remind people of also clinical trials as well. Now on the right here, you see some recommended treatments. We talked about CAR T-cells, Selinexor. Certain other interesting drugs, such as venetoclax, while not approved for myeloma, is one that we do consider in the relapsed setting for patients that T-11, 14 translocation. You have listed here belantamab mafodotin, but as many of you know, that that drug was recently withdrawn from the market for patients with the current label indication of belantamab, which was for prior therapies.

Now, let's talk about targets in myeloma, and we are discovering many more targets. We started with CD-38, and that really formed a backbone of our myeloma therapy options. And we also SLAMF7 – those are really our first two naked antibodies that were approved in the treatment of myeloma. We've now moved beyond those, to certainly BCMA-targeting being a real backbone of myeloma therapy, and in the near future you'll see GPRC-5D and FCRH-5 also becoming very much standard approaches in the treatment of relapsed

multiple myeloma.

So what are bispecific antibodies? Well, exactly that. The bi referring to the fact that there are two bindings. One to the tumor cell antigen, and currently BCMA is the one that is really most advanced, but also some of the other targets. We talked about GPRC-5D and FCRH-5 are in trial with bispecific antibodies.

And the other target is the CD-3 positive T-cell. Now having said that, in the future, there are also bispecifics binding other targets such as NK cells, and so again, the field is really moving quite quickly. But the idea is really a T-cell redirection mechanism to help augment the anti-tumor effects of the antibody. We also are going to see trispecific antibodies, so they include a T-cell costimulatory molecule, so all further augment and stabilize the immunologic effects of the antibody.

Here you can see that I mentioned we have one approved – teclistamab – so we actually need to update this to mention it was approved. There is a phase 3 ongoing with teclistamab, as well. But also, a phase 3 with elranatamab. And then there's several other ones who are a little bit earlier in development, but nonetheless also show promising results, and I've listed some of them below.

And then I mentioned earlier, trispecifics. So those are much earlier in development, but you can see here a couple of them that are being tested, and they have different third targets, again, to increase persistence in the stimulatory effects. The one that we have, for example, at our institution is the one with CD-38, CD-3 and CD-28 targeting. Here the non-BCMA-targeted bispecific antibodies currently in phase 1 with FCRH-5, and then we have talquetamab with GPRC5D. That has been presented as phase 1/phase 2, and a phase 3 trial is ongoing with it.

There's some common toxicities associated with T-cell redirection, namely in terms of T-cell activation leading to cytokine release, and this happens in about 75% of patients treated with these bispecific antibodies. Fortunately, in the majority of cases, the CRS is grade 1 and grade 2. Neurologic toxicity tends to be relatively low – certainly on the order of less than 10%, and so far, we've not seen any late neurologic toxicities with any of these agents. Hematologic toxicities is not uncommon in the majority of patients. It tends to be transient and self-limited, generally during the early cycles, which in part may represent extensive marrow infiltration in these patients with advanced disease, and also probably some immunologic effects as well with T-cell trafficking.

I think the biggest thing that we're struggling to understand and learn how to modify our treatments is the issue with infections. And we see now, with longer-term data, about 75% of patients treated with these bispecifics ultimately have some sort of infectious complication. Those can be bacterial, but it can also be viral infections representing in part this idea, probably, of the T-cell exhaustion.

And so, we're learning how to use mitigation strategies to minimize that risk. That includes the use of prophylactic medication such as prophylaxis and PJP prophylaxis, the use of immunoglobulins for patients. There's a majority of patients, especially with BCMA bispecifics, tend to be hypogamma. And then, infusion-related reactions – those tend to be somewhat less common.

So in summary, bispecific antibodies represent a huge step forward for us in multiple myeloma. We are still learning how to optimize their use, with many questions remaining about schedule and duration of therapy. Thank you.

Dr. Usmani:
So, in this section, it's titled, "Preparing for Future T-Cell Redirecting Therapies with Bispecific Antibodies," I'm going to be highlighting data that's emerging with teclistamab as well as other bispecific antibodies targeting BCMA that are making their way towards a regulatory approval. So it could be good for us to learn a bit more about each of those strategies. I do want to highlight that most of this data is in the relapsed/refractory setting, primarily focused in more of our triple-class exposed – triple-class refractory patients – but I will point out where the data is in earlier lines of treatment. Before we start talking about teclistamab, I do want to share some of the proof of principle work that was done early on by our German myeloma colleagues. First with a compound called AMG 420, which was the first BCMA-directed bispecific that was reported on in literature. This was a continuous IV formulation being given for 4 out of 6 weeks. The early data was shared in roughly 42 patients and the overall response rate at the most therapeutic dose was about 70%. You know, the challenge with this kind of approach was really logistic care. It was not feasible for us to give patients IV formulations as a continuous infusion for 28 consecutive days. And so, a weekly dosing formulation, or extended half-life formulation called AMG 701 was then studied in clinical trials, but around the same time, there were several other bispecific platforms that were in development. So even though AMG 701 did show clinical activity, as I'll show you over the next few slides, it wasn't at par with some of the other bispecifics that were in clinical development.

And here they are, so you can see teclistamab, elranatamab, the Regeneron compound, the BMS compound, and the AbbVie compound. All of those different bispecific antibodies actually demonstrated high overall response rate in a very refractory – triple-class refractory – percentage. You can see well over 60% in most of these data sets showing very high response rates, kind of unprecedented for this patient population. Where we were used to seeing response rates of anywhere from 20 to 30%, we were now seeing responses in two-thirds of this patient population.

So, let me walk you through some of the data with teclistamab. We first heard about teclistamab in the MajesTEC-1 trial. This trial had a dose escalation, first in human portion, and then a phase 2 dose expansion portion. So, both IV and subcutaneous formulations were examined in this dose escalation portion of the study. There were 2 step-up doses of teclistamab that were given and the idea behind that step-up dosing was to reduce the likelihood of cytokine release syndrome as well as degrading of the cytokine release syndrome. And then the second part – the phase 2 portion – was expanding the expedience of the recommended phase 2 dose in a larger cohort of patients. So eventually, a total of 165 patients were treated at the recommended phase 2 dose of 1.5 milligrams per kilogram dose of teclistamab, given on a weekly basis.

And these are the salient features. The overall response rate at that dose was 62%, with vast majority of patients – 58% – getting VGPR or higher. The median follow-up at the time of this particular report was 7.8 months with the median time to first response being only 1.2 months. And really high MRD-negativity rates at 10^{-5} – 24.7% of the patients being MRD-negative, and 16.7% at 10^{-6}.

And at the time of this ASH report, the 9-month EFS and 9-month PFS rates were quite high, but more recently in the NEJM publication, we now know that the median PFS for this study is a little under 12 months. So, quite impressive results with teclistamab, if we look at the ANSA patterns, the infection appears to be, about half of the patients – a little over half of the patients – 61% in fact. 72% of the patients had evidence of hypogammaglobulinemia. There were nine deaths due to AEs none were related to teclistamab. Again, you can see seven patients passed away from COVID, one from pneumonia, one from hemoperitoneum episode.

If we look at the CRS, it occurred in about 70-odd percent of the patients, but it was all grade 1 and 2. There was only one patient who had a grade 3 event. The median time of onset of CRS is about two days. And the neurotoxicity profile is quite favorable. If you look at the data compared to the CAR T-cell data, as well as some of the bispecific data we are seeing in the B-cell malignancies, the neurotoxicity was seen in about 12.7% of the patients, and in vast majority of those, it was headache. So, ICANS was only seen in 5 out of the 165 patients, encephalopathy in 2, and all of these were grade 1 or 2 and median onset was 2.5 days, and they resolved with supportive care measures.

What is also interesting to see is data in previously BCMA-targeted agent-treated patients, so patients who got an antibody drug conjugate or a CAR T-cell therapy. What was observed in this particular cohort was a response rate of well over 50 percent – so 55% in ADC-exposed, 53% in CAR T-exposed, if we look at the whole cohort, it was 52.5, with high rates of EGPR. Something again, unprecedented. As you can see in the summer slot below, several of the responses are well beyond 12 months, and sustained. So, important data with this bispecific.

Then more recently at ASH this year, we saw the combination of teclistamab with daratumumab and lenalidomide in a group of 32 patients. This is early lines of treatment, so median prior lines of 2, with very high response rate of 93.5% and a CR rate of 54.8%. CRS was seen in 81% of the patients, but this was grade 1 and 2, and infections were seen in about 75% of the patients. So this is something that all of us have to be cognizant of as we're thinking about bringing these treatments into the earlier lines of treatment, and I'll love to get some feedback from my colleagues during the Q&A session, about the duration of treatment in light of the responses we are seeing with the bispecific antibodies.

Similarly, the combination of teclistamab with daratumumab on its own showed very high response rates – as you can see. Regardless of whether patients were treated with the 1.5 milligram per kilogram dose on a weekly basis, or the 3 milligram per kilogram dose every 2 weeks, the overall response rates were the 75 to 74% range. The CRS and again, infections were similar to what has been described with teclistamab.

And I do want to talk about elranatamab, which is not far behind in terms of clinical development, and we are seeing some really good data. Just like teclistamab, this particular bispecific antibody targeting BCMA was examined in a dose escalation phase 1, first-in-human study with subcutaneous dosing. And then there was an expansion part of this, particular study as well. One can see that in terms of the common side effects from hematologic CRS side effect perspective, very similar to what we are seeing, and priming dosing was utilized for elranatamab as well, which mitigated the degree and the grading of the CRS that has been observed. And another important thing to note in this particular data set is prior BCMA exposure, and ADCs and CAR T's were allowed in this particular data set and study.

So what we find is an overall response rate of 64%, and overall response rate in the patients who had BCMA – prior BCMA-directed therapy was 54%. So similar to teclistamab, we are seeing responses with elranatamab as well. And then, if we look at the cohort of patients who did not have prior BCMA exposure, we are seeing the over 60% response, even in this patient population, at the recommended monotherapy dose. Looking at the various, adverse events within hematologic and non-hematologic categories, again the most common issue, similar to what has been described for teclistamab, is cytokine release syndrome.

Looking at the combination of subcutaneous elranatamab with subcutaneous daratumumab, what has been reported so far, in the Magnificent 5 safety lead-in is that it's fairly safe to proceed with this combination. All grade 3 or 4 neutropenia, seen in about 29% of the

patients grade 3 or 4 TEAEs were observed in 46% of the patients, and CRS was seen in about 50% of this patient population, and it was all grade 1 and 2. So the bottom line is that there are several bispecific antibody platforms in clinical trials. We have one that already FDA-approved, others that are making their way. I think compared to CAR T-cell therapies, the potential advantages with bispecifics are the off-the-shelf, better safety profile and subcutaneous administration. But the potential disadvantage is the continuous therapy as the infection risk for these patients does go up over time; as you can see, well over half of the patients do have an infection during the course of these treatments.

Now we are seeing BCMA-directed bispecifics having shown impressive you know, efficacy and safety. They are being examined in early lines of treatment, in combination with monoclonal antibodies and immunomodulatory drugs. And there are even frontline studies being planned, with high-risk myeloma patients in mind. So it's quite possible that we can have bispecific antibody combinations as frontline treatment for many of our patients, and I'd love to have more discussions around that with my colleagues, and I would welcome you all to actually submit questions to us during the live Q&A portion of this program. Thank you so much.

Dr. Ailawadhi:
Hello, everyone. I'm Sikander Ailawadhi from Mayo Clinic in Jacksonville, Florida, and in this section, we'll be talking about addressing access to care in multiple myeloma.

Over the years, outcomes have been improving in multiple myeloma, but as this study from one of my colleagues in Mayo-Arizona, Dr. Fonseca, shows myeloma patients still do significantly worse than the general population, so the thought being that we still have ways to go before we can make it into, hopefully, a curable disease. But, we know that the outcomes are improving. Still, we know that there are disparities that exist. So this was a study that we did about, now, 10 or so years ago looking at the national CR database, showing how outcomes are different for patients according to their race and ethnicity. What we found was that Asians have the best survival, then African Americans, then whites, and Hispanics had the worst survival. And these differences became much more pronounced when the patients became older in our elderly patients, above the age of 75.

When we talk about healthcare access, utilization, impact, there are several factors that come into play. These can be social, cultural, economic, etc. Some are related to disease biology, which may not be modifiable, but there are other that are socioeconomic, sociocultural – some of which may actually be modifiable, but it's important first, to figure out where those disparities and differences exist, and how we can hopefully overcome those barriers. So I'll talk about some of these factors, which are quite interrelated and very complex, but hopefully we can tease something out of them.

When we look at disease biology, there have been many studies showing that the African Americans, for example, have a lower incidence of high-risk disease. So for example, TP-53 mutations, 17P deletion – those are seen much less frequently in African Americans, so the playing field is okay. Is it the same? African Americans should actually have the better survival, which is something I showed you in the previous slide.

We also looked at differences in clinical presentation, and while we talk about African Americans having a younger age at onset, we know that Hispanics have an even younger age as compared to whites – even younger than African Americans, at a median age of onset for myeloma. We also found out in this study that we did 4 or 5 years ago now, that African Americans, at the time of presenting for myeloma or during treatment, are much more likely to present with myeloma-related complications, like hypercalcemia, kidney dysfunction, anemia, need for dialysis. But it's important to know that fractures are seen less frequently in African Americans, at presentation or during treatment because they tend to have a higher bone density as compared to whites.

We also looked at the access to care, and specifically treatment using novel agents. And although utilization over time has been increasing, we noted in this analysis, which was about 4 or 5 years ago that African Americans have the lowest utilization of any race ethnicity type for lenalidomide. Similarly, the median time to the first dose of bortezomib – a cornerstone drug in myeloma – is about 102 days in Hispanics, significantly longer as compared to other race ethnicity subgroups.

We then redid the analysis with a larger data from the CR Medicare, utilizing also other newer agents like carfilzomib and pomalidomide, and this data was a couple of years ago. And we found that still, African Americans and Hispanics had a lower utilization of novel agents, and over time, the increase in utilization was the least in our analysis in Hispanics.

There have been many, many studies looking at stem cell transplant utilization, and the healthcare disparities by race ethnicity. Now it's important to note that according to certain analyses, only about 20-25% of transplant-eligible patients in the U.S. get a transplant. So, we have a huge gap there, but even there, although over time the utilization has been increasing for everybody, Hispanics, for example, have the lowest utilization of all race ethnicity for myeloma. Similarly, African Americans get referred to transplant centers significantly later, as compared to whites. And we know deferred transplant, or delayed transplant, can have an effect on patient outcomes. So, many data showed that disparity.

But an important disparity is with clinical trial enrollment, where the study from a couple of years ago showed that while African Americans make up 20% or so of the myeloma population in the U.S., only about 5% African American representation in clinical trials that lead to FDA drug approval. We did this analysis a little bit later – just last year – out of the same FDA data looking at it a little bit differently, and what we noticed – that although in the most recent past, the number of race reporting in trials has been increasing, it still has a long way to go. We also looked at age – so demographics – and race reporting, and we noted that where race was not reported, the patient population in the clinical trials was much farther and less representative of the true U.S. population of that cancer. We looked at all different cancers, but I have highlighted multiple myeloma on the left for you of this slide.

We also looked at financial toxicity a couple of years ago, and patients who are race and ethnic minorities – so African Americans and Hispanics – they tend to have a higher out-of-pocket cost and financial impact of treatments, as compared to whites. In this particular analysis, that finding was most stark for Hispanics.

Now, I would like to point out – just take a case example of CAR T-cell treatment, which is important. Newly available, very effective and desirable for myeloma, but we used to talk about the T's of disparity – trials, triplets and transplant – but now I think we can add a fourth T as per my colleague, Dr. Joe Mikhael, who shared this language with me, and I took it to heart – the four T's of disparity now including CAR T. So I'll just point out that as this is just data I quickly put together myself looking at online information, and there are about 116 CAR T centers in the U.S. That means about 2.3 per state. But if you take out some of the larger states, like California, Florida, Illinois, New York, Pennsylvania, Texas – there are only about 73 CAR T centers in the country – about 1.6 per state. And there are 12 states in the U.S. that have only one CAR T center in the whole of that state. Now you can imagine insurances are a lot of times state-limited, so hence, disparities issues, workflow logistic problems. Also, only one to two CAR T slots per month per site or product – there are two products available. In the best-case scenario, that means we would be able to do about 5.5 thousand CAR T's a year. We have about 35,000 new myeloma patients in the U.S. diagnosed every year, so in the best case scenario, utilization for myeloma will be less than 15% of the patients getting to CAR T in a given year. Access is very limited. Cost and reimbursement models are still being looked at. Sometimes patients need to travel long distances. There are huge wait lists, and when we talk about racial ethnic disparities there are already studies showing that only about 6% of real-world African American patients are getting CAR T. I mentioned previously, African Americans make up about 20% of myeloma patients in the country. So, logistic and disparate challenges that need to be overcome, but at least we are trying to figure out what the challenges are so we can come up with strategies.

It's important to note – I'm a huge proponent of clinical trials – it's important to note that in clinical trials – we did this analysis a few years ago, pooling all the cooperative group clinical trial data – that when you look at clinical trial data – this is specifically for myeloma – no overall survival or progression-free survival benefit based on race ethnicity. So it seems clinical trials are a great equalizer in some way.

And similarly, this data from the VA a couple of years ago, showing that, again, a level playing field like – right? The VA system. African Americans tend to do better when given the equal access opportunity.

Going back to this slide I had started from, that we found racial ethnic disparities in survival, and African Americans tend to do slightly better. But, access needs to be addressed. So, there are quite a few things we can do about access. For example, the social determinants of health need to be addressed in patient care. There could be strategies to engage community healthcare providers, certain centers that may be in underrepresented areas that could get more resources to come to clinical trials and get access to newer treatments.

But I'll use a quick case study from a forthcoming clinical trial we have – S2209. This will be an intergroup NCS-supported clinical trial for newly diagnosed myeloma, for frail patients comparing VRd light and DRdS induction, and then Rev single-agent with Dararev as the maintenance. But importantly, we have changed the inclusion criteria so that patients with even lower counts can go in, even with growth factors. Any amount of kidney dysfunction is allowed. High-risk patients are allowed, and the study will be opening at the VA also along with cooperative groups across the country, to try and get a real-world population.

So making the plan is good, but do we really want– to wait for the end of the study to find out if we did okay? Well, for this particular clinical trial, we've actually come up with an active monitoring plan also. So, centers – wherever the study's opened – will be divided into different categories, depending upon a projected minority accrual. And we will do an interim analysis, not just for safety and efficacy, but more importantly, also for minority accrual, so that if centers are meeting their target, or are not meeting their target, we'll ask them – why or why not? And hopefully, with all of these learnings, we'll be able to come up with a strategic plan of how we can improve minority accrual into clinical trials, and again, go back to getting the right treatment to the right patient at the right time. Thanks a lot for this and I look forward to the Q&A session.

Dr. Usmani:
Alright. Welcome to our live panel discussion. You know, you've heard all three of us discuss several topics that are relevant to the BCMA-directed strategies, and I wanted to get my colleagues to give their takes on some specific questions that each of us have raised

in our respective talks. So the first one is kind of an elephant in the room. You know, when we started this year, we had a BCMA-directed ADC that we were utilizing in our clinics, and we were hoping that we'll get the second BCMA CAR approved, and maybe, if we get lucky, we might get a BCMA bispecific approved.

But, we were talking about, okay, how do we take ADC versus CAR versus bispecifics. And now, we're at the end of the year, and the discussion has totally changed, so ADC is out of the picture, and now we are trying to figure out the logistics of bispecifics versus CAR. So, Amrita, what do you think? How are you picking one strategy versus the other, because there are logistic challenges to both?

Dr. Krishnan:
I think – thank you, sir – I think, some of it's not dictated by me, it's dictated by the pace of the disease, to your point about logistic challenges. Someone who's relapsing pretty aggressively, I mean, I am going to use the BCMA-directed bispecific. Someone where I can still kind of control the disease – I think many of us are, in fact, sort of looking at CAR, while the person's on their – starting the fourth line of therapy, thinking, okay, let me put you on the wait list, and then the minute it stops working, you know, you may have a spot. So, I think it tends to be – the CAR T people tend to be somewhat slower progressors, who can wait for a slot, and then the manufacturing time, which is also, unfortunately, still a bit of a challenge for us.

Dr. Usmani:
What about you, Sikander? Have you guys started to treat commercial bispecifics yet, or…?

Dr. Ailawadhi:
So no, actually, not yet. But in fact, Saad, it is so timely, because earlier today my colleagues in Rochester and Arizona and myself in Florida – we were all exchanging emails about logistics, and we were still trying to figure out inpatient, outpatient, how many days inpatient outpatient, short-stay unit, how do we monitor, etc. But I think too, at this point, sometimes the disease just presents itself, but I'll take it one step forward and say, if we are in that perfect state – that we have CAR T availability, manufacturing, logistics sorted out, bispecific, everything sorted out – I have thought to myself, how will I talk to a patient and present this? And I guess the way I think about it is, we have data with both teclistamab and elranatamab, post-CAR T. We don't have post-elranatamab or teclistamab or bispecific treatment with CAR T. So, the disease – how it progresses out of each one of these would be different, I would think. So, at this point, if all else similar – if I can consider, if I can try to, if I can get the patient to CAR T, I will try to get them to CAR T, just because evidence is, I can come to a bispecific later. But again, with time, I think we'll have more data.

Dr. Usmani:
No, I agree with both of you. I think, you know, that the other caveat to that BCMA exposed experience with bispecifics is we don't know what those of the CAR patients received, and how long ago they received before progressing, so again, if they're progressing a year later, then I think they got the most from the BCMA CAR strategy and they're probably going to be still responsive to a BCMA-directed therapy, whereas if someone who's progressing within 2 or 3 months of receiving a BCMA CAR, that's where I think we're going to be a little bit wary about changing up the mechanism of action that they're going to give to the patients.

Dr. Krishnan:
But, I mean, to Sikander's point, there was an abstract presented from MD Anderson retrospectively looking at ide-cel outcomes, after prior T-cell directed strategies. I grant you, I think there was only about 6 patients that had a prior BCMA-bi – or, even – they didn't say BCMA, but it just said bispecific. And, it seems like in 6 months, if you waited, the patients got a CAR T less than 6 months, they really had a very low response, and short PFS on the matter of 3 or 4 months. So, suggesting also T-cell health probably with T-cell exhaustion after just bispecific exposure may be important.

Dr. Usmani:
Yeah, and that may impact the quality of leukapheresis for the products, too, I think. Alright, so I have a question for you, Amrita. It's in context of Sikander's presentation, and the fact that you have this new wonderful role, and you're probably thinking about strategies to address the diversity and inclusion in clinical trials. So, what are your thoughts around some of those strategies in your part of the country? How are you thinking about increasing the inclusion of diverse populations?

Dr. Krishnan:
Yeah, that's a great and tough question, Saad, right? I think, and if Sikander can speak to just the diversity of population in L.A., but also just geographically how far apart we all are in L.A. I think to those with challenges in regards to access of care. I think one of the things is having a different model that we have. You know, we have a lot of satellite clinics, and changing this idea of clinical trials being centralized, and trying to decentralize them is a key part of this in terms of opening up access to care, because it's unrealistic to expect every patient to have the resources to be able to drive 60 miles, you know, once a week – twice a week – for treatment. So I think that's a major part.

Obviously, patient education – we have a big commitment to that in regards to awareness of patients and awareness in the community of physicians to refer patients. So I think those are some of the steps that we're certainly taking. You know, we've amended some of the trials, like the SWOG SAT node 3 trial, to be a little bit more inclusive as well. So hopefully all those steps will again make inroads into some of the challenges we face.

Dr. Usmani:
Yeah, I think, absolutely. I think this decentralization, and then site selection, those are going to be very important, and then again, I think with nod to Ed Kim at City of Hope – he's actually overseeing a very similar model being developed in North Carolina – so I think, I really look forward to how you guys really expand that model in your nook of the woods. So, I'm going to go to Dr. Ailawadhi for the next question. You kind of highlighted bela-maf in your presentation. So where do we go from here? You know, because the drug is active. We know it's safety profile, and we were just learning how to use it in the clinics in an effective manner. In someone who's benefiting from it, you don't necessarily need to give it, you know, every 3 weeks. You can delay it to every 8 weeks, or even every 12 weeks, you know, and kind of manage that safety bit of it. So where do we go from here?

Dr. Ailawadhi:
Sure. I think, Saad, that's an extremely important question, and in fact I would bring our listeners and all of us back to the point that the DREAMM-3 trial, which did not pan out and led to the voluntary withdrawal of this drug as a single agent from the market by the company – that did not pan out because of an efficacy as compared to the comparator arm. There was not a new safety signal or a concern that came up. Now why is this important? Because those patients who are deriving benefit are still continuing. Yeah, it's a little bit cumbersome for us to keep them on – more paperwork, and all that – but we're continuing them on that. And in a way, I also appreciate that all the clinical trials with this drug, the clinical trial drug platform, is continuing to be supported by the pharma company, because that ways, I think we'll understand a little bit better how to use this, what to use it with, how to bring it back, and maybe it'll – I pointed out in my presentation that maybe the drug will come back as a combination. But, even if it comes back as in combination, there are currently clinical trials ongoing where we are trying to see how to most effectively and safely give this drug. So maybe there will be a future for this drug in some way, shape or form, and this is kind of a new problem that we have. There are so many drugs coming up, and there is a want, there is a need, to get the drug to market and to patients as fast as possible, to hopefully get the patients benefit from that, and sometimes some trials will pan out, others will not. In fact, in the past year or so, we've seen more drugs in myeloma that have either decided not to move forward, or have been pulled back, and that is because there are so many drugs. So in a way, maybe this is a good problem to have that we are trying to come up with the right and the best, most appropriate drugs for our patients.

Dr. Usmani:
No, very well said, and again, and I share your view that we are probably going to see this drug come through in combinations, and perhaps DREAMM-3, if it had been designed as a non-inferiority study, we wouldn't be in this situation, because we are using this drug after patients have been treated with palmolidomide. Alright, so one question I have for Dr. Krishnan, and it's going to be probably a long-winded answer because we saw a lot of teclistamab data at ASH. We saw a lot of BCMA-bispecific data at ASH, and we saw combination therapy data, in early alliance. Can you just share a little bit of what excited you about some of those combinations Amrita?

Dr. Krishnan:
So, I mean, we saw some of the early phase run-in of MajesTEC-7, right? Which is tec-dara-len. And we've already seen data, not at this ASH, but prior meetings, of tec-dara combinations, and those are including patients who have been dara-refractory, suggesting you can still get response rates about 70%. So the combination does seem to have some degree of synergy. So, I think those are the good things. The challenges remain this infection issue, and the question of when you add more agents, specifically dara, in fact, because we know that patients become fairly hypogamma, it's fairly, of the agents, particularly immunosuppressive, so I think infection risks still remain to be – how to best mitigate that, especially viral infections, right? I think we are better about bacterial infections. We can use antibiotic prophylaxis, we can give IV IG, but we're pretty helpless in terms of viral infections.

Dr. Usmani:
Yeah, and this is where we've had a lot of conversation around response-driven, fixed duration treatment with some of these bispecifics. So, I guess our audience will be hearing more about it in the coming years. Thank you so much, Dr. Krishnan and Dr. Ailawadhi, for your wonderful insights as well as your respective talks. And thank you, our audience, for joining us today. We hope you found the information informative and beneficial to your practice. Just as a reminder, you will receive an email later today with a link to the post-test. Once you complete the post-test, you'll be able to claim your credit and download your certificate.

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