FAQs on Bispecific Antibodies in Multiple Myeloma

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Transcript

Mary DeRome (MMRF): Welcome everybody and thank you for joining us for today's session on frequently asked questions about bispecific antibodies therapy in multiple myeloma. I'm Mary DeRome, Senior Director of Medical Communications and Education at the Multiple Myeloma Research Foundation (MMRF). Today, I am joined by Dr. Jesus Berdeja, MD from Tennessee Oncology in Nashville, Tennessee and Dr. Melissa Alsina, MD from Moffitt Cancer Center in Tampa, Florida. Patients and caregivers have a lot of questions about bispecific antibody therapies and their expanding role in the various stages of multiple myeloma. So, let's take a stab at answering some of the questions we received in our recent webinar on bispecific antibodies. Let's begin our discussion by first reviewing what bispecific antibody therapy is. Dr. Berdeja, can you broadly explain how bispecific antibody therapy works—and what treatments have been approved for multiple myeloma and the stage of treatment that they are used for?

Jesus Berdeja, MD: This is obviously a very good question. So, bispecific antibodies are monoclonal antibodies that have 2 targets, unlike the antibodies daratumumab (Darzalex) or isatuximab (Sarclisa), which are monoclonal antibodies that have just 1 target. Usually the target is a myeloma cell, then the antibody flags the immune system to come and kill the myeloma cell. The bispecifics on the other hand have 2 targets. One target binds the myeloma cell and the other target binds the T cells. By doing so, it activates the T cells, and it's almost like lassoing the T cells to come and kill the myeloma cell. You're basically kind of forcing or redirecting the T cells to the myeloma cells. These therapies are actually quite good and 3 are currently FDA-approved in the United States—2 against BCMA and 1 against GPRC5D. The bispecific antibodies targeted against BCMA all have the same indication, which is 4 prior lines of therapy and have had a prior proteasome inhibitor, like a bortezomib (Velcade)-type drug; a prior immunomodulatory drug (IMiD); a lenalidomide (Revlimid)-type drug; and a prior anti-CD38 antibody like Darzalex. Teclistamab (Tecvayli) and elranatamab (Elrexfio) are the BCMA-targeted bispecific antibodies and talquetamab (Talvey) is the GPRC5D-targeted bispecific.

Mary DeRome (MMRF): So, these are the "big" bispecific antibodies right now. And, I think we're probably on the verge of having a couple more approved in the near future. We'll talk a little bit more about that later. Dr. Alsina, can you give an overview about how bispecific antibody therapies are administered and what a patient can expect when they're starting on this type of therapy? How often are they administered, and how long should they expect to be on this therapy?

Melissa Alsina, MD: Sure. The 3 bispecific antibodies that have been approved are given as a subcutaneous injection, which is an injection under the skin. The frequency of administration varies depending on which therapy it is. What is common to all 3 of them is that when patients are first exposed they are at a higher risk of having a reaction. We call that cytokine release syndrome, which is caused when your immune system is very active, similar to when you have an infection. So, patients can get a fever. Because of that, it's recommended that the initial doses of bispecific antibodies are given inpatient, starting with a low dose and then waiting 48 hours between each of the first, second, and third doses. For teclistamab, we administer the first 4 doses while inpatient. After that the patient is treated in the clinic, where the BCMA-targeting antibodies Elrexfio and Tecvayli are given weekly and Talvey can be given weekly or every other week.

The risks with the initial doses are very, very common, but they're not severe, so they're very manageable. In many centers we are moving to giving the initial doses outpatient. I think in the future bispecific antibodies will be administered to outpatients through the whole course of therapy, particularly if they’re not having toxicity. Usually, patients stay on this treatment until disease progression; however, we can change the dosing frequency in those patients who are responding well, and that helps actually the toxicity.

Mary DeRome (MMRF): Great. Dr. Berdeja, regarding the BCMA-targeted bispecific antibody therapies, does every patient express BCMA on their myeloma cells? Or, are there ways to enhance its expression that might enhance the activity of these bispecific antibodies?

Jesus Berdeja, MD: The short answer is yes. BCMA is a very important pathway for the survival and development of plasma cells. Technically, all plasma cells should express it. There are variances, so some patients may express it less than others. But, luckily, the immune system is so potent that what we think is low expression of BCMA is usually sufficient expression. So, we don't usually test for BCMA expression.

We can augment BCMA expression. There are these products called gamma secretase inhibitors, which can lead to an increased expression of BCMA in service of the cells. But, it's unclear if we need them and early studies done with them showed that these drugs have toxicities of their own. So, it's unclear how well of a partner they might be. The only other time that BCMA expression might become a problem is when the patient has had a prior BCMA therapy, there is a very small risk that they might lose expression of BCMA.

Mary DeRome (MMRF): That makes sense. Dr. Alsina, are there patient populations for whom bispecific antibody therapies work better or worse? For example, are bispecific antibodies appropriate for older patients? How well do they work in patients who have high-risk multiple myeloma?

Melissa Alsina, MD: These bispecific antibodies do not work as well in high-risk myeloma or patients who have disease outside of the bone marrow, which we call extramedullary disease. They also don't work as well in patients who are over 75, have a very high tumor burden, or rapidly progressing myeloma. We see lower response rates in these patients. However, if the patient does respond, the ratio of response is about the same as in other patients. So, I would say that while these types of myeloma are challenging to treat with any treatment, I would suggest that we should still try bispecific antibody treatment in these patient populations. The median time to response is about a month, so we would know fairly quickly if the treatment is working or not. Then we can switch gears if it's not.

The other thing that I've found is in patients who have rapidly progressing myeloma where the myeloma is moving faster than the antibody can work, it's helpful to try to give a different treatment. For example, chemotherapy to control the disease before you can actually start the bispecific antibody. But, these are not published data; it's just what I've seen, in my experience.

Mary DeRome (MMRF): More like real world.

Jesus Berdeja, MD: Which is better than published data.

Melissa Alsina, MD: Right. Dr. Berdeja, do you have that experience?

Jesus Berdeja, MD: I agree. I think the patients who are rapidly progressing should be treated with all types of treatment modalities. I would argue that because of the intricacies of CAR-T therapy sometimes the bispecifics are easier. But, you are right that those patients who are progressing quickly, sometimes they don't get that initial response and then we have to move on, and maybe we didn't really give them a fair chance. I think that's why it's nice now that these bispecific antibodies are approved. We don't have to be as strict as the clinical trials. In general, patients who have controlled disease tend to do better. So, if we had some kind of a bridging therapy for bispecifics—even though we talk about bridging therapy for CAR Ts more so—it is not necessarily an unreasonable thing to do because of what you just mentioned.

Mary DeRome (MMRF): Right. It's interesting that we've seen a lot of real-world data presented recently at some of the meetings. What they're really looking for is whether or not the real-world use of the drug mirrors what happens in the clinical trials where the patient population that is given the drug in the trial is much more prescribed. It's a very small percentage of patients actually who can enroll in trials based on the inclusion and exclusion criteria. From what I've seen recently, it looks like real-world data are actually mirroring pretty well what happens in the clinical trials, which is a good thing.

Melissa Alsina, MD: One could argue that it's a little bit better because the condition of the population that we treat in the real world is much worse than the population we treat in the trials. So, it's reassuring to see that even in this real-world patient population that we see, that these treatments still work in a very similar way.

Mary DeRome (MMRF): In our previous bispecific antibody webinar that we had a few weeks ago, several patients had questions regarding sequencing of bispecific antibodies. I know this is a very important question. Sequencing is very important when you start thinking about all of these anti-BCMA therapies especially. Dr. Berdeja, can you speak to some of the data regarding when it's best to use bispecifics, particularly the timing, relative to other novel treatments like CAR T-cell therapy that may target the same antigen on the cell surface, like BCMA?

Jesus Berdeja, MD: This is a very hot button topic. This question is asked at every conference we go to now and the truth is we have very little data to help us. Basically, the majority of the BCMA trials with bispecifics and CAR Ts excluded patients who had prior BCMA therapy, although some allowed a small group in a separate cohort. When you're switching the target, though, then that's a little bit different. We do have good data with talquetamab, which targets GPRC5D and that allows inclusion of patients with prior BCMA therapy. Actually, half the patients on that initial trial that got the drug approved had prior BCMA treatment and it seems to work quite well.

A lot of the data that we have are from small cohorts and from real-world data that was brought up earlier. Obviously, in the real-world we go with what we have, so we can't be as specific and say, "Oh, you've had this before; you can't have this. In my opinion, if you're sticking to the same target—let's say BCMA because that's where we have different classes of drugs towards it—there definitely is a drop-off of the effectiveness of a second BCMA-directed therapy. I would argue that this happens more so if you've had a bispecific antibody and then you move on to something else like a CAR T versus the opposite. So, when in doubt, I'd say give your CAR T first and then your bispecific.

What it boils down to is the mechanism of resistance. We are finding the question becomes if you're getting the bispecific and it stops working, is it because the T cells are so exhausted they don't work anymore? You go and collect those T cells for CAR-T therapy and now that won't work because the T cells are exhausted. The bispecifics, as we're finding out, can induce these mutations on the binding site at least.

Mary DeRome (MMRF): That was interesting data they were shown recently.

Jesus Berdeja, MD: So, if that's the case, technically going with another BCMA may not work, but there's no reason why you couldn't go with a different target

like GPRC5D. As we're learning more, I think it will help us. But right now, we all just kind of work with what we have. There definitely are good data, especially with the bispecifics, that after a CAR T against BCMA, for example, you still have very good responses.

Mary DeRome (MMRF): Okay. I have seen some interesting work where patients are given both the GPRC5D-targeted bispecific and the BCMA-targeted specific at the same time and those are also really interesting data. Dr. Alsina, can you address those data?

Melissa Alsina, MD: That's in clinical trials, early on in the course of the disease. You're trying to target 2 different pathways to different cell surface proteins, so it's a very interesting approach. We're not there yet but I think that would be in the future. The other interesting thing would be not only administering these treatments at the same time, but sequencing them—giving a few months of 1 and then a few months of the other. We're definitely looking forward to seeing those results.

I agree with Dr. Berdeja that even though we need more data, if you have the option of giving a bispecific versus a CAR T, I would definitely do the CAR T first because there are data in the real world and also in clinical trials where CAR T was specifically started after BCMA-targeted therapy and doing this definitely decreases how long the CAR-T response lasts. Until we get more information that's the way we should go. The timing is also important—how long ago you received the BCMA-targeted therapy. There were some real-world data presented at the hematology meeting in December that showed if you had received BCMA-targeted therapy more than 6 months prior to receiving another BCMA-targeted bispecific (which in this case was teclistamab), that the response rate was sustained. I would say these data show that it’s not that you cannot receive drugs like elranatamab and teclistamab sequentially, but the time that you wait between 1 drug and the other is an important factor. We need to learn a little bit more about that.

Mary DeRome (MMRF): That makes sense. Let's talk a little bit now about the toxicity and side effects of bispecific antibodies. We have seen some reports of unique toxicities with bispecific antibodies. Dr. Alsina, how have these treatment toxicities seen with the bispecifics compare with those seen with CAR T-cell therapy?

Melissa Alsina, MD: Both CAR T and bispecifics are immunotherapy—drugs that will use your immune system to kill the myeloma cells. The typical side effects that we get with immunotherapies is that your immune system becomes super-active—killing the myeloma and of course this releases a lot of proteins. We call that cytokine release syndrome. Most commonly, the patients have fever but it could also be more than that, like hypotension, low oxygen, shortness of breath. It can be quite severe. We learned a lot about this with CAR-T

treatments over the past, I don't know, how many years now?

Jesus Berdeja, MD: Seven years or so.

Melissa Alsina, MD: Seven, right? With the CAR-T treatments, these effects seem to be more significant even though they're very manageable. But yeah, it requires more aggressive therapy in many patients. The other thing is neurotoxicity, which means it affects your central nervous system, causing patients to get anything from headaches to mental status changes. These effects can be seen with CAR T and bispecifics, but in CAR T it's more significant. With bispecifics, it usually tends to occur only during those initial doses, like in the first month of therapy. Even though it's common, we can see that in around 70% of the patients the cytokine release syndrome is mild, so it's very manageable. Rarely, we will see a patient with a severe reaction. The same is true with the neurotoxicity. We see very little neurotoxicity with the bispecifics. With the bispecifics, the more concerning thing is infections. These drugs are suppressing your immune system. With CAR T the same thing happens, but you do it once and then you recover, especially in patients who achieve complete remission. But, with the bispecifics, the patient is on treatment month after month so this is an issue. The rate of really severe infections, meaning those requiring intervention (eg, going to the hospital to be treated) is over 50%. With the BCMA-targeted bispecifics, elranatamab and teclistamab, and the GPRC5D-targeted bispecific, talquetamab, the side effects are actually different.

Essentially, to me the main thing is infections. We have to be very aggressive trying to prevent these infections in these patients. The other thing that we can do is to back off a little bit when the patient achieves a response. In some cases, we can reduce the dose or we can lengthen the time between doses. For example, instead of administering treatment weekly try every other week in some cases, or even once a month, which will definitely decrease the risk of infection.

There aren’t a lot of data published on managing infections in patients on bispecific antibodies, but each center follows its own protocol. In our center, we administer acyclovir as prophylaxis for herpes zoster to every patient. We check the CD4 count, which are cells in your immune system that are more active in dealing with infections. If that number is low, we give the patients a medication to prevent opportunistic pneumonias. This requires taking an additional drug or sometimes an infusion in the vein. If the patients have low immunoglobulins and are getting frequent infections, we give IVIG to these patients with an infusion of an immune system booster, which the patients have to take once a month. Then, any time the patient develops a fever or any sign of infection, we’re very aggressive with treating this.

Mary DeRome (MMRF): Okay. Great. So, some patients during our webinar also asked about the toxic hematologic effects seen with bispecifics and how those are managed.

Dr. Berdeja, can you address that?

Jesus Berdeja, MD: Sure. I think it's important to note that all of these therapies—both CAR Ts and bispecifics—lead to significant drops in your blood cell counts. I think the idea is that it tends to happen early and it likely has to do with the immune system being activated, going into the bone marrow, killing myeloma cells, causing some stunning of the bone marrow that leads to these very quick drops in the blood counts. But, as we're seeing, even though you continue to give the bispecific, the blood counts usually recover, suggesting that it's not the bispecific antibody—again, it's more this new mediated, initial effect of killing myeloma cells.

This can take a while, so it is very important to make sure that your blood counts are checked very frequently, and some people will need transfusions or growth factors to help them bridge this period of time. If a patient does become neutropenic, meaning they lose neutrophil counts, that adds an extra level of immune deficiency than what Dr. Alsina just mentioned in terms of cellular and humoral immune deficiencies, meaning the antibodies and the T-cells. But when neutrophils are also down that usually means we're going to have to introduce antibiotics and maybe some antifungals during that period of time. So, again, it's all sort of tied together in terms of the toxicities, blood cell counts, as well as the infections.

Mary DeRome (MMRF): Okay. We've talked a little bit about how to prevent infections. Dr. Alsina, several patients asked in our webinar about how important it is to repeat their vaccinations. Can you speak to that?

Melissa Alsina, MD: Yes, definitely. After CAR T, we do start vaccinations all over similar to after you have a transplant. You do all the baby shots. Usually patients are vaccinated for 2 years at different intervals.

After bispecifics we don't necessarily repeat all the baby vaccinations, but we make sure patients are up to date on their vaccines. It’s definitely super important to get the COVID boosters, the pneumonia shots, the flu shot, and now most recently the RSV shot. So, that's even more important in these patients who are getting treatments that are compromising their immune system.

Mary DeRome (MMRF): Yes.

Melissa Alsina, MD: The other important thing is that the infections that we see after bispecifics are different than those we typically see in myeloma. These are more opportunistic infections, viral infections we normally are not used to seeing. It's a different part of your immune system, the one that is more affected by bispecific treatment, so we have to pay more attention to that. For example, cytomegalovirus is a virus that most of us are colonized by, but if your immune system is normal you would not get an infection from this virus. That is something

we have to pay attention to, thinking a little bit out of the box when a patient develops a fever and the clinical picture is suggestive of an infection.

Jesus Berdeja, MD: I completely agree with what Dr. Alsina just said, but the only thing I would also mention is that response to vaccines is not going to be as good for someone who is on these treatments. So, if at all possible, if you haven't had your vaccines recently, you want to get them before you start the treatment.

Mary DeRome (MMRF): Right. Some patients wrote in with some pretty specific questions about issues with some of the infection prophylaxis measures. One patient said they couldn't tolerate the IVIG. Another patient who couldn't tolerate dapsone and is on pentamidine is wondering if they could discontinue that. What are some of the options for patients who have issues on some of these standard prophylactic measures? Is reducing the frequency of administration of the bispecific antibody an option for that, Dr. Berdeja?

Jesus Berdeja, MD: That's obviously a difficult situation. Dr. Alsina mentioned all the reasons why patients on these treatments are so heavily immunocompromised and at risk for infection. Different types, but especially these sort of odd, atypical infections that we used to see in the old AIDS days. We're talking about that level of immunodeficiency. But actually, I would argue even more so because that was all T-cell deficiency, which we have here, but remember, the target is actually your plasma cells, which are the cells that make your antibodies.

You have not only T-cell deficiencies but you also have antibody deficiencies, or what are called humoral deficiencies. Bispecific antibody treatment brings an increased risk of those. I agree that not everybody will be able to tolerate all of the prophylaxis, but the important thing is that we find something that can be tolerated, because the alternative is essentially a life-threatening infection. As Dr. Alsina mentioned, one of these things that we can do is check a CD4 count, which are the cells that are suppressed that increase the risk for pneumocystis jiroveci pneumonia (PJP), which is what the trimethoprim/sulfamethoxazole (Bactrim), the dapsone, and the pentamidine are for. If that patient's CD4 count has recovered, then they could potentially come off the prophylaxis and be monitored. If not, then yes, we need to figure this out. The alternative is that if the patient is in complete remission, then there's a potential to increase the dosing interval or potentially even hold there. That's not the actual indication, but we all have data. There are actually some data with some of the bispecifics where there's a limited duration of therapy and then we stop. We know that responses can be maintained off therapy, so that potentially is another option as well. You have to weigh the pros and cons with your doctor and decide what makes the most sense.

Mary DeRome (MMRF): There was an FDA approval for teclistamab, for increasing the interval between doses to 3 weeks or something like that? Is that right?

Jesus Berdeja, MD: It's actually for patients in complete remission after 6 months of teclistamab therapy. If teclistamab is given weekly, then you can go to every other week, which is interesting because elranatamab actually has it built into their indication already that after a certain amount of therapy you can go from weekly treatment to every other week. This all goes back to how the studies were done. The good news is that we're all finding out that perhaps we don't need to give it as frequently as we've been doing. There's one particular antibody that is only administered for a year and then it’s stopped.

Mary DeRome (MMRF): That was the cevostamab data that was really, really interesting. We had Dr. Trudell on a webinar not too long ago who was talking about that. It was fascinating data. A year of treatment and then patients have gone off, and everybody who was in a complete remission at the time that they discontinued the therapy is still doing well. So, that bodes well for this class of drugs.

Dr. Alsina, patients were wondering about changes to their sense of taste after being on a bispecific and whether or not that will ever resolve itself. Can you speak to that? I'm assuming these are probably patients who have been on Talvey, or talquetamab, because that's really where that effect comes from.

Melissa Alsina, MD: Right. That is a very common and difficult question that we are getting recently, but unfortunately we don’t have a really good answer or solution for that. Yes, that is from talquetamab, which is a bispecific antibody that targets the GPRC5D protein. This protein is expressed in the skin, in follicles and the mucous membranes, so patients get side effects associated with that. The nails and skin get really bad and patients frequently can get a rash that could be very bothersome. Then, they get this loss of taste and weight loss as a result of that.

These are a different set of side effects and unfortunately we don't have any good way of managing them. What I do in my practice, is have all the patients take biotin and do biotin washes. Then, I have them use a lotion to try to keep the skin super hydrated when they start therapy. It's interesting, though, that even though these side effects are difficult to manage in the studies, and in my experience also, we rarely adjust treatment based on them. If the treatment is working, the patients manage and put up with it. I wish we had a better solution, but in the study with talquetamab they also looked at changing the frequency or decreasing the dose from 0.8 mg/kg to 0.4 mg/kg and then seeing what happens with these side effects. That intervention helped with the skin. The skin didn't continue to get worse when you did that. It really did not cause a huge difference in terms of the weight loss or loss of taste. I guess those are things that we could

try and the physical measures. It's a very challenging side effect to manage. What is your experience, Dr. Berdeja?

Jesus Berdeja, MD: I completely agree with that. I guess the short answer to that patient's question is “it will go away when you're off the drug.” So, that's the good news, that it actually is because of the drug and it will go away. I think just talking to patients and saying, "The fact that you're getting these side effects actually shows us that this drug is working" often really helps them psychologically in terms of "Okay, well, this is sort of part of it."

I agree with Melissa that at least in my experience, very similar to low blood counts, the flares are worse at the beginning. Whether it's because the patient starts trying different measures or the toxicity is diminishing some, it doesn't seem as severe as you go along. The only other thing I would add is that patients can get very dry mouths. Taking lots of liquids with their foods and avoiding dry bread by itself, I think those modifications really help with the nutrition. But yeah, ultimately, the way to stop the toxicities is stopping the drug unfortunately.

Mary DeRome (MMRF): Well, okay. So, let's talk a little bit about what's next for bispecifics. We currently have 3 approved bispecific antibodies and there are probably at least 3 additional ones in the pipeline edging toward approval. Several patients asked about the use of bispecifics in earlier lines of therapy. So, Dr. Berdeja, how close are we to that being an option? I know that we're thinking about that with CAR-T therapy as well and the FDA is addressing that next month in their public hearings. So, that'll be an interesting day on March 15th when the FDA talks both about Carvykti (ciltacabtagene autoleucel) and Abecma (idecabtagene vicleucel) in earlier lines of therapy on the same day.

Jesus Berdeja, MD: Yes. The short answer is we're not as close with the bispecifics as with CAR T. But, there are ongoing trials currently looking at CAR T, bispecific antibodies, and earlier lines of therapy by themselves or in combination with some of the other drugs that people are used to, like bortezomib, carfilzomib, and pomalidomide. Those trials are ongoing and we actually have some pretty interesting data for the early patients that are enrolling that's starting to come to and be presented, which actually look quite good. The response rates that we're seeing are actually much higher than what we’ve seen in the relapsed refractory population that got these drugs approved to begin with—often in populations where the companion drug had already been given and the patient was already refractory. For example, patients who were refractory to Darzalex, and then got Darzalex with talquetamab actually had very high response rates, more than we would expect with either drug alone. That's actually encouraging from that standpoint.

Even now there are some protocols potentially looking at frontline therapy. When we diagnose patients, in combination, and even some by themselves, because we're seeing these profound responses, I think you can sort of entertain the

possibility of do we even need to combine? The caveat here is that any time you start to move to a different indication, you want to make sure that the treatment is safe. We've been talking about these infections. If we get a little bit too careless and we give bispecifics to a newly diagnosed patient and they have a bad infection and don't survive, that's not a good outcome. So, we need to be very careful with these drugs and really learn how to use them.

The other thing is that these treatments are so powerful, I'm still unclear as to the actual benefit of combination and whether that's just adding toxicity compared to giving them separately. Lots to learn still. So, I don't think we're ready for prime time yet for moving bispecific antibodies into earlier lines of therapy. What I'm hoping will happen, is that we move away from this line of therapy. It's very clear that patients who have had prior treatment with the 3 big classes of drugs—the proteasome inhibitors, the immunomodulating therapies, and the anti-CD38 antibodies—do very poorly with standard of care therapies, and these bispecifics and CAR Ts work so much better. We're really hoping that as these early data start coming in that maybe we'll move away from the requirement that you have so many lines as opposed to just having been exposed to the classes of drugs. I think that's where we're headed. So, hopefully, more to come.

Mary DeRome (MMRF): That was a really interesting outcome from that conference. Moving away from lines of therapy, and just looking at what the patient has been exposed to and what they're potentially refractory to, instead of how many lines of therapy they've had makes good sense.

Dr. Alsina, in this webinar that we had a few weeks ago there were a couple of patients who were scheduled for autologous stem cell transplant and they were wondering if they should have bispecific antibody therapy instead. Are there any trials that are addressing that? I know there are trials that are addressing patients having a CAR T instead of a transplant, but I have not heard anything about patients having a bispecific instead of a transplant. That seems to be a little advanced at this point.

Melissa Alsina, MD: The short answer is no. Induction therapy nowadays includes treating myeloma with 4 drugs, so including a CD38 antibody, followed by transplant followed by maintenance therapy, is what we call the minimum residual disease (MRD) adaptive approach. That means I'm going to push until I get to the best possible response, hopefully a deep response, to give the patients a long time without disease.

Until proven otherwise, we should not change that approach because it is a really, really good approach. I'm super impressed by the data presented at ASH and that PERSEUS study that looked at 4-drug combinations followed by transplant followed by maintenance. These studies do not have enough follow-up to tell me, okay, this is going to last 10 years. So, how long? But it looks so good, that even studies that are looking at substituting transplant for CAR T, they're

going to take a long time to show that that is better than transplant because that initial approach is so good. So, I think we still have some treatments that are very effective that are standard of care especially for newly diagnosed patients. We should not move away from that until we get data. But the data, again, are going to take a long, long time because the bar is very high. And it's getting higher as we speak.

In the relapse setting, that's a completely different story. Once you have a patient with relapsed myeloma, it's a completely different challenge. I would agree that we should not wait until a patient has failed everything to introduce these treatment modalities that are so effective. They're going to work better when we use them early. They're also going to work better when we use them as consolidation, meaning after initial therapy, my patient did not get to that deep response that I'm looking for. Being able to do consolidation with those drugs, there are trials right now looking at that. For example, let's say in a patient who is not going to get a transplant, I do my best possible treatment—let's say daratumumab, lenalidomide, and dexamethasone—and I don't get the response I need. Then, a possible option may be sequencing with a bispecific antibody to see if I can get a deep response associated with better survival and so on. I hope that I answered your question.

Mary DeRome (MMRF): Yes, I think so.

Jesus Berdeja, MD: I'll just add that I completely agree. This is not standard of care, so you don't equate them. If you are interested in other approaches to treatment, there are clinical trials looking at that. So, if you find those clinical trials, you may be able to get data for a CAR T or bispecific plus or minus a transplant, but again, it would only be under a clinical trial. This would not be a standard of care. It would not be recommended.

Mary DeRome (MMRF): Absolutely. So, I know we've discussed the 3 big bispecific antibodies so far: teclistamab, elranatamab, and talquetamab. I know that there are newer ones in the pipeline. We've talked a little bit about cevostamab, which seems like it's probably going to be pretty good and it's pretty far along so it probably will be approved fairly soon. There are other ones, too, like alnuctamab and others. Have I missed any?

Jesus Berdeja, MD: Yes. But I'm blanking on the name.

Jesus Berdeja, MD: Yes. So, there's about 6 BCMA-targeted bispecifics, right?

Mary DeRome (MMRF): Right.

Jesus Berdeja, MD: So, we have 2 approved and 4 that have quite good data . They all look quite similar, so it'll be interesting to see what happens—whether

the FDA approves all of them or they have to prove something different. That's the question. But in terms of the efficacy data, it all looks very similar. I think what we're excited about is that cevostamab has a different target.

Mary DeRome (MMRF): Exactly.

Jesus Berdeja, MD: It's like what we were talking about before—having that extra target that we can go after, if and when a patient no longer has a response. So, cevostamab targets FcRH5, so those are the 3 big targets in myeloma right now.

Mary DeRome (MMRF): Right. So, that'll be really interesting. A couple of final thoughts... Dr. Berdeja, how have bispecifics, both the BCMA-targeted and the non-BCMA-targeted, affected the outcomes of patients that you manage? Have you been really impressed with how active they are and how much they've helped the patients so far?

Jesus Berdeja, MD: I am. I was lucky and my patients were lucky enough to be able to participate in and receive these bispecific drugs in clinical trials, so, we've been using them for years now. They're very impressed with them. It's very similar to when CAR Ts came in and made a big splash in terms of the efficacy we're seeing. I think patients really like them. I have to say, it's like we keep talking about which is the best patient for this or that, but ultimately it comes down to patient preference, too. I have patients who are "addicted to" CAR Ts and will not have anything but a CAR T. Luckily, in clinical trials you can't do CAR Ts against different targets, so patients have gone serially with CAR Ts. Then I have patients where we talk about the 2 options and they're petrified of the CAR T and they say "I want to do the bispecific. I don't want to do the CAR T." So, just remember that, again, it's a conversation. Because both options are very good, I think it's hard to be very dogmatic about it. If you want to maximize the available therapies, that's when we start talking about which one do you do first, etc. Especially with the BCMA-targeted bispecific, I think it's very well tolerated. Once you get beyond that initial step-up, most people come in for an injection, leave, and that's it. The infections are the big concern here, but obviously those are not side effects necessarily. Those are just risks that if managed properly, you hopefully stay away from.

I've had patients who have been on talquetamab for 3 years and they will never stop it. I try to stop it and they won't, even though they have some off-tumor, on-target effects—these side effects of the taste, skin, and nails. I've had patients who have never been in a complete response and all of a sudden they're in a complete response and going for years. So, yes, so we do see these dramatic potential responses with these bispecific antibody therapies and it's just a matter of learning how to use them best. Ideally, the plus of CAR Ts versus bispecifics is the idea that with CAR T you get treatment and then you're off therapy, which is

unusual for a patient. Whereas, the bispecifics follow the same modality with all of our therapies in that it is continuous.

Mary DeRome (MMRF): At least for now.

Melissa Alsina, MD: I have a question for Dr. Berdeja. Based on the combination data, like with talquetamab-daratumumab, for example, or from those studies, do you ever have a patient, for example, that is progressing on talquetamab and you add daratumumab or Pomalyst (pomalidomide)? If you've done it, do you see a response?

Jesus Berdeja, MD: Those are not FDA-approved combinations. But having said that, I haven't done that mostly because I think if the bispecific is not working already and you add something like Pomalyst or talquetamab, the likelihood of achieving enough of a new response is pretty low in my mind. But, I think it's different in the beginning when you're trying to get ahold of the disease where I think the combination makes the most sense. Then, you kind of can peel it off and just go to the bispecific. It's different if you have a patient who maybe has a partial response and not a complete response. I think at that point you could argue, "Well, what if we add something? Can we deepen the response?" But once the patient is progressing, I don't think adding just pomalidomide or daratumumab is going to do that, especially if they're already refractory.

Melissa Alsina, MD: Okay. I was just curious.

Mary DeRome (MMRF): I'm glad that we're providing a forum so you can have this professional interaction and discuss your treatment modalities of your patients.

Jesus Berdeja, MD: Your patients should know that this is what we do. This is what's great about the myeloma community. We know each other well. We'll pick up the phone. We'll talk and say, "Hey, I've got a patient. What do you do? Have you ever done this?" It's' important that we have those kind of conversations.

Mary DeRome (MMRF): Totally agree.

Melissa Alsina, MD: In the past, our challenge was "Okay, what do we do when the patients have their first relapse?" Now the challenge is "What do we do when the patients have their whatever, 14th relapse?" That's our new challenge. "What's my next step when my patients progress after that?" Even though of course there a are lot of clinical trials.

Jesus Berdeja, MD: Yeah.

Mary DeRome (MMRF): Okay. So, that's a great segue to my final question. Dr. Alsina, if you had a crystal ball and could see what's going to be happening with

bispecific therapies in the next few years, what do you predict we will see with some of them?

Melissa Alsina, MD: I don't need a crystal ball because it has been our experience for over 30 years now of myeloma therapy, that every treatment that works in the relapse setting, we move up front and do it in earlier lines of therapy. It works better and it deepens our responses and that's the reason we got where we are right now with first-line therapy in myeloma. So, I think that's what's going to happen. It's happening already in clinical trials, moving these drugs to earlier lines of therapy, even in the newly diagnosed They're even doing this in high-risk smoldering myeloma. In that setting, those drugs are going to work better and also in combination with other classes of drugs, and hopefully it will give the patients deeper responses and more time as a result of that. So, these are definitely very exciting times. I think it's incredible how far we've come. I think the hope is that it continues.

Mary DeRome (MMRF): It's kind of amazing. Dr. Berdeja was talking before about this joint FDA/International Myeloma Society (IMS) meeting that took place this past week, and there was a lot of talk about the fact that we've had 19 drug approvals in myeloma in the last 20 years, which is a phenomenal number. When people ask me about that I always say that I think the reason that the progress has been so amazing is that multiple myeloma is such a challenging disease. The best medical minds gravitate to working on myeloma because it's so challenging. Like you were saying, you guys all know and talk to each other. It's a great community. This has really helped move the myeloma community forward because you all work so hard, and you're so smart, and these great drugs come out and all the patients get them. It's just amazing to see how far these things have come in 20 years. Twenty years ago, if you had myeloma you had maybe 3 years to live or so. And, that is no longer the case.

Melissa Alsina, MD: Well, it takes a village. We are a little part of this along with the pharmaceutical companies, the foundations, and more than anything, the patients who decide they're going to participate in these clinical trials.

Mary DeRome (MMRF): Right. The trials, yes.

Melissa Alsina, MD: That's the only way that the field moves forward.

Mary DeRome (MMRF): Yes. Agreed.

Jesus Berdeja, MD: I was just going to say that I really love what Dr. Alsina said about how amazing the data look for newly diagnosed patients, especially for patients on the current regimens and how long it's going to take to prove that something else would be better. It's a double-edged sword. So, just a reminder to our patients that if you're newly diagnosed you have excellent therapies. Don't get discouraged at the fact that you can't get a CAR T or you can't get a

bispecific because those trials are ongoing now and it may be proven 10 years from now that this is what we need to be doing. Again, we're sort of a victim of our own success from that standpoint. That's a good problem to have.

Mary DeRome (MMRF): It is a very good problem to have. Okay. So, on behalf of the MMRF I'd like to thank Dr. Berdeja and Dr. Alsina for joining me today. I'd like to thank everyone for taking the time out of their day to watch our presentation.