Patient Webinar – BCMA-targeted Bispecific Antibodies in Multiple Myeloma

March 21, 2023

Transcript

Mary DeRome (MMRF): Welcome to the Patient Webinar–BCMA-targeted Bispecific Antibodies in Multiple Myeloma brought to you by the Multiple Myeloma Research Foundation (MMRF). I'm Mary DeRome, Senior Director of Medical Communications and Education at the MMRF. Thank you for making the time to participate in today's webinar.

Our faculty today include Dr. Jesus Berdeja of the Sarah Cannon Research Institute at Tennessee Oncology, located in Nashville, Tennessee, and Dr. Amrita Krishnan of the Judy and Bernard Briskin Center for Multiple Myeloma Research at the City of Hope, located in Duarte, California. We will also hear from Tonya, a patient who will share her perspective on receiving bispecific antibody treatment. Let's get started with Dr. Berdeja.

Dr. Jesus Berdeja: Great. Thank you, Mary. Well, it's always a pleasure to talk with the MMRF. I was tasked with giving an introduction about bispecific antibodies. Most of you probably know monoclonal antibodies like Darzalex or Sarclisa, which are antibodies that bind to a protein in the myeloma cell. They then wait for the immune system, in particular T cells, to kill the myeloma cell. This works for a while, but unfortunately, the T cells then become agnostic and don't recognize that antibody anymore. So, the question is, how can we try and convince or force these T cells to go after myeloma? Bispecific antibodies have CD3 and BCMA on the ends, which bind to two different places. One part of the antibody binds to BCMA, a protein on the myeloma cell, and the other binds to CD3, a protein on T cells. So, by binding the T cell, it activates it to see the other part of the antibody bound to the myeloma cell and kills the myeloma cell. So, you're basically forcing that T cell to go and kill the myeloma cell.

There are many proteins on myeloma cells that can be used for treatment. BCMA has become one of the more important targets because it is very specific to plasma cells, which are the cells that become myeloma cells. Also, it has very little or no expression in other tissues in the body so it's very specific to myeloma. So, it's a great target for therapies, which is why we now have several FDA-approved therapies against BCMA. Bispecific antibodies, just like the monoclonal antibodies before it are off-the-shelf and they're ready to go for treatment, which obviously makes them a nice therapy as well. Bispecific antibodies, are probably the most advanced antibodies against BCMA. So, we have Tecvayli, which is now approved by the FDA for use in myeloma patients. On its heels, we have several others, including elranatamab, linvoseltamab, alnuctamab, ABBV-383, and a couple of others as well.

The first to the gate, Tecvayli (teclistamab) was approved based on the MajesTEC-1 study, which enrolled 165 patients. They had to have had a prior proteasome inhibitor

(PI), an IMiD (immunomodulatory drug), and anti-CD38 antibody therapy, so at least three prior lines of therapy. They were relatively advanced patients who had failed most FDA-approved treatments. In this heavily pretreated population, the overall response rate was 63%. Most of those responses were quite deep with 39.4% of the patients achieving complete responses (CR), and 60% of patients, achieving a very good partial response (VGPR) or better, which means at least a 90% decrease in their myeloma.

Now that it's been approved, how do we move it forward? Part of the MajesTEC-1 study had a group of patients who had been treated with prior BCMA therapies. So, that included obviously CAR T-cell therapies which are usually against BCMA, and an antibody drug conjugate (ADC) belantamab mafodotin (Blenrep), which some of you may have heard was actually FDA-approved, but unfortunately now has been removed. But it's still in clinical trials and is still an active drug. Patients who had prior BCMA therapies responded very well to Tecvayli with an overall response rate of 50% to 55%. If you recall, in the group who had not had prior BCMA, the response rate was about 60%. So, a very good response, which tells us that perhaps we can sequence these therapies and give one after the other.

Patients who were getting standard-of-care treatment had much lower response rates than patients on Tecvayli. Now, these are not direct comparisons of a study, so you always take it with a grain of salt, but it just gives us a little bit of a look into how effective this therapy is. So, in myeloma, of course, most patients don't get treated with just one drug, although that has changed a little bit with bispecifics and CAR T-cell therapy. But in general, we tend to do combination therapies, so we are starting to see some data with combinations. Tecvayli was combined with Darzalex, which is the anti-CD38 antibody in the TRIMM-2 study. Several schedules were tried with Tecvayli, and the overall response rates were quite good ranging from 74% to 100% depending on schedule and dose. So, an average response of 75% is what we would expect with the combination. Again, it’s quite impressive. A lot of these patients had prior anti-CD38 antibodies, so theoretically they would not be responsive to that therapy again.

Myeloma is notorious for triplets and quadruplets. Combined Tecvayli, Darzalex, and Revlimid has been used in patients who were a little bit earlier, so they had only one to three prior lines of therapy in the MajesTEC-2 study. A total of 32 patients have been dosed so far with very impressive response rates of 93.5%. These will likely continue to deepen with time. Again, very encouraging data in combination as well.

The one that's sort of furthest along following Tecvayli is elranatamab, which is a bispecific antibody against BCMA as well. The MagnetisMM-1 study, which is the initial study showed an overall response rate of 64%, again, with stringent CR rates and CR rates of about 30%, almost 40%. Most of the patients achieved VGPR or better.

The MagnetisMM-3 study is our phase 2 study looking at patients who had a prior IMiD and an anti-CD38 antibody, but no prior BCMA therapy. They had a response rate of 61%, so again, a very effective therapy in very heavily pretreated patients. Based on

this data, the FDA has granted priority review for elranatamab for the treatment of patients with relapsed refractory multiple myeloma.

Another one is called alnuctamab, also a BCMA×CD3 bispecific antibody. Initially there was the IV (intravenous) formulation, and now there's also a subcutaneous formulation. I forgot to mention that Tecvayli is given subcutaneously, but all these bispecifics start intravenously, and then as we hone down the dose, they become subcutaneous. That's how most of these are getting approved in the subcutaneous form. With IV alnuctamab, 70 patients were treated, and the 30 mg or higher dose had a 65% overall response. Again, very similar to what we're seeing with the others.

About toxicity, these types of therapies can cause cytokine release syndrome, neurotoxicity, a drop in blood counts, and infections.

Linvoseltamab, another CD3×BCMA bispecific antibody at the higher doses of 200 mg to 800 mg has a 75% overall response rate. One of the things that is interesting with these last two is the CRS rates are a little bit on the lower side of about 38%. Most of the others are in the 70% to 80% range. It is unclear why that is, but there's probably some nuances in the structure of the antibodies that lead to that.

The last one, ABBV-383 is a very active bispecific antibody with an overall response rate of 57%, with the patients who are in the higher dose level getting responses up to 60% and very deep remissions as well.

Mary DeRome (MMRF): Okay, great. Thank you. It's amazing to see this proliferation of BCMA-directed bispecific antibodies, lots of choices out there. I can imagine that we'll have some approvals of more of these agents soon. Of course, there's plenty of bispecifics that do not target BCMA, and we'll be having another webinar about those later in the year. I'm going to hand over to Dr. Amrita Krishnan to talk to us about bispecific antibodies and their expected toxicities.

Dr. Amrita Krishnan: Thank you, Mary. Dr. Berdeja talked about the great promise and excitement about these drugs in terms of response rates in patients who have advanced myeloma. We're thrilled that we have new options that seem to be effective in over 50% of patients. As with any new therapy, it's a learning curve for all of us. Part of that learning curve is how to best manage side effects because the response rate is not the end of the story. We think about toxicities in four major categories as follows: cytokine release syndrome (CRS); neurologic toxicity, which is fortunately in a minority of patients; infection, which is something that we see more. It's a catch 22. Patients are staying on treatment, so their myeloma is responding. But now we are seeing the other part of this equation, which is the infections; and then cytopenia or low blood count, which is not a predominant problem, in my opinion. It's generally manageable. For me, the CRS and the infections are the major things I think about with these drugs.

As Dr. Berdeja showed, most of these drugs cause CRS in about 75% of patients. The good news is, in most cases, it is mild. Part of the importance of recognizing it early, is to treat it early so you don't go from mild to severe.

So, what are the things that we see? Most commonly, we see fever. Generally, most of us have a low threshold for treating patients with tocilizumab (Actemra) at the first signs of either a high or persistent fever. Because of this, the FDA has put in a recommendation that patients should be treated inpatient for the step-up dosing as well as the first full dose so that the CRS can be recognized and treated quickly. Some of the other things that can happen, fortunately it's rare, if CRS gets worse, is patients can become hypoxic, so low oxygen. They can start to develop low blood pressure. Further, you start to see organ dysfunction in terms of liver, kidneys and then some neurologic signs as well. But generally, with most of these drugs, the most common thing we see is fever.

Neurologic toxicity is something we think about with any kind of T cell-directed therapy. It again tends to be mild with this class of drugs, but we see it in anywhere between 5% to 28% of patients, and that's a broad number. Some of it is because it's sometimes hard to sort out. If someone gets a fever and then they become a little bit confused, is that neurologic toxicity or is it just the fever causing that? Patients can have electrolyte abnormalities. Sometimes those can cause some changes in thinking.

So, there's a lot of interplay when you're looking at neurologic toxicity. Headache probably is the most common thing I do see and sometimes some confusion in some of the more severe cases that I've seen. Again, it's just important to recognize it and treat it quickly in the same way that we treat patients who have had CAR T-cell therapy. We tend to use steroids for neurologic toxicity. I personally have not had anyone with such severe neurologic toxicity. But, clearly it has been recognized and likely we'll see it more as we treat more patients in the community, especially patients who have a very large tumor burden, one could guess, or patients who have other risk factors that were not included in the clinical trials. Certainly, it is important to be aware of it.

The biggest thing, though, I think we all agree, is the risk of infection. Because BCMA is also in B cells, which are part of our immune function, we see low IgG levels in the majority of patients, and we see infections in 75% of patients. I think this is the biggest thing, and there's multiple ongoing studies on how to reduce that risk. So, some of the things that we think about in terms of reducing risk are IVIG (intravenous immunoglobulin) for patients who have low IgG levels, and COVID-19 prevention, which is very important. In the original studies, severe infections and death were related to COVID-19. We know patients with myeloma get more severe COVID-19. Patients treated with these types of drugs probably also do because one, they don't mount the same immune response, and two, if they do get COVID-19, they get very sick. We should recognize that and try to prevent it or treat aggressively and early if needed for those patients.

All patients need to be on prophylaxis for herpes zoster. Something that we're recognizing more and more now is PJP pneumonia. It used to be called pneumocystis pneumonia. It was something we saw in immunocompromised patients like our transplant patients. We now have seen it in some patients treated with bispecific antibodies. So, most of us now routinely will put patients on prophylaxis for PJP, and that could be either with Bactrim or with Mepron. Everyone's favorite drug is generally what we use at our center.

Other common sense things for infection prevention we think about is obviously avoiding crowds, good handwashing, and certainly think about wearing masks, especially if you're going to be in a crowd. Anything you can do to mitigate infection risk because beyond COVID-19, I can tell you, I see many patients constantly coming in with other respiratory viruses and often they get it from their children, who are out and about and meet more people. These are the things that challenge us. If the patients on bispecifics get an infection, it tends to linger longer, especially with viral infections.

The biggest question we get asked a lot is how do you choose which one to use and what are the similarities between them? For some of the choices, the side effects are somewhat similar in terms of CRS and neurologic toxicity. I think of neurologic toxicity a little bit less with bispecifics and a little bit more with the CAR T-cell therapy. The biggest pro with CAR T-cell therapy is it's a one-and-done, which patients certainly find very attractive if they can be near the CAR T-cell center for the time required. For most centers it's about two months. The availability of a CAR T-cell spot is also very rate limiting. As many of you know, there are waiting lists to get your T cells collected and then you wait for them to be manufactured. Bispecific antibodies, now that we have the technology, are available off-the-shelf. Most people get their initial dose at a hospital that has experience with it, but then can be seen often in the community to continue therapy.

So, the challenge is the continued therapy. Right now, it's given weekly until disease progression, though many of us spread it out to every two weeks in patients who have had a very good response. But nonetheless, it's still given until disease progression, and that's part of some future discussions. Do you really need to keep giving it indefinitely? I think there is more to follow on that.

As I said, for advantages versus disadvantages, CAR T-cell therapy is one-and-done, but you need to stay near a specialized center. You can't drive for two months so you need caregiver support. Then there is time for manufacturing and manufacturing failures, which are some of the challenges. Bispecifics, as I mentioned are off-the-shelf, easy to get, and have sort of a manageable toxicity profile. But the ongoing treatment, I think, is the biggest challenge, and the risks of infection with ongoing treatment don't diminish.

To sum it up, we're very excited about bispecific antibodies. Today we were talking about BCMA-directed bispecifics. But you're going to hear about a whole bunch of other targets that hopefully will also get FDA approval, and we will have a plethora of choices.

We don't yet know how to best sequence these drugs, and that's also part of our future state of understanding. Side effects like CRS, infection, neurologic toxicity, and low blood counts are all treatable, but certainly require early recognition and close management. We look forward to having more options for our patients. Thank you.

Mary DeRome (MMRF): Great. Thank you, Dr. Krishnan. That was fantastic. It's interesting to hear about these toxicities. They're quite effective drugs, but they're certainly not without their issues, for sure. We're going to turn our attention to our patient speaker, Tonya. Tonya is currently on a BCMA bispecific antibody and she's going to tell us about her patient experience.

Tonya: Thank you, Mary. I'll just go backwards and talk about when I was diagnosed and a little bit of the history so that you can get an overall picture of the situation. So, in 2015, eight years ago, I was diagnosed. I had three kids who were all little—two-, four-, and five-year-olds at the time, so it was very stressful. I went through a lot of different treatment options. I had a bone marrow transplant in 2016, and that was not simple, unfortunately. At the time my disease was not super aggressive. I had IgG kappa, no lesions and was stable but required treatment. After the transplant, I tried several different lines of therapy, and they would all control it for a while and then they would just stop working which led me to this clinical trial and it's been amazing.

I have been on it for a year and a half, and initially it wasn't a big deal. The toxicity was exactly what was mentioned, just a fever. I believe I was in the hospital for two or three days, came home for the weekend and then had the second infusion. Then I've been going consistently every two weeks for a year and a half. The side effects have been minimal for me, just a cough, and the odd infection that was quickly treated with Z-Pak (azithromycin). I also did the IVIG infusions that you had mentioned. The frequency varied depending on what my IgG levels were, and my neutrophils would determine that. But I would say I've had a dozen of those infusions and they were helpful. I didn't have any side effects from them, and I had them on the day of the treatment.

Not sure if you want me to keep going, but I had a recent bone marrow biopsy done at the year and a half mark on the trial, and I was myeloma-free for the first time in eight years. Also, my FISH studies came back, and the seven high-risk features had all been eliminated for the first time as well. It was amazing to hear that I was myeloma-free and all the aggressive features had been eliminated. So, now I'm just continuing to go every two weeks and have the infusion and hope that it keeps everything at bay. That's about it. It's nice to be on a single agent.

Mary DeRome (MMRF): That's great. That's an amazing story, Tonya. Thank you so much for being with us. We really appreciate that. We're going to start our Q&A. We're going to have our faculty back.

Dr. Berdeja, after being treated with teclistamab and achieving complete remission, how long should the treatment continue?

Dr. Jesus Berdeja: Unfortunately, we don't know. As Dr. Krishnan mentioned, this is a treatment not too dissimilar to most of what we do in myeloma, where we treat till progression or intolerance. So, the depth of remission does not necessarily matter from that standpoint. It only matters if you're not responding or progressing on the therapy. Having said that, I think we all have anecdotes and there's some data with one of the non-BCMA antibodies that has a limited duration of therapy that has looked at patients who have come off the treatment, and the responses seem to be durable. There are patients who come off the treatment for an infection or for whatever reason and remain in remission. So we all hope that in the near future, and there are studies now that are starting to look at a limited duration of therapy or guiding therapy based on the depth of response. For example, if you are in complete response and you're MRD-negative and it's sustained, would you be the person we would want to stop therapy in and then just watch and then restart at a later time if the myeloma progresses? Ideally, that's how we would do it. Tecvayli was approved five months ago. So, obviously we're in the early stages of this. But that's an excellent question and hopefully the answer will be yes.

Mary DeRome (MMRF): Great. Speaking of people who have been on teclistamab (Tecvayli) and then have gone off, there's a patient who has an interesting story. The patient had five full doses of teclistamab, but then broke their arm and needed to have surgery. So, the surgeon was concerned that teclistamab would increase exposure to infections, so they cancelled treatment. Dr. Krishnan, what are the effects of missing doses and its relation to exposure to infection?

Dr. Amrita Krishnan: I honestly don't see it as regular chemotherapy where I give a patient a dose of Cytoxan and seven days later their white counts are 200 and two weeks later their white counts are better. It's not like that. The effects on the immune system are more long standing. So, I think that's a big part of it. I don't think holding a dose a week before surgery is going to do anything. Now, having said that, we do hold it in people who have active infections, but it's more about not further diminishing the immune function. Conversely, I have had patients who have had certain infections, COVID-19 being the one I think about the most. I just have someone right now who had COVID-19. It took three months for him to clear it. They did multiple different treatments. But the nice thing that I've seen with these drugs, and I've had someone else who had a lung infection six months off the treatment, is that patients can maintain their responses.

Mary DeRome (MMRF): Amazing. Okay, great. Tonya, one questioner is asking what is your quality of life like? Energy levels, muscle strength, sleep quality, activities of daily living, et cetera? Also, the second question from the same patient. Does single agent mean that you are on one drug now for treatment?

Tonya: Yeah, it is one drug, which is nice. So, I go in and have the infusion and it only takes 30 minutes for the infusion. Additional time is required for the IVIG infusion if my numbers are low, and my immune system needs it. For example, last week I went, and I was in and out very quickly. The blood work turnaround was fast. I had my 30-minute infusion and drove myself home an hour and a half later.

I did a 5K road race on Saturday and I felt fine. I ran the whole thing. I was always a runner. So, I'm very active. I go to all my kids' games and I drive. I mean, sometimes I don't know if it's just my age and that I'm busy with my kids that I'm tired because some of my friends are equally as tired. I feel like the treatment does not make me more tired than just normal life. I think that my myeloma burden is so low now it must just be my active lifestyle with running, hiking, and biking. I have three dogs and a horse, so I'm busy and I feel good. I have sometimes had this mild cough that was or wasn't treated. It would be annoying and my biggest complaint just because I felt like I had to be really careful when I was out. I didn't want anyone to think I was contagious or had COVID-19 or something. So, other than that, I would say my quality of life is pretty good. I hope that helps.

Mary DeRome (MMRF): Yes, very good. Another question for you, Tonya. Did you have CAR T-cell therapy? Was it offered to you but you decided to go for the bispecific instead?

Tonya: We weighed both options. The CAR T-cell therapy had some appeal. I left it up to my doctor to make the decision over which one he thought my myeloma would respond to. That's ultimately the path we went down. I was offered CAR T-cells and I was offered the BCMA (bispecific) therapy. Sometimes I think about CAR T-cell therapy and if I should have done it and be done. But this is working well, so it's great too.

Mary DeRome (MMRF): Excellent. Thank you. Dr. Berdeja, a patient asks, "If CAR T did not work for me and the target was BCMA, will the BCMA bispecific treatment work?"

Dr. Jesus Berdeja: Another excellent question. The answer is maybe. So, the good news is we do have data, which I glossed over quickly. But we do have data with the bispecifics that are going against the BCMA target in patients who have had prior CAR T-cell therapy or the antibody drug conjugate belantamab mafodotin (Blenrep). They had good responses and very deep responses. What we don't know is who those patients are. There is a little bit of a drop off in the response. It's unclear whether the duration of response would be the same as someone who's never had BCMA therapy. So, there is no short answer. The long answer is just because you didn't respond to one does not mean you will not respond to the other. But I will caution that if you have an option for a different target, then probably go for a different target. But if you don't, it's worth trying.

Mary DeRome (MMRF): Great. Thank you. So, Dr. Krishnan, Dr. Berdeja did the introduction to our webinar today, and he discussed how T cells become agnostic. Can you expound upon that a little bit? What does that mean? How do they become agnostic?

Dr. Amrita Krishnan: I think of them as more exhausted than agnostic. There's a lot of studies done in the lab of what they call markers of T cell activation. We can't keep activating T cells. At some point they become tired, and they stop functioning as well.

That's sort of why these bispecifics stop working. That adds further weight to this idea maybe that you don't keep treating people indefinitely and that you give treatment holidays. There are a few trials in the future that will look at three months on, two months off schedules. Some of it is hand-waving. We don't know how long it takes for T cells to really recover a lot of function. Balancing T-cell function while keeping the myeloma under control is what we're aiming for.

Mary DeRome (MMRF): Thank you. Dr. Berdeja, Tonya spoke about her treatment. She said that all her high-risk markers have now disappeared after a year and a half of treatment with a bispecific. Can you tell us a little bit about high-risk disease and what the implications are for people who are taking bispecifics? Do we have data showing that it works well for people who have high-risk disease?

Dr. Jesus Berdeja: Congratulations, Tonya. That's excellent. We do have evidence that high-risk patients do respond to treatment. The way I think about it is immunotherapy like this is using T cells. The T cells come from outside and kill. It is not a treatment from within, like chemotherapy, where the cells can become resistant and the chemotherapy doesn't work anymore. So technically, immunotherapies should be able to kill the myeloma cell, whether it has resistant features or not.

Now, having said that, we do have some data, especially with CAR T-cell therapy. Now, we're starting to see that with the bispecifics, patients who have high-risk features still don't do as well as patients who don't have high-risk features. So there still is something to those cells that allows them to survive a little more and relapses tend to occur a little bit sooner. But absolutely, in terms of responding, these are very effective therapies even for patients with high-risk features.

Mary DeRome (MMRF): Okay. One patient writes that they have kidney disease. "And I heard the patient say that her myeloma treatment affected her kidneys. So do you have any suggestions for what I need to consider for my treatment?"

Dr. Jesus Berdeja: Well, sticking to the bispecifics here, of course, the kidneys are an important consideration when we're choosing different therapies. For example, for CAR T-cell therapy, if your kidney function is very poor, we're not able to give the lymphodepleting chemotherapy that is required to allow the CAR T cells to expand. So that may perhaps not be the best treatment for someone with poor kidneys. But bispecifics technically do not get cleared through the kidneys. So even though the studies require a certain kidney function level, these should be more tolerable treatments for someone with kidney disease. So, talk to your doctor because the allowance for how good your kidneys must be is better for bispecific therapies.

Mary DeRome (MMRF): Great. Thank you. So, here's another good question. Dr. Krishnan, with so many patients getting quadruple therapy prior to stem cell transplant, where do you see bispecific antibodies fitting into relapsed treatment? Would it be in early relapse or later relapses?

Dr. Amrita Krishnan: So there are trials going on in early relapse. We have one right now. It's called MajesTEC-3, which has patients who have been on one to three prior lines of therapy. One arm gets Tecvayli and daratumumab (Darzalex), the other arm is getting Darzalex, dexamethasone, Pomalyst (pomalidomide), and Velcade (bortezomib). So, it's really in that early relapse setting. There are also some trials using bispecifics in the frontline setting. I think this is a common theme in myeloma. A drug gets approved in very advanced disease, but the interest is, "This is a great drug. Can it work better earlier?", which makes sense because T-cell function is better earlier in myeloma. So maybe you can get even better bang for that earlier. Dr. Berdeja can speak to the same thing which has been happening with CAR T-cell therapy as well. Certainly, I think that's where the future will be—T cell-directed therapy earlier in the myeloma process.

Mary DeRome (MMRF): It's good that we have trials ongoing that answer that question because it's a question that many patients ask.

Dr. Jesus Berdeja: Just to add to what Dr. Krishnan said, I think right now we all talk about lines of therapy, but as the person that asked the question said, we're starting to use quadruplets. So, in these lines of therapy that we normally would go to, we're starting to use up some of their components, and the lines of therapy become very murky. We're hoping that at some point we'll be talking more about patients in terms of their myeloma being refractory to two types of therapy so that if you are progressing and you've had a prior PI and anti-CD38, then that would be the person in whom I think the BCMA-directed therapies would be very effective. Whether it's second-line or third-line, it shouldn't matter. But right now, Dr. Krishnan is correct. It's just where we are.

I saw a question asking that I specify the population Tecvayli is FDA-approved for. It's approved for patients with relapsed refractory multiple myeloma who had a prior PI, IMiD, and an anti-CD38 who have had at least four lines of therapy. It must be your fifth line of therapy, so it is very late in the game.

Mary DeRome (MMRF): Okay. So, then here's another good question. I think we've talked a little bit about this, but still, it asks "After being treated with teclistamab (Tecvayli) and achieving a CR, how long should the teclistamab treatment continue? Does the risk of infection continue if treatment continues every day?"

Dr. Amrita Krishnan: I think many of us know they allow you to go every two weeks if you've had a deep response. I think it was after cycle seven. I think many of us certainly would back down the frequency. The question is how low can you go? The other part is the risk of infection continues, unfortunately, for as long as you're on treatment.

Mary DeRome (MMRF): A lot of people in the Q&A are talking about being infected. So, I know that this has been just a hot topic with the bispecifics at some of the meetings that we've been at recently. It's an unfortunate side effect. Although Tonya, you said that you really haven't had much in the way of difficulty with colds or anything like that, which is amazing for somebody that has three small kids.

Tonya: Yes. Just a low-grade cough that would come and go. I only had it treated a couple of times when it got to something a little more advanced, but it was never pneumonia or anything like that. I've been lucky so far.

Mary DeRome (MMRF): You must have a strong immune system, to begin with.

Tonya: Well, like Dr. Krishnan was saying too, with the COVID-19 vaccines, I've been up-to-date and been boosted with the maximum allowable. I've had my pneumonia and shingles vaccine. So, I try to stay on top of those as well for prevention.

Mary DeRome (MMRF): Great. It's a good plan. Dr. Berdeja, what is the overall survival of Tecvayli for patients who had prior BCMA treatment? Also, what tests are done to determine if a prior BCMA-exposed patients still has the antigen? Does that really matter?

Dr. Jesus Berdeja: I don't know if that's been reported on the study.

Dr. Amrita Krishnan: I don't know either. I'm pulling up the paper right now.

Mary DeRome (MMRF): I don't think we have that piece of data.

Dr. Amrita Krishnan: They didn't report overall survival at all as a group.

Dr. Jesus Berdeja: The duration of response is 11 months or so for the entire group but for the group on prior BCMA, we don't know that information yet. That data has just been presented at meetings. It hasn't been fully published just yet, so stay tuned. I don't know the answer to that, but that's good that we don't have an overall survival for the entire study. It means patients are living long enough that we haven't reached that median. That's what we saw also with CAR T-cell therapy. We saw the progression-free survival, but the overall response went much further out. A testament, again, to how well these therapies are working.

The second part of the question was, do we need to test for BCMA? We do know of a few case reports where people have had prior therapy against BCMA, and when their myeloma comes back, those cells no longer express BCMA. But luckily that is incredibly rare and most patients still express BCMA when their myeloma comes back. So, we don't routinely test and it's not necessary to test the tissue for BCMA expression. There is a test called the soluble BCMA that probably will become something that can be done easily and that will be sort of a surrogate test for when your plasma cells recover or your myeloma progresses. BCMA is shed from the surface of the cells and can be detected in the bloodstream. So that would be like a surrogate way of doing it. But the truth is that it should be very rare that that happens.

Dr. Amrita Krishnan: Mary, can I just jump in? Because I misspoke. Talquetamab doesn't have an overall survival, but for teclistamab, they report a median overall

survival of 18 months, but they don't break it down into whoever had prior BCMA. My recollection is that study didn't allow prior BCMA in the original group.

Mary DeRome (MMRF): Got it. Okay. Another question is, "Did Tonya say that she had a bone marrow transplant or a stem cell transplant? Also, does she have any nerve damage from that?"

Tonya: No, I do not have any nerve damage. In 2016, I had a bone marrow transplant with my own cells, and it was unsuccessful. So, my myeloma remained the same when I was tested. I believe it was two or three months after the bone marrow was done.

Mary DeRome (MMRF): That's amazing. How often do people's stem cell transplants not work? Do you see that routinely in your practice?

Dr. Amrita Krishnan: No, not routinely. I'd say less than 10% of patients don't have at least a 50% response.

Mary DeRome (MMRF): Right. Okay. Dr. Berdeja, "Is the risk of infection higher with the bispecifics than with CAR T?"

Dr. Jesus Berdeja: Good question. I think the short answer is, we don't know. But they both have a high risk of infections. I think CAR T-cell therapy is a little bit easier to rein in, in my opinion, because it has such a limited duration of therapy. There is the chemotherapy that is given before the CAR T cells that can lead to suppression of your T cells and then you have the CAR T cells, which can obviously lead to suppression of all the B cells and the immunoglobulins just like the bispecifics. But then the CAR T cells are expanded and then about two to three months later, they are basically gone from your system or very low levels remain. As Dr. Krishnan talked about, unlike with chemotherapy you're no longer getting an active therapy. Eventually, the immune system recovers in about six to 12 months depending on the cell lines we're talking about. So, we tend to tailor our prophylactic therapy based on that. I would say about a year after CAR T-cell therapy, most patients have sort of regained their T cell immunity. Because B cells are just killed with the CAR T-cells. They remain nonexistent for a long time.

With the bispecifics, each time you give them, you see T cell redirection. So, you're taking T cells out of the circulation to go kill myeloma cells. These effects last for the entire time that you're on the treatment. So, that, in my opinion, that effect would be much more continuous.

Mary DeRome (MMRF): Yes. Okay. That makes sense. I'd like to thank our audience for tuning in today. I'd like to thank our speakers Dr. Jesus Berdeja, Dr. Amrita Krishnan, and our patient speaker, Tonya, for their time and their contributions. Thank you so much.