

### Transcript Details

This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: <https://reachmd.com/programs/project-oncology/myeloma-matters-bispecific-antibody-horizons-dosing-strategies-and-meeting-updates-in-myeloma-care/24428/>

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Myeloma Matters: Bispecific Antibody Horizons: Dosing Strategies and Meeting Updates in Myeloma Care

### Announcer:

Welcome to ReachMD. This activity titled Myeloma Matters: Bispecific Antibody Horizons, Dosing Strategies, and Meeting Updates in Myeloma Care, is jointly provided by RedMedEd and the Multiple Myeloma Research Foundation. Prior to beginning the activity, please be sure to review the faculty and commercial support statement as well as the learning objectives.

Welcome to the Myeloma Matters podcast hosted by the Multiple Myeloma Research Foundation and focusing on topics related to improving outcomes for myeloma patients. This podcast is based on a round table discussion by, Dr. Saad Usmani, Chief of Myeloma Service at Memorial Sloan Kettering Cancer Center, Dr. Joshua Richter, Associate Professor of Medicine at Tisch Cancer Center Icahn School of Medicine at Mt. Sinai, and Ashley Steinberger, a nurse practitioner at Memorial Sloan Kettering Cancer Center. This episode of Myeloma Matters reviews the latest data on bispecific antibody therapy for relapsed/refractory multiple myeloma, as discussed at the 2024 American Society of Clinical Oncology and European Hematology Association annual meetings, including information about the use of fixed duration dosing to mitigate adverse events.

### Dr. Usmani:

Hello, I'm Dr. Saad Usmani, the chief of the Myeloma Service at Memorial Sloan Kettering Cancer Center. Welcome to this episode of Myeloma Matters entitled Bispecific Antibody Horizons, Dosing Strategies, and Meeting Updates in Myeloma Care. Joining us today are my colleagues, Dr. Joshua Richter and Ashley Steinberger. I would welcome them to introduce themselves, starting with Dr. Richter.

### Dr. Richter:

Thank you so much for having me here today. My name is Josh Richter. I'm an Associate Professor of Medicine at the Tisch Cancer Institute Icahn School of Medicine at Mt. Sinai and the director of Myeloma at the Blavatnik Family Chelsea Medical Center at Mt. Sinai, and excited to be talking about myeloma today.

### Dr. Usmani:

Ashley?

### Ms. Steinberger:

Hi, my name is Ashley Steinberger. I am a nurse practitioner at Memorial Sloan Kettering Cancer Center in New York City.

### Dr. Usmani:

Wonderful. Thank you, Josh and Ashley, for joining. We'll start our discussion with, you know, a couple of abstracts that were featured recently on teclistamab. We'll start with the MajesTEC-1 updates specifically, focusing on the prophylactic use of tocilizumab and the incidence of CRS in severity. If, you know, you recall MajesTEC-1 was the pivotal trial that led to the FDA approval of teclistamab back in the fall of 2022. The original cohort of patients was a total of 165 that had not received prophylactic dosing. Subsequently, there was a cohort of 24 patients that went on to receive prophylactic tocilizumab. This particular abstract that was presented at ASCO highlighted was the reduction in the overall cytokine release syndrome with prophylactic dosing, went from 72% of overall CRS down to 25% and grade 1s were around 50% in the original trial, went down to 8.3 in this toci prophylactic cohort. However, the grade 2 percentage was about the same, 16.7%. So, you know, there were no disease characteristic differences between the groups but, you know, I found this, you know, data, you know, quite intriguing.

They also presented on the responses in the two cohorts and, you know, the response appears to be comparable compared to, you know, the overall original patient population of 72 versus 63%. If you look at the follow-up time period between the cohorts, it was little

different and so you do see some differences in the quality or depth of response here. The median follow-up was only 8 months or so, and on the original cohort, the median follow-up is, you know, reaching close to 3 years now. You know, what are your thoughts about these findings, you know? We can start with Josh, maybe providing some comments and then, you know, I'll go to Ashley.

**Dr. Richter:**

Sure. So, you know, one of the things is that the three of us work in institutions where we treat dozens, and dozens, and dozens of myeloma patients per day and have whole teams set up to deal with things like cytokine release. One of the things that makes me very excited about this data is I think by bringing down the overall rates of CRS, there's a better chance of getting it in the hands of some of our community colleagues who may not, just like you, Dr. Usmani, who just came from seeing, you know, 30 myeloma patients in your clinic with an amazing group of doctors and nurses and nurse practitioners. So, to me that's the biggest thing about. A better pathway to outpatient dosing and community dosing.

**Dr. Usmani:**

All right, Ashley, what are your thoughts?

**Ms. Steinberger:**

So, I definitely agree. I think that it's going to bring down some of the barriers in starting the step-up dosing. I think some patients are hesitant because of the admission to the hospital, so if we can somehow mitigate the cytokine release syndrome and make it safer for patient to get it as outpatient, then more patients would be more willing to proceed with the drug. I also think it's better for the hospitals as well and to not burden the floors with more admissions.

**Dr. Usmani:**

I'll ask both of you, you know, have you started to use teclistamab in the outpatient setting yet? Or if you're doing it, you know, how are you picking patients for that? So, you know, Josh, how are you guys thinking about this at Sinai?

**Dr. Richter:**

We haven't quite delved into the full outpatient dosing just yet, because I think a lot of patients that we tend to give commercial teclistamab, may be a little bit higher burden, so a little bit higher risk overall. We have what I like to call the early release program, which is we admit you to the hospital and almost everyone will get CRS within the first one or two step-up doses. And within 24 hours of that, we'll actually send them home because our internal data shows the likelihood of any severe CRS to recur after is extremely low. In fact, most people don't get any given the long half-life and only a handful will get only grade 1 CRS, so we send them home with some steroids just in case.

**Dr. Usmani:**

Ashley, what are your thoughts?

**Ms. Steinberger:**

Yeah, we have done a few as outpatient, actually, where they'll get the dose outpatient and then they go home with a vital-signs monitoring machine that we can, kind of closely monitor their vitals and be notified if any of the vitals are abnormal. So, it makes it safer for them but, like Josh said, they have to fit a strict criteria and have a low burden of disease and the people that go on this drug typically have a higher burden, so most of them are getting admitted, but some of them do fit the criteria to have as outpatient safely.

**Dr. Usmani:**

I know that, you know, some of the Sinai colleagues have done this for CAR-T cell therapies as well and, you know, we are doing the same for both, you know, the bispecifics and there's a CAR program. The other important abstract, you know, was actually presented at EHA from our colleague at MSK, Carlyn Tan. This was the MSK experience of less frequent dosing. So, one of the, you know, concerns that has been raised by, you know, our BCMA-directed bispecifics is patients getting increased risk of infections, both bacterial, viral, and, you know, even opportunistic infections, you know, with ongoing treatment with teclistamab and other BCMA-directed bispecifics requiring IVIg support for hypogammaglobulinemia, etc. So, I think we, you know, in this cohort of 86 patients who got at least one dose of teclistamab, you know, with the median of six prior lines of treatment. And 1/3 of the patients had received a previous bispecific-directed therapy as well, you know, they were, you know, a couple different, you know, groups of patients, you know, the early initiators were the patients that were treated in the first 4 months and, Josh, Ashley, you guys know how desperate we were for other options at that time and, you know, we all had long wait list for CAR-T cells and we just let, you know, we just let teclistamab loose on that area patient population. Then we had, you know, subsequent, you know, patients where we had more experience with tec, you know, and started to switch patients from Q-week to Q2-week or Q4-week dosing. And what, Carlyn Tan, demonstrated is that even after that switch that tended to happen around the 3-month mark with subsequent follow-up of, you know, further 6 months, more than 90% of the patients actually maintained their initial responses.

So, our group had initially decided that, you know, since the median time to best response is within, you know, is about three cycles or so, in patients who are already demonstrating responses of VGPR or better, let's start dialing down the frequency of treatment. And, you know, in our experience it appears that patients continue to maintain responses. And I know that, you know, Carlyn will also be updating the infection data, but I thought the fact that, you know, you know, more than 90% of the patients actually have sustained responses was, you know, pretty neat after that switch.

So, you know, Josh, what are your thoughts around this data and, you know, how has, you know, the Sinai experience been with the less frequent dosing? Is it any different?

**Dr. Richter:**

I think one of the things that this data brings up is, you now, we have to stop thinking about all of these drugs like we did classical chemotherapy. It's not all about dose intensity. It's not all about doses higher, dosing lower, it's about getting your immune system to do what you need it to do and trying to find that Goldilocks zone between forcing every T-cell to wake up and fight cancer and then taking every T-cell away from fighting infection. So, I think your description of the landscape is perfect.

When these first came out we were desperate to get these drugs into the hands of our patients and now we have taken a very similar path, just as you guys have, which is kind of quickly getting to less frequent doses. I think a lot of try to follow the daratumumab-like scheduled, you know, 2 months of weekly, 4 months or every other week, and then monthly. But there are, you know, patients that are in CR or better within a few cycles. For some of those we feel absolutely fine going right, pretty quickly, to monthly dosing.

**Dr. Usmani:**

Ashley, what are your thoughts? Because, you know, you actually take care of a lot of these patients.

**Ms. Steinberger:**

Yeah, so I have similar experiences so definitely patients are tolerating the drugs better when they are given a little bit less frequent, and they are getting less sick and the immunoglobulins come up a little bit better. So, it just seems like, and they seem to continue with a good response. So, we have a patient that sometimes will go travel for 3 months and come back and still have undetectable disease, so it seems to be that they get, some of them, very deep durable responses.

**Dr. Usmani:**

Thank you. And, you know, just staying on that, you know, theme here, with these amazing results with BCMA-bispecifics and the relapse stated was only a matter of time, you know, that we started to think about combining them with other therapies in earlier lines of treatment and we actually got the first glimpse of the MajesTEC-7 safety cohort. Josh, I would love your comments on this front-line treatment regimen. What was the regimen and, you know, what were the data?

**Dr. Richter:**

So, I think it's been an exciting, you know, about 6 months or so. We've seen, you know, many years of everyone focusing on the relapsed space and then within the last 6 months between seeing transplant-eligible studies like Isa-KRd, transplant ineligible like Isa-VRd, and now with MajesTEC-7 giving teclistamab, Darzalex, and lenalidomide, I think we've really seen this, kind of, push to, you know, get these unbelievably deep responses upfront. Maybe so deep that we don't even need to get to the relapsed setting. So, MajesTEC-7 was a multi-arm study but what they really put forward data-wise was the teclistamab, Darzalex, lenalidomide cohort, and, you know, median follow-up now of almost 14 months. And the data's, you know, not unexpected.

From a safety standpoint, you know, about 2/3 of patients are going to have CRS. Most of this occurs in \_\_\_ [LB2] [LN3] cycle 1. ICANS is very rare. I think they had only one case that was a grade 1. Most of these patients are able to maintain good dose intensity. Really the big side effects, besides heme toxicity and lowered blood counts, is infections. I think we saw a fair amount of infectious complications in this and not unexpected when you start to mix CD38 and BCMA. And, I think, what Ashley alluded to before was perfect, is that, you know, with BCMA therapies, you know, we have to be concerned hypogamma and the infection. And when you mix Darzalex in it, it can make it a little more profound.

But you know, I think one of the things that we really liked was the efficacy of this regimen and ultimately the overall response rate was 92.3% with more than 92% of patients having a VGPR or better. So, you know, a highly effective regimen and so far, no one has progressed. So, you know, I think T-cell redirection with the recent approval on first relapse established the dominance there and now we're starting to see some great data in front-line.

**Dr. Usmani:**

Ashley, what do you think about these data? And, you know, oh one thing that, you know, I do want to highlight, you know, with this regimen, I think the teclistamab dosing follows that of daratumumab, Josh. So I think, you know, you go from weekly to every other

week, to, you know, monthly dosing. And that's the piece that I also liked about how this being a cohort was run and designed because, you know, that will help mitigate that infection risk, you know, issue. Ashley, what do you think?

**Ms. Steinberger:**

This is really interesting and it could change a lot of what we do as upfront treatments for multiple myeloma if the response rate is this high. And I think we're learning more about how to, kind of, combat infections and prevent them.

**Dr. Usmani:**

And this was, you know, interesting. So MajesTEC-7, you know, is like a multi-cohort phase 1 to figure out safety and then there's a randomized trial. And this regimen is being developed for the transplant ineligible or older patients. So, and it's going to challenge MAIA so DRd. I'm really looking forward to the phase 3 portion of this trial opening and for us all to enroll patients on it because, you know, the depth of response we're seeing is, you know, amazing. And the fact that, you

know, MAIA has already, you know, made such a big impact for that older myeloma patient population, seeing a regimen that can even supersede that is, you know, I'm really looking forward to that. So, you know, I'll be curious to see how this plays out and, you know, what that, you know, final clinical trial design looks like.

Let's turn our attention to data on other BCMA-directed bispecifics. Dr. Mohty presented updated efficacy and safety results from the MagnetisMM-3 trial that has now had more than 2 years of follow-up after the last patient was originally dosed. So, this is long-term survivorship from that original clinical trial. A total of 123 BCMA treatment-naïve patients with relapsed or refractory disease were treated with elranatamab. A third of those patients had extramedullary disease, 15% had high-risk karyotypic abnormalities. And the median prior lines of treatment was five triple-class refractory made up vast majority of patients; almost 97% of this patient population. Overall response rate was very similar to what had been reported with teclistamab, you know, it was around, you know, 61%. But MRD negativity was 90.3% in the evaluable patients who had complete responses or better. And the complete responses or better were there and around, you know, 38 or 39% of the patients if I remember correctly. The median PFS was, you know, quite impressive at 17.2 months and median OS for this population was over 2 years. And just for context for, you know, for this triple-class refractory patient population. The median OS we would expect is only 8 to 9 months. So, you know, amazing results and I don't think that they reported any new safety signals from an infection risk or long-term follow-up respective. Josh, what are your thoughts about the elra long-term follow-up?

**Dr. Richter:**

So, I think this confirms the data we've seen all along. You know, with some of the great data presented by Dr. \_\_\_ at your center, we've seen a lot of the great data. It's nice to see the follow-up. It's really nice to see no increase in second primary malignancies because we've seen that, unfortunately, with the Carvykti product. You know, head-to-head between this and teclistamab, hard to say a lot, although the nice features are that it's a shorter step-up dose and fixed dosing as opposed to weight-based, but again, another great asset to have in our toolbelt.

**Dr. Usmani:**

Ashley, what do you think? You know, we've had experience at our site with elra, you know, doing the clinical trial phase and now, you know, with the commercial product.

**Ms. Steinberger:**

So, I think that, you now, this is, again what Josh said, just confirms that people do get deep and durable responses to these bispecifics and this is in BCMA-naïve patients so I would be interested to kind of learn more about the patients that have had BCMA and had elra and if they did respond because, with tec, I think that you still could respond even if you had prior BCMA.

**Dr. Usmani:**

And I'm going to now turn to Josh to review data on BCMA-directed bispecifics.

**Dr. Richter:**

Let's take a look at what's on the horizon for treatment for relapsed and refractory myeloma. So, Saad, as you have already pointed it out, we already have a two FDA-approved BCMA-targeting bispecifics: teclistamab and elranatamab. But there's some good data coming down the pike on a couple others including linvoseltamab and ABBV-383. And we recently saw some data presented by Dr. Lynch over at Columbia from some of the updated phase I/II results of the LINKER-MM1 study.

So, at a median follow-up of around 14.3 months, we saw very high efficacy, and again, it's, you know, in myeloma you're never supposed to compare trial-to-trial, so you have to say that statement, then you take a deep sigh, and you go on to compare trial to trial. So, shouldn't do trial-to-trial comparisons, ahh. So, we see an overall response rate here of 71% which is, so far, the highest in class.

But, again, there are noticeable differences between the different trials, so it is a quite high number, but the others being around 63-64% are also in the same ballpark. You saw a CR rate of 50%, median duration of response was almost 30 months, and progression-free survival was not yet reached, 70% of patients were still in remission at the 12-month mark, median OS of 31 months. So a very efficacious drug.

In terms of the safety profile, you know, again like with all the bispecifics, the big treatment adverse events are things like CRS and ICANS. Overall, the CRS rates were relatively low. And the majority, just like the other assets, grade 1 and grade 2. And, you know, I think that in terms of efficacy and safety, teclistamab, elranatamab, linvoseltamab, all very, very similar. You know, maybe one drug is slightly higher in the perimeter, one is slightly low in that parameter, but I think the three are all great drugs. And we're really waiting for the LINKER-MM3 study comparing against elo/pom as a registration phase 3 for future data.

The next abstract drug we're going to discuss is the ABBV-383 bispecific antibody. This was presented by Dr. Isoken and this was another large trial; 220 BCMA-naïve patients with a median number of lines of five. And exactly, as Ashley pointed out, you know, we know this great data in a BCMA-naïve population, we really need more data about evaluating these drugs in patients who have had other BCMA assets like CAR-T therapy.

So, one of the really nice things about the ABBV-383 drug is that it goes right away to a monthly dosing. So, I think that's a really nice feature of the drug. A really great quality of life thing for patients because the other drugs will stay weekly and/or go to every other week. You know, we do have data for extending out teclistamab and elranatamab to monthly. Linvoseltamab actually has built-in, when you get to week 24, if you are in a VGPR or better you go to monthly dosing, but here with the 383 compound you go right away to monthly dosing well within perimeters.

So in terms of CRS, overall very well in line with some of the previous assets. When we looked at the 40-mg and 60-mg doses given every 3 weeks, we saw CRS rates of 71 and 70%, respectively, but at the Q4-week dosing it goes all the way to 43%, so really well-tolerated drug overall. So, when we talk about the overall response rate, looking at the different dosing strategies, this is very much in line with the other bispecifics and with the 60-mg Q4-week dosing, we see an overall response rate of 65% with more than half of the patients achieving a VGPR or better. And, you know, a little bit of a shorter follow-up with this cohort, but overall responding very quickly, median time to first response of around a month. So again, overall, I think we can find little perimeters here and there that may be subtly different between the different BCMA assets, but they're all pretty much in line safety- and efficacy-wise.

**Dr. Usmani:**

So the key takeaways from the BCMA-directed bispecific data, it looks like prophylactic tocilizumab may be able to help mitigate frequency of with teclistamab. The elranatamab, I don't see any reason why we won't be able to utilize the same approach for that FDA-approved BCMA-directed bispecific. I think the real-world data shows that less frequent dosing is doable and does not impact the durability of response, you know, at least at the 6-month mark after the change. And then combining bispecifics with standard myeloma treatment looks promising given the depth of response we're seeing in those early cohorts and MajesTEC-7 look great. And then early-phase trials of the investigational BCMA-directed antibodies look promising. The linvo data, again the CRS pattern from that experience appears to be the most impressive out of the lot, but then we have ABBV-383, which is the monthly dosing convenience. So, a lot is going on in that space and we're moving to phase 3 trials with these bispecifics.

Josh and Ashley, would you like to add any other key takeaways?

**Ms. Steinberger:**

So I think that, you know, what these trials are showing is that these drugs work very well. And I think, in the real world, that is what we're seeing; we're seeing people respond quickly and have long responses. I think also these abstracts are pointing to kind of trying to make this safer for patients, easier for patients, and easier for healthcare providers. So, all good things in the pipeline.

**Dr. Usmani:**

So, let's move on and review recent abstracts on non-BCMA-directed bispecific antibodies that are represented at ASCO and EHA. Dr. Leo Rasche shared long-term efficacy and safety results from the phase 1/2 MonumentAL-1 study of talquetamab in relapsed/refractory multiple myeloma. As you all know, talquetamab is a GPRC5D-directed bispecific antibody that was approved by the FDA based on the MonumentAL-1 clinical trial. The approval came about a year ago and it was based off the two cohorts of patients who received the 0.4 mg/kg weekly dose of talquetamab. And then there was a second cohort of 0.8 mg/kg of talquetamab given every 2 weeks. The median PFS reported with the 0.4 mg cohort was 7.5 months and it was around 11 months with the 0.8 Q2-week dosing. In patients who had triple-class refractory disease, the median progression-free survival was about a little less than 8 months. The overall response were quite impressive. They were in the, you know, 60 to 70 odd percent range. You know, I'm going to call out the most significant one or more the relevant in terms of the population that we treat, almost 67% for the triple-class refractory population. And each of the cohorts

had almost, you know, 55 to 60% of the patients achieving a VGPR or better, so really impressive depth of response. From an A standpoint I don't think CRS was as significant an issue as were some GPRC5D associated AEs.

So, you know, I want to actually go to Ashley and just, you know, get your thoughts on the GPRC5D specific side effects that we see in clinic, you know. Can you share, you know, the talquetamab experience on the clinical trial data as well as your own?

**Ms. Steinberger:**

People are responding well to this drug, but they have a hard time staying on it because of the side effects. So, you really have to be upfront with them at the beginning when they're going on it and tell them what to expect. Personally, what I see the most in clinic is the taste changes and people losing a lot of weight. So, usually when we hold a dose or spread out the dosing, the patient's kind of can tolerate it better. There also can get nail changes and skin changes. So, the skin changes can be peeling on the hands and feet, which will present a little bit later, and then also, the nails can kind of separate from the nail bed. There can be nail pitting and also a generalized rash which I haven't seen as much, but yeah, the skin and nail changes and taste are very common with this drug.

**Dr. Usmani:**

So, Josh, are there any other safety issues you want to highlight from the MonumentAL-1 study or with talquetamab?

**Dr. Richter:**

No, I think overall, Ashley did a great job. I think her assessment of this is really accurate. It's not the easiest drug to keep people on so the way I think about it is, you know, some drugs in myeloma are an ends to a mean and some drugs are a means to an end. And right now, a lot of the patients that we use talquetamab is a means to an end to get them to a CAR-T, to get them to the next type of therapy.

**Dr. Usmani:**

Yeah, and speaking of safety profiles, you know, there is, you know, data relevant to infectious complications of bispecifics and CAR-T cell therapies. Ashley, do you want to comment on some of that new data?

**Ms. Steinberger:**

Yes. So, as we've mentioned multiple times, infections are kind of one of the biggest things with CAR-T cells and bispecifics. So, there was a retrospective analysis that [Julien Mercey](#) and colleagues evaluated infectious complications of any grade in 137 patients treated with either BCMA or GPRC5D-directed bispecific antibodies or CAR-T cell therapy. So of these 137 patients, 58 were CAR-T, 47 were BCMA-targeted bispecific, and 32 received GPRC5D-targeted antibody. Kind of what they saw was that there were less infections in the patients that received the GPRC5D versus the BCMA antibodies. So the rates were 76% for CAR-T therapy, 85% for BCMA, and 59% for GPRC5D-targeting bispecific antibodies. So, most of the infections were of the respiratory tract viral infections. So, you know, while the talquetamab can cause a lot of other side effects that are unwanted, like the nail changes, the taste, etc., one thing it does do, is it doesn't put you as high of a risk as the other bispecifics.

Now we're going to transition over to cevostamab, and Josh is going to cover that.

**Dr. Richter:**

Sure. So, we saw the CAMMA 2 data presented at EHA by Shaji Kumar. The CAMMA 2 data was specifically looking at cevostamab, which is a FcRH5/CD3 bispecific, but the CAMMA 2 data was only looking at patients who had had prior BCMA therapy.

So, what we saw is early data, small number of patients. No real post bispecifics in this cohort. It was really either patients receiving ADC with belantamab mafodotin or prior CAR-T therapy. And overall, you know, the drug is well-tolerated. Similar toxicity profile to the other bispecifics, so it doesn't have the nail, skin, and dysgeusia that we see with talquetamab, but it does cause CRS and ICANS at similar rates to the other assets. In terms of infection, if I had to rank them, I think BCMA causes the most infection, GPRC5D the least, and cevostamab is probably somewhere in between, but overall, a fairly well-tolerated drug.

In terms of efficacy, for the entire cohort we saw an overall response rate of 67%, but this was higher in patients who had had prior CAR-T rather than the ADC. So, it was 73% in prior CAR-T, 60% in prior ADC. And this is really in line with what we are seeing when you even go from BCMA-to-BCMA asset, that the longer the distance in between that attack, the better you do. And when you're on an ADC or on it more regularly, so the time in between dosing between the ADC and cevostamab was shorter and that probably impacted the response rate. But overall, response rates were quite high with about 20% of patients getting VGPR or better. And, again, 73% response rate post-CAR-T is a really exciting thing especially as CAR-Ts are moving earlier and earlier on that we have some great therapies as salvage when we need them.

Saad, your key thoughts on takeaway points.

**Dr. Usmani:**

You know, I think the long-term efficacy and safety of talquetamab is confirmed based on the longer follow-up that was presented. The

points that both you and Ashley made about the infectious complications with bispecifics, you know, where BCMA bispecifics rank higher than GPRC5D and, you know, cevostamab is somewhere in between. And the CAR-T related infections that we see with CARs is actually lower than what we see with the bispecifics. So I think it's important to appreciate that. And, you know, the early data with cevostamab is in cohorts of patients with prior, you know, bispecific and CAR exposure, so, you know, I look forward to seeing a little bit more of that data in those cohorts with longer follow-up because, you know, relapsed disease beyond these therapies still remain an area of unmet need and we, you know, have many of those patients in our respective clinics.

In the previous sections we discussed key clinical trial data that was presented at ASCO and EHA. Let's try to see if we can talk about a patient scenario and illustrate how to optimize the use of BCMA-directed bispecific therapy in clinical practice and, you know, we are going to have robust discussions with my two esteemed colleagues.

So, we have a 72-year-old woman with high-risk multiple myeloma. Performance status is 2. At the most recent progression, the patient has amplification of 1q21 along with deletion 17p. In terms of treatment history, the patient started with

DRd as initial treatment like the MAIA trial, but then daratumumab was discontinued and len maintenance was continued. VGPR was the best response, but the patient progressed after 1.5 years, then they received a dose-attenuated regimen of bortezomib, selinexor, and dexamethasone, which resulted in a duration of response for about 1 year, response. Then the patient went back to daratumumab with pomalidomide and dexamethasone for another 9 months or so, before progressing. And the last line of treatment was a dose-attenuated carfilzomib with cyclophosphamide and dexamethasone, but they only got it for about 5 months before, you know, showing clinical progression.

What would be the considerations of treatment for this patient? You know, this is a transplant ineligible patient, likely being considered for BCMA-directed bispecific therapy here. And I'm going to turn to, you know, Ashley and Josh. Ashley, do you agree? You know, this fourth-line treatment patient whose had, you know, all the drugs, but you know, in different doses and schedules probably because of the performance status and not being, you know, transplant eligible. But, you know, what are your thoughts? What are the options for this patient? And would you consider a BCMA-directed bispecific?

**Ms. Steinberger:**

I think we would because the performance status is still 2. It's not terrible so I think we would. We would just need to be careful about giving them, maybe not weekly treatment, maybe every other week. I'm not sure, you know, it's selecting between elranatamab and teclistamab. Elranatamab maybe has a shorter hospital stay. I'm not sure if that would be a better option. What do you guys think?

**Dr. Usmani:**

So, Josh, you know, I'm going to ask you, you know, would you treat this kind of patient in the outpatient setting or you would start inpatient and then transition to outpatient?

**Dr. Richter:**

You know, I think the devils in the details. I mean I think if the PET scan showed, you know, a whole bunch of lesions that was really bulky, I would treat the patient inpatient, but if this is simply a serologic relapse, which it's likely going to be, I think that we certainly could treat them as an outpatient. Again, it depends on comorbidities and how much they can tolerate and access to a center that could treat CRS if it up, but definitely reasonable.

**Dr. Usmani:**

Okay, and then Ashley brought up, you know, whether to dose them less frequently from the get-go or start weekly and then go less frequent. How would you do it?

**Dr. Richter:**

So, I actually kind of approach all BCMA therapy, also belantamab, the same way, which is those initial doses I give kind of on schedule. And once we get the response we need, then we back off. So, I would start off with the, you know, weekly dosing. The reason to make sure to, kind of, keep that a little bit is the prior therapies really hasn't had a deep response, never got those CR MRD-negative responses, so I would really try to eke out a CR or better here, if possible, before switching to less frequent dosing.

**Dr. Usmani:**

All right. And then, you know when trying to modify dosing, Ashley, you know, what would be your biggest, you know, concern? You know, suppose the patient is responding, what would be your thoughts around, you know, the less frequent dosing?

**Ms. Steinberger:**

So, less risk for neutropenia and infection would be the reason to back off eventually once they have a good response.

**Dr. Usami:**

And, you know, what's the current dosing schedule for elra at the moment?

**Ms. Steinberger:**

So, this is a typical dosing scheduled of where it's given on day 1, 4, and 8. So, the step-up dose on day 1 is 12 mg and then step-up dose on day 4 is 32 mg. And at MSK they will be discharged, I believe, at this point and they come back for the first treatment dose on day 8 as outpatient, and that's 76 mg. And then, after that, it's given weekly up until week 25, where we will switch to every other week.

**Dr. Usmani:**

So we have become comfortable in dosing patients now on days 1, 3, and then 5. Just like, you know, we did for tec as well, you know, so that we can transition patients out, you know, sooner than later. But we do that, you know, on a case-case basis as well. Josh, are you guys trying to do that as well?

**Dr. Richter:**

Yeah, you know, doses on day 1 and 3, and then 48 hours later, discharged on day 5. And yeah, I think, assuming the patient is stable without active CRS, I think we're all kind of taking that approach.

**Dr. Usmani:**

Yeah, you know, instead of elra with teclistamab, you know, what are your thoughts around the dosing and the step-up period? Ashley, what are the differences and are they going to be any different? Or about the same?

**Ms. Steinberger:**

So, they are similar. So, the dosing is about day 1, 4, and 7 as well, except the patient is in the hospital the entire time and for 48 hours after the 7<sup>th</sup> dose. So, day 1 would be, it's dosed by weight, so 0.06 mg/kg and then day 4, second dose, is 0.3 mg/kg, and then the first treatment dose is given on day 7, and it's 1.5 mg/kg. That continues as weekly as outpatient after that. So after day 7 they keep them in the hospital for about 48 hours to monitor for CRS. And if no CRS and they're stable, they discharge 48 hours after day 7. Also, it's been updated that patients who have maintained a CR or better after 6 months, that we will reduce dosing to 1.5 mg/kg every 2 weeks. So, this is the standard dosing, but also step-up doses can be administered between 2 to 4 days after the previous dose, given that the patient is stable and maybe given up to 7 days after the previous dose to allow for resolution of any adverse reactions.

**Dr. Usmani:**

Josh, what has been your clinical experience with CRS and ICANS in patients who are receiving bispecific antibodies?

**Dr. Richter:**

So, as far as CRS, it seems that most people get it. The majority is grade 1 and grade 2 and I think a lot of this has to do with your tocilizumab approach. At Sinai, the minute you spike a figure with grade 1, we pounce on you with toci. I've spoken to other myeloma experts who have used the phrase, "We let them sizzle a little." I'm not a fan of letting people sizzle. And then once they get toci, they tend not to have anything else in terms of CRS after. ICANS though, you know how the rates are very low in the clinical trials, I have to be honest, it's been a little bit higher on clinical practice, and I think this is related to an overall higher burden disease, sicker patient that we're treating, which standard of care bispecifics then what was done in some of the clinical trials. But still, overall, grade 1, grade 2, most of this is managed across the board. You know, tocilizumab and/or steroids for CRS. For ICANS, usually steroids and occasionally needing to use anakinra. And, you know, I think if we look at, you know, the trial data, we'll see that, you know, CRS was, you know, the majority of patients, but you know, almost no grade 3 or 4 CRS and really no grade 3 or grade 4 ICANS.

**Dr. Usmani:**

So, Ashley, as your patients start the treatment with elra, what principals should inform infection prevention?

**Ms. Steinberger:**

So, these kind of remain the same, as far as I know, with teclistamab and elranatamab. So, there are a lot of things that we do, kind of, to mitigate infections and decrease the risk. So, first is, just education for the patient and letting them know that they will be at a higher risk for infection, so tell them, you know, be more careful in certain situations, in crowded areas, wash their hands frequently, things like that. So, just kind of neutropenic precautions. We also, if they are neutropenic, give growth factor, like Neupogen or Neulasta, to help combat that. We will give PJP pneumonia prophylaxis. So, whether it's Bactrim or atovaquone or pentamidine, they'll receive one of those to make sure they don't develop PJP. We also will give them acyclovir to prevent shingles reactivation. We monitor hepatitis B as well, and if they have a positive core antibody, we will likely give them entecavir to prevent reactivation of hepatitis B. Also, we monitor CMV levels to make sure there's no activation of CMV. And lastly, most patients on teclistamab or elranatamab will have to go on IVIg and have close monitoring of IgG levels.



**Dr. Usmani:**

So, to summarize the key points from this section, bispecific antibodies as monotherapies are efficacious in relapsed/refractory multiple myeloma. We are seeing early, deep, and durable responses, and these therapies are off the shelf. So, you know, whether it's a clinical or a biochemical relapse, you know, they're easily accessible for us to utilize in our clinical practices. Overall management strategies, you know, that may mitigate CRS and ICANS are important, so early recognition is the key. Tends to happen, you know, during the step-up dosing or the first dose of treatment. But what's encouraging is that unlike CAR-T cell therapies, most of the events are grade 1 or 2, and ICANS, you know seldom happens with, you know, any of these products. So, vigilant monitoring, prophylaxis, and treatment can prevent infections. And, you know, Ashley rightly highlighted the VZV and PGP prophylaxis strategies and for patients for, you know who may require, you know, entecavir for hep B core antigen positivity, these antiviral and antimicrobial strategies need to be continued throughout the treatment. And for patients developing hypogammaglobulinemia, IVIg replacement is strongly encouraged for all patients.

Let's move on and discuss how to optimize the use of GPRC5D-directed antibodies. So, let's take, you know, essentially, a similar kind of a case. So, we have a patient who is 74 years. They have a good performance status with an ECOG of 1. So, in terms of treatment history, patient got VRD as induction, then transplant, and then len maintenance. And then 3.5 years later the disease was relapsing, so they were switched over to daratumumab with pomalidomide and dexamethasone, remained in a duration of response of about 18 months or so. VGPR was the best response even with this line of treatment. Then patient went on to have another relapse, and received carfilzomib with cyclophosphamide and dexamethasone as their next line of treatment before progressing 1 year later and then being placed on selinexor and dexamethasone for about 4 months before progressing and then received a BCMA-directed CAR-T cell therapy. They remained in response for about a year before progressing and they're now considered for GPRC5D-directed antibodies with talquetamab.

So, Josh and Ashley, assuming the patient starts talquetamab, what are the unique side effects that we would need to discuss with the patient? Josh, maybe we can start with you first.

**Dr. Richter:**

Sure. So, you know, anytime we're talking about any targeted antibody-based therapy, the question is always, "Where else is that target expressed other than the malignant plasma cells?" And for GPRC5D we know, besides plasma cells, it's expressed on the squamous epithelium of the hands and feet, so dermatologic side effects are something we note. The desquamating rash that people can get actually reminds me of Xeloda back when we used to use more Xeloda, back in fellowship for me, and then some nail-related issues, where the nails can become brittle, even fall off, or become discolored and have ridging. The other thing is that GPRC5D is expressed in the oropharynx and salivary glands, and dysgeusia, weight loss, anorexia. These are really the big issues that we see. You know, I think there's a lot of work ongoing to figure out the optimal mitigation strategies. Right now, it's you know, working with a nutritionist, small frequent meals, making sure that things like artificial saliva to help with making sure that dry mouth is not an issue. And then there's a lot of ad-hoc experimentation, you know, lemon and sour or MSG or oral dexamethasone washes.

I would love to know, Ashley, if you have any tips and tricks that have worked particularly well for you with your patients.

**Ms. Steinberger:**

So, for the skin-related changes we see a lot of, as Josh had said, peeling of the hands and the feet. So, they do suggest that the patients can use ammonium lactate 12% cream twice a day. And then, also, patients can have more of a generalized rash and if there's a change, they may need to apply some triamcinolone. Also, you know, just adding in any thicker-based ointments, like Eucerin or Vaseline can help hydrate the skin. And oral antihistamines of course can be used if there's any generalized itching as well. With nail-related changes, as we stated prior, they can fall off, they become very brittle, they can have nail pitting, or separation from the nail bed. And this usually can start around cycle 2 and last, from what I see, for most of the time that they're on the medication. They should avoid long, frequent durations of water immersion, and can also apply Vaseline or Aquaphor, vitamin E oil, nail hardeners, and then Biotin can also help with nail growth and hardening, and then also just filing the nail edges to be more smooth.

And then another side effect that they can get is dysgeusia and xerostomia. So, dysgeusia is the change in taste that people can have, and this is a little bit difficult to combat. So usually, dose modifications in the drug, reductions or delays, or skipping a dose can help with the management of this, and then just telling patients to have things high in calorie and small, frequent meals. So, also you need to monitor nutritional, like vitamins, make sure they're not becoming iron deficient, B12 deficient, folate deficiency. And then xerostomia is dry mouth, which is also, can be seen. Increasing hydration and having water throughout the day to keep the mouth more moist and then also using topical agents like saliva sprays or sugar-free chewing gums or candies to help stimulate saliva flow. And then, lastly, they can use sodium lauryl sulphate-free toothpaste which might be better tolerated than the other toothpastes. But, like Josh said, referring to the dietitian or nutritionist early is encouraged.

And then, we're also going to go over the dosing of talquetamab. Similar to the other medications, there's a standard dosing, but it can be given a little bit earlier if there's no adverse reaction. So, the standard would be giving it on day 1, and it's body weight based so it's 0.01 mg/kg on day 1, day 4 is 0.06 mg/kg, day 7, it's 0.4 mg/kg, and then given weekly thereafter. You would not want to give it earlier than 6 days after the full dosage, the first treatment dose. And it can also have a bi-weekly or every 2 weeks schedule. So similar to the weekly in the beginning, it's 0.01 mg/kg on day 1, 0.06 mg/kg on day 4, and then 0.4 mg/kg on day 7, and then the first treatment dose is 0.8 mg/kg on day 10. And then it's given bi-weekly as 0.8 mg/kg. And in this one you would want to maintain at least a minimum of at least 12 days between the biweekly dosing, but the doses can be administered between 2 to 4 days after the previous dose, if there is not CRS or adverse reactions.

**Dr. Usmani:**

So, the key takeaways from, you know, this section, it's very important to educate the patient to be their own advocate. The best prepared patients as they're starting these new therapies are going to help mitigate and manage these side effects. They need to know what to look for and how to best reach the healthcare team. Preparing patients for possibility of off-tumor on-target effects of talquetamab is very important. So, you know, again, repetition is going to be the key here and patients who know these are common are usually able to cope much better because they can anticipate, you know, what is coming down the pike.

Ashley, any other thoughts to what I have shared?

**Ms. Steinberger:**

Yeah, that's pretty much that it. If they kind of know what to expect, they're going to be able to reach out and ask for help more easily.

**Dr. Usmani:**

Any other pearls of wisdom, Josh?

**Dr. Richter:**

You know the only pearls of wisdom I would say is just ongoing communication with your healthcare team. You know, I think, you know, we have some tools to help mitigate a lot of the side effects of the bispecific antibodies and you don't get extra points for suffering. So reaching out because of a myeloma community, even though these drugs are new, we're all sharing at even events like this, where we share our little tips and tricks about how to make the treatment better for everyone. So open line of communication always.

**Dr. Usmani:**

Absolutely, Josh. I think, you know that's the case, especially in this late relapse setting where our patients may think, "Oh I'm benefiting from this treatment, maybe I shouldn't tell that, you know, this is something happening, you know, I may be taken off of treatment." No that's not the goal. The goal here is to find the right recipe, the schedule and then help manage your, you know, side effects as they come along. And the sooner we know about them, you know, the more time we have to actually come up with a game plan with you.

So this concludes our discussion entitled Bispecific Antibody Horizons, Dosing Strategies and Meeting Updates in Multiple Myeloma Care. Thank you for joining us. Please make sure to complete the evaluation. This information will help guide the development of future educational activities and resources.

**Announcer:**

Thank you for listening to this episode of Myeloma Matters on the latest data on bispecific antibody therapy hosted by the Multiple Myeloma Research Foundation. We would like to thank Dr. Saad Usmani, Dr. Joshua Richter, and Ashley Steinberger, for sharing their insights on bispecific therapy for myeloma treatment. The Multiple Myeloma Research Foundation also thanks Johnson & Johnson and Pfizer Incorporated for their support of this educational podcast. If you have questions about anything you have heard today, please call the Multiple Myeloma Research Foundation Patient Navigation center at 1-888-841-6673 for more information.

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