**Myeloma Matters: A Podcast Series from the Multiple Myeloma Research Foundation**

**Episode: *Prevention and Management of Bispecific Antibody–Associated Adverse Events in Multiple Myeloma***

> ***Amy****: The other thing that I think that is important to bear in mind …[the] patient's point of view –and their own mental management of the rollercoaster ride that we [all] go through with this disease [and] that a lot of times it's all relative. Like, "How do I feel about these side effects right now as relative to what other side effects I've had in the past and how bad they felt at the time?" [Currently] this feels better than the last drug that I was just on because the side effects of that felt more severe to me. …This feels more tolerable to me. …Based on our responses from previous treatments and how soon that last round of bad side effects [was]… affects our mental psyche while trying to manage current treatment*

**Narrator**: Welcome to the *Myeloma Matters* podcast, hosted by the Multiple Myeloma Research Foundation and focusing on topics related to improving outcomes for myeloma patients.

In this podcast, we'll examine the role of bispecific antibodies in relapsed/refractory multiple myeloma and strategies for recognizing, preventing, and managing bispecific antibody–associated adverse events.

This podcast is based on a roundtable discussion between Dr. Jesus Berdeja, Director of Multiple Myeloma Research at Tennessee Oncology; Dr. Ajai Chari, Director of the Multiple Myeloma Program and Professor of Clinical Medicine at the University of California in San Francisco; and Nick Barkemeyer, a physician assistant at Tennessee Oncology. Drs. Berdeja and Chari will review the clinical efficacy and safety of approved and emerging bispecific antibody therapies. They'll also look at a sample case to explore patient and disease considerations when sequencing therapy for patients with relapsed/refractory multiple myeloma. Nick Barkemeyer will provide his perspective on the role of advanced practice providers in administering bispecific antibody therapy. We'll also hear from myeloma patients Amy, Harvey, and Steve, who will describe their personal experiences with bispecific therapy.

The topics we'll cover in this podcast are clinical advances in the use of bispecific antibody therapy for patients with relapsing and refractory multiple myeloma; recognizing and managing common and potentially serious adverse events; and the future of bispecific and similar antibody therapies in the management of difficult-to-treat multiple myeloma.

Bispecific antibodies—or bispecifics—are bifunctional T-cell–engaging antibodies. The unique feature of bispecifics is that they can target two cell surface molecules at the same time—one on the myeloma cell and one on a T cell. Although many different bispecifics are in clinical development, three have been approved for the treatment of refractory multiple myeloma. Two are B-cell maturation antigen or BCMA-targeted

bispecifics and one targets GPRC5D, another epitope found predominately on the surface of myeloma cells.

First, let's take a look at the BCMA-directed bispecific antibody therapies approved for the treatment of relapsed or refractory myeloma.

**Clinical Advances in BCMA-Directed Bispecific Antibody Therapy**

Bispecific antibodies that target BCMA on myeloma cells are from a promising class of agents in the management of relapsed/refractory multiple myeloma. BCMA is highly expressed on myeloma cell membranes. Two BCMA bispecifics, teclistamab and elranatamab, have been approved by the FDA for weekly subcutaneous administration in the treatment of relapsed and refractory patients.

In clinical studies, BCMA bispecifics have shown impressive response rates in heavily treatment patients.

> ***Dr. Chari****: These are relatively large, single-arm studies with over 100 patients heavily treated with a median of five lines of therapy and essentially 80% to 100% triple-class refractory. And what we're seeing strikingly across all of the BCMA assets is this response rate of around 60% at the recommended phase II dosing. The progression-free survival is really so impressive for an off-the-shelf product with such heavily treated disease.*
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> *We're seeing PFS anywhere from 12.5 to 17.2 months, and we already have some encouraging [overall survival] OS data for teclistamab because it has a little bit longer follow-up of 22 months and a really very impressive duration of response of 24 months.*
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> *… I think this is really what's so exciting for these off-the-shelf products because we know there's also CAR Ts out there that are also targeting BCMA, but for an off-the-shelf product to be giving these kinds of results it's great.*

BCMA bispecifics are not without the risk of potentially serious side effects, however.

> ***Dr. Chari****: …as a class, all the bispecifics I would say not just in myeloma but in lymphoma have the cytokine release syndrome, which is when the T cells are activated and can create symptoms such as fever or in higher grades hypotension, hypoxia.*
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> *Fortunately, with bispecifics in myeloma they generally tend to be low grade and you can see 60% to 70% all-grade, but very, very few high grade, three or more in BCMA bispecifics, Infections is a big one here. We're seeing all-grade infections of about 70% to 80%, including high-grade infections of 40% to 50%.*

Cytopenia is another potentially concerning adverse event of BCMA bispecific therapy. Clinical studies show that cytopenia affects 50% to 70% of patients overall, with 50% to 60% of these being high-grade events. Yet many cytopenias tend to emerge during the first cycle of bispecific therapy, when the patient is being debulked of the disease.

Harvey—one of Dr. Berdeja's myeloma patients—responded well to bispecific therapy. Harvey was diagnosed with multiple myeloma in 2021. It initially presented as a 5-cm tumor on his femur. He was treated with several therapies, each of which eventually failed, including the proteasome inhibitor carfilzomib and the CD38-targeting monoclonal antibody daratumumab. With few options remaining, Harvey was enrolled in a clinical trial for treatment with the BCMA bispecific teclistamab.

> ***Harvey****: in August of' 23, I finished my first 6-month cycle, had a PET scan. No issues, no new tumors, no active cancer. Dr. Berdeja considers me in deep remission—or, deep response is what he calls it. And so, that has really been the case since, probably three or four weeks after I had my first full dose of teclistamab. The tumor goes away literally within a couple of weeks.*
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> *…I have not had really any kind of side effects outside of just fatigue… And that has just been something that's followed me since I started the journey back in '21.*

Steve, another of Dr. Berdeja's patients, was first diagnosed with multiple myeloma in 2012. He ended up on BCMA-targeted bispecific therapy after several lines of therapy failed, including proteasome inhibitors, anti-CD38 monoclonal antibodies, immunomodulatory agents, and CAR T.

Steve epitomized the type of patient who may be a prime candidate for BCMA bispecific therapy and the type of reactions that typically follows. He was started on a clinical trial to receive elranatamab but was warned by his physician to be prepared for the possibility of potentially serious side effects.

> ***Steve:*** *He [the physician] said  he basically said, "You know all those terrible things that happened to you during the CAR T?" And I said, "Yeah." "Well, it's that but less. And so—and it shouldn't be anywhere near as bad. But there's a scale-up dose and reactions tend to happen in those scale-up doses and—but you'll be in the hospital for observation. And then, if you have a reaction then we treat it." "Okay." Of course, he said almost the exact same thing for the CAR T.*

Fortunately, the side effects from elranatamab were relatively mild.

> ***Steve:*** *Yeah, it was not bad. It's—I had quite a few different symptoms but none of them lasted a long time or were extremely, extremely severe. My biggest complaint about the whole ride is the dexamethasone pretreatment—because I'm a diabetic, so it kind of spikes your blood glucose, makes it hard to manage—it gives you insomnia and then that makes you irritable. The good thing about it was, is after the third dose I was kind of pushing "When can I get off the Dex?" And they said, "Oh, okay. Today."*

But Steve did experience fever, chills, and fatigue, which are possible signs of cytokine release syndrome.

> **Steve:** *My reactions were not the first night but the second night, and that happened [also] to me on the second dose. It was kind of odd. They kind of started right around—both times about sundown as the sun's going down, the*

*room's cooling off, and I would get chills and shivering and a fever that … night, the second night after the ... dose. [After the first dose, I had] a fever of 100.9℃. And I think they gave me steroids and the night nurse stayed with me two or three hours getting that under control. But then it was under control and I went to sleep. But it did smooth out pretty quickly. So, they use the ice packs and things like that.*

*I've been more fatigued and—I don't know if you would call it malaise… Well, one, you're getting some Benadryl, so you're sleeping and that sort of thing, but you're kind of—you're more fatigued usually that day of injection. It's not exactly like getting the flu once a week– probably not that bad.*

During therapy, Steve also showed evidence of cytopenia.

***Steve:*** *My last IG level was in the 300s…and low normal is about 600 or something. And so, they said, "This would be a good idea [to receive IVIG]. My other blood counts are somewhat depressed than what they were, but not much from what they were before I started. And so, what I really like is—on almost every other kind of treatment I had before CAR T—is that I would have trouble maintaining levels of neutrophils. And so, my neutrophils are low normal right now and my blood counts are borderline normal.*

Thus far, Steve has responded well to elranatamab, and his adverse events have been relatively mild and not dose-limiting. Steve has not experienced any notable infections, perhaps because during his course of treatment, he received prophylactic antibiotic treatment.

**Clinical Advances in GPRC5D-Directed Bispecific Antibody Therapy**

GPRC5D is a relatively recently identified target for the treatment of refractory multiple myeloma. Currently, talquetamab is the only GPRC5D-targeted bispecific currently approved by the FDA. Not much is known about the function or signaling of the GPRC5D protein receptor, but it is overexpressed on myeloma cells. It is also heavily overexpressed on keratinized tissues such as nails and to a lesser extent in hair follicles, setting the stage for possible dermatologic side effects. Importantly, GPRC5D expression is independent of BCMA, and this difference has ramifications for sequencing the use of bispecific therapies.

Talquetamab efficacy was demonstrated in the MonumenTAL-1 study, which provided the basis for its approval. This study included a heavily pretreated population, with a median of six previous lines of therapy. Talquetamab was administered subcutaneously on a weekly schedule at doses of 0.4 mg/kg weekly or 0.8 mg/kg every 2 weeks. Progression-free survival was impressive, ranging from 7.5 months at the lower dose to 14.2 months at the higher dose.

***Dr. Chari****: And in this heavily-treated population we're seeing a single-agent activity of over 70%. And I think many of us are using the every-two-week dosing,*

*because there's quite a bit of difference, what we see in the PFS 7.5 versus 14.2 months.*

*Now, again, we always say avoid cross-study comparisons, but we do think based on emerging data that perhaps the less frequent dosing might not only be more convenient for patients, but it may also be associated perhaps with less T-cell exhaustion. And so, I think many of us are doing that every-two-week dosing. Although there is that option of weekly dosing, we don't have a median duration of response.*

In one cohort of this study involving 51 patients who had either prior CAR T or bispecific therapy, 65% achieved a response with talquetamab therapy. However, patients who had prior CAR T therapy had a 75% response rate compared with only 44% for patients who had prior therapy with a bispecific antibody.

***Dr. Chari**: This third cohort is really interesting because one of the unmet needs…is patients who've had prior T-cell redirection. … So, I think this may be shedding some light on the fact that when you give somebody a bispecific their T-cells may be exhausted. And if possible, it may be good to have some interceding therapy before going to yet another bispecific, if possible, recognizing that sometimes we don't have that option.*

***Dr. Berdeja**: We're left with really the decision of which one do we use first and how do they work one after the other? And I think the data, as you pointed out, is showing us that it does matter.*

For talquetamab, side effects are similar to what is seen with BCMA bispecifics in terms of the risk for CRS. After a follow-up period of up to one and a half years, the incidence of CRS ranged 75% to 80%, but most cases were considered low grade and manageable. Only a small percentage of these cases, about 2%, were considered serious. Infections also were common, affecting about three quarters of patients overall. And about a quarter of these infections were considered serious. However, over time the infection incidence appeared to decline. In addition, neutropenia affected half the patients overall, with the highest risk in the prior T-cell redirection cohort—the most heavily pretreated group.

***Dr. Chari:** This drug does have unique toxicities, which are important to discuss. Perhaps this is less dirty in terms of the B-cell expression and maybe that's why we're not seeing as much of infection. Even the hypogamma signal seems to be lower or less IVIG. So, that infection signal is less, but we have other AEs that we need to discuss, and this likely has to do with the GPRC5D expression on other tissues. So we know that dysgeusia, or loss of taste, can be as high as 70%. And admittedly, I think we've done a poor job of characterizing this because NCI CTCAE criteria only have a grade one and two. There is no grade three and four. And we need to have more granularity in the patient experience for this. But this can also be associated with dry mouth difficulty, swallowing.*

Skin and nail disorders affected about two thirds of patients in the MonumenTAL-1 study. Skin reactions were divided into two types and were usually quite manageable. Rashes

tended to emerge early in treatment and then disappear, and palmar/plantar peeling—a side effect unique to talquetamab—occurred throughout treatment. Although nail reactions like fragility or nail loss were common in the MonumenTAL-1 study, none of these adverse events were considered severe.

Oral toxicities such as dysgeusia, ageusia, and hypogeusia, as well as weight loss have been reported in the MonumenTAL-1 study and other clinical trials. Dose modifications of talquetamab allow patients to continue therapy to maintain clinical benefit while potentially reducing the severity of dysgeusia and other oral events based on investigator experience. Nutritional monitoring, such as for iron deficiencies, should be undertaken with appropriate supplementation. High caloric shakes should be considered to ensure adequate nutritional intake and to prevent weight loss due to dysgeusia or other oral events.

With GPRC5D-targeted therapy, dysgeusia and skin reactions should be anticipated by the physician and patient and managed as effectively as possible. Interestingly, patients who experienced palmar/plantar peeling and dysgeusia actually had a 20% higher likelihood of responding to talquetamab therapy.

Amy is another patient of Dr. Berdeja's who is currently receiving treatment for multiple myeloma. Like the other patients we've discussed, Amy has gone through multiple lines of therapy, including CAR T and teclistamab. Amy may typify what can be expected with talquetamab therapy in terms of side effects for patients who have had previous T cell–redirection therapy.

> ***Amy**: I think—yes, I felt that it [the CRS reaction] was [easier than with CAR T] because … it was a shorter duration. And also, having had it before, I … knew what to expect. And with the step-up dosing I was in the hospital already for observation, so I knew that the nurses, one, knew exactly what to do and how to handle it and were there and could react to it very quickly.*
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> *But beyond the CRS I've had dry mouth; I've had mouth sores. I've had—I did lose my taste. [But]not 100%. There are a few things that I can get a little bit of flavor from but for the most part there's no taste. I have not lost my appetite though, so for me, weight loss on this drug has not been a problem. I've had some issues with my nails but not awful. And I had issues with bloody noses which probably related more to my low platelets than [this drug]. And I had some randomized bone pain that was fairly severe, only happened for a couple of weeks, a couple of times, but it was in my thighs and my shins and my hips. …With a small dose of dexamethasone, I was able to resolve that pretty quickly. And then it stopped. Once the cancer was under control, a lot of those side effects reduced or stopped.*

**Consideration for Selecting Bispecific Antibody Therapy for RRMM Management**

Let's take a look at some of the considerations for choosing a bispecific to treat resistant multiple myeloma. We'll start by examining the case of a 70-year-old man with rapidly progressive multiple myeloma. His ECOG performance status was two at the most

recent progression. This patient has had multiple prior lines of therapy, including daratumumab, the proteasome inhibitor bortezomib, and an immunomodulator—followed by a stem cell transplant and lenalidomide maintenance therapy.

The patient relapsed and received elotuzumab, a humanized IgG-1 monoclonal antibody that specifically targets the SLAMF7 protein, the immunomodulator pomalidomide, and dexamethasone. This regimen produced a partial response that lasted for about six months. Subsequent therapy included the proteasome inhibitor carfilzomib and dexamethasone. Again, only a partial response was achieved, which lasted for about 4.5 months. Isatuximab, an anti-CD38 monoclonal antibody, was then added to the carfilzomib-dexamethasone regimen. It induced a response, but it lasted only three months.

The patient's disease is progressing quickly. The question to be answered now is, Should we consider immediate bispecific antibody therapy or initiate bridging therapy for CAR T-cell therapy?

> ***Dr. Chari****: …I think the important message is that if you're at all considering this you should refer, right? Ideally, if there's somebody who's CAR T-eligible, don't preclude them from getting a CAR T by doing a treatment. So, it's good to have that collaborative discussion before you either include or exclude a patient from CAR T.*

In this case, the most important consideration appears to be the pace of the disease. The main difference between these treatment options is that CAR T therapy will not be immediately available without bridging therapy, and the patient's disease may be progressing extremely rapidly. CAR T therapy has a vein-to-vein time—that is, the time from T-cell collection to the time when the CAR T cells are ready for infusion into the patient. This delay may have consequences for a patient like this, where the myeloma is progressing rapidly.

Unlike bispecific therapy, CAR T is not off-the-shelf. In our case example, speed of treatment may be of the essence, and the manufacturing time for CAR T therapy for this patient may be totally incompatible with the pace of his disease, leading to a poor outcome or even death.

> ***Dr. Chari:*** *In somebody like this where the vein-to-vein time may be totally incompatible with the pace of the disease, the CAR Ts can lead to worse outcomes or even deaths by the time patients get to CAR T.*
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> *So, I think it really highlights where bispecifics really need to be, which is rapidly progressive disease is really the standout for this off-the-shelf class.*

Another consideration is the difference in adverse event profiles between CAR T and bispecific therapies. For all T cell–redirection therapies, including CAR T, we have limited safety data for subgroups such as frail patients, older patients, and patients with comorbidities such as renal failure and heart failure. In the absence of data, bispecific antibody therapy may be a better option because the treatment can be stopped if the patient develops a serious adverse event.

> ***Dr. Chari:*** *And I think the concern is with the CAR Ts you kind of have this—their amazing efficacy but you don't get to pull back or stop the drug. Once you've given it you lose all control over the AE profile and just—it's the hope and prayer approach. And yes, you've got to manage the AEs as much as possible. The beautiful thing about bispecifics [is that] if you have an AE that's challenging, you just stop the drug and then you have some breathing room. Because when you're getting a high-grade CRS, for example, with a CAR T, you can't go back. [0:20:00] But if you're seeing somebody with CRS or even HLH or something like that, you just don't have to give the next drug.*
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> *So, I think that's, I think, an important differentiating factor.*

For older, frail patients, and patients more susceptible to drug side effects, a case can be made for the use of bispecifics over CAR T therapy. It should be kept in mind, however, that patients who have had prior T cell–redirection therapy tend to be sicker, so the addition of a bispecific may yield a less robust therapeutic response.

> ***Dr. Berdeja:*** *I think with the older patient, the more frail patient, bispecific is probably the way to go, but I would like to remind the audience that that older patients can do very well with CAR T. And actually there's some data showing that the age alone is not does not lead to more adverse effects or worse outcomes with CAR Ts. It's probably more about frailty and about ~~…~~ organ function, like you mentioned before. And I will mention also that I think that kidney function is important.*
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> *So, remember with CAR Ts we have to give lymphodepleting chemotherapy, especially fludarabine, which…does require adequate renal function … to minimize toxicity and for clearance. ~~…~~ I think that is probably the most salient organ dysfunction that would sway me potentially to go to a bispecific versus CAR T.*

There is a concern in the myeloma treatment community about giving a bispecific before CAR T because a lot of the benefits are lost. The effects of sequencing CAR T and bispecifics are still under investigation. For bispecifics, mature clinical data is not available, but the data we do have shows that the response rate for teclistamab, which is 63%, does not decline much if patients received prior CAR T or antibody-drug conjugate therapy. Optimally sequencing T cell–redirection therapies is critical; however, the best available therapy should be offered to the patient based on practical considerations such as drug logistics, access, and availability.

> ***Dr. Berdeja****: Just to get back to our case, as a reminder, we have a 70-year-old man with rapidly progressive multiple myeloma with four prior lines of therapy, a prior PI IMiD and an anti-CD38 antibody. So, this patient is a candidate for both CAR T and bispecific. ~~…~~ I suspect I know what Dr. Chari would use here first, but I'll let him tell us what he would use, either CAR T or bispecific, in this particular scenario.*
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> ***Dr. Chari****: Probably given the pace of disease I think a bispecific. And maybe because we don't want to completely close the door on a BCMA CAR T down the*

*road, maybe start with the non-BCMA. But I think you could easily justify doing the other order as well.*

**Mitigating Cytokine Release Syndrome During Bispecific Antibody Therapy**

Cytokine release syndrome is a common reaction associated with T cell–redirection therapies and is characterized by hypersecretion of pro-inflammatory cytokines, which leads to activation of bystander immune and non-immune cells as monocyte, macrophages, dendritic cells, NK and T cells, and endothelial cells. These cells further release pro-inflammatory cytokines, triggering a cascade reaction. CRS symptoms may occur immediately after the administration of T-cell-engaging therapies or may be delayed until days or weeks after treatment. CRS can manifest as mild, with flu-like symptoms like fever, nausea, and chills, or it may be life-threatening and severe with shock and respiratory compromise, leading to multisystem organ failure and even death The question naturally arises, What strategies can be considered to mitigate CRS during bispecific antibody therapy?

All T-cell-engaging therapies have a risk evaluation and mitigation strategy or REMS programs in their label. These programs require procedures to lower the risk for CRS, such as administering gradual step-up dosing instead of initially administering the full dose. During the up-titration phase, patients are hospitalized so they can be monitored for side effects like CRS.

In addition, reduced overall drug exposure may be another step toward reducing the risk for CRS and other adverse events.

> ***Dr. Chari****: Some of the current products are all given till [disease] progression, but there's great interest in fixed duration of therapy because if these remissions are so deep and durable, do we need to keep treating or can we give people breaks?*

For T cell–redirection therapies like bispecifics, CRS is the adverse event most prescribers fear, especially if they do not have experience with this reaction. But it should be kept in mind that these events, though frequent, are typically low-grade and occur early in therapy. Once the first course of therapy is completed, CRS is rarely encountered.

> ***Dr. Chari:*** *CRS is really in that priming phase, and after you finish the first cycle these patients can do very well in the community. And the other point I would make is I think we're today talking about myeloma bispecifics, but if you zoom out, take the 1,000-foot view, this is the wave of the future.*
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> *I remember the skittishness when we had the first monoclonal antibodies like rituximab and daratumumab and now, in the words of Fergie, those are 2000 and late.*
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> *So, if people don't jump on board, this is really going to affect access to therapies because the bulk of oncology patients are not treated at academic centers and we need community practices to get on board with these quickly so that*

*everybody can benefit, because I think bispecifics are the new monoclonal, and it's just going to increase across diseases.*

CRS occurring with bispecific therapy, though common, can be quite variable. Let's hear from Amy once more, this time regarding her experience with CRS.

> ***Amy****: And we all react differently, each of us patients, so I might not get all of the side effects but I could get a number of them. I wasn't fearful of most of them. Cytokine release syndrome can be concerning but I had been through it with … CAR T and I knew how well the team was able to respond to that and pull me out of it, so I didn't have any fear of those.*

Amy did experience one episode of CRS when initially treated with talquetamab.

> ***Amy:*** *I did have one day of it and I think it was only grade one whereas the CAR T was grade two. With the CAR T, I had to have two doses of the [immunosuppressive] tocilizumab. With the talquetamab I got one dose of tocilizumab and some dexamethasone as part of the treatment. And that…resolved it within a day.*

**Mitigating Infections During Bispecific Antibody Therapy**

Infections are another concerning and common set of adverse events associated with bispecifics. There are three basic strategies for managing bispecific-associated infections: the first is decreasing treatment intensity. In one single-arm study, patients who maintained weekly teclistamab dosing had a 33% risk of getting a new-onset severe infection. However, when the dosing frequency was switched to every two weeks in treatment-responsive patients, the incidence decreased to about 16%, with no loss of treatment response. This finding has yet to be confirmed in a randomized trial, but it implies that decreasing dose intensity can be a reasonable approach for reducing infection risk in patients who respond to the initial regimen.

The second strategy for managing bispecific-related infections is supportive care with intravenous immunoglobulin or IVIG.

> ***Dr. Chari****: Our work from Mount Sinai shows that the role of IVIG in reducing [serious] grade three to five infections was about 80% if you look at the rates of infections when patients were on IVIG versus not. And if you look at specifically high-grade bacterial infections, it's almost a 90% reduction. And this data set was also replicated by our colleagues in Europe*.

Prophylactic antibiotics and antivirals represent a third strategy and are a must when patients are treated with bispecifics to prevent not only common infections but uncommon infections such as *Pneumocystis* pneumonia, herpes simplex, and cytomegalovirus.

These strategies have helped ensure that patients can remain on therapy while minimizing the rates of high-grade infections associated with bispecifics. However, as Dr Chari noted earlier, a brief pause in bispecific antibody therapy is another strategy for managing treatment-related side effects.

> ***Steve****: What I heard was most people have to stop treatment because they get an infection or something. [0:25:00] …That's why I'm taking the Bactrim and—and I really—I've been still circulating with friends and family and things like that.*

Nick Barkemeyer, a nurse practitioner and a colleague of Dr. Berdeja at Tennessee Oncology, offers this perspective on preventing infections in patients receiving bispecific antibody therapy:

> ***Nick Barkemeyer****: …I obviously tell the patients, especially in the beginning, it probably is in your best interest to avoid large crowds. I emphasize good hand washing and just hygiene in general. I explain that we can give growth factors for things like neutropenia. Obviously, you guys touched on the IVIG earlier in the discussion and the need for that. And obviously, that's sometimes an ongoing battle with the insurance company but hopefully that's becoming easier as time goes on here. We talk about being immunized. Obviously, COVID-19 prevention. Prophylactically being treated for herpes, Zoster, and PJP. And then, monitoring the patient's CD4 count too, just as we do in our CAR T patients.*
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> *…I agree. All those are great points. One thing, if at all possible, if patients can get immunized before they start the therapy, that would be advisable, as response to vaccines after starting some of these therapies is not great. It's not always possible, but when it is I think it's a good—good to remember.*

**Mitigating GPRC5D-Directed Bispecific Antibody Therapy-Related Adverse Events**

Let's examine the unique side effects linked to GPRC5D-directed bispecific antibodies like talquetamab. Because the GPRC5D epitope is also expressed in the skin and keratinized tissue cells, talquetamab treatment is associated with a unique set of adverse reactions, including dysgeusia, skin toxicity, and nail dysmorphia.

Let's turn to Amy once again, who had her own experience with side effects due to talquetamab therapy.

> ***Amy:*** *…I'd say the first six weeks of the treatment were pretty tough and I really didn't feel well, but then all of a sudden it seemed like week seven or eight a light switch went off and my energy started coming back and I just felt so much better. And so, I feel really good right now and I feel like I've got my quality of life back. And so, yeah, it took me six, seven weeks to get there but it was definitely worth it.*

Again, with talquetamab, reductions in treatment intensity—either the dose or the dosing frequency—can reduce the risk of these adverse events while maintaining efficacy. Clinical study data shows that decreasing the starting dose of talquetamab from 0.8 mg/kg every two weeks to 0.4 mg/kg every two weeks or from 0.8 mg/kg every two weeks to 0.8 mg/kg every month maintained efficacy while reducing the risks for skin, oral, and nail toxicity.

> ***Dr. Chari****: I think the starting dose is important because we are not getting 100% response rates. We do need to capture the disease. These are very, very sick*

*patients. But once that disease is captured, perhaps we have the luxury now of backing off on the dose intensity. And that's the same theme for BCMA- and GPRC5D-directed bispecifics—that would be my take-home message.*

Dermatologic side effects such as rash or peeling tend to be mild and can usually be managed with topical creams.

Here's Nick Barkemeyer sharing his experience with managing dermatologic adverse events.

**Nick Barkemeyer**: *…when it comes to the skin, if they develop a rash or we have kind of the peeling going on, it's usually relatively benign. Some people will say that it's itchy. I've never heard anyone say that it was painful, but I kind of say that "Okay, well this is hopefully a self-limiting process."*

*We can send in something like triamcinolone cream, and I encourage them to use good over-the-counter moisturizers to keep their skin nice and moist. Kind of the same thing with the nails. It's mostly an aesthetic complication. But there are some products out there… that you can apply to your nails to hopefully try and keep them from splitting or sloughing off, so to speak. And then, when it comes to taste, obviously all the difficulties with swallowing and the dry mouth and the dysgeusia, that kind of goes hand in hand with weight loss, though they can be independent of each other as well. But that's probably the one that affects their quality of life the most. And so, using supportive measures is key.*

Oral side effects may be managed with over-the-counter sodium chloride mouthwash and artificial saliva spray. If taste issues disrupt normal food intake, patients and clinicians should be sensitive to weight loss and take steps to ensure good nutrition through therapy. For patients with taste disturbances, it may be helpful to encourage patients to set reminders to eat and hydrate regularly. Nutritionist consultation should be considered at talquetamab initiation to provide nutritional support throughout treatment and to encourage active patient and caregiver engagement in the management of oral events affecting diet and food consumption.

Here are Nick's and Amy's insights on managing dry mouth and dysgeusia.

**Nick Barkemeyer**: B*efore you started, I said make sure that you have a good mouthwash on hand. Make sure that you're using hard candies to promote salivary production. And eat whenever you can that's gonna give you calories, because that's really the most crucial thing, is just getting nutrition of any kind. Protein is great, but when you're just trying to keep weight on anything will suffice until it hopefully plateaus out.*

***Amy:*** *Yeah, absolutely. And we also talked about eating saucy foods, something that has more moisture, because I've found that protein is the toughest part. You have to really chew it a lot in order to be able to swallow properly.*

**Role of APPs in Helping Patients During Bispecific Antibody Treatment**

Now let's look at the role of advanced practice providers in the care of patients with myeloma receiving bispecific antibody therapy. The primary role of an APP is helping

with patient education and informing patients about what to expect while on this form of therapy.

In addition, APPs are involved in monitoring the patient's response to treatment through laboratory testing and checking for the emergence of adverse events. APPs also coordinate with other health care providers such as oncology nurses, social workers, and palliative care specialists to provide comprehensive supportive care services aimed at optimizing treatment outcomes and patient quality of life and well-being.

> ***Nick Barkemeyer****: I feel like our primary role in the process of these bispecific patients is to help with things such as education and just informing them on what's on the horizon while they're on this therapy. Some of the symptom management and supportive care that we get into is how do we address things such as pain, fatigue, nausea, neuropathy, and other side effects.*
>
> *We're also monitoring their response to the therapy…through lab testing, through imaging studies, clinical symptoms to kind of help us track the disease and assess the efficacy. And then, of course, … we're collaborating with physicians and the nurses… to be involved in the process to kind of help these patients along the way in their journey.*

Amy highlights the importance of understanding the patient's perspective, an important role for an APP.

> ***Amy:*** *The other thing that I think that is important to bear in mind …[the] patient's point of view –and their own mental management of the rollercoaster ride that we go through with this disease is that a lot of times it's all relative. Like, "How do I feel about these side effects right now as relative to what other side effects I've had in the past and how bad they felt at the time?" And so this feels better than the last drug that I was just on because the side effects of that felt more severe to me. And so, this feels more tolerable to me. And so, based on our responses from previous treatments and how soon that last round of bad side effects … affects our mental psyche while trying to manage current treatment.*

Harvey points out how APPs prepared him for what to expect with teclistamab treatment.

> ***Harvey****: By the time I got to Dr. Berdeja I had already gone through that really initial couple of doses and then really through the hospital had gotten every kind of information I could it on teclistamab. So, they [the APPs] probably did more of the educational part than Dr. Berdeja did. we talked a little bit about the psychological kind of impacts that the drug could have and making sure I'm thinking the process through and my mind is okay. That was really probably the most significant thing that we talked about ....* They're still asking me the questions to make sure I know what year it is and all that good stuff.

Caregivers (partners, family members, and close friends) play a crucial role in the treatment process. They ensure that the patient attends appointments, serve as another set of ears for information relayed to the patient, and take detailed notes or record each visit. They also note symptoms and side effects and can report them to the health care team. Additionally, caregivers can ensure that the patient takes any prescribed

medications in the correct dosages and at the appropriate time. Above all, the caregiver helps the patient optimize nutrition, self-care, sleep, and exercise. Therefore, it is important to educate and empower caregivers to advocate for the treatment options supportive care strategies that are most likely to yield the best outcome for their loved ones.

### Emerging Bispecific Antibody Constructs and New Combinations

What does the future hold for bispecifics? Not only do we have three approved bispecifics currently, but there are a lot more in development, and combination monoclonal antibody therapies have also shown promise in the treatment of refractory multiple myeloma.

Cevostamab is a bispecific in development that targets a different epitope, FcRH5, a protein that is abundant on myeloma cells and also on B cells. The action of cevostamab is independent of BCMA and, as a result, it is being evaluated for patients with multiple myeloma who have received prior anti-BCMA therapy. Results from an early phase one study in patients with multiple myeloma who had an average of six lines of prior therapy found that cevostamab yielded a response rate of 57% after 12-month treatment. In this study, only about 8% of patients received prior bispecific therapy, however. Although 80% of patients experienced CRS, the vast majority of these cases were either mild or moderate. Interestingly, the administration of a single dose of tocilizumab 2 hours before cevostamab administration lowered the overall incidence of CRS from about 90% to 36%, though no clinically meaningful change was detected in the incidence of severe CRS. However, the incidence of neutropenia increased in the tocilizumab pretreatment group from about 40% to 70%. Most of these cases, however, were manageable and reversible and tocilizumab did not impair cevostamab anti-tumor activity.

> ***Dr. Berdeja:*** *I think the most exciting thing about cevostamab is of course it's a new target, so hopefully it's something that can be used as well as people have gone through BCMA and GPRC5D targets. [A recent clinical trial evaluating] cevostamab has introduced us to the potential to do a limited duration therapy. On this study, patients only were treated for 12 months and then that treatment was stopped. [0:58:00] And I think some of that data on the patients who were stopped looks quite intriguing, which I think will help us as we sort out how to best give these therapies.*

Another bispecific in development, Harpoon or HPN 217, contains three binding domains: anti-BCMA for multiple myeloma cell binding, anti-albumin for half-life extension, and anti-CD-3 for T-cell engagement and activation. In addition, there are other bispecifics in development—such as forimtamig—that are unique because they have a two-to-one binding domain. That is, they have two binding sites for either the BCMA or GPRC located on myeloma cells and a binding site for CD3 on T cells.

Other bispecific constructs in development include those with trispecific and tetravalent formats that, as their names imply, can bind to three or four epitopes simultaneously.

Finally, there are BCMA-targeted bispecifics in development that redirect NK cells and enhance their ability to kill myeloma cells. Early efficacy findings for some of these newer agents suggest a 60% to 70% response rate, but whether there will be a lower risk for infections or cytopenias remains unclear at this time. It's encouraging, though, to see so many antibodies with bispecific constructs in the pipeline.

> ***Dr. Berdeja****: I'm especially excited about the modulations that are being done to minimize toxicity to keep that efficacy. So, I think as we're learning more…[and] that will be great. And of course, targeting several things at once. In myeloma we like combination therapy.*

There is mounting evidence that combining bispecific antibodies with other monoclonal antibodies or another bispecific antibody enhances anti-tumor activity and potentially overcomes resistance mechanisms by targeting multiple pathways simultaneously.

In early clinical trials, teclistamab has been examined in combination with daratumumab alone or with the addition of lenalidomide. Only safety data was available for these combinations, and they did not show much improvement in the risk for infections and cytopenia.

In other early clinical trials, talquetamab yielded impressive progression-free survival of about 20 months when combined with either daratumumab or teclistamab.

In a study of talquetamab combined with pomalidomide, the follow-up period was too short to determine progression, but the response was 94%. Importantly, the rate of adverse events did not appear to be elevated in a clinically significant way with these forms of talquetamab combination therapy.

Because all three bispecifics on the market—teclistamab, elranatamab, and talquetamab—were approved by the FDA through the accelerated approval pathway, the manufacturers are required to conduct full phase 3 clinical trials in the multiple myeloma population. Many of those trials are now under way, and their findings should more clearly elucidate the safety and efficacy profiles of these bispecifics in the treatment of refractory myeloma.

> ***Dr. Chari****: if we look at the phase three studies for bispecific, they fall into one of three buckets. First bucket is non-transplant—so, transplant ineligible and newly diagnosed [patients], where the bispecifics are being combined with daratumumab and lenalidomide to kind of compete against triple therapy with daratumumab, lenalidomide, and dexamethasone. Second bucket is after transplant, either with or to displace lenalidomide maintenance, and that's the post-transplant setting. And finally, bispecifics are being compared either as monotherapy or in combination—for example, talquetamab, daratumumab and pomalidomide versus control arms of standard-of-care options. And obviously, we'll see those will lead to the definitive approval of these, but it's nice to see so much activity. And hopefully we'll get these readouts soon.*

***Dr. Berdeja**: Couldn't agree more. And I think, again, underscoring that these are still—in some of these combinations, especially in the frontline there's thoughts about just doing limited duration of the therapy as a maintenance or as a consolidation which—as we alluded to, I think, may help us sort of understand how these therapies work best with minimal toxicity, hopefully less infection.*

Thank you for listening to this episode of *Myeloma Matters* on the prevention and management of bispecific antibody–associated adverse events in multiple myeloma, hosted by the Multiple Myeloma Research Foundation. We would like to thank Amy, Harvey, and Steven for sharing their stories and unique perspectives on bispecific therapy for myeloma treatment. The Multiple Myeloma Research Foundation also thanks Johnson & Johnson and Pfizer, Inc 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.