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Released: 04/15/2024
Valid until: 04/15/2025
Time needed to complete: 30 minutes

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

GPRC5D-Targeted Bispecifics in Relapsed/Refractory Multiple Myeloma: Practical Expert Consensus on a New Target with Unique Adverse Events

Announcer:
Welcome to CME on ReachMD. This activity, titled “GPRC5D-Targeted Bispecifics in Relapsed/Refractory Multiple Myeloma: Practical Expert Consensus on a New Target with Unique Adverse Events” is provided by Prova Education.

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Dr. Matous:
The inclusion of bispecific antibodies into the treatment algorithm for relapsed refractory myeloma has really revolutionized patient care. It is therefore crucial that clinicians recognize and effectively manage patients who have unique treatment-emergent adverse events that occur on some of these agents. So, this is CME on ReachMD, and I'm Dr. Jeff Matous.

Dr. Chari:
Hi, I'm Dr. Ajai Chari.

Ms. Catamero:
And I'm Donna Catamero.

Dr. Matous:
So, to start us off, talquetamab is a first-in-class novel bispecific antibody directed against both CD3 on T-cells and GPRC5D on plasma cells. And Ajai, can you tell us about the rationale for targeting GPRC5D in our myeloma patients?

Dr. Chari:
Sure. I think we're in this really exciting era of T-cell redirection therapies. And while we have two bispecifics targeting BCMA and two CAR T's targeting BCMA, there's only one product targeting GPRC5D and that's talquetamab. And what makes GPRC a great target is, as with all immunotherapy targets, we want something that's overexpressed on myeloma, but not so much on other cells. And

GPRC actually does meet those criteria. Uh, the responses are really impressive for an off-the-shelf product with a median of five to six lines of therapy. We're seeing responses of around 70%, PFS 14 months, and an important cohort of prior T-cell redirection, so prior bispecific and CAR T’s, really encouraging 65% response rate, PFS of around 5 months. So, those are really great. And I would also at that talquetamab is one of the few, if not only, products in myeloma where the PFS for high risk and standard risk are nearly overlapping.

There are some important AEs that we need to talk about. But the main ones to keep in mind – and these we think these are on-target off-tumor, include basically oral, skin, and nails.

Importantly, these are all typically low-grade toxicities, so patients are able to stay on drug, and benefit. And interestingly, also unique about talquetamab in myeloma armamentarium is these AEs seem to correlate with response. And so, patients with for example,

palmoplantar peeling, dysgeusia, there's a 20% higher likelihood they'll have a response.

Dr. Matous:
Donna, you have a lot of experience with talquetamab. Comments?

Ms. Catamero:
I would just add the on-target off-tumor effect, it's – just to keep in mind that GPRC, yes, it's heavily expressed on myeloma cells, but we're also seeing it's on keratinized cells.So, we want to keep that in mind when we're looking at toxicities. And we are going to talk more about the oral toxicities and the skin toxicities. But I also think this gives us a great option for patients. I have patients who are in deep durable responses. My longest patient is over 5 years and is doing quite well. So, this is a great option for patients.

Dr. Matous:
And we have more GPRC5D-directed therapies around the corner besides talquetamab. Dr. Chari?

Dr. Chari:
Yeah. So, as a monotherapy, there's another bispecific-targeting GPRC known as forimtamig, and this has two binding domains for GPRC. There's also CAR T's that have GPRC as a monotherapy target. Those actually have similar AE profile, but perhaps less so with the exception of maybe cerebellar toxicity. And then there's also combination efforts. So, there's CAR T's with both targeting BCMA and GPRC. And there's also T-cell engagers for example, trispecific, that's targeting both GPRC and BCMA. So, I think this target and it's AE profile is essential for everybody to learn about.

Dr. Matous:
How do the BCMA-directed therapies contrast with respect to toxicity with talquetamab? Ajai?

Dr. Chari:
BCMA is a little bit more dirty in terms of the immune microenvironment, I would say, that it seems to be overexpressed on more immature B cells. And the reason I bring that up as we see more hypo gamma, more infections. In fact, with the most mature follow-up from the teclistamab dataset, the rates of grade 3 infections are 55% which is strikingly high. These are crazy opportunistic and unusual infections. And also, we've seen a fair number of deaths with those that are not due to progression.

Interestingly, talquetamab was accrued at the same time as teclistamab, and yet we don't see the COVID deaths that we see, for example, with the BCMA bispecifics. We don't see as high-grade toxicities with the talquetamab, at probably more 20 to 30% grade 3, neutropenia is less with this compound, maybe 20 to 30% grade 3 and higher instead of, say, 60% with some of the BCMA bispecifics.

Dr. Matous:
Donna, can you talk to our audience about some practical aspects of, targeting GPRC5D versus uh, BCMA?

Ms. Catamero:
Yeah. Ajai was talking about infection, so yes, we do absolutely see less infection when we target GPRC5D. But we can't forget that these are myeloma patients, these are heavily pretreated patients so, there still is an underlining risk of infection. But unlike BCMA-targeted therapies, I'm not necessarily prophylaxising above and beyond what I would do for my typical myeloma patients. So yes, we're going to keep on the shingles prophylaxis, we're going to monitor IgG levels. And for patients who are below 400 or 500, I'm going to supplement monthly IVIG. I'm going to make sure my patients maintain an ANC level at least above 1000. And, you know, adding growth factor support to maintain an adequate ANC

And then I want to make sure that my patients are up to date on their vaccinations.

So, I'm going to make sure if my patients are eligible to get vaccines, I'm going to give it to them, even though they may not amount as a robust response to the vaccines as, say, a healthy patient, but you know, some response to vaccines are better than no response.

Dr. Matous:
And then a common question that I get, and you, our experts, might get the same one is how do we deal with PJP prophylaxis or even CMV monitoring?

Dr. Chari:
Yeah, I think as Donna alluded to, these are heavily treated patients for the initial four or more lines of therapy, which is the label currently, triple class exposed, four or more lines of therapy. So, of course, with advanced myeloma, you get those kinds of issues. However I don't think we have seen as many opportunistic infections. In the MonumenTAL-1 study, it's less than 5%. And the rates of hypo gamma are less. So, I tend to be a little bit less aggressive with prophylaxis with talquetamab, and CMV also does not seem to be occurring at a higher level. With BCMA bispecifics, I definitely do the IVIG repletion for everybody. Because everybody gets hypo

gamma, PJP prophylaxis for all BCMA, and CMV monitoring we do once monthly on the BCMA. But it's very different, I think, which is what makes this compound easier to use in terms of an infection management.

Dr. Matous:
Similar for us. So, we like to do PJP prophylaxis in our patients while they're on a T-cell redirecting antibody. We don't see much CMV reactivation in any of our patients, and particularly with talquetamab. And so, we're very similar. And we really need to, involve our infectious disease colleagues in the management of these patients. And so, I think the GPRC5D patients, I think they're quite different from the BCMA patients, personally, there been a number of studies done as part of MonumenTAL-2 or TRIMM uh, so forth, combining talquetamab with other agents. And so, what happens when we do that?

Dr. Chari:
In TRIMM-2, we combined both tal and tec with daratumumab, as well as with pom and with dexamethasone. What we saw with the TRIMM-2 with tal plus dara was a really encouraging PFS of around 19 months, which is quite impressive. We didn't see any additional toxicities in terms of no worsening of CRS, no increased rates of cytopenias. You do see a little bit more infections when you add dara, but I think the IMiD combinations were a little challenging in TRIMM-2.

Dr. Matous:
One of the arms of MonumenTAL-2 for patients who are less heavily pretreated, median of, of two to three priors was combining talquetamab with pomalidomide. And in that study, the pomalidomide was added at cycle 2 at a dose of 2 mg and, in general, that was well tolerated from the perspective of cytopenias. It didn't increase CRS or any other obvious toxicities. And attempts were made to escalate the dose of pom beyond 2 mg. And those those were fraught with more cytopenias in general. But the response rates, again, were impressive. I mean, really impressive, including deep responses and durable responses and among different patients..

Dr. Chari:
You know, I think when we talked about combination strategies, some of the early data that we're seeing highlights the differential AE profile. So, when the BCMA bispecifics have been combined with the IMiDs, for example, say the sister study to what you presented, we see and sometimes with CD38, we're seeing very high rates of neutropenia, like 80% plus, high rates of infections, high rates of COVID-related deaths. So, I think the combinations where you have to really keep in mind each individual compound's toxicity profile before you just combine everything willy nilly. And that's what's nice about GPRC5D as a target.

Dr. Matous:
I couldn't agree more. I think of interest to a lot of us myeloma docs and to our clinician colleagues is, how do we mitigate and manage these talquetamab-related toxicities? You know, using dosing or scheduling modification. So, let's start with Dr. Chari.

Dr. Chari:
I would start with the recommended doses for talquetamab of either 0.4 mg/kg weekly or 0.8 mg/kg every 2 weeks. And those initial doses were selected to get that optimal response in these heavily treated patients.

What we've shown at ASH is that, in a retrospective look, patients who had dose reductions did not seem to have any compromise. But there's always a caveat, I always joke that, you know, people who do better do better. So, we wanted to confirm that in a prospective cohort. And you could either reduce the dose from 0.8 to 0.4 and keep it at every 2 weeks. Or you could go from 0.4 to point, 0.4 every 2 every week to less frequently. So, you could change either the dosing or the intensity. What that showed preliminarily, with this about 20 patients or so, no change in response, no change in PFS; and yet we saw improvements in the skin toxicities, both rash and non-rash, some improvement in the oral and nail toxicities, as well in terms of AEs resolving.

We didn't see that much change in weight loss, whether that's due to the kind of kinetics of how long it takes to develop and how long it takes to improve.

But I think what this tells me is that the drug is very active. We know that the responses actually are very high and brisk, but also correlate with the AEs correlate with better efficacy. So, when you have this response, what the study showed is at the maximal response, which occurs almost as early as 3 months we can then think about reducing the intensity of the drug without compromising efficacy.

Dr. Matous:
When are you comfortable making dose modifications and schedule modifications?

Dr. Chari:
So, in the prospective cohort, patients have to have had at least a VGPR or better but it tended to be around that 3- to 4-month time period. And I think it seemed to be really well tolerated.

Dr. Matous:
And Donna, you may have one of the world's greatest experiences managing patients dealing with some of these side effects from talquetamab. What can you tell us further about how you take care of these patients and keep them on effective therapy?

Ms. Catamero:
Yeah, and I know the oral toxicities is what really impacts patient's quality of life. we've tried several interventions in our institution. There's no silver bullet, per se, that will eliminate the oral toxicities, but we can help manage our patients through so that when a patient achieves a VGPR or a CR that we can decrease the dose or decrease the frequency, because I believe really that's how patients tolerate the drug best. Because we don't necessarily need to be treating so frequently; these responses are very durable.

In the real-world setting and in my experience, really, it's all patients that have some degree of oral toxicity. And this can start as early as step-up dosing, patients will start noticing some taste changes. So, what we've initiated in, our institution is, with that first dose we're giving patients dexamethasone and Nystatin swish and spit. And we're not waiting for a patient to have symptoms, we're telling them to start this at the initiation of therapy. And we've had anecdotally notice that patients have a lesser degree of these taste changes. We're also encouraging patients good oral hygiene. Patients will complain of some dry mouth so, we're adding in saliva substitutes. Patients with dysphagia, or difficulty swallowing, we really work with our nutritionists and modifying diets. And again, that saliva substitute may also help as well.

Weight loss is problematic, and I want to try to avoid that. So, getting nutrition in early on for someone who might be susceptible to weight loss is important to really make sure you have counsel the patient to have adequate nutrition intake.

And I think what's most important is to set expectations. explaining not if this happens, but when this happens because as I said, the majority of my patients, if not all, do have some degree of oral toxicity.

Dr. Matous:
I couldn't agree more. That's been our experience as well. And the other problem that we occasionally encounter is dysphagia in patients where they have difficulty swallowing, which I think can be another challenging problem. So, I agree that involving the dietitians and taking a really detailed taste disorder history can be very helpful sometimes, because there are different things that we can try, depending on how taste alterations are affecting any given patient.

But I think that one of the keys here, as you so eloquently pointed out, is to educate our patients what to look for, encourage them to report everything they get and remind them, like Dr. Chari said earlier in the talk, is if you're getting a lot of these side effects, it probably is an, you know, indicating factor that your therapy is quite effective. And so, I think that there's a lot to be learned still in my opinion, still about how we're going to manage these side effects.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Jeff Matous, and here with me today are Dr. Ajai Chari and Donna Catamero. We're about to delve into, you know, deeper into the identification and management of skin and nail changes reported with GPRC5D-directed therapies.

So, moving on. We talked earlier about on-target AEs related to talquetamab. And what about the toxicities involving the cutaneous tissues, integumentary tissues, skin and nails, and what have we seen in clinical trials, Dr. Chari?

Dr. Chari:
So, I think there's a different pattern. So, the skin toxicity, the rash I feel is very manageable., These patients can get sometimes just localized rash, or sometimes it's higher grade but localized rashes, like so grade 1/2 can be managed with topical steroids like low or medium potency. Higher grade rashes, which is uncommon, can respond beautifully to a course of oral steroids like a Medrol Dosepak, for example. So, those I think are helpful for the initial AE of skin rash. The palmoplantar peeling occurs a little bit later, but also can be very responsive to topical steroids. And that's quite resolvable. The nail I'm going to – Donna, I think, has a lot more experience with nails, but I know it's nail hardeners, vitamin E oil have been tried.

And then I think the important thing for these toxicities is that they're uncomfortable orthe nails may not look cosmetically pleasing, of course. But in general when we looked at our dataset at Sinai, for example, I think out of 70 patients at that time, only 1 patient had come off for nonprogression. And I think more than the three of us talking about it, it's those kinds of numbers, right? And in general, I would say tal discontinuation due to AE is quite uncommon, speaking to the manageability with, I think, especially now that we've formally studied the dose intensity, I'm curious if that's been both of your experience as well.

Dr. Matous:
Donna, any other words of wisdom about managing these patients?

Ms. Catamero:
Yeah. So, these dermatological side effects, we typically can see them in that first month. patients will be complaining of some dry skin. we advise patients to even prior to starting their therapy to start with the heavy barrier moisturizers. And then, we can see these body rashes, which a steroid taper can also be helpful. for the hand and foot peeling ammonia lactate 12% lotion to the soles and the palms we do that twice a day. And these are quite reversible. So at least dermatological side effects, we can manage very well. They're self-limiting, they're reversible.Also if patients, , with the rash, if there's pruritis, we can add loratadine for several days to help with that. general, with these dermatological side effects, we see them earlier on, within that first three cycles of therapy, and they're self-limiting and reversible, well managed.

Dr. Matous:
And occasionally, I'll put gloves on patients for occlusion at nighttime if they're really having trouble with dryness.

So, let's, now, let's tackle a different problem. And this is one I think that we have seen most of our patients experience, which is the oral toxicities observed with talquetamab. We've talked about this a little bit, but let's spend just a couple of minutes talking about how we tackle these problems. So, Dr. Chari?

Dr. Chari:
Yeah. So, I think this is probably the most challenging one to deal with. Because we don't really know, first, the mechanism honestly, and secondly, how to manage it. But I think it's some of the things we've alluded to are, well, first is quite common and occurs quite early as well. just, I guess, from a medical perspective, that I think this too is responsive to dose reductions and also can correlate with efficacy. But I do think that part of the limitation is that we don't really have the tools to study it. We're hematologists/oncologists community, and dysgeusia is not an AE that we've really done a lot with. And so, grade 1 and 2 is all we have in CTC. So, there's efforts to first better characterize the patient experience with the study that will be coming out, and then trying to understand the pathophysiology to really get definitive treatments. But until then, I would say dose reduction, dose intensity reduction has been the mainstay of management.

Dr. Matous:
And Donna, you talked to us just a few minutes ago about some of the strategies to use, when do you involve nutrition?

Ms. Catamero:
If there's dysphagia, so any type of difficulty swallowing and those patients who are at higher risk for weight loss or if I start seeing weight loss, I'm going to involve them early. This way,we can manage a diet that might be high in protein and calories, so that we can maintain a patient's weight.

I think most importantly, when educating patients, you really, really need to set the expectations for patients. You know, this will occur, this is how we're going to manage it, this is what you need to report to us. So, really, I think education is key. And like any signs of infections in the mouth you know, early in intervention because we want to prevent infection. But it's very challenging. Like I said, no proven intervention has shown effectiveness as yet; everything is anecdotal. I think the swishes, we even are trying icing for patients. We did see some uptake in the salivary glands on a PET scan post treatment. So, you know, there are changes happening and, you know, we're trying icing. So, there are several things that we're looking at.

Dr. Matous:
When I talk to my colleagues in the community, one of the big concerns that they have is the management of cytokine release syndrome, or CRS, and a lot of our colleagues have been hesitant to take up some of these T-cell redirecting therapies because of – of CRS. So, what about the CRS in patients getting bispecific antibody therapy?

Ms. Catamero:
For the most part patients will be treated on an inpatient setting, but I know more and more institutions are doing bispecifics outpatient. Of course these institutions all need to be REMS certified. So, the staff, the nursing staff, everyone needs to know how to manage CRS, or cytokine release. We mitigate upfront by doing the step-up dose approach, we premedicate our patients with steroids, diphenhydramine and acetaminophen, that we keep up throughout this step-up dosing and with the first full dose. And this will mitigate you know, the CRS. But we are seeing there is still a large percentage of patients that will experience CRS, mainly grade 1 and 2. And patients will present with fever, you know, 100.5. And at our institution, what we're doing as soon as a patient has that fever, we're adding the acetaminophen and tocilizumab so that, the patient doesn't progressively get worse with hypoxia or hypertension.

So, in my experience, we see more with that second step-up dose, but a patient's at risk up through the first full dose. patients need to be monitored 48 hours post-dose. So, right now, we're doing this at our institution as an inpatient basis. Our staff is fully educated on how to manage. what patients have told me, what CRS feels like, it's essentially, you know, when you get your flu vaccine and you feel a

low-grade fever coming on with muscle aches. we're always picturing the worst-case scenario, but the majority of these patients are presenting with a fever, which we can quickly intervene and prevent from getting worse.

Dr. Matous:
So, Donna, I use the exact same analogy with my patients describe the CRS is as either mild flu or a bad flu, depending on the grade of the CRS. So, you guys are using tocilizumab for grade 1 CRS, is that what I heard?

Ms. Catamera:
Yes, we are.

Dr. Matous:
Dr. Chari, are you seeing the same thing with your referral colleagues about, how to get the bispecifics out, more in the community?

Dr. Chari:
Yeah, it's been really a struggle, I think. I would start with the fact that we were just talking about myeloma bispecifics of which there are three. There's also I think at least three lymphoma bispecifics. So, to me, I almost feel like where we were maybe 20-25 years ago when monoclonal antibodies were just coming out, and there was so much skittishness about infusion-related reactions, and then everybody, like got over it, and everybody's getting rituximab and daratumumab intravenously without issues in the community. But I think– we're there now. And we need to get to the point where these bispecifics can be started, because the vast majority of the patients who need these products are not going to be treated in academia.

And the REMS programs, while well intentioned and appropriate I think can also be a deterrent. I would say that the need for tocilizumab after this first cycle is almost zero, right? So yes, people need to do the REMS program, but it's not that you're going to be needing to give tocilizumab throughout the journey of a bispecific in the long term. And I hope that these kinds of programs and other efforts will make it easier for people to train. It is important, as Donna mentioned, you've got to train the entire team, nurses, pharmacy your consultants with infectious disease, and neurology, and ER. And all of those people need to be trained, but it shouldn't be a barrier. And it's you know, the words of Fergie, if you don't step up, you will be 2000-late, right? You've got to start sometime. And it's super important because these patients' lives are dependent on these really highly efficacious products.

Dr. Matous:
So, what's your approach to treating CRS?

Dr. Chari:
So, we actually even standardize it just because the inpatient teams are not necessarily disease specific. So, the APPs and the hospitalists cover all diseases and we have decided to just standardize it. And basically, if you have a whiff of fever, we don't wait for complications, they get the toci. Especially in the myeloma bispecifics where there's multiple step-up doses being given close together, we think that that early toci use dials down the grade, decreasing the recurrence.

Other institutions are using that REMS liberalness, like patients should be monitored for 48 hours and interpreting it differently. I think if you're at a site where you can give toci at any time, you don't need to be in the hospital, but I think right now, we're still figuring it out on each institutional basis. How about yourself, what are you doing?

Dr. Matous:
So, we give our bispecifics almost uniformly on an outpatient basis. And we're set up to do that. we're not as liberal with – with tocilizumab for grade 1 CRS but, we give it a little more than we used to give it. Because in MonumenTAL-1 and MajesTEC-1, the toci use was about 1/3 of patients, if I recall correctly. And I think the actual clinical utilization is a little bit higher than that.

And there is interest in premedication with tocilizumab. There'll be an abstract from MajesTEC-1 for teclistamab with toci premedication presented at ASCO. There's an ongoing study called Optec addressing the same question, which I think will be very helpful, because that may help for you know, get broader adapting or incorporating of these bispecifics in the community.

Let's go on and talk about, best practices for managing AEs with talquetamab, because we're goingto bring the whole program together here and try to help our listeners, feel confident that they know what these AEs are and how to manage them. So, Dr. Chari, can you please summarize for us, best practices are for dose and schedule modifications to keep people on therapy to, get these optimal responses?

Dr. Chari:
So, I would start with the 0.8 every 2 weeks, and then the median time to response is 1 month, median time to best response is about 3 months, and about 70% of patients are responding to this as a monotherapy. All of that tells me that by around 3 months, if somebody's responding, I'm going to feel comfortable reducing that dose. I typically go to monthly dosing because that's easier for the patient, and

then keep people on until progression or intolerance. And fortunately most patients are able to stay on therapy in spite of the AE profile that we've discussed.

Dr. Matous:
And Donna, again, summarizing some of the great thoughts you've had during this program, you know, regarding the management of CRS or skin or nail toxicities, oral toxicities and so forth some best practices?

Ms. Catamero
Yeah, I think to educate and anticipate and set expectations with your patients. So, oral toxicities, just anticipate it will happen with your patient and intervene early with the first dose of therapy. I think because the oral toxicities is really what's going to, patients are going to affect their quality of life. And that's when patients want to come off therapy. So, I think if we can, manage the oral toxicities, and what Ajai was saying, in our practice too, once we get a patient into a deep response, we're decreasing the frequency. And I really think that intervention helps with these other side effects.

Dr. Matous:
And so, to wrap things up, I really want to thank the audience for listening. I really thank Ajai and Donna for their expertise and sharing all their great insights into how to use talquetamab for treating our patients with multiple myeloma. And it was really great having you on our panel today. So, thank you so much.

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