

Patient Webinar: Non-BCMA-Targeted Bispecific Antibodies in Multiple Myeloma

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Transcript

Mary DeRome (MMRF): Hello and welcome to the MMRF Patient Webinar, *Non-BCMA- Targeted Bispecific Antibodies in Multiple Myeloma*, brought to you by the Multiple Myeloma Research Foundation. I'm Mary DeRome, senior director of medical communications and education at the MMRF.

During this webinar, you will hear from two myeloma experts who will discuss non-BCMA-targeted bispecific antibodies like Talvey or talquetamab and cevostamab for use in multiple myeloma treatment, as well as describe the latest advancements with these agents and discuss their exciting potential. Our speakers are Dr. Ajai Chari from the University of California San Francisco, and Dr. Suzanne Trudel from the Princess Margaret Cancer Center in Toronto, Ontario, Canada. We will also hear from a patient who will share his experience of being on a non-BCMA bispecific antibody.

Let's get started with our first speaker, Dr. Ajai Chari.

Dr. Ajai Chari: Thank you so much, Mary, for the kind invitation. I'm really excited about our topics today and really welcome questions from the patients.

Let's start with, what are bispecific antibodies? As the name implies, it's two targets. The two major cells we are concerned about for this topic are the T cells that are characterized by a protein called CD3 and the myeloma cell. There are different targets we could go after. BCMA is one that many may be familiar with, but today we're going to be talking about non-BCMA targets.

If your immune system is working well, which includes the T cells, they should recognize the myeloma as a foreign entity and then release perforin and granzymes, and that pokes holes in the membrane of the myeloma cell or whatever target you're going after—bacteria, virus, et cetera. That results in the death of the target cell. So in a way, these are like targeted therapies. It's using your immune system to—rather than having a broad swath of killing everything in its path—zoom in on the target. You can design different molecules. A bispecific antibody targeting CD3 and myeloma brings these two cells into proximity, and those T cells wake up and realize that they should be killing the target.

The other way to do it is to use what's called a non-IgG-like bispecific antibody, which is a much smaller molecule. There was one under development in myeloma, but the problem with these is that they have what we call a very short half-life, and you have to give them continuously IV.

We now have three bispecific antibodies approved for myeloma. Many people have heard about CAR T and are super excited, but the challenge there is that from the day you get a slot for CAR T to when it is actually given, it can be anywhere from 4 to 6 weeks. These, on the other hand, are off-the-shelf and ready-to-go, and they can be used for all myeloma patients.

So what are the targets? We talked about CD3. For myeloma targets, there are three potential ones that are in either approved or in advanced development. BCMA stands for B-cell maturation antigen; it's a protein. All of these are overexpressed on the myeloma cell, and maybe also a little bit on B cells. We know that you can detect BCMA in the blood and on the serum. That's important, because you can, in some new diagnostic tests, trend BCMA and show that as you kill myeloma, you can actually decrease that level.

Then there is GPRC5D, which stands for G-protein receptor coupled class 5D. This is overexpressed on myeloma and also on hair follicles. This target is independent of BCMA. That's good, because we have this issue of sequencing. Like, if you do one of these, can you go to another one? That's an important question that we will also answer here.

Finally, we have FcRH5, which is selectively overexpressed on B cells and plasma cells. Dr. Trudel will be covering the really exciting drug for that target.

So what are the bispecifics that we have under study? We have the three different targets we talked about. You have five different antibodies that target BCMA. Of those, two are FDA approved, teclistamab and elranatamab. Then there are three others that are following on their heels: linvoseltamab, alnuctamab, and ABBV-383. Those three are still in clinical trials. Some also will be submitting application shortly.

The two targeting GPRC5D are talquetamab, also known as Talvey, and forimtamig or RG6234. Talquetamab is approved, and forimtamig is still being studied.

Finally, cevostamab is the only one targeting FcRH5. It is in clinical trials.

What's really amazing is that all of these drugs work in 60% to 70% of very heavily treated patients—not only responding, but deep remissions, like very good partial response or even complete responses.

The phase 1/2 MonumenTAL study looked at about 300 patients from three different cohorts—one group got 0.4 mg/kg every week, one group got 0.8 mg/kg every 2 weeks, and a third group are patients who got prior T-cell redirection. These are, in other words, typically patients who had prior BCMA-directed CAR Ts or bispecifics, which is the new unmet need. Across the board for all three cohorts, you have response rates of 65% to 75%.

This drug is now available. It's for patients who have had relapsed/refractory myeloma and at least four lines of therapy, a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti- CD38 antibody.

I'm sure many people will ask why that many lines of therapy, and we'll talk about that. It has to do with how we get new drugs approved. We start, usually, in advanced myeloma patients where, truth be told, you don't know if a new drug's going to work. But once you have that safety and efficacy profile... There are studies going on for all of these products in less heavily treated patients.

Why are we so excited about the bispecifics, and the CAR Ts for that matter? To put into context this really unprecedented era in myeloma therapy, consider the drugs that have been approved recently, prior to the immunotherapy age: pomalidomide, carfilzomib, daratumumab, selinexor. When those drugs were initially studied in advanced patients, progression-free survival (PFS) ranged from 3 to 4 months. The duration of response was about 4 to 8 months.

Now, whether you're talking about bispecifics or CAR Ts, the results are astounding. In patients for whom many therapies have failed—at least four lines of therapy; they have had IMiD, PIs, and CD38. IMiDs meaning lenalidomide and pomalidomide or Revlimid and Pomalyst; PIs like bortezomib and carfilzomib, or Velcade and Kyprolis; and then the CD38 being daratumumab or isatuximab, brand names Darzalex and Sarclisa.

In such heavily treated patients, you're getting remissions of anywhere from 11 to almost 35 months—so, 3 years—and the duration of response has either not been reached or is, again, as long as almost 3 years. This is really a paradigm-shifting time in myeloma.

Many of you may know, I actually recently moved from New York to San Francisco, and I saw a patient on the portal already. The most difficult and also striking thing was saying goodbye to so many patients who had at one point exhausted all their therapies, and now they're in their most deep and durable remissions. It's really a game-changing, paradigm-shifting time.

Today we'll talk about efficacy, but also safety. What are some of the side effects? We have cytokine release syndrome (CRS), infections—which Dr. Trudel will be covering—low blood counts, and neurotoxicity known as ICANS.

The good news is these typically, if they occur, tend to be low grade and short-lived. But I also want to spend a brief moment on GPRC5D-related side effects. GPRC5D is overexpressed, as we said, on the myeloma cell, particularly the malignant myeloma cell. That's important, because we don't see a lot of infections with this product. But it is overexpressed also on other things that express a lot of keratin, which is a protein that's in skin and nails. So that'll explain a little bit of the side effects.

The two doses are 0.4 and 0.8. If you recall, the 0.4 was weekly, and the 0.8 was every 2 weeks. Surprisingly, the remission duration is almost double. So the PFS of the every-2-week dosing is about 14 months, whereas the PFS for the weekly dosing is 7½ months. I'm preferentially using the every-2-week dosing.

The side effects of this included lowering of blood counts. Myeloma is a bone marrow cancer. When you traffic T cells to the myeloma, which is primarily in the marrow, you are going to have a little bit of count impairment, like red cells, white cells, and platelets. It tends to happen early, and then it improves.

CRS occurs quite commonly—for the bispecifics, almost 75%. But it's almost all low grade, which is quite manageable.

Other things like issues with the skin and nails, and also taste occurred in almost 50% to 70% of patients. But again, they were typically low grade. In particular, we can see taste issues in 71%, weight loss in about 40%, skin issues in about 73%, nail issues in 55% or so, and fatigue. Now, one thing regarding infections: with this drug, even in the Covid era, we did not see serious complications. So while there were infections, we have to remember that myeloma patients are at risk of getting infections just because of the nature of the disease. But this particular product, we're not seeing a lot of Covid-related complications or death. We've shown in the laboratory that people can actually make Covid antibodies when they get vaccines.

What are the skin, nail, and oral toxicities? With the skin, you can have rashes or peeling. This tends to be benign, self-limited, not painful, and it also tends to go away. With the nails, we see thinning and loss, primarily aesthetic, that can take time to resolve. Oral issues in some ways are perhaps more challenging, because they can lead to dryness, difficulty swallowing, and taste changes, and that can also lead to weight loss. The mainstay of managing this is dose modification but also supportive care measures like artificial saliva, diet changes, high-caloric shakes, et cetera.

What I really want to emphasize, and this is hot-off-the-presses information, is that with this agent we've noticed that people who get these side effects are more likely to respond, have a more durable response, and actually tend to live longer. We will be presenting this data at an upcoming meeting. But what this means is that if patients have these side effects, we can probably lower the dose very safely, because we know that these side effects are also dose-related, and that way we can continue to benefit from the drug but try to minimize those side effects. So stay tuned for that.

As examples of the side effects, you sometimes see some redness at the injection site. Many of you have seen this with other drugs like bortezomib or daratumumab. It is not super common, but self-limited.

You sometimes see patients who have redness and a rash. At Mount Sinai, only five patients out of about a hundred had this. It's uncommon to have a distributed rash; it tends to be more limited.

You sometimes see peeling of the hands and feet. How do we manage these? Hydrating creams, topical steroids, and, if needed, antihistamines like Benadryl or Claritin to prevent itching. But again, people who have these tend to have better responses.

Regarding nail changes—typically nails grow from the base of your finger bed, and then the new nail grows out. The good news is that nail issues generally don't cause pain and are reversible.

When patients stop talquetamab, these side effects go away. We think these are probably dose-related. Some things that our nursing team recommends are using clear nail polish or nail hardeners, biotin, among other options.

Cytokine release syndrome, which Dr. Trudel will talk about in more detail, can occur because, when you give the drug, the T cells kill the myeloma, and they release those chemicals. Those chemicals can cause fever. How do we mitigate that? We don't give the full dose all at once. We do what's called step-up dosing. For the weekly dose, there are two step-ups. For the every-2-week dosing of that 0.8, there are three step-ups. So we give these at a low dose, and then a slightly higher dose and a slightly higher dose.

There is a certification program called the REMS that requires physicians, pharmacists, and everybody to be trained on it. The facility needs to have REMS training experience. The REMS program mentions that patients should be hospitalized after each of these step-up doses, for a total of ideally 48 hours after each one. Maybe we can talk about some efforts in the discussion of how some sites are doing this as an outpatient process.

Finally, when we study these new drugs, we start them as a single agent, but we are also doing combinations. There are two combinations that I want to highlight. One is the two drugs in combination. The sisters, if you will: Tecvayli, which targets BCMA, and talquetamab (Talvey), which targets GPRC5D. When you combine these, there are outstanding responses—86%, 96%, including patients who have extramedullary disease, and that's about 86%. Not only are those responses very high, they're also durable. Progression-free survival is 20.9 months, which is really outstanding. The side effect profile is similar for each drug. We don't see any additive problems, no increase in CRS, no other unusual things that we would expect.

Another option, which is more readily doable because it's a commercially available product that's been used for a while, is talquetamab with daratumumab. The response rate is 71%, 84%. Remission duration, perhaps even more impressive, is 19.4 months. Having these kinds of remissions, for an off-the-shelf

product, is incredible. It rivals some of the CAR T products. But, of course, there's no question that CAR T has its own tremendous benefit. But it's just this, being off-the-shelf, does not require going to an academic medical center like for the CAR T, so does not have that wait time. It's a great option for patients.

What's the future direction? Obviously, these combinations are going on. There are efforts to rescue minimal residual disease (MRD) positivity, but the pivotal phase 3 study is actually going to compare this to, for example, talquetamab with daratumumab or daratumumab and pomalidomide or talquetamab plus pomalidomide. So, different combinations. We'll await those confirmatory phase 3 studies for full approval.

But I'll stop there and thank you for your attention. And I'll hand it over to Dr. Trudel.

Dr. Suzanne Trudel: Great, thank you. I'd like to thank the MMRF for the invitation to present today, and for all of you for participating in this seminar.

I'll be talking about some additional non-BCMA bispecifics, focusing on their efficacy and side effect profiles, and then finishing off about just general safety concerns with the bispecifics in general and how we can manage them.

First I'll talk about forimtamig, which is another bispecific that, similarly to the ones that Dr. Chari just mentioned, also binds to CD3 on immune T cells but also binds to GPRC5D like Talvey does. We know that GPRC5D is a molecule that's present on the myeloma cells and therefore targets the T cell to the myeloma cell, causing the T cells to destroy the myeloma cells. It's being tested in a phase 1 study. For those of you who are not familiar with phase 1 studies, they are basically clinical trials that are aimed at trying to find the optimal dose for patients by using small doses and incrementally increasing the doses and monitoring for safety to find a dose that will be safe and hopefully show some efficacy.

In a presentation from Dr. Harrison, he reported on 105 patients that were treated with various doses of forimtamig. Of the 49 patients who received forimtamig as an intravenous infusion every 2 weeks, 71.4% responded. Comparable responses were seen in patients who received forimtamig as a subcutaneous injection; that is, an injection just under the skin on the tummy area. These results are quite encouraging and are similar to what was reported for Talvey.

Half the patients in this study were over 65, and the response rate in those patients was 71%, which is equivalent to what was seen in the overall patients. This suggests that both patients that are younger and older than 65 benefited from forimtamig.

To summarize the other subgroups in this study, patients who are really heavily pretreated—who had more than four different regimens of treatment, did not respond to the three major classes or to carfilzomib, bortezomib, pomalidomide,

lenalidomide, and anti-CD38—all of those patients respond well to forimtamig, with responses that are pretty close to what was seen in the overall patient population. Importantly, about 29 patients in this study had received prior BCMA-targeted therapy, and those patients responded to treatment.

Finally, patients who have high-risk disease or extramedullary disease, which tends to be very difficult to treat, are responding to forimtamig. The conclusion is that forimtamig has a good anti-myeloma activity in patients that are heavily advanced in their disease, and many have not responded to most available therapies. The activity looks similar to what's been reported with the approved drug Talvey.

Next we're going to talk about cevostamab, which is another bispecific antibody that also binds to CD3 on T immune cells. In contrast to talquetamab, which targets GPRC5D, and to elranatamab and teclistamab, which target BCMA, cevostamab has a novel target called FcRH5, which is also present on the surface of myeloma cells, as well as their normal counterpart plasma cells, and also on B cells, which are also immune cells. The expression is very selected to those tissues, and it's not present in other normal tissues such as skin and nails. That will be important to keep in mind when we go over the side effect profile.

In a phase 1 study where patients who had not responded to all available therapy were given cevostamab intravenously every 3 weeks, at doses between 20 to 90 milligrams, 36% of those patients responded. The responses were even better when higher doses of cevostamab were administered. When between 132 and 198 milligrams were administered, 56.7% of the patients responded.

The most commonly reported adverse event or side effect was CRS, reported in just over 80% of the patients. Severity of the CRS, which we grade between 1 and 4, varied. The majority of patients who experienced CRS had grade 1, meaning that the symptoms were mild, mainly a temperature of 38 degrees Celsius, and could be managed without intervention.

Quite a lot of patients experienced grade 2 CRS, which would be considered moderate, meaning that it needing minimal or non-invasive interventions. For CRS, that would mean a temperature above 38 with a blood pressure that's a bit lower. It can be usually managed with intravenous fluids or low doses of oxygen. These are usually managed non-invasively. But sometimes patients can receive a drug called tocilizumab or dexamethasone to manage CRS.

Only 2% of patients experienced grade 3 CRS, which would be considered severe but not life-threatening. Those patients have blood pressures that require management with medication to help bring up their blood pressure or high-flow oxygen and usually ICU admission.

Other commonly reported toxicities included lowering of the blood counts, as mentioned earlier by Dr. Chari. There was a high incidence of patients

experiencing low neutrophil count anemia or low platelet count. Nearly 50% of patients experienced infection, including about 20% of patients who experienced grade 3, meaning severe, or grade 4, potentially life-threatening, infections.

Overall, the safety profile for cevostamab is consistent with what has been seen with other bispecifics in myeloma. Unlike with Talvey, we don't see the issues with skin and nails, because FcRH5 is not found on the surface of skin and nail cells.

Currently, bispecifics are given indefinitely as long as the disease is responding to treatment. Some physicians are opting to give it less frequently—every 2 weeks or even every month depending on the patient's response. But really the bispecifics are continued until the disease is no longer controlled.

One of the interesting aspects of the study of cevostamab was that it required that patients stop cevostamab after 17 cycles or approximately 1 year of treatment. This past year, we reported on 18 patients who completed their 17 cycles of treatment. These patients are continuing to remain in response despite having stopped cevostamab—for one patient, approximately 2 years from starting treatment and 2 years after stopping cevostamab.

So this really has led to us looking at studies to evaluate whether all bispecifics can be discontinued after a period of time and when is the best time to discontinue bispecifics: after a certain number of cycles or after patients achieve a certain type of response? This will hopefully help us to reduce the side effects of these bispecifics, as they do tend to accumulate over time.

The common side effects seen with bispecifics in general include CRS, which is reported in approximately 80% of patients, and mostly are low grade, so mild to moderate grade 1 or 2. Over time, we have really learned as physicians how to manage the CRS with the use of tocilizumab and dexamethasone. As well, we see a lot of low blood counts, which tend to be reversible with the use of growth factor support for the white blood cell count or platelet or blood transfusions as required. But these are really short-lived. This is in contrast to what we see with CAR T-cell therapy, where cytopenias or low blood counts can sometimes persist for several months.

Neurotoxicities or ICANS are symptoms where patients can be confused, have difficulties expressing themselves, or following certain tasks. These occur at low frequency with bispecifics, generally 10% or less, and are almost exclusively low grade, meaning mild to moderate. Unlike CAR T-cell therapy, we very infrequently see long-term neurotoxicity with patients who receive bispecifics.

Finally, infections have really emerged as a challenge for patients who receive bispecifics, and I will speak to that in more detail.

But first I'll just talk to you about how we are trying to reduce the severity and the risk of CRS. So first, one way that we've done this is, as Dr. Chari mentioned, is using the step-up dosing approach where patients get a small dose, an intermediate dose, and a full dose. We've previously shown that by doing this, we reduced the severity of CRS. But in another study what we did is we looked at using the drug that we use to treat CRS, which is tocilizumab, and we give it before we give the bispecific to see whether we could reduce the incidence of CRS. That is indeed what happened in the study.

We treated 31 patients with tocilizumab prior to receiving cevostamab. In those patients, the incidence of CRS was 38.7%, which was markedly contrasted to the patients who did not receive tocilizumab prior to cevostamab, where the incidence of CRS was 90.9%. So, really, the use of tocilizumab prior to the administration of bispecifics reduces the risk of CRS by about two thirds.

Importantly, the use in tocilizumab prior to using a bispecific does not negatively affect its activity, as 54.8% of patients who received tocilizumab responded, which is comparable to 37.2% of patients responding for those that did not receive tocilizumab prior to the administration of cevostamab. These types of results have also been mirrored in another study that used tocilizumab prior to teclistamab.

Switching to the topic of infections and looking at an analysis of over a thousand patients who received bispecifics: most of them received BCMA-targeted bispecifics. In this large cohort of patients, 50% experienced infection and nearly a quarter of patients had severe to life-threatening infection. In fact, 28 patients died due to infection in this large cohort of patients. Importantly, as Dr. Chari mentioned, severe infections tend to be less of an issue with Talvey. That may be because we see that patients who receive Talvey have fewer issues with hypogammaglobinemia. What that means is that their normal antibody levels are suppressed. You see that, with Talvey, fewer patients have very low levels of antibodies, which is in contrast to what you see with BCMA-targeted bispecifics. So it made sense that maybe we could reduce the risk of infection by giving patients what we call IVIG, which is basically giving patients back intravenous antibodies from normal donors.

In a study reported by one of my colleagues, Dr. Lancman, patients who had very low levels of IgG antibodies, less than 400, had a higher risk of getting grade 3 to 5 infections. If we gave patients IVIG, the incidence of getting grade 3 or 4 infections of all types or bacterial infection was markedly reduced compared to the patients who did not receive IVIG.

Other recommendations to prevent infections are avoiding crowds, especially right now with Covid being really rampant, using good hand-washing hygiene, and the use of growth factor support when the white cell count is low.

We talked about the important benefit of receiving IVIG. Immunizations also are recommended, especially at this time of year for RSV, flu, and Covid. With Talvey, patients do seem to mount responses to vaccines, maybe less so with some of the other bispecifics. Monitor for symptoms of Covid. Do Covid testing at home if you have symptoms, because you can be treated with medications such as Paxlovid. We see quite a lot of shingles and *Pneumocystis jirovecii* pneumonia (PJP) for patients who are on bispecifics who are not receiving preventative treatments. It's important that you take preventative treatment for those types of infections. We do see cytomegalovirus reactivation, and some physicians are considering monitoring patients on a regular basis, as there are treatments available for CMV infection.

Finally, I'd like to talk about the combination studies with cevostamab. It has shown really promising activity on its own. However, we do know in myeloma that when we combine drugs, they tend to work better.

In one study combining cevostamab with pomalidomide and dexamethasone in a very small number of patients, all 8 patients that received the combination responded. It is important to note that there was no unexpected side effects or toxicities when combining with pomalidomide. The side effects most commonly reported were as expected, CRS and low neutrophil count.

The bispecifics obviously have been transformative and are showing, as Dr. Chari nicely illustrated, unprecedented activity in patients with advanced myeloma for whom previous treatments failed. But they are not curative, and not all patients respond. So there's still work to do. An approach that others are developing is to use what we call trispecific antibodies, which are antibodies that bind three different targets. These trispecific antibodies have the ability to bind two different immune cells, such as a T cell and a natural killer cell, or to bind to the T cell and then two different targets on the myeloma cells. We hope to see some data on this approach in the near future.

To summarize, bispecific antibodies are very active, even in heavily pretreated patients. The side effects of bispecifics include CRS, neurotoxicities—which tend to be rare—and low blood counts, all of which are very treatable and reversible. Infections have emerged as a more challenging toxicity but, with experience, some comprehensive strategies are being formed to mitigate the risks. Bispecifics are an off-the-shelf immunotherapy—in contrast to CAR T-cell therapy, they can be given right away. There are new modalities that are being explored, and several additional bispecifics are under clinical evaluation.

Mary DeRome: Thank you so much, Dr. Trudel, and thank you, Dr. Chari. We're going to move on now to our patient speaker. Mr. Nick Lenoir.

Can you tell us your experience of being on a bispecific?

Nick Lenoir: I want to start by saying that I'm glad I was on here to hear from Dr. Chari that the more side effects you have, the better it reacts, because I check off a lot of boxes.

Quick history, I was diagnosed almost 8 years ago at 31; I'm looking at 40 coming up. I've run through a lot of drugs, stem cell transplant, CAR T... Finally, talquetamab came to my area, and I did 11 days' inpatient for the step-up dosing. I went in with my kappa light chains at about 170, and I came out after just step-up dosing at 7.34, so I had a great response to it, but also I have a great amount of side effects. The taste loss and dry mouth are probably the worst.

I'm 2½ months into this with step-up dosing. Friday will be my 3-month dose. I'm getting it every other week. haven't tasted food in a long time. I did the soups and finally got tired of soups, and now I'm basically forcing myself to eat. But it's like I've told people over time: I have found that if I can smell it, it's almost like I can taste it. So I try to eat more fragrant foods just to trick my mind. But the dry mouth has changed the texture of foods. So chicken is pretty much out the window. It's a lot of protein shakes every morning. I was a big guy. I'm down 30 pounds from the time I went into the hospital, but I could afford to lose it. So now I just have to maintain.

Skin peeling was a big deal. I looked like I was trying to be a ninja turtle and had dunked myself in some toxic goo. The skin just peeling off my hands, and my feet are still peeling—I'm using lots of lotion.

For those of you that might know me other than here, I had a big, beautiful beard that fell out. I talked to a few doctors about that, and that's not necessarily a side effect but a skin condition. With as dry as I am and other conditions, it came out in handfuls. Now I just got to be a clean-shaved guy for a while.

As an outpatient, you go to the full dose from step-up. I now have the site reaction. It's pretty painful when I first get my injections on Friday morning or Friday afternoon; by Saturday evening, I have a baseball- or softball-sized red mark. By Sunday evening, it's spread across my whole belly. By Tuesday, it starts getting better. It's horrible. You can't touch it.

But it's like I tell everybody: my kappa light chains went from here to here, and they're still going down, and they're maintaining. My M spike's dropped, and everything's looking great. I'll fight through the side effects. I just had my fifth kid, so I will keep taking this drug as long as I need to. We've seen the presentations here: there are a lot of drugs coming up. So if I have to deal with the bad side effects now and maybe there's a drug coming up, I'll do it.

Find little tricks like the fragrant foods. For dry mouth, drink a lot of water, get a lot of hydration. Biotène was recommended for dry mouth, but it didn't work for me. Put a lot of lotion on the skin. Just always remember that the treatment is working, especially for a high-risk myeloma guy like myself—I mean, multiple

times I've relapsed. So it's a battle, but we're doing it. I am happy this drug's here, as nasty and ugly as it can be. I'm happy it's here, it's working. We'll see what comes up next.

Mary DeRome: Thank you so much, Nick, for sharing your experience. I'm sure that they got some great nuggets out of that.

Let's move to the Q&A portion of our program. We've got a lot of questions.

I'll give this one to you Dr. Chari. Should bispecifics and CAR T be viewed as separate therapies that both can be used? Is there a suggested sequence?

Dr. Ajai Chari: It's a great question. As a general rule in myeloma, we've been so busy getting drugs approved that sequencing has not been addressed adequately. It's challenging to do sequences, because there's not always going to be two patients with the exact same sequence. If somebody has one study or treatment and then they have, let's say some side effect or need to travel, they may not be able to immediately do the next therapy for that reason. So it's a really tough question, but I would say my personal bias and approach is that our single best therapy today in myeloma has been cilta-cel. But it takes a while to get to that.

If you have somebody that has generally slow-growing disease, and you have a slot, and they meet the eligibility for a clinical trial, that would be nice to get to. But if for some reason it's somebody who's rapidly exploding and you can't wait for a slot, then the bispecifics are much more practical. But the ideal sequence would start with cilta-cel, because it has such a great duration, 3 years typically. After that, you could potentially go back to all of these therapies. Because that time interval of therapy, which is first and foremost amazing for patients, may also then allow the body and immune system to reset so that you can come in with these other therapies.

There's a joke that if you ask two myeloma doctors, you'll get three opinions. Dr. Trudel, any thoughts?

Dr. Suzanne Trudel: I completely agree with what you've said. The data on cilta-cel is so impressive that, if the patient is suitable and it's very important that they be able to not have this aggressive explosive disease, they're not going to be able to get the product back and then really be in trouble. Also, the data does suggest that patients who have more bulky disease don't respond as well. There are select patients for whom maybe CAR T is not optimal. But for those that are the right patients, I would do cilta-cel first. For those other patients, bispecifics are a great option.

I don't think people should get discouraged if they get a bispecific first. There is still activity with CAR T after, based on some preliminary studies in that patient population. There are other types of CAR Ts coming out with different targets, as

well. So if that's what recommended, and that's the best plan for you, I don't think you should be discouraged by it. It's a good treatment, and there are lots of good options coming down the line, as well.

Mary DeRome: What you presented, Dr. Trudel, about the fixed duration of therapy with cevostamab was very interesting. I'd like to hear from both of you what you think about that type of fixed-duration therapy with any of the other bispecifics, and would they work as well? That seems like it would be an important thing to be able to bring to patients, similar to CAR T. You would have a treatment for a fixed period of time and then you'd be done for a period of time.

Dr. Suzanne Trudel: That's the way the future is going to go. The data is very impressive for patients who achieve a complete response; they really maintain it. We still don't know yet, though, if that's going to be applicable for the other bispecifics. There are some differences. FcRH5 is present on the earlier B cells and maybe on the progenitors and is maybe one of the reasons that these responses are sustained. But I do think that it will likely be the case with all the other bispecifics. It's a question, too, of when the optimal time to stop is. That's not really clear, either.

Dr. Ajai Chari: I completely agree. One of the fascinating parts—the fact that we've been asking this question—has to do with historically never having the luxury of asking when you can stop, right? Because the responses were typically below 50%, and it didn't last long enough. So the option to stop was never even on the table. Now we have these durable responses, and you have to think about the pros and cons.

Theoretically, remissions could be potentially longer lasting if you continue. Maybe somebody who has really aggressive disease like extramedullary disease—those patients tend to relapse faster with all of these therapies—that might not be a group that you would normally do it. But, again, there are some folks who I know personally that have had extramedullary disease and are doing well. So I don't think we know.

The flip side to why you might want to discontinue is a couple of things. Number one, and there was a really good question about T-cell fatigue or exhaustion, right? We call it exhaustion scientifically, but it really is fatigue for laypeople, too. Perhaps you can avert that by giving the T cells a break.

Then there's also this other concern, which fits in into the previous question about CAR T. There's also the impact of these bispecifics on the target. There's been some emerging and really early great data. Dr. Trudel always tells me that I'm an honorary Canadian, and some of this work came from Canada, actually. What they have shown is that one of the downsides of bispecifics relative to CAR T is that the repetitive targeting may result in loss of that target. So that may have

ramifications, let's say if you're going from bispecific for target A to CAR T for target, A. That is something that we're also needing to investigate.

Long story short, the duration of therapy is going to be guided by the immune system, the target, the patient side effects—all of those things. So there's not going to ever be a one-size-fits-all. It's nice to have these options. It's the first time that myeloma patients are actually getting treatment-free intervals. That is amazing, even after transplant, right? We ask people to take lenalidomide maintenance. These data are so encouraging, and what's better than for your quality of life than being off all therapy?

Mary DeRome: Last question for you both. Can you talk about the activity of bispecifics in high-risk disease patients? Do these bispecifics have any impact on AL amyloidosis?

Dr. Trudel, I'll let you go first.

Dr. Suzanne Trudel: Studies so far seem to suggest that the patients that tend not to do as well are the patients who have extramedullary disease, disease that's growing outside of the bone marrow. At least for the BCMA patients that have a lot of disease in their bone marrow and then those with ISS stage 3, but the higher-risk cytogenetics didn't seem to matter as much in those subgroup analyses that they did. Right now, the ones that are most concerning are the extramedullary disease patients. But the responses in those patients are not zero, as mentioned by Dr. Chari. They still see responses, but they may be not as high and they don't last as long. We have to continue to work out strategies. Maybe the combination strategy that Dr. Chari mentioned of talquetamab and Tecvayli would be particularly good for that patient population.

Dr. Ajai Chari: The challenge with doing high risk is a couple of things. First is there's a bias, because truly high-risk patients are getting to a sixth line of therapy. That tells us that their disease is actually manageable, right? About half the patients in all of these studies, CAR Ts and bispecifics, are high risk. In spite of that, we're getting these responses. So standard high-risk definitions are actually less relevant in this population because almost half the patients are high risk by the standard, t(4;14), deletion 17p, chromosome 1 amplification, et cetera.

The second comment I would make is that we really need to distinguish between responses and durability in high risk. A lot of studies will show good responses but the durability is less. What's fascinating is that some of these products are not showing that. I actually just had the privilege of presenting, on behalf of my colleagues at our IMS meeting in Greece, that with talquetamab or Talvey, the PFS curves of high risk and standard risk are super imposable, which is unprecedented. We almost never see that, because, yes, everybody responds, but then high-risk patients typically relapse faster than the standard risk. So this is really exciting preliminary data.

But the final thing I'll say is that, to truly answer this question, you need a randomized phase 3 study. Because these are all single-arm studies, and so you need a bunch of patients that are randomized to treatment A versus B, and you compare a standard risk and high risk in each group. Because if you don't have all four of those groups, you can't really discern whether the drug is preferentially benefiting that subgroup. That's a nerdy policy wonk response. But our current data are really encouraging, and it's great that all of these patients have options that they didn't have before.

Mary DeRome: Thank you. Unfortunately, that's all the time that we have for questions. I'd like to thank our audience for their attention and for the great questions that were submitted. I'd like to thank our speakers, Dr. Ajai Chari Dr. Dr. Suzanne Trudel, and our patient speaker Nick Lenoir for their time and their contributions to today's program.

This concludes today's patient webinar. Thank you.