

FAQs on Non-BCMA-Targeted Bispecific Antibodies in MM

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Transcript

Mary DeRome: Welcome, everyone, and thank you for joining us for today's livestream session, *Frequently Asked Questions on Non-BCMA-Targeted Bispecific Antibodies in Multiple Myeloma*. I'm Mary DeRome, senior director of medical communications and education at the Multiple Myeloma Research Foundation.

Today, I'm joined by Dr. Hearn Jay Cho from the Icahn School of Medicine in Mount Sinai in New York City. He is also the chief medical officer of the Multiple Myeloma Research Foundation. Also joining us is Chloe Ray, nurse practitioner from the Icahn School of Medicine at Mount Sinai in New York City, and Susan Thompson, a myeloma patient from New York City.

Patients and caregivers have a lot of questions about these newer non-BCMA-targeted bispecific antibodies and their role in the various stages of multiple myeloma management. Our panel is going to answer some of these questions, so let's get started.

I'd like to begin by first reviewing what is a non-BCMA-targeted bispecific antibody. Dr. Cho, can you broadly explain the difference between BCMA-targeted antibodies that we may have heard more about and the newer non-BCMA-targeted bispecific antibodies?

Dr. Hearn Jay Cho: These are good questions, because there's an important role played by the target of the bispecific antibody. Bispecific antibodies, at a very broad level, are engineered antibodies that bring myeloma cells together with T cells and turn on the T cells. They're engineered to have two ends. One end sticks to a target on the myeloma cell; the other end sticks to a target on the T cell called CD3, which is one of the on switches for a T cell that activates it to kill a target cell. BCMA is broadly expressed on myeloma cells, so that's a good target to bring together with the T cells to kill them, but there are alternatives. GPRC5D and FcRH5. These are two proteins that are on the surface of myeloma cells, and antibodies that are engineered to stick to those targets—with the other end engineered to stick to CD3— will bring myeloma cells together with T cells, turn on the T cells, and allow the T cells to kill the myeloma cells.

Mary DeRome: Ms. Ray, is administration of a non-BCMA-targeted bispecific antibody largely the same as administration of a BCMA-targeted bispecific? What should patients expect with regards to treatment administration and monitoring, both initially when they first start the therapy and later when they've been on the therapy for a while? How often can they expect to be monitored while receiving this treatment?

Chloe Ray: They're administered either subcutaneously or intravenously, like BCMA-targeted bispecifics. In the beginning, the monitoring is going to be a bit more rigorous than later on, once the patient becomes accustomed to the drug. But they can expect to be admitted to the hospital for at least the first 48 hours, sometimes up to a week, while they receive the initial doses of the drug in what's called a step-up dose. The BCMA bispecifics typically have this, as well, where you get a baby dose and then you work your way up to the target dose.

During that time, you still run the risk of cytokine release syndrome (CRS) and neurotoxicities, just as you would with BCMA bispecifics, so they can expect close monitoring. Once they become accustomed to the drug, they would expect to come weekly, sometimes biweekly, and occasionally bimonthly, depending on how tight their remission is, later on.

Mary DeRome: Ms. Thompson, I understand that you are on Talvey (talquetamab), which is the bispecific that targets GPRC5D, and you've had a stringent complete response. Can you tell us about how the treatment process impacted your quality of life with regard to hospitalization or clinic visits when you first started and now that you're 5 years out with ongoing monitoring.

Susan Thompson: When I got the first dose, I was in the hospital for 3 days. I probably had some sort of event, because I remember being sedated a bit, and towards the end, I just had a headache and they gave me medication for it and I went home. After that, I came back to the hospital every other week to get my infusion.

I have been doing that for most of the time until about 4 months ago. Now I only have to come once a month.

Mary DeRome: It's great to hear that these therapies are working so well for people.

Dr. Cho, we've had several patients asking about the sequencing of non-BCMA-targeted bispecifics relative to other novel treatments. Can you tell us when a non-BCMA-targeted bispecific would be considered, and whether, for example, it would likely be effective in a patient who has had prior BCMA-directed immunotherapy or CAR T therapy?

Dr. Hearn Jay Cho: That's a good question, too. The two latest and greatest myeloma therapies are CAR T cells, which are engineered T cells that are taken from the patient—artificial receptors are inserted into the T cells so that they can recognize myeloma cells, and then they're infused back into the patient.

Then, of course, bispecifics, several of which have been now approved by the FDA. Both of the CAR T cells that are currently approved by the FDA target BCMA, so both of those are BCMA-targeted agents. Two of the three approved bispecific agents target BCMA. That's teclistamab and elranatamab. Happily, talquetamab, which Ms. Thompson is getting on the clinical trial, was also recently approved, and that one targets GPRC5D.

The current approval for talquetamab is for patients who've received at least four prior lines of therapy. Many of these patients have already gotten the standard Velcade, Kyprolis, Revlimid, Pomalyst, Darzalex, and other standard therapies. If a patient has previously received either a CAR T cell or a bispecific that targets BCMA, and they've progressed after BCMA-targeted therapy, sometimes their progression is accompanied by loss of BCMA on the surface of the myeloma cells or mutations of BCMA that prevent either the artificial receptor or the bispecific antibody from recognizing it, so it doesn't stick to them. It makes sense to switch targets in that setting. If someone has progressed on a BCMA-directed therapy, having an option for either a GPRC5D- or an FcRH5-targeted bispecific antibody is a good one.

Mary DeRome: Ms. Thompson, talk to us about your myeloma journey and what was going on when you started on Talvey. What treatments had you previously been on when you started Talvey?

Susan Thompson: I was diagnosed the beginning of 2012, and initially I was treated with Velcade and Revlimid for several cycles. They were gearing me up for autologous bone marrow transplant, which I received 8 months later. It worked very well for 3 years, and I also took Revlimid (maintenance) at that same time. After that, my numbers started going up, so I started getting other medications. I was on Ninlaro, daratumumab, elotuzumab, and I was also on atezolizumab very briefly. Also, I had to get Velcade again, sometime during those couple of years. By then, it was 6 years since I'd been diagnosed, and they offered me this trial with the—I always call it GPRC, but now it's an FDA-approved drug.

Mary DeRome: Dr. Cho, we've been hearing data about treatment responses in relapsed/refractory myeloma from fixed-duration cevostamab, which is the FcRH5 bispecific. Can you tell us about that and what that might mean for patients? Currently, most bispecifics are given to patients until they relapse, but that wasn't the case in at least one cevostamab study.

Dr. Hearn Jay Cho: Historically, myeloma treatments have been continuous very consistent and ongoing, because we know that, for most of the medications that were approved for myeloma in the last 10 or 15 years, if we stopped treatment, patients would relapse quickly, so ongoing treatment was required to keep the disease under control. When we entered into this new era of T cell–directed therapies with CAR T cells and bispecifics, the intention, at least with the bispecifics, was to continue treatment because, as we’ve known historically, myeloma patients relapse if we take them off treatment. But interestingly, bispecifics are being used in other diseases, and in a related disease called non-Hodgkin’s lymphoma, it has been observed that if they go into remission, you can stop treatment and they won’t necessarily relapse. We don’t need to do ongoing treatment to keep that disease under control.

Now, we did not know that when we were going into the clinical trials for these bispecific agents, so the great success we were seeing with very deep remissions and very long durations of remissions was an important new finding, which then led to the idea that, perhaps, this is a type of therapy that we can give for a limited amount of time, patients go into remission, they don’t necessarily have to continue the treatment. This is needs to be examined individually for each of these agents, because they’re different. The early results from the cevostamab trial are very important, because they give us a hint that perhaps there’s a subset of patients who will do well for a long time on a limited duration of treatment.

That means a lot for patients’ quality of life, as Ms. Thompson related. She was coming in to the clinic every other week to get an infusion. Now she comes once every 4 weeks. Wouldn’t it be great if we could give that treatment for x amount of months or a year and then, if the patients are in remission, stop the treatment? It’s an important thing to know. We were taken by surprise by the great success of these agents.

We now have to think differently about how we’re going to apply these in clinical trials. We need that data from clinical trials that will tell us it’s safe to stop treatment after x amount of treatment, so that’s really an important ongoing area of research.

Mary DeRome: Ms. Ray, aside from studies looking at fixed-duration treatment, how long should patients typically expect to stay on a non–BCMA-targeted bispecific therapy?

Chloe Ray: As Dr. Cho was just saying, we’re hoping to cut it from forever to a finite number of months, hopefully after 12 months. With cevostamab, it’s 17 cycles and then stop. In Ms. Thompson’s case, we’ve been on the drug for 5 years and still going strong, but we do still need the data to tell us when it’s safe

to stop. Patients typically will be on it for as long as they're in remission. If their numbers start to go up or they have side effects that are intolerable, we may take them off or decrease the frequency that they're coming in. A lot of these patients, even though Talvey is not approved for monthly administration right now, do go to every-4-weeks dosing, because they're in such a stringent remission and the side effects were such that they do better at a reduced frequency. It is still case-by-case, but hopefully we'll get the data where we can safely give people a year and then get them off.

Mary DeRome: Dr. Cho, what do we know about the use of non-BCMA-targeted bispecifics in high-risk myeloma patients, such as those that have a 17p deletion or a 4;14 translocation, both newly diagnosed and relapsed/refractory? Has this been well studied? Are they being dosed in trials in newly diagnosed patients?

Dr. Hearn Jay Cho: A small number of trials have been initiated that are giving bispecifics in very early lines of treatment, so not necessarily with the first treatment. For example, for patients who don't have a great response to a transplant after induction chemotherapy, there are trials that are putting patients onto a bispecific as a consolidation of the transplant step. We're hoping to, for example, take advantage of patients' immune systems being more fit. If they're earlier in treatment, they haven't had a lot of chemotherapy or other types of therapy. That's an important question that we're investigating now.

High-risk patients, we know them based on certain genetic features of their tumors. We know that patients, for example, whose tumor has a translocation of 4:14 or amplification of chromosome 1 or deletion of chromosome 17—these are patients whose disease tends to behave more aggressively. How do these patients do with immunotherapy, which is fundamentally different from chemotherapy? Instead of trying to poison the tumor cells with these toxins that'll kill them and hopefully have relatively few side effects on normal tissue, we're guiding the patient's own immune system to these cells and having the immune system eradicate the disease. It's an important question, because about 10% to 20% of patients have high-risk features, and it's important to understand what the role of immunotherapy is going to be for them.

In the clinical trials that have been published—and this is for teclistamab and elranatamab, which are BCMA bispecifics, and with talquetamab, which is a GPRC5D bispecific—there were patients with high-risk features that were part of these clinical trials. What they do in these trials is something called subset analysis, so they report on the response rates and the duration of responses for all the patients in the trials. But for certain groups that might be of special interest—for example, patients who are over 75, patients who have renal failure, patients who have high-risk features—in the subset analysis, in the published trials, the response rates in the high-risk group were similar to the response rate

of the overall group. In other words, there was not a statistically significant deviation that it was lower response rates or shorter durations of response.

But the caveat is there weren't enough high-risk patients to make that finding statistically significant. We have early information that suggests that these bispecific agents are just as effective in high-risk patients, but we don't know that with statistical certainty. There are efforts under way to specifically test high-risk populations with these new immune therapy agents, so that we know for certain whether they're just as good in the high-risk patients as they are in standard-risk patients. That's an important question that we are also trying to answer.

Mary DeRome: Let's switch gears and talk about side effects, because there are some side effects seen with the non-BCMA-targeted bispecifics that are similar to what we viewed previously with the BCMA-targeted bispecifics, effects like CRS and cytopenias, but we are seeing some adverse events that are unique to some of these newer agents.

Dr. Cho, can you tell us about the on-target off-tumor effects seen with GPRC5D and FcRH5 bispecifics? We learned, recently, that some of the more severe skin and nail side effects that are seen with the GPRC5D bispecifics may actually correlate with better treatment efficacy. Has that been your experience, as well?

Dr. Hearn Jay Cho: That's a good question. These agents are very powerful, because they are targeting proteins and other markers that are expressed on myeloma cells, so they're present on the surface of myeloma cells. Unfortunately, we don't have targets that are exclusively expressed in myeloma cells, so targets like BCMA, GPRC5D, and FcRH5 are also expressed on other tissues, so there is the risk that the bispecifics will direct immune responses to those normal cells, including other immune cells. Because they deplete certain populations of immune cells, patients are vulnerable to infection. We know that.

In the case of GPRC5D, it's also expressed in epithelial tissue, so this is why we see these effects in the nail beds, on the skin, in the mucous membranes, and this is why it can do things like cause the nails to become brittle, it can affect taste and salivation, it can affect the sense of smell. These are side effects that are on the target but they're not on the tumor. Similarly, FcRH5 may have effects in other types of immune cells, which may predispose for, for example, inflammatory side effects. These are important to understand, because we need to manage those side effects to effectively deliver these therapies.

About the rash, we have seen some correlation between skin and nail side effects with GPRC5D and efficacy. In other words, patients who show these effects are also showing better responses in the myeloma, as well. It could be that this would be an early indicator of effectiveness. Obviously, we don't want it to become so severe that it interferes with patients' quality of life, but these are

important observations. It makes sense, with the biology of these agents in myeloma patients.

Mary DeRome: Dr. Chari was telling us about this, and we had a patient in a webinar who was on Talvey who had these side effects, but he felt much better after he found out from Dr. Chari that that meant that the drug was working.

Ms. Ray, there were several questions about patients' loss of taste with these drugs. What do you tell your patients who are experiencing this? What should they prepare for?

Chloe Ray: In the beginning, I think, is the most difficult time, because they're receiving the drugs so frequently. Loss of taste is pretty universal among all the patients that I've seen on Talvey. It does typically improve with reduced frequency or reduced dose. Whether it's 100% resolved by coming off the therapy is case-by-case. Certain patients I know have reported that they get monthly dosing, and then for 2 days after their dose, they have a bit of an off taste, and then it goes away completely. Everybody is a bit different that way, but generally, with the reduced dosing frequency, they do see improvement.

In terms of dental issues, I think across the board with all chemotherapies, immunotherapies, you're affecting the oral mucosa, you're drying out the mucous membranes, and that puts you at risk for dental issues. We don't do anything more than encourage oral hydration. Lozenges helps with taste and keeping everything moist, and then seeing your dentist every 6 months, making sure that your general dental hygiene is up to date.

Mary DeRome: Ms. Thompson, I understand that you had some of these taste issues, and also some aches, while you were on Talvey. But they were worse in the beginning, as Ms. Ray mentioned, and they have subsided some now that you're not being dosed as frequently. Can you tell us about these side effects and how they may have changed over the 5 years that you've been on this drug?

Susan Thompson: Usually, every time I get treatment, I do experience some change in taste for a couple of days. I've noticed that now, these last couple of months, the time period has shortened, so maybe it's only 1 day. If I get the medication on Friday, then Saturday I have the little taste changes, and then by Sunday it's gone. As far as pain goes, I think every now and then I might get a little headache, but it's really not a big thing.

Usually, it's when I get up in the morning. I get up, I go downstairs, get something to drink, and then it subsides. I'm pretty okay, but there is one thing I always tell the people who are caring for me, that I do have changes to my hair. My hair, the texture has changed somewhat.

Mary DeRome: Can you elaborate on that?

Susan Thompson: My hair is curlier since I started taking the medication. I used to wear very short hair. Dr. Cho has not seen me in about a year, he said, “Oh, my God, you have long hair.” I let my hair grow so that the curls aren’t as tight. Then, when it’s longer, it drops down a little. It’s curly.

Mary DeRome: Dr. Cho, this year there was some data on pre-treatment with tocilizumab and its effects on reducing incidence of CRS in relapsed/refractory patients receiving cevostamab, and we’ve seen that now at a couple of different meetings. What can you tell us about that, and what does it mean?

Dr. Hearn Jay Cho: CRS is one of the most prominent and common side effects of these classes of agents, and they come about because, in the initial treatments when a patient has a lot of tumor cells, the wholesale activation of T cells against these tumor cells causes a lot of inflammation, a lot of immune activation. This can mimic a very bad infection. It’s called cytokine release syndrome because T cells make a lot of signaling molecules called cytokines, which mediate things like fever, low blood pressure, body aches, confusion—all these are hallmarks of the CRS.

One of the big cytokines that is involved in this is called IL-6, and tocilizumab is an antibody that sticks to IL-6 and takes it out of circulation, reducing some of those symptoms, and so it is one of the mainstay treatments for the management of CRS. Historically what we do is we would carefully administer the early doses of these agents. If the patient developed fever and other symptoms, we would give them tocilizumab and observe—this was all in the hospital—and we would observe and make sure that they stabilize and don’t have any further CRS symptoms. Fortunately, tocilizumab lasts a long time, so it usually rides out the first couple of treatments and then, often, because the number of tumor cells is drastically reduced by those first couple of treatments, we don’t see cytokine release with later treatments. But there was a lot of interest in using tocilizumab before the symptoms develop, to prevent these symptoms from occurring at all, and maybe ultimately keeping patients out of the hospital.

There are clinical trials where they are giving tocilizumab a couple of hours before the first treatment to see if that prevents the CRS. This is important and we need to understand if that’s feasible, because ultimately, for quality of life we want to keep patients out of the hospital.

There is another side to that question, because there are some theoretical reasons to believe that maybe that first burst of inflammatory activity is important to the long-term effectiveness of these agents. We need to do this in clinical trials to ensure that giving tocilizumab as a prophylactic—in other words, before the symptoms occur—doesn’t interfere with the overall effectiveness of these agents.

Mary DeRome: Ms. Thompson, I know that risk of infection is also higher when you're taking these agents, and I know that you take precautions to decrease your risk of infection. You've been on this drug for 5 years; can you tell us your methodology for decreasing risk of infection?

Susan Thompson: I've been practicing my decreased risk of infection since I had my bone marrow transplant. If I go for a pedicure, I don't allow them to cut the cuticles. I try not to go into a big crowd. If I go to a gathering, I try not to let people hug me, and so forth. I also try not to be around very young children, because they have a lot of germs.

Basically, that's it. I'm very lucky in that I live in the suburbs right now, and I'm retired, so I don't have to go on the subway in New York City and get exposed to a lot of people. Also, I'm very careful about what I eat, because if I eat food that's been sitting around a long time, I could get some stomach issues, so I try to eat food that's fresh.

Chloe Ray: Really good advice for everyone.

Mary DeRome: Have you had any issues with Covid or anything like that? Because you were taking this right through that.

Susan Thompson: I didn't have any issues with Covid, although when I went for treatment, the nurse told me that my antibodies had gone. She said I must have been exposed to Covid, but I didn't have any symptoms.

One more issue, when I do travel, for instance, since Covid, I went to Jamaica and then I also went to Europe. Both times when I came back, I did end up with an upper respiratory infection of some sort. But it wasn't Covid either time.

Chloe Ray: A lot of our patients will get monthly intravenous immunoglobulin (IVIG), patients on bispecifics and not on bispecifics, just in the myeloma community, because we know that their immunoglobulins are suppressed by the myeloma and that they are at increased risk of infection. Most patients, at least at some point in their myeloma journey, will receive IVIG. But the GPRC5D patients have a lower risk of infection than the ones taking BCMA bispecifics, generally, so that is one upside of the GPRC5D bispecific, I guess.

Dr. Hearn Jay Cho: Before we move on... Ms. Ray, what are some of the other prophylactic things that we do for our patients who are getting these immunosuppressive agents?

Chloe Ray: They're all going to be on antivirals, so acyclovir, Valtrex, those sorts of things, they'll be on indefinitely. With a lot of these immunosuppressive agents, we will put them on *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis, so something like Bactrim or Mepron, for the duration of them being on this therapy, in addition to the IVIG.

Mary DeRome: We're going to move on, now, to our final thoughts.

Ms. Ray, how have bispecifics, both the BCMA-targeted and the non-BCMA-targeted, affected the outcomes of the patients that you manage? Are things getting better for these patients?

Chloe Ray: Absolutely. Our enrollment in research trials is down because so many patients are doing well.

Patients are in sustained remissions for years now. Darzalex did that, too, the same, you know, even better. It's very exciting and it's great for the patients, because it's not a pill they have to take, it can be minimized to monthly the way Ms. Thompson is living her life, and it's extending people's lifespan by who knows how many years.

Mary DeRome: Things have really come a long way since I joined the myeloma field in 2014. Back then, there wasn't much, but now there are all kinds of new drugs.

Ms. Thompson, after your 5 years on this drug, it sounds like you've had a largely positive experience, with a favorable outcome and side effects that aren't so horrible. Is there anything you want to say to other patients who might be considering this class of treatment and might be concerned about some of these side effects?

Susan Thompson: It's been great for me. After I got the first dose, my numbers went down tremendously. I haven't had any really bad side effects. If your food tastes different for 1 or 2 days, you just put some hot sauce on it and continue to eat. Especially if you only have to go, like I do now, once a month, you're still able to continue with other activities and be around your family and friends. I think if you can have this medication, then you probably won't have a lot of other side effects and you'll live your life.

Chloe Ray: One thing to note is that we also do have prophylactic and treatment measurements for the nail, skin, and oral toxicities. Starting those up front, like Vitamin E oil and certain heavy moisturizers for the skin, can be really effective. Lozenges for keeping your mouth moist. We're trying to roll out an icepack, parotid gland icepack that patients would wear as a headband around the parotid glands, after treatment, which might lead to some improvements but is also a commitment from the patient. They have to do it for, like, 3 hours a day for a period of time, so, if you want to try that, you can. Anecdotally, we've had a few patients that have said that it does help with taste changes. That's just on the research side of things.

Mary DeRome: Dr. Cho, we've seen a lot of data recently with non-BCMA-targeted bispecifics in combination with other treatment regimens. I've even been

hearing about trispecific antibodies. What do you think that we can expect from the non-BCMA bispecifics or trispecifics, both in the near future and further down the road?

Dr. Hearn Jay Cho: I think we're very fortunate that we're in an era where we have effective treatments, treatments that are effective even in patients who've had multiple prior treatments. That patients are getting deep remissions and long-lasting remissions with these new treatments. I fully expect that there will be more approvals for bispecific agents in the very near future, hopefully within the next year or so. The next step is to make them even more effective. There are a number of clinical trials with combinations of bispecifics with other types of treatments for myeloma. I think there's really a lot of interest in combining them with other immunotherapy agents so that you can get a complete immune response against the myeloma, the diseased cells.

When we put things all together, we are seeing even greater effectiveness, but we are also seeing more serious side effects. The next challenge is understanding how to combine bispecifics with other therapies in a way that maximizes their effectiveness but minimizes those side effects, particularly things like infections. That's one thing we're very conscious of. There's really an ultimate goal to arrive at combinations of therapies that can be delivered for a limited period of time, so that patients can have long durable remissions even they have stopped therapy. I'm grateful, every day, that we have these agents that we are now able to give to patients, even ones who've had all the standard chemotherapy agents.

There are new agents coming that may be added to the armamentarium against myeloma. There are trispecific antibodies that are trying to harness other aspects of the immune response against myeloma cells. So it's a very exciting time to be working in this field. Many of us have hope that we are going to arrive at treatments that will confer long-lasting remissions—ultimately cures in this disease. There's reason for optimism. There's a lot of work that still needs to be done, but we do this in collaboration with our patients and our colleagues. We are hopeful for the future.

I want to thank Ms. Thompson and all the patients who participate in clinical trials. It takes a lot of courage to do this, but it's necessary for us to move the field forward. I'm incredibly grateful that our patients trust us and work with us on these clinical trials, because we're trying to make better therapy for everybody.

Susan Thompson: Well, thank you all for taking care of me.

Mary DeRome: I would also like to thank Dr. Hearn Cho and also Chloe Ray for being with us today.