Title: MMRF Patient Webinar Bispecific Antibodies in Multiple Myeloma

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Mary DeRome: Hello and welcome to the MMRF Patient Webinar 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.

Today we'll be hearing from two myeloma experts who will discuss the bispecific antibodies used in multiple myeloma treatment and the findings on these agents that were presented during the recent International Myeloma Society and American Society of Hematology meetings.

We'll hear from Dr. Noa Biran from the John Theurer Cancer Center at Hackensack University Medical Center in Hackensack, New Jersey, and Dr. Gurbakhash Kaur from the University of Texas Southwestern Medical Center in Dallas, Texas.

Let's get started with our first speaker.

Dr. Noa Biran: Hi there. Nice to be on this important talk about all the novel therapies we have that were recently approved for our patients.

It is quite an exciting time in the world of multiple myeloma, because we have therapies that are really changing what we call the standard of care. I'm going to go through some of these treatments today.

Bispecific antibodies: what are they? To refresh your memory, an antibody is a therapy that directly targets a receptor or a protein on a specific cell. A simple type of antibody would be a CD38 monoclonal antibody, which targets one part of the cell; examples are daratumumab and isatuximab. Another monoclonal antibody approved in myeloma, elotuzumab, targets a different protein called SLAMF7—CS1 is the other name for it.

But now we have a new type of antibody, a bispecific, which doesn't only target a protein or an antigen on a multiple myeloma cell but also target your own body's T cells or immune cells. There are a lot of different names for them, because they target two different receptors: you can call them dual-specific antibodies, bifunctional antibodies, T-cell engagers, or T-cell engaging antibodies.

The way they work is that they target two cell surface molecules simultaneously. They bring the multiple myeloma cell right next to the T cell, which causes a number of things to occur. First of all, it allows the T cell to directly kill the multiple myeloma cell, but the T cell also becomes activated, so it starts to produce a lot of proteins. Some of the proteins are called perforin or granzyme proteins that target not only the multiple myeloma cells it's attached to but other

myeloma cells in the vicinity. It also can recruit other T cells to the area, because it's causing inflammation in the body. Then other T cells flock to the area, because it's a warning that something is wrong, and they kill the myeloma cell, as well, or the other myeloma cells in the vicinity. It has multiple target ways of working, multiple mechanisms of action, and it's very useful in our clinical practice, because they are very effective in terms of response.

The other benefit of bispecific antibodies is that you don't have to wait. They're not a cellular therapy. For example, CAR T cells, you have to extract the T cells, you have to wait for them to be manufactured. It can take anywhere from 5 to 8 weeks. It's a more cumbersome process, whereas these types of therapies are what we call off-the-shelf or readily available and can be administered at any time.

What is a good target? How do we identify an ideal target for these bispecific antibodies? One of the arms attaches to CD3, which is on the T cell, but for the other one, we have to find a target that's highly expressed on myeloma cells. You don't want it to be expressed on only 10% of myeloma cells. You want almost all cells to express this receptor. But you also don't want it to be expressed on healthy cells, because that's where you get side effects. If it's expressed on healthy, for example, taste buds, you're going to have problems with taste. If it's expressed on skin or nail cells, you're going to have problems in that regard. Sometimes we can't help it. But when we're looking to develop an ideal antibody target, we want something that's highly expressed on myeloma cells and not highly expressed on healthy cells.

One of these targets that we've been working with for quite some time is called BCMA. We know that myeloma patients have significantly higher serum BCMA levels than healthy individuals, and that's how this target was identified. Another target is GPRC5D, and those two have FDA-approved bispecific antibodies. BCMA- and GPRC5D-target bispecific antibodies are already identified to be effective and safe and are approved. GPRC5D is expressed on myeloma cells in the bone marrow. It has low expression on hair follicles but not on other cells. Also, this has no correlation with BCMA, so it doesn't matter if you express BCMA or not. GPRC5D is still highly expressed.

Another antigen or receptor that we have been evaluating as a potential target for bispecific antibodies is called FCRH5, and this receptor is expressed on some B cells and on plasma cells. There are ongoing trials looking at bispecific antibodies targeting this receptor.

What is the current state of bispecific antibodies? First of all, before I tell you this, we need to look at what is the expectation in patients for whom the three most common classes of drugs—proteasome inhibitors, immunomodulating agents, and monoclonal antibodies—have failed. When we looked at other therapies

such as Selinexor or other agents in that patient population, triple-class exposed or triple-class refractory, we expected about a 30% response rate, and that was enough to get the therapy FDA approved.

Now we have therapies in the same type of patients where we're seeing double or more of the overall response rate, 60% to 70%. This is seen in patients that are triple-class exposed or triple-class refractory, which is our heavily pretreated patients. Not only are we seeing the therapy work, but there are a significant number of patients who are achieving complete response (CR), which is a much deeper level of response, or a very good partial response (VGPR), which is a 90% reduction in tumor burden.

The two approved BCMA CD3 bispecifics are Tecvayli (teclistamab) and Elrexfio (elranatamab). Several more bispecifics targeting BCMA and CD3 are in ongoing trials, including linvoseltamab, alnuctamab, and ABBV-383. We're going to look at some of the studies and the preliminary data on these three drugs.

Tecvayli was the first FDA-approved bispecific T-cell engager; it targets BCMA, its name is teclistamab. The studies that evaluated teclistamab were named MajesTEC—all therapies have their own names of clinical trials. The MajesTEC-1 study evaluated teclistamab in patients who never had a prior BCMA-targeted treatment.

What drugs around the time of the study were BCMA-targeted treatments? There were two. One was belantamab, which is not on the market at this time. It's a BCMA antibody–drug conjugate (ADC) that works differently. BCMA-directed CAR T cells, of which there were two—not many had seen those drugs at the time. This study removed patients who had prior exposure to a BCMA-targeted therapy, and it saw a response rate—meaning what percentage of all the patients responded—of 63%. That was remarkable in this particular patient population, double what we would expect.

In the LocoMMotion study that compared teclistamab to real-world clinical practice, we saw that when the same group of triple-class exposed or refractory patients got the standard of care, they had a 26.8% response to therapy. With teclistamab, we saw double that response rate, with 32% achieving a CR.

In the MajesTEC-1 study, 32.7% achieved a stringent complete response (sCR)—that means, a CR that was confirmed by bone marrow aspiration. Of 165 patients, almost 40% achieved a CR. The median duration of response was 18.4 months. In this particular patient population: very, very, very good results.

Now, what happens in patients who have had prior BCMA-targeted therapy? Of the 165 patients in the MajesTEC-1 study, 29 had prior BCMA, the ADC belantamab; maybe they had a different one. But 55% responded. Maybe slightly

less of a response, but you're still seeing effectiveness of the therapy even in patients that had prior belantamab, which is important.

Then what about CAR T-cell patients? Patients that already had a CAR T and then received Tecvayli had a 53.3% response rate. The same with ADC and/or CAR T. More than 50% of the 40 patients who had one or the other had a response. That's very important, and it proves a principle that maybe prior BCMA therapy reduces the rate of response, but it doesn't take away from the fact that it's still likely to work.

That's single-agent teclistamab. What about combining it? We have a lot of ongoing studies looking at many different combinations with teclistamab combined with other therapies. Tecvayli plus daratumumab in patients with three or more prior lines, that's the TRIMM-2 study. We're seeing responses approaching 74% with this dose every 2 weeks. If you lower the dose to 1.5 mg/kg but give it weekly, you see a 75% response rate. But if you are giving it at 3 mg/kg subcutaneously, injected under the skin in the area over the stomach once weekly, you see a 100% response rate. This is still early data, but this is certainly remarkable and very promising. What's going to be more important is the durability—not just does it work, but for how long.

Now if we combine it with a triplet—so teclistamab plus daratumumab plus lenalidomide—in patients with one to three prior lines—so this is an earlier line of therapy; the patients are not as heavily pretreated—we see a very high response rate, 93.5%.

It's not just about how well it works. It's also about how long it will work and what the side effects are. We don't want to cause a lot of infections. Infections are really the main concern, and we're going to go through a lot of these side effects shortly. We want to make sure we don't give our patients severe infections or quality-of-life–altering infections where they can't live a good quality of life. [00:19:00] Ninety percent got infections, but only about 40% were severe; grade 3 or 4 means severe. Real-world experience.

This study asked the question, is what we see in reality comparable to what the trials show? Because trials do tend to pick really good patients with good kidney function, good blood counts, very compliant patients. Are we seeing the same thing in the real world? Pretty much, yes, we are. They looked at a cohort of patients that was similar. The response rate was the same. The median progression-free survival (PFS) was 5.4 months in the real-world data. In the trial, it was longer; it was 11.3. Again, we need to see whether there are patients that aren't exactly the same as they were in the clinical study.

What about prior BCMA therapy? One real-world study looked at patients who received teclistamab and had a prior BCMA therapy and compared the results to the MajesTEC-1 trial. At about 3 months, about half of the patients who had prior

BCMA therapy had already progressed compared to 90% of BCMA-naive patients. This shows that it still works in patients who had prior BCMA therapy, but maybe not as well and not as long.

Now, the Horizon study is going to be open very shortly. It's an adaptive platform trial, meaning that the study design changes based on the results. It's a good way of evaluating a new therapy. It looks at different therapies at the same time in the relapse setting. The control arm is going to be a teclistamab treatment with different schedules and dosing to see if maybe we can evaluate the efficacy in a safer way, reduce infections, and improve patient quality of life.

Elrexfio (elranatamab) is another BCMA CD3 bispecific T-cell engager. The studies that look at elranatamab are called MagnetisMM; there's all different numbers of MagnetisMM studies. This drug is FDA approved. The MagnetisMM-1 was the phase 1 study, a dose-finding study. Ninety one percent of patients were triple-class refractory, meaning that we expected a less than 30% response rate in these patients and a median duration of response or median PFS around 3 to 5 months. The response rate was 64%, with a median duration of response of 17.1 months. That's not the median PFS, but it's still an important end point. It speaks to the efficacy of this class of drugs. This particular one is effective, as well.

Elrexfio in patients without prior BCMA, that was part of the MagnetisMM-3 study. This was the phase 2, so we already knew the correct dose. These patients were refractory to at least one proteasome inhibitor, one immunomodulator, and one anti-CD38. They had no prior BCMA. Sixty one percent responded.

Another analysis looked at all the MagnetisMM studies of patients who had prior BCMA therapy, and we're still maintaining response rates around 50% in those patients. In patients who had ADCs or prior CAR T cell, we're seeing response rates between 42% and 53%.

In terms of PFS—PFS means at a point in time where patients have not yet relapsed—at 21 months, 50% had still not relapsed, which is impressive in a very heavily pretreated patient population. Median PFS was 17.2 months. Patients less likely to respond were those with a higher burden of disease and/or high-risk cytogenetics: patients with ISS stage 1 or 2 at diagnosis, high-risk cytogenetics, extramedullary disease—that means disease outside of the bone, which tends to not respond as well to therapy—and/or more than 50% bone marrow involvement still responded. Penta-refractory—that means refractory to five classes of drugs—patients are a harder-to-treat population, and you're still getting adequate response. Patients who are ISS stage 3, where all of those high-risk features make a difference—high-risk cytogenetics, extramedullary disease, and penta-refractory—still not a great response. We have to do better for those patients. Maybe it's going to be combination therapy, like we saw before.

For side effects, in 123 patients we saw low blood counts. That's expected. Also, 67% had infections, 47% of which were severe. Diarrhea was common, not severe, but we do see it in 44%. Fatigue. Decreased appetite. We need to work on preventing infections in these patients.

The LINKER-MM1 study evaluated another BCMA CD3 bispecific T-cell engager called linvoseltamab in patients with relapsed/refractory myeloma. This study started as a phase 1 to find the appropriate dose and then opened into an expansion cohort of phase 2 once the appropriate dose was found. It enrolled patients who had three or more lines of therapy, and they had to be triple exposed or triple-class refractory. Again, a very hard-to-treat patient population less likely to respond.

In this study, linvoseltamab was given through a step-up dosing schedule starting at once a week. For patients who achieved a VGPR, meaning a 90% reduction in tumor burden, the drug was switched to monthly or, if less than a 90% response, every 2 weeks.

We're looking at increasing the intervals between dosing and determining how that affects response. The response was high, at 69.2%, with 33% of patients achieving an sCR and median time—that means how long it took to achieve a partial response or better—of 1 month. We're seeing deep responses very quickly. There were 10 patients who previously had belantamab, which is the BCMA ADC, and their response rate was 70%. Prior BCMA exposure didn't appear to affect response in a small patient population. There were 37 patients with CR or sCR who were evaluated for minimal residual disease (MRD), and 50% were MRD negative. That's very impressive in a relapsed patient population, patients who were heavily pretreated and triple-class exposed or refractory.

The side effects seen in this study included cytokine release syndrome (CRS), diarrhea, cough, and fatigue. The incidence of low blood counts were a little bit lower than in the previous study but still significant. In terms of infections and opportunistic infections—that means infections caused by very low blood counts and an immunocompromised state—there were some rare infections that we don't typically see in myeloma patients, such as *Pneumocystis jirovecii* pneumonia (PJP) or cytomegalovirus. Upper respiratory infections were fairly common; not many were severe.

Alnuctamab, another BCMA CD3 bispecific, was investigated in a dose-finding phase 1 study. There were different responses with different doses, but at the 30-mg target dose, the response rate was near 70% with similar side effects, infections, CRS, and low blood counts.

ABBV-383 was evaluated in a phase 1 dose-finding study. They looked at different dose schedules: 20 mg every 3 weeks, 40 mg every 3 weeks, 60 mg

every 3 weeks, or 60 mg every 4 weeks. Response rates appeared similar, though once you get beyond 20 mg, there was a little bit of a reduction in CR when you stretch it out to 4 weeks. That may not be the ideal dose, but we also have to look at toxicity.

For side effects, at the every-3-week doses, there were similar grade 3 or 4 infections: 22%, 24%, and 34%. At the monthly dose, that was reduced to 10%. That schedule might be worth considering, even if we're not getting as deep a remission. Pneumonia was seen at the 3-week doses, with levels much lower at the every-4-week schedule.

What are these side effects that I've been referring to? CRS is a phenomenon that occurs not just with bispecific T-cell engagers but with many types of immunotherapy, including CAR T-cell therapy. What happens is, once you start activating those T cells, you can have what's called cytokine storm. Those cytokines or proteins trigger inflammation everywhere in the body. That can lead to difficulty breathing, liver enzyme abnormalities, kidney problems, low blood counts, fevers, fatigue, headaches. You can also have neurologic issues from all of that inflammation; for example, tremors and forgetfulness. Some people, if it's severe, have a seizure and/or cardiovascular effects. Any part of the body can be affected, and that's why we do what's called step-up dosing. We start really low and we slowly increase the dose while you're in the hospital, so that if you develop CRS, it's treated right away.

There is an early intervention that makes a big difference and reduces irreversible damage and significantly reduces CRS. A therapy called tocilizumab reduces the cytokines, in particular interleukin (IL)-6, which drives a lot of this process.

The other expected toxicities are infections, so it depletes your lymphocytes and a lot of other healthy immune cells. We have to be proactive, get vaccines. We have to ensure proper hand-washing. Avoid crowds. We use growth factors as needed, granulocyte-colony stimulating factor (G-CSF) or even red cell growth factors. We give immune globulin for people who have low IgG. COVID prevention and vaccinations are important, but no live vaccines. We check your CD4 count, which tells us if you need a medication to prevent PJP. We give acyclovir or valacyclovir for zoster or shingles prevention.

Other side effects are low blood counts and neurotoxicity, which is part of CRS, but it can be more severe and affect the brain. It's extremely rare in this type of therapy. Centers that are certified to administer bispecific T-cell engagers are well versed in how to treat neurotoxicity and immune effector cell-associated neurotoxicity syndrome (ICANS), and it can be prevented or treated with tocilizumab or steroids, dexamethasone, without affecting response.

To give you a summary about BCMA bispecifics, these are excellent therapeutic options. They're off-the-shelf; two of them are approved, Tecvayli (teclistamab) and Elrexfio (elranatamab). The differing factors between the BCMA bispecifics include the route of administration and step-up dosing. You have to be in the hospital for the step-up dosing to prevent adverse events. We have to be very careful with managing infections, preventing infections, being proactive. If we see the start of an infection, we treat accordingly. We have ongoing studies that are going to benefit response, help improve response rates with combinations and newer BCMA-targeted bispecifics, and hopefully reduce infection, if we can alter the schedule and the dose a little bit.

Okay, so I'm going to hand it over to Dr. Kaur, and then we'll have question time at the end. Thank you.

Dr. Gurbakhash Kaur: The focus of my talk will be more on the non–BCMA-directed bispecific antibodies. As Dr. Biran highlighted earlier, we have developed specific ways to target myeloma cells, and bispecific technology is one of them.

On the myeloma cell is an antigen called GPRC5D, and Talvey (talquetamab), which is currently approved for patients with relapsed or refractory multiple myeloma who have received at least four lines of therapy, has been tested in the phase 1/2 MonumenTAL-1 study.

There were 288 patients, both with or without prior T-cell redirecting therapies, who received Talvey at two different subcutaneous doses, 0.4 mg/kg every week and 0.8 mg/kg every other week. There is a trend to decrease the weekly infusions without compromising efficacy. For the 0.4 mg/kg-weekly and the 0.8 mg/kg-every-2-weeks doses, the response rates were 74.1% and 71.7%, respectively. For patients who had a prior T-cell redirection—whether a BCMA antibody or a bispecific antibody or CAR T—the response rate was slightly lower, at 64.7%. That is still pretty remarkable to get this degree of response. We did not see the depth of responses that we're seeing with bispecific therapies in general with prior therapies that were studied in multiple myeloma.

With each bispecific therapy, depending on the target, we have a diverse presentation of side effects. As Dr. Biran highlighted, one of the main concerns is infections, because that is the pattern that we saw. When it came to Talvey or talquetamab in patients with relapsed/refractory myeloma, aside from the general low blood counts—the anemia, neutropenia, and thrombocytopenia—what stood out was the skin-related and the GI-related side effects that were seen. CRS, which is commonly seen with immunotherapy with both CAR T as well as with bispecific therapy, was observed, and any grade was about 79%. Most of it is grade 1 and 2; the high grade, which is grade 3 and 4, was only 2.1%. That is one of the common side effects that we see with immunotherapy. It's good to see

that this mostly was grade 1 and grade 2. Taste disorder (dysgeusia), skin-related toxicity—we'll discuss that toxicity further down the presentation—and nail-related changes were anywhere between 55% and 72%.

When taste is affected, what else is affected? Your weight is affected. We saw that 41% of the patients had a reduction in their weight with the 0.4 mg/kg dose, and it was comparable to the 0.8 mg/kg dose. It was similar with taste, but slightly higher with skin-related effects when it came to the 0.8-milligram dosing.

There was a prospective way to see the depth of response if you reduced the dose. The Talvey dose reduction typically occurred after patients achieved a response, because we did not want to compromise the efficacy, how well the drug works. The depth of the response and the median time to dose reduction was about 3.2 months if you were on the weekly regimen, 4.5 months if you were on the every-2-week dosing. If you had a prior T cell–receptor therapy, that was about 4.7 months. Patients still maintained responses following the prospective dose reduction, with some patients still going on to have deeper responses. For responders with dose reduction, outcomes in terms of their median follow-up and their duration of response, 19.8 months in the weekly, and 24.2 months in the 10 patients who had prior T-cell redirection therapy (TCR).

When you did a dose reduction, did the patients actually benefit from that in terms of the toxicity? Did the rashes or the skin toxicity go down in the ones where the dose reduction was done? About 66.7% of patients had a reduction in their skin toxicity in comparison to 41.2%, and that's total resolution. A higher percentage of patients who did not have a dose reduction did not see a change in their skin toxicity, and that was about 58.8%, and that was mostly in terms of rash. There was a higher percentage of patients, about 50%, who saw a resolution in their non-rash toxicity versus only 15.3%. Similarly, 74.1% of patients without a dose reduction did not see a change. That percentage was higher. And 6%, in fact, actually had a worsening of non-rash skin toxicities if you did not do a dose reduction. Oral toxicity was improved, 33.3% versus only 26.9% who kept the same dose. Nail toxicity was similar. Keep in mind that only 3.3% of the patients actually had worsening nail toxicity if they did not have a dose reduction. Weight loss, as well. What this highlights is that most of the GPRC5D-related adverse events trended towards improvement or resolution, except for weight loss, with the dose reduction.

Further defining these side effects, you have skin, which could be rash, it could be skin peeling. The management is generally benign, and it could be self-limiting. You can use emollients, and we'll explain some of that down the line. Then you have nail toxicity; you can have nail thinning and loss. This is aesthetic, and it can take time to resolve.

When it comes to oral toxicity, patients have difficulty swallowing; there's dry mouth, there are taste changes. This can lead to weight loss, as we have seen in the trial and in the data that I have shared so far. They have longer duration and can affect quality of life. This is where we can try to do the dose modification and use supportive measures to help with increasing oral intake.

The summary is that myeloma patients respond well to treatment. GPRC5D therapy–related side effects do happen. They are very different from what we experience or see with the BCMA bispecifics. They do improve over time. Dose reductions may be warranted. Some of the side effects may be tolerable, and others may not. If you are on this therapy, this is an ongoing discussion to have with your provider, to let them know what is really affecting your quality of life and how to get it addressed.

For patients who have skin toxicity, whether it's skin peeling of the hands and feet or rash, ammonium lactate, 12% cream triamcinolone—which is a steroid cream—other emollients, or even antihistamines like Claritin or Zyrtec can be used.

Nail-related toxicity—for example, thinning of the nails—usually starts in about cycle two, and it can last for months. The way health care providers manage this is you tell patients to avoid frequent and long durations of water immersion. Also, patients can use frequent applications of emollients, such as Vaseline, Aquaphor, or vitamin E oil. You can file to smooth the edges and corners of the nail plates, and clear nail polish or nail hardeners can be applied. Biotin supplements may be helpful.

When you get started on these therapies, have a discussion with the pharmacy team at your cancer center, as well as with your provider, to get a head start on these side effects and what side effects management options you will need.

Talvey is administrated subcutaneously. Patients have to be hospitalized, because of the risk of CRS and neurotoxicity. The drug is slowly ramped up, and the doctors and your treatment team can anticipate those side effects. Patients are generally hospitalized for 48 hours for monitoring of side effects after they have completed their step-up dosing at a Risk Evaluation and Mitigation Strategy (REMS)–certified facility.

In clinical trials, talquetamab is being studied in combination with other therapies that are currently approved for myeloma. One trial evaluated Tecvayli, the BCMA-targeted bispecific, combined with Talvey, which is a GPRC5D bispecific, in patients with relapsed/refractory myeloma. At all dose levels, the overall response rate was about 86.6%. For the recommended phase 2 dose, which is teclistamab 3 mg/kg every 2 weeks plus talquetamab 0.8 mg/kg every 2 weeks, the overall response rate was much higher, 96.3%.

Something unique is that 86% of patients with extramedullary disease responded. If you talk to most myeloma docs or providers, you will know that they will identify extramedullary disease as a high-risk marker. To exceed this level and depth of response in this patient population is quite promising. The PFS is 20.9 months, and the duration of response is not yet evaluable.

Low blood counts were seen, mostly it was neutropenia, 65.6%, and the majority were grade 3 and 4. Non-hematologic toxicity is what we want to pay attention to; 76.3% of patients experienced CRS, with only 3.2% being grade 3 and 4. At the recommended phase 2 dose, that was about 74%, and there was no grade 3 or 4 toxicity seen.

What is adding two immune therapies going to do to the inflammatory response that happens in the body? Would it be higher? Not manageable? The data shows that the combination therapy can be safely administered from that perspective, in terms of CRS. What we have seen with Talvey, because of the target it addresses, is dysesthesia in 61.3% in all dose levels and about 47% in patients with the recommended phase 2 dose. Skin toxicity at very similar levels, as well as nail disorders. You still see skin, nail, and oral toxicity with them.

Talvey was also utilized with Darzalex, a monoclonal antibody that targets CD38 on plasma cells, in patients who had three or more prior lines of therapy. Response rates were going from 71.4% with Talvey 0.4 mg/kgweekly dosing. That was in about 14 patients. When you use a higher dose, which is the Q2 weekly dosing, the overall response rate was about 84.0%, and the sCR rate was higher. VGPR, which is an approximately 90% reduction in M protein or light chains, was similar.

The future direction with Talvey is that there’s a phase 2 pilot study of Talvey plus Darzalex and Tecvayli plus Darzalex in patients with high-risk newly diagnosed multiple myeloma, with an early rescue intervention that’s guided by the MRD assessment. You’ll see that’s a pattern in oncology, particularly myeloma. Newer therapies are usually tested and studied in late lines of therapies, then, over time, as they show that they’re effective and that they’re safe, those therapies are studied in earlier lines. Going from four lines of therapy where many of these bispecifics were first studied to now going to the second line, and then eventually to newly diagnosed multiple myeloma.

Turning our attention to another GPRC5D bispecific, forimtamig, that was given to 105 patients. There was an IV cohort as well as a subcutaneous cohort. The response rate was 63.6% in patients on the subcutaneous arm versus 71% in the IV arm. Looking at response based on specific characteristics, 52 patients were over 65 years of age, and the response rate in that patient population was 71.2%. There were 49 patients who had more than four prior lines of therapy, so heavily refractory, and their response rate was about 63%. Response rate was

57.8% in penta-drug refractory patients. In patients who had prior BCMA target therapy, so if they had teclistamab or they had a CAR T or an ADC like belantamab, it's all specified, the highest response was seen in patients who had prior CAR T; that was about 66.7%, about 42% if they had a prior bispecific antibody, and about 47% if they were previously treated with an ADC. In the high-risk patient population, the response rate was also very reasonable, about 63.4%. Patients who had extramedullary disease—another marker of high-risk disease—had a 50% overall response rate.

What all of this tells you is that these therapies are extremely effective, despite being studied and utilized in patients who are heavily refractory. It's a good thing to have effective therapies in this space.

Shifting gears from the GPRC5D space, cevostamab is another bispecific antibody. It targets the FCRH5 receptor, and that's been studied in a clinical trial, as well. The response rate at the 20-to-90-mg dose level was about 36.1%, but at a higher dose level, it was about 56.7%, with a VGPR rate of almost 33.3%.

Reduced blood counts—that's a common side effect that you see with a lot of myeloma therapies, and then additionally non-hematologic toxicity such as CRS, which tends to be more grade 1 and 2. There were electrolyte issues as well as fatigue. These were some of the observed side effects.

Currently, we give therapies until you either progress or you have toxicity from those therapies, whether it's Darzalex, pom/dex, maintenance therapy, or bispecific therapy. One trial evaluated whether we could give fixed-duration therapy. What if we set a limit on, say, "Hey, these patients are going to get X number of cycles, and after that we're going to stop, and we're going to see if their responses actually deepen." Do they go from a VGPR to a CR, or do they lose those responses? This was done with cevostamab—assessing the duration of response in patients who've completed a set line of therapy.

Patients completed 17 cycles. Some patients got into sCRs. At the time of this presentation, no patients who had achieved an sCR have relapsed. This is very important; maybe we ought to move into a space where limited-duration therapy is done for toxicity's sake, because we have to find a balance between toxicity, efficacy, and quality of life. This is very promising.

Right now, the three officially approved bispecific therapies—Tecvayli (teclistamab), Talvey (talquetamab), and elranatamab—are all given in the hospital to mitigate CRS, as it cannot really be managed outpatient. With cevostamab, you can reduce the rate of CRS if you pretreat the patients with tocilizumab. The CRS rate was about 90.9%, but in patients that got tocilizumab, it was 38.7%. Tocilizumab is an IL-6 antibody, and it's usually the antidote that we give when we notice that patients are starting to experience CRS, which can be very mild from having fevers, to extreme, where your blood counts blood

pressure is low, you require oxygen, and occasionally even an ICU stay. They decreased the overall rate of CRS. Most CRS was grade 2 and grade 1.

One of the fears is that we want the inflammatory response that happens when bispecific therapy or immune therapy is given, but we don't want to blunt the response by giving something that may decrease the efficacy. Patients who were pretreated with tocilizumab had no negative impact on response rates. In non-tocilizumab patients, the overall response rate was 37.2%, with a VGPR of 25.6%. The overall response rate was 54.8% in patients who had received tocilizumab.

Cevostamab is also being studied in combination with other therapies. There's a phase 1B study called CAMMA 1 in patients who have two prior lines of therapy, including an IMiD and a proteasome inhibitor, where cevostamab is combined with pomalidomide as well as dexamethasone in patients with relapsed/refractory multiple myeloma. Eight patients received this regimen. The number is too low, this is too early, but the overall response rate is about 100%. One patient had a CR, three patients achieved VGPR, and four patients had a PR. CRS was observed in 87.5%. Only two out of the eight experienced grade 3, so 25%.

One interesting concept that has to be panned out as time goes on is that, if in patients who are getting standard-care CAR T, could you give them post CAR T consolidation to deepen their responses? That's being studied in this phase 2 investigator-initiated study by Dr. Cohen. The key inclusion criteria of that trial is that you have relapsed/refractory multiple myeloma with more than four prior lines of therapy, triple-class exposed. You have stable disease after CAR T, you have good performance status. The primary end point is to evaluate for MRD-negative CR rate at 12 months post CAR T. That's currently in process.

The take-home points are that bispecific antibodies are very active, even in heavily pretreated patients. Side effects of bispecific antibodies are CRS, low blood counts, and confusion, all of which are treatable. Infections have emerged as a more challenging toxicity, but with experience and mitigating strategies, we've been able to limit those.

Bispecific antibodies are an off-the-shelf immunotherapy, they're readily available; you don't need to wait for manufacturing.

Three bispecific antibodies have been approved since October 2022. Several more are under investigation.

On that note, we can move on to the question-and-answer phase of our webinar today, and I will turn it over to Mary.

Mary DeRome: Thank you so much, Dr. Kaur.

We have limited time for questions, but I would like to ask just a couple, because there were a number of patients who asked the same question. One of the things

they asked is whether the age of the patient plays a role in being able to receive a bispecific antibody.

Dr. Gurbakhash Kaur: The age of the patient and the performance status go hand in hand and do impact what therapy we recommend for patients. Someone who's more fit and has an improved performance status may be more suitable for a CAR T therapy that is slightly more intense, whereas someone who's slightly frail may be more suitable for bispecific therapies. Ultimately, as of right now, I don't see that there would be a limitation on age. Of course, extremes of age, we have to be mindful and have a discussion with the patient and the doctor. They need to engage on what's in line with goals of care, at extreme older age. But I would think that if you have a good performance status and your disease needs it, I don't see bispecifics being limiting to that.

Mary DeRome: Another question that was addressed during the presentations, regards sequencing. Is it better to have a bispecific first and then a CAR T or a CAR T first and then a bispecific?

Dr. Gurbakhash Kaur: That's the million-dollar question that the whole myeloma community is trying to answer. We have gotten some retrospective data, and earlier I highlighted—it may have been with cevostamab—where, based on the prior bispecific therapy, the overall response rate was actually higher in patients who had gotten CAR T. More concrete data needs to come out, but what the myeloma community believes is that you can do CAR T first because you hit the target one time, and then if you relapse post CAR T, you can do bispecific.

But that's a sequencing approach that most myeloma physicians are trying to evaluate. If we do bispecific versus, let's say, a BCMA bispecific—and the currently FDA-approved targets when it comes to CAR T is also a BCMA—it may not be prudent to do bispecific first, and then do CAR T. Usually, it's CAR T first followed by bispecific. But every situation is unique. I've had a patient where I had nothing else to give; CAR T cells were being manufactured and the disease was exploding. I had to use a cycle of a bispecific therapy, so I could keep it calm before CAR T cells could be infused. Every situation ends up being unique.

Mary DeRome: I've got one last question: what is the most recent data for bispecific antibodies in high-risk patients? For example, patients who have deletion 17p or patients who are 1q amplified, patients who have high-risk chromosomal rearrangements. What is the data on the efficacy of bispecific antibodies in that high-risk population?

Dr. Gurbakhash Kaur: The generic answer is that by the time patients are fourth- and fifth-line relapse, they're already pretty high-risk, because the disease is pretty advanced—extramedullary, disease manifestations like that actually are telling us more. These drugs are effective in those spaces. That is why they're currently being moved up, because while we've moved the needle in terms of

overall survival when it comes to myeloma patients or in standard-risk myeloma patients, there's a long way to go when it comes to moving the needle in the high-risk myeloma patients. That's why you have the HORIZON platform. That is why there is this call to the myeloma community, "Hey, we need new concept, new designs. We want to see how immunotherapy can change the outcomes for those patients," [00:66:00] to see what happens in that space. There is a lot of interest from companies, from organizations, and myeloma docs to study this.

Mary DeRome: It'll be interesting to see how those HORIZON studies can help the high-risk patient population moving forward, because it really is an area of high unmet need for myeloma patients. We're all looking forward to having those trials up and running and recruiting very soon.

I don't want to keep people any longer. That's all the time we have for Q&A. I would like to thank our two faculty for today's presentation on bispecific antibodies, Dr. Noa Biran and Dr. Gurbakhash Kaur for their contributions.