

FAQs From the IMS Annual Meeting

October 17, 2023

Transcript

Mary DeRome: Welcome and thank you for joining us for today's session, *Frequently Asked Questions From the International Myeloma Society Annual Meeting*. I am Mary DeRome, senior director of medical communications and education at the Multiple Myeloma Research Foundation. Today I am joined by Dr. Jesus Berdeja and Nick Barkemeyer from Tennessee Oncology in Nashville, Tennessee.

We've invited them here today to answer some of the frequently asked questions we receive from patients and caregivers about the data presented at this year's International Myeloma Society (IMS) annual meeting, so let's jump in.

We're going to start by talking about minimal residual disease. Several presentations at IMS focused on the importance of minimal residual disease (MRD) negativity, including using peripheral blood to measure MRD.

Dr. Berdeja, can you tell us how the use of MRD is evolving in myeloma and how close we are to being able to measure MRD with a simple blood draw instead of a bone marrow biopsy?

Dr. Jesus Berdeja: MRD, just to back up, is a deeper way of measuring a response. When you get a complete response, there are often cells that are residual; MRD is just a way to get a deeper read into that response.

By definition, the deeper remission you have, the longer it takes for your disease to come back. The traditional way of assessing MRD is with bone marrow biopsy and either flow cytometry or a procedure called next-generation sequencing (NGS). That's the traditional MRD that people probably have come to see and know for most clinical trials—but it does require a bone marrow biopsy.

Other things can tell us how deep the remission is, especially in patients that have disease outside of the bone marrow, for example. Imaging is important to assist MRD with things like positron-emission tomography (PET) scans and magnetic resonance imaging (MRI). In patients who have extramedullary disease outside the bone marrow, sometimes bone marrow MRD is not indicative of the true response, so something like a blood test that can actually assess cells everywhere—not just in bone marrow—is very attractive.

Luckily, new tools that we have at our disposal are starting to yield excellent results. In the data that was presented at IMS, we saw a lot of the traditional bone marrow MRD being used. Can it help us guide therapy; for example, the duration of maintenance, which is a question I get asked a lot by my patients: “Can I come off my Revlimid?”

There were some really nice studies looking at patients who achieve MRD negativity—not just at one time point, but actually several time points. In one study, it was three time points, where basically we called that sustained MRD negativity. So the patient that has a complete response, who is MRD negative and potentially PET negative—those patients, after 3 years of Revlimid, have their lenalidomide stopped, and the majority of those patients were able to stay in response. That’s encouraging, that perhaps at some point we can use MRD to help guide how long our treatments continue.

I will caution, though, that there are some studies looking at patients who have high-risk disease where that has been tried. We know that in patients, especially with ultra-high-risk disease—meaning that you have more than one traditional high-risk feature—stopping therapy quickly led to progression of disease. So, again, in myeloma, as in everything else, one size does not fit all, so it’s important to make sure you treat the data with caution.

In terms of the blood test, which is what Mary actually asked, there are several things that are ongoing right now. One of the tests that we’re all very excited about is called mass spectrometry, and that’s a test that’s designed to replace the traditional serum protein electrophoresis (SPEP) and urine protein electrophoresis (UPEP), which you all have come to love. We know that mass spectrometry technology is much more sensitive—if it’s truly negative, we know that the patient has a much deeper remission, and so that actually is used for that reason.

Can achieving a complete response by mass spectrometry actually equate to MRD negativity by bone marrow? The short answer to that is, we don’t know. The longer answer is that—and the Spanish have led this effort—it does seem to be just as powerful as MRD in the bone marrow, but they don’t seem to be equivalent, meaning that they’re complementary. So using both perhaps would be better. But, again, this is all retrospective data, so as usual, we need studies to help us determine how to best use it.

Mary DeRome: This is something that patients are eagerly awaiting; I don’t think any patients enjoy having a bone marrow biopsy.

Nick, are there some patients for whom a blood draw instead of a bone marrow biopsy to measure MRD would make a big difference? For example, do you have patients who are basically unable or unwilling to undergo a bone marrow biopsy?

Certainly in these events we've had patients who have come on and said that bone marrow biopsies can be very painful, and I think that the way that their care teams try to help mitigate that pain differs from center to center.

Nicholas Barkemeyer: There really are patients who would much rather have a blood test than a bone marrow biopsy—I think that number would probably be 100%, because who wants to go through a bone marrow biopsy?

But from a practical standpoint, the ability to do that via bloodwork, as opposed to biopsy, would benefit them in the sense that, maybe the patient is very frail. Maybe they have difficulty dealing with the sedation required for the bone marrow biopsy procedure. Maybe they have had difficulty with anesthesia in the past. Maybe they're on a blood thinner: they have to hold their blood thinner for so many hours prior to the procedure.

Also, as Dr. Berdeja mentioned, if you could have the ability to check for disease outside of the marrow, broadening that scope is actually going to be more beneficial to the person than just doing a bone marrow biopsy.

Mary DeRome: Right. More to come on that, and looking forward to seeing interesting data from mass spec and MRD measurement in blood biopsy instead of bone biopsy.

So let's pick up on the data that was presented for different drug combinations for both newly diagnosed and relapsed refractory myeloma. There were a couple of presentations on venetoclax in combination Kyprolis and dexamethasone specifically in patients with the t(11;14) chromosomal translocation.

Dr. Berdeja, it seems like we've been waiting forever for this drug to be approved in myeloma, so can you remind our audience what venetoclax is and why it's being studied only in this specific patient population? When is this drug going to be approved for myeloma patients, even though many myeloma patients already use it who have t(11;14) in compassionate use settings.

Dr. Jesus Berdeja: Correct, but don't say that too loudly!

As you all know, one patient's myeloma is different from another's, but in about 20% percent of patients with myeloma, there is a translocation with chromosomes 11 and 14, meaning that parts of chromosomes 11 and 14 broke off and came together to form the new chromosome, and that is considered the 11;14 translocation. We know that in patients who have that translocation, their myeloma cells are specifically dependent on this protein called BCL-2, and BCL-2 allows those cells to survive.

Venetoclax is a drug that was approved for a different type of cancer, specifically chronic lymphocytic leukemia (CLL) and now also acute myeloid leukemia (AML), where we know that BCL-2 is an important component of the survival of those

cells. So it made sense that, in myeloma, it should work, and it does. It works very well, but only in the subset of patients with t(11;14). The reason this drug is not approved is that when the original study to hopefully take it to approval to the FDA was done, it was done in all patients, not just patients with t(11;14). That was the BELLINI study, which was venetoclax with Velcade and dexamethasone compared to Velcade and dexamethasone. And although the study achieved its primary end point of improving progression-free survival (PFS), it actually showed a worse overall survival (OS) for the patients on the venetoclax arm, mostly because of the increased toxicity.

But when you look at the subset of patients with just t(11;14), those patients actually benefited both with PFS and OS, thus proving the point that that's what you need.

Actually, at the IMS this year, I think that probably the most important presentation was actually—what we're all waiting for—was the CANOVA study. That study looks specifically at patients with t(11;14), and they were randomized to receive either venetoclax with dexamethasone alone, as a doublet, versus pomalidomide and dexamethasone in patients who had prior proteasome inhibitors (PIs) and immunomodulatory drugs (IMiDs). And although the venetoclax arm outperformed the other arm, the PFS was 9.9 months compared to 5.8. The overall response rate (ORR) was doubled. The time to progression to next treatment—I believe it was double, as well. The PFS benefit did not meet statistical significance, which was the primary end point of the study, and so it is considered a negative study, so we'll see how the FDA views this in light of the information I just told you.

This was very frustrating, though what's interesting is actually at the same meeting, we also had data presented with venetoclax in addition to Kyprolis-dexamethasone. There we're seeing some very impressive results compared to just Kyprolis-dex, with ORRs in the mid 90s, with PFS that is approaching almost 3 years—very similar to some of the more powerful combinations we have, and so in my mind, I think that's what's required.

Remember that t(11;14)—although present in 20% of patients—in the individual patient, this mutation is not present in all myeloma cells, meaning that if you just used BCL-2 as a target by itself, you may only affect those cells with this mutation. But then the other cells without this mutation will actually cause progression, so I feel venetoclax needs to be used in combination. I think that's how we're going to get it approved, so hopefully it will be approved because it is a very powerful drug. It just hasn't been tested appropriately, in my mind.

Mary DeRome: There was data on some other triplet and quadruplet combinations in both high-risk newly diagnosed myeloma and relapsed refractory

patient populations. What were some of the take-home messages from some of those studies?

Dr. Jesus Berdeja: The high-risk patient population is a very difficult population, and usually “high”-risk means that the patient’s myeloma cells have these high-risk mutations, in particular, t(4;14) translocation, t(14;16) translocation, deletion 17p, and amplification or extra copies of chromosome 1q. Having disease outside of the bone marrow—extramedullary disease—is also considered a high-risk feature. In that patient population, duration of response is always a problem: you get responses, but the responses don’t last very long.

We had some updates at IMS from two larger trials, one from the Germans, and one from the French. The Germans conducted the CONCEPT trial, and they are looking at patients with just high-risk disease from the very beginning: newly diagnosed. They’re using what we consider the four most powerful drugs we have right now, so they’re using an anti-CD38 antibody—in this case they’re using isatuximab—Kyprolis, Revlimid, and dexamethasone as an induction, and then if the patient goes on to have a stem cell transplant—not all patients need a transplant—they got transplanted, and then they get several more cycles of the four-drug combination, then they continue maintenance with three drugs, the anti-CD38 antibody, Kyprolis, and Revlimid—so a very aggressive approach. And basically they showed that it can induce deep remissions, and those remissions seem to be lasting much longer than what we see historically for this patient population. More to come in that. I think that following these patients longer will really help us determine how much better this is potentially than our standard.

The French are doing a similar thing, but instead of isatuximab, they’re using daratumumab (Darzalex), but one of the differences is that they’re not giving the maintenance with those three drugs. They’re only doing maintenance with Darzalex and Revlimid.

I think this will help us, looking at both of these studies to determine how important the addition of the proteasome inhibitor is as maintenance. But more to come; currently, early data from these studies looks very good.

And then the same in the relapsed/refractory settings. When disease comes back, some patients already have some high-risk features, but those can also be acquired. Each time the disease comes back, you can get high-risk features, and patients with high-risk features tend to do worse with any particular treatment, so there’s a lot of work, as well.

But at least we’re seeing data with the similar combinations that we just talked about. We had the final OS analysis of the IKEMA trial, which is isatuximab, Kyprolis, and dexamethasone versus Kyprolis and dexamethasone in patients who had one to three prior lines of therapy. That’s probably the best PFS, it

would seem, still about 3 years for the triplet combination, and the OS even after almost 5 years of follow-up has not been reached. When they looked at patients with high-risk disease, those patients also benefited from the triplet, so I think the moral of the story is, the more the better for high-risk patients, and also keeping the treatment ongoing, unfortunately, is important.

Mary DeRome: We had a podcast that we did with patients who were high risk, and two out of the three patients were actually having triplet maintenance therapies. They were actually doing okay on them.

Nicholas, talk about managing these patients with high-risk myeloma. Do some of these emerging combinations provide you with more options for managing this population, and are there more toxicities you have to worry about?

Nicholas Barkemeyer: All these therapies that are emerging are definitely the more therapies, the better, as Dr. Berdeja said for these patients. I think the key thing that was already mentioned was yes, keeping these patients on therapy and having those patients understand why they need to go on therapy compared to other myeloma patients. I get a lot of cases where somebody will come in and say, “Oh, well, my friend has multiple myeloma,” but they’re doing this, this, and this, and then I have to explain to them, “Well, that’s because not all myeloma is the same.”

Particularly with the high-risk group, I try to tell them, “We’re going to try and keep you on an IMiD. We’re going to try and keep you on a PI. We’re going to maybe incorporate an anti-CD38.” It will be interesting to see some of these studies head-to-head, and hopefully that will show the importance of having the PI involved, as opposed to just the anti-CD38 and the IMiD.

As far as toxicities go, any time you’re on a multiple-drug regimen there’s always the increased risk for more toxicity, but what I’m seeing is that a lot of the patients with these newer therapies that have been coming come up the past 5 years, they tend to do a lot better than, say, those patients who had high-risk features 10 years ago or so.

Dr. Jesus Berdeja: The other thing is that we’ve seen the importance of continuing the multidrug agents, so adjusting doses for toxicity is important—but to try and maintain them, as opposed to stopping one—to try and maintain all of them going is important.

I just wanted to add that, because I’m sure patients will have questions about it.

Mary DeRome: New and emerging classes of agents. We saw several presentations on CAR T-cell therapies, and it looks like companies are really trying to speed up the manufacturing process and using imaging to predict relapse.

We also saw data on the use of CAR T therapies earlier. That is, in patients who've only had one to three prior lines of therapy, and right now, they're only approved in patients who have had four or more therapies, right?

Last but not least, there was some phase 2 data on a new CAR T-cell target, GPRC5D, which is actually the target for an approved bispecific antibody treatment.

Dr. Berdeja, what are some of the major takeaways from IMS regarding CAR T-cell therapy for treating multiple myeloma?

Dr. Jesus Berdeja: We saw a lot of updates from what we've seen before, but I think that you are correct. In terms of CAR T, there are a lot of great things about CAR T, but one of the downsides with the autologous CAR T—meaning CAR T-cell therapy that is using your T cells—is that there's a requirement for collecting the T cells, then you have to manufacture the T cells to have the chimeric antigen receptors before they are ready to use as treatment, and that is usually, on average, taking about 4 to 6 weeks. During that time, myeloma can progress, and so people may need to treat patients with chemotherapy, and so we always try and figure out, how can we make this process better?

Obviously, the idea would be an allogeneic CAR T, which is basically a CAR T that's off the shelf, but so far, those have not been as effective as the autologous CAR Ts. We did see two presentations at IMS with new faster manufacturing, with fancy names like T-Charge and InstanCART. These CAR Ts can be manufactured in 1 to 2 days, which is amazing.

Now the problem is, because these are cell products, they still require that you do all this infectious disease testing to make sure that they're not contaminated, right?

Mary DeRome: It's really that QA that takes the longer time, right?

Dr. Jesus Berdeja: Correct, and if you're the patient, you want that, right? You do not want a part that's contaminated. Unfortunately, that still adds time, so the fastest turnaround, even in the clinical trials, is still about 2 weeks. But if it's 2 weeks versus 6 weeks, that's a significant improvement, and that will make a big difference for some of our patients.

If anyone's heard me give talks about bispecifics versus a CAR T, sometimes the patient that goes on to take a bispecific is a patient that's progressing very quickly and can't wait for that CAR T. Well, manufacturing these CAR T treatments faster may open that treatment up to more patients.

But in terms of the earlier use of CAR T, I think that's actually the most exciting thing that's happened right now. We saw some updates on the CARTITUDE-4 trial, which is basically enrolling patients with one to three prior lines of therapy,

giving Carvykti, which is a BCMA autologous CAR T—that's currently approved for patients who have received four-plus lines of therapy—versus standard of care, and most patients in the standard-of-care arm got Darzalex, pomalidomide/dex, and I believe pomalidomide, Velcade, dex, and so on. We saw the data earlier, and we know that the CAR T outperforms the standard of care, and so it's looking very promising. Basically, it's telling us that it's better than any other option you have, so that's the good news. This data is being looked at by the FDA as we speak, so we're all hoping that within the next year that we will have the availability to use CAR Ts, certainly as second line, but hopefully earlier than waiting until after four lines of therapy.

One of the things we saw here at IMS that was new was they looked at different patient groups to see if one group benefited more than others because, unfortunately, high-risk features are still important for the effectiveness of CAR T and bispecifics. The good news is, at least on the CARTITUDE-4 trial, the patients with extramedullary disease, with stage 3 disease, high-risk cytogenetics, all of these patient groups benefited from the CAR T and it was superior to standard of care.

We'll just have to wait and see, but usually these treatments do not benefit these patient groups as much as the patients without these high-risk features, but nonetheless, it helps us or at least reassures us that we can still choose this treatment over another, just even if they have these high-risk features.

Then finally, I think you mentioned the GPRC5D CAR T. We saw two studies presented at IMS, and again, these were updates. One is a Chinese company that's looking at GPRC5D, and they presented their update, and then the other one is a BMS product that also was updated at this meeting, and both are looking quite impressive.

The GPRC5D target we know is a good one, as Mary said. We have a bispecific that's good for that, but the CAR T is just as efficacious. We're seeing some very high response rates in the 80% to 90% response range. The important thing is that a lot of the patients on these trials actually have had prior BCMA therapies, and the efficacy was just as good, or it seems to be just as good. It tells us that we can use a similar therapy with an alternate target, and I think especially with CAR Ts, I've had patients who've had a BCMA CAR T, and had an excellent response. They come and demand a second CAR T, and we put them on the GPRC5D CAR T and they have had amazing responses. Hopefully, that's what this will translate to. More options, the better, as usual.

Mary DeRome: One of the things that I thought was amazing was they had a presentation on giving patients a much lower dose of CAR T, just many fewer cells, and then basically letting the cells grow and expand in the patient instead

of growing and expanding them in the dish before you give it to patients, which will then shorten the manufacturing time.

Dr. Jesus Berdeja: Actually, it does bring up a good point; that's part of the way they're decreasing this manufacturing time. It's called in vivo (a process performed in a living organism) expansions. With in vitro (a process performed in a test tube or culture dish) expansion, CAR T cells are expanded in the petri dish, and then they're infused back into the patient where they expand in vivo, as well. But what we're finding out is when the cells expand in the petri dish, they actually become activated at that time. So, often what happens is you give them to the patient, and many of those CAR T cells already can be exhausted, meaning they don't work as well and/or cause more toxicities. Allowing for the CAR T-cell expansion to happen in the patients instead of a petri dish is what's driving a lot of this research, and at least the data early on looks like this approach may result in more effective CAR T cells.

Mary DeRome: Now that potentially CAR T will be approved for a new indication, where it'll be available to patients who are in earlier lines, that is probably going to affect availability of CAR T, which has never been that easy in the first place.

Nick, from a practical perspective, has the process of getting patients access to CAR T therapy gotten any easier, and what will faster manufacturing mean to some of these myeloma patients?

Nicholas Barkemeyer: Access to CAR T has gotten much better now that we've gotten commercial approval through the FDA for Carvykti and Abecma compared to just having a clinical trial option a few years ago. Obviously, faster manufacturing can mean life and death to some patients. Unfortunately, there are those, as we talked about, high-risk patients who can progress very quickly, and if you have to wait weeks before you can get these products, that could potentially be the difference between life and death. It's really going to make an impact if manufacturing can be sped up. As Dr. Berdeja alluded to, 2 weeks would be at least a 50% reduction in production time in some cases.

Hopefully, one day we will get to an allogenic CAR T where it can be just off the shelf. In the meantime, if autologous CAR T is what we have to do but we can make it faster, then that's going to mean better outcomes for people.

Mary DeRome: There were also several findings presented for bispecific antibodies, including their role in treating high-risk myeloma, causes of drug resistance and strategies to overcome that resistance, as well as data on a new GPRC5D bispecific agent and an update on Tecvayli.

Dr. Berdeja, what can you tell patients about these recent findings for bispecifics?

Dr. Jesus Berdeja: Yes, so I think that's the other pillar. It seems like every meeting we go to, it's everything myeloma, and then about half the meeting is about CAR Ts or bispecifics.

The good news is that we have three bispecifics that are FDA approved in the United States. Two against BCMA—teclistamab and elranatamab—and one against GPRC5D, which is the target we just talked about with the new CAR T, as well, and that's called talquetamab or Talvey.

The data does look fantastic, but obviously we're all struggling with how do we give these drugs? They have the exact same indication as CAR Ts. Now we have five—two CAR Ts and three bispecifics—with the same indication, and the question is, is it better to give one versus the other? Which one do we give first? A lot of the data that was presented is really being geared towards those questions.

We've speculated over why patients stopped responding to both CAR Ts and bispecifics, but we really don't know the reasons why someone's disease becomes resistant. More recently, we've seen some publications and now some data presented that tells us that the mechanisms of resistance may be very different between the CAR Ts and the bispecifics.

For example, after CAR T, when a patient's disease progresses, it's rare that they lose the target. For example, if you get a BCMA CAR T, chances are at the time of relapse, you can still express BCMA. What we're finding out more is that patients who are getting bispecifics and then their disease progresses, we are seeing a much higher rate of negative antigen escape, meaning that the myeloma has lost that target, which would tell you that, if that's the case, then going in against the same target after a bispecific is unlikely to be effective as opposed to after a CAR T.

We've actually seen that with some of the data that is now being presented both from clinical studies and from the real world where the sequence does matter, where patients who've had a prior CAR T seem to respond very well to a bispecific in the same target, but the reverse is not the case. From that standpoint, it makes sense that we pay attention to those kinds of details, because I think that will be important.

Changing the target, obviously, is another strategy. That's why it's so nice that we now have GPRC5D, with talquetamab approved. But also we saw some data representative for forimtamig, which is another GPRC5D bispecific that is being developed that is also looking very active, so that's important.

We talked about the GPRC5D CAR T, so again, we will have options against GPRC5D, but also not presented at this meeting, but presented in past meetings, we know we have another bispecific that goes against a different target called

FcRH5, or cevostamab. So, again, having the option of treatments aimed at multiple targets is important.

We've also seen data in other meetings where combining bispecifics against multiple targets may be beneficial. We're starting to see that. Can we prevent this antigen escape by hitting two or three or more different targets, and now with all these, we have that possibility. Similar to what we do with the PIs and the IMiDs. We never give them by themselves. We always give them combined. So why not these?

I think that's all the data that's going to be forthcoming. It's going to be combinations and multitargeted, but we're also starting to see that maybe you don't have to give multiple drugs. There are actually now studies with CAR Ts and bispecifics that are looking at multitargeted bispecifics and CAR Ts, and with one drug, it can hit multiple targets. So again, I think that's just the proof of a concept, and that's what the data with the bispecifics is really showing us, is that they're effective, but how do we use them best?

Mary DeRome: Dosing is a big issue too. We had a webinar last week on non-BCMA-targeted bispecific antibodies, and we had Dr. Ajai Chari and also Dr. Suzanne Trudel. They had amazing things to say about Talvey and cevostamab, which is still in clinical trials.

I was especially impressed by the cevostamab data, particularly the fact that many of the patients who were on that study were only dosed for 1 year. They had 17 cycles of 3 weeks, and then they stopped treatment. Every patient had reached a stringent complete response by the time they stopped the therapy, many of them had still not relapsed, and it's been 2 years since they were treated. They were basically on drug holiday—some of them as long as 2 years—and they had no relapse. Any patients interested in looking at that, just make sure you go to our website and check out some of our resources, and you can see a recording of that webinar.

Speaking of interesting data, Nick, we heard about some of the nail and skin side effects with the GPRC5D-targeted agents, and we recently heard from Dr. Chari in that webinar that these effects may be correlated with good activity of the bispecific.

We had a patient on the webinar who was also taking Talvey, and he had been really plagued with some of these side effects, and he was so thrilled to hear Dr. Chari say that it probably means the drug's going to work.

How do you prepare patients to anticipate these side effects?

Nicholas Barkemeyer: Up front, before they even get the drug, we have a chat—you know, "You're probably going to experience some side effects

involving your tastebuds, your skin, your fingernails, potentially just one of the three, potentially all three. Potentially it lasts a couple weeks, and then it'll fade out or plateau, or this can be something that lasts for months.”

But me just telling them that isn't necessarily the best thing to do, so we've also—if both parties are amenable—had patients talk to each other and share their experiences to let them know what possibly could be coming.

If a patient does have those side effects, first of all, they don't like them, but they do take solace in the fact that if it is working against their disease, it's something that they can manage and deal with.

But as far as preparing them, having them talk to other patients, explaining it to them up front, teaching them what to look for, some strategies to help mitigate the side effects—whether it's hard candy to try and increase saliva to help with the tastebuds or there are lots of things to help keep the fingernails from becoming so brittle. It's just about preparing them to have a plan of action before those issues arise, because they know that one of them is going to arise.

Dr. Jesus Berdeja: Can I jump on something?

First of all, Nick didn't tell you about—because we had this cevostemab study open, as well, and how long has our patient been off the cevostamab?

Nicholas Barkemeyer: Oh, it's been over 2 years, two and a half years. We saw her a couple of weeks ago.

Dr. Jesus Berdeja: She's getting close to three.

That brings up a good point: that a lot of the research now is also looking at—because it's not just with cevostamab—so it's not planned, but there are some patients on some of the other clinical trials with the bispecifics that come off for whatever reason, toxicity or they get an infection—which is something that is a concern; infections are a big problem—who actually have achieved a response. They come off, and they stay in remission for a very long time.

We're all hoping that this means that we could do limited duration of therapy for these bispecifics, and then preemptively restart or hopefully we just have to give it for 6 months and you're done after you reach a certain remission. Those are the kind of questions that we still have, because these toxicities that we're talking about do not always go away until you stop the therapy. We talked about the GPRC5D toxicities, but the infection toxicity is think the most important, and so that risk of infection continues indefinitely while the person's on the bispecifics, so if we could get to shorter durations of treatment, I think that would be optimal.

Mary DeRome: Okay, so finally we saw a few presentations on a new class of drugs called the CELMoDs.

Dr. Berdeja, for CELMoDs like iberdomide and mezigdomide—or mezi—what have we learned about their use in both newly diagnosed and relapsed/refractory patients, and how soon might this be a treatment option?

Dr. Jesus Berdeja: Yeah, so these are exciting drugs. These are in the same class as the IMiDs, which we know very well: thalidomide, lenalidomide, and pomalidomide. When Revlimid, when Pomalyst—and definitely Thalomid—were first—when we first found out that they worked for myeloma, we had no idea how. We just knew they worked. Later on, these brilliant scientists realized that it was by inhibiting cereblon, which led to degradation of these proteins important for the survival of the myeloma.

The CELMoDs are drugs that have been developed after learning this. These drugs are specifically directed to inhibit cereblon, and so they're much cleaner and much more powerful in that sense, and that's why they're no longer called IMiDs. Now they're called CELMoDs, but they're a similar class.

The CELMoDs that's most advanced is iberdomide, and we're hoping it's getting close to approval. But that was presented here in combination, even in patients who were previously untreated, and in combination with Velcade and dexamethasone, showing that you can combine it, as well as you can Revlimid or Pomalyst with our usual classes.

What we're seeing is that, unfortunately, they do have issues with low blood counts, and that's actually by definition, because cereblon and Ikaros and Aiolos are important for neutrophil recovery, so it's not unusual that we would expect that. Maybe Nick can eventually tell us that, I think, we're seeing less toxicity, and that's what this trial seemed to indicate, is that it seemed to have fewer off-target effects.

The other drug, mezigdomide, is an even more powerful CELMoD that is also being looked at in combination, and that one seems to have more toxicity from a standpoint of the cell counts. Because it is more powerful, we would expect that. What's encouraging about mezigdomide is that when you look at patients with heart diseases, like a subset of patients with extramedullary disease, meaning tumors outside of the bones and bone marrow, which often are very refractory to most treatments, mezigdomide seems to be very effective for that subset of patients. That will be quite impressive and nice if we had a drug that can benefit that patient population.

These are looking fantastic. There are clinical trials ongoing, not only to look at combinations, trying to prove to the FDA that they should be approved, but eventually being looked at even as early maintenance therapy after transplant instead of Revlimid, for example, along with what we have right now, looking at a head-to-head comparison between Revlimid and iberdomide, so some more to

come from these drugs, but these will probably replace, potentially, even some of our current IMiDs with the more specific and more powerful drugs.

Mary DeRome: We talked about the neutropenia that these drugs cause.

Nick, are there any other side effects that people who are taking CELMoDs need to worry about, and are those side effects similar to what you might see with Revlimid or Pomalyst?

Nicholas Barkemeyer: No. I would actually say that the CELMoDs are much better tolerated than the IMiDs overall. I'll give you a real-life example. We had a patient who was on a clinical trial. He got a BCMA CAR T, and then he received iberdomide maintenance after, or he was supposed to.

He took the medication. Unfortunately, the neutropenia was a major side effect, so much to the point that he did have to come off, but at no point while he was on the medication did he complain of anything that you would traditionally see with an IMiD like Revlimid, like he wasn't having any diarrhea. His fatigue was no worse than it had been while he was going through the CAR T. He didn't have a rash, for example, so overall, I think that the CELMoD category is much better tolerated than the pomalidomide, lenalidomide, things like that.

Mary DeRome: That's good news for patients who have to put up with those, sometimes for years, for maintenance therapy.

Nicholas Barkemeyer: He was actually wanting to stay on the drug. He's like, "Why can't I stay on it?" I said, "Well, you don't have anything to fight infection, and that's a more serious problem."

Mary DeRome: Anything to add, Dr. Berdeja?

Dr. Jesus Berdeja: No, I agree, but I was just going to say that notice how I say they *may* be better tolerated, whereas Nick said they're *definitely* better tolerated.

Nicholas Barkemeyer: Well, there's always something...

Dr. Jesus Berdeja: Well, while Mary makes me travel and go to meetings, Nick has to see my patients, so—

Nicholas Barkemeyer: Exactly.

Dr. Jesus Berdeja: But he has much more hands-on experience.

Nicholas Barkemeyer: That's not true.

Dr. Jesus Berdeja: I really do think that the CELMoDs are going to significantly affect how we treat myeloma, and it's going to be more of a replacement. Because we still have the PIs and the IMiDs/CELMoDs, which are still the two big pillars. Now with the anti-CD38 antibody, and those are the three big targets. I do think that the BCMA and GPRC5D and all these other classes of drugs either will

be complementary or be next in line for the foreseeable future, but potentially even frontline, especially for the high-risk population. But I think making each class of drugs the best I think is important.

Mary DeRome: We're getting closer to the top of the hour, so I have one more question for both of you: was there any data presented at the IMS meeting overall that will immediately affect how you manage your patients? And what is the take-home message that you see from the meeting for patients?

Nick, I'll start with you.

Nicholas Barkemeyer: I would keep it very brief, because I'll leave it to the expert to give all the details, but I think that the data—and Dr. Berdeja touched on it earlier—was having the CAR T prior to doing bispecifics and not losing that efficacy by having to eventually transition to the bispecific and still getting a response. The whole thing with myeloma obviously is sequencing, sequencing, sequencing—especially patients who have multiple lines of therapy or are high risk, and so I think that the major takeaway, looking at the data presented, is that you can still have benefits post-CAR T by using other therapies such as a bispecific.

Mary DeRome: Dr. Berdeja, your thoughts?

Dr. Jesus Berdeja: I thought it was an excellent meeting. I think we were all disheartened by the CANOVA results, which was venetoclax-dex versus pomalidomide-dex. But, having said that, I think when you actually look at the data, you still see how much more powerful that drug is for that subset of patients. And like we discussed before, the more optimistic take on this is that venetoclax in combination with Kyprolis looks fantastic, and these are the early reports. Looks just as powerful as any three-drug combination we've had in relapsed/refractory, so I still think there's life for this drug, and I think in the subset of t(11;14) patients, it just needs to be dosed appropriately. It should be looked at, and it is being looked at in clinical trials as a maintenance drug in this population, for example, and again, in combinations.

But I have to agree with Nick. The other thing that at least I learned the most about was the data coming out from the German groups and from Dr. Bahlis's labs in Canada, looking at mechanisms of resistance between CAR Ts and bispecifics, which is really helping us determine how to best sequence these drugs, so I think that is fantastic work that is going there, and really, it's going to translate to optimal care for the patient with myeloma.

Mary DeRome: The IMS meeting, I think, is getting better every year. It's good that they're doing it every year instead of doing it every other year.

Dr. Jesus Berdeja: It's also a great meeting because, it's not just about the data presented, but you bring the entire myeloma community together in a forum where we're not being pulled in all different directions.

Mary DeRome: It's highly collaborative, and there's a lot of opportunity for people to collaborate on different topics and talk about patients and sequencing and all these different things. It's a great learning opportunity, and I thought there was more new data that came out from IMS this year than I've seen in some of the previous meetings, which I thought was great.

Dr. Jesus Berdeja: Right, and that's actually a push to try and encourage people to present more data. You know, traditionally, everything had to be presented at ASH. Now we're starting to see more at ASCO. But the truth is, there's no reason to pile everything at once now we have this meeting in between the two. The IMS, if it's myeloma-specific data, all the myeloma eyes are in this meeting, and so hopefully that will translate to continuation. I think that's why you're seeing this, and we're hoping that it will translate to even further, more novel data that will be presented at this meeting.

Mary DeRome: On behalf of the MMRF, I'd like to thank Dr. Berdeja and Nick Barkemeyer for joining me today. I'd also like to thank everyone for taking time out of your day to watch this session.

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