FAQs From the 2022 American Society of Hematology Annual Meeting

January 6, 2023

Transcript

Mary DeRome (MMRF): Welcome and thank you for joining us for today's session, Frequently Asked Questions From the 2022 American Society of Hematology Annual Meeting. I'm Mary DeRome, Senior Director of Medical Communications and Education at the Multiple Myeloma Research Foundation.

Today, I am joined by Dr. Jesus Berdeja from the Sarah Cannon Research Institute in Nashville, Tennessee, and Dr. Sham Mailankody from the Memorial Sloan Kettering Cancer Center in New York City.

First, we're going to talk a little bit about precursor conditions, meaning, smoldering multiple myeloma (SMM) and monoclonal gammopathy of undetermined significance (MGUS).

Dr. Mailankody, how common is MGUS? Does it always precede multiple myeloma?

Sham Mailankody, MBBS: About 3% of the population over the age of 50 years has MGUS, and the number increases as people grow older. In people in their 70s and 80s, that number probably approaches 5% to 6%. I caveat that by saying, as we get more sensitive tests like mass spectrometry to detect monoclonal spikes, we will likely see an even higher proportion of people, probably closer to 4% to 5% of the population over 50 years. It's a little more common in men than women. It's twice as common in Black patients than other groups. But it's a common condition. Most people are not diagnosed with this, because it is not part of a routine physical to do M-spikes and light chains. But if you did population screening, it's a common condition.

Mary DeRome (MMRF): So, it doesn't always translate into active myeloma. How long would it take someone diagnosed with MGUS before they are diagnosed with active multiple myeloma?

Sham Mailankody, MBBS: So, the important thing is most patients who have MGUS will never develop multiple myeloma, so that's key to remember. About 10% of individuals who have MGUS would be expected to develop myeloma in about a 10-year follow-up, so that's 1 in 10 over a 10-year period. Probably about 15% to 20% in a 20-year period. So, it's very infrequent for MGUS to progress into multiple myeloma, so that should give some degree of reassurance for individuals who are diagnosed with MGUS. The reverse is true, which is that every patient with multiple myeloma probably had MGUS preceding it, which has

been shown by some very nice studies in the past. But having MGUS in most cases does not lead to multiple myeloma.

Mary DeRome (MMRF): Dr. Berdeja, should healthy adults over 40 years old with a close family member with multiple myeloma get tested for the presence of MGUS?

Jesus Berdeja, MD: No. As Dr. Mailankody said, this is an infrequent event. Even though patients who have a family member with myeloma have an increased risk of developing MGUS, that risk is still quite small. The iStopMM study at ASH was interesting because they showed that there was a significant percentage of MGUS patients who had transient MGUS. So, oftentimes, we will pick up something that truly is insignificant and may go away, and so, I think the stress of having it and dealing with it is probably more than the actual risk. So, I would just continue with routine follow-up with the primary care doctors, but I wouldn't necessarily look for MGUS.

Mary DeRome (MMRF): Dr. Mailankody, is there any link between COVID-19 vaccination and progression of MGUS to active myeloma? I sat through that presentation at ASH, and I thought it was an interesting connection people were looking for there.

Sham Mailankody, MBBS: Even before that presentation, there's little clinical or preclinical data to suggest that it would lead to progression. Dr. Berdeja alluded to the iStopMM Study, a large population-based screening study that's ongoing in Iceland, where about 75,000 or more individuals over the age of 40 have been screened for MGUS. The primary objective is to follow these individuals over a period of time, in two or three different ways, to identify if early diagnosis of MGUS leads to clinical benefits. Now, the advantage of the study is also that it allows us to ask many more questions related to MGUS and its natural history. So, one of the many questions that was asked at ASH, and answered, was if there is an impact of COVID-19 vaccination on progression of MGUS in individuals.

They had about 1,800 patients who had a diagnosis of MGUS. They collected their M-spike and light chain values prior to COVID-19 vaccination, then after. This allowed them to ask if the M-spike increase rate accelerated after the vaccination. The short answer is it did not. This gives enough confidence and comfort, hopefully, to our patients, that there is no reason to believe that COVID-19 vaccination would lead to an acceleration of, or progression from MGUS to multiple myeloma. That's consistent with what we have seen since the vaccines have been available for the last 2, almost 3 years now.

Mary DeRome (MMRF): Interesting data, there. Dr. Berdeja, are there certain patients with SMM who should be aggressively treated? I know that this is sort of

a loaded question in the field right now. If they should be aggressively treated, how do you determine which patients might require treatment?

Jesus Berdeja, MD: The key is which patients should be treated. So, I think there is a subset of patients who should be treated; but the question is how to truly determine who those patients are. SMM is a diagnosis of multiple myeloma, but with no clinical symptoms or signs of active multiple myeloma. Traditionally patients with this diagnosis have been monitored closely and not treated. There is some data showing that not all patients with SMM are equal. There is a group of patients who are considered high-risk, and those are patients who by definition, have a 50% chance of converting to active multiple myeloma in the next 2 years.

That group is where interventions may be helpful. There are two large studies from Spain and from ECOG, here in the United States, that looked at intervening with lenalidomide, plus or minus dexamethasone. It showed that you could prevent or delay the onset of active multiple myeloma, and there was a survival advantage in those patients.

The problem has been with the definition of high-risk SMM, and we continue to struggle with how to interpret study results in the general population.

As we get better and start incorporating more cytogenetic and clinical data, we'll have a better idea about what group will benefit. Some studies are looking at the possibility that maybe, once we have identified this population, maybe we should be treating them much more aggressively. At ASH this year, we actually saw that study from Spain, where patients, just like in active myeloma were on drug inductions, et cetera.

Dr. Kumar presented the data with daratumumab-KRD in those patients. And again, it's looking quite promising, but again the question is whether you can make an impact in these patients this early and cure them. Because if you can’t, then you are exposing patients to toxicity unnecessarily.

Mary DeRome (MMRF): Yeah, I think that's going to be on the docket at ASH, for many years, as people really begin to sort this out. I think that the one thing that is true is that patients with SMM should be treated on a clinical trial, if at all, right?

Jesus Berdeja, MD: Ideally.

Mary DeRome (MMRF): All right. Dr. Mailankody, how do you determine if a patient has high-risk multiple myeloma? What does that mean for prognosis?

Sham Mailankody, MBBS: This is also somewhat evolving and challenging. Classically, I guess we've used cytogenetic FISH studies that many patients who have myeloma may be familiar with. From a bone marrow biopsy, we look at

certain genetic changes that a subset of patients with multiple myeloma have that put them at high risk. For instance, deletion of 17p chromosome where a protein called p53, which is a critical protein in the body resides, is considered high risk. This is probably presented in about 5% to 10% of patients. Others, for instance, translocation (14;16) or (4;14) have also been considered high-risk. Depending on which cytogenetic abnormalities are included and how you define them, probably about 25% or so of patients who are newly diagnosed with multiple myeloma have one or more of these high-risk features.

The revised ISS staging, which has been developed over the last few years, groups patients with multiple myeloma into three stages. Many of us consider stage III, which to be fair, includes cytogenetics among other factors, high-risk. We also consider things like plasma cell leukemia. Patients who present with circulating plasma cells on diagnosis, I think have for all intents and purposes, high-risk disease. These patients tend to not do as well with conventional treatments like in standard-risk myeloma. Similarly, I think patients who have extramedullary disease, which is myeloma lesions outside of the bone and the bone marrow, would in many instances have high-risk disease.

As I mentioned, I think the definitions are somewhat evolving and different maybe from center-to-center, but these are broad parameters for high-risk disease in newly diagnosed myeloma. One last caveat would be what many of us call functional high-risk disease. These are patients who do not fit into any of these categories but inexplicably have disease that does not respond as well or as long as we would expect to standard treatment. For instance, if they progress within 6 to 12 months after initial treatments, which is typically not the case for standard-risk disease, they would be considered as functional high-risk patients.

I think the implications are patients with high-risk myeloma tend not to respond as well or for as long as patients with standard-risk myeloma to available standard treatments. Therefore, many of us in the field feel that these are patients who would benefit from earlier adoption of novel therapies and integration of novel therapies, as they tend to achieve deeper and longer-lasting responses with them.

These patients should strongly consider participating in clinical trials of these novel treatments for newly diagnosed multiple myeloma when available. I will caveat by saying for patients who are listening in, I think not all high-risk disease mean bad outcomes. There are patients in my practice, and all our practices, who have one or more of these high-risk features, and they do well with available treatments.

So I wouldn't necessarily consider high-risk disease to have an absolute bad outcome. There are exceptions, there are differences, and there are nuances to it. The best available treatments, whether on trials or off trials, are still the best

possible options for patients with high-risk myeloma, as they are for our standard-risk patients.

Mary DeRome (MMRF): When you go to meetings like ASH and you see clinical trial data presented, they always have a high-risk cohort. It's always interesting to see how those patients respond to the treatment versus patients who aren't in that cohort. So, I think it's good the field is really looking into that because it's like 20% to 25% of patients fit into that sort of definition, however you define it, right?

Dr. Berdeja, are there specific ways to treat high-risk patients, however it's defined? Does risk change when patients relapse from a treatment that they might be on?

Jesus Berdeja, MD: I think the important thing is for patients to realize that when you are considered a high-risk patient, the goals are still the same. It's to get you to the deepest remission possible because that sometimes can overcome that high-risk status in this subset of patients. So, I think the issue here is not necessarily going beyond what the standard treatments are, but I think it's the de-escalation of therapy that's probably more important. Oftentimes, with high-risk patients, I will continue the same four-drug induction, and proceed with transplant.

A lot of standard-risk patients get de-escalated to single-agent lenalidomide, for example. But with the high-risk patients, there are data showing you need to continue multiagent drugs throughout consolidation, and even maintenance, if possible. That has been shown by the Emory group with Velcade and Revlimid combinations, and the FORTE Trial, with carfilzomib and lenalidomide. So, in general, I try to keep my higher-risk patients on multiagent therapy longer than I do my standard-risk patients. That's really the main difference, from my standpoint.

Unfortunately, the outcomes are still not great. So, I completely agree with Dr. Mailankody, this is the patient population where there are clinical trials looking at incorporating novel therapies, including things like CAR T-cell therapy and bispecifics, as consolidation, even, in first-line therapy. So, I would encourage patients to seek out clinical trials, if possible.

In terms of whether the risk changes over time, the answer is, yes. There are high-risk features that can become more overt, as the clone that basically survives that initial treatment has higher-risk features. As we know, each time the patient gets treated with subsequent relapses, the duration of remissions get shorter and shorter. So, by definition, those are higher-risk clones, already. I would say any patient who has had several lines of therapy is a high-risk patient. High-risk cytogenetics can increase with subsequent relapses.

Mary DeRome (MMRF): Some interesting data came out of ASH on stem cell transplants. Dr. Mailankody, with the variety of treatments now available, would

you still consider a second transplant for patients who experienced an early relapse?

Sham Mailankody, MBBS: This varies across the country, and I think across the world, depending on where you are and the preferences of patients and doctors. But in broad terms, at our site and in my practice, we don't typically do tandem transplants, where there's two transplants back-to-back about 3 months apart. Second consolidative transplants are few and far between at our center, across my practice and those of my colleagues. So, that's one way of doing two transplants.

The second way is if you had a transplant in the past and your disease were to come back after some time, would you consider a second transplant? Again, this is in the context of available treatments. As more treatments become available, I think the use of a second transplant is expected to go down and has gone down. At our site, we would consider a second transplant for somebody who's had a more than 2-year interval after the first one. In other words, where we think that the first transplant had a reasonable duration of remission, we would consider it. That does not mean we would do it, but we would consider it. The longer the duration of remission after the first transplant, let's say patients who have done well for 5 to 7 years and are still transplant-eligible, the more we would consider doing a second transplant.

I think objectively, different groups have shown that the rates of second transplants have gone down over time, and this directly correlates with more treatments becoming available. You know, we've had so many new treatments that have now become available for myeloma, including CAR-T cells, bispecifics, and other non-immunotherapy treatments. We're fortunate that we don't often need to go to a second transplant, even when patients relapse. But that's the broad parameters at our practice for considering a second transplant.

Mary DeRome (MMRF): Dr. Berdeja, this has been a hot topic as well. What are your thoughts on doing or not doing a transplant for newly diagnosed patients?

Jesus Berdeja, MD: From the time the DETERMINATION study was presented at ASCO 2022, that has become an even hotter topic. The DETERMINATION trial was the American counterpart to the French IFM 2009 trial with RVD induction, transplant, followed by maintenance arm versus longer-term RVD going straight to maintenance.

They found a progression-free survival (PFS) advantage to the transplant arm of over 50%, but no overall survival benefit. Because of that, the question is who the patients who should be treated with transplant are, or if they should all be treated with transplant. I will argue though that consistently, transplant trials have shown a PFS benefit, regardless of the induction.

As our inductions get better, I think that overall survival becomes less of a concern, mostly because we have such great salvage therapies. But there is that concern of potential increased toxicity with transplant, and potentially secondary issues down the line that may mitigate some of the benefits in the standard-risk patient. For high-risk patients, I generally would recommend that they proceed with first-line transplant, unless they are in a clinical trial that's looking at something novel or different that may obviate that. If you're a standard-risk patient, I think that's where the conversation really becomes a little more fluid in terms of the risks, benefits, and the preferences of the patient. But I think transplant is still a very viable option for all patients with active myeloma.

Mary DeRome (MMRF): Dr. Mailankody, a common question from patient viewers is: What other options exist for patients on maintenance, besides Revlimid? I think this is because a lot of patients experience side effects from taking Revlimid, which is not always a pleasant drug to take.

Sham Mailankody, MBBS: There are emerging options. To be clear, I think a preponderance of data to date at least supports Revlimid use. There are multiple randomized studies, large ones, both here in the US and elsewhere that have shown PFS and overall survival benefits with lenalidomide maintenance compared with standard surveillance. That's what led to the establishment of lenalidomide as a standard-of-care for maintenance.

The challenges, as you alluded to are the side effects, GI (gastrointestinal) side effects, fatigue, but also this increased risk of second primary cancers with long-term use of lenalidomide, which is the reason why patients and doctors are looking for alternatives.

Two agents that have been studied would be Ninlaro (ixazomib), which is an oral proteasome inhibitor. This was tested against placebo, not against Revlimid, where there was an improvement in PFS benefit, but not in overall survival benefit. It had a modest improvement in PFS, which is why it has not yet been approved by the FDA for this indication. We do occasionally use it in patients who are intolerant to or cannot get Revlimid for other reasons. This is an oral option, something that patients can take at home. So, although it does not have an approval from the FDA, it does have randomized data supporting improvement in PFS compared with placebo.

The other agent that has been studied and is being studied, is daratumumab as maintenance. Patients can come in once a month and get it in their doctor's office. Again, some of the studies are ongoing.

The best study, probably, at this point, is the CASSIOPEIA study, which was a large European study looking at two randomizations. The second randomization was daratumumab maintenance versus placebo in patients who got initial induction therapy with a triplet or a quadruplet. There appeared to be some PFS

benefit with daratumumab maintenance compared with placebo, particularly in patients who had not had daratumumab as part of their initial induction therapy. I think we're waiting for some more definitive maintenance studies to establish the role of daratumumab in this setting, if at all.

The other thing I think we already covered for high-risk patients is the idea of doublet maintenance from the FORTE Study, for instance, using carfilzomib and Revlimid versus Revlimid alone. Patients in the FORTE Study appeared to have a PFS benefit to doing a two-drug maintenance. So that's the landscape of maintenance treatments.

As new treatments become available, I think we should hopefully start questioning the paradigm of indefinite maintenance for our patients. Timebound maintenance can use things like MRD to define durations of maintenance. All these things that are coming hopefully will also be an answer to the toxicity question, which could be alleviated by using fixed maintenance of these existing treatments or more novel therapies. One last point, my colleague, Dr. Neha Korde presented at ASH 2022 this study of lenalidomide cessation. This is for patients who were MRD-negative. Patients who stopped lenalidomide maintenance were monitored very closely with bloodwork and bone marrow biopsy.

Reassuringly, most patients, albeit after a short follow-up of 1 or 1.5 years, did not relapse and were doing very well. So, ideas of this kind where you can stop and then perhaps restart therapy if there's any change in clinical scenario would be another way to mitigate the toxicities associated with lenalidomide or other drugs.

Mary DeRome (MMRF): Yeah. There were more data on maintenance therapy presented at ASH 2022 than I've seen in some previous meetings. That is great because a lot of patients ask, "How long do I have to keep taking this therapy?"

Dr. Berdeja, about second primary malignancies that might be caused by Revlimid maintenance therapy in myeloma, patients want to know what they should expect or what they should be screened for during doctor's visits, if they're on long-term Revlimid maintenance therapy. What are their chances of having a second primary malignancy?

Jesus Berdeja, MD: What is interesting is we've always known from studies in both transplant and nontransplant patients that Revlimid can be associated with secondary malignancies. It's usually a small percentage and perhaps higher after use of alkylating agents like melphalan in transplant. Traditionally, we've seen skin cancers and secondary blood disorders like myelodysplastic syndrome, leukemia, et cetera. But what was interesting at ASH 2022 is the Myeloma XI study, which is this humongous study from the UK that enrolled 4,420 transplant-eligible and transplant-ineligible patients. They followed them up and they gave

us a couple of very interesting presentations at ASH 2022.

One was about the length of lenalidomide use. They showed us that the toxicity related to lenalidomide was not only from when it was used but also for how long it was used. Also, they showed that as patients get beyond the third and fourth year, the benefit of that continuation may not be as great as the initial year. So, I would be intrigued to see the long-term follow-up after cessation of therapy at 3 years. But they also looked at secondary malignancies in both groups. Secondary malignancies were more common in patients who got Revlimid versus those who did not, both in the transplant and nontransplant groups. Interestingly, the percentage of patients who got secondary malignancies was higher in the patients who had Revlimid induction and maintenance, as opposed to just using one or the other. So, we know that that risk does increase.

Most of the secondary malignancies were skin cancers, either squamous cell or basal cell carcinomas, which can be very easily managed. So, that was reassuring. In the transplant side, as we expected, they saw more potential myelodysplastic syndromes and leukemias compared with the nontransplant arm. Interestingly, the nontransplant arm had a higher incidence of secondary malignancies, but that could be because usually these are older patients who don't get transplant. So, even without treatment, patients who got observation still had secondary malignancies. So, there's a baseline of malignancies to expect.

The take-home point from my standpoint was that the highest risk to the patient was still myeloma. Most patients died of myeloma more than secondary malignancies during follow-up. So even though we should be considering secondary malignancies very aggressively, the benefit still outweighs the risk. So, I recommend very close follow-up, skin evaluations, and routine screening. Do not forget screening of other malignancies, just because patients have myeloma.

Mary DeRome (MMRF): Dr. Mailankody, are there any data that indicate waiting a little bit longer, say, 6 months versus 3 months after a transplant to start maintenance therapy with Revlimid might decrease the incidence of secondary malignancies?

Sham Mailankody, MBBS: As Dr. Berdeja alluded to, there's an increased risk with the back-to-back transplant and Revlimid maintenance. I'm not aware of any high-quality data that would suggest that delaying Revlimid by 6 months would decrease the risk of second cancers. It's also more cumulative over time, unfortunately. I'm not sure that you can completely decouple the Revlimid toxicity of second primary malignancies from the efficacy, which is a clear benefit in overall survival.

So unfortunately, I think with this maintenance, particularly posttransplant but also in nontransplant patients, there is an increased risk. We think that, despite the increased risk, most patients benefit from being on Revlimid maintenance.

Most patients died from myeloma, not from secondary cancer, so the overall survival benefit offsets the serious but, fortunately, rare side effect of second primary hematologic cancers.

Mary DeRome (MMRF): We're going to move a little bit into disease monitoring, and there were actually quite a number of presentations on that at ASH 2022.

Dr. Berdeja, can a patient ask for mass spectrometry testing? Are there certain cancer centers where this is routinely being used? Are you using it at Sarah Cannon? If it's not being routinely used, how far off do you think it is before it will be routinely used?

Jesus Berdeja, MD: So, the short answer is, yes, a patient can ask, but they would have to go to a particular center that has capabilities for this technology. So, at Sarah Cannon, unfortunately, we do not have it. The hope is that this will be soon available at all centers, but at this time, we're really talking about specific centers. So, you want to ask your doctor. Obviously, we send things to other centers all the time, if we want to get a specific result, so it doesn't hurt to ask, for sure.

Mary DeRome (MMRF): Great. It's a test that can be done from a blood sample. Dr. Mailankody, will this test pick up light-chain only myeloma?

Sham Mailankody, MBBS: In principle, it should, and it does because mass spectrometry, as the name suggests, is based on the mass of the abnormal proteins. So, it separates out higher masses from lower masses. Light-chain amyloidosis, for instance, can all be tracked and picked up by mass spectrometry, which has many advantages, including faster turnaround time, quick reporting, and less manpower required to read compared with gel electrophoresis. Also, it is more sensitive than blood-based testing, currently. There's hope that, at some point, it will get sensitive enough to supplement or replace some of the bone marrow biopsies our patients get. We're not there, yet, to be clear, but I think the hope is we'll get more sensitive blood-based testing that will, at some point, obviate the need for frequent bone marrow biopsies. Hopefully, that'll happen in the next several years. But there are several potential advantages to a mass spectrometry-based assessment.

Mary DeRome (MMRF): It seems like this could potentially be used for MRD testing, at some point in the future, right? Dr. Berdeja, should MRD negativity after treatment be a standard goal?

Jesus Berdeja, MD: Correct. But to remind everybody, MRD currently is measured with a bone marrow biopsy, which looks at deeper levels of remission. This is not what we mean when we tell patients they are in complete remission, which allows for some cells to be detected. Whereas, with MRD, depending on the depth of that detection, we're talking, potentially, up to 10^{-6}, or one in a million

cells where you don't detect myeloma. So, it's basically just a measure of deeper remission. As was noted before, patients who do get MRD negativity tend to stay in remission longer, and most of the studies have borne that out. So, the short answer is, yes, MRD negativity should be our goal. The long answer is, we don't know what to do, necessarily, with that information.

Now, the trials are starting to tell us a little more. We don't know if one gets to MRD negativity if we should stop treatment. Or, if you're not MRD-negative, should we be augmenting therapy? We still don't have that answer. Also, the caveat is, it may depend on your original risk stratification.

We saw from the MASTER trial, a study where they took high-risk patients on aggressive therapy that was stopped once they met the criteria of at least two MRD-negative assessments. Although a subset of patients appeared to be doing well with longer-term follow-up, a significant proportion of patients with ultra high-risk disease, or at least two high-risk features who had achieved an MRD-negative status relapsed during observation. This suggests that we should not stop therapy for those patients, even when they are MRD-negative. We're still in the early stages of determining how to use MRD testing, but when I talk to my patients who are MRD-negative, it definitely feels good.

Mary DeRome (MMRF): For the patient, too, I'm sure.

So, Dr. Mailankody, is it possible to have a small percentage of multiple myeloma cells in the bone marrow after treatment? So, a patient is not necessarily MRD-negative, but they have a small percentage of cells there that might not progress; but just sort of sit there?

Sham Mailankody, MBBS: So, this is the counterpart of the first argument. Yes, we all like to see MRD-negative responses, no question about it. You do a bone marrow biopsy, you get the reports back, it's all clear, no minimal residual disease. It's great to tell patients that. The patients like it, doctors like it, and the teams like it. I will say, though, that it's not a prerequisite to have MRD-negative responses to do well, and that's what the question alludes to. There are patients in whom we don't achieve MRD negativity with our available treatments who end up doing very well. They may have a small M-spike, and are possibly MRD-positive after transplant or other treatments, but then have a very long period of remission, where they don't need any additional intensive treatments around maintenance for a long period of time.

This is more so with standard-risk patients. Typically, patients who have had no high-risk features do well, even without the MRD-negative responses. The challenge is we don't yet know what to make of the information, beyond saying you're MRD-negative or MRD-positive. Should we be adding more treatments to patients who are MRD-positive? Maybe, maybe not. Should we be de-escalating treatments for MRD-negative patients? Maybe in some patients, not all.

So I think the next few years will be important in integrating the high-risk features, the responses to treatments, the sustained responses to treatments, and available therapies into one, to determine what's best for our patients. It is probably not going to be the same for every single patient. Maybe it will be determined based on all these factors and others that are emerging.

Mary DeRome (MMRF): Dr. Berdeja, if a patient has bony lesions, can they still be considered MRD-negative? Does MRD negativity, in this instance have a favorable prognosis?

Jesus Berdeja, MD: I think it goes back to the definition of MRD. So, I think it's important to realize that when we talk about MRD, usually, we're talking about getting a bone marrow sample and looking for cells in the bone marrow. That's the traditional MRD. We talked about mass spectrometry as a different method that may be broader because it's a blood-based test that maybe will give us more information. But remember, there is MRD by imaging in the IMWG, which is especially important for patients with disease outside of the bone marrow.

The bony lesion question is a little bit tricky, because it depends on the modality you are using. If you're using CT or x-ray, oftentimes, those bone lesions will remain, whether myeloma is in remission or not. So just because you have detectable bone lesions does not mean there's active myeloma. PET-CT or diffuse-weighted MRI, which are not available throughout, are much more sensitive techniques that look at the evolution of the disease, and so basically they can detect active myeloma in patients if it is still there. So, those will probably make it easier for us to determine whether patients have active disease in the bones or not. But technically, yes, if you have disease by x-ray or CT scan, it can still be MRD-negative.

Mary DeRome (MMRF): CAR T-cell therapy and bispecific antibodies, were the highlight at ASH 2022. Dr. Mailankody, how close are we to having additional CAR T-cell therapy options with shortened manufacturing times? Are we going to have better access to the two currently approved agents? I've talked to a lot of physicians who find the availability issue a tough one for them and for their patients.

Sham Mailankody, MBBS: With the two available products, things are looking up, at least at our site and others. We have more availability now such that we're no longer dealing with a long waitlist of patients trying to get the product. That's a positive. There's obviously room for improvement because there's still the manufacturing bottleneck and other things that need to be overcome, and we're anticipating that these products might be moved to earlier lines of therapy, which would open it up as an option for more patients. So, there's certainly no room for complacency in terms of access. It's getting better hopefully as the field is continuing to move forward.

There were several interesting presentations at ASH that hopefully will lead to potential future standards-of-care soon. There were a couple of different BCMA-directed autologous CAR T-cells that looked very promising. So, if those make it to approval in the future, they will add to the 2 currently available options, and more options mean more availability. There are platforms of rapid manufacturing of autologous products, so, instead of taking 2 to 3 weeks, typically, for manufacturing, and then another 2 to 3 weeks for quality check and other things, there are now platforms where cells can be manufactured in 2 to 5 days.

These are still in clinical trials, but again, the early results of both feasibility of rapid manufacturing as well as the efficacy look promising, so that adds to the options. There are allogeneic products. For instance, we presented the update on the ALLO-715, which is a BCMA CAR T-cell off-the-shelf. So, that means rapid turnaround time and efficacy. That's yet another approach. There are other companies looking at off-the-shelf allogeneic CAR T-cells.

Lastly, almost all the focus in the preceding years has been on BCMA. We're now starting to look at other targets as well. For instance, Dr. Berdeja presented results from a GPRC5D-directed CAR T-cells, a multicenter study that looks very promising. This is now in addition to BCMA, and an option for patients who have or have not received BCMA therapies. There were several new updates at ASH 2022 that gives us a lot of hope for the next 2 to 3 years.

Mary DeRome (MMRF): Sure. I think that sequencing of these agents is becoming a much more interesting and important question as more of these agents become available. Dr. Berdeja, what is the experience with Carvykti in a patient who relapsed after having Abecma, or vice-versa? Can a patient who's previously had a CAR T-cell therapy be eligible for bispecific antibody treatment?

Jesus Berdeja, MD: So, the shorter answer is yes. The good news is there are good sequencing data. I think all of us who've had clinical trials for a long time have done this in clinical trials and seen that some patients can respond to a subsequent therapy that has the same target. But it's hard to tell between these commercial products. We know that retreatment with Abecma and Carvykti was not good. I would not recommend it.

A lot of the real-world data that we're seeing in terms of sequencing are pretty recent. So, we don't have patients who potentially got a remission that lasted 3-plus years. Would that patient potentially then be able to take Abecma then go on to Carvykti? Most likely the answer is yes, and it goes back to the mechanisms of resistance or why the patient progressed. But looking at single-institution data, it does look to me that if patients have had prior CAR T-cell therapy then go to another one the responses are just not as good and durable.

Whereas, with the bispecifics, we're seeing that the responses tend to be very similar and may be durable. Obviously, there is now data from clinical trials

allowing prior BCMA. In my mind, if you have a patient that has all the options and your plan is to give CAR T-cell therapy, you want to give the CAR T-cell first. If that patient for some reason is not a candidate or can't wait or needs something off-the-shelf, then you go with bispecifics. The caveat is if you go with the bispecific and then the BCMA-directed CAR T-cell therapy, you may not get the same results.

Dr. Mailankody alluded to the GPRC5D study, where if you have a patient who relapsed from a BCMA-directed CAR T-cell therapy, they can be treated with a different one and get excellent responses. Although we don't know the durability with some of those responses. So again, they're still completely in flux, but I think it really depends on how they responded and how long it has been since the therapy before you consider going back to the same target. So, there's a lot of nuances to it that we're still learning, but the short answer is, yes, they can be sequenced.

Mary DeRome (MMRF): Great. Dr. Mailankody, can T-cells be collected and frozen to be reused for future CAR T-cell therapy?

Sham Mailankody, MBBS: Scientifically, the answer is yes. There's nothing to stop us from collecting, freezing, and manufacturing as needed. The challenge is logistics and financial considerations. Logistics being where do we store all these T-cells and who's going to pay for them. Right now, at our site we don’t do that. I am not aware of any other sites that will offer to collect T-cells and store them in anticipation of needing them down the line. As the treatments evolve and we use CAR T-cells earlier, that might change, but for now, you know, I think we're limited by the logistics and finances of doing it. I would also say most of the experience of manufacturing CAR T-cells has been in fresh or relatively recent apheresis. So, I would caveat by saying, although there's no scientific reasons to believe that you cannot store them, we don't know how successful manufacturing after collecting T-cells 3 or 4 years earlier would be.

There may be challenges to viability and other potential issues that would need to be ironed out before we say this is something we want to do for our patients regularly. So, for now it's not an option, but that might change as more data become available.

Mary DeRome (MMRF): Dr. Berdeja, do you see CAR T-cell therapy replacing stem cell transplantation? I know, another hard question.

Jesus Berdeja, MD: I think there has been movement towards CAR T-cells replacing transplant in a subset of patients. So, I think it could happen. The trials are ongoing now in high-risk patients who can’t get a transplant.

Mary DeRome (MMRF): Those are going to be some interesting data when they come out.

Jesus Berdeja, MD: Yes, absolutely. We'll wait and see. But remember there must be significant benefit, right? I mean, we're talking about a $500,000 treatment versus a $50,000 treatment. So, if patients get a PFS improvement of 6 months, is that sufficient to replace something like a transplant? This is possible in places where we have this embarrassment of riches like the US, but throughout the world, obviously, this would be a much more difficult thing to do. So, in that case, transplant, I don't think, will be replaced by CAR T-cells. But could I foresee a future where CAR T-cells will take the place of transplant? The answer is yes. I would love to see that, because I think it is a much better treatment.

Mary DeRome (MMRF): I think it's going be a while before we come up with something that's going to take the place of transplant, which is still an extremely effective therapy for many patients. Certainly, in the rest of the world it's much more available than CAR T-cells.

Dr. Mailankody, what are the distinguishing attributes of the various bispecific antibodies under investigation?

Sham Mailankody, MBBS: There are many bispecific antibodies, and the way I keep track of them in my head are if the target is BCMA or non-BCMA. There are many BCMA-directed treatments, but there are two non-BCMA ones that look promising. One is talquetamab, which is a GPRC5D-targeting bispecific antibody. Another one is cevostamab, which is an FcRH5-targeting bispecific antibody. There were updates for both of those products at ASH, and both looked quite promising with responses in the order of above 60% in patients. Being non-BCMA targets makes them quite an attractive option because there are plenty of BCMA-directed therapies.

Talquetamab is a subcutaneous injection. Cevostamab is intravenous (IV) but it is given every 3 weeks, so it has the convenience of being a less frequent treatment. Its toxicity profile CRS (cytokine release syndrome) and neurologic toxicity is like the BCMA bispecifics. Talquetamab has some GI side effects of dry mouth and loss of taste, plus skin and nail changes, which are unique to talquetamab.

There's probably half-a-dozen BCMA-targeted therapies if not more in development. One that's FDA-approved already is teclistamab. My impression of the data is that they're similarly effective and have a similar toxicity profile, by and large. The caveat is that they have not been tested head-to-head. We're comparing phase 1 and 2 studies across-board, done at different times and different places. But the high-level numbers for toxicity and efficacy look comparable across the board.

So, what's different about them? I think one is mode of administration. There are

some subcutaneous formulations, some IV, so that's different and people might prefer one or the other. There are differences between the frequency of administrations, once a week versus some that are now every 3 or even 4 weeks. So obviously, less frequent administration would be more desirable. Ultimately, I guess it is easier to pick what's readily available than what's not. So, teclistamab is approved and therefore does not need trial eligibility or enrollment to get access to. The other products, right now, are available only in the context of clinical trials.

The bottom line I think is, across-board, these half-a-dozen or more bispecifics have a response rate in the order of 50% to 75% in patients with relapsed refractory multiple myeloma–triple-class exposed, triple-class refractory myeloma. The rates of CRS and neurologic toxicities appear lower than we see with CAR T-cells, and so that's good. All these products, at this point, require inpatient stay for the initial admission step-up dosing, to mitigate or lower the risk of CRS and neurologic toxicity. Lastly, as a point of caution, although they're very effective, they also have the tendency and the potential to cause serious infections in patients. That's true for all these bispecific antibodies. So, infections like severe COVID-19, pneumonia, and other opportunistic infections appear to be common and increasing as patients stay on this drug for a longer period of time.

One of the challenges for us will be to monitor patients for infections that we may not necessarily expect in patients with multiple myeloma. So, typically PCP pneumonia, fungal infections, and others. We must be able to identify those infections early, intervene appropriately, and come up with strategies for immune prophylaxis surveillance. So, we maximize benefits and lower the potential harmful side effects of these treatments.

Mary DeRome (MMRF): My final question for both of you is, based on what you may have seen at ASH 2022, is there anything that you're going to do differently in your practice?

Jesus Berdeja, MD: It was a great ASH annual meeting, but at the same time, there was no presentation that I thought was practice-changing. So, from that standpoint, no. One of the things that both of us deal with a lot are the bispecifics and the CAR T-cells, right? We always get that question about which of these is going to be the winner. One of the potential benefits of the bispecifics was that they're off-the-shelf, so they are going to be easier and maybe more translatable to the community. What we found out so far from teclistamab since its approval is that it's actually been a little bit difficult to give because of the mandate to hospitalize patients.

So, the same issues have remained with CAR T-cells, which is interesting. One of the presentations that I felt would help me potentially modify how we do this was a presentation from Dr. Trudel with cevostamab. We've been thinking about how we can do this all outpatient, right? Because as Dr. Mailankody alluded,

CRS, even though it's present in most patients, tends to be mostly grade 1 and rarely grade 2. So, it is very manageable as an outpatient.

Mary DeRome (MMRF): That was an interesting presentation.

Jesus Berdeja, MD: In that presentation, they gave tocilizumab as a prophylaxis, and they showed that you can decrease the risk of CRS in half. Tocilizumab is still a very expensive medication and may not be available to all clinics, but the nice thing about bispecifics is that you're going to keep giving it. So, I think we can come up with a more aggressive prophylaxis, like the use of steroids, perhaps with dose escalation. I think this gives us proof that potentially we can come up with that magic solution of how to do this all outpatient because I think that will expand its potential use. But we must remain cautious. We worry about that initial CRS, but I think that the increasing infections Dr. Mailankody mentioned are going to become a bigger problem when we think that we're over that initial hump and the patient can go back to their clinic 3 hours away and continue. This is going to need a lot of education to make sure people are looking out for those infections.

Mary DeRome (MMRF): Agree. Dr. Mailankody, final thoughts on any practice-changing information from ASH 2022?

Sham Mailankody, MBBS: I echo what Dr. Berdeja said, which is that although it was a very interesting ASH with lots of good data, they were not immediately practice-changing.

Two themes stood out for me. First, there's still a lot of uncertainty, as this discussion alluded to. Do we transplant everybody or not? What maintenance do we give patients? What's the optimal induction? There's a lot of uncertainty despite the progress that has been made. So, one of the lessons for me, as I go to these meetings is there's room for shared decision-making with patients. Patients are smart and they can choose transplant versus no transplant. The best we can do is to provide them as much information as possible to make those decisions, and these meetings help us give data to back our recommendations or the different options that patients are facing.

Second, think about both benefits and risk. We've been incredibly excited about CAR T-cells and bispecific antibodies, which we've been using for many years now in clinical trials. But now that these treatments are available in clinical practice, we've had to treat several patients with tocilizumab. Patients are eager to get these treatments, and are doing well. The meeting was a highlight of all the great efficacy that we see. But like Dr. Berdeja, I do worry about the longer-term infection risk quite a bit as patients stay on these treatments for long. How do we best manage infections? How do we reduce the risk?

If patients are getting these at lower-volume centers where they may not have

the same level of comfort or expertise managing these side effects, will we see more infections and complications from infections? How do we best educate patients, caregivers, and doctors to minimize that risk? I think it is going to be a big real-world challenge in the next year or two, as more of these treatments become available.

Mary DeRome (MMRF): On behalf of the MMRF, I'd like to thank our guests today, Dr. Jesus Berdeja and Dr. Sham Mailankody and our viewers.