FAQs on Multiple Myeloma Diagnosis and Prognosis

June 28, 2023

Transcript

Mary DeRome (**MMRF):** Welcome. Thank you for joining us for today's session, Frequently Asked Questions from the American Society of Clinical Oncology. I'm Mary DeRome, Senior Director of Medical Communications and Education at the Multiple Myeloma Research Foundation. Today I am joined by Dr. Nisha Joseph, Danielle Roberts, and Rosie Pruitt from the Winship Cancer Institute at Emory. We've invited all of these ladies here today to answer some of our frequently asked questions that we've received from caregivers about the recent multiple myeloma clinical study data at this year's American Society of Clinical Oncology Meeting, or ASCO. So, let's jump in. I'd like to begin our discussion focusing on patients with newly diagnosed myeloma. There were only a couple presentations this year offering new insights on this topic. My first question is to you, Dr. Joseph about a phase 3 study that compared a three drug regimen to a four-drug regimen that includes elotuzumab, or Empliciti, as induction therapy. Could you tell us whether a four-drug regimen is part of the standard of care for newly diagnosed patients? And if so, what is the advantage of a four-drug regimen over a three-drug regimen, and what did the trial with Empliciti tell us?

Nisha Joseph, MD: Yes, absolutely. So first, I just want to say thank you so much, Mary, and everyone, for organizing this, and to Danielle and Rosie for joining me today. So, you are asking about, in the newly diagnosed space, the role of triplet versus quadruplet, or three-drug versus four-drug regimens. And specifically, from ASCO this past June, to talk about the abstract that looked at the addition of elotuzumab with carfilzomib (Kyprolis), lenalidomide (Revlimid), and dexamethasone (KRd).

As things have evolved in myeloma, we have continued to add drugs. We started with doublets, then we went to triplets, and now we're looking at quadruplets. And in general, we have noted that when you add additional drugs, we see improved efficacy, and that's the goal, particularly in the upfront setting. The caveat is we want to improve that efficacy, or how effective the regimen is, while minimizing overlapping toxicities. Meaning, every time we add a drug, we're potentially adding side effects, so we want to be really careful about that. Keeping that in mind, for standard-risk patients, historically, the standard of care has been RVd, which is lenalidomide, bortezomib (Velcade), and dexamethasone.

And so, the Griffin Trial, which is a recent phase II trial, looked at the addition of daratumumab (dara; Darzalex), which is now a subcutaneous injection, in addition to RVd, and this really showed improved efficacy in terms of depth of response or minimal residual disease (MRD) negativity, both postinduction and later in treatment (post-transplant, post-maintenance, et cetera). And so, for us, dara-RVd is pretty routine for standard-risk patients. I think the question of triplet versus quadruplet is a little up for debate in the high-risk patients. We tend to use triplets, namely, KRd, but we've also

started using a little bit of dara-KRd, but I think that's in a select group of patients, just given some of the toxicity issues.

In terms of this abstract, this was a study out of Germany, a randomized phase III study. It was a large study, looking at KRd (carfilzomib, lenalidomide, and dexamethasone), versus elotuzumab plus KRd. And elotuzumab is a monoclonal antibody similar to daratumumab or isatuximab (Sarclisa), but it has a different target, which is SLAMF7. The endpoint of the study was looking at depth of response or MRD negativity. Minimal residual disease is the most sensitive tool we have for detecting myeloma. At the most sensitive level, asking can we even see one myeloma cell. And they met that endpoint: they saw higher rates of MRD negativity in the group with elotuzumab plus KRd versus KRd alone. And these were patients who received induction therapy with either the quadruplet or triplet, they had a transplant, there was an option for second transplant in patients with high-risk disease. Then they got consolidation with the same regimen they were assigned to, and then they received maintenance with either elotuzumab plus lenalidomide or lenalidomide alone, until progression.

So, it was similar to what we do for upfront patients. And they saw better depth of response. In terms of toxicity, they saw similar toxicity between both arms, but I'll just point out that there were several deaths on study, and there was a non-zero rate of cardiotoxicity, which we see with carfilzomib. And I don't think it has anything to do with elotuzumab, but it's really the KRd backbone. So I think the bigger question is, do we need KRd in the upfront setting, knowing that the point is to get patients successfully through induction to get them to transplant. So, if we're having heart failure or cardiotoxicity that is preventing or delaying people from getting to transplant, is that really the best regimen to use upfront? So, I don't think it has anything to do with elotuzumab, but it's still worth noting. I think the bigger take-home message for me is, yes, a quad versus a triplet regimen seems to be better. But I think, again, the goal is finding a quad regimen that we can deliver safely.

Mary DeRome (**MMRF):** Thank you for that very complete response. I have heard similar things from other folks in the myeloma space, so it was really great. So, Danielle, in general, would giving four drugs instead of three increase a patient's risk of side effects? I think we've gone over that a little bit. In your experience, what have you seen?

Danielle Roberts: In our experience, we use a quad therapy for upfront therapy for standard-risk patients prior to transplant. We're using dara-RVd, as Dr. Joseph stated, and it's overall very well tolerated. The goal is to increase their response and decrease the side effect profile, and I think we're doing a good job of doing that. Patients work full time while receiving these regimens.

As with everything that we give, there is going to be some toxicity associated with it, but I think the toxicity, especially in the upfront setting, is minimal, and we're able to use the appropriate supportive medications, whether it be diphenoxylate and atropine (Lomotil) or loperamide (Imodium) for diarrhea, and using things like ondansetron and prochlorperazine (Compazine) to help with nausea. But in general, in the upfront setting,

I think the quad therapy is very well tolerated; we're obtaining great responses and getting patients to transplant. If we take that same information and move it later on down the line to when people have had more and more therapies, I think that changes the discussion a little bit. But even still, we've used it successfully in the relapsed/refractory setting for certain patients, maintaining responses and addressing the side effect profile with supportive medications and able to allow people to still have a good quality of life while coming in and receiving their therapy.

Mary DeRome (**MMRF):** So, we've already talked about elotuzumab-KRd, and now you were just telling us about dara-RVd. Are there other four-drug regimens that you have used in your clinic?

Nisha Joseph, MD: I think the main other four-drug regimen that we've used besides dara-RVd is dara-KRd, which was studied in the MASTER trial and the CONCEPT trial and other trials, I think particularly for high-risk patients. So, I don't think we're doing that routinely. I think it's an ongoing discussion, because some of those data are a little early, but that's a very effective regimen. There were high rates of MRD negativity in those trials, in the 60% range, and I think it's just a little bit about toxicity. I think there's a select patient that maybe can tolerate that. Carfilzomib is twice weekly and daratumumab is weekly, and it could be a little much for some patients. But for the most part, I think the quad we use most commonly is dara-RVd.

Mary DeRome (**MMRF):** Rosie, following an induction regimen, and, in most patients, a stem cell transplant, patients will receive some form of treatment known as maintenance therapy. Before we get into the details of the next presentation that looked at maintenance therapy regimens at ASCO, can you remind us why maintenance therapy is necessary for patients? And what is the current standard of care for maintenance?

Rosie Pruitt: Sure. Currently, our standard of care for standard-risk myeloma patients would be single-agent lenalidomide, in most cases. For patients with high-risk myeloma, we typically recommend a triplet regimen, whether that's RVd, or, like Dr. Joseph alluded to, KRd, something like that. We don't always do the triplet maintenance indefinitely. Sometimes we aim for three years and then reassess disease status and downgrade to single-agent lenalidomide if it's safe to do so. I personally believe maintenance therapy is so important, and I often tell patients that I compare this to the one-two knockout punch. So, induction and transplant is us knocking out the myeloma, the maintenance is us keeping pressure on it so that we can make sure, as best we can, it doesn't get back up any time soon.

Our institutional data have shown that patients with standard-risk myeloma that have gone on to single-agent lenalidomide maintenance achieve about six years, on average, of progression-free survival (PFS) on maintenance. And we know that a deeper and a longer first remission leads to better overall survival (OS) for our patients. Maintenance can sometimes deepen that response over time, and it appears to certainly lengthen that response, and it's definitely why we think it's so important. And for many of our patients, like we said, we can do things to make maintenance very tolerable and not

significantly impact quality of life, so that we're having patients living the lives they want but still maintaining control of their myeloma. And, keeping quality of life in mind, we are starting to investigate if and when discontinuation of maintenance therapy or even treatment breaks would be appropriate.

There are very limited data on the role of stopping maintenance therapy, but I'm hopeful, with more time and data analysis, that we'll be able to identify a population of patients where it would be safe to stop or take a maintenance break after a certain period of time.

Mary DeRome (**MMRF):** I've seen some presentations at some meetings with some of that data, which are really interesting. We'll have to see how that plays out over time. Dr. Joseph, there was a phase II study of a three-drug regimen as maintenance therapy for patients with high-risk myeloma, presented by your colleague at Emory, Dr. Ajay Nooka. First, can you tell us what constitutes high-risk myeloma?

Nisha Joseph, MD: Yes. That, honestly, is being debated, and I think it's changing. In general, we can think about it in two ways, and that's genetic high-risk myeloma and biologic high-risk myeloma. There are certain genetic changes in your plasma cell that make it a myeloma cell. People often get confused when we say “genetics,” because some cancers are hereditary, and that's not what we're talking about here. We're talking about the specific change in that plasma cell that made it malignant. And some of those changes make a “smarter” myeloma cell, and so, as a result, we have to be smarter and a little bit more aggressive. The most common changes are translocation of (4;14) and translocation of (14;16). “Translocation” just means a swap of genetic material between chromosomes. Other common changes are deletion 17p, which is a deletion of a part of chromosome 17, and gain of 1q, particularly high numbers, is often thought of as high risk, though not in this abstract. Biologically, we think of things like extramedullary disease, which is having myeloma outside of the bone marrow, and plasma cell leukemia, which is circulating plasma cells; we often think of these as high risk. In this trial specifically, Rosie already alluded to our approach of risk-stratified maintenance therapy, which we've been doing for over 15 years, and Dr. Nooka has previously published on RVd maintenance. After the FORTE trial, we've started using KRd maintenance a little more regularly.

The idea behind this trial was using the most effective, potent drugs we have to try to prolong PFS in these patients, particularly the ultrahigh-risk patients, which are patients who have more than one of these high-risk features, because they really don't do as well as the standard-risk patient: they tend to relapse sooner. Again, the goal is to try to get the best and longest remission that we can, particularly that first remission. In this trial, Dr. Nooka defined high risk as having deletion 17p, translocation (4;14), translocation (14;16), or plasma cell leukemia. The idea was, post-transplant, these patients were on maintenance therapy with carfilzomib, pomalidomide (Pomalyst), and dexamethasone for three years. I think about 60% of the patients had two high-risk features (a “double hit”), and about 60% of the patients were also Black, which I think is notable because of where we are. Emory is in Atlanta, and so for a lot of our trials we are very fortunate to have a diverse patient population enrolled. That's not always the

case, not for a lack of trying, but based on patient populations. It's really important to have patients that are representative of the community on these trials. Otherwise it's just not applicable to everybody.

What Dr. Nooka found was really impressive. After three years, approximately 60% of patients still hadn't progressed and the rate of OS was in the 70s, which might not seem great, but it actually is very impressive in such a high-risk group of patients. And this was a particularly high-risk group. I think it's a very promising initial report of a way we can manage these patients better. In general, particularly for ultrahigh-risk patients, what we do doesn't seem to work, so we need to start thinking out of the box.

Mary DeRome (**MMRF):** Agreed. Danielle, for patients that are taking only lenalidomide as maintenance, would there be a time when they should consider adding other agents to their maintenance, for example, if their M protein values start to go up a little bit?

Danielle Roberts: That's a great question. It's a really common question that we get in our clinics. When patients are on maintenance lenalidomide, we are typically checking labs anywhere between every month to every three months, and it depends on where they are post-transplant and how stable they've been. It's not uncommon for us to see a biochemical relapse, and what we mean by that is that your M spike may be slowly increasing, or maybe if it's your free kappa light chains or your lambda light chains that's your marker, we're watching those numbers slowly start to trend up. But if somebody's completely asymptomatic, with no bone pain, and if we've done additional PET scans and we're not finding any evidence of bone disease, and if the rest of their labs are all completely normal, especially looking at the CRAB criteria (calcium elevation, renal insufficiency, anemia, and bone abnormalities), then our trend is to continue to monitor that slow progression of numbers.

What we want is to extend the amount of time for these patients where they have a good quality of life and they're tolerating the lenalidomide. If we're adding additional agents at that point, we may be starting that too soon, which can shorten that relapse-free time period. We also could be increasing toxicity at that point too. So really, what we're doing is slowly watching those numbers, trying to limit the amount of anxiety and stress that it may cause the patient. But at the point we start to see what we consider more organ damage, which is what the CRAB criteria indicate (the calcium levels increasing, the patient becoming more anemic, or their renal function declining), at that point, we are now looking to say, "Okay, your myeloma tends to be causing more issues. Now is when that we need to start thinking about making a treatment change."

Mary DeRome (**MMRF):** Thank you. So, Rosie, as we're discussing these regimens, should patients who are taking more than one drug as maintenance expect to have a higher instance of side effects from taking all of these medications at once? And what do you suggest for patients for their quality of life while they're on maintenance, whether it's a single agent or more than one agent?

Rosie Pruitt: Technically, yes, as you add more agents, you're increasing the potential for side effects. But I wouldn't necessarily say that it's additive or that patients that are on doublet or triplet maintenance necessarily have more intolerance issues. I think whether it's single-agent maintenance, triplet maintenance, whatever it is, the most important thing is being followed by a provider who is knowledgeable and comfortable in managing those side effects. And on the patient's side, it's just being open and communicative about what's most disruptive to their quality of life. So, for example, with an infusion-based maintenance therapy, if the patient is trying to work around a work schedule, that can be accommodated. We can talk about timing of treatments or infusions, possibly including weekend infusions, if that allows for better quality of life.

And then thinking about side effects, there's a lot that we can manage. We can do dose reductions, interval reductions, [different] timing of medications, those kinds of things, and just appropriately managing supportive interventions. Like Danielle said, we love our diphenoxylate and atropine, we love our colestipol (Colestid); there are just certain tricks that we have that are really effective at making these maintenance therapies tolerable. It's very rare that we have a patient that really can't tolerate anything. It does happen, and for those patients, we just observe them. But I think for the most part, we're able to manage side effects so patients are living the lives that they want to be living.

Mary DeRome (**MMRF):** It's great that we've gotten to this point where there are so many medications to help people get past these side effects so that they can receive appropriate therapies. That's really a good thing.

Let's move on, now, to talk about relapsed/refractory patients and chimeric antigen receptor (CAR) T-cell therapies. Just like last year, this year's ASCO meeting brought us several updates on the CAR T-cell therapies and also a lot of information on bispecific antibodies. First, let's talk about data relating to the two FDA-approved CAR T-cell therapies that are currently available to patients, idecabtagene vicleucel (ide-cel; Abecma) and ciltacabtagene autoleucel (cilta-cel; Carvykti). There was a presentation on the final results of the trial that led to Carvykti's approval, and another presentation on the real-world experiences with the use of Abecma. Dr. Joseph, I have a couple of questions for you on these presentations. The first is, what key takeaway should patients know about the Carvykti study? And how is it possible that Carvykti got approved before these final results were complete?

Nisha Joseph, MD: Carvykti got approved and it had a priority review and an early designation because we saw such promising results early. But these were the final results of the study. I think the one thing I heard everyone talk about was "35 months." The medium PFS, or the average survival, of patients receiving cilta-cel on the study was almost three years, which is really impressive, particularly in the relapsed/refractory space. This was a heavily pretreated patient population; these were not newly diagnosed patients. That was kind of the buzz around it, and I think it remains a really effective tool in the relapsed/refractory space. I think the challenge of CAR T-cell therapy in general is about logistics and access. We are going to talk about a few [areas in which] that's evolving.

But right now, both cilta-cel and ide-cel are approved for patients who have progressed through four or more lines of therapy, and as many of you might know, as myeloma continues to come back, it gets a little trickier, and sometimes things take off a little faster than they might've in earlier lines, and so, having the time to wait for the manufacturing and delivery of CAR T cells can be really challenging. And so, moving into the next abstract that was presented, this was looking at the role of bridging therapy in ide-cel. This was a retrospective analysis in the real world, with over 200 patients, and the data were gathered across the US–this was from the myeloma CAR T-cell consortium. Approximately 80% of patients received bridging therapy in this group, so they were able to compare patients who had received bridging therapy with those who had not. The aim of the analysis was to see whether bridging therapy had an effect. And they grouped the bridging therapy into immunomodulatory-based therapy, protease-inhibitor–based therapy, alkylators, and selinexor (Xpovio). The patients who received bridging therapy, not surprisingly, tended to have higher-stage disease, so R-ISS II or III higher-risk disease, they tended to have worse performance status, and there was a higher risk of extramedullary disease, which is not overly surprising, if you think about it. Bridging therapy is therapy that we use to control a patient's disease while the cells are being manufactured. It makes sense that those patients have a little bit more aggressive disease.

What they found in terms of toxicity was no significant differences, except there tended to be longer hospitalizations in the bridging-therapy group, and there were slightly higher rates of neurotoxicity (immune effector cell–associated neurotoxicity syndrome; ICANS) in patients who had received selinexor. This was a very small group of patients, but I thought that was interesting, because selinexor crosses the blood-brain barrier. And so, I think it's worth keeping in mind, if you're using selinexor right before CAR T-cell therapy, maybe that's not ideal, or maybe we need to think about longer washouts. But in general, there wasn't significant toxicity, and I'll also point out there wasn't a lot of responses to bridging therapy. So then, when we looked at response, in general, the bridging-therapy group didn't do as well. The PFS and the OS was not as great.

When comparing the subgroups defined by type of bridging therapy, the alkylator group did the worse, but there were small numbers of patients, so it's a little hard to tease out, but that's what we tended to see. The patients with immunomodulatory-based therapy tended to do a little better.

But regarding the question of whether bridging therapy affects efficacy, I don't really think that's the question. I think all we're seeing here is that if you need bridging therapy, you might not be the best patient for CAR T-cell therapy, because we're forcing it, for lack of a better word.

Mary DeRome (**MMRF):** Right. That is a patient like that would be in kind of bad shape to begin with, right, so the results might not be as good.

Nisha Joseph, MD: It's not ideal. But the problem is we don't often have options, and so that might be what we're pushing for, because that's the best we have. But I think

what we're working on is getting access to CAR T-cell therapy in earlier lines, and we're starting to be able to manufacture CAR T cells in a shorter period of time. Currently, we're waiting anywhere from four to eight weeks. That's a long time if you have rapidly evolving myeloma. Being able to manufacture that in a couple of days really makes a difference. I think that's where we're moving, and I think those are some of the bigger take-homes from that study.

Mary DeRome (**MMRF):** I agree. That's great. So, Danielle, from a practical perspective, has the process of getting patients access to ide-cel and cilta-cel gotten easier? When these drugs were first approved, it was very difficult. There were very long waiting lists to be able to get into the manufacturing facility, and each center got maybe one or two spots per month, and it was very difficult for patients to access these therapies. Has that gotten easier? And are there more patients who are able to access these therapies from their myeloma specialist or their oncologist? So, what have experiences been like at Emory?

Danielle Roberts: I think the access has gotten a little easier recently. Even in our own practices here, we're seeing higher numbers of patients using commercial FDA-approved CAR T-cell therapy, and we're having more slots available to us. We're getting these patients taken care of. Like Dr. Joseph said, from a manufacturing standpoint, there is still the time between the collection of T cells to the time we're able to administer them. So that part is definitely still there, but the overall patient access and the number of patients that we're taking through has definitely increased more recently, which is great for our patients.

Mary DeRome (**MMRF):** That is a really great thing. Dr. Joseph, many in the audience are curious to know when the next generation of CAR T cells might be available. We've heard about three new CAR T-cell therapies at ASCO, all with numeric designations for now: PHE885, GC012F, and CT103A. What can you tell us about these agents, and how are they similar or different from ide-cel and cilta-cel?

Nisha Joseph, MD: When we're trying to improve upon CAR T-cell therapy, we're thinking about improving the persistence of these CAR T cells, the efficacy, and reducing the toxicity. And then, of course, trying to get these cells with reduced manufacturing time to get them to the patients sooner. All of these new therapies hit one of those boxes. The PHE885 and the GC012F are using newer manufacturing to make these CAR T cells in two to three days. And across the board, of all these trials, you're seeing very high response rates, very promising in terms of efficacy, duration of response, depth of response, so, those are all good things, but also, being able to access these things earlier. The third, CT103A, is using a fully human CAR T-cell receptor. That's really relevant in terms of reducing immunogenicity and reducing toxicity. These are just all different ways of how we can make these CAR T cells more effective and tolerable, but also get them to the patients sooner. I don't know when they'll be available, unfortunately. These are mostly early-phase trials and they take some time, but I think it’s really exciting and encouraging that we're seeing such promising results.

Mary DeRome (**MMRF):** For sure. Speed is of the essence to be able to get our patients these therapies. Let's talk about the late-breaking abstract that was presented on the use of cilta-cel in patients who had previously had one to three prior lines of therapy, which is actually much earlier than what it's currently approved for, which is four. Everybody was really excited for this data. What did we learn from that study? And do you think that CAR T-cell therapy will eventually be used earlier in the treatment plan, as a result of this data?

Nisha Joseph, MD: The take-home was that we used cilta-cel in an earlier line, with one to three prior lines, and we compared it to standard of care (daratumumab, pomalidomide, and dexamethasone or pomalidomide, bortezomib, and dexamethasone), and cilta-cel won, in short. There was better depth of response and duration of response. The point of this trial is that we're showing that it's more effective than some standard of care regimens in earlier lines, so we can gain access to this therapy earlier. So, my expectation is that's where we're going.

Mary DeRome (**MMRF):** Right. I think that Janssen, the company that makes cilta-cel, has already applied to the FDA for this new indication, and ide-cel has also applied for approval as an indication in earlier lines of therapy. So, we'll see how that works out with the FDA in the coming months.

We're going to talk now about bispecific antibodies, which was, arguably, the main class of therapies that was discussed in myeloma at ASCO this year. First, let's review the data that were presented on teclistamab-cqyv (Tecvayli), which is the bispecific that is approved by the FDA for myeloma. Danielle, what more did we learn about teclistamab at ASCO?

Danielle Roberts: Teclistamab, I think, is very exciting for our patients. You know, you get to that third or fourth line where patients have had multiple lines of therapy and the options start decreasing, and OS rate and the rate of durable response actually decrease, typically, in this patient population. And then this study actually proved that, for these patients who have multiple lines of therapy, we can extend some response rates up until almost 24 months, somewhere between 11 and 24 months, depending on your risk factors and how many lines of therapy that you had. But for our patients, this is a great option for them, especially when we look at the amount of time it takes for patients to get CAR T-cell therapy. For somebody that needs therapy quickly, we're able to move to teclistamab and have response rates and a great side effect profile and less toxicity. As with CAR T-cell therapy, the bispecifics do carry the risk for having symptoms of cytokine release syndrome, so our protocol is to do the ramp-up dosing schedule inpatient, so that we can adjust for that.

Once the patient has successfully had the ramp-up schedule, we're doing this in an outpatient setting, which is fantastic for our patients. They're coming in once a week, and it's a subcutaneous injection, usually in your abdomen, so, no infusions and a lot of injections and things like that. And typically, it’s pretty well tolerated. There is a group of

patients that we've seen have some injection site reactions, but we're able to manage that, a lot of times, using some antihistamines both orally and topically to correct for that.

I think the other really important piece for this clinical trial was the fact that, over time, when patients had attained a response, they were able to decrease the frequency of giving the injections. So if you had had a partial response after cycle four, instead of getting it weekly, they started decreasing it and doing it every other week. And that's great for patients, for two reasons. One, they're not coming into the clinic every week, so in terms of quality of life and time spent with us, less time is always going to be better. But then also, from a toxicity standpoint, when we look at the infection risk associated with this class of medications, maybe decreasing the amount of times that they're coming in, giving their T cells a chance to recover, is actually going to help improve that toxicity profile. But in general, I think we're all super excited about the bispecifics and having access for this for our patients, and more of these are going be coming into market and we're going to be using them more and more in the years to come.

Mary DeRome (**MMRF):** Sure. Speaking of more of these coming along the pike, Rosie, you've heard about two, additional, B-cell maturation antigen (BCMA)-targeted bispecific antibodies that are in development right now, linvoseltamab and elranatamab, both of which are not yet approved for patients with myeloma. Did the information that we saw at ASCO on these tell us anything new about this class of drugs, particularly, how effective they are in patients who have already received a BCMA-targeted treatment such as a CAR T-cell therapy or maybe belantamab mafodotin-blmf (bela-maf; Blenrep)?

Rosie Pruitt: Yes, I think they just continue to show that this class of medications is really promising, in general. The linvoseltamab study showed an overall response rate (ORR) of about 64% at the 200-mg dose, which is a pretty high response for patients that have been heavily pretreated. And the probability of maintaining that response at 6 months was as high as 85% to 89%, which is really encouraging. Looking at side effects, it's all very comparable to what we're seeing with the other BCMA therapies. The rates of cytokine release syndrome, fatigue, and anemia are about the same; the safety profile is comparable. When we think about more severe neurotoxicity side effects, the severe side effects, ICANS ratings of greater than a grade three, were 1% to 2%. That's pretty small. I think it showed a good tolerance, promising results.

Elranatamab was part of a study that showed a pooled analysis for efficacy and safety in patients that had already received BCMA-targeted therapy. So, patients that had received antibody-drug conjugates or CAR T-cell therapies, specifically, and looking at how effective this drug was in that patient population. And overall, the response rate was a little bit lower, but it was still around 45%, which is really good. I think it shows us that, again, in a heavily pretreated patient population that has already received a BCMA-targeted therapy, there might be a role for rechallenging them with another BCMA-targeted therapy or bispecific. And we might just need to look at, more specifically, the timing between those therapies, or potentially an interim therapy with a drug from a different class. But it did show success, which is really exciting.

Nisha Joseph, MD: I just wanted to add, for comparison, we're getting spoiled with bispecifics when we think about ORRs in the 60% to 70% range. Usually, drugs that receive approval in myeloma have an ORR around 30%, which is what daratumumab had and which is what bela-maf had, et cetera. And so, 60% or higher is very impressive. I just can't overstate that.

Mary DeRome (**MMRF):** Yes, certainly, in these heavily pretreated patient populations.

So, Dr. Joseph, we did hear about another bispecific antibody called talquetamab, at ASCO, and this drug has a different target. It targets GPRC5D on myeloma cells. What is GPRC5D, and how was talquetamab used in the studies that were presented?

Nisha Joseph, MD: The BCMA-targeted therapies are great. We're very excited about them. The downside of BCMA-targeted therapy is we need something else to salvage patients who progress after that therapy. Although as Rosie alluded to, there's probably a role for rechallenging, certainly not right away. And so, we've started looking at different targets that we can use, both in bispecifics and in CAR T-cell therapy. And so, GPRC5D stands for G protein–coupled receptor 5D. It's another antigen on the surface of myeloma cells, so it's just another way of targeting myeloma cells. It otherwise works in the same way as teclistamab or BCMA-targeted bispecifics. And so, a couple of different abstracts came out about talquetamab. One was the RedirecTT-1 study, which was looking at talquetamab plus teclistamab in relapsed/refractory myeloma. This was the first time that we looked at two different bispecific therapies with different targets.

I think we're going to see more and more studies looking at bispecifics in combination with each other, bispecifics in combination with other standard agents in myeloma, and moving bispecifics up. That's always how things go, if they work in the relapsed/refractory setting, we're going to combine them and move them forward.

So, there's going to be a lot more data coming out like this. But the RedirecTT-1 study was interesting, because you're dual-targeting the myeloma cell at the same time. I think the main kind of concern is about toxicity. It was very effective; there were high ORRs. The GPRC5D agents do have some slightly different side effects that we see. Very commonly, we see dysgeusia, or changes in taste buds and appetite.

And we also see, commonly, skin and nail changes, which can be upsetting for some patients. One of the questions was, does adding teclistamab increase that, and we didn't see that, which is good. The other thing we always think about in bispecifics is infections. And so, there was about one quarter of patients with grade three or higher infections. But I think the other point to make is that infections are just going to happen, and I think we need to make sure we're not crossing a threshold and also make sure we're optimizing management.

So the other study was talquetamab with daratumumab. I think using daratumumab and then using talquetamab is a little concerning in terms of infection risk, so that's important. But, it was effective; we saw good response rates. It's a little early, I think, for that study.

A good number of these patients had low antibody levels, which we call hypogammaglobulinemia. But I think about one quarter of those patients received what we call intravenous immunoglobulin (IVIG), which is a way to give antibodies back. So, I think there's still room to improve upon that.

I think we're going to see more and more of those types of comparisons to optimize the drugs and minimize toxicity. And it's gonna change if they move to earlier lines, but you're still gonna have infection risk.

Mary DeRome (**MMRF):** So, if you had to guess, how soon do you think we'll have another bispecific antibody approved for myeloma patients? Do you think it'll be this year?

Nisha Joseph, MD: I think it'll be this year. Yes. Now it's almost July. If you asked me a few months ago, I would definitely say this year, but I think this year or early next. There are several BCMA-targeted therapies and we have mounting data on not only talquetamab but also cevostamab, which we didn't talk about today, but that's a bispecific that targets Fc receptor–homolog 5 (FcRH5). I think the take-home is this is a very optimistic time to be in the myeloma world, because we have a lot of therapies coming down the pike. And not only that, I'm jumping the gun, but the real take-home from ASCO, I think, is, there weren't as many novel therapies, but we're learning so much more about the therapies that have recently come out, and how to better deliver them and deliver them safely. I think that's equally as exciting as having brand-new therapies. We have a lot of those, too, but having really effective drugs that we can use more effectively is the goal, and so I think that's a really exciting piece that came out of the meeting.

Mary DeRome (**MMRF):** Yes, totally agree. So, Danielle, we've been talking about bispecific antibodies and increased risk of infection. Can you tell us why taking a bispecific antibody increases the risk of infection for patients?

Danielle Roberts: Sure. I think this is actually two separate issues that occur in the same patient. When we look at the backgrounds of the patients that were receiving the bispecific, they all had greater than three lines of prior therapy. So, when we think about the immune system, it’s already taken a hit. Most of these patients have had autologous stem cell transplants, they’ve had multiple lines of therapy, which can lower their immune system, and some may or may not have had CAR T-cell therapy also prior to getting to the bispecifics, which we know is going to impact their immune system. And then, when we start giving them either bispecific, you’re targeting their T cells, and our T cells are really what’s responsible for recognizing foreign infection and helping our bodies fight it off.

So when we have suppression of that, then we're going to increase the risk for infection in our patient population. When we think about the clinical trials that just came out, looking at both teclistamab and talquetamab, there was about a 50% risk of total infections in these patient populations. And when we're talking about infections, we're talking about bacterial infections, viral infections, and fungal infections. And in both studies, bacterial infections were the majority, followed by viral, and then fungal was about 7% in each one of the studies. But what they did note, also, is about 64% of the patients had hypogammaglobulinemia, or low immunoglobulin G (IgG) levels. And so, looking at the results and taking that information to heart and asking how can we use that information to take better care of our patients, it's changing those protocols of what we're doing post induction therapy and how we need to protect our patients.

At our institution, all of our patients are on some type of antiviral therapy to prevent shingles reactivation, and we use mostly valacyclovir (Valtrex). We start patients on prophylaxis for *Pneumocystis jirvecii* pneumonia, an opportunistic infection that you see in the severely immunocompromised patient. If you don't have a sulfa allergy and have fairly good counts, then sulfamethizole and trimethoprim (Bactrim) tends to be our go-to. And there are other medications that we can use if somebody has an allergy or intolerance to Bactrim. And we're also starting our patients on IVIGs monthly, especially for those who have IgG levels less than 400 mg/dL, and then we monitor those IgG levels. If they're getting above 600 mg/dL or in those higher ranges, then we can look at how much we want to continue on with that.

In addition to that, we've added in looking at some viruses like cytomegalovirus, and so we're monitoring for that as well. If we're starting to see you mount viral loads, expressing that virus in your bloodstream, we can adjust for that and do the treatments to prevent you from having any systemic side effects like diarrhea or gastrointestinal systems or further count drops that we can see with cytomegalovirus viraemia. When you look at the two studies head-to-head, looking at teclistamab and talquetamab, there was a little bit less risk of infections with talquetamab versus teclistamab, but overall, there was a similar infection risk with both drugs.

Mary DeRome (**MMRF):** Yes, it's a recurring theme, and there's a lot of talk about how to better protect patients who become so much more susceptible to infection while they're taking these bispecifics. Hopefully, we'll be able to solve that issue moving forward.

Nisha Joseph, MD: It's not just prophylaxis, but also the interval, which Danielle already mentioned, so that gives the patient's immune system a little bit of break, as well, so.

Mary DeRome (**MMRF):** Yes, some time to recover from that.

Danielle Roberts: And then, like Dr. Joseph mentioned before, as we add in other drugs to these, are we going to increase the risk for infections, as well, too? So, I think it's also looking at how we're using the medications: is it a single agent, are we using it

in combination with other medications, too, and how do we prophylactically take care of our patients in that population or in that setting, as well.

Mary DeRome (**MMRF):** Yes, that makes sense. Okay, so let's talk, finally, about a couple of studies that were mentioned on belantamab mafodotin, also known as Blenrep or bela-maf. Many in our audience might not understand why this is still being investigated, since this compound was approved for myeloma patients but was withdrawn from the market last year. Dr. Joseph, what is bela-maf ? And is this drug still being used for myeloma patients?

Nisha Joseph, MD: Belantamab mafodotin is an antibody-drug conjugate and it's an anti-BCMA drug, so it basically delivers a chemotoxic agent directly to the myeloma cell. So, it gloms onto the myeloma cell and then says, "Here's some poison. Here you go." It got accelerated approval. Unfortunately, in the DREAMM-3 randomized trial, which was supposed to be a confirmatory trial looking at bela-maf versus pomalidomide plus dexamethasone, there wasn't a statistically significant benefit of bela-maf over pomalidomide plus dexamethasone. Having said that, I'm a little optimistic that the nail is not in the coffin yet, and so, GlaxoSmithKline is continuing to run the studies that were already open, with the hope that this might change.

And I will say, anecdotally, though I think there are challenges with bela-maf, I have several patients who have really benefited from it, particularly more frail, older patients who are penta-refractory. It can be a really helpful tool. So, I'm hopeful that we'll able to use it again. But for the two trials that were updated, one was the original trial that I just mentioned, DREAMM-3, I don't think there were significant changes in the data. It continued not to show a statistically significant benefit in PFS (it was 11 months versus 7 months). It did show better duration of response in the bela-maf arm, as well, for what it's worth. I think we need more time, and we'll see.

The second trial is DREAMM-9, looking at bela-maf in addition to RVd, which is a standard induction regimen, in transplant-ineligible patients upfront. And it showed reasonable efficacy. Actually, it was 100% at the highest bela-maf dose. And in terms of toxicity, the main side effect of bela-maf that was a little different from what we typically see was ocular toxicity. For a lot of these drugs, hematologic toxicities and gastrointestinal toxicities we can manage. We're hematologists, so, low platelets don't bother us. With bela-maf, we had a lot of vision changes, and I think that can be challenging, particularly in older patients who might have baseline vision changes in general, like cataracts and things like that.

About 50% of patients on this trial had ocular events of grade three or higher. So, I just point that out in terms of using bela-maf in the upfront setting; for me, I worry a little bit about that, because we have other drugs that are better tolerated, like daratumumab. That's a very easy drug to deliver, even in a frail patient. I have a 91-year-old patient on daratumumab, lenalidomide, and dexamethasone right now, and he’s doing very well. He's very active. But I would not give him bela-maf.

This is an early trial and we have more to learn about the drug. It's impressive that it's so effective, but I think also quads can be quite effective, so I think it's really about finding the right quad. The DREAMM trials are still open, and hopefully we'll see, still, a role for bela-maf.

Mary DeRome (**MMRF):** Yes. Every myeloma doctor that I've talked to has at least one patient who's had great responses with bela-maf, and thankfully, even though the drug has been removed from the market, these patients are still able to receive the drug with an individual investigational new drug application. We'll see what happens as more data is gathered from some of the other DREAMM trials.

I've got my final question for all of you. Were there any data presented at this meeting, overall, that will immediately affect how you manage your patients? And what is the take-home message for patients from ASCO? Rosie, I'll start with you.

Rosie Pruitt: I think a lot of the data were really exciting, really promising, and I'm lucky to work in a place where we're constantly evaluating our practice and updating our recommendations based on the most recent literature. That's what I absolutely love about my job. And I think the take-home message is that there are really promising developments in both existing therapies and new therapies. And that patients just need to stay informed, be their best advocates, and I think exciting things are to come.

Mary DeRome (**MMRF):** Yes, agreed. Danielle?

Danielle Roberts: I have to echo Rosie. I've been at Emory for a long time, and it's great to see the advances that we've made in the myeloma landscape for treatment, going from just lenalidomide and bortezomib to now having these bispecifics and CAR T-cell therapy. You know, we never want patients to have an oncology diagnosis, and it would be great to be out of a job because we have cures for everything. But at least for our patients that we do have, we have all these drugs not only give them good quality of life, but that have these longer durations of response. I think from ASCO, right now, really the most exciting thing is all these bispecifics and the easy access that we can actually get to our patients. CAR T-cell therapy is great, but it takes just a little longer, and so for that patient that needs the treatment now, we can get them on teclistamab fairly easily and get them going, and they're responding and they're doing well. So, it's exciting for our patients.

Mary DeRome (**MMRF):** Agree, totally agree. Dr. Joseph, I'll give you the last word.

Nisha Joseph, MD: Sure. I agree with all of that. I need to say a few additional things. I think in terms of practice changing, I think the two things that I would think about is the dosing of teclistamab, and probably CARTITUDE-4. I think those are the two things that are probably most immediately going to change our practice. I think the rest is evolving. But like they said, a lot of optimism, a lot of exciting things.

I think the last thing I'll just say is, if you have myeloma or you have a loved one with myeloma or smoldering myeloma or plasma cell disorder, I really think it's worthwhile to have at least a consultation at an academic center. Because things are changing in myeloma so quickly. There are a lot of clinical trials, there's a lot of new development, even just management, even if your therapy's working for you but you're having side effects, you know, this is all we do every day. There are actually data out there showing that people who are comanaged within an academic center tend to have better outcomes.

And so, if you're willing, sometimes we're not always close, but several academic centers do telehealth out of state, including Mayo. So, there are really opportunities to get insight and more information, which I think is the best thing you can do, as a patient, to equip yourself with knowledge and advocate for yourself.

Mary DeRome (**MMRF):** I agree with all of your points. I just think that, as we run through our schedule of major meetings for the year, it seems like every time we get to a major meeting like that of ASCO or the American Society of Hematology or even the International Myeloma Society, there are always more extremely exciting data coming together for myeloma patients. There's a lot of room for hope for myeloma patients, with all these new therapies and new combinations of therapies and using therapies in earlier lines of treatment, that I think is really going to go a long way to improving quality of life for myeloma patients, moving forward.

So, on behalf of the MMRF, I'd like to thank our panelists today, Dr. Joseph, Rosie, and Danielle. And I'd like to thank everyone for listening today, thank you for taking time out of your day.

Finally, I'd like to thank our sponsors, Adaptive Biotechnologies, BMS, CURE, GSK, Karyopharm, Regeneron, Sanofi, and Takeda Oncology for their sponsorship.

If you have additional questions about what you heard today, please don't hesitate to call our Patient Navigation Center and talk to our experienced oncology professionals on the phone. Their number is 1-888-841-6673