MMRF Patient Webinar Series – *Management of Patients Who Have Relapsed After One to Three Prior Lines of Therapy*

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Transcript

Mary DeRome (MMRF): Hello, and welcome to the MMRF Patient Webinar Series, brought to you by the Multiple Myeloma Research Foundation. I'm Mary DeRome, Senior Director of Medical Communications and Education at the MMRF.

We have with us today two myeloma experts who will be discussing options in relapsed/refractory multiple myeloma for patients who have had one to three lines of prior therapy: Dr. Larry Anderson from the University of Texas Southwestern Medical Center Simmons Comprehensive Cancer Center in Dallas, Texas, and Dr. Faith Davies from the Perlmutter Cancer Center, New York University Langone Health in New York City. We will also hear from a patient speaker who will describe their patient journey. Let's get started with our first speaker.

Faith Davies, MBBCh, MD: I'm Faith Davies, and I would like to talk about treatment of relapsed disease, particularly for patients who are relapsing between one and three previous treatments.

It's important to remember that multiple myeloma presents in patients very differently. Although when we start our first treatment with that first line of therapy, we're hoping that it's going to induce a long remission. Unfortunately, some patients actually go on to relapse. When they relapse, we need to start a second line of therapy. Patients can actually have a number of different relapses.

The important thing to say is, it's obviously disappointing when a patient's disease comes back. But it's also important to remember that we have lots of effective therapies now, so we can get that disease back into a response and have patients getting back to their normal everyday lives.

I want to explain a couple of the words that we often use when we're talking about relapsed disease.

The first is *relapse,* which essentially is recurrence of disease. It may be that we see the M component come back in the blood after treatment. Or the patient may present with new bone pain or new kidney problems.

We'll also often use the term *refractory,* which refers to the disease continuing to be a problem despite having treatment.

We also often talk about *progression,* and that's when we will see that the M component or the light chains just change a little bit in therapy.

Another term we'll often use is *line of therapy.* This really talks about the number of different treatments a patient has had. Often, we use maybe three different treatments in one course of treatment; so, for instance, VRd would be called one line of therapy. Just to make life more complicated, if a patient is having some form of induction therapy, followed by a stem cell transplant, followed by maintenance treatment—so for instance, VRd followed by a transplant followed by R or lenalidomide maintenance—that would actually also be called one line of therapy.

When we're thinking about a patient's disease coming back or relapsing, we'll often describe this in two different ways. The first is to say that the patient's disease has relapsed, but this is a biochemical relapse. That means that the patient is actually well, asymptomatic, but the doctors have spotted indicators of myeloma in the blood or the urine. Essentially, to some extent, we've caught the relapse early.

The second kind of relapse we talk about is a clinical relapse, which is usually something that patients notice first. For instance, they may find that they have new bone pain or that their kidneys have gone off a bit. However, whichever of these relapses it is, it's really important to remember that when the disease has been quiet and the patient is in remission, they should continue seeing their doctor regularly so that the doctor can perform these tests to try and catch this relapse early.

We treat the two different kinds of relapses slightly differently. If the patient has symptoms, we definitely need to start therapy. If the patient's blood counts have just come up a little, so maybe we're now seeing a light chain that we haven't seen before, this may mean that we need to treat the disease, but it also may mean that we can just closely monitor the patient.

Now when we're thinking about choosing a therapy, be it for their first relapse or the second relapse, we'll often think about lots of different things. We need to pay particular attention to the actual kind of myeloma that the patient has. You'll remember that we often test a patient's genetics to find out if they have a translocation or something like that.

We also need to think about the way the disease has relapsed. Has it relapsed in the bones? Has it been a quiet relapse? Has it been an explosive relapse, or has it just crept up?

We also need to think about how the patient wants to handle these things. Does the patient want to have oral tablets, or does the patient want to have frequent treatments, an inpatient schedule, an outpatient schedule? All of those kind of things need to be taken into consideration.

When we actually think about the precise treatments we're going to use, we then think

about what treatments the patients previously had. Have they had a stem cell transplant? What treatments have they had? Did they respond well to them, or did they have any side effects?

We also then need to think about what other problems the patient has. Does he or she have diabetes? Heart problems? We need to think about the patient's social circumstances. Is the patient still working? Will treatment impact that? Also, where does the patient live? is it a long travel to the clinic? Would an oral regimen be more appropriate?

All of these different things are things that the doctors are considering when we see a patient relapsing. The reason is that we're actually very fortunate now that there are a lot of different treatments that we can use. Some treatments we may just give on their own. For instance, the cellular therapies. Whereas many other drugs we'll often use in a combination. It may mean that we give two drugs or three drugs at once. For instance, we might give one of the monoclonal antibodies along with either an immunomodulatory drug (IMiD) or a proteasome inhibitor (PI) with a steroid.

We'll often pick different drugs from different drug categories to make up the best regimen for that particular patient. That best regimen is going to depend on what they've had before, what side effects they've had, but also the different ways that the drugs work together. It's also really important to remember that everybody's myeloma is very different. It may be that the combination of drugs the doctor chooses for one patient's relapse is slightly different from those used for another patient's relapse.

We do have some guidelines in this. We'll use a combination of drugs. The drugs we choose may depend on whether this is the first relapse or a second, third, fourth, or fifth relapse.

The other thing we look at is whether a patient has had Velcade, which is also called bortezomib, or Revlimid, which is also called lenalidomide. If the patient has had those drugs, how did they get on with them, and would they still respond to them? If we think that the patient wouldn't respond to them, we call that refractory. If that's the case, we wouldn't want to offer that patient that drug again. We make those different decisions, and when we've made those different decisions, we end up with a number of different drugs that we could potentially use. I'll come back to that in a moment.

The other thing to remember is that many patients will have had a stem cell transplant in their first line of therapy, and if they responded well to it, there's certainly the option to have a transplant again in their second line of therapy. Or patients may have decided not to have a transplant in their first line of therapy and therefore potentially could have a transplant in their second line of therapy.

What I'd like to do for the next few minutes is concentrate on some of the combinations we can use in this setting. I'm going to concentrate on the PIs, and those are the drugs that act like a recycling process. They stop the cell recycling the different proteins;

therefore, when this is stopped, the cell actually goes on to die.

Now we have a number of different PIs, and they've been tested in quite a large number of clinical trials. Some of the more common PIs are Velcade (bortezomib),Kyprolis (carfilzomib), and Ninlaro (ixazomib). These drugs usually are given with another drug, and we'll come to those in a moment. It can sometimes be one of the IMiDs, which is Revlimid (lenalidomide) or Pomalyst (pomalidomide). Or they can be given with one of the newer drugs, one of which is called Xpovio (selinexor). Sometimes, rather than giving the drugs as a triplet—so, three drugs—they can be given as a doublet, so two drugs.

Important things to know about these different drugs are that they're all effective and they all induce deep remissions that last for a reasonable length of time.

There are, however, some important differences between the drugs. One issue we know can happen with the PIs is what we call peripheral neuropathy (PN). That is essentially pins and needles in the fingers or the toes or a burning sensation in the skin of the fingers or the toes. It can particularly happen with bortezomib and tends to not be such a problem with Kyprolis (carfilzomib). One of the ways that we'll often deal with it is to give the drug as a subcutaneous injection and just to give it weekly. If a patient does get problems, then it may be that we give the drug less often.

With all of these drugs, shingles can certainly be a problem, so we usually recommend that patients have the shingles vaccination and/or take some tablets to stop shingles happening. These drugs are usually pretty kidney friendly, so they're often one of the go-to drugs that we will use for patients that have problems with their kidneys.

The other PIs also tend to have a few little side effects. One of the ones that can sometimes happen with carfilzomib is that it can sometimes cause problems with shortness of breath or a problem with high blood pressure. This one is usually given as an infusion and can be given either once or twice weekly. The nursing staff will usually monitor patients quite closely after the drug to keep a close eye on their blood pressure.

Ixazomib has a slightly different side effect profile. One of the things that sometimes can occur is that patients can feel nausea or get gastric irritation. So usually there's a suggestion to take it at least an hour before meals.

There are other drugs that we can also use with them; these are the IMiDs. In this instance, we have both Revlimid or Pomalyst. Both of these drugs are tablets that are given once a day, often for 21 days followed by a week off. They have quite distinct side effects, which may be different from those of the PIs. Some patients can have a rash. If it's a mild rash, then it might be manageable with some antihistamines. If it's a severe rash, then we'll often maybe need to stop the Revlimid altogether. Both of the drugs can cause potentially a blood clot, and so we'll often need to think about putting the patient either on an aspirin or a blood thinner. Also, there is the suggestion that these drugs can cause another cancer. So we usually suggest that patients use a good sunscreen

when receiving these medications to try and stop any sun damage.

With Revlimid, we have to be careful with kidney function, but we don't need to do that with Pomalyst. Revlimid also has a slightly unusual side effect in that sometimes when patients have been on it for a while, it can cause explosive diarrhea. There is a medication that can help with that.

The final drug I want to talk about is Xpovio (selinexor), which is able to stop the cell moving different proteins around in the cell and stop proteins and messages moving between the cell nucleus and the cytoplasm. When this happens, the cell dies. Although it's an extremely effective drug, it has its own unique set of side effects, including gastrointestinal side effects. We usually try to be very careful and give patients antinausea medicines, particularly in the first cycle, to try and stop these. Some patients have also found it caused some tiredness and some low blood counts.

When we use these different drugs together, we'll often decide which is the best PI for our particular patient and then try and decide which other drugs to add to it. Do we want to add an IMiD? Do we want to add Xpovio? Or do we want to just use it as a doublet? Our decisions will be based on whether the patients had these different drugs before, how well they got on with them, but also what kind of side effects these drugs may cause, and therefore, what those implications are for a given patient. The important message is that there are lots of different options, but the options need to be tailored to a given patient. Not all relapses are exactly the same.

I'll hand it on over to Dr. Anderson, who's going to talk about some of the other drugs that we can use in this relapse setting.

Larry Anderson, Jr, MD, PhD: This is Dr. Larry Anderson at UT Southwestern Medical Center in Dallas. We have a lot of great options for relapsed multiple myeloma these days, and many of these options include multiple myeloma–directed monoclonal antibodies. We have at least three of these that have been approved.

One of the main ones that we use currently in clinical practice is Darzalex (daratumumab), which targets CD38 on the myeloma cell. Several trials have proven that adding Darzalex to other standard therapies improves outcomes, such as progression-free survival. The patients stay in remission longer by adding monoclonal antibodies.

For example, the POLLUX study added Darzalex to Revlimid and dex. The CASTOR study added Darzalex to Velcade and dex. The CANDOR study added Darzalex to Kyprolis and dex. The APOLLO study added Darzalex to pomalidomide and dex. All three of these studied compared three-drug therapies with a monoclonal versus two-drug therapy without the monoclonal antibody.

As far as increased side effects with the addition of Darzalex to these therapies, really, we only have a couple things that we watch for. One would be an infusion reaction,

which is often less likely when we give this medication through a subcutaneous route instead of intravenous. Giving it subcutaneously decreases the risk. Also, we give a lot of premedications to prevent that. Usually, it's just with the first or sometimes second injection or infusion and really not a problem after that.

Also, there is an increased risk of infections such as shingles. We want to be on preventive medications for that and make sure the vaccines are up to date. There is also increased risk of upper respiratory infections.

But other than that, Darzalex doesn't add a lot of toxicity, and it adds a significant amount of time in remission for these patients. Studies have shown that the main risk of adding Darzalex would be potentially lowering the blood counts more and increasing the risk of upper respiratory infections. But other than that, it's pretty well tolerated.

Two other monoclonal antibodies have been approved for treatment of relapsed myeloma: Sarclisa, which targets CD38, and Empliciti, which targets SLAMF7. Multiple trials have shown that adding one of these monoclonal antibodies to other standard therapies significantly prolongs remissions.

In the ELOQUENT-2 study, Empliciti was combined with Revlimid and dex. In the ELOQUENT-3 study, Empliciti was combined with pomalidomide and dex. In the ICARIA study, Sarclisa was combined with pomalidomide and dex. In the IKEMA study, Sarclisa was combined with Kyprolis and dex. All of these studies showed that three drugs were better than two without significantly worsening the risk of side effects. The main side effects that we see, just like with Darzalex, are infusion reactions or increased risk of infections like shingles or upper respiratory infections. All of these studies showed very impressive improvements in the length of time that patients remain in remission, known as progression-free survival, without significant worsening of risks of side effects.

Other therapies in ongoing clinical trials—actually, a few have been approved—are antibody–drug conjugates and chimeric antigen-receptor T cells. For example, we have an FDA-approved product known as Blenrep that targets B–cell maturation antigen (BCMA). It's an antibody, but it has a toxin conjugated to it. It helps deliver that toxin to the myeloma cells and kill the myeloma without killing other cells. The only downside to that one is that it can potentially cause eye toxicity. Patients receiving this agent need to have frequent eye exams before each infusion and could potentially have blurry vision, and that has to be monitored very carefully. But it is an option for patients that may not have other good options—for example, patients that have increased risk of toxicities from CAR T cells or don't have a slot to get CAR T cells. It can sometimes be a bridge while waiting on a slot for other therapies.

We have been blessed to have two different CAR T cells FDA approved for the treatment of relapsed/refractory multiple myeloma, Abecma and Carvykti. Both target BCMA on the myeloma, just like Blenrep, but these are genetically modified cells that take about a month to produce, because they require the T cells from the patient to be

shipped off and genetically engineered and trained to recognize and kill the myeloma. These agents are both approved, but they require four prior lines of therapy. These are used for significantly advanced myeloma. Trials are ongoing looking at those in earlier lines.

Other very promising therapies that we have coming along are bispecific antibodies. For these, you essentially have the business end of one antibody binding to BCMA and the other end binding to the T cell and forcing the patient's own T cells in their body to recognize the myeloma. It's sort of like having the benefit of the CAR T cells but without the genetic engineering, without the month of production; it's off-the-shelf. These are very exciting.

Potentially, these can cause some similar side effects to CAR T cell therapies, but generally not as severe. They also require less time in the hospital. Those are coming along nicely, and we're hoping in the next year that we'll have these available for patients outside of a trial.

We also have other exciting molecules like the CELMoDs that are essentially the next generation of Revlimid and Pomalyst. They target cereblon and decrease the resistance that we see with some of the other IMiDs.

We also have some exciting molecules that target pathways in specific mutated myeloma cells; for example, venetoclax that is very active in patients with BCL2 molecule overexpression, which is typically seen with translocation (11;14). That molecule has been combined with other medications and looks very promising.

In summary, we now have many different options for relapsed/refractory multiple myeloma, which will all depend on the factors present at relapse. These therapy decisions will depend on teamwork between the patient and the provider and caregivers and will be based on multiple decision points. Combinations with PIs with either IMiDs or selinexor improved progression-free survival. Also, we have three different monoclonal antibodies that are approved that improve progression-free survival when added to other standard therapies without significantly increasing the risk of side effects. In general, three-drug combinations are going to work better than two drugs, especially when we're combining monoclonal antibodies with other therapies. Also, I just want to highlight that we have many other exciting immunotherapy options that are currently in trials and look very promising. Thank you very much.

Mary DeRome (MMRF): Thank you very much.

I would like to introduce our next speaker, Pamela Jones, a myeloma patient who is going to share about her patient journey.

Pamela Jones (Patient): Hello. My name is Pamela Jones, and I live in the Dallas, Texas area. I am a patient at the Simmons Cancer Center at UT Southwestern Medical Center and am very fortunate to have Dr. Larry Anderson as my myeloma specialist.

I was diagnosed with multiple myeloma in March of 2018. I had an autologous stem cell transplant in July of 2018. Unfortunately, the stem cell transplant did not result in me achieving a full, complete remission. Instead, I was considered to be in very good partial remission. While disappointing, it was still good to hear that I at least achieved some form of remission from the myeloma. In November of 2018, I began a maintenance program on Revlimid only. I continued that treatment until May of 2020, when my labs indicated that my free light chains were starting to progress, so we had to look at going back into a full treatment.

That was a bit of a shock. I knew that the myeloma was going to come back at some point. It's just that, in the back of my mind, I thought it would be longer than nearly a 2-year period. But in September of 2020, I began a treatment of Pomalyst, Ninlaro, Darzalex, and dexamethasone. I'm happy to say that in May of 2021, I actually achieved full complete stringent remission for the very first time, and I'm still enjoying that remission.

Right now, I'm continuing the treatment. We haven't changed the treatment plan at all; really, I am in a maintenance phase. But there's still that concern every month when I go for my visits over whether it is still going to be in complete remission. I don't think any myeloma patient doesn't have that same concern each time you have labs drawn. It's just something that we have to get used to as myeloma patients.

If there were things that I wish that I knew then from what I know now, it's just knowing that every myeloma patient's situation is different, and relapse is not a certain amount of time. In my case, it was 2 years, but I understand that there are probably patients that may relapse within a year.

The good thing to know is that there are so many more treatments available to us than there were years ago, and there are so many treatments on the horizon. But it's just knowing that it's going to happen. There's no set time period as to when it will happen, but there are options available if and when you have to go back into treatment. I certainly feel better about that now, about relapse. Certainly, I am not looking forward to it happening, but I feel better knowing that, if it does occur anytime soon, there are other options. That the treatment that I have now is not my last hope. That's probably the one thing that I wish I would have known back then that I realize now.

But fortunately, the treatment that I'm on is working well. I've not had many side effects, if any at all. I'm thankful for that and hoping that this treatment will last for a long time from now.

Thank you for allowing me to share my brief patient journey with you, and hopefully it will be helpful to someone to hear it while they're going through their journey. Thank you.

Mary DeRome (MMRF): Pamela, thank you so much.

We're going to have both of our faculty, Dr. Anderson and Dr. Davies, give us some updates from more recent data that has come out. Dr. Anderson, we'll let you go first.

Larry Anderson, Jr, MD, PhD: I want to talk first about an update on the Sarclisa trial known as the IKEMA study. In this large, randomized study, Sarclisa was combined with Kyprolis and dexamethasone (Sarclisa-Kd) and compared with Kyprolis and dexamethasone (Kd).

This combination has now been tested in early relapse as well as late relapse. The take home message is Sarclisa-Kd works well whether it's early or late relapse. Even the late relapse patients on Sarclisa-Kd have a 90.4% overall response rate (ORR) and 37.5% are in molecular remission. So, the results were much better than without the CD38 antibody.

I also wanted to touch on CAR T-cell therapy. Essentially what we're doing is taking cells from the patient and shipping them off to a company that uses a virus to insert a gene into those cells that forces the T cells to recognize the myeloma. The two therapies that are at this point FDA approved are Abecma (ide-cel) and Carvykti (cilta-cel). Both of these drugs target B-cell maturation antigen (BCMA) on the surface of myeloma.

Both of them are already in clinical production and we're already using these in clinical practice. They require four prior lines of therapy. So these are not right now for early relapse patients. They're for patients who have had four relapses. Right now these products are using the patient's own T cells. But other products down the road are also looking at using donor T cells to speed up the process.

Some insights and updates from our KarMMa study of Abecma were presented at the last American Society of Hematology (ASH) meeting. We've now found that the patients who've had the longest progression-free survival (PFS) are the ones who achieved molecular remissions or minimal residual disease (MRD) negativity. So, they tested negative for MRD at one month. That was more important than even just having disappearance of their monoclonal protein after a month. However, for the most sustained responses, it's also necessary to see patients in not only molecular remission, but monoclonal protein remission at the one-year time point.

We've also been participating in some real-world outcome studies, and some of these have been reported, including Dr. Ferrari’s presentation at the ASH meeting showing that for patients who got Abecma in the real world after FDA approval, the risk of having BCMA-directed therapy prior to Abecma is that those patients have significantly inferior duration of their response or PFS.

We don't yet know if that's going to be the same now that we have FDA approval of a bispecific against BCMA. Many of these patients may still be responding to BCMA-directed therapy. So, further testing is needed to know if that will affect outcomes. But we at least know that patients who had prior BCMA and failed it or relapsed after it,

those patients had inferior outcomes with Abecma treatment.

We also now know that patients who relapse after CAR-T can still do well. In the KarMMa study, the overall survival (OS) was 24.8 months. But in patients who had progressed after Abecma on the KarMMa study, the OS was 14.8 months and in those who had received subsequent BCMA- directed CAR-T or bispecific antibodies, the OS was 18 months, so they still did pretty well, even with subsequent BCMA-directed therapy.

Other studies are looking at low blood cell counts and trying to find reasons for that. Mostly it's patients who we found were heavily pretreated and received more than one stem cell transplant. Now, the KarMMa-2 study has been read out at ASH and actually also the KarMMa-3 study at a recent meeting. We're finding that if we're using these Abecma CAR T-cells earlier in the course of disease, we can see significant improvements compared to standard of care.

I mentioned that we have two approved products, but yet we have many products that are under investigation, including next generations of CAR T-cells such as the NEXT-T or BMS-986354. This study was presented at ASH as well in which we saw the expected rates of cytokine release syndrome (CRS) about 80%. Fortunately only 10.9% experienced neurotoxicity, which is about half of what we expect with other CAR T-cell products. Fortunately, we saw a 98.1% ORR with 57.4% achieving a deep remission or very good partial response (VGPR) and 29.6% achieving a complete response (CR).

Other FasT CAR-T treatments include one that targets both BCMA and CD19 and its manufacturing process takes as little as 24 hours. A phase 1 trial of this treatment showed 100% of patients achieved VGPR deep remissions and 69% stringent complete responses (sCR). All patients were MRD negative and fortunately CRS occurred in 23% of patients, all low grade. That's compared to about 80% plus with other products.

Now that we've gotten so saturated with BCMA-targeting therapies, we need other targets either for patients who have failed BCMA or who don't have access to them. Other products, such as BMS-98633, are now looking at targeting GPRC5D. One of these studies that we read out at ASH found that in heavily pretreated patients with relapsed refractory multiple myeloma (RRMM) who receive this therapy, 86% responded overall. However, if you look at the highest doses, response rates are close to 100%. Even in those patients who had prior BCMA-targeted therapies, seven out of 11 responded to this non-BCMA-directed therapy against GPRC5D.

The other types of therapies that we're looking at now are bispecific antibodies. As of the last meeting, we didn't have one approved. Now, we fortunately have FDA approval of teclistamab or Tecvayli that targets BCMA. It's an off-the-shelf product. Bispecifics are like two different antibodies joined together.

One binds to a target on the tumor, in this case BCMA and the other end binds to CD3 on the T cells and forces the patient's own T cells in their body to snuggle up and kill

and attack the myeloma. Then they can get teclistamab for immediate treatment, especially patients who can't wait for production of CAR T-cells, patients who have rapidly growing myeloma, patients that don't have a slot for CAR T-cells. It's exciting times to have one of these approved. Dr. Davies is next going to go through the data from investigational products in this area.

Faith Davies, MBBCh, MD: Thank you, Dr. Anderson. We don't just have BCMA as our target on the myeloma cell. We also have two other potential targets, GPRC5D and FcRH5. Those are areas on the myeloma cell. and another is on the T-cell, which is the CD3.

There was a lot of data presented at ASH on lots of new drugs. The top one, teclistamab, is now approved and can be used. But, there is also data on four other drugs (elranatamab, linvoseltamab, alnuctamab, ABBV-383) targeting BCMA, as well as two (talquetamab, forimtamig) targeting GPRC5D, and one (cevostamab) targeting FCRH5. They're all slightly different and they're all made slightly differently, so they have different ways of binding. They also all get given slightly differently. Some are intravenous, some are subcutaneous, some get given every week, some get given every two weeks. So, they have slightly different schedules and slightly different side effects.

But the key, important thing is that the patients who have already received an immunomodulary drug (IMiD), a protease inhibitor (PI), and a monoclonal antibody seem to be having response rates of somewhere between 60% and 70%. So many, many patients are able to respond to this approach, presumably because it's a novel way of attacking the myeloma cell.

Other data that was presented for these studies was that it was found that we could actually give many of these drugs after a patient has had a previous CAR T-cell, which is important. Indeed, it appeared that maybe if a patient had had a previous BCMA bispecific, they could actually go on and get one of the other bispecifics. Patients often ask whether they have to take the therapies that we give forever. Another piece of data that was shown at ASH was from a nice study looking at one of the bispecifics, where they just gave that drug for a year and then stopped. When they reported the data, it looked like the patients who'd had a really good response to treatment were still in remission, even though they had just had that one year of therapy.

As everybody knows, we often combine our drugs up. There was phase 1b study, MajesTEC-2, suggesting that you can use bispecifics with many of the drugs we already had. This particular study combined teclistamab with daratumumab (Darzalex) and Revlimid and the response rate then went up to 93.5%. So certainly lots of exciting things going on—some already here, some need to be explored.

I just want to talk about some of the toxicities of these bispecific therapies as well as the CAR T-cells, because they do have an unusual and slightly different toxicity. The two slightly unusual ones, CRS, where you have a high temperature or a low blood

pressure, and the neurotoxicity, which presents in a slightly unusual way where patients can either have difficulty naming things or don't have such great cognition and thought processes.

Those two side effects, if they're going to occur, happen just in the first week. Once you get past that first week, the risk of those side effects really drops off. However, we do know that sometimes patients can struggle with their blood cell counts as they move forward. There was a very nice study at ASH talking about the different infections (cytomegalovirus, Epstein-Barr virus, Pneumocystis carinii/ Pneumocystis jirovecii pneumonia) that patients can get. It suggested that we need to be really observant for some of these rare infections that we don't see very often in myeloma patients, but we might actually see quite often in patients who have allogeneic transplants.

Some of the slightly more unusual side effects, particularly with the GPRC5D, are where patients can get issues with their skin peeling, with their nails getting very brittle, or indeed with some difficulty with their sense of taste. There is some work about how we might reduce some of these side effects, which I think is really important and there are lots of studies looking at that at the moment as well.

The final one I want to mention is a slightly different drug. Many of you will have had an IMiD before, so be that lenalidomide, Revlimid, or pomalidomide (Pomalyst). This is like a cousin, I guess. It's called a CELMoD (mezigdomide). It's got a very long name, so we call it mezi for short. Essentially again, it's a tablet that can get given usually for three weeks on and a week off. So, very similar to the other drugs.

When they tested this in patients that had received all sorts of other treatments, so the majority of those had seen at least six other treatments, the response rate for this was very good as well, with much less side effects as well. So another drug that's going to be added to our mix, hopefully, as I say, many of the ones we've just been talking about are still going through the clinical trials. I'm going to hand it back to Mary. Thank you.

Mary DeRome (MMRF): Now we're going to the Q&A portion.

Dr. Anderson, I'm going to start with you on this one. Pamela mentioned that when she had her stem cell transplant, it did not put her into a complete response. How many patients do not respond when they have a stem cell transplant? If they do not respond, what is your option for therapy?

Larry Anderson, Jr, MD, PhD: As far as how many don't respond, it's a minority that doesn't get some level of response from the transplant. Maybe 10%. Most will get some response. It's just a question of how many will get a complete or the deepest response, which is maybe closer to 30% or 40% will have that complete remission.

It also depends on what therapy you've had before the transplant. We are starting to see that including some of these monoclonal antibodies up front may enhance the odds of getting into the deepest remissions after stem cell transplant, as well. But as Pam

noted, just because you don't achieve a complete remission doesn't mean that you won't have years of ongoing, stable, low-level disease and absence of symptoms. Just because you don't achieve a complete response doesn't mean you have to throw your hands up and do something completely different. A lot of times even just going on maintenance therapy can deepen that remission over time.

We don't really have data saying that, oh, just because you're not in a complete remission, we need to completely change your treatment. But certainly, monitor closely and consider changing things up if the markers are starting to go in the wrong direction. We do have a lot of options if that remission occurs sooner than later. But I've got many patients—especially those that have achieved very good partial response after transplant—that do quite well on maintenance for years. it's not the end of the world if it's not a complete remission.

Mary DeRome (MMRF): Dr. Davies, I'm going to go to you for the next question. There was a question about extramedullary disease and what the treatment might be for that.

Faith Davies, MBBCh, MD: I just wanted to start off by saying thank you to Pamela. I thought that was a really important message for everybody to hear about how myeloma can come back, but that, as she really quite clearly said, how we can get patients back into a remission, and maybe sometimes, like herself, actually get a better remission with the second treatment than the first treatment.

As to extramedullary disease... Theoretically, myeloma cells are supposed to grow in the bone marrow, so within the bones. But sometimes they can go a little crazy and learn to grow outside of the bones. Sometimes it can be a lesion that started off in the bone and has grown outside the bone. Or sometimes it can just be some cells that somehow have learned to not be dependent on the bone marrow. It might be a little lump under the skin or in the muscle.

Generally, we get a little worried when that happens, because it tends to mean that the myeloma might be more aggressive. It does depend on whether that lesion's connected to the bone or not. But if we notice that patients have that, then we're usually going to go in and change our therapy to make sure that we can try and kill those cells off using a different kind of treatment. Something in our toolbox—one of the ones we've talked about today—but it may be that we just need to tweak things because those cells have got used to our regular treatment, and we need to go in and confuse them so that they go on and die.

Mary DeRome (MMRF): Great. Thank you.

Dr. Anderson, what about patients who have a hard time tolerating maintenance therapy, have to go off maintenance therapy, then have a relapse of their disease? Sometimes that relapse can be aggressive. What is the best type of treatment under that scenario?

Larry Anderson, Jr, MD, PhD: We do have a subset of patients that can't stand maintenance because it's too toxic. Although I will put in my two cents that a lot of times it might just need to be adjusted heavily to be able to help them tolerate that. The dosing might need to be adjusted: bile acid sequestrants for diarrhea, different things like that, can really help patients stay on at least some level of maintenance in most cases.

Whether they're off maintenance or not and they've relapsed, obviously if they had a lot of trouble with that class of medication, you'll probably want to switch classes to something different. If they've not had a monoclonal antibody with frontline therapy, it would be pretty standard to include a monoclonal antibody with the second line therapy these days, because we're seeing such good results even in the front line, and we just want to make sure they get the best foot forward.

That being said, it really goes back to all of those same questions that Faith mentioned earlier. How far away does the patient live? What are they willing to do? What is their level of comfort with these therapy options? If someone lives 3 hours away, it's going to be difficult to come in for antibody injections every week without partnering with someone locally. It takes a lot of factors into consideration. The blanket answer would be probably switching to a different class and probably a three-drug combination.

Mary DeRome (MMRF): Great.

Dr. Davies, what are your thoughts about patients who never become minimal residual disease (MRD) negative but have standard or "low-risk" myeloma?

Faith Davies, MBBCh, MD: It's a question that doctors and researchers are trying to work out.

As many of you know, we have a myeloma-related condition called monoclonal gammopathy of uncertain significance (MGUS), where there's a low level of M component, but the patient's well and there's no damage.

We all have patients in our practice who we give all of this treatment to, and as the guest mentioned, the proteins come down and then they just stay stable. The patient doesn't become unwell. They just stay like that. What we think happens is that we're maybe able to kill off those cells, the aggressive cells that were the myeloma cells and essentially leave the patient with those quieter ones, which I often describe as being asleep and just sit there, and were not able to kill those off. From my side of things, that's fine. That's great. As long as the patient is stable.

The key thing we need to work out, which we're working on with lots of different tests, is identifying the patients who have had all of that treatment, have a little bit of disease remaining, but are going to be stable for 10 or so years. Or which patients still have that little bit of disease but are only going to be stable for a few months or a little bit longer. That's what we need to try and figure out, because we don't know the answers at the

moment.

Certainly for patients, as Dr. Anderson said and as Pamela has shown, it's not the end of the world if you don't reach a complete response. But if you do have a very good partial response, the key is to have the regular follow-ups to make sure that it's staying nice and stable.

Mary DeRome (MMRF): Great; thank you.

Dr. Anderson, we're going to move on to CAR T therapy. Can you elaborate on the difference between CAR T and bispecific antibodies and how those treatments work? This is particularly important, because we may be on the threshold of the first approval of a bispecific antibody.

Larry Anderson, Jr, MD, PhD: We could talk for a whole hour on the difference between CAR T and bispecifics. But just in a nutshell, CAR T is where we take the patient's own T cells and genetically modify them to force them to recognize myeloma. It takes about a month, then the modified cells get shipped back to the site. The patient usually ends up in the hospital for 1 to 2 weeks after the CAR T infusion so we can monitor for side effects like cytokine release syndrome and neurotoxicity. Patients can't drive for 2 months because of the risk of neurotoxicity. They have to be within 2 hours of the medical center for a month because of the risk of cytokine release syndrome.

It's a big deal. It can have really great payoffs. I have a patient who's four and a half years out and still in remission after CAR T. But it is not off-the-shelf. It does require the patients to be at least stable enough to make it a month to wait for that infusion, which is where the bispecific antibodies come in, because they're off-the-shelf, and a lot of them are anti-BCMA on one end and anti-CD3 on the other. The bispecific antibody brings the T cell to the myeloma cell and forces it to attack the myeloma. That can cause any T cell that's floating around in the body near the myeloma to become an antimyeloma killer.

It can have some of the same side effects as CAR T cells. It generally requires hospitalization for one or two nights the first week and possibly another one or two nights the second week because patients still can have cytokine release syndrome, which is where these T cells attack the myeloma and release large levels of cytokines and can cause high fevers. Sometimes we have to use an antibody against interleukin-6 called tocilizumab. The incidence of these side effects is higher with CAR T, but we definitely see it with bispecific antibodies, as well. But generally, it's going to be less severe on average and less durable. So those patients don't have to stay in the hospital as long. We do see occasional neurotoxicity with bispecific antibodies, but it's certainly less common than with CAR T.

Now one of the main benefits of CAR T cells over bispecifics is that it's one infusion and you're done, whereas bispecifics often require ongoing infusions or injections either every week or every other week, depending on the product. So you're not necessarily

done with treatment, whereas patients that go into remission after CAR T may potentially stay off all their myeloma therapy for potentially years.

There are pros and cons to either option. There's no study directly comparing one versus the other. The jury's still out on which one is going to show the longest, most durable remissions. That may be important. Another question is whether and/or how to sequence these therapies. Should we use one to bridge to the other? Should we use one and not worry about the other? There are a lot of trials looking into these things.

Mary DeRome (MMRF): Yes.

Let's talk, Dr. Davies, about the mechanics and the ins and outs of these CAR T therapies. What have you experienced as far as availability of the two approved CAR T therapies, Abecma and Carvykti? Are you having trouble getting your patients onto those drugs?

Faith Davies, MBBCh, MD: It's getting much better, which is great. Unfortunately, there are quite a lot of myeloma patients who have relapsed disease. When the first drug came onto the market, there was a lot of demand for it. Essentially more patients than they could make the drug for. Whereas now we have the second company also making it, as well as a large number of clinical trials going on, it's getting much easier. It's not perfect, but it's getting much easier.

In addition to that, there are a few other things that patients need to take into consideration. One is that you often have to go to a larger center to have that procedure. If you're fortunate enough to live in a big city, that's not so bad. But if you're in a smaller community, that may be more problematic.

The second consideration is that the procedure for making CAR T cells is quite complex. We have to collect the T cells from the patient and then send them off to the laboratory, which then engineers them and sends them back to the hospital so the hospital can infuse them. That can take about 4 weeks. You have to make sure that when the patient is going through all of that procedure, their myeloma's actually quiet enough for them to be able to go and have that time off treatment while they're waiting for that to come back.

There are a few different bits and pieces in there, which are all getting sorted out with time. There are lots of trials with different ways of making these CAR T cells, hoping to make them better. Or indeed, not use the patient's cells but somebody else's cells, all of which are designed to either make them better or to make it a quicker process so that we can reach more patients with it.

Mary DeRome (MMRF): As a follow-up question, you mentioned how complex the manufacturing process is. Have you had the experience where you've sent patient cells out for manufacturing and the manufacturing process has failed? If so, what happens then?

Faith Davies, MBBCh, MD: I haven't had the experience of it failing. I've had the experience of it actually being contaminated. The laboratories work very hard to try and fix that. If that's not possible, the patient will often have another harvest procedure. It's actually quite rare. As I say, sometimes just as a stem cell harvest doesn't work for everybody, sometimes it's just not possible to make these cells. Dr. Anderson, anything to add?

Larry Anderson, Jr, MD, PhD: No, that's correct. I'd probably say less than 1%. I've had one patient that their production failed, but then they were able to reharvest and production went fine the second time.

There's other patients that I believe had some issues with production, but then they had enough frozen from their first collection that they were able to use those. it can be a number of different scenarios.

Mary DeRome (MMRF): Pamela, did you have additional neuropathy symptoms when you relapsed, if it you'd previously experienced them because of what you had taken previously?

Pamela Jones (Patient): I experienced neuropathy during my initial treatment when I was first diagnosed. My treatment was Revlimid and dex and Velcade. But with the current treatment that I'm on, I've been fortunate in that I've experienced hardly any side effects. But no, I do not have any neuropathy issues right now.

Mary DeRome (MMRF): Another question for you, Pamela. How frequently are your myeloma labs done?

Pamela Jones (Patient): Monthly.

Mary DeRome (MMRF): And how frequently do you have imaging and bone marrow biopsy?

Pamela Jones (Patient): I have monthly labs done. Imaging I had at the beginning of the new treatment. I've had a couple of imaging sessions done, but it's been because I've had back pain, and it was just to make sure that there were no new lesions from myeloma. But outside of that, it's really just been as needed.

Mary DeRome (MMRF): Great. Thank you.

Dr. Davies, when can we expect CAR T therapy to be used in earlier lines of therapy, such as after first relapse?

Faith Davies, MBBCh, MD: Those studies are ongoing at the moment, actually. We always try to test or work out whether a treatment's going to be effective in a patient who's relapsed on a number of occasions. We're also very excited about the results

with both the CAR T cells and the bispecific antibodies; we're very keen to bring them further forward not only to first relapse, but potentially to newly diagnosed patients. Particularly patients where we don't think our current therapies are maybe going to be the best. The trials are ongoing, and we just have to wait for those results. Hopefully soon.

Mary DeRome (MMRF): Dr. Anderson, getting back to maintenance therapy, do you recommend that patients stay on maintenance therapy, even if they reach a complete stringent response?

Larry Anderson, Jr, MD, PhD: As long as they tolerate it okay, it's my general recommendation to stay on maintenance just because there are so many studies looking at patients that came off maintenance earlier and had less-durable remissions. In my opinion, it would be the best to stay on maintenance as long as they're able to tolerate it. That being said, if they have a lot of issues and they're in a complete remission, maybe even MRD negative, then certainly more of a leg to stand on to take them off therapy. I do have patients who've had to come off therapy, and even one lady who's 12 years out from transplant and not on maintenance and still in complete remission. Just coming off therapy doesn't always mean you're going to relapse earlier, but on average.

Mary DeRome (MMRF): Okay. Great.

A final question for Pamela: if you could, please repeat the medications that you're currently taking.

Pamela Jones (Patient): Currently, I am on Pomalyst, Ninlaro, Darzalex infusions, and dexamethasone.

Mary DeRome (MMRF): If you've had one drug in a class and you're refractory to it, does that mean that you will also be refractory to another drug in that class?

Faith Davies, MBBCh, MD: No, definitely not, and that's important. We often talk about class refractory. Sometimes you'll hear us talking about triple class or quadruple refractory. The IMiDs are a good example. Many patients can receive lenalidomide, and then their myeloma gets used to it and they stop responding, but they can then swap onto pomalidomide and continue on that one. If their myeloma stops responding to that, mezigdomide has actually been effective in patients who were refractory to both pomalidomide and lenalidomide. So these drugs work in slightly different ways, meaning that we can still confuse the myeloma cell and convince it to die.

Mary DeRome (MMRF): Dr. Anderson, how might treatment differ for patients who are high risk and have high-risk cytogenetic abnormalities?

Larry Anderson, Jr, MD, PhD: Well, we're still trying to figure that out, to be honest. For the most part, we treat those patients more aggressively. We'll typically use a four-

drug combination for front-line therapy instead of a three-drug combination for many patients with high-risk chromosomes. We're being aggressive about making sure they have a chance to get an autologous stem cell transplant. Often we'll give them more than the standard maintenance therapy after that as well. It really depends on which high-risk feature they have. There can potentially be variations, but essentially, we try to increase the potency of the treatment according to the risk factors.

Mary DeRome (MMRF): Dr. Davies, is there any data on the success of CAR-T therapy in patients who are considered to be high-risk patients? Is it better, worse, or the same than in patients who are considered to be standard risk?

Faith Davies, MBBCh, MD: We're still working our way through that. There are a number of clinical studies now specifically for high risk, and the idea is that those patients will be compared to, as you say, the standard-risk patients. Anecdotally, we know that patients who are high risk still do respond. indeed, many of the patients who were in the studies actually had plasmacytomas and myeloma outside of the bone, and they did respond to treatment. In some cases, maybe the response didn't last quite as long as for those patients who have standard-risk disease, but they still did respond.

Mary DeRome (MMRF): Dr. Anderson, can you talk a little bit about venetoclax and the use of that particular drug, which in myeloma is not approved for patients with the t(11;14) translocation and how that works?

Larry Anderson, Jr, MD, PhD: Venetoclax is a BCL-2 protein inhibitor. Often BCL-2 is overexpressed or upregulated in patients with translocation t(11;14) myeloma. It's a drug that's approved for leukemia, lymphoma—diseases besides myeloma. It's already on the market. A lot of times we'll use it as an “off-label” treatment for myeloma. We can combine it with other drugs, for example, daratumumab or carfilzomib, as well. This makes it work even better. Essentially, even in patients who have failed multiple other lines of therapy or even all lines of therapy, we can often get a response to venetoclax combinations in those patients if they have translocation t(11;14). Probably the earlier we use it, the more likely they are to respond. It can cause low blood counts, maybe some fatigue, an increased risk of infections, but otherwise it’s pretty well tolerated.

Mary DeRome (MMRF): Dr. Davies, let's talk a little bit about patients who might be non-secretory. It's a fairly rare type of patient, but these are patients who don't really have biomarkers so that their level of disease can be easily assessed. There's really no M-spike protein and maybe you can't even see serum free light chains. Aside from looking at a bone marrow biopsy, are there any new techniques to assess a relapse in a patient like that?

Faith Davies, MBBCh, MD: Yes. There are some really cool ones undergoing investigation. Unfortunately, they're not available everywhere yet, but people are working on that. The main one is called mass spectrometry, which is one that's done on a blood test. They take the fluid from the blood test and they can actually still detect serum free light chains in that, even though you can't see it with our standard tests.

They did a very nice study looking at 50 nonsecretory myeloma patients. In 95% of them, they could actually see a level. So, those patients could get away without having to have a bone marrow biopsy. They're also potentially going to use a similar test for MRD detection as well, because it's much more sensitive than the blood tests we currently have. This is very much done in a number of places around the country, often in clinical trials at the moment. Certainly, once the test has gone through the rest of its approval processes, we hope it's going to be much more widely used.

Mary DeRome (MMRF): What is the most up to date combination of therapies to use at first relapse? Dr. Davies, can you address that question for standard risk and also for high risk?

Faith Davies, MBBCh, MD: I think the answer is that there's no correct answer. My answer would be that it depends what you had for your first treatment and how you got on with that treatment and what side effects you had for it and how long you were in remission. We've got our combinations of IMiDs, PIs, and anti-CD38 antibodies, which we can pick from the most appropriate one from them.

But now, there are also some clinical trials that are comparing those standard treatments to either a CAR T-cell or indeed one of those bispecifics. I think currently the standard would be one of the combination of three drugs based on your IMiD, PI, and monoclonal antibody. However, I think clinical trials might find that we change our tack with the CAR-T's and the bispecifics as they come through.

Larry Anderson, Jr, MD, PhD: I completely agree with everything you said. It also somewhat depends on how aggressively the relapse is happening. For example, we might want to go with a more infusional therapy that might work faster than an oral therapy and someone that may be relapsing less aggressively or less high-risk disease. Certainly, it also goes back to patient preferences and how far do they live, and all those things come into play. If they're not able to come in every week for injections, that might affect things.

Basically in a nutshell, it's going to be a monoclonal antibody combination in most situations, but we certainly also have some other triple oral therapies and things like that. Down the road, hopefully immunotherapies will be moved earlier in the course of therapy. I think the other correct answer would be a clinical trial.

Mary DeRome (MMRF): Thank you so much. That is all the time that we have for questions.

I'd like to thank our faculty, Dr. Larry Anderson and Dr. Faith Davies, and our patient, Ms. Pamela Jones, for being with us today.