MMRF Patient Webinar Series – *High-Risk Disease*

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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.

The MMRF has several important new research initiatives focused on the needs of high-risk patients that I would like to briefly discuss. Last year, the MMRF launched a request for applications for the MMRF Myeloma Accelerator Challenge grants in two areas of high unmet medical need. The first is optimizing first-line therapy for high-risk, newly diagnosed multiple myeloma patients. And the second is in high-risk smoldering multiple myeloma. Applicants were asked to form multi-institutional collaborative research networks with a minimum of three participating centers in each network for preclinical and translational research projects with a primary goal of developing novel hypothesis-driven clinical trial concepts in each of these two areas of high unmet need.

This program will provide funding up to $10 million over three years for one network in each area and will result in clinical trials that are ready for startup. This work is vitally important because it is filling a gap that is not otherwise supported, and the level of funding is designed to accelerate work in these areas of high need. The awardees of these grants will be announced in the coming weeks, and we will keep the myeloma community updated on their progress.

The second area of research that is focused on high-risk patients is the innovative Horizon Adaptive Platform Trials initiative, which will be carried out in collaboration with the Multiple Myeloma Research Consortium (MMRC) and in partnership with some of the most influential pharmaceutical partners and scientific and medical experts in the field of multiple myeloma. The MMRC Horizon Adaptive Platform Trials, which may evolve from Myeloma Accelerator Challenge grant initiatives and results, will be designed to rapidly test multiple agents simultaneously while evolving in response to clinical outcomes and scientific advances. The goal is to identify the most effective and safe therapies for multiple myeloma patients, especially the 25% of patients in the high-risk category where need is the greatest.

Today, we have with us two myeloma experts who will be explaining high-risk disease, including what treatment options are available. We also have a patient speaker, Nicholas Lenoir, who will talk about his patient journey with high-risk disease. Dr. Melissa Alsina is a professor of medicine and head of the myeloma section within the Bone Marrow Transplant and Cellular Immunotherapy Program at the Moffitt Cancer Center in Tampa, Florida. She is a specialist in multiple myeloma, bone marrow transplantation, and cellular immunotherapy. Dr. Alsina's clinical research focuses on the evaluation of novel drugs and combinations to treat myeloma. Dr. Craig Hofmeister is a professor of the Department

of Hematology and Medical Oncology at Emory University School of Medicine in Atlanta, Georgia. In clinical practice, he focuses on plasma cell cancers such as multiple myeloma. As a researcher, Dr. Hofmeister studies early drug development and has worked on clinical trials exploring novel diagnostics and treatments. We are grateful to have Dr. Melissa Alsina, Dr. Craig Hofmeister, and Nicholas with us today. Let's get started with our first speaker, Dr. Craig Hofmeister .

Craig Hofmeister, MD, MPH: Good afternoon. My job is to talk about high-risk multiple myeloma, and overall, I think my task here is to provide a foundation upon which you can talk about more complexities [with respect to] what is high-risk multiple myeloma. Doctors and patients, especially myeloma doctors, use the word *risk* in a lot of different ways, and we just expect you, as the patient, to understand what we're talking about, which I think is wrong. Sometimes we can say, “This patient has high-risk monoclonal gammopathy of undetermined significance (MGUS). I want you to come back in three months for a blood test.” There, we're using the word *risk* to mean the likelihood of developing the blood and bone marrow cancer, multiple myeloma.

Or a doctor can say, “Because of your high-risk myeloma, we'll always need to treat you with three- or four-drug chemotherapy cocktails,” and there, the word *risk* means that you're less likely to respond to chemotherapy and you'll respond for a shorter time to treatment. *Low-risk* would mean that the myeloma is easier to treat and patients, on average, tend to live longer. Finally, we sometimes say, “Your only lytic lesion is in your skull, so your myeloma bone disease is low risk.” And here we mean that you only have a few bones that are affected or are known to be affected by your myeloma, and they're not weight-bearing, so they’re at low risk for a fracture.

So, risk generally describes how quickly the disease, in this case multiple myeloma, will become resistant to treatment. Low-risk patients live longer, and their treatment is more effective, whereas those patients with higher-risk (more difficult-to-treat) myeloma have a two- to five-year overall survival with treatment. Try not to worry about the predictions about how long people live, because that's never accurate. What is accurate is the relationship between patients with lower-risk and higher-risk multiple myeloma.

We've tried to define risk in a lot of different ways. Oncologists are bottom-line people. We want to know what we are dealing with. At its most basic, the first staging system was [created] in 1975. The 2005 update from that uses two blood tests, beta-2 microglobulin and albumin, to try to predict how patients would do. These are markers of patient health and how proliferative or how active the myeloma is. Patients who have a low beta-2 microglobulin level (less than 3.5 mg/L) and a serum albumin level of less than 3.5 g/dL have the lowest-risk (easiest-to-treat) myeloma. Whereas those patients who have a beta-2 microglobulin level of at least 5.5 mg/L have higher risk (more difficult-to-treat) disease. And this is just based on a blood test at the time of diagnosis, prior to receiving any treatment.

What this leaves out is the other half of the story: what kind of myeloma do you have? It's based primarily on genetics. And these are not your genetics, necessarily. These are the

genetics of your myeloma cells, and you get access to these myeloma cells, in the vast majority of patients, through a bone marrow biopsy. You can do two different types of testing, but we sometimes do three different types of testing.

First is just to throw the myeloma cells in a dish and see if they start dividing. Now, this is rare; it happens 10% of the time. But this is just a karyotype, just looking for the myeloma cells to divide. The next step is doing FISH testing (fluorescent in situ hybridization). This is staining specific mutations in a patient's myeloma cell and trying to look for indicators of higher-risk disease. You could look for five or ten different known mutations, each with a different color, in the patient's plasma cells. Each one of these puts the patient at a little higher risk of having more difficult-to-treat myeloma. And the last thing is to do sequencing, which is, instead of looking for specific mutations, just en masse looking for the actual DNA in a variety of different, more complex ways. Sometimes it's just looking at specific segments. Sometimes it's literally sequencing the whole genome. And this can provide a ton of data, but a lot of it is hard for clinicians to use right at the moment in upfront care.

The next staging system that we use more commonly now is called the Revised International Staging System (R-ISS). This combines the blood tests (in the *Criteria* column) with some basic genetics. So, these are the results (in general) of the FISH, and we've added on a lactate dehydrogenase test, which is another blood test also shown to align with how proliferative or active the patient's myeloma is. Here, we use a combination of blood tests plus the genetics of the patient's myeloma on bone marrow biopsy to try to more accurately define those patients who are stage I, who have easier-to-treat myeloma, and stage III, harder-to-treat myeloma. The corresponding overall survivals, you can see on the right-hand side of the slide. Again, these survivals are not accurate today, but they're relatively accurate in terms of low versus high or high versus low.

On the left-hand side, you can see patients who have so-called standard-risk myeloma. These patients have less inflammation in their blood and no high-risk genetics seen on FISH. On the right-hand side, you can see those patients who are high risk. And [in between is] everyone who doesn't fit the standard-risk or high-risk categories; 60% of newly diagnosed patients are in this middle category, which is R-ISS stage II. We're working to figure out, of these patients who have stage II disease, which ones are really closer to standard risk and which ones are closer to high risk.

The MMRF has looked at another concept, which is a little bit difficult to think about, which is those patients who have so-called double hit myeloma. They have two problems. For instance, for chromosome 17, you can have one chromosome out versus both chromosomes out. And the more chromosomes that are affected in a plasma cell, the higher-risk, or the more aggressive, the patient's myeloma will be. This is a complicated concept, but you'll hear the words *double hit* used to describe any number of ways to look at abnormalities in a particular chromosome involving one or both [copies of that chromosome].

Finally, when we use the word *stage*, it's different than how patients with breast, lung, colon, or prostate cancer [use] the word stage. Those oncologists, when they describe that a patient has early-stage breast cancer, the location [of the cancer] is linked inextricably with outcome. That means early-stage breast cancer is generally curable and has a very good five-year survival rate, whereas for patients with metastatic breast cancer (stage IV cancer), their breast cancer has spread throughout their body and is not currently curable. In solid tumors (in breast, colon, lung, and prostate cancer), stage and location are linked to outcome, but that doesn't make sense in patients with myeloma and leukemia, where stage really does not depend on location.

For us, easier-to-treat myeloma is stage I, harder-to-treat myeloma is stage III, and everyone else is dumped into the stage II category, if you look at the R-ISS. Staging and risk are different from control. In our clinic, we often talk about, “Is your myeloma in control or not?” Meaning, are there more myeloma cells being made per day? Are you at more risk to have fractures, anemia, and kidney failure? For patients who are out of control, their myeloma markers are increasing every day, and they're at risk for fractures, anemia, and kidney failure. Whereas, if their myeloma's in control, there are no new myeloma cells being made at that time. So, there's no risk that the patient's kidney function or bone disease is going to get worse.

How can we enumerate control? Our favorite patients in the myeloma world are engineers, because they love numbers. And myeloma, in the vast majority of patients, involves numbers. You're looking at your IgA (immunoglobulin A), you're looking at your monoclonal protein, you're looking at your serum-free light chains. One or two out of three of these numbers best approximates the status of the patient's myeloma. And over time, even in patients who are not in great control, with a very slow increase [in these markers] in years one and two, the numbers slowly get worse, but these patients are generally asymptomatic. It's only when these numbers start changing rapidly that patients develop symptoms.

I often get the question, “When do we need to start treating my myeloma? Is it when my IgA is 500 mg/dL? Is it when my IgA is a 1000 mg/dL?” It's not the number that's so important. It's actually the slope of this curve that is the best indicator for the patient's status; [when it] starts increasing rapidly, that's when the patient is at risk for developing symptoms, and that's when we usually need to start treatment.

Do patients relapse differently? A little bit. This curve is very similar. It's just like the one you saw on the previous slide. For patients with low-risk or easier-to-treat myeloma, their myeloma can both present at diagnosis or at the time of first, second, or third relapse can slowly get worse very linearly. And right before this starts increasing rapidly (on the right-hand side) and before symptoms develop, that's a good time to start a novel treatment to see if there are better ways to control the myeloma with fewer symptoms.

For patients with high-risk myeloma, [the curve] shrinks. It's very difficult to treat their myeloma, so you get very little warning when the patients with high-risk or difficult-to-treat myeloma start relapsing. The time period you have between [noticing], “Uh-oh, the

myeloma's out of control," and the patient developing symptoms is very, very short. Patients who have high-risk smoldering myeloma, who are likely to develop into multiple myeloma, and patients with multiple myeloma who have very aggressive disease are both high-risk patients, but using the word *risk* differently.

The focus in this webinar is primarily multiple myeloma patients who are high risk, who have more proliferative disease. They require more treatment, and the focus on them is ever present. Thank you so much.

Mary DeRome (MMRF): Thanks, Dr. Hofmeister, for that great explanation of what *risk* really means. And now we're going to move on to a presentation by Dr. Melissa Alsina on how to treat high-risk multiple myeloma.

Melissa Alsina, MD: Good afternoon, everyone. Thank you to the MMRF for the invitation. I'm going to talk, after this introduction by Dr. Hofmeister, about how do we approach a patient with high-risk multiple myeloma. We always talk about a risk-adapted therapy, and it's aimed to treat patients differently, especially patients that have high risk. Patients with high-risk myeloma locally are not the majority of myeloma patients, probably about 15% or 20% of the patients.

And among all the studies that have shown significant improvements in how myeloma patients respond and how long patients live, the majority of the studies include both patients with standard risk and high risk. But again, the majority of those patients are going to be patients with standard risk. And when we see results, they're including all the patients, but probably the good results are mainly based on the number of patients with standard risk that are in the studies.

And so, when we think of treating a patient with standard risk, we should not be backing off therapy. We should offer these patients the best effective treatment that is available and try to get those patients the deepest response possible. And with high-risk patients, we will do the same. We're going to try to offer these patients the best effective therapy as we know or has been proven. But in these patients, achieving a deep response is probably even more important. And these patients usually would stay on therapy longer, and we would be more hesitant to back off therapy when we're trying to treat a patient with high-risk disease.

So, if I'm seeing a patient with high-risk myeloma, especially a newly diagnosed patient, I will push a lot more to try to get those patients in remission. Whereas, in a patient with standard risk, if I get a very good response and I'm not able to get where I need, I might feel more comfortable backing off sooner. But I just want to make clear that patients with standard risk still should receive the best therapy possible with the goal of getting the patients in a deep response.

This [slide shows] many studies that were done in newly diagnosed myeloma, and this is just to show that the majority of the studies include a small number of high-risk patients compared to the whole population, probably all of them except for this first study

comparing the combination of lenalidomide (Revlimid), bortezomib (Velcade), and dexamethasone with the combination of lenalidomide, bortezomib, dexamethasone, and elotuzumab (Empliciti). The total number of patients is 500, 700, [or] 1000, and then just a small number of patients with high risk. This is representative of the myeloma population. But this is also the reason it's hard to study this group of patients and understand exactly how these patients are going to do. So, we definitely need studies that are dedicated to high-risk patients, like Mary was referring to at the beginning.

This is a meta-analysis. *Meta-analysis* means that I take many different studies and I analyze them together if they study the same patient population. This is a summary of six trials that compare regimens [with or without] daratumumab (Darzalex). You probably know that Darzalex is a CD38-targeted monoclonal antibody. It's like immunotherapy against the protein that is exposed in myeloma cells. And Darzalex really has changed the way we treat myeloma, both in the newly diagnosed and in the relapse setting, because it's a great addition to the regimens that we use like the immunomodulatory drugs and the proteasome inhibitors like Revlimid or Velcade for example, or carfilzomib (Kyprolis).

And these [studies] analyzed how patients did when [they] used Darzalex or when [they] didn't use it, in patients with high risk (defined based on the cytogenetics of the myeloma cells). And it was shown that if you add Darzalex to these treatments, that would improve how long the patients stay with the disease under control, both in the frontline setting, with newly diagnosed patients, and in the relapse setting.

I think what is important is that we know that Darzalex is an important drug to use, both when you're a newly diagnosed patient or in relapse, and more so in high-risk patients. I think most of us are incorporating Darzalex to treat newly diagnosed patients and relapse patients. The main challenge, sometimes, is that Darzalex in combination with Revlimid and Velcade is still not an FDA-approved regimen for newly diagnosed patients. Sometimes we have a challenge, but there are studies available using these regimens. If you're a newly diagnosed patient or a relapsed patient, you should always ask your doctor if are there any studies that will give you a better opportunity, especially if you have high-risk myeloma.

How do we treat high-risk myeloma? What are some of the regimens? It's usually a combination of three drugs or four drugs, and that includes a proteasome inhibitor like Kyprolis or Velcade, an immunomodulatory drug like Revlimid or pomalidomide (Pomalyst), and dexamethasone. And as I mentioned, some of the studies include Darzalex. [One] particular study, for example, compares using Kyprolis, Revlimid, and dexamethasone versus Velcade, Revlimid, and dexamethasone. It was a retrospective study, and they reviewed 154 patients with high-risk newly diagnosed myeloma. They showed that patients that were getting Kyprolis had a deeper response, and that translated into a longer period before the disease would progress. Even though it's not a perfect study, because it's retrospective, it does suggest that Kyprolis may be a better option than Velcade for patients that have high-risk myeloma.

And on the right, there's the OPTIMUM study of about a hundred patients with very high-risk myeloma or plasma cell leukemia, which means that the myeloma cells are in the blood. Patients received Darzalex in combination with cyclophosphamide (Cytoxan), Velcade, Revlimid, and dexamethasone. So, we're talking here about five-drug regimen, followed by transplant, followed by more treatment with daratumumab, Velcade, and Revlimid. As you can see, about 50% of the patients got to minimal residual disease (MRD) negativity, which is a very, very deep response and probably what should be the goal of therapy, especially for patients with high-risk myeloma. And 77% of the patients had not progressed at 30 months after the initiation of therapy. So, more intensive therapy is likely to result in deeper responses and likely to translate into better outcomes for patients with high-risk myeloma.

Isatuximab-irfc (Sarclisa) is a drug that is similar to Darzalex; it is also an antibody against CD38, and so it works the same as Darzalex. It has been used in combinations for patients with newly diagnosed high-risk myeloma. This particular study included both patients that were transplant eligible and transplant ineligible.

It’s a very intensive regimen, where patients got a four-drug combination followed by transplant (if they were transplant eligible) or no transplant. And then they received more treatment as consolidation and then maintenance. Probably, most of you have heard that we use Revlimid as maintenance, usually as a single agent. But with this study, with patients with high risk, patients received a more intense maintenance regimen that included three drugs. There were very high response rates (94% for the patients that were eligible for transplant) and also a very high rate of MRD negativity. That, again, means that you have the deepest response possible. I think most myeloma doctors would agree that that should be the goal of therapy in the majority of patients.

This is another study that is very interesting, and I know these slides are super complicated, but I just want to bring up a point with this. This is a study that also was for newly diagnosed myeloma patients, but instead of doing a risk-adapted approach to adjusting the treatment based on risk, they adapted the treatment based on the response. And having that deep response, MRD negativity, as a goal, patients were treated with induction therapy with four drugs followed by transplant, and they checked MRD at all these points.

And if the patient achieved MRD negativity, then the patient stopped therapy. But if the patient did not get to MRD negativity, they received more intensive therapy. So it's a more response-adapted approach. This is changing what we normally use. We normally would keep patients on maintenance therapy indefinitely, but this study would say, well, if you achieve a very deep response, I don't have to keep you on therapy indefinitely, and I'm going to stop therapy. This regimen works very well; 80% of the patients got to that deep response that we were looking for. However, when you look at patients that had high-risk cytogenetics, the rate of MRD negativity goes down.

I don't like to show these curves very much; [this shows] the percent of patients that were without progression at 30 months. If patients had only one [high-risk cytogenetic

abnormality], they were not really high risk, and they were doing very well. But for patients who had ultra–high-risk myeloma, this [percentage] goes down even if they get MRD negativity, which suggests that for patients with high-risk disease, we have to be careful about stopping therapy. And that would be the reason why maybe when you talk to your doctor, if you have high risk, your doctor would be less comfortable with backing off therapy completely, even if you're in remission or you're MRD negative. For high-risk patients, there's definitely a lot of work to do. We definitely have to do a lot better.

The MyDRUG study is a good example of the efforts to try to get there. It's a study sponsored by the MMRF. Essentially, what they're trying to see is, okay, I'm not going to treat all the patients the same, but I'm going to try to identify what are mutations, or genetic changes, in the cells that I could target, not necessarily with the classic myeloma drugs, but with other drugs that target some of these mutations. So, it's a very important study that would help patients that have already received all the drugs that are the standard of care and for whom we don't know exactly in which direction to go. This could guide how the treatment should be directed, and it depends on the particular mutation. For translocation (11;14), which results in expression of a gene that makes myeloma cells grow, there is a drug, not approved for myeloma, but approved for leukemia, that can target this mutation. We use that drug in myeloma patients that have this mutation, and patients respond very well.

This [slide shows] an example of a patient that participated in one of these studies. The patient had received a first-line Velcade, Revlimid, dexamethasone/Kyprolis, Revlimid, dexamethasone induction, transplant, and maintenance. The patient achieved a good response, a complete remission, but progressed within less than three years. The second line had elotuzumab, Pomalyst, and dexamethasone, with very minimal response. The patient did not respond very well and progressed very quickly. And then, as a third line, it's very difficult to decide, right? This patient had received many good drugs. So, the patient enrolled in this study, and it was shown that the patient had a particular mutation that could be targeted with these drugs. That's what the patient received, and they responded very well to therapy. So, it's a helpful way of approaching myeloma, particularly patients with high-risk myeloma.

Just to mention very quickly, if a myeloma patient has translocation (11;14), venetoclax (Venclexta) is an excellent drug. It inhibits this gene that is called BCL-2 that makes the myeloma cells grow. And we actually combine venetoclax with either a proteasome inhibitor like Kyprolis or Velcade, or we combine it with Darzalex, a CD38 antibody, and it works very well. We don't see this [mutation] very commonly. In myeloma, it's only about 15% of the patients with myeloma, but those that have it definitely benefit from this drug.

And this is another example: patients that have translocation (4;14), which is considered high risk [and is present] in about 15% of the patients. This results in the increase in a gene that is called MMSET that makes the myeloma cells grow. [KTX-1001] is a drug that is not readily available, but this drug can inhibit that particular mutation and is being evaluated now in patients with relapsed myeloma.

Understanding those genetic changes in the myeloma cells that Dr. Hofmeister was talking about initially is very important to try to direct the therapy, particularly in patients with high-risk myeloma that do not have any other options. And there are many studies for high-risk myeloma. We do understand that this is a challenging type of myeloma. So, there are many studies, for example, moving chimeric antigen receptor (CAR) T-cell therapy early. Some of these have already been completed, and results are coming out soon. And some of these are ongoing. For example, [some studies are looking at] if a patient, by genetics, has high-risk myeloma, doing CAR T-cell therapy up front, or if a patient has functional high risk, meaning the patient don't necessarily have bad cytogenetics, but the disease is not behaving well and the patient is relapsing quickly after first-line therapy or is not having an optimal response. There are several trials looking at CAR T-cell therapy in those settings.

High-risk disease, again, is not just one definition. The most common that we have, probably the only one that we can use when we see a newly diagnosed patient for the first time and we don't know how the disease is going to behave, is based mainly on these staging systems that Dr. Hofmeister defined at the beginning or on whether the patient has high-risk cytogenetic abnormalities. But, the best test is time and seeing how patients respond to therapy and how long those remissions last.

And we use combinations of these therapies. I think for patients with high-risk myeloma, the goal of therapy should be to achieve the deepest response possible, MRD negativity, and then try to keep it. So, maintenance therapy continues. In many cases, doublet maintenance therapy is very important in high-risk myeloma. And definitely, this personalized medicine approach, like in the MyDRUG trial, is helpful to address what, exactly, in a particular patient, is the mutation that is driving the disease-refractory events or making that disease be more aggressive, so that we can target that in particular. Thank you very much for your attention.

Mary DeRome (MMRF): Thank you, Dr. Alsina, for that great presentation on all the treatments that are currently available for high-risk patients. Clearly, this is an area of high unmet need and there's a lot of work going on in this area in the myeloma field. Now we're going to hear from Nicholas, who's going to tell us about his patient experience as a person with high-risk multiple myeloma.

Nicholas Lenoir: Hi. I was diagnosed in 2016. I had to do kyphoplasty in my T2 vertebrae. I did Kyprolis, Revlimid, and dexamethasone, and I did an allogeneic stem cell transplant. I got a year of remission out of that, relapsed, went back into treatment, and finally CAR T-cell therapy opened up after quite a while. I did CAR T-cell therapy and got a year of remission out of that. I went back into treatment and had to do some radiation on my hips. Through all this, I still work every day. I am still raising a family. We've had three kids. Even with high-risk myeloma, you can still have your treatment days, you can still go on family vacations, you can still have a normal life. I'm not saying you don't have bad days. I'm not saying you don't have days where you just don't feel like doing it, but it's still possible.

I mean, there are so many treatments out there right now. I'm on a trial right now because we're looking at the next step, trying to make sure I'm here well past those five years that they're saying for high risk. I know every time we meet with my doctor; my fiancé tells her we need 40 more years. So with all the science that's out there, all the trials, all the medicines that are coming together, there are lots of options. These were just a few of them. There are so many drugs that have hit the market for the myeloma world in the last two years. It's pretty fantastic.

Mary DeRome (MMRF): Thanks, Nick, for that message of hope for other high-risk patients that there's a lot of options for them out there. Now we're going to move on to our Q & A, and we do have a lot of questions. Let me just start here at the top. A number of patients asked about 1q amplification. I know this is an area of study, and there's a number of trials ongoing. Dr. Hofmeister, what can you tell us about 1q amplification and what's out there for patients who have that chromosomal abnormality?

Craig Hofmeister, MD, MPH: 1q amplification is not just a one-size-fits-all situation. There is sometimes one copy, there are sometimes multiple copies, and the more copies there are in the patient's myeloma cells, the worse it is. A significant number of patients have some abnormality in 1q, the long arm of chromosome one. And the more copies that you have, in essence, the more abnormal it is, the more resistant in general the patient's myeloma cells are, and the worse the outcomes are. And 1q [amplification] alone, without anything else, seems to be one of those factors that pushes the patient's myeloma to be more resistant to treatment and to require more drugs to keep the patient's myeloma in control. I don't know of any specific 1q-targeted treatments that have shown significant success yet, but it's an ongoing area.

Mary DeRome (MMRF): Yes. Dr. Alsina, what can you tell us about a patient who has a 1q gain and a simultaneous translocation (14;16), as far as prognosis?

Melissa Alsina, MD: That patient is considered high risk. As Dr. Hofmeister just mentioned, 1q amplification, by itself, perhaps, is not easy to understand whether it's high risk or not. And in fact, the R-ISS was revised once more, and there was a publication last year to account for those patients that have 1q amplification. It's like a point system. It's complicated, but it allows us to not look [only] at that [amplification], but at whether it's associated with other cytogenetic abnormalities and so on. And it allows us to separate those patients that are in stage II, for whom it is difficult to know if they are more [like] stage I or more [like] stage III. But a (14;16) translocation is clearly a high-risk cytogenetic abnormality, so if someone has that in combination with 1q amplification, that would definitely be considered high risk.

Mary DeRome (MMRF): There is a question about allogeneic transplant in patients who have high-risk multiple myeloma. I know that allogeneic transplant is not really something that a lot of myeloma patients undergo, but Dr. Alsina, would that be something that you might recommend to a high-risk myeloma patient if it was a possibility?

Melissa Alsina, MD: That is a very controversial question, and it's a subject that has changed a lot over the years. In the past, when we did not have as many good drugs and combinations as we have right now, allogeneic transplantation was definitely considered, usually in the setting of a clinical trial for patients with high-risk myeloma, if they were fit and so on. The results are controversial; they're not definitive. A big national study went on to look at that, and accrual was closed early because not enough patients were accrued. But some patients do benefit from that.

As I'm sure Dr. Hofmeister has, I have patients with the 17p deletion that have been in remission 10 years after an allogeneic transplant. But I don't think it's something for all [patients], and I would only consider it in the setting of a clinical trial. I think right now we have other options, and if I had to choose a novel therapy for high-risk patients, I probably would choose CAR T-cell therapy before I would consider an allogeneic transplant. Allogeneic transplant is also a very aggressive therapy, and patients can have many bad complications down the road from receiving an allogeneic transplant. And it requires you to be in the hands of a very experienced allogeneic transplant physician, which most myeloma doctors are not. I would not say absolutely not, but that would not be my first choice, especially outside of a clinical trial.

Mary DeRome (MMRF): Dr. Hofmeister, how important is it, as a patient, to learn whether or not you are double hit and how would that inform your treatment? (*Double hit* meaning having two different chromosomal abnormalities at the same time.)

Craig Hofmeister, MD, MPH: Well, I have to say that the vast majority of my patients are not genomic experts, oddly enough. And as my PhD colleagues will characterize us clinicians, they make fun of us for being simpletons. Because oncologists just want to know if this is going to be difficult, what's going to happen, and what can I do to get the myeloma under control? So, I think it's very important if you can be engaged with, ideally, a myeloma expert and have upfront communication about whether your disease is easy to treat, intermediate, or hard to treat. I wouldn't worry so much about exactly which chromosomes [are involved], but try to stay active with what type of myeloma you have in terms of easy, intermediate, or hard to treat, and what clinical trials are available in your region. These are the types of high-yield activities for patients to improve management.

Mary DeRome (MMRF): Dr. Alsina, can a patient move from being in the high-risk category to being in the low-risk category after treatment?

Melissa Alsina, MD: Usually, the answer to that question is no. Even if you're diagnosed with myeloma, and they do your bone marrow, and they show you have high-risk [disease, with deletion of] 17p, for example, and you get treatment and you get in remission and then we repeat a bone marrow, well, the 17p deletion is going to be gone. But it's gone because there are no myeloma cells there. We cannot look for it anymore. But usually, if that disease gets active again, we will see that abnormality again; the disease will come back again with that 17p deletion. We don't see it in the absence of myeloma cells. It's not really that it's gone, but just that there are no myeloma cells.

Now, the opposite is true. A patient can have standard risk, [without] those abnormalities. And then when the disease relapses, they can develop a high-risk abnormality. And that is the importance of, when that disease becomes active, repeating the bone marrow biopsy so that we understand exactly what we're dealing with and understand that the disease is changing, is becoming more aggressive, and what we should do about that.

Mary DeRome (MMRF): Dr. Hofmeister, how often do you recommend Darzalex for maintenance after stem cell transplant?

Craig Hofmeister, MD, MPH: This is something we argue about at the moment quite a lot. We talk about this in upfront therapy. We still don't know if the addition of Darzalex really provides a patient-level outcome that's important. We love it because it improves responses, and it improves the proportion of patients who are MRD negative. We don't quite know whether it really improves survival, and it may be quite a while before we get that information.

On the back end, in terms of patients who are fit and patients who are transplant candidates, after transplant, do you do single-drug maintenance, two-drug maintenance, or three-drug maintenance? And for which patients do you do it? We have these same, somewhat enthusiastic, discussions about who's high risk, who's standard risk, and who's low risk, and how this affects their long-term maintenance. Primarily, we generally have the idea that patients who have two-drug or three-drug maintenance have higher-risk disease or harder-to-treat disease. So, the more drugs that you're on continuously, the harder your myeloma is to treat. And with the drugs that we currently have, you can control or adjust and take somebody who has one or two high-risk features and make them have as good an outcome as those patients without those high-risk features. But that only goes up to a point.

And there are patients who have too many high-risk features, and our current crop of drugs are not as effective [for them] in the maintenance setting based on the data published so far. That's a long answer to your question. Yes, we do have patients on long-term CD38 antibody therapy, and trying to find exactly the right patients who are most likely to benefit with the least amount of infections remains a big task. I think the biggest change in the maintenance setting is trying to divorce the patient from their abusive partner of dexamethasone in the maintenance setting. Because everyone loves to say goodbye to dexamethasone whenever they can, and that's something that more data have been in support of.

Mary DeRome (MMRF): Yes. I've seen some of those data, and that's actually good news. Speaking of dexamethasone, Dr. Alsina, what is the importance of taking a steroid like dexamethasone with treatment?

Melissa Alsina, MD: Yes, well, dexamethasone kills the myeloma cells. That is the answer. It is a very effective drug in myeloma, and that's why we want to use it in combination with the other drugs, especially when the patients have active disease. But once we get control of the disease, we back off as soon as we can. I know a lot of patients

have this love-hate relationship with the drug, and we do too. We like the drug because it helps; it's going to kill the myeloma cells. Patients, when they take it, feel better. A lot of times their bone pain improves. But then it has other, detrimental effects. It doesn't let you sleep because of leg swelling; it suppresses your immune system.

So, again, we use it because it kills the myeloma cells. We do have to give pre-medication with Darzalex, especially at the beginning, to prevent a reaction. So we use it for both things, but as soon as we have control of the disease, we back off. But it's a really good drug to treat myeloma.

Mary DeRome (MMRF): Dr. Hofmeister, we talked a little bit about whether high-risk disease can turn into standard-risk disease. But if a patient starts out being standard risk, can they then convert to high risk? And is that patient then treated differently because of their phenotype?

Craig Hofmeister, MD, MPH: Great question. The idea is that so much of what clinical oncologists do borrows from what we learned about evolution: oncologists are always focused on killing the myeloma cells, and myeloma cells are always focused on surviving. So, if somebody is newly diagnosed with proliferative, difficult-to-treat disease and you treat them and then they relapse, whatever they relapse with is usually even more difficult to treat than what they initially presented with. And that continues to move forward with each relapse. And that really doesn't change in the setting of low-risk, newly diagnosed myeloma; at each relapse, the myeloma becomes more difficult to treat. But they're starting from a less proliferative, less aggressive starting point. So even if they become more difficult to treat at relapse, at their third relapse, they still may not be as aggressive as somebody who is newly diagnosed with numerous high-risk features.

Mary DeRome (MMRF): Dr. Hofmeister, I know that at Emory, there is some interesting cutting-edge research ongoing about the importance of the microbiome in multiple myelomas. This patient asks, “What can you share about the research on the importance of the patient's gut microbiome in the maintenance of multiple myeloma?”

Craig Hofmeister, MD, MPH: There's lots to know, and certainly, there's a lot of associations between the gut microbiome, which is a fancy way of saying the bacteria and immune interactions that are primarily going on in our intestines, and the immunology and the response to immunotherapies in both solid tumors like kidney cancer, melanoma, lung cancer, et cetera, as well as blood cancers like myeloma. It's associative. What we really want to know as clinicians is what we can find to be causative and how we can manipulate the microbiome for the patient's benefit. That's the focus of the research here at Emory.

Dr. Madhav Dhodapkar, a card-carrying immunologist and myeloma clinician, his focus is primarily looking at patients with MGUS, with precursor disease, those who haven't yet developed myeloma, and trying to take a look at their microbiome, studying manipulations of the microbiome with medications that are primarily isolated to the intestinal tract, like rifaximin (Xifaxan), and see if the use of that or a change of diet has a way to change the

microbiome and perhaps alter the course for patients with precursor disease to ideally delay their development of multiple myeloma and improve outcomes.

Mary DeRome (MMRF): That's going to be an interesting area of research, I'm sure, moving forward. Dr. Alsina, I wanted to talk a little bit about the two myeloma drugs that were recently approved over the past week or so, the two bispecifics talquetamab-tgvs (Talvey) and elranatamab-bcmm (Elrexfio), and the implications of using those two newly approved drugs for high-risk patients.

Melissa Alsina, MD: We got very excited. We had two drugs approved within a week, which is really amazing. These drugs are called bispecific antibodies. On one side, they bind a protein in the myeloma cell, and on the other side, they bind cells from your immune system. They put those cells together so that the immune system can kill the myeloma cells. And that protein in the myeloma cell, the target that we have been using more (for example, for most CAR T-cell therapies), is a protein that is called BCMA. So, we have CAR T-cell therapy, and then we have teclistamab (Tecvayli), which is one that was approved in December of last year that has the same target [and] is another bispecific, and then the one, (Elrexfio), that was just approved last week. But the other one, talquetamab (Talvey), has a different target.

For patients that received CAR T-cell therapy and then relapsed and maybe their myeloma cells are no longer expressing that BCMA protein, talquetamab becomes a really good opportunity. These drugs, all of the bispecifics, are quite effective and induced relapse rates of over 60%, with many patients going into complete remission. These are effective drugs. The only issue is that right now we have so many treatments that we don't know exactly how we should sequence them. And these drugs have not been studied, for example, following a relapse after CAR T-cell therapy. But now that the drugs are approved, we're gathering real-world experience, and we have treated many patients, as I'm sure Dr. Hofmeister's institution has done as well. But we have treated many patients, for example, with teclistamab after relapse following CAR T-cell therapy, and patients do respond. And now that talquetamab, the one that has a different target, is available, we'll be doing the same thing.

These definitely represent a great opportunity. As with everything in myeloma, if the drug is very effective in the relapse setting, it is likely to be more effective early in the course of the disease. And these drugs are already being studied for newly diagnosed myeloma in clinical trials, even for high-risk smoldering myeloma. These are effective drugs, so they are likely to move up for earlier stages of the disease once we learn more about how they should be used in these settings and in combination with the backbone, like the proteasome inhibitors, immunomodulatory drugs, and so on.

Mary DeRome (MMRF): I know that we have a couple of applications in for earlier use of CAR T-cell therapies for patients who maybe are in their second or third line as opposed to being after their fourth. And there was some very hopeful data that was presented at the ASCO (American Society of Clinical Oncology) meeting about that. It will be interesting to see how that all works out.

I'd like to thank our amazing speakers, Dr. Craig Hofmeister, Dr. Melissa Alsina, and Nick Lenoir for their time and their contributions.