FAQs on Biomarkers in Multiple Myeloma

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Transcript

Mary DeRome (MMRF): Welcome everyone and thank you for joining us for today's session of frequently asked questions on biomarkers in multiple myeloma. I'm Mary DeRome, Senior Director of Medical Communications and Education at the Multiple Myeloma Research Foundation (MMRF). Today, I'm joined by Dr. Alexander Lesokhin from the Weill Cornell Medical College and Memorial Sloan Kettering Cancer Center (MSKCC) in New York City and Dr. Joshua Richter of the Tisch Cancer Center and Icahn School of Medicine at Mount Sinai in New York City. We've received quite a few questions from patients and caregivers about biomarkers and their role in multiple myeloma prognosis and management from our previous webinar a couple of weeks ago, so today we're going to try to answer some of these questions.

Let's get started. We're going to start off by talking about standard multiple myeloma biomarkers. Dr. Lesokhin, can you briefly define what a biomarker is for listeners who may not know and what distinguishes, for example, a diagnostic biomarker from a prognostic or predictive biomarker?

Alexander Lesokhin, MD: There's a lot in that question actually. A biomarker is basically a blood or tissue feature that is associated with a clinical situation. The clearest biomarker is having plasma cells in your bone marrow associated with or diagnostic of multiple myeloma. There are other biomarkers that are, for example, predictive of a particular outcome—an example of that in myeloma is something that we use commonly in International Staging System (ISS) staging. Beta 2-microglobulin distinguishes stage 3 versus not stage 3 or stage 1. Those have some prognostic significance when evaluated in the context of the therapies where those biomarkers were developed. I'll leave it to Dr. Richter to talk about the biomarkers that we commonly use.

Mary DeRome (MMRF): That's a lovely segue. Very nice. Dr. Richter, what are some of the common biomarkers that have historically been used in diagnosing and monitoring myeloma? What do they tell us about a patient's disease?

Joshua Richter, MD: As Dr. Lesokhin pointed out perfectly, plasma cells in the bone marrow are one of the ways we define myeloma, but nobody wants bone marrow biopsies constantly to find out what's going on. They are figuratively and literally a pain in the butt. So, the biomarkers that we tend to use are chemicals that are made by the bad cells. We actually have a pecking order according to something called the International Myeloma Working Group (IMWG), of which we're both members. The top biomarker we look for is that M spike in the blood, that monoclonal protein, and that's usually a combination of a heavy chain like an

immunoglobulin G (IgG) or an immunoglobulin A (IgA) with a light chain, a kappa or a lambda, and it gives us an M spike. We usually look for that in the blood and typically more of that means the disease is growing. If it goes down, we're killing the bad cells in the bone marrow that made it.

The second ranked biomarker is a urine M spike that looks for that bad protein in the urine. That's when we give people those giant orange jugs and say come back in 24 hours and please fill it to the brim. Everybody hates those. We don't do that as often as we used to because of the third tier biomarker, the serum-free light chains. That's that kappa and lambda. Again, more of this protein means the disease is growing. If it goes down, it means it's getting better. For years they talked about prognostics of non-IgG types or IgA types, and this may have some impact for the precursor disorders, like monoclonal gammopathy of undetermined significance (MGUS) or smoldering multiple myeloma progressing to active multiple myeloma. I don't think it really has much of an impact for myeloma nowadays, because we have so many other predictors that have a much greater impact than what type of bad protein you make.

Mary DeRome (MMRF): Okay. Dr. Lesokhin, can any of these standard biomarkers indicate who might respond to transplant or to certain therapies at this time? I think that work is ongoing to try to ramp up the predictive nature of some of these data. We're not quite there yet, but we're sort of getting there.

Alexander Lesokhin, MD: So, there's been some iterative evaluation of some of these biomarkers as a way to stage disease. The ISS stage is the key feature based on blood biomarkers like beta 2-microglobulin and albumin, which could distinguish stage 1, 2, or 3 based on the combination of those levels. It would therefore serve as a predictive model of overall outcome in the context of the available therapy at that time. That has now been expanded upon with the addition of Revised International Staging System (R-ISS) staging and the addition of lactate dehydrogenase (LDH) values—again, a blood marker that can be evaluated, as well as an additional feature that can only be defined in the bone marrow, looking at the cytogenetic features of plasma cells. In terms of the blood markers themselves, I would say that there isn't really a feature that says, "Oh, this person is or isn't likely to respond to therapy X, Y, or Z or to transplant." I think that is one of the main reasons that our initial treatment approaches are fairly uniform, with "fairly" being a key word there. Of course, there's variation, but the idea of induction, consolidation, and then some sort of maintenance, that overall arching treatment approach is fairly uniform.

Mary DeRome (MMRF): Yes. Yes.

Joshua Richter, MD: Can I throw in one little peek towards the future?

Mary DeRome (MMRF): You may.

Joshua Richter, MD: Thank you. So, what Dr. Lesokhin and I have talked about so far are very standard biomarkers. There are some newer ones, something called soluble BCMA, which we're starting to measure in our patients in the clinic. It's not on the routine list of "Okay, you're in a complete remission or partial remission," but we're starting to look at it. This is an important thing because a lot of the treatments we use, including a very amazing treatment that was recently approved, elranatamab (Elrexfio), are anti-BCMA therapies. Dr. Lesokhin was the lead author on an article about elranatamab. Although we don't have all the "nitty gritty" just yet, we know that when soluble BCMA is sky high people tend not to respond as well. If it's zero, we do know that there's a small group of people who have a 16p deletion who don't express the BCMA, so they're not going to respond. You can theoretically order this test and if it's zero or sky high, we don't think you'll respond as well, but it's not the end-all-be-all. So, this is more of a peek into the future, not a standard test just yet.

Mary DeRome (MMRF): I hadn't heard about that 16p deletion. That's a new one for me.

Alexander Lesokhin, MD: It's a location for BCMA. Right?

Joshua Richter, MD: Yes. This is from a lot of work that was done by Dr. Nikhil Munshi and his group at Harvard in Boston.

Mary DeRome (MMRF): Interesting. Okay. Dr. Richter, I know we were just talking with Dr. Lesokhin about how it's important to get cells from the bone marrow so you can do a lot of testing on them and look for different biomarkers in myeloma. We had a couple of patients who wrote in during the webinar that we just had about biomarkers who said that they've had bone marrow biopsies, but there weren't enough cells gotten from their marrow to be able to do important testing like the fluorescent in situ hybridization, or FISH, which is really interesting genomically to tell what's happening in your own personal myeloma. So, if this happens to a patient on your service, how do you then help them? Do you have to give them another biopsy?

Joshua Richter, MD: Well, I think Dr. Lesokhin pointed this out perfectly, that right now for the majority of our decisions we're not using this information and we can still provide therapy choices without it. The problem is once that sample is used you can't really go back and repeat the FISH test on it. The problem is usually sometime after a bone marrow biopsy people are going on treatment and the amount of myeloma in their bone marrow is heading towards zero. So if a bone marrow is repeated at that time, if there's not a lot of myeloma or no myeloma present you're not going to find abnormalities. We talk about repeating a bone marrow biopsy for patients for whom we think we're going to need this information at the time of a relapse, because we know that the burden of disease in the marrow is likely to be such that we're likely to find abnormalities.

Mary DeRome (MMRF): Okay, that makes sense. We discussed a little about the predictive properties of genetic biomarkers. Dr. Lesokhin, can you go into a little more detail on what some of those markers might be genomically? For example, what are the high-risk genetic biomarkers and what are the implications of the presence of those biomarkers for a patient's treatment?

Alexander Lesokhin, MD: Yes. So I think this is a field that's continuously evolving because of the advent of our ability to sequence the entire genome of a cell in a few weeks at a reasonable cost. What we look for in the standard FISH test are the things called immunoglobulin heavy chain (IgH) translocations, so 4;14, 14;16, and also 11;14. These are important for prognosis. Some are high-risk, some are not. A 17p deletion is another genetic biomarker that is very important, as are abnormalities of the first chromosome, so an amplification of 1q and deletions of 1p. What are the high-risk features? Traditionally, 4;14 and 14;16 translocations and the 17p deletion have been considered high-risk features. These are the ones that are included in the R-ISS staging criteria and they imply a more aggressive phenotype. It's certainly a disease phenotype where individuals will respond to their initial treatment, but the disease tends to recur earlier than in patients who don't have some of these abnormalities. That doesn't necessarily change our approach in terms of initial treatment or initial induction treatment, but it does when we get into a maintenance phase. There we understand that patients will have disease recurrence more rapidly than we want. There have been several treatment approaches that have been developed to try to prevent early relapse that have shown benefit—namely, the combination of lenalidomide and proteasome inhibitor-based maintenance approaches rather than lenalidomide alone. The 11;14 translocation fits in its own class because the drug venetoclax (Venclexta) or other BCL-2 inhibitors seem to have preferential efficacy in this subset of individuals. Venetoclax is currently approved for chronic lymphocytic leukemia, not myeloma; however, we will commonly use it in individuals with myeloma with the 11;14 translocation, so it offers another therapeutic opportunity there. In that sense, this translocation is predictive of response to venetoclax.

Mary DeRome (MMRF): Yes. I have been seeing a lot more on combination maintenance therapy, which is interesting. There are a number of patients whom we've had on some of our podcasts lately that have been on these combination maintenance therapies based on level of risk that was genetically determined. It's a kind of interesting and more recent development.

Dr. Richter, can a patient's genetic biomarkers change over time? In particular, can they go from having high-risk biomarkers to not having them? That's probably less likely than going from not having high-risk to having high-risk as the disease progresses.

Joshua Richter, MD: Sure. Can biomarkers change? Absolutely. Oftentimes,

some of these abnormal cytogenetic changes are part of the spark that may set off the development of myeloma. You tend to carry these through as you go along, but you can certainly acquire new ones. The most common one to acquire is a gain or amplification of chromosome 1q. As Dr. Lesokhin mentioned, this is unfortunately a higher risk abnormality and it tends to occur pretty frequently over time. In terms of can you ever go from high-risk to standard-risk biomarkers, I don't really see it that way. We look at patients initially as having high risk or standard risk status, and if you look at the website of our colleagues at the Mayo Clinic, mSMART.org, it includes the risk factors that determine if a patient is considered high or standard risk. The only thing different from going from upfront to relapse is a concept of functional high risk, which is separate from cytogenetics. If you relapse within 12 months of your initial diagnosis or transplant, you are considered high risk. But again, it doesn't mean that you're going to have a poor prognosis. I have many patients who have 17p, 4;14, or 1q genetic biomarkers that do quite amazingly. So, that doesn't define your disease and there are a lot of other factors that have an influence in there.

Mary DeRome (MMRF): Okay. In our recent webinar we had on biomarkers, which was done with the group from Miami with Dr. Francesco Maura and Dr. Ben Diamond, we talked a lot about this new model that they've come up with for prognostication. It is just a research model, it's not in clinical use yet. They call it Individualized Risk Model for Multiple Myeloma (IRMMa). Dr. Lesokhin, have you done any reading about this model or do know anything about it? What are the implications regarding what it can tell clinicians about a patient's multiple myeloma?

Alexander Lesokhin, MD: Yes. I appreciate that question. Some of those data were developed using the genomic information acquired from patients treated at our center, as well as many other centers around the world. If you Google it, that's what you'll find.

Mary DeRome (MMRF): Okay. I will do that.

Alexander Lesokhin, MD: But that aside, this is a model that is based on targeted sequencing. So, let me take a step back because it's complicated. When we do the bone marrow biopsy we pull out myeloma cells. We also pull out everything else that's around the myeloma cells. There are tools available to isolate the myeloma cells and to look at everything else there, which is the microenvironment. These days we can look at the myeloma cells with really fine detail. These newer ways to evaluate the genomes of those myeloma cells allow us to not only sequence the entire genome, but we can also sequence it in a targeted way to look at specific genes or segments of DNA that we know drive cancer development. They're called driver or tumor oncogenes, right?

Mary DeRome (MMRF): Right.

Alexander Lesokhin, MD: There are targeted panels and whole genome approaches. Then, there is something in between that doesn't look at the whole genome and isn't targeted, but only looks at what I'll call the accessible genome. I'm going to stop there for fear of sounding too much like a textbook. Suffice it to say that when you put all of these together and you also look at standard FISH results and the ISS stage, what you find is that one feature is associated with a certain outcome and another is associated with another outcome, so it's really hard to integrate all of them.

Mary DeRome (MMRF): Yes. It's like looking at patients and what treatments they might respond to best? That's part of that picture, right?

Alexander Lesokhin, MD: Absolutely. Right. All of these features, any sort of biomarker is going to be dependent on the treatment the individual gets. The utility of a biomarker that's predictive or prognostic is it tells you what treatment is going to work or not. So, any of these prognostic models are going to be highly dependent on what treatment context they're evaluated in. There are several layers of complexity there. How do you integrate all of that information in a way to remove the noise? That's the stuff that goes together. If it's raining outside and it's wet, those 2 conditions go together. They go together and you have to think of them together. So, when you think about the genetic models and clinical variables that predict for a higher risk of some outcome in the context of some therapy, you need to think about what's separate and what goes together.

This is a long preamble to say that what the IRMMa did is try to integrate all of these different variables and come up with a prognostic tool that says, "Hey, if this person got Velcade (bortezomib), then their outcome is going to be X." Or, if they had this particular genetic fingerprint or ISS stage and so on and so forth. They characterized a bunch of different groups, and honestly, for most clinicians and certainly for most patients and regular people it's really complex.

Mary DeRome (MMRF): Yes, very complex.

Alexander Lesokhin, MD: But, it's moving toward the place we want to go, it's moving to a place where we can say, "Okay, we know these features from a patient's diagnostic presentation. We know their age. We know their ISS stage. We've obtained the genetic panel." That's not something we do routinely, so we're not there yet. That's why this is very much a research test.

Mary DeRome (MMRF): Yes.

Alexander Lesokhin, MD: We have obtained this genetic panel and we know that if we use a treatment such as Velcade, Revlimid (lenalidomide), transplant, and chronic therapy after that, their outcomes based on their combination of genetic and clinical features are going to be this. On some level, that theoretically allows us to say, "Okay, well, this patient is unlikely to benefit or more likely to

benefit from transplant. We should or should not use this." I think this is very avant garde at this point, but it is definitely a direction. At this point, it's kind of looking back at treatment that has been delivered thus far.

Mary DeRome (MMRF): Correct. It's looking backward.

Alexander Lesokhin, MD: It doesn't incorporate newer things like daratumumab. Right?

Mary DeRome (MMRF): Yes. Much of this data was collected some time ago, especially all of the data they used from the CoMMpass study. There's aren't that many patients in that study who were on the more modern therapies at the time. Darzalex (daratumumab) or Empliciti (elotuzumab) were the only more modern things that were in there.

Alexander Lesokhin, MD: Absolutely.

Mary DeRome (MMRF): It has some catching up to do.

Alexander Lesokhin, MD: That's the nature of these type of models. They're always going to have some catching up to do, but they still teach us on an individual level that you are more or less likely to achieve a good response with this or that therapy. I think it's similar to what we do now. We know that if someone has a 4;14 translocation, it's important to add a proteasome inhibitor to their therapy. We know if someone has an 11;14 translocation that venetoclax is going to be very useful for their treatment. Similarly, these types of models need to be looked at prospectively because that 4;14 and 11;14 data and information come from studies where folks looked at these translocations and realized that these folks benefit from this type of therapy. So, the IRMMa is a move to create a fingerprint that we can then look at and say, "Okay, based on this fingerprint we can give treatment A or B or C and look and see what happens there."

Mary DeRome (MMRF): Yes. They have a lot of patients' data already and they're asking doctors and researchers to add as much data as possible to the model because it's a machine learning model. The more data you put in, the better it gets at predicting. I think eventually this is one of the ways that myeloma may someday be cured. Or, at least patients will take medicines and treatments they know are going to work based on their fingerprint and this model. We're not there yet, but we'll get there eventually. It's pretty interesting stuff.

Alexander Lesokhin, MD: I think that's the key point. The idea is that you can try to optimize who needs what therapy for how long because that's really the goal. As physicians treating patients, how can we use this information to define treatment? We're not there yet so granularly, but we're making strides.

Mary DeRome (MMRF): I think we'll eventually get there. It'll take some time, but it's big for quality of life for patients—that they're not going to be treated with something that is not going to work for them, which happens sometimes now. So, hopefully we'll get away from that when we have more data about what works for which patients and why, based on their genetics. Because myeloma is different in every person, this is the way that it has to be done.

Okay, moving on a little bit. Dr. Richter, when a patient has high-risk biomarkers, does that have implications for what they should be treated with? How does a patient go about finding a doctor to treat high-risk multiple myeloma if they are defined as being a high-risk patient?

Joshua Richter, MD: I'll take the second part first. Anyone who treats myeloma or specializes in myeloma treats all types. I think this is where we would differ from obstetricians/gynecologists, where patients have a clear delineation of high- and standard-risk obstetrics in terms of who treats them. If we all treat myeloma, we treat high-risk just the same. In terms of how this drives treatment decisions, for the broad swath we don't have clear guidelines, but we're starting to chip away at that. We have a couple of inklings about it. One of the really great studies done recently was done by a colleague of ours, Dr. Luciano Costa, who did this trial called the MASTER trial. He looked at an induction regimen of daratumumab, KRd (carfilzomib + lenalidomide + dexamethasone), and transplant followed by consolidation and maintenance. He looked at people and would stop them if they were minimal residual disease (MRD)-negative. Then, he'd look back and say, "All right, well, what did this look like if you had no high-risk cytogenetic abnormalities? One? Two or more?"

One of the things that's come out of this study so far is that for the people with 2 or more cytogenetic abnormalities, you probably need to keep your foot on the gas pedal. They may need more than just Revlimid. They may need daratumumab + Revlimid or proteasome inhibitor + Revlimid to keep things going. What was interesting is that the 0 and 1 high-risk cytogenetic abnormality groups behaved fairly similarly, not 100%, but they were very, very close on the lines. It may be that we're starting to figure out that patients with high-risk cytogenetic abnormalities may need a little bit more, but standard- or even 1 high-risk cytogenetic abnormality may need less, meaning that you may be able to stop maintenance. If you're MRD-negative and you're standard-risk with induction, do you really need transplant? I think with anything in myeloma, we can find 10 doctors to give us 12 opinions and argue over what this means. I think these are questions that we're on the precipice of having real data to drive decisions.

Mary DeRome (MMRF): Agreed. The more I talk to patients on these podcast episodes, the more I'm seeing patients who are diagnosed, go through induction, have their transplant, then they're on maintenance for a couple of years, and they have long-term MRD negativity, and they say to their doctor, "I'm done. I'm not

going to take any more." They've discussed this with their care teams and say, "This is my decision. I really don't want to have any more therapy. I will continue to be watched closely just to make sure that if I start to relapse it will be caught early." I think a lot of patients are doing that now.

Joshua Richter, MD: There's a study, SWOG S1803, being led by Dr. Amrita Krishnan at City of Hope. It's also known as the DRAMMATIC study. It's one of the fastest accruing phase 3 studies in myeloma history. Dr. Krishnan is looking at people after transplant to be randomized to Revlimid alone or daratumumab + Revlimid. She has MRD stopping rules along the way. It'll probably take us about 3 to 5 years until we start getting meaningful information from this study, but this is one of the big steps toward understanding all of the studies until now. For example, if you do 2 years versus staying on maintenance, staying on is better or 3 years versus just staying on maintenance, staying on is better. Now, with these powerful techniques we may really get granular saying, "No, no, no. If you have this risk and this level of depth or MRD negativity, you may be able to stop." So crossing fingers for that data.

Mary DeRome (MMRF): Agreed. So, now we're going to talk about one of the newer biomarkers on the block over the past few years. We've already just mentioned MRD in the myeloma world. Dr. Lesokhin, can you briefly explain what MRD is and what it means when a result comes back as MRD-negative at a level of 10^{-4}, 10^{-5}, 10^{-6}? These numbers are kind of tossed around and patients don't understand what that means. Is an MRD-negative result the same result as below the limit of detection?

Alexander Lesokhin, MD: I'll take the very first and then the last part of your question. Is it below the limit of detection? The answer is yes, using that particular assay. You're asking about 10^{-4}, 10^{-5}, 10^{-6}. Really, this is a bone marrow-based test at the current time where the liquid portion of the bone marrow is evaluated using historically either something called a polymerase chain reaction (PCR) test that had a lower sensitivity threshold, 10^{-4}, which is not something we do now, or a flow-based cytometry test, which is something where there's a special machine that looks at what's displayed on the surface of myeloma cells. This can differentiate them from normal plasma cells, the cells they derive from, or from other cell types and can identify those abnormal cell types typically at a threshold of 10^{-5}. Then, 10^{-6} is a threshold that's defined using these genetic approaches where the entire sequence of the specific antibody that myeloma cell is making is looked at. Now, for that last test, as well as for the PCR test, you need to know what you're looking for, so you need to first identify that specific sequence. So, you can only do those kinds of tests if you have a diagnostic sample where that clone was identified.

These are the most sensitive MRD tests that we have. The sequencing-based test and the flow cytometry test doesn't require the prior diagnostic specimen. Suffice it to say that the current 10^{-5} accepted criteria for MRD negativity by the

IMWG defines these biomarkers with us having an understanding that 10^{-6} is probably better. Studies looking at 10^{-6}, like the MASTER trial, are able to say, "Okay, if we have below the limit of detection once or we have below the limit of detection on 2 consecutive tests, then we have a sustained MRD response and those folks will achieve a better outcome. MRD negativity at the 10^{-5} level, has been evaluated across several clinical trials, and consistently those that achieve that end point fare better than those that don't in the retrospective way that these things are analyzed. We took a population, we gave them a fixed treatment, and we said, "How many achieved the endpoint?" The ones that got there did better than the one that didn't.

We also know now to look at those 2 tests consecutively 12 months apart. There's some variability in terms of whether 6 or 12 months are enough to define sustained MRD negativity. That's probably what we now consider to be the best sort of prognostic outcome or the best outcome group in response to any particular treatment—those that achieve that sustained MRD negativity end point. What we are now starting to do, as Dr. Richter has alluded to, is to try to use this biomarker as a way to evaluate whether we can stop a treatment or should we add a treatment. As you've heard, those kind of studies are ongoing.

I would like to put in a shameless plug for a study that one of my colleagues at MSKCC, Dr. Neha Korde, is running. In this study, we are actually looking at MRD negativity in the context of maintenance therapy as a potential biomarker that can be used in association with other biomarkers, as well as to stop maintenance therapy with careful subsequent observations. This is something you alluded to as something that we should try to do. This is a trial that we are currently accruing.

Mary DeRome (MMRF): Interesting. Okay. Dr. Richter, who should have MRD testing? Every patient or just like some patients at some points of their therapy? It's not really being routinely used to guide clinical practice at this time. Although, I think there are some physicians who have a lot of experience with MRD who are doing that. But, there really aren't any guidelines per se of what to do with MRD results at this time. So, in a way it's a little bit "seat of the pants" stuff. We will at some point get to where there are guidelines regarding when to change treatment or stop maintenance based on MRD. So, is that being done more in the big academic medical centers or in the community at all?

Joshua Richter, MD: I think MRD is being utilized a lot more in academia. There's a spectrum of doctors and even the myeloma centers who do it multiple times a year on every patient and use it to inform decisions. I tend to use it as little as possible. I think it's a piece of the puzzle. It's not necessarily the main driver, at least for me. I think the bigger question is there's a very basic medical precept that we all learn in training, which is if you're going to do a test, will it change what you do? If the answer is no, do you really need to do it?

if I have a discussion with a patient up front and we discuss that based on risk, cytogenetics, lifestyle, and disease whether we're going to do a transplant or not, I don't need a bone marrow biopsy to guide that decision if we've already made it. If somebody is on maintenance therapy and they're not tolerating it despite dose reductions and supportive care, I don't need a bone marrow biopsy to tell me that we haven't found any cells to justify stopping it. I think that it's part of a discussion. If you have somebody who's on the fence about transplant and they're standard risk and they want to know if they are MRD negative because that would help them make a decision about a transplant, we can absolutely do it. If it's going to impact your decision-making, you should do it at inflection points, such as at presumed complete remission or presumed relapse. My concern about doing it haphazardly is that I have a lot of patients post-transplant on maintenance that we do a bone marrow biopsy and we find 3 cells out of 10,000,000 and it's upsetting. They're still going to do amazing. But finding out that your positron emission tomography (PET) scan is negative, your M spike is zero, your light chains look normal, the bone marrow looks negative, everyone is cheering, and then, "Wait. Hold on. We found 3 bad cells." It's not going to change anything, but that's an upsetting thing to find out. So, I'm not inclined to do as much MRD as some of my other colleagues.

Alexander Lesokhin, MD: Can I add to that?

Mary DeRome (MMRF): You may.

Joshua Richter, MD: Please.

Alexander Lesokhin, MD: I agree with the precept that if you're not going to change your management based on a test, then don't do the test. I also would say that MRD is a very important test, but it's not yet a test that we can use to say, "Oh, where should we change to therapy A, B, C, or D?" That is my current thinking. I think it's a very important test to study and to utilize in our clinical studies to try to understand what we can do and when. Particularly since right now for all our patients as soon as we start treatment it's lifelong; it's indefinite. Is that really necessary? Can we stop?

Mary DeRome (MMRF): Yes, I mean, that's the question. Right?

Alexander Lesokhin, MD: Yes. But, I would also say that there's a missing piece of the puzzle. There's more to it and there are other biomarkers and other things that are incompletely explored as of yet that can predict whether or not someone may have a durable remission or a disease recurrence. They are not focused on the plasma cell, but are focused a little bit on the microenvironment and dare I say, the microbiome and other things that that may also impact how folks do overall.

Mary DeRome (MMRF): Okay, that makes sense. Some data has been emerging on the use of peripheral blood and mass spectrometry as a possible alternative to current methods of sampling from a bone marrow biopsy. This seems like good news for patients who are reluctant to have a bone marrow biopsy. Dr. Richter, can you discuss where the state of the science is on this? How close is it to being used clinically? We're going to discuss a number of presentations about these new biomarkers that took place at the American Society of Hematology (ASH) meeting this year. So, please expound.

Joshua Richter, MD: Sure. So, mass spectrometry allows us to do a number of things besides just finding small amounts of disease in the blood. It also lets us know what that is. What I mean by that is that you can't turn on the television nowadays without seeing commercials for some drug ending in "mab" for all different types of diseases: rheumatologic, dermatologic, gastrointestinal—the list goes on and on. Any "mab" drug is a monoclonal antibody and pretty much all of these are IgG kappa monoclonal antibodies and the most common type of myeloma is IgG kappa. If you order immunofixation and serum protein electrophoresis (SPEP) on people getting mab therapies for dermatologic and rheumatologic disease, you find an M spike. Then, they get referred to a cancer center and that could be concerning. One of the great things is that because we know the chemical makeup and weight of these drugs you can use mass spectrometry. The Mayo Clinic has been doing this for some time. They're one of the big proponents of this technology. They get a referral for an M spike, they'll order this technology and say, "No, this is your infliximab that's being used to treat your rheumatological disease. It's not a distinct power protein. Nothing to worry about." So, there are really nice little caveats you get with this. I believe Mayo Clinic Labs, which is, you know, one of the main third-party major centers for sending laboratory studies, have actually converted their SPEP technology to a mass spectrometry-like technology to give finer detail. I think that happened within the last few weeks, if I'm not mistaken.

Mary DeRome (MMRF): Really? Wow.

Joshua Richter, MD: Then there's quantitative immunoprecipitation mass spectrometry (QIP MS). And there's a commercial one out there that's being advertised a lot. These tests are wonderful. But, the long and the short of it is that we have so much data with the standard evaluations we don't know what the results for these tests really mean. We have no standardization to define response, relapse, depth of response. These are good adjunctive tools, but as Dr. Lesokhin pointed out, we need more prospective data with them to figure out how we can incorporate them on a day-to-day basis.

Mary DeRome (MMRF): Agreed. Okay. So, speaking about some of this data from ASH, it indicated that biomarkers may be able to predict outcomes from CAR-T cell therapies, including treatment response and toxicity. We already talked a little bit about soluble BCMA, which is one of the biomarkers. Dr. Richter,

can you summarize some of these other data that were in some of these abstracts?

Joshua Richter, MD: Sure. So, CAR Ts are some of the most exciting therapies that we have. And, next week is one of the biggest meeting days for myeloma in history—the FDA's Oncologic Drugs Advisory Committee (ODAC) meeting next Friday, where there will be presentations on both Abecma (idecabtagene vicleucel) and Carvykti (ciltacabtagene autoleucel) to try to convince the FDA that we ought to be able to use these treatments in earlier lines of therapy. There's a good likelihood that by April we're going to start giving people CAR-T cell therapy at first relapse. So, the question is who's going to do better, who's going to do worse, and who's going to have some of the big side effects?

There were a number of really cool presentations at ASH, including by Dr. Penn, who is one of our fellows, who is going to be joining Drs. Martin, Chari, and Wolf at University of California San Francisco (UCSF) this coming July. He looked at inflammatory biomarkers prior to going into CAR T and observed that elevated levels of fibrinogen and ferritin (markers that our body cranks up when we're inflamed) may predict for worse outcomes after CAR T and higher baseline levels of the inflammatory markers, C-reactive proteins (CRPs). He also looked at the lymphocyte level in the blood, and found that higher lymphocyte levels in the blood may predict for some other toxicities that we call immune effector cell-associated neurotoxicity syndrome (ICANS).

There were a few other great presentations by Dr. Zhao and Dr. Hansen looking at other predictors on the back end for who will have longer cytopenia. People going into CAR T who had more myeloma tend to have longer cytopenia and low blood counts afterward. We do know that there are a number of patients for whom the count stays so low, for so long, we have to give them back the original stem cells that we collected up front many years prior. Those are really the main ones that they found. Also, looking into the presence of extramedullary disease, if you have big solid masses of myeloma, you tended not to do quite as well with CAR T. At the end of the day it's all Goldilocks. We don't want this porridge to be too hot or too cold, so we are looking at ways that if the porridge it too hot, to cool it off before you go into CAR T.

Mary DeRome (MMRF): Yes. Makes sense. Okay. There were some abstracts at ASH suggesting that markers of T-cell health can predict outcomes with the BCMA-targeted bispecific antibody, teclistamab. Dr. Lesokhin, are the results of those studies likely to result in biomarker testing that will be used to predict treatment response to bispecifics?

Alexander Lesokhin, MD: In the future, I would hope so, but I think that these data that were presented are certainly encouraging in that they highlight features that suggest somebody might respond versus somebody who is less likely to respond, as well as potential ways that one may try to overcome that lack of

response. One abstract was an analysis of patients we treated as soon as teclistamab came out at our center and then obtained their peripheral blood and did flow cytometry. This is the kind of testing I was referring to earlier where you look at what's displayed on particular cell populations that are circulating in the blood, and based on that you can identify what kind of cell it is. This was focused on the T cells understandably, because this is a T-cell-directed therapy. This was work done by a really excellent fellow at our place, Dr. Ross Firestone. What he found was that folks who respond tend to have T cells that have more of these kind of effector molecules on them. These are T cells that have already seen a target. We don't know what that target is, but they've gotten activated and they have all of the machinery ready to kill something. Having those cells around at a higher frequency makes sense logically. When they're redirected toward the myeloma cell and "licensed to kill" it, then they do it and people get a response. Conversely, folks who have a population of cells that are typically like, "Hey, hey, hold on, chill, we don't want to get activated," which are called regulatory (Treg) cells were less likely to respond. There were particular markers on those Tregs, one of them being T-cell immunoreceptor with immunoglobulin and ITIM domain (TIGIT), for which there are checkpoint blockade drugs that are available to block those molecules. This would suggest the possibility that maybe that's a rational combination partner, at least in some ways, with something like teclistamab or another bispecific perhaps. So, that's one story.

There's also another set of work that was based on the MajesTEC-1 trial, sort of a correlative analysis run by Dr. Niels van de Donk. They also looked at the T cells, again looking at what they expressed in the blood and bone marrow, both at the time that treatment was started, then sequentially and then also at relapse. What they found was that dynamic changes in how T cells behave seemed to be predictive of whether or not folks would respond or not. So, if someone had transient activation and they looked at if CD38 (a marker of T-cell activation), went up and came back down, that suggested there was efficacy and response and less ongoing activation; whereas, if the cells go up and continue to stay up and accumulate markers of exhaustion or basically chronic activation, then those folks were less likely to achieve a durable response. Again, from a T-cell biology perspective, this sort of makes sense. T cells are designed to go out, do their business, and then relax. If they are chronically active, that means they're ineffective initially, so they're unable to get rid of what they're targeted against, then they stay chronically active and there are other mechanisms intrinsic to the T cells to keep them from doing harm essentially and that lock their efficacy. Cancers like myeloma utilize those things to cause T cells to be like, "Hey, yo, I'm cool. I want to hang out here."

Mary DeRome (MMRF): You can just see the T-cells in there talking to each other.

Alexander Lesokhin, MD: Well, they do. That's what cytokines and chemokines do.

Mary DeRome (MMRF): Maybe not with words. Right. Exactly. I'm just going to ask for some final thoughts here to wrap up. Dr. Lesokhin, what is the most important thing for patients to take away about biomarkers and multiple myeloma?

Alexander Lesokhin, MD: I think the fundamental take-home message is to talk to your doctor, because this is highly complicated. It's an evolving field and these biomarkers including cytogenetics, ISS stage, MRD, and all the newer testing that we've touched on, all need to be put into context of what's your treatment? How are you doing on the treatment? How well have you responded so far? Are you tolerating the treatment? All of that needs to be put together to formulate a personalized treatment plan for every individual, and these biomarkers help, but they don't define anyone. Having high-risk cytogenetic biomarkers doesn't mean automatically that you're going to do badly. These are statistical, kind of like, "The chances are X or Y" or "X-ish and Y-ish" is probably the better way to describe it. So I think that's the fundamental message. There's a lot of information that your doctor has. Ask them.

Mary DeRome (MMRF): Ask them. Okay. Good idea. Dr. Richter, for the final word, if you were to look into your crystal ball and try to predict what exciting developments there might be in the future for biomarkers in multiple myeloma, what's next?

Joshua Richter, MD: The future is saying no to the needle. Right now, we still glean some of the most potent information from the bone marrow, because myeloma cells, in general, don't like to hang out in the blood too often. Some of them go out to take a peek but most of them stay in the marrow. But thanks to evolving technologies, including mass spectrometry, PCR sequencing, soluble BCMA, we're starting to be able to put together a picture, a better picture than from the blood alone. I can envision a time when bone marrow biopsies are not a routine phenomenon. We are not there yet, but I think we are getting closer and closer to having the type of technology that would allow us to do away with them on a regular basis. That's deep in my crystal ball.

Mary DeRome (MMRF): That's good news for patients, right? It's always amazing to think about how much the science of multiple myeloma has really advanced in just such a short period of time. Ten years ago when I joined MMRF and started working in this area, we didn't have any of these things. Now, there's so much to talk about. I think it's great. It's very hopeful and there's just a lot of really good things coming as the science continues to develop. On behalf of the MMRF, I'd like to thank Dr. Lesokhin and Dr. Richter for joining me today. I'd like to thank everybody for taking some time out of their day to join us on this program.