Frontline Updates From the Annual Hematology Meeting: Advances in the Treatment of Multiple Myeloma
DR. WILLIAM MENCIA: Hello, I’m Dr. William Mencia and welcome to Med-IQ’s coverage of the American Society of Hematology’s annual meeting. I’m joined here today with Dr. Joseph Mikhael, hematologist at the Mayo Clinic in Arizona. Welcome Joseph.

DR. JOSEPH MIKHAEL: Thank you for having me.

DR. MENCIA: Let’s start today by discussing the PETHEMA trial. What are your thoughts concerning this study, and did you have any issues or concerns regarding the design?

DR. MIKHAEL: This is a great study. I think it’s helping us understand a little bit more about how we should approach patients with high-risk smoldering multiple myeloma. We’ve known for a long time that multiple myeloma is not a single disease, and there’s a huge spectrum ranging from patients who have just a monoclonal gammopathy—or what we sometimes call monoclonal gammopathy of undetermined significance—through smoldering myeloma and genuine multiple myeloma, and this study was designed to try and capture the patients who were in the highest risk category of smoldering [myeloma] but still not demonstrating symptomatic disease or organ damage but perhaps soon to be demonstrating those things. They were treated with a regimen of lenalidomide and dexamethasone and, when compared to those individuals who were not treated with lenalidomide and dexamethasone, indeed had an improved progression-free and even overall survival. In general we thought it was a very important study to address this issue of high-risk smoldering disease. That being said, as you intimated, there are some concerns. One, their definition of high-risk smoldering multiple myeloma is not one that we can typically use in community practice. They have some very sophisticated techniques to detect evidence of high-risk disease and that makes it a little bit challenging to apply it day to day. Second, we also want to be careful that it doesn’t send the message that we should be treating all monoclonal gammopathies. That being said, we think it’s a very important study to explore the notion of where one draws the line between smoldering disease and active disease, and that’s what brings us to the meeting this year where we’ll discuss other studies that are trying to explore that same concept.
As a myeloma community, we’re trying to better define what active myeloma really is versus smoldering myeloma and to follow very closely studies like PETHEMA that are being presented here at this meeting—including a study looking at carfilzomib, lenalidomide, and dexamethasone—not just as therapeutic studies for this high-risk group but to measure markers of bone activity or myeloma activity and even minimal residual disease. Not that, again, people should walk away saying this is how I’m going to treat my smoldering myeloma patient tomorrow but to help us as a community better define that group of patients. I think it’s early yet to make any new changes. I would still tell people that we should wait until people meet the formal CRAB criteria that we discussed for myeloma, but these studies are pointing us in the direction of how we’re going to, in the future, likely treat patients with earlier myeloma.

DR. MENCIA: Based on these trials that are being presented here at ASH, the take-home point—if I’m hearing correctly—is that out in the community right now we should not be doing anything differently than what is currently being done in practice. Is that correct?

DR. MIKHAEL: Yes, I think that is correct. I think right now we don’t treat smoldering multiple myeloma. We don’t have the tools easily accessible to all to make that discrimination between true high-risk smoldering and regular smoldering myeloma patients, but we do anticipate that will come soon. So, I think it should be on people’s radar, but, currently, I completely agree with you. We do not change current practice.

DR. MENCIA: Joseph, let’s turn our focus now to the French study with lenalidomide that is looking at long-term maintenance therapy. What are your thoughts concerning the results of that trial and how it compared to the US trial?

DR. MIKHAEL: It was a very provocative study and one that we’ve been highly anticipating. Individuals watching this will remember that there were two very similarly designed studies: one in the states and one in France randomizing patients to lenalidomide versus placebo as maintenance therapy posttransplant. Thus far, we have seen that both studies were almost identical in prolonging progression-
free survival, but there was not an overall survival signal seen in the French study and there was a small one demonstrated in the US study. Very interesting here, Michele Attal presented the updated data from the French study, which looked longer term at what happened to these patients. The short version is that, even though patients had a prolonged progression-free survival on lenalidomide maintenance, in the long run their outcomes were really no different and in some cases were inferior to those in patients who had been started on placebo. This means that their next progression happened more quickly even though they had been on lenalidomide.

We need longer-term data from this. We need more understanding of the details of all that this study is showing to us. I think it’s starting to raise a bit of a caution flag about saying that we have to now look at patients in the longer term. Although maintenance therapy provides an improvement in the short term for progression-free survival, it’s still unclear whether or not it makes a long-term difference. What that means for practice today is still up in the air. Lenalidomide may and is still considered standard in many settings, particularly in North America. It’s still recommended by various groups, although there is still a split vote on that recommendation. I think that, to be honest, this study is going to make it even a little bit more complicated because people do have concerns about long-term toxicity. People also have concerns about second primary malignancies, so I think it’s going to make us very carefully review whether maintenance therapy in any individual patient is the right thing to do.

We also anticipate the long-term results of the US study because there were some differences between the two, and maybe the US strategy will be different from that of the French study.

DR. MENCIA: Along those lines, to help clarify was the fact that the US study was broken out by the level of risk of the patient and whether this ultimately had any impact on the type of maintenance therapy or whether maintenance therapy should be used or not?

DR. MIKHAEL: That’s a fantastic question and one that I think a lot of us want an answer to. The water is still murky on
that, but I think there is still a sense that patients with higher-risk myeloma are the ones who are going to relapse more quickly after transplant. In these patients it’s more justified to pursue some kind of maintenance therapy—be it with lenalidomide or now as being presented using bortezomib or bortezomib-based regimens for maintenance therapy, especially in the higher-risk patients. Again, there’s a lot of confusing data and sometimes differing data, but I think it goes back to the important point of individualizing therapy for each patient and to not use a simple blanket approach—that everyone receives maintenance therapy—posttransplant. We need to look at those patients who still have a burden of disease after transplant, patients with a higher risk, and patients in whom we are concerned that the progression-free interval is going to be shorter. I think we’re willing to accept some of the challenges and maybe even the risks associated with maintenance therapy, but more is to come.

We’ll be hearing further updates on both of these studies over the coming year, and we’ll probably have a better understanding of the best use of maintenance therapy. For now, I think the take-home message is that lenalidomide maintenance is still an excellent strategy posttransplant, but it’s not likely necessary in all patients.

DR. MENCIA: That’s also a great segue to looking into the future. Here at ASH and from other studies that are going to be upcoming over the next few years, we will get a lot of exciting data on newer agents, newer mechanisms of action, and newer therapeutic targets. What is exciting to you right now Joseph?

DR. MIKHAEL: There are a lot of things that are exciting me about the future of multiple myeloma, and I think that this meeting has been a breakthrough meeting for the myeloma community on a lot of different levels. First, I think that we’re getting better at using the agents that we currently have. We’re fortunate that two agents, pomalidomide and carfilzomib, have recently been approved by the FDA. Although we initially used them, of course, as single agents, we’ve seen a lot of data presented about how they can be combined and furthermore how they can be used at different stages of multiple myeloma. We’re seeing a number of studies being presented using carfilzomib as frontline
therapy—be it combined with lenalidomide, combined with cyclophosphamide, or even combined with melphalan in older patients. So, a number of studies are validating the use of carfilzomib up front.

Similarly, we’re now seeing carfilzomib being used in multiple combinations in relapsed therapy with those agents I’ve mentioned, and carfilzomib and pomalidomide together are demonstrating promise. Furthermore, a number of studies with pomalidomide in combination with other agents are being presented—in combination with cyclophosphamide and in combination with bortezomib and other agents. I think that we are able to use the tools that we have even more effectively to improve patient outcomes for multiple myeloma.

DR. MENCIA: In addition to these agents that you’re talking about and all of the exciting data that’s coming out, are we also looking now at next-generation versions of these products?

DR. MIKHAEL: Absolutely, and I think that this is one of the most exciting things we’ve seen at the meeting this year. We’re very thankful to have these agents, including carfilzomib and pomalidomide, but now we’re beginning to see further generations of these drugs, in particular the proteasome inhibitors. We’ve seen a lot of data presented at this meeting for one drug in particular, which has sometimes been referred to as MLN9708 but has now been given the name ixazomib. This drug is another proteasome inhibitor, much like bortezomib, but it’s given orally. We think this is a tremendous step forward for our patients, because it will allow a more convenient delivery of a class of agents that, until now, always had to be given either intravenously or subcutaneously.

At this meeting we’ve seen ixazomib presented as frontline therapy, relapsed therapy, maintenance therapy, and even as combination therapy. Thus, it really has a broad profile and is a drug that has activity on its own and indeed in combination. There’s another drug called oprozomib, which is an oral version of carfilzomib that is a little bit earlier on in development, but already data are being presented in this meeting of its activity in multiple myeloma and in our cousin disease Waldenstrom.
macroglobulinemia. We’re excited about the fact that this class of drugs, which has been so critical to the care of patients with myeloma, might be developed so that we will be able to provide it to our patients in an oral fashion.

DR. MENCIA: That’s fantastic news. There are also new targets that we’re looking at—monoclonal antibodies for example. What are some of the data showing in this area?

DR. MIKHAEL: Absolutely. I think it’s great to have newer versions of the drugs that we have, because they’re more effective and less toxic, but we need new classes of drugs in myeloma. Perhaps the most exciting are the ones that you mentioned, monoclonal antibodies. Currently, there are three monoclonal antibodies in development against a very well known myeloma target called CD38, which is pretty well universally expressed on all myeloma cells. The first is daratumumab, and it has generated a lot of excitement and even has been given designation at the FDA for further review. It’s not being highlighted as much at this meeting because the data are maturing. The “new kid on the block” for an anti-CD38 molecule is one developed by Sanofi called SAR650984, or SAR for short. I think this is one of the most exciting abstracts being presented here at this meeting, because this agent—even as a single agent in very heavily pretreated patients—has a response rate of greater than 30%. Again, most of us in the community of hematology and oncology are familiar with the concept of monoclonal antibodies, but to be able to introduce it in myeloma patients is very exciting. A third monoclonal antibody, directed against CD38, is much earlier in development and is only being presented here in very early form.

Furthermore, there’s already work underway looking at these agents not only as single agents but in combination with other drugs, so I think that is going to be something we all want to watch very carefully. The other monoclonal antibody is one that’s well known to us, elotuzumab, which is directed against a cell surface marker on the outside of the cell, CS1. Again, at this meeting, we’re still just waiting for data. There’s been completion of a very large study evaluating the efficacy of this drug in combination with lenalidomide and dexamethasone, and we anticipate the results of that study in the new year. I guess, if we’re looking broadly, there are still other compounds that are...
quite exciting in multiple myeloma.

The KSP inhibitor known as ARRY520 is perhaps the other sort of class and agent that has provided a lot of excitement in the myeloma community, and there are a number of abstracts presented here at this meeting regarding this drug. It has a completely different mechanism, and you mentioned from the start—and I think that’s really important—that we really need a different approach to myeloma or an additional approach to myeloma. This is a drug that has been really well tolerated by patients and is already showing quite a bit of activity on its own and is now being combined with a whole host of agents, even including carfilzomib. I think it’s too early for these drugs to be used in clinical practice, but it’s encouraging that there are so many coming down the line, many of which are already showing promise, that we could spend the rest of the day talking about them. They have come out of basic science research and are now being developed to approach myeloma in a different way.

DR. MENCIA: It sounds like we may see a change in how we approach myeloma treatment based on all of the data that we’re starting to see. Let’s bring this back home to the reality of the community practitioner. What do all of these data being presented here at ASH regarding these new agents and the new mechanisms of action mean to them right now?

DR. MIKHAEL: I think, in the short term, it means that we’re using more effectively the tools that we have. The two agents most recently approved by the FDA, carfilzomib and pomalidomide, are drugs that we’re now going to be able to use more effectively in combination and to even use carfilzomib up front. The other agents that we’ve discussed are not going to change practice immediately, but they will give practicing oncologists and hematologists in the community and their patients hope that other options may be available in the near future, perhaps even through clinical trials, but more importantly that may receive FDA approval and become available to patients and that more oral drugs or other combinations may also become available.

It’s really up to us in the myeloma community to use the additional tools in the toolbox to determine the best sequence. As we discussed earlier, who should receive
maintenance therapy and with what, what is the best frontline therapy, and what is the best therapy at relapse? We are really on the cusp of starting to build a better algorithm for myeloma. One other angle that we haven’t really discussed today, which is also not going to immediately change practice but which has come out of this meeting, is a better understanding of the basic science of this disease. You mentioned earlier how we often treat patients differently based on their risk status, so understanding high-risk disease a little bit more, understanding the genetics of the disease using tools like gene expression profiling, or even using more conventional tools like MRI and PET scan are all important. A lot of the studies that are being conducted may not immediately change practice, but we anticipate in the near future that their results will allow the practitioner to differentiate their myeloma patients so that they can determine which groups would be best treated with proteasome inhibitors, IMiDs, monoclonal antibodies, or whatever it is that we have at our disposal.

I know this sounds more complicated, but it’s more hopeful. There aren’t very many diseases in which we’ve doubled, if not even tripled, the average survival of patients in the last decade, but myeloma is one of them and it’s because of the kind of work that we’ve been discussing today.

DR. MENCIA: Thank you very much for your time today Joseph. I think that your conclusion really wraps up well the focus that we should be having in myeloma now and in the next couple of years as more and more information becomes available.