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Hello and welcome to *Managing Myeloma*. My name is Dr. Sagar Lonial, and I am a Professor at the Winship Cancer Institute of Emory University in Atlanta, Georgia. Today, I am introducing a series of interviews highlighting selected sessions at the European School of Haematology 3rd International Conference on Multiple Myeloma that was held earlier this year between October 7th and 9th in Milan, Italy. The purpose of this meeting was to bring together many thought leaders in the context of new treatments and new approaches for myeloma, and try and have important discussions of how to put this important data into clinical context. So, I am going to begin hitting with a few highlights that are going to be described in greater detail during the sessions that you are going to hear and see recorded in the rest of this activity.

So, there were really four big key sessions that were discussed at this meeting, and let's start off with the earliest forms of disease, and that is patients with smoldering or monoclonal gammopathy of unknown significance, also known as MGUS. What we talked at length about in that session was really the importance of the new revised definition of symptomatic myeloma. In that revised definition, we now no longer include just the CRAB criteria—hypercalcemia, renal insufficiency, anemia, and bone disease—we have now added three disease-defining or myeloma-defining criteria. These include an abnormal free light chain ratio of greater than 100, greater than 60% plasma cells in the bone marrow, or greater than one focal lesion as seen by MRI. I think what is really key about these is that you are seeing introduction of biomarkers into the management and risk stratification of patients with smoldering myeloma, and why that is really important is certainly from the perspective of management of bone disease. We know that x-rays alone have really been inadequate to identify patients with bone disease in the context of myeloma, and so now using CAT scans (whether it is low-dose whole-body CAT scans or whether it is MRIs or PET-CTs) these clearly are more effective modalities for trying to understand whether patients have bone disease that would otherwise require treatment, rather than observing a typical patient with smoldering myeloma. The second piece is that we now have treatments that are tolerated well enough that early intervention is certainly a reasonable strategy in the context of a clinical trial. One point that I think is really important to raise at this time is that it remains the standard of care to continue to observe patients with smoldering myeloma whether they fit into the high-risk, intermediate-risk, or low-risk categories that have been defined by the ECOG and the Mayo Clinic group. I think that is really important because there is a question about whether the Spanish randomized trial has changed the current standard of care, and my answer to that question would be at this time in 2016 that is not the case, and you will hear more about this from Dr. Mateos in another segment of this website.

Now, the second area that I think is really important to talk a little bit about was the management of newly diagnosed myeloma. What we have learned about the management of patients with newly diagnosed myeloma is that clearly triplets are better than doublets for fit or younger patients with myeloma. Now, one area that came up of significant interest at this conference was the idea of "What is the definition of transplant eligible?" The reason I bring this up is that in

Europe and in Canada, the definition has typically been younger than age 65, but we have now seen two or three data sets, including data from our own center here at Emory, suggesting that patients over the age of 65 can in fact gain benefit from transplant similar to patients who are younger than 65. So one of the key discussion points at this meeting was that age alone should not be a discriminator between eligible or ineligible for high-dose therapy and transplant. The second is the almost universal acceptance now that an IMiD/proteosome inhibitor combination represents the standard of care for patients with newly diagnosed symptomatic myeloma if they are not frail, and I think that is an important distinction and an important point going forward. Our current standard of approach is to use the RVD-based regimen with lenalidomide, bortezomib, and dexamethasone, but as long as there is an IMiD and a proteosome inhibitor in the combination, you can come up with whatever flavor of IMiD/PI combination you want to use. Those are clearly now superior to bortezomib in combination with cyclophosphamide or doublets using just lenalidomide and dexamethasone.

The third session that I think was really important and worth discussing was the treatment of patients who are elderly, and in my definition are frail. These are patients that are not eligible for high-dose therapy or autologous transplant, and even more importantly are patients that are not really eligible for aggressive three-drug high-dose dexamethasone-based approaches for newly diagnosed myeloma. In these frail patients, the current data supports the use of lenalidomide and dexamethasone as a standard approach. Certainly in the US, the use of oral melphalan has been supplanted by the use of lenalidomide-dexamethasone for these frail older patients. What I think there was great hope and excitement about in the future was the idea that perhaps the addition of monoclonal antibodies — whether they are daratumumab or elotuzumab — may add to the benefit of lenalidomide-dexamethasone for these frail patients without significantly adding toxicity, allowing these older frailer patients to receive triplet-based therapy but with a kinder, gentler triplet-based therapy. There was also some discussion about an RVD “light” which is a modification of bortezomib dosing and schedule that has been presented by the group of Mass General at ASH in the past, and this is certainly being evaluated and looked at as well. What is clear is that for true frail patients, the addition of standard three-drug aggressive regimens does not necessarily improve their outcomes, and so thinking about kinder, gentler ways, such as incorporation of monoclonal antibodies, represents an important step forward for these patients.

Now, the last category that I think was really important and was discussed in great detail was the management of patients in the setting of either early or refractory relapse. I think that there really are a couple of important take-home messages from this. The first is that clearly with the use of carfilzomib (either at standard dose or higher dose) and the use of pomalidomide, we have seen significant improvements in outcomes for patients in the early relapse as well as in the late relapse setting as part of combination therapy. What I think was really quite exciting was seeing updated data on daratumumab in combination with lenalidomide or in combination with bortezomib, the so-called CASTOR or POLLUX trials, that showed the best hazard ratios and progression-free survival we have seen in myeloma trials in the modern era. There was great excitement about the use and ability to incorporate daratumumab in early relapse and again early data suggesting that incorporation in the context of newly diagnosed myeloma might also be very exciting and encouraging as well. The other area that was discussed at length was the role of immune-based therapies. Immune-based therapies in addition to the monoclonal antibodies can include things such as the PD-1 inhibitors like pembrolizumab. At this meeting, Dr. Mateos actually updated her data on pembrolizumab in combination with lenalidomide and dexamethasone. What was really quite striking was the overall 50% response rate from all

patients, but a response rate of about 38% for patients who are resistant to lenalidomide-dexamethasone when pembrolizumab was added to lenalidomide and dexamethasone, suggesting one could overcome lenalidomide resistance through the addition of the PD-1 antibody pembrolizumab. This is an area of extreme excitement in myeloma with the use of both PD-1 and PD-L1 antibodies being tested in the context of newly diagnosed and relapsed/refractory myeloma. I think that these types of approaches will ultimately help us to revolutionize the care of patients with myeloma in all phases of their disease and really does begin to usher in the era of immune-based therapy in myeloma. So as you can see, there was a lot of information covered in the 3 days in addition to some oral abstracts and other information, but this was a really exciting and important conference and I think it highlighted a lot of the rapidly changing standard-of-care approaches for the management of myeloma, not just in the US, but around the world, and how we can incorporate those changes in standard of care to our routine daily practice. So, I look forward to discussing some of these and reviewing these in the upcoming segments that you are going to see. So, thank you very much for viewing this introduction, and we hope you enjoy the meeting highlights.