Sagar Lonial, MD, FACP
Chair and Professor
Department of Hematology and Medical Oncology
Chief Medical Officer
Winship Cancer Institute
Emory University School of Medicine
Atlanta, Georgia

María-Victoria Mateos, MD, PhD
Associate Professor of Medicine
University of Salamanca
Salamanca, Spain

Dr. Sagar Lonial: Hello. I am Dr. Sagar Lonial from the Winship Cancer Institute of Emory University in Atlanta, Georgia, and I would like to welcome you to *Managing Myeloma*. We are here today to talk about highlights from the European School of Haematology (ESH) meeting focused on myeloma that was held in Milan in October of 2016. I am joined today by my colleague Dr. María-Victoria Mateos who is an Associate Professor at the University of Salamanca and Director of the Myeloma Program in the University of Salamanca, and a major thought leader in terms of how we manage both smoldering and MGUS or other precursor plasma cell disorders. Welcome Dr. Mateos.

Dr. María-Victoria Mateos: Hello, Sagar. Thank you for the invitation to be here to discuss the most relevant findings of the European School of Haematology that took place in Milan in October of 2016.

Dr. Sagar Lonial: So, Dr. Mateos, you chaired a session that focused a little bit on not just MGUS and smoldering myeloma, and if you can talk us through a couple of the important take-home clinical messages from first the MGUS session and then we will talk a little bit more about smoldering.

Dr. María-Victoria Mateos: Okay. Thank you again, Sagar, and the session I chaired, as you said, was mainly focused on monoclonal gammopathy and smoldering, and also Elena Zamagni from Bologna in Italy discussed the role of new imaging techniques in the diagnosis and staging of multiple myeloma. Starting with monoclonal gammopathy, the new criteria for the definition of myeloma and plasma cell disorders published at the end of the year 2014 updated the criteria for diagnosis of smoldering and monoclonal gammopathy in myeloma. I would like to start in saying that the criteria for the definition of monoclonal gammopathy has not changed, and in fact, the patient required the presence of a monoclonal component inferior to 3 grams and plasma cell bone marrow infiltration inferior to 10% with no myeloma-defining event. However, what is important to note is that the concept of myeloma-defining event has changed. In addition to the classical CRAB symptomatology, new myeloma-defining events were published in this publication based on the new criteria. These new myeloma-defining events include the presence of serum-free light chain ratio higher than 100, or plasma cell bone marrow infiltration higher than 60%, or presence of two or more focal lesions in MRI. So, I would say that there are no major changes for patients with monoclonal gammopathy. I would say yes to one important take-home message, and that is the problem for patients with monoclonal gammopathy is not only that they can evolve to myeloma, to active disease, but it is important to consider that smoldering myeloma can also evolve to other diseases mainly focused on the role of the monoclonal gammopathy because the monoclonal component to be allocated in different tissues resulting, for example, in amyloidosis or light chain disease deposition or even the role of the monoclonal component with auto antibody activity resulting in cryoglobulinemia, ITP,

hemolytic anemia, or even peripheral neuropathy. Also important is that there are some MGUS associated conditions like infections, osteoporosis, fractures, and venous and arterial thrombosis, that all these entities are also related with small end component percentage in MGUS, and this would be from my point of view the most clear take-home message coming from monoclonal gammopathy.

Dr. Sagar Lonial: So, Dr. Mateos, I think the re-classification of some of the high-risk smoldering as you described into symptomatic myeloma is really an important step forward for the field because it is the first time we have not required symptoms in order to diagnose myeloma, and I think that is an important message, but I think there are many in the community that are asking about the role of genetics or FISH in terms of risk of progression or whether any of those can be used to distinguish smoldering from symptomatic myeloma, and based on available data, what would be your response to that?

Dr. María-Victoria Mateos: Yes, so, you are completely right, and in fact, if we focus now more in smoldering myeloma, I think that the most significant change is that now a group of patients with smoldering has to be considered myeloma because they have an imminent risk of progression to active disease. As I previously said, these biomarkers are not clearly related with symptomatology for assessing the patients because patients continue being asymptomatic, but we know that the presence of plasma cell bone marrow infiltration higher than 60, serum-free light chain ratio higher than 100, or two or more focal lesions are associated with imminent risk of myeloma. What about other new biomarkers as you mentioned, FISH or genetic abnormalities? So, I think that we are now in the process of confirmation of the role of new biomarkers because from my point of view, the future will be to expand more and more the definition of myeloma. What is the problem? The problem is that, as you know, in order for a new biomarker to be considered as a new criteria for the definition of myeloma, it has to predict approximately 70% or 80% of risk of progression to myeloma within the first 2 years after the diagnosis of smoldering myeloma, and in addition, this new biomarker has to validated by at least two independent groups. So, I think that we are now in this process and my feeling is that in the future the definition of myeloma will be expanded more and more because new biomarkers will be added. Concerning, for example, FISH and abnormalities we know that when a patient with smoldering myeloma has deletion 17 or deletion 17p or 4;14 translocation we know that the risk of progression is higher approximately 50% at 2 years. So, this means that this group of patients is at high risk of progression to myeloma, and from my point of view, I think that the research has to be focused a little bit beyond the disease in order to evaluate probably more detailed genetic changes like mutation or other type of genetic abnormalities.

Dr. Sagar Lonial: So, I think it is certainly a very important time as we again review the definitions and criteria for what it means to be each of these subsets of disease. I think that one area that has been overlooked for decades in myeloma has been imaging because we so rarely were able to achieve deep and sustained responses from a biochemical perspective, but with many of the new drugs we have, imaging now has become even more important. So, can you give us a bit of a take-home message from the imaging discussion and how we can use it in our daily practice?

Dr. María-Victoria Mateos: Yes, I feel that the incorporation of the new imaging assessment changes also the diagnostic criteria for myeloma because x-ray and skeletal survey has been the standard imaging assessment for the evaluation of bone disease in patients with multiple

myeloma. The problem is that we know that 30% of bone loss is required in order to detect a new lytic lesion. So, the incorporation of the new imaging assessment and I would say the low-dose CT or even PET-CT, I think that are technically valid for the detection of lytic lesions, but in addition, the sensitivity level is much higher. So, we do not need to lose 30% of bone to detect the lytic lesions, and in line with this, the new criteria for the definition of multiple myeloma bone lytic lesions is not only required by x-ray as it was in the past, but it is possible to evaluate the lytic lesions by PET-CT or just CT. What is also important is that for example, PET-CT is an optimal assessment to evaluate not only the diagnosis of myeloma but also the follow-up, the metabolic response to the different options of therapy. From the classical point of view, we evaluated the response to the treatment according to the end component, and when the end component disappears, we went into the bone marrow to evaluate even the stringent or even the immunophenotypic or the molecular complete response, but what about the disease outside the bone marrow? We did not evaluate it because we did not have any optimal assessment to do this, and now, it seems that with the PET-CT, we can do it and in fact we know that the new criteria for the evaluation of the response of patients with multiple myeloma include now the minimal residual disease activity by imaging using PET-CT. So, I think that the implementation of prospective clinical trials with these new imaging techniques will help us to address several issues, standardize the interpretation of the results, and of course will contribute to optimize the use of these new imaging assessments.

Dr. Sagar Lonial: So, just from a practical perspective as we wrap this up, I think it is really important, would you recommend that patients all have PET-CT done as part of their initial diagnostic workup, and if so, how often would you repeat them as part of the follow-up for patients?

Dr. María-Victoria Mateos: So, I would say that at the moment of diagnosis all patients can have low-dose CT or PET-CT, but from my point of view, I would recommend to always do, if possible, a PET-CT at the moment of diagnosis in order to know in which specific sites the PET is positive or not. If the patient is going to receive an induction therapy followed by transplant, I would consider it relevant to do PET-CT again before autologous stem cell transplantation to know well the response to the induction, but from the general point of view, I would say that when the patient is in complete response from the serological point of view and because in the bone marrow there is not any disease, I think that at this moment it would be of course mandatory to repeat again the imaging assessment in order to confirm even the complete response is only at the bone marrow level or also outside of the bone marrow.

Dr. Sagar Lonial: Thank you very much Dr. Mateos. That has been very helpful, and it was really an exciting session at ESH. So, thank you again for listening to this highlight from the European School of Haematology meeting in Milan in October of 2016. Please go to *ManagingMyeloma.com* to see other updates from this meeting and other meetings, and thank you for your attention.