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Immunotherapy, PROs and Prognostication with PET

Hello, my name is Dr. Sagar Lonial, and I am a Professor at the Winship Cancer Institute of Emory University in Atlanta, Georgia. I am reporting to you live at the ASCO 2016 meeting in Chicago, Illinois, from the *Managing Myeloma* booth. Today, I am going to discuss a few brief highlights on some of the exciting advances in multiple myeloma and review some of the new data revealed here at ASCO in 2016. So, let's start off.

The first abstract I would like to cover is Abstract 8008 which is a phase 1/2 study of ixazomib, pomalidomide, and dexamethasone in relapsed and refractory myeloma, and this was a very early study presented by Amrita Krishnan on behalf of the MMRC, or the Multiple Myeloma Research Consortium, and this is a really interesting concept because it takes two very active and important oral agents, ixazomib, an oral proteosome inhibitor, in combination with the third-generation IMiD pomalidomide, and what we demonstrated was that full doses of both drugs could be given in combination, but more importantly in a relapsed and refractory patient population, the overall response rate in the first 25 patients was 44%, with a clinical benefit rate of over 70%. This really exciting data I think is actually quite important, and it highlights some important issues that will make things easier for patients as they think about convenience and minimum side effects associated with therapy. What was noted was that there were some infections which we know occur in patients with relapsed and refractory myeloma. About 20% of patients appear to have some level of the hematologic toxicity, not unexpected for the combination of a proteasome inhibitor and an IMiD, and again, I think this raises the question about the role of triplet-based therapy in the context of relapsed and refractory myeloma. Very exciting preliminary data, and we look forward to additional patients being treated on this small phase 1/phase 2 trial.

The next abstract I want to talk about is the plenary abstract, and this is the Castor study, which is a randomized phase 3 trial of daratumumab plus bortezomib and dexamethasone versus bortezomib and dexamethasone. And what was really quite striking about this was not only the very high overall response rate, very high complete remission rate, but actually a relative lack of significant safety signals with the addition of the third drug, daratumumab. What I think is really the most impressive part of this abstract is the hazard ratio. This trial had a hazard ratio of 0.39 with a median progression-free survival of 7 months for the group that received bortezomib and dexamethasone, and the addition of daratumumab has not even yet reached the median progression-free survival with a median followup of over 12 months. What this says to me is that daratumumab clearly is an active drug, we know that in the relapsed and refractory setting. But the addition of daratumumab in earlier lines of therapy in the context of the Castor study suggests that daratumumab may in fact be a rituximab for myeloma, that it can be incorporated in many different phases, and in earlier and earlier phases and stages of disease treatment. This I think is significantly a practice-changing abstract.

So, the next abstract I want to talk a little bit about is a meta-analysis, actually from our group, that looked at three drugs versus two drugs in a meta-analysis of all the large randomized phase 3 trials. And there has been brewing a controversy in the myeloma community about whether patients even in the early relapse setting should preferentially be treated with a triplet versus a doublet. I think we have settled this discussion in the context of newly diagnosed myeloma where almost all experts now agree that a triplet is superior to a doublet for patients that can tolerate intensive therapy, and I think we have agreed that an IMiD and proteasome inhibitor (PI) represent the best triplet for newly diagnosed myeloma. What Dr. Nooka and his colleagues did was actually look at all the phase 3 trials that have gotten our drugs approved in the last 12 months and put them together and demonstrated that that hazard ration of progression-free survival clearly favored triplets, with a hazard ratio of 0.674 and an odds ratio of 1.8 for doublets versus triplets in terms of overall response rate. When we begin to look at adverse events, there is no question that triplet-based therapy is associated with more adverse events, typically more diarrhea, fatigue, and thrombocytopenia, but again, the significant benefit in terms of progression-free survival and overall response rate I think really do begin to favor triplets. And given the fact that we have so many new treatment approaches to make, trying to have a significant impact on disease burden, even in the context of early relapse, I think is becoming an important endpoint favoring the use of triplet-based therapy in the context of early relapsed myeloma, and I think this meta-analysis helps us to put that together.

The next abstract I want to talk about is a really important emerging area, and that is the role of the imaging in the management of multiple myeloma. For years, even decades, we have focused mostly on the M-protein or the bone marrow assessment to understand disease status, but we have now identified that even in patients who are MRD negative, whether it is by flow cytometry or by next-generation sequencing, there may be islands of residual disease that remain, and those can only be picked up by more sensitive imaging techniques. In this abstract, they were trying to understand how to use PET scans and predict outcomes based on PET positivity. And this was a very complicated analysis that I think really does call into question the ease with which PET scans can be used in routine clinical practice. What they did was come up with a number of criteria, diffuse versus focal, SUV (standardized uptake value) numbers, SUV versus baseline numbers, and put that into an algorithm that helped to provide some insight about how we can use a PET scan in terms of positivity versus negativity to guide potential therapeutic options. I know that the International Myeloma Working Group is looking at a larger dataset and will in fact very soon have recommendations on how to manage and use imaging in the context of newly diagnosed, relapsed, and assessment of disease response. I think we are going to need larger studies to understand how best to fit PET scans into the larger scheme, but this analysis gets us started down that road, and I think PET scans are being used relatively routinely now by a number of practitioners, and we will soon have guidance on how best to incorporate them into response criteria as well as prognostic criteria over time.

The next abstract I am going to talk about is an update from ELOQUENT-2 study. This was a randomized phase 3 trial of elotuzumab in combination with lenalidomide and dexamethasone versus lenalidomide and dexamethasone. This was a study that I published last year in *The New England Journal of Medicine* in June, and this was actually a really important study because it did lead to the FDA approval of elotuzumab in the 1 to 3 prior lines of therapy group of patients. What we did was we began to go back and look at subsets of patients that may have gained greater benefit from the use of elotuzumab versus lenalidomide and dexamethasone. As you can see from this data, it actually is quite striking that the role of

transplantation time since diagnosis high-risk cytogenetics, there are a number of important subsets that clearly seem to gain significant benefit with median progression-free survival well in excess of the average that we saw in the trial, in some cases almost 27 and 28 months for the elotuzumab/lenalidomide/dexamethasone arm compared to the lenalidomide and dexamethasone control arm. I think what this tells us is that there clearly are subsets of patients who benefit from an immuno-oncology treatment-based approach, and elotuzumab is important not only for directly targeting the myeloma cell but also for activating immune function, particularly NK cells, and activation of immune function may lead to a prolonged tail on the curve as opposed to just a higher overall response rate. And identifying some of these subsets that may be particularly prone to that longer tail on the PFS curve I think is critically important and will help guide us into which patient should preferentially be treated with an elotuzumab/ lenalidomide/dexamethasone approach in the early relapsed multiple myeloma setting.

Now, the last abstract I am going to talk about is an abstract presented by Paul Richardson, and this was an update of an analysis from the PANORAMA-1 trial. What this really sought to do was to look at PROs (patient reported outcomes), using a number of different validated instruments looking at neurotoxicity, disease symptoms, and global health assessment. What Paul did in this analysis was look at the PROs, which were done prospectively in this trial, in both the triplet arm of panobinostat with bortezomib and dexamethasone, and the doublet arm of just bortezomib and dexamethasone. And what Paul clearly showed was that among the patients that did gain significant benefit, there was not a significant reduction in patient-reported quality of life or other potential outcomes. There obviously was some diminution usually earlier on in the treatment phase, but those patients that seemed to gain the most benefit from the use of panobinostat did not have significant reductions in quality of life over the long term associated with the study. Additionally, the patients were able to have a long treatment-free interval on this, which may have further contributed to improvements in quality of life and improvements in patient-reported outcomes as well, and I think this is an important study as we try to best understand who is best suited for use in treatment with panobinostat. In my view, that is probably not an early relapse patient population, that may be a later patient population, and combinations with drugs such as ixazomib or carfilzomib may be better partners than the intravenous bortezomib that we saw in the PANORAMA1 clinical trial overall.

So, in general, I think it has been a great meeting. There are lots of very interesting data, some practice-changing data as we suggested as well, and I would like to thank you for joining me in this activity. Please stay tuned for more information and resources available at *ManagingMyeloma.com.*