**EHA Highlights from Paul G. Richardson, MD**

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Welcome to *Managing Myeloma*. My name is Dr. Paul Richardson, and I am the Clinical Program Leader and Director of Clinical Research at the Jerome Lipper Multiple Myeloma Center here at Dana-Farber Cancer Institute in Boston, Massachusetts. I also serve as the R.J. Corman Professor of Medicine at Harvard Medical School. It is truly my pleasure to be with you today, and I will be reviewing three abstracts that were presented at the European Hematology Association 2018 Annual Congress in Stockholm. First, I will review the results from the phase 2 ELOQUENT-3 study, looking at the activity of elotuzumab combined with pomalidomide and dexamethasone, compared to pomalidomide and dexamethasone alone in relapsed/refractory multiple myeloma. I will then be discussing the OPTIMISMM phase 3 trial in which we studied the combination of pomalidomide, bortezomib, and low-dose dexamethasone compared to bortezomib and dexamethasone in relapsed/refractory myeloma. Finally, I will be reviewing some very promising data regarding a combination of isatuximab plus pomalidomide and dexamethasone as part of a phase 1b study in relapsed/refractory multiple myeloma.

First, I will review the results from the phase 2 ELOQUENT-3 study which examined the role of elotuzumab plus pomalidomide and dexamethasone compared to pomalidomide and dexamethasone in relapsed/refractory myeloma. As everyone in the audience is aware, while we have made great progress in the treatment of relapsed/refractory myeloma, treatment choices remain very challenging, particularly once patients have had one or two, or even three or more, prior lines of therapy. This study, in a randomized prospective fashion, sought to evaluate patients who had to have had at least two prior lines of treatment. In the context of that, they had to have progressive refractory disease that is refractory either to a PI and an IMiD combined or either a PI or IMiD alone, but most importantly, they had to have had prior lenalidomide but could not have had prior pomalidomide. Most certainly they could have had prior proteasome inhibitors, and so this population of patients were heavily pre-treated. In that context, pomalidomide and dexamethasone was given in a one-to-one fashion to the control arm at the usual dose and schedule (4 mg three weeks on and one week off, and dexamethasone 40 mg a week if the patient was under the age of 75, and 20 mg if the patient was aged over 75). This was compared to the combination of elotuzumab, pomalidomide, and dexamethasone, where the pomalidomide and dexamethasone was given in the traditional fashion that I just described. The elotuzumab was given at 10 mg/kg once a week for two months and then after that at 20 mg/kg every four weeks. This represented an important step for patients, because this was a very convenient schedule when it

came to the monthly approach. This obviously builds on the success that we have seen with elotuzumab combined with lenalidomide and dexamethasone, and exploits the mechanism of action that we think is so important with elotuzumab, which is this targeting of SLAMF7 in this true immunomodulatory approach that appears to be enhanced by immunomodulatory treatments. By that I mean, particularly the activity of natural killer cells for which we believe pomalidomide in particular may be an IMiD of choice.

One-hundred and seventeen patients were enrolled in this multicenter international trial, 60 patients were assigned to elotuzumab, pomalidomide, and dexamethasone, and 57 to the control arm. The results were particularly interesting. While the combination of elotuzumab, pomalidomide, and dexamethasone was generally well-tolerated and the incidence of infections between both arms were very similar, the primary endpoint of the study – progression-free survival (PFS) – was strikingly favorable for the three drugs compared to the two. Specifically, the PFS for pomalidomide and dexamethasone was 4.7 months, much as expected based upon previous data in the relapsed/refractory population; but encouragingly, an almost six-month gain was seen for the three drugs, with a median PFS at the time of this analysis of 10.3 months. The hazard ratio for that was particularly favorable at 0.54, and this was obviously highly statistically significant. Now when one looks at the response rates, and this, too, was commensurate with clinical benefit, with the response rates overall being approximately 55% for the elotuzumab, pomalidomide, and dexamethasone combination compared to the Pd alone where the response rate for that group was 26%. In that same context, the very good partial response (VGPR) rate was higher for the three drugs compared to the two. Basically, with a VGPR rate of 20% for elo-Pd compared to 9% for the two drugs alone. Now as I mentioned, the side-effect profile was generally favorable for both arms, and most importantly, the rates of infection between both groups for all grades were exactly the same.

In conclusion, in this first randomized trial of elotuzumab, pomalidomide, and dexamethasone compared to pomalidomide and dexamethasone, we see a meaningful and significant reduction in the risk of progression or death compared to control for this combination approach. Very importantly, we have a number of patients who remain on the three-drug combination going forward at the time of our cutoff analysis, and this suggests that survival data in terms of longer follow-up will be important to know. Furthermore, the safety profile critically appeared to be very similar for both arms, and I think this is encouraging. These data overall suggest that elo, pomalidomide, and dexamethasone may be an important new treatment option for our patients with relapsed/refractory myeloma and, in particular, for those patients in whom lenalidomide has failed them and they have had prior proteasome inhibition. It may be looking to the future as we think about the mechanisms underlying this and importantly the effects on natural killer cells that we believe elotuzumab has as well as pomalidomide, that this is an important option for us as treating physicians for our patients when prior therapies have failed them. In that regard, there may be a role to consider this combination or combinations like it, for example, when other monoclonal antibody therapies have exhausted their benefit. Going forward, we look forward to more studies into this

combination approach in this setting, as well as the opportunity to bring it arguably earlier into our therapeutic armamentarium.

Next, I would like to discuss the results of the OPTIMISMM phase 3 trial in which we evaluated pomalidomide, bortezomib, and low-dose dexamethasone compared to bortezomib and dexamethasone in patients who have received at least one to three prior lines of therapy. All patients had to not only have been lenalidomide-exposed but also in the vast majority LEN-refractory. It was my privilege to present this on behalf of a global network of investigators. It is the largest phase 3 trial of its kind performed in this unique population which is becoming more and more important; specifically, those patients who have received prior lenalidomide, are on lenalidomide-based therapy and are progressing on the lenalidomide therapy. As lenalidomide establishes itself as an upfront regimen and as part of maintenance, it is therefore all the more important that we now know what our best options are when lenalidomide treatment fails our patients. With that in mind, this was a multicenter international trial in which a total of 559 patients were enrolled; 281 patients received the three-drug combination of pomalidomide, bortezomib, and dexamethasone, compared to 278 patients who received the control therapy, bortezomib and dexamethasone. The regimens were very well-balanced in terms of duration and dose intensity. Bortezomib and dexamethasone for the control patients was given according to the classical schedule but then continued as part of the maintenance approach, so there was no fixed duration of therapy between bortezomib and dexamethasone. Similarly, for pomalidomide, bortezomib, and dexamethasone, the classical bortezomib and dexamethasone schedule was followed, with the pomalidomide given two weeks on and one week off. Again, treatment was continuous after initial treatment had been well-tolerated and had been shown to be active, patients could continue on treatment thereafter. With that in mind, the median age of the patients was about 68 years for both arms, so these were very well-balanced. As for other features, not least of which all patients have to have received prior lenalidomide and, in fact, 70% were refractory in both arms. Most importantly, a similar proportion of patients have received prior bortezomib, but critically, they were not bortezomib refractory in the context of their last treatment to the therapeutic dosing schedule as applied. In terms of the median number of lines treatment, that was actually two. In that same context, we were able to show that the combination of the three drugs significantly outperformed the two drugs in terms of the primary endpoint, which was progression-free survival. We showed that the median progression-free survival for the three drugs was 11.2 months compared to 7.1 months for the combination of the two drugs, bortezomib and dexamethasone. This was an early look and for the whole population; the hazard ratio for this was 0.61. The overall response rate was 82% for the three drugs and 50% for the two drugs. The VGPR or better was 53% for the three-drug combination versus just 18% for the two-drug combination, showing a correlation between clinical benefit in the form of PFS and also quality of response in this relapsed/refractory population. Very importantly, let’s drill down to the one prior treatment group, those patients who had one line of therapy; typically lenalidomide plus a proteasome inhibitor and dexamethasone, followed then by either further intensification with transplant and then some form of continuous treatment

thereafter, typically lenalidomide with or without other agents as clinically appropriate. If you looked at this one prior treatment group, the results were quite striking. What we showed is that the three-drug combination of pomalidomide, bortezomib, and dexamethasone generated a median progression-free survival of approximately 21 months compared to approximately 12 months for the bortezomib and dexamethasone. This represented in itself an approximate 10-month increase compared to control, and the hazard ratio for this group is particularly favorable at 0.54. If we look at the overall response rate in this group, that was 90% for the three-drug combination compared to 55% for the two drugs. If you look at the VGPR rates or better, it was 61% for the three drugs compared to just 23% for the two drugs. This is clear evidence of clinical benefit as reflected by progression-free survival and also the correlative which was the quality of response.

In terms of tolerability, this was particularly favorable. We were able to show that the addition of pomalidomide to the bortezomib and dexamethasone backbone did not result in excess toxicity. The treatment-emergent adverse events proved manageable and very much in keeping with what we have typically seen for pomalidomide and bortezomib combined in other settings. Overall, the conclusions of the OPTIMISMM study to date have been that this three-drug combination clearly shows clinically significant and meaningful benefit compared to the two-drug combination in this particularly important population of lenalidomide-exposed and lenalidomide-refractory patients. It therefore provides an important platform from which we can build. This could be not only in the context of a three-drug combination but also with a rational combination such as other monoclonal antibodies as to how they may be best positioned to be combined with this three-drug platform. I think this bodes very well for further optimizing salvage regimens in this particularly important subgroup of patients.

Finally, I will review a phase 1b study of isatuximab plus pomalidomide and dexamethasone in relapsed/refractory multiple myeloma that was presented by my colleague Dr. Joe Mikhael as an oral session at the EHA Meeting in Stockholm. This study was a phase 1 effort to evaluate several dose levels of isatuximab combined with pomalidomide and dexamethasone in relapsed/refractory myeloma. Given the remarkable success of daratumumab as a monoclonal antibody in relapsed/refractory disease and its rapid development into the upfront setting, isatuximab provides us with another CD38 targeting antibody that may have some important advantages compared to other monoclonal antibodies in this space. In particular, isatuximab has clinical benefits in terms of convenience of administration; it is administered weekly for the first month and then every two weeks thereafter. Scientifically though, there may be some subtle but important differences in the way it works. In particular, its effects on the apoptotic pathway in myeloma may be quite strong and, in that regard, it does not appear to be so complement activating as is, for example, daratumumab. That may mean that the rates of infusion reactions are perhaps a little lower, and it means that we are able to infuse isatuximab more quickly by the intravenous route than is typically the case for daratumumab when it’s given intravenously. With that in mind, this study sought to explore the combination of

three drugs and in an exquisitely vulnerable population, ie, patients with relapsed/refractory multiple myeloma in whom not only had lenalidomide and a proteasome inhibitor failed, but also other lines of treatment had similarly run out of benefit. In this study of approximately 45 patients with a median of three prior lines of treatment (including IMiDs, proteasome inhibitors and other drugs), we evaluated several dose levels of isatuximab in combination with the classical pomalidomide backbone of 4 mg three weeks on, one week off and dexamethasone partnered accordingly.

We examined three dose levels for isatuximab: 5 mg/kg, 10 mg/kg and 20 mg/kg, and while all three dose levels were well-tolerated and all showed activity, 10 mg/kg was chosen for our dose expansion and taking forward into phase 2 and 3 evaluation.

In short, what we were able to demonstrate with this study is not only that the rates of infusion reactions were very low and that generally the combination was well-tolerated, but encouragingly, response rates in this particularly vulnerable and sick population were quite encouraging. Specifically in that regard, the overall response rate was 62%. Interestingly, in the patients with high-risk cytogenetics, it was approximately 35%, and this benefit was consistent whether the patients were IMiD-refractory, PI-refractory, or otherwise. Excitingly, we also saw that 30% of patients achieved a very good partial response or better, including two complete responses and one stringent complete response. The median time to first response was approximately one month. The median duration of response was approximately 19 months. That is particularly important, because what it meant was that the median progression-free survival overall is almost 18 months at 17.6 months. Very interestingly, we were also able to look at isatuximab pharmacokinetics as part of this study, and we were able to show that it was unaffected by the co-administration of the pomalidomide and dexamethasone. These final results confirm the promising clinical activity and manageable safety profile of isatuximab in combination with pomalidomide and dexamethasone in heavily pretreated relapsed/refractory myeloma patients. A phase 3 confirmatory trial is ongoing and has completed enrollment. Analysis is eagerly awaited, but we are hoping for results if not later this year, certainly early next year.

In summary, these three oral presentations at the 2018 Annual Congress for EHA in Stockholm were very informative for the management of relapsed/refractory myeloma. First, we were able to show that combining pomalidomide and dexamethasone with elotuzumab was remarkably active in a very vulnerable population of relapsed/refractory myeloma patients, with promising progression-free survival benefits seen and excellent tolerability. We were also able to show that the combination of pomalidomide, dexamethasone, and bortezomib in relapsed/refractory disease was particularly effective; especially in first relapse after lenalidomide failure and, in particular, in lenalidomide-refractory patients. Very strikingly, in the first relapse group of patients, not only was the PFS overall approximately 21 months, but in the lenalidomide-refractory group of patients in that first line, it was also very impressive at 17.5 months. This clearly shows that this platform is one that in principle is validated in the phase 3 setting going forward. This is

important for US practitioners, but I think it has importance outside of the US as well when one considers how the availability of proteasome inhibitors in different settings may limit some of the choices that some of our non-US caregivers have available to them. Finally, the combination of isatuximab plus pomalidomide and dexamethasone in relapsed/refractory myeloma shows really promising activity for another CD38 targeting monoclonal antibody. This builds upon the success of daratumumab and shows here, with some meaningful differences in both administration, time spent, and so on, that this particular antibody in combination with pomalidomide and dexamethasone will hopefully provide a very exciting new platform of treatment for relapsed/refractory patients.

**Abstracts**

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