Managing Myeloma

Future Treatments in RRMM: Isatuximab and Melflufen

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Welcome to *Managing Myeloma*. My name is Dr. Paul Richardson and I am live here at the ASH Annual Meeting in Atlanta Georgia. Today, I will be reviewing the results of two important phase 2 studies with you. The first review will be the updated results from a phase 1B/2 study of isatuximab plus pomalidomide and dexamethasone in relapsed/refractory myeloma. The second is the first report on survival and progression-free survival in a phase 2 study of melflufen combined with dexamethasone in advanced relapsed/refractory disease.

Let's start first with the results from the phase 1B/2 study of isatuximab plus pomalidomide and dexamethasone. Isatuximab, just like daratumumab, targets CD38, but importantly, it has a variety of different properties. Most importantly, it can be infused over a relatively short period of time, and once the weekly administration is complete in the first month, it can then be given every two weeks. In terms of its activity, one of the most interesting aspects of its pathway is it is particularly potent in targeting the apoptotic mechanism that we think is so important for CD38 antibody-targeting treatment. In the context of this study, we tried to combine isatuximab with pomalidomide and dexamethasone using a phase 1 design to appropriately explore a dose escalation with isatuximab. This was done, and we were able to define a maximum tolerated dose of 10 mg/kg; pomalidomide was administered at 4 mg, three weeks on and one week off. The primary and secondary objectives of this study were basically safety, and the secondary objectives were to look at activity. What we found, remarkably, was a high overall response rate, approximately 65%, and in terms of follow-up, these responses were durable. What was really important to note was that in terms of the next steps with this study, we have an ongoing phase 3 trial that is rapidly accruing, comparing pomalidomide/dexamethasone with or without isatuximab. I think what is so exciting about this combination is not only was it well-tolerated and highly active, but it clearly was active in high-risk disease as well. In terms of community practitioners, the key points to take away from this study are that we have another CD38 targeting antibody that has a favorable infusion schedule, an excellent tolerability profile recognizing that chest infections and counts can be a challenge (but we see that with daratumumab as well), and very interestingly, the infusion reactions are limited and minimal. In that context, I think it provides us potentially with an important new advance for our patients.

Moving on to the next study, this is the first report on overall survival and progression-free survival in a recently completed phase 2A study of melflufen and dexamethasone in advanced relapsed/refractory myeloma. Melflufen is a fascinating peptidase potentiated molecule that is a derivative of melphalan but has critical differences. What is most important is that its uptake into myeloma onto the tumor cells is preferentially higher than it is to surrounding tissue, making it an ideal targeted novel cytotoxic. In this context it is also highly active when combined with dexamethasone. In terms of treatment-emergent adverse events with this drug, what we see is what we would expect, which is predominately myelosuppression; however, it is generally very manageable. What is very interesting is there is minimal, if any, mucositis from it, and at the same time it is generally otherwise very well-tolerated. What we saw in this trial, which was a large

multicenter effort, was a remarkable response signal. By classic intent-to-treat analysis, the overall response rate was around 30%. If you look at the protocol-treated patients, as per protocol, the response rate was substantially higher. What was also very interesting was that these proved durable. If you look at the per-protocol treated patients, including those achieving minimal response or better, the clinical benefit rate was remarkable at around 60%. What is also very important is that the progression-free survival was particularly impressive at around 6 months. Particularly striking has been the overall survival data where the median currently sits at 20 months, suggesting this platform is a very important next-step in the treatment of relapsed/refractory myeloma. To this end, there are a number of important trials ongoing. One is called the OCEAN study, which is a randomized prospective comparison of melflufen and dexamethasone compared to pomalidomide and dexamethasone in relapsed/refractory disease. There is a companion trial, the so-called HORIZON study, which is looking at the use of melflufen and dexamethasone in a single-arm phase 2 experience in patients of unmet medical need. In terms of challenges going forward, we are looking forward to partnering melflufen with other novel drugs to make it that much more potent in the context of triplets and quadruplets. In terms of our community-based practice and where this might land, this might be a very important cytotoxic that we will have that is relatively targeted and well-tolerated to help salvage patients who have become resistant to either proteasome inhibitors, immunomodulators, antibodies, or both. Thank you very much for viewing this activity and we do hope the discussion and the data have been both informative and helpful. Thank you.

References:

Richardson PG, Mikhael J, Usmani SZ, et al. Updated Results from a Phase Ib Study of Isatuximab Plus Pomalidomide (Pom) and Dexamethasone (dex) in Relapsed/Refractory Multiple Myeloma (RRMM). *Blood*. 2017;130. Abstract1887.

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