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Translocation 11;14 and High BCL2 Expression Are Predictive Biomarkers of Response to Venetoclax in Combination with Bortezomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma: Biomarker Analyses from the Phase 3 BELLINI Study

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Welcome to *Managing Myeloma*. I'm Dr. Shaji Kumar and I'm live at the 61st ASH conference in Orlando, Florida. Today I will be reviewing the results of the study titled, "Translocation 11;14 and High BCL2 Expression Are Predictive Biomarkers of Response to Venetoclax in Combination with Bortezomib and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma: Biomarker Analyses from the Phase 3 BELLINI Study."

Venetoclax has been shown to be effective in myeloma, particularly in patients with t(11;14) in single arm studies, as well as in combination with bortezomib in the context of relapsed myeloma. As a single agent in patients with t(11;14), you can observe up to 40% response rate in the setting of relapsed disease and this was observed in the context of patients with multiple prior lines of therapy with the median of five previous lines. When you add dexamethasone to venetoclax, this response rate goes up to almost 65% in patients with relapsed disease who also had the t(11;14). When you combine venetoclax with bortezomib, you see responses upwards of 90% in patients who are naïve to bortezomib or have not previously been exposed to this drug, and also have had one to three prior lines of therapy.

Based on these observations, a phase 3 trial called BELLINI was designed that randomized patients with one to three prior lines of therapy and relapsed/refractory myeloma who are not refractory to bortezomib to receive either bortezomib and dexamethasone along with placebo or venetoclax. The primary goal of this phase 3 trial was to see if additional venetoclax would improve the progression-free survival. The results of the BELLINI study that was initially presented earlier this year and then updated at the current ASH meeting demonstrates that addition of venetoclax to bortezomib and dexamethasone significantly improved the progression-free survival, almost two years versus one year with and without venetoclax. However, it was observed that patients treated with venetoclax in combination with bortezomib and dexamethasone had a higher mortality rate compared to the patients receiving placebo in combination with bortezomib and dexamethasone. Based on this finding, additional studies were performed on the samples from patients enrolled in the clinical trial to get a better understanding of the basis of these findings. Of the 291 patients who were enrolled on the trial, 194 were randomized to receive venetoclax in combination with bortezomib and dexamethasone, and 97 patients received placebo, a 2:1 randomization. Amongst these patients, almost 61 of these patients could be evaluated using immunohistochemistry to assess the degree of expression of BCL2 protein in the myeloma cells. Nearly 88% of these patients

also were assessable using quantitative PCR to look at the expression of BCL2 in the myeloma cells, and 90% of the patients also had FISH testing available that allowed us to determine who had the t(11;14). A broad range of BCL2 gene expression was observed and this did correlate very strongly with the protein expression as well.

As expected and has been described before, t(11;14) myeloma had the highest BCL2 expression, both by immunohistochemistry as well as by the quantitative PCR. However, it was important to note that the high BCL2 expression was not limited to the t(11;14) subgroup, but also nearly another 30% of these patients also had a high expression of BCL2 based on the quantitative PCR.

A variety of statistical tools were used to estimate the threshold value for BCL2 expression by quantitative PCR for the subsequent analysis to correlate this with the outcomes of the study. What was observed was that the biomarker subgroups with the greatest progression-free survival improvement were those with the t(11;14) and those with a high BCL2 expression by PCR.

A variety of additional analysis was done to better understand how these different subgroups performed, both in terms of progression-free survival as well as the overall survival. As was seen before, venetoclax did lead to a higher overall response rate, better VGPR, and a better CR rate compared to placebo for the overall patient group.

When you look at the patients with the t(11;14) or a high BCL2 expression, the median progression-free survival was not reached in the venetoclax arm compared to 9.9 months in the placebo arm, translating to a hazard ratio of 0.26. It was important to note that the MRD negativity rate was also significantly higher for the t(11;14) or the high BCL2 patients who are receiving the venetoclax compared to the placebo arms. What was really of interest was that the median overall survival, even though it was not reached in either arm, it was very similar for venetoclax and the placebo in patients who were either t(11;14) positive or had high BCL2 expression. In contrast, what we found was that the t(11;14)-negative patients or those with a low BCL2 expression, the overall survival was in favor of placebo, again, giving us a better sense of what really happened in the BELLINI trial.

When you look at these individual subgroups, what was clear was that the patients with t(11;14) clearly had a better progression-free survival and no deleterious effect on the overall survival. When you look at the BCL2 high patients who are not t(11;14), we had a similar finding in the sense that the progression-free survival was better with the venetoclax and the overall survival was quite comparable. In contrast, when you look at the patients who are t(11;14), negative and low BCL2, the progression-free survival was not in favor of venetoclax, suggesting that this might be a good biomarker-based approach for treating patients with venetoclax-based combinations.

The takeaway point from this study is that this now really opens up the opportunity for us to do a biomarker-based approach in myeloma. So, clearly, if you have a t(11;14) or if you have high expression of BCL2 by PCR, these patients are likely to benefit from venetoclax, at least used in combination with bortezomib as was done in the BELLINI trial. Whether these findings apply across the board, including other combinations like the daratumumab and the carfilzomib combinations that have been studied, is yet unknown. We know that when you use the venetoclax alone or in combination with dexamethasone, we do clearly see that the t(11;14) patients benefit. What is unknown is that whether the high BCL2 expressing patients also

benefit in a similar fashion with single-agent venetoclax or the combination. These findings cannot yet be translated into the practice today since venetoclax is still not approved for use in myeloma. Hopefully, with the ongoing clinical trials, we will be able to make this drug available for patients in the future, along with a biomarker that can be used to decide who benefits from the use of this particular drug, both in the newly diagnosed setting and in the relapsed setting, as well as other plasma cell disorders like amyloidosis and plasma cell leukemia where the prevalence of t(11;14) is fairly high.

Thank you for your attention.