Managing Myeloma

Abstract 1888

Updated Analysis of BELLINI, a Phase 3 Study of Venetoclax or Placebo in Combination with Bortezomib and Dexamethasone, in Patients with Relapsed/ Refractory Multiple Myeloma

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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, "Updated Analysis of BELLINI, a Phase 3 Study of Venetoclax or Placebo in Combination with Bortezomib and Dexamethasone, in Patients with Relapsed/Refractory Multiple Myeloma."

Venetoclax is a small molecule inhibitor of BCL2 protein, which is one of the major anti-apoptotic proteins in the cell. BCL2 plays an important role in the survival of a variety of different tumor cells and in myeloma. Also, it is believed to play an important role in resistance to various therapies as well as survival of the myeloma cells. Preclinical studies have shown that use of venetoclax can inhibit the BCL2 and lead to myeloma cell death. Additional studies had subsequently been done, which revealed that when you combine venetoclax with dexamethasone there is a phenomenon that's called BCL2 priming, which is because of all the beam shifting to BCL2, thus making the cell more susceptible to the inhibition from venetoclax. Preclinical studies have also shown that addition of bortezomib to venetoclax can lead to simultaneous inhibition of MCL-1 leading to significant synergy for the combination of bortezomib and venetoclax. Based on this preclinical work, early phase 1 studies have demonstrated that venetoclax alone can lead to about 40% response rate in patients with t(11;14). With the addition of dexamethasone, this would go up to almost 65% and, in combination with bortezomib in patients who have previously never been exposed to bortezomib, the combination can lead to response rate of upwards of 90% in patients with 1 to 3 prior lines of therapy.

Based on all these initial study results, a phase 3 trial was designed which randomized patients with 1 to 3 prior lines of therapy in a 2:1 fashion to bortezomib and dexamethasone in combination with placebo or venetoclax. Overall, 291 patients, the median age of 66 years were randomized. Nearly half of the patients received one prior line of therapy, and the other half had two to three lines of prior therapy. Nearly 60% of these patients had previous stem cell transplant, two-thirds of the patients had been exposed to a proteasome inhibitor or an immunomodulatory drug, and almost 40% had both these drugs.

The initial results of the BELLINI trial presented earlier this year at the European Hematology Association had demonstrated a progression-free survival of 22.4 months for venetoclax versus 11.5 months for placebo, with a hazard ratio of 0.63 that was significant, allowing this study to meet its primary endpoint. However, at that time, it was also noted that the patients on the

venetoclax arm had an inferior survival primarily related to deaths due to infections that was seen early on after start of therapy.

At the current meeting, an updated analysis of the trial with the data cut off of March 18th is being presented with a confirmation of the previous results, again showing a near doubling of the progression-free survival with the addition of venetoclax to bortezomib and dexamethasone compared to placebo. This correlated well with a significantly higher overall response rate for venetoclax compared to placebo, a nearly 84% response rate versus 70%, and also deeper responses as indicated by 61% VGPR rate compared to 40% for placebo. MRD testing was also done by next-generation sequencing and was found to be present in about 13% of the venetoclax-treated patients compared to just 1% in the bortezomib and dexamethasone. The median duration of response was nearly twice as long for venetoclax at almost two years compared to a year for placebo. And when you look at the overall survival, the median overall survival was not reached in either arm, but continued to favor the placebo with the hazard ratio of 1.5. Now, this is clearly a more narrowing of the curve than what was reported at the initial analysis. Overall, there have been 70 deaths in the clinical trial, 26% in the venetoclax arm compared to 20% in the placebo arm.

Based on the initial data suggesting that the activity of venetoclax is primarily seen in the t(11;14) patients when used as a single agent, additional subgroup analysis that were preplanned showed that patients with the t(11;14) had a progression-free survival that was not reached with venetoclax compared to just 9.3 months for the placebo, translating to a hazard ratio of 0.1. In contrast, when you look at the patients without the t(11;14), the median progression-free survival for venetoclax was 22.4 months compared to 10.7 months for placebo, consistent with the results seen with the overall study, and when you look at the median overall survival, it was not reached for either arm, and the hazard ratio was more in favor of Ven in the t(11;14) patients compared to placebo, whereas it was in the opposite direction in the t(11;14)-negative patients.

In addition, we also looked at the low BCL2 expressing myeloma. So, what was found was that if the BCL2 expression in the myeloma cells were low, and if they also had high-risk cytogenetics, this was associated with a significantly decreased progression-free survival and overall survival with the use of venetoclax arm. Particularly in the high-risk cytogenetics, there was no improvement in the progression-free survival, and the overall survival favored the placebo arm.

As part of the original plan, the impact of high-risk cytogenetics as well as the BCL2 expression was also examined in the study. In the patients with the low expression of BCL2 by immunohistochemistry, the progression-free survival was only 11.7 months for venetoclax compared to 17 months for placebo, and the median overall survival was 21 months for the venetoclax arm versus not reached, suggesting that the patients with low expression of BCL2 on the myeloma cells actually do not benefit and, in fact, may be harmed by the use of venetoclax in combination. A similar finding was also seen in patients with high-risk cytogenetics, particularly the t(4;14) and these patients appear to have a decreased overall survival with comparable median progression-free survival with or without the interventional arm.

Overall, when you look at the safety data from the clinical trials, the GI toxicity was the most common, and especially diarrhea and nausea seem to be increased with the use of venetoclax.

Hematological toxicity was more commonly seen with the venetoclax-treated patients, particularly neutropenia, which are seen in twice as many patients as the placebo. And this is particularly true for the grade 3 and 4 neutropenia. The rates of serious adverse events as well as serious infections were comparable between the two arms. There were 69 deaths in the safety population. In the venetoclax arm, 14 of these deaths were treatment related or treatment emergent, suggesting that this happened within 30 days of discontinuation. Thirty-six of the deaths were considered to be non-treatment emergent, meaning this happened beyond 30 days after discontinuing the treatment. In the placebo arm, only one was considered to be treatment emergent and 18 were non-treatment emergent. And these findings are consistent with what was originally reported with majority of the deaths seen in the venetoclax arm happening early on within the first six months after starting therapy, and primarily being related to infection, particularly in the context of disease progression.

The findings from this study are relevant because it clearly demonstrates the efficacy of venetoclax in patients with multiple myeloma. What we have found is that the benefit appears to be limited to these patients with t(11;14) or BCL2 high expression, a finding that is comparable to what was seen with a single agent and also the studies which looked at venetoclax in combination with dexamethasone. Currently, the results of the BELLINI trial will not be used for obtaining a regulatory approval for this drug, but the ongoing phase 3 trials that are looking at the role of venetoclax in combination with dexamethasone in the t(11;14) patients will hopefully lead to eventual approval of this drug and the ability for the clinicians to use the drug in the clinic for patients, particularly those who are t(11;14) positive or high BCL2 expressors, where we believe that the maximum efficacy of this drug would be observed.

Thank you for your attention.