Immune Checkpoint Approaches in MDS: Data from the Phase 2 Trial of Nivolumab/ Azacitidine vs Ipilimumab/Azacitidine

Naval Daver, MD
Assistant Professor
Department of Leukemia
The University of Texas MD Anderson Cancer Center
Houston, Texas

Welcome to *Managing MDS*. My name is Dr. Naval Daver, and I am an Assistant Professor in the Department of Leukemia at the University of Texas MD Anderson Cancer Center in Houston, Texas. Today, I will be reviewing the phase 2 study of nivolumab or ipilimumab with azacitidine in patients with previously treated or untreated MDS. This was a study that we performed in patients with myelodysplastic syndrome. This was one of the first studies to evaluate immune checkpoint treatment in patients with MDS. In parallel, there were studies ongoing with other PD1 inhibitors such as pembrolizumab, or PDL1 inhibitors such as durvalumab. We developed the study to be a very broad study looking at multiple subsets of MDS, including frontline high-risk MDS patients who would receive either azacitidine with nivolumab; or azacitidine with ipilimumab; or azacitidine with nivolumab and ipilimumab. These were three nonrandomized parallel and sequential cohorts. We also had patients who had post hypomethylating agent failure. These are people who had 4 to 6 cycles of azacitidine or decitabine and then progressed. These patients would again receive either nivolumab alone in the first cohort; or ipilimumab alone in the second cohort; or eventually, once we showed the safety and efficacy of the single agents, the combination of nivolumab and ipilimumab. We presented the initial data at ASH, this was presented by the PI of the study Dr. Guillermo Garcia-Manero. At this EHA meeting, we have an update of the study where we are focusing on the frontline groups. What we see is in the frontline setting, the combination of azacitidine-nivolumab is producing a response rate of about 80% (when the responses are looked at by the IWG criteria looking at CR, CRi hematological improvement). Now, this is about double the response rate you would get with azacitidine alone in a similar high-risk frontline MDS. The azacitidine and ipilimumab combination has a response rate of about 55% to 60%, which is also better than azacitidine alone (as has been shown in our institution in other three phase 3 studies in high-risk MDS), but was lower than the azacitidine-nivolumab.

The regimen was very well-tolerated. We did see immune toxicities, but these were manageable with early evaluation, recognition, and treating with steroids. In most cases, immune toxicities resolve within 48 to 72 hours of steroids. We were able to taper the steroids within about 12 to 14 days, which is a quicker taper than is usually

done in solid tumors. Most of these people actually stayed on study; we had less than 5% discontinuation due to immune-mediated toxicities when these were appropriately managed. We think that the further direction for this combination is going to be a combination of azacitidine with nivolumab and ipilimumab, a very similar approach that we have started in AML. The reason we think this will be important is because when we treat these patients with the azacitidine plus PD1 inhibitor, we see that, uniformly in most patients who are not responding, there is significant upregulation of CTLA-4 on T-cells; indicating that this was the major immune mechanism of resistance. Potentially by using the combination, we could prevent or overcome such resistance. If this does turn out to be true, this could be a very important breakthrough for development in frontline MDS, a disease that has needed new drugs, just like in AML. Thank you for viewing this activity.

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