Carfilzomib, Dexamethasone, and Daratumumab Versus Carfilzomib and Dexamethasone for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma: Primary Analysis Results from the Randomized, Open-Label, Phase 3 Study CANDOR

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Welcome to *Managing Myeloma.* I'm Dr. Saad Usmani, and I'm live at the 61st ASH conference in Orlando, Florida. Today, I will be reviewing the results of the late-breaking abstract titled "Carfilzomib, Dexamethasone, and Daratumumab Versus Carfilzomib and Dexamethasone for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma: Primary Analysis Results from the Randomized, Open-Label, Phase 3 Study CANDOR."

Let me talk to you about the rationale of combining these two therapies. Of the current available six options in the early relapsed setting, four options contain lenalidomide as one of the partners in the triplet regimen. In the United States specifically, lenalidomide maintenance is utilized for majority of the frontline patients. And as patients start progressing on an IMiD, if you look at the options available to us, they are somewhat limited compared to patients who may be IMiD sensitive or IMiD non-exposed. So with that in mind, knowing that Dara has good activity in the relapsed/refractory myeloma setting and so does carfilzomib, it made sense to look at this combination and compare it with carfilzomib-dexamethasone that is already a standard of care approved on the basis of the ENDEAVOR trial. To set the stage for this, a phase 1 study called EQUULEUS was done that looked at this combination, but carfilzomib was given on a weekly basis. There were no safety signals with that phase 1 study, and the overall response rates were impressive, and that set the stage for this phase 3 trial.

The design of this phase 3 trial was a 2:1 design. So for every patient who was getting Kd, two were randomized to receive Kd along with daratumumab. A total of 466 patients were randomized, and the baseline characteristics were fairly balanced across the two arms. The median age was 64%. Of the randomized patients, 90% had received bortezomib-containing regimens, 42% had received lenalidomide-containing regimens, and in fact 33% of the patients were refractory to lenalidomide.

After a median follow up of roughly 17 months, the primary endpoint of the study, which was PFS, was met. For the control arm, the PFS was 15.8 months and that for the experimental arm, which was not reached, and the hazard ratio for the study was 0.63. What that means is that there was 37% reduction of risk of death or progression in favor of the three-drug arm compared to the two-drug arm. Most importantly, across the pre-specified subgroups, Len-exposed and Len-refractory patients also did not have their median PFS reached in the three-drug arm, whereas the median PFS for those respective populations was 12.1 months and 11.1 months with Kd.

If you look at the median time to response, it was about a month on both studies. At a median follow-up of 17 months, median overall survival has not been reached.

When we look at the safety profile, there was a difference and increase in the grade 3 or higher adverse events on the Kd-Dara arm and those AEs were primarily infections as well as myelosuppression with low hemoglobin, white blood cell count, and platelet counts.

One interesting finding that that we observed was a lower incidence of grade 3 or higher cardiac failure on the Kd-Dara arm compared to the Kd arm. And we're still trying to figure out the reasons why this observation happened by looking at it, taking a deeper dive at the patient characteristics. There were five deaths reported that were treatment related on the Kd-Dara arm compared to none on the Kd arm, and four out of five of those events were infection related.

So, how are these findings clinically relevant? We have another very good option that's Dara-based that we can utilize for patients in the relapsed setting, especially for those that are Len-exposed or Len-refractory. I think one of the key elements that we have to consider is the initial administration of carfilzomib with daratumumab as we are starting the first cycle. And in this particular study, the dose of daratumumab was split over the first two days of only the first cycle. And that is probably also why we saw a lower incidence of infusion-related reactions at about 18% in the Kd-Dara arm. From a community standpoint, I think for the Len-exposed and Len-refractory patients as well as the younger patients who are not frail and who don't have recurrent infections, this would be a very good potential option in our armamentarium.

Thank you for your attention.