Managing Myeloma

Efficacy of Daratumumab in RRMM: Two- vs Three-Drug Combinations and Cytogenetic Risk

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My name is Professor San Miguel. I am the Director of Clinical and Translational Medicine at the University of Navarra in Spain. Today, it is my pleasure to discuss with you the efficacy of daratumumab in combination with what are the standards of care - lenalidomide and dexamethasone or bortezomib and dexamethasone in relapsed/refractory patients - making special emphasis on dose with high-risk cytogenetics. As you know, the overall survival in myeloma has significantly improved in the last decade; however, patients with high-risk cytogenetics continue to have poor outcomes. Daratumumab is a monoclonal antibody with a dual mechanism of action, direct antitumor, and immunomodulatory effects that has recently been approved both as monotherapy and in combination with standards of care. The approval in a single agent was based on the efficacy in highly refractory patients. In this context, one third of these patients responded to daratumumab single agent with a median PFS of 4 months, 15 months for responding patients, and overall survival of 20 months. The approval in combination was based on two large phase 3 randomized trials in which the standard of care - lenalidomide dexamethasone (Rd) or bortezomib-dexamethasone (Vd) - were compared with the same schemes, but adding daratumumab.

The first study, the Rd study, is the POLLUX trial in which treatment was given until disease progression. The second study based on Vd, the CASTOR trial, was given the Vd or daratumumab-Vd (DVd) for 8 cycles, and then in the experimental arm, daratumumab was continued until progression. Let me now provide the results of the daratumumab lenalidomide dexamethasone (DRd) study, the POLLUX study. With a median follow-up of 24 months, the progression-free survival (PFS) at 2 years is 68% in the experimental arm versus 41% in the control arm, Rd, with a similar outcome for the total population as compared to patients that have received one prior line of therapy. The CASTOR study, the one based on Vd, showed also a significant benefit for the addition of daratumumab with a median PFS of 16.7 months as compared to 7 months in the control arm. In this setting, a clear benefit was seen for those patients that received daratumumab after just one prior line of therapy, with a median PFS that has not been reached yet.

As I mentioned, one of the goals of our study was to identify the efficacy of daratumumab according to cytogenetic risk status. We defined high-risk cytogenetics based on the presence of translocation 4;14, 14;16, or deletion 17p, and this was assessed either at the local labs by FISH or centralized by NGS. The incidence of high-

risk cytogenetics was approximately 20% and was well-balanced among the four different arms. What is very interesting to see is the high degree of concordance, over 90%, between the two techniques, the conventional FISH and the new NGS.

Now, let me focus on the results. First, the overall survival. In both the studies, the addition of daratumumab was associated with a significant increase in the overall response rate, both in the high- and in the standard-risk patients. I want you to focus on the high-risk population because I think in this population there is a more unmet medical need. As you can see, 37% of the patients receiving DRd achieved a stringent complete response, while only 6% of patients receiving conventional Rd achieved a complete response. In a similar figure, 34% complete response was observed with DVd, which is also significantly superior to the 9% observed with Vd.

If we now focus on the PFS, we can see that the addition of daratumumab to Rd prolongs the PFS regardless of the cytogenetic risk. The continuous line corresponds to the standard-risk patients, and within the standard-risk patients, those that received daratumumab do significantly better than those that receive only Rd. Similarly, it is observed for the high-risk patients, and in fact, high-risk patients receiving daratumumab do better than standard-risk patients that receive only Rd. Nevertheless, it should be also mentioned that the addition of daratumumab is not able to completely abrogate the adverse prognosis of high-risk cytogenetics, and almost the same picture is observed when you analyze the combination of daratumumab plus Vd. Again, daratumumab prolongs the PFS significantly, regardless of the cytogenetic risks. Again, the continuous line reflects the outcome of patients receiving DVd - significantly longer PFS - as compared to just Vd in the standard-risk patients. The other line corresponds to the high-risk patients, and once again, we can see that high-risk patients receiving DVd do better than standard-risk receiving just Vd, but once again, daratumumab was not able to completely abrogate this adverse prognosis of high-risk because the high-risk patients do worse than the standard-risk patients.

We have very preliminary data on overall survival, and I should emphasize that the data is still very immature, but if you look to the number of events, both in the DRd and in the DVd arms, you can see that the number of events is lower than in the control arm, particularly in this high-risk population.

Finally, let me analyze the impact of these new regimens on minimal residual disease (MRD). We know that minimal residual disease is probably one of the best, if not the best, markers to predict survival. This has been mainly demonstrated in the upfront setting. The data in the relapsed setting is still very scant, and these are the largest studies in which minimal residual disease has been explored in the relapsed setting. First, I will analyze the impact in the high-risk population and first in the POLLUX trial, the DRd. As you can see, an MRD-negative status with a sensitivity of 10 to -5 was only achieved in 21% of patients that received daratumumab, as compared to none of the patients treated with only Rd, and this was associated with a significantly longer

survival. Again, a very similar picture is observed when you analyze the CASTOR trial. The DVd, 14% of the patients achieved MRD negativity, none of the patients receiving Vd with high-risk cytogenetics achieved an MRD negative status, and again, MRD negativity is associated with a significantly longer survival. In fact none of these patients has relapsed so far.

Finally, a comment about the standard-risk cytogenetic groups, and here you can see on the PFS curve the continuous line curve corresponds to the MRD-negative patients, and in both the DRd and the Rd arms, those patients that achieve an MRD-negative status show a significantly longer progression free survival, which indicates the value of achieving MRD-negative status. Probably, you can conclude that it does not matter what drug you use, if eventually you achieve an MRD-negative status. This is partially true because if you look at the chances that you have to achieve an MRD negative status, you can see on the columns that this possibility is three times more frequent in the context of daratumumab treatment, and almost the same applies in the DVd arm; 2% of the patients receiving Vd achieve an MRD negative status versus 14% (seven times more frequent) with DVd, and in both arms, an MRD negative situation is associated with a significantly longer survival. I think we can conclude that in these two large randomized phase 3 trials, the addition of daratumumab to the standard of care showed a significant benefit, both in standard risk and in high-risk patients, and this was demonstrated based on PFS data, overall response rate data, and MRD-negative rates. In the high-risk patients, MRD negativity was achieved only when daratumumab was added, and preliminary data indicate that possibly daratumumab is also associated with an overall survival benefit. Thank you very much for your attention.