ASCO Highlights from Sagar Lonial, MD, FACP

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I am Dr. Sagar Lonial from the Winship Cancer Institute of Emory University in Atlanta, Georgia, I am at ASCO 2018, and we are going to talk about new data presented at the meeting.

Let us start off talking a little bit about a very interesting abstract from the group in Massachusetts that looked at the combination of pomalidomide, bortezomib, and dexamethasone with elotuzumab in a patient population that was relapsed and refractory. This was a phase 2 study and many patients were resistant to either pom or bortezomib, or had previously seen these drugs in other combinations, and the real question was, “Can you add in elotuzumab and potentially enhance the overall response?” The response rate in this phase 2 trial was actually quite good. Over 50% of patients had a response, with about 43% of patients responding who were resistant to daratumumab, suggesting that we may be able to gain benefit through the use of elotuzumab in the post-dara patients as well. This is certainly a very interesting trial and given data at this meeting on the use of PVd (pomalidomide, bortezomib, and dexamethasone) from the OPTIMISMM trial, establishing another standard in the relapsed and refractory setting, the addition of elo as a quad regimen is quite interesting and we are looking forward to additional data with larger patient cohorts.

The next trial I want to talk about is a follow-up on the ELOQUENT-2 study, a randomized phase 3 trial that I led several years ago looking at elotuzumab plus len-dex versus lenalidomide and dexamethasone in one to three prior lines of therapy. This is the trial that ultimately led to the FDA approval of elotuzumab in combination with lenalidomide and dexamethasone. What we are seeing now with much longer follow-up than we have ever had before is that the difference in progression-free survival, that 30% benefit with the addition of elotuzumab, is continuing to hold up with four plus years of follow-up now. What we are also beginning to see is that there was no increase in infectious or other complications with longer follow-up, and the survival curves are continuing to separate. This really continues to establish the benefit of elo in combination with len-dex over len-dex with long-term follow-up now, suggesting that the benefit is continuing to be sustained.

The next trial I want to talk about is the ALCYONE trial and this is the trial that was presented initially at ASH and was published in the *New England Journal of Medicine* simultaneously. It was a randomized phase 3 trial of VMP – bortezomib, melphalan, and prednisone – versus dara plus VMP (VMP plus or minus daratumumab). This was a large phase 3 trial done in transplant-ineligible patients predominantly enrolled in Europe, and as you can tell, the use of melphalan and prednisone does not occur quite frequently in the US, but it is used frequently in Europe. This randomized phase 3 trial demonstrated a significant improvement in progression-free survival, depth of response, and actually MRD negative complete remission. For one of the first times ever, the FDA actually recognized MRD negativity as a major benefit of the VMP plus

daratumumab combination. We have seen dara in other partners does achieve MRD negativity in the newly diagnosed and in the relapsed and refractory setting, making this a really exciting newer regimen. This led to the FDA approval of daratumumab in newly diagnosed myeloma in combination with VMP. Very interesting data, and there are other partners with dara that we are looking at in future therapies such as VRd, Rd or even carfilzomib and dexamethasone, to better understand where daratumumab may add benefit in the newly diagnosed myeloma setting.

The other trial I want to talk about is the AQUILA trial, and this is a trial in progress. This is being presented by Dr. Rajkumar and is a randomized phase 3 trial of subcutaneous daratumumab versus observation for patients with high-risk smoldering myeloma. We know that there are a lot of clinical investigations in high-risk smoldering myeloma. Things that have been done include aggressive VRd, KRd, tandem transplant, long-term maintenance. There are also more gentle approaches such as single-agent lenalidomide versus observation, and daratumumab versus observation, in a number of different studies. The advantage this ongoing trial has is: A) the use of subcutaneous daratumumab and B) the fact that there is a control arm, because I do not think that we have established clearly that early intervention for high-risk smoldering impacts short-term and long-term outcome. We are all looking forward to results in the future, which will help us to understand how best to approach smoldering myeloma.

Finally, as we are talking about monoclonal antibody-based therapy across the spectrum in myeloma, we know that there were a couple of hiccups with the pembrolizumab trials in the context of newly diagnosed and relapsed refractory myeloma partnered with either lenalidomide or pomalidomide; and some of that was discussed by the FDA at ASCO 2018. What we also know is that very recently the nivolumab trials were just reopened, further trying to assess the benefit of PD-1 inhibition in combination with an immunomodulatory agent in patients with relapsed and refractory myeloma, suggesting further clinical investigation is currently ongoing.

Abstracts:

Yee AJ, Laubach J, Campagnaro E, et al. A phase II study of elotuzumab in combination with pomalidomide, bortezomib, and dexamethasone in relapsed and refractory multiple myeloma. ASCO 2018. Abstract 8012.
https://meetinglibrary.asco.org/record/160701/abstract

Lonial S, Dimopoulos M, Weisel K, et al. Extended 5-y follow-up (FU) of phase 3 ELOQUENT-2 study of elotuzumab + lenalidomide/dexamethasone (ELd) vs Ld in relapsed/refractory multiple myeloma (RRMM). ASCO 2018. Abstract 8040.
https://meetinglibrary.asco.org/record/160720/abstract

Cavo M, Iida S, Blade J, et al. Daratumumab plus bortezomib-melphalan-prednisone (VMP) in elderly (≥75 y) patients (Pts) with newly diagnosed multiple myeloma (NDMM) ineligible for transplantation (ALCYONE). ASCO 2018. Abstract 8031.
https://meetinglibrary.asco.org/record/160738/abstract

Randomized, open-label, phase 3 study of subcutaneous daratumumab (DARA SC) versus active monitoring in patients (Pts) with high-risk smoldering multiple myeloma (SMM): AQUILA. ASCO 2018. Abstract TPS8062.
https://meetinglibrary.asco.org/record/165532/abstract