ASCO Highlights from Saad Z. Usmani, MD, FACP

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Hi, my name is Saad Usmani. I am the chief of Plasma Cell Disorders at the Levine Cancer Institute in Charlotte, North Carolina, and I'm here at the ASCO Annual Meeting 2018 in Chicago. I am presenting an abstract on the KEYNOTE-185 trial which compared pembrolizumab-lenalidomide-dexamethasone versus lenalidomide-dexamethasone given to newly diagnosed transplant-ineligible multiple myeloma patients. Both the KEYNOTE-185 study, as well as the KEYNOTE-183 study in the relapsed/refractory setting with pembrolizumab and pomalidomide in combination, were held by the FDA last year because of concerns about high numbers of deaths on the study, as well as immune-related adverse events on the pembrolizumab arms. This is the final analysis on the 301 patients that were accrued to the pembrolizumab-lenalidomide-dexamethasone versus pembrolizumab-Rd study. The study was stopped less than halfway through the accrual. There appeared to be a higher number of high-risk patients, 16% versus 7%, on the pembrolizumab arm. There was a higher percentage of patients who were older than the age of 75 on the pembrolizumab arm as well, and one would expect these numbers to even out by the time that study finishes complete accrual, but the study was halted early. There was no difference found in terms of overall response rates, median progression free survival, or the overall survival at that point in time. In terms of the immune-related adverse events, the most common ones were hypothyroidism and hyperthyroidism. There were also some increased infections and pneumonitis observed. The overarching message from this experience is that there was no efficacy observed in this group of patients, with the caveat that the study was less than half accrued and therapy was stopped before optimal exposure to the drug could have taken place.

I am going to be talking about two specific abstracts: the first being presented by my colleague, Dr. Ajai Chari, on the phase 1B experience with subcutaneous daratumumab. I had originally presented these data at ASH in 2016 on two cohorts of patients with subcutaneous infusion at an infusion rate between 20 to 30 minutes. The data that Dr. Ajai Chari is presenting is on the new formulation which has only 15 mL of volume and can be given in three to five minutes subcutaneously. The cohort of 25 patients that Dr. Chari is reporting on had a median of three prior lines of treatment, and the overall response rate that was reported at ASH of 2017 was around 44% with subsequent follow-up of a little over eight months. The response rate has deepened in patients, it is now about 52%. The PK/PD (pharmacokinetic/pharmacodynamic) data appears to be similar to IV daratumumab. This leads into the second study which is actually a trial in progress being reported at ASCO, which is called the COLUMBA trial. It is comparing IV daratumumab to subcutaneous daratumumab in a large randomized phase 3 study. At the time that the abstract was submitted, the study was still accruing. The study will finish accruing roughly 488 patients by the end of July, and we are hoping that we will have a readout in another year or year and a half. We are hoping that we can bring this easier and more convenient option for patients through an FDA approval.

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I'm going to be sharing some details about an abstract being presented by my colleague, Dr. Joseph Mikhael, and a study that I participated in. It's a phase 1B data study combining isatuximab, an anti-CD38 monoclonal antibody, with pomalidomide and dexamethasone. We are reporting on 45 patients with a median of three prior lines of treatment who received isatuximab initially in a dose escalation cohort, and then in a dose expansion cohort of 10 mg/kg dosing. The overall response rate was over 60% in this patient population. Over 80% of the patients were refractory to a previous line of treatment, and a majority of these patients were IMiD and PI refractory. The most common side effects that were observed were fatigue and neutropenia, and infusion-related reactions were observed in about 42% of patients but were mostly grade 1 and 2 and well-managed. Overall, the main message is that this monoclonal antibody combination is quite potent. There is a large randomized phase 3 trial that has finished accrual comparing isatuximab-pomalidomide-dexamethasone with pomalidomide-dexamethasone, and we should be learning about those results hopefully by late 2019 or early 2020.

I am going to be commenting and highlighting an abstract that was presented by my colleague, Dr. Paul Richardson, on the OPTIMISMM trial which compared pomalidomide-bortezomib-dexamethasone to bortezomib-dexamethasone in patients who received one to three prior lines of treatment. A total of 559 patients were randomized to this phase 3 study and the primary endpoint was progression-free survival. This is a very important abstract because it addresses our need for options for lenalidomide refractory patients. 100% of the patients enrolled on the study were lenalidomide exposed, and about 70% on both arms were lenalidomide refractory, so this is very relevant to practice in the U.S. What was observed was a median PFS of about 11 months versus 7 months in favor of pomalidomide-bortezomib-dexamethasone for the overall population. Specifically, for patients who were in the first prior line of treatment, the median PFS was a little more than 20 months compared to 11 months. In terms of overall response rates, again the higher overall response rate with pomalidomide-bortezomib-dexamethasone was observed a little north of 80%, and there was durability of responses for this early line of treatment, especially in the first relapsed patient population. The bottom line in terms of safety profile, no new safety signals were observed. Most of the side effects we would anticipate for pomalidomide or bortezomib were seen and managed with adequate dose adjustments. This hopefully will add a new option for us, especially for the U.S. myeloma patient population where most patients are on lenalidomide maintenance. When they are relapsing, they are lenalidomide refractory and we are struggling on how to pick treatments, this would be a very reasonable option for those patients.

Abstracts:

Usmani S, Schjesvold F, Rocafiguera AO, et al. A phase 3 randomized study of pembrolizumab (pembro) plus lenalidomide (len) and low-dose dexamethasone (Rd) versus Rd for newly diagnosed and treatment-naive multiple myeloma (MM): KEYNOTE-185. ASCO 2018. Abstract 8010.
https://meetinglibrary.asco.org/record/160702/abstract

Chari A, Usmani S, Mateos MV, et al. Subcutaneous daratumumab (DARA) in patients (Pts) with relapsed or refractory multiple myeloma (RRMM): Part 2 update of the open-label, multicenter, dose escalation phase 1b study (PAVO). ASCO 2018. Abstract 8013.
https://meetinglibrary.asco.org/record/160706/abstract

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