The AETHERA Trial: Results of a Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Brentuximab Vedotin in the Treatment of Patients at Risk of Progression

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My name is Craig Moskowitz. I am attending physician on the Lymphoma Service at Memorial Sloan Kettering Cancer Center and a professor of medicine at Weill Medical College of Cornell University. I am going to discuss the AETHERA study which is the largest and only placebo-controlled random assignment trial in patients with Hodgkin lymphoma. The study patient population are those with relapsed or primary refractory Hodgkin lymphoma. All these patients were at risk to have a suboptimal response to an autologous stem cell transplant. Three cohorts of patients were enrolled on study. Those patients with a remission duration of less than a year after primary therapy, those patients with primary refractory Hodgkin lymphoma, and those patients with a remission duration of greater than a year but with disease outside of the lymph node system and/or extranodal disease. The patients were enrolled on study, and all received salvage chemotherapy. Those patients without evidence of disease progression, meaning either a complete, partial, or stable disease to salvage chemotherapy, were transplanted and then randomly assigned to receive placebo or 16 doses of study drug called brentuximab vedotin. Brentuximab vedotin is an antibody drug conjugate to CD30 which is approved for patients where stem cell transplant fails. This is a multicenter multinational study, 78 centers were involved, 329 patients were enrolled on study and then stratified. Treatment was given every 3 weeks, and patients were seen at that time in clinic. Interestingly, this is a crossover design study. Those patients who have progression of disease and were randomized to the placebo, they were able to sign consent and be treated on a companion study to receive brentuximab vedotin free of charge. Study endpoints were imaging studies done at 3, 6, 9, and 12 months followed by CAT scans at 18 and 24 months. Thereafter, patients were followed. The primary endpoint of the study is progression-free survival measured at the 2-year time point. Secondary endpoints are overall survival as well as safety. Concerning the status of patients, nearly half the patients on study finished all the treatment, 69 patients on the placebo arm were taken off study for progression and 50 patients on the brentuximab vedotin arm were taken off the study for toxicity. The primary endpoint of the study is progression-free survival based upon independent review. Secondary is based upon investigator review. The concordance between investigator and the dependent review was 87%. The major differences were at times because physicians took patients off study because of clinical progression. New treatment was received. Later on, this was felt not necessarily to be a progression based upon independent review. Be that as it may, the

hazard ratio for progression-free survival based on independent review is 0.57, and the hazard ratio based upon investigator review is 0.5. There is a 19-month improvement and freedom from progression on the independent review with progression-free survival rate at 2 years of 65% versus 51%. Based upon the investigator review, the median time to progression has not been reached. Overall survival as expected at 24.4 months was not different. The reasons for this are obvious. Number one, patients were able to receive brentuximab vedotin in a companion study in a crossover design. When we wrote the study originally back in late 2009 early 2010, the median survival of Hodgkin lymphoma patients where a stem cell transplant had failed was 28 months. The median survival now for a patient where a stem cell transplant fails is between 42 and 48 months. The reason for that is there is a host of new agents patients can receive. Obviously, they can receive brentuximab vedotin. The HDAC inhibitors are active, and now as you have heard at this meeting, the checkpoint inhibitors are active, both nivolumab and pembrolizumab. So, it is impossible at this particular time for there to be an overall survival difference.

Concerning toxicity, the most common toxicity on this treatment program was peripheral neuropathy seen in patients getting brentuximab vedotin. In 85% of the patients, this was reversible. I want to stress that this is a very unfavorable patient population. If one looks at five risk factors of known prognostic import which includes primary refractory disease, having less than a complete response to salvage chemotherapy, having extranodal involvement, having these symptoms or needing more than one salvage regimen to achieve chemosensitive disease to undergo a transplant, half the patients on this study had at least three risk factors. If one just looks at typical transplant studies in the literature in patients with three risk factors, the progression-free survival ranges from 25% to 30%.

From my point of view, the conclusion of this study is that the treatment program was well tolerated. The primary endpoint was met for progression-free survival. Overall survival is too soon but will be read out in 2016, and lastly, based upon the PFS data, I do believe that this will become standard of care in patients who are eligible to be enrolled on this study, and I will stress that again, patients with an initial remission duration of less than a year, patients with primary refractory Hodgkin lymphoma, or patients with Hodgkin lymphoma with extranodal involvement. As always, we want to thank the patients and their families for participating in this study. It was a difficult study to do. Patients were seen every 3 weeks for up to a year, that is 16 to 17 visits and frequently thereafter, but at the end of the day, consolidation with this study drug called brentuximab vedotin is likely to help up to 15% of patients. Thank you for your attention.

Reference:

Abstract #673: The Aethera Trial: Results of a Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Brentuximab Vedotin in the Treatment of Patients at Risk of Progression. *https://ash.confex.com/ash/2014/webprogram/Paper67040.html*