Managing Hodgkin Lymphoma

Immunotherapy

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Welcome to *Managing Hodgkin Lymphoma*. My name is Dr. Stephen Ansell. I am a Professor of Medicine at Mayo Clinic in Rochester, Minnesota. I am live at the 58th Annual American Society of Hematology Meeting. Today, I would like to talk about four abstracts in the area of immunotherapy for Hodgkin lymphoma.

The first abstract I would like to talk about is an update on the Phase 2 data that came from the CheckMate 205 study using nivolumab in relapsed and refractory Hodgkin lymphoma. Many folks may be familiar with nivolumab. For those that might not be, nivolumab is anti-PD-1 antibody. It blocks the PD-1 protein that is on Hodgkin lymphoma cells and prevents T-cells that are present within the Hodgkin lymphoma microenvironment from being shut down and preventing an effective immune response. The blockade liberates those T-cells and allows the cells to target the malignant cell. This is an important clinical trial because it is looking at the data from nivolumab that was very promising in the Phase 1 study and confirming it in the Phase 2 trial. Early data from this study was presented, but it is important as longer followup has gone on, to ensure that with this longer followup the data remains good and the results are as good as initially promised. In this trial, there are a number of different cohorts. There is a cohort of patients that had an autologous stem cell transplant and then received brentuximab vedotin, and then nivolumab was used and tested. There are subsequent cohorts for whom they did not receive an autologous stem cell transplant or they received an autologous stem cell transplant but did not receive brentuximab vedotin. The updated efficacy data is from the cohort B. These are people that received an autologous stem cell transplant and brentuximab vedotin; 80 patients are included in this cohort of patients. Most patients had received multiple therapies, the average being four previous regimens, and the encouraging data is that the efficacy and durability of treatment remains good; 54% of patients remain on therapy, now with more than a year, actually 15 months of followup. Also very encouraging is the fact that the overall response rate remains high at 68%. Most of these however are partial responses with only an 8% complete response rate. For the responding patients, the median duration of response now exceeds a year.
All of these results are very encouraging. They continue to confirm the efficacy and tolerability and also durability of benefit for this agent and supports the label that this agent has received for use in clinical practice. In clinical practice, the place where nivolumab now has an established role is in patients who with Hodgkin lymphoma have

failed front-line therapy, failed an autologous transplant, have received brentuximab vedotin, and still have persistent disease. This data supports the efficacy of nivolumab in these particular patients.

The second abstract that is important to highlight is the update of Phase 2 data from the KEYNOTE-087 study. This is using a PD-1 antibody called pembrolizumab. Pembrolizumab also targets PD-1. It blocks the interaction of PD-L1, the ligand for PD-1 with PD-1 on the T-cells. Many will know that PD-L1 is very highly expressed in Hodgkin lymphoma. This makes it a very important target, and pembrolizumab similar to nivolumab has had excellent results, initially reported in a Phase 1 trial and now is substantiated and further confirmed in a Phase 2 trial. This again is a study that has multiple cohorts of patients, patients who have received an autologous stem cell transplant, received brentuximab vedotin, and then received pembrolizumab. There are also cohorts for patients who had primary refractory disease who could not have a transplant and received pembrolizumab. There are studies in a cohort of patients who have not received brentuximab vedotin. The safety data from this updated study shows that the drug is well tolerated. Common immune side effects were seen but only in a minority of patients. These immune side effects are due to the body reacting at multiple sites, particularly the skin, the bowel, and the lung, and sometimes the thyroid, but the adverse events that were severe at a grade 3 or 4 level were very minimal. The most encouraging part about this particular abstract is the fact that the response rates remain high and the responses are durable. Per investigator review, the response rate was 67%, and in each of the cohorts mentioned, the response rates were very similar. Across all cohorts, what was further interesting was when patients who had relapsed were compared to people who had primary refractory disease. Response rates were very similar, suggesting that prior chemotherapy does not in any way affect the efficacy of this therapy. This gives us another agent that is likely to be approved for patients with relapsed Hodgkin lymphoma. Pembrolizumab has excellent efficacy with durable responses and is well tolerated. This will likely be incorporated into the standard of care for patients with Hodgkin lymphoma with the fact that nivolumab is also likely to be an agent in the similar population of patients. Further studies are going to need to be done to see whether there is really a difference between the two agents, but provisionally at this point, the results suggest that both are highly active, both are well tolerated, and the responses are very durable.

As one moves to look to the future and wonders how much one can improve on the results, there is some data now looking at combination studies. The abstract that I would like to highlight is a Phase 1 trial that was part of the CheckMate 39 study. One might remember that the initial cohort of patients in this study with Hodgkin lymphoma received nivolumab alone. Now, there has been a further cohort of patients who were

treated with two immune checkpoints using the PD-1 antibody nivolumab but also adding a second immune checkpoint therapy that targets CTLA-4, an anti CTLA-4 antibody called ipilimumab. The combination of ipilimumab and nivolumab was tested in a variety of different patients with both Hodgkin lymphoma, diffuse large B-cell lymphoma, T-cell lymphoma, and multiple myeloma. The rationale for why connecting or combining these two therapies would be useful is that CTLA-4 blockade works more where there is an interaction between antigen presenting cells and the T-cells, so in the activation phase. Nivolumab works more in the suppression phase where activated T-cells could be switched off by PD-1 signaling. If one thinks about how you could put these two agents together, the one agent, ipilimumab, increases activation and the second agent, nivolumab, prevents suppression. This would keep cells active in targeting the malignant cell. This is a sequential cohort that followed the original nivolumab cohort. The results from this study showed that the agents could be combined together with little difficulty or complications with increased immune effects. The majority of patients did have some side effects, but in the vast majority, these were grade 1 and grade 2. Only a very small minority, less than 20% of patients, had any grade 3 toxicities. The Hodgkin lymphoma population was again a focus, and in 31 patients in the Hodgkin lymphoma cohort, the overall response rate was very promising at 74% with a 19% complete response rate. All told, the agent combination was effective, toxicity was modest, but additional studies are going to need to be done to really see whether this is better than the nivolumab therapy alone. In the study, however, many patients did not have a previous transplant because they had primary refractory disease. This may have been a more sort of difficult population to treat and hence these results could be very promising, but clearly, a randomized comparison will be needed.

The further abstract that is important to highlight is the long-term followup from the Phase 1B KEYNOTE-013 trial of pembrolizumab in classical Hodgkin lymphoma after brentuximab vedotin failure. This again was the original study that showed the efficacy of the PD-1 antibody pembrolizumab. This is now a long-term followup study with approximately 2½ years of followup. The initial studies have suggested a response rate of around 65%. I think what is very encouraging is that the investigator assessed responses have remained high at about 65% with long-term followup. With ongoing review of the patients, there has been confirmation of an excellent result. I think when one takes all of these data and puts them together and says what does this tell us about the use of pembrolizumab? Both the phase 1 data and the phase 2 data continue to show that this is a highly effective therapy, well tolerated, and responses are very durable.

With that, I thank you for viewing this activity. I would like to highlight that there are additional resources which you can access if one looks at *ManagingHodgkinLymphoma.com*, and thank you for your time and for your attention.