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Interim Update on the PET/CT Adapted Treatment After 3 Cycles of ABVD for All Stages of HL

I want to welcome the audience. Good afternoon. My name is Astrid Pavlovsky. I am from Buenos Aires, Argentina. I am a hematologist with special interest in lymphomas, and I am part of the GATLA group which is a cooperative group throughout all of Argentina, and I would like to share with you this interim analysis of a trial that we have started in 2005. It is a PET-CT adapted therapy after 3 cycles of ABVD for all stages of Hodgkin lymphoma.

So, we know that PET-CT is an important tool for treatment-response assessment in Hodgkin lymphoma, and it can predict therapy response and overall outcome early in the treatment. And the negative predictive value for PET-CT is very high, higher than 90% or 94% according to different studies and the new recommendations for complete remission, the fine complete remission with a negative PET-CT. So, what we are approaching in this clinical trial is to see whether a negative PET-CT after 3 cycles of ABVD is a sufficiently important biomarker to decide to stop therapy in all stages of Hodgkin lymphoma. So we are trying to reduce therapy in patients who achieve an early complete remission with a negative PET-CT and continue therapy only in those who are not in complete remission. And we have our historical control to compare the efficacy of this treatment. Patients with confirmed diagnosis of Hodgkin lymphoma age 16 or older and no previous treatment were included in this trial, and all patients received 3 cycles of ABVD and a PET scan was performed. If PET was negative, no further treatment was offered. This is for all stages of Hodgkin lymphoma. If PET was positive and we considered chemo-sensitivity and a partial response, patients went on with ABVD to complete 6 cycles plus involved-field radiotherapy and hypermetabolic lesions. If patients were considered chemo-refractory with stable disease or advanced disease after 3 cycles of ABVD, they went on to a salvage chemotherapy regimen according to their physician. Due to the design of the trial, we considered a negative PET-CT to be a Deauville score 1 and 2. At this moment, more than 350 patients have been included, and 305 are evaluable, the median age is 31. We have 187 patients in early stage and 118, 40%, in advanced age with almost 20% with bulky disease at diagnosis. Of all these patients, 71% had a negative PET-CT after 3 cycles of ABVD and ended treatment, 29% had persistent hypermetabolic lesions, most of them in partial remission, so they continued with ABVD. Of these patients that had to continue therapy after finishing 6

cycles of ABVD, 75% of the patients achieved a negative PET-CT and were in complete remission, and 8 patients went on to salvage therapy and transplantation. For the whole group of patients, and with a median followup of 55 months, the event-free survival at 4 years is 80%. As in other clinical trials, we see a plateau from there on. The overall survival in this group of patients was 96%. We only had five patients die of Hodgkin disease, and these were patients who had a refractory disease from the diagnosis. They never achieved complete remission. Two of them had transplantation with active disease, and all five patients died of progressive disease. If we look at the event-free survival according to the result of PET after the third ABVD, the PET-negative group, independent of their stage, had an event-free survival of 86% and the PET positive had an event-free survival of 63%, and the overall survival at 4 years is 98% for patients in the PET-negative group and 88% for patients in the PET-positive group. And if we divide, and we have four curves with a localized stage and PET negative, the event free survival is 88%, and advanced stage and PET-negative patients, we have an event-free survival at 4 years of 85%. So, most of these advanced-stage patients were treated with only 3 cycles of ABVD with 85% event-free survival at 4 years. Patients with early stage who had positive PET-CT and continued therapy have a 75% event-free survival at 4 years, and their worst prognosis group is those patients with advanced stage and positive PET-CT which is only 22 patients who have an event-free survival of 53% at 4 years. The overall survival according to PET and stage is the same for all groups, which is around 87%, except for the worst prognosis which is advanced stage and positive PET-CT which is 80% at 4 years. So some of these patients were rescue. In a multivariant analysis for event-free survival, and if we take into account age, stage, extranodal areas, bulky disease, and PET-CT, clearly PET-CT is the most powerful statistically prognostic factor, and age and extranodal areas lose significant prognosis. And risk also is also inferior as a prognostic factor when it is compared to PET-CT after 3 cycles of ABVD. When I say risk, I mean stage. So, if we look at the result of PET-CT after three ABVD according to stage, yes, patients with early stage have a higher probability of obtaining a negative PET CT, and that is 78% of early stage had a negative PET-CT and 59% of advanced stage had a negative PET-CT after 3 cycles of ABVD. So this has a *P*-value which is less than 0.001. Bulky disease was not an important factor regarding the possibility of obtaining a negative PET-CT in this trial.

We compared this without historical control when patients were treated with 3 or 6 cycles of ABVD according to stage and where all patients had received radiotherapy, and the results are exactly the same with an event-free survival of 86% for localized stage with 99 and 98 overall survival and 72% event-free survival for advanced stage in both clinical trials. What is the difference between these two clinical trials? The results are the same, but on our previous clinical trial, 100% of the patients received involved-field radiotherapy, and in this clinical trial, only 30% received involved-field radiotherapy, and

only 30% of the patients received more than 3 cycles of ABVD. So what we believe is that we are having the same efficacy with 3 cycles of ABVD which is adequate treatment for patients who achieve early complete remission with a negative PET-CT. Continuing with ABVD is acceptable in early stage but might be insufficient in advanced-stage Hodgkin lymphoma, so we might have to escalate therapy in these patients. Also this trial, I think, questions, the relevance of previous clinical factors and we need to reexamine this in the era of PET. Interim PET-CT is a powerful prognostic factor which can help us predict which patients can safely spare radiotherapy, even in advanced stage.

So the highlights or the take-home message is that we have seen that the most patients have an excellent outcome after just 3 cycles of ABVD or meeting a more treatment in the large group of patients, and that the high-risk group of patients are those with advanced stage and who do not achieve complete remission with a negative PET-CT early during the treatment. Thank you very much.