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Hello, my name is Bastian von Tresckow. I am a physician at Cologne University Hospital, and I am a German Hodgkin Study Group Trial physician. At this year's International Symposium on Hodgkin lymphoma that has taken place in Cologne in October, I gave a presentation on the *Therapy of Relapsed and Refractory Hodgkin Lymphoma*. I will now briefly summarize my talk. So, first, I started with the treatment of first relapsed or refractory patients. The standard so far had been two cycles of salvage therapy followed by BEAM and autologous stem cell transplant. The results with the strategy were proven, and that was PFS at 3 years of about 50%. That is why a large European multicenter study had been performed, the HDR2 trial, and this trial intensified treatment regimen with the single-agent high-dose chemotherapy, was compared to the standard with 2 cycles of induction therapy followed by BEAM. So, there were 120 patients in each arm, a really large trial. In this trial unfortunately, the intensified regimen could not be shown to be superior. The results were the same; and with the intensified treatment, there were more side effects, more treatment delays, so we can conclude from that that the standard treatment of first relapsed or refractory Hodgkin lymphoma remains 2 cycles of induction therapy followed by BEAM and high-dose chemotherapy. It is important to note that in this trial, the high-risk patients were not included, that means primary refractory patients and patients not responding to the salvage therapy. So, in the trial, the patients had excellent results with the PFS of 70% at 3 years, but that was only in the non-high-risk patients.

There have also been risk-adaptive strategies, and I will just summarize the risk factors we know in relapsed or refractory Hodgkin lymphoma. The most important factor is time to relapse. The primary refractory patients have the worst prognosis, and there are other risk factors such as remission status of the salvage, clinical stage at relapse and others, and more recently, PET has been characterized as one of the most important risk factors in patients of the salvage. So, with the positive PET of the salvage patients, we have a very poor prognosis.

For the risk-adaptive strategies, I will present the results of two trials, the H96 trial performed by the French GELA group. In this trial, the high-risk patients, that means patients with primary refractory disease or at least two of the risk factors, early relapse, stage III or IV at relapse, or relapse with previously irradiated sites, those high-risk patients received double autologous transplant, and this trial showed quite favorable

results in comparison to historical controls. There was an overall survival of 53% at 5 years for primary refractory patients. It is a really good result, and at the OSHO-9, we have the 10 years' long-term follow-up presented of these patients, and there were only very few more relapses in the follow-up time. So we can conclude that this is a good strategy for high-risk patients.

Another risk-adaptive approach is that pursued by Memorial Sloan Kettering. In this approach, the patients receive risk-adaptive therapy. The risk factors of these symptoms, extranodal disease, are remission time shorter than 1 year, and then they receive either standard ICE followed by augmented ICE or 2 cycles of augmented ICE depending on the number of risk factors. Then the PET-CT is performed; and if there is response to PET, then it is just following the standard path high-risk chemotherapy and autologous stem cell transplant; however, if the PET is positive, the non-cross-resistant chemotherapy is given consisting of gemcitabine, vinorelbine, and doxorubicin. The results of this trial have just been presented, and the trial demonstrated that the patients receiving a non-cross-resistant salvage chemotherapy that achieved negative PET afterwards did equally well than the patients who were PET negative after first salvage. The authors concluded that the aim of our salvage therapies should be a negative PET. So, another strategy has also been reported recently for patients with positive PET after salvage. This is a retrospective analysis from France; 111 patients were included. They received either single or double autologous transplant; and according to the PET result, if you look at the PET-positive patients only, then the 5-year progression-free survival is 43% with the tandem transplant, but there are no patients with progression-free survival with the single transplant. So from that we can conclude from those two trials that second-line salvage or tandem autologous transplant might improve the prognosis of patients with positive PET after salvage therapy. However, we still need randomized evidence to really establish this as a standard.

Regarding new drugs and perspectives, of course, the most important new drug we have in Hodgkin lymphoma is brentuximab vedotin. It is an anti-CD30 monoclonal antibody, and it is coupled to a vinca alkaloid, and this drug really specifically targets cancer cells and kills them. So, there has been a pivotal phase II trial published recently by Anas Younes, and in this trial, the drug as a single agent for multiple relapsed patients, had an excellent outcome; 94% of the patients achieved tumor reductions. The side effects of this drug are also very favorable in the phase II trial; that was 14% and 6% grade 3 and 4 for neutropenia, respectively. There was a peripheral sensory neuropathy of 8% of the patients, but most of these patients recovered, so we can truly say that the side effect profile of the drug is really very favorable. In the relapsed or refractory setting, there are other strategies that are currently being evaluated with brentuximab vedotin, for example, brentuximab vedotin as bridge to allogeneic transplant. There has

been a very small study with just 18 retrospectively in the last patients, but in this patient the patients with multiple relapsed responded to brentuximab vedotin and were able to go on to allogeneic transplant and these patients after very short follow-up of one year had PFS of 92% and overall survival of 100%. Of course, this is a small case number, but it is the proof of principal for brentuximab vedotin as bridge to allogeneic transplant. So, brentuximab is further evaluated in the combination with DHAP, this EORTC trial is starting enrolling soon; and at the OSHO-9, there was also a presentation on a sequential salvage therapy with brentuximab vedotin followed by augmented ICE, and in this trial, some of the patients could proceed directly to high-dose chemotherapy and autologous transplant after brentuximab vedotin so they could spread out the toxicity of ICE. It did not work in all patients; that is why the authors of the trial now concluded that an additional cycle of brentuximab vedotin before transplant should be given, so they are currently evaluating a new schedule with 3 cycles of brentuximab vedotin before transplant. The third strategy which was evaluated with brentuximab is maintenance strategy. The AETHERA Trial is a trial in which patients received brentuximab vedotin or placebo if they are at high risk for relapse, and this trial has complete recruitment in September 2012, and we hope to get the results in about one year. So, if this trial is successful, we will, of course change management.

Regarding new drugs, there was also a very interesting presentation on everolimus. Phase II trial was presented at OSHO-9 with 57 patients, and in these patients, the progression free survival was remarkable with 9 months, so the authors concluded that further studies should be performed with this drug. The German Hodgkin Study Group is currently using everolimus to enforce DHAP. We are currently running a phase I trial with everolimus-DHAP combination with currently 7.5 mg. We will go up to 10 mg, and if that can be demonstrated to be safe, we will perform a randomized trial of everolimus-DHAP versus placebo-DHAP. So, there are other drugs which are currently evaluated. Of course, there are the HDAC inhibitors, panobinostat and mocetinostat. I think both are very interesting and effective drugs; but unfortunately, none of those are approved for Hodgkin lymphoma, and there are new antibody construct. For example, at OSHO-9, there had been presentation on the CD60 and CD30 antibody targeting natural killer cells. I think we will hear more about the substance in the future. There has been a trial on bendamustine recently published in the JCO, and there is increasing data on lenalidomide for the treatment of relapsed or refractory Hodgkin lymphoma patients. Thank you for your attention.