Managing Hodgkin Lymphoma

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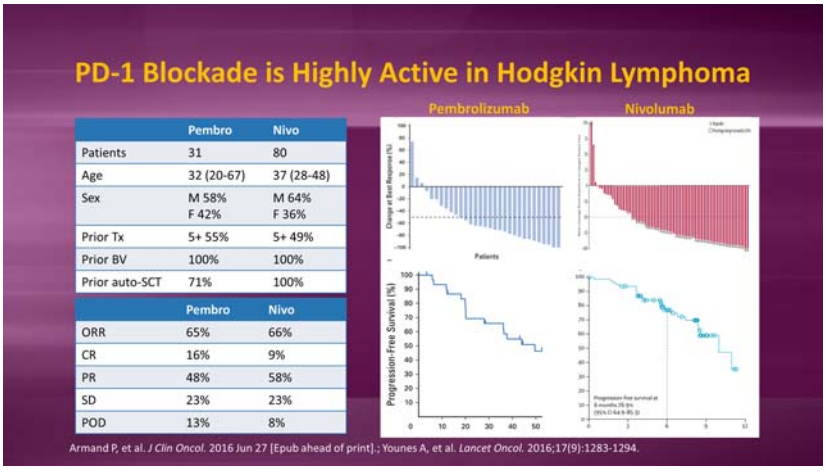
Welcome to *Managing Hodgkin Lymphoma*. My name is Dr. Alison Moskowitz, and I am an Assistant Attending at Memorial Sloan Kettering Cancer Center. I am speaking live from the 10th International Symposium on Hodgkin Lymphoma, and I would like to take a few minutes to provide an overview of the data presented at the immunotherapy session. Immunotherapy was a hot topic at this conference, and that is based upon the recent data showing the activity of checkpoint inhibitors in Hodgkin lymphoma.

The phase 2 data for nivolumab was recently published in *Lancet Oncology* showing an overall response rate of 66% in 80 patients that were presented in that publication. These were all patients with relapsed/refractory Hodgkin lymphoma that had failed prior transplant as well as brentuximab. Data regarding pembrolizumab also looks promising as well, also associated with an overall response rate of 65%. This was recently published in *Journal of Clinical Oncology* in 2016 and hopefully will lead to approval of this drug.



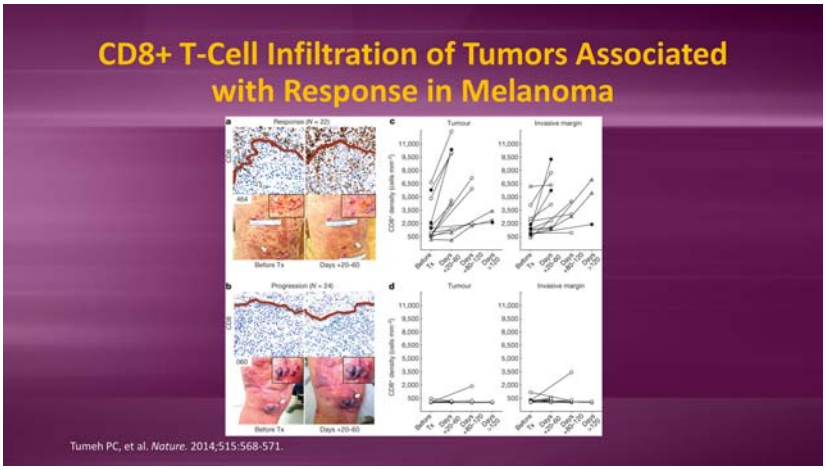
	Pembro	Nivo
Patients	31	80
Age	32 (20-67)	37 (28-48)
Sex	M 58% F 42%	M 64% F 36%
Prior Tx	5+ 55%	5+ 49%
Prior BV	100%	100%
Prior auto-SCT	71%	100%

	Pembro	Nivo
ORR	65%	66%
CR	16%	9%
PR	48%	58%
SD	23%	23%
POD	13%	8%

Based upon the activity of these drugs in relapsed/refractory Hodgkin lymphoma, there is a lot of interest in trying to incorporate these drugs earlier on into the treatment schema. Even though these drugs are so active in Hodgkin lymphoma, we also do have a lot of unanswered questions, and answering these questions will help us figure out how to best incorporate these drugs earlier on into the treatment schema and also to just

optimize the response to these drugs. In particular, one of the questions we have about these drugs is that even though the overall response rate is quite high, a minority of the patients actually have complete response to these drugs. Understanding the mechanism of how these drugs work will actually help us. In addition, we need to know why do patients progress on these drugs and which drugs we should be combining with checkpoint inhibitors, and finally are there patients for whom it is likely they are not going to respond to checkpoint inhibitors and we should avoid the treatment altogether. If we understand the mechanism of action of checkpoint inhibitors, this can help us answer these questions and optimize this therapy for our patients.

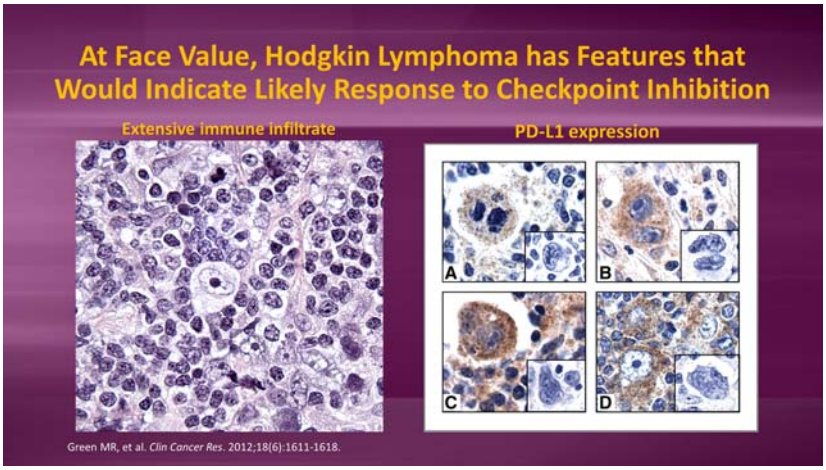
What do we know about the mechanism of action? We believe we know how it works in solid tumors. In particular in melanoma, there is data that shows that PD-1 blockade really does release the brakes on anti-tumor immunity, and this mechanism is mediated by CD8 positive cytotoxic T-cells, and an intact antigen presentation by MHC class I is required for this to occur. Now, in Hodgkin lymphoma, it appears to be a different story. The data that we have in melanoma is really based upon the fact that the mechanism was worked out because patients who responded to therapy and also who progressed on therapy had biopsies that were performed and these were analyzed and they were able to work out the mechanism.



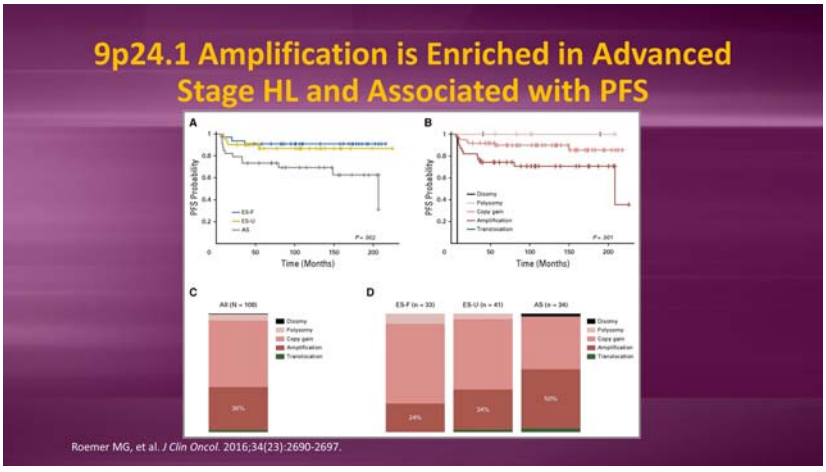
We do not have that data in Hodgkin lymphoma yet. However, there are some features of Hodgkin lymphoma that indicate that the mechanism of action is likely very different than it is in melanoma.

Hodgkin lymphoma at face value does have some features that would indicate that it is likely to respond to checkpoint inhibition. That includes the fact that it is characterized

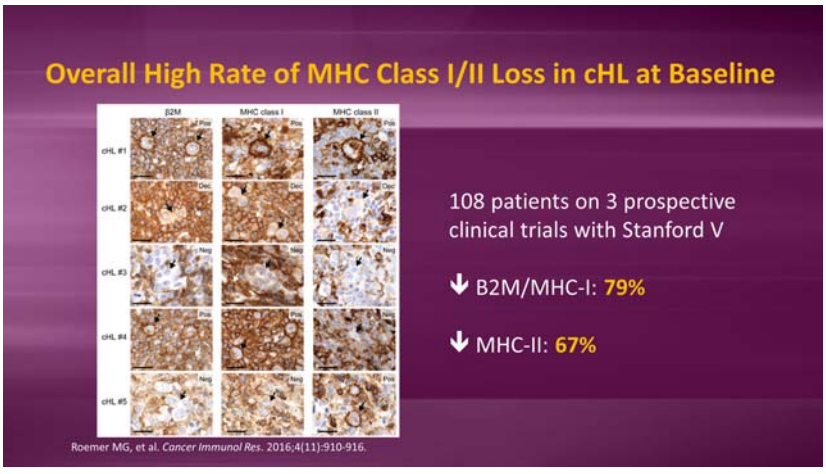
by an extensive immune infiltrate and also there is almost universal expression of the ligands for PD-1 or PD-L1 and PD L2.



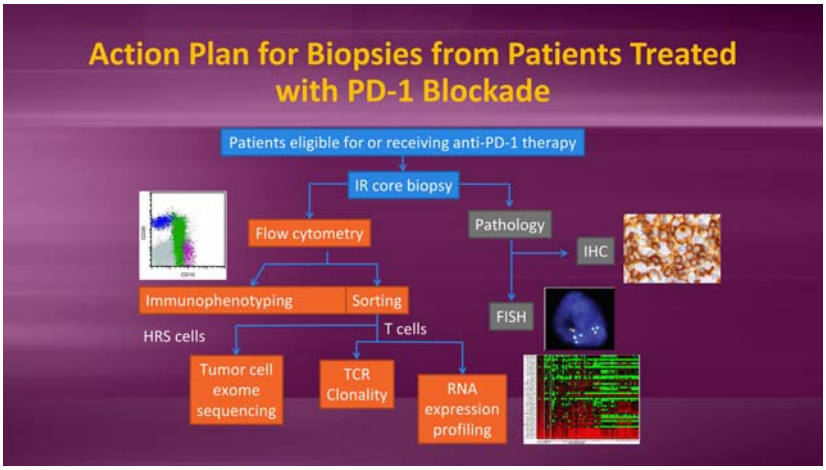
The mechanism for expression of PD-L1 and PD-L2 in Hodgkin lymphoma has been found to be very commonly related to alteration in the 9p24 chromosome which is in a series of patients in the front-line setting which has been published by Dr. Roemer and Dr. Shipp in the *Journal of Clinical Oncology* in 2016. Almost every patient in their series which included 108 patients treated on perspective clinical trials in which they received Stanford V chemotherapy. Almost all of those patients had alterations in 9p24. However, some of those patients had more significant alteration, which they termed amplification, which was associated with a higher expression of PD-L1 or PD-L2. It was interesting that the patients with amplification were more likely to have an inferior progression-free survival and these patients were more likely to have advanced-stage disease.



Now, the presence of PD-L1 and PD-L2 on the surface of Reed-Sternberg cell in Hodgkin lymphoma would suggest that Hodgkin lymphoma was likely to respond to PD-1 blockade, but some of the pieces of the puzzle are missing in Hodgkin lymphoma. I mentioned that in melanoma the mechanism is mediated by the CD8 positive T-cells. However, CD8 positive T-cells are actually quite absent in the Hodgkin lymphoma infiltrator. At least they represent the minority, and actually, the T-cells in the Hodgkin lymphoma infiltrate are more dominated by CD4 positive cells. The other piece of the puzzle that is missing in Hodgkin lymphoma is antigen presentation. I mentioned that antigen presentation appears to be important in melanoma with regard to its mechanism in checkpoint inhibition, but now, we have data that antigen presentation in Hodgkin lymphoma is actually quite perturbed, and this is based upon the fact that there is loss of expression of MHC class I and class II in the majority of cases of Hodgkin lymphoma. Once again, this was shown very nicely by Dr. Roemer and Dr. Shipp's group in that same series of 108 patients who were treated with Stanford V chemotherapy, immunohistochemical staining for MHC class I and class II was reduced in a significant number of patients. The MHC class I was reduced or absent in 79% of the patients, and MHC class II was absent or reduced in 67% of the patients. The lack of this expression would make us believe that Hodgkin lymphoma really should not respond to checkpoint inhibitors or at least the mechanism has to be different than what we see in solid tumors, and so, that is something that we really need a lot more research to figure out how these drugs work, and in the future, I think we will see many more studies where analyzing biopsies of patients both at baseline as well as on treatment for patients who are responding to treatment as well as those who develop disease progression on treatment.



By analyzing these tumors by gene expression profiling and immunohistochemical staining, I think we will be able to figure out the mechanism and also really be able to figure out which patients are most likely to respond to these drugs.



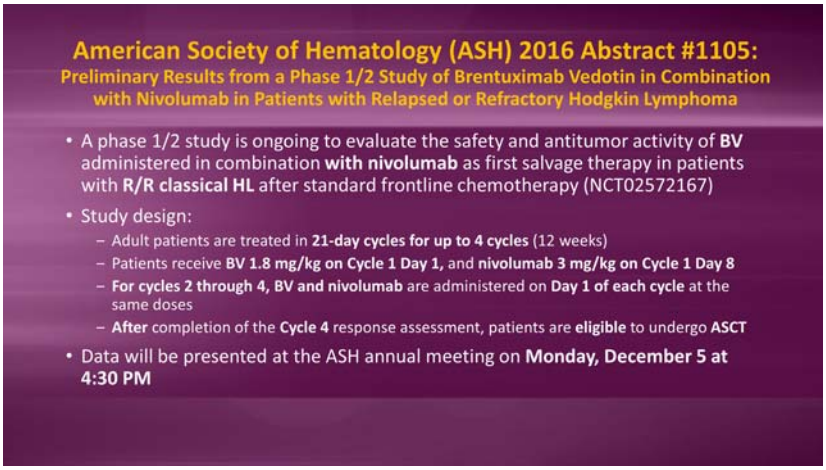
One of the abstracts that was presented in this session in addition highlights the problem with antigen presentation in Hodgkin lymphoma. This was a presentation by Dr. Diepstra from the Netherlands in which he presented data on 361 cases in which there was loss of both MHC class I and MHC class II expression in many of these cases, and in fact, there were only 12% of the patients in his series that actually showed HLA expression that was compatible with antigen presentation, so indicating a very small minority of the group in his series which would be expected to be able to respond to a checkpoint inhibitor in the way that it potentially works in solid tumors. One hypothesis from this was that maybe it is that very small minority of the patients who actually have a complete response to treatment. Another possibility is that the mechanism of action of checkpoint inhibitors is really quite different than in solid tumors and is mediated in a way that it is not dependent upon expression of MHC class I and class II.

I want to highlight another abstract that was presented in this series, which is off the topic of checkpoint inhibition, but it was presented in another target that looks promising in Hodgkin lymphoma. This was Dr. Casagrande from Italy, who provided data regarding CCR5 which is a marker that is expressed on Hodgkin Reed Sternberg cells and contributes to cell growth. She presented data indicating that it contributes the cell growth and proliferation. This represents a potential target and in fact she showed data that blocking CCR5 by an FDA-approved drug for HIV called maraviroc led to reduced proliferation in Hodgkin lymphoma cell lines. They also found that this drug synergized

with doxorubicin in their cell lines. So certainly, this is an interesting target that warrants further exploration in the clinical setting.

So, looking toward the future with regard to immunotherapy, there are a lot of interesting studies that are either already undergoing or soon to be opening that will help us figure out how to best incorporate these drugs into the treatment schema for Hodgkin lymphoma. At this point, nivolumab is the one approved drug in the U.S., and it is approved really only in the setting of the patient who fails transplant as well as brentuximab. However, I think that we will be seeing multiple combination studies in the relapsed setting, as well as studies that are incorporating nivolumab as well as pembrolizumab in the second-line and front-line setting.

One of the studies that looks promising is a combination of brentuximab plus nivolumab which is a study for patients who have failed their front-line treatment and this regimen is being used as a salvage therapy bridging patients to autologous stem cell transplant. We are going to see initial results from this study at this upcoming ASH. Other studies looking at nivolumab as well as pembrolizumab are underway in the front-line setting as well.



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