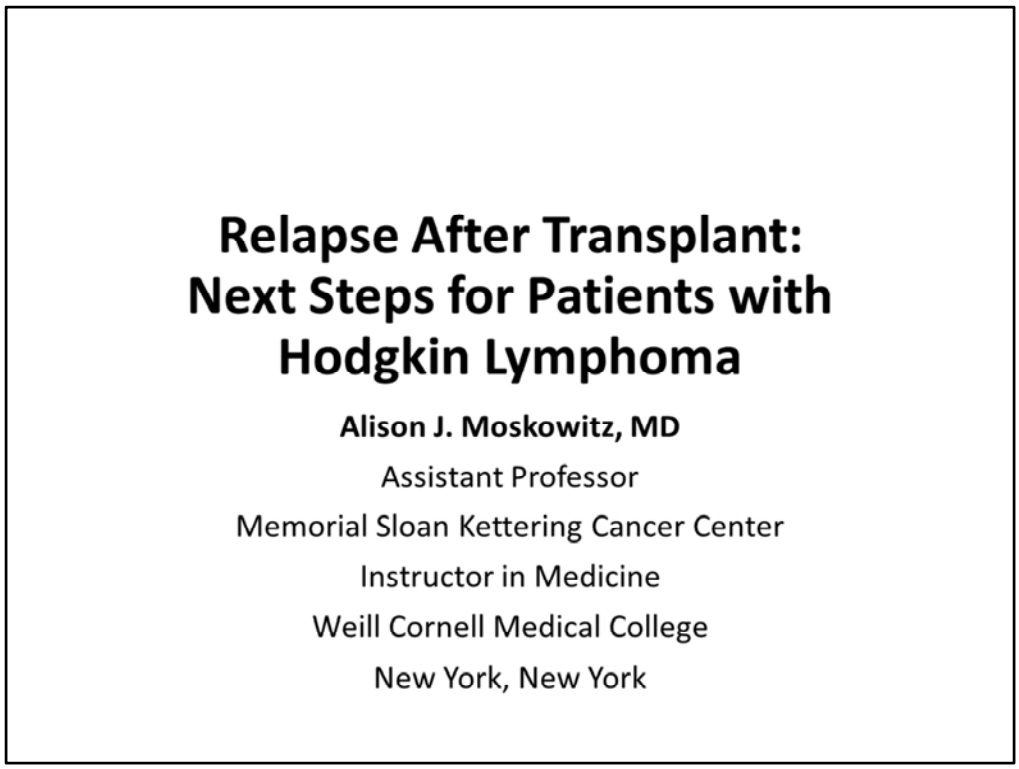
Relapse After Transplant:
Next Steps for Patients with Hodgkin Lymphoma



Hi! My name is Alison Moskowitz. I am an attending at Memorial Sloan Kettering Cancer Center within the Lymphoma Department. I am speaking on behalf of *ManagingHodgkinLymphoma.com*. I will be discussing the next steps for patients with Hodgkin lymphoma who have relapsed after autologous stem cell transplant.

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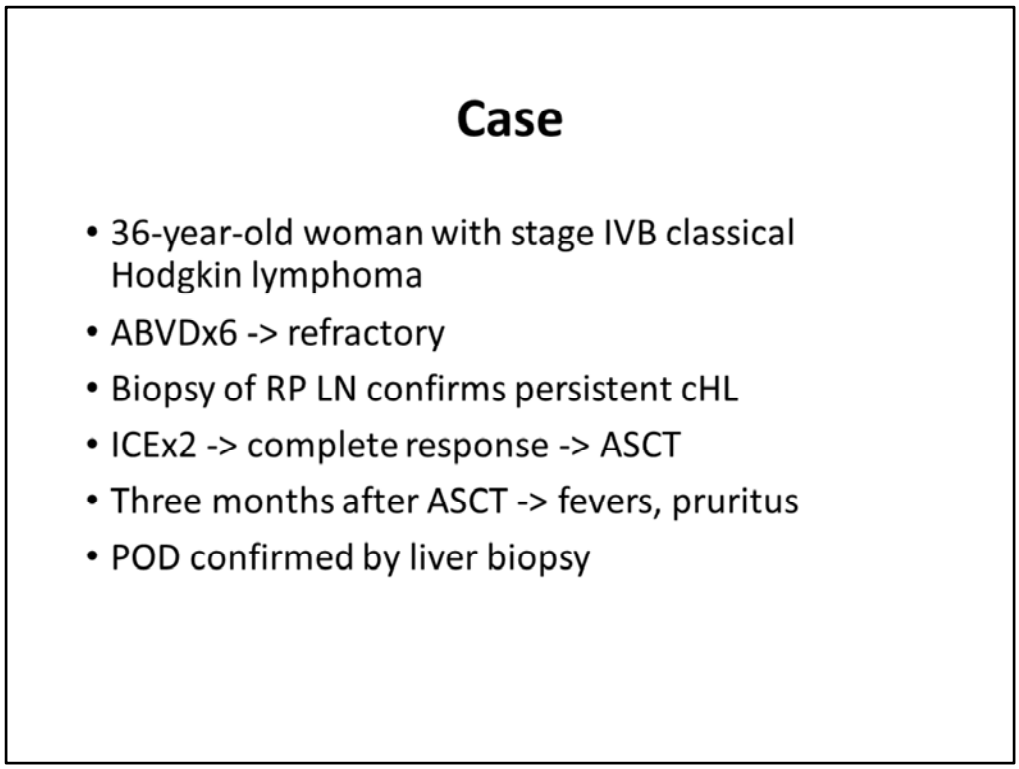

To begin with a case, this is a 36-year-old woman who initially was diagnosed with stage IVB classical Hodgkin lymphoma. She received treatment with ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) to which she was unfortunately refractory. She had a biopsy at the end of treatment of a retroperitoneal lymph node that confirmed persistent classical Hodgkin lymphoma. She went on to receive two cycles of ICE (ifosfamide, carboplatin, etoposide) chemotherapy to which she achieved a complete response and then went on to an autologous stem cell transplant. Unfortunately, 3 months after transplant, she developed fevers and pruritus, and a scan showed evidence of disease progression. She underwent a repeat biopsy of a liver lesion that confirmed disease progression.

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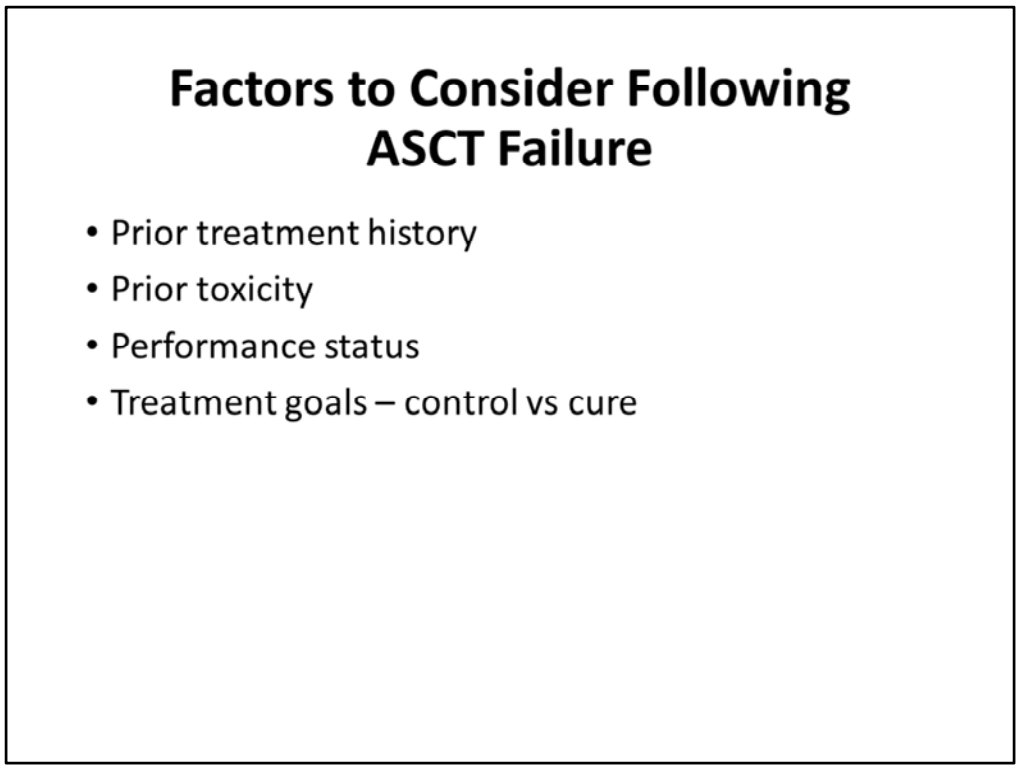

What are the factors that we consider when deciding upon the next treatment for this patient? Well, one of the most important factors is what treatment she has already received. In this era, many patients have already received brentuximab, but this patient had not received brentuximab. Given that it is very effective in this setting, it is one of the common next treatments that we would choose. We would also consider prior toxicities, for example, prior neuropathy when choosing our next treatment, the patient's performance status, their age, and whether our goal of treatment is to try to cure the disease with a potential allogeneic stem cell transplant or whether we are trying to aim for more of disease control. This might be dependent upon the patient age, their comorbidities, and also their own desires.

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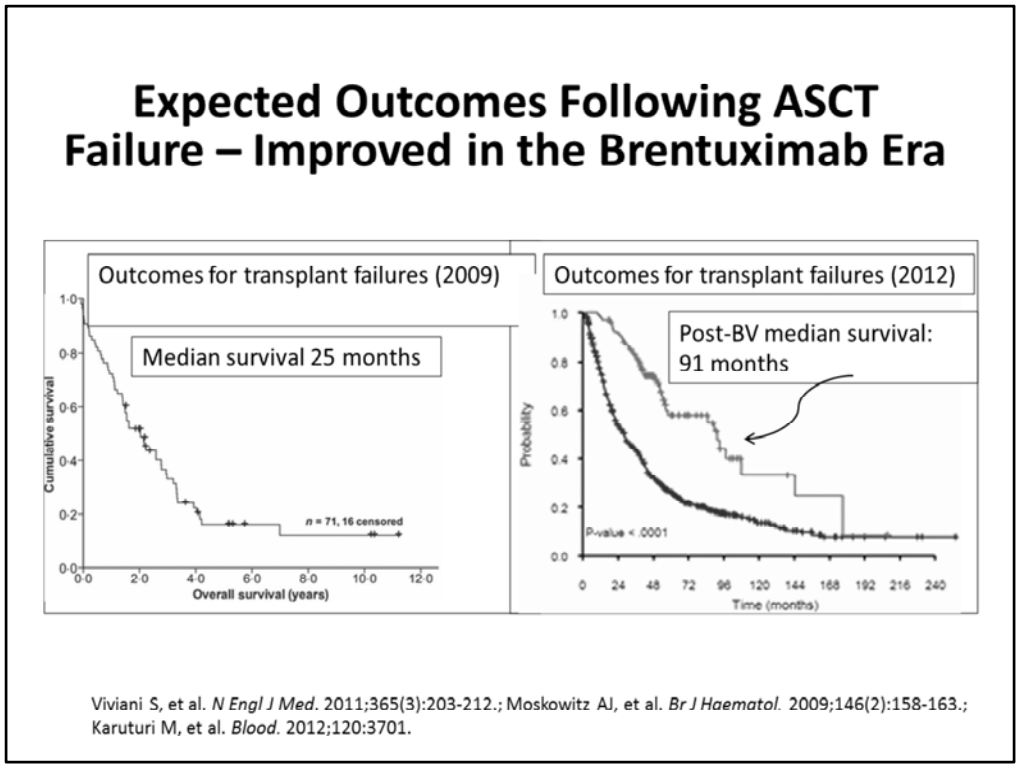

What are the expected outcomes for a patient who relapses after an autologous stem cell transplant? In the past, before we had some of the newer agents that we have available now, the outcomes for these patients were actually quite dismal. The median survival for a patient who had failed a transplant was only about 25 months. More recently, now that we have the availability of brentuximab, that has changed significantly. It is now estimated the median survival in the post-brentuximab era is about 91 months for patients who relapse after transplant, and it is probably even better now that we have anti-PD-1 therapy for Hodgkin lymphoma.

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Summary of Active Agents in Rel/Ref HL

	Drug	n	ORR	Reference
	Brentuximab vedotin	102	75%	Younes, et al. *J Clin Oncol*. 2012
Anti-PD1	Nivolumab	23	87%	Ansell, et al. *N Engl J Med*. 2015
Anti-PD1	Pembrolizumab	31	66%	Moskowitz CH, et al. ASH 2014
	Bendamustine	36	53%	Moskowitz AJ, et al. *J Clin Oncol.* 2013
mTOR	Everolimus	57	42%	Johnston, et al. ASH 2012
HDAC	Vorinostat	25	4%	Kirschbaum, et al. ASH 2007
HDAC	Panobinostat	129	27%	Younes, et al. *J Clin Oncol.* 2012
HDAC	Entinostat	38	12%	Batlevi, et al. *Haematologica*. 2016
HDAC	Mocetinostat	51	33%	Younes, et al. *Lancet Oncol*. 2011
	Lenalidomide	36	19.5%	Fehniger, et al. *Blood*. 2011

With regard to the agents that are available for patients with relapsed and refractory Hodgkin lymphoma, this is just a summary of some of the agents that have been evaluated in clinical trials in the relapsed and refractory setting. The agents that I am going to go into in more detail are brentuximab vedotin which is one of the most active single agents for Hodgkin lymphoma as well as the anti-PD-1 therapy which also is very active in Hodgkin lymphoma as well. The other agents have been evaluated and have activity in Hodgkin lymphoma, but I am not going to go into them in more detail.

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Characteristics for Patients Enrolled on Phase II Study with Brentuximab Vedotin in Rel/Ref HL

	N=102
Age, median (range)	31 yr (15–77)
Gender	48 M / 54 F
ECOG status	
0	42 (41%)
1	60 (59%)
Refractory to frontline therapy	72 (71%)
Refractory to most recent treatment	43 (42%)
Prior chemotherapy regimens*	3.5 (1–13)
Prior radiation	67 (66%)
Prior ASCT	102 (100%)
Time from ASCT to first post-transplant relapse*	6.7 mo (0–131)

Younes A, et al. *J Clin Oncol.* 2012;30:2183-2189.

With regard to brentuximab, it was approved for relapsed and refractory Hodgkin lymphoma in 2011. That was based upon the results of this phase 2 study that enrolled 102 patients, all of whom had prior transplant.

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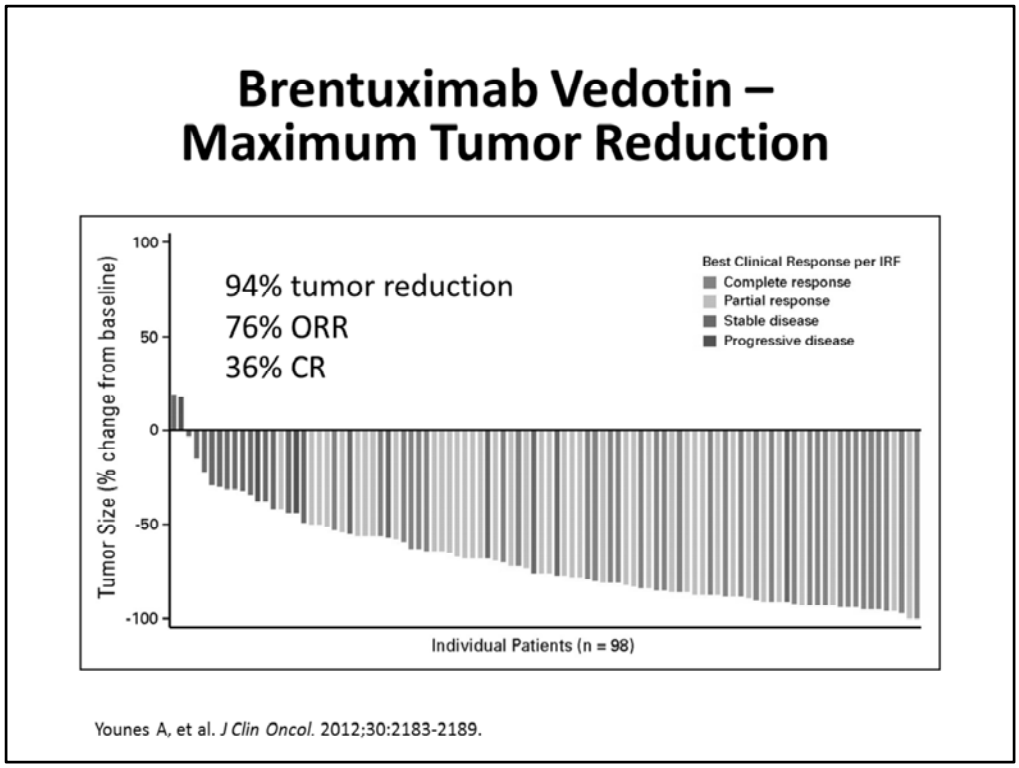

The response rates in the study were quite impressive. Over about 94% of the patients had some degree of tumor reduction. The overall response rate was 76% with about 36% of the patients having a complete response. Based upon these results, this led to approval of the brentuximab in 2011.

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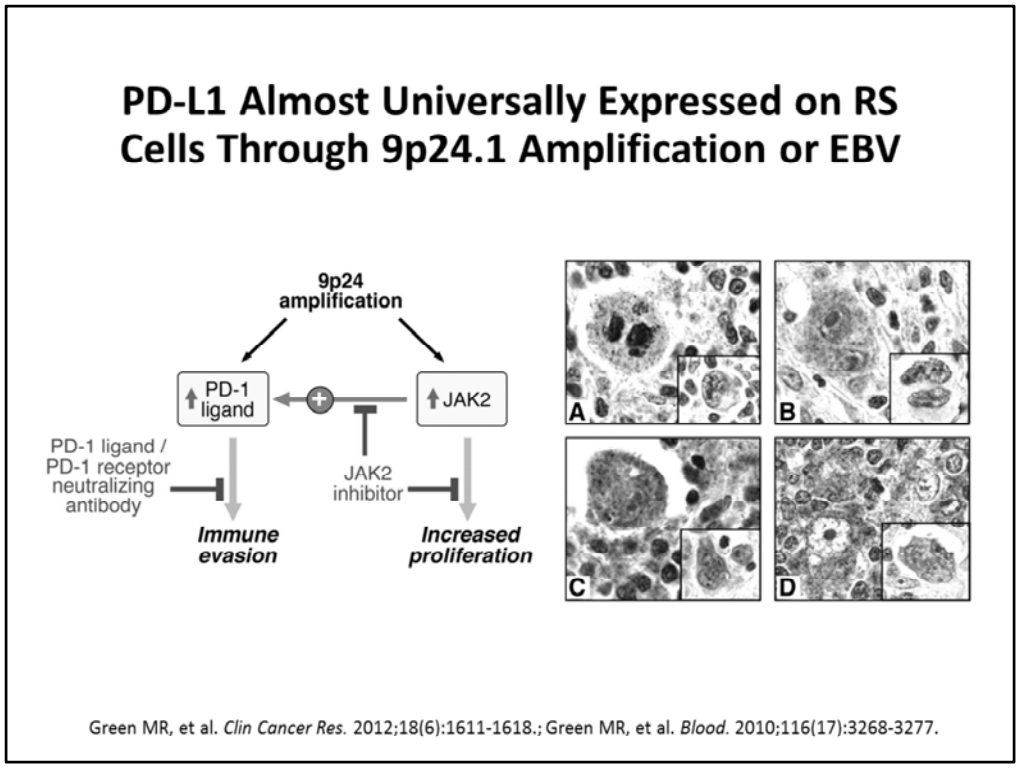

With regard to anti-PD-1 therapy, it has more recently shown significant activity in Hodgkin lymphoma. It turns out that Hodgkin lymphoma is a good example of a disease in which to evaluate anti-PD-1 therapy because the ligand for PD-1 is almost universally expressed on Reed-Sternberg cells. It is likely that this is the mechanism by which Hodgkin lymphoma is able to evade immune responses. The chromosome 9p24 is the chromosome that is often amplified in Hodgkin lymphoma. This contains a gene for JAK2 as well as PD-L1, and this is responsible for the overexpression of PD-L1 on Reed-Sternberg cells. In addition, the upregulation of JAK2 itself further drives expression of PD-L1.

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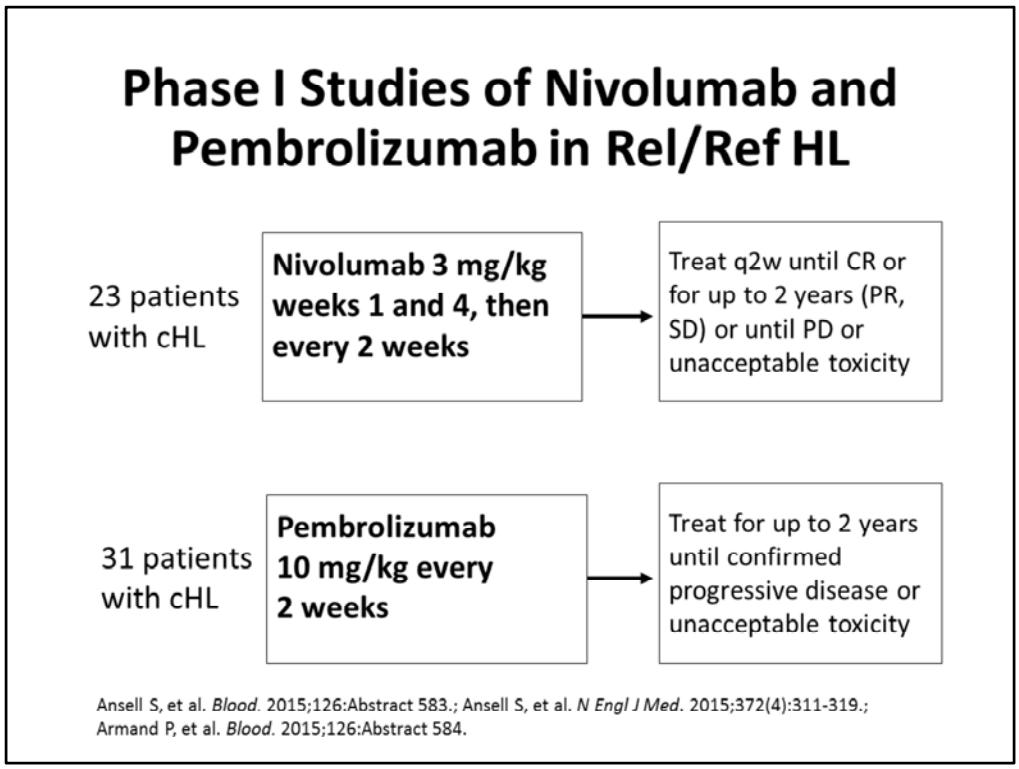

Both nivolumab and pembrolizumab which are both monoclonal antibodies against PD-1 have been evaluated in Hodgkin lymphoma. Both of these were evaluated in phase 1 studies that included cohorts for Hodgkin lymphoma. For the nivolumab study, there were 23 patients and pembrolizumab study, there were 31 patients.

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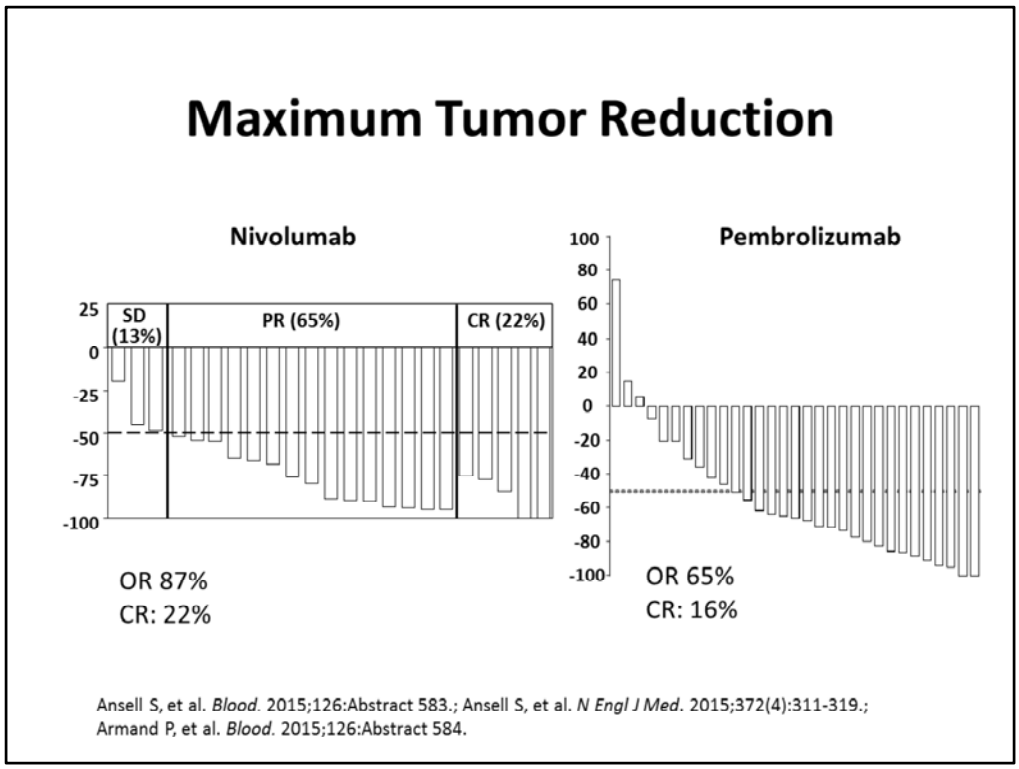

The response to both agents were quite impressive. Again, this is a highly pretreated patient population. Many of them had previously had transplant, and many of them had previously had brentuximab. The overall response rate on this study to nivolumab on the phase 1 study was 87% with 22% of the patients having complete response. Likewise, with pembrolizumab, the overall response rate was 65%, with 16% of the patients having complete response. Based upon this activity, both drugs have been evaluated or are ongoing evaluation in phase 2 studies.

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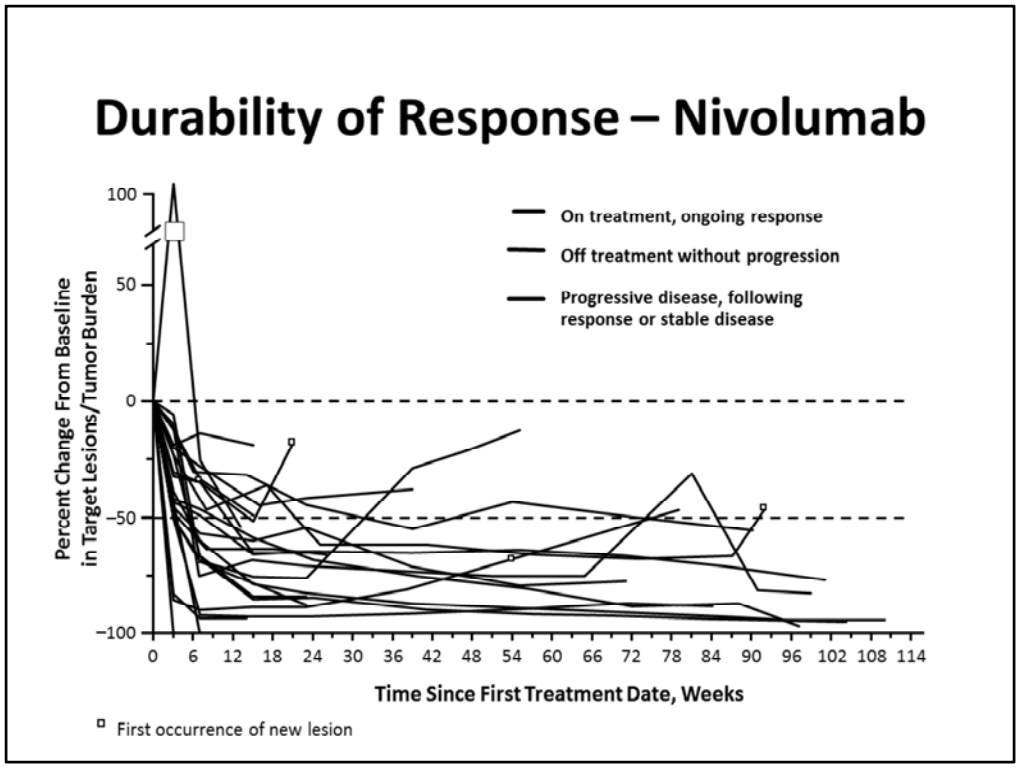

Actually, the durability of the response to nivolumab just going back to the phase 1 study was quite impressive, and this was seen with both nivolumab and pembrolizumab. As you can see, particularly you see the green and the blue lines here. They stretch out to as far as 108 weeks. This is showing the durability of response to treatment. Patients are really achieving long-term benefit from these drugs. Both of these drugs are being evaluated in phase 2 studies.

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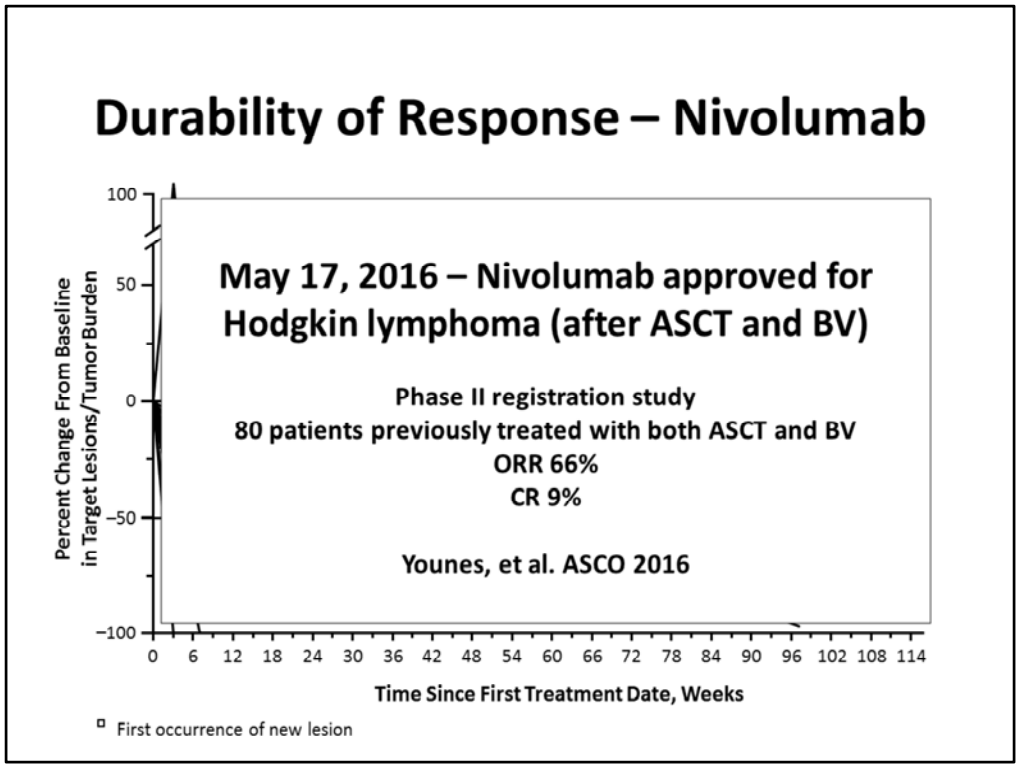

Nivolumab was actually approved for relapsed and refractory Hodgkin lymphoma in May of 2016. This was based upon the results of a phase 2 registrational study that enrolled 80 patients who had previously received both autologous stem cell transplant and brentuximab. The overall response on the study was 66%, with 9% of the patients having a complete response.

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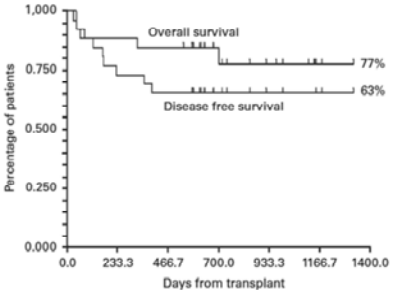
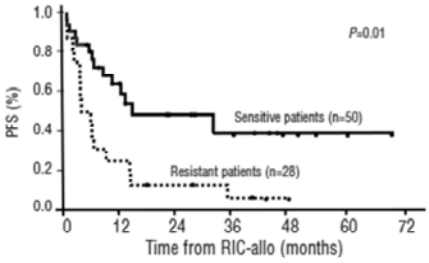
Allogeneic Stem Cell Transplant for Rel/Ref cHL

- Carefully selected patients
- Chemosensitivity predicts outcome[1]





- Haploidentical transplants – outcomes potentially appear more favorable[2]

[1]Sureda A, et al. *Haematologica.* 2012;92:310-317.; [2]Raiola A, et al. *Bone Marrow Transplant*. 2014;49: 190-194.

What about allogeneic stem cell transplant for relapsed and refractory Hodgkin lymphoma? This does represent one of the potential curative options for patients in the relapse setting; however, given the toxicity associated with transplant, it is important that we carefully select patients who are going to be referred for transplant. For Hodgkin lymphoma, the data is quite variable with progression-free survival, and disease-free survival rates reported from anywhere between 26% to 63% following allogenic stem cell transplant. The factors that seem to impact whether or not a patient is going to be cured with an allogenic stem cell transplant is whether or not they have chemosensitive disease going into the transplant. Those patients tend to do better. There is some data that suggest potentially that haploidentical transplants may be associated with a more favorable outcome for patients with Hodgkin lymphoma.

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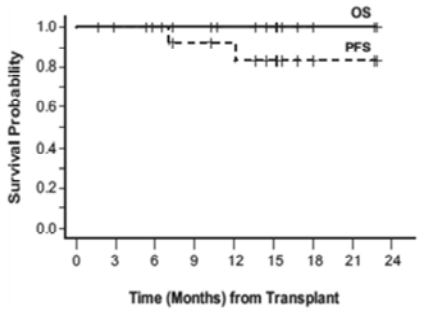
Allogeneic Stem Cell Transplant After Newer Agents

- Brentuximab followed by allogeneic SCT[1]
  - 18 patients; retrospective
  - Reduced intensity
  - Excellent outcomes but short median follow-up



- PD-1 therapy followed by allogeneic SCT[2]
  - 19 patients; retrospective; various histologies
  - Grade 2-4 acute GVHD 32%; chronic GVHD at 1 year 30%
  - 4 treated-related deaths
    - 3 severe acute GVHD within 14 days
    - 1 VOD

[1]Chen R, et al. *Blood*. 2012;119:6379-6381.; [2]Merryman R, et al. ASH 2015.

With regard to allogenic stem cell transplant following the newer agents that are now available for Hodgkin lymphoma, there was a retrospective study evaluating brentuximab followed by allogenic stem cell transplant for patients with relapsed and refractory Hodgkin lymphoma. With 1-year followup, the results look quite good, with progression-free survival at about 93%. However, we really need longer followup on the study to see if these results are going to pan out. With regard to allogenic stem cell transplant following anti-PD-1 therapy, the data is not quite mature. We still need more experience in this area. There was a retrospective analysis of 19 patients who were treated at Dana-Faber who had various different lymphoma histologies and who all went on to an allogenic stem cell transplant. While the 1-year overall survival for these patients was about 78%, there were some early treatment-related deaths observed within this group, with three patients having severe acute graft-versus-host disease within the first 14 days of transplant, and one patient having venoocclusive disease. Clearly, there is a suggestion that there might be more toxicity with an allogenic stem cell transplant following the anti-PD-1 therapy, and we need to be using these with caution.

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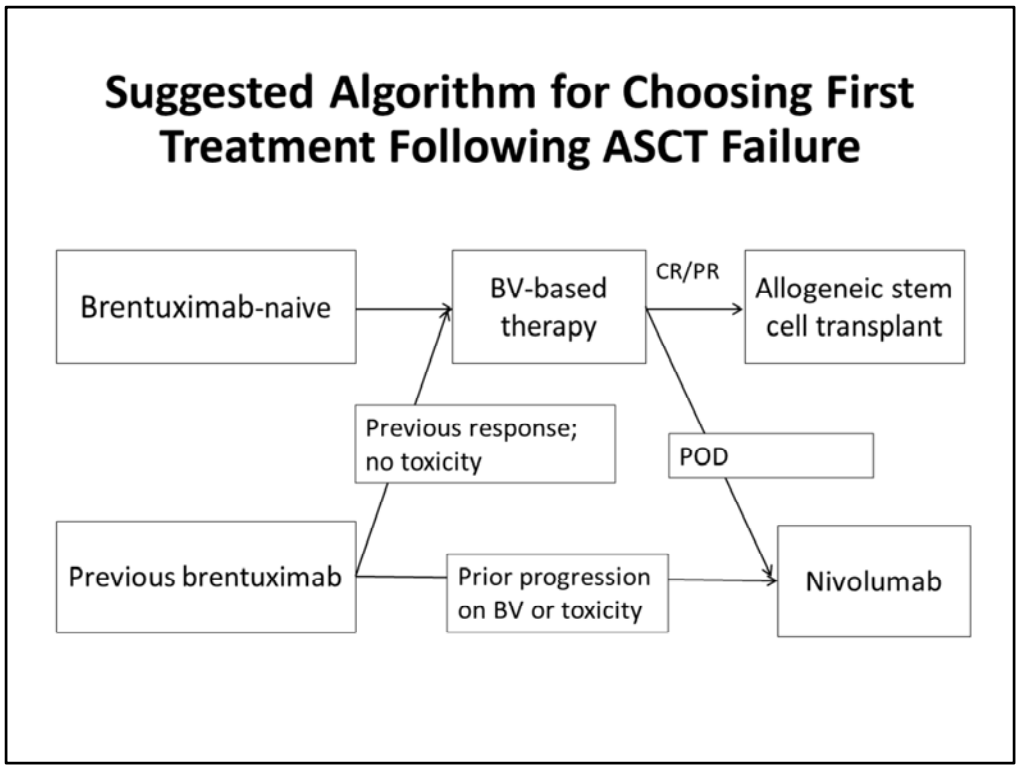

How would I approach a patient who has failed an autologous stem cell transplant or has relapsed after an autologous stem cell transplant and has not previously received brentuximab, as is the case for our patients in this talk? A patient who has not previously received brentuximab, it is pretty straightforward that brentuximab would be my first option for them after relapsing after an autologous stem cell transplant. I would choose either single-agent brentuximab, or if there is a clinical trial available evaluating a brentuximab combination, I think that that would even be a better choice. If they achieve a complete or partial response to treatment, I do think it is reasonable to consider consolidation with an allogenic stem cell transplant if they are otherwise healthy, have no significant comorbidities, I think that is a reasonable thing to consider. Now, there is recent data from the phase 2 brentuximab study that a small subset of those patients who had a complete response to brentuximab have remained in remission 5 years out from their initial treatment. There is a suggestion that single-agent brentuximab alone can potentially be curative, even without an allogenic stem cell transplant. This is a very small group amongst these patients that were enrolled in the study, but it is intriguing to consider this as a possible curative treatment on its own. For a patient who is unwilling to go for a transplant or for whom a donor is not available, you can consider monitoring these patients if they achieve complete response. For patients who previously received brentuximab either as part of their frontline or second-line treatment, which is now being done more and more as part of clinical trials, I would still at times consider treating with brentuximab again if they had a good response to brentuximab in the past and they do not have significant toxicity from it. If they have had prior progression on brentuximab or they have had toxicity associated with it, then I would consider anti-PD-1 therapy. Nivolumab is now approved in this setting, and so that would be the treatment I would use outside of a clinical trial. I would also be looking for clinical trials, potentially including anti-PD-1 therapy in combination with other agents. With regard to what we do after anti-PD-1 therapy for a patient who responds and with a complete response or partial response, I am often continuing their treatment, particularly if they have a partial response, which is the case for the majority of the patients. I would continue them on treatment as long as they are tolerating the treatment and not having significant toxicity to the treatment. Given my concerns about the role of allogenic stem cell transplant after a PD-1 therapy, and in particular the potential of toxicities associated with it, I am not excited about offering an allogenic stem cell transplant to a patient directly following anti-PD-1 therapy. That currently is not my practice, although I think we need more data in this area.

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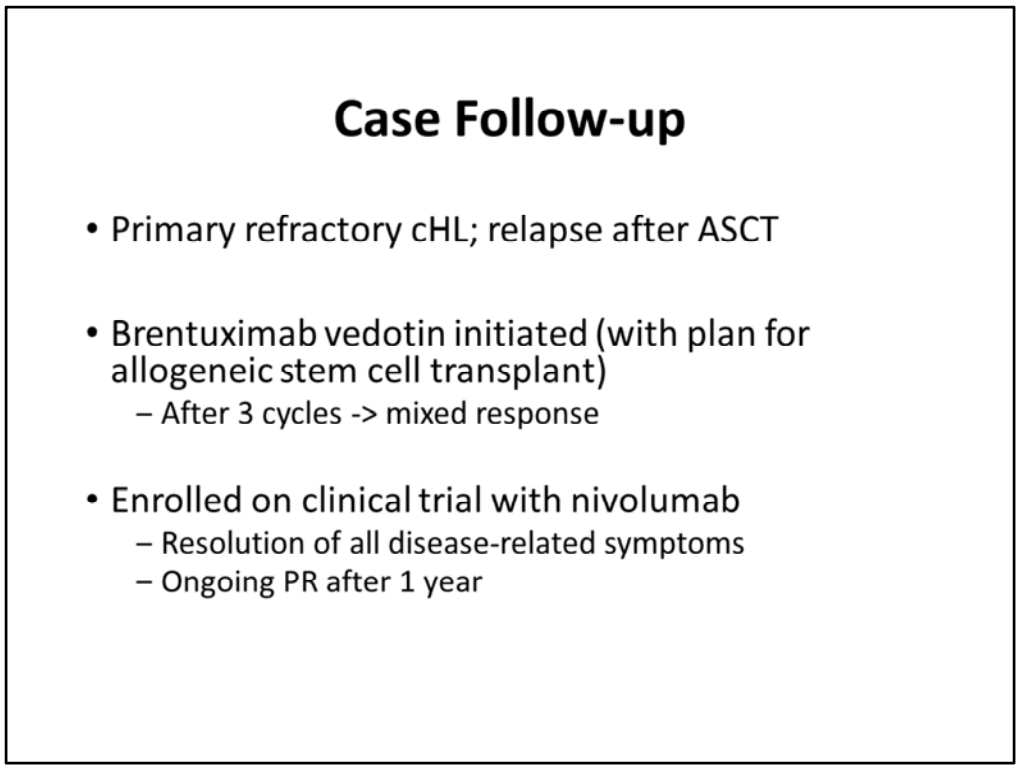

To follow up on our patient, this was our patient with primary refractory classical Hodgkin lymphoma who had relapsed after an autologous stem cell transplant. Following transplant, as I mentioned, we decided to treat her with brentuximab with the plan for a potential allogenic stem cell transplant. However, unfortunately, after three cycles of brentuximab, she underwent re-imaging that showed only a mixed response with some areas of progression. At that point, she was, therefore, enrolled in a clinical trial with nivolumab because it was not yet FDA approved. Fortunately, she had resolution of all her disease-related symptoms, and she achieved a partial response when she had repeat imaging after 12 weeks. At this point, 1 year after treatment, she remains with a partial response. After discussions with her regarding the pros and cons of allogenic stem cell transplant and other treatments, we have decided to keep her on treatment because she is having ongoing favorable clinical benefit from the treatment, and she is feeling quite well.

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