Incorporating Immunotherapy in the Treatment of Hodgkin Lymphoma

Welcome to *Managing Hodgkin Lymphoma*. My name is Dr. Craig Moskowitz. In this presentation, I will be discussing the potential role of immunotherapy in the treatment of Hodgkin lymphoma and outlining the efficacy and safety of cancer immunotherapy studied thus far in clinical trials for this disease.

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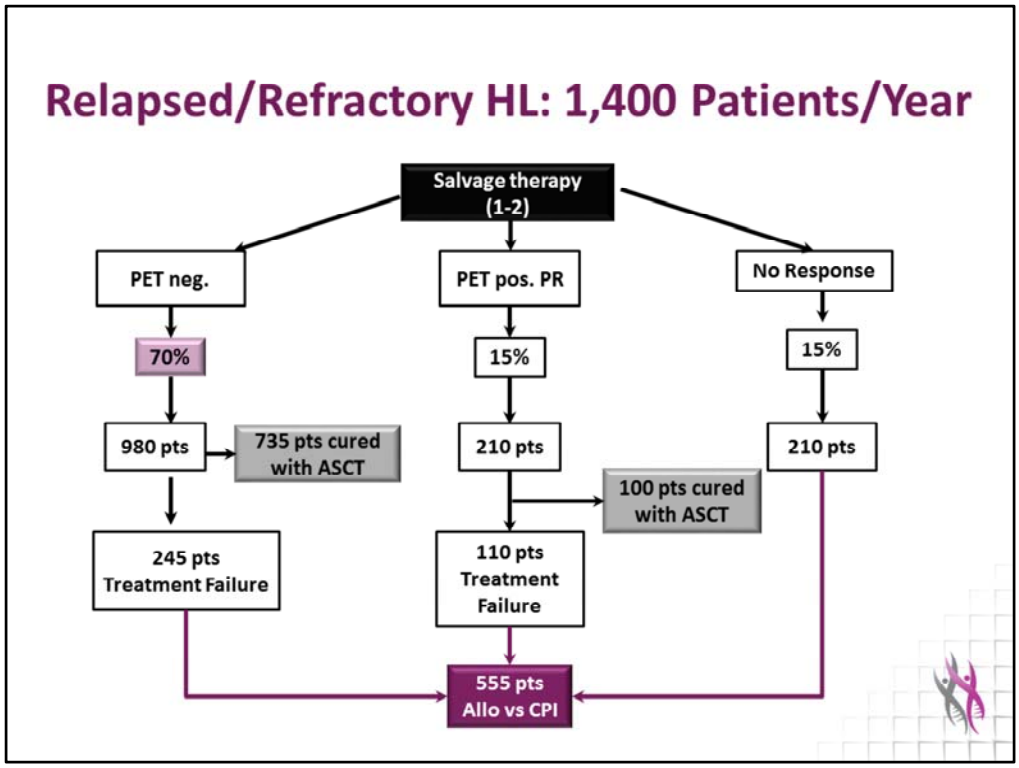
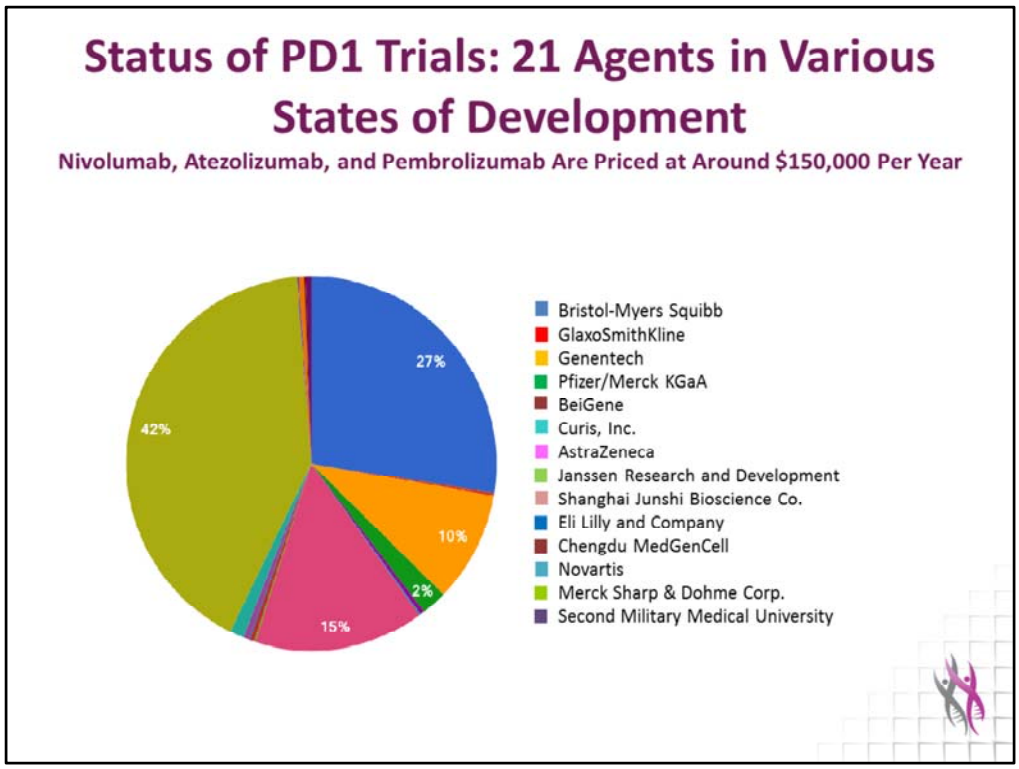


The patient population that we are going to be discussing is relapsed and refractory Hodgkin lymphoma, which is approximately 1,400 patients each year in the United States. About 8,500 patients each year are diagnosed with this disease in our country. The number one treatment is salvage chemotherapy. This is usually platinum-based chemotherapy. I am willing to give one or two different salvage regimens to achieve a complete response to salvage chemotherapy, and a complete response is defined as a PET-negative outcome. There are three possibilities: patients who have a complete remission, patients who have a PET-positive partial remission, or this treatment will not work. Luckily for the patients, about 70% of these folks achieve a complete response after salvage chemotherapy. If you do the numbers, approximately 1,000 patients will have a PET-negative response, and of those 1,000 patients, about three-quarters of them will be cured with high-dose therapy and autologous stem cell transplant. In patients who have a partial response, approximately half of those patients will be cured with stem cell transplant. If one does the math of these 1,400 patients, roughly 850 or so will be cured with second-line therapy followed by autologous stem cell transplantation; that leaves about 500 to 600 patients each year in the United States that need to receive additional therapy. Currently, that therapy is to receive a variety of outpatient chemotherapy programs which bridge the patient to an allogenic stem cell transplant. Now in the past year, we also have checkpoint inhibitors available to us, and this is a competing patient population.



It is interesting. This is a fascinating paper from *The Cancer Letter*. There are 21 different agents being studied in the United States with either PD1 or PD-L1 inhibitors. The majority of these studies and trials are being done with nivolumab or pembrolizumab. However, atezolizumab is also fairly commonly used and was recently approved for bladder cancer, but 21 different agents with the same target is what I find fascinating. If one compares this to statins for example, there are only seven statins approved in the United States, and really, only two statins are used, atorvastatin (Lipitor) and rosuvastatin (Crestor). Whether we need 21 different PD1 inhibitors is a matter of debate, but in Hodgkin lymphoma we have two that are approved.

At my center, which is Memorial Sloan Kettering Cancer Center, we have 75 prospective clinical trials open with a variety of checkpoint inhibitors in solid and liquid tumors. I oversee the scientific advisory board at our center, and I am perfectly comfortable with having this amount of clinical trials open with this target. However, it is critical if we are going to open a new clinical trial that we are going to learn something in addition to clinical efficacy.

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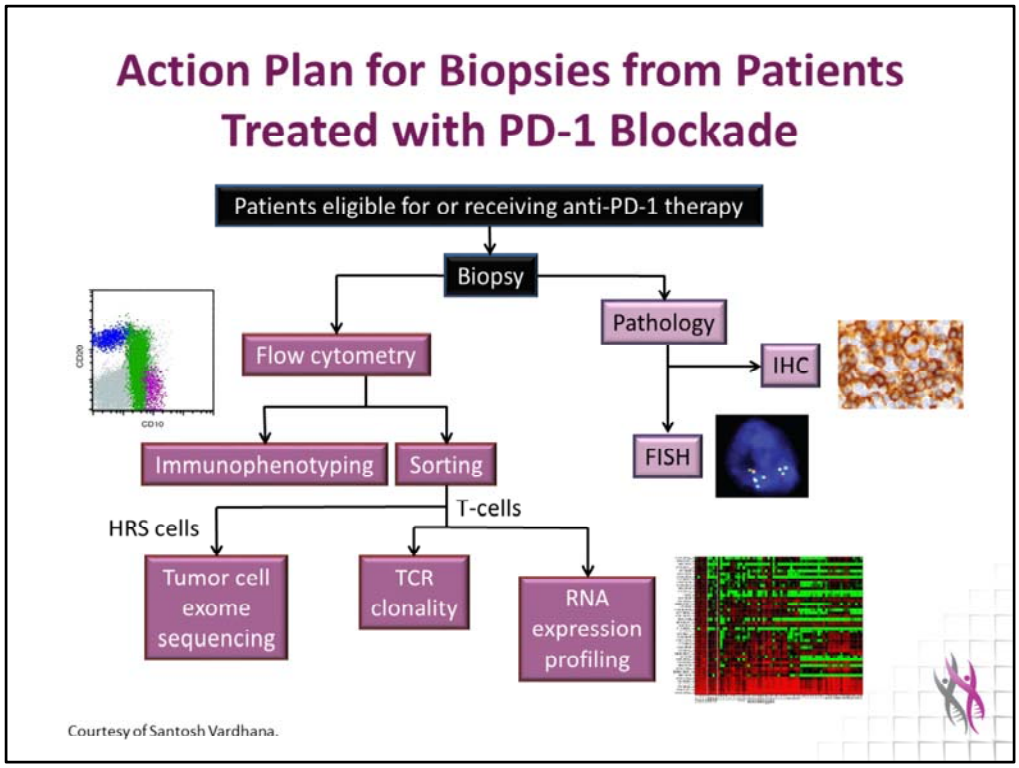
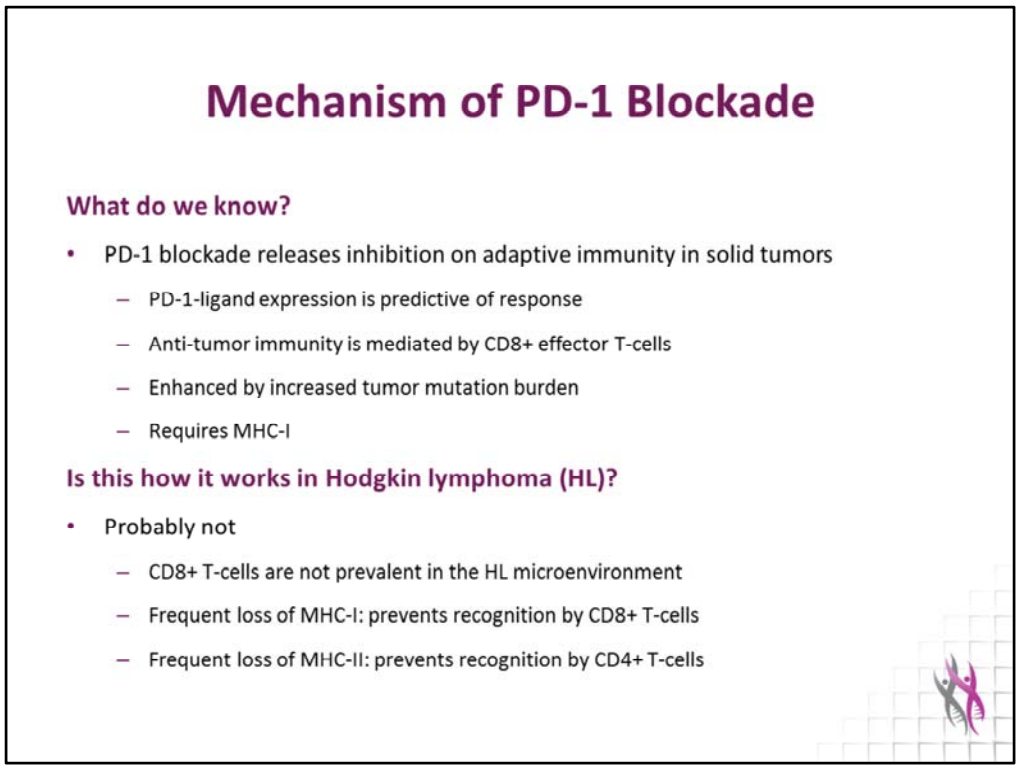
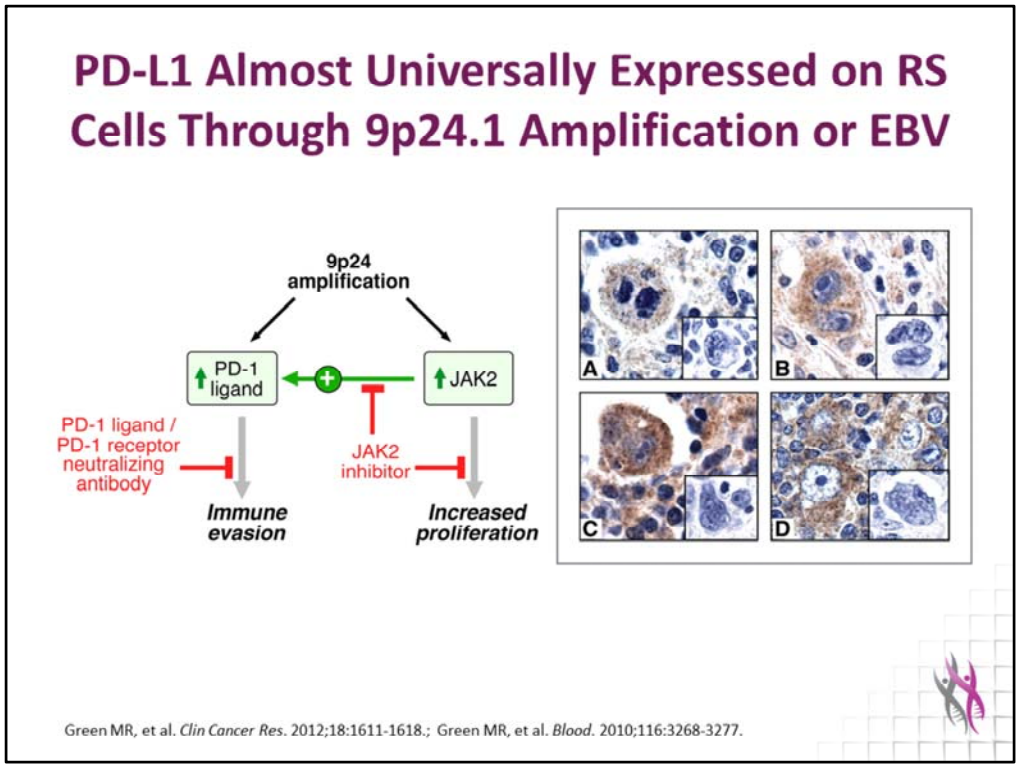


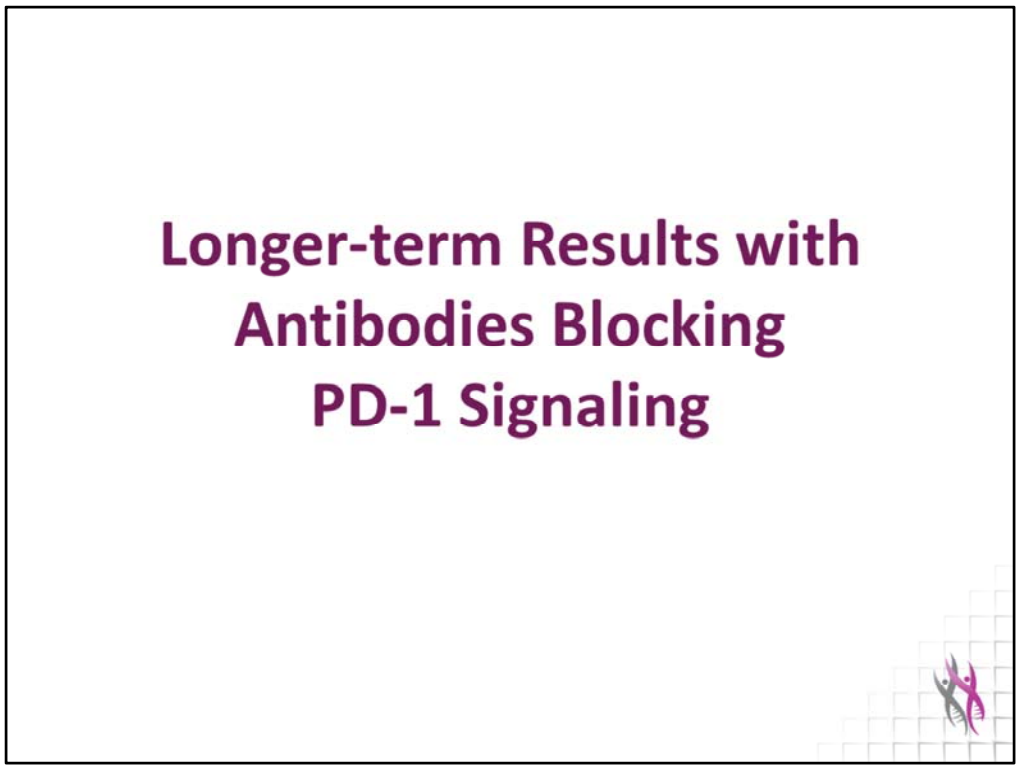
When I write a study using checkpoint blockade, invariably I will incorporate biopsies that are prospective into the clinical trial. If one looks at this schema here, when a biopsy is done we can do classic pathology, immune histochemistry, or FISH analysis on the sample. In addition, we can do flow cytometry, we can sort out T-cells, and we can look at RNA expression profiling. If we do this on all the patients getting checkpoint inhibitors, at least we will learn something, and it is very important because there are probably some subtle differences between these agents.



How does PD1 blockade work? Well, there is a lot of information in solid tumors. What we know is that PD1 blockade releases inhibition on adaptive immunity in solid tumors. It is very clear, especially in lung cancer and some of the other solid tumors, that PD1 ligand expression predicts for response to a checkpoint inhibitor. We also know that anti-tumor immunity is mediated by CD8-positive T-cells. In melanoma, it is very clear that response to a PD1 inhibitor is enhanced or increased by an increased tumor mutational burden. Lastly, this whole process requires MHC-I. How does it work in Hodgkin lymphoma? This is quite debatable. It certainly does not work the way it works in solid tumor. Number one, if one does biopsies prior to incorporating nivolumab or pembrolizumab in patients with Hodgkin lymphoma, there is a paucity of CD8-positive T-cells in the microenvironment. Number two, unfortunately, there is loss of MHC-I and MHC-II in the Reed-Sternberg cells and microenvironment, so this prevents recognition of CD8-positive T-cells or CD4-positive T-cells. It is very clear that in Hodgkin lymphoma, the checkpoint inhibitors do not work this way. One can take this a step further. There is a variety of positive and negative signals in this pathway. For example, LAG-3 binds to MHC class I and class II, that would make no sense to use in a patient with Hodgkin lymphoma.



What do we know in Hodgkin lymphoma? Well, we know that PD-L1 is uniformly expressed on Reed-Sternberg cells. This has been borne out in the clinical trials. In fact, at Memorial, it is part of our standard panel in a workup for a patient with Hodgkin lymphoma, as well as for primary mediastinal large cell lymphoma and some other rare types of diffuse large B-cell lymphoma. The reason that PD-L1 is overexpressed on the Reed-Sternberg cell is that there is a unique genetic abnormality in Hodgkin lymphoma samples, where there is amplification at the PD-L1 and PD-L2 locus because of abnormalities on chromosome 9p24. If one looks at this schema, one can see that PD-L1 is quite close to JAK2, and PD-L1 is also increased on tumor cells by EBV (Epstein-Barr virus) infection. As the audience knows, about half of the patient's tumors in Hodgkin lymphoma express on EBV. The right panel is just some staining of PD-L1 in Reed-Sternberg samples. If the checkpoint inhibitors do not work in Hodgkin lymphoma, scientifically that would make no sense because this is a disease set up for cytoreduction from these agents.

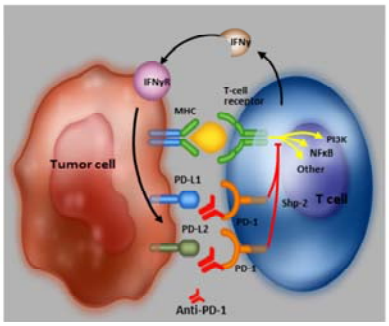


What I am going to do today, clinically, is just look at some of the long-term results with the PD1 inhibitors in classical Hodgkin lymphoma. Much of the data was presented at ASH in 2016, and some of this work is in press now.

Incorporating Immunotherapy in the Treatment of Hodgkin Lymphoma

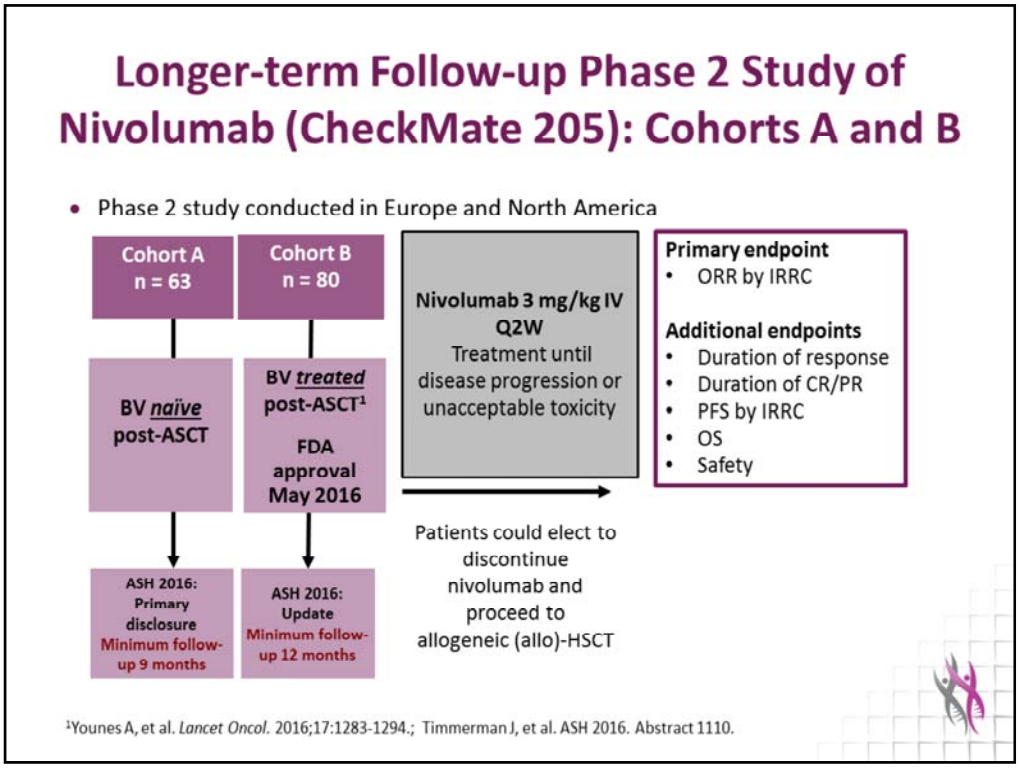
Immune Checkpoint Blockade: Blocking PD-1

- PD-1 ligands are overexpressed in inflammatory environments and attenuate the immune response via PD-1 on immune effector cells[1]
- PD-L1 expressed on malignant cells and/or in the tumor microenvironment suppresses tumor infiltrating lymphocyte activity[2]



[1]Francisco LM, et al. *J Exp Med*. 2009;206:3015-3029. [2]Andorsky DJ, et al. *Clin Cancer Res*. 2011;17:4232-4244.

This is a classic cartoon just showing the yin and yang between the tumor cell and the T-cell. In our particular case, the tumor cell expresses PD-L1 and PD-L2. It rarely presents MHC class I or II and the T-cells express PD1.



The first study that was updated at ASH in 2016 is what we called the CheckMate 205 clinical trial which was a three-cohort study. Cohorts A and B were updated at the meeting. Cohort A is an interesting cohort where patients had not previously received brentuximab vedotin, a drug that is approved in relapsed and refractory Hodgkin lymphoma, but all the patients previously had a stem cell transplant. Cohort B, which is the cohort I like to call the registration cohort with nivolumab, is for patients where both brentuximab vedotin and autologous stem cell transplantation failed. This led to approval of this agent, now 11 months ago. Nivolumab was given at a standard 3 mg/kg, given biweekly and in this particular study, which is the first that I know of using checkpoint inhibitors in lymphoma. Patients were able to stay on study drug until there was evidence of disease progression or toxicity. In both the phase 1B studies, the maximum amount of time on treatment was 2 years. The primary endpoint was overall response rate by independent review, and there was a variety of secondary endpoints.

Best Overall Response

Cohort A: Nivolumab in BV-Naïve Post-ASCT Patients

	Cohort A (n = 63)
	IRRC assessed
ORR, n (%) 95% CI	43 (68) 55, 79
CR, n (%)	14 (22)
PR, n (%)	29 (46)
SD, n (%)	13 (21)
PD, n (%)	7 (11)

Timmerman J, et al. ASH 2016. Abstract 1110.

In the primary endpoint, the complete response rate was 14%. Interestingly, when that was reassessed by investigators, it was 22%. The overall response rate was 68%, and the majority of patients are still on study at the present time.

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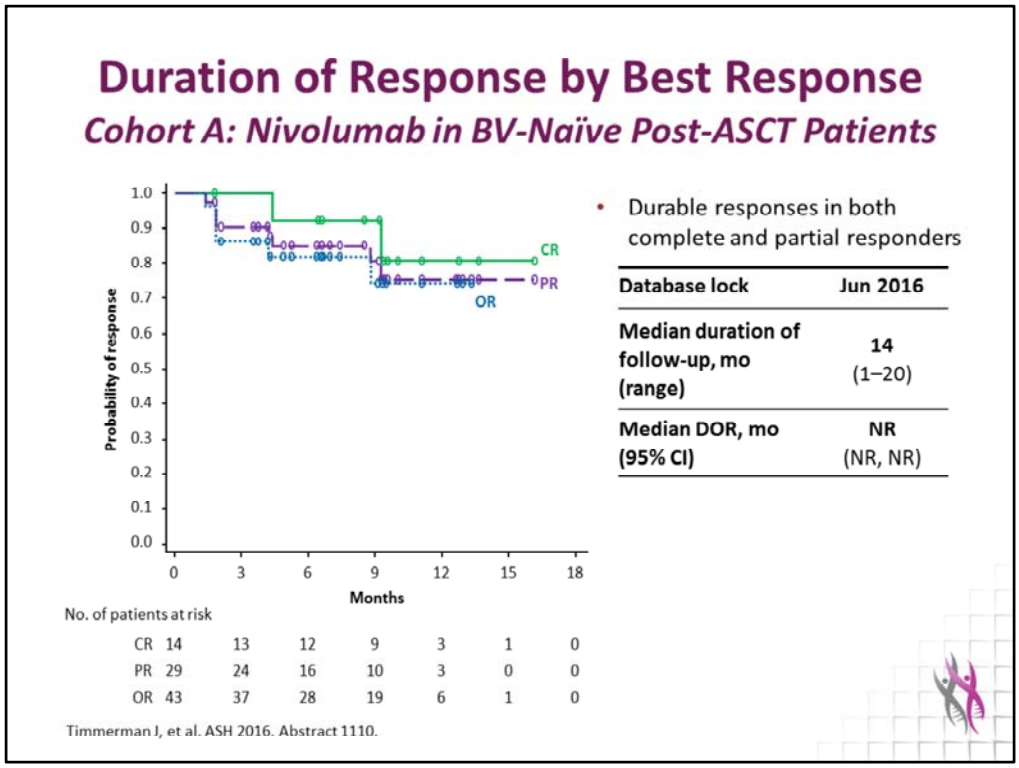
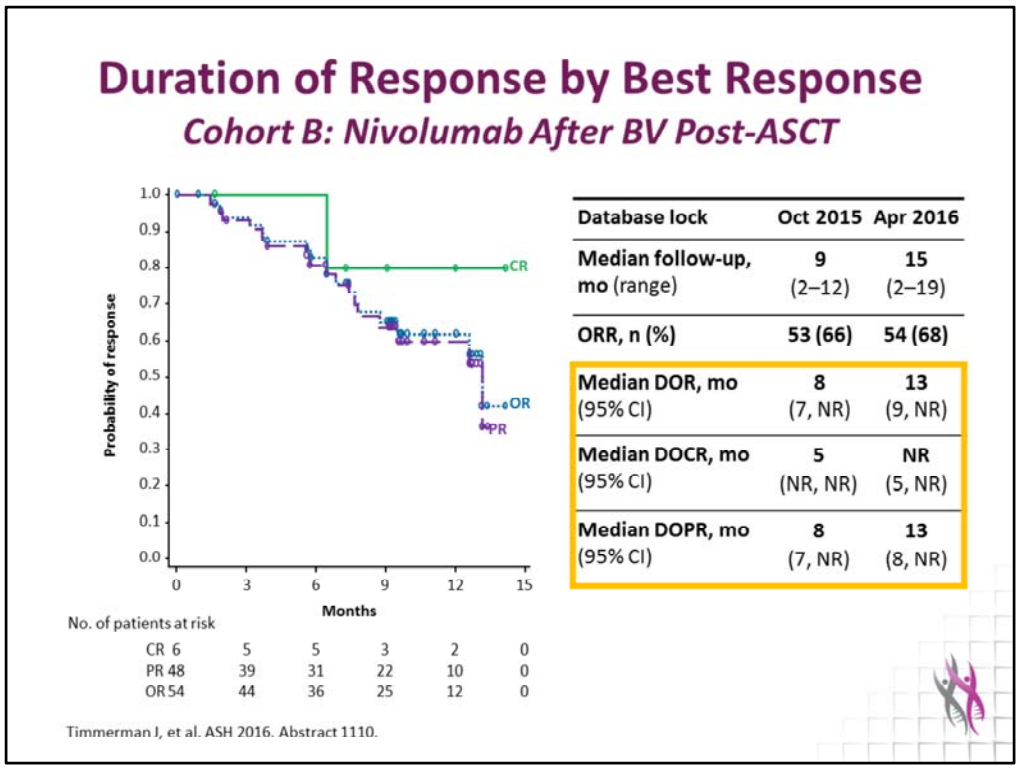


If one looks at outcome based upon either complete, partial, or partial response, it is very interesting that patients who have a partial response stay on treatment nearly as long as patients who had a complete response.



Database lock	Oct 2015	Apr 2016
Median follow-up, mo (range)	9 (2–12)	15 (2–19)
ORR, n (%)	53 (66)	54 (68)
Median DOR, mo (95% CI)	8 (7, NR)	13 (9, NR)
Median DOCR, mo (95% CI)	5 (NR, NR)	NR (5, NR)
Median DOPR, mo (95% CI)	8 (7, NR)	13 (8, NR)

If one looks at the duration of response based upon whether or not a complete response was achieved, it is clear that it is more favorable to have a complete response. Reminding the audience, for most patients who are treated with a checkpoint inhibitor, a complete response is uncommon. What is even more important is that nearly all patients have some evidence of clinical benefit from a checkpoint inhibitor, and there is a tremendous sense of well-being when folks get this treatment. For example, for Hodgkin lymphoma patients, these symptoms, either fever or night sweats, usually resolve within a day or two.

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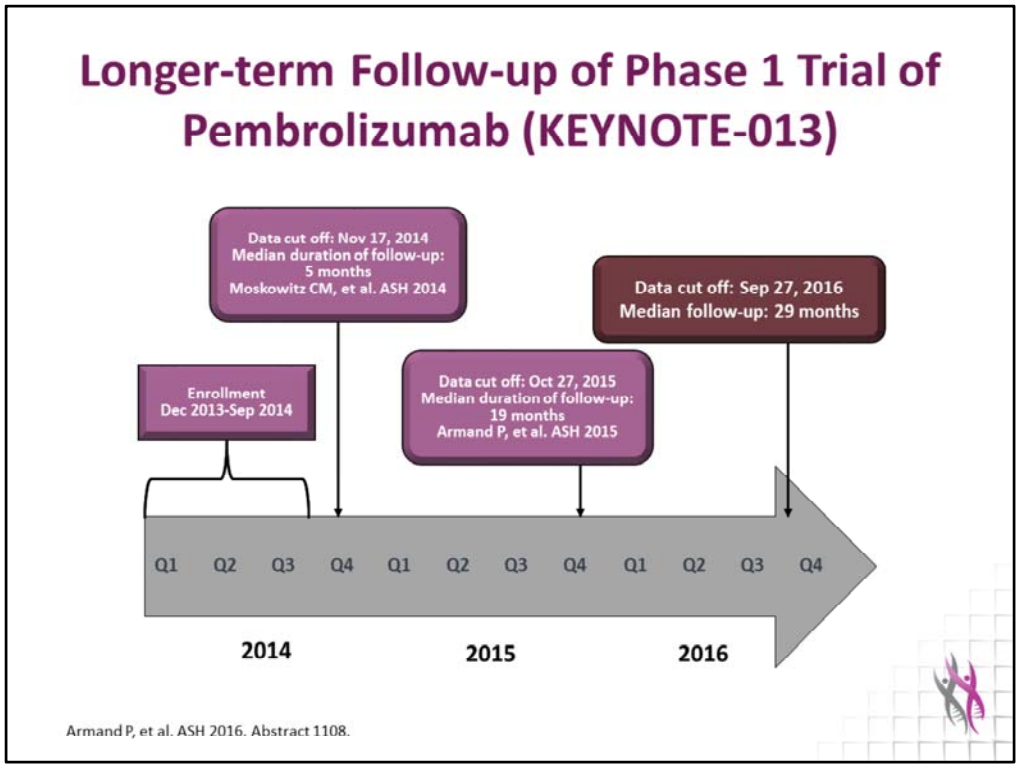


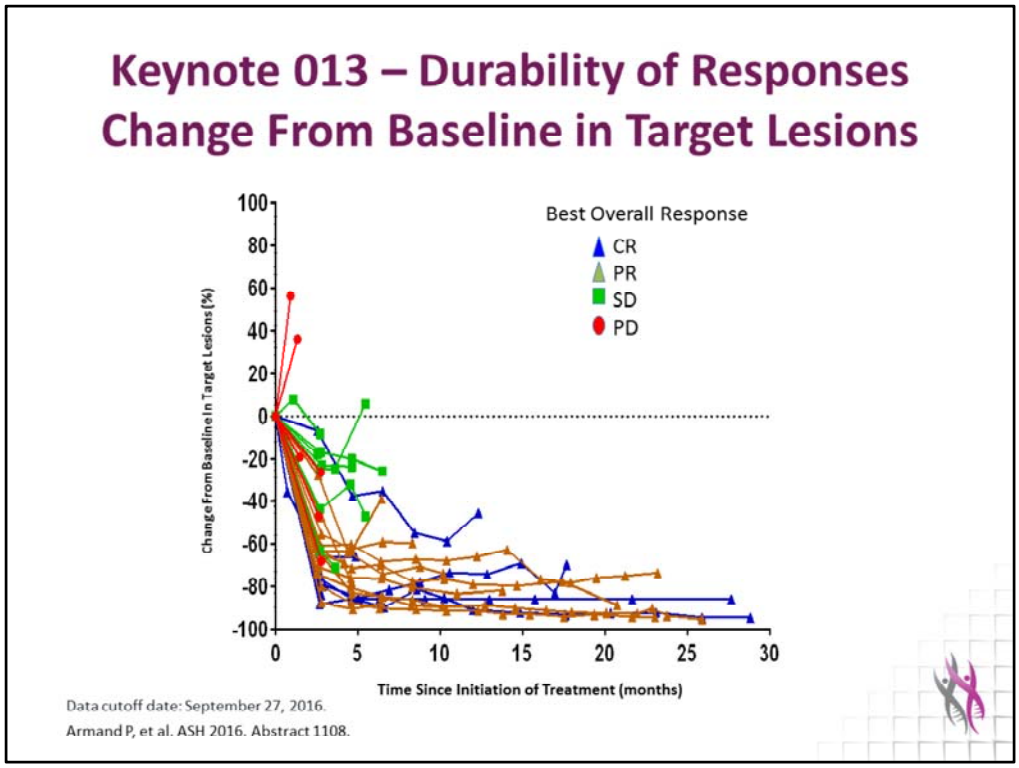
The second checkpoint inhibitor that was approved in Hodgkin lymphoma is pembrolizumab that was approved in March of 2017. This is an update of the phase 1B study where patients receive standard pembrolizumab, which was given on an every 3-week schedule and was administered for up to 2 years. Now, this particular study has the longest followup of any of the checkpoint inhibitor studies in Hodgkin lymphoma.

Keynote 013 - Best Overall Response

	All Patients N = 31		Prior ASCT, BV Post ASCT n = 16		ASCT Ineligible, Failed BV n = 8		Prior ASCT, BV Pre ASCT n = 7	
	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI	n (%)	95% CI
ORR	**18 (58%)**	39-76	**11 (69%)**	41-89	**3 (38%)**	9-76	**4 (57%)**	18-90
CR	**6 (19%)**	8-38	**3 (19%)**	4-46	**2 (25%)**	3-65	**1 (14%)**	0.4-58
PR	**12 (39%)**	22-58	**8 (50%)**	25-75	**1 (13%)**	0.3-53	**3 (43%)**	10-82

Data cutoff date: September 27, 2016.
Armand P, et al. ASH 2016. Abstract 1108.

What is interesting is, it is a small data set, only 31 patients**.** Overall response rate was 58% and the complete response rate was 19%. There were a number of different cohorts, either patients who had brentuximab vedotin and a stem cell transplant, those that were ineligible for stem cell transplant, and those who had brentuximab vedotin prior to a stem cell transplant. I know that that is a mouthful; in general, the results are about the same in all three cohorts.



This is a spider plot on that pembrolizumab study. One can see the tremendous amount of clinical benefit that is achieved from this drug, and these spider plots are superimposable to that of the nivolumab data set.

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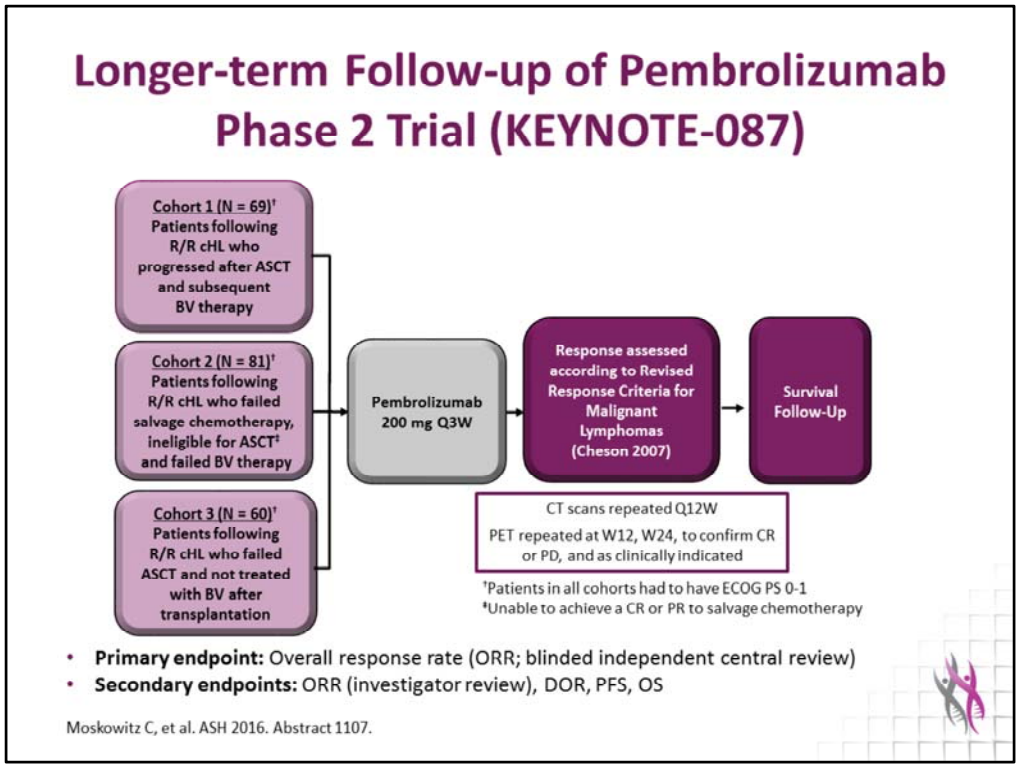

The phase 2 data with pembrolizumab which allowed this drug to get approved was presented at ASH this year. It is a 200 patient study. I am the principal investigator of that study, which led to the drug approval. In general, it was a fairly straightforward clinical trial, very comparable to the checkmate studies.

Keynote 087: ORR by Cohort (BICR)

	Cohort 1 Progressed after ASCT and subsequent BV therapy N = 69		Cohort 2 Failed salvage chemotherapy, ineligible for ASCT and failed BV therapy N = 81		Cohort 3 Failed ASCT and not treated with BV after transplantation N = 60	
	n (%)	95% CI†	n (%)	95% CI†	n (%)	95% CI†
ORR	**51 (73.9)**	**61.9-83.7**	**52 (64.2)**	**52.8-74.6**	**42 (70.0)**	**56.8-81.2**
Complete remission‡	15 (21.7)	12.7-33.3	20 (24.7)	15.8-35.5	12 (20.0)	10.8-32.3
Partial remission	36 (52.2)	39.8-64.4	32 (39.5)	28.8-51.0	30 (50.0)	36.8-63.2
Stable disease	11 (15.9)	8.2-26.7	10 (12.3)	6.1-21.5	10 (16.7)	8.3-28.5
Progressive disease	5 (7.2)	2.4-16.1	17 (21.0)	12.7-31.5	8 (13.3)	5.9-24.6
Unable to determine	2 (2.9)	0.4-10.1	2 (2.5)	0.3-8.6	0 (0)	–

Data cutoff: September 25, 2016.
†Based on binomial exact confidence interval method.
‡For complete remission, a residual mass was permitted for patients who were negative on PET scanning.
Moskowitz C, et al. ASH 2016. Abstract 1107.

In fact, the overall response rate in all three cohorts was over 70%. The complete response rate was over 20% in all the cohorts. In general, patients have stayed on drug for a long period of time.

Keynote 087: ORR by Blinded Central Review: Subgroup Analyses†

	Primary Refractory Disease (n = 73)		Relapsed After ≥3 Lines of Therapy (n = 146)	
	n (%)	95% CI‡	n (%)	95% CI‡
ORR	58 (79.5)	68.4-88.0	99 (67.8)	59.6-75.3
Complete remission	17 (23.3)	14.2-34.6	31 (21.2)	14.9-28.8
Partial remission	41 (56.2)	44.1-67.8	68 (46.6)	38.3-55.0
Stable disease	4 (5.5)	1.5-13.4	24 (16.4)	10.8-23.5
Progressive disease	8 (11.0)	4.9-20.5	20 (13.7)	8.6-20.4
Unable to determine	3 (4.1)	0.9-11.5	3 (2.1)	0.4-5.9

Data cutoff: September 25, 2016.
†These subgroups are not mutually exclusive.
‡Based on binomial exact confidence interval method.
Moskowitz C, et al. ASH 2016. Abstract 1107.

This is an interesting data set with primary refractory disease, which will be presented at the Lugano Meeting, which is an every other year lymphoma conference. Showing in the patient population that is deemed to be very unfavorable, the response rate is the same with pembrolizumab. I suspect that it will be exactly the same with nivolumab where patients have a complete response rate over 20% and overall response rate that is close to 80%.

Now, this is old news, and I think it is very important to discuss some of the newer data. In general, in lymphoma, we almost never give single-agent therapy except for palliation. If we are going to use drugs in the curative setting, we give combination therapy. I am going to discuss some of the combinations I feel are important for this seminar. One in particular, which I will discuss in a few minutes.

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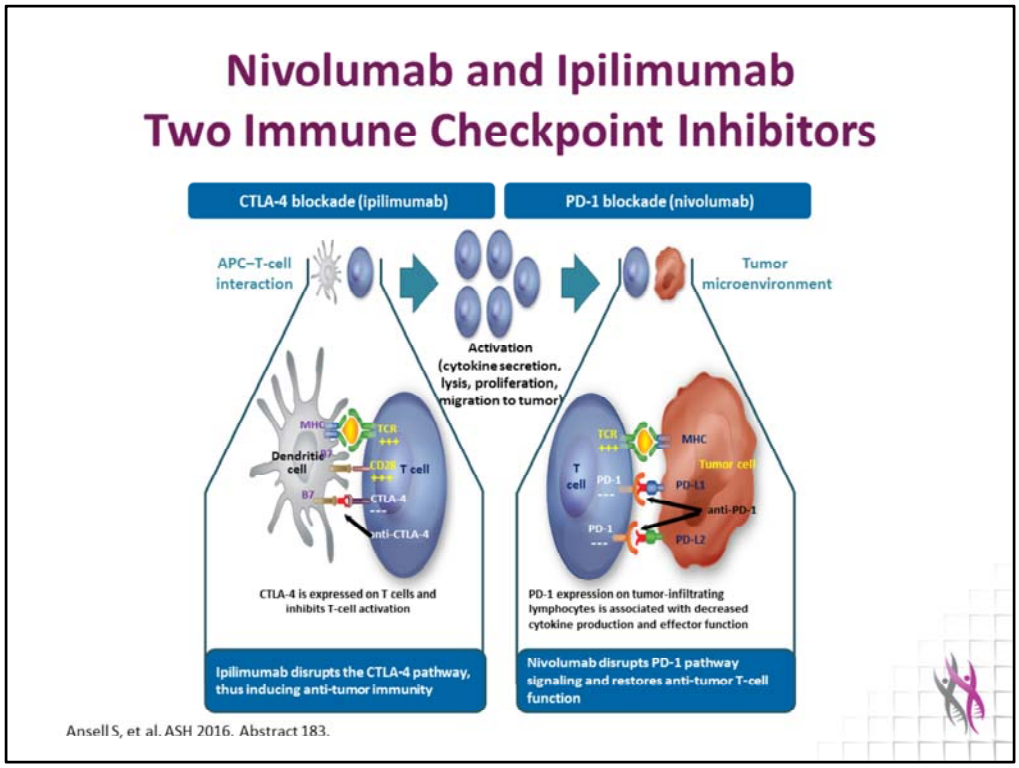
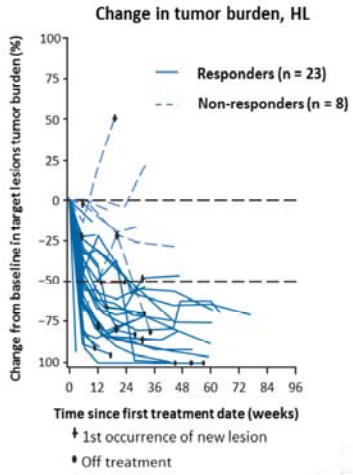


This particular one, however, may not be the optimal combination program in lymphoma. Nivolumab and ipilimumab, which as the audience knows is approved in melanoma and works on two distinct pathways in the T-cell system, has been looked at now in Hodgkin lymphoma.

Incorporating Immunotherapy in the Treatment of Hodgkin Lymphoma

HL: Best Overall Response

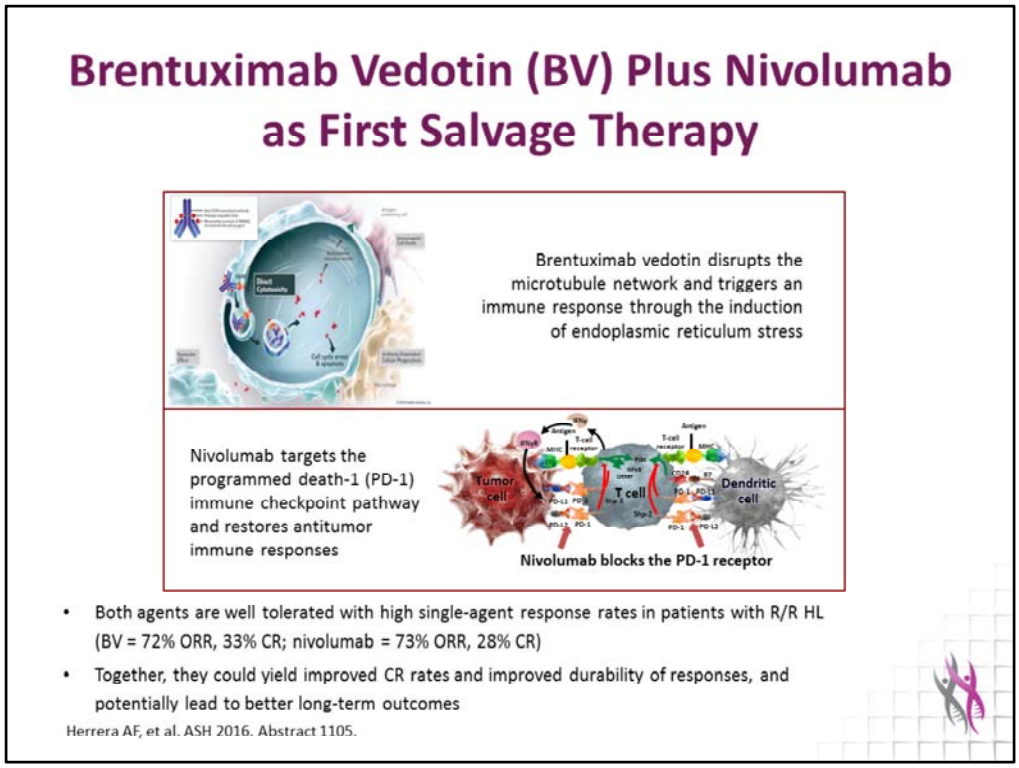
	HL (N = 31)
ORR, n (%)	23 (74)
Complete response	6 (19)
Partial response	17 (55)
Stable disease	3 (10)
Relapsed or progressive disease	3 (10)
Median duration of OR, months (range)	NR (0.0+, 13.4+)
	Transplant naïve (n = 18)
ORR, n (%)	12 (67)



Ansell S, et al. ASH 2016. Abstract 183.

This is a small data set of 31 patients. The complete response rate, the partial response rate, and the median time on treatment is fairly similar to getting nivolumab alone. That would be fine except the combination of ipilimumab and nivolumab is more toxic than nivolumab by itself. Although this is scientifically intriguing to use in patients, I do not see this moving forward in Hodgkin lymphoma management with nivolumab as such a well-tolerated and excellent drug.

Incorporating Immunotherapy in the Treatment of Hodgkin Lymphoma



On the other hand, from my point of view this was of the more important abstracts presented at ASH, this will be updated at the Lugano Meeting. This is a combination program of brentuximab vedotin and nivolumab being used as first salvage therapy in patients with classical Hodgkin lymphoma. This is now nivolumab being moved up in the treatment paradigm in this disease whereas these drugs, nivolumab and pembrolizumab, are approved for palliation. Now, we are trying to use these drugs in the curative setting. In this particular setting, the goal is to achieve a complete response prior to a stem cell transplant. The science behind this is very straightforward. By administrating brentuximab vedotin upfront, it is very likely that this will enhance the immune response to nivolumab. This is a combination program. It is not what people would like to call chemotherapy-free. Brentuximab vedotin is an antibody-drug conjugate or some people would like to say this is chemotherapy on a stick or targeted chemotherapy.

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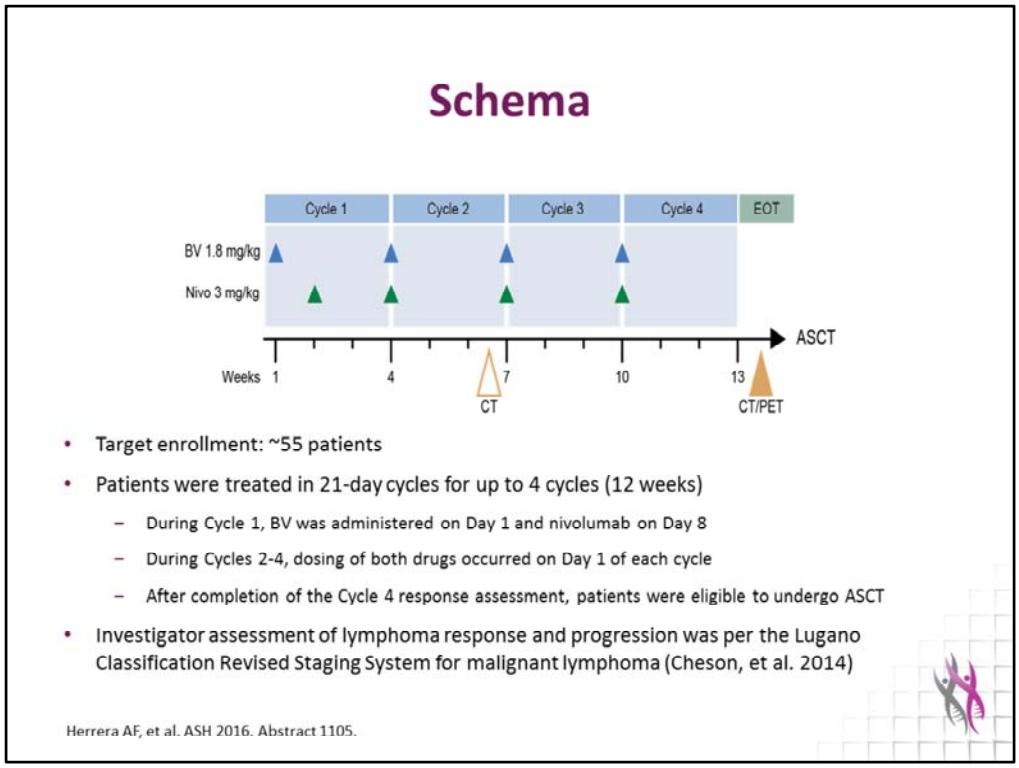
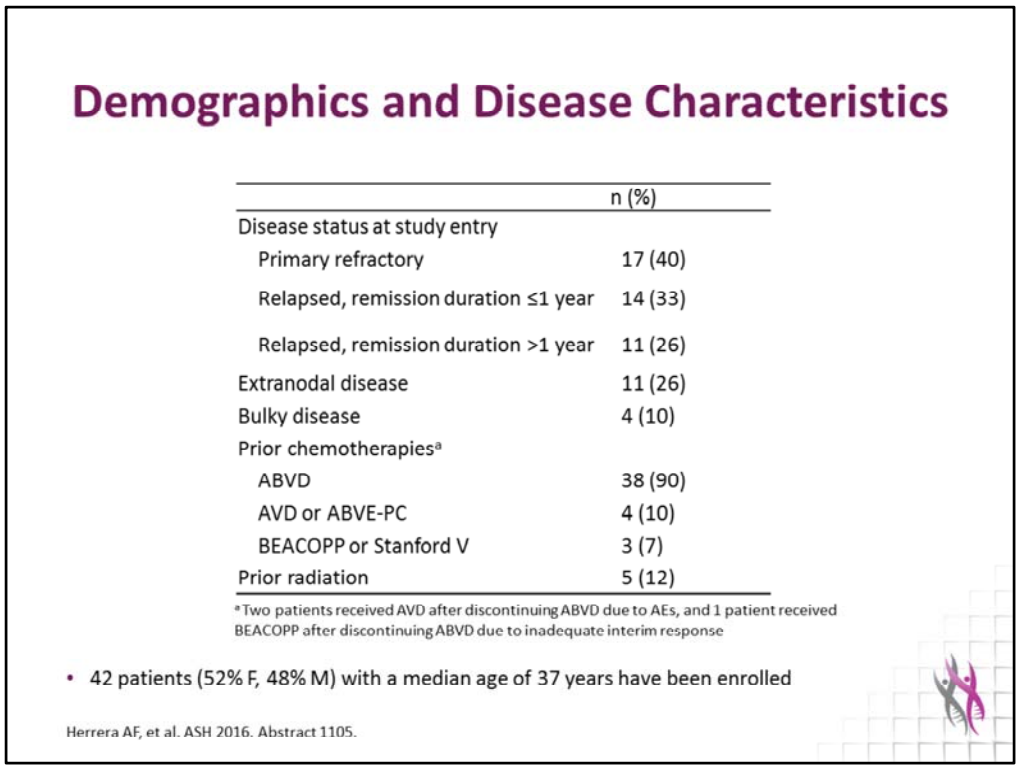


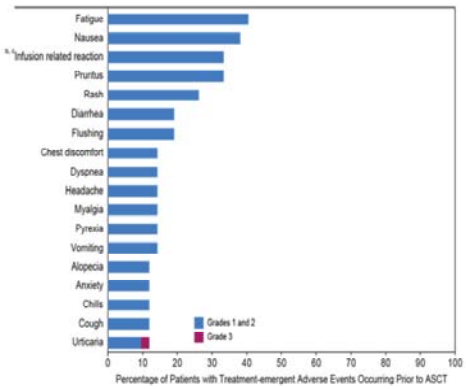
The schema was fairly straightforward. This study was led by Dr. Herrera from the City of Hope as well as from our group at Sloan Kettering. This is a combination program which used four cycles of brentuximab vedotin and nivolumab, followed by repeat imaging with the goal of this treatment program to achieve a complete response, which we know, as borne out by many studies, will improve the outcome with stem cell transplant.



In this particular study, typical patient population, about 40% of the patients had primary refractory disease, a number of patients had extranodal involvement, and nearly all the patients previously had ABVD chemotherapy.

BV + Nivolumab: Adverse Events

- AEs occurring in ≥10% of patients (N = 42) **pre-ASCT**[a] were all Grade 1 or 2 in severity with the exception of one Grade 3 urticaria event
- AEs occurring in ≥50% of patients **post-ASCT** completion (N = 6) included anemia (G3), vomiting (G1), diarrhea (G1), febrile neutropenia (G3), and neutropenia (G4)
- One patient with treatment-related **serious adverse event** after Cycle 1 BV: dehydration (G3), asthenia (G1), hypercalcemia (G2), malaise (G2), nausea (G1)



[a]3 patients (7%) experienced peripheral sensory neuropathy (Grade 1).
[b]Includes 1 occurrence of Grade 3 urticaria.
[c]One PT of IRR not reported as associated with infusion.
Herrera AF, et al. ASH 2016. Abstract 1105.

This is a fairly well-tolerated treatment program. We have a number of patients on this study**.** Rash is fairly common with both brentuximab vedotin and nivolumab, so it is not a surprise that one-third of patients had a rash, but it was manageable. Our biggest fear with these drugs is shortness of breath. Both agents have been reported to cause pneumonitis; however, in this particular treatment strategy, thus far, that has been minimal.

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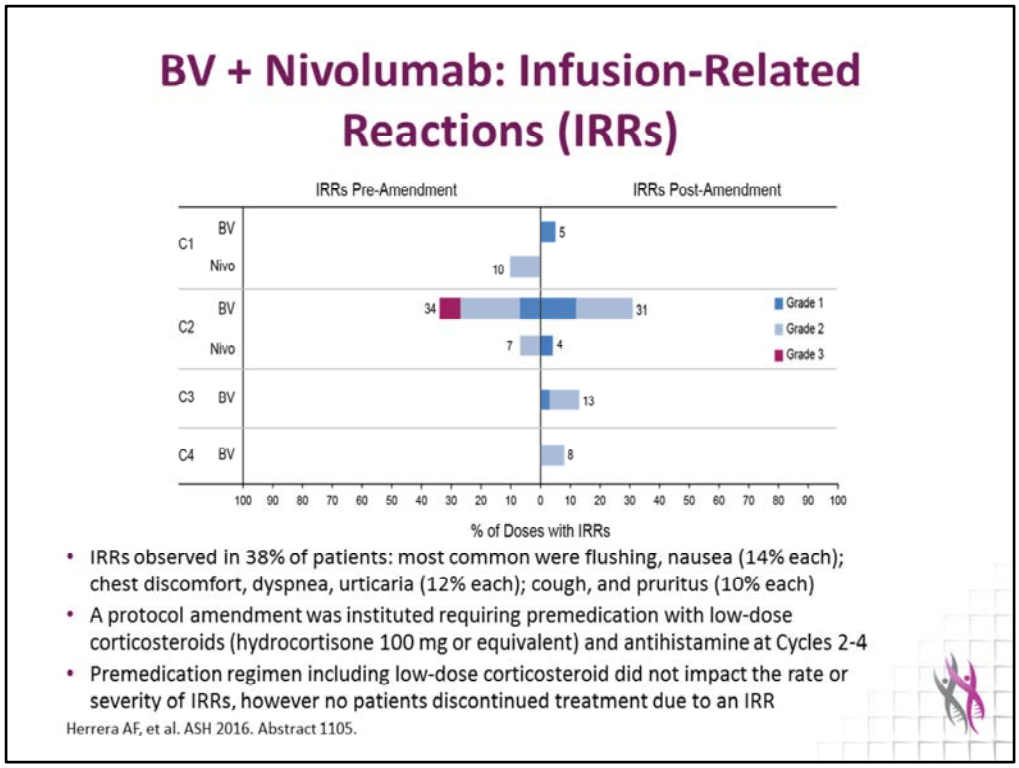

Unexpectedly, there was an increased amount of infusion reactions with brentuximab vedotin and nivolumab which led to an amendment and steroid requirement prior to giving this combination in treatment strategy.

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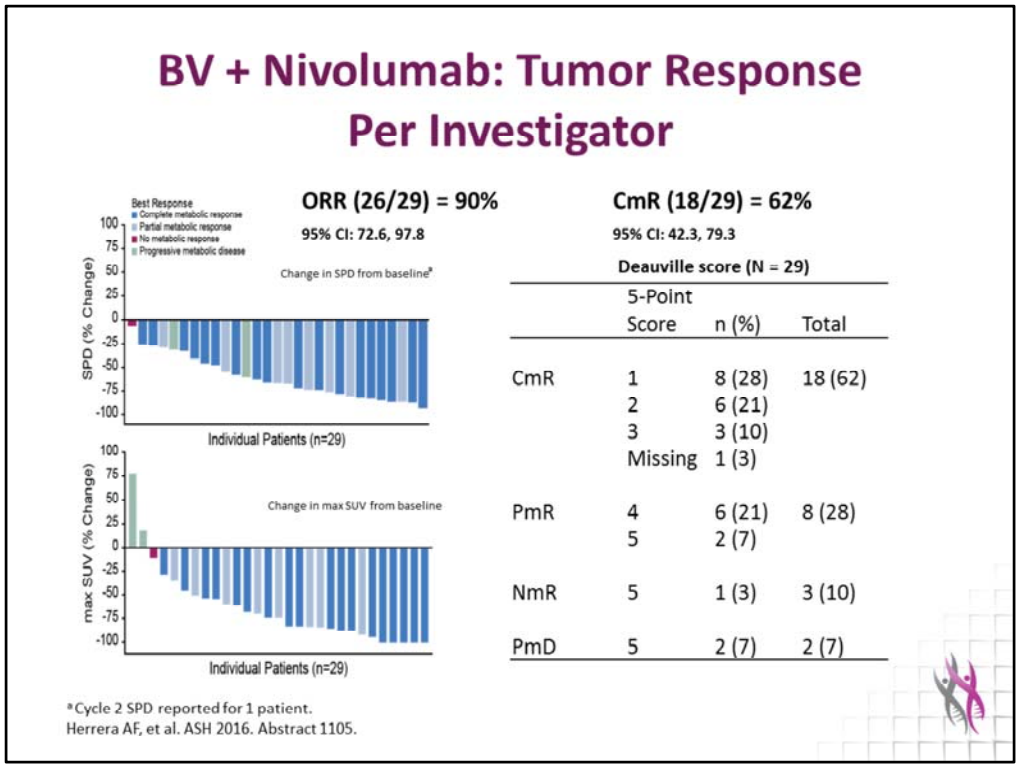
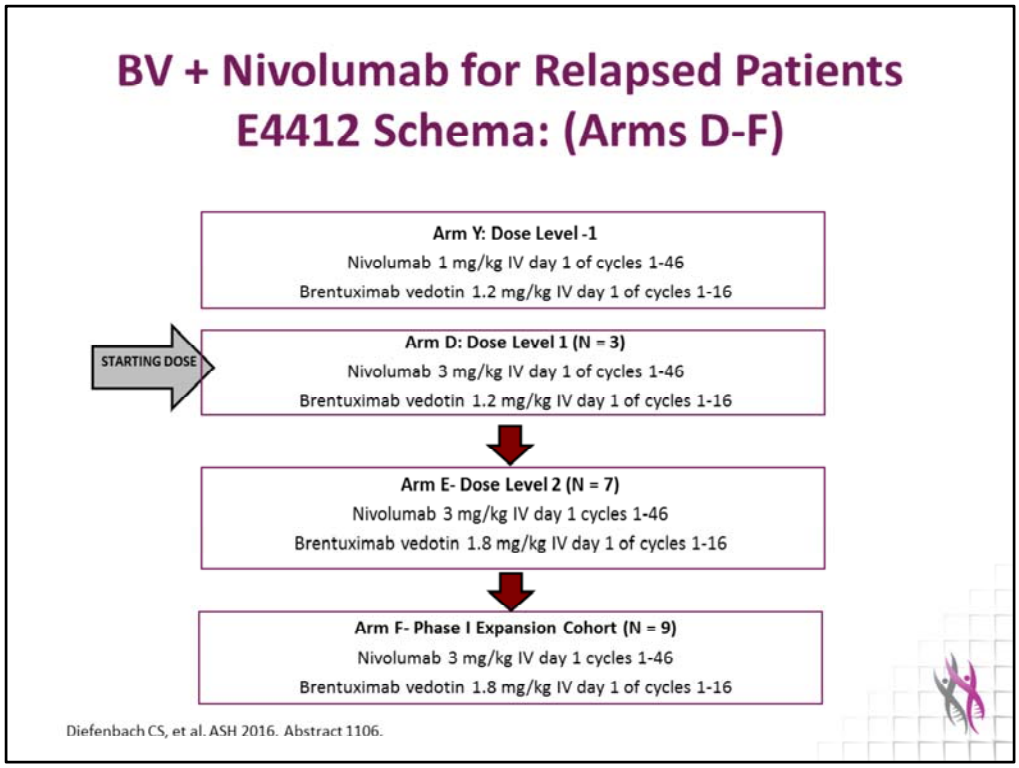


Deauville score (N = 29)

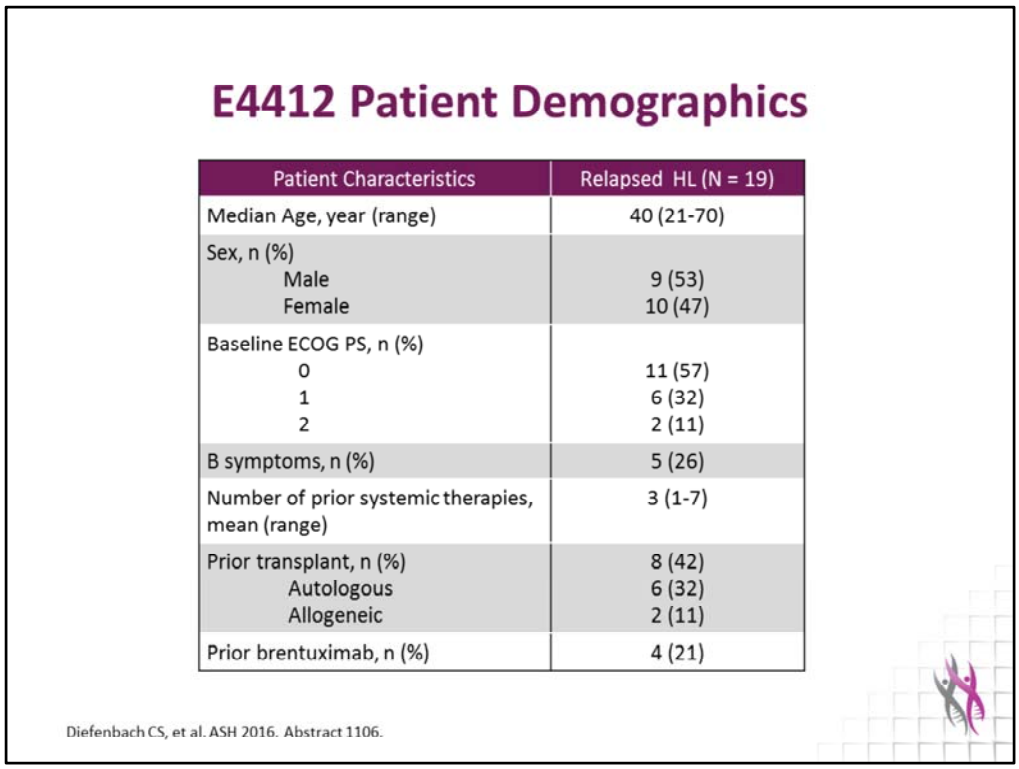
	5-Point Score	n (%)	Total
CmR	1	8 (28)	18 (62)
	2	6 (21)	
	3	3 (10)	
	Missing	1 (3)	
PmR	4	6 (21)	8 (28)
	5	2 (7)	
NmR	5	1 (3)	3 (10)
PmD	5	2 (7)	2 (7)

Here are the phenomenal waterfall plots in this program. So, 26 of the 29 patients had evidence of clinical benefit. The complete response rate was 62%. Now, it is very similar to what we have out there in the literature using inpatient platinum-based chemotherapy, which has a 25% neutropenic fever incidence and nearly a similar amount of platelet transfusion requirements. Here, we have an outpatient program which is well-tolerated and causes no hematologic side effects, so it is very likely that this will be studied further. We will see an update of this data set with twice as many patients at Lugano.

Incorporating Immunotherapy in the Treatment of Hodgkin Lymphoma

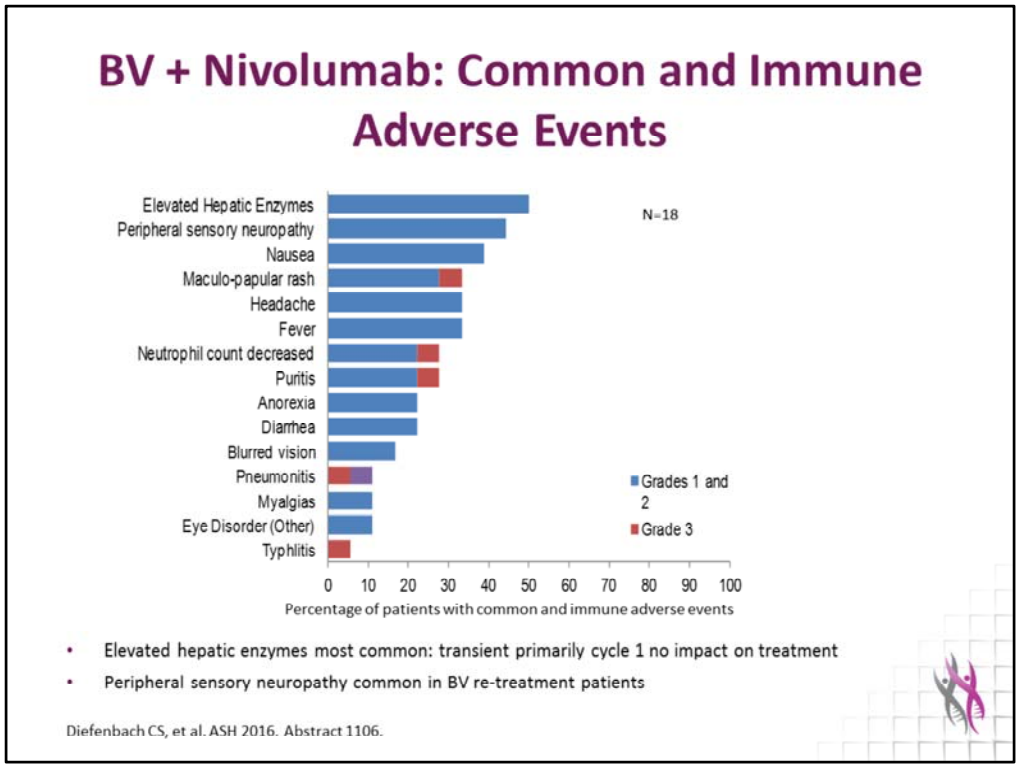


Now, in the palliative setting, the ECOG group looked at brentuximab vedotin and nivolumab for heavily pretreated patients in a dose-expansion study and in fact adding ipilimumab after doses were stable

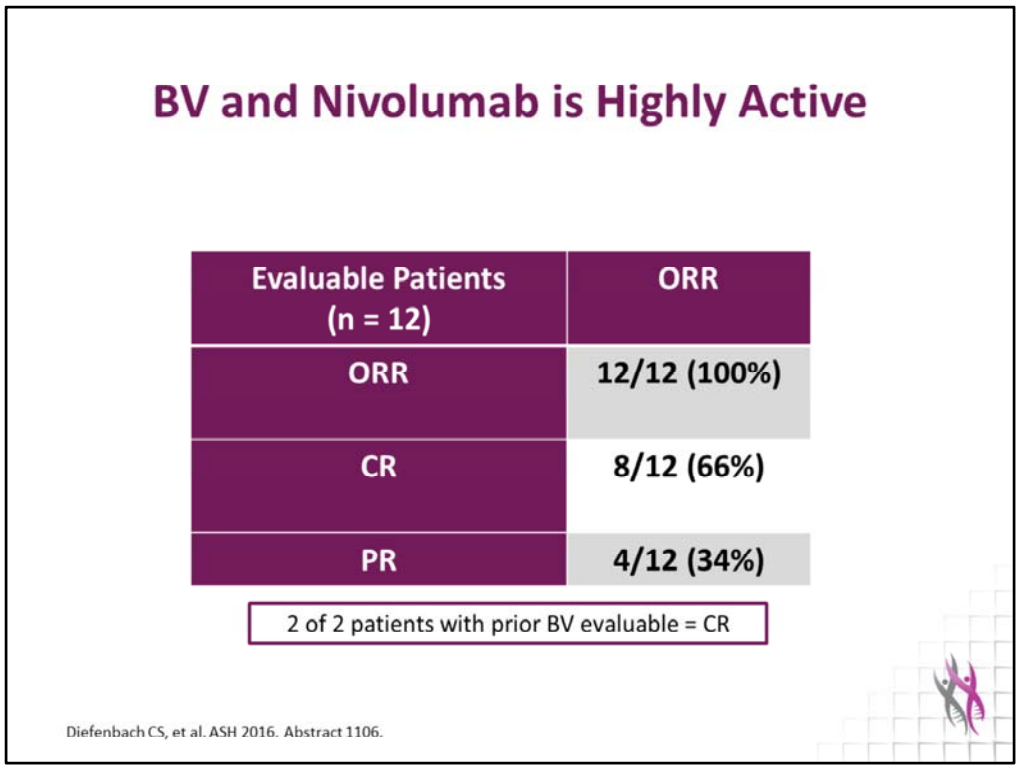


In general, this is a small patient population of 19 patients. Although most of the patients had not had an autologous stem cell transplant, which I find unusual since nearly every patient can be transplanted for Hodgkin lymphoma sooner or later.

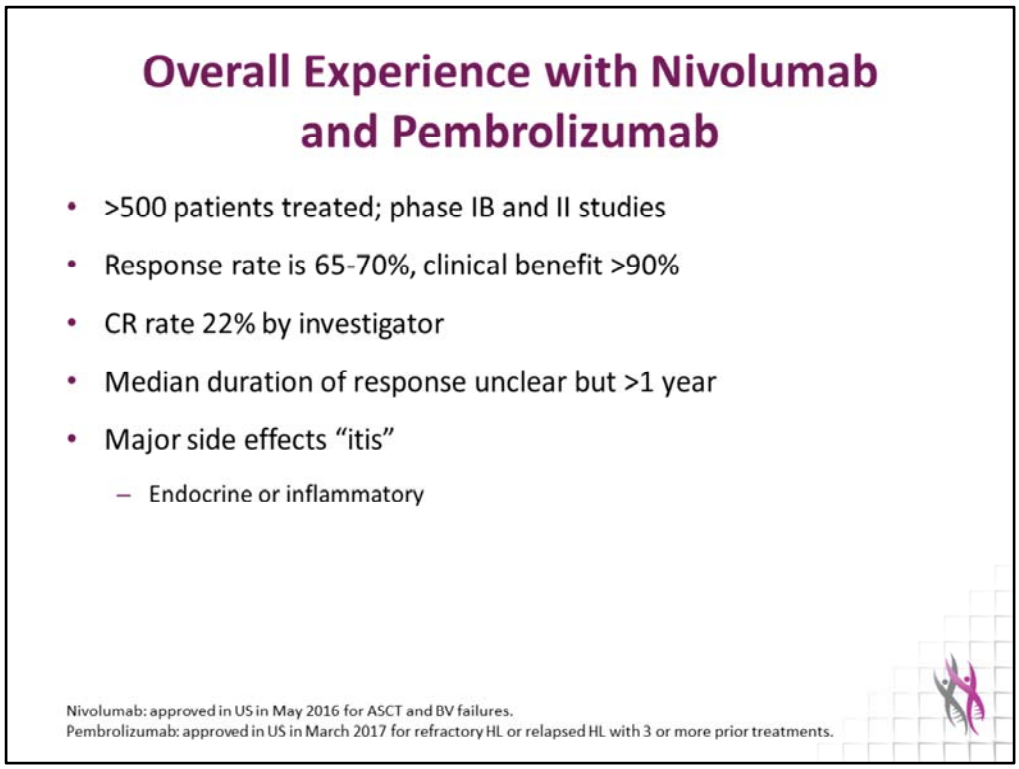
Incorporating Immunotherapy in the Treatment of Hodgkin Lymphoma



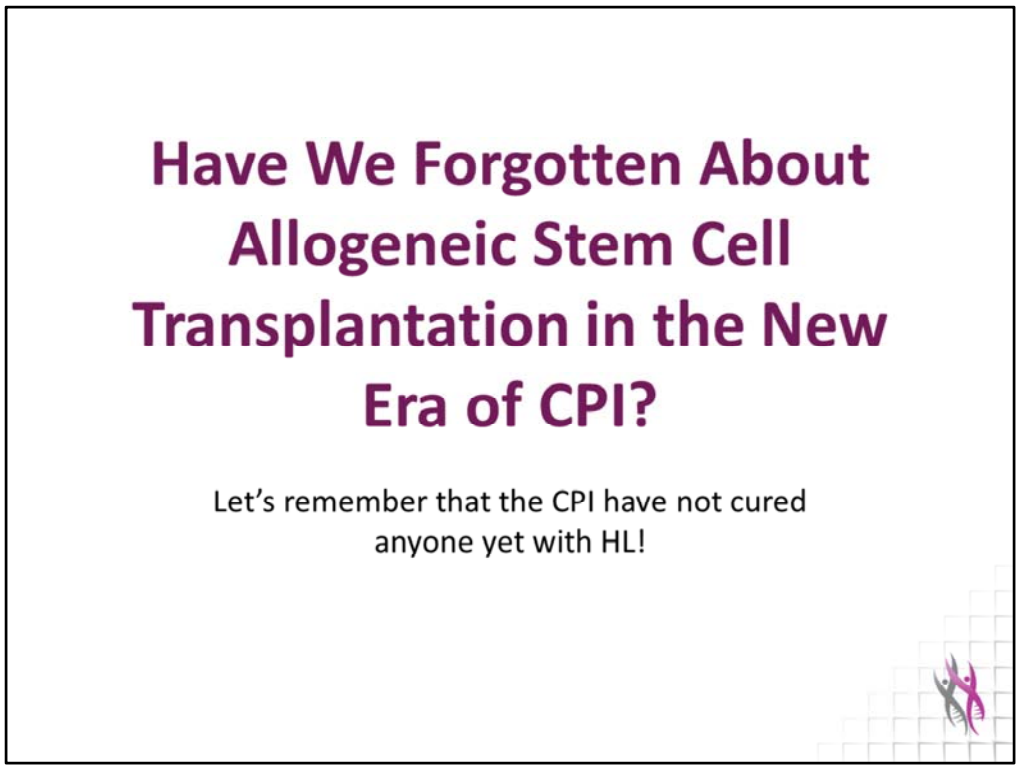
A fairly well-tolerated chemotherapy program, although there was one death on study from multisystem organ failure.



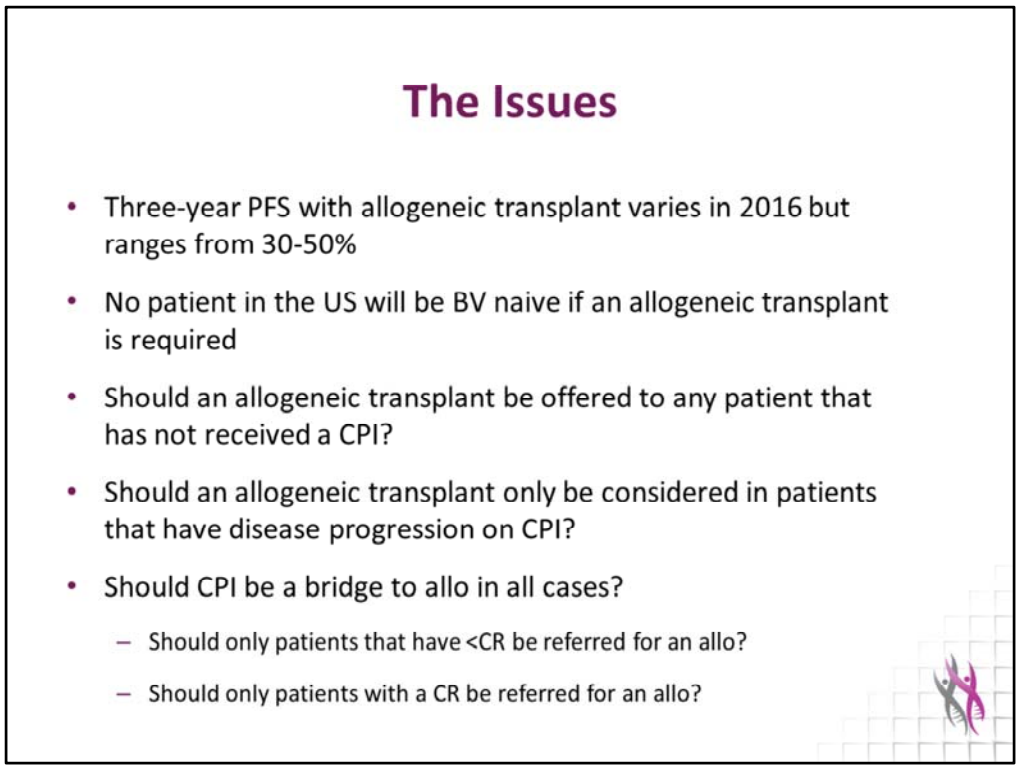
Response rate was high. The complete response rate was the same as in the pre-transplant setting. Durability of response is unclear at this time.



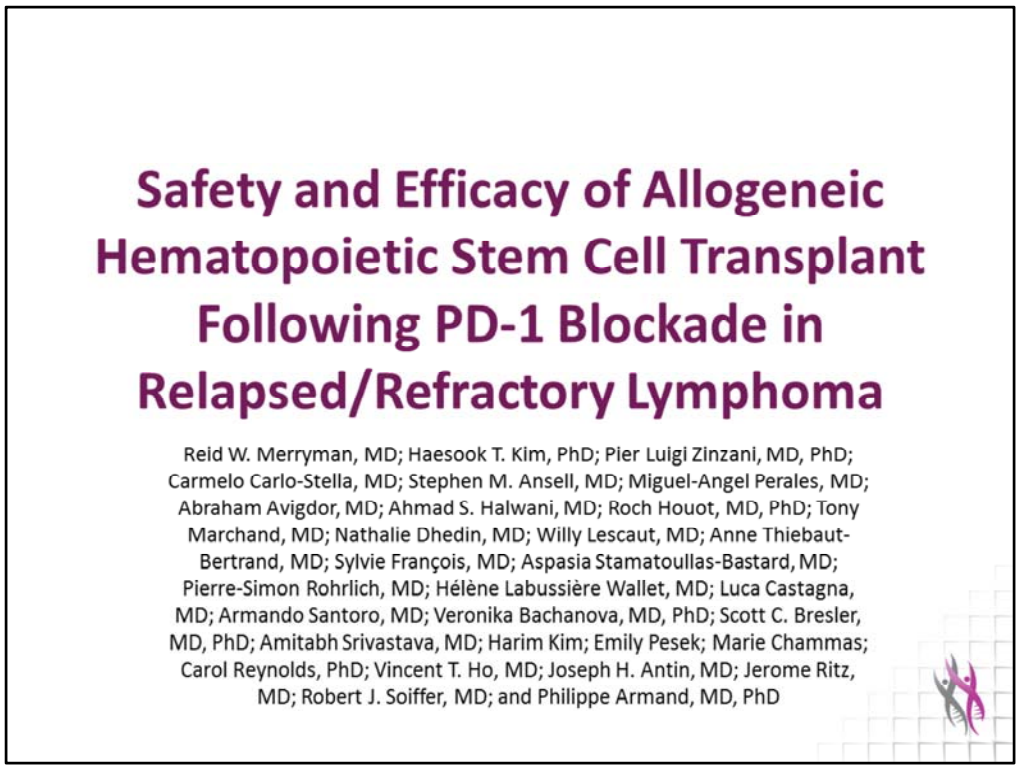
What I like to do, which I think is interesting, is just to summarize the data that we have, and this will be as of December 2016, the clinical trial patients who received nivolumab and pembrolizumab. There are over 500 patients that have been treated on the phase 1B and 2 studies. The response rate is about 70%. However, the more important clinical benefit rate is nearly universal. The complete response rate by investigator is 22%. The median duration of response is at least a year. I just saw a patient who is up to treatment #71 of nivolumab, so you can do the math that is week 142. The major side effect is inflammatory, that is either endocrinopathies, which are thyroiditis, adrenalitis, or hypophysitis. For a lymphoma doctor who classically takes care of thyroid dysfunction, I have never seen TSH abnormalities as I have seen in the pembrolizumab and nivolumab data sets. I recommend endocrine consultation for any patient with an endocrinopathy from these agents. Of course, nobody is going to die, in general, from an endocrinopathy. It is the other inflammatory syndromes that we need to be careful about, and the classics are pneumonitis and colitis. Pneumonitis can happen early or late. It needs to be evaluated fully with CT imaging. I recommend pulmonary consultation and possible steroid use. If a patient is started on steroids, then the checkpoint inhibitor should be held. Colitis is a little bit trickier, that can happen at any time and sometimes it is confused for typical viral gastroenteritis or C. diff colitis (Clostridium difficile colitis). I would recommend a colonoscopy and biopsy if this is not short-lived. As you know, nivolumab was approved in 2016 and pembrolizumab was approved in 2017.



What about the competition for checkpoint inhibitors, which are at the present time an allogeneic stem cell transplant. Are we ever going to do these treatments again? Let's remember, as far as I know, no patient has been cured with a checkpoint inhibitor and patients are cured with an allogeneic stem cell transplant.

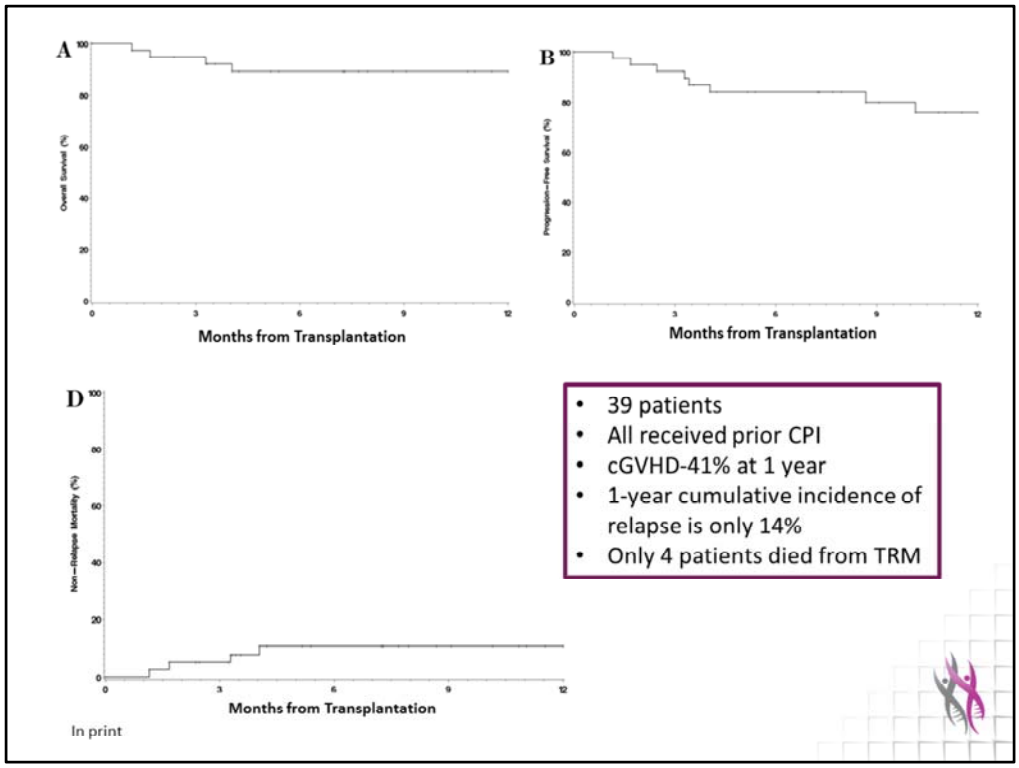


Here are the issues. When I started doing clinical trials with these agents, all the patients came to discuss, “How am I going to get to an allogeneic stem cell transplant?” Now, those same patients are very happy getting nivolumab or pembrolizumab and do not want an allogeneic stem cell transplant. In all likelihood, this scenario is going to have to fall somewhere in the middle. Here are the issues. The 3-year progression-free survival with an allogeneic stem cell transplant ranges from 30% to 50%. No patient in the United States will be brentuximab vedotin-naive if an allogeneic stem cell transplant is required. Should we be offering an allogeneic transplant to any patient that has not received a checkpoint inhibitor? It is debatable. Should an allogeneic transplant only be considered in a patient who has disease progression on a checkpoint inhibitor? Should a checkpoint inhibitor be a bridge to an allogeneic stem cell transplant in all cases? That is how it is done in Europe. In the United States, it is very uncommon. To make matters even more difficult to understand, should only patients that have less than a complete response to a checkpoint inhibitor be referred for an allogeneic stem cell transplant? Because almost no patient who receive these agents will have a partial response converted to a complete response. Should only patients that achieve a CR to a checkpoint inhibitor be referred to an allogeneic transplant? Well, that is very difficult to do because these patients are doing fine in remission.

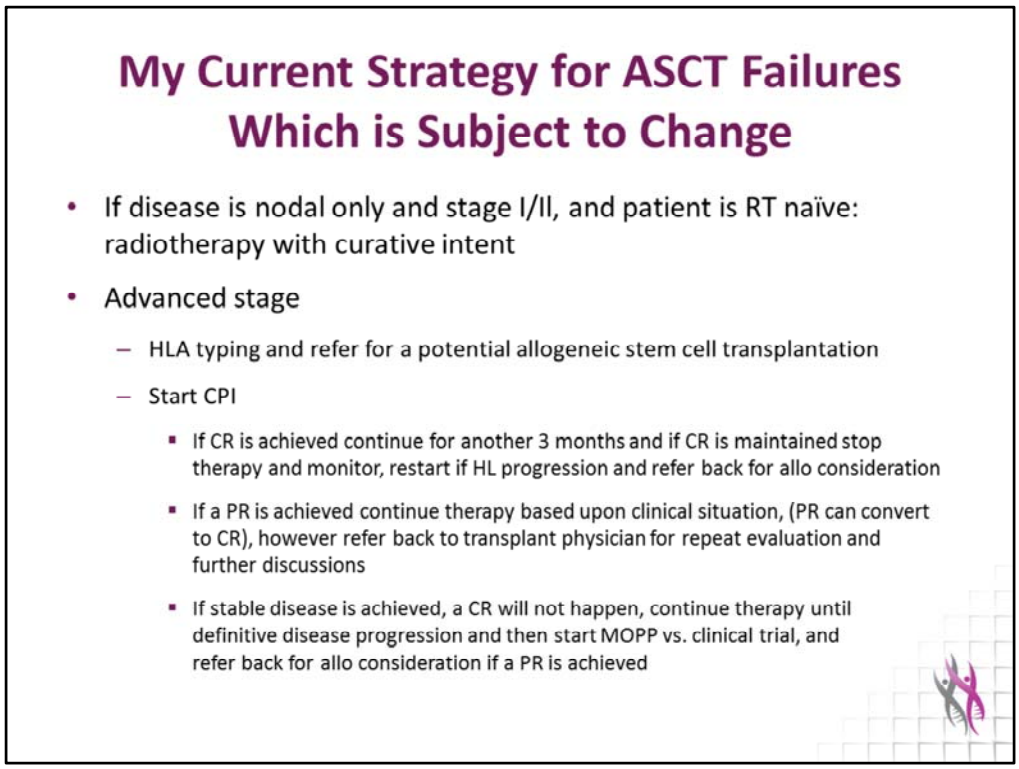


For a while, most investigators were giving checkpoint inhibitors to disease progression because of all of the issues with allogeneic stem cell transplant, with graft-versus-host (GVH) disease, and assorted other toxicities, and the possibility that giving a checkpoint inhibitor prior to a transplant was associated with an increase in incidence of GVH.

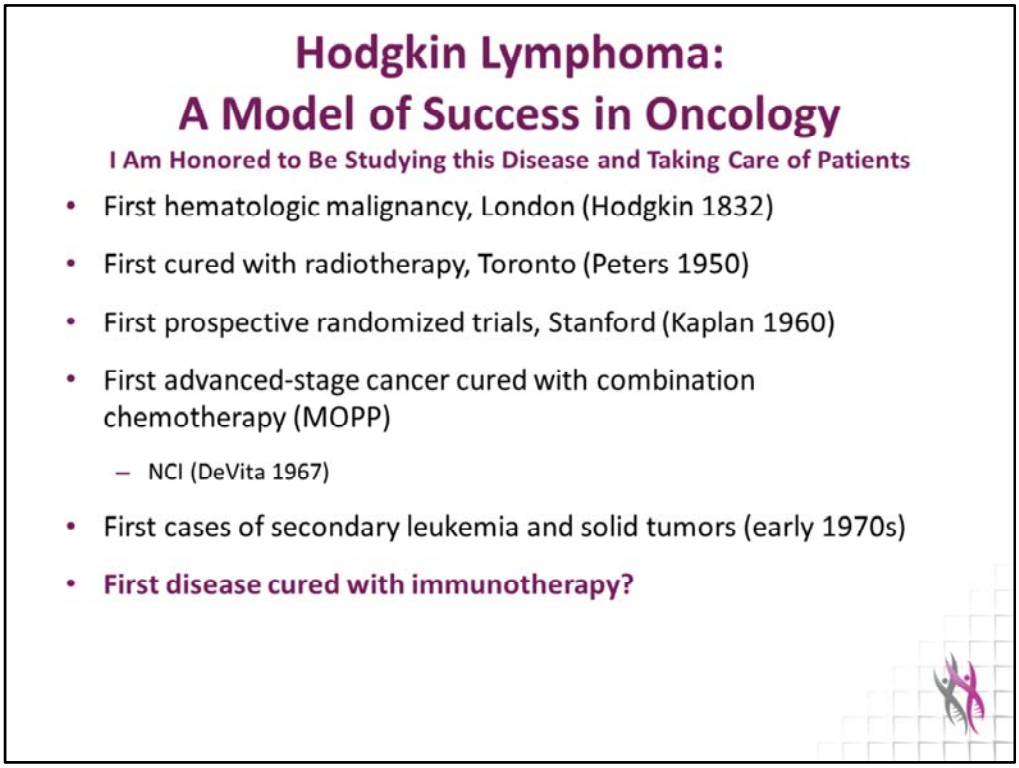
Incorporating Immunotherapy in the Treatment of Hodgkin Lymphoma



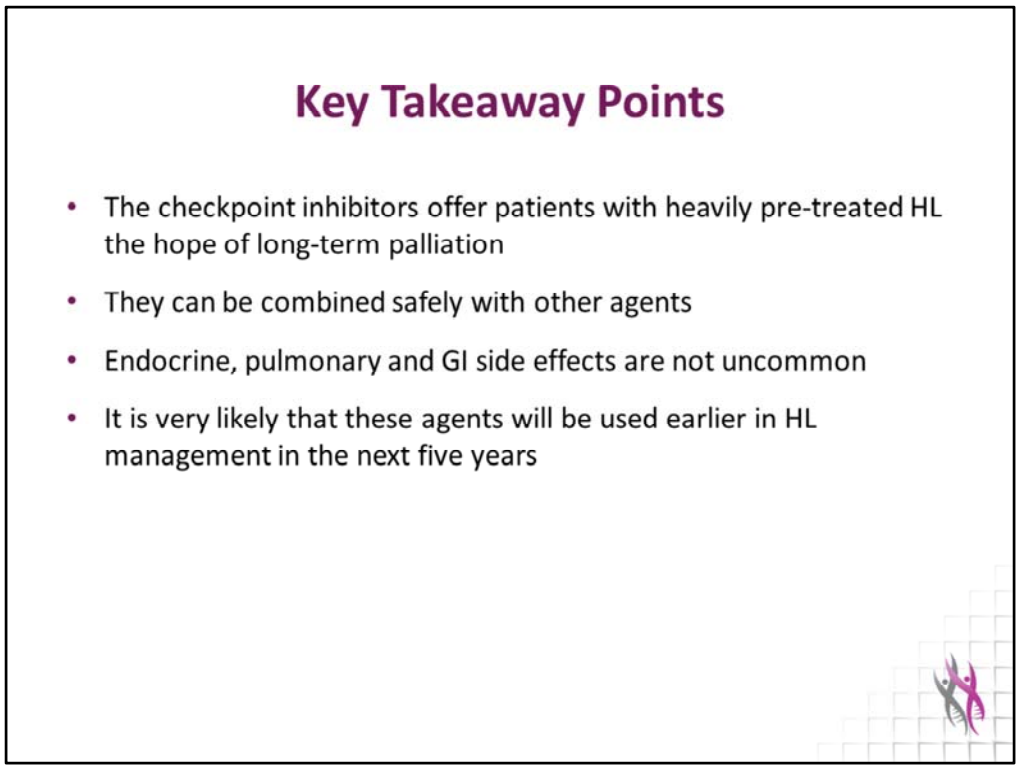
This is data that is in press. This is the data set of 40 patients who have received nivolumab and a subsequent allogeneic stem cell transplant. One can readily see that the incidence of chronic GVH at 1 year is 40%, which is no different than in patients who have not received a checkpoint inhibitor. The incidence of relapse is low, and there have only been four patients who had treatment-related mortality, which is no different than patients who do not get these drugs. That is food for thought and interesting because, remember, an allogeneic transplant is curative but with side effects.



Here is my current strategy as of April 18, 2017 when the seminar is being taped. If a patient has disease which is only nodal and is early stage, and that area has not been radiated, the first thing to do is to give radiation therapy to that Hodgkin lymphoma patient with curative intent. For patients with advanced-stage disease, the first thing the clinician should do is a HLA (human leukocyte antigen) typing and refer the patient for an allogeneic stem cell transplant consult. At the same time, I would recommend starting nivolumab. If a complete response is achieved, I will continue this for another 3 months. If the complete response is maintained, I would actually try to stop nivolumab or pembrolizumab and monitor, and restart if there is Hodgkin lymphoma progression. If there is progression, refer back to an allotransplant doctor. If a partial remission is achieved, I will just continue therapy until disease progression. However, make sure that your allogeneic stem cell transplant doctor knows about this patient. Not dissimilar to stable disease, which will never compare to a complete response, and continue therapy to progression. It is very interesting and I do not have the answer to this; however, response rate to chemotherapy after nivolumab or pembrolizumab is very high. I give MOPP chemotherapy; others are giving bendamustine-based treatment, but most patients will respond to that treatment and consider referring the patient back for a transplant.



I have been studying Hodgkin lymphoma now for 25 years, and it really is an honor taking care of these patients and studying this disease. You may not know this, but it was the first malignancy diagnosed by Thomas Hodgkin in 1832. It is the first malignancy that has been cured by radiotherapy by the Princess Margaret Group. It is the first malignancy where there was a prospective random assignment trial. This was done at Stanford by Henry Kaplan. It is the first cancer that was cured with combination chemotherapy. Remember ALL (acute lymphoblastic leukemia) in kids was cured with one drug, and this was done with MOPP by Vincent DeVita at the NCI. It is unfortunately the first cancer where we now study secondary cancers, especially secondary leukemia and solid tumors. I hope that it will be the first disease that is cured with immunotherapy.



I want to conclude by leaving it with these take-home messages. The checkpoint inhibitors offer patients tremendous palliation for long term with a sense of well-being. I believe they can be combined safely with other drugs. This is being done in both Hodgkin lymphoma and non-Hodgkin lymphoma, which we did not discuss today. Be wary of endocrine, pulmonary, and GI side effects. There is no doubt in my mind that these drugs will be used in our armamentarium, especially earlier in Hodgkin lymphoma management, in the next 5 years.