Year in Review

Proceedings from a Multitumor CME Symposium Focused on the Application of Emerging Research Information to the Care of Patients with Common Cancers

Hodgkin Lymphoma — Craig Moskowitz, MD

Select Publications

Ansell SM et al. **PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma.** *N Engl J Med* 2015;372(4):311-9.

Moskowitz AJ et al. **PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosfamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: A non-randomised, open-label, single-centre, phase 2 study.** *Lancet Oncol* 2015;16(3):284-92.

Moskowitz CH et al. **Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): A randomised, double-blind, placebo-controlled, phase 3 trial.** *Lancet* 2015;385(9980):1853-62.

Moskowitz CH et al. **PD-1 blockade with the monoclonal antibody pembrolizumab (MK-3475) in patients with classical Hodgkin lymphoma after brentuximab vedotin failure: Preliminary results from a Phase 1b study (KEYNOTE-013).** *Proc ASH* 2014;**Abstract 290**.

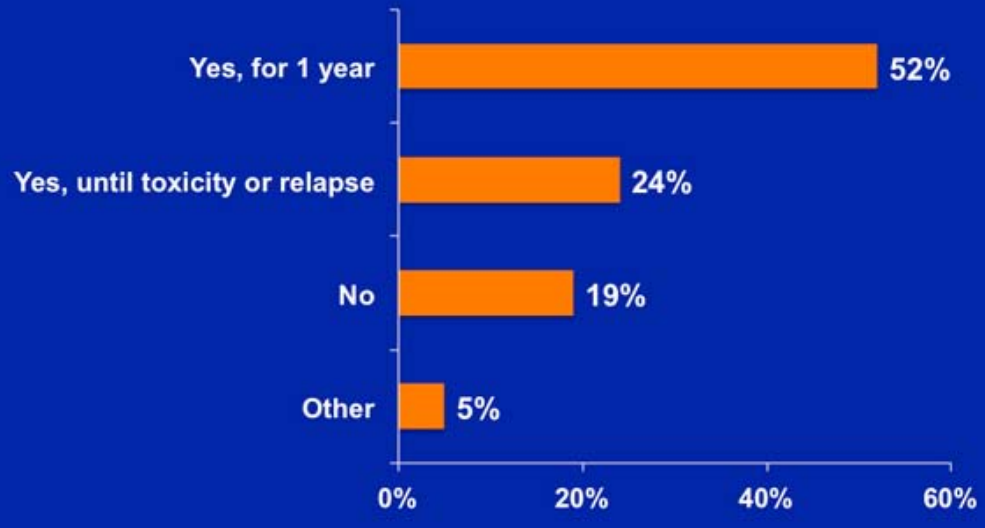
Walewski JA et al. **Multivariate analysis of PFS from the AETHERA trial: A phase III study of brentuximab vedotin consolidation after autologous stem cell transplant for HL.** *Proc ASCO* 2015;**Abstract 8519**.

Disclosures

Consulting Agreements	Celgene Corporation, Genentech BioOncology, Merck, Seattle Genetics
Contracted Research	Merck, Pharmacyclics Inc, Seattle Genetics

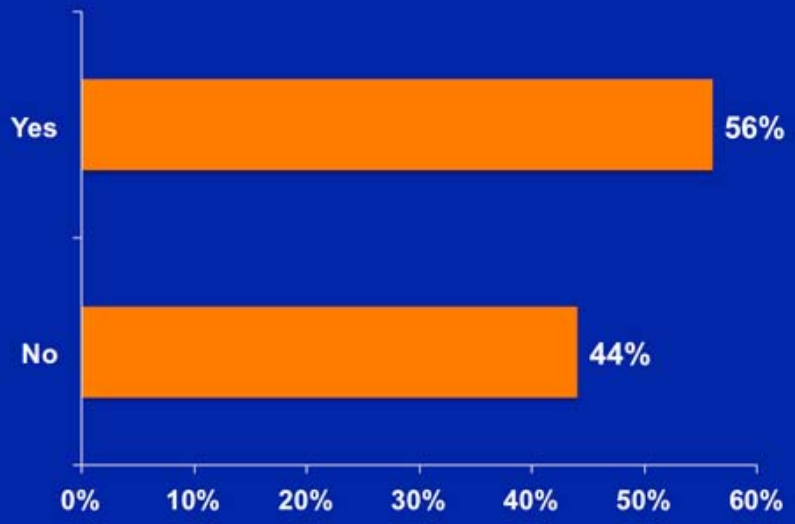
AUDIENCE POLL

A 38-year-old man with Hodgkin lymphoma (HL) receives ABVD chemotherapy but experiences recurrent disease in the liver and multiple nodes 12 months later. The patient receives ICE chemotherapy followed by autologous stem cell transplant and achieves a complete response. Would you recommend consolidation brentuximab vedotin?



AUDIENCE POLL

If you could access an anti-PD-1/anti-PD-L1 antibody, are there patients in your practice with HL for whom you would like to use it?

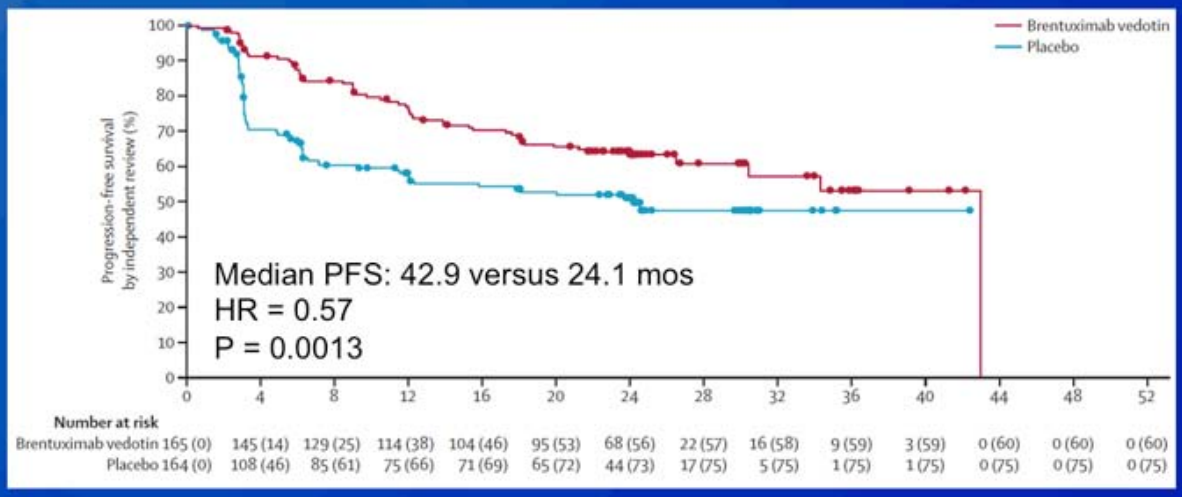


Brentuximab vedotin as consolidation therapy after autologous stem-cell transplantation in patients with Hodgkin's lymphoma at risk of relapse or progression (AETHERA): a randomised, double-blind, placebo-controlled, phase 3 trial

Craig H Moskowitz, Auayporn Nademanee, Tamas Masszi, Edward Agura, Jerzy Holowiecki, Muneer H Abidi, Andy I Chen, Patrick Stiff, Alessandro M Gianni, Angelo Carella, Dzhelil Osmanov, Veronika Bachanova, John Sweetenham, Anna Sureda, Dirk Huebner, Eric L Sievers, Andy Chi, Emily K Larsen, Naomi N Hunder, Jan Walewski, for the AETHERA Study Group

Lancet 2015; 385: 1853–62

Progression-Free and Interim Overall Survival (ITT) by Independent Review



Interim analysis of overall survival: No significant difference between treatment groups (p = 0.6204).

Moskowitz CH et al. *Lancet* 2015;385(9980):1853-62.

Multivariate Analysis of PFS from the AETHERA Trial: A Phase III Study of Brentuximab Vedotin Consolidation After Autologous Stem Cell Transplant for HL

Walewski JA et al.

Proc ASCO 2015;Abstract 8519.

AETHERA: PFS by Subgroups

PFS by…	N	Hazard ratio
Response to Front-Line Therapy		
Refractory	196	0.55
Relapse <12 mo	107	0.55
Relapse ≥12 mo (with extranodal disease)	26	0.30
Number of Risk Factors		
≥1	329	0.50
≥2	280	0.40
≥3	166	0.37
Presence of B Symptoms		
No	239	0.56
Yes	87	0.30
Extranodal Disease Involvement		
No	222	0.57
Yes	107	0.37

Walewski JA et al. *Proc ASCO* 2015;Abstract 8519.

Conclusions

Critical finding(s): This is the largest Phase III study done in relapsed/refractory HL and the only placebo-controlled trial ever done in HL. Primary endpoint is PFS, and there is a near doubling in time to progression in patients receiving BV. There is no difference in OS at this time, the primary reason being that in this patient population median OS is about 5 years. BV was approved by the FDA in this setting and has Level I evidence in the NCCN guidelines. Patients are eligible if they have presalvage risk factors of remission duration less than 1 year, primary refractory disease or extranodal involvement. In addition, 3 other risk factors predicted for added benefit for BV: B symptoms, lack of CR to salvage

Conclusions

therapy or needing more than 1 salvage regimen to achieve chemosensitive disease. Ninety percent of patients on study had at least 1 risk factor and 50% had 3 or more. As the number of factors increases the magnitude of BV maintenance is amplified.

Clinical implication(s): The general oncologist will be administering BV. Sixteen doses are planned with 1 dose reduction for Grade 2 neuropathy. Rash is common and may require steroids. There is no mention of previous BV therapy prior to ASCT and the use of BV post-ASCT on the label. In a patient who had a good response pre-ASCT I administer BV as per AETHERA but usually will reduce the number of cycles to 10 to 12. Patients refractory to BV-AVD or BV-based salvage should not receive this agent.

Conclusions

Research relevance: The checkpoint inhibitors have only been given for palliation and have not been combined with salvage therapy. A number of studies are beginning:

1. BV/nivolumab for salvage pre-ASCT
2. ICE/pembrolizumab for salvage
3. Pembrolizumab post-ASCT for consolidation
4. I will initiate a small study of pembrolizumab/ISRT for favorable relapsed HL, trying to avoid ASCT

PET-adapted sequential salvage therapy with brentuximab vedotin followed by augmented ifosamide, carboplatin, and etoposide for patients with relapsed and refractory Hodgkin's lymphoma: a non-randomised, open-label, single-centre, phase 2 study

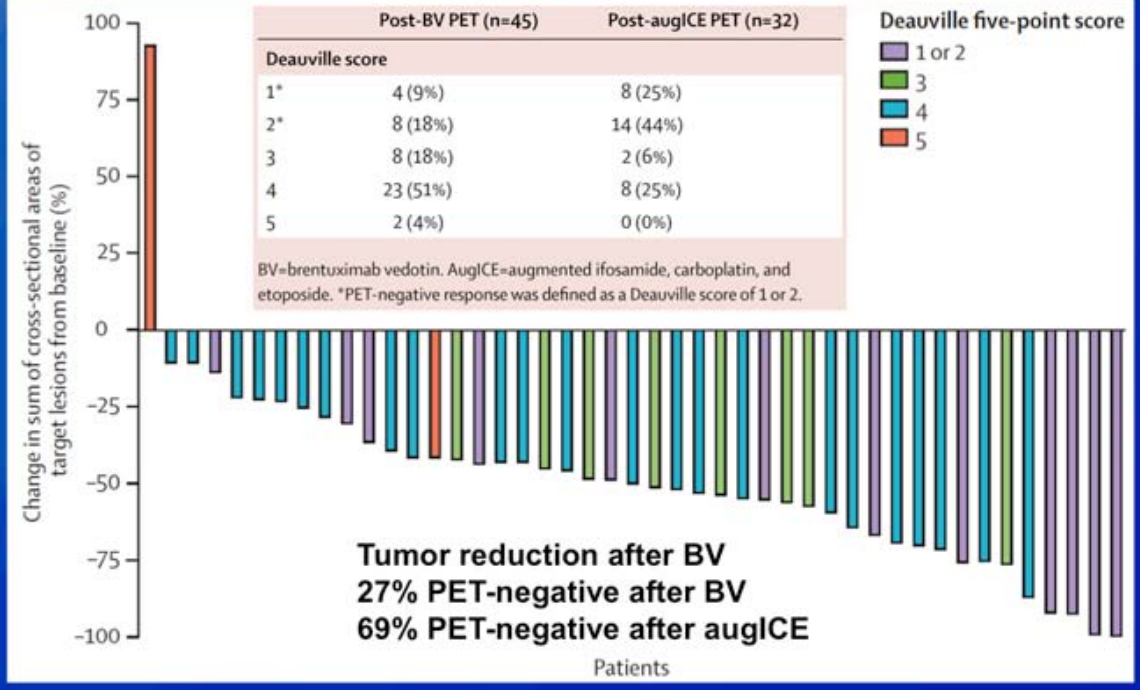
Alison J Moskowitz, Heiko Schöder, Joachim Yahalom, Susan J McCall, Stephanie Y Fox, John Gerecitano, Ravinder Grewal, Paul A Hamlin, Steven Horwitz, Rachel Kobos, Anita Kumar, Matthew Matasar, Ariela Noy, M Lia Palomba, Miguel-Angel Perales, Carol S Portlock, Craig Sauter, Neerav Shukla, Peter Steinherz, David Straus, Tanya Trippett, Anas Younes, Andrew Zelenetz, Craig H Moskowitz

Lancet Oncol 2015; 16: 284–92

Response to Salvage Therapy and Tumor Reduction after Brentuximab Vedotin (BV)

	Post-BV PET (n=45)	Post-augICE PET (n=32)
Deauville score		
1*	4 (9%)	8 (25%)
2*	8 (18%)	14 (44%)
3	8 (18%)	2 (6%)
4	23 (51%)	8 (25%)
5	2 (4%)	0 (0%)

BV=brentuximab vedotin. AugICE=augmented ifosamide, carboplatin, and etoposide. *PET-negative response was defined as a Deauville score of 1 or 2.



Moskowitz AJ et al. *Lancet Oncol* 2015;16(3):284-92.

Conclusions

Critical finding(s): First salvage study reported combining BV and chemotherapy. BV was administered weekly x 6, and if a CR was achieved then ICE was not given. CR was seen in 40% of patients. The remaining patients received an augmented version of ICE. Overall CR rate pre-ASCT was 80%, and 90% of the CR patients remain in remission 2 years post-ASCT.

This study was initiated to see if ICE could be avoided and hence long-term side effects might be minimized, and in fact 3 pregnancies have been reported thus far. It is somewhat disappointing that the CR rate was low, but it is consistent with previous reports.

Conclusions

Clinical implication(s): Weekly BV, especially for patients with favorable relapse, is a reasonable option as first salvage, and there are confirmatory data from City of Hope, albeit with a q3wk schedule, in press. If BV is administered as per the MSKCC paper and a CR is achieved either with 6 doses of BV or after ICE and the response to BV is a Deauville 3 or 4, then BV should be administered post-ASCT for 8 to 12 doses provided there is no contraindication.

Research relevance: The CR rate with BV alone is suboptimal, and combining with checkpoint inhibitors makes sense. Combination with chemo, as with bendamustine/BV, does not solve the problem of potential long-term side effects.

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PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin's Lymphoma

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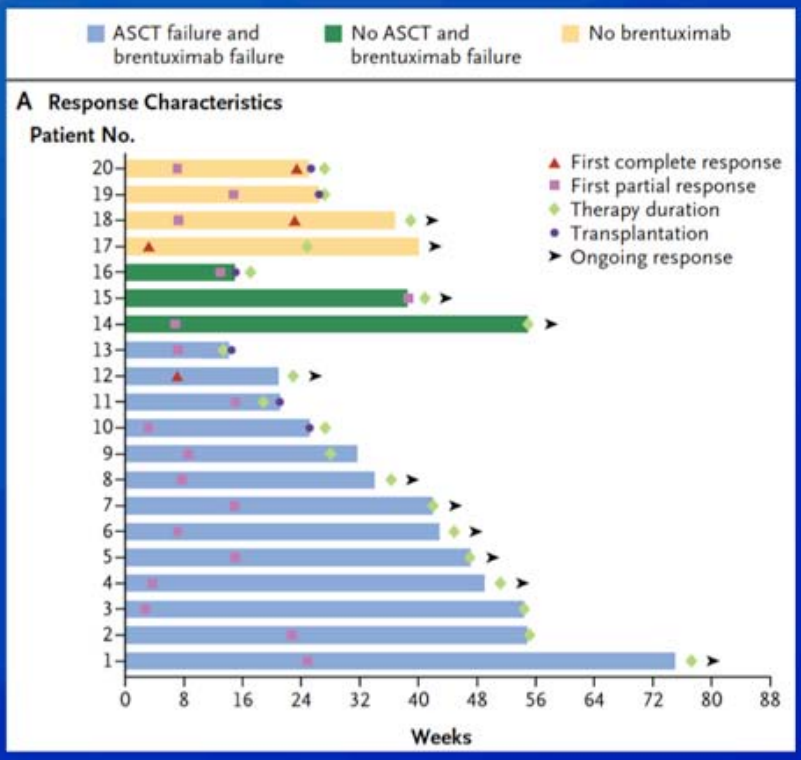
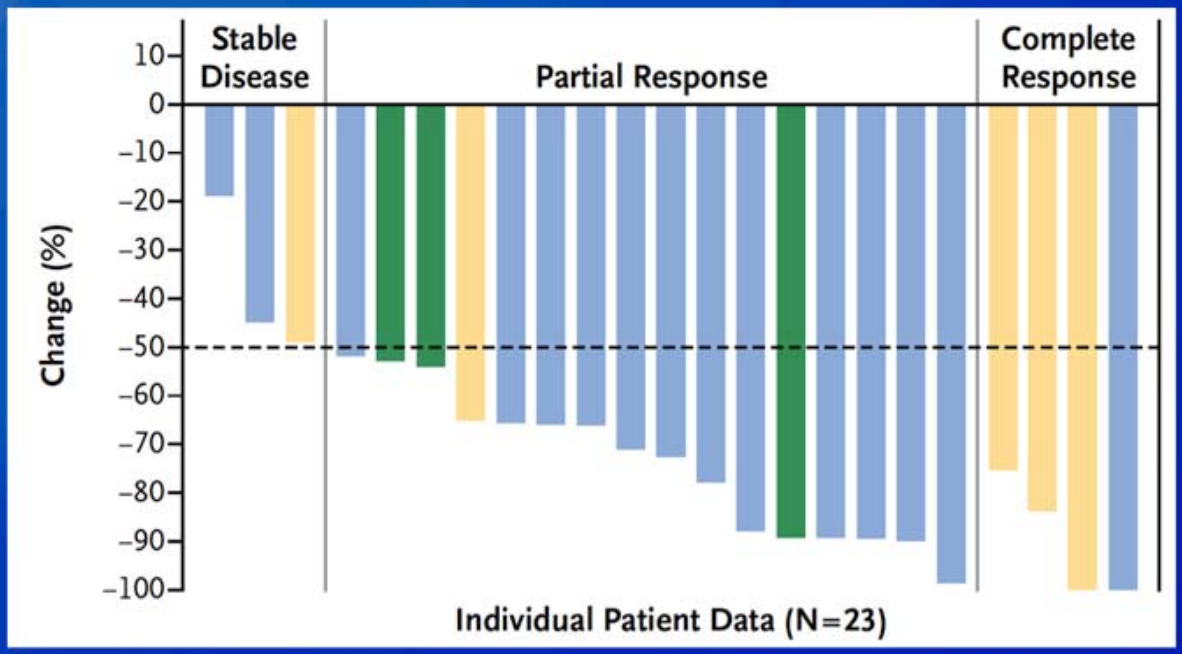
Onset and Duration of Response to Nivolumab



Ansell SM et al. *N Engl J Med* 2015;372(4):311-19.

Reduction of Tumor Burden with Nivolumab

ORR = 87%



Ansell SM et al. *N Engl J Med* 2015;372(4):311-19.

Conclusions

Critical finding(s): Very small study in a poor-risk HL population. The results are outstanding. An update of this paper at Lugano has a median time to progression of 95 weeks. CR rate is low, half that of BV, but stable PRs and stable disease can mean very long time to progression. The use of a consolidative allogeneic stem cell transplant in these patients has yet to be reported in a peer-reviewed format.

Clinical implication(s): Very well tolerated. However, here are some of my rules: Any patient with a history of steroid-necessitating pneumonitis should not receive this drug, and if pneumonitis develops, pulmonary support is needed and I would stop the agent.

Conclusions

Significant endocrinopathies happen and TFTs should be checked ever other cycle. Endocrine consultative support may be necessary.

All patients have a sense of well-being on this drug and B symptoms resolve quickly. Weight gain is common.

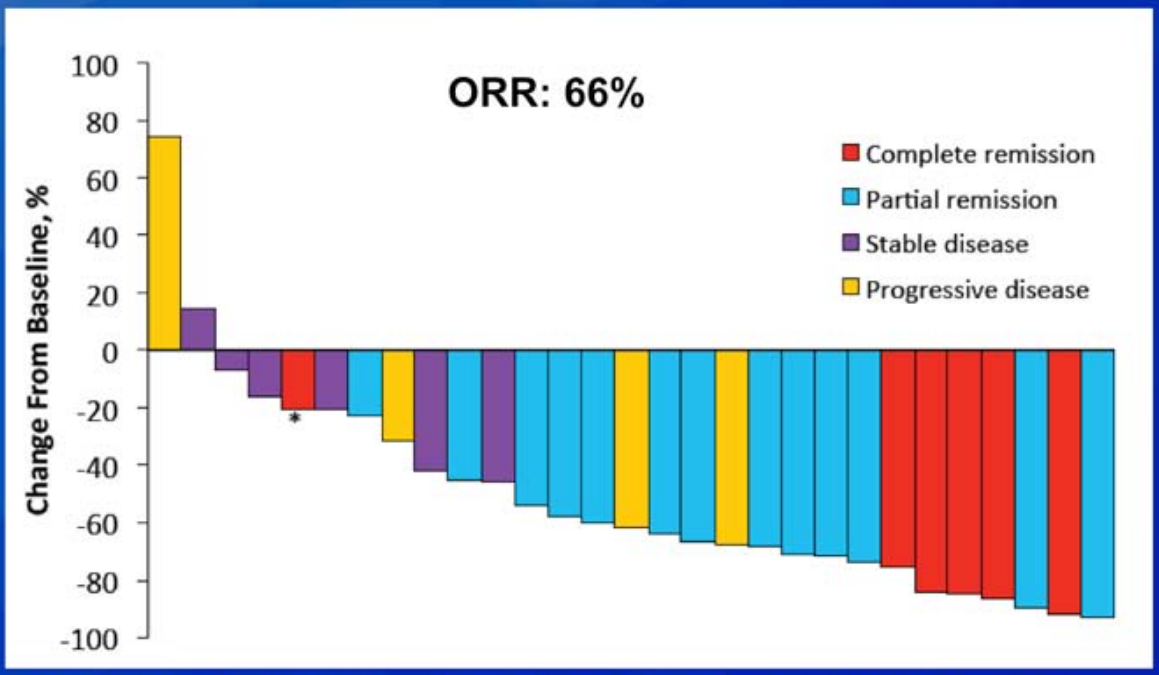
Research relevance: A registration trial for nivolumab with 150 patients is accrued and will almost certainly lead to approval for patients for whom ASCT has failed.

PD-1 Blockade with the Monoclonal Antibody Pembrolizumab (MK-3475) in Patients with Classical Hodgkin Lymphoma After Brentuximab Vedotin Failure: Preliminary Results from a Phase 1b Study (KEYNOTE-013)

Moskowitz CH et al.

Proc ASH 2014;Abstract 290.

Response and Best Percentage Change from Baseline in Tumor Size



* Patient became PET negative and was therefore declared to be in complete remission

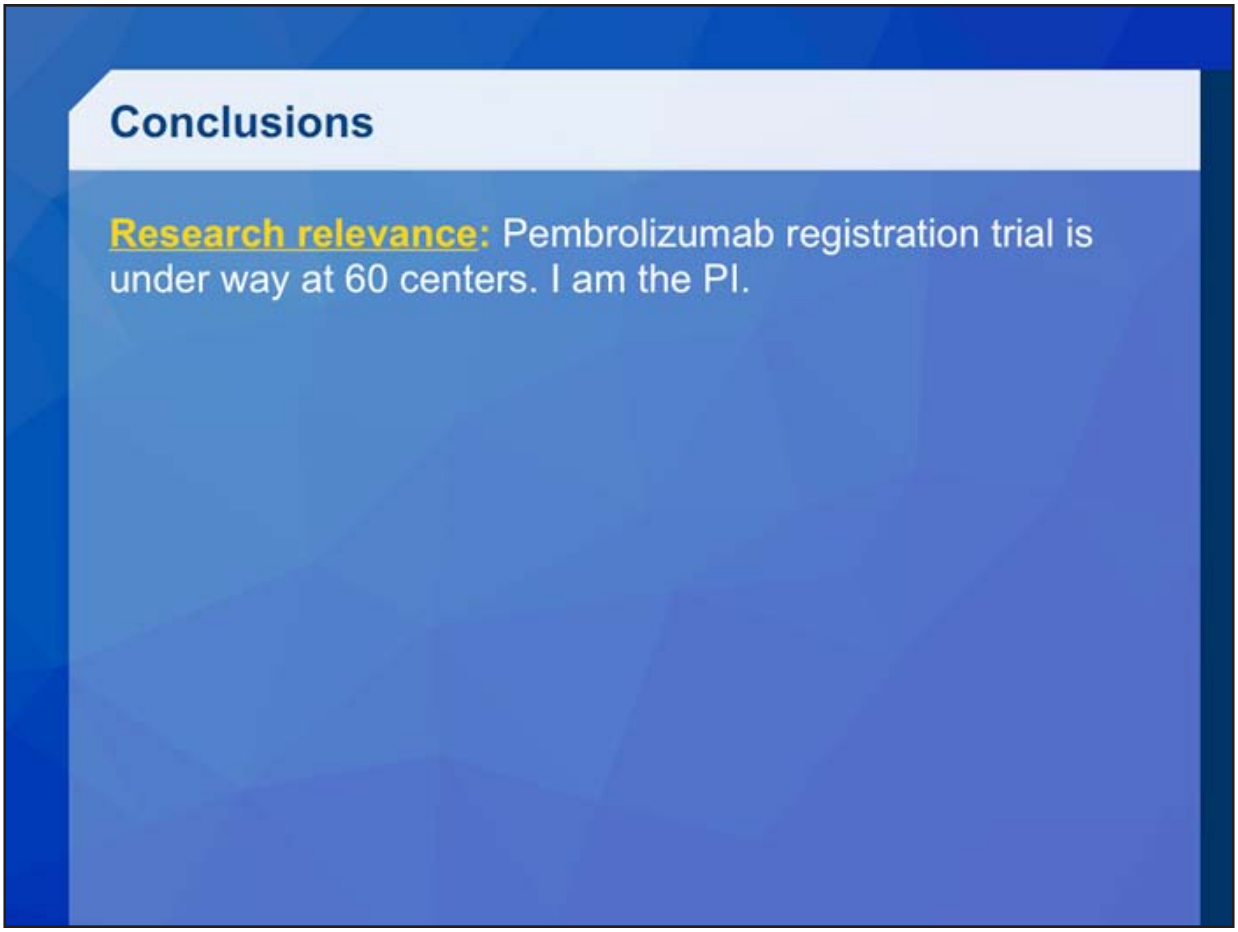
Moskowitz CH et al. *Proc ASH* 2014;Abstract 290.

Conclusions

Critical finding(s): Slightly larger study than nivolumab in same patient population. CR rate is higher but overall response somewhat less. In general, this study is 1 year behind nivolumab program in HL.

Data will be updated at ASH 2015 and manuscript has been submitted. Median time to progression has not been reached.

Clinical implication(s): Same as with nivolumab. However, dose used was high in pembrolizumab HL study, and now all pembrolizumab studies have fixed dosing of 200 mg. I honestly do not see any difference between these drugs, and it is unclear to me why we need 2 PD-1 inhibitors in HL. I have treated 40 patients with these agents in HL thus far on study.


Conclusions
Research relevance: Pembrolizumab registration trial is under way at 60 centers. I am the PI.