

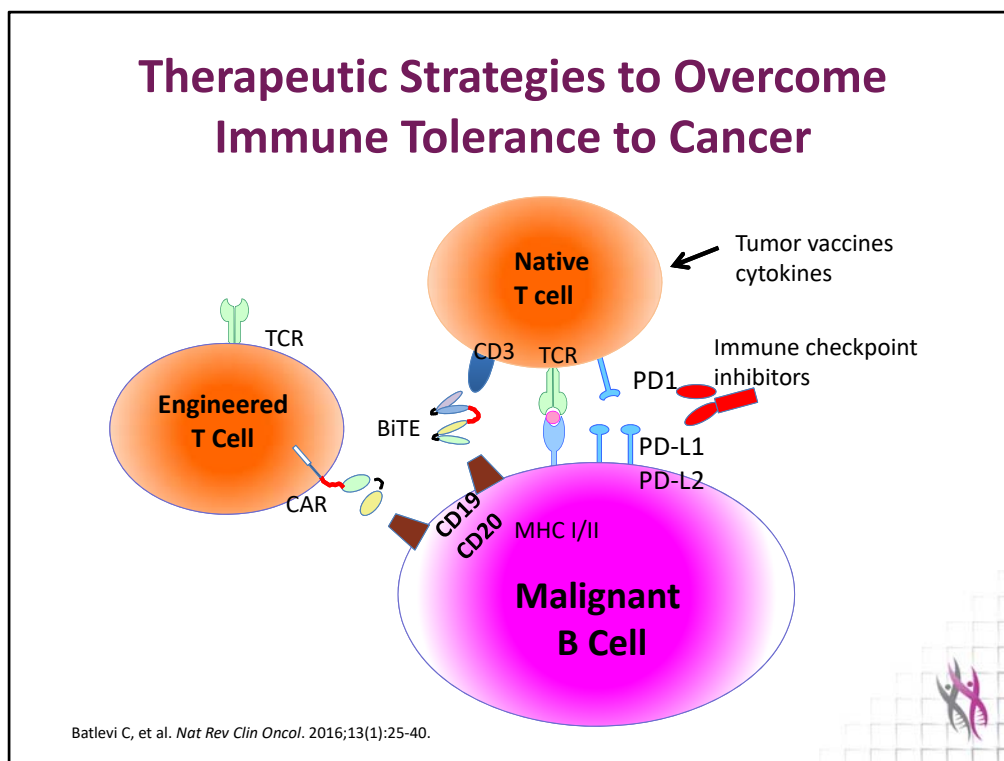
Immunotherapy in Hodgkin Lymphoma: Current and Future Approaches to Treatment



Welcome to *Managing Hodgkin Lymphoma*. I am Dr. Anas Younes.

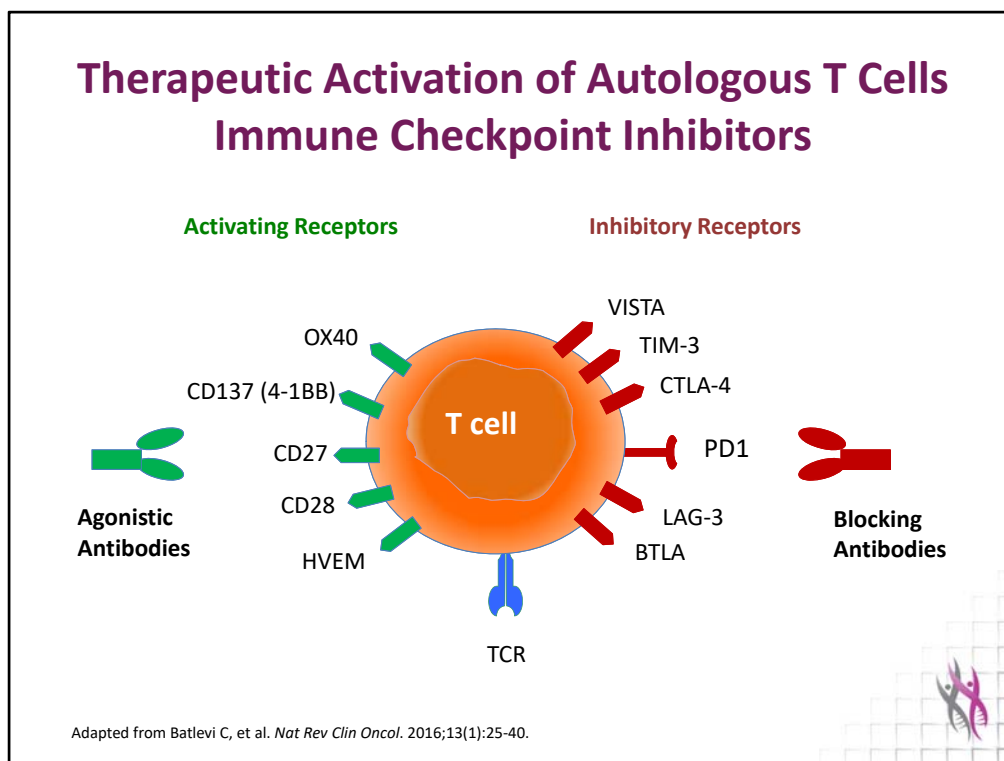
Today, I will review immune therapy in Hodgkin lymphoma, the current and future approaches to treatment. In this presentation, I will review the rationale of targeting PD-1/PD-L1 in classical Hodgkin lymphoma, summarize the data on activity and safety profile in the treatment of elapsed and refractory classical Hodgkin lymphoma and review ongoing prospective trials, looking at combination therapy with brentuximab vedotin and future directions.

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When we talk about immune therapy of Hodgkin lymphoma, and this is really applicable for all types of cancer, it is not unique for Hodgkin or non-Hodgkin lymphoma, we mainly talk about multiple platforms. One of them is immune checkpoint inhibitors, but there are other emerging platforms that are making news and demonstrating benefit to patients with Hodgkin lymphoma and other types of cancers. These include the CAR T cells, these are engineered CAR T cells. The bispecific antibody drug conjugates, and an example brentuximab vedotin, and naked antibodies, and of course within the naked antibodies, the immune checkpoint inhibitors. The focus today will be mainly on the immune checkpoint inhibitors and we will also talk about brentuximab vedotin as the combination of these two strategies are now showing interesting results.

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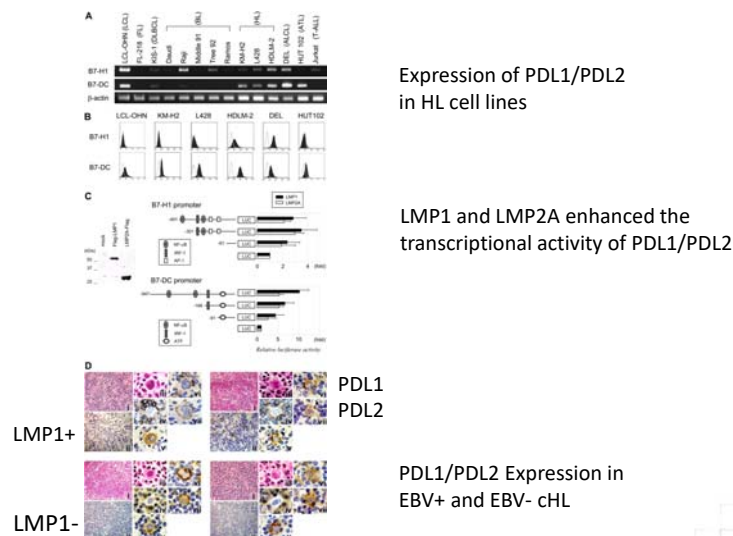


When we talk about immune checkpoint inhibitors, we are mainly talking about ways or tricks to activate the patient's own immune cells, in this example, his own or her own T-lymphocytes. T-lymphocyte activation is regulated by a set of receptors that can trigger either activation or inactivation of T-cells. It is a normal physiologic function and so after let us say, fighting a pathogen or infection, T-cells get activated, but after killing the offending pathogen, the T-cells need to tone down their activation and this is regulated by these sets of receptors.

In this cartoon, the green ones are the activating receptors and the red ones are the inactivating or inhibitory receptors. If you want to activate T-lymphocytes, you need to either use agonistic antibodies to activate the activating receptors or blocking antibodies to block or inhibit the inhibitory receptors. Examples here are the antibodies targeting PD-1 like nivolumab or pembrolizumab, both are blocking antibodies; same thing for antibodies targeting CTLA-4, they are blocking antibodies. You can see there is now a trend to combine more than one antibody like a blocking antibody and activating antibody, and these are ongoing efforts in clinical trials. The only combination antibodies that are accrued by regulatory agents including FDA are two blocking antibodies, one targeting PD-1 and the other one targeting CTLA-4 but there are more of these combinations being tested in context of clinical trials.

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Expression and Gene Regulation of PDL-1 (CD273) and PDL-2 (CD274) in HL

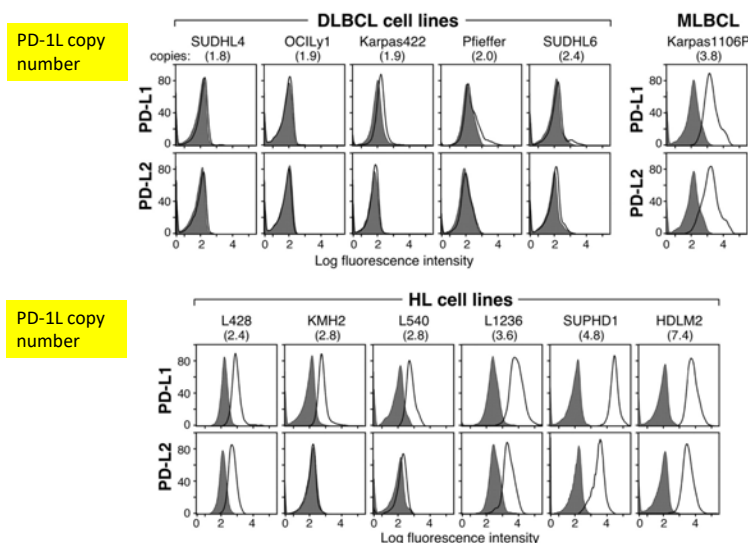


Yamamoto R, et al. *Blood*. 2008;111:3220-3224.

The story behind investigating the activity of PD-1, PD-L1 antibodies in Hodgkin lymphoma started around 2008 where a Japanese group reported their observation that for some reason, Hodgkin lymphoma cell lines had a high level of expression of a messenger RNA of PD-L1 and PD-L2 and a protein as detected by flow cytometry. Also, they could see that by immunohistochemical staining from primary Hodgkin lymphoma section which is shown in the lower part of this slide. They also found that it did not matter whether the disease expressed EBV or not, PD-L1 and PD-L2 expression were observed regardless of EBV infection status.

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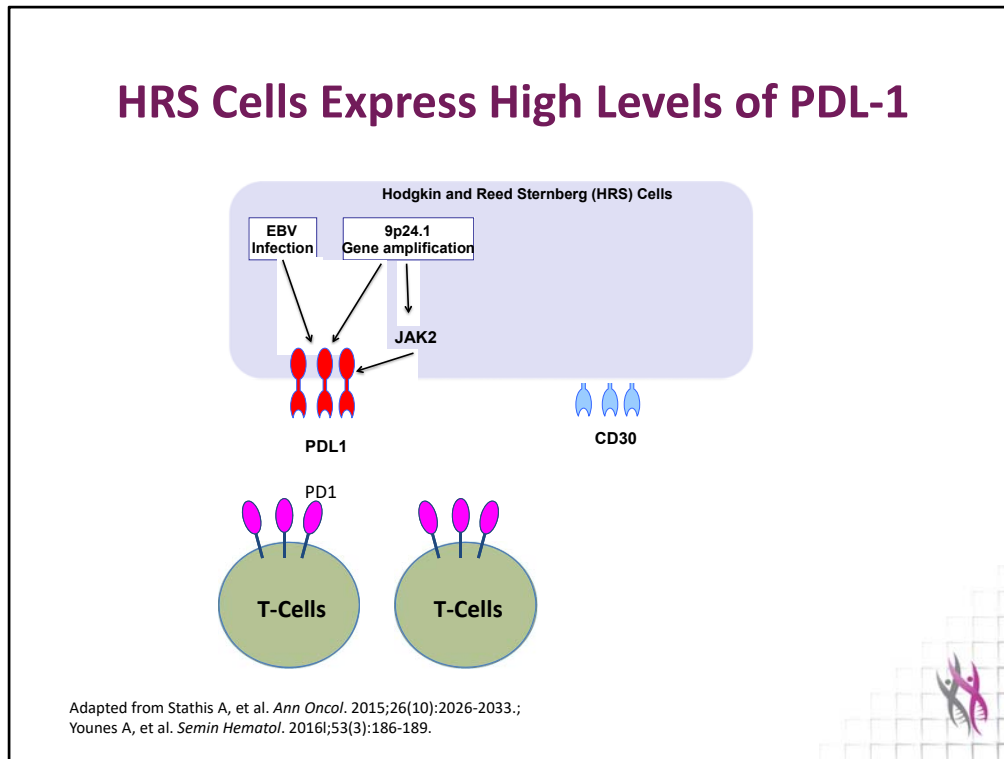
9p24.1 Amplification and PD-1L Cell-surface Expression in HL and MLBCL Cell Lines



Green MR, et al. *Blood*. 2010;116:3268-3277.

About a year later, the group from Boston led by Margaret Shipp linked the over-expression of PD-L1 and PD-L2 proteins to genetic abnormalities which is an amplification of the amplicon 9p24.1 and this amplicon, the genes for PD-L1 and PD-L2, and also JAK2 reside. So, if you have amplification of this region than you have an amplification of PD-L1 and PD-L2 gene and also JAK2. If you have a PD-L1 increase in PD-L1 copy numbers, as shown in the top part of the slide in MLBCL (which is primary mediastinal large lymphoma), you can see there is about 3.8 copies of PD-L1 gene and therefore you have a nice expression of the protein PD-L1 shown in the white histogram. Whereas, in the common variety diffuse large B-cell lymphoma cell lines, you do not see amplification of PD-L1 because the copy number is ranging to 1.8 to 1.9 which is normal two copies per cell and you do not see much of the PD-L1 expression. In contrast, what you see in the lower part of this slide, in Hodgkin lymphoma cell lines, you can see most of these cell lines have a high copy number of PD-L1, ranging from 2.4 to 7.4 copies, and you can see there is association with high level of PD-L1 expression on the surface, measured by flow cytometry.

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So now we have genetic explanation why the malignant Hodgkin and Reed-Sternberg cells express high levels of PD-L1 and PD-L2. This is mainly because they have an amplification in the 9p24 region that I just mentioned. To put to this together, now we can see in this cartoon, Hodgkin lymphoma expressed now high levels of PD-L1. They also express high levels of CD30 and presumably the target for PD-L1 is PD-1 which is presumably expressed on the infiltrating T-lymphocytes in the microenvironment of Hodgkin lymphoma. The question was, “Would interruption of this interaction between PD-1 and PD-L1 lead to therapeutic benefit?”

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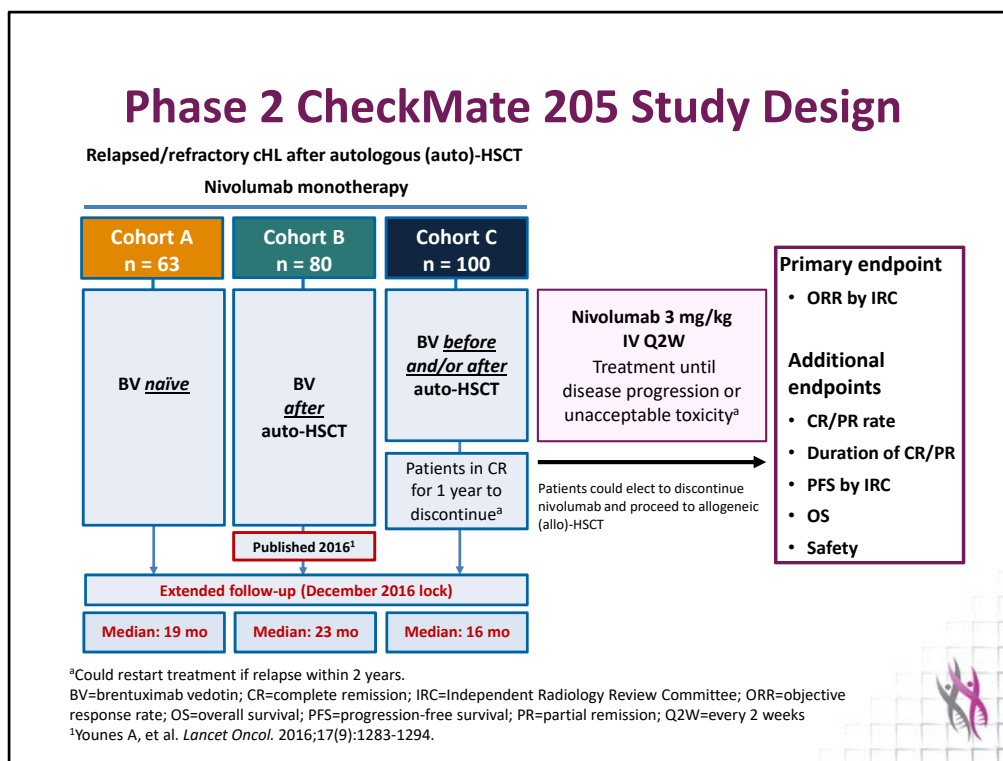
Current and Future Approaches to Treatment

Results of PD1 Blocking Antibodies in Relapsed HL: Phase-I Studies

Drug	Dose/ Schedule	N	% ORR	% CR	ORR in BV treated HL	1 st Author
Pembrolizumab (humanized IgG4)	10 mg/kg IV Q 2 wks	29	66%	21%	66% (n =1 9)	Armand P. JCO 2016
Nivolumab (fully human IgG4)	3 mg/kg IV Q 2 wks	23	87%	17%	70% (n = 16)	Ansell S. NEJM 2015

The question was tested initially in two phase I trials. These phase I trials were multi-arm phase I trials that included non-Hodgkin lymphoma, Hodgkin lymphoma, multiple myeloma, myelodysplastic syndrome and other hematologic malignancies, mainly looking for a therapeutic signal. To everyone's pleasant surprise, the highest response rate was seen in the cohort of Hodgkin lymphoma. What you can see here is a summary slide of two segments of the phase I trials, one with pembrolizumab and one with nivolumab. Each included about 29 or 23 patients but the response rate in this relatively small cohort was strikingly high with pembrolizumab with 66% response rate and with nivolumab with 87% response. Most responses were partial, few had complete responses, but this was like enough signal to get everyone excited.

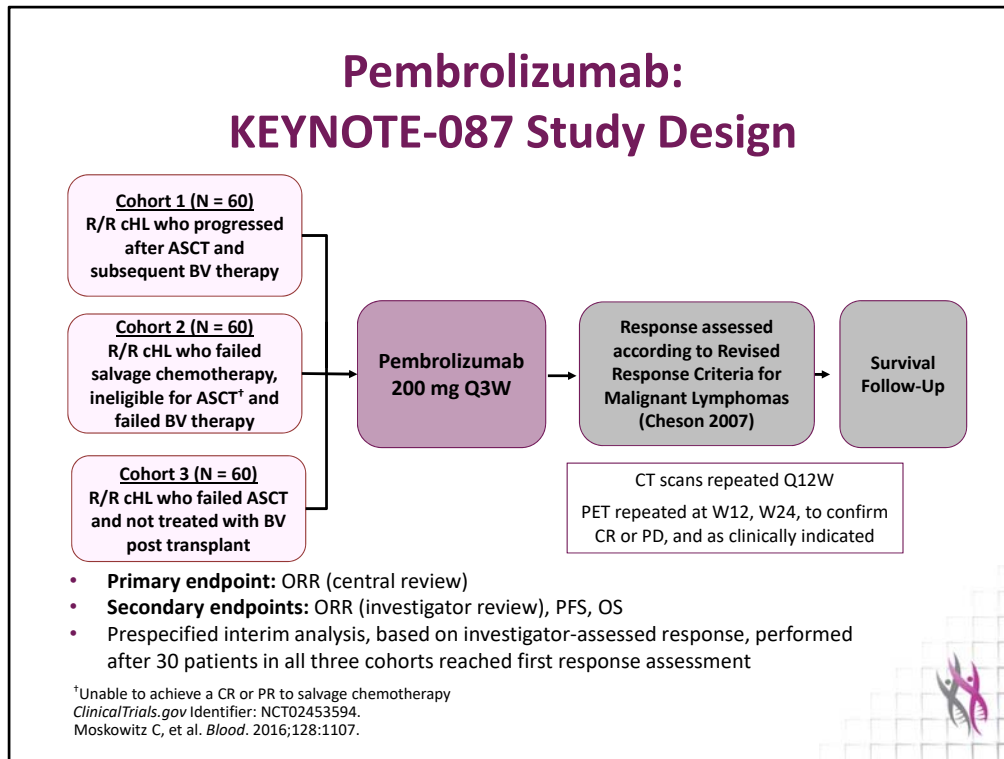
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That led quickly to two pivotal trials, phase II trials, seeking registration by the FDA and other regulatory agencies. These phase II trials also included multiple cohorts, looking at different clinical scenarios. The first one with nivolumab which is called CheckMate 205 included three different cohorts, all cohorts are required to have failure after autologous transplant. Cohort B, which led to the initial approval, required patients to fail both autologous transplant and brentuximab vedotin. Eventually, the other cohorts also showed similar responses.

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Pembrolizumab also was conducted in a phase II trial with multiple cohorts. Different clinical scenarios, one of them also included patients who failed both autologous transplant and brentuximab vedotin.

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Results of PD1 Blocking Antibodies in Relapsed HL: Results of Phase-II Studies

Post ASCT and Brentuximab Vedotin

Drug	Dose/Schedule	N	% ORR	% CR	1 st Author/Ref
Pembrolizumab (humanized IgG4)	200 mg IV Q 3 wks	69	72%	21%	Moskowitz C. ASH 2016
Nivolumab (fully human IgG4)	3 mg/kg IV Q 2 wks	80	66%	9%	Younes A. Lancet Oncology 2016

The bottom line, if you look at the activity of these agents in similar cohorts, in this example here we are showing you responses in patients who failed both autologous transplant and brentuximab vedotin. You could see with pembrolizumab, there were 69 patients treated, and with nivolumab, there were 80 patients treated. The overall response rate was 72% and 66%, very similar. The complete response rate was at 21% and 9% respectively with these two agents. You really should not compare these results head to head, especially the CR rate because this could be probably an underestimation because these agents can induce a local inflammation that may give you false positive PET scan and we are using PET scan to determine CR in these patients, but the bottom line, you can achieve a high response rate regardless whether you use pembrolizumab or nivolumab and CR rate is relatively low with both agents.

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Results of PD1 Blocking Antibodies in Relapsed HL: Results of Phase-II Studies

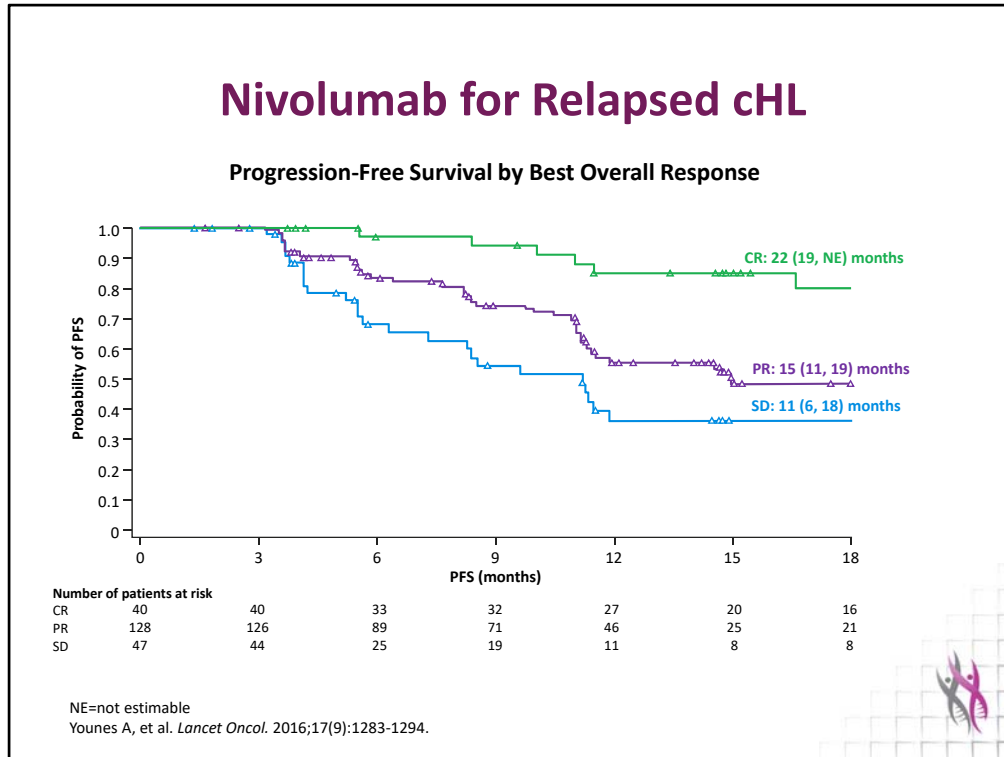
Post ASCT but No PRIOR Brentuximab Vedotin

Drug	Dose/Schedule	N	% ORR	% CR	1 st Author/Ref
Pembrolizumab (humanized IgG4)	200 mg IV Q 3 wks	60	67%	21%	Moskowitz C. ASH 2016
Nivolumab (fully human IgG4)	3 mg/kg IV Q 2 wks	63	68%	22%	Timmerman J. ASH 2016

The same thing if you look at the different cohort, now looking at patients who failed autologous transplant but had no prior brentuximab vedotin. With pembrolizumab, 60 patients treated and with nivolumab, 63 patients treated. Overall response rate is almost identical at 67% and 68% and the CR rate almost identical at 21% and 22%. So regardless, whether you have brentuximab or no brentuximab, if you failed autologous transplant, you have a response rate in the neighborhood of 60% to 70%.

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What is also interesting is that these responses are durable, we have seen data with brentuximab vedotin. If you achieve a complete response, you can have a durable response duration but if you do not achieve a CR with brentuximab vedotin, even partial remission, the median duration of response is measured in a few months, about four to five months. Here with checkpoint inhibitors, in this example is nivolumab but the same story with pembrolizumab. Even if you achieve a partial remission or even a stable disease, you can have a good duration of response, sometimes exceeding a year. This is good to remember because even stable disease which is technically minor response can give the patients good mileage in terms of time to progression.

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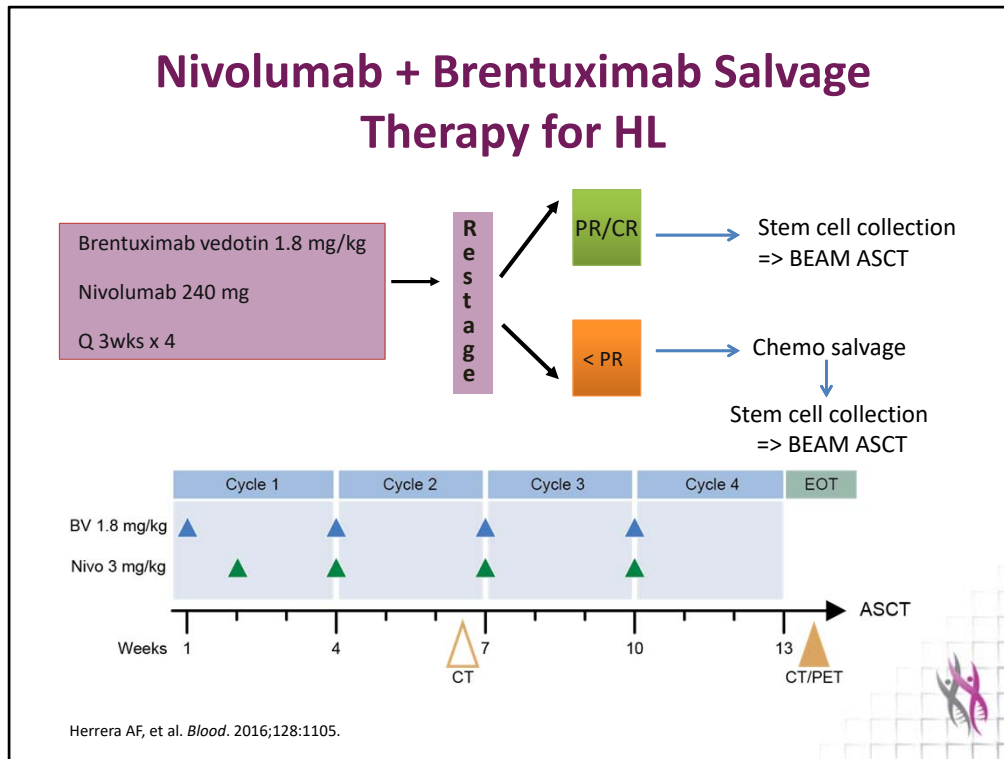
1105 Preliminary Results from a Phase 1/2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Hodgkin Lymphoma

Alex F Herrera, MD, Nancy L Bartlett, MD, Radhakrishnan
Ramchandren, MD, Julie M Vose, MD, Alison J Moskowitz, MD,
Tatyana A Feldman, MD, Ann S LaCasce, MD, Stephen M Ansell,
MD, PhD, Craig H. Moskowitz, MD, Keenan Fenton, Kazunobu Kato,
MD, Abraham Fong, MD, PhD and Ranjana H Advani, MD



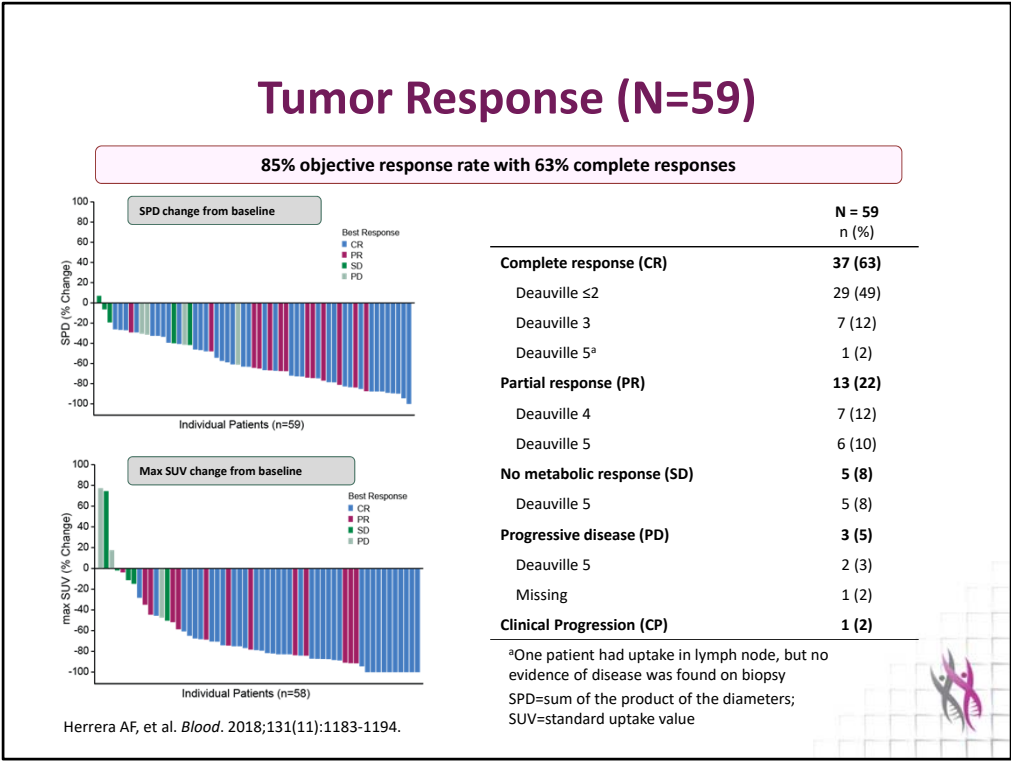
Now we have checkpoint inhibitors, pembrolizumab and nivolumab, both give you about 60% to 70% response rate. We previously had brentuximab vedotin which was the first drug approved by the FDA for relapsed Hodgkin lymphoma with the response rate also about 75%. Everybody wants to see these agents combined because, a) you can combine them at full doses without overlapping toxicity, and b) they have a different mechanism of action. The question is, “If we combine both of them, would we get a higher response rate or longer duration of response?” To answer this question, the group from City of Hope led a multi-center trial that did this combination trial, brentuximab vedotin plus nivolumab but as salvage therapy before autologous transplant.

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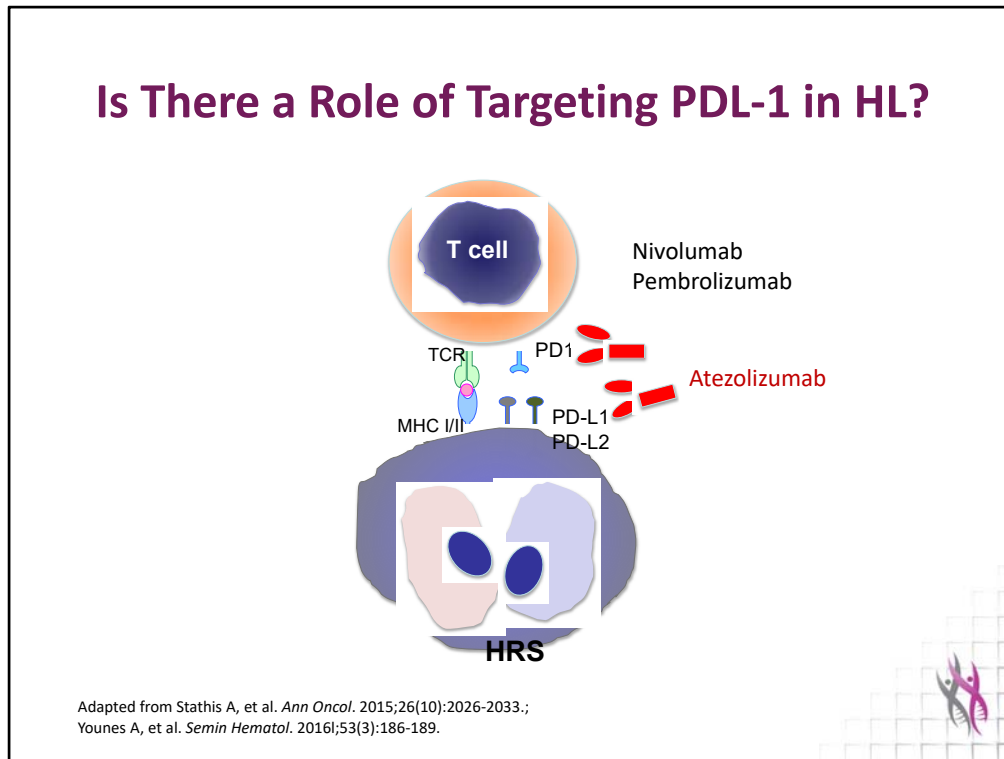
In this trial, patients were treated with four doses of these two drugs, and if you respond, you can go to autologous transplant. This trial can give you an idea about the response rate but unfortunately, does not give you an idea about the median time to progression because patients who responded were then offered autologous transplant, but regardless, the data was very impressive.

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The overall response rate was 85% and a complete response rate is 63% which is higher than what we see with each drug alone, higher than what we have seen with brentuximab vedotin because the CR rate is about 35% and higher than what we have seen with pembrolizumab or nivolumab with a CR rate ranging between 12% to 21% response. That has really created a lot of excitement, and based on this data, there is now an international randomized trial comparing brentuximab alone with brentuximab plus nivolumab in patients failing after autologous transplant.

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Another question that came up is that what about PD-L1 antibodies? We know that PD-L1 antibodies have been approved for several solid tumor indications. Can we use PD-1 and PD-L1 antibodies interchangeably in Hodgkin lymphoma? The reason why this question was important is because Hodgkin lymphoma, as I mentioned before, expressed both PD-L1 and PD-L2 because of the genetic amplification. There was concern that if you block PD-L1 alone, PD-L2 may compensate and then therefore PD-L1 target agents may not be as effective.

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Blockade of the PD-1 checkpoint with anti-PD-L1 avelumab is sufficient for clinical activity in relapsed/refractory classical Hodgkin lymphoma (cHL)


Robert Chen¹, Adam Gibb², Graham P. Collins³, Rakesh Popat⁴, Dima El-Sharkawi⁴, Cathy Burton⁵, David Lewis⁶, Fiona Miall⁷, Alison Forgie⁸, Anna Compagnoni⁹, Giovanna Andreola⁹, Satjit Brar¹⁰, Aron Thall¹⁰, Adrian Woolfson¹¹, and John Radford²

¹City of Hope Medical Center, Duarte, California, USA; ²The Christie NHS Foundation Trust, Manchester, United Kingdom; ³Churchill Hospital, Cancer and Haematology Centre, Oxford, United Kingdom; ⁴University College London Hospitals NHS Foundation Trust, London, United Kingdom; ⁵St. James's University Hospital, Leeds, United Kingdom; ⁶Plymouth Hospital NHS Trust, Plymouth, United Kingdom; ⁷University Hospitals of Leicester NHS Trust, Leicester, United Kingdom; ⁸Pfizer Oncology Research and Development, San Francisco, California, USA; ⁹Pfizer Oncology, Milano, Italy; ¹⁰Pfizer Oncology, La Jolla, California, USA; ¹¹Pfizer Oncology, New York, New York, USA

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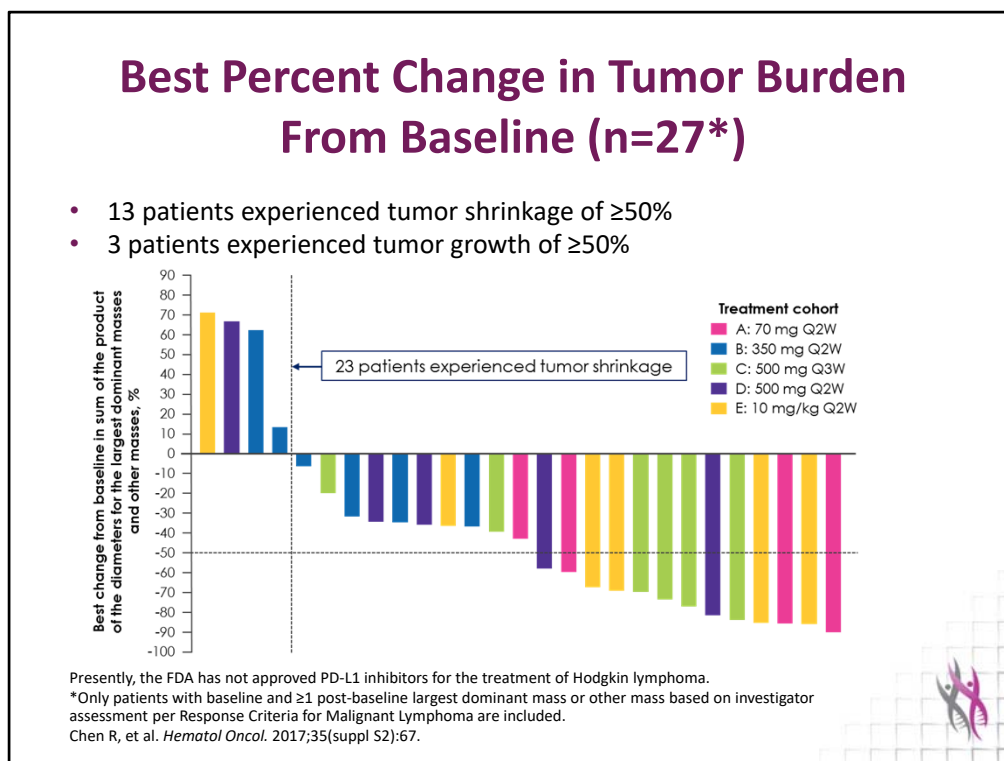
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A phase I trial was conducted and reported about a year ago by Robert Chen from City of Hope, it was a multi-centered trial.

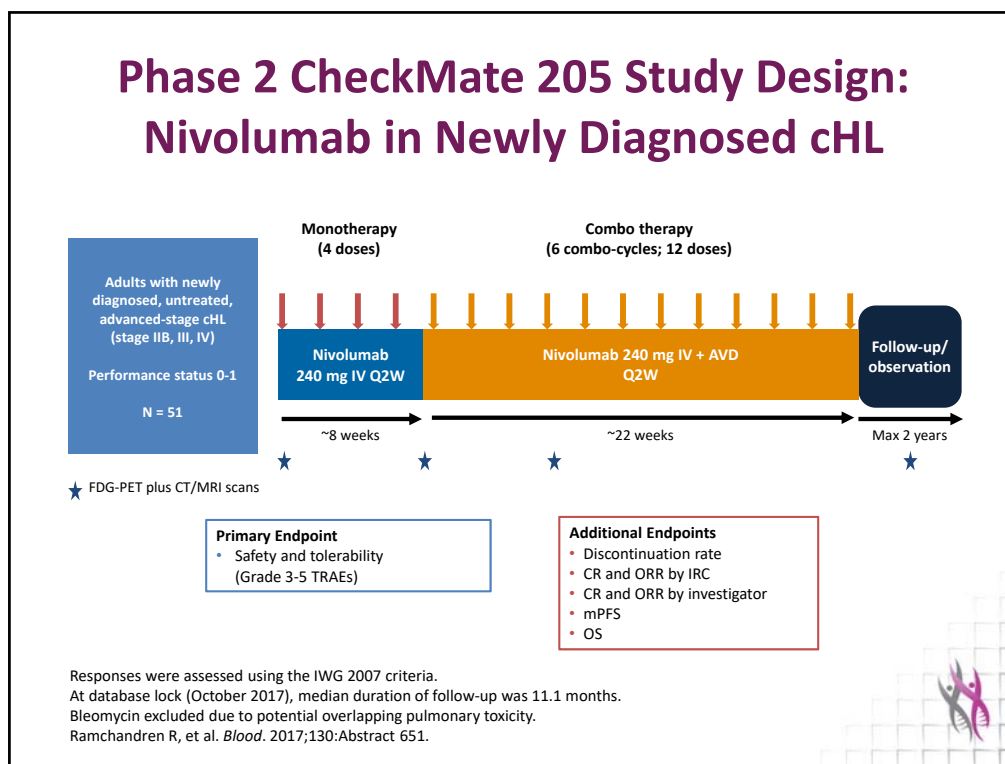
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This is a gist of the trial, it is a phase I trial so that is multi-dose escalation, but it was very interesting to see that the majority of patients had some responses, seen in this waterfall plot. What we know from this trial that PD-L2 may not completely compensate for PD-L1. We do not know the exact overall response rate because it is a phase I trial. We do not know the phase II data yet, but it is interesting to know at the least if you block PD-L1 alone, you could still see good response rate in patients with Hodgkin lymphoma. Keep in mind, PD-L1 targeted agents are not approved for Hodgkin lymphoma at present.

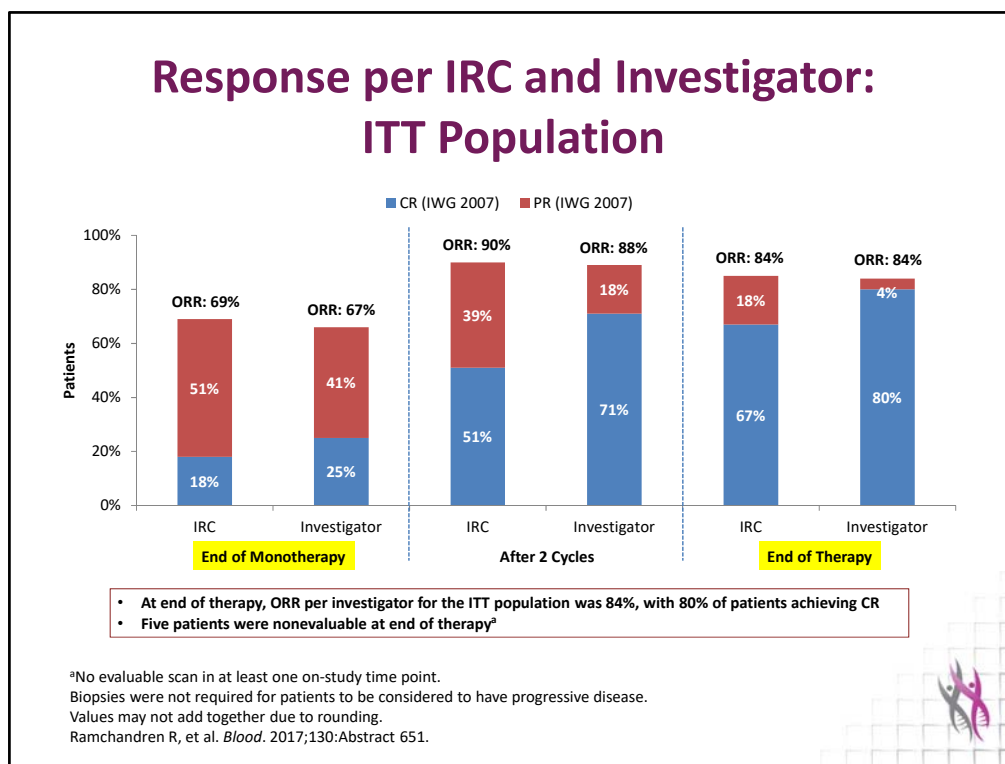
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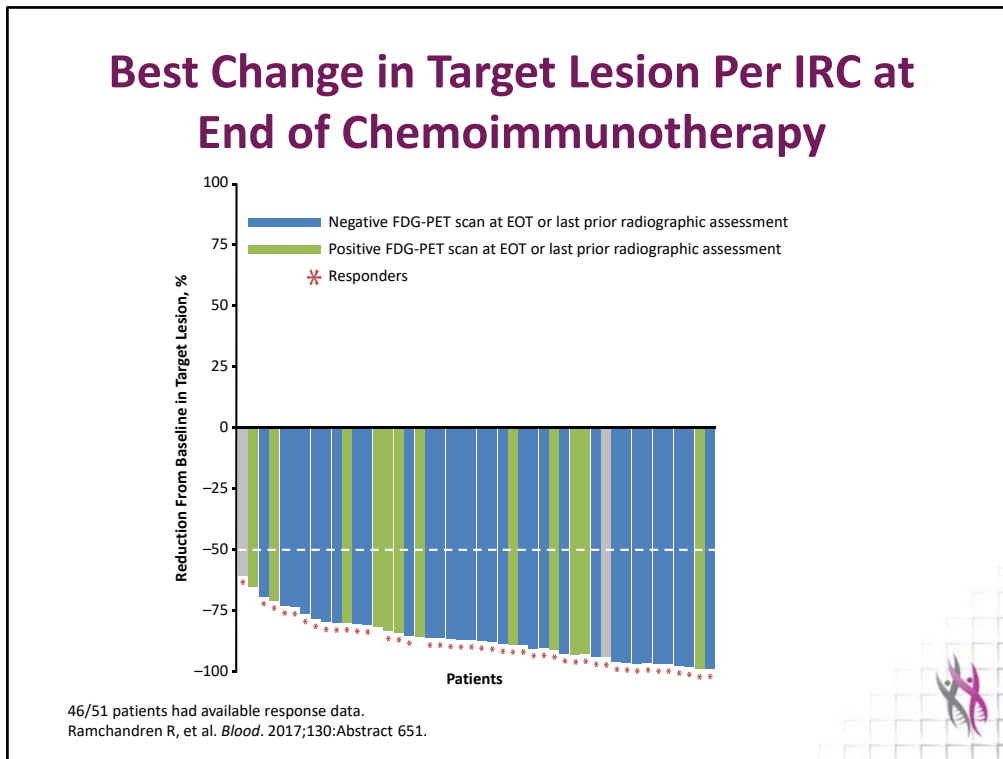
Another question came up with the ECHELON-1 trial, which combined brentuximab vedotin plus ABVD or AVD in newly diagnosed patients. Can we or should we combine checkpoint inhibitors with ABVD or AVD in newly diagnosed patients, and what is the safety in these patients and what is the efficacy? And again, there is a cohort in the CheckMate 205, it is called cohort D which included patients with newly diagnosed classical Hodgkin lymphoma. It had a window design, meaning that the patients received nivolumab for two months, four doses, before they started chemotherapy. After four doses of nivolumab, they received a concurrent AVD plus nivolumab for the six cycles and then the patients were followed up. There is no maintenance strategy whatsoever.

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This is the data which was published last ASH meeting. If you look at the end of monotherapy, nivolumab alone four doses which is shown on the left side of this slide, you could see that the overall response rate was almost 70%. Most responses were also partial, which is shown in the red color and the blue color were the CRs. So as single agent in newly diagnosed, untreated patients with classical Hodgkin lymphoma, four doses produced same response rate as what we have seen in patients who failed autologous transplant and patient who failed both autologous transplant and brentuximab vedotin. Now when you combine both AVD and brentuximab vedotin, you can see at the end of therapy, at the end of six cycles of AVD plus nivolumab, the response rate now goes up to 84% with the majority of responses being complete responses about 70% complete response.

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The question is what do you do with this data? This is the waterfall plot for this data, almost all patients responded which is not surprising. There are now trials looking at the combination of these agents, pembrolizumab or nivolumab with AVD or ABVD, and then there may be plans to do randomized trial to see if this adds value over brentuximab AVD or maybe even could be considered in the future to be compared head to head with the ECHELON-1 data, but this is an ongoing discussion at this present time.

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Most Common Treatment-Related Adverse Events with PD-I Inhibitors in cHL

Common Therapy-Related Grade 1-2 occurring in 10% to 15%	Most Common Grade 3 or greater
Fatigue	Neutropenia
Infusion reaction	Dyspnea
Rash	Diarrhea
Thrombocytopenia	Pancreatitis
Hypothyroidism	
Fever	
Diarrhea	
Immune Related Adverse Events	
Pneumonitis	
Colitis	
Hepatitis	
Hypophysitis	

Younes A, et al. *Lancet Oncol.* 2016;17(9):1283-1294.
Chen R, et al. *J Clin Oncol.* 2017; 35:2125-2132.

Side effects of checkpoint inhibitors are the same thing that what has been reported in any other cancers including solid tumors. The class effective for a PD-1 target agent, mainly at grade 1 and grade 2, fever, diarrhea, neutropenia, fatigue, cough, hypothyroidism is seen in about 7% or so, sometimes skin rash, some nausea. What we are mainly concerned about is what we call the 'itis' (hepatitis, pneumonitis, colitis). These are typically rare, a grade 3 and 4. Less than 2% to 3% usually, but those require usually steroid administration, dose interruption, and sometimes dose termination if they are severe or recurrent side effects. One should be aware of these side effects when using checkpoint inhibitors.

OPDIVO (nivolumab) Highlights of Prescribing Information. Bristol-Myers Squibb Company.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125554lbl.pdf

KEYTRUDA (pembrolizumab) Highlights of Prescribing Information. Merck & Co., Inc.

https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125514s012lbl.pdf

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Conclusions

- Antibodies targeting PD1 demonstrated significant clinical activity in HL, leading to regulatory approval
- Anti PD1/PDL1 antibodies have modest single-agent activity in NHL => combination strategies
- The role of immune checkpoint inhibitors in eradicating MRD/ctDNA in HL and NHL is being investigated

Conclusions, antibodies targeting PD-1 demonstrated significant clinical activity in Hodgkin lymphoma leading to regulatory approval of both nivolumab and pembrolizumab. Anti-PD-1 and PD-L1 antibodies have modest single-agent activity in non-Hodgkin lymphoma, we did not talk about that, and therefore multiple combination strategies are now being investigated. So, none of these agents have been approved for non-Hodgkin lymphoma. The approval right now, only for classical Hodgkin lymphoma. The role of immune checkpoint inhibitors in eradicating minimal residual disease or circulating tumor DNA in both Hodgkin lymphoma and non-Hodgkin lymphoma being investigated. Again, we did not have much time to talk about this but there is lot of interest in looking at the value of adding checkpoint inhibitors to frontline regimens as a concurrent administration, AVD plus nivolumab, I mentioned that. There are trials combining that with R-CHOP for example and G-bendamustine for non-Hodgkin low-grade B-cell lymphoma, plus maintenance strategies looking at the effect of these agents on circulating tumor DNA in both Hodgkin and non-Hodgkin lymphomas and also in solid tumors. With this, I thank you for watching this program.