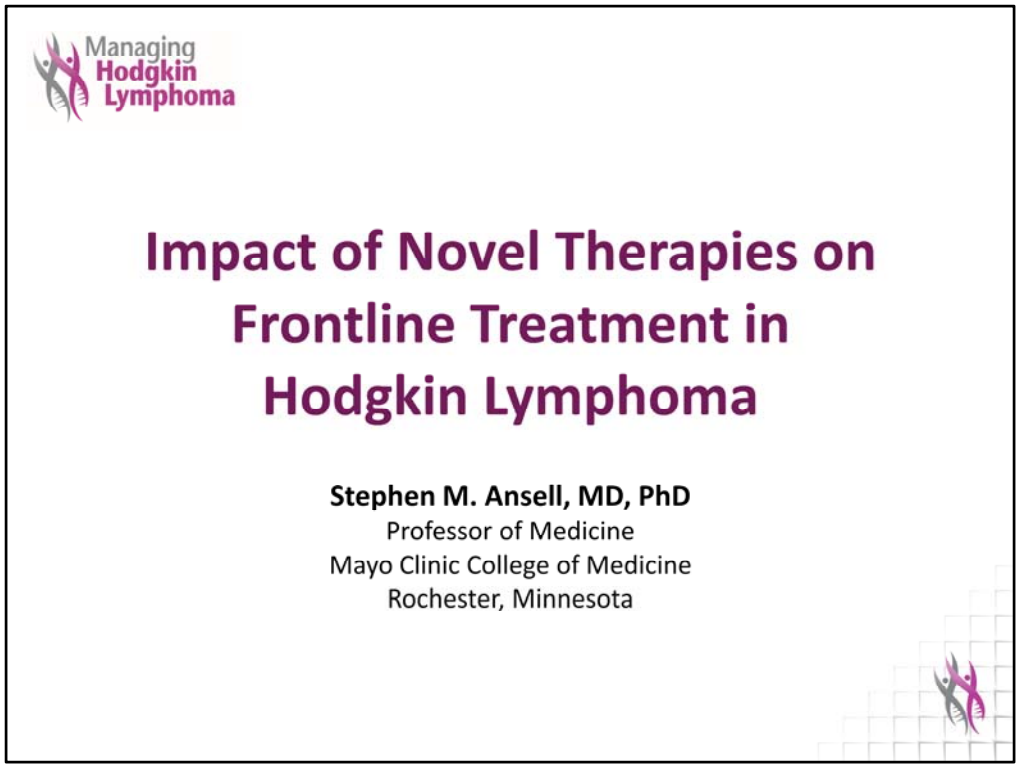
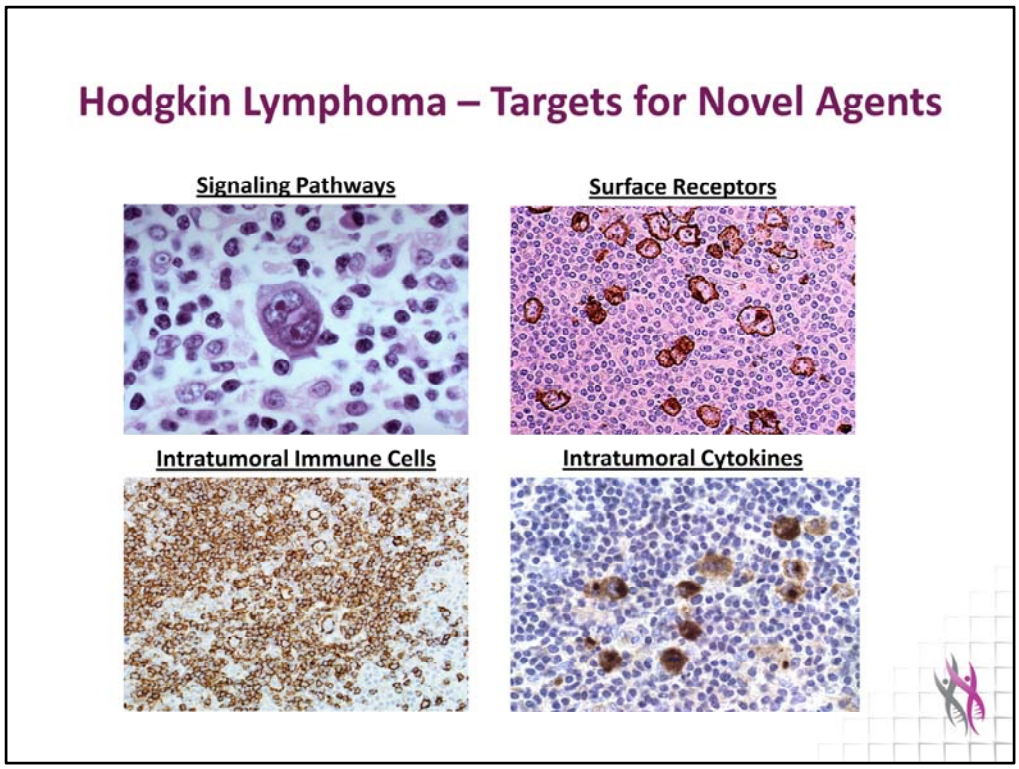
The Future Impact of Novel Therapies on the Frontline Treatment of Hodgkin Lymphoma



Welcome to *Managing Hodgkin Lymphoma*. I am Dr. Stephen Ansell. In today's presentation, I will be discussing novel agents and drug combinations being investigated in the frontline therapy for patients with Hodgkin lymphoma, and I will be discussing the potential impact of investigational therapies on the standard of care and on the existing treatment paradigms in newly diagnosed Hodgkin lymphoma. Let’s begin.



One of the things that is really important to know is that Hodgkin lymphoma is quite a unique disease. Within the tumor microenvironment, only a small percentage, 1% to 2% of cells are actually malignant Reed-Sternberg cells. The vast majority of cells present within the microenvironment are actually inflammatory normal immune cells that are being recruited there. Within this normal immune microenvironment, there are a number of opportunities to target the interactions between the malignant cell and the tumor infiltrate of normal cells. These opportunities are to either target specific signaling pathways within the malignant cells or within the infiltrating cells to target some of the receptors on the outside of both the Reed-Sternberg cells and the immune cells to actually specifically try and deplete the cells that appear to be assisting the malignant cell, or to work in on trying to get rid of cytokines and other proteins that are stimulating the entire process. As we talk about some of the novel therapies, we will talk about some of the ways in which this is being explored.

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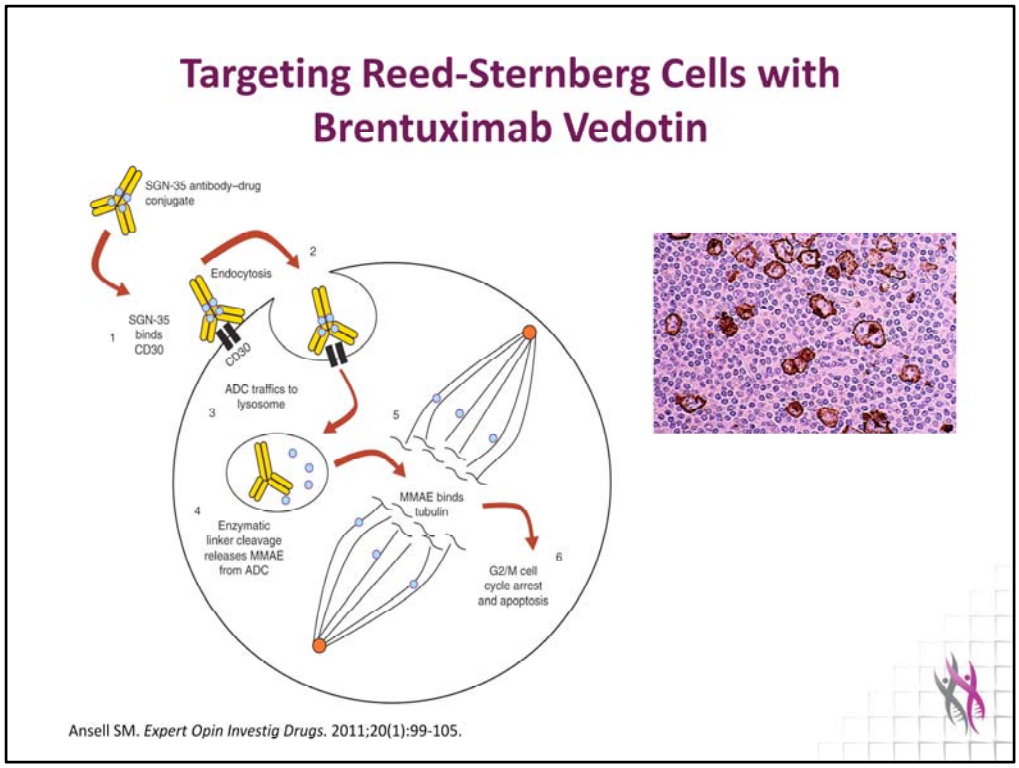
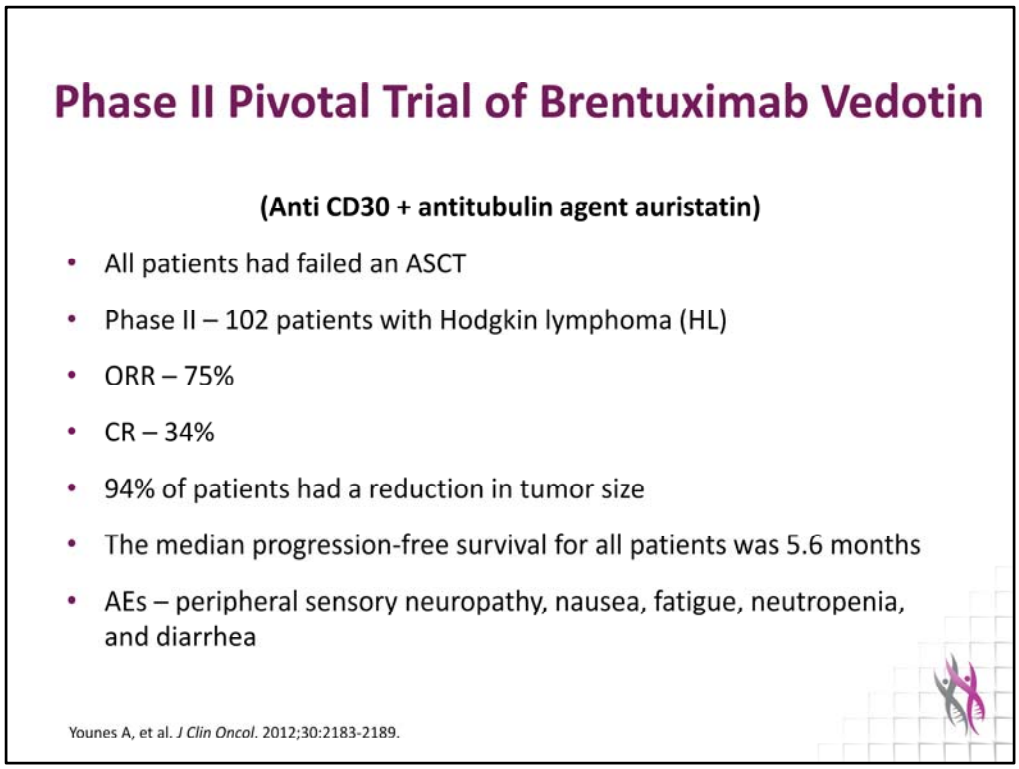
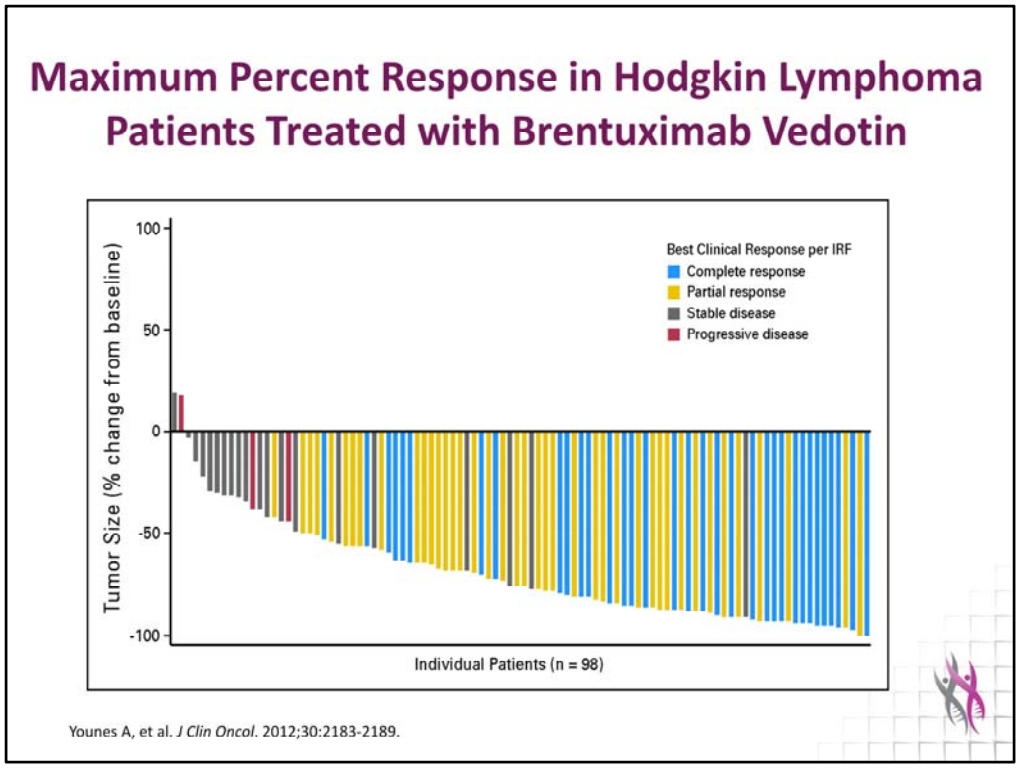


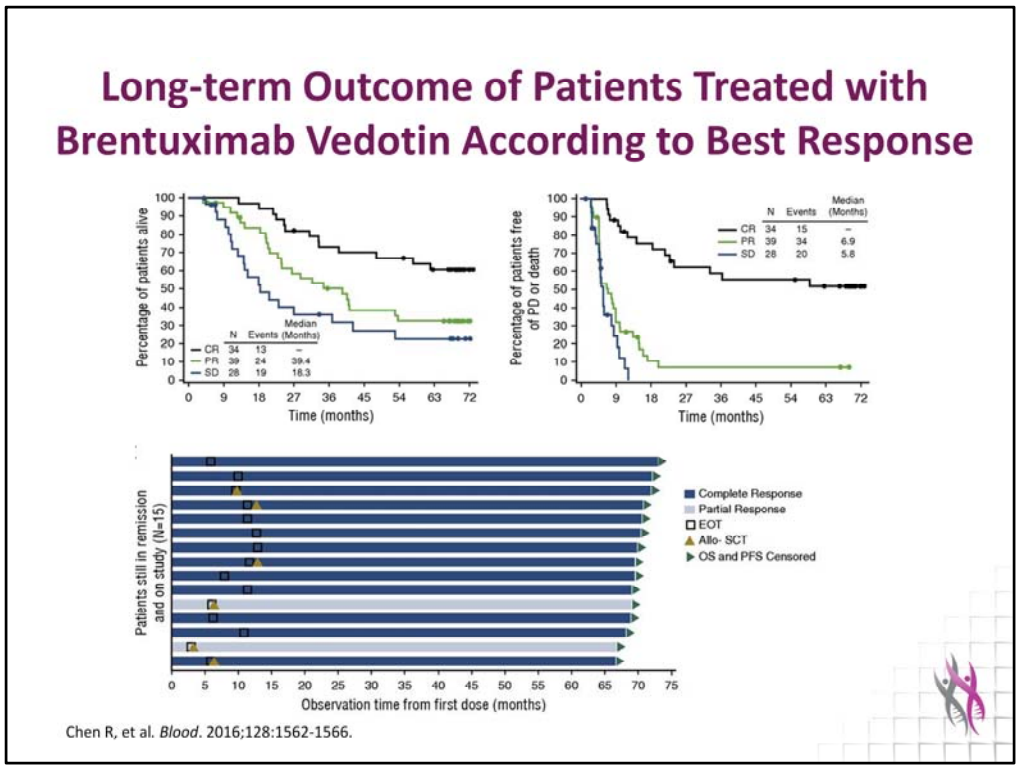
First it is very important to realize that Reed-Sternberg cells have a unique protein on the outside called CD30, and CD30 is the target of the agent brentuximab vedotin. As shown in the slide, CD30 is highly expressed, but really limited just to Reed-Sternberg cells, very few other cells within the microenvironment or within the patient express CD30. The unique thing about brentuximab vedotin is that as it binds to CD30, CD30 is internalized. With the internalization process, the antibody then releases its payload which is MMAE, this is a toxin which inhibits microspindle and microtubulin function and then induces the apoptosis of the cell. Interestingly, even after the cell becomes apoptotic, some of the toxin and the chemotherapy then spills out and is eaten up by some of the other cells including macrophages within the tumor microenvironment. This has a further bystander effect on some of the cells that surround the malignant cell.



Utilizing brentuximab vedotin has proven to be very useful in Hodgkin lymphoma. After very promising initial studies in the phase I trials of brentuximab vedotin with promising results seen in Hodgkin lymphoma, a standard phase II trial was then done in patients with classical Hodgkin lymphoma who had failed frontline therapy and had failed an autologous stem cell transplant. This pivotal trial included 102 patients with Hodgkin lymphoma and had an outstanding overall response rate of 75%. Of the patients, 34% had a complete response to treatment, but even more interesting was the fact that 94% of patients had some degree of reduction in the size of the tumor. At the time of the initial presentation, progression-free survival for all patients was approximately six months. The treatment was well tolerated. Specifically, peripheral neuropathy, some mild nausea and fatigue, neutropenia and diarrhea were most of the side effects seen, but in general, the agent was well-tolerated and felt to be highly effective.

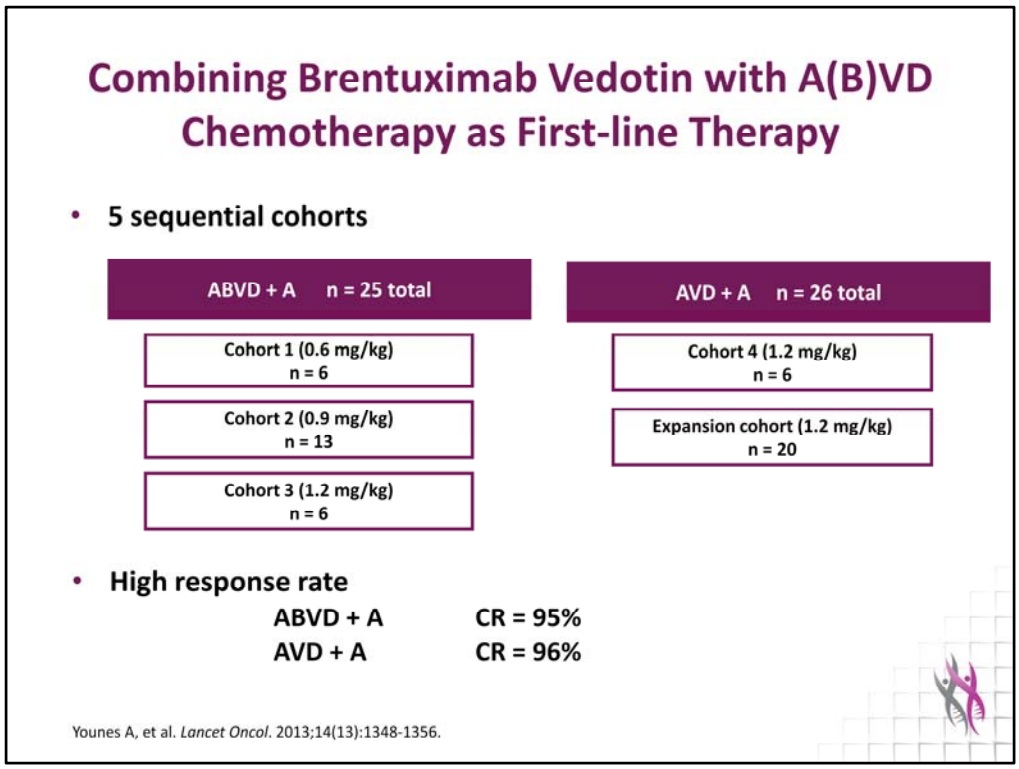


As shown here in this waterfall plot, you can see the vast majority of patients benefited from therapy. Aside from just a small number of patients, almost everybody benefited from therapy. The key question however was, “Is this a durable response and are these therapies, particularly brentuximab vedotin, going to induce prolonged responses in patients with Hodgkin lymphoma?”

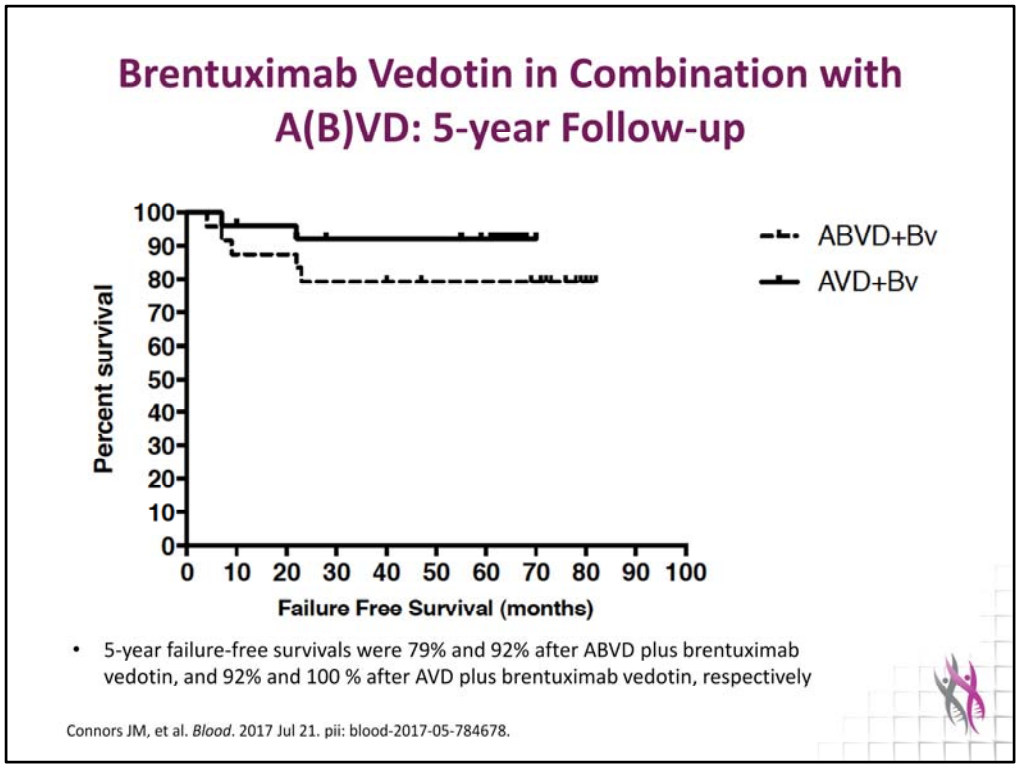


Chen R, et al. *Blood*. 2016;128:1562-1566.

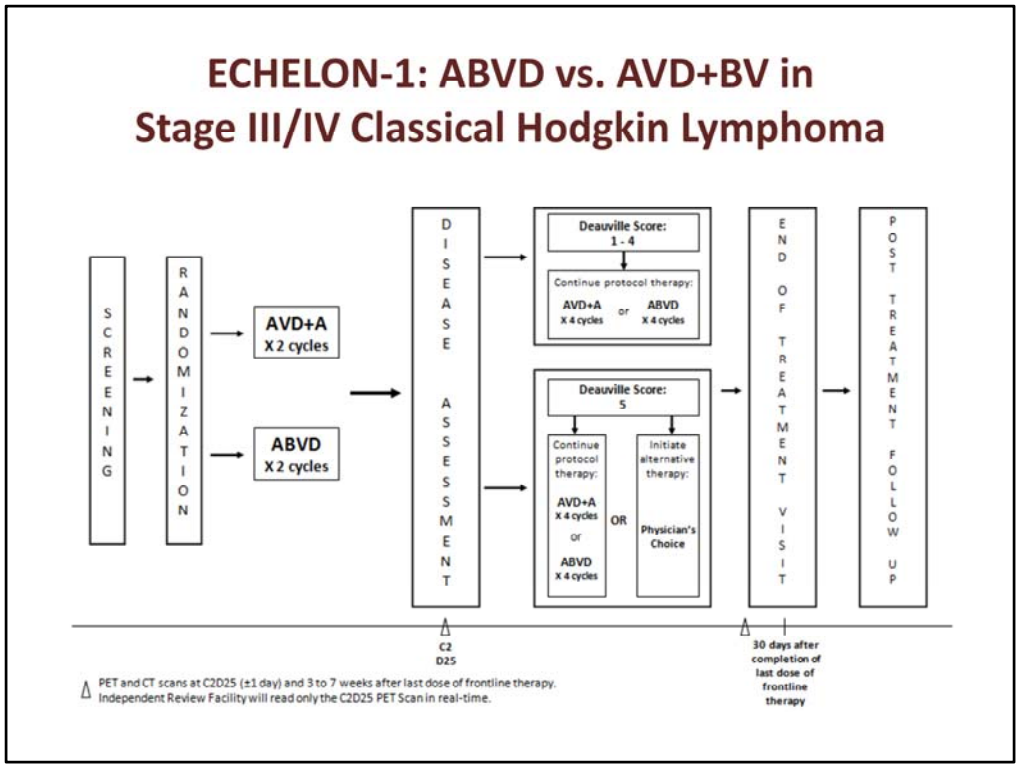
We now have the advantage of almost 5 years of follow up after that initial trial. Shown here are those five-year follow-up data that are presented which showed that patients who had a complete response to therapy had a very promising long-term outcome. Complete responding patients clearly did far better than patients that had only a partial response or no response. I think what is most interesting is that a subset of patients remain in remission now with five years of follow up, and these patients potentially could even be cured with the use of brentuximab vedotin. I think an important lesson to learn is that when patients are treated in the relapsed and refractory setting, the patients achieving a complete remission may have very durable benefits from brentuximab vedotin.



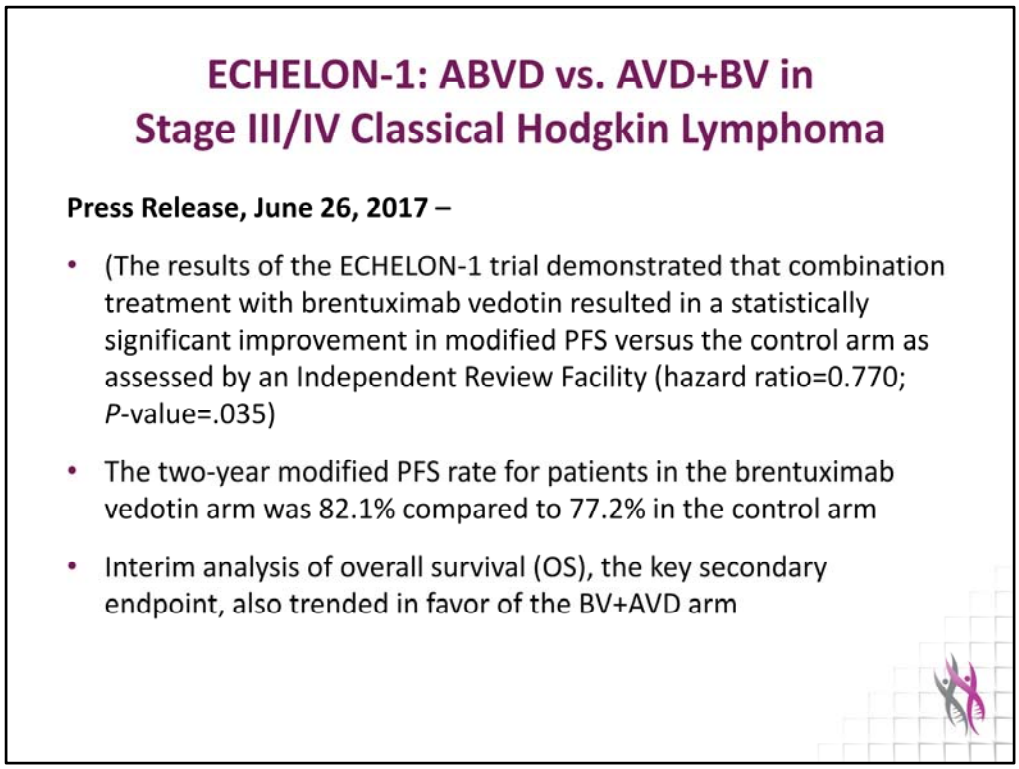
Clearly this was very exciting and promising data. It allowed us to then take this unique novel therapy and utilize it in the frontline setting. To do that, brentuximab vedotin was combined with a standard frontline therapy, ABVD chemotherapy. Initially, the chemotherapy was given in two cohorts. The first cohort utilized brentuximab vedotin in combination with ABVD, 25 patients were treated in this cohort. One of the challenges, however, was the fact that brentuximab vedotin and bleomycin had interactions resulting in an unacceptably high percentage of patients that had bleomycin lung toxicity. Because of that, a second cohort was explored leaving out bleomycin and instead continuing with brentuximab vedotin as it were in the place of bleomycin. The AVD chemotherapy plus brentuximab vedotin was then explored in a further 26 patients. I think that what was extremely encouraging from this trial was the complete response rate with both cohorts was 95% and 96%, respectively, suggesting that the addition of brentuximab vedotin further improved the outcomes of patients that were treated with atypical ABVD chemotherapy. For context, it is important to know that approximately 75%, possibly 80%, of patients would be expected to have a complete response to ABVD chemotherapy alone. This clearly looked as an advance over the use of standard therapy.



With longer-term follow up, now recently published was the five-year follow up of that phase 1 trial. As shown in these curves, you can see the failure-free survival was very promising in both cohorts, 79% and 92%, respectively, in the ABVD plus brentuximab vedotin or the AVD plus brentuximab vedotin. If one looked at the overall survival, patients continued to do extremely well when treated with this combination. I think all told, this study showed us that combining brentuximab vedotin with frontline chemotherapy was feasible. The lesson we learned was that brentuximab vedotin and bleomycin were not able to be utilized in the same combination but that the use of AVD chemotherapy plus brentuximab vedotin was a highly effective regimen with high response rates. These response rates were very durable with excellent results now with five years of follow up.

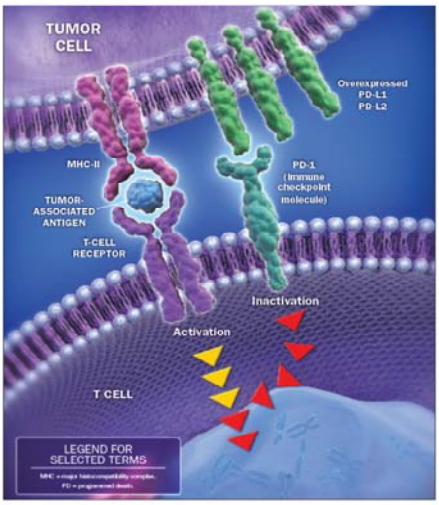


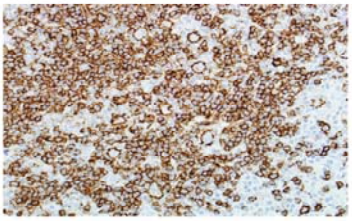
This clearly led to a large randomized trial comparing the standard ABVD chemotherapy to AVD chemotherapy plus brentuximab vedotin. This trial was called ECHELON-1, it was a very large study with more than 1000, in fact 1300 patients enrolled in the study, an international study. The study specifically looked at giving two cycles of treatment, doing a disease assessment in patients responding to treatment, continuing on then with one of those two arms. In patients with evidence of disease progression, there was the opportunity to go off study onto other therapy.



This trial has not been reported at this point in all detail yet. A press release released at the end of June 2017 showed that the results were (for the combination of brentuximab vedotin plus AVD) met the primary endpoint. This was a significant improvement in the modified progression-free survival versus the control arm with a *P*-value that was significant. Modified progression-free survival here was very similar to what we would call inventory survival. This modified progression-free survival in patients who received brentuximab vedotin plus AVD chemotherapy was 82% compared to the control ABVD arm, which was 77%. At the time of the press release, there was also an interim analysis of overall survival, which was a secondary endpoint, and this also proved the report favored the combination of brentuximab vedotin plus AVD chemotherapy. Clearly, this is limited data at this point, a more complete assessment will need to be done as new data emerges. I think it further supports the phase I evidence, which say that AVD chemotherapy plus brentuximab vedotin was a highly effective therapy, and based on the initial press release, this appears superior to patients who were treated with ABVD chemotherapy.

Targeting T-cells and the PD-1/PD-L1 Pathway





- PD-1 is expressed on the surface of activated T-cells
- Its ligands, PD-L1 and PD-L2, are overexpressed in certain tumor cells
- Binding of PD-1 to its ligands inhibits T-cell activation, allowing tumors to evade the immune response

I think, all told, the important thing to note here is the targeting CD30 on Reed-Sternberg cells utilizing brentuximab vedotin is a highly effective approach with very promising results as a single agent and even more promising results when used in frontline in combination with standard chemotherapy, such as AVD chemotherapy. A second approach might now be to target cells in the microenvironment. One of the cell types that are very prevalent within the microenvironment are cytotoxic T-cells, and T-cells within the microenvironment as they become activated may express PD-1. PD-1 is a negative regulatory receptor, and signaling through PD-1 by one of the ligands PD-L1 or PD-L2 results in deactivation and suppression of the T-cells. The ligands of PD-L1 and PD-L2 are commonly overexpressed and Reed-Sternberg cells, particularly, can have a very high expression of PD-L1 and PD-L2. This is mostly due to amplifications and copy number gains of chromosome 9p24.1, which is seen in most patients with Hodgkin lymphoma present within the Reed-Sternberg cells. As I said, when PD-L1 or PD-L2 binds to PD-1 on T-cells, this results in decreased T-cell activation, and this is one of the ways in which tumors effectively evade the immune response.

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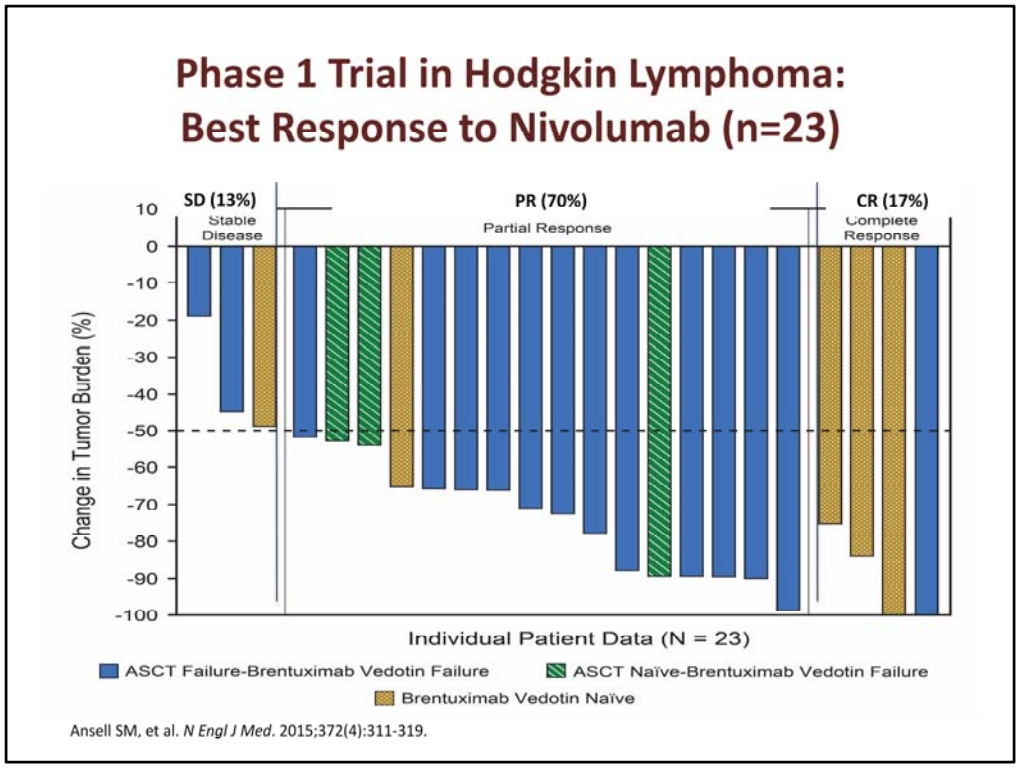
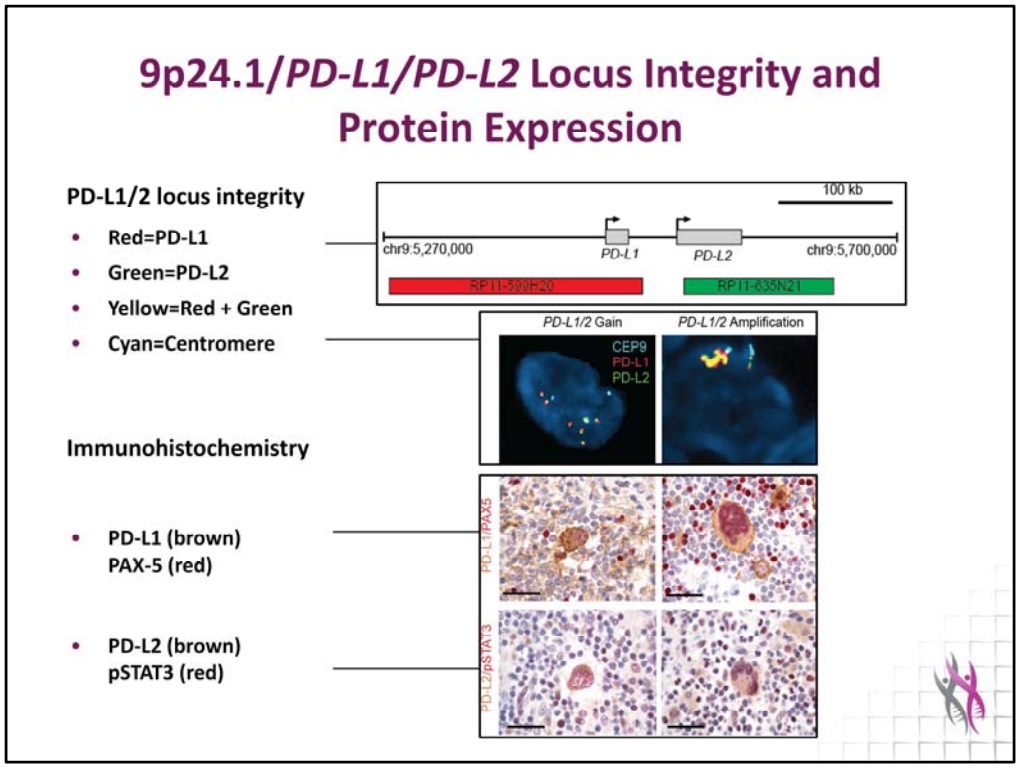


One of the potential options is to block PD-L1/PD-L2 interactions with PD-1. This is being done with a number of anti-PD-1 antibodies, the first of them being nivolumab, the results are shown here in the slide. In an initial phase 1 trial of many hematologic malignancies, a subset of 23 patients with Hodgkin lymphoma had an excellent response to therapy. In this study, 87% of patients had benefit from therapy in the way of a partial or complete response. Virtually all patients had some degree of benefit with PD-1 blockade.



As I mentioned earlier, chromosome 9p24.1 is the locus at which PD-L1 and PD-L2 is present, and this results in overexpression of PD-L1 and PD-L2. Shown in the top part of this slide is the copy number gain or amplification that can be seen. Shown in the immunohistochemistry slides is co-staining for PD-L1 and PD-L2 and also for PAX5 and STAT3 which shows us that in the Reed-Sternberg cells, the large cells present in the tumor, these are the cells that show very high expression of PD-L1 and PD-L2. These ligands are what shut down the activity of the T-cells and are very highly expressed, and this accounts for the fact that nivolumab therapy is highly effective. In 10 patients in whom specimens were available in the phase 1 trial, overexpression of PD-L1 and PD-L2 was seen in every case.

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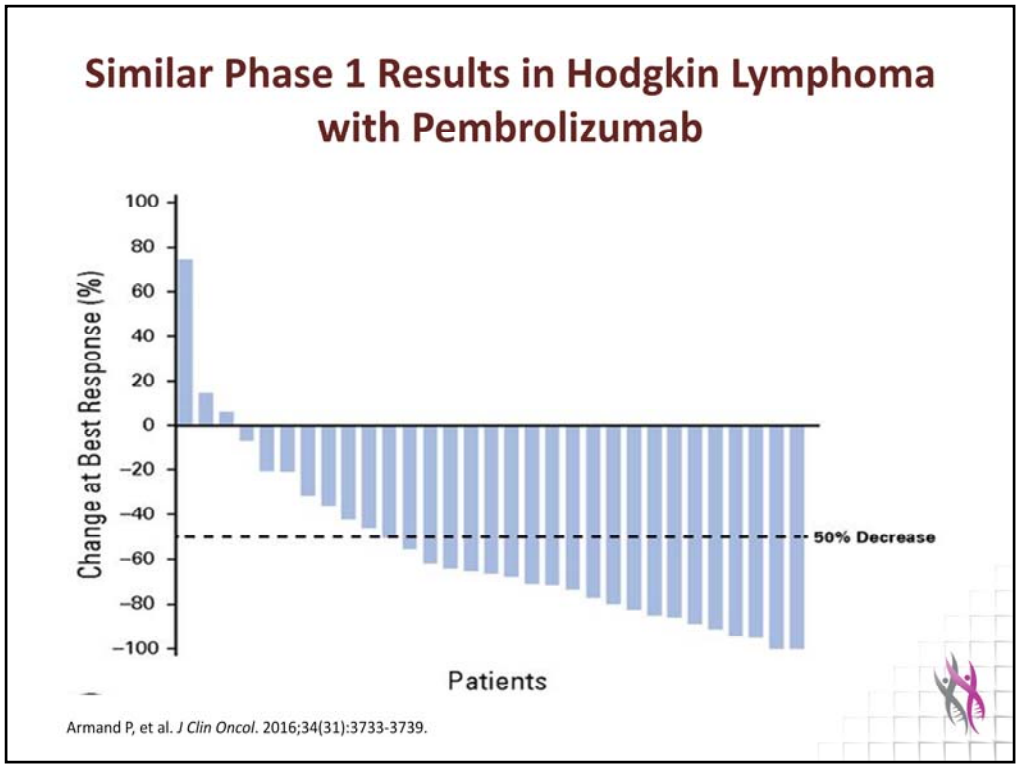
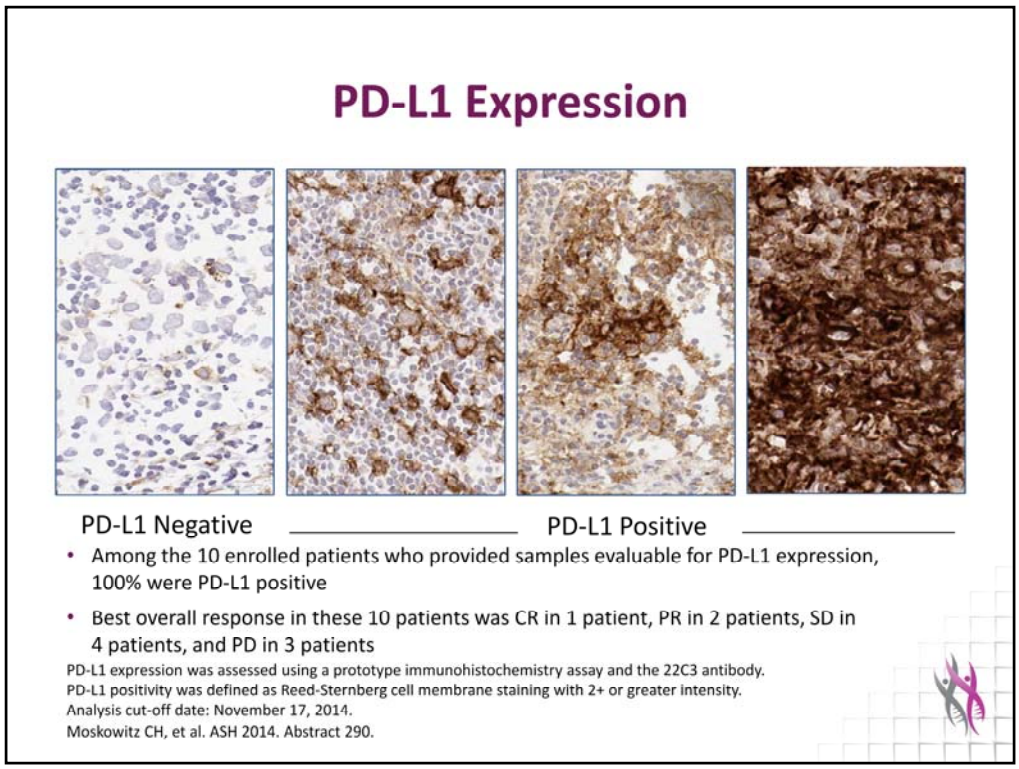


Subsequent studies were done with another PD-1 antibody, pembrolizumab. Here are the results from the initial phase 1 trial, again in a cohort of patients with Hodgkin lymphoma. Similar to the results seen with nivolumab, excellent results were seen with PD-1 blockade using pembrolizumab. Again, the majority of patients showing a significant response to therapy, and approximately two-thirds of patients having at least a partial or complete response to the treatment in this phase 1 trial



Immunohistochemistry for PD-L1 and PD-L2 was done in the study. In a subset of 10 patients, every patient in whom PD-L1 could be tested, high levels of expression were seen in every single case. Shown here is three of three cases, and you can see significant overexpression of PD-L1 present in each of the patient biopsies that were obtained.

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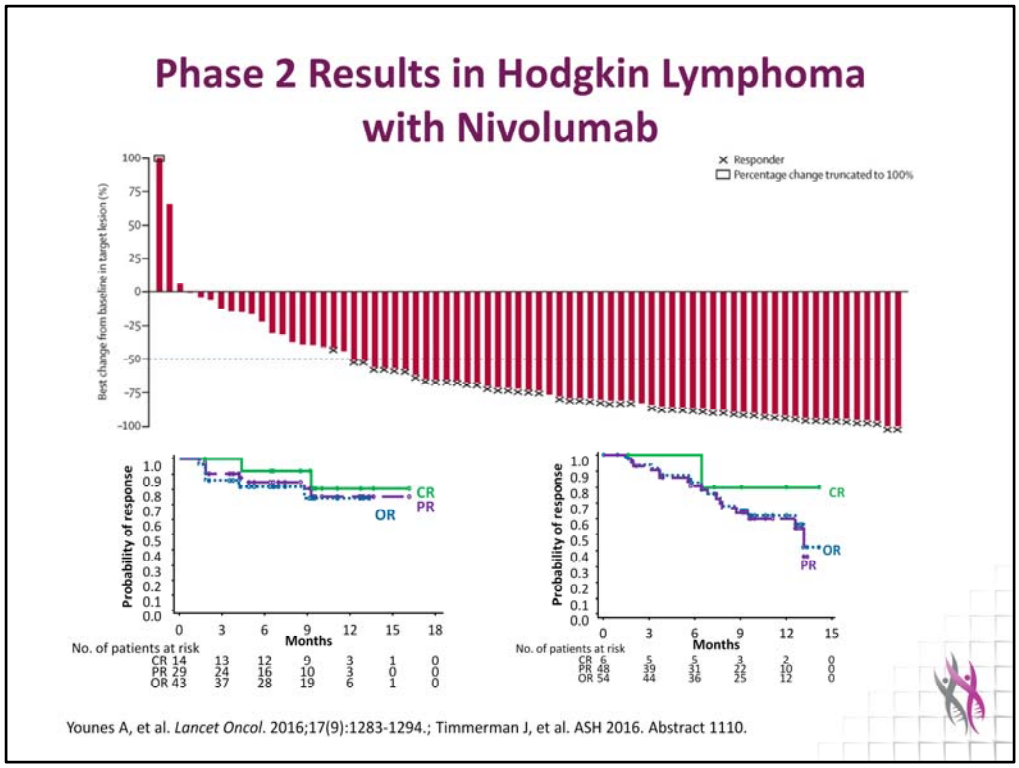

Phase 2 trial was then subsequently done with nivolumab. Here are the data from that trial, and you can see the results were confirmed. In the phase 2 trial a number of cohorts of patients were enrolled, some patients who had received brentuximab vedotin and had undergone autologous stem cell transplant, others who had received brentuximab vedotin and had not proceeded to a transplant, and some patients who had had a transplant but had not received brentuximab vedotin. I think all told, in each of these cohorts, excellent results were seen, with approximately 65% to 70% of the patients having a partial or complete response to therapy. As shown in the Kaplan-Meier curves, it did not really seem to be significantly different in patient outcome whether you had a complete response or partial response, with partial responding patients benefiting as much as patients who had a complete response to therapy.

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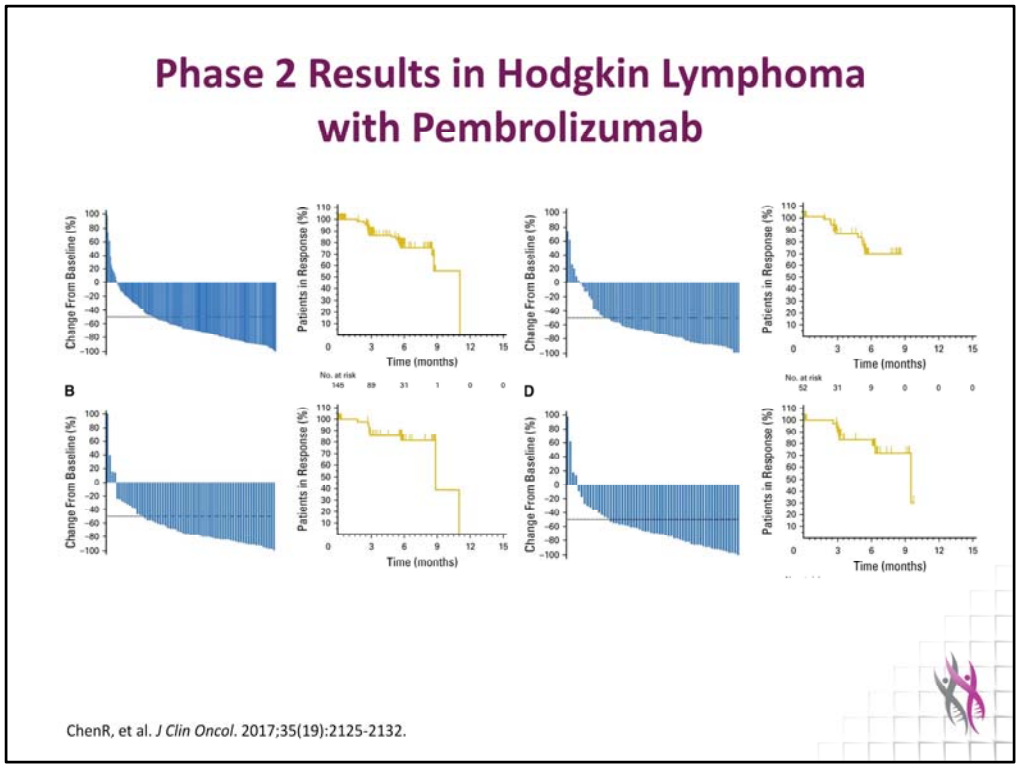

The phase 2 data with pembrolizumab are also similarly encouraging. You can see here again the waterfall plots from the multiple cohorts addressed in that trial. The patients had either undergone a transplant and brentuximab vedotin; the patients might have not received a transplant due to primary refractory disease, or patients may have received a transplant without brentuximab vedotin. Similar to the results with nivolumab, excellent results were seen with pembrolizumab, with response rates in the 65% to 70% rate in each of the cohorts. A further analysis done in this trial compared people with primary refractory disease to people with chemo sensitive disease, and responses were seen in both cohorts at a very similar level. This really suggested that pembrolizumab and nivolumab work in an entirely different way and therefore they are not ineffective when patients have chemo resistant disease and are a great choice for patients with disease that has progressed on standard therapies.

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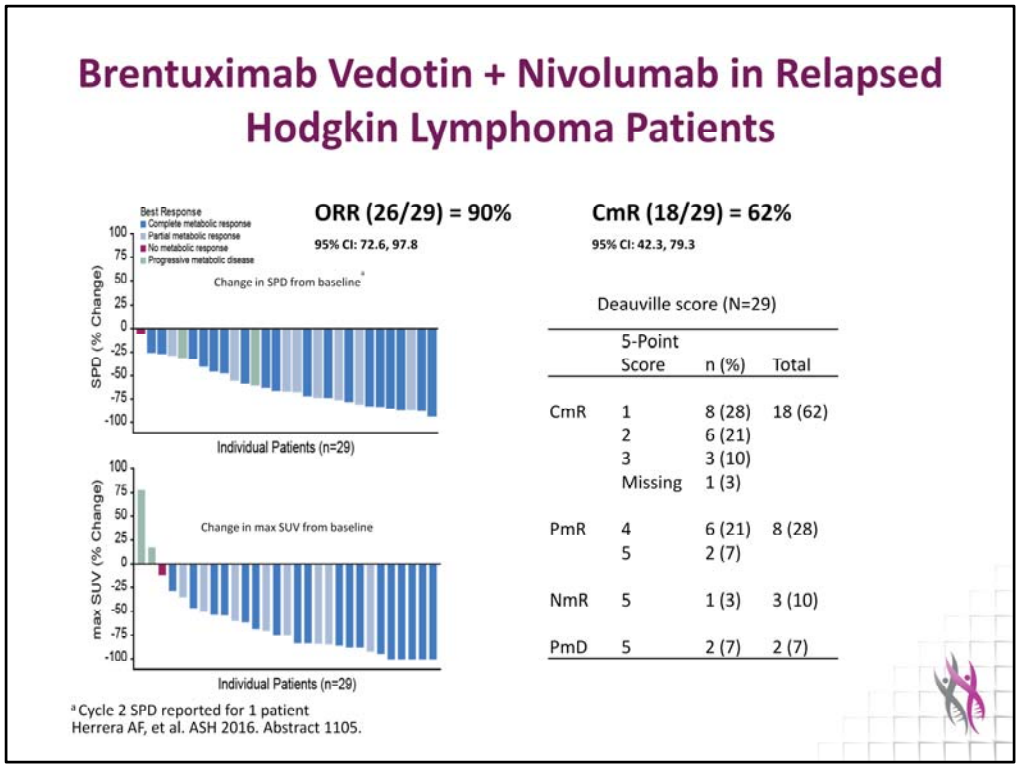
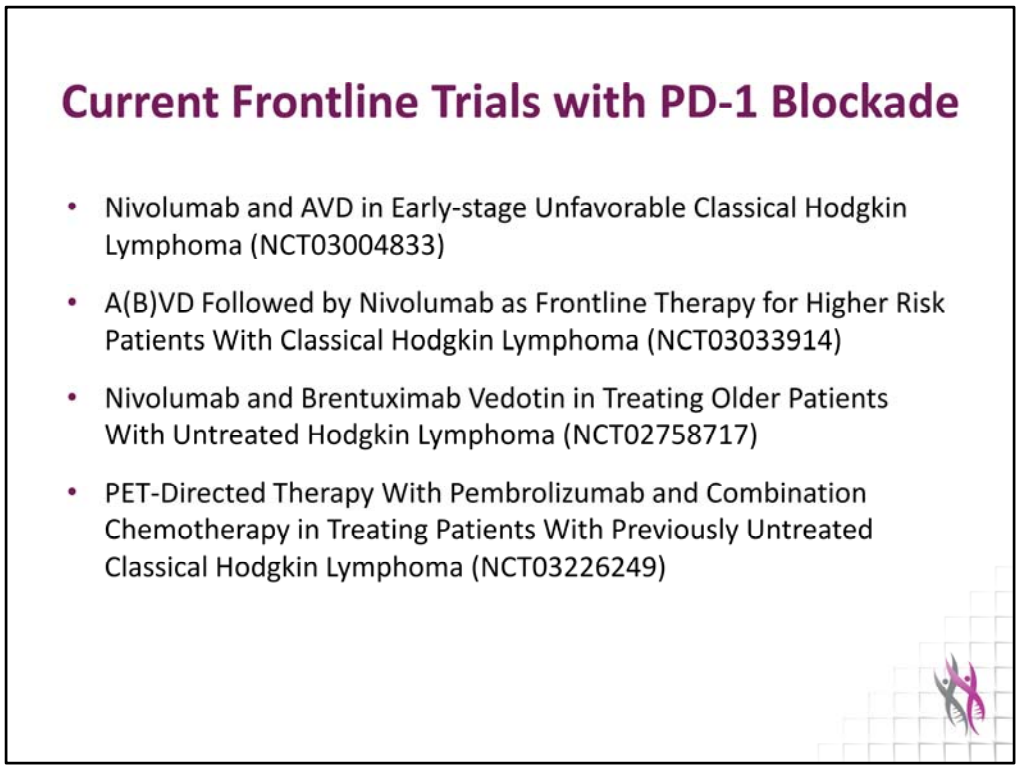
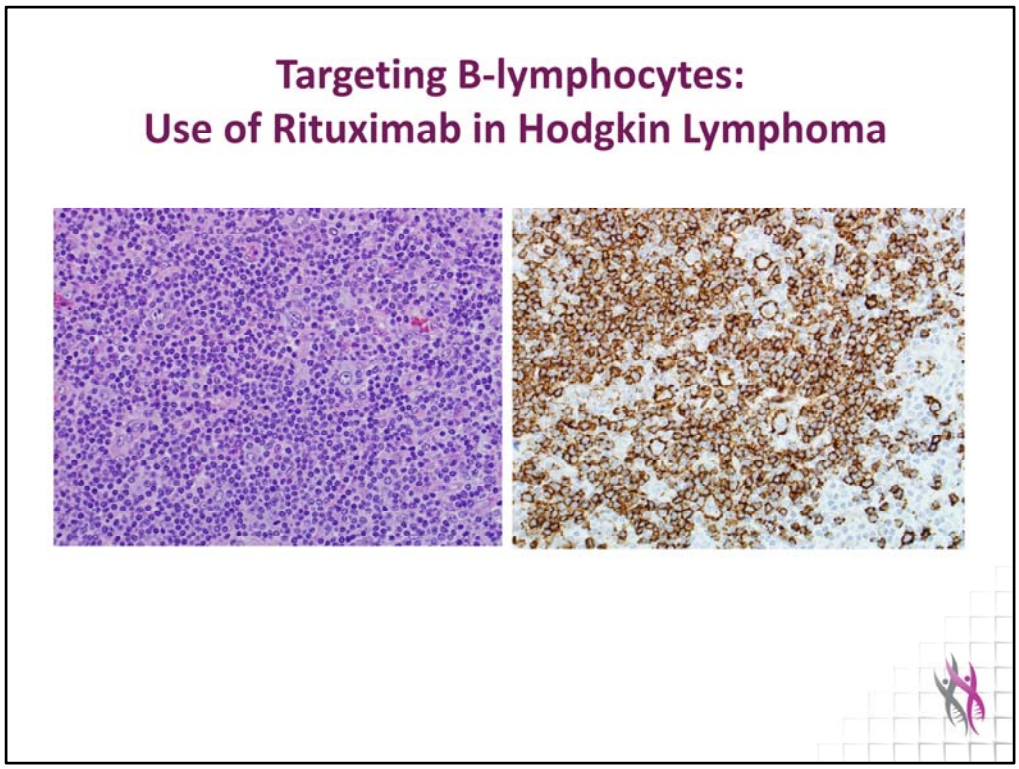


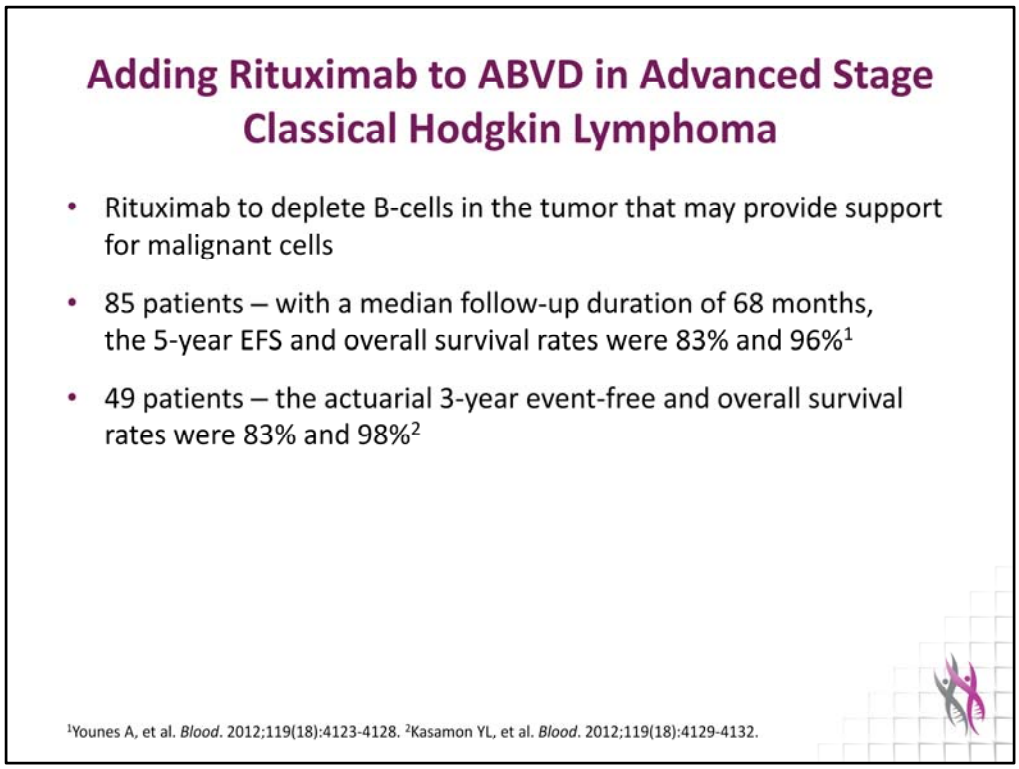
Further evaluation has now looked at taking these novel therapies and utilizing them in combination. Shown here is data presented at the most recent ASH meeting, utilizing brentuximab vedotin targeting CD30 on the Reed-Sternberg cell and nivolumab targeting PD-1 on the T-cells present within the microenvironment, and looked at utilizing this as the first therapy for patients who had progressed after initial treatment. Very encouragingly, a high overall response rate was seen in this trial of 29 patients, 90% of them responded to therapy. Important also was that the complete metabolic response rate was 62% in this trial. This showed that, firstly, one could combine these two novel agents effectively. There were some infusion reactions, but in general this was well-tolerated. More encouragingly, this was shown to be a highly effective regimen and very promising a high rate of complete responses.



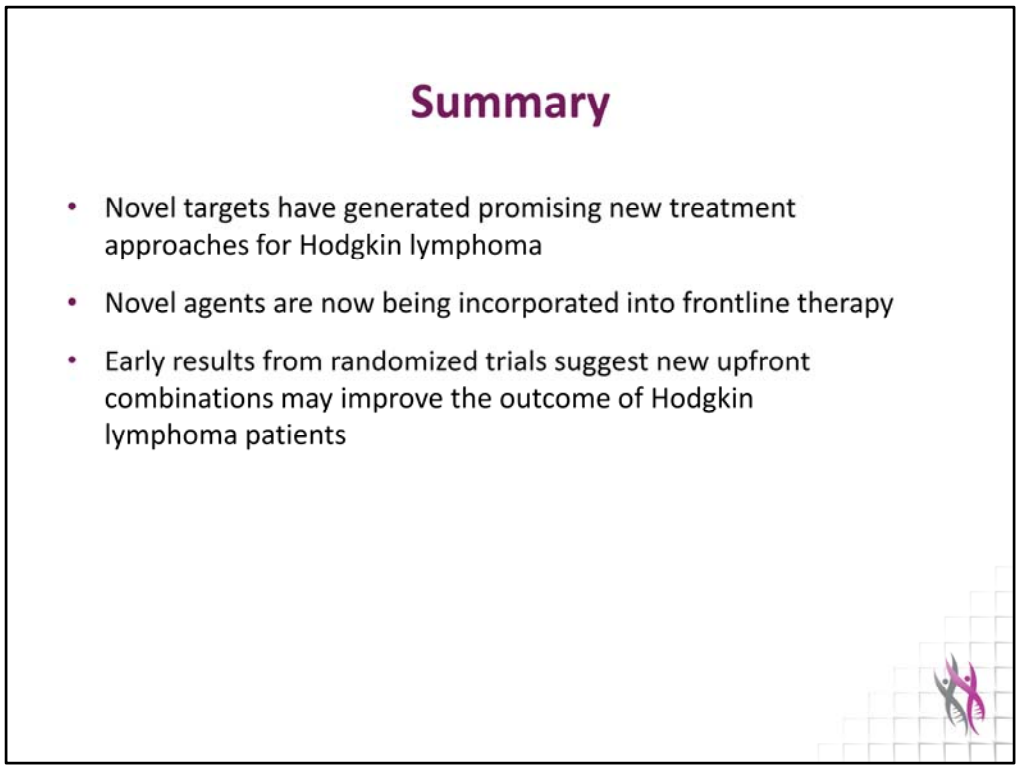
Further steps are taking the PD-1 antibodies, very similar to the approach with brentuximab vedotin, and utilizing this in frontline therapy. There are a variety of different trials, I have highlighted four of them here. In some cases, taking AVD chemotherapy and adding nivolumab to that treatment combination, again, avoiding bleomycin due to the fact that bleomycin lung toxicity could potentially be exacerbated with the use of nivolumab. There are trials utilizing the same combination, but now not just in early unfavorable stage patients, but now in patients with higher risk and more advanced disease. There is a combination utilizing brentuximab vedotin and nivolumab, similar to what I just showed in the relapse setting in the frontline sitting, as first-line therapy, particularly for elderly patients who do not tolerate ABVD chemotherapy very well. Furthermore, there is a PET-directed approach utilizing chemotherapy and pembrolizumab in patients with untreated disease. All told, the agents nivolumab and pembrolizumab are being used in combination with chemotherapy as frontline treatment to test and see whether this approach improves the outcome of patients with classical Hodgkin lymphoma.



What we discussed so far in the presentation has been looking at targeting CD30 on the Reed-Sternberg cell, targeting T-cells by blocking PD-1; but a further cell component that is present within the microenvironment are B-lymphocytes and high numbers of CD20 positive B-cells are also present within the tumor microenvironment. A number of trials have looked at targeting these B-lymphocytes with the use of an anti-CD20 antibody commonly used in non-Hodgkin lymphoma, now being tested in combination in frontline therapy in Hodgkin lymphoma.



There have been two trials reported a few years ago utilizing rituximab to actually deplete all of the B-cells present within the tumor microenvironment. These B-cells seemingly providing support for the malignant Reed-Sternberg cell. In the first trial of 85 patients with a median duration of follow up of almost 5 years, the patients had an excellent long-term outcome. The five-year of event-free survival and overall survival rates were 83% and 96%, respectively, in patients with advanced-stage classical Hodgkin lymphoma. These results really look very promising, and similar results were seen in 49 patients treated in a similar trial using rituximab in combination with ABVD chemotherapy, where similar 3-year event-free and overall survival rates of 83% and 98% was seen. This is a combination that kind of has not really been explored in a randomized setting to date, partly because of the huge enthusiasm for the results seen with brentuximab vedotin and nivolumab. Maybe in the future this will be explored further in utilizing this approach to deplete malignant B-cells.



So all told, I think as we have discussed targeting CD30 on the outside of Reed-Sternberg cells using brentuximab vedotin, as we have discussed targeting PD-1 on intratumoral T-cells, and as we discuss targeting CD20 on intratumoral B-cells; one can see that novel targets in Hodgkin lymphoma have generated significant promising new data that suggests new treatment approaches are possible and very promising for patients with classical Hodgkin lymphoma. These novel agents, specifically brentuximab vedotin and the PD-1 antibodies nivolumab and pembrolizumab, are now being incorporated into frontline therapy for patients with classical Hodgkin lymphoma. So far, the early results from randomized trials, notably the results from the ECHELON-1 trial comparing brentuximab vedotin in combination with AVD chemotherapy to standard ABVD chemotherapy, have suggested an advantage for the combination, and the final reports of that trial is being awaited. This suggests a very promising future for this combination approach utilizing new agents in combination with standard therapy as frontline treatment for classical Hodgkin lymphoma.

Thank you for listening to this activity and for viewing this presentation. I thank you for your time.