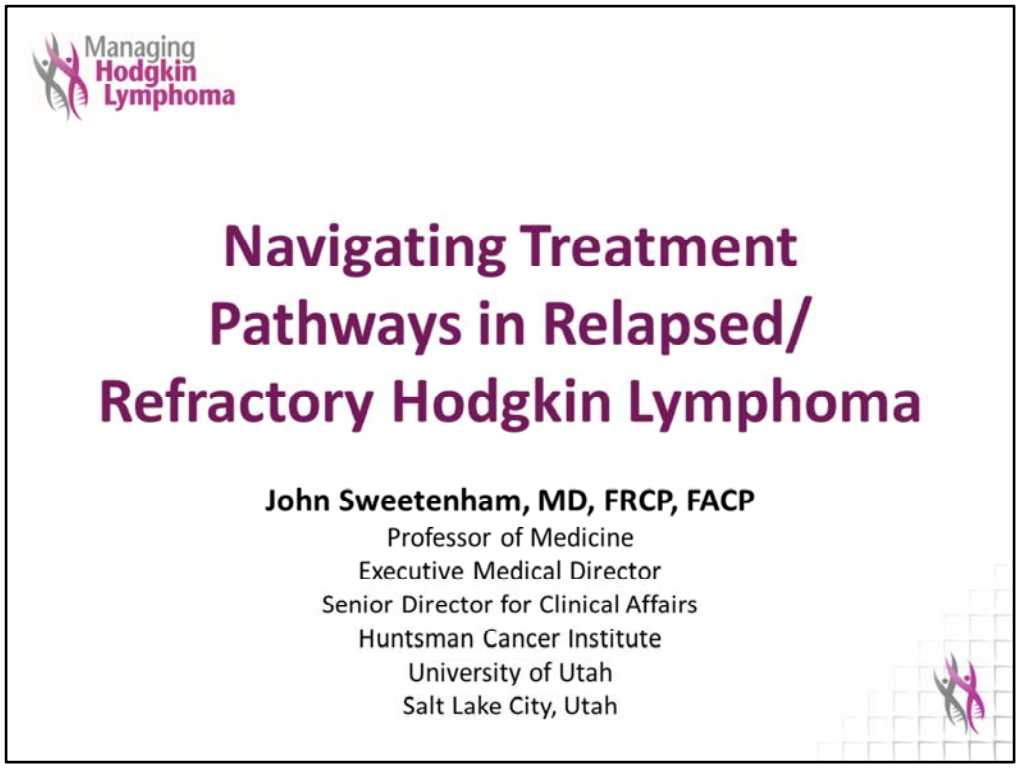
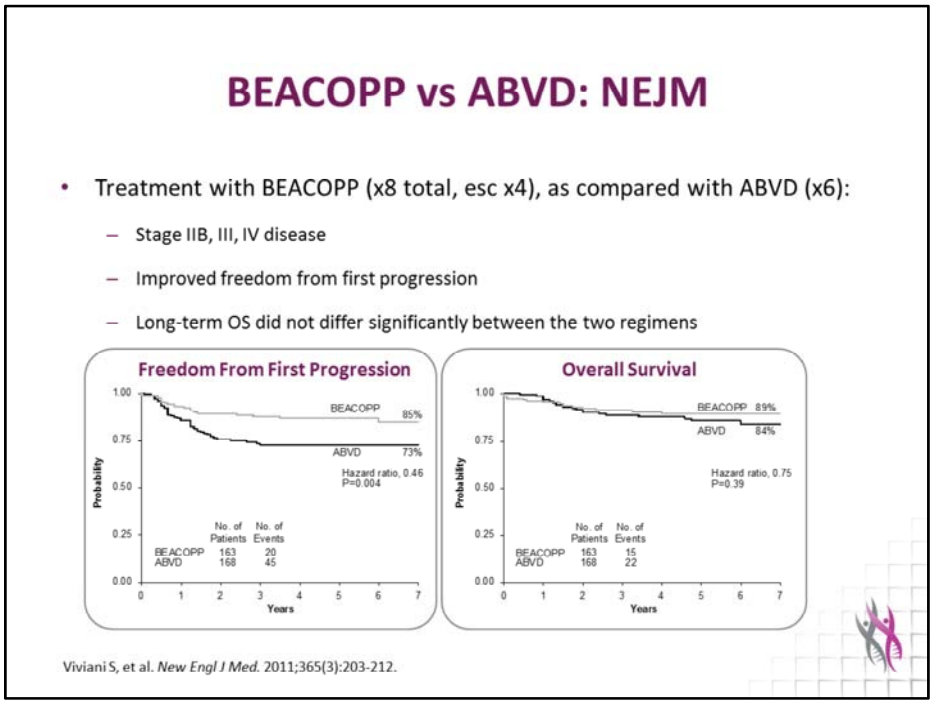
Navigating Treatment Pathways in Relapsed/Refractory Hodgkin Lymphoma



Welcome to *Managing Hodgkin Lymphoma*. I am Dr. John Sweetenham from Huntsman Cancer Institute at the University of Utah. In today's presentation, I will be discussing navigating treatment pathways in relapsed and refractory Hodgkin lymphoma and outlining potential treatment strategies and therapeutic algorithms for drug selection and sequencing in patients with relapsed and refractory Hodgkin lymphoma. I will also differentiate between therapies in patients with relapsed and refractory Hodgkin lymphoma based on patient- and disease-related factors to help individualize treatment plans. So, let's begin.



If you look at the overall outcomes in patients with Hodgkin lymphoma in 2017, they are very good. The slide I show here is an example of the excellent outcomes achieved with combination chemotherapy for patients with advanced Hodgkin lymphoma. This particular slide shows the results of a randomized trial of ABVD, generally regarded as standard therapy for advanced Hodgkin lymphoma in the United States, versus the escalated BEACOPP regimen widely regarded as a standard treatment in Germany and other parts of Europe. The bottom line is that both of these regimens produce excellent results with overall survival figures of 80% or higher according to both regimens. The optimal regimen still remains unclear but nevertheless in the U.S.A., ABVD is still regarded as standard.

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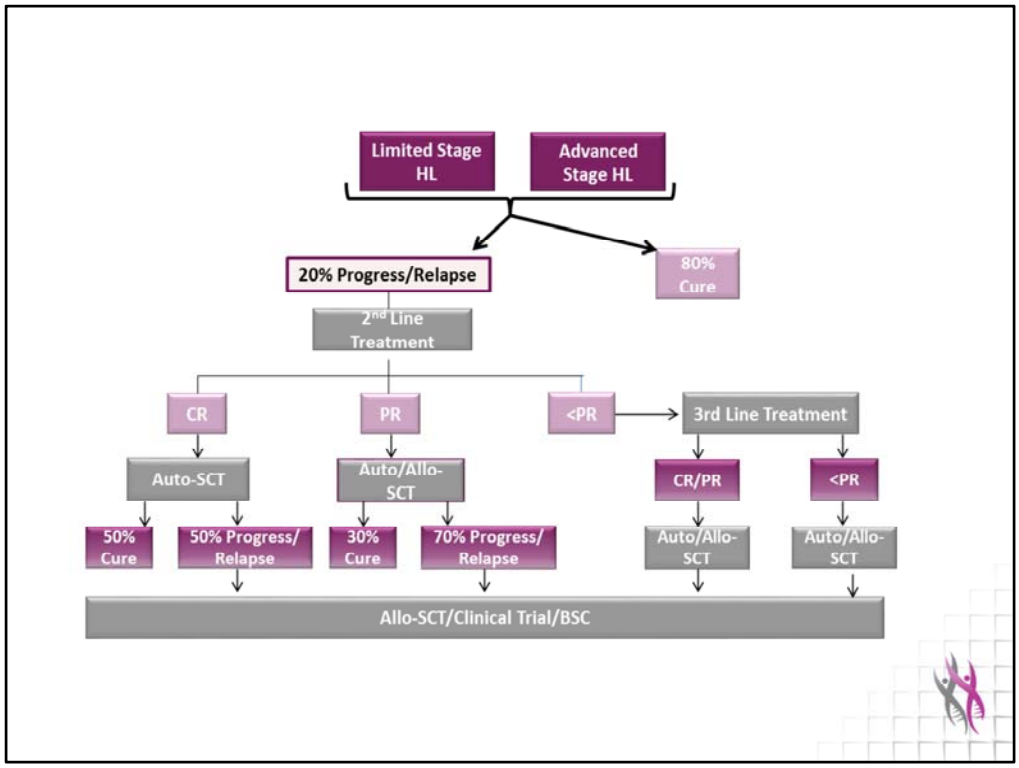

Although the treatment outcomes are very good, the fact is that around 20% of patients with advanced Hodgkin lymphoma, as shown on this slide, are still destined to have either progressive or relapsing disease. This group of patients will need subsequent second-line treatment. In general, as shown on this treatment algorithm, the approach is to give a second-line salvage chemotherapy regimen. Then depending upon the response to that, a patient may proceed to an autologous stem cell transplant if they achieve a complete response or to other transplant strategies based on less than a complete response to this therapy. Ultimately, patients who fail after an autologous transplant may also be considered for allogeneic transplant, which is widely regarded at present as the only curative option for that group of patients whose disease relapses after autologous stem cell transplantation.

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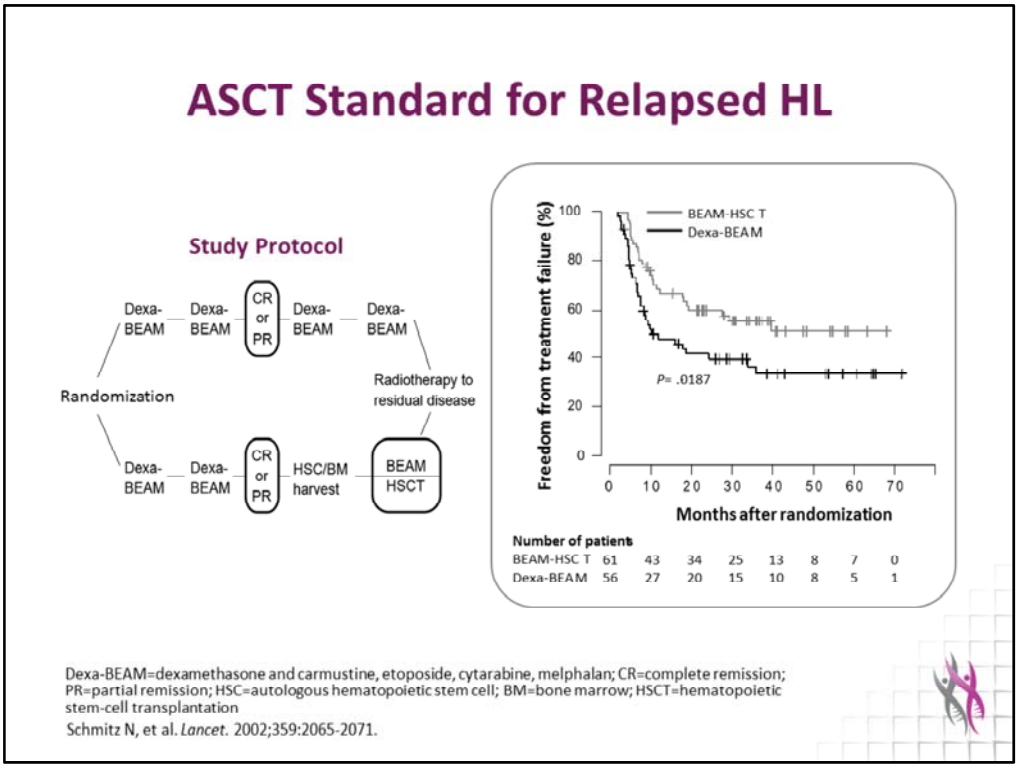

Autologous transplantation is, of course, a standard of care for patients with relapsed Hodgkin lymphoma and it was established as a standard many years ago. This slide shows the results of one of the two randomized trials that address the issue of whether conventional dose therapy was inferior or superior to high-dose therapy with autologous stem cell transplant for patients with relapsed or refractory Hodgkin lymphoma. In this study, patients who responded to second-line salvage therapy were randomized to continue with the conventional dose salvage or proceed to high-dose therapy with stem cell transplantation. Both, this study and another British study, demonstrated an improvement in progression-free survival for those patients who underwent transplant. Although no overall survival difference was identified in this or in the other study from the U.K., this is thought to be because those patients who did not receive a transplant in randomization subsequently crossed over and received the transplant if they progressed after conventional dose therapy.

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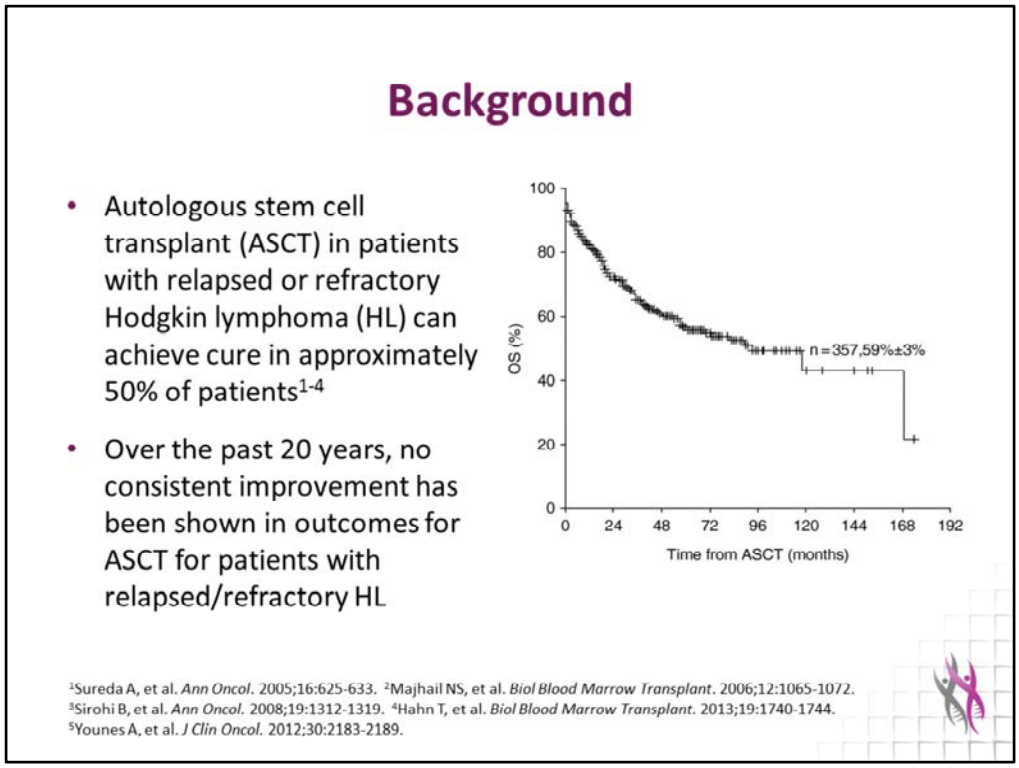

At the moment, as shown on this slide, we anticipate that approximately 50% of patients who undergo autologous stem cell transplantation for relapsed or refractory Hodgkin lymphoma can expect to be cured. If we look over the past 20 years, that figure really has not moved. The data shown here is from the early 2000s, but there are comparable data from the early 1990s and indeed from recent years, which show essentially the exact same outcome. Although around 50% of these patients are cured, we have not had a significant impact on that over the last 20 years.

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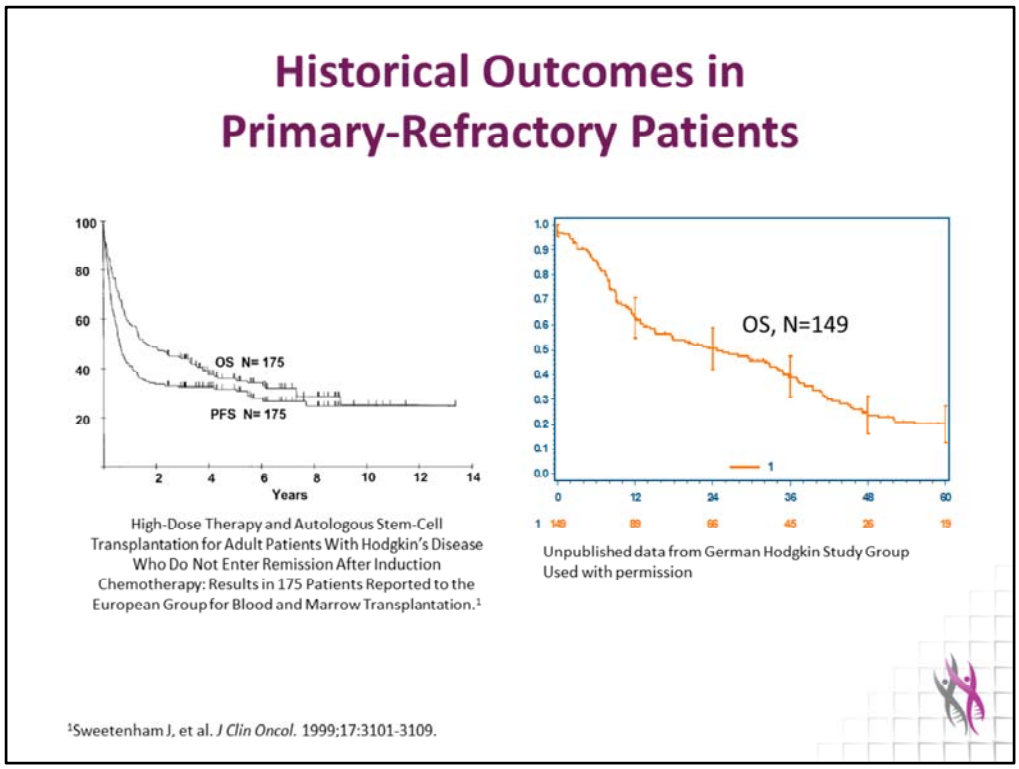

Similarly, for those patients who have primary refractory disease, the outcomes are relatively poor and again have not significantly improved over the last 20 years. Shown in this slide are two datasets, one from the 90s and one from the 2000s, for the outcome of patients with primary refractory Hodgkin lymphoma undergoing autologous stem cell transplant. In both studies, the long-term disease-free survival is around 20% to 30%, lower than for that group of patients who have relapsed rather than refractory disease but nevertheless still poor. As mentioned previously, these figures really have not changed over the last several years.

Salvage Therapy for Relapsed/Refractory HL

- Inability to achieve a CR with salvage therapy has been associated with worse outcomes post-transplant[1,2]

Salvage chemotherapy regimens in relapsed or refractory Hodgkin lymphoma[1,3]

Chemotherapy Regimen	N	CR (%), 95% CI	ORR (%), 95% CI
ICE	65	26 (16-39)	85 (74-92)
ICE/Augmented ICE	97	60	n/a
DHAP*	102	21 (13-29)	89 (83-95)
GDP	23	17 (5-39)	69 (47-87)
GVD	91	19	70
IEV	51	76 (60-88)	84 (71-93)

*Q2 week

CI=confidence interval; ICE=ifosfamide, carboplatin, etoposide; DHAP=dexamethasone, ara-C, cisplatin; GDP=gemcitabine, dexamethasone, cisplatin; GVD=gemcitabine, vinorelbine, doxil (liposomal doxorubicin); ORR=overall response rate

[1]Moskowitz CH, et al. *Blood.* 2012;119(7):1665-1670. [2]Josting A, et al. *Ann Oncology.* 2002;13(10):1628-1635.
[3]Kuruvilla J, et al. *Blood.* 2011;117(16):4208-4217.

In the path to getting somebody to a transplant, the standard approach as shown on one of the earlier slides is to treat that patient with a conventional dose salvage chemotherapy regimen first, and then, they would progress to transplant based on their response to that regimen. Listed on this slide, there are a number of commonly used second-line regimens which are all chemotherapy-based for the treatment of relapsed Hodgkin lymphoma. For the most part, these are regarded as regimens given to cytoreduce a patient prior to high-dose therapy and autologous stem cell transplantation. As you can see, most of these regimens will produce an overall response rate in the 70% to 80% range with approximately 25% to 30% of those responses typically being complete responses. Although, response assessment in Hodgkin lymphoma can be difficult because of the presence of residual nodal masses, and that is an issue we will return to shortly when we consider the use of functional imaging.

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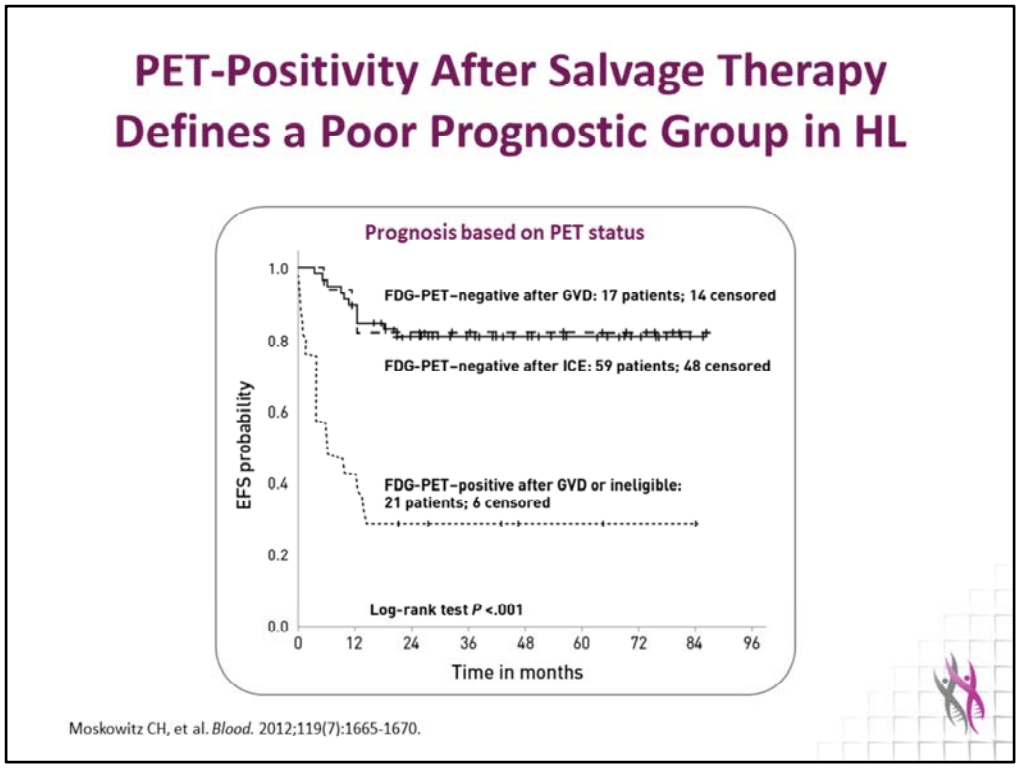
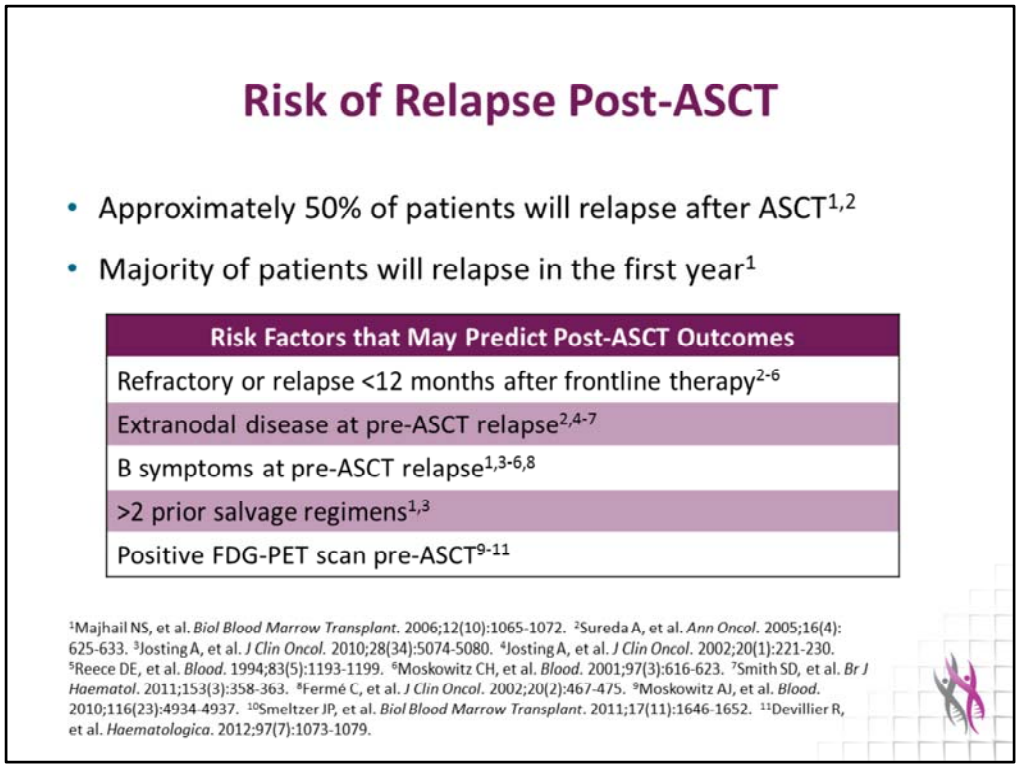
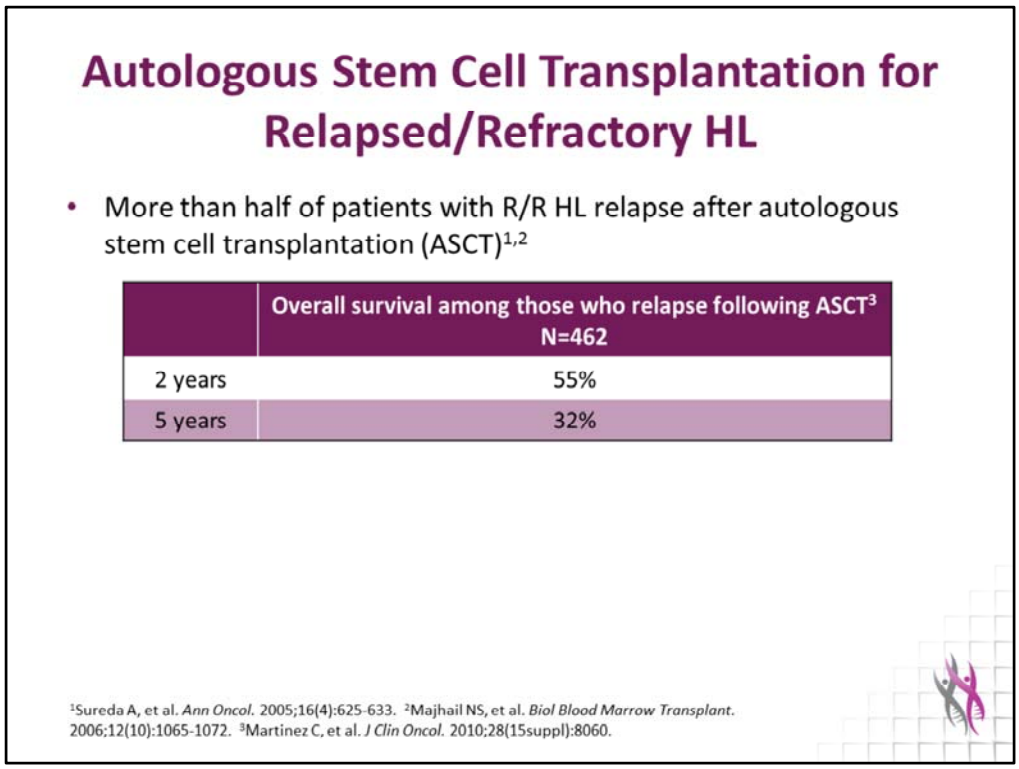


As far as functional imaging is concerned, it is important to point out that we now have very solid data; predominantly from Dr. Craig Moskowitz of Memorial Sloan Kettering Hospital in New York, which has shown us the status of functional imaging of a patient prior to autologous transplantation is an important predictor of the subsequent outcome. What is shown on this slide is the results of FDG-PET scanning in patients with relapsed or refractory Hodgkin lymphoma. The PET scanning is performed at the time the patient has completed their salvage chemotherapy regimen, but before they undergo high-dose therapy. As you can see from this slide, those patients who go into their transplant PET positive have a significantly inferior outcome to that group of patients who are PET negative at the time they undergo transplantation. Not only has this become a significant prognostic factor, which is now recognized as important in this group, but increasingly, we believe that the achievement of PET negativity prior to autologous transplantation should probably be the goal of our initial cytoreductive therapy. If the patient does not achieve a PET positive status, one should probably consider an alternative regimen prior to taking the patient to transplant.



In addition to PET positivity as one of those factors which predicts the risk of relapse after transplantation, there are a number of other more classical risk factors which are listed here. It is being demonstrated reproducibly in most studies of autologous transplants in Hodgkin lymphoma that the presence of refractory disease or early relapse, typically defined as a patient relapsing within 12 months of their initial induction therapy, that these two factors predict for a worse outcome after transplantation. Similarly, the presence of extranodal disease at the time of relapse of Hodgkin lymphoma confers a poor prognosis as does the presence of B symptoms at the time of relapse. Any patient who has had more than two prior salvage regimens also appears to have a poorer outcome. As I have already mentioned, the FDG-PET status immediately prior to stem cell transplantation is also an important predictive factor for the outcome after transplantation.



It is also important to remember, as we have already pointed out, that more than half of the patients who relapse after autologous transplant will do so relatively early. Furthermore, the overall survival for those patients who relapse after a transplant, as shown on this slide, is relatively poor. Only half of those patients will be alive at 2 years, and by 5 years, only around 30% of those patients relapsing after a transplant will still be alive.

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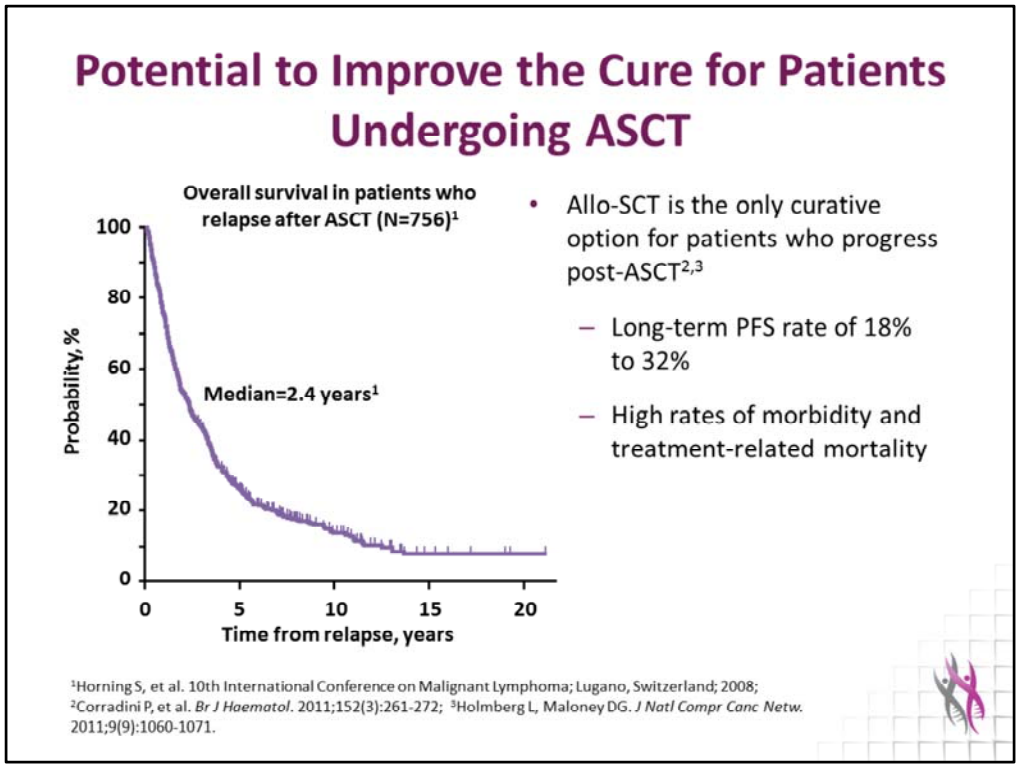

On the next slide, you can see in graphical form the outcome for patients who relapse after autologous stem cell transplantation, with a median 2-year overall survival in this series of about 2.4 years, which is representative of many other series that have been published addressing this issue. For these patients in 2017, the only known curative option is an allogeneic stem cell transplant. In most series, this is being reported to produce a long-term progression-free survival rate of somewhere between 18% and 32%, but of course, this is associated with very high rates of morbidity and mortality.

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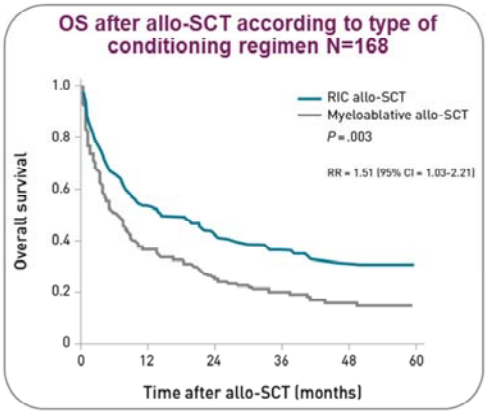
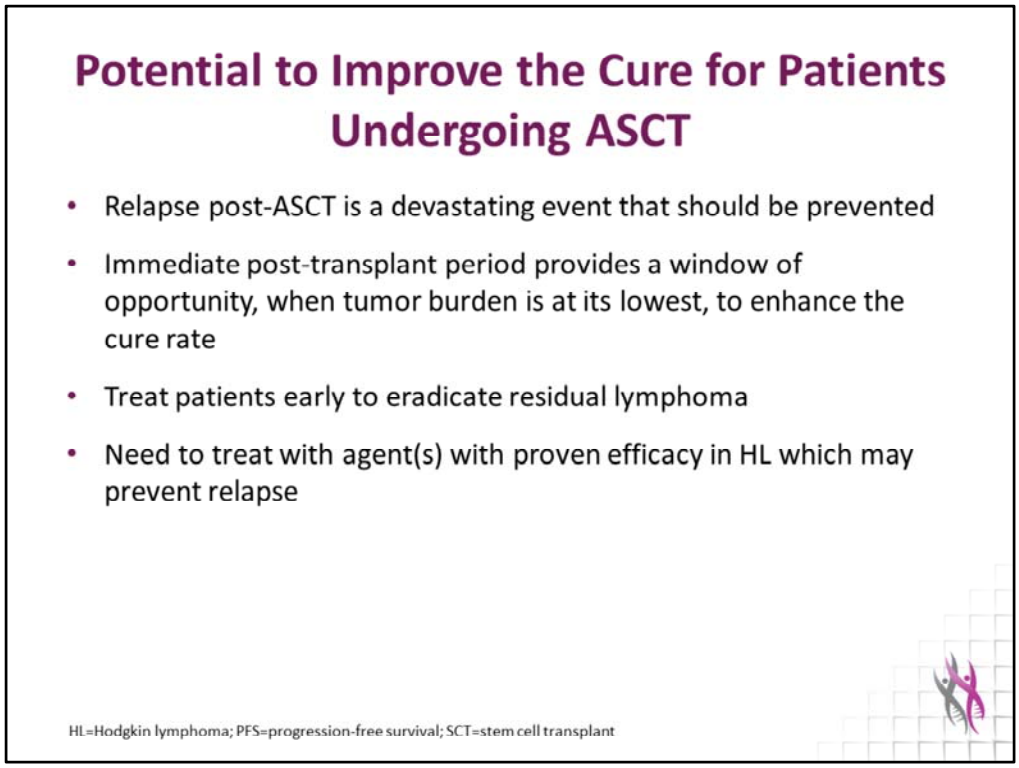
Myeloablative vs Reduced-Intensity Conditioning Allo-SCT in HL: Overall Survival

- 5-year OS:
  - 22% for myeloablative allo-SCT
  - 28% for reduced-intensity conditioning allo-SCT



Sureda A, et al. *J Clin Oncol.* 2008;26(3):455-462.

Shown on this slide is a typical result for patients undergoing either a myeloablative or a reduced intensity allograft for relapsed or refractory Hodgkin lymphoma, showing the overall survival with a slight advantage for patients undergoing a reduced-intensity conditioning regimen.



We really need to look for options for improving the cure rate of patients undergoing autologous stem cell transplantation for Hodgkin lymphoma because relapse following autologous transplant is a devastating event for the patient. Particularly, since many of these patients are in their 20s and 30s, in many respects in the most productive part of their lives with small families. This can be devastating for them even though they may potentially have some chance at long-term survival and salvage of their recurrent disease. The immediate posttransplant period provides a window of opportunity when the tumor burden is minimal because of the effects of high-dose therapy. There is a chance there to potentially enhance the cure rate with an appropriate intervention, and treating patients early in this period to eradicate residual lymphoma has a strong rationale, particularly if one uses an agent with proven efficacy in Hodgkin lymphoma.

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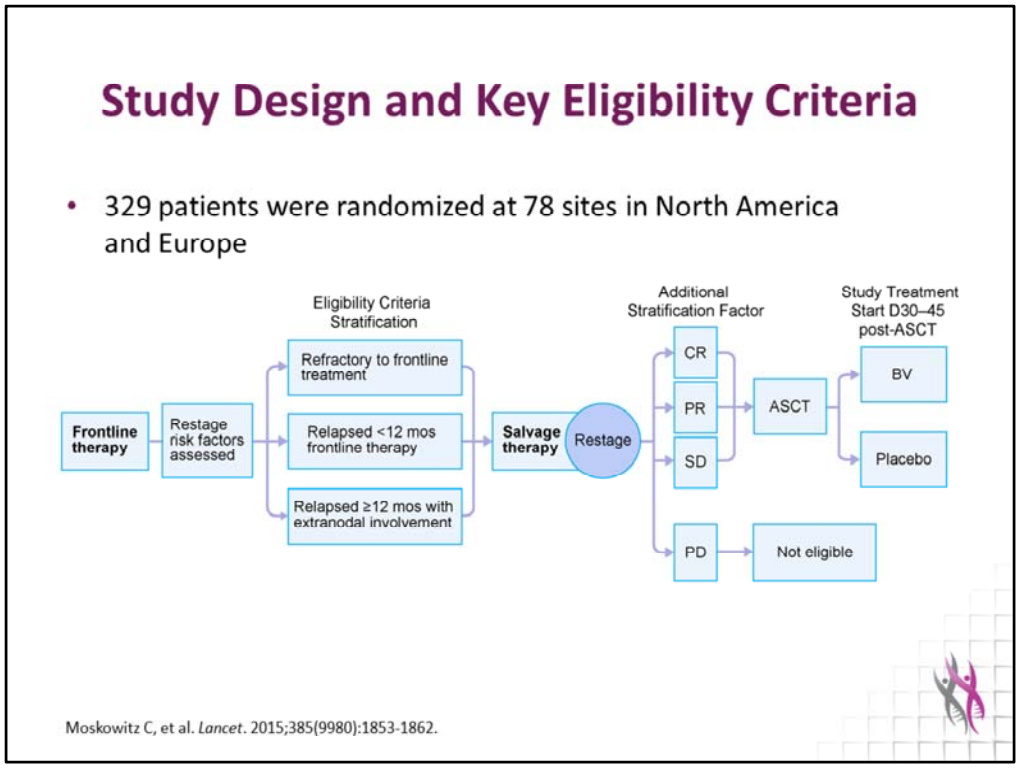
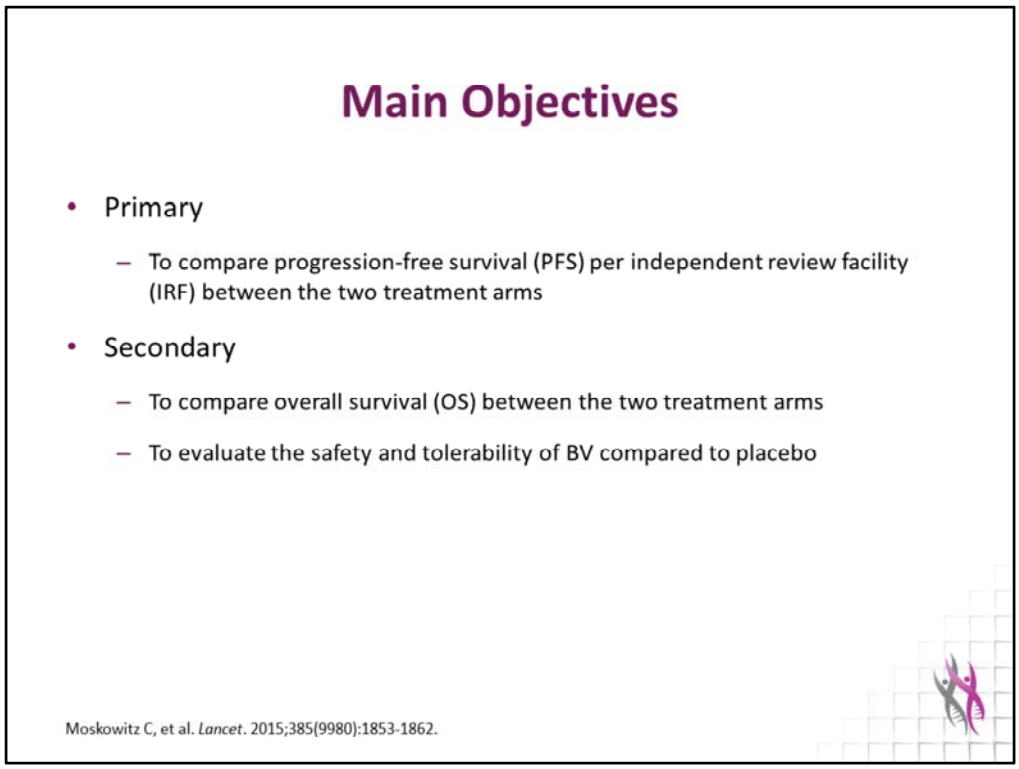


It was on this basis that the AETHERA study was developed. This is a study addressing the use of an agent, brentuximab vedotin, an antibody-drug conjugate directed at the CD30 antigen for patients undergoing autologous transplant at high risk of relapse of their Hodgkin lymphoma. Briefly to summarize the study design, these patients had undergone their frontline therapy and had subsequently relapsed. At the time of relapse, patients with poor-risk features were entered in to this study and stratified according to those poor-risk features which were as listed on this slide, those who were refractory to frontline therapy, those who relapsed within 12 months of their frontline therapy or those who relapsed at greater than 12 months but had evidence of extranodal disease at the time of relapse. These patients underwent a conventional-dose salvage regimen and then were restaged. Those patients who achieved a complete partial response or stable disease proceeded to autologous stem cell transplantation. Following transplantation, they were randomized to 1 year of brentuximab vedotin, a 21-day interval for 16 cycles or on the same schedule to receive placebo.



The primary objective of this study was to compare progression-free survival between the two treatment arms. Important secondary objectives included overall survival and safety and tolerability of brentuximab vedotin in this patient population.

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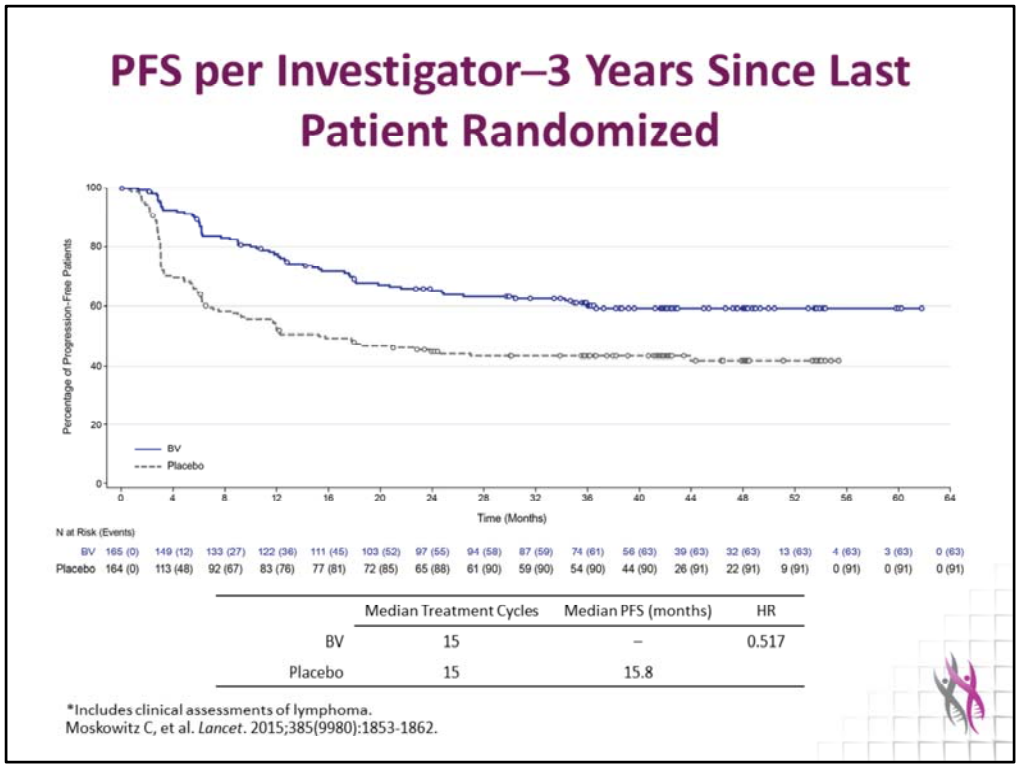

There is a progression-free survival as shown on this slide, showing a clear advantage in progression-free survival for those patients receiving consolidated therapy with brentuximab vedotin compared with those who received placebo.

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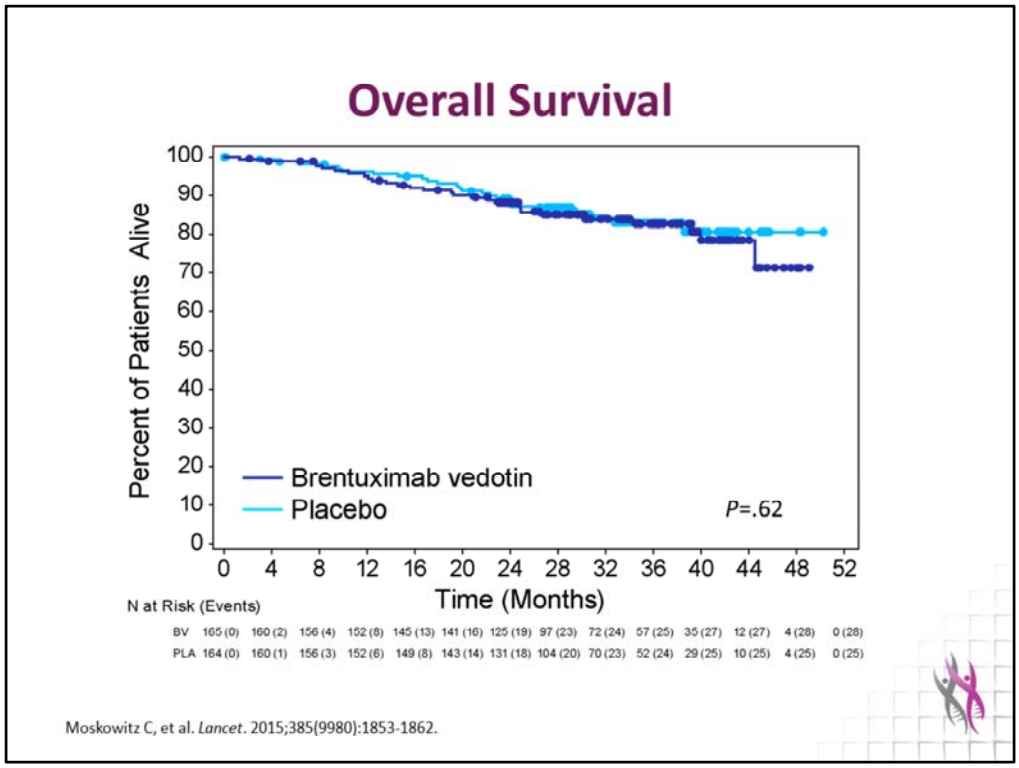
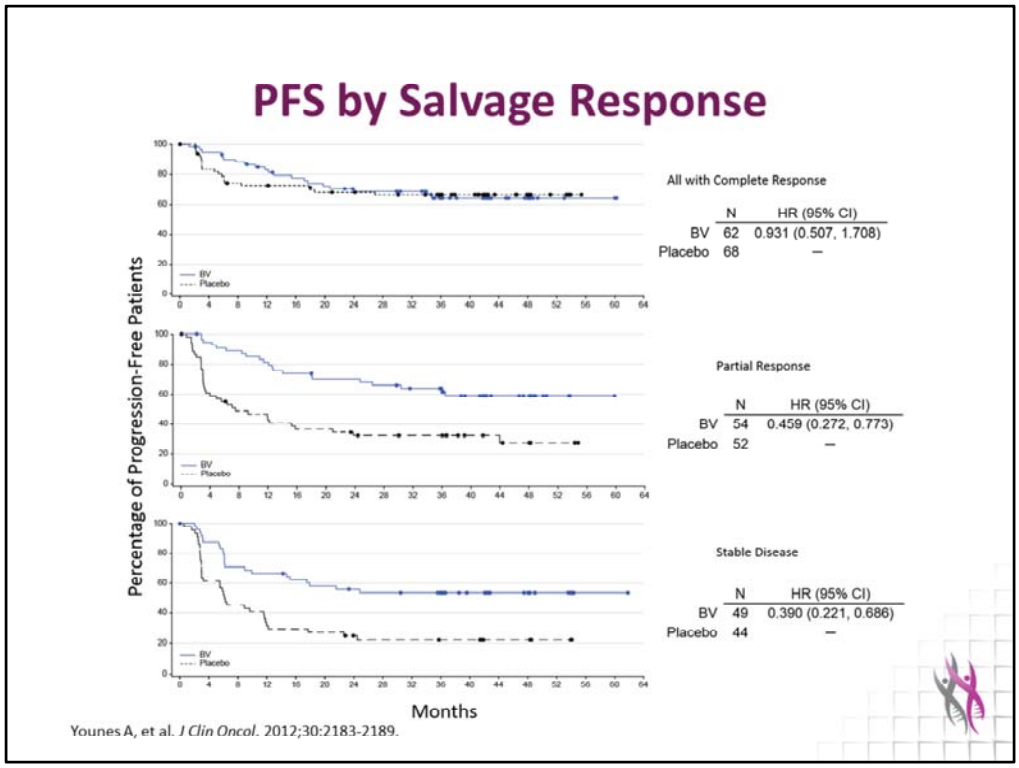
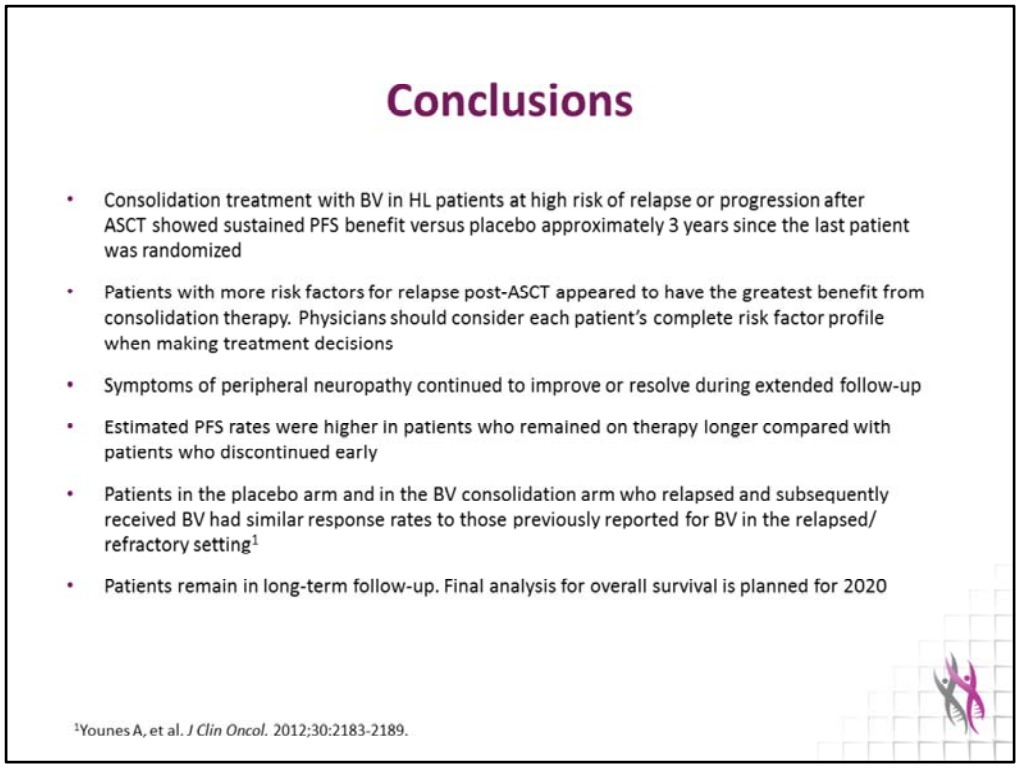


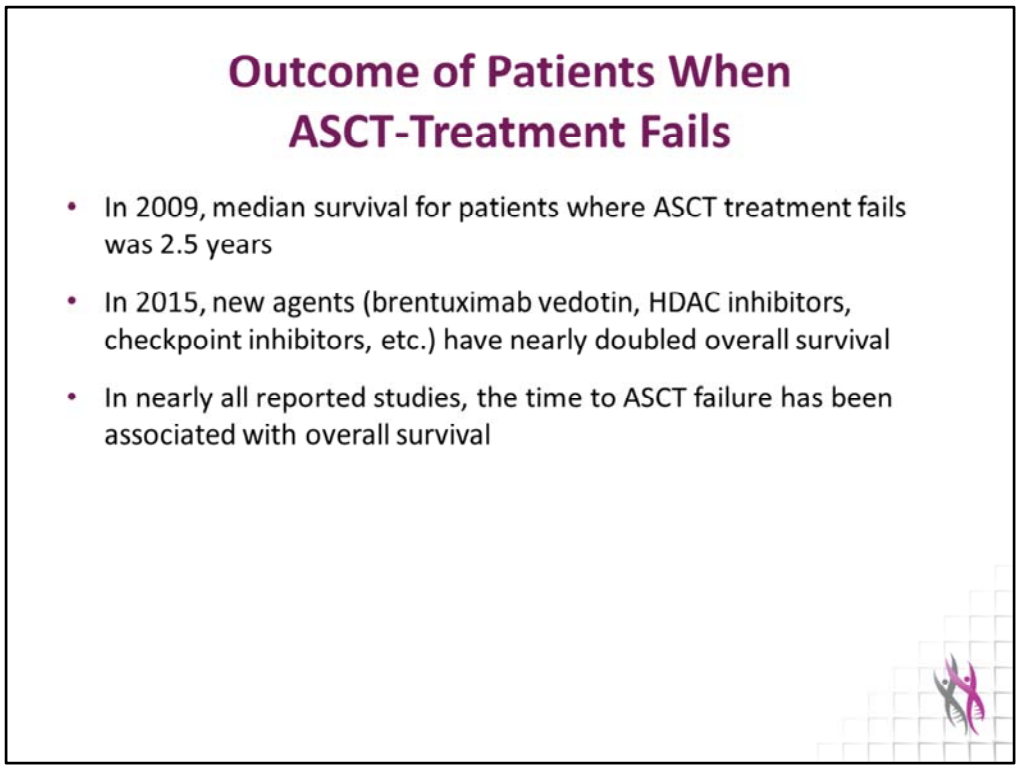
To date, this is not converted into an improvement in overall survival and the final analysis for overall survival is planned in the year 2020.



If one looks according to subgroups, this slide shows an unplanned subset analysis of these data, demonstrating significant improvements in progression-free survival in those patients who demonstrated a partial response or stable disease prior to going into transplant. For those patients in complete remission entering into transplant, at this point, there does not appear to be a difference in progression-free survival, but one should caution against these unplanned subset analyses, particularly as a number of prognostic factors interplay here. It is difficult to draw firm conclusions about any specific subset of patients.



Overall, the conclusions of the study were the consolidation treatment with brentuximab vedotin in these patients at high risk of relapse showed a sustained progression-free survival benefit when compared with placebo. Those patients who had more risk factors following autologous stem cell transplantation appeared to be the ones who benefited the most from consolidation therapy and the toxicity of the regimen was comparable to that shown in the previous phase 1 and phase 2 studies. Patients in the placebo arm and in the brentuximab vedotin consolidation arm who relapsed and subsequently received further brentuximab vedotin had similar response rates to those in the early phase 1 and 2 trials conducted in the relapsed and refractory setting. As I mentioned, final analysis for overall survival is planned in 2020.



When autologous stem cell transplant fails, what is the outcome for these patients? Things have definitely changed. In 2009, the median survival for patients who relapsed after an autologous stem cell transplant was 2.5 years. By 2015 with the introduction of a range of new agents, including brentuximab vedotin, HDAC inhibitors, checkpoint inhibitors, and other drugs which we will list shortly, the survival has nearly doubled during that time. In nearly all reported studies, the time to failure after autologous stem cell transplantation has been associated with overall survival.

What are some of these novel agents? When we are in a situation where consolidative therapy is not an option or fails, what other options do we have as alternatives or as bridges to stem cell transplantation?

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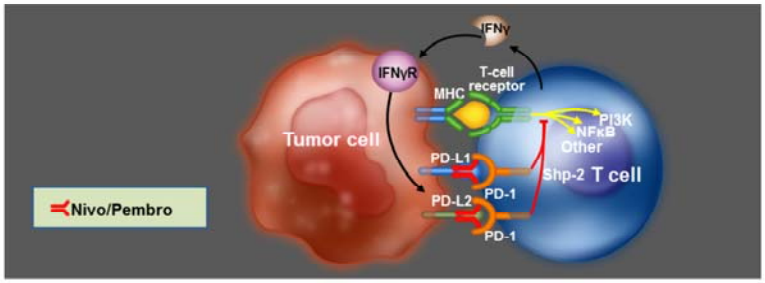
Background

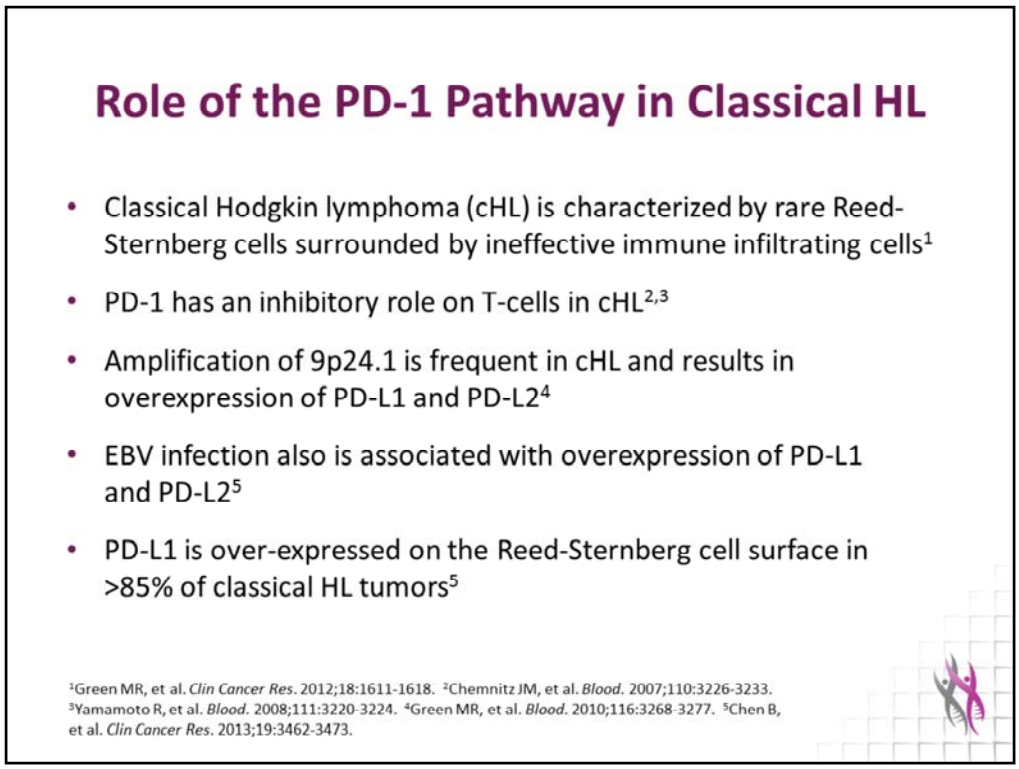
- PD-1 engagement by its ligands results in transient down-regulation of T-cell function (T-cell exhaustion)
- Nivolumab is a fully human IgG4 anti-PD-1 antibody which selectively blocks the PD-1 and PD-L1/PD-L2 interaction
- Pembrolizumab (MK-3475) is a humanized, monoclonal IgG4 antibody against PD-1



- PD-1 blockade through monoclonal antibody therapy has single-agent activity in a range of solid tumors

Brahmer JR, et al. *N Engl J Med*. 2012;366:2455-2465.; Topalian SL, et al *N Engl J Med*. 2012;366:2443-2454.

Without a doubt, the agents which have created the most buzz recently are checkpoint inhibitors. Just to demonstrate some background, PD-1 engagement by its ligands is known to result in transient downregulation of T-cell function known as T-cell exhaustion. This is thought to be an important mechanism in the immune paralysis that is associated with Hodgkin lymphoma. Two drugs, nivolumab and pembrolizumab, are both agents directed against PD-1, and PD-1 blockade through monoclonal antibody therapy is being shown to have single-agent activity now in a range of solid tumors



We also know the PD-1 pathway to be important in classical Hodgkin lymphoma. The rare Reed-Sternberg cells are surrounded by an ineffective immune infiltrate which suggests that PD-1 is active in this disease. As I already mentioned, it is known to have an inhibitory role in T-cells in classic Hodgkin lymphoma. Furthermore, amplification of 9p24.1 is frequent in classical Hodgkin lymphoma and is known to result in overexpression of PDL-1 and PDL-2. An EBV infection is also associated with overexpression of these ligands. PDL-1 is overexpressed on the Reed-Sternberg cell surface in more than 85% of Hodgkin lymphoma tumors.

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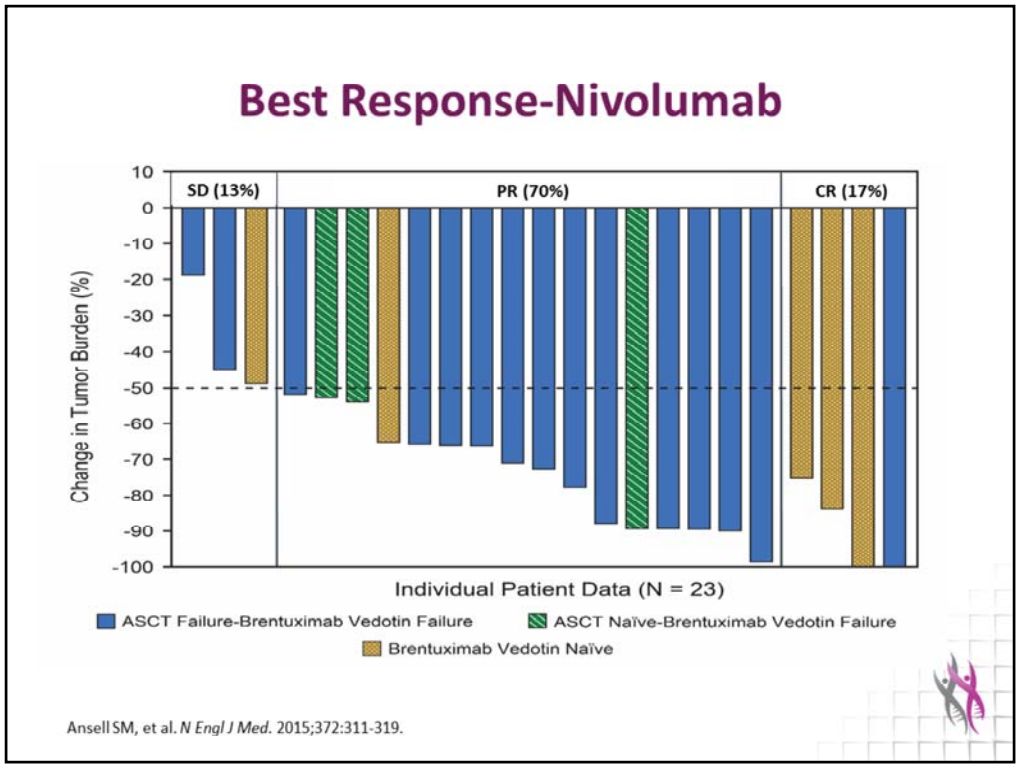

The use of nivolumab and pembrolizumab is being relatively extensively investigated in Hodgkin lymphoma. This shows a water flow plot, demonstrating responses in patients with relapsed Hodgkin lymphoma who have either failed an autologous stem cell transplant plus brentuximab vedotin or without exposure to brentuximab vedotin. As you can see, almost all the patients here demonstrated an impressive response.

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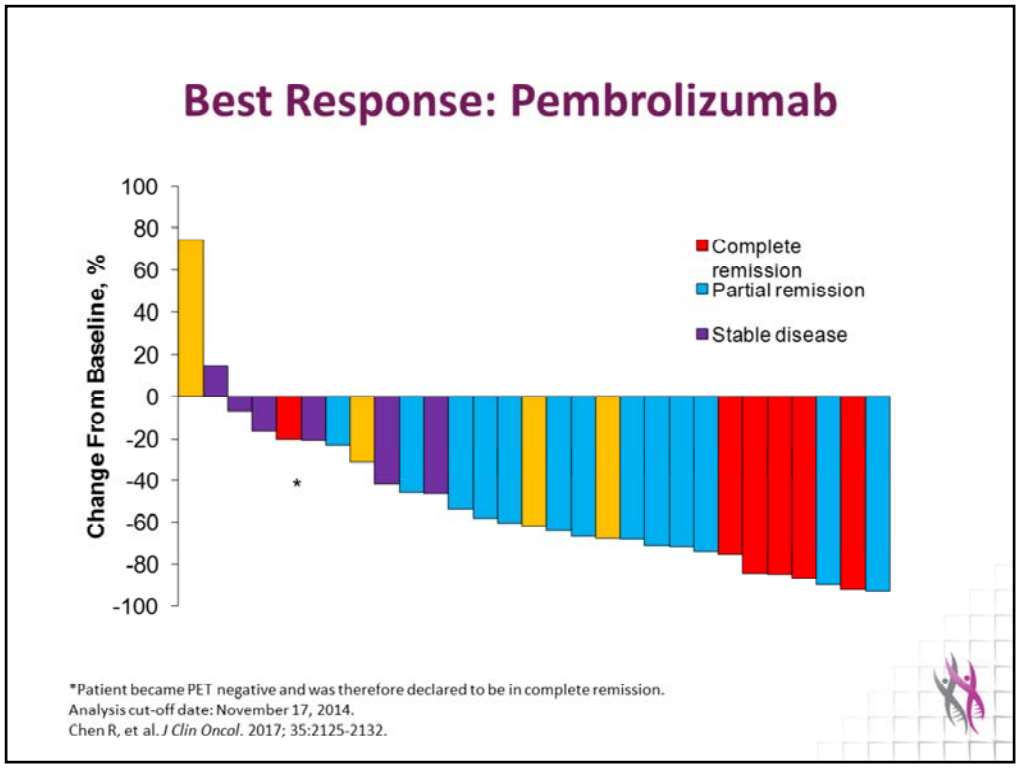

In a similar study with pembrolizumab, there were very similar findings with the majority of patients achieving a response to checkpoint inhibition.

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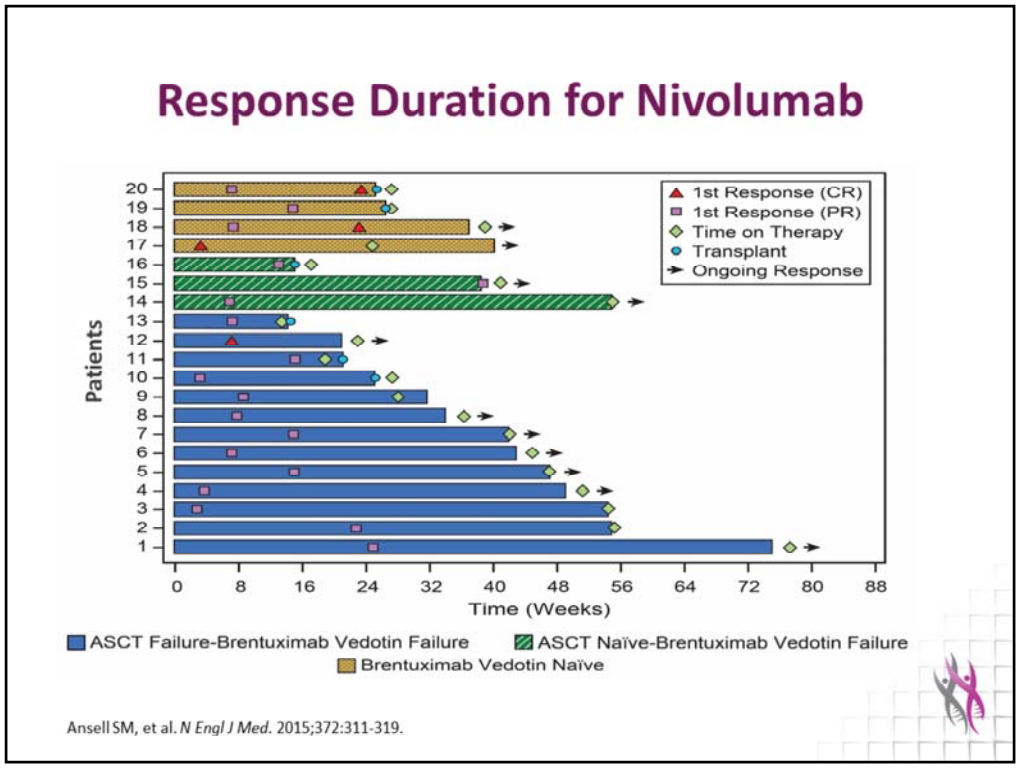
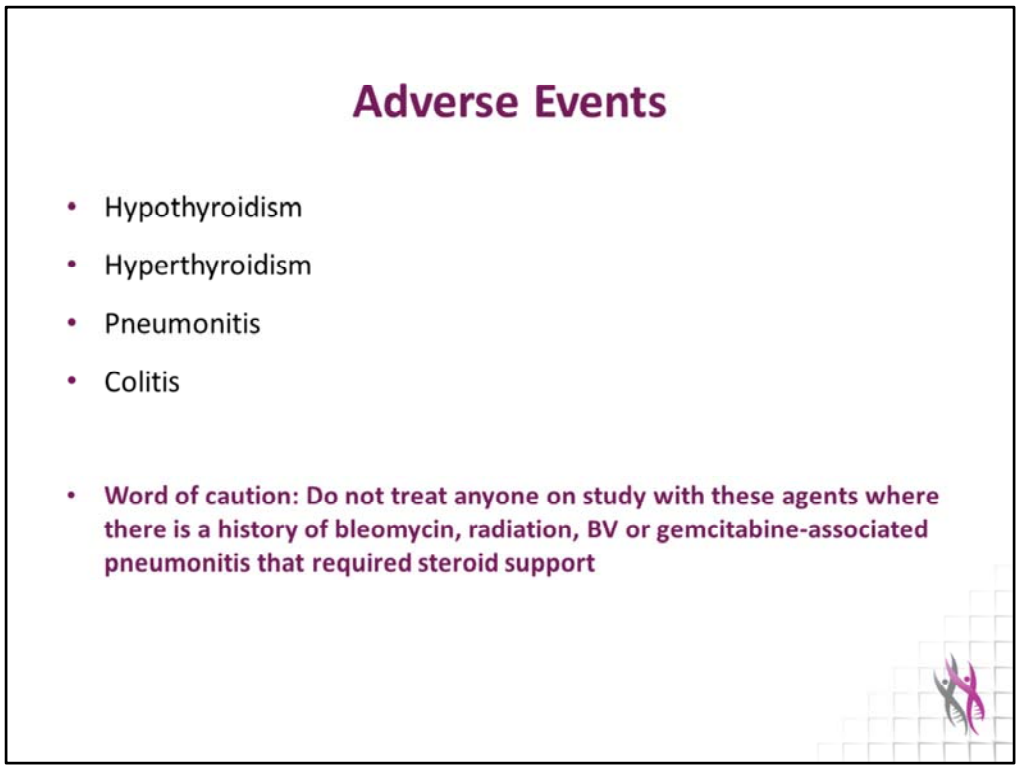


What is more? Just showing one representative example here for nivolumab. You can see that for many of these patients these have been very sustained responses. Many of these patients have been bridged to a further therapy based on the use of checkpoint inhibitors.



There are problems with these drugs, in particular those listed here. Particularly, because many patients with Hodgkin lymphoma will have a history of lung toxic interventions, including bleomycin, radiation therapy, brentuximab, or drugs such as gemcitabine. It is very important to be aware of the risk of pneumonitis and, for the most part, to try to avoid these drugs in patients who have been exposed to these agents.

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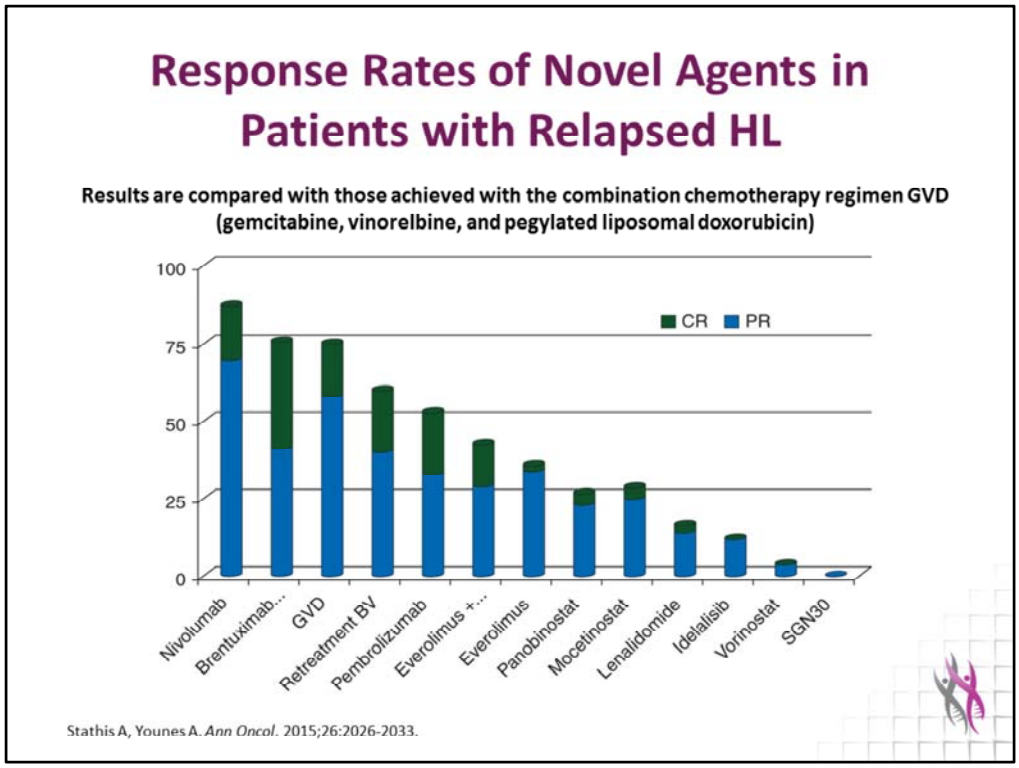
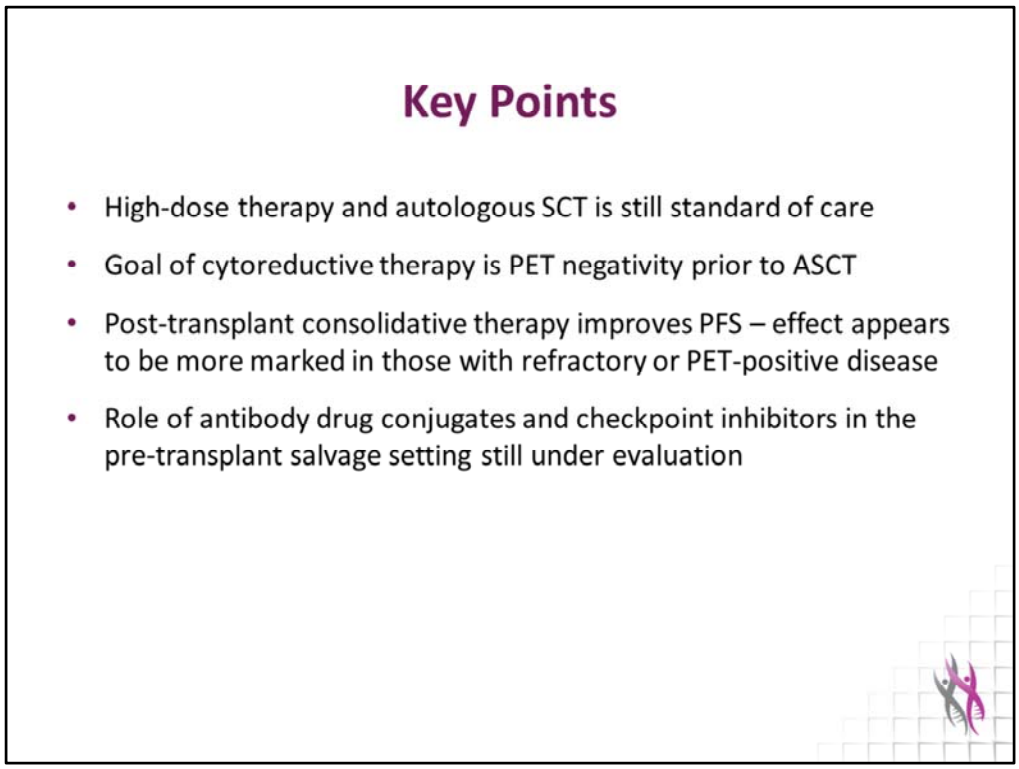


On this slide, I have listed a number of the agents which are currently in use for relapsed and refractory Hodgkin lymphoma and compared response rates, and so, they are stacked up here according to their response rates. As you can see, there are many drugs which as single agents have very significant activity in relapsed and refractory Hodgkin lymphoma. At the moment, those which have the most promising single-agent activity include the checkpoint inhibitors, brentuximab vedotin, and then other drugs such as everolimus and panobinostat also show intriguing activity. The real question for these drugs at the moment is how do we use them in the relapsed and refractory setting, either prior to an autologous stem cell transplant as a part of the initial cytoreductive regimen, or how do we use them in those patients who relapse after autologous stem cell transplant? At this point, all we can say is many of these drugs have single-agent activity and combinations of these drugs, including checkpoint inhibitors plus brentuximab vedotin, are now being actively explored in the pre- and post-autologous stem cell transplant setting.



To conclude, I would like to leave you with some key take-away points. First of all, for those patients with relapsed and refractory Hodgkin lymphoma, the use of high-risk therapy and autologous stem cell transplantation should still be regarded as the standard of care. Our current knowledge suggests that the goal of our cytoreductive therapy given prior to transplant should be PET negativity. This raises the question as to whether a patient who has a chemotherapy regimen which does not get them to PET negativity should be treated with an alternative agent prior to transplant such as brentuximab vedotin or a checkpoint inhibitor. This is actively under investigation at this time. Posttransplant consolidative therapy improves progression-free survival, at least in the case of brentuximab vedotin, and this effect appears to be more marked in those with refractory or PET positive disease. The role of antibody drug conjugates and checkpoint inhibitors in the pre-transplant salvage setting, as I have said, is still under evaluation. It certainly is looking promising, and we anticipate that new data will be emerging very soon. Thank you for your attention and for viewing this activity.