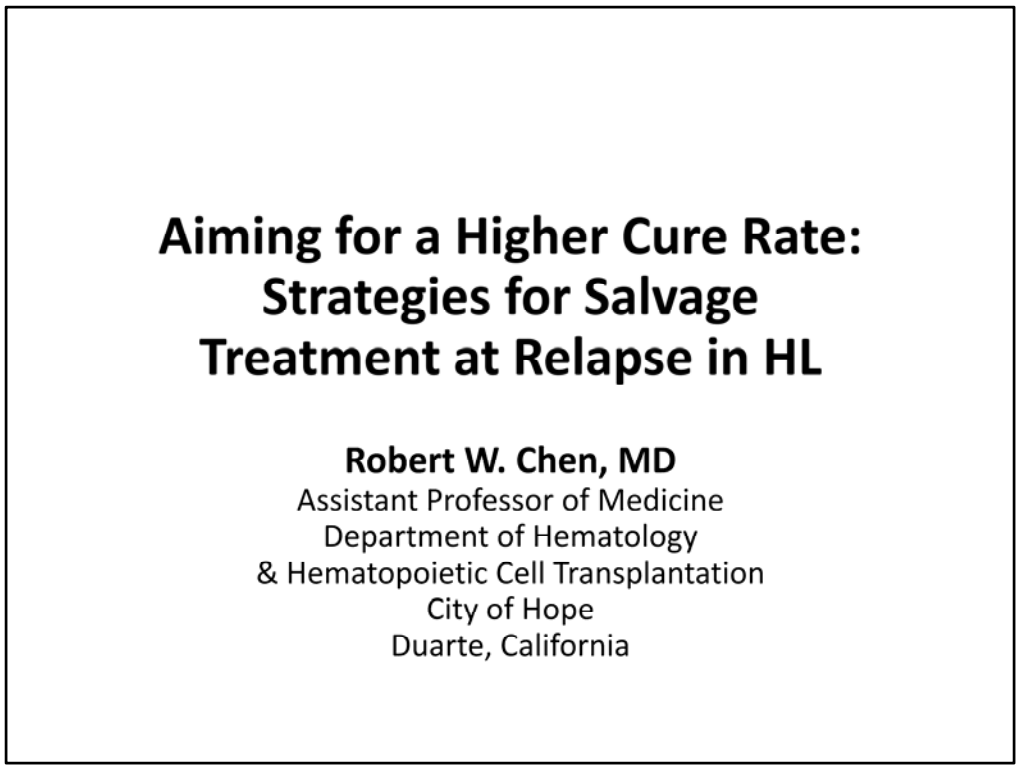
Aiming for a Higher Cure Rate: Strategies for Salvage Treatment at Relapse in HL

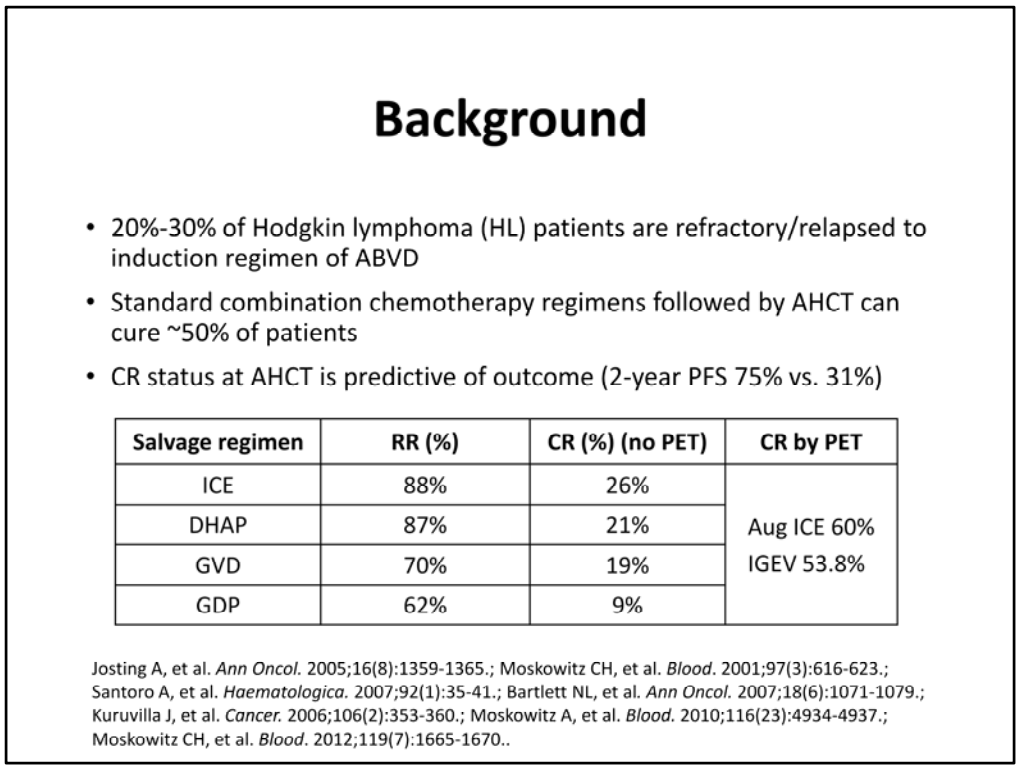


Hi, my name is Dr. Robert Chen. I am an assistant professor at City of Hope Medical Center. I am also a co-leader of our lymphoma disease team. It is my honor to present to you this topic titled “Aiming for a Higher Cure Rate: Strategies for Salvage Treatment at Relapse in Hodgkin Lymphoma.”

Learning Objectives

- Outline current standards for salvage therapies at relapse after first-line therapy, prior to high-dose marrow-ablative chemotherapy and autologous SCT
- Identify the rationale behind increasing the fraction of PET-negative metabolic CR patients prior to ASCT

In this talk, we will talk about the standard for salvage therapy at relapse after first-line therapy prior to high-dose marrow-ablative chemotherapy and autologous transplant, and also identify the rationale behind increasing the fraction of PET-negative metabolic CR patients prior to transplant.



Background

- 20%-30% of Hodgkin lymphoma (HL) patients are refractory/relapsed to induction regimen of ABVD
- Standard combination chemotherapy regimens followed by AHCT can cure ~50% of patients
- CR status at AHCT is predictive of outcome (2-year PFS 75% vs. 31%)

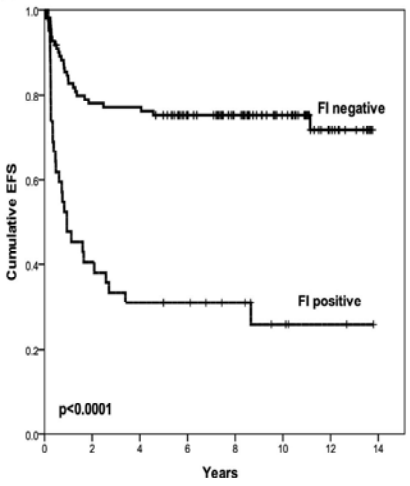
Salvage regimen	RR (%)	CR (%) (no PET)	CR by PET
ICE	88%	26%	Aug ICE 60% IGEV 53.8%
DHAP	87%	21%	
GVD	70%	19%	
GDP	62%	9%	

Josting A, et al. *Ann Oncol.* 2005;16(8):1359-1365.; Moskowitz CH, et al. *Blood*. 2001;97(3):616-623.; Santoro A, et al. *Haematologica.* 2007;92(1):35-41.; Bartlett NL, et al. *Ann Oncol.* 2007;18(6):1071-1079.; Kuruvilla J, et al. *Cancer.* 2006;106(2):353-360.; Moskowitz A, et al. *Blood.* 2010;116(23):4934-4937.; Moskowitz CH, et al. *Blood*. 2012;119(7):1665-1670..

Up to 20-30% of Hodgkin lymphoma patients are refractory or relapsed to induction regimen ABVD. The standard therapy, at this time, is combination chemotherapy followed by autologous hematopoietic cell transplant, and it can cure about 50% of the patients. We also know that the CR status at the time of transplant can be predictive of outcomes. Here is a table that shows you the four typical salvage regimens that we use: ICE, DHAP, GVD, and GDP. As you can see, the overall response rates are quite high ranging from 60-80%. The CR rate appears to be low from 9-26%. However, that was done in an era without PET scans. Since PET scans have come about, the CR rates of these regimens are a bit higher. For augmented ICE, it is about 60%, and for IGEV it is about 54%.

Background

- Risk-adapted therapy administered based upon risk factors:
  - B symptoms
  - Extranodal disease
  - Relapse <1 year
- Pre-transplant functional imaging was the most significant determinant of outcome

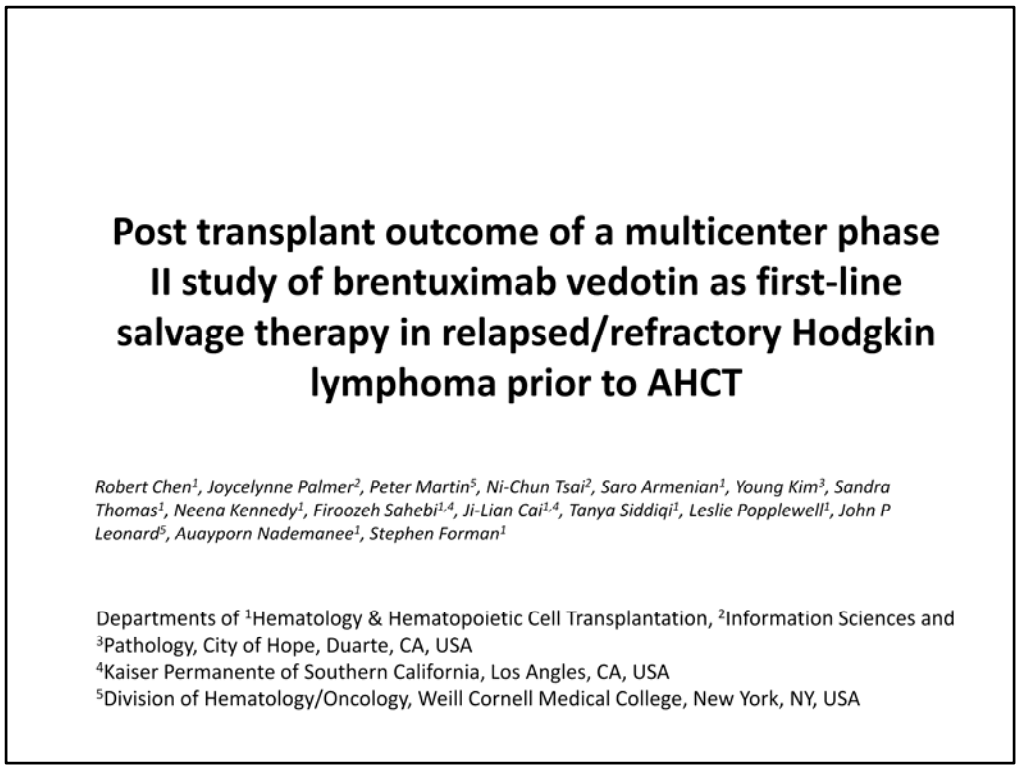


From previous studies, we know that there are different risks that can be predictive of outcomes posttransplant. One is, do the patients have these symptoms at the time of relapse? The other is, do they have extranodal disease at the time of relapse, or did relapse happened less than 1 year from the time of induction therapy? However, the most important factor is their pre-transplant PET status. Patients who are PET-negative oftentimes will have a much better outcome compared to PET-positive patients. This graph that you see here was done by Dr. Alison Moskowitz at Memorial Sloan-Kettering showing that PET-negative patients had a much higher 2-year event-free survival as compared to PET-positive patients.

PET- vs. PET+

Reference	PFS/EFS PET+	PFS/EFS PET-
Gentzler, BJH 2014	52%	85%
Akhtar, BMT 2013	49%	74%
Smeltzer, BBMT 2011	41%	82%
Moskowitz, Blood 2010	31%	75%
Jabbour, Cancer 2007	27%	69%

Besides Dr. Alison Moskowitz, all of the investigators have looked at the importance of PET scan at the time of transplant. This table shows you a compilation of studies. You can see that again, patients who are PET-positive have a lower PFS or event-free survival posttransplant compared to the patients who are PET-negative.



Post transplant outcome of a multicenter phase II study of brentuximab vedotin as first-line salvage therapy in relapsed/refractory Hodgkin lymphoma prior to AHCT

Robert Chen[1], Joycelynne Palmer[2], Peter Martin[5], Ni-Chun Tsai[2], Saro Armenian[1], Young Kim[3], Sandra Thomas[1], Neena Kennedy[1], Firoozeh Sahebi[1,4], Ji-Lian Cai[1,4], Tanya Siddiqi[1], Leslie Popplewell[1], John P Leonard[5], Auayporn Nademanee[1], Stephen Forman[1]

Departments of [1]Hematology & Hematopoietic Cell Transplantation, [2]Information Sciences and [3]Pathology, City of Hope, Duarte, CA, USA
[4]Kaiser Permanente of Southern California, Los Angles, CA, USA
[5]Division of Hematology/Oncology, Weill Cornell Medical College, New York, NY, USA

We also performed a study that was presented at last year's ASH that had a posttransplant outcome of a multicenter, phase 2 study of brentuximab vedotin as first-line salvage therapy in relapsed/refractory Hodgkin lymphoma prior to autologous hematopoietic cell transplantation. Brentuximab vedotin is an antibody drug conjugate that targets CD30-positive cells, and Hodgkin lymphoma universally expresses the CD30-positive cells in a classical variety.

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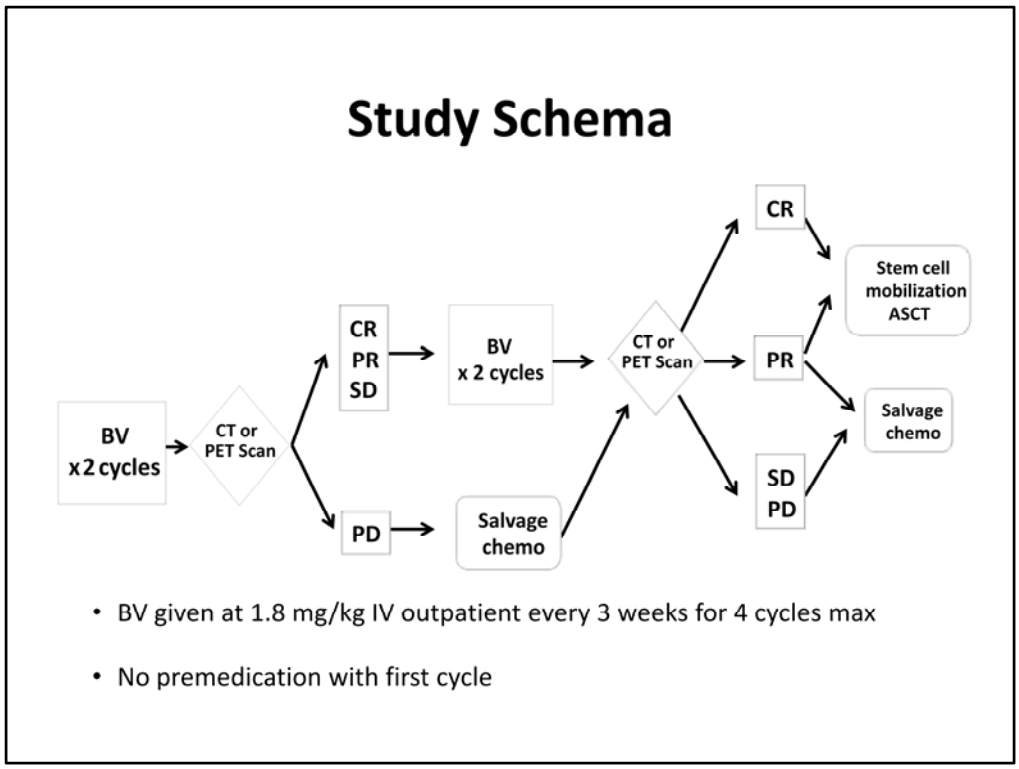

In our trial, we knew that brentuximab vedotin has a higher response rate in patients posttransplant, so we had postulated that we can give this drug prior to transplantation and the study schema is as follows: Patients would get brentuximab vedotin for 2 cycles followed by the CT or PET scan. If they achieved a CR, PR, or stable disease, then they can get 2 more cycles of brentuximab vedotin. At that point, they will be staged for CT or PET scan. If they are in CR, they can move directly to stem cell mobilization and transplant, and if they are in PR, they have an option of going straight to transplant or getting further salvage therapy. If they have stable disease or progressive disease, then they would go through salvage therapy, and brentuximab vedotin here, was given at the approved dosing of 1.8 mg/kg intravenously, outpatient every 3 weeks for 4 cycles maximum.

Response Rates

	Best response to BV, N=37	Response to combination chemotherapy (ICE/DICE/IGEV/GND) post-BV, N=18
ORR	25/37 (68%)	16/18 (89%)
CR	13/37 (35%)	10/18 (56%)
PR	12/37 (32%)	6/18 (33%)
SD	10/37 (27%)	1/18 (6%)
PD	2/37 (5%)	1/18 (6%)

- Univariate analysis: no differences in terms of age, sex, disease stage, response to induction, bulky disease, or B symptoms

In our study as a single agent, brentuximab vedotin had an overall response rate of 68%, a CR rate of 35%, and a PR or partial response rate of 32%. In a univariate analysis, there was no difference in terms of age, sex, disease, stage, response to induction, bulky disease, or B symptoms. For the patients that did not achieve a complete remission, they went on to further salvage chemotherapy such as ICE/DICE/IGEV or GND. The overall response rate was 89%, and the CR rate was 56%. It is important to note that by delaying giving these patients the combination chemotherapy the overall response rate and CR rate did not appear to suffer, so they are not different if they were given in second-line or third-line setting.

AHCT Results

Characteristics	N or Range
Types of HCT	
- AHCT	32 (86%)
- AlloHCT	2 (5%)
- No HCT	3 (8%)
Disease Status at AHCT	
- CR	23/32 (72%)
- PR	8/32 (25%)
- SD	1/32 (3%)
Salvage regimen	
- BV only	15/32 (47%)
- BV followed by chemotherapy	16/32 (50%)
- BV followed by radiation	1/32 (3%)
AHCT centers	
- COH	25/32 (78%)
- Cornell	5 (16%)
- UCLA	1 (3%)
- UCSD	1 (3%)

In terms of the patients that moved to transplant, out of a total 37 patients, 32 went to autologous hematopoietic cell transplant, and two patients went to allogeneic transplant, and three patients could not proceed to transplant. Overall, 72% of patients were in complete remission at the time of transplant and as we eluded earlier, people who were in CR at the time of transplant have a better outcome posttransplant. In terms of the therapy they received, 47% or almost half of the patients went to transplant receiving brentuximab vedotin only, and the other 50% received brentuximab vedotin followed by chemotherapy.

AHCT Outcomes

	All patients (32)	COH patients (25)
Median f/u	20.9 months (10.1, 41.1)	24.2 months (10.1, 39.6)
OS	18 months -96.9% (79.8, 99.6)	2 yrs -89.1% (61.5, 97.3)
PFS	18 months -71.9% (52.9, 84.3)	2 yrs -68.0% (46.1, 82.5)
NRM	D100 -3.1% (0.5, 21.5)	D100 -4% (0,6, 27.3)

In terms of the outcome posttransplant, for all patients, the median followup was about 21 months. For City of Hope patients, it was about 24 months. I want to show you the different columns because the study was active at City of Hope earlier, so we have longer followup for the City of Hope patients. But in terms of all patients, the overall survival of 18 months was about 97% and the PFF was about 72% in 18 months, whereas for City of Hope only patients, the median followup was longer at 24 months so we can report a 2-year overall survival of 89%, but a 2-year PFS of 68%. As you can see, they are very similar with the exception that City of Hope patients had a little slightly longer followup. Also, the day 100 non-relapse mortality was low at 3-4%.

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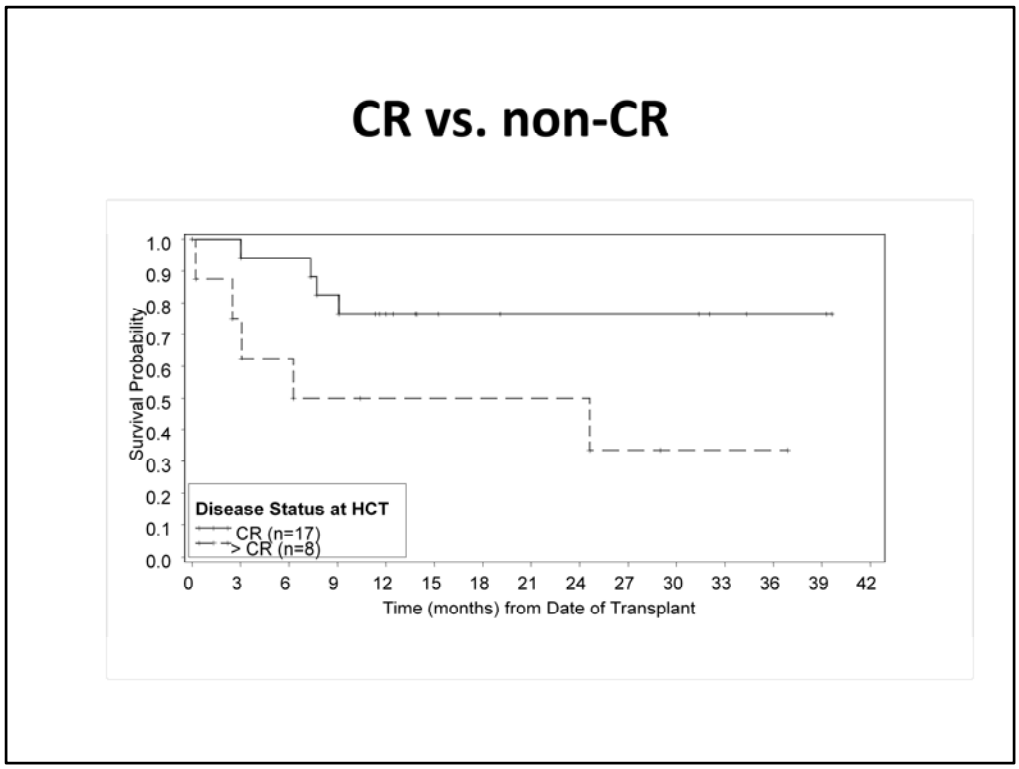

I also told you earlier that patients who were in CR had better outcome posttransplant. So, among the patients that got transplanted, we broke it down to two different curves. The curve above is the patients in CR at the time of the transplant. The curve below is the patients not in CR. You can see that patients who are already in CR did much better. The 2-year PFS was about 75% compared to 50% for patients not in CR.

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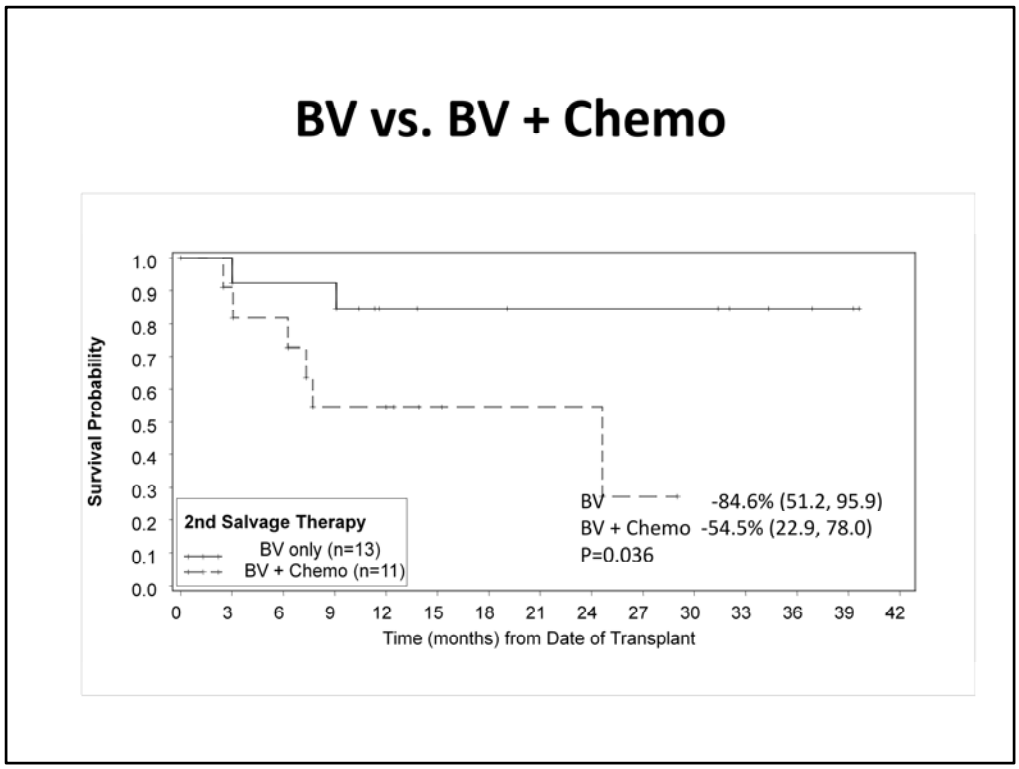

We also broke it down into patients who received brentuximab vedotin only versus patients that received brentuximab vedotin followed by chemotherapy. The patient that received brentuximab vedotin only also did very well. Their 2-year PR was 85% compared to 55% for the patients that required brentuximab vedotin plus other forms of chemotherapy, and I show you this slide not to tell you the point that BV only is better than BV plus chemo, but the fact is there are people that were concerned that the CR to brentuximab vedotin may not be as good as CR to combination salvage chemotherapy, but our trial showed that if you receive CR from brentuximab vedotin only the 2-year PFS rates actually compare very favorably.

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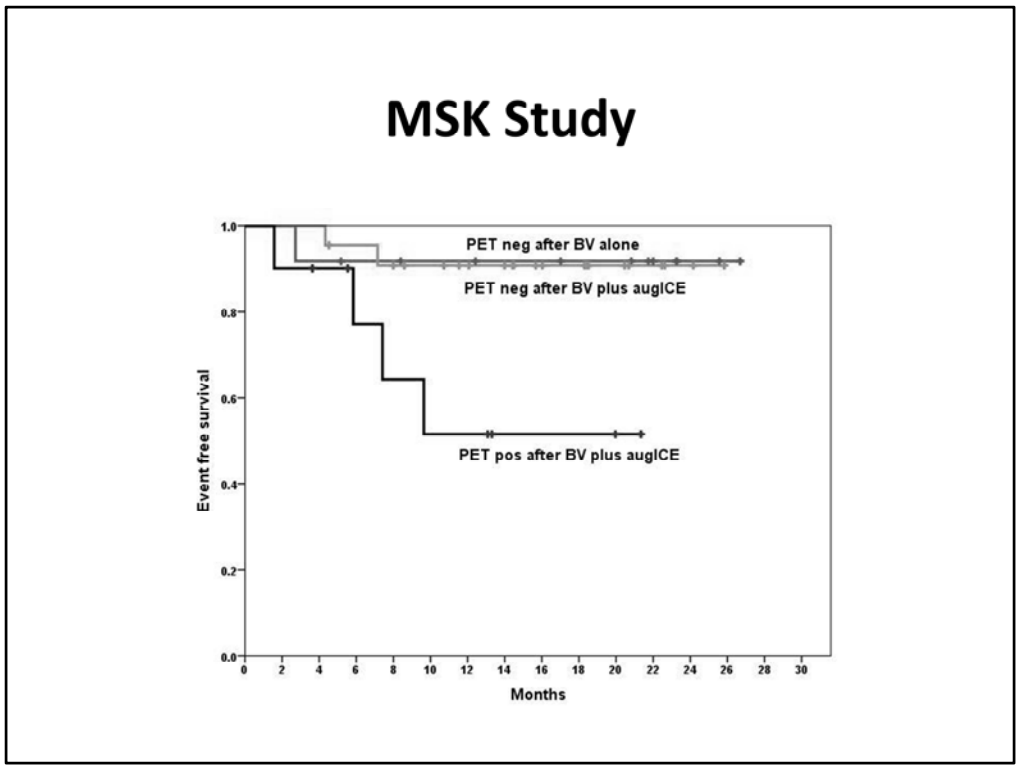
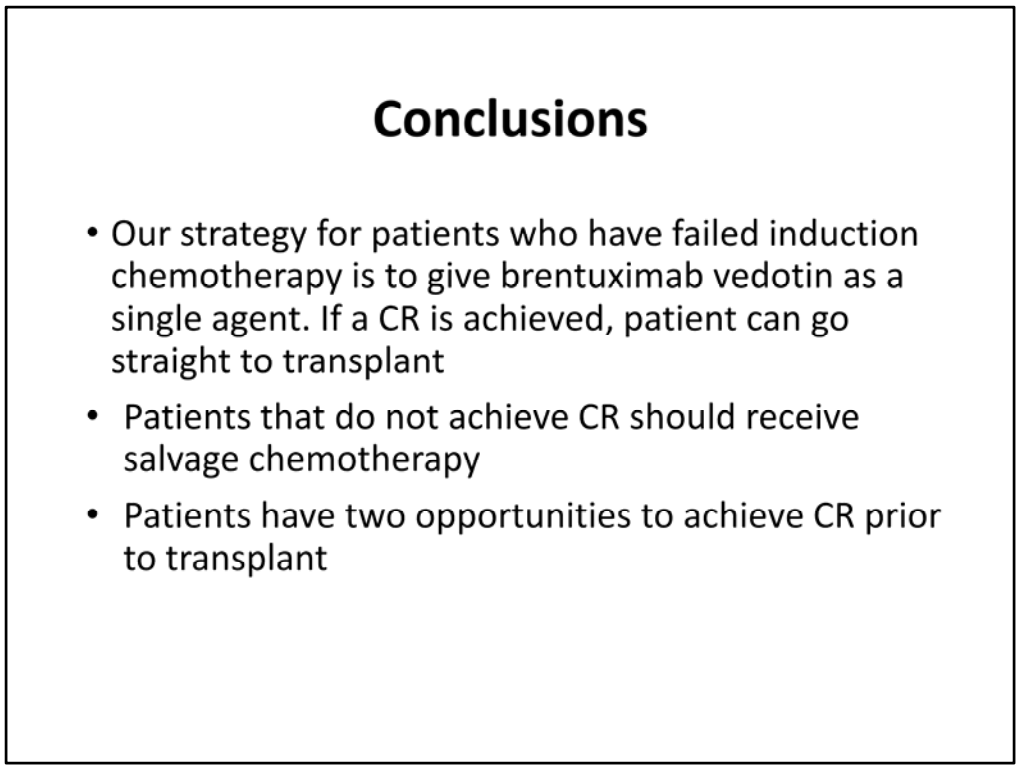


Dr. Alison Moskowitz at Memorial Sloan-Kettering also performed a similar study. The difference was they gave brentuximab vedotin as 1.2 mg/m once a week, rather than the way we did, which is 1.8 mg/kg every 3 weeks. They also found out that patients who had achieved PET-negative status, or CR status, did much better compared to people who were PET positive, and the patients who got PET negative after brentuximab vedotin alone were just as good as patients who got PET negative after BV plus chemotherapy.



So, basically, at this time, our strategy for patients who have failed induction chemotherapy is to give them brentuximab vedotin first, as a single agent, and if they achieve a CR they can go straight to transplant. If they do not achieve CR, then we can give them first salvage chemotherapy. So, these patients had two opportunities to achieve CR prior to transplant, and the patients who achieve CR at the time of transplant, again, would have the best outcome posttransplant.

Thank you for your attention on this presentation. If you have any further questions, please visit our website as there will be other activities and also resources on how to help you manage Hodgkin lymphoma.