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Does BV as part of salvage impact outcome?

Craig Moskowitz, MD
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Member, Memorial Sloan Kettering Cancer Center
Professor of Medicine, Weill Medical College of Cornell University

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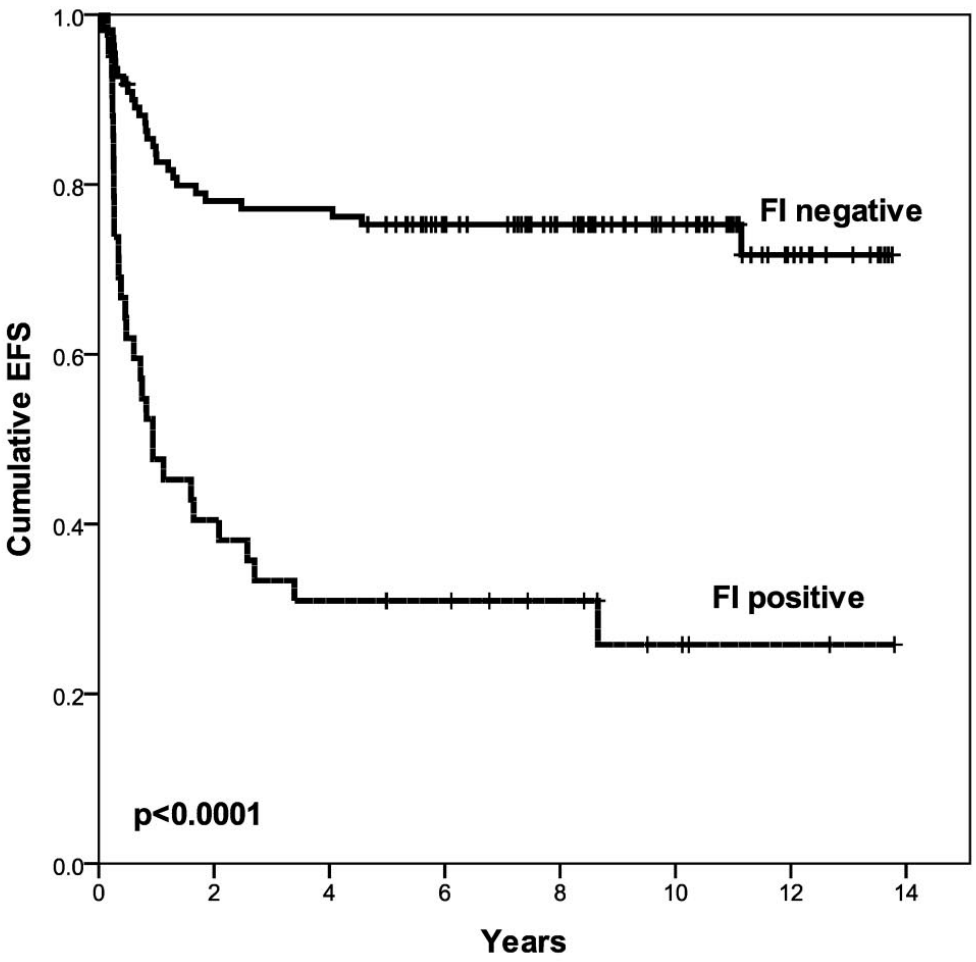
How important is pre-ASCT PET status in HL

Very, but not the whole story

Pretransplant functional imaging in rel/ref HL (1994-2003)



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

Moskowitz, AJ. Blood 2010.

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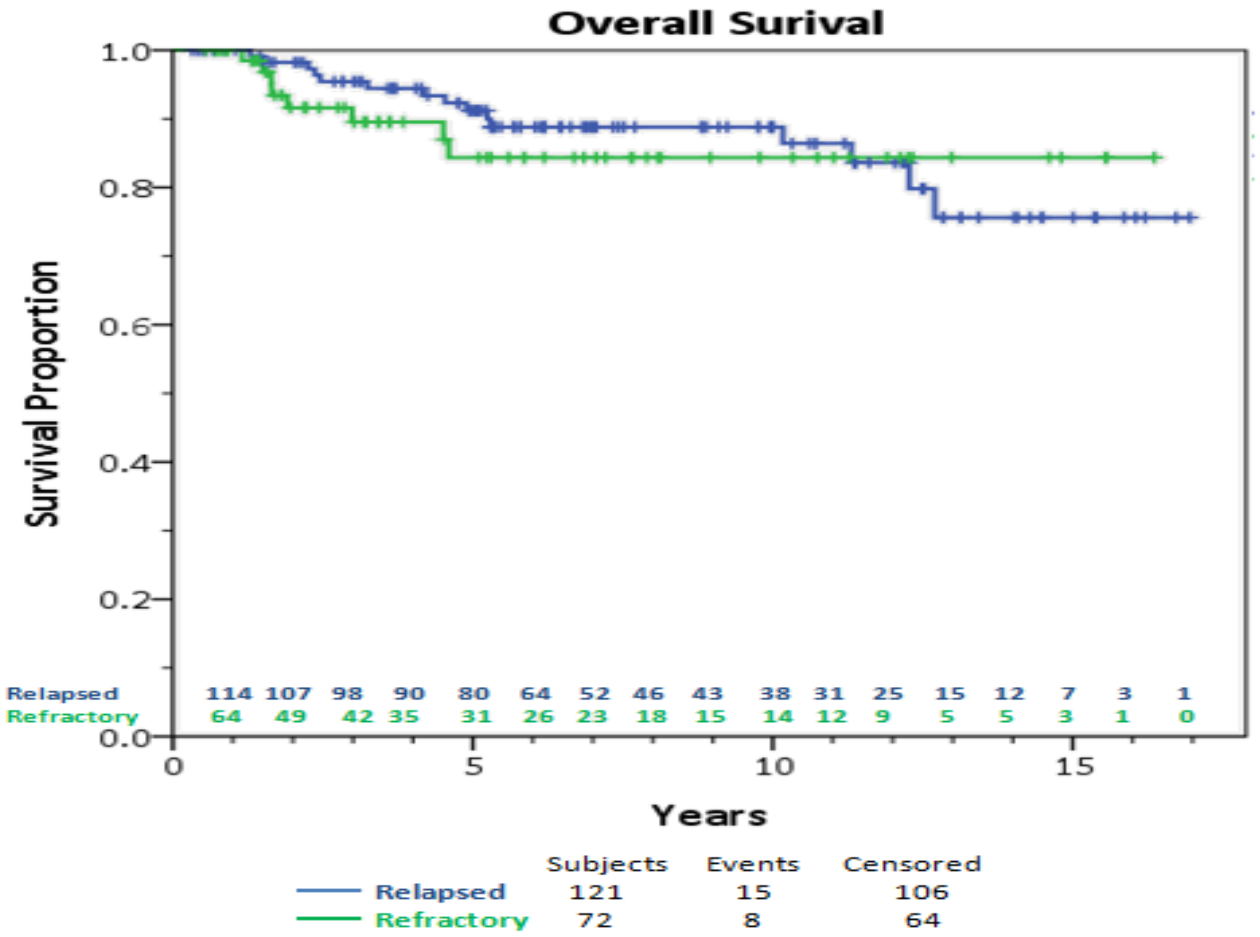
Patients transplanted in CR at MSKCC 1994-2012
Brentuximab Vedotin naïve , nodal only disease at time of salvage therapy



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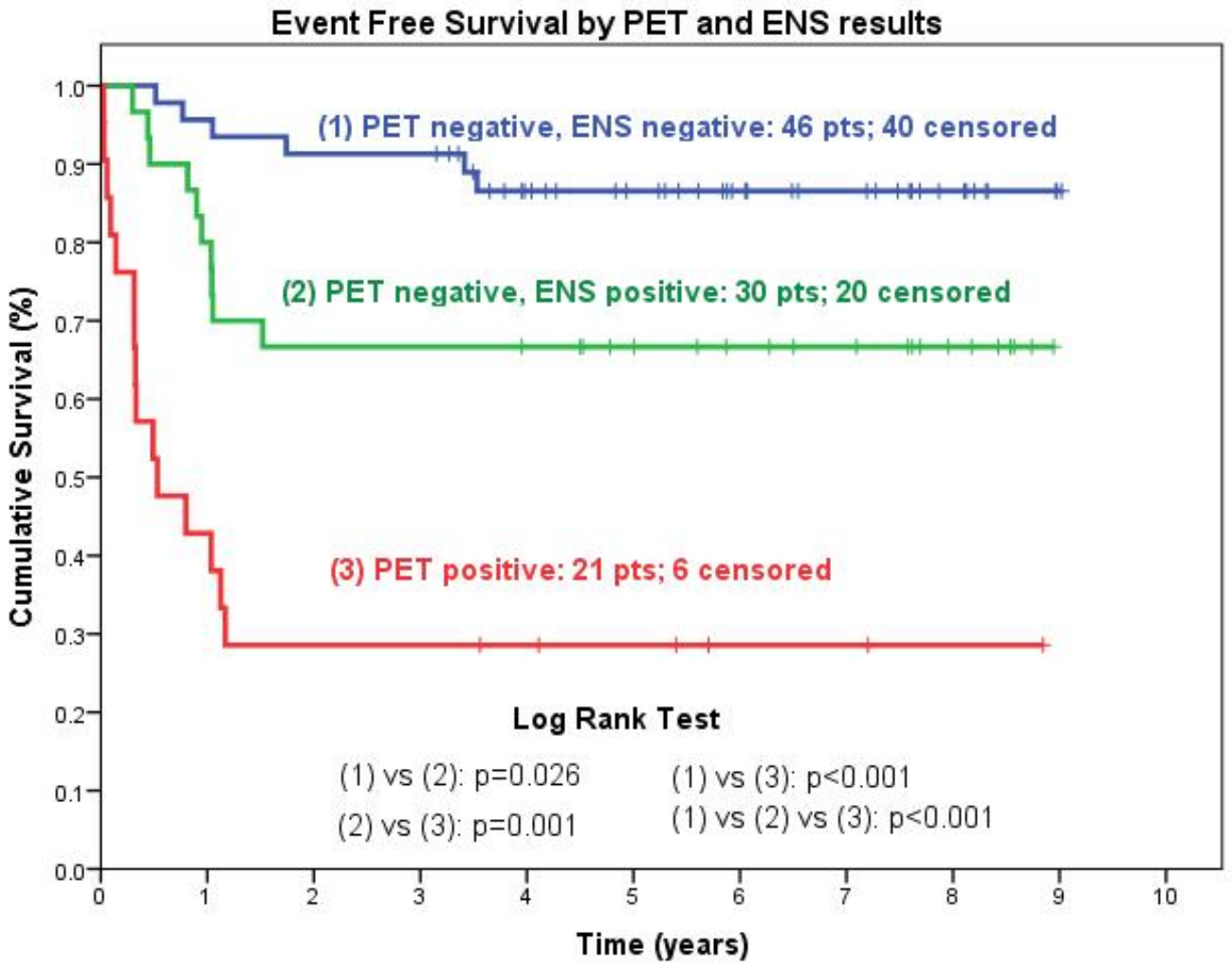
FDG-PET and ENS



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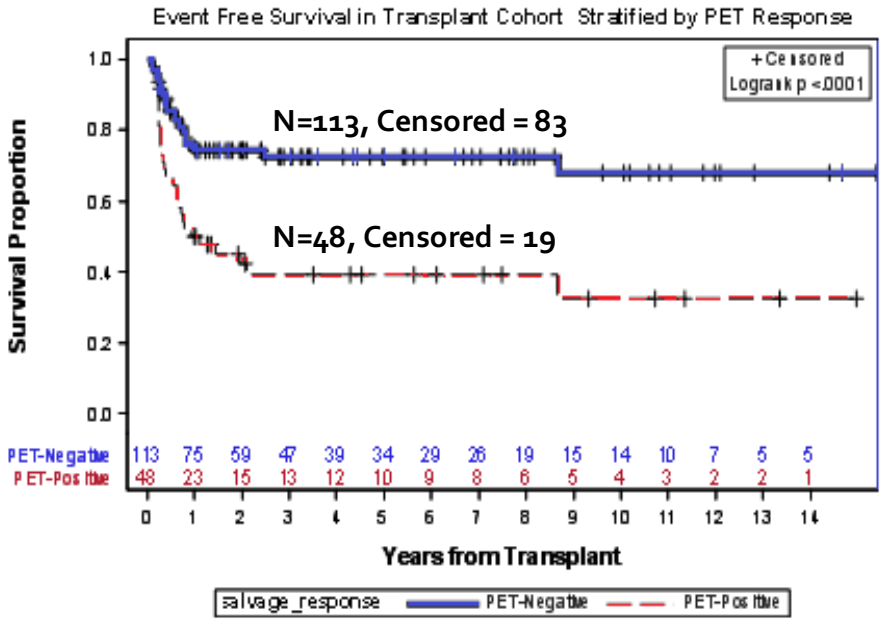
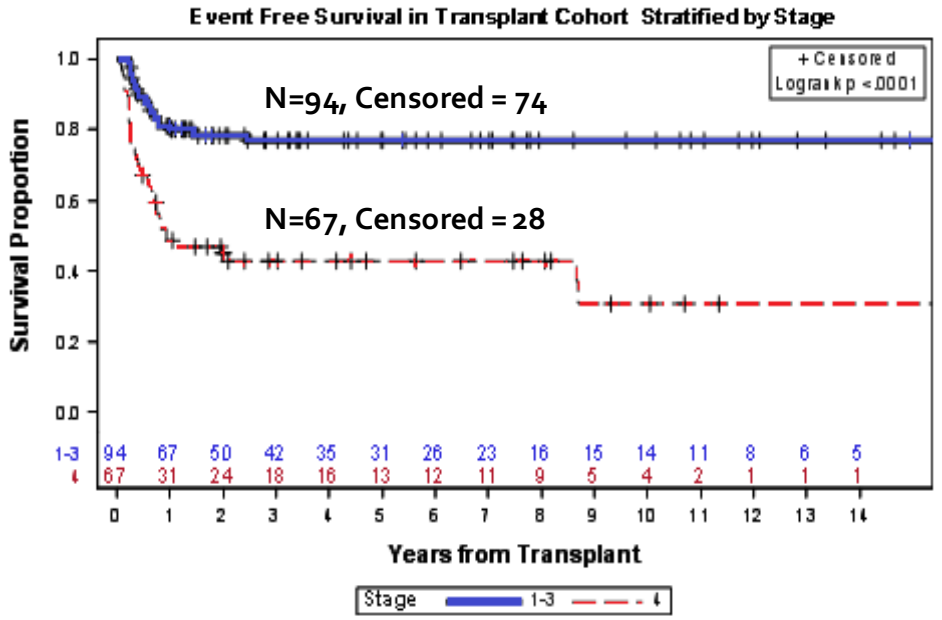
Primary Refractory, chemosensitive, Transplanted Patients at MSKCC: Multivariate EFS Analysis

Multivariate EFS		HR	[95% CI]	p-value
Ann Arbor Stage of Refractory Disease	IV	2.55	[1.43 - 4.57]	0.002
Response to Salvage	PET Positive	2.00	[1.16 - 3.44]	0.013



Median EFS: Not Reached 1.03yrs



Median EFS: Not Reached 0.95 yrs

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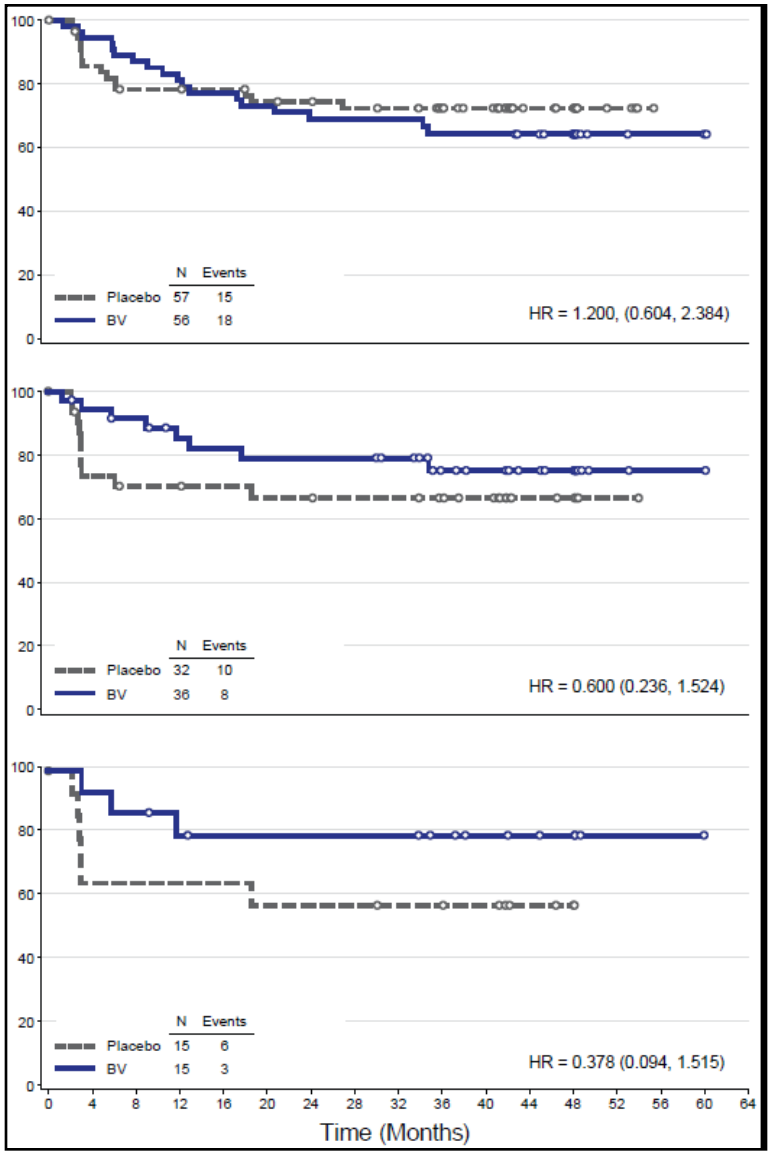
Pre-ASCT PET Negative



All

≥ 2 Risk Factors

Extranodal Disease at Relapse

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FDG-PET assessment

Deauville criteria or 5 point scale

Score	FDG-PET/CT scan result
1	No uptake above background
2	Uptake ≤ mediastinum
3	Uptake > mediastinum but ≤ liver
4	Uptake moderately more than liver uptake, at any site
5	Markedly increased uptake at any site or new sites of disease

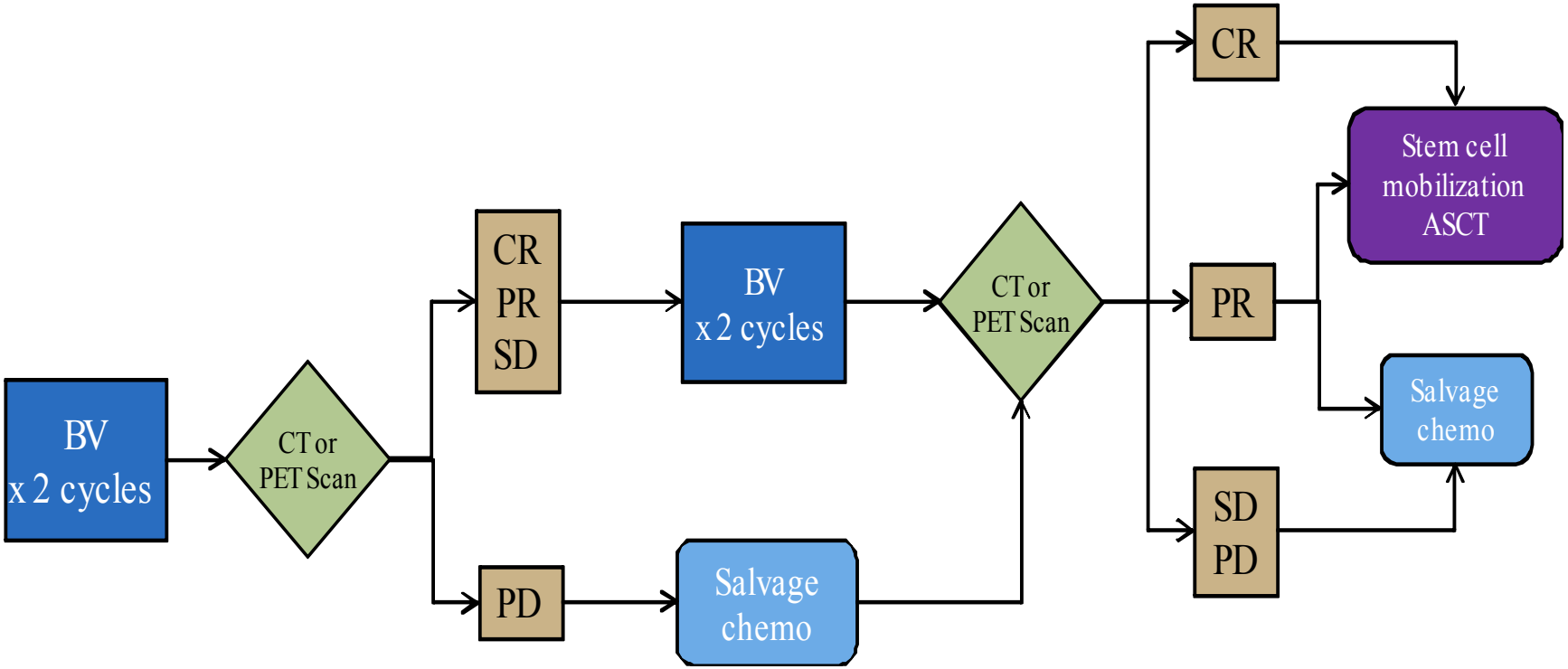
5 studies: same goal-PET negative CR

- An attempt to avoid salvage therapy (published)
  - BV as a single agent
  - BV administered sequentially with if necessary

- Adding multiple active agents (abstract only)
  - BV + bendamustine
  - BV+ DHAP
  - BV+ICE

COH

Chen et al Biol Blood Marrow Transplant 21 (2015) 2136e2140



- BV given at 1.8 mg/kg IV outpatient every 3 weeks for 4 cycles max
- No premedication with first cycle

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Response Rates

(CR Deauville 2)

	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.

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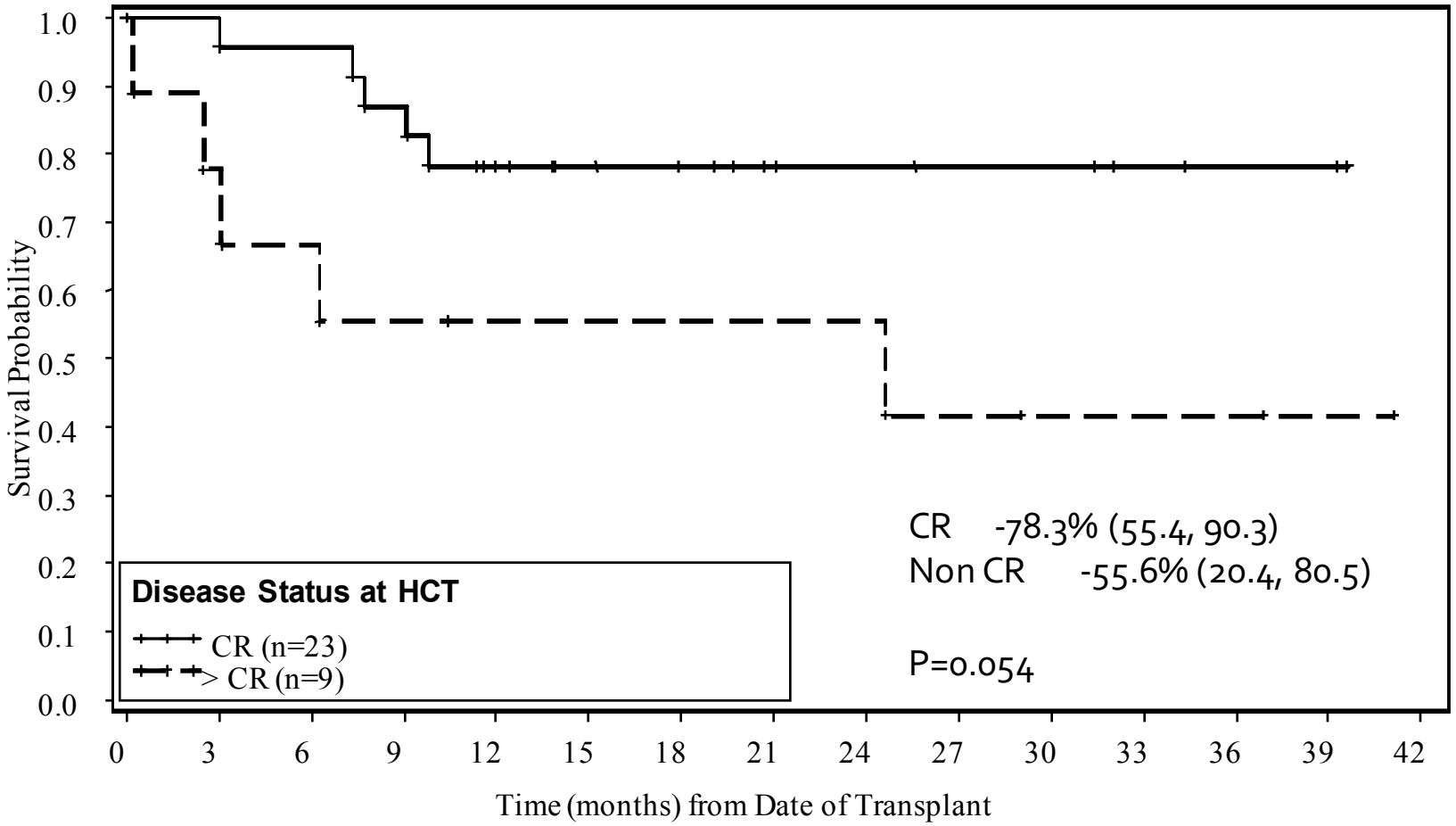
All patients-PFS
CR. Vs. non-CR



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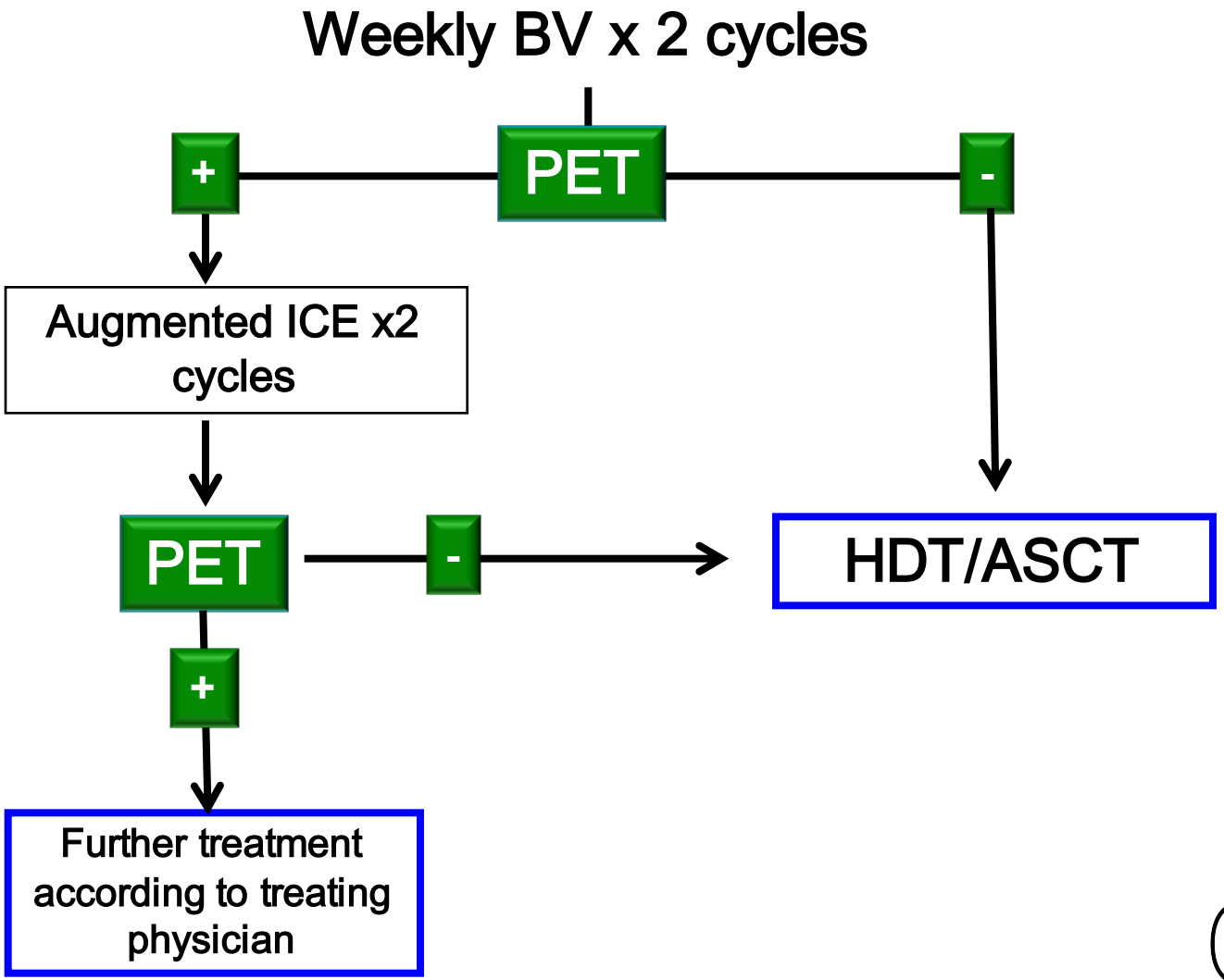
MSKCC 11-142: Relapsed/refractory HL

First TX following upfront therapy

Moskowitz, AJ, et al. Lancet Oncol 2015;16: 284-92



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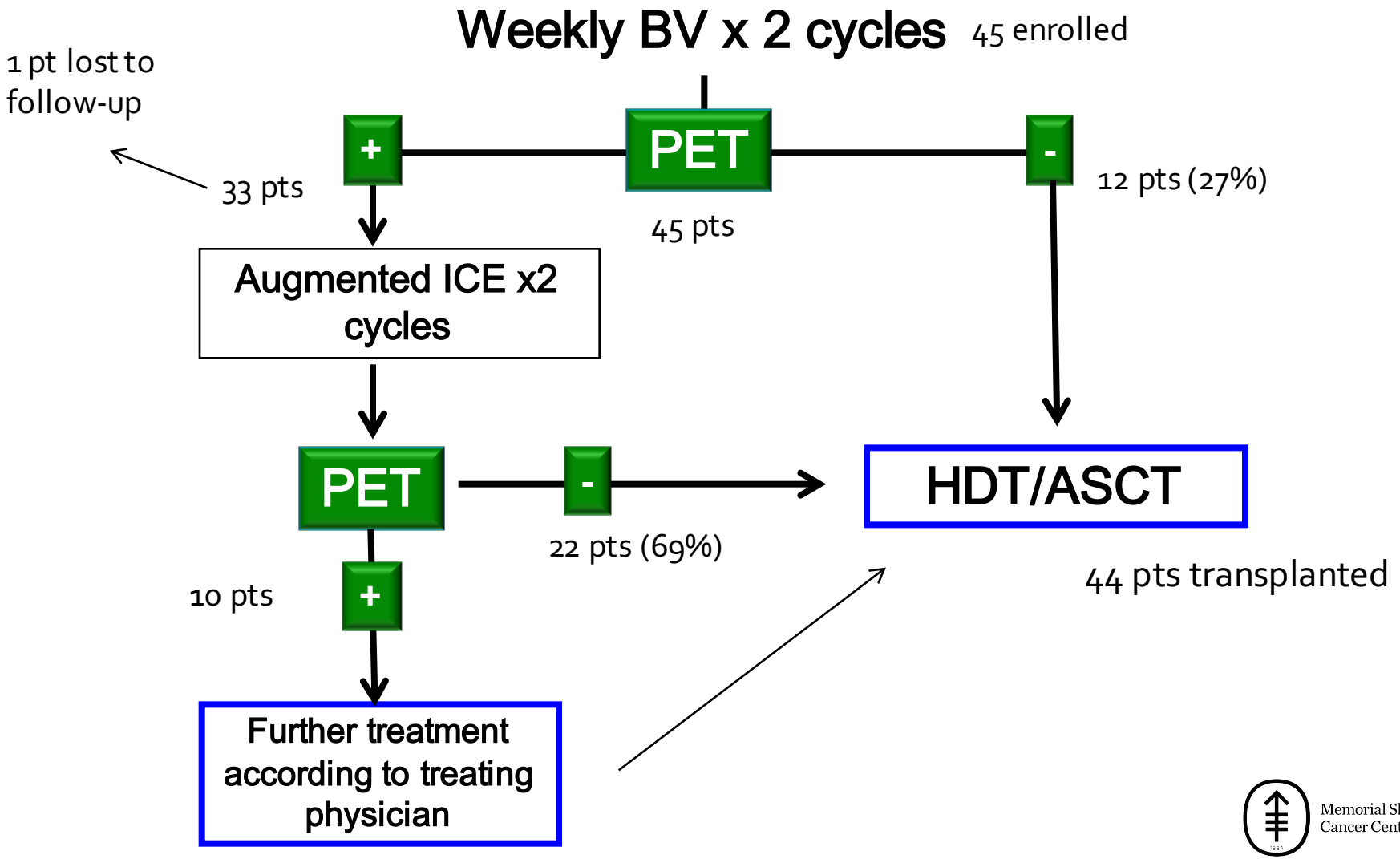
MSKCC 11-142

45 evaluable patients (CR Deauville 2)



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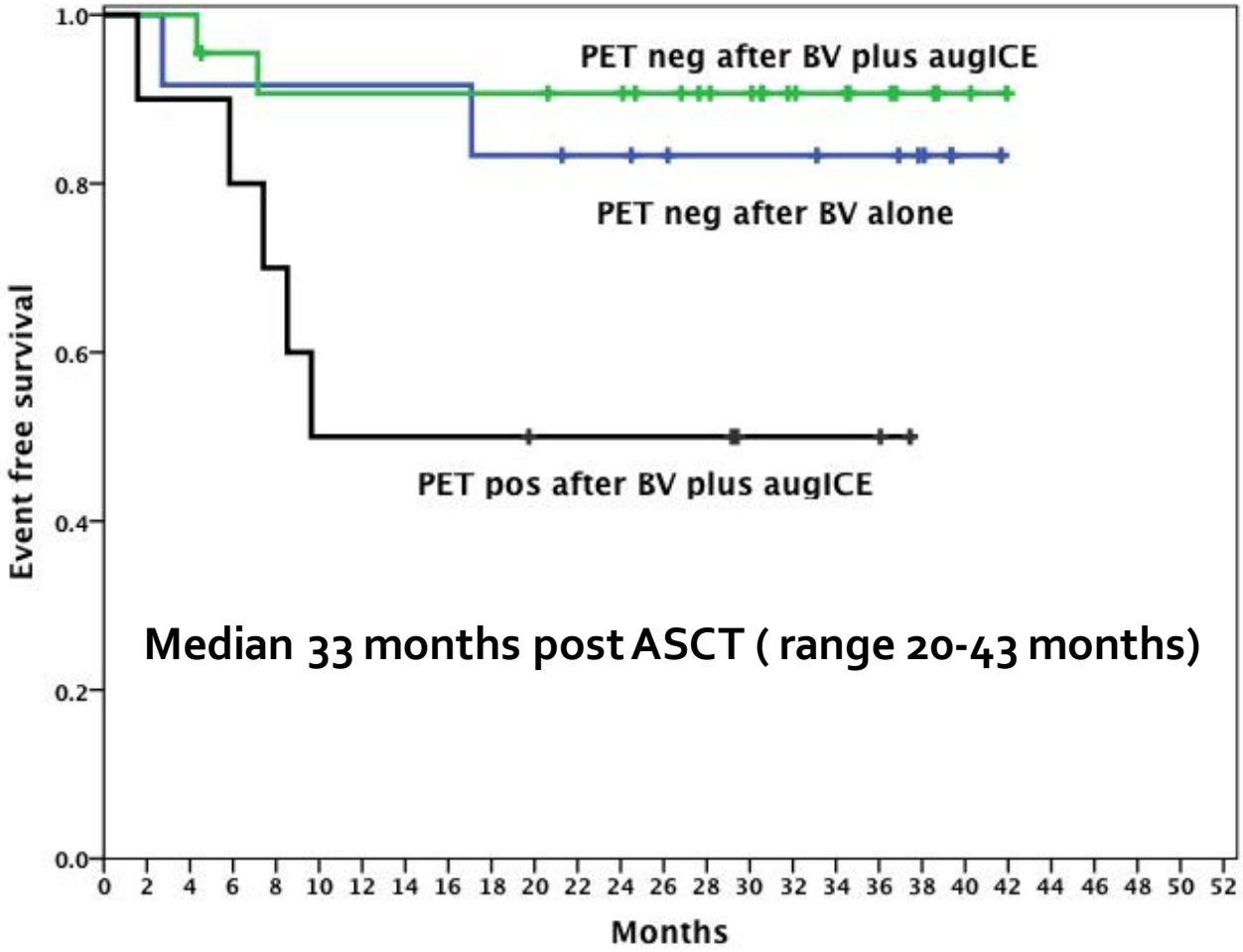
PET adapted therapy with BV and augICE
Updated results



Median 33 months post ASCT (range 20-43 months)

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Cytokine/Chemokine changes following BV

Cytokine/chemokine (normal)	Pre-brentuximab vedotin (pg/ml)		Post-brentuximab vedotin (pg/ml)	
	median	range	median	range
IL-6 (<17.4)	2.27	0.10 – 154	1.41	0.09 - 34
IL-10 (<2)	0.38	0.09 – 112	0.45	0.14 – 18
TNF-α (<5.6)	2.55	0.55 - 15.15	2.25	0.58 – 22
IFN-γ (<2)	8.66	1.45 - 1554	9.01	2.62 - 113
TARC (<500)	8250	236 - 220773	1027	241 - 34453

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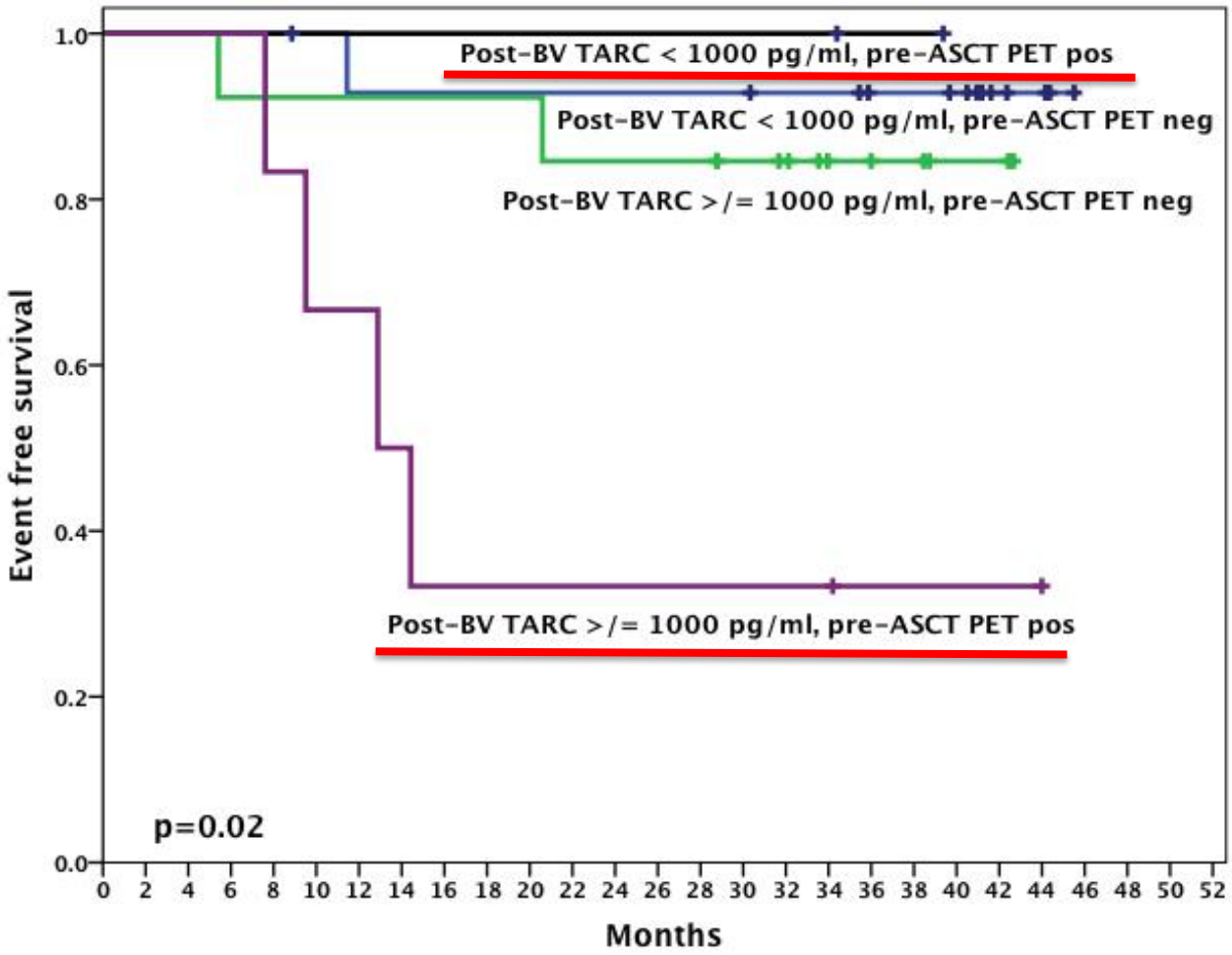
Post-BV TARC and pre-ASCT PET



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Abstract only

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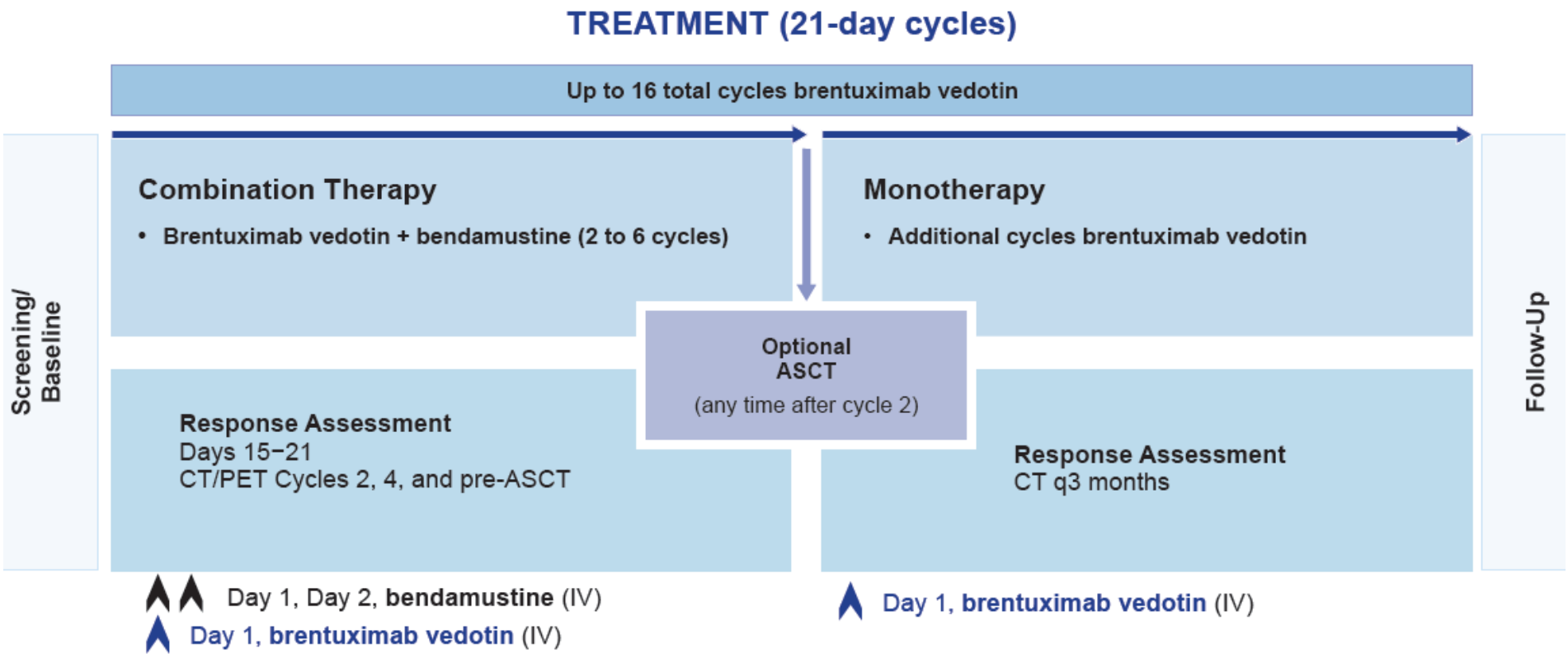
Brentuximab Vedotin Plus Bendamustine: A Highly Active Salvage Treatment Regimen for Patients with Relapsed or Refractory Hodgkin Lymphoma

Ann LaCasce[1], R. Gregory Bociek[2], Ahmed Sawas[3], Paolo Caimi[4], Edward Agura[5], Jeffrey Matous[6], Stephen Ansell[7], Howland Crosswell[8], Miguel Islas-Ohlmayer[9], Caroline Behler[10], Eric Cheung[11], Andres Forero-Torres[12], Julie Vose[2], Owen A. O'Connor[3], Neil Josephson[13], Ranjana Advani[14]

[1]Dana-Farber Cancer Institute, Boston, MA, USA; [2]University of Nebraska Medical Center, Omaha, NE, USA; [3]Columbia University Medical Center, New York, NY, USA; [4]University Hospitals Case Medical Center, Cleveland, OH, USA; [5]Charles A. Sammons Cancer Center, Dallas, TX, USA; [6]Colorado Blood Cancer Institute, Denver, CO, USA; [7]Mayo Clinic, Rochester, MN, USA; [8]St. Francis Hospital, Greenville, SC, USA; [9]The Jewish Hospital-Mercy Health, Cincinnati, OH, USA; [10]Pacific Hematology Oncology Associates, San Francisco, CA, USA; [11]The Oncology Institute of Hope & Innovation, Whittier, CA, USA; [12]University of Alabama at Birmingham, Birmingham, AL, USA; [13]Seattle Genetics, Inc., Bothell, WA, USA; [14]Stanford Cancer Center, Stanford, CA, USA

American Society of Hematology 2015, December 5–8, 2015, Orlando, FL, Abstract No. 3982

Study Design



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Patients

	N=55
Median age, (range)	36 years (19–79)
Gender (% female/male)	56/44
ECOG status, n (%)	
0	36 (65)
1	18 (33)
2	1 (2)
Median time since HL diagnosis, (range)	13.8 months (3–98)
Stage III/IV at diagnosis, n (%)	29 (53)
Baseline disease status, n (%)	
Primary refractory	28 (51)
Relapsed	27 (49)
No. of patients with remission duration ≤ 1 yr	11 (20)
B symptoms, n (%)	12 (22)
Bulky disease, n (%)	5 (9)
Extranodal disease, n (%)	17 (31)
Bone marrow involvement, n (%)	
PET	8 (15)
Bone marrow biopsy	4 (19)[a]
Median International Prognostic Score (IPS[b]) at enrollment, (range)	2 (0-5)

Extranodal disease = extra-lymphatic disease; lymphomatous infiltration of anatomic sites other than lymph nodes and other lymphatic organs

[a] Percentage is relative to the number of patients who had a bone marrow biopsy performed (n=21); 3 of 4 patients with bone marrow involvement by biopsy also had bone marrow involvement by PET

[b] Includes the following 7 parameters (1 point each; maximum score =7): male sex, age ≥45 years, stage IV, hemoglobin <105 g/L, WBC count >15 X 10^9/L, lymphocyte count <0.6 X 10^9/L or <8% differential, albumin < 40g/L

- 50 of 55 (91%) patients received ABVD as their frontline therapy

Safety

Results on Combination Therapy

- Patients received a median of 2 cycles (range, 1–6) of bendamustine 90 mg/m^2 in combination with brentuximab vedotin 1.8 mg/m^2
- Main toxicities on combination were infusion-related reactions (IRRs)

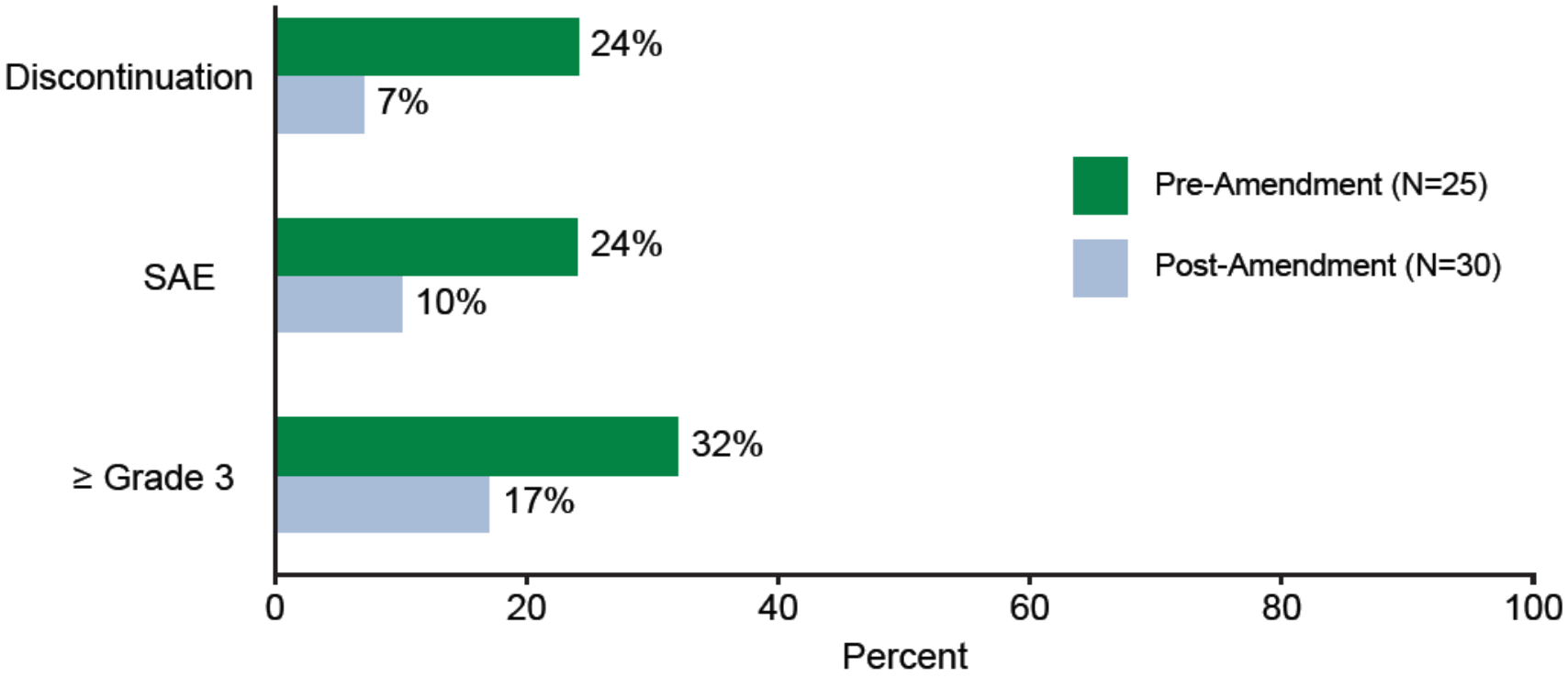
Infusion-Related Reactions

- IRRs observed in 58% of pts overall, most common symptoms (≥15%) were pyrexia, chills, dyspnea, flushing, and nausea
- IRRs occurred at a greater rate and severity than that which would be expected for either drug given as a single-agent[a,b]
- A protocol amendment requiring premedication with corticosteroids and antihistamines resulted in a decrease in IRR severity

a TREANDA Prescribing Information, Cephalon, Inc., a wholly owned subsidiary of Teva Pharmaceutical Industries Ltd., or its affiliates, September 2015

b ADCETRIS Prescribing Information, Seattle Genetics, Inc., August 2015

Adverse Events



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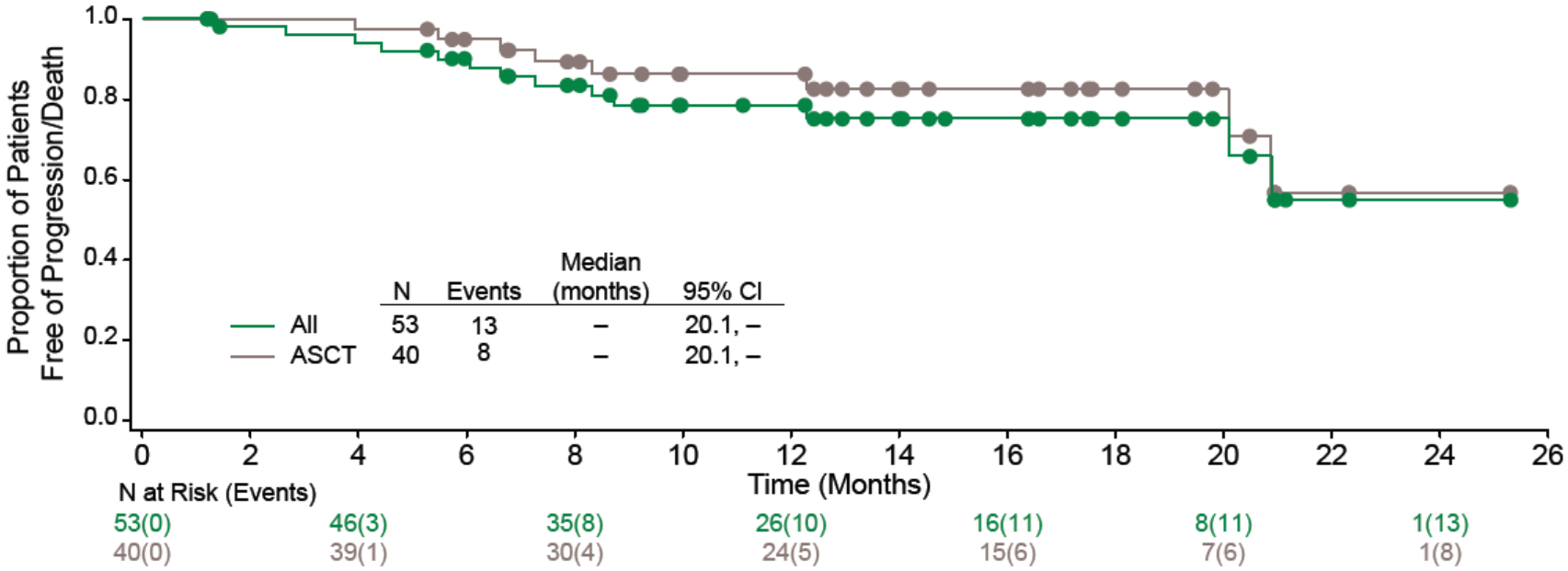
Long-Term Follow Up

- Patients have been followed for a median of approximately 15 months from first dose (N=53) and 13 months from ASCT (n=40)

- Thirty patients received a median of 10 cycles (range, 1–14) of brentuximab vedotin as monotherapy 25/40 pts who underwent transplant and 5/13 pts who did not undergo transplant

Progression-Free Survival – All Patients and in ASCT Subset



- Overall 18-month PFS rate of 75% (95% CI: 59, 86), 83% in ASCT subset
- 9 of 11 pts (82%) observed ≥18 months remain free of progression

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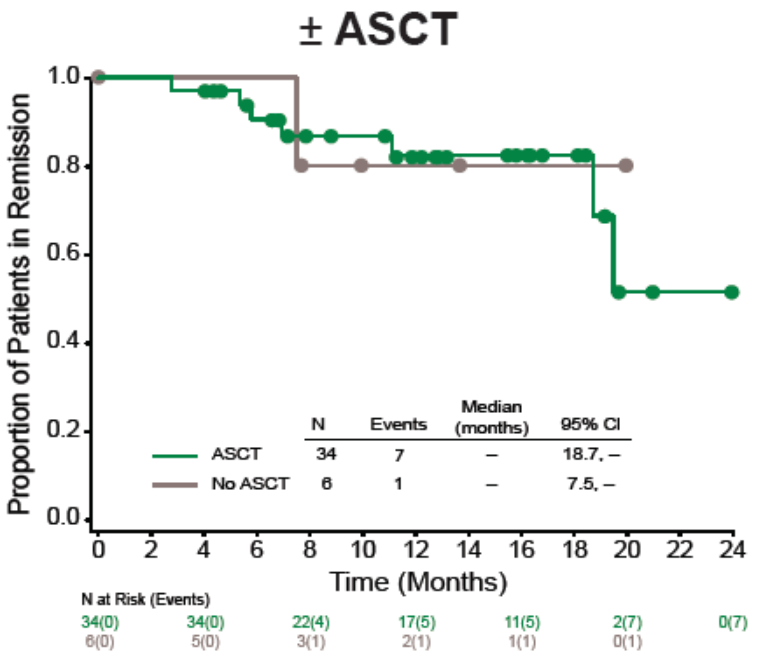
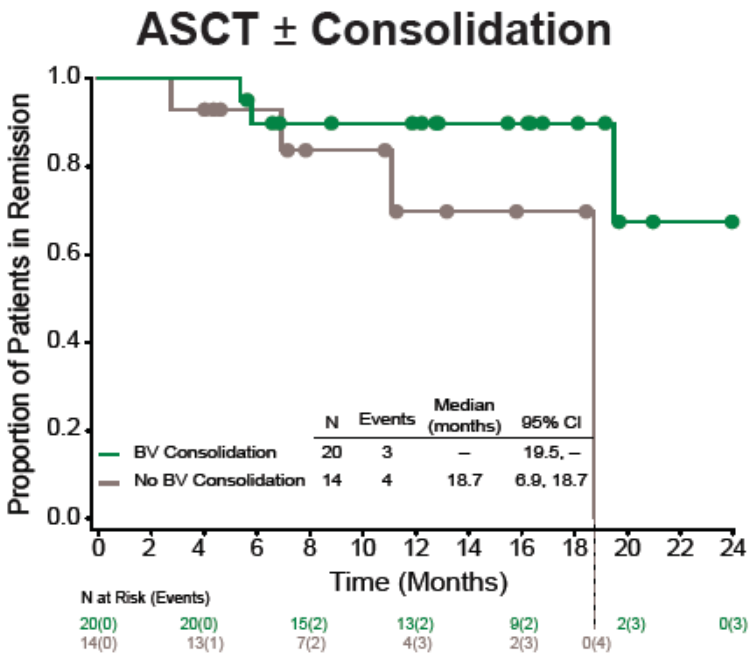
Duration of Remission for Patients with CR



- Similar percentage of events in pts with CR who did (21%) and did not (17%) undergo ASCT



- Greater percentage of events observed in pts who did not receive consolidation (29%) relative to pts who did (15%)

- For pts with a best response of PR (n=9), events were observed in 1/4 pts (25%) who underwent ASCT and 3/5 pts (60%) who did not undergo ASCT

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Best Response on Combination Therapy

N=53	n (%)	95% CI
Best clinical response		
Complete remission (CR)	40 (76)	61.7, 86.2
Partial remission (PR)	9 (17)	
Stable disease (SD)	3 (6)	
Progressive disease (PD)	1 (2)	
Objective response rate (ORR [CR + PR])	49 (93)	81.8, 97.9

- 76% CR rate and 93% ORR
- CR rates were 88% in relapsed pts and 64% in primary refractory pts

Stem Cell Harvest and Marrow Engraftment

Median number of apheresis sessions, (range)	2 (1–5)
Median CD34+ cell yield (cells/kg), (range)	4.1 x 10^6 (1.7–11.8)
<2 x 10^6 Cells Collected, n	1[a]
Plerixafor required after failure to collect/harvest CD34+ cells with first-line agent(s), n	1
Median number of cycles before mobilization (range)	2 (2–6)
Median time (days) to neutrophil engraftment (range)	11 (9–21)
Median time (days) to platelet engraftment (range)	13 (9–39)

[a] Patient with 1.7 x10^6 cells collected was able to undergo transplant with engraftment

- 95% of pts who underwent mobilization (39/41) had successful stem cell collection with first-line agent(s) (G-CSF ± plerixafor)
  - 1 pt required rescue plerixafor
  - 1 pt underwent bone marrow harvest due to failure of G-CSF (rescue plerixafor not used)
- 40 pts underwent transplant
  - 1 pt had disease progression after mobilization and was not transplanted
  - 1 pt died from septic shock subsequent to transplant and never engrafted

Summary and Conclusions

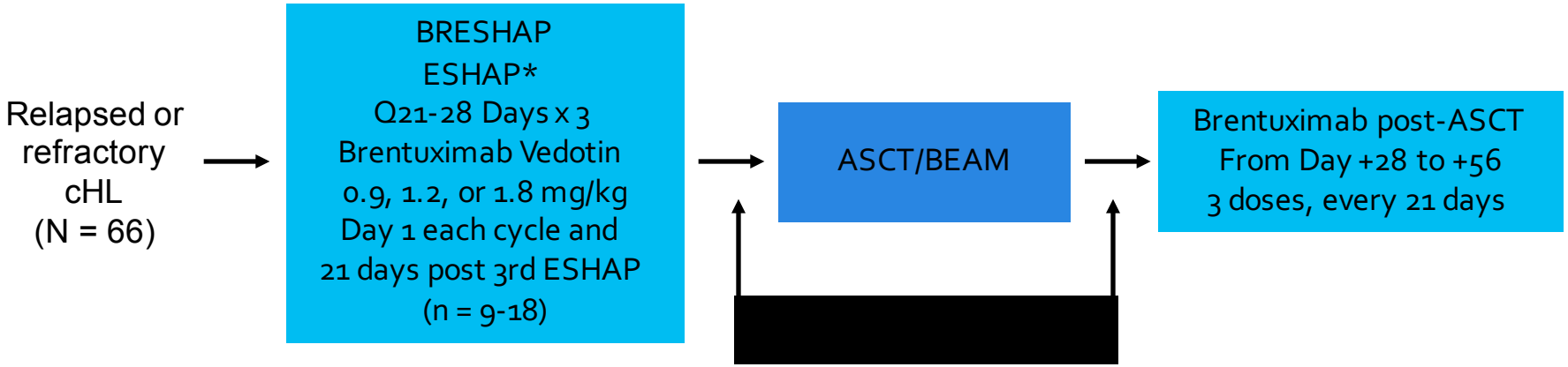
- Combination therapy produced a high response rate (76% CR, 93% ORR) with manageable toxicity and enablement of stem cell mobilization and engraftment
- 75% estimated 18-month PFS rate demonstrates durability of response
- Early trend suggesting benefit for post-transplant consolidation with brentuximab vedotin
- Duration of remission for the few patients who achieved CR and did not proceed to ASCT will continue to be followed
- Outpatient regimen of brentuximab vedotin in combination with bendamustine represents a promising salvage regimen for patients with HL who have R/R disease after frontline therapy

Brentuximab Vedotin + ESHAP for R/R cHL Pts

- Approved for
  - cHL that has failed ASCT or, if transplantation ineligible, after failure of 2 or more multiagent chemotherapy regimens
  - sALCL after failure of 1 or more multiagent chemotherapy regimens
- Current study evaluated the role of brentuximab vedotin + ESHAP (BRESHAP) in transplantation-eligible pts with R/R cHL[2]

1. Younes A, et al. Hematol Oncol Clin North Am. 2014;28:27-32.
2. Garcia-Sanz R, et al. ASH 2015. Abstract 582.

Brentuximab Vedotin + ESHAP for R/R cHL: Phase I/II Open-Label Study



*ESHAP: etoposide 40 mg/m^2, 2-hr infusion Days 1-4; methylprednisone 200 mg/day Days 1-4; cytarabine 2 g/m^2, 2-hr infusion, 1 dose Day 5; cisplatin 25 mg/m^2, continuous infusion Days 1-4; G-CSF support.

- Autologous PBSC collection before cycles 2, 3 of ESHAP; CD34+ quantification: ≥ x 106/kg CD34+ cells
- Neutropenia prophylaxis: mandatory G-CSF from Day +7, peg-filgrastim recommended
- Phase II: up to 66 pts
- Primary objectives: phase I, MTD; phase II, ORR/CR after BRESHAP salvage therapy before ASCT
- Secondary objectives: toxicity and stem cell mobilization capacity after BRESHAP; and TRM, TTF, PFS, and OS after BRESHAP, chemotherapy, ASCT, and brentuximab vedotin

Garcia-Sanz R, et al. ASH 2015. Abstract 582.

Slide credit: clinicaloptions.com

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Brentuximab Vedotin + ESHAP for R/R cHL Lymphoma: Phase I + Phase II

- N = 36
- Median age: 33 yrs (range: 18-60)
- Male/female: 20/16
  - Primary refractory: 58%
  - Relapsed: 42% (6 early, 9 late)
- 145 courses of BRESHAP have been administered
  - Serious AEs (n = 19), febrile neutropenia (n = 9); all resolved
  - No deaths, 1 discontinuation due to PD
- Stem cell collection (n = 24); no mobilization failures
- Evaluable for pre-ASCT response (n = 24)
  - ORR: 96%; CR: 83%

Garcia-Sanz R, et al. ASH 2015. Abstract 582.

Slide credit: clinicaloptions.com

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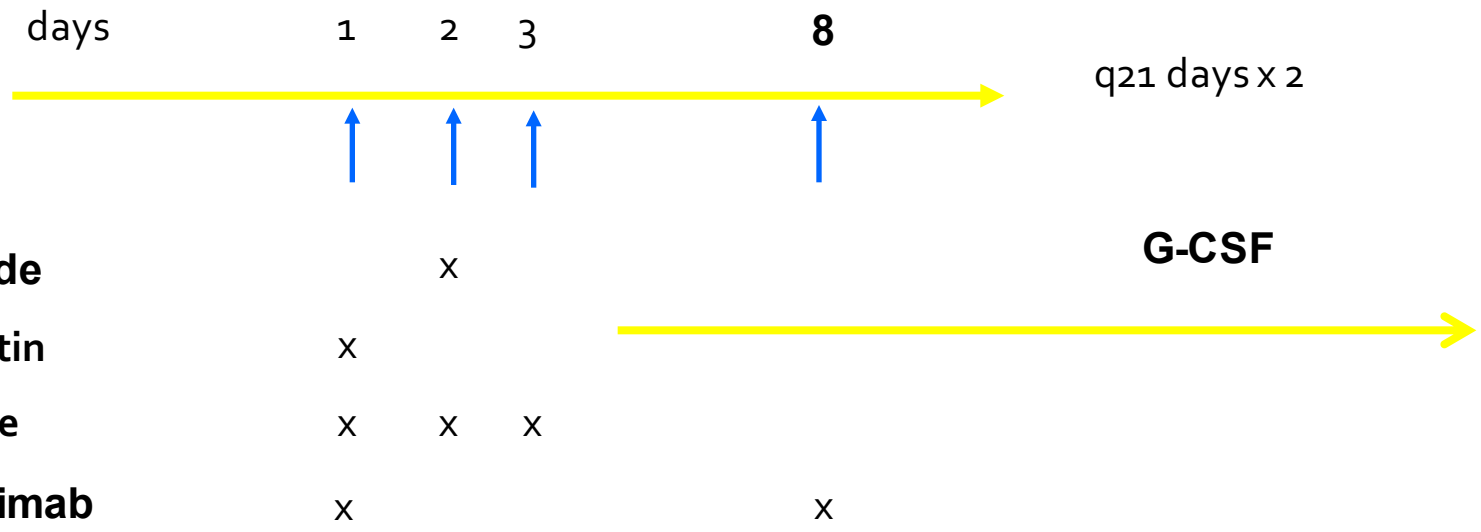
Phase I/II: ICE + BV



	Dose Level	Day 1 BV Dose	Day 8 BV Dose
	-1	1.8 mg/kg	None
Phase II dose	1	1.2 mg/kg	1.2 mg/kg
	2	1.5 mg/kg	1.5 mg/kg

ICE, ifosfamide, carboplatin, etoposide.
Cassaday, et al (UW/FHCRC). Trial in progress.

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I see very little evidence that BV should be "required" as part of salvage therapy

- If administered, however this is my strategy
  - If a CR is reached with BV and pt meets criteria for Aethera then I give 7-10 doses post-ASCT
  - If a PR is reached with BV/chemo then I administer full course therapy post-ASCT
  - If a patient is not sensitive to BV as part of salvage then no post-ASCT treatment

If BV is not administered

  - In a patient that does not receive BV as part of salvage one and has PET avid disease after ICE it is unlikely that a complete response will be achieved with BV (in its approved setting) and I do not use it as such, I administer GVD
    - If a pt has persistent nodal stage I/II disease after 2 salvage programs we radiate and take to auto with post-ASCT BV
    - If a pt has persistent PET avid extranodal disease after 2 salvage we refer to allo or administer a checkpoint inhibitor

Lymphoma* and Lymphoma Transplant** Services-MSKCC

- John Gerecitano*
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- Alison Moskowitz*
- Craig Moskowitz*/**
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