Relapsed and Refractory HL
Will we be able to avoid transplant:
Living in the past-Jethro Tull

Craig Moskowitz, MD
Stephen A. Greenberg Chair in Lymphoma Research
Member, Memorial Sloan-Kettering Cancer Center
Professor of Medicine, Weill Medical College of Cornell University

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FDG-PET assessment in HL

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	Uptake markedly more than liver uptake (>2 times SUVmax of liver) at any site or new sites of disease

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New data with Brentuximab Vedotin

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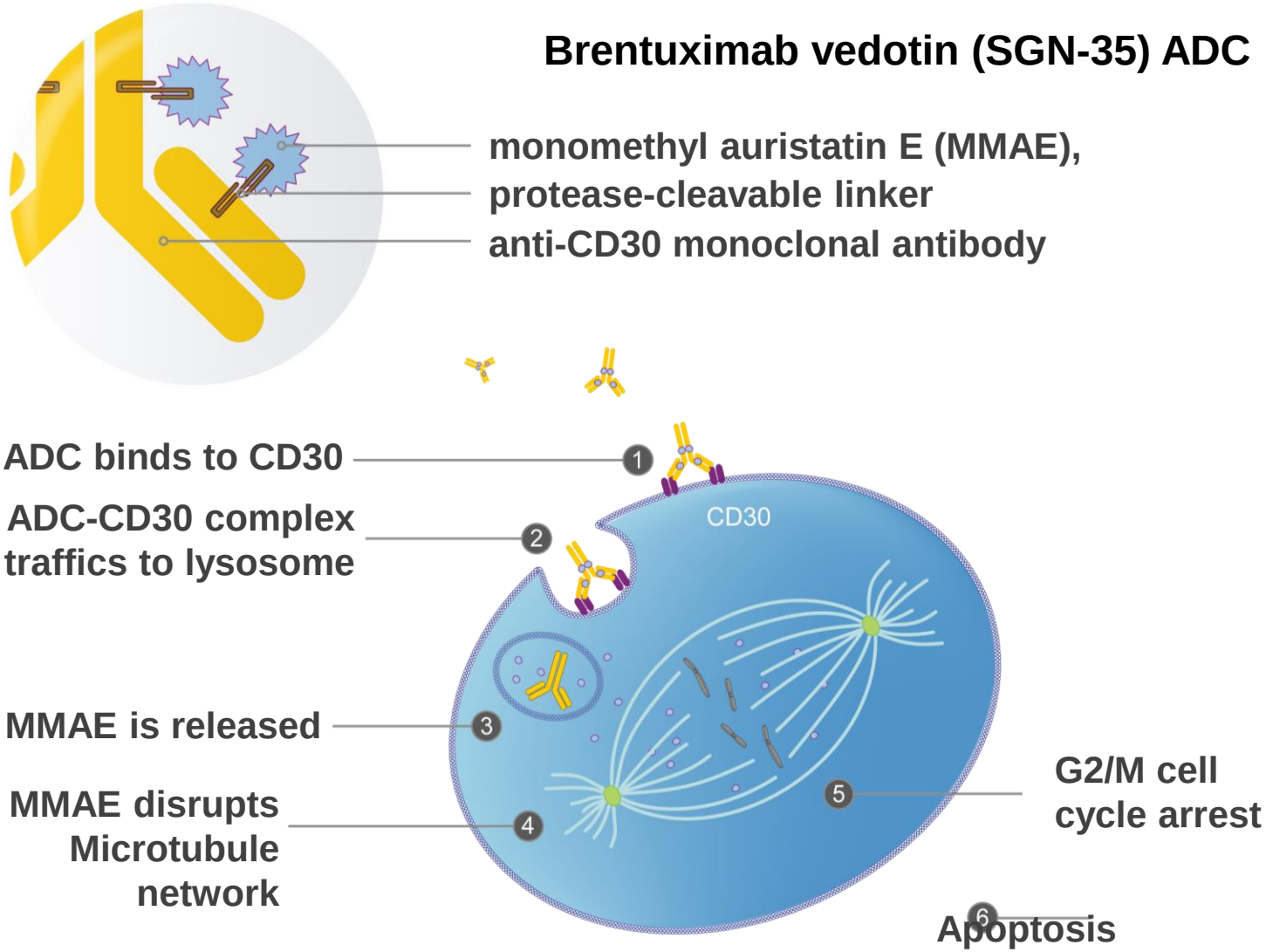
Brentuximab Vedotin Mechanism of Action



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Five recent clinical trials

- **Update on ASHL with BV-AVD**
- **BV administered as a single agent for salvage treatment for HL**
- **BV administered post ASCT for consolidation after and ASCT**
- **BV administered sequentially with ICE as salvage treatment for HL**
- **BV administered concomitantly with bendamustine for salvage treatment for HL**

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ASHL

Will BV-AVD win?

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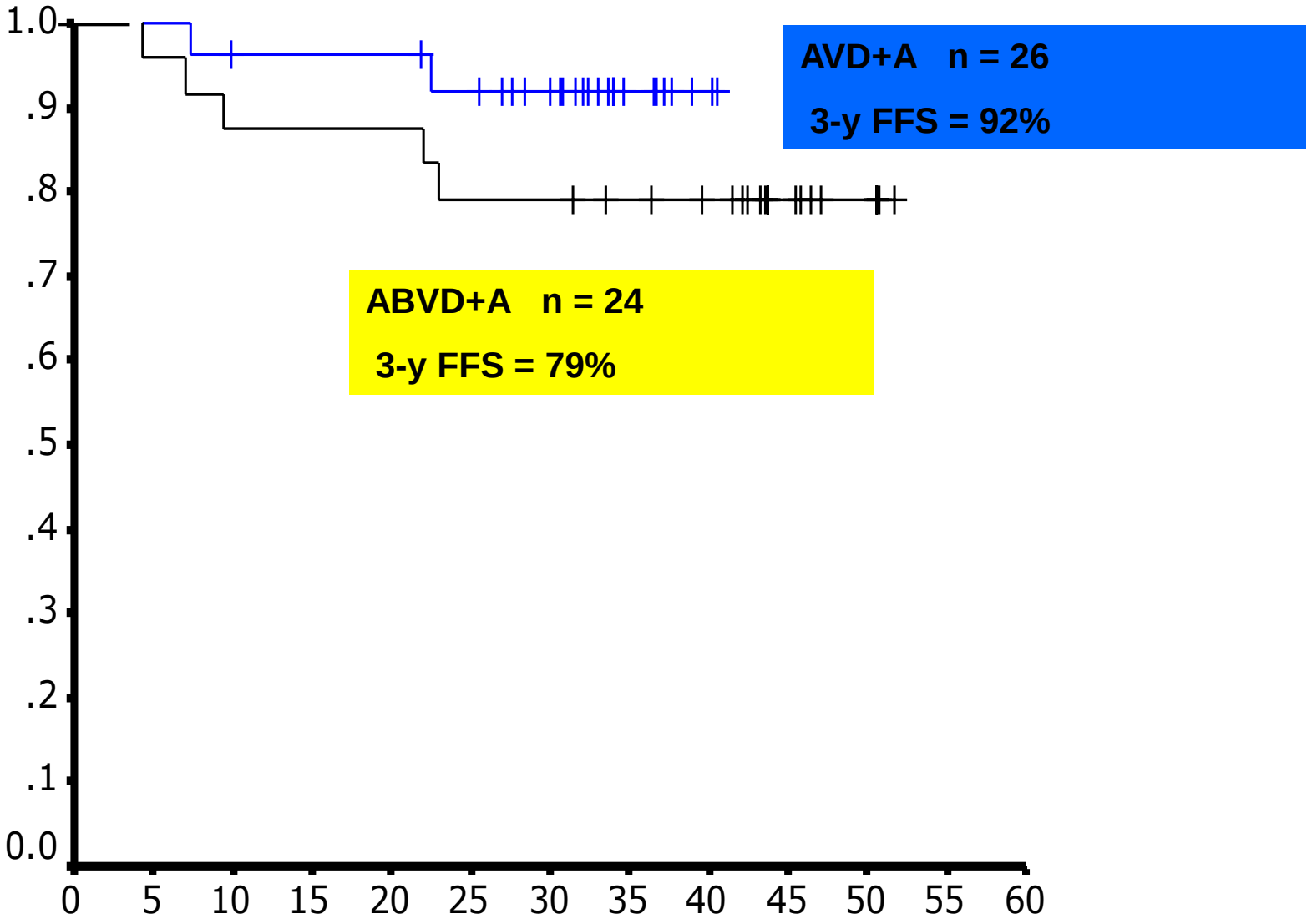

Failure-free Survival (months)

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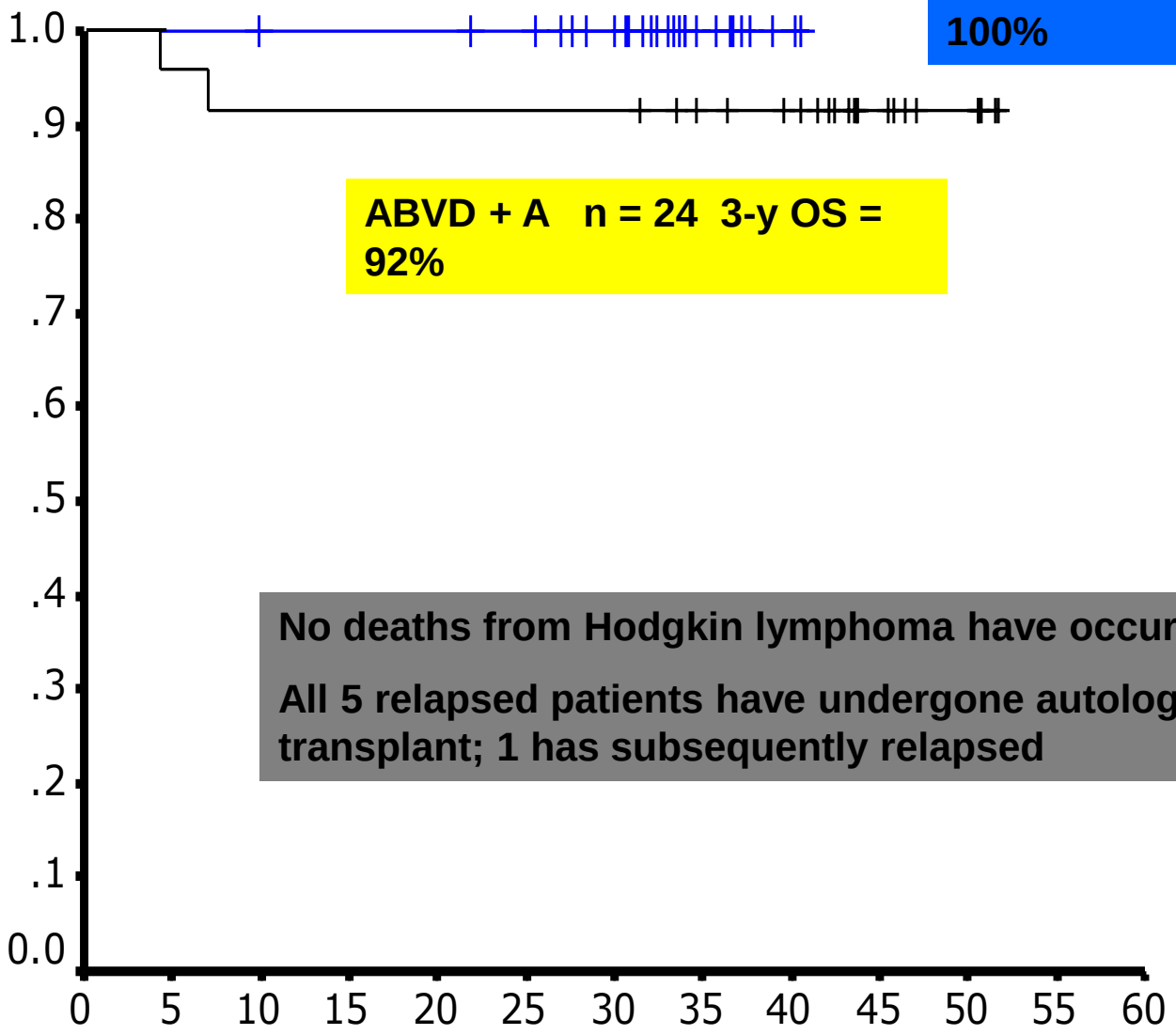

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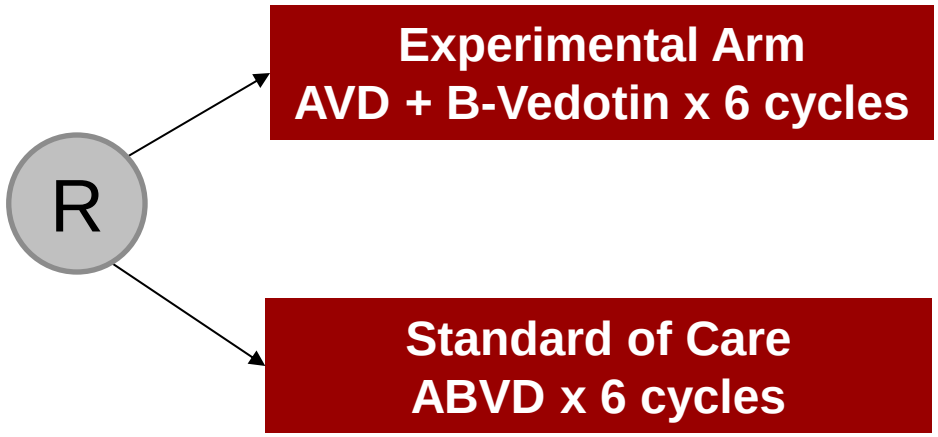
Phase III Frontline HL (ECHELON-1)

- **Design**

Newly Diagnosed Advanced Stage cHL Patients
≥18 y



- **Target n = 1040**
- **Primary outcome measure: Modified progression free survival (mPFS)**

Slide adapted from Takeda/Seattle Genetics

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My Critique

- **Follow-up is short**
- **Stage IIB patients were included**
- **BV should never be combined with Bleomycin and likely Gemcitabine; Studies will be initiated to see if BV can be safely combined with checkpoint inhibitors**

- **BV-AVD should be administered with growth factors, I prefer G-CSF days 6-9**

- **The design of the Echelon study leads one to believe that all patients will benefit from BV it the study is positive, one could argue that patients could receive 2 cycles of BV-AVD and if the interim PET is negative, de-escalate to AVD**

COH phase II trial of BV as first salvage therapy in relapsed/refractory HL prior to ASCT

Robert Chen[1], Joycelynne Palmer[2], Peter Martin[5], Ni-Chun Tsai[2], Young Kim[3], Sandra Thomas[1], Michelle Mott[1], Firoozeh Sahebi[1,4], Tanya Siddiqi[1], Saro Armenian[1], Yuan Shan[1], Leslie Popplewell[1], Stephen Forman[1]

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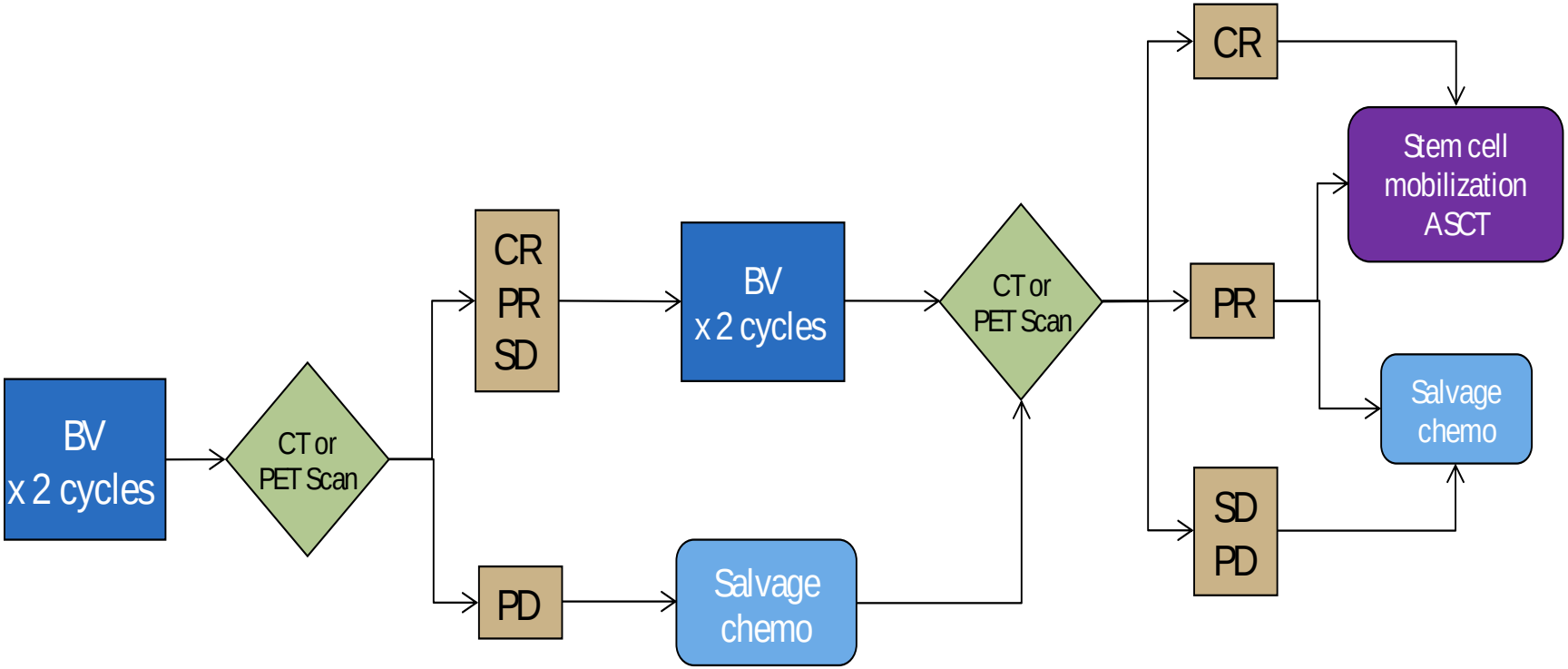
Study Schema



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Response Rate

	Best response	Best response at cycle 2	Response at cycle 4 or EOT
ORR	25/36 (69%)	24/36 (67%)	22/36 (61%)
CR	13/36 (36%)	13/36 (36%)	13/36 (36%)
PR	12/36 (33%)	11/36 (31%)	9/36 (25%)
SD	10/36 (28%)	11/36 (31%)	10/36 (27%)
PD	1/36 (3%)	1/36 (3%)	4/36 (11%)

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

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ASCT

- **33/37 successfully proceeded to ASCT (89%): 1 went to allo-HCT, 3 could not be salvaged**
- **17/33 (52%) received BV only**
- **16/37 (48%) received additional salvage chemotherapy (ICE/DICE/IGEV/GVD)**
- **13 CR and 4/12 PR went to ASCT directly**
- **24/33 (73%) were in CR at time of ASCT**

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My Critique

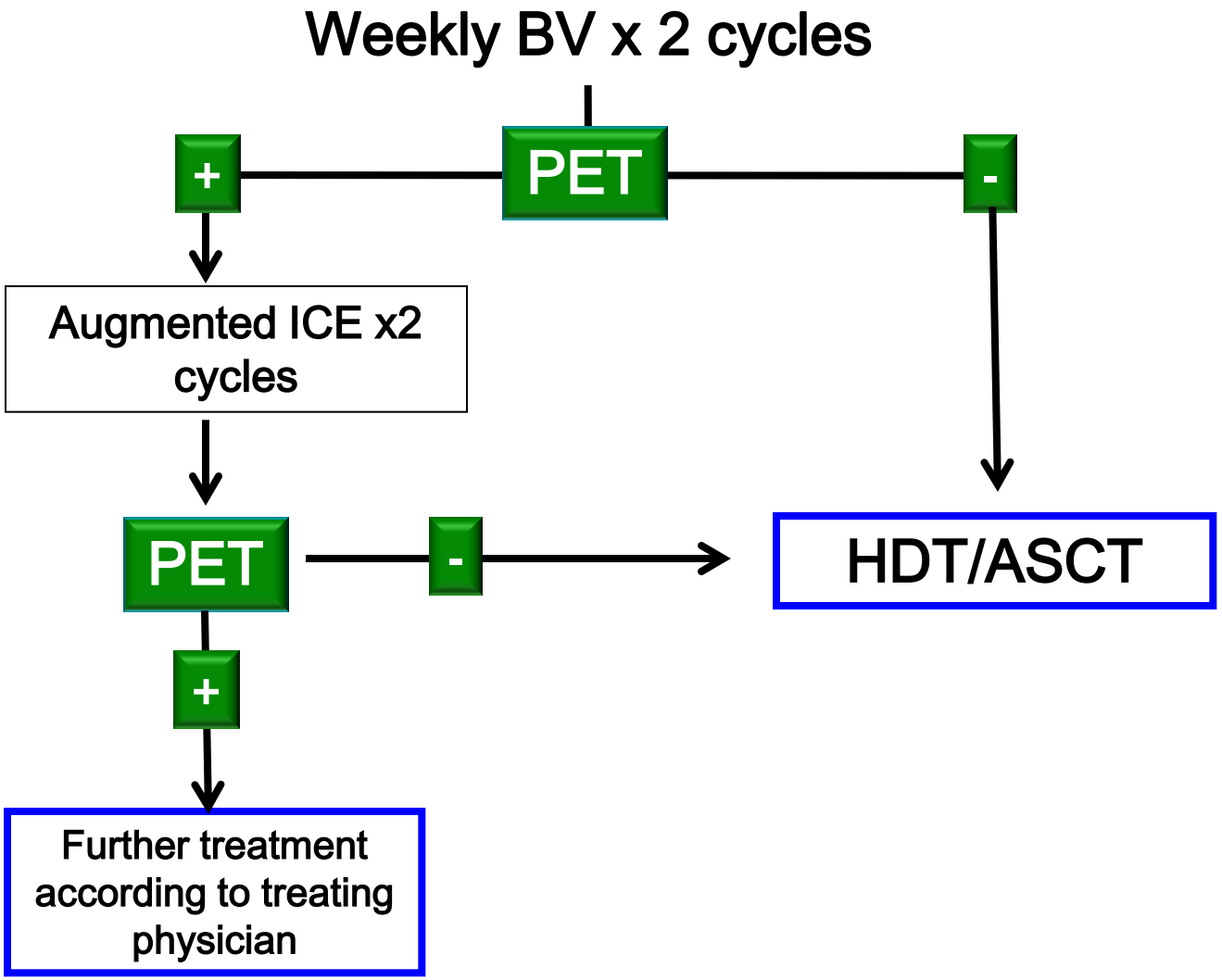
- **The CR rate is most important endpoint for salvage tx in H; 36% with BV; luckily it nearly always happens at the first restaging, hence no “bridge burning”**

- **Study is not an intent to treat design and the chemotherapy-based salvage regimen was not fixed for type, dose, or number of cycles**

MSKCC 11-142: Relapsed/refractory HL

First TX following upfront therapy

Lancet Oncology 16, No 3, 284-292, March 2015



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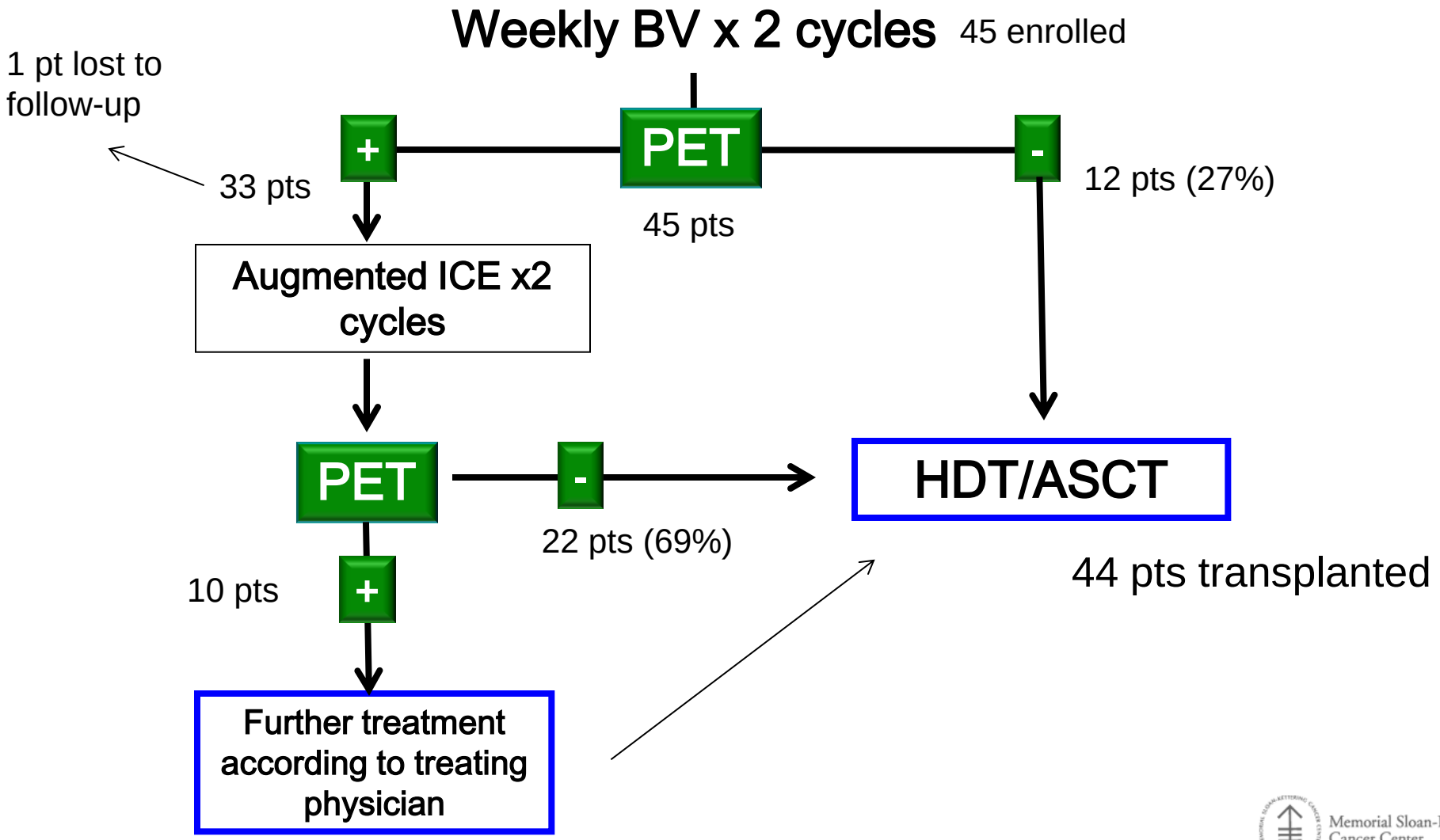
MSKCC 11-142

45 evaluable patients



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Deauville response to salvage therapy

BV (n=45)

Deauville score	n
1	4
2	8
3	8
4	21
5	4

AugICE (n=32)

Deauville score	n
1	8
2	14
3	2
4	8
5	

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Adverse events due to BV in at least 10% of patients

- **Neuropathy: 58%**
  grade 1: 17 (43%)
  grade 2: 6 (15%)

- **Rash: 73%**
  grade 1: 22 (55%)
  grade 2: 6 (15%)
  grade 3: 1 (3%)

- **Systemic steroids administered: 10 (25%)**

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Post-salvage outcome

- 80% CR (Deauville 2) following BV +/- AugICE
- 10 patients did not achieve CR
  - 3 proceeded directly to ASCT (2 deauville 3, 1 deauville 4)
  - 6 received involved field RT followed by ASCT
  - 1 (not eligible for RT) received 3rd AugICE (SD) then ASCT
- Stem cell collection
  - BV alone:
    - Median 6.3 x 10^6/kg (range 2.96-13.29 x10^6/kg)
  - BV-> AugICE
    - Median 9.4 x 10^6/kg (range 5.15-31.43 x10^6/kg)
- Conditioning
  - Chemo (BEAM, CBV): 36
  - TLI/cytoxan/etoposide: 7
  - Pre-transplant IFRT: 17

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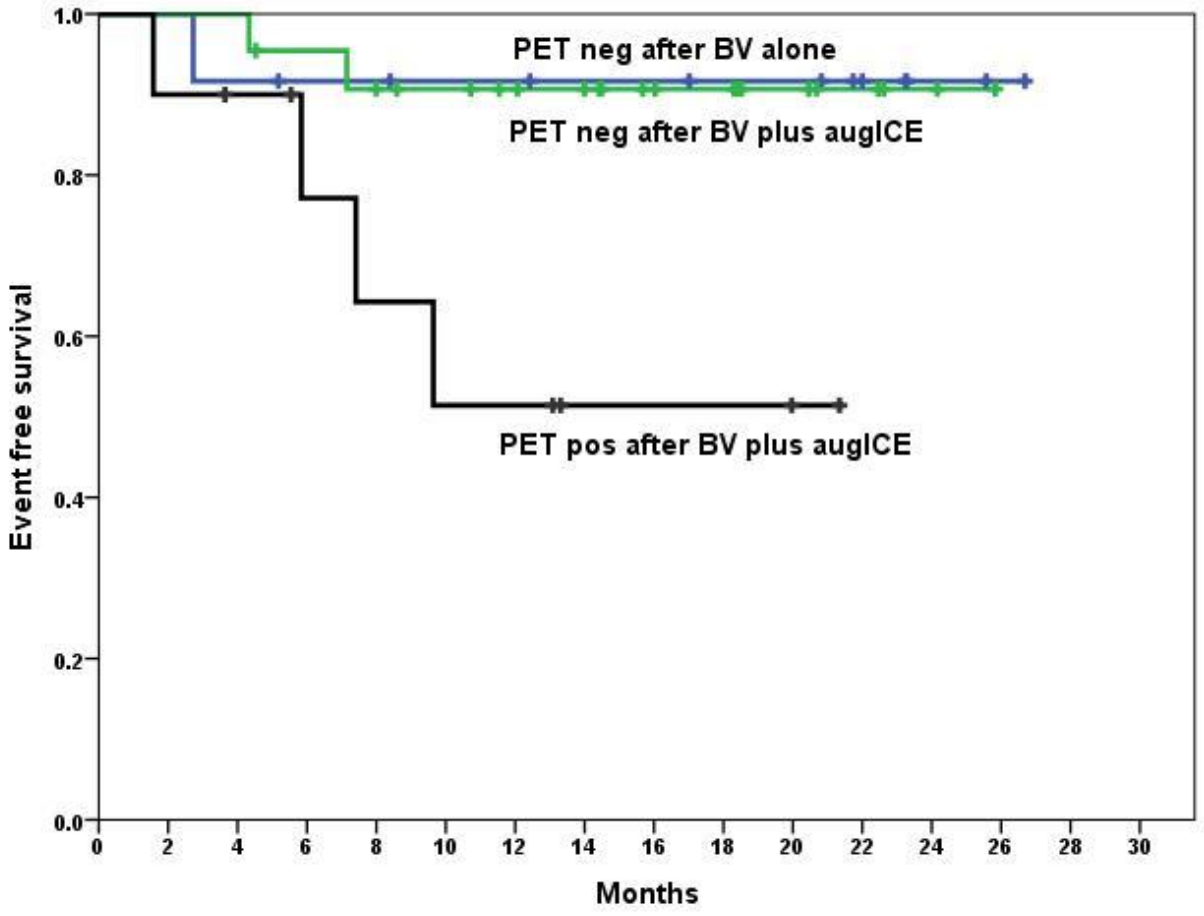
EFS according to treatment and PET status



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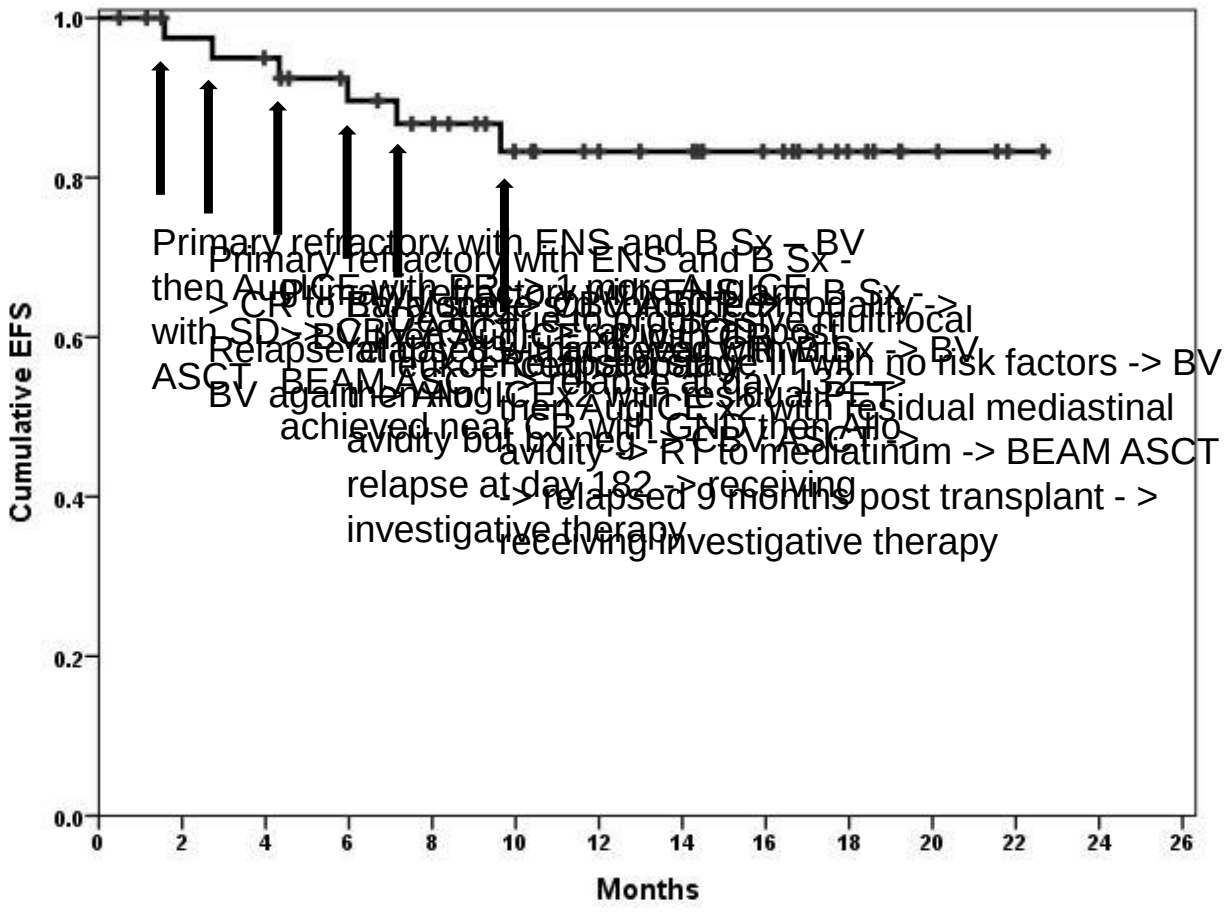
EFS for transplanted patients



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Brentuximab Vedotin in Combination with Bendamustine for Patients with Rel/Ref HL

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

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

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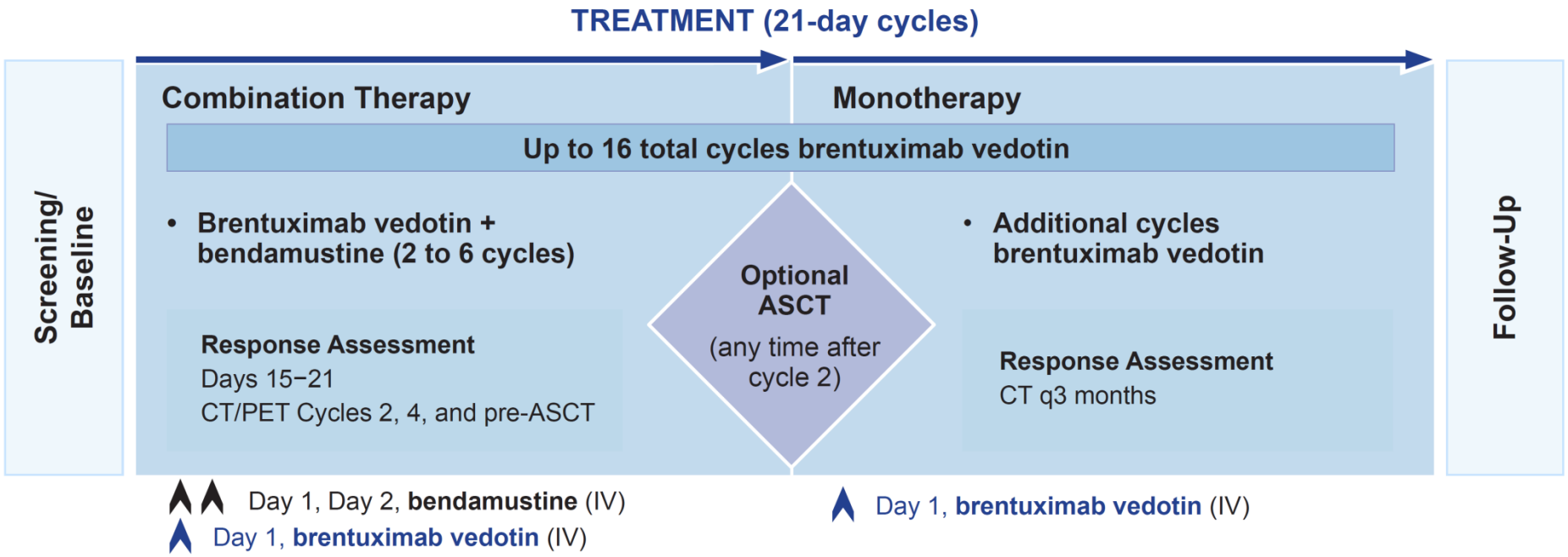
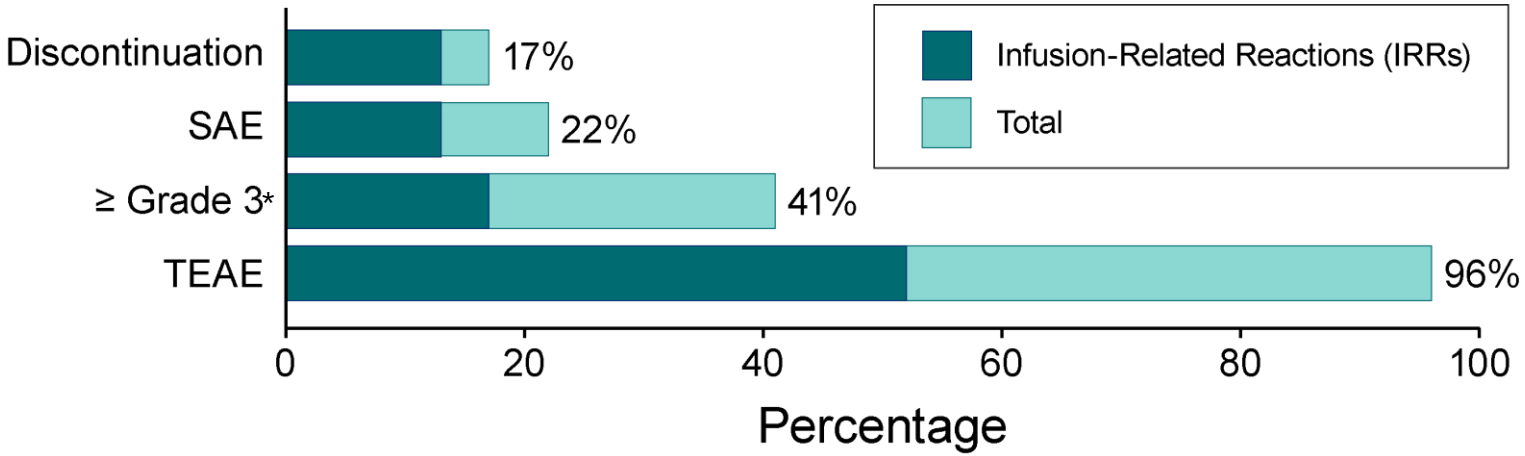
Study Design



Main eligibility: ≥18 years old, Classical HL, R/R disease after frontline chemotherapy, ECOG performance status 0–2

CT.gov #NCT01874054

Adverse Events on Combination Therapy

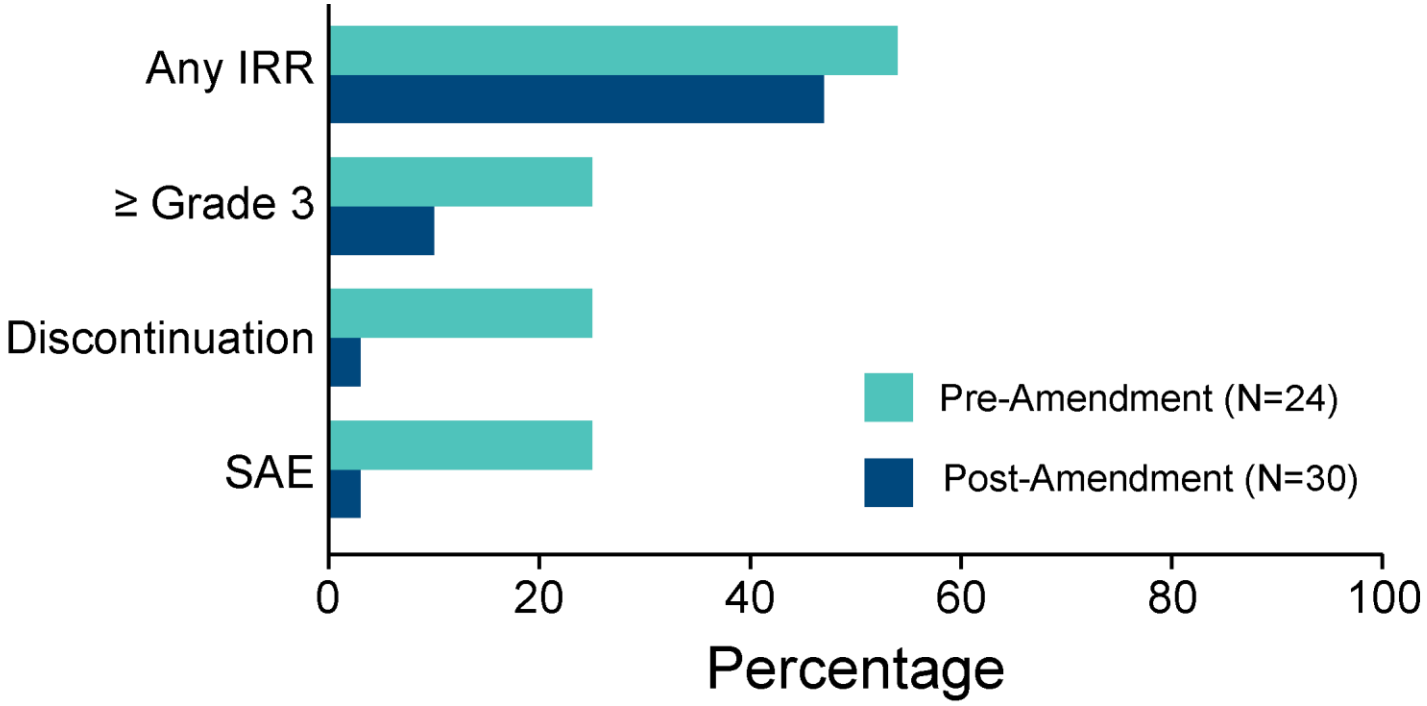


* Grade 3 IRR per NCI CTCAE 4.03: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae

- Main toxicities observed on combination treatment were IRRs
  - Dyspnea (15%), chills (13%) and flushing (13%) were most common symptoms; hypotension requiring vasopressor support also occurred
  - Majority of reactions occurred within 24 hrs of Cycle 2 infusion and were considered related to both agents
- Delayed hypersensitivity reactions also occurred, the most common of which was rash (14 patients up to 22 days after infusion)

IRR Premedication

- Protocol was amended to require premedication with corticosteroids and antihistamines
- Premedication decreased severity of IRRs



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Best Response on Combination Therapy

	N=48	
	n (%)	95% CI
Best clinical response*		
Complete remission (CR)	40 (83)	69.8. 92.5
Partial remission (PR)	6 (13)	
Stable disease (SD)	1 (2)	
Progressive disease (PD)	1 (2)	
Objective response rate (ORR [CR + PR])	46 (96)	85.8, 99.5

*Prior to ASCT

- Majority of CRs (34/40) achieved at Cycle 2 restage

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Stem Cell Mobilization and Collection

	N=33
Median number of apheresis sessions, (range)	2 (1–5)
Median CD34+ cell yield (cells/kg), (range)	4.0×10^6 (1.7–11.8)
$>2 \times 10^6$ Cells Collected, n	32*

*Patient with 1.7 $x10^6$ cells collected was able to undergo transplant with engraftment

- First-line mobilization (G-CSF alone or combined with plerixafor) successful in all but 1 patient*
- Approximately half of patients who underwent mobilization (17/33) did so after 2 treatment cycles
- Median time to platelet and neutrophil engraftment <2 weeks

* Patient underwent bone marrow harvest due to failure of G-CSF (rescue plerixafor not used)

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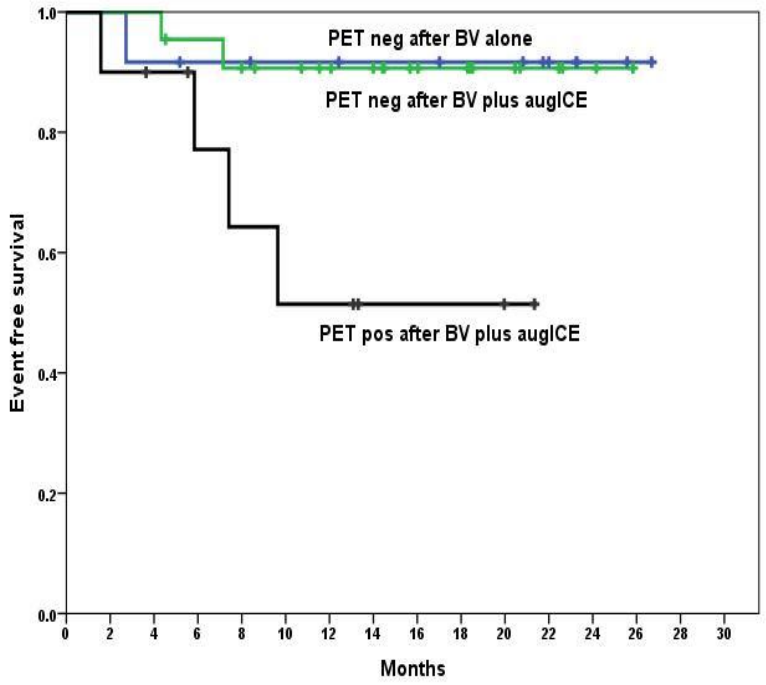
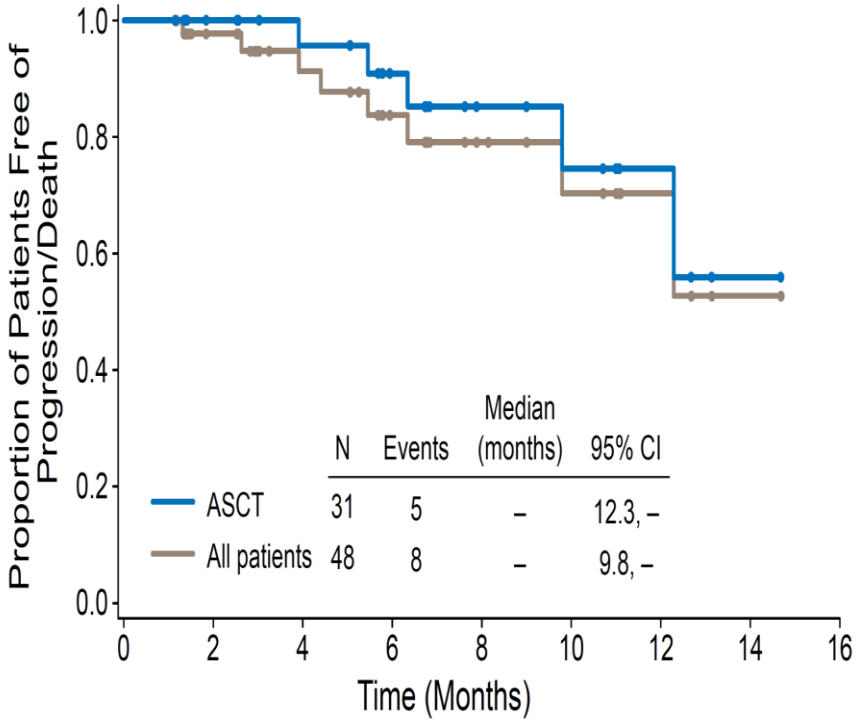
EFS: MSKCC 11-142 vs. Benda-BV





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My Critque

- **I am concerned that there is a number of relapses early post-ASCT in pts that were in CR pre-ASCT this has not been seen in other cohorts**

- **PBPC mobilization as expected is not robust**

The AETHERA Trial: Results of a Randomized, Double-Blind, Placebo-Controlled Phase 3 Study of Brentuximab Vedotin in the Treatment of Patients at Risk of Progression Following Autologous Stem Cell Transplant for HL

CH Moskowitz, A Nademanee, T Masszi, E Agura, J Holowiecki, MH Abidi, AI Chen, P Stiff, AM Gianni, A Carella, D Osmanov, V Bachanova, J Sweetenham, A Sureda, D Huebner, EK Larsen, NN Hunder, and J Walewski

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In press: The Lancet, March 19, 2015

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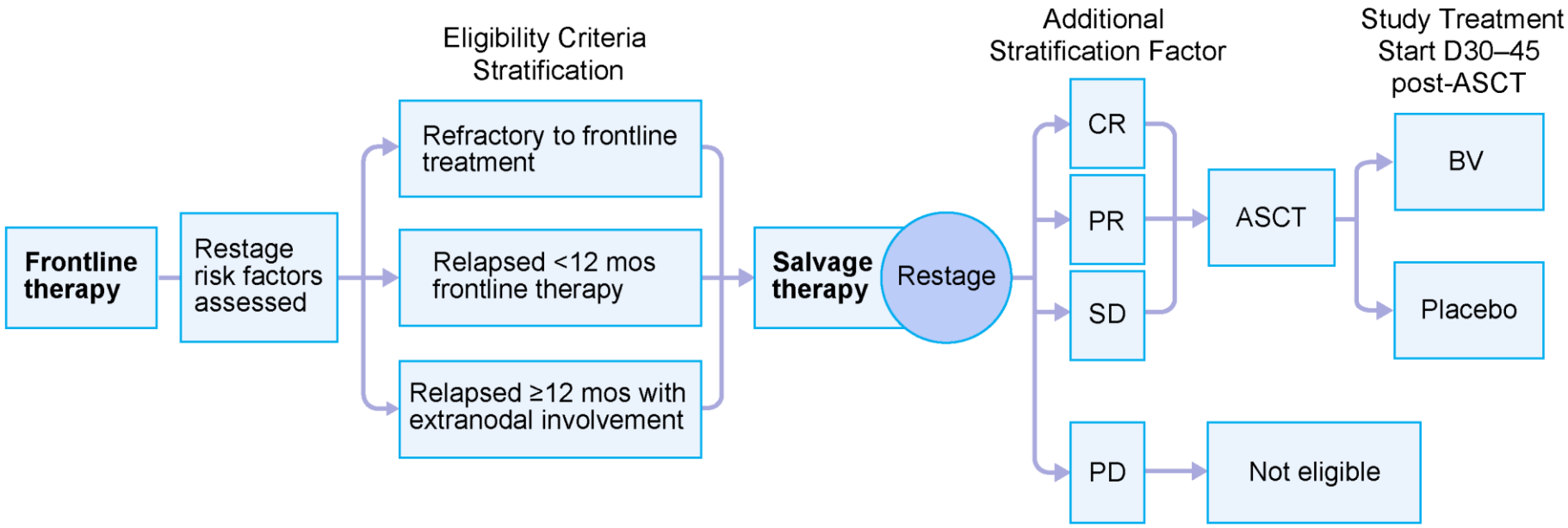
Study Design and Key Eligibility Criteria

- **329 patients were randomized at 78 sites in North America and Europe**



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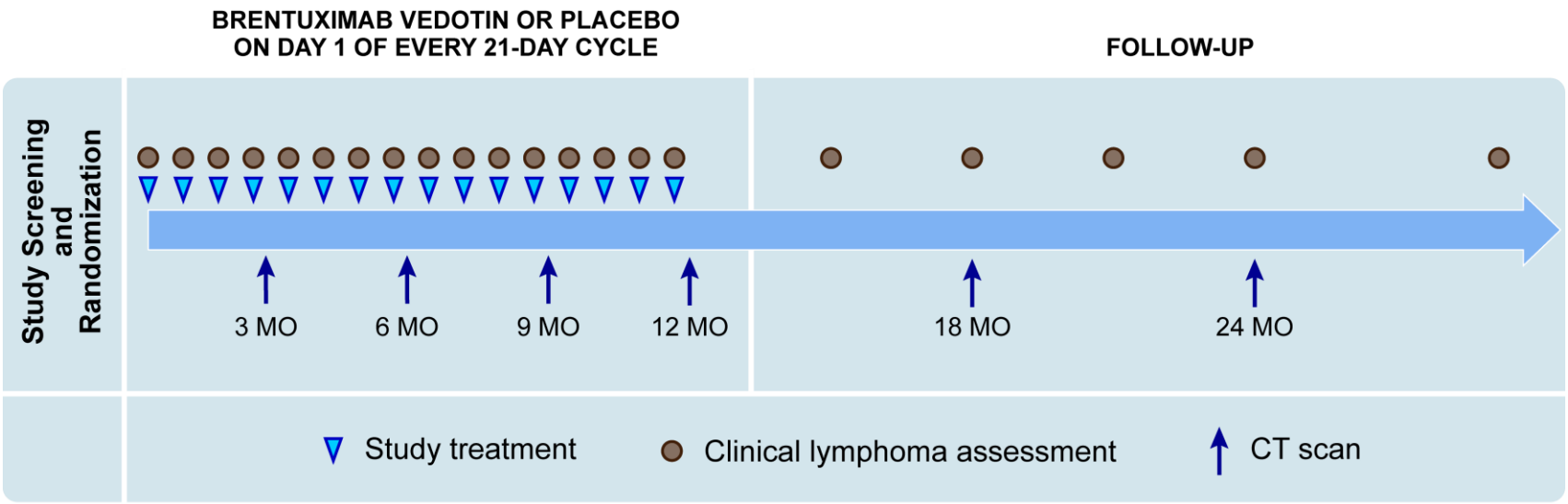
Treatment and Assessment Schedule

- Patients were randomized to receive 16 cycles of BV or placebo
- They were evaluated and treated every 21 days
- Imaging quarterly for first year, then at 18 and 24 months
- Importantly, patients who progressed on the placebo arm could subsequently receive BV on another trial



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Main Objectives

- **Primary**
  - **To compare progression-free survival (PFS) per independent review facility (IRF) between the 2 treatment arms**
- **Secondary**
  - **To compare overall survival (OS) between the 2 treatment arms**
  - **To evaluate the safety and tolerability of BV compared to placebo**

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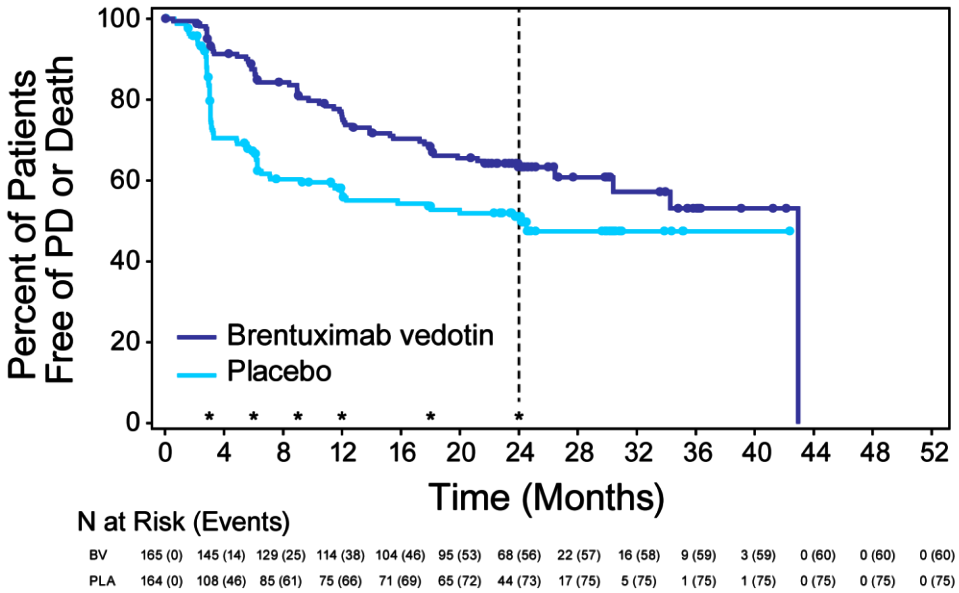
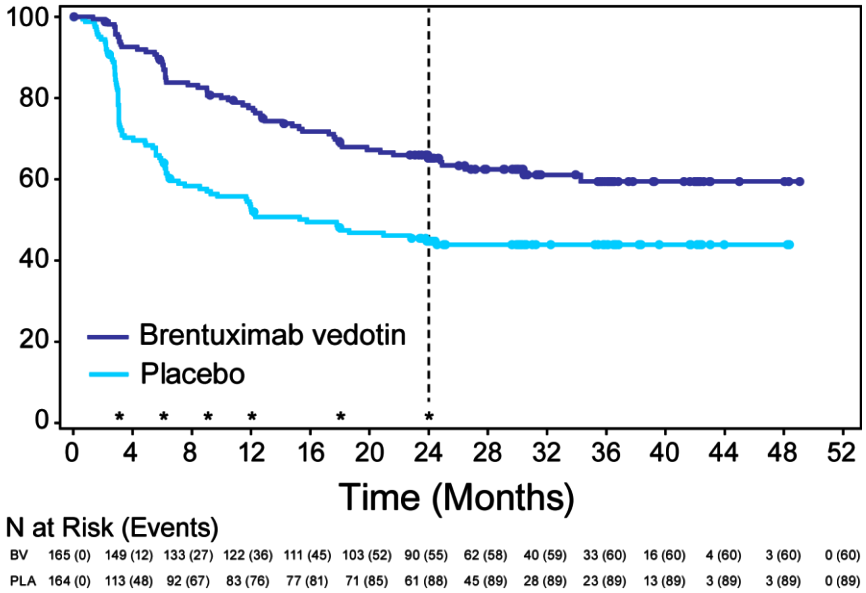
Progression-Free Survival





	BV (N=165)	Placebo (N=164)
Hazard Ratio (95% CI)	0.57 (0.40–0.81, P=0.001)	
Events	60	75
Median PFS (months)	43	24
2-year PFS rate	63%	51%

	BV (N=165)	Placebo (N=164)
Hazard Ratio (95% CI)	0.50 (0.36–0.70)	
Events	60	89
Median PFS (months)	--	16
2-year PFS rate	65%	45%

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Censoring Rules

Analysis	CT Scans (per IRF)	CT Scans (per INV)	Biopsy Reports	Lymphoma Assessments	Death
IRF	X		X		X
Investigator		X	X	X	X

	Number of Patients at Risk after 24 Months				
	28 Months	32 Months	36 Months	40 Months	44 Months
PFS per IRF	39	21	10	4	0
PFS per investigator	107	68	56	29	7

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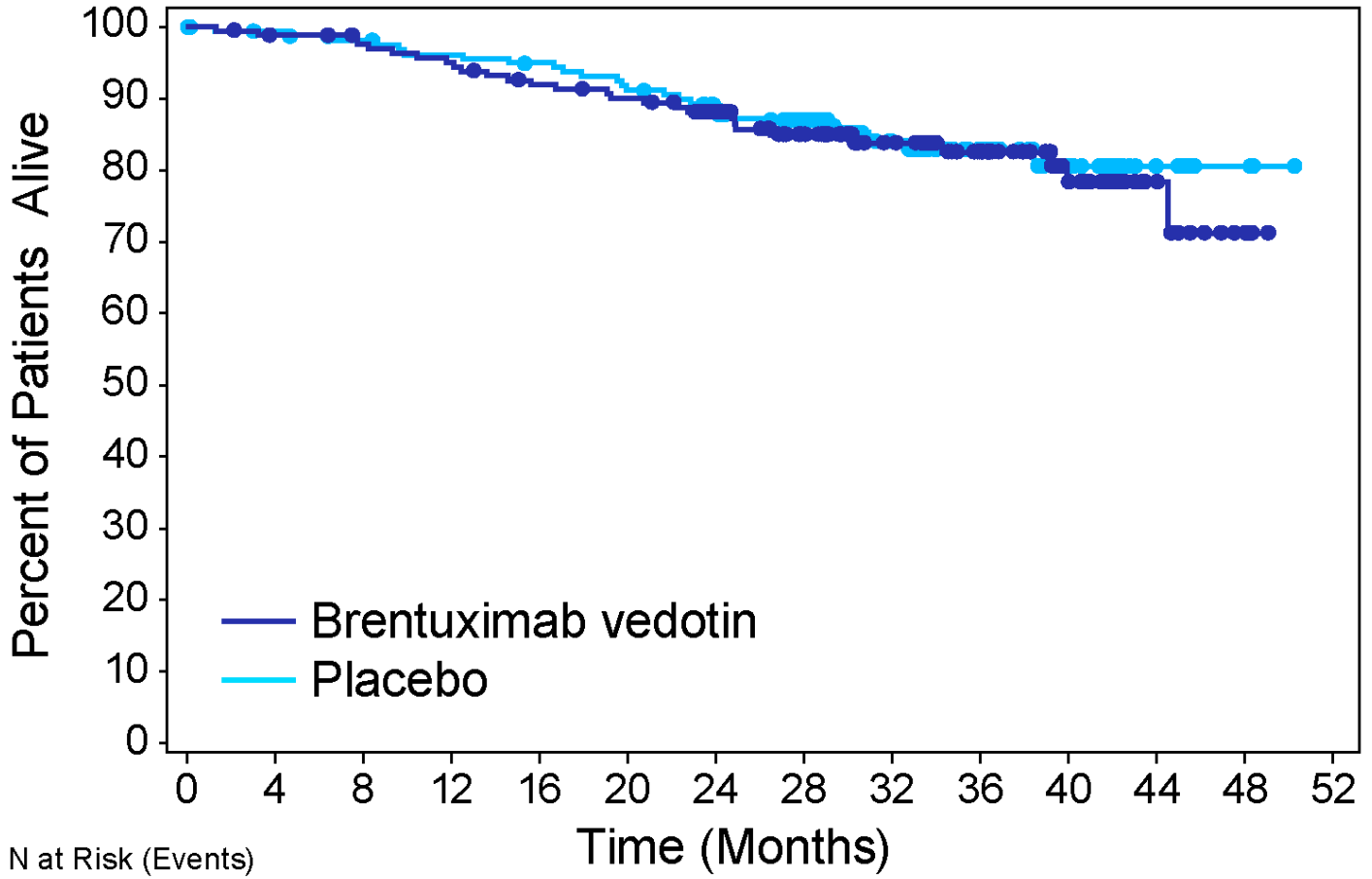
Overall Survival



N at Risk (Events)

BV	165 (0)	160 (2)	156 (4)	152 (8)	145 (13)	141 (16)	125 (19)	97 (23)	72 (24)	57 (25)	35 (27)	12 (27)	4 (28)	0 (28)
PLA	164 (0)	160 (1)	156 (3)	152 (6)	149 (8)	143 (14)	131 (18)	104 (20)	70 (23)	52 (24)	29 (25)	10 (25)	4 (25)	0 (25)

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PFS and OS by Number of Risk Factors

No. Risk Factors	N	PFS per IRF HR (95% CI)	PFS per Investigator HR (95% CI)	OS HR (95% CI)
≥1	329	0.57 (0.40–0.81)	0.50 (0.36, 0.70)	1.15 (0.67–1.97)
≥2*	280	0.49 (0.34–0.71)	0.40 (0.28, 0.57)	0.94 (0.53–1.67)
≥3*	166	0.43 (0.27–0.68)	0.38 (0.25, 0.58)	0.92 (0.45–1.88)

Risk Factors

- **Relapsed <12 months or refractory to frontline therapy**
- **Best response of PR or SD to most recent salvage therapy**
- **Extranodal disease at pre-ASCT relapse**
- **B symptoms at pre-ASCT relapse**
- **Two or more prior salvage therapies**

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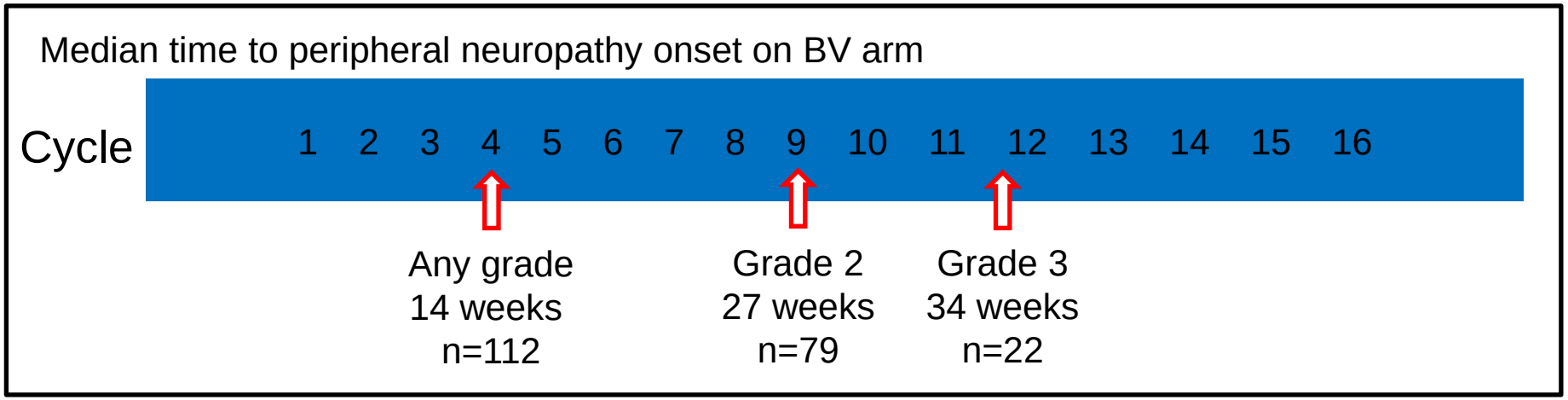
Peripheral Neuropathy*

	BV (N=167) n (%)	Placebo (N=160) n (%)
Any treatment-emergent peripheral neuropathy	112 (67)	31 (19)
Grade 3	22 (13)	2 (1)
Grade 4	0	0



*Standardized MedDRA Query (SMQ) analysis

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Conclusions

- **Early consolidation post-ASCT with BV demonstrated improved PFS per IRF in HL patients with risk factors for relapse or progression (HR=0.57, P=0.001)**
  - **PFS benefit was sustained, with 2-year PFS rates per investigator of 65% and 45% on the BV and placebo arms, respectively**
  - **Consistent benefit was observed across subgroups**
- **Interim analysis of overall survival did not show a significant difference between treatment arms (P=0.62)**
  - **Analysis limited by small number of events and the large number of patients on the placebo arm crossing over to BV after progression**
  - **More patients on the placebo arm received subsequent anti-tumor therapy and/or allogeneic stem cell transplant**
- **Consolidation therapy was generally well tolerated**
  - **Peripheral sensory neuropathy and neutropenia were common, and were manageable with dose reductions or delays**
  - **Two deaths occurred within 40 days of dosing with BV**
- **BV consolidation therapy is an important therapeutic option for HL patients undergoing ASCT to reduce the risk of relapse or progression**

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Interesting Case

Segue to checkpoint inhibition in HL

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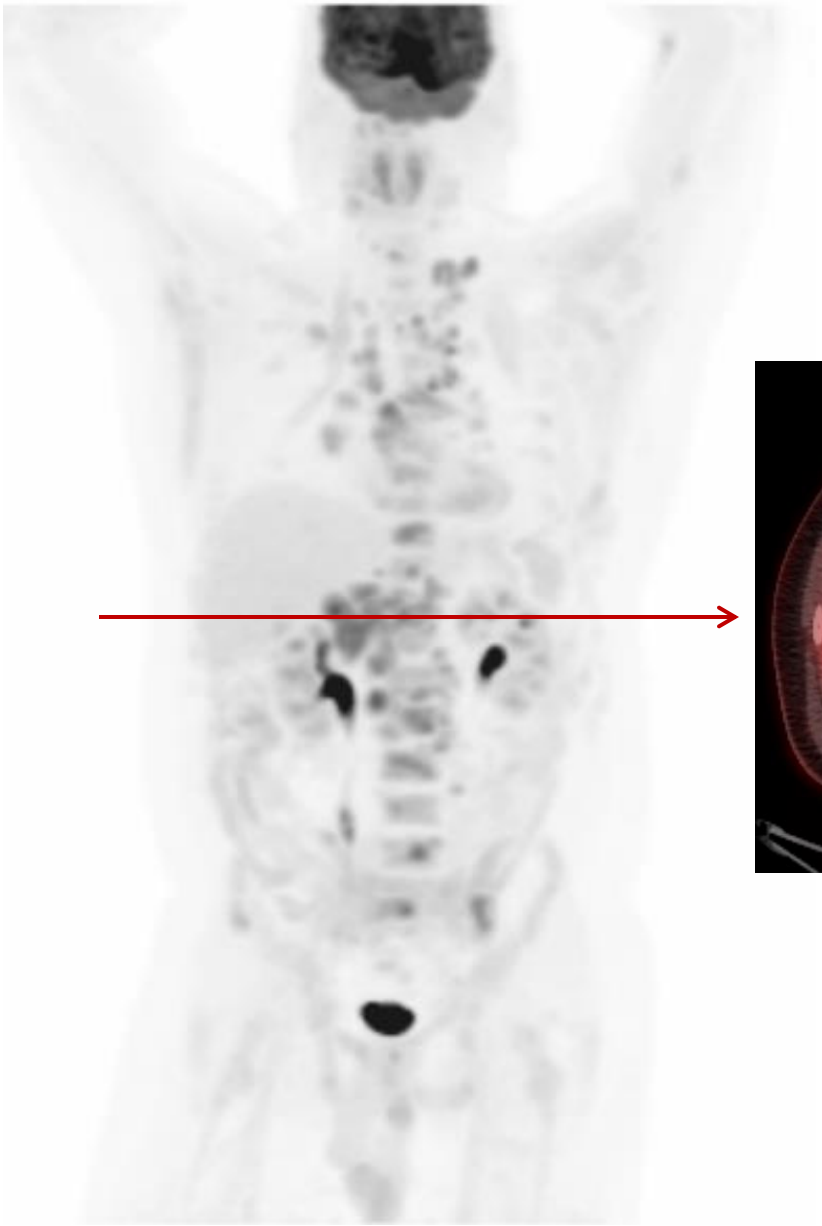
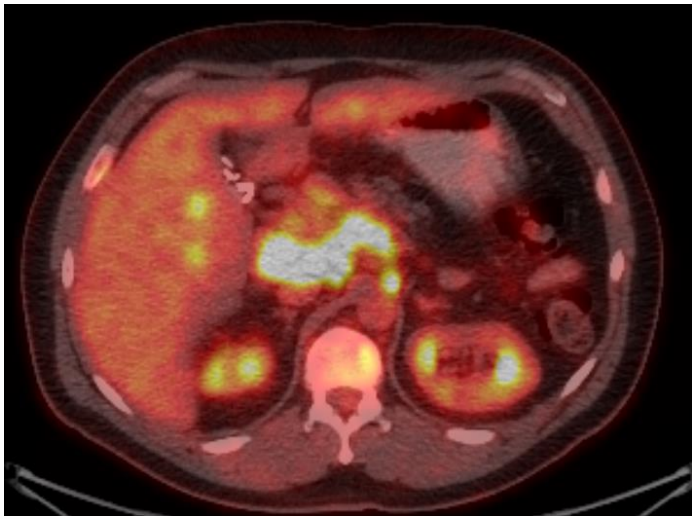
Patient: AH, Primary Ref HL

- **ABVD, DHAP, BV-PR**
- **8/2013: BEAM → auto-SCT with plan for post-SCT axillary XRT**
- **11/2013: PET-CT with worsening R axillary LAD**
- **11-12/2013: XRT 4400 cGy to R axilla**
- **2/14, 6/14, 9/14: slowly progressive PET-avid LAD in mediastinal, hilar, RP LN and bone disease in 9/2014**
  - **Mediastinal surgical biopsy 9/22/14: relapsed dz**



PET-CT (9/14)

1. increased mediastinal LAD including subcarinal LN 2.8 x 2.1 intensely avid, L supraclavicular, innumerable RP LN including conglomerate portocaval LN 4.1 x 2.6 from 3.4 x 1.6 cm
2. multiple foci of FDG activity within axial skeleton.



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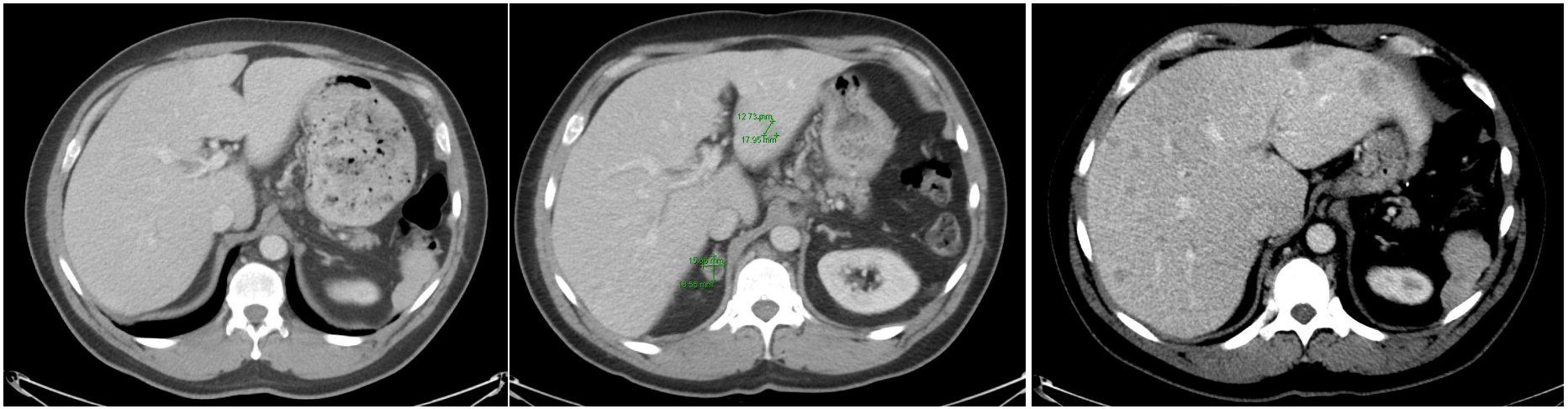
Patient: AH, continued

- **Off protocol salvage options: MOPP, GVD, Bendamustine**
- **Enrolled in 12-142: Ipilimumab + Nivolumab**
  - **11/13/14: Ipi/Nivo C1 (c/b leukocytosis, fevers)**
  - **12/3/14: Ipi/Nivo C2**
  - **12/24/14: Ipi/Nivo C3**
  - **1/2014: Ipi/Nivo C4**



- **12/2014 CT: mixed response with new hypointense liver lesions but stable by immune response criteria: continued nivolumab alone q2w x2c**
- **02/2015: increase and development of multiple new liver lesions**
  - **Given dramatic clinical improvement (resolution of B symptoms), arranged for liver biopsy**
- **2/20/15: Liver, right lobe biopsy: benign liver parenchyma with mild, predominantly portal chronic inflammation. No evidence of lymphoma seen. Note: Additional deeper levels were obtained. Performed immunohistochemical stains reveal that the majority of inflammatory cells are CD3 positive T cells.**

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Lymphoma* and Lymphoma Transplant** Services-MSKCC

- John Gerecitano*
- Paul Hamlin*
- Steve Horwitz*
- Anita Kumar*
- Matthew Matasar*/**
- Alison Moskowitz*
- Craig Moskowitz*/**
- Ariela Noy*
- Lia Palomba*
- Miguel Perales**
- Carol Portlock*
- Craig Sauter**
- David Straus*
- Joachim Yahalom*/**
- Anas Younes*
- Andrew Zelenetz*