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The status of HL in the near future

Impact of Brentuximab vedotin, the Checkpoint inhibitors

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Professor of Medicine, Weill Medical College of Cornell University

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Rel/Ref HL

Major changes are here!

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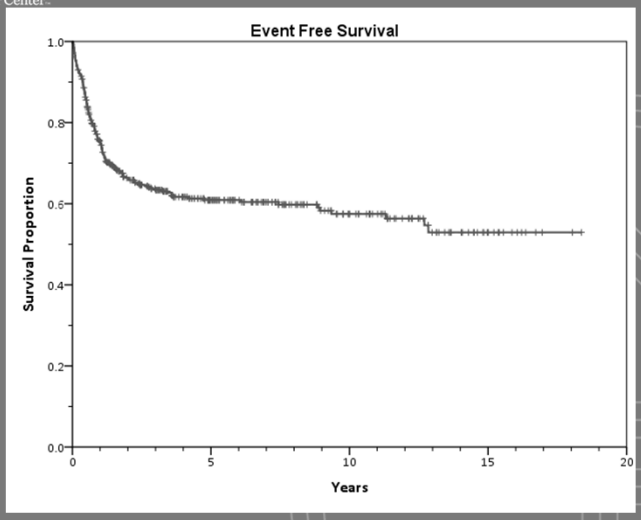

MSKCC- Intent to treat data EFS: 1994-2014,
Primary Refractory and Relapsed HL pts enrolled on ICE-based salvage regimen clinical trials

Subjects	Events	Censored
431	164	267

Current Patient Populations with Rel/Ref HL

- Relapsed ASHL
- Primary refractory ASHL
- Relapsed or primary refractory ESHL treated with full course chemotherapy or CMT-4 cycles of ABVD and ISRT

- *Relapsed or primary refractory ESHL treated with short course chemotherapy or 2+2 now with stage III-IV disease*
- *Primary Refractory ESHL treated with short course chemotherapy or 2+2 now with stage III-IV disease*

- **Relapsed ESHL treated with short course chemotherapy (3 or 4 cycles of ABVD) or 2 cycles of ABVD and 20Gy ISRT (2+2) now with stage I-II disease –out of field if radiated**
- **Primary Refractory ESHL treated with short course chemotherapy or 2+2 now with stage I-II disease-out of field if radiated**

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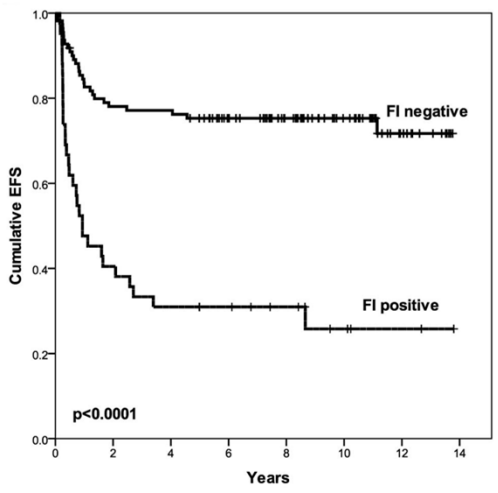
How important is pre-ASCT PET status in HL

Very, but not the whole story

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



Moskowitz, AJ. Blood 2010.

- 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

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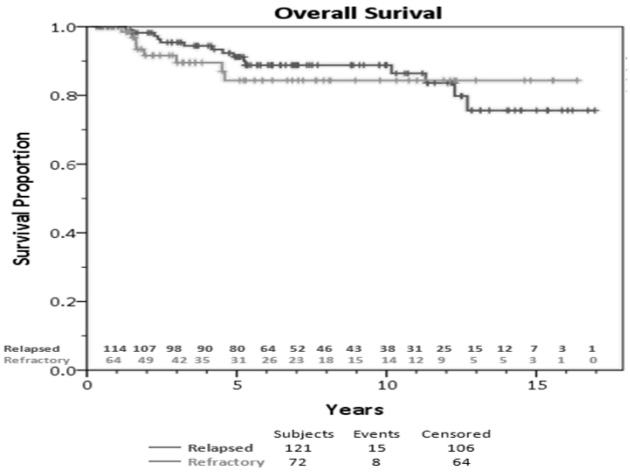
Patients transplanted in CR at MSKCC 1994-2012
Brentuximab Vedotin naïve , nodal only disease at time of salvage therapy



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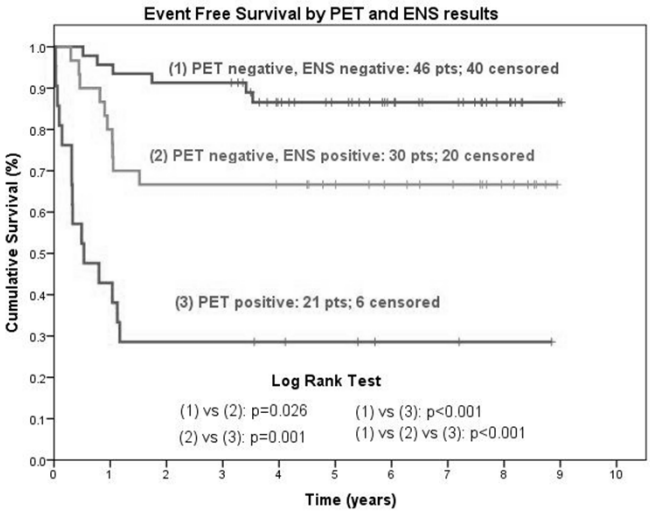
FDG-PET and ENS



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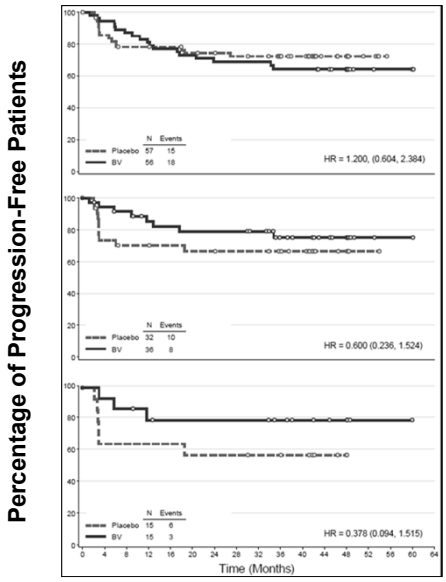
Pre-ASCT PET Negative



All

≥ 2 Risk Factors

Extranodal Disease at Relapse

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PET and rel/ref HL

- Maximum of 2 different salvage regimens can be used to achieve PET neg response
  - If 2 regimens needed definitely give post ASCT BV
- 80% of patients with nodal only disease in remission at time of ASCT are cured
  - Post-ASCT BV not likely needed
- Stage IV or EN disease predicts for an unfavorable outcome in PET negative patients
  - Post-ASCT BV should be given
- Pts with PET-avid disease have <50% cure and if stage IV disease then outcome is poor
  - All pts with PET avid disease should receive post-ASCT BV

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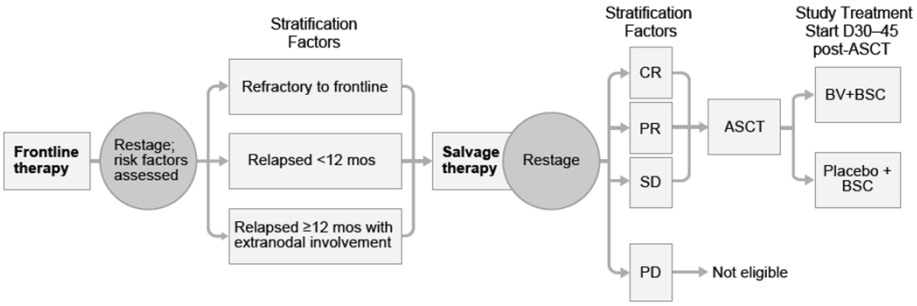
Updated Efficacy and Safety Data from the AETHERA Trial of Consolidation with Brentuximab Vedotin after Autologous Stem Cell Transplant (ASCT) in Hodgkin Lymphoma Patients at High Risk of Relapse

Should post-ASCT consolidation with BV be administered to all patients?

Key Eligibility Criteria and Stratification



- Randomization stratified by
  - Risk factors after frontline therapy
  - Best clinical response to salvage therapy before ASCT
- Patients with progressive disease after salvage therapy were not eligible

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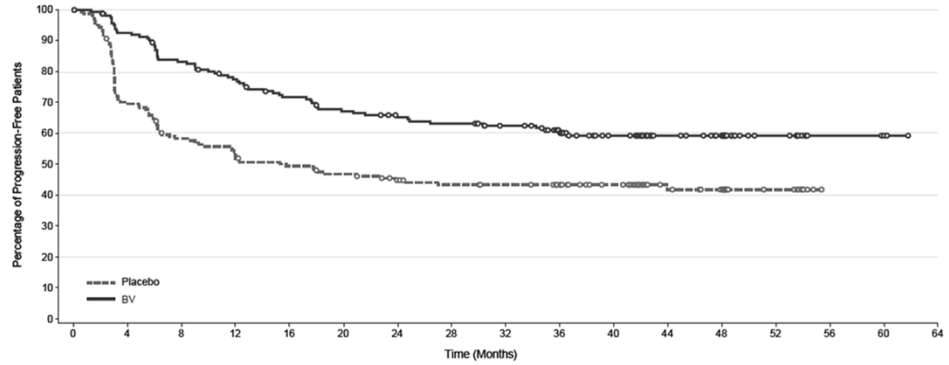
Results

PFS* per Investigator – 3 Years Since Last Patient Randomized



N at Risk (Events)

BV	165 (0)	149 (12)	133 (27)	122 (36)	111 (45)	103 (52)	97 (55)	94 (58)	87 (59)	74 (61)	56 (63)	39 (63)	32 (63)	13 (63)	4 (63)	3 (63)	0 (63)
Placebo	164 (0)	113 (48)	92 (67)	83 (76)	77 (81)	72 (85)	65 (88)	61 (90)	59 (90)	54 (90)	44 (90)	26 (91)	22 (91)	9 (91)	0 (91)	0 (91)	0 (91)

	Treatment cycles (median)	Events	PFS Rate, % (95% CI) 24 months	PFS Rate, % (95% CI) 36 months	Median PFS (mos)	Hazard ratio
BV (N=165)	15	63	65 (57, 72)	61 (53, 68)	–	0.52
Placebo (N=164)	15	91	45 (37, 52)	43 (36, 51)	15.8	

*Includes clinical assessments of lymphoma

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
- 2 or more prior salvage therapies

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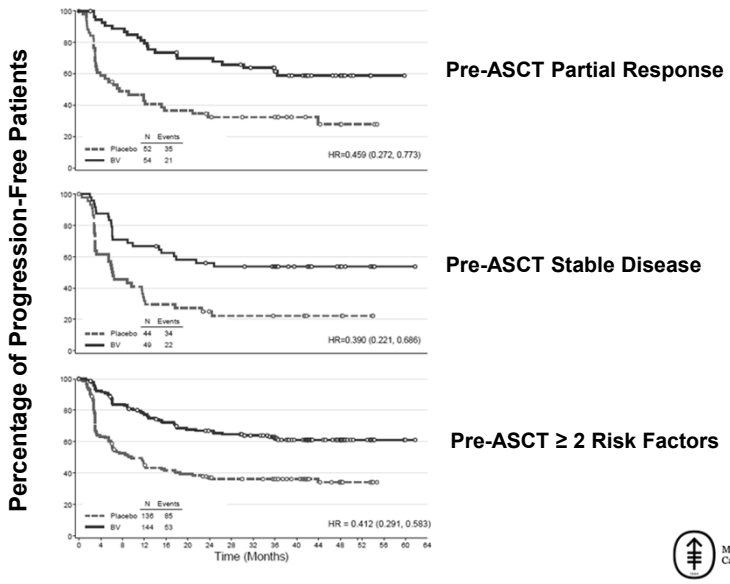
Pre-ASCT Subgroup Analysis



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PET data and Aethera

- Not prospectively done but about 2/3 had one pre-ASCT
- Not centrally read
- No standard criteria for what is positive or negative

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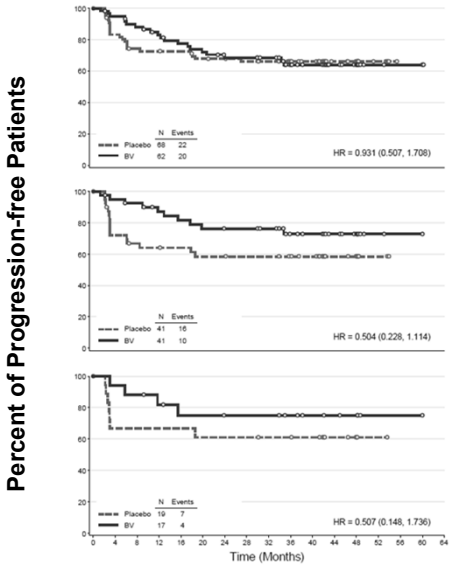
Pre-ASCT Complete Response



All

≥ 2 Risk Factors

Extranodal Disease at Relapse

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Peripheral Neuropathy (SMQ)—BV Arm

- 112/167 (67%) patients reported PN; 22 of these patients reported a maximum Grade 3 event. No PN event was ≥ Grade 4

N = 112	Sep 2014 n (%)	Oct 2015 n (%)
Resolution or improvement	95 (85)	99 (88)
Complete resolution	66 (59)	74 (66)

- 38/112 patients had ongoing PN at last assessment
  - 15 are off study and can no longer be followed for resolution
  - 23 patients remaining on study have ongoing PN
- Of patients remaining on study with ongoing PN
  - 17 have maximum Grade 1
  - 5 have maximum Grade 2
  - 1 has maximum Grade 3 (patient has ongoing Grade 3 radiation myelitis confounding assessment of PN)

SMQ = standardized MedDRA query; includes peripheral sensory neuropathy, peripheral motor neuropathy, paresthesia, muscular weakness, hypoesthesia, gait disturbance, neuralgia, amyotrophy, decreased vibratory sense, hyporeflexia, peroneal nerve palsy, and sensory disturbance

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BV-AVD or BV as part of salvage

- Common Sense approach
  - CR to BV-AVD with a remission duration of a least 6 months then I use an Aethera approach provided that pts have risk factors
  - CR < 6 months or primary refractory disease then no more BV
  - Less than a PR to pre-ASCT, BV makes no sense to use post-ASCT, regardless of risk factors

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The issue of OS

- In the era of BV, Checkpoint inhibition, HDACs, and MTOR inhibitors median survival at MSKCC is greater than 5 years
- The wait will be long for Aethera but it will be assessed till 2019

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The issue of neuropathy

- Any pt who has grade II neuropathy pre-BV should not get it
- If Grade II develops reduce to 1.2 mg/kg
- If grade III develops stop BV

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Does BV as part of salvage impact outcome?

5 studies: same goal-PET negative CR

- CR rate with 2 cycles of ICE is 60%
- An attempt to avoid salvage therapy (published)
  - BV as a single agent
  - BV administered sequentially with ICE if necessary
- Adding multiple active agents (abstract only)
  - BV + bendamustine
  - BV+ DHAP
  - BV+ICE

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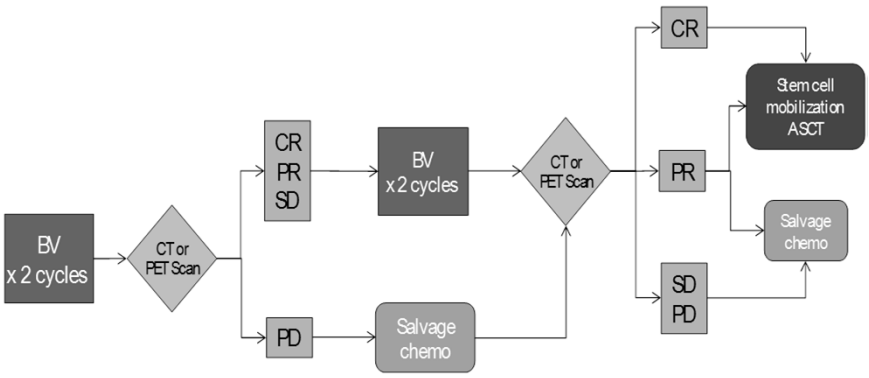
COH

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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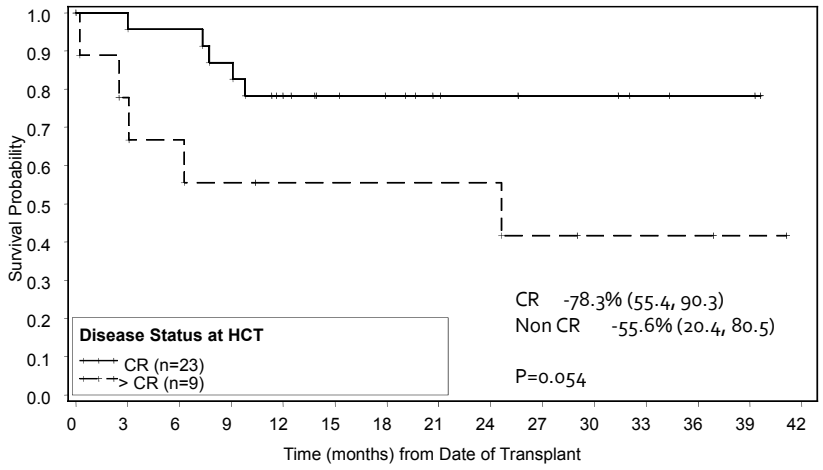
All patients-PFS
CR. Vs. non-CR



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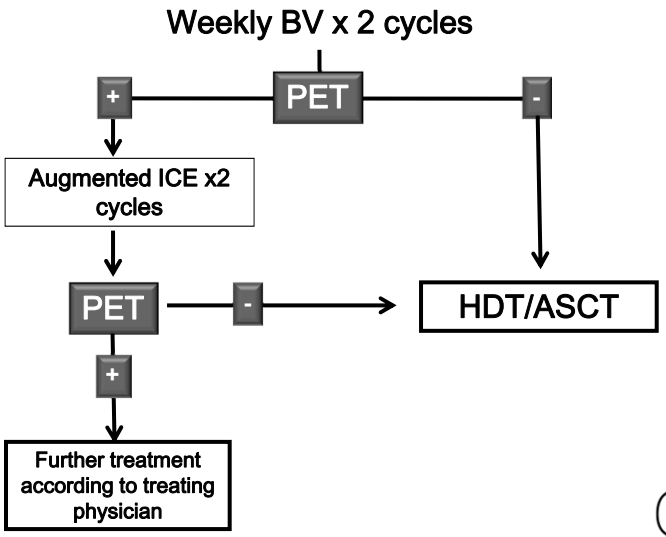
MSKCC 11-142: Relapsed/refractory HL

First TX following upfront therapy

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



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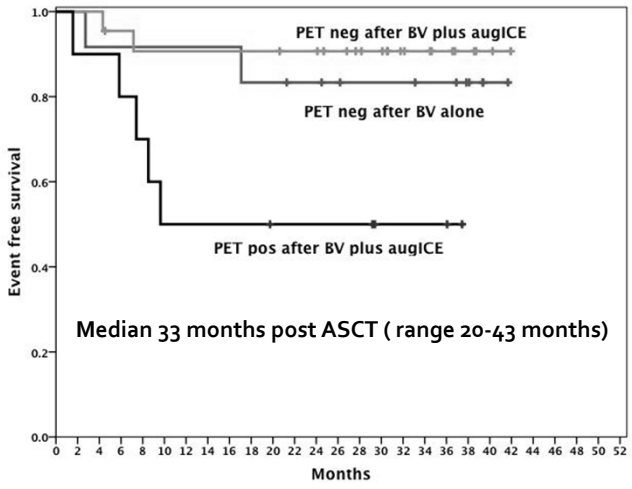
PET adapted therapy with BV and augICE Updated results



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

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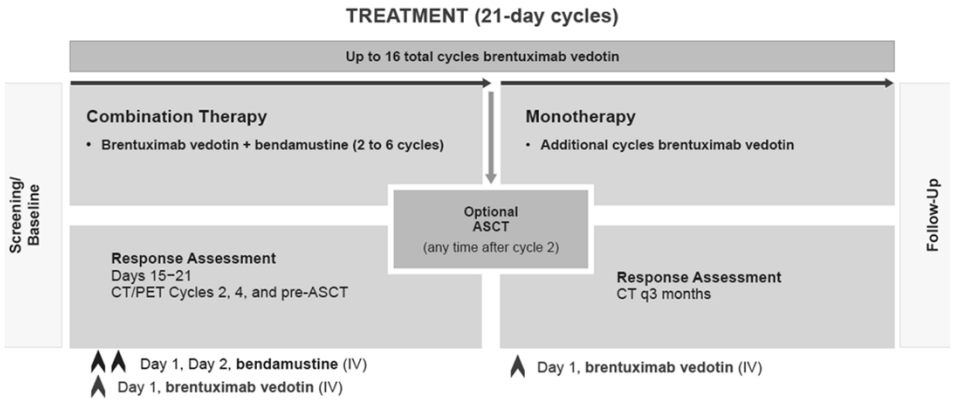
Brentuximab Vedotin Plus Bendamustine: A Highly Active Salvage Treatment Regimen for Patients with Relapsed or Refractory Hodgkin Lymphoma

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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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

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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
  - 5/13 pts who did not undergo transplant

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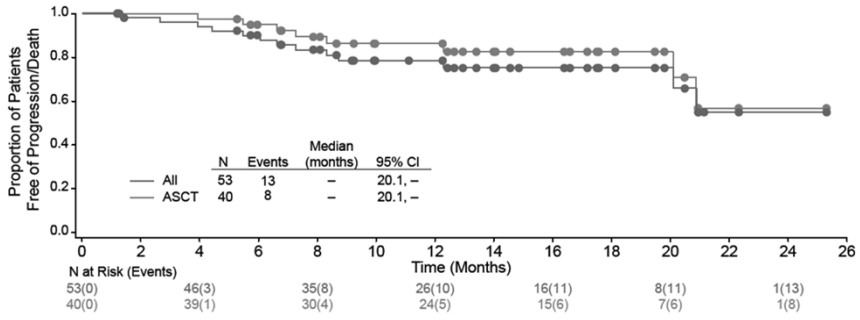
Progression-Free Survival – All Patients and in ASCT Subset



- 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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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 x10^8 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

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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

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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.

Slide credit: clinicaloptions.com

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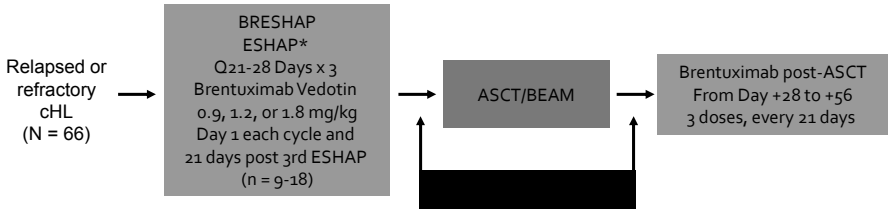
Brentuximab Vedotin + ESHAP for R/R cHL: Phase I/II Open-Label Study



*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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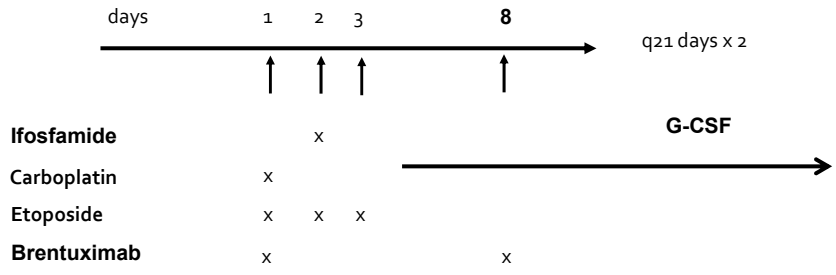
Phase I/II: ICE + BV



	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 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

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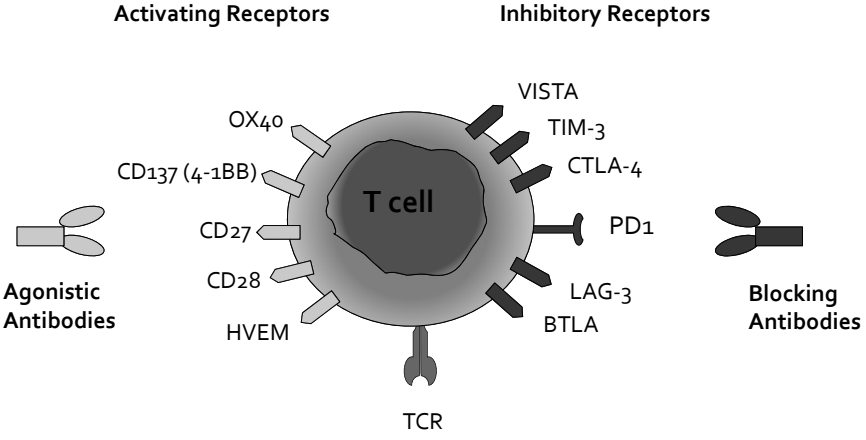
The Checkpoint Inhibitors in Lymphoma

Everyone wants some: Van Halen

Nivolumab vs. Pembrolizumab

Therapeutic Activation of Autologous T Cells
Immune checkpoint inhibitors



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General Facts :

There are currently 186 open studies with these agents on Clinicaltrials.gov

- PD-1 signaling inhibits T-cell activation, leading to reduced proliferation, cytokine production, and T-cell cytolysis
- The negative regulation of lymphocytes by PD-1 is mediated by the interaction with its ligands and B7-like proteins, PD-L1 and PD-L2.
  - HL and PMBL are unique, however since there is near uniform expression of PDL1 and 2
  - Amplification of 9p24.1 is frequent in cHL and results in overexpression of PD-L1 and PD-L2
  - EBV infection also is associated with overexpression of PD-L1 and PD-L2
- A major strength in studying the clinical benefit of PD-1/PD-L1 blockade and its combinations is the rapidity of response relative to other immunotherapies
  - The majority of responders to PD-1 pathway blockade appear to do so in the first 8 to 12 weeks of treatment

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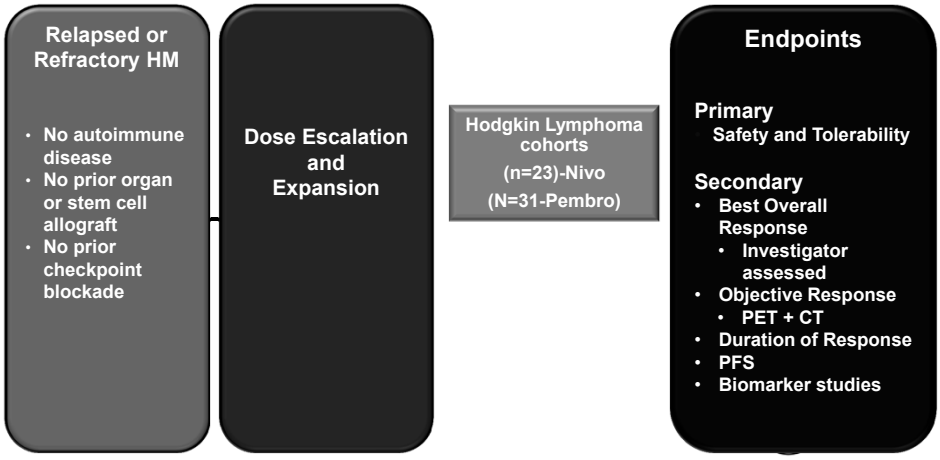
Rationale and Design of both Phase I Studies

- Based on potential vulnerability to PD-1 blockade, cHL included as independent expansion cohort in Phase 1b study of nivolumab in hematologic malignancies.



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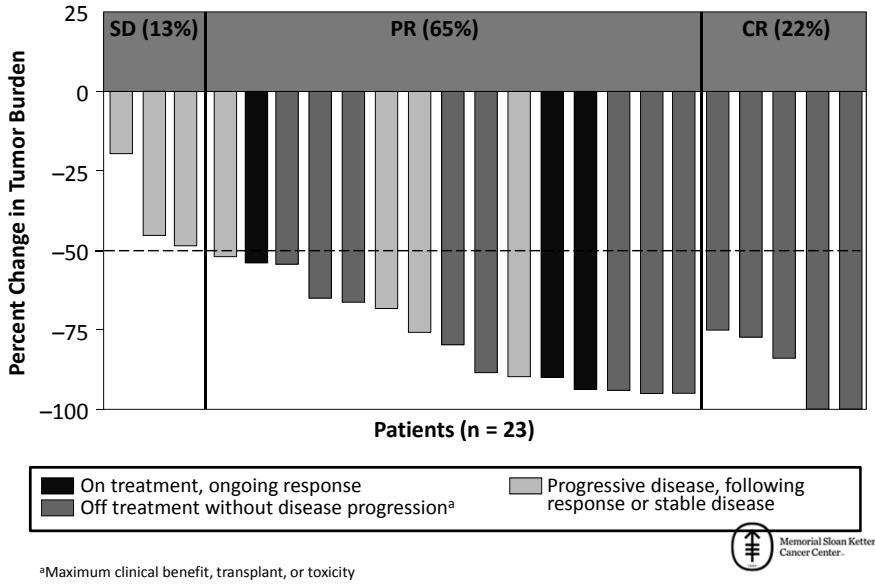
Nivolumab

Likely the first to the finish line

Best Response



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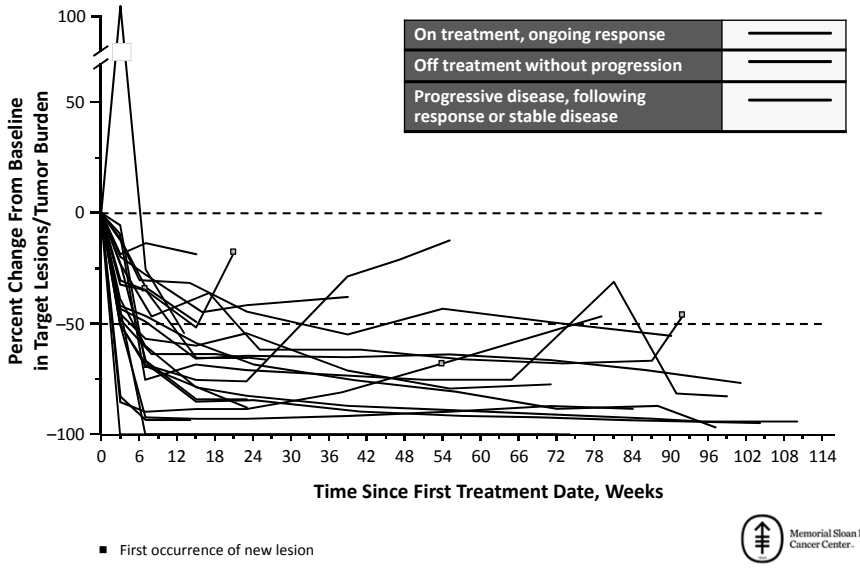
[a]Maximum clinical benefit, transplant, or toxicity

Durability of Response



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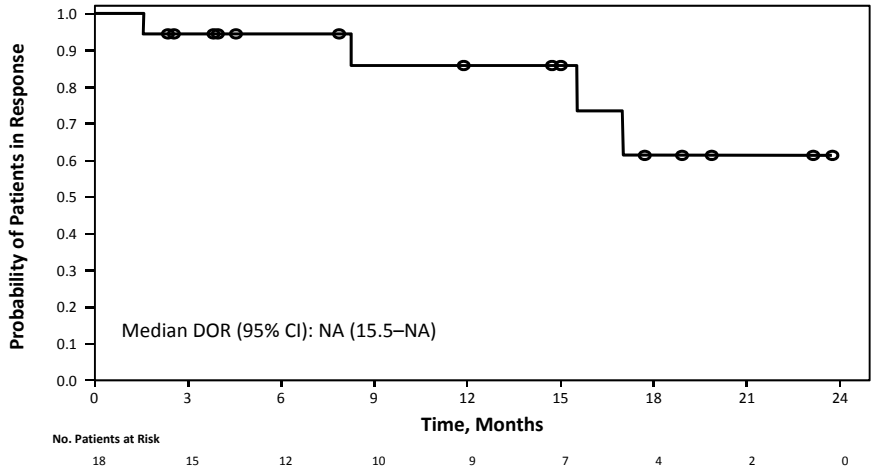
■ First occurrence of new lesion

Duration of Response



- **Median follow-up: 101 wks**
- **Median DOR not reached**

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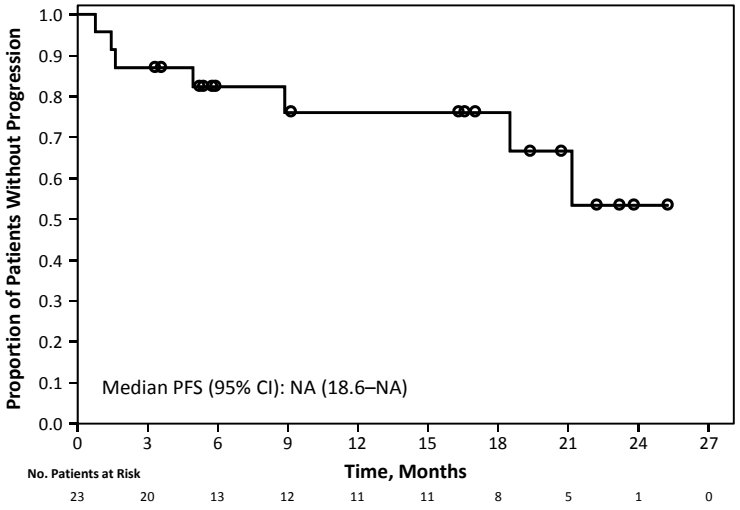
Progression-Free Survival



- **Median follow-up: 101 wks**
- **Median PFS not reached**

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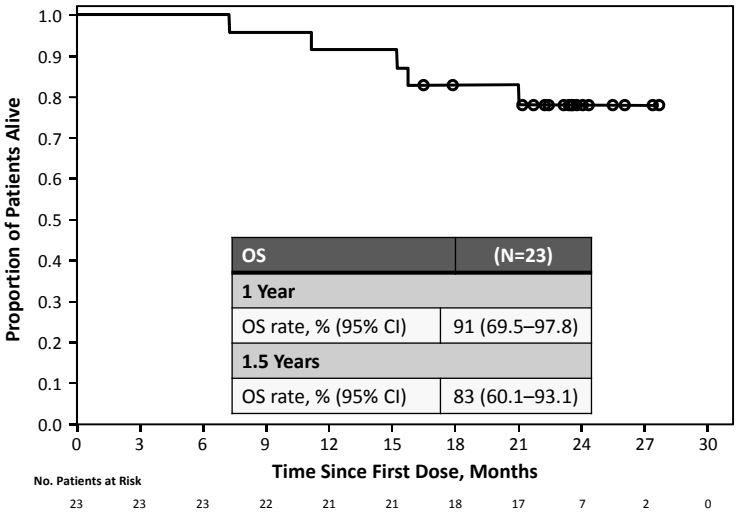
Overall Survival



OS	(N=23)
1 Year	
OS rate, % (95% CI)	91 (69.5–97.8)
1.5 Years	
OS rate, % (95% CI)	83 (60.1–93.1)

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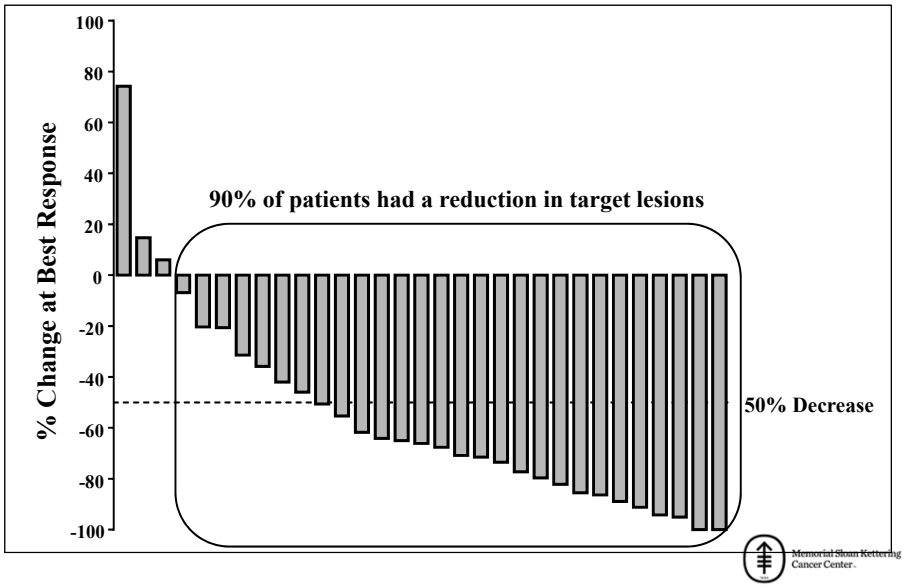
Pembrolizumab

Trying to catch up

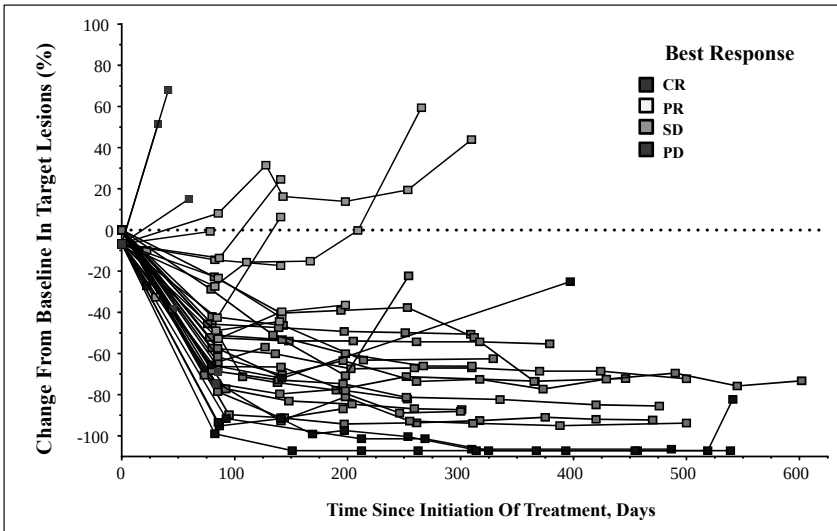
Efficacy

	Brentuximab Failure		
	Transplant Failure N = 22	**Transplant Ineligible/ Refused N = 9**	**Total N = 31**
Overall Response Rate	**16 (73%)**	**4 (44%)**	**20 (65%)**
Complete Remission	3 (14%)	2 (22%)	5 (16%)
Partial Remission	13 (59%)	2 (22%)	15 (48%)
Stable Disease	4 (18%)	3 (33%)	7 (23%)
Progressive Disease	2 (9%)	2 (22%)	4 (13%)

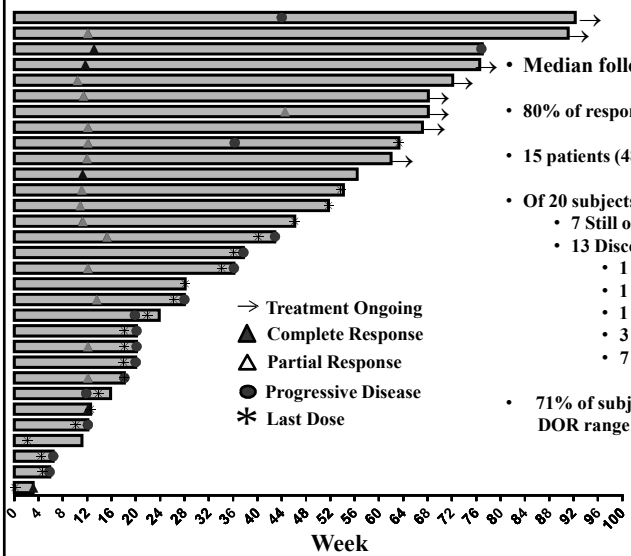
Efficacy



Change From Baseline in Target Lesions



Time Since Initiation of Treatment



- Median follow-up for survivors: ~18 months
- 80% of responses occurred by 12 weeks
- 15 patients (48%) progressed
- Of 20 subjects who achieved CR or PR:
  - 7 Still on treatment
  - 13 Discontinued treatment:
    - 1 CR no longer on treatment
    - 1 PR switched treatments
    - 1 adverse event
    - 3 allogeneic transplant
    - 7 (35%) progressive disease
- 71% of subjects have a DOR ≥ 24 weeks
  DOR range 0.14+ to 74+ weeks

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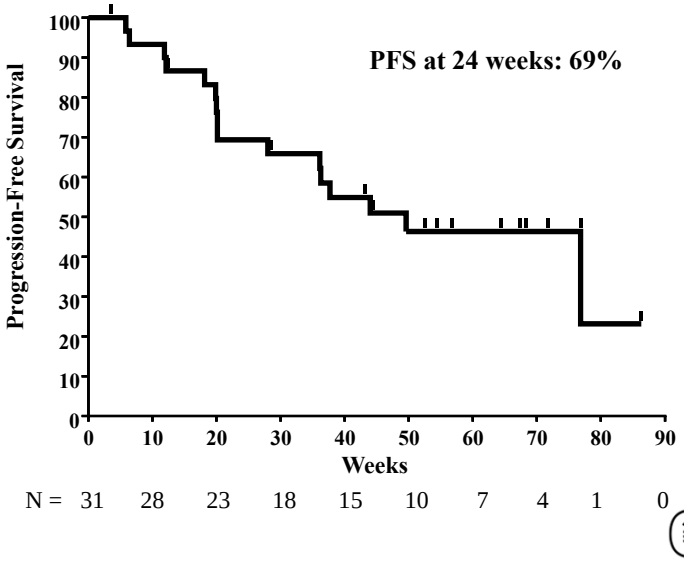
Progression-Free Survival



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"ITIS"

- Hypothyroidism
- Hyperthyroidism
- Pneumonitis
- Colitis

- Word of Caution: Do not treat anyone on study with these agents where there is a history of Bleomycin, Radiation, BV or Gemcitabine associated pneumonitis that required Steroid Support

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Conclusions

- Nivolumab and Pembrolizumab demonstrate promising antitumor activity in patients with heavily pretreated HL
- CR rates are low but waterfall plots are impressive as are response durations
- Acceptable safety and tolerability profile was observed
- Among enrolled patients, PD-L1 expression was observed in 100% of the evaluable samples
- I see very little difference between the agents
- Results support the continued development in patients with HL and phase II results will be reported at ASCO and EHA
  - Nivo-60 pts
  - Pembro- 60 pts

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What are we studying in HL

- BV-AVD and ISRT for unfavorable ESHL-AK PI : 41 pts
- BV-NIVO for salvage pre-ASCT: 7 centers-AM PI-just opened
- Pembro Registration trial: many centers, I am global PI, first 2 cohorts accrued 120 pts
- Pembro and ISRT for Favorable relapse HL (non-transplant study)-I am PI
  - My baby
- Sequential ABVD-nivo-AM PI-approved by BMS
- Pembro-post-ASCT-with DFCI, Philip Armand is P-I12 pts enrolled

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Continued……

- 13-034 BV-AVD x4 and ISRT for unfavorable ESHL with at least a 7 cm mass
  - Multicenter IST Rochester, COH and Stanford
- BV-NIVO for salvage: 7 centers
- Pembro Registration trial: many centers
- Pembro and ISRT for Favorable relapse HL (non-transplant study)
- A new version of RAPID (RADAR): Randomizing Pts to BV-AVD vs. ABVD for 3 cycles in same pt population

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Chronic HL
an entity to be avoided

- In 2009 the median survival of patient where an ASCT failed was 30 months
- In 2016 that same patient has a median survival of 60 months
- Thus the chronic HL patient has emerged
- This patient bares no resemblance to any other chronic lymphoma patient
- This patient is not living with lymphoma but slowly dying from HL

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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*

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