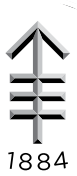

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The status of Relapsed and Primary Refractory Hodgkin Lymphoma in the near future

Impact of Brentuximab vedotin, and the Checkpoint inhibitors

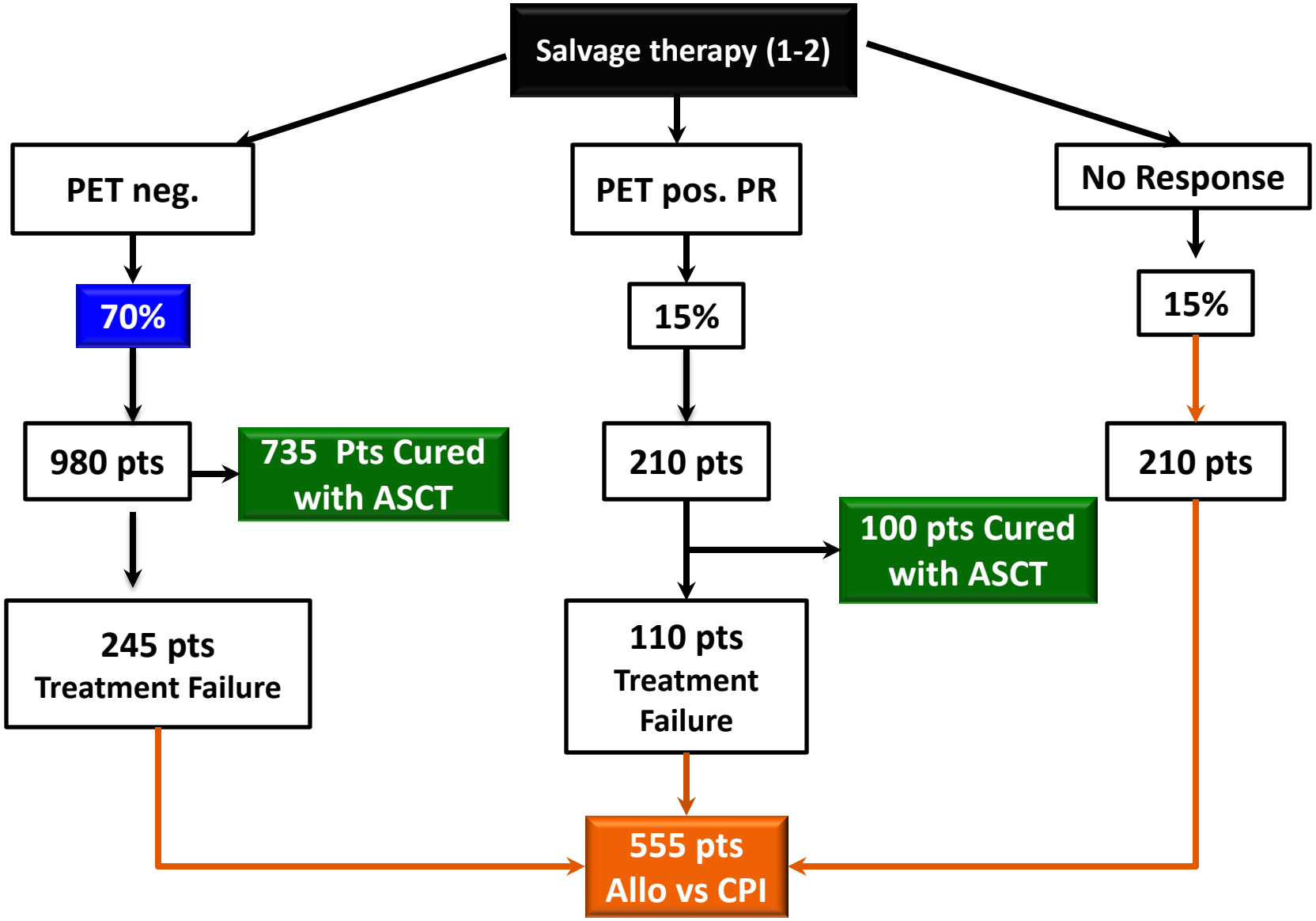
Craig Moskowitz, MD
Stephen A. Greenberg Chair in Lymphoma Research
Member, Memorial Sloan-Kettering Cancer Center
Professor of Medicine, Weill Medical College of Cornell University

Disclosures

- Research Funding: Merck, Seattle Genetics, BMS

- SAB: Novartis, Seattle Genetics, Celgene, Merck, BMS, Genentech

Relapsed/Refractory HL: 1400 pts/year



HL: Spring 2017-current status

The issues:

- Who should get post-ASCT maintenance therapy?
- Why is pre-ASCT PET status so important?
- Should BV be administered as part of salvage therapy?
- How will the checkpoint inhibitors be used?
- Is there a home for allogeneic stem cell transplantation?

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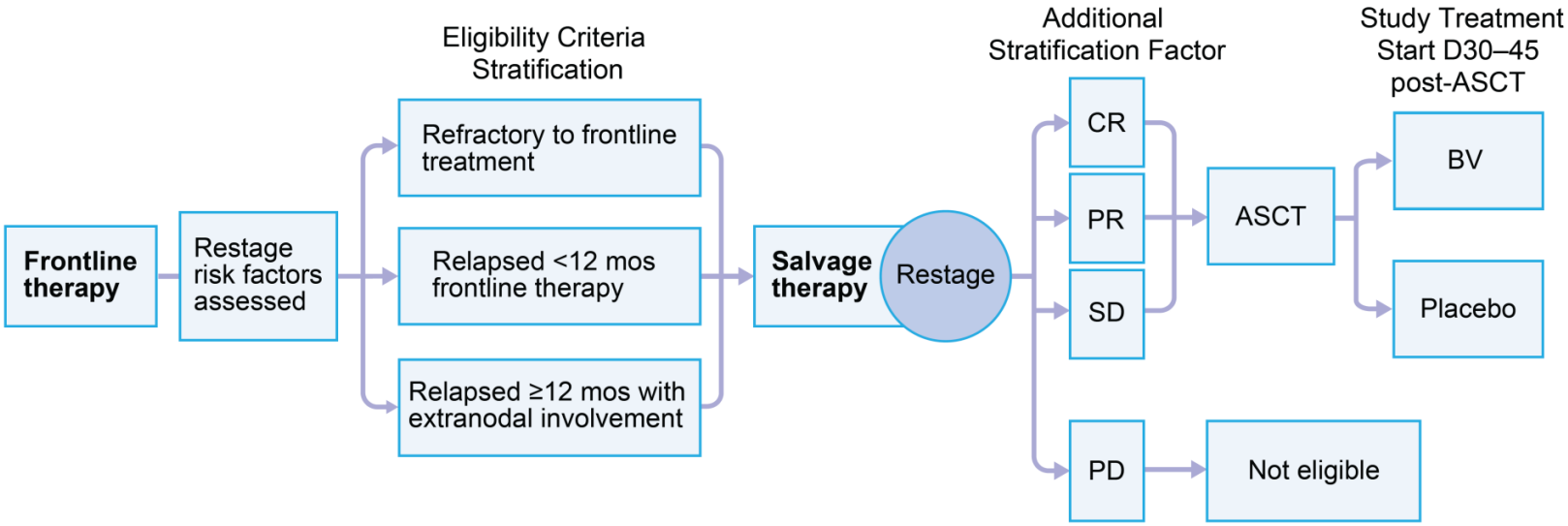
When evaluating patients for ASCT the 2 most important issues are:

Is there stage IV disease pre-salvage therapy?

Is the patient in CR: PET negative post-salvage therapy?

AETHERA Trial Design

Moskowitz CH, et al. Lancet,385; 1852-1862, 9 May 2015



- 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.

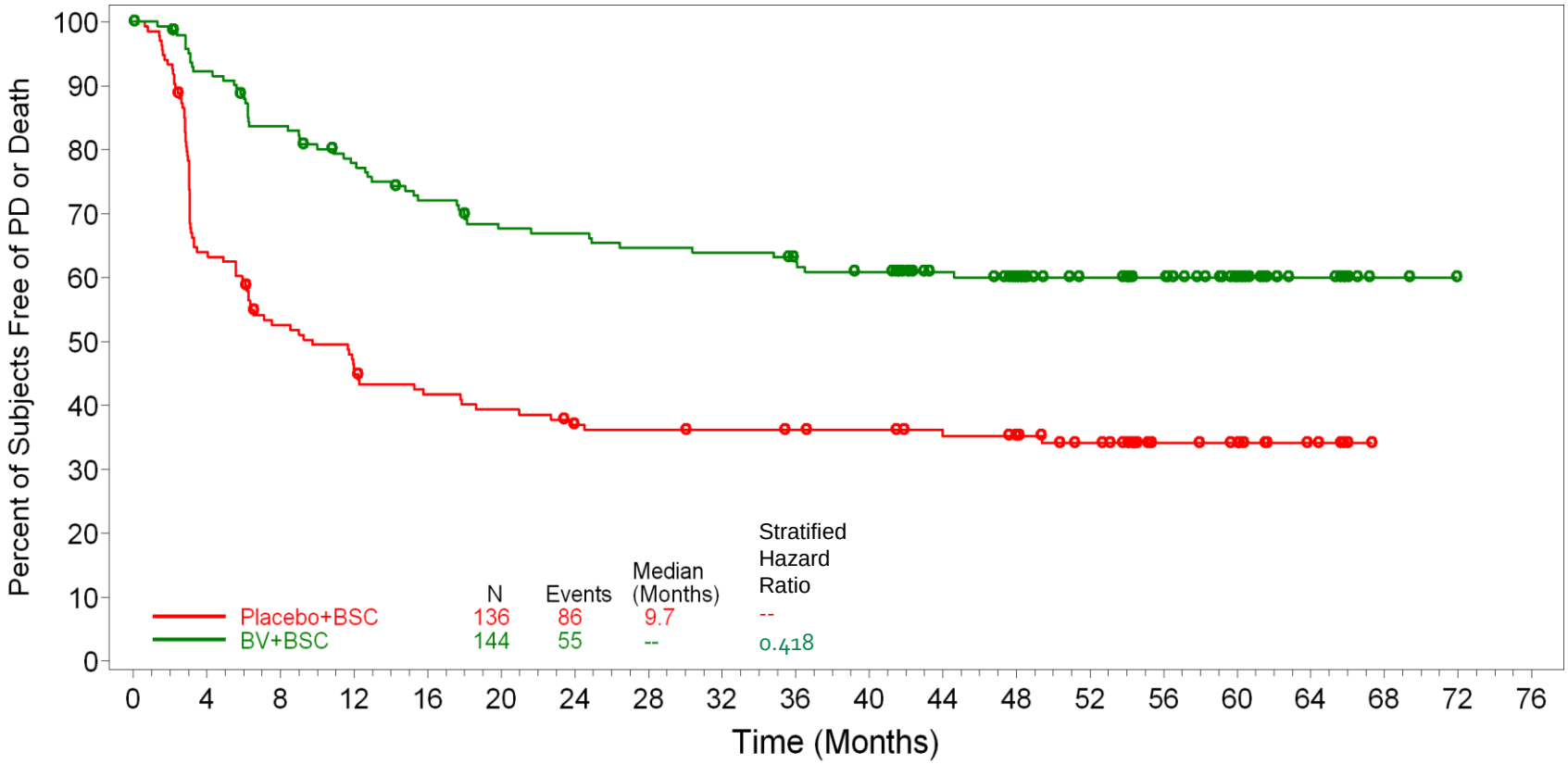
Risk Factors on AETHERA

Only 10% of patients had one unfavorable prognostic factor

- Initial remission duration < 1 year
- PET positive response to most recent salvage therapy
  - 1 of 5 risk factors
- ≥2 salvage therapies
- Extranodal disease at pre-ASCT relapse
- B symptoms at pre-ASCT relapse

- I administer maintenance to patients with >1 risk factor

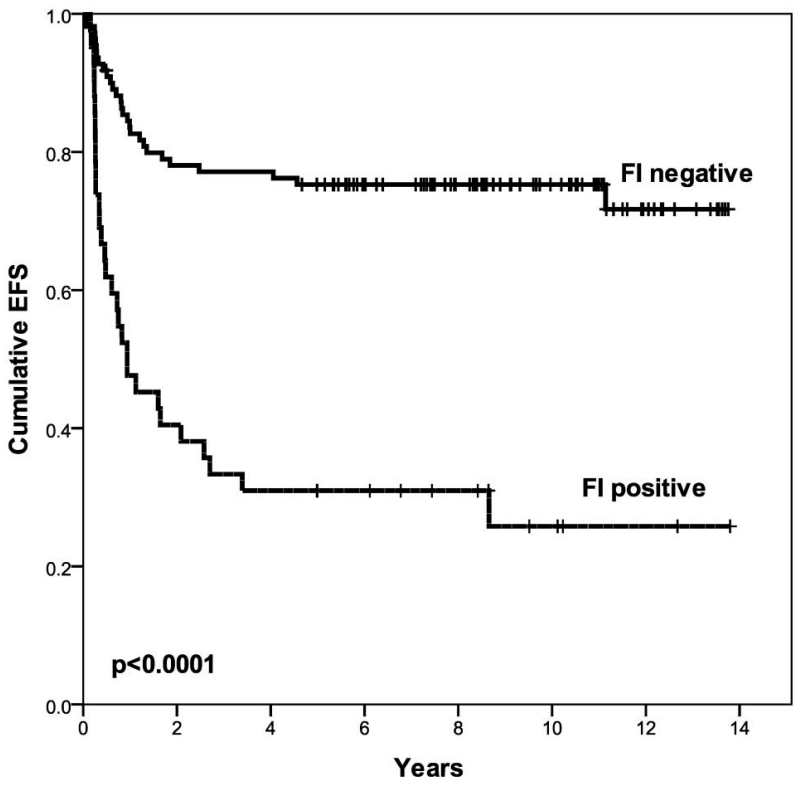
PFS Per Investigator: ≥ 2 Risk Factors*



N at Risk (Events)

Pla+BSC	136 (0)	85 (48)	68 (63)	59 (72)	53 (77)	50 (80)	45 (83)	44 (84)	43 (84)	42 (84)	41 (84)	38 (85)	36 (85)	28 (86)	14 (86)	12 (86)	5 (86)	0 (86)	0 (86)	0 (86)
BV+BSC	144 (0)	130 (11)	117 (23)	107 (31)	98 (39)	91 (45)	90 (46)	87 (49)	86 (50)	83 (51)	79 (54)	69 (54)	61 (55)	46 (55)	34 (55)	22 (55)	9 (55)	2 (55)	0 (55)	0 (55)

Functional imaging prior to HDT/ASCR in relapsed/refractory HL (1994-2003)



- Second-line therapy was risk-adapted based on the MSKCC 3 factor model:
  - B symptoms
  - Extranodal disease
  - Relapse < 1year
- Pre-transplant functional imaging was the most significant determinant of outcome

Moskowitz AJ et al. Blood 2010;116:4934-7

Pre-ASCT PET is consistently prognostic

Reference	n	PET neg definition	PFS/EFS PET pos	PFS/EFS PET neg
Gentzler, et al. BJH 2014	32	Deauville 2**	52%	85%
Akhtar, et al. BMT 2013	141	< Mediastinal blood pool	49%	74%
Devillier, et al. Haematologica 2012	111	Harmonization	23%	79%
Smeltzer, et al. BBMT 2011	46	Harmonization	41%	82%
Mocikova, et al. Leukemia&Lymphoma 2011	76	Harmonization	36%	73%
Jabbour, et al. Cancer 2007*	211	< Background	27%	69%

*Publications included gallium scans

**Results similar when PET negative defined as Deauville 3

What are the results when standard salvage therapy includes Brentuximab Vedotin?

6 studies: same goal-PET negative CR

- Sequential immuno-chemotherapy (published)
  - BV as a single agent and sequential administration of ICE or other salvage therapy only if < CR is achieved (MSKCC, COH studies respectively)

- Concomitant immuno-chemotherapy (abstract only)
  - BV + bendamustine-in review
  - BRAVE: BV+ DHAP-presented at ISHL
  - BR-ESHAP-ASH-oral presentation Monday night
  - BV+ICE-(Seattle) poster at ASH-Saturday night

Current State of Salvage Therapy

Regimen	Pt #	Rel	Primary Ref	CR-PET neg pre-ASCT	CD34	ASCT %	PFS ITT
BV-ESHAP	66	26	40	70%	5.75	92	Too soon
Benda-BV	54	27	27	74%	4	74	63% at 2 years
BV-ICE	16	5	11	69%	11	75	Too soon
BV-DHAP	12	10	2	90%	5.3	100	Too soon
BV → Sequential ICE	66	33	33	73%	6.2	95	79% at 3 yrs
BV → Sequential Salvage therapy	37	13	24	73%	5.6	89	72% at 18 mo
ICE/GVD	97	56	41	76%	6.3	88	68% at 8 yrs
Benda-GV	59	27	32	73%	8.8	73	63% aat 2 yrs

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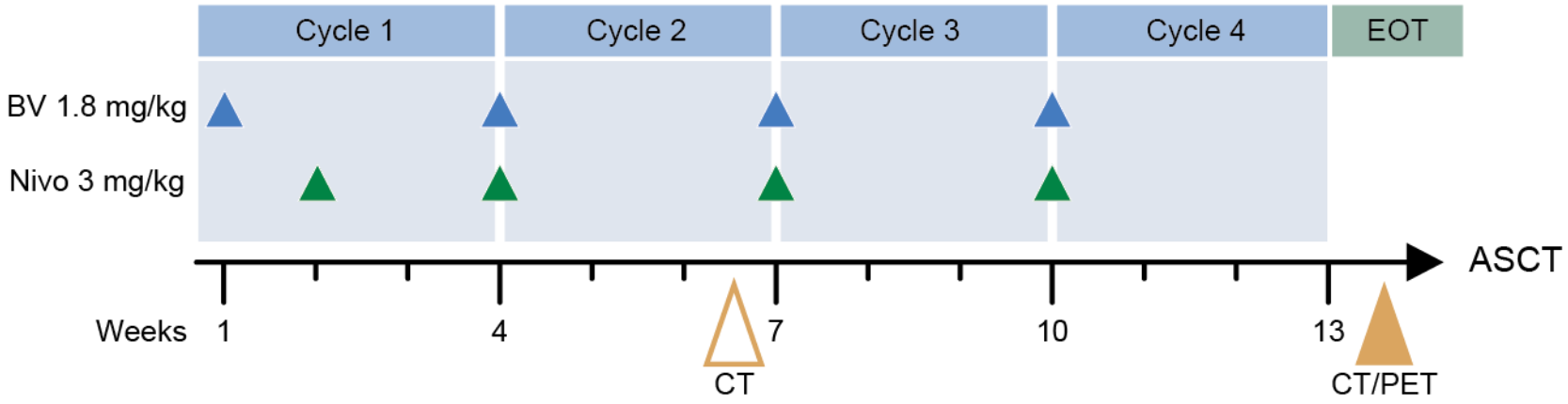
Preliminary Results from a Phase 1/2 Study of Brentuximab Vedotin in Combination with Nivolumab in Patients with Relapsed or Refractory Hodgkin Lymphoma

Alex F. Herrera[1], Nancy L. Bartlett[2], Radhakrishnan Ramchandren[3], Julie M. Vose[4], Alison J. Moskowitz[5], Tatyana A. Feldman[6], Ann S. LaCasce[7], Stephen M. Ansell[8], Craig H. Moskowitz[5], Keenan Fenton[9], Kazunobu Kato[10], Abraham Fong[9], Ranjana H. Advani[11]

[1]City of Hope National Medical Center, Duarte, CA, USA; [2]Washington University School of Medicine, St. Louis, MO, USA; [3]Karmanos Cancer Institute, Detroit, MI, USA; [4]University of Nebraska Medical Center, Omaha, NE, USA; [5]Memorial Sloan Kettering Cancer Center, New York, NY, USA; [6]Hackensack University Medical Center, Hackensack, NJ, USA; [7]Dana Farber Cancer Institute, Boston, MA, USA; [8]Mayo Clinic, Rochester, MN, USA; [9]Seattle Genetics, Inc., Bothell, WA, USA; [10]Bristol-Myers Squibb, Princeton, NJ, USA; [11]Stanford University Medical Center, Palo Alto, CA, USA

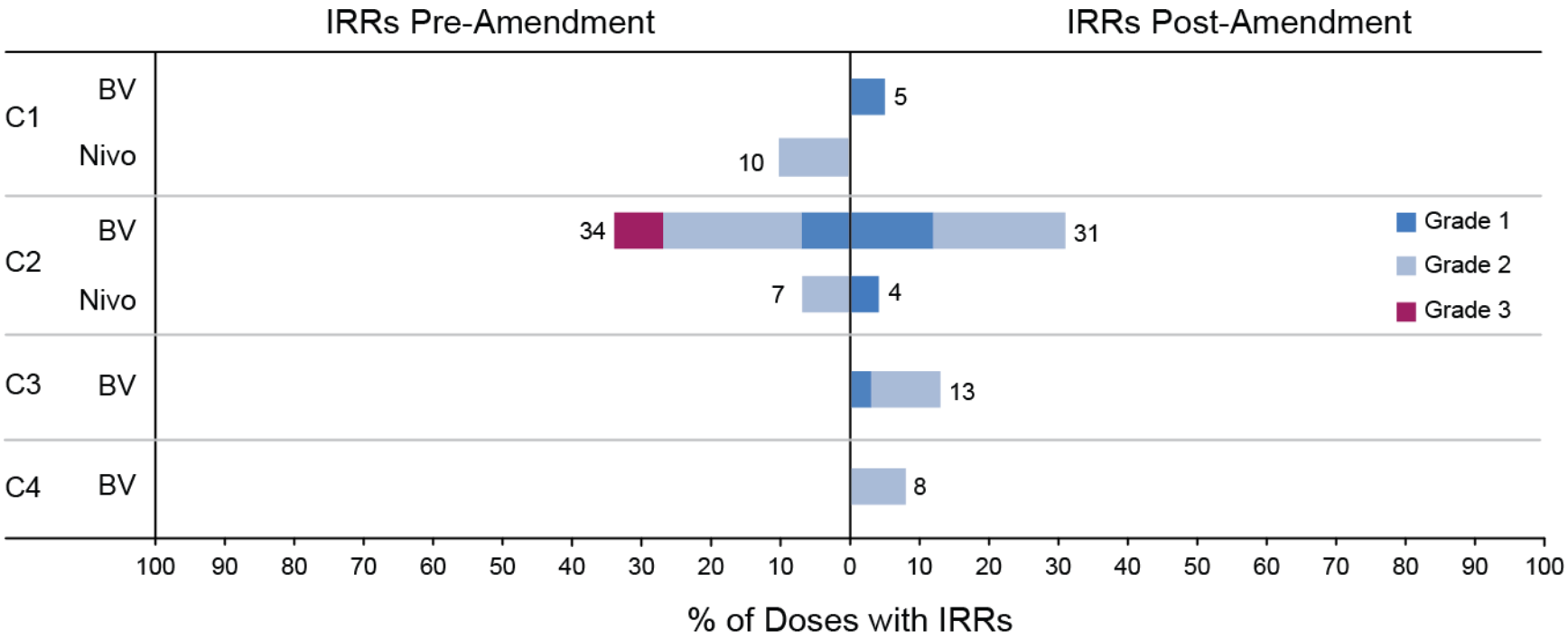
American Society of Hematology, San Diego, California, December 3–6, 2016, Abstract No. 1105

Methods



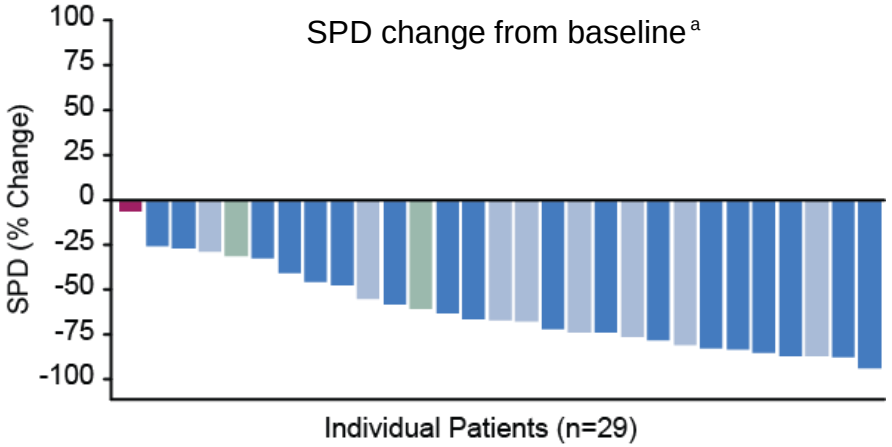
- Target enrollment: ~55 patients
- Patients were treated in 21-day cycles for up to 4 cycles (12 weeks)
  - During Cycle 1, BV was administered on Day 1 and Nivo on Day 8
  - During Cycles 2-4, dosing of both drugs occurred on Day 1 of each cycle
  - After completion of the Cycle 4 response assessment, patients were eligible to undergo ASCT
- Investigator assessment of lymphoma response and progression was per the Lugano Classification Revised Staging System for malignant lymphoma (Cheson et al., 2014)

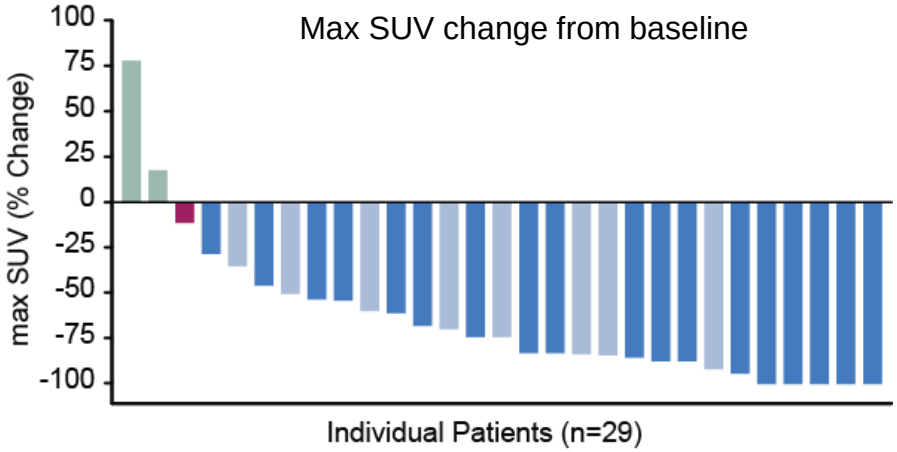
Infusion-Related Reactions (IRRs) and Associated Symptoms



- IRRs were observed in 38% of patients overall, most common symptoms were flushing, nausea (14% each); chest discomfort, dyspnea, urticaria (12% each); cough, and pruritus (10% each)
- A protocol amendment was instituted requiring premedication with low-dose corticosteroids (hydrocortisone 100 mg or equivalent) and antihistamine at Cycles 2-4
- Premedication regimen including low-dose corticosteroid did not impact the rate or severity of IRRs, however no patients discontinued treatment due to an IRR

Tumor Response per Investigator





ORR (26/29) = 90%

95% CI: 72.6, 97.8

CR (18/29) = 62%

95% CI: 42.3, 79.3

Deauville score (N=29)

5-Point Score	Best Metabolic Response	n (%)	Total n (%)
1	CR	8 (28)	18 (62)
2		6 (21)	
3		3 (10)	
Missing		1 (3)	
4	PR	6 (21)	8 (28)
5		2 (7)	
5	SD	1 (3)	1 (3)
5	PD	2 (7)	2 (7)

Best Metabolic Response:

Complete response (CR) | Partial response (PR) | Stable disease (SD) | Progressive disease (PD)

[a] Cycle 2 SPD reported for 1 patient

Conclusions

- **Early data suggest the combination of BV and Nivo is an active and well-tolerated outpatient regimen**
  - **90% ORR and 62% CR (same as all other regimens?)**
  - **38% of patients have experienced IRRs, however the overall safety profile is manageable with no dose reductions or discontinuations due to AEs**
  - **The incidence of immune-related adverse events is low**
- **Preliminary biomarker results indicate**
  - **No antagonism between BV and Nivo**
  - **Decrease in Treg cells with BV**
- **The promising activity of the BV and Nivo combination supports further exploration of this chemotherapy-free regimen for R/R HL patients**

BV+Nivolumab for Relapsed Patients
E4412 Schema: (Arms D-F)

Arm Y: Dose Level -1

Nivolumab 1mg/kg IV day 1 of cycles 1-46

Brentuximab vedotin 1.2 mg/kg IV day 1 of cycles 1-16

STARTING DOSE

Arm D: Dose Level 1 (N=3)

Nivolumab 3 mg/kg IV day 1 of cycles 1-46

Brentuximab vedotin 1.2 mg/kg IV day 1 of cycles 1-16

Arm E- Dose Level 2 (N=7)

Nivolumab 3 mg/kg IV day 1 cycles 1-46

Brentuximab vedotin 1.8 mg/kg IV day 1 of cycles 1-16

Arm F- Phase I Expansion Cohort (N=9)

Nivolumab 3 mg/kg IV day 1 cycles 1-46

Brentuximab vedotin 1.8 mg/kg IV day 1 of cycles 1-16

ECOG-ACRIN cancer research group

NYU Langone MEDICAL CENTER

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Diefenbach et al. ASH 2016 abstract #1106

BV and Nivolumab is Highly Active

Evaluable Patients (n = 12)	ORR
ORR	12/12 (100%)
CR	8/12 (66%)
PR	4/12 (34%)

2 of 2 patients with prior BV evaluable= CR

ECOG-ACRIN cancer research group
Reshaping the future of patient care

NYU Langone MEDICAL CENTER

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Diefenbach et al. ASH 2016 abstract #1106

Current State of Salvage Therapy

Regimen	Pt #	Rel	Primary Ref	CR-PET neg pre-ASCT	CD34	ASCT %	PFS ITT
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BV + Chemotherapy							
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Chemotherapy							
ICE/GVD	97	56	41	76%	6.3	88	68% at 8 yrs
Benda-GV	59	27	32	73%	8.8	73	63% at 2 yrs

Why do I recommend sequential therapy?

- There is no evidence that a CR to single agent BV is inferior to that of chemotherapy or chemo-immunotherapy
- 1/3 of patients can avoid chemotherapy for salvage if BV is used first
- Chemotherapy alone without BV offers a CR rate of 60-73% with ICE or BeGV
  - BV can be used as salvage number 2
- Bendamustine-BV seems no better than BeGV
- Platinum based salvage regimens combined with BV are "challenging"

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The Checkpoint Inhibitors

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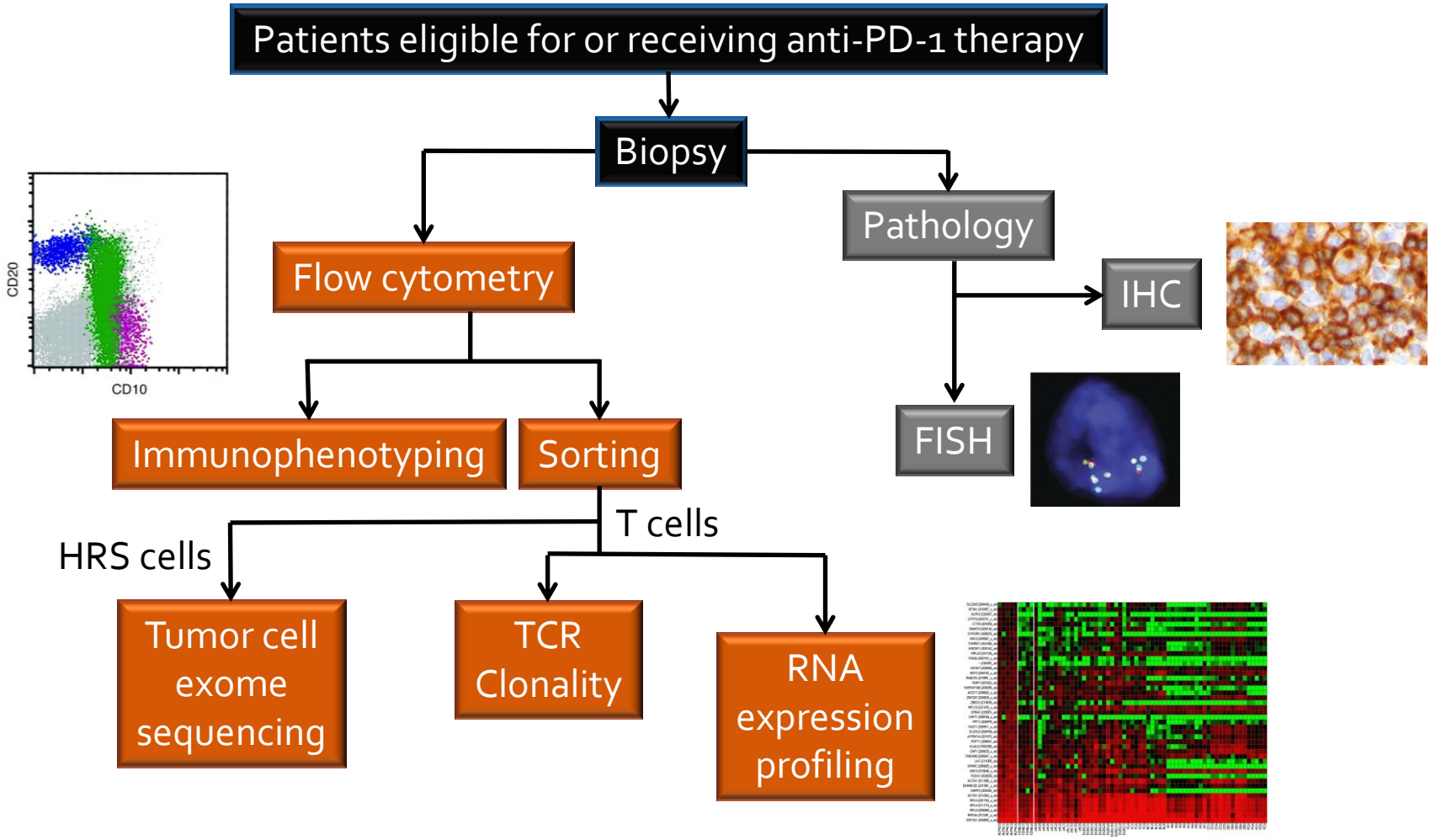
As pf March 1, 2017, there are currently 79 prospective clinical trials open at MSKCC studying checkpoint inhibitors in solid and liquid tumors

Please only open studies where there are prospective biopsies being done!

Action plan for biopsies from patients treated with PD-1 blockade



Courtesy of Santosh Vardhana

Overall experience with nivolumab and pembrolizumab

- >500 patients treated; phase IB and II studies
- Response rate is 65-70%, Clinical Benefit >90%
- CR rate 22% by investigator
- Median duration of response unclear but >1 year
- Major side effects "itis"
  - Endocrine or Inflammatory

Nivolumab: approved in US for ASCT and BV failures

Pembrolizumab: approved in US for refractory HL or failure of 3 previous regimens

I have some reservations on the Pembrolizumab label

- There is an implication that patients with primary refractory, transplant-eligible disease can receive this therapy prior to salvage chemotherapy
- **This would be a MISTAKE in clinical judgement**
- As far as I know, no patient has been cured with a CPI
- Reserve Pembrolizumab for HL having a poor response to salvage chemotherapy or for ASCT failures

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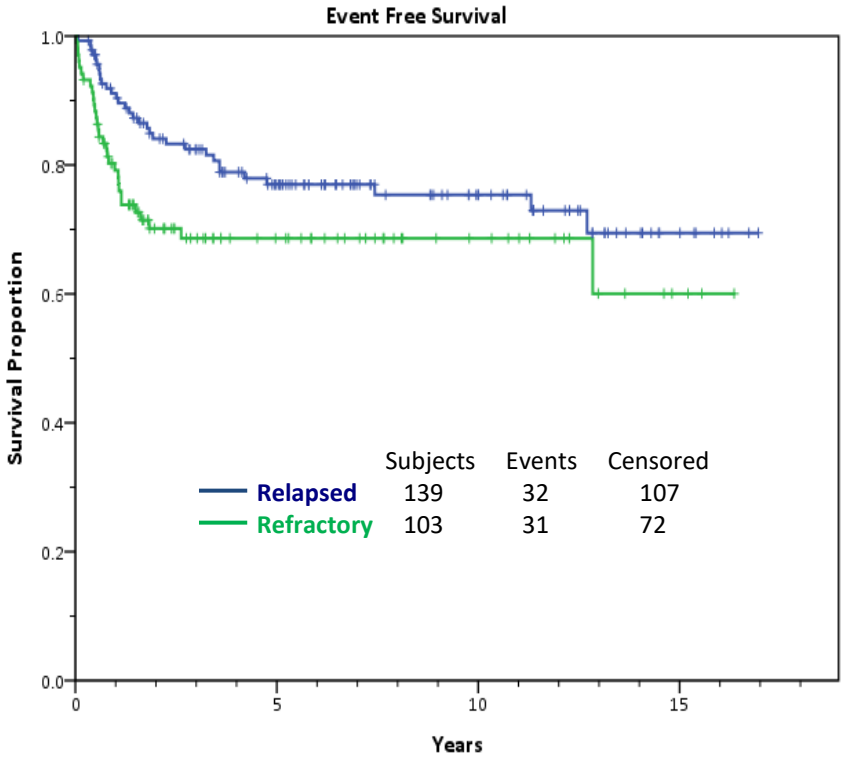
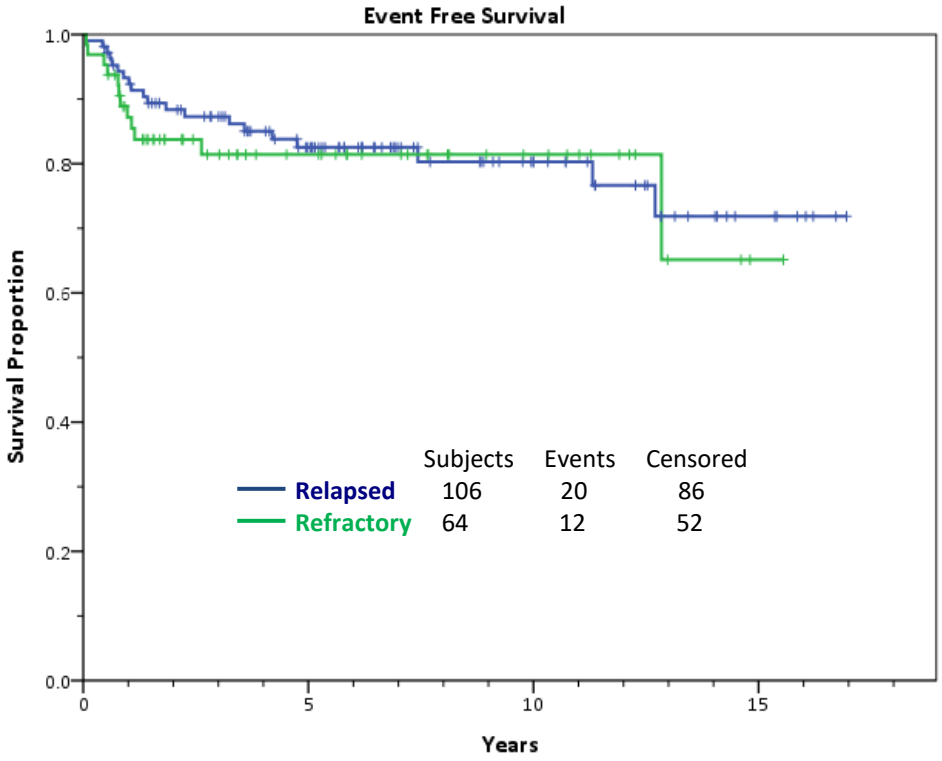
Should all transplant-eligible patients undergo HDT/ASCT with the availability of CPI?

Maybe not: A research question

An intent to treat analysis of outcome for relapsed and primary refractory HL with stage I/II disease at MSKCC



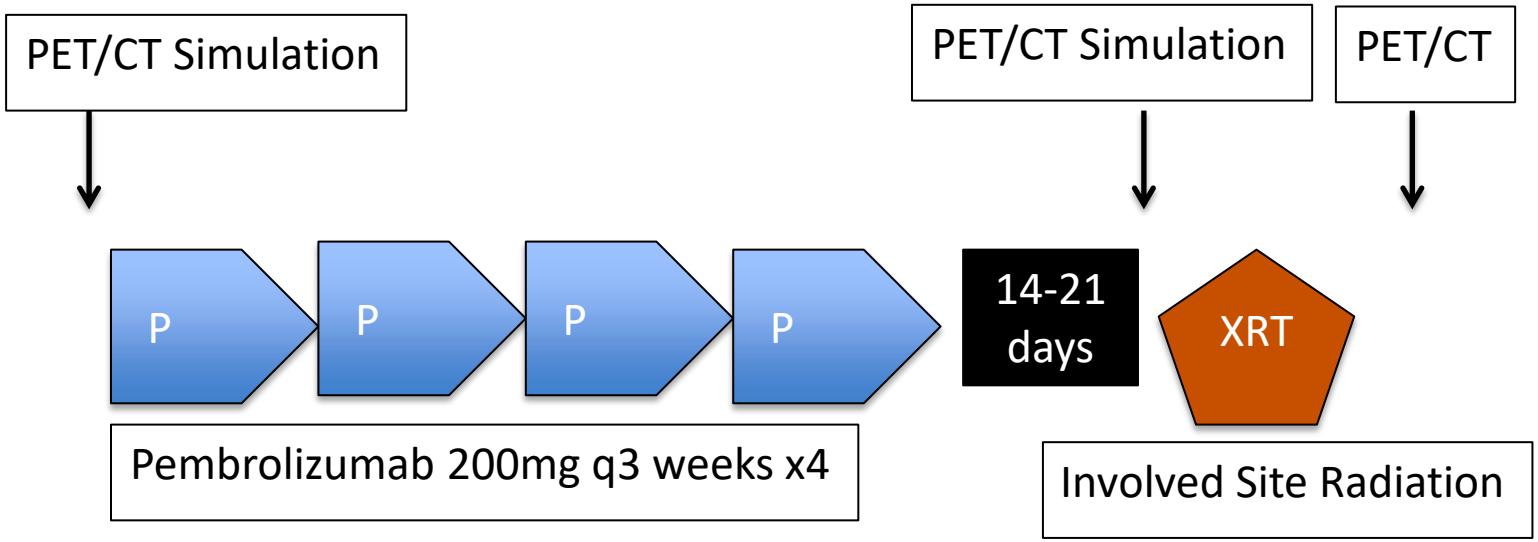


All Patients

PET Negative, ASCT pts

* Only 10 pts (1 relapsed and 9 primary refractory) did not go on to Auto HSCT

Study, Patient populations and statistics



ESHL, treated with < 6 cycles of chemotherapy alone and relapsed or refractory early stage disease

- **RAPID failures for example**
  - **Where ISRT is commonly administered**

Simon 2-Stage Design

- **CR rate will increase from 20% with pembrolizumab alone to 50% with the use of pembrolizumab + ISRT**

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Have we forgotten about allogeneic stem cell transplantation in the new era of CPI?

Let's remember that the CPI have not cured anyone yet with HL!

The issues

- 3 yr. PFS with allogeneic transplant varies in 2016 but ranges from 30-50-%
- No patient in the US will be BV naive if an allogeneic transplant is required
- Should an allogeneic transplant be offered to any patient that has not received a CPI?
- Should an allogeneic transplant only be considered in patients that have disease progression on CPI?
- Should CPI be a bridge to allo in all cases?
  - Should only patients that have <CR be referred for an allo?
  - Should only patients with a CR be referred for an allo?

My current strategy for ASCT failures which is subject to change

- If disease is nodal only and stage I/II, and pt is RT naïve: radiotherapy with curative intent
- Advanced stage
  - HLA typing and refer for a potential allogeneic stem cell transplantation
  - Start CPI
    - If CR is achieved continue for another 3 months and if CR is maintained stop therapy and monitor, restart if HL progression and refer back for allo consideration
    - If a PR is achieved continue therapy based upon clinical situation, (PR can convert to CR), however refer back to transplant physician for repeat evaluation and further discussions
    - If stable disease is achieved, a CR will not happen, continue therapy until definitive disease progression and then start MOPP vs. clinical trial, and refer back for allo consideration if a PR is achieved

SAVE THE DATE

MSK SYMPOSIUM ON LYMPHOMA

STATE-OF-THE-ART IN BIOLOGY, THERAPY AND PATIENT CARE

May 5-6, 2017

Memorial Sloan Kettering Cancer Center
Zuckerman Research Center
417 East 68th Street
New York, NY 10065

Course Director
Anas Younes, MD, Chief, Lymphoma Service

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