Memorial Sloan Kettering Cancer Center

Checkpoint Inhibitors in Lymphoma

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Professor of Medicine, Weill Medical College of Cornell University

Case 1 – 48-year-old female

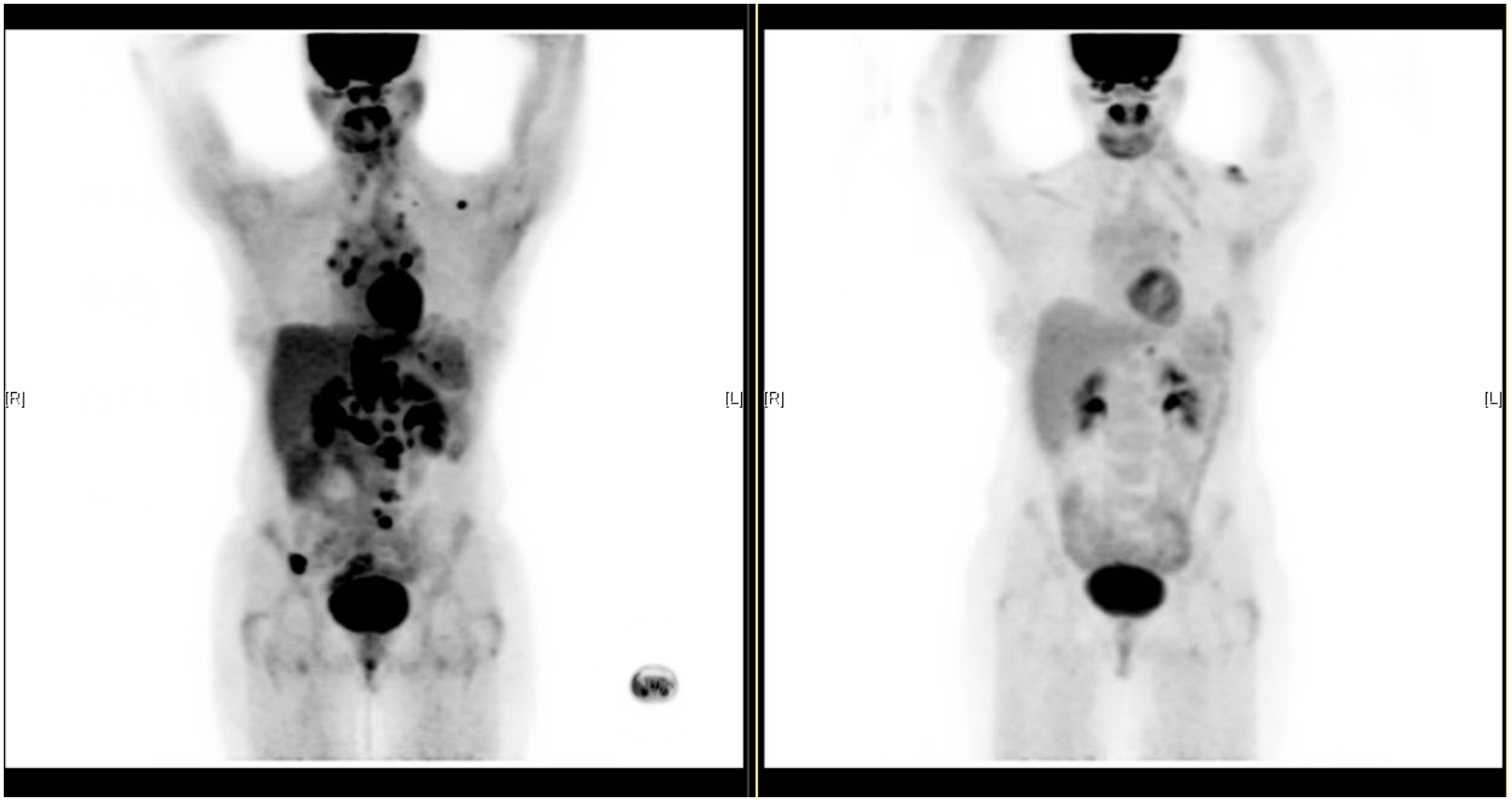
- March 2010 dx with stage IIA nodular sclerosing Hodgkins lymphoma
- 5/6/10 BM Bx without involvement
- She received 5 cycles of ABVD followed by IFRT to bilateral neck, supraclavicular fossa, mediastinum.
- Restaging at completion of treatment demonstrated residual disease
- 11/4/10 right level 4 LN bx with atypical lymphoid proliferation, compatible with residual classical Hodgkin lymphoma.
- late 2011 ICE chemotherapy
- Feb 2012 autologous SCT (conditioning regimen unknown).

Case 1 cont'd

- Upon first restaging post-transplant, the patient had refractory disease.
- 7/3/12 R cervical LN bx: classical Hodgkin Lymphoma, CD30+
- July 2013: initiated brentuximab. Imaging after two cycles demonstrated VGPR. However, at the next restaging, she had progressive disease.
- Therapy was changed to Gemcitabine, vinorelbine, and doxorubicin. She received 6 cycles, completed 7/24/13.
- PET/CT 8/23 revealed CR.
  - Her sister, who is HLA-matched was pregnant at that time. She delivered in December 2013. Patient refused cord blood transplant as alternative

Case 1 cont'd

- PET on 1/14/14 revealed hypermetabolic thoracic and abdominal lymphadenopathy suspicious for malignant involvement
- 3/31/14 initiated pembrolizumab 10mg/kg on phase I clinical trial
- 6/20/14 PET/CT CR
- Second restaging 10/17/14 NED. CT 6/25/15 NED
- 10/16/2015 dose #50 pembrolizumab on study → study end
  - Received 50 doses over 2 year period of time
  - Tx discontinued due to finite dosing schedule per protocol
  - Toxicities related to treatment: none.
- 2/2017 NED



Baseline 3/21/2014

2/5/2015

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Disclosures

Consulting Agreements	Bristol-Myers Squibb Company, Celgene Corporation, Genentech BioOncology, Merck, Seattle Genetics
Contracted Research	Bristol-Myers Squibb Company, Merck, Pharmacyclics LLC, an AbbVie Company, Seattle Genetics

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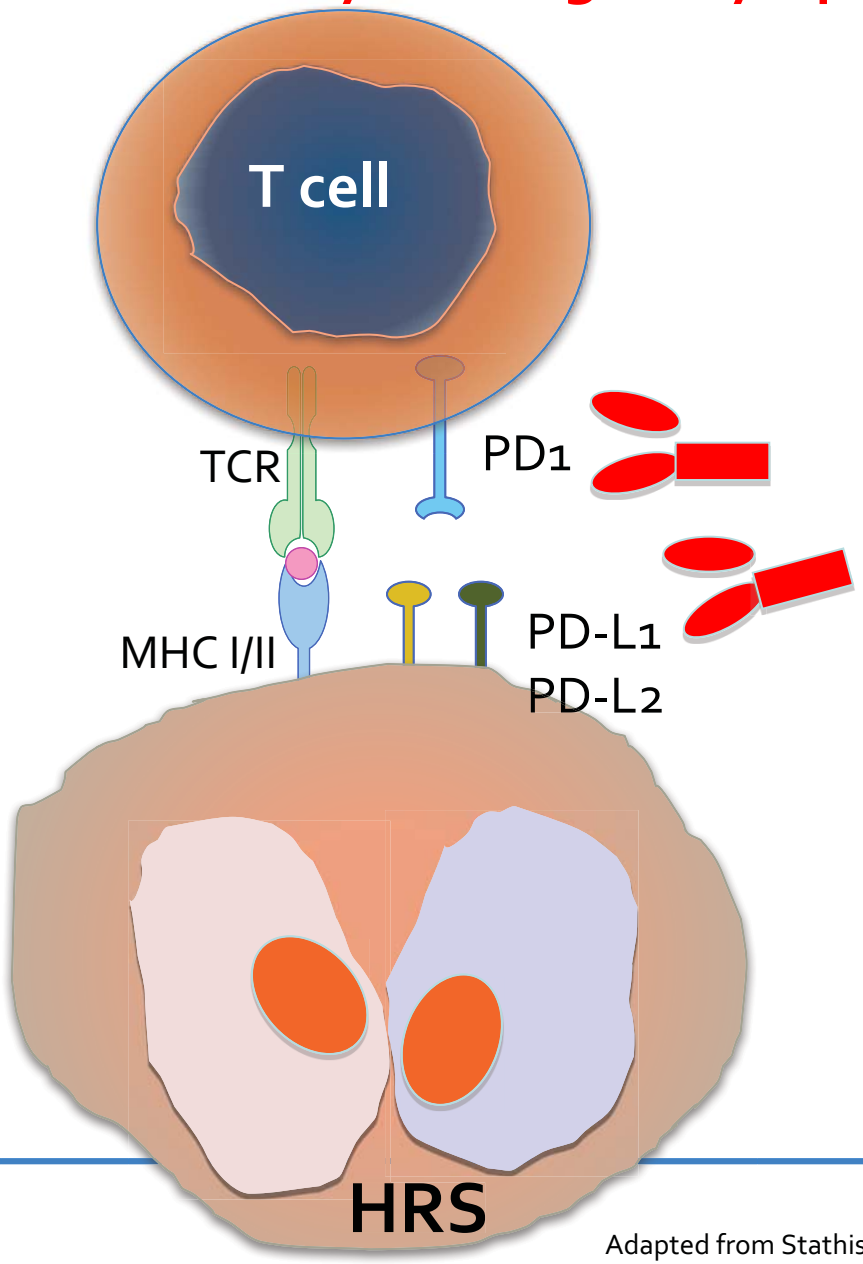
There are currently 75 prospective clinical trials open at MSKCC studying checkpoint inhibitors in solid and liquid tumors

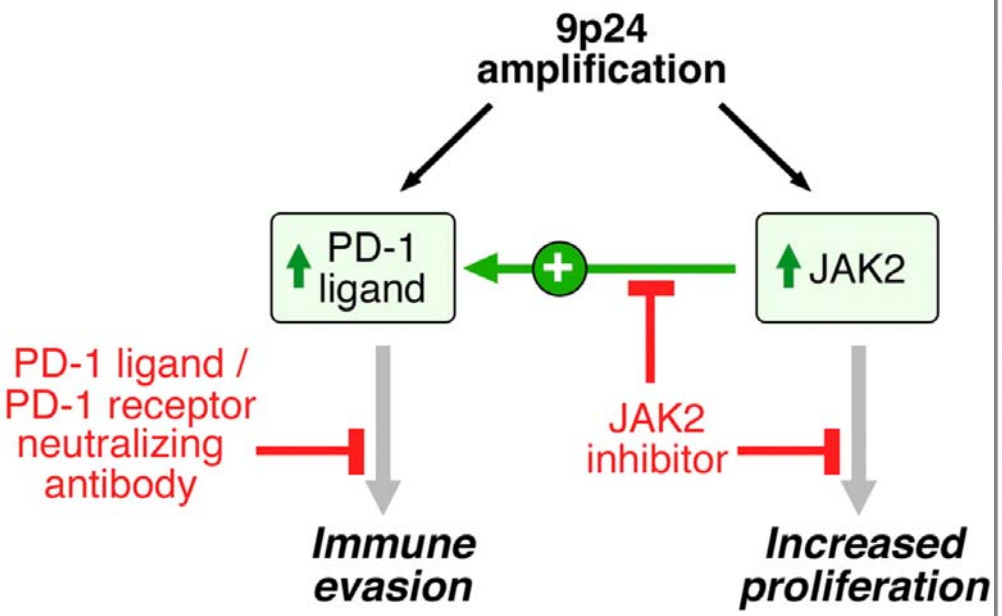
Please only open studies where there are prospective biopsies being done!

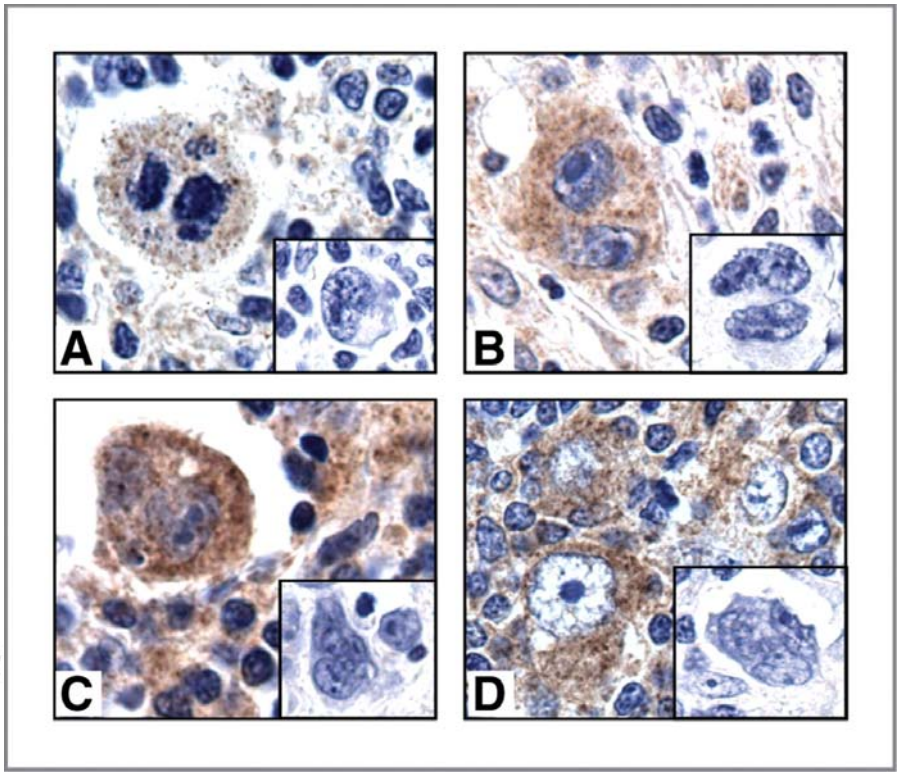
Targeting PD1/PDL1 Pathway in Hodgkin Lymphoma



Adapted from Stathis & Younes: Ann Oncology 2015

PD-L1 Almost Universally Expressed on RS Cells Through 9p24.1 Amplification or EBV





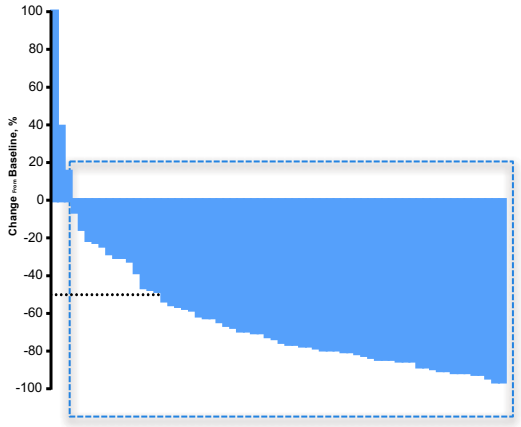
Michael R. Green et al. Clin Cancer Res 2012;18:1611-1618
Michael R. Green et al. Blood 2010;116:3268-3277

Best comparison phase II studies, ASCT and BV failure

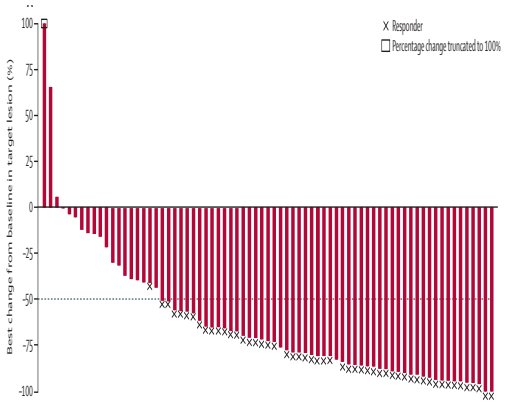
	Pembro	Nivo
Patients	69	80
Age	34 (19-64)	37 (28-48)
Prior Tx	4 (2-12)	4 (3-15)
Prior BV	100%	100%
Prior auto-SCT	100%	100%

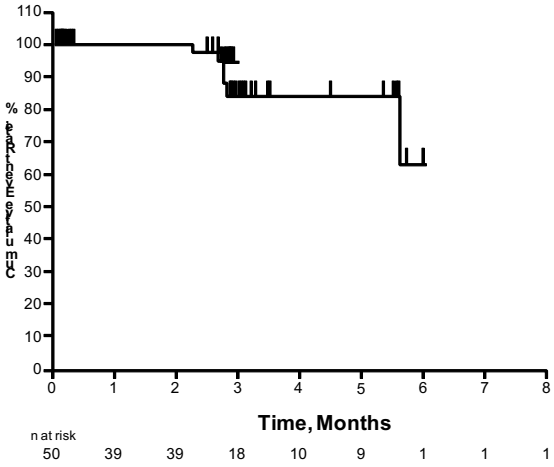
	Pembro	Nivo
ORR	72%	66%
CR (IR) CR (doc)	22% 22%	9% 22%
PR	51%	58%
SD	13%	23%
POD	6%	8%

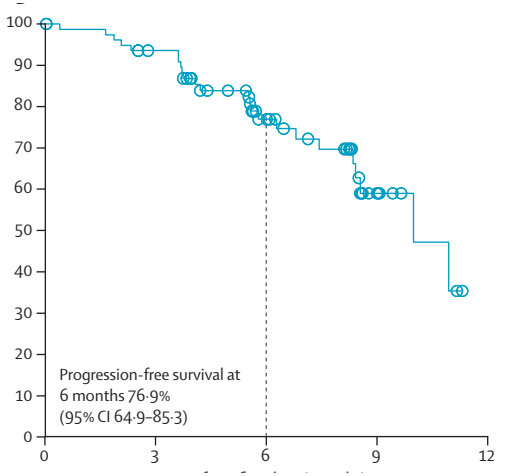
Pembrolizumab



Nivolumab







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Moskowitz et al, *ISHL* 2016
Younes et al, *Lancet Oncol* 2016

Overall experience with nivolumab and pembrolizumab

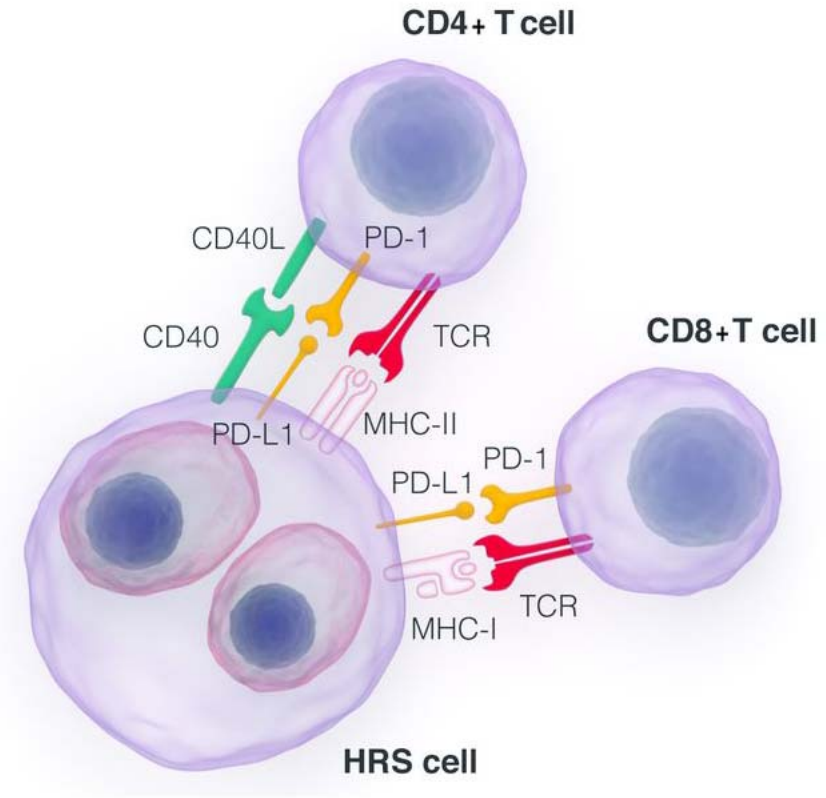
- >500 patients treated; phase IB and II studies
- Response rate is 65-70%, Clinical Benefit >90%
- CR rate 22% by investigator
- Median duration of response unclear but >1 year
- Major side effects "itis"
  - Endocrine or Inflammatory

Nivolumab: approved in US for ASCT and BV failures

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

Hodgkin lymphoma does not fit the immunotherapy paradigm

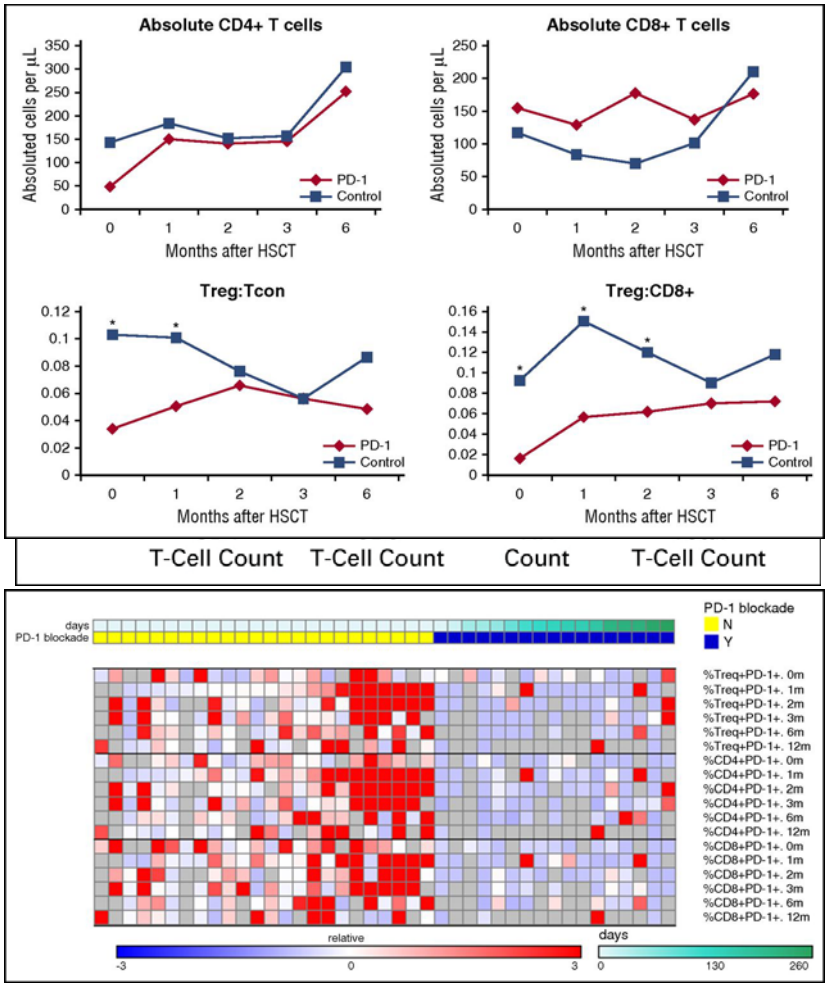
- Anti-PD-1 therapy acts in solid tumors by enhancing CD8+ T-cell recognition of tumor antigens presented by MHC-I on tumor cells
- 70-95% of HL cases lack MHC-I expression on HRS cells due to mutations in the B2M gene
- Up to 60% of HL cases lack MHC-II expression for multiple reasons including epigenetic silencing
- **How PD-1 blockade acts in HL is not known**



Vardhana and Younes, *Haematologica* 2016

Known biomarkers of response to anti-PD-1 therapy in HL

- **Evidence of T-cell activation**
  - Increase in T and NK cells in the peripheral blood
  - Increased IFN-γ response signature
  - Decreased Treg: Teff ratio
  - Decreased PD-1 expression
- These did not correlate with response to therapy



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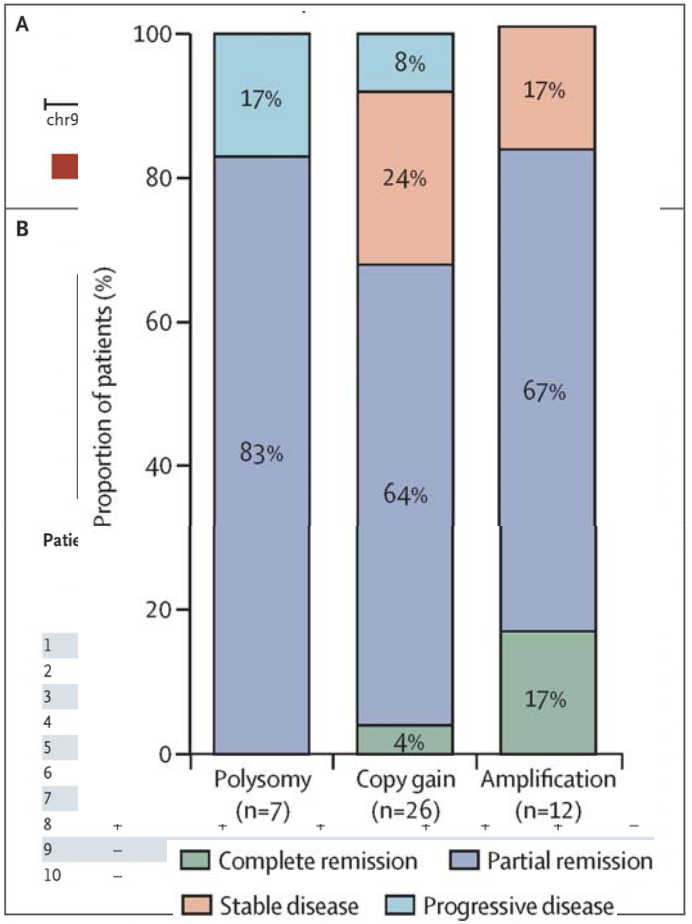
Armand et al, *J Clin Oncol* 2016
Merryman et al, *Blood* 2017

Known biomarkers of response to anti-PD-1 therapy in HL

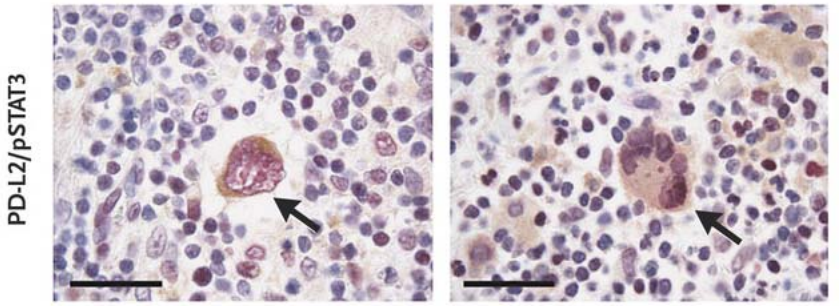
- Evidence of T-cell activation
- **Alterations in HRS cells**
  - PD-L1 expression
    - The majority of patients have multiple copies of PD-L1 (gain or amplification)
    - Polysomy, low expression by IHC may identify primary non-responders



Ansell et al, *N Engl J Med* 2015
Younes et al, *Lancet Oncol* 2016

Known biomarkers of response to anti-PD-1 therapy in HL

- Evidence of T-cell activation
- **Alterations in HRS cells**
  - PD-L1 expression
  - JAK/STAT activation
    - All patients on both a phase I and phase II study of nivolumab had nuclear pSTAT3 suggestive of constitutive JAK/STAT activation

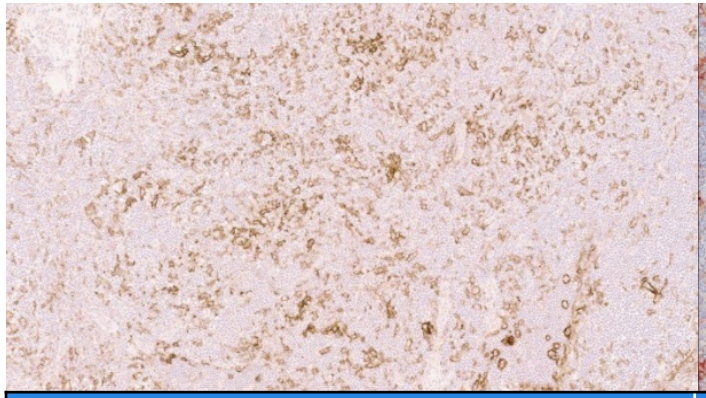


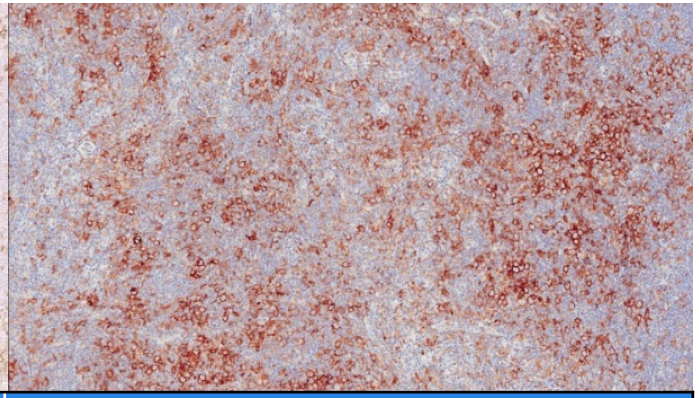
Patient No.	Cytogenetic Alterations			IHC-positive HRS cells		Nuclear pSTAT3	EBER
	Polysomy 9p	*PDL1/2* Gain	*PDL1/2* Amplification	PD-L1	PD-L2		
1	+	–	–	+	+	+	–
2	+	–	–	+	+	+	–
3	+	–	–	+	+	+	–
4	+	+	–	+	+	+	–
5	+	+	–	+	+	+	–
6	+	+	–	+	+	+	+
7	+	+	+	+	+	+	–
8	+	+	+	+	+	+	–
9	–	+	+	+	+	+	–
10	–	–	+	+	+	+	–

Ansell et al, *N Engl J Med* 2015
Younes et al, *Lancet Oncol* 2016

Immunohistochemistry

- Baseline tumor samples (n=9)

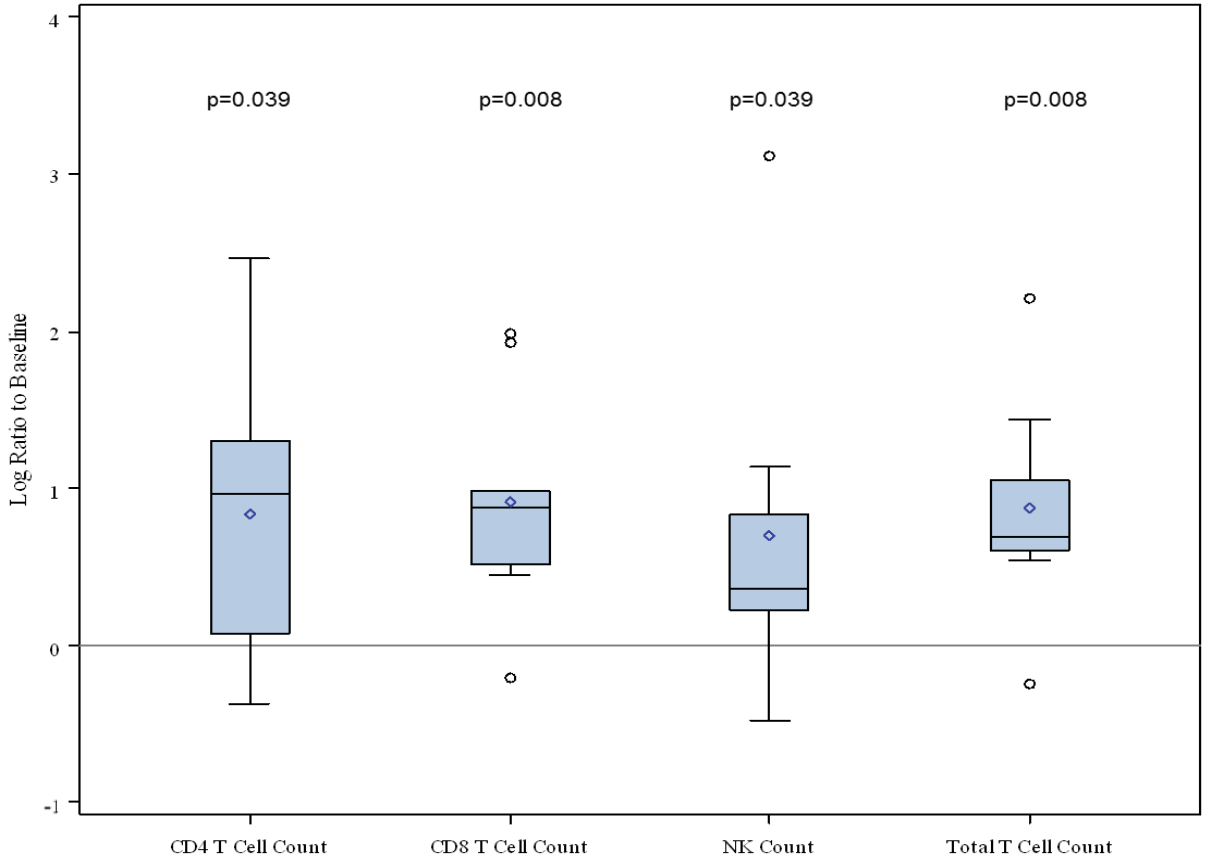




PD-L1 IHC % Tumor Cells Positive	PD-L2 IHC Score Tumor and Microenvironment
100%	4.5
100%	4.5
100%	5
0%	5
100%	5
100%	3
100%	5
30%	4.5
80%	4.5

Peripheral Blood Immunophenotyping

- PB samples baseline and cycle 7 (n=9)
- Change in circulating lymphocyte subsets by flow



NanoString Analyses

- Baseline FFPE tumor biopsies (n=19)
- 680 immune-related gene platform

IFN-γ	Expanded Immune		T-Cell Receptor Signaling	
IDO1	CD3D	NKG7	CD27	CD4
CXCL10	IDO1	HLA-E	TIGIT	CCL5
CXCL9	CIITA	CXCR6	CD8a	IL2RB
HLA-DRA	CD3E	LAG3	CD3D	IKZF3
STAT1	CCL5	TAGAP	GRAP2	CD3G
IFNG	GZMK	CXCL10	LCK	CD74
	CD2	STAT1	PTPRCAP	
	HLA-DRA	GZMB		
	CXCL13	IL2RG		

NanoString Analyses

- Baseline FFPE tumor biopsies (n=19)
- 680 immune-related gene platform

Signature	Direction	Signed Rank Test Adjusted p-value
Expanded Immune Score	Positive	0.0028
TCR Score	Positive	0.0038
IFN-γ Score	Positive	0.0052

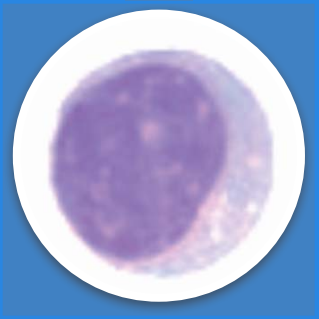
Unanswered questions regarding the MOA of anti-PD-1 therapy in HL

1. Does anti-PD-1 therapy activate anti-tumor immunity in HL, and if so, what is the effector cell?
   - CD_4+ T cells?
   - NK Cells?
2. Do immunosuppressive features of either R-S cells or the HL microenvironment predict response to anti-PD-1 therapy?
   - PD-L1 expression/genetic amplification
   - MHC-I and MHC-II expression
   - R-S cell mutational burden
   - Regulatory T-cells

Patients eligible for or receiving anti-PD-1 therapy

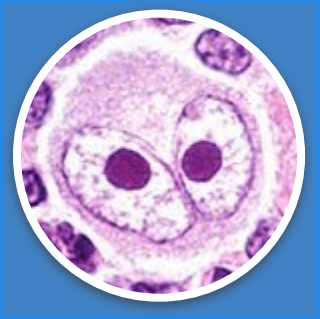
Multiple core biopsies

FFPE sections | Single cell sorting



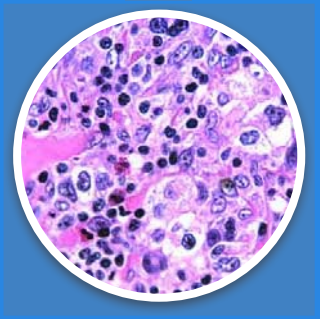
T-cells

- Immunophenotype
- Gene expression
- Clonality



HRS cells

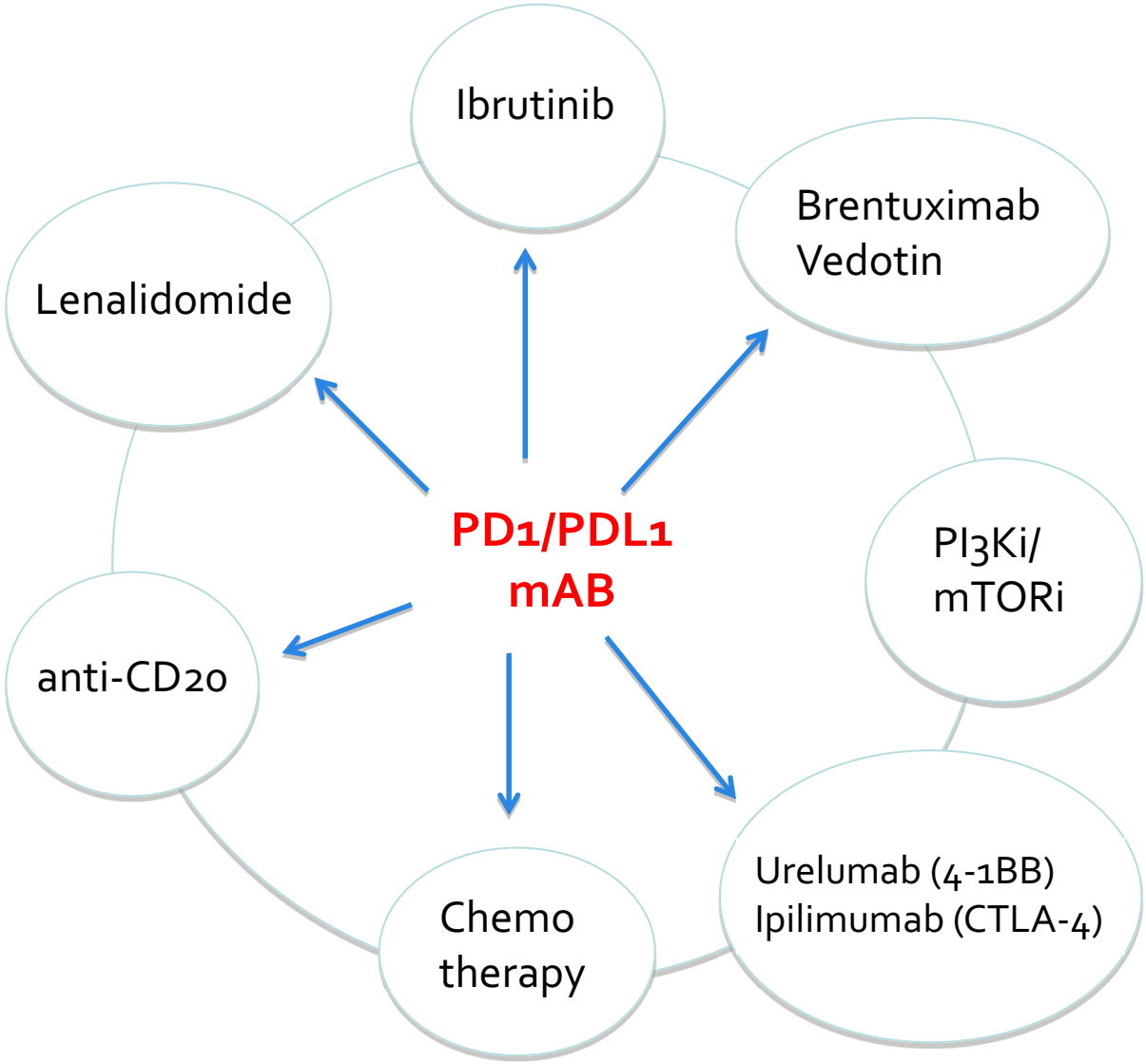
- PD-L1/2 expression
- MHC-I/II expression
- Mutational and neoantigen burden
- Gene expression



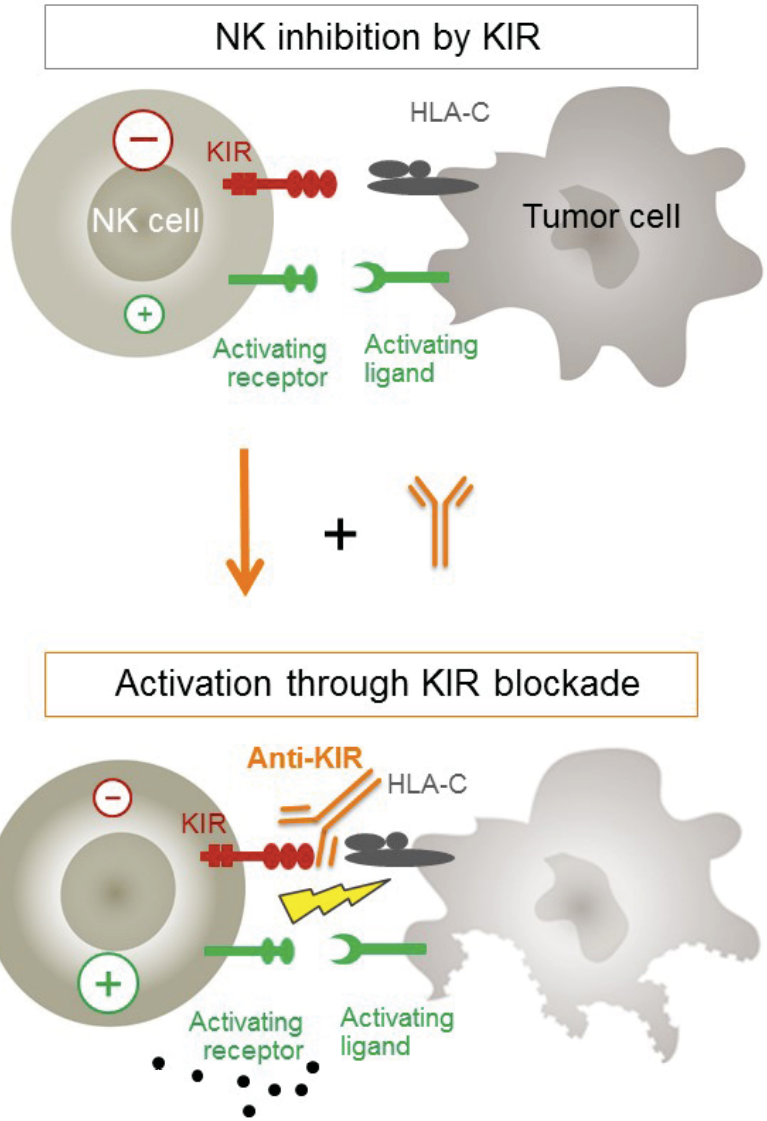
Microenvironment

- PD-L1/2 expression
- NK cell infiltration
- Treg infiltration
- Gene expression

Development of Anti-PD1/PDL1-Based Therapy



Combination Strategies
Nivolumab Plus Lirilumab



PCI32765-LYM-1002: Study Design

Nivolumab + Ibrutinib in relapsed B-cell malignancies

Part A n=18
(Dose Optimization)

A-1
I: 420 mg , po, qd
N: 3mg/kg , i.v., q14d

A-2
I: 560 mg, p.o., qd
N: 3 mg/kg, i.v., q14d

Part B (n=30 in each cohort)
(Expansion Cohort: Two-stage design)

B 1: I: 420 mg/qd PO + N: 3 mg/kg/q14d

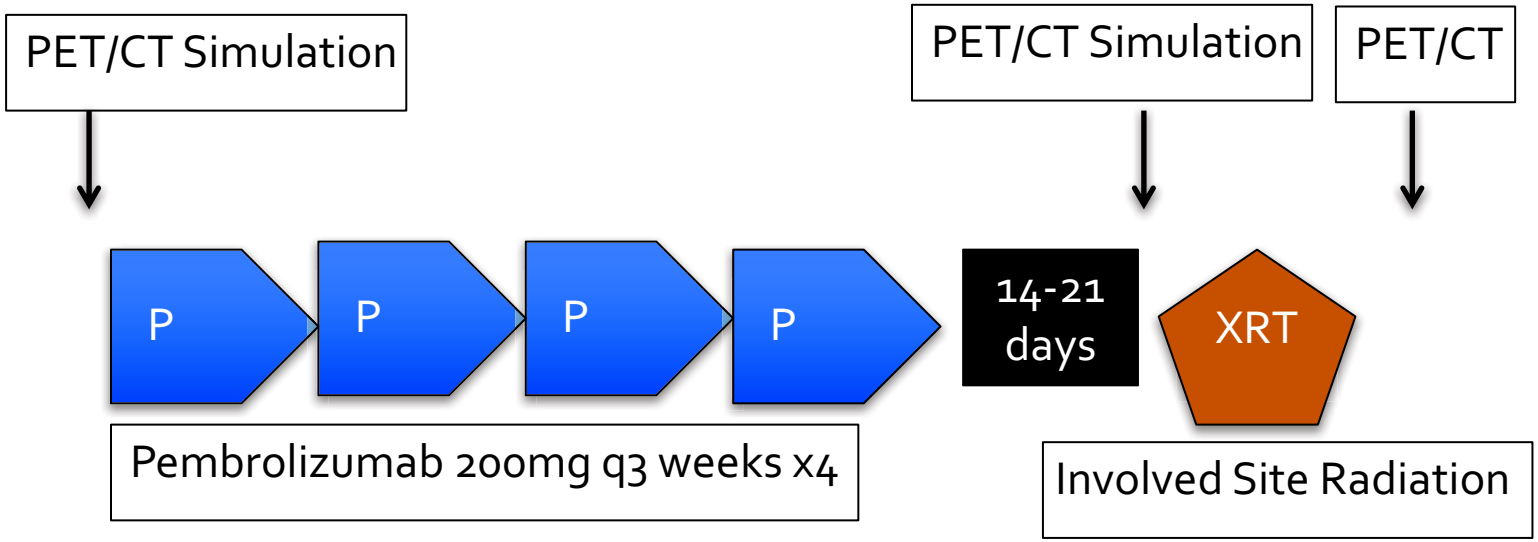
B1: CLL (del 17p or del 11q)

B 2 and B 3: I: 560 mg/qd PO + N: 3 mg/kg/q14d

B2: Follicular Lymphoma

B3: DLBCL

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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Case 2 – 66-year-old female

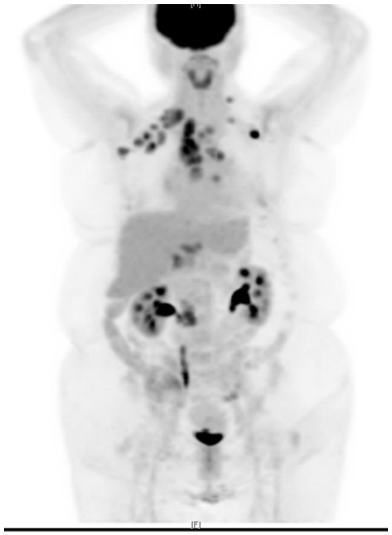
- Diagnosed with stage IIIA mixed cellularity HL in 1972.
  - treated with splenectomy and cobalt radiation
- Early 2010: developed anorexia, weight loss, fevers, sweats, rash, and pruritus
- 3/6/2010: biopsy of right groin LN consistent with mixed cellularity Hodgkin lymphoma, stage IIIB
  - treated with ABVD x 6 cycles -> CR
- Early 2011: developed left posterior cervical LN. Biopsy confirmed recurrent disease, stage IIIA
  - Received ICE x 4 months (no. of cycles unknown), complicated by bilateral PE
  - Did not go to transplant

Case 2 cont'd

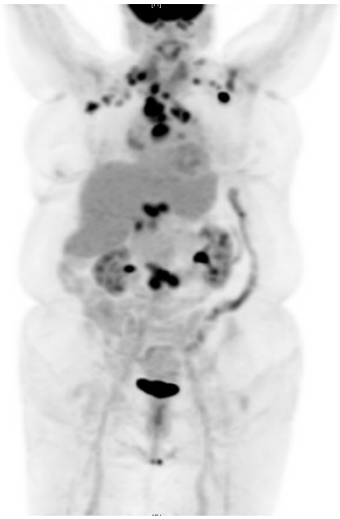
- Late 2012: recurrent disease
  - treated with EVAC x 4; critical illness following cycle 4 with pneumonia/meningitis
- 5/15/2012 - 5/24/2013: Brentuximab vedotin
- 9/2014 – 4/2015: CUDC (dual HDAC & PI3K Inhibitor) on protocol

Case 2 cont'd

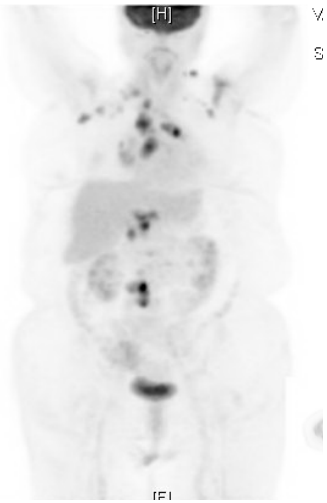
- 11/24/15: Initiated Pembrolizumab 200mg q 3 weeks on Phase 2 clinical trial
  - Received 19 doses
  - Toxicities related to treatment: hypothyroidism, rash
- 10/21/16: POD, but continued tx on study
- 1/2017: further POD →off study



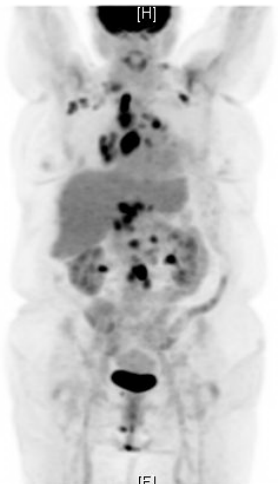
Baseline 11/16/2015



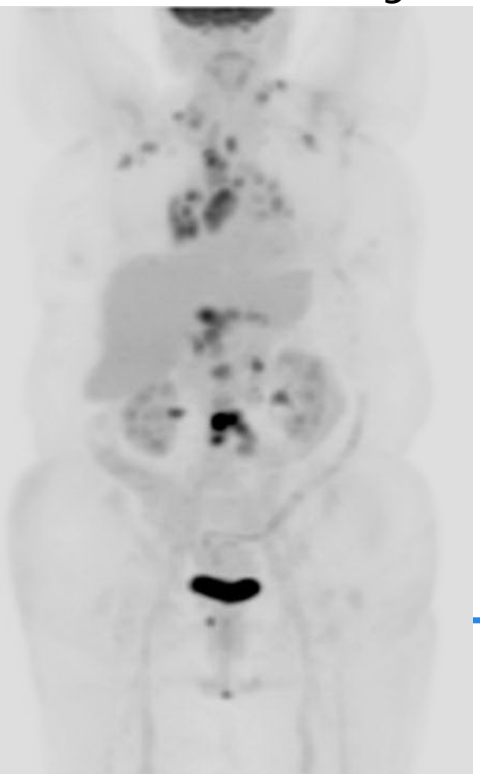
2/12/2016



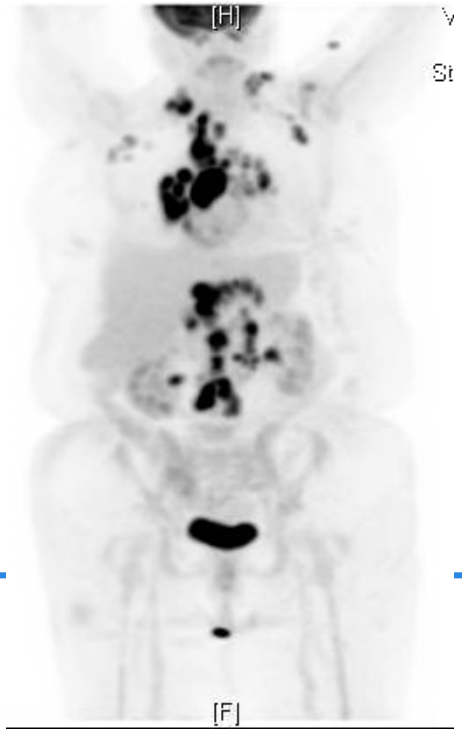
Best response 5/6/2016



8/1/2016



12/9/2016



2/2017