Origins and Organization of PD-1: PD-L1 Interactions in Classical Hodgkin lymphoma

Scott Rodig MD, PhD

Center for Immuno-Oncology, Dana-Farber Cancer Institute
Department of Pathology, Brigham & Women’s Hospital
Harvard Medical School
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- and -

I will not discuss off label use and/or investigational use in my presentation.
Classical Hodgkin Lymphoma

**Definition:**
Malignancy of B-cell lineage with a unique clinical presentation, histomorphology, phenotype, and genetics.

**Diagnosis:**
Identification of Reed-Sternberg (HRS) cells in a mixed inflammatory background

20-30% are EBV+

**Treatment:**
ABVD, Stanford V, BEACOPP

**Outcome:**
Cure rate approx. 80%.
But survival for relapsed/refractory disease is very low (20%)

ABVD=adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPP=bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, prednisone; EBV=Epstein-Barr virus.
PART I: The HRS Cell
9p24.1 Amplicon Block in cHL

Green et al, Blood 2010; 116:3268
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PD-1 :PD-L1 Signaling

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Adapted from: Freeman G et al., Proc Natl Acad Sci 2008
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PD-1 :PD-L1 Signaling

Dephosphorylation

T Cell

ITSM - P

SHP-2

P

Proximal signaling kinases

T-cell Activation

Antigen Presenting Cell (APC)

PD-1

PD-1 ligand

ITIM - P

CD3

TCR

MHC

CD8

Adapted from:
Freeman G et al., Proc Natl Acad Sci 2008
PD-1 : PD-L1 Signaling

Adapted from: Freeman G et al., Proc Natl Acad Sci 2008
PD-1 :PD-L1 Signaling

T Cell

Deactivation of T-cell signaling

ITSM

SHP-2

ITIM

Proximal signaling kinases

T-cell Activation

Nivolumab (Opdivo)
Pembrolizumab (Keytruda)
Atezolizumab; anti-PDL1 (Tecentriq)

PD-1

PD-L1

PD-L2

CD3

TCR

MHC

CD8

Adapted from:
Freeman G et al., Proc Natl Acad Sci 2008
PD-1 :PD-L1 Signaling

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PD-1

PD-L1

PD-L2

ITSM

SHP-2

ITIM

CD3

TCR

MHC

CD8

Tumor cell

Adapted from:
Freeman G et al., Proc Natl Acad Sci 2008
Robust PD-L1 Expression is characteristic of Reed-Sternberg cells in Primary cHL

1. 87% of primary cHL show PD-L1 expression by the HRS cells
2. 11% of primary non-Hodgkin lymphomas show PD-L1 expression by the malignant B-cells

**PD-L1 and PD-L2 Genetic Alterations Define Classical Hodgkin Lymphoma and Predict Outcome**

1. 108 Patients enrolled in a trial of Stanford V (chemotherapy +/- radiation)

2. Uniform treatment and clinical/radiological follow-up

3. We performed FISH and IHC analysis on FFPE diagnostic biopsy samples collected as part of the trial

PD-L1 and PD-L2 Genetic Alterations Define Classical Hodgkin Lymphoma and Predict Outcome

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**B**
- Disomy
- Polysomy
- Copy Gain
- Amplification

**C**
- PD-L1/PAX5
- PD-L1/PAX5
- PD-L1/PAX5
- PD-L1/PAX5

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Frequency of 9p24.1 Genetic Alterations in cHL Cohort

Alterations of 9p24 is a defining characteristic of HRS cells in cHL

Roemer M et al. JCO. 2016
Highest PD-L1 Expression among HRS cells is Correlated with the Lowest Residual Disomy for PD-L1/ PD-L2
Progression-Free Survival (PFS) by 9p24.1 Genetic Alterations

1. Significant differences in outcome (PFS) by 9p24.1 genetic alteration -
2. **PD-L1/PD-L2** amplification most unfavorable, $p<0.001$
3. Results suggest a role for immune evasion in the progression of cHL and response to chemotherapy

Rationale for PD-1 Blockade in cHL

1. Gain of 9p24.1 is a genetic basis for PD-Ligand expression by Reed-Sternberg cells.

2. Gain of 9p24.1 is a defining characteristic of Reed-Sternberg cells.

3. PD-L1 and PD-L2 protein expression is promoted by multiple, re-enforcing mechanisms and highly expressed by Reed-Sternberg cells in the majority of cHLs

4. PD1 Blockade is likely to be more effective than PD-L1 blockade in cHL due to co-expression of PD-L2
PD-1 Blockade with Nivolumab in Relapsed or Refractory Hodgkin’s Lymphoma

Change in Tumor Burden

<table>
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<tr>
<th>Change (%)</th>
<th>Stable Disease</th>
<th>Partial Response</th>
<th>Complete Response</th>
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Individual Patient Data (N=23)

Nivolumab ORR= 87%
Pembrolizumab ORR= 65%

**PD-L1/PD-L2 Copy Number Alterations and Protein Expression**

<table>
<thead>
<tr>
<th>Case</th>
<th>PD-L1/PD-L2 copy gain</th>
<th>PD-L1 in HRS</th>
<th>PD-L2 in HRS</th>
<th>pSTAT3 in HRS</th>
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Ansell et al, NEJM 2015; 372:311
### Phase 1: Durability of Response in R/R cHL

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<th>Overall response, n (%)</th>
<th>76 Weeks</th>
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<td>20 (87)</td>
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<th>24-week progression-free survival, %</th>
<th>87%</th>
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<th>Duration of response, median (range)</th>
<th>NR (18–82+)</th>
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Phase 2: PD-1 Blockade in R/R cHL

• 80 patients
• Short clinical follow-up

Younes et al., Lancet Onc, 2016
Phase 2: PD-1 Blockade in R/R cHL

Younes et al., Lancet Onc, 2016
Phase 2: PD-1 Blockade in R/R cHL

Younes et al., Lancet Onc, 2016
Conclusions: PD-1 Blockade in R/R cHL

1. Gain of 9p24.1 and near universal expression of PD-L1 and PD-L2 provides a biological rationale for the efficacy of PD-1 blockade in patients with relapsed/ refractory cHL.

2. PD-1 blockade is effective treatment for patients with relapsed/ refractory cHL
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FDA Approves Nivolumab for Heavily Pretreated Classical Hodgkin Lymphoma

By The ASCO Post
May 25, 2016 (/issues/may-25-2016/)
9p24.1 Alterations in NHL

1. Primary mediastinal (thymic) large B-cell lymphoma

2. Primary CNS lymphoma

3. Primary Testicular lymphoma
9p24.1 Alterations in NHL

1. Primary mediastinal (thymic) large B-cell lymphoma

Shi et al. AJSP., 2014.
9p24.1 Alterations in Solid Tumors

Cervical cancer

Howitt et al. JAMA Oncol., 2016.
PART II: The Microenvironment
PART II: The Microenvironment

PD-L1
Quantitative Analysis of the Tumor Microenvironment in cHL
PD-L1 co-localizes with CD30+ HRS cells and with CD68+ TAMs
TAMs and HRS cells Contribute to the Pool of PD-L1 in cHL

The **majority** of PD-L1 in cHL is derived from CD68+ TAMs not HRS cells
PD-L1+ TAMs form an **Immuno-Protective Niche** for HRS cells in Classical Hodgkin Lymphoma

CHL is characterized by multiple, re-enforcing mechanisms that ensure a tolerant immune microenvironment in the immediate vicinity of HRS cells
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<td>Brigham and Women’s Hospital</td>
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<td>Evisa Gjini</td>
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