Anti-PD1 Therapy **AFTER** allogeneic stem cell transplant

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Conflicts of Interest

• Research Funding from –
  – Bristol Myers Squibb
  – Celldex Therapeutics
  – Seattle Genetics
PD-1 Blockade after Allo Transplant

- Preclinical data regarding the role of PD-1/PD-L1 interactions in allo patients
  - Some data suggests benefit
  - Some data suggests risk
- Clinical data with anti-PD-1 antibodies post allogeneic transplant.
Benefit? Relapsed Myeloid leukemia cells post allogeneic transplant express PD-L1

Benefit? Blocking PD1 post allogeneic transplant restores T-cell function

A  PD-L⁺ AML Pt 9

B  PD-L1⁺/L2⁺ mDC

A

3H-Thymidine incorporation (cpm x 10⁴)

C  3H-Thymidine incorporation (cpm x 10³)

D  3H-Thymidine incorporation (cpm x 10³)

Allogenic CD3⁺ T cells

C

IFN-γ production, pg/mL

D  IFN-γ production, pg/mL

Medium  Isotype  αPD-1  αPD-L1

Medium  Isotype  αPD-1  αPD-L1

Medium  Isotype  αPD-1  αPD-L1

Medium  Isotype  αPD-1  αPD-L1

Risk? The PD-1 Axis Creates Tumor Niches after Allogeneic Hematopoietic Stem Cell Transplantation.
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**PD-1 Blockade**

- PD-1 ligands are overexpressed in inflammatory environments and attenuate the immune response via PD-1 on immune effector cells.¹
- PD-L1 expressed on malignant cells and/or in the tumor microenvironment suppresses tumor infiltrating lymphocyte activity and interferes with host antitumor immunity.²

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Table 1: Clinical characteristics of the two patients with advanced cHL and history of allogeneic stem cell transplant treated with pembrolizumab

<table>
<thead>
<tr>
<th></th>
<th>PATIENT 1</th>
<th>PATIENT 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PRE-TREATMENT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Male</td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td>2007</td>
<td>2008</td>
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<tr>
<td>Autologous SCT</td>
<td>March 2008</td>
<td>April 2009</td>
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<tr>
<td>Allogeneic SCT</td>
<td>January 2009</td>
<td>January 2014</td>
</tr>
<tr>
<td>Number of other prior systemic therapies</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Previous brentuximab vedotin</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic GVHD (location; stage)*</td>
<td>Liver (score 1)</td>
<td>None</td>
</tr>
<tr>
<td>Prednisone dosage</td>
<td>2.5 mg daily</td>
<td>2.5 mg daily</td>
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<tr>
<td>Date of first pembrolizumab infusion</td>
<td>October 21, 2014</td>
<td>July 7, 2015</td>
</tr>
<tr>
<td><strong>POST-TREATMENT</strong></td>
<td></td>
<td></td>
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<tr>
<td>Best overall response</td>
<td>Complete response</td>
<td>Partial Response</td>
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<tr>
<td>Chronic GVHD (location; stage)*</td>
<td>Liver (score 1)</td>
<td>None</td>
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<tr>
<td>Date of last infusion</td>
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<td>Number of total infusions</td>
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<td>7</td>
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<td>Date of last radiological assessment</td>
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<td>October 5, 2015</td>
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<td>Treatment status</td>
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<td>Ongoing</td>
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Villasboas et al. Oncotarget 2016
Clinical Results with PD-1 Blockade post Allo

Angenendt et al. Bone Marrow Transplantation (2016) 51, 443–445
Cautionary note –
Fatal graft vs host disease induced by PD-1 inhibitor pembrolizumab in a patient with Hodgkin's lymphoma
Case report – post allogeneic transplant for Hodgkin lymphoma

Singh et al. Bone Marrow Transplant 2016
Ipilimumab (CTLA-4 blockade) after allogeneic hematopoietic cell transplantation

- 29 patients with relapsed hematologic disease.
- Three patients with lymphoid malignancy developed objective disease responses following ipilimumab:
  - CR in 2 patients with Hodgkin disease
  - PR in a patient with refractory mantle cell lymphoma.
- Ipilimumab did not induce or exacerbate clinical GVHD

Conclusions

• PD-1 blockade can be given safely post allogeneic transplant
• However, severe toxicity with PD-1 blockade post allogeneic transplant has also been described.
• Cautious if active GVHD present?
• Needs a clinical trial