Immune checkpoint inhibitors in Hodgkin and non-Hodgkin Lymphoma: How do they work? Where will we use them?

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Mayo Clinic
Conflicts of Interest

• Research Funding from –
  – Bristol Myers Squibb
  – Celldex Therapeutics
  – Seattle Genetics
Immune checkpoint inhibitors in Hodgkin and non-Hodgkin Lymphoma

• What’s the rationale for using them?
• How do they work?
• How well do they work?
• Where will we use them?
  – Alone?
  – In combinations?
What’s the rationale for using Immune Checkpoint Inhibitors in Lymphomas?
How do they work?

Targets for immune modulation

How does blocking inhibitory signals work?

Does Immune Checkpoint Blockade work?

Blocking CTLA4

• Treated 18 patients with ipilimumab 3mg/kg
• 2 patients responded; 1 CR (>31 months), 1 PR (19 months)
• In 5 of 16 cases (31%), T-cell proliferation to recall antigens was increased (>2-fold)

Ipilimumab to treat relapse 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

Does Immune Checkpoint Blockade work? Blocking PD-1

- 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.\(^2\)

\(^2\)Andorsky DJ et al. Clin Cancer Res 2011;17:4232-44
Pidilizumab After Autologous Hematopoietic Stem-Cell Transplantation for DLBCL

- Pidilizumab is an anti–PD-1 humanized IgG1 monoclonal antibody
- Sixty-six eligible patients were treated.
- PFS at 16 months was 0.72 (90% CI, 0.60 to 0.82), meeting the primary end point.
- Among the 24 high-risk patients who remained positive on PET after salvage chemotherapy, the 16-month PFS was 0.70 (90% CI, 0.51 to 0.82).
- Among the 35 patients with measurable disease after AHSCT, the overall response rate after pidilizumab treatment was 51%.

Armand et al. JCO 2013;31:4199-4206
32 patients enrolled.
The combination was well tolerated.
Of 29 evaluable patients, 19 (66%) achieved an objective response: CRs in 15 (52%) patients and PRs in four (14%).
Nivolumab – Phase I/II Study Design

Relapsed or Refractory HM (N=105)
- No autoimmune disease
- No prior organ or stem cell allografting
- No prior checkpoint blockade

Dose Escalation
Nivolumab 1mg/kg → 3mg/kg
Wks 1,4 then q2w
(N=13)
- B-Cell Lymphoma (n=8)
- CML (n=1)
- Multiple Myeloma (n=4)

Dose Expansion (3mg/kg)
Hodgkin Lymphoma (n=23)

Endpoints

Primary
- Safety and Tolerability

Secondary
- Best Overall Response
- Investigator assessed
- Objective Response
- Duration of Response
  - PFS
- Biomarker studies

Lesokhin et al. ASH 2014, abstract 291
Nivolumab - Drug-related Adverse Events

Overview

- Safety profile similar to other nivolumab trials
- The majority of pneumonitis cases were Grade 1 or 2
- No clear association between pneumonitis and prior radiation (28 patients), brentuximab vedotin (9 patients) or gemcitabine

<table>
<thead>
<tr>
<th>Nivolumab (N=82)</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Grade Related AE</td>
<td>51 (62)</td>
</tr>
<tr>
<td>Any Grade Drug-related AE Occurring in ≥ 5% of Patients</td>
<td>n (%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (13)</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>9 (11)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Rash</td>
<td>7 (9)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Anemia</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>5 (6)</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>5 (6)</td>
</tr>
</tbody>
</table>

Lesokhin et al. ASH 2014, abstract 291
## Nivolumab - Best Overall Response

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>Objective Response Rate, n (%)</th>
<th>Complete Responses, n (%)</th>
<th>Partial Responses, n (%)</th>
<th>Stable Disease n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>B-Cell Lymphoma</strong> (n=29)</td>
<td>8 (28)</td>
<td>2 (7)</td>
<td>6 (21)</td>
<td>14 (48)</td>
</tr>
<tr>
<td><strong>Follicular Lymphoma</strong> (n=10)</td>
<td>4 (40)</td>
<td>1 (10)</td>
<td>3 (30)</td>
<td>6 (60)</td>
</tr>
<tr>
<td><strong>Diffuse Large B-Cell Lymphoma</strong> (n=11)</td>
<td>4 (36)</td>
<td>1 (9)</td>
<td>3 (27)</td>
<td>3 (27)</td>
</tr>
<tr>
<td><strong>T-Cell Lymphoma</strong> † (n=23)</td>
<td>4 (17)</td>
<td>0 (0)</td>
<td>4 (17)</td>
<td>10 (43)</td>
</tr>
<tr>
<td><strong>Mycosis Fungoides</strong> (n=13)</td>
<td>2 (15)</td>
<td>0 (0)</td>
<td>2 (15)</td>
<td>9 (69)</td>
</tr>
<tr>
<td><strong>Peripheral T-Cell Lymphoma</strong> (n=5)</td>
<td>2 (40)</td>
<td>0 (0)</td>
<td>2 (40)</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>Multiple Myeloma</strong> (n=27)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>18 (67)</td>
</tr>
<tr>
<td><strong>Primary Mediastinal B-Cell Lymphoma</strong> (n=2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (100)</td>
</tr>
</tbody>
</table>

*includes other B-cell lymphoma (n=8)
†includes other cutaneous T-cell lymphoma (n=3) and other non-cutaneous T-cell lymphoma (n=2)

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Hodgkin Lymphoma - Response to Nivolumab

Response Duration - Nivolumab

9p24.1/PD-L1/PD-L2 Locus Integrity and Protein Expression

**PD-L1/2 locus integrity**
- Red=PD-L1
- Green=PD-L2
- Yellow= Red + Green
- Cyan=Centromere

**Immunohistochemistry**
- PD-L1 (brown)
  - PAX-5 (red)
- PD-L2 (brown)
  - pSTAT3 (red)
**Hodgkin Lymphoma - Response to Pembrolizumab (n=29)**

*Patient became PET negative and was therefore declared to be in complete remission.
Analysis cut-off date: November 17, 2014.

*Patient became PET negative and was therefore declared to be in complete remission.

Moskowitz et al. ASH 2014, abstract 290
Treatment Exposure and Response Duration

- Median time to response: 12 weeks
- 89% (17 of 19) of responses were ongoing as of November 17
- Duration of response
  - Median: not reached
  - Range: 1+ to 185+ days

Moskowitz et al. ASH 2014, abstract 290
## Treatment-Related Adverse Events of Any Grade Observed in ≥2 Patients

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>n (%)</th>
<th>N = 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypothyroidism</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>3 (10)</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>2 (7)</td>
<td></td>
</tr>
<tr>
<td>Hematuria</td>
<td>2 (7)</td>
<td></td>
</tr>
</tbody>
</table>

- 16 (55%) patients experienced ≥1 treatment-related AE of any grade

Analysis cut-off date: November 17, 2014.
Among the 10 enrolled patients who provided samples evaluable for PD-L1 expression, 100% were PD-L1 positive.

Best overall response in these 10 patients was CR in 1 patient, PR in 2 patients, SD in 4 patients, and PD in 3 patients.

PD-L1 expression was assessed using a prototype immunohistochemistry assay and the 22C3 antibody. PD-L1 positivity was defined as Reed-Sternberg cell membrane staining with 2+ or greater intensity.

Analysis cut-off date: November 17, 2014.

Moskowitz et al. ASH 2014, abstract 290
All B-Cell Lymphoma Patient Responses

Percent Change from Baseline

Time since First Dose (Weeks)

Diffuse Large B-Cell lymphoma
Follicular B-Cell Lymphoma
Other B-Cell Lymphoma
All T-Cell Lymphoma Patient Responses

Lesokhin et al. ASH 2014, abstract 291
Does activating immune stimulatory signals work? – CD27 and CD40

Phase I trial of an agonist anti-CD27 antibody (Varlilumab/CDX-1127) in lymphoma patients

- 24 patients enrolled
- No significant depletion in absolute lymphocyte counts, T cells or B cells
- Evidence of increased immunologic activity, consistent with expected mechanism of action:
  - Increased soluble CD27
  - Reduction of circulating Tregs
  - Induction of pro-inflammatory cytokines
- Anti-lymphoma activity – 1 CR in a patient with Hodgkin Lymphoma

Ansell et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 3024)
Phase I study of humanized anti-CD40 monoclonal antibody dacetuzumab in recurrent non-Hodgkin's lymphoma.

• 50 patients treated.
• Two DLTs: conjunctivitis and ALT elevation.
• Six objective responses (one complete response, five partial responses).
• Tumor size decreased in approximately one third of patients.

Advani et al. JCO 2009;27:4371-4377
How will use Immune Checkpoint Inhibitors in the future? - Reprogramming Approach

- Reprogramming Approach
  - Depletion of malignant cells
  - Inhibition of critical pathways
  - Immune activation
How can the Depletion Approach be improved by Immune Checkpoint Blockade?

- Sequencing standard chemotherapy before or after immune checkpoint blockade
- Using antibody-drug conjugates for targeted killing – Brentuximab vedotin plus PD-1 blockade
- Giving immune checkpoint inhibition post transplant – pidilizumab
How can the Pathway Inhibition Approach be improved by Immune Checkpoint Blockade?

- Use small molecule inhibitors that potentially upregulate immune receptors/ligands – HDAC inhibitors
- Using inhibitors that have off target effects that promote immune (T-cell) function – ibrutinib, idelalisib
- Blocking downstream signaling induced by immune checkpoints – mTOR inhibitors, PI3 Kinase inhibitors
How can the Immune Optimization Approach be improved by Immune Checkpoint Blockade?

- Inhibit more than one immune checkpoint – PD-1/PD-L1 and CTLA4/LAG-3/TIM-3
- Block an inhibitory signal and simultaneously give an activating signal – PD-1/PD-L1 and 4-1BB or OX-40
- Use a different immune activator – CART/bispecific antibody/BITE/viral therapy/vaccine in combination with an immune checkpoint inhibitor.
Conclusions

• Optimizing immune function is the new therapeutic “frontier” in B-cell lymphomas
• Immune checkpoint inhibitors hold real promise in Hodgkin and non-Hodgkin lymphoma.
• Multiple new agents (anti-PDL1, anti-LAG3, anti-TIM3) are in development to block immune suppression or induce immune stimulation.
• Incorporating promising immunologic agents into combination approaches will be the next clinical challenge.