Immunotherapy: Myth or Reality?

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**Abstract**

Intratumor heterogeneity may foster tumor evolution and adaptation and hinder personalized-medicine strategies that depend on results from single tumor-biopsy samples.

**Methods**

“One may ultimately have to consider each advanced malignancy as an individual therapeutic problem....Immunotherapy becomes a leading candidate for the easiest means of destroying the remainder of the neoplastic clone...it is more feasible to produce specific cytotoxic antiserums or lymphocytes against a particular tumor than to design a specific chemotherapeutic agent for each neoplasm.”
Heterogeneity – Burden or Asset?

- Development of a sufficiently large arsenal of molecularly targeted therapies is a technical and clinical challenge.

- Resistance to targeted therapies can develop due to clonal diversity and evolution.

*Immune-based therapy is uniquely suited to addressing the challenge of cancer heterogeneity.*
Phase I Nivolumab: RCC cohort (n=34)

- Generally tolerable: fatigue, rash, pruritus, diarrhea
  - 3 deaths: pneumonitis (non-RCC)

- Preliminary efficacy in heavily pre-treated patients:
  - 29% objective responses
  - Median PFS 7.3 months

[Graph showing treatment-free survival (TFS)]

All stopped therapy

Treatment - Free Survival (TFS)

Drake ASCO 2013
Meeting the goal of the patient

Nivo RCC Phase 2: Duration of response

0.3 mg/kg (n=12)  2 mg/kg (n=12)  10 mg/kg (n=11)

Motzer et al, ASCO 2014
Making PD-1 Pathway Blockade Based Immunotherapy a Reality

• Efficacy data
  – Will the clinical activity = improved OS?
  – How many responses are durable off therapy?
    • As seen with IL-2 and ipilimumab

• Predictive Biomarkers
  – Can we improve patient selection and move PD-1 pathway blockade to the first-line?

• Combination Therapy
  – Can we produce more durable responses?
## PD-L1 Expression and Response

<table>
<thead>
<tr>
<th>Agent(s)</th>
<th>Tumor Type</th>
<th>n</th>
<th>RR (%)</th>
<th>RR(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>PD-L1 pos</td>
<td>PD-L1 neg</td>
</tr>
<tr>
<td>Nivolumab¹</td>
<td>Multiple Solid Tumors</td>
<td>42</td>
<td>36%</td>
<td>0%</td>
</tr>
<tr>
<td>MPDL3280A²</td>
<td>Kidney Cancer</td>
<td>47</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Nivolumab³</td>
<td>Melanoma</td>
<td>34</td>
<td>44%</td>
<td>17%</td>
</tr>
<tr>
<td>Nivo/Ipi⁴</td>
<td>Melanoma</td>
<td>27</td>
<td>40%</td>
<td>47%</td>
</tr>
</tbody>
</table>

Making PD-1 Pathway Blockade Based Immunotherapy a Reality

• Efficacy data

• Predictive Biomarkers
  – Are they ready to guide clinical development?
  – Should we stratify patients on pivotal trials based on PD-L1 expression?
  – Can we develop a reliable response prediction (PRP) model?
    • Incorporating tumor and immune infiltrate
    • Incorporating multiple platforms:
      – IHC + IF + Mutational signature + Gene Expression

• Combination Therapy
Towards a Multi-factor PRP Model: Tumor + Infiltrate

Representative confocal images of triple immunofluorescence labeling for CD8, PD-1 and TIM-3 in a FFPE clear cell RCC sample. A subset of T-cells co-expressing CD8, PD-1 and TIM-3 is identified.

S Signoretti, with permission
MPDL3280A Phase Ia: Response by Smoking and Mutational Status

Tumor grade and response to PD-1 Blockade in RCC

- Nivolumab Phase 1 Trial
  - ORR = 29% (n=34)
  - ORR by tumor grade – based on path reports
    - Grade 1/2 – 18%
    - Grade 3/4 – 45% (9/20)
    - Grade 4 – 62% (5/8)
Somatic mutations by tumor type

MS Lawrence et al. Nature 2013
Somatic mutations have the potential to generate neoantigens
Making Immunotherapy a Reality

All Patients

Biomarker +, responsive:
Single agents PD-1/PD-L1 Ab

Immune response

Tumor Defense

PD-L1
Making Immunotherapy a Reality

• Efficacy data

• Predictive Biomarkers

• Combination Therapy
  – Which will improve durable response rate?
  – Will toxicities limit potential?
Making Immunotherapy a Reality

Biomarker+, Rx Sensitive: Single agents PD-1/PD-L1 Ab

Biomarker+, Rx Resistant: Combination Therapy

1) Elimination of Tregs: anti-GTR, CCR4
2) Inhibition of VEGF/MDSC: anti-VEGF, HDM2
3) Support effector T cells: IL-2, CD137 Ab, IL-21
4) Support DCs: GM-CSF
5) Other checkpoint inhibitors (CTLA4, TIM3 etc)
Rationale to Combine PD-L1 + VEGF Abs

- Anti-VEGF therapy has immunomodulatory properties
  - Increases trafficking of T cells into tumors\(^1,2\)
  - Reduces suppressive cytokines and infiltrating Tregs and MDSCs\(^3,4\)

Cloudman melanoma model\(^5\)

RAPID: A Randomised phase II study investigating anti-PDL-1 alone or in combination with bevacizumab in mRCC

Eligibility
Metastatic clear cell renal cancer
Measurable disease (RECIST v1.1)
Archived or fresh tissue available
PDL-1 +ve and – ve patients eligible
No previous therapy for metastatic disease

Primary endpoint
Progression free survival
N=150 in 40 sites
PD-1 Ab + VEGF TKI = more efficacy?

Responders at first assessment (6 weeks):
S + N = 7/17 (41.2%)
P + N = 5/9 (55.6%)

Ongoing responders:
S + N = 10/17 (58.8%)
P + N = 3/9 (33.3%)

Median follow-up: S + N2, 91 weeks; S + N5, 53 weeks; P + N, 76.5 weeks

Amin, et al ASCO 2014
Making Immunotherapy a Reality

Biomarker +, Rx Sensitive:
Single agents PD-1/PD-L1 Ab

Biomarker +, Rx Resistant:
Combination Therapy

1) Elimination of Tregs: anti-GTR, CCR4
2) Inhibition of VEGF/MDSC: VEGF RTK, HDM2
3) Support effector T cells: IL-2, CD137 Ab, IL-15, IL-21
4) Support DCs: GM-CSF
5) Other checkpoint inhibitors CTLA4, LAG3, TIM3 etc

All Kidney Tumors

Immune Response
Phase I study of nivolumab in combination with ipilimumab in metastatic renal cell carcinoma (mRCC)

## Treatment-related select AE categories

<table>
<thead>
<tr>
<th>Category, n (%)</th>
<th>N3 + I1 (n=21)</th>
<th></th>
<th>N1 + I3 (n=23)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3-4</td>
<td>All</td>
<td>Grade 3-4</td>
</tr>
<tr>
<td>Endocrinopathy</td>
<td>3 (14.3)</td>
<td>0</td>
<td>8 (34.8)</td>
<td>0</td>
</tr>
<tr>
<td>Gastrointestinal disorder</td>
<td>6 (28.6)</td>
<td>1 (4.8)</td>
<td>9 (39.1)</td>
<td>4 (17.4)</td>
</tr>
<tr>
<td>Hepatic</td>
<td>1 (4.8)</td>
<td>0</td>
<td>9 (39.1)</td>
<td>6 (26.1)</td>
</tr>
<tr>
<td>Infusion reaction</td>
<td>2 (9.5)</td>
<td>0</td>
<td>2 (8.7)</td>
<td>0</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1 (4.8)</td>
<td>0</td>
<td>2 (8.7)</td>
<td>0</td>
</tr>
<tr>
<td>Renal disorder</td>
<td>2 (9.5)</td>
<td>0</td>
<td>3 (13.0)</td>
<td>0</td>
</tr>
<tr>
<td>Skin disorder</td>
<td>8 (38.1)</td>
<td>0</td>
<td>9 (39.1)</td>
<td>0</td>
</tr>
</tbody>
</table>

- No high-grade pulmonary AEs, including pneumonitis, were observed

Hammers, et al ASCO 2104
PD-1 + CTLA-4 Blockade = more efficacy?

Responders at first assessment (6 weeks):
N3 + I1 = 4/9 (44.4%)
N1 + I3 = 6/11 (54.5%)

Ongoing responders:
N3 + I1 = 7/9 (77.8%)
N1 + I3 = 9/11 (81.8%)

Patients discontinuing treatment (not due to progression) who continued to respond:
N3 + I1 = 3/9 (33.3%)
(23.3, 16.4, & 0.3 weeks)
N1 + I3 = 5/11 (45.5%)
(17, 22, 12.3, 7.2 & 4.1 weeks)

- Median duration of response (DOR) for N3 + I1 was 31 weeks
- Median DOR was not reached in the N1 + I3 arm at 40.1 weeks follow-up
## Current PD-1 Pathway Trials in RCC

<table>
<thead>
<tr>
<th>Trial</th>
<th>Sponsor</th>
<th>Status</th>
<th>NCT #</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab vs. Everolimus Phase III</td>
<td>BMS</td>
<td>Enrolled</td>
<td>01844505</td>
</tr>
<tr>
<td>Phase I/II Pazopanib + Pembro</td>
<td>GSK</td>
<td>Enrolling</td>
<td>02014636</td>
</tr>
<tr>
<td>Phase II PD-L1 vs. Bev/PD-L1 vs. Sunitinib</td>
<td>Genentech</td>
<td>Enrolling</td>
<td>01984242</td>
</tr>
<tr>
<td>Phase I Axitinib + Pembro</td>
<td>Pfizer</td>
<td>Enrolling</td>
<td>02133742</td>
</tr>
<tr>
<td>Nivo/Ipi vs. Sunitinib Phase III</td>
<td>BMS</td>
<td>Coming Soon</td>
<td>02231749</td>
</tr>
<tr>
<td>PD-1 Adjuvant Trial</td>
<td>NCI/Coop</td>
<td>In Development</td>
<td></td>
</tr>
</tbody>
</table>
Making Immunotherapy a Reality

High expression of vascular markers, macrophages, fibroblasts +
Low inflammation and chemokines, few lymphocytes =
Poor effector cell trafficking

Gajewski, Curr Opin Immun 2011
Making Immunotherapy a Reality

All Kidney Tumors

Non-Inflamed Tumors (Biomarker neg)
Induce Antitumor Immunity
1) Enhance Antigen Expression:
   Demethylating Agents
   SBRT, IT IFN
2) Focus Immune Response:
   DC Vaccines
   Neo-antigen based vaccines
RCC Vaccine Approaches

- **IMA901:**
  - Multiple tumor associated peptide vaccine + GM-CSF

- **Dendritic Cell (DC) Vaccines**
  - AGS-003: autologous DC vaccine + sunitinib

Adapted from Dranoff Cancer Cell 2012
The specificity of antigens underlying tumor immunotherapy

**Increasing tumor specificity**

**Decreasing autoimmunity**

- Allogeneic HSC transplant & DLI
- Whole tumor cells as antigens
- Over-expressed tumor proteins as antigens
- Tumor-specific mutant proteins as antigens

Tumor Neoantigens
Developing NeoVax: based on multiple coding mutations unique to each pt tumor

High-risk melanoma, IND (Wu CJ); PI (Ott PA)
NCT 01970358

Hacohen et al, Can Imm Res 2013
Neoantigen Based Vaccine Summary

• Next-generation sequencing capabilities now enable systematic mining of the genome for potential neoantigens

• Tumor neoantigens are a potentially important class of immunologic targets against which tumor-specific responses can be generated

• Further characterization of the immunogenicity of neoantigens and association with clinical response is in progress

• Phase I clinical trials to test a personalized cancer neoantigen vaccine are planned – Cathy Wu (DFCI)
  – Melanoma – Patrick Ott (PI)
  – RCC – Toni Choueiri (PI)
Making Immunotherapy a Reality

**Biomarker +, Sensitive:**
Single agents PD-1/PD-L1 Ab

**Biomarker +, Resistant:**
Combination Therapy
1) Elimination of Tregs: CTLA4 Ab, anti-GTR
2) Inhibition of MDSC (VEGF TKI, HDM2 Antagonists)
3) Support effector T cells: IL-2, CD137 Ab, IL-15, IL-21
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5) Other checkpoint inhibitors (PDL2, LAG3, TIM3 etc)

**Non-Inflamed Tumors (PD-L1 neg)**
Induce Antitumor Immunity
1) Enhance Antigen Expression: Demethylating Agents
   - SBRT, IT IFN
2) Focus Immune Response: DC Vaccines
   - NeoAntigen Based

**Selection**
Identify the patients in the overlap through translational research
Making Immunotherapy a Reality for Patients with RCC

• Until we develop better tools, immunotherapy is the best method for achieving the patient’s goal – “Treatment-Free Survival”

• ITH may be associated with relatively increased activity of immunotherapy
  – Mutational load = predictive biomarker?

• ITH generates neoantigens that could be used as immunotherapies?
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