Tumor Site Immune Modulation Therapy

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Disclosures

• Consultant: MedImmune, Pfizer, Symphogen, Boehringer Ingelheim

• Sponsored research: Amplimmune, Eli Lilly
Tumor Site vs. Systemic Immune Modulation

**Tumor site modulation:**

*PD-L1/PD-1*

**Systemic modulation:**

*CTLA-4, Lag-3, Tim-3, 4-1BB, OX40, etc.*
The B7-H1/PD-1 pathway in tumor site immune modulation

Cancer

APCs

Lymphoid Organs

IFN-\(\gamma\)

PD-1

B7-H1 (PD-L1)

\(T_E\)
The B7-H1/PD-1: A “peace keeper” pathway

- Low level of B7-H1 in normal cells and tissues
- Up-regulation of B7-H1 in tissues by neighboring T-cells via IFN-γ
- B7-H1 suppresses T cell activity via PD-1 to control inflammation
- Over-expression of B7-H1 by cells in tumor site to prevent immune attack
PD-1/PD-L1 antibody therapy

- Regression of large solid tumors
- A therapy for a broad spectrum of human cancer
- Durable response
- Tolerable toxicity
What are the next steps?

- A therapy for a broad spectrum of human cancer
- Predictive biomarkers to enrich responders
- Frontline therapy (chemo/radiation-free)
- Treatment of early diseases
- Mechanism-based combination therapy
<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Single Agent</th>
<th>Combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma (n&gt;2,000)</td>
<td>40-50%</td>
<td>&gt;60%</td>
</tr>
<tr>
<td>Lung cancer (n&gt;1,000)</td>
<td>20-35%</td>
<td></td>
</tr>
<tr>
<td>Renal cancer (n&gt;200)</td>
<td>40-55%</td>
<td></td>
</tr>
<tr>
<td>Gastric cancer (n&gt;50)</td>
<td>~30%</td>
<td></td>
</tr>
<tr>
<td>Bladder cancer (n&gt;30)</td>
<td>~50%</td>
<td></td>
</tr>
<tr>
<td>Head &amp; neck cancer (n&gt;30)</td>
<td>~30%</td>
<td></td>
</tr>
<tr>
<td>Hodgkin’s/non-Hodgkin’s (n&gt;50)</td>
<td>~50%</td>
<td></td>
</tr>
<tr>
<td>Colorectal cancer (n&gt;50)</td>
<td>&lt;10%</td>
<td></td>
</tr>
<tr>
<td>Prostate cancer (n&gt;50)</td>
<td>&lt;10%</td>
<td></td>
</tr>
</tbody>
</table>

*With durable clinical responses and <5% autoimmune toxicity*
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Membrane PD-L1 on Tumor Is A Potential Predictive Biomarker for Response to Anti-PD-1/PD-L1 therapy

PD-L1 staining patterns

- Negative or Cytosolic only (n=18)
- Membranous (n=23)

NSCLC (17)
Mel (30)
RCC (9)
CRC (8)
CRPC (4) (n=41)

Clinical Benefit Rate (CR+PR+SD)

= 6%
1/18 responders

= 48%
11/23 responders

Taube et al, Clin Cancer Res. 20:5064, 2014
Challenges to use B7-H1 expression in tumor site as a biomarker

- Heterogenic expression
  - Limited size of biopsy specimens
  - Timing
  - Denatured B7-H1 protein in FFPE

- Future approaches
  - In vivo imaging
  - CTC
Somatic mutation frequencies in exomes from 3,083 tumor–normal pairs


High ORR

Low ORR
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## B7-H1 expression and TILs in lung cancer by disease stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>N</th>
<th>TILs</th>
<th>B7-H1&lt;sup&gt;hi&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>169</td>
<td>44%</td>
<td>33%</td>
</tr>
<tr>
<td>II</td>
<td>102</td>
<td>40%</td>
<td>34%</td>
</tr>
<tr>
<td>III</td>
<td>129</td>
<td>35%</td>
<td>21%*</td>
</tr>
<tr>
<td>IV</td>
<td>44</td>
<td>24%</td>
<td>23%*</td>
</tr>
</tbody>
</table>

# Total 444 patients with non-small cell and small cell lung cancer in both Yale and Greece cohort were analyzed

*Velcheti et al, Lab Invest 2014*
What are the next steps?

- A therapy for a broad spectrum of human cancer
- Predictive biomarkers to enrich responders
- Frontline therapy (chemo/radiation-free)
- Treatment of early diseases
- Combination (mechanism-based)
PD-L1 expression/TIL infiltration in 110 human melanoma and their functional implications

I  
B7-H1 -  
TIL-  
41%

II  
B7-H1+  
TIL+  
38%

III  
B7-H1-  
TIL+  
20%

IV  
B7-H1+  
TIL-  
1%

Lack of inflammation  Adaptive resistance  other inhibitors?  Intrinsic induction

PD-L1 expression pattern in 457 lung cancer (tissue microarray analysis)

Velcheti et al, Lab. Invest. 2014
Mechanism-based combination therapy

**TIL-/PD-L1-** (lack of inflammation): anti-CTLA-4, local radiation, chemoattraction, cancer vaccine, adoptive T cell therapy

**TIL+/PD-L1+** (adaptive resistance): Anti-PD-1 +/- anti-PD-L1, new inhibitory pathways

**TIL+/PD-L1-** (non-PD-L1 mediated immune tolerance): New inhibitory pathways

**TIL-/PD-L1+** (intrinsic induction of PD-L1): EGFR inhibitors etc.
Platforms for discovery of tumor site
T-Cell inhibitory pathways

Over-expressed molecules of human cancer
(identified by microarray, proteomics and bioinformatics)

T-Cell Activity Array

The Receptor Array

Immunobiology *in vitro* and *in vivo*

Mouse tumor /PDX models