Immunotherapy in Cancer: How It All Began

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Johns Hopkins School of Medicine
Immunotherapy: History, Present Status & Future
“Ten years from today, >50% of patients with inoperable cancer will be receiving some form of immunotherapy”
- Drew Pardoll
  January, WSJ, 2014
Advances in Cancer Immunology & Immunotherapy

Clinical Immunotherapy Milestones

- Coley’s toxins
- Discovery of antibodies/magic bullet theory
- TIL for melanoma
- Approval of IL-2 for melanoma
- αCTLA-4 approved for melanoma
- Elucidation of tumor-associated antigens
- Elucidation of how T cells recognize antigen

Basic Immunology/Cancer Immunology

- Monoclonal antibodies
- Elucidation of immune checkpoints
- Elucidation of tumor-associated antigens

TIL, tumor-infiltrating lymphocytes
Immune Checkpoint Blockade: Anti-CTLA-4

- 10% objective response rate (mel and RCC)
- 23%-33% grade 3/4 autoimmune toxicities
- 1st approved checkpoint inhibitor but ONLY melanoma as single agent

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**PRE-RX**

**POST-RX**

- Dermatitis
- Colitis
- Hepatitis

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Role of CTLA-4 vs PD-1 in Suppressing Antitumor Immunity

- **Activation** (cytokines, lysis, prolif., migration)

Inhibition

- PD-1 expressed
- Traffic to tumor

**Tumor** or Vaccine

- APC
- T cell
  - MHC-Ag
  - B7.1/2
  - CD28
  - TCR Signal 1
  - (+)Signal 2 dominates

- PD-L1
- (-)

**Inhibition**
### Patient-Years of Tumor Remission for Solid Cancers in US: PD-1 Blockade vs Mutant Oncogene-Targeted Drugs

#### Anti-PD-1/L1

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>#Annual cases</th>
<th>%mutated</th>
<th>Resp. Rate</th>
<th>Durability (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung (NSC, SC)</td>
<td>155,000</td>
<td>20%</td>
<td>1.5</td>
<td>46,500</td>
</tr>
<tr>
<td>Mesothelioma</td>
<td>5000</td>
<td>30%</td>
<td>1.5*</td>
<td>2250</td>
</tr>
<tr>
<td>Breast (TN)</td>
<td>12,000</td>
<td>20%</td>
<td>1.5*</td>
<td>3600</td>
</tr>
<tr>
<td>Bladder</td>
<td>16,000</td>
<td>30%</td>
<td>1.5*</td>
<td>7200</td>
</tr>
<tr>
<td>Melanoma</td>
<td>9000</td>
<td>40%</td>
<td>2.5</td>
<td>9000</td>
</tr>
<tr>
<td>Kidney</td>
<td>14,000</td>
<td>25%</td>
<td>1.5</td>
<td>5250</td>
</tr>
<tr>
<td>Liver</td>
<td>25,000</td>
<td>20%</td>
<td>1.5*</td>
<td>7500</td>
</tr>
<tr>
<td>Gastric</td>
<td>11,000</td>
<td>25%</td>
<td>1.5*</td>
<td>4125</td>
</tr>
<tr>
<td>Esophageal</td>
<td>15,000</td>
<td>25%</td>
<td>1.5*</td>
<td>5625</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>9000</td>
<td>25%</td>
<td>1.5*</td>
<td>3375</td>
</tr>
<tr>
<td>Ovarian</td>
<td>14,000</td>
<td>15%</td>
<td>1.5*</td>
<td>3150</td>
</tr>
<tr>
<td>Merkel Cell</td>
<td>1000</td>
<td>70%</td>
<td>1.5*</td>
<td>1050</td>
</tr>
<tr>
<td>MSI (multiple)</td>
<td>15,000</td>
<td>65%</td>
<td>3.0*</td>
<td>29,250</td>
</tr>
</tbody>
</table>

Total: 127,875 pt yrs

* Estimated as DOR not available yet

#### Mutation-targeted drugs

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>#Annual cases</th>
<th>%mutated</th>
<th>Resp. Rate</th>
<th>Durability (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSCLC (EGFR+ALK+ROS1+BRAF)</td>
<td>128,000</td>
<td>15%</td>
<td>60%</td>
<td>.6</td>
</tr>
<tr>
<td>Melanoma (BRAF+cKIT)</td>
<td>9000</td>
<td>60%</td>
<td>60%</td>
<td>.6</td>
</tr>
<tr>
<td>Pap. thyroid ca/CRC (BRAF)</td>
<td>3500</td>
<td>60%</td>
<td>50%</td>
<td>.6</td>
</tr>
<tr>
<td>GIST (cKIT)</td>
<td>1500</td>
<td>60%</td>
<td>70%</td>
<td>1</td>
</tr>
<tr>
<td>Basal cell ca (Hh)</td>
<td>2000</td>
<td>60%</td>
<td>45%</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Total: 10,611 pt yrs
Conservative Predictions for the Future of Cancer Immunotherapy

- >50% of cancer patients will receive immunotherapy by 2025
- >$80B market by 2025
- Chemotherapy market will decrease >50% by 2025
- Oncogene-targeted therapy will become a “primer” for immunotherapy
Long-Term Survival of Patients With Melanoma Receiving Immune Checkpoint Blocking Drugs

At 5 yrs, 50% will have died
Duration of Response and Overall Survival
Lung Cancer

NSCLC Responders\(^a,b\) by Histology

| Time, Week | 0 | 8 | 16 | 24 | 32 | 40 | 48 | 56 | 64 | 72 | 80 | 88 | 96 | 104 | 112 | 120 | 128 | 136 | 144 | 152 | 160 |
|------------|---|---|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|----|
| Squamous   |   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Nonsquamous|   |   |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |    |

Vertical line at 96 weeks = maximum duration of continuous nivolumab therapy

\(^a\) Responses were assessed by modified RECIST v1.0

\(^b\) All efficacy analyses based on data collected as of September 2013

All Treated Subjects With NSCLC

<table>
<thead>
<tr>
<th>Died/Treated</th>
<th>Median (95% CI)</th>
</tr>
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<tr>
<td>94/129</td>
<td>9.90 (7.80, 12.40)</td>
</tr>
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</table>

At 4 yr, 85% will have died

Median OS: 9.9 Months (7.8, 12.4)

1-Year OS Rate 42% (48 pts at risk)

2-Year OS Rate 24% (20 pts at risk)

Innate (Tumor-Cell Intrinsic) Resistance

Constitutive tumor signaling induces PD-L1 on tumor cells

Adaptive Resistance

T cell–induced PD-L1 upregulation

Implication: The immune surveillance hypothesis was half right – patients DO have an extant repertoire of antitumor T cells

Genetic Mutations In Cancer Encode Altered Proteins

- Some can be “tumor-specific antigens” – the biochemical signature that the immune system uses to recognize the tumor as “foreign”

Many mutations → Many antigens → Stronger immune response
Mutational Heterogeneity in Cancer: Altered Proteins Contain Neoepitopes for Immune Recognition

Does mutational load correlate with responsiveness to immune checkpoint blockade?

Colorectal Cancers Are Generally Unresponsive to PD-1 Blockade, but the MSI-High Subset Has a High Mutational Load

- **Microsatellite instability (MSI):** genetic hypermutability resulting from impaired DNA mismatch repair, present in ~15% colon cancers, 5%-20% of multiple other tumor types

### Objective Responses

<table>
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<tr>
<th></th>
<th>MMR-Deficient CRC (MSI)</th>
<th>MMR-Proficient CRC (MSS)</th>
<th>MMR-Deficient Non-CRC (MSI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>13</td>
<td>25</td>
<td>10</td>
</tr>
<tr>
<td><strong>Objective Response Rate</strong></td>
<td>62%</td>
<td>0%</td>
<td>60%</td>
</tr>
<tr>
<td><strong>Disease Control Rate</strong></td>
<td>92%</td>
<td>16%</td>
<td>70%</td>
</tr>
</tbody>
</table>

Even in Tumors With a Lower # of Mutations, One or Two Will Likely Produce a Tumor Antigen

More Than 90% of Patients Possess Tumor-Specific T Cells

Much evidence for T-cell responses against shared tumor-associated antigens – ie, self antigens upregulated in tumors (cancer-testes Ag), but their role in antitumor immunity remains to be determined
Viral antigens in virus-induced cancers are the other type of neoantigen

- EBV (Hodgkin, Burkitt, NPC)
- HPV (cervical, vulvar, anal, H&N)
- MCPyV (Merkel cell cancer)
- HBV, HCV (liver cancer)
Overview: Merkel Cell Carcinoma

• ~ 2,000 cases/year in the US
• UV exposure, age >50, immune suppression
• Merkel cell polyomavirus present in 80% of cases

> 40% of MCC patients develop distant disease...
Virus-positive vs negative MCC: at the extremes of mutational frequency compared to TCGA data for other cancers.

MCC antigens:

- Virus-positive tumors have a low mutational burden, but express viral oncoproteins that are strong immune stimulants (ORR = 62%)
- Virus-negative tumors have a very high carcinogen-induced mutational burden (UV light) (ORR = 44%)

Why Don’t More Patients Respond to Anti-PD-1?

How do we capture the remaining 80%-90%?

1) Multiple checkpoints on antitumor T cells
   Solution – multicheckpoint blockade (>500 trials)
Antitumor Cytotoxic T Cell Responses Against Tumors Are Suppressed by Multiple Mechanisms

- **Tumor**
  - EGFR, Stat3
  - Raf/MEK

- **Tumor Antigens**
  - PD-L1

- **Dendritic Cell**
  - PD-L1
  - IL-10, TGFβ
  - IL-35
  - Neuropilin
  - CTLA4
  - TIGIT
  - GITR

- **Treg**
  - Foxp3

- **T helper Cell**
  - Tbet

- **MΦ/MDSC**
  - IDO
  - Arginase

- **Tumor-specific CTL**
  - PD-1
  - LAG-3
  - Tim3
  - TIGIT

- **“Help” to promote CTL**
Why Don’t More Patients Respond to Anti-PD-1?
How do we capture the remaining 80%-90%?

1) Multiple checkpoints on antitumor T cells
   Solution – multichannel checkpoint blockade (>500 combo trials, $\alpha$PD-1 + $\alpha$CTLA-4 promising, but high toxicity)

2) Suppressive cells in the tumor microenvironment:
   a) Treg, b) myeloid-derived suppressor cells/MΦ
   Solution – block receptors that promote these cells or block suppressive molecules they produce

3) Endogenous antitumor T-cell response too weak
   Solution – Activate the T cells the patient has:
   a) vaccines
   b) intra-tumor injection (endogenous vaccine)
   c) targeted therapy (BRAF, EGFR, MEK in clinic)

4) Chimeric antigen receptor and TCR-engineered ACT
Considerations for Predictive Biomarker Use in Clinical Development of Immunotherapies

• No obvious clean selection biomarker such as oncogene mutation. MSI best current biomarker, PD-L1 second best – 4 PD-L1 tests approved. CD8 infiltrate a possibly simpler biomarker.

• In the absence of a “clean” biomarker, imperfect biomarkers useful in prioritizing (ie, 1st vs 2nd line)

• If biology suggests the target is acting in the tumor microenvironment, the likely biomarker will be in the tumor biopsy

• Retrospective analysis of biomarker expression and its correlation with response are the first step in defining useful biomarkers
Pretreatment Tumor PD-L1 Expression Correlates With Response to Anti-PD-1 Pembrolizumab) in NSCLC: Individualizing Treatment Strategy

≥ 50% tumor cells PD-L1+
  - Response rate 45%
  - Median survival not reached

< 50% tumor cells PD-L1+
  - Response rate 11%-17%
  - Median survival 8.8 months

Bloomberg-Kimmel Institute for Cancer Immunotherapy at Johns Hopkins

Thanks to patients and collaborating clinical trial centers.