Recent Successes in Cancer Immunotherapy and Future Perspectives

Marco Donia, M.D., PhD
DTU June 13th 2016

A conceptual change

<table>
<thead>
<tr>
<th>Immunotherapy</th>
<th>Chemo- radio- and targeted therapy</th>
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</thead>
<tbody>
<tr>
<td>Target host immunity</td>
<td>Target tumor</td>
</tr>
</tbody>
</table>
Profound and Durable Responses: Cure?

Antitumor Activity of Pembrolizumab (one anti PD-1 immunotherapy)

• Is there a natural immune response to cancer?

• Can the immune system reject cancer?

Presentation Outline

• Cancer and the Immune System

• Immunotherapy of Melanoma

• Prediction Criteria for response to checkpoint blockade

• Conclusions
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The Hallmarks of Cancer
The Immune System

A complex system that is responsible for distinguishing us from everything foreign to us, and for protecting us against infections and foreign substances. The immune system works to seek and kill invaders.

www.als.net/als101/glossary.asp

Can the immune system see this tumor as foreign?
Priming and Effector Phase of Cancer Immunity

Wolchok J, ASCO Annual Meeting 2015

Priming and Effector Phase of Cancer Immunity

Couzin-Frankel, Science 2012
Tumor infiltrating lymphocytes (TILs)

T cells infiltrate Solid tumors

TILs have the potential to recognize multiple targets on tumor cells

Don’t worry, knowing the acronyms does not help that much!!
Improved Survival with “high” TILs in all solid tumors

...in Melanoma

...in Ovarian Cancer

...in Breast Cancer

...in Colon Cancer

Erdag G et al., Cancer Res 2012;72(5):1070-80

Galon J et al., Science 2006

Mahmoud SM et al., Journal of Clinical oncology 2011

Tumor Immune Escape in the Tumor MicroEnvironment (TME)

Cousin-Berlingue J, Science 2010;330:448-53

Immunosuppressive Shield
• Is there a natural immune response to cancer?

• Can the immune system reject cancer?

The Immune System’s balance

Activating Receptors
- CD40L
- ICOS
- CD28
- OX40
- TCR

Inhibitory Receptors
- LAG3
- PD-1
- CTLA-4

Activation

Tolerance

Autoimmune diseases

Infections
PD-L1: Molecular Immune Shield

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13/06/16

Key Events in the History of Cancer Immunotherapy

1890  First cancer vaccine developed (Coley)
1960s Adjuvants (e.g., BCG) shown to eradicate some tumors
1980s IFN-α approved as cancer immunotherapy
1985 Adoptive immunotherapy for patients with cancer
1992 IL-2 approved as cancer immunotherapy
1991 First tumor-associated antigen cloned (MAGE-1)

Immune Checkpoint Inhibitors

Multiple Costimulatory and Inhibitory Interactions Regulate T-Cell Responses

Activating Receptors
- CD28
- OX40
- GITR
- CD137
- CD27
- HVEM

Inhibitory Receptors
- CTLA-4
- PD-1
- TIM-3
- BTLA
- VISTA
- LAG-3

Agnostic antibodies
Blocking antibodies
T-cell stimulation

**Immune Checkpoint Inhibitors**

The big stars of melanoma immunotherapy

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**How PD-1 immunotherapy works**

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CTLA-4 and PD-1/L1 Checkpoint Blockade

Clinical Results with combination anti-CTLA4 and anti PD-1


Wolchok J, ASCO Annual Meeting 2015
Larkin et al, NEJM 2015
Pattern Response-Relapse with Targeted Therapy

Before Treatment  + 3 months  + 6 months

Wagle N et al., J Clin Oncol 2011;29(22):3085-96

Pts-at-Risk, n
Ipilimumab 1861 839 370 254 192 170 120 26 15 5 0

3-yr OS rate: 22% (95% CI: 20-24)

Median OS: 11.4 mos (95% CI: 10.7-12.1)


downloaded from clinicalcareop5ions.com
Immunotherapy + Targeted Therapy

Overall Survival Metastatic Melanoma

1-year OS Phase 3 Studies

<table>
<thead>
<tr>
<th>Year</th>
<th>OS Rate</th>
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<tbody>
<tr>
<td>2010</td>
<td>30-35%</td>
</tr>
<tr>
<td>2011</td>
<td>46%</td>
</tr>
<tr>
<td>2012</td>
<td>47%</td>
</tr>
<tr>
<td>2013</td>
<td>56%</td>
</tr>
<tr>
<td>2014</td>
<td>70%</td>
</tr>
<tr>
<td>2015</td>
<td>73%</td>
</tr>
</tbody>
</table>

68% Pembrolizumab 10 mg/kg Q2W
74% Pembrolizumab 10 mg/kg Q2W
74% Dabrafenib + Trametinib
83% Vemurafenib + Cetuximab

2-year OS

3-year OS

4-year OS

Sharma and Allison, Cell 2015
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Immunogenic Tumor microenvironment

Sharma and Allison, Science 2015
Immunogenic Tumor Microenvironment Biomarkers

High Mutational Burden

PD-L1 expression

Rooney et al., Cell 2015

Taube et al., Science Transl Med 2012
Genetic Basis of Response to Immunotherapy

adapted from:
Schumacher and Schreiber, Science 2015
Alexandrov et al., Nature 2013
DNA Mismatch repair (MMR) and Response

<table>
<thead>
<tr>
<th></th>
<th>MMR-deficient CRC</th>
<th>MMR-deficient non-CRC</th>
<th>MMR-proficient CRC</th>
<th>non-CRC</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>13</td>
<td>25</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Objective Response Rate</td>
<td>62%</td>
<td>0%</td>
<td>60%</td>
<td>70%</td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>92%</td>
<td>16%</td>
<td>60%</td>
<td>70%</td>
</tr>
</tbody>
</table>

% Change from Baseline BLD

Tumor Antigens

Adapted from Coule et al, Nat Rev Cancer 2013
• The immune system does not care of tumor histology but of level of foreignness

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• So, is there a natural immune response to cancer?

• Can the immune system reject cancer?
Management of Cancer in the Post Anti–PD-1/PD-L1 Era

Anti–PD-1/anti–PD-L1

Generate T cells:
+ Anti–CTLA-4
+ Immune-activating antibodies or cytokines
+ TLR agonists or oncolytic viruses
+ IDO or macrophage inhibitors
+ Targeted therapies

Bring T cells into tumors:
- Vaccines
- TCR-engineered ACT
- CAR-engineered ACT
- TIL-based ACT

Cancer Immunotherapy: What Is Next?

Anti–PD-1/PD-L1

Your favorite treatment

The future of cancer therapy
Thank you for your attention!

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