Immunotherapy for the Treatment of Cancer

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Oncology for Scientists
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Holy Grail of Tumor Immunity

- Exquisite specificity for target; limit collateral damage
- Target non-resectable tumors
- Systemic immunity; target tumors throughout the body
- Long-lasting protection
Kidney Cancer and Skin Cancer are the most responsive to state-of-the-art (checkpoint blockade, DC) and traditional (IL-2) immunotherapy.
Multiple Obstacles Must be Overcome for Effective Anti-Tumor Immunity

1. T cell recognition of tumor antigens (Ag) presented by DC
2. T cell Activation
3. T cell infiltration into lymph nodes & tumors
4. Lysis of Ag⁺ tumor targets

<table>
<thead>
<tr>
<th>Tumor cell destruction</th>
<th>Tumor Ag</th>
<th>Soluble factors</th>
<th>Dendritic cells (DC)</th>
</tr>
</thead>
</table>

Draining Lymph Node

CD8 effector T cells
Multiple Obstacles Must be Overcome for Effective Anti-Tumor Immunity

- PD-1 Blockade
- PD-L1 Blockade

Tumor Ag
Soluble factors
Dendritic cells (DC)

1. T cell recognition of tumor antigens (Ag) presented by DC
2. T cell Activation
3. T cell infiltration into lymph nodes & tumors
4. Lysis of Ag+ tumor targets

CD8 effector T cells

DC Vaccines
- CTLA-4 blockade
- HD IL-2

Tumor cell destruction

T cell expansion

Draining Lymph Node

Tumor

T cell infiltration into lymph nodes & tumors

1. T cell recognition of tumor antigens (Ag) presented by DC
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CD8 effector T cells

DC Vaccines
- CTLA-4 blockade
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Tumor cell destruction

T cell expansion
• IL-2
  - Only FDA-approved therapy against mRCC and melanoma for decades
  - Curative in up to 15%
  - Highly toxic
  - Mechanism of action largely unknown

**Treatment**
- Days 1 - 5
  - Cycle 1 IL-2 q8h
  - No Tx
- Days 15 - 19
  - Cycle 2 IL-2 q8h

**Recovery**
- ~ 4 weeks
  - No Treatment

Monitor for severe side-effects that result from capillary-leak syndrome

Continue Tx?
<table>
<thead>
<tr>
<th>Response Type</th>
<th>Criteria</th>
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<tbody>
<tr>
<td>Complete Response</td>
<td>Disappearance of all measurable tumors for more than 4 weeks</td>
</tr>
<tr>
<td>Partial Response</td>
<td>&gt;30% tumor size reduction of all lesions</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>Small changes that do not meet above criteria</td>
</tr>
<tr>
<td>Progressive Disease:</td>
<td>&gt;20% tumor size increase or appearance of new lesions</td>
</tr>
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</table>
Objective Response Rates of Available Immunotherapy Options for RCC

Total Number of Treated Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Objective Response %</th>
<th>Total Number of Treated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>17%</td>
<td>259</td>
</tr>
<tr>
<td>Anti-PD-L1</td>
<td>7%</td>
<td>17</td>
</tr>
<tr>
<td>Anti-PD-1</td>
<td>33%</td>
<td>33</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>10%</td>
<td>40</td>
</tr>
</tbody>
</table>

1st enrolled Pt.:
- IL-2: 1986
- Anti-PD-1: 2008
- CTLA-4: 2007


Immune Checkpoint Blockade
Objective Response Rates of Available Immunotherapy Options for RCC

IL-2 has the greatest level of cytotoxicity and patient management.
Complete Response Rates of Available Immunotherapy Options for RCC

Immune Checkpoint Blockade
IL-2 remains an effective stand alone strategy to induce long term responses

More than 80% of complete responders are still disease free > 2 years post treatment

Rosenberg et al Annals of Surgery 1998
Klapper et al Cancer 2008
Muhitch and Schwaab Immunotherapy 2014

Complete Response Rates of Available Immunotherapy Options for RCC

Complete Response %

- IL-2: 259
- Anti-PD-L1: 17
- Anti-PD-1: 33
- CTLA-4: 40

IL-2 remains an effective stand alone strategy to induce long term responses
Characterizing Tumor Immune Responses

T cell recognition of tumor antigens

Tumor sites are often characterized by poor T cell infiltration

- Limited CD8 infiltration correlates with poor prognosis in melanoma.

*Human Melanoma (CD45/Hematoxylin)*

Repasky and Hylander

*Piras et al. Cancer. 2005*
Removing a Tumor’s Cloak of Invisibility: Overcoming Tumor Immunosuppression

- Antibody immune-based therapeutics
  - PD-1
  - PD-L1
  - CTLA-4

- Dendritic cell vaccinations

- Adoptive transfer of tumor-specific T cells
Removing a Tumor’s Cloak of Invisibility: Overcoming Tumor Immunosuppression

- MHC
- TCR
- PD-L1
- PD-L2
- T cell

Tumor Cell

- MHC
- Ag
- PD-L1
- PD-L2

T cell

- TCR
- PD-1
Antibody-mediated Therapies: PD-1 & PD-L1

◆ PD-1

Bristol-Myers Squibb - BMS-936558 nivolumab
Phase I clinical trial, advanced patients demonstrated:
  ▪ Cumulative response rates: 18% of non–small-cell lung, 28% melanoma, and 27% renal-cell cancer patients.
  ▪ Durable responses observed in 20 out of 31 patients
    Topalian et al, NEJM 2012

Merck – Permbrolizumab née Lambrolizumab (MK-3475)
  ▪ In Phase I clinical trial, response rate of 38% in patients with advanced melanoma
    Hamid et al, NEJM 2013

◆ PD-L1

Roche, Genentech: MPDL320A
  ▪ 45% of patients progression free at 24 weeks.
  ▪ Patients with melanoma had a 29% response rate
    http://am.asco.org/daily-news
Tumors from Responders to Lambrolizumab Treatment Had Dense CD8 T Cell Infiltration

Tumors from Responders to Lambrolizumab Treatment Had Dense CD8 T Cell Infiltration

Brahmer J R et al. JCO 2010;28:3167-3175
Vitiligo is Associated with Complete Response

Removing a Tumor’s Cloak of Invisibility: Overcoming Tumor Immunosuppression

Yervoy (anti-CTLA-4, ipilimumab)

Bristol-Myers Squibb
Yervoy (anti-CTLA-4, ipilimumab)

- Approved by FDA as first-line or second-line treatment for advanced melanoma.
- Blocks inhibitory signal for activated T cells.
- Enhances survival & durable responses (>2.5 y) in 15-20% of patients.
- Response can be delayed.
- Associated with immune-mediated side effects.
  - Colitis
  - Dermatitis

Bristol-Myers Squibb

Hodi et al NEJM 2010
Dendritic Cell Vaccinations: Orchestrating Immune Responses from the Battleground

Palucka et al Nat Rev Cancer 2012
- FDA approved for treatment of metastatic castrate resistant prostate cancer
- Induces antibody and T cell responses
- Overall 4 month prolonged median survival benefit
- Few objective biological responses


*Di Lorenzo Nature Reviews Clinical Oncology 2011*
How can therapy be improved to obtain > 20% response?

Can responding patients be identified prior to therapy?
Clinical and Immunologic Effects of Intranodal Autologous Tumor Lysate-Dendritic Cell Vaccine with Aldesleukin (Interleukin 2) and IFN-α2a Therapy in Metastatic Renal Cell Carcinoma Patients

Thomas Schwaab et al.

Clin Cancer Res 2009
Heterogeneous Patient Responses in Clinical Trial

Clinical and Immunologic Effects of Intranodal Autologous Tumor Lysate-Dendritic Cell Vaccine with Aldesleukin (Interleukin 2) and IFN-α2a Therapy in Metastatic Renal Cell Carcinoma Patients

Thomas Schwaab, Adrian Schwarzer, Benita Wolf, et al.

_Clin Cancer Res_ 2009

Schwaab et al. _Clin Cancer Res_ 2009
Combining Targeted Therapy with Immune Checkpoint Blockade to Improve Patient Responses

Axitinib in combination with pembrolizumab in patients with advanced renal cell cancer: a non-randomised, open-label, dose-finding, and dose-expansion phase 1b trial

Atkins, Plimack, Puzanov […] Choueiri

*Lancet Oncol.* 2018

Tyrosine Kinase Inhibitor + PD-1 Inhibitor

Photo from pemr.com

Photo from Mims.co.uk
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*Lancet Oncol.* 2018

✓ “At data cutoff, 38 (73%; 95% CI 59·0–84·4) patients achieved an objective response (complete or partial response).”

✓ 8% complete response rate
Combining Immune Checkpoint Strategies to Improve Patient Responses

**CheckMate 214: Efficacy and safety of nivolumab + ipilimumab (N+I) v sunitinib (S) for treatment-naïve advanced or metastatic renal cell carcinoma (mRCC), including IMDC risk and PD-L1 expression subgroups**

Escudier, Tannir, McDermott […] Motzer

*Annals of Oncology 2017*
Combining Immune Checkpoint Strategies to Improve Patient Responses

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9.4 % complete response in N+I vs. 1.2% in S

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<tr>
<td><strong>Intermediate/poor risk</strong></td>
</tr>
<tr>
<td><strong>N+I</strong></td>
</tr>
<tr>
<td>N = 425</td>
</tr>
<tr>
<td><strong>ORR per IRRC, n (%) [95% CI]</strong></td>
</tr>
<tr>
<td>P&lt;0.0001</td>
</tr>
<tr>
<td>Odds ratio (95% CI)=1.50 (1.04-2.17)</td>
</tr>
<tr>
<td><strong>Median PFS per IRRC, mo (95% CI)</strong></td>
</tr>
<tr>
<td>P=0.0331</td>
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<tr>
<td><strong>HR (99.1% CI)</strong></td>
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*Percentage based on number of PD-L1 evaluable patients;  
Descriptive analysis
Genomic correlates of response to immune checkpoint therapies in clear cell renal cell carcinoma

Miao, Margolis, Gao [...] Van Allen

*Science 2018*

- Sequencing of met RCC from 35 patients reviewing anti-PD-1
- Clinical Benefit associated with loss-of-function of *PBRM1* gene
How can therapy be improved to obtain > 20% response?
- Combined treatments (anti-PD-1 + anti-CTLA-4)

Can responding patients be identified prior to therapy?
- Genomic markers of response