Developing Novel Immunotherapeutic Cancer Treatments for Clinical Use

Oncology for Scientists
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Disclosures

• Muhitch Laboratory Support:
  – Dendreon
  – Argos Therapeutics
Holy Grail of Tumor Immunity

Realized in 1987 in a subset of RCC and melanoma patients treated with HD IL-2
Rosenberg, S et al. NEJM 1987

RCC and Melanoma are the most responsive to state-of-the-art (checkpoint blockade, DC, adoptive transfer) and traditional (IL-2) immunotherapy
Rosenberg, S. J Immunol 2014
Requirements for Effective Anti-Tumor Immune Responses

1. T cell recognition of tumor Ags presented by DC
2. T cell Activation
3. T cell infiltration into tumors
4. Lysis of tumor targets

Tumor Ag
Soluble factors
Dendritic cells

CD8 effector T cells

Tumor cell destruction

T cell expansion

Draining Lymph Node

Tumor vessel
Requirements for Effective Anti-Tumor Immune Responses

Part I
1. T cell recognition of tumor Ags presented by DC
2. T cell Activation

Part II
3. T cell infiltration into tumors
4. Lysis of tumor targets

Tumor Ag
Soluble factors
Dendritic cells

Draining Lymph Node
HEV

T cell expansion

CD8 effector T cells

Tumor cell destruction

Tumor vessel

Tumor
IL-2 Treatment Protocols

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

**Recovery**
- Days 15 - 19
- ~ 4 weeks: No Treatment

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

Continue Tx?
Comparison of Conventional Cytokine Therapy with Kinase Inhibitors for Treatment of Metastatic RCC

IL-2 has the greatest level of cytotoxicity and patient management

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Objective Response %</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>259</td>
</tr>
<tr>
<td>Pazopanib</td>
<td>557</td>
</tr>
<tr>
<td>Sunitinib</td>
<td>553</td>
</tr>
</tbody>
</table>


Klapper Cancer 2008

Tyrosine Kinase Inhibitors

Motzer NEJM2013
Comparison of Conventional Cytokine Therapy with Kinase Inhibitors for Treatment of Metastatic RCC

- IL-2: 259
- Pazopanib: 557
- Sunitinib: 553

Complete Response %

1st enrolled Pt.
- IL-2: 1986
- Pazopanib: 2008
- Sunitinib: 2008

Klapper Cancer 2008
Tyrosine Kinase Inhibitors Motzer NEJM2013

Motzer NEJM2013
Removing a Tumor’s Cloak of Invisibility: Overcoming Tumor Immunosuppression

- Antibody immune-based therapeutics (3 of top 10 2013 experimental cancer drugs)
  - ✓ CTLA-4
    - ▪ Yervoy (Merck)
  - ✓ PD-1
    - ▪ Nivolumab (BMS-936558) (Bristol-Myers Squibb)
    - ▪ *Permbrolizumab née Lambrolizumab* (MK-3475)
  - ✓ PDL-1
    - ▪ *MPDL320A* (Roche, Genentech)

- Dendritic cell vaccinations
Improving T cell Activation Through CTLA-4 Inhibition

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
Requirements for Effective Anti-Tumor Immune Responses

1. T cell recognition of tumor Ags presented by DC
2. T cell Activation
3. T cell infiltration into tumors
4. Lysis of tumor targets

Part I

Part II

Tumor Ag
Soluble factors
Dendritic cells

Draining Lymph Node

T cell expansion

CD8 effector T cells

Tumor vessel

Tumor cell destruction
Enhancing T cell Function within the Tumor Microenvironment through PD-1/PD-L1 Axis Blockade

Nature Medicine 18, 993 (2012)
Comparison of Checkpoint Inhibitors for Treatment of Metastatic RCC

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total Number of Treated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-2</td>
<td>259</td>
</tr>
<tr>
<td>Anti-PD-L1</td>
<td>17</td>
</tr>
<tr>
<td>Anti-PD-1</td>
<td>406</td>
</tr>
<tr>
<td>CTLA-4</td>
<td>40</td>
</tr>
</tbody>
</table>

1st enrolled Pt.
- IL-2: 1986
- Anti-PD-1: 2012
- CTLA-4: 2007


Immune Checkpoint Blockade
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)
Improving Immunotherapy Through Combinatorial Approaches and Patient Selection

➢ How can immune-based treatments be improved to obtain > 20 - 30% response?

➢ Can responding patients be identified prior to therapy?
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

# Targeted by anti-CTLA-4
* Targeted by anti-PD-1/PD-L1
### Table 3. Clinical Activity in Patients Who Received the Concurrent Regimen.

<table>
<thead>
<tr>
<th>Cohort No.</th>
<th>Dose</th>
<th>Patients with a Response(^a)</th>
<th>Stable Disease for ≥24 Wk</th>
<th>Immune-Related Stable Disease for ≥24 Wk(^\dagger)</th>
<th>Objective-Response Rate (95% CI)(^\ddagger)</th>
<th>Aggregate Clinical-Activity Rate (95% CI)(^\ddagger)</th>
<th>≥80% Tumor Reduction at 12 Wk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Nivolumab, 0.3; ipilimumab, 3</td>
<td>14</td>
<td>2</td>
<td>2</td>
<td>21 (5–51)</td>
<td>50 (23–77)</td>
<td>4 (29)</td>
</tr>
<tr>
<td>2</td>
<td>Nivolumab, 1; ipilimumab, 3</td>
<td>17</td>
<td>6</td>
<td>0</td>
<td>2</td>
<td>65 (38–86)</td>
<td>7 (41)</td>
</tr>
<tr>
<td>2a</td>
<td>Nivolumab, 3; ipilimumab, 1</td>
<td>15</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>73 (45–92)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>3</td>
<td>Nivolumab, 3; ipilimumab, 3</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>83 (36–100)</td>
<td>0</td>
</tr>
<tr>
<td>All</td>
<td>—</td>
<td>52</td>
<td>16</td>
<td>4</td>
<td>3</td>
<td>65 (51–78)</td>
<td>16 (31)</td>
</tr>
</tbody>
</table>

\(^a\) Data are for patients who had a response that could be evaluated, defined as patients who received at least one dose of study therapy, had measurable disease at baseline, and had one of the following: at least one tumor evaluation during treatment, clinical progression of disease, or death before the first tumor evaluation during treatment.

\(^\dagger\) Data include patients who had a reduction in the target tumor lesion in the presence of new lesions, which was consistent with an immune-related partial response or stable disease.\(^1\)

\(^\ddagger\) The objective-response rate was calculated as the number of patients with either a complete response or a partial response, divided by the number of patients with a response that could be evaluated, times 100. Unconfirmed or immune-related responses were not included in this calculation. Confidence intervals (CIs) were estimated by the Clopper-Pearson method.

\(^\ddagger\) The aggregate clinical-activity rate was calculated as the number of patients with a complete response, a partial response, an unconfirmed complete response, an unconfirmed partial response, an immune-related partial response, stable disease for at least 24 weeks, or immune-related stable disease for at least 24 weeks, divided by the number of patients with a response that could be evaluated, times 100.

\(^\dagger\) Data include patients who had a partial response after one tumor assessment but did not have sufficient follow-up time for confirmation of the initial partial response.

\(^\ddagger\) Two additional patients in cohort 2 had tumor reduction of 80% or more at their first scheduled assessment, which was conducted after week 12.
Boosting Tumor Immune Responses

- Antibody immune-based therapeutics (3 of top 10 experimental cancer drugs)
  - ✓ CTLA-4
    - Yervoy (Merck)
  - ✓ PD-1
    - Nivolumab (BMS-936558) (Bristol-Myers Squibb)
    - _Permbrolizumab née Lambrolizumab (MK-3475)_
  - ✓ PDL-1
    - _MPDL320A_ (Roche, Genentech)

- Dendritic cell vaccinations
Dendritic Cell Vaccinations: Orchestrating Immune Responses from the Battleground

- **Endogenous vaccination**
  - Immunogenic chemotherapy
  - Radiotherapy
  - Anti-tumour antibodies
  - T cell immune checkpoint blockade

- **Ex vivo-generated cytokine-driven DCs**
  - Ex vivo instruction to generate and maintain cytotoxic effector and helper T cells

- **Reprogramming inflammation**
  - Targeting DCs with TLR ligands
  - Cytokine blockade

- **Targeting antigens to DC subsets in vivo**
  - DC antibody linked to pathogen and/or cancer-specific antigens and DC activators

*Palucka et al Nat Rev Cancer 2012*
Sipuleucel-T

- **FDA approved** for treatment of metastatic castrate resistant prostate cancer
- Induces antibody and T cell responses against a single antigen
- Overall 4 month prolonged median survival benefit
- Few objective biological responses


Di Lorenzo Nature Reviews Clinical Oncology 2011
Sipuleucel-T

- 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

Purification of Monocytes

Peripheral Blood

Ex Vivo Culture into Dendritic Cells (IL4, GMCSF)

Electroporate Dendritic Cells with Tumor RNA and CD40L

i.d. injection, every week for 4 weeks

Goal: Boost Anti-Tumor Immune-Response

State-of-the-art Dendritic Cell Vaccination Utilizing Tumor RNA and Costimulation Signals (AGS-003)
Dendritic Cell Vaccination (AGS-003) Combined with Sunitinib Treatment Extends Long-Term Survival in mRCC

Amin et al. Journal for ImmunoTherapy of Cancer 2015

Median OS from registration 30.2 months for all patients

NCT00678119
Dendritic Cell Vaccinations: Orchestrating Immune Responses from the Battleground

Ongoing phase I clinical trial at RPCI (Dr. Schwaab) utilizing dendritic cells electroporated with tumor RNA for treatment of localized Renal Cell Carcinoma

Palucka et al Nat Rev Cancer 2012
Combining Cytokine and Dendritic Cell Vaccination to Improve Patient Responses

Purification of Monocytes

Peripheral Blood

Ex Vivo Culture into Dendritic Cells (IL-4, GM-CSF)

Pulsing with Autologous Tumor Cell Lysate

Injection into Patient’s Lymph Node + IFN-α and IL-2 therapy

T cell activation

Goal: Boost Anti-Tumor Immune-Response

NCT00085436
Schwaab …Ernstoff Clin Cancer Res 2009
Heterogeneous Patient Responses to DC Vaccination

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

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Description</th>
</tr>
</thead>
<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>&lt;30% tumor size reduction and &lt;20% tumor size increase</td>
</tr>
<tr>
<td>Progressive Disease:</td>
<td>&gt;20% tumor size increase or appearance of new lesions</td>
</tr>
</tbody>
</table>

N = 18
How can immune-based treatments be improved to obtain > 20 - 30% response?
✓ Improve and combine immune-based treatments:
  • Dendritic Cell Vaccination + IL-2
  • Anti-CTLA-4 + anti-PD-1

Can responding patients be identified prior to therapy?
Requirements for Effective Anti-Tumor Immune Responses

1. T cell recognition of tumor Ags presented by DC
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CD8 effector T cells

Tumor vessel

Tumor cell destruction

Tumor

Draining Lymph Node

HEV

T cell expansion
Immunogenic Antigens Represent Key Targets for Effector T cells

➢ Tumor-associated antigens
  ✓ Increased expression in tumors with restricted expression in normal tissues
  ✓ Shared expression, can be expressed in multiple tumor types as well as amongst multiple patients
  ✓ Allows for broad treatment protocols that target tumor-associated antigens

➢ Neoantigens
  ✓ Originate from mutations in the tumor microenvironment
  ✓ Rarely shared/expressed in different patients or tumor types
  ✓ Likely to be more immunogenic due to higher frequency of circulating neoantigen-specific T cells
Neoantigen Expression in Non-small Cell Lung Cancer (NSCLC) Identifies Patients with a Clinical Benefit from PD-1 Treatment

Adapted from McGranahan...Swanton et al. Science 2016

- Homogeneous Neoantigen Expression
  - Neoantigen expression is consistent even in different regions of tumor

- Heterogeneous Neoantigen Expression
  - Neoantigens expressed only in specific regions of tumors
Neoantigen Expression in Non-small Cell Lung Cancer (NSCLC) Identifies Patients with a Clinical Benefit from PD-1 Treatment

Adapted from McGranahan...Swanton et al. *Science* 2016
Clonal Neoantigen Expression in Tumors Identifies Patients with a Clinical Benefit from PD-1 Treatment

Adapted from McGranahan...Swanton et al. *Science* 2016
How can immune-based treatments be improved to obtain >20 - 30% response?

✓ Improve and combine immune-based treatments (IL-2, Intralymphatic injections) to attack multiple targets

Can responding patients be identified prior to therapy?

✓ Increased neoantigens identify patients likely to respond to checkpoint blockade