The Potential of “Targeted” Immunotherapy for Cancer

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Harvard Medical School
Disclosures of: David McDermott

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<td>Employment</td>
<td>No conflict of interest to disclose</td>
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<tr>
<td>Research support</td>
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<td>Scientific advisory board</td>
<td>BMS, Pfizer, Genentech</td>
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<td>Travel support</td>
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Presentation includes discussion of the following off-label use of a drug or medical device: N/A
Why should you care?

• Most compelling story in Oncology.

• Targeted immunotherapy =
  – durable remissions of solid tumors

• Coming to a cancer near you
Immunotherapy Made Simple

Cytokine Therapy
e.g. IL-2, IFN

Vaccine Therapies
e.g. Sipuleucel-T

CTLA-4 Pathway Blockade
e.g. Ipilimumab, Yervoy

PD-1 Pathway Blockade
e.g. nivolumab, MK-3475
Approaches to Cancer Immunotherapy: Pressing on the gas

Cytokine Therapy
  e.g. IL-2, IFN

Limited Application
Cytokines

Antibody production

Dendritic cells
Macrophages
B lymphocytes

Intracellular organisms in
Macrophages

Virally infected
cells and some
tumor cells

B

TH

TC

NK

Antigen presentation

Cytokines

Activation

Cytotoxicity
Case Example of Metastatic Melanoma Treated With IL-2

Baseline

After Treatment

Provided by D. Schwartzentruber, MD
The High-Dose Aldesleukin “Select” Trial in Patients with Metastatic RCC

D McDermott, M Ghebremichael, S Signoretti, K Margolin, J Clark, J Sosman, J Dutcher, M French and M Atkins on behalf of the Cytokine Working Group
Activity of IL-2 is greater than 20 years ago

<table>
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<tr>
<th>Response</th>
<th>%</th>
</tr>
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<tbody>
<tr>
<td>Historical rate</td>
<td>14</td>
</tr>
<tr>
<td>IL-2 Select Trial (all pts n=120)*</td>
<td>25</td>
</tr>
<tr>
<td></td>
<td>p=0.0014</td>
</tr>
<tr>
<td></td>
<td>95% CI=17.5-33.7%</td>
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Likely explanations for improved RR include:

1) Improved screening  
   - smaller non-clear cell population  
2) Impact of new therapies on IL-2 referral patterns  
3) Fewer patients treated with original tumor in place

*Using WHO Criteria
### Six Years of Impressive Progress

<table>
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<tr>
<th>Setting</th>
<th>Phase III</th>
<th>Alternative</th>
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<td><strong>1st-Line Therapy</strong></td>
<td>Good or intermediate risk*</td>
<td>Sunitinib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pazopanib</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bevacizumab + IFNα</td>
</tr>
<tr>
<td>Poor risk*</td>
<td>Temozolomide</td>
<td>Sunitinib</td>
</tr>
<tr>
<td><strong>2nd-Line Therapy</strong></td>
<td>Prior cytokine</td>
<td>Sorafenib</td>
</tr>
<tr>
<td></td>
<td>Prior VEGFR inhibitor</td>
<td>Everolimus</td>
</tr>
<tr>
<td></td>
<td>Prior mTOR inhibitor</td>
<td>Clinical Trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Axitinib</td>
</tr>
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</table>

Does Immunotherapy have any role?
Approaches to Cancer Immunotherapy: Improving the steering

Vaccine Therapies - gp100
A  Progression-free Survival

Progression-free Survival (%)

Years

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>94</th>
<th>5</th>
<th>3</th>
<th>2</th>
<th>2</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interleukin alone</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interleukin-2 + vaccine</td>
<td>91</td>
<td>13</td>
<td>10</td>
<td>8</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

P = 0.008

Douglas Schwartzentruber and Larry Kwak
On the trail of a cancer vaccine

I will never forget the day I heard the words “You have cancer.” They are three of the most chilling words you can ever hear, stripping you of control over your life, not to mention any confidence that life will even continue.
Vaccine Therapy for Cancer 2014

• Is this result proof of concept that the immune response can be focused and will it be relevant with novel immunotherapies?
  – IL-2 + novel vaccine
  – Novel immunotherapy (eg CTLA 4 ab) + vaccine – not yet

• Sipuleucel-T – a step forward?
  – Improves survival in CRPC
  – Impact small (median 4.1 mo)
  – Cost high (93K/pt to prepare)
Novel approach to Cancer Immunotherapy: Releasing the Brakes

CTLA-4 = “The Brakes”
The normal rhythms of an immune response

- **Effector response**: production of antibodies and killer T cells
- **Clonal expansion**: increase in numbers of antigen-specific lymphocytes
- **Decline** (homeostasis)
- **Memory**

Designed to shut off
Ipilimumab augments the antitumor immune response

Pivotal 2\textsuperscript{nd} Line Phase III Trial

Study Design

Pre-treated Metastatic Melanoma (N=676)

\begin{itemize}
  \item Ipilimumab + gp100 (N=403)
  \item Ipilimumab + placebo (N=137)
  \item gp100 + placebo (N=136)
\end{itemize}

Hodi et al NEJM, 2010
Blocking CTLA-4 in Melanoma: Releasing the Brakes = Improved Outcomes

- First drug to improve survival in MM patients
- Treating the Immune System, not the cancer
- Outpatient therapy, but associated with significant toxicity
Approval for Drug That Treats Melanoma

The drug, Yervoy, was developed by Bristol-Myers Squibb, and is a novel type of cancer drug that works by unleashing the body’s own immune system to fight a tumor.

By ANDREW POLLACK
Published: March 25, 2011

The first drug shown to prolong the lives of people with the skin cancer melanoma won approval from the Food and Drug Administration on Friday.
**Most Common Immune-Related Adverse Events (irAEs; All Grades)**

<table>
<thead>
<tr>
<th>irAE</th>
<th>% of Patients</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Lpi + gp100</td>
</tr>
<tr>
<td></td>
<td>N=380</td>
</tr>
<tr>
<td><strong>All grades</strong></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>57</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>39</td>
</tr>
<tr>
<td>GI</td>
<td>31</td>
</tr>
<tr>
<td>Endocrine</td>
<td>3</td>
</tr>
<tr>
<td>Hepatic</td>
<td>2</td>
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</table>
Ipilimumab Toxicity can be Severe
Commentary - CTLA-4 Antibodies

- Enables immune responses and anti-tumor responses in some individuals
- Activity powerful enough to work in CNS and overcome concurrent immunosuppression
- May augment effects of XRT
- Phase III trials ongoing in NSCLC, CRPC

Ipilimumab represents an option for the majority of patients with advanced melanoma; timing of therapy, severe autoimmune toxicities require attention
Approaches to Cancer Immunotherapy: Avoiding the Wheel Spikes

PD-L1 = Wheel Spikes
PD-1/PD-L1: Immune Checkpoint Pathway

- There are positive and negative signal pathways that regulate T cells
- The Programmed Death (PD)-1/PD-L1 ligand pathway is an immune checkpoint that suppresses activated T cells and promotes tolerance

PD-L1 can be expressed on tumor cells either endogenously or induced by association with T cells (adaptive immune resistance)\(^1,2\)

In RCC, PD-L1 expression has been shown to be associated with adverse clinical/pathologic features, including\(^3\):
- More aggressive disease
- Shorter survival

Anti-PD-1: Blocking T cell Suppression

PD-L1 Is Broadly Expressed in Solid Tumors

- Positive PD-L1 staining in RCC (proprietary Genentech/Roche PD-L1 IHC)
- High sensitivity and specificity in FFPE samples

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Estimated PD-L1 Prevalence, (\approx) %*</th>
</tr>
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<tbody>
<tr>
<td>NSCLC (SCC)</td>
<td>50%</td>
</tr>
<tr>
<td>NSCLC (adenocarcinoma)</td>
<td>45%</td>
</tr>
<tr>
<td>Colon</td>
<td>45%</td>
</tr>
<tr>
<td>Melanoma</td>
<td>40%</td>
</tr>
<tr>
<td>RCC</td>
<td>20%</td>
</tr>
</tbody>
</table>

- PD-L1 not expressed in normal human kidney cells but is aberrantly expressed in primary and metastatic RCC
- Tumor expression of PD-L1 is associated with poor prognosis

* Based on staining of archival tumor tissue from patients with metastatic cancer (Genentech data).
**Study Design: Phase I Multi-dose Regimen**

8-wk treatment cycle

- Day 1
- 15
- 29
- 43
- 57

* Dose administered IV Q2wk

- Rapid PD or clin. deterioration
- Unacceptable toxicity
- CR/PR/SD or PD but clinically stable

- Follow-up every 8 wks x 6 (48 wks)
- Off Study

Treat to confirmed CR, worsening PD, unacceptable toxicity, or 12 cycles (96 wks)

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**Eligibility:** Advanced MEL, RCC, NSCLC, CRC, or CRPC with PD after 1-5 systemic therapies
### Nivolumab-related adverse events

<table>
<thead>
<tr>
<th>Drug-Related Adverse Event</th>
<th>All Grades</th>
<th>Grades 3-4</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Tot Pop*†</td>
<td>RCC</td>
</tr>
<tr>
<td></td>
<td>N (%) of Patients, All Doses</td>
<td></td>
</tr>
<tr>
<td>Any adverse event</td>
<td>220 (72)</td>
<td>29 (85)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>78 (26)</td>
<td>14 (41)</td>
</tr>
<tr>
<td>Rash</td>
<td>41 (14)</td>
<td>9 (27)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>36 (12)</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>31 (10)</td>
<td>6 (18)</td>
</tr>
<tr>
<td>Nausea</td>
<td>24 (8)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Appetite ↓</td>
<td>24 (8)</td>
<td>3 (9)</td>
</tr>
<tr>
<td>Hemoglobin ↓</td>
<td>18 (6)</td>
<td>2 (6)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>16 (5)</td>
<td>3 (9)</td>
</tr>
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</table>

*AEs occurring in ≥5% of the total population.

†Drug-related renal failure/nephritis occurred in 1% of the total population, with no grade 3-4 drug-related events, based on an analysis on July 3, 2012.

‡The most common grade 3-4 AEs were respiratory system disorders (2 patients) and hypophosphatemia (2 patients). An additional 10 grade 3-4 drug-related AEs (pruritus, rash macular, alanine aminotransferase, blood alkaline phosphatase increased, hypophosphataemia, muscular weakness, acute respiratory failure, cough, hypercapnia, hypoxia) were observed and one or more occurred in a single patient.
Pulmonary Complications with PD-1 Blockade
Summary of Key Safety Results

In the total treated patient population across all tumor types:

• Grade 3-4 drug-related AEs occurred in 14%

• Discontinuation of treatment due to drug-related AE occurred in 18/304 (6%) of patients

• Three drug-related deaths occurred in patients with pneumonitis (2 with NSCLC and 1 with CRC)

In RCC patients:

• Safety profile was similar to the total treated patient population

• Grade 3-4 drug-related AEs occurred in 21% of patients
Update: Phase I Nivolumab: RCC cohort (n=34)

- Generally tolerable: fatigue, rash, pruritus, diarrhea
  - 3 deaths: pneumonitis (non-RCC)

- Preliminary efficacy in heavily pre-treated patients:
  - 29% objective responses
  - Median PFS 7.3 months