Cancer Immunotherapy

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Disclosure

• Research Support Bristol-Myers Squibb
Cancer Immunotherapy:

Cancer Vaccines (Sipuleucel-T)
Cytokines (IL-2, Interferon)
Adoptive T cell Therapy

**Checkpoint Blocking Antibodies**

- CTLA-4
- PD-1

**Checkpoint Molecules Regulate T cell Activation**

Mellman et al. Nature 2011
**Checkpoint Molecules Regulate T cell Activation**

CD28 is a Costimulatory molecule that has a positive impact on T cell activation.

CTLA-4 and PD-1 are “Checkpoints” or Inhibitory molecules that negatively regulate T cell activation.

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**CTLA-4 Blockade Augments T cell Activation**

Adapted from O'Day et al. Plenary session presentation, abstract #4, ASCO 2010.
CTLA-4 Blockade Augments T cell Activation

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CTLA-4 Blockade Augments T cell Activation

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CTLA-4 Blocking Antibodies in the Clinic

Antibodies that Block CTLA-4 attenuate negative feedback for T cells and results in more sustained T cell activation.

**Ipilimumab**
- Fully human monoclonal IgG1 kappa antibody
- Half-life ~12-14 days

**Tremelimumab**
- Fully human monoclonal IgG2 antibody
- Half-life ~ 22 days

11/28/06  1/9/07
Tumorous nodule with melanin pigment (macrophages and lymphocytes; no melanocytes)

Macrophages and lymphocytes are present, but no tumor cells

CD8-positive T-cells

CD4-positive T-cells (macrophages are also weakly pos for CD4)
Ipilimumab – Pathway to FDA Approval

Inclusion

HLA-A*02:01 pretreated, metastatic melanoma (N = 676)

Pretreated, unresectable stage III or IV melanoma
Pretreated central nervous system metastases allowed
Any LDH level

Endpoints

Primary endpoint: overall survival
Secondary objectives:
Best overall response rate
Duration of response
Progression-free survival
Safety

Ipilimumab + gp100
Q2W x 4
(n = 403)

Ipilimumab + placebo
Q2W x 4
(n = 137)

gp100 + placebo
Q2W x 4
(n = 136)

Ipilimumab + gp100
Q3W x 4
(n = 6)

Ipilimumab + placebo
Q3W x 4
(n = 39)

gp100 + placebo
Q3W x 4
(n = 3)

FOLLOW-UP

Hodi et al. NEJM 2010

Ipilimumab – Pathway to FDA Approval

A

Comparison Hazard ratio P value
Arm A vs C 0.68 < 0.001
Arm B vs C 0.66 0.003

Proportion alive (%)

0 20 40 60 80 100

Years

Ipilimumab + gp100
(n = 403)

Ipilimumab + placebo
(n = 137)

gp100 + placebo
(n = 136)

1-year OS rate (%) 44 46 25
2-year OS rate (%) 22 24 14
Median OS (months) 10.0 10.1 6.4

Hodi et al. NEJM 2010
Ipilimumab – Pathway to FDA Approval

- Overall survival benefit demonstrated in 2 Phase 3 studies of patients with advanced melanoma
- Approved by the FDA in March 2011
- Approved dose of 3 mg/kg administered every 3 weeks for 4 doses

Hodi et al. NEJM 2010

Ipilimumab – Unique Mechanism Based Toxicities

<table>
<thead>
<tr>
<th>TABLE 19.3 Immune-related Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Common</strong></td>
</tr>
<tr>
<td>Colitis</td>
</tr>
<tr>
<td><strong>Infrequent</strong></td>
</tr>
<tr>
<td>Hepatitis</td>
</tr>
<tr>
<td><strong>Rare</strong></td>
</tr>
<tr>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Uveitis</td>
</tr>
<tr>
<td>Nephritis</td>
</tr>
<tr>
<td>Red Blood Cell Aplasia</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Meningitis/Encephalopathy</td>
</tr>
</tbody>
</table>

Callahan et al. 2013
Ipilimumab – Unique Mechanism Based Toxicities

Management of Toxicities According to Published Algorithms

Generally Reversible with appropriate treatment – i.e. systemic steroids – or rarely stronger immunosuppressants

Evaluate Severity

↓

Initiate Appropriate Treatment (i.e. Steroids)

↓

Reassess

Ipilimumab – Unique Kinetics of Response

Baseline (Day 0)  Week 12 (Day 84)

Week 16 (Day 112)  Week 72 (Day 503)
Ipilimumab – Unique Kinetics of Response

- Delayed Kinetics of Response (compared to Chemotherapeutics)
- Mixed Responses (Heterogeneity in the Rate of Response between lesions)
- Responses (when they happen) are typically durable, lasting for years.
- Development of Immune Related Response Criteria

CTLA-4 Blockade: A Case Study for Immunotherapy in Need of Biomarkers

Knowns
- Clinical benefit for a subset of patients with refractory melanoma
- Reversible mechanism-based side effects
- Tumor responses tend to be durable
- Kinetics of response unlike cytotoxics

Unknowns
- Biomarkers for response
- Biomarkers for toxicities
- Effect on effector vs regulatory T cells in humans
- Antigens recognized after infusion
- Importance of vaccination before treatment
- Relevance of PBMC vs tumor site findings

Hoos et al. 2009
Checkpoint Molecules Regulate T cell Activation

CTLA-4 and PD-1 Act at Different Steps in T cell Activation
Checkpoint Blocking Antibodies in Clinical Development

Callahan et al. 2013

<table>
<thead>
<tr>
<th>Antibody *fusion protein</th>
<th>Target</th>
<th>Isotype</th>
<th>Clinical Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab (BMS)</td>
<td>CTLA-4</td>
<td>IgG1k</td>
<td>FDA approved</td>
</tr>
<tr>
<td>Tremelimumab (Pfizer, Medimmune)</td>
<td>CTLA-4</td>
<td>IgG2</td>
<td>Completed Phase 3</td>
</tr>
<tr>
<td>Nivolumab/BMS-936550/MDX1106 (BMS)</td>
<td>PD-1</td>
<td>IgG4</td>
<td>Phase 1 interim, Phase 3 open</td>
</tr>
<tr>
<td>CT-011 (CureTech)</td>
<td>PD-1</td>
<td>IgG1</td>
<td>Completed Phase 1</td>
</tr>
<tr>
<td>MK-3475 (Merck)</td>
<td>PD-1</td>
<td>IgG4</td>
<td>Phase 1 ongoing, interim results</td>
</tr>
<tr>
<td>AMP-224* (Ampimmune)</td>
<td>PD-1</td>
<td>NA</td>
<td>Phase 1 ongoing</td>
</tr>
<tr>
<td>BMS-936550/MDX-1105 (BMS)</td>
<td>PD-L1</td>
<td>IgG4</td>
<td>Completed Phase 1</td>
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<tr>
<td>MEDI4736 (Medimmune/AstraZeneca)</td>
<td>PD-L1</td>
<td>IgG1k</td>
<td>Phase 1 ongoing</td>
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<tr>
<td>MPDL3280/PG7446 (Genentech/Roche)</td>
<td>PD-L1</td>
<td>NA</td>
<td>Phase 1 ongoing</td>
</tr>
</tbody>
</table>

*fusion protein

Checkpoint Blockade Moves Beyond Melanoma

Safety, Activity, and Immune Correlates of Anti–PD-1 Antibody in Cancer

Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Lemaing, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Szol, M.D.

<table>
<thead>
<tr>
<th>Cancer</th>
<th>Objective Response</th>
<th>Objective Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>26/94</td>
<td>28 (19-38)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>14/76</td>
<td>18 (11-29)</td>
</tr>
<tr>
<td>RCC</td>
<td>9/33</td>
<td>17 (13-46)</td>
</tr>
</tbody>
</table>
Checkpoint Blockade in Combinations

Immunologic Correlates of the Abscopal Effect in a Patient with Melanoma

Michael A. Postow, M.D., Margaret K. Callahan, M.D., Ph.D., Christopher A. Baker, M.D., Yoshia Yamada, M.D., Jianfa Yuan, M.D., Ph.D., Shehhrza Khan, M.D., Ph.D., Zhenyu Mu, M.D., Teresa Rasslan, B.S., Matthew Adamson, B.S., Erika Ritter, B.S., Christine Szabolcs, B.S., Ashim A. Jungbluth, M.D., Damon Chua, B.S., Amin S. Yang, M.D., Ph.D., Nathanael Kerman, R.N., Samuel Rizzone, Brenna Benson, James F. Allison, Ph.D., Alexander M. Leszokh, M.D., Sacha Gejy, Ph.D., and Jedd D. Wolchok, M.D., Ph.D.

Hepatotoxicity with Combination of Vemurafenib and Ipilimumab

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Unexpected Benefits

Unexpected Toxicities

Summary

• CTLA-4 blockade is an effective treatment that confers a benefit in overall survival in patients with advanced melanoma.

• Unique Toxicities are managed with a published algorithm that employs immunosuppressive agents such as steroids.

• Unique Kinetics of Response, including delayed responses and long-term durability of responses are characteristic.

• PD-1 (or PD-L1) blockade appears to have activity in melanoma, NSCLC, and RCC.

• Further studies are needed to develop biomarkers for these agents.
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Ruth Halaban

MD Anderson
Pam Sharma

Learning Objectives:

What is a checkpoint blocking antibody and how do these antibodies work in the treatment of cancer?

What checkpoint blocking antibody is approved by the FDA for the treatment of cancer?

What is the side-effect profile for checkpoint blocking antibodies?
Multiple Choice Question 1:

Question: The following molecules are negative regulators (or checkpoints) of T cell activation

A. CTLA-4
B. CD-28
C. PD-1
D. A and B
E. A and C
F. B and C

Answer: E (A &C)
Explanation: CTLA-4 and PD-1 are both checkpoint molecules that negatively regulate T cell activation. CD28 is a costimulatory molecule that positively regulates T cell activation.

Multiple Choice Question 2:

Question: How does Ipilimumab work ?

A. By blocking CTLA-4, Ipilimumab turns off a negative regulator (or checkpoint) and results in more T cell activation
B. By blocking PD-1, Ipilimumab turns off a negative regulator (or checkpoint) and results in more T cell activation
C. Ipilimumab is a vaccine that generates a new anti-tumor immune response
D. Ipilimumab is a cytokine that

Answer: A
Explanation: Ipilimumab is a checkpoint blocking antibody. It blocks the negative regulatory molecule CTLA-4 (not PD-1).
Multiple Choice Question 3:

Question: How should ipilimumab related colitis be treated?

A. By following published algorithm for ipilimumab-related toxicity management
B. Promptly initiating a course of systemic corticosteroids according to the published algorithms
C. With close followup after initiation of appropriate intervention until symptoms resolve.
D. All of the above
Answer: D

Explanation: Ipilimumab related colitis should be managed according to published algorithms. Corticosteroids are utilized in the management of ipilimumab-related colitis and with prompt, appropriate treatment symptoms are typically transient and reversible. Close followup is warranted.

Multiple Choice Question 4:

Question: Responses to ipilimumab are generally expected to be ___ traditional chemotherapies or targeted inhibitors.
A. Faster than
B. Slower than
C. The same as

Answer: B

Explanation: Responses to Checkpoint blockade may be delayed or slower than typically seen with chemotherapies or targeted inhibitors.