Use of CTLA-4 Blockade in Metastatic Melanoma

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CANCER BREAKTHROUGH

INTERLEUKIN-2, HUMAN
(des-alanyl, serine-125)

Lyophilized Preparation
- For single use
- With sterile Water for Injection

Cetus Corp.'s
Tumor-zapping
Interleukin-2
High-Dose IL-2 Therapy

- RR: 16% (43/270)
- Durable responses
  - Median 8.9 mos
  - CR: not reached

Atkins et al., J Clin Oncol, 1999
Ipilimumab Augments T-Cell Activation and Proliferation

Adapted from O'Day et al. Plenary session presentation, abstract #4, ASCO 2010.
Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma

Leach DR et al., Science, 1996
Clinical Response in Melanoma: NCI

Experienced complete resolution of 2 subcutaneous nodules, 31 lung metastases and 0.5 cm brain metastasis.
Immune-Related Adverse Events

- Rash (approx 20%)
- Colitis/enteritis (approx 15%)
- Elevated AST/ALT (approx 10%)
- Endocrinopathies: Thyroiditis, Hypophysitis, Adrenal insufficiency (2-5%)

Severity is inversely related to vigilance of surveillance. If detected early, most are easily treated and reversible.
Rapid Clinical Response to Ipilimumab

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

Klaus Busam, MSKCC Dermatopathology
CD8-positive T-cells

CD4-positive T-cells (macrophages are also weakly pos for CD4)
Ipilimumab Pattern of Response: Responses After the Appearance and Subsequent Disappearance of New Lesions

Pre-treatment

July 2006

Week 12: Progression

3 mg/kg ipilimumab Q3W X 4

New lesions

Week 20: Regression

Week 36: Still Regressing

Source: 2008 ASCO Abstract #3020 Wolchok.
Four Patterns of Response to Ipilimumab Therapy Observed

• 2 conventional:
  – Response in baseline lesions
  – ‘Stable disease’ with slow, steady decline in total tumor volume

• 2 novel:
  – Response after initial increase in total tumor volume
  – Response in index plus new lesions at or after the appearance of new lesions
irRC Identifies Survivors in Patients with Progressive Disease by mWHO

Pooled data from phase II studies CA184-008 and CA184-022: ipilimumab monotherapy 10 mg/kg (N=227)

Kaplan-Meier Analysis of Survival
MDX-010-20: Hodi et al, NEJM, 2010

Survival Rate | Ipilimumab + gp100 | Ipilimumab alone | gp100 alone
--- | --- | --- | ---
1-year | 44% | 46% | 25%
2-year | 22% | 24% | 14%

Comparison | HR | P-value
--- | --- | ---
Arm A vs C | 0.68 | 0.0004
Arm B vs C | 0.66 | 0.0026
Arm A vs B | 1.04 | 0.7575
Study 024: Overall Survival

Estimated Survival Rate

<table>
<thead>
<tr>
<th></th>
<th>1 Year</th>
<th>2 Year</th>
<th>3 Year*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab + DTIC</td>
<td>47.3</td>
<td>28.5</td>
<td>20.8</td>
</tr>
<tr>
<td>Placebo + DTIC</td>
<td>36.3</td>
<td>17.9</td>
<td>12.2</td>
</tr>
</tbody>
</table>

*3-year survival was a post-hoc analysis
Ipilimumab Long Term Pooled Survival Analysis: 4846 Patients

Median OS (95% CI): 9.5 (9.0–10.0)

3-year OS Rate (95% CI): 21% (20–22%)

Hodi et al., ESMO, 2013
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
10 mg/kg Ipilimumab is More Biologically Active than 3 or 0.3 mg/kg

Mean absolute lymphocyte count (ALC) versus time

- Thick curves show fitted means as a function of time and dose
- Thin curves are bounds of 95% confidence bands for the mean

Wolchok et al., Lancet Oncology, 2010
This patient population comprises all patients (N=73) available at the Immune Monitoring Facility (IMF) of Memorial Sloan-Kettering Cancer Center, New York.

Ku et al., Cancer, 2010
Changes by Lymphocyte Phenotype

CD4+

CD4+ CD8+ CD4+CD25+

CB NCB CB NCB CB NCB

P = 0.14
P = 0.0094
P = 0.54

Yang et al. ASCO, 2010
Correlation of NY-ESO-1 antibody with clinical course following anti-CTLA-4 treatment

Patients with NY-ESO-1 antibodies at any time point during study

<table>
<thead>
<tr>
<th>Response</th>
<th># patients Status at wk24 (%)</th>
<th># NY-ESO-1 SERONEGATIVE Status wk24 (%)</th>
<th># NY-ESO-1 SEROPOSITIVE Status wk24 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>6 (5.1%)</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>PR</td>
<td>14 (12.0%)</td>
<td>9</td>
<td>5</td>
</tr>
<tr>
<td>SD</td>
<td>25 (21.4%)</td>
<td>19</td>
<td>6</td>
</tr>
<tr>
<td>Clinical Benefit</td>
<td>45 (38.5%)</td>
<td>32 (33.7%)</td>
<td>13 (59.1%)</td>
</tr>
<tr>
<td>No Clinical Benefit</td>
<td>72 (61.5%)</td>
<td>63 (66.3%)</td>
<td>9 (40.9%)</td>
</tr>
<tr>
<td>Total</td>
<td>117 (100%)</td>
<td>95</td>
<td>22</td>
</tr>
</tbody>
</table>

According to Immune-related response criteria:

CR: Complete Response  
PR: Partial Response  
SD: Stable Disease  
POD: Progression of Disease (includes MR: mixed response)  
DOD: Dead of Disease  

Fisher's exact test:  
P value 0.0498

Yuan et al., *PNAS*, 2011
ICOS expression in CD4⁺ T cells

With clinical benefit (7/7)

No clinical benefit (1/7)

Carthon et al, Clin Cancer Res, 2010
Metastatic Melanoma Patients Have Increased Quantity of MDSC


p=0.02

med OS not reached (95% CI: 8.6, not reached)

med OS 6.3 months (95% CI: 3.4, 18.8)

n=26 pts

• April 2004: 33 woman w/ pT2aNo (Stage IB) melanoma arising in upper back (non-ulcerated, 2mf)

• October 2008: Left pulmonary nodule detected incidentally by CXR with CT scan/PET confirmation (also with additional RLL 3mm nodule)

• December 2008: 2 cycles of Cisplatin, Vinblastine, Temodar

• February 2009: Left lower lobectomy

• August 2009: Unresectable recurrence

Postow and Callahan, NEJM, 2012
A-A''

B-B''

C-C''

D-D''

E-E''

Radiation

Unresectable Recurrence

Ipilimumab

Induction

Maintenance

Radiation

Maintenance

Stable

Slow Progression

Response

Stable

August 2009

November 2010

January 2011

April 2011

October 2011

8/09

9/09

12/09

11/10

12/10

1/11

4/11

10/11

A-A''

B-B''

C-C''

D-D''

E-E''

Radiation

Maintenance
Mutations and Immunogenicity

- *In silico* analysis of 1,152 peptides with missense mutations in breast and CRC:
  - 7-10 unique HLA-A*0201 epitopes per tumor
- Carcinogen-induced sarcoma cell line in mice featured highly immunogenic peptides ("rejection antigens")
  - ~1% of mutations constituted “rejectable clones”

Alexandra Snyder, M.D.
Mutations and Immunogenicity

• Study of melanoma patient with PR to ipilimumab:
  – 1,075 nonsynonymous mutations
  – Computational + *in vitro* strategies to narrow down 448 candidate neoantigens to one
## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Long-Term Benefit</th>
<th>Minimal or No Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td><strong>Age at start of treatment (median, range)</strong></td>
<td>63 (39-70)</td>
<td>59.5 (48-79)</td>
</tr>
<tr>
<td><strong>LDH at start of therapy (n, %)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>8 (73)</td>
<td>8 (57)</td>
</tr>
<tr>
<td>Above normal</td>
<td>2 (18)</td>
<td>5 (33)</td>
</tr>
<tr>
<td>Not available</td>
<td>1 (9)</td>
<td>1 (7)</td>
</tr>
<tr>
<td><strong>Duration of response (median weeks, range)</strong></td>
<td>59 (42-361+)</td>
<td>0 (0-24)</td>
</tr>
<tr>
<td><strong>Prior therapies (median number, range)</strong></td>
<td>1 (0-3)</td>
<td>1 (0-2)</td>
</tr>
<tr>
<td><strong>Stage at Diagnosis (n, %)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M1a</td>
<td>0 (0)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>M1b</td>
<td>5 (45)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>M1c</td>
<td>6 (55)</td>
<td>12 (86)</td>
</tr>
<tr>
<td><strong>Overall Survival (median years, range)</strong></td>
<td><strong>4.4 (2-6.9)</strong></td>
<td>0.9 (0.4-2.7)</td>
</tr>
</tbody>
</table>

Presented by: Alexandra Snyder, M.D.
**Exome Analysis Pipeline**

Memorial Sloan Kettering Cancer Center

**Overall process:**
1. Alignment
2. Exclude SNPs
3. Select nonsynonymous coding mutations
4. Manually review
5. Identify ("call") mutations

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1. **Alignment**
   - BWA
   - GATK
   - Somatic Sniper

2. **Exclude SNPs**
   - 1000 Genomes
   - ESP5400
   - dBSNP 132

3. **Select nonsynonymous coding mutations**
   - ANNOVAR
     - Intronic/Intergenic
     - Noncoding
     - Synonymous Coding

4. **Manually review**
   - Minimum 11x depth
   - Manual IGV Curation

5. **Identify ("call") mutations**
   - (5) non-synonymous, coding point mutations
## Mutational Load Correlates with Clinical Benefit

<table>
<thead>
<tr>
<th>Number of Exonic Missense Mutations</th>
<th>Long-term Benefit</th>
<th>Minimal or No Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$P = 0.01$</td>
</tr>
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</table>
Neoepitope Signature in Discovery Set

Long-term Benefit

Minimal or No Benefit

Wild type: TKSPFEQHI

Mutant: TESPFEQHI

Alexandra Snyder, M.D.
The Cancer–Immunity Cycle

Summary and Future Directions

- Checkpoint blockade with ipilimumab is an effective treatment with durable responses in metastatic melanoma.
- Induction of ICOS on CD4+ T cells, pre-existing immunity to surrogate antigens and increases in peripheral lymphocyte counts are promising pharmacodynamic markers.
- MDSCs represent a potential predictive biomarker.
- Mutational load may confer a significant effect on outcomes from CTLA-4 blockade.