Endogenous and Exogenous Vaccination in the Context of Immunologic Checkpoint Blockade

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Disclosure

• Consultant: Bristol-Myers Squibb
CTLA-4 Blockade Enhances Tumor-Specific Immune Responses

Attenuated or Terminated Proliferation

Unrestrained Proliferation

Necrotic Death
Vaccines
Chemotherapy
Irradiation
Hormone therapy
Anti-angiogenesis
Antibodies
“Targeted” Therapies
Anti-CTLA-4 Induces Regression of Transplantable Colon Carcinoma

Average Tumor Size (mm²)

Days After Tumor Injection

Leach
Anti-CTLA-4 and GM-CSF Tumor Cell Vaccine Synergize to Eradicate Established B16 Melanoma

Days After Tumor Injection

Average Tumor Size (mm²)

No Rx
GM-Vaccine
Anti-CTLA-4
Both

van Elsas, Hurwitz
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.
Hypopigmentation
MDX010-20: Study Design

Pre-treated Metastatic Melanoma (N=676)

Randomize

Ipilimumab + gp100 (N=403)

Ipilimumab + placebo (N=137)

gp100 + placebo (N=136)
Kaplan-Meier Analysis of Survival

<table>
<thead>
<tr>
<th>Survival Rate</th>
<th>Ipi + gp100 N=403</th>
<th>Ipi + pbo N=137</th>
<th>gp100 + pbo N=136</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year</td>
<td>44%</td>
<td>46%</td>
<td>25%</td>
</tr>
<tr>
<td>2 year</td>
<td>22%</td>
<td>24%</td>
<td>14%</td>
</tr>
</tbody>
</table>
**PFS: Impact of Both Ipilimumab Regimens vs gp100**

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Hazard Ratio (C.I.)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arms A vs C</td>
<td>0.81 (0.66–1.00)</td>
<td>0.0464</td>
</tr>
<tr>
<td>Arms B vs C</td>
<td>0.64 (0.50–0.83)</td>
<td>0.0007</td>
</tr>
<tr>
<td>Arms A vs B</td>
<td>1.25 (1.01–1.53)</td>
<td>0.0371</td>
</tr>
</tbody>
</table>

**Graph**

- **Ipi + gp100 (A)**
- **Ipi alone (B)**
- **gp100 alone (C)**

- **Y-axis:** Proportion Not Progressed
- **X-axis:** Years

**Note:**

- The graph shows the proportion of patients not progressed over time for each arm of the study.
- The hazard ratios and p-values indicate the impact of different treatment regimens on progression-free survival.

ASCO 2010
# Ipilimumab Improves Best Objective Response Rate (BORR)

<table>
<thead>
<tr>
<th></th>
<th>Arm A Ipi + gp100 N=403</th>
<th>Arm B Ipi + pbo N=137</th>
<th>Arm C gp100 + pbo N=136</th>
</tr>
</thead>
<tbody>
<tr>
<td>BORR, %</td>
<td>5.7</td>
<td>10.9</td>
<td>1.5</td>
</tr>
<tr>
<td>P-value: A vs C</td>
<td>0.0433</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value: B vs C</td>
<td>0.0012</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DCR‡, %</td>
<td>20.1</td>
<td>28.5</td>
<td>11.0</td>
</tr>
<tr>
<td>P-value: A vs C</td>
<td>0.0179</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value: B vs C</td>
<td>0.0002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

‡Disease control rate: percentage of patients with CR, PR, or SD
Vaccines and CTLA-4 Blockade

- Pre-clinical models in melanoma support synergy
- Clinical trial shows equivalent overall survival but inferior response and disease control rates
  - Correct vaccine?
  - Antigen escape?
  - Polarization of response?
  - Antigen sink?
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
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)

Klaus Busam
NY-ESO-1 antibody and CD4 T-cell response were detected after full-length NY-ESO-1 protein vaccination

NY-ESO-1 CD4 and CD8 T-cell specific response after CTLA-4 blockade (Patient IMF-11)
Grand Serology in CTLA-4 treated patients (peak response):
Correlation with clinical benefit
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><strong>Clinical Benefit</strong></td>
<td><strong>45 (38.5%)</strong></td>
<td><strong>32 (33.7%)</strong></td>
<td><strong>13 (59.1%)</strong></td>
</tr>
<tr>
<td><strong>No Clinical Benefit</strong></td>
<td><strong>72 (61.5%)</strong></td>
<td><strong>63 (66.3%)</strong></td>
<td><strong>9 (40.9%)</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>117 (100%)</strong></td>
<td><strong>95</strong></td>
<td><strong>22</strong></td>
</tr>
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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

Gnjatic & Wolchok, Ludwig Center/MSKCC
Halaban and Sznol, Yale
Polyfunctional NY-ESO-1 Specific T cells in Blood Of Melanoma Patients Treated with aCTLA-4

% IFN-γ+ MIP-1β+ T-cell

% IFN-γ+ TNF-α+ T-cell

% of total CD4+ T cell response

% of total CD4+ T cell response

Yuan, Gnjatic, Wolchok
NY-ESO-1 antigen-specific CD4 T cell response

P=0.127 by Fisher’s Exact Test
NY-ESO-1 antigen-specific CD8 T cell response

No Clinical Benefit (3/9)  Clinical Benefit (10/11)

P=0.016 by Fisher’s Exact Test
NY-ESO-1 seropositivity with a CD8+ T-cell response correlates with survival (median survival not reached vs. 8 months, p=0.0158).
Tumor 1
Tumor 2
Primary Site
PHENOTYPE OF PBMCS (PT. IMF-91E) & TUMORS (00-144-413)
PHENOTYPE OF PBMCS (PT. IMF-91E) & TUMORS (00-144-413)

**CD4⁺ T CELLS**

- PBMC
- Tumor 1
- Tumor 2

**CD8⁺ T CELLS**

- PBMC
- Tumor 1
- Tumor 2
Tyrosinase and gp100 specific immunity in patient IMF-32

DNA vaccination trial 00-142
GM-CSF DNA + gp100 and tyrosinase peptides

Anti-CTLA-4 antibody trial (CA184-008)
Ipilimumab
10 mg/kg
Every 3 weeks x four doses ++
Tyrosinase and gp100 antigen-specific response during GM-CSF DNA and CTLA-4 blockade

GM-CSF DNA

<table>
<thead>
<tr>
<th>HLA/A*0201 Tyrosinase tetramer</th>
<th>Pre-vaccine</th>
<th>Post-vaccine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.004</td>
<td>0.001</td>
<td></td>
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<td>0.05</td>
<td>1.31</td>
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CTLA-4 blockade

<table>
<thead>
<tr>
<th>HLA/A*0201 Tyrosinase tetramer</th>
<th>Pre-therapy</th>
<th>Wk12</th>
<th>Wk36</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.001</td>
<td>0.09</td>
<td>0.1</td>
<td></td>
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<th>Pre-therapy</th>
<th>Wk12</th>
<th>Wk36</th>
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</thead>
<tbody>
<tr>
<td>0.001</td>
<td>0.61</td>
<td>14.1</td>
<td></td>
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Gp100 specific CD8 T-cell response during GM-CSF DNA and CTLA-4 blockade

GM-CSF DNA

- Pre-vac: 0.12
- Post-vac: 0.28

CTLA-4 blockade

- Pre-therapy: 0.14
- Wk12: 0.37
- Wk36: 4.93
CD8 gp100\textsuperscript{209} specific T-cell response during gp100 DNA vaccine and CTLA-4 blockade (patient IMF-24)
Summary

• CTLA-4 blockade with ipilimumab results in prolonged survival of patients with refractory melanoma.
• Clinical response has been associated with: changes in ALC, NY-ESO-1 immunity and induction of ICOS expression on CD4+ T cells. These require prospective evaluation in ongoing clinical trials.
• De novo immune responses to self antigens has been manifest by autoimmune hypopigmentation.
• Tumor microenvironment is fertile ground to study the mechanism underlying immunologic checkpoint blockade.
Ludwig Center for Cancer Immunotherapy

Jim Allison  Lloyd Old  Alan Houghton

Sacha Gnjatic  Charlotte Ariyan  Jianda Yuan & the IMF Crew

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