Cancer Immunotherapy: Accomplishments and Challenges

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CTL-4 Blockade Enhances Tumor-Specific Immune Responses

Attenuated or Terminated Proliferation

Unrestrained Proliferation

Tumor

Necrotic Death
Vaccines
Chemotherapy
Irradiation
Hormone therapy
Anti-angiogenesis
Antibodies
“Targeted” Therapies

TCR
CD28
CTLA-4

Peptide/MHC

B7-1,2
Tumorous nodule with melanin pigment (macrophages and lymphocytes; no melanocytes)

Macrophages and lymphocytes are present, but no tumor cells

Klaus Busam
CD8-positive T-cells

CD4-positive T-cells
(macrophages are also weakly pos for CD4)

Klaus Busam

Ipilimumab Pattern of Response:
Responses After the Appearance and Subsequent Disappearance of New Lesions

Pre-treatment

July 2006

3 mg/kg ipilimumab Q3W X 4

Week 20: Regression

Week 12: Progression

New lesions

Week 36: Still Regressing

Source: 2008 ASCO Abstract #3120 Wolchok.
Four Patterns of Response to Ipilimumab Therapy were 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
Proportion of Response to Ipilimumab

Patients randomized to 10 mg/kg ipilimumab monotherapy: CA184-008 and -022
n = 227

mWHO PD at Week 12
n = 123

Followed beyond mWHO PD
n = 97

Response in baseline lesions
n = 14
6 ongoing
3 decline with intermittent progression

Response after initial increase in total tumor volume
n = 1

Response of index plus new lesions after the appearance of new lesions
n = 3
1 ongoing

**Unknown (No follow-up scan)**
n = 41

mWHO Disease control in baseline lesions
n = 63

Response in baseline lesions
n = 18
12 ongoing *
1 response with intermittent progression

mWHO SD in baseline lesions
n = 45
25 ongoing

**Response in baseline lesions**
n = 18
8 ongoing *
12 ongoing *
1 response with intermittent progression

**Response after initial increase in total tumor volume**
n = 1

**Response of index plus new lesions after the appearance of new lesions**
n = 3
1 ongoing

14 patients with evidence of clinical activity
(13 after mWHO PD = 1 who follow-up beyond mWHO PD)

**Ongoing = response or SD ongoing at the last evaluable tumor assessment (prior to alternate non-ipilimumab therapy) unless patient died. Slow steady decline is defined as a > 25% reduction from baseline in total tumor volume at the last evaluable tumor assessment, unless otherwise noted.**

**Response of index plus new lesions after the appearance of new lesions**

15 ongoing
1 decline with intermittent progression

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)

Wolchok et al, Clin Cancer Res, 2009
Immune-Related Adverse Events

- Rash (approx 20%)
- Colitis/enteritis (approx 15%)
- Elevated AST/ALT (approx 10%)
- Thyroiditis (2 cases)
- Adrenal insufficiency (1 case)
- Hypophysitis (4 seen in 170 patients at MSKCC)

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

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

Source: Dr. David Berman, BMS: CA184007, CA184008, CA184022

Mean longterm ALC

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
Clinical response week 24

Changes by Lymphocyte Phenotype

Yang et al. ASCO, 2010
ICOS and FOXP3 in Blood of Metastatic Melanoma Patient after anti-CTLA-4 Treatment

Carthon et al., Clin Cancer Res, 2010

ICOS expression in CD4 T cells obtained from 14 melanoma patients with CTLA-4 blockade

With clinical benefit (7/7) No clinical benefit (1/7)

Jianda Yuan and Geoffrey Ku
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)

Reciprocal titer

Percent of IFN-γ+ MIP-1β+ or IFN-γ+TNF-α+ T cells

Pre-tx wk7 wk20 Pre-tx wk7 wk20
CD8 T cells CD4 T cells

Grand Serology in CTLA-4 treated patients (peak response):
Correlation with clinical benefit

Clinical Benefit
No Clinical Benefit
Awaiting

NY-ESO-1
LAGE-1
MAGE-1
MAGE-3
MAGE-4
MAGE-10
Melan-A
CT7
CT10
CT14
CT46
CT47
SSX1
SSX2
SSX4
PLAC1
SOX2
p53
XAGE-1
ZH1347
ZH_P24
DHFR
GAGE7
CXorf48
PASD1
CXorf61
CSAG2
ERG
NXF2
SAGE1
ACTL8

Clinical Benefit
PR
Pod
DOD
Awaiting

Clinical Benefit
No Clinical Benefit

POD
SD
CR
PR
DOD
Awaiting

POD
SD
CR
PR
DOD
Awaiting
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>
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</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

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

Yuan, Gnjatic
NY-ESO-1 seropositivity with a CD8+ T-cell response correlates with survival (median survival not reached vs. 8 months, p=0.0158).

NY-ESO-1 antigen-specific B cell epitope response before and after CTLA-4 therapy (pt. IMF-16)
PHENOTYPE OF PBMCS (PT. IMF-91E) & TUMORS (00-144-413)

<table>
<thead>
<tr>
<th>Tumor 1</th>
<th>Tumor 2</th>
<th>PBMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.7</td>
<td>11.5</td>
<td>1.3</td>
</tr>
<tr>
<td>56.6</td>
<td>26.4</td>
<td>2.99</td>
</tr>
<tr>
<td>33.1</td>
<td>19.6</td>
<td>7.32</td>
</tr>
<tr>
<td>49.5</td>
<td>17.1</td>
<td>7.79</td>
</tr>
</tbody>
</table>
PHENOTYPE OF PBMCS (PT. IMF-91E) & TUMORS (00-144-413)

Elevation in IL-17 serum level correlates temporally with colitis symptoms

Patient Example 1

Elevation in IL-17 serum level correlates temporally with colitis symptoms
Elevation in IL-17 serum level correlates temporally with colitis symptoms

Patient Example 1

Th17 cells mirror IL-17 levels
Positive and Negative Signals Regulate T cell Activation

Ipilimumab, tremelimumab

BMS-663513

OX-86

Dendritic cell

Combination therapy reduces intratumoral Tregs and leads to a favorable Teff:Treg ratio
Combination therapy induces Treg-specific activation induced cell death in vivo

Day 0
Thy1.1 recipient
B16

6
Thy1.2 CFSE purified CD4+
+ OX86 or IgG

CTX

7

12

Flow analysis

B16

Day 0
Thy1.1 recipient

Thy1.2 CFSE purified CD4+
+ OX86 or IgG

Combination therapy induces Treg-specific activation induced cell death in vivo

TNF family members Represent potential targets for cancer immunotherapy

• Member of the TNF family of co-stimulatory T cell receptors
• Constitutively expressed at high levels on regulatory T cells
• Expressed at low levels on resting CD4 and CD8 T cells
• Upregulated following T cell activation (24-48hrs)
• GITR-L is expressed on macrophages, DCs, B cells
• *Agonist anti-GITR antibody DTA-1 can break tolerance to self antigens* Shimizu et al. Nature 2002
Agonist anti-GiTR antibody DTA-1 can enhance xenogeneic melanoma antigen DNA vaccines:

**Human gp100 vaccination + DTA1**

<table>
<thead>
<tr>
<th>gp100 + Rat IgG</th>
<th>gp100 + DTA 1mg</th>
<th>gp100 + DTA 0.25mg</th>
<th>No treat</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td>80</td>
<td>60</td>
<td>40</td>
</tr>
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**Human TRP2 vaccination + DTA1**

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Cohen et al, Cancer Res. 2006 May 1;66(9):

**DTA-1 treatment of established tumors:**

**B16 Melanoma**

- DTA1 Day 4
- Rat IgG
- p<0.001

**A20 lymphoma**

- DTA1 day 7
- No treat

**MethA sarcoma**

- 10/15 (66.6%)*
- 13/15 (66.0%)*

Ko et al, JEM 2005 202 (7): 885

Cohen et al, PloS ONE 2010 May 3;5(5)

**DTA-1 Treatment Reduces Intra-tumoral Treg Infiltration**

- B16 melanoma
- 500K in matrigel
- 4x10^6 pmel-1 CD8 T cell
- Adaptively transferred
- 1mg DTA1 or Rat IgG
- Isolate spleen, tumor draining lymph node (TDLN) and tumor

**IgG**

- Fo xp3
- CD25
- 48.8%
- 22.4%

**DTA1**

- Fo xp3
- CD25
- 48.8%
- 22.4%

- Reduced Treg number only seen in the tumor
- Intra-tumor Tregs do not appear apoptotic but are Ki67+

PloS ONE 2010 May 3;5(5)
Intra-tumor examination shows that after DTA-1 treatment, Tregs display aberrant Foxp3-GFP cytosolic localization

- Foxp3 is a transcription factor and is normally found in the nucleolus
- Aberrant GFP localization is not seen in TDLN of treated animals

Conclusions

- Trials of immunotherapies require novel endpoints
- Each new agent may necessitate different correlatives
- Combination strategies will present new opportunities for biomarker evaluation
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