Exploring Therapeutic Combinations with anti-CTLA-4 Antibody

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iSBTc
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Disclosures

• Served on advisory board, BMS, received honorarium
• Served on advisory board, Dendreon, received honorarium
Improving on CTLA-4 blockade

• CTLA-4 blockade has a consistent anti-tumor response rate of ~10% and survival benefit of ~20-30%; Phase III trial with documented survival benefit

• Durable partial and complete regression of disease observed in a subset of patients

• How can we do better?
  – Identify immunologic markers that predict which patients will benefit and provide therapy to those patients
  – Explore combination therapies to increase the numbers of patients who will benefit
Part I
Identification of immunologic markers:
Pre-surgical clinical trial
with anti-CTLA-4 monotherapy

<table>
<thead>
<tr>
<th>Study Week</th>
<th>anti-CTLA-4 antibody</th>
<th>Surgery</th>
<th>Post-operative follow-up visits</th>
</tr>
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<tr>
<td>0</td>
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<tr>
<td>7</td>
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Pre-therapy blood*  After dose #1 blood*  After dose #2 blood*

Blood  Blood

*Blood drawn prior to antibody dose administered and prior to surgery
Core biopsy (~ 1 cm x 1mm x 1mm)

Histology sections

IF in frozen sections

IHC in paraffin sections

Core biopsy

TIL expansion

Fine needle aspiration and chunks

RNA later
Clinical Trial

• Patients who are surgical candidates (N=12)
  – 6 patients dosed at 3mg/kg/dose and 6 patients dosed at 10 mg/kg/dose
  – Organ-confined localized disease; did not require any therapy other than surgery as treatment

• Primary endpoint: safety

• Secondary endpoint: immunologic correlates
Choosing biomarkers for immune monitoring
Immune Monitoring

• Assessed T cell markers including: HLA-DR, CD69, CD45RA, CD45RO, PD-1, etc. and

• Inducible costimulator (ICOS)
  - belongs to CD28 family
  - expression increased on activated T cells
  - plays a role in function of Th1, Th2, Th17, Tfh, Treg cells
  - is not a marker of a particular T cell subset but plays a role in the function of a given T cell subset that has been activated
Increased frequency of ICOS\textsuperscript{hi} T cells in tumors from anti-CTLA-4 treated patients

Non-malignant tissues: untreated

\begin{tabular}{|c|c|}
\hline
\textbf{ICOS} & \textbf{CD4} \\
\hline
13\% & \textbf{} \\
\hline
\end{tabular}

Tumor tissues: untreated

\begin{tabular}{|c|c|}
\hline
\textbf{ICOS} & \textbf{CD4} \\
\hline
16\% & \textbf{} \\
\hline
\end{tabular}

Tumor tissues: anti-CTLA-4 treated

\begin{tabular}{|c|c|}
\hline
\textbf{ICOS} & \textbf{CD4} \\
\hline
40\% & \textbf{} \\
\hline
\end{tabular}

Liakou et al., *Proc Natl Acad Sci*, 2008
ICOS expression increases in tumor tissues of treated patients

Liakou et al., *Proc Natl Acad Sci*, 2008
FOXP3 expression is lower in tumor tissues from anti-CTLA-4 treated patients

Non-malignant tissues: untreated

Tumor tissues: untreated

Tumor tissues: anti-CTLA-4 treated

Liakou et al., *Proc Natl Acad Sci*, 2008
FOXP3 expression decreases in tumor tissues of treated patients

Liakou et al., *Proc Natl Acad Sci*, 2008
Increased IFN-γ and T-bet mRNA in treated tissues with concomitant decrease in FOXP3 mRNA levels

Liakou et al., Proc Natl Acad Sci, 2008
What is the function of ICOS$^{\text{hi}}$ cells in tumors?: Expression of NY-ESO-1 antigen allowed for functional analyses of TILs

H & E  
CD4 T cells  
NY-ESO-1

Chen et al., Proc Natl Acad Sci, 2009
Recognition of NY-ESO-1 by TILs

Chen et al., Proc Natl Acad Sci, 2009
What about immunologic events in the systemic circulation?

Do they correlate with observed changes in tumor tissues?
ICOS expression significantly increases on T cells in peripheral blood after treatment with anti-CTLA-4 antibody.
ICOS<sup>hi</sup> T cells in peripheral blood from anti-CTLA-4 treated patients produce IFN-γ

Liakou et al., *Proc Natl Acad Sci*, 2008
ICOS\textsuperscript{hi} T cells from peripheral blood recognize NY-ESO-1 tumor antigen
Are changes in ICOS expression associated with clinical benefit?
<table>
<thead>
<tr>
<th>Patient Number</th>
<th>Pre-Therapy Pathology (UC, HighGrade)</th>
<th>Post-Therapy Pathology</th>
<th>Pre-Therapy Cytology Fluorescence in situ hybridization (FISH)</th>
<th>Post-Therapy Cytology Fluorescence in situ hybridization (FISH)</th>
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<tr>
<td>1</td>
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<td>T0N0M0</td>
<td>Positive Cytology, Positive FISH</td>
<td>Negative Cytology, Negative FISH</td>
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<td>4</td>
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<td>T3N1M0</td>
<td>Negative Cytology, Non-contributory FISH</td>
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<tr>
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<td>TaN0M0</td>
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<td>6</td>
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<td>Negative Cytology, Negative FISH</td>
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<tr>
<td>7</td>
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<td>pTXN0M1</td>
<td>Positive Cytology</td>
<td>Positive Cytology</td>
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<td>12</td>
<td>T2N0M0, UC &amp; Micropapillary Disease</td>
<td>T2N1M0, UC, Sarcomatoid &amp; Micropapillary Disease</td>
<td>Positive Cytology</td>
<td>Positive Cytology, Positive FISH</td>
</tr>
</tbody>
</table>
Metastatic Melanoma: Sustained elevation of CD4^{+}ICOS^{hi} T cells correlates with survival

Carthon et al., *Clinical Cancer Research*, 2010
Part II
Combination Therapies
Why Combination Therapy?

• Each tumor has multiple (90?) mutations resulting in coding changes (Vogelstein et al. Science 2006)

• Many of these, depending on MHC type of host, will represent neoantigens
Neoepitopes generated by genomic instability inherent in cancer

• Algorithms predict 9/tumor for HLA-0201
• 6 MHC alleles/tumor, so assuming even distribution predicts 54 total neoepitopes/tumor
• Assuming algorithm is wrong 90% of time, would predict 5-6 neoepitopes/tumor

*Effective checkpoint blockade with anti-CTLA-4 therapy may turn 1 drug/therapy into 6-7, raising the possibility of combinatorial therapies to improve anti-tumor responses*

Segal N and Allison JP
Rationale for Combination Therapy

Agents that kill tumor cells (e.g. chemotherapy, radiation, hormone therapy, antibodies, “targeted” therapies) can be used to prime an immune response against multiple antigens.

In combination with checkpoint blockade, can unleash the immune system to maximize T cell responses to multiple targets.
Combination Studies with Ipilimumab

- Phase III study with Ipilimumab plus XRT in patients with metastatic prostate cancer
- Phase III study with Ipilimumab plus DTIC in patients with melanoma
- Phase II study with Ipilimumab plus Temozolamide in patients with metastatic melanoma
- Phase II study with Ipilimumab plus Taxol plus Paraplatin in patients with lung cancer
- Phase II study with Ipilimumab plus androgen blockade in patients with metastatic prostate cancer
- Pre-surgical Phase IIa study with Ipilimumab plus Lupron in patients with localized prostate cancer
- Phase I study with Ipilimumab plus MDX-1106 (anti-PD-1) in patients with melanoma
- Phase I/II study with Ipilimumab plus cryoablation in patients with breast cancer
- Planned study with Ipilimumab plus Sipuleucel-T in patients with prostate cancer
- Planned study with Ipilimumab plus BRAF inhibitor in patients with melanoma
Phase III clinical trial with Ipilimumab + XRT vs. Placebo + XRT in CRPC

800 patients
Bone Mets

Randomize

XRT + Placebo

Overall Survival

XRT + anti-CTLA-4 antibody (administered within 2 days of XRT)

Immune Monitoring

Estimate participation of 145 sites

No crossovers allowed
Pre-surgical trial: Lupron + Ipilimumab

Clinical Trial for Patients with Localized Prostate Cancer
Conclusions

• CTLA-4 blockade increases ICOS expression on T cells in tumor tissues and peripheral blood

• ICOS\textsuperscript{hi} T cells from treated patients contain a population that are IFN\textsubscript{γ}-producing effector T cells and can recognize tumor antigen

• ICOS may serve as a biologic marker of disease response but, this has to be tested in a larger cohort of patients

• ICOS/ICOSL may serve as another immunotherapy target

• Pre-surgical clinical trials provide a feasible platform to study biologic effects on tumor tissues thus providing data that can be applied to the metastatic disease setting and improve our understanding of mechanisms

• Pre-clinical data supports the development of combination therapies with anti-CTLA-4 and any agent that is capable of killing tumor cells to prime a T cell response
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  – Chrysoula Liakou
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  – Qiuming He
  – Abdol Hossein
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• MSKCC and LICR Collaborators
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  – Jim Allison, Jedd Wolchok, Jianda Yuan (LCCI, MSKCC)
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