Coordinating Immune Checkpoint Blockade For Cancer Immunotherapy In Combination

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March 25, 2015
Choices.....!
Overview

- Introduction - what is the goal of combination therapy?
- Combining immune checkpoint therapies
- Combinations of immunotherapy with targeted therapies and vaccines
- Future directions for combinations
- Strategies for selecting combinations
What do we want to achieve with combinations?

Increase the percentage of patients achieving durable complete responses

Ai et al Cancer Immunol Immunother 2014
Multiple Pathways Modulate T cell and APC Activity

- **Bispecifics**
- **T-Cell Co-Inhibitory Receptors**
  - TIM-3
  - LAG-3
  - TIGIT
  - PD-1
  - CTLA-4
  - PD-L1
  - BTLA
  - VISTA

- **T cell**
  - 4-1BB
  - OX40
  - CD27
  - TIM-1
  - CD28
  - HVEM
  - GITR
  - ICOS

- **Vaccines**
- **T-Cell Co-Stimulatory Receptors**
  - Dendritic Cell Co-Stimulatory Receptors
  - CAR T cells
  - APC
  - CD40
  - 4-1BB
Combinations can be beneficial: early evidence

**CTLA-4 and 41-BB blockade enhance tumor rejection, reduce AI**


MC38 colon model
Combo therapy = rapid and durable responses in clinic

*Increased percentage of ORR with manageable safety profile*

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**Metastatic Melanoma**

<table>
<thead>
<tr>
<th>Therapy</th>
<th>ORR</th>
<th>&gt;80% Tumor Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipilimumab (CTLA-4)</td>
<td>7%</td>
<td>&lt;3%</td>
</tr>
<tr>
<td>Nivolumab (PD-1)</td>
<td>28%</td>
<td>&lt;2%</td>
</tr>
<tr>
<td>Combination (cohort 2)</td>
<td>53%</td>
<td>41%</td>
</tr>
</tbody>
</table>

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1 mg/kg nivolumab (anti-PD-1) + 3 mg/kg ipilimumab (anti-CTLA-4)

Wolchok et al NEJM 2013
Antibody Combinations
Dual Blockade of T-Cell Co-Inhibitory Pathways

Synergy of anti-LAG-3 and PD-1 in Sa1N and MC38 models

Control

Anti-LAG-3

Anti-PD-1

Anti-LAG-3/anti-PD-1

High co-expression of LAG-3/PD-1 restricted to infiltrating TILs.
Will LAG-3/PD-1 combo immunotherapy promote tumor-specific responses?

BMS LAG-3 +/- PD-1 in clinic for 18 months - data awaited
Antagonizing Co-Inhibitory Receptors on Multiple Cell Types

TIM-3/PD-L1 co-blockade demonstrates synergy in CT-26 colon model

Target modulation on multiple cell types may promote anti-tumor activity through T cell extrinsic paths


Adapted from Makouk and Weiner 2015 Cancer Res 75:5
ImmunoTherapy for Hematological Cancers

*Immune Checkpoint Blockade Combos for Multiple Myeloma*

- Early days for immunotherapy in heme cancers
- Breakthrough Therapy Designation for Nivolumab in Hodgkin’s- Phase I ORR = 87% in 23 patients

![Graph showing survival rates and statistical significance](image)

- PD-L1 blockade combined with anti-LAG-3 or TIM-3 see synergistic or additive increases in survival in 5T33 model of multiple myeloma
- Increased survival rates correlated with increased frequencies of tumor-reactive CD8 and CD4 T cells

*Jing et al J Immunother Cancer 2015*
Co-Inhibitory and Co-Stimulatory Targeting Synergy

**PD-1 Antagonist Combined with GITR Agonist**

- GITR antibodies increase proliferation and function of effector T cells
- Ligation of GITR on Tregs abrogates suppression of tumor specific effector T-cells
- Combination of anti-PD1 and anti-GITR antibodies is synergistic in 1D8 tumor model

**1D8 Ovarian model**

Mice were treated with 250ug of control, anti-PD-1, anti-GITR or combination on day 8, 11 and 15. Lu et al. J of Translational Med 2014

GITR=glucocorticoid-induced tumor necrosis factor receptor related protein
Combining T-cell and Macrophage Targeting

Anti-CSF1 and Anti-PD-1 synergize in pancreatic cancer model

- Colony-stimulating factor 1 receptor (CSF1R) expressed by monocytes, Mo-MDSCs, and macrophages
- Can CSF1 targeting alleviate local tumor-induced immune suppression and bolster response to immunotherapy?

- Depletion of TAMs- (tumor associated macrophage) improves response to chemotherapy by activating CD8+ T cells, but can also upregulate PD-L1 expression
- Anti-CSF1 neutralizing Ab in combination with PD-1 checkpoint inhibitor effective in pancreatic ductal adenocarcinoma model

Combination of Checkpoints plus Vaccine

Shifting the Tumor Microenvironment from Suppressive to Inflammatory

- Anti-PD-1/CTLA-4/PD-L1/Fvax resulted in 65% tumor-free mice in B16 melanoma model
- Increased frequency of IFNγ+TNFα+ TILs and increased CD4/CD8 proliferation
- Increased ratio of Teffs : Tregs and MDSCs

- Vaccines activate a *de novo* antitumor immune response
- Tumors respond by upregulating immune-checkpoint ligands
- Combining the two approaches may induce tumor regressions in patients that would not have responded to either treatment alone
Improving outcomes in patients with advanced prostate cancer

Will combo of immune checkpoint inhibitors and vaccines increase anti tumor activity?

See significant improvement in OS with no evidence of short-term clinical benefit

Three prostate cancer trials of Prostvac + ipilimumab in patients

Bristol-Myers Squibb Signs Exclusive Agreement with Bavarian Nordic for PROSTVAC®, a Prostate-Specific Antigen-Targeting Cancer Immunotherapy

Category: Partnering News, R&D News

Wednesday, March 4, 2015 1:30 am EST

Ongoing Trials (Clinicaltrials.gov)

- Sipuleucel-T and Ipilimumab for Advanced Prostate Cancer- Phase I
- A Randomized Phase 2 Trial of Combining Sipuleucel-T With Immediate vs. Delayed CTLA-4 Blockade for Prostate Cancer
Antibody and Targeted Therapy Combinations
Immune responses against tumors occur in a stepwise manner

Why combine targeted and checkpoint therapies?

mTOR, GSK3β inhibitors, loaded DC (Provenge®, XRT)

Cancer antigen presentation (dendritic cells/ APCs)

Priming and activation (APCs & T cells)

 Trafficking of T cells to tumors (CTLs)

Infiltration of T cells into tumors (CTLs, endothelial cells)

Recognition of cancer cells by T cells (CTLs, cancer cells)

Release of cancer cell antigens (cancer cell death)

Killing of cancer cells (Immune and cancer cells)

Tumor microenvironment reset (e.g. IFNγ, IL-15)

Sunitinib, JAK2 inhibitors, anthracyclines or XRT combinations

IAP, HSP90, PI3K inhibitors, Checkpoint blockade (e.g. PD1, LAG3)

Decrease Tumor derived immunosuppression/Antagonize Treg/MDSCs

Gemcitibine, sunitinib

Chen and Mellman: Immunity 2013
Immuno- and Targeted Therapies for Melanoma

Can we achieve response rates which are high AND durable?

Robert et al NEJM 2015
Improved Overall Survival in Melanoma with Combined Dabrafenib and Trametinib

- Phase III metastatic melanoma
- 52% ORR, Median PFS 7.3 months, OS 65%

Robert et al NEJM 2015 Nivolumab in Previously Untreated Melanoma without BRAF Mutation

- Phase III study ipilimumab-refractory metastatic melanoma
- 40% ORR, Median PFS 5.1 months, OS 73%
Challenges to Consider for Combo Therapy

*Ipilimumab and Vemurafenib Combo*

- Concurrent administration of ipilimumab and vemurafenib = liver toxicity
- *March 2015 Yervoy/IDO inhibitor PhI/II trial stopped due to liver toxicity

### Appropriate timing, dosage and sequencing of these agents is crucial to the success of combinatorial approaches

**Table 1. Data for Patients with Grade 3 Elevations in Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) Levels While Receiving Combination Therapy with Vemurafenib and Ipilimumab.

<table>
<thead>
<tr>
<th>Study Cohort and Patient No.</th>
<th>No. of Doses of Ipilimumab before ALT-AST Elevation</th>
<th>Time to Onset of ALT-AST Elevation after First Dose of Ipilimumab</th>
<th>Treatment</th>
<th>Time to Resolution of ALT-AST Elevation</th>
<th>Toxicity Relapse with Repeated Ipilimumab</th>
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</thead>
<tbody>
<tr>
<td>First cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>21 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 3 days and then restarted with dose reduction; ipilimumab permanently discontinued</td>
<td>4 days</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>36 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (2 doses)</td>
<td>6 days</td>
<td>No</td>
</tr>
<tr>
<td>6†</td>
<td>1</td>
<td>21 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 5 days and then restarted with dose reduction; ipilimumab continued (1 dose)</td>
<td>6 days</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>1</td>
<td>19 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 4 days and then restarted with dose reduction; ipilimumab continued (2 doses)</td>
<td>12 days</td>
<td>Yes</td>
</tr>
<tr>
<td>Second cohort</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>15 days</td>
<td>Glucocorticoids; vemurafenib discontinued for 7 days and then restarted with dose reduction; ipilimumab permanently discontinued</td>
<td>10 days</td>
<td>NA</td>
</tr>
<tr>
<td>16‡</td>
<td>1</td>
<td>13 days</td>
<td>Vemurafenib and ipilimumab permanently discontinued</td>
<td>20 days</td>
<td>NA</td>
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</tbody>
</table>

Ribas et al NEJM 2013
**Competitor Landscape: PD-1 Pathway/Targeted Agent Combos**

*Registered Anti PD-1/Anti-PD-L1 combo trials according to ClinicalTrials.gov*

<table>
<thead>
<tr>
<th>Combination</th>
<th>Targets</th>
<th>Sponsor</th>
<th>Phase</th>
<th>Indication</th>
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</thead>
<tbody>
<tr>
<td>Nivolumab + Pazopanib/Sunitinib/Ipilimumab</td>
<td>PD1 + CTLA4/RTK</td>
<td>BMS</td>
<td>I</td>
<td>RCC</td>
</tr>
<tr>
<td>Nivolumab + Dasatinib</td>
<td>PD1 + BCR/Abl</td>
<td>BMS</td>
<td>IB</td>
<td>CML</td>
</tr>
<tr>
<td>Pembrolizumab + INCR024360</td>
<td>PD1 + IDO1</td>
<td>Merck</td>
<td>I/II</td>
<td>NSCLC</td>
</tr>
<tr>
<td>Pembrolizumab + pazopanib</td>
<td>PD1 + RTK</td>
<td>Merck</td>
<td>I</td>
<td>RCC</td>
</tr>
<tr>
<td>Pembrolizumab + PegIFN-2b</td>
<td>PD1+JAK/STAT</td>
<td>Merck</td>
<td>I/II</td>
<td>RCC</td>
</tr>
<tr>
<td>MEDI4736 + Dabrafenib/Trametinib</td>
<td>PDL1+BRAF/MEK</td>
<td>Medimmune/NVS</td>
<td>I/II</td>
<td>Mel</td>
</tr>
<tr>
<td>MPDL3280A + Tarceva</td>
<td>PDL1+EGFR</td>
<td>Roche/Genentech</td>
<td>I</td>
<td>RCC</td>
</tr>
<tr>
<td>MPDL3280A + Cobimetinib</td>
<td>PDL1+ MEK</td>
<td>Roche/Genentech</td>
<td>I</td>
<td>NR</td>
</tr>
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</table>
The Future of Combinations
Bispecific approaches

Potential for increased potency, but complex to produce

Early evidence: Removab® (Catumaxomab)

Dec 2014 FDA approves Blinatumomab

- Bispecific T-cell engager (BiTE) immunotherapy binds CD19 on the surface of B-cell lymphoblasts and CD3 on T cells.

- In clinical trials in acute B-cell lymphoblastic leukemia (B-ALL), 32% had complete remissions for an average of 6.7 months

What are the advantages of the bispecific format over combinations of co-stimulatory or co-inhibitory targeting Abs?

Potential for greater efficacy by modulating multiple pathways, preventing the development of resistance, unique mechanisms of action.

Challenges with stability, dosing, production and half-life
Combining Co-Inhibitory Receptors with Cytokines

Combinations versus bi-functional approach

- IL-21 plus PD-1 blockade enhances efficacy in hepatocarcinoma model
- Combination boosts cytotoxicity of tumor-specific CD8 T cells

Pan X et al. Onc Letters. 2013

BMS – anti-PD-1 + IL-21 Phase I advanced or metastatic tumor (RCC, NSCLC, melanoma)

William E. Carson III Clin Cancer Res 2010;16:5917-5919
Chimeric Antigen Receptor (CAR) T cell therapy

CD19 directed CAR-T cells
CAR T cell system developed at UPenn

- Engineered T cells are a powerful new form of cancer therapy that combine specific targeting with long-lived memory – “living drug”
- CAR T cells directed to CD19 have achieved unprecedented responses in B cell malignancies
- Penn has received Breakthrough Designation to develop CART19/CTL019 for adult and pediatric ALL
Challenges in treating solid tumors with CARTs

Can combinations with immune checkpoint blockade increase efficacy?

- CAR T cells are potentially immunogenic
- Need to improve persistence and antitumor activity
- Monitoring CAR T cell activity in vivo is more complex

Combining Checkpoint Blockade with CAR-T cells

Anti-PD-1 enhances antitumor effects mediated by CAR Her-2 T cells

- No effect of PD-1 blockade on the percentage of CAR T cells at the tumor site
- Reduction of MDSCs in tumors of mice treated with CAR T cells and anti-PD-1 antibody
- No structural damage or increased immune cell infiltration for mice treated with CAR Her-2 T cells and anti-PD-1 or isotype antibody in mammary or brain tissues

John et al Clin Can Res 2013

CAR Her2 T cells and anti-PD-1 antibody led to inhibition of 24JK-Her-2 sarcoma tumors and long-term survival (~63%)

CAR-Her-2 T cell and anti-PD-1 reduced growth of established Her-2 breast carcinoma tumors
Bioinformatics approach to combination selection

*RNA-based immunophenotyping*

gene expression-based immune cell markers

<table>
<thead>
<tr>
<th>T-cell</th>
<th>B-cell</th>
<th>PMN</th>
<th>Treg</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3</td>
<td>CD79</td>
<td>ELANE</td>
<td>FOXP3</td>
</tr>
<tr>
<td>M2 Mac</td>
<td>M1 Mac</td>
<td>DC</td>
<td>NK cell</td>
</tr>
<tr>
<td>CD163</td>
<td>IL-12</td>
<td>FLT3</td>
<td>NCR1</td>
</tr>
</tbody>
</table>

use immune cell marker compendium to:
- **immunophenotype** patient samples
- infer target expression by cell type

correlate immune phenotype to prognosis
correlate immune phenotype to patient genetics

Anti-PD-1 Anti-CSF1

BRAF mutation status

Anti-PD-1 BRAF inhibit
Summary

Intense Industry Focus on Immunotherapy

• Many “breakthrough” immunotherapies
• Field is incredibly competitive
• New targets, new modalities
• Still unmet medical need - will combinations improve efficacy and/or safety?
Our challenge – to make the right choices