OX40 Immunotherapy in Cancer Patients: Immunological Observations and Implications for T Cell Immunotherapy
Earle A. Chiles Research Institute accepted grants from BMS, MedImmune, Prometheus and Merck to cover costs of clinical trials.

I am neither employed nor do I have equity interests in any company or entity whose products/drugs will be discussed today.

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Speakers Bureau: Prometheus

Unpaid Consultant: Agonox
Overview

- Selective summary of preclinical OX40 data
- Summary of phase I immunological and clinical monitoring from anti-OX40 phase I trial
- OX40-based combinations entering the clinic
OX40 Background: Expression

A) OX40 is a T cell activation protein that is expressed upon TCR engagement (a TNF-receptor family member).
   1) Primarily on activated CD4^+ and CD8^+ T cells
   2) Engaging CD28 increases OX40 expression
   3) Also expressed on Tregs, PMNs, and monocytes/DCs

B) OX40 expression is transient, peaking 24-48 hr after TCR engagement and down-regulated 72-96 hr later.

C) The OX40 ligand is transiently expressed on activated APC.
   1) B cells, macrophage, endothelial cells, and dendritic cells
   2) Engaging CD40 or TNF up-regulates OX40 ligand expression
   3) Low OX40L in vivo limits OX40 enhancement of T cell function
A) Engagement of OX40 costimulates activated T cells.
   1) OX40 ligand expressed on APC or soluble OX40L:Ig and antibodies to OX40 are all costimulatory.

B) Engagement of OX40 will costimulate both TH1 and TH2 cells and increase cytokine production and proliferation.
   1) Enhances Ag-specific Ab production

C) OX40 costimulation during primary immunization leads to increased survival of memory T cells through inhibition of activation-induced cell death.
Human Tumors with OX40+ TIL

- Breast Cancer
- Colon Cancer
- Melanoma
- Head and Neck Cancer
- Prostate Cancer
- Bladder Cancer
- Lung Cancer
- Ovarian Cancer

Ramstad et al., Am J Surg 179:400, 2000
Pre-clinical Models Showing Anti-Tumor Activity of OX40 Agonists

- Breast (4T1, SM1, EMT-6)
- Sarcoma (MCA 303, 205, 203)
- Colon (CT-26)
- Glioma (GL261)
- Melanoma (B16/F10)
- Prostate (TRAMP-C1)
- Lung (Lewis lung)
Summary of OX40 Immunological Effects:

Tumor Immunity

- Increased T-cell proliferation and migration
- Increased memory T-cell survival
- Increased cytokine production
- CD4⁺ effector T cell
- TCR
- MHC class II
- Tumour peptide
- APC
- CD8⁺ T cell
- MHC class I
- Perforin
- Granzyme
- Tumour fragments
- Tumour

Nature Reviews | Immunology
OX40 Is a Potent Immune-Stimulating Target in Late-Stage Cancer Patients

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OX40 Dose Levels

- 0.1 mg/kg, 0.4 mg/kg, 2 mg/kg
- Consecutive enrollment to cohorts
- 10 patients per cohort (random assignment to arms A and B)
- KLH and tetanus used as reporter antigens
  - Arm A
    - Anti-OX40 on days 1, 3 and 5
    - KLH on day 1
    - Tetanus on day 29
  - Arm B
    - Anti-OX40 on days 1, 3 and 5
    - Tetanus on day 1
    - KLH on day 29
<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
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<tr>
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<tr>
<td>Fatigue</td>
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<td>12</td>
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<tr>
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<tr>
<td>Nausea/Vomiting</td>
<td>4</td>
<td>3</td>
<td></td>
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<tr>
<td>Increased AST, ALT or alkaline phosphatase</td>
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<tr>
<td>Anemia</td>
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<td>8</td>
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Tumor Response Illustrations
Anti-OX40 on PBMC

**Day 0**
- FITC Anti-mouse IgG: 0%
- FITC Anti-rat IgG: 0.2%

**Day 5**
- FITC Anti-mouse IgG: 20.4%
- FITC Anti-rat IgG: 0.1%

**% of cells with surface Anti-OX40**
- **OX24**: Patients 0, 1, 2, 3
- **OX25**: Patients 0, 1, 2, 3
- **OX28**: Patients 0, 1, 2, 3
- **OX29**: Patients 0, 1, 2, 3
- **OX30**: Patients 0, 1, 2, 3

**Legend**
- White: CD4+ T cells
- Black: CD8+ T cells
T-Cell Proliferation

**CD4$^{+}$ Foxp3$^{neg}$ T cells**

- Cohort 1 (0.1mg/kg)
- Cohort 2 (0.4mg/kg)
- Cohort 3 (2mg/kg)
- Controls

**CD4$^{+}$ Foxp3$^{pos}$ T cells**

- Cohort 1 (0.1mg/kg)
- Cohort 2 (0.4mg/kg)
- Cohort 3 (2mg/kg)
- Controls

**CD8$^{+}$ T cells**

- Cohort 1 (0.1mg/kg)
- Cohort 2 (0.4mg/kg)
- Cohort 3 (2mg/kg)
- Controls

**CD3$^{−}$ cells**

- Cohort 1 (0.1mg/kg)
- Cohort 2 (0.4mg/kg)
- Cohort 3 (2mg/kg)
- Controls
**Reporter Antigen Responses**

- **Arm A**
  - Anti-OX40 on days 1, 3 and 5
  - KLH on day 1
  - Tetanus on day 29

- **Arm B**
  - Anti-OX40 on days 1, 3 and 5
  - KLH on day 29

**Anti-Tetanus Ab**

- Fold Increase (Post/Pre)
- Arm A, Arm B

**Anti-KLH Ab**

- Fold Increase (Post/Pre)
- Arm A, Arm B

**Tetanus-specific T cell Proliferation**

- Fold change in TT specific proliferation (CPM)
- Arm A, Arm B

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**Earle A. Chiles Research Institute**

**Providence Cancer Center**
T-Cell Proliferation by “Response”

A. CD4⁺ Foxp³⁻⁻⁻⁻ T cells
   - Non-Progressor
   - Progressor

B. CD8⁺ T cells
   - Percent Change in Tumor Size Compared to Baseline

C. CD4⁺ Foxp³⁺⁺⁺ T cells

D. CD3⁻ cells
Antigen-Exposed T-Cell Proliferation
Tumor-Specific Antibody Response
Summary: Anti-OX40 Clinical and Immunological Effects

• Anti-OX40 was well tolerated.
• Humoral and cellular immune responses to reporter antigens were enhanced by anti-OX40.
• Peripheral blood CD4+ and CD8+ T cells with effector and memory phenotypes proliferated after anti-OX40 without T_{reg} proliferation.
• We saw these immunological changes with a *mouse* monoclonal antibody that we gave for only one cycle.
Human OX40 Agonist

Published in final edited form as:

**Development and Characterization of Recombinant Human Fc:OX40L fusion protein linked via a coiled-coil trimerization domain**

Nicholas P. Morris, Carmen Peters, Ryan Montler, Hong-Ming Hu, Brendan D. Curti, Walter J. Urba, and Andrew D. Weinberg*
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[Image of OX40L trimers and c.p.m. vs OX40 agonist (nM) graph]
A Phase I Study of MEDI6383 in Adult Subjects with Select Advanced Solid Tumors

- Opened September 2014
- Metastatic bladder, colorectal, non-small cell lung or squamous cell head and neck cancer with disease progression after standard therapy.
  - Restrictions on prior anti-CTLA-4, anti-PD-1, anti-PDL1, anti-4-1BB, GITR, OX40 and CD27
- Phase I dose escalation and dose expansion
- MEDI6383 dosing every 2 weeks for 6 months
OX40 Combinations
= -1?

= +1?
- Modest Hypothesis:
  \(-(-1) + 1 = 2\)

- Hopeful Hypothesis:
  \((-(-1) + 1)^2 = 4\)

- Hypothesis of Maximum Hope:
  \((-(-1) + 1)^n = \text{Cure}\)
Selected Published Pre-Clinical Anti-OX40 Combinations

- Anti-OX40 + anti-CTLA4
- Anti-OX40 + anti-PD1
  - Guo et al., PLOSone 9:e89350, 2014
- Anti-OX40 + antiPDL-1 + anti-41BB
  - Morales-Kastresana et al., Clin Cancer Res 19:6151, 2013
- Anti-OX40 + TGF beta inhibition
  - Garrison et al., Cancer Immunol Immunother 61: 511, 2012
Clinical Trials Investigating OX40 Combinations

- Phase 1b/2 Safety and Tolerability of MEDI6469 in Combination with Therapeutic Immune Agents or Monoclonal Antibodies
  - Tremelimumab
  - MEDI4736 (anti-PDL1)
  - Rituximab

- Stereotactic Body Radiation and Monoclonal Antibody to OX40 in Breast Cancer Patients with Metastatic Lesions
EACRI/Providence Cancer Center