Phase I Trial of a Monoclonal Antibody to OX-40 in Patients with Advanced Cancer

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Collaborators

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Supporters of the RWFCRC
NIH Grant # R01 CA109563-01
Selected OX40 Biology

- OX40 is a T cell activation protein expressed after TCR engagement primarily on CD4+ and CD8+ T cells.
- OX40 expression is transient, peaking 24-48 hr after TCR engagement and downregulated 72-96 hr later.
- OX40 engagement results in proliferation and enhanced survival of CD4 T cells and mediates anti-tumor effects against breast, sarcoma, melanoma and colon cancers in murine models.
- T cells expressing OX40 found in many human cancers (breast, colon, melanoma, prostate, bladder, lung, head and neck).
OX40 Pathway in Tumor Immunity
Anti-OX40 Antibody

- IgG1 kappa murine monoclonal antibody (150 kd) that recognizes the human OX40 receptor (CD134)
- Well-tolerated in non-human primates at doses up to 10/mg/kg (IV on days 1, 3 and 5)
  - Increased LN and spleen size in some animals
  - Serum levels of anti-OX40 increased in a dose-related fashion.
  - Monkey anti-mouse antibodies observed in all animals
Clinical Trial Objectives

- Determine the maximal tolerated dose of anti-OX40 in patients with advanced malignancy.
- Determine if antigen-specific T cell and antibody responses to KLH, tetanus and CMV are enhanced via anti-OX40.
- Measure pharmacokinetics of anti-OX40
- Determine the most biologically active dose of anti-OX40 to induce antigen-specific responses
- Monitor for tumor regression.
Patient Eligibility

• Metastatic carcinoma not curable with standard treatment
• ECOG 0-2
• WBC > 2000, HGB >8, platelets >100,000
• AST, ALT, alk phos < 2.5x ULN
• Negative for HIV, hepatitis
• No autoimmune disease (except hypothyroidism or vitiligo)
Exclusion Criteria

- Not yet recovered from prior treatment toxicities
- Active brain mets (treated mets OK) or primary brain cancer
- Requirement for steroids
- Previous mouse monoclonal abs
- Allergies to shellfish or tetanus
- Splenomegaly
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)
Treatment Plan

• 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
Planned Immunologic Monitoring

- Antibody responses to KLH and tetanus
- T cell responses to KLH, tetanus, CMV
- Cytometry on peripheral blood
- HAMA
Exploratory Monitoring

- Serum cytokine analysis (complicated by HAMA)
- Tumor-specific immune responses
- Proliferation of naïve and memory CD4+ and CD8+ T cells
<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age</th>
<th>Surgery</th>
<th>Radiation</th>
<th>Chemo</th>
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<tbody>
<tr>
<td>Melanoma</td>
<td>54</td>
<td>WLE and SLN</td>
<td>no</td>
<td>IFN, IL-2, CTLA-4</td>
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<tr>
<td>NSCLCA</td>
<td>55</td>
<td>RUL-ectomy</td>
<td>Gamma knife (brain XRT)</td>
<td>Carboplatin, paclitaxel, pemetrexed, gemcitabine, gefitinib, erlotinib, Xyotac</td>
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<tr>
<td>Ovarian CA</td>
<td>63</td>
<td>Debulking, TAH, BSO</td>
<td>no</td>
<td>Paclitaxel, carboplatin, liposomal adriamycin, gemcitabine</td>
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</tbody>
</table>
Toxicities

• Constitutional symptoms: 2 pts (grade I)
• Hypercoagulable state and infection: 1 patient*

*Multiple thromboembolic strokes, deep venous thrombosis, elevated PT/PTT/INR, elevated rheumatoid factor, pneumonia, Rapidly progressive cancer
WBC Subsets Following anti-OX40 (OX1, OX2, OX3)

**Lymphocyte counts**
- OX01
- OX02
- OX03

**Neutrophil counts**
- OX01
- OX02
- OX03

**Monocyte counts**
- OX01
- OX02
- OX03
Tetanus-Specific ELISA

OX01 vs OX02

Titer

1/300 (ARM A)
1/15000 (ARM B)
Patient Serum Western Blot (OX1) Melanoma (femex) and Kidney (293) lysates

Day 0             Day 8           Day 15          Day 29        Day 36

Patient Serum Western Blot (OX1)
Melanoma (femex) and Kidney (293) lysates
“IR” in Melanoma Patient

March 2006

July 2006
Examination of T Cell Subsets By Expression of:

- CD95 (fas)
  - Naïve vs memory
- CD28
  - Central vs effector memory
- Ki-67
  - Proliferation

Strategy adapted from Louis Picker (SIV monkey studies)

Gating Strategy for OX-40 Clinical Trial: Part I
Gating Strategy: Part II

CD4 Gated

CD8 Gated

Memory Gated

Naive Gated
OX01
(Gated on CD95⁺)

CD4

Pre
Day 5
Day 8
Day 15
Day 29
Day 43
Post

CD8

CD28

Ki-67

CD28

Ki-67

0.00%
OX02
(Gated on CD95⁺)

CD4

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<tr>
<th></th>
<th>Pre</th>
<th>Day 5</th>
<th>Day 8</th>
<th>Day 15</th>
<th>Day 29</th>
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<tbody>
<tr>
<td>CD28</td>
<td>2.1%</td>
<td>0.15%</td>
<td>0.2%</td>
<td>0.26%</td>
<td>0.18%</td>
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<tr>
<td>Ki-67</td>
<td>91.41%</td>
<td>88.48%</td>
<td>78.69%</td>
<td>86.18%</td>
<td>87.68%</td>
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CD8

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Day 5</th>
<th>Day 8</th>
<th>Day 15</th>
<th>Day 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD28</td>
<td>20.44%</td>
<td>23.15%</td>
<td>24.06%</td>
<td>20.93%</td>
<td>19.04%</td>
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<tr>
<td>Ki-67</td>
<td>74.82%</td>
<td>71.64%</td>
<td>69.33%</td>
<td>65.93%</td>
<td>73.98%</td>
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</table>
OX03
(Gated on CD95+)

CD4

Pre       Day 5       Day 8       Day 15       Day 29       Day 43       Post

86.17%  10.65%  84.27%  11.57%  77.16%  19.89%  75.45%  18.82%  80.47%  12.51%  81.33%  13.23%  84.69%  11.88%

CD28      Ki-67

3.02%  0.16%  3.97%  0.19%  2.76%  0.18%  4.8%  0.93%  6.76%  0.27%  5.26%  0.19%  3.29%  0.13%

CD8

41.78%  15.54%  36.72%  12%  40.88%  14.01%  31.42%  13.87%  32.54%  10.64%  39.35%  9.35%  45.43%  12.86%

CD28      Ki-67

36.55%  6.12%  45.81%  5.47%  40.98%  4.13%  43.01%  11.7%  50.56%  6.26%  47.77%  3.54%  47.24%  4.48%
Fold Increase of Ki-67+ CD4+CD28+, CD8+CD28+ and CD8+CD28-
Preliminary Conclusions

- More patients needed
- Immune events occurring
  - Antibody responses to tumor and reporter antigens
  - Increased proliferation of T cell subsets
- Dose-limiting toxicity not yet found