A PHASE 1 STUDY OF TRC105 (ANTI-CD105 ANTIBODY) IN PATIENTS WITH ADVANCED SOLID TUMORS

Premiere Oncology, Santa Monica, CA; Pinnacle Oncology Hematology, Scottsdale, AZ; Duke University Medical Center, Durham, NC; Roswell Park Cancer Institute, Buffalo, NY; TRACON Pharmaceuticals, Inc., San Diego, CA

Presented at the 2011 ASCO Annual Meeting. Presented data is the property of the author.
Introduction

• TRC105 is a chimeric IgG1 anti-CD105 monoclonal antibody with very high avidity (5 pM, 1 ng/mL)

• CD105, also known as endoglin, is a membrane receptor that is essential for angiogenesis and highly expressed by proliferating vascular endothelial cells in solid tumors (Seon 2011)

• TRC105 inhibits angiogenesis and tumor growth by inhibiting endothelial cell proliferation and inducing antibody-dependent cellular cytotoxicity and apoptosis

• Like VEGF, CD105 is upregulated by hypoxia and is knockout lethal; mice that lack CD105 die in utero from absent vascular development (Li 1999)
Introduction

• High tumor microvessel density as measured by CD105 immunohistochemistry correlates with poor prognosis across more than 10 solid tumor types, including breast, colorectal, prostate and lung cancer

• In mouse models of human cancer, CD105 expression is upregulated by VEGF inhibitors (Bockhorn 2003, Davis 2004)

• TRC105 potentiates the activity of VEGF inhibitors in preclinical models

• CD105 is expressed on renal cell cancer stem cells (Bussolati 2008)
Objectives

• Evaluate the safety and tolerability of escalating doses of intravenous TRC105 in patients with advanced solid tumors
• Evaluate pharmacokinetics, tumor response and immunogenicity
Methods

Study Design

• Phase 1, open-label, dose-escalation, first-in-human study conducted at 4 US institutions
# Methods

## Key Inclusion Criteria
- Advanced incurable solid cancer
- ECOG PS of 0 or 1
- Adequate organ function
- Hemoglobin $\geq 10$ g/dL

## Key Exclusion Criteria
- Lung cancer with central tumor
- CNS disease
- Clinically significant effusions
- Prior cancer therapy within 4 wks
- Major surgery within 4 wks
- Major bleeding within 4 wks
**Methods: Dose Escalation Schema**

### NS0-Produced TRC105
- 0.01 mg/kg q2 wks (N=3)
- 0.03 mg/kg q2 wks (N=3)
- 0.1 mg/kg q2 wks (N=6)
- 0.3 mg/kg q2 wks (N=3)
- 1 mg/kg q2 wks (N=6)

### CHO-Produced TRC105
- 0.3 mg/kg q2 wks (N=6)
- 1 mg/kg q2 wks (N=6)
- 3 mg/kg q2 wks (N=3)
- 10 mg/kg q2 wks (N=3)
- 15 mg/kg q2 wks (N=4)
- 10 mg/kg q wk (N=3)
- 15 mg/kg q wk (N=4)
## Patient Demographics

### Baseline Patient Characteristics (N=50)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>Median: 64</td>
</tr>
<tr>
<td></td>
<td>Range: 25 - 84</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Female: 15</td>
</tr>
<tr>
<td></td>
<td>Male: 35</td>
</tr>
<tr>
<td><strong>Baseline ECOG Performance Status</strong></td>
<td>ECOG PS 0: 15</td>
</tr>
<tr>
<td></td>
<td>ECOG PS 1: 35</td>
</tr>
<tr>
<td><strong>Number of Prior Regimens</strong></td>
<td>Median: 4</td>
</tr>
<tr>
<td></td>
<td>Range: 1-13</td>
</tr>
<tr>
<td><strong>Cancer Type</strong></td>
<td>Colorectal: 10</td>
</tr>
<tr>
<td></td>
<td>Prostate: 9</td>
</tr>
<tr>
<td></td>
<td>Renal: 5</td>
</tr>
<tr>
<td></td>
<td>Lung: 4</td>
</tr>
<tr>
<td></td>
<td>Ovarian: 3</td>
</tr>
<tr>
<td></td>
<td>Sarcoma: 3</td>
</tr>
<tr>
<td></td>
<td>Breast: 2</td>
</tr>
<tr>
<td></td>
<td>Pancreatic: 2</td>
</tr>
<tr>
<td></td>
<td>Other: 12</td>
</tr>
</tbody>
</table>
Immunogenicity

<table>
<thead>
<tr>
<th>TRC105 Source</th>
<th>HAMA Positive</th>
<th>HACA Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS0 cells</td>
<td>2 of 21 (9.5%)</td>
<td>7 of 20 (35%)</td>
</tr>
<tr>
<td>CHO cells</td>
<td>0 of 28 (0 %)</td>
<td>0 of 26 (0 %)</td>
</tr>
</tbody>
</table>

- HAMA and HACA rarely detected in 21 patients treated with NS0-produced TRC105 and did not correlate with infusion reactions or other adverse events.
- Neither HAMA nor HACA detected in 29 patients treated with CHO-produced TRC105 to be used for all future clinical trials.
Pharmacokinetics

- TRC105 concentrations that engage ADCC (1 ng/mL) were achieved at all dose levels.
- The target concentration for maximum effect (200 ng/mL) was achieved at doses of 0.3 mg/kg and higher.
- Serum concentrations expected to saturate CD105 binding sites (>200 ng/mL) were achieved continuously at 15 mg/kg q2 weeks and 10 mg/kg weekly.
- TRC105 accumulated with weekly dosing.
Pharmacokinetics

![Graph showing TRC105 Concentration (ng/mL) over days for different dosing frequencies: 15 wkly, 10 wkly, 15 q2wk, 10 q2wk, 3 q2wk, and target concentration. The graph includes data points at days 0, 7, 14, 21, 28, and 35.]
<table>
<thead>
<tr>
<th>Drug Supply</th>
<th>TRC105 Dose</th>
<th>Schedule</th>
<th>Preferred Term</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>NS0</td>
<td>0.03 mg/kg</td>
<td>Every 2 Weeks</td>
<td>Fatigue</td>
<td></td>
<td></td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>NS0</td>
<td>0.1 mg/kg</td>
<td>Every 2 Weeks</td>
<td>Gastrointestinal hemorrhage</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS0</td>
<td>0.3 mg/kg</td>
<td>Every 2 Weeks</td>
<td>Anemia</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS0</td>
<td>1 mg/kg</td>
<td>Every 2 Weeks</td>
<td>Diarrhea</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NS0</td>
<td>1 mg/kg</td>
<td>Every 2 Weeks</td>
<td>Fatigue</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHO</td>
<td>0.3 mg/kg</td>
<td>Every 2 Weeks</td>
<td>Infusion related reaction</td>
<td></td>
<td>1</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>CHO</td>
<td>1 mg/kg</td>
<td>Every 2 Weeks</td>
<td>Headache</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHO</td>
<td>10 mg/kg</td>
<td>Every 2 Weeks</td>
<td>Infusion related reaction</td>
<td>2</td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>CHO</td>
<td>10 mg/kg</td>
<td>Every 2 Weeks</td>
<td>Anemia</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHO</td>
<td>15 mg/kg</td>
<td>Every 2 Weeks</td>
<td>Epistaxis</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHO</td>
<td>15 mg/kg</td>
<td>Weekly</td>
<td>Fatigue</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHO</td>
<td>15 mg/kg</td>
<td>Weekly</td>
<td>Anemia</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHO</td>
<td>15 mg/kg</td>
<td>Weekly</td>
<td>Headache</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHO</td>
<td>15 mg/kg</td>
<td>Weekly</td>
<td>Pyrexia</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>CHO</td>
<td>15 mg/kg</td>
<td>Weekly</td>
<td>Telangiectasia</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>CHO</td>
<td>15 mg/kg</td>
<td>Weekly</td>
<td>Infusion related reaction</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>CHO</td>
<td>15 mg/kg</td>
<td>Weekly</td>
<td>Epistaxis</td>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHO</td>
<td>15 mg/kg</td>
<td>Weekly</td>
<td>Telangiectasia</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>
Safety: Summary of Grade 3 & 4 Adverse Events

- Grade 4 hemorrhage from a gastric ulcer occurred in one patient on Study Day 5 after the initial TRC105 infusion at 0.1 mg/kg
  - The bleeding had resolved by the time of upper endoscopy after 2 units PRBCs
  - No other Grade 3 or 4 hemorrhage
- Grade 3 infusion reactions in Cycle 1 at 0.3 to 1.0 mg/kg
  - Dexamethasone-based premedication regimen allowed dose escalation to 15 mg/kg weekly
  - Dexamethasone can be safely tapered and discontinued with weekly TRC105 administration
Safety: Summary of Grade 3 & 4 Adverse Events

• Grade 3 anemia during Cycle 2 in 3 of 3 patients at 15 mg/kg weekly, with one patient progressing to Grade 4 by Cycle 3
  • Gradually progressive hypoprophic anemia was associated with TRC105 accumulation to very high levels
  • Dose-limiting anemia is likely the result of TRC105 suppression of CD105-positive proerythroblasts (RBC precursors) in marrow
  • Anemia is reversible, treatable, and easily monitorable allowing modification of TRC105 dose relative to the degree of anemia
Efficacy: Prostate Cancer

- A patient with metastatic castrate-resistant prostate cancer and multiple painful skeletal metastases has been on TRC105 therapy for over 3 years
- Complete PSA response
- Resolution of bone pain
- Bone scan normalization
Efficacy: Prostate Cancer

Bone Scan

Baseline

After 2.5 years
Efficacy: Endometrial Cancer

- A patient with lung metastases from endometrial cancer remains on study after 10+ months of treatment with a reduction in the maximum dimension of all 8 tumors including this 5.8 cm tumor.
- Overall tumor burden reduction was 7%, 9%, 13%, and 8% at Month 2, 4, 6, and 8, respectively.
- Progression-free survival on TRC105 exceeds that for all 3 prior systemic regimens including:
  - Carboplatin/paclitaxel (4 months)
  - Anastrozole (8 months)
  - Ifosfamide (2 months)
Efficacy: Endometrial Cancer

Chest CT Scan

Baseline

Month 2
Summary and Conclusions

• Safety and Tolerability
  • Dose-limiting hypoprotective anemia occurred at 15 mg/kg weekly
  • Grade 3 infusion reactions controlled with premedications
  • Isolated Grade 4 hemorrhage at 0.1 mg/kg every 2 weeks did not recur at higher doses
  • TRC105 was tolerated at doses up to 15 mg/kg every 2 weeks and 10 mg/kg weekly

• Pharmacokinetics and Immunogenicity
  • Serum concentrations expected to saturate CD105 binding sites (>200 ng/mL) were achieved continuously at 15 mg/kg every 2 weeks and 10 mg/kg weekly.
  • HAMA /HACA not detected in patients administered CHO-produced TRC105 to be used in all future studies
Summary and Conclusions

• Pharmacodynamics and Efficacy
  • Global decrease in key angiogenic biomarkers with treatment (ASCO 2011 Poster #10565)
  • SD ≥ 2 months in 22 of 45 pts (49%), SD ≥ 4 months in 6 of 44 pts (14%)
  • One patient with castrate-resistant metastatic prostate cancer remains on TRC105 therapy for >3 years with a complete PSA response, bone scan normalization and resolution of bone pain
  • One patient with refractory endometrial cancer remains on TRC105 therapy in Month 10 with reduced tumor burden
  • Tumor marker decreases (CEA, PSA or CA125) in 8 of 21 pts (38%)
References

- Davis DW, Cancer Research 64:4601-4610, 2004
- Li DY, Science 284:1534-1537, 1999
- Seon BK, Current Drug Delivery 8:135-143, 2011