A PHASE 1B DOSE-ESCALATION STUDY OF TRC105 (ANTI-ENDOGLIN ANTIBODY) IN COMBINATION WITH PAZOPANIB IN PATIENTS WITH ADVANCED SOFT TISSUE SARCOMA (STS)

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Endoglin is Expressed on Tumor Vessels and Targeting Endoglin Complements VEGF Inhibition

- Essential angiogenic target
- Up-regulated following VEGF inhibition
- Persistent expression on tumor vessels allows progression in face of VEGF inhibition
- Genetic knockdown and knockout of endoglin sensitizes tumors to VEGF inhibition
- Targeting VEGF and endoglin concurrently improves angiogenesis inhibition
## Endoglin (CD105) Expression on STS

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Number Patient Samples</th>
<th>CD105 IHC 3+</th>
<th>CD105 IHC 2+</th>
<th>CD105 IHC 1+</th>
<th>Tumor vessels CD105+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chondrosarcoma</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td>13/14</td>
</tr>
<tr>
<td>Ewing sarcoma</td>
<td>7</td>
<td>1</td>
<td>5</td>
<td></td>
<td>7/7</td>
</tr>
<tr>
<td>Osteosarcoma</td>
<td>20</td>
<td>2</td>
<td>2</td>
<td></td>
<td>20/20</td>
</tr>
<tr>
<td>Leiomyosarcoma (non-gynecologic)</td>
<td>20</td>
<td>2</td>
<td>1</td>
<td></td>
<td>20/20</td>
</tr>
<tr>
<td>Gynecologic leiomyosarcoma</td>
<td>20</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td>18/20</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>20</td>
<td></td>
<td>3</td>
<td></td>
<td>20/20</td>
</tr>
<tr>
<td>Angiosarcoma</td>
<td>20</td>
<td>13</td>
<td>3</td>
<td>3</td>
<td>17/17</td>
</tr>
<tr>
<td>Undifferentiated pleomorphic sarcoma</td>
<td>20</td>
<td>1</td>
<td>4</td>
<td>3</td>
<td>20/20</td>
</tr>
</tbody>
</table>

- Endoglin is densely expressed on certain STS, particularly angiosarcoma.

Study Rationale

- Pazopanib is an oral multikinase VEGFR inhibitor that is approved for the treatment of STS and demonstrated a partial response rate of 4% and progression free survival (PFS) of 4.6 months by RECIST 1.1 following treatment with chemotherapy in the pivotal PALETTE study.

- Endoglin is densely expressed on tumor vessels and on certain STS tumor tissue, particularly angiosarcoma, by immunohistochemistry (IHC).

- By targeting the endoglin pathway that is upregulated following VEGF inhibition and is expressed directly on sarcoma tissue, TRC105 may complement pazopanib, particularly in angiosarcoma.

- Tumor endoglin expression by IHC may serve as a biomarker that predicts highly responsive STS subtypes.
Phase 1b Sarcoma: Study Design

- **ENROLLMENT COMPLETE**
- Open-label, dose finding (N=18)
- Unresectable STS that progressed following chemotherapy
- GIST & adipocytic sarcomas excluded
- Prior pazopanib allowed
- 1° Endpoint: Recommended Phase 2 Dose (RP2D) and safety

**COHORT 1 (N=3)**
- TRC105 8 mg/kg IV weekly
- Pazopanib 800 mg/day PO
  (2-4 week run-in period)

**COHORT 2 (N=3)**
- TRC105 10 mg/kg IV weekly
- Pazopanib 800 mg/day PO
  (2-4 week run-in period)

**RP2D EXPANSION COHORT (N=12)**
- TRC105 10 mg/kg IV weekly
- Pazopanib 800 mg/day PO
  (2-4 week run-in period)
## Phase 1b Sarcoma: Study Results

### Baseline Patient Characteristics (N=18)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>• Median: 55&lt;br&gt;• Range: 25-71</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>• Male: 8&lt;br&gt;• Female: 10</td>
</tr>
<tr>
<td><strong>ECOG</strong></td>
<td>• ECOG 0: 7&lt;br&gt;• ECOG 1: 11</td>
</tr>
<tr>
<td><strong>Number of Lines of Previous Systemic Therapies</strong></td>
<td>• Median: 2&lt;br&gt;• Range: 1-7</td>
</tr>
<tr>
<td><strong>Histology</strong></td>
<td>• Leiomyosarcoma: 9&lt;br&gt;• Angiosarcoma: 2&lt;br&gt;• Synovial Sarcoma: 2&lt;br&gt;• Myxofibrosarcoma: 2&lt;br&gt;• Epithelioid Sarcoma: 1&lt;br&gt;• Epithelioid Hemangioendothelioma: 1&lt;br&gt;• Myxoid Spindle Cell Sarcoma: 1</td>
</tr>
</tbody>
</table>
Most Common (n > 1) and all Grade 3 and Above TRC105 Drug-Related Adverse Events by Preferred Term and by Grade

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Maximum Grade</th>
<th>Total N = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Gr 1</td>
<td>Gr 2</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Anemia</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Gingival bleeding</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Headache</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Flushing</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Gingival pain</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Erythema</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lymphocyte count decreased</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

- Dose limiting toxicity was not observed
- Expected events of epistaxis, gingival bleeding and headache are known features of the Osler-Weber-Rendu syndrome of endoglin heterozygosity
- Anemia reflects endoglin expression on the proerythroblast, an erythrocyte precursor
Phase 1b Sarcoma: Study Results

Study Duration*

- Epithelioid Sarcoma
- Leiomyosarcoma
- Angiosarcoma
- Leiomyosarcoma
- Leiomyosarcoma
- Leiomyosarcoma
- Leiomyosarcoma
- Leiomyosarcoma
- Leiomyosarcoma
- Synovial Sarcoma
- Leiomyosarcoma
- Leiomyosarcoma
- Myxofibrosarcoma
- Leiomyosarcoma
- Myxoid Spindle Cell Sarcoma
- Leiomyosarcoma
- Angiosarcoma
- Myxofibrosarcoma
- Synovial Sarcoma

TRC105 Dose Level
- 8 mg/kg Weekly
- 10 mg/kg Weekly
- Prior pazopanib treatment

Median PFS is 5.5 months
Duration ranged from 2 to 18+ months

PFS of pazopanib in PALETTE was 4.6 months (19.7 Wks)

* Duration on study is calculated from date of consent to date of withdrawal or most recent visit if pt is ongoing
Phase 1b Sarcoma: Study Results

Maximum percentage change in target lesion size

- Progressive Disease by RECIST 1.1
- Partial Response by RECIST 1.1

<table>
<thead>
<tr>
<th>Best Response (N=18)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response (CR) by RECIST 1.1</td>
<td>1</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>15</td>
</tr>
<tr>
<td>Progressive Disease</td>
<td>2</td>
</tr>
</tbody>
</table>

- 8 mg/kg TRC105
- 10 mg/kg TRC105
- Prior pazopanib treatment
- Ongoing treatment

TRACON
Phase 2 Sarcoma: Study Design

- Open-label, non-randomized, metastatic STS
- Progression following anthracycline chemotherapy, up to four prior lines of systemic therapy
- TRC105 RP2D of 10 mg/kg weekly with pazopanib at 800 mg/day
- 1° Endpoint: PFS, stratified by tumor endoglin expression by IHC

- Enrollment ongoing, 62 of 63 patients enrolled
- Angiosarcoma cohort added (N=13)
Phase 1b/2: Angiosarcoma Experience

Maximum percentage change in target lesion size

Positive IHC staining in 3/3 patients with available samples

Pt #1: CD105, IHC 2+
Pt #3: CD105, IHC 3+
Pt #5: CD105, IHC 1+

Pt #1
Visceral PD at 10 wks

Pt #2
Visceral PD at 34 wks

Pt #3
Cutaneous Withdrawn due to unrelated AE at 10 wks

Pt #4
Cutaneous ongoing at week 62

Pt #5
Cutaneous ongoing at week 31

10 mg/kg TRC105
Prior Pazopanib
Ongoing treatment

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Partial Response by RECIST 1.1
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Progressive Disease by RECIST 1.1

Pt #3: CD105, IHC 1+
Pt #5: CD105, IHC 1+

Withdrew due to unrelated AE at 10 wks
ongoing at week 62
ongoing at week 31

PD at 10 wks
PD at 34 wks
PD at 10 wks
PD at 34 wks
PD at 10 wks
PD at 34 wks
Phase 1b/2 Angiosarcoma: Durable Complete Responses

Phase 1b Angiosarcoma patient with CR at TRC105 RP2D

Day 0
Day 48
Ongoing CR at week 62

Phase 2 Angiosarcoma patient with CR at TRC105 RP2D

Day 0
Day 37
Ongoing CR at week 31
Conclusions

• TRC105 at its RP2D of 10 mg/kg weekly was well tolerated with pazopanib without dose limiting toxicity

• Adverse events characteristic of each individual drug were not increased in frequency or severity when the two drugs were administrated concurrently

• TRC105 and pazopanib demonstrated encouraging preliminary signs of activity in a highly pretreated population, including durable complete responses in patients with cutaneous angiosarcoma

• A randomized phase 3 trial of TRC105 and pazopanib is planned in angiosarcoma
References

• Fritchie K, EORTC-AACR-NCI 2013
• Davis DW, Cancer Res 64:4601-10, 2004
• Li DY, Science 284:1534-37, 1999
• Nolan-Stevaux O, PLOS One 7:1-12, 2012
• Seon BK, Current Drug Del 8:135-43, 2011