A Phase 1/2 Study Of TRC105 In Combination With Sorafenib In Hepatocellular Carcinoma (HCC)

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Introduction
Sorafenib is an oral multi-kinase inhibitor of vascular endothelial growth factor (VEGF) receptor, the platelet-derived growth factor (PDGF) receptor, and Raf and was the first systemic medical therapy to prolong survival in HCC based on the SHARP study which demonstrated a median overall survival benefit compared to placebo (10.7 months vs 7.9 months; HR 0.69; P<0.001). Since the SHARP study, attempts to combine agents with sorafenib have been disappointing.

Endoglin (CD105) is a transmembrane receptor overexpressed by proliferating endothelial cells that is required for angiogenesis and upregulated by hypoxia in response to VEGF inhibition. TRC105 is a chimeric IgG1 monoclonal antibody that binds CD105 with high avidity and inhibits binding of its key ligand, bone morphogenic protein. TRC105 inhibits angiogenesis and mediates apoptosis and antibody-dependent cell-mediated cytotoxicity (ADCC) of proliferating endothelium.

Preclinical data: (1) CD105 expression after sorafenib treatment.
BNL tumors in Balb/c mice were treated with Sorafenib (10 mg/kg/d). Tissue was harvested after 3 days and analyzed. As shown in Figure 1, sorafenib treatment induced an increase in endoglin expression compared to control.

Preclinical data (2): Anti-mouse endoglin antibody in combination with sorafenib daily.
Based on the observation that sorafenib causes endoglin expression we tested the combination of anti-mouse endoglin antibody (clone M2J/18) + sorafenib. As shown in Figure 2 the combination of anti-CD105 + sorafenib was more effective than sorafenib treatment alone.

Clinical trial:
- To establish the MTD for TRC105 when given with sorafenib in HCC.
- Pharmacodynamic Biomarkers:
  - VEGF, PIGF, sFGF, sVEGFR1, soluble CD105
  - DCE-MRI
- Preliminary Evidence of Anti-Tumor Response:
  - Response rate and DFS

Preclinical trial: Patients with HCC were enrolled in a phase I study of TRC105 given at 3, 6, 10, 15mg/kg every 2 weeks plus sorafenib 400mg po bid.

Results:
N=20 pts were enrolled. N=2 were ineligible for DLT. Baseline characteristics for evaluable patients summarized in Table 1.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of pts</th>
<th>Toxicity (Grade ≥ 3)</th>
<th>Dose levels (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td>MTD</td>
</tr>
<tr>
<td>Male/Female</td>
<td>12/6</td>
<td></td>
<td>1000</td>
</tr>
<tr>
<td>Age (Range)</td>
<td>60 (18 – 76)</td>
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</tr>
<tr>
<td>Weight (kg)</td>
<td>70 (50 – 90)</td>
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<td>250</td>
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<td>Performance</td>
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<td></td>
<td>125</td>
</tr>
<tr>
<td>Karnofsky</td>
<td>70</td>
<td></td>
<td>62.5</td>
</tr>
<tr>
<td>ECOG</td>
<td>5</td>
<td></td>
<td>31.25</td>
</tr>
<tr>
<td>Disease stage</td>
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<td>15.625</td>
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<tr>
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<td>40</td>
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<tr>
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<tr>
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<td>Hematologic</td>
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</tr>
</tbody>
</table>

Toxicity:
- Grade 1-2:
  - Fatigue
  - Gastrointestinal:
    - Diarrhea
    - Hepatic failure
    - Cardiac ischemia infarct
    - Hypertension
  - Dermatologic:
    - Hand-foot syndrome
    - Anemia
    - Hand-foot syndrome
  - Hematologic:
    - Lymphopenia
    - Thrombocytopenia

- Grade 3-4:
  - Hepatic failure
  - Cardiac ischemia infarct
  - Hypertension

CONCLUSIONS:
TRC105 combined with sorafenib was well tolerated at the recommended single agent doses of both drugs. Encouraging evidence of activity was observed and the study is proceeding to the phase 2 stage.