A Phase 1/2 Dose Escalation and Expansion Study of Cabiralizumab (FPA008), an anti-CSF1R antibody, in Tenosynovial Giant Cell Tumor (TGCT, Diffuse Pigmented Villonodular Synovitis D-PVNS)

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Study Design

This was a Phase 1/2 dose escalation and dose expansion study designed to evaluate the pharmacokinetics (PK), pharmacodynamics (PD), safety, and efficacy of cabiralizumab in patients with TGCT.

- **Phase I**: consisted of a 3:3 dose escalation at dose levels of 3, 6, and 12 mg/kg.
- **Phase 2**: was对外开放 at 4 mg/kg and included both patients with and without prior exposure to imatinib.

The protocol was approved by each site’s institutional review board.

Study Schema

**PK of Cabiralizumab Key Non-Linear Clearance and Steady-State CSF1R or Lesch Dose Escaping**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>PK Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 mg/kg</td>
<td>Clearance 0.25 L/h</td>
</tr>
<tr>
<td>6 mg/kg</td>
<td>Clearance 0.15 L/h</td>
</tr>
<tr>
<td>12 mg/kg</td>
<td>Clearance 0.05 L/h</td>
</tr>
</tbody>
</table>

**Safety of All Treated Patients (N=38)**

<table>
<thead>
<tr>
<th>Event</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>DLT</td>
<td>No DLT</td>
<td>25%</td>
<td>12%</td>
<td>10%</td>
</tr>
</tbody>
</table>

**Key Eligibility Criteria**

- **Inclusion**:
  - ECOG performance status ≤1
  - Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 Grade ≤ 1
  - Male or female, ≥ 18 years old
  - Measurable or non-measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
  - Other investigations:
    - Alanine aminotransferase ≤ 1.5 upper limit of normal (ULN)
    - Aspartate aminotransferase ≤ 1.5 ULN
    - Alkaline phosphatase ≤ 1.5 ULN
    - Total bilirubin ≤ 1.5 ULN
    - Hemoglobin ≥ 10 g/dL
    - Platelet count ≥ 100,000/mm²
    - **Prior anti-VEGFR inhibitors:**
      - Nilotinib: ≤ 3 months
      - Imatinib: ≤ 2 cycles

- **Exclusion**:
  - **Prior anti-CSF1R inhibitors:**
    - Nilotinib: ≤ 3 months
    - Imatinib: ≤ 2 cycles

**Study Endpoints**

- **Primary**:
  - Response assessed by RECIST v1.1 on MRI and Clinical Evaluation
  - Disease control rate (DCR) as per RECIST v1.1 on MRI
  - Efficacy evaluations by MRI and Clinical Evaluation (CE) continue up to approximately 12 months in the absence of radiographic disease progression, even if drug is discontinued.

- **Secondary**:
  - PK and PD of cabiralizumab
  - Dose-related and dose-limiting toxicities
  - Duration of response
  - Baseline MRI assessment, per Investigator assessment
  - Quality of life

**Demographics and Prior Tyrosine Kinase Inhibitor Therapy of All Enrolled Patients (N=38)**

<table>
<thead>
<tr>
<th>Category</th>
<th>0 (0%)</th>
<th>1 (17%)</th>
<th>2 (22%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>17 (45%)</td>
<td>17 (45%)</td>
<td>5 (13%)</td>
</tr>
<tr>
<td>Asian</td>
<td>11 (29%)</td>
<td>11 (29%)</td>
<td>6 (16%)</td>
</tr>
<tr>
<td>Other</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>7 (18%)</td>
</tr>
</tbody>
</table>

**Conclusions**

- **PK and PD of cabiralizumab**
  - **Cabiralizumab is safe and well-tolerated at 4 mg/kg in TGCT with no dose-limiting toxicities**
  - Dose-related toxicities included fatigue, pain, rash, pruritus, and increased alanine aminotransferase

- **Efficacy**
  - **10 of 11 Efficacy evaluable patients including 4 of 5 patients with PR had baseline Ogilvie-Harris score improvement in median Ogilvie-Harris composite score was reported in both responders and non-responders (per RECIST v1.1 on MRI)**

- **References and Acknowledgements**

- **Acknowledgements**
  - The patients and their families, investigators, co-investigators, and the study teams at each participating center

- **Patient with 10% Tumor Reduction by MRI Showed Improvement in Median Ogilvie-Harris Composite Score v1.1 on MRI (Figure 6) 3**

- **20-year-old Female with PVNS of Right Hand Demonstrating Dose-Related Clinical Efficacy**

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