**A First-in-Human Phase 1 Study of Receptor Tyrosine Kinase (RTK) Inhibitor MGCD516 in Patients with Advanced Tumors**


**Study Objectives**

- **Primary Objectives:**
  - To characterize the safety profile and tolerability of sitravatinib
  - To characterize the PK of sitravatinib in patients with advanced solid tumors
  - To evaluate the clinical activity of sitravatinib in patients selected based upon diagnosis, tumor type, and genetic alterations

- **Secondary Objectives:**
  - To characterize sitravatinib metabolites
  - To explore potential biomarkers of response in plasma
  - To identify sitravatinib dose and regimens for investigation of clinical activity

**Study Design**

- **Phase 1:**
  - Open-label, open-label Phase 1/2 study evaluating Safety, PK, Metabolism, PD and Activity of sitravatinib in patients with advanced solid tumors.
  - Dose escalation: 20 mg/kg once daily for 21 days
  - Dose expansion: 150 mg once daily for 21 days

- **Phase 2:**
  - Evaluation of sitravatinib in selected patient populations
  - Phase 1b: Tumors with a Molecular Profile of interest: NSCLC, CRC, HNSCC, MET, CTG-0838, DU145, A549, PANC1, H1437, and Hs746T
  - Phase 2a: Tumors with a Molecular Profile of interest: NSCLC and other tumors harboring genetic alteration in RET, MET, VEGFR, etc., respectively

**Results**

- **Dose and Dose Limiting Toxicity:**
  - 32 pts were enrolled in the dose escalation phase. Doses ranged from 10 to 200 mg/kg on day 1, and 10 pts were enrolled at 200 mg/kg, exceeding the MTD (Table 3).
  - Phase 1 dose of 20 mg/kg in cycles of 21 days

- **Targeted Activity:**
  - Sitravatinib strongly demonstrates tumor growth inhibition in a variety of cancer models driven by tumor regression/plasma levels in patients selected based upon diagnosis.
  - Post-Treatment CT imaging observed in clear cell renal cell carcinoma (Figure 5); and significant bone modulation with exposure (Figure 3).

**Conclusions**

- Sitravatinib is a potent inhibitor of several RTKs that act as oncogenic drivers.
- Phase 1 dose escalation has been completed with recommended Phase 1 dose of 150 mg QD.
- Pharmacokinetic/cytokinetic dose limiting modulation.
- Tolerable safety profile with manageable AEs consistent with target inhibition.
- Further evaluation of sitravatinib is warranted in phase II trials in VEGFR-positive RCC and selected pts with NSCLC and other tumors harboring genetic alterations in RET, VEGF, DDR2, CRL, or Chromosome 4 amplification.

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**Key Entry Criteria:**

- Advanced metastatic or unresectable solid tumor malignancy
- ECOG performance status 0, 1 or 2
- Adequate bone marrow and organ function
-决不使用

**Study Details:**

- **MGCD516:** Sitravatinib is an oral drug that inhibits a spectrum of related RTKs including: VEGFR2, Axl, and PDGFRα.
- **Targeted activity:**
  - MGCD516 is a potent inhibitor of several RTKs that act as oncogenic drivers.
  - Post-Treatment CT imaging observed in clear cell renal cell carcinoma (Figure 5); and significant bone modulation with exposure (Figure 3).

**Table 1:** Patient Characteristics and Disposition

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>No.</th>
<th>Gender</th>
<th>Race</th>
<th>Prior Therapy</th>
<th>Progression-Free Survival</th>
<th>PFS Median</th>
<th>Overall Survival</th>
<th>OS Median</th>
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<tbody>
<tr>
<td>NSCLC</td>
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<td>Female</td>
<td>White</td>
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<td>14</td>
<td>12</td>
<td>24</td>
<td>32</td>
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<tr>
<td>CRC</td>
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<td>Male</td>
<td>Black</td>
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<td>5</td>
<td>10</td>
<td>12</td>
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</table>

**Table 2:** Phase 1b Patients with Advanced Stratifactor Targets in Tumor Tissue

<table>
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<th>Gene</th>
<th>Tumor Type</th>
<th>No.</th>
<th>Complete Response</th>
<th>Partial Response</th>
<th>No Response</th>
<th>Median Tumor Response</th>
<th>Tumor Type</th>
<th>No.</th>
<th>Complete Response</th>
<th>Partial Response</th>
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<td>2</td>
<td>1</td>
<td>30</td>
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<td>4</td>
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<td>2</td>
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<tr>
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**Table 3:** Dose Levels and Dose Limiting Toxicity

<table>
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<th>Group</th>
<th>Dose Level</th>
<th>Dose (mg/kg)</th>
<th>No.</th>
<th>Grade 3/4 Adverse Events</th>
<th>DLT</th>
<th>Metabolites</th>
<th>Plasma Levels</th>
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<td>5</td>
<td>1</td>
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</tbody>
</table>

**Conclusions:**

- Sitravatinib is an oral drug that inhibits a spectrum of related RTKs including: VEGFR2, Axl, and PDGFRα.
- Targeted activity: MGCD516 is a potent inhibitor of several RTKs that act as oncogenic drivers.
- Post-Treatment CT imaging observed in clear cell renal cell carcinoma (Figure 5); and significant bone modulation with exposure (Figure 3).