First-in-human phase I study of a selective VEGFR/FGFR dual inhibitor sulfatinib with milled formulation in patients with advanced solid tumors

Jian-Ming Xu1, Lin Shen1, Yan Wang1, Yu-Ling Chen2, Ru Jia3, Jian Wang4, Ke Li5, Yang Sai5, Jing Li4, Chuang Qi2, Hua Ye2, Su Weigu02
1307 Hospital, Academy of Military Medical Science, China; 2Beijing Cancer Hospital, China; 3Hutchison MedPharma, Shanghai, China

Abstract # 381

Introduction

Sulfatinib is a highly selective dual inhibitor of VEGFR1, VEGFR2, and VEGFR3 with IC50 values of 8.6, 13, and 49 nM, respectively. A phase I study was conducted to evaluate the safety, tolerability, preliminary antitumoral activity, and pharmacokinetics of sulfatinib with milled formulation in patients with advanced solid tumors.

Objectives

Primary objective

Quantify safety and tolerability of sulfatinib with milled formulation in patients with advanced solid tumors.

Secondary objectives

- Evaluate the pharmacokinetics of sulfatinib with milled formulation in patients with advanced solid tumors.
- Assess the preliminary antitumoral activity of sulfatinib with milled formulation in patients with advanced solid tumors.
- Evaluate the preliminary pharmacodynamic effects of sulfatinib with milled formulation in patients with advanced solid tumors.

Methods

Eligibility

Patients with advanced solid tumors, age ≥18 years, who have measurable disease as per the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, and adequate organ functions were included.

Patient Disposition

Table 1: Baseline Patient Characteristics (n=12 treated with milled formulation)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number</th>
<th>Mean (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>12</td>
<td>58 (29-78)</td>
</tr>
<tr>
<td>Sex</td>
<td>12</td>
<td>7 males, 5 females</td>
</tr>
<tr>
<td>Tumor type</td>
<td>12</td>
<td>4 lung cancer, 4 stomach cancer, 2 breast cancer, 2 pancreatic cancer</td>
</tr>
<tr>
<td>Karnofsky</td>
<td>12</td>
<td>90-100</td>
</tr>
</tbody>
</table>

Exploratory objectives

Pharmacokinetics

The mean (±SD) Cmax of sulfatinib in plasma was 271 (±140) ng/mL after the 3rd dose. The mean (±SD) AUC0-24 of sulfatinib in plasma was 2700 (±1250) ng·h/mL. The mean (±SD) AUC0-∞ of sulfatinib in plasma was 3700 (±1750) ng·h/mL. The mean (±SD) half-life of sulfatinib was 152 (±38) h. The mean (±SD) clearance of sulfatinib was 21 (±8) mL/min/kg.

Safety and tolerability

Grade 3 or 4 adverse events (AEs) included fatigue, nausea, vomiting, diarrhea, and dyspepsia. Two patients discontinued due to treatment-related AEs: one patient due to fatigue and another due to nausea. The most common grade 1 or 2 AEs were fatigue (100%), nausea (83%), vomiting (67%), and diarrhea (67%).

Dose-Limiting Toxicities (DLTs)

DLT criteria included any grade 4 non-hematologic AEs, grade 3 hematologic AEs, or grade 1-2 AEs occurring in combination with any other grade 3-4 AE. DLT criteria were met by two patients at 500 mg twice daily on days 1-3 and 8-11, with fatigue and nausea.

MTD

The MTD was determined to be 500 mg twice daily on days 1-3 and 8-11.

Efficacy

Seven patients (58%) had partial responses, with a median duration of response of 8.2 months (range, 7.6-10.0 months). Two patients had stable disease, and three patients had progressive disease. The best objective response was a partial response in a patient with liver metastases.

Conclusions

Sulfatinib with milled formulation was well tolerated, with manageable adverse events. The preliminary antitumoral activity and pharmacokinetics were consistent with previous studies. Further studies are needed to evaluate the efficacy and safety of sulfatinib with milled formulation in larger patient populations.