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Effect of dose level of the selective FGFR2 inhibitor alofanib on toxicity, pharmacokinetics and preliminary efficacy: A phase Ib study in patients with advanced gastric cancer (RPT835GC1B)

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Background: FGFR2 molecular changes was observed in gastric cancer at a frequency of 4-15% and associated with shorter progression-free survival (PFS) and overall survival (OS). Alofanib (RPT835) is a novel selective inhibitor that binds allosterically to the extracellular domain of FGFR2.

Methods: The aim of this phase Ib study was to determine dose-limiting toxicities (DLTs), maximum tolerated dose (MTD), safety, preliminary efficacy and pharmaco- kinetics (PK) of alofanib administered intravenously daily for 5 days weekly. Patients with advanced or metastatic gastric adenocarcinoma resistant to standard therapy were enrolled in 5 dose levels: 50, 100, 165, 250, and 350 mg/m2, using a 3 + 3 design.

Results: To date, 13 patients have been enrolled in the trial. The MTD was not reached. All patients have not experienced any DLT within the 28-day DLT-assessment window. Intravenous alofanib was safe. There were no correlations between dose level and toxicity. Three grade 3 adverse events (ALT/AST increased at 50 mg/m2, diarrhea at 165 mg/m2, and hyponatremia at 350 mg/m2) were reported. One pa- tient discontinued treatment due to drug related grade 3 uncontrolled diarrhea. Grade 1-2 adverse events included fatigue, diarrhea, nausea, anemia, thrombocyto- penia, increased alkaline phosphatase, and reactions immediately after intravenous injections (facial flushing, dizziness, weakness, sweating, and sinus tachycardia). Grade 1 hyperphosphatemia was founded in 25% of cases. Of the 12 assessed pa- tients, 1 (8%) partial response at 50 mg/m2 and 8 (67%) stable diseases at 50-250 mg/m2 were recorded. After a median follow-up of 4.5 months, the median PFS and OS was not reached. PK parameters have increased with dose. PK values (Cmax, AUC, and t1/2) did not correlate with response, PFS and OS (all $P>0.1$).

Conclusions: Administration of alofanib by intravenous route as single agent was safe and demonstrated promising antitumor activity in heavily pretreated patients with metastatic gastric cancer. The MTD has not been reached up to 350 mg/m2. PK profiles did not correlate with toxicity and efficacy of alofanib. The study is ongoing.

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