First-in-human study of BLU-554, a potent, highly selective FGFR4 inhibitor designed for hepatocellular carcinoma (HCC) with FGFR4 pathway activation

**Hypothesis and objectives**

- FGFR4 pathway activation in HCC is a potential HCC driver
- 5% of HCCs have genetic amplification of the FGFR4/2 complex (FGFR4/2C), and 23% of HCCs overexpress FGFR4 in the absence of genetic amplification (HCC-FGFR4).

**Methods**

- Phase I study was initiated in advanced HCC to explore the hypothesis that BLU-554, a potent, highly selective FGFR4 inhibitor designed for HCC, will have therapeutic benefit in HCC driven by the FGFR4 pathway.
- The key objectives were to determine the maximum tolerated dose (MTD) and to evaluate the safety, pharmacokinetics (PK), pharmacodynamics (PD), and preliminary antitumor activity of BLU-554, an investigational, potent, highly-selective, oral FGFR4 inhibitor.

**Key inclusion criteria**

- Advanced HCC
- Ki-67 ~5%
- Normal liver does not express FGF19, but expresses high levels of FGFR4 and klotho-beta (KLB).

**Key exclusion criteria**

- Patients who had undergone surgical resection of their HCC
- Patients with disease progression on systemic therapy within 4 cycles of prior sorafenib
- Patients with untreated jaundice
- Patients with active ascites
- Patients with uncontrolled active intra-abdominal infection
- Patients with coagulopathy requiring therapeutic anticoagulation

**Results**

- 18 patients had Grade 3-4 AEs which were treatment-related in 12 patients.
- 17 patients had Grade ≥3 AEs which were treatment-related in 12 patients.
- ALP increased (5 of 28), hyperbilirubinemia (4 of 14), and hyponatremia (4 of 14) were most common.
- 17 patients had Grade ≥3 AEs which were treatment-related in 12 patients.
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**Pharmacodynamics**

- FGF19 IHC+ 11q13.3 FISH-
- Ki-67 ~5%
- ALP = 1000
- ALT = 1000
- AST = 1000

**Conclusions**

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