Title:

Preliminary safety, pharmacokinetics, and efficacy results from an open-label, multicenter, Phase I/II study of avapritinib in Chinese patients with unresectable or metastatic gastrointestinal stromal tumors (GIST)

Authors:

Jian LI[1], Jifang GONG[1], Xicheng WANG[1], Jie LI[1], Yan LI[1], Changsong QI[1], Lin SHEN[1], Wenxiao REN[2], Wanqi ZHAO[2], Yedong WANG[2], Jin HU[2], Chunli REN[2], Wenjie SONG[2], Jianxin YANG[2]

1. Department of Gastrointestinal Oncology, Beijing Cancer Hospital, Beijing, China
2. CStone Pharmaceuticals (Suzhou), Suzhou, China

Background:

More than 85% of GIST patients (pts) have tumors associated with KIT or PDGFRA mutations. Avapritinib is a potent, selective, small-molecule inhibitor that targets KIT/PDGFRA activation loop mutants. Recently FDA approved avapritinib for pts with unresectable or metastatic GIST harboring a PDGFRA exon 18 mutation, including D842V mutations based on a robust ORR (84%) in the NAVIGATOR study. This abstract reports preliminary results from the dose escalation part of the bridging study in Chinese pts with advanced GIST.

Methods:

Adult pts with unresectable or metastatic GIST that progressed after imatinib and ≥ 1 other tyrosine kinase inhibitor, or could not tolerate the standard treatment or had PDFGRA D842V mutation were enrolled and treated with avapritinib once daily (QD) in continuous 28-day cycles following a modified 3+3 dose escalation design. Primary objectives included determination of Recommended Phase II dose (RP2D) and assessment of safety. PK parameters and response per mRECIST v1.1 for GIST were also assessed.

Results:

As of 25 Dec 2019, 12 pts were treated with avapritinib QD at a starting dose of 200 mg or 300 mg (6 per group). No dose-limiting toxicities were observed. Most treatment-emergent adverse events (TEAEs) were Grade (G) 1-2, most commonly blood creatine phosphokinase increased (n=9) and blood bilirubin increased (n=8). There were no G4-5 TEAEs. The most frequent G3 treatment-related TEAE was anaemia (n=2). Serious adverse events were observed in 1 pt (renal hydrocele) in 200 mg group and 2 pts (abdominal distension and anaemia) in 300 mg group, all were G3 and considered unrelated to avapritinib. No AEs leading to drug discontinuation occurred. Avapritinib was rapidly absorbed (median T_{max} 2.0-4.0 h) and the exposure increased proportionally with doses at the steady state. The mean half-life of avapritinib ranged 42.2-44.4 h, supporting QD dosing. Of the 3 pts with PDGFRA D842V mutation (all in the 300 mg group), 2 pts achieved PR, and 1 had SD, as assessed by investigators at the first tumor assessment.

Conclusions:

Avapritinib appears generally tolerable at 200 mg and 300 mg QD and shows clinical activity in Chinese pts with PDGFRA D842V mutation. Based on the safety profile in Chinese pts and dose selection results in NAVIGATOR study, 300 mg QD was determined to be the RP2D for Chinese pts. The preliminary safety, PK, and efficacy data support further investigation of avapritinib in Chinese pts with GIST.

NCT Number: NCT04254939