TREETOPP: A phase 2/3 study of varlitinib plus capecitabine versus placebo plus capecitabine as second-line treatment in patients with advanced or metastatic biliary tract cancers (BTCs).

Milind M. Javle, Do-Youn Oh, Masafumi Ikeda, Shukui Qin, Wei-Peng Yong, Yee Chao, Nicola McIntyre, Chih-Yi Hsieh, Lilian Chow, Alyssa Chang, Mark McHale, Bertil Lindmark

University of Texas MD Anderson Cancer Center, Houston, TX, USA; Seoul National University Hospital, Seoul, Korea, Republic of (South); National Cancer Center Hospital East, Kashiwa, Japan; People’s Liberation Army 81 Hospital, Nanjing, China; National University Cancer Institute, Singapore, Singapore; Taipei Veterans General Hospital, Taipei, Taiwan; ASLAN Pharmaceuticals, Singapore, Singapore; ASLAN Pharmaceuticals, Taipei, Taiwan

Background

- BTCs are heterogeneous and highly lethal malignancies including a spectrum of invasive carcinomas arising in the gallbladder and bile ducts (intrahepatic and extrahepatic), and variably, ampullary carcinoma. These tumors are very uncommon, representing less than 1% of all cancers in the developed countries.
- BTCs are often diagnosed at advanced stage with limited treatment options and the 5-year overall survival rates are 10% to 40% for cholangiocarcinomas (CCAs) and 5% to 10% for gallbladder cancers.
- Overexpression of epidermal growth factor receptor (EGFR), human epidermal growth factor receptor (HER2), HER3, and HER4 vary from 23-57%, 4-13%, 12-23% and 59-60% of BTCs, respectively. Blockade of EGFR and HER2 by laptatinib leads to growth inhibition of intrahepatic CCA in the pre-clinical rat model if administered early. Thus, co-inhibition of EGFR and HER2 represents a new therapeutic approach for BTCs.

About Varlitinib

- Varlitinib is a small molecular tyrosine kinase inhibitor of EGFR, HER2 and HER4 with potent antitumor effect in preclinical BTC models. Varlitinib also demonstrated tumor shrinkage responses and durable disease stabilization in BTC patients in Phase I/II study.

Study Objectives

Primary objectives:

- Part 1
  - To assess the efficacy of varlitinib in combination with capecitabine as measured by co-primary endpoints of objective response rate (ORR) and progression-free survival (PFS), both assessed by an Independent Central Review (ICR).

Secondary objectives:

- Part 1
  - To evaluate the efficacy of varlitinib in combination with capecitabine, as measured by duration of response (DoR), and disease control rate (DCR) as assessed by ICR, and OS and ORR as assessed by the site.
  - To assess the safety and tolerability of varlitinib when combined with capecitabine.
  - To explore exposure-response relationships for varlitinib (and any relevant circulating metabolites) for measures of efficacy, safety, and pharmacological responses.
  - To examine the effects of varlitinib, when added to capcitabine on electrocardiography (ECG) parameters including QTcF, QTcB, HR (heart rate) and RQS.

- Part 2
  - To evaluate the efficacy of varlitinib in combination with capecitabine, as measured by ORR, DoR, DCR and PFS, all based on site assessment.
  - To evaluate the safety and tolerability of varlitinib when combined with capecitabine.
  - To explore exposure-response relationships for varlitinib (and any relevant circulating metabolites) for measures of efficacy, safety, and pharmacological responses via sparse pharmacokinetics (PK) sampling and population PK analyses.

Exploratory objectives:

- Part 1
  - To explore the role of HER family status as a predictor of benefit to varlitinib.
  - To explore possible relationships between HER family and downstream signaling protein and phospho-protein expression levels and clinical outcomes.
  - To explore possible relationships between gene mutational status and clinical outcomes.

- Part 2
  - If a relationship is found between biomarker(s) expression and clinical outcomes in Part 1 of the study, the biomarker(s) could be prospectively evaluated in Part 2 of the study.

Major Criteria

- Have histologically or cytologically confirmed advanced (unresectable) or metastatic BTC, including intrahepatic or extrahepatic CCA, gallbladder cancer and carcinoma of Ampulla of Vater. This includes clinical diagnosis of BTC with histological confirmation of adenocarcinoma.

- Have received and failed one and only one prior line of systemic treatment for advanced or metastatic disease with radiologic evidence of disease progression. This prior line of systemic treatment must also contain gemcitabine.

- Have received at least 6 doses of gemcitabine containing treatment in first line (Adjuvant therapy is not regarded as first line therapy).

- Have radiographically measurable disease based on Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 as assessed by ICR (For Part 1).

- Have no evidence of biliary duct obstruction, unless obstruction is controlled by local treatment or, in whom the biliary tree can be decompressed by endoscopic or percutaneous stenting with subsequent reduction in bilirubin to below or equal to 1.5 x upper level of normal.

- Have no known metastatic brain lesion(s), including asymptomatic and well controlled lesion(s).

- Have no evidence of multiple (≥ 2) peritoneal metastases or ascites at baseline as assessed by ICR (For Part 1). (Ascites which can be attributed by non-malignant causes is not excluded.)

Statistical Analysis

- Co-primary endpoints of Part 1, ORR, and PFS, will be analyzed using data from an ICR of radiological data. A Hochberg procedure will be used to control the familywise type I error rate for Part 1 at the 10% level (one-sided).

- The primary endpoint of Part 2, OS, will be tested at the two-sided 5% significance level

Study Progress

- The study is intended to recruit approximately 490 patients in around 70 centers

- Patient enrolment is in progress, the first patient was enrolled in June 2017.

- Topline data will be available in 2019.

Other Information

- Clinical trial identification: ClinicalTrials.gov NCT03093870
- Contact information:
  - mjavle@mdanderson.org
  - Chih-Yi.Hsieh@aslanpharma.com

Acknowledgement

This study was sponsored by ASLAN Pharmaceuticals.

References