JADETREE*: A phase 2A, single arm, multicenter, study of the panHER inhibitor varlitinib plus capecitabine in Chinese patients with advanced or metastatic biliary tract cancer (BTC).

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Background:
BTC is a rare and aggressive malignancy arising from the biliary epithelium, characterized by poor prognosis and poor response to current treatments. The 5-year overall survival rate is 5% to 10% for advanced BTC (ref). Human epidermal growth factor receptor (HER) family receptors are expressed at high levels in BTC and may be driving tumor proliferation and survival. In fact, overexpression of epidermal growth factor receptor (EGFR/HER1), HER2, HER3, and HER4 range from 23-57%, 4-13%, 12-23%, and 59-60% of BTCs, respectively. Varlitinib (VAR) is a well-tolerated, nanomolar small molecular tyrosine kinase inhibitor of EGFR, HER2, and HER4 with potent anti-tumor effect in preclinical BTC models. The recently published ABC-06 study from the UK in 2nd line (2L) Caucasian BTC patients showed promising efficacy using mFOLFOX regimen, however, the toxic profile from doublet chemotherapy may be highly selective for a fitter 2L western population and might not represent the real-world situation for patients with aggressive BTC in China. Here we present a phase 2A, single arm, multicenter, study using VAR plus capecitabine (VC) in unselected Chinese patients with 2L BTC.

Method:
Patients with advanced or metastatic BTC having failed on prior 1st line gemcitabine containing regimens were given VAR (300 mg twice daily in a 21-day cycle) plus capecitabine (1,000mg/m² twice daily for 2 weeks followed by a 7-day rest period). Patients with no evidence of biliary duct obstruction (unless controlled by local treatment or endoscopic or percutaneous decompression), ECOG PS 0-1 and adequate organ function were eligible. The primary endpoint was to assess the objective response rate (ORR) as defined by RECIST v1.1 criteria. Secondary endpoints include duration of response, progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and the safety and tolerability of VC. Clinical trial information: NCT03231176.

Result:
As of 16-Jun-19, 61 pts were treated, 31 (50.8%) intrahepatic, 19 (31.3%) gallbladder, 9 (14.8%) extrahepatic, and 2 (3.3%) ampulla of Vater. Gender M/F is 33(54.1%)/28 (45.9%); median (range) age was 56 (22-77); ECOG PS was 0/1 in 23 (37.7%)/38 (62.3%) pts. The ORR for evaluable patients with advanced BTC receiving VC was 10.8% and the DCR was 70.2%. This is higher than observed with mFOLFOX in the ABC-06 study (ORR = 5% and DCR = 33%) VC in 2L led to a similar ORR versus JadeTree historical data for gem/cis in 1L (10.8% vs. 10.3%). Median PFS in JadeTree was 2.7 months and median OS was 5.8 months. 12-month OS for JadeTree was 36%, versus 26% for ABC-06. All causes Grade 3 or more events in 2 or more pts include blood bilirubin increase (19.7%), GGT increase (6.6%), Anemia (4.9%), and 2 pts (3.3%) each for abdominal pain, ascites, AST increase, conjugated bilirubin increase, disease progression, hyponatremia, Jaundice, malaise and UGI bleeding.
Conclusion
JadeTree provides the first “real world” data in Chinese patients with 2nd Line BTC and shows that Varlitinib plus Capecitabine is efficacious and well tolerated compared to previously reported studies.

*: JADETREE: Joint Assessment of Drug Efficacy of Pan-Her inhibition using Varlitinib in second line BTC in China

Keywords biliary tract cancer, HER2, EGFR, varlitinib, capectabine