Abstract 1311
A phase I study of varlitinib (VAR; ASLAN001) an oral pan-HER tyrosine kinase inhibitor (TKI) combined with mFOLFIRI chemotherapy in advanced solid tumors
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Background
VAR is a potent TKI against EGFR, HER2 and HER4. Efficacy of VAR combined with fluoropyrimidine and platinum chemo in colorectal cancer (CRC) and biliary tract cancer (BTC) has been reported (ESMO 2018 430P, GI ASCO 2019 #319).

Methods
Patients (pts) ECOG PS 0–1 with advanced solid tumors and adequate organ function were eligible. Homozygous UGT1A1*6/*6 and *28/*28 pts were excluded. VAR was combined with mFOLFIRI up to 9 cycles followed by VAR monotherapy. Each cycle was 14 days with dose limiting toxicity (DLT) period of 28 days. VAR was evaluated at 3 dose levels (DL): DL1 200mg/BD D1-14; DL2 200mg/BD D4-11; DL3 300mg/BD D4–11. Dose escalation by 3+3 design. Primary endpoint was safety and maximum tolerated dose (MTD). Secondary endpoints were pharmacokinetics (PK) and response. Tumor NGS (Oncomine OCP v3) and IHC (HER2, cMET, PTEN) were performed.

Results
As of 15-Feb-19, 16 pts were treated, 5 (31%) BTC, 5 (31%) CRC, 3 (19%) gastroesophageal, 2 (13%) pancreatic and 1 (6%) ovarian clear cell cancer (OCCC). Sex M/F 13/3, median (range) for age was 62yrs (45–79), ECOG 0 (0–1) and lines of prior therapy was 3 (0–6). 4/4 pts at DL1 had G3/4 neutropenia on cycle 2 D1 lasting <7 days, possibly by VAR inhibition of UGT1A1 mediated clearance of SN-38. Intermittent dosing of VAR in DL2 (n=5) and DL3 (n=6) was tolerable with a DLT of G3 stomatitis (HSV co-infection) at DL3. PK study showed widely variable VAR levels but no VAR accumulation. VAR was not escalated as prior studies showed limited tolerability at 400mg/BD combined with chemo. G3/4 treatment related adverse events (TRAE) seen in ≥10% of pts was neutropenia (44%; 4 DL1, 1 DL2, 2 DL3) with no events of neutropenic sepsis. Of the 16 pts, 2 (13%) had PR (BTC, 1 prior line; HER2 over-expressing OCCC, 6 prior lines) maintained at 7.5 and 6.1 mths respectively, 9 (56%) had disease control (PR+SD) of which in 4 (25%) DCR was >6 mths, and median PFS was 4.2 mths. HER2 alterations were seen in 4 pts (1 PR, 2 SD, 1 PD).

Conclusions
VAR 300mg/BD D4–11 combined with mFOLFIRI is the MTD and well tolerated. Durable response in HER2 positive OCCC was seen and warrants further investigation.

Clinical trial identification
NCT02435927

Editorial acknowledgement