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Clinical Activity Of BLU-554, A Potent, Highly-Selective FGFR4 Inhibitor In Advanced Hepatocellular Carcinoma (HCC) With FGFR4 Pathway Activation.

Introduction: FGFR4 and its ligand, FGF19, normally promote hepatocyte proliferation and regulate bile acid homeostasis; however, emerging data show FGF19 overexpression in ~30% of HCC and implicate FGF19-dependent FGFR4 activation as a driver of hepatocarcinogenesis. A phase 1 study (NCT02508467) was initiated to assess the safety, pharmacokinetics (PK), pharmacodynamics (PD) and preliminary clinical activity of investigational agent BLU-554, a potent, highly-selective, irreversible FGFR4 inhibitor.

Methods: Adult patients (pts) with advanced HCC, ECOG PS 0-1 and well-preserved liver function, who had received sorafenib, or could not access or declined sorafenib were given BLU-554 orally once daily on a 4-week cycle following a 3+3 design with dose expansion at the MTD. Adverse events (AEs) per CTCAE v4.03, PK and PD (changes in blood C4 (bile acid precursor), total cholesterol, FGF19) were assessed. Baseline tumor FGF19 expression was analyzed via immunohistochemistry (IHC) as a marker of pathway activation. FGF19 gene amplification was assessed via FISH. Response was determined by RECIST 1.1 every 8 weeks.

Results: At a 31-MAR-2017 cutoff, 55 pts have been treated with BLU-554 at doses of 140 to 900 mg/day (25 in dose escalation; 30 in dose expansion); enrollment to dose expansion continues. 43 (78%) pts had metastatic disease, 42 (76%) had ECOG PS = 1, 13 (24%) had vascular invasion and 49 (89%) had failed ≥1 prior systemic therapies (median 1; range 0-6), most commonly sorafenib 43 (78%). 23 (42%) pts had pathway activation based on positive FGF19 IHC (IHC+). BLU-554 is rapidly absorbed (median Tmax ~2 h), exposure increases linearly with dose, and mean half-life is ~17 h. Dose-dependent pathway modulation (←C4,↓cholesterol,←FGF19) was observed from dose level 1, 140 mg. Based on safety profile, PK, PD and preliminary anti-tumor activity, 600 mg was the MTD and recommended dose for expansion.
Radiographic tumor reduction and partial response (PR) per RECIST 1.1 were observed in IHC+ pts in both dose escalation and dose expansion. Of 18 IHC+ pts with ≥ 1 radiographic assessment, 10 (56%) pts had radiographic tumor shrinkage including 4 with PR (22%). 4 IHC+ pts were FISH positive (gene copy # 5, 8, 12, 15), 1 had PR, and 3 remain on treatment. Duration of treatment for the IHC+ pts ranged from 1-9 cycles with 8 treated for ≥ 5 cycles. In contrast, only 4 (16%) of 25 IHC negative (IHC-) pts had tumor shrinkage and none had PR. Duration of treatment for the IHC- pts was 1-9 cycles with 5 treated for ≥ 5 cycles. Most AEs were Grade (Gr) 1 or 2, including diarrhea (65%), nausea (42%), vomiting (38%), ALT increase, fatigue (29% each), abdominal pain, AST increase (27% each), and decreased appetite (24%). BLU-554-related Gr 3-4 AEs occurring in ≥5% of pts included AST increase (15%), ALT increase (11%), anemia, diarrhea (7% each), and vomiting (5%). 2 pts experienced DLT (1 Gr 3 abdominal pain; 1 Gr 3 fatigue lasting > 7 days) at 900 mg indicating the MTD had been exceeded at this dose level. 33 (60%) pts have discontinued treatment, 24 due to disease progression, 4 due to AE, 3 due to investigator's decision, and 2 withdrew consent.

Conclusion: BLU-554, a potent, highly-selective, FGFR4 inhibitor is well tolerated at the recommended dose of 600 mg and demonstrates important clinical activity in FGF19 IHC+ advanced HCC pts. These

compelling proof of concept data validate FGFR4 as a therapeutic target and FGF19 IHC as a selection marker for pathway activation.