TPS3171 **Poster Session**

A first-in-human multi-center phase 1/2 study of a selective FGFR2/3 inhibitor, CGT4859, in patients with intrahepatic cholangiocarcinomas or other advanced solid tumors.

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Background: Genetic alterations in fibroblast growth factor receptors 2 and 3 (*FGFR2/3*) occur in nearly all cancer types. *FGFR2* fusions and rearrangements occur in up to 10-15% of intrahepatic cholangiocarcinomas (iCCA) and alterations in *FGFR3* occur in 15-30% of urothelial cancers. The clinical benefit from currently approved FGFR inhibitors (FGFRi) is often curtailed by development of acquired resistance, which may arise through on-target mutations in the *FGFR2/3* kinase domain. Additionally, off-tumor effects on FGFR1 by pan-FGFRi can lead to hyperphosphatemia and consequently to dose reductions or dose holds. Thus, there is an unmet clinical need for a selective FGFR2/3 inhibitor that has clinical efficacy against activating alterations and resistance mutations without causing FGFR1-mediated hyperphosphatemia. CGT4859 is an orally bioavailable, ATP-competitive, reversible inhibitor of FGFR2/3, with potency against clinically relevant *FGFR2/3* kinase domain mutations. In addition, CGT4859 demonstrates >140 fold selectivity over FGFR1, and shows robust efficacy in target altered *in vivo* tumor models without increases in serum phosphorus. Nonclinical pharmacokinetics (PK) and safety data support evaluating CGT4859 in a first-in-human, open-label, dose-escalation and signal-seeking Phase I/II study (NCT06777316). Safety, tolerability, PK, pharmacodynamics, and antitumor activity of CGT4859 will be assessed in adults with histologically confirmed unresectable or metastatic iCCA or other solid tumors with *FGFR2/3* alterations. **Methods:** CGT4859 will be administered orally continuously in 28-day cycles to patients (N=~50) at a starting dose of 1 mg QD, and dose escalation will not exceed 40 mg QD as determined using a Bayesian optimal interval design with backfill (BF-BOIN). This approach will be used to guide dose escalation and establish the maximum tolerated dose (MTD) and recommended Phase 2 Dose (RP2D). BF-BOIN enables backfilling of participants to doses that are cleared for safety during the dose escalation, generating additional data on safety and tolerability below the MTD. Objective response rate (ORR) and disease control rate will be determined based on investigator assessment using RECIST v1.1. Phase II will enroll up to 4 cohorts, each enrolling ~15 patients. Proposed cohorts will include participants who have iCCA and are either FGFRi-naïve or FGFRi-exposed. Two additional cohorts with other advanced solid tumors harboring *FGFR2/3* alterations may be included based on signals detected in dose escalation. The primary efficacy endpoint for Phase II is ORR per RECIST v1.1. The preclinical data support the study of CGT4859 in this patient population with solid tumors harboring *FGFR2* and/or *FGFR3* genetic alterations. The phase I dose escalation study is currently enrolling at sites in the United States. Clinical trial information: NCT06777316. Research Sponsor: Cogent Biosciences.