TPS3169 **Poster Session**

A phase 1/2 study of FOG-001, a first-in-class direct β-catenin: TCF inhibitor, in patients with colorectal cancer (CRC) and other locally advanced or metastatic solid tumors.

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Background: Activation of the Wnt/β-catenin pathway, often as truncal APC mutations, in 80–90% of CRCs and other solid tumors, is known to be a key driver of cancer progression and has been associated with immune exclusion and resistance to immunotherapy. Development of agents targeting this pathway at the key β-catenin: T-cell factor (TCF) node has eluded the pharmaceutical industry to date. FOG-001 is a Helicon peptide that competitively inhibits interaction between β-catenin and TCF transcription factors. Helicon peptides are hyper-stabilized α-helices that can be tuned for picomolar binding affinities, robust cell penetration, broad tissue distribution, no immune recognition, and long *in vivo* half-lives. In studies in a wide range of patient-derived xenograft (PDX) CRC and HCC models, FOG-001 inhibited tumor growth and promoted tumor regression as monotherapy. Combinations with immune checkpoint inhibitors or standard-of-care therapies, including bevacizumab and 5-FU, showed strong additivity/synergy in PDX CRC models. **Methods:** This first-in-human, phase 1/2, multicenter, open-label, dose-escalation (part 1) and dose-expansion (part 2) study evaluates the safety/tolerability, pharmacokinetics (PK), pharmacodynamics (PD), and anti-tumor effects of FOG-001 monotherapy and combined with other anti-cancer therapies in patients with microsatellite stable (MSS) CRC or advanced/metastatic solid tumors known to harbor a Wnt pathway-activating mutation (WPAM). Eligible patients must have received at least one prior systemic anti-cancer therapy and either progressed on, not responded to, or be unfit for available therapies. In Part 1, FOG-001 is administered intravenously every week, at escalating dose levels evaluated sequentially in a standard 3+3 design as monotherapy in patients with MSS CRC or any solid tumor with documented WPAM. PD effects are evaluated in a separate cohort of approximately six patients with MSS CRC. Combination cohorts will evaluate FOG-001 + FOLFOX/bevacizumab (1L MSS CRC), FOG-001 + nivolumab (3L MSS CRC or anti-PD-1/PD-L1-resistant CRC and solid tumors), and FOG-001 + trifluridine/tipiracil + bevacizumab (3L MSS CRC). Part 2 dose expansion will evaluate FOG-001 monotherapy in patients with MSS CRC and other solid WPAM+ tumors. Combination dose expansion will evaluate combinations initially studied in Part 1. Primary endpoints are safety/tolerability of FOG-001 alone or in combination. Secondary endpoints are PK, PD, recommended phase 2 dose and schedule, and preliminary anti-tumor activity (e.g., ctDNA changes, overall response rate, best objective response, duration of response, and progression-free survival). 156 patients are planned to be enrolled in Part 1, which is currently enrolling in the USA. Clinical trial information: NCT05919264. Research Sponsor: Parabilis Medicines.