A phase 1b/2 study to evaluate the safety and efficacy of TTI-101 as monotherapy and in combination in advanced hepatocellular carcinoma.

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Background: STAT3 (signal transducer and activator of transcription 3) is a key regulatory protein positioned at the intersection of many signaling pathways integral to the survival and immune evasion of cancer cells. Persistent STAT3 activation has been linked to pathological conditions, including chronic inflammation and fibrosis, both of which play essential roles in the pathogenesis of hepatocellular carcinoma (HCC), and is observed in up to 95% of HCC cases. TTI-101 is a first-in-class, orally delivered, small molecule, direct inhibitor of STAT3 activation. TTI-101 monotherapy demonstrated tumor growth arrest as well as reversal of liver injury and fibrosis in a genetically modified mouse model (Hep*Pten*$^{-}$) which recapitulates the pathogenesis of HCC in non-alcoholic fatty liver disease (NAFLD), as well as in combination with immune checkpoint inhibition in a humanized HCC mouse model.[1,2] TTI-101 monotherapy was found to be well tolerated in a Phase 1 trial conducted in patients (pts) with advanced solid tumors (NCT03195699). Of 15 evaluable HCC pts, 60% demonstrated clinical benefit, including 20% confirmed partial responses (median duration=10.5 months). All pts were relapsed/refractory to standard of care (SOC; median prior systemic therapy=2), including anti-PD-(L)1 based therapy. **Methods:** NCT05440708 is a multicenter, open-label, study with primary endpoints including safety and efficacy of TTI-101 as monotherapy and in combination with SOC agents. Patients are enrolled to one of three treatment cohorts based upon prior therapy. Cohort A: TTI-101 (monotherapy), pts who have received up to 3 prior lines of systemic therapy. Cohort B: TTI-101 + pembrolizumab, pts who have progressed following ≥ 2 cycles of first-line anti-PD-(L)1 based therapy. Cohort C: TTI-101 + atezolizumab/bevacizumab, patients who are systemic treatment-naïve. The study consists of 2 parts for each cohort (Phase 1b and Phase 2). During Phase 1b, up to 3 dose levels of TTI-101 will be tested for each cohort to determine the RP2D, using a 3+3 design. Subsequent to RP2D determination, enrollment to Phase 2 will commence (Cohort A n=30, Cohort B n=30, Cohort C n=40). Treatment will continue until disease progression, unacceptable toxicity, withdrawal of consent, discontinuation based on investigator discretion, or study termination. Secondary and exploratory endpoints include pharmacodynamic effects of TTI-101 and evaluation of candidate biomarkers for anti-tumor activity. Enrollment is simultaneously ongoing in Cohorts A, B, and C of the Phase 1b study. 1. Jung KH, et al. *Clin Cancer Res.* 2017;23(18):5537-5546. 2. Zhao Y, et al. *Hepatology.* 2021. Clinical trial information: NCT05440708. Research Sponsor: Tvardi Therapeutics.