First-in-man phase I clinical trial evaluating TTI-101, an orally bioavailable, small molecule inhibitor of STAT3, in patients with advanced solid tumors.

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Background: Signal transducer and activator of transcription 3 (STAT3) is a transcription factor that is a key signaling node and a master regulator of the key hallmarks of cancer, including tumor angiogenesis, resistance to apoptosis, metastasis, and immune evasion. STAT3 activation is observed in ~70% of all cancers and up to 95% of hepatocellular carcinomas (HCC). Thus, inhibition of STAT3 signaling is expected to have a therapeutic effect against a wide range of cancers. TTI-101 is a first-in-class, orally bioavailable, selective small molecule that binds STAT3 and prevents phosphorylation, homodimerization, nuclear translocation, and ultimately, STAT3-mediated transcriptional activity. TTI-101 has demonstrated anti-tumor activity across a broad range of preclinical cancer models, including a Hep*Pten*$^{-}$ (hepatocyte-specific deletion of *Pten*) murine model of liver cancer, which recapitulates the pathogenesis of HCC in non-alcoholic fatty liver disease (NAFLD) with chronic inflammation and liver fibrosis leading to cancer at 11 months. TTI-101 treatment starting at 11 months arrested tumor growth as well as reversed liver injury and fibrosis (1). Given these findings, a clinical trial is being conducted examining the effect of this novel, targeted therapeutic agent in patients with advanced solid malignancies. **Methods:** This single-site Phase I trial (NCT03195699) is evaluating TTI-101 as monotherapy in patients with advanced solid tumors who are refractory to prior therapies. The primary objectives of this dose-escalation study include establishing tolerability and safety at each dose level, pharmacokinetics (PK), and establishing the recommended phase 2 dose (RP2D). The secondary and exploratory objectives include assessing clinical outcomes of patients and pharmacodynamics (PD) of TTI-101 via timed, paired tumor biopsies. The initial dose-escalation study is stratified by disease type (HCC and non-HCC) with independent dose-escalation schemas and will be followed by dose expansion cohorts where safety, PK and PD will be evaluated. TTI-101 is administered orally, twice daily for a 28-day cycle. Key eligibility criteria include: 18 years of age or older, having metastatic or unresectable solid tumor refractory to standard therapies, and measurable disease as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, an Eastern Cooperative Oncology Group (ECOG) score of 0-2, and normal organ function. Additional criteria are specified for patients with HCC including Child-Pugh class A. HCC cohorts 1-4 and non-HCC cohorts 1-3 have been completed without dose limiting toxicities (DLTs). Enrollment to the HCC dose expansion began in February 2021. 1. Jung KH, et al. Multifunctional Effects of a Small-Molecule STAT3 Inhibitor on NASH and Hepatocellular Carcinoma in Mice. Clin Cancer Res. 2017;23(18):5537-46. Clinical trial information: NCT03195699. Research Sponsor: Cancer Prevention and Research Institute of Texas, Other Foundation.