3018 **Poster Discussion Session**

Phase 1 trial evaluating TTI-101, a first-in-class, 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 at the critical intersection of signaling pathways controlling gene networks integral to the survival and immune sequestration of cancer cells. Given the integral role of STAT3 in tumorigenesis and immune suppression, STAT3 signaling inhibition may have dual antitumor activity. TTI-101 is a first-in-class, orally bioavailable, selective small molecule that binds to STAT3 and prevents STAT3-mediated transcriptional activation. A first-in-human, Phase 1, dose escalation and expansion study of TTI-101 monotherapy was conducted in patients with advanced/refractory solid tumors (NCT03195699). **Methods:** Patients with advanced metastatic cancer who had failed standard therapy were treated with TTI-101 twice daily in 28-day cycles at dose levels (DL) 1-4: 3.2 (DL1), 6.4 (DL2), 12.8 (DL3), and 25.6 (DL4) mg/kg/d ("3+3" design). Three different formulations of TTI-101 were used stepwise, beginning with formulation 1 (F1). A second-generation formulation (F2) was introduced at DL3 during dose escalation and patients were stratified into two cohorts: hepatocellular carcinoma (HCC) and other solid tumors. A third-generation formulation (F3) was evaluated once the recommended phase 2 dose (RP2D) was determined. Treatment continued until disease progression, unacceptable toxicity, or study withdrawal. **Results:** Key patient characteristics included a median age of 63 years (range, 33-78), 52% male, and a median number of 3 (range, 1-9) prior systemic therapies. No dose limiting toxicities (DLTs), or fatal treatment-related adverse events (TRAEs) were observed. Diarrhea was the only TRAE observed in ≥30% of the safety population (n=64) with events being mostly Grade 1/2. F3 was better tolerated than F1 and F2 with no events ≥Grade 3. One patient experienced transient Grade 4 hyperglycemia which resolved with insulin and metformin. Five patients had serious TRAEs (all Grade 3), which resolved. TTI-101 showed linear pharmacokinetics from DL1-3 plateauing at DL3. The RP2D was determined to be 12.8mg/kg/d (DL3) for both the HCC and other solid tumor cohorts. Of the 39 patients evaluable for response, 5 (13%) patients had confirmed partial responses (cPR) and 16 (41%) stable disease (SD). Of the 15 patients with HCC, 3 (20%) had a cPR with a median duration of 10.5 months. The other two cPRs were in ovarian cancer (n=1) and gastric cancer (n=1). **Conclusions:** TTI-101 was well-tolerated and no DLTs were noted. cPRs were observed across tumor types. The antitumor activity of TTI-101 monotherapy in the relapsed/refractory setting is promising, particularly in HCC. Two Phase 2 oncology studies of TTI-101 in STAT3-driven cancers (HCC and metastatic breast cancer) are underway. Clinical trial information: NCT03195699. Research Sponsor: Tvardi Therapeutics, Inc.; V Foundation; U.S. National Institutes of Health; Cancer Prevention and Research Institute of Texas (CPRIT).