TWT-101: A PHASE 1 STUDY OF THE NOVEL HPK1 INHIBITOR CFI-402411 IN PATIENTS WITH ADVANCED CANCER

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Background CFI-402411 is an orally available small molecule potent inhibitor of HPK1 (Hematopoietic progenitor kinase 1). T-cells are negatively-regulated at different junctures of cancer-immunity cycle by this regulatory kinase. HPK1, (also mitogen activated protein kinase kinase kinase 1 (MAP4K1)) is a protein serine/threonine kinase predominantly expressed in hematopoietic cells. In T-cells, following T-cell receptor activation, HPK1 is recruited to the plasma membrane where it phosphorylates the adapter protein SH2 domain-containing leukocyte protein of 76 kDa (SLP-76), down-regulating signaling events required for T cell activation and proliferation. Selected for development based on its pharmacologic properties and preclinical activity in a variety of syngeneic cancer models and assays, with an IC₅₀ = 4.0±1.3 nM, CFI-402411 is expected to relieve HPK1-mediated inhibition of T and B cells, facilitating an anti-tumor immune response.

Methods Phase 1, 3 + 3 design in patients. Patients have acceptable laboratory, other parameters for study entry. Single agent dose daily oral escalation cohort (A1) in advanced tumors, then dose expansion (A3) with biomarker backfill (A2) in select advanced tumors; combination with PD-1 Inhibitor (pembrolizumab) (B1, pembrolizumab eligible tumors with no prior grade ≥3 related to CPI) and expansion (B2, PD-1/PD-L1 naïve pembrolizumab eligible tumors). DLT defined as any grade ≥3 toxicity in first cycle of therapy (21d cycles). Standard assessments for response per RECIST v1.1 or iRECIST. The starting dose level was 80mg.

Results At 10 June 2021 data is available for 12 patients from A1. Median age 61.5 years (range 33–73), 8 patients female, and 10 white. Diagnoses were pancreatic cancer, colorectal (3 pts), ovarian, basal cell, cholangiocarcinoma, sigmoid, salivary and breast cancer (1 pt). Six patients (50%) had 4 prior therapies, 1 patient (basal cell) had prior treatment with immune checkpoint inhibitor, pembrolizumab. Four doses studied: 80, 120, 180 and 270mg. TEAEs across all CTCAE grades, (in >2 patients) were diarrhea (6 patients), nausea (4 patients), dyspepsia (3 patients), fatigue (3 patients). No related grade 3–5 events, one immune related event (grade 1, weight loss). 3 grade 3 events all unrelated to study drug - pleural effusion, rash, thromboembolic event. Discontinuation due to disease progression was main reason (7 patients). PK and PD assessments will be updated at time of presentation.

Conclusions CFI-402411 is a potent inhibitor of HPK1 that is well tolerated with a manageable adverse event profile and dose escalations continue. Further safety and efficacy results will be presented at the meeting including additional cohorts if available.

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Trial Registration ClinicalTrials.gov Identifier: NCT04521413

Ethics Approval This study obtained has obtained ethics approvals at multiple institutions globally including;USAWCG IRB - Western Institutional Review Board - MOD00002618 (Submission ID)IntegReview Institutional Review Board - N/AAdvarra Central IRB - SSU00130103IntegReview Institutional Review Board N/AAdvarra Central IRB - SSU00137751Advarra Central IRB - SSU00143275The University of Texas MD Anderson Cancer Center Institutional Review Board - 2020-0678 (IRB ID Number)Hong KongJoint Chinese University of Hong Kong - New Territories East Cluster Clinical Research Ethics Committee - 2020.367 (Ref Number)CanadaOntario Cancer Research Ethics Board - 3320 (Project ID)Health Research Ethics Board of Alberta, HREBA Cancer Committee - HREBA.CC-20-0504 (Ethics ID Number)South KoreaimCORE - Seoul National University Hospital Institutional Review Board - H-2012-094-1182 (IRB Number)National Cancer Institute Review Board - 2020-0525-0001 (Receipt Number) All participants gave informed consent before taking part in this clinical trial.

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