741 **TWT-101: A FIRST-IN-CLINIC STUDY OF CFI-402411, A HEMATOPOIETIC PROGENITOR KINASE-1 (HPK1) INHIBITOR, AS SINGLE AGENT OR COMBINED WITH PEMBROLIZUMAB IN SUBJECTS WITH ADVANCED SOLID MALIGNANCIES**

[1]Kyriakos P Papadopoulos, [2]Scott A Laurie, [3]Alexander Spira, [4]Siqing Fu, [5]Erika Hamilton, [6]Brigette Ma, [7]Judy S Wang, [8]Manish Sharma, [9]Quincy Chu, [10]Anna Spreafico, [11]Mark R Bray, [12]Dih-Yih Chen, [12]Emily Roberts-Thomson, [12]Roger Sidhu, [13]Omid Hamid*. *[1]START San Antonio, San Antonio, TX, USA; [2]The Ottawa Hospital Cancer Center, Ottawa, ON, Canada; [3]Virginia Cancer Specialists, Fairfax, VA, USA; [4]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [5]Sarah Cannon Research Institute, Nashville, TN, USA; [6]The Chinese University of Hong Kong, Hong Kong, Hong Kong; [7]Florida Cancer Specialists/SCRI, Sarasota, FL, USA; [8]START Midwest, Chicago, IL, USA; [9]University of Alberta, Edmonton, AB, Canada; [10]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; [11]Treadwell Therapeutics, Toronto, ON, Canada; [12]Treadwell Therapeutics Inc, New York, NY, USA; [13]The Angeles Clinic and Research Institute, A Cedars-Sinai Affiliate, Los Angeles, CA, USA*

Background CFI-402411, a potent HPK1 inhibitor, may promote T-cell response to tumors through a variety of mechanisms that enhance T-cell function in the cancer immunity cycle, and potentially in settings where antigens are expressed poorly and heterogeneously.[1] Preliminary results demonstrated tolerable safety profile with efficacy signals in select tumor types.[2]

Methods In this ongoing phase 1/2 study, part A evaluates CFI-402411 daily dose (3+3 design) and dose expansion; part B evaluates CFI-402411 in combination with pembrolizumab (200mg) as BOIN design and dose expansion in pembrolizumab eligible tumors. Dose limiting toxicity (DLT) is any grade ≥3 toxicity in cycle 1. Starting dose was 80mg.

Results At 02-May-2023 the study enrolled 59 patients (pts; A, 40pts; B, 19pts). In US, checkpoint inhibitor (CPI) pretreated patients were eligible. Diagnoses in ≥2pts for A: colorectal (11pts), melanoma (6pts), pancreatic (5pts) and non-small cell lung and prostate (2pts each) cancers; for B: head and neck squamous cell (HNSCC; 3pts) and esophageal, non-small cell lung and small cell lung cancers (2pts, each). Part A tested 9 dose levels (80 - 800mg). B tested 5 dose levels (60 - 400mg) to date. Immune-related AEs (irAE) were reported in 7 pts (A; 18%) and 5 pts (B; 26%). Grade ≥3 AEs occurred in 25 pts (A: 63%) and 10pts (B: 53%). SAE's occurred in 21 pts (A: 53%) and 11 pts (B: 58%). Diarrhea was the most common TEAE (A: 73%; B: 47%), related AE (A: 63%; B: 42%), irAE (A: 15%; B: 11%), and grade ≥3 AE in A (18%). Most common grade ≥3 AE in B was pulmonary embolism (PE) and AST increase (11% both). The most common SAE was sepsis (A: 15%) and PE (B: 11%). Diarrhea was the most common DLT occurring at 400mg+pembro; 800mg, 720mg, 640mg monotherapy doses. Disease control rates (CR, PR, or SD ≥ 6 weeks from baseline) at 3 months were 18% (A) and 29% (B). Two HNSCC pts achieved a PR (A: 400mg) and confirmed CR (B: 60mg+pembro). A third HNSCC pt's (B: 400mg+pembro) tumor lesion size reduced 16% at week 5 and pt remains on study. One RCC pt achieved long term SD, 2 years. All 4 pts had prior CPI exposure.

Conclusions CFI-402411 is well-tolerated with a manageable AE profile. Responses as monotherapy and in combination with CPI in CPI exposed patients were seen. Monotherapy part A expansion at 560 mg is underway in HNSCC and RCC.

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Trial Registration NCT04521413

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Ethics Approval This study obtained ethics approvals; Papadopoulos; ID: Pro00051609 Fu; ID2020–0678 Hamilton; ID: Pro00051611 Spira; ID: Pro00043629 Laurie; CTO Project ID 3320 Wang; ID: Pro00051611 Ma; CREC Ref: 2020.367-T Spreafico; CTO Project ID 3320 Sharma; ID Pro00051609 Chu; ID: HREBA.CC-20–0504_REN1 Hamid; IRB: 2020236

Consent As evidenced by verified clinical database information all subjects gave informed consent before taking part in this clinical trial.

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