Background CFI-402411 is a potent inhibitor of HPK1 (Hematopoietic progenitor kinase 1), a protein serine/threonine kinase that negatively-regulates T-cell activation. Following T-cell receptor engagement, HPK1 phosphorylates SLP-76, to down-regulate signals required for T-cell activation and proliferation. CFI-402411 is expected to relieve HPK1-mediated inhibition of T-cell activation, facilitating an anti-tumor immune response.

Methods In this ongoing phase 1 study, part A evaluates CFI-402411 daily dose in dose escalation cohort (3+3 design) and dose expansion, part B evaluates CFI-402411 in combination with pembrolizumab in dose escalation (BOIN design) and dose expansion, part B evaluates CFI-402411 in combination with pembrolizumab in dose escalation (BOIN design) and dose expansion in pembrolizumab eligible patients. Dose limiting toxicity (DLT) is any grade ≥3 toxicity in the first cycle of therapy (21d cycles). Starting dose was 80mg.

Results As of 14 May 2022 (data cutoff), 25 and 9 patients (pts) enrolled to A and B respectively. Median age was 62 (30-79). Median cycles of treatment were 3 (range: 0-20). Majority of patients were male (A, 60% and B, 78%). Median prior regimens were 2 (range: A, 1-4; B, 1-3). 6pts (A, 24%) and 5pts (B, 56%) received prior anti-PD-1/anti-PD-L1 inhibitor. Diagnoses in A (5pts): colorectal (6pts), pancreatic (5pts); for B: small cell lung cancer (2pts). 8 dose levels (80 mg) have been studied in A, 2 dose levels (60 and 80 mg) in B. TEAEs occurring in ≥40% of A pts: diarrhea (n=17, 68%), nausea (n=11, 44%), decreased appetite (n=10, 40%); and B: vomiting (n=4, 44%). 19pts (76%) in A and 6pts (67%) in B experienced CFI-402411 related AEIs. Immune-related AEIs were reported in 1pt (A; 4% [ALT and AST increase]) and 2pts (B; 22% [febrile illness, flu-like symptoms]). Grade ≥3 AEIs and serious AEIs occurred in 14pts (56%) and 10pts (40%) in A; and 3pts (33%) and 4pts (44%) in B. DLTs occurred in 2pts (A [800mg]: diarrhea, spinal cord compression) and 1pt (B [80mg+pembro]: flu-like symptoms). No novel toxicity signals were seen. Disease control rates were 24% in A (6/25) and 44% in B (4/9). One B patient (11%), squamous head and neck cancer (H&N) previously treated with pembrolizumab, has confirmed partial response (PR) and remains on treatment, 8 cycles. An additional H&N patient treated with monotherapy CFI-402411 achieved unconfirmed PR after data cut.

Conclusions CFI-402411 is a well-tolerated, potent inhibitor of HPK1 with a manageable AE profile and initial evidence of activity. RP2D and additional safety and efficacy data will be reported at conference presentation.

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Trial Registration NCT04521413

REFERENCES

Ethics Approval This study obtained ethics approvals at the following ethics/IRB’s; Papadopoulos, KP; Advarra IRB ID: Pro00051609 Fu, S; University of Texas MD Anderson Cancer Center Office of Human Subject Protection IRB ID 2020-0678 Hamilton, E; Advarra IRB ID: Pro00051611 Spira, A; Advarra IRB ID: Pro00043629 Laurie, S; Ontario Cancer Research Ethics Board, CTO Project ID 3320 Wang, J; Advarra IRB ID: Pro00051611 Ma, B; Joint Chinese University of Hong Kong-New Territories East Cluster Clinical Research Ethics Committee CREC Ref. No.: 2020.367-T Sprefacio, A; Ontario Cancer Research Ethics Board, CTO Project ID 3320 Sharma, M; Advarra IRB: ID Pro00051609 Chu, Q; Health Research Ethics Board of Alberta Ethics ID: HREBA.CC-20-0504_REN1 Hamid, O; WCG, IRB: IRB Tracking Number: 2020236 As evidenced by verified clinical database information all subjects gave informed consent before taking part in this clinical trial.