Interim safety and efficacy results of a phase II clinical trial on trametinib and low-dose dabrafenib in patients with advanced BRAFV600 wild-type melanoma

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19O A phase Ib trial of CFI-402257 in combination with weekly paclitaxel in patients with advanced HER2-negative (HER2-) breast cancer (aBC)

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Background: CFI-402257 is a selective oral inhibitor of TTK protein kinase, a critical regulator of the mitotic spindle assembly checkpoint. TTK is overexpressed in breast cancer (BC); CFI-402257 has anti-proliferative and cytotoxic activity as monotherapy. Synergy has been identified between TTK inhibitors and taxanes; CFI-402257 enhances the antitumor activity of paclitaxel in BC xenograft models.

Methods: The primary objective was to establish the safety and recommended phase 2 dose (RP2D) of CFI-402257 combined with weekly paclitaxel. Patients with HER2-ve aBC with adequate organ function, PS 0-1, previously treated with >1 non-taxane chemotherapy, not appropriate for endocrine therapy, were eligible. A 3+3 design was used with dose limiting toxicities (DLTs) assessed during cycle 1 (28 days). Starting dose CFI-402257 was 84mg on 2-day on, 5-day off schedule with paclitaxel 80mg/m^2 day 1, 8, and 15. Safety assessments were performed weekly (CTCAE v5.0) and response (RECIST 1.1) every 2 cycles.

Results: 13 patients received a total of 39 cycles at 3 dose levels (84mg, 112mg, 168mg). Median age was 51, 85% ER+/HER2-ve, 54% PS1, 50% $\geq$3 prior lines of chemotherapy, and 54% with $\geq$4 sites of metastatic disease. One grade 4 neutropenia DLT was seen at DL3; no related serious adverse events (AEs) were seen. The most frequent ($\geq$30%) non-hematological AEs were alopecia (82%), diarrhea (55%), nausea (55%), fatigue (55%), vomiting (45%), sensory neuropathy (45%), headache (45%), constipation (45%), back pain (36%), and extremity pain (36%). Grade $\geq$3 hematological AEs were neutropenia (27%) and anemia (9%). The overall response rate for evaluable patients was 1/9 = 11.1%.

Conclusions: CFI-402257 and paclitaxel is well tolerated. Dose escalation is ongoing and the RP2D has not yet been defined. Updated safety and efficacy data will be presented at the meeting.

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Legal entity responsible for the study: Canadian Cancer Trials Group.

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20P Interim safety and efficacy results of a phase II clinical trial on trametinib and low-dose dabrafenib in patients with advanced BRAFV600 wild-type melanoma

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Background: Preclinical and clinical data suggest MEK-inhibition (MEKi) to be effective in NRAS-mutant (mt) and NRAS wild-type (wt) melanoma. However, MEKi causes considerable cutaneous treatment-related adverse events (TRAE) which are less present if MEKi is combined with BRAFi.

Methods: This open-label, dual-stratum, single-center phase 2 clinical trial investigated trametinib (T; 2 mg QD) in patients (pts) with advanced BRAF^{V600} wt, NRAS$^{Q61R/K/L}$ mt/wt melanoma who had progressed following or were ineligible for immune checkpoint inhibitors. In case of T-related cutaneous TRAE, low-dose dabrafenib (ld-D; 50 mg BID) was added to prevent further skin TRAE. The trial was amended in June 2019 to administer ld-D upfront with T. The primary endpoint was the confirmed objective response rate (ORR; per RECIST 1.1); secondary endpoints were progression-free and overall survival and safety.

Results: Between Jan and Dec 2019, 9 pts initiated T monotherapy and 8 pts initiated T + ld-D. TRAE were seen in 15 pts (29% G3-4; 29% SAE). One pt permanently interrupted T due to G3 pneumonitis. All 9 pts who initiated T monotherapy developed G1-2 acneiform rash which resolved (to G0: 6 pts; to G1: 3 pts) with temporary interruption of T, local metronidazole therapy and subsequent addition of ld-D to T. One pt had a G1 recurrence of acneiform rash that was managed with local therapy. Of 8 pts who initiated T + ld-D upfront, 1 developed G1 acneiform rash that resolved with local therapy only. Other TRAE are shown in the table. T dose was reduced in 4 pts for TRAE (1 pt with left ventricular ejection fraction decrease; 1 with central serous retinopathy; 1 with AST/ALT increase; 1 with hyponatremia and syncope). The unconfirmed ORR is 4/15 and the disease control rate is 7/15 evaluable pts.

Table 20P: TRAE in ≥2 pts

TRAE	G1-2 (n[%])	G3-4 (n[%])
CPK increase	10 (59)	0
Diarrhea	5 (29)	0
AST increase	4 (24)	1 (6)
Lipase increase	4 (24)	0
Arterial hypertension	4 (24)	0
Hyponatremia	2 (12)	2 (12)
ALT increase	3 (18)	1 (6)
Fatigue	2 (12)	1 (6)
Anemia	3 (18)	0
Chills	3 (18)	0
Nausea	3 (18)	0
Central serous retinopathy	3 (18)	0
Syncope	0	2 (12)
Acute kidney injury	2 (12)	0
Thrombocytopenia	2 (12)	0
Fever	2 (12)	0

Conclusions: No unexpected toxicities were seen with T or T + ld-D. ld-D is able to prevent T-related skin toxicity. Thus, combining ld-D with T is a safe approach to increase tolerance of and optimize exposure to T.

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