

RESULTS FROM AN ONGOING OPEN-LABEL, MULTICENTER, PHASE 1 TRIAL OF CCX559, AN ORALLY ADMINISTERED SMALL MOLECULE PD-L1 INHIBITOR, IN PATIENTS WITH ADVANCED SOLID TUMORS

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Background The novel small molecule CCX559 is a highly potent and selective PD-L1 inhibitor that induces dimerization and internalization of cell-surface PD-L1. CCX559, when orally administered in animal models, demonstrated anti-tumor efficacy, including the ability to induce complete responses.¹ Initial results from a phase 1 study of CCX559 indicated on-target pharmacodynamic (PD) effects consistent with PD-L1 inhibition, including peripheral T cell activation and stimulation of cytokines.^{2,3}

Methods This phase 1, first-in-patient, dose-escalation trial is evaluating safety, tolerability, pharmacokinetics (PK), PD, and preliminary anti-tumor activity of CCX559 in patients with advanced solid tumors. CCX559 is dosed orally once daily in repeated 21-day cycles with a starting dose level of 30 mg. PBMC and plasma samples are collected from patients over the first 2 cycles of treatment for PD assessments, including quantification of T cell proliferation and measurement of plasma cytokines and chemokines. Principal component analysis (PCA) was used to identify patient clusters with discrete cytokine/chemokine profiles.

Results As of July 12, 2022, a total of 17 patients were dosed with CCX559, including 13 patients across the 120 mg and 180 mg dose groups. No DLTs, treatment-related SAEs, or severe (Grade 3 or higher) treatment-related AEs were reported. The observed PK exposures were generally dose-proportional from 30 mg to 180 mg and in line with projections based on nonclinical data.

PD assays were performed with samples from the 30 mg (n=1), 60 mg (n=1), 120 mg (n=8) and 180 mg (n=2) cohorts. Patients in all four cohorts showed 1.5-fold or greater increases in peripheral CD4 and CD8 T cell proliferation starting in the first cycle (21 days) of treatment, as measured by Ki67 positivity. In patients treated with CCX559 120 mg or 180 mg, plasma levels of IFN γ , IFN γ -stimulated factors CXCL10 and CXCL11, and soluble PD-L1 were significantly increased (p<0.05) during the first treatment cycle, and changes in these factors were positively correlated with each other. PCA of the 120 mg cohort showed that patients with increased IFN γ -stimulated factors formed a cluster with a differentiated global cytokine/chemokine response, including upregulation of CXCL13, CXCL8, and IL-1 β .

Conclusions Interim results from the phase 1 dose-escalation trial of CCX559 indicate on-target PD effects consistent with PD-L1 inhibition. Peripheral IFN γ -stimulated responses were observed in the 120 mg and 180 mg cohorts, consistent with the expected activity profile for immune checkpoint inhibitors. Additional PD data, together with the safety and PK profile, will be presented.

Trial Registration ANZCTR registration
ACTRN12621001342808

REFERENCES

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Ethics Approval This study was approved by the central Human Research Ethics Committee Bellberry Limited; approval numbers 2021-04-374, 2021-04-374-AB, 2021-04-374-AC, and 2021-04-374-AD.

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