

**THE SMALL MOLECULE PD-L1 INHIBITOR CCX559
PREFERENTIALLY ACCUMULATES IN TUMORS,
RESULTING IN DEPLETION OF CELL-SURFACE PD-L1 IN
A MURINE PRECLINICAL MODEL**

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Background The small molecule CCX559 is a novel, highly potent inhibitor of human PD-L1 (hPD-L1) in development as an oral treatment for cancer patients.^{1,2} *In vitro* studies showed that CCX559 inhibits PD-L1 binding to PD-1 and induces PD-L1 internalization from the cell surface. To investigate the mechanism of action *in vivo*, we examined the effect of CCX559 distribution and clearance on tumor cell PD-L1 dynamics and anti-tumor activity.

Methods CCX559 was administered orally at the clinically relevant dose of 30 mg/kg once daily for 7 days to human PD-L1 knock-in mice bearing MC38 tumors (average volume 60-100 mm³). The MC38 cells were engineered to express hPD-L1, as CCX559 does not cross-react with mouse PD-L1. CCX559 levels in tumors and organs, including lung, liver, kidney, spleen, heart, and brain, were quantitated by mass-spectrum analysis at 1, 5 and 12 days after the last dose. Cell surface and intracellular PD-L1 were detected using flow cytometry and immunohistochemistry.

Results Dosing CCX559 for 7 days significantly reduced hPD-L1-MC38 tumor growth compared to vehicle control, and the reduction in tumor volume persisted post dosing until the end of study. The average CCX559 level on day 1 post dose was significantly higher in tumors than plasma and other organs (27.9 µg/g tissue vs. 0.007 – 1.4 µg/g). In tumors CCX559 induced hPD-L1 internalization into intracellular vesicles and reduced the cell surface level by over 90% compared to vehicle control. CCX559 levels dropped 98% in plasma, tumor and tissues by day 5 post dose, but the level in the tumors was still above the IC₉₀ for inhibiting PD-L1; consistent with this, intracellular PD-L1 was also observed. The drug was completely cleared by day 12 post dose, but tumor cell surface hPD-L1 in the CCX559 arm was only partially recovered compared to the vehicle control.

Conclusions In a preclinical model, higher levels of CCX559 were observed in tumors than in plasma and other organs. Cessation of dosing led to clearance of CCX559 within days, but recovery of tumor cell surface PD-L1 levels was delayed, perhaps as a result of higher CCX559 levels in the tumor. The *in vivo* properties of CCX559 suggest that PD-L1 inhibition in tumors may be achieved at relatively low drug levels in the periphery, thus mitigating potential risk of adverse events. No DLTs, treatment-related SAEs or severe (Grade 3 or higher) AEs have been reported in an ongoing first-in-human dose escalation trial with CCX559 (ACTRN12621001342808).

REFERENCES

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2. Gonzalo Tapia *et al.* Preliminary data from an ongoing phase 1 dose-escalation study of CCX559, an orally administered small molecule PD-L1 inhibitor, in patients with advanced solid tumors. *Journal of Clinical Oncology* 2022;**40**(16_Suppl): 2593.

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