**Background**

HGF/c-MET signaling mobilizes neutrophils in response to cancer immunotherapies. Neutrophils recruited to T-cell-inflamed microenvironments acquire immunosuppressive properties. c-MET+ neutrophils suppress therapy-induced T-cell expansion and effector functions. Glodde N et al (2017) have shown that c-MET inhibition promotes adoptive T-cell transfer in murine cancer models by increasing effector T-cell infiltration in tumors. This therapeutic effect was independent of tumor cell-intrinsic c-MET dependence. In cancer patients, high serum levels of HGF correlated with high neutrophil counts and poor responses to checkpoint blockade therapies. Therefore, c-MET inhibitor (CBT-101) co-treatment may improve responses to cancer immunotherapy in settings beyond c-MET-dependent tumors.

- c-MET inhibitor co-treatment may improve responses to cancer immunotherapy in settings beyond c-MET-dependent tumors
- HGF/c-MET signaling mobilizes neutrophils in response to cancer immunotherapy
- Neutrophils acquire immunosuppressive properties in T-cell inflamed tissues
- Concomitant c-MET inhibition enhances the efficacy of cancer immunotherapies

**Pre-Clinical Rationale**

Safety and efficacy of CBT-101, anti-PD-1 Ab and combination were evaluated in three syngeneic mouse models, MC-38 (colorectal), H-22 (liver) and RENCA (renal). Tumor cells were inoculated in C3HBL/6 mice and treatment was initiated when tumors reached a mean volume of approximately 100 mm³. Mice were randomized into four groups of 10 animals per group and treated with either vehicle, CBT-101 (10 mg/kg oral daily in MC-38 and H-22 models and 20 mg/kg oral daily in RENCA), anti-PD-1 Ab (10 mg/kg intraperitoneally twice weekly), or a combination of CBT-101 plus anti-PD-1. Animals were checked daily for morbidity and mortality. Body weights (BW) and tumor volumes (TV) were measured twice weekly. In the MC-38 model, tumor tissue was collected at the end of the study and formalin fixed. Double IF analysis of c-MET and neutrophils was used to quantify the expression of Met+ neutrophils.

**Biomarker Studies**

In the MC-38 model, tumor tissue was collected at the end of the study and formalin fixed. Double IF analysis of c-MET and neutrophils was used to quantify the expression of Met+ neutrophils.

**Summary**

CBT-101 and Anti-PD-1 Ab combination treatment enhances host anti-tumor response in murine tumor models. Our findings reveal a role for the MET pathway in neutrophil recruitment and function and suggest that c-MET inhibitor co-treatment may improve responses to cancer immunotherapy in settings beyond c-MET-dependent tumors. Encouraged by these results, a Phase 1/2 clinical trial has been initiated to establish a safe dose combination of CBT-501 (anti-PD-1 antibody) + CBT-101 primarily and nivolumab + CBT-101, secondarily in select solid tumors. NCT03655613.

**Reference**


**Contact / Further Information**

Please visit CBT Pharmaceutical’s website at [www.cbppharma.com](http://www.cbppharma.com) for a PDF version of the poster presentation.