Combination immunotherapy anti-PD-1 antibody with CBT-101 (c-MET inhibitor) demonstrates enhanced activity in tumors not dependent on c-MET

Poster No: 377

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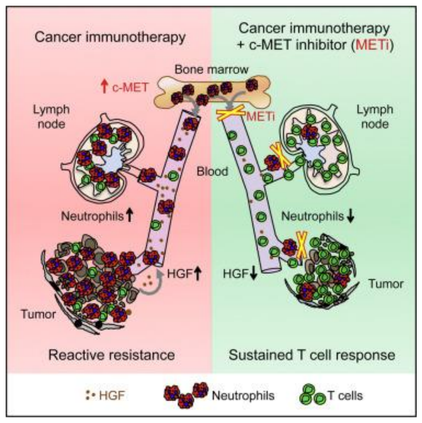
Background

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 promoted 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.



Glodde et al. Immunity Oct 2017

- 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

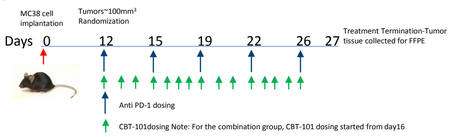
Pre-Clinical Rationale

Safety and efficacy of CBT-101, anti-PD-1Ab and combination were evaluated in three syngeneic mouse models, MC-38 (colorectal), H-22 (liver) and RENCA (renal). Tumor cells were inoculated in C57BL/6 mice and treatment was initiated when tumors reached a mean volume of approximately 100 mm^3. Mice were randomized into four groups of ten 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.

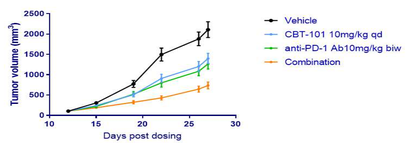
Mean % TGI = ((Mean TVcontrol-Mean TVtreated)/MeanTVcontrol) x 100

Figure 1: Antitumor activity in MC-38 syngeneic colon cancer model

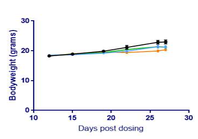
A. Study Design



B. Tumor Volume



C. Body Weight

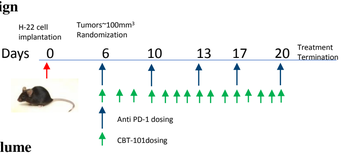


D. Mean Percent Tumor Growth Inhibition

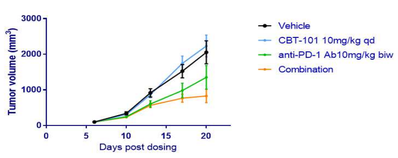
Vehicle	
CBT-101 10mg/kg qd	33.6
Anti-PD-1 Ab 10mg/kg biw	39.9
Combination	65.1

Figure 2: Antitumor activity in H-22 syngeneic hepatocellular carcinoma model

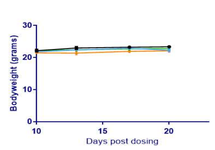
A. Study Design



B. Tumor Volume



C. Body Weight

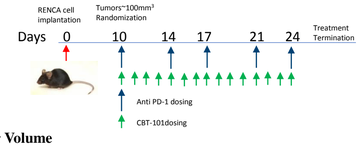


D. Mean Percent Tumor Growth Inhibition

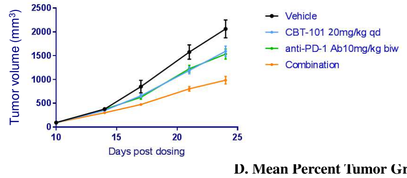
Vehicle	
CBT-101 10mg/kg qd	-8.3
Anti-PD-1 Ab 10mg/kg biw	34.2
Combination	59.6

Figure 3: Antitumor activity in RENCA syngeneic renal cell carcinoma model

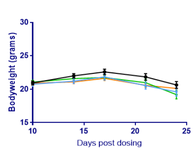
A. Study Design



B. Tumor Volume



C. Body Weight



D. Mean Percent Tumor Growth Inhibition

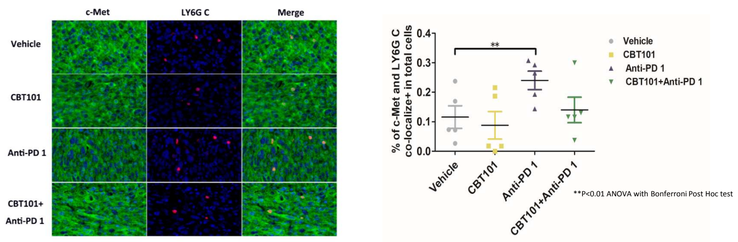
Vehicle	
CBT-101 10mg/kg qd	23.0
Anti-PD-1 Ab 10mg/kg biw	28.3
Combination	52.3

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.

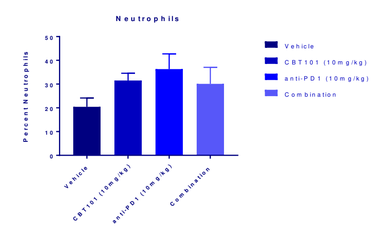
Figure 4: Double IF staining on MC38 syngeneic colon tumors (c-Met and Neutrophil (LY6G C))

Representative Images of Met+ Neutrophils in Tumor Tissue



Anti-PD1 increased c-Met positive neutrophils, and anti-PD1+c-Meti decrease this neutrophil percentage in tumor microenvironment.

Figure 5: Circulating blood Neutrophils in MC38 syngeneic colon cancer model



Anti-PD1 increased c-Met positive neutrophils, and anti-PD1+c-Meti decrease this neutrophil percentage in peripheral circulation. This difference was not statistically significant

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

Glodde N, Bald T, van den Boorn-Konijnenberg D, et al. Reactive neutrophil responses dependent on the receptor tyrosine kinase c-MET limit cancer immunotherapy. Immunity 2017; 47: 789–802e9.

Contact / Further Information

Please visit CBT Pharmaceutical's website at www.cbtpharma.com for a PDF version of the poster presentation.

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Society for Immunotherapy of Cancer (SITC) Annual Meeting 2018, November 7–11, 2018, Walter E. Washington Convention Center, Washington, D.C.