793 TREATMENT OF ANTI-SIRPα IN COMBINATION WITH ANTI-TAA EXERTS SUPERIOR ANTI-TUMOR ACTIVITY

Xiaofeng Niu, Chunnian Wang, Jinfeng Zhao, Haiying Wang, Li Zhang, Jiahui Hu, Jingfeng Yu, Yefeng Lu, Xiaoli Guo, Haixia Jiang, Rui Gao, Zhihao Wu, Yangsheng Qiu, Quan Qiu, Zheng Song, Dawei Sun, Hongtao Lu*. *Elpiscience Biopharma, Shanghai, China*

Background Signal-regulatory protein alpha (SIRPα), is an inhibitory receptor expressed on myeloid cells and dendritic cells. Ligation of CD47 to SIRPα delivers a "don't eat me" signal to suppress phagocytosis. Tumor cells frequently overexpress CD47 to evade macrophage-mediated destruction. Currently, agents targeting CD47 have proceeded to clinical trials and demonstrated promising anti-tumor results. However, these agents have been associated with hemolytic anemia and thrombocytopenia. In addition, universal expression of CD47 causes antigen sink, which leads to reduced efficacy. We therefore consider targeting CD47 receptor SIRPα to achieve improved efficacy with better safety profile. We have developed a pan-allele anti-SIRPα competitive functional antibody ES004-B5 that potently potentiates antibody dependent cellular phagocytosis (ADCP) activity of antibodies against tumor associated antigens (TAAs) *in vitro* and *in vivo*.

Methods Pan-allele SIRPα reactivities, SIRP family homologue binding properties, and cross-species reactivity were evaluated by ELISA and FACS. Antigen binding affinity was determined by surface plasmon resonance system (Biacore). Blocking activity was determined by competition assay and SHP-1 recruitment assay. *In vitro* functional activity was determined by phagocytosis assay. The impact on T cell function was evaluated by mixed lymphocyte reaction (MLR). *In vivo* efficacy was evaluated in a syngeneic mouse tumor model with human CD47/human SIRPα double knock-in mice. Epitope analysis was performed by competitive ELISA and hydrogen deuterium exchange mass spectrometry (HDX-MS). Lead clone was humanized via CDR grafting and back mutation screening. Non-human primates (NHPs) models were used to assess the safety and pharmacokinetics of the humanized candidate.

Results ES004-B5 recognizes pan-allele human SIRPα with high affinity, and cross reacts well with cynomolgus SIRPα. It binds a unique epitope on SIRPα that is distinct from known competitor molecules. Although ES004-B5 binds to SIRPγ expressed on T cell surface, it doesn't cause negative impact on T cell activation. ES004-B5 potently blocks CD47-SIRPα interaction as well as CD47 mediated SHP-1 recruitment to phosphorylated SIRPα intracellular tail. Through blocking CD47-induced inhibitory "don't eat me" signals, ES004-B5 potently potentiates ADCP activity of anti-TAA antibodies like rituximab and cetuximab. In a syngeneic mouse tumor model, the combination of ES004-B5 plus anti-Claudin18.2 significantly inhibited tumor growth *in vivo*. ES004-B5 has favorable pharmacokinetics and safety profile in NHPs.

Conclusions In summary, the functional anti-SIRPα mAb ES004-B5 has great potential to be used in combinations with multiple anti-TAA antibodies in cancer treatment. We are currently advancing the development of ES004-B5 into clinical candidate.

http://dx.doi.org/10.1136/jitc-2022-SITC2022.0793