DUAL TARGETING OF INNATE AND ADAPTIVE IMMUNE CHECKPOINTS WITH A PD-L1/SIRPα BISPECIFIC MACROPHAGE ENGAGER TO PROMOTE ANTI-TUMOR ACTIVITY

Dawei Sun*, Hongtao Lu, Haixia Jiang, Yanan Geng, Jiahui Hu, Ziqiao Ding, Jinfeng Zhao, Xiang Xu, Wengiang Lu, Xiaofeng Niu, Rui Gao, Zhihao Wu, Quan Qiu, Zheng Song, Yangsheng Qiu. Elpiscience Biopharma, Shanghai, China

Background Tumor-associated macrophages are major component of immune cells in the tumor micro-environment that express an array of effector molecules leading to the inhibition of anti-tumor immune responses. Signal regulatory protein α (SIRPα) is a myeloid-lineage inhibitory receptor that restricts phagocytosis through engagement of its ligand CD47 expressed on tumors and normal tissues. Compared to anti-CD47 therapeutics, targeting myeloid-restricted SIRPα may provide a differential pharmacokinetic, safety, and efficacy profile. Here, we report the construction of a SIRPα antagonist-based bispecific macrophage engager (BiME) called ES019, which uses PD-L1 antibody as a tumor associated antigen (TAA) targeting arm and also as a tool to relieve the inhibition of T cell. The PD-L1/SIRPα bispecific macrophage engager aims to promote macrophage phagocytosis against PDL1 expressing tumor cells, and to activate T cell adaptive immunity resulting in further tumor cell killing.

Methods Through Elpiscience proprietary BiME platform, we have generated a panel of single domain antibody (sdAb) based anti-PDL1/SIRPα bispecific antibodies, including different orientations, ratios, and IgG isotypes of anti-PDL1 arm and anti-SIRPα arm. These bispecific antibodies were evaluated for PDL1, SIRP family homologue binding, PD1-PDL1 and CD47-SIRPα blocking properties by ELISA and FACS. In vitro function activity was determined by phagocytosis assay using human monocyte derived macrophage and mouse bone marrow derived macrophage. In vivo anti-tumor efficacy was tested in a syngeneic tumor model with hSIRPα knock-in mice. The pharmacokinetic (PK) and safety profile were assessed in hSIRPα knock-in mice or cynomolgus monkeys.

Results In this study, we demonstrated that anti-PDL1/SIRPα bispecific antibodies bound to PD-L1 expressing tumor cell and macrophage simultaneously, effectively inhibited CD47-SIRPα signal and triggered strong macrophage phagocytosis. ES019 showed potent in vitro macrophage and T cell tumor killing activity in the presence of peripheral blood mononuclear cells, but without nonspecific killing in PDL1 negative cells. Remarkably, ES019 showed almost 100% tumor growth inhibition in in vivo SIRPα knock-in syngeneic models. On the other hand, ES019 did not induce phagocytosis of normal immune cells like activated T cells. In summary, we demonstrated that ES019 exhibited super anti-cancer effects, evidenced by potent phagocytosis in vitro and almost complete tumor regression in vivo.

Conclusions Using our bispecific macrophage engager (BiME) platform, we have developed a PD-L1/SIRPα bispecific antibody that is capable of activating both macrophages and T cells to kill cancer cells with the potential to overcome the limitations of traditional anti-PD1 therapies.