Dual Targeting of Innate and Adaptive Immune Checkpoints with a PD-L1/SIRPα Bispecific Macrophage Engager to Promote Anti-tumor Activity

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BACKGROUND

Tumor-associated macrophages are major component of immune cells in the tumor micro-environment (TME) 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 SIRPs 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, which, together with PD-L1 blockade, will eventually lead to an activation of T cell adaptive immunity resulting in further tumor cell killing.

METHODS

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, SIRPα family homologue binding, ligand and receptor blocking properties. Function activity was determined by phagocytosis assay using human and mouse 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.

RESULTS

BIME Provides Solutions to the Challenges of BITE

Figure 1. ES019 Phagocytosis Activity Is Correlated With PD-L1 Level on Tumor Cells

Figure 2. ES019 Leads to Better Phagocytosis Capability of Tumor Cells By M2-like Than M1-like Macrophage

Figure 3. ES019 Activates T cells Without Induction Phagocytosis of T Cells

Figure 4. ES019 Shows Favorable Pharmacokinetics In Mouse Model

Figure 5. ES019 Demonstrates Single Agent Anti-Tumor Efficacy In Animal Model

Conclusion

Based on our bispecific macrophage engager (BIME) platform, we have developed a PD-L1/SIRPα bispecific antibody that is capable of reactivating macrophages and T cells to kill cancer cells with the potential to overcome the limitations of traditional anti-PD1 therapies. The anti-PD1/SIRPα bispecific antibody, designed for tumor cell and immune cell dual targeting, demonstrated significantly enhanced tumor therapeutic efficacy versus combo or monotherapies.