1176 BSI-510, A NOVEL BISPECIFIC MOLECULE COMBINING AN ANTI-SIGLEC-15 ANTIBODY WITH CYTOKINE GM-CSF FOR ENHANCED ANTITUMOR EFFICACY

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Background Siglec-15 has increased expression levels not only in solid tumors but also in tumor associated macrophages. It is an immune suppressive molecule that inhibits T cell activity in the tumor microenvironment (TME). Siglec-15 blockade can increase T cell proliferation and activity. In the TME there is an accumulation of tumor suppressed M2 macrophages; thus, therapies that can convert M2 to M1 macrophages can enhance tumor killing. GM-CSF is a key cytokine that induces differentiation of pro-tumor M2 macrophages into anti-tumor M1 macrophages. Here we report the development of a novel bispecific fusion molecule composed of a newly discovered anti-Siglec-15 antibody fused with GM-CSF. BSI-510 is expected to target Siglec-15 on M2 macrophages and to reprogram M2 to M1 through GM-CSF stimulation, thus boosting antitumor efficacy through activating both T cells and macrophages.

Methods An anti-Siglec-15 mAb was identified from humanized mice immunized with recombinant Siglec-15-ECD-Fc and screened by our proprietary H^3 (High-throughput, High-content and High-efficiency) platform. Human GM-CSF was fused to the C-terminus of the anti-Siglec-15 antibody via a flexible linker. The affinities of the fusion molecule to Siglec-15 and GM-CSFR were determined by SPR. The binding of the molecule to Siglec-15 was further confirmed by ELISA and FACS. *Ex vivo* T cells proliferation assay was used to evaluate the function of anti-Siglec-15 antibody portion of the molecule, and TF-1 proliferation assay and macrophage polarization assay were used to evaluate the function of GM-CSF part. MC38-Siglec15 and MC38-mSiglec15 syngeneic murine models were used to evaluate the tumor inhibition activity of a surrogate bispecific fusion molecule (anti-Siglec15/mouse GM-CSF).

Results BSI-510 demonstrated comparable potency to the parental anti-Siglec-15 antibody regarding Siglec-15 binding and T cell proliferation. It also exhibited comparable potency to recombinant protein GM-CSF in GM-CSFR binding and TF-1 proliferation. In addition, treatment with BSI-510 induced a significant shift from M2 to M1 macrophages, whereas anti-Siglec-15 alone did not show any repolarization activity. A BSI-510 surrogate (anti-Siglec-15/mouse GM-CSF) showed superior antitumor efficacy in syngeneic murine models with a shift of M2 macrophages to M1. Expression of Siglec-15 in M2 macrophages was confirmed in human tumor samples.

Conclusions BSI-510 is a first-in-class anti-Siglec-15×GM-CSF bispecific fusion molecule combining simultaneous reversal of T cell inhibition and M2/M1 macrophage repolarization. BSI-510 demonstrates favorable biophysical and functional characteristics, supporting the initiation of development activities including manufacturing and IND-enabling studies.

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