Background Programmed death-ligand 1 (PD-L1) and programmed cell death protein 1 (PD-1) blockade therapy has been approved for the treatment of many malignancies whereas the majority of patients with solid tumors do not respond well.1 B7-H3, another newly identified immune checkpoint molecule, has limited expression in normal human tissues while highly expressed on cancer cells and tumor-infiltrating antigen-presenting cells (APCs), which is associated with T-cell exhaustion in cancer patients. In addition, B7-H3 is overexpressed by the tumor-associated vasculature and stromal fibroblasts, and contributes to the development of cancer through both immune-dependent and nonimmune routes.2 However, clinical therapeutic antibodies targeting B7-H3, such as Enobituzumab, have not shown an immune checkpoint blockade effect. ATG-027, a novel B7-H3/PD-L1 bispecific antibody, was designed to exert the anti-tumor efficiency through reinforcing T cell activation by dual-blocking of B7-H3 and PD-L1, antibody-dependent cellular cytotoxicity (ADCC), complement dependent cytotoxicity (CDC), and antibody-dependent cellular phagocytosis (ADCP).

Methods ATG-027 was developed by introducing high-affinity PD-L1 scFv into a human IgG1 B7-H3 monoclonal antibody (mAb). The bispecific antibody employed wild type Fc domain which enables ADCC and ADCP effects. A series of in vitro studies were performed to evaluate the immune regulating function and anti-tumor efficacy of ATG-027. The in vivo efficacy of ATG-027 was evaluated in mice bearing syngeneic MC38 colorectal cancer cells overexpressing human B7-H3 (MC38-hB7-H3).

Results In the cell-based assay, ATG-027 binds with nanomolar affinity to both B7-H3 and PD-L1 expressing cells. ATG-027 demonstrated higher ADCC/CDC activity compared with anti-PD-L1 and anti-B7-H3 parental antibodies. ATG-027 also demonstrated greater ADCP potency than anti-PD-L1, anti-B7-H3, or the combination. Interestingly, in a Mixed Lymphocyte Reaction (MLR) experiment to assess the T cell activation, the B7-H3 parental antibody (30-C7) or the Fab region of 30-C7 induced interferon gamma (IFNγ) production, indicating T cell activating function, whereas Enobituzumab showed no effect in the experiment (figure 1). ATG-027 also demonstrated superior in vivo anti-tumor activity in mouse MC38-hB7-H3 models compared to parental antibodies. Bi-weekly dosing of 7.5mg/kg ATG-027 induced tumor shrinkage or complete tumor regression.

Conclusions By binding to a specific epitope of B7-H3, ATG-027 blocks the protein’s inhibitory function, leading to strong T cell activation. ATG-027 can also inhibit the interaction between PD1/PD-L1 to rescue T cell activity suppression. ATG-027’s dual T cell activation function and powerful ADCC, CDC, and ADCP properties contribute to its promising anti-tumor efficacy in preclinical models.

REFERENCES