ATG 027 A FIRST IN CLASS B7 H3 PD L1 BISPECIFIC ANTIBODY SHOWS POTENT T CELL ACTIVATION CAPABILITY AND IN VIVO ANTI TUMOR EFFICACY

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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 (30-C7-Fab) induced robust IL-2 and 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 colorectal cancer cells overexpressing human B7-H3 (MC38-hB7-H3). Biweekly 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

Ethics Approval The protocol and any amendment(s) or procedures involving the care and use of animals in this study were reviewed and approved by the Institutional Animal Care and Use Committee (IACUC) of CrownBio to execution with an AUP number or IACUC approval number for each animal study. All studies were conducted following an approved IACUC protocol. AUP NO. 2104-09-2186.

Abstract 1397 Figure 1 B7H3 Mab 30-C7 activates T cells in MLR assay
Human T cells were isolated and co-cultured with mature DCs (mDC), ATG-027 parental anti-B7-H3 antibody (30-C7) or Fab region of 30-C7 induced potent IFNγ (left) and IL2 (right) production after 24 hours of co-culturing. Enobituzumab or IgG1 control showed no effect.