1221 BP1202-NF2, A NOVEL ADCC-ENHANCING CD39 ANTIBODY, INDUCES DESTRUCTION OF REGULATORY T CELLS AND ENHANCES CYTOTOXIC T LYMPHOCYTESINDUCTION

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Background The immune suppression in the tumor microenvironment (TME) was promoted by the adenosine signaling in metabolites downstream of CD39 (ENTPD1). CD39, an extracellular enzyme, is one of the surface markers of regulatory T cells (Tregs). Tregs were suppressive immune cells that induce inhibitory and anti-proliferative effects on effector cells. Therefore, selective reduction of tumor-infiltrating Tregs is expected to re-invigorate anti-tumor immunity. Here, we describe the development of BP1202-NF2, a novel glycosylation-modified monoclonal antibody (mAb) targeting human CD39 that induces Treg depletion through antibody-dependent cellular cytotoxicity (ADCC) followed by antigen specific cytotoxic T lymphocytes (CTLs).

Methods Anti-human CD39 antibodies were screened by sorting B cells of mice immunized with human CD39 protein. The clones that inhibited the enzyme activity of CD39 were humanized on IgG1. A glycosylation modification was then introduced to the antibody during its production. Binding to human CD39 and Treg was evaluated via surface plasmon resonance (SPR) or flow cytometry. Functional assay was performed by Promega CD16 (V/F variants) ADCC signaling assay. Treg depletion and CTL induction were assayed using peripheral blood mononuclear cells (PBMCs) from healthy donors.

Results The humanized anti-CD39 antibody, BP1202 has a high affinity for the recombinant CD39 protein (K_D: 481 pM) and inhibits the enzyme activity on CD39-expressing cells and human Tregs (IC_{50}: 1 nM). BP1202-NF2, a glycosylation-modified version of BP1202, binds to CD39 on activated Treg with a K_D value in the nano-molar range, and demonstrated a robust ADCC activity in a dose-dependent manner. The ADCC activity was conferred by the glycolyration-modification and peaked at 1 μg/mL in PBMCs with either of V and F variants of FcγRIIIa receptor. By using ADCC assay, BP1202-NF2 selectively depleted $CD39^{hi}$ T cell populations and completely $CD39^{hi}$ Tregs in PBMCs from healthy donors. Further stimulation with CMV peptide robustly induced antigen-specific cytotoxic T lymphocytes. Their exhaustion level was lower than the reference antibodies.

Conclusions The humanized anti-CD39 antibody with glycosylation modification, BP1202-NF2 specifically binds to CD39 and targets $CD39^{hi}$ Tregs for depletion via ADCC and subsequently enhances CTL induction. Our results suggest that BP1202-NF2 modulates the TME to promote immune response in human tumors via Treg depletion and inhibition of CD39 enzymatic activity.

Ethics Approval The present study was approved by the Institutional Ethics Committee of BrightPath Biotherapeutics Co., Ltd. (approved number: ERD-01).

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