BGBA3055, an afucosylated anti-CCR8 antibody, preferentially depletes intratumoral regulatory T cells and inhibits tumor growth in preclinical models

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Abstract

Background: Regulatory T cells (Tregs) is a well-known key immune suppressive cell population enriched in tumor microenvironment (TME) that inhibits the anti-tumor immunity. Accordingly, specific depletion of Tregs in TME is considered as an attractive strategy to enhance the efficacy of immunotherapy such as PD-(L)1 treatment. C-C motif chemokine receptor 8 (CCR8), a G-protein coupled receptor, is predominately upregulated in intratumoral Tregs while CCR8 level in peripheral Tregs is relatively low. Therefore, CCR8 is widely explored as a promising therapeutic target for intratumoral Treg depletion. BGB-A3055 is a novel humanized afucosylated immunoglobulin G (IgG) 1 monoclonal antibody against human CCR8 (hCCR8). Here, we present the in vitro and in vivo data of BGB-A3055 in preclinical models.

Methods: The cellular binding of BGB-A3055 was determined by fluorescence-activated cell sorting (FACS) on 293T cells that overexpress hCCR8 or primary human Treg cells. The blocking activity of BGB-A3055 on CCL1-CCR8 induced signaling was determined by Path Hunter eXpress HuCCR8 CHO-K1ß-Arrestin GPCR Assay kit. Antibody-dependent cellular cytotoxicity (ADCC) effect was evaluated on primary Treg cells. In vivo intratumoral Treg depletion and anti-tumor efficacy was assessed in GL261 and MC38 syngeneic models using hCCR8 knock-in mice.

Results: BGB-A3055 exhibited a potent cellular binding to hCCR8 overexpressing cells and primary human Treg cells. BGB-A3055 can also efficiently block CCL1-CCR8 signaling and induce potent ADCC effect against CCR8 expressing primary Treg cells. Furthermore, in preclinical in vivo models, BGB-A3055 preferentially depleted Tregs in TME, demonstrated potent single agent and synergistic anti-tumor effect in combination with PD-1 antibody.

Conclusions: BGB-3055 is a novel fully humanized afucosylated antibody that has high binding affinity to hCCR8, strong CCL1-CCR8 blocking capacity and potent ADCC effect. BGB-A3055 demonstrated strong anti-tumor activity as single agent or in combination with PD-1 antibody. A Ph1 study evaluating BGB-A3055 alone and in combination with Tislelizumab in participants with solid tumor is ongoing (NCT05935098).