BGB-A3055, 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.

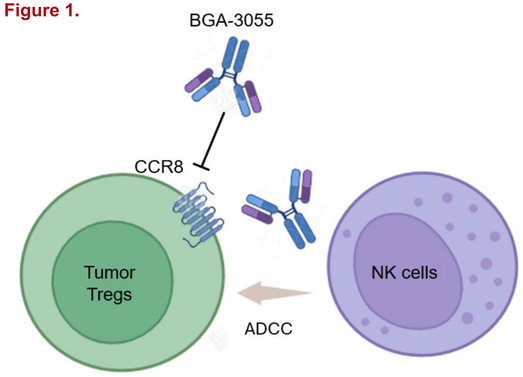
Methods: The cellular binding of BGB-A3055 was determined by fluorescence-activated cell sorting (FACS) on 293T cells that overexpress hCCR8 or primary human Treg cells. The blocking activity of BGB-A3055 on CCL1-CCR8 induced signaling was determined by Path Hunter eXpress HuCCR8 CHO-K1ß-Arrestin GPCR 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-A3055 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).

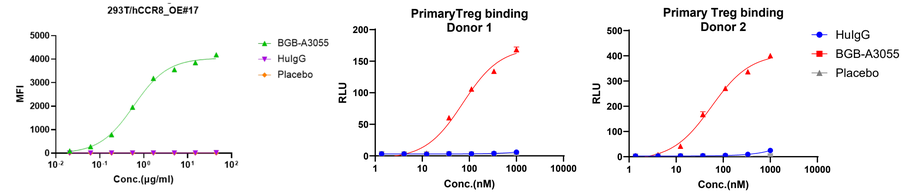
Mechanism of Action

Figure 1.



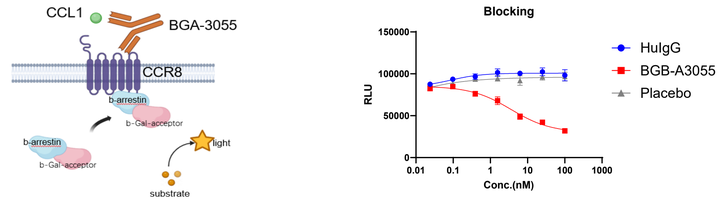
BGB-A3055 Strongly Binds to CCR8 Expressing Cells and Primary Tregs

Figure 2. The binding activity of BGB-A3055 was examined by FACS on 293T cells that overexpress hCCR8. BGB-A3055 exhibited a dose-dependent response with an EC50 of 4 nM. In addition, the binding activity of BGB-A3055 to primary Treg cells derived from human T was also examined by FACS. BGB-A3055 exhibited a dose-dependent binding with an average EC50 of 74.71 nM.



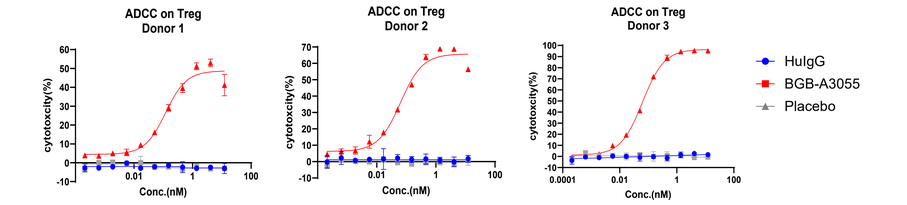
BGB-A3055 Potently Blocks CCL1-CCR8-Induced Signaling

Figure 3. CCR8 expressing cells were incubated with CCL1 in the presence of increasing concentrations of BGB-A3055, the signal was inhibited dose dependently with a IC50 of 2.41 nM.



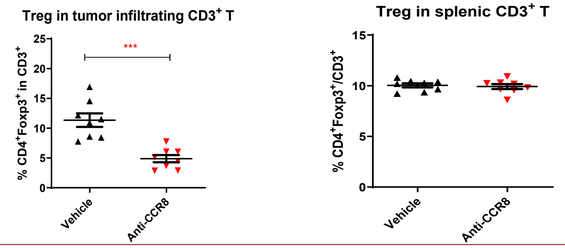
BGB-A3055 Induces Strong ADCC Against CCR8 Expressing Primary Tregs

Figure 4. CCR8-expressing primary Treg cells were co-cultured with NK92 cells for 24 hours in the presence of increasing concentrations of BGB-A3055. Treg cells were depleted during the incubation time served as a readout of the ADCC activity of BGB-A3055. The results showed BGB-A3055 induced potent ADCC activity against primary Treg cells with an average EC50 of 0.08 nM.



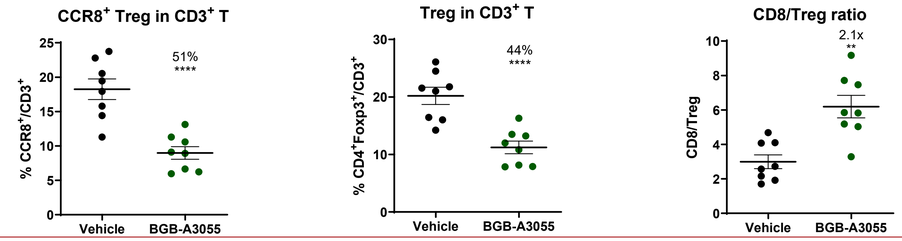
Anti-CCR8 Antibody Specifically Depletes Tumor Infiltrating Treg

Figure 5. CT26WT cells were implanted into BALB/c mice. The mice were treated once with vehicle or anti-mouse CCR8 surrogate antibody. Anti-CCR8 antibody treatment specifically depleted tumor infiltrating Treg, while spare splenic Treg.



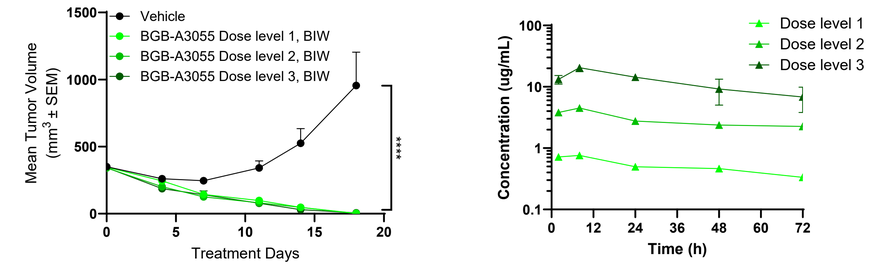
BGB-A3055 Shows Effective Intratumoral Treg Depletion Effect

Figure 6. MC-38 cells were implanted into hCCR8 knock-in mice. The mice were treated with single dose of BGB-A3055. 72 hours after treatment, tumor infiltrating lymphocytes (TILs) were isolated and immune cell population was measured. BGB-A3055 significantly depleted Treg and increased CD8/Treg ratio in TILs.



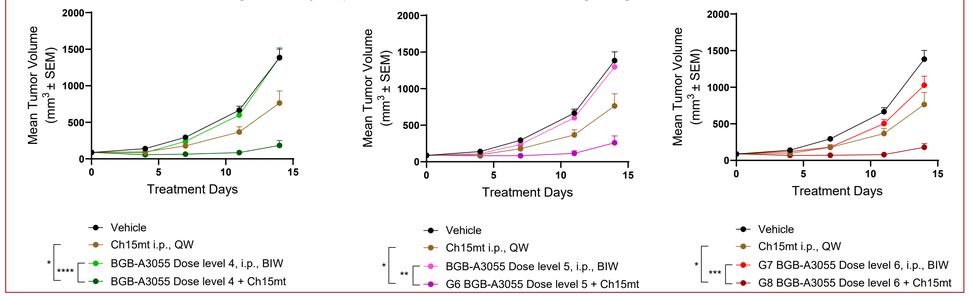
BGB-A3055 Exhibits Significant Anti-tumor Monotherapy Activity

Figure 7. GL261 were implanted into hCCR8 knock-in mice. The mice were treated with different doses level (DL) of BGB-A3055 twice weekly (DL3>DL2>DL1). BGB-A3055 effectively inhibited tumor growth in all three DL and demonstrated dose dependent PK property.



BGB-A3055 Enhances Anti-tumor Activity Combined with Anti-PD1

Figure 8. MC-38 cells are implanted into hCCR8 knock-in mice. The mice were treated with different doses level of BGB-A3055 (DL6>DL5>DL4), anti-mouse PD-1 antibody Ch15mt, or the combination of both. BGB-A3055 in combination with Ch15mt significantly improved anti-tumor effect of single-agent in the MC-38 model.



Conclusion

- BGB-A3055 is a fully humanized afucosylated antibody that has high binding affinity to hCCR8.
- BGB-A3055 strongly inhibited CCL1-CCR8 signaling and induced potent ADCC effect.
- Targeting CCR8 specifically depleted intratumoral Tregs while spare peripheral normal Tregs.
- 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).