491 GENERATION OF AN INNOVATIVE BISPECIFIC ANTIBODY TARGETING CCR8/CTLA4

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Background Regulatory T cells (Tregs) are indispensable for preventing autoimmunity and maintaining self-tolerance. In tumor settings, Tregs abundantly infiltrate into tumor tissues and suppress effective anti-tumor responses. Thus, specific removal of intra-tumor Tregs is highly desired in order to promote anti-tumor immunity without inducing severe adverse effects. CCR8 has recently been found to be predominantly expressed on intra-tumor Tregs but not on peripheral Tregs nor on activated Tconv. Anti-CCR8 antibody monotherapy has shown significant anti-tumor activity in pre-clinical studies. To specifically target intra-tumoral Tregs, we have developed a novel bispecific antibody (bsAb), GBD201, against CCR8/CTLA-4.

Methods Anti-CTLA-4 nanobody lead molecules were generated from alpaca and anti-CCR8 antibodies were generated from hybridoma. The bsAb, GBD201, has been assembled with high binding for CCR8 and fine-tuned for the potency of CTLA-4 inhibition. The Fc is afucosylated IgG1 to enhance ADCC. The in vivo efficacy and toxicity were determined in hCCR8/hCTLA-4 mice.

Results GBD201 has been generated after multiple rounds of lead screening and modifications of engineered tri-specific molecular structures. A unique partial blocker was selected for the CTLA-4 arm. The CCR8 arm was a full blocker and strong binder (which has BIC potential as mAb, compared to other anti-CCR8 mAbs in clinic). GBD201 was intentionally designed to lower its binding activity to CTLA-4 single positive cells (EC50 of 21nM) while maintaining its high binding to CCR8/CTLA-4 double positive cells (EC50 of 0.08 nM), which directs GBD201 to preferentially bind to $CCR8^{+}CTLA\text{-}4^{+}$ cells Tregs in tumor sites. GBD201 exhibited potent depletion of intra-tumor Tregs but spared peripheral Tregs and Tconv in tumor models of hCCR8/hCTLA-4 mice. In addition, GBD201 fully blocked CCL1/CCR8 interactions, but only partially blocked CTLA-4 binding to its ligands, which resulted in better tolerability compared with ipilimumab, shown by in vivo studies using hCCR8/hCTLA-4 mice. Furthermore, GBD201 exhibited significantly better in vivo anti-tumor efficacy compared to anti-CCR8 Abs or anti-CTLA4 mAbs including ipilimumab.

Conclusions GBD201, an anti-CCR8/CTLA-4 bsAb with FIC potential, exhibited potent anti-tumor activity in preclinical models. The bsAb has been fine tuned to reduce the peripheral toxicity associated with CTLA-4 blockade. GBD201 may present a novel immunotherapy approach to direct CTLA-4 inhibition or Treg depletion within the tumor microenvironment, and improve clinical benefits of other anti-cancer agents such as PD-1 inhibitors or ADCs in the treatment of cancers.

http://dx.doi.org/10.1136/jitc-2023-SITC2023.0491