BT7480, a synthetic Bicycle tumor-targeted immune cell agonist (Bicycle TICA®), induces reprogramming of the tumor immune microenvironment through tumor localized CD173 agonism

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Abstract
Bicycles are fully synthetic constrained peptides with antibody-like affinities and specificities, readily penetrate tumor tissue, have relatively short half-lives, and can be chemically linked together to make functional molecules. BT7480 is a first-in-class, Nectin-4/CD173 Bicycle tumor-targeted immune cell agonist® (Bicycle TICA®) designed to activate CD173 through co-igation of CD173 on immune cells and Nectin-4 on tumor cells. Nectin-4 is reported as highly expressed in wide range of solid tumors including bladder, pancreas, breast, ovary, esophagus, head and neck, stomach, and lung cancers (1, 2). Nectin-4 and CD173 are co-expressed in many of these tumor types (3, 4) and thus may benefit from Nectin-4 targeted CD173 agonism.

We used a suite of in vitro and in vivo assays to characterize BT7480 pharmacology and mechanism of action. These include primary human peripheral blood mononuclear cell (PBMC)/tumor cell co-culture assays and efficacy and transcriptional profiling studies in a syngeneic mouse tumor model.

BT7480 elicited potent Nectin-4-dependent CD173 agonist activity in vitro as measured by increase in interferon gamma and interleukin-2 production from stimulated PBMCs in Nectin-4 dependent manner. Treatment of immunocompetent mouse bearing Nectin-4 expressing tumors with BT7480 led to a wide reprogramming of the immune microenvironment including an early increase in several T-cell chemotactic cytokines that we demonstrated that BT7480 anti-tumor activity with complete tumor regressions was not dependent on continuous circulating drug levels but that plasma drug exposure for approximately two days per weekly cycle was sufficient for optimal anti-tumor activity. In rat and non-human primate safety studies BT7480 appears well tolerated at doses that are far greater than those we believe to be clinically relevant.

Results

BT7480 binds potently and specifically to both tumor and immune cell targets and elicits potent Nectin-4-dependent CD173 agonist activity in vitro

Figure 1: (A) Human PBMCs were pre-stimulated with anti-CD3 and treated for 1 hour with vehicle or BT7480. Unbound and total CD173 receptors were detected by flow cytometry using an AlexaFlur 488-labeled CD173 Bicycle dye (BCY15410) and a non-competitive CD173 antibody, respectively. (B) HT1376 and T-420 cells were treated with BT7480 or a non-Nectin-4 binding analog of BT7480 (BCY13144) for 1 hour. BT74880 induced cell clustering and activation of a competitive Nectin-4 antibody. CD173 and Nectin-4 receptor occupancy was carried out as shown. (C) Human PBMCs were stimulated with anti-CD3 and co-cultured with HT-1376 cells and treated with BT7480. BCY12759 (non-binding/BCY, or anti-CD173 antibody agonist) and IFNγ and IL-2 in the cell supernatants were measured after 48 hours. Gray bars indicate untreated control levels. Data were fit using log(agonist) versus response (three parameter) or log(agonist) versus response–variable slope (four parameter). (D) Simulated plasma concentration profiles for 1 and 10 mg/kg BT7480 administered Q2D. (E) BT7480 was maintained at or above the average EC50 required to induce FcγR and t-2 secretion in PBMCs (1.18 nM) for approximately 1 day of the Q3D dosing cycle. (F) LOQ of BT7480 detected in plasma using a competitive Nectin-4 antibody. Nectin-4 and CD173 receptor occupancy was carried out as shown. (G) Mouse T cells were stimulated with anti-CD3 and co-cultured with MC38 cells and treated with BT7480. BCY12759 (non-binding/BCY), or anti-CD173 antibody agonist and IFNγ and L-2 in the cell supernatants were measured after 48 hours. Gray bars indicate untreated control levels. Data were fit using log(agonist) versus response (three parameter) or log(agonist) versus response–variable slope (four parameter).

BT7480 leads to CD8+ cell infiltration into tumor tissue

Figure 2: (A) Simulated predicted potential target coverage in human with a weekly (BIW) dosing regimen of 0.3 mg/kg in mice that with 0h and 24h dosing at 5 mg/kg in mice. (B) Simulated tumor cell occupancy profile of BT7480 dosed at 5 mg/kg at 0h and 24h in mice overlayed with the MC38-Nectin-4 tumor growth in hucD137-C786/mice treated with vehicle or GW dosing of BT7480 at 0h and 24h.

Conclusions
We have demonstrated that BT7480 is potent, specific, effective, and well tolerated in preclinical species and are therefore uniquely positioned to test the hypothesis that intermittent CD173 agonism may benefit cancer patients. BT7480 entered first-in-human clinical trial at the end of 2021 (NCT05163041).

References