A Combined Phase I/II Study of a Novel *Bicycle* Tumor-targeted Immune Cell Agonist® BT7480 in Patients with Nectin-4 Associated Advanced Malignancies

ABSTRACT# TPS2689

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BACKGROUND

- BT7480 is a novel, first-in-class, Nectin-4/CD137 *Bicycle* tumor-targeted immune cell agonist® (*Bicycle* TICA™) that activates CD137 through CD137 and Nectin-4 co-ligation
- Nectin-4 is overexpressed in urothelial, pancreatic, breast, ovarian, esophageal, head and neck, gastric and lung cancers[1-4], among others
- Nectin-4 and CD137 are co-expressed in a variety of human tumors[5,6]
- BT7480 is designed to have rapid tumor penetration and a short terminal half-life
- BT7480 exhibited a favorable preclinical profile supporting the initiation of a FIH study to investigate safety and efficacy in indications associated with Nectin-4 expression

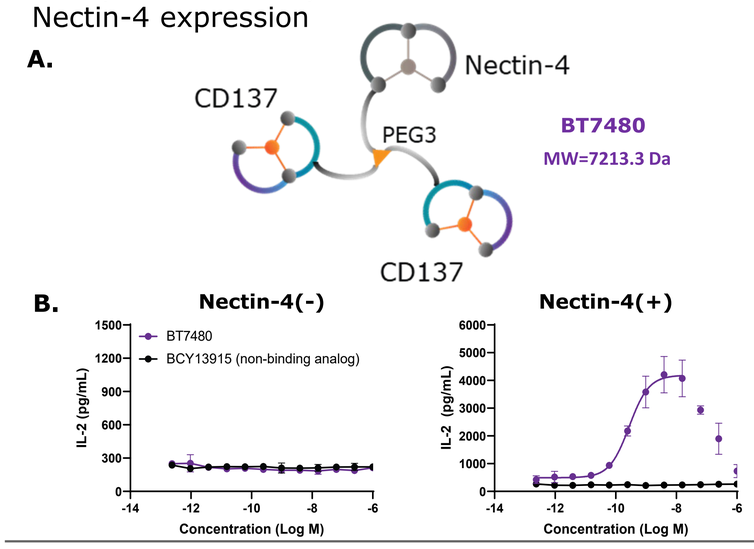


Figure 1. BT7480 is a novel, fully synthetic, Nectin-4-dependent *Bicycle* tumor-targeted immune cell agonist® (*Bicycle* TICA™). A) BT7480 is a heterotrimeric conjugate comprised of 1 Nectin-4 and 2 CD137 binding *Bicycles*. **B)** BT7480 led to potent activity (increased IL-2 production) in an *in vitro* model system that co-cultured primary peripheral blood mononuclear cells (PBMCs) with human tumor cells that express Nectin-4 (right panel). BT7480 did not induce IL-2 production when PBMCs were co-cultured with tumor cells that did not express Nectin-4 (left panel). A non-binding analogue of BT7480 was not active in the assay (black curves).

ENROLLMENT CRITERIA

- Solid tumors associated with Nectin-4 expression (including urothelial, NSCLC, ovarian, breast, gastric, HNSCC, or esophageal)
- Fresh or archival tumor tissue
- Acceptable hematologic and organ function
- Exclusion criteria include uncontrolled brain metastasis, uncontrolled hypertension, autoimmune disease, or prior CD137 targeted therapy

OBJECTIVES

Primary

Phase 1
- Safety and tolerability of BT7480 as monotherapy and in combination or in patients with renal insufficiency

Phase 2
- Clinical activity of BT7480 as monotherapy and in combination

Secondary

Phase 1
- Clinical activity of BT7480 as monotherapy and in combination or in patients with renal insufficiency

Phase 2
- Safety and tolerability of BT7480 as monotherapy and in combination

Phase 1 and Phase 2
- Assess additional measures of antitumor efficacy
- PK parameters of BT7480 as monotherapy and in combination or in patients with renal insufficiency
- Incidence of anti-drug antibody development
- CD137 target engagement in peripheral blood

First-in-Human Study with a *Bicycle* Tumor-targeted Immune Cell Agonist® targeting Nectin-4 and CD137

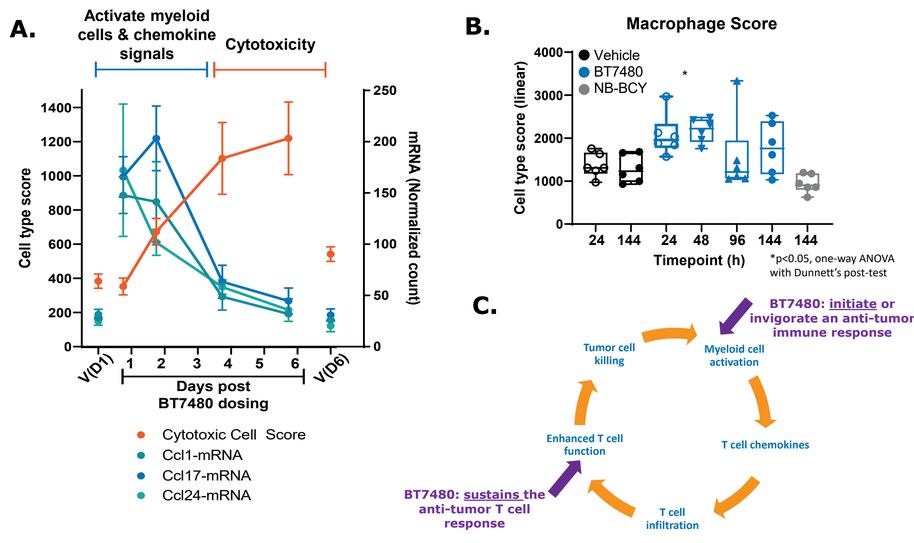
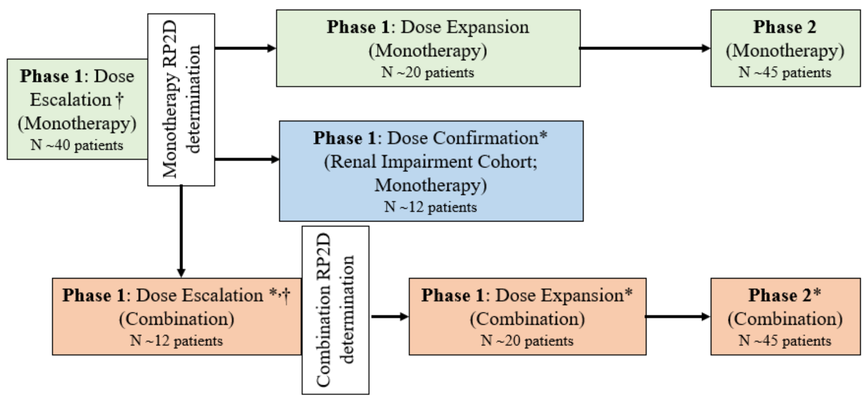


Figure 2. BT7480 treatment led to significant immunomodulation in tumor tissue, including an early activation of myeloid cells that preceded the activation of cytotoxic cells. A) MC38-Nectin-4 tumor bearing mice (huCD137-C57Bl/6) were treated with vehicle or 5 mg/kg BT7480 iv at 0h and 24h. Tumors were harvested at 24, 48, 96, or 144h as indicated, and processed for transcriptional analysis by NanoString. The cytotoxic cell score (left y-axis) and Ccl1, Ccl17, and Ccl24 mRNA counts (right y-axis) were overlaid over the course of the study (days post dosing). **B)** Macrophage cell score in response to BT7480 or a non-binding control (NB-BCY) in MC38-Nectin-4 bearing mice. **C)** In the cancer immunity cycle, BT7480 likely acts to both initiate as well as sustain the anti-tumor immune response.

STUDY DESIGN

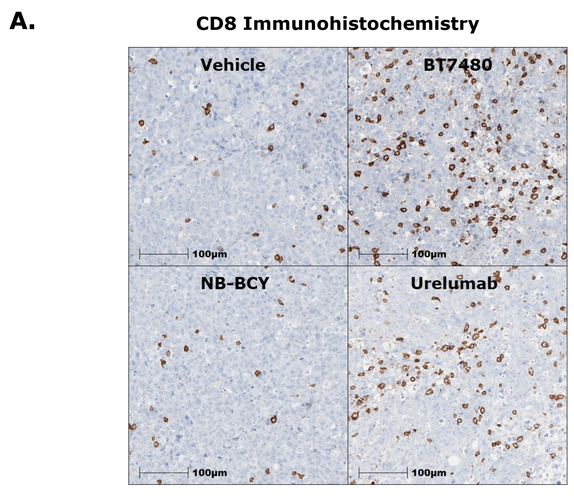
- Open-label dose escalation, dose confirmation, and dose expansion study of BT7480 given as a single agent or in combination with a checkpoint inhibitor
- Up to 200 patients are expected to be enrolled in approximately 20 sites globally
- Study initiated in BT7480 monotherapy dose escalation with accelerated single-subject cohorts followed by 3+3 design
- Following monotherapy RP2D, study parts include:
  - Phase 1 optional combination dose escalation
  - Phase 1 optional dose confirmation in patients with renal insufficiency
  - Phase 1 and Phase 2 BT7480 monotherapy and optional combination dose expansions
- BT7480 is administered as an intravenous infusion QW in a 28-day cycle
- Tumor response assessed per RECIST every 8 weeks



*** indicates optional cohorts; † indicates optional backfill**

- **Monotherapy dose escalation is ongoing**

BACKGROUND



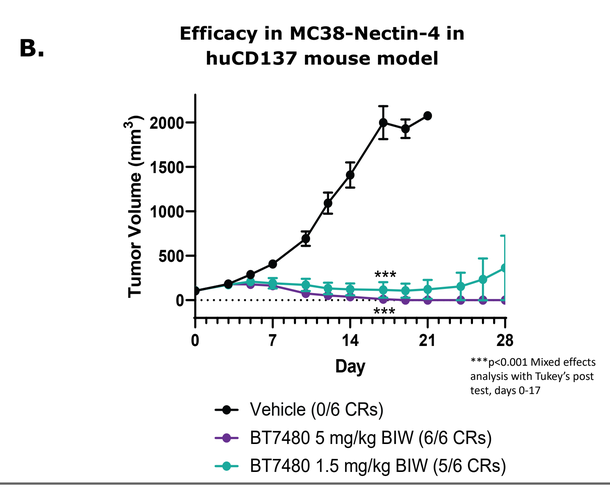
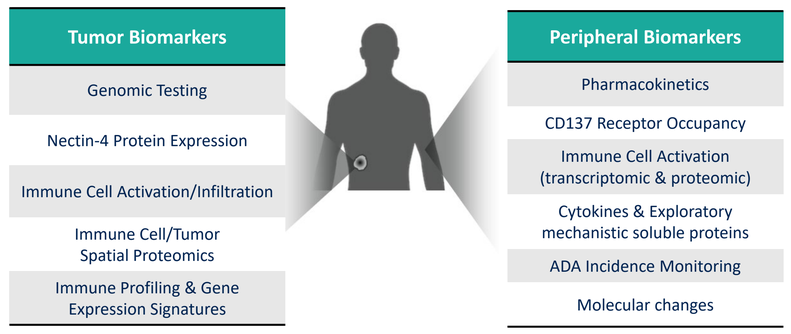


Figure 3: BT7480 treatment led to increased T cell infiltration and robust antitumor activity in a syngeneic mouse model. A) Representative images of tissue sections harvested at 144h from MC38-Nectin-4 tumor bearing mice and stained for CD8. NB-BCY is a CD137 non-binding analogue of BT7480. T cell infiltration in response to the CD137 monoclonal antibody agonist, urelumab, is shown for comparison. **B)** BT7480 led to significant anti-tumor activity including complete responses (CRs) in 11/12 MC38-Nectin-4 tumor bearing mice dosed twice a week (BIW).

STUDY DESIGN

Robust biomarker plan to monitor BT7480 activity



- Tumor biomarkers collected at baseline for retrospective assessment of Nectin-4 and CD137 expression in patients treated with BT7480
- Peripheral biomarkers collected pre- and post-dose to assess PK, CD137 target engagement and immune cell PD profiling to support safety monitoring, study objectives and RP2D

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