Phase 1/2 study of the safety, pharmacokinetics, and preliminary clinical activity of BT7480 in patients with Nectin-4 associated advanced malignancies

Abstract #CT253

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BACKGROUND

- *Bicycles* are a novel class of chemically synthesized molecules
- BT7480 is a first-in-class *Bicycle* tumor-targeted immune cell agonist® (*Bicycle* TICA™)[1]
  - Trimer composed of one *Bicycle* that binds to Nectin-4 and two identical *Bicycles* that bind and agonize CD137
  - Stimulates an anti-tumor immune response in the presence of both Nectin-4-expressing tumor cells as well as CD137-expressing immune cells
- Nectin-4 is highly expressed in many solid tumors including urothelial, NSCLC, gastric/esophageal, ovarian, breast, and head and neck cancers[2-6]; overexpression is a marker for poor prognosis
- CD137 is a costimulatory receptor expressed on immune cells
- Co-ligation of Nectin-4 and CD137 by BT7480 is hypothesized to induce oligomerization and activation of CD137, resulting in a tumor-localized costimulatory signal leading to anti-tumor immunity

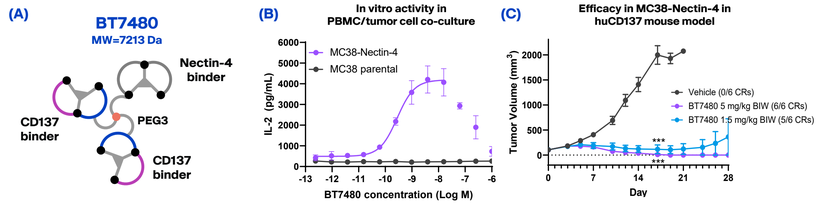

Figure 1. BT7480 is a novel, fully synthetic, Nectin-4-dependent *Bicycle* TICA™. **A)** BT7480 is a heterotrimeric conjugate comprised of 1 Nectin-4 and 2 identical CD137 binding *Bicycles*. **B)** BT7480 led to potent activity (increased IL-2 production) in an in vitro model system that co-cultured primary peripheral blood mononuclear cells (PBMCs) with human tumor cells that express Nectin-4 (purple). BT7480 did not induce IL-2 production when PBMCs were co-cultured with tumor cells that did not express Nectin-4 (black). **C)** BT7480 led to significant anti-tumor activity including complete responses in 11/12 MC38-Nectin-4 tumor bearing mice dosed twice a week. ***p<0.001 mixed effects analysis with Tukey's post test, days 0-17.

KEY ELIGIBILITY CRITERIA

Inclusion

- Advanced malignancy associated with Nectin-4 expression ineligible for standard therapy
- Fresh or archival tumor tissue
- ≥18 years of age
- ECOG PS of 0 or 1
- Adequate organ function
  - eGFR 30-59 mL/min by the CKD-EPI equation in the optional renal impairment cohorts

Exclusion

- Prior CD137-targeted therapy
- History of autoimmune disease
- Uncontrolled:
  - Symptomatic brain metastases
  - Diabetes
  - Hypertension

REFERENCES

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STUDY DESIGN

PHASE 1

Dose Escalation: Monotherapy†
N ~80 patients

Monotherapy RP2D determination

Dose Confirmation: Monotherapy
Renal Cohort*
N ~12 patients

Dose Escalation: Combination with nivolumab*†
N ~12 patients

Combination RP2D determination

Primary: Safety and tolerability of BT7480 as monotherapy and in combination, or in patients with renal insufficiency

Secondary: Clinical activity of BT7480 as monotherapy and in combination, or in patients with renal insufficiency

† indicates optional backfill; * indicates optional cohorts. Note: Combination therapy will occur after a RP2D for monotherapy has been identified.

PHASE 2

Monotherapy
N ~45 patients

Combination with nivolumab
N ~45 patients

Primary: Clinical activity of BT7480 as monotherapy and in combination
Secondary: Safety and tolerability of BT7480 as monotherapy and in combination

Figure 2. Study schema.

Phase 1+2 Objectives

Secondary:

- 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

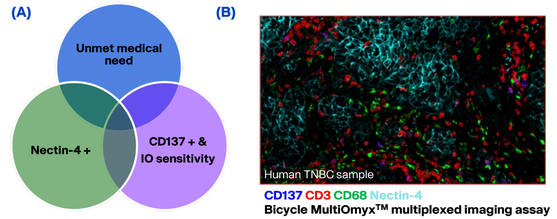
Exploratory:

Evaluate biomarkers in blood and tumors associated with pharmacological activity, including signals of immune activations, target expression, ctDNA and pharmacogenomics

- Monotherapy: Patients are treated with weekly 60-min IV infusions of BT7480 in 28-day cycles
  - Starting dose of 0.002 mg/kg, escalating up to a maximum of 7.5 mg/kg
- Combination: BT7480 will be given at the RP2D in combination with nivolumab 240 mg administered as a 30-min IV infusion once every 2 weeks
- Disease assessments per RECIST v1.1 performed every 8 weeks for the first year, every 12 weeks thereafter

TUMOR TYPE SELECTION AND BIOMARKER STRATEGY

Bicycle Translational Infrastructure & Informatics Pipeline → **Tumor Selection**



(C)
Top tumor types most likely to benefit include:
Breast
Urothelial
Head & Neck Squamous Cell
Ovarian
Non-Small Cell Lung
Esophageal
Gastric

Figure 3. Tumor type selection strategy. **A)** Tumor types most likely to benefit include high unmet need indications associated with a high prevalence of Nectin-4 expression and sensitivity to IO. **B)** A custom multiplexed imaging assay was developed to evaluate Nectin-4 and CD137 protein expression and immune infiltrate within human tumors. Multiple samples and indications tested preclinically; representative image shown from TNBC.[1,6] **C)** Top tumor types most likely to benefit from BT7480 treatment were identified using forward and reverse translational analyses.

Tumor Biomarkers	Peripheral Biomarkers
Nectin-4 protein expression	CD137 receptor occupancy
CD137 protein expression & immune infiltration	T/NK/Myeloid cell activation (transcriptomic & proteomic)
Immune cell/tumor spatial proteomics	Cytokines & soluble mechanistic proteins
Immune activation profiling & gene expression signatures	ADA incidence monitoring
	Molecular changes/ctDNA

Figure 4. Biomarker strategy. Tumor tissue (archival or fresh) submitted at baseline is used for retrospective assessment of Nectin-4 and CD137 expression and immune infiltrate. Optional on-treatment biopsy collections are used to monitor pharmacodynamic changes at the primary site of action (Left panel). Peripheral biomarker samples are collected pre- and post-dose to evaluate biomarkers in blood associated with pharmacological activity (Right panel).

SUMMARY

- BT7480 is a *Bicycle* TICA™ targeting Nectin-4 and CD137
- This phase 1/2 study is evaluating the safety, pharmacokinetics, and preliminary clinical activity of BT7480 in patients with Nectin-4 associated advanced malignancies (NCT05163041)
- This study is actively recruiting

ACKNOWLEDGMENTS

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- For additional information please contact Jeff Evans at J.Evans@beatson.gla.ac.uk