BT8009-100 Phase I/II Study of the Safety, Pharmacokinetics, & Preliminary Clinical Activity of BT8009 in Patients with Nectin-4 Expressing Advanced Malignancies

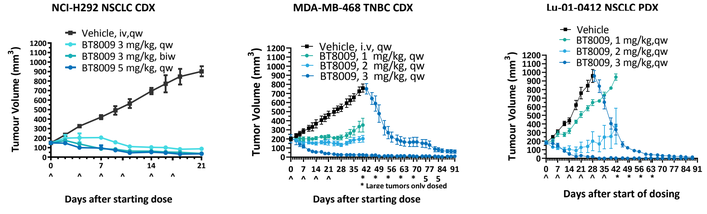
Meredith A. McKean, MD, MPH[1,2]; Johanna C. Bendell, MD[1,2]; Daniel P. Petrylak, MD[3]; Thomas Powles, MD[4]; Guru Sonpavde, MD[5]; Amy Dickson[6]; Lola Dosunmu, MD, MPH, MLA[7]; Meliessa G. Hennessy[6]; Phil Jeffrey[8]; Michael Rigby[8]; Shawn Watson[6]; Terrence West[6]; Geoffrey Shapiro, MD, PhD[5,9]

[1]Sarah Cannon Research Institute, Nashville, TN, USA; [2]Tennessee Oncology, PLLC, Nashville, TN, USA; [3]Yale Cancer Center, New Haven, CT, USA; [4]Barts Cancer Institute, London, UK; [5]Dana Farber Cancer Institute, Boston, MA, USA, [6]Bicycle Therapeutics, Lexington, MA, USA, [7]Sarah Cannon Development Innovations, Nashville, TN, USA; [8]Bicycle Therapeutics, Cambridge, UK; [9]Brigham and Women's Hospital and Harvard Medical School, Boston, MA

Background:

- BT8009 is a *Bicycle*® Toxin Conjugate (BTC) in which a Nectin-4 binding *Bicycle* (bicyclic peptide) is conjugated through an inert sarcosine spacer chain and a cleavable linker to the antimitotic toxin MMAE.
- Nectin-4 is expressed in bladder, NSCLC, esophageal, pancreatic, ovarian and breast cancers[1-4].
- Overexpression of Nectin-4 in tumor tissue is a marker for poor prognosis[1-4].
- BT8009 is designed to have rapid tumor penetration, release and prolonged retention of MMAE in tumor and short terminal plasma half-life to reduce exposure to tissues outside of tumor.
- BT8009 exhibited a satisfactory preclinical profile supporting the initiation of a FIH study to investigate safety and efficacy in indications with evidence of Nectin-4 expression.

BT8009 in Xenograft Tumor Models



Enrollment Criteria:

Part A (Dose Escalation) Specific Inclusion Criteria

- Urothelial carcinoma naïve to Nectin-4-directed therapies; or confirmed Nectin-4 expression on fresh biopsy or archived tissue (<12 months) without intervening anti-cancer therapies or solid tumors known to frequently express Nectin-4 (pancreatic, TNBC, NSCLC, gastric, esophageal or ovarian.)

Part B Patients

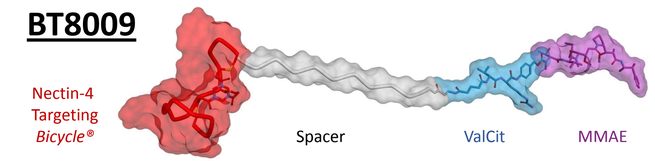
- Confirmed Nectin-4 expression on fresh biopsy or archived tissue (< 12 months) without intervening anti-cancer therapies

Part C Patients

- Renal insufficiency

First-in-Human Study with a *Bicycle*® Toxin Conjugate targeting Nectin-4 with an MMAE cytotoxic payload. Patient enrollment ongoing.

BT8009



Primary objectives

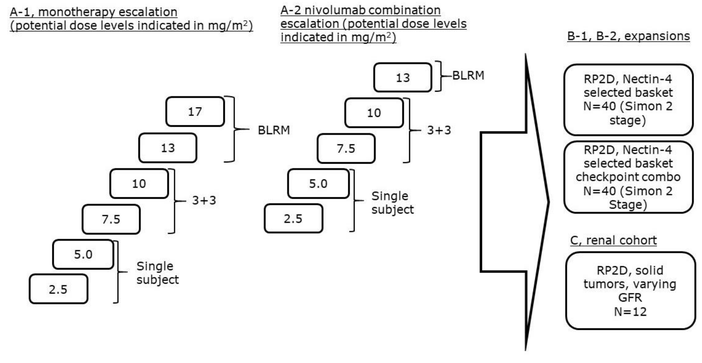
- Dose escalation
  - -Safety and tolerability of BT8009 as monotherapy and in combination with nivolumab or in patients having renal insufficiency.
  - -MTD and RP2D of BT8009 as monotherapy and in combination with nivolumab
- Dose expansion
  - -Clinical activity of BT8009 as monotherapy and in combination with nivolumab

Secondary objectives

- **Dose escalation**
  - -Preliminary signals of activity of BT8009 as monotherapy and in combination with nivolumab or in patients having renal insufficiency.
  - -PK parameters of BT8009 and MMAE
  - -Incidence of anti-drug antibody (ADA) development
- Dose expansion
  - -Safety and tolerability of BT8009 as monotherapy and in combination with nivolumab
  - -PK parameters of BT8009 and MMAE
  - -Incidence of ADA development

Study Design

- Phase I/II, first-in-human, open-label dose-escalation study of BT8009 given as a single agent or in combination with nivolumab.
- Up to 146 patients (up to 66 in Phase I and 80 in Phase II) are expected to be enrolled in this study in approximately 20 sites globally.
- Three parts to this study:
  - -Phase I: dose escalation
    - Part A-1: BT8009 monotherapy dose escalation (34 patients)
    - Part A-2: BT8009 plus nivolumab dose escalation (20 patients)
  - -Phase II: dose expansion
    - Part B-1: BT8009 monotherapy dose expansion (40 patients)
    - Part B-2: BT8009 plus nivolumab dose expansion (40 patients)
  - -Phase I: patients with renal insufficiency (12 patients)



References

1. Nishiwada, S, Sho M, Yasuda S, et al. (2015). J Exp Clin Cancer Res 34: 30.
2. M-Rabet M, Cabaud O, Josselin E, et al. (2017). Ann Oncol 28(4): 769-776.
3. Zhang Y, Zhang J, Shen Q, et al. (2018). Oncol Lett 15(6): 8789-879
4. Deng H., Shi H, Chen L, et al. (2019). Cancer Cell Int 19: 106.

ESMO Abstract Number: 3716

For additional information, please contact Dr. McKean at mmckean@tnonc.com

Dr. McKean declares the following conflicts of interest-institutional funding from ArrayBioPharma, Ascentage Pharma Group, Bicycle Therapeutics, Epizyme, Exelixis, Genentech, GlaxoSmithKline, IDEAYA Biosciences, Ikena Oncology, Jacobio Pharmaceuticals, MedPage Today, Moderna, Oncorus, Prelude Therapeutics, Regeneron Pharmaceuticals, Tizona Therapeutics, TopAlliance Biosciences