Initial results from a Phase 1/2 study of BT7480, a novel Nectin-4/CD137 Bicycle tumor-targeted immune cell agonist®, in patients with advanced solid tumors

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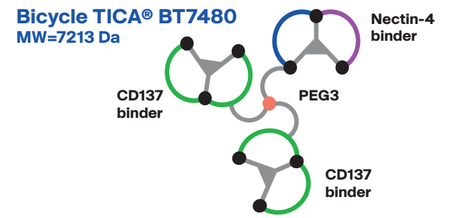
Kyriakos P. Papadopoulos[1], Afshin Dowlati[2], Juanita Lopez[3], Jordi Rodón[4], Alexander Spira[5], Mark Stein[6], Matthew Zibelman[7], Waldo Ortuzar Feliu[8], Amy Dickson[9], Ananya De[10], Xuemin Gu[11], Heather Cohen[12], Mengyao Li[13], Justin Bader[13], Cara Bray[12], Sean Santos[12], Jeffrey Smith[12], Roger Lis[14], Thomas Jeffry Evans[15]

[1]Clinical Research Department, START San Antonio, San Antonio, TX, USA; [2]Oncology Department, University Hospitals of Cleveland Medical Center, Cleveland, OH, USA; [3]Drug Development Unit, Royal Marsden NHS Foundation Trust, Sutton, UK; [4]Drug Development Department, MD Anderson Cancer Center, Houston, TX, USA; [5]Research Department, Virginia Cancer Specialists Research Institute, Fairfax, VA, USA; [6]Irving Medical Center, Columbia University, New York, NY, USA; [7]Temple Health, Fox Chase Cancer Center, Philadelphia, PA, USA; [8]Clinical Development, Bicycle Therapeutics, Cambridge, MA, USA; [9]Medical Affairs, Bicycle Therapeutics, Cambridge, MA, USA; [10]Clinical Science, Bicycle Therapeutics, Cambridge, MA, USA; [11]Biostatistics, Bicycle Therapeutics, Cambridge, MA, USA; [12]Translational Sciences, Bicycle Therapeutics, Cambridge, MA, USA; [13]Quantitative Pharmacology, Bicycle Therapeutics, Cambridge, MA, USA; [14]Clinical Operations, Bicycle Therapeutics, Cambridge, MA, USA; [15]Institute of Cancer Sciences, University of Glasgow, Glasgow, UK

INTRODUCTION

- Bicycle® molecules are an innovative therapeutic class in development that offers the manufacturing and pharmacokinetic (PK) properties of a small molecule with the high binding specificity of a biologic,[1-3] making them ideally suited for the targeted delivery of a range of payloads such as cytotoxins to solid tumors
- The Bicycle® molecule BT7480 is a novel, synthetic Bicycle tumor-targeted immune cell agonist® (Bicycle TICA®) comprising three bicyclic peptides, one targeting Nectin-4 and two targeting CD137, conjugated by a three-arm branched trimeric polyethylene glycol (PEG3) linker **(Figure 1)**[4,5]
  - Nectin-4 is overexpressed in many cancers including lung, breast, esophageal, and head and neck cancers, and urothelial carcinoma[6–9]
  - CD137 is a member of the tumor necrosis factor (TNF) receptor superfamily; on ligation, CD137 provides costimulatory signals for immune cells, such as T cell proliferation, anti-apoptosis, cytokine secretion, chromatin remodeling, and mitochondrial fitness; it is expressed on activated immune cells, with high expression in tumors[10–13]
  - Nectin-4 and CD137 coligation by BT7480 is hypothesized to cause tumor-localized CD137 agonism (based on preclinical findings)[4]
- Presented here are the results of the monotherapy dose escalation part of the Phase 1/2 study (NCT05163041) of BT7480 ± nivolumab in patients with advanced solid tumors associated with Nectin-4 expression

FIGURE 1. BT7480 STRUCTURE



METHODS

- Adults with advanced solid tumors associated with Nectin-4 expression and refractory to/ineligible for standard therapy were included in this open-label study; patients with prior CD137 targeted therapy were excluded
- BT7480 was administered as an IV infusion, starting at 0.002 mg/kg QW; patients were enrolled sequentially to increasing doses, with a 3 + 3 design, to 3.5 mg/kg QW
- The primary endpoint was incidence and severity of treatment-emergent AEs (TEAEs; per NCI CTCAE v5.0); secondary endpoints included antitumor activity (per RECIST v1.1) based on investigator assessment, PK, and CD137 target engagement in peripheral blood
- Additional biomarker analyses were exploratory endpoints

RESULTS

Patient demographics and clinical characteristics

- As of 12 February 2024, 39 patients had received BT7480 (0.002–3.5 mg/kg QW IV), with a median age of 62 years **(Table 1)**
- NSCLC was the most common tumor type (n=11; 28%) of which all patients with available IHC data (n=8) were Nectin-4+

TABLE 1. BASELINE PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Characteristic	All patients (N=39)
Median age, years (range)	62 (29–83)
Sex, n (%)	
Female	24 (62)
Male	15 (38)
Race, n (%)	
White	32 (82)
Black or African American	5 (13)
Other	2 (5)
ECOG PS, n (%)	
0	12 (31)
1	27 (69)
Median prior lines of therapy (range)	4 (1–9)
Target expression, n (%)	
Nectin-4+	26 (77)[a]
Nectin-4+ CD137+	19 (63)[b]

[a]Of 34 IHC evaluable patients, positivity ≥1 TPS. [b]Of 30 mIF evaluable patients, positivity ≥1%.

Safety

- Any grade treatment-related AEs (TRAEs) occurred in 49% of patients, the most common being fatigue (23%) and headache (10%) **(Table 2)**
  - None of the patients receiving BT7480 3.5 mg/kg (n=4) experienced these TRAEs; TRAEs were only reported in one patient (25%) in this group
- A low rate of Grade ≥3 TRAEs (5%) and of TRSAEs (8%) were reported **(Table 2)**, with none among patients receiving BT7480 3.5 mg/kg
- Two patients experienced a DLT (0.6 mg/kg: mucosal inflammation; 2.6 mg/kg: increased ALT/AST)
- The maximum tolerated dose has not yet been reached

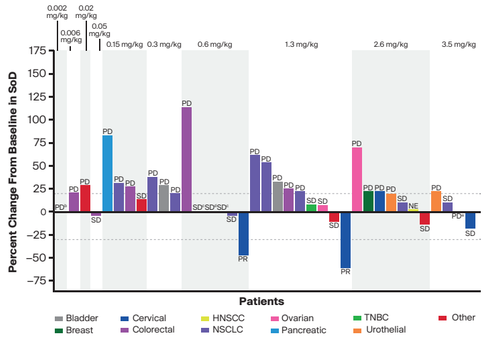
Efficacy

- Best overall response of SD was reported in 13 patients, and there were two unconfirmed PRs, both in patients with cervical cancer **(Table 3)**
- Among patients with NSCLC, five patients (45%) reported a best overall response of SD **(Figure 2)**
- SD was prolonged (>8 months) for three patients **(Figure 3)**, two treated with 0.6 mg/kg (NSCLC) and one treated with 1.3 mg/kg (anal squamous cell carcinoma)

TABLE 2. SAFETY SUMMARY FOR BT7480

Category, n (%)	All patients (N=39)	Patients (3.5 mg/kg; n=4)
TEAEs	38 (97)	4 (100)
TRAEs	19 (49)	1 (25)
TEAEs Grade ≥3	16 (41)	2 (50)
TRAEs Grade ≥3	2 (5)	0
SAEs	14 (36)	2 (50)
TRSAEs	3 (8)	0
DLTs	2 (5)	0
TEAEs leading to dose interruption	8 (21)	1 (25)
TEAEs leading to dose reduction	0	0
TEAEs leading to dose discontinuation	2 (5)	0
TRAEs reported in ≥5% of patients in either group, n (%)		
Fatigue	9 (23)	0
Headache	4 (10)	0
Arthralgia	3 (8)	0
Decreased appetite	3 (8)	0
Lethargy	3 (8)	0
Nausea	3 (8)	0
Amylase increased	2 (5)	0
Anemia	2 (5)	0
Blood alkaline phosphatase increased	2 (5)	0
Hypomagnesemia	1 (3)	1 (25)
Urinary tract infection	1 (3)	1 (25)

FIGURE 2: MAXIMUM PERCENT REDUCTION FROM BASELINE IN TARGET LESION[a]



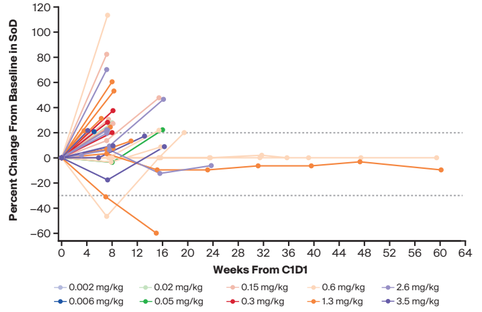
[a]Unconfirmed best overall response; only patients with at least one postbaseline assessment are represented. NE indicates patient was not evaluable for best overall response. [b]Other. [c]NSCLC. [d]HNSCC. [e]Urothelial.

TABLE 3. BEST OVERALL RESPONSE

Best overall response, n (%)	All patients (N=40[a])
CR	0 (0)
PR	2 (5)[b]
SD[c]	13 (33)
PD	20 (50)
NE	5 (13)
ORR (CR+PR)	2 (5)
CBR (CR+PR+SD [≥ 8 weeks])	15 (38)

[a]Data cleaning efforts identified one additional unconfirmed partial response from the 12 February 2024 data cut, which was rectified as of a data cutoff date of 15 April 2024, with one additional patient enrolled as of this date. [b]Unconfirmed. [c]For ≥6 weeks from the start of study drug to assessment date.

FIGURE 3. PERCENT CHANGE FROM BASELINE IN TUMOR SIZE OVER TIME[a]



[a]Only patients with at least one postbaseline assessment are represented.

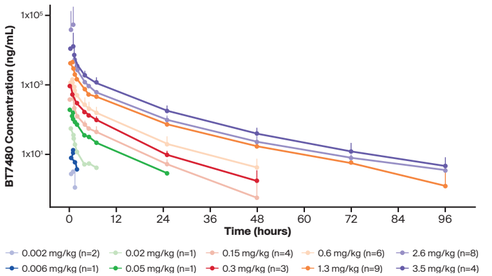
Pharmacokinetics/Pharmacodynamics

- Approximately dose proportional PK was observed across the tested dose range at C1D1 **(Figure 4)**
- Terminal half-life at 1.3–3.5 mg/kg was approximately 13–16 hours, with minimal BT7480 accumulation at steady state (C1D15) following QW dosing

CONCLUSIONS

- BT7480 was generally well tolerated and showed preliminary antitumor activity in patients with advanced Nectin-4–associated solid tumors
- BT7480 exhibited dose-dependent increase in PK with minimal accumulation at steady-state with a QW regimen
- Preliminary biomarker analyses support BT7480 dual targeting of CD137 and Nectin-4 as demonstrated by enhanced immune cell activation, aligned with the proposed mechanism of action of BT7480
- This study remains ongoing, with additional cohorts planned to investigate BT7480 in combination with nivolumab

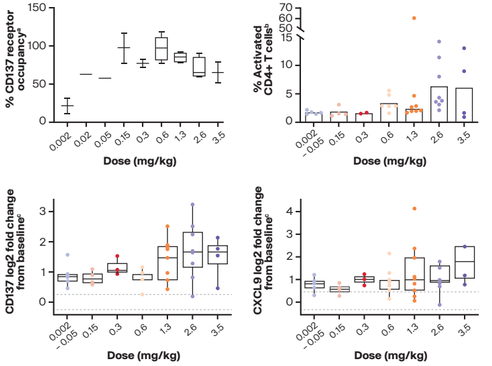
FIGURE 4: BT7480 PLASMA CONCENTRATION OVER TIME BY DOSE AT C1D1[a]



[a]Data presented as mean ± standard deviation.

- Preliminary biomarker analyses showed target saturation in peripheral blood at doses ≥0.15 mg/kg **(Figure 5)**
- Maximum induction of circulating immune activation markers (soluble CD137, CXCL9, and CD4+ T cells) was observed at doses ≥1.3 mg/kg with no hook effect at higher doses **(Figure 5)**

FIGURE 5: BT7480 DEMONSTRATES TARGET ENGAGEMENT AND INDUCTION OF IMMUNE ACTIVATION SIGNALS IN PATIENT BLOOD



[a]Measured at C1D1, 20 minutes post-end of infusion, divided by the baseline value. [b]Maximum value reported, through C2. [c]Maximum value reported through C2D15. Each dot represents one patient; bars and horizontal lines represent the median; whiskers show the maximum and minimum values. Dashed lines = 1 standard deviation from baseline.

ABBREVIATIONS

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CBR, clinical benefit rate; CR, complete response; C, cycle; D, day; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; HNSCC, head and neck squamous cell carcinoma; IHC, immunohistochemistry; IV, intravenous; mIF, multiplex immunofluorescence; MW, molecular weight; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; NSCLC, non-small cell lung cancer; NE, not evaluable; ORR, objective response rate; PD, progressive disease; PEG3, trimeric polyethylene glycol; PK, pharmacokinetics; PR, partial response; QW, weekly; RECIST, Response Evaluation Criteria in Solid Tumors; SAE, serious AE; SD, stable disease; SoD, sum of diameters; TEAE, treatment-emergent AE; TICA, tumor-targeted immune cell agonist; TPS, Tumor Proportion Score; TRAE, treatment-related AE; TRSAE, treatment-related SAE.

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Presenting author:
Kyriakos P. Papadopoulos
kyri.papadopoulos@startsa.com

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