EphA2-targeting Bicycle® Toxin Conjugate BT5528 in patients with advanced solid tumors: A Phase 1/2 study

647P

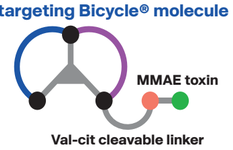
Elisa Fontana[1], Judy S. Wang[2], Meredith McKean[3], Raid Aljumaily[4], Jean-Pascal Machiels[5], Bernard Doger de Spéville[6], Maria Vieito[7], Louise Carter[8], Hans Prenen[9], Gerald S. Falchook[10], Alastair Greystoke[11], Waldo Ortuzar Feliu[12], Ananya De[13], Xuemin Gu[14], Mengyao Li[15], Assunta De Rienzo[16], Babar Bashir[17]

[1]Drug Development, Sarah Cannon Research Institute UK, London, UK; [2]Drug Development Unit, Florida Cancer Specialists/Sarah Cannon Research Institute, Sarasota, FL, USA; [3]Melanoma and Skin Cancer Research Program, Sarah Cannon Research Institute, Nashville, TN, USA; [4]Department of Internal Medicine, Division of Hematology-Oncology, OU Health Stephenson Cancer Center, Oklahoma City, OK, USA; [5]Department of Oncology, Saint-Luc University Hospitals, Brussels, Belgium; [6]Start-Madrid Phase 1 Unit, START Madrid-FJD and Hospital Universitario Fundacion Jimenez Diaz, Madrid, Spain; [7]Medical Oncology Department, Vall d'Hebron Barcelona Hospital Campus, Barcelona, Spain; [8]Division of Cancer Sciences, The University of Manchester and Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK; [9]Oncology Department, Antwerp University Hospital (MOCA), Edegem, Belgium; [10]Drug Development Unit, Sarah Cannon Research Institute at HealthONE, Denver, CO, USA; [11]Medical Oncology Department, Newcastle University, Newcastle upon Tyne, UK; [12]Clinical Development, Bicycle Therapeutics, Cambridge, MA, USA; [13]Clinical Science, Bicycle Therapeutics, Cambridge, MA, USA; [14]Biostatistics, Bicycle Therapeutics, Cambridge, MA, USA; [15]Quantitative Pharmacology, Bicycle Therapeutics, Cambridge, MA, USA; [16]Translational Sciences, Bicycle Therapeutics, Cambridge, MA, USA; [17]Medical Oncology, Sarah Cannon Research Institute, Nashville, TN and Sidney Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA, USA

BACKGROUND

- 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
- BT5528 is a Bicycle® Toxin Conjugate comprising a bicyclic peptide targeting EphA2 linked to the cytotoxin MMAE[1] **(Figure 1)**
- EphA2 is overexpressed in many cancers leading to oncogenesis, angiogenesis, and metastasis, and its expression correlates with poor clinical outcome[4–7]
- Prior selected therapies targeting EphA2 have been associated with significant toxicity and limited efficacy[8–10]
- Preclinical tumor models have shown antitumor activity with BT5528, with rapid systemic clearance and tumor retention[1]
- These favorable preclinical studies supported this Phase 1/2 first-in-human dose escalation and dose expansion study to assess safety and efficacy of BT5528 monotherapy or in combination with nivolumab in patients with advanced solid tumors (NCT04180371); results from the monotherapy cohorts of dose escalation and dose expansion are reported here

FIGURE 1. SCHEMATIC OF BT5528



METHODS

- Adults with recurrent metastatic solid tumors known to express EphA2 who have exhausted all standard treatment options were included
- For dose escalation, patients received BT5528 IV at a starting dose of 2.2 mg/m² QW and were enrolled sequentially to increasing doses of BT5528; a 3 + 3 design was used for the first two dose levels, and then a Bayesian Logistic Regression Model was used for the remaining dose levels up to a maximum dose of 8.5 mg/m² QW or 10.0 mg/m² Q2W
  - The RP2D of 6.5 mg/m² Q2W was further evaluated in select tumor types as part of dose expansion
  - For dose optimization, 5 mg/m² QW was selected as a potentially efficacious dose with an acceptable safety profile, for further evaluation in select tumor types for dose escalation
- The primary endpoints for dose escalation were incidence and severity of treatment-related adverse events (TRAEs) and dose-limiting toxicities with the objective of defining the maximum tolerated dose and RP2D; secondary objectives included preliminary antitumor activity and PK
  - For dose expansion, the primary objective was to assess clinical activity of BT5528, including objective response rate (ORR), clinical benefit rate (CBR), and duration of response (DoR); secondary objectives were to assess safety and PK
- Plasma concentrations of BT5528 and MMAE were assessed, and key PK exposure metrics were obtained, including maximum plasma concentration (C_{max}), area under the concentration-time curve (AUC), and drug elimination half-life

RESULTS

Demographics

- As of 14 March 2024, 128 patients had received BT5528 monotherapy across the dose escalation and dose expansion parts of the study; baseline demographics and disease characteristics are reported in **Table 1**

TABLE 1. BASELINE PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Characteristic	All monotherapy (N=128)[a]
Age, years, median (range)	63 (33–82)
Sex, n (%)	
Female	78 (61)
Male	50 (39)
Race, n (%)	
Asian	7 (5)
Black or African American	3 (2)
White	96 (75)
Other/unknown/not disclosed	22 (17)
ECOG PS, n (%)	
0	52 (41)
1	76 (59)
Primary diagnosis, n (%)	
Ovarian cancer	47 (37)
Urothelial cancer	34 (27)
Lung cancer	11 (9)
Breast cancer	9 (7)
Head and neck cancer	8 (6)
Pancreatic cancer	8 (6)
Esophageal cancer	5 (4)
Gastric/upper GI cancer	3 (2)
Other/unknown	3 (2)
Median prior lines of therapy (range)	4 (1–13)
Types of prior therapy, n (%)	
Platinum-based	118 (92)
Taxane-based	84 (66)
Checkpoint inhibitor	67 (52)
PARP inhibitor	25 (20)
Sacituzumab govitecan	12 (9)
Enfortumab vedotin	8 (6)
FGFR inhibitor	4 (3)

[a]Includes dose escalation and expansion.

Safety

- Any grade TRAEs occurred in 88% of patients (all monotherapy; 91% for 6.5 mg/m² Q2W and 83% for 5 mg/m² QW); the most common TRAEs were nausea, fatigue, and diarrhea **(Table 2)**, which were Grade 3 in ≤5% of patients
- Incidence of treatment-related peripheral neuropathy (TRPN) was 20% (all monotherapy), with 19% for 6.5 mg/m² Q2W and 29% for 5 mg/m² QW (any grade), and no Grade ≥3 events **(Table 3)**
- No treatment-related hemorrhage events of any grade were reported following treatment with BT5528
- Other TRAEs of interest (neutropenia, skin reactions, ocular disorders, and hyperglycemia) were Grade ≥3 in ≤5% of patients **(Table 3)**

TABLE 2. SAFETY SUMMARY FOR BT5528

Category, n (%)	All monotherapy dose esc+exp N=128	6.5 mg/m² Q2W dose esc+exp n=74	5 mg/m² QW dose esc n=24
TEAEs	124 (97)	71 (96)	23 (96)
TRAEs	112 (88)	67 (91)	20 (83)
TEAEs Grade ≥3	64 (50)	36 (49)	11 (46)
TRAEs Grade ≥3	34 (27)	16 (22)	3 (13)
SAEs	39 (31)	19 (26)	8 (33)
TRSAEs	12 (9)	6 (8)	0
DLTs	7 (5)	1 (1)	1 (4)
TEAEs leading to dose interruption	39 (31)	16 (22)	6 (25)
TEAEs leading to dose reduction	12 (9)	2 (3)	1 (4)
TEAEs leading to dose discontinuation	4 (3)	2 (3)	0
TRAEs reported in ≥15% of patients, n (%)			
Nausea[a]	58 (45)	37 (50)	7 (29)
Fatigue	44 (34)	27 (37)	8 (33)
Diarrhea	35 (27)	23 (31)	3 (13)
Vomiting[a]	27 (21)	13 (18)	3 (13)
Anemia	25 (20)	15 (20)	3 (13)
Decreased appetite	21 (16)	15 (20)	3 (13)
Alopecia	20 (16)	12 (16)	2 (8)
Pyrexia	17 (13)	13 (18)	0

[a]Prophylactic anti-emetics were required in the dose expansion phase and for the 5 mg/m² QW dose.

TABLE 3. TRAES OF INTEREST FOR BT5528

Category, n (%)	All monotherapy dose esc+exp N=128		6.5 mg/m² Q2W dose esc+exp n=74		5 mg/m² QW dose esc n=24	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Peripheral neuropathy[a]	26 (20)	0	14 (19)	0	7 (29)	0
Neutropenia	13 (10)	6 (5)	6 (8)	2 (3)	2 (8)	1 (4)
Ocular disorders[b]	3 (2)	0	2 (3)	0	1 (4)	0
Hyperglycemia[c]	4 (3)	1 (<1)	3 (4)	1 (1)	1 (4)	0
Skin reactions[d]	13 (10)	0	10 (14)	0	0	0
Hemorrhage[e]	0	0	0	0	0	0

[a]Peripheral neuropathy SMQ [broad]. [b]Preferred terms defined in Eye Disorders SOC. [c]Hyperglycemia/new onset diabetes mellitus SMQ [broad]. [d]Includes the SCAR SMQ and the preferred terms defined in Skin and Subcutaneous Disorders SOC, excluding alopecia. [e]Hemorrhage SMQ (excluding laboratory terms) [narrow].

Efficacy

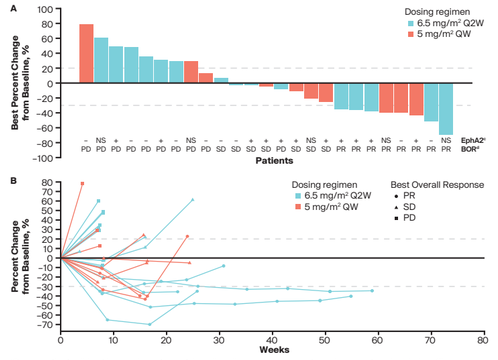
- Objective responses were observed in 14 of 113 efficacy-evaluable patients (12%) with 10 of these observed in 29 efficacy-evaluable patients with urothelial cancer (34%) **(Table 4)**
- The highest antitumor activity was observed in urothelial cancer with ORRs of 31% and 27% (confirmed + unconfirmed) in efficacy-evaluable patients in the 6.5 mg/m² Q2W and 5 mg/m² QW cohorts, respectively **(Figure 2a** and **2b)**
- No objective responses were observed in patients with ovarian cancer who received 5 mg/m² QW at the time of data cutoff, however, 5 patients (42%) maintained stable disease
- Amongst the patients with urothelial cancer with available IHC and response data (n=24), ORR was 43% (6/14) (unconfirmed & confirmed) among patients who were EphA2+, compared with 20% (2/10) among patients who were EphA2- **(Figure 2A)**

TABLE 4. BEST OVERALL RESPONSE IN EFFICACY-EVALUABLE PATIENTS

BOR[a], n (%)	All cancers			
	All monotherapy dose esc+exp N=113[b]	6.5 mg/m² Q2W dose esc+exp n=66[c]	6.5 mg/m² Q2W dose exp n=52[c]	5 mg/m² QW dose esc n=21[d]
CR	1 (<1)	0	0	0
PR	13 (12)	8 (12)	7 (13)	3 (14)
SD	47 (42)	26 (39)	21 (40)	9 (43)
PD	50 (44)	32 (49)	24 (46)	8 (38)
ORR	14 (12)	8 (12)	7 (13)	3 (14)
CBR[e]	30 (27)	19 (29)	15 (29)	5 (24)
BOR[a], n (%)	**Urothelial cancer**			
	All monotherapy dose esc+exp N=29[c]	6.5 mg/m² Q2W dose esc+exp n=16	6.5 mg/m² Q2W dose exp n=11	5 mg/m² QW dose esc n=11[d]
CR	0	0	0	0
PR	10 (34)	5 (31)	5 (45)	3 (27)
SD	7 (24)	3 (19)	1 (9)	4 (36)
PD	11 (38)	8 (50)	5 (45)	3 (27)
ORR	10 (34)	5 (31)	5 (45)	3 (27)
CBR[e]	12 (41)	6 (38)	5 (45)	4 (36)

[a]Confirmed and unconfirmed responses reported; data cutoff date of 26 April 2024 for efficacy. [b]Two patients in the all monotherapy group were not evaluable (1 with urothelial cancer and one with "other" cancer). [c]In dose expansion phase, anti-emesis prophylaxis was made mandatory (unlike dose escalation, where it was not allowed) leading to improved response profile. [d]one patient was NE. [e]CR + PR + SD ≥4 months.

FIGURE 2. (A) CHANGE FROM BASELINE IN TUMOR SIZE AND (B) DURATION OF RESPONSE IN EFFICACY-EVALUABLE UROTHELIAL CANCER PATIENTS[a,b]



[a]Seven patients did not have adequate post-baseline disease assessments and were not evaluable for efficacy. [b]Confirmed and unconfirmed responses per RECIST v1.1. [c]EphA2+ expression used a cutoff of TPS >1 by IHC using mAbs; NS indicates no sample available for testing. [d]Confirmed and unconfirmed.

Pharmacokinetics

- BT5528 and MMAE exhibited dose-dependent increases in PK **(Figure 3)**
- There was no or limited accumulation after multiple doses of BT5528 and MMAE, respectively
- PK exposure metrics of BT5528 and MMAE from the two tested dose regimens are presented in **Table 5**; half-life was <1 hour for BT5528 and 39–42 hours for MMAE

FIGURE 3. CONCENTRATION-TIME PROFILES OF BT5528 AND MMAE

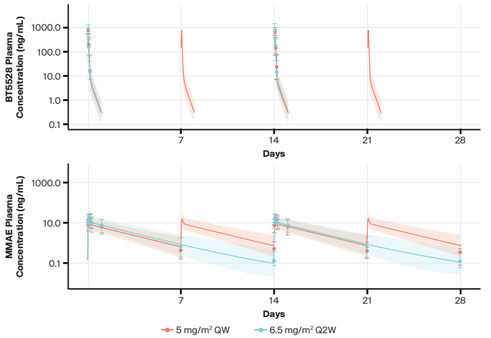


TABLE 5. MEAN PK PARAMETERS OF BT5528 AND MMAE

Parameter	6.5 mg/m² Q2W		5 mg/m² QW	
	$AUC_{0-28day}$ (ng*h/mL)	C_{max} (ng/mL)	$AUC_{0-28day}$ (ng*h/mL)	C_{max} (ng/mL)
Conjugate (BT5528)	2836	1041	4363	801
Unconjugated MMAE	1928	25.2	2890	20.4

CONCLUSIONS

- BT5528 demonstrated an emerging differentiated safety profile and antitumor activity in patients with advanced solid tumors, particularly in urothelial cancer
  - BT5528 was not associated with safety concerns that have been reported for other EphA2-targeting therapies, such as hematological toxicities[8–10]
  - In addition to the RP2D (6.5 mg/m² Q2W) a dose of 5 mg/m² QW also demonstrated antitumor activity and an acceptable and differentiated safety profile
- These results support further development of BT5528 as monotherapy and in combination with nivolumab and potentially other agents in select tumor types

ABBREVIATIONS

ADC, antibody-drug conjugate; AUC, area under the concentration-time curve; CBR, clinical benefit rate; C_{max}, maximum plasma concentration; CR, complete response; DLTs, dose-limiting toxicities; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EphA2, ephrin type-A receptor 2; esc, escalation; exp, expansion; FGFR, fibroblast growth factor receptors; GI, gastrointestinal; IHC, immunohistochemistry; IV, intravenous; mAB, monoclonal antibody; MedDRA, Medical Dictionary for Regulatory Activities; MMAE, monomethyl auristatin E; NCI-CTCAE, National Cancer Institute-Common Terminology Criteria for Adverse Events; NE, not evaluable; NS, no sample; ORR, objective response rate; PARP inhibitor, poly (ADP-ribose) polymerase inhibitor; PD, progressive disease; PK, pharmacokinetics; PR, partial response; Q2W, every 2 weeks; QW, weekly; RP2D, recommended Phase 2 dose; SAE, serious adverse event; SCAR, severe cutaneous adverse reactions; SD, stable disease; SMQ, Standardized MedDRA Queries; SOC, NCI-CTCAE system-organ class; TEAE, treatment-emergent adverse event; TPS, tumor proportion score; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.

ACKNOWLEDGEMENTS

The authors would like to thank the participating patients and their families, clinicians, and the BT5528-100 study investigators. Medical writing support was provided by Becky Bradley, PhD, and Rebecca L. Crepeau, PhD, of Avalere Health Global Limited, and funded by BicycleTx Ltd.

EF discloses the following relationships: Employment - HCA/Sarah Cannon. Consulting or Advisory Role - Astellas; Pfizer. Research Funding (institution) - Acerta; ADC; Amgen; Arcus; Array; Artios; Astellas; Astex; AstraZeneca; Basilea; Bayer; BeiGene; Bicycle; BioNTech SE; Blueprint; Boehringer Ingelheim; Calithera; Carrick; Casi; Clovis Oncology; Crescendo; CytomX; Daiichi Sankyo; Deciphera; Eli Lilly; Ellipses; Exelixis; F. Hoffman-La Roche; Fore; G1; Genentech; GSK; H3 Biomedicine; Hutchinson MediPharma; Ignyta/Roche; Immunocore; Immunomedics; Incyte; Instil Bio; IOVANCE; Janssen; Jiangsu Hengrui Medicine; Kronos Bio; Lupin Limited; MacroGenics; Menarini; Merck KGaA; Mereo; Merus; Millennium; MSD; Nerviano; Nurix; Oncologie; Oxford Vacmedix; Pfizer; Plexxikon; PMVPharma; QED; Relay; Repare; Ribon; Roche; Sapience; Seagen; Servier; Stemline; Synthon; Taiho; Tesaro; Turning Point; Takeda. Patents, Royalties, Other Intellectual Property - Patent No: 1716712.3 pending. Speaker fees: CARIS Life Science. Travel, Accommodations, Expenses - Bicycle; CARIS Life Sciences; Repare; Sapience; Seagen. Other Relationship - European Organization for Research and Treatment of Cancer (EORTC); Hospital Corporation of America (HCA) International.

REFERENCES

1. Bennett G, et al. *Mol Cancer Ther*. 2020;19(7):1385–1394.
2. Mudd GE, et al. *J Med Chem*. 2020;63(8):4107–4116.
3. Walsh SJ, et al. *Cancer Res*. 2024;84(6_Suppl):5807.
4. Wilson K, et al. *Oncogene*. 2021;40(14):2483–2495.
5. Wykosky J, Debinski W. *Mol Cancer Res*. 2008;6(12):1795–1806.
6. Abraham S, et al. *Clin Cancer Res*. 2006;12(2):353–360.
7. Kinch MS, et al. *Clin Cancer Res*. 2003;9(2):613–618.
8. Shitara K, et al. *J Immunother Cancer*. 2019;7(1):219.
9. Annunziata CM, et al. *Invest New Drugs*. 2013;31(1):77–84.
10. Merrimack Pharmaceuticals, Inc. Press release 4th April 2019. http://investors.merrimackpharma.com/node/11941/pdf

Presenting author:
Elisa Fontana, MD
elisa.fontana@hcahealthcare.co.uk

Presented at the European Society for Medical Oncology (ESMO) Annual Meeting, Barcelona, Spain, 13–17 September 2024