UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

October 7, 2021
Date of Report (Date of earliest event reported)

Bicycle Therapeutics plc
(Exact name of registrant as specified in its charter)

England and Wales	**001-38916**	**Not applicable**
(State or other jurisdiction of incorporation)	(Commission File Number)	(IRS Employer Identification No.)

B900, Babraham Research Campus **Cambridge CB22 3AT** **United Kingdom**	**Not Applicable**
(Address of principal executive offices)	(Zip Code)

Registrant's telephone number, including area code: **+44 1223 261503**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Ordinary shares, nominal value £0.01 per share	n/a	The Nasdaq Stock Market LLC*
American Depositary Shares, each representing one ordinary share, nominal value £0.01 per share	BCYC	The Nasdaq Stock Market LLC

***** Not for trading, but only in connection with the listing of the American Depositary Shares on The Nasdaq Stock Market LLC.

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Item 8.01 Other Events.

On October 7, 2021, Bicycle Therapeutics plc (the "Company") issued a press release announcing interim results from its phase I clinical trial of BT5528 and preliminary results from its ongoing phase I clinical trial of BT8009. A copy of the press release is filed as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated into this Item 8.01 by reference.

Also on October 7, 2021, the Company hosted a conference call and webcast to discuss the above-mentioned clinical trial results. A copy of the presentation used for the conference call and webcast is attached as Exhibit 99.2 to this Current Report on Form 8-K and is incorporated into this Item 8.01 by reference.

Item 9.01 Financial Statements and Exhibits

(a) Exhibits

99.1	Press Release issued October 7, 2021
99.2	Presentation dated October 7, 2021
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Date: October 7, 2021

BICYCLE THERAPEUTICS PLC

By: /s/ Lee Kalowski
Name: Lee Kalowski
Title: Chief Financial Officer

Exhibit 99.1

Bicycle Therapeutics Announces Interim BT5528 Phase I Clinical Trial Results and Preliminary Results from Ongoing BT8009 Phase I Clinical Trial

- *BT5528 Phase I anti-tumor activity observed in late line patients, with 2 partial responses out of 2 urothelial cancer patients dosed and an 80% disease control rate in 5 EphA2-positive ovarian cancer patients, including 1 partial response*

-A recommended BT5528 Phase II dose (RP2D) range has been established at 6.5-8.5mg/m^2 every other week; expansion cohorts expected to initiate in 2022

- *In the ongoing BT8009 Phase I trial in monotherapy cohorts, 4 out of 11 urothelial patients had partial responses; Phase I dose escalation remains ongoing, with no dose limiting toxicities (DLTs) yet observed*

- *BT5528 data to be presented at a virtual plenary session today at 1:25pm ET at the AACR-NCI-EORTC meeting; conference call scheduled for 3:00pm ET*

CAMBRIDGE, England, & BOSTON, October 7, 2021 – Bicycle Therapeutics plc (NASDAQ: BCYC), a biotechnology company pioneering a new and differentiated class of therapeutics based on its proprietary bicyclic peptide (*Bicycle*®) technology, today provided a clinical update of its wholly-owned, next-generation *Bicycle* Toxin Conjugates (BTCs), reporting interim Phase I trial results for BT5528 and preliminary findings from the ongoing dose escalation portion of the of the BT8009 clinical trial.

“We are pleased to provide a clinical update for two of our wholly-owned BTCs currently undergoing Phase 1 dose escalation trials in late line cancer patients,” said Dominic Smethurst, MA, MBChB, MRCP, MFPM, Chief Medical Officer of Bicycle Therapeutics. “We are delighted to see preliminary anti-tumor activity in both trials and across two tumor types, as well as to report tolerability profiles that may demonstrate differentiation from antibody-based approaches.”

“These data support our belief that the Bicycle platform offers a potentially differentiated approach to traditional toxin delivery. The data generated from these molecules provide a wealth of information and insights as we continue to expand the application of our technology and generate additional *Bicycle*- targeted therapeutics with the intention of making a meaningful difference to cancer patients,” said Kevin Lee, Ph.D., Chief Executive Officer of Bicycle Therapeutics. “We look forward to providing additional clinical data on BT5528 and BT8009 next year, and initiating our Phase I/II study for BT7480 later this year.”

BT5528, a BTC targeting EphA2, a target for which prior antibody-based approaches have been unsuccessful, has demonstrated preliminary anti-tumor activity. Bicycle has established an RP2D range and is pursuing enrollment in expansion cohorts

- **Preliminary signs of anti-tumor activity observed.** A total of 24 patients were dosed both prior to, and after, the implementation of the EphA2 immunohistochemistry (IHC) assay, with a median of seven prior lines of therapy. Amongst these patients, preliminary anti-tumor activity was observed in urothelial and ovarian cancer patients.

- A total of two BT5528 monotherapy urothelial patients were dosed. Both (100%) were observed to have tumor reductions constituting a partial response under Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The administered doses in these patients ranged from 6.5mg/m^2 to 10 mg/m^2 every other week.

- A total of eight BT5528 monotherapy ovarian cancer patients were dosed. Of these eight, five were determined to be EphA2-positive based on the IHC assay. Anti-tumor activity was observed in four of the five (80%) patients, including one (20%) that constituted a partial response under RECIST version 1.1 criteria. The range of administered doses in these patients was 6.5-8.5mg/m^2 every other week.

- **Doses of BT5528 administered to date have been tolerated in the ongoing Phase I portion of the Phase I/II trial.** In addition, and in contrast to the toxicities observed with MedImmune's EphA2 antibody-drug conjugate (ADC) MEDI-547, Bicycle has observed no signs of coagulopathy to date.

- **Based on the Phase I results, Bicycle has established an RP2D range.** BT5528 has been dosed up to 8.5mg/m^2 every week and 10mg/m^2 every other week. Some mild and transient neutropenia was observed at 8.5mg/m^2 every week, although this did not constitute a DLT. At 10mg/m^2 every other week, two DLTs were observed (Grade 3 fatigue and Grade 3 pneumonitis). The most common Grade 3 and above events were neutropenia, anemia and pneumonitis and there were two Grade 5 events: tumor lysis syndrome and renal failure caused by GI-related dehydration. Based on the totality of the findings, the RP2D is expected to be in the range of 6.5 mg/m^2 to 8.5mg/m^2 every other week, a dose that is believed to be within the therapeutic range based on both preclinical studies and preliminary clinical anti-tumor activity.

- **Bicycle to advance BT5528 in expansion cohorts.** Based on the findings from the Phase I trial, Bicycle plans to initiate expansion cohorts in urothelial and ovarian cancers as well as a basket that includes head and neck, non-small cell lung, gastroesophageal and triple negative breast cancers in 2022. The trial will enroll up to 56 patients in the initial expansion cohorts, with the ability to further expand enrollment based on the results of the initial expansion cohorts.

BT8009, a Nectin-4 targeting BTC with a potentially differentiated profile as compared to a Nectin-4 targeting ADC has shown preliminary anti-tumor activity in the ongoing Phase I portion of its Phase I/II trial.

- **Preliminary signs of anti-tumor activity in urothelial patients observed.** As of September 30, a total of 11 response evaluable urothelial cancer patients have been dosed in monotherapy cohorts of 2.5mg/m^2 and 5.0mg/m^2 weekly in the ongoing trial. Of these, four patients were in the 2.5mg/m^2 dose cohort and seven in the 5.0mg/m^2 dose cohort. Prior to enrollment, all patients had previously received at least two prior lines of therapy, with a median of two and a range of two-to-six prior therapies. A total of four patients (36%) were observed to have tumor reductions that constituted partial responses under RECIST 1.1, with a range in tumor reductions from 37% to 89% among these patients.

- Four response evaluable patients were dosed at 2.5mg/m^2 weekly. Among these four patients, three patients were observed to have at least stable disease, with a disease control rate of 75% and one patient (25%) was observed to have a tumor reduction of 37%, meeting the criteria of a partial response under RECIST 1.1.

- Seven response evaluable patients were dosed at 5.0mg/m^2 weekly. Among these seven patients, five were observed to have at least stable disease, with a disease control rate of 71% and three patients (43%) were observed to have tumor reductions meeting the criteria of a partial response under RECIST 1.1. The magnitude of tumor reductions ranged from 44% to 89%.

- **Dose escalation remains ongoing.** At both 2.5mg/m^2 weekly and 5.0mg/m^2 weekly, BT8009 has been tolerated, with no DLTs observed to-date. At 5.0mg/m^2 weekly, BT8009 is estimated to administer over 35% more MMAE per four-week dosing cycle compared to the antibody-based drug conjugate, enfortumab vedotin. The escalation remains ongoing, and patients are currently being enrolled in 7.5mg/m^2 weekly and every other week cohorts.

- **BT8009 enrollment ongoing.** A total of 14 clinical sites are active globally, including nine outside of the United States. Bicycle expects to have up to 21 sites active this year.

Conference Call Details

Bicycle Therapeutics will host a conference call and webcast on Thursday, October 7 at 3:00 p.m. ET to review the BT5528 trial data being presented at the AACR-NCI-EORTC meeting and provide an update on preliminary findings from the BT8009 trial. To access the call, please dial (800) 377-9118 (domestic) or (409) 937-8920 (international) and provide the Conference ID 2287246. A live webcast of the presentation will be available on the Investors & Media section of the Bicycle website, bicycletherapeutics.com.

About Bicycle Therapeutics

Bicycle Therapeutics (NASDAQ: BCYC) is a clinical-stage biopharmaceutical company developing a novel class of medicines, referred to as Bicycles, for diseases that are underserved by existing therapeutics. Bicycles are fully synthetic short peptides constrained with small molecule scaffolds to form two loops that stabilize their structural geometry. This constraint facilitates target binding with high affinity and selectivity, making Bicycles attractive candidates for drug development. Bicycle is evaluating BT5528, a second-generation Bicycle Toxin Conjugate (BTC™) targeting EphA2, and BT8009, a second-generation BTC™ targeting Nectin-4, a well-validated tumor antigen, in company-sponsored Phase I/II trials. In addition, BT1718, a BTC™ that targets MT1-MMP, is being investigated in an ongoing Phase I/IIa clinical trial sponsored by the Centre for Drug Development of Cancer Research UK. Bicycle is headquartered in Cambridge, UK, with many key functions and members of its leadership team located in Lexington, MA. For more information, visit bicycletherapeutics.com.

Forward Looking Statements

This press release may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as “aims,” “anticipates,” “believes,” “could,” “estimates,” “expects,” “forecasts,” “goal,” “intends,” “may,” “plans,” “possible,” “potential,” “seeks,” “will” and variations of these words or similar expressions that are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Forward-looking statements in this press release include, but are not limited to, statements regarding Bicycle’s anticipated advancement of its product candidates, including BT5528, BT8009 and BT7480; the advancement of Bicycle’s product candidate pipeline; ; anticipated design of, initiation of, enrollment in and progression of Bicycle’s clinical trials; the availability of data from clinical trials; and the therapeutic potential of Bicycle’s product candidates. Bicycle may not actually achieve the plans, intentions or expectations disclosed in these forward-looking statements, and you should not place undue reliance on these forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in these forward-looking statements as a result of various factors, including: risks to site initiation, clinical trial commencement, patient enrollment and follow-up, as well as to Bicycle’s abilities to meet other anticipated deadlines and milestones, presented by the ongoing COVID-19 pandemic; uncertainties inherent in the initiation and completion of clinical trials and clinical development of Bicycle’s product candidates ; the risk that Bicycle may not realize the intended benefits of its technology; availability and timing of results from clinical trials; whether the outcomes of preclinical studies will be predictive of clinical trial results; whether initial or interim results from a clinical trial will be predictive of the final results of the trial or the results of future trials; the risk that trials may be delayed and may not have satisfactory outcomes; potential adverse effects arising from the testing or use of Bicycle’s product candidates; and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, are described in greater detail in the section entitled “Risk Factors” in Bicycle’s Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 5, 2021, as well as in other filings Bicycle may make with the SEC in the future. Any forward-looking statements contained in this press release speak only as of the date hereof, and Bicycle expressly disclaims any obligation to update any forward-looking statements contained herein, whether because of any new information, future events, changed circumstances or otherwise, except as otherwise required by law.

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Exhibit 99.2

Interim Phase I Update on BT5528 and Preliminary Findings from BT8009 Program

October 7, 2021

bicycle therapeutics

Forward-looking statements

This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as "aims," "anticipates," "believes," "could," "estimates," "expects," "forecasts", "goal," "intends," "may" "plans," "possible," "potential," "seeks," "will," and variations of these words or similar expressions that are intended to identify forward-looking statements. All statements other than statements of historical facts contained in this presentation are forward-looking statements, including statements regarding our future financial or business performance, conditions, plans, prospects, trends or strategies and other financial and business matters; our current and prospective product candidates, planned clinical trials and preclinical activities, current and prospective collaborations and the timing and success of our development of our anticipated product candidates.

Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results, our plans to initiate clinical trials and the designs of the planned trials and other future conditions, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, risks related to the ongoing COVID-19 pandemic, the risk that any one or more of our product candidates will not be successfully developed or commercialized, the risk of cessation or delay of any ongoing or planned clinical trials, the risk that we may not realize the intended benefits of our technology, including that we may not identify and develop additional product candidates for our pipeline, the risk that we may not maintain our current collaborations or enter into new collaborations in the future, or that we may not realize the intended benefits of these collaborations, the risk that our product candidates or procedures in connection with the administration thereof will not have the safety or efficacy profile that we anticipate, the risk that prior results will not be replicated or will not continue in ongoing or future studies or trials, the risk that we will be unable to obtain and maintain regulatory approval for our product candidates, the risk that the size and potential of the market for our product candidates will not materialize as expected, risks associated with our dependence on third-parties, risks regarding the accuracy of our estimates of expenses, risks relating to our capital requirements and needs for additional financing, and risks relating to our ability to obtain and maintain intellectual property protection for our product candidates. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our Quarterly Report on Form 10-Q, filed with the Securities and Exchange Commission on August 5, 2021, as well as in other filings we may make with the SEC in the future, as well as discussions of potential risks, uncertainties and other important factors in our subsequent filings with the Securities and Exchange Commission. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

Agenda

Introduction	**Kevin Lee** Chief Executive Officer
Review monotherapy trials to date: **BT5528** **BT8009**	**Dominic Smethurst** Chief Medical Officer
Beyond BT5528 and BT8009	**Nick Keen** Chief Scientific Officer
Closing remarks	**Lee Kalowski** President and Chief Financial Officer
Q&A	**Executive Management Team**

Robust proprietary and partnered pipeline

Target / Product	Partner / Sponsor	Indication	Modality	Pre-clinical	IND-enabling	Phase I	Phase II
Internal programs							
BT5528 (EphA2)		Oncology	Bicycle® Toxin Conjugate				
BT8009 (Nectin-4)		Oncology	Bicycle® Toxin Conjugate				
BT7480 (Nectin-4/CD137)		Immuno-oncology	Bicycle TICA™				
BT7455 (EphA2/CD137)		Immuno-oncology	Bicycle TICA™				
Partnered programs							
THR-149 (Kallikrein inhibitor Bicycle)	OXURION	Ophthalmology					
BT1718 (MT1-MMP)	CANCER RESEARCH UK	Oncology	Bicycle® Toxin Conjugate				
BT7401 (multivalent CD137 systemic agonist)	CANCER RESEARCH UK	Immuno-oncology					
Undisclosed	Genentech A Member of the Roche Group	Immuno-oncology					
Inhaled Bicycles	AstraZeneca	Respiratory					
Novel anti-infectives	Innovate UK	Anti-infectives					
Novel CNS targets	Dementia Discovery Fund IONIS	CNS					
Novel neuromuscular targets	IONIS	Neuromuscular					

BT5528 Monotherapy

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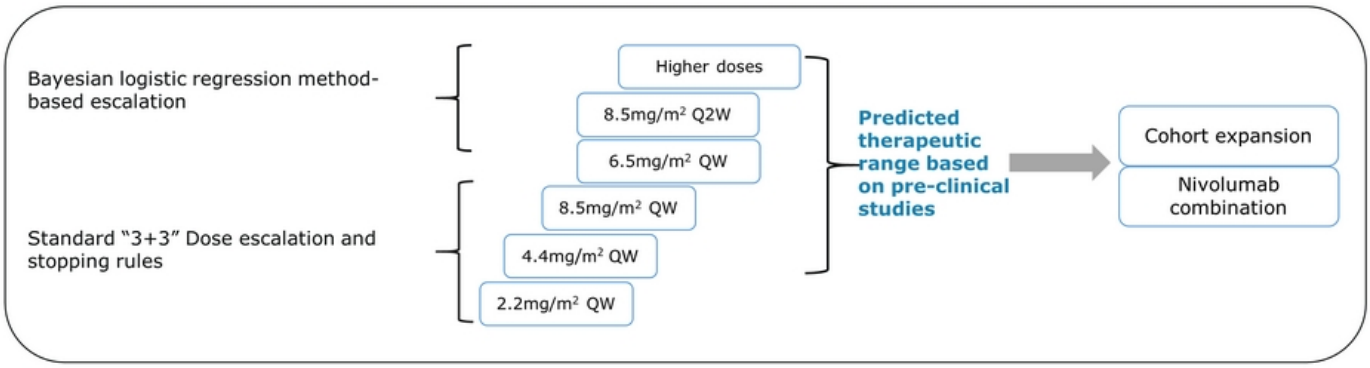
Background to BT5528 and ADC target: EphA2

- Erythropoietin-producing hepatocellular A2 receptor: member of Eph subfamily of receptor tyrosine kinases
- Regulates cell migration, adhesion, proliferation and differentiation
- Overexpressed in human cancers and correlates with tumor progression
- Development of MEDI-547 (MedImmune) in ovarian cancer was halted following serious bleeding events in phase I

"The bleeding and coagulation events observed in humans showed similarities to those evident in rats and monkeys. In all three species, increased activated partial thromboplastin time, increased fibrinogen/fibrin degradation product, and increased fibrin D-dimer were reported. Monkeys had red/ blood discharge from the nose, mouth, gums."[1]

1. Annunziata, Christina M., et al. "Phase 1, open-label study of MEDI-547 in patients with relapsed or refractory solid tumors." *Investigational new drugs* 31.1 (2013): 77-84.
Zelinski, Daniel P., et al. "EphA2 overexpression causes tumorigenesis of mammary epithelial cells." *Cancer research* 61.5 (2001): 2301-2306.

BT5528 phase I dose escalation: trial design



Inclusion/Exclusion criteria:

- Standard first-in-human criteria
- **Prior neuropathy must have returned to ≤Grade 1**
- IHC based enrichment for EphA2(+) tumors introduced mid-trial

Objectives:

- Primary – Safety and tolerability
- Secondary – PK, PD and preliminary signs of efficacy

ClinicalTrials.gov Identifier: NCT04180371

Overview of key demographics for patients enrolled in BT5528 phase I dose escalation trial

Demographics	
Total	24 (100%)
Age, years, median (range)	65.5 (49-76)
Sex, n (%)	
Male	7 (29%)
Female	17 (71%)
ECOG, n (%)	
0 (Good performance status)	11 (46%)
1	13 (54%)
2+	0 (0%)
Prior therapies, median (range)	**7 (1-16)**

Data as of 14Jul21, not fully QCed

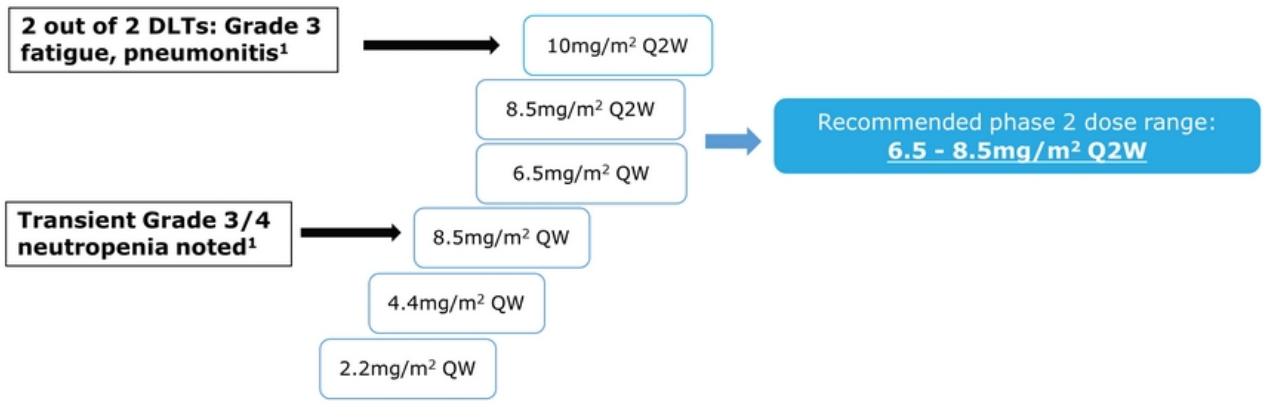
Overview of key adverse events observed in BT5528 phase I dose escalation trial

Adverse Events	Related Gr ≥3 AE N=13 patients[1]
Neutropenia	N=8
Anemia	N=2
Pneumonitis	N=2
Fatigue	N=1
Ileus	N=1
Tumor Lysis Syndrome	N=1
Bleeding disorders	**N=0**
Conjunctival disorders	**N=0**
Cutaneous events	**N=0**
Neuropathy	**N=0**

- Total number of adverse events: 235[1]
- Adverse events related to BT5528: 101[1]
- Other toxicities (<Gr 3) were predominantly hematological and GI[1]
- Two Gr 5 events observed, one following data cut-off

1. Data as of 14Jul21, not fully QCed

BT5528 phase I dose escalation – establishment of RP2D range



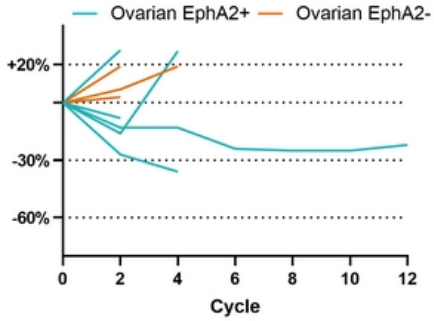
1. Data as of 14Jul21, not fully QCed

BT5528: Preliminary responses observed during phase I dose escalation trial

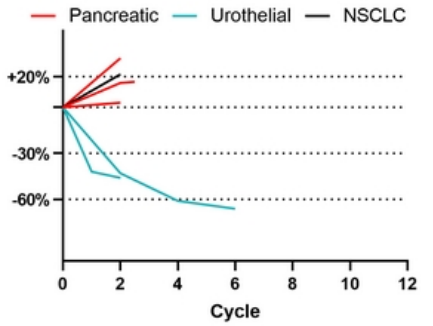
Responses observed:

- **Ovarian**
  - 1 PR[1] of 8 ovarian cancer patients, PR observed by month 4
  - 4 of 5 with EphA2 staining showed some shrinkage

Change in target lesion size relative to baseline



- **Urothelial**
  - 2 of 2 PRs[1], both at 2 months
  - Both responses by first scan



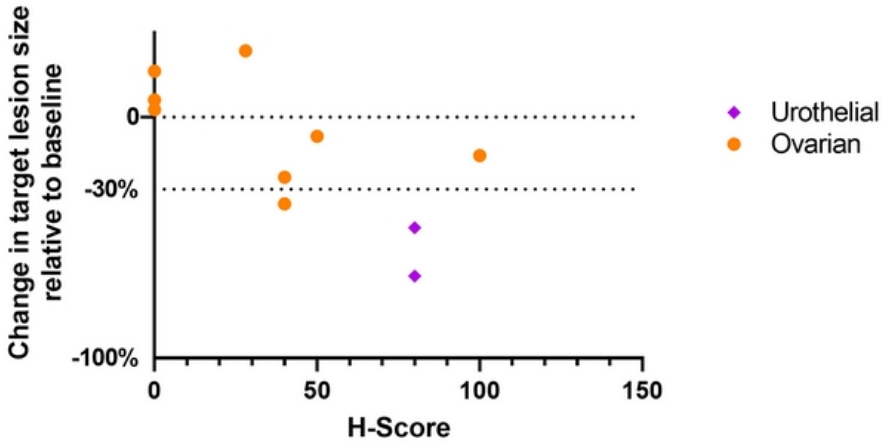
1. Partial responses under response evaluation criteria in solid tumors (RECIST) version 1.1.
Data as of 14Jul21, not fully QCed

October-21

bicycle therapeutics

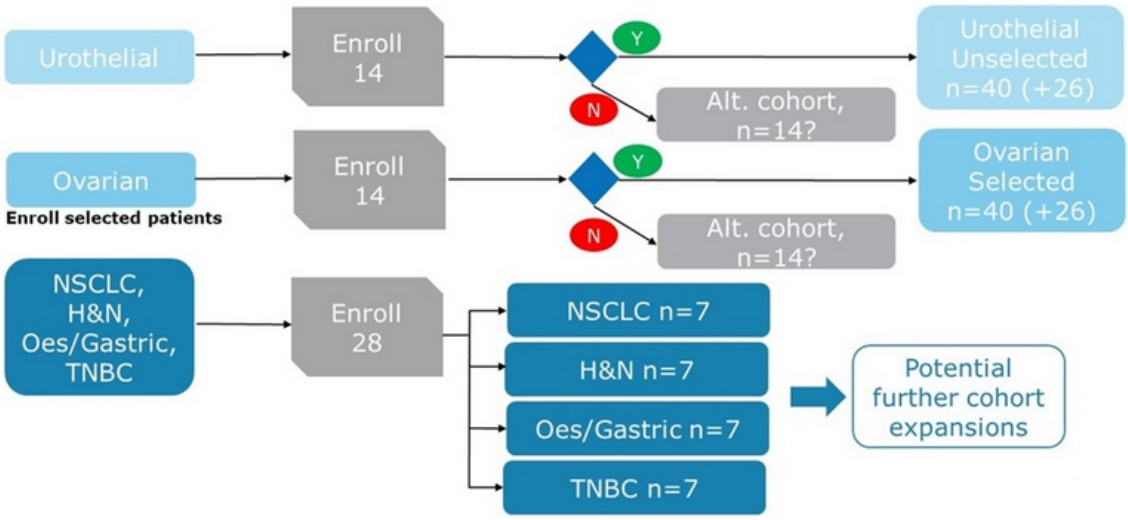
Emerging observed relationship between EphA2 staining and responses

- More EphA2 staining = more tumor shrinkage
- Early relationship with low numbers



Data as of 14Jul21, not fully QCed

BT5528 expansion: overall trial design



BT5528 – Phase I dose escalation preliminary conclusions and next steps

- BT5528 is a first-in-class *Bicycle*® toxin conjugate
- No evidence of BT5528 clotting abnormalities vs multiple disseminated intravascular coagulation events for MEDI-547 ADC
- Doses tolerated within expected therapeutic range; preliminary anti-tumor activity observed in two tumor types (ovarian and urothelial)
- Additional potential points of differentiation: to date, neuropathy, eye and skin toxicities not observed in BT5528 clinical trial
- Preliminary findings indicate activity associated with tumor expression
- Preparations underway for expansion cohorts in multiple tumor types

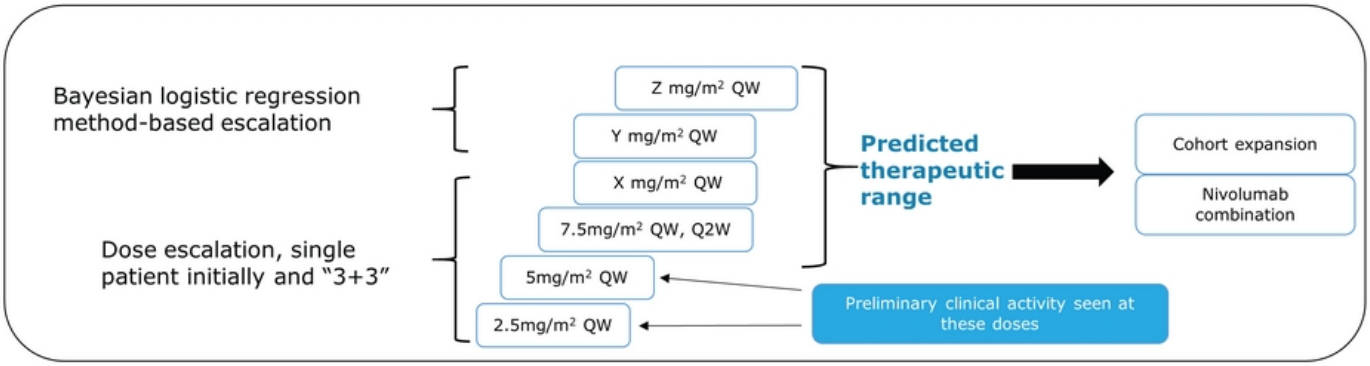
BT8009 Monotherapy

bicycle therapeutics

Background to BT8009 and ADC target: Nectin-4

- A cell adhesion molecule and one of four members of the nectin family
- All nectins share the same overall structure defined by three extracellular immunoglobulin domains, a single transmembrane helix and an intracellular domain
- Overexpressed in human cancers and correlated with tumor progression
- Solid tumors with high levels of Nectin-4 expression are urothelial, TNBC, ovarian, head & neck and NSCLC
- Target for Padcev (enfortumab vedotin), an FDA approved ADC

BT8009 phase I dose escalation trial design – currently escalating to 7.5mg/m² QW and Q2W



Inclusion/Exclusion criteria:

- Standard first-in-human criteria
- Any prior Nectin-4 target therapy excluded
- Urothelial patients were not IHC screened for Nectin-4

Objectives:

- Primary – Safety and tolerability
- Secondary – PK, PD and preliminary signs of efficacy

Overview of key demographics for evaluable patients enrolled in BT8009 phase I dose escalation trial

Demographics	
Total	26 (100%)
Age, years, median (range)	66 (44-81)
Sex, n (%)	
Male	15 (58%)
Female	11 (42%)
ECOG, n (%)	
0 (Good performance status)	11 (42%)
1	15 (58%)
2+	0
Prior therapies, median (range)	**5 (2-12)**

Data as of 30Sept21, not fully QCed

BT8009 phase I dose escalation trial: evaluable patients enrolled by tumor type

Demographics	
Total	26 (100%)
By tumor type:	
Urothelial	11 (42%)
Pancreatic	6 (23%)
NSCLC	4 (15%)
TNBC	3 (12%)
Head & Neck	1 (4%)
Ovarian	1 (4%)

Data as of 30Sept21, not fully QCed

Key demographics of evaluable urothelial cancer patients participating in BT8009 phase I dose escalation trial

Demographics	
Total	11 (100%)
Age, years, median (range)	69 (54-81)
Sex, n (%)	
Male	9 (82%)
Female	2 (18%)
ECOG, n (%)	
0 (Good performance status)	7 (64%)
1	4 (36%)
2+	0
Prior therapies, median (range)	2 (2-6)

Data as of 30Sept21, not fully QCed

Overview of key adverse events observed in BT8009 phase I dose escalation trial across all patients (N=27)

Adverse Events	Related Gr ≥3 AE N=10 events
Anemia	N=4
Neutropenia	N=3
Hypertension	N=1
Hypokalemia	N=1
Asthenia	N=1

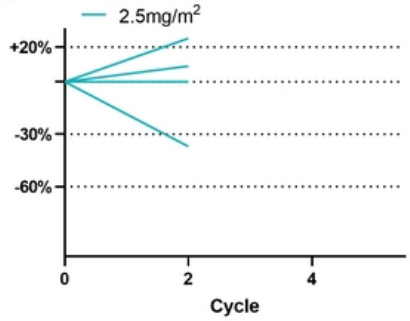
Data as of 30Sept21, not fully QCed

BT8009: preliminary responses observed in phase I dose escalation by dose in response evaluable urothelial cancer patients

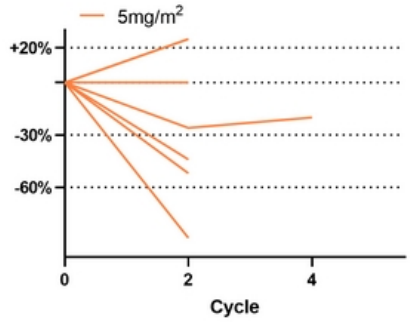
Responses observed:

- **2.5mg/m²**
  - 1 of 4 PR[1]: -37% tumor reduction
  - 2 of 4 SD
  - 75% disease control

Change in target lesion size relative to baseline



- **5mg/m²**
  - 3 of 7 PR[1]
    - -89% tumor reduction
    - -52% tumor reduction
    - -44% tumor reduction
  - 2 of 7 SD
  - 71% disease control



1. Partial responses under response evaluation criteria in solid tumors (RECIST) version 1
Data as of 30Sept21, not fully QCed

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Comparison of BT8009 to enfortumab vedotin (Padcev©) phase I dose escalation – urothelial cancer

Comparison*	BT8009 2.5mg/m²	BT8009 5mg/m²	BT8009 both cohorts	Enfortumab (1mg/kg and below)**	Enfortumab (All cohorts)**
No of patients	4	7	11	26	33
Median age	75	68	69	67	67
≥2 prior lines (%)	4 (100%)	7 (100%)	11 (100%)	N/A	25 (60%)
IHC pre-screen (%)	0	0	0	26 (100%)	33 (100%)
Partial or Complete Response (ORR %)	1 (25%)	3 (43%)	4 (36%)	6 (23%)	10 (30%)
Stable Disease or better (DCR %)	3 (75%)	5 (71%)	8 (73%)	N/A	N/A
Adverse event commentary			No eye tox, no DLTs		21% had Gr1/2 eye tox, 6% had DLTs

BT8009 data as of 30Sept21, not fully QCed

* This comparison is for illustrative purposes only. This table does not depict a head-to-head trial.

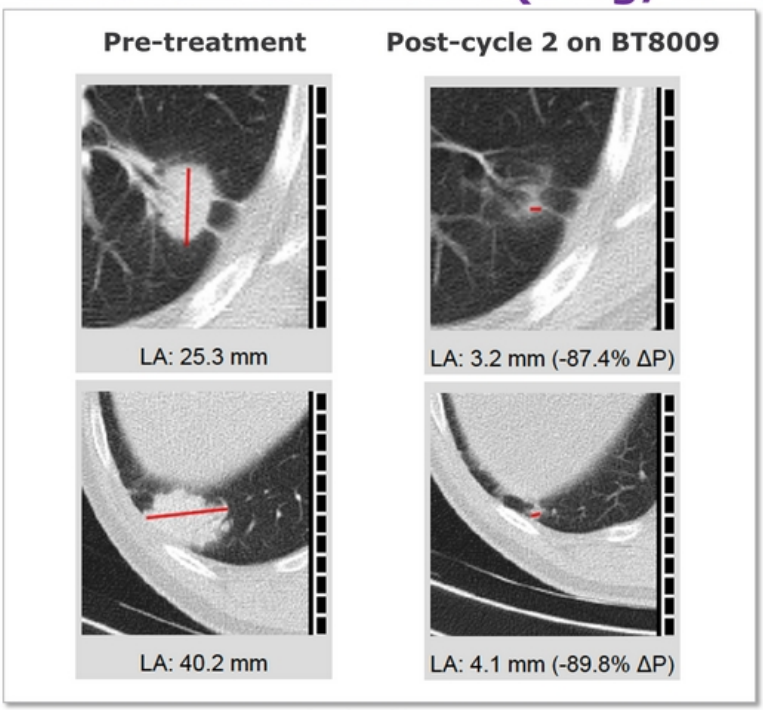
** Rosenberg, Jonathan, et al. "Interim analysis of a phase I dose escalation trial of ASG-22CE (ASG-22ME; enfortumab vedotin), an antibody drug conjugate (ADC), in patients (Pts) with metastatic urothelial cancer (mUC)" *Annals of Oncology 27 (Supplement 6): vi266-vi295*, 2016

More information on preliminary responses observed for urothelial cancer patients in BT8009 phase I dose escalation trial

	Patient A	Patient B	Patient C	Patient D
Dose (mg/m^2)	2.5	5.0	5.0	5.0
Age	81	68	66	62
Sex	M	M	M	M
Prior lines of therapy	2	2	2	2
Partial response	-37%	-89%	-44%	-52%

Data as of 30Sept21, not fully QCed

Comparison of Patient B pre-dose tumor images with tumor images after 2 months treatment (5mg/m² Q2W)



Non-target lung lesion was reduced by -89% after two cycles of BT8009 treatment

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BT8009 phase 1 dose escalation summary as of Sept 30

- No DLTs observed and escalation remains ongoing, with patients currently being enrolled in 7.5 mg/m^2 weekly and every-other-week cohorts
- BT8009 anti-tumor activity observed in pre-treated, urothelial cancer patients in both cohorts
- Doses tolerated within the expected therapeutic range; most common side effects GI-related
- Expect to present additional Phase I data in 2022

Beyond BT5528 and BT8009

bicycle therapeutics

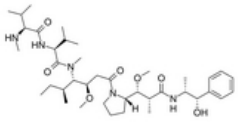
We believe we are well positioned to be the next generation of targeted oncology therapeutics

Tumor targeting *Bicycles*

DEPTH

Building depth in internal library of tumor antigen binding Bicycles

Bicycle Toxin Conjugates®

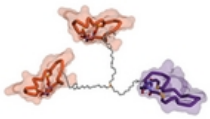


- Clinical signal observed
- Generalizable to other payloads
- Intend to build on current clinical trial observations with "wave" of 3rd Gen molecules

3rd Gen BTCs

- Broaden indications with additional targets and payloads

Bicycle® TICAs



- BT7480 expected to enter phase I 4Q21
- BT7455 in IND enabling studies
- We believe our platform uniquely suited to tumor specific IO modulation
- Generalizable to multiple receptor classes

2nd Gen IO

- Tumor cell specific NK cell engagers in optimization
- Multi-targeted molecules in discovery

Internal & external pipeline combinations

- Short $t_{1/2}$ critical for sequencing
- Current data provides compelling biological rationale for combination of cytotoxic BTC with TICAs and / or PD1

BREADTH

Looking forward

- Plan to initiate BT5528 expansion cohorts in 2022
- BT8009 dose escalation to 7.5 mg/m^2 will continue during Q4. Expect to present additional Phase I data in 2022
- BT7480 - a Nectin-4-CD137 Bicycle TICA® - anticipate dosing first patient by year end 2021
- Third generation Bicycle Toxin Conjugates® and NK cell engagers are in development

Question and Answer

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