

**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

November 20, 2019

Date of Report (Date of earliest event reported)

Bicycle Therapeutics plc

(Exact name of registrant as specified in its charter)

England and Wales
(State or other jurisdiction
of incorporation)

001-38916
(Commission
File Number)

Not applicable
(IRS Employer
Identification No.)

B900, Babraham Research Campus
Cambridge CB22 3AT
United Kingdom
(Address of principal executive offices)

Not Applicable
(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:

<u>Title of each class</u>	<u>Trading Symbol(s)</u>	<u>Name of each exchange on which registered</u>
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 x

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. x

Item 7.01 Regulation FD Disclosure

On November 20, 2019, Bicycle Therapeutics plc (the “Company”) posted an updated corporate presentation on the Company’s website. In such presentation, the Company announced key events it expects to occur in 2020. The Company expects to initiate a Phase IIa clinical trial of its BT1718 product candidate, provide interim data regarding its Phase I clinical trial of BT5528, initial a Phase I clinical trial of BT8009, and advance Investigational New Drug application enabling activities regarding BT7480 in 2020. A copy of the presentation is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference.

The information furnished under this Item 7.01, including Exhibit 99.1, shall not be deemed “filed” for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, or subject to the liabilities of that section. The information shall not be deemed incorporated by reference into any other filing with the Securities and Exchange Commission made by the Company, regardless of any general incorporation language in such filing.

Item 9.01 Financial Statements and Exhibits

<u>Exhibit No.</u>	<u>Description</u>
99.1	Presentation dated November 20, 2019

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: November 20, 2019

BICYCLE THERAPEUTICS PLC

By: /s/ Lee Kalowski

Name: Lee Kalowski

Title: Chief Financial Officer



Constrained peptides **Unconstrained thinking**

November 2019

bicycle
therapeutics

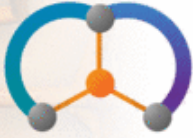
Forward-looking statements

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 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, 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 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 (SEC) on November 7, 2019, as well as in other filings Bicycle 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.

Our goal is to create transformational medicines

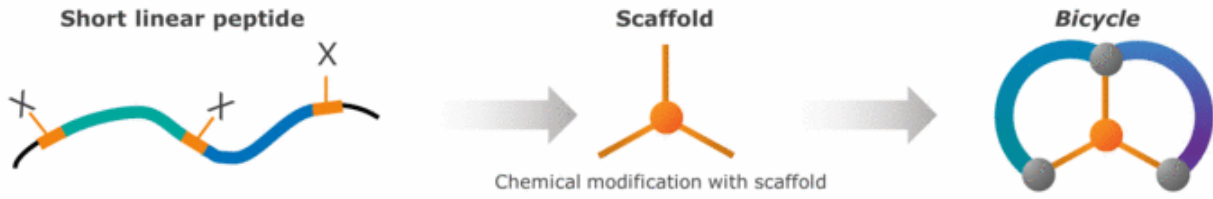
We aim to redefine what's possible for people with cancer and other serious diseases by pioneering a new and differentiated class of innovative treatments



Engineering *Bicycles*[®]
to solve unique therapeutic
challenges

- Advancing wholly-owned oncology pipeline of multiple clinical assets
- Exploring broad potential beyond oncology through partnerships
- Developing world's first fully synthetic immuno-oncology (IO) platform
- Led by world class management team, supported by strong financial foundation

Bicycles® are a new therapeutic modality for addressing intractable challenges



	Chemical synthesis	Rapid tissue distribution	Complex protein targets druggable	Route of elimination
Small molecules	+++	+++	---	Liver
Antibodies	---	+	+++	Liver
Bicycles	+++	+++	+++	Renal



Built-in tolerance to conjugation

- Generalizable approach
- Versatility to adopt multiple formats



Phage-based screening platform

- Nobel Prize-winning technology
- Rapid selection from $>10^{17}$ potential candidates



Robust patent protection

- >90 patent families
- Expiration into 2030s

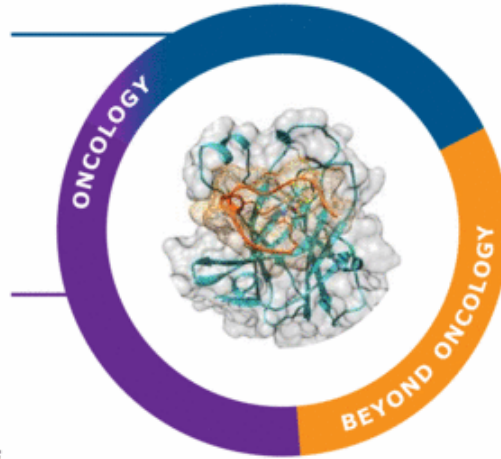
Internal focus on oncology, partnerships to explore additional applications across therapeutic areas

Bicycle® Toxin Conjugates

- Toxin delivery system with unique mechanism of action
- Potentially improved safety & efficacy over other modalities

Bicycle Tumor-targeted Immune Cell Agonists

- Differentiated approach to agonizing immune cells
- May overcome limitations of antibody & biologic therapies











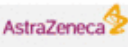





- Leverage platform's versatility
- More efficiently bring novel medicines to patients

OXURION® AstraZeneca

Dementia
Discovery
Fund

Innovate UK

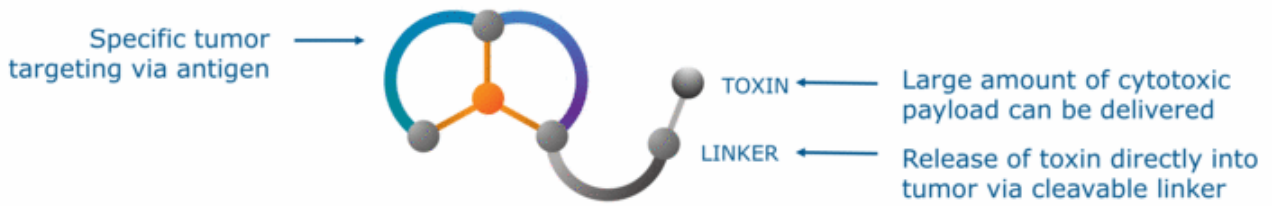
Robust proprietary and partnered pipeline

Product/Target	Therapeutic Interest	Collaborator	Stage	
			Discovery/ Preclinical	Clinical
Bicycle® Toxin Conjugates				
BT1718 (MT1-MMP)	Oncology			
BT5528 (EphA2)	Oncology			
BT8009 (Nectin-4)	Oncology			
Bicycle Tumor-targeted Immune Cell Agonist (TICAs™)				
BT7480 (Nectin-4/CD137 TICA)	Oncology			
EphA2/CD137 TICA	Oncology			
Beyond Oncology				
THR-149 (Kallikrein inhibitor <i>Bicycle</i>)	Ophthalmology			
Inhaled <i>Bicycles</i>	Respiratory			
Novel anti-bacterials	Anti-infectives			
Novel CNS targets	CNS diseases			

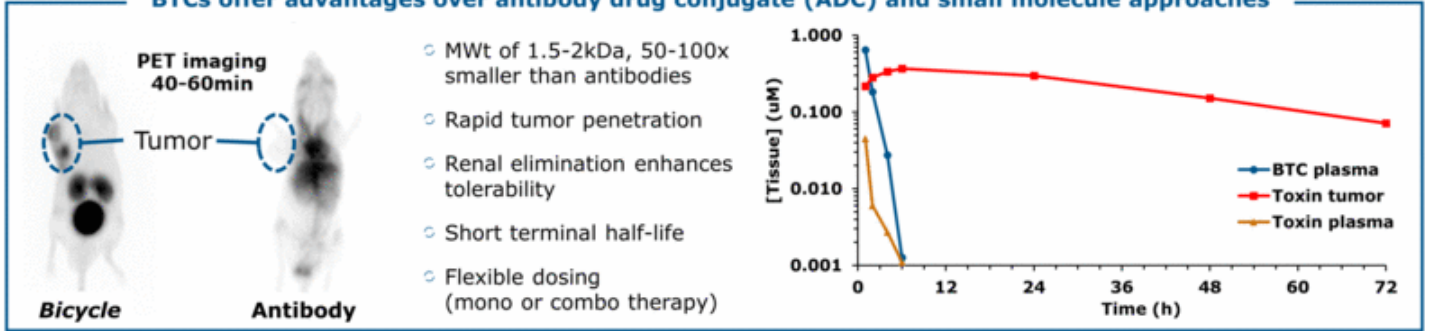


Bicycle[®]
Toxin Conjugates

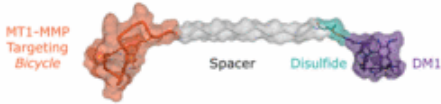
Bicycle[®] Toxin Conjugates – designed to be selective tumor targeting therapeutics



BTCs offer advantages over antibody drug conjugate (ADC) and small molecule approaches



BT1718: Potential first-in-class *Bicycle*[®] Toxin Conjugate targeting key tumor antigen

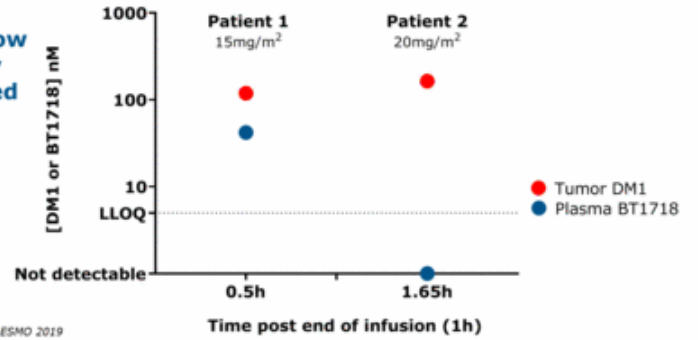


- Highly selective for MT1-MMP (MMP-14)
 - Cell-surface matrix metalloprotease
 - Established role in cell invasion and metastasis
- Dosing ongoing in Phase I escalation of PhI/IIa open-label, multicenter study in patients with advanced solid tumors

Ongoing all-comers PhI trial in patients with advanced solid tumors

- Includes patients with advanced solid tumors
- Dosing continues, within therapeutic range
- Manageable adverse events with once-weekly dosing*
- PhIIa expansion arms are in preparation (squamous lung cancer and an all-comers "basket" cohort)

Tumor biopsies show payload selectively delivered & retained in tumor



*Data cutoff of August 7, 2019, as reported at ESMO 2019

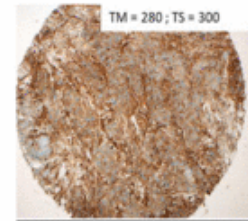
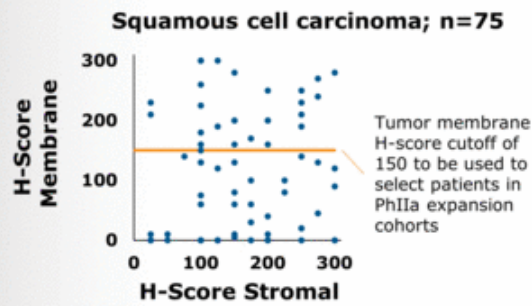
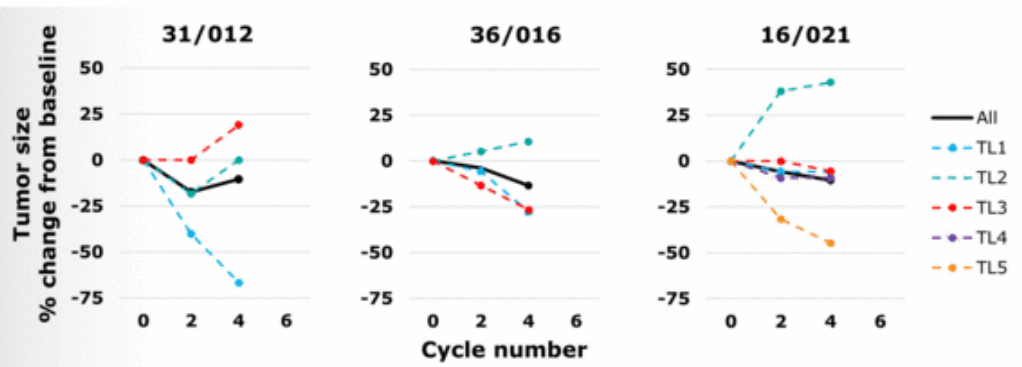
Clinical data from BT1718 validates Bicycle platform



At early doses, anti-tumor activity observed in individual target lesions

Initial analysis reported at ESMO 2019 shows stable disease in 54% of evaluable patients at 8 weeks*

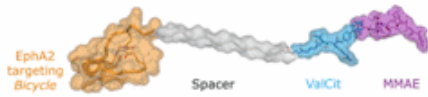
Analysis of historical, primary tumor microarray (TMA) tissue series indicates squamous cancers as preferred tumor subtype for PhIIa



Representative image of lung cancer core with corresponding tumor membrane (TM) and tumor stroma (TS) H-scores

Tumor membrane H-score cutoff of 150 to be used to select patients in PhIIa expansion cohorts

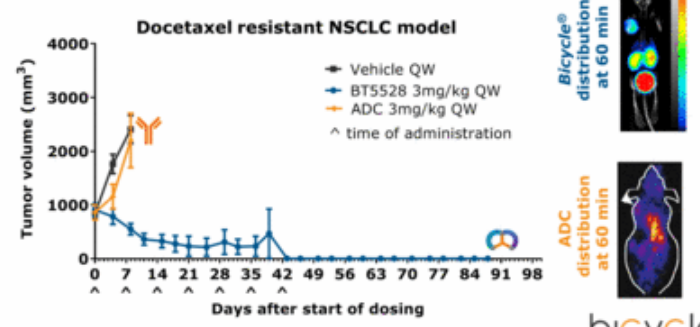
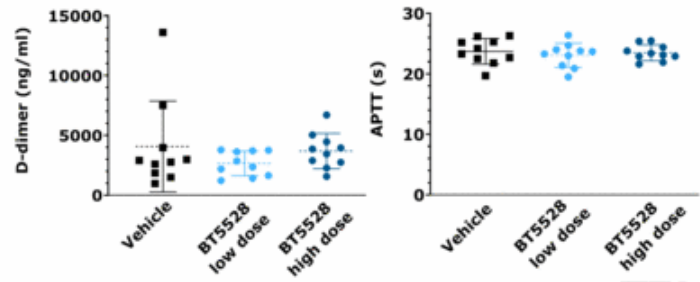
BT5528: EphA2 BTC delivers improved preclinical safety and efficacy over comparator ADCs



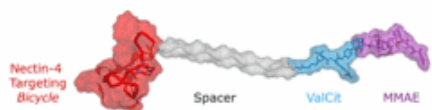
- EphA2 is overexpressed in many difficult to treat tumors
- Previous antibody drug conjugate projects, notably MEDI-547, have failed due to bleeding events
- Preclinical models are predictive
- Findings from BT5528 GLP tox study show no coagulation problems at toxin equivalent doses >150x clinical dose of MEDI-547 used in patients
- Dosing is underway in Phase I/II open-label, multicenter study in patients with advanced solid tumors evaluating BT5528 as a monotherapy and in combination with nivolumab

No signs of coagulopathy or bleeding

Displayed superior activity to EphA2 ADC in large tumor xenografts

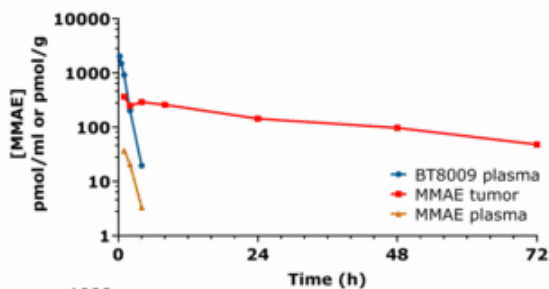


BT8009: Nectin-4 BTC fast follower with differentiated profile to clinical ADC

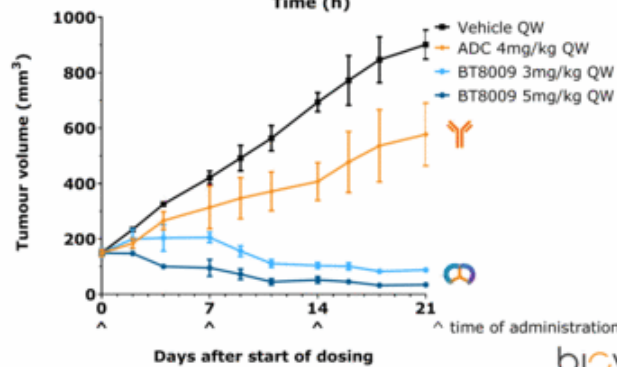


- Nectin-4 is involved in establishing cell-cell contact and tumor cell survival, overexpressed in common types of cancer (e.g. bladder, breast, gastric, lung and ovarian)
- Target validated in the clinic by enfortumab vedotin (Astellas/SeaGen)
- BT8009 designed to avoid hepatic exposure, may overcome stromal barrier in pancreatic cancer, easily manufactured
- IND-enabling studies ongoing

Impressive selective delivery of toxin to tumor



Improved activity over Nectin-4 ADC



bicycle
therapeutics

Nov-19

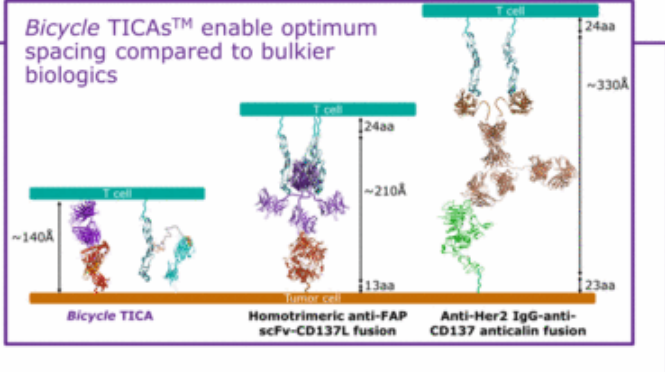


Bicycle[®]
Tumor-targeted
Immune Cell Agonists
(TICAs[™])

Properties of *Bicycles*[®] are uniquely suited to IO modulation



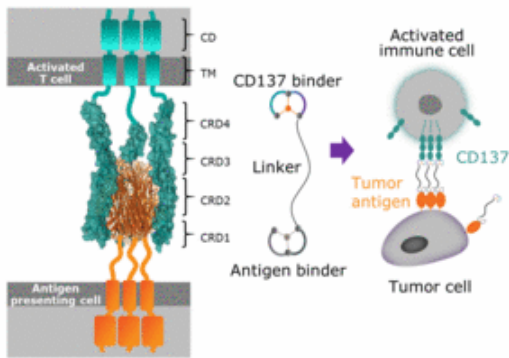
- Designed for optimal immune cell engagement
- Rapid tumor penetration
- Renal elimination avoids liver toxicity
- Small molecule COGS
- Short half-life
- Flexible dosing (mono or combo therapy)
- Tuneable PK to vary degree of activation
- Fully synthetic
- Generalizable format



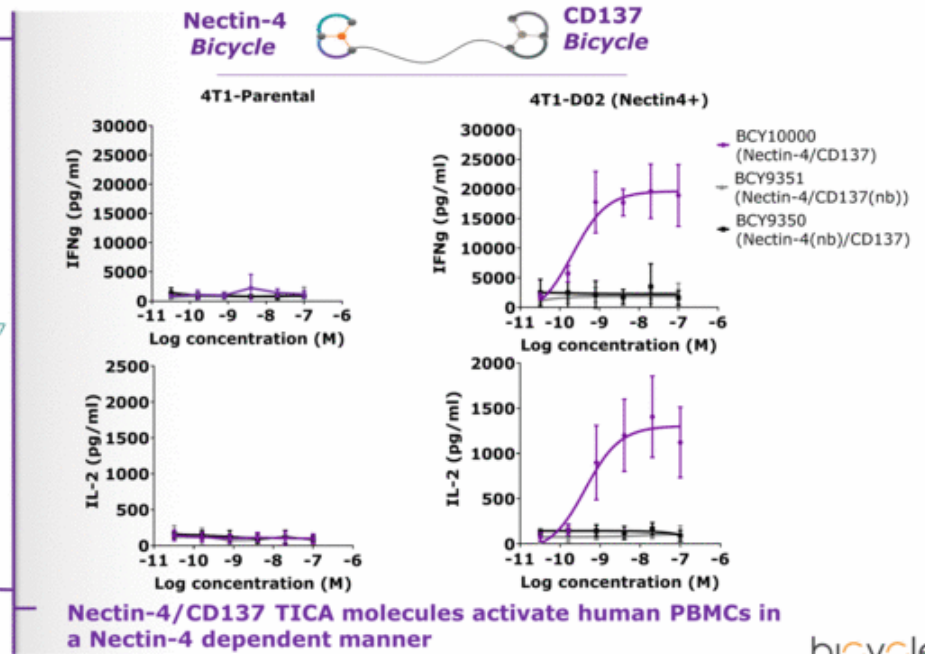
Bicycle® Tumor-targeted Immune Cell Agonists are potent and selective modulators of CD137



TICA™ molecules could achieve potent activity through receptor cross-linking across the immune synapse



CD137 provides robust anti-tumor T cell and NK cell effects



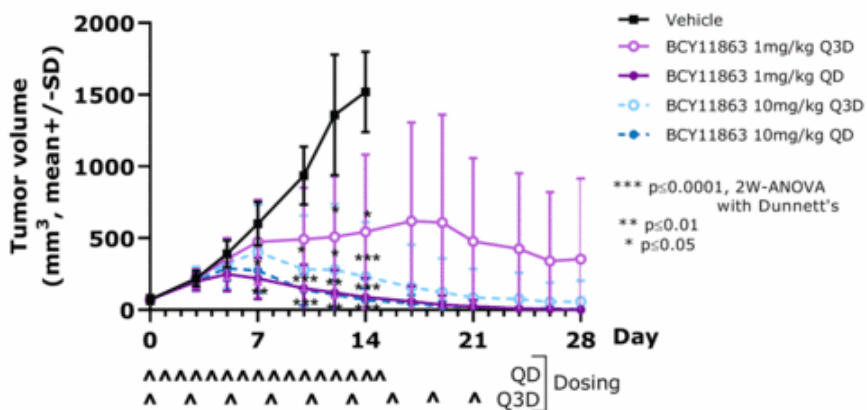
Nov-19

bicycle
therapeutics

Dosing of BT7480 leads to robust anti-tumor activity and immune memory in a syngeneic model

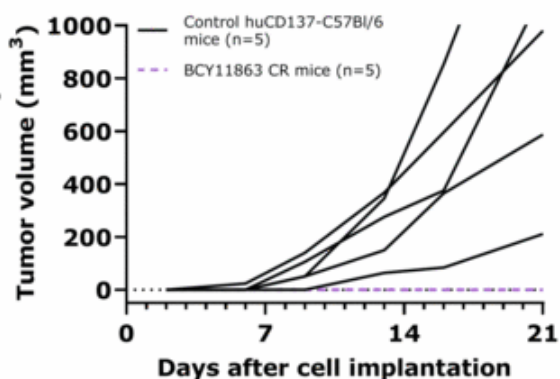


MC38 #13 in huCD137 C57Bl/6 mice



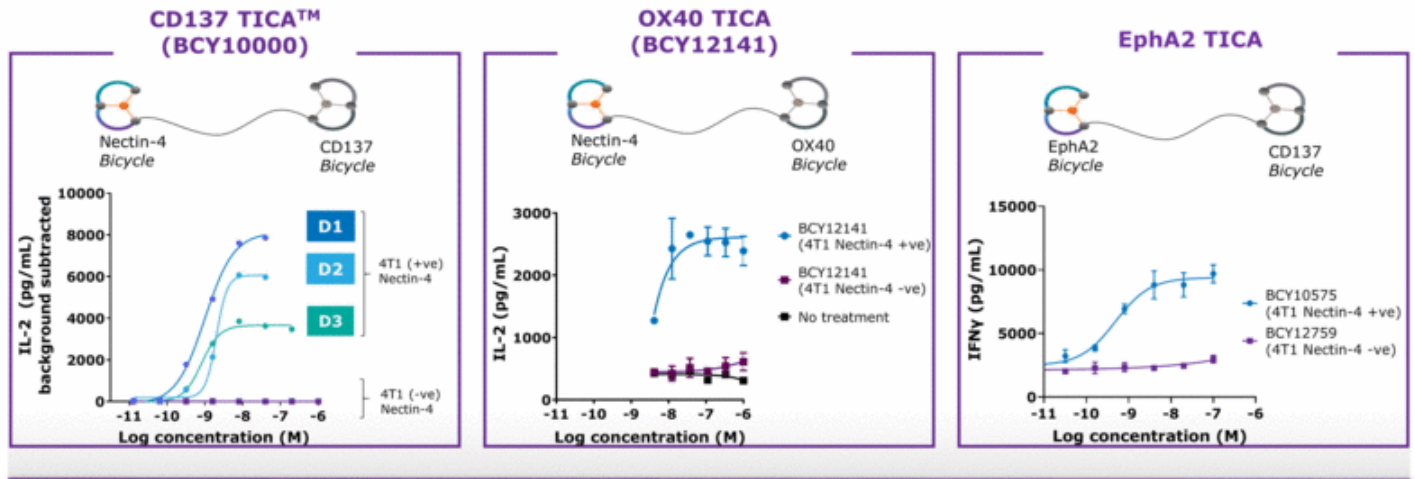
Nectin-4-CD137 TICA™ achieves rapid tumor regression

Re-challenge of CR mice with MC38#13 cells



Rechallenge of "cured" mice with tumor reimplantation shows no tumor growth, implying immunogenic memory

Immune cell engaging *Bicycles*[®] and tumor antigen engaging *Bicycles* can be readily interchanged



Potential to rapidly and efficiently generate multiple clinical candidates

The background of the top section is a light beige color with a subtle pattern of various chemical structures, including rings and chains, rendered in a slightly darker beige tone. Overlaid on this is a large, bright orange circular graphic that is not fully closed, with two gaps. The text "Beyond Oncology" is centered within this graphic.

Beyond Oncology

bicycle
therapeutics

Partnerships with leading therapeutic experts to explore broad application of *Bicycles*[®] beyond oncology



+

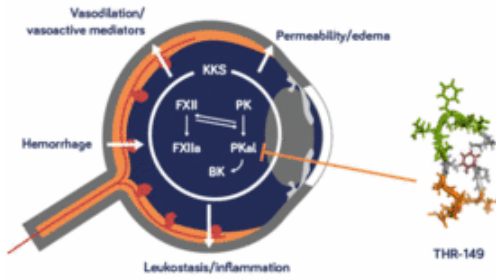


Bicycle's unique technology & deep technical understanding

Development & therapeutic expertise

Differentiated treatments for diseases with high unmet need

THR-149: Novel Pkai inhibitor provides validation of *Bicycle*[®] platform for ophthalmological diseases



Phase I trial evaluated safety of a single intravitreal injection of THR-149 at 3 ascending dose levels in 12 patients with visual impairment due to center-involved diabetic macular edema (DME)

Topline data show that THR-149 is well-tolerated and safe

No dose-limiting toxicities or drug-related serious adverse events reported

Rapid onset of action starting at Day 1

Increasing **average improvement in BCVA of up to 7.5 letters at Day 14** following a single injection of THR-149

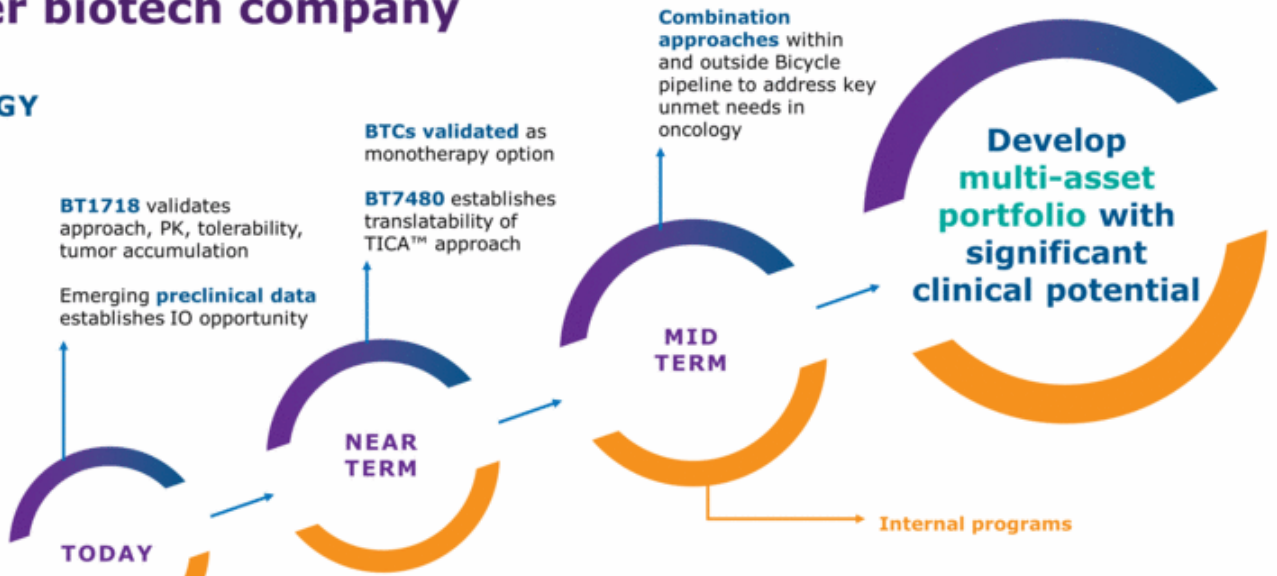
Activity maintained

An average **improvement in BCVA of 6.5 letters at Day 90** following a single injection of THR-149

*BCVA = Best Corrected Visual Acuity

Establishing Bicycle as an integrated, top tier biotech company

ONCOLOGY



Bicycle Therapeutics is led by an experienced team, growth is enabled by robust financial profile



Experts in drug development with executive experience at leading companies



Cash balance of \$96.0M* provides runway to support multiple clinical milestones



Clinical data readouts at medical meetings and trial initiations expected in 2020 across BTC, IO and partnered programs

2020 Key Events

- **BT1718** PhIIa start
- **BT5528** interim PhI data
- **BT8009** PhI start
- **BT7480** IND enabling activities



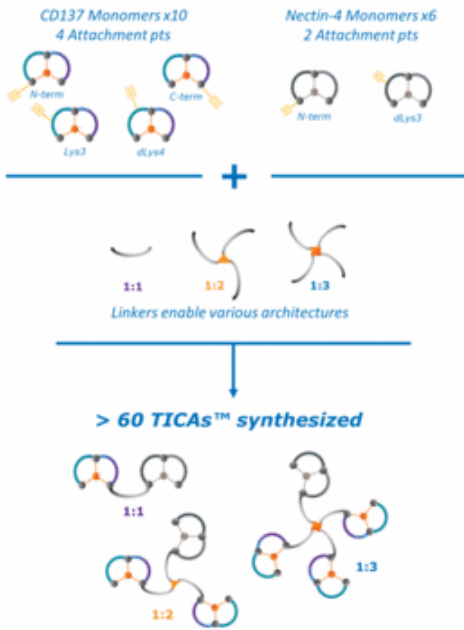
Thank you

bicycle
therapeutics



Appendix

Chemical nature of platform allows rapid “dialing in” of most desirable properties



>90 Nectin-4 TICAs molecules synthesized in combinatorial manner

Reporter cell assay data for 30 Nectin-4/CD137 TICAs in co-culture with HT1376

