Constrained peptides
Unconstrained thinking

NASDAQ: BCYC
March 2022

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 Annual Report on Form 10-K, filed with the Securities and Exchange Commission on March 1, 2022, 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.

Clinical stage biopharma company pioneering *Bicycles* – *a new differentiated class of innovative medicines*

Unique Platform

Generating Bicycles – a novel synthetic peptide modality that enables complex previously undruggable targets to be drugged.

Bicycle® modular format platform based on Nobel Prize science.

Strong intellectual property portfolio.

Internal Programs

Focused on oncology and immuno-oncology with multiple Phase I/II clinical assets (BT5528, BT8009 and BT7480).

BT5528 and BT8009 have shown preliminary signs of anti-tumor activity.

Trial updates for BT5528 and BT8009 in 2022.

Validating Partnerships

Extending the clinical utility of Bicycle® platform into diverse range of therapeutic areas.

Genentech – A Member of the Roche Group
AstraZeneca
OXURION
Innovate UK
Dementia Discovery Fund
CANCER RESEARCH UK
IONIS

Ambitious Company

Deeply experienced team

Located Cambridge UK and Lexington, MA

~119 Employees

NASDAQ: BCYC

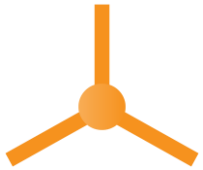
Cash balance $438.7M* (expected cash runway into 2024)

* as of December 31, 2021

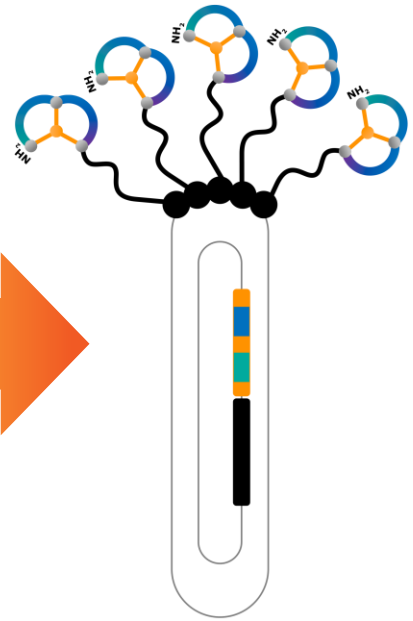
Bicycles are a new therapeutic modality – bicyclic peptides

Short linear peptide

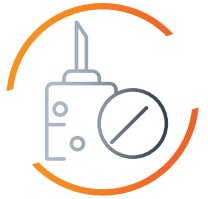
+



Scaffold
Chemical modification with scaffold



Diverse *Bicycle*® phage libraries (>10^{20})



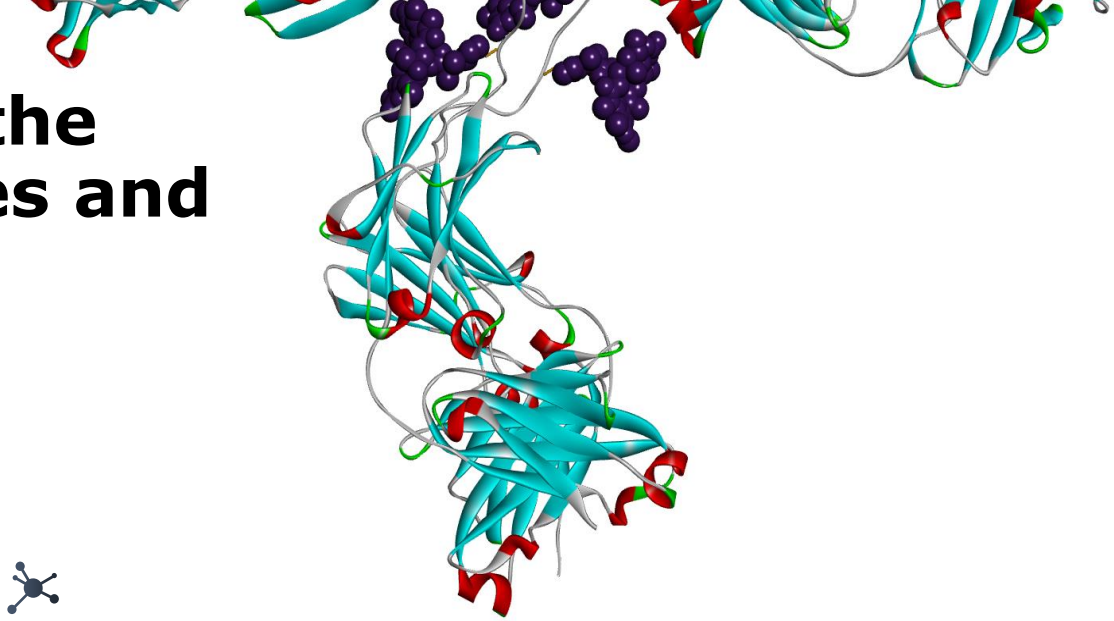
Powerful/versatile platform
- Immense combinatorial potential
- Combines advantages of both small molecules and antibodies

Multi-formats
- Monomeric Bicycles
- *Bicycle* Toxin Conjugates® (BTCs)
- Tumor-Targeted immune cell agonists (*Bicycle* TICAs)

Robust patent protection
with 122 patent families*

* as of December 31, 2021

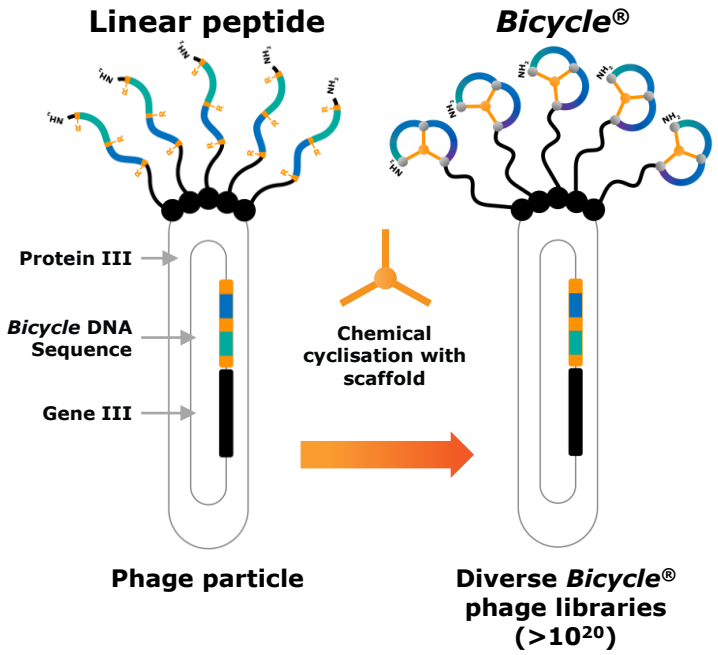
Bicycles are designed to combine the advantages of both small molecules and antibodies



	Bicycle®	Small molecule	Antibody
Small size	**Yes – 1.5-2kDa**	Yes – <0.8kDa	No – >150kDA
Specificity	**High**	Low	High
Chemical synthesis (NCEs)	**Yes**	Yes	No
Rapid tissue penetration	**Yes**	Yes	No
Complex protein targets druggable	**Yes**	Limited	Yes
Route of elimination	**Renal**	Liver	Liver

Bicycle® platform delivers a toolkit of building blocks to create novel medicines

Bicycle® Phage Display - Discovery



Peptide & Medicinal Chemistry

Optimize *Bicycle*® monomers

Non-natural Amino Acids

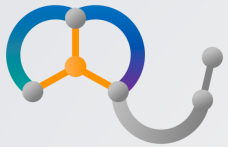
Tumor Targeting and Effector *Bicycles*

Build and Optimize Therapeutic *Bicycles*

Easy conjugation Linkers and Payloads

Potential *Bicycle*® Medicines

Monomeric *Bicycles*



Targeted Drug Conjugates

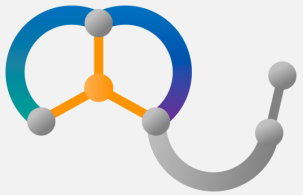
Targeted/Multi-specific *Bicycles*

bicycle therapeutics

Bicycle® formats for Oncology and Immuno-Oncology

Monomeric Bicycles

THR-149
(Kallikrein inhibitor)

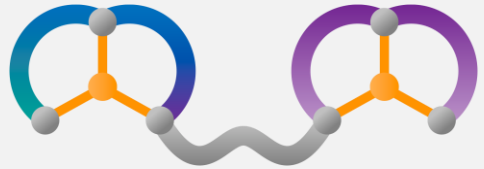


***Bicycle* Toxin Conjugates® (BTCs)**

BT5528
(EphA2)

BT8009
(Nectin-4)

BT1718
(MT1-MMP)



Multi-specific Bicycles / Tumor-targeted immune cell agonists (*Bicycle* TICAs)

BT7480
(Nectin-4/CD137)

BT7455
(EphA2/CD137)

BTCs – preclinical data indicates higher potency and specificity with fewer side effects than ADCs

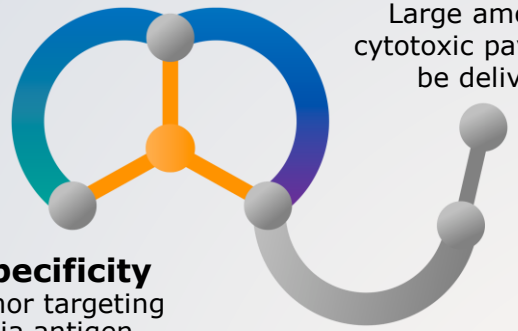
MWt of 1.5-2kDa

50-100x smaller than antibodies

High selectivity

Allows more potent toxin to be delivered directly to tumor

***Bicycle*® Toxin Conjugate (BTC™)**

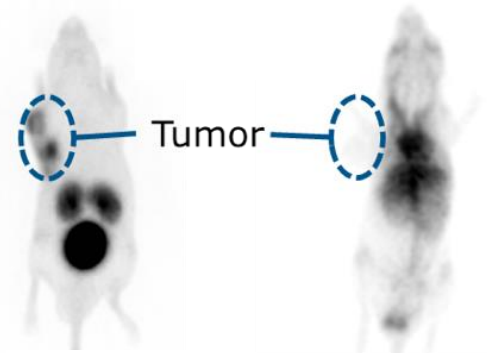


Toxin
Large amount of cytotoxic payload can be delivered

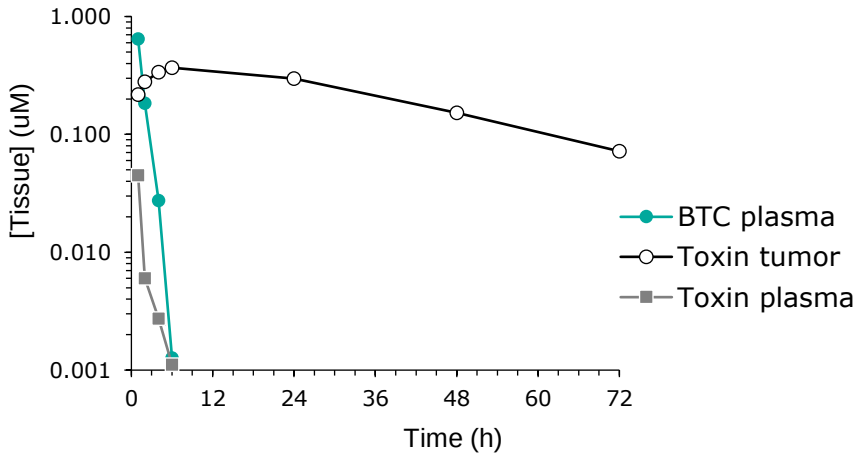
Specificity
tumor targeting via antigen

Linker
Release of toxin directly into tumor via cleavable linker

PET Imaging 40-60min

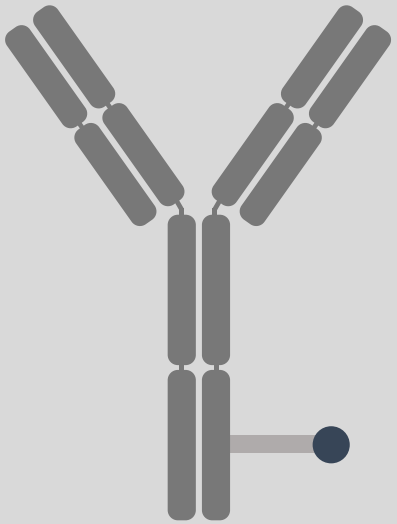


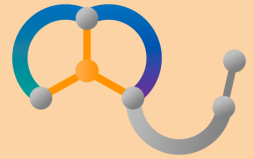
***Bicycle*®** **Antibody**



bicycle therapeutics

BTCs address limitations of antibody drug conjugates

ADC			BTC™
	?	**Tumor penetration** Accesses site of action	✓
	?	**Tumor retention** Maintenance at site of action, lower total body burden	✓
	✘	**Short systemic exposure** Maintenance at site of action, lower total body burden	✓
	✘	**Reduced liver metabolism** Improved safety profile	✓
	✘	**Renal elimination** Improved safety profile	✓
	✘	**Flexible dosing** Tailored dosing regimen minimizing toxicity	✓



BTCs designed to provide:

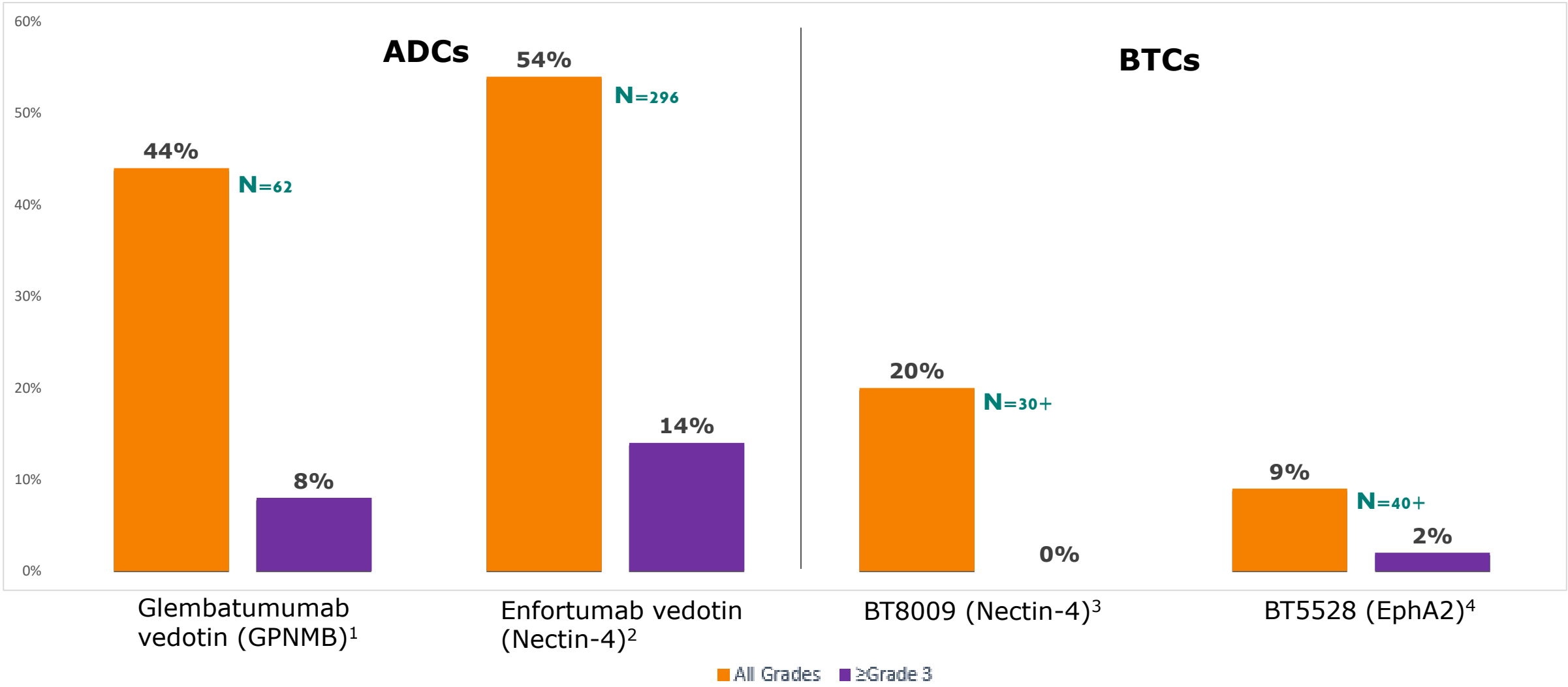
Precision targeting

Maximal therapeutic window

Optimal patient experience

We believe that the unique properties of BTCs, which are now being demonstrated in clinical trials, may lead to superior clinical outcomes for patients

Cross-study reporting of cutaneous adverse event rate

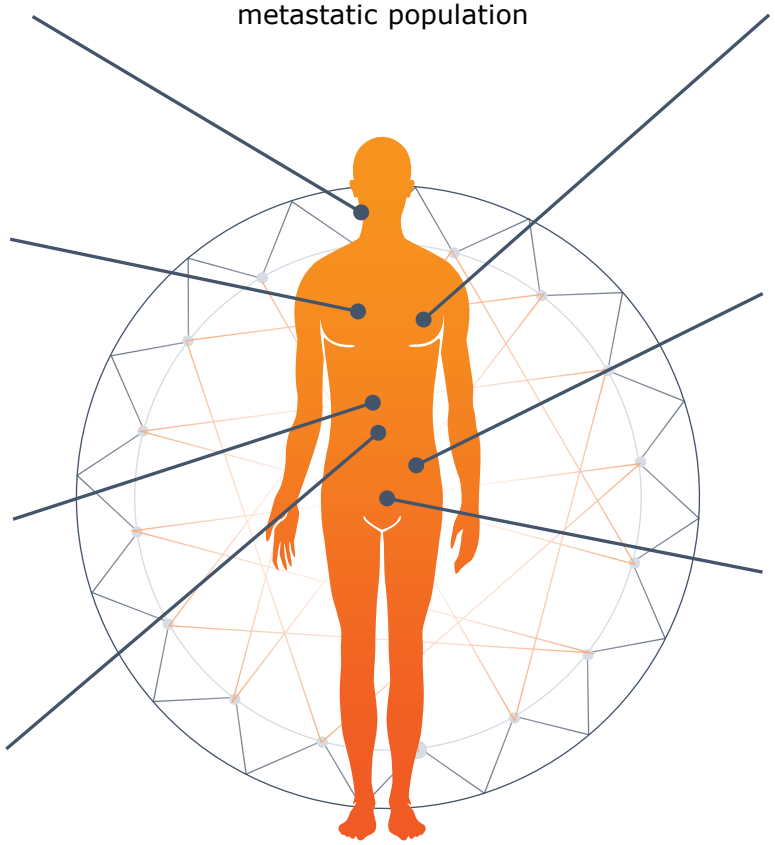


1. Ott, Patrick A., et al. "A phase 2 study of glembatumumab vedotin, an antibody-drug conjugate targeting glycoprotein NMB, in patients with advanced melanoma" *Cancer* 125.7 (2019): 1113-1123.
2. Padcev FDA Label, revised 7/2021, Table 3, Page 10
3. BT8009 Phase I/II Clinical Trial, Dec 21
4. BT5528 Phase I/II Clinical Trial, Dec 21

bicycle therapeutics

Large market potential for all BTCs

Market size (US/5EU)
Based on size of 1L drug-treated advanced / metastatic population



H&N
~45,000 patients
- 27-37%
- 53-63%

NSCLC
~230,000 patients
- 22-32%
- 34-44%
- 53-63%

Pancreatic
~80,000 patients
- 47-57%
- 14-24%

Gastric
~70,000 patients
- 22-32%
- 2-8%

TNBC
~17,000 patients
- 15-25%
- 81-91%
- 85-95%

Ovarian
~45,000 patients
- 15-25%
- 41-51%
- 91-99%

Bladder
~40,000 patients
- 31-41%
- 72-82%
- 91-99%

Detectable levels of target expression (%)

TARGET	EphA2[1]	Nectin-4[2]	MT1-MMP[3]
BTC	**BT5528**	**BT8009**	**BT1718**

[1] 6/22/20 BCYC publication (EphA2 expression by IHC in TMAs)
[2] 4/10/21 BCYC poster (Multi-Tumor Survey of Nectin-4 Expression)
[3] Market research conducted by Global Life Sciences Ltd (May 2021), on behalf of BCYC

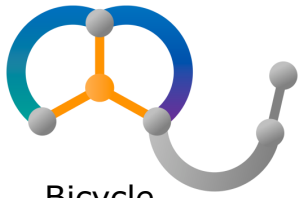
Pipeline

bicycle
therapeutics

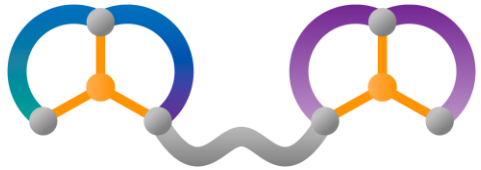
Business strategy designed to explore full potential of *Bicycle*® technology

Oncology

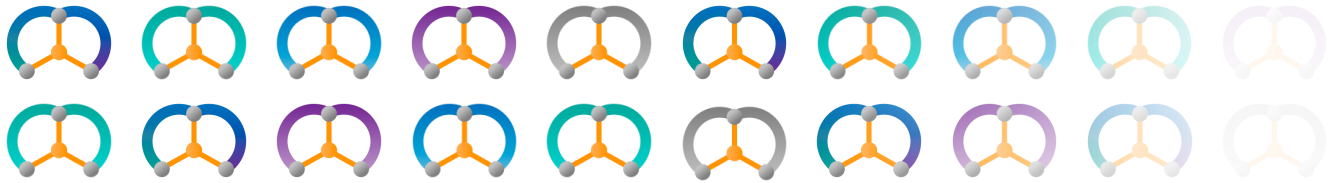
Bicycles are well suited for solid tumors, which are the majority of all cancers. Limited established treatments and high-medical need.



Bicycle Toxin Conjugates® (BTCs)



Tumor Targeted immune cell agonists (*Bicycle* TICAs)



Binders e.g., Tumor Antigens, T-Cell Receptors, NK-Cell Receptors, Transporters

CANCER RESEARCH UK

Genentech
A Member of the Roche Group

Other serious diseases

Exploring broad application of *Bicycles* beyond oncology through partnerships with leading therapeutic experts

AstraZeneca

OXURION®

Innovate UK

Dementia Discovery Fund

IONIS™

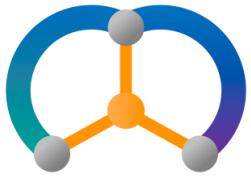
Robust proprietary and partnered pipeline

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					

bicycle therapeutics

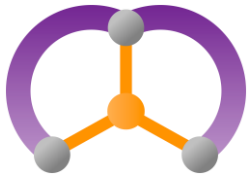
Bicycle TICA™ – Tumor-Targeted Immune Cell Agonists join immune cell-engaging and tumor-targeting Bicycles

Immune cell receptor engaging *Bicycle*®
CD137



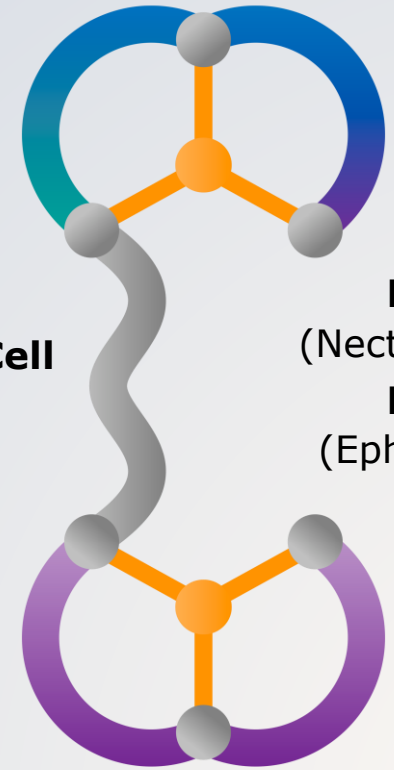
Linker

+



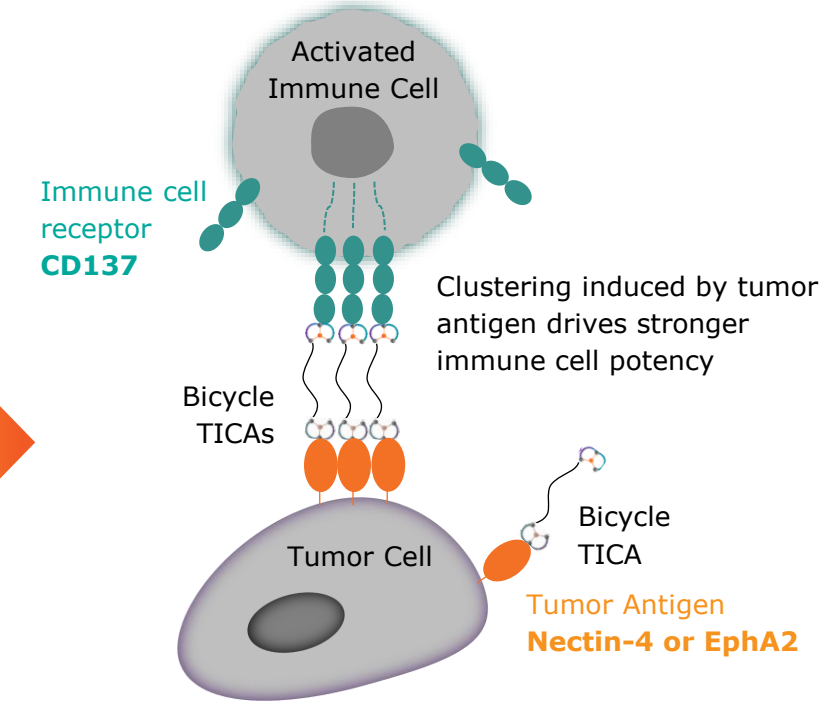
Tumor Antigen Targeting *Bicycle*®
Nectin-4 or EphA2

Tumor Targeted Immune Cell Agonists (*Bicycle* TICA™)



BT7480
(Nectin-4/CD137)

BT7455
(EphA2/CD137)



CD137 validated target
Signal 2 costimulatory receptor – drives T-cell function and survival, also expressed on NK cells and myeloid cells

bicycle therapeutics

BT7480

Nectin-4/CD137

bicycle therapeutics

BT7480: entered clinic Q4 2021

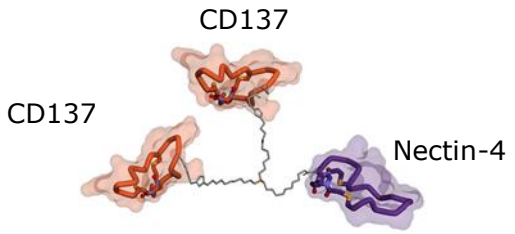
Nectin-4 and CD137 co-expressed in a variety of human tumors

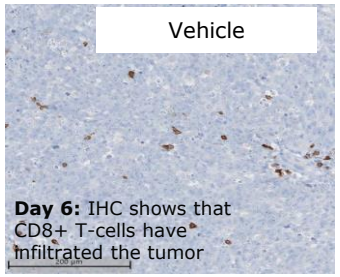
- BT7480 binds to Nectin-4 (across species) and CD137 (human, non-human primates) with high affinity. Exquisite selectivity observed in pre-clinical studies – no binding seen with >5,000 other membrane proteins.

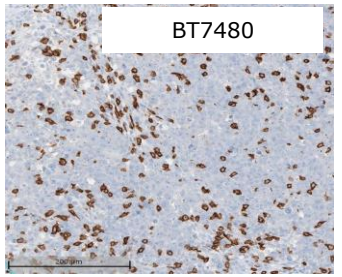
- BT7480 well-tolerated in preclinical species, with no liver tox
- BT7480 is ca. 30x smaller than comparator biologics
- US IND approved 17Sept21
  - 9 sites selected
  - QW dosing initially with dosing adjustment to Q2W

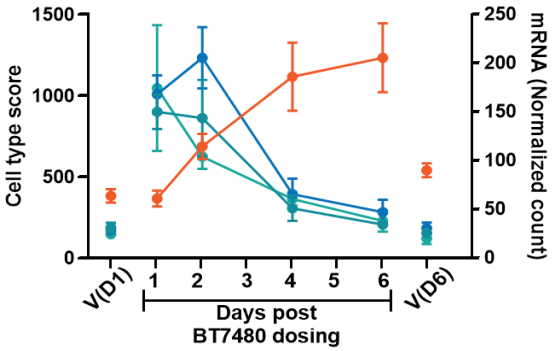
Entered clinic Q4 2021

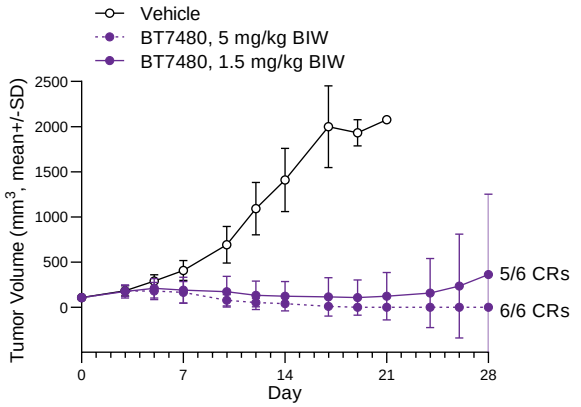
Internal	Target	Modality	Pre-clinical	IND-enabling	Phase I	Phase II
bicycle therapeutics	Nectin-4 /CD137	*Bicycle* TICA™				











BT5528 Monotherapy

EphA2

bicycle therapeutics

BT5528: EphA2 background - Target for BT5528 and MEDI-547 ADC

Erythropoietin-producing hepatocellular A2 receptor: member of Eph subfamily of receptor tyrosine kinases

Internal	Target	Modality	Pre-clinical	IND-enabling	Phase I	Phase II
bicycle therapeutics	EphA2	*Bicycle*® Toxin Conjugate				

- 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.

BT5528: Phase I dose escalation trial; overview of patient demographics and key adverse events

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)**

Adverse Events (AEs)	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 AEs: 235[1]**
- **AEs related to BT5528: 101[1]**
- **Transient Gr3/4 neutropenia at 8.5mg/m² dose[1]**
- **DLTs at 10mg/m²: pneumonitis and fatigue[1]**
- **Other toxicities (<Gr 3) predominantly hematological and GI[1]**
- **Two Gr5 events observed, one following data cut-off**

1. Data as of 14Jul21

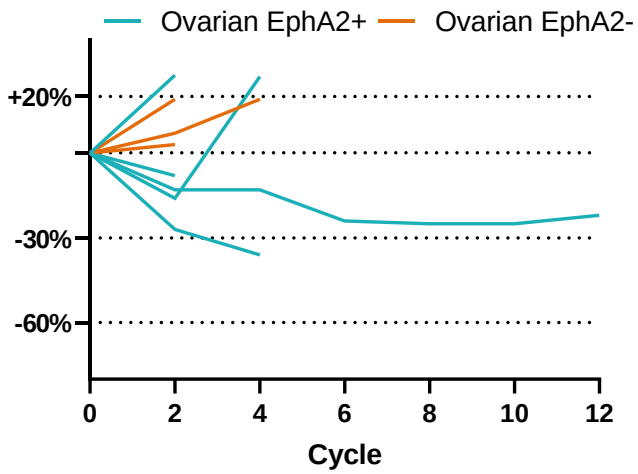
BT5528: Preliminary responses observed during phase I dose escalation trial

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

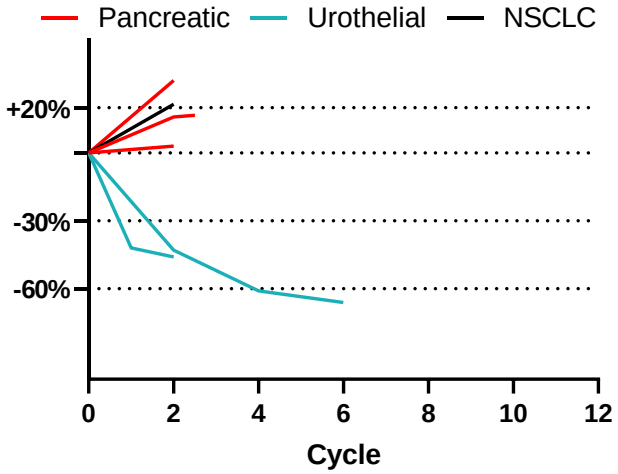
Change in target lesion size relative to baseline



Urothelial

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

Change in target lesion size relative to baseline

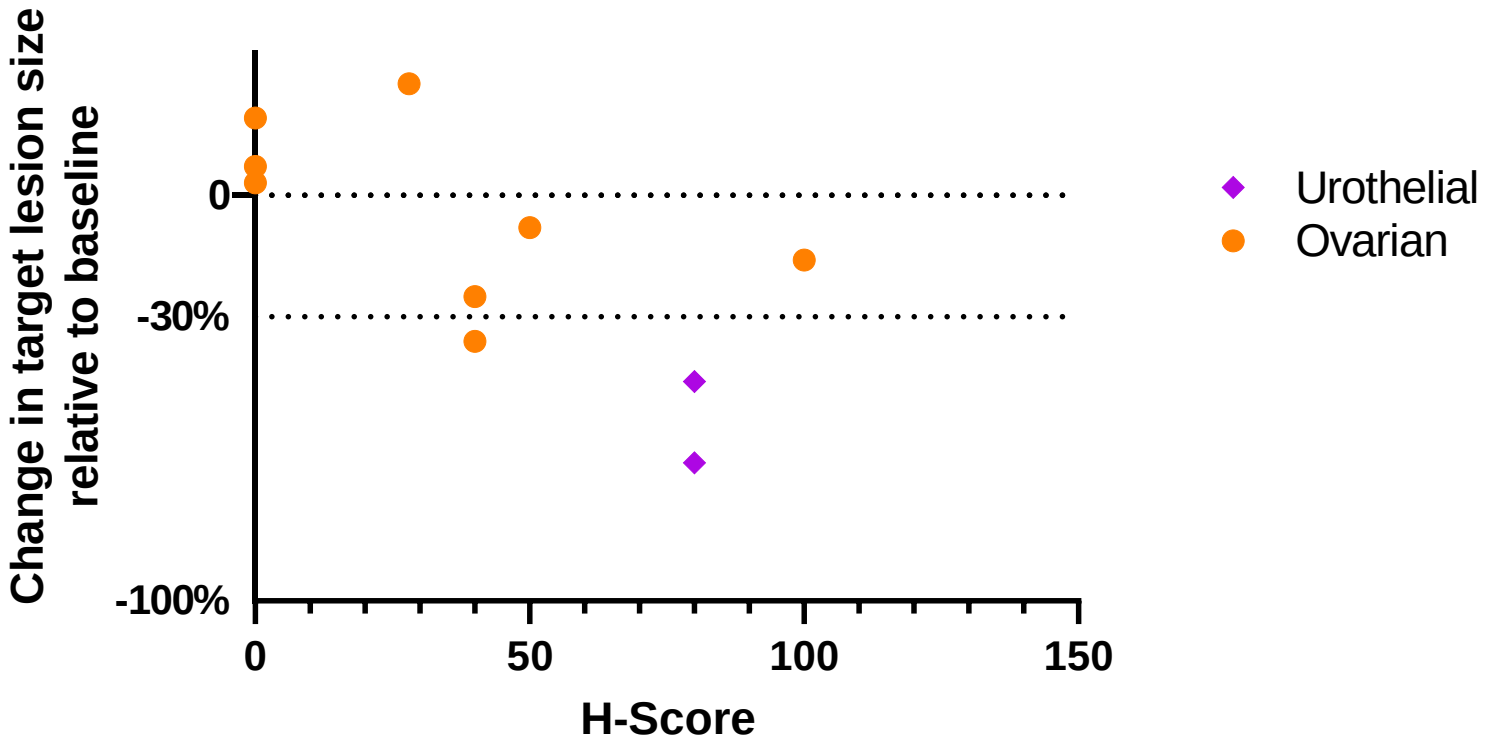


1. Partial responses under response evaluation criteria in solid tumors (RECIST) version 1.1. Data as of 14Jul21

bicycle therapeutics

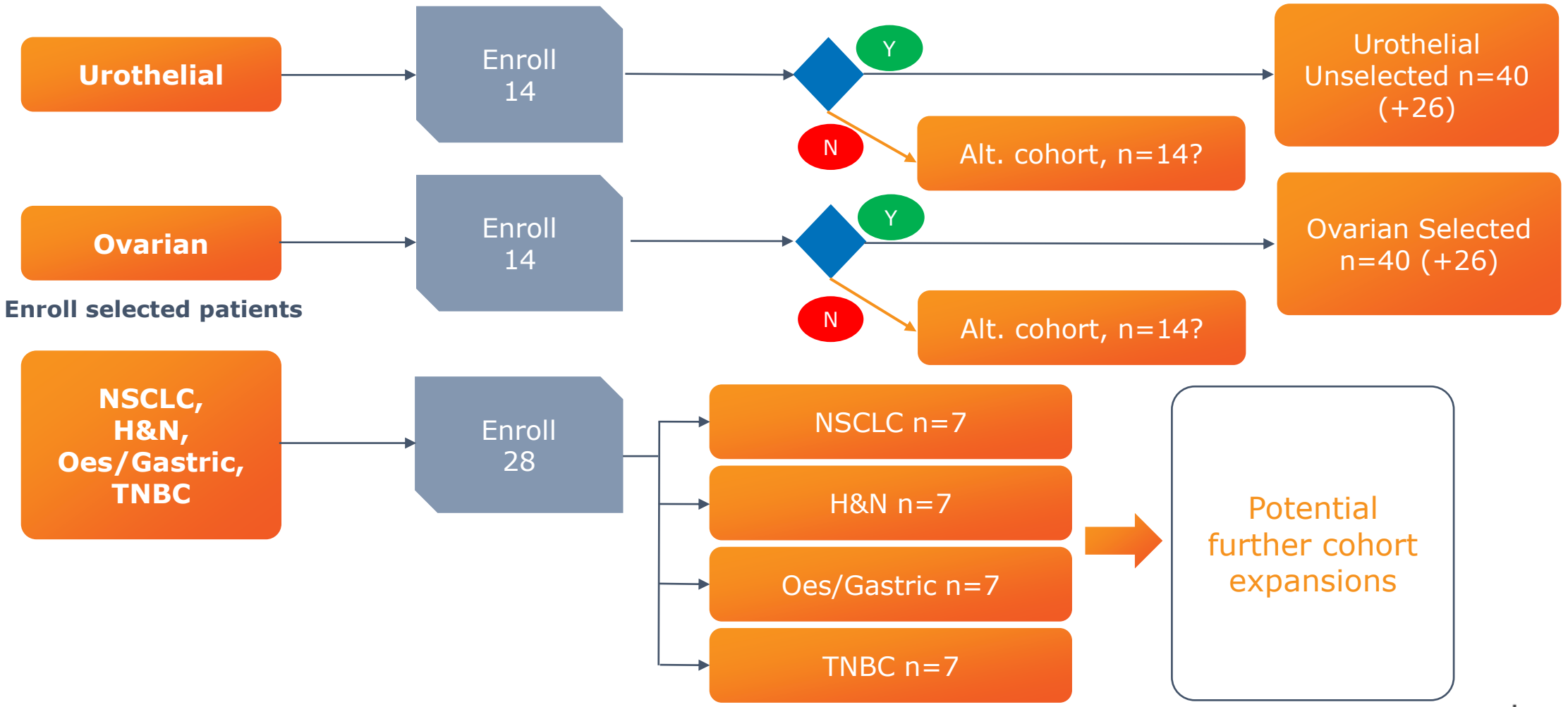
BT5528: Emerging observed relationship between EphA2 staining and responses

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



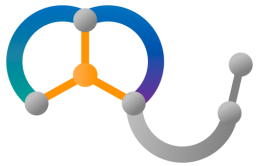
Data as of 14Jul21

BT5528 expansion: overall trial design



BT5528: Phase I dose escalation preliminary conclusions and next steps

BT5528 is a first-in-class *Bicycle*® toxin conjugate



Preliminary conclusions

- 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: no significant indications of neuropathy, eye and skin toxicities observed in BT5528 clinical trial as reported in interim Phase I dose escalation trial update on 7Oct21.
- Preliminary findings indicate activity associated with tumor expression

Preparations underway for expansion cohorts in multiple tumor types

Expected recommended Phase II dose of 6.5mg/m^2 Q2W

BT8009 Monotherapy

Nectin-4

bicycle therapeutics

BT8009: Nectin-4 background - target for BT8009 and Padcev® (enfortumab vedotin), an FDA-approved ADC

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

Internal	Target	Modality	Pre-clinical	IND-enabling	Phase I	Phase II
bicycle therapeutics	Nectin-4	*Bicycle*® Toxin Conjugate				

- 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

"PADCEV can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Immediately withhold PADCEV and consider referral for specialized care for suspected SJS or TEN or severe skin reactions. Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions."[1]

1. Padcev FDA boxed warning label, revised 7/2021

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

Demographics	All evaluable	Evaluable urothelial
Total	26 (100%)	11 (100%)
Age, years, median (range)	66 (44-81)	69 (54-81)
Sex, n (%)		
Male	15 (58%)	9 (82%)
Female	11 (42%)	2 (18%)
ECOG, n (%)		
0 (Good performance status)	11 (42%)	7 (64%)
1	15 (58%)	4 (36%)
2+	0	0
Prior therapies, median (range)	**5 (2-12)**	**2 (2-6)**

Data as of 30Sept21

BT8009: 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

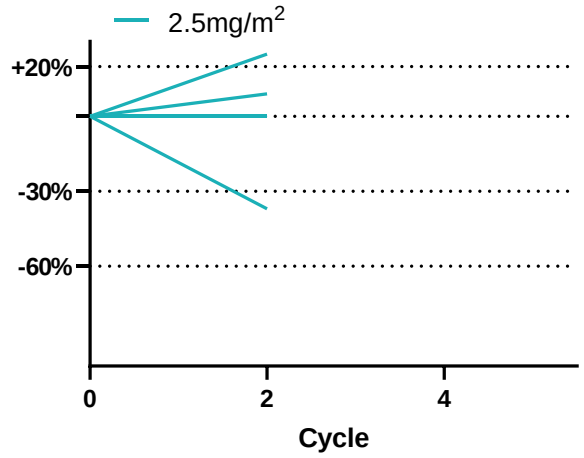
BT8009: preliminary responses observed in phase I dose escalation by dose in response evaluable urothelial cancer patients

Responses observed:

2.5mg/m²

- 1 of 4 PR[1]: -37% tumor reduction
- 2 of 4 SD
- 75% disease control

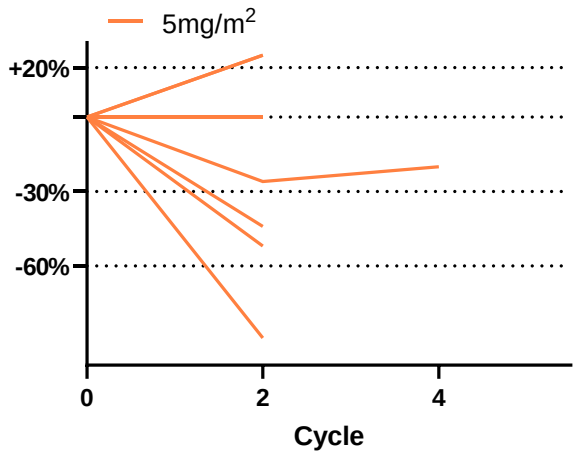
Change in target lesion size relative to baseline



5.0mg/m²

- 3 of 7 PR[1]
  - -89% tumor reduction
  - -52% tumor reduction
  - -44% tumor reduction
- 2 of 7 SD
- 71% disease control

Change in target lesion size relative to baseline



1. Partial responses under response evaluation criteria in solid tumors (RECIST) version 1.1
Data as of 30Sept21

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

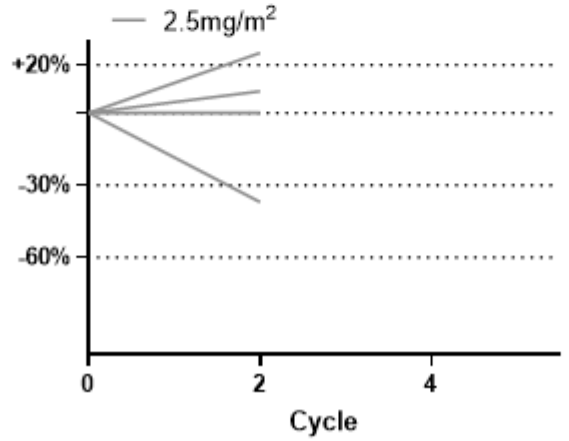
All responses have been confirmed as of 5Jan22

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



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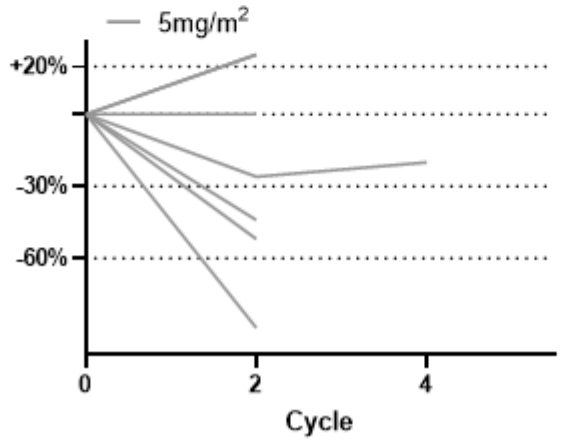


1. Partial responses under response evaluation criteria in solid tumors (RECIST) version 1.1
Data as of 30Sept21

BT8009: 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

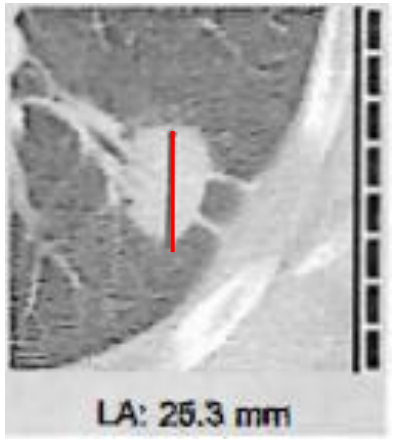
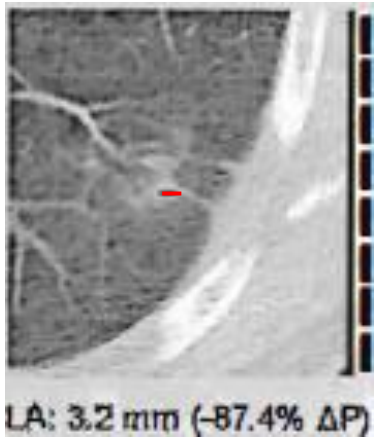
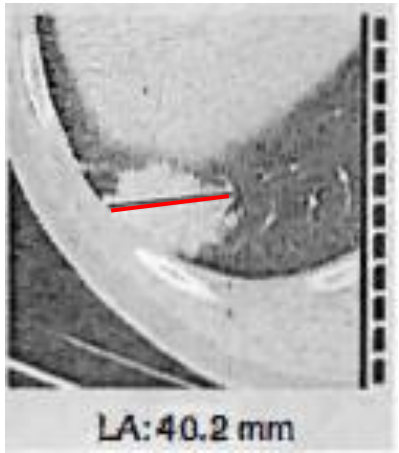
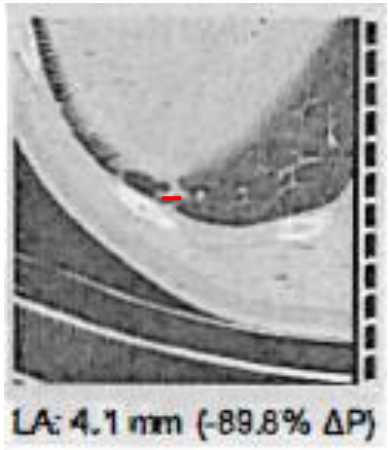
* This comparison is for illustrative purposes only. This table does not depict a head-to-head trial.
** Rosenberg, Jonathan, et al. "Interim analysis of a phase I dose escalation trial of ASG-22CE (ASG-22ME; enfortumab vedotin), an antibody drug conjugate (ADC), in patients (Pts) with metastatic urothelial cancer (mUC)" *Annals of Oncology 27 (Supplement 6): vi266-vi295*, 2016

BT8009: 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

BT8009: Comparison of Patient B pre-dose tumor images with tumor images after six months treatment (5mg/m² QW)

	Baseline	Follow-up 1	Follow-up 2	Follow-up 3
Lung lower lobe left			**Disappeared**	**Disappeared**
Lung lower lobe right			**Disappeared**	**Disappeared**

Target lesions were reduced by -100% after four months of BT8009 treatment.

Data as of 5Jan22.

BT8009: phase 1 dose escalation summary as of Sept 30 2021

No DLTs observed and escalation remains ongoing, with patients currently being enrolled in 7.5 mg/m^2 weekly and every-other-week cohorts

Data expected in 2022

- Preliminary BT8009 anti-tumor activity observed in pre-treated, urothelial cancer patients in both cohorts
- Doses within therapeutic range have been well-tolerated; most common treatment related adverse events GI-related

Expect to present additional Phase I data in 2022

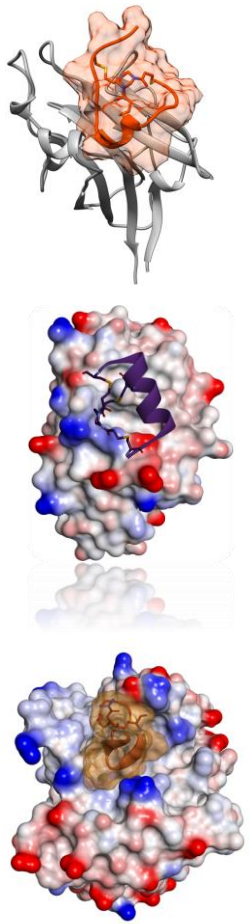
Beyond BT5528 and BT8009

Upcoming Milestones

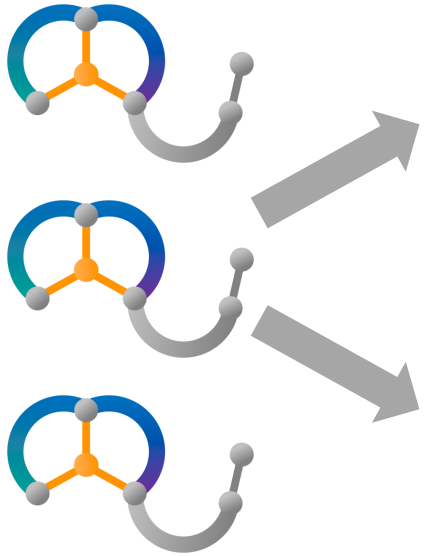
bicycle therapeutics

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

Tumor targeting *Bicycles*

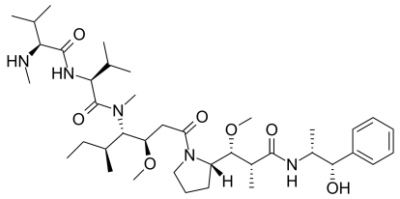


DEPTH



Building depth in internal library of tumor antigen binding Bicycles

Bicycle Toxin Conjugates®

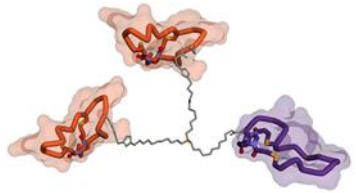


- Clinical signal observed
- Generalizable to other payloads
- Intend to build on current clinical trial observations with "wave" of 3rd Gen molecules

3rd Gen BTCs

- Broaden indications with additional targets and payloads

Bicycle® TICAs



- BT7480 entered phase I Q4 2021
- 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 *Bicycle* TICAs and / or PD1

BREADTH

Looking forward

BT5528 - plan to initiate expansion cohorts in 2022

BT8009 - dose escalation is ongoing; expect to present additional Phase I data in 2022

BT7480 – dose escalation is ongoing (first patient dosed in Q4 2021)

Third generation *Bicycle* Toxin Conjugates® and NK cell engagers are in development