Bicycle Therapeutics
Investor Presentation

November 2023

Bicycle®

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, 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 (the “SEC”) on November 2, 2023, 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 SEC. 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.

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Bicycle Therapeutics

- Science, Platform and Pipeline

Bicycle®

Bicycle Therapeutics: A clinical-stage company pioneering a new, differentiated class of innovative medicines

Unique Platform

Developing Bicycles – a novel synthetic peptide modality that enables the drugging of complex targets

Bicycle® modular format platform based on Nobel Prize science

Strong intellectual property portfolio

Internal Programs

Focused on oncology, with multiple Phase I/II clinical assets

BT8009 and BT5528 have shown signs of anti-tumor activity

Expedited development and regulatory pathway for BT8009

Trial updates for BT8009, BT5528 and BT7480 in 2H23

Validating Partnerships

Extending use of Bicycle® platform into diverse range of therapeutic areas like radiopharmaceuticals and neurology

Genentech – A Member of the Roche Group
NOVARTIS
Bayer
IONIS
OXURION
Innovate UK
dkfz.
CANCER RESEARCH UK

Ambitious Company

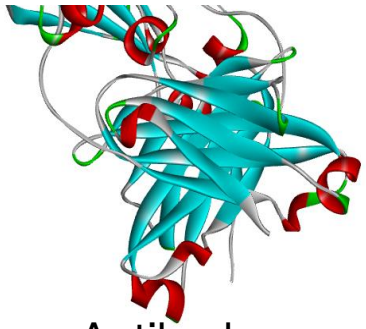
Deeply experienced team

Located in Cambridge, UK and Cambridge, MA

NASDAQ: BCYC

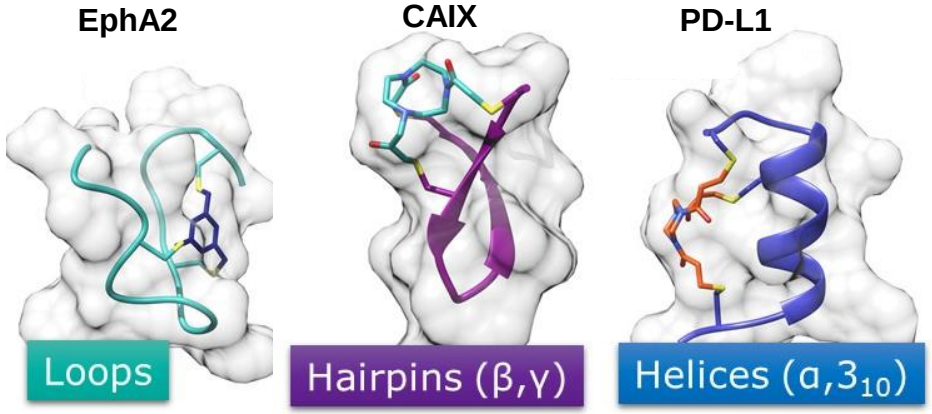
Cash and cash equivalents of $572.1M as of Sept. 30, 2023

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



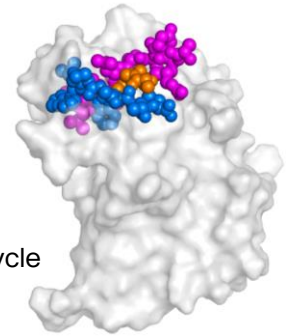
	Bicycle®	Small molecule	Antibody
Small size	**Yes 1.5 to 2 kDa**	Yes <0.8 kDa	No >150 kDa
Specificity	**High**	Low	Multiple
Chemical synthesis (NCEs)	**Yes**	Yes	No
Rapid tissue penetration	**Yes**	Yes	No
Complex protein targets druggable	**Yes**	Limited	Yes
Ease of Conjugation	**Simple**	Complex	Complex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

Biologically relevant tertiary structures

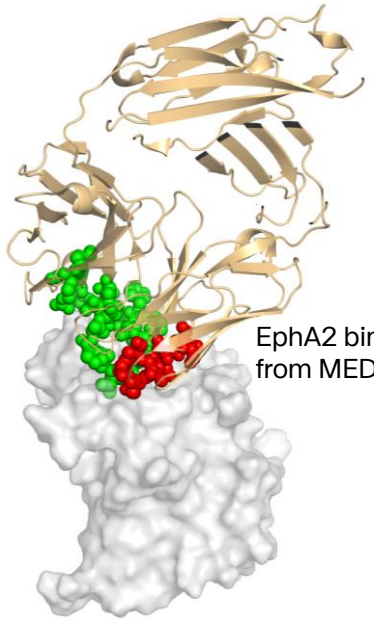


Very high ligand efficiency

	Bicycles	Fab
Weight	2.3kDa	48kDa
Size	19aa	445aa
Binding residues	16aa (85%)	24aa (5%)



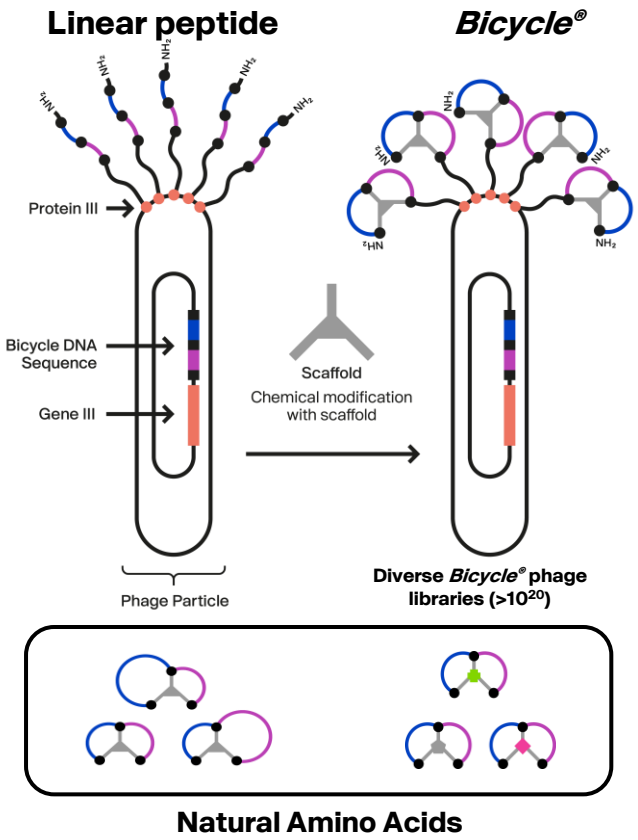
EphA2 binding bicycle from BT5528



EphA2 binding Fab from MEDI-547

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

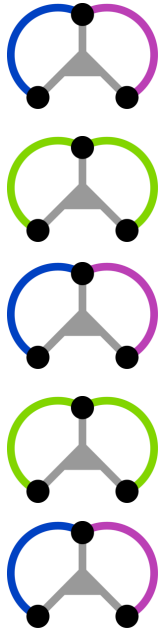
Bicycle® Phage Display - Discovery



Peptide & Medicinal Chemistry

Optimize *Bicycle® monomers*

Non-natural Amino Acids

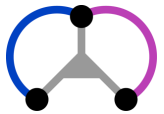


Tumor Targeting and Effector *Bicycles*

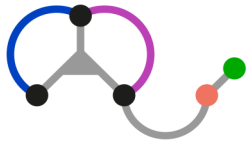
Build and Optimize Therapeutic *Bicycles*

Easy conjugation of Linkers and Payloads

Potential *Bicycle®* Medicines



Monomeric *Bicycles*



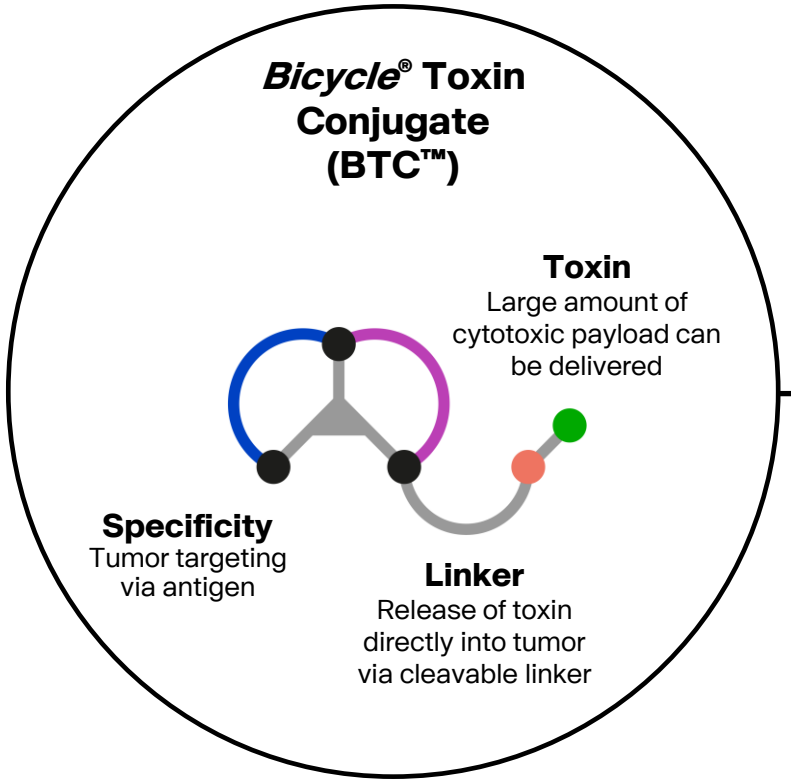
Targeted Drug Conjugates

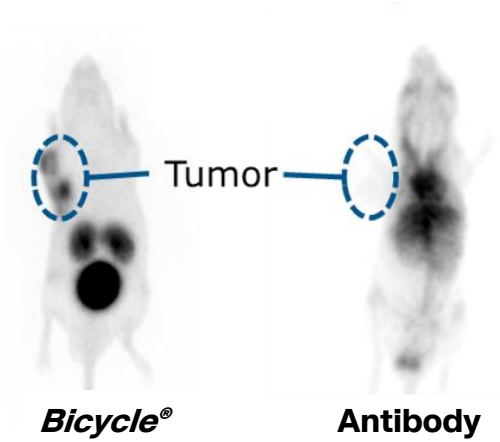
Targeted/ Multi-specific *Bicycles*

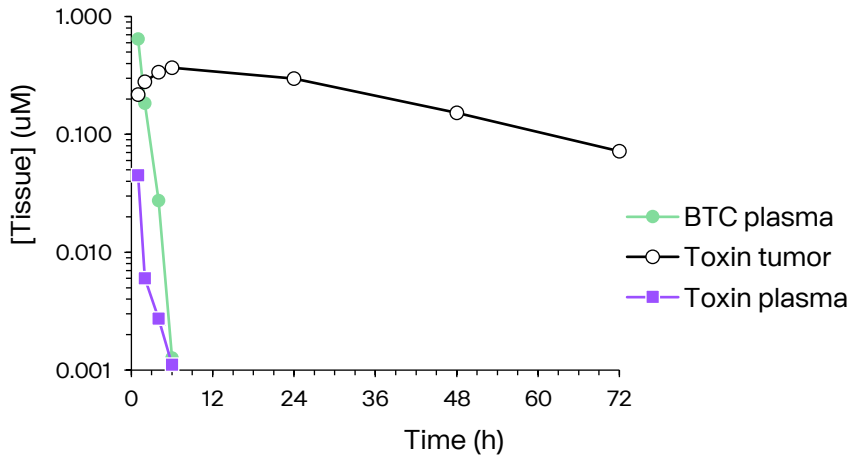
BTCs – preclinical data indicates higher potency and specificity with fewer side effects than ADCs

- **MW of 1.5-2kDa**
- **50-100x smaller than antibodies**

- **High selectivity**
- **Allows more potent toxin to be delivered directly to tumor**

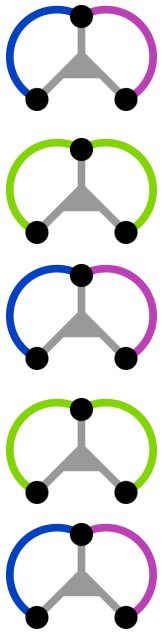






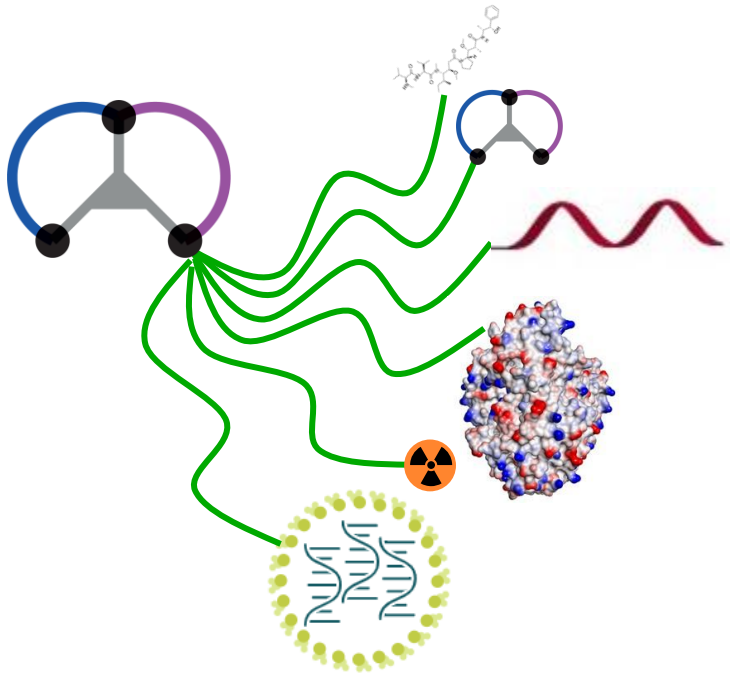
Creating a franchise of unique and industry leading opportunities

Conjugation for precise cell targeting



Antigen/tissue targeting system where we have *Bicycles* in hand
Tumor antigens
Dendritic antigens
NK cell antigens
T cell antigens
Fibroblast antigens
Skeletal Muscle antigens
Cardiac Muscle antigens
Neuromuscular antigens
Kidney antigens
Ubiquitously expressed antigens
Vascular antigens
Viral antigens
Bacterial antigens
.....but any other cell / tissue type of interest potentially can be enabled

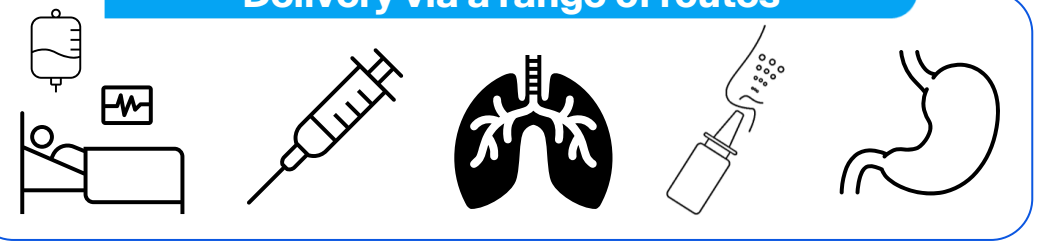
Bicycle delivers payload optionality



Precise cell targeted therapies

Therapeutic areas & applications

Delivery via a range of routes



Broad range of programs supports robust nature of Bicycle® platform

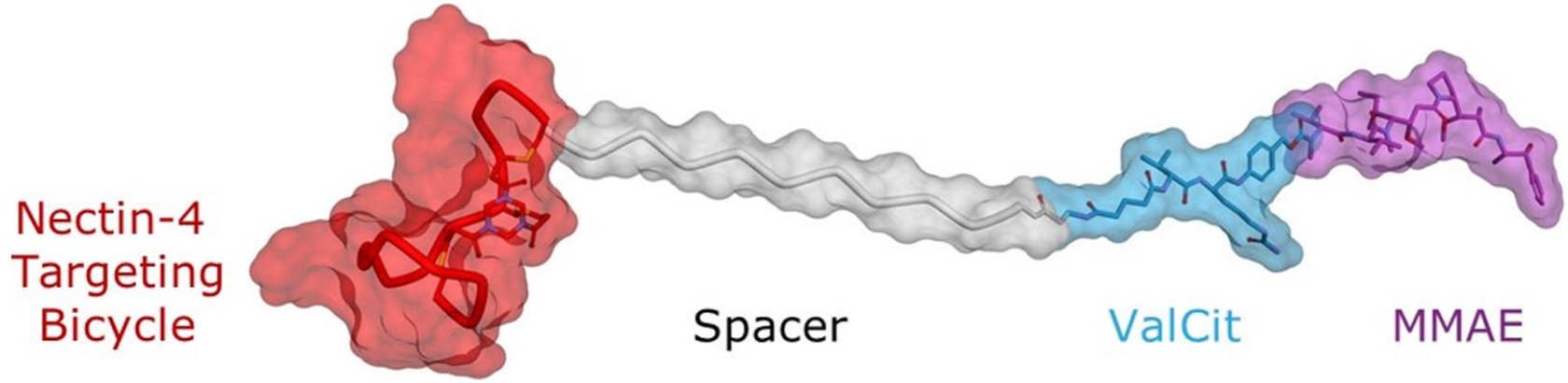
Target / Product	Partner/Sponsor	Indication	Modality	Preclinical	IND-enabling	Phase I	Phase II/ Expansion	Phase III
Internal Programs								
BT5528 (EphA2)		Oncology	Bicycle® Toxin Conjugate					
BT8009 (Nectin-4)		Oncology	Bicycle® Toxin Conjugate					
BT7480 (Nectin-4/CD137)		Immuno-oncology	Bicycle TICA™					
BT7455 (EphA2/CD137)		Immuno-oncology	Bicycle TICA™					
Undisclosed	dkfz.	Radiopharmaceutical	Bicycle® Radio Conjugate					
Partnered Programs								
THR-149 (Kallikrein inhibitor)	OXURION	Ophthalmology						
BT1718 (MT1-MMP)	CANCER RESEARCH UK	Oncology	Bicycle® Toxin Conjugate					
BT7401 (multivalent CD137 system agonist)	CANCER RESEARCH UK	Immuno-oncology						
Undisclosed	Genentech A Member of the Roche Group	Immuno-oncology						
Novel anti-infectives	Innovate UK	Anti-infectives						
Novel CNS targets	IONIS	CNS						
Novel neuromuscular targets	IONIS	Neuromuscular						
Undisclosed	NOVARTIS	Radiopharmaceutical	Bicycle® Radio Conjugate					
Undisclosed	Bayer	Radiopharmaceutical	Bicycle® Radio Conjugate					

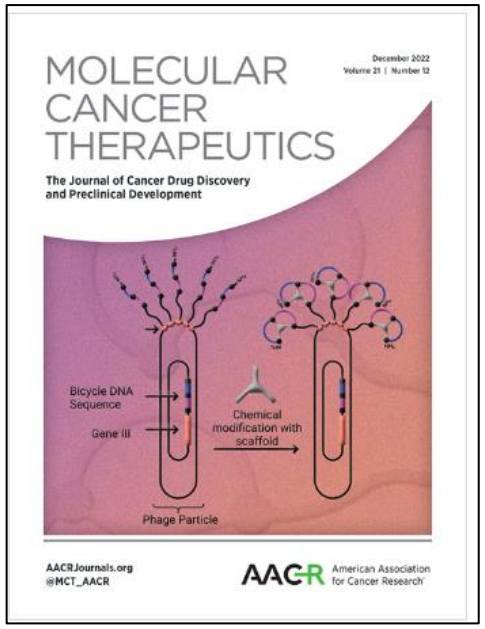
BT8009, a Bicycle® Toxin Conjugate (BTC™) targeting Nectin-4

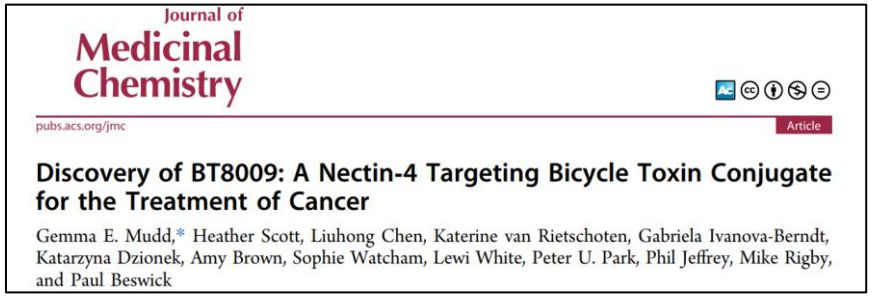
* All BT8009 data as of 20Sep22 except as otherwise noted

Bicycle®

BT8009, a Nectin-4 targeting BTC™ with excellent preclinical performance





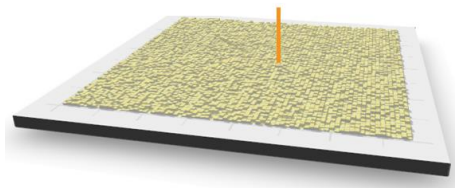


- Fully synthetic molecule
- 4kDa (vs >150kDa for mAb)
- Defined synthetic route
- Homogeneous product, single molecular species
- Cost of goods much lower than comparator biologics
- Highly stable with excellent pharmaceutical properties

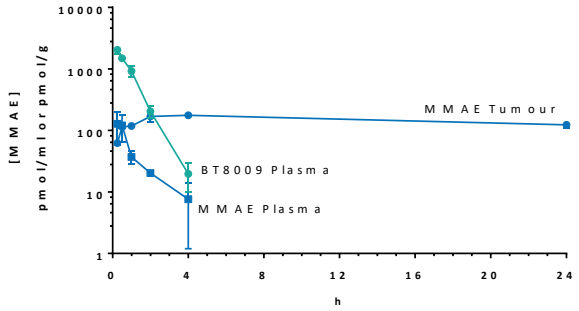
Bicycle conjugates exhibit superior preclinical performance

Selectivity

- Antibodies bind to multiple receptors (Fc, c-type lectin receptors and others)
- In internal comparator studies, Bicycles are completely selective for their biological target while mAbs can bind to more than 6 additional proteins

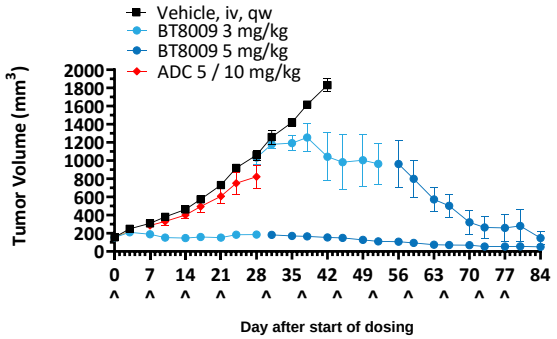


Unique and advantageous PK profile



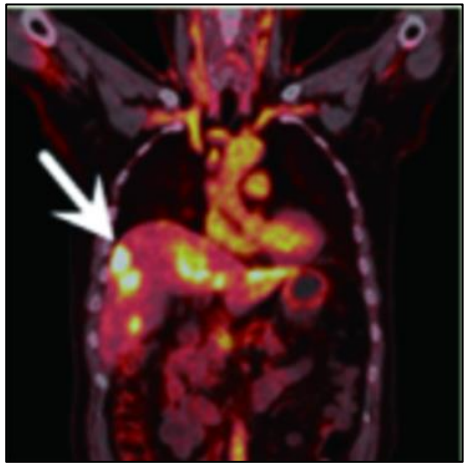
- Efficient and durable tumor MMAE delivery
- Minimal exposure to parent drug minimizes off target delivery

Potent anti-tumor activity



- Significant anti-tumor effects in multiple preclinical models including patient derived tissue
- Superiority to EV observed in preclinical patient derived xenografts

Validated tumor penetration

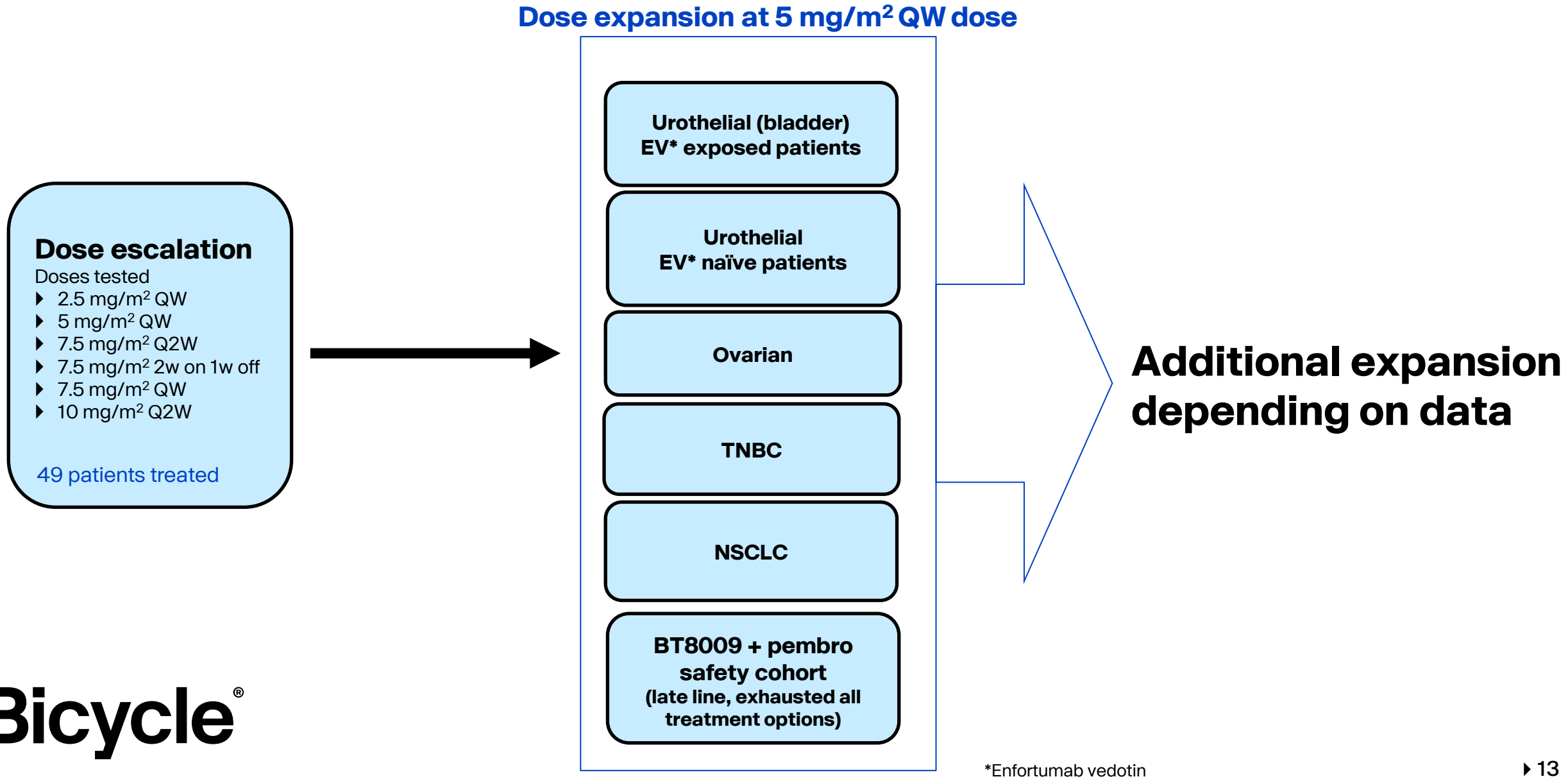


Duan *et al.* Clin Cancer Res. 2023 Apr 24

- Imaging shows Nectin-4 Binding Bicycle rapidly penetrates human tumors (15 mins) and is selectively retained

Bicycle®

Phase 1/2 study is currently in dose expansion phase, combination BT8009 dose with anti-PD1 being assessed in parallel



*Enfortumab vedotin

Overview of key demographics and disease history for all patients enrolled in Phase I dose escalation trial

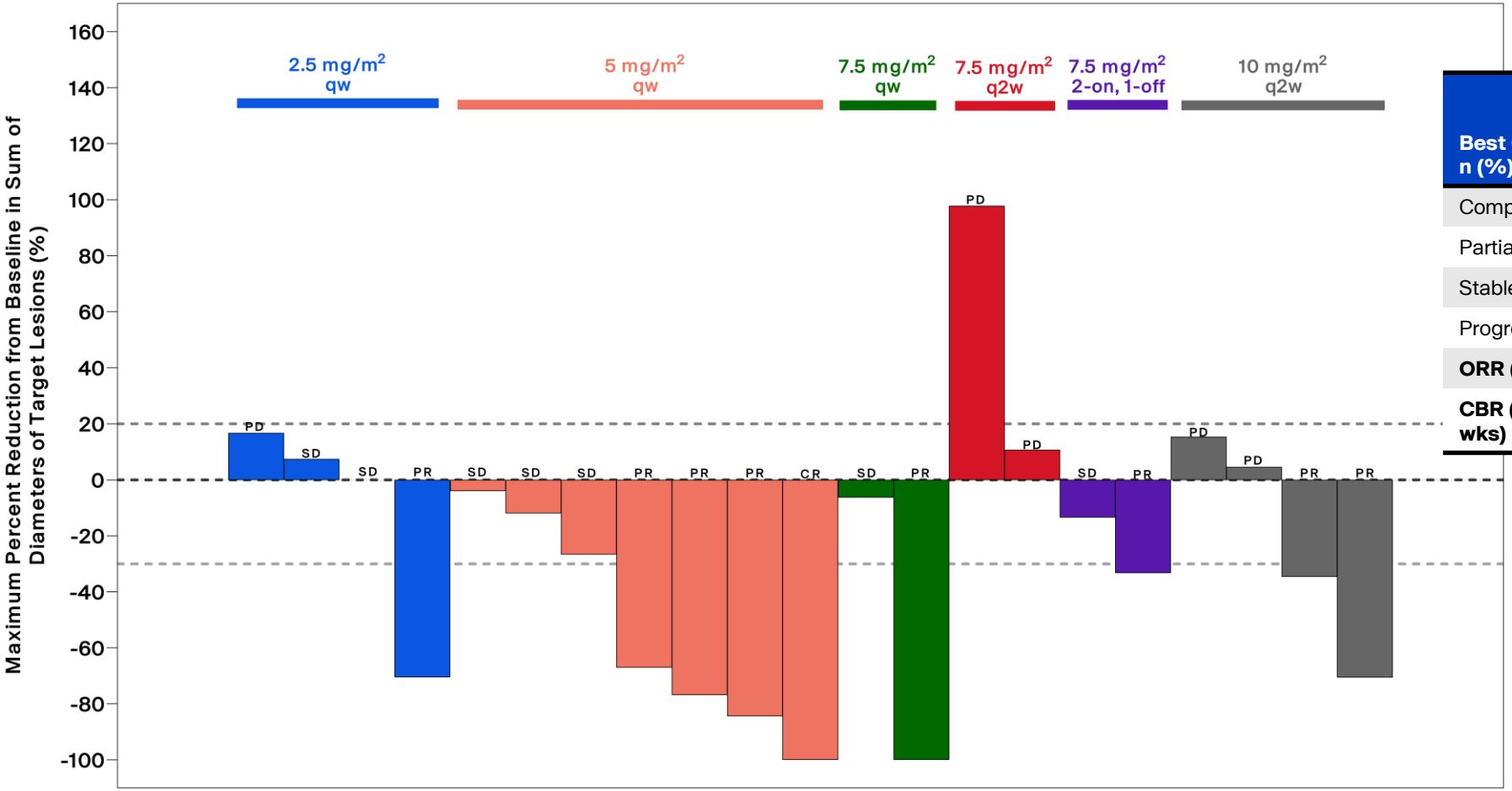
Demographics	
Total	N=49
Age, years, median (range)	66 (35-83)
Sex, n (%)	
Male	29 (59%)
Female	20 (41%)
ECOG, n (%)	
0 (Good performance status)	20 (41%)
1	29 (59%)
Prior lines of therapy, median	3

Disease history, n (%)*	
Total	N=49
Tumor type	
Breast	7 (14)
Esophageal	1 (2)
Head & Neck	3 (6)
Lung	6 (12)
Ovarian	1 (2)
Pancreatic	6 (12)
Renal	1 (2)
Urothelial	**24 (49)**

- Sum of percentages does not add to 100 due to rounding

BT8009 activity data in late line urothelial cancer

BT8009 waterfall plots across all urothelial patient dose cohorts (response evaluable patients only)



Best Overall Response[1], n (%)	Part A-1 BT8009 5 mg/m² QW (N=7)	Part A-1 BT8009 All doses (N=21)
Complete Response (CR)	1 (14)	1 (5)
Partial Response (PR)	3 (43)	8 (38)[2]
Stable Disease (SD)	3 (43)	7 (33)
Progressive Disease	0	5 (24)
ORR (CR+PR)	**4 (57)**	**9 (43)[2]**
CBR (CR+PR+SD≥16 wks)	**6 (86)**	**13 (62)**

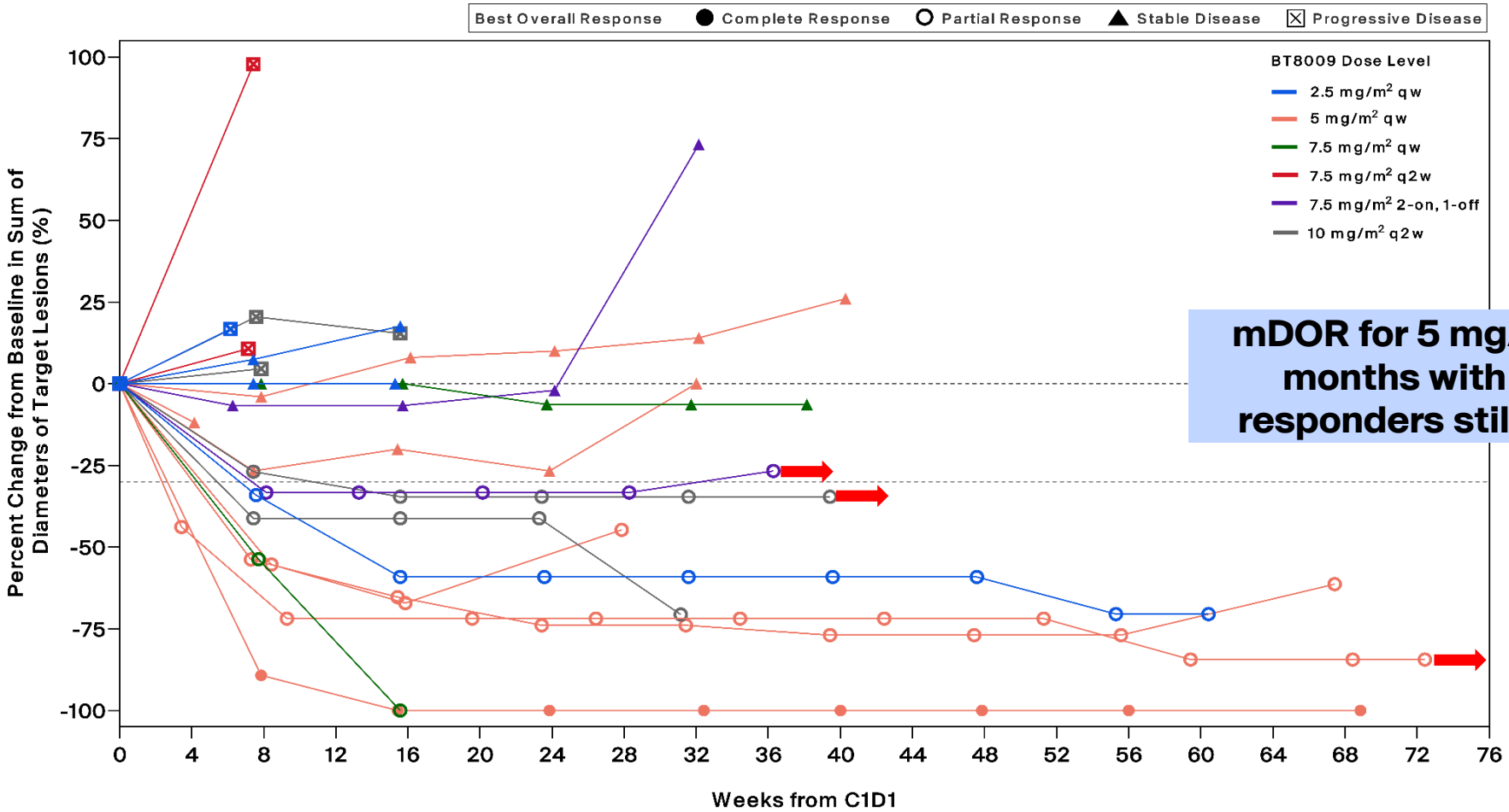
ORR = overall response rate; CBR = Clinical Benefit Rate

1. Responses under response evaluation criteria in solid tumor (RECIST) version 1.1. Response evaluable set is used which is defined as all enrolled patients with measurable disease at baseline who received at least one dose of BT8009 and had at least one adequate post-baseline disease assessment. Three patients were excluded due to no post-baseline assessments.
2. Responses under response evaluation criteria in solid tumor (RECIST) version 1.1. Includes 1 unconfirmed PR (7.5 mg/m² qw)

Data cut off date: 31Mar2023

BT8009 shows long duration of response in urothelial cancer

Spider plot across all Part A-1 urothelial patient dose cohorts (n = 21)



Active at time of data cut

mDOR for 5 mg/m² is ~14 months with 1 out of 4 responders still on therapy

Among the 9 responders[1] (CR or PR) treated in any dose level cohort, 5 (55.5%) showed responses (CR or PR) maintained ≥6 months.

[1] Responses under response evaluation criteria in solid tumor (RECIST) version 1.1. Includes 1 unconfirmed PR (7.5 mg/m² qw)

- The DOR for the CR patient in 5mg/m² who had discontinued treatment was estimated using the last disease assessment in Nov 2022. The actual DOR should be longer because the patient had another disease assessment in Jan 2023 which had not been entered into EDC by the time of data cutoff

Bicycle®

Data cut off date: 31Mar2023

Response[1] rates in urothelial cancer

Best overall response, n (%)	2.5 mg/m² qw (N=4)	5 mg/m² qw (N=8)[2]	7.5 mg/m² qw (N=4)[3]	7.5 mg/m² q2w (N=2)	7.5 mg/m² 2-on, 1-off (N=2)	10 mg/m² q2w (N=4)	Total (N=24)
Complete Response (CR)	0	1 (13)	0	0	0	0	1 (4)
Partial Response (PR)[4]	1 (25)	3 (38)	1 (25)	0	1 (50)	2 (50)	8 (33)
Stable Disease (SD)[5]	2 (50)	3 (38)	1 (25)	0	1 (50)	0	7 (29)
Progressive Disease	1 (25)	0	0	2 (100)	0	2 (50)	5 (21)
Not Evaluable	0	1 (13)	2 (50)	0	0	0	3 (13)
ORR (CR+PR)	**1 (25)**	**4 (50)**	**1 (25)**	**0**	**1 (50)**	**2 (50)**	**9 (38)**
CBR[6] (CR+PR+SD≥16 wks)	**2 (50)**	**6 (75)**	**2 (50)**	**0**	**1 (50)**	**2 (50)**	**13 (54)**

1. Responses under response evaluation criteria in solid tumors (RECIST) version 1.1
2. One patient deemed non-evaluable due to missed end of trial RECIST assessment
3. Two patients deemed non-evaluable due to coming off trial before their first scans
4. Includes 1 unconfirmed PR (7.5 mg/m² qw) and 2 that were confirmed post the 20Sep22 data cut off: 7.5 mg/m² 2-on, 1-off and 10 mg/m² q2w
5. The following patients had SD<16 wks: 1 patient at 2.5 mg/m², 1 at 5 mg/m² and 1 at 7.5 mg/m² 2-on, 1-off
6. Clinical Benefit Rate

BT8009: Anti-tumor activity outside of urothelial*

Lung cancer

Cohort (dose)	H-Score	Outcome
2.5 mg/m^2 qw	0	Progressive disease
2.5 mg/m^2 qw	240	Unconfirmed stable disease
2.5 mg/m^2 qw	180	Stable disease: >9 mos on therapy
5 mg/m^2 qw	120	Not evaluable
7.5 mg/m^2 2-on, 1-off	100	Partial response: >10 mos on therapy
7.5 mg/m^2 qw	120	Stable disease: >6 mos on therapy

Anti-tumor activity in all Nectin-4 positive, evaluable lung cancer patients

Breast cancer

Cohort (dose)	H-Score	Outcome
5 mg/m^2 qw	N/A	Not evaluable
5 mg/m^2 qw	135	Progressive disease
5 mg/m^2 qw	120	Unconfirmed stable disease
7.5 mg/m^2 q2w	165	Progressive disease
7.5 mg/m^2 2-on, 1-off	145	Unconfirmed stable disease
10 mg/m^2 q2w	100	Progressive disease
10 mg/m^2 q2w	160	Partial response: >8 mos on therapy

*Best response data, as of 31Mar23

Overview of adverse events

Number of patients with at least one, n (%)	All Cohorts[4] N=49	5 mg/m^2 qw N=20	7.5 mg/m^2 2-on, 1-off N=5
Any TEAEs[1]	49 (100)	20 (100)	5 (100)
Any TEAE, ≥ Grade 3	33 (67)	13 (65)	4 (80)
BT8009 Related TEAE	46 (94)	17 (85)	5 (100)
BT8009 Related TEAE, ≥ Grade 3	18 (37)	4 (20)	3 (60)
Any TESAE[2]	12 (24)	4 (20)	2 (40)
Any TESAE, ≥ Grade 3	9 (18)	3 (15)	2 (40)
BT8009 Related TESAE[3]	5 (10)	1 (5)	1 (20)
BT8009 Related TESAE, ≥ Grade 3	3 (6)	0	1 (20)

1. Treatment-emergent adverse event
2. Treatment-emergent serious adverse event
3. Treatment-related SAEs occurred in 5 patients. 2 were at the RP2Ds: vomiting (1) at 5 mg/m^2 qw; and nausea and neutropenia (1) at 7.5 mg/m^2 2-on, 1-off. 3 were at doses greater than the RP2Ds: pyrexia (1), sepsis (1); and febrile neutropenia and vomiting (1) at 10 mg/m^2 q2w
4. 2 DLTs occurred in 2 patients: 1 Gr3 asthenia at 7.5 mg/m^2 qw and 1 Gr4 sepsis at 10 mg/m^2 q2w

BT8009: Most frequent treatment-related adverse events (≥15%) and treatment-related adverse events of specific monitoring

Treatment-Related Adverse Event, n (%)	All Cohorts N=49 All Grades	All Cohorts N=49 Grade ≥3	5 mg/m² qw N=20 All Grades	5 mg/m² qw N=20 Grade ≥3	7.5 mg/m² 2-on, 1-off N=5 All Grades	7.5 mg/m² 2-on, 1-off N=5 Grade ≥3
Nausea	23 (47)	1 (2)	7 (35)	0	4 (80)	1 (20)
Fatigue	18 (37)	3 (6)	5 (25)	1 (5)	3 (60)	0
Diarrhea	13 (27)	1 (2)	3 (15)	0	2 (40)	0
Decreased appetite	12 (24)	1 (2)	5 (25)	0	2 (40)	0
Asthenia	11 (22)	2 (4)	3 (15)	1 (5)	0	0
Pyrexia	11 (22)	0	4 (20)	0	2 (40)	0
Neutrophil count decreased	11 (22)	3 (6)	4 (20)	1 (5)	0	0
Alopecia	11 (22)	0	5 (25)	0	2 (40)	0
Neutropenia	8 (16)	7 (14)	1 (5)	1 (5)	3 (60)	2 (40)
TRAEs of Specific Monitoring						
Neuropathy	13 (27)	1 (2)	6 (30)	0	2 (40)	0
Skin rash	6 (12)	0	2 (10)	0	0	0
Eye disorders	4 (8)	1 (2)	1 (5)	0	2 (40)	1 (20)
Pneumonitis	0	0	0	0	0	0

Limited number of treatment-related dose modifications at doses ≤ RP2Ds

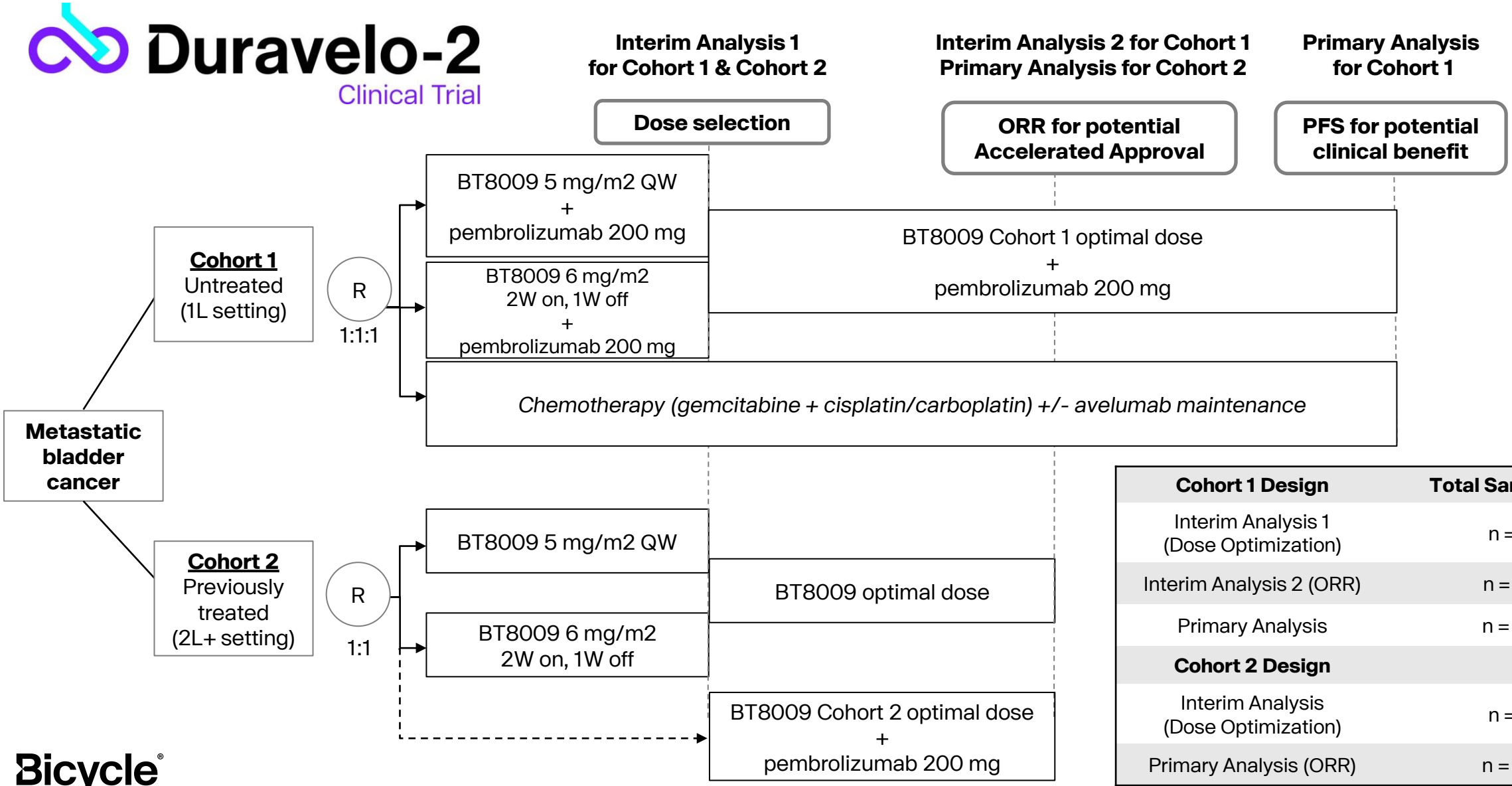
Treatment-related modifications, n (%)	(N=37)
Discontinuations	0
Interruptions	9 (24)
Reductions	6 (16)

Expediting development of BT8009 for metastatic urothelial cancer

- **Robust and innovative clinical development plan for BT8009** that is in line with the philosophy of the FDA's Project FrontRunner and follows the agency's recent draft guidance on accelerated approval of oncology therapeutics
- Alignment with the FDA on the registrational trial design, dose selection and clinical trial endpoints that could support **potential accelerated approval in a broad metastatic urothelial cancer population**
- Clinical infrastructure established, allowing **registrational trial start in 1Q 2024**
- Selected for inaugural cohort of FDA's CMC Development and Readiness Pilot (CDRP) Program to help **expedite commercial manufacturing readiness**
- **Our goal: Get this much-needed therapy to patients as quickly as possible**

Innovative trial design allows for efficient path-to-market

Duravelo-2
Clinical Trial



Cohort 1 Design	Total Sample Size
Interim Analysis 1 (Dose Optimization)	n = 60
Interim Analysis 2 (ORR)	n = 292
Primary Analysis	n = 566
Cohort 2 Design	
Interim Analysis (Dose Optimization)	n = 60
Primary Analysis (ORR)	n = 240

Bicycle®

BT8009: Clear path to establish a new standard of care in urothelial cancer and beyond

Enter market and establish clinical value

Fast Track designation supports an ambitious development program with **parallel indication assesment in mUC**

- 1L combo PD1/PDL1*
- 2L+ combo PD1/PDL1 and monotherapy

* BT8009 tolerability allows flexibility in combinations

Innovate administration and move to earlier treatment

Technology potentially allows development of **highly sought after formulations, combinations and methods of administration** in earlier lines of therapy for UC

Expand indications and explore areas of unmet need

Early and promising **signals in additional solid tumors** will be rigorously explored in monotherapy and novel combination therapy

- Non small cell lung cancer
- Triple negative breast cancer
- Ovarian cancer

Focused on maximizing the development and commercialization of BT8009

BT5528-100: End of Phase I escalation top-line results*

* All BT5528 data as of 01Aug22

Bicycle®

Overview of key demographics and disease history for all patients enrolled in Phase I dose escalation trial

Demographics	All Cohorts N=45 n (%)	6.5 mg/m^2 q2w N=15 n (%)
Age, years, mean (range)	62 (49-76)	61 (51-75)
Sex, n (%)		
Male	15 (33)	9 (60)
Female	30 (67)	6 (40)
ECOG at baseline, n (%)		
0 (Good performance status)	18 (40)	5 (33)
1	27 (60)	10 (67)
Prior lines of therapy, median (range)	4 (1-13)	4 (2-13)

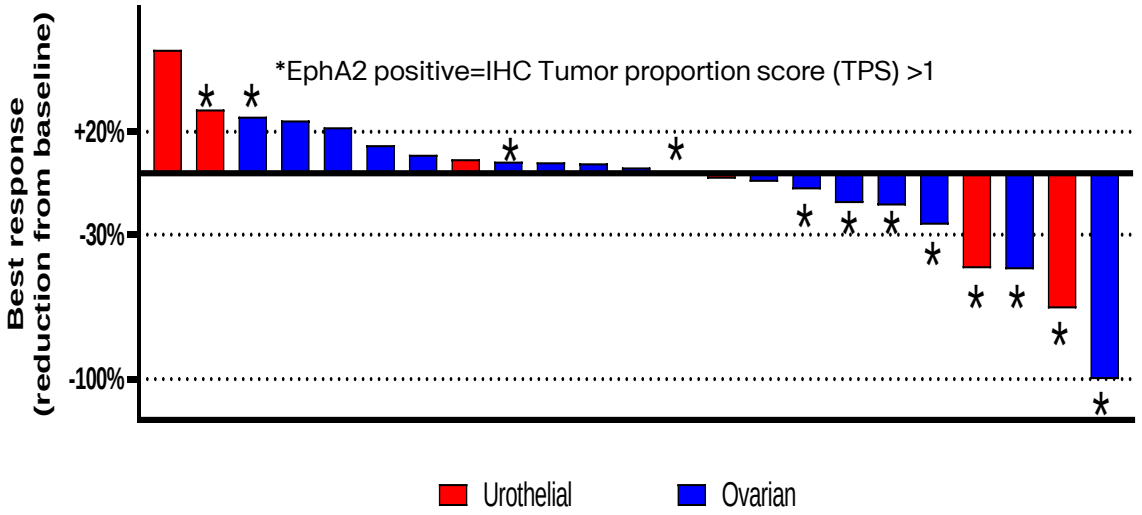
Primary Diagnosis (tumor type)	All Cohorts N=45 n (%)[1]	6.5 mg/m^2 q2w N=15 n (%)
Ovarian[2]	21 (47)	3 (20)
Urothelial[3]	8 (18)	6 (40)
Pancreatic	8 (18)	1 (7)
Lung[4]	4 (9)	2 (13)
Other[5]	4 (9)	3 (20)

1. Sum of percentages does not add to 100 due to rounding
2. Includes ovarian, fallopian tube
3. Includes bladder, urethra, urinary bladder, and urothelial carcinoma
4. Includes lung, NSCLC
5. Includes bone, rectal, stomach, and squamous of unknown origin

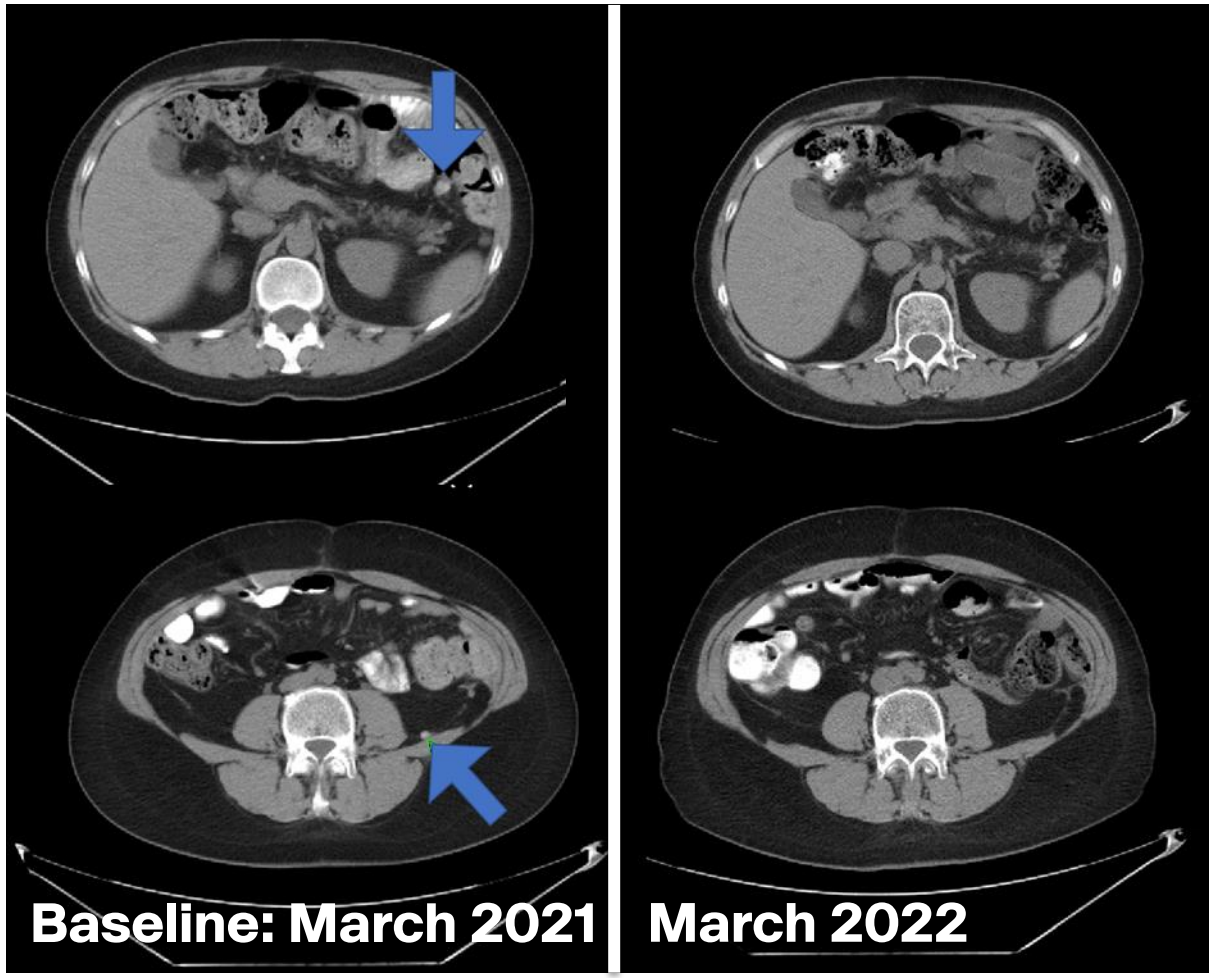
Bicycle®

BT5528: Emerging relationship between EphA2 expression and response in ovarian and urothelial cancers

Best response by RECIST in response evaluable patients



CT scans-abdomen. First in human dose escalation trial.



- Waterfall plot showing best response among urothelial and ovarian cancer patients in first in human study
- Immunohistochemistry data suggest EphA2 positive patients more likely to respond to BT5528
- Scan showing complete responder with ovarian cancer

Bicycle®

Summary of responses among EphA2+ response evaluable patients across cohorts

Best overall response	Ovarian EphA2+ N=9 n (%)	Urothelial EphA2+ N=3 n (%)
Complete Response (CR)	1 (11)[1]	0
Partial Response (PR)	1 (11)[2]	2 (67)[3,4]
Stable Disease (SD)	4 (44)	0
Progressive Disease	3 (33)	1 (33)
ORR (CR+PR)	**2 (22)**	**2 (67)**
DCR (CR+PR+SD)	**6 (67)**	**2 (67)**

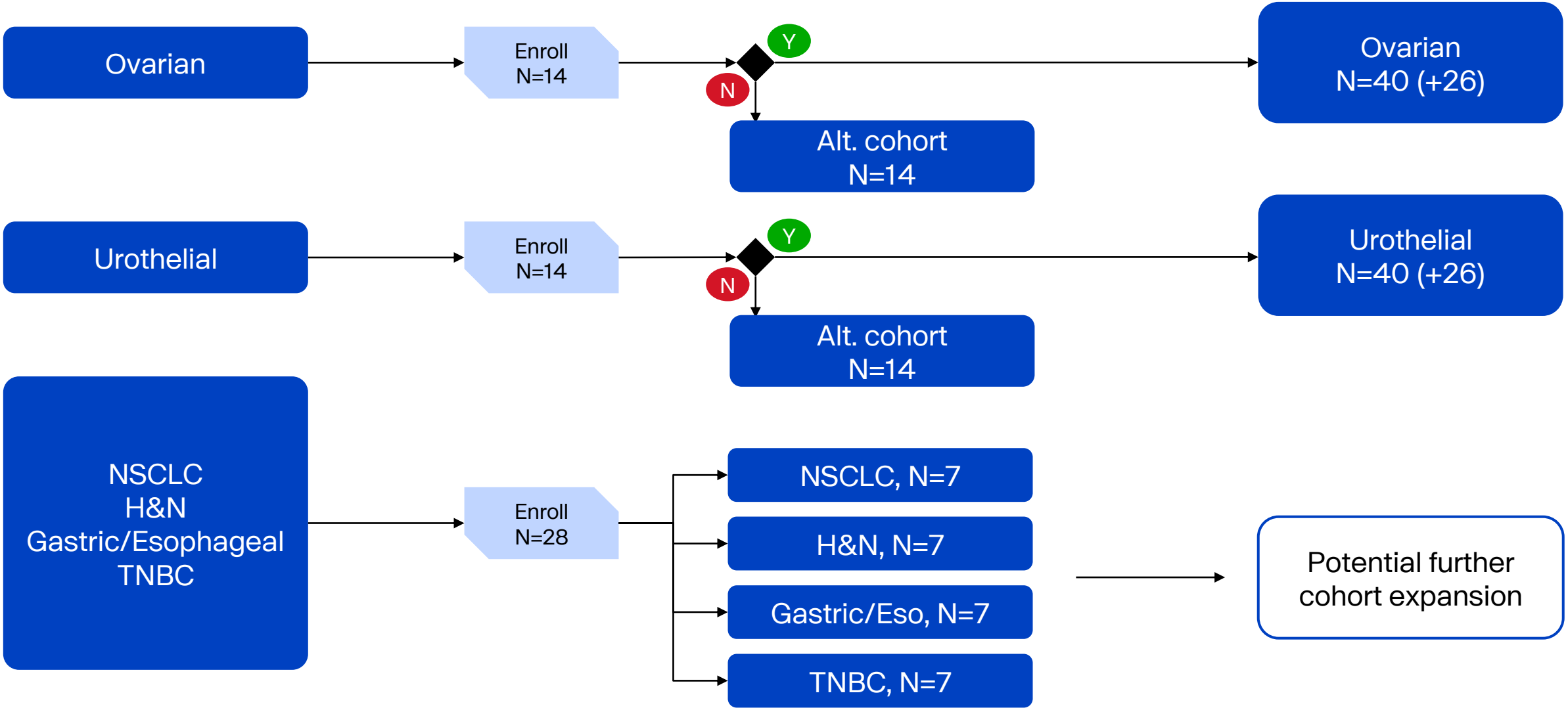
1. Ovarian CR patient started at 8.5 mg/m^2 q2w and reduced to 6.5 mg/m^2 q2w after 12 28-day cycles. Patient remains on therapy >16 months
2. Ovarian PR patient started at 6.5 mg/m^2 q2w and remains on therapy >4 months
3. A urothelial responder started at 8.5 mg/m^2 q2w and reduced to 6.5 mg/m^2 q2w after 1 dose. They remained on therapy ~6 months
4. A urothelial responder started at 10 mg/m^2 q2w and reduced to 6.5 mg/m^2 q2w after 1 dose. They remained on therapy ~3 months

BT5528: Most frequent treatment-related adverse events (≥15%) and treatment-related adverse events of specific monitoring

Treatment-Related Adverse Event, n (%)	All Cohorts N=45 All Grades	All Cohorts N=45 Grade ≥3	6.5 mg/m² q2w N=15 All Grades	6.5 mg/m² q2w N=15 Grade ≥3
Nausea	20 (44)	1 (2)	8 (53)	0
Diarrhea	16 (36)	1 (2)	7 (47)	1 (7)
Fatigue	15 (33)	2 (4)	6 (40)	0
Vomiting	12 (27)	1 (2)	3 (20)	0
Anemia	10 (22)	4 (9)	4 (27)	2 (13)
Neutrophil count decreased	8 (18)	7 (16)	0	0
Decreased appetite	7 (16)	0	4 (27)	0
Alopecia	7 (16)	0	1 (7)	0
Peripheral neuropathy[1]	7 (16)	0	2 (13)	0
TRAEs of Specific Monitoring				
Skin rash[2]	2 (4)	0	0	0
Eye disorders[3]	2 (4)	0	1 (7)	0
Hemorrhage	0	0	0	0

1. Peripheral neuropathy events include neuropathy peripheral, muscular weakness, peripheral sensory neuropathy, gait disturbance, neuralgia, paresthesia
2. Both skin rash TRAEs were maculopapular
3. Eye disorder TRAEs were dry eye, visual impairment, and visual blurred

BT5528 Expansion: Overall trial design



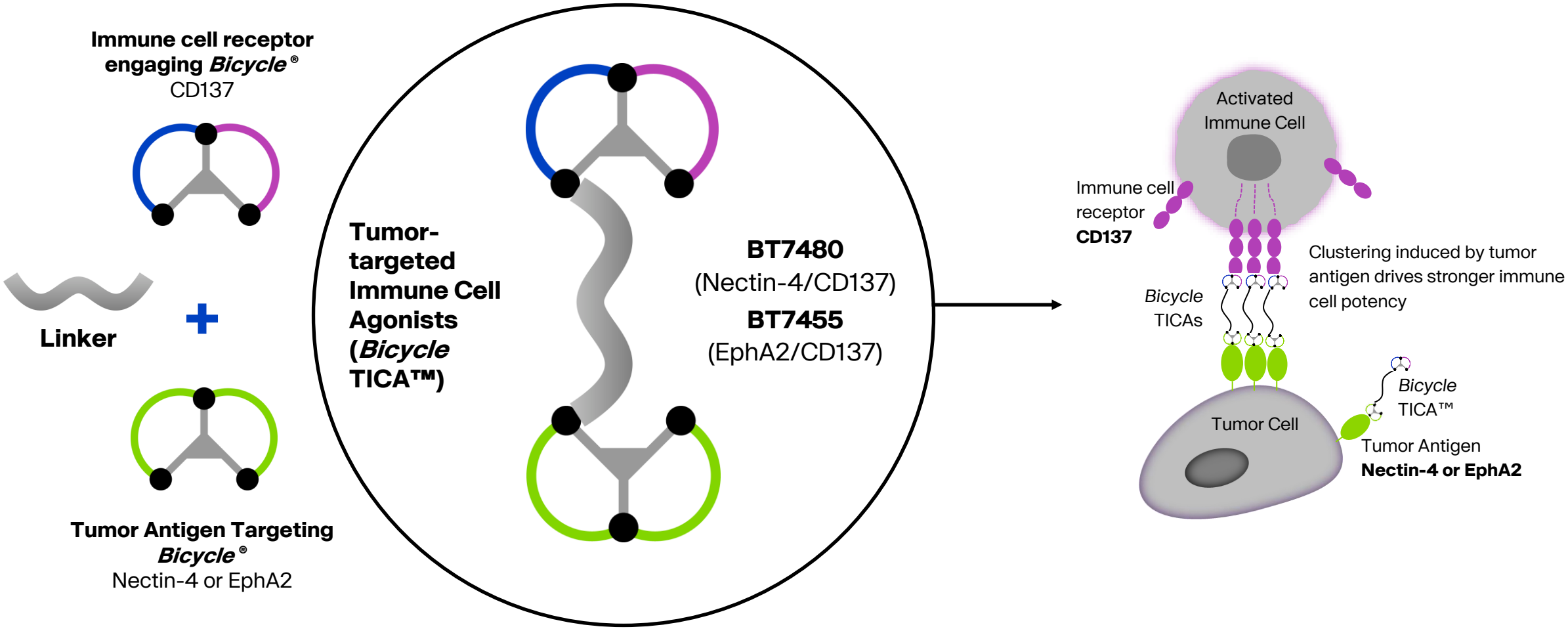
Bicycle®

Bicycle Therapeutics

- BT7480: Nectin 4/CD137

Bicycle®

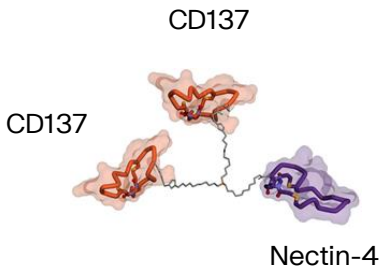
Beyond BTCs: *Bicycle* TICA™ – Tumor-targeted Immune Cell Agonists enable precision guided activation of the immune system

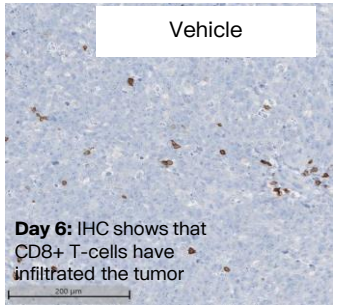


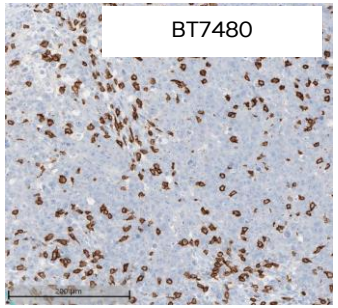
BT7480 currently in early clinical testing

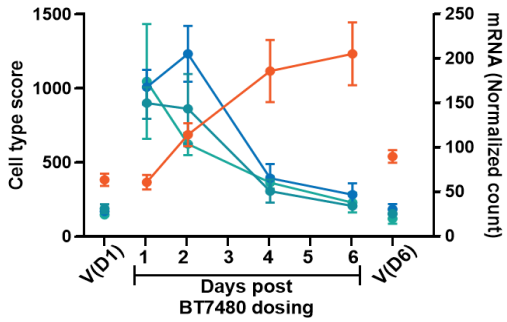
Nectin-4 and CD137 co-expressed in a variety of human tumors

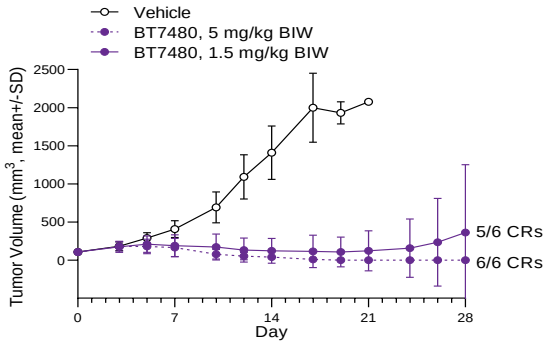
- BT7480 binds to Nectin-4 (across species) and CD137 (human, non-human primates) with high affinity. Exquisite selectivity observed in pre-clinical studies – no binding seen with >5,000 other membrane proteins
- BT7480 well-tolerated in preclinical species, with no liver tox
- BT7480 is ca. 30x smaller than comparator biologics
- Will give Phase I clinical update in Dec 2023











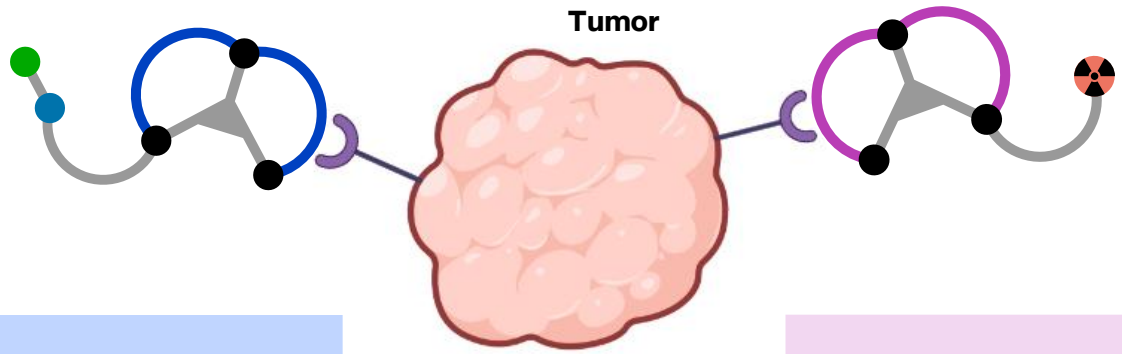
IHC stainings and charts depict pre-clinical results

Bicycle Therapeutics

- Bicycle Radio Conjugates

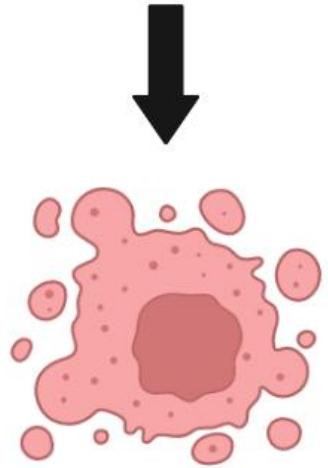
Bicycle®

Bicycles have demonstrated clinical anti-tumor activity delivering cytotoxic payloads and are ideally suited to delivering radionuclide payloads



Bicycle Toxin Conjugates (BTCs)

- Delivering cytotoxic small molecule
- Cleavable linker
- Early clinical validation



Tumor cell death

Bicycle Radio Conjugates (BRCs)

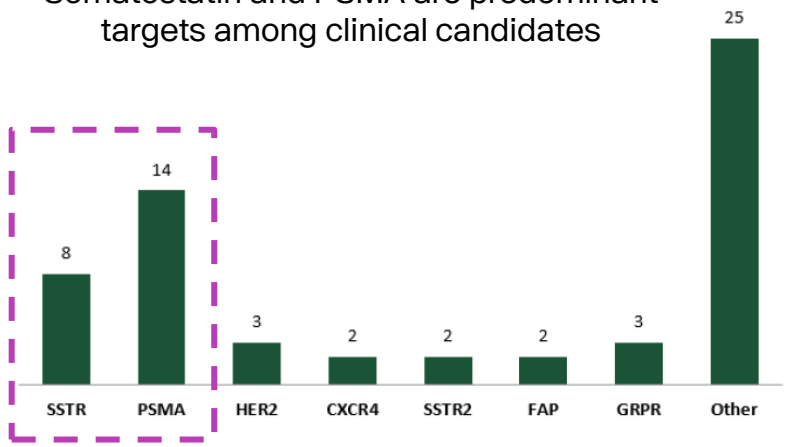
- Delivering cytotoxic radioisotope
- No cleavable linker
- Potentially effective in different patient population / cancers

The (Bicycle®) radiopharm opportunity

- Therapeutic PSMA & SSTR2 radioligands have achieved **clinical and commercial validation**
  - Clear clinical benefit in advanced cancers
  - Pluvicto annual run-rate beyond initial expectations despite manufacturing bottlenecks
- KOLs believe isotope manufacturing & supply challenges can be overcome
- Novel ligands would open target space beyond PSMA/SSTR2 and drive long-term growth → **Bicycles**

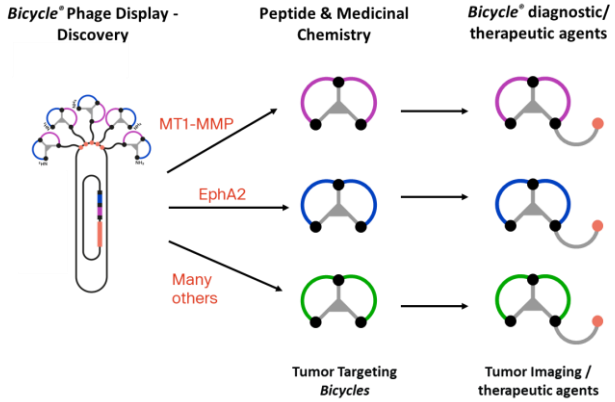
Suitable binders to new tumor targets are needed

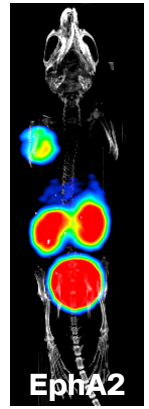
Somatostatin and PSMA are predominant targets among clinical candidates



Source: TD Cowen

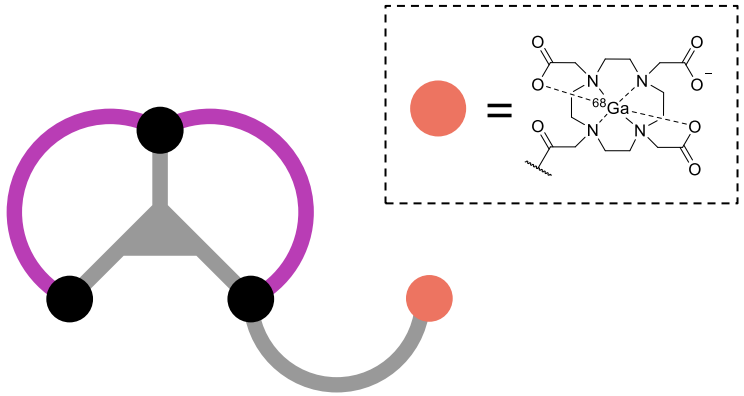
Bicycle platform well positioned to deliver such binders



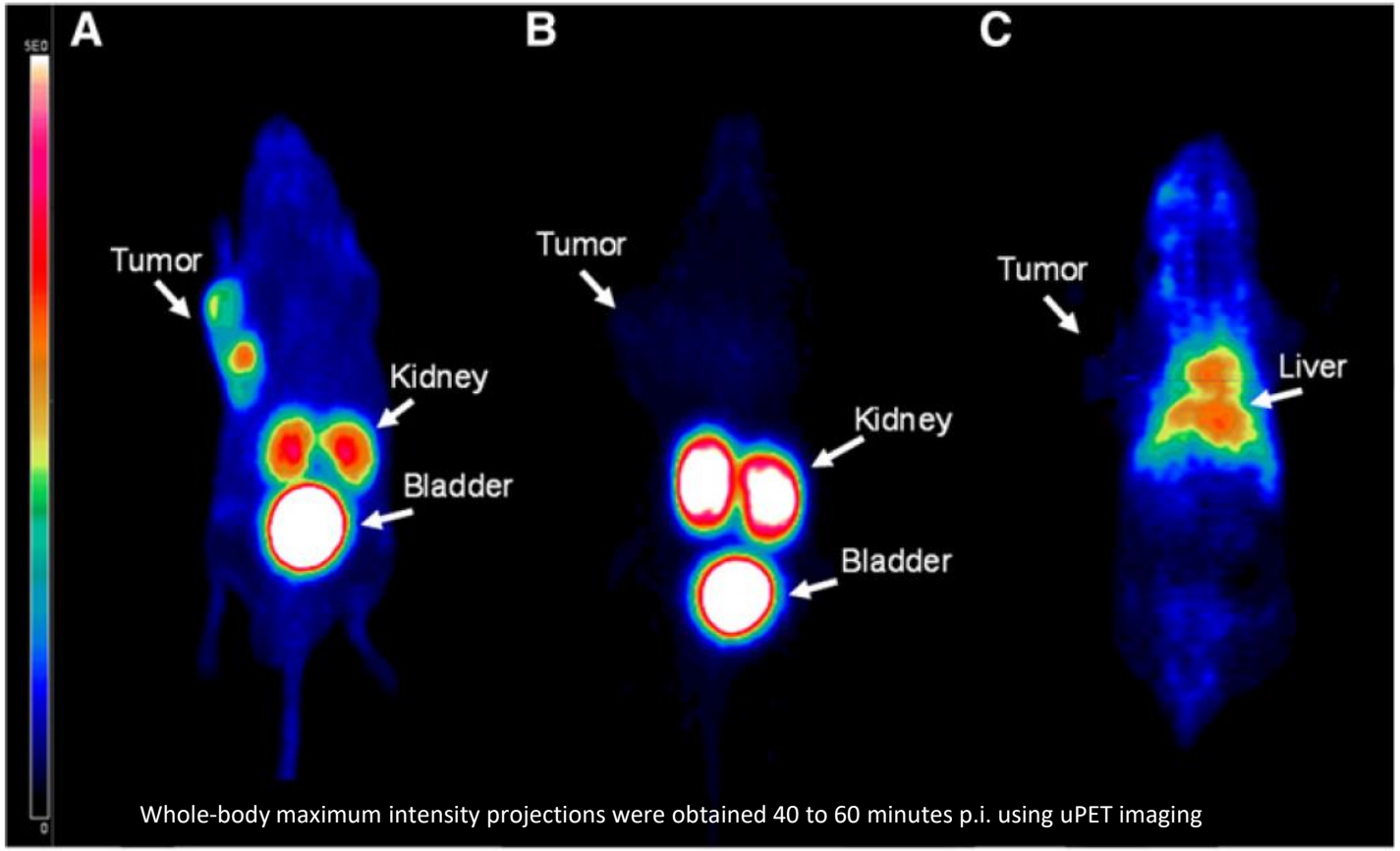


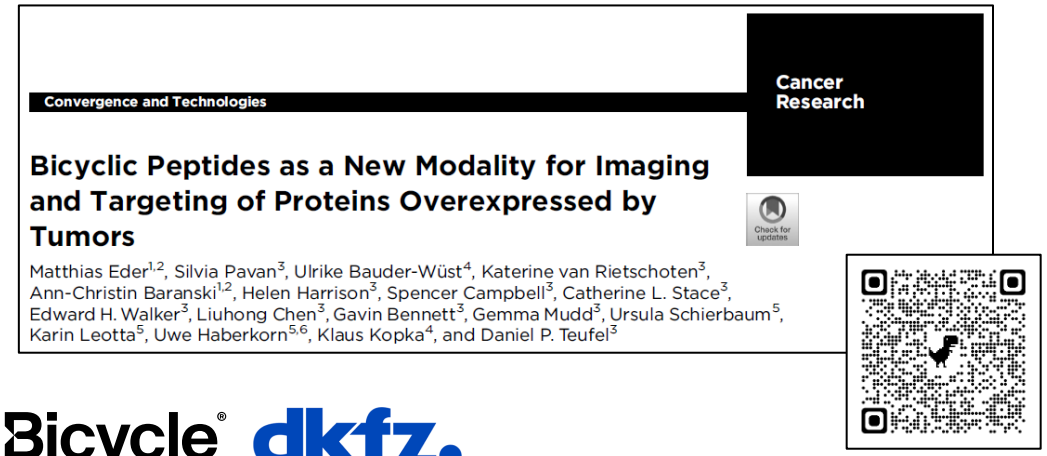
- Rapid and high tumor accumulation
- Rapid excretion of non-tumor bound molecule
- High contrast imaging / efficient payload delivery to tumors

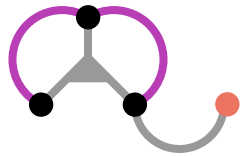
MT1-MMP targeting BRC shows far superior tumor uptake and contrast versus mAb



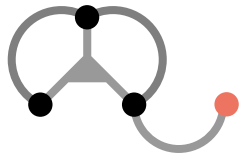
- MT1-MMP overexpressed in variety of cancers (non–small cell lung, gastric and breast)



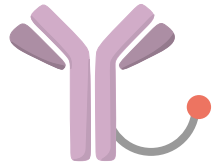




MT1-MMP targeting BRC



Non-binding BRC



MT1-MMP targeting mAb conjugate

Bicycle® dkfz.

Potent anti-tumor activity of a Lead-212 labelled MT1-MMP targeting Bicycle Radio Conjugate in mouse model

MT1-MMP targeting *Bicycle*

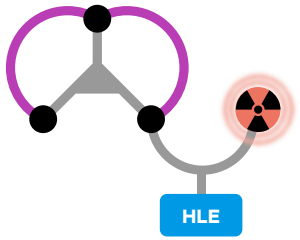
- **High affinity** (5 nM) binding to MT1
- Allows **precision** targeting of BRC™ to tumor cells

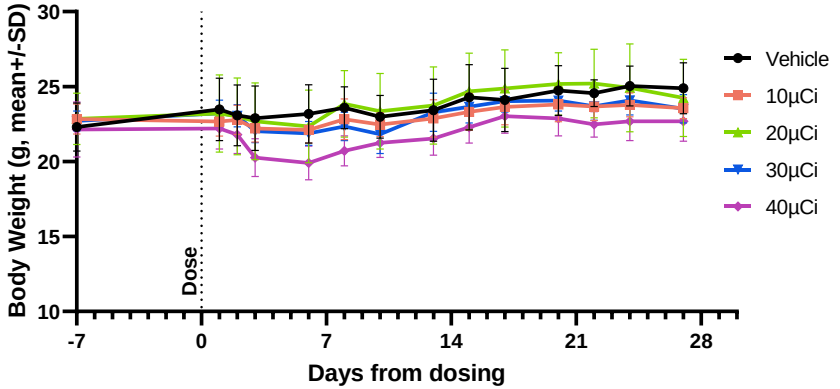
Lead-212

- **Potent radioisotope** causes dsDNA break through single alpha emission
- Decay half life 10 hours

Half-life extending (HLE) moiety

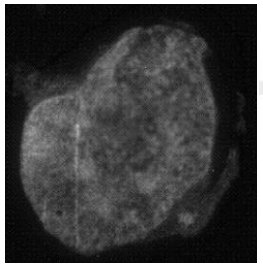
- Reversible albumin binding motif
- Prolongs circulating half-life of conjugate



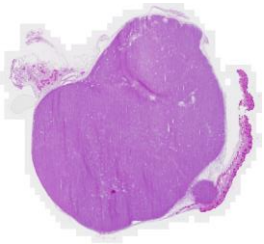


Alpha imaging

1 hour

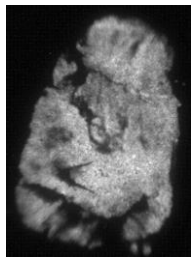


Dark image



H&E

4 hours



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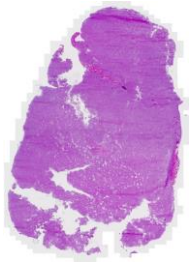
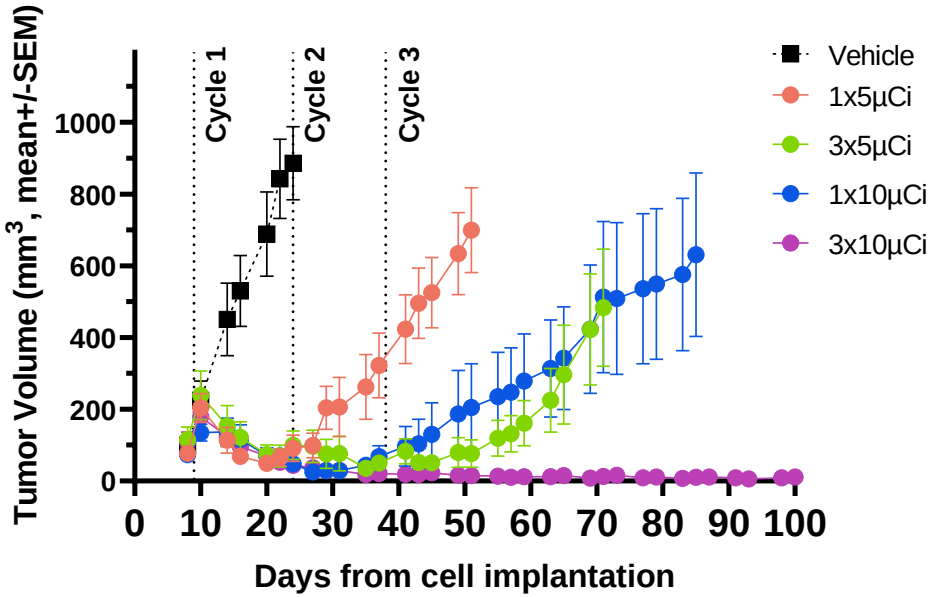


H&E

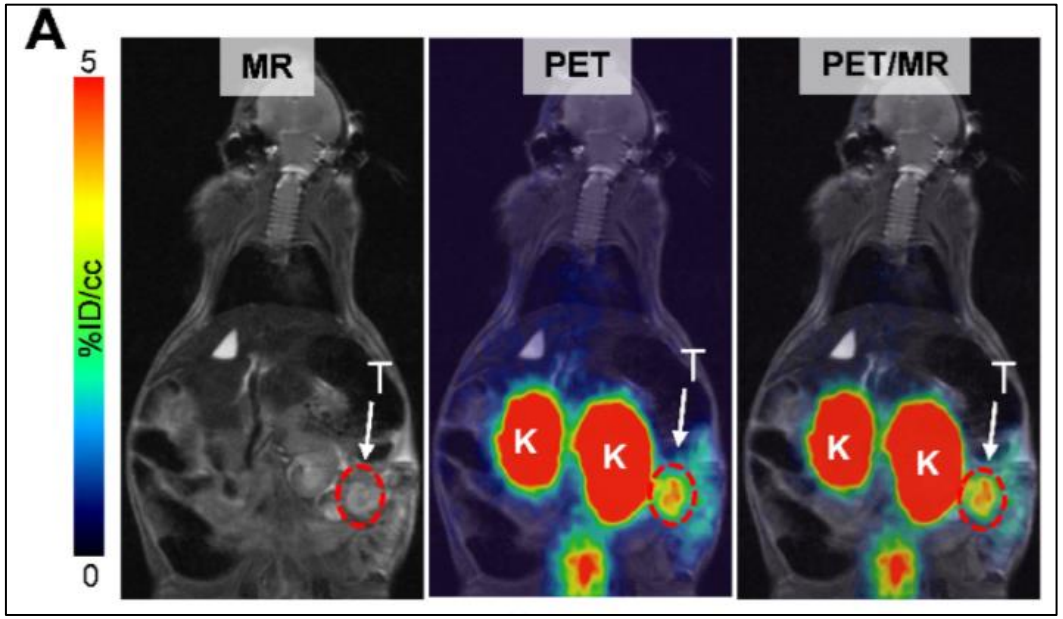


Bicycle®

oranomed

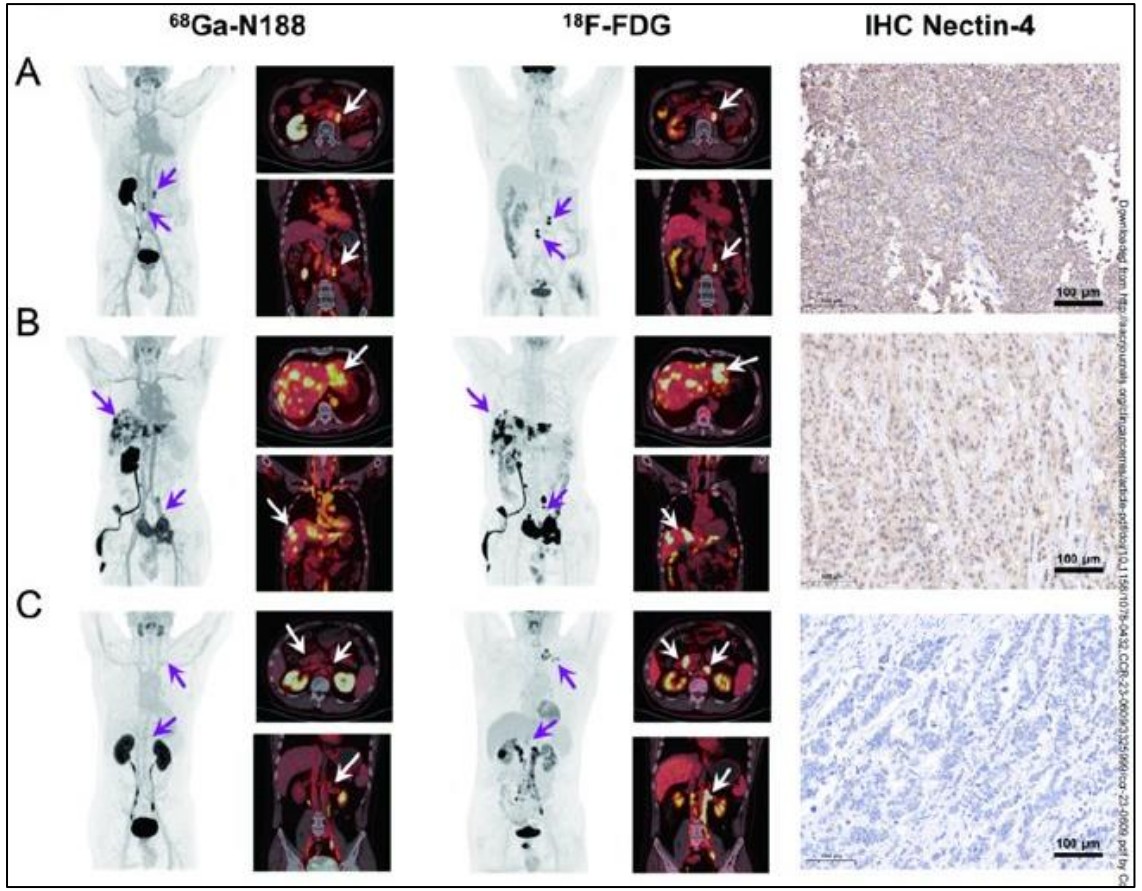
Independent groups publishing on BRCs (including FIH imaging)

EphA2 BRC able to image pancreatic cancer in orthotopic mouse model



Data builds confidence in potential clinical utility of BRCs

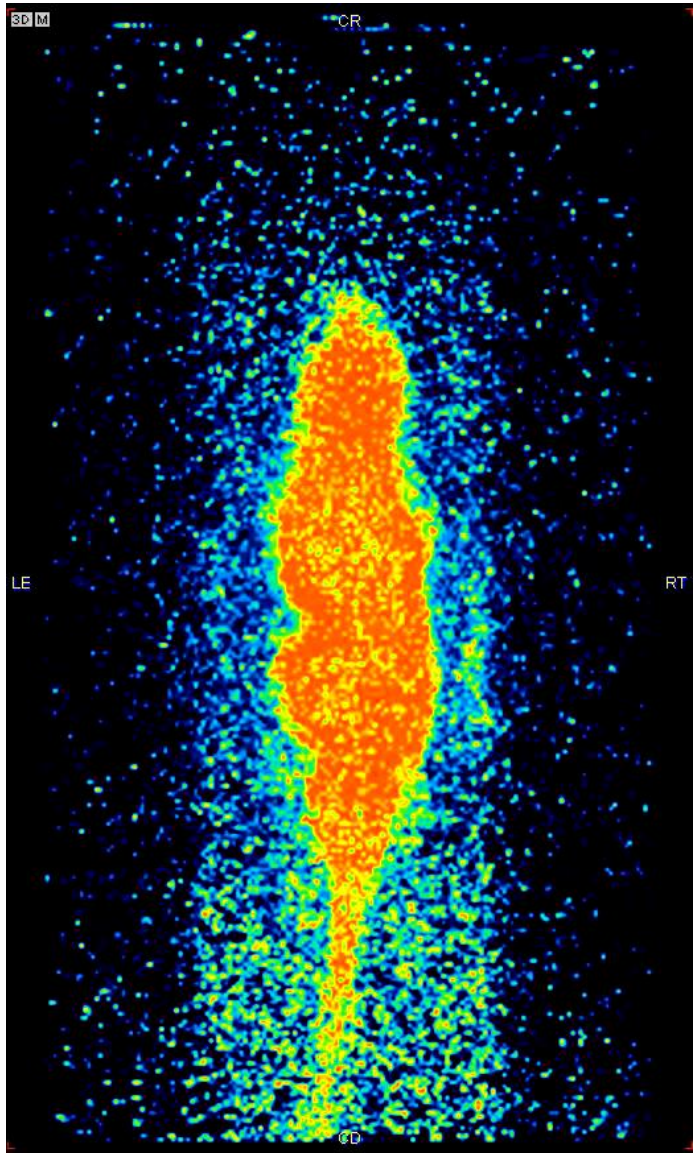
BRC selectively images Nectin-4 expressing metastases in urothelial cancer patients



Sharma, A. K. et al. *Cancer Research* (2023),
Duan, X. *et al. Clinical Cancer Research* (2023)

BRCs - Summary

- Bicycles have ideal properties for targeted radionuclide delivery
- Bicycle platform can provide binders to novel targets for radioligand therapeutics
- Will potentially allow treatment of different patient populations versus BTCs



MT1-MMP targeting BRC
Dynamic scan recording
0-60 mins P.I.

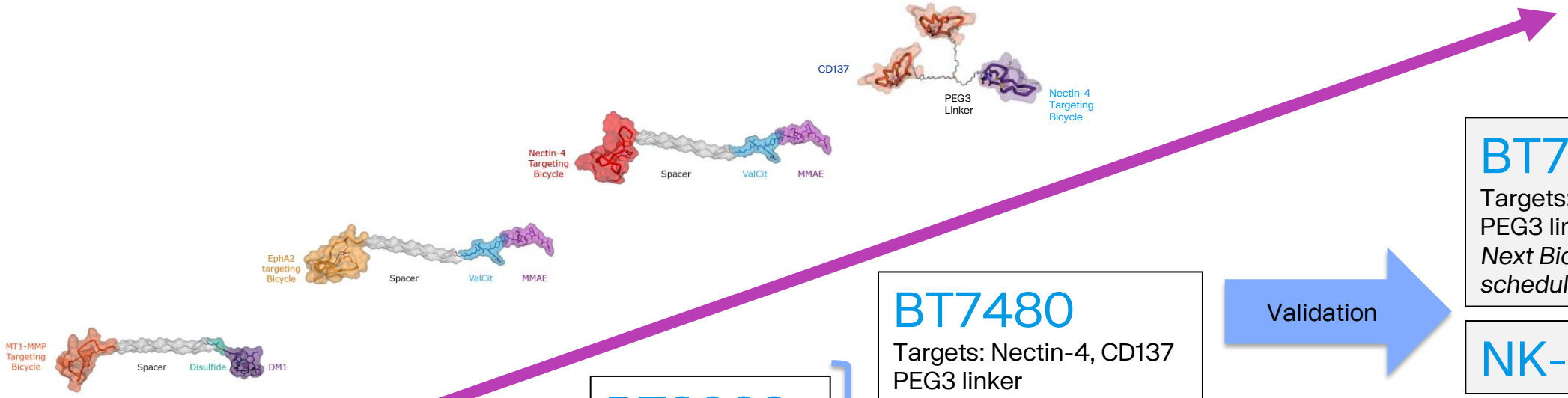
Bladder not evacuated due to anesthesia

Bicycle Therapeutics

- Upcoming Milestones

Bicycle®

Elevating the platform



BT1718
Target: MT1-MMP
DM1 payload
Disulfide linker

BT5528
Target: EphA2
MMAE payload
Val-Cit linker

BT8009
Target: Nectin-4
MMAE payload
Val-Cit linker

BT7480
Targets: Nectin-4, CD137
PEG3 linker

Validation

BT7455
Targets: EphA2, CD137
PEG3 linker
Next Bicycle TICA™ scheduled for clinic

NK-TICA™

Validation

Next-gen BTCs
Different targets, linkers and payloads

Radiopharm

FIH 2018 2019 2020 2021 2023 and beyond

Looking forward

- Clinical updates expected in December 2023 for BT8009, BT5528 and BT7480
  - BT8009 – initiated expansion cohorts in 4Q22
  - BT5528 - initiated expansion cohorts in 2Q22
  - BT7480 – dose escalation ongoing
- Third generation Bicycle Toxin Conjugates® and NK cell engagers are in development

Thank you

Bicycle®