Bicycle Therapeutics Investor Presentation

- October 2024

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, including expected financial runway; 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 current and prospective product candidates; the safety and efficacy profile of our product candidates; and the size and composition of the potential market for any of our product candidates, if approved.

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 or preclinical activities, 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 partnerships or enter into new partnerships in the future, or that we may not realize the intended benefits of these partnerships, 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 and financial runway, 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 October 31, 2024, 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: Pioneering a new, differentiated class of innovative medicines

Unique Platform

Developing Bicycle® molecules – a novel synthetic peptide modality that enables the drugging of complex targets

Technology based on Nobel Prize-winning science

Strong intellectual property portfolio

Internal Programs

Focused on oncology, with multiple clinical molecules

Expedited development and regulatory path for zelenectide pevedotin (zele, formerly BT8009) in mUC

zele, BT5528 and BT7480 have shown anti-tumor activity and emerging differentiated safety profiles

First human imaging data validates potential of MT1-MMP as a novel radiopharmaceuticals target

Validating Partnerships

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

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

Ambitious Company

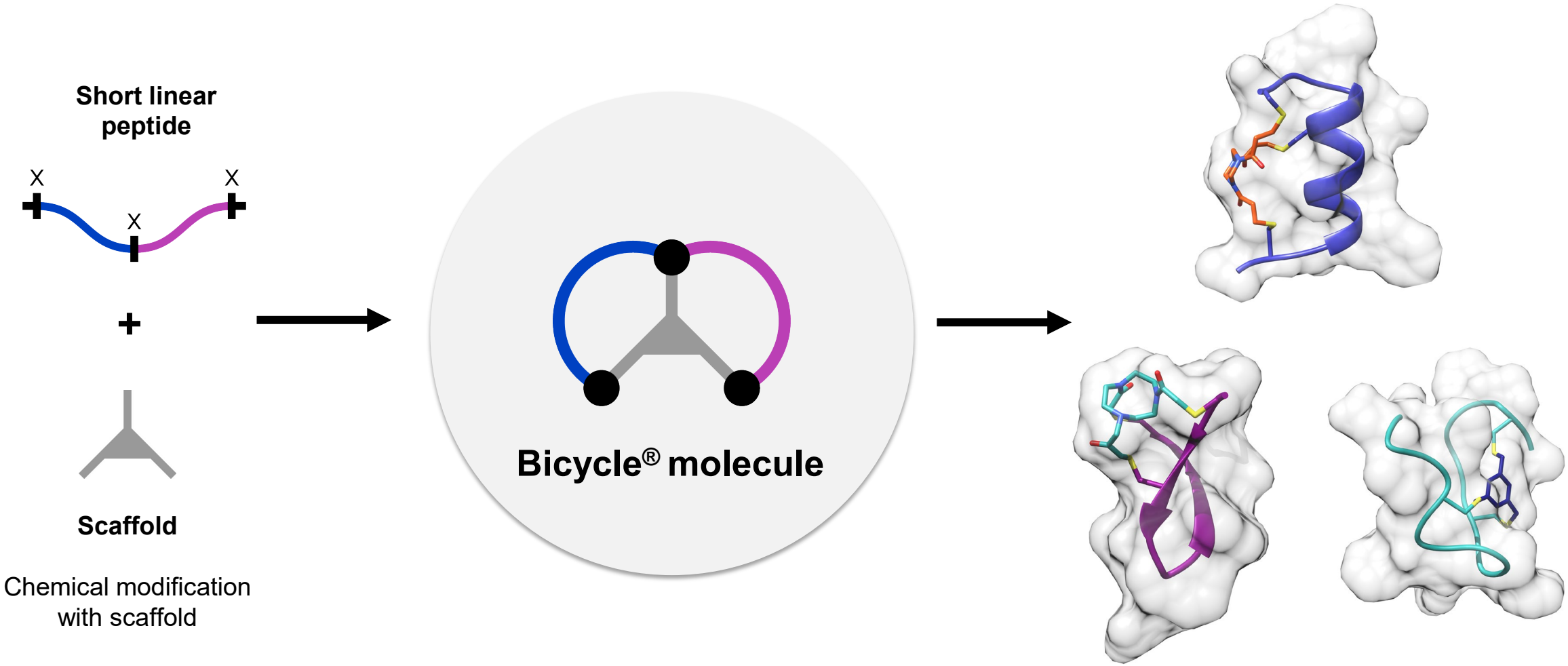
Deeply experienced team

Located in Cambridge, UK, and Cambridge, MA

NASDAQ: BCYC

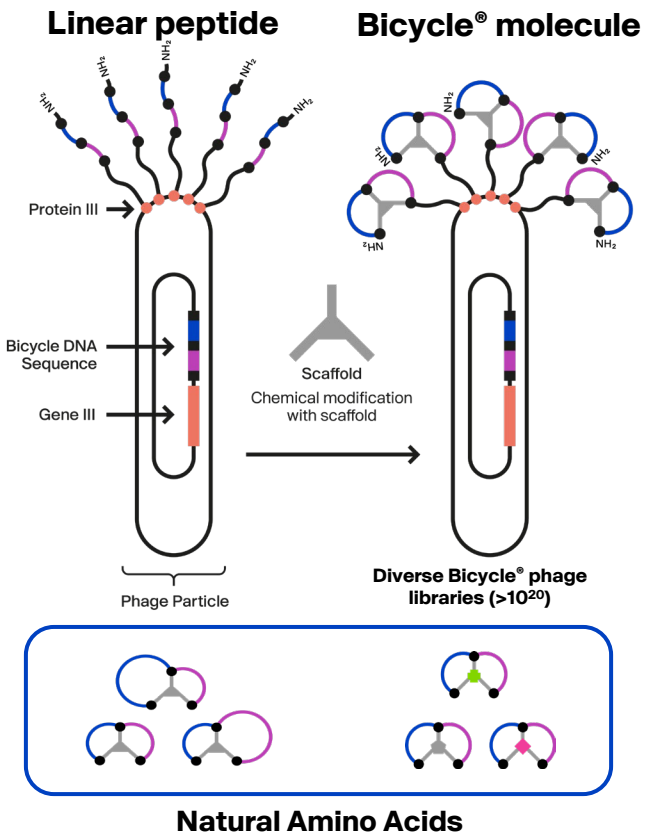
Cash and cash equivalents of $890.9M as of Sept. 30, 2024, with expected financial runway into 2H 2027

Bicycle® molecules are short peptides chemically constrained with a central scaffold that can induce diverse structures



Bicycle® platform delivers a toolkit of modular building blocks to create novel precision-guided medicines

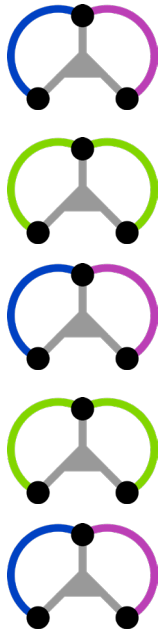
Bicycle® Phage Display Discovery



Peptide & Medicinal Chemistry

Optimize Bicycle® monomers

Non-natural Amino Acids

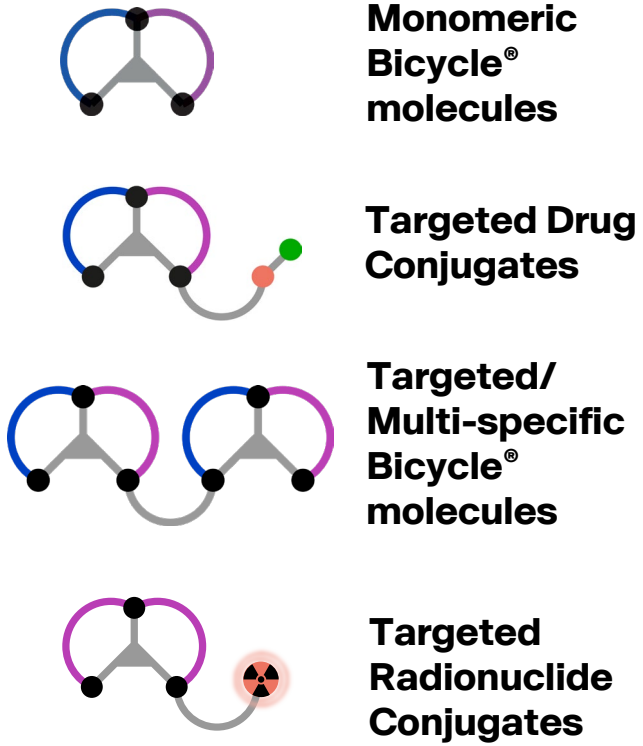


Targeting and Effector Bicycle® molecules

Build and Optimize Therapeutic Bicycle® molecules

Easy conjugation of Linkers and Payloads

Potential Bicycle® Medicines



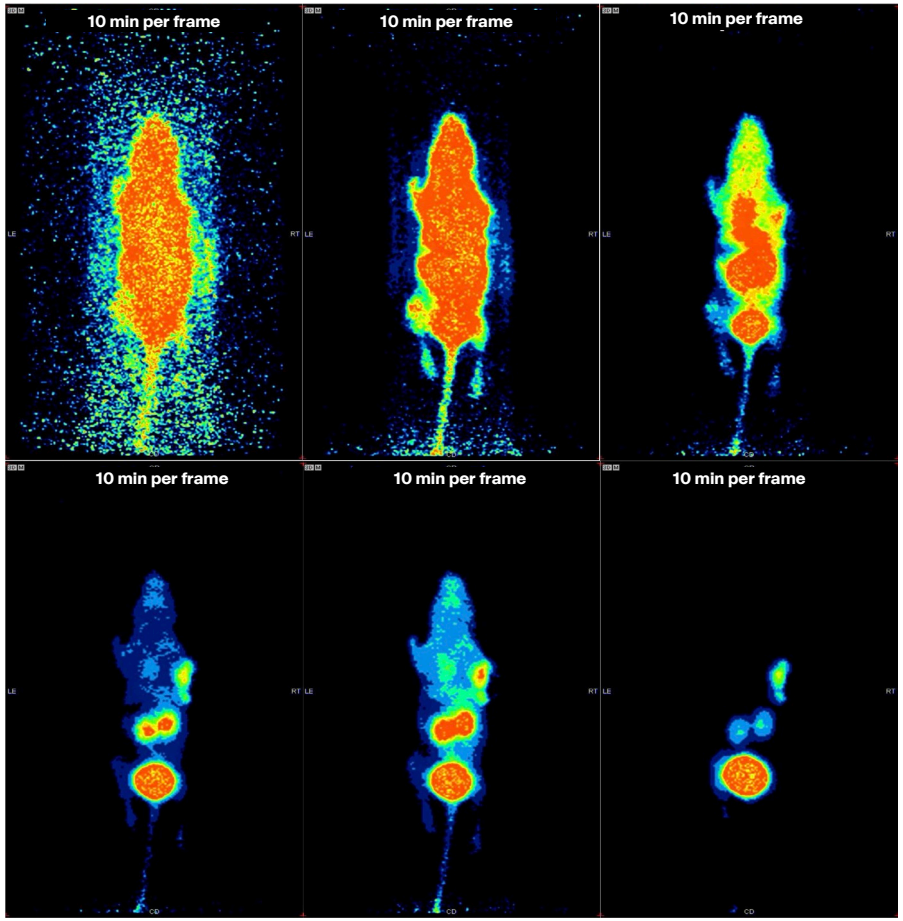
Monomeric Bicycle® molecules

Targeted Drug Conjugates

Targeted/ Multi-specific Bicycle® molecules

Targeted Radionuclide Conjugates

The Bicycle® Advantage



Stills from dynamic PET scan following injection of ^{68}Ga labelled BRC® molecule targeting MT1-MMP (60 min time course)

- **Small size for rapid tissue penetration**
- **Tunable PK for optimized target vs. systemic exposure**
- **High affinity and selectivity for precision targeting and tumor retention**

We believe The Bicycle® Advantage will lead to enhanced patient benefits

Precision Guided Therapeutics

- Rapid tumor penetration
- Minimized systemic exposure
- Minimal off-target activity
- Tumor retention

Greater Tolerability

- Improved adherence to optimized dosage regimen
- Better combinability

Enhanced Patient Benefit

- Longer responses
- Deeper/broader responses

Turning The Bicycle® Advantage into reality

Execute

Translate our Nobel Prize-winning science into therapies

Expand

Address numerous solid tumors and improve outcomes for patients through our Nectin-4 and EphA2 portfolios and by bringing forward next-generation molecules

Explore

Establish high-value collaborations that enable clinical development for oncology and beyond

We are building a leading precision-guided therapeutics company

Broad range of programs supports robust nature of the Bicycle® platform

Target / Product	Partner/Sponsor	Indication	Modality	Preclinical	IND-enabling	Phase I	Phase II/ Expansion	Phase III
Internal Programs								
zelenectide pevedotin (Nectin-4)		Oncology	Bicycle® Toxin Conjugate					
BT5528 (EphA2)		Oncology	Bicycle® Toxin Conjugate					
BT7480 (Nectin-4/CD137)		Immuno-oncology	Bicycle TICA® molecule					
MT1-MMP	dkfz.	Radiopharmaceutical	Bicycle® Radio Conjugate					
EphA2	dkfz.	Radiopharmaceutical	Bicycle® Radio Conjugate					
Partnered Programs								
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					

Nectin-4 Portfolio

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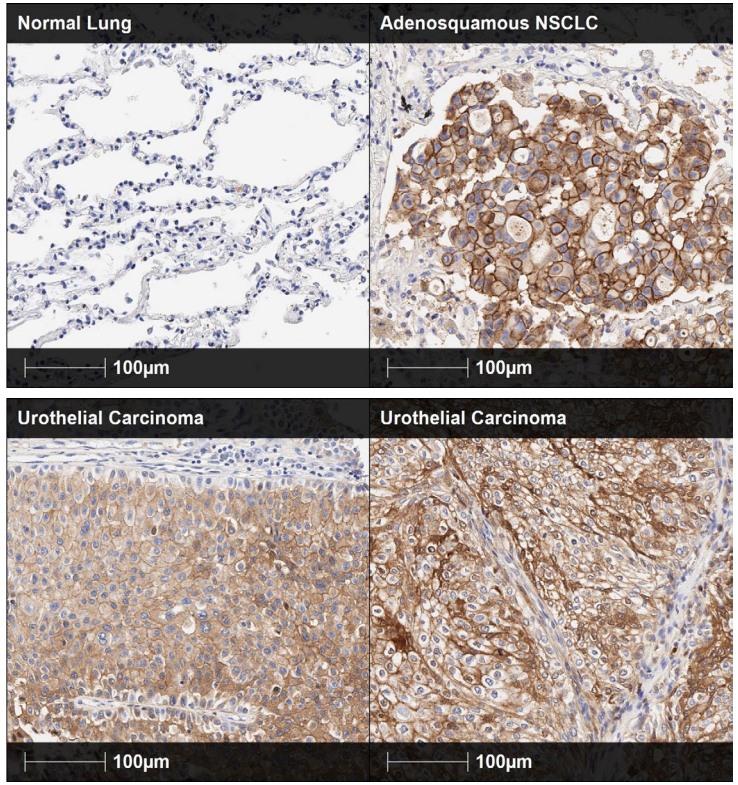
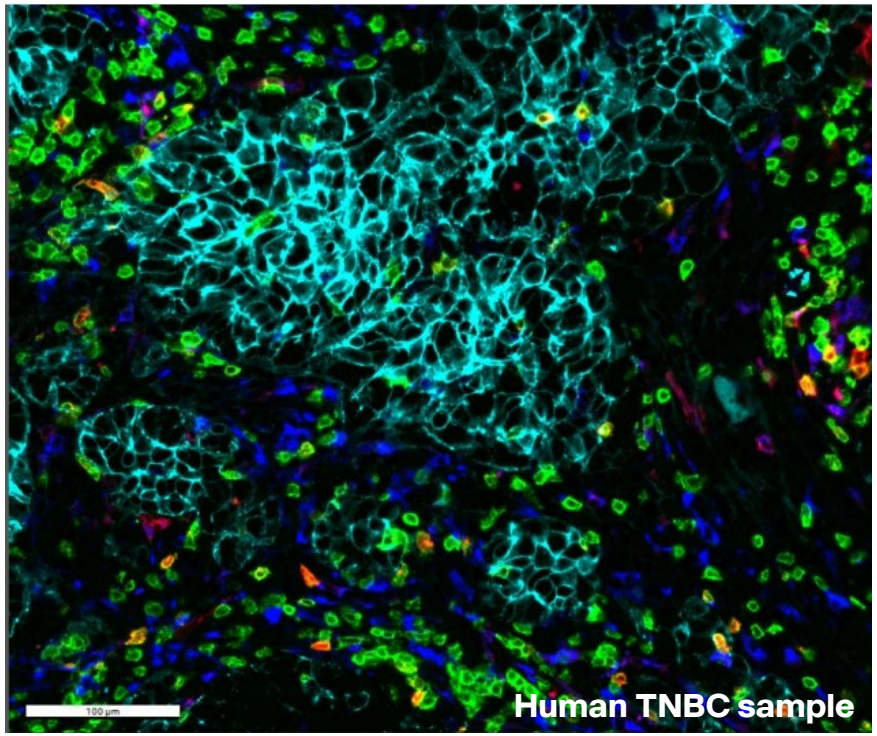
Nectin-4 is a high value target expressed in many tumors

A vector for toxin delivery...



MMAE-sensitive tumor types include **bladder, NSCLC, TNBC** and others

...and for immune cell activation



Key: Nectin-4 CD137 CD3 CD68

Tumor types include **cervical, NSCLC, TNBC** and others

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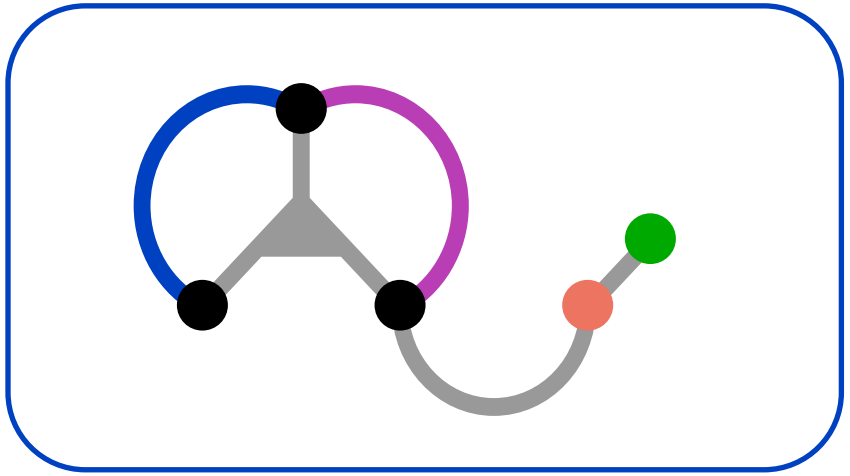
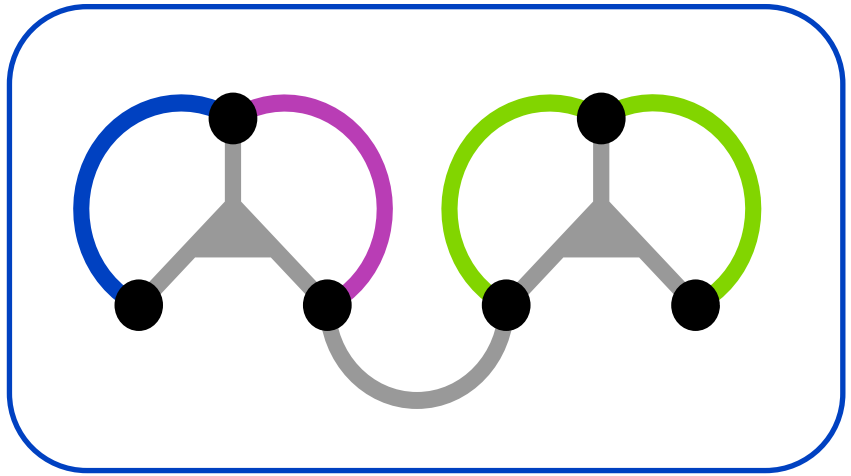
1. Challita-Eid PM et al. 2016. *Cancer Res*, 76(10):3003-3013. 2. Campbell CT et al. 2020. *Cancer Res*, 80(16 Suppl):5300. 3. Cohen H et al. 2021. *J Immunother Cancer*, 9(Suppl 2):A2.
MMAE: monomethyl auristatin E; NSCLC: non-small cell lung cancer; TNBC: triple-negative breast cancer.

We have taken two approaches to try and address the broadest Nectin-4 expressing population of patients

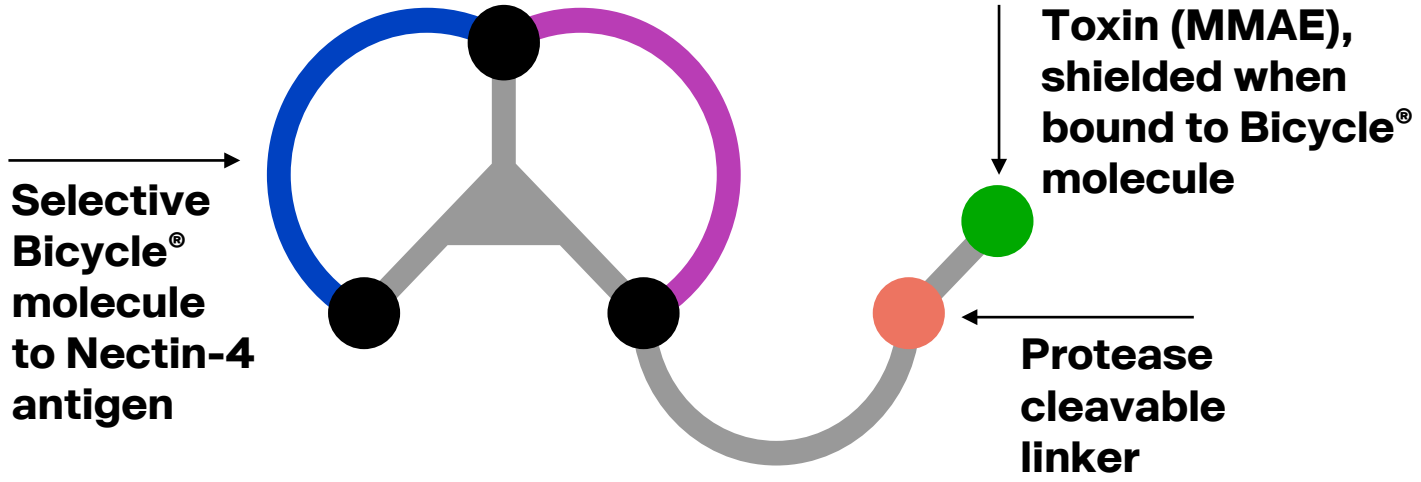


zelenectide pevedotin is a Nectin-4 targeted Bicycle toxin conjugate (BTC®) designed to overcome the significant toxicity associated with other toxin conjugate approaches.



BT7480 is a Nectin-4 targeted CD137 agonist designed to overcome immune agonist toxicities and activate the immune system in Nectin-4 expressing tumors.

Zelenectide pevedotin, our approach to addressing the broadest Nectin-4 expressing population of patients



- 3-4 kDa versus 150+ kDa for ADCs
- Synthetic, defined manufacture
- Cost of goods much lower than comparator biologics, and highly stable with excellent pharmaceutical properties

Highly differentiated preclinical performance:

- **Superior selectivity**
- **Reduced skin/eye toxicity**
- **Reduced parent exposure**
- **Excellent activity in multiple tumor models**

1. Rigby M et al. 2022. *Mol Cancer Ther*, 21(12):1747-1756. 2. Mudd GE et al. 2022. *J Med Chem*, 65(21):14337-14347.
MMAE: monomethyl auristatin E

Improved selectivity may lead to differentiated tolerability

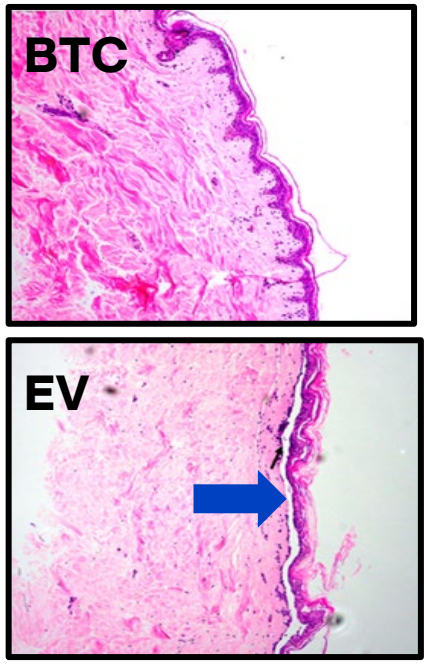
Selectivity[1]

Receptor	BT8009	Enfortumab vedotin
Nectin-4	✓	✓
Human SCLC16A2	✗	✓
Human FCGR1A	✗	✓
Human FCGR2A	✗	✓
Human FCGR2B	✗	✓
Human FCGR3A + FCER1G	✗	✓

✓ Binds ✗ Does not bind

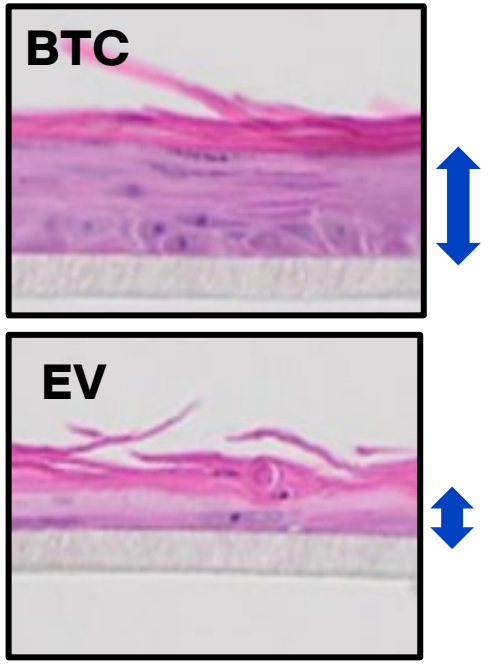
- EV binds to 6+ extracellular receptors expressed in non-target tissue
- These include multiple Fc receptors and a key thyroid hormone transporter SLC16A2
- Bicycle® molecules are completely selective for their target in the same assay

Human skin model[2]



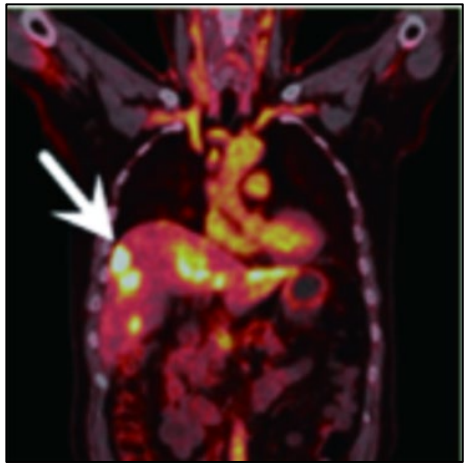
- EV induces dermal/epidermal separation in-vitro
- BTC® molecule does not

Human corneal model[2]



- EV induces corneal thinning in-vitro
- BTC® molecule does not

Human imaging[3]



- Nectin-4 Binding Bicycle® binder rapidly penetrates human tumors (15 min) and is selectively retained

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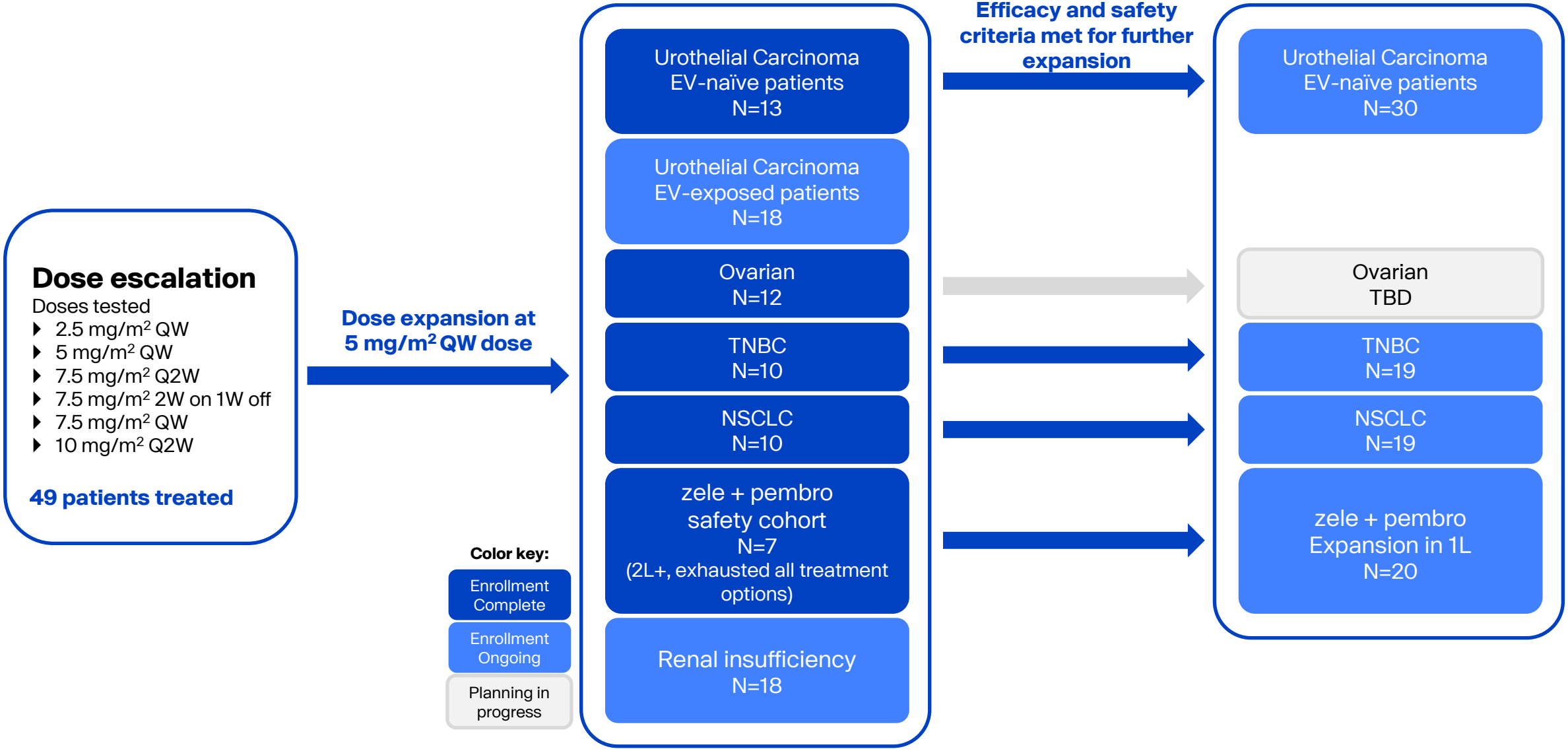
1. Assessed using the Retrogenix assay platform, enfortumab vedotin (EV) and zelenectide pevedotin (BTC) (2 µg/ml) were assessed for binding to ~6,500 secreted and cell surface-tethered human secreted proteins expressed on cells. Binding was detected using an anti-MMAE antibody. Bicycle Therapeutics unpublished data.
2. Skin and eye adverse events were modelled *in vitro* using human tissue *ex vivo*. Bicycle Therapeutics unpublished data.
3. Duan et al., Clin Cancer Res. 2023 Sep 1;29(17):3395-3340.

Duravelo-1: Phase 1/2 zelenectide pevedotin study



Number of patients enrolled as of 01Dec2023.
1L: 1st line; 2L+: 2nd line or later; EV: enfortumab vedotin; NSCLC: non-small cell lung cancer; QW: weekly; Q2W: every other week; TNBC: triple-negative breast cancer.

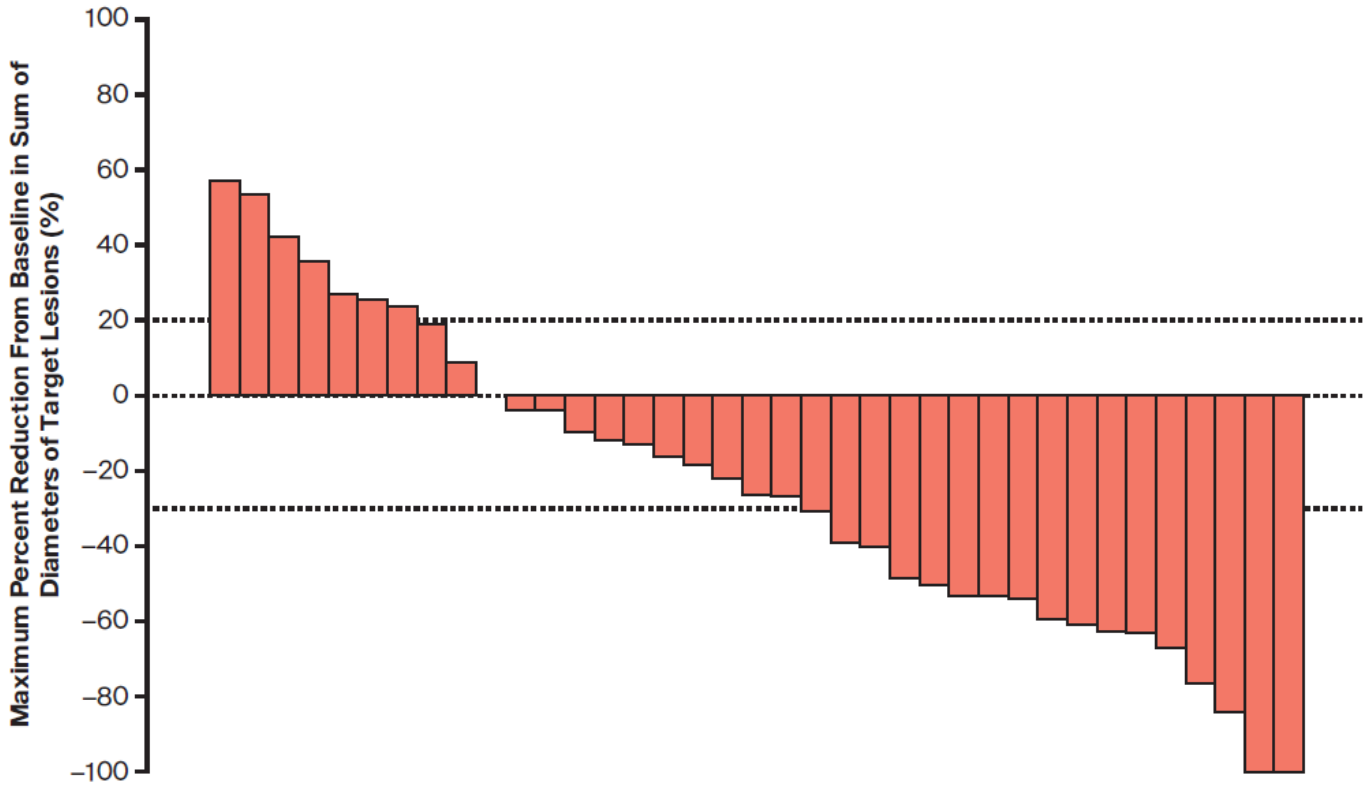
Baseline characteristics of EV-naïve mUC patients

Characteristic	EV-naïve mUC 5 mg/m^2 QW[a] N=45
Median age, yrs (range)	67 (42-84)
Sex, n (%)	
Male	34 (76)
Female	11 (24)
Race, n (%)	
White	27 (60)
Black or African American	0
Other/missing[b]	18 (40)
ECOG, n (%)	
0	21 (47)
1	24 (53)
Median prior lines of therapy (range)	2.5 (1-7)
Prior therapy, n (%)	
Checkpoint inhibitor	42 (93)
Platinum-based therapy	42 (93)
Sacituzumab govitecan	6 (13)
FGFR inhibitor	1 (2)
Enfortumab vedotin[c]	0

Torras OR et al. ESMO 2024. Data as of 22Mar2024.
[a]Including data from dose escalation and dose expansion phases. [b]Due to French ethics laws, data on race is recorded as Other for patients enrolled in France.
[c]Patients with prior exposure to enfortumab vedotin were excluded from this cohort of the study.
EV: enfortumab vedotin; mUC: metastatic urothelial cancer; QW: weekly.

Zelenectide pevedotin response data in EV-naïve mUC

Waterfall plot of change from baseline in tumor size in efficacy-evaluable EV-naïve patients with mUC treated with zelenectide pevedotin 5 mg/m² QW (n=37[a])



Best Overall Response[b], n (%)	Total EV-naïve mUC 5 mg/m² QW N=38
Complete Response (CR)	1 (3)
Partial Response (PR)	16 (42)
Stable Disease (SD)	9 (24)
Progressive Disease	12 (32)
ORR (CR+PR)	17 (45)
CBR (CR+PR+SD≥16 wks)	23 (61)

mDOT is currently 16.1 weeks (range 1-101.4)

mDOR is currently 11.1 months (95% CI [3.9, NR])

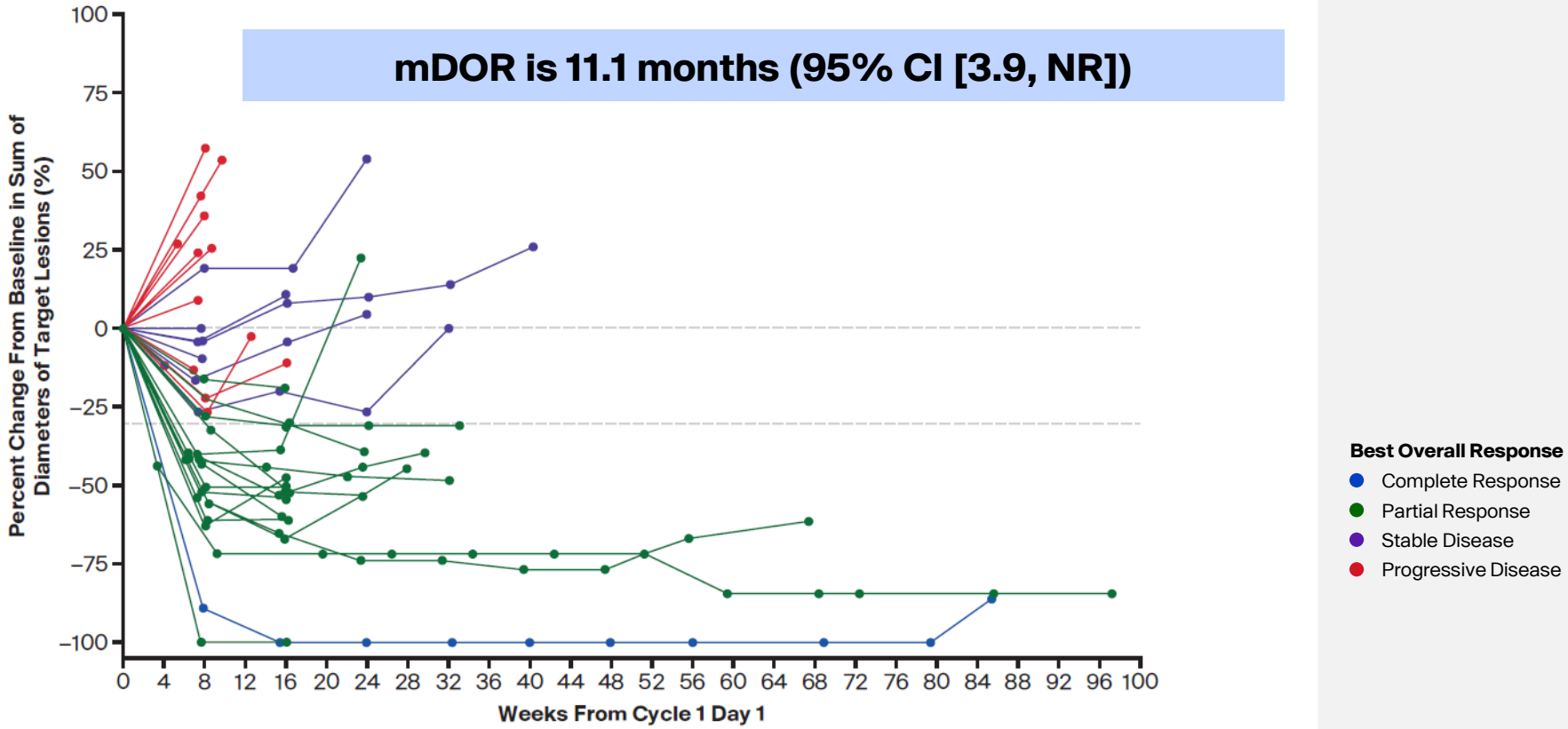
Torras OR et al. ESMO 2024. Data as of 22Mar2024.

[a]Number of efficacy-evaluable patients with at least one postbaseline target lesion measurement. One patient had progressive disease because of a new lesion, but this individual did not have a postbaseline target lesion measurement. [b]Responses under response evaluation criteria in solid tumor (RECIST) v1.1.

CBR: clinical benefit rate; EV: enfortumab vedotin; mDOT: median duration of treatment; mUC: metastatic urothelial cancer; ORR: objective response rate; QW: weekly.

Zelenectide pevedotin shows an emerging profile that may support long duration of response

Duration of response and change from baseline in tumor size in efficacy-evaluable EV-naïve patients with mUC treated with zelenectide pevedotin 5 mg/m^2 QW (n=37[a])



Median duration of follow-up is 4.2 months (range, 0.5–28.6)

Torras OR et al. ESMO 2024. Data as of 22Mar2024.

[a]Number of efficacy-evaluable patients with at least one postbaseline target lesion measurement. One patient had progressive disease because of a new lesion, but this individual did not have a postbaseline target lesion measurement. Responses under response evaluation criteria in solid tumor (RECIST) version 1.1.

C1D1: Cycle 1, Day 1; EV: enfortumab vedotin; mDOR: median duration of response; mUC: metastatic urothelial cancer; QW: weekly.

Zelenectide pevedotin continues to demonstrate an emerging differentiated safety profile in mUC

Category, n (%)	5 mg/m^2 QW in EV-naïve mUC patients[a] N=45
TEAEs	42 (93)
Grade ≥3	24 (53)
TRAEs	36 (80)
Grade ≥3	10 (22)
TRAEs reported in ≥15% of patients, n (%)	
Nausea[b]	15 (33)
Asthenia	10 (22)
Fatigue	9 (20)
Pyrexia	9 (20)
Diarrhea	8 (18)
Appetite decreased	7 (16)
Alopecia	7 (16)
Dose modifications, n (%)	
TEAEs leading to dose interruption	24 (53)
TEAEs leading to dose reduction	12 (27)
TEAEs leading to dose discontinuation	2 (4)
Time to dose modification, months (range)	
Median time to first dose reduction	2.3 (1.0–14.1)

Torras OR et al. ESMO 2024. Data as of 22Mar2024.
[a]Including data from dose escalation and dose expansion phases. [b]Prophylactic antiemetics are prohibited during Cycle 1 of dose escalation, and use of antiemetics associated with QT prolongation is prohibited during the study.
EV: enfortumab vedotin; mUC: metastatic urothelial cancer; QW: weekly.

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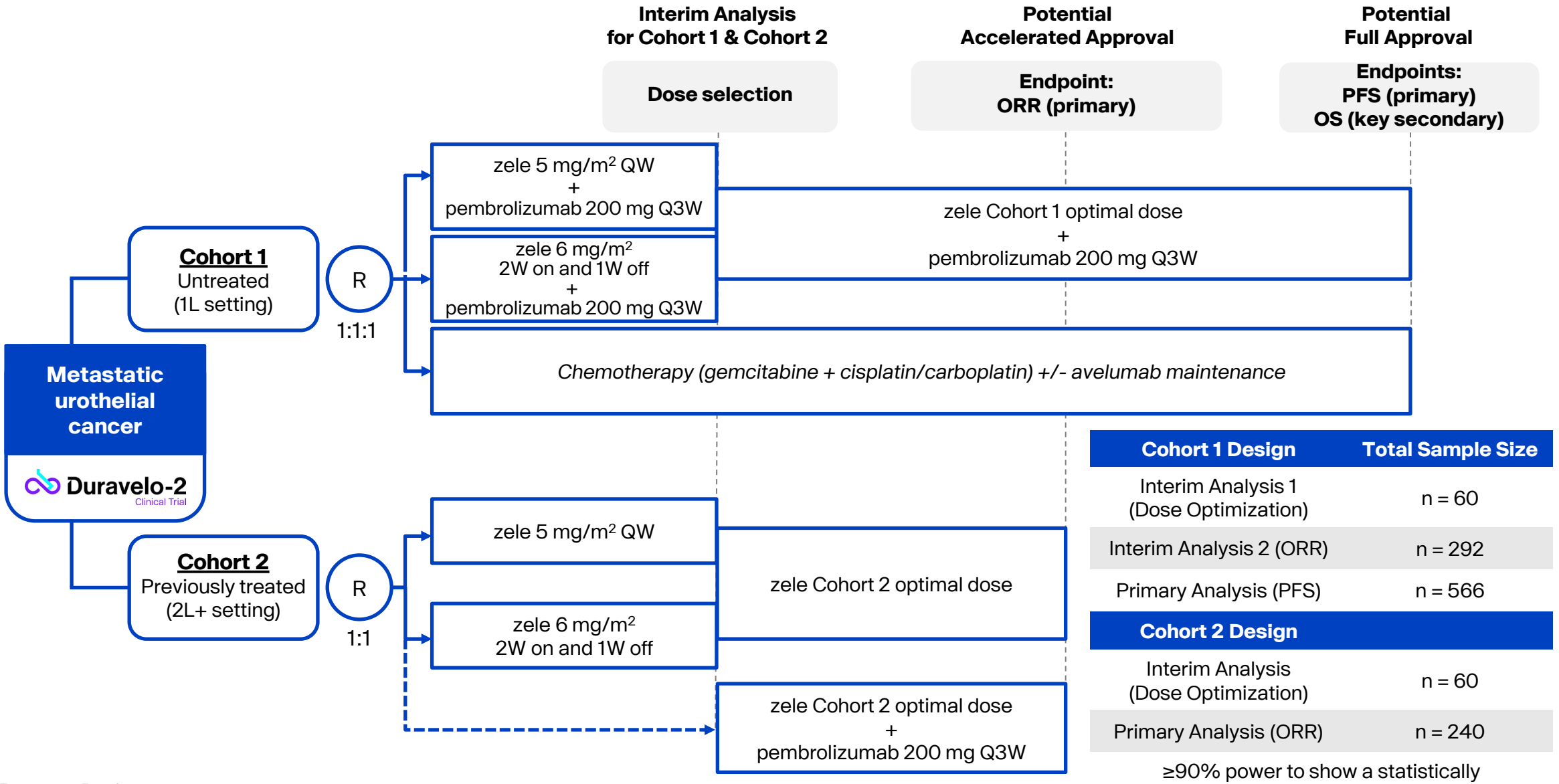
Treatment-related adverse events of interest seen with other Nectin-4 targeted therapies were of low frequency and severity

Event type	5 mg/m² QW in EV-naïve mUC patients[a] N=45 n (%)					
	Grade 1, n (%)	Grade 2, n (%)	Grade 3, n (%)	Grade 4, n (%)	Grade 5, n (%)	Total, n (%)
Peripheral neuropathy[b]	9 (20)	7 (16)	0	0	0	16 (36)
Peripheral sensory neuropathy[c]	6 (13)	0	0	0	00	6 (13)
Hyperglycemia[c]/diabetes mellitus[c]	2 (4)	0	1 (2)	0	0	3 (7)
Skin reactions[d]	6 (13)	2 (4)	0	0	0	8 (18)
Neutropenia[c]	2 (4)	2 (4)	2 (4)	0	0	6 (13)
Eye disorders[e]	2 (4)	1 (2)	0	0	0	3 (7)

Torras OR et al. ESMO 2024. Data as of 22Mar2024.
[a]Including data from dose escalation and dose expansion phases. [b]Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQ) [broad]. [c]Preferred term. [d]Includes the MedDRA term of Severe Cutaneous Adverse Reactions (SCAR) SMQ and events that fell into the MedDRA system organ class (SOC) of Skin and Subcutaneous Tissue disorders, excluding alopecia. [e]SOC of eye disorders.
EV: enfortumab vedotin; mUC: metastatic urothelial cancer; QW: weekly.

Phase 2/3 trial design allows for efficient path-to-market



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

≥90% power to show a statistically significant benefit in ORR, PFS and OS

1L: 1st line; 2L+: 2nd line or later; PFS: progression-free survival; ORR: objective response rate; OS: overall survival; mUC: metastatic urothelial cancer; QW: weekly; Q2W: every other week; Q3W: once every 3 weeks.

Zelenectide pevedotin, a first-in-class BTC® molecule, has significant potential to treat Nectin-4 expressing tumors

SUMMARY

- zelenectide pevedotin has the potential to provide a best-in-class clinical benefit profile in mUC
- Promising early signals emerging in ovarian, TNBC and NSCLC provide first-in-class opportunities
- FDA alignment on Duravelo-2 pivotal study design in mUC
- Intent to pursue options for accelerated approval in other indications

NEXT STEPS

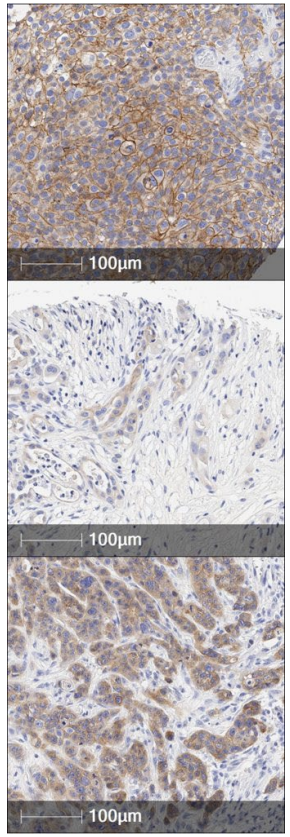
- ✓ **1Q 2024: Initiated Ph2/3 Duravelo-2 trial**
- **2H 2024: Data from ongoing open-label expansion cohorts**
  - ✓ zele monotherapy in LL mUC
  - – zele + pembrolizumab in 1L mUC
  - – zele monotherapy in TNBC and NSCLC
- **2024: Start expansion study in combination with checkpoint inhibitors in TNBC and NSCLC**

1L: 1st line; LL: late-line; mUC: metastatic urothelial cancer; NSCLC: non-small cell lung cancer; TNBC: triple-negative breast cancer.

BT5528, a potential first-in-class EphA2 targeting BTC® molecule

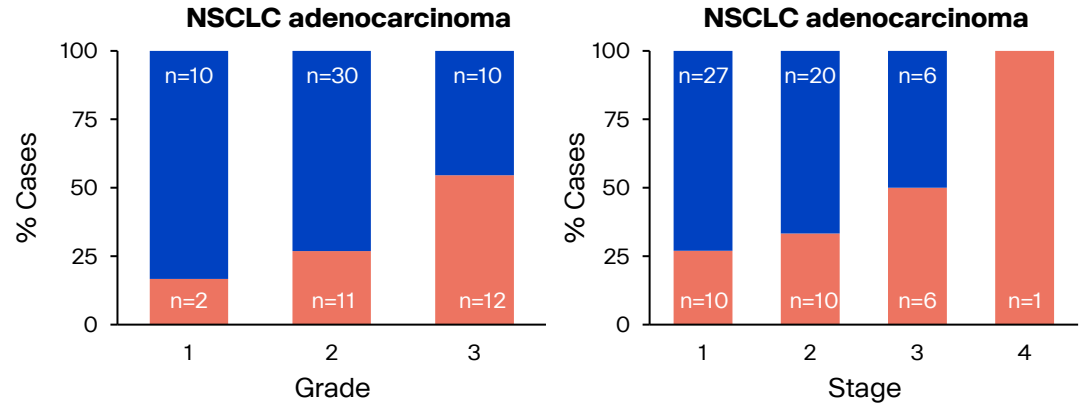
Bicycle®

EphA2 is a tumor antigen that is widely expressed in many cancers and whose expression is believed to increase with stage



Data were generated internally with an IHC assay using EphA2 (D4A2) monoclonal antibody (CST #6997) on commercially purchased tumor tissue microarray samples.[1]

- Literature describes the association of overexpression of EphA2 with higher grade and/or stage in a variety of cancers[2,3]
- Internal data suggests an increase with grade/stage in lung adenocarcinoma



Percent of EphA2-expressing NSCLC adenocarcinoma cases from commercially obtained tumor tissue microarrays, shown by tumor grade or by stage of disease.[4]

EphA2 Negative (H-score <20)
EphA2 Positive (H-score ≥20)

Bicycle®

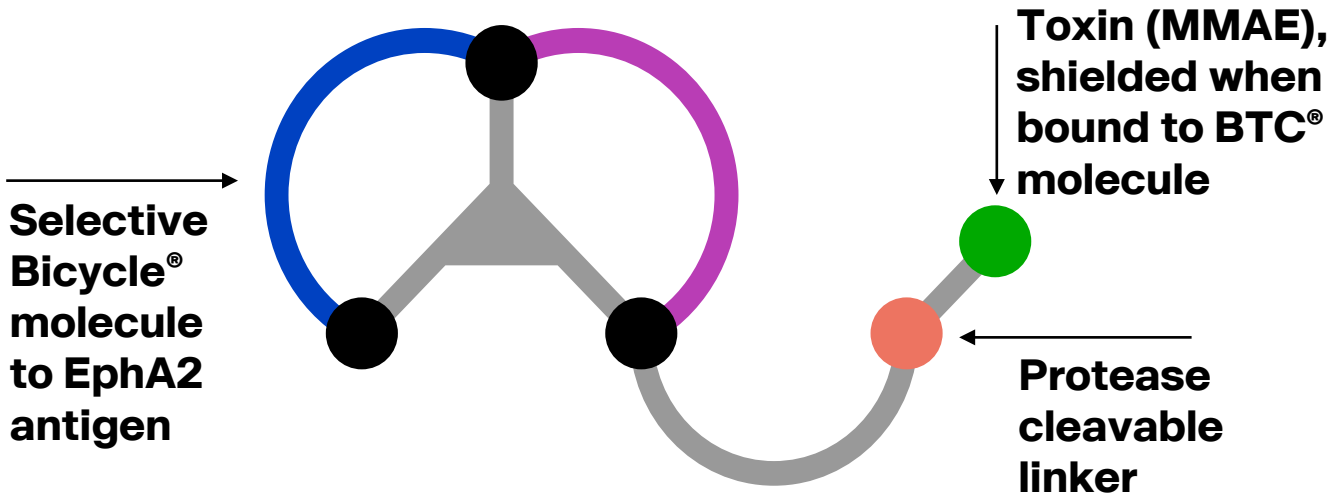
1. Bicycle Therapeutics unpublished data. 2. Zhou L et al. 2021. *Int J Clin Exp Pathol*, 14(4):484-49. 3. Cioce M and Fazio VM. 2021. *Cancers (Basel)*, 13(4):700. 4. Campbell CT et al. 2020. *Cancer Res*, 80(16 Suppl):5300.
NSCLC: non-small cell lung cancer.

Multiple approaches to targeting EphA2 have been unsuccessful, creating a first-in-class opportunity

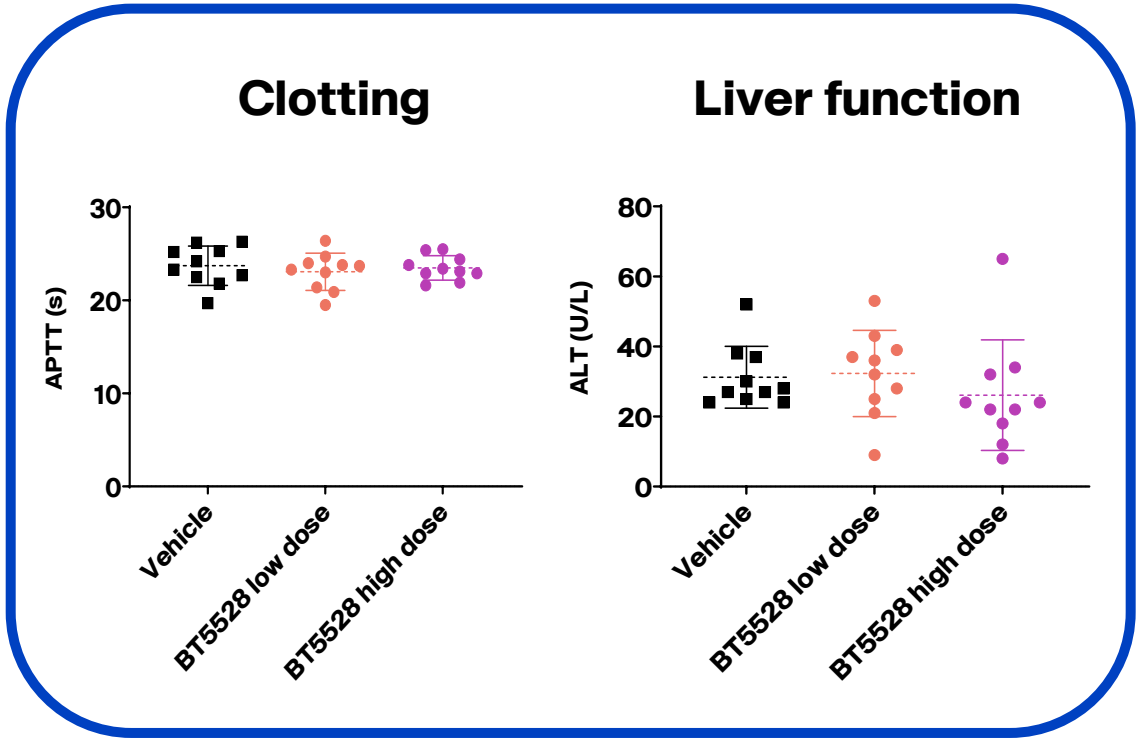
Molecule and company	MEDI-547 **Medimmune**	DS-8895a **Daiichi Sankyo**	ATRC-301 **Atreca**
Modality	EphA2-directed ADC carrying MMAF payload	Afucosylated humanized anti-EphA2 mAb, recognizing extracellular juxtamembrane region of EphA2	EphA2-directed ADC (recognizing unique epitope) carrying auristatin payload
Outcome	6 patients were dosed with MEDI-547 0.8 mg/kg; all discontinued treatment and dose escalation was not pursued **Treatment-related bleeding and coagulation events** were seen (N=3 hemorrhage related; N=2 epistaxis)[1]	Limited efficacy in EphA2+ gastric and esophageal cancer, significant infusion reactions.[2] Discontinued because of **poor risk-benefit profile & low tumor uptake,**[3] consistent with lack of substantial tumor inhibition	Nonhuman primate study revealed safety signals, including **bleeding**, that led to decision to stop development[4]

1. Annunziata et al. *Invest New Drugs*. 2013 Feb;31(1):77-84. 2. Shitara et al. *J ImmunoTherapy Cancer*. 2019 7:219-230. 3. Gan et al. *Invest New Drugs*. 2022 40(4):747-755. 4. Atreca press release, 10Nov2022.

Aiming to drug the undruggable: BT5528, an EphA2-targeting BTC® molecule



- **Highly differentiated preclinical performance with robust anti-tumor activity**
- **No liver or clotting effects observed preclinically**



aPTT and ALT measured on Day 32, following BT5528 i.v. dosing to cynomolgus monkeys on Days 1, 8, 15, 22, and 29.

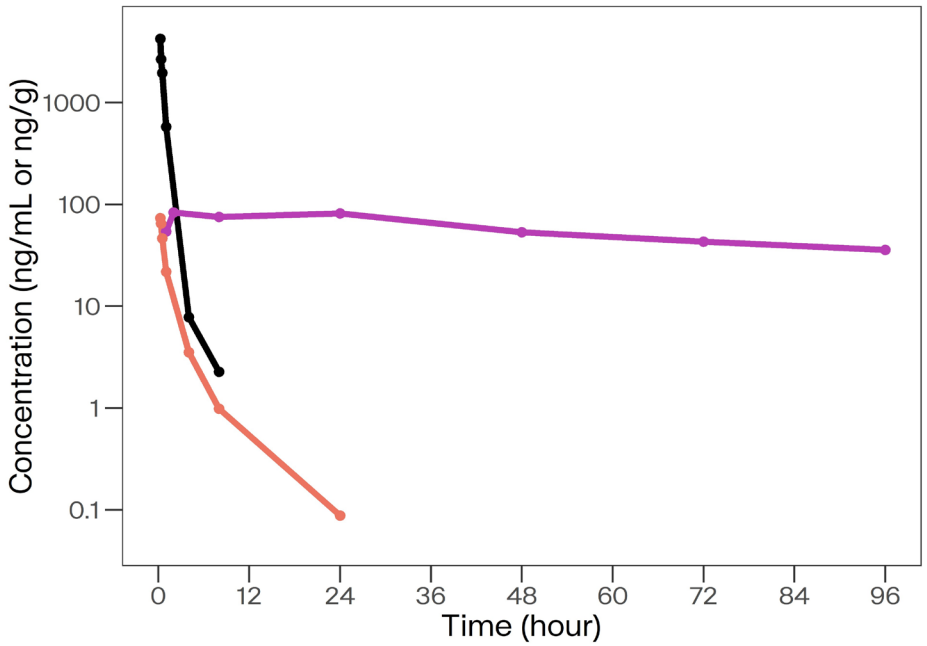
BT5528 low dose = 0.75 mg/kg, human equivalent dose 9 mg/m2
BT5528 high dose = 1.5 mg/kg, human equivalent dose 18 mg/m2

Mudd GE et al. 2020. *J Med Chem*, 63(8):4107-4116.

BT5528 delivers 10x more toxin to the tumor compared to plasma in patients

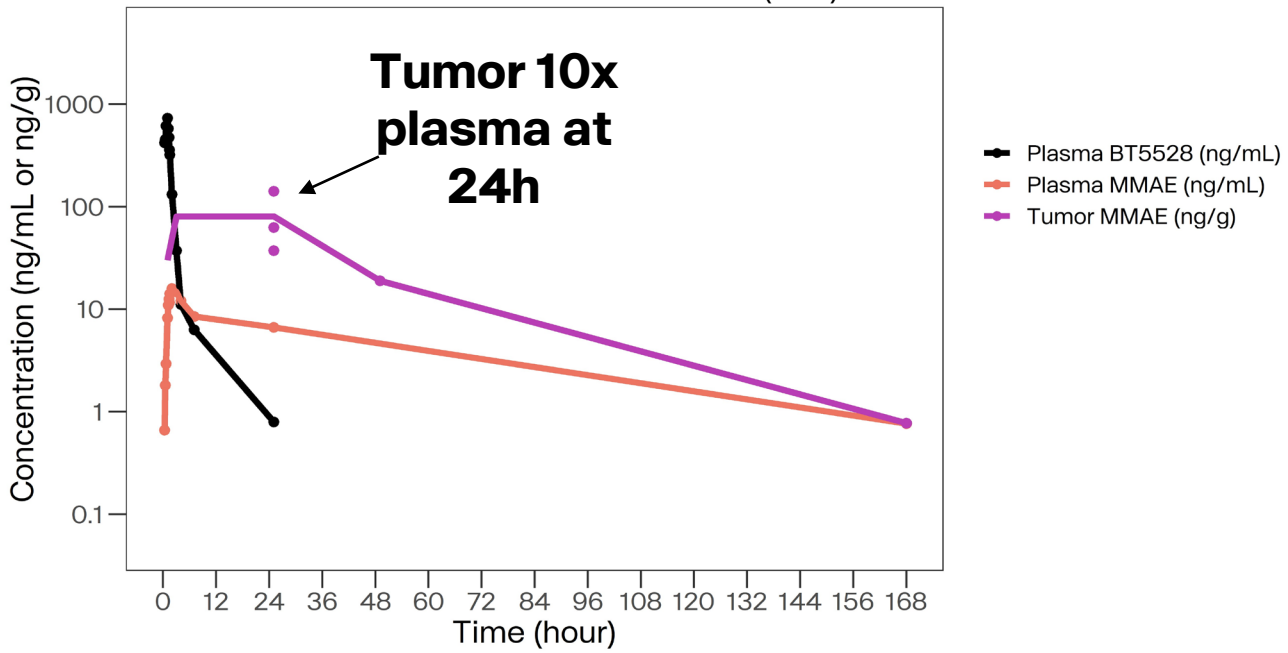
BT5528 PK in **Mouse** (1.5 mg/kg)

Mouse PK following treatment with BT5528 1.5 mg/kg



BT5528 PK in **Human** (5 mg/kg)

Human PK following treatment with BT5528 at 5 mg/kg, the estimated minimum efficacious dose (MED)



- **Efficient and durable tumor MMAE delivery**
- **Minimal exposure to parent drug minimizes off target delivery**
- **Demonstrated translation to human**

Bicycle®

BT5528 Phase 1/2 monotherapy dose escalation and expansion

Dose escalation	
2.2 mg/m^2 QW	(N=3)
4.4 mg/m^2 QW	(N=3)
8.5 mg/m^2 QW	(N=4)
6.5 mg/m^2 QW	(N=8)
6.5 mg/m^2 Q2W	(N=15)
8.5 mg/m^2 Q2W	(N=10)
10 mg/m^2 Q2W	(N=2)
5 mg/m^2 QW	(N=5)
2.2 mg/m^2 QW + nivolumab	(N=3)
4.4 mg/m^2 QW +nivolumab	(N=4)

Expansion cohorts at 6.5 mg/m^2 Q2W	
Ovarian	(N=14)
Urothelial	(N=14)
NSCLC	(N=7)
HNSCC	(N=8)
Gastric/Upper GI	(N=7)
TNBC	(N=9)

Expansion cohorts at 5 mg/m^2 QW	
Urothelial	(N=12)
Ovarian	(N=12)

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GI: gastrointestinal; HNSCC: head and neck squamous cell carcinoma; NSCLC: non-small cell lung cancer; QW: weekly; Q2W: every other week; TNBC: triple-negative breast cancer.

BT5528 patient demographics and clinical characteristics

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

Bicycle®

Fontana E et al. ESMO 2024. Data as of 14Mar2024.
[a]Includes dose escalation and expansion.
ECOG PS: Eastern Cooperative Oncology performance status; FGFR: fibroblast growth factor receptors; GI: gastrointestinal; PARP: poly (ADP-ribose) polymerase.

BT5528 demonstrated anti-tumor activity in patients with advanced solid tumors, particularly in mUC

BEST OVERALL RESPONSE IN EFFICACY-EVALUABLE PATIENTS

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

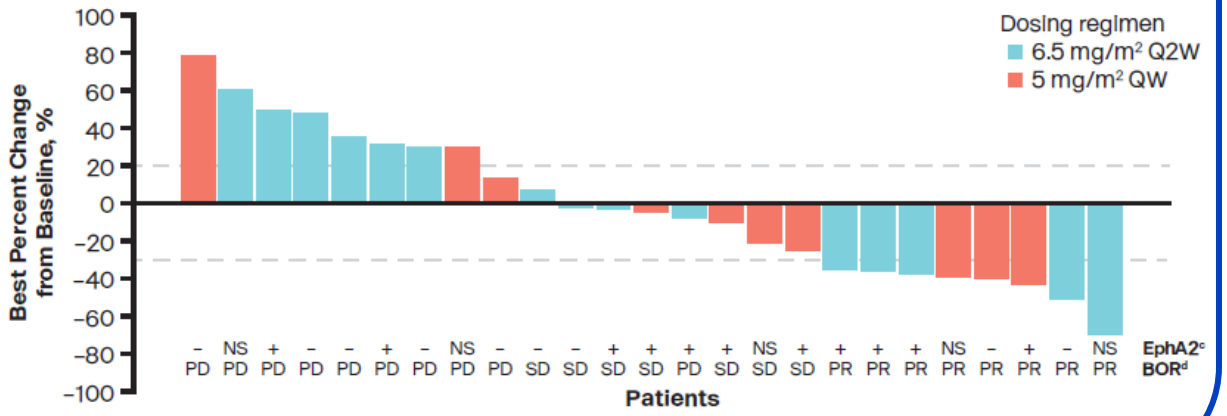
Fontana E et al. ESMO 2024.

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

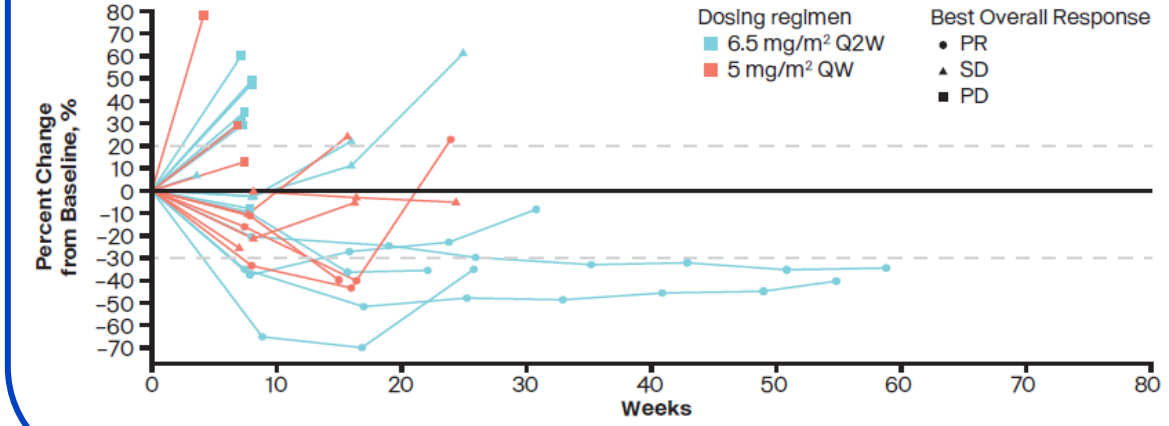
BOR: best overall response; CBR: clinical benefit rate; CR: complete response; esc: escalation; exp: expansion; mUC: metastatic urothelial cancer; ORR: objective response rate; PD: progressive disease; PR: partial response; QW: every week; Q2W: every 2 weeks; SD: stable disease.

BT5528 demonstrated anti-tumor activity in patients with advanced solid tumors, particularly in mUC

CHANGE FROM BASELINE IN TUMOR SIZE IN EFFICACY-EVALUABLE mUC PATIENTS[a,b]



DURATION OF RESPONSE IN EFFICACY-EVALUABLE mUC PATIENTS[a,b]



Fontana E et al. ESMO 2024.
[a]Seven patients did not have adequate post-baseline disease assessments and were not evaluable for efficacy. [b]Confirmed and unconfirmed responses per RECIST v1.1. [c]EphA2+ expression used a cutoff of TPS >1 by IHC using mAbs; NS indicates no sample available for testing. [d]Confirmed and unconfirmed.
BOR: best overall response; mUC: metastatic urothelial cancer; PD: progressive disease; PR: partial response; QW: every week; Q2W: every 2 weeks; SD: stable disease.

BT5528 demonstrated an emerging differentiated safety profile in patients with advanced solid tumors

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

Fontana E et al. ESMO 2024. Data as of 14Mar2024.
[a]Prophylactic anti-emetics were required in the dose expansion phase and for the 5 mg/m^2 QW dose.
DLTs: dose-limiting toxicities; esc: escalation; exp: expansion; QW: weekly; Q2W: every 2 weeks; SAEs: Serious adverse events; TRAEs: treatment-related adverse events; TRSAEs: treatment-related serious adverse events.

BT5528 treatment-related adverse events of interest were of low frequency and severity

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

Fontana E et al. ESMO 2024. Data as of 14Mar2024.
[a]Peripheral neuropathy SMQ [broad]. [b]Preferred terms defined in Eye Disorders SOC. [c]Hyperglycemia/new onset diabetes mellitus SMQ [broad]. [d]Includes the SCAR SMQ and the preferred terms defined in Skin and Subcutaneous Disorders SOC, excluding alopecia. [e]Hemorrhage SMQ (excluding laboratory terms) [narrow].
esc: escalation; exp: expansion; QW: weekly; Q2W: every 2 weeks; SMQ: Standardized MedDRA Queries; SCAR: severe cutaneous adverse reactions; SOC: skin and subcutaneous disorders; TRAEs: treatment-related adverse event; TRPN: treatment-related peripheral neuropathy.

BT5528, a first-in-class BTC® molecule, has a promising emerging efficacy and tolerability profile

SUMMARY

- BT5528 has shown an emerging differentiated safety profile, in contrast to other EphA2-targeted agents
- Promising antitumor activity seen in advanced solid tumors, particularly in mUC
- In addition to the RP2D of 6.5 mg/m^2 Q2W, a dose of 5 mg/m^2 QW also demonstrated antitumor activity and an acceptable and differentiated safety profile
- There appears to be a relationship between EphA2 expression and activity, providing a clear potential path forward in tumors where EphA2 is expressed

NEXT STEPS

✓ **Expect 5 mg/m^2 QW data in urothelial and ovarian cancer in 2H 2024**

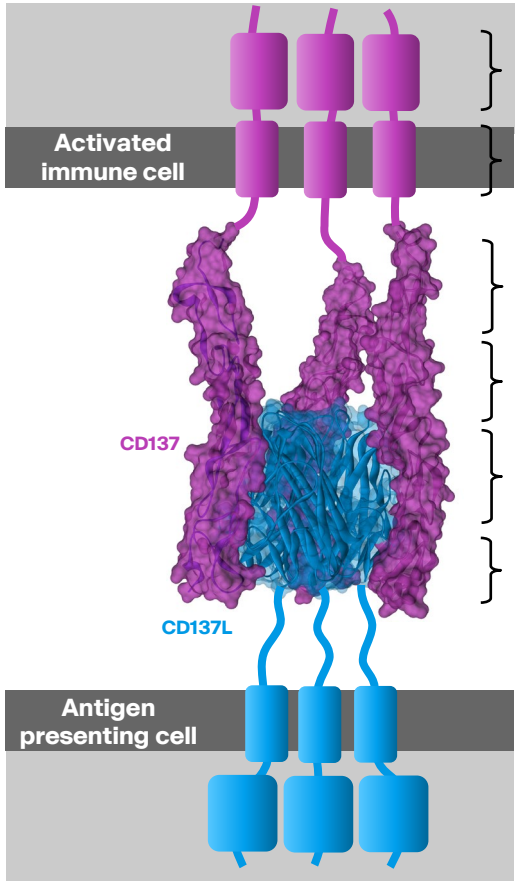
- Enables decision-making on dose regime and expansion plans in line with the FDA's Project Optimus initiative
- Enables decision on drug combinations
- Potential to expand to other indications of high interest (HNSCC, Gastric/Upper GI, NSCLC, TNBC)

GI: gastrointestinal; HNSCC: head and neck squamous cell carcinoma; mUC: metastatic urothelial cancer; NSCLC: non-small cell lung cancer; RP2D: recommended Phase 2 dose; QW: every week; Q2W: every 2 weeks; TNBC: triple-negative breast cancer.

BT7480, a potential first-in-class Bicycle TICA® molecule

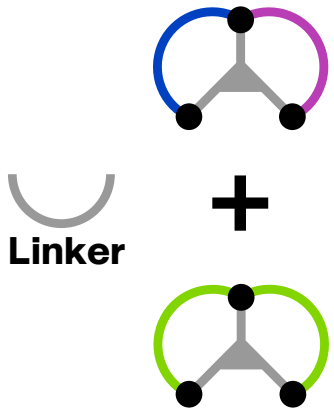
Bicycle®

Bicycle TICA® molecules: Tumor-Targeted Immune Cell Agonists join immune cell and tumor targeting Bicycle® molecules



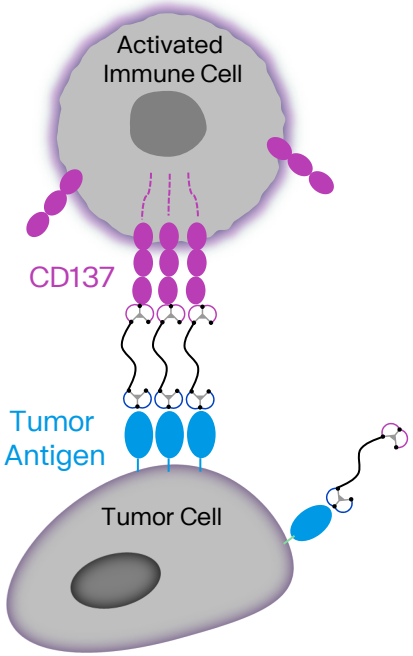
Activation induced by clustering of **CD137** by trimeric **CD137L**

CD137-engaging Bicycle® molecule



Tumor-targeting Bicycle® molecule

Tumor Target/CD137 Bicycle TICA® molecule

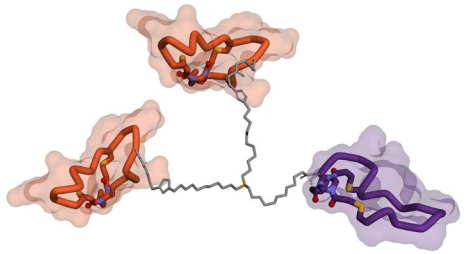


CD137 clustering induced by tumor antigen

BT7480 is a fully synthetic context-dependent CD137 agonist

Small

Bicycle TICA® molecule BT7480

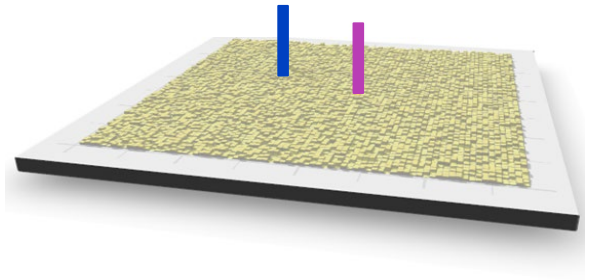


7.2 kDa

~30x smaller than other targeted agonists

Selective

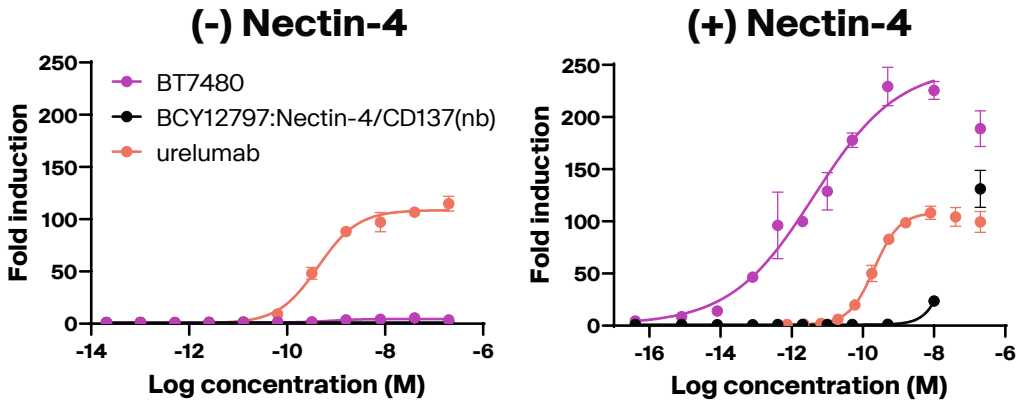
BT7480 only binds Nectin-4 and CD137



Retrogenix membrane protein array: no binding of biotinylated-BT7480 @1µM to 5,482 other proteins.

No off-target Fc directed agonism in normal tissue

Potent and Nectin-4 dependent



In vitro bioactivity assay measuring CD137 agonism: BT7480 activity is dependent on Nectin-4 in cell-based assays.

More potent than mAb agonists, but only where needed

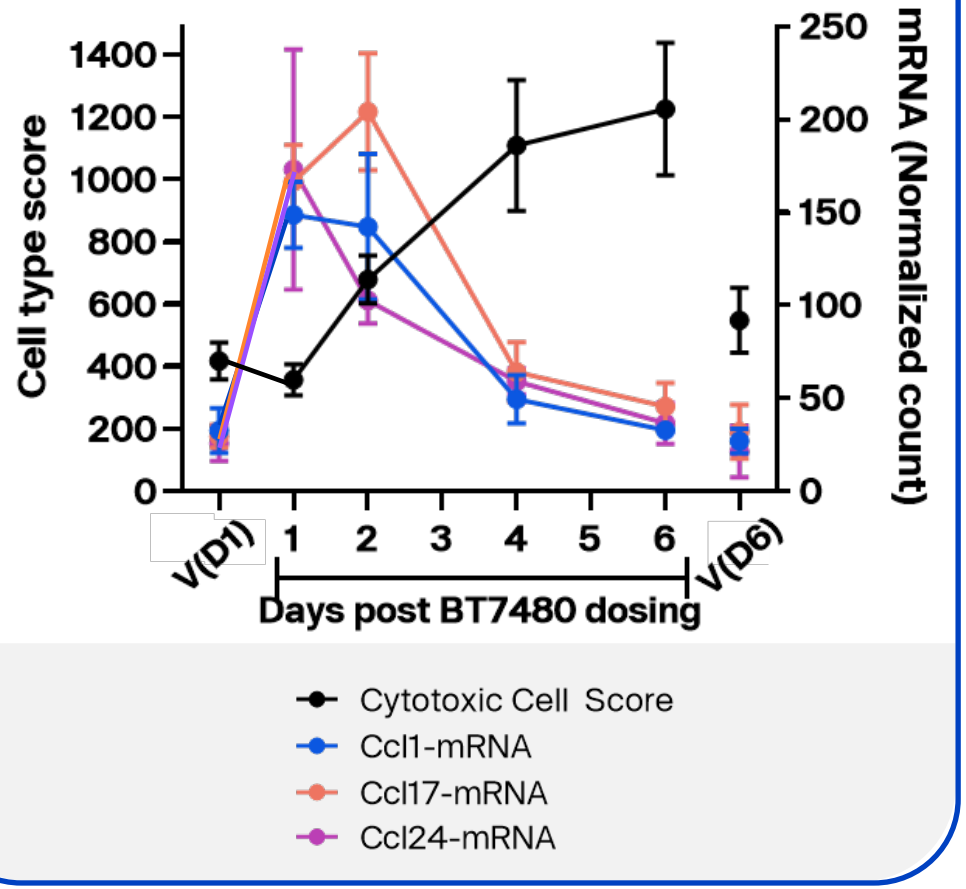
BT7480 is well-tolerated in preclinical species, with no evidence of liver effects

Hurov K et al. 2021. *J Immunother Cancer*, 9(11):e002883.
mAb: monoclonal antibody.

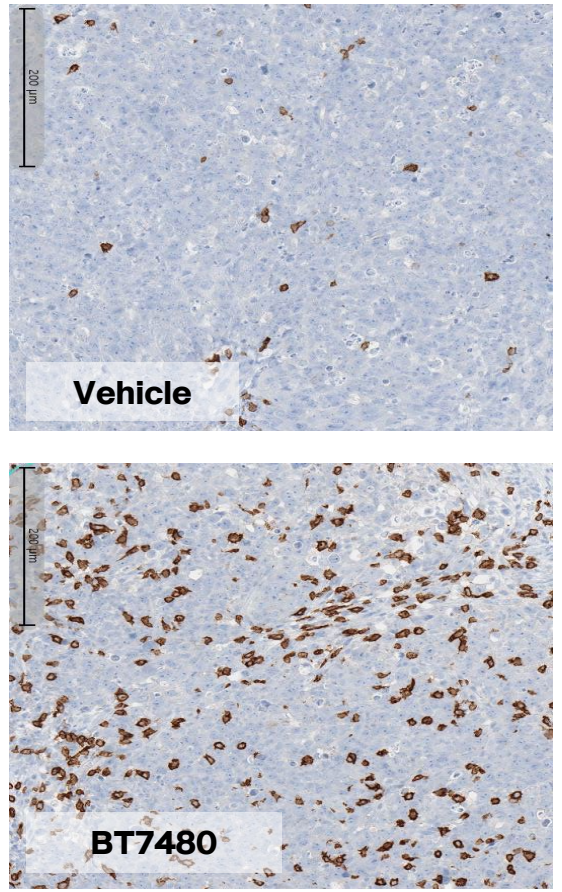
Bicycle TICA® molecules have a unique MOA that is different from, and complementary to, that of current checkpoint inhibitors

- BT7480 induces a rapid pulse of chemokine/cytokine signaling (hours)
- This signals to, attracts and activates effector cells

Increase in chemotactic cytokine transcription, followed by increased cytotoxic cell score

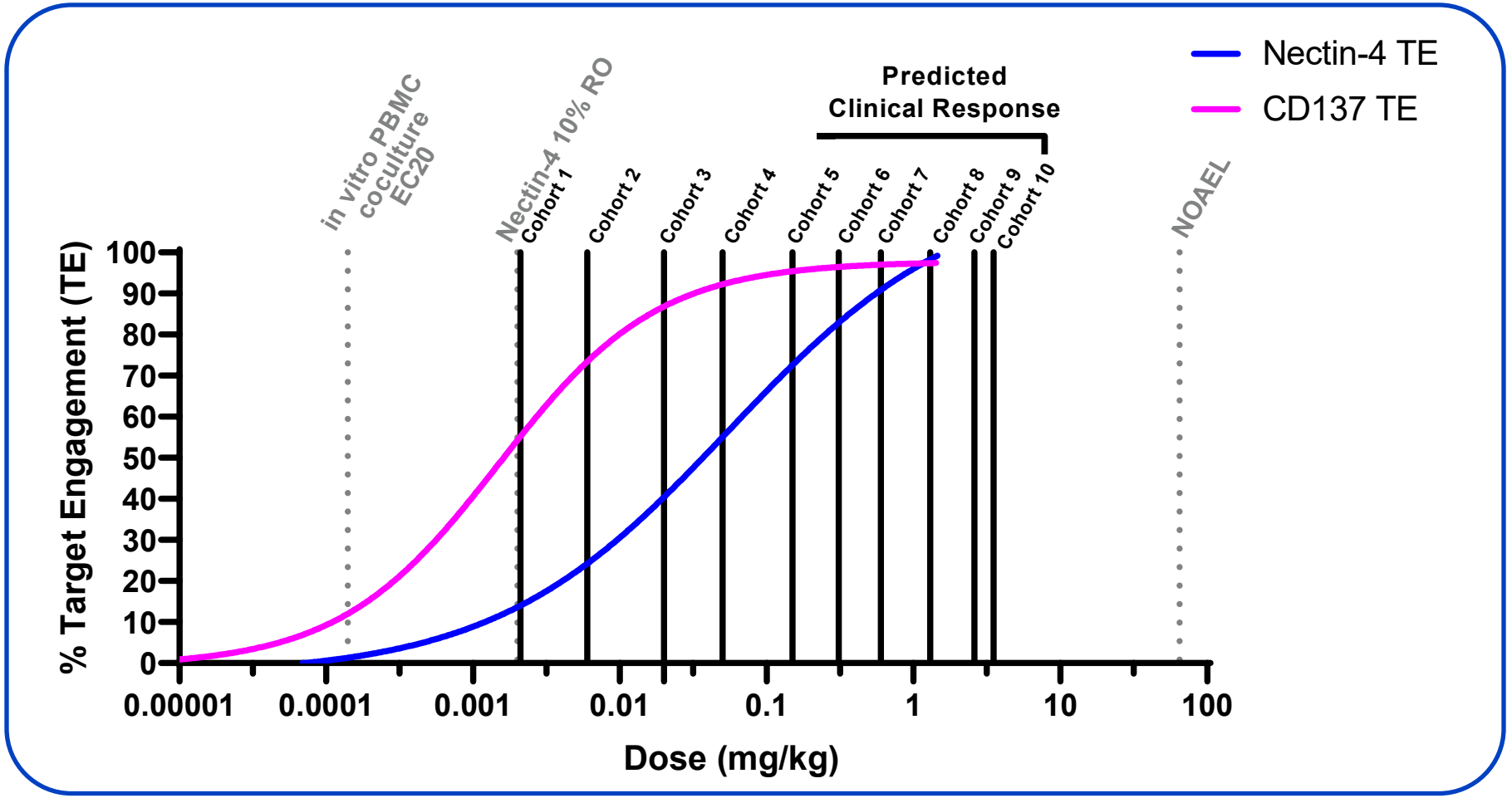


CD8+ T cells on Day 6



MC38-Nectin-4 tumor bearing huCD137 C57Bl/6 mice were dosed with BT7480, and then transcriptionally profiled.
Hurov K et al. 2021. *J Immunother Cancer*, 9(11):e002883.
MOA: mechanism of action.

We built a robust preclinical PK/PD model to provide a roadmap for BT7480 clinical dose selection



Predicted clinical response based on tumor growth inhibition detected in BT7480 administered huCD137 mice bearing Nectin-4+ MC38 tumors. NOAEL based on 100 mg/kg NOAEL in NHP based on exposure. Nectin-4 and CD137 TE based on *in vitro* cell-based RO studies.
EC20: 20% effect concentration; NOAEL: no observed adverse effect level; PBMC: peripheral blood mononuclear cells; RO: receptor occupancy; TE: target engagement.

BT7480 Phase 1/2 study design

Dose escalation (monotherapy)
Safety, PK, Biomarker focus

Cohort 1‡:	0.002 mg/kg QW	(N=2)
Cohort 2‡:	0.006 mg/kg QW	(N=1)
Cohort 3‡:	0.02 mg/kg QW	(N=1)
Cohort 4‡:	0.05 mg/kg QW	(N=1)
Cohort 5†:	0.15 mg/kg QW	(N=4)
Cohort 6†:	0.3 mg/kg QW	(N=3)
Cohort 7†,*:	0.6 mg/kg QW	(N=6)
Cohort 8†,*:	1.3 mg/kg QW	(N=9)
Cohort 9†:	2.6 mg/kg QW	(N=7)
Cohort 10†:	3.5 mg/kg QW	(N=4)

Combination escalation (BT7480 + nivolumab)
Safety, PK, Biomarker focus

Monotherapy RP2D minus 1	3+3
Monotherapy RP2D	3+3

Future expansion
Ph2 clinical efficacy

- Cervical cancer (monotherapy and combination)
- NSCLC (monotherapy and combination)

Enrollment numbers as of 12Feb2024. Study is actively recruiting.
‡Single subject cohorts
†3+3 design cohorts
*Cohorts with backfill enrollment to further evaluate PK and biomarker data

Future cohorts/trials

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BT7480 baseline patient demographics and clinical characteristics: Cohorts 1-10 (0.002-3.5 mg/kg QW)

- As of 12 February 2024, 39 patients had received BT7480 (0.002–3.5 mg/kg QW IV)
- Median age: 62 years
- NSCLC was the most common tumor type (n=11; 28%) of which all patients with available IHC data (n=8) were Nectin-4+

Characteristic	All patients (N=39)
Median age, years (range)	62 (29–83)
Sex, n (%)	
Female	24 (62)
Male	15 (38)
Race, n (%)	
White	32 (82)
Black or African American	5 (13)
Other	2 (5)
ECOG PS, n (%)	
0	12 (31)
1	27 (69)
Median prior lines of therapy (range)	4 (1–9)
Target expression, n (%)	
Nectin-4+	26 (77)[a]
Nectin-4+ CD137+	19 (63)[b]

Papadopoulos KP et al. ESMO 2024. Data as of 12Feb2024.
[a]Of 34 IHC evaluable patients, positivity ≥1 TPS. [b]Of 30 mIF evaluable patients, positivity ≥1%.
ECOG PS: Eastern Cooperative Oncology Group performance status; IHC: immunohistochemistry; IV: intravenously; mIF: multiplex immunofluorescence; NSCLC: non-small cell lung cancer; QW: once every week; TPS: Tumor Proportion Score.

Bicycle®

BT7480 was generally well-tolerated
Safety summary: Cohorts 1-10 (0.002-3.5 mg/kg QW)

- Any grade treatment-related AEs (TRAEs) occurred in 49% of patients, the most common being fatigue (23%) and headache (10%)
  - None of the patients receiving BT7480 3.5 mg/kg (n=4) experienced these TRAEs
  - TRAEs were only reported in one patient (25%) in this group
- A low rate of Grade ≥3 TRAEs (5%) and TRSAEs (8%) were reported, with none among patients receiving BT7480 3.5 mg/kg
- Two patients experienced a DLT:
  - 0.6 mg/kg: mucosal inflammation
  - 2.6 mg/kg: increased ALT/AST
- The maximum tolerated dose has not yet been reached

Category, n (%)	All patients (N=39)	Patients (3.5 mg/kg; n=4)
TEAEs	38 (97)	4 (100)
TRAEs	19 (49)	1 (25)
TEAEs Grade ≥3	16 (41)	2 (50)
TRAEs Grade ≥3	2 (5)	0
SAEs	14 (36)	2 (50)
TRSAEs	3 (8)	0
DLTs	2 (5)	0
TEAEs leading to dose interruption	8 (21)	1 (25)
TEAEs leading to dose reduction	0	0
TEAEs leading to dose discontinuation	2 (5)	0
TRAEs reported in ≥5% of patients in either group, n (%)		
Fatigue	9 (23)	0
Headache	4 (10)	0
Arthralgia	3 (8)	0
Decreased appetite	3 (8)	0
Lethargy	3 (8)	0
Nausea	3 (8)	0
Amylase increased	2 (5)	0
Anemia	2 (5)	0
Blood alkaline phosphatase increased	2 (5)	0
Hypomagnesemia	1 (3)	1 (25)
Urinary tract infection	1 (3)	1 (25)

Bicycle®

Papadopoulos KP et al. ESMO 2024. Data as of 12Feb2024.
AE: adverse events; ALT: alanine aminotransferase; AST: aspartate aminotransferase; DLT: dose-limiting toxicity; SAE: serious adverse events; TEAEs: treatment-emergent adverse events; TRAEs: treatment-related adverse events; TRSAEs: treatment-related serious adverse events.

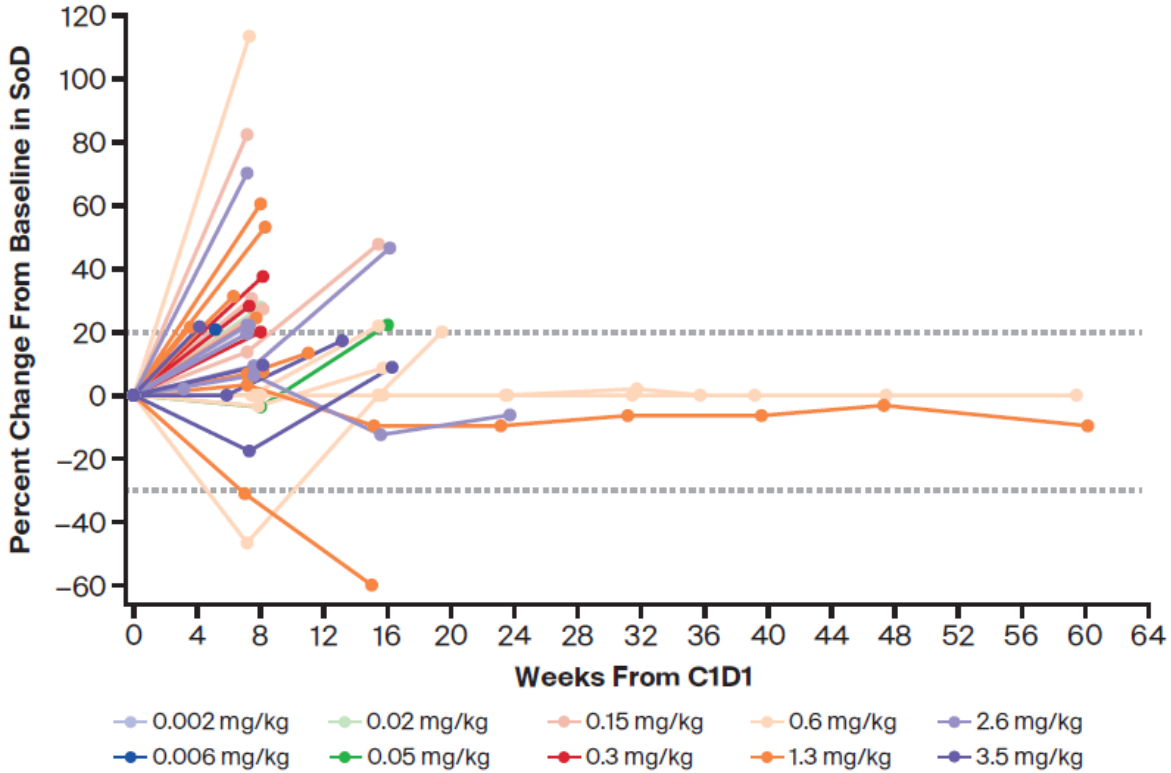
BT7480 showed preliminary antitumor activity in patients with advanced Nectin-4–associated solid tumors

- Best overall response of SD was reported in 13 patients, and there were two unconfirmed PRs, both in patients with cervical cancer
- SD was prolonged (>8 months) for three patients, two treated with 0.6 mg/kg (NSCLC) and one treated with 1.3 mg/kg (anal squamous cell carcinoma)

BEST OVERALL RESPONSE

Best overall response, n (%)	All patients (N=40[a])
CR	0 (0)
PR	2 (5)[b]
SD[c]	13 (33)
PD	20 (50)
NE	5 (13)
ORR (CR+PR)	2 (5)
CBR (CR+PR+SD [≥ 8 weeks])	15 (38)

PERCENT CHANGE IN TUMOR SIZE FROM BASELINE OVER TIME[d]

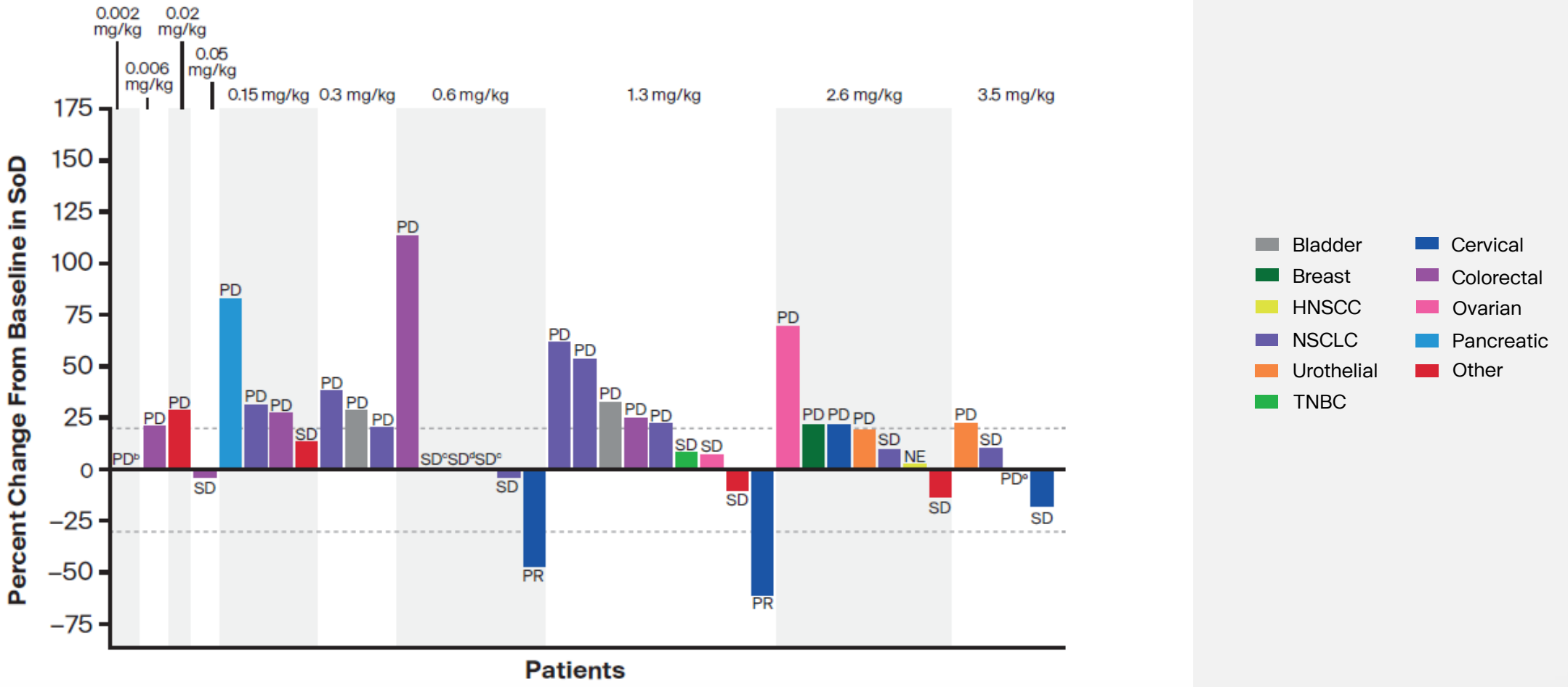


Papadopoulos KP et al. ESMO 2024. Data as of 12Feb2024.
[a]Data cleaning efforts identified one additional unconfirmed partial response from the 12 February 2024 data cut, which was rectified as of a data cutoff date of 15 April 2024, with one additional patient enrolled as of this date. [b]Unconfirmed. [c]For ≥6 weeks from the start of study drug to assessment date. [d]Only patients with at least one post-baseline assessment are represented.
CBR: clinical benefit rate; CR: complete response; NE: not evaluable; ORR: objective response rate; PD: progressive disease; PR: partial response; SD: stable disease.

Bicycle®

Among BT7480-treated patients with NSCLC, five reported a best overall response of SD

MAXIMUM PERCENT REDUCTION FROM BASELINE IN TARGET LESION[a]



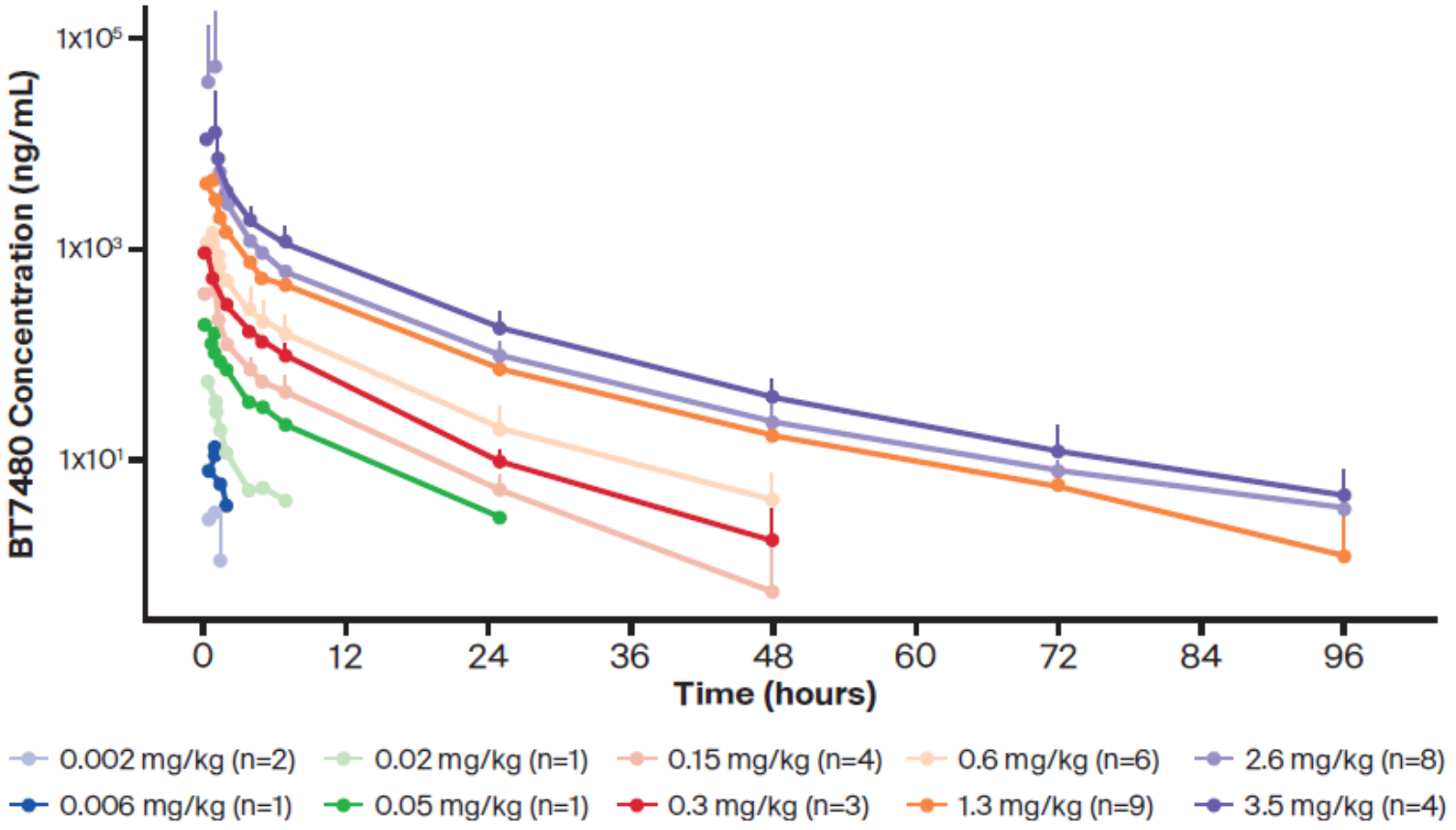
Papadopoulos KP et al. ESMO 2024. Data as of 12Feb2024.

[a]Unconfirmed best overall response; only patients with at least one postbaseline assessment are represented. NE indicates patient was not evaluable for best overall response. [b]Other. [c]NSCLC. [d]HNSCC. [e]Urothelial.

BT7480 exhibited a dose-dependent increase in PK with minimal accumulation at steady-state with a QW regimen

- Approximately dose proportional PK was observed across the tested dose range at C1D1
- Terminal half-life at 1.3–3.5 mg/kg was approximately 13–16 hours, with minimal BT7480 accumulation at steady state (C1D15) following QW dosing

BT7480 PLASMA CONCENTRATION OVER TIME BY DOSE AT C1D1[a]



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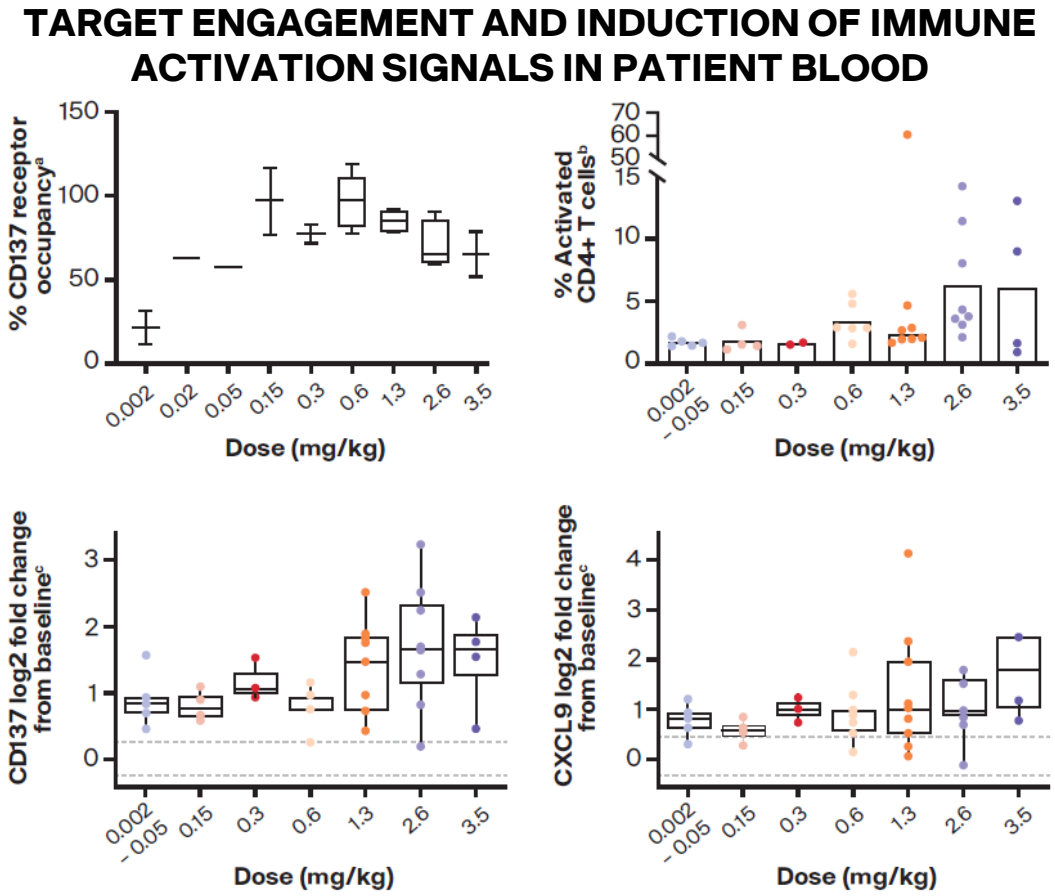
Papadopoulos KP et al. ESMO 2024. Data as of 12Feb2024.
[a]Data presented as mean ± standard deviation.
C: cycle; D: day; PK: pharmacokinetics; QW: every week.

Preliminary biomarker analyses support BT7480 dual targeting of CD137 and Nectin-4 as demonstrated by enhanced immune cell activation, aligned with molecule's proposed mechanism of action

- Preliminary biomarker analyses showed target saturation in peripheral blood at doses ≥0.15 mg/kg
- Maximum induction of circulating immune activation markers (soluble CD137, CXCL9, and CD4+ T cells) was observed at doses ≥1.3 mg/kg with no hook effect at higher doses



Papadopoulos KP et al. ESMO 2024. Data as of 12Feb2024.
[a]Measured at C1D1, 20 minutes post-end of infusion, divided by the baseline value. [b]Maximum value reported, throughC2. [c]Maximum value reported through C2D15. Each dot represents one patient; bars and horizontal lines represent the median; whiskers show the maximum and minimum values. Dashed lines = 1 standard deviation from baseline.
C: cycle; D: day; PK: pharmacokinetics; QW: every week.

BT7480 has a promising emerging efficacy and tolerability profile

SUMMARY

- In contrast to other CD137 targeted agents, BT7480 has shown an emerging safety and tolerability profile with a low number of severe adverse events
- BT7480 showed preliminary antitumor activity in patients with advanced Nectin-4–associated solid tumors
- BT7480 exhibited dose-dependent increase in PK with minimal accumulation at steady-state with a QW regimen
- Preliminary biomarker analyses support BT7480 dual targeting of CD137 and Nectin-4 as demonstrated by enhanced immune cell activation, aligned with the proposed mechanism of action of BT7480

NEXT STEPS

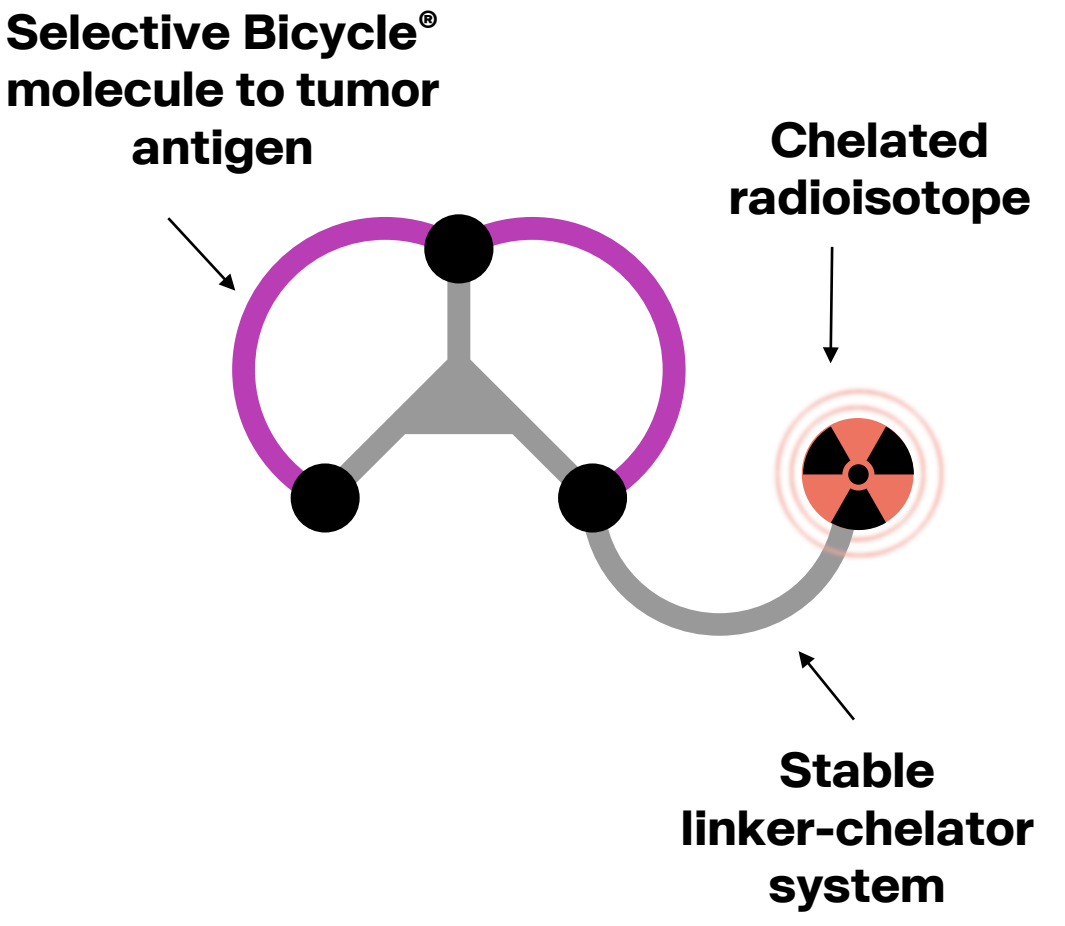
- ✓ **Define RP2D (or maximum dose) and a dose range**
- ✓ **Enroll combination cohorts with nivolumab**
- **Design Phase 2 trial with potential for accelerated approval**

QW: every week; RP2D: recommended Phase 2 dose

Bicycle Radionuclide Conjugates (BRC®)

Bicycle®

Bicycle® molecule advantages for delivering cytotoxic payloads are also advantages for delivering radionuclide payloads



- Highly selective and tumor penetrant
- Pipeline of Bicycle® molecules to novel tumor antigens
- Minimal systemic exposure

BRC® molecules show selective tumor uptake and ideal PK across a range of targets and tumor models

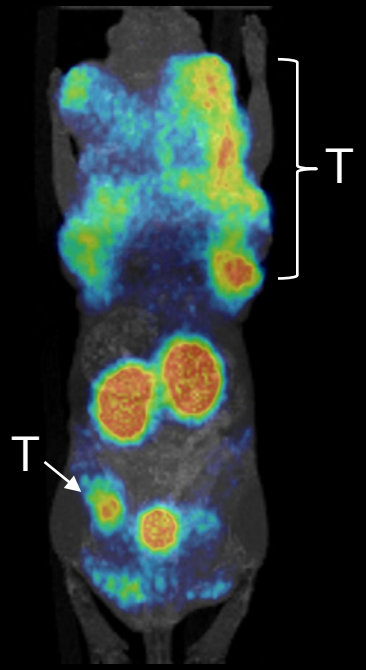
MT1-MMP

Fibrosarcoma

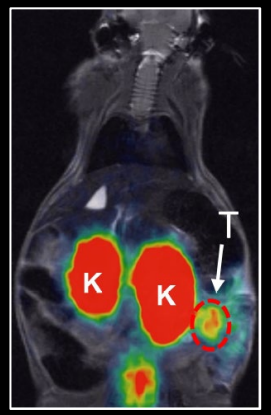
Left: HT1080 tumor model, 2h P.I. (DKFZ unpublished data)
Right: HT1080 tumor model, 40 to 60 min P.I. Eder M et al. 2019. *Cancer Res.* 79(4):841-852

EphA2

Breast



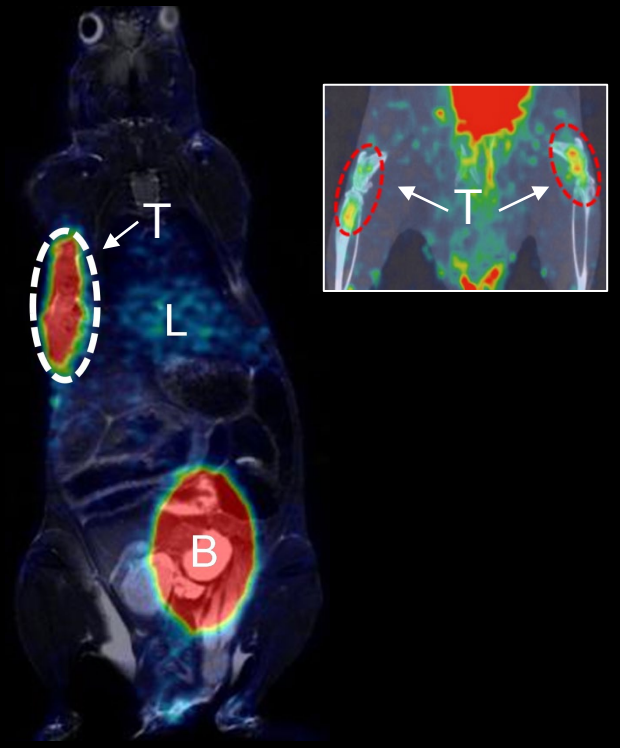
Pancreatic



Left: MMTV-PyMT transgenic mouse model, 2h P.I.
Right: Panc-1 orthotopic tumor model 1h P.I.
Sharma AK et al. 2023. *Cancer Res,* 83(7 Suppl):2768

CD38

Multiple myeloma



Left: MOLP8 tumor xenograft, 90 min P.I.
Right: MOLP8 disseminated tumor model (Sharma AK et al. BioRxiv)

Bicycle® dkfz.

Our strategy in radiopharmaceuticals

Partner with leaders in the field

- Build our understanding through strategic partnerships

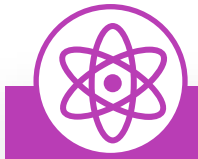
  NOVARTIS Bayer

- Partner with academia to deepen our knowledgebase
- Build unique internal portfolio guided by KOLs

  dkfz.

Pursue novel targets with first-in-class potential

- Platform proven to identify novel peptide ligands
- Use early imaging data to direct indication selection for theranostics and build programs in a data-driven manner
- Enable optimal clinical and commercial positioning of BRCs



Use the isotope best suited for the target

- Test BRCs with a range of isotope payloads and select the best
- Establish arrangements with leading isotope suppliers and manufacturers

  Eckert & Ziegler [1]

- Scale to support broad portfolio of clinical applications

1. Letter of intent in place as of October 10, 2024.

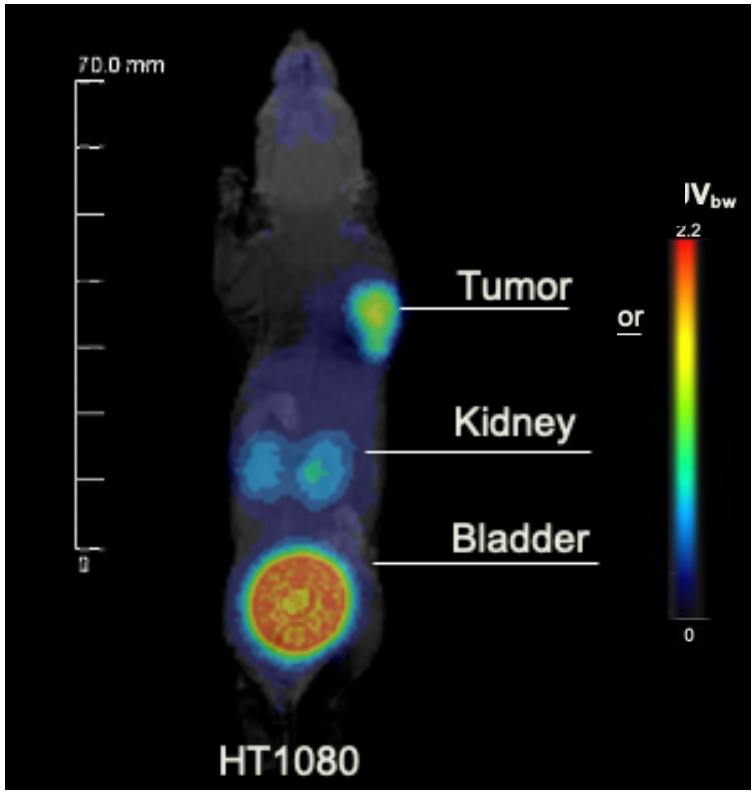
MT1-MMP is a novel target in the treatment of cancer

- Membrane type 1 matrix metalloproteinase (MT1-MMP)
- Overexpressed in variety of cancers and associated with poor prognosis
- Potential first-in-class opportunity

Tumor Type	Number of cases tested	MT1-MMP positive
Lung squamous	76	**59%**
Bladder	96	**56%**
Esophageal	66	**55%**
Triple negative breast cancer	81	**43%**
Ovarian cancer	82	**11%**
Lung adenocarcinoma	69	**9%**

MT1-MMP expression was determined using IHC performed with in house validated antibody, positive cases were defined as H-score ≥ 50 in tumor cell membrane.

Early MT1-MMP targeting BRCs show high tumor enrichment in PET imaging studies

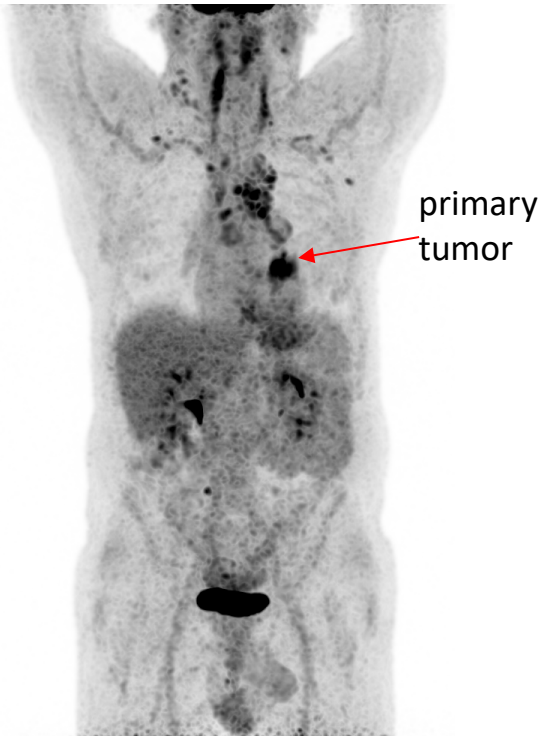


Whole-body maximum intensity projection of ^{68}Ga-labeled BRC targeting MT1-MMP 60 min. p.i. obtained from PET/MR imaging

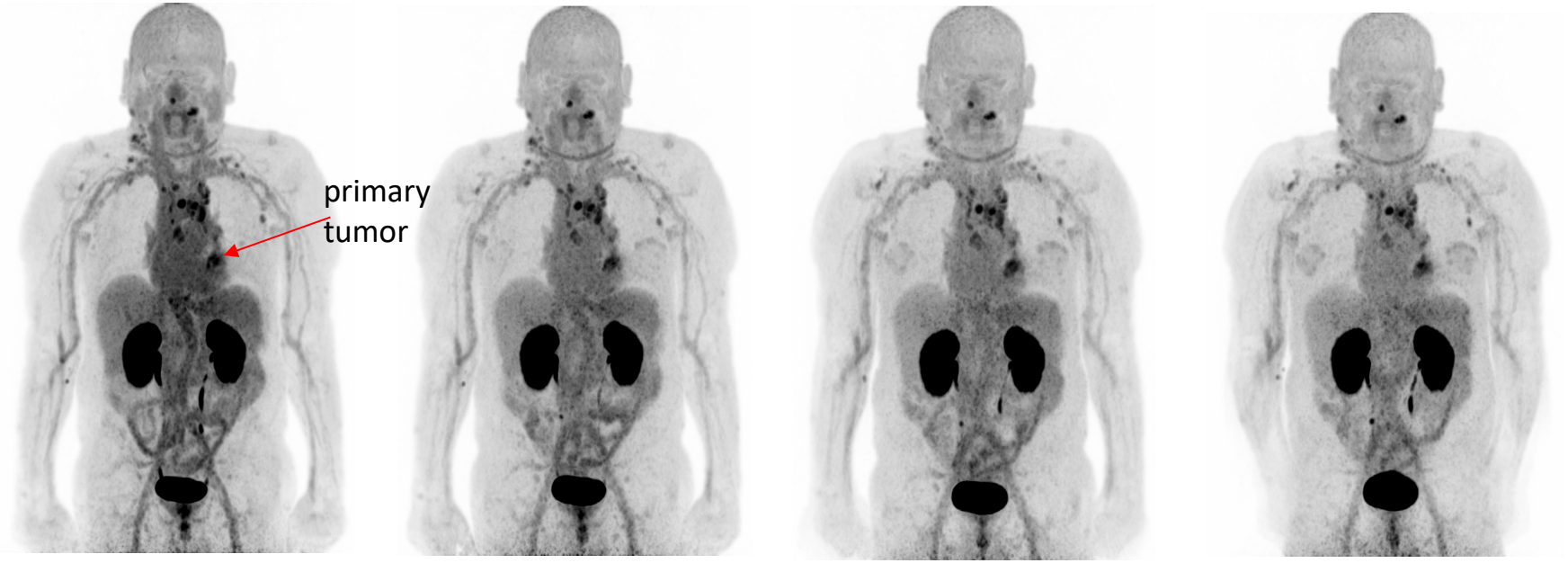
1. Gelb T et al. 2019. *Mol Cancer Ther*, 18(12_Suppl):A047. 2. Eder M et al. 2019. *Cancer Res*. 79(4):841-852.

First in Human MT1-MMP imaging

[^{18}F]FDG-PET/CT



[^{68}Ga]Ga-MT1-MMP-PET/CT



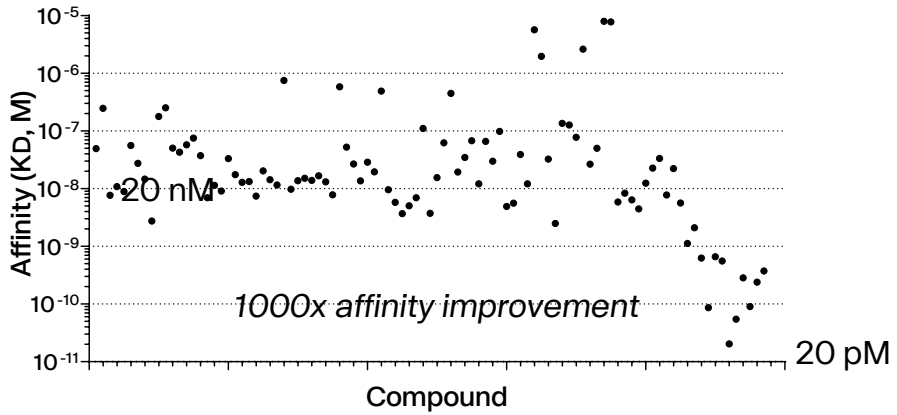
15 min. p.i. | 30 min. p.i. | 45 min. p.i. | 60 min. p.i.

Maximum Intensity Projections

Advanced left lower lobe lung adenocarcinoma; EBUS biopsy: 2R, 4R, 3P and primary tumor confirmed

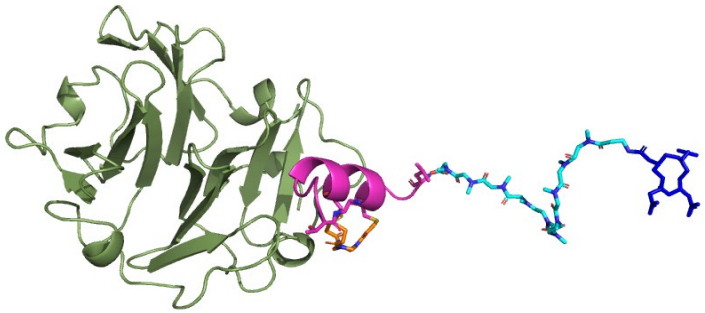
Generation of an MT1-MMP BRC® molecule with potential theranostic applications

Binding properties



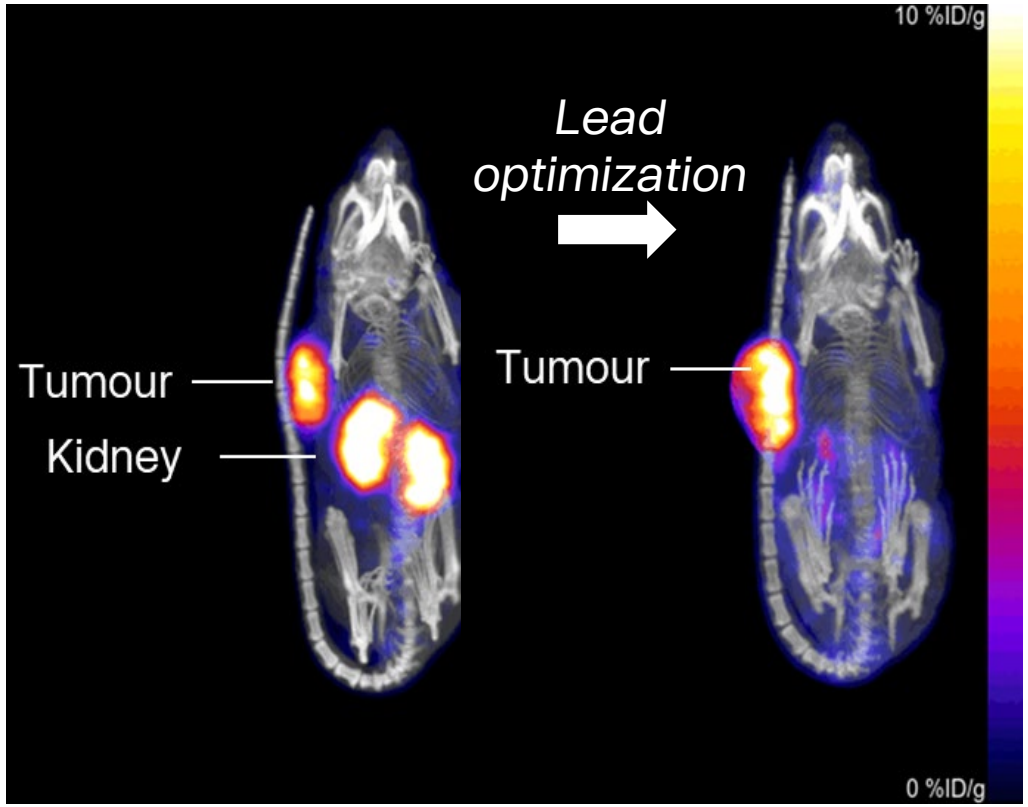
Binding affinities of compounds synthesized during lead optimization, as determined by surface plasmon resonance.

Structurally enabled



A co-crystal structure of MT1-MMP protein and bicyclic peptide was obtained And used to study molecular interactions and guide chemical optimisation

Kidney uptake / retention



^{111}In SPECT images of early (left) versus optimized (right) BRCs 24 hours post injection. Optimized BRC shows reduced payload levels in the kidneys and maintains high payload levels in the tumor.

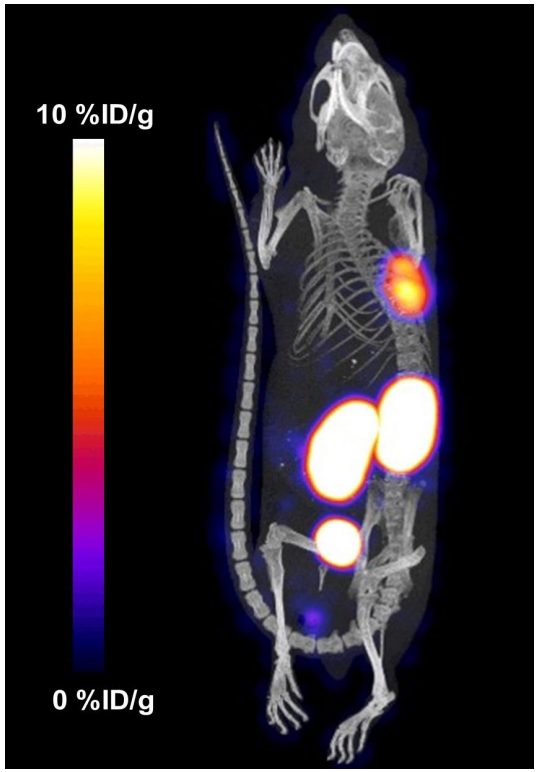
Our next BRC® molecule target: EphA2, a first-in-class opportunity

- EphA2 overexpression associated with higher grade and/or stage in a variety of cancers[1,2]
- Moving into human imaging in 2025

Tumor Type	Number of cases tested	EphA2 positive
Pancreatic	80	**60%**
Bladder	139	**58%**
Head and Neck	61	**46%**
Lung squamous	88	**30%**
Stomach	57	**30%**
Ovarian	73	**29%**

EphA2 expression was determined using IHC with pAb (RnD AF3035) on tissue microarrays. Positive cases were defined as TPS score >1 in tumor membrane or cytoplasm. For lung cancer, only samples annotated for adenocarcinoma or squamous subtype were included. TMAs included: Pancreatic - PA2081b, Bladder - BL2082a, Head and Neck - HN803f, Lung squamous – LC1921b and ATGC1118, Stomach - ST1001a, Ovarian - BC11115c, Esophageal - ES2081, TNBC - BR1301, Lung adenocarcinoma – LC706b, LC1921b, and ATGC1118. Cores with ambiguous results were removed. Top 6 indications were listed.

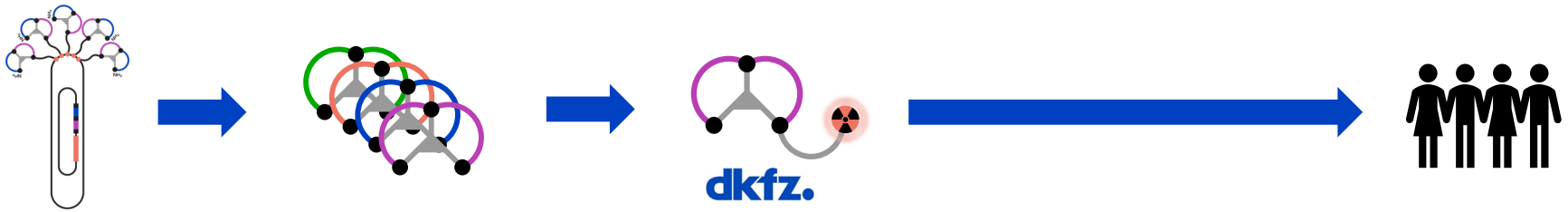
High tumor uptake and low uptake in non-tumor tissues



Example SPECT/CT Maximum Intensity Projection (MIP) 60 min. p.i. of 230 pmol of [111In]In labeled BRC

1. Zhou L et al. 2021. *Int J Clin Exp Pathol*, 14(4):484-49. 2. Cioce M and Fazio VM. 2021. *Cancers (Basel)*, 13(4):700.

Next steps are to advance the pipeline and align with the relevant clinical indication



Target	Discovery / POC	BRC™ Lead Optimization	Human Imaging/ IND enabling
MT1 (Im)			
MT1 (Tx)			
EphA2 (Im)			
EphA2 (Tx)			
Target 1			
Target 2			
Additional			

Im – imaging, Tx = theranostic

Advance portfolio into human studies and leverage experts in the field to position molecules in optimal clinical indication(s)

Bicycle Clinical Advisory Board

Charles Swanton (Chair)
The Francis Crick Institute

Solange Peters
University Hospital Lausanne

Toni K. Choueiri
Dana-Farber Cancer Institute

Sherene Loi
Peter MacCallum Cancer Centre

We believe Bicycle Radionuclide Conjugates are well-positioned to deliver novel radiopharmaceuticals

SUMMARY

- Our technology platform is well-suited to develop radiopharmaceutical medicines, enabling us to pursue novel targets and remain isotope agnostic
- First human imaging data 1) validates the potential of MT1-MMP as a novel target and first-in-class opportunity and 2) helps us understand how BRC® molecules are being distributed throughout the human body
- Our next target will be EphA2, another potential first-in-class opportunity

NEXT STEPS

- **EphA2 molecule ready for human imaging in 2025**
- **Additional imaging data in mid-2025**
- **First Bicycle-sponsored clinical trial in 2026/2027**

Looking Ahead

Bicycle®

We expect 2024 to be a catalyst-rich year

zelenectide pevedotin	✓ Initiate Ph 2/3 Duravelo-2 in 1Q 2024 ✓ Report updated clinical data from ongoing dose expansion study in mUC ❑ Report updated clinical data in other indications (NSCLC, breast) ❑ Initiate novel combination studies in certain indications
BT5528	✓ Report clinical data at 5 mg/m^2 in urothelial and ovarian cancer in 2H 2024 ✓ Complete dose-finding work and identify optimal dose for future studies ❑ Consider initiating studies on other indications of high interest (HNSCC, Gastric/Upper GI, NSCLC, TNBC)
BT7480	✓ Define the RP2D (or max dose) and a dose range ✓ Enroll combination cohorts with nivolumab ❑ Design a Phase 2 trial that could support potential accelerated approval
Platform	❑ Advance our next-generation programs ❑ Select a bicycle toxin conjugate clinical candidate using our next-generation technology ❑ Continue to seek additional partnerships

Bicycle®

GI: gastrointestinal; HNSCC: head and neck squamous cell carcinoma; mUC: metastatic bladder cancer; NSCLC: non-small cell lung cancer; RP2D: recommended Phase 2 dose; TNBC: triple-negative breast cancer.

Bicycle Therapeutics: Pioneering a new, differentiated class of innovative medicines

Bicycle®

Thank you

Bicycle®