Bicycle Therapeutics Investor Presentation

- May 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 cash 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 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 and cash 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 May 2, 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.

This presentation does not constitute an offer to sell or a solicitation of an offer to buy securities, nor shall there be any sale of any securities in any state or jurisdiction in which such offer, solicitation or sale would be unlawful prior to registration or qualification under the securities laws of any such state or jurisdiction.

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 assets

Expedited development and regulatory pathway for BT8009 in metastatic urothelial cancer

BT8009, BT5528 and BT7480 have shown signs of anti-tumor activity and emerging differentiated safety profiles

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

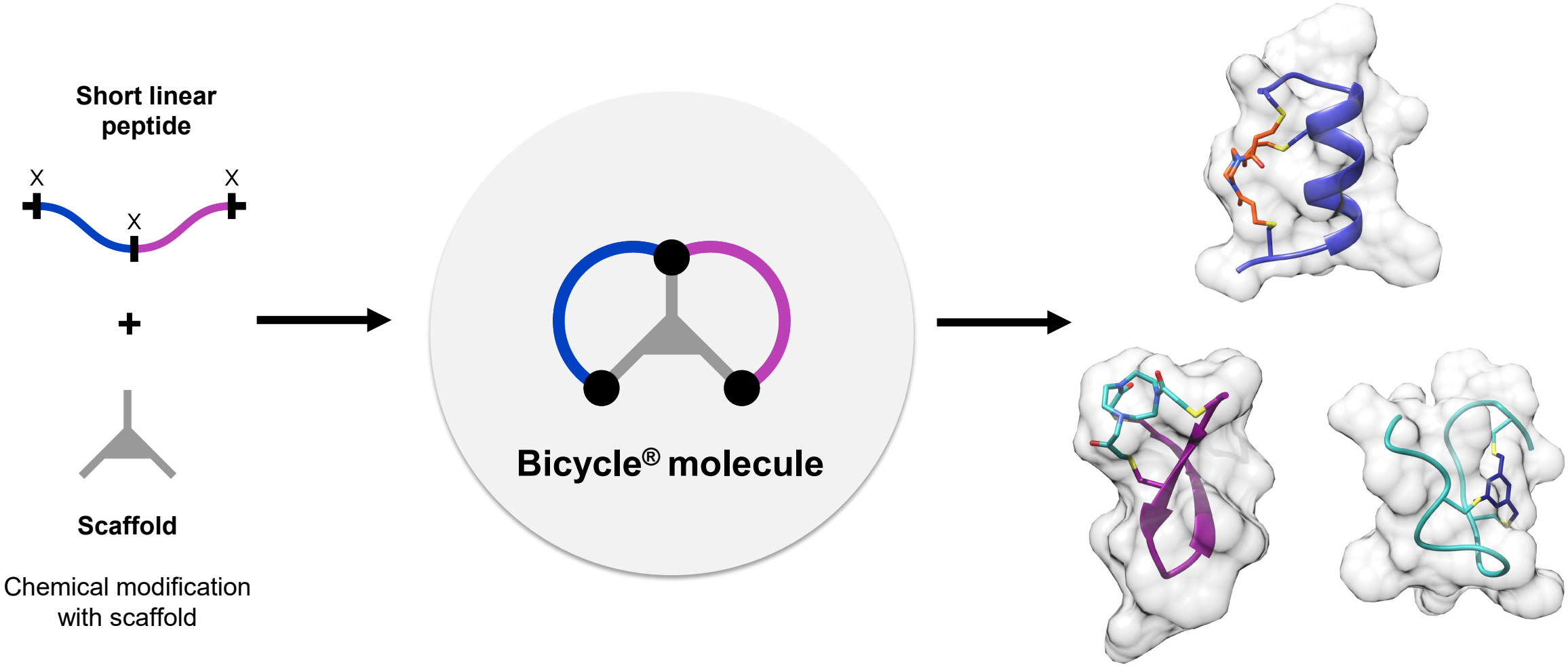
Deeply experienced team

Located in Cambridge, UK, and Cambridge, MA

NASDAQ: BCYC

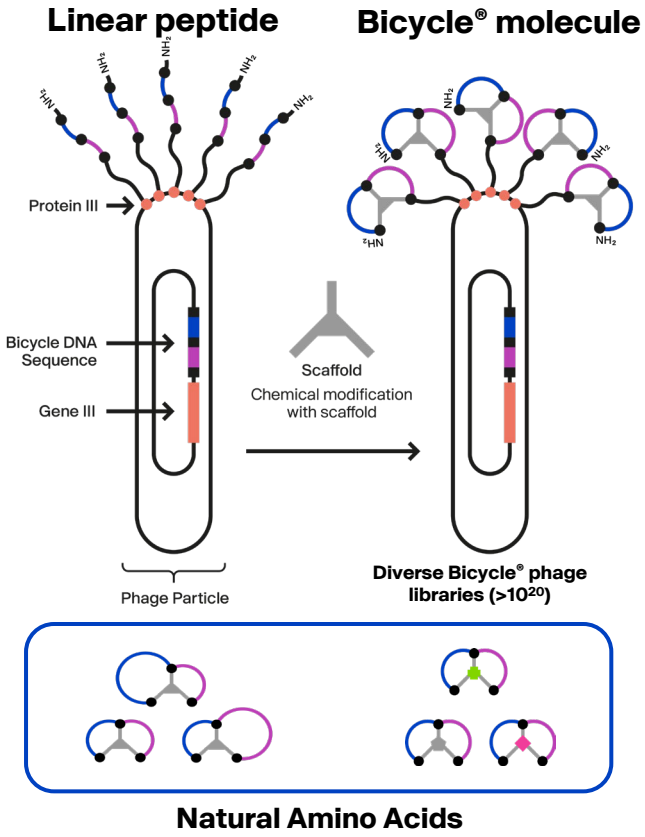
Cash and cash equivalents of $457.0M as of March 31, 2024, with expected cash runway into 2026

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

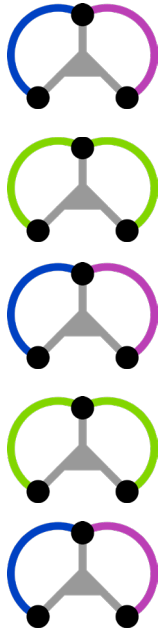
Bicycle® Phage Display Discovery



Peptide & Medicinal Chemistry

Optimize Bicycle® monomers

Non-natural Amino Acids



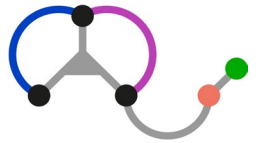
Targeting and Effector Bicycle® molecules

Build and Optimize Therapeutic Bicycle® molecules

Easy conjugation of Linkers and Payloads

Potential Bicycle® Medicines

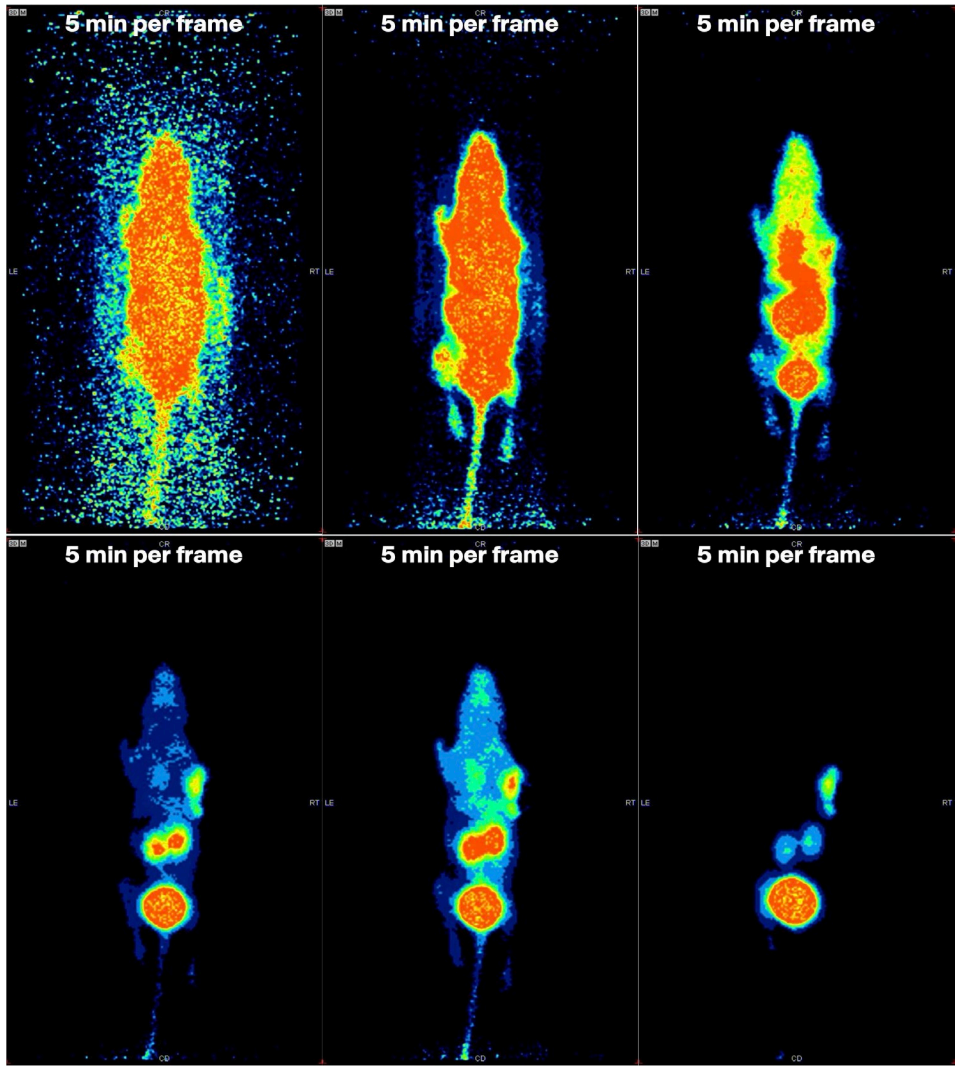
Monomeric Bicycle® molecules



Targeted Drug Conjugates

Targeted/ Multi-specific Bicycle® molecules

The Bicycle® Advantage



- 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 beyond oncology

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								
BT8009 (Nectin-4)		Oncology	Bicycle® Toxin Conjugate					
BT5528 (EphA2)		Oncology	Bicycle® Toxin Conjugate					
BT7480 (Nectin-4/CD137)		Immuno-oncology	Bicycle TICA® molecule					
BT7455 (EphA2/CD137)		Immuno-oncology	Bicycle TICA® molecule					
Undisclosed	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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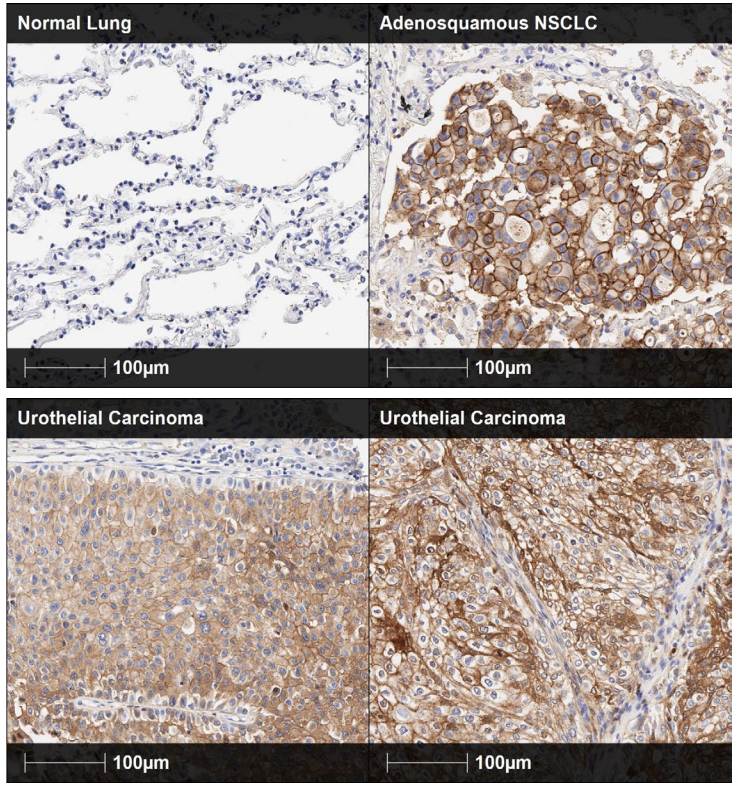
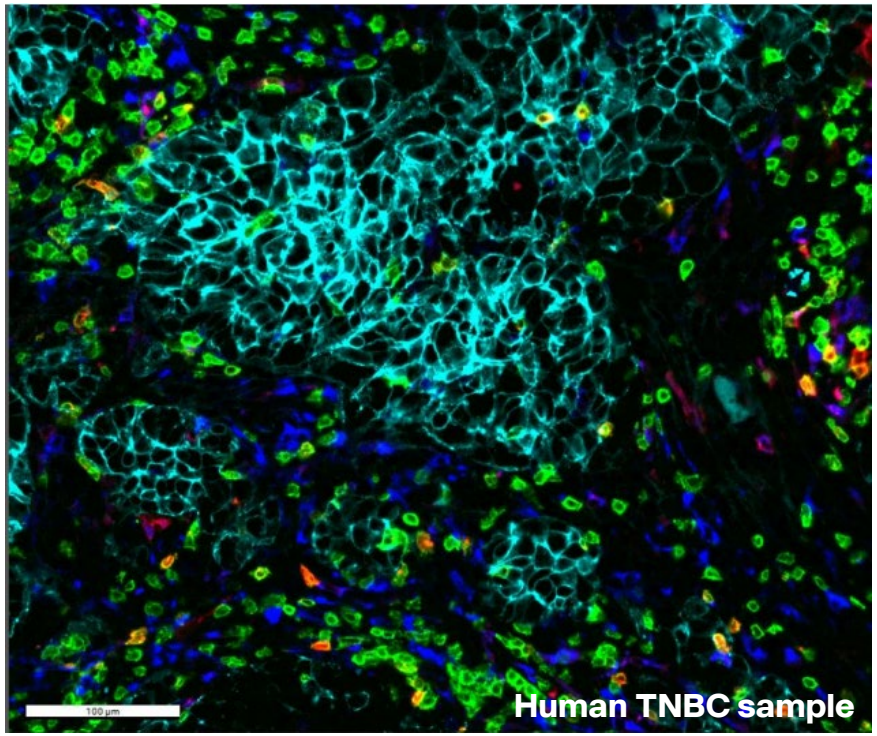
Nectin-4 is a high value target expressed in many tumors

A vector for toxin delivery...



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

...and for immune cell activation



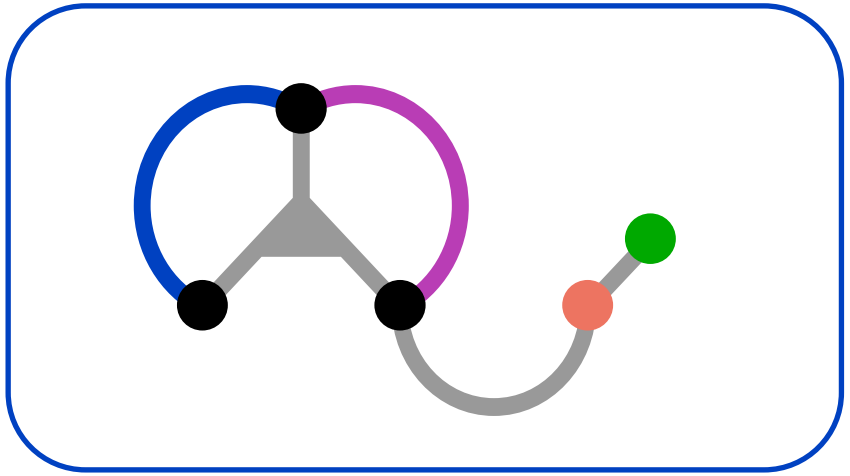
Key: Nectin-4 CD137 CD3 CD68

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

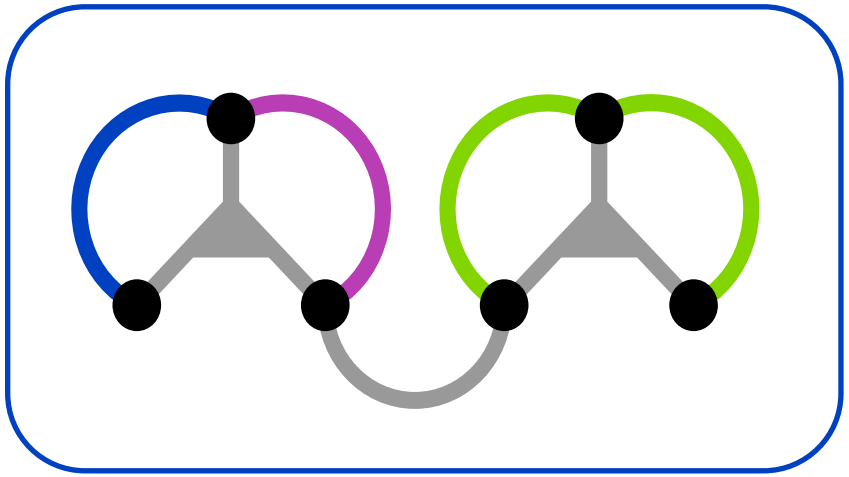
Bicycle®

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.
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

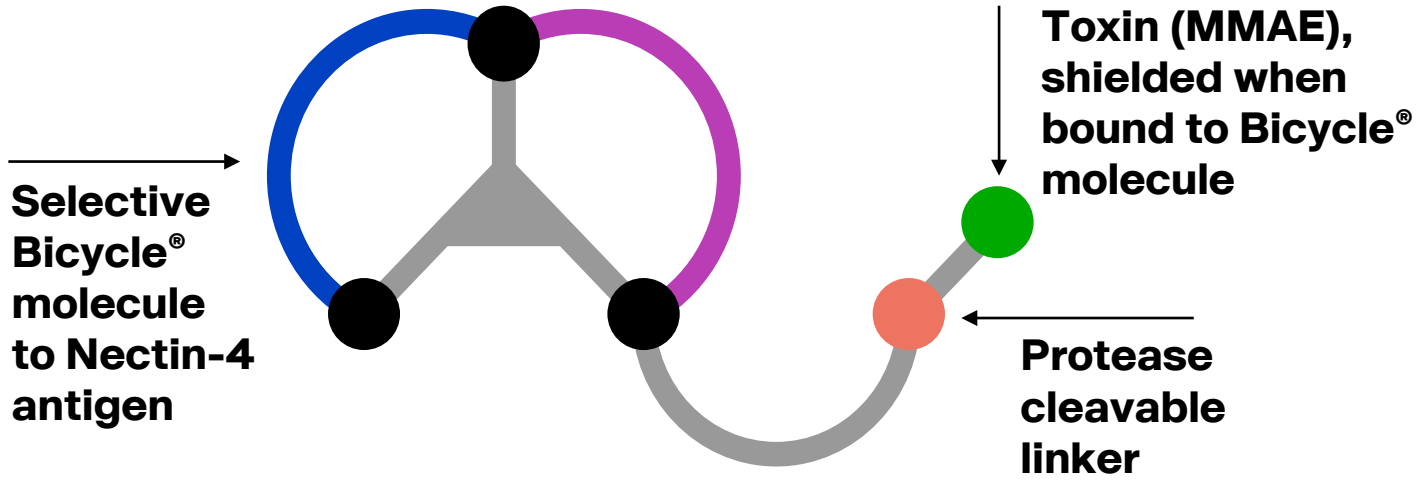


BT8009 is a Nectin-4 targeted Bicycle toxin conjugate (BTC®) designed to overcome the significant toxicity associated with other toxin conjugate approaches.



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

BT8009, a Nectin-4 targeting BTC® molecule



- 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.

Improved selectivity may lead to differentiated tolerability

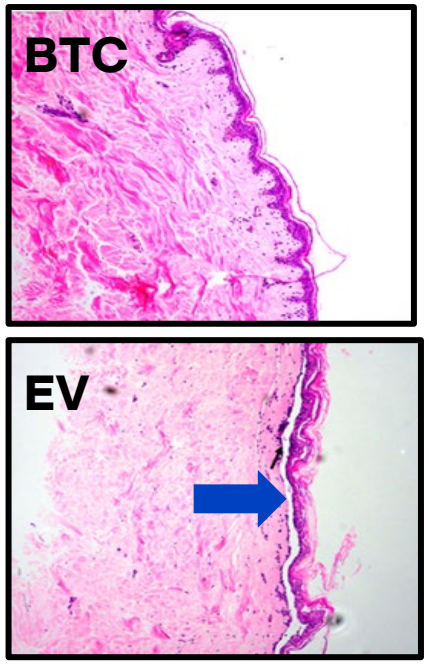
Selectivity[1]

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

✓ Binds ✗ Does not bind

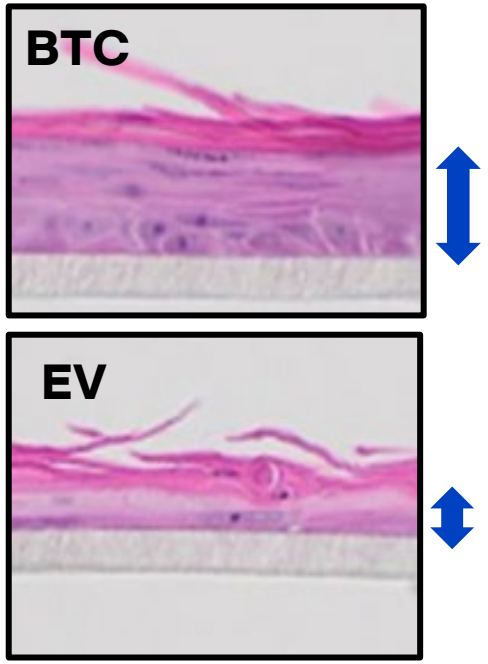
- EV binds to 6+ extracellular receptors expressed in non-target tissue
- These include multiple Fc receptors and a key thyroid hormone transporter SLC16A2
- Bicycle® molecules are completely selective for their target in the same assay

Human skin model[2]



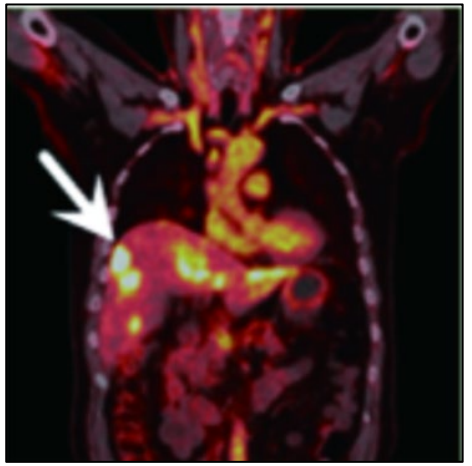
- EV induces dermal/epidermal separation in-vitro
- BTC® molecule does not

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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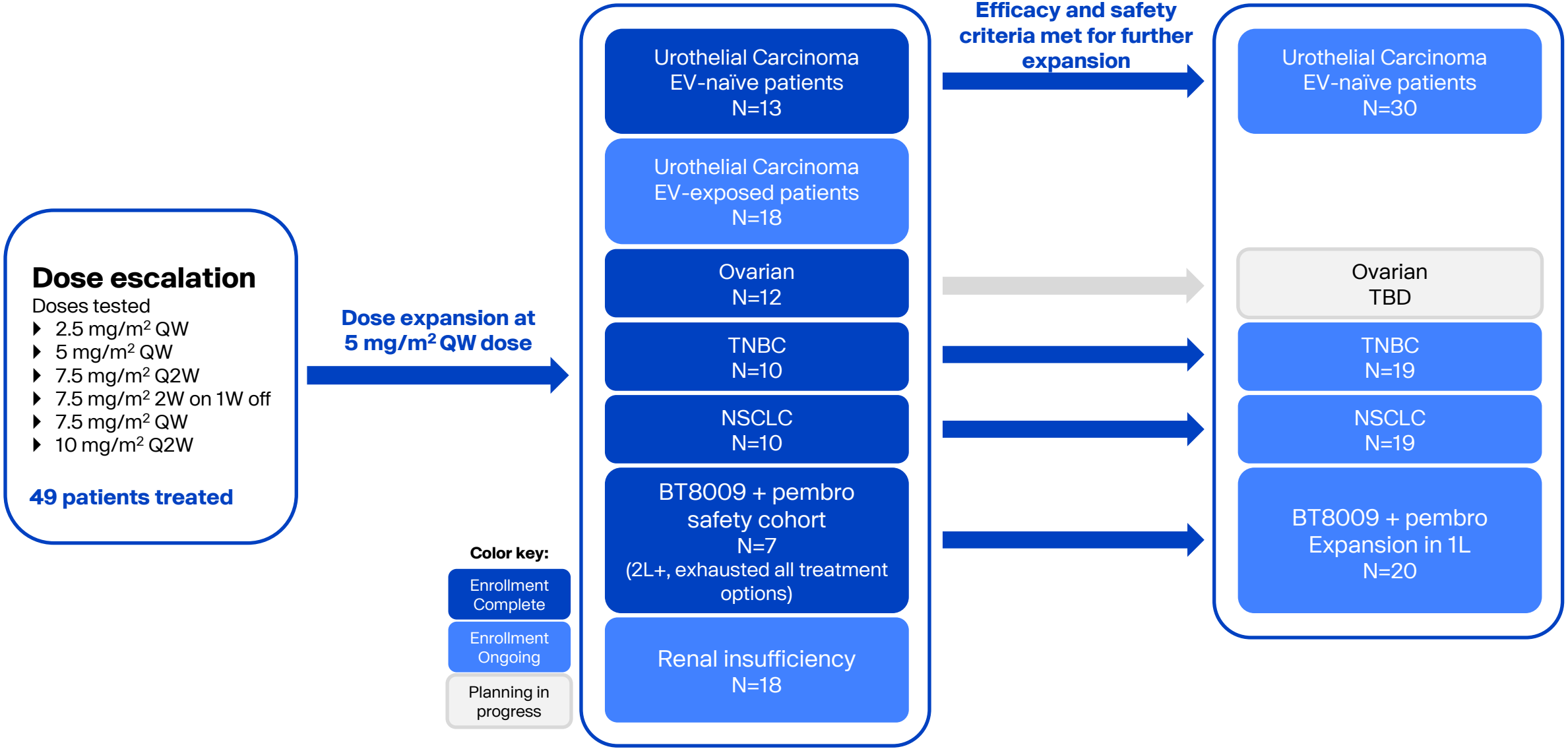
1. Assessed using the Retrogenix assay platform, enfortumab vedotin and BT8009 (2 µg/ml) were assessed for binding to ~6,500 secreted and cell surface-tethered human secreted proteins expressed on cells. Binding was detected using an anti-MMAE antibody. Bicycle Therapeutics unpublished data.
2. Skin 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 BT8009 study



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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/m² QW[a] N=34
Median age, yrs (range)	67 (42-84)
Sex, n (%)	
Male	27 (79)
Female	7 (21)
Race, n (%)	
White	21 (62)
Black or African American	0
Other[b]	10 (29)
Missing	3 (9)
ECOG, n (%)	
0	13 (38)
1	21 (62)
Median prior lines of therapy (range)	2.5 (1-7)

Characteristic	EV-naïve mUC 5 mg/m² QW[a] N=34
Metastatic sites, n (%)	
Brain	0
Breast	0
Bone	9 (27)
Central nervous system	0
Distant lymph nodes	11 (32)
Liver	8 (24)
Local or regional lymph nodes	9 (27)
Lung	15 (44)
Skin or subcutaneous	1 (3)
Other	8 (24)
Visceral disease[c], n (%)	
Yes	23 (68)
No	9 (27)
Missing	2 (6)

Data as of 16Nov2023.
[a]Contains data from dose escalation and dose expansion.
[b]Due to French ethics laws, data on race is recorded as Other for patients enrolled in France.
[c]Visceral disease: Brain, Bone, Central nervous system, Liver, Lung and some sites in Other.
EV: enfortumab vedotin; mUC: metastatic urothelial cancer; QW: weekly.

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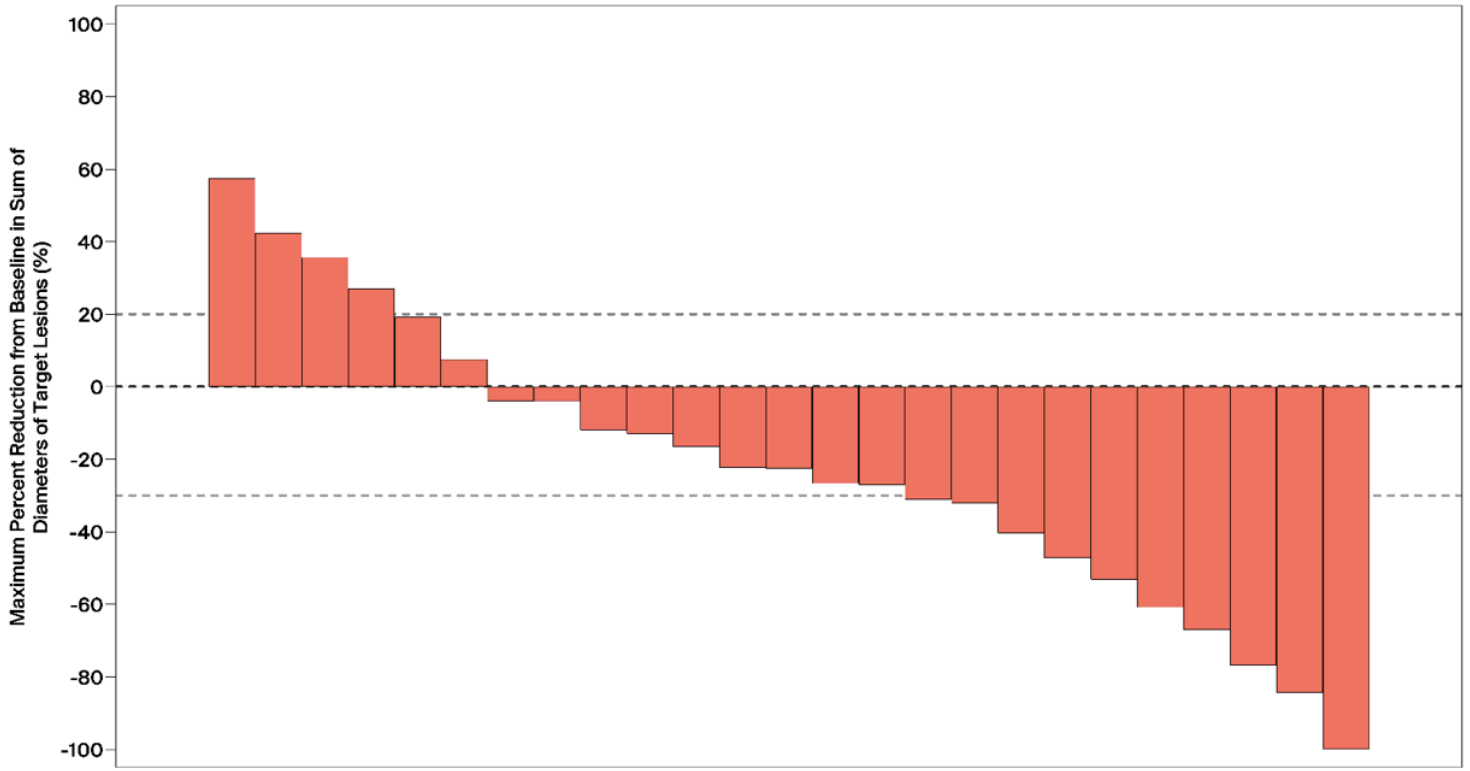
BT8009 response data in EV-naïve mUC

BT8009 waterfall plot across all EV-naïve mUC patients dosed at 5 mg/m² QW
(efficacy evaluable patients only; includes 2 unconfirmed PRs)



Best Overall Response[a,b], n (%)	Total EV-naïve mUC 5 mg/m² QW N=26
Complete Response (CR)	1 (4)
Partial Response (PR)	9 (35)
Stable Disease (SD)	7 (27)
Progressive Disease	9 (35)
ORR (CR+PR)	10 (38) 95% CI (20, 59)
CBR (CR+PR+SD≥16 wks)	15 (58)

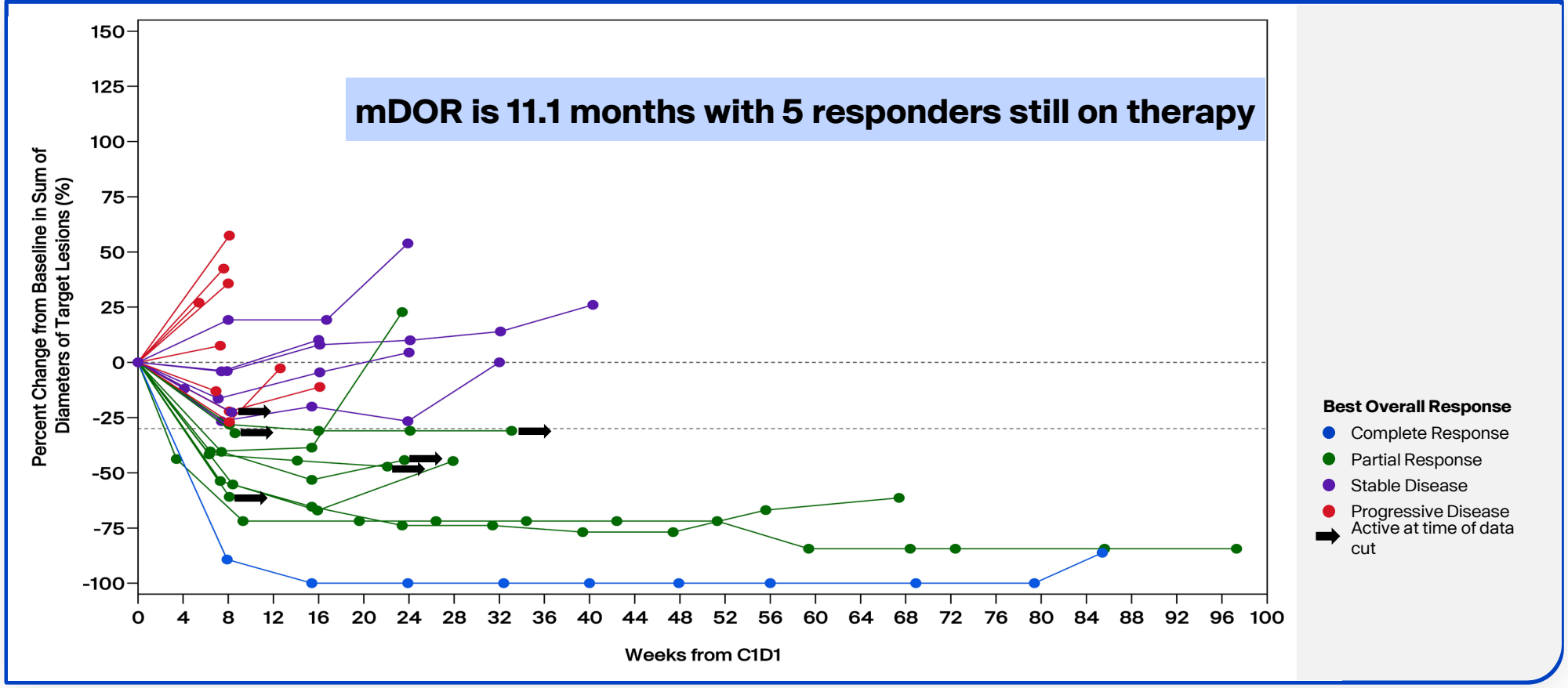
mDOT is currently 11 weeks (range 1-101)

mDOR is currently 11.1 months with 5 responders still on therapy

Data as of 16Nov2023.
[a]Efficacy evaluable set 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. Eight patients were excluded due to no post-baseline assessment. A ninth patient was excluded from the waterfall plot as target lesion data was non-evaluable in the single post-baseline assessment.
[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.

BT8009 shows an emerging profile that may support long duration of response

BT8009 spider plot across all EV-naïve mUC patients at 5 mg/m^2 QW



Median duration of follow-up is 3.3 months

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Data as of 16Nov2023.
Responses under response evaluation criteria in solid tumor (RECIST) version 1.1. Includes 2 unconfirmed PR.
C1D1: Cycle 1, Day 1; EV: enfortumab vedotin; mDOR: median duration of response; mUC: metastatic urothelial cancer; QW: weekly.

BT8009 treatment-related adverse events in mUC patients were low, including those of interest seen with other Nectin-4 targeted therapies

Treatment-related Adverse Events	EV-naïve mUC BT8009 5 mg/m² QW[a] N=34 n (%)	
	Any Grade	≥Grade 3
Ocular disorders[b]	1 (3)	0
Peripheral neuropathy[c]	10 (29)	0
Skin reactions[d]	3 (9)	0
Lab-related		
Hyperglycemia	1 (3)	0
Neutropenia	3 (9)	1 (3)

Data as of 16Nov2023
[a]Contains data from dose escalation and dose expansion; [b]Preferred terms defined in Eye Disorder System Organ Class (SOC) used; [c]Peripheral neuropathy SMQ [broad] used, fifty percent of Any Grade was Grade 1; [d]All preferred terms defined in Skin and Subcutaneous Tissue SOC, excluding Alopecia, and SCAR MedDRA SMQ [broad] used, Any Grade: two Grade 1, one Grade 2
Lab related treatment-related adverse events by Preferred Term
EV: enfortumab vedotin; mUC: metastatic urothelial cancer; QW: weekly.

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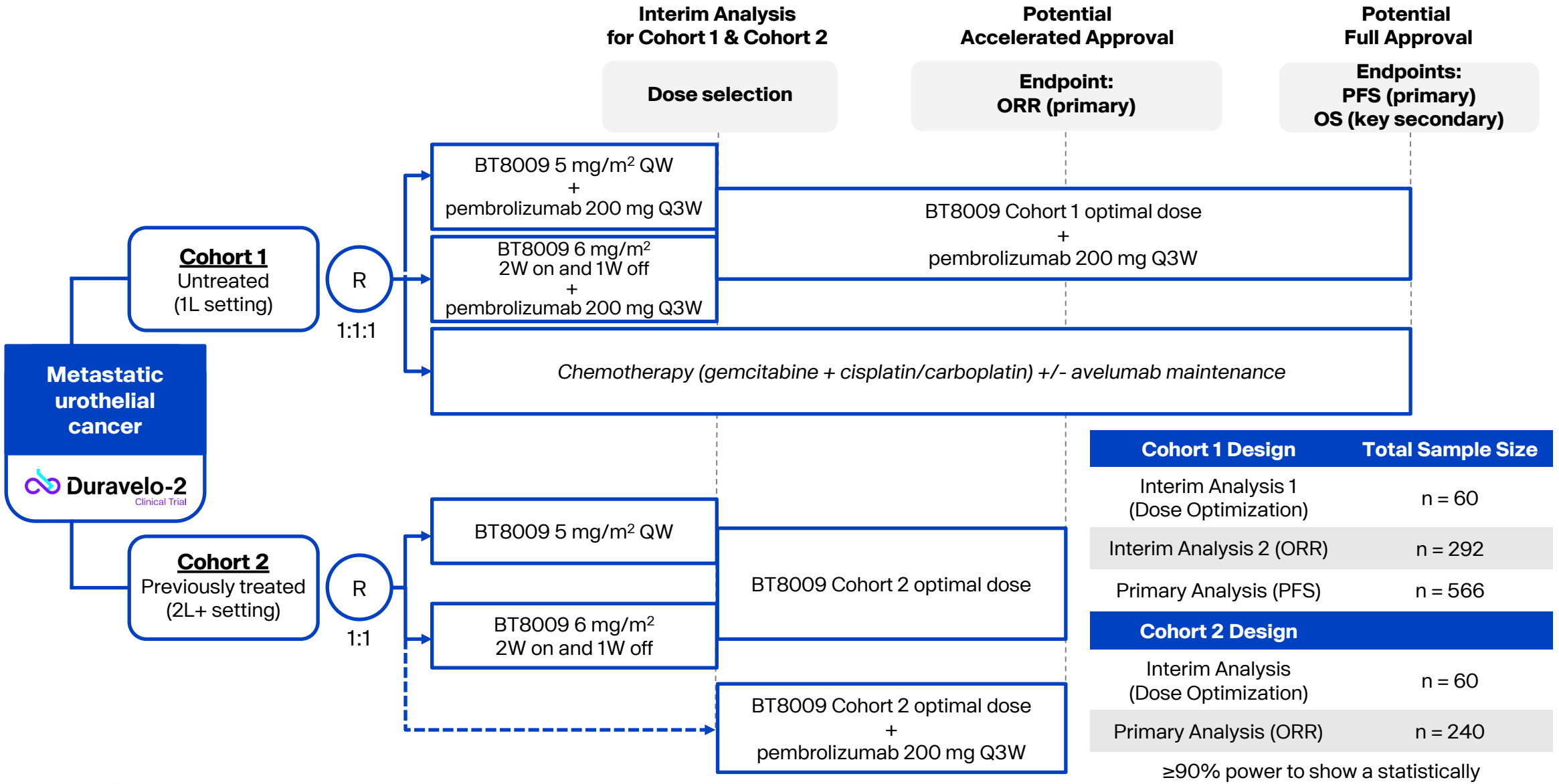
Phase 2/3 trial design allows for efficient path-to-market



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.

BT8009, a first-in-class BTC® molecule, has significant potential to treat Nectin-4 expressing tumors

SUMMARY

- BT8009 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
- Promising data in combination with Pembrolizumab
- 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**
  - BT8009 monotherapy in LL mUC
  - BT8009 + pembrolizumab in 1L mUC
  - BT8009 monotherapy in ovarian, TNBC, NSCLC
- **2024: Start expansion study in combination with checkpoint inhibitors in TNBC and NSCLC**

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

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

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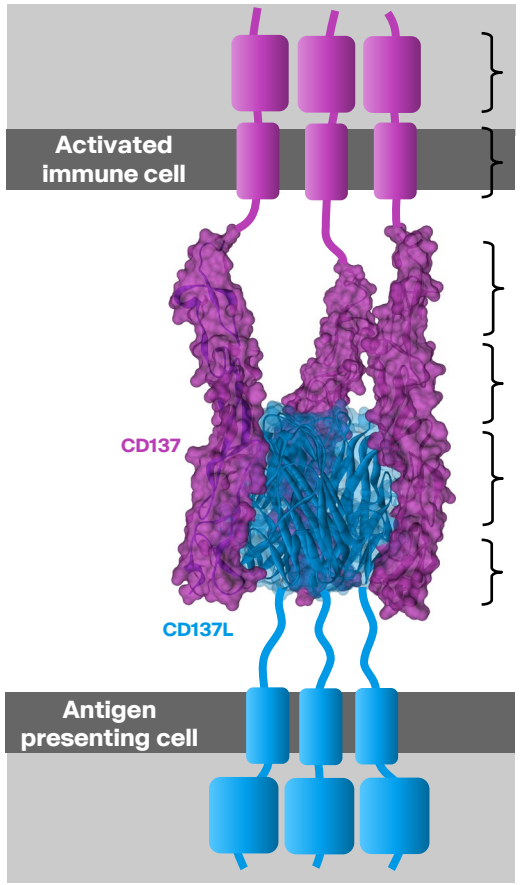
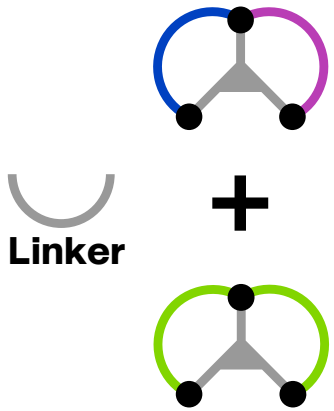
Bicycle TICA® molecules: Tumor-Targeted Immune Cell Agonists join immune cell and tumor targeting Bicycle® molecules



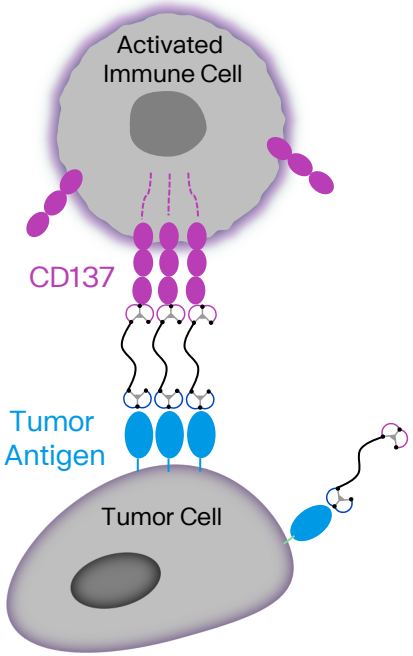
Activation induced by clustering of **CD137** by trimeric **CD137L**

CD137-engaging Bicycle® molecule



Tumor-targeting Bicycle® molecule

Tumor Target/CD137 Bicycle TICA® molecule

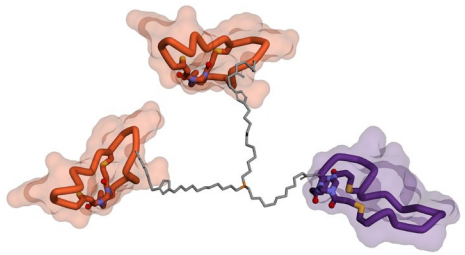


CD137 clustering induced by tumor antigen

BT7480 is a fully synthetic context-dependent CD137 agonist

Small

Bicycle TICA® molecule BT7480

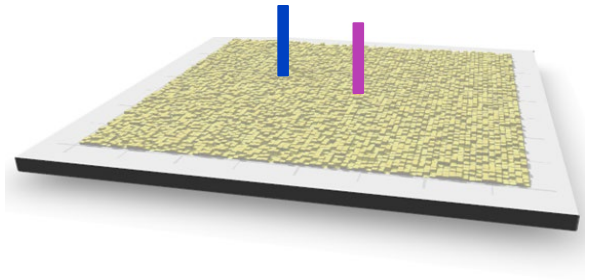


7.2 kDa

~30x smaller than other targeted agonists

Selective

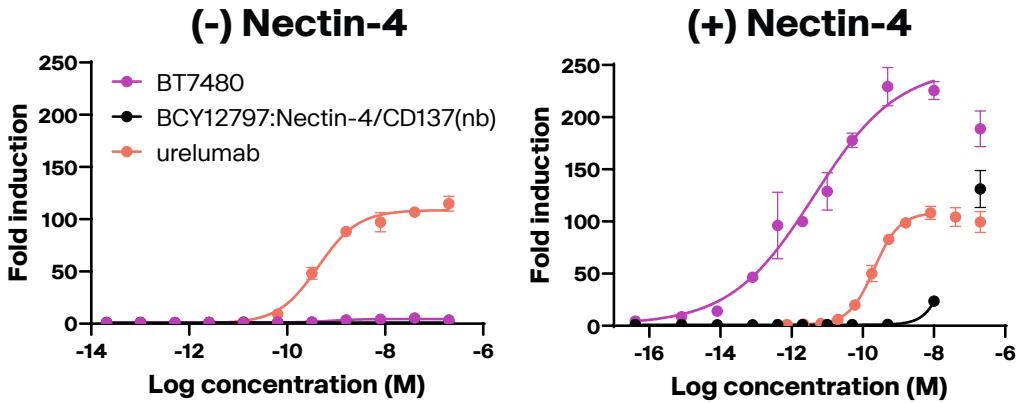
BT7480 only binds Nectin-4 and CD137



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

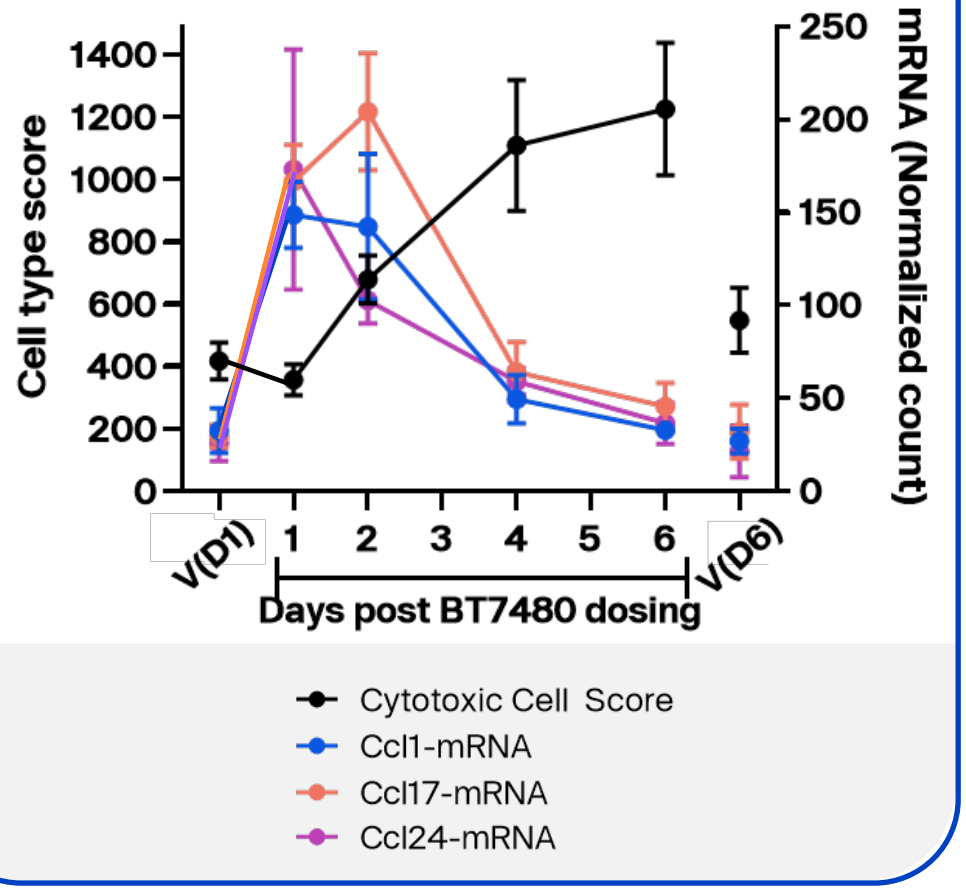
Bicycle®

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

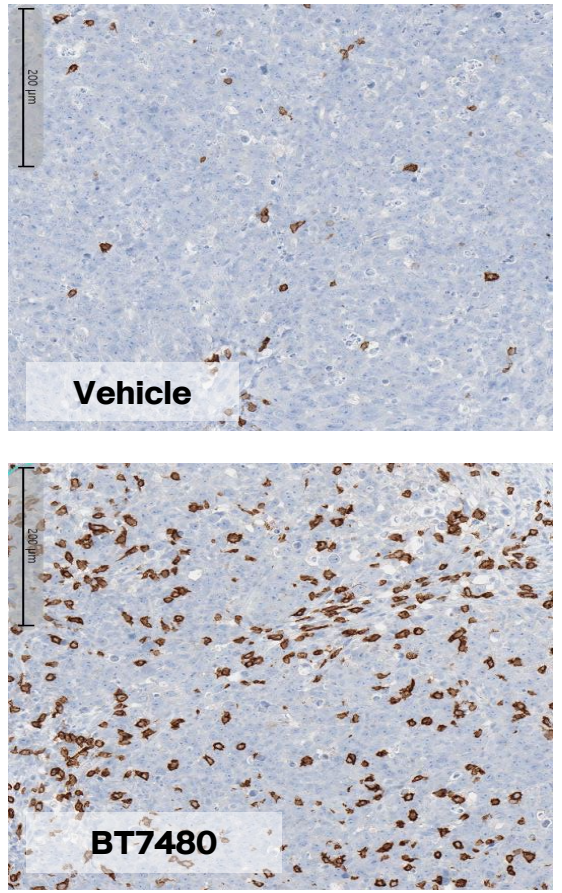
Bicycle TICA® molecules have a unique MOA that is different from, and complementary to, that of current checkpoint inhibitors

- 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

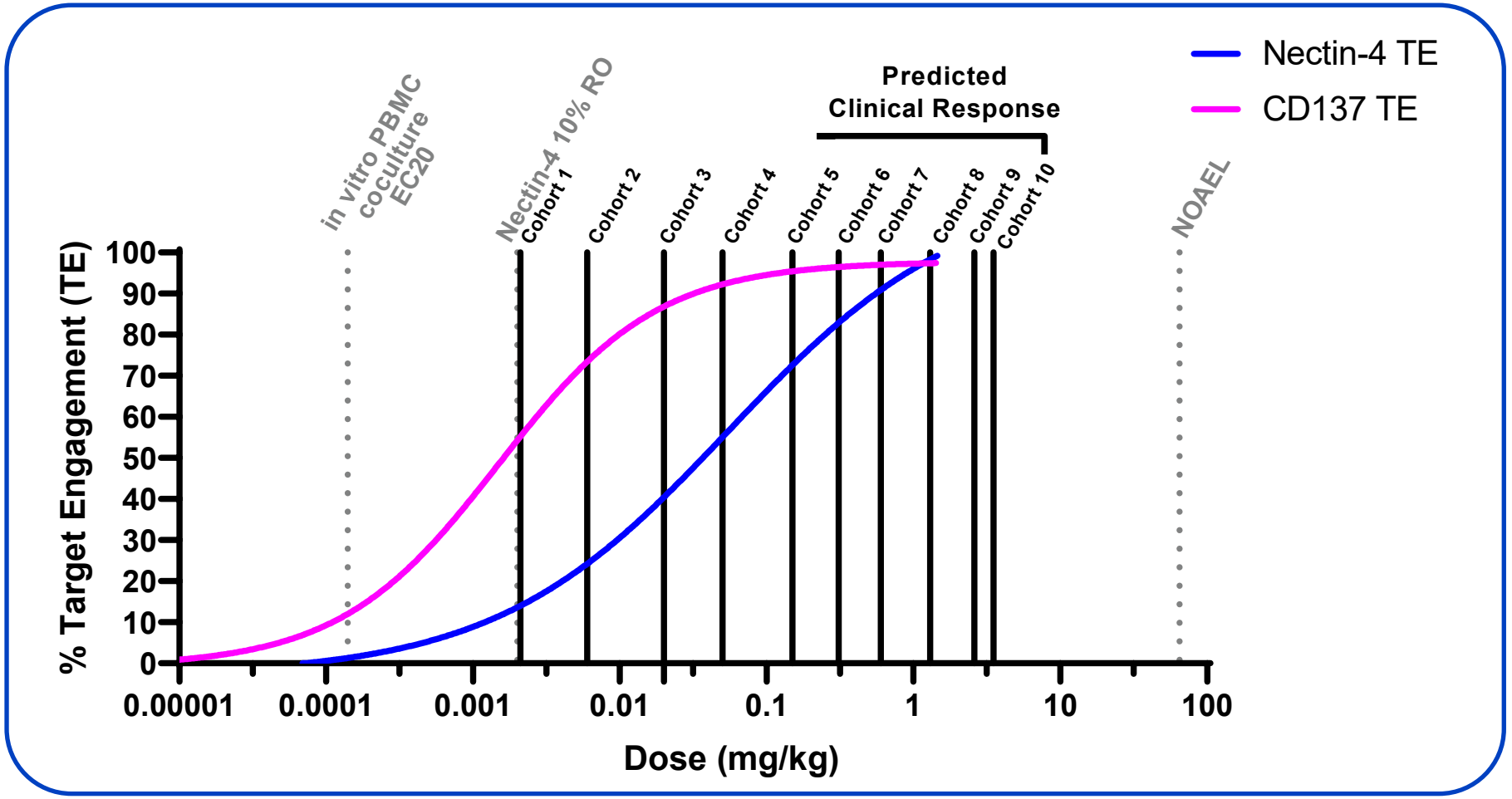


CD8+ T cells on Day 6



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 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=3)

Combination escalation (BT7480 + PD-1 inhibitor)
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 08Nov2023. 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 Characteristics: Cohorts 1-9 (0.002-2.6 mg/kg QW)

Characteristic	Cohorts 1-9 N=33
Median age, yrs (range)	61 (29-83)
Sex, n (%)	
Male	13 (39)
Female	20 (61)
Race, n (%)	
Black or African American	4 (12)
White	27 (82)
Other	2 (6)
ECOG, n (%)	
0	10 (30)
1	23 (70)
Median prior lines of therapy (range)	4 (1-9)

>60% of patient tumors express Nectin-4 and CD137*

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Data as of 24Sep2023.
*As assessed by Bicycle Therapeutics' proprietary Nectin-4 IHC and MultiOmyx methods. Data cutoff 03Nov2023.
QW: weekly.

BT7480 was generally well tolerated

Safety summary: Cohorts 1-9 (0.002-2.6 mg/kg QW)	
TEAEs in ≥10% Patients by Preferred Term	**N=33 n (%)**
Headache	7 (21)
Abdominal Pain	6 (18)
Decreased appetite	6 (18)
Fatigue	6 (18)
Dizziness	5 (15)
Nausea	5 (15)
Tumor Pain	5 (15)
Anemia	4 (12)
Dyspnea	4 (12)

Related TEAEs by Preferred Term in ≥10% Patients	N=33 n (%)
Fatigue	4 (12)

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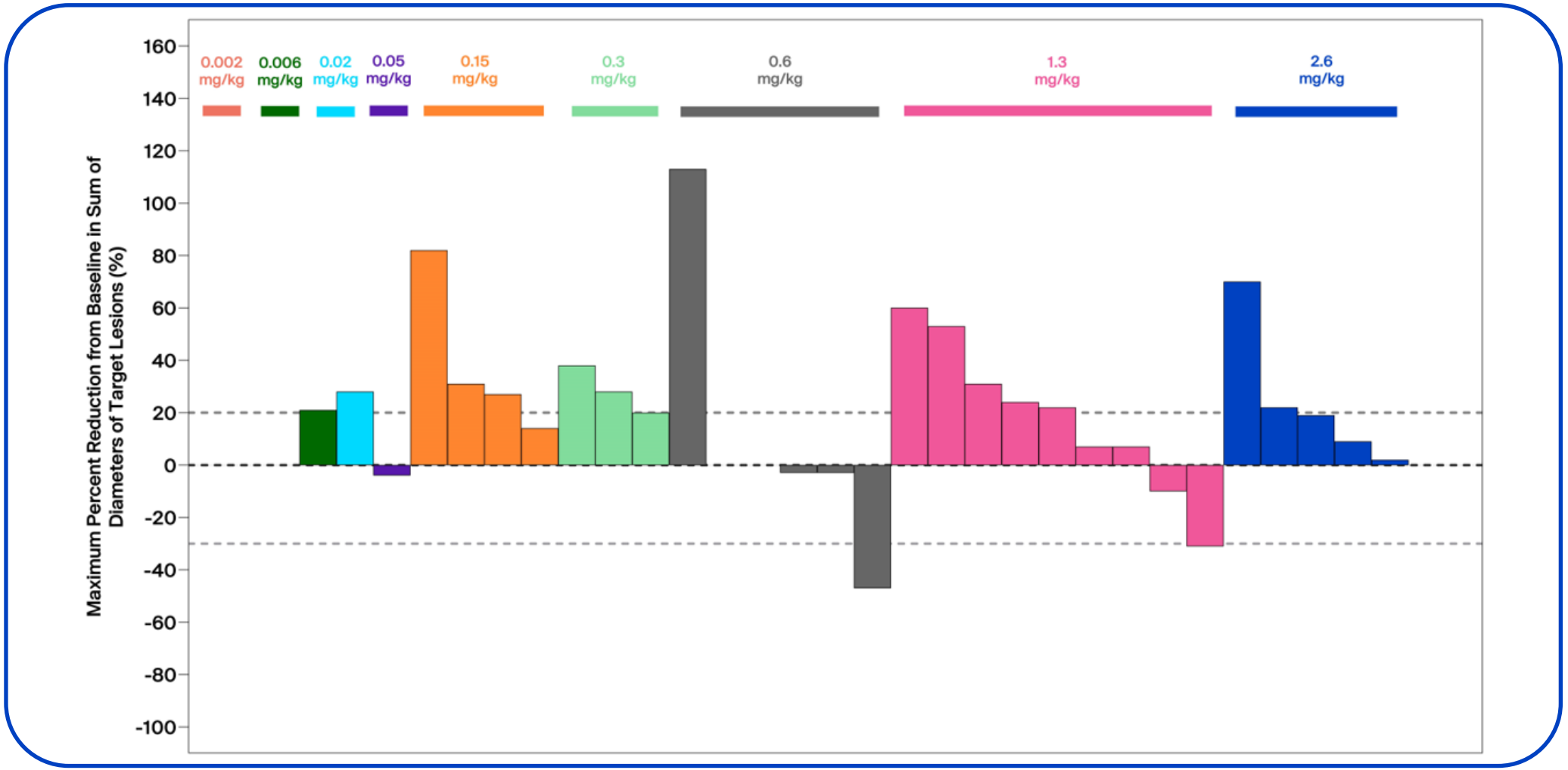
Data as of 25Sep2023.
QW: weekly; TEAE: treatment-emergent adverse event.

BT7480 response by dose across Cohorts 1-9*



Data as of 08Nov2023
Responses under response evaluation criteria in solid tumor (RECIST) version 1.1
*Efficacy evaluable patients, defined as all enrolled patients with measurable disease at baseline who received at least one dose of BT7480 and had at least one adequate post-baseline disease assessment. As of 08Nov23, 34 patients were enrolled in Cohorts 1-9; three patients were excluded due to no post-baseline assessments or lack of adequate post-baseline disease assessment. Both cervical responses are unconfirmed.
QW: weekly.

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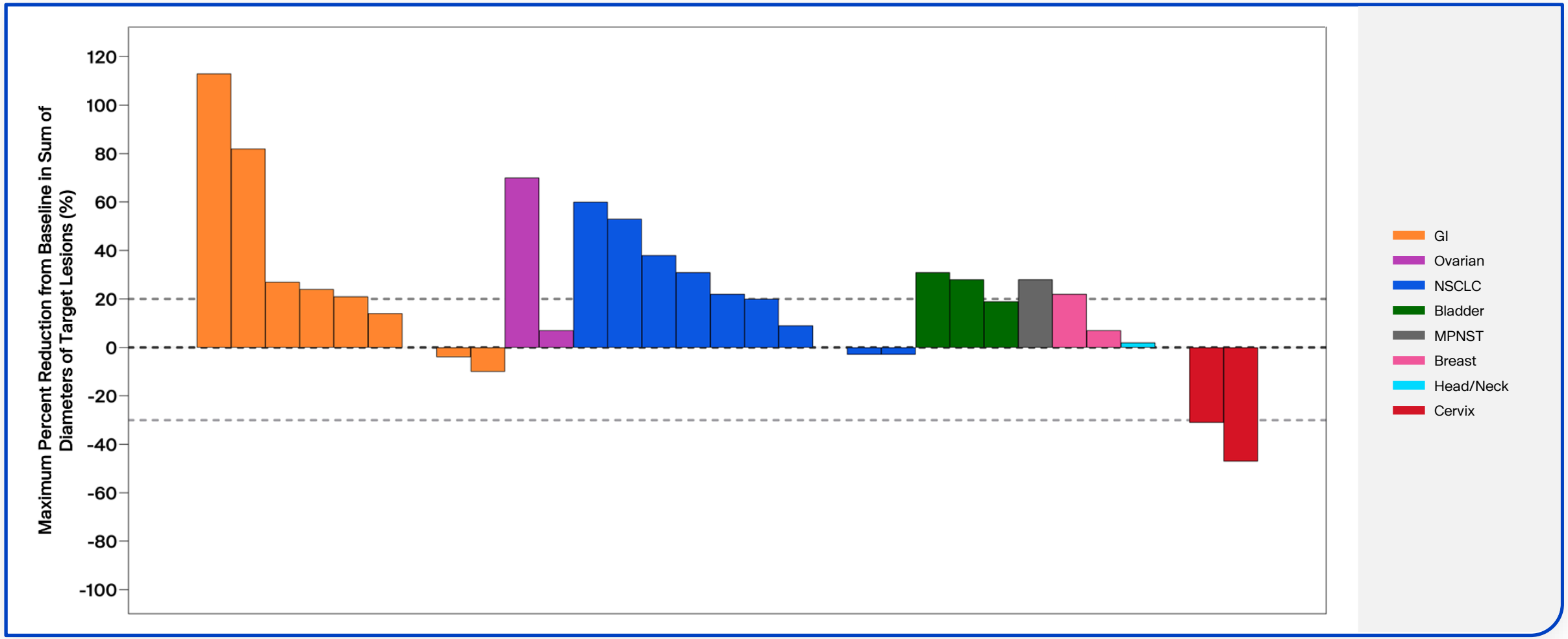
BT7480 response by tumor across Cohorts 1-9



Data as of 08Nov2023
Responses under response evaluation criteria in solid tumor (RECIST) version 1.1
*Efficacy evaluable patients, defined as all enrolled patients with measurable disease at baseline who received at least one dose of BT7480 and had at least one adequate post-baseline disease assessment. As of 08Nov23, 34 patients were enrolled in Cohorts 1-9; three patients were excluded due to no post-baseline assessments or lack of adequate post-baseline disease assessment. Both cervical responses are unconfirmed.
QW: weekly.

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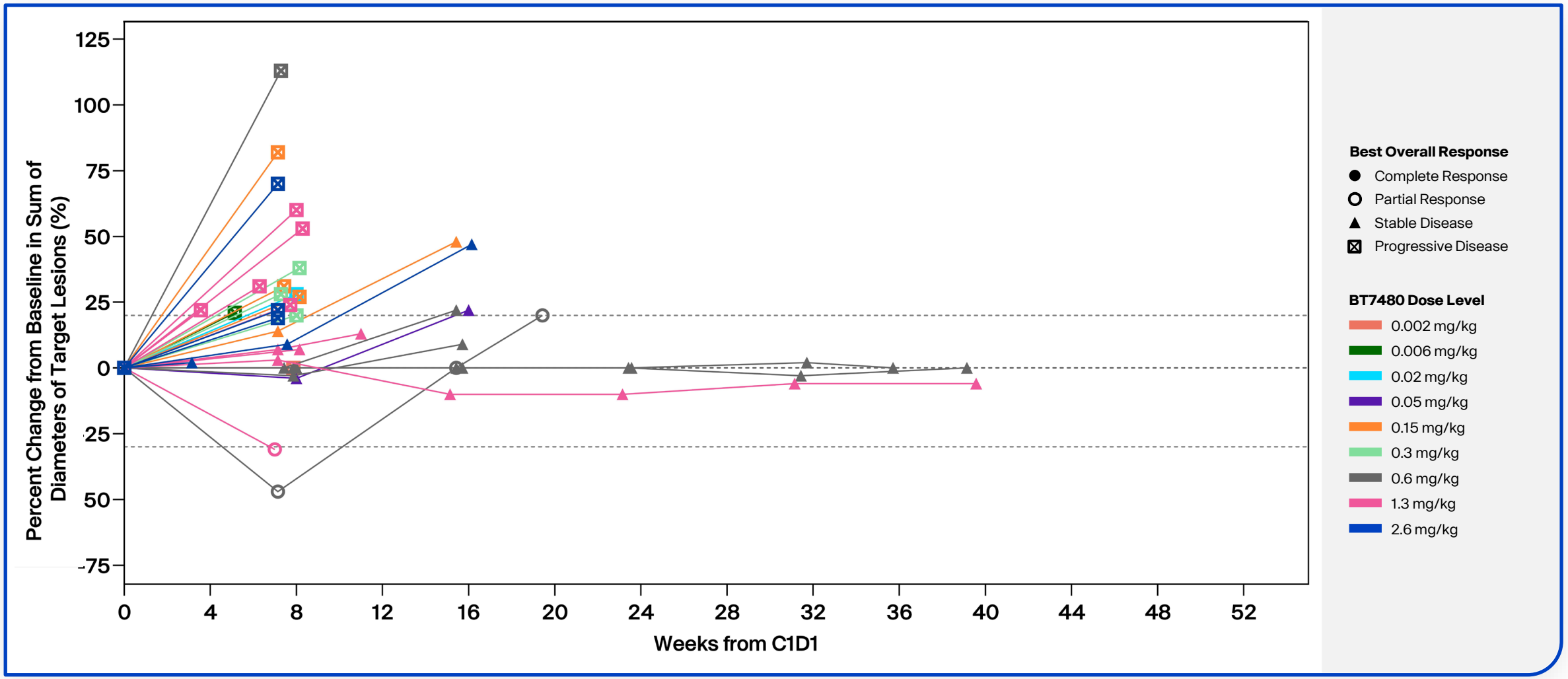
BT7480 responses in Cohorts 1-9 (N=31)

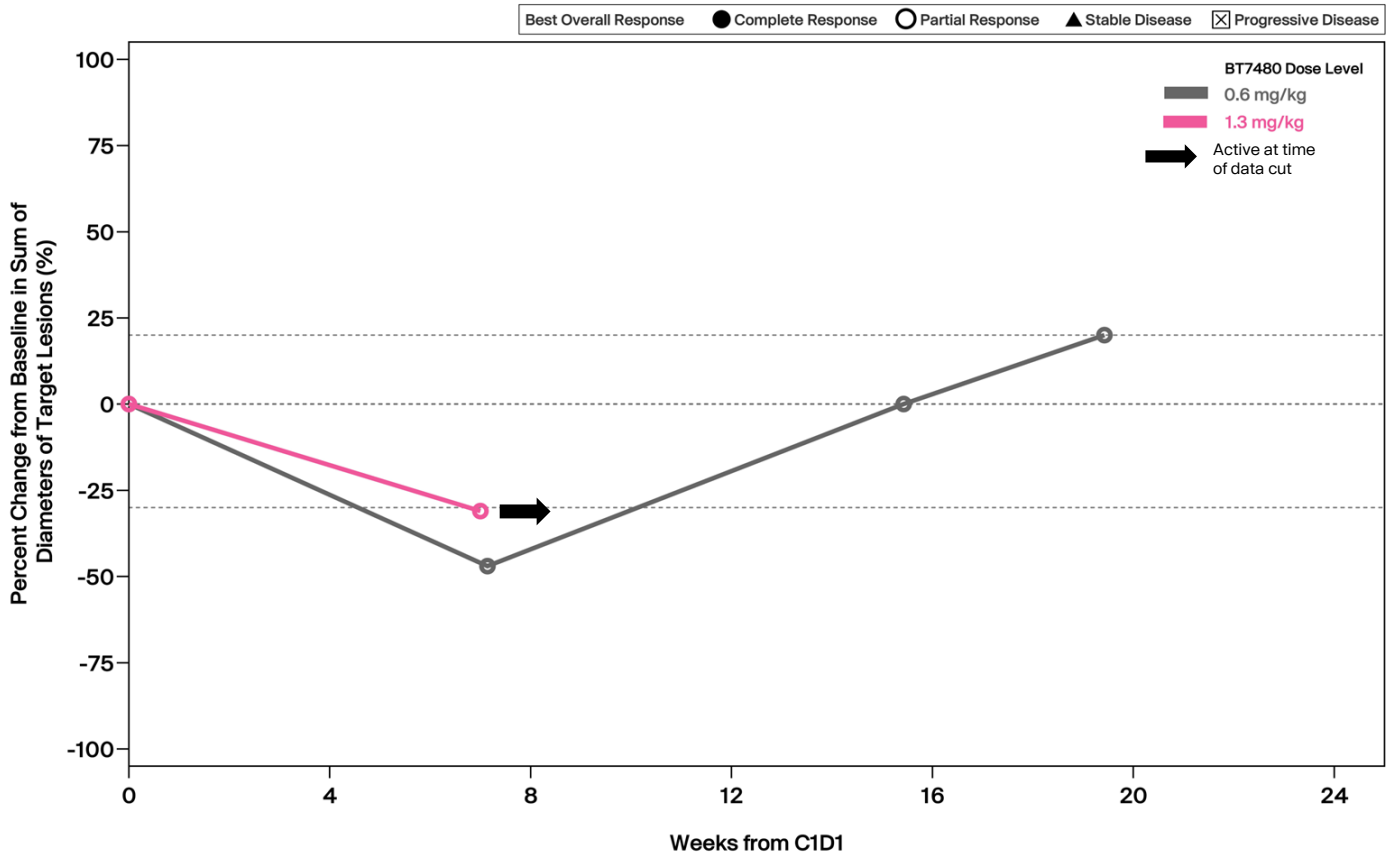


Median duration of follow-up is 3.3 months

Data as of 08Nov2023.
Responses under response evaluation criteria in solid tumor (RECIST) version 1.1. As of 08Nov23, 34 patients were enrolled in Cohorts 1-9; three patients were excluded due to no post-baseline assessments or lack of adequate post-baseline disease assessment. Includes 2 unconfirmed responses.
C1D1: Cycle 1 Day 1.

BT7480 has demonstrated 2 out of 2 unconfirmed partial responses in heavily pretreated cervical cancer patients

- Patient: Female, 75, enrolled in Cohort 7 (0.6 mg/kg QW) , Stage IV squamous cell carcinoma of cervix
  - Prior lines of therapy: Adjuvant cisplatin plus 3 lines of therapy in metastatic setting including prior CPI
  - Nectin-4 score: 110
- Patient: Female, 42, enrolled in Cohort 8 (1.3 mg/kg QW), Stage IV squamous cell carcinoma of cervix
  - Prior lines of therapy: Neo-adjuvant carboplatin + paclitaxel, adjuvant cisplatin, plus 2 lines of therapy in metastatic setting including prior CPI
  - Nectin-4 score: 265



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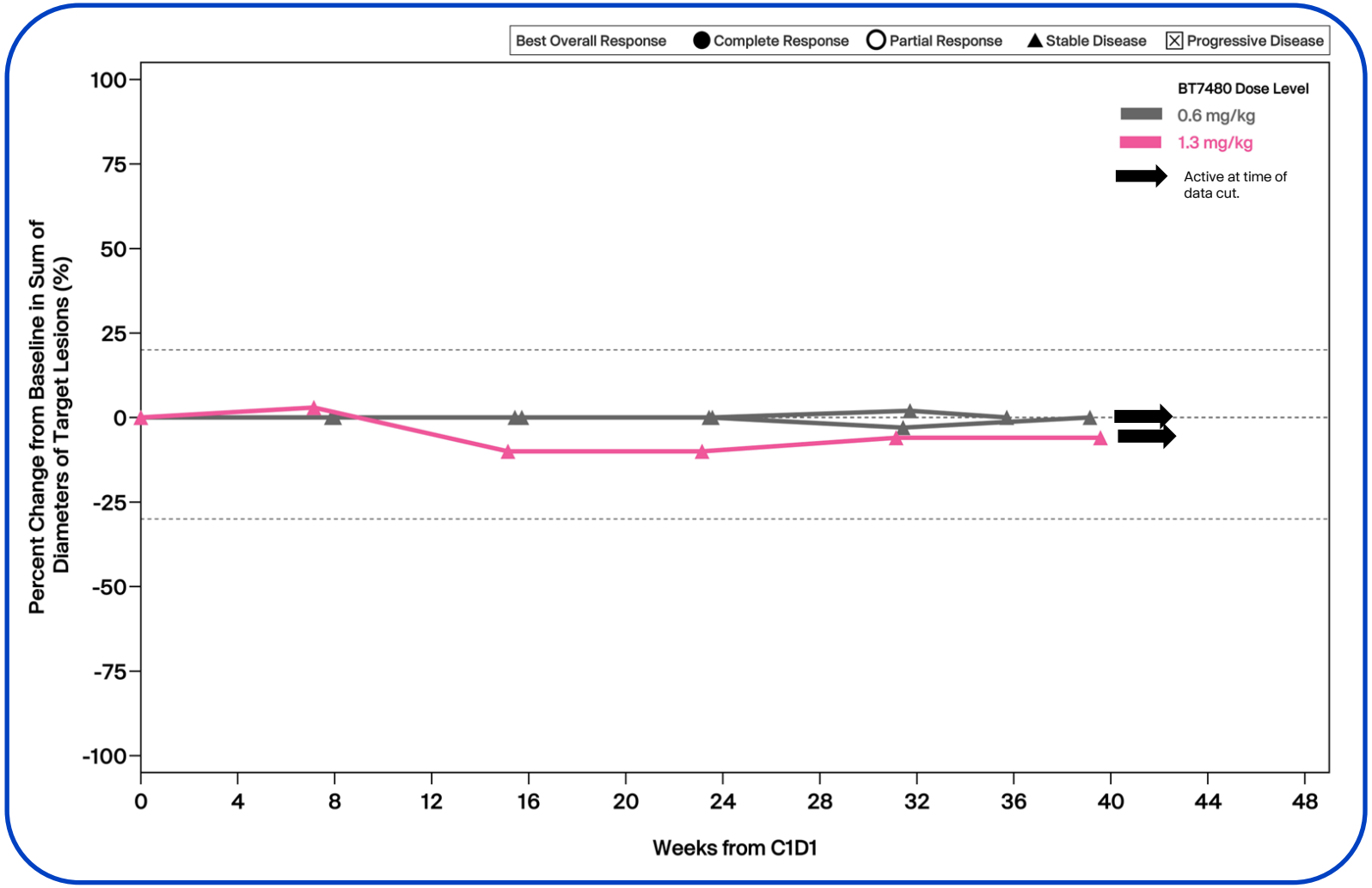
Data as of 08Nov2023.
Responses under response evaluation criteria in solid tumor (RECIST) version 1.1.
CPI: checkpoint inhibitor; QW: weekly.

BT7480 has demonstrated stable disease ≥7 months in 3 heavily pretreated patients



- Patient: Female, 77, enrolled in Cohort 7 (0.6 mg/kg QW), Stage IV NSCLC (adenocarcinoma)
  - 3 prior lines of therapy in metastatic setting, including prior CPI
  - Nectin-4 score: 225
- Patient: Female, 45, enrolled in Cohort 7 (0.6 mg/kg QW), Stage IV NSCLC (adenocarcinoma)
  - 4 prior lines of therapy in metastatic setting, including prior CPI
  - Nectin-4 score: 110
- Patient: Female, 53, enrolled in Cohort 8 (1.3 mg/kg QW), Stage IIIC squamous cell carcinoma of anus
  - 3 prior lines of therapy
  - Nectin-4 score: 200

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Data as of 08Nov2023.
Responses under response evaluation criteria in solid tumor (RECIST) version 1.1.
C1D1: Cycle 1 Day 1; CPI: checkpoint inhibitor; NSCLC: non-small cell lung cancer; QW: weekly.

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
- Robust clinical biomarkers indicate that BT7480 is a pharmacologically active compound with signals of blood immune activation associated with potential clinical benefit
- Two unconfirmed clinical responses have been observed in cervical cancer
- Three prolonged stable disease (≥ 7 months) have been observed in NSCLC and anal cancer

NEXT STEPS

- **Define RP2D (or maximum dose) and a dose range**
- **Enroll combination cohorts with checkpoint inhibitor therapy in 2024**
- **Design Phase 2 trial with potential for accelerated approval**

NSCLC: non-small cell lung cancer; RP2D: recommended Phase 2 dose

EphA2 Portfolio

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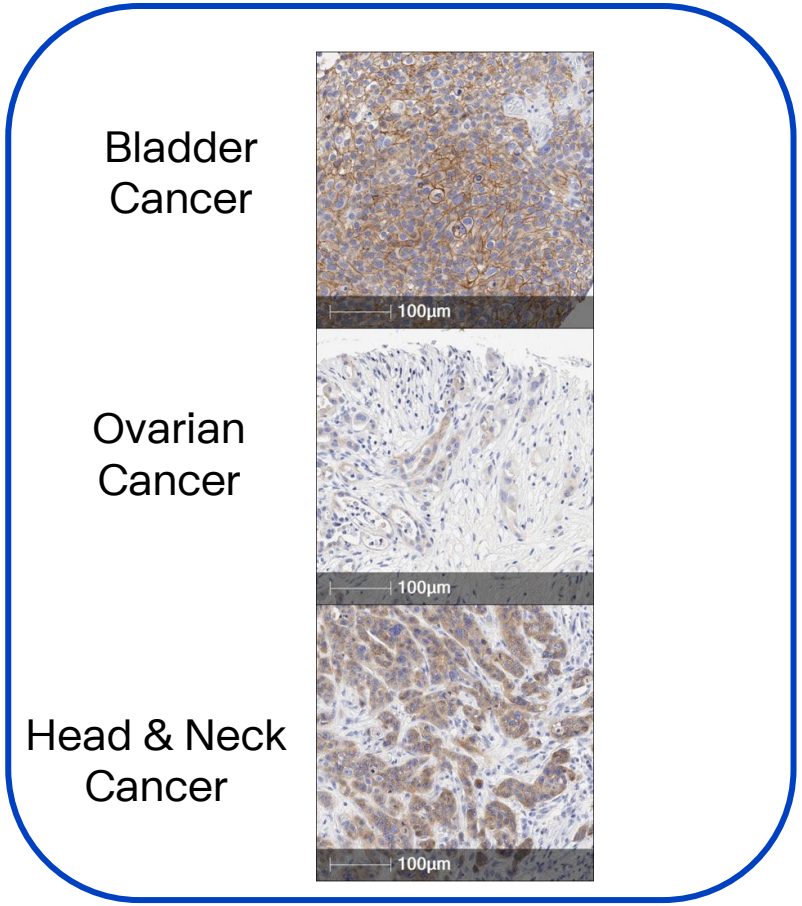
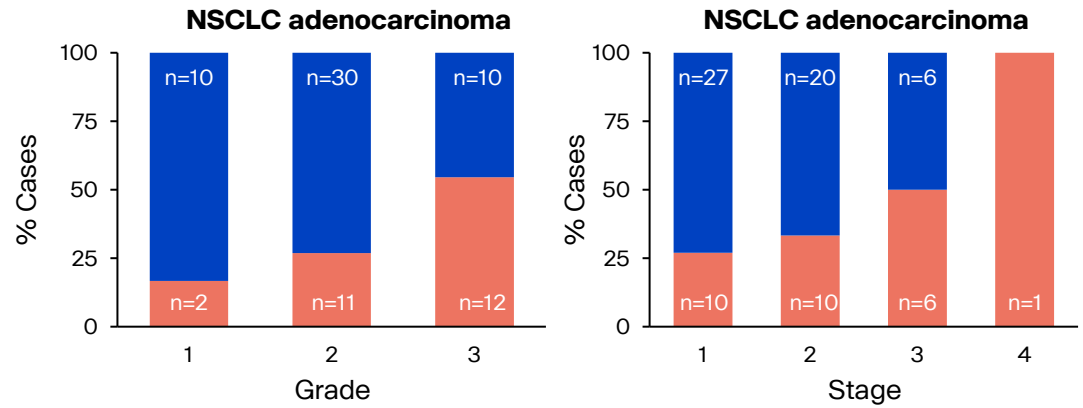
EphA2 is a tumor antigen that is widely expressed in many cancers and whose expression is believed to increase with stage



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)

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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]

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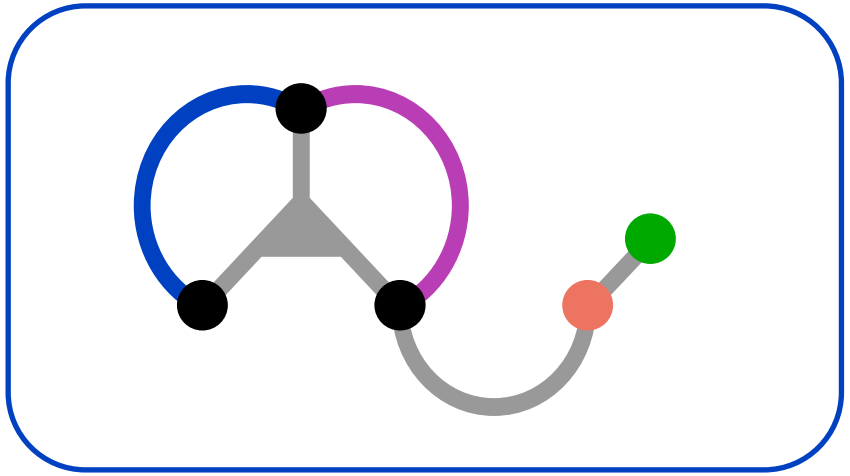
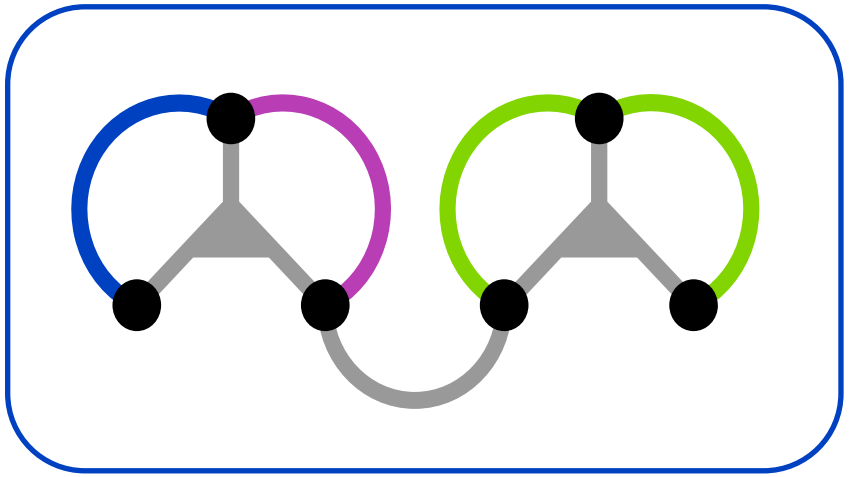
1. Annunziata et al. *Invest New Drugs*. 2013 Feb;31(1):77-84. 2. Shitara et al. *J ImmunoTherapy Cancer*. 2019 7:219-230. 3. Gan et al. *Invest New Drugs*. 2022 40(4):747-755. 4. Atreca press release, 10Nov2022.

We have taken two approaches to try and address the broadest EphA2-expressing population of patients

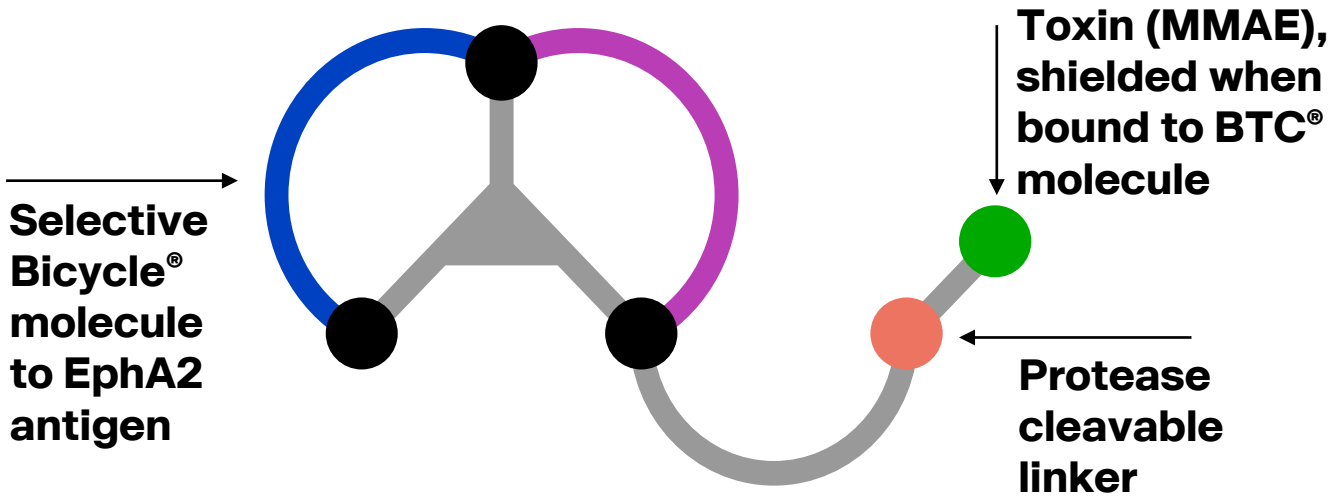


BT5528 an EphA2-targeted BTC® molecule designed to overcome the significant toxicity associated with other toxin conjugate approaches.

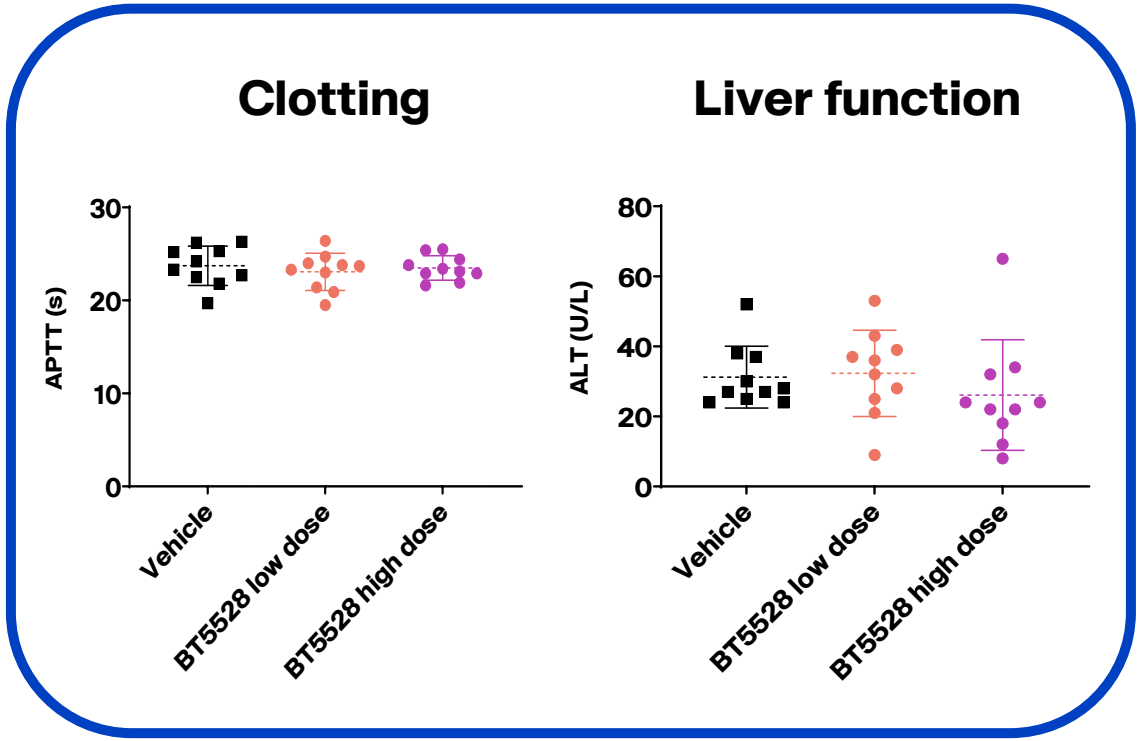


BT7455 an EphA2-targeted CD137 agonist designed to overcome immune agonist toxicities and activate the immune system in EphA2-expressing tumors. IND-enabling work to be completed.

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.

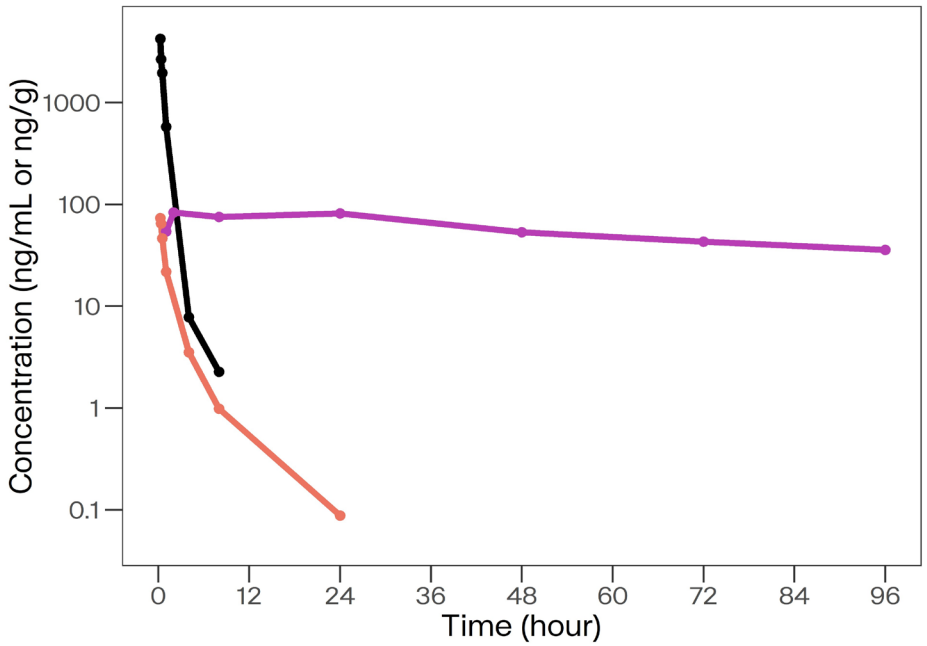
BT5528 low dose = 0.75 mg/kg, human equivalent dose 9 mg/m2
BT5528 high dose = 1.5 mg/kg, human equivalent dose 18 mg/m2

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

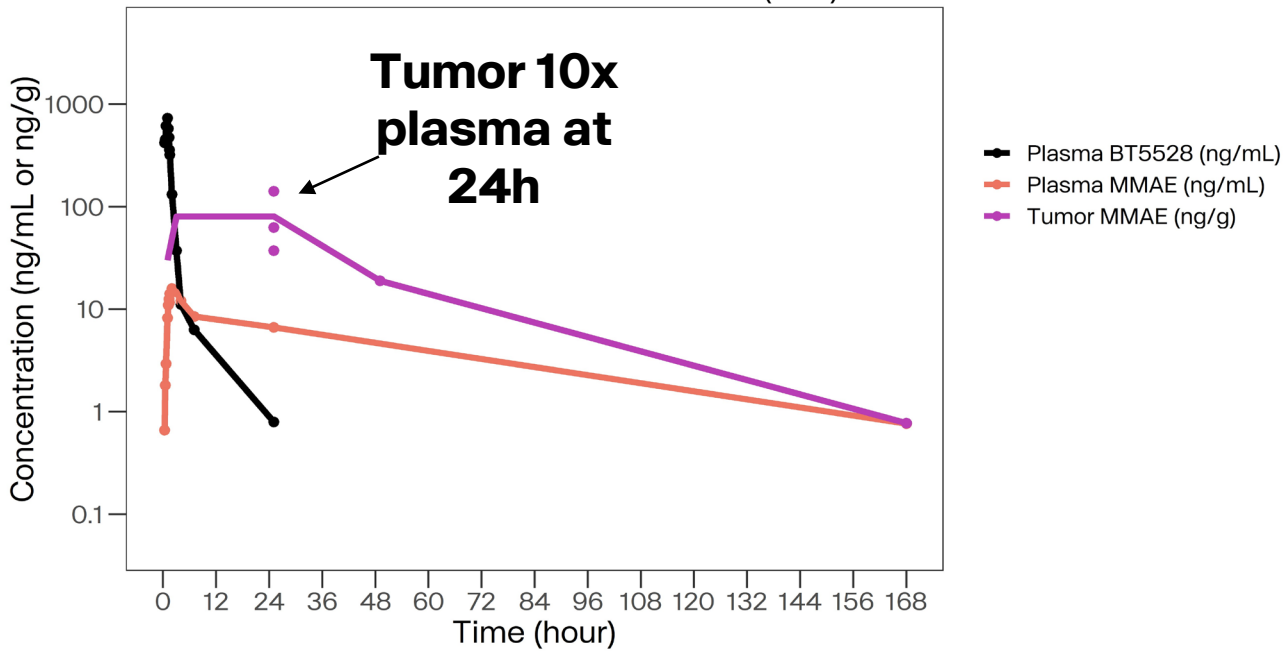
BT5528 PK in **Mouse** (1.5 mg/kg)

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**

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BT5528 monotherapy dose escalation

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)

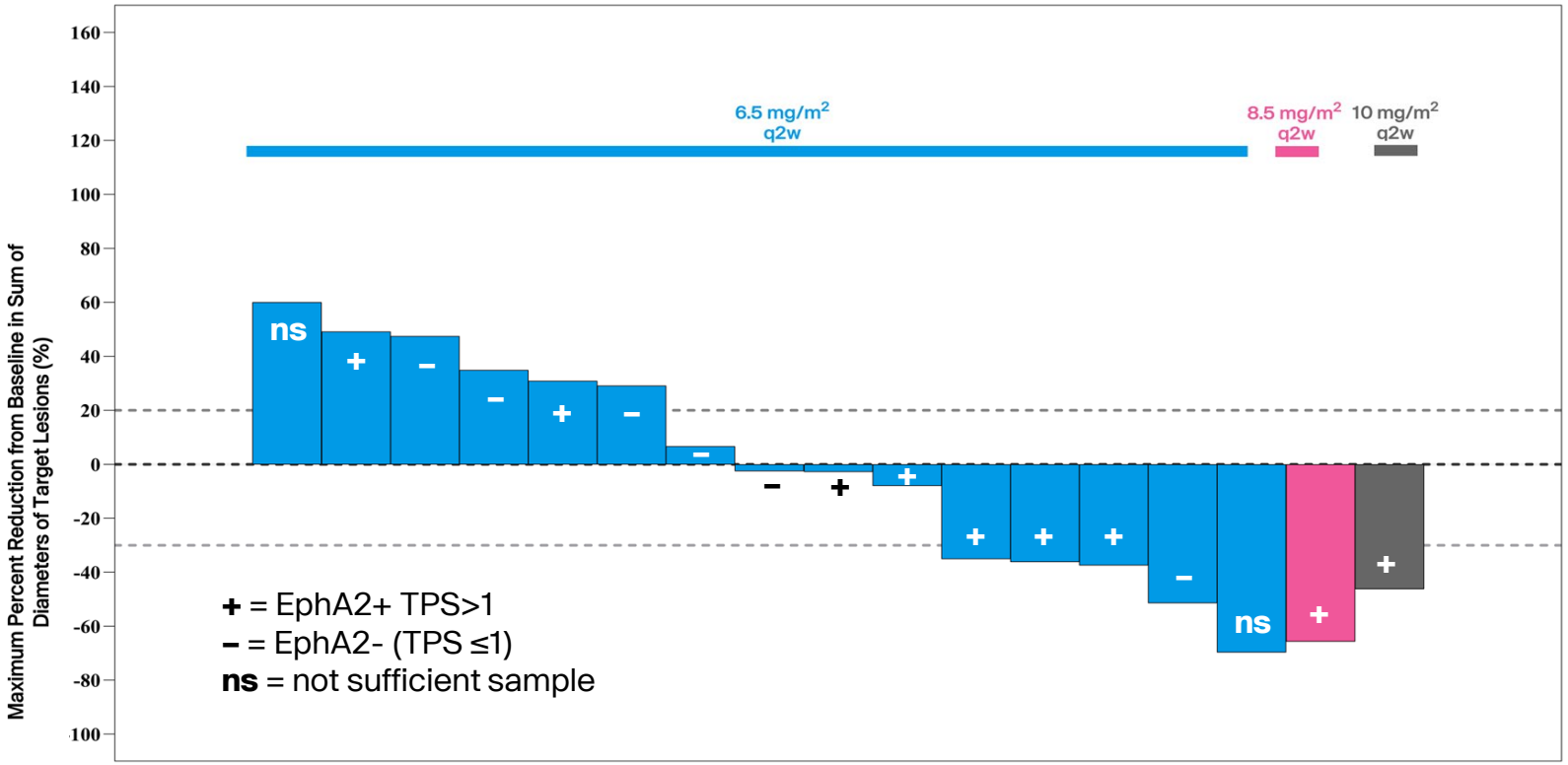
Expansion cohorts at 6.5 mg/m^2 Q2W	
Ovarian	(N=14)
Urothelial	(N=14)
NSCLC	(N=7)
HNSCC	(N=8)
Gastric/Upper GI	(N=7)
TNBC	(N=9)

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

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.

Enrollment ongoing.

BT5528 response data in mUC
(Efficacy evaluable patients only; includes 1 unconfirmed response)



mUC Best Overall Response[a,b]	BT5528 Monotherapy Cohorts[c] N=18 n (%)	BT5528 6.5mg/m² Q2W[d] N=16 n (%)
Complete Response (CR)	0	0
Partial Response (PR)	7 (39)	5 (31)
Stable Disease (SD)	3 (17)	3 (19)
Progressive Disease	8 (34)	8 (50)
ORR (CR+PR)	39%	31%
CBR (CR+PR+SD ≥ 16 wks)	39%	31%

Median duration of treatment is 14 weeks (range 2-59)

Data as of 27Sep2023.
[a]Efficacy evaluable set is defined as all enrolled patients with measurable disease at baseline who received at least one dose of BT5528 and had at least one adequate post-baseline disease assessment. Four patients were excluded due to no post-baseline assessment. A fifth patient was excluded from the waterfall plot as target lesion data was non-evaluable in the single post-baseline assessment.
[b]Responses under response evaluation criteria in solid tumor (RECIST) v1.1.
[c]Contains data from 6.5 mg/m² Q2W, 8.5 mg/m² Q2W and 10 mg/m² Q2W.
[d]Contains data from dose escalation and dose expansion.
mUC: metastatic urothelial cancer; ORR: objective response rate; Q2W = every other week.
+ EphA2+ (TPS>1), - EphA2- (TPS≤1) ns not sufficient sample, using in-house monoclonal IHC assay.

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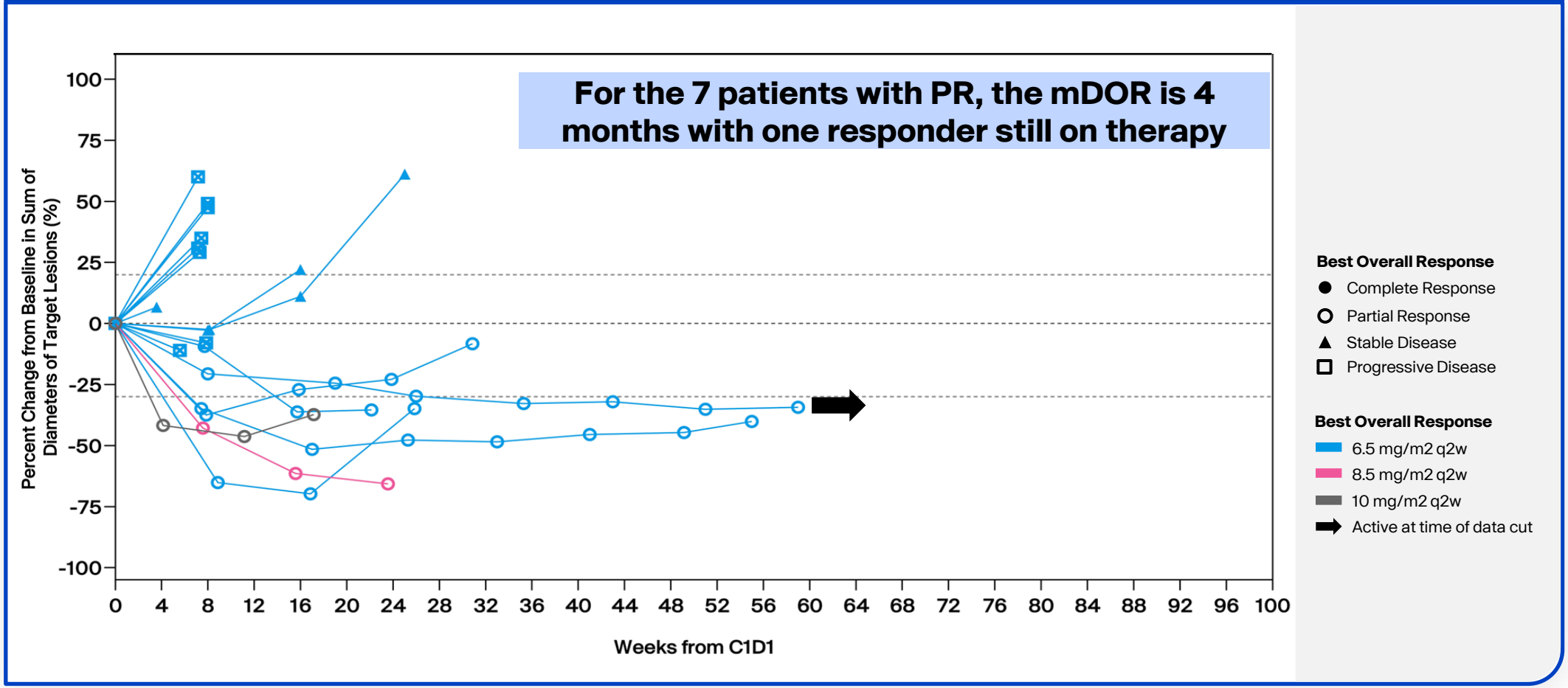
BT5528: Spider plot for tumor response in urothelial cancer

BT5528 spider plot for tumor response in urothelial cancer



Median duration of follow-up is 3 months

Data as of 27Sep2023.
Responses under response evaluation criteria in solid tumor (RECIST) 1.1. Contains data from 6.5 mg/m^2 Q2W, 8.5 mg/m^2 Q2W and 10 mg/m^2 Q2W.
Includes 1 unconfirmed PR.
C1D1: Cycle 1 Day 1; mDOR: median duration of response; PR: partial response; Q2W: every other week.

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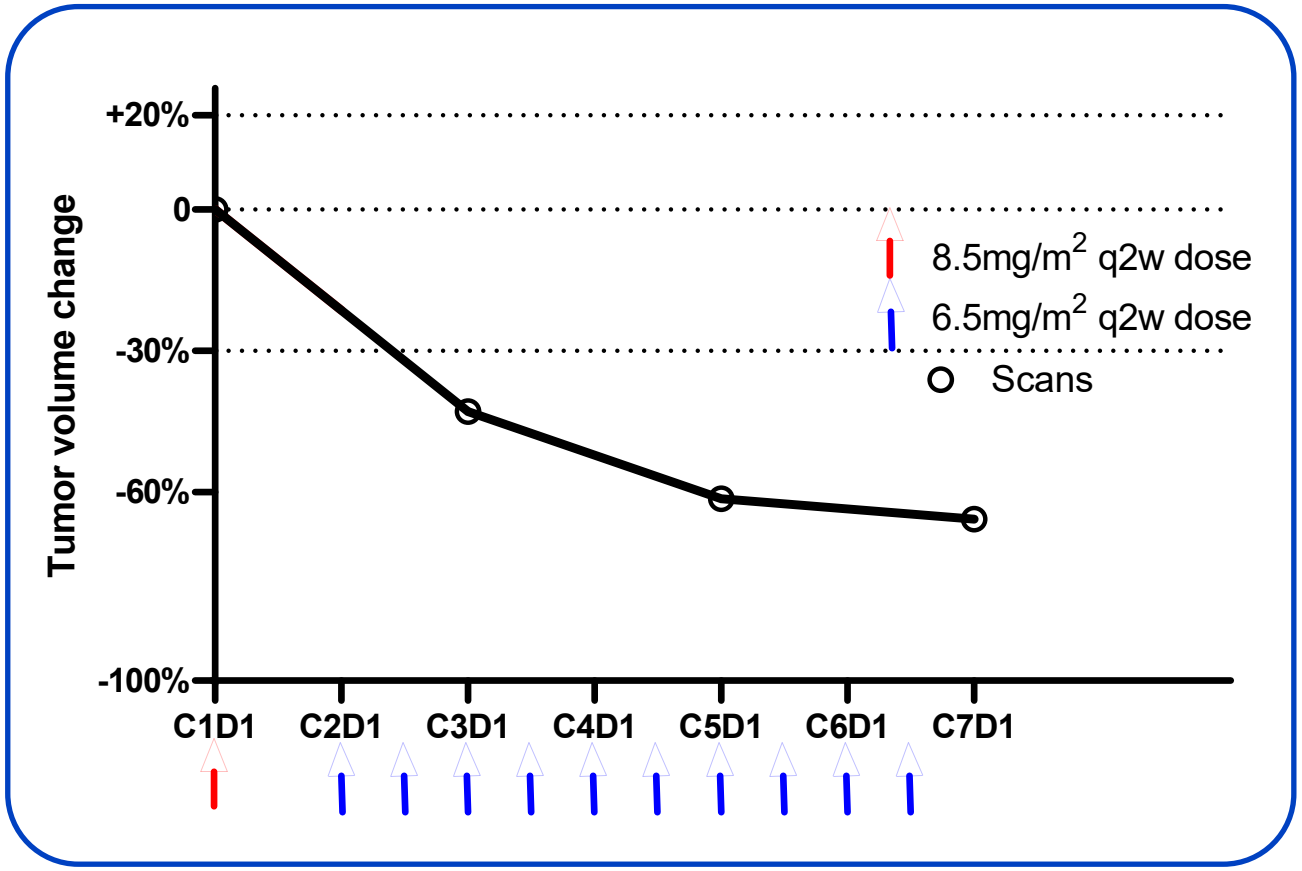
BT5528 shows potential in heavily pre-treated patients, including post-EV exposure

Patient: Female, 76

- 4 prior lines of therapy
  - Neoadjuvant: cisplatin + gemcitabine (14 weeks): PD
  - 1st Line: Pembrolizumab (32 weeks): PD
  - 2nd Line: Enfortumab vedotin (15 weeks): PR (stop due to tox, pancreatitis)
  - 3rd Line: Carboplatin + gemcitabine (17 weeks): CR (stop due to tox)
- Tumor at Study entry: metastatic urothelial cancer. Target lesions: Lung and adrenal gland; Non target lesions: Lymph nodes and liver
  - Patient enrolled in Cohort 5 (8.5 mg/m2 Q2W)
  - C1D1 at 8.5 mg/m2 Q2W
  - Dose interrupted C1D15 due to neutropenia Gr3
  - Dose reduced to 6.5 mg/m2 Q2W, C2D1-C6D15
  - Reason for discontinuation: progression due to brain metastases



C1D1: Cycle 1 Day 1; C1D15: Cycle 1 Day 15; CR: complete response; EV: enfortumab vedotin; mDOR: median duration of response; PD: progressive disease; PR: partial response; Q2W: every other week.

BT5528 overall safety population baseline characteristics

Characteristic	BT5528 All Monotherapy Cohorts N=109	BT5528 6.5 mg/m^2 Q2W[a] N=74
Median age, yrs (range)	64 (33-78)	63 (33-78)
Sex, n (%)		
Male	41 (38)	34 (46)
Female	68 (62)	40 (54)
Race, n (%)		
White	84 (77)	55 (74)
Black or African American	2 (2)	0
Others	23 (21)	19 (26)
Missing	0	0
ECOG, n (%)		
0	43 (39)	30 (41)
1	66 (60)	44 (59)
Median prior lines of therapy (range)	4 (1 - 13)	4 (2 - 13)
Median duration of treatment (range)	6 weeks (0.14-84)	7 weeks (0.14-84)

Data as of 27Sep2023.
[a]Includes dose escalation and dose expansion.
Q2W: every other week.

BT5528 has an acceptable emerging tolerability profile

Treatment-related Adverse Events in ≥10% Patients by Preferred Term	BT5528 All Monotherapy Cohorts N=109 n (%)		BT5528 6.5 mg/m^2 Q2W N=74[a] n (%)	
	Any Grade	≥Grade 3	Any Grade	≥Grade 3
Nausea	52 (48)	2 (2)	35 (47)	1 (1)
Fatigue	38 (35)	6 (6)	27 (37)	3 (4)
Diarrhea	33 (30)	1 (1)	23 (31)	1 (1)
Vomiting	26 (24)	3 (3)	13 (18)	2 (3)
Anemia	22 (20)	6 (6)	15 (20)	3 (4)
Alopecia	18 (17)	0	12 (16)	0
Decreased appetite	18 (17)	1 (1)	15 (20)	0
Pyrexia	17 (16)	0	13 (18)	0
Headache	13 (12)	0	7 (10)	0
Neutrophil count decreased	12 (11)	5 (5)	4 (5)	3 (4)
Myalgia	10 (9)	0	9 (12)	0

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Data as of 27Sep2023.
[a]Includes dose escalation and expansion.
Q2W: every other week.

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

Treatment-related Adverse Events	BT5528 All Monotherapy Cohorts N=109 n (%)		BT5528 6.5 mg/m^2 Q2W N=74[a] n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Peripheral neuropathy[b]	19 (17)	0	14 (19)	0
Skin reactions[c]	11 (10)	0	9 (12)	0
Hemorrhage[d]	0	0	0	0
Ocular disorders[e]	2 (2)	0	2 (3)	0
Lab-related				
Hyperglycemia	3 (3)	1 (1)	3 (4)	1 (1)
Neutropenia	11 (10)	5 (5)	6 (8)	2 (3)

Data as of 27Sep2023.
[a]Includes dose escalation and expansion; [b]Peripheral neuropathy SMQ [broad] used; [c]All preferred terms defined in Skin and Subcutaneous Tissue SOC, excluding Alopecia, and SCAR MedDRA SMQ [broad] used, Any Grade: one patient was Grade 2, all others Grade 1; [d]Hemorrhage SMQ used; [e]Preferred terms defined in Eye Disorder System Organ Class (SOC) used.
Lab-related treatment-related adverse event by Preferred Term.
Q2W: every other week.

BT5528 treatment-related peripheral neuropathy was low-grade and often reversible

Treatment-related Adverse Events	BT5528 All Monotherapy Cohorts N=109 n (%)	BT5528 6.5 mg/m^2 Q2W[a] N=74 n (%)
Peripheral neuropathy (Any grade)[b]	**19 (17)**	**14 (19)**
TRAE by PT		
Peripheral Sensory Neuropathy (Any grade)	**6 (6)**	**4 (5)**
Grade 1	**3 (3)**	**2 (3)**
Grade 2	**3 (3)**	**2 (3)**
Grade ≥3	**0**	**0**
Muscular weakness (Any grade)	**0**	**0**

Data as of 27Sep2023.
[a]Contains data from dose escalation and dose expansion; [b]Peripheral neuropathy SMQ [broad] used.
PT: Preferred Term; Q2W: every other week; TRAE: treatment-related adverse event.

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 early signals seen in urothelial cancer and in a variety of tumor types
- Continued review of safety and PK demonstrates that there is sufficient headroom to explore a higher dose regimen (5 mg/m^2 QW)
- Trend in relationship between EphA2 expression and activity observed but complicated by technical issues of accessing archival tissue and likely sub-optimal dose levels

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)

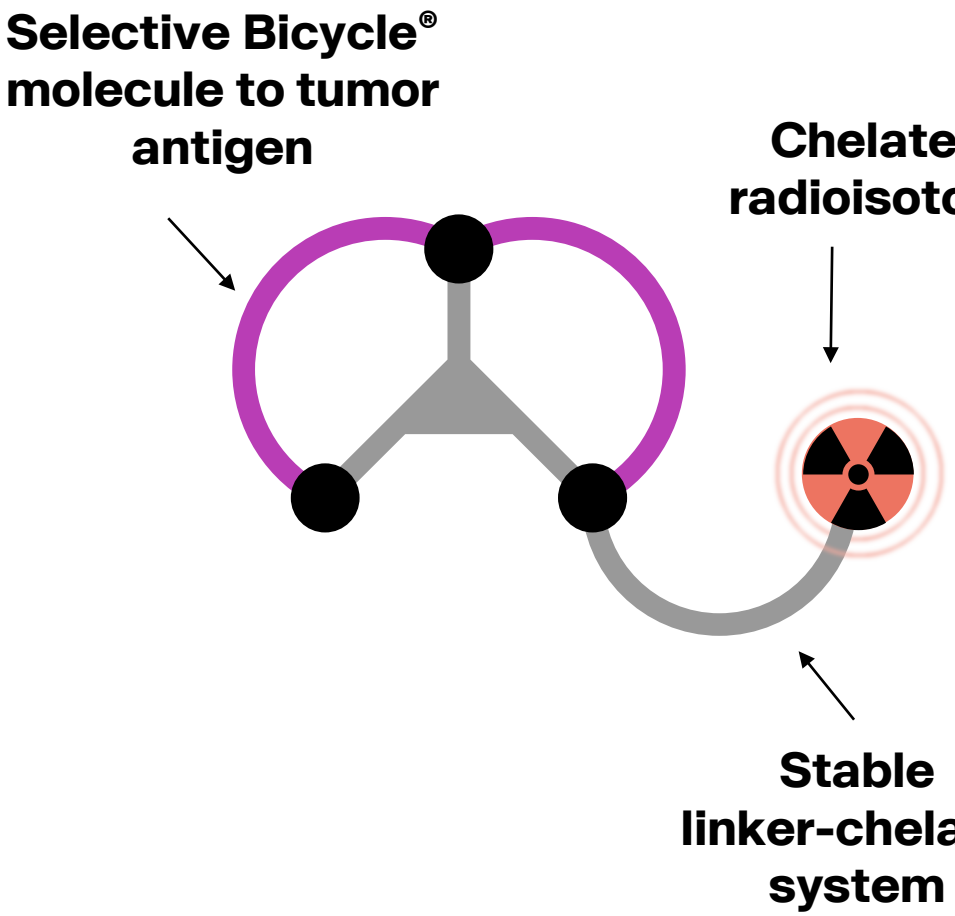
Bicycle®

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

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

Access to multiple development paths provides opportunity for full potential of BRC™ molecules to be unlocked

Collaboration

- Multiple oncology targets
- Benefit from Bayer's scale, expertise and supply chain
- Bayer responsible for downstream development, manufacturing and commercialization

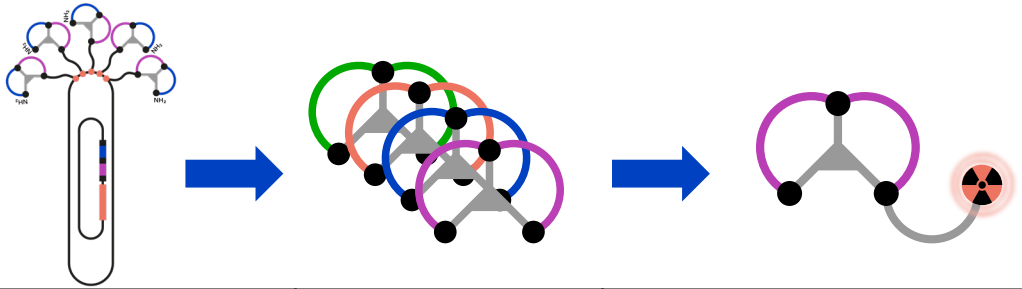
Collaboration

- Multiple oncology targets
- Benefit from Novartis' scale, expertise and supply chain
- Novartis responsible for further development, manufacture and commercialization

Internal Pipeline

- Wholly owned assets (in collaboration with DKFZ)
- Control over target, isotope
- Control over downstream development

We are building a deep portfolio of Bicycle® tumor antigen binders for novel targets



Target	Indications	Affinity	Discovery / POC	BRC™ Lead Optimization	IND enabling
MT1 (Im)	Multiple cancers	20 pM			
MT1 (Tx)	Multiple cancers	20 pM			
EphA2	Pancreatic, ovarian, head and neck	170 pM			
CD38	Hematological	100 pM			
Target 1	Not disclosed	3 nM			
Target 2	Not disclosed	1 nM			
Target 3	Not disclosed	100 pM			
Target 4	Not disclosed	7 nM			
Additional	Various				

Im – imaging, Tx = therapeutic

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

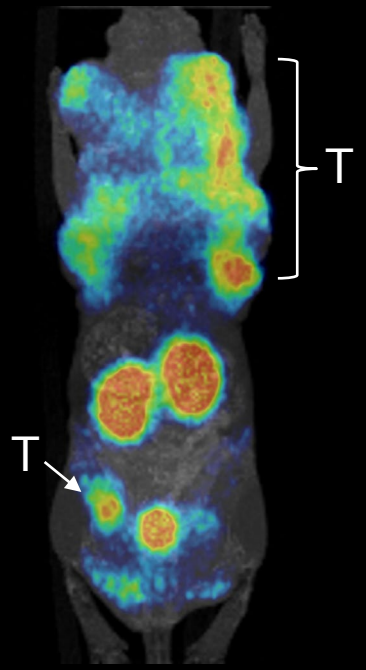
MT1-MMP

Fibrosarcoma

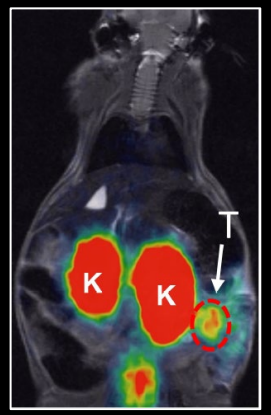
Left: HT1080 tumor model, 2h P.I. (DKFZ unpublished data)
Right: HT1080 tumor model, 40 to 60 min P.I. Eder M et al. 2019. *Cancer Res.* 79(4):841-852

EphA2

Breast



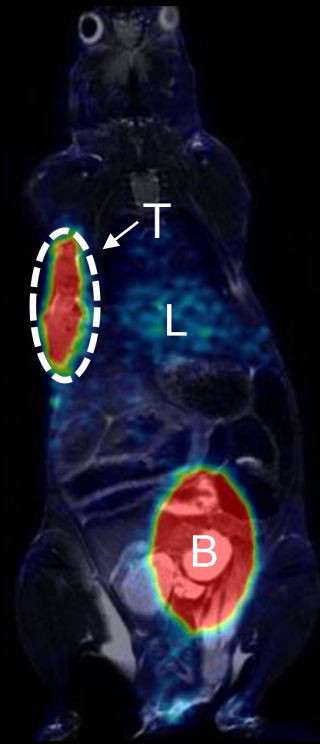
Pancreatic

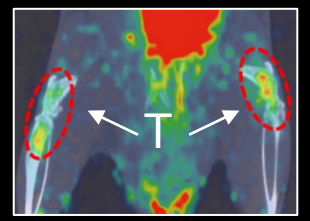


Left: MMTV-PyMT transgenic mouse model, 2h P.I.
Right: Panc-1 orthotopic tumor model 1h P.I.
Sharma AK et al. 2023. *Cancer Res,* 83(7 Suppl):2768

CD38

Multiple myeloma





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

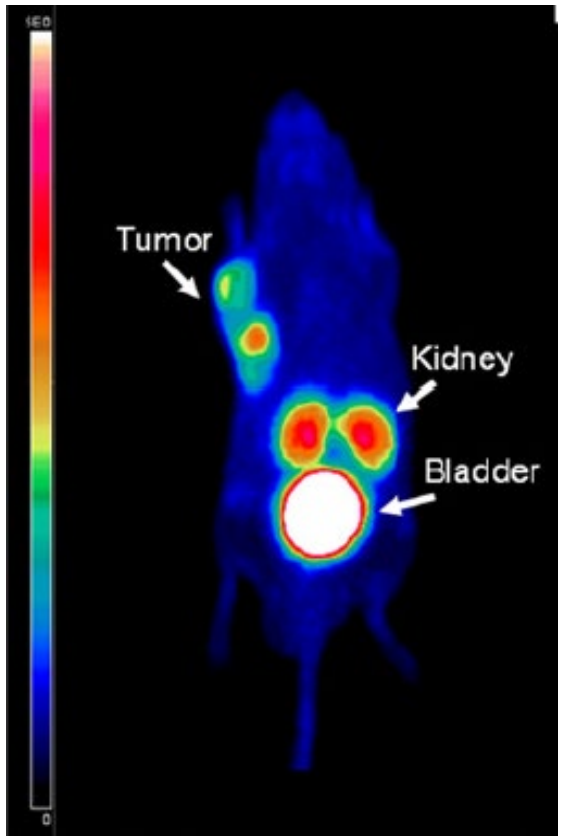
Bicycle® dkfz.

MT1-MMP is a high value target in the treatment of cancer

- Membrane type 1 matrix metalloproteinase MT1-MMP (or matrix metallopeptidase 14, MMP14)
- Overexpressed in variety of cancers (e.g., HCC, NSCLC, gastric, breast)
- Associated with poor prognosis

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

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.

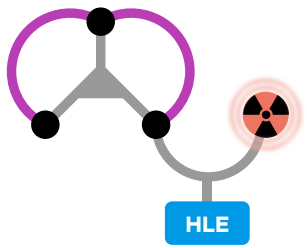


Early MT1-MMP targeting BRCs show high tumor enrichment in PET imaging studies

Bicycle®

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.
HCC: hepatocarcinoma; NSCLC: non-small cell lung cancer.

^{212}Pb labelled MT1-MMP targeting BRC™ molecule shows potent anti-tumor activity and is well tolerated in preclinical studies



MT1-MMP targeting Bicycle® molecule

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

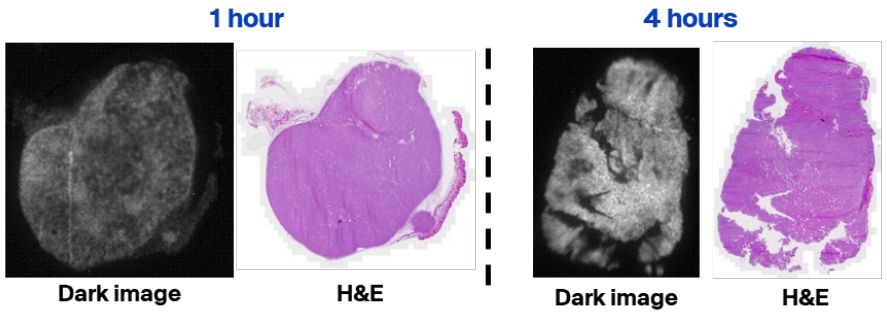
Half-life extending moiety

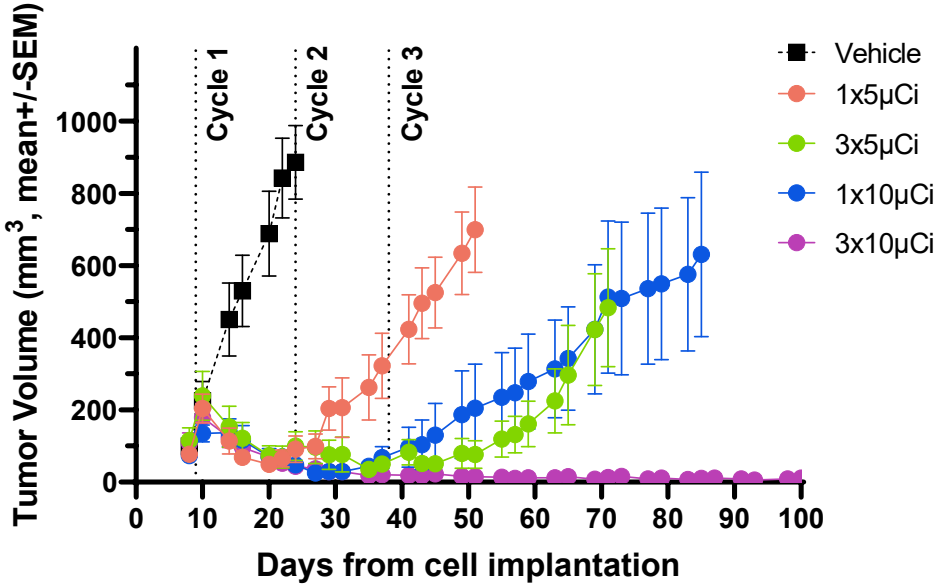
- Reversible albumin binding motif
- Prolongs circulating half-life of conjugate

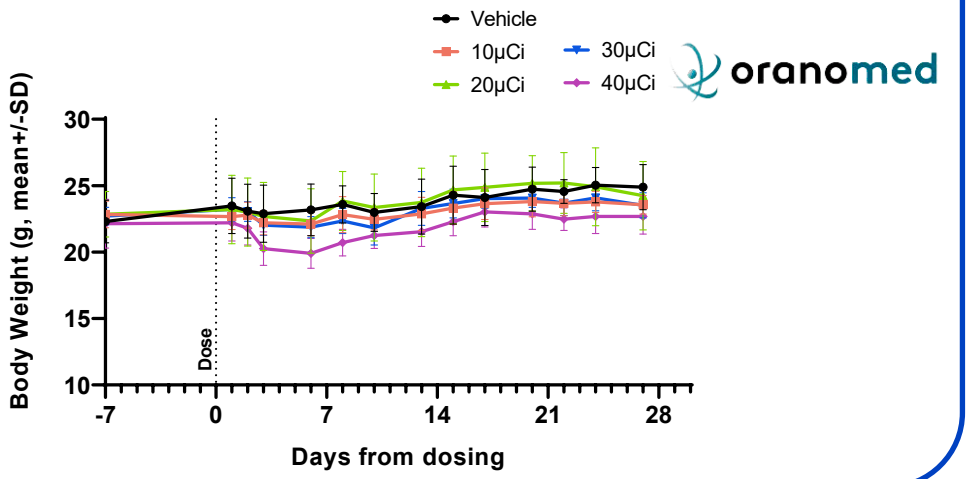
Lead-212 payload

- Decay half-life 10 hours
- Double stranded DNA break *via* single alpha particle emission

Payload distribution in tumor







Bicycle®

Mudd, G. et al. TIDES 2023.
BRC: Bicycle Radio Conjugate; H&E: hematoxylin and eosin; HLE: half-life extension; MT1-MMP: membrane type 1 matrix metallopeptidase; SD: standard deviation; SEM: standard error of the mean.

We believe our BRC™ molecules are well-positioned to deliver novel radiopharmaceuticals

SUMMARY

- We have a pipeline of novel Bicycle® binders with ideal properties for radioisotope delivery
- Validation through entry into multiple collaborations including Novartis (March 2023), Bayer (May 2023), DKFZ (May 2023) and independent studies
- An MT1-MMP targeting BRC™ molecule shows potent anti-tumor activity and is well tolerated in preclinical studies
- In 2023, we generated $95M in non-dilutive capital leveraging our BRC™ platform

NEXT STEPS

- **2024: Generate early human imaging data from our wholly owned BRC pipeline**

BRC: Bicycle Radio Conjugate; MT1-MMP: membrane type 1 matrix metallopeptidase.

Looking Ahead

Bicycle®

We expect 2024 to be a catalyst-rich year

BT8009	✓ 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, ovarian) ❑ 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 checkpoint inhibitor therapy ❑ 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

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®