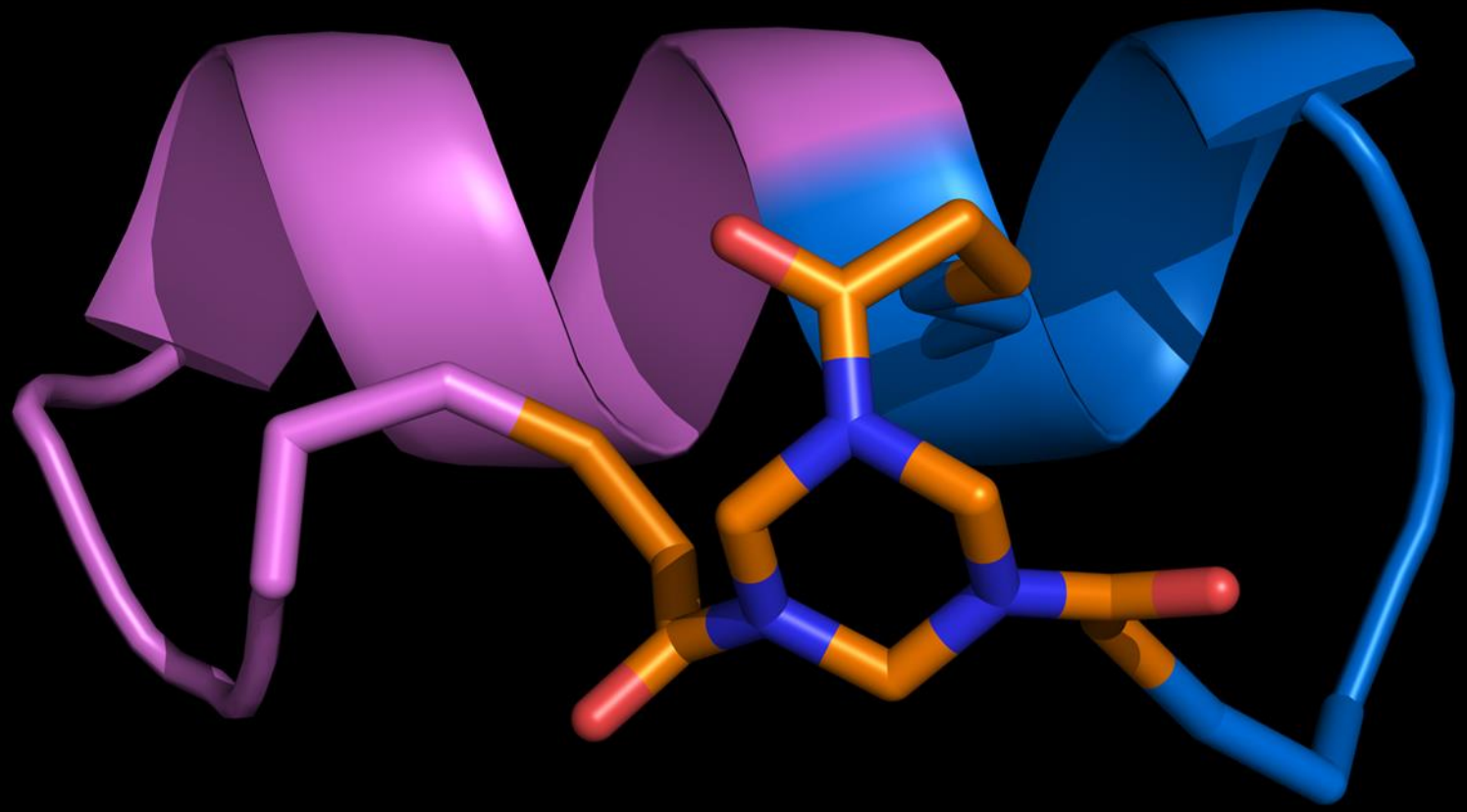
R&D Day

December 14, 2023



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Forward-looking statements

This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as “aims,” “anticipates,” “believes,” “could,” “estimates,” “expects,” “forecasts”, “goal,” “intends,” “may” “plans,” “possible,” “potential,” “seeks,” “will,” and variations of these words or similar expressions that are intended to identify forward-looking statements. All statements other than statements of historical facts contained in this presentation are forward-looking statements, including statements regarding: our future financial or business performance, conditions, plans, prospects, trends or strategies and other financial and business matters; our current and prospective product candidates, planned clinical trials and preclinical activities, current and prospective collaborations, and the timing and success of our development of our 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 November 2, 2023, as well as in other filings we may make with the SEC in the future, as well as discussions of potential risks, uncertainties and other important factors in our subsequent filings with the SEC. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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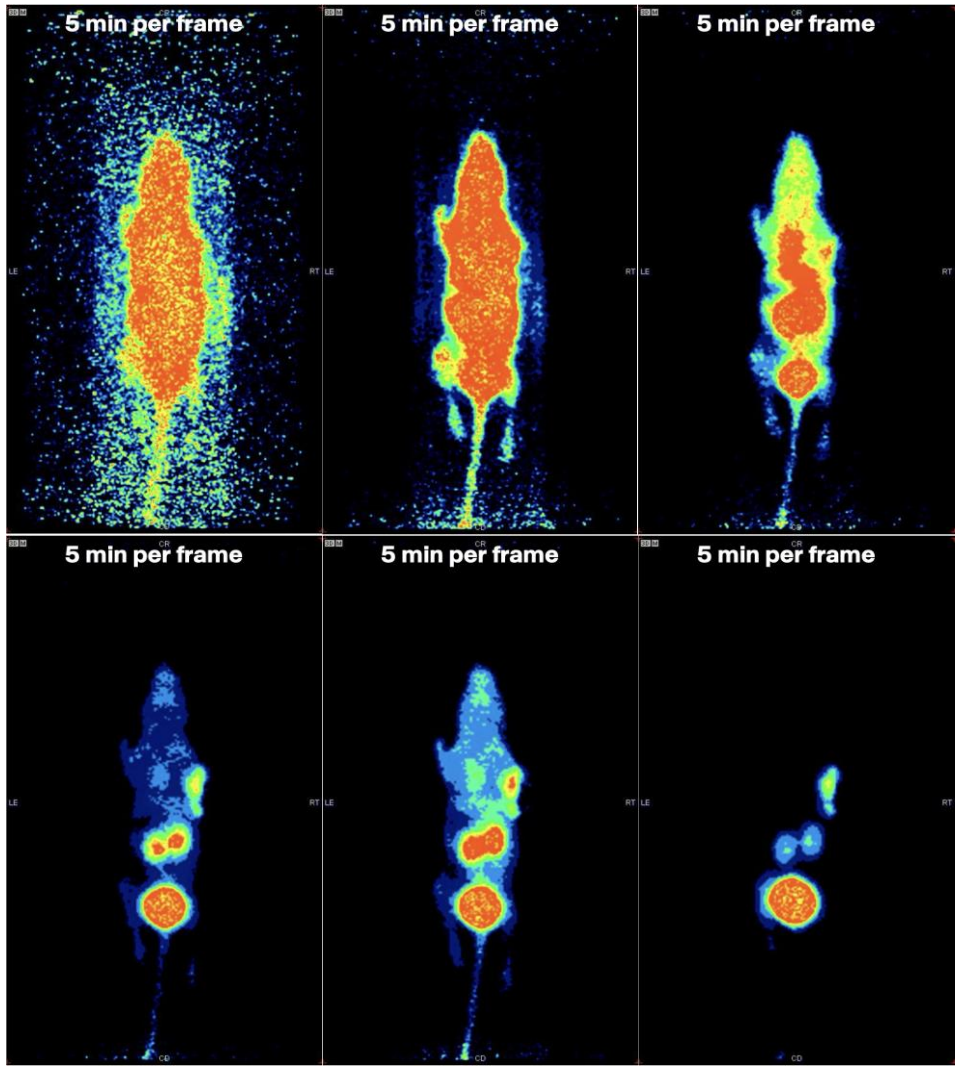
Bicycle Therapeutics: A clinical-stage company pioneering a new, differentiated class of innovative medicines

Bicycle®

Sir Greg Winter

Nobel Prize Winner
Founder/Director of Bicycle Therapeutics

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

We are primed to accelerate from our strong foundation since IPO

>85% **SUCCESS RATE** in identifying Bicycle® binders to targets	**3** **WHOLLY OWNED PROGRAMS** in clinical testing	**5** **PARTNERSHIPS** with leading biopharma and life sciences organizations
#11 **IN ESG** out of 885 pharma companies evaluated by Morningstar Sustainalytics[2]	**$628M** **RAISED** through equity financing	**$213M** **GENERATED** from non-dilutive financing

[1]

Bicycle® molecules have demonstrated potential in

- ✓ Oncology
- ✓ Neurology
- ✓ Neuromuscular disorders
- ✓ Infectious disease (bacterial and viral)
- ✓ Metabolic disease

We believe there is immense potential for Bicycle Therapeutics

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1. Statements in table refer to period since company IPO, except where noted. 2. Ranking based on Nov2023 assessment by Morningstar Sustainalytics; total pool as of 12Dec2023. Legal Disclaimer (sustainalytics.com)

Our strategy to deliver on the promise of Nobel Prize-winning science

Execute

plan to become leader in next-gen solid tumor therapeutics and combinations

- Initiate Duravelo-2 registrational trial for BT8009 in metastatic bladder cancer
- Further studies to assess BT8009, BT7480 and BT5528 in emerging tumors of interest

Expand

opportunities in oncology

- Advance the next generation of BTCs
- Validate the radiopharm opportunity and partner for success
- Advance immuno-oncology program through innovative partnerships

Explore

platform potential beyond oncology

- Continue strong track record of collaboration
- Partner with leading academic, government and life sciences organizations

Today’s speakers

Kevin Lee, Ph.D., MBA

Chief Executive Officer

Nick Keen, Ph.D.

Chief Scientific Officer

Santiago Arroyo, M.D., Ph.D.

Chief Development Officer

Jennifer Perry, Pharm.D.

SVP, Head of Commercial

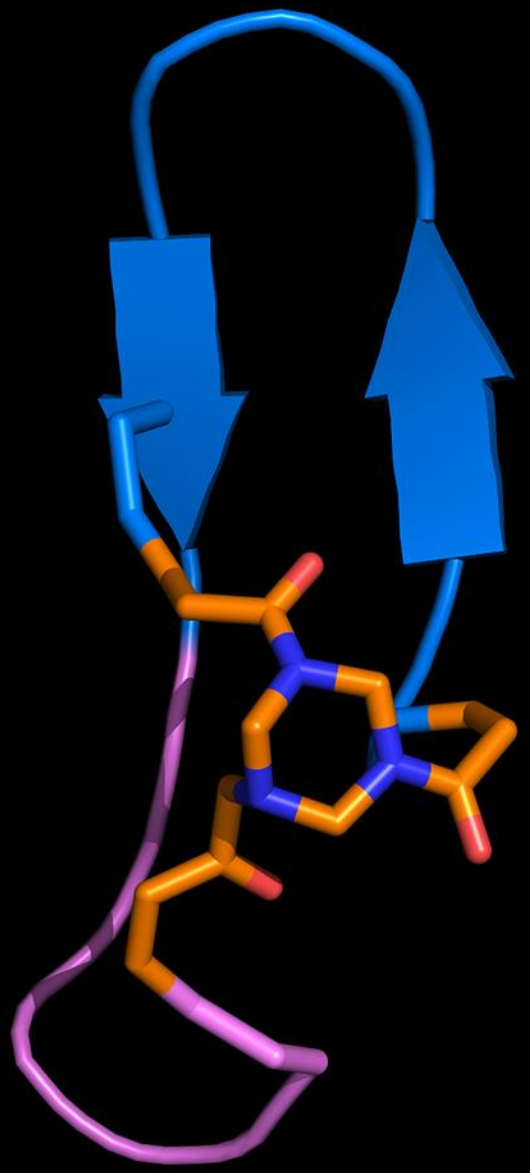
Mike Skynner, Ph.D.

Chief Technology Officer

Agenda

Time	Topic	Speaker(s)
8 a.m.	Welcome and Company Overview	Kevin Lee
8:15 a.m.	Our Nectin-4 Portfolio ▸ BT8009 and BT7480	Nicholas Keen Santiago Arroyo Jennifer Perry
9:30 a.m.	Q&A	Management Team
10:00 a.m.	Break	
10:10 a.m.	Our EphA2 Portfolio ▸ BT5528 and BT7455	Nicholas Keen Santiago Arroyo Jennifer Perry
10:50 a.m.	Q&A	Management Team
11:05 a.m.	Our Platform Opportunities	Nicholas Keen Michael Skynner
11:40 a.m.	Q&A	Management Team
11:50 a.m.	Summary and Close	Kevin Lee

Nectin-4 Portfolio



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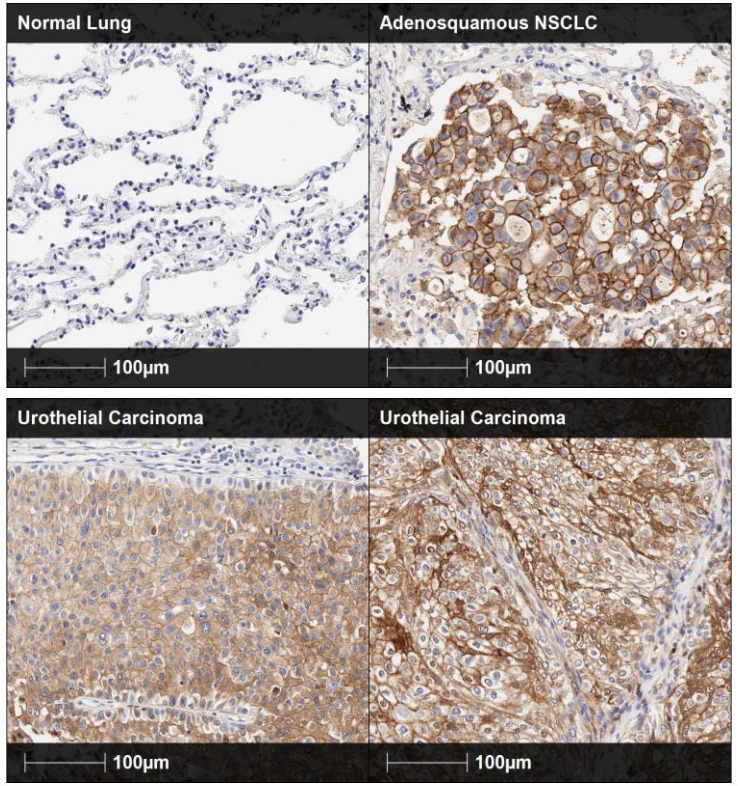
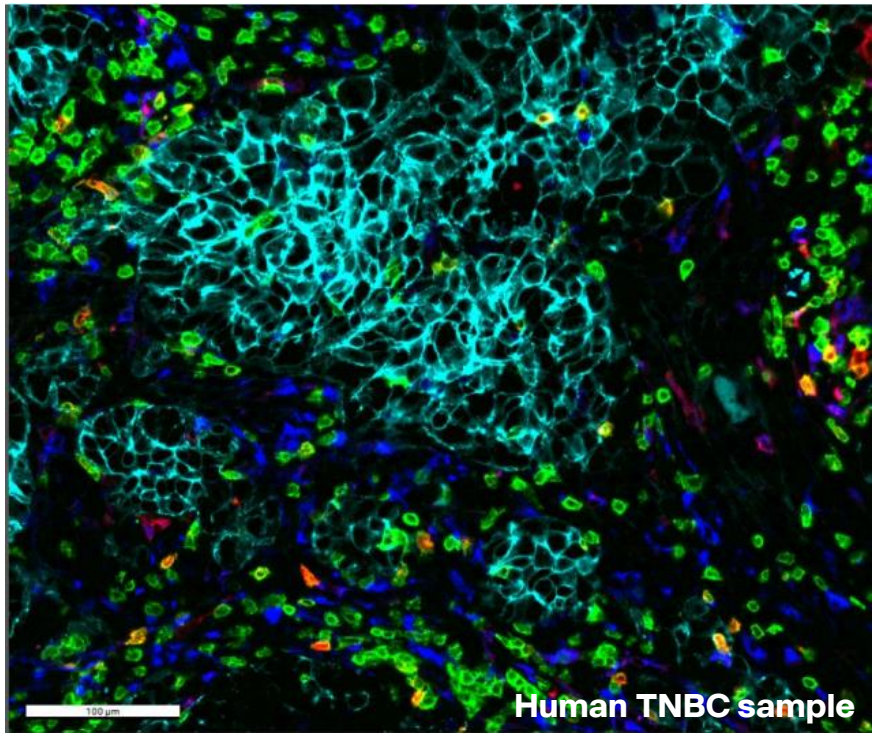
Nectin-4 is a high value target expressed in many tumors

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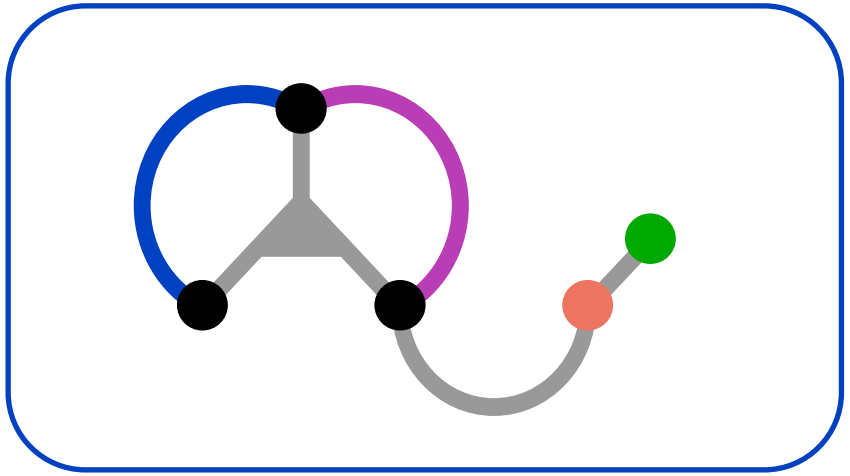
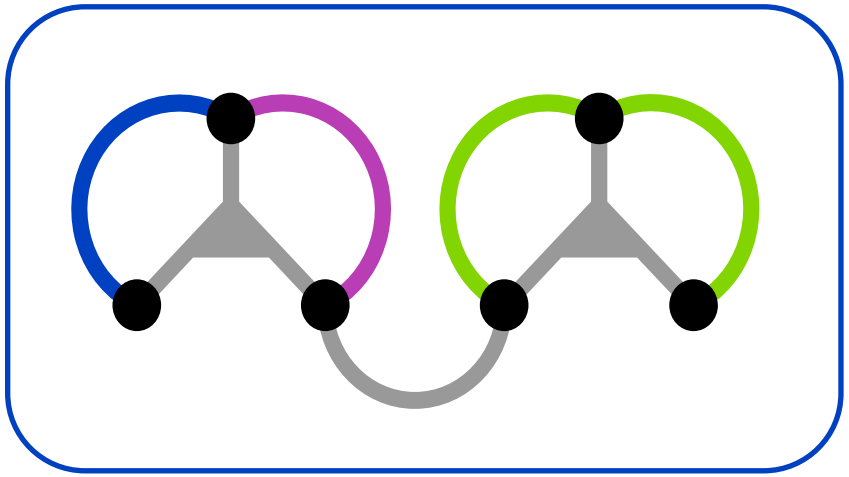
1. Challita-Eid PM et al. 2016. *Cancer Res*, 76(10):3003-3013. 2. Campbell CT et al. 2020. *Cancer Res*, 80(16 Suppl):5300. 3. Cohen H et al. 2021. *J Immunother Cancer*, 9(Suppl 2):A2.
NSCLC: non-small cell lung cancer; TNBC: triple-negative breast cancer.

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

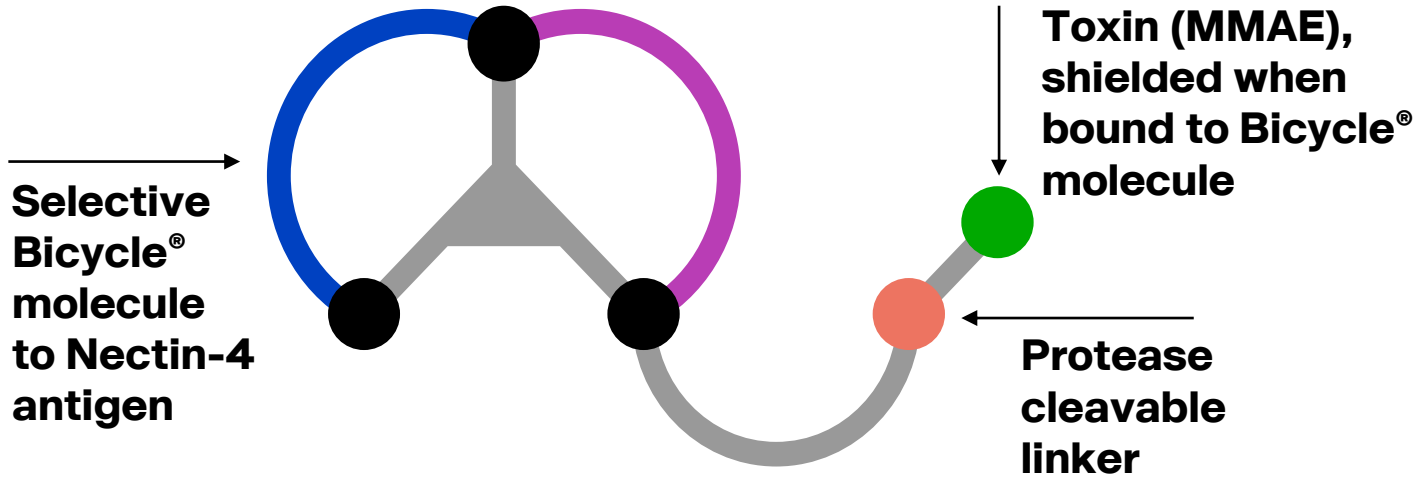


BT8009 is a Nectin-4 targeted Bicycle toxin conjugate (BTC®) designed to overcome the significant toxicity associated with other toxin conjugate approaches.



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®



- 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

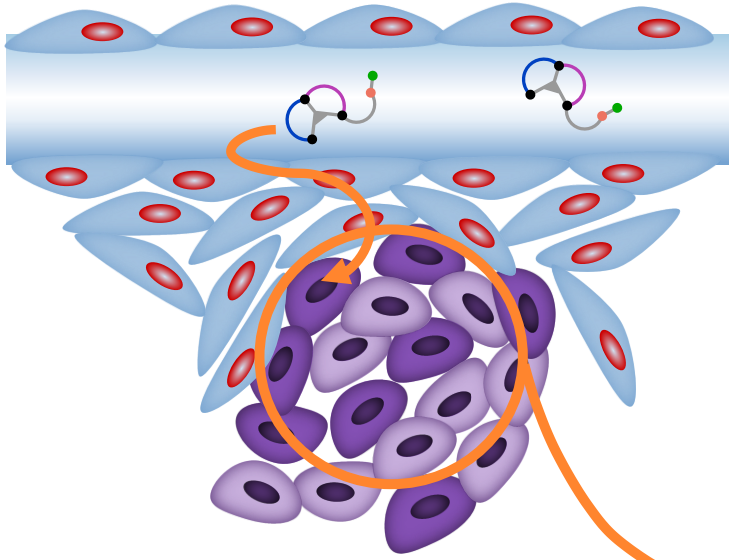
Highly differentiated preclinical performance:

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

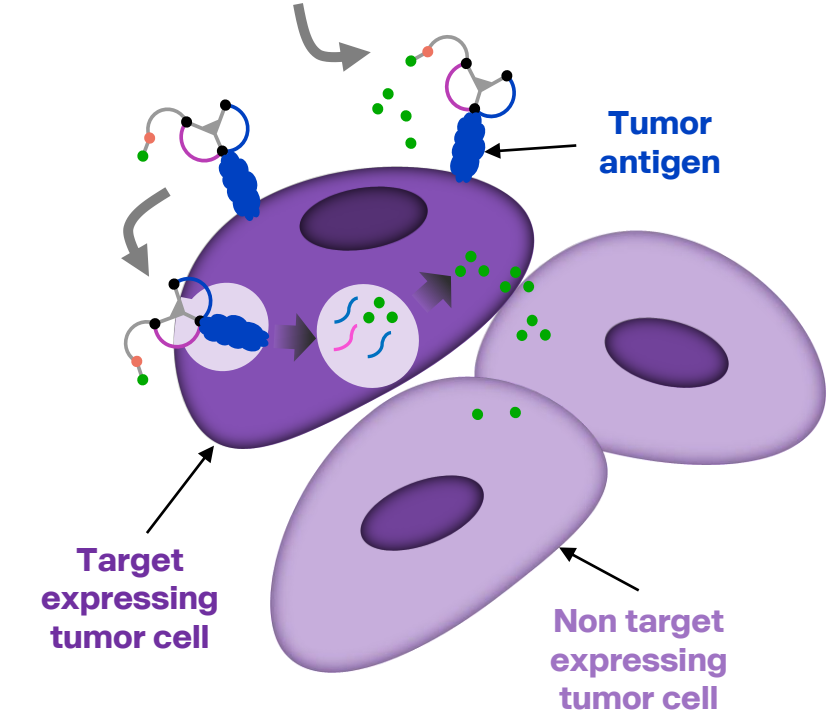
1. Rigby M et al. 2022. *Mol Cancer Ther*, 21(12):1747-1756. 2. Mudd GE et al. 2022. *J Med Chem*, 65(21):14337-14347.

BTCs have a unique mechanism of action

1 **Bicycle® molecules rapidly extravasate to penetrate the whole tumor**

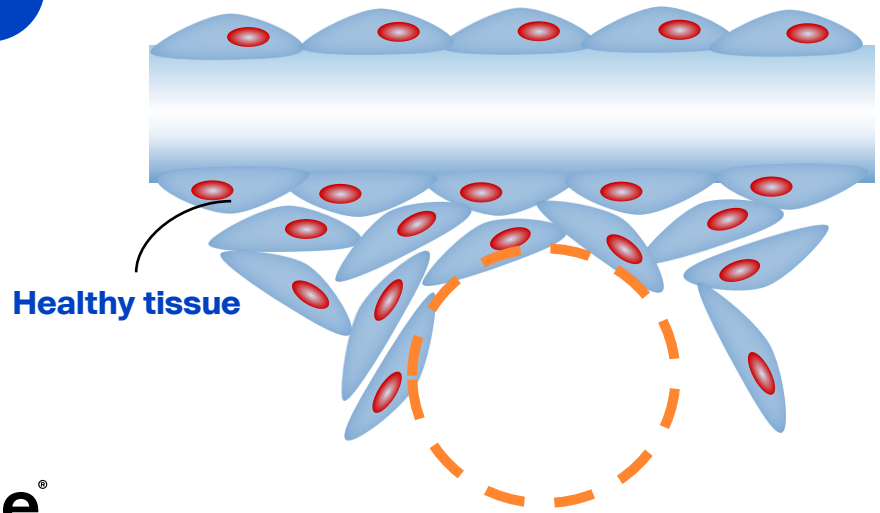


2 **Toxin activation through cell surface linker cleavage and internalization**



3 **Bystander effect can address tumor heterogeneity**

4 **Tumor reduction**



Bicycle® molecules are designed to be more selective than antibodies

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

✓ Binds ✗ Does not bind

- Antibodies have evolved to interact with multiple receptor systems which may give rise to unwanted toxicities – eye, skin, liver, lung, etc.
- Bicycle® molecules are highly selective for their intended target
- This may decrease toxicity, increase duration of response and the ability to combine with IO agents

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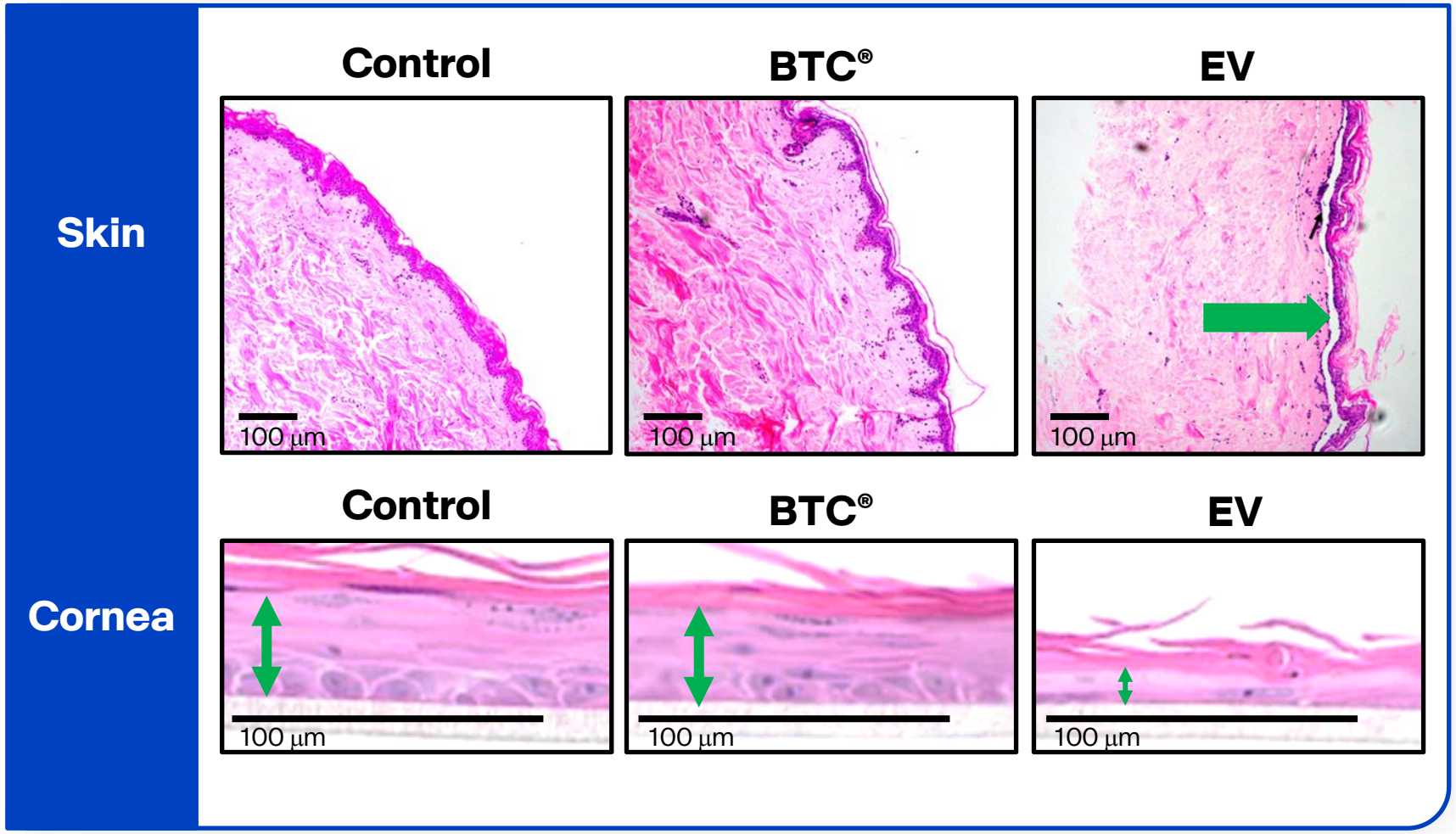
Assessed using the Retrogenix assay platform, enfortumab vedotin and BT8009 (2 μg/ml) were assessed for binding to ~6,500 secreted and cell surface-tethered human secreted proteins expressed on cells. Binding was detected using an anti-MMAE antibody. Bicycle Therapeutics unpublished data.

Improved selectivity may lead to differentiated tolerability



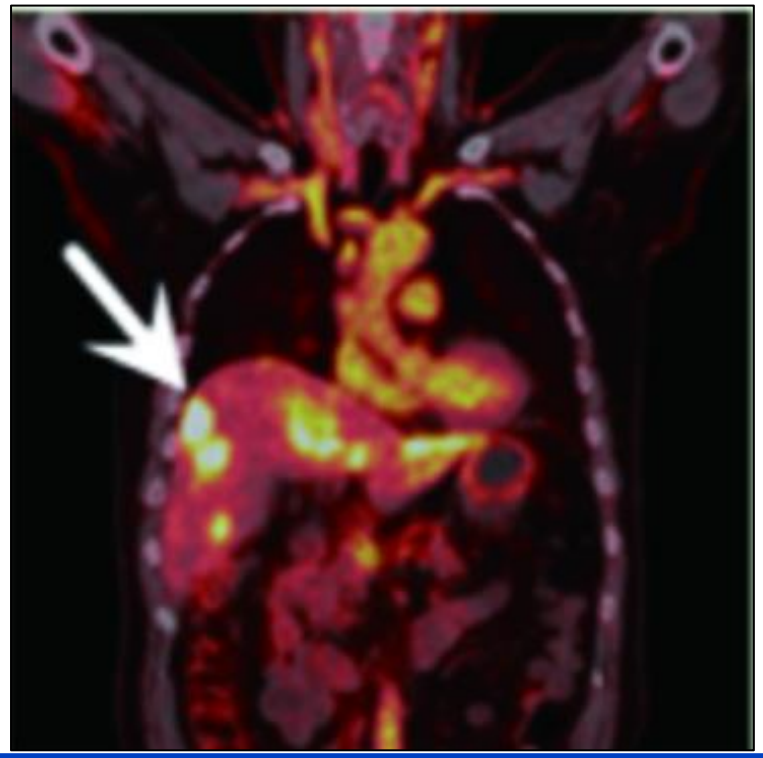
Skin and eye adverse events were modelled *in vitro* using human tissue *ex vivo*

Skin assay
Human skin explants were incubated, at the basolateral surface, with enfortumab vedotin (EV) or a Nectin-4 binding Val-Cit MMAE Bicycle Toxin Conjugate (BTC®) under conditions to simulate their potential human exposures with respect to concentration and duration. For 2 weeks (2 dosing intervals). Samples were processed, routine histology (H and E staining) performed and separation of epidermal and dermal interface assessed.

EpiCorneal Assay
EpiCorneal model consists of human corneal epithelial cells cultured on a substrate to mimic the cornea. Samples were incubated, at the basolateral surface, with EV or a Nectin-4 binding Val-Cit MMAE BTC® under conditions to simulate their potential human exposures with respect to concentration and duration. For 1 week (1 dosing period). Samples were processed and routine histology (H and E staining) performed. Thickness of the corneal epithelial layer was assessed.

Bicycle Therapeutics unpublished data.

External data demonstrate Bicycle® conjugates can rapidly and selectively target human tumors



Imaging shows a Nectin-4 Bicycle® binder rapidly penetrating human tumors (15 mins) with selective retention

Bicycle® conjugates are designed to:

- Be highly selective, minimizing off-target toxicity
- Minimize systemic exposure and toxicity
- Penetrate human tumors rapidly
- Offer a new modality with advantageous properties that may increase duration of response and be far more combinable, particularly with IO agents

Duan X et al. 2023. *Clin Cancer Res*, 29(17):3395-3407.

BT8009 Phase 1/2 clinical trial update

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Our BT8009 clinical strategy is to deliver a first-in-class differentiated treatment in Nectin-4 expressing tumors

Execute
in metastatic urothelial cancer

- Understand optimal dosing
- Establish differentiation through improved patient benefit
- Potentially become first-line treatment of choice

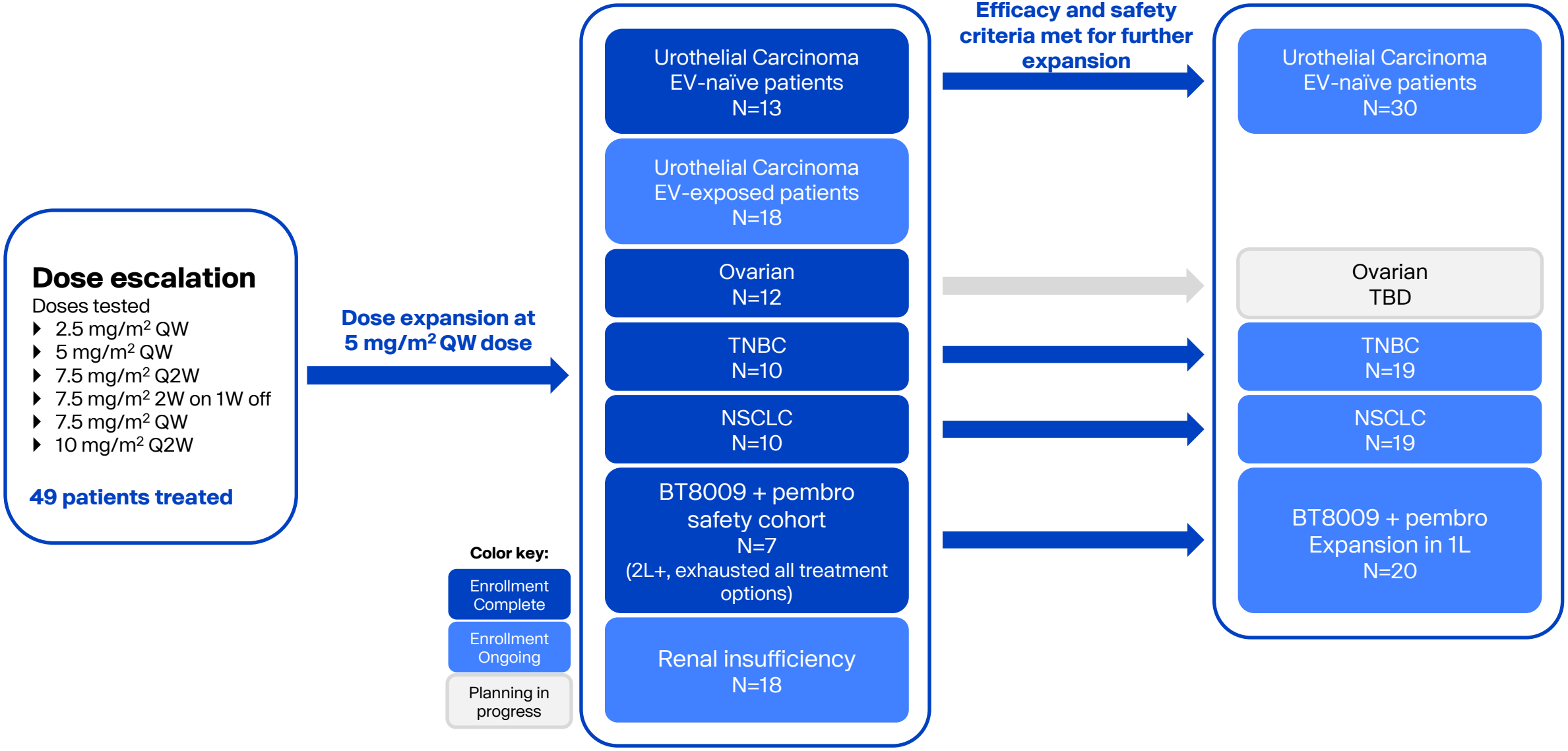
Expand
beyond metastatic urothelial cancer

- Undertake signal finding in other solid tumors to enable accelerated approval where appropriate
- Expand to earlier stage of bladder cancer

Explore
lifecycle management

- Investigate novel combinations
- Investigate alternate dosing routes

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.

Study populations included in this update

- Efficacy:
  - EV-naïve mUC monotherapy at 5 mg/m^2 QW (N=26)*
  - Ovarian (N=10)
  - TNBC (N=15)
  - NSCLC (N=16)
- Safety:
  - 5 mg/m^2 QW patients in monotherapy [dose escalation and dose expansion] (N=113)
  - 5 mg/m^2 QW EV-naïve mUC in monotherapy [dose escalation and dose expansion] (N=34)
  - 5 mg/m^2 QW 2L+ mUC patients in combination (N=7)
  - Analysis on AEs of interest

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*Study is actively enrolling and currently 7 ongoing patients with EV-naïve mUC at 5 mg/m^2 QW have not had follow-up scans.
2L+: 2nd-line or later; AE: adverse event; EV: enfortumab vedotin; mUC: metastatic urothelial cancer; NSCLC: non-small cell lung cancer; QW: weekly; 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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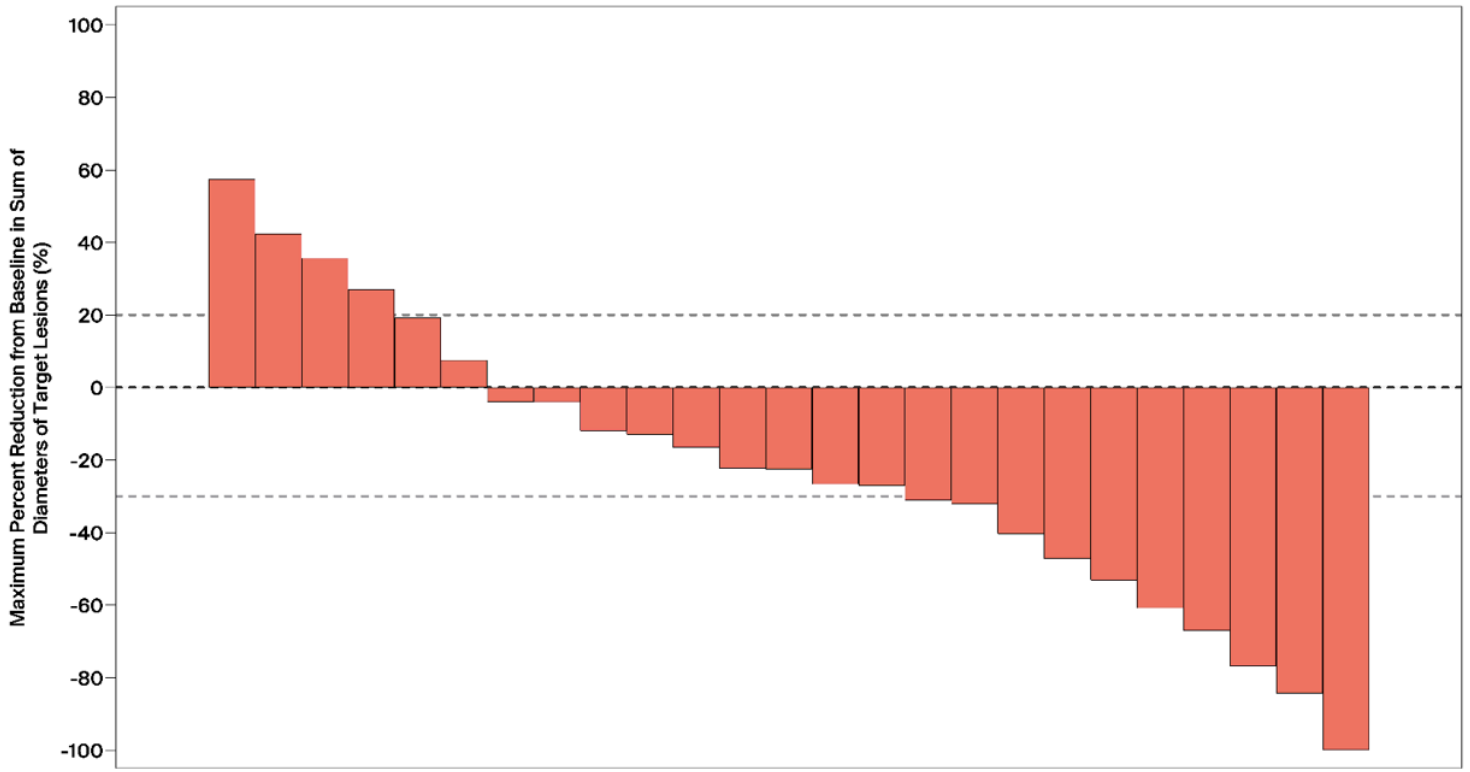
BT8009 response data in EV-naïve mUC

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)

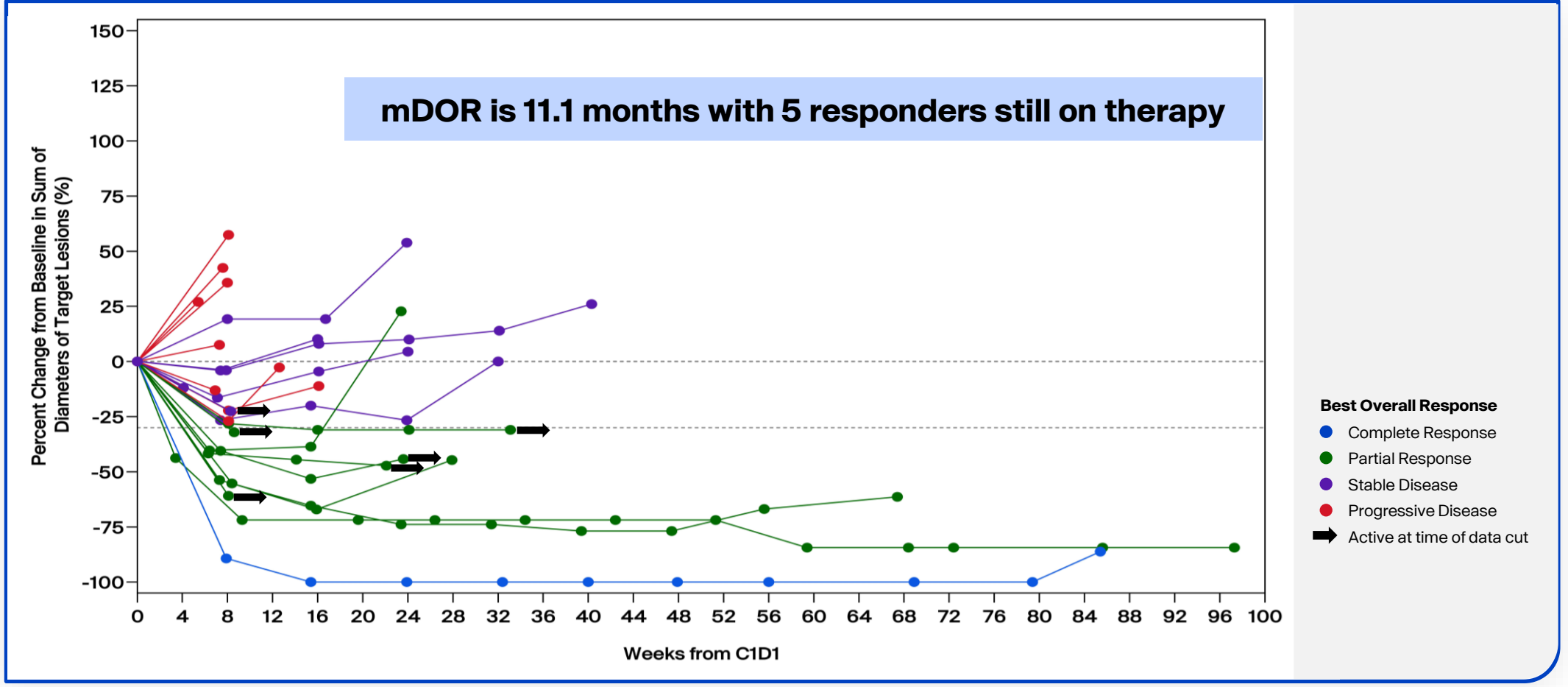
mDOT is currently 11 weeks (range 1-101)

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 a long duration of response in EV-naïve mUC

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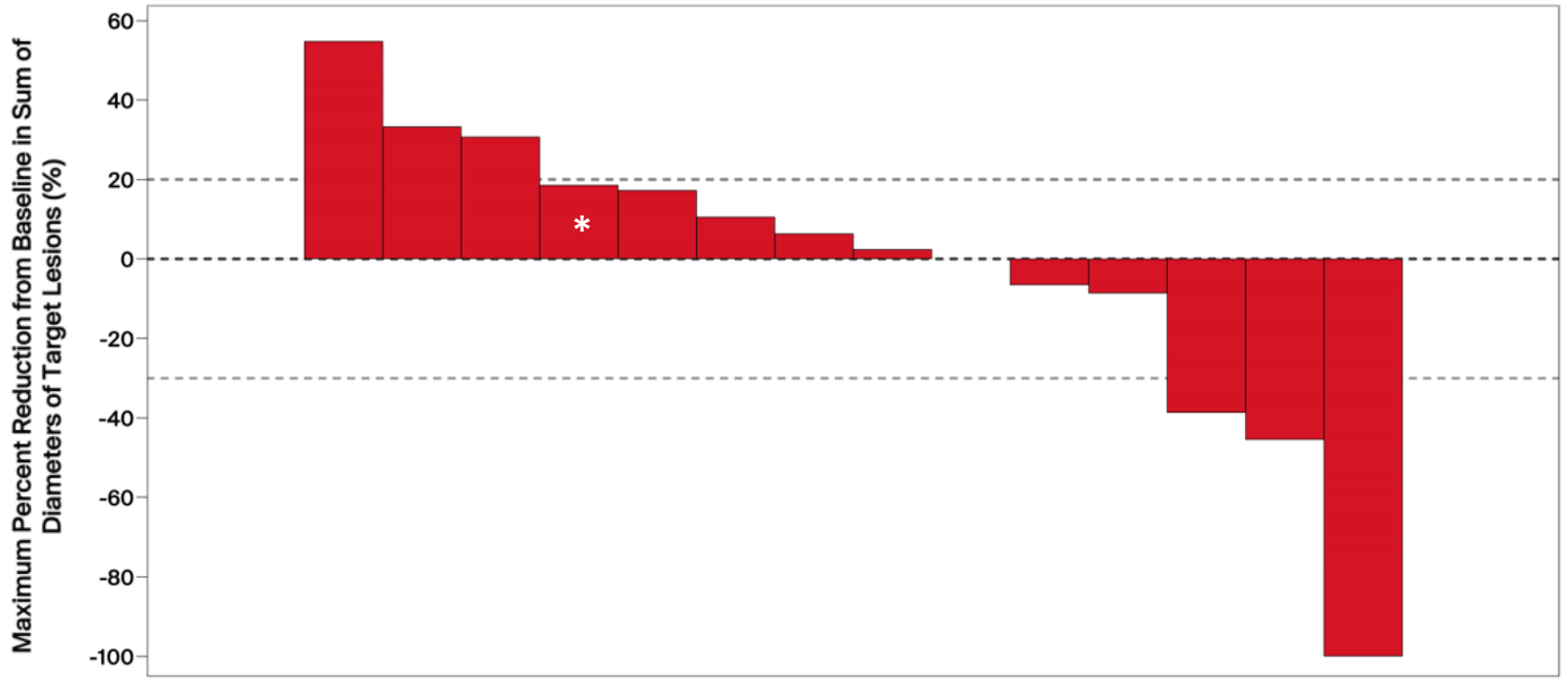
Data as of 16Nov2023.
Responses under response evaluation criteria in solid tumor (RECIST) version 1.1. Includes 2 unconfirmed PR.
C1D1: Cycle 1, Day 1; EV: enfortumab vedotin; mDOR: median duration of response; mUC: metastatic urothelial cancer; QW: weekly.

BT8009 shows promising responses in TNBC

Emerging data (efficacy evaluable patients only)

TNBC (N=15)

ORR: 20% | CBR (CR+PR+SD ≥ 16 weeks): 27% | mDOR: 4.2 months
(includes 1 unconfirmed PR; 1 patient with PR ongoing)



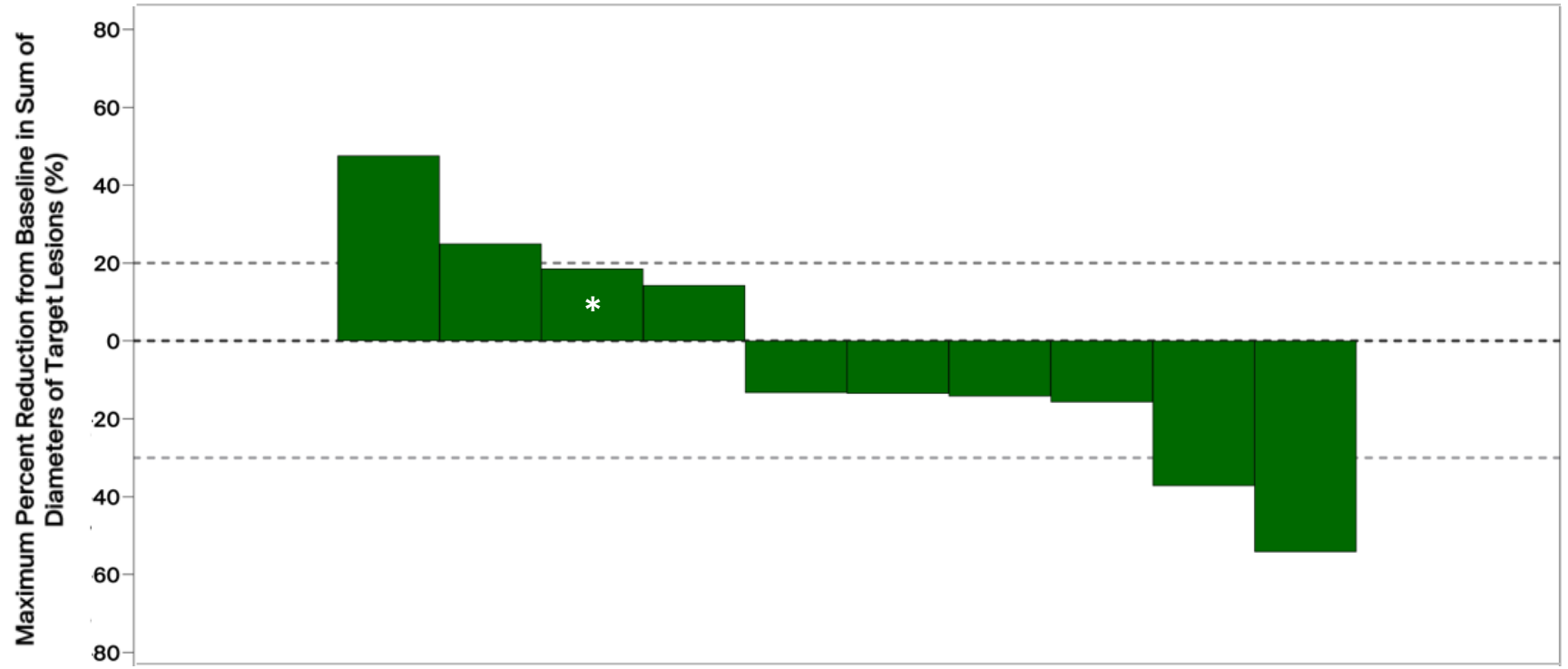
Data as of 16Nov2023.
Efficacy evaluable set is defined as all enrolled patients with measurable disease at baseline who received at least one dose of BT8009 and had at least one adequate post-baseline disease assessment. Responses under response evaluation criteria in solid tumor (RECIST) v1.1. Five patients were excluded due to no post-baseline assessment. All the excluded patients were ongoing except 2 patients. One additional TNBC patient is excluded from the figure as measurement of all target lesions was not performed at the single post-baseline assessment.
*All patients dosed at 5 mg/m^2 QW with exception of those indicated with asterisk.
CBR: clinical benefit rate; CR: complete response; mDOR: median duration of response; ORR: objective response rate; PR: partial response; SD: stable disease; TNBC: triple-negative breast cancer.

BT8009 shows promising responses in ovarian cancer

Emerging data (efficacy evaluable patients only)

Ovarian (N=10)

ORR: 20% | CBR (CR+PR+SD ≥ 16 weeks): 50% | mDOR: 1.8 months
(includes 2 unconfirmed PR)



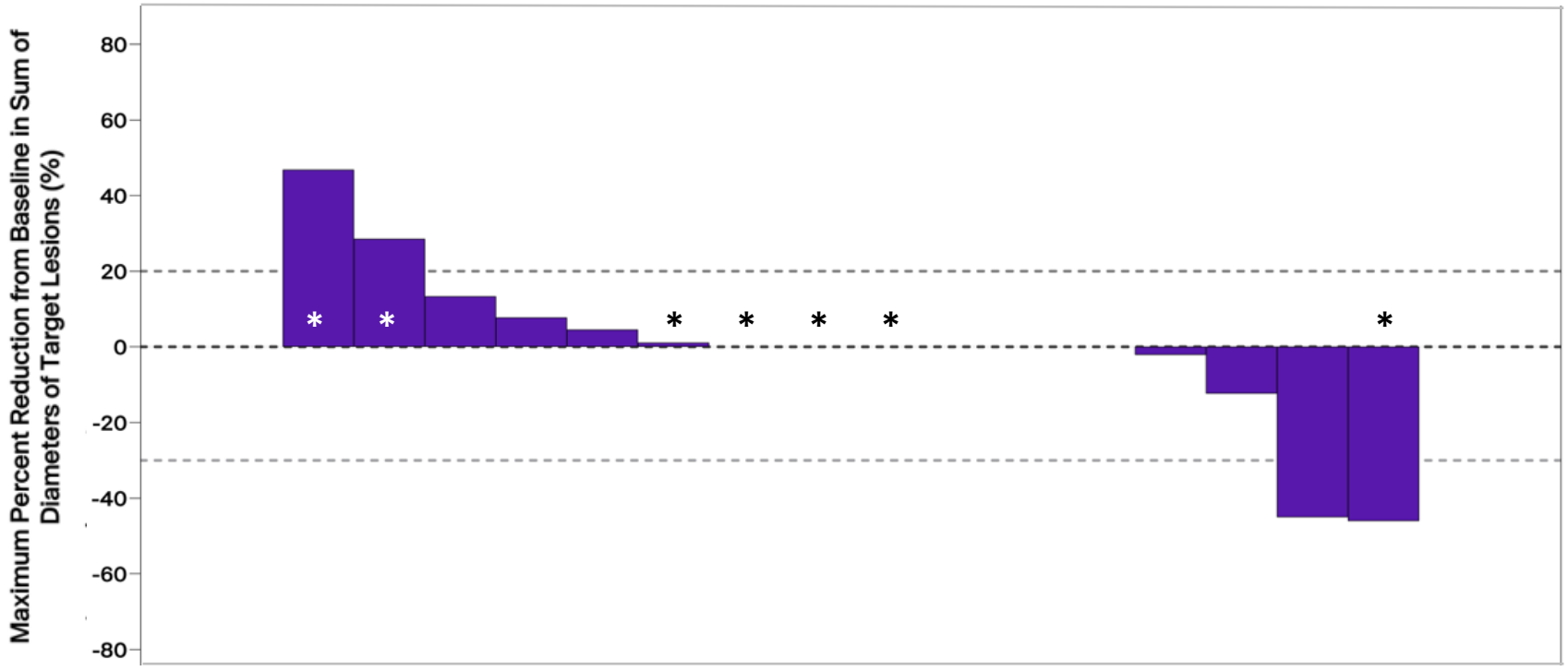
Data as of 16Nov2023.
Efficacy evaluable set is defined as all enrolled patients with measurable disease at baseline who received at least one dose of BT8009 and had at least one adequate post-baseline disease assessment. Responses under response evaluation criteria in solid tumor (RECIST) v1.1. Two patients were excluded from ovarian due to no post-baseline assessment. Neither patient was ongoing at the time off data cut.
*All patients dosed at 5 mg/m^2 QW with exception of those indicated with asterisk.
CBR: clinical benefit rate; CR: complete response; mDOR: median duration of response; ORR: objective response rate; PR: partial response; SD: stable disease.

BT8009 shows promising responses in NSCLC

Emerging data (efficacy evaluable patients only)

NSCLC (N=16)

ORR: 13% | CBR (CR+PR+SD ≥ 16 weeks): 63% | mDOR: 3.4 months
(includes 1 unconfirmed PR)



Data as of 16Nov2023.
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. Responses under response evaluation criteria in solid tumor (RECIST) v1.1. Twelve patients were excluded due to no post-baseline assessment. All but 4 of the excluded patients were ongoing.
*All patients dosed at 5 mg/m^2 QW with exception of those indicated with asterisk.
CBR: clinical benefit rate; CR: complete response; mDOR: median duration of response; NSCLC: non-small cell lung cancer; ORR: objective response rate; PR: partial response; SD: stable disease.

BT8009 overall safety population baseline characteristics

Characteristic	BT8009 5 mg/m^2 QW[a] N=113
Median age, yrs (range)	63 (31-84)
Sex, n (%)	
Male	53 (47)
Female	60 (53)
Race, n (%)	
White	53 (47)
Black or African American	1 (1)
Other[b]	55 (49)
Missing	4 (4)
ECOG, n (%)	
0	40 (35)
1	73 (65)
Median prior lines of therapy (range)	3 (1-11)
Median duration of treatment (range)	8 weeks (1-101)

Data as of 16Nov2023.
[a]Contains data from all patients dosed at Cycle 1 Day 1 with BT8009 5 mg/m^2 QW monotherapy.
[b]Due to French ethics laws, data on race is recorded as Other for patients enrolled in France.
QW: weekly.

BT8009 overall safety and tolerability profile

Event Type	BT8009 5 mg/m^2 QW[a] N=113 n (%)
TEAEs Overall	100 (89)
TEAEs ≥Grade 3	55 (49)
BT8009 Related TEAEs	82 (73)
BT8009 Related TEAEs ≥Grade 3	28 (25)
Any TESAE	36 (32)
BT8009 Related TESAE	14 (12)
TEAEs Leading to BT8009 Dose Modification	64 (57)
TEAEs Leading to BT8009 Dose Reduction	22 (20)
TEAEs Leading to BT8009 Dose Interruption	53 (47)
TEAEs Leading to BT8009 Dose Withdrawn	4 (4)
Median relative dose intensity (%)	90

Data as of 16Nov2023.
[a]Contains data from all patients dosed at Cycle 1 Day 1 with BT8009 5 mg/m^2 QW monotherapy.
QW: weekly; TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse event.

Most BT8009 treatment-related adverse events were GI-related and low grade

Treatment-related Adverse Events in ≥10% Patients by Preferred Term	BT8009 5 mg/m2 QW[a] N=113 n (%)	
	Any Grade	≥Grade 3
Nausea	33 (29)	3 (3)
Fatigue	25 (22)	6 (5)
Diarrhea	23 (20)	1 (1)
Pyrexia	22 (20)	1 (1)
Decreased appetite	16 (14)	2 (2)
Asthenia	15 (13)	6 (5)
Anemia	15 (13)	2 (2)
Alopecia	14 (12)	0
Myalgia	11 (10)	0
Vomiting	11 (10)	2 (2)

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Data as of 16Nov2023.
[a]Contains data from all patients dosed at Cycle 1 Day 1 with BT8009 5 mg/m^2 QW monotherapy.
QW: weekly.

BT8009 treatment-related adverse events of interest were of low frequency and severity

Treatment-related Adverse Events	BT8009 5 mg/m^2 QW[a] N=113 n (%)	
	Any Grade	≥Grade 3
Ocular disorders[b]	6 (5)	0
Peripheral neuropathy[c]	25 (22)	1 (1)
Skin reactions[d]	11 (10)	0
Lab-related		
Hyperglycemia	3 (3)	2 (2)
Neutropenia	10 (9)	6 (5)

Data as of 16Nov2023.
[a]Contains data from all patients dosed at Cycle 1 Day 1 with BT8009 5 mg/m^2 QW monotherapy; [b]Preferred terms defined in Eye Disorder System Organ Class (SOC) used; [c]Peripheral neuropathy SMQ [broad] used; [d]All preferred terms defined in Skin and Subcutaneous Tissue SOC, excluding Alopecia, and SCAR MedDRA SMQ [broad] used, Any Grade: all except two patients (Grade 2) were Grade 1.
Lab-related treatment-related adverse events by Preferred Term.
QW: weekly.

BT8009 treatment-related peripheral neuropathy was low-grade and often reversible

Treatment-related Adverse Events	BT8009 5 mg/m^2 QW[a] N=113 n (%)
Peripheral neuropathy (Any grade)[b]	**25 (22)**
TRAE by PT	
Peripheral sensory neuropathy (Any grade)	**8 (7)**
Grade 1	**6 (5)**
Grade 2	**2 (2)**
Grade ≥3	**0**
Muscular weakness (Any grade)	**1 (1)**

- Median time to onset of peripheral neuropathy was 1.7 months
- Peripheral neuropathy resolved or improved (Grade 1 or better) in 44% patients with a median time of resolution/improvement of 2.6 weeks
- Only 11% of the patients with a history of baseline peripheral neuropathy developed related worsening peripheral neuropathy while on treatment and 2 of 3 cases ended with complete resolution

Data as of 16Nov2023
[a]Contains data from all patients dosed at Cycle 1 Day 1 with BT8009 5 mg/m^2 QW monotherapy.
[b]Peripheral neuropathy SMQ [broad] used.
PT: Preferred Term; QW: weekly; TRAE: treatment-related adverse event.

BT8009 overall safety and tolerability profile in mUC patients

Event Type	EV-naïve mUC BT8009 5 mg/m^2 QW[a] N=34 n (%)
TEAEs Overall	28 (82)
TEAEs ≥Grade 3	16 (47)
BT8009 Related TEAEs	23 (68)
BT8009 Related TEAEs ≥Grade 3	5 (15)
Any TESAE	9 (27)
BT8009 Related TESAE	3 (9)
TEAEs Leading to BT8009 Dose Modification	18 (53)
TEAEs Leading to BT8009 Dose Reduction	7 (21)
TEAEs Leading to BT8009 Dose Interruption	15 (44)
TEAEs Leading to BT8009 Dose Withdrawn	1 (3)
Median relative dose intensity (%)	80

Data as of 16Nov2023.
[a]Contains data from dose escalation and dose expansion.
mUC: metastatic urothelial cancer; QW: weekly; TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse event.

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BT8009 treatment-related adverse events in mUC patients were low, similar to 5 mg/m^2 QW study population

Treatment-related Adverse Events in ≥10% Patients by Preferred Term	EV-naïve mUC BT8009 5 mg/m^2 QW[a] N=34 n (%)	
	Any Grade	≥Grade 3
Nausea	9 (27)	0
Pyrexia	7 (21)	1 (3)
Asthenia	6 (18)	2 (6)
Diarrhea	6 (18)	0
Fatigue	5 (15)	0
Myalgia	5 (15)	0
Decreased appetite	4 (12)	0
Anemia	4 (12)	0
Alopecia	4 (12)	0
Vomiting	4 (12)	0
Neuropathy peripheral	4 (12)	0
Dysgeusia	4 (12)	0

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Data as of 16Nov2023
[a]Contains data from dose escalation and dose expansion
EV: enfortumab vedotin; mUC: metastatic urothelial cancer; QW: weekly.

BT8009 treatment-related adverse events of interest in mUC patients were low, similar to 5mg/m^2 QW study population

Treatment-related Adverse Events	EV-naïve mUC BT8009 5 mg/m^2 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.

BT8009 + pembrolizumab combination: Overall safety profile in 2L+ mUC

Event Type	BT8009 (5 mg/m^2 QW) + pembrolizumab (200 mg Q3W) N=7 n (%)
TEAEs Overall	7 (100)
BT8009 Related TEAEs	6 (86)
Pembrolizumab Related TEAEs	5 (71)
TEAEs ≥Grade 3	5 (71)
BT8009 Related TEAEs ≥Grade 3	2 (29)
Pembrolizumab Related TEAEs ≥Grade 3	1 (14)
Any TESAE	3 (43)
BT8009 Related TESAE	2 (29)
Pembrolizumab Related TESAE	1 (14)
TEAEs Leading to BT8009 Dose Modification	4 (57)
TEAEs Leading to Pembrolizumab Dose Modification	3 (43)
Median prior lines of therapy (range)	4 (1-9)

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Data as of 16Nov2023.
2L+: 2nd line or later; mUC: metastatic urothelial cancer; QW: weekly; Q3W: once every 3 weeks; TEAE: treatment-emergent adverse events; TESAE: treatment-emergent serious adverse event.

BT8009 + pembrolizumab combination shows limited severe treatment-related adverse events in 2L+ mUC

Treatment-related Adverse Events by Preferred Term in ≥2 Patients	BT8009 (5 mg/m^2 QW) + pembrolizumab (200 mg Q3W) N=7 n (%)	
	Any Grade	≥Grade 3
Nausea	4 (57)	0
Diarrhea	4 (57)	0
Fatigue	3 (43)	0
Vomiting	3 (43)	0
Abdominal pain	2 (29)	0
Neuropathy peripheral	2 (29)	0
Decreased appetite	2 (29)	0
Hyponatremia	2 (29)	1 (14)
Anemia	2 (29)	1 (14)

Bicycle®

Data as of 16Nov2023.
2L+: 2nd line or later; mUC: metastatic urothelial cancer; QW: weekly; Q3W: once every 3 weeks.

BT8009 + pembrolizumab combination shows limited severe treatment-related adverse events of interest in 2L+ mUC

Treatment-related Adverse Events	BT8009 (5 mg/m^2 QW) + pembrolizumab (200 mg Q3W) N=7 n (%)	
	Any Grade	≥Grade 3
Ocular disorders[a]	1 (14)	0
Peripheral neuropathy[b]	2 (29)	0
Skin reactions[c]	1 (14)	0
Lab-related		
Hyperglycemia	0	0
Neutropenia	1 (14)	1 (14)

Data as of 16Nov2023.
[a]Preferred terms defined in Eye Disorder System Organ Class (SOC) used, Any Grade: Grade 1; [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.
Lab-related treatment-related adverse events by Preferred Term.
2L+: 2nd line or later; mUC: metastatic urothelial cancer; QW: weekly; Q3W: once every 3 weeks.

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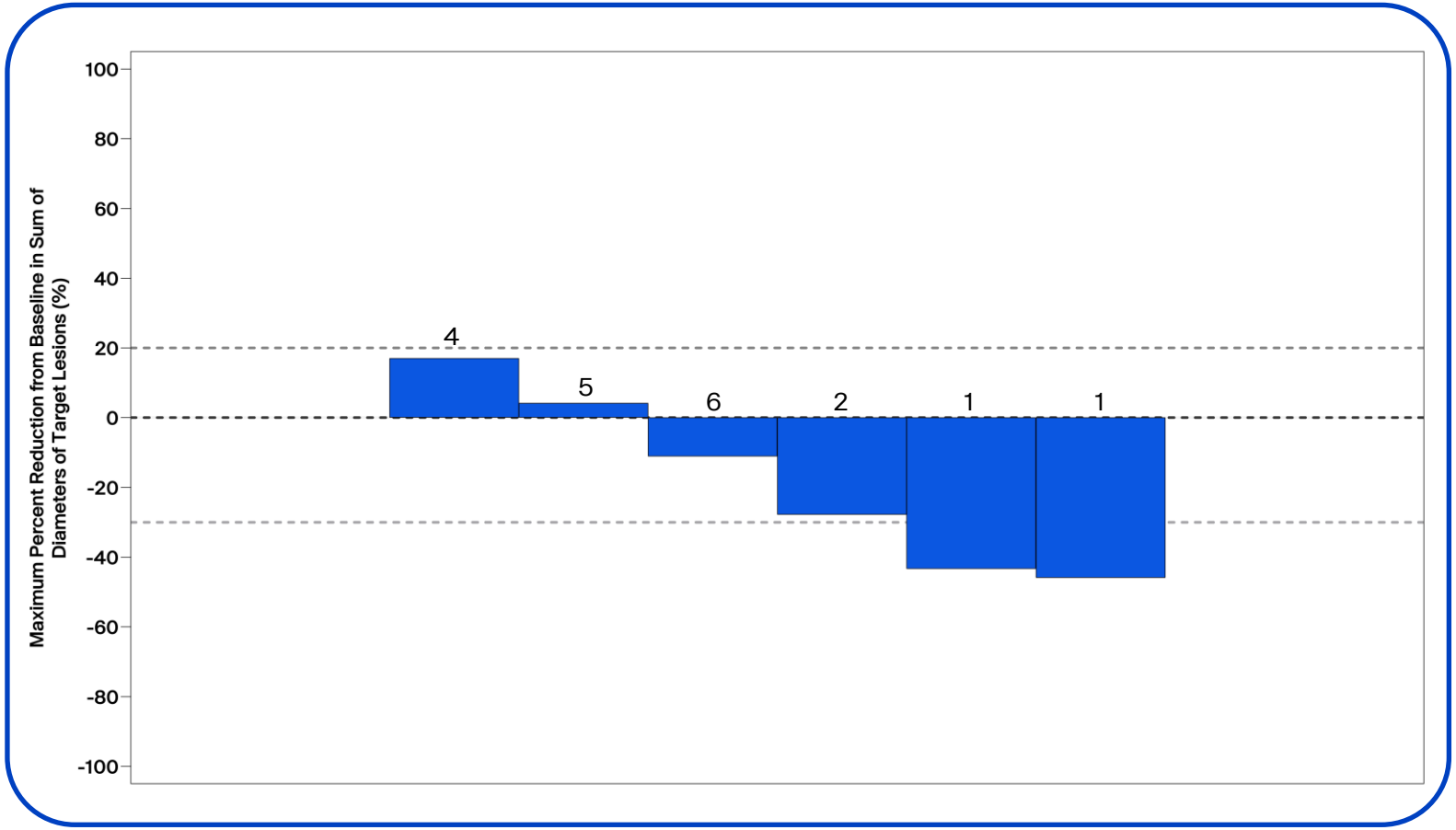
BT8009 + pembrolizumab combination response data in 2L+ mUC

Emerging data (efficacy evaluable patients only)

In 6 evaluable patients:

- 2 patients responded, both had 1 prior line of therapy
  - Both were previously treated with platinum chemotherapy[a]
  - 1 patient was previously treated with a checkpoint inhibitor
- 1 patient had stable disease (-28%) and had received 2 prior lines of therapy
- The remaining had stable disease and had received 4-6 prior lines of therapy



Data as of 16Nov2023

[a]One patient received platinum chemotherapy in the neoadjuvant setting.

Efficacy evaluable set is used which is defined as all enrolled patients with measurable disease at baseline who received at least one dose of BT8009 and had at least one adequate post-baseline disease assessment. One patient was excluded due to no post-baseline assessment.

Number of prior lines of therapy listed for each patient.

Responses under response evaluation criteria in solid tumor (RECIST) v1.1. Confirmation of objective tumor response is not required for this summary presentation.

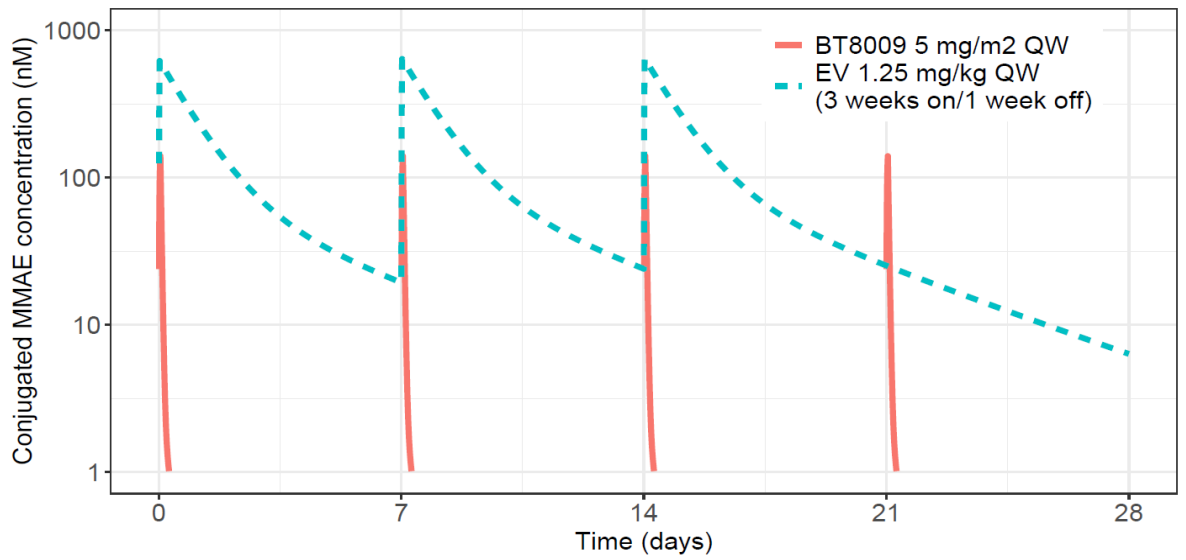
Includes 1 PR that was confirmed after the data cut date.

2L+: 2nd line or later; mUC: metastatic urothelial cancer

BT8009 demonstrates a unique PK profile which may contribute to its emerging differentiated safety profile

- BT8009 is rapidly cleared from circulation and is not likely to have broad nonspecific tissue distribution
- No dose adjustment needed for patients with renal impairment (CrCL > 30 mL/min) compared to normal
- PK modelling and simulation demonstrates that:
  - BT8009 exposure (AUC in Cycle 1) is substantially lower than enfortumab vedotin (EV)
  - Unconjugated MMAE exposure for BT8009 (AUC in Cycle 1) is ~25% higher than EV

Parent molecule PK profiles



PK profiles of a typical subject simulated from population PK models of BT8009 and enfortumab vedotin (EV).
BT8009 population PK based on BT8009-100 2023-10-30 data cut; EV is simulated from population PK model reconstructed from BLA dossier (https://www.ema.europa.eu/en/documents/assessment-report/padcev-epar-public-assessment-report_en.pdf; https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761137Orig1s000MultiDisciplineR.pdf).
AUC: area under the concentration-time curve; CrCL: creatinine clearance; EV: enfortumab vedotin; PK: pharmacokinetic; QW: weekly.

Duravelo-1 key takeaways

In an ongoing Phase 1/2 study involving heavily pre-treated patients, BT8009 shows:

- An emerging differentiated safety profile
- A promising response profile at 5 mg/m^2 QW
  - ORR of 38%
  - mDOR of 11.1 months
- Encouraging initial data in other tumors (ovarian, TNBC and NSCLC) that supports expansion beyond mUC
- Acceptable tolerability in combination with pembrolizumab

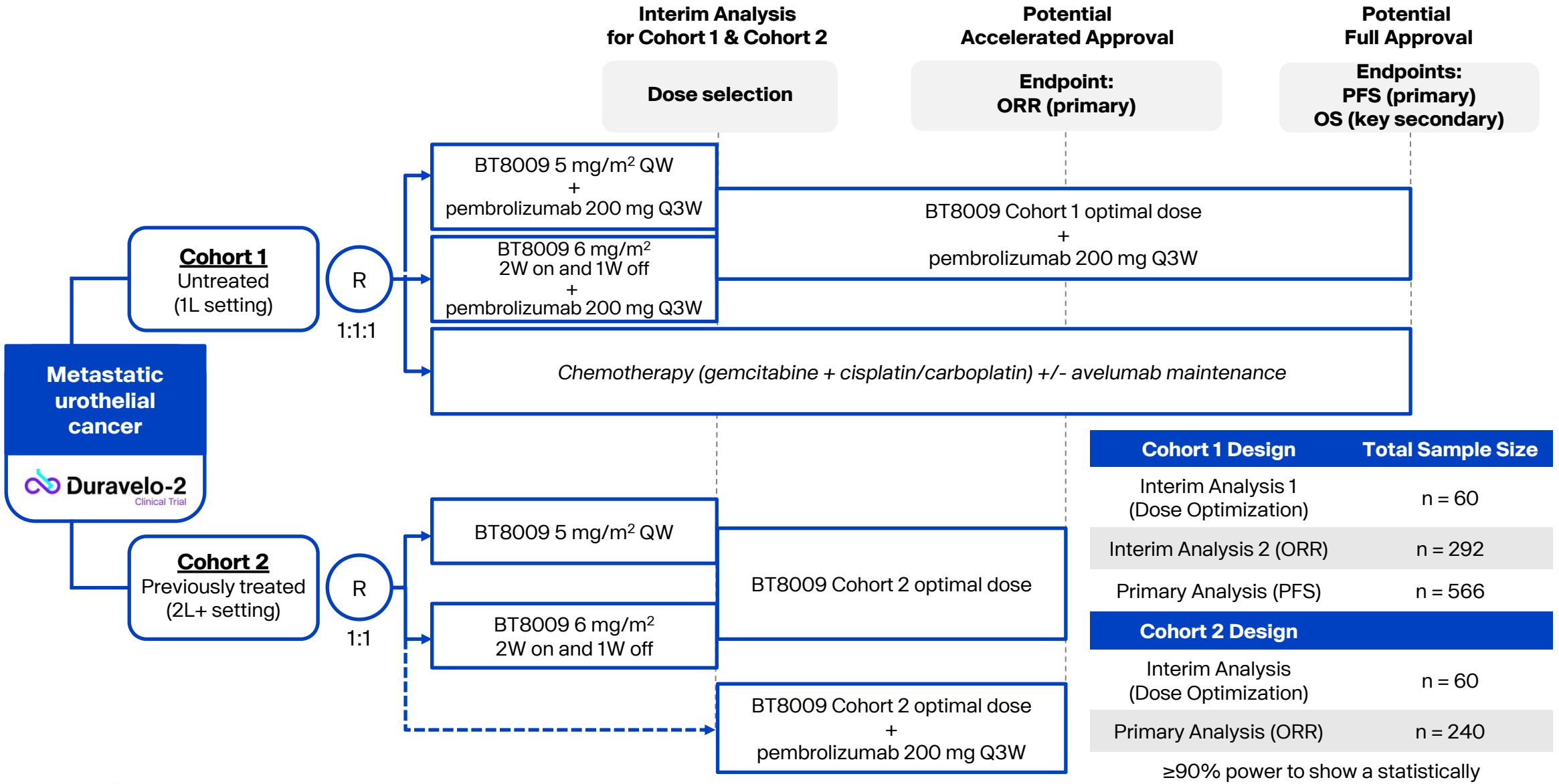
mDOR: median duration of response; mUC: metastatic urothelial cancer; NSCLC: non-small cell lung cancer; ORR: objective response rate; QW: weekly; TNBC: triple-negative breast cancer.

We had numerous positive and collaborative interactions with the FDA this year

- Fast Track designation granted for BT8009 for treatment of adult patients with previously treated locally advanced or metastatic urothelial cancer
- FDA meetings to discuss Duravelo-2 clinical trial:
  - Alignment on overall design, populations and endpoints consistent with Project FrontRunner initiative and Draft Guidance on Clinical Trial Considerations to Support Accelerated Approval of Oncology Therapeutics
  - FDA considered that the active control chemotherapy + avelumab arm is appropriate and reflects current standard of care
  - FDA may consider accelerated approval for both 1L and 2L+ on the basis of overall clinical benefit/risk
  - Alignment on doses to be tested in the study
- Acceptance into CMC Development and Readiness Pilot (CDRP) Program

1L: 1st line; 2L+: 2nd line or later; CMC: Chemistry, Manufacturing and Controls.

Innovative 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®, has significant potential for the treatment of 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
- FDA alignment on Duravelo-2 pivotal study design in mUC, which is scheduled to commence in 1Q 2024
- Intent to pursue options for accelerated approval in other indications

NEXT STEPS

- **Expect to start Duravelo-2 in 1Q 2024**
- **Expect to receive complete data sets from ongoing open-label expansion cohorts in 2H 2024**
  - BT8009 monotherapy in LL mUC
  - BT8009 + pembrolizumab in 1L mUC
  - BT8009 monotherapy in ovarian, TNBC, NSCLC
- **Expect to start expansion study in combination with checkpoint inhibitors in TNBC and NSCLC in 2024**

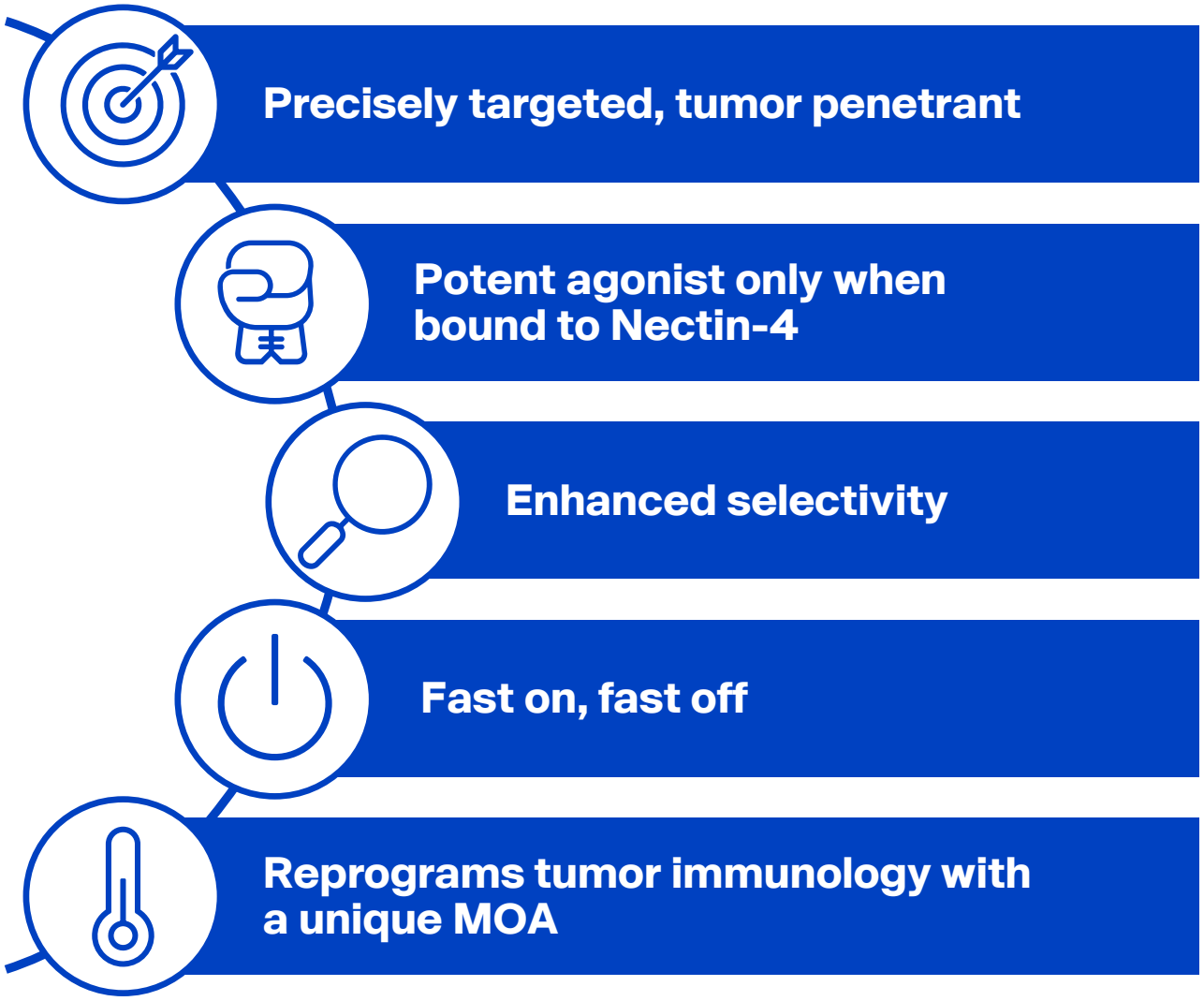
1L: 1st line; LL: late-line; mUC: metastatic urothelial cancer; NSCLC: non-small cell lung cancer; TNBC: triple-negative breast cancer.

BT7480, a first-in-class Bicycle TICA®

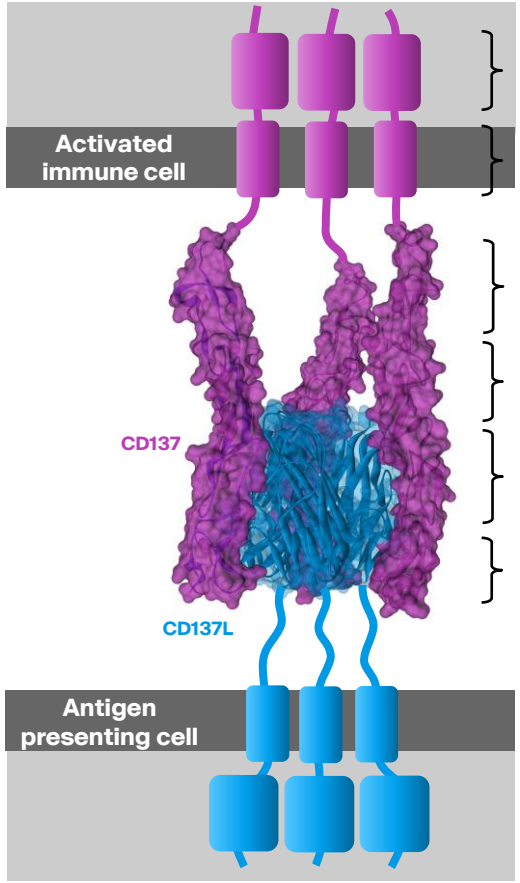
Bicycle®

BT7480, a first-in-class, highly differentiated immune agonist targeting Nectin-4 expressing tumors

- CD137 provides a powerful co-stimulatory signal to not just **T cells**, but also **dendritic** and **NK** cells
- CD137 agonism can induce anti-tumor responses – **but is toxic when engaged systemically**
- **Offers an alternative way** to target Nectin-4 expressing tumors

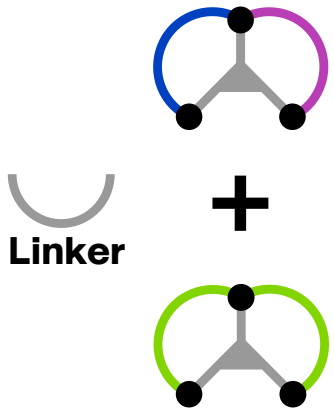


Bicycle TICA®: Tumor Targeted Immune Cell Agonists join immune cell and tumor targeting Bicycle® molecules



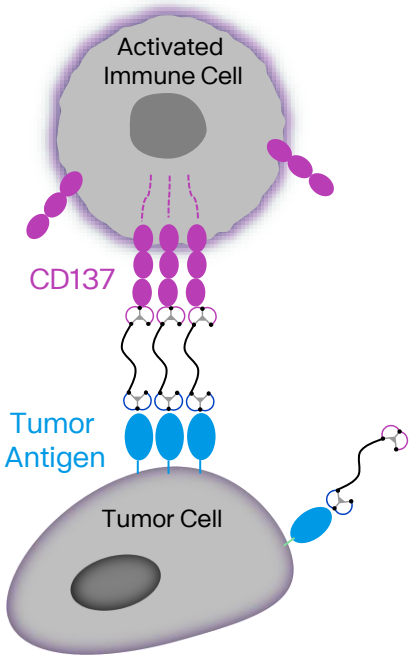
Activation induced by clustering of **CD137** by trimeric **CD137L**

CD137-engaging Bicycle® molecule



Tumor-targeting Bicycle® molecule

Tumor Target/CD137 Bicycle TICA®

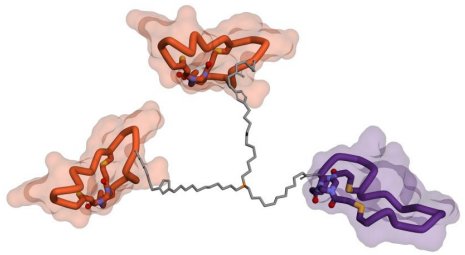


CD137 clustering induced by tumor antigen

BT7480 is a fully synthetic context-dependent CD137 agonist

Small

Bicycle TICA®
BT7480

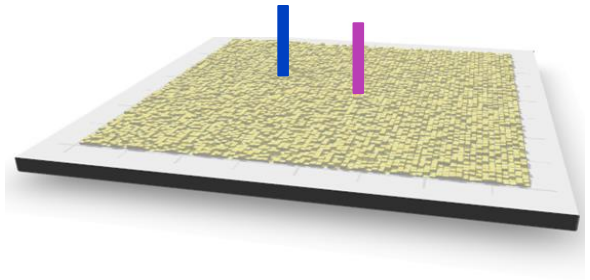


7.2 kDa

~30x smaller than other targeted agonists

Selective

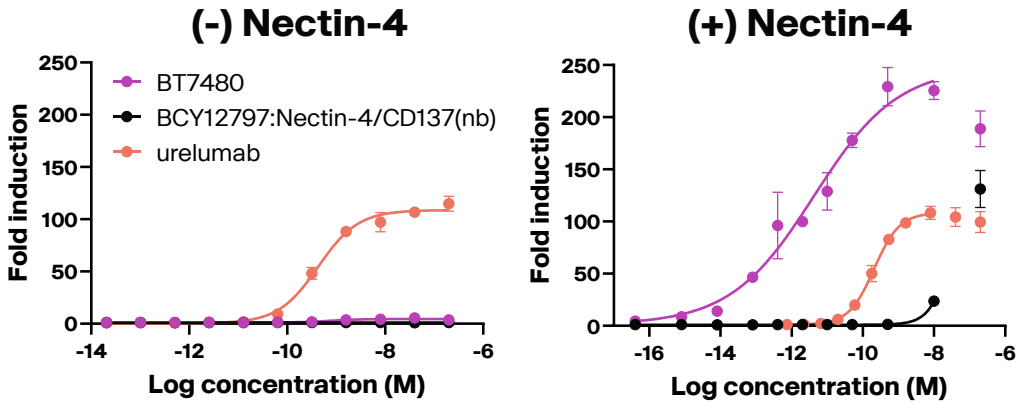
BT7480 only binds Nectin-4 and CD137



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

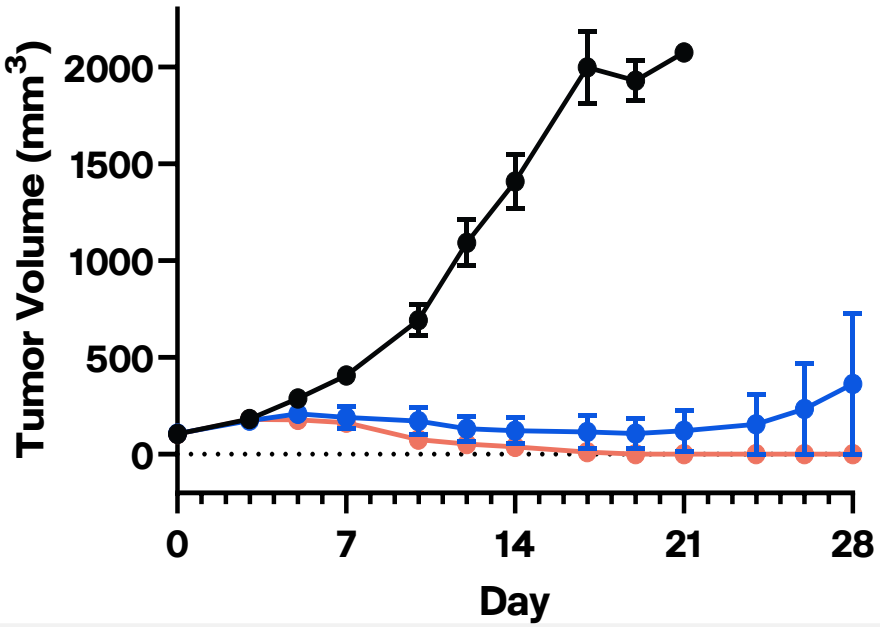
BT7480 is well-tolerated in preclinical species, with no evidence of liver effects

Bicycle®

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

BT7480 induces complete responses and memory *in vivo*

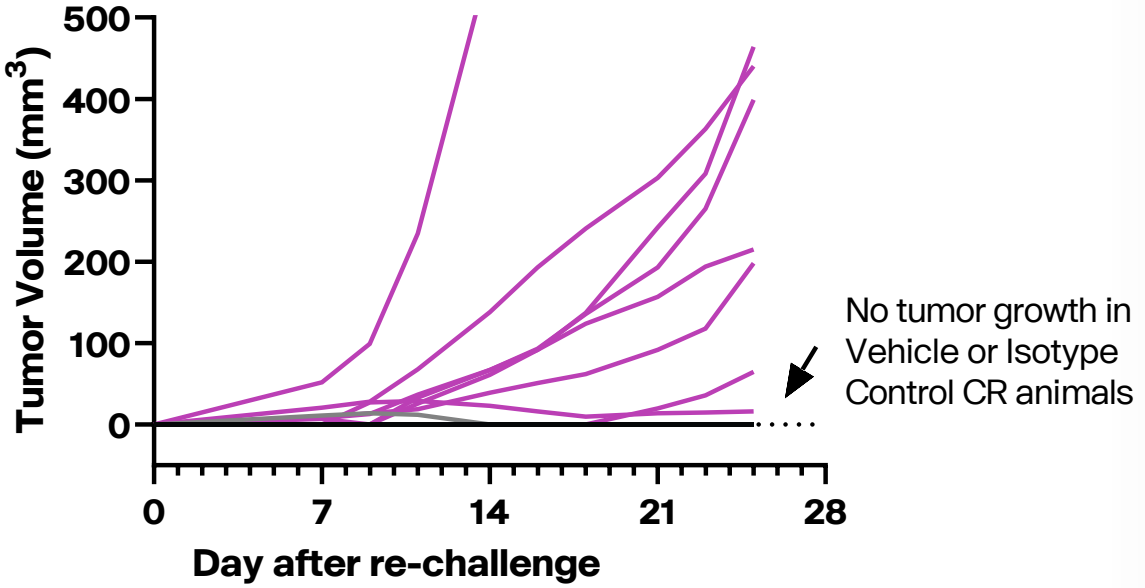
Anti-tumor activity of BT7480 in mouse model



- Vehicle (0/6 CRs)
- BT7480 5 mg/kg BIW (6/6 CRs)
- BT7480 1.5 mg/kg BIW (5/6 CRs)

Day 59

BT7480 treatment led to rejection of tumor re-challenge in CR animals



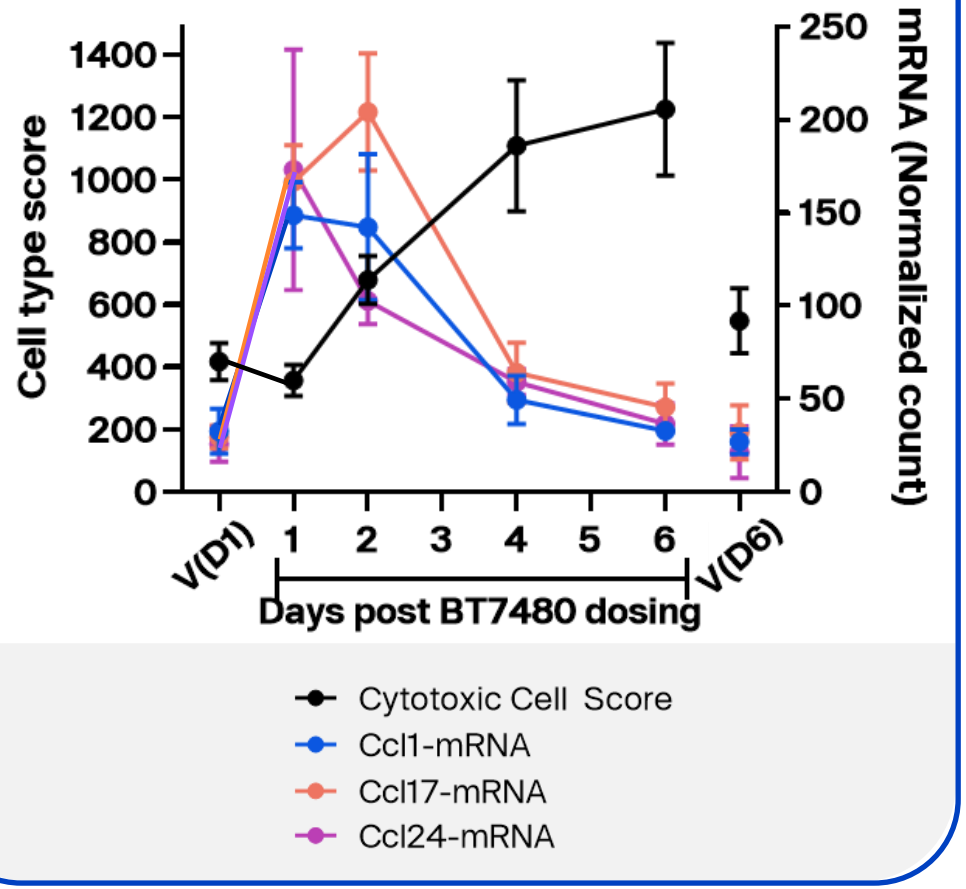
- CRs Vehicle (n=7)
- CRs Isotype Control (n=7)
- CRs with CD8 depletion (n=10)

MC38-Nectin-4 tumor growth in huCD137 C57Bl/6 mice with twice a week dosing of BT7480, and then upon re-challenge 59 days after dosing initiation. CR mice were treated with a depleting anti-mouse CD8a antibody or an isotype control antibody 5 days prior to tumor re-challenge. Hurov K et al. 2021. *J Immunother Cancer,* 9(11):e002883.
BIW: twice a week; CR: complete responder.

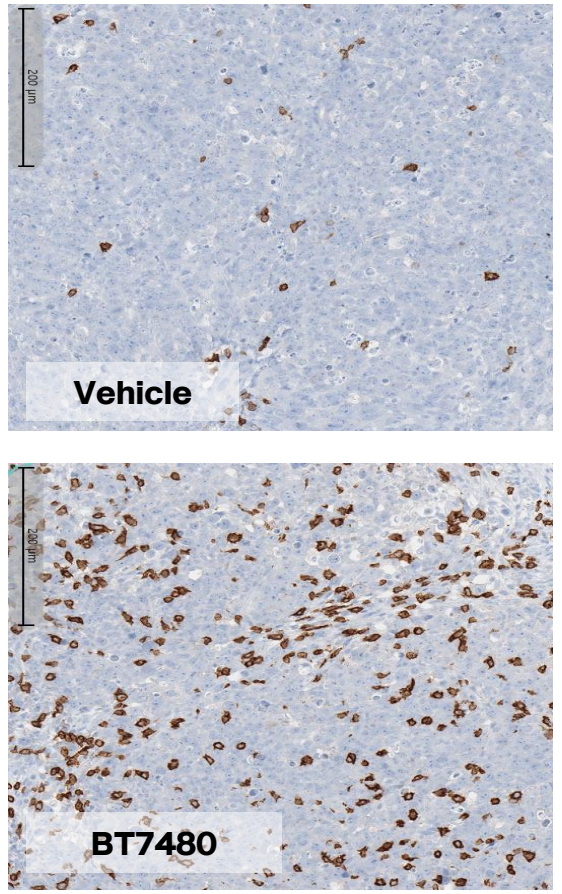
Bicycle TICAs have a unique mechanism of action, different from, and complementary to that of current checkpoint inhibitors

- 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

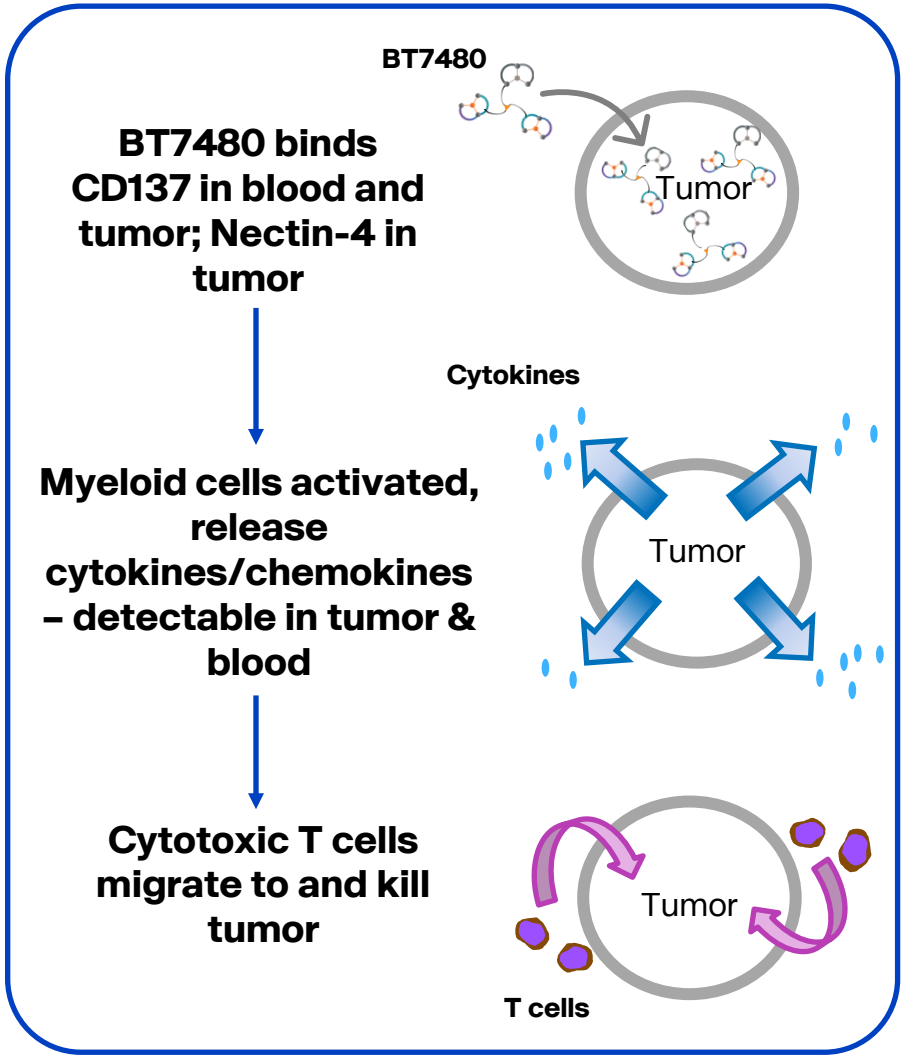


CD8+ T cells on Day 6



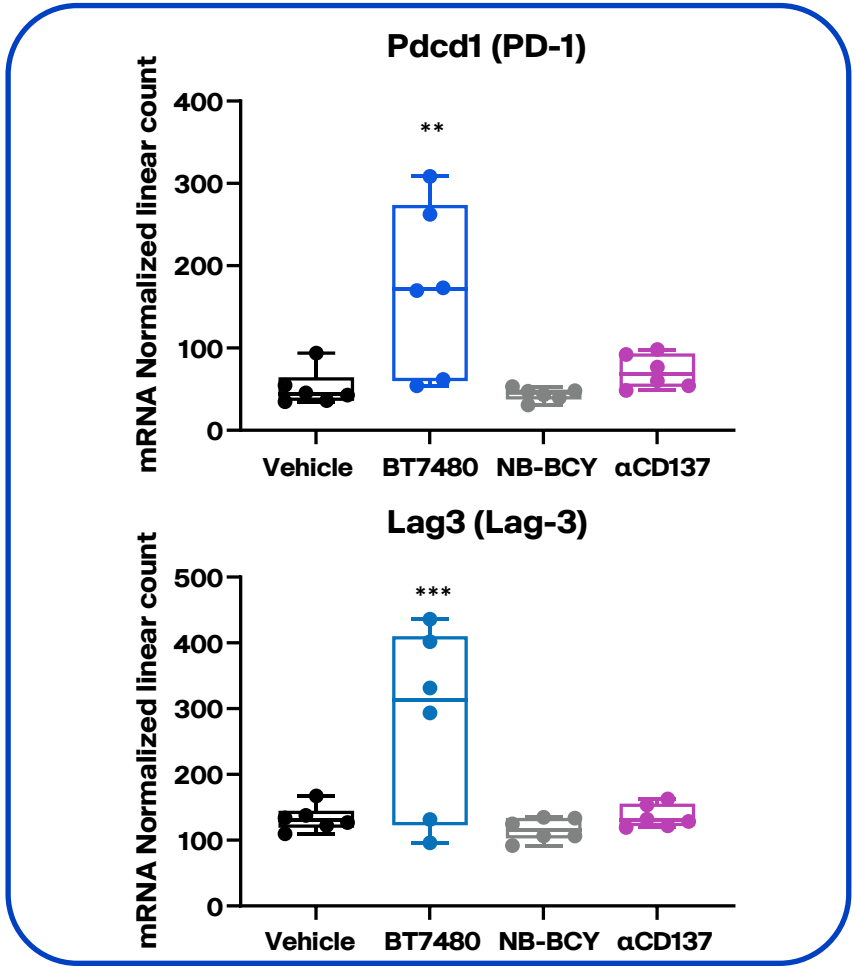
MC38-Nectin-4 tumor bearing huCD137 C57Bl/6 mice were dosed with BT7480, and then transcriptionally profiled.
Hurov K et al. 2021. *J Immunother Cancer*, 9(11):e002883.

BT7480 is a unique molecule with a unique mechanism revealed in mouse models



- Key cytokines/chemokines induced include **CXCL9 (a predictor of PD1 response),** CXCL10, CCL22, CCL24
- Our clinical biomarker strategy includes monitoring cytokines/chemokine levels and cell populations within patient tumors and in blood
- **The "pulse" does not require resident CD8+ T cells**
- Key cell populations identified as the likely source of this signal include key dendritic cell subtypes
- **This may set up an ideal microenvironment for checkpoint combination (including "newer" checkpoints such as LAG3)**

BT7480's unique mechanism leads to increased immune checkpoint gene expression in mouse models



MC38-Nectin-4 bearing huCD137-C57Bl/6 mice administered with BT7480 or controls, and transcriptionally analyzed 6 days after administration initiation. NB-BCY: non-binding Bicycle TICA®.[1]

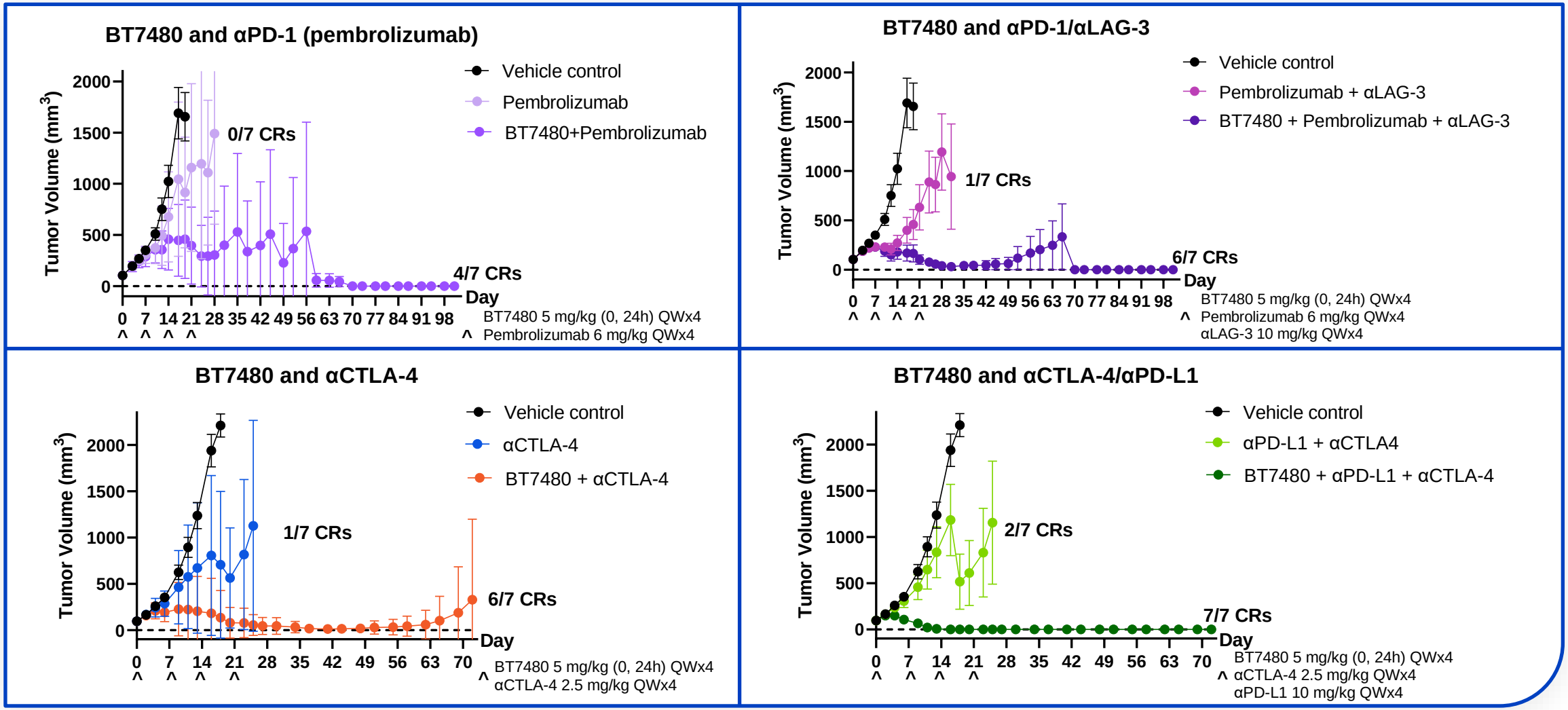
Gene	CD137 mAb (urelumab analog)	BT7480
PD-1	✗	✓
CTLA-4	✗	✓
LAG-3	✗	✓
TIGIT	✗	✓
CXCL9	✗	✓

Significantly ($p<0.05$, one-way ANOVA with Dunnett's post-test, compared to vehicle) increased mRNA levels in MC38-Nectin-4 bearing huCD137-C57Bl/6 mice 6 days after BT7480 or CD137 mAb administration.[1]

Published work indicates upregulated CXCL9 is a strong predictor of checkpoint inhibitor response across many tumor types.[2]

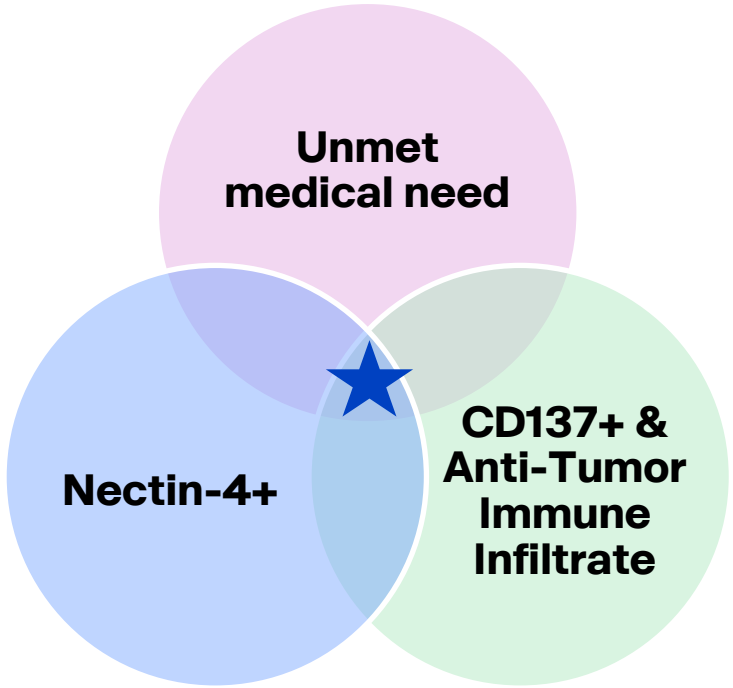
1. Hurov K et al. 2021. *J Immunother Cancer,* 9(11):e002883. 2. Litchfield K et al. 2021. *Cell,* 184(3):596-614.

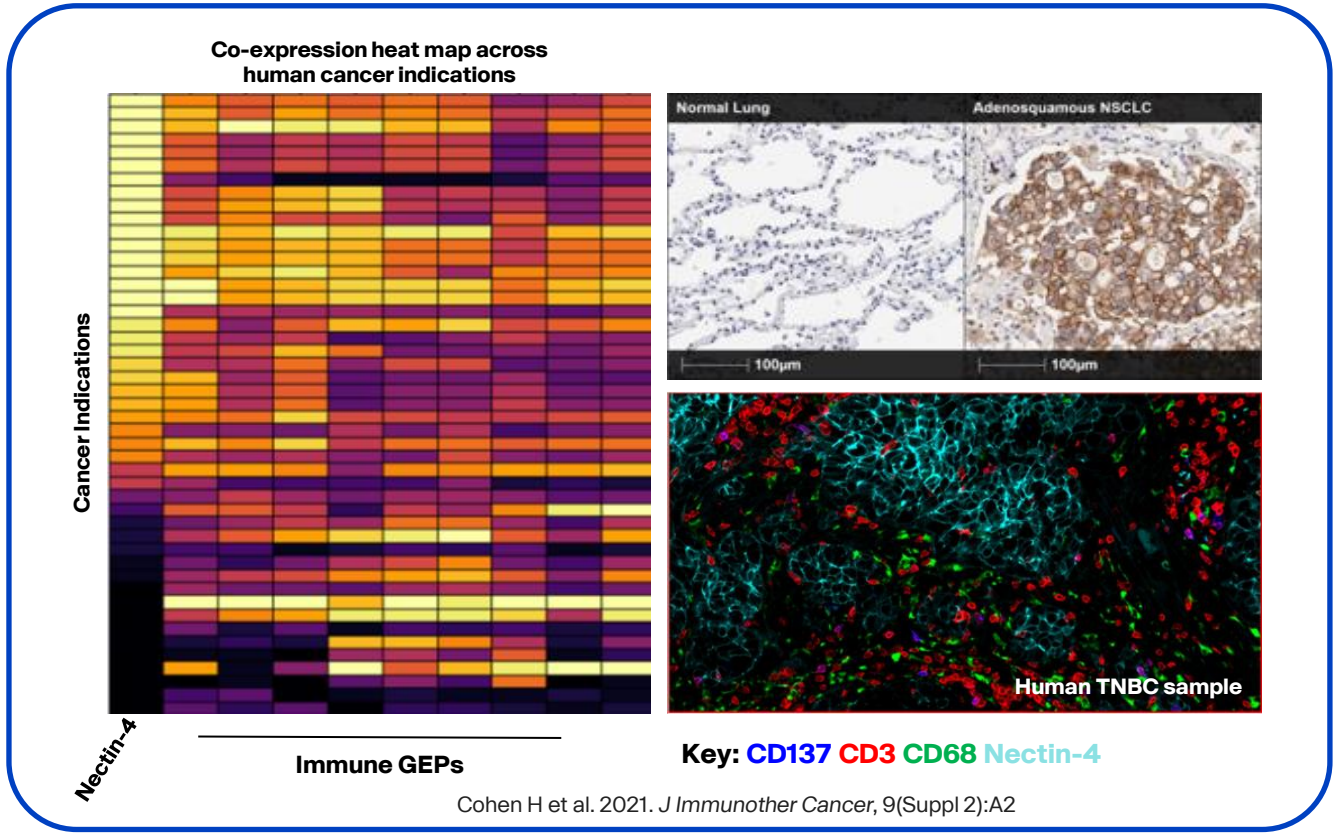
Rational combination of BT7480 and checkpoint inhibitors show remarkable activity in mouse models



MC38-Nectin-4 tumor volume in huCD137/(huPD-1)/C57Bl/6 mice was measured following administration with BT7480 +/- checkpoint inhibitor.
Bicycle Therapeutics unpublished data.
CR: complete response; QW: weekly.

BT7480 could broaden the opportunity to address Nectin-4 expressing tumors





Cohen H et al. 2021. *J Immunother Cancer*, 9(Suppl 2):A2

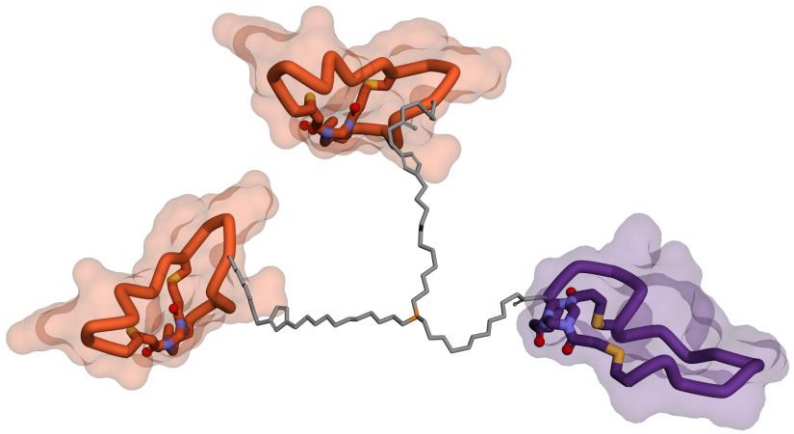
- Top indications that may benefit from BT7480 treatment include **NSCLC, cervical, head & neck, bladder, ovarian and breast cancers**
- BT7480 only requires low levels of Nectin-4 on tumor cells for activity

Bicycle®

GEP: gene expression profile; NSCLC: non-small cell lung cancer; TNBC: triple-negative breast cancer.

BT7480, a novel molecule with a new mechanism of action

Bicycle TICA®
BT7480



7.2 kDa

- BT7480 is a **first-in-class, novel, Nectin-4 dependent** CD137 agonist
- It has a **unique mechanism of action**, distinct from that reported for other CD137 agonists or checkpoint molecules
  - Induces signaling from tumor resident immune cells, and does not require resident CD8+ T cells for this
- **Monotherapy activity** in preclinical systems with intermittent dosing and excellent combination data
- Remarkable **selectivity** and well-tolerated in preclinical species
- Fully synthetic; far **smaller** and more efficient than comparators

BT7480 Phase 1 clinical trial update

Bicycle®

Approach to BT7480 clinical development

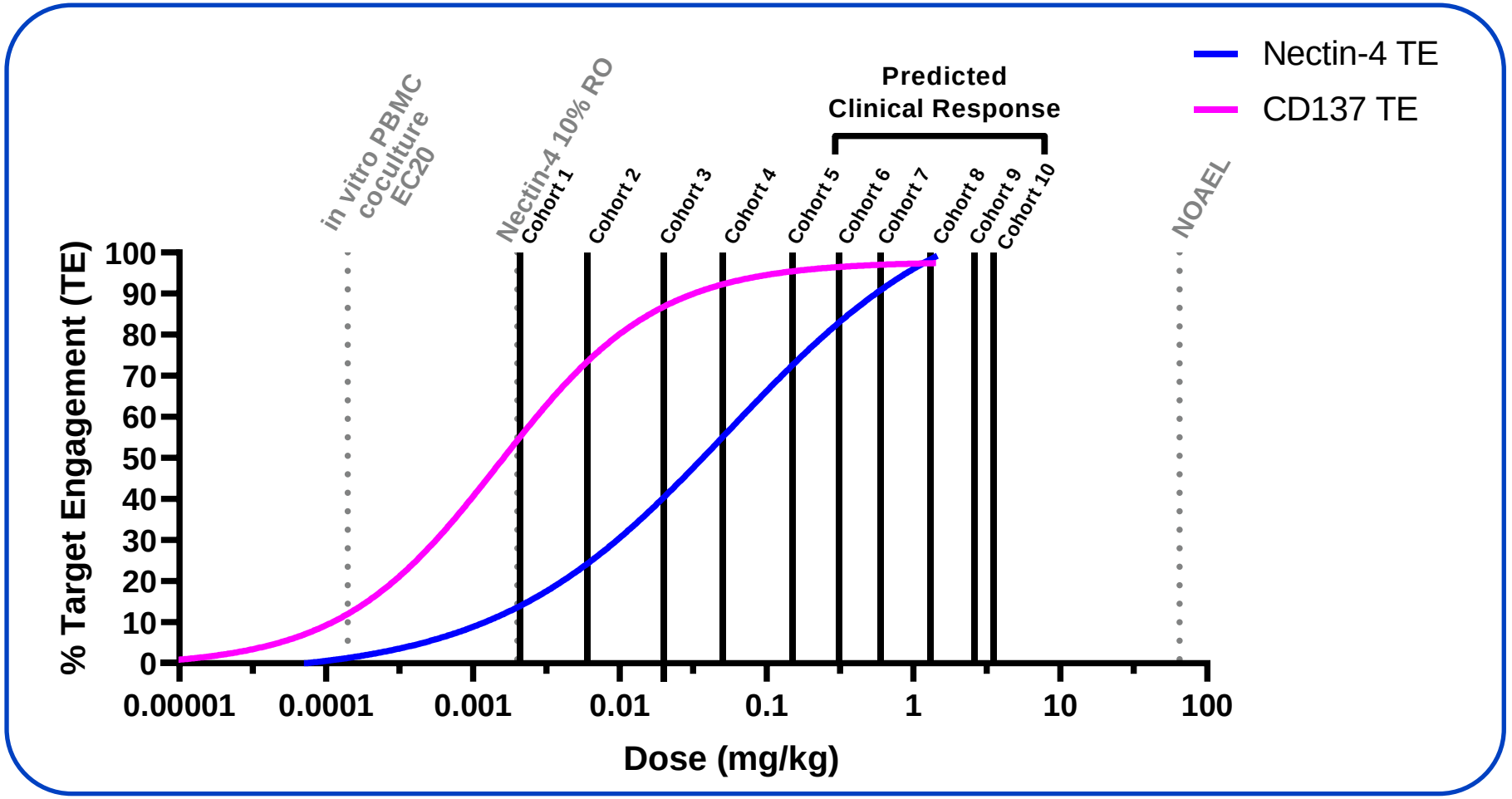
- **CD137 agonists have had a checkered history**
  - First-generation CD137 agonists (non-tumor targeted monoclonal Abs) experienced dose-limiting hepatic toxicity (urelumab) or limited efficacy (utomilumab)
  - Recent strategies focused on next-generation CD137 monoclonal and bispecific antibody agonists

- **BT7480 initial development was guided by safety considerations, the novelty of our Bicycle® technology and FDA's Project Optimus guidance**
  - Dose escalation was cautious, with initial doses believed to be minimally pharmacologically active
  - Assessment of dose response aided by predictive biomarkers (target engagement and immune activation biomarkers)

- **As we have approached the zone for predicted activity, we have expanded some cohorts to obtain additional biomarker information**

1. Etxeberria I et al. 2020. *ESMO Open,* 4(Suppl 3):e000733. 2. Chester C et al. 2018. *Blood*, 131(1):49-57. 3. Segal NH et al. 2017. *Clin Cancer Res*, 23(8):1929-1936.

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 Overall safety data: low number of related TEAEs and ≥Grade 3 TEAEs

Safety summary: Cohorts 1-9 (0.002-2.6 mg/kg QW) N=33 n (%)		
Event Type	**Overall**	**Related**
TEAEs	**31 (94)**	**14 (42)**
TEAEs ≥Grade 3	**12 (36)**	**2 (6)**
SAEs	**11 (33)**	**2 (6)**
Dose Modifications		
TEAEs leading to Interruptions	**5 (15)**	
TEAEs leading to Reductions	**0**	
TEAEs leading to Discontinuation	**1 (3)**	

No AESI reported

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Data as of 25Sep2023.
AESI: adverse events of special interest; QW: weekly; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

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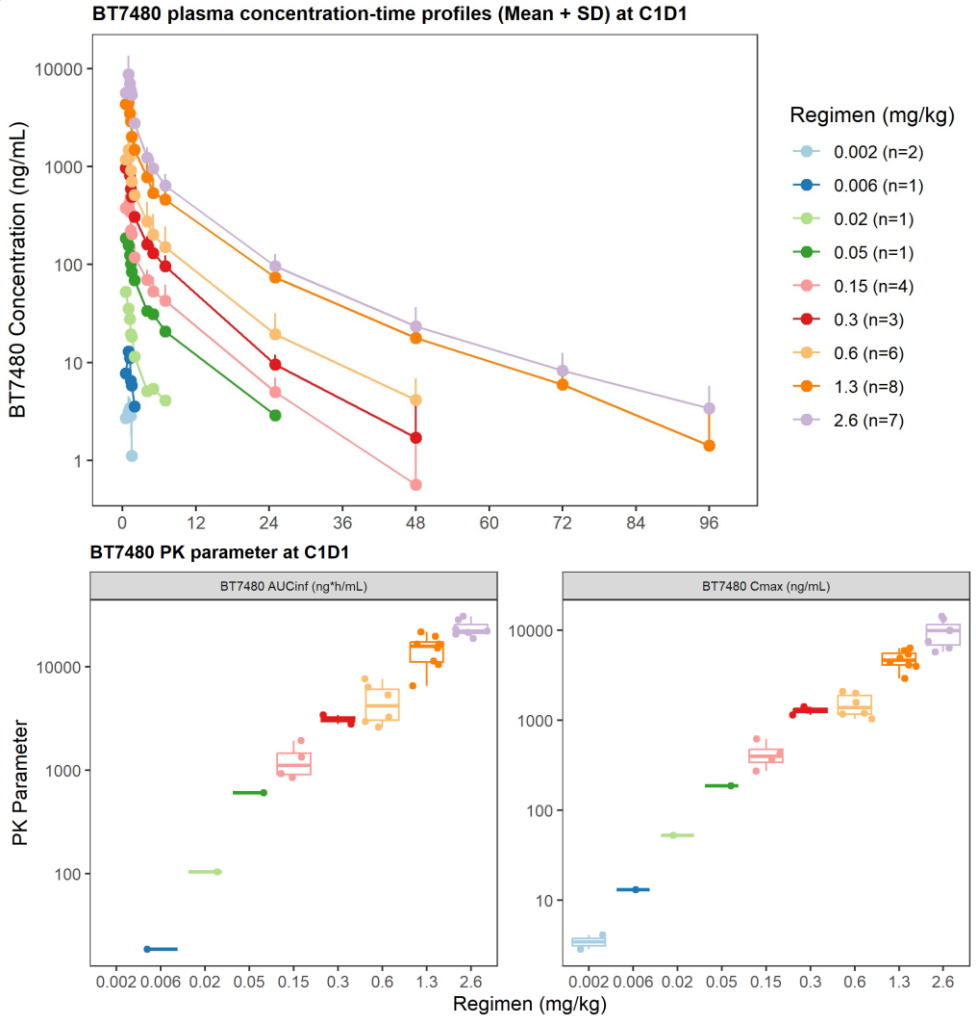
Data as of 25Sep2023.
QW: weekly; TEAE: treatment-emergent adverse event.

BT7480 clinical PK profile has been consistent and predictable across dose escalation

- Preliminary BT7480 PK appears dose proportional — indicating exposures are increasing consistently with dose escalation
- Between subject PK variability is moderate
- The vast majority of BT7480 exposures are eliminated over a t1/2 of ~6-17 hours
- No/limited accumulation after once weekly dosing



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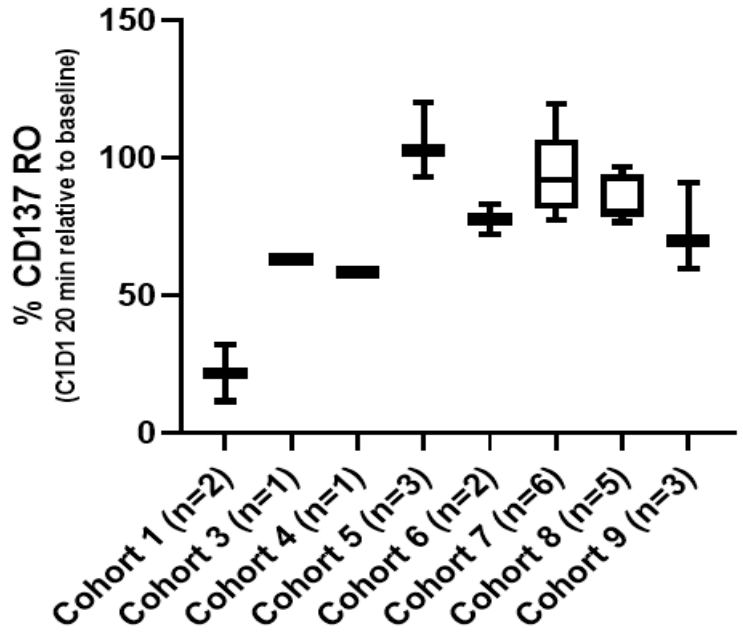
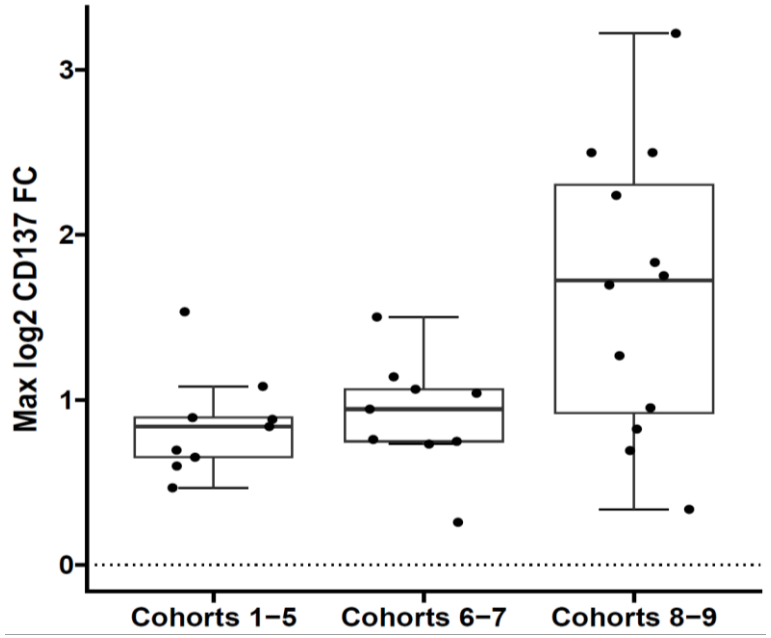
Bicycle Therapeutics unpublished data.
C1D1: Cycle 1 Day 1; PK: pharmacokinetic; SD: standard deviation; t1/2: half-life.

BT7480 demonstrates full target engagement in patient blood samples at doses ≥0.15 mg/kg

CD137 Target engagement saturated in blood in Cohorts 5 and above



sCD137 induction

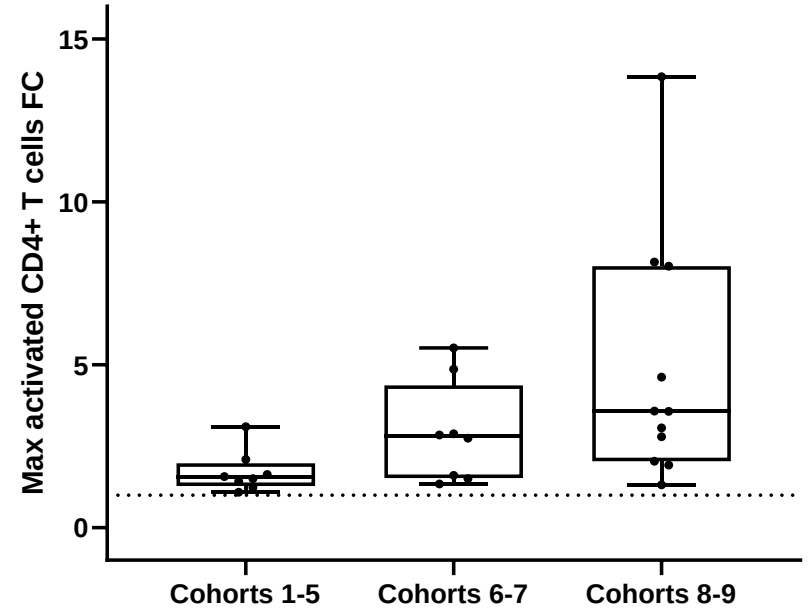


Soluble CD137 induction following BT7480 indicates downstream biological effect from target engagement and shows dose response

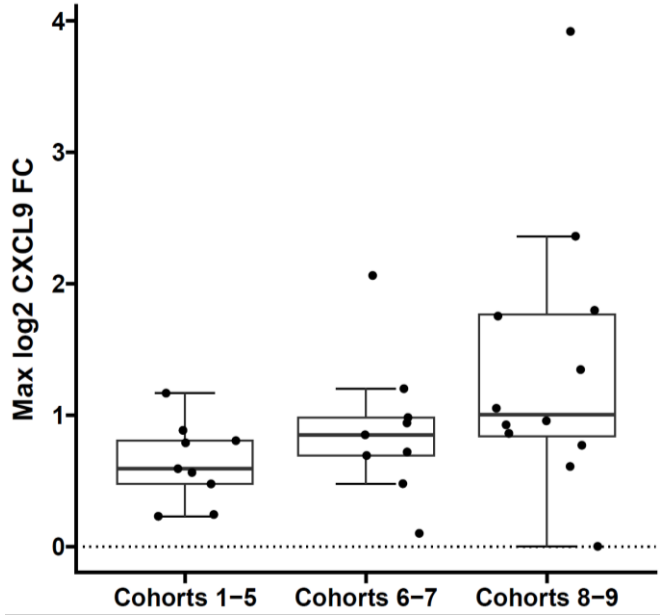
Exploratory analysis (Data as of 28Sep2023)
Bicycle Therapeutics unpublished data.
C1D1: Cycle 1 Day 1; FC: fold-change; RO: receptor occupancy.

BT7480 demonstrates robust blood PD signals at doses ≥0.3 mg/kg in possible association with clinical benefit

CD4+ T cell activation



CXCL9 induction



Dose-dependent increase in circulating activated CD4+ T cells and CXCL9 following BT7480. All patients in Cohorts 6-9 had either CXCL9 and CD4+ T cell activation, majority had increase in both.

Exploratory analysis (Data as of 28Sep2023)
Max PD signal: fold-change relative to baseline; Dashed line: fold-change relative to baseline=2 (left).
Bicycle Therapeutics unpublished data.
FC: fold-change; PD: pharmacodynamic.

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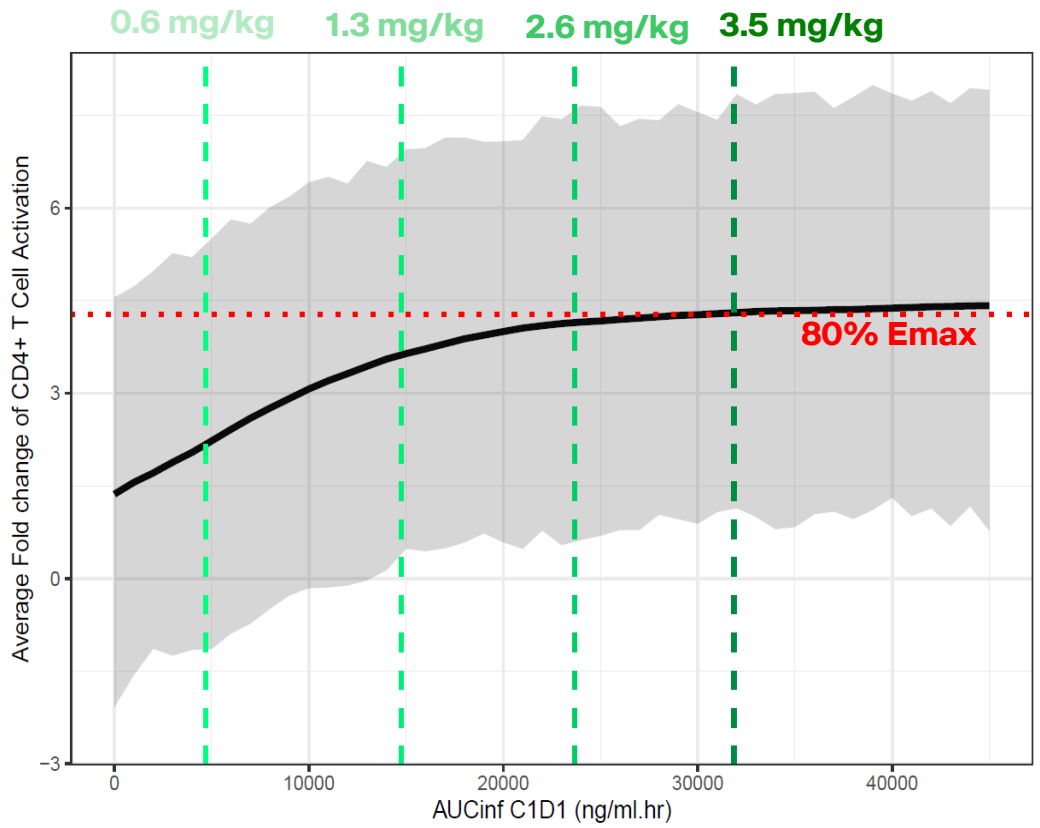
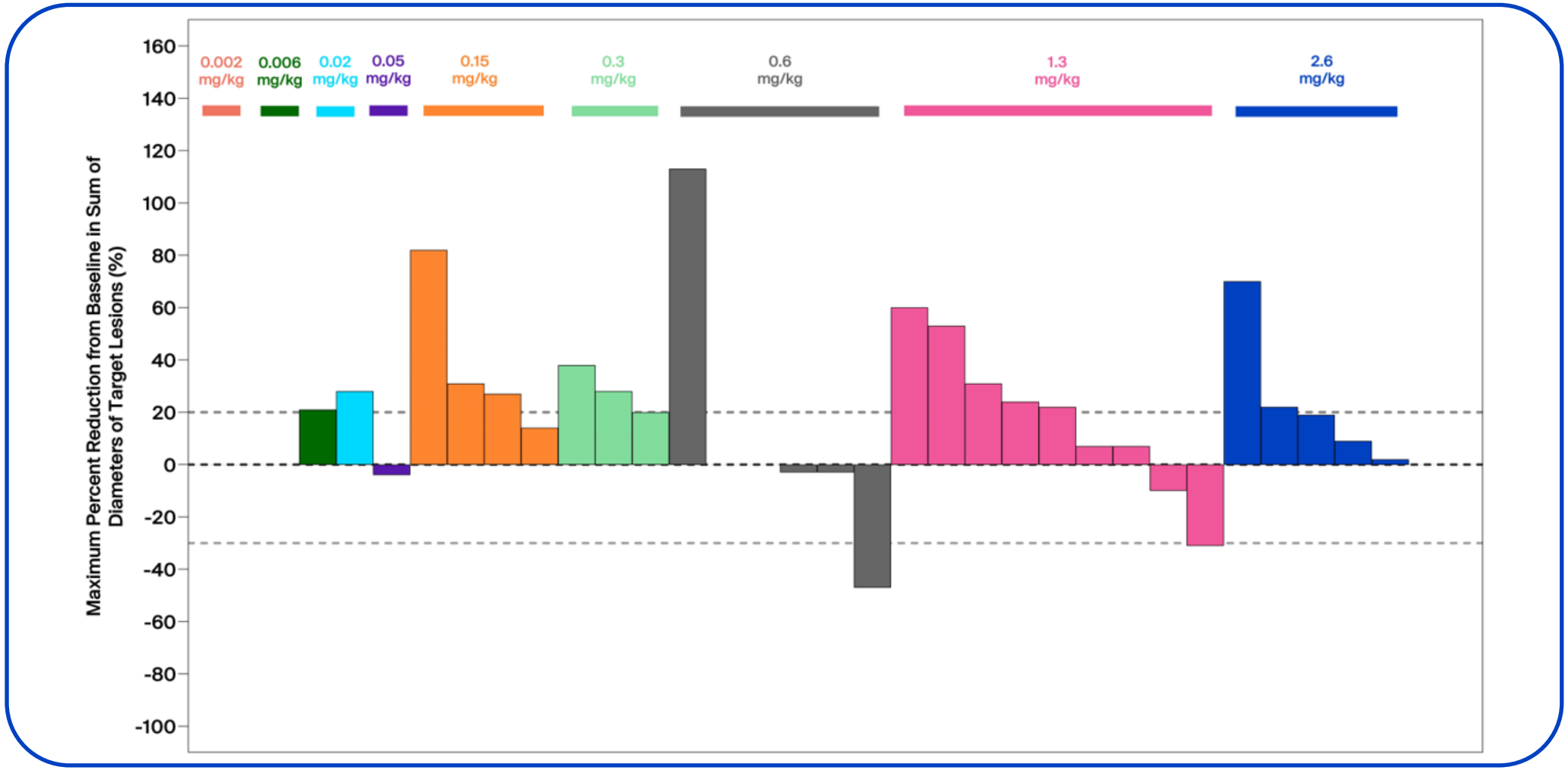
Clinical PK quantitative modelling of BT7480 confirms our potential therapeutic dose range

Exposure-response modeling to identify clinical doses that provide near maximal biomarker change



Data from all sources. Preclinical: PK, biomarkers, activity in xenograft models, toxicology. Clinical: PK, biomarkers (eg, CD4+ T cell activation, CXCL9, cytokines), tumor shrinkage, safety/tolerability. Black line: median prediction (no residual error); shaded area: 95% prediction interval (with residual error); dashed lines: mean AUC_{inf} C1D1 at 0.6, 1.3, 2.6 and 3.5 mg/kg (AUC_{inf} C1D1 of 3.5 mg/kg extrapolated based on AUC_{inf} C1D1 at 2.6 mg/kg, assuming dose-proportional PK); y-axis represents average fold change (relative to baseline) of FOXP3+CD25+CD4+ T cells at Week 1-4.

BT7480 response by dose across Cohorts 1-9 (0.002-2.6 mg/kg QW)*



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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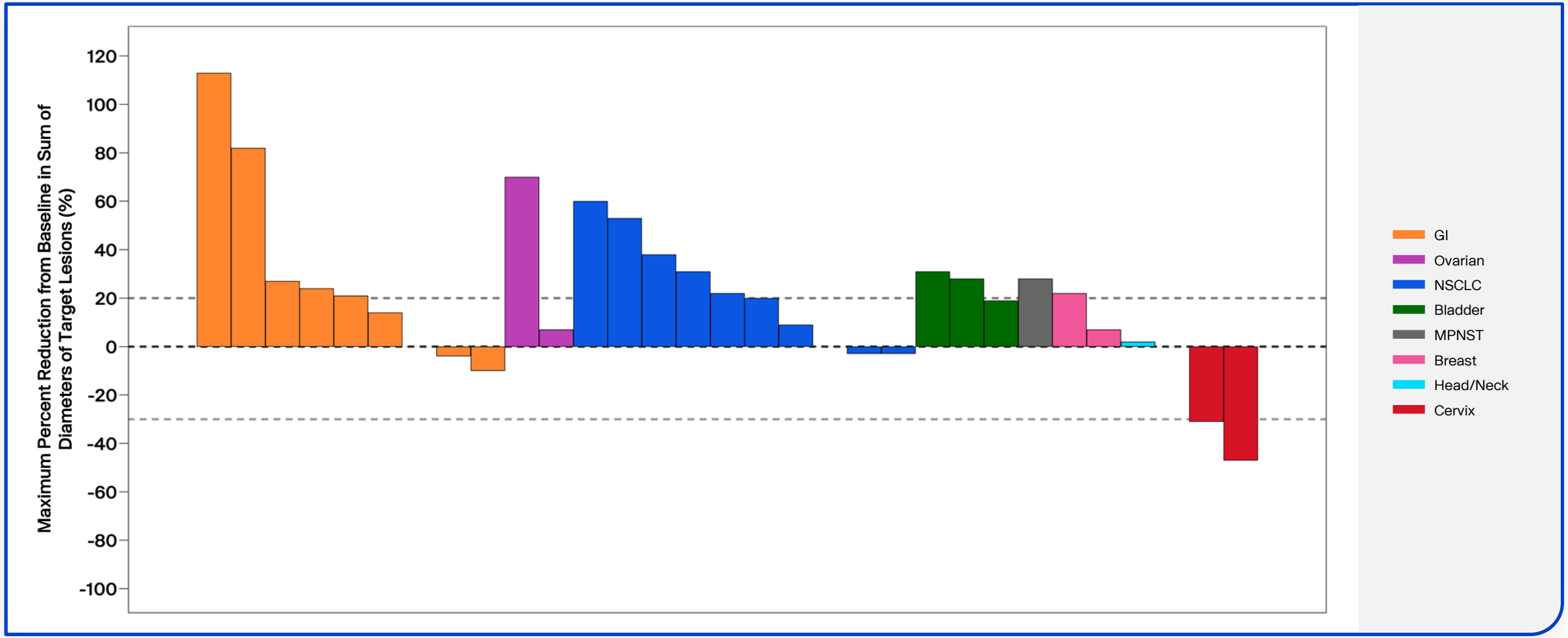
BT7480 response by tumor across Cohorts 1-9 (0.002-2.6 mg/kg QW)*



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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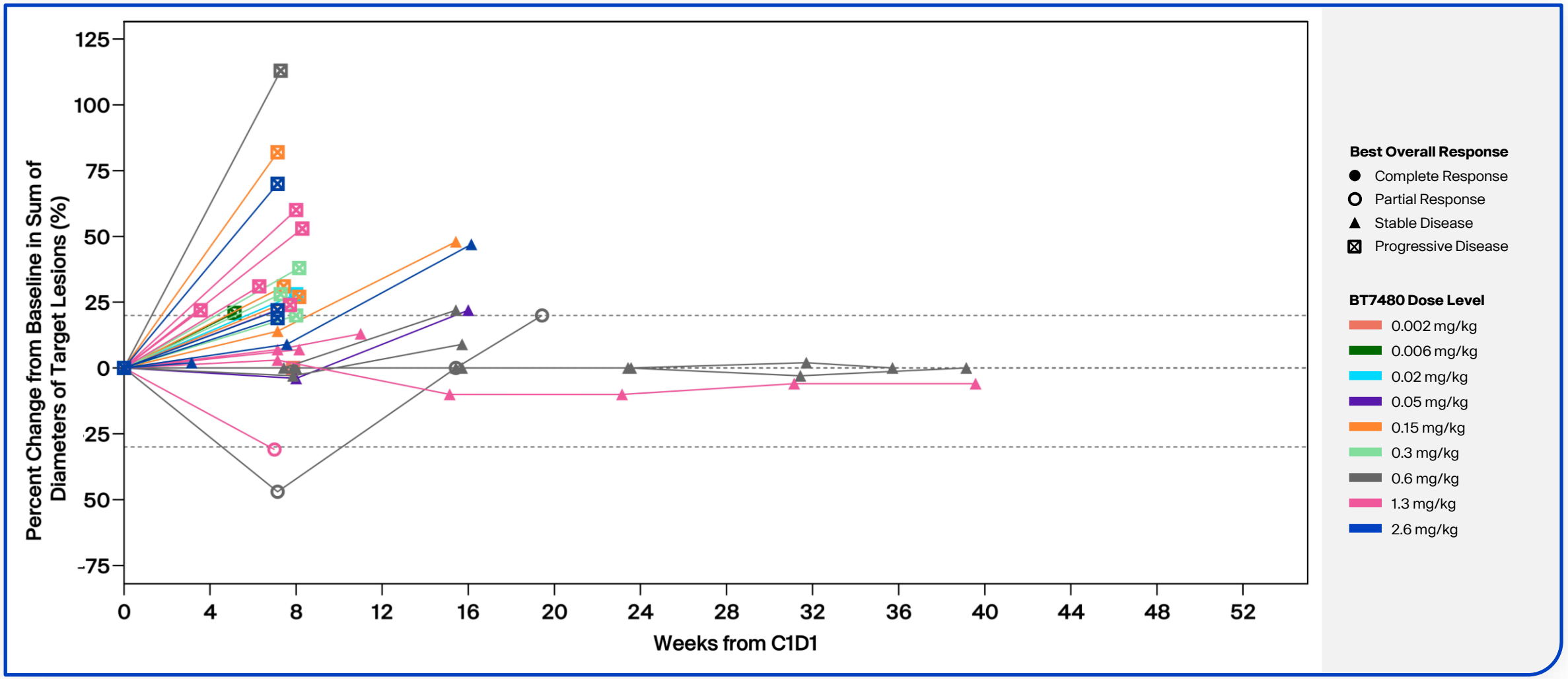
BT7480 responses in Cohorts 1 through 9 (0.002-2.6 mg/kg QW; N=31)

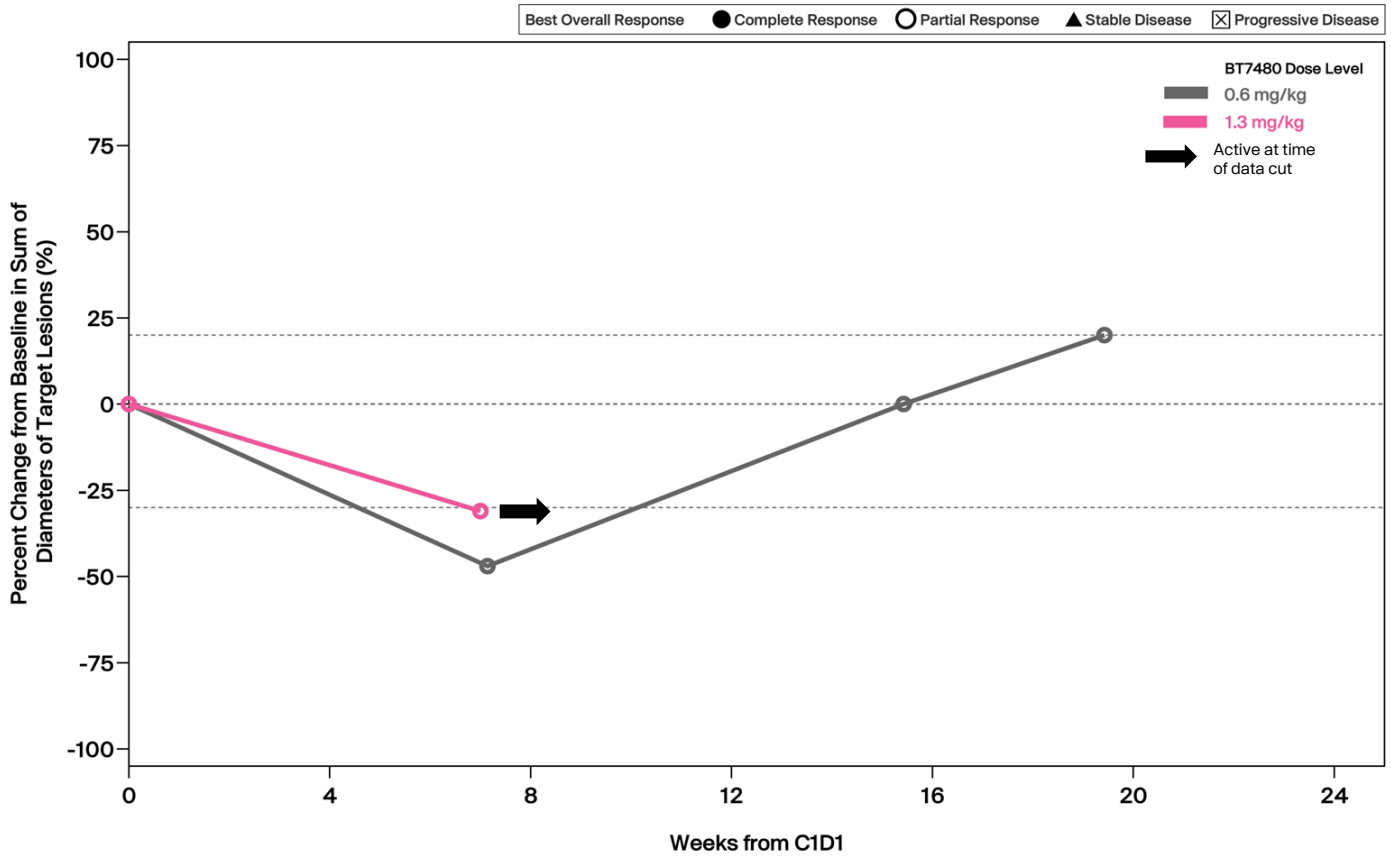


Median duration of follow-up is 3.3 months

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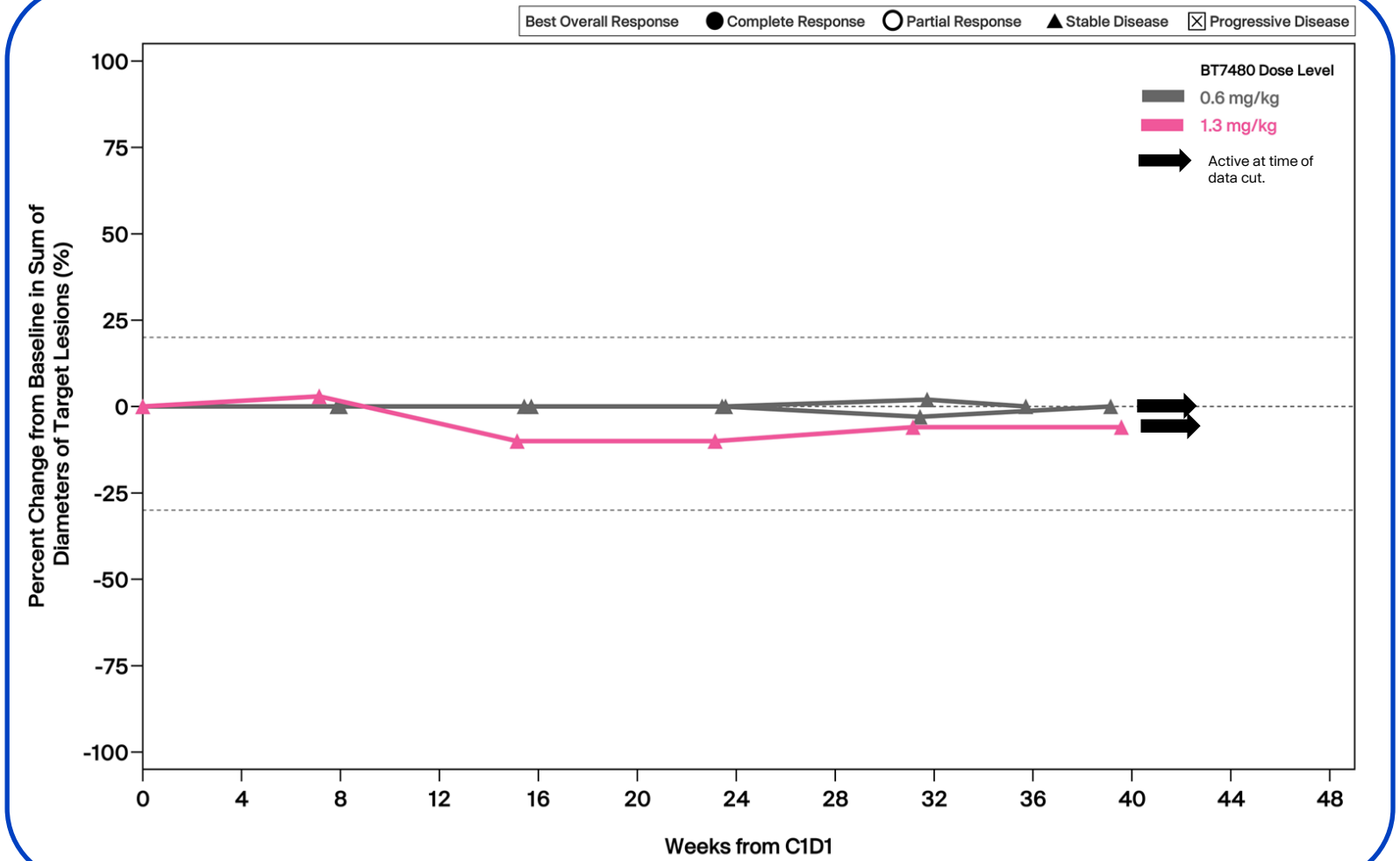
Data as of 08Nov2023.
Responses under response evaluation criteria in solid tumor (RECIST) version 1.1.
CPI: checkpoint inhibitor; QW: weekly.

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

Nectin-4 Portfolio Market Opportunity

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Bicycle® molecules targeting Nectin-4 could represent a high value approach across multiple solid tumors

BT8009

First-in-class
Next generation Nectin-4 agent

Market leading potential

Lead tumor
Urothelial

Additional tumors
NSCLC, TNBC, Ovarian

BT7480

First-in-class
Innovative Nectin-4 CD137 agent

Significant monotherapy and combination opportunities

Lead tumor
Cervical

Additional tumors
NSCLC, HNSCC

HNSCC: head and neck squamous cell carcinoma; NSCLC: non-small cell lung cancer; TNBC: triple-negative breast cancer.

BT8009 has the potential to transform care in urothelial cancer and additional Nectin-4 expressing tumors

BT8009

First-in-class
Next generation Nectin-4 agent

Market leading potential

Lead tumor
Urothelial

Additional tumors
NSCLC, TNBC, Ovarian

- Novel, powerful and selective small peptide
- Potential for long mDOR and improved tolerability
- Unique properties for flexible administration
- Parallel regulatory path available in mUC
- Promising early signals in NSCLC, TNBC, Ovarian

mDOR: median duration of response; mUC: metastatic urothelial cancer; NSCLC: non-small cell lung cancer; TNBC: triple-negative breast cancer

Metastatic urothelial cancer could provide an important opportunity for BT8009 to bring The Bicycle® Advantage to patients

Annual Incidence (Stages 0-IV)[1]

573,000 Worldwide

85,503 United States

Rank among all cancers (Incidence)

10 Worldwide

6 United States

Patients developing metastatic disease

25%

5-year Survival

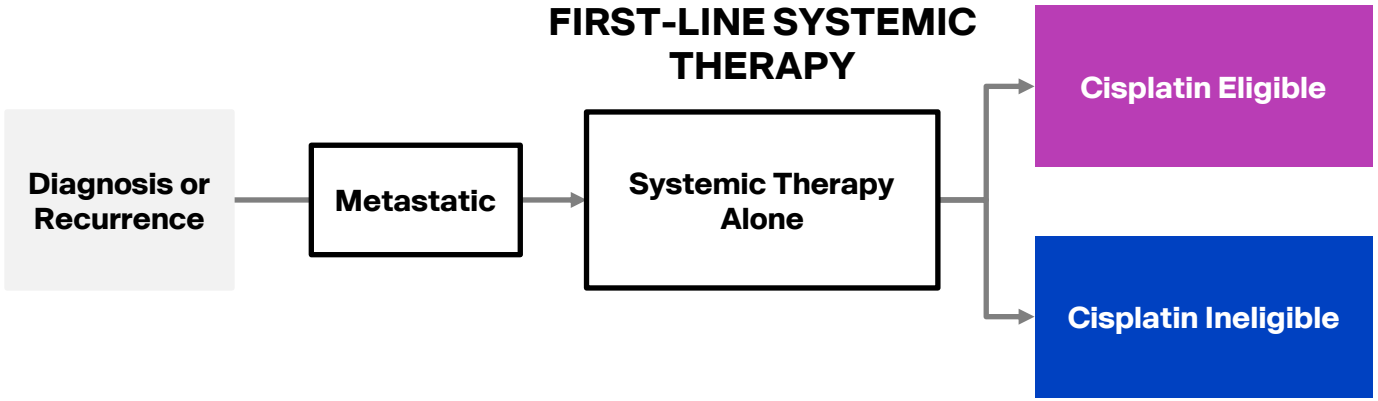
63% / 12%

Stages 0-IV Stage IV

- One of the highest lifetime treatment costs per patient of all cancers[2]
- High recurrence rate and ongoing invasive monitoring lead to economic and human toll of this disease[2]
- **Improved safety profiles are needed to bring the promise of chemotherapy free treatment options to mUC**

1. Cerner Enviza CancerMPact, Treatment Architecture US Bladder Cancer, Nov2022. Sources: Based on CancerMPact® Patient Metrics U.S., accessed Feb2023. Ranking is based on relative incidence of 31 tumors; Risk factors from National Cancer Institute (cancer.gov), NCCN Guidelines *Bladder Cancer* v2.2022, ASCO's patient information website (Cancer.Net), American Cancer Society (cancer.org).
2. Journal of Urology, Adult Urology, Late Recurrences Following Radical Cystectomy Have Distinct Prognostic and Management Considerations, Sep2020.
mUC: metastatic urothelial cancer.

Current metastatic urothelial cancer treatment journey is dominated by chemotherapy in 1L



Cisplatin Eligible

Chemotherapy use[1,2] ~70-80%

Top 3 modalities[2]
gemcitabine, cisplatin
gemcitabine, carboplatin
pembrolizumab

Cisplatin Ineligible

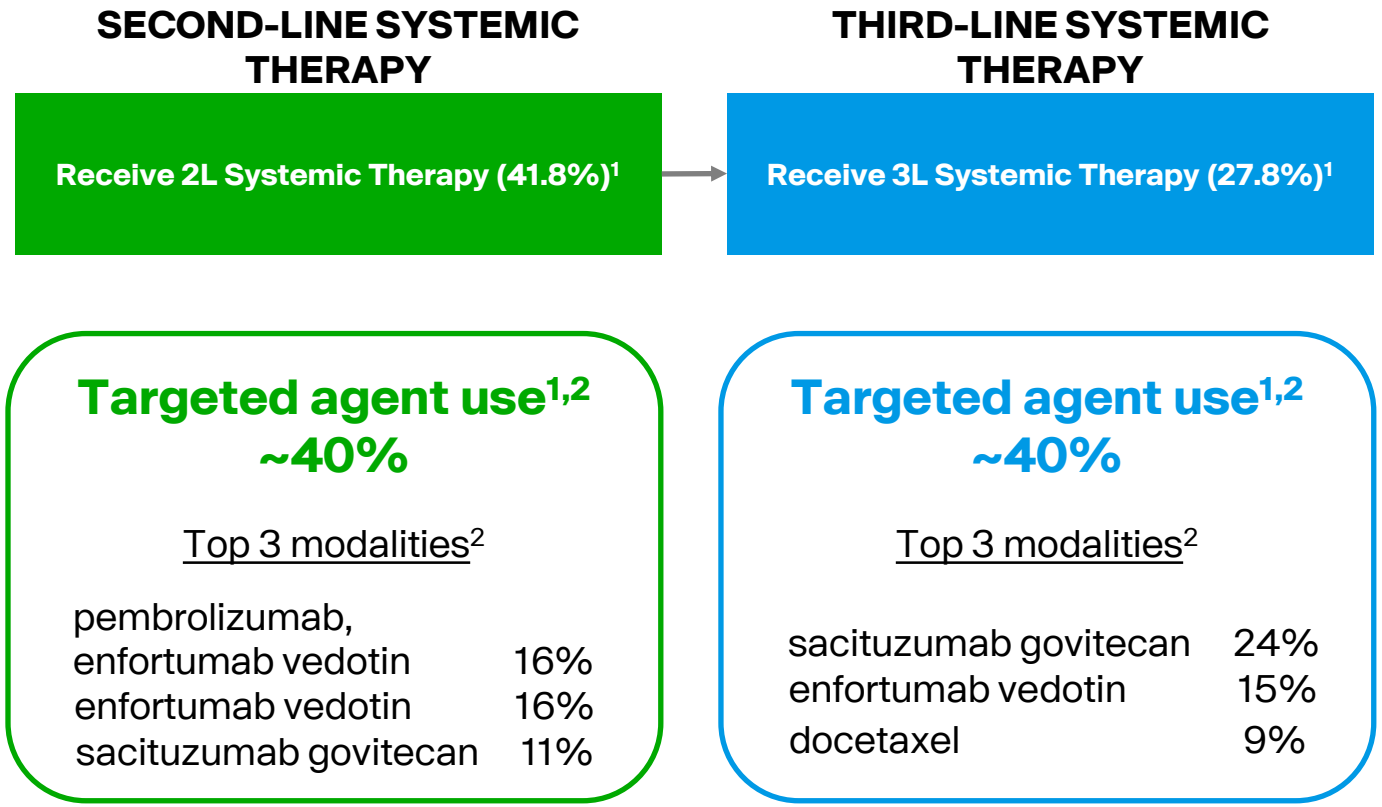
Chemotherapy use[1,2] ~50%-60%

Top 3 modalities[2]
gemcitabine, carboplatin
pembrolizumab
pembrolizumab, enfortumab vedotin

- **Using the most effective regimen in 1L is one important treatment consideration[3]**
- **Toxicity profile also matters because patients often progress to 2L therapy[3]**

1. Cerner Enviza CancerMPact Treatment Architecture Nov2022, US Bladder Cancer, Source: survey 103 physicians treating 3920 bladder cancer patients.
2. Cerner Enviza CancerMPact, Future Trends and Insights, Dec2023 US Bladder Cancer Only top 3 active modalities are shown for first-line therapy. Regimen boxes refer to use of systemic therapy when given alone or combined with other therapies.
3. Combination, Sequencing and the Contribution of Components: New Frontline Standards for Metastatic Urothelial Carcinoma, JCO Jul2023.
Chemotherapy data shown is regardless of PD-L1 status.
1L: 1st line; 2L: 2nd line.

Despite targeted agent availability, 2L and 3L treatment use is fragmented in mUC showing ongoing unmet need



- **Clinicians are seeking more tolerable treatments in 2L and 3L mUC even though more efficacious agents exist[3]**

1. Cerner Enviza CancerMPact Treatment Architecture Nov2022, US Bladder Cancer, Source: survey 103 physicians treating 3920 bladder cancer patients.
2. Cerner Enviza CancerMPact, Future Trends and Insights, Dec2023 US Bladder Cancer, Only top 3 active modalities are shown for second-line and third-line therapy. Regimen boxes refer to use of systemic therapy when given alone or combined with other therapies.
3. Return on Focus Insight Mining and Target Product Profile Testing Research Jul2023, Oct2023.
2L: 2nd line; 3L: 3rd line; mUC : metastatic urothelial cancer.

BT8009 is a potential new option that could address unmet need and build on the chemotherapy free treatment paradigm

Clinician feedback on unmet need in mUC[1,2]	BT8009 Target Product Profile[2]
Desire for novel therapies that have **improved efficacy and toxicity**	✓
Need for **innovative approaches to existing targets** and new targets	✓
Better toxicity profiles especially for patients with poor performance status	✓
Improvement in treatment limiting AEs including skin rash, neuropathy	✓
More durable treatments and improved adherence that furthers efficacy	✓

Many clinicians report a product with **improved safety and tolerability would lead them to use it over one with similar efficacy[2]**

Bicycle®

1. ESMO Oct2023, Bicycle Bladder Cancer Key Opinion Leader Meetings.
2. Return on Focus Insight Mining and Target Product Profile Testing Research Jul2023, Oct2023.

AE: adverse event; mUC: metastatic urothelial cancer.

Experts continue to support the ongoing development of BT8009 as a potential differentiated treatment option after ESMO 2023

KOL views on efficacy[1]

"If this drug maintains a **DOR beyond 9-12 months**, it could be **given more chronically** and be better tolerated"

"In metastatic, **long DOR matters along with stable disease and partial responses** especially when combined with a **true improvement in quality of life**"

KOL views on safety[1]

"**Tolerability matters in all lines of treatment** because patients become frail as they progress... **and this drug could be used before more challenging drugs**"

"If you have developed a less toxic EV **with at least a 20-30% improvement in rash and neuropathy**, people will jump on it"

Clinician views from ESMO 2023[2]

"EV data is a proof of concept for 8009 and [Duravelo-2] is a nice study design, patient preference is always important"

"Likely we will realize in a short time not all patients' benefit [on EV-P] and we can do a lot to furthering the efficacy by improving the adherence"

"Patients decisions are not just about benefit but also harms and how bothersome [toxicities] are for ADLs and QOLs"

"Reducing tox and improving tolerability is very important to this disease. These are older patients, are already challenged physically and need better options"

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1.ASCO GU Feb2023, ASCO June 2023 Bladder Cancer Key Opinion Leader Meetings.
2. ESMO Oct2023 Bladder Cancer Key Opinion Leader Meetings and Twitter accessed 25Oct2023.
ADL: activities of daily living; DOR: duration of response; EV: enfortumab vedotin; EV-P: enfortumab vedotin plus pembrolizumab; QOL: quality of life.

Powerful brands have differentiated on safety and tolerability to become best-in-class treatments for patients in oncology

	CALQUENCE® acalabrutinib 100 mg tablets	CABOMETYX® (cabozantinib) tablets 60 mg | 40 mg | 20 mg
Profile Positioning	▸ Best-in-class BTKi for CLL, 5 years after Imbruvica ▸ Higher selectivity, less off target effects, favorable tolerability	▸ Best-in-class TKI for RCC, 4 years after Inlyta ▸ 'A Balance of Data', similar OS, improved tolerability and quality of life
Differentiation Approach	**Safety advantage, including treatment limiting atrial fibrillation[1]**	**Safety advantage including overall tolerability, significant improvement in patient report quality of life[5]**
Patient Reach	**30%+ share of new patient starts within 9 months post launch[2,4]** **50%+ share of new patient starts as market leaders in 2022[3,4]**	

1. AstraZeneca press release published 02Feb2016. 2. FiercePharma, "AstraZeneca touts Calquence safety win against Imbruvica in leukemia trial showdown"; 25Jan2021. 3. AstraZeneca Q4 2022 Earnings Call. 4. IQVIA Script Trends for the Week Ended 19Aug2022, SVB Securities 29Aug2022. 5. Cabometyx HCP website aRCC accessed Nov2023.
BTK: Bruton's tyrosine kinase; CLL: chronic lymphocytic leukemia; OS: overall survival; RCC: renal cell carcinoma; TKI: tyrosine kinase inhibitor.

BT8009 combination and monotherapy has potential to be a market leading treatment for bladder cancer

PRODUCT VISION

- First-in-class Bicycle® technology targeting Nectin-4 to be indicated for 1L and 2L+ mUC
- Powerful and durable responses as combination and monotherapy
- Better tolerability allowing for longer treatment, improved efficacy and a better patient experience

Key areas of opportunity

1. **Standard of care in first line combination**
2. **Standard of care in previously treated**
3. **Expand beyond metastatic disease***

We believe BT8009 has potential to become the preferred and next generation treatment for bladder cancer and additional Nectin-4 expressing tumors

Bicycle®

*For example, earlier lines of bladder cancer, or additional Nectin-4-expressing tumors such as triple negative breast cancer and non-small cell lung cancer.
1L: 1st line; 2L+: 2nd line or later; mUC: metastatic urothelial cancer.

BT8009 could be the first Nectin-4 targeted therapy in NSCLC, TNBC, ovarian cancer

	US Statistics	Unmet Need
Metastatic Non-Small Cell Lung Cancer	130,000 diagnosed annually[3] 5-year survival rate 7% mNSCLC[1]	**60% will progress after 1 year when receiving immune checkpoint inhibitors in 1L***
Metastatic Triple Negative Breast Cancer	23,000 diagnosed annually[3] 5-year survival rate 12% mTNBC[1]	**50% of 1L patients who progress will not receive 2L treatment****
Advanced Ovarian Cancer	12,000 women diagnosed[1,2] 5-year survival rate 19%[1]	**New efficacy benchmarks have been set with top priority now being more tolerable treatments**

1. Cerner Enviza CancerMPact US Future Trends and Insights, Ovarian Cancer Oct2023, Breast Cancer Aug2023, NSCLC Nov2023
2. American Cancer Society, Key Statistics: Ovarian, revised Oct2023, Lung, revised Jan2023, TNBC, revised Mar2023
3. Patient metrics source: Global Data, Global Drug Forecast and Market Analysis

*patients treated with immune checkpoint inhibitor with no actionable mutation
**2L+ regardless of mutational status
NSCLC: non-small cell lung cancer; TNBC: triple-negative breast cancer.

As part of the Nectin-4 portfolio, BT7480 could expand The Bicycle® Advantage beyond BT8009 into additional solid tumors

BT7480

First-in-class, innovative Nectin-4 targeting CD137 agent

Significant monotherapy and combination opportunities

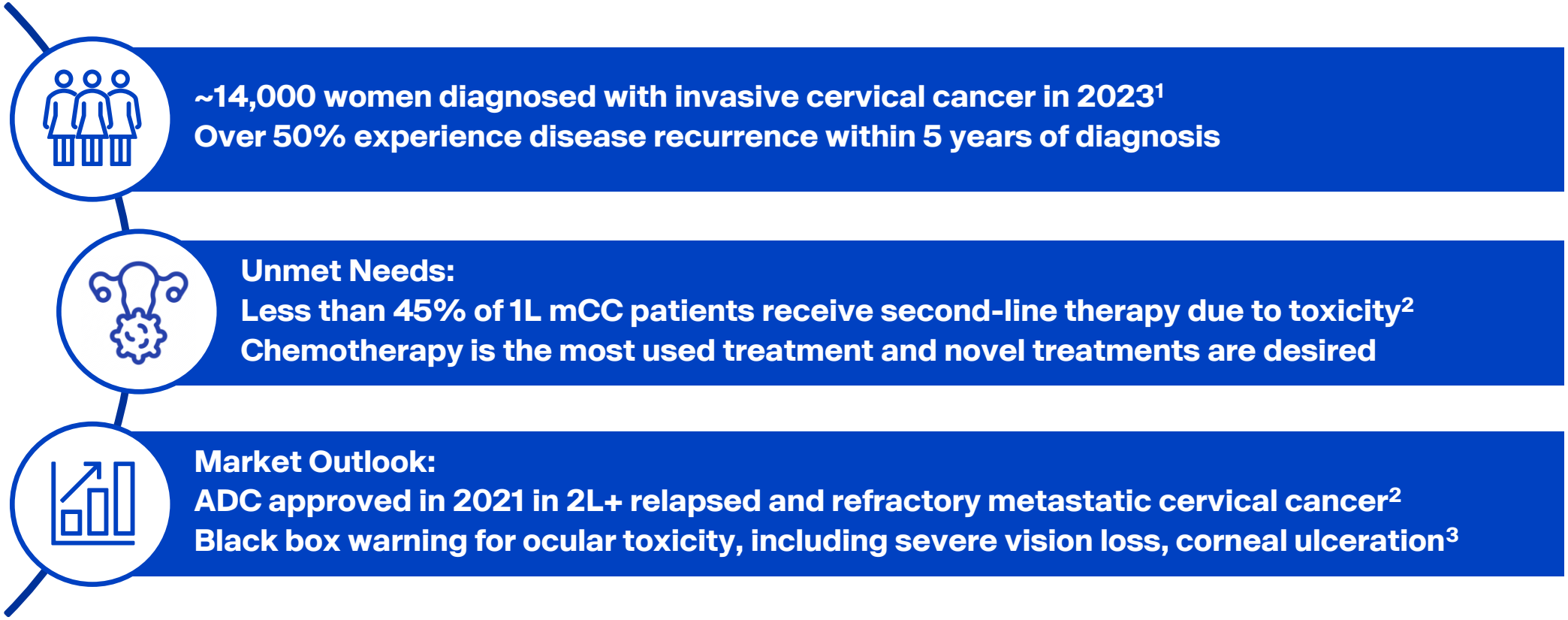
Lead tumor
Cervical

Additional tumors
NSCLC, HNSCC

- New modality, unique potential therapy
- Early responses as monotherapy
- Minimal safety events
- Opportunity to combine with other agents and potentially:
  - Enhance anti-tumor effect
  - Prolong duration of response
  - Achieve improvement in PFS and OS

HNSCC: head and neck squamous cell carcinoma; NSCLC: non-small cell lung cancer; OS: overall survival; PFS: progression free survival.

We believe BT7480 could fill a gap in cervical cancer where unmet need remains high and few novel treatments are in development



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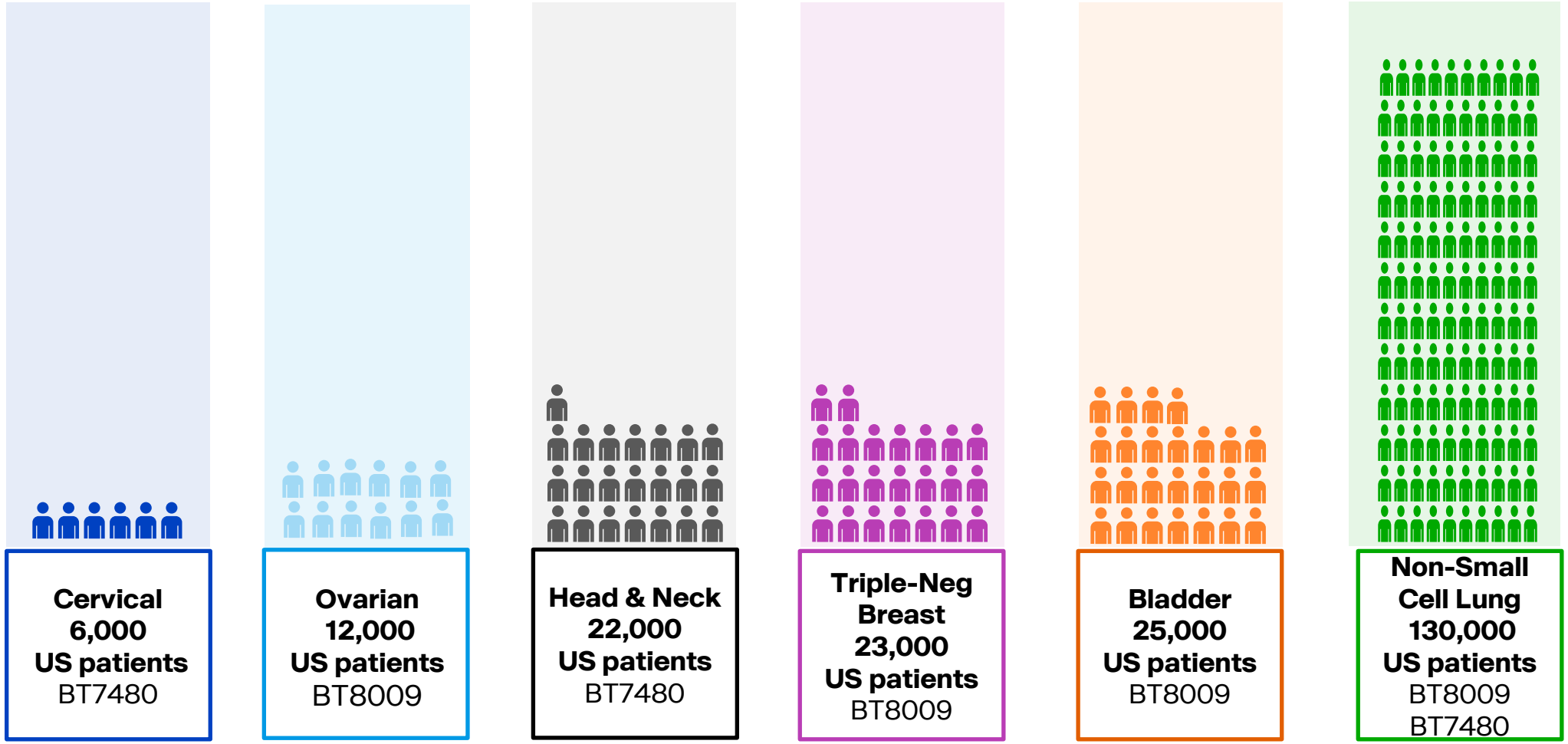
1. The American Cancer Society Statistics Center 2023, accessed Nov2023. 2. Cerner Enviza, Future Trends and Insights, Cervical Cancer, published Oct2023.
3. Seagen Inc. and Genmab US, Inc. Tivdak HCP website.
1L: 1st line; 2L+: 2nd line or later; ADC = antibody drug conjugate; mCC = metastatic cervical cancer.

The Bicycle® Advantage: We believe our emerging Nectin-4 portfolio could improve patient care in the metastatic setting across multiple solid tumors



Patient metrics source: Global Data, Global Drug Forecast and Market Analysis.
SEER US Incidence Data Surveillance Research Program, National Cancer Institute, Nov2022 Submission.
Populations represent potentially addressable patient population in the metastatic or advanced stage for the US population annually.

Q&A

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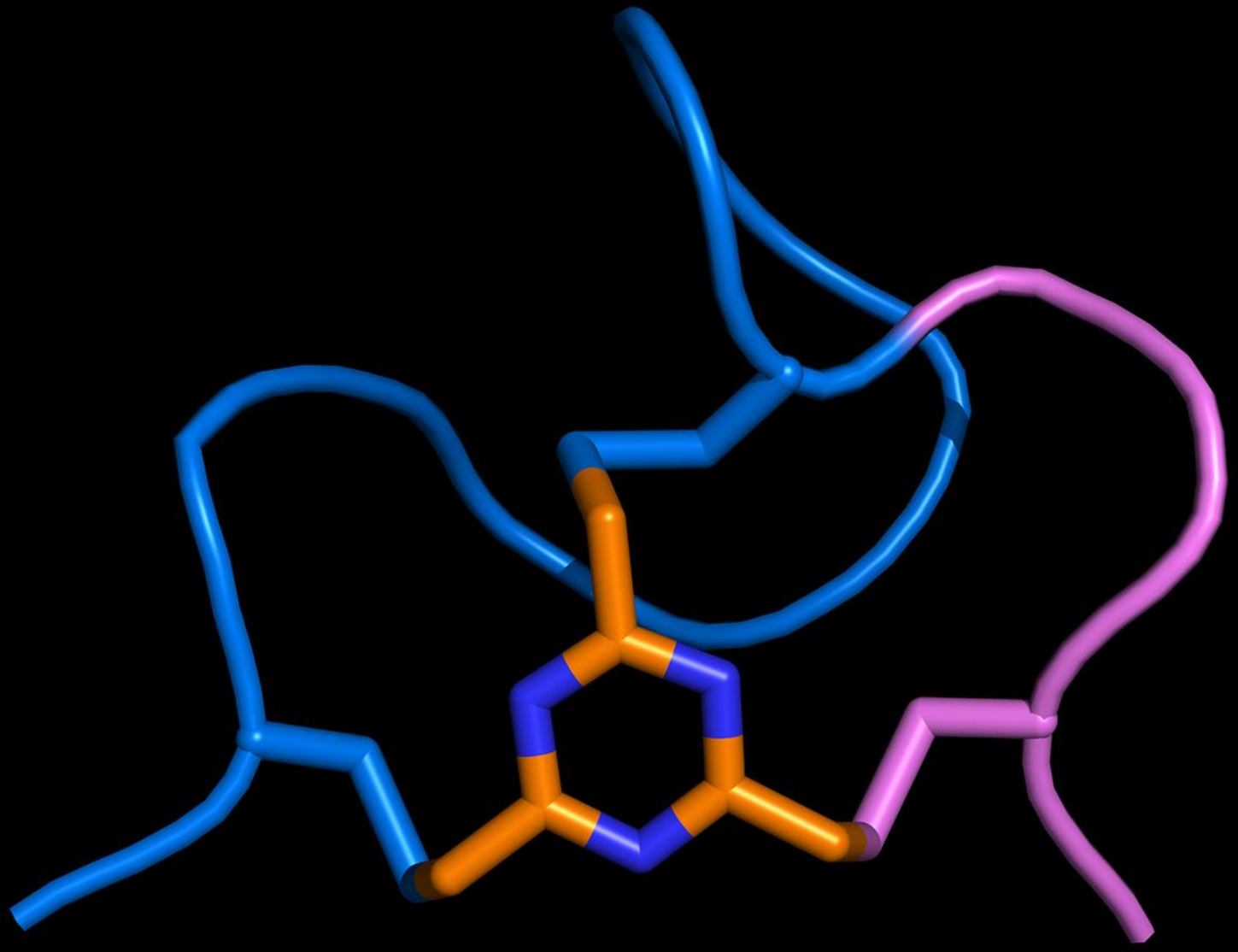
Agenda

Time	Topic	Speaker(s)
8 a.m.	Welcome and Company Overview	Kevin Lee
8:15 a.m.	Our Nectin-4 Portfolio ▸ BT8009 and BT7480	Nicholas Keen Santiago Arroyo Jennifer Perry
9:30 a.m.	Q&A	Management Team
10:00 a.m.	Break	
10:10 a.m.	Our EphA2 Portfolio ▸ BT5528 and BT7455	Nicholas Keen Santiago Arroyo Jennifer Perry
10:50 a.m.	Q&A	Management Team
11:05 a.m.	Our Platform Opportunities	Nicholas Keen Michael Skynner
11:40 a.m.	Q&A	Management Team
11:50 a.m.	Summary and Close	Kevin Lee

EphA2 Portfolio Overview



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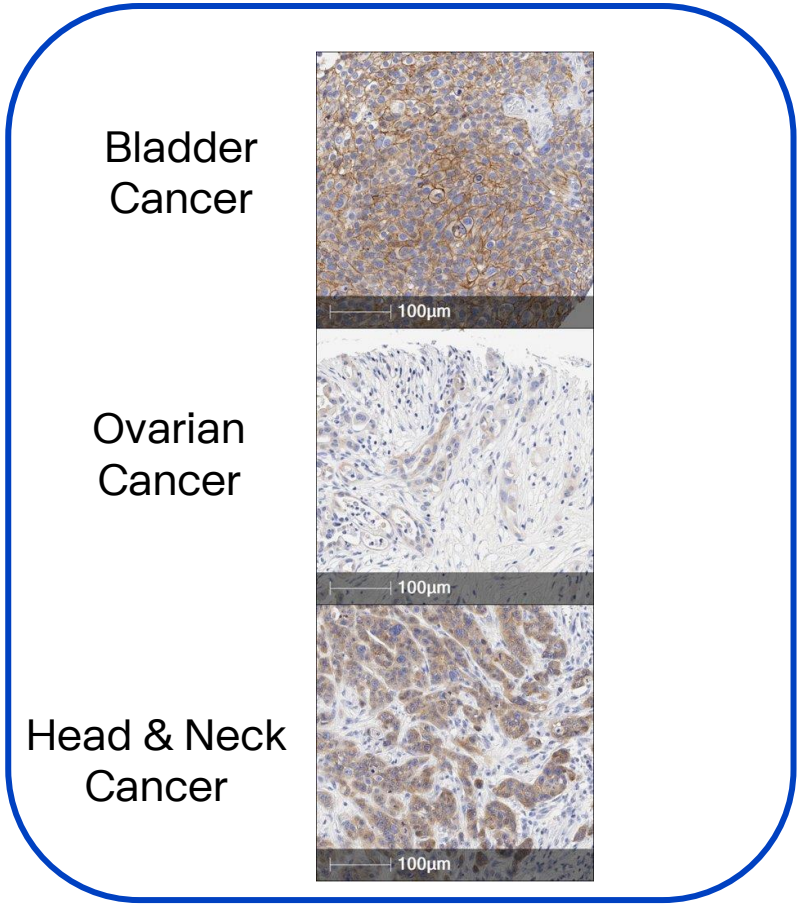
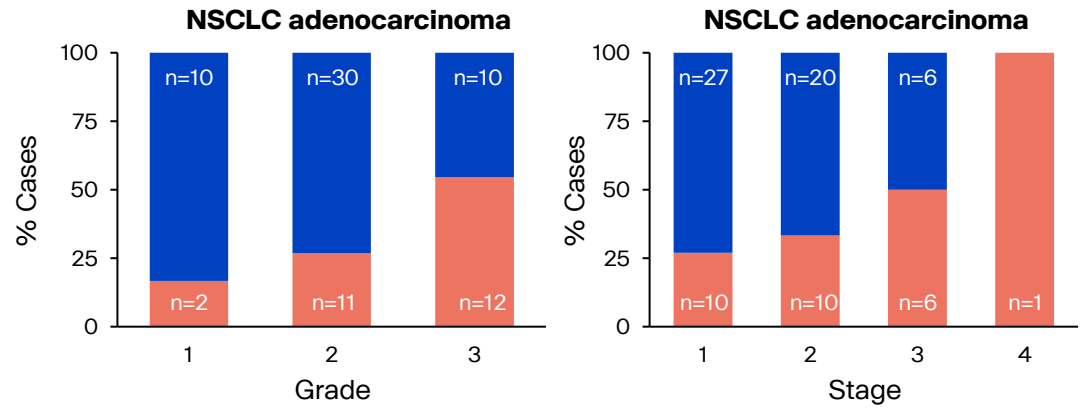
EphA2 is a tumor antigen that is widely expressed in many cancers and whose expression is believed to increase with stage



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

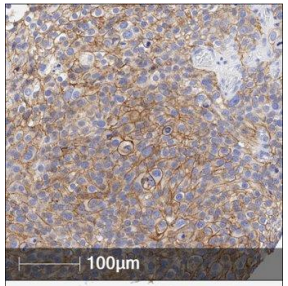
Molecule and company	MEDI-547 **Medimmune**	DS-8895a **Daiichi Sankyo**	ATRC-301 **Atreca**
Modality	EphA2-directed ADC carrying MMAF payload	Afucosylated humanized anti-EphA2 mAb, recognizing extracellular juxtamembrane region of EphA2	EphA2-directed ADC (recognizing unique epitope) carrying auristatin 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]

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.

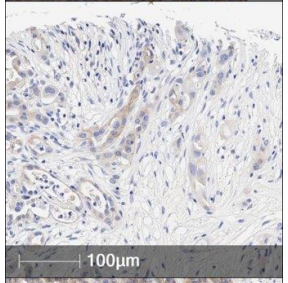
EphA2 offers the opportunity for multiple first-in-class approaches

A vector for toxin delivery...

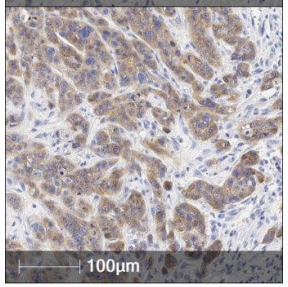
Bladder Cancer



Ovarian Cancer



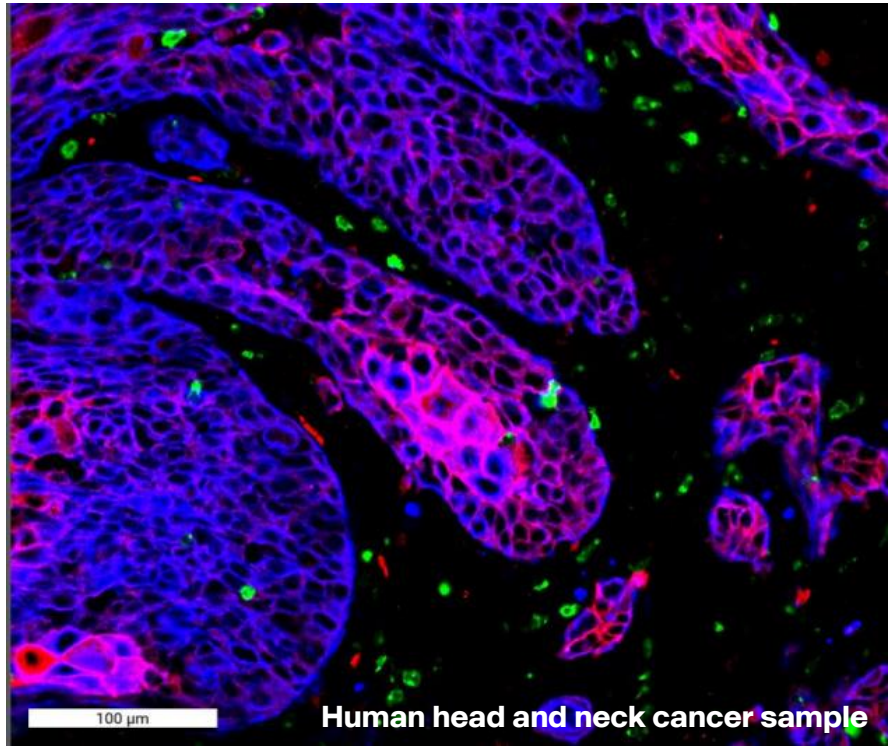
Head & Neck Cancer



Bladder, NSCLC, ovarian, breast

Data was generated internally with an IHC assay using EphA2 (D4A2) monoclonal antibody (CST #6997) on commercially purchased tumor tissue microarray samples. NSCLC: non-small cell lung cancer. Bicycle Therapeutics unpublished data.

...and for immune cell activation



Key: PanCK EphA2 CD137

Tumor types include **head and neck, stomach, colon** and others

Internal data of a head & neck tumor sample stained with anti-EphA2 polyclonal antibody (R&D Systems AF3035) along with antibodies detecting PanCK and CD137 using Mulitomyx (TM) multiplexed immunofluorescence technology. Bicycle Therapeutics unpublished data.

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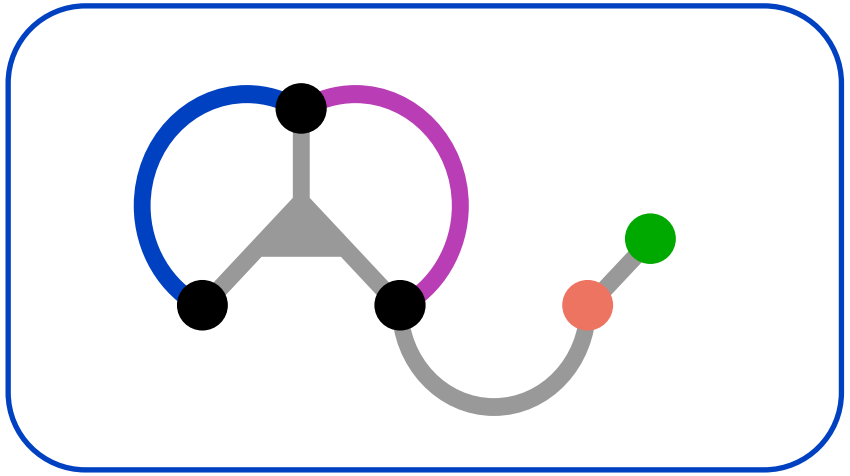
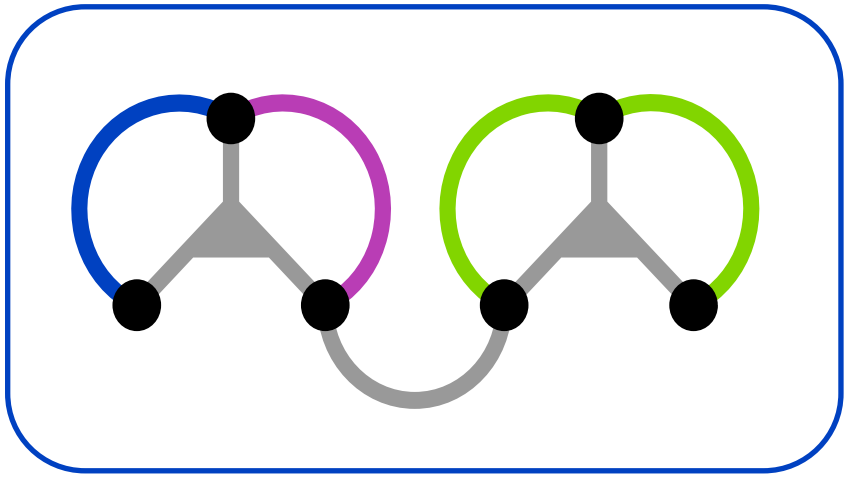
We have taken two approaches to try and address the broadest EphA2-expressing population of patients

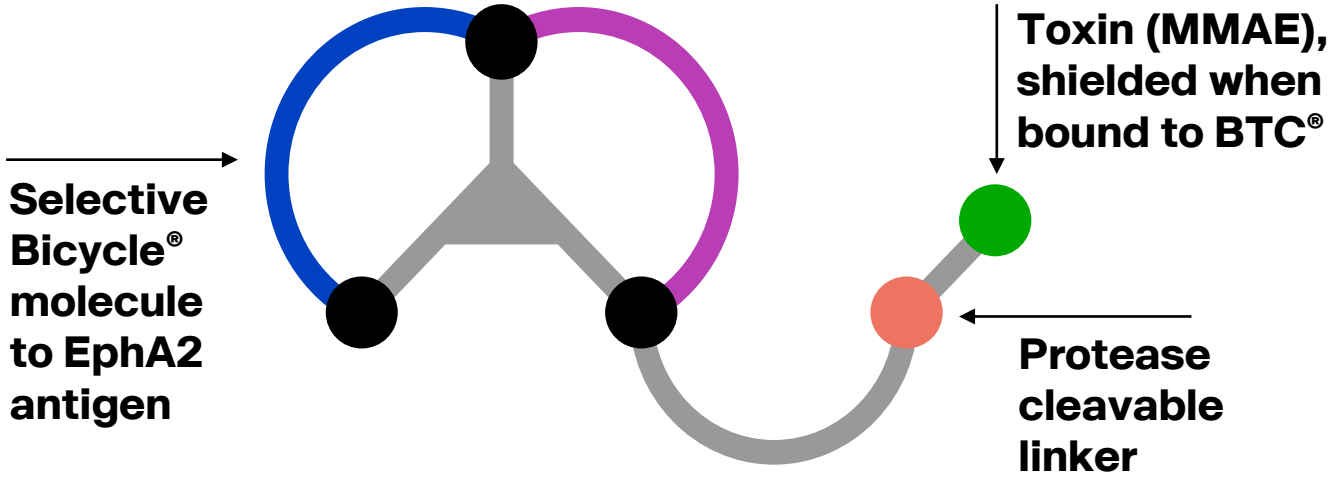


BT5528 an EphA2-targeted BTC® designed to overcome the significant toxicity associated with other toxin conjugate approaches.

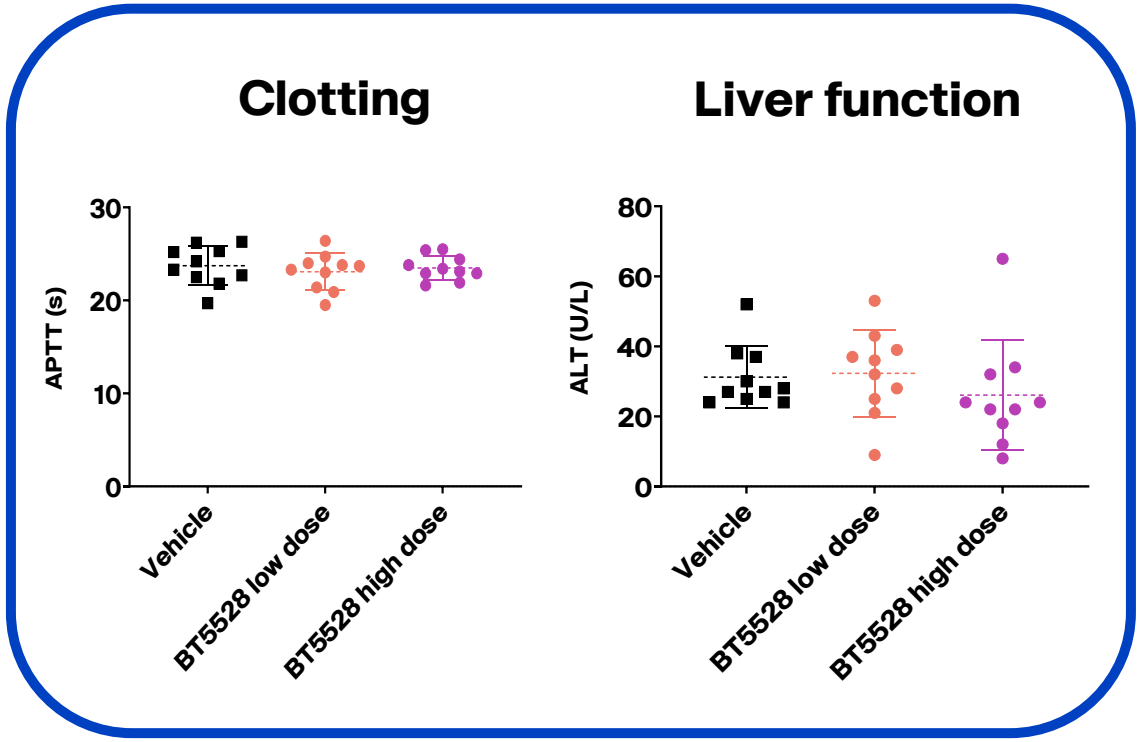


BT7455 an EphA2-targeted CD137 agonist designed to overcome immune agonist toxicities and activate the immune system in EphA2-expressing tumors. IND-enabling work to be completed.

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



- **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.

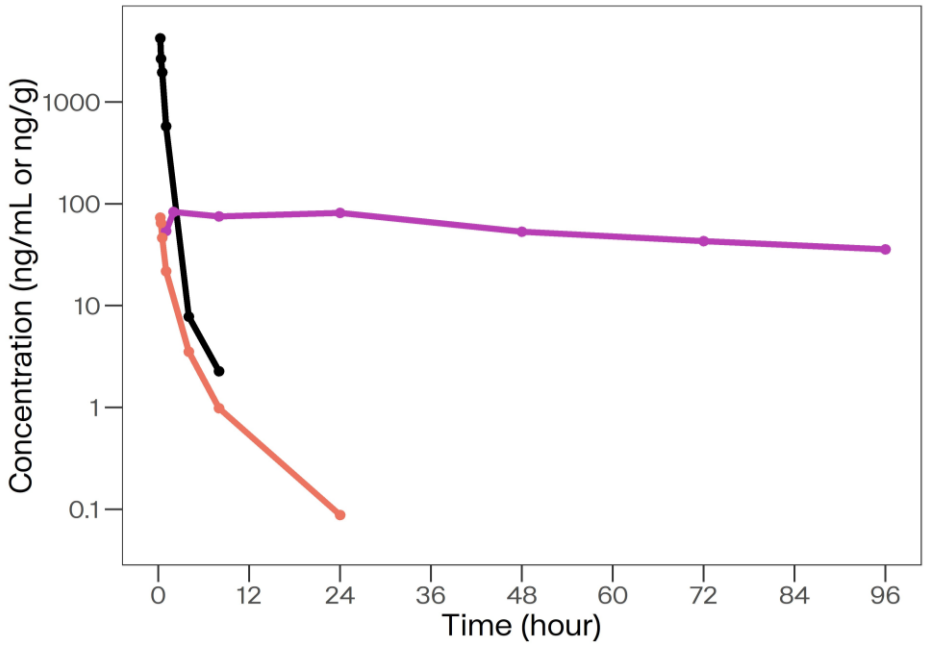
BT5528 low dose = 0.75 mg/kg, human equivalent dose 9 mg/m2
BT5528 high dose = 1.5 mg/kg, human equivalent dose 18 mg/m2

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

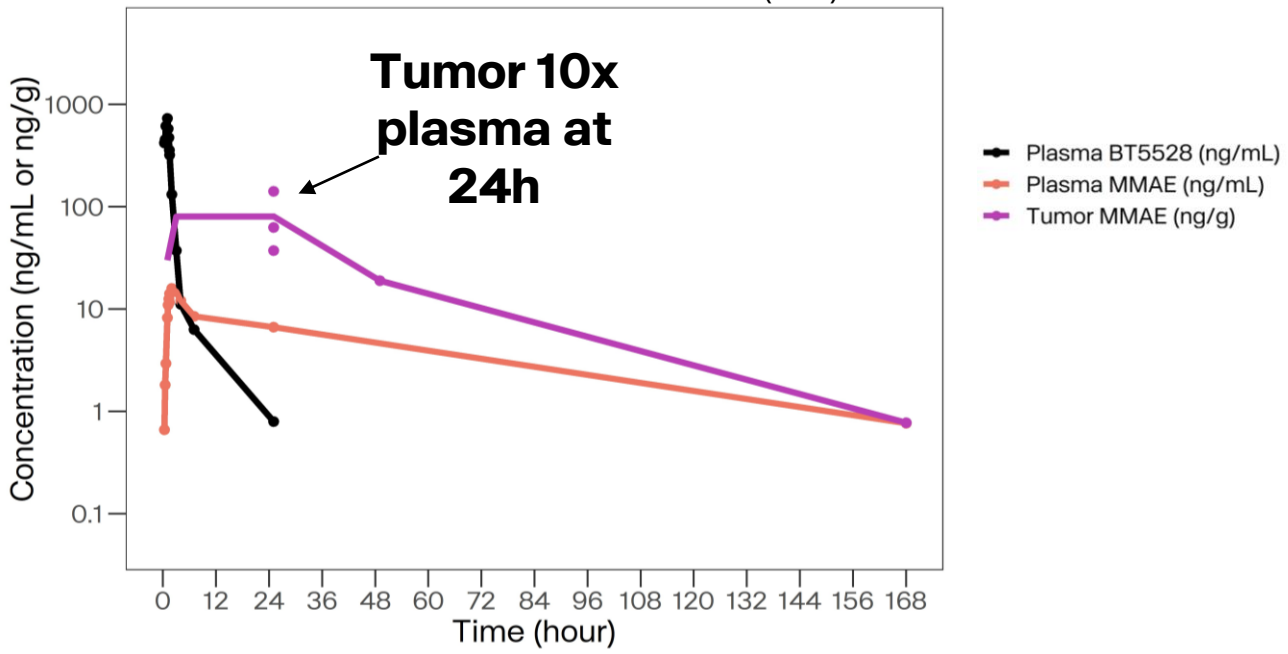
BT5528 PK in **Mouse** (1.5 mg/kg)

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 Ph1/2 clinical trial update

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Approach to BT5528 clinical development

- EphA2 is considered 'undruggable' with severe and life-threatening toxicity when targeted with ADC approaches

- Consequently, BT5528 initial development was guided by safety considerations, the novelty of the Bicycle® technology and FDA's Project Optimus initiative

- As we have approached the zone for predicted activity, we have expanded to obtain additional information in different tumor types and have used PK modelling for further dose optimization

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.

Study populations included in this update

- Efficacy:
  - BT5528 monotherapy in mUC (N=18)
  - Ovarian (N=31)
  - NSCLC (N=8)
  - TNBC (N=9)
  - HNSCC (N=7)
  - Gastric/upper GI (N=7)
- Safety:
  - BT5528 monotherapy
    - All patients (N=109)
    - Patients treated at 6.5 mg/m^2 Q2W (N=74)
  - Analysis of AEs of interest

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Study is ongoing, 5 patients enrolled at 5 mg/m^2 QW at time of data cut.
AE: adverse event; GI: gastrointestinal; HNSCC: head and neck squamous cell carcinoma; mUC: metastatic urothelial cancer; NSCLC: non-small cell lung cancer; Q2W: every other week; TNBC: triple-negative breast cancer.

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)

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

BT5528 was studied in multiple solid tumors

	BT5528 All Monotherapy Cohorts N=109 n (%)[a]	BT5528 6.5 mg/m^2 Q2W N=74[b] n (%)
Ovarian[c]	37 (34)	17 (23)
Urothelial[d]	24 (22)	20 (27)
Pancreatic	8 (7)	1 (1)
NSCLC[e]	10 (9)	8 (11)
TNBC[f]	9 (8)	9 (12)
HNSCC[g]	8 (7)	8 (11)
Gastric/Upper GI[h]	8 (7)	8 (11)
Other[i]	5 (5)	3 (4)

Data as of 27Sep2023.
[a]Sum of percentages does not add to 100 due to rounding; [b]Includes dose escalation and expansion; [c]Includes ovarian, fallopian tube; [d]Includes bladder, urethra, urinary bladder, pyelum, renal pelvis transitional cell cancer, and urothelial carcinoma; [e]Includes lung and non-small cell lung cancer; [f]Triple Negative Breast Cancer; [g]Head & Neck Squamous Cell carcinoma, Includes head/neck, salivary, tongue and nasopharyngeal; [h]Gastric includes esophageal, gastric and stomach; [i]Includes bone, rectal, uterus, renal, and unknown.
Q2W= every other week.

BT5528 overall safety profile

Event Type	BT5528 All Monotherapy Cohorts N=109 n (%)	BT5528 6.5mg/m^2 Q2W N=74[a] n (%)
TEAEs Overall	106 (97)	71 (96)
TEAEs ≥Grade 3	54 (50)	34 (46)
BT5528 Related TEAEs	98 (90)	67 (91)
BT5528 Related TEAEs ≥Grade 3	29 (27)	14(19)
Any TESAE	34 (31)	19 (26)
BT5528 Related TESAE	12 (11)	6 (8)
TEAEs Leading to BT5528 Dose Modification	41 (38)	20 (27)
TEAEs Leading to BT5528 Dose Reduction	11 (10)	2 (3)
TEAEs Leading to BT5528 Dose Interruption	35 (32)	17 (23)
TEAEs Leading to BT5528 Drug Withdrawn	5 (5)	2 (3)

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Data as of 27Sep2023.
[a]Includes dose escalation and expansion.
Q2W: every other week; TEAE: treatment-emergent adverse event; TESAE: treatment-emergent serious adverse event.

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/m² 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)

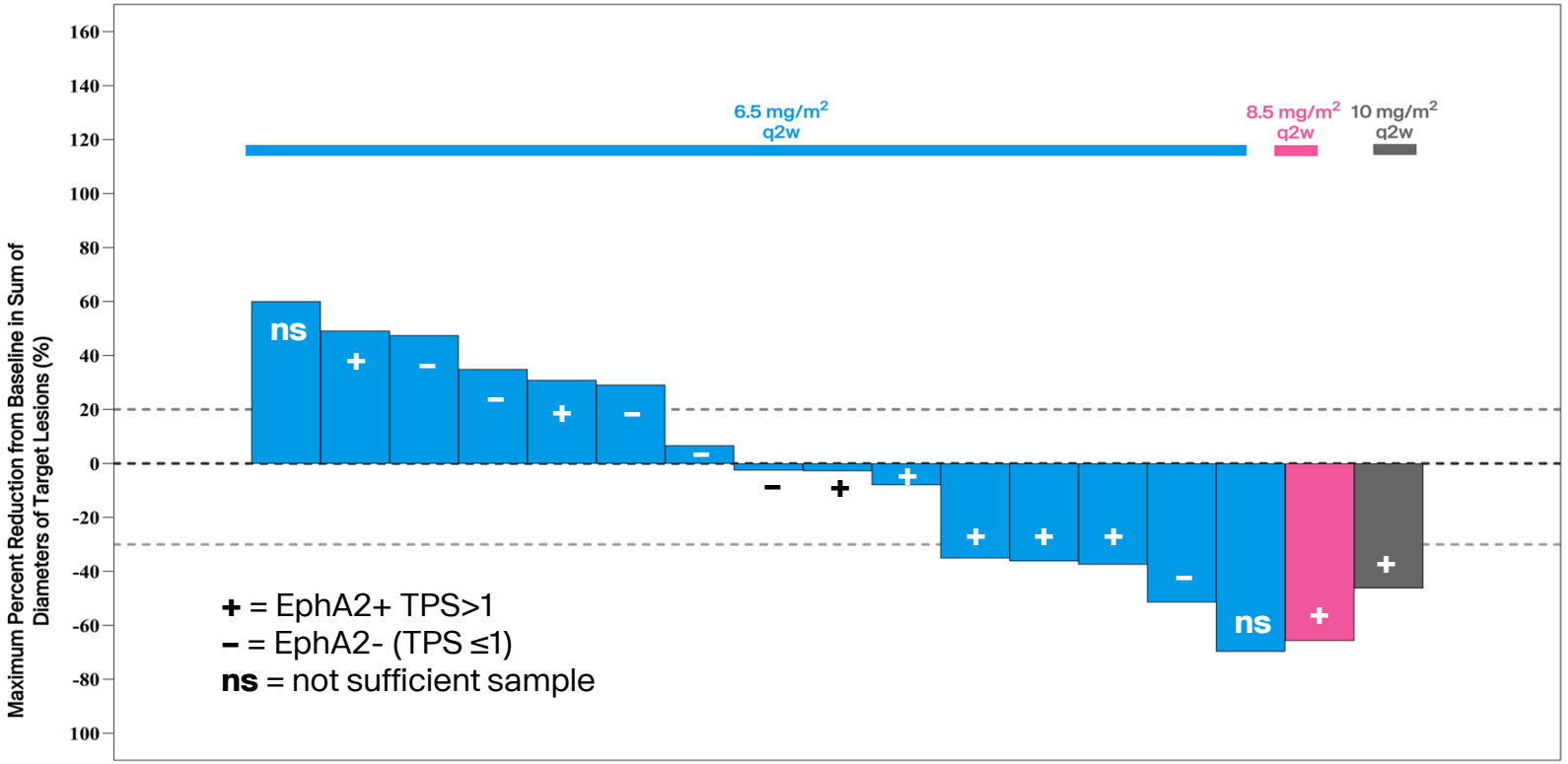
Data as of 27Sep2023.
[a]Includes dose escalation and expansion; [b]Peripheral neuropathy SMQ [broad] used; [c]All preferred terms defined in Skin and Subcutaneous Tissue SOC, excluding Alopecia, and SCAR MedDRA SMQ [broad] used, Any Grade: one patient was Grade 2, all others Grade 1; [d]Hemorrhage SMQ 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 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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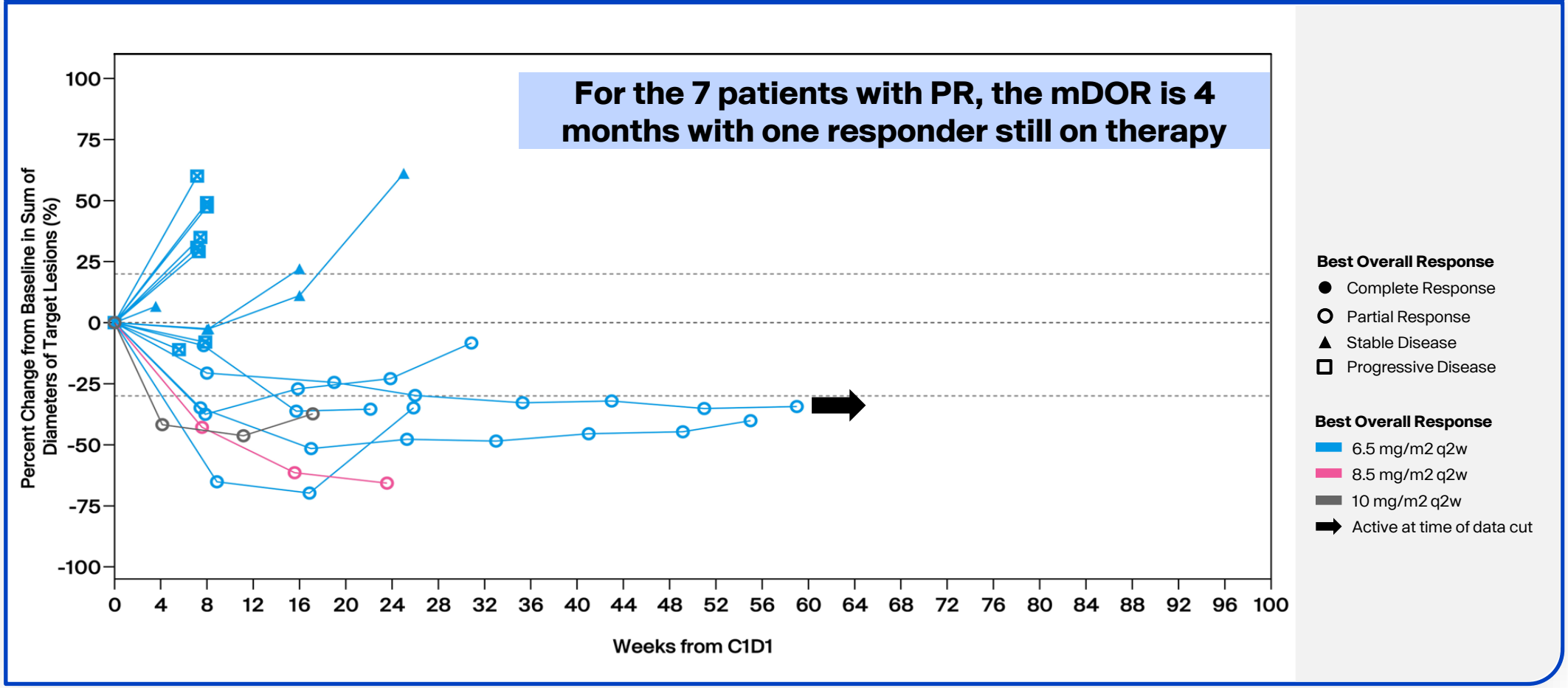
BT5528: Spider plot for tumor response in urothelial cancer

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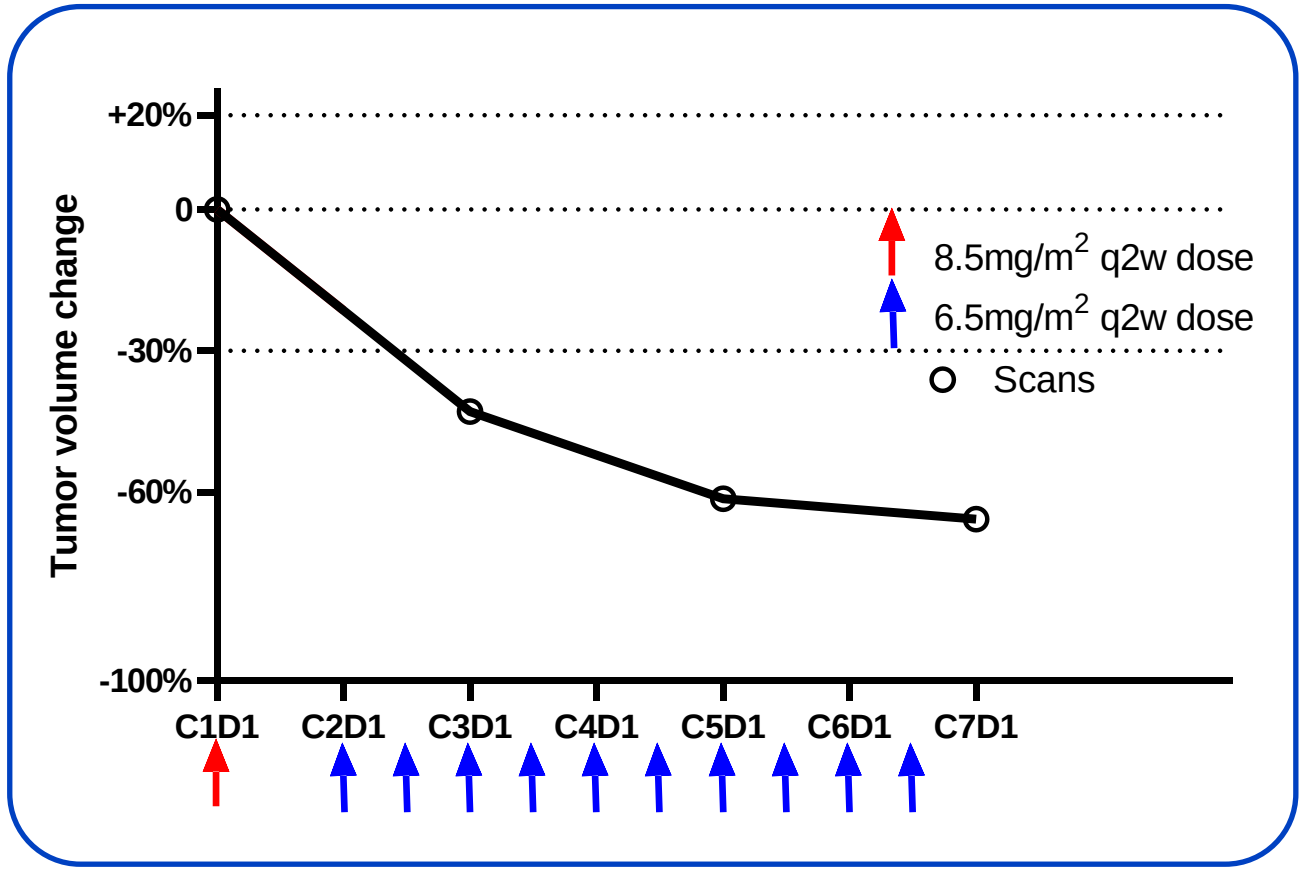
BT5528 shows potential in heavily pre-treated patients, including post-EV exposure

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



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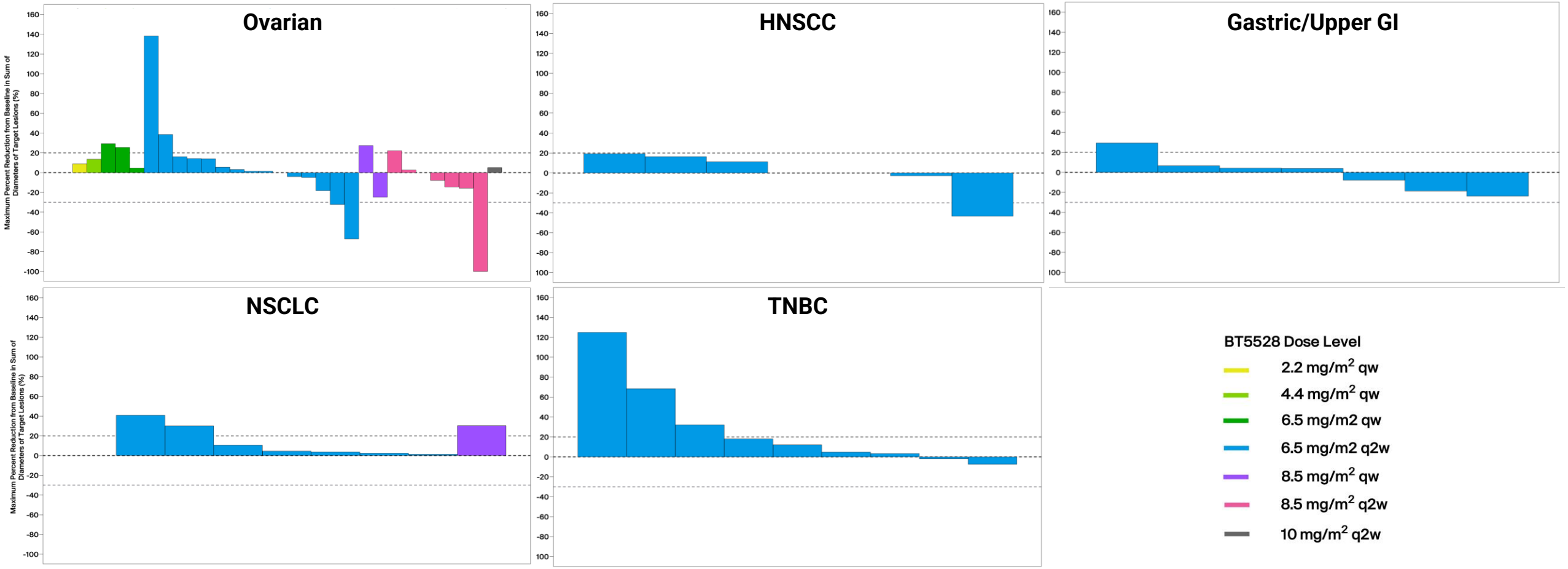
C1D1: Cycle 1 Day 1; C1D15: Cycle 1 Day 15; CR: complete response; EV: enfortumab vedotin; mDOR: median duration of response; PD: progressive disease; PR: partial response; Q2W: every other week.

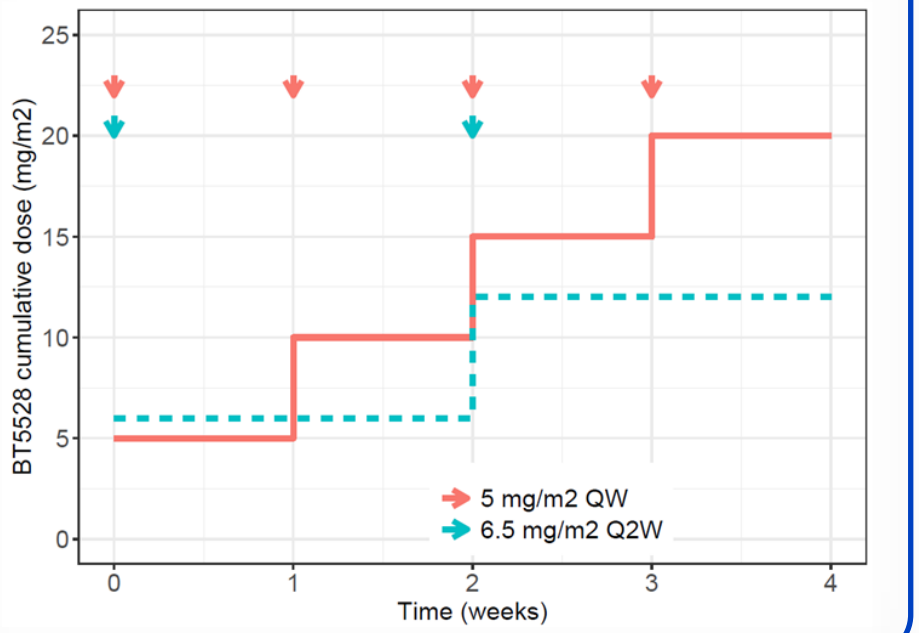
Emerging data with BT5528 in other solid tumors is informing our dose optimization strategy



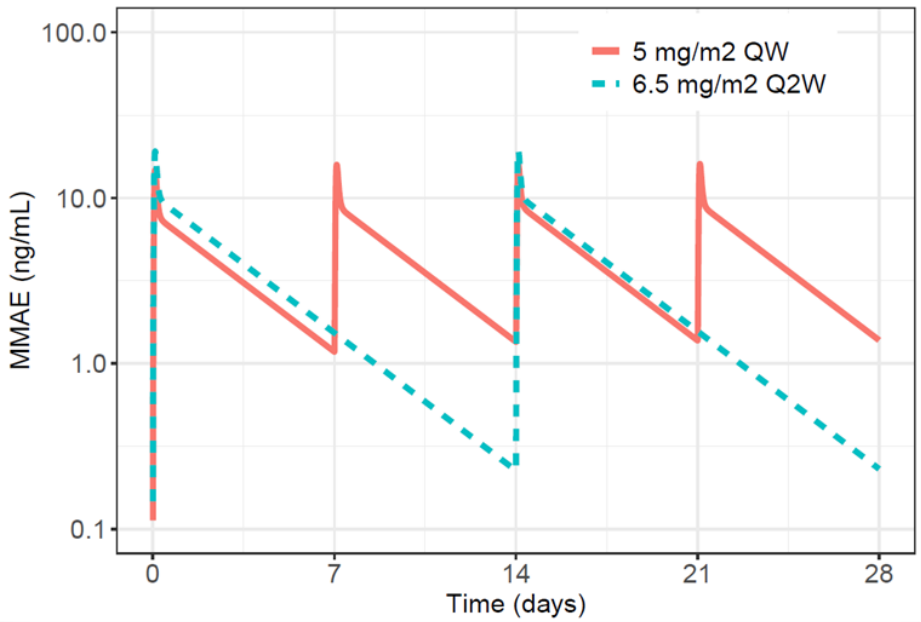
Data as of 27Sep2023.
Efficacy evaluable set used, defined as all enrolled patients with measurable disease at baseline who received at least one dose of BT5528 and had at least one adequate post-baseline disease assessment.
Other tumor types investigated: pancreatic, Ewing's sarcoma, rectal. No significant response or sustained stable disease seen.
NSCLC: non-small cell lung cancer; TNBC: triple-negative breast cancer. QW: weekly; Q2W: every other week.

BT5528 at 5 mg/m² QW may offer higher exposure to potentially further enhance response

Dosing frequency and cumulative dose



PK profile of MMAE



Ongoing 5 mg/m² QW cohort predicted to offer ~54% higher dose/exposure compared to 6.5 mg/m² Q2W dosing tested

Bicycle®

Data as of 27Sep2023.
MMAE PK profiles are simulated in a typical subject (with BSA = 1.8 m^2) using the population PK model.
PK: pharmacokinetic; QW: weekly; Q2W: every other week.

BT5528, a first-in-class BTC®, 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.

EphA2 Portfolio Market Opportunity

Bicycle®

Bicycle® molecules are evolving into a portfolio that could change the treatment landscape across solid tumors

BT8009

Next generation Nectin-4 agent

First-in-class BTC®

Market-leading potential

Lead tumor:
Urothelial

Additional tumors:
NSCLC, TNBC, Ovarian

BT7480

Innovative Nectin-4 CD137 IO agent

First-in-class Bicycle TICA®

Significant monotherapy and combination opportunities

Lead tumor:
Cervical

Additional tumors:
NSCLC, HNSCC

BT5528

EphA2 agent going where ADCs have been unable to go

First-in-class BTC®

Differentiated candidate targeting the 'undruggable'

Lead tumor:
Urothelial

Additional tumors:
Ovarian, HNSCC, Gastric/Upper GI

Bicycle®

ADC: antibody drug conjugate; Bicycle TICA: Bicycle tumor-targeted immune cell agonist; BTC: Bicycle toxin conjugate; GI: gastrointestinal; HNSCC: head and neck squamous cell carcinoma; IO: immuno-oncology; NSCLC: non-small cell lung cancer; TNBC: triple-negative breast cancer.

BT5528: Potential first-in-class treatment for an ‘undruggable’ target providing new innovation and opportunity

Product Vision

BT5528, a first-in-class agent targeting EphA2, demonstrates game changing clinical activity across multiple solid tumors addressing areas of high clinical unmet need

Strategic Imperatives

1. **Meaningful efficacy in urothelial cancer with an improved tolerability profile**

2. **Greater efficacy potential and safety gains in additional tumors**
   Ovarian, HNSCC, Gastric/Upper GI

GI: gastrointestinal; HNSCC: head and neck squamous cell carcinoma.

BT5528 could provide a novel therapy for patients and strengthens our commitment to treating urothelial cancer

Priority

Develop an efficacious and tolerable treatment for patients who progress or have intolerance to current 1L or 2L+ metastatic urothelial cancer treatments

Key areas of opportunity

- Leverage our infrastructure and resources deployed for BT8009 in urothelial cancer
- Demonstrate responses in sequence or combination and/or primary vs secondary resistance
- **Develop a portfolio of solutions in urothelial cancer for patients**

1L: 1st line; 2L+: 2nd line or later.

Along with BT8009, BT5528 could establish the foundation for a urothelial franchise and external expert enthusiasm is high

KOL feedback on target

"**Potential for two targets in UC** since 80%+ express Nectin-4 but only 40% ORR. **EphA2 could close gap in ORR**"

"**Novel target with potential to generate enthusiasm in UC for 2L+,** current alternative is sacituzumab govitecan which carries a black box warning for neutropenia and diarrhea"

KOL views on approach

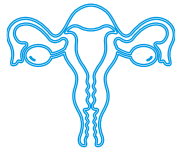
"Look at EV naïve and EV exposed, sequence or combination, and primary vs secondary resistance…"

"If you see a durable response post EV, good tolerability and **ORR 25-30%, it could drive potential accelerated approval in this space**"

Bicycle®

ASCO GU February 2023, ASCO June 2023 Bladder Cancer Key Opinion Leader Meetings
2L+: 2nd line or later; EV: enfortumab vedotin; mUC: metastatic urothelial cancer; ORR: objective response rate.

The cancer treatment landscape is evolving, but the need for new druggable targets that improve patient outcomes remains



US Ovarian cancer
- 12,000 metastatic[1,3]
- 5-year survival rate of 19%[2]
- Top priority is tolerable agents[2]

US Gastric cancer
- 21,000 metastatic[3]
- 5-year stage IV survival rate of 3%[2]
- Limited therapies, limited efficacy[2]

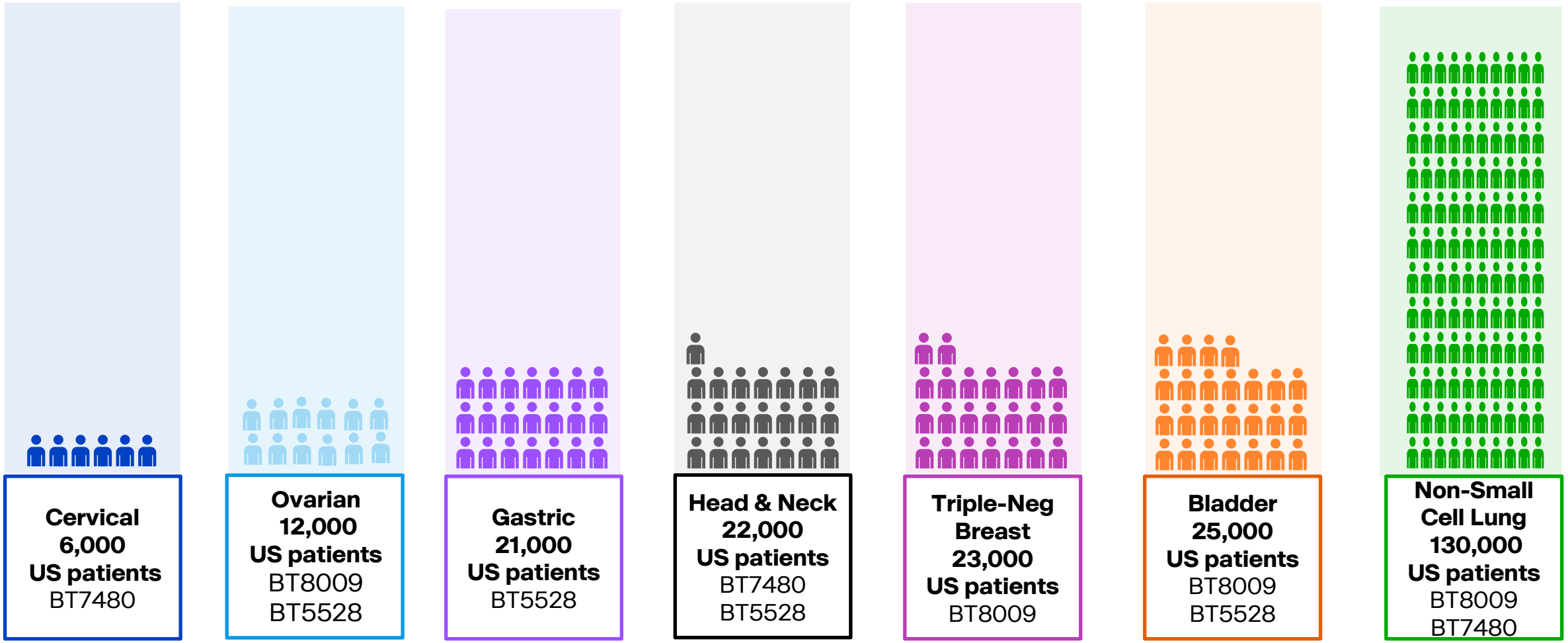
US Head and Neck cancer
- 22,000 metastatic[3]
- 5-year stage IV survival rate of 14%[2]
- High reoccurrence rates, low survival benefit[2]

Unmet Need

- **New efficacy benchmarks have been set in ovarian cancer, but tolerability improvements are still needed[2]**
- **Newer treatment regimens in gastric and head and neck cancers only offer ~1-2 month improvements in efficacy endpoints along with ongoing toxicity challenges[2]**

1. The American Cancer Society Statistics Center 2023, accessed Nov 2023
2. Cerner Enviza, Future Trends and Insights: Ovarian, published Oct2023, Gastric, published Nov2023, Head and Neck, published Sep2023
3. Patient metrics source: Global Data, Global Drug Forecast and Market Analysis

The Bicycle® Advantage: We believe our emerging clinical programs have the potential to benefit nearly a quarter of a million US patients in the metastatic setting across multiple solid tumors



Patient metrics source: Global Data, Global Drug Forecast and Market Analysis.
SEER US Incidence Data: Surveillance, Epidemiology, and End Results Program, National Cancer Institute, Nov2022 Submission.
Populations represent potentially addressable patient population in the metastatic or advanced stage for the US population annually.

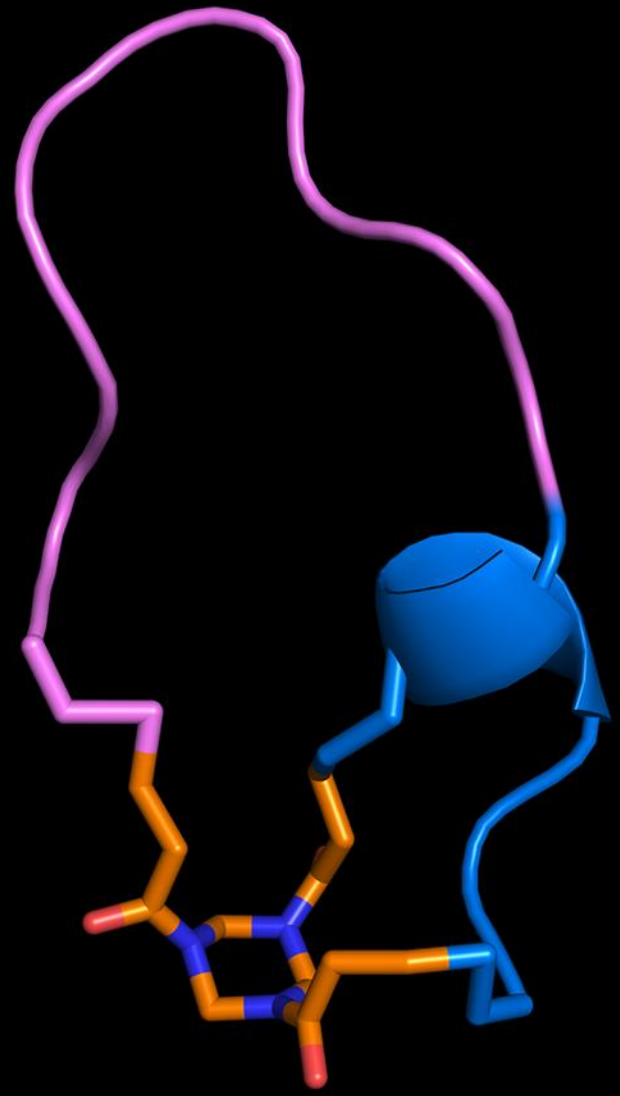
Q&A

Bicycle®

Agenda

Time	Topic	Speaker(s)
8 a.m.	Welcome and Company Overview	Kevin Lee
8:15 a.m.	Our Nectin-4 Portfolio ▸ BT8009 and BT7480	Nicholas Keen Santiago Arroyo Jennifer Perry
9:30 a.m.	Q&A	Management Team
10:00 a.m.	Break	
10:10 a.m.	Our EphA2 Portfolio ▸ BT5528 and BT7455	Nicholas Keen Santiago Arroyo Jennifer Perry
10:50 a.m.	Q&A	Management Team
11:05 a.m.	Our Platform Opportunities	Nicholas Keen Michael Skynner
11:40 a.m.	Q&A	Management Team
11:50 a.m.	Summary and Close	Kevin Lee

What’s next for Bicycle



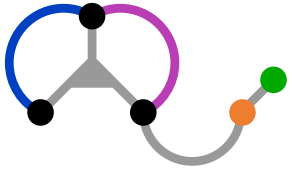
Bicycle®

Next-generation BTCs

Bicycle®

The oncology challenge: Achieving the optimal balance between efficacy and toxicology

ADC

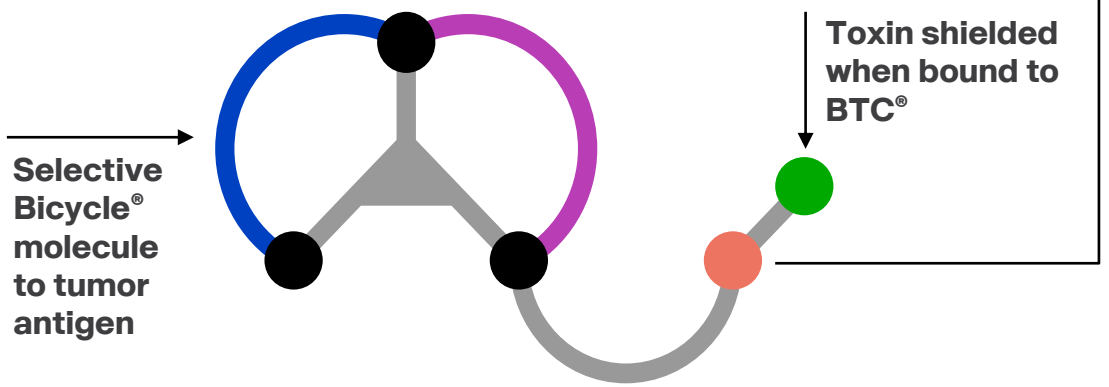


BTC®

Antigen expression in non-target tissue (target-mediated toxicology)	Reduced parent exposure may reduce normal tissue delivery. No severe skin tox observed with BT8009, and no bleeding events observed with BT5528.	✓
Target independent cellular uptake	Unlikely given clearance mechanisms are mostly mAb specific	✓
Payload de-conjugation and release	Free MMAE may drive neutropenia, some neuropathy. Design linkers with increased systemic stability, efficient tumor payload release	Focus for next generation BTCs

We are identifying a suite of proprietary linkers to address non-specific payload release

Next-gen BTCs: linker focus



1st Generation Val-Cit linkers

- Val-Cit linkers were designed for ADCs

2nd generation linkers

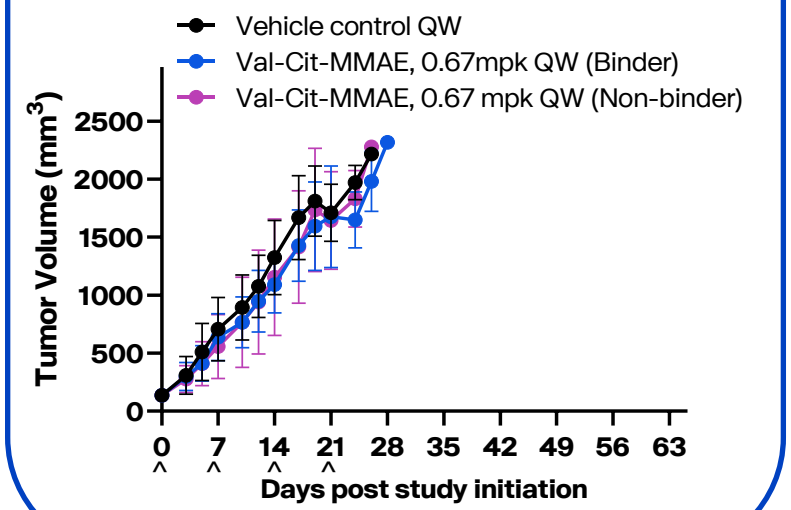
- Designed for BTCs, likely target specific
- Unlikely to be "one size fits all"
- Peptide platform enables discovery (hundreds of linkers evaluated)

- We have identified linkers with improved stability/cleavage trade off in model systems

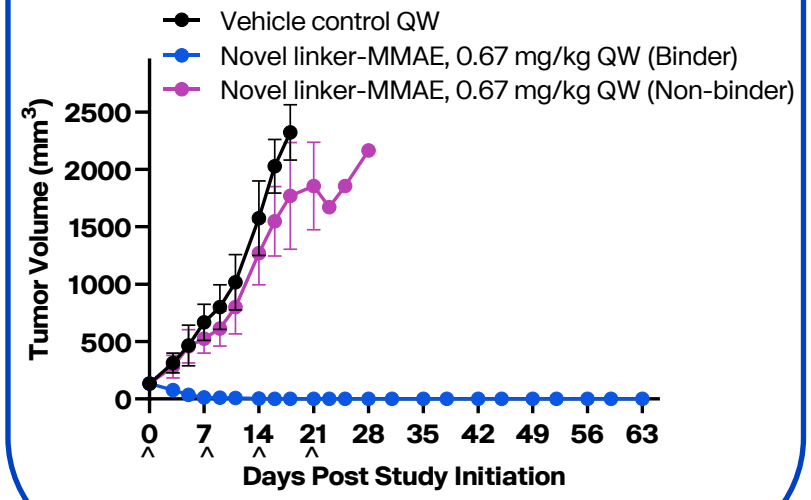
New proprietary linkers drive improved performance in preclinical models

- **Novel linker improves anti-tumor activity and reduces MMAE exposure in preclinical models**
- **This may translate to better efficacy and reduced MMAE-driven toxicities**

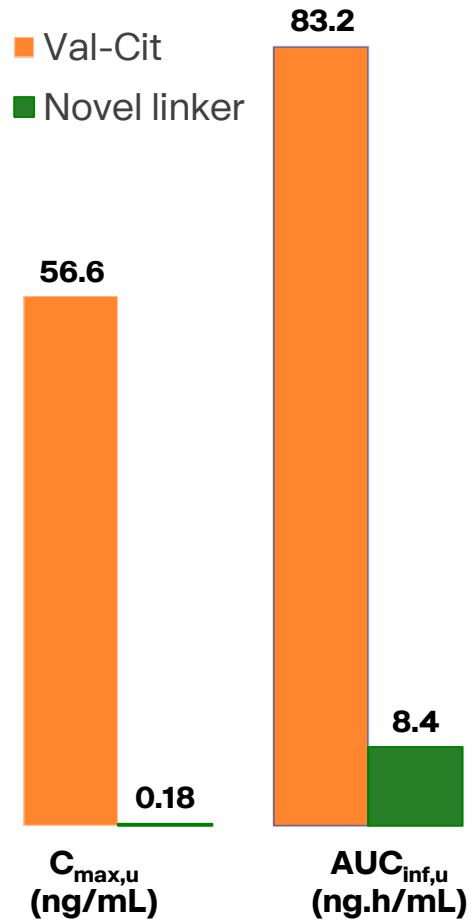
Val-Cit



Novel linker



MMAE exposure



HT1080 mice were treated with Bicycle® binder vs. non-binder and followed for up to 9 weeks.

Mouse PK (dose normalized) at the estimated minimum efficacious dose (MED) – 5 mg/kg for Val-Cit, 0.67 mg/kg for novel linker.

Bicycle®

Bicycle Therapeutics unpublished data.
QW: weekly

Next-generation BTCs: We have a deep portfolio of tumor antigen Bicycle® binders which we believe have the potential to transform the targeted delivery field

SUMMARY

- We believe that our 1st generation BTCs represent a significant step forward in tumor targeting and an emerging differentiated clinical profile
- We believe that our 2nd generation molecules will deliver further improvements

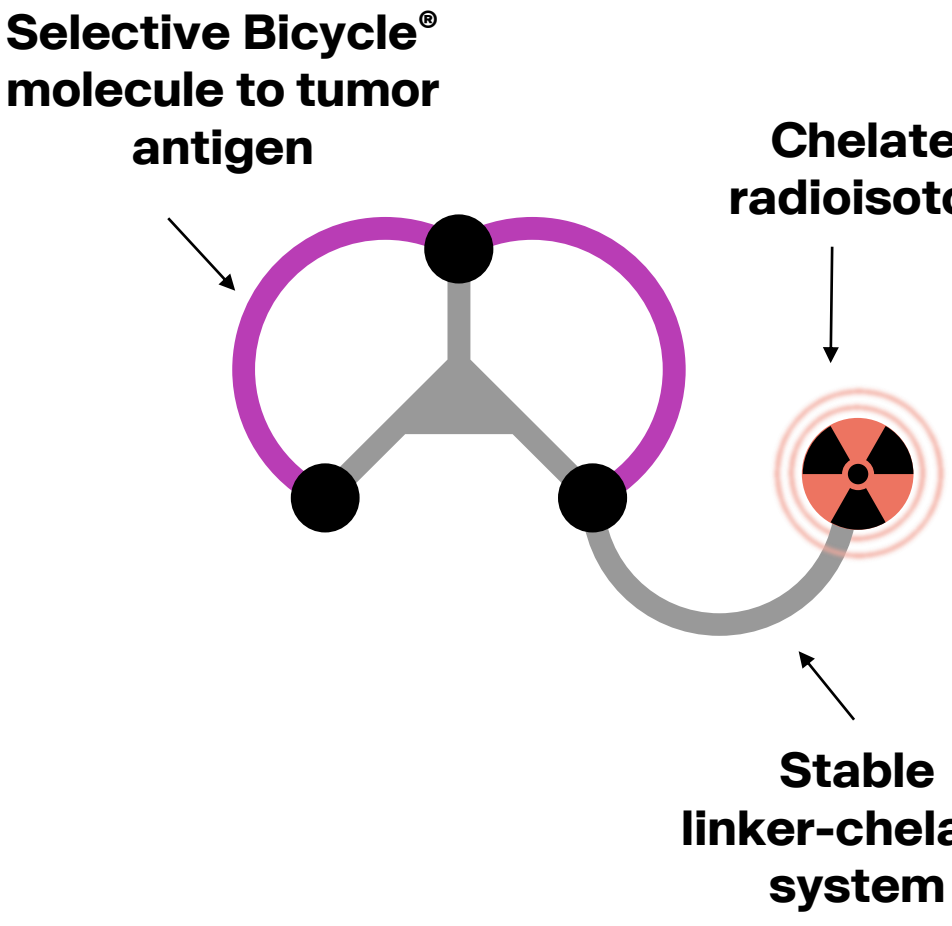
NEXT STEPS

- **Incorporate next generation linkers into future molecules**
- **Select a clinical candidate using our next-generation technology in 2H 2024**

Bicycle Radionuclide Conjugates

Bicycle®

Bicycle® 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

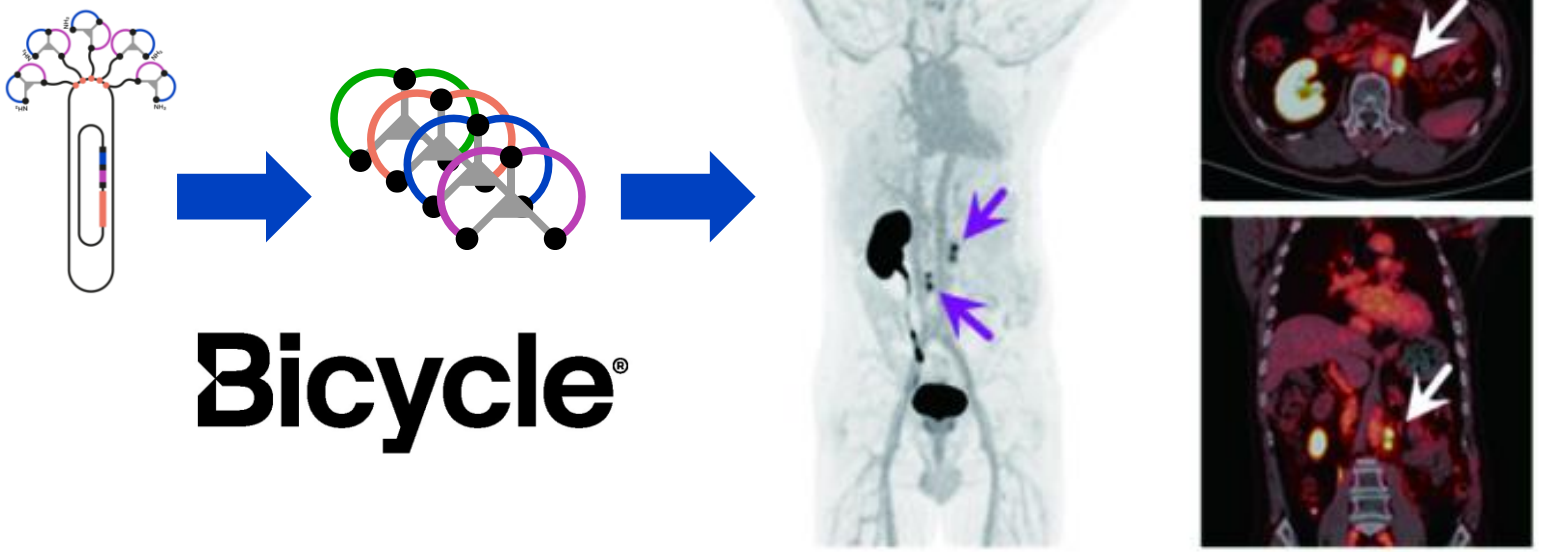
We are ideally positioned to deliver new ligands for radiopharmaceutical use

Therapeutic radiopharmaceuticals shown **clinical potential** and **commercial opportunity** in NETs and mCRPC (SSTR and PSMA)

Majority of industry focusing on **small** number of targets, typically those with pre-existing ligands

There are multiple opportunities for **novel** radioligands

Given desired characteristics, **peptides well suited** for radiopharmaceuticals targeting **solid tumors**



Duan X et al. 2023. *Clin Cancer Res*, 29(17):3395-3407.
mCRPC: metastatic castration-resistant prostate cancer; NET: neuroendocrine tumor; PSMA: prostate specific membrane antigen; SSTR: somatostatin receptor.

Access to multiple development paths provides opportunity for full potential of BRCs to be unlocked

Collaboration

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

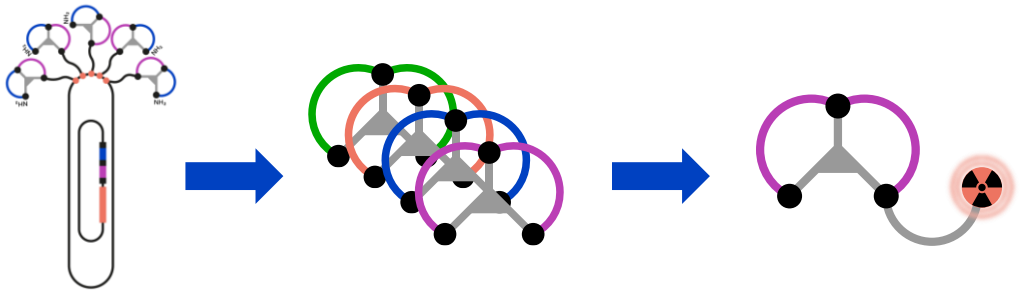
Collaboration

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

Internal RP Pipeline

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

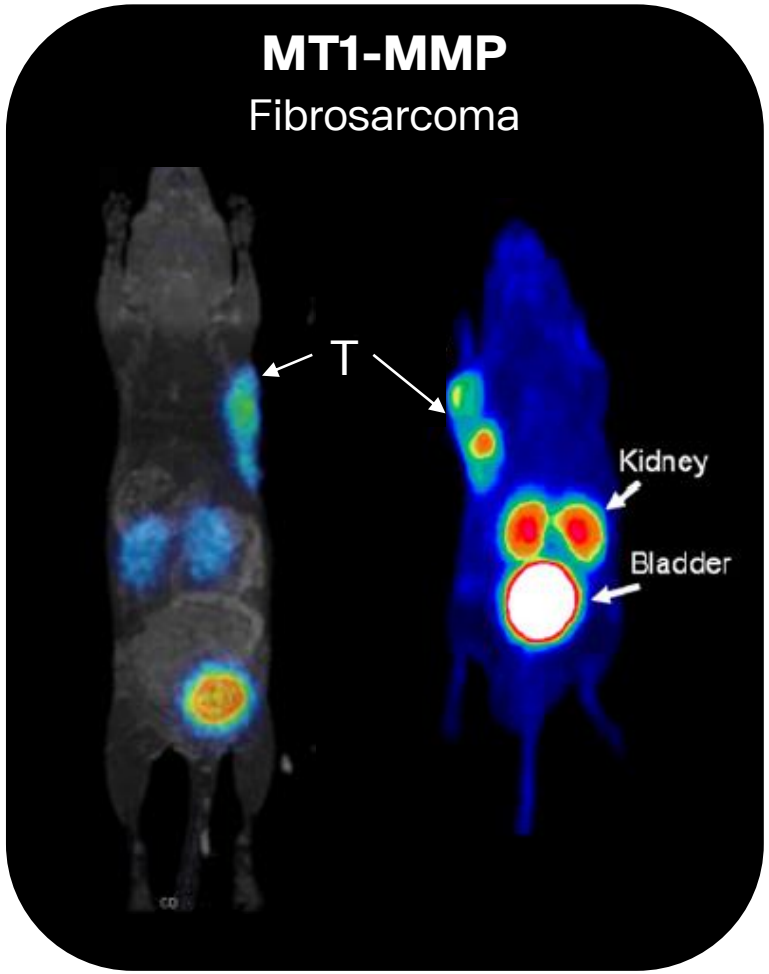
We are building a deep portfolio of Bicycle® tumor antigen binders



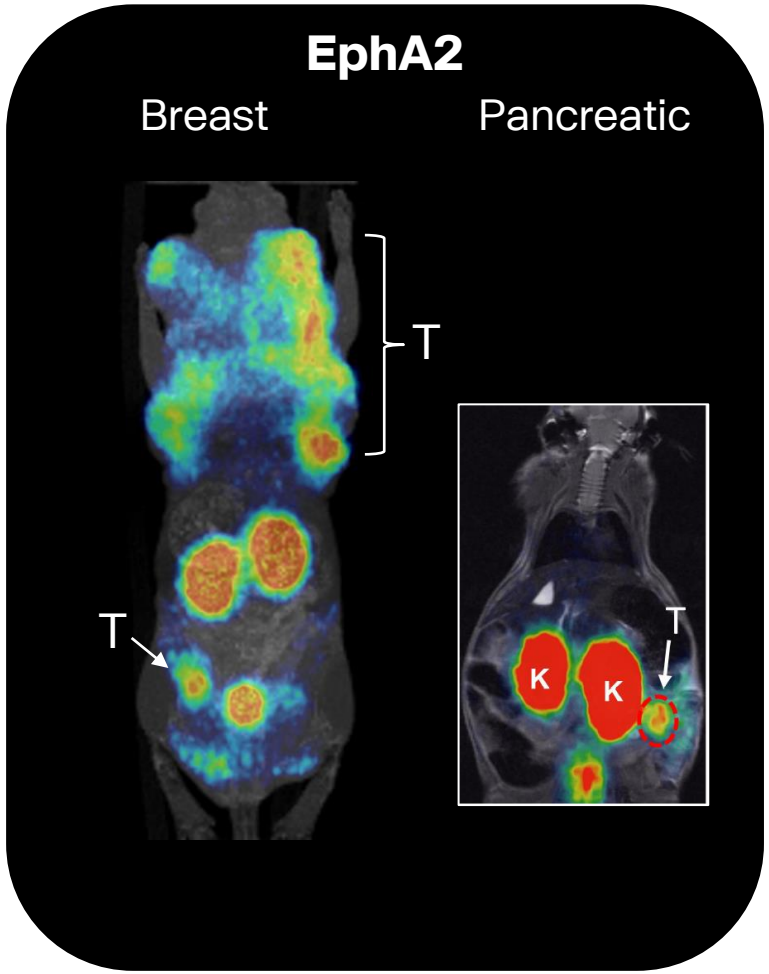
Target	Indications	Affinity	Discovery / POC	BRC™ Lead Optimization	IND enabling
MT1 (Im)	Multiple cancers	20 pM			
MT1 (Tx)	Multiple cancers	20 pM			
EphA2	Pancreatic, ovarian, head and neck	170 pM			
CD38	Hematological	100 pM			
Target 1	Not disclosed	3 nM			
Target 2	Not disclosed	1 nM			
Target 3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

Im – imaging, Tx = therapeutic

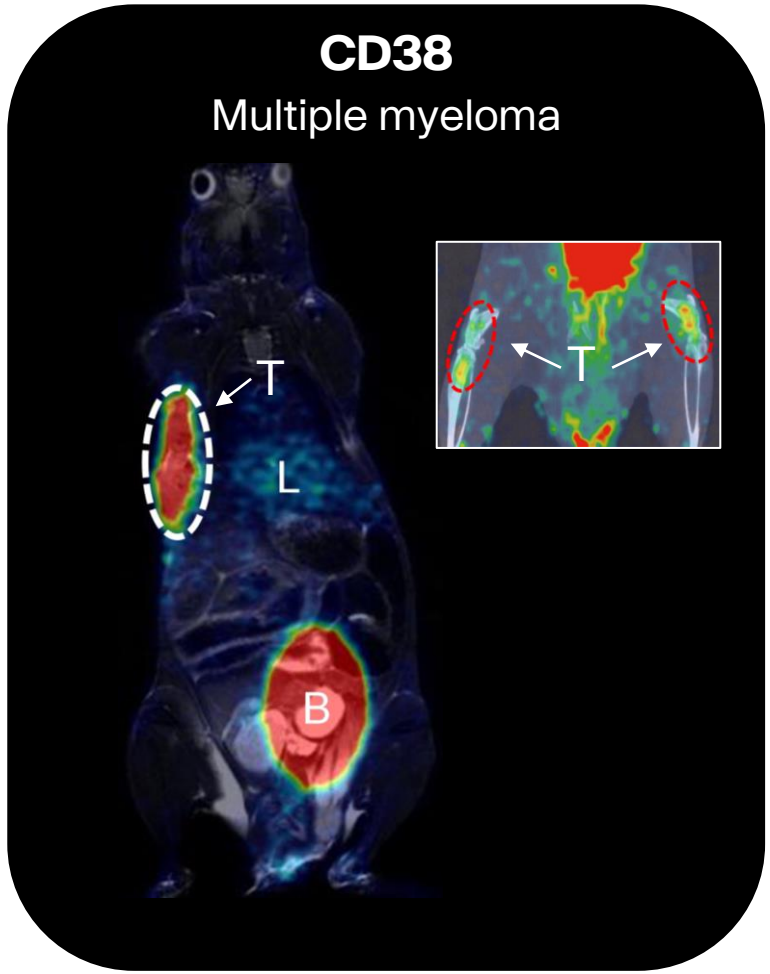
Bicycle® molecules show selective tumor uptake and ideal PK across a range of targets and tumor models



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



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

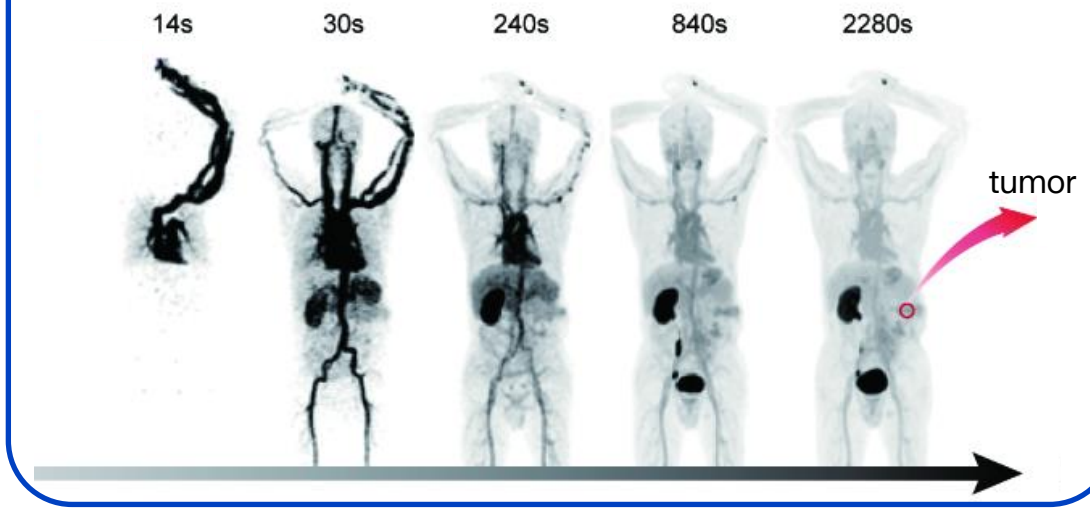


Left: MOLP8 tumor xenograft, 90 min P.I.
Right: MOLP8 disseminated tumor model (Sharma AK et al. BioRxiv)

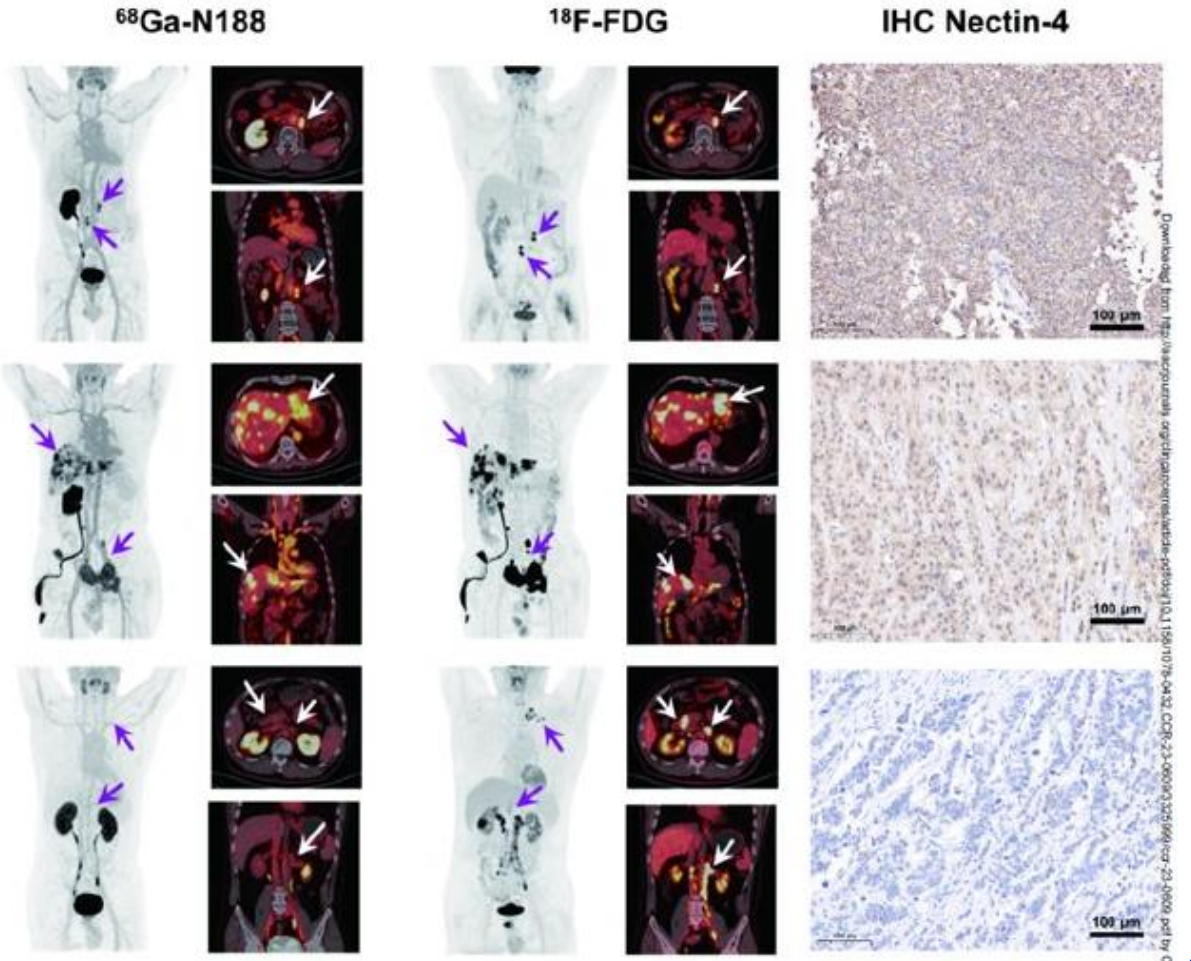
BRC™ favorable properties translate well in clinical imaging studies

- BRC™ using a Nectin-4 Bicycle® binder able to image metastatic urothelial cancer in human patients
- Selective tumor uptake which correlates with target expression

Nectin-4 BRC™ pharmacokinetics



Tumor uptake correlates with target expression



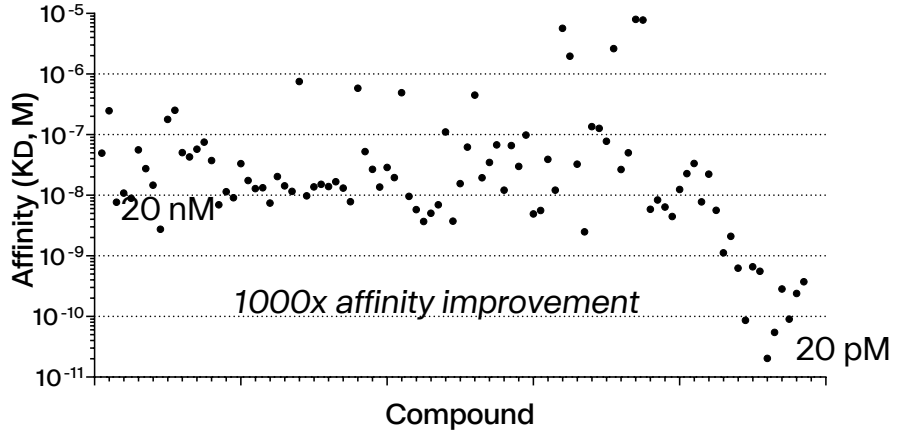
Bicycle®

Duan X et al. 2023. *Clin Cancer Res*, 29(17):3395-3407.
BRC™: Bicycle Radio Conjugate; FDG: fludeoxyglucose F18; IHC: immunohistochemistry.

A key component of The Bicycle® Advantage: Properties can be engineered via medicinal chemistry

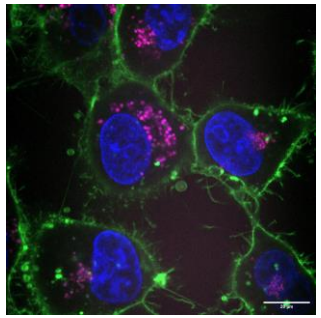
Binding properties

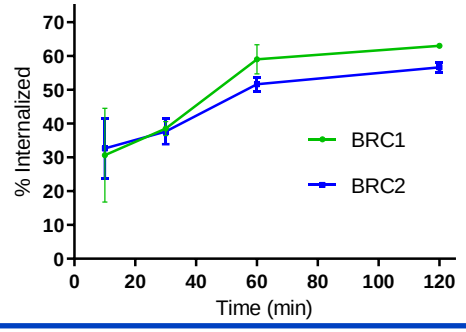
Binding affinities of compounds synthesized during lead optimization, as determined by surface plasmon resonance.



Internalization

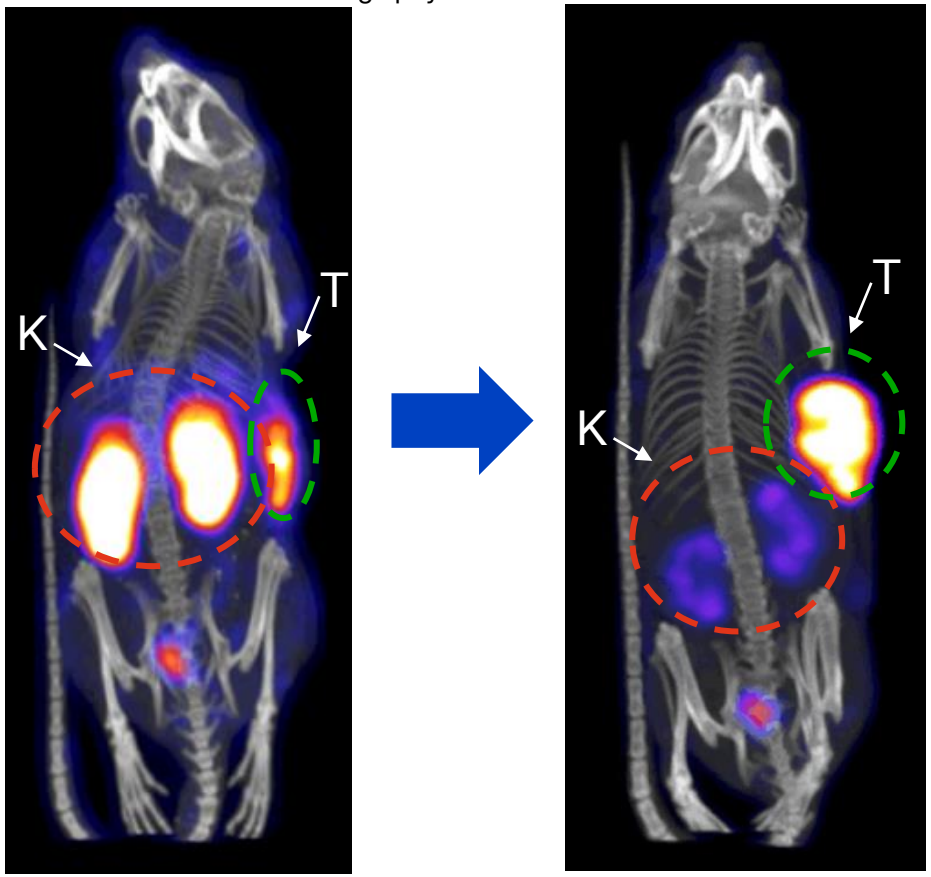
Left – Fluorescently labelled Bicycle® molecules are efficiently internalized into target expressing cells *in vitro*, as determined by confocal microscopy. *Right* – Lu-177 labelled BRCs are rapidly internalized into target expressing cells *in vitro*.





Kidney uptake / retention

In-111 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.



Bicycle®

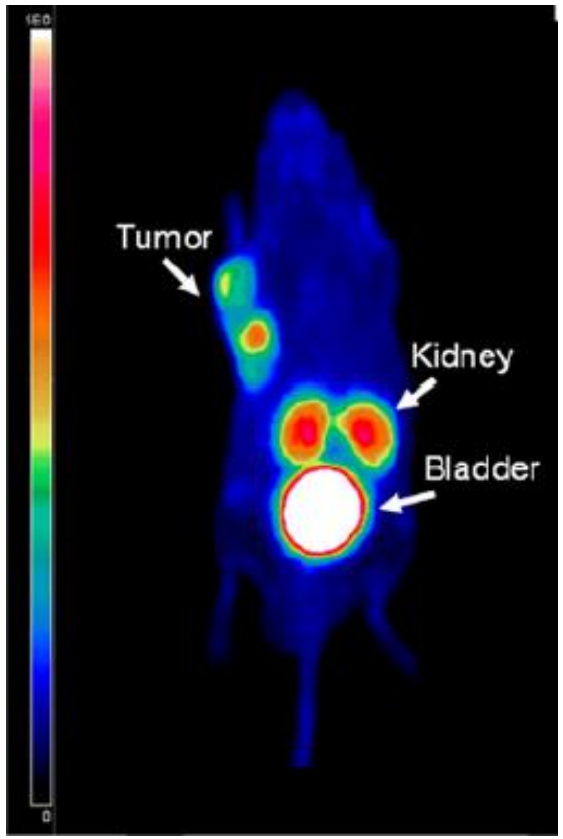
Bicycle Therapeutics unpublished data.
BRC: Bicycle Radio Conjugate.

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 (eg, 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%**

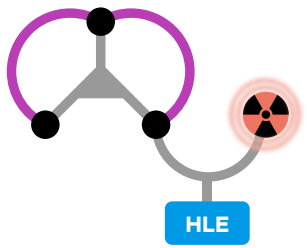
MT1-MMP expression was determined using IHC performed with in house validated antibody, positive cases were defined as H-score ≥ 50 in tumor cell membrane.



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

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™ 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™ to tumor cells

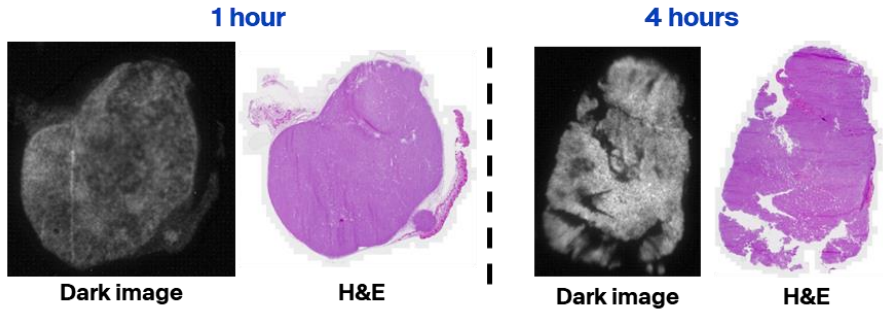
Half-life extending moiety

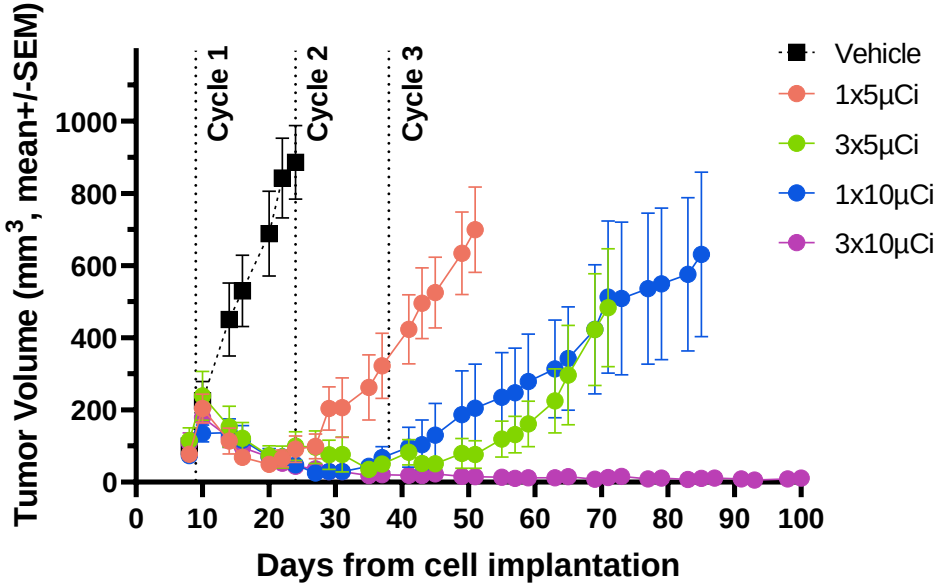
- Reversible albumin binding motif
- Prolongs circulating half-life of conjugate

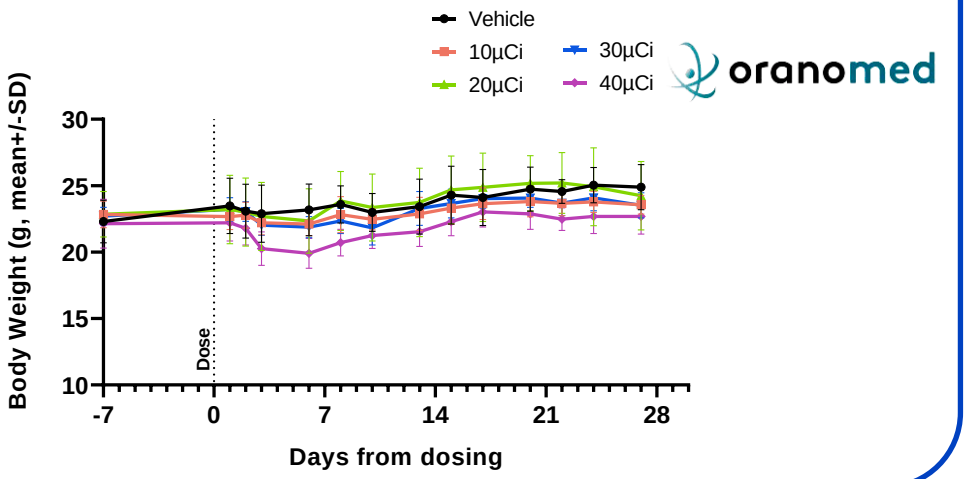
Lead-212 payload

- 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 Bicycle Radio Conjugates (BRCs) 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™ shows potent anti-tumor activity and is well tolerated in preclinical studies
- In 2023, we have generated $95M in non-dilutive capital leveraging our BRC™ platform

NEXT STEPS

- **Expect to generate early human imaging data from our wholly owned BRC pipeline over 2024**

Bicycle®

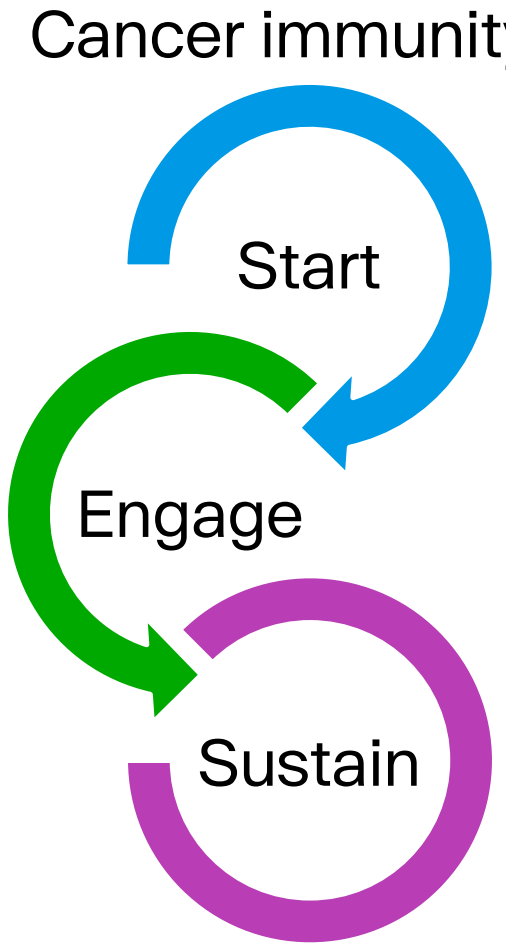
BRC: Bicycle Radio Conjugate; MT1-MMP: membrane type 1 matrix metallopeptidase.

Next-generation immuno-oncology

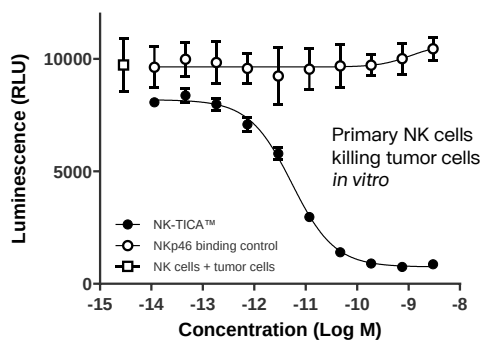
Bicycle®

Driving immune activation across the cancer immunity cycle: Potential to transform the space

- Immune activation occurs via activating receptors on immune cells → drug targets
- The industry has not succeeded in drugging these receptors to treat cancer
- The properties of Bicycle® molecules match the design goals dictated by the biology

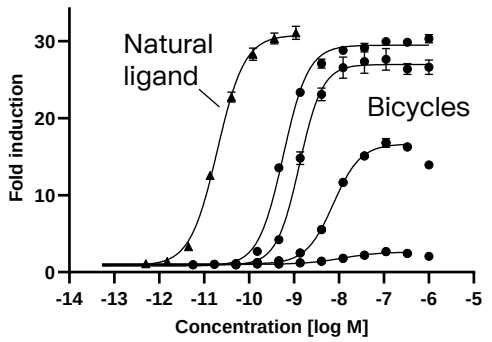


NK cell engagers



Dufort F et al., 2023. *Cancer Res*, 83(7 Suppl) :1806.

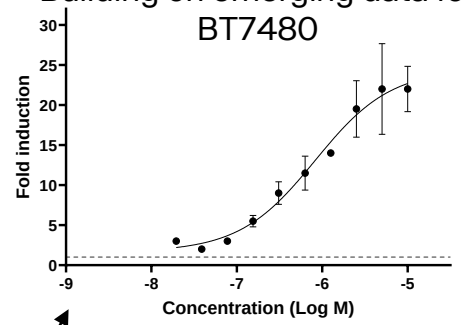
Cytokines



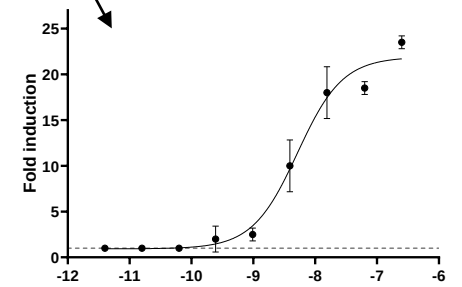
Reporter cell assay

"Dual active" CD137 Bicycle TICA®

Building on emerging data for BT7480



Block PD-L1/PD-1 signaling
Activate CD137 signaling

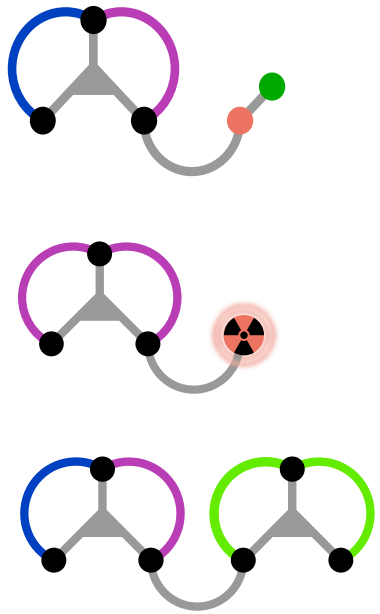


Reporter cell assays, same cpd in both assays

We are building a deep portfolio of Bicycle® tumor antigen binders and effector molecules

OPPORTUNITY

Target	Indications	Affinity
MT1	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	mM to pM



STRATEGY

- Orthogonal approaches for widely expressed tumor antigens based on knowledge of tumor biology (e.g., Nectin-4)
- Focussed approaches for high value targets with narrow expression in single tumor types (e.g., radioisotope conjugates)

Beyond oncology

Bicycle®

The Bicycle® Advantage: Additional horizons beyond oncology

Platform

Nobel-prize winning technology

- Platform has screened over 150 highly diverse targets
- >85% screening success rate since IPO across a range of challenging target classes
- Majority of the targets successfully screened are unprecedented with Lipinski-compliant small molecules

Properties

Unique new bicyclic modality

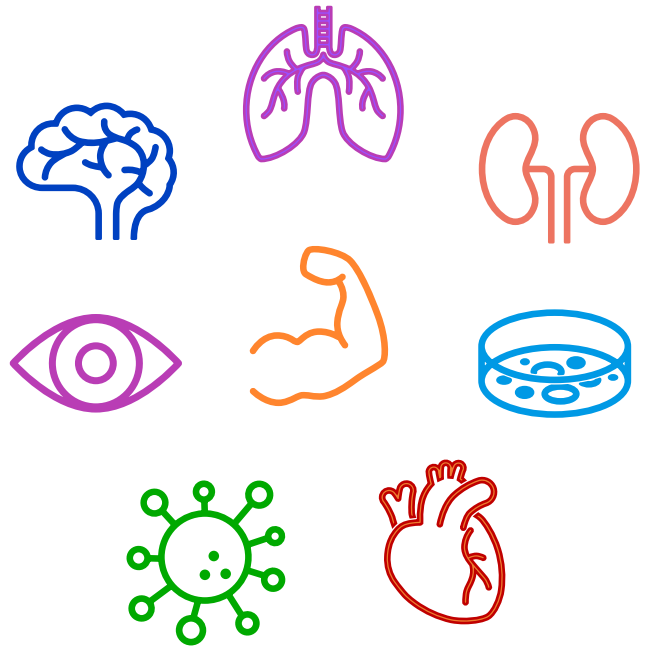
- Bicycle® molecules can be optimized to have high affinity/selectivity
- Bicycle® molecules can be "tuned" to have appropriate drug-like properties
- Bicycle® molecules have multiple potential applications and therapeutic uses

Partnerships

Validate platform and provide non-dilutive funding

- Collaboration brings expertise from the partner
- Collaboration brings non-dilutive funding
- Collaboration can help us to get innovative medicines to as many patients as possible

Since our founding, Bicycle has successfully explored other therapeutic applications using non-dilutive funding



THERAPEUTIC AREAS

IONIS

AstraZeneca

Innovate UK

OXURION

Bioverativ
A SANOFI COMPANY

Dementia Discovery Fund

lifeArc

UKRI Biotechnology and Biological Sciences Research Council

INDUSTRIAL PARTNERS AND FUNDERS

UNIVERSITY OF CAMBRIDGE

UNIVERSITY OF OXFORD

Imperial College London

UCL

WARWICK
THE UNIVERSITY OF WARWICK

UNIVERSITY OF LIVERPOOL

UKRI MRC Laboratory of Molecular Biology

Newcastle University

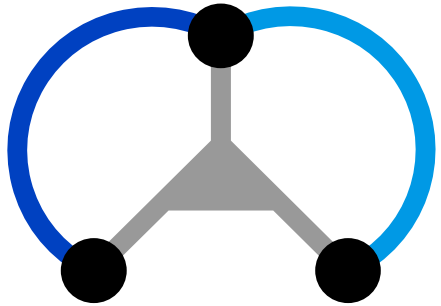
Alzheimer's Research UK
The Power to Defeat Dementia
UNIVERSITY OF OXFORD
DRUG DISCOVERY INSTITUTE

ACADEMIC COLLABORATORS

Our work outside oncology has generated ~$88M in non-dilutive funding

The Bicycle® Advantage: A plug-and-play approach to precision targeting

Bicycle® molecule



Bicycle® molecule generation against hard to drug targets

- Small molecule
- Toxin
- Radiological
- Bicycle® molecule
- Antisense oligonucleotide
- siRNA
- Lipid nanoparticle
- Protein
- Cell
- Virus, gene therapy

Choice of payloads

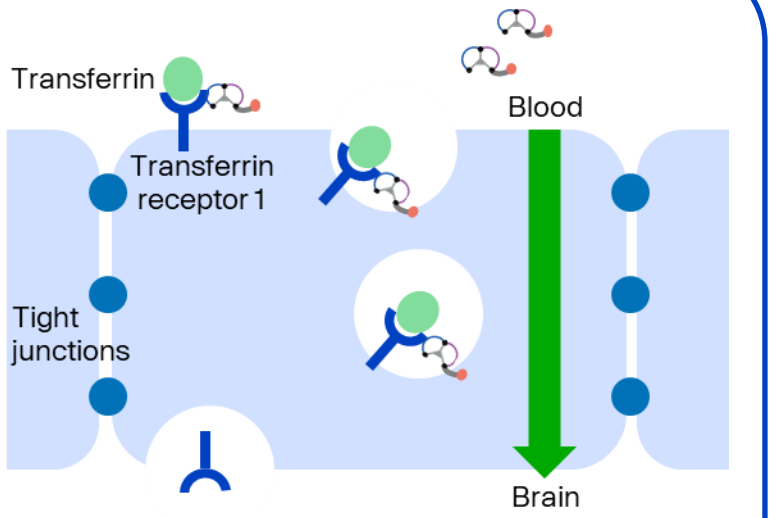
Cell specific antigens enable precision targeting of diseased cells

Enabled by high affinity & exquisite selectivity

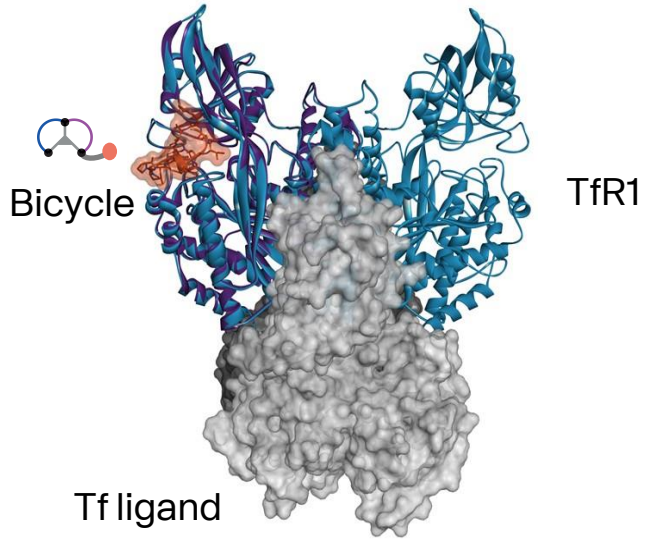
Generate novel therapeutics with new mechanisms of action

Precision-targeted therapeutics

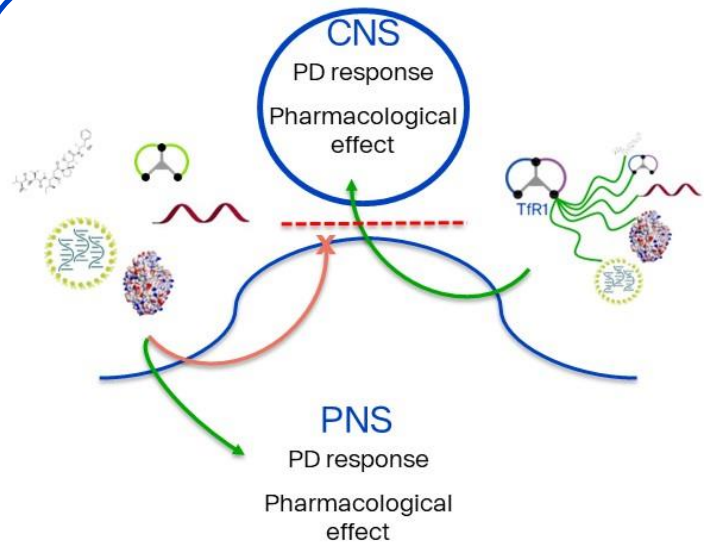
Precision targeting exemplified by transferrin receptor (TfR1) for delivery into the CNS



TfR1 receptor enables CNS delivery



We successfully drugged TfR1, developing molecules binding to a novel unprecedented site



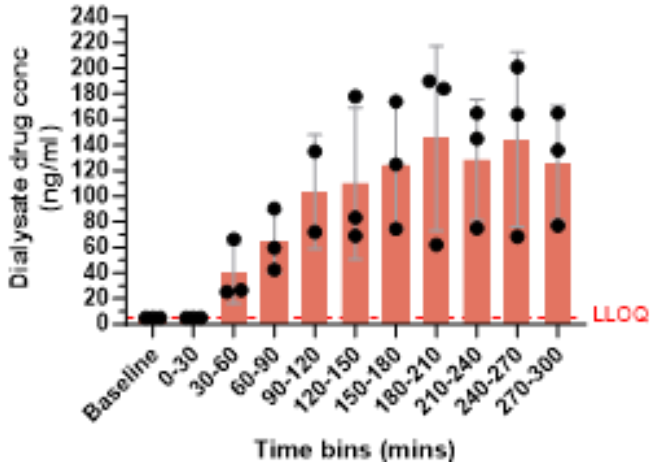
We are using this technology to deliver a range of peripherally restricted molecules

Non-dilutive funding provided by the Dementia Discovery Fund.
CNS: central nervous system; PNS: peripheral nervous system; PD: pharmacodynamic; Tf: transferrin; TfR1: transferrin receptor.

CNS delivery can be achieved through precision targeting by Bicycle® TfR1 molecules

- Bicycle® molecules are able to cross the blood brain barrier in significant quantities
- TfR1 has successfully delivered peripherally restricted payloads
- A range of additional tissue delivery Bicycle® molecules are under optimization in Neuroscience and other therapeutic areas

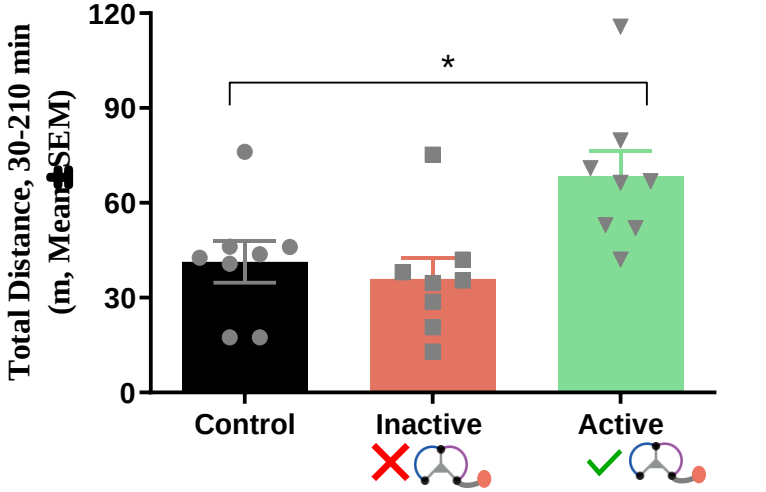
Brain TfR1 Bicycle® molecule levels after peripheral administration



Bicycle® molecule infused I.V. at 10 mg/kg/h for 5 hours in NHP

PK: Bicycle® molecules identified in CNS

Peripheral delivery, central activity of small molecule



Bicycle® molecule administered s.c. at 30 mg/kg in hTfR1 mice

PD: Small molecules delivered/active in CNS

Target	Cell/tissue
Undisclosed	Next gen CNS
Undisclosed	Universal delivery
Undisclosed	Kidney
ACE2	Lung
Undisclosed	Fibroblasts
NKp46	NK cells
Undisclosed	Dendritic cells
Undisclosed	Vascular

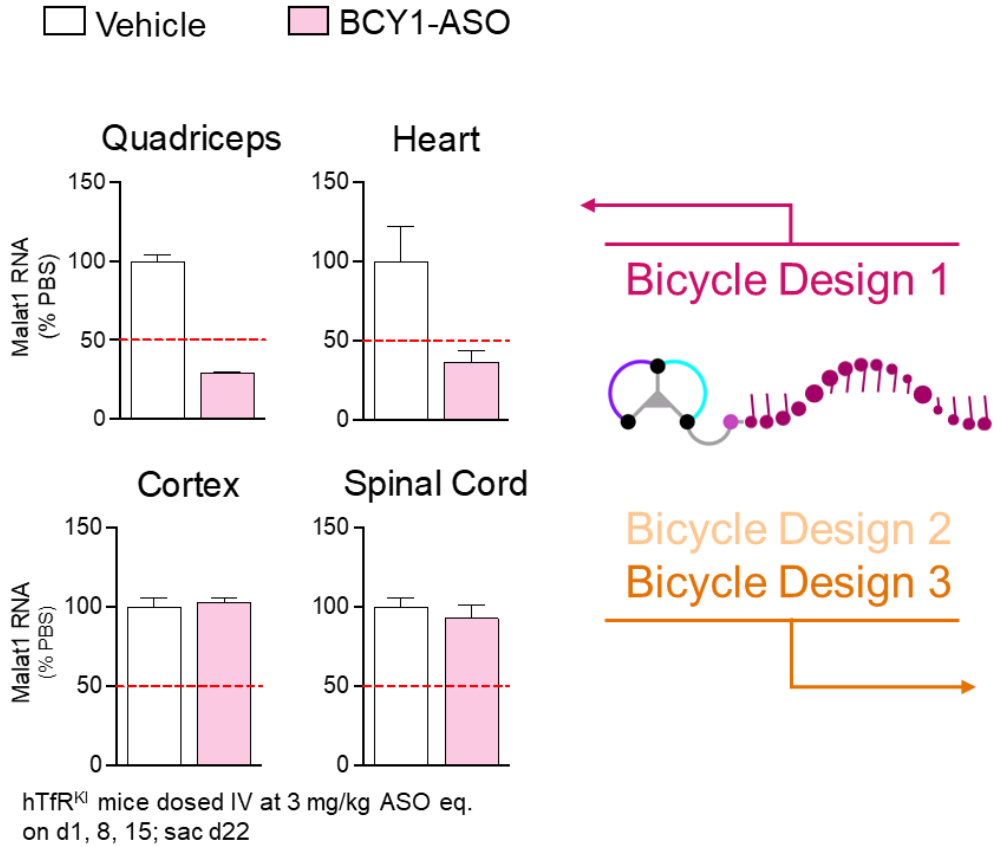
Our cell-targeting portfolio is growing

Bicycle®

Bicycle Therapeutics unpublished data.
CNS: central nervous system; I.V.: intravenous; LLOQ: lower limit of quantitation; NHP: non-human primate; PD: pharmacodynamics; PK: pharmacokinetics; s.c.: subcutaneous; TfR1: transferrin receptor.

Through our partnership with Ionis, we are optimizing TfR1-mediated antisense oligonucleotide delivery

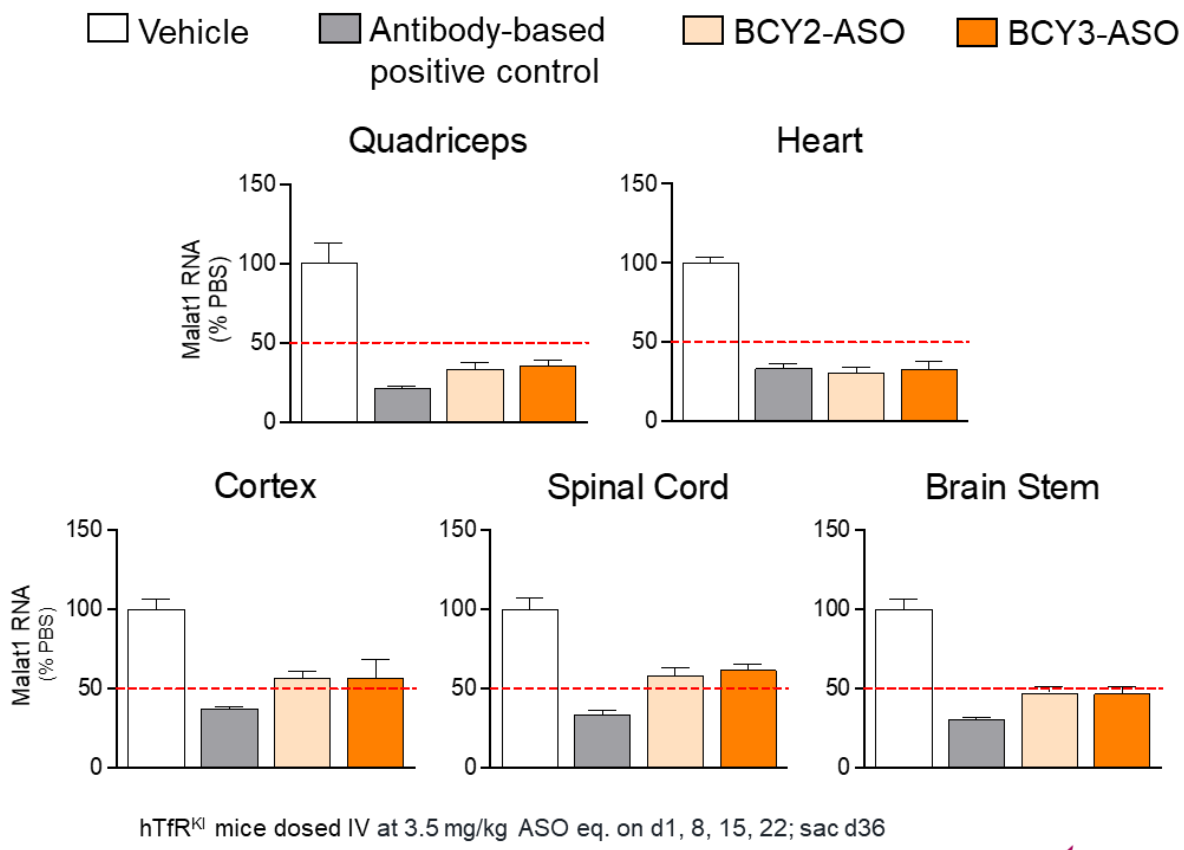
Muscle targeted Bicycle design does not cross the BBB



hTfR^{KI} mice dosed IV at 3 mg/kg ASO eq. on d1, 8, 15; sac d22

Other Bicycle designs can cross the BBB

Small structure with no antibody/protein

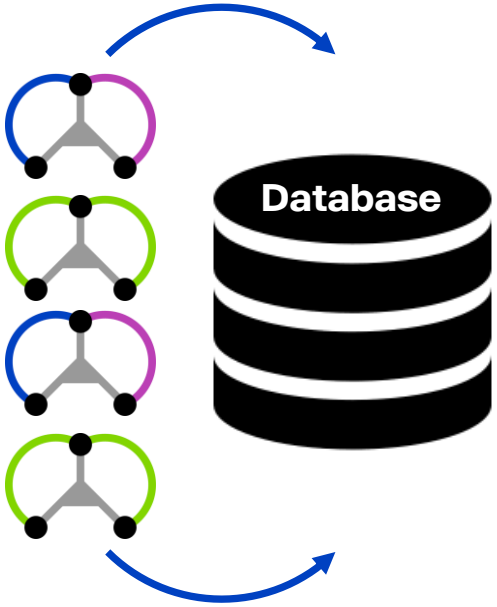


hTfR^{KI} mice dosed IV at 3.5 mg/kg ASO eq. on d1, 8, 15, 22; sac d36

As shared by Ionis on Oct 4, 2023.
ASO: antisense oligonucleotide; BBB: blood brain barrier; TfR: transferrin receptor.

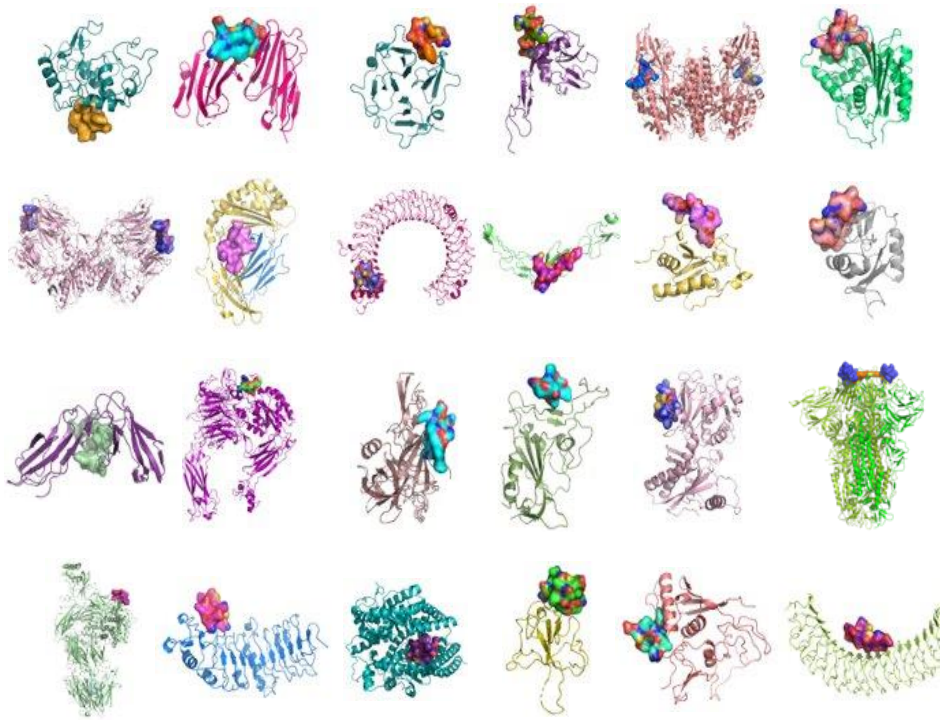
The next chapter: Building on our proprietary knowledge to accelerate discovery through machine-learning and AI

Proprietary data



>150 screening campaigns

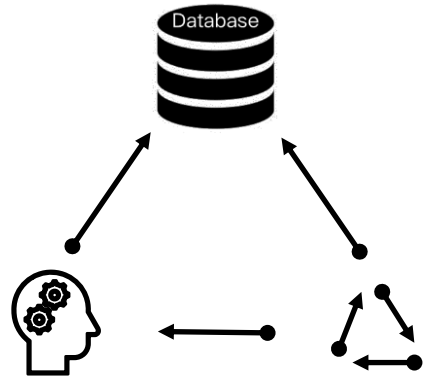
Deep repository of detailed structural information



Growing collection of cryoEM data

Use proprietary data, AI and machine learning to optimize

Training data



Google Cloud

Next-generation Bicycle® molecules

We have successfully utilized non-dilutive financing to make significant advances beyond oncology

SUMMARY

- We have investigated Bicycle® molecules beyond oncology through partnerships with leading pharma companies and funding from not-for-profit organizations
- Bicycle® molecules have shown potential in a wide range of therapeutic areas[1,2,3,4,5]
- This work has allowed us to further develop and evolve our platform technology

NEXT STEPS

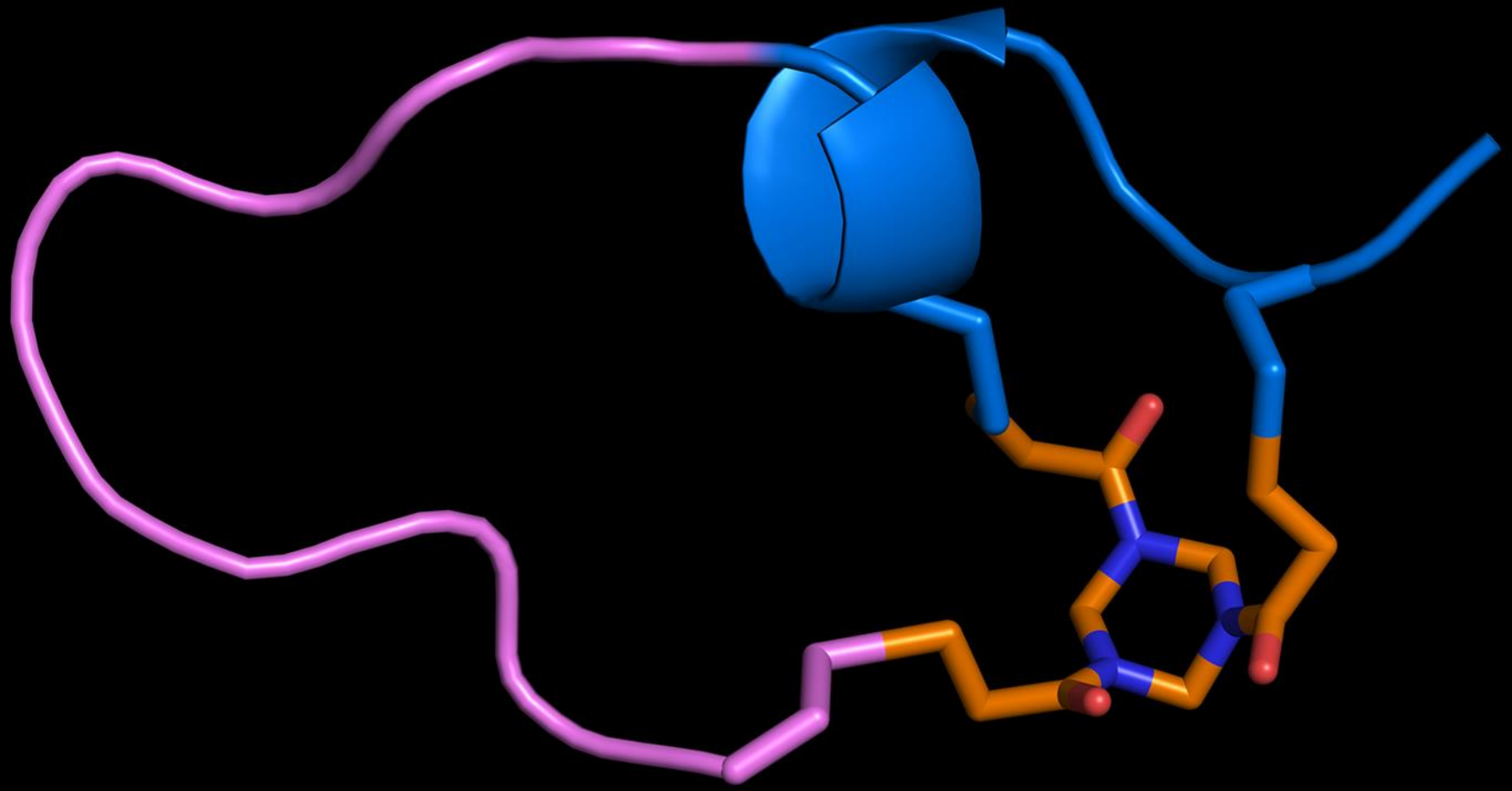
- **We will continue to seek additional partnerships**
- **We plan to use our data, combined with *in silico* methods, to augment Bicycle® molecule identification and optimization**

1. Gaynor KU et al. 2023. *Nat Commun,* 14(1):3583-3598. 2. Harman MAJ et al. 2023. *J Med Chem*, 661(14):9881-9893. 3. Hadjicharalambous A et al. 2022. *Antibiotics*, 11(11):1636-1662. 4. Teufel DP et al. 2018. *J Med Chem*, 61(7):2823-2836. 5. Wagstaff JM et al. 2020. *ACS Infect Dis*, 6(9):2355-2361.

Q&A

Bicycle®

Closing



Bicycle®

We expect 2024 to be a catalyst rich year, broadening our reach significantly beyond BT8009 in mUC

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 clinical candidate using our next generation technology in 2H 2024 ❑ 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.

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

Thank you

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