Constrained peptides
Unconstrained thinking

NASDAQ: BCYC
May 2022

bicycle therapeutics

Forward-looking statements

This presentation may contain forward-looking statements made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995. These statements may be identified by words such as "aims," "anticipates," "believes," "could," "estimates," "expects," "forecasts", "goal," "intends," "may" "plans," "possible," "potential," "seeks," "will," and variations of these words or similar expressions that are intended to identify forward-looking statements. All statements other than statements of historical facts contained in this presentation are forward-looking statements, including statements regarding: our future financial or business performance, conditions, plans, prospects, or strategies and other financial and business matters; and our current and prospective product candidates, ongoing and planned clinical trials and preclinical activities, current and prospective collaborations and the timing and success of our development of our anticipated product candidates.

Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results, our plans to initiate clinical trials and the designs of the planned trials and other future conditions, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, risks related to the ongoing COVID-19 pandemic, the risk that any one or more of our product candidates will not be successfully developed or commercialized, the risk of cessation or delay of any ongoing or planned clinical trials, the risk that we may not realize the intended benefits of our technology, including that we may not identify and develop additional product candidates for our pipeline, the risk that we may not maintain our current collaborations or enter into new collaborations in the future, or that we may not realize the intended benefits of these collaborations, the risk that our product candidates or procedures in connection with the administration thereof will not have the safety or efficacy profile that we anticipate, the risk that prior results will not be replicated or will not continue in ongoing or future studies or trials, the risk that we will be unable to obtain and maintain regulatory approval for our product candidates, the risk that the size and potential of the market for our product candidates will not materialize as expected, risks associated with our dependence on third-parties, risks regarding the accuracy of our estimates of expenses, risks relating to our capital requirements and needs for additional financing, and risks relating to our ability to obtain and maintain intellectual property protection for our product candidates. For a discussion of these and other risks and uncertainties, and other important factors, any of which could cause our actual results to differ from those contained in the forward-looking statements, see the section entitled "Risk Factors" in our Annual Report on Form 10-K, filed with the Securities and Exchange Commission on March 1, 2022, as well as in other filings we may make with the SEC in the future, as well as discussions of potential risks, uncertainties and other important factors in our subsequent filings with the Securities and Exchange Commission. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

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

Unique Platform

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

Bicycle® modular format platform based on Nobel Prize science.

Strong intellectual property portfolio.

Internal Programs

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

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

Trial updates for BT5528 and BT8009 in 2022.

Validating Partnerships

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

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

Ambitious Company

Deeply experienced team

Located in Cambridge UK and Lexington, MA

~149 Employees*

NASDAQ: BCYC

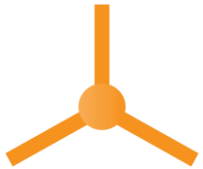
Cash balance $407.4M* (expected cash runway through 2024)

* as of March 31, 2022

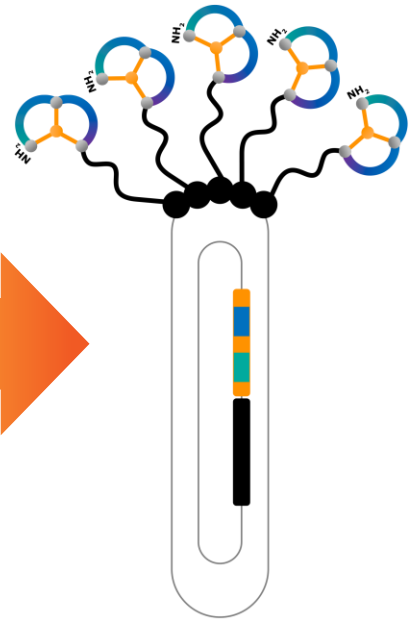
Bicycles are a new therapeutic modality – bicyclic peptides

Short linear peptide

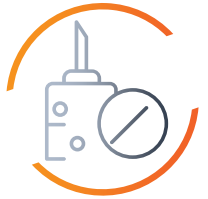
+



Scaffold
Chemical modification with scaffold



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



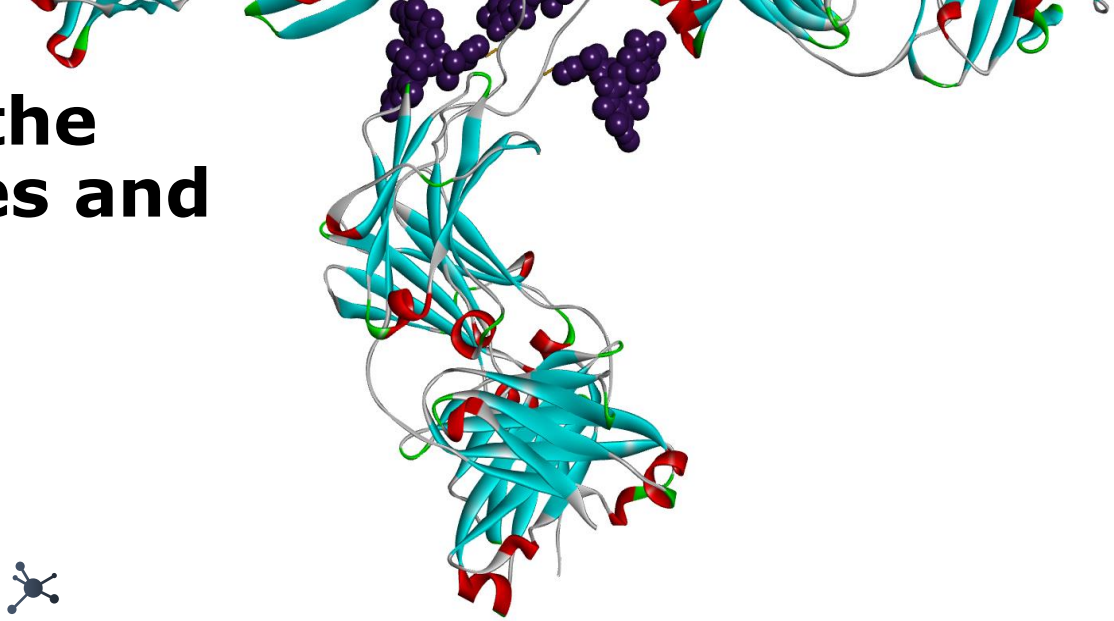
Powerful/versatile platform
- Immense combinatorial potential
- Combines advantages of both small molecules and antibodies

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

Robust patent protection
with 120 patent families*

* as of March 31, 2022

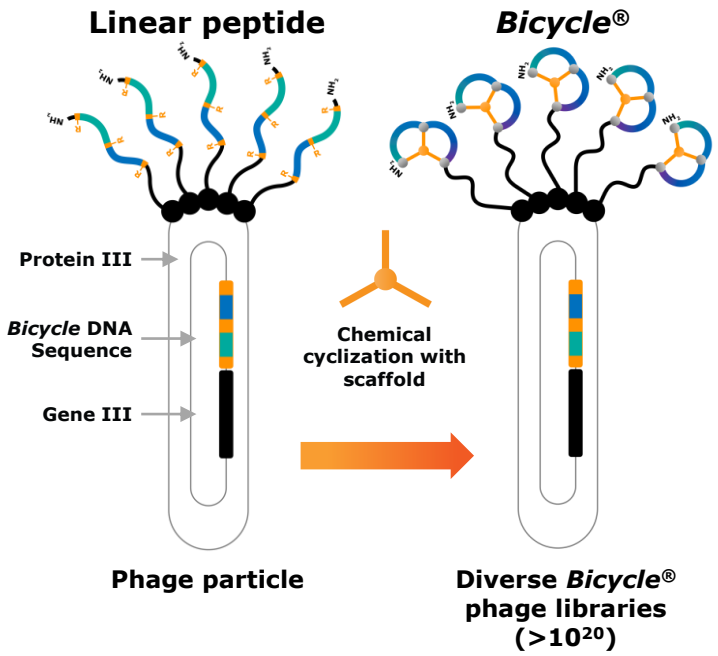
Bicycles are designed to combine the advantages of both small molecules and antibodies



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

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

Bicycle® Phage Display - Discovery



Peptide & Medicinal Chemistry

Optimize *Bicycle*® monomers

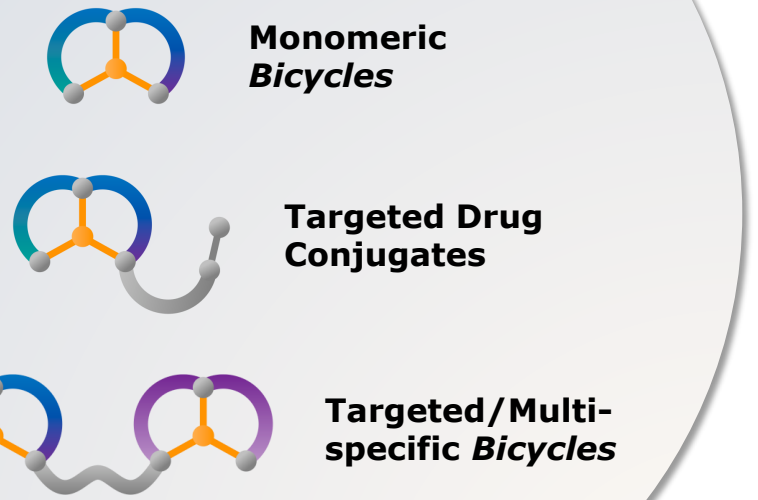
Non-natural Amino Acids

Tumor Targeting and Effector *Bicycles*

Build and Optimize Therapeutic *Bicycles*

Easy conjugation of Linkers and Payloads

Potential *Bicycle*® Medicines



Monomeric *Bicycles*

Targeted Drug Conjugates

Targeted/Multi-specific *Bicycles*

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

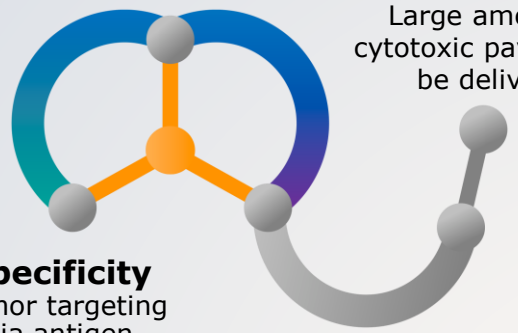
MW of 1.5-2kDa

50-100x smaller than antibodies

High selectivity

Allows more potent toxin to be delivered directly to tumor

***Bicycle*® Toxin Conjugate (BTC™)**

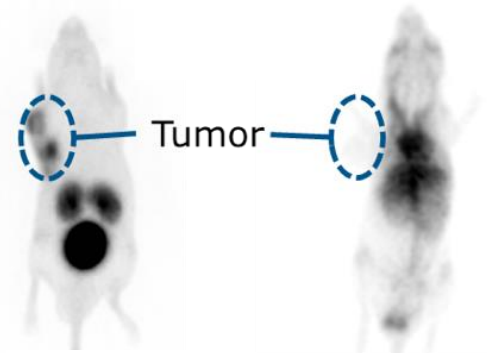


Toxin
Large amount of cytotoxic payload can be delivered

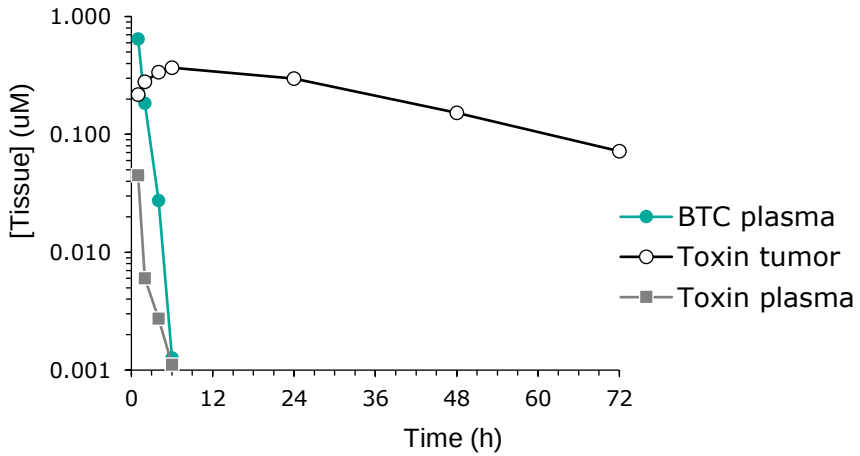
Specificity
Tumor targeting via antigen

Linker
Release of toxin directly into tumor via cleavable linker

PET Imaging 40-60min



***Bicycle*®** **Antibody**



bicycle therapeutics

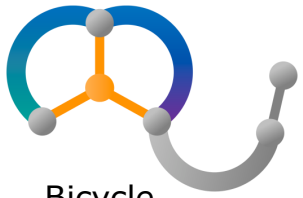
Pipeline

bicycle
therapeutics

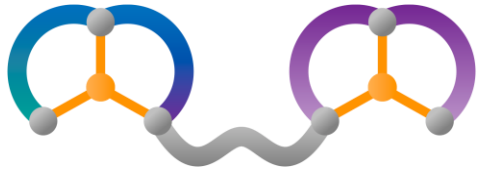
Business strategy designed to explore full potential of *Bicycle*® technology

Oncology

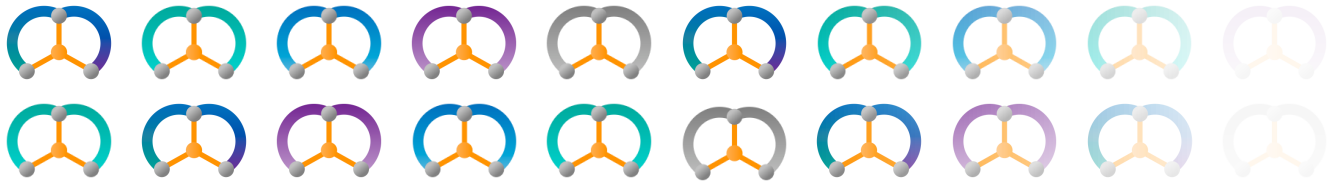
Bicycles are well suited for solid tumors, which are the majority of all cancers. Limited established treatments and high-medical need.



Bicycle Toxin Conjugates® (BTCs)



Tumor-targeted immune cell agonists (*Bicycle* TICAs)



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

CANCER RESEARCH UK

Genentech
A Member of the Roche Group

Other serious diseases

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

AstraZeneca

OXURION®

Innovate UK

Dementia Discovery Fund

IONIS™

Robust proprietary and partnered pipeline

Target / Product	Partner / Sponsor	Indication	Modality	Pre-clinical	IND-enabling	Phase I	Phase II
Internal programs							
BT5528 (EphA2)		Oncology	Bicycle® Toxin Conjugate				
BT8009 (Nectin-4)		Oncology	Bicycle® Toxin Conjugate				
BT7480 (Nectin-4/CD137)		Immuno-oncology	Bicycle TICA™				
BT7455 (EphA2/CD137)		Immuno-oncology	Bicycle TICA™				
Partnered programs							
THR-149 (Kallikrein inhibitor Bicycle)	OXURION	Ophthalmology					
BT1718 (MT1-MMP)	CANCER RESEARCH UK	Oncology	Bicycle® Toxin Conjugate				
BT7401 (multivalent CD137 systemic agonist)	CANCER RESEARCH UK	Immuno-oncology					
Undisclosed	Genentech A Member of the Roche Group	Immuno-oncology					
Inhaled Bicycles	AstraZeneca	Respiratory					
Novel anti-infectives	Innovate UK	Anti-infectives					
Novel CNS targets	Dementia Discovery Fund IONIS	CNS					
Novel neuromuscular targets	IONIS	Neuromuscular					

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BT8009 Monotherapy

Nectin-4

bicycle therapeutics

BT8009: Status of Phase I dose escalation*

Promising clinical activity seen at 5mg/m² QW in urothelial carcinoma (UC); dose well tolerated, with signs of differentiation compared to antibodies and potential for industry-leading product profile

- 50% ORR and 75% disease control, including 1 (13%) complete response
- Durable responses, with tumor reductions maintained over time

Expect to declare 5mg/m² QW recommended Phase II dose (RP2D)

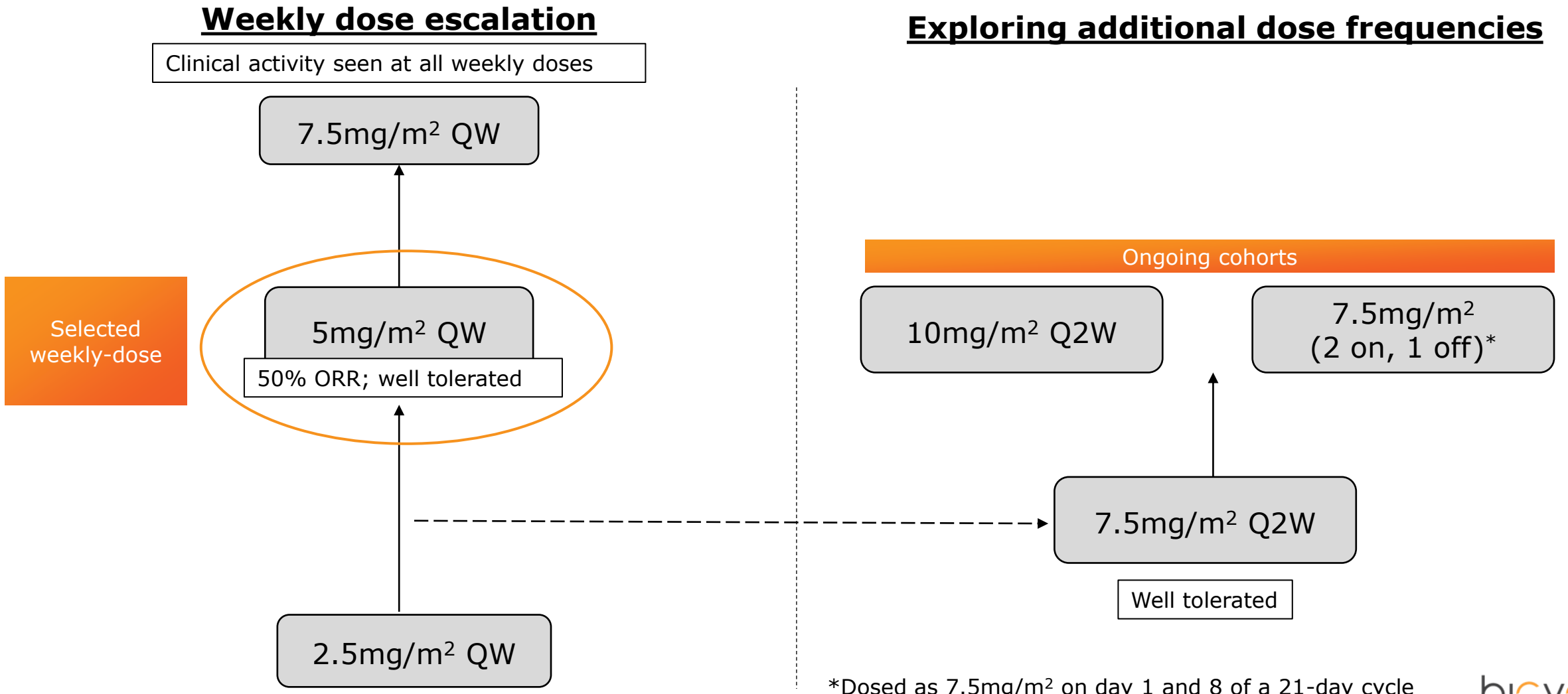
Also exploring additional, less frequent doses and one additional dose could be selected for Phase II

Expect to provide further updates on clinical progress later in 2022

* All BT8009 data as of 7Mar22

BT8009: Dose escalation progress and strategy

3+3 escalation design: MTD reached for weekly schedule and one go-forward dose identified. Currently investigating alternative dosage regimens as per FDA's Project Optimus guidelines



*Dosed as 7.5mg/m² on day 1 and 8 of a 21-day cycle

BT8009: Overview of key demographics for all patients enrolled in Phase I dose escalation trial

Demographics	
Total	N=37
Age, years, median (range)	66 (44-83)
Sex, n (%)	
Male	22 (59%)
Female	15 (41%)
ECOG, n (%)	
0 (Good performance status)	15 (41%)
1	22 (59%)
Prior therapies, median	3
Screened for Nectin-4, n (%)	0

BT8009: Overview of disease history for all patients enrolled in Phase I dose escalation trial

Demographics	
Total	N=37
Tumor type	
Breast	4 (11%)
Esophageal	1 (3%)
Head/Neck	2 (5%)
Lung	5 (14%)
Ovarian	1 (3%)
Pancreatic	6 (16%)
Urothelial	**18 (49%)**

BT8009: Response-evaluable response[1] rates in urothelial cancer

Best overall response, N (%)	2.5mg/m² QW (N=4)	5mg/m² QW (N=8)	7.5mg/m² Q2W (N=2)	7.5mg/m² QW (N=2)[2]	Total (N=16)
Complete Response	0	1 (13)	0	0	1 (6)
Partial Response	1 (25)	3 (38)	0	1 (50)	5 (31)
Stable Disease	2 (50)	2 (25)	0	1 (50)	5 (31)
Progressive Disease	1 (25)	2 (25)	2 (100)	0	5 (31)
ORR (CR+PR)	**1 (25)**	**4 (50)**	**0**	**1 (50)**	**6 (38)**
DCR[3] (CR+PR+SD)	**3 (75)**	**6 (75)**	**0**	**2 (100)**	**11 (69)**

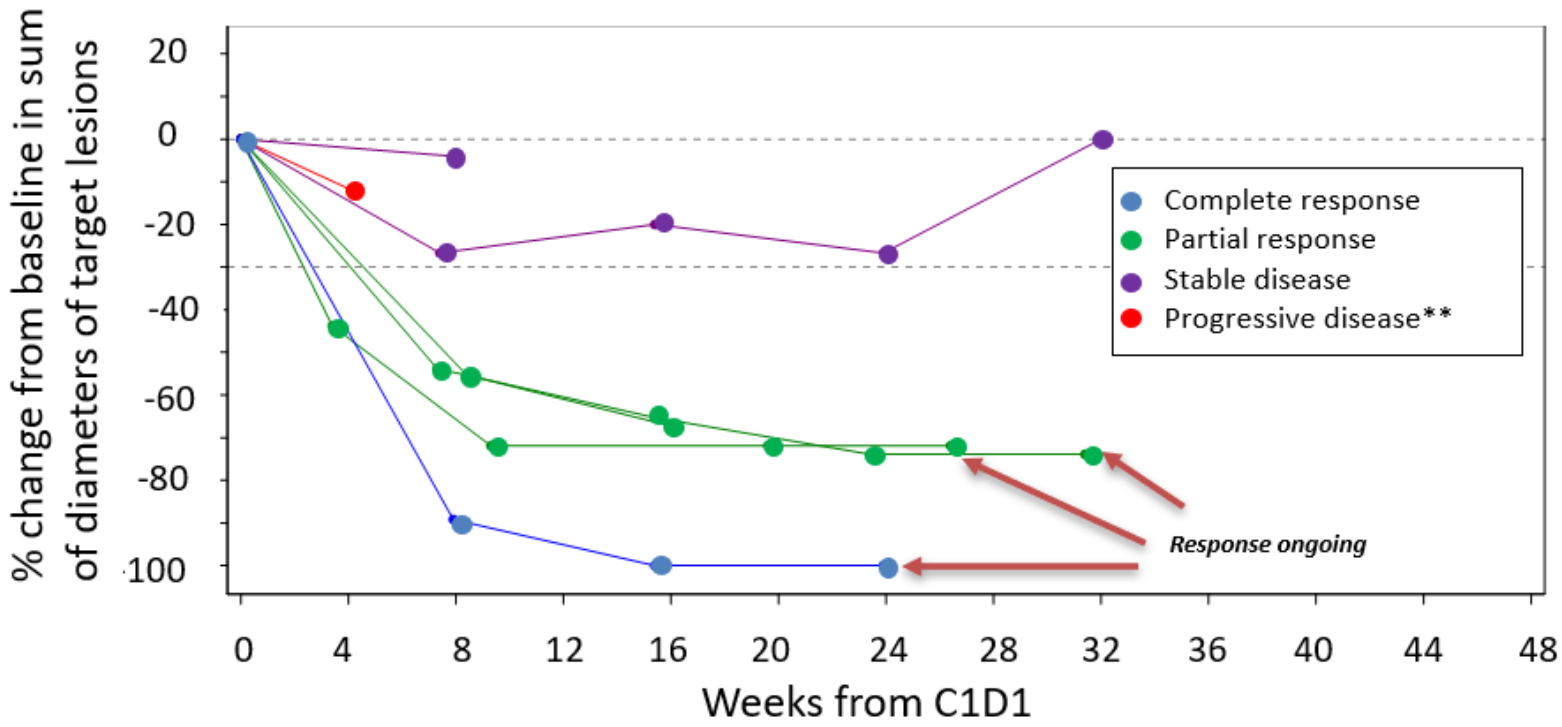
1. Responses under response evaluation criteria in solid tumors (RECIST) version 1.1
2. Excludes two non-evaluable patients who came off trial before their first scans
3. Disease control rate

BT8009: Responses* observed in 5mg/m² QW cohort Phase I dose escalation in response-evaluable urothelial patients

Urothelial responses:

- 4 responses in 8 patients
  - 1 Complete response
  - 3 Partial responses
    - 71% tumor reduction

      (100% reduction in target lesion)
    - 65% tumor reduction
    - 54% tumor reduction
- Median DoR not reached
  - 3 responses ongoing
  - 1 progression at ~3 months



One subject who had clinical progression did not have post-baseline RECIST assessment data and is thereby omitted from this figure.
**In Sept 2021, site entered patient as progressive disease (PD) in target lesion. Subsequent to the Oct 2021 BT8009 update, the site updated patient as stable disease (SD) in target lesion but PD in non-target lesion.

* Responses under response evaluation criteria in solid tumors (RECIST) version 1.1

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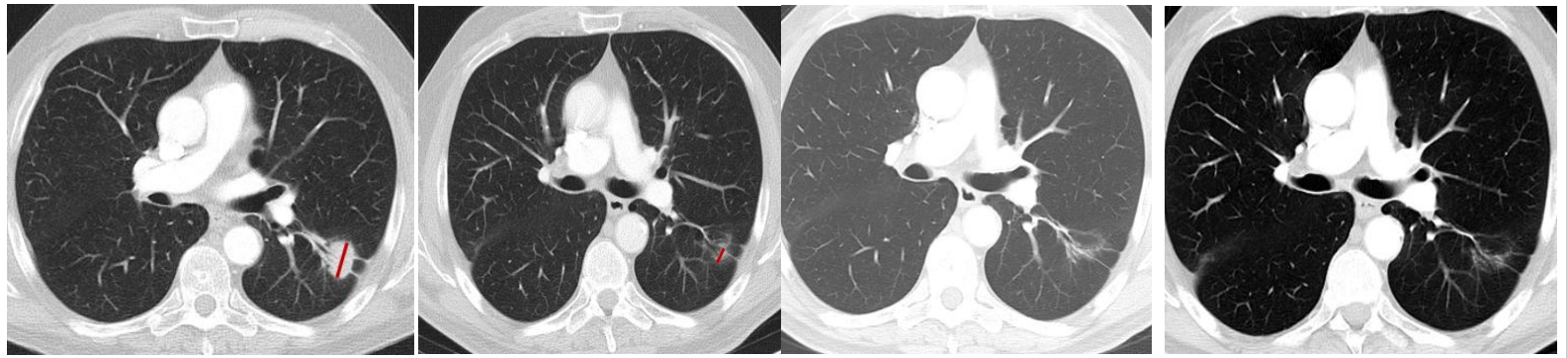
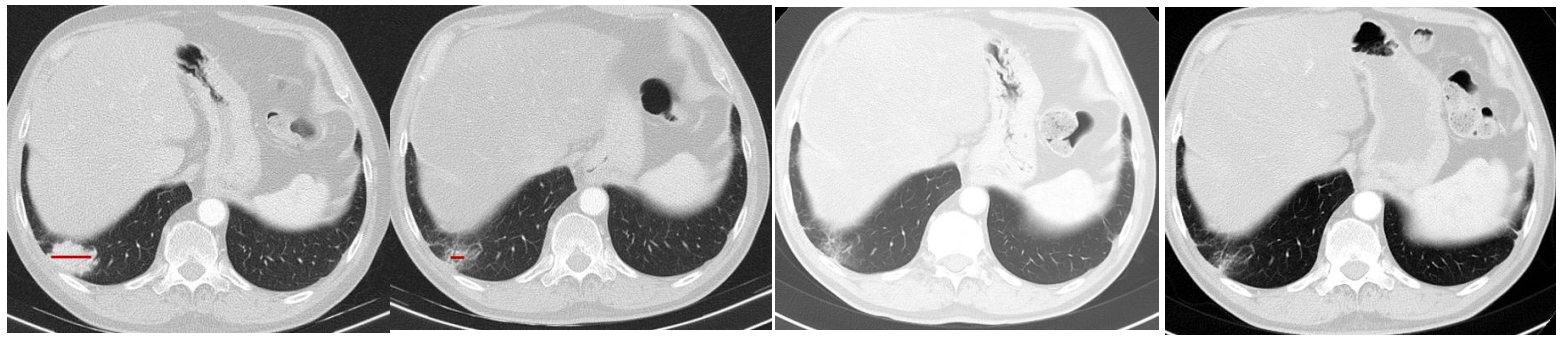
BT8009: Comparison of complete responder* pre-dose tumor images with tumor images after six months treatment (5mg/m² QW)

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

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

* Response under response evaluation criteria in solid tumors (RECIST) version 1.1

BT8009: Overview of adverse events across all cohorts. Well tolerated below 7.5mg/m² QW

Treatment Emergent Adverse Events and Treatment Related Adverse Events														
Dose Cohort	All Cohorts		2.5mg/m² QW		5mg/m² QW UC		5mg/m² QW non-UC		5mg/m² QW		7.5mg/m² Q2W		7.5mg/m² QW	
N	37		7		8		12		20		5		5	
TEAE ≥15%	Total N (%)	Treatmt Rel N (%)	Total N (%)	Treatmt Rel N (%)	Total N (%)	Treatmt Rel N (%)	Total N (%)	Treatmt Rel N (%)	Total N (%)	Treatmt Rel N (%)	Total N (%)	Treatmt Rel N (%)	Total N (%)	Treatmt Rel N (%)
Fatigue	15 (41)	12 (32)	4 (57)	4 (57)	1 (13)	0	7 (58)	5 (42)	8 (40)	5 (25)	2 (40)	2 (40)	1 (20)	1 (20)
Nausea	14 (38)	13 (35)	5 (71)	4 (57)	3 (38)	3 (38)	4 (33)	4 (33)	7 (35)	7 (35)	1 (20)	1 (20)	1 (20)	1 (20)
Diarrhea	12 (32)	9 (24)	4 (57)	3 (43)	3 (38)	2 (25)	2 (17)	1 (8)	5 (25)	3 (15)	0	0	3 (60)	3 (60)
Pyrexia	12 (32)	8 (22)	2 (29)	1 (14)	4 (50)	2 (25)	1 (8)	2 (25)	5 (25)	4 (20)	2 (40)	1 (20)	3 (60)	2 (40)
Anemia	12 (32)	6 (16)	2 (29)	1 (14)	2 (25)	0	6 (50)	4 (33)	8 (40)	4 (20)	0	0	2 (40)	1 (20)
Decreased appetite	12 (32)	8 (22)	3 (43)	3 (43)	1 (13)	1 (13)	8 (67)	4 (33)	9 (45)	5 (25)	0	0	0	0
Constipation	11 (30)	2 (5)	2 (29)	1 (14)	2 (25)	0	3 (25)	0	5 (25)	0	1 (20)	0	3 (60)	1 (20)
Urinary tract infection	10 (27)	0	2 (29)	0	5 (63)	0	1 (8)	0	6 (30)	0	1 (20)	0	1 (20)	0
Neutrophil count decrease[1]	8 (22)	8 (22)	0	0	0	0	4 (33)	4 (33)	4 (20)	4 (20)	1 (20)	1 (20)	3 (60)	3 (60)
Asthenia	9 (24)	9 (24)	1 (14)	1 (14)	2 (25)	2 (25)	1 (8)	1 (8)	3 (15)	3 (15)	2 (40)	2 (40)	3 (60)	3 (60)
Peripheral neuropathy[2,3]	9 (24)	7 (19)	2 (29)	2 (29)	4 (50)	4 (50)	1 (8)	1 (8)	5 (25)	5 (25)	1 (20)	0	1 (20)	0
--Peripheral sensory neuropathy	4 (11)	3 (8)	0	0	2 (25)	2 (25)	1 (8)	1 (8)	3 (15)	3 (15)	0	0	1 (20)	0
--Other peripheral neuropathy	5 (14)	4 (11)	2 (29)	2 (29)	2 (25)	2 (25)	0	0	2 (10)	2 (10)	1 (20)	0	0	0
Abdominal pain	8 (22)	1 (3)	2 (29)	1 (14)	1 (13)	0	3 (25)	0	4 (20)	0	0	0	2 (40)	0
Pruritus	7 (19)	5 (14)	3 (43)	3 (43)	0	0	1 (8)	0	1 (5)	0	2 (40)	1 (20)	1 (20)	1 (20)
Alopecia	7 (19)	7 (19)	0	0	3 (38)	3 (38)	1 (8)	1 (8)	4 (20)	4 (20)	1 (20)	1 (20)	2 (40)	2 (40)
Rash	7 (19)	5 (14)	2 (29)	2 (29)	2 (25)	2 (25)	2 (17)	0	4 (20)	2 (10)	1 (20)	1 (20)	0	0
Back pain	6 (16)	0	1 (14)	0	2 (25)	0	2 (17)	0	4 (20)	0	0	0	1 (20)	0
Hypokalemia	6 (16)	2 (5)	1 (14)	0	0	0	4 (33)	1 (8)	4 (20)	1 (5)	0	0	1 (20)	1 (20)
Hypomagnesia	6 (16)	2 (5)	1 (14)	1 (14)	1 (13)	0	3 (25)	0	4 (20)	0	0	0	1 (20)	1 (20)

1. Previous neutrophil count decrease total included neutrophilia leukocytosis (neutrophil count increase). This event has been removed from current total.
2. Peripheral neuropathy includes peripheral sensory neuropathy (4 total, 3 related), paresthesia (1,1), hypoesthesia (1,1), neuropathy peripheral (1,1), neurotoxicity (1,1), and hemiparesis (1,0)
3. Due to rounding, the sum of the percentages of peripheral sensory neuropathy and other sensory neuropathy do not equal peripheral neuropathy for all cohorts TEAE

In enfortumab vedotin Phase I trial: "Peripheral neuropathy (of any form)…occurred in 76 patients (49%)"[1]

- "Peripheral sensory neuropathy was the most common reason for discontinuation as a result of an AE (5 of 16 patients)"[1]

TABLE 2. Incidence of TRAEs That Occurred in ≥ 20% of Patients With mUC Treated With 1.25 mg/kg EV (N = 112)[1]

	Grade, No. (%)							
	EV 0.50 mg/kg (n = 2)		EV 0.75 mg/kg (n = 14)		EV 1.0 mg/kg (n = 27)		EV 1.25 mg/kg (n = 112)	
TRAE	All	≥ 3	All	≥ 3	All	≥ 3	All	≥ 3
Fatigue	0	0	3 (21)	0	9 (33)	1 (4)	59 (53)	2 (2)
Alopecia	0	0	2 (14)	0	7 (26)	0	52 (46)	0
Decreased appetite	0	0	1 (7)	0	8 (30)	0	47 (42)	1 (1)
Dysgeusia	0	0	2 (14)	0	7 (26)	0	43 (38)	0
Nausea	0	0	4 (29)	0	12 (44)	0	42 (38)	1 (1)
Peripheral sensory neuropathy[2]	0	0	2 (14)	0	5 (19)	0	42 (38)	1 (1)
Pruritus	0	0	1 (7)	0	11 (41)	0	39 (35)	1 (1)
Diarrhea	1 (50)	0	3 (21)	0	7 (26)	0	37 (33)	1 (1)
Maculopapular rash	0	0	0	0	3 (11)	2 (7)	30 (27)	3 (3)
AST increased	0	0	0	0	5 (19)	0	25 (22)	1 (1)
Dry skin	0	0	1 (7)	0	1 (4)	0	24 (21)	0

49% incidence of Any Peripheral Neuropathy, across all cohorts. Supplemental Appendix, Table S2[1]

1. Rosenberg, *et al.*, "EV-101: A Phase I Study of Single-Agent Enfortumab Vedotin in Patients With Nectin-4–Positive Solid Tumors, Including Metastatic Urothelial Carcinoma" Journal of Clinical Oncology, 2020 Apr 1; 38(10): 1041–1049
2. This definition excludes other forms of peripheral neuropathy (PN) that are included in BT8009's definition of PN: paresthesia, hypoesthesia, neuropathy peripheral, neurotoxicity, and hemiparesis

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BT8009 patients on trial experienced limited dose modifications below 7.5mg/m² QW

N (%)	2.5mg/m² QW (N=7)	5mg/m² QW (N=20)	7.5mg/m² Q2W (N=5)	7.5mg/m² QW (N=5)	All Cohorts (N=37)
Discontinuations[1]	1 (14)	1 (5)	0	0	2 (5)
Interruptions[2]	2 (29)	6 (30)	0	3 (60)	11 (30)
Reductions[3]	0	4 (20)	0	2 (40)	6 (16)

1. Neither incident was treatment-related
2. 19 of 28 incidents were treatment related: fatigue (4), asthenia (3), anemia (3), paresthesia, neurotoxicity-hands, transaminitis, creatinine increase, fever, neutropenia, neutrophil count decrease, neutrophilia leukocytosis, myalgia
3. All incidents were treatment related: neutropenia (2), asthenia (2) neutrophil count decrease, hypokalemia, neurotoxicity

BT8009: Summary of treatment-related and serious adverse events

# of patients with at least one:	2.5mg/m² QW (N=7)	5mg/m² QW (N=20)	7.5mg/m² Q2W (N=5)	7.5mg/m² QW (N=5)	Total (N=37)
Related TEAE	7 (100)	17 (85)	5 (100)	5 (100)	34 (92)
Related TEAE, ≥Gr3	1 (14)	3 (15)	1 (20)	4 (80)	9 (24)
Related TEAE, Gr3[1]	1 (14)	2 (10)	1 (20)	4 (80)	8 (22)
Related TEAE, Gr4[2]	0	2 (10)	0	3 (60)	5 (14)
Related TEAE, Gr5	0	0	0	0	0
TESAE	2 (29)	4 (20)	1 (20)	0	7 (19)
TESAE, ≥Gr3	1 (14)	3 (15)	1 (20)	0	5 (14)
Related TESAE[3]	0	1 (5)	0	0	1 (3)
Related TESAE, ≥Gr3	0	0	0	0	0
Dose Limiting Toxicity[4]	0	0	0	2 (40)	2 (5)

1. 2.5mg/m² QW: fatigue. 5mg/m² QW: fatigue, asthenia. 7.5mg/m² Q2W: hypertension. 7.5mg/m² QW: asthenia, diarrhea, neutrophil count decrease, neutropenia.
2. 5mg/m² QW: neutrophil count decrease, hypokalemia. 7.5mg/m² QW: neutrophil count decrease, hypokalemia, neutropenia.
3. Vomiting
4. DLTs: asthenia and neutrophil count decrease

BT8009: The incidence of neutropenia* was dose dependent and low below 7.5mg/m² QW

- Neutrophil decrease findings were transient in nature and monitorable, measurable and treatable; prophylactic G-CSF was not utilized in the Phase I but will be in Phase II
- Incidence of lab recorded neutropenia was 2 of 37 or 5%, with 0% incidence of febrile neutropenia

Cohort-by-cohort description of neutropenia* incidence		
Dose (mg/m²)	**Grade 2-4**	**Grade 3-4**
2.5 QW	0/7 (0%)	0/7 (0%)
5 QW	**4/20 (20%)**	**2/20 (10%)**
7.5 Q2W	0/5 (0%)	0/5 (0%)
7.5 QW	3/5 (60%)	3/5 (60%)
All doses	7/37 (19%)	5/37 (14%)
Below 7.5 QW	**4/32 (13%)**	**2/32 (6%)**

* Neutropenia includes 8 cases of neutrophil count decreases and 2 cases recorded as neutropenia

Enfortumab vedotin: Neutropenia incidence and severity from label*

Neutrophil count decrease at 1.25mg/kg		
Study (N)	**Grade 2-4**	**Grade 3-4**
EV-201 C1 (125)	14%	5%
EV-201 C2 (89)	34%	5%
EV-301 (296)	27%	12%

*Padcev FDA Label, July 2021

BT8009: Low incidence and severity of rash

Treatment Emergent Adverse Events and Treatment Related Adverse Events														
Dose Cohort	All Cohorts		2.5mg/m^2 QW		5mg/m^2 QW UC		5mg/m^2 QW non-UC		5mg/m^2 QW		7.5mg/m^2 Q2W		7.5mg/m^2 QW	
N	37		7		8		12		20		5		5	
	Total	Treatmt Rel	Total	Treatmt Rel	Total	Treatmt Rel	Total	Treatmt Rel	Total	Treatmt Rel	Total	Treatmt Rel	Total	Treatmt Rel
TEAE ≥15%	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Fatigue	15 (41)	12 (32)	4 (57)	4 (57)	1 (13)	0	7 (58)	5 (42)	8 (40)	5 (25)	2 (40)	2 (40)	1 (20)	1 (20)
Nausea	14 (38)	13 (35)	5 (71)	4 (57)	3 (38)	3 (38)	4 (33)	4 (33)	7 (35)	7 (35)	1 (20)	1 (20)	1 (20)	1 (20)
Diarrhea	12 (32)	9 (24)	4 (57)	3 (43)	3 (38)	2 (25)	2 (17)	1 (8)	5 (25)	3 (15)	0	0	3 (60)	3 (60)
Pyrexia	12 (32)	8 (22)	2 (29)	1 (14)	4 (50)	2 (25)	1 (8)	2 (25)	5 (25)	4 (20)	2 (40)	1 (20)	3 (60)	2 (40)
Anemia	12 (32)	6 (16)	2 (29)	1 (14)	2 (25)	0	6 (50)	4 (33)	8 (40)	4 (20)	0	0	2 (40)	1 (20)
Decreased appetite	12 (32)	8 (22)	3 (43)	3 (43)	1 (13)	1 (13)	8 (67)	4 (33)	9 (45)	5 (25)	0	0	0	0
Constipation	11 (30)	2 (5)	2 (29)	1 (14)	2 (25)	0	3 (25)	0	5 (25)	0	1 (20)	0	3 (60)	1 (20)
Urinary tract infection	10 (27)	0	2 (29)	0	5 (63)	0	1 (8)	0	6 (30)	0	1 (20)	0	1 (20)	0
Neutrophil count decrease	8 (22)	8 (22)	0	0	0	0	4 (33)	4 (33)	4 (20)	4 (20)	1 (20)	1 (20)	3 (60)	3 (60)
Asthenia	9 (24)	9 (24)	1 (14)	1 (14)	2 (25)	2 (25)	1 (8)	1 (8)	3 (15)	3 (15)	2 (40)	2 (40)	3 (60)	3 (60)
Peripheral neuropathy	9 (24)	7 (19)	2 (29)	2 (29)	4 (50)	4 (50)	1 (8)	1 (8)	5 (25)	5 (25)	1 (20)	0	1 (20)	0
--Peripheral sensory neuropathy	4 (11)	3 (8)	0	0	2 (25)	2 (25)	1 (8)	1 (8)	3 (15)	3 (15)	0	0	1 (20)	0
--Other peripheral neuropathy	5 (14)	4 (11)	2 (29)	2 (29)	2 (25)	2 (25)	0	0	2 (10)	2 (10)	1 (20)	0	0	0
Abdominal pain	8 (22)	1 (3)	2 (29)	1 (14)	1 (13)	0	3 (25)	0	4 (20)	0	0	0	2 (40)	0
Pruritus	7 (19)	5 (14)	3 (43)	3 (43)	0	0	1 (8)	0	1 (5)	0	2 (40)	1 (20)	1 (20)	1 (20)
Alopecia	7 (19)	7 (19)	0	0	3 (38)	3 (38)	1 (8)	1 (8)	4 (20)	4 (20)	1 (20)	1 (20)	2 (40)	2 (40)
Rash*	7 (19)	5 (14)	2 (29)	2 (29)	2 (25)	2 (25)	2 (17)	0	4 (20)	2 (10)	1 (20)	1 (20)	0	0
Back pain	6 (16)	0	1 (14)	0	2 (25)	0	2 (17)	0	4 (20)	0	0	0	1 (20)	0
Hypokalemia	6 (16)	2 (5)	1 (14)	0	0	0	4 (33)	1 (8)	4 (20)	1 (5)	0	0	1 (20)	1 (20)
Hypomagnesia	6 (16)	2 (5)	1 (14)	1 (14)	1 (13)	0	3 (25)	0	4 (20)	0	0	0	1 (20)	1 (20)

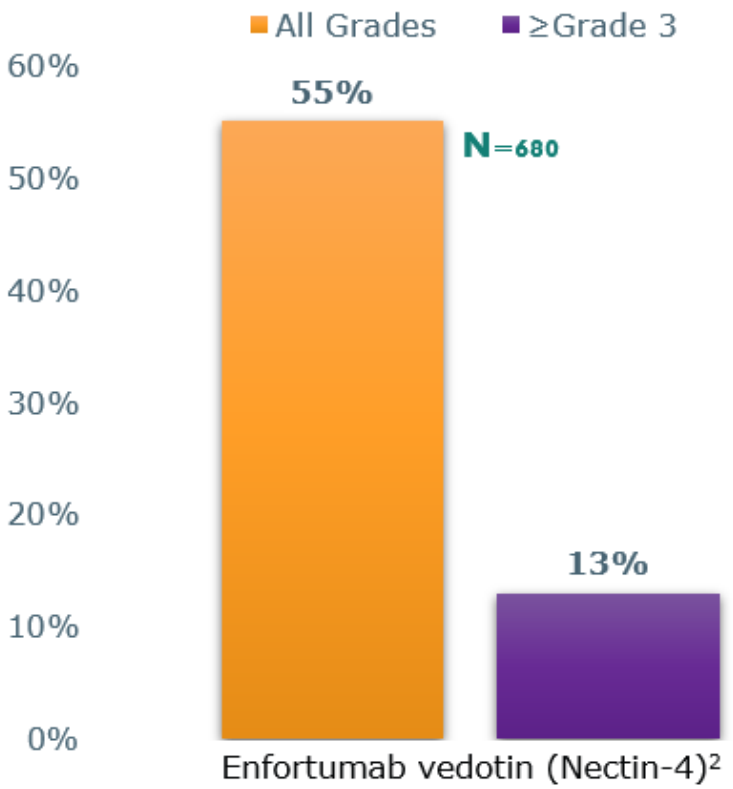
*Of the 7 rash TEAEs, 6 were Gr1 and 1 was Gr2. Of the 5 rash TRAEs, 4 were Gr1 and 1 was Gr2.
Rash patients in 5mg/m^2 QW UC cohort were rash chest (Gr1) and eczema (Gr2). Remaining rash cases in other cohorts were rash bilateral forearms, maculopapular, photosensitivity, urticaria, rash chest and rash not otherwise specified.

Enfortumab vedotin: Rash incidence in Phase 1 and label

Table S2. Treatment-Emergent Adverse Events of Special Interest [1]

	Metastatic Urothelial Carcinoma (N=155)	
	All Grades	Grade ≥3
Any Rash	**70 (45)**	**10 (6)**
Maculopapular rash	39 (25)	5 (3)
Rash	11 (7)	0
Blister	7 (5)	0
Bullous dermatitis†	5 (3)	1 (1)
Erythema	5 (3)	0
Erythematous rash	5 (3)	2 (1)
Palmar-plantar erythrodysaesthesia	4 (3)	1 (1)
Papular rash	4 (3)	0
Vesicular rash	4 (3)	0
Eczema	3 (2)	1 (1)
Macular rash	3 (2)	0
Dermatitis	2 (1)	0
Generalised rash	2 (1)	0
Maculovesicular rash	2 (1)	0
Skin irritation	2 (1)	0
Allergic dermatitis	1 (1)	0
Erythema multiforme	1 (1)	0
Pemphigoid	1 (1)	0

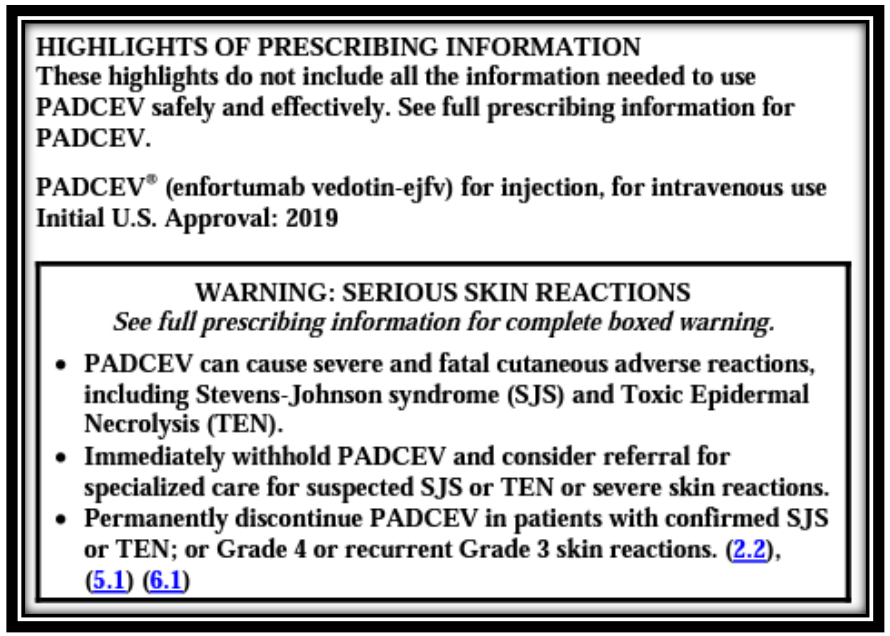
†Grade 4



1. Rosenberg, *et al.*, "EV-101: A Phase I Study of Single-Agent Enfortumab Vedotin in Patients With Nectin-4–Positive Solid Tumors, Including Metastatic Urothelial Carcinoma" Journal of Clinical Oncology, 2020 Apr 1; 38(10): 1041–1049
2. Padcev FDA Label, July 2021

Enfortumab vedotin: Rash incidence, severity, warning label and recent articles

- FDA Label revised July 2021 to include Black Box warning
- Event reports have since been published



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PADCEV safely and effectively. See full prescribing information for PADCEV.

PADCEV® (enfortumab vedotin-ejfv) for injection, for intravenous use
Initial U.S. Approval: 2019

WARNING: SERIOUS SKIN REACTIONS
See full prescribing information for complete boxed warning.

- **PADCEV can cause severe and fatal cutaneous adverse reactions, including Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN).**
- **Immediately withhold PADCEV and consider referral for specialized care for suspected SJS or TEN or severe skin reactions.**
- **Permanently discontinue PADCEV in patients with confirmed SJS or TEN; or Grade 4 or recurrent Grade 3 skin reactions. (2.2), (5.1) (6.1)**

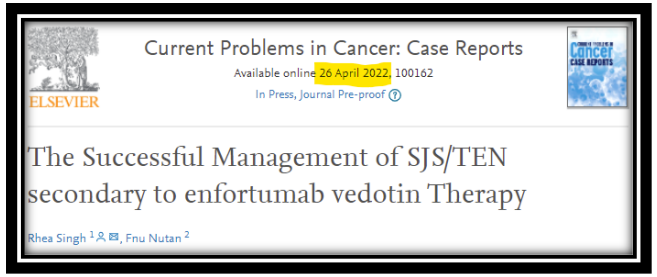
ELSEVIER

European Journal of Cancer
Volume 167, May 2022, Pages 168-171

Letter to the Editor

Life-threatening skin reaction with Enfortumab Vedotin: Six cases

Florine Guerrois [a, b, 1], Constance Thibault [c, 1], Coralie Lheure [b, 1], Pierre Sohier [d, 1], Benoit Bensaid [e, f], Saskia Ingen-Housz-Oro [a, f, g, 1], Nicolas Dupin [b, h, 1]
Collaborations[2]

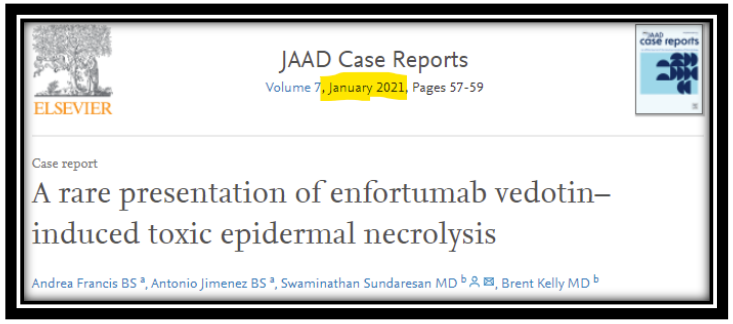


ELSEVIER

Current Problems in Cancer: Case Reports
Available online 26 April 2022, 100162
In Press, Journal Pre-proof

The Successful Management of SJS/TEN secondary to enfortumab vedotin Therapy

Rhea Singh [1], Fnu Nutan [2]



ELSEVIER

JAAD Case Reports
Volume 7, January 2021, Pages 57-59

Case report

A rare presentation of enfortumab vedotin–induced toxic epidermal necrolysis

Andrea Francis BS [a], Antonio Jimenez BS [a], Swaminathan Sundaresan MD [b], Brent Kelly MD [b]

The Oncologist, 2022, **27**, e223–e232
https://doi.org/10.1093/oncolo/oyac001
Advance access publication 26 Febuary 2022
Review Article

OXFORD

Management of Dermatologic Events Associated With the Nectin-4-directed Antibody-Drug Conjugate Enfortumab Vedotin

Mario E. Lacouture[1,2,*], Anisha B. Patel[3], Jonathan E. Rosenberg[1,2], Peter H. O'Donnell[4]

BT5528 Monotherapy

EphA2

bicycle therapeutics

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

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

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

- Regulates cell migration, adhesion, proliferation and differentiation
- Overexpressed in human cancers and correlates with tumor progression
- Development of MEDI-547 (MedImmune) in ovarian cancer was halted following serious bleeding events in phase I

"The bleeding and coagulation events observed in humans showed similarities to those evident in rats and monkeys. In all three species, increased activated partial thromboplastin time, increased fibrinogen/fibrin degradation product, and increased fibrin D-dimer were reported. Monkeys had red/ blood discharge from the nose, mouth, gums."[1]

1. Annunziata, Christina M., et al. "Phase 1, open-label study of MEDI-547 in patients with relapsed or refractory solid tumors." *Investigational new drugs* 31.1 (2013): 77-84.

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

Demographics	
Total	24 (100%)
Age, years, median (range)	65.5 (49-76)
Sex, n (%)	
Male	7 (29%)
Female	17 (71%)
ECOG, n (%)	
0 (Good performance status)	11 (46%)
1	13 (54%)
2+	0 (0%)
Prior therapies, median (range)	**7 (1-16)**

Adverse events (AEs)	Related Gr ≥3 AE N=13 patients[1]
Neutropenia	N=8
Anemia	N=2
Pneumonitis	N=2
Fatigue	N=1
Ileus	N=1
Tumor Lysis Syndrome	N=1
Bleeding disorders	**N=0**
Conjunctival disorders	**N=0**
Cutaneous events	**N=0**
Neuropathy	**N=0**

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

1. Data as of 14Jul21

bicycle therapeutics

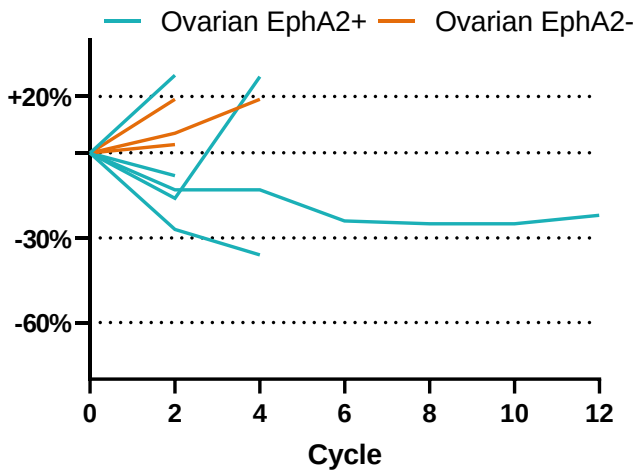
BT5528: Preliminary responses observed during Phase I dose escalation trial

Responses observed:

Ovarian

- 1 PR[1] of 8 ovarian cancer patients, PR observed by month 4
- 4 of 5 with EphA2 staining showed some shrinkage

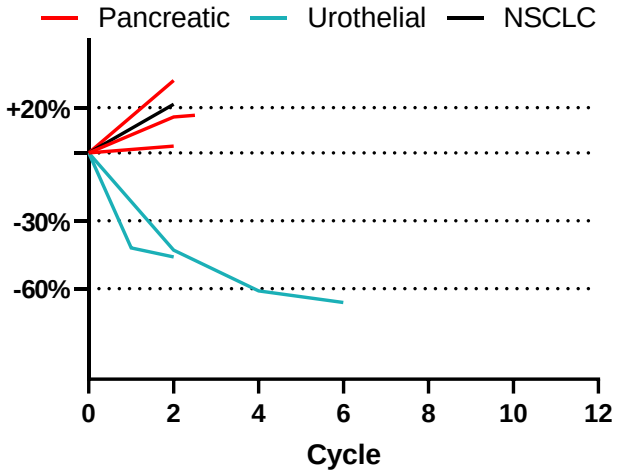
Change in target lesion size relative to baseline



Urothelial

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

Change in target lesion size relative to baseline

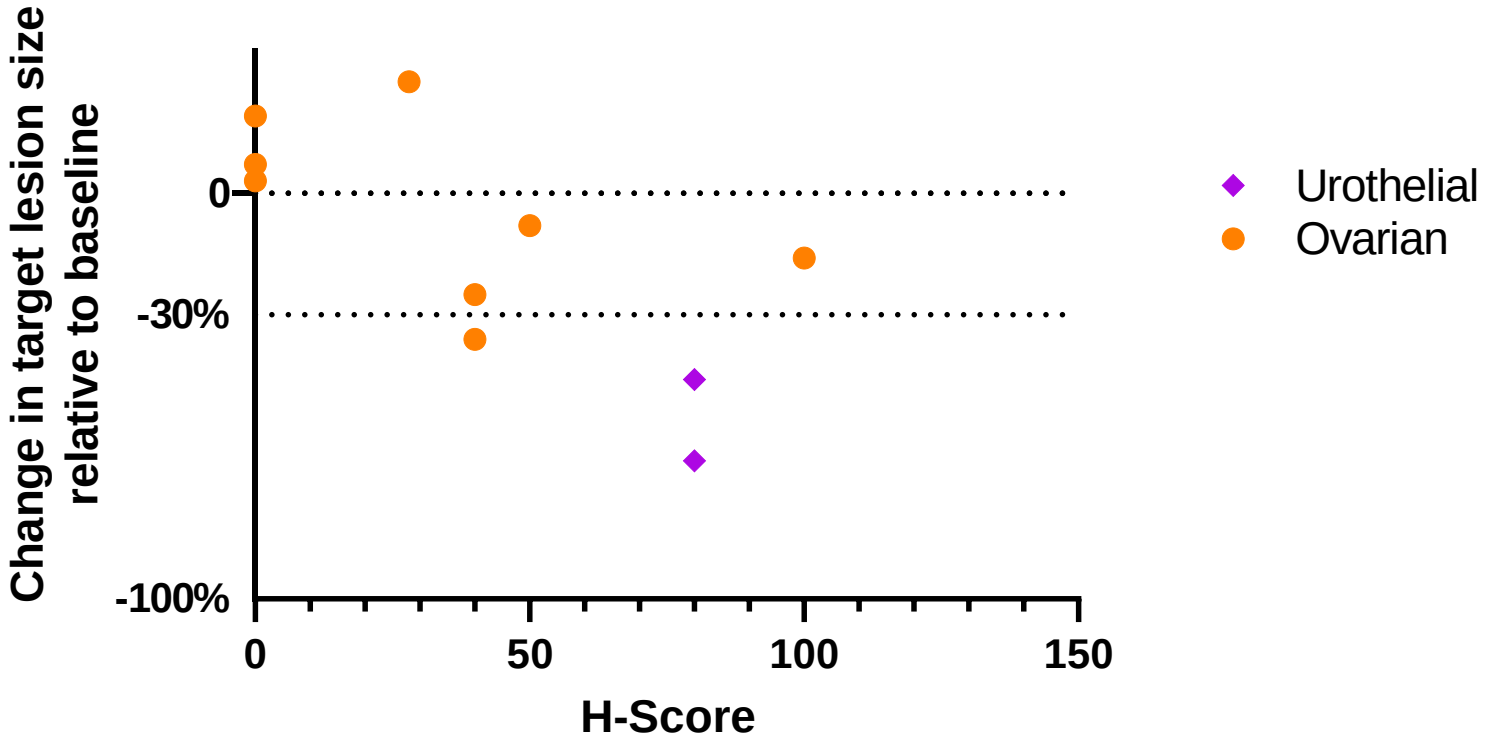


1. Partial responses under response evaluation criteria in solid tumors (RECIST) version 1.1. Data as of 14Jul21

bicycle therapeutics

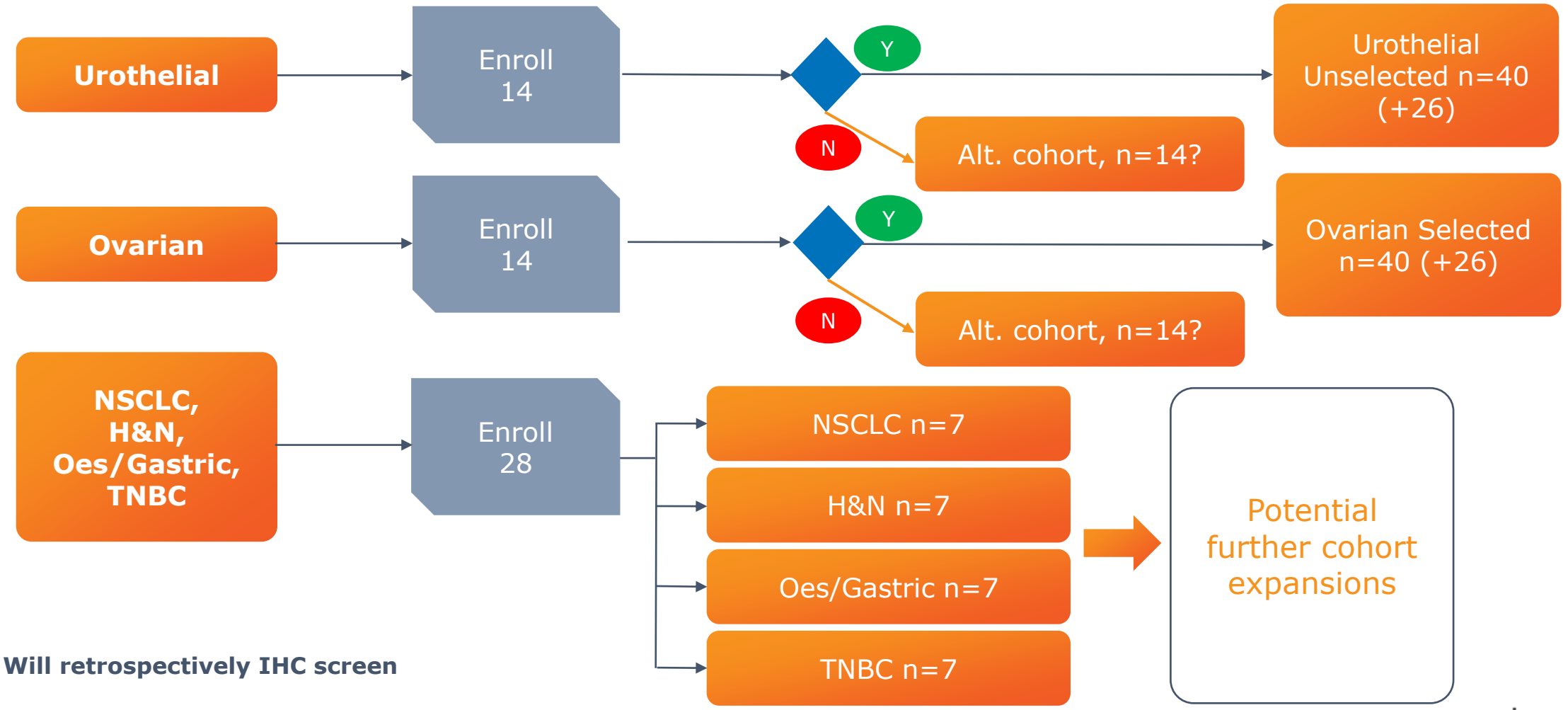
BT5528: Emerging observed relationship between EphA2 staining and responses

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



Data as of 14Jul21

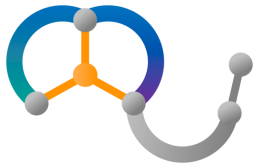
BT5528 expansion: overall trial design



Will retrospectively IHC screen

BT5528: Phase I dose escalation preliminary conclusions and next steps

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



Preliminary conclusions

- No evidence of BT5528 clotting abnormalities vs multiple disseminated intravascular coagulation events for MEDI-547 ADC
- Doses tolerated within expected therapeutic range; preliminary anti-tumor activity observed in two tumor types (ovarian and urothelial)
- Additional potential points of differentiation: no significant indications of neuropathy, eye and skin toxicities observed in BT5528 clinical trial as reported in interim Phase I dose escalation trial update on 7Oct21.
- Preliminary findings indicate activity associated with tumor expression

Preparations underway for expansion cohorts in multiple tumor types

Recommended Phase II dose of 6.5mg/m^2 Q2W

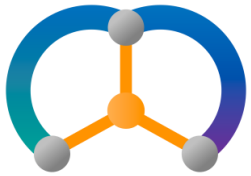
BT7480

Nectin-4/CD137

bicycle therapeutics

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

Immune cell receptor engaging *Bicycle*®
CD137



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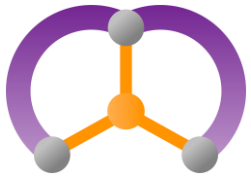
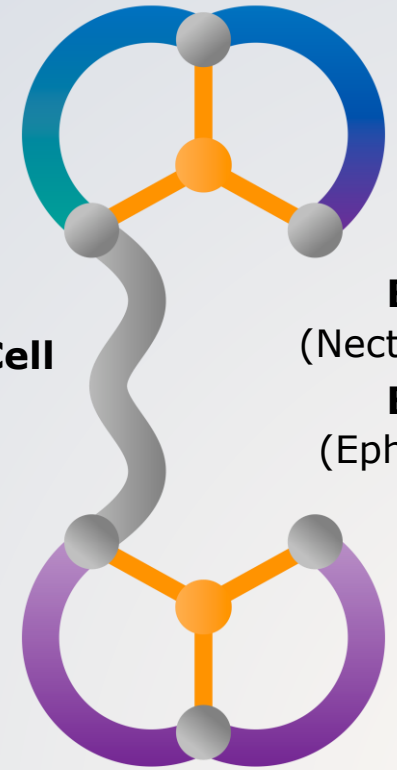


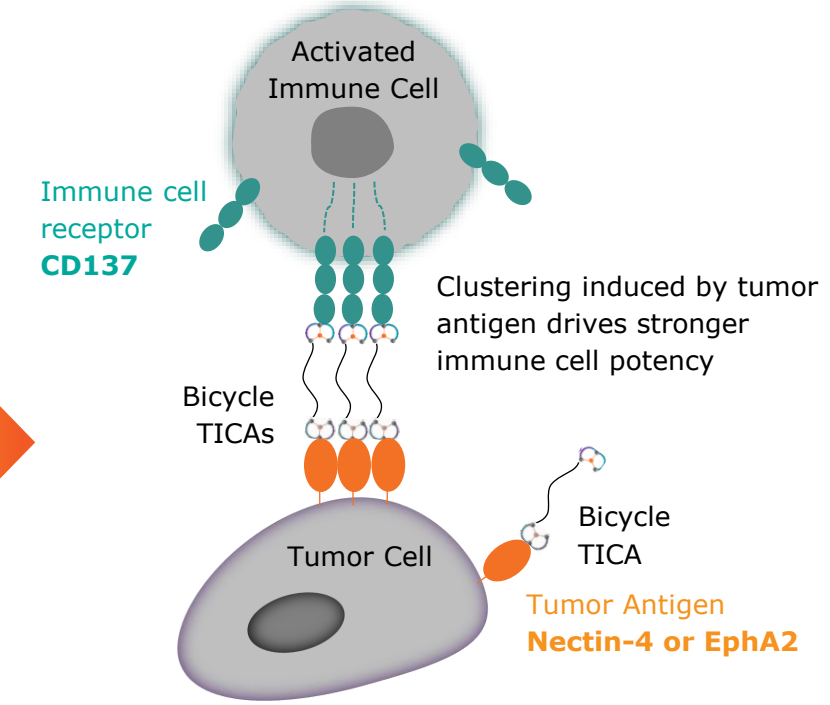
Tumor Antigen Targeting *Bicycle*®
Nectin-4 or EphA2

Tumor-targeted Immune Cell Agonists (*Bicycle* TICA™)



BT7480
(Nectin-4/CD137)

BT7455
(EphA2/CD137)



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

bicycle therapeutics

BT7480 entered clinic Q4 2021

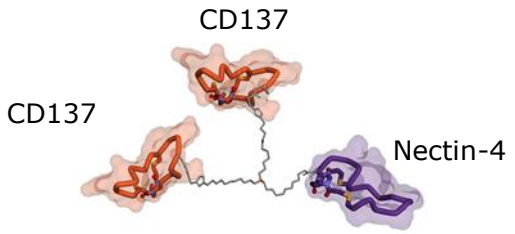
Nectin-4 and CD137 co-expressed in a variety of human tumors

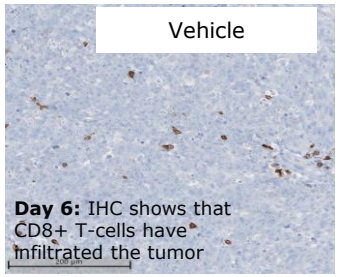
- BT7480 binds to Nectin-4 (across species) and CD137 (human, non-human primates) with high affinity. Exquisite selectivity observed in pre-clinical studies – no binding seen with >5,000 other membrane proteins.

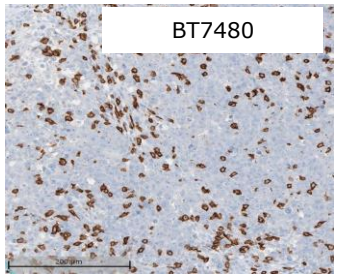
- BT7480 well-tolerated in preclinical species, with no liver tox
- BT7480 is ca. 30x smaller than comparator biologics
- US IND cleared 17Sept21
  - 9 sites selected
  - QW dosing initially with dosing adjustment to Q2W

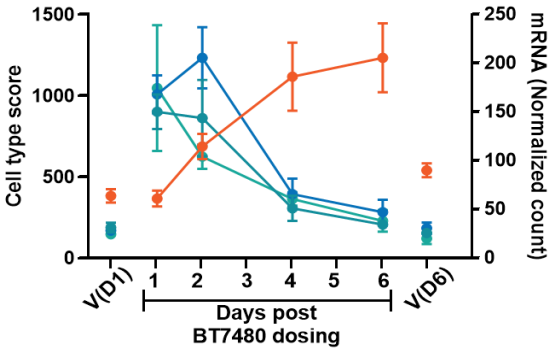
Entered clinic Q4 2021

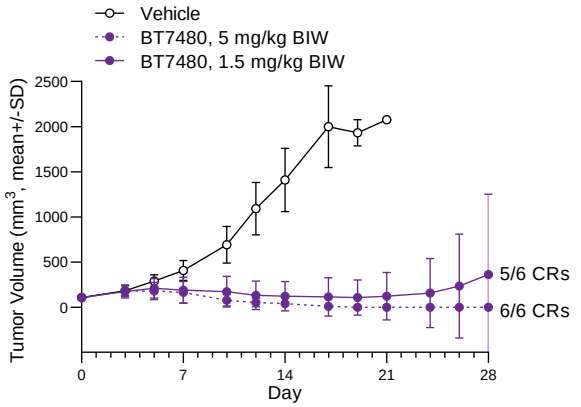
Internal	Target	Modality	Pre-clinical	IND-enabling	Phase I	Phase II
bicycle therapeutics	Nectin-4 /CD137	*Bicycle* TICA™				









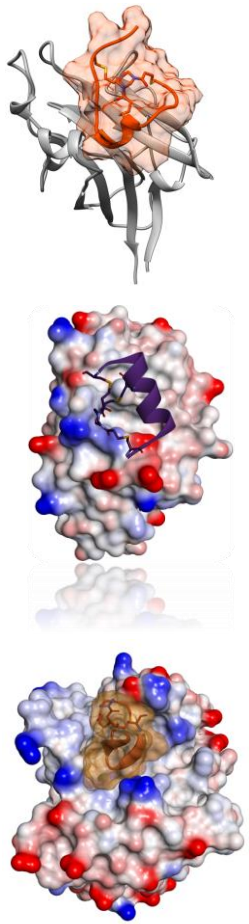


Upcoming Milestones

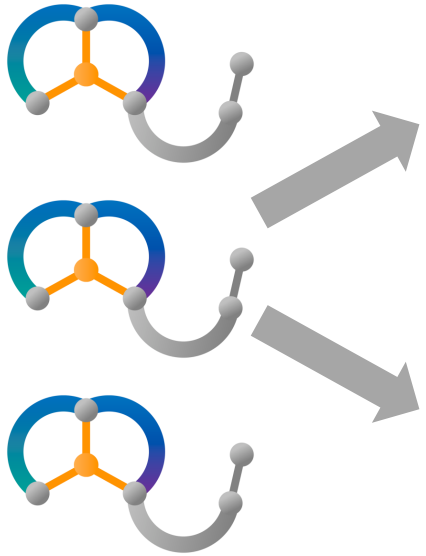
bicycle
therapeutics

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

Tumor targeting *Bicycles*

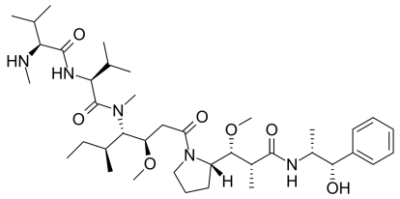


DEPTH



Building depth in internal library of tumor antigen binding Bicycles

Bicycle Toxin Conjugates®

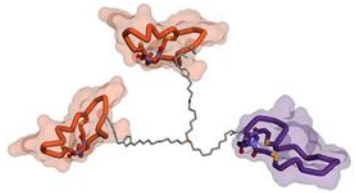


- Clinical signal observed
- Generalizable to other payloads
- Intend to build on current clinical trial observations with "wave" of 3rd Gen molecules

3rd Gen BTCs

- Broaden indications with additional targets and payloads

Bicycle® TICAs



- BT7480 entered Phase I Q4 2021
- BT7455 in IND enabling studies
- We believe our platform uniquely suited to tumor specific IO modulation
- Generalizable to multiple receptor classes

2nd Gen IO

- Tumor cell specific NK cell engagers in optimization
- Multi-targeted molecules in discovery

Internal & external pipeline combinations

- Short $t_{1/2}$ critical for sequencing
- Current data provides compelling biological rationale for combination of cytotoxic BTC™ with *Bicycle* TICAs and / or PD1

BREADTH

bicycle therapeutics

Looking forward

BT5528 - plan to initiate expansion cohorts in 2022

BT8009 – further update later in 2022

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

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

Appendix

bicycle
therapeutics

BT8009: Low incidence of neutropenia[1] below 7.5mg/m^2 QW

Dose (mg/m^2)	Tumor	Highest Grade	Day of Onset	Resolved?	Dose Reduced?
5 QW	Pancreatic	4	20	Yes	Yes
5 QW	Breast	2	8	No	No
5 QW	Pancreatic	2	6	No	No
5 QW	NSCLC	1	21	No	No
5 QW	Ovarian[2]	4	14	Yes	Yes
7.5 Q2W	Bladder	1	15	Yes	No
7.5 QW	Bladder[2]	4	14	Yes	Yes
7.5 QW	Bladder	3	15	Yes	No
7.5 QW	NSCLC	1	64	No	No
7.5 QW	Bladder	4	15	Yes	No

1. Neutropenia includes 8 cases of neutrophil count decreases and 2 cases recorded as neutropenia
2. Recorded as neutropenia patients

BT8009: Neuropathy was limited to Grade 1-2 treatment-related events in patients with prior history of nerve damaging therapies

Dose (mg/m^2)	Tumor	Highest Grade	Dose Reduced?	# Prior Lines of Therapies*
2.5 QW	Bladder (PD)	2	No	2
2.5 QW	Bladder (PR)	1	No	2
5 QW	Bladder (PR)	1	No	3
5 QW	Bladder (PR)	2	Yes	2
5 QW	Bladder (SD)	1	No	2
5 QW	Bladder (PR)	1	No	3
5 QW	Pancreatic (PD)	1	No	3

* All patients previously treated with platinum (60-90% neuropathy incidence: Kanat O, Ertas H, Caner B. World J Clin Oncol. 2017;8(4):329-335).

BT8009 parent and payload PK profile

- BT8009 demonstrates linear pharmacokinetics in humans. BT8009 has an elimination half-life of ~0.7 h
- The mean per dose exposure (AUC) of unconjugated MMAE from BT8009 dosed at 5mg/m^2 (equivalent to a dose 0.86 mg/m^2 of MMAE) was 829 ng.h/ml (CV 75%)
- Mean MMAE Cmax from BT8009 dosed at 5mg/m^2 was 18.4 ng/mL (CV 46%)
- The elimination half-life for MMAE was 2.3 days after BT8009 dosed at 5mg/m^2

Molecular weight is 4174 Da for BT8009

Enfortumab vedotin parent and payload PK profile*

- Enfortumab vedotin has an elimination half-life of ~3.6 days
- The per dose exposure (AUC) of unconjugated MMAE from enfortumab vedotin dosed at 1.25mg/kg (equivalent to a dose 0.85 mg/m^2 MMAE) was estimated to be 680 ng.h/mL* (CV 59%)
- Mean MMAE Cmax from a 1.25mg/kg dose of enfortumab vedotin was 5.5 ng/mL (CV 55%)
- The elimination half-life for MMAE was 2.6 days after enfortumab vedotin dosed at 1.25mg/kg

*Enfortumab vedotin data are from Padcev USPI (Nov 2021). MMAE data estimated from MMAE AUC0-28d [mean(±SD): 85(50) ng·d/mL] after 1st treatment cycle of 1.25 mg/kg EV on days 1, 8 and 15 of a 28-day cycle.

Molecular weight is 149022 Da for enfortumab vedotin with a drug antibody ratio of 3.8