BT8009 clinical trial update

NASDAQ: BCYC
April 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, trends or strategies and other financial and business matters; our current and prospective product candidates, planned clinical trials and preclinical activities, current and prospective collaborations and the timing and success of our development of our anticipated product candidates.

Forward-looking statements are neither historical facts nor assurances of future performance. Instead, they are based on our current beliefs, expectations and assumptions regarding the future of our business, future plans and strategies, our development plans, our preclinical and clinical results, our plans to initiate clinical trials and the designs of the planned trials and other future conditions, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to, 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.

Agenda

Introduction	**Kevin Lee** Chief Executive Officer
Technology overview	**Nick Keen** Chief Scientific Officer
BT8009 clinical experience to date	**Dominic Smethurst** Chief Medical Officer
Q&A	**Executive Management Team**

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 Cambridge UK and Lexington, MA

~119 Employees*

NASDAQ: BCYC

Cash balance $438.7M* (expected cash runway into 2024)

* as of December 31, 2021

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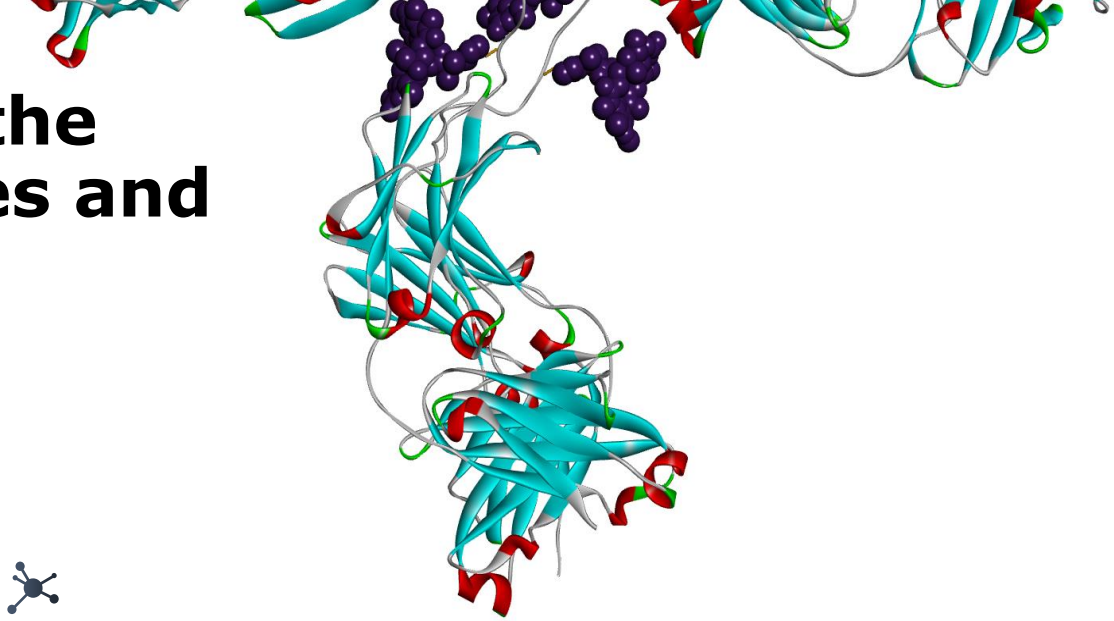
Bicycles are designed to combine the advantages of both small molecules and antibodies



	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

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

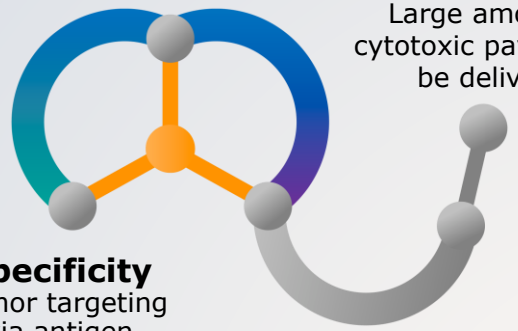
MWt of 1.5-2kDa

50-100x smaller than antibodies

High selectivity

Allows more potent toxin to be delivered directly to tumor

***Bicycle*® Toxin Conjugate (BTC™)**

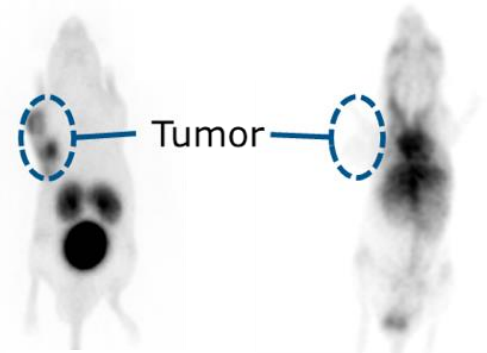


Toxin
Large amount of cytotoxic payload can be delivered

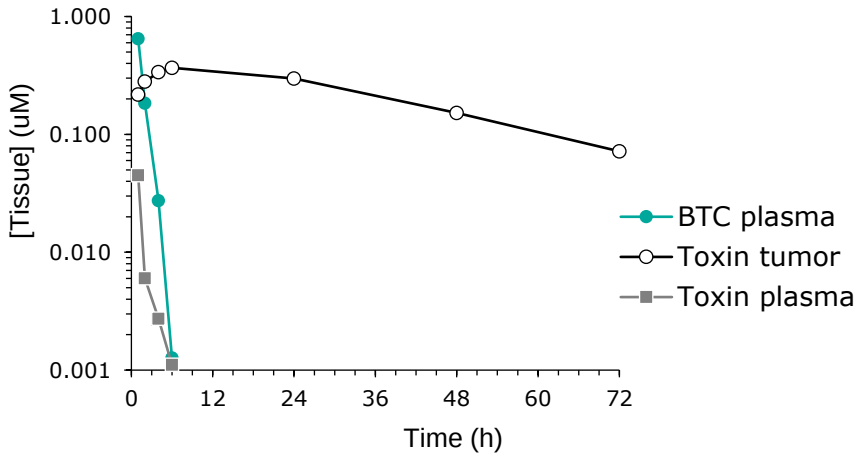
Specificity
Tumor targeting via antigen

Linker
Release of toxin directly into tumor via cleavable linker

PET Imaging 40-60min



***Bicycle*®** **Antibody**



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BT8009 Monotherapy

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Key takeaways from phase I dose escalation trial to date*

Promising clinical activity seen at 5mg/m^2 weekly; dose tolerated, with potential for differentiated and industry-leading product profile

- 50% ORR and 75% disease control, including 1 (13%) complete response
- Durable responses, with tumor reductions maintained over time
- No DLTs, low incidence of skin toxicity, ocular toxicity and neuropathy

7.5mg/m^2 weekly cohort identified as a non-tolerated dose, with GI and fatigue related 'soft DLTs' being observed

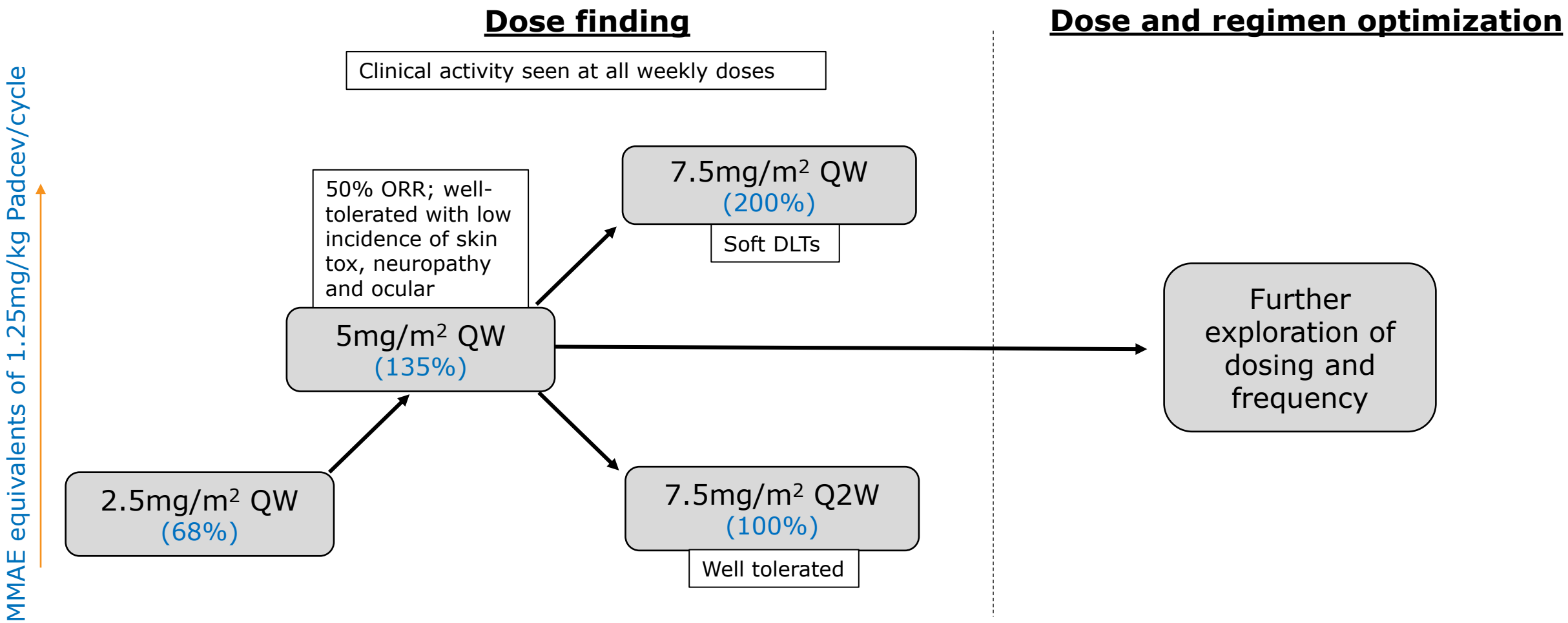
As predicted from preclinical data, BT8009 demonstrates linear pharmacokinetics. In contrast to ADCs, it also demonstrates a short terminal half-life.

Alternative dosing frequencies being explored while nearing a recommended Phase 2 dose

Expect to provide further updates on clinical progress later in 2022

* All BT8009 data as of 7Mar22

Dose escalation progress and strategy



Overview of key demographics for all patients enrolled in BT8009 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

Overview of disease history for all patients enrolled in BT8009 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%)**

Responses* observed in 2.5, 5 and 7.5mg/m² phase I dose escalation in response evaluable urothelial cancer patients

Update of First Two Cohorts

2.5mg/m² QW (N=4)
- 1 of 4 responses (25% ORR)
  - 59% tumor reduction
  - Deepened from 37% at 30Sept21
  - Remains on therapy; approaching 11 months
- 2 of 4 stable disease
- 75% disease control

5mg/m² QW (N=8)
- 4 of 8 responses (50% ORR)
  - 1 complete response
  - 3 partial responses
- 2 of 8 stable disease
- 75% disease control
- Greater detail on next slide

Newer Two Cohorts

7.5mg/m² Q2W (N=2)
- Well tolerated

7.5mg/m² QW (N=2)
- 1 PR prior to dose reduction
- 1 stable disease

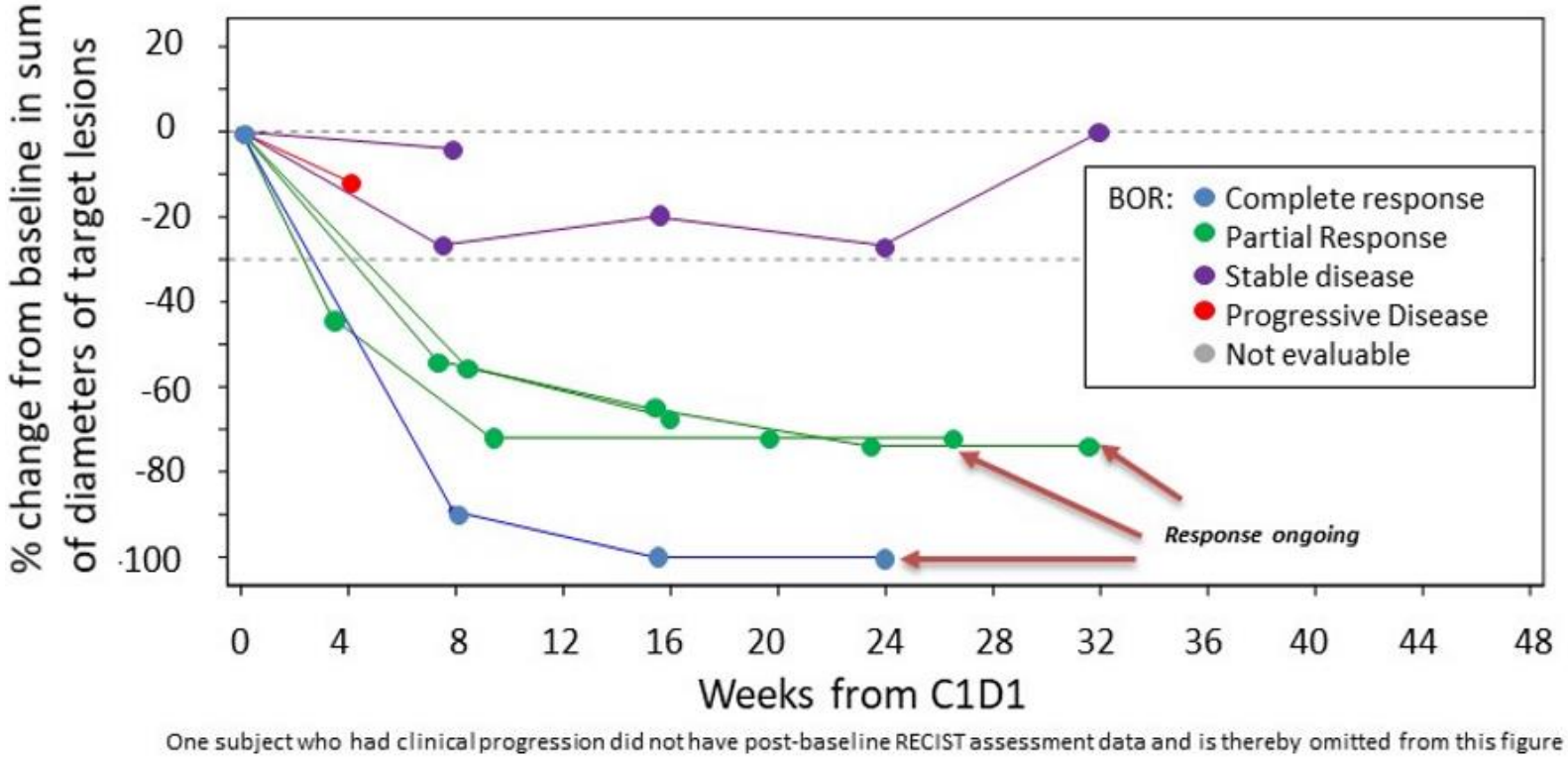
* Responses under response evaluation criteria in solid tumors (RECIST) version 1.1

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

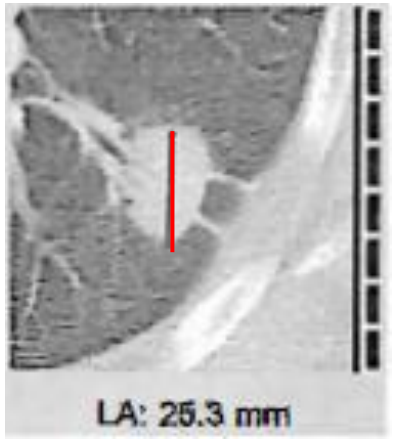
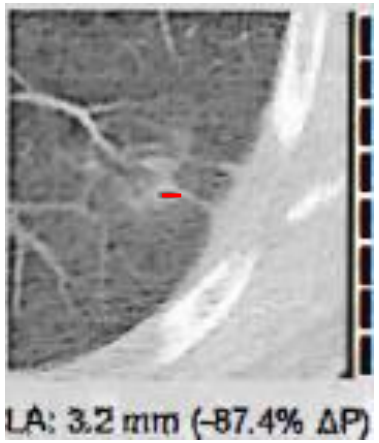
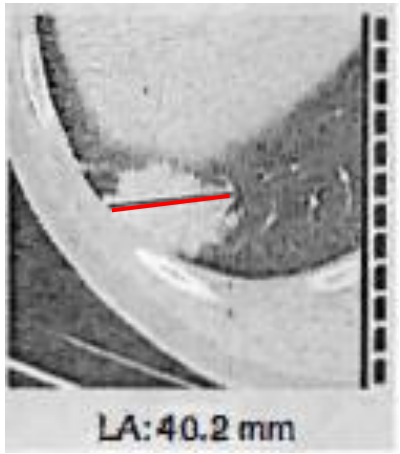
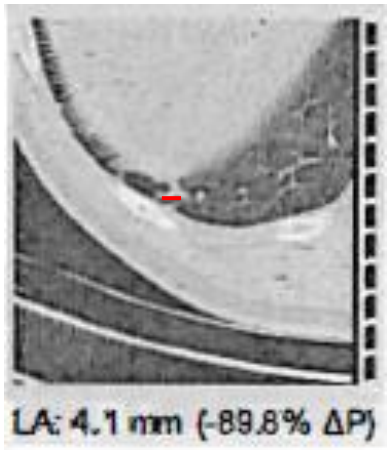
      (100% reduction in target lesion)
    - 65% tumor reduction
    - 54% tumor reduction
- Median DoR not reached
  - 3 responses ongoing
  - 1 progression at ~3 months



One subject who had clinical progression did not have post-baseline RECIST assessment data and is thereby omitted from this figure

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

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	 LA: 25.3 mm	 LA: 3.2 mm (-87.4% ΔP)	**Disappeared**	**Disappeared**
Lung lower lobe right	 LA: 40.2 mm	 LA: 4.1 mm (-89.8% ΔP)	**Disappeared**	**Disappeared**

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

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Phase I interim results from enfortumab vedotin (Padcev®)

Annals of Oncology 27 (Supplement 6): vi266–vi295, 2016
doi:10.1093/annonc/mdw373.16

genitourinary tumours, non-prostate

788P **Interim analysis of a phase I dose escalation trial of ASG-22CE (ASG-22ME; enfortumab vedotin), an antibody drug conjugate (ADC), in patients (Pts) with metastatic urothelial cancer (mUC)**

J.E. Rosenberg[1], E. Heath[2], R. Perez[3], J. Merchan[4], J. Lang[5], D. Ruether[6], D. Petrylak[7], R. Sangha[8], D.C. Smith[9], S. Sridhar[10], E. Gartner[11], M. Vincent[12], R. Chu[13], B. Anand[13], F. Donate[14], A. Melhem-Bertrandt[15], J. Zhang[16]

[1]Genitourinary Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [2]Medical Oncology, Karmanos Cancer Institute, Detroit, MI, USA, [3]Medical Oncology, University of Kansas Cancer Center, Fairway, KS, USA, [4]Medical Oncology, University of Miami Sylvester Comprehensive Cancer Center, Miami, FL, USA, [5]Genitourinary Oncology, UW Carbone Cancer Center, Madison, WI, USA, [6]Medical Oncology, Tom Baker Cancer Centre, Calgary, AB, Canada, [7]Medical Oncology, Smilow Cancer Hospital at Yale-New Haven, New Haven, CT, USA, [8]Oncology, University of Alberta Cross Cancer Institute, Edmonton, AB, Canada, [9]Internal Medicine and Urology, University of Michigan, Ann Arbor, MI, USA, [10]Oncology, Princess Margaret Hospital, Toronto, ON, Canada, [11]Development, Seattle Genetics, Inc., Seattle, WA, USA, [12]Clinical Research and Development, Agensys, Inc., Santa Monica, CA, USA, [13]Development, Agensys Inc., Santa Monica, CA, USA, [14]Translational Research, Agensys Inc., Santa Monica, CA, USA, [15]Clinical Research, Astellas Pharma, Northbrook, IL, USA, [16]Medical Oncology, H. Lee Moffitt Cancer Center University of South Florida, Tampa, FL, USA

Background: Nectin-4 is a protein expressed on several tumors, including mUC. Enfortumab vedotin is an ADC that delivers a small molecule microtubule-disrupting agent, monomethyl auristatin E (MMAE), to tumors expressing Nectin-4.

Methods: Pts with solid tumors, including mUC, treated with ≥ 1 prior chemo were enrolled using a modified continual reassessment method design. Pts were prescreened for Nectin-4 expression (IHC assay) and enrolled if H-score ≥150. Disease assessments were performed every 8 weeks (wks) using RECIST v 1.1. Enfortumab vedotin was administered IV wkly for 3 out of every 4 wks. 4 dose levels were studied: 0.5, 0.75, 1, or 1.25 mg/kg.

Results: As of 4/29/16, 49 solid tumor pts were enrolled; 42 with mUC reported here. Of analyzed tumor tissues, 98% were Nectin-4 positive (93% had H-score ≥ 150). Median age 67 y; 100% ECOG PS ≤ 1; 25 mUC pts (60%) had ≥ 2 prior therapies (tx). Of 33 response evaluable pts, 10 had a partial response (PR) (ORR =30%), including 4/10 pts (40%) with liver metastasis and 3/12 (25%) who failed checkpoint inhibitor tx. Antitumor activity is seen at all dose levels. Median duration on treatment is 12 wks. Both median progression free survival and duration of response are 16 wks. 38 pts (91%) had adverse events (AEs). The most common tx related AE was fatigue (38%). 23 pts (55%) had Grade (G) 3/4 AEs, 10 pts (24%) considered related. 9 pts (21%) had ocular AEs (G1/2). 2 pts had protocol defined dose limiting toxicities. There were 2 deaths, unrelated to tx. Serum concentration of enfortumab vedotin decreased multi-exponentially with half-life ~1.6 days. Exposure was dose proportional. Expansion cohorts are open at 1.25 mg/kg: updated results will be presented.

Table: 788P mUC Pts Only

Dose (mg/kg)	0.5	0.75	1	1.25
Evaluable pts* (n = 33)	2	12	12	7
ORR (CR + PR) n (%)	1 (50)	4 (33)	1 (8)	4 (57)

* ≥ 1 dose of drug and ≥ 1 post-baseline DA.

Conclusions: This novel Nectin-4 targeted ADC, enfortumab vedotin, is well tolerated in mUC pts with encouraging antitumor activity. These results warrant further studies in mUC.

Clinical trial identification: ASG-22CE-13-2

Legal entity responsible for the study: Agensys Inc.

Funding: Agensys Inc. and Seattle Genetics Inc.

Disclosure: J.E. Rosenberg: Boehringer Ingelheim, Bristol Meyers Squibb, Dendreon, Janssen Oncology, Johnson & Johnson, Oncogenex, Onyx, Lilly, Merck, Genentech/Roche, Illumina, Agensys and Mirati Therapeutics E. Heath: Agensys Inc., Bayer, Dendreon, Sanofi, Tokai Pharma, Seattle Genetics, Genentech/Roche, Millennium, Celdex, Inovio Pharma and Celgene. R. Perez, B. Anand, F. Donate: Agensys Inc. J. Merchan: Lilly, Tracon Pharmaceutical, Acceleron, Agensys, Rexahn Pharmaceutical. J. Lang: Salus Discovery, Agensys, Medivation, Innocrin Pharmaceutical, and Salus LLC. D. Petrylak: Bayer, Bellicum Pharma, Dendreon, Sanofi, Johnson & Johnson, Exelixis, Ferring, Millenium, Medivation, Pfizer, Porgenics, Genentech Inc., Astellas, Oncogenix, Merck, GTX and Novartis. R. Sangha: Boehringer Ingelheim, Astra Zeneca, Merck, Bristol Meyers Squibb, Pfizer, and Roche Glycart. D.C. Smith: Agensys Inc., Aragon Pharma, Atterocor, Bayer, Boston Biomedical, Celgene, Eisai, Exelixis, ImClone Systems, Incyte, Lilly, Millennium, Novartis, Oncogenex, Oncomed, PSMA, Puma Biotech, Seattle Genetics, Regeneron, Teva, Tekmira and BMS/Medarex. S. Sridhar: Astellas Pharma, Janssen, Sanofi, Bayer, Roche/Genentech and BMS. E. Gartner: Seattle Genetics Inc. M. Vincent: Pfizer and Amgen. R. Chu: Agensys Inc., Vertex, and Gilead. A. Melhem-Bertrandt: Astellas Pharmaceutical. J. Zhang: Bayer and Astellas Pharma. All other authors have declared no conflicts of interest.

Median PFS and DoR both 16 weeks

ORR 10/33 or 30%

100% patients pre-screened

60% patients ≥2 prior therapies

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Data from BT8009 interim phase I dose escalation trial to date in response-evaluable urothelial cancer patients

	2.5mg/m²	5mg/m²
No of patients	4	8
Median age	75	67
≥2 prior lines (%)	4 (100%)	8 (100%)
IHC pre-screen (%)	0	0
Partial or Complete Response (ORR %)	1 (25%)	4 (50%)
Stable Disease or better (DCR %)	3 (75%)	6 (75%)
Median duration of response (weeks)	Not reached	Not reached

Overview of adverse events observed in BT8009 phase I dose escalation trial across all patients

Preferred Term	Incidence (≥15%)
Fatigue	40.5%
Nausea	37.8%
Diarrhea	32.4%
Pyrexia	32.4%
Anemia	32.4%
Decreased appetite	32.4%
Constipation	29.7%
Urinary tract infection	27.0%
Neutrophil count decreased	24.3%
Asthenia	24.3%
Abdominal pain	21.6%
Pruritus	18.9%
Alopecia	18.9%
Back pain	16.2%
Hypokalemia	16.2%
Hypomagnesmia	16.2%

Summary of adverse event information from Padcev® FDA label

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)**

Adverse Event	Median time to onset (months)*	Padcev incidence*	Padcev severity (Gr≥3)*	Which trial(s)	N subjects
Skin tox	0.6	55%	13%	All	680
Neuropathy	4.6	52%	4%	All	680
Ocular disorders	1.6	40%	N/A	EV-201, EV-101, EV-102	384
Hyperglycemia	0.6	14%	7%	All	680
Pneumonitis	2.9	3%	1%	All	680

*Data from Padcev FDA approved product label

Overview of key adverse events observed in BT8009 phase I dose escalation trial across all cohorts

Adverse Event	Incidence	Severity (Gr≥3)	Related
Skin tox	19%	0%	14%
Neuropathy	24%	3%	19%
Ocular disorders	3%	0%	3%
Hyperglycemia	8%	0%	5%
Febrile neutropenia	0%	0%	0%
Pneumonitis	0%	0%	0%

Other adverse events of interest in BT8009 phase I dose escalation trial across all cohorts

Adverse Events	Incidence	Severity (Gr≥3)	Related
Neutropenia	30%	14%	30%
Gastrointestinal Disorders:			
Nausea	38%	3%	36%
Diarrhea	32%	5%	24%
Vomiting	11%	3%	11%

Potential efficacy in other tumor types will be explored more thoroughly in Phase II expansion trial

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

- 1 SD at 7.5mg Q2W. Disappearance of non-target lesions

- 1 SD at 2.5mg. 9+ months on therapy
- 1 SD at 7.5mg QW. 6+ months on therapy

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