A phase 2/3 study of Bicycle® Toxin Conjugate zelenectide pevedotin (BT8009) targeting Nectin-4 in patients with locally advanced or metastatic urothelial cancer (la/mUC) (Duravelo-2)

Abstract ▶TPS4619

Yohann Loriot, MD, PhD[1], Arlene O. Siefker-Radtke, MD[2], Terence W. Friedlander, MD[3], Andrea Necchi, MD[4], Alexander Z. Wei, MD[5], Srikala S. Sridhar, MD[6], Benjamin Garmezy, MD[7], Santiago Arroyo, MD, PhD[8], Emma Gartside, BSc (Hons)[9], Jie Liu, MSc[8], Carly Campbell, BSc[8], Justin Bader, PharmD, MBA[8], Daniel P. Petrylak, MD[10]

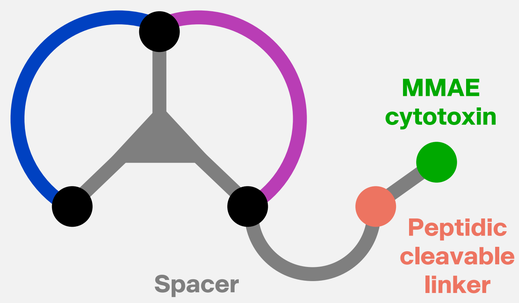
[1]Gustave Roussy Institute, University Paris-Saclay, Villejuif, France; [2]The University of Texas MD Anderson Cancer Center, Houston, TX, USA; [3]University of California San Francisco, Helen Diller Family Comprehensive Cancer Center, San Francisco, CA, USA; [4]Vita-Salute San Raffaele University, Milan, Italy; [5]Columbia University Irving Medical Center, New York, NY, USA; [6]Princess Margaret Cancer Center, Toronto, ON, Canada; [7]Sarah Cannon Research Institute, Nashville, TN, USA; [8]Bicycle Therapeutics, Cambridge, MA, USA; [9]BicycleTX Ltd, Cambridge, UK; [10]Yale School of Medicine, New Haven, CT, USA

BACKGROUND

- Bicycle Toxin Conjugates® (BTCs) are a new class of investigational anticancer agents that allow targeted delivery of cytotoxic payloads to tumors[1]
  - Synthetic, highly constrained, tumor-targeting bicyclic peptides linked to cytotoxic payloads enable payload release in the tumor microenvironment
  - Small, with molecular weight ~40 times less than antibody-drug conjugates
  - Rapidly distributed
  - Short plasma half-lives that limit systemic exposure
- Nectin-4 is a cell adhesion molecule that is overexpressed in multiple cancers, including la/mUC, and is a validated therapeutic target[2-4]
- Zelenectide pevedotin (BT8009) is a BTC which comprises a bicyclic peptide targeting Nectin-4 linked to the cytotoxin MMAE via a sarcosine spacer chain and a valine-citrulline cleavable linker (**Figure 1**)[5]
- With a low molecular weight and short plasma half-life, zelenectide pevedotin has the potential to rapidly penetrate solid tumors and reduce toxicity by minimizing prolonged exposure of conjugated drug to normal tissue[1,5]
- In the phase 1/2 Duravelo-1/BT8009-100 study (NCT04561362), patients with advanced malignancies (N=149) including la/mUC, had a tolerable safety profile and promising preliminary antitumor activity when treated with zelenectide pevedotin monotherapy at 5 mg/m^2 weekly.[6,7] Please see ASCO poster #3088 for updated PK and safety data from BT8009-100

FIGURE 1. SCHEMATIC AND CHARACTERISTICS OF ZELENECTIDE PEVEDOTIN[1]

Nectin-4 targeting Bicycle® molecule



Molecular weight[5]	4.2 kDa
Half-life[1]	<1 hr
Affinity for Nectin-4 (K_D)[1]	2.5 nM

OBJECTIVE

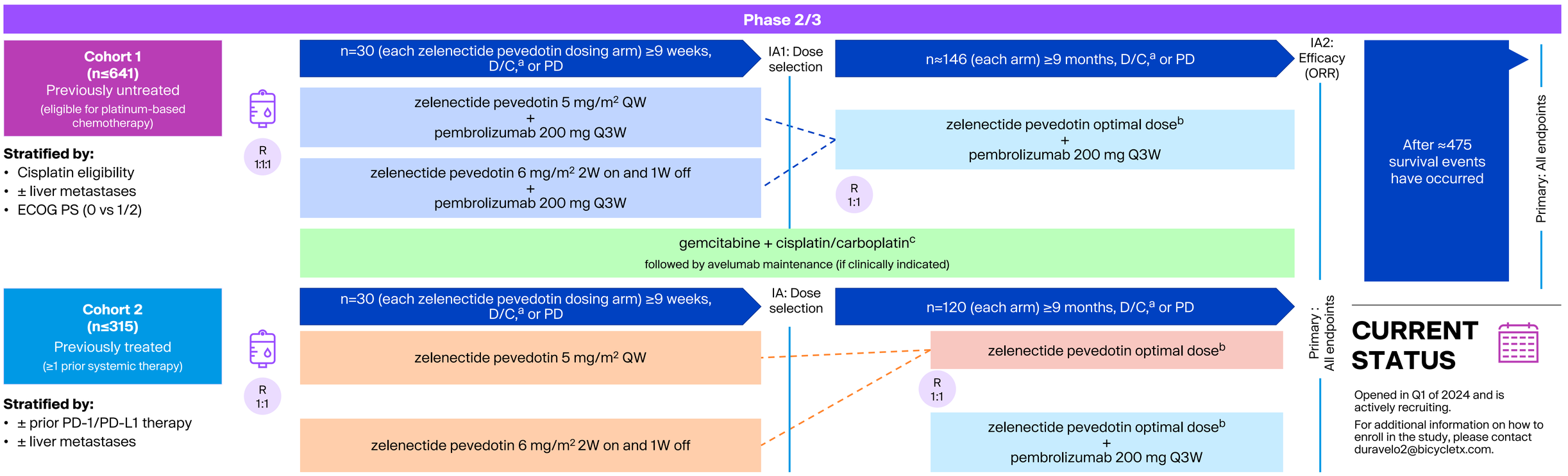
- Duravelo-2/BT8009-230 (NCT06225596) is designed to measure efficacy and safety of zelenectide pevedotin as monotherapy and in combination with pembrolizumab vs chemotherapy in patients with la/mUC (**Figure 2**)

2/3 **Phase**

Open-label **Randomized**

Global **Multicenter**

FIGURE 2. DURAVELO-2 (BT8009-230) STUDY DESIGN



[a]Discontinuation criteria include planned completion of therapy, progressive disease, and intolerable toxicity. [b]Optimal dose based on the total clinical and PK data available from the first 30 patients in each zelenectide pevedotin combination (Cohort 1) or monotherapy (Cohort 2) arm. [c]Dose and regimen in accordance with their respective US prescribing information and EU summary of product characteristics label, followed by avelumab maintenance (800 mg on day 1 and day 15 of each 28-day cycle) within 10 weeks after the last dose of platinum chemotherapy (if clinically indicated).

CURRENT STATUS

Opened in Q1 of 2024 and is actively recruiting.

For additional information on how to enroll in the study, please contact duravelo2@bicycletx.com.

STUDY ENDPOINTS BY COHORT

Cohort 1	Cohort 2
Primary: PFS (BICR)	**Primary: ORR (BICR)**
Secondary: • OS (key secondary) • ORR, DoR, and DCR (BICR, INV) • PFS (INV) • Safety/tolerability • HRQoL (EQ-5D, EORTC QLQ-C30)	**Secondary:** • ORR (INV) • OS • DoR, DCR, and PFS (BICR, INV) • Safety/tolerability • HRQoL (EQ-5D, EORTC QLQ-C30)
Exploratory: • PK of zelenectide pevedotin and MMAE • Incidence of ADA • Tumor and peripheral biomarkers • Exposure-response relationships	

KEY ELIGIBILITY CRITERIA

Inclusion	Exclusion
• Aged ≥18 years • Histologically/cytologically confirmed la/mUC of the renal pelvis, ureter, bladder, or urethra • Measurable disease per RECIST v1.1 • Archival or fresh tumor tissue available • Adequate organ and hematological function, including eGFR ≥30 mL/min **Cohort 1 only:** • ECOG PS ≤2 • No prior treatment for la/mUC[a] and eligible to receive platinum-based chemotherapy **Cohort 2 only:** • ECOG PS ≤1 • ≥1 prior systemic treatment[b] for la/mUC • Progression/recurrence of UC during or following most recent therapy	• Active keratitis/corneal ulcerations, ILD/pneumonitis, or untreated CNS metastases • Prior treatment with a CPI or with any systemic anticancer therapy or investigational agent within 2 weeks or 5 half-lives • Uncontrolled diabetes (HbA1c ≥8%), hypertension, or pleural/pericardial effusion • Grade ≥2 peripheral neuropathy • Prior Grade ≥3 irAE while receiving CPI **Cohort 1 only:** • Prior treatment with a CPI for any other malignancy within the last 12 months **Cohort 2 only:** • Received >1 prior platinum-based chemotherapy regimen for la/mUC[c] • Prior treatment with EV or any other MMAE-based therapy • Ongoing Grade ≥2 toxicity associated with prior treatment for UC

[a]Patients with prior neoadjuvant/adjuvant chemotherapy, MMAE-based therapy, immune checkpoint inhibitor therapy with recurrence >12 months from completion of therapy were allowed. [b]Including neoadjuvant/adjuvant platinum-based chemotherapy if recurrence occurred <12 months. [c]The percentage of patients with prior PD-1/PD-L1 inhibitor is capped at 50%.

ABBREVIATIONS

ADA, antidrug antibody; BICR, blinded independent central review; BTC, Bicycle Toxin Conjugate; CNS, central nervous system; CPI, checkpoint inhibitor; D/C, discontinuation; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; eGFR, estimated glomerular filtration rate; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30; EQ-5D, EuroQol-5 Dimensions; EV, enfortumab vedotin; HbA1c, hemoglobin A1C; hr, hours; HRQoL, health-related quality of life; IA, interim analysis; ILD, interstitial lung disease; INV, per investigator; irAE, immune-related adverse event; K_D, equilibrium dissociation constant; la/mUC, locally advanced or metastatic urothelial carcinoma; MMAE, monomethyl auristatin E; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD-1, programmed cell death protein-1; PD-L1, PD-ligand 1; PFS, progression-free survival; PK, pharmacokinetics; Q1, quarter 1; QW, weekly; Q3W, every 3 weeks; R, randomized; RECIST, Response Evaluation Criteria in Solid Tumors; UC, urothelial carcinoma; W, weeks.

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ACKNOWLEDGEMENTS

The authors would like to thank the participating patients and their families, clinicians, and the BT8009-230 study investigators. Medical writing support was provided by Rebecca L. Crepeau, PhD, of Fishawack Communications Ltd, part of Avalere Health, and funded by BicycleTx Ltd.

Presented at the American Society of Clinical Oncology (ASCO) 2024 Annual Meeting, Chicago, IL, USA, May 31–June 4, 2024