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)

Yohann Loriot, MD, PhD1, Arlene O. Sieffer-Radtke, MD2, Terence W. Friedlander, MD3, Andrea Necchi, MD4, Alexander Z. Wei, MD5, Sirkala S. Sridhar, MD6, Benjamin Garnemez, MD7, Santiago Arroyo, MD, PhD8, Emma Gartside, BSc (Hons)9, Jie Liu, MSc5, Carly Campbell, BSc10, Justin Bader, PharmD, MBA10, Daniel P. Petrylak, MD10

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

Zelenectide pevedotin (BT8009) is a BTC which comprises a bicyclic peptide targeting Nectin-4 linked to the cytotoxic MMAE via a saronic spacer chain and a valine-citrulline cleavable linker (Figure 1).

With a low molecular weight and short plasma half-lives, zelenectide pevedotin has the potential to rapidly penetrate solid tumors and reduce toxicity by minimizing prolonged exposure of conjugated drug to normal tissue.

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/m² weekly.

Please see ASCO poster #3088 for updated PK and safety data from BT8009-100

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)

FIGURE 1. SCHEMATIC AND CHARACTERISTICS OF ZELENECTIDE PEVEDOTIN

Molecular weight: 4.2 kDa
Half-life: <1 hr
Affinity for Nectin-4 (Kₐ): 2.5 nM

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

Phase 2/3
- Cohort 1 (n=64)
  - Previously untreated (eligible for platinum-based chemotherapy)
  - Stratified by:
    - Cisplatin eligibility
    - a liver metastases
    - ECOG PS (0 vs 1/2)
- Cohort 2 (n=310)
  - Previously treated (at prior systemic therapy)
  - Stratified by:
    - a prior PD-1/PD-L1 therapy
    - a liver metastases

IA1: Dose selection
- n=30 (each zelenectide pevedotin dosing arm) ≥9 weeks, D/C, or PD
  - zelenectide pevedotin 5 mg/m² QW
  - zelenectide pevedotin 6 mg/m² 2W on and 1W off
- gemcitabine + cisplatin/carboplatin
  - followed by avalubavum maintenance (if clinically indicated)

IA2: Efficacy (ORR)
- n=146 (each arm) ≥9 months, D/C, or PD
  - zelenectide pevedotin optimal dose
  - pembrolizumab 200 mg Q3W

IA3: Efficacy (OS)
- n=120 (each arm) ≥9 months, D/C, or PD
  - zelenectide pevedotin optimal dose
  - pembrolizumab 200 mg Q3W

STUDY ENDPOINTS BY COHORT

<table>
<thead>
<tr>
<th>Cohort 1</th>
<th>Cohort 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary: PFS (BICR)</td>
<td>Primary: ORR (BICR)</td>
</tr>
<tr>
<td>Secondary: OS (key secondary)</td>
<td>Secondary: ORR (BICR)</td>
</tr>
<tr>
<td>ORR, DoR, and DCR (BICR, INV)</td>
<td>OS, DCR, and PFS (BICR, INV)</td>
</tr>
<tr>
<td>PFS (INV)</td>
<td>Safety/tolerability</td>
</tr>
<tr>
<td>Safety/tolerability</td>
<td>HRQoL, (EQ-5D, EORTC QLQ-C30)</td>
</tr>
<tr>
<td>Exploratory: PK of zelenectide pevedotin and MMAE</td>
<td>Exploratory: PK of zelenectide pevedotin and MMAE</td>
</tr>
<tr>
<td>Incidence of ADA</td>
<td>Incidence of ADA</td>
</tr>
<tr>
<td>Tumor and periphery biomarkers</td>
<td>Tumor and periphery biomarkers</td>
</tr>
<tr>
<td>Exposure-response biomarkers</td>
<td>Exposure-response biomarkers</td>
</tr>
</tbody>
</table>

KEY ELIGIBILITY CRITERIA

**Inclusion**
- 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:
  - EGFR PS ≤2
  - No prior treatment for la/mUC and eligible to receive platinum-based chemotherapy
- Cohort 2 only:
  - EGFR PS 0
  - ≥1 prior systemic treatment for la/mUC
  - Progression/recurrence of UC during or following most recent therapy

**Exclusion**
- Active keratitis/conjunctival ulcerations, ILLD/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
- Prior and concurrent treatment with a CPI or any other malignancy within the last 12 months
- Ongoing Grade 2 toxicity associated with prior treatment for UC

*Patients with prior nadir-adjusted platinum-based chemotherapy, MMAE-based therapy, immune checkpoint inhibitor therapy with response >12 months from completion of therapy were allowed. Including nadir-adjusted platinum-based chemotherapy if unreccurrence occurred ≥12 months. The percentage of patients with prior PD-1/PD-L1 inhibitor is capped at 50%.

REFERENCES
8. Emma Gartside, BSc (Hons)9, Jie Liu, MSc8, Carly Campbell, BSc8, Justin Bader, PharmD, MBA8, Daniel P. Petrylak, MD10

ACKNOWLEDGEMENTS
The authors would like to thank the participating patients and their families, clinicians, and the BT8009-230 study team. Medical writing support was provided by Medical Writing Services, Inc. Presented at the American Society of Clinical Oncology (ASCO) 2024 Annual Meeting, Chicago, IL, USA, May 31–June 4, 2024.