Zelenectide pevedotin (BT8009) monotherapy in enfortumab vedotin–naïve patients with metastatic urothelial carcinoma: Updated results of Duravelo-1

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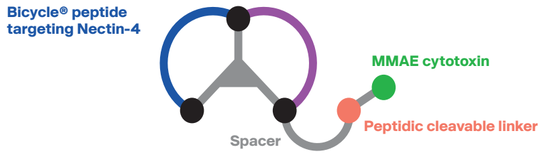
BACKGROUND

- Bicycle® molecules are an innovative therapeutic class in development that offers the manufacturing and pharmacokinetic (PK) properties of a small molecule with the high binding specificity of a biologic,[1–3] making them ideally suited for the targeted delivery of a range of payloads such as cytotoxins to solid tumors
- Zelenectide pevedotin, formerly BT8009, is a first-in-class Bicycle® Toxin Conjugate, comprising a highly selective Nectin-4–targeted Bicycle® peptide conjugated to the cytotoxic drug monomethyl auristatin E (MMAE) via a cleavable linker **(Figure 1)**[2,4]
- Nectin-4 is overexpressed in a range of solid tumors, including metastatic urothelial carcinoma (mUC)[5–8]
- Zelenectide pevedotin provides a novel targeted therapeutic option for Nectin-4–associated tumors with the potential for similar or better efficacy and an improved safety profile compared with currently available MMAE antibody-drug conjugates based on preclinical models[4]
- This ongoing Phase 1/2 study (NCT04561362) is evaluating zelenectide pevedotin ± pembrolizumab in patients with advanced solid tumors associated with Nectin-4 expression
- Updated results from zelenectide pevedotin monotherapy 5 mg/m^2 weekly in enfortumab vedotin (EV)-naïve patients with mUC are reported

FIGURE 1. ZELENECTIDE PEVEDOTIN STRUCTURE



METHODS

- Eligible adult patients have recurrent, unresectable mUC, prior anti-programmed death-1/programmed death ligand-1 (PD-1/PD-L1) exposure, have progressed after or are ineligible for platinum-based chemotherapy, and have received no prior EV
- The primary endpoint for this part of the study is objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1; secondary endpoints include incidence and severity of treatment-emergent adverse events (TEAEs); duration of response (DoR) and clinical benefit rate (CBR); and PK
  - In this study, CBR is defined as the rate of complete response + partial response + stable disease lasting ≥16 weeks
- All patients with mUC receiving 5 mg/m^2 zelenectide pevedotin monotherapy weekly across dose escalation and expansion phases are included for safety analysis; of these, patients who received any dose of study drug and had ≥1 adequate postbaseline response assessment are efficacy-evaluable

RESULTS

Patient demographics and characteristics

- As of 22 March 2024, in total, 45 patients with median age 67 years (range, 42–84) and a median of 2.5 prior lines of therapy (range, 1–7) have been included **(Table 1)**
- The PK of EV-naïve patients with mUC is consistent with PK observed across the entire study

TABLE 1. PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Characteristic	Patients (N=45)
Median age, years (range)	67 (42–84)
Sex, n (%)	
Male	34 (76)
Race, n (%)	
White	27 (60)
Black or African American	0
Other/missing	18 (40)
ECOG PS, n (%)	
0	21 (47)
1	24 (53)
Median prior lines of therapy (range)	2.5 (1–7)
Prior therapy, n (%)	
Checkpoint inhibitor	42 (93)
Platinum-based therapy	42 (93)
Sacituzumab govitecan	6 (13)
FGFR inhibitor	1 (2)
Enfortumab vedotin[a]	0

[a]Patients with prior exposure to enfortumab vedotin were excluded from this cohort of the study.

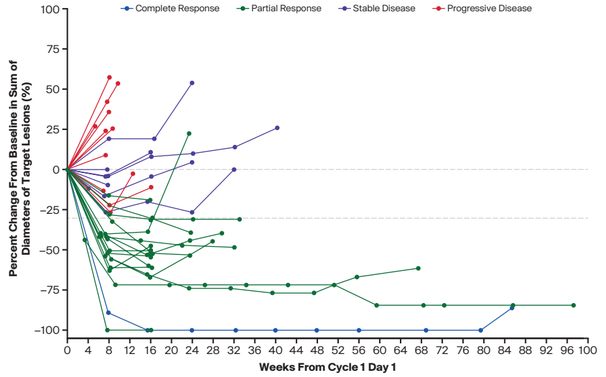
Efficacy

- Median time on treatment is 16.1 weeks (range, 1–101.4) **(Figure 2)**
- Median follow-up time is 4.2 months (range, 0.5–28.6)
- Among 38 efficacy-evaluable patients, ORR is 45% (n=17) and CBR is 61% (n=23), including 1 confirmed complete response and 16 partial responses; stable disease is maintained in 9 patients, and 12 patients have experienced progressive disease
- Median DoR is 11.1 months (95% confidence interval [CI] 3.9, not reached [NR]), among patients with confirmed responses (n=14) **(Figures 2 and 3)**

Safety

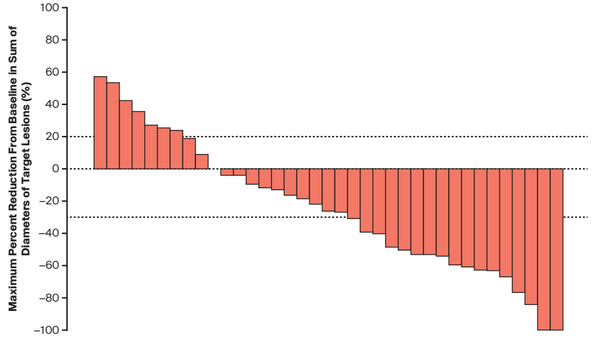
- The most common treatment-related AEs (TRAEs) are nausea (33%), asthenia (22%), pyrexia and fatigue (20% each) **(Table 2)**
- There have been no Grade ≥3 TRAEs of peripheral neuropathy (any kind), skin reactions, or eye disorders **(Table 3)**
  - TRAEs of peripheral neuropathy were low-grade; 82% of patients with mUC who had peripheral neuropathy at baseline did not develop treatment-related peripheral neuropathy
- There have been no treatment-related deaths

FIGURE 2. DoR AND CHANGE FROM BASELINE IN TUMOR SIZE IN EFFICACY-EVALUABLE EV-NAÏVE PATIENTS WITH mUC TREATED WITH ZELENECTIDE PEVEDOTIN 5 mg/m^2 ONCE PER WEEK (n=37[a])



[a]Number of efficacy-evaluable patients with at least one postbaseline target lesion measurement. One patient had progressive disease because of a new lesion, but this individual did not have a postbaseline target lesion measurement.

FIGURE 3. WATERFALL PLOT OF CHANGE FROM BASELINE IN TUMOR SIZE IN EFFICACY-EVALUABLE EV-NAÏVE PATIENTS WITH mUC TREATED WITH ZELENECTIDE PEVEDOTIN 5 mg/m^2 ONCE PER WEEK (n=37[a])



[a]Number of efficacy-evaluable patients with at least one postbaseline target lesion measurement. One patient had progressive disease because of a new lesion, but this individual did not have a postbaseline target lesion measurement.

TABLE 2. SAFETY SUMMARY OF ZELENECTIDE PEVEDOTIN IN EV-NAÏVE PATIENTS WITH mUC

Category, n (%)	Patients (N=45)[a]
TEAEs	42 (93)
Grade ≥3	24 (53)
TRAEs	36 (80)
Grade ≥3	10 (22)
TRAEs reported in ≥15% of patients, n (%)	
Nausea[b]	15 (33)
Asthenia	10 (22)
Fatigue	9 (20)
Pyrexia	9 (20)
Diarrhea	8 (18)
Appetite decreased	7 (16)
Alopecia	7 (16)
Dose modifications, n (%)	
TEAEs leading to dose interruption	24 (53)
TEAEs leading to dose reduction	12 (27)
TEAEs leading to dose discontinuation	2 (4)
Time to dose modification, months (range)	
Median time to first dose reduction	2.3 (1.0–14.1)

[a]Including data from dose escalation and dose expansion phases. [b]Prophylactic antiemetics are prohibited during Cycle 1 of dose escalation, and use of anti-emetics associated with QT prolongation is prohibited during the study.

TABLE 3. TRAEs OF SPECIFIC MONITORING RELATED TO TREATMENT WITH ZELENECTIDE PEVEDOTIN

	Patients[a] (N=45)					
Event type	**Grade 1, n (%)**	**Grade 2, n (%)**	**Grade 3, n (%)**	**Grade 4, n (%)**	**Grade 5, n (%)**	**Total, n (%)**
Peripheral neuropathy[b]	9 (20)	7 (16)	0	0	0	16 (36)
Peripheral sensory neuropathy[c]	6 (13)	0	0	0	0	6 (13)
Hyperglycemia[c]/diabetes mellitus[c]	2 (4)	0	1 (2)	0	0	3 (7)
Skin reactions[d]	6 (13)	2 (4)	0	0	0	8 (18)
Neutropenia[c]	2 (4)	2 (4)	2 (4)	0	0	6 (13)
Eye disorders[e]	2 (4)	1 (2)	0	0	0	3 (7)

[a]Including data from dose escalation and dose expansion phases. [b]Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries (SMQ) [broad]. [c]Preferred term. [d]Includes the MedDRA term of Severe Cutaneous Adverse Reactions (SCAR) SMQ and events that fell into the MedDRA system organ class (SOC) of Skin and Subcutaneous Tissue disorders, excluding alopecia. [e]SOC of eye disorders.

CONCLUSIONS

- This ongoing Phase 1/2 study of zelenectide pevedotin monotherapy at 5 mg/m^2 weekly shows promising response and a generally well-tolerated safety profile in EV-naïve patients with mUC
  - No Grade ≥3 treatment-related peripheral neuropathy has been reported
  - As of median 4.2 months (range, 0.5–28.6) follow-up time, patients with pre-existing peripheral neuropathy were unlikely to develop worsening peripheral neuropathy during treatment with zelenectide pevedotin
- A Phase 2/3 study of zelenectide pevedotin in patients with mUC (NCT06225596; Duravelo-2) is currently enrolling

ABBREVIATIONS

AEs, adverse events; CBR, clinical benefit rate; CI, confidence interval; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EV, enfortumab vedotin; FGFR, fibroblast growth factor; MedDRA, Medical Dictionary for Regulatory Activities; MMAE, monomethyl auristatin E; mUC, metastatic urothelial carcinoma; NR, not reached; ORR, objective response rate; PD-1, programmed death 1; PD-L1, programmed death ligand 1; PK, pharmacokinetics; QT, time between Q and T waves on an electrocardiogram; RECIST, Response Evaluation Criteria in Solid Tumors; SCAR, Severe Cutaneous Adverse Reactions; SMQ, Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries; SOC, MedDRA system-organ class; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; UC, urothelial carcinoma.

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