Peripheral neuropathy following treatment with Bicycle Toxin Conjugates® zelenectide pevedotin (formerly BT8009) or BT5528 monotherapy in patients with advanced solid tumors

654P

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BACKGROUND

- Bicycle® molecules are an innovative therapeutic class in development that offers the manufacturing and pharmacokinetic 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, and BT5528 are Bicycle Toxin Conjugates® (BTCs) comprising bicyclic peptides that target Nectin-4 and EphA2, respectively, linked to monomethyl auristatin E (MMAE) via a cleavable linker[4,5]
- Nectin-4 and ephrin type-A receptor 2 (EphA2) are overexpressed in many tumors[6-9]
- Peripheral neuropathy (PN) is a known adverse event in approximately 65% (7% Grade 3/4) of patients treated with MMAE-based antibody-drug conjugates[10]
- Owing to short plasma half-lives and high selectivity, BTCs have the potential to limit MMAE-related toxicity by reducing non-tumor tissue exposure[2,5]
- Here we report on treatment-related PN (TRPN) from two ongoing, Phase 1/2 studies of zelenectide pevedotin (NCT04561362) and BT5528 (NCT04180371) in patients with advanced solid tumors; additional trial results are presented in posters 652P and 647P, respectively

METHODS

- Patients with tumors associated with Nectin-4 or EphA2 expression who had progressed on ≥1 prior therapy were eligible
- Patients with ongoing Grade ≥2 PN from prior therapy were not included in either study
- Patients received the recommended Phase 2 monotherapy dose: zelenectide pevedotin 5 mg/m^2 QW or BT5528 6.5 mg/m^2 Q2W
- Dose interruptions were required for Grade 2 (zelenectide pevedotin/BT5528) or Grade 3 (BT5528) PN; treatment was withdrawn for Grade 3 (zelenectide pevedotin) or Grade 4 (BT5528) PN
- PN was reported using Medical Dictionary for Regulatory Activities (MedDRA) standardized MedDRA queries (SMQ) (broad) and preferred terms were graded per National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0

RESULTS

PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

- Both study populations had clinical characteristics consistent with those expected of a Phase 1/2 study. In the zelenectide pevedotin study, 149 patients were treated, most with urothelial cancer; in the BT5528 study, ovarian cancer was most common among the 74 patients. Platinum-based therapies were the most common prior therapy in each trial **(Table 1)**
- Median time on treatment was 10.0 weeks (N=149; range 1.0–101.4) for zelenectide pevedotin and 8.5 weeks (N=74; range 1.3–106.0) for BT5528 (as of 22 March and 14 March 2024, respectively)

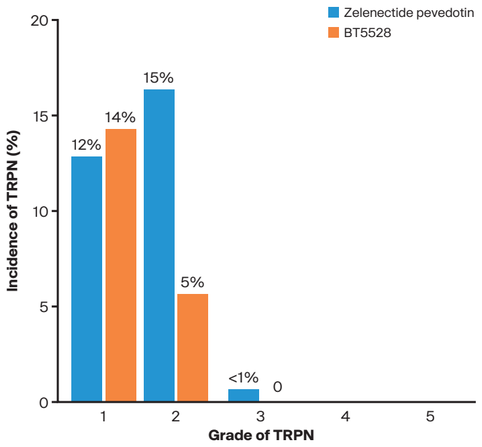
TABLE 1. PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Characteristic	Zelenectide pevedotin (N=149)	BT5528 (N=74)
Age, years, median (range)	62 (31–84)	63 (33–78)
Sex, n (%)		
Female	77 (52)	40 (54)
Male	72 (48)	34 (46)
Race, n (%)		
Asian	2 (1)	5 (7)
Black or African American	1 (<1)	0
White	68 (46)	55 (74)
Other/missing	78 (52)	14 (19)
ECOG PS, n (%)		
0	59 (40)	30 (41)
1	89 (60)	44 (59)
Prior lines of therapy, median (range)	3 (1–13)	4 (1–13)
Types of prior therapy, n (%)		
Platinum-based	121 (81)	66 (89)
Checkpoint inhibitor	107 (72)	44 (60)
Taxane-based	79 (53)	50 (68)
Sacituzumab govitecan	29 (20)	10 (14)
Enfortumab vedotin	20 (13)	5 (7)
FGFR inhibitor	5 (3)	2 (3)

FREQUENCY AND SEVERITY OF TRPN

- Per SMQ (broad), TRPN was reported in 42/149 (28%) patients treated with zelenectide pevedotin and 14/74 (19%) patients treated with BT5528 **(Figure 1)**
  - One Grade 3 event (neuralgia) was reported in a patient treated with zelenectide pevedotin following prior therapy with enfortumab vedotin; no Grade 3–4 events were observed for BT5528
- Of patients with TRPN, 7/42 (16%; zelenectide pevedotin) and 5/14 (36%; BT5528) had ongoing Grade 1 PN at baseline
- 80% of zelenectide pevedotin-treated patients with PN at baseline did not develop TRPN during treatment (median follow-up 3.3 months [range 0.4–28.6])

FIGURE 1. INCIDENCE AND BREAKDOWN OF TRPN BY GRADE



- In patients receiving zelenectide pevedotin, <1% of cases were considered as motor-related TRPN, while 1% were considered sensorimotor. There were no motor or sensorimotor cases of TRPN in patients receiving BT5528 **(Table 2)**

TABLE 2. INCIDENCE OF TRPN

Characteristic	Zelenectide pevedotin (N=149)		BT5528 (N=74)	
	Grade 1 n (%)	Grade 2 n (%)	Grade 1 n (%)	Grade 2 n (%)
SMQ [broad]				
Patients with TRPN	18 (12)	23 (15)	10 (14)	4 (5)
Preferred terms				
Peripheral sensory neuropathy	13 (9)	8 (5)	2 (3)	2 (3)
Dysesthesia	3 (2)	0	0	0
Peripheral neuropathy	2 (1)	4 (3)	6 (8)	1 (1)
Paresthesia	1 (<1)	0	1 (1)	1 (1)
Neuralgia	0	3 (2)	0	0
Neurotoxicity	0	3 (2)	0	0
Peripheral sensorimotor neuropathy	0	2 (1)	0	0
Polyneuropathy	0	2 (1)	1 (1)	0
Muscular weakness	0	1 (<1)	0	0
Peripheral motor neuropathy	0	1 (<1)	0	0

- The median time to onset of TRPN was similar for zelenectide pevedotin and BT5528 (7.4 and 5.7 weeks, respectively) **(Table 3)**

TABLE 3. TIME TO ONSET OF TRPN

Characteristic	Median time to onset, weeks (range)			
	Zelenectide pevedotin		BT5528	
TRPN, any grade	n=42	7.4 (0–61.3)	n=14	5.7 (0.4–37.8)
Grade ≥2 TRPN	n=24	12.2 (0.4–79.6)	n=4	13.9 (3.0–18.3)

TRPN-RELATED CHANGES TO DOSING

- TRPN resulted in few dose modifications across the overall patient populations for zelenectide pevedotin and BT5528; no drug withdrawals were necessary for either BTC® molecule **(Table 4)**

TABLE 4. DOSE MODIFICATIONS DUE TO TRPN IN THE OVERALL PATIENT POPULATIONS

Characteristic	Zelenectide pevedotin (N=149) n (%)	BT5528, (N=74) n (%)
Dose modifications	16 (11)	0
Interruption[a]	13 (9)	0
Reduction[a]	6 (4)	0
Withdrawn	0	0

[a]Patients could be included in more than one category of modification.

RESOLUTION OF TRPN

- TRPN had completely resolved in 14% (zelenectide pevedotin) and 21% (BT5528) of patients, and 26% and 21%, respectively, had some resolution or improvement at time of reporting, though post-treatment follow-up was limited **(Table 5)**
- Median time to resolution or improvement of TRPN was 2.2 weeks for zelenectide pevedotin (range 0–42.2 weeks) and 1.7 weeks for BT5528 (range 0.4–29.1 weeks); improvement or resolution of zelenectide pevedotin-related TRPN was seen as a result of dose interruptions

TABLE 5. RESOLUTION OR IMPROVEMENT IN TRPN

Characteristic	Zelenectide pevedotin (N=42) n (%)	BT5528 (N=14) n (%)
Complete resolution	6 (14)	3 (21)
Residual TRPN	36 (86)	11 (79)
Some resolution or improvement	11 (26)	3 (21)
No resolution or improvement	25 (60)	8 (57)

CONCLUSIONS

- Frequency and severity of TRPN were relatively low following zelenectide pevedotin or BT5528 monotherapy, contributing to an emerging differentiated safety profile for BTCs
- Most events were mild to moderate, even in patients with baseline PN, required no withdrawals, and patients were often able to continue treatment without modification

ABBREVIATIONS

BTC®, Bicycle® Toxin Conjugate; ECOG PS, Eastern Cooperative Oncology Group performance status; EphA2, ephrin type-A receptor 2; FGFR, fibroblast growth factor receptor; MedDRA, Medical Dictionary for Regulatory Activities; MMAE, monomethyl auristatin E; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; PN, peripheral neuropathy; Q2W, every 2 weeks; QW, weekly; SMQ, standardized MedDRA queries; TRPN, treatment-related peripheral neuropathy

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