Enhanced anti-tumor activity of zelenectide pevedotin in triple negative breast cancer (TNBC) patients with *NECTIN4* gene amplification

Poster

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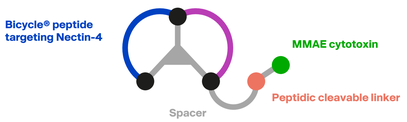
BACKGROUND

- Bicycle® molecules are a new class of therapeutics under clinical evaluation 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, is a first-in-class Bicycle® Toxin Conjugate (BTC), 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]
- BTC® molecules have lower molecular weight and shorter plasma half-life than antibody-drug conjugates, with distinct pharmacokinetics/dynamics, i.e., potential for rapid tumor penetration and minimal healthy tissue exposure[4–7]

FIGURE 1.



- Nectin-4 is expressed in a range of solid tumors, including metastatic urothelial carcinoma (mUC) and breast cancer (BC)[7–9]
- *NECTIN4* amplification has been proposed as a predictive biomarker of response to Nectin-4 targeted therapy in mUC[10]
- An analysis of *NECTIN4* amplification in a large, independent cohort of 245 patients with BC indicates that *NECTIN4* amplification is common: 19% (30/161), 14% (5/36), and 23% (11/48) of patients with HR+/HER2-, HER2+, and TNBC, respectively[11]
- Increased *NECTIN4* copy number was associated with high Nectin-4 protein expression (H-score ≥100) in 100 human TNBC tumor samples[12]
- This post-hoc analysis assesses the utility of *NECTIN4* amplification as a predictor of response to zelenectide pevedotin in heavily pretreated patients with BC

METHODS

- Zelenectide pevedotin is being evaluated in an ongoing Phase 1/2 study (BT8009-100/Duravelo-1; NCT04561362) assessing safety and efficacy in patients with advanced solid tumors associated with Nectin-4 expression, including those with BC
- Across the monotherapy dose escalation and dose expansion parts of the study, patients with BC received zelenectide pevedotin monotherapy, with most receiving the recommended phase 2 dose (RP2D) of 5 mg/m^2 weekly
- Response was assessed by the investigator per RECIST v1.1; the efficacy evaluable population included those who received any dose of study drug and had ≥1 adequate post-baseline response assessment
- *NECTIN4* amplification testing using fluorescence in situ hybridization (FISH) was performed on archival tissue from patients with BC who had available tumor tissue and who had consented to optional future research; *NECTIN4* amplification was defined as a ratio of *NECTIN4*:*CEN1* of ≥2; testing was performed at a laboratory accredited under DIN EN ISO/IEC 17020, using a standard protocol, as previously described[10]
- All patients with BC were included in the safety analysis, including assessment of the incidence and severity of treatment-related adverse events (TRAEs)

RESULTS

Patient demographics and clinical characteristics

- As of September 13, 2024, 38 heavily pretreated patients with BC were enrolled and treated with zelenectide pevedotin:
  - 33 treated with 5 mg/m^2 weekly
  - 1 treated with 7.5 mg/m^2 every other week
  - 2 treated with 7.5 mg/m^2 on Day 1 and Day 8 of a 21-day cycle
  - 2 treated with 10 mg/m^2 every other week
- Thirty-two patients were confirmed to have TNBC, and 6 patients had non-TNBC (**Table 1**)
- Thirty-one patients with TNBC were treated with zelenectide pevedotin 5 mg/m^2 weekly, and 1 was treated with zelenectide pevedotin 7.5 mg/m^2 on Day 1 and Day 8 of a 21-day cycle
- Nineteen patients with TNBC were tested for *NECTIN4* amplification, 6 of whom were amplified (31.6%); 4 non-TNBC patients were tested for *NECTIN4* amplification, one of whom was amplified (25%) (**Table 2**)

TABLE 1. PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Patient characteristic, n (%)	Patients with BC (N=38)	Patients with TNBC (N=32)
Median age, years (range)	52.5 (30-83)	52.0 (30-76)
Sex, n (%) Female	38 (100.0)	32 (100.0)
Race,[a] n (%) White Asian Black or African American Other	14 (36.8) 2 (5.3) 1 (2.6) 20 (52.6)	11 (34.4) 2 (6.3) 0 18 (56.3)
ECOG PS, n (%) 0 1	18 (47.4) 20 (52.6)	16 (50.0) 16 (50.0)
Median prior lines of therapies (range)	6 (1-15)	6 (2-13)
Prior therapy, n (%) Taxane-based ADC (any) Sacituzumab govitecan T-DXd Platinum-based Checkpoint inhibitor Endocrine therapy HER2-targeted therapy CDK4/6 inhibitor	35 (92.1) 27 (71.1) 26 (68.4) 5 (13.2) 18 (47.4) 17 (44.7) 14 (36.8) 7 (18.4) 7 (18.4)	30 (93.8) 27 (84.4) 26 (81.3) 5 (15.6) 15 (46.9) 16 (50.0) 9 (28.1) 6 (18.8) 2 (6.3)

[a]Information for one patient was missing

Efficacy

- Of the 38 patients treated with zelenectide pevedotin, 35 were efficacy evaluable and the majority were treated at the RP2D of 5 mg/m^2 weekly
  - 5 patients had a partial response (PR; 4 confirmed and 1 unconfirmed) for an objective response rate (ORR) among efficacy evaluable patients of 14.3% (95% CI: 4.8, 30.3) (**Table 2**)
  - 4 of 30 efficacy evaluable patients with TNBC had a PR for an ORR of 13.3% (95% CI: 3.8, 30.7)
  - Median duration of response in BC was 5.6 months (range: 2.4, 9.2) (**Figure 2**)
  - Median duration of treatment was 8.6 weeks (range 1.0, 51.9)
- 23 samples were available for *NECTIN4* FISH testing and passed QC; 7 (30.4%) demonstrated a *NECTIN4* amplification
  - All 7 patients who were *NECTIN4* amplified had stable disease (SD) or better: 4 patients had PRs (including 1 unconfirmed PR), and 3 patients had SD
  - The ORR for patients who were *NECTIN4* amplified was 57.1% (95% CI: 18.4, 90.1) and the disease control rate (DCR) was 100.0%
  - Prolonged responses were seen in all patients with *NECTIN4* amplification who responded (**Figure 2**)
  - One patient with *NECTIN4* polysomy (*NECTIN4* copy number ≥6; ratio *NECTIN4*:*CEN1* <2.0) had a confirmed PR and was the only responder among 16 patients who were not *NECTIN4* amplified
  - The ORR for patients who were *NECTIN4* amplified and/or polysome was **62.5%** (**Table 2, Figure 3**)
- Of 19 TNBC samples that were available and passed QC, 6 were *NECTIN4* amplified
  - All 6 patients who were *NECTIN4* amplified had SD or better: 3 patients had a PR (including 1 unconfirmed PR), and 3 patients had SD
  - The ORR for patients who had TNBC and were *NECTIN4* amplified was 50.0%
  - All 3 patients with TNBC and *NECTIN4* amplification who achieved a PR had received prior sacituzumab govitecan treatment

TABLE 2. BEST OVERALL RESPONSE AMONG PATIENTS WITH BC

Patient population, n (%)	Patients with BC N=38	Patients with TNBC N=32
Efficacy evaluable, n PR SD PD ORR [95% CI] DCR[c]	35[a] 5 (14.3)[b] 14 (40.0) 15 (42.9) 5 (14.3)[b] [4.8–30.3] 19 (54.3)[b]	30[a] 4 (13.3)[b] 13 (43.3) 12 (40.0) 4 (13.3)[b] [3.8–30.7] 17 (56.7)[b]
Samples tested and passed QC for *NECTIN4* amplification, n	23	19
With *NECTIN4* amplification, n PR SD PD ORR [95% CI] DCR[c]	7 4 (57.1)[b] 3 (42.9) 0 **4 (57.1)**[b] [18.4–90.1] 7 (100.0)[b]	6 3 (50.0)[b] 3 (50.0) 0 **3 (50.0)**[b] [11.8–88.2] 6 (100.0)[b]
Without *NECTIN4* amplification, n PR SD PD ORR [95% CI] DCR[c]	16 1 (6.3)[d] 4 (25.0) 11 (68.8) 1 (6.3)[d] [0.2–30.2] 5 (31.3)	13 1 (7.7)[d] 3 (23.1) 9 (69.2) 1 (7.7)[d] [0.2–36.0] 4 (30.8)
With *NECTIN4* amplification and/or polysomy **ORR**	**8** **5 (62.5%)**[b]	**7** **4 (57.1%)**[b]

[a]Efficacy evaluable patients had at least one postbaseline scan available for RECIST v1.1 review. One patient's postbaseline scan was not evaluable per RECIST v1.1. [b]Includes one unconfirmed PR; [c]DCR, disease control rate, defined as the proportion of patients with a CR, PR, or SD according to RECIST v1.1; [d]This patient harbored a polysomy.

FIGURE 2. DoR AND CHANGE FROM BASELINE IN TUMOR SIZE IN EFFICACY EVALUABLE PATIENTS WITH BC WHO WERE TREATED WITH ZELENECTIDE PEVEDOTIN AND WERE TESTED FOR *NECTIN4* AMPLIFICATION (N=23)

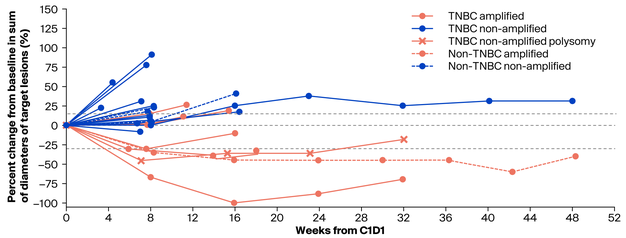
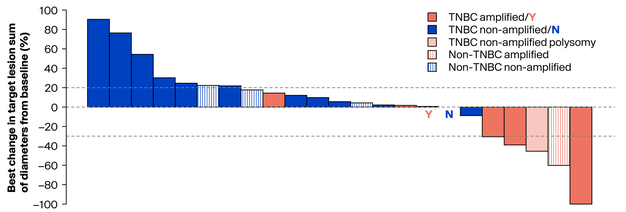


FIGURE 3. BEST PERCENT CHANGE FROM BASELINE IN TUMOR SIZE IN EFFICACY EVALUABLE PATIENTS WITH BC WHO WERE TREATED WITH ZELENECTIDE PEVEDOTIN AND WERE TESTED FOR *NECTIN4* AMPLIFICATION (N=23)



Safety

- In heavily pretreated patients with BC, safety and tolerability of zelenectide pevedotin was similar to a previously reported cohort of patients with bladder cancer[13]
- Grade ≥3 TRAEs occurred in 34.2% of all patients with BC, and Grade ≥3 treatment-related serious adverse events (TRSAEs) occurred in 10.5% of patients with BC (**Table 3**)
  - In 32 patients with TNBC, Grade ≥3 TRAEs occurred in 34.4%, and Grade ≥3 TRSAEs occurred in 12.5% of patients
  - In 23 patients with BC tested for *NECTIN4* amplification, Grade ≥3 TRAEs occurred in 34.8%, and Grade ≥3 TRSAEs occurred in 4.3% of patients
- Patients who were *NECTIN4* amplified appeared to have similar frequency and type of TRAEs to the overall BC population; however, no patients who were *NECTIN4* amplified had a zelenectide pevedotin-related SAE
- TRAEs of clinical interest, including peripheral neuropathy (any kind) and skin reactions, were low grade in patients with BC (**Table 4**)
- There have been no treatment-related deaths

TABLE 3. SAFETY SUMMARY OF ZELENECTIDE PEVEDOTIN IN PATIENTS WITH BC

Category, n (%)	Patients with BC (N=38)			
TEAEs Grade ≥3	38 (100.0) 20 (52.6)			
TRAEs Grade ≥3	35 (92.1) 13 (34.2)			
TESAEs TRSAEs TRSAEs Grade ≥3	12 (31.6) 6 (15.8) 4 (10.5)			
TRAEs (≥15%)[a]	All Grades	Grade 1	Grade 2	Grade ≥3
Pyrexia	15 (39.5)	15 (39.5)	0	0
Nausea	14 (36.8)	10 (26.3)	3 (7.9)	1 (2.6)
Diarrhea	13 (34.2)	12 (31.6)	1 (2.6)	0
Asthenia	9 (23.7)	5 (13.2)	3 (7.9)	1 (2.6)
Fatigue	9 (23.7)	4 (10.5)	4 (10.5)	1 (2.6)
Alopecia	7 (18.4)	4 (10.5)	3 (7.9)	0
Decreased appetite	7 (18.4)	3 (7.9)	2 (5.3)	2 (5.3)
Neutropenia	7 (18.4)	0	2 (5.3)	5 (13.2)
Abdominal pain	6 (15.8)	4 (10.5)	2 (5.3)	0
Anemia	6 (15.8)	1 (2.6)	5 (13.2)	0
Dose modifications Dose interruptions Dose reductions Dose discontinuation	21 (55.3) 18 (47.4) 8 (21.1) 0			
Median time to first dose reduction, months (range)	1.2 (0.5-11.0)			

[a]System Organ Class (SOC) Preferred Terms MedDRA: v27.0

TABLE 4. ZELENECTIDE PEVEDOTIN TRAEs OF CLINICAL INTEREST

TRAEs of clinical interest, n (%)	Patients with BC (N=38)			
	All Grades	Grade 1	Grade 2	Grade ≥3
Peripheral neuropathy[a]	12 (31.6)	4 (10.5)	7 (18.4)	1 (2.6)
Neuropathy peripheral	5 (13.2)	3 (7.9)	2 (5.3)	0
Peripheral sensory neuropathy	5 (13.2)	2 (5.3)	3 (7.9)	0
Neuralgia	4 (10.5)	0	3 (7.9)	1 (2.6)
Dysesthesia	1 (2.6)	1 (2.6)	0	0
Paresthesia	1 (2.6)	1 (2.6)	0	0
Skin reactions[b]	6 (15.8)	6 (15.8)	0	0
Erythema	2 (5.3)	2 (5.3)	0	0
Stomatitis	2 (5.3)	2 (5.3)	0	0
Dermatitis acneiform	1 (2.6)	1 (2.6)	0	0
Dry skin	1 (2.6)	1 (2.6)	0	0
Eczema	1 (2.6)	1 (2.6)	0	0
Erythema multiforme	1 (2.6)	1 (2.6)	0	0
Hyperhidrosis	1 (2.6)	1 (2.6)	0	0
Hyperglycemia[c]	3 (7.9)	1 (2.6)	2 (5.3)	0
Eye disorders[d]	2 (5.3)	0	2 (5.3)	0

Patients can have multiple preferred terms within a category. [a]Peripheral neuropathy Standardised MedDRA Queries (SMQ) [broad]. [b]Includes the MedDRA term of Severe Cutaneous Adverse Reactions (SCAR) SMQ [broad] and events that fell into the MedDRA SOC of Skin and Subcutaneous Tissue disorders, excluding alopecia. [c]Preferred term. [d]SOC of eye disorders.

CONCLUSIONS

- *NECTIN4* amplification appears to be a frequent genomic event in BC. In this study, 30% of tested patients with BC and 32% of tested patients with TNBC were *NECTIN4* amplified
- Increased *NECTIN4* copy number appears to predict response to zelenectide pevedotin, with an ORR of 62.5% among patients with *NECTIN4* amplification and/or polysomy; however, the significance of *NECTIN4* polysomy is uncertain
- *NECTIN4* amplification appears to show predictive clinical utility in identifying heavily pretreated patients with TNBC who will have an enhanced response to zelenectide pevedotin, with an ORR of 57.1% in *NECTIN4* amplified patients including polysomy versus an ORR of 13.3% in biomarker unselected patients with TNBC
- In this study zelenectide pevedotin was generally well tolerated in patients with BC
- Despite the limited sample size, this post-hoc analysis underscores the promising anti-tumor activity of zelenectide pevedotin in patients with *NECTIN4* amplified TNBC, who continue to have significant unmet medical need for effective, well-tolerated therapy
- These findings support further exploration of zelenectide pevedotin and *NECTIN4* amplification stratification strategies in patients with BC; a phase 2 study evaluating zelenectide pevedotin in patients with BC and *NECTIN4* amplification is planned

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ABBREVIATIONS

BC, breast cancer; BTC, Bicycle® Toxin Conjugate; C, cycle; CEN1, centromere 1; CI, confidence interval; CR, complete response; D, day; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; FISH, fluorescence in-situ hybridization; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; MedDRA, Medical Dictionary for Regulatory Activities; MMAE, monomethyl auristatin E; mUC, metastatic urothelial carcinoma; N, negative; NR, not reached; ORR, objective response rate; PD, progressive disease; PR, partial response; QC, quality control; RECIST, Response Evaluation Criteria in Solid Tumors; RP2D recommended Phase 2 dose; SCAR, Severe Cutaneous Adverse Reactions; SD, stable disease; SMQ, Standardized Medical Dictionary for Regulatory Activities (MedDRA) Queries; SOC, MedDRA system-organ class; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse events; TNBC, triple negative breast cancer; T-DXd, trastuzumab deruxtecan.

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