Enhanced anti-tumour activity of zelenectide pevedotin in non-small cell lung cancer (NSCLC) patients with *NECTIN4* gene amplification

▶ 96P

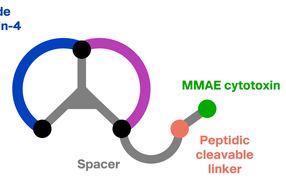
Loic Verlingue,[1] Niklas Klümper,[2] Markus Eckstein,[3] Johannes Brägelmann,[4] Meredith McKean,[5] Antoine Italiano,[6] Louise Carter,[7] Gerald S. Falchook,[8] Valentina Boni,[9] Afshin Dowlati,[10] Bernard Doger de Spéville,[11] Elisa Fontana,[12] Jordi Rodón Ahnert,[13] Leslie R. DeMars,[14] Gladys Brown,[14] Cong Xu,[14] Carly Campbell,[14] Tara Gelb,[14] Sean Santos,[14] Capucine Baldini[15]

[1]Centre Léon Bérard, Lyon, France; [2]University Hospital Bonn, Bonn, Germany; [3]Institute of Pathology, University Hospital Erlangen & Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [4]University Hospital Cologne, Cologne, Germany; [5]Sarah Cannon Research Institute, Nashville, TN, USA; [6]Institut Bergonié and University of Bordeaux, Bordeaux, France; [7]The University of Manchester and Department of Medical Oncology, The Christie NHS Foundation Trust, Manchester, UK; [8]Sarah Cannon Research Institute at HealthONE, Denver, CO, USA; [9]NEXT Oncology Madrid, Quirónsalud Madrid University Hospital, Madrid, Spain; [10]University Hospitals of Cleveland Medical Center, Cleveland, OH, USA; [11]START Madrid-FJD-Hospital Universitario Fundacion Jimenez Diaz, Madrid, Spain; [12]Sarah Cannon Research Institute UK, London, UK; [13]The University of Texas MD Anderson Cancer Centre, Houston, TX, USA; [14]Bicycle Therapeutics, Cambridge, MA, USA; [15]DITEP, Gustave Roussy Cancer Campus, Villejuif, France.

BACKGROUND

- Bicycle® molecules are an innovative therapeutic class 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 tumours
- Zelenectide pevedotin (zele; formerly BT8009), is a first-in-class Bicycle® Drug Conjugate (BDC™), comprising a highly selective Nectin-4–targeted bicyclic peptide conjugated to the cytotoxic drug monomethyl auristatin E (MMAE) via a cleavable linker (**Figure 1**)[4]
- Bicycle® molecules have lower molecular weight and shorter plasma half-life than antibody-drug conjugates, with distinct pharmacokinetics/dynamics, i.e., potential for rapid tumour penetration and minimal healthy tissue exposure[4-7]

FIGURE 1. ZELENECTIDE PEVEDOTIN STRUCTURE[4]



- Nectin-4 is overexpressed in a range of solid tumours, including metastatic urothelial carcinoma (mUC) and NSCLC[4,6,8] and is considered a diagnostic and therapeutic target for lung cancer[9]
- *NECTIN4* amplification has been found in up to 17% of solid tumours, including 7% of lung adenocarcinomas, and has been proposed as a predictive biomarker of response to Nectin-4-targeted therapy in mUC[10]
- This *post-hoc* analysis assesses the utility of *NECTIN4* amplification as a predictor of response to zelenectide pevedotin in heavily pretreated patients with NSCLC from the Phase 1/2 Duravelo-1 study (BT8009-100; NCT04561362)

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 tumours associated with Nectin-4 expression, including NSCLC
- Across dose escalation and dose expansion, patients with NSCLC received zelenectide pevedotin monotherapy, with most receiving the recommended Phase 2 dose (RP2D) of 5 mg/m^2 once weekly
- Response was assessed by the investigator per RECIST v1.1; the efficacy-evaluable population (EE) included those who received any dose of study drug and had ≥1 adequate post-baseline response assessment (34 EE; 29 EE and treated at RP2D or higher)
- *NECTIN4* amplification, determined by fluorescence in situ hybridisation (FISH) testing, was performed on archival tissue from patients with NSCLC who had available tumour 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 NSCLC who received a dose of zelenectide pevedotin were included in the safety analysis

RESULTS

PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

- As of 13 September 2024, 40 heavily pretreated patients with NSCLC were enrolled and treated with zelenectide pevedotin (**Table 1**):
  - n=3 treated with 2.5 mg/m^2 once weekly
  - n=32 treated with 5.0 mg/m^2 once weekly
  - n=1 treated with 7.5 mg/m^2 once weekly
  - n=4 treated with 7.5 mg/m^2 on Days 1 and 8 of a 21-day cycle
- Of 19 patients with NSCLC who were tested for *NECTIN4* amplification, 6 were amplified (6/19, 31.6%)

TABLE 1. PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Patient characteristic, n (%)	Patients with NSCLC (N=40)
Age, median years (range)	63.5 (34–80)
Sex, n (%) Male Female	 19 (47.5) 21 (52.5)
Race, n (%) White Asian Black or African American Other	 15 (37.5) 2 (5.0) 1 (2.5) 22 (55.0)
ECOG PS, n (%) 0 1	 10 (25.0) 30 (75.0)
Prior lines of therapy, median (range)	3 (1–8)
Prior therapy, n (%) Platinum-based Checkpoint inhibitor Taxane-based EGFR Inhibitor ≥ 3 prior lines in all settings	 39 (97.5) 36 (90.0) 27 (67.5) 2 (5.0) 21 (52.5)

- Median follow-up time and median time on treatment for all patients (N=40) was 4.5 months (range 0.5, 32.8) and 15.4 weeks (range 1.0, 41.7), respectively
- Of the 40 patients treated with zelenectide pevedotin, 29 were EE and treated at the RP2D of 5 mg/m^2 or higher (n=25 at 5 mg/m^2 once weekly, n=3 at 7.5 mg/m^2 on Days 1 and 8 of a 21-day cycle, and n=1 at 7.5 mg/m^2 once weekly)
  - Of these, 3 patients had a partial response (PR; 2 confirmed and 1 unconfirmed) for an overall response rate (ORR) of 10.3% (3/29; 95% CI: 2.2, 27.4) (**Table 2; Figure 2**)
- Of 19 patients who had samples available for *NECTIN4* amplification testing, 17 had been treated at 5 mg/m^2 or higher; of these, samples from 6 patients (35.3%) were *NECTIN4* amplified
- Of the 5 EE patients with amplified tumours, all had stable disease (SD) or better: 2 patients had a confirmed PR, and 3 patients had SD (**Figure 2**)
  - The histology of both responding patients was adenocarcinoma
  - Of the 3 patients with SD, the histology included: 1 adenocarcinoma, 1 carcinoma, and 1 squamous cell carcinoma
- The ORR for patients with NSCLC and *NECTIN4* amplified tumours was 40.0% (2/5; 95% CI 5.3, 85.3) and the disease control rate (DCR) was 100.0% (5/5; **Table 2**)
- Response durations were 3.2 months (unconfirmed response), 5.5 months, and 9.3 months (2 confirmed responses, respectively) (**Table 2; Figure 3**)

TABLE 2. BEST OVERALL RESPONSE

Best overall response, n (%)	Patients with NSCLC
EE patients, n PR SD PD **ORR** [95% CI] **DCR**[c]	29 3 (10.3)[a] 19 (65.5) 7 (24.1) **3 (10.3)**[a] [2.2, 27.4] **22 (75.9)**[a]
EE patients tested for *NECTIN4* amplification, n	13
With *NECTIN4* amplification, n PR SD PD **ORR** [95% CI] **DCR**[b]	5 2 (40.0) 3 (60.0) 0 (0.0) **2 (40.0)** [5.3, 85.3] **5 (100.0)**
Without *NECTIN4* amplification, n PR SD PD **ORR** **DCR**[b]	8 0 (0.0) 7 (87.5) 1 (12.5) **0 (0.0)** **7 (87.5)**

[a]Includes one unconfirmed PR. [b]DCR is defined as the proportion of patients with a CR, PR, or SD according to RECIST v1.1.

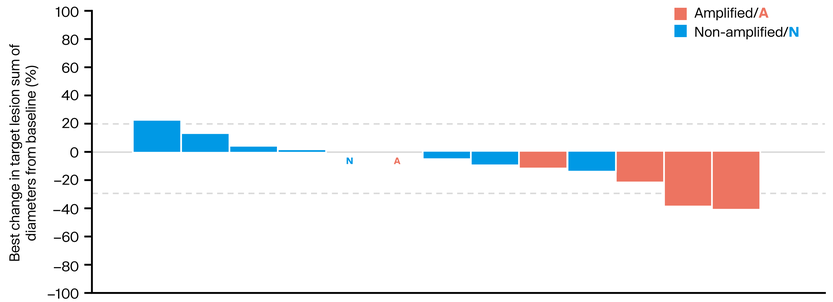
- In N=40 heavily pretreated patients with NSCLC, zelenectide pevedotin demonstrated adequate safety and tolerability
- Grade ≥3 treatment-related adverse events (TRAEs) occurred in 37.5% and Grade ≥3 treatment-related serious adverse events (TRSAEs) occurred in 12.5% of all patients with NSCLC (**Table 3; Table 4**)
- Treatment discontinuation due to TRAEs was reported in 3 patients; reasons included Grade 3 fatigue, Grade 2 peripheral sensory neuropathy, and Grade 2 arthralgia
- No Grade ≥3 TRAEs of clinical interest for zelenectide pevedotin were observed (**Table 5**)

TABLE 3. SAFETY SUMMARY

Category, n (%)	Patients with NSCLC	
	NECTIN4 amplified (n=6)	Total[a] (N=40)
TEAEs Grade ≥3	6 (100) 4 (66.7)	40 (100) 26 (65.0)
TRAEs Grade ≥3	6 (100) 4 (66.7)	37 (92.5) 15 (37.5)[b]
SAEs Grade ≥3	4 (66.7) 3 (50.0)	16 (40.0) 14 (35.0)
TRSAE Grade ≥3	4 (66.7) 4 (50.0)	7 (17.5) 5 (12.5)
Dose modifications TEAEs leading to dose reduction TEAEs leading to dose discontinuation	 1 (16.7) 2 (33.3)	 10 (25.0) 3 (7.5)

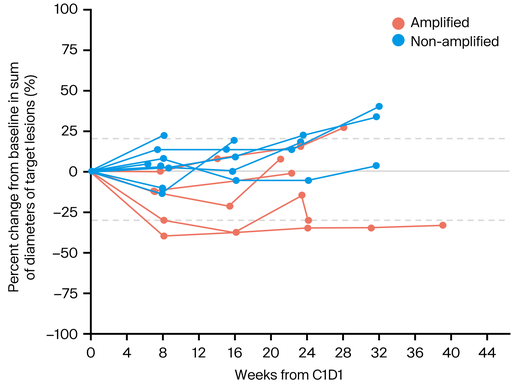
[a]Includes all patients, tested and untested for *NECTIN4* amplification. [b]One event of Grade 5 diarrhoea was reported in a 69-year-old male, *NECTIN4* non-amplified patient on C1D15. Patient had a history of Grade 1 immune-related colitis. Ongoing conditions at the time of enrolment were emphysema, amnesia, anaemia, diarrhoea, and fatigue. Patient received a single dose of zelenectide pevedotin (7.5 mg/m^2) and 5 days later was hospitalised for infectious enterocolitis. The patient was found to be *Clostridium difficile* positive, was treated, and discharged; however, the diarrhoea later worsened, and the patient passed away 14 days after first/last dose of zelenectide pevedotin. A relationship with zelenectide pevedotin could not be excluded and the event was considered related. No other Grade 4 or 5 TRAE occurred.

FIGURE 2. BEST % CHANGE FROM BASELINE IN TUMOUR SIZE IN EE PATIENTS TREATED WITH ≥5 MG/M^2 ZELENECTIDE PEVEDOTIN AND TESTED FOR *NECTIN4* AMPLIFICATION (N=13)



Dashed lines represent response or progression thresholds.

FIGURE 3. DOR AND CHANGE FROM BASELINE IN TUMOUR SIZE IN EE PATIENTS TREATED WITH ≥5 MG/M^2 ZELENECTIDE PEVEDOTIN AND TESTED FOR *NECTIN4* AMPLIFICATION (N=13)



Dashed lines represent response or progression thresholds.

TABLE 4. TRAES OCCURRING IN ≥20% PATIENTS TREATED WITH ZELENECTIDE PEVEDOTIN

TRAEs, n (%)	Patients with NSCLC (N=40)	
	All Grades	Grade ≥3
Fatigue	21 (52.5)	5 (12.5)
Nausea	14 (35.0)	2 (5.0)
Diarrhoea	12 (30.0)	2 (5.0)
Alopecia	10 (25.0)	0 (0.0)
Decreased appetite	10 (25.0)	1 (2.5)
Peripheral sensory neuropathy	9 (22.5)	0 (0.0)
Pyrexia	9 (22.5)	0 (0.0)
Anaemia	8 (20.0)	1 (2.5)
Abdominal pain	8 (20.0)	1 (2.5)

TABLE 5. TRAES OF CLINICAL INTEREST FOR ZELENECTIDE PEVEDOTIN

TRAE of clinical interest, n (%)	Patients with NSCLC (N=40)			
	All Grades[a]	Grade 1	Grade 2	Grade ≥3
Peripheral neuropathy[b]	14 (35.0)	5 (12.5)	9 (22.5)	0 (0.0)
Sensory neuropathy	9 (22.5)	4 (10.0)	5 (12.5)	0 (0.0)
Neuralgia	2 (5.0)	0 (0.0)	2 (5.0)	0 (0.0)
Neuropathy peripheral	2 (5.0)	1 (2.5)	1 (2.5)	0 (0.0)
Muscular weakness	1 (2.5)	0 (0.0)	1 (2.5)	0 (0.0)
Motor neuropathy	1 (2.5)	0 (0.0)	1 (2.5)	0 (0.0)
Eye disorders[c]	8 (20.0)	4 (10.0)	4 (10.0)	0 (0.0)
Skin reactions[d]	7 (17.5)	6 (15.0)	1 (2.5)	0 (0.0)
Hyperglycaemia[e]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a]Patients can have multiple preferred terms within a category. [b]Based on MedDRA SMQ [Broad] for peripheral neuropathy. [c]SOC of Eye disorders. [d]Includes the MedDRA SMQ [broad] for Severe Cutaneous Adverse Reactions (SCAR) and MedDRA SOC of Skin and Subcutaneous Tissue disorders, excluding alopecia. [e]Preferred term.

CONCLUSIONS

- Approximately one-third (6/19) of tested patients with NSCLC had *NECTIN4* amplified tumours
- *NECTIN4* amplification appears to show predictive clinical utility in identifying patients with NSCLC in the EE population who will have an enhanced response to zelenectide pevedotin, with an ORR of 40% in patients with *NECTIN4* amplified tumours
- Zelenectide pevedotin is generally well tolerated in patients with NSCLC, with no Grade ≥3 peripheral neuropathy or skin reactions observed
- These findings support further exploration of zelenectide pevedotin in patients with NSCLC who have *NECTIN4* amplified tumours; a Phase 2 study evaluating zelenectide pevedotin in previously treated patients with squamous and non-squamous cell lung cancer and *NECTIN4* amplification is planned

ABBREVIATIONS

AEs, adverse events; BDC™, Bicycle® Drug Conjugate; C1D1, Cycle 1 Day 1; C1D15, Cycle 1 Day 15; CI, confidence interval; DCR, disease control rate; DIN, Deutsches Institut für Normung (German Institute for Standardisation); DOR, duration of response; EE, efficacy evaluable; EN, Europäische Norm (European Standards); FISH, fluorescence in situ hybridization; IEC, International Electrotechnical Commission; ISO, International Organization for Standardization; MedDRA, Medical Dictionary for Regulatory Activities; MMAE, monomethyl auristatin E; mUC, metastatic urothelial carcinoma; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PR, partial response; RP2D, recommended phase 2 dose; SAE, serious adverse event; SD, stable disease; SMQ, Standardised MedDRA Queries; SOC, system organ class; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.

REFERENCES

1. Eder M, et al. *Cancer Res.* 2019;79(4):841–852.
2. Mudd GE, et al. *J Med Chem.* 2020;63(8):4107–4116.
3. Walsh SJ, et al. *Cancer Res.* 2024;84(6_Suppl):5807–5807
4. Rigby M, et al. *Mol Cancer Ther.* 2022;21(12):1747–1756.
5. Baldini C, et al. *J Clin Oncol.* 2023;41(6_Suppl):498.
6. Mudd GE, et al. *J Med Chem.* 2022;65(21):14337–14347.
7. Bader J, et al. *J Clin Oncol.* 2024;42(16_Suppl):3088.
8. Duan X, et al. *Clin Cancer Res.* 2023;29(17):3395–3407.
9. Takano A, et al. *Cancer Res.* 2009;69(16):6694–6703.
10. Klümper N, et al. *J Clin Oncol.* 2024;42(20):2446–2455.

Presenting author:
Loic Verlingue, MD, PhD;
loic.verlingue@lyon.unicancer.fr

ACKNOWLEDGEMENTS

Bicycle Therapeutics would like to thank the patients and their families for participating in this study. Medical writing support was provided by Rebecca L. Crepeau, PhD, of Avalere Health Global Limited, which was funded by BicycleTx Ltd.

This study was sponsored by BicycleTx Ltd.

LV discloses the following financial relationships: personal fees from Adaptherapy, CEO of RESOLVED, received non-personal fees from Pierre-Fabre and Servier, and a grant from BMS, all outside the submitted work. LV is Principal-Investigator in the Phase 1 unit at CLB of studies with Genmab, Bicycle Therapeutics, Revolution Medicine, Daiichi, Astra Zeneca, Hoffmann La Roche.