# Phase 1/2 Duravelo-1 study: Preliminary results of Nectin-4 targeting zelenectide pevedotin (BT8009) plus pembrolizumab in previously untreated, cisplatin-ineligible patients with locally advanced or metastatic urothelial cancer

Abstract # 4567

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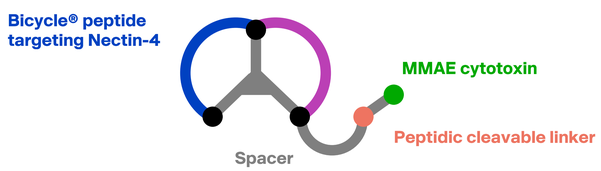
## INTRODUCTION

- For patients with locally advanced or metastatic urothelial cancer (la/mUC), first-line treatment may be limited by tolerability, and additional options are needed
- 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 (zele, formerly BT8009) is a first-in-class Bicycle® Drug Conjugate (BDC™), comprised of a highly selective Nectin-4–targeting bicyclic peptide conjugated to the cytotoxin monomethyl auristatin E (MMAE) via a cleavable linker (**Figure 1**)[4]

**FIGURE 1: ZELENCTIDE PEVEDOTIN STRUCTURE[4]**




- Zele monotherapy has shown an objective response rate (ORR) of 45% and a generally tolerable safety profile in previously treated enfortumab vedotin-naïve patients with la/mUC in the ongoing Phase 1/2 study, Duravelo-1 (NCT04561362)[5]
- Here, we present preliminary data from expansion Cohort B-7 of Duravelo-1, investigating zele plus pembrolizumab (pembro) in patients with previously untreated, cisplatin-ineligible la/mUC (**Figure 2**)

**FIGURE 2: DURAVELO-1 (BT8009-100) STUDY DESIGN**


## METHODS

- Adults with la/mUC who were cisplatin-ineligible based on Galsky criteria[6] and who had not received any prior systemic anti-cancer treatment for la/mUC were eligible
- Patients were cisplatin-ineligible if they fulfilled at least one criterion[6]:
  - Creatinine clearance (CrCl) of 30–59 mL/min
  - Hearing loss of ≥25 decibels at two contiguous frequencies
  - New York Heart Association (NYHA) ≥Class III heart failure
  - Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 (must have hemoglobin ≥10 g/dL, CrCl ≥50 mL/min, and no NYHA Class III heart failure)
- Patients received intravenous zele 5 mg/m² on Days (D) 1, 8, and 15 plus pembro 200 mg on D1 of a 21-day cycle
- The primary endpoint was investigator-assessed ORR per RECIST v1.1. The efficacy-evaluable (EE) population includes patients who received any dose of study drug and had ≥1 adequate post-baseline response assessment
- Secondary endpoints include safety (treatment-related adverse events [TRAE] per CTCAE v5.0), duration of response (DoR), and disease control rate (DCR)

## RESULTS

### PATIENT DEMOGRAPHICS AND CHARACTERISTICS

- As of January 3, 2025, 22 patients were enrolled (between November 2023 and July 2024) (**Table 1**)

**TABLE 1: PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS**

| Patient characteristic, n (%) | Patients (N=22) |
|---|---|
| Median age, years (range) | 77 (61–85) |
| Sex, n (%) | |
| Male | 15 (68.2) |
| Female | 7 (31.8) |
| Race, n (%) | |
| White | 18 (81.8) |
| Asian | 1 (4.5) |
| Black or African American | 0 (0.0) |
| Other/missing | 3 (13.6) |
| ECOG PS, n (%) | |
| 0 | 5 (22.7) |
| 1 | 7 (31.8) |
| 2 | 10 (45.5) |
| CrCl , n (%) | |
| ≥60 mL/min | 10 (45.5) |
| <60 mL/min | 12 (54.5) |

### EFFICACY

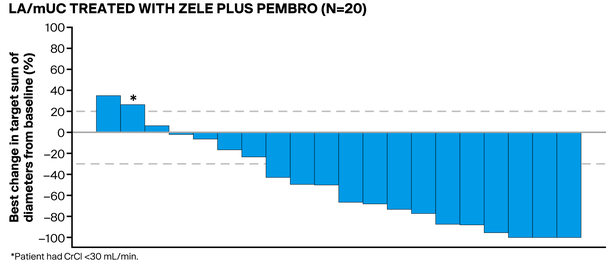
- Among 20 patients with EE disease, ORR was 65.0% (n=13 responses; **Table 2**; **Figure 3**)
  - Twelve patients remained on treatment as of data extraction, including 4 patients with stable disease
  - Median DoR was not mature, as 8 responders were ongoing at the time of analysis (**Figure 4**)
- Median duration of treatment was 22.9 weeks (range 1.0–58.1)
- Median duration of follow-up was 7.1 months (range 1.0–13.2)

**TABLE 2: BEST OVERALL RESPONSE IN EE PATIENTS WITH LA/mUC TREATED WITH ZELE PLUS PEMBRO**

| Best overall response in EE patients, n (%) | Patients (N=20) |
|---|---|
| **ORR** [95% CI] | **13 (65.0)** [40.8, 84.6] |
| Complete response | 5 (25.0)[a] |
| Partial response | 8 (40.0)[b] |
| Stable disease | 5 (25.0) |
| DCR[c] | 18 (90.0) |

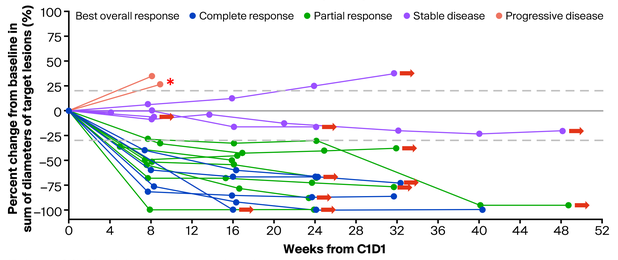
[a]Includes 1 unconfirmed complete response; second confirmatory scan not completed as of data extraction. [b]Includes 2 unconfirmed partial responses; both patients have discontinued treatment. [c]DCR includes all patients who had a complete response, partial response, or stable disease.

**FIGURE 3: BEST % CHANGE FROM BASELINE IN TUMOR SIZE IN EE PATIENTS WITH LA/mUC TREATED WITH ZELE PLUS PEMBRO (N=20)**




*Patient had CrCl <30 mL/min.

**FIGURE 4: DOR AND CHANGE FROM BASELINE IN TUMOR SIZE IN EE PATIENTS WITH LA/mUC TREATED WITH ZELE PLUS PEMPRO (N=20)**




*Patient had CrCl <30 mL/min. Arrows indicate ongoing patients.

### SAFETY

- TRAEs occurred in all patients; however, serious zele-related AEs (SAEs; including zele- and pembro-related) occurred in only 9.1% of patients (**Table 3**)

**TABLE 3: SAFETY SUMMARY OF PATIENTS TREATED WITH ZELE AND PEMBRO**

| Category, n (%) | Patients (N=22) | | |
|---|---|---|---|
| TEAEs Grade ≥3 | 22 (100.0) 16 (72.7) | | |
| | Any | Zele-related[a] | Pembro-related[b] |
| TRAEs Grade ≥3 | 22 (100.0) 15 (68.2) | 20 (90.9) 13 (59.1) | 21 (95.5) 11 (50.0) |
| SAEs Grade ≥3 | 12 (54.5) 11 (50.0) | 2 (9.1) 2 (9.1) | 5 (22.7) 4 (18.2) |
| | Zele modifications | Pembro modifications | |
| Dose modifications | | | |
| TEAEs leading to dose reduction | 11 (50.0) | 0 | |
| TEAEs leading to dose discontinuation | 1 (4.5) | 2 (9.1) | |

[a]Includes AEs related to zele and zele + pembro. [b]Includes AEs related to pembro and zele + pembro.

- TRAEs of Grade 4 hypomagnesemia and neutropenia were reported in one patient each, both zele-related
- There were no Grade 5 TRAEs (**Table 4**)

**TABLE 4: TRAES OCCURRING IN ≥20% PATIENTS TREATED WITH ZELE PLUS PEMBRO**

| | Patients (N=22) | | | |
|---|---|---|---|---|
| TRAEs, n (%)[a] | Any Grade | Grade 1 | Grade 2 | Grade ≥3 |
| Asthenia | 14 (63.6) | 4 (18.2) | 8 (36.4) | 2 (9.1) |
| Anemia | 13 (59.1) | 5 (22.7) | 8 (36.4) | 0 |
| Diarrhea | 11 (50.0) | 6 (27.3) | 3 (13.6) | 2 (9.1) |
| Decreased appetite | 9 (40.9) | 5 (22.7) | 3 (13.6) | 1 (4.5) |
| AST increased | 8 (36.4) | 5 (22.7) | 2 (9.1) | 1 (4.5) |
| Nausea | 8 (36.4) | 4 (18.2) | 3 (13.6) | 1 (4.5) |
| Rash | 7 (31.8) | 5 (22.7) | 1 (4.5) | 1 (4.5) |
| ALT increased | 6 (27.3) | 3 (13.6) | 0 | 3 (13.6) |
| Neutropenia | 6 (27.3) | 1 (4.5) | 2 (9.1) | 3 (13.6) |
| Pruritus | 6 (27.3) | 4 (18.2) | 2 (9.1) | 0 |
| Alopecia | 5 (22.7) | 3 (13.6) | 2 (9.1) | 0 |
| Hyperglycemia | 5 (22.7) | 4 (18.2) | 1 (4.5) | 0 |
| Vomiting | 5 (22.7) | 4 (18.2) | 0 | 1 (4.5) |

[a]Includes AEs related to zele, pembro, or zele + pembro.

**TABLE 5: TRAES OF CLINICAL INTEREST IN PATIENTS TREATED WITH ZELE PLUS PEMBRO**

| | Patients (N=22) | | | |
|---|---|---|---|---|
| TRAE of clinical interest[a,b] | Any Grade | Grade 1 | Grade 2 | Grade ≥3 |
| Skin reactions[c] | 13 (59.1) | 8 (36.4) | 4 (18.2) | 1 (4.5) |
| Rash | 7 (31.8) | 5 (22.7) | 1 (4.5) | 1 (4.5) |
| Pruritus | 6 (27.3) | 4 (18.2) | 2 (9.1) | 0 |
| Rash erythematous | 2 (9.1) | 0 | 2 (9.1) | 0 |
| Erythema | 1 (4.5) | 1 (4.5) | 0 | 0 |
| Dry skin | 1 (4.5) | 1 (4.5) | 0 | 0 |
| Peripheral neuropathy[d] | 11 (50.0) | 6 (27.3) | 3 (13.6) | 2 (9.1) |
| Neuropathy peripheral | 3 (13.6) | 1 (4.5) | 1 (4.5) | 1 (4.5) |
| Polyneuropathy | 3 (13.6) | 1 (4.5) | 2 (9.1) | 0 |
| Peripheral sensory neuropathy | 1 (4.5) | 1 (4.5) | 0 | 0 |
| Peripheral motor neuropathy | 1 (4.5) | 1 (4.5) | 0 | 0 |
| Acute polyneuropathy | 1 (4.5) | 0 | 0 | 1 (4.5) |
| Hyperglycemia[e] | 5 (22.7) | 4 (18.2) | 1 (4.5) | 0 |
| Eye disorders[f] | 4 (18.2) | 3 (13.6) | 1 (4.5) | 0 |

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

- Skin reactions were mostly Grade 1 or 2 and occurred more frequently with the addition of pembro than was previously reported with zele monotherapy in la/mUC[5] (**Table 5**)
  - Non-serious Grade 3 rash was reported in 1 patient
  - No events of rash maculopapular were reported
  - No events of Stevens-Johnson Syndrome were reported
- TRAEs of peripheral neuropathy occurred in 50.0% of patients, mostly Grade 1 (**Table 5**)
- All Grade 3 TRAEs of clinical interest were reversible; no Grade 4 TRAEs of clinical interest were reported
- Immune-mediated AEs:
  - Non-serious Grade 3 hepatitis (n=1; pembro-related)
  - Serious Grade 3 hepatotoxicity (n=1; pembro-related; discontinued pembro, remains on zele)
  - Serious Grade 3 increased alanine aminotransferase, aspartate aminotransferase, and bilirubin (n=1; pembro-related; remains on zele and pembro)

## CONCLUSIONS

- The combination of zelenectide pevedotin and pembrolizumab shows promising preliminary anti-tumor activity in a cohort of patients who historically have poor prognosis with first-line therapies, with nearly 50% of enrolled patients having an ECOG PS of 2
- The safety profile was generally tolerable and consistent with previous reports of each respective agent
- No new safety signals were observed with the combination
- These data support a randomized, multicenter, open-label Phase 2/3 study of zelenectide pevedotin as monotherapy and in combination with pembrolizumab vs chemotherapy in patients with la/mUC (NCT06225596; Duravelo-2), which is currently enrolling

### 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. Reig Torras O, et al. *Ann Oncol.* 2024;35(2_Suppl):S515–S516.
6. Galsky MD, et al. *J Clin Oncol.* 2011;29(17):2432–2438.

### ABBREVIATIONS

AEs, adverse events; CrCl, creatinine clearance; CTCAE, Common Terminology Criteria for Adverse Events; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EE, efficacy-evaluable; la/mUC, locally advanced/metastatic urothelial carcinoma; MedDRA, Medical Dictionary for Regulatory Activities; MMAE, monomethyl auristatin E; NYHA, New York Heart Association; ORR, objective response rate; pembro, pembrolizumab; 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; zele, zelenectide pevedotin.

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