

# Interim Analysis Results From Duravelo-2: Zelenectide Pevedotin + Pembrolizumab in Patients With Previously Untreated Locally Advanced/Metastatic Urothelial Carcinoma

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# Key Takeaway Points

1

## *Urothelial Carcinoma*

An unmet need remains for more tolerable first-line treatment options for locally advanced or metastatic disease

2

## *Safer Option*

Zelenectide pevedotin at the optimized dose of 6 mg/m<sup>2</sup> + pembrolizumab demonstrated favorable tolerability and substantially reduced toxicity

3

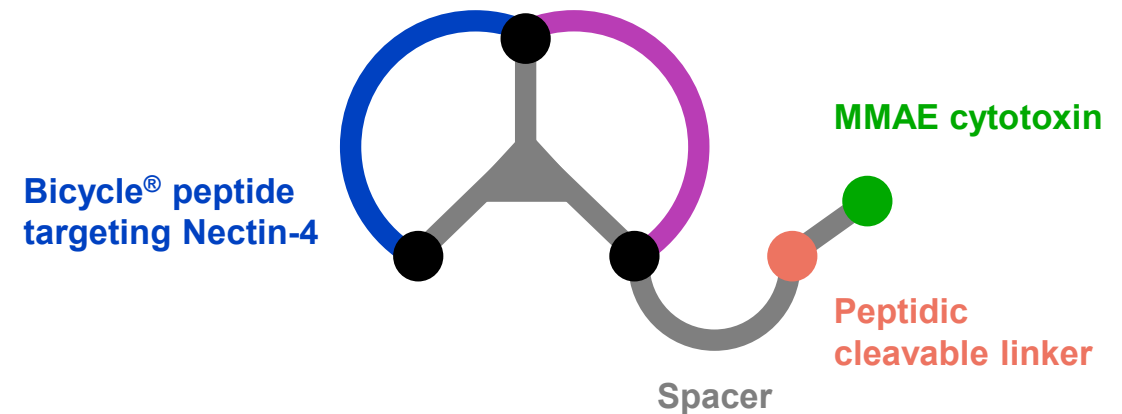
## *Favorable Responses*

Response rates with zelenectide pevedotin + pembrolizumab were promising, supporting its benefit-risk profile and potentially meeting the need for a more tolerable option

# Introduction

- First-line options for la/mUC may be limited by tolerability, and there remains an unmet need for safer treatments
  - The current standard-of-care ADC is associated with high rates of Grade  $\geq 3$  skin reactions, and ADC-related events led to 30% of patients discontinuing therapy<sup>1</sup>
- Zelenectide pevedotin (zele; BT8009) is a highly selective Bicycle<sup>®</sup> Drug Conjugate (BDC<sup>®</sup>) targeting Nectin-4, a protein overexpressed in la/mUC<sup>2</sup>
- In an expansion cohort of the Phase 1 Duravelo-1 study in cisplatin-ineligible patients, many with poor performance status, zele + pembro showed promising preliminary anti-tumor activity (50% cORR) and a potentially differentiating safety profile from currently available ADCs<sup>3</sup>
- Here, we report an interim analysis for zele + pembro (Cohort 1) dosage selection from the randomized Phase 2 Duravelo-2 study (NCT06225596/BT8009-230) in previously untreated patients with la/mUC

## Zelenectide Pevedotin Structure<sup>2</sup>



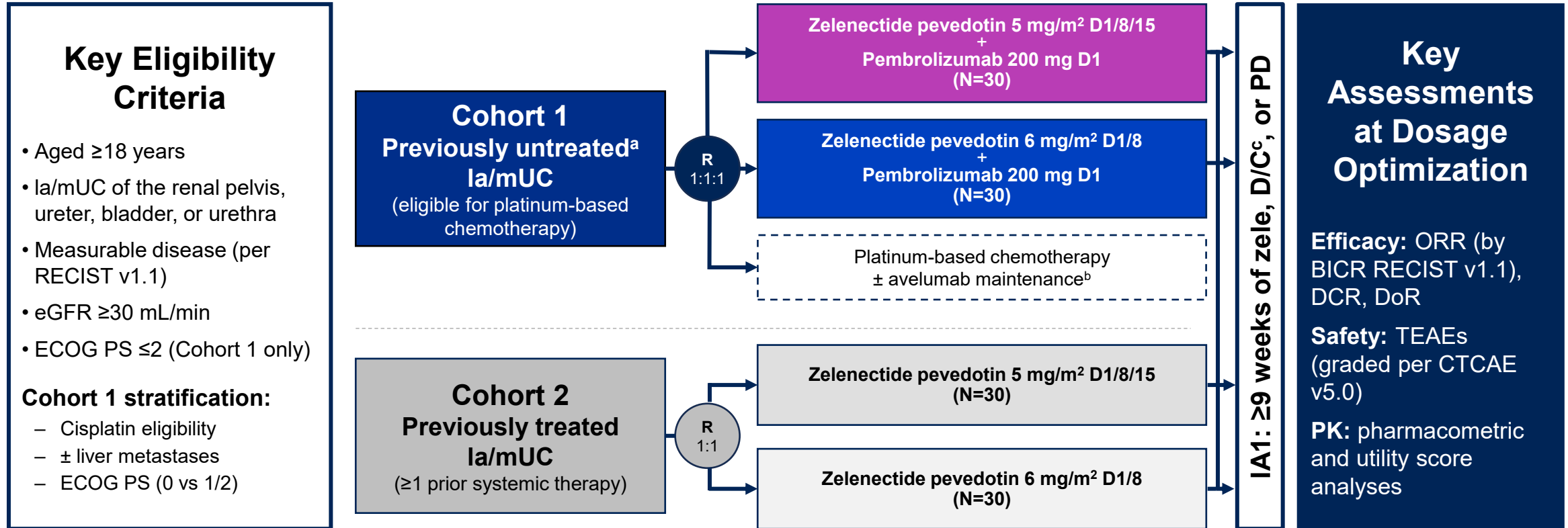
Molecular weight: 4.2 kDa

1. Powles T et al. *New Engl J Med*. 2024;390(10):875-888. 2. Rigby M, et al. *Mol Cancer Ther*. 2022;21(12):1747–1756. 3. Giannatempo P, et al. ASCO 2025. Abstract 4567.

ADC, antibody–drug conjugate; BDC, Bicycle Drug Conjugate; cORR, confirmed objective response rate; la/mUC, locally advanced or metastatic urothelial carcinoma; MMAE, monomethyl auristatin E; zele, zelenectide pevedotin.

# Duravelo-2: Study Design for Dosage Optimization

## Cohort 1: Previously Untreated la/mUC



### Cohort 2 is reported separately.

Treatments were based on 21-day cycles. <sup>a</sup>Patients with prior neoadjuvant/adjuvant chemotherapy, MMAE-based therapy, and immune checkpoint inhibitor therapy with recurrence >12 months from completion of therapy were allowed. <sup>b</sup>Gemcitabine + cisplatin/carboplatin 4-6 cycles ± avelumab maintenance. This arm is not included in this dosage optimization interim analysis. <sup>c</sup>Discontinuation criteria include planned completion of therapy, progressive disease, and intolerable toxicity.

BICR, blinded independent central review; D, day; D/C, discontinuation; DCR, disease control rate; DoR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status;

eGFR, estimated glomerular filtration rate; IA1, interim analysis 1; la/mUC, locally advanced or metastatic urothelial carcinoma; MMAE, monomethyl auristatin E; ORR, objective response rate; PD, progressive disease;

PK, pharmacokinetic; R, randomized; TEAE, treatment-emergent adverse event; zele, zelenectide pevedotin.

# Patient Demographics and Clinical Characteristics

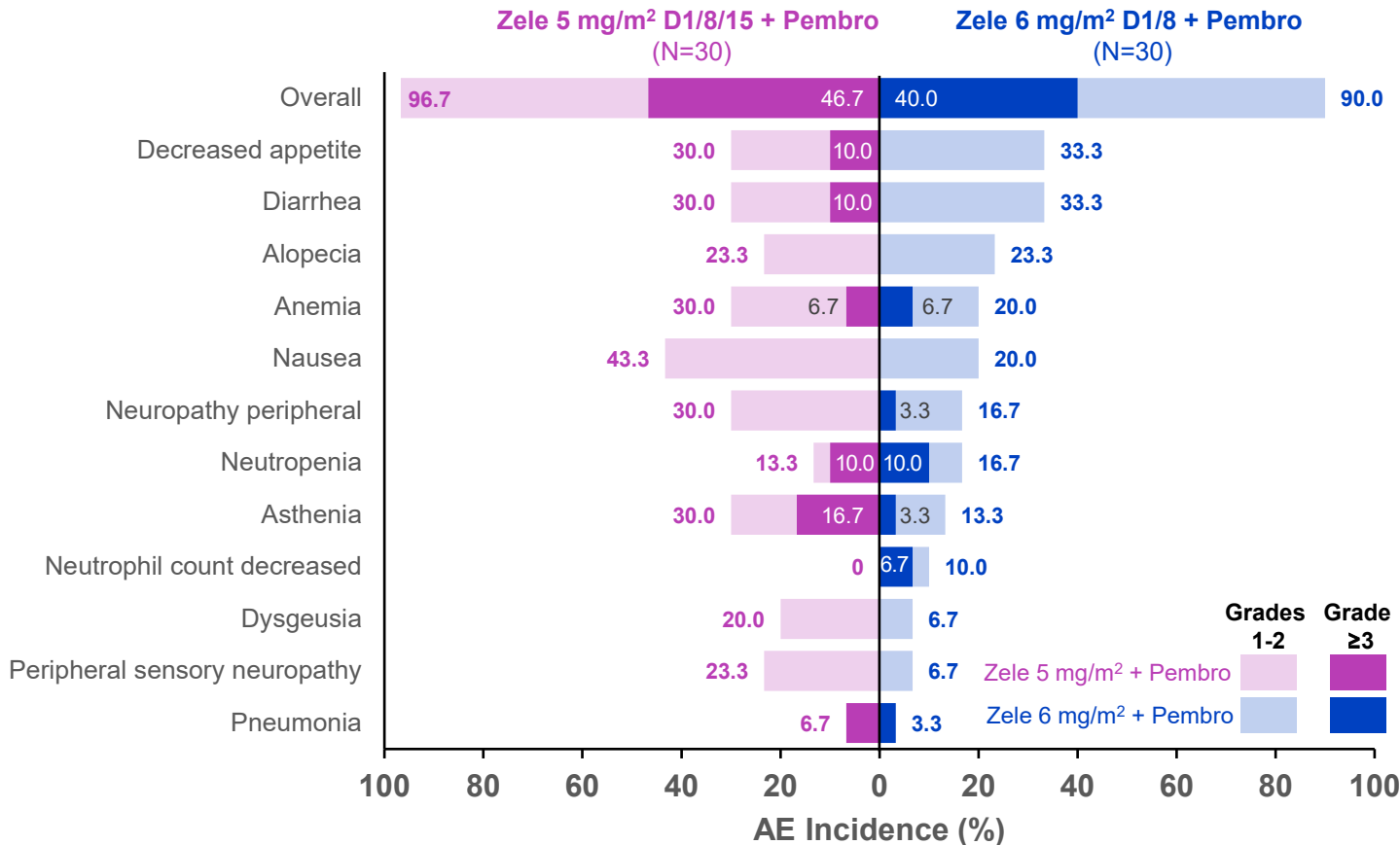
Patient characteristic		Zelev 5 mg/m <sup>2</sup> D1/8/15 + Pembro (N=30)	Zelev 6 mg/m <sup>2</sup> D1/8 + Pembro (N=30)
Age, years	Median (range)	70 (44-81)	68 (29-87)
	≥65 years, n (%)	25 (83.3)	20 (66.7)
Sex, n (%)	Male	24 (80.0)	20 (66.7)
	Female	6 (20.0)	10 (33.3)
Race, n (%)	White	23 (76.7)	22 (73.3)
	Asian	6 (20.0)	6 (20.0)
	Black or African American	0	1 (3.3)
	Not reported	1 (3.3)	1 (3.3)
ECOG PS, n (%)	0	16 (53.3)	19 (63.3)
	1-2	14 (46.7)	11 (36.7)
Disease status at diagnosis	Locally advanced	4 (13.3)	5 (16.7)
	Metastatic	26 (86.7)	25 (83.3)
Liver metastases, n (%)	Present	5 (16.7)	7 (23.3)
	Absent	25 (83.3)	23 (76.7)
Primary site of disease origin, n (%)	Upper tract	5 (16.7)	8 (26.7)
	Lower tract	25 (83.3)	22 (73.3)
Cisplatin eligibility status, n (%)	Eligible	12 (40.0)	10 (33.3)
	Ineligible	18 (60.0)	20 (66.7)

- As of 23, July 2025, median follow-up was 7.0 months (range 1.1-12.6) with zelev 5 mg/m<sup>2</sup> D1/8/15 and 7.0 months (range 1.2-10.5) zelev 6 mg/m<sup>2</sup> D1/8

D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; pembro, pembrolizumab; zelev, zelelectide pevedotin.

# Safety Summary of Zelenectide Pevedotin + Pembrolizumab in la/mUC

## Common Zele-Related AEs<sup>a</sup>



- Median relative dose intensity in patients receiving 6 mg/m<sup>2</sup> was 97.0%
- Zele-related AEs were mostly Grades 1-2
- Grade ≥3 TEAEs occurred in 66.7% and 60.0% of patients receiving zele at 5 mg/m<sup>2</sup> and 6 mg/m<sup>2</sup>, respectively
- SAEs related to zele occurred in 7 patients (23.3%) receiving the 5 mg/m<sup>2</sup> and 5 patients (16.7%) receiving the 6 mg/m<sup>2</sup> dosage
- Only 1 patient discontinued zele due to a zele-related AE at the 6 mg/m<sup>2</sup> dosage
  - Zele-related AEs led to discontinuation in 5 patients (16.7%) receiving the 5 mg/m<sup>2</sup> dosage

<sup>a</sup>Includes AEs related to zele or zele + pembro of any grade that occurred in ≥20% of patients or of Grade ≥3 that occurred in ≥5% of patients in either arm. Patients with multiple AEs are counted only once by the worse NCI-CTCAE category within a preferred term.

AE, adverse event; la/mUC, locally advanced or metastatic urothelial carcinoma; pembro, pembrolizumab; SAE, serious adverse event; TEAE, treatment-emergent adverse event; zele, zelenectide pevedotin.

# Zeletide-Related AEs of Clinical Interest With Zeletide Pevedotin 6 mg/m<sup>2</sup> D1/8 + Pembrolizumab

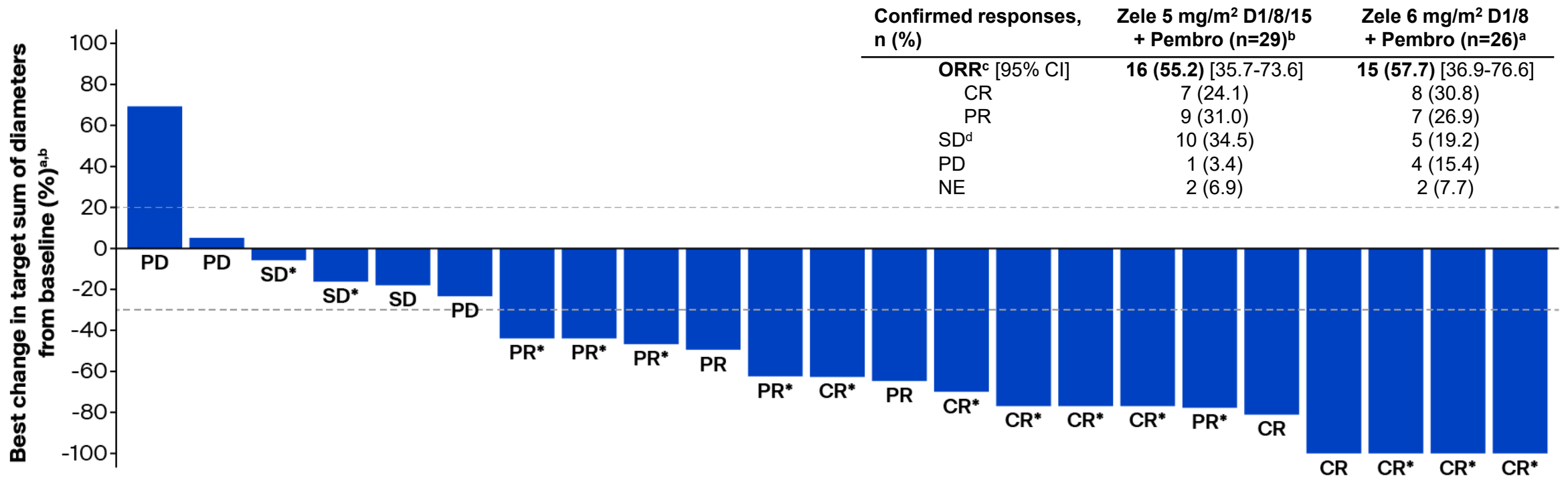
Category, n (%) <sup>a,b</sup>	Zeletide 6 mg/m <sup>2</sup> D1/8 + Pembro (N=30)					
	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
<b>Peripheral neuropathy<sup>c</sup></b>	11 (36.7)	6 (20.0)	4 (13.3)	1 (3.3)	0	0
Sensory events	10 (33.3)	6 (20.0)	3 (10.0)	1 (3.3)	0	0
Motor events	1 (3.3)	0	1 (3.3)	0	0	0
<b>Skin reactions<sup>d</sup></b>	5 (16.7)	3 (10.0)	2 (6.7)	0	0	0
<b>Eye disorders<sup>e</sup></b>	3 (10.0)	3 (10.0)	0	0	0	0
<b>Hyperglycemia<sup>f</sup></b>	0	0	0	0	0	0

- No zeletide-related severe skin reactions of any grade were reported at the 6 mg/m<sup>2</sup> D1/8 dosage
  - No events of Stevens-Johnson syndrome or toxic epidermal necrolysis occurred
- One patient had Grade 3 peripheral neuropathy that resolved to Grade ≤1 in 8.4 weeks
- The occurrence of zeletide-related AECIs was similar between arms, though any-grade peripheral neuropathy events occurred less frequently with the 6 mg/m<sup>2</sup> dosage

<sup>a</sup>Includes AEs related to zeletide or zeletide + pembro. <sup>b</sup>Patients can have multiple preferred terms within a category. <sup>c</sup>MedDRA SMQ [Broad] for peripheral neuropathy. <sup>d</sup>MedDRA SMQ [broad] for SCAR and high level terms of 'bullous conditions,' 'dermatitis and eczema,' 'rashes, eruptions and exanthems NEC,' 'erythemas,' and 'dermatitis ascribed to specific agent.' <sup>e</sup>SOC of eye disorders. <sup>f</sup>Preferred Term.

AE, adverse event; AECl, adverse event of clinical interest; D, day; NEC, not elsewhere classified; pembro, pembrolizumab; SCAR, Severe Cutaneous Adverse Reactions; SOC, system organ class; zeletide, zeletide pevedotin.

# Responses to Zelenectide Pevedotin 6 mg/m<sup>2</sup> D1/8 + Pembrolizumab in Evaluable Patients (n=23)<sup>a</sup>

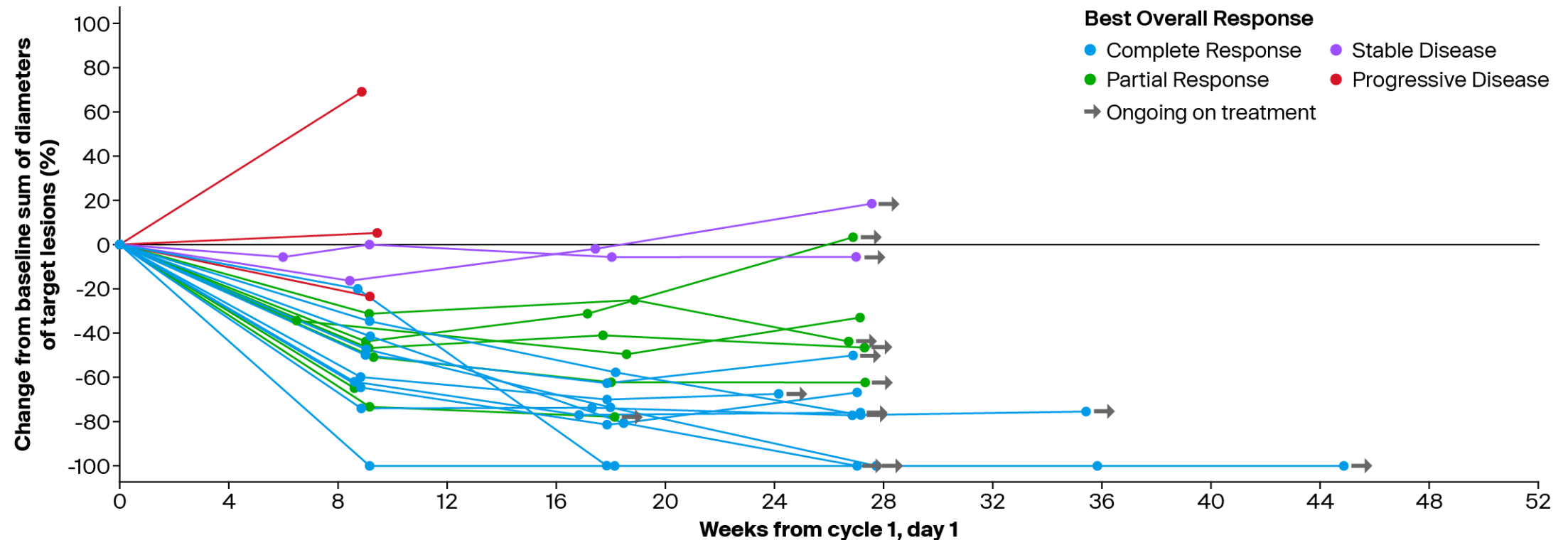


- Median duration of zelev treatment at 6 mg/m<sup>2</sup> was 6.3 months (range, 0.7-10.6)

<sup>a</sup>In the 6 mg/m<sup>2</sup> D1/8 dosage, 4 patients had no measurable disease at baseline per BICR and were excluded from the efficacy analysis. Three patients had no post-baseline sum of diameter target lesion measurements. A total of 23 patients are included in the waterfall plot. <sup>b</sup>In the 5 mg/m<sup>2</sup> D1/8/15 dosage, 1 patient had no measurable disease at baseline per BICR and was excluded from the efficacy analysis. <sup>c</sup>Confirmed ORRs assessed by BICR per RECIST v1.1 are reported. <sup>d</sup>SD must be documented as present at least once on or after 6 weeks post first dose for BOR to be SD. Asterisks denote ongoing on treatment.

BICR, blinded independent central review; BOR, best overall response; CR, complete response; NE, not evaluable; ORR, objective response rate; PD, progressive disease; pembro, pembrolizumab; PR, partial response; SD, stable disease; zelev, zelenectide pevedotin.

# Duration of Response and Change from Baseline in Tumor Size With Zelenectide Pevedotin 6 mg/m<sup>2</sup> D1/8 + Pembrolizumab



- 15/23 (65.2%) efficacy evaluable patients receiving the 6 mg/m<sup>2</sup> dosage remained on treatment at data extraction<sup>a</sup>

<sup>a</sup>Patients with best response of PD were excluded from the number of patients on treatment and assessed at time of data extraction. PD, progressive disease.

# Conclusions

- Zele at 5 mg/m<sup>2</sup> on D1/8/15 + pembro and 6 mg/m<sup>2</sup> on D1/8 + pembro demonstrated encouraging response rates and favorable safety profiles with the potential to differentiate from ADCs in previously untreated patients with la/mUC
- The 6 mg/m<sup>2</sup> on D1/8 dosage of zele was identified as the optimized dosage, demonstrating a favorable benefit-risk profile, and meeting the need for safer and more tolerable treatments
  - Zele + pembro had low rates of AEs, especially those which limit the administration of other ADCs used in la/mUC<sup>1</sup>
  - Tolerability was improved with 6 mg/m<sup>2</sup> over the 5 mg/m<sup>2</sup> dose, with increased potential for combinability and enhanced convenience
- Skin toxicity with zele + pembro was low grade and manageable
  - As of 18 June 2025, in 595 patients treated with zele, no events of Stevens-Johnson syndrome or toxic epidermal necrolysis were reported, demonstrating an improved safety profile compared with currently available ADC regimens<sup>1</sup>

1. Powles T, et al. *N Engl J Med*. 2024;390(10):875-888.

ADC, antibody-drug conjugate; AE, adverse event; D, day; la/mUC, locally advanced or metastatic urothelial carcinoma; pembro, pembrolizumab; zele, zelenectide pevedotin.

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