An EphA2-targeting Bicycle® Drug Conjugate (BDC®), nuzefatide pevedotin, in combination with nivolumab in patients with advanced solid tumors: results from a Phase 1/2 study

▶ CT063

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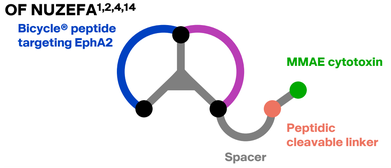
BACKGROUND

- Bicycle® molecules are an innovative therapeutic class in development that offers the manufacturing and pharmacokinetic (PK) properties of a small molecule with the high binding specificity of an antibody,[1–4] making them ideally suited for the targeted delivery of a range of payloads such as cytotoxins to solid tumors
- Nuzefatide pevedotin (nuzefa; formerly BT5528) is a Bicycle® Drug Conjugate (BDC®) comprising a bicyclic peptide targeting erythropoietin-producing hepatocellular receptor A2 (EphA2) linked to the cytotoxin monomethyl auristatin E (MMAE) via a cleavable linker[1] (**Figure 1**)
- EphA2 is overexpressed in various solid tumors leading to oncogenesis, angiogenesis, and metastasis, and correlates with poor clinical outcomes[5–8]
- Other EphA2-targeted therapies have been associated with significant toxicity that limited efficacy analysis[9–12]
- BDCs have the potential to limit toxicity by reducing non-tumor tissue exposure because of their low molecular weight and high selectivity[1–3]
- In the first-in-human Phase 1/2 dose-escalation study of nuzefa in patients with advanced solid tumors (NCT04180371), treatment was well tolerated and demonstrated preliminary anti-tumor activity[13]; favorable dose escalation safety data with nuzefa monotherapy[13] supported the initiation of the nuzefa + nivolumab (nivo) dose escalation part of the study (Part A-2)

FIGURE 1. SCHEMATIC AND CHARACTERISTICS OF NUZEFA[1,2,4,14]



Molecular weight	4.4 kDa[1]
Half-life	<1 hr[14]
Affinity for EphA2 (K_D)	1.9 nM[1,a]
Specificity of binder	Binds to a single protein in over 5500 surface-expressed targets[15,b]

[a]As assessed by fluorescence polarization.[1] [b]As assessed by Retrogenix membrane array.[15] EphA2, erythropoietin-producing hepatocellular receptor A2; K_D, dissociation constant; kDa, kiloDalton; MMAE, monomethyl auristatin E; nuzefa; nuzefatide pevedotin.

OBJECTIVE

- To evaluate the safety and efficacy of nuzefa plus nivo in patients with advanced solid tumors associated with EphA2 expression

METHODS

- Eligible adults were those who had recurrent metastatic solid tumors, tumor tissue available for EphA2 expression testing, and exhausted all appropriate treatment options
- Patients received intravenous (IV) infusions of nuzefa at 2.2 or 4.4 mg/m^2 once weekly (QW) or 6.5 mg/m^2 once every two weeks (Q2W)[13] plus nivo (480 mg IV once every four weeks, Q4W)
- The primary endpoint was to assess treatment-emergent adverse events (TEAEs) and dose-limiting toxicities (DLTs)
- Secondary endpoints were objective response rate, duration of response, clinical benefit rate, time to tumor progression, progression-free survival (PFS), PFS rate at 6 months, overall survival, and PK parameters
  - Plasma concentrations of nuzefa and MMAE were assessed, and key PK exposure metrics were evaluated, including maximum plasma concentration (C_{max}), area under the concentration-time curve (AUC), and drug elimination half-life
- EphA2 immunohistochemistry (IHC) was performed retrospectively using tumor proportion score (TPS) >1 to determine positivity for expression

RESULTS

PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

- As of February 9, 2026, 21 patients had received nuzefa + nivo across all doses in Part A-2 of the study; baseline demographics and disease characteristics are reported in **Table 1**
- Median age was 65 years (range, 41–83); 57% had an ECOG PS 1; median prior lines of therapy in the locally advanced or metastatic setting was 2 (range, 1–7)
- In the 18 analyzed tumor samples, EphA2-positivity was observed in 61% (10 of 14 metastatic urothelial carcinoma [mUC] samples and 1 of 4 non-mUC samples)
- All patients in the 6.5 mg/m^2 cohort had mUC and previously progressed on a checkpoint inhibitor; 10 patients had progressed while on enfortumab vedotin (EV)
- Median duration of treatment for nuzefa + nivo was 58.0 days (range, 15–525); as of the data cut-off, 4 patients remain on treatment

TABLE 1. PATIENT DEMOGRAPHICS AND CLINICAL CHARACTERISTICS

Patient characteristic, n (%)	All patients (N=21)	Nuzefa 6.5 mg/m^2 Q2W + nivo 480 mg Q4W (n=14)
Age, median years (range)	65 (41–83)	69 (56–83)
Sex, n (%)		
Male	14 (67)	11 (79)
Female	7 (33)	3 (21)
Race, n (%)		
White	19 (91)	13 (93)
Black or African American	1 (5)	0
Other	1 (5)	1 (7)
Baseline ECOG PS, n (%)		
0	9 (43)	8 (57)
1	12 (57)	6 (43)
Tumor type, n (%)		
Urothelial	14 (67)	14 (100)
Non-small cell lung	3 (14)	0
Breast	3 (14)	0
Pancreas	1 (5)	0
PD-L1 status, n (%)		
Positive	5 (24)	5 (36)
Negative	6 (29)	6 (43)
Unknown	10 (48)	3 (21)
Prior lines of therapy in the locally advanced/metastatic setting, median (range)	2 (1–7)	2 (1–6)
Prior therapy, n (%)		
Checkpoint inhibitor	17 (81)	14 (100)
Platinum	17 (81)	13 (93)
Antimetabolite	17 (81)	12 (86)
Antibody-drug conjugate	11 (52)	11 (79)
Taxane	6 (29)	1 (7)
Antineoplastic	5 (24)	2 (14)
FGFR inhibitor	2 (10)	2 (14)
Endocrine therapy	2 (10)	0

ECOG PS, Eastern Cooperative Oncology Group performance status; EphA2, erythropoietin-producing hepatocellular receptor A2; EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; mUC, metastatic urothelial carcinoma; nivo, nivolumab; nuzefa, nuzefatide pevedotin; PD-L1, programmed death-ligand 1; Q2W, once every 2 weeks; Q4W, once every 4 weeks.

SAFETY

- Nuzefa-related and nivo-related adverse events (AEs) were reported in 76% and 67% of patients, respectively (**Table 2**)
- The most common (≥10%) nuzefa treatment-related adverse events (TRAEs) are shown in **Table 2**
- One DLT of Grade 3 fatigue that lasted for 5 days was reported in 1 patient (7%) in the nuzefa 6.5 mg/m^2 plus nivo cohort
- Grade ≥3 TRAEs were infrequent and included fatigue (n=2, 10%), anemia (n=1, 5%), and alanine/aspartate aminotransferase (ALT/AST) increase (n=1, 5% each); no Grade 4 or Grade 5 nuzefa-related TEAEs were reported
- Serious adverse events (SAEs) of pneumonia were reported in 2 (10%) patients; all other SAEs were reported in 1 patient each

TABLE 2. SAFETY SUMMARY

Category, n (%)	All patients (N=21)		Nuzefa 6.5 mg/m^2 Q2W + nivo 480 mg Q4W (n=14)	
TEAEs Grade ≥3	21 (100) 14 (67)		14 (100) 11 (79)	
TESAEs Grade ≥3	11 (52) 11 (52)		8 (57) 8 (57)	
	Nuzefa-related	**Nivo-related**	**Nuzefa-related**	**Nivo-related**
TRAEs Grade ≥3	16 (76) 4 (19)	14 (67) 3 (14)	12 (86) 4 (29)	10 (71) 3 (21)
TRSAEs Grade ≥3	1 (5) 1 (5)	2 (10) 2 (10)	1 (7) 1 (7)	2 (14) 2 (14)
Dose modifications	**Nuzefa**	**Nivo**	**Nuzefa**	**Nivo**
TEAEs leading to dose reduction	2 (10)	0	2 (14)	0
TEAEs leading to drug interruption	11 (52)	7 (33)	10 (71)	6 (43)
TEAEs leading to drug withdrawn	0	2 (10)	0	2 (14)
Nuzefa-related AEs reported in ≥10% of patients, n (%)	**All patients (N=21)**		**Nuzefa 6.5 mg/m^2 Q2W + nivo 480 mg Q4W (n=14)**	
	All Grades	**Grade ≥3**	**All Grades**	**Grade ≥3**
Fatigue	6 (29)	2 (10)	4 (29)	2 (14)
Nausea	5 (24)	0	3 (21)	0
Diarrhea	4 (19)	0	4 (29)	0
Anemia	3 (14)	1 (5)	3 (21)	1 (7)
Vomiting	3 (14)	0	2 (14)	0
Myalgia	2 (10)	0	2 (14)	0
Pruritus	2 (10)	0	2 (14)	0
Rash	2 (10)	0	2 (14)	0

AE, adverse event; nivo, nivolumab; nuzefa, nuzefatide pevedotin; Q2W, once every 2 weeks; Q4W, once every 4 weeks; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.

- TRAEs of clinical interest included skin reactions (29%, all Grade 1 or 2) and peripheral neuropathy (10%, all Grade 1, and no motor events were reported) (**Table 3**)
- No Grade ≥3 TRAEs of clinical interest were reported (**Table 3**)
- No TRAEs of hemorrhage occurred (**Table 3**)

TABLE 3. TRAEs OF CLINICAL INTEREST IN PATIENTS TREATED WITH NUZEFA + NIVO

TRAE of clinical interest[a,b]	All Patients (N=21)		Nuzefa 6.5 mg/m^2 Q2W + nivo 480 mg Q4W (n=14)	
	All Grades	**Grade ≥3**	**All Grades**	**Grade ≥3**
Skin reactions[c]	6 (29)	0	5 (36)	0
Peripheral neuropathy[d]	2 (10)	0	2 (14)	0
Hyperglycemia[e]	1 (5)	0	1 (7)	0
Eye disorders[f]	2 (10)	0	1 (7)	0
Hemorrhage	0	0	0	0

[a]Includes AEs related to nuzefa. [b]Patients can have multiple PT 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]Hyperglycemia/new onset diabetes mellitus [broad] (SMQ). [f]SOC of Eye disorders.
AE, adverse event; PT, Preferred Term; MedDRA, Medical Dictionary for Regulatory Activities; nivo, nivolumab; nuzefa, nuzefatide pevedotin; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SCAR, Severe Cutaneous Adverse Reactions; SMQ, Standardized MedDRA Queries; SOC, system organ class; TRAE, treatment-related adverse event.

EFFICACY

- In patients treated with nuzefa 6.5 mg/m^2 plus nivo (all mUC), 4/10 (40%) with EphA2+ tumors responded
- In the subset of patients with EphA2+ tumors that were MMAE-naïve, 3/3 achieved a confirmed partial response ([PR]; Objective response rate [ORR] 100%) (**Table 4**)

TABLE 4. BEST OVERALL RESPONSE IN PATIENTS WITH MEASURABLE DISEASE AT BASELINE

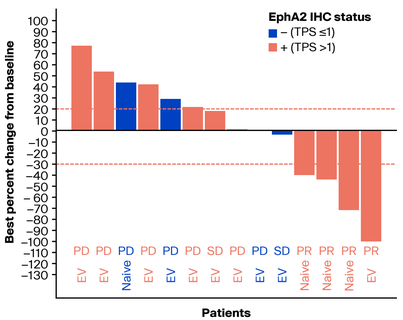
Best overall response, n (%)	All patients (n=19)	Nuzefa 6.5 mg/m^2 Q2W + nivo 480 mg Q4W					
		All (n=14)	**EphA2+ (n=10)**	**EphA2+ Prior MMAE (n=7)**	**EphA2+ MMAE-naïve (n=3)**	**EphA2- Prior MMAE (n=3)**	**EphA2- MMAE-naïve (n=1)**
CR	0	0	0	0	0	0	0
PR	4 (21)	4 (29)	4 (40)	1 (14)	3 (100)	0	0
SD	2 (11)	2 (14)	1 (10)	1 (14)	0	1 (33)	0
ORR[a] [95% CI]	**4 (21)** [6.1, 45.6]	**4 (29)** [8.4, 58.1]	**4 (40)**	**1 (14)**	**3 (100)**	**0**	**0**
CBR[a,b] [95% CI]	**5 (26)** [9.1, 51.2]	**5 (36)** [12.8, 64.9]	**4 (40)**	**1 (14)**	**3 (100)**	**1 (33)**	**0**

[a]Confirmed. [b]CBR is defined as the proportion of patients with a confirmed CR, PR, or SD ≥16 weeks from Cycle 1 Day 1 (C1D1).
C1D1, Cycle 1 Day 1; CBR, clinical benefit rate; CI, confidence interval; CR, complete response; EphA2, erythropoietin-producing hepatocellular receptor A2; ORR, objective response rate; MMAE, monomethyl auristatin E; nivo, nivolumab; nuzefa, nuzefatide pevedotin; PR, partial response; Q2W, once every 2 weeks; Q4W, once every 4 weeks; SD, stable disease.

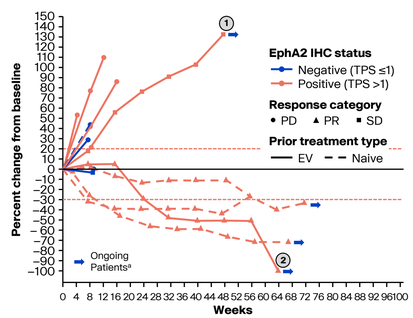
- Patients who achieved a PR or at least 16 weeks of SD were on treatment for a minimum of 56 weeks, and most continued on treatment at the time of data cut-off (**Figure 2**)

FIGURE 2. A) BEST PERCENT CHANGE FROM BASELINE IN TUMOR SIZE IN PATIENTS WITH mUC TREATED WITH NUZEFA 6.5 mg/m^2 + NIVO, AND B) OVER TIME

A. Waterfall plot by EphA2 status (Nuzefa 6.5 mg/m^2 Q2W + nivo, n=14)



B. Percent change from baseline in tumor size over time (Nuzefa 6.5 mg/m^2 Q2W + nivo, n=14)



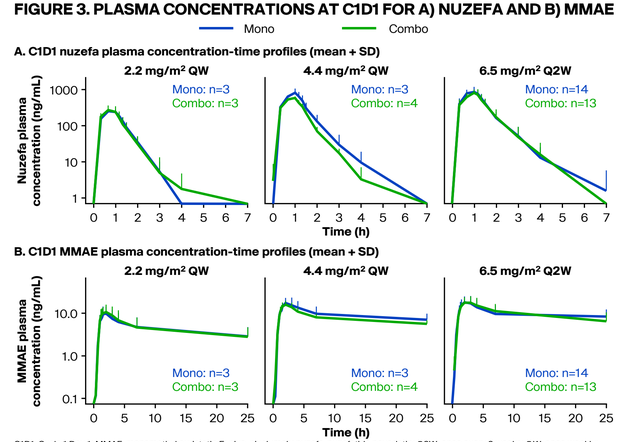
[a]Status of ongoing patients as of February 9, 2026.
[1]Line 1 represents a patient treated beyond progression with symptomatic relief and bladder lesion clearance.
[2]Line 2 represents a patient with a complete response in target lesions with persistent non-target lesions.

Data as of February 9, 2026. Best post baseline response status from EDC was used for the response category for both figures.
EDC, electronic data capture; EphA2, erythropoietin-producing hepatocellular receptor A2; EV, enfortumab vedotin; IHC, immunohistochemistry; mUC, metastatic urothelial carcinoma; nivo, nivolumab; nuzefa, nuzefatide pevedotin; PD, progressive disease; PR, partial response; Q2W, once every 2 weeks; SD, stable disease; TPS, tumor proportion score.

PHARMACOKINETICS

- PK of nuzefa and MMAE are similar with and without nivo, indicating no apparent PK interaction for the combination (**Figure 3**)

FIGURE 3. PLASMA CONCENTRATIONS AT C1D1 FOR A) NUZEFA AND B) MMAE



C1D1, Cycle 1 Day 1; MMAE, monomethyl auristatin E; nivo, nivolumab; nuzefa, nuzefatide pevedotin; Q2W, once every 2 weeks; QW, once weekly; SD, standard deviation.

CONCLUSIONS

- These results demonstrate that the nuzefa + nivo combination demonstrates a safety profile with the potential to differentiate across the range of nuzefa dose levels tested, in contrast to prior EphA2-targeted therapies that demonstrated less favorable safety profiles
  - Most TRAEs were Grade 1 or 2; only 4 (19%) patients experienced Grade 3 TRAEs
  - No Grade ≥3 TRAEs of clinical interest and no TRAEs of hemorrhage occurred
- Preliminary anti-tumor activity was demonstrated in patients with mUC at a dose of nuzefa 6.5 mg/m^2 Q2W + nivo 480 mg Q4W, especially in patients with EphA2+ tumors
  - All patients with EphA2+ tumors who were MMAE-naïve achieved confirmed PRs and durable disease control
  - All patients who achieved a PR had a history of progression on prior immune checkpoint inhibitor, including one patient with prior progression on EV, indicating that nuzefa may support immune resensitization
  - Patients who achieved a PR or at least 16 weeks of SD were on treatment for a minimum of 56 weeks, with most continuing on treatment at the time of data cut-off

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ABBREVIATIONS

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; AUC, area under the concentration-time curve; BDC®, Bicycle® Drug Conjugate; C1D1, Cycle 1 Day 1; CBR, clinical benefit rate; CI, confidence interval; C_{max}, maximum plasma concentration; CR, complete response; DLT, dose-limiting toxicity; ECOG PS, Eastern Cooperative Oncology Group performance status; EphA2, erythropoietin-producing hepatocellular receptor A2; EV, enfortumab vedotin; FGFR, fibroblast growth factor receptor; IHC, immunohistochemistry; IV, intravenous; K_D, dissociation constant; kDa, kiloDalton; MedDRA, Medical Dictionary for Regulatory Activities; MMAE, monomethyl auristatin E; mUC, metastatic urothelial carcinoma; nivo, nivolumab; nuzefa, nuzefatide pevedotin; ORR, objective response rate; PD, progressive disease; PD-L1, programmed death-ligand 1; PFS, progression-free survival; PK, pharmacokinetics; PR, partial response; PT, Preferred Term; Q2W, once every 2 weeks; Q4W, once every 4 weeks; QW, once weekly; SAE, serious adverse event; SCAR, Severe Cutaneous Adverse Reactions; SD, stable disease; SD, standard deviation; SMQ, Standardized MedDRA Queries; SOC, system organ class; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; TPS, tumor proportion score; TRAE, treatment-related adverse event; TRSAE, treatment-related serious adverse event.

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