Phase 2 Study of Nuzefatide Pevedotin, an EphA2-targeting Bicycle® Drug Conjugate, in Patients With Metastatic Pancreatic Ductal Adenocarcinoma

Poster #

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BACKGROUND

- Bicycle Drug Conjugate (BDC®) 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 a biologic, making them ideally suited for the targeted delivery of a range of payloads, including cytotoxins, to solid tumors[1-3]
- Nuzefatide pevedotin (nuzefa; BT5528) is a BDC® comprising a bicycle peptide targeting Ephrin type-A receptor 2 (EphA2) linked to cytotoxic monomethyl auristatin E (MMAE; **Figure 1, Table 1**)[2,4]
  - EphA2 is a member of the receptor tyrosine kinase family that mediates bidirectional signaling through interactions with ephrin ligands to regulate cellular processes, such as cell proliferation, migration, and epithelial-mesenchymal transition[5]
  - EphA2 is expressed in up to 95% of pancreatic ductal adenocarcinoma (PDAC) cases, and its overexpression is correlated with poor prognosis[6-9]
  - With a low molecular weight and short plasma half-life, nuzefa has the potential to rapidly penetrate solid tumors with minimal exposure to healthy tissue[2]
- In a Phase 1/2 trial, nuzefa monotherapy demonstrated antitumor activity and was generally well tolerated in patients with advanced solid tumors (NCT04180371)[10]
- This open-label, multicenter, single-arm Phase 2 study (NCT07450859) aims to evaluate efficacy and safety of nuzefa monotherapy in previously treated patients with metastatic PDAC (**Figure 2**)

INTRODUCTION

FIGURE 1. NUZEFATIDE PEVEDOTIN (NUZEFA) STRUCTURE[10,11]

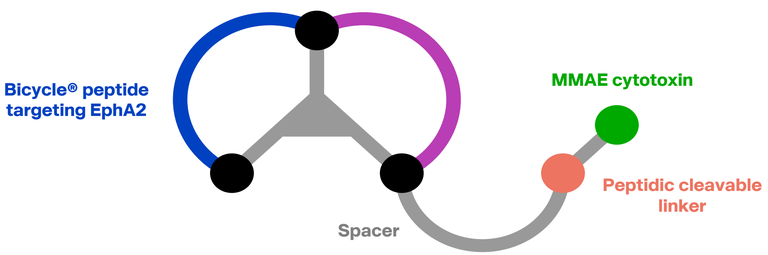


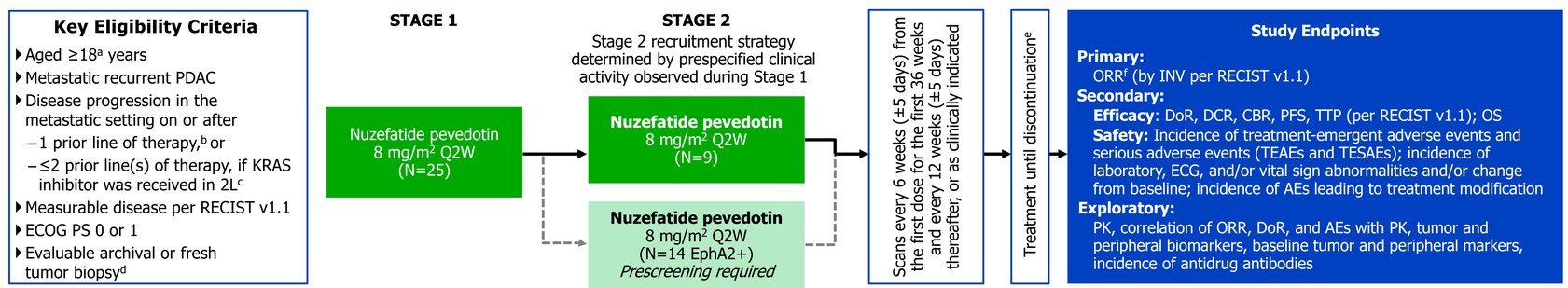
TABLE 1. NUZEFA MOLECULAR CHARACTERISTICS

Molecular weight	4.4 kDa[4]
Half-life	<1 hour[12]
Affinity for EphA2 (K_D)	1.9 nM[a,4]
Specificity of binder	Binds to single protein in more than 5500 surface-expressed targets[b,11]

[a]Assessed by fluorescence polarization. [b]Assessed by Retrogenix membrane array.

TRIAL DESIGN

FIGURE 2. STUDY DESIGN AND ENDPOINTS (NCT07450859)



Nuzefa will be administered via IV infusion on days 1 and 15 of a 28-day cycle; study visits for safety assessments will be conducted at each dosing visit and as clinically indicated throughout study treatment.
[a]At the time of signing the informed consent, participants must be of locally defined age of consent. [b]Neoadjuvant or adjuvant systemic therapy may count as the first line if the participant progressed <6 months from the end of systemic therapy. [c]Participants who received prior treatment with a KRAS inhibitor (either as monotherapy or in combination with chemotherapy) in the first-line setting are also permitted with no intervening treatment before enrollment. [d]Although evaluable tissue and blood samples are required, prospective testing for EphA2 positivity in tumor cells is not required for study entry at Stage 1. [e]Treatment discontinuation may occur due to disease progression, irreversible or intolerable toxicity, investigator or participant decision, death, or study termination. [f]A complete or partial response should be confirmed by repeat tumor imaging ≥4 weeks after the date the initial response was first documented; after the confirmatory scan, resume the original RECIST scan schedule.

Inclusion criteria

- Histologically confirmed metastatic recurrent PDAC
- Disease progression on or after 1 prior line of systemic therapy or on or after 2L therapy with a KRAS inhibitor, with evidence of radiographic progression
  - Neoadjuvant or adjuvant systemic therapy may count as the first-line therapy if the disease progressed <6 months from the end of systemic treatment
  - Prior treatment with a KRAS inhibitor in the first-line setting is permitted with no intervening treatment before enrollment
- ≥1 measurable target disease lesion per RECIST v1.1
- ECOG PS 0 or 1
- Adequate organ function
- Sufficient tumor tissue available for analysis of EphA2 expression or other biomarkers
  - During Stage 1, analysis of EphA2 will be retrospective

Exclusion criteria

- Chemotherapy within 14 days or radiotherapy within 28 days before the first dose of study treatment
- Experimental treatments within 28 days or 5 half-lives (whichever is longer) of the first dose of study treatment
- Prior taxane and/or MMAE exposure
- Patients with known microsatellite instability-high status eligible for immune checkpoint inhibitor treatment
- Untreated central nervous system metastases

Study recruitment is ongoing in 8 global study centers

- Mayo Clinic Arizona, Phoenix, AZ, USA
- Mayo Clinic Florida, Jacksonville, FL, USA
- Seoul National University Hospital, Seoul, Korea
- Mayo Clinic Rochester, Rochester, MN, USA
- Memorial Sloan Kettering Cancer Center, New York, NY, USA
- Samsung Medical Center, Seoul, Korea
- Siteman Cancer Center, Washington University School of Medicine, St Louis, MO, USA
- Thomas Jefferson University, Sidney Kimmel Comprehensive Cancer Center, Philadelphia, PA, USA

For more information, please visit https://clinicaltrials.gov/study/NCT07450859

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ABBREVIATIONS

2L, second line; AE, adverse event; BDC®, Bicycle® Drug Conjugate; CBR, clinical benefit rate; DCR, disease control rate; DoR, duration of response; ECG, electrocardiogram; ECOG PS, Eastern Cooperative Oncology Group performance status; EphA2, Ephrin type-A receptor 2; INV, investigator; IV, intravenous; MMAE, monomethyl auristatin E; nuzefa, nuzefatide pevedotin; ORR, objective response rate; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PFS, progression-free survival; PK, pharmacokinetics; Q2W, every 2 weeks; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event; TTP, time to progression.

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