Poster 1014eP

Histological biomarker analysis of nonclinical and baseline tumor samples from the phase 1 dose escalation study using micvotabart pelidotin (MICVO) in advanced solid tumors

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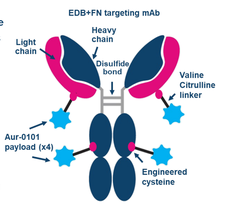
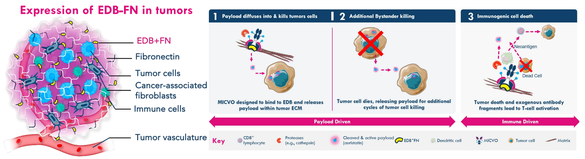
BACKGROUND

- Micvotabart pelidotin (MICVO, aka PYX-201) is a first-in-concept antibody-drug conjugate (ADC) targeting extradomain-B of fibronectin (EDB+FN), a non-cellular structural component within the tumor extracellular matrix (ECM) that is highly expressed in tumors compared to normal adult tissues.[1]
- MICVO is composed of a fully human IgG1 monoclonal antibody conjugated to an optimized Auristatin-0101 payload via a cleavable linker (DAR of 4).[2,3]
- MICVO is designed to achieve anti-tumor activity via three mechanisms of action: 1) the cytotoxic, cell-permeable Auristatin-0101 payload directly kills tumor cells through disruption of microtubule formation, 2) the payload promotes additional tumor cell killing via the bystander effect, and 3) release of neoantigens from dying tumor cells induces immunogenic cell death.



Mechanism of Action for MICVO



- PYX-201-101 is a first-in-human, open-label, multicenter, Phase 1 clinical study (NCT05720117) to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of MICVO monotherapy in participants with advanced solid tumors. Study PYX-201-101 comprises two parts: Part 1 dose escalation and Part 2 dose expansion. Data from the Part 1 dose escalation is reported in ESMO Poster # 965P.
- **Objective: Histological biomarkers were evaluated using baseline clinical biopsy samples and nonclinical tumor samples to identify stromal features that could confer sensitivity to treatment with MICVO.**

Clinical Study Design

- Treatment with MICVO IV Q3W until unacceptable toxicity or disease progression
- As of 04Oct2024, a total of 77 participants were treated with MICVO across 9 dose levels ranging from 0.3-8.0 mg/kg Q3W IV during the dose-escalation part of the study.
- Dose escalation study identified the range of potentially effective doses to be 3.6-5.4 mg/kg

Part 1 Dose Escalation

Key Eligibility Criteria	Eligible Tumor Types		Objectives & Endpoints
• All-comers with no biomarker selection • Histologically or cytologically confirmed solid tumors • Locally advanced, recurrent/metastatic disease progressed on SoC • RECIST v1.1 measurable disease • ECOG PS 0-1 • Adequate organ function • Grade >2 neuropathy excluded	HCC	HNSCC	**Primary** • Safety & tolerability • MTD • Determine dose(s) for next phase of development **Secondary** • ORR, PFS, DCR, DOR, TTR per RECIST v1.1 by Investigator • PK: C_{max}, T_{max}, half-life, total Antibody, free payload • OS **Exploratory** • Blood and tumor tissue biomarker
	HR+ Breast Cancer	NSCLC	
	Ovarian Cancer	PDAC	
	Renal Cancer*	Sarcoma	
	Thyroid Cancer	TNBC	

*No patient was dosed in this Phase 1 study for Renal Cancer

Methods

Baseline biopsies from participants in the phase 1 dose escalation study were evaluated for histological biomarkers and correlation to drug response. Tumor biopsies tested by H&E for tumor stroma and IHC for EDB+FN were scored by a board-certified pathologist for percent of tumor stroma and EDB+FN, quantified as H scores in tumor stroma, cancer cell membrane, and cancer cell cytoplasm. Scores were evaluated for correlation to clinical response. Best overall response (BOR) was per RECIST v1.1 criteria. Nonclinical human biopsy samples from tumor types of interest were evaluated for histologic features that may confer sensitivity to MICVO. AI powered digital pathology was deployed on H&E images of commercially-sourced nonclinical samples of HNSCC, NSCLC, ovarian cancer, and PDAC to annotate tissue regions and cell types and evaluate stromal architecture.

EDB+FN is robustly expressed in tumor stroma in baseline biopsy samples from participants enrolled in phase 1 dose escalation study

Table 1. Baseline biopsy sample metrics

Efficacy evaluable participants	Total (N=65)
Evaluable baseline biopsies	**50**
Fresh	17
Archival*	33
Evaluable baseline biopsies by indication	
HCC	1
HR+ Breast Cancer	3
Ovarian Cancer	5
Thyroid Cancer	3
HNSCC	5
NSCLC	7
PDAC	12
Sarcoma	8
TNBC	6

*Archival biopsies collected >1 month prior to first dose of MICVO.

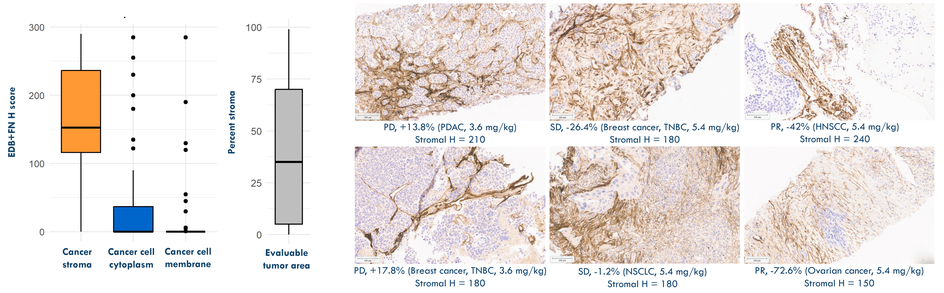


Figure 1. EDB+FN is robustly expressed in tumor stroma in baseline biopsies. A novel IHC assay was developed to quantify the intensity and distribution of EDB+FN protein expression in the tumor stroma, cancer cell membrane, and cancer cell cytoplasm, reported as EDB+FN H-scores.[4] All evaluable baseline biopsy samples were evaluated and scored by a board-certified pathologist for EDB+FN protein expression (A) using this assay and for percent stroma (B) using H&E staining. Cancer stroma was the predominant region of EDB+FN expression (median stromal H = 150, range 0-290), with broad expression observed across indications and clinical responses (C). Values below images reflect best overall response and best percent change from baseline.

Stromal EDB+FN expression is not directly correlated with clinical response to MICVO

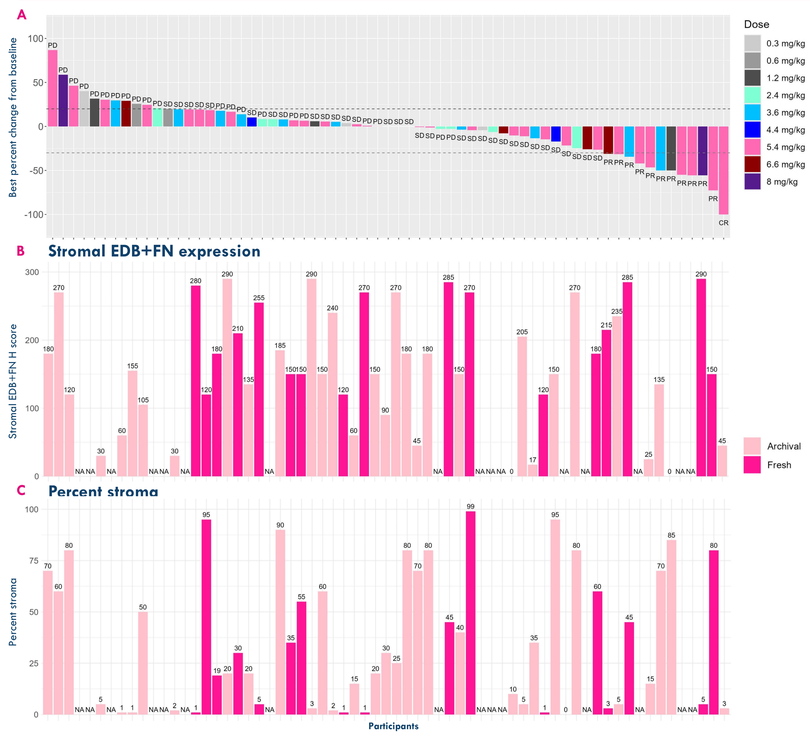
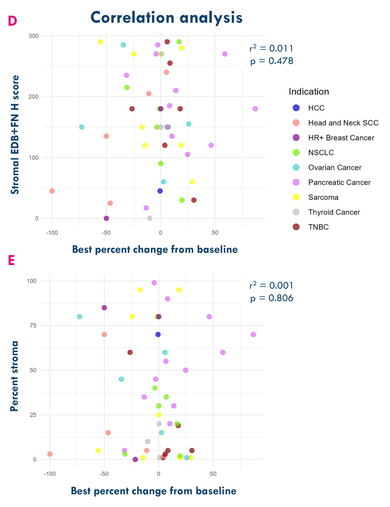


Figure 2. Clinical outcome is not directly correlated with either stromal EDB+FN expression or percent stroma. Of 67 participants with evaluable responses to MICVO per Resist v1.1 (A), 51 evaluable baseline biopsies were tested and scored by a board-certified pathologist for EDB+FN protein expression by IHC (B) and stromal density by H&E (C)*. EDB+FN protein was broadly detected in tumor stroma regardless of clinical response. Clinical response was not correlated with either EDB+FN protein expression (D) or stromal density (E), either overall or for any individual indication.

*In plots A-C, each bar reflects one participant, and bars are ordered by best percent change from baseline. NA indicates samples not available or not evaluable due to poor sample quality. Values above bars in A reflect best overall response per RESIST v1.1. CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease.



Features of stromal architecture differ across indications in nonclincal samples

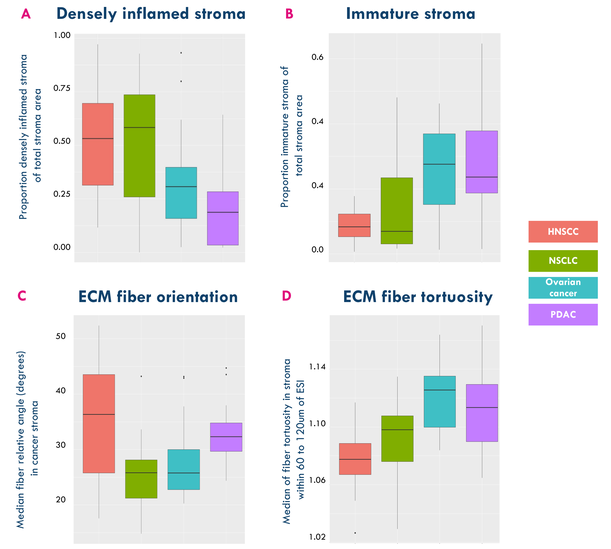


Figure 3. Digital pathology analysis of nonclinical samples revealed differences in stromal morphology between indications. To explore additional stromal features that may confer sensitivity to MICVO, AI powered digital pathology was deployed on H&E images of commercially-sourced nonclinical human tumor samples to evaluate stromal architecture across indications. Stromal subtyping analysis using PathAI PathExplore revealed that the HNSCC tumors have a higher proportion of densely inflamed stroma (A) and a lower proportion of immature stroma (B) compared to tumors from the other indications evaluated. When examined using the PathAI PathExplore fibrosis model, ECM fiber organization in HNSCC tumors showed a higher median relative fiber angle (C) and lower median fiber tortuosity (straighter fibers) 60-120 µm from the epithelial-stromal interface (ESI) (D) compared with the fiber organization in tumors of the other indications evaluated.

SUMMARY & CONCLUSIONS

- EDB+FN is broadly expressed in tumor stroma in biopsy samples from participants in the phase 1 dose escalation study.
- In this heterogeneous dataset, the level of EDB+FN protein expression and percent stroma did not correlate with clinical response.
- In certain tumor types such as HNSCC, features of stromal architecture detected using digital pathology may contribute to sensitivity to MICVO.
- Studies with participant tumor samples correlating features besides EDB+FN such as protease expression, payload sensitivity, drug resistance mechanisms, or other histologic features such as those identified here using PathAI with sensitivity to MICVO are on-going and will be further investigated in tumor specific expansion cohorts.

Link to PYX-201-101 (NCT05720117) at CT. gov

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ABBREVIATIONS

HCC – hepatocellular carcinoma
HNSCC – head and neck squamous cell carcinoma
NSCLC – non-small cell lung cancer
PDAC – pancreatic ductal adenocarcinoma
TNBC – triple negative breast cancer
CR – complete response
PR – partial response
SD – stable disease
PD – progressive disease

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2. Graziani et al., Mol Cancer Ther 2020 Oct; 19(10):2068-2078.
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DECLARATIONS OF INTEREST

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