Micvotabart pelidotin, a non-cellular targeting ADC, remodels the tumor microenvironment in tumors from participants in a phase 1 dose escalation study

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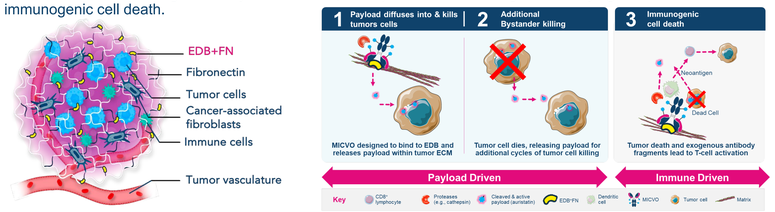
Abstract: A113

PYXIS ONCOLOGY

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 that is highly expressed in tumors compared to normal adult tissues. EDB+FN, a splice variant of fibronectin, is known to be involved in tumor angiogenesis, proliferation, and metastasis.
- 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.



- MICVO is currently being evaluated in a Phase 1 monotherapy trial (NCT05720117) and a Phase 1/2 combination trial with pembrolizumab (NCT06795412) for advanced solid tumors [1,2].
- Part 1 of the phase 1 dose escalation study assessed the safety, tolerability, pharmacokinetics, pharmacodynamics, and preliminary efficacy of MICVO monotherapy in participants with advanced solid tumors [3].

Key Eligibility Criteria

- 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

Eligible Tumor Types

HCC	HNSCC
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

Objectives & Endpoints

Primary
- Safety & tolerability
- MTD
- Determine dose(s) for next phase of development

Secondary
- ORR, DCR, DOR, TTR per RECIST v1.1 by Investigator
- PK: C_{max}, T_{max}, half-life, total Antibody, free payload

Exploratory
- Blood and tumor tissue biomarker

- Dose escalation study design: Treatment with MICVO IV Q3W until unacceptable toxicity or disease progression.
- This study has evaluated a wide range of doses from 0.3 mg/kg through 8.0 mg/kg, with 3.6-5.4 mg/kg identified as the potentially effective dose response range.
- Histologic approaches to characterize the tumor and stromal compartments were recently evaluated on nonclinical human tumor samples and in animal models [4-7].
- **The objective of this poster is to deploy histological approaches [Poster A117] on the clinical tumor biopsies from the dose escalation study to characterize the pharmacodynamic response to MICVO in the TME.**

Methods

Baseline and matched on-treatment biopsies from participants in the dose escalation study were collected from the same anatomic locations prior to study treatment and during Cycle 2 of MICVO treatment, respectively. Biopsies were evaluated for pharmacodynamic biomarkers and correlation to clinical response. Best overall response (BOR), per RECIST v1.1 criteria, and best percent change from baseline were both as of 10/4/2024. H&E-stained tumor sections were evaluated by a board-certified pathologist for percent stroma and using PathAI PathExplore, stromal subtyping, and fibrosis models to annotate tissue regions and cell types and evaluate stromal architecture. EDB+FN immunohistochemistry (IHC) was performed using a novel assay [4] and scored by a board-certified pathologist to assess EDB+FN target expression, reported as stromal H scores. Custom multiplex-immunofluorescence (mIF) staining, coupled with digital pathology analysis [Poster A117], was deployed to assess changes in the TME.

MICVO induces pharmacodynamic changes in the tumor epithelium after two cycles of treatment

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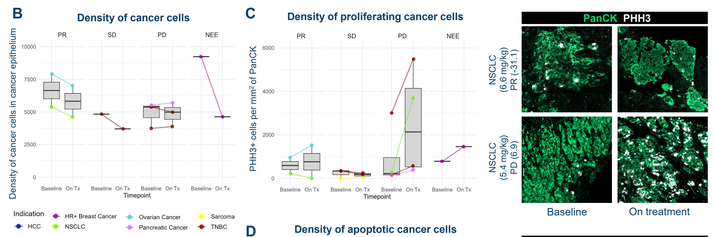
Indication	Evaluable pairs H&E (AI)	IHC	mIF
HCC	0	1	0
HR+ breast cancer	1	2	1
NSCLC	1	3	2
Ovarian cancer	1	2	1
PDAC	1	1	1
Sarcoma	0	1	1
TNBC	3	4	4
TOTAL	7	14	10



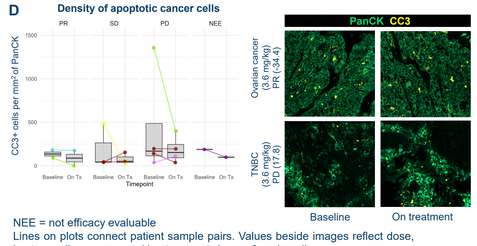


Figure 1. MICVO induces response-specific changes in the tumor epithelium after two cycles of MICVO.
(A) Matched biopsy samples collected from study participants prior to study enrollment and during cycle 2 of MICVO treatment were histologically evaluated. (B) AI powered digital pathology evaluation of H&E-stained slides showed decreased density of cancer cells in the tumor epithelium in participants with partial response (PR) or stable disease (SD). (C) Evaluation using mIF revealed increased proliferation, measured by phospho-histone H3 (PHH3), in PanCK-expressing tumor cells in participants with progressive disease (PD). (D) Apoptosis, measured by cleaved caspase 3 (CC3), was unchanged in PanCK-expressing tumor cells regardless of clinical response.

NEE = not efficacy evaluable
Lines on plots connect patient sample pairs. Values beside images reflect dose, best overall response, and best percent change from baseline.

MICVO reduces the density of cells in EDB+FN+ tumor stroma, but does not deplete expression of its target EDB+FN

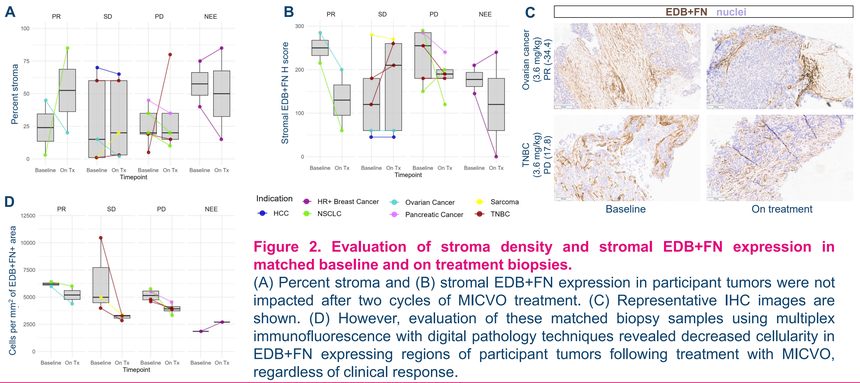


Figure 2. Evaluation of stroma density and stromal EDB+FN expression in matched baseline and on treatment biopsies.
(A) Percent stroma and (B) stromal EDB+FN expression in participant tumors were not impacted after two cycles of MICVO treatment. (C) Representative IHC images are shown. (D) However, evaluation of these matched biopsy samples using multiplex immunofluorescence with digital pathology techniques revealed decreased cellularity in EDB+FN expressing regions of participant tumors following treatment with MICVO, regardless of clinical response.

Histological changes in tumor stroma reflective of drug activity and clinical outcome were evident after two cycles of MICVO treatment

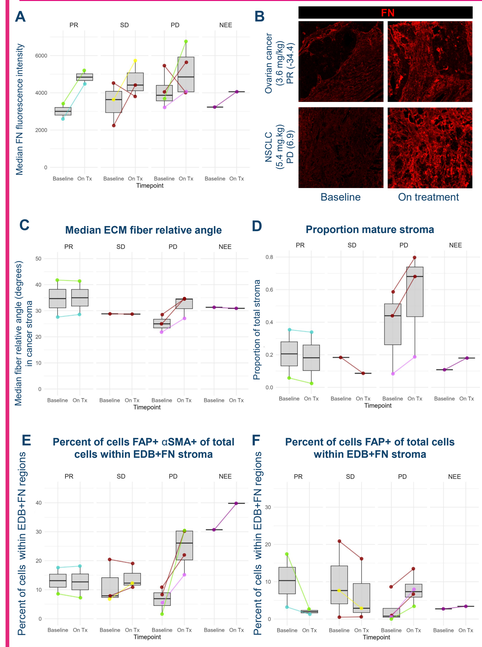


Figure 3. Stromal organization and composition changes in response to MICVO treatment and reflective of clinical response.
(A) mIF analysis revealed increased median fluorescence intensity of fibronectin (FN) staining in on-treatment samples compared to matched baseline biopsies, regardless of clinical response, reflective of a pharmacodynamic effect of MICVO to remodel tumor stroma. (B) Representative IF images are shown. Digital pathology analysis of H&E-stained biopsy sections showed changes in stromal organization, including (C) an increase in median fiber angle in cancer stroma and (D) an increased proportion of mature stroma subtype in tumors from participants with PD, while these metrics remained unchanged in participants with PR or SD. mIF analysis of stromal cell composition within the EDB+FN-expressing region of cancer stroma found an increased percentage of (E) FAP+αSMA+ and (F) FAP+ cancer associated fibroblasts in participants with PD. The percentage of these cells decreased or remained stable in participants with PR or SD. (G) Proportion of αSMA+ cells showed the opposite trend. These changes are reflective of disease progression in participants with PD.

Conclusions

- Histological evaluation of a limited set of matched pair biopsies from participants treated with MICVO in the dose escalation study demonstrated pharmacodynamic effects on both tumor cells and stromal remodeling across clinical responses, reflective of the mechanism of action of this novel non-cellular targeting ADC.
- Notably, MICVO reduced cellular density in both tumor epithelium and stroma compartments after two cycles of treatment but did not deplete EDB+FN expression in the cancer stroma, maintaining target expression.
- Pharmacodynamic effects of MICVO on stroma included increased FN fluorescence intensity and changes in stromal cell composition, reflective of stromal remodeling.
- MICVO's ability to mobilize an anti-tumor immune response is also under investigation in these biopsies [Poster A114].
- These pharmacodynamic changes will be further characterized in indication-specific expansion cohorts from the ongoing clinical evaluation of MICVO as monotherapy (NCT05720117) and in combination with pembrolizumab (NCT06795412).

References
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