Micvotabart pelidotin, an ADC targeting non-cellular EDB+FN, induces an immune response in tumors from participants in a phase 1 dose escalation study

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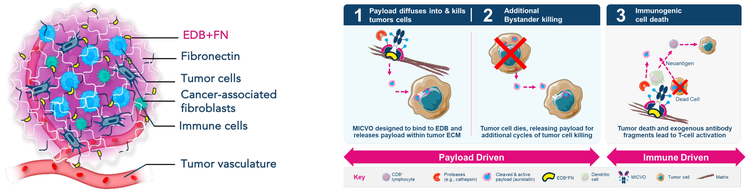
Abstract: A114

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 [1,2]. 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.



- Preclinical studies have shown evidence of MICVO inducing an immunogenic cell death response in cancer cells in culture and syngeneic mouse models treated with a mouse analog of MICVO showed increased infiltration of activated CD3+ T-cells. [Posters: A112 & A115].
- 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 [3,4].
- 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 [5].

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 participant with renal cancer was dosed in this Phase 1 study

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 biomarkers

- 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.
- **The objective of this poster is to confirm MICVO's ability to mobilize an anti-tumor immune response in tumor samples from clinical trial participants with advanced solid tumors in the dose escalation study to characterize this pharmacodynamic response to MICVO in the tumor microenvironment.**

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 time on study were both as of 10/4/2024. H&E-stained tumor sections were evaluated using PathAI's PathExplore models to annotate tissue regions and cell types. Multiplex-immunofluorescence (mIF) staining, coupled with digital pathology analysis, was deployed using a custom panel designed to characterize changes in the tumor immune microenvironment [Poster A117]. Gene expression (GE) analysis on RNA isolated from tumor biopsies was evaluated using the Nanostring IO360 panel. Differentially expressed genes on treatment were determined using DESeq2 on raw counts of genes above the limit of detection (LOD) accounting for unwanted factors with RUVSeq, % stroma, and participant in the design formula. Over-representation analysis used all genes above LOD as background.

	Evaluable pairs		
Indication	H&E	mIF	GE
HR+ breast cancer	1	1	1
NSCLC	1	2	1
Ovarian cancer	1	1	1
PDAC	1	1	1
Sarcoma	0	1	1
TNBC	3	4	3
TOTAL	7	10	8

MICVO increases density of lymphocytes infiltrating the tumor epithelium

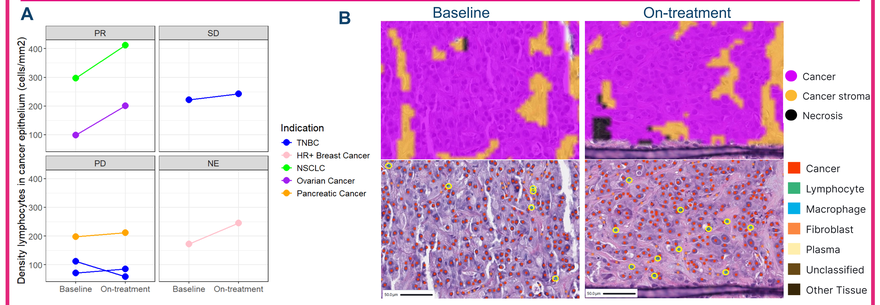


Figure 1: AI-powered digital pathology on H&E-stained slides reveals an increased density of lymphocytes within the tumor parenchyma on treatment, particularly within participants with better clinical response (A). Longitudinal change in density of lymphocytes within cancer epithelium. Lines connect paired samples from the same participant between baseline and on-treatment timepoints. Panels are split by participant's BOR. **(B)** Representative H&E slide images of tumor biopsies from a participant with TNBC (BOR = SD) annotated with PathAI's PathExplore features before (left) and on (right) treatment with MICVO. Top rows show annotated tissue regions and bottom rows show annotated cell types. Yellow circles highlight annotated lymphocytes.

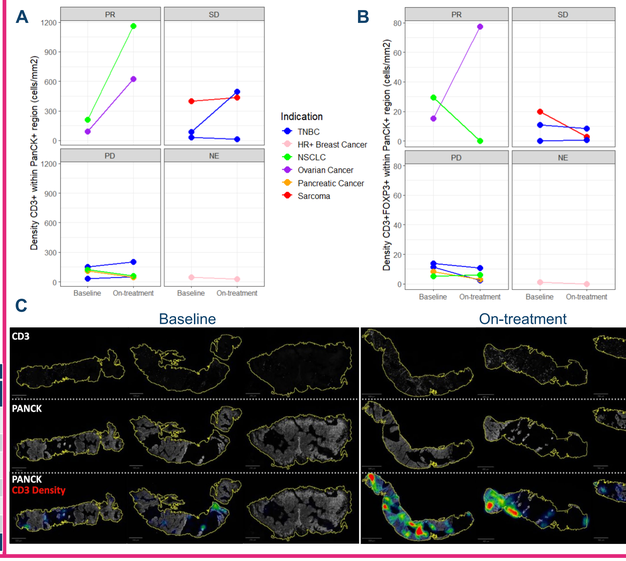


Figure 2: mIF reveals an increased density of non-immunosuppressive (FOXP3-) T-cells (CD3+) within tumor cell regions (PanCK+) on treatment, particularly with better clinical response. Longitudinal changes in density of CD3+ staining **(A)** and CD3+ FOXP3+ dual staining **(B)** cells within PanCK+ regions. Lines connect paired samples from the same participant between baseline and on-treatment timepoints. Panels are split by participant's BOR. **(C)** Representative CD3 density maps on a tumor biopsy slide from a participant with ovarian cancer (BOR = PR).

Abbreviations
BOR = Best overall response
PR = Partial response
SD = Stable disease
PD = Progressive disease
NE = Not efficacy evaluable
TNBC = Triple-negative breast cancer
NSCLC = Non-small cell lung cancer
FC = Fold change

MICVO-induced T-cell infiltration associates with time on study

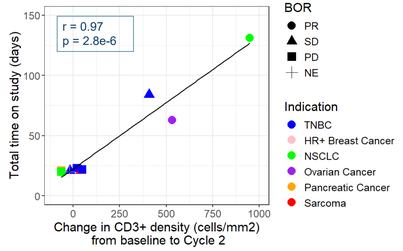


Figure 3: A greater increase in T-cell (CD3+) density in tumor cell regions at cycle 2 (from baseline) is associated with longer time on study. Correlation plot of change in CD3+ density within tumor cell regions from baseline with total time on study across participants with matched, paired samples with Pearson's correlation listed and linear regression best fit line.

MICVO upregulates immune response gene expression in tumors

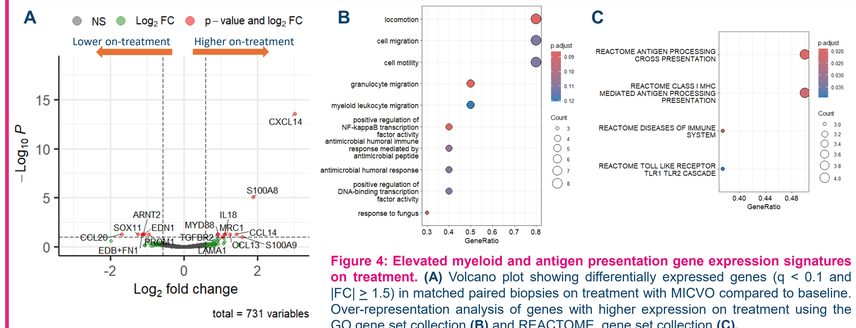


Figure 4: Elevated myeloid and antigen presentation gene expression signatures on treatment. (A) Volcano plot showing differentially expressed genes ($q < 0.1$ and $|FC| \geq 1.5$) in matched paired biopsies on treatment with MICVO compared to baseline. Over-representation analysis of genes with higher expression on treatment using the GO gene set collection **(B)** and REACTOME gene set collection **(C)**.

Conclusions

- Collectively, these results support MICVO's ability to mobilize an anti-tumor immune response in participants with solid tumors, which associates with improved clinical outcome, and confirm preclinical observations [Posters A112 & A115].
- MICVO's induction of T-cell infiltration, as well as elevated immune gene expression signatures, in participants' tumors provide further rationale for the ongoing clinical trial in combination with pembrolizumab across cancer types and are supported by preclinical studies [Poster A115].
- MICVO's ability to remodel the tumor stroma is also under investigation in these biopsies [Poster A113].
- These pharmacodynamic responses will be further characterized in tumor-specific expansion cohorts from the ongoing clinical evaluation of MICVO as monotherapy (NCT05720117) and in combination with pembrolizumab (NCT06795412).

References
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