Abstract 1004eP

Longitudinal changes in circulating tumor DNA in a phase 1 dose escalation study of micvotabart pelidotin, a first-in-human ADC targeting EDB+FN

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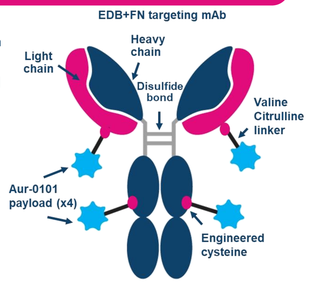
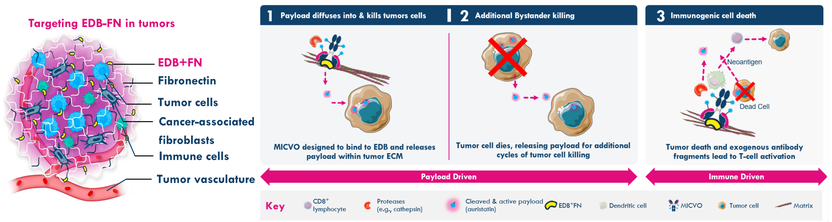
Background

- Micvotabart pelidotin (PYX-201, aka MICVO) 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. The study 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.
- Longitudinal circulating tumor DNA (ctDNA) profiling is increasingly being utilized as an aid to monitor treatment response, with changes serving as a quantitative measurement of molecular response[4].
- **Objective: Changes in ctDNA were evaluated as a pharmacodynamic biomarker of response to MICVO in this heterogeneous population consisting of different tumor types treated at different dose levels.**

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

- 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

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 & tumor tissue biomarkers

*No participant with renal cancer was dosed in this Phase 1 study

Methods

- Blood was collected from trial participants at baseline, within +/- 7 days of pre-dose cycle 3 day 1(C3D1) of treatment, and at the end of treatment.
- Plasma cell-free DNA (cfDNA) was extracted and analyzed using Tempus' xF+ liquid biopsy assay and associated algorithms.
- Paired (n = 37 of 65 efficacy evaluable participants with measurements for both timepoints) samples were assessed for longitudinal changes in ctDNA tumor fraction (ctDNA TF), as well as blood tumor mutation burden (bTMB) with MICVO treatment.
- Best overall response (BOR) and overall response at first on-treatment scan were per RECIST v1.1 criteria and as of October 4th, 2024.
- Paired samples Wilcoxon test with alternate hypothesis as "greater" (i.e., baseline values higher than on-treatment) was used to test for significant reduction in measurements with treatment.

Reduction in ctDNA TF was observed after MICVO treatment

Participants with HNSCC across dose levels showed a median reduction of 35.3% in ctDNA tumor fraction around C3D1

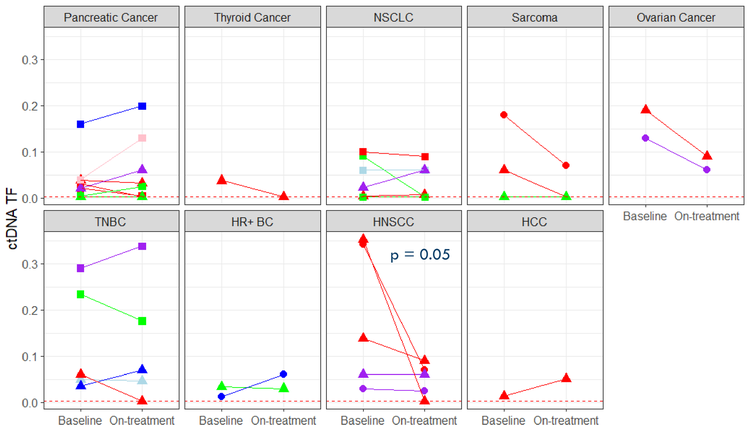


Figure 1: ctDNA TF values at baseline and on-treatment by indication. Paired samples from the same participant are connected by a solid line between the baseline and on-treatment timepoints. Dot shape represents the best overall response for the participant and color represents the dose of MICVO received. Dashed red lines signify the limit of detection of ctDNA TF.

Participants across multiple indications receiving the 5.4 mg/kg dose of MICVO showed a median reduction of 68.5% in ctDNA tumor fraction around C3D1

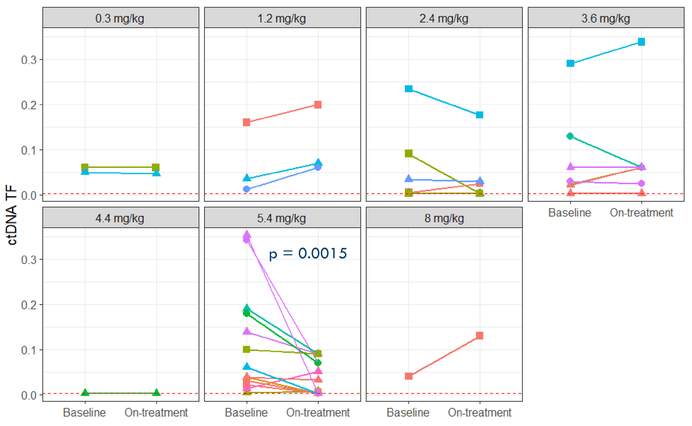


Figure 2: ctDNA TF values at baseline and on-treatment by MICVO dose received. Paired samples from the same participant are connected by a solid line between the baseline and on-treatment timepoints. Dot shape represents the best overall response for the participant and color represents cancer indication. Dashed red lines signify the limit of detection of ctDNA TF.

Reductions in ctDNA tumor fraction were observed in all participants who had a partial overall response at the first radiological scan

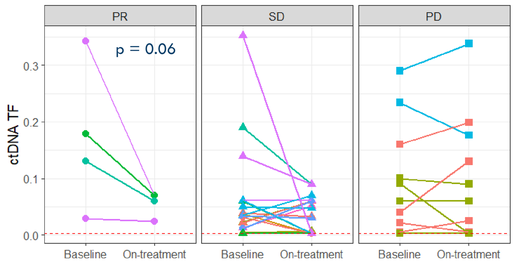


Figure 3: ctDNA TF values at baseline and on-treatment by overall response at first scan. Paired samples from the same participant are connected by a solid line between the baseline and on-treatment timepoints. Color represents cancer indication. Dashed red lines signify the limit of detection of ctDNA TF. First radiological scan occurred around the same time period as the on-treatment ctDNA sample collection.

Minor decrease in bTMB was observed after MICVO treatment

All participants with HNSCC showed a reduction (median = 10.7%) in bTMB around C3D1

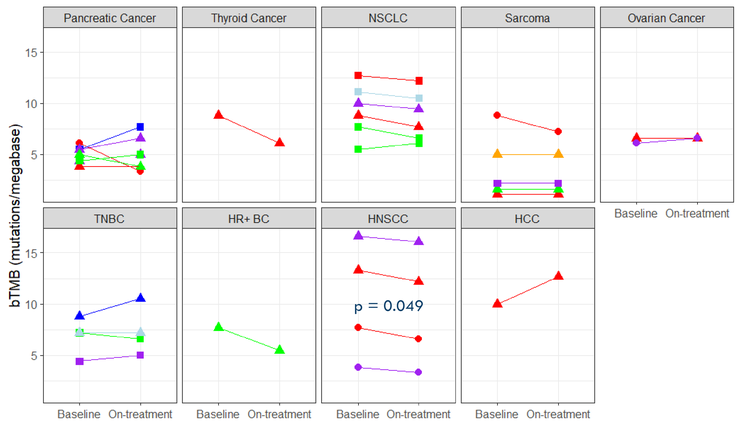


Figure 4: bTMB values at baseline and on-treatment by indication. Paired samples from the same participant are connected by a solid line between the baseline and on-treatment timepoints. Dot shape represents the best overall response for the participant and color represents the dose of MICVO received.

Many participants receiving the 5.4 mg/kg dose of MICVO across indications showed a minor reduction in bTMB around C3D1

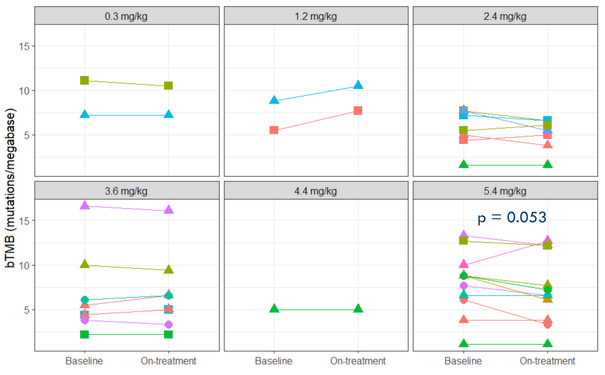


Figure 5: bTMB values at baseline and on-treatment by MICVO dose received. Paired samples from the same participant are connected by a solid line between the baseline and on-treatment timepoints. Dot shape represents the best overall response for the participant and color represents cancer indication.

Key

BOR
- PR
- SD
- PD

Dose
- 0.3 mg/kg
- 1.2 mg/kg
- 2.4 mg/kg
- 3.6 mg/kg
- 4.4 mg/kg
- 5.4 mg/kg
- 8 mg/kg

Indication
- Pancreatic Cancer
- Thyroid Cancer
- NSCLC
- Sarcoma
- Ovarian Cancer
- TNBC
- HR+ BC
- HNSCC
- HCC

Summary & Conclusions

- Plasma cfDNA was profiled from a heterogeneous population consisting of different tumor types, and treated with MICVO at different dose levels, at baseline and with treatment.
- Reductions in ctDNA TF, around C3D1 of treatment compared to baseline, occurred both in participants with HNSCC and in the cohort dosed at 5.4 mg/kg.
  - ➢ Supports a positive molecular response to MICVO, as ctDNA TF is a surrogate for tumor burden.
  - ➢ Provides further support for the 5.4 mg/kg dose, the dose level determined to be safe and well tolerated with preliminary signs of efficacy that has been selected for Part 2 of the study.
- bTMB showed decrease with treatment within the HNSCC cohort and a trend of reduction in the cohort dosed at 5.4 mg/kg.
  - ➢ Further exploration of the implication of this signal will be investigated.
- Further characterization of ctDNA as a minimally invasive liquid biomarker of pharmacodynamic response to MICVO will be performed in tumor specific expansion cohorts.

ABBREVIATIONS

HCC = Hepatocellular carcinoma
HNSCC = Head and neck squamous cell carcinoma
NSCLC = Non-small-cell lung cancer
TNBC = Triple-negative breast cancer
PR = Partial response
SD = Stable disease
PD = Progressive disease
HR+ BC = HR+ breast cancer

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4. Showbaki et al., Journal for Immunotherapy of Cancer. 2023;11(2):e005854.

DECLARATIONS OF INTEREST

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Advisory boards: Eisai, ADC Therapeutics, Abbvie

CONTACT

For additional questions on the study, please contact Marsha Crochiere (mcrochiere@pyxisoncology.com)

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