Presentation #965P

First-in-Human Study of the First-in-Class Non-cellular Targeting Antibody-Drug Conjugate (ADC), Micvotabart Pelidotin (MICVO), in Patients With Select Solid Tumors

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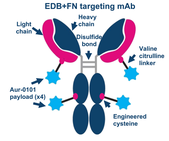
BACKGROUND

- 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[1]
- EDB+FN is overexpressed in several solid tumor types yet negligibly present in healthy adult tissues, making it a promising therapeutic target[1,2]
- MICVO is composed of a fully human IgG1 monoclonal antibody conjugated to an optimized Auristatin-0101 payload via a cleavable linker (DAR of 4)[3,4]
- MICVO is designed to achieve anti-tumor activity via three mechanisms of action: 1) the cell-permeable Auristatin-0101 payload directly kills tumor cells by disrupting microtubule formation, 2) the payload promotes additional tumor cell killing via a bystander effect, and 3) release of neoantigens from dying tumor cells induces immunogenic cell death
- In preclinical studies, MICVO demonstrated broad antitumor activity across 10 solid tumor patient-derived xenograft models[5]
- Exploratory biomarker analyses for EDB+FN protein expression in participant baseline tumor biopsies and longitudinal changes in ctDNA from blood are presented in ESMO ePosters 1014eP and 1004eP



Mechanism of Action for MICVO (Micvotabart Pelidotin)

Targeting EDB-FN in Tumors

STUDY DESIGN

- 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
- Patients were treated with MICVO IV Q3W until unacceptable toxicity or disease progression

Part 1 Dose Escalation

Key Eligibility Criteria

- All-comers with no biomarker selection
- Histologically or cytologically confirmed solid tumors
- Locally advanced recurrent / metastatic disease that 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 and Endpoints

Primary
- Safety and 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

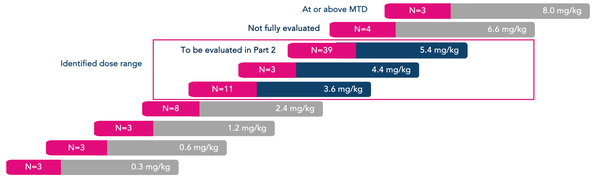
Exploratory
- Blood and tumor tissue biomarkers

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

PATIENT DISPOSITION

- Data from Part 1 dose escalation of the study is reported
- As of 04Oct2024, a total of 77 participants were treated with MICVO across 9 dose levels ranging from 0.3-8.0 mg/kg IV Q3W during the dose escalation part of the study (**Figure** 1)
- Median treatment duration: 85 days (12 weeks)
- The dose escalation part of the study identified the range of potentially effective doses to be 3.6-5.4 mg/kg

Figure 1. Enrollment in the Dose Escalation Part of Study



RESULTS

Antitumor Activity

- In the efficacy evaluable population across all dose levels, responses were seen in 6 of the tumor types evaluated including HNSCC, ovarian cancer, sarcoma, PDAC, NSCLC, and HR+ BC (**Figure** 2)
- In the identified dose range (3.6-5.4 mg/kg) in 6 responding tumor types (N=31), ORR was 26%
- In HNSCC, in the efficacy evaluable set across the 3.6-5.4 mg/kg dose range (N=6), confirmed ORR was 50% (2 PR, 1 CR) and DCR was 100% by RECIST 1.1, with responses in both HPV+ and HPV- participants; 4/6 (67%) participants were on treatment as of data cutoff (**Figure** 3)

Figure 2. Tumor Response in Participants Treated With MICVO (All Dose Levels) (Efficacy Evaluable Set)

Numbers on each bar represent dose level in mg/kg.
Efficacy population (N=63): dose level for patients who escalated or de-escalated = starting dose.
12/77 patients not included in the waterfall for the following reasons: 3 patients had their 1st scan after data cutoff, 1 patient's scan was delayed beyond protocol-allowable timeframe, 3 patients discontinued prior to 1st scan due to non-TRAEs, 1 patient withdrew from study prior to 1st scan, and 4 patients discontinued due to clinical progression prior to 1st scan.
*Confirmed response as of 04Oct2024 data cutoff. **Confirmed response after 04Oct2024 data cutoff (-47% tumor regression). ***Confirmed response after 04Oct2024 data cutoff (-73% tumor regression).
†Does not include patient dosed at 5.4 mg/kg who received scan on Day 97 after receiving 1 dose and whose scan was disallowed per protocol due to excessive time between dosing and scan. This patient showed stable disease with -15.5% tumor reduction after 1 dose given 97 days prior to the scan.

Pharmacokinetics

- MICVO is engineered with site-specific conjugation to Auristatin-0101 via a protease-cleavable mcValCitPABC linker, which improves linker-payload stability resulting in lower levels of free payload in circulation and a longer half-life compared to conventionally conjugated ADCs
- Plasma PK was dose linear
- The half-life of MICVO at 5.4 mg/kg was ~5.2 days

Figure 4. Plasma PK of MICVO Across All Dose Levels in Dose Escalation

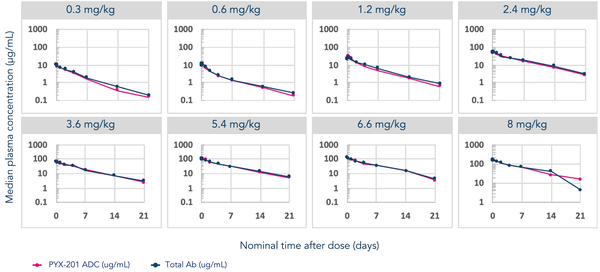
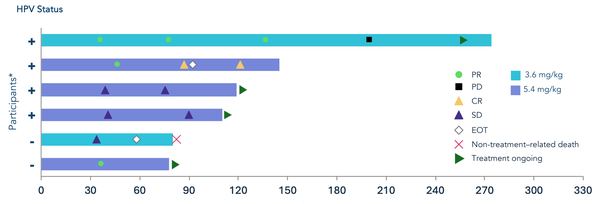


Figure 3. Tumor Response in HNSCC Participants Treated With MICVO at the Identified Dose Range (3.6-5.4 mg/kg) (Efficacy Evaluable Set, N=6)



*Does not include patient dosed at 5.4 mg/kg who received scan on Day 97 after receiving 1 dose and whose scan was disallowed per protocol due to excessive time between dosing and scan. This patient showed stable disease with -15.5% tumor reduction after 1 dose given 97 days prior to the scan.

Baseline Characteristics

- This was a heterogeneous patient population with 9 tumor types evaluated
- Patients were heavily pretreated, with a median of 4 prior lines of therapy

Table 1. Demographics and Baseline Characteristics (Safety Analysis Set)

Demographics	Total (N=77)
Race	n (%)
Asian	6 (8)
Black or African American	5 (6)
White	56 (73)
Other/unknown/not reported	10 (13)
Age	Years
Median (min-max)	65 (34-81)
Baseline weight	kg
Median (min-max)	68 (39-117)

Prior Therapy	Total (N=77)
Prior lines of cancer therapy	Count
Median (min-max)	4 (0-10)
Prior therapy type	n (%)
Taxane	55 (71)
Platinum	53 (69)
IO agent	33 (43)
ADC agent*	14 (18)

Disease Characteristics	Total (N=77)
Cancer type	n (%)
PDAC	17 (22)
NSCLC	14 (18)
Sarcoma	11 (14)
HNSCC	9 (12)
TNBC	9 (12)
Ovarian cancer	8 (10)
HR+ breast cancer	4 (5)
Thyroid cancer	4 (5)
HCC	1 (1)
Renal cancer	0 (0)
Baseline ECOG PS	n (%)
0	31 (40)
1	46 (60)
Time from initial diagnosis	Years
Median (min-max)	3 (0.2-36)

*Includes sacituzumab govitecan, trastuzumab deruxtecan, IMG-151 (FRα ADC), ifinatamab deruxtecan, ELU001 (FRα ADC), ASN004 (5T4 ADC).

Safety

- MICVO was generally well tolerated with a manageable safety profile. The observed safety signals are consistent with known toxicities associated with other ADCs with auristatin payloads
- As of 04Oct2024, the majority of TRAEs were of low grades (**Table 2**)
- There were no treatment-related deaths (**Table 2**)
- The most common auristatin payload-related TRAEs were cutaneous toxicity (skin rash), peripheral neuropathy, and neutropenia (**Table 3**)
- No grade 3/4 treatment-related ocular toxicity or neuropathy was observed

Table 2. TRAEs in the Dose Escalation Part of the Study (Safety Analysis Set)

	Identified Dose Range								
	0.3 mg/kg	0.6 mg/kg	1.2 mg/kg	2.4 mg/kg	3.6 mg/kg	4.4 mg/kg	5.4 mg/kg	6.6 mg/kg	8.0 mg/kg	TOTAL
N	3	3	3	8	11	3	39	4	3	77
All TRAEs, n (%)	1 (33)	1 (33)	3 (100)	6 (75)	9 (82)	3 (100)	36 (92)	4 (100)	3 (100)	66 (86)
Grade 1/2 TRAEs, n (%)	1 (33)	1 (33)	3 (100)	4 (50)	8 (73)	2 (67)	22 (56)	1 (25)	2 (67)	44 (57)
Grade 3/4 TRAEs, n (%)	0	0	0	2 (25)	1 (9)	1 (33)	14 (36)	3 (75)	1 (33)	22 (29)
TRAEs leading to treatment discontinuation, n (%)	0	0	0	0	0	0	1 (3)*	0	0	1 (1)
TRAEs leading to dose reduction, n (%)	0	0	0	1 (13)	1 (9)	0	11 (28)	1 (25)	1 (33)	15 (20)
TRAEs leading to dose delay, n (%)	0	0	0	1 (13)	0	0	7 (18)	3 (75)	1 (33)	12 (16)
Dose-limiting toxicity, n (%)	0	0	0	0	0	0	3 (8)†	1 (33)‡	1 (33)‡	5 (6)
Treatment-related deaths (grade 5), n (%)	0	0	0	0	0	0	0	0	0	0

*Discontinuation due to grade 3 pneumonitis in a heavily pretreated patient with NSCLC.
†3 TRAEs: grade 3 neutropenic enterocolitis (n=1), grade 2 dehydration (n=1), and grade 2 myalgia (n=1).
‡TRAE: grade 4 hyponatremia.
§Non-TRAE: grade 5 sepsis.

Table 3. Most Common Grade 3/4 TRAEs (Safety Analysis Set)

	Identified Dose Range								
	0.3 mg/kg	0.6 mg/kg	1.2 mg/kg	2.4 mg/kg	3.6 mg/kg	4.4 mg/kg	5.4 mg/kg	6.6 mg/kg	8.0 mg/kg	TOTAL
N	3	3	3	8	11	3	39	4	3	77
Auristatin payload-related toxicity, n (%)										
Cutaneous*	0	0	0	0	0	0	3 (8)	0	0	3 (4)
Neuropathy	0	0	0	1 (13)	0	0	0	1 (25)	0	2 (3)
Neutropenia	0	0	0	0	0	0	3 (8)	1 (25)	1 (33)	5 (6)
Ocular	0	0	0	0	0	0	0	0	0	0
Non-payload-related toxicity, n (%)										
Anemia†	0	0	0	0	0	0	2 (5)	2 (50)	0	4 (5)
Pneumonitis†	0	0	0	0	0	0	1 (3)	0	0	1 (1)
Other	All other non-payload-related grade 3/4 toxicities with a frequency of <5%									

*Reversible and easily treated; not immunologically mediated. Limited to skin surface; no mucosal membrane involvement and no desquamation involvement.
†AEs of interest for ADC. Grade 3 pneumonitis occurred in a heavily pretreated patient with NSCLC who discontinued therapy.

CONCLUSIONS

- MICVO was generally well tolerated in the Phase 1 Part 1 dose escalation study, with a low incidence of dose discontinuation, interruptions, or delays due to TRAEs, and a low rate of grade 3/4 payload-related TRAEs
- 3.6-5.4 mg/kg is the identified dose range
- Promising antitumor activity was seen in multiple tumor types of high unmet medical need
- MICVO monotherapy achieved significant clinical response in 3 out of 6 heavily pretreated patients with recurrent/metastatic HNSCC at the identified dose range of 3.6-5.4 mg/kg Q3W, including 1 patient with a confirmed CR and 2 patients with confirmed PRs by RECIST v1.1
- Based on the totality of safety and antitumor activity date, 5.4 mg/kg was selected as the dose for expansion. The dose expansion part of the PYX-201-101 study is ongoing, prioritizing HNSCC due to the high medical need in this disease state. Data are maturing
- Combination treatment with MICVO and pembrolizumab is currently being evaluated in Phase 1 trials for patients with recurrent/metastatic HNSCC and other advanced solid tumors for potential enhanced antitumor activity (NCT06795412)

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

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ABBREVIATIONS

ADC, antibody-drug conjugate; AEs, adverse events; BC, breast cancer; CR, complete response; CRO, contract research organization; DAR, drug:antibody ratio; DCR, disease control rate; DOR, duration of response; ECM, extracellular matrix; ECOG PS, Eastern Cooperative Oncology Group performance status; EDB+FN, extra-domain-B of fibronectin; EOT, end of treatment; FRα, folate receptor α; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; HPV, human papillomavirus; HR+, hormone receptor positive; IO, immuno-oncology drug; IV, intravenous; mAb, monoclonal antibody; MICVO, micvotabart pelidotin; MTD, maximum tolerated dose; NSCLC, non-small cell lung cancer; ORR, objective response rate; PD, progressive disease; PDAC, pancreatic ductal adenocarcinoma; PK, pharmacokinetics; PR, partial response; Q3W, every 3 weeks; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; SOC, standard of care; TNBC, triple negative breast cancer; TRAEs, treatment-related adverse events; TTR, time to response.

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DECLARATIONS OF INTEREST

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