1025eTiP

A Phase 1/2 Study of a First-in-Class Non-Cellular Antibody-Drug Conjugate, Micvotabart Pelidotin (MICVO), in Combination with Pembrolizumab in Select Advanced Solid Tumors

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BACKGROUND

- Antibody-drug conjugates (ADCs) are transforming cancer therapy; combination of ADCs with checkpoint immunotherapy has also demonstrated enhanced clinical benefit in several tumor types (1, 2, 3).
- Micvotabart pelidotin (PYX-201, aka MICVO) is a first-in-concept 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).
- 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, 4).
- EDB+FN is overexpressed in several solid tumor types yet negligibly present in healthy adult tissues, making it a promising therapeutic target (5).
- In preclinical studies, MICVO demonstrated broad anti-tumor activity in patient-derived xenograft (PDX) models across numerous solid tumor indications (6).
- A mouse analog of MICVO showed monotherapy anti-tumor activity and combination with anti-PD-1 resulted in superior tumor clearance in a syngeneic triple negative breast cancer model (7).
- MICVO as a single agent 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 treatment related adverse events (TRAEs), and a low rate of Grade 3 or 4 payload-related TRAEs. (ESMO Poster 965P).
- MICVO demonstrated single-agent activity confirmed by RECIST 1.1 in heavily pretreated R/M HNSCC patients (cORR=50%, cDCR=100%) within the 3.6-5.4 mg/kg IV Q3W identified dose response range (ESMO Poster 965P).
- MICVO is being evaluated for safety, tolerability, pharmacokinetics, pharmacodynamics, and antitumor activity in patients with select advanced solid tumors in a Phase 1 monotherapy study (PYX-201-101, NCT05720117, ESMO 1031eTiP).
- The current trial-in-progress is a Phase 1/2 study of MICVO in combination with pembrolizumab in patients with R/M HNSCC and other advanced solid tumors (PYX-201-102, NCT06795412), enrolling in Part 1.

MICVO CONSTRUCT AND MECHANISM OF ACTION

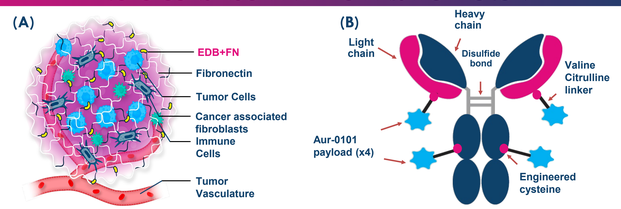

Figure 1: (A) The extradomain-B splice variant of fibronectin (EDB+FN) is a non-cellular structural component of the extracellular matrix (ECM) that is highly differentially expressed in several solid tumors. (B) MICVO is an anti-EDB+FN, fully human IgG1 mAb engineered with site-specific conjugation to Auristatin-0101 via a protease-cleavable mcVal Cit PABC linker, enhancing linker-payload stability and reducing off-target toxicities compared to conventionally conjugated ADCs.

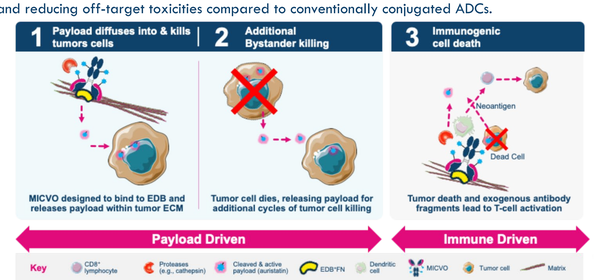

Figure 2: MICVO is designed to achieve anti-tumor activity via three mechanisms of action: 1) the cytotoxic, cell-permeable Auristatin-0101 payload directly kills tumor cells through disruption of microtubule formation, 2) the payload promotes additional tumor cell killing via the bystander effect, and 3) release of neoantigens from dying tumor cells induces immunogenic cell death.

STUDY DESIGN

Study Design

ESCALATION

1L or 2L+ R/M HNSCC, TNBC, HR+/HER2- Breast Cancer, Gastric Cancer, Cervical Cancer and Sarcoma

BACKFILL

Cohorts focused on R/M HNSCC

Part 1: Dose Escalation
micvotabart pelidotin q3w + pembrolizumab 200 mg q3w

- 5.4 mg/kg + 200 mg → 5.4 mg/kg Backfill
- 4.4 mg/kg + 200 mg → 4.4 mg/kg Backfill
- 3.6 mg/kg + 200 mg → 3.6 mg/kg Backfill

Part 2
Dose Expansion

Part 2 dose expansion cohorts will be opened based on emerging Part 1 dose escalation data

Key Eligibility Criteria

Key Inclusion Criteria

- Male or non-pregnant, non-lactating female participants age ≥18 years
- ECOG PS of 0-1
- Life expectancy of >3 months, in the opinion of the investigator
- At least one measurable, non-irradiated lesion *(RECIST v1.1)*
- **1L HNSCC*** (with PDL1 CPS ≥1)
- **2L+ HNSCC**

Locally advanced/refractory:

- **Triple Negative Breast Cancer**
- **HR+ and HER2-** (IHC 0, IHC 1+ or IHC 2 +/ISH-) **Breast Cancer**
- **Gastric or GEJ** (adenocarcinoma only)
- **Cervical** (adeno, adenosquamous, SCC only)
- **Sarcoma** (chordoma, LMS, EES, UPS and osteosarcoma only)

**Participants must not have received prior systemic therapy for advanced or metastatic HNSCC with the following 3 exceptions: a) neoadjuvant chemotherapy and/or immunotherapy with recurrence >12 months from completion of therapy, b) adjuvant chemotherapy and/or immunotherapy following surgical resection with recurrence >12 months from completion of therapy, c) prior concurrent chemoradiation with recurrence >6 months is permitted.*

Key Exclusion Criteria

- Known active CNS metastases
- Known active HBV, HCV, HIV or AIDS
- Failure to recover to CTCAEv5.0 G≤1 from acute non-hematologic toxicity due to previous therapy
- History of noninfectious pneumonitis/ILD that required steroids or are under current treatment
- Contraindications to receive pembrolizumab

STUDY DESIGN CONTINUED

Study Treatment

Micvotabart Pelidotin (aka MICVO) IV Q3W + **Pembrolizumab 200 mg IV Q3W**

Treatment may continue until:

- Radiographically documented evidence of disease progression*
- Clinical disease progression
- Unacceptable toxicity
- The start of new anticancer treatment
- Study discontinuation
- Any other criteria for withdrawal from the study or study drug
- Reaching a maximum of 2 years of treatment duration.

*Treatment beyond disease progression may be considered in participant who are deriving clinical benefit based on mutual agreement between Investigators and the Sponsor.

Study Objectives and Endpoints

	Objectives	Endpoints
PRIMARY	• Determine RP2D and MTD of MICVO in combination with pembrolizumab	• DLT Rate • Incidence of AEs characterized overall and by type, seriousness, relationship to study treatment, timing and severity graded according to the NCI-CTCAE v5.0 • Change in clinical laboratory parameters, vital signs, and ECG parameters
SECONDARY	• Evaluate preliminary efficacy • Assess PK profile • Characterize immunogenicity	• ORR, DOR, DCR, CBR, TTR by Investigator per RECIST v 1.1 • PK parameters: C_{max}, T_{max}, CL, AUC_{0-tf}, AUC_{tau}, AUC_{0-inf}, and $t_{½}$ for ADC, tAb, and free payload • Incidence of anti-MICVO antibodies
EXPLORATORY	• Explore predictive and pharmacodynamic biomarkers • Explore preliminary survival outcomes	• Exploratory biomarkers: protein, RNA, & DNA analyses • PFS, OS • Expression of EDB+FN • Expression of PD-L1

Link to CT. gov (NCT05720117)

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ABBREVIATIONS

ADC: Antibody-Drug Conjugate
AIDS: Acquired Immune Deficiency Syndrome
AUC_{0-tf}: Area Under the Concentration-Time Curve from time zero extrapolated to infinity
AUC_{tau}: Area Under the Concentration-Time Curve from time zero to time
AUC_{0}: Area Under the Concentration-Time Curve over a dosing interval
BC: Breast Cancer
CBR: Clinical Benefit Rate
CL: Clearance
C_{max}: Maximum Observed Concentration
CNS: Central Nervous System
CPS: Combined Positive Score
DAR: Drug-Antibody Ratio
DLT: Dose Limiting Toxicity
DNA: Deoxyribonucleic Acid
DOR: Duration of Response
ECG: Electrocardiogram
ECM: Extra-cellular Matrix
ECOG: Eastern Cooperative Oncology Group
EDB+FN: Extra Domain-B Fibronectin
EES: Endometrial Stromal Sarcoma
ESMO: European Society for Medical Oncology
GC: Gastric Carcinoma
GEJ: Gastroesophageal Junction
HER2: Human Epidermal Growth Factor Receptor 2 Negative
HBC: Hepatitis B Virus
HCV: Hepatitis C Virus
HIV: Human Immunodeficiency Virus
HNSCC: Head and Neck Squamous Cell Carcinoma
HR+: Hormone Receptor Positive
IHC: Immunohistochemistry
IgG1: Immunoglobulin G1
ILD: Interstitial Lung Disease
ISH: In Situ Hybridization
IV: Intravenous
LMS: Leiomyosarcoma
MICVO: Micvotabart Pelidotin
MTD: Maximum Tolerated Dose
NCI-CTCAE: National Cancer Institute – Common Terminology Criteria for Adverse Events
ORR: Overall Response Rate
OS: Overall Survival
PFS: Progression Free Survival
PK: Pharmacokinetics
Q3W: Every 3 weeks
RECIST: Response Evaluation Criteria in Solid Tumors
RNA: Ribonucleic Acid
RP2D: Recommended Phase 2 Dose
R/M: Recurrent / Metastatic
$t_{½}$: Half-life
T_{ab}: Total Antibody
T_{max}: Time to Reach Maximum Concentration
TNBC: Triple-Negative Breast Cancer
TEAE: Treatment-Related Adverse Events
TTR: Time to Response
UPS: Undifferentiated Pleomorphic Sarcoma

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DECLARATIONS OF INTEREST

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