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Phase 1 Expansion Study of the First-in-Concept Extracellular Antibody-Drug Conjugate (ADC), Micvotabart Pelidotin (MICVO), in Patients with 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 recurrent/metastatic HNSCC patients (cORR=50%, cDCR=100%) within the 3.6-5.4 mg/kg IV Q3W identified dose response range (ESMO Poster 965P).
- The current trial-in-progress is a Phase 1 dose-expansion study of MICVO monotherapy in patients with previously treated recurrent/metastatic HNSCC.
- A Phase 1/2 study of MICVO in combination with pembrolizumab in patients with R/M HNSCC and other advanced solid tumors is ongoing (NCT06795412).

MICVO CONSTRUCT AND MECHANISM OF ACTION

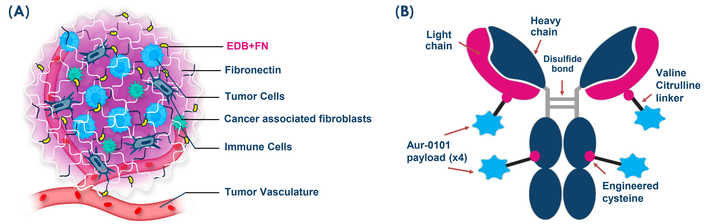

Figure 1: (A) The extradomain-B splice variant of fibronectin (EDB+FN) is a non-cellular structural component of the extracellular matrix (ECM) that is highly differentially expressed in several solid tumors. (B) MICVO is an anti-EDB+FN, fully human IgG1 mAb engineered with site-specific conjugation 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.

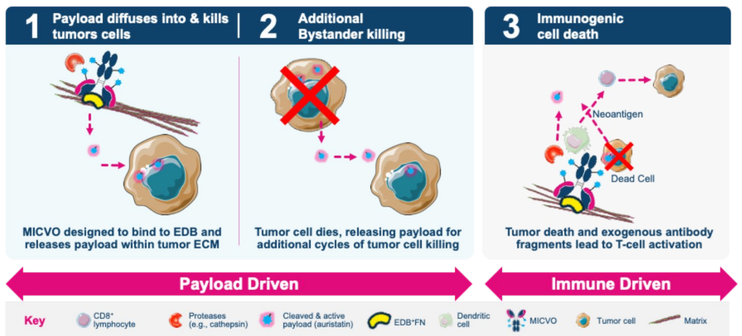

Figure 2: MICVO is designed to achieve anti-tumor activity via three mechanisms of action: 1) the cytotoxic, cell-permeable Auristatin-0101 payload directly kills tumor cells through disruption of microtubule formation, 2) the payload promotes additional tumor cell killing via the bystander effect, and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

STUDY DESIGN

Overview

Design: Phase 1, first-in-human, open-label, multicenter, non-randomized, dose-expansion study.

Target Population: Participants with recurrent/metastatic HNSCC tumors that have relapsed, been non-responsive, or have progressed through select standard of care regimens.

Study Treatment: MICVO will be administered intravenously (IV) Q3W at a dose of 5.4 mg/kg. Treatment continues until radiographically documented evidence of disease progression per RECIST v 1.1, clinical progression, unacceptable toxicity, the start of new anticancer treatment, study discontinuation, or any other criteria for withdrawal from the study or study drug, or for a maximum of 2 years, whichever occurs first.

Expansion Cohorts – Treatment with MICVO 5.4 mg/kg IV Q3W

N≈20	HNSCC 2/3L Post PD1 inhibitor + platinum-based therapy
N≈20	HNSCC 2/3L Post PD1 inhibitor + EGFR-directed therapy

Key Inclusion Criteria

- Histologically or cytologically confirmed squamous cell carcinoma
- Locally advanced recurrent/metastatic disease progression on SoC
- RECIST v1.1 measurable disease
- ECOG PS 0-1
- HNSCC patients must have received at least 1 but no more than 2 prior lines of systemic therapy for recurrent and/or metastatic disease, with oropharynx, oral cavity, hypopharynx, or larynx as primary tumor locations:
  - Arm 1: have received platinum-based therapy and a PD-1 inhibitor
  - Arm 2: have received one prior PD-1 inhibitor and one prior EGFR-directed therapy

Key Exclusion Criteria

- Primary HNSCC tumor sites of nasopharynx or sinonasal (any histology)
- Any active or prior CNS metastases
- Known active HBV, HCV, HIV or AIDS
- Failure to recover to CTCAE v5.0 G≤1 from acute non-hematologic toxicity due to previous therapy
- Previous or active pneumonitis / interstitial lung disease (ILD) requiring steroids

	Objectives	Endpoints
PRIMARY	• Determine the ORR	• ORR by Investigator per RECIST v. 1.1
SECONDARY	• Evaluate antitumor activity • Assess PK • Evaluate safety profile • Characterize immunogenicity	• DOR, DCR, CBR, TTR by Investigator per RECIST v. 1.1 • PK parameters: C_{max}, T_{max}, C_{trough} • Incidence of AEs characterized overall and by type, seriousness, relationship to study treatment, timing, and severity • Change in clinical laboratory parameters and vital signs • Incidence of ADAs
EXPLORATORY	• Explore predictive and pharmacodynamic biomarkers • PROs	• Expression of EDB+FN • Exploratory biomarkers • General changes to PRO measures

Study of PYX-201 in Solid Tumors
NCT05720117

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ABBREVIATIONS
MMAE: Monomethyl Auristatin E
ADC: Antibody-drug conjugates
EDB+FN: extra-domain-B fibronectin
PDX: patient-derived xenograft
TRAEs: treatment related adverse events

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DECLARATIONS OF INTEREST
DRP received honorarium or funds for advisory/consulting from: None

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