A First-in-Human Phase 1 Clinical Study Evaluating Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of the EDB+FN targeting ADC PYX-201 in Participants with Advanced Solid Tumors

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Abstract #: 762

BACKGROUND

Fibronectin (FN) is a ubiquitously expressed, high-molecular-weight, extracellular matrix glycoprotein. The extra domain B splice variant of FN (EDB+FN) is a novel therapeutic target that is upregulated in the tumor microenvironment (TME) of multiple solid tumor types with restricted expression in normal tissues.

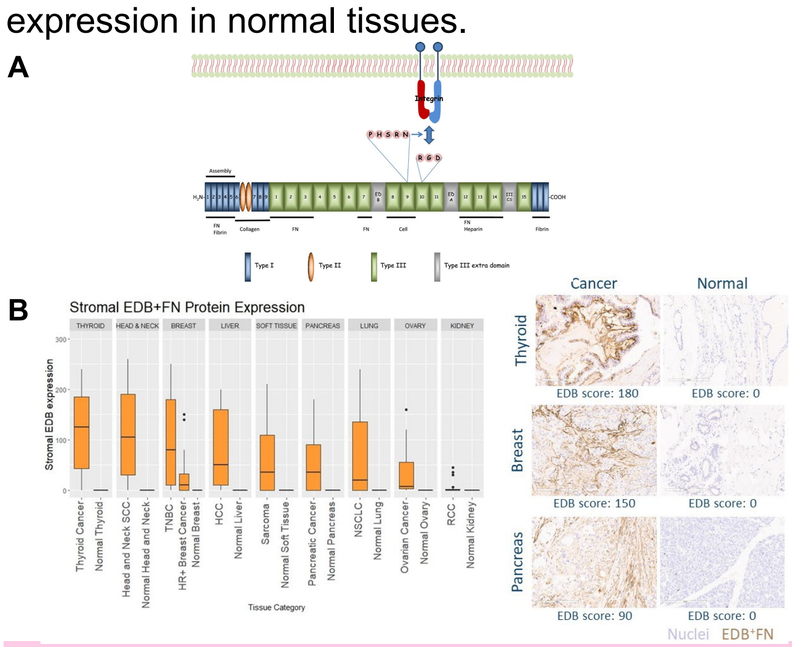


Figure 1: Expression of EDB+FN. A) Overview of extra domain B of FN (1). FN contains repeats of 3 types of domains: types I, II, and III. EDB+FN is a type III domain of 91 amino acids inserted between FN domains 7 and 8 of the oncofetal FN isoform. B) Immunohistochemistry (IHC) analysis demonstrates EDB+FN protein is highly differentially expressed in tumor stroma versus normal tissue

RATIONALE

PYX-201 is an investigational antibody-drug conjugate (ADC) consisting of an EDB+FN-targeting monoclonal antibody engineered for site-specific conjugation to vc0101, which showed improved linker-payload stability and bystander activity in preclinical studies (2). The linker-payload vc0101 is completely synthetic and, via a cleavable linker, delivers auristatin PF-06380101 (Aur0101), a microtubule depolymerizing agent with potent anti-mitotic and cytotoxic properties. PYX-201 induced tumor regression in xenograft mouse models of non-small cell lung cancer and pancreatic cancer. In a syngeneic model of breast cancer, a mouse analog of PYX-201 induced upregulation of PD-L1 and infiltration of CD3+ T cells in tumors (2).

The PYX-201-101 clinical trial is in progress in participants with advanced cancers (NCT05720117).

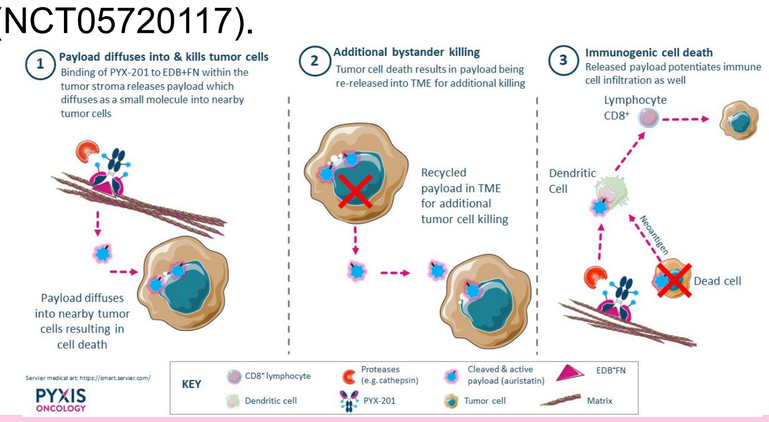


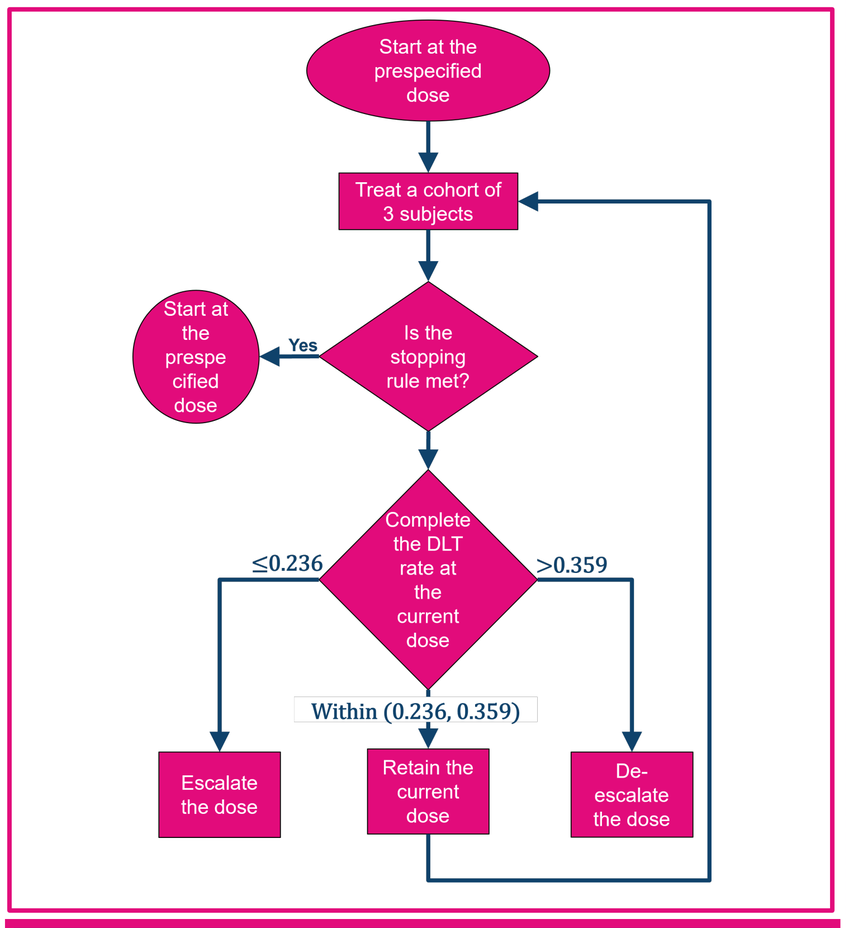
Figure 2: PYX-201 may have multiple mechanisms of action: 1) promoting cell destruction by directly binding to EDB+FN, 2) releasing payload into the TME and nearby cancer cells, and 3) potentiating immune cell infiltration upon release of the payload.

STUDY DESIGN

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

Target Population: Participants with advanced solid tumors who have relapsed, been non-responsive, or have progressed with all available therapies, with a focus on those tumor types known to have expression of the target antigen

Sample Size: Up to 45 subjects (including backfill enrollment) will be enrolled into the dose escalation cohorts



INDICATIONS

Non-small cell lung cancer	Head and Neck Squamous Cell Cancer
Pancreatic Ductal Adenocarcinoma	Ovarian cancer
Hepatocellular Carcinoma	Thyroid cancer
Soft Tissue Sarcoma	Kidney cancer
Breast Cancer (hormone receptor positive (HR+) and human epidermal growth factor receptor 2 (HER2)- breast cancer, HR- and HER2+ breast cancer, triple negative breast cancer)	

OBJECTIVES

Primary Objective:

- To determine the recommended dose(s) of PYX-201 for participants with relapsed or refractory solid tumors

Secondary Objectives:

- To characterize the PK profile of PYX-201 as a single agent
- To evaluate the preliminary antitumor activity of treatment with PYX-201 at the recommended dose(s) of PYX-201
- To evaluate the immunogenicity of PYX-201 as measured by the incidence of ADAs in participants treated with PYX-201

Exploratory Objectives:

- To explore predictive and pharmacodynamic biomarkers of response to PYX-201

ENDPOINTS

Primary Endpoints:

- Dose Limiting Toxicity rate
- Incidence of adverse events characterized overall and by type, seriousness, relationship to study treatment, timing, and severity graded according to the NCI-CTCAE Version 5.0
- Change in clinical laboratory parameters, vital signs, and ECG parameters

Secondary Endpoints:

- Single-dose and multiple-dose PK parameters (such as C_{max}, t_{max}, AUC_{0-t}, AUC_{T}, $AUC_{0-\infty}$, and $t_{½}$) for antibody and/or relevant metabolites
- Overall Response Rate
- Duration of Response
- Progression Free Survival
- Disease Control Rate (defined as Complete Response, Partial Response, or Stable Disease).
- Time to response (defined as the time from the first dose of PYX-201 to the time of response [CR/PR] first observed)
- Overall Survival
- Incidence of anti-PYX-201 antibodies

Exploratory endpoints:

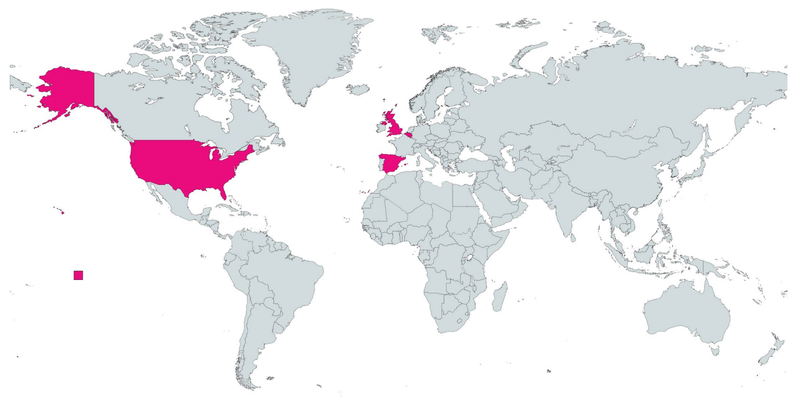
- Evaluate predictive and pharmacodynamic biomarkers of response to PYX-201

STUDY PROGRESS

Enrollment opened:

- February 2023

Up to 20 sites planned to be activated in the Unites States, Spain, Belgium and the United Kingdom



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REFERENCES

1) Nishida T, Inui M, Nomizu M. Peptide therapies for ocular surface disturbances based on fibronectin–integrin interactions. Progress in Retinal and Eye Research. 2015; 47:38-63

2) Hooper, A. T., Marquette, K., Chang, C. P. B., Golas, J., Jain, S., Lam, M. H., ... & Sapra, P. (2022). Anti-extra domain B splice variant of fibronectin antibody–drug conjugate eliminates tumors with enhanced efficacy when combined with checkpoint blockade. Molecular Cancer Therapeutics, 21(9), 1462-1472.

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