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. PYX-201 is an investigational antibody drug conjugate consisting of a site-specific engineered EDB+FN-targeting monoclonal antibody conjugated to vc0101, which shows improved linker-payload stability and bystander activity in preclinical studies. The linker-payload vc0101 is completely synthetic and delivers auristatin PF-06380101 (Aur0101), a microtubule depolymerizing agent with potent anti-mitotic and cytotoxic properties. PYX-201 may have multiple mechanisms of action: promoting cell destruction by directly binding to EDB+FN, releasing payload into the TME and into nearby cancer cells, and potentiating immune cell infiltration upon release of the payload. PYX-201 has been shown to induce tumor regression in xenograft mouse models of non-small cell lung cancer (NSCLC) and pancreatic cancer. In a syngeneic model of breast cancer, a mouse analogue of PYX-201 induced upregulation of PD-L1 and infiltration of CD3+ T cells in tumors.

Methods PYX-201 is being evaluated in a first-in-human, open-label, non-randomized, Phase 1 dose-escalation (Part 1) study in participants with advanced solid tumors. Part 1 utilizes a Bayesian optimal interval design to explore ascending doses of PYX-201 administered as an intravenous infusion to evaluate safety and efficacy and to identify the recommended Part 2 dose(s). The study is designed to characterize safety and pharmacokinetics and will incorporate a robust translational biomarker plan. Upon completion of Part 1 and depending upon data obtained, a Part 2 dose expansion part of the study may be initiated. The PYX-201–101 study began enrolling participants in February 2023 and will be conducted in the US and Europe. Adverse events are assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events Version 5.0 and protocol-specific ophthalmic complications table. Tumor response is determined according to Response Evaluation Criteria in Solid Tumors 1.1 criteria and safety findings are reviewed by the dose escalation steering committee, which will monitor safety and recommends dose(s) for Part 2. The study population will include participants with NSCLC, hormone receptor positive breast cancer, triple negative breast cancer, head and neck squamous cell carcinoma, ovarian cancer, thyroid cancer, pancreatic ductal adenocarcinoma, soft tissue sarcoma, hepatocellular carcinoma, and kidney cancer.

Trial Registration NCT05720117

Reference