A phase 1/2, first-in-human study of STX-478 monotherapy or in combination with fulvestrant in patients with breast cancer or other advanced solid tumors (trial in progress)

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Background

- Phosphoinositide 3-kinase α (PI3Kα) is one of the most commonly mutated genes across multiple cancers[1,2]
- Mutations occur throughout the PI3Kα gene, but hotspot mutations predominate in the helical and kinase domains[1,2]
- Activating PI3Kα mutations are most prevalent in breast, gynecological, and squamous cell cancers of the head and neck[3-6]
- The therapeutic benefit of isoform-selective PI3Kα inhibition was established with alpelisib (PIQRAY®), which has equipotent activity against the wild-type (WT) and mutant enzyme[7]
- Inhibition of WT PI3Kα is associated with severe toxicities, including hyperglycemia, rash, and diarrhea that limit widespread alpelisib use[7]
- By selectively targeting mutant PI3Kα, a potent small-molecule inhibitor could demonstrate an improved safety- and anti-tumor efficacy profile

STX-478: Profile

- STX-478 binds to a novel, cryptic allosteric site present in both mutant and WT PI3Kα isoforms[8]
- STX-478 has activity against the most common PI3Kα kinase-domain mutation H1047R (inhibitory concentration [IC_{50}] = 9.4 nmol/L), with 14-fold selectivity over WT PI3Kα (IC_{50} = 131 nmol/L)[8]
- In a 900-tumor cell line screen, STX-478 selectively inhibited the *in vitro* proliferation of cell lines with kinase-domain and helical-domain mutations compared with cells expressing WT PI3Kα[8]
- *In vivo*, STX-478 monotherapy or STX-478 in combination with fulvestrant and/or cyclin-dependent kinase 4/6 inhibitors showed robust and durable tumor regres- sion in human tumor xenograft models harboring PI3Kα kinase- or helical-domain mutations[8]
- No toxicities indicative of WT PI3Kα inhibition were observed in preclinical animal models within the expected therapeutic STX-478 dose range
- STX-478 entered clinical development with the potential to provide the best-in-class treatment for patients with PI3Kα mutant cancers

Methods

Study Overview

- Multi-part Phase 1/2, first-in-human study ongoing in the USA with expansion into Europe
- Study Design: Traditional 3+3 design for dose escalation with (i) back-fill cohorts and (ii) dose expansion cohorts
- Intra-patient dose escalation allowed
- Study conduct guided by Safety Evaluation Team of participating investigators and sponsor personnel

Study Objectives

- **Primary Objective**: Determine the Optimal Biologic Dose and Maximum Tolerated Dose and select the Recommended Phase 2 Dose of STX-478 administered as (i) monotherapy and (ii) in combination with fulvestrant
- **Secondary Objectives**: Characterize the overall safety, tolerability, pharmacokinetics, and preliminary antitumor activity (including exploratory circulating tumor DNA measurements) of STX-478 administered as (i) monotherapy and (ii) in combination with fulvestrant

Study Therapy

- STX-478 once daily oral dosing
- STX-478 in combination with intramuscular administration of fulvestrant (500 mg) on Days 1, 15, 29 and once monthly thereafter

STX-478: Mechanism of Action

Figure 1. STX-478 – Molecular structure[8]

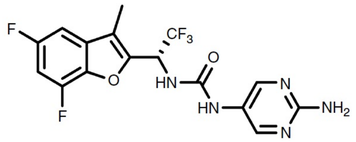


Figure 2. X-ray structure of STX-478 bound in a novel, allosteric site within PI3Kα (p110 purple/silver; p85 orange). Inavolisib bound in the adenosine triphosphate site[8]

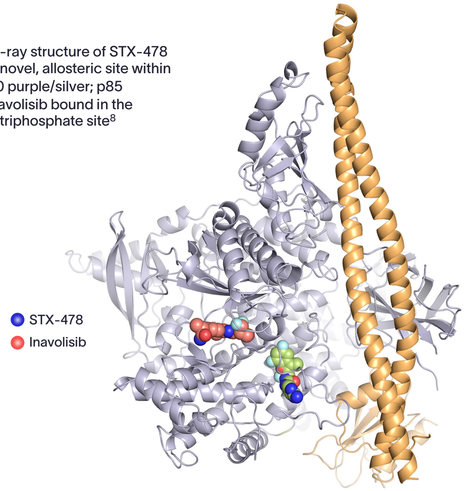
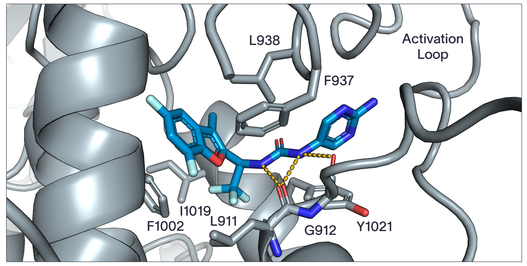


Figure 3. X-ray structure showing facilitated STX-478 binding to the allosteric site by mutation in the kinase domain of PI3Kα[8]



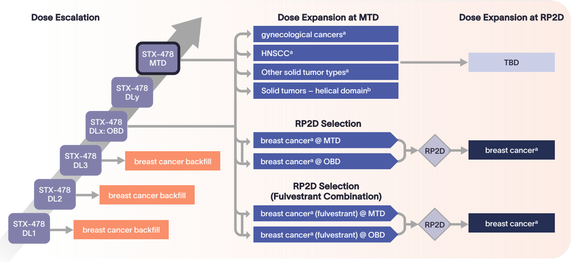
Enrollment

- Recruitment opened in April 2023 and ongoing in the USA
- Expansion to Europe is underway

Study Information

- Clinical Trials.gov: https://clinicaltrials.gov/study/NCT05768139
- Contact clinicaltrials@scorpiontx.com for additional information

Figure 4. Phase 1/2 Study Design



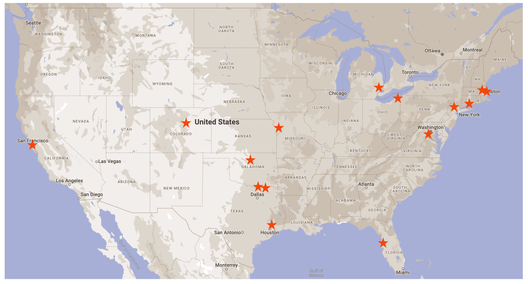
[a] PI3Kα kinase domain mutations
[b] PI3Kα helical domain mutations

Abbreviations: DL, dose level; HNSCC, head and neck squamous cell carcinoma; MTD, maximum tolerated dose; OBD, optimal biologically active dose; RP2D, recommended Phase 2 dose; TBD, to be determined.

Table1. Key eligibility criteria

Key inclusion criteria
• Metastatic or locally advanced and unresectable solid tumor
• Confirmed PI3kα-mutation in the kinase and/or helical domain
• Received standard therapy option(s)
• Measurable or evaluable disease
• The Eastern Cooperative Oncology Group (ECOG) performance status score of 0 to 1
• Adequate hematologic and organ function, including fasting glucose <140 mg/dL (7.7 mmol/L) and hemoglobin A1c (glycated hemoglobin; HbA1c) <7.0%
Key exclusion criteria
• Known phosphatase and tensin homolog (PTEN) mutation/deletion or activating AKT mutation
• No prior use of PI3K/AKT/mTOR inhibitors (except prior intolerance)
• Type 1 diabetes or uncontrolled type 2 diabetes
• Symptomatic brain or spinal metastases

Figure 5. Participating sites in the USA



Clinical Sites

California: University of California, San Francisco
Colorado: University of Colorado Anschutz Medical Center
Connecticut: Yale University
Massachusetts: Massachusetts General Hospital; Dana Farber Cancer Center
Michigan: Karmanos Cancer Institute
Missouri: Saint Luke's Cancer Institute
New York: Memorial Sloan Kettering Cancer Center
Ohio: University Hospitals/Seidman Cancer Center Case Western Reserve University
Oklahoma: University of Oklahoma
Texas: Mary Crowley Cancer Research; Texas Oncology-Baylor Charles A. Sammons Cancer Center; The University of Texas MD Anderson Cancer Center
Virginia: NEXT Virginia
Florida: Moffitt Cancer Center

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Disclosures

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