LOXO-783

PI3Kα INHIBITOR

LOXO@Lilly

The safety and efficacy of the agents under investigation have not been established. There is no guarantee that the agents will receive regulatory approval and become commercially available for the uses being investigated.

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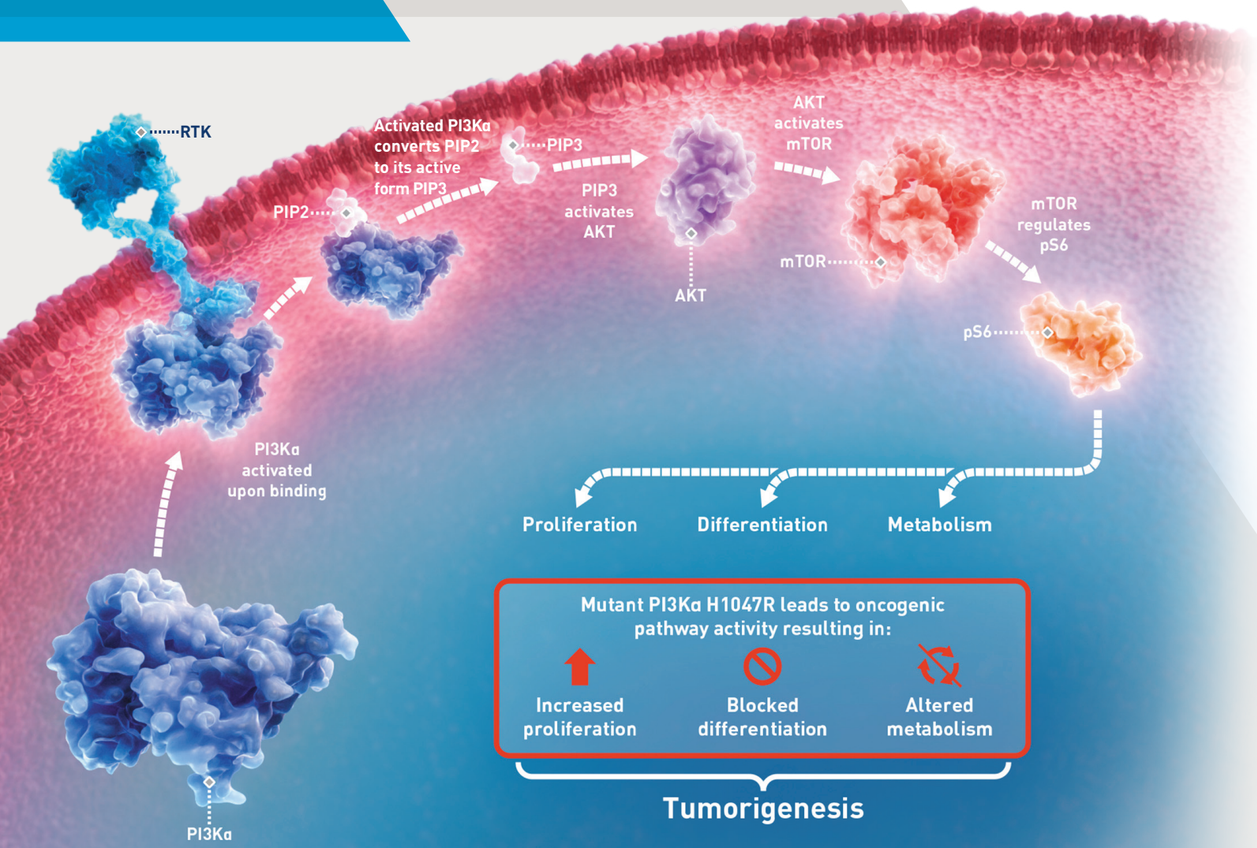

Gkeka P, et al[1]; Karakas B, et al[2]; Vasan N, et al[3]

TARGET

Phosphoinositide 3-kinase alpha (PI3Kα) H1047R mutations are activating oncogenic events that occur in ~15% of breast cancers and less commonly in other cancers.[4]

MOLECULE

LOXO-783 is a potent, highly mutant-selective, brain-penetrant, allosteric small molecule PI3Kα H1047R inhibitor.[4]

CLINICAL DEVELOPMENT

LOXO-783 is being investigated in an open-label, multicenter, phase 1a/1b study in patients with *PIK3CA* H1047R-mutant advanced breast cancer and other solid tumors.

References: 1. Gkeka P, et al. *PLoS Comput Biol*. 2014;10(10):e1003895. **2.** Karakas B, et al. *Br J Cancer*. 2006;94(4):455-459. **3.** Vasan N, et al. *Ann Oncol*. 2019;30(Suppl_10):x3–x11. **4.** Klippel A, et al. Preclinical characterization of LOXO-783 (LOX-22783), a highly potent, mutant-selective, and brain-penetrant allosteric PI3Kα H1047R inhibitor. Presented at AACR-NCI-EORTC Virtual Meeting 2021; October 7, 2021.

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PIKASSO-01

A Study of LOXO-783 Administered as Monotherapy and in Combination With Anticancer Therapies for Patients With Advanced Breast Cancer and Other Solid Tumors With a *PIK3CA* H1047R Mutation*

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Phase 1a

Dose escalation of LOXO-783†

Primary endpoints:
Dose-limiting toxicity (DLT) rate and DLT-equivalent toxicities

Phase 1b

Dose expansion:

Part A
LOXO-783† + fulvestrant‡ (A1)
LOXO-783† + imlunestrant§ (A2)
LOXO-783† + aromatase inhibitor‖ (A3)

Part B
LOXO-783† + aromatase inhibitor‖ + abemaciclib¶ (B1)
LOXO-783† + fulvestrant‡ + abemaciclib¶ (B2)
LOXO-783† + imlunestrant§ + abemaciclib¶ (B3)

Part C
LOXO-783† + fulvestrant‡ (C1)

Part D
LOXO-783† + paclitaxel# (D1)

Part E
LOXO-783† monotherapy (E1)

Part F
LOXO-783† + fulvestrant‡ (F1)**

* This clinical trial is being conducted globally.
† LOXO-783 is administered PO.
‡ Fulvestrant is administered intramuscularly.
§ Imlunestrant is administered PO.
‖ Aromatase inhibitor (anastrozole, exemestane, or letrozole) is administered PO.
¶ Abemaciclib is administered PO.
# Paclitaxel is administered intravenously.
** Multiple randomized dose levels of LOXO-783 with fulvestrant.

KEY INCLUSION CRITERIA

- Advanced breast cancer or another solid tumor with the presence of a *PIK3CA* H1047R mutation (or other sponsor and SRC-approved, activating *PIK3CA* mutations other than H1047R mutation)
- Adequate archival tumor tissue sample available or be approved by the sponsor for enrollment if no tumor sample is available
- Stopped all cancer treatment and have recovered from the major side effects
- Adequate organ function, as measured by blood tests
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Patients must have measurable disease (patients with non-breast tumor types must have at least 1 measurable lesion) OR non-measurable bone disease (at least one bone lesion in breast cancer patients only)
- For patients with an estrogen-receptor-positive (ER+) breast cancer diagnosis, if female, must be postmenopausal; if male, must agree to use hormone suppression
- Phase 1a: Dose escalation and backfill patients
  - Advanced solid tumor
  - Patients may have had up to 5 prior regimens for advanced disease
- Phase 1b: Part A
  - ER+/HER2- advanced breast cancer
  - Patients may have had up to 5 prior regimens for advanced disease, depending on cohort. Prior cyclin-dependent kinase (CDK) 4 & 6 inhibitor therapy required
- Phase 1b: Part B
  - ER+/HER2- advanced breast cancer
  - Patients may have had up to 2 prior regimens for advanced disease
- Phase 1b: Part C
  - ER+/HER2- advanced breast cancer
  - Patients may have had up to 5 prior regimens for advanced disease. Prior CDK4 & 6 inhibitor therapy required
  - Have a diagnosis of diabetes mellitus Type 2
- Phase 1b: Part D
  - Advanced breast cancer
  - Patients may have had up to 5 prior regimens for advanced disease
- Phase 1b: Part E
  - Advanced solid tumor
  - Patients may have had up to 3 prior regimens for advanced disease
- Phase 1b: Part F (randomized)
  - ER+/HER2- advanced breast cancer
  - Patients may have had up to 5 prior regimens for advanced disease. Prior CDK4 & 6 inhibitor therapy required

KEY EXCLUSION CRITERIA

- Medical conditions
  - Colorectal cancer
  - Endometrial cancers with specific concurrent oncogenic alterations
  - A history of known active or suspected: diabetes mellitus Type 1; diabetes mellitus Type 2 requiring antidiabetic medication (phase 1a and all parts of phase 1b, except part C); serious concomitant systemic disorder
- Known or suspected history of untreated or uncontrolled central nervous system (CNS) involvement
- Active uncontrolled systemic bacterial, viral, fungal, or parasitic infection, or other clinically significant active disease process
- Prior exposure to PI3K/AKT/mTOR inhibitor(s), except in certain circumstances

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT05307705].

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Pipeline information is current through November 2, 2023

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