LOXO-435

FGFR3 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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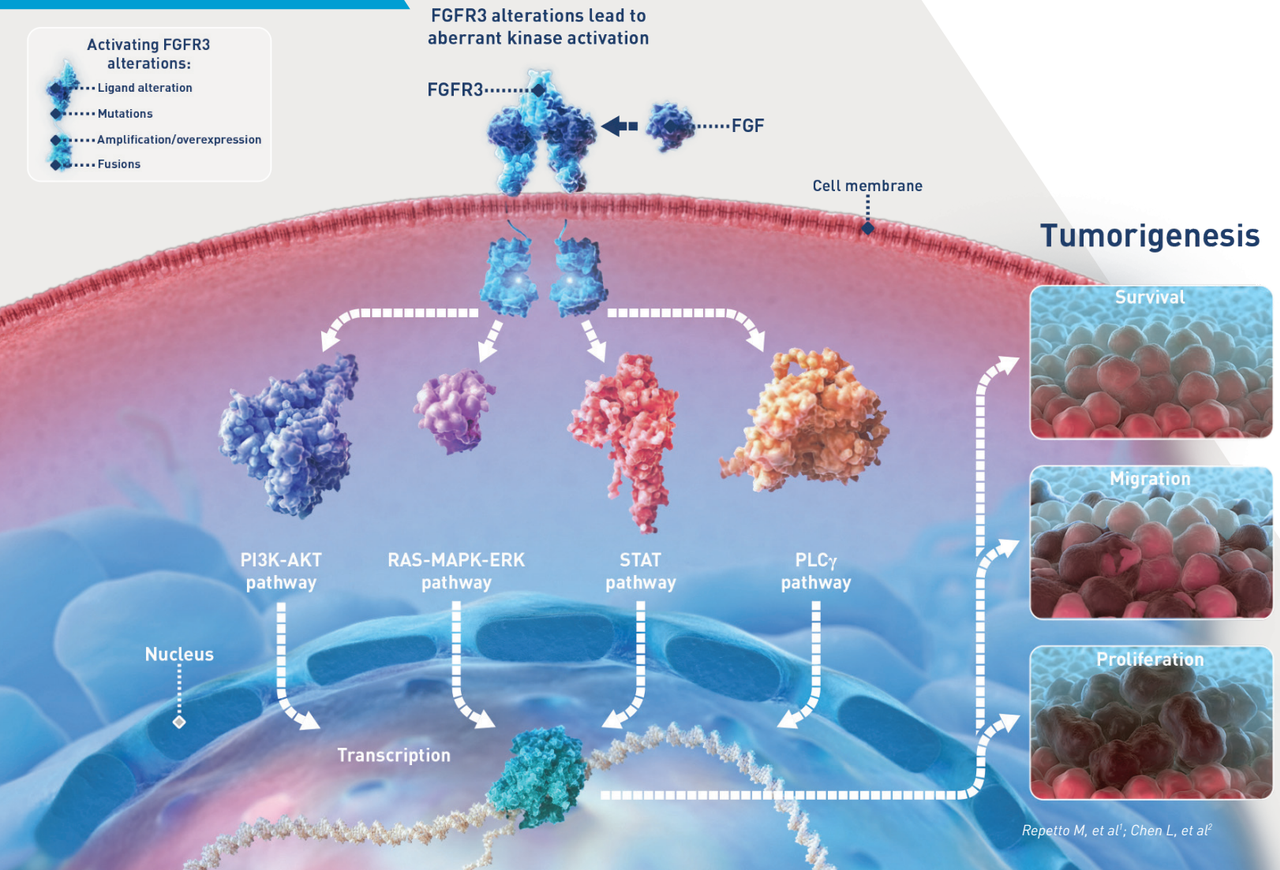
VV-OTHR-US-DEL-1411 11/2023 PRINTED IN USA



TARGET

Fibroblast growth factor (FGF) receptor 3 (FGFR3) is a member of the highly conserved FGFR family of transmembrane receptors.[2-4] There are four FGF receptors, FGFR1-4, that each consist of an extracellular ligand-binding domain, transmembrane domain, and an intracellular tyrosine kinase domain.[3,4] Receptor dimerization induced upon binding of the extracellular domain with a high-affinity member of the FGF family of ligands leads to phosphorylation of the intracellular domain and phospholipase Cγ, PI3K-AKT, RAS-MAPK-ERK, and STAT pathways activation, playing a critical role in several biological and developmental processes.[2,4,5] FGFR3 aberrations act as oncogenes across tumor types and have been identified in 15% to 20% of advanced urothelial bladder cancers, ~15% of uterine carcinosarcomas, ~5% of endometrial cancers, and less frequently (<5%) in other solid tumor malignancies.[3,4,6,7] Activating FGFR3 alterations are diverse and include point mutations, fusions, amplifications, and overexpression.[2-5] Dysregulation of FGFR3 promotes oncogenesis and tumor cell proliferation, migration, and survival.[2-5,8] Inhibition of oncogenic FGFR3 shows clinical benefit in patients with advanced urothelial cancer; however, currently approved FGFR targeted therapies that are not specific to FGFR3 demonstrate limited efficacy, dose-limiting off-target toxicities, and susceptibility to resistance mutations.[7,9]

MOLECULE

LOXO-435 is an isoform-selective FGFR3 inhibitor that has shown antitumor activity across FGFR3-mutant in vivo preclinical models, with preserved potency against FGFR3 gatekeeper resistance mutants.[7] LOXO-435 spares FGFR1 and FGFR2 in preclinical in vivo models, with the goal of avoiding dose-limiting hyperphosphatemia and other clinical adverse events that drive chronic intolerance to pan-FGFR inhibitors.[7]

CLINICAL DEVELOPMENT

LOXO-435 is being investigated in an open-label, multicenter, phase 1a/b study in patients with FGFR3-altered advanced urothelial carcinoma and other solid tumors.

References: 1. Repetto M, et al. *Expert Rev Clin Pharmacol.* 2021;14(10):1233-1252. **2.** Chen L, et al. *J Exp Clin Cancer Res.* 2021;40(1):345. **3.** Krook MA, et al. *Br J Cancer.* 2021;124(5):880-892. **4.** Katoh M. *Nat Rev Clin Oncol.* 2019;16(2):105-122. **5.** Glaser AP, et al. *Nat Rev Urol.* 2017;14(4):215-229. **6.** Helsten T, et al. *Clin Cancer Res.* 2016;22(1):259-267. **7.** Ballard JA, et al. *Mol Cancer Ther.* 2021;20(12_Suppl):P141. **8.** Haugsten EM, et al. *Mol Cancer Res.* 2010;8(11):1439-1452. **9.** Loriot Y, et al. *N Engl J Med.* 2019;381(4):338-348.

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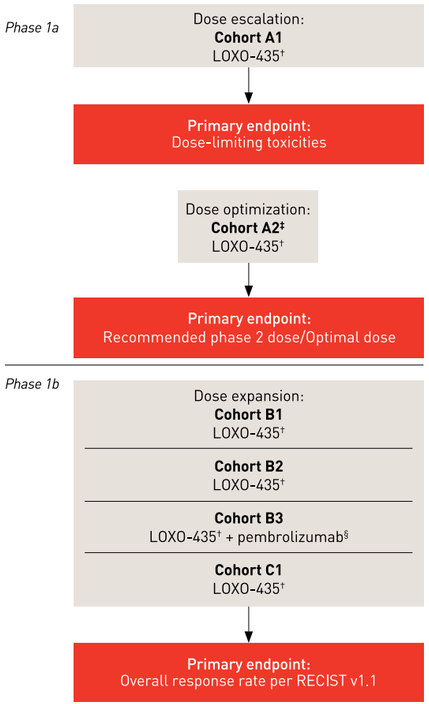
NCT05614739

An Open-Label, Multicenter Study of LOXO-435 (LY3866288) in Advanced Solid Tumor Malignancies With FGFR3 Alterations*



* This clinical trial is being conducted globally.
† LOXO-435 is administered PO.
‡ Patients in cohort A2 will be randomized to dose levels chosen by the investigator.
§ Pembrolizumab is administered intravenously.

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KEY INCLUSION CRITERIA

- Solid tumor cancer with an FGFR3 pathway alteration on molecular testing in tumor or blood sample that is deemed as actionable
  - Cohort A1 (dose escalation): Presence of an alteration in FGFR3 or its ligands
  - Cohort A2 (dose optimization): Histological diagnosis of urothelial cancer that is locally advanced or metastatic with a qualifying FGFR3 alteration
  - Cohorts B1, B2, and B3 (dose expansion): Histological diagnosis of urothelial cancer that is locally advanced or metastatic with a prespecified activating FGFR3 alteration
  - Cohort C (dose expansion): Histological diagnosis of a non-urothelial solid tumor malignancy that is locally advanced or metastatic with a prespecified activating FGFR3 alteration
- Measurability of disease:
  - Cohort A1: Measurable or non-measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
  - Cohorts A2, B1, B2, B3, and C1: Measurable disease as defined by RECIST v1.1
- Adequate archival tumor tissue sample available or undergo a screening biopsy, if allowed per country-specific regulations
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
- Prior systemic therapy criteria:
  - Cohorts A1 and C1: Participant has received all standard therapies for which the participant was deemed to be an appropriate candidate by the treating Investigator; OR there is no standard therapy available for the disease. There is no restriction on number of prior therapies
  - Cohorts A2, B1, B2, and B3: Participants must have received at least one prior regimen in the advanced or metastatic setting. There is no restriction on number of prior therapies
- FGFR inhibitor specific requirements:
  - Cohorts A1 and A2: Prior FGFR inhibitor treatment is permitted, but not required
  - Cohort B1: Participants must have been previously treated with a FGFR inhibitor
  - Cohorts B2, B3, and C1: Participants must be FGFR inhibitor naïve

KEY EXCLUSION CRITERIA

- Primary central nervous system (CNS) malignancy
- Uncontrolled CNS metastases
- Current evidence of corneal keratopathy or retinal disorder
- History and/or current evidence of extensive tissue calcification
- Any unresolved serious toxicities from prior therapy
- Significant cardiovascular disease
- Prolongation of the QT interval corrected for heart rate using Fridericia's formula (QTcF)
- Active uncontrolled systemic infection or other clinically significant medical conditions
- Pregnant, lactating, or plan to breastfeed during the study or within 6 months of the last dose of study treatment. Participants who have stopped breastfeeding may be enrolled

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT05614739].

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Pipeline information is current through November 2, 2023.

VV-OTHR-US-DEL-1411 11/2023 PRINTED IN USA

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