LOXO-435
(LY3866288)

FGFR3 INHIBITOR

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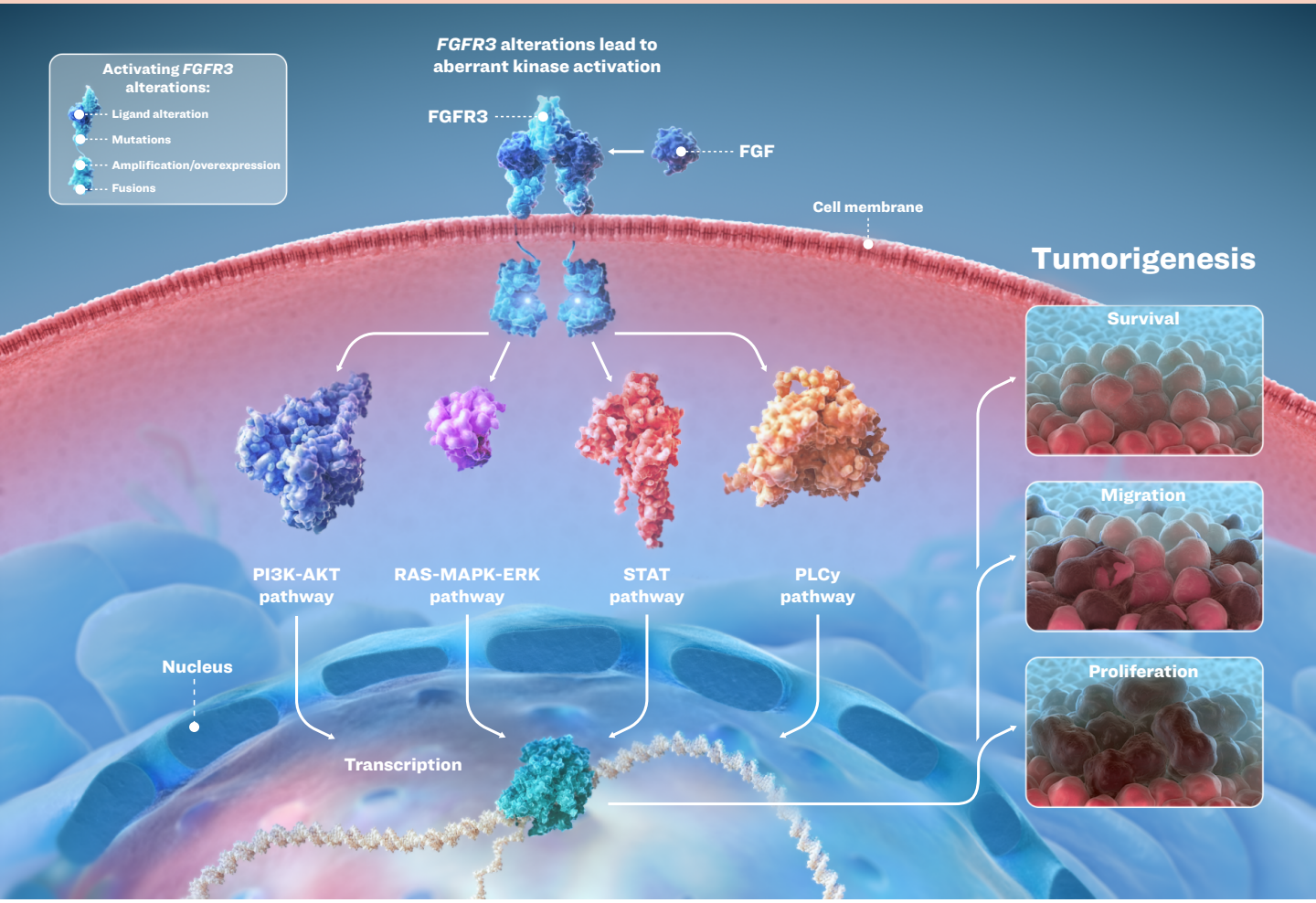
LOXO-435 FGFR3 INHIBITOR (LY3866288) | MECHANISM OF ACTION[1,2]



Repetto M, et al[1]; Chen L, et al[2]

Abbreviations: FGF=Fibroblast Growth Factor; FGFR3=Fibroblast Growth Factor Receptor 3; PLCγ=Phospholipase C gamma.

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.

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TARGET

Fibroblast growth factor (FGF) receptor 3 (FGFR3) is a member of the highly conserved FGFR family of transmembrane receptors.[1-3] There are four FGF receptors, FGFR1-4, that each consist of an extracellular ligand-binding domain, transmembrane domain, and an intracellular tyrosine kinase domain.[2,3] 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.[1,3,4] *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.[2,3,5,6] Activating *FGFR3* alterations are diverse and include point mutations, fusions, amplifications, and overexpression.[1-4] Dysregulation of FGFR3 promotes oncogenesis and tumor cell proliferation, migration, and survival.[1-4,7] 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.[6,8]

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.[6] 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.[6]

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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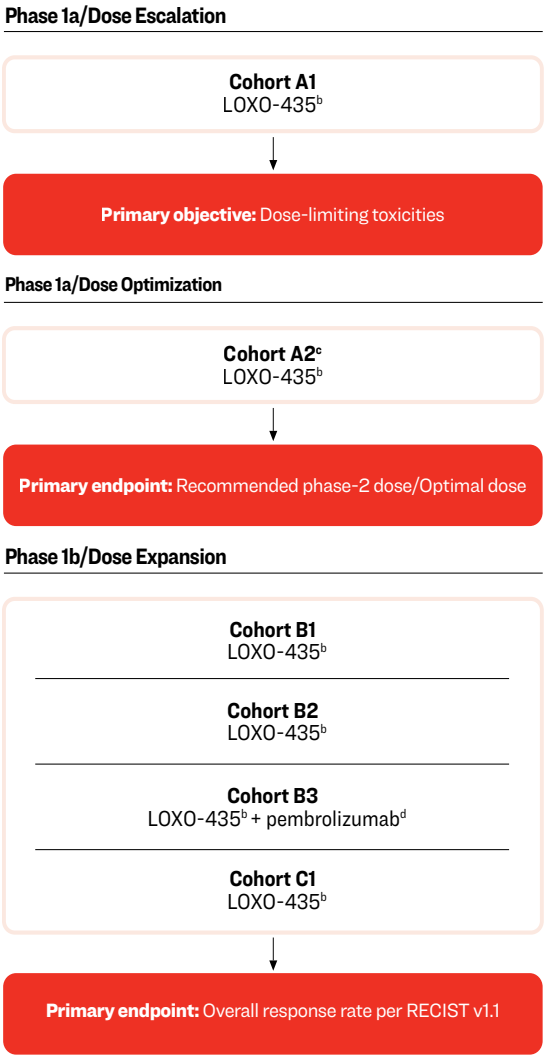
LOXO-435 FGFR3 INHIBITOR (LY3866288)

NCT05614739

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



[a]This clinical trial is being conducted globally. [b]LOXO-435 is administered PO. [c]Patients in cohort A2 will be randomized to dose levels chosen by the investigator. [d]Pembrolizumab is administered intravenously. **Abbreviations:** PO=orally; RECIST v1.1=Response Evaluation Criteria in Solid Tumors version 1.1.

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

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

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

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Pipeline information is current through February 6, 2023.