LY3866288 (LOXO-435)

FGFR3 INHIBITOR

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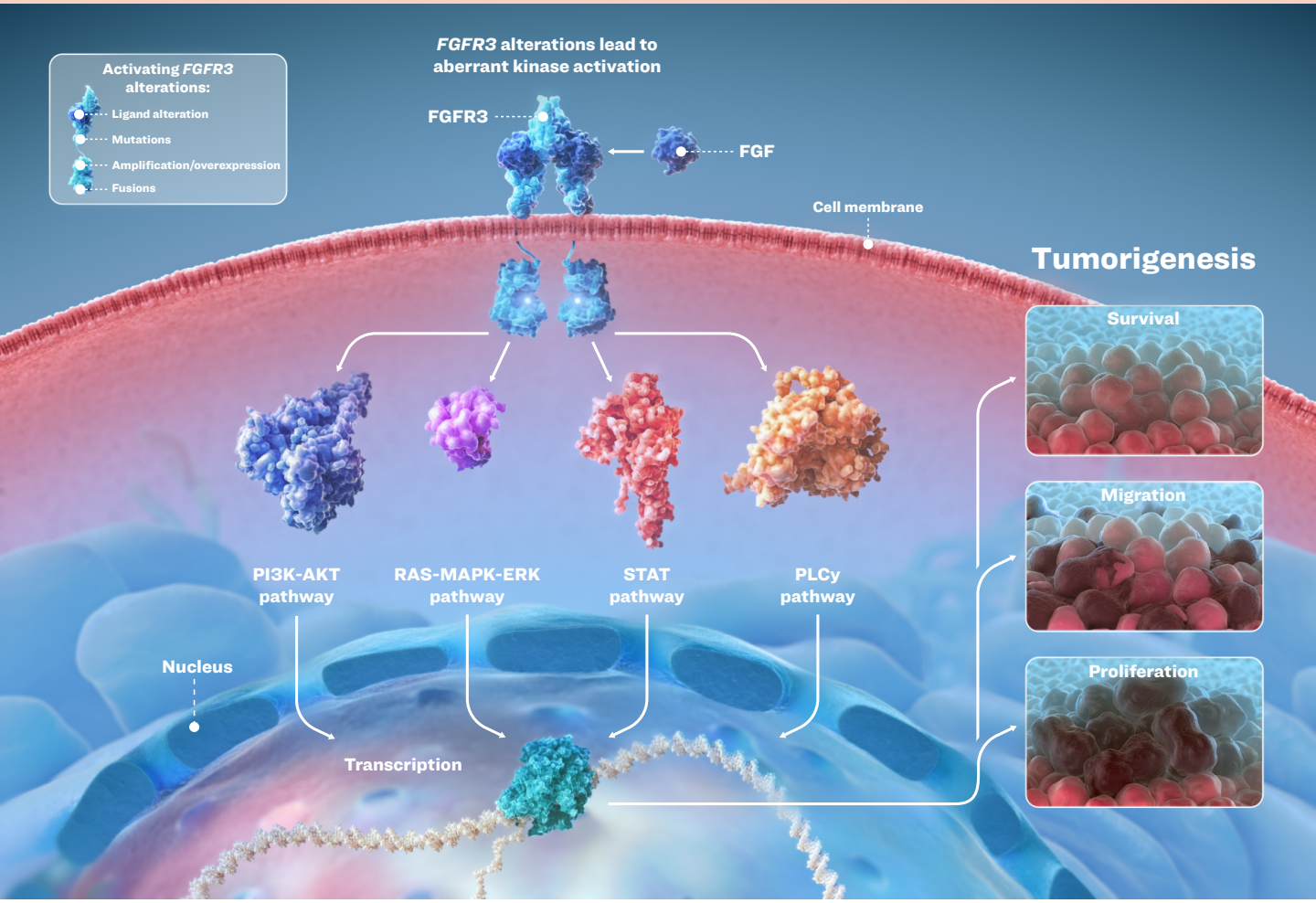
LY3866288 FGFR3 INHIBITOR (LOXO-435) | MECHANISM OF ACTION[1,2]



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.[6,8,9]

MOLECULE

LY3866288 (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] LY3866288 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

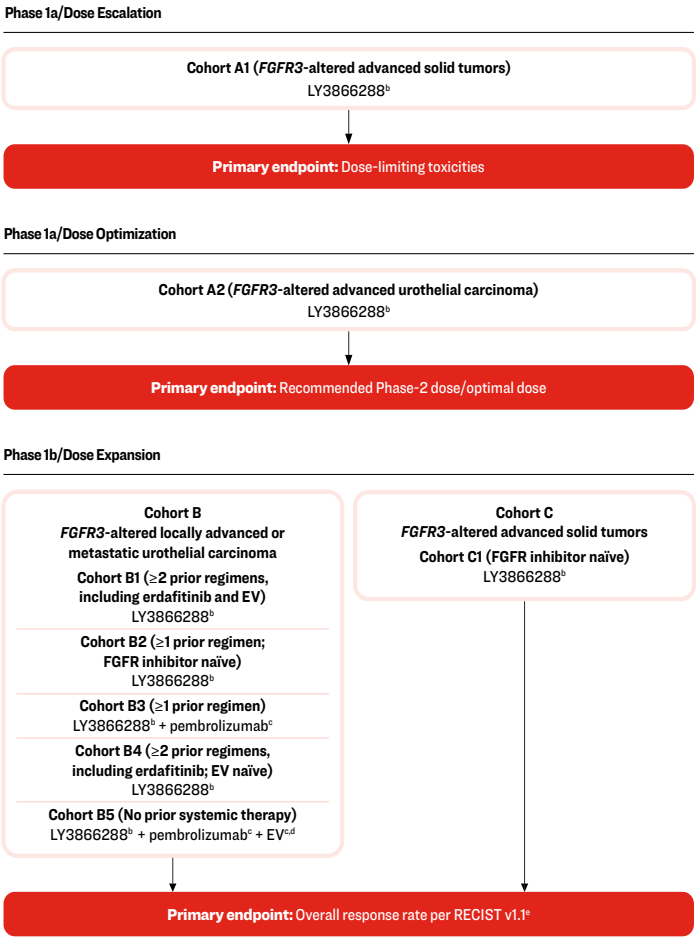
LY3866288 is being investigated in an open-label, multicenter, phase 1a/b study in patients with *FGFR3*-altered advanced urothelial carcinoma and other solid tumors.

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.

LY3866288 FGFR3 INHIBITOR (LOXO-435)

NCT05614739

FORAGER-1: A Phase 1, Open-label, Multicenter Study of LY3866288 (LOXO-435) in Locally Advanced or Metastatic Solid Tumors Including Urothelial Cancer with *FGFR3* Alterations[a]



[a]This clinical trial is being conducted globally. [b]Administered orally. [c]Administered intravenously. [d]Up to 2 cycles of EV plus pembrolizumab prior to study are allowed for cases where immediate treatment is clinically indicated. [e]Cohorts B3 and B5 will assess safety and tolerability as co-primary endpoints in addition to overall response rate.

Abbreviations: EV=Enfortumab Vedotin; FGFR3=Fibroblast Growth Factor Receptor 3; 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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FORAGER-1: A Phase 1, Open-label, Multicenter Study of LY3866288 (LOXO-435) in Locally Advanced or Metastatic Solid Tumors Including Urothelial Cancer with *FGFR3* Alterations (Cont.)

KEY INCLUSION CRITERIA

- Solid tumor cancer with an *FGFR3* pathway alteration (where applicable) 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
  - **Cohorts A2, B2, B3, and B5:** Histological diagnosis of urothelial cancer (UC) that is locally advanced or metastatic with a qualifying *FGFR3* genetic alteration
  - **Cohorts B1 and B4:** Histological diagnosis of UC that is locally advanced or metastatic
  - **Cohort C1 :** Histological diagnosis of a non-urothelial solid tumor malignancy that is locally advanced or metastatic with a qualifying *FGFR3* genetic alteration
- **Measurability of disease:**
  - **Cohorts A1 and B3:** Measurable or non-measurable disease as defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1)
  - **Cohorts A2, B1, B2, B4, B5, and C1:** Measurable disease as defined by RECIST v1.1
- Adequate archival tumor tissue sample available
- Eastern Cooperative Oncology Group (ECOG) performance status of:
  - 0 or 1 for Cohorts A1, A2, B3, and B5, or
  - ≤2 for Cohorts B1, B2, B4, and C1
- **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, B2, and B3:** Participants must have received at least one prior regimen in the locally advanced or metastatic setting. There is no restriction on number of prior therapies
  - **Cohort B1:** Participant must have received at least two prior regimens, including erdafitinib and enfortumab vedotin; AND must also have received all other standard therapies deemed appropriate by the treating investigator
  - **Cohort B4:** Participants must have received at least two prior regimens, including erdafitinib, but have not received enfortumab vedotin; AND must also have received all other standard therapies deemed appropriate by the treating investigator
  - **Cohort B5:** Participants must not have received prior systemic therapy for locally advanced or metastatic UC
- **FGFR inhibitor specific requirements:**
  - **Cohorts A1, A2, and B3:** Prior FGFR inhibitor treatment is permitted, but not required
  - **Cohorts B1 and B4:** Participants must have been previously treated with erdafitinib
  - **Cohorts B2, B5, and C1:** Participants must be FGFR inhibitor naïve

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

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FORAGER-1: A Phase 1, Open-label, Multicenter Study of LY3866288 (LOXO-435) in Locally Advanced or Metastatic Solid Tumors Including Urothelial Cancer with *FGFR3* Alterations (Cont.)

KEY EXCLUSION CRITERIA

- Primary central nervous system (CNS) malignancy (glioma)
- Untreated or uncontrolled CNS involvement
- Current evidence of corneal keratopathy or retinal disorder
- Any unresolved serious toxicities from prior therapy, exceptions for individuals with:
  - Alopecia
  - Peripheral neuropathy
  - Hearing loss
  - Grade 2 nail loss
  - Grade ≥2 skin toxicity by body surface area (BSA) alone
  - Endocrinopathies developed due to prior immunotherapies
- 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 January 30, 2025.