



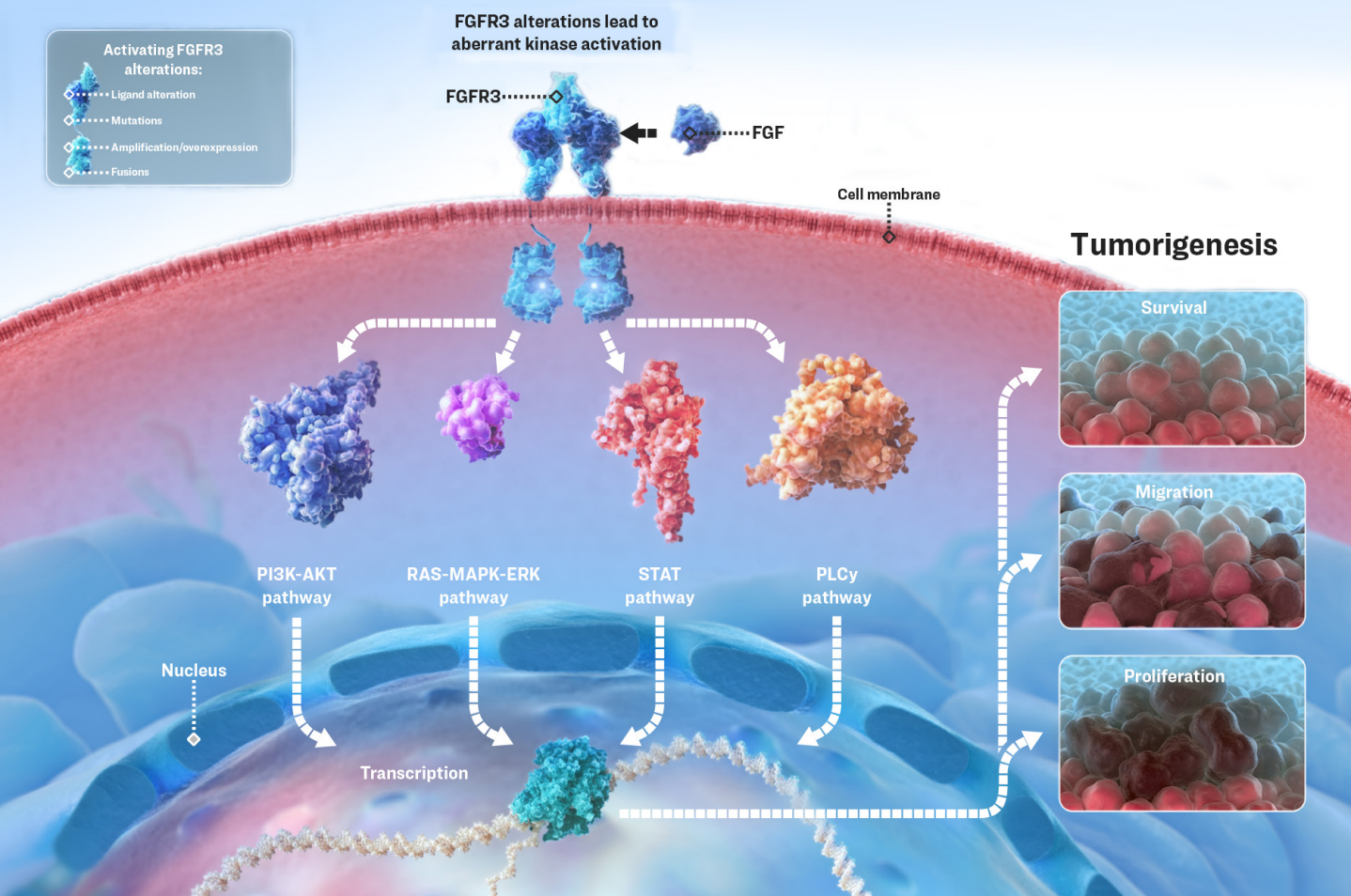
VEPUGRATINIB **(LY3866288)**

FGFR3 INHIBITOR

The safety and efficacy of the agents for uses under investigation have not been established. Pipeline molecules may not receive regulatory approval and become commercially available for the uses being investigated. The information provided about new molecules being studied is for scientific information exchange purposes only with no commercial intent. For more information on our pipeline, please visit lillyoncologypipeline.com.

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VEPUGRATINIB **FGFR3 INHIBITOR** (LY3866288) | MECHANISM OF ACTION^{1,2}



Repetto M, et al¹; Chen L, et al²

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 C γ , 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

Vepugratinib (LY3866288) 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 Vepugratinib 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

Vepugratinib 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.

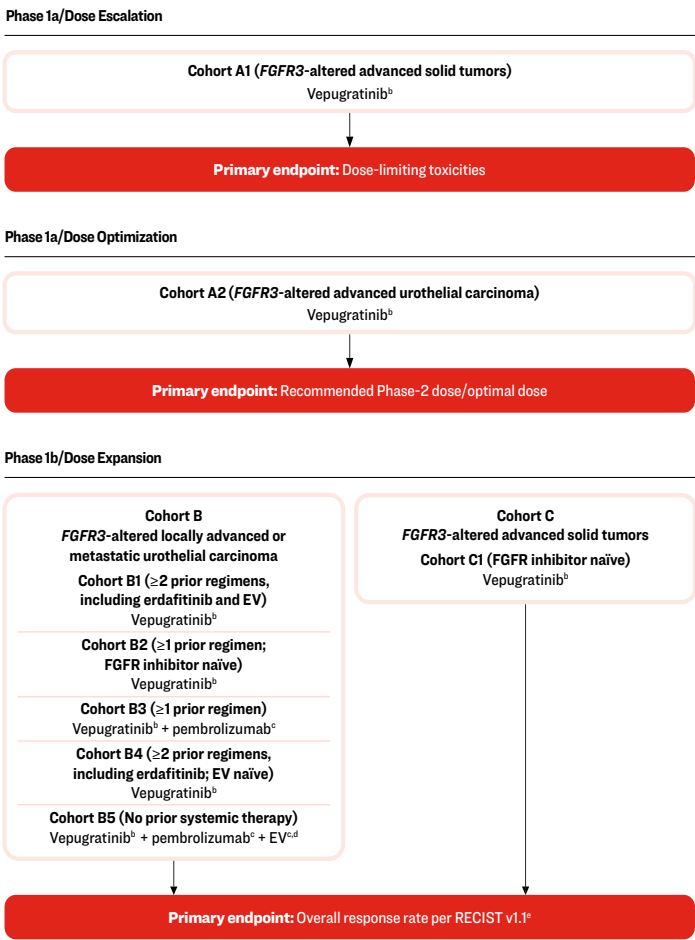
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VEPUGRATINIB FGFR3 INHIBITOR (LY3866288)

NCT05614739

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



^aThis clinical trial is being conducted globally. ^bAdministered orally. ^cAdministered intravenously. ^dUp to 2 cycles of EV plus pembrolizumab prior to study are allowed for cases where immediate treatment is clinically indicated. ^eCohorts 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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VEPUGRATINIB FGFR3 INHIBITOR (LY3866288)

NCT05614739

FORAGER-1: A Phase 1, Open-label, Multicenter Study of Vepugratinib (LY3866288) 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 Vepugratinib (LY3866288) 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 July 31, 2025.

