LOXO-260

NEXT-GENERATION RET 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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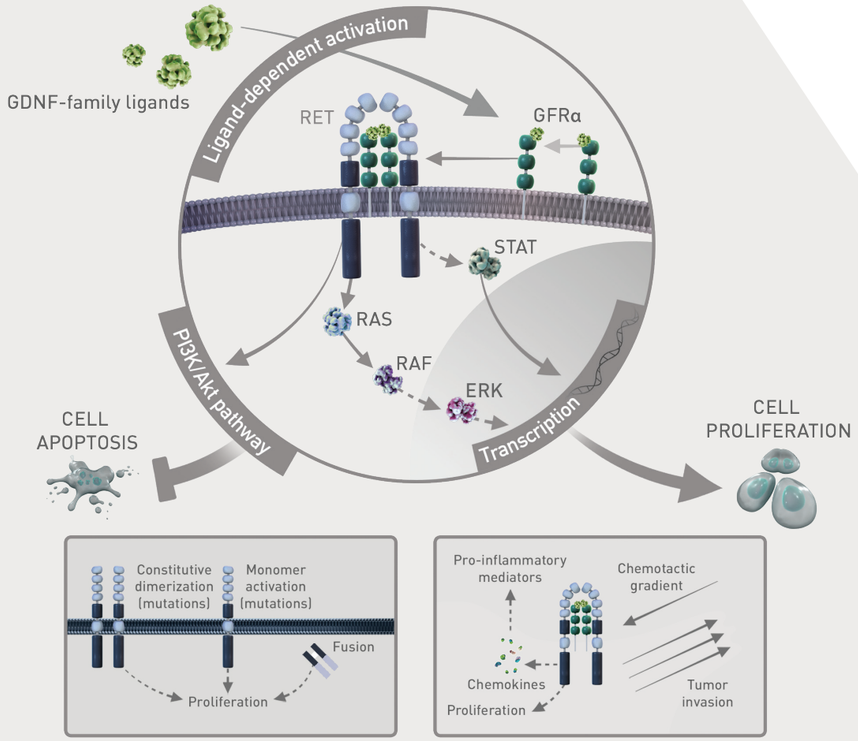

Mulligan LM[1]

TARGET

Rearranged during transfection *(RET)* fusions have been identified in approximately 2% of non-small cell lung cancer,[2,3] approximately 10% of papillary thyroid cancer,[4,5] and less than 1% in other solid tumors including pancreatic and colorectal cancer.[6-8] *RET* point mutations account for approximately 60% of medullary thyroid cancer.[9-11] Cancers that harbor activating *RET* fusions or *RET* mutations depend primarily on this single constitutively activated kinase for their proliferation and survival. This dependency renders such tumors highly susceptible to small-molecule inhibitors targeting *RET*.

Recently, resistance to targeted RET treatment has been described in the clinic with secondary solvent front mutations or other oncogenic pathway activations emerging.[12-14]

MOLECULE

LOXO-260 is a selective small-molecule inhibitor of the RET receptor tyrosine kinase, developed to have activity against both solvent front and gatekeeper mutations, expressed alone or together, while maintaining the potency and selectivity of current selective RET inhibitors.[15] LOXO-260 has demonstrated in vitro and in vivo activity as a selective inhibitor of both wild-type and oncogenic activated RET, including *RET* fusions, activating *RET* point mutations, and anticipated acquired resistant mutations.

CLINICAL DEVELOPMENT

LOXO-260 is being investigated in a clinical trial in patients with *RET* fusion-positive solid tumors, medullary thyroid cancer, and other tumors with RET activation refractory to selective RET inhibitors.

References: 1. Mulligan LM. *Nat Rev Cancer.* 2014;14:173-186. **2.** Lipson D, et al. *Nat Med.* 2012;18(3):382-384. **3.** Takeuchi K, et al. *Nat Med.* 2012;18(3):378-381. **4.** Drilon A, et al. *Nat Rev Clin Oncol.* 2018;15(3):151-167. **5.** Parimi V, et al. *NPJ Precis Oncol.* 2023;7(1):10. **6.** Yang SR, et al. *Clin Cancer Res.* 2021;27(5):1316-1328. **7.** Kohno T, et al. *Carcinogenesis.* 2020;41(2):123-129. **8.** Li AY, et al. *Cancer Treat Rev.* 2019;81:101911. **9.** Hofstra RM, et al. *Nature.* 1994;367(6461):375-376. **10.** Agrawal N, et al. *J Clin Endocrinol Metab.* 2013;98(2):E364-E369. **11.** Taccaliti A, et al. *Curr Genomics.* 2011;12(8):618-625. **12.** Solomon BJ, et al. *J Thorac Oncol.* 2020;15(4):541-549. **13.** Subbiah V, et al. *Ann Oncol.* 2021b;32(2):261-268. **14.** Rosen EY, et al. *Clin Cancer Res.* 2021;27(1):34-42. **15.** AACR disclosure. Kolakowski et al. Pre-clinical characterization of potent and selective next-generation RET inhibitors. Presented at AACR Annual Meeting 2021; April 10, 2021.

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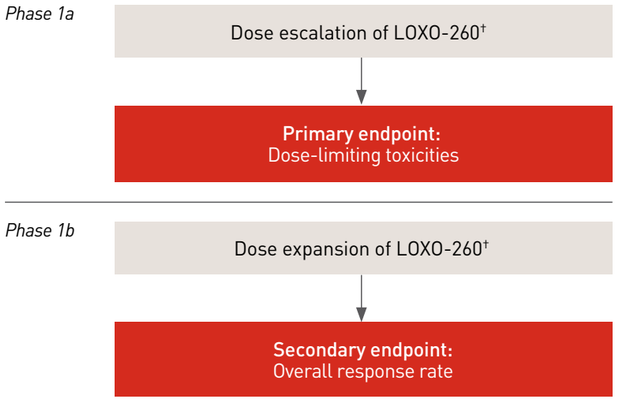
NCT05241834

A Phase 1 Study of Oral LOXO-260 in Patients with *RET* Fusion-Positive Solid Tumors, Medullary Thyroid Cancer, and Other Tumors With RET Activation Refractory to Selective RET Inhibitors*



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* This clinical trial is being conducted in the United States.

† LOXO-260 is administered PO.

KEY INCLUSION CRITERIA

- ≥18 years of age at the time of signing the informed consent (phase 1a and phase 1b). Patients 12 years and older may be enrolled in phase 1b for countries and sites where approved
- Evidence of a previously documented *RET* fusion (solid tumors) or *RET* mutation (MTC or MEN2-associated cancers) that is a histological or a cytological proven diagnosis of locally advanced, unresectable and/or metastatic cancer and meet cohort-specific criteria
- Prior treatment with selective RET inhibitor
- Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 (age >16 years), Karnofsky Performance Status (KPS) ≥80 (age >16 years), or Lansky Performance Status (LPS) ≥40% (age <16 years)
- Discontinued all previous treatments for cancer with resolution of any significant adverse events (AEs) and of all clinically significant toxic effects of prior locoregional therapy, surgery, radiotherapy, or systemic anticancer therapy
- Adequate organ function
- Phase 1b (dose expansion): Patients must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1
- Phase 1b (dose expansion): Molecular pathology results (including RET and other genes) from a sample (blood or tissue) taken on or after RET selective treatment

KEY EXCLUSION CRITERIA

- Disease suitable for local therapy administered with curative intent
- Active fungal, bacterial, and/or active untreated viral infection
- Serious preexisting medical condition(s)
- Symptomatic central nervous system (CNS) malignancy or metastasis
- Treatment with drugs known to be strong inhibitors or inducers of cytochrome P450 3A (CYP3A)
- Progression of disease within 4 months of starting a prior selective RET inhibitor
- Phase 1b (dose expansion): Patients harboring known activating bypass alterations outside RET that may confer resistance to LOXO-260

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT05241834].

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