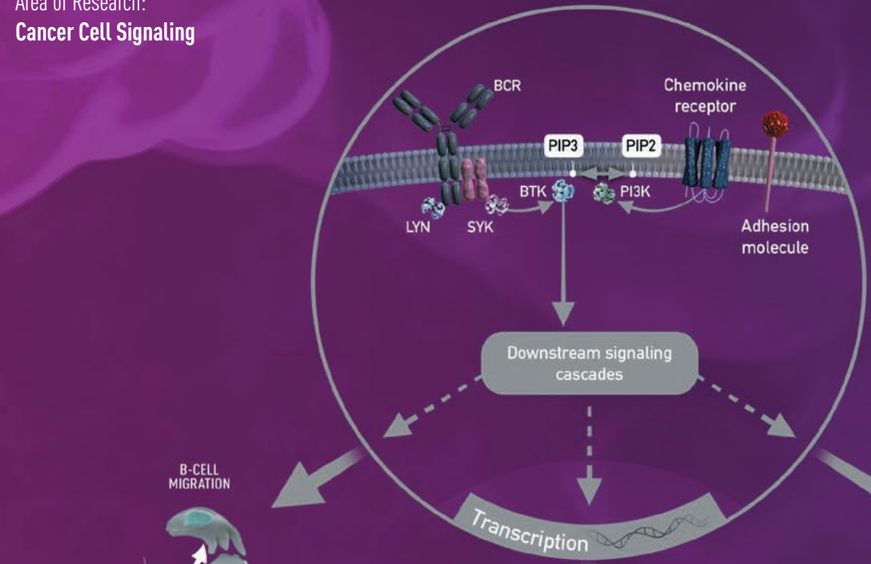
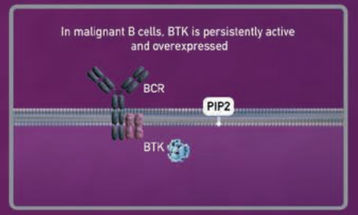
BTK Inhibitor

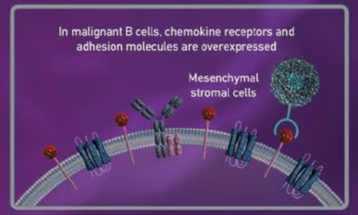
LOXO-305

LOXO ONCOLOGY at Lilly

Area of Research:
Cancer Cell Signaling







Wu J, et al[1]; Singh SP, et al[2]

Target

Bruton tyrosine kinase (BTK) inhibitors represent a major therapeutic advance in the treatment of patients with chronic lymphocytic leukemia (CLL) and other B-cell malignancies by inducing durable responses.[1-5] BTK is critical for the propagation of B-cell receptor signaling and is upregulated in CLL cells as compared with normal B cells. BTK inhibition, both in vitro and in vivo, decreases proliferation and survival signals.[3]

Molecule

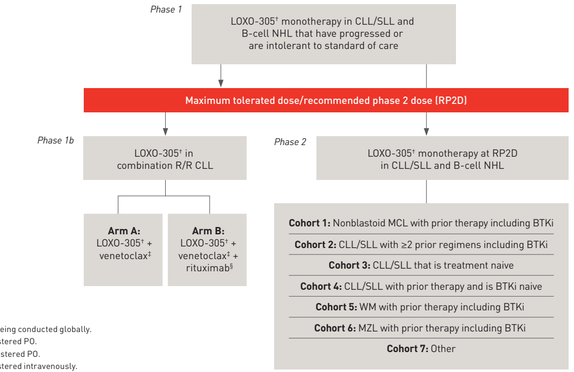
LOXO-305 is a next-generation, highly selective, oral, noncovalent BTK inhibitor. It possesses nanomolar potency against wild-type and C481-mutated BTK in enzyme and cell-based assays. LOXO-305 has been shown in vitro to be 300-fold more selective for BTK, for over 98% of the 370 kinases tested, with no significant inhibition of nonkinase off targets at 1 μM.[6]

Clinical Development

LOXO-305 is being investigated in a clinical trial in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma or non-Hodgkin's lymphoma.

References: 1. Wu J, et al. *J Hematol Oncol*. 2016;9(1):80. **2.** Singh SP, et al. *Mol Cancer*. 2018;17(1):57. **3.** Woyach JA, et al. *J Clin Oncol*. 2017;35(13):1437-1443. **4.** Mato AR, et al. *Blood*. 2016;128(18):2199-2205. **5.** Byrd JC, et al. *N Eng J Med*. 2016;374(4):323-332. **6.** Gomez EB, et al. *Blood*. 2019;134(suppl 1):4644.

BRUIN: A Phase 1/2 Study of Oral LOXO-305 in Patients With Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin's Lymphoma (NHL)*



* This clinical trial is being conducted globally.
† LOXO-305 is administered PO.
‡ Venetoclax is administered PO.
§ Rituximab is administered intravenously.

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.

Key Inclusion Criteria

- Phase 1/2 LOXO-305 monotherapy: B-cell malignancies that have failed or are intolerant to either ≥2 prior standard-of-care regimens given in combination or sequentially, or received one prior BTK inhibitor (BTKi) regimen when a BTKi is approved as first-line therapy (phase 1) OR with prior treatment defined by phase 2 cohort (phase 2 patients only)
- Phase 1b arm A: Relapsed/refractory (R/R) CLL and venetoclax is appropriate salvage treatment
- Phase 1b arm B: R/R CLL and venetoclax + rituximab is appropriate salvage treatment
- At least 18 years of age
- Phase 1/1b: Adequate hematologic function that is responsive to transfusion support for thrombocytopenia or anemia
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- Adequate hepatic and renal function
- Able to receive oral study drug
- Willing to use conventional and effective birth control

Key Exclusion Criteria

- Concurrent investigational agent or anticancer therapy within 5 half-lives prior to planned start of specified study treatment; therapeutic monoclonal antibody treatment must be discontinued ≥4 weeks prior to the first dose of study treatment; no concurrent systemic anticancer investigational therapy is permitted
- Major surgery within 4 weeks prior to planned start of study treatment
- Radiotherapy with a limited field of radiation for palliation within 7 days of study treatment
- Pregnant or breastfeeding
- Require therapeutic anticoagulation with warfarin
- Any unresolved ≥ grade 2 toxicities as defined by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 5.0 attributed to prior therapy (other than alopecia) at the start of study treatment
- History of allogeneic or autologous stem-cell transplant or chimeric antigen receptor-modified T-cell therapy within the past 60 days (180 days before the PK trigger) prior to planned start of specified study treatment
- Known central nervous system (CNS) involvement by systemic lymphoma. Patients with previous treatment for CNS involvement who are neurologically stable and without evidence of disease may be eligible and enrolled to phase 2 cohort 7 if a compelling clinical rationale is provided by the investigator and with documented sponsor approval
- Active uncontrolled autoimmune cytopenia when new or concomitant therapy was introduced or escalated to maintain adequate blood counts within 4 weeks prior to study enrollment
- Uncontrolled cardiac or cardiovascular disease, or myocardial infarction within 6 months prior to planned start of study treatment
- HIV or active uncontrolled systemic bacterial, viral, fungal, or parasitic infection
- Active malabsorption syndrome
- Current treatment with certain strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers
- Treatment with proton pump inhibitors within 7 days of starting study treatment
- Phase 1b arm A or B: Patients with prior treatment with venetoclax or other BCL-2 inhibitors
- Active second malignancy unless in remission and with life expectancy >2 years
- Phase 1b arm B: Prior significant hypersensitivity to rituximab/biosimilar requiring discontinuation, or prior allergic or anaphylactic reaction to rituximab

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT03740529].

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Pipeline information is current through October 27, 2020.

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