PIRTOBRUTINIB (LY3527727)

BTK INHIBITOR

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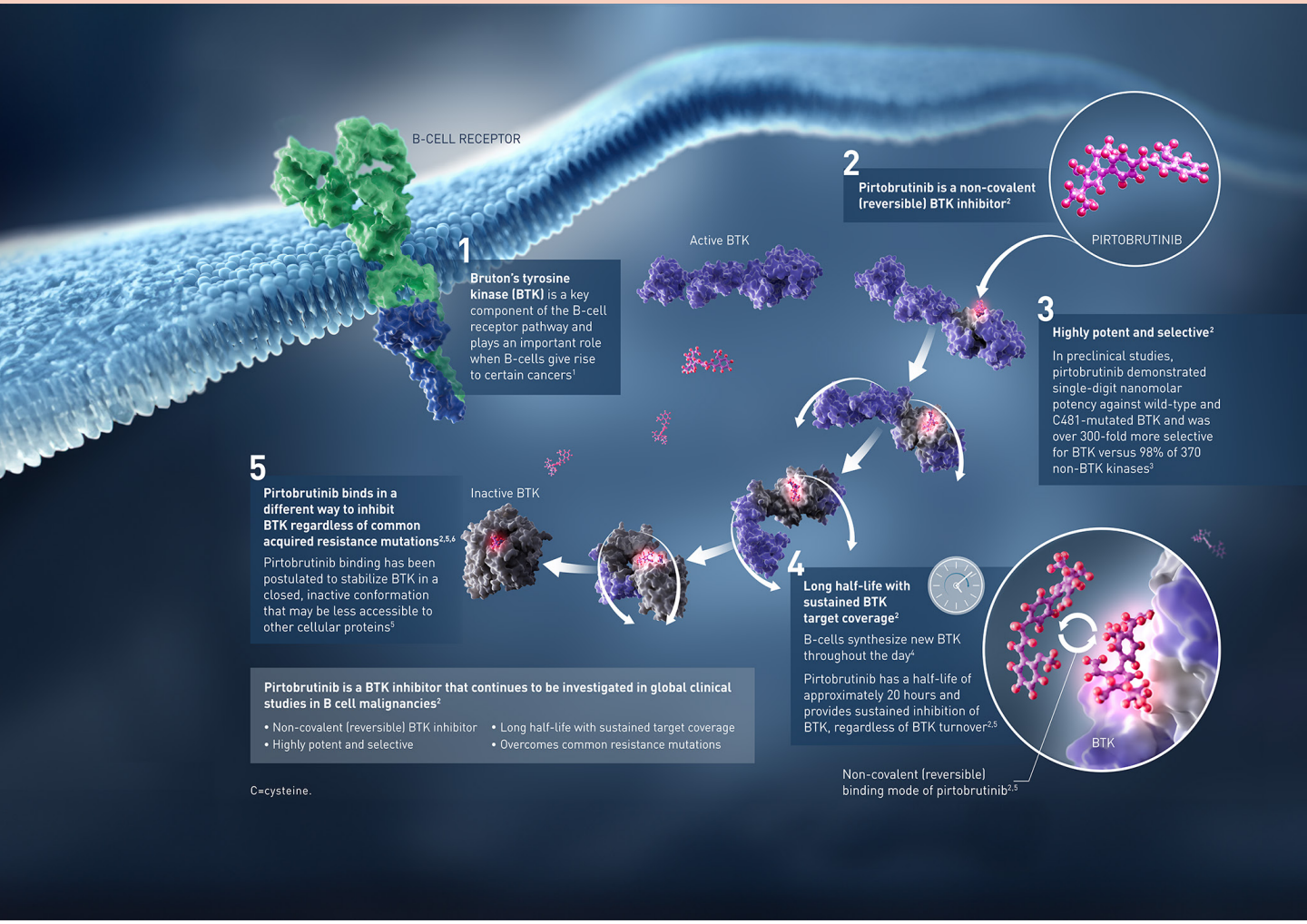
PIRTOBRUTINIB BTK INHIBITOR (LY3527727) | MECHANISM OF ACTION[1]



Estupiñán HY, et al[1], Mato AR, et al[2], Brandhuber B, et al[3], Alsadhan A, et al[4], Gomez EB, et al[5], Gomez EB, et al[6]

References: 1. Estupiñán HY, et al. *Front Cell Dev Biol*. 2021;9:630942. **2.** Mato AR, et al. *Lancet*. 2021;397(10277):892-901. **3.** Brandhuber B, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:S216. **4.** Alsadhan A, et al. *Clin Cancer Res*. 2020;26(12):2800-2809. **5.** Gomez EB, et al. *Blood*. 2023;142(1):62-72. **6.** Gomez EB, et al. *Blood*. 2019;134(suppl 1):4644.

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TARGET

Bruton's tyrosine kinase (BTK) is critical for the propagation of B-cell receptor signaling and is upregulated in many B-cell malignancies as compared with normal B-cells. BTK inhibition, both *in vitro* and *in vivo*, decreases proliferation and survival signals.[1]

MOLECULE

Pirtobrutinib is an investigational, oral, highly selective (in preclinical studies, over 300-fold more selective for BTK vs 98% of 370 non-BTK-kinases),non-covalent (reversible) BTK inhibitor.[2,3] It possesses nanomolar potency independent of BTK C481 status in enzyme and cell-based assays.[2-4] Pirtobrutinib has been shown in preclinical studies to reversibly bind BTK, have high target coverage regardless of BTK turnover rate, preserve activity in the presence of the C481 acquired resistance mutations, and predominantly avoid off-target kinases.[2]

CLINICAL DEVELOPMENT

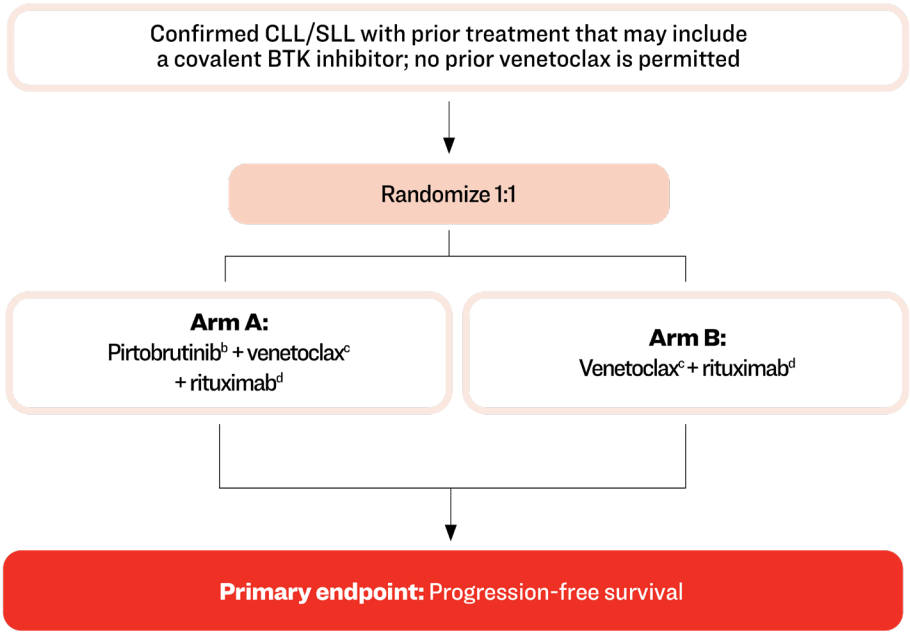
Pirtobrutinib is being investigated in clinical trials in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma, mantle cell lymphoma, and non-Hodgkin's lymphoma.

References: 1. Woyach JA, et al. *J Clin Oncol*. 2017;35(13):1437-1443. **2.** Mato AR, et al. *Lancet*. 2021;397(10277):892-901. **3.** Brandhuber B, et al. *Clin Lymphoma Myeloma Leuk*. 2018;18:S216. **4.** Gomez EB, et al. *Blood*. 2019;134(suppl 1):4644.

PIRTOBRUTINIB BTK INHIBITOR (LY3527727)

BRUIN CLL-322

A Phase 3 Open-Label, Randomized Study of Fixed Duration Pirtobrutinib (LOXO-305) Plus Venetoclax and Rituximab Versus Venetoclax and Rituximab in Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma[a]



[a]This clinical trial is being conducted globally. [b]Pirtobrutinib is administered PO QD. [c]Venetoclax is administered PO QD. [d]Rituximab is administered intravenously. **Abbreviations:** BTK=Bruton Tyrosine Kinase; CLL=Chronic Lymphocytic Leukemia; PO=orally; QD=once daily; SLL=Small Lymphocytic Lymphoma.

Please visit clinicaltrials.gov for more information on this clinical trial [NCT04965493].

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A Phase 3 Open-Label, Randomized Study of Fixed Duration Pirtobrutinib (LOXO-305) Plus Venetoclax and Rituximab Versus Venetoclax and Rituximab in Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (cont.)

KEY INCLUSION CRITERIA

- Confirmed diagnosis of chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL) requiring therapy as defined by the International Workshop on Chronic Lymphocytic Leukemia (iwCLL) 2018 criteria
- Previously treated with at least one line of therapy that may include a covalent BTK inhibitor
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- Platelets ≥50 x 10^9/L, hemoglobin ≥8 g/dL, and absolute neutrophil count ≥1.0 x 10^9/L
- Adequate organ function
- Estimated creatinine clearance ≥30 mL/min

KEY EXCLUSION CRITERIA

- Known or suspected Richter's transformation at any time preceding enrollment
- Uncontrolled immune thrombocytopenic purpura (ITP) or autoimmune hemolytic anemia (AIHA)
- Central nervous system (CNS) involvement
- Significant cardiovascular disease
- History of allogeneic stem cell transplantation (SCT) or chimeric antigen receptor-modified T-cell (CAR-T) therapy within the past 60 days
- Active hepatitis B or C
- Known active cytomegalovirus (CMV) infection
- Active uncontrolled systemic bacterial, viral, fungal, or parasitic infection
- Known HIV infection, regardless of cluster of differentiation 4 (CD4) count
- Previously treated with venetoclax
- Prior exposure to a non-covalent (reversible) BTK inhibitor
- Patients requiring therapeutic anticoagulation with warfarin or another vitamin K antagonist
- Current treatment with strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers
- Vaccination with a live vaccine within 28 days prior to randomization
- Patients with the following hypersensitivity:
  - Known hypersensitivity to any component or excipient of pirtobrutinib and venetoclax
  - Prior significant hypersensitivity to rituximab
  - Known allergy to allopurinol and inability to take uric acid lowering agents

Please visit clinicaltrials.gov for more information on this clinical trial [NCT04965493].

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ACTIVE TRIALS CURRENTLY NOT ENROLLING

[NCT03740529] Hematologic Cancer
BRUIN: A Study of Oral LOXO-305 in Patients With Previously Treated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma (CLL/SLL) or Non-Hodgkin's Lymphoma (NHL)

[NCT05254743] Hematologic Cancer
A Study of Pirtobrutinib (LOXO-305) Versus Ibrutinib in Participants With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

[NCT05023980] Hematologic Cancer
A Study of Pirtobrutinib (LOXO-305) Versus Bendamustine Plus Rituximab (BR) in Untreated Patients With Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

[NCT04662255] Hematologic Cancer
Study of BTK Inhibitor LOXO-305 Versus Approved BTK Inhibitor Drugs in Patients With Mantle Cell Lymphoma (MCL)

[NCT04666038] Hematologic Cancer
Study of LOXO-305 Versus Investigator's Choice (IdelaR or BR) in Patients With Previously Treated Chronic Lymphocytic Leukemia (CLL)/Small Lymphocytic Lymphoma (SLL)

[NCT05024045] Hematologic Cancer
Study of Oral LOXO-338 in Patients With Advanced Blood Cancers

[NCT04849416] Hematologic Cancer
A Study of LOXO-305 in Chinese Participants With Blood Cancer (Including Lymphoma and Chronic Leukemia)

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Pipeline information is current through August 16, 2024.