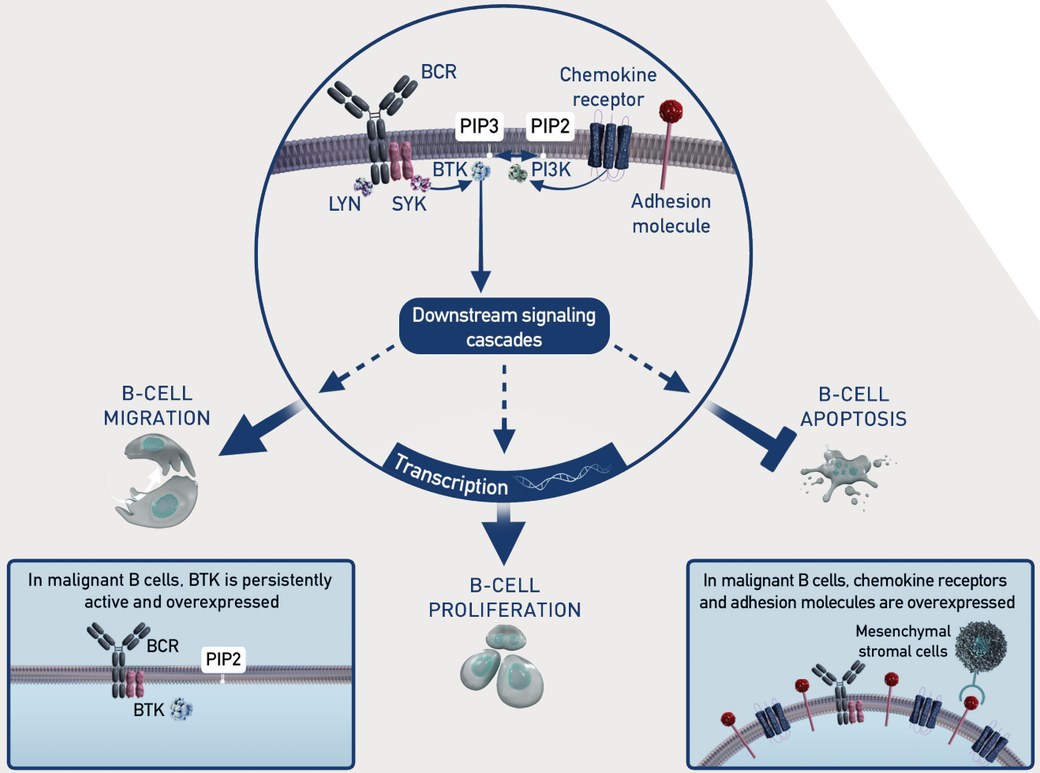
PIRTOBRUTINIB
LOXO-305

BTK 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.



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), mantle cell lymphoma (MCL), and B-cell malignancies by inducing responses.[3-8] 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.[3]

MOLECULE

Pirtobrutinib (LOXO-305) is an investigational, oral, highly selective (over 300-fold more selective for BTK vs 98% of 370 non-BTK-kinases), non-covalent (reversible) BTK inhibitor. It possesses nanomolar potency independent of BTK C481 status in enzyme and cell-based assays. Pirtobrutinib has been shown in preclinical studies to reversibly bind BTK, deliver consistently high target coverage regardless of BTK turnover rate, preserve activity in the presence of the C481 acquired resistance mutations, and avoid off-target kinases.[9]

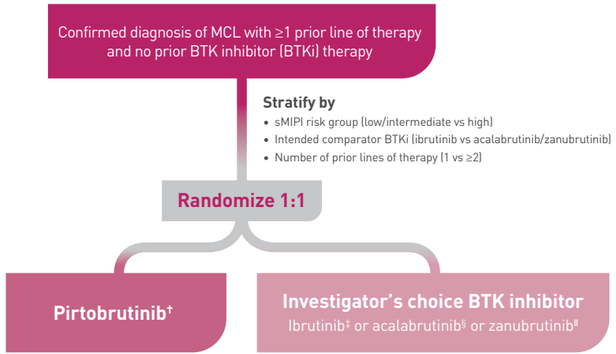
CLINICAL DEVELOPMENT

Pirtobrutinib (LOXO-305) 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. 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.** Rule S, et al. *Haematologica*. 2019;104(5):e211-e214. **7.** Wang M, et al. *Leukemia*. 2019;33(11):2762-2766. **8.** Noy A, et al. *Blood*. 2017;129(16):2224-2232. **9.** Gomez EB, et al. *Blood*. 2019;134(suppl 1):4644.

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.

A Phase 3 Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) Versus Investigator's Choice of BTK Inhibitor in Patients With Previously Treated BTK Inhibitor-Naïve Mantle Cell Lymphoma*



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.

* This clinical trial is being conducted globally.
† Pirtobrutinib is administered 200 mg PO QD until therapy discontinuation.
‡ Ibrutinib is administered 560 mg PO QD.
§ Acalabrutinib is administered 100 mg PO BID.
|| Zanubrutinib is administered 160 mg PO BID or 320 mg PO QD.

KEY INCLUSION CRITERIA

- Confirmed mantle cell lymphoma (MCL) diagnosis that has been previously treated with at least one prior line of systemic therapy
- Measurable disease per Lugano criteria
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- Absolute neutrophil count ≥0.75 x 10^9/L without granulocyte-colony stimulating factor support within 7 days of screening
- Hemoglobin ≥8 g/dL and platelets ≥50 x 10^9/L not requiring transfusion support or growth factors within 7 days of screening
- AST and ALT ≤3.0 x upper limit of normal (ULN); total bilirubin ≤1.5 x ULN
- Creatinine clearance of ≥30 mL/min according to Cockcroft-Gault formula

PRIMARY ENDPOINT

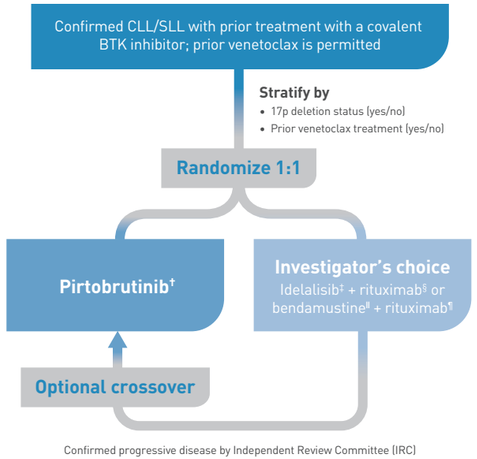
- Progression-free survival

KEY EXCLUSION CRITERIA

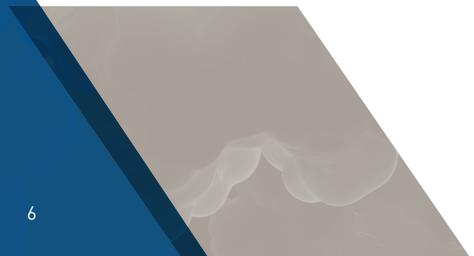
- Prior treatment with an approved or investigational BTK inhibitor
- History of bleeding diathesis
- History of stroke or intracranial hemorrhage within 6 months of randomization
- History of allogeneic or autologous stem cell transplant (SCT) or chimeric antigen receptor-modified T-cell (CAR-T) therapy within 60 days of randomization
- Clinically significant cardiovascular disease
- Prolonged QT interval corrected using Fridericia's formula (QTcF) >470 ms on two out of three consecutive ECGs, and mean QTcF >470 ms on all three ECGs
- Known HIV infection or active HBV, HCV, or CMV infections
- Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption
- Ongoing chronic treatment with strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers, which cannot be stopped within 3-5 half-lives of the CYP3A inhibitor therapy prior to start of study treatment
- Patients requiring therapeutic anticoagulation with warfarin or another vitamin K antagonist
- Vaccination with live vaccine within 28 days prior to randomization

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT04662255].

A Phase 3 Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) Versus Investigator's Choice of Idelalisib Plus Rituximab or Bendamustine Plus Rituximab in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma*



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.



* This clinical trial is being conducted globally.
† Pirtobrutinib is administered 200 mg PO QD until progression or unacceptable toxicity.
‡ Idelalisib is administered 150 mg PO BID.
§ Rituximab is administered intravenously (IV) as 8 total infusions.
‖ Bendamustine is administered 70 mg/m^2 IV on days 1 and 2 of cycles 1-6.
¶ Rituximab is administered IV as 6 total infusions.

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 a covalent BTK inhibitor
- Eastern Cooperative Oncology Group (ECOG) status of 0-2
- Absolute neutrophil count ≥0.75 x 10^9/L without granulocyte-colony stimulating factor support
- Hemoglobin ≥8 g/dL not requiring transfusion support or growth factors within 14 days of cycle 1 day 1
- Platelets ≥50 x 10^9/L not requiring transfusion support or growth factors within 14 days of cycle 1 day 1. If the investigator has chosen rituximab + bendamustine as the arm B treatment, platelets must be ≥75 x 10^9/L
- AST and ALT ≤3.0 x upper limit of normal (ULN); total bilirubin ≤1.5 x ULN
- Estimated creatinine clearance of ≥30 mL/min

PRIMARY ENDPOINT

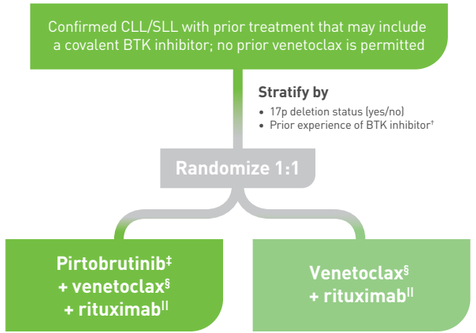
- Progression-free survival

KEY EXCLUSION CRITERIA

- Known or suspected Richter's transformation at any time preceding enrollment
- Known or suspected history of central nervous system (CNS) involvement by CLL/SLL
- Ongoing drug-induced liver injury
- Active uncontrolled autoimmune cytopenia
- Significant cardiovascular disease
- History of allogeneic or autologous 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
- Clinically significant active malabsorption syndrome or inflammatory bowel disease
- 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 and/or strong P-gp inhibitors
- Vaccination with a live vaccine within 28 days prior to randomization
- Patients with the following hypersensitivity:
  - Known hypersensitivity, including anaphylaxis, to any component or excipient of pirtobrutinib, idelalisib, and bendamustine
  - Prior significant hypersensitivity to rituximab

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT04666038].

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*



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.

* This clinical trial is being conducted globally.
† Discontinuation due to progression of disease vs discontinuation due to other reasons vs no prior BTK inhibitor.
‡ Pirtobrutinib is administered PO QD.
§ Venetoclax is administered PO QD.
ǁ Rituximab is administered intravenously.

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

PRIMARY ENDPOINT

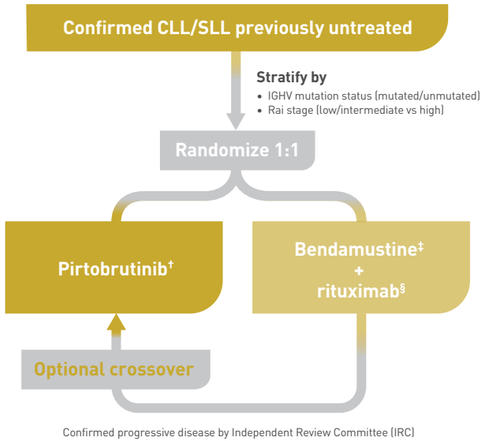
- Progression-free survival

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

A Phase 3 Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) Versus Bendamustine Plus Rituximab in Untreated Patients With Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma*



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.

* This clinical trial is being conducted globally.
† Pirtobrutinib is administered PO.
‡ Bendamustine is administered intravenously (IV).
§ Rituximab is administered IV.

KEY INCLUSION CRITERIA

- 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
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- Platelets ≥75 x 10^9/L (≥50 × 10^9/L for patients with evidence of bone marrow infiltrate), hemoglobin ≥8 g/dL, and absolute neutrophil count ≥0.75 x 10^9/L
- Adequate organ function
- Kidney function: Estimated creatinine clearance ≥40 mL/min

PRIMARY ENDPOINT

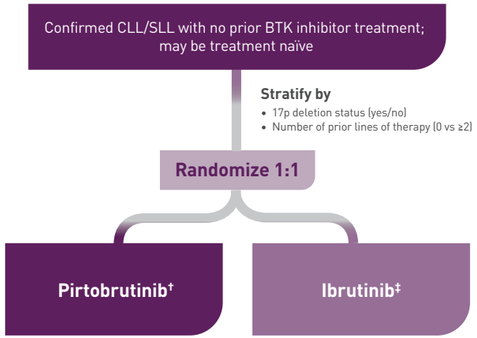
- Progression-free survival

KEY EXCLUSION CRITERIA

- Known or suspected Richter's transformation at any time preceding enrollment
- Prior systemic therapy for CLL/SLL
- Presence of 17p deletion
- Central nervous system (CNS) involvement
- Active uncontrolled autoimmune cytopenia (eg, autoimmune hemolytic anemia [AIHA], idiopathic thrombocytopenic purpura [ITP])
- Significant cardiovascular disease
- Active hepatitis B or C
- Active cytomegalovirus (CMV) infection
- Active uncontrolled systemic bacterial, viral, fungal, or parasitic infection
- Known HIV infection, regardless of cluster of differentiation 4 (CD4) count
- Concurrent use of investigational agent or anticancer therapy except hormonal therapy
- Patients requiring therapeutic anticoagulation with warfarin or another vitamin K antagonist
- Vaccination with a live vaccine within 28 days prior to randomization
- Patients with the following hypersensitivity:
  - Known hypersensitivity, including anaphylaxis, to any component or excipient of pirtobrutinib or bendamustine
  - Prior significant hypersensitivity to rituximab

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT05023980].

A Phase 3 Open-Label, Randomized Study of Pirtobrutinib (LOXO-305) Versus Ibrutinib in Patients With Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma*



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.

* This clinical trial is being conducted globally.
† Pirtobrutinib is administered PO.
‡ Ibrutinib is administered PO.

KEY INCLUSION CRITERIA

- 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
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
- Platelets ≥50 x 10^9/L, hemoglobin ≥8 g/dL, and absolute neutrophil count ≥0.75 x 10^9/L
- Adequate organ function
- Kidney function: Estimated creatinine clearance ≥30 mL/min

PRIMARY ENDPOINT

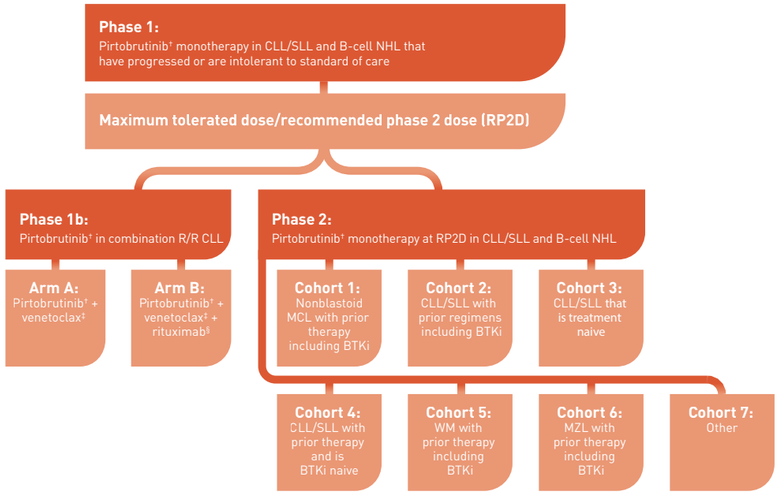
- Overall response rate as assessed by Independent Review Committee (IRC)

KEY EXCLUSION CRITERIA

- Known or suspected Richter's transformation to diffuse large B-cell lymphoma (DLBCL), prolymphocytic leukemia, or Hodgkin's lymphoma at any time preceding enrollment
- Known or suspected central nervous system (CNS) involvement
- Significant history of renal, neurologic, psychiatric, endocrine, metabolic, or immunologic disease
- Active uncontrolled autoimmune cytopenia (eg, autoimmune hemolytic anemia [AIHA], idiopathic thrombocytopenic purpura [ITP])
- Significant cardiovascular disease
- Active hepatitis B or C
- Active cytomegalovirus (CMV) infection
- Active uncontrolled systemic bacterial, viral, or fungal infection
- Known HIV infection, regardless of cluster of differentiation 4 (CD4) count
- Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal absorption
- Ongoing inflammatory bowel disease
- Prior exposure to BTK inhibitor (covalent or non-covalent)
- Concurrent use of investigational agent or anticancer therapy, except hormonal therapy
- Patients requiring therapeutic anticoagulation with warfarin or another vitamin K antagonist
- Use of ≥20 mg prednisone daily or equivalent dose of steroid with the first dose of study treatment
- Vaccination with a live vaccine within 28 days prior to randomization
- Chronic therapy with a strong cytochrome P450 3A (CYP3A) inhibitor (except posaconazole and voriconazole), which cannot be stopped within 3-5 half-lives of the CYP3A inhibitor therapy prior to start of study drug
- Known hypersensitivity, including anaphylaxis, to any component or excipient of pirtobrutinib or ibrutinib

Please visit www.clinicaltrials.gov for more information on this clinical trial [NCT05254743].

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



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.

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

KEY INCLUSION CRITERIA

- Phase 1/2 pirtobrutinib monotherapy: B-cell malignancies that have failed or are intolerant to either ≥2 prior standard of care regimens given in combination or sequentially, OR have received 1 prior BTK inhibitor-containing regimen when a BTK inhibitor 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/recurrent CLL and venetoclax is appropriate salvage treatment; no prior venetoclax is permitted
- Phase 1b arm B: Relapsed/refractory CLL and venetoclax + rituximab is appropriate salvage treatment; no prior venetoclax is permitted
- 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

- Investigational agent or anticancer therapy within 5 half-lives or 14 days, whichever is shorter, 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 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 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
- Clinically significant, 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
- Clinically significant active malabsorption syndrome
- Current treatment with certain strong cytochrome P450 3A4 (CYP3A4) inhibitors or inducers and/or strong P-gp inhibitors (phase 1b only)
- 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
- Prior treatment with pirtobrutinib or known hypersensitivity to any component or excipient of pirtobrutinib

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

LOXO@Lilly

Pipeline information is current through April 27, 2023.

VV-OTHR-US-DEL-1052 04/2023 PRINTED IN USA

© Lilly USA, LLC 2023. All rights reserved.

Printed on post-consumer recycled paper.