A Phase 3 Open-Label, Randomized Study of LOXO-305 versus Investigator Choice of BTK Inhibitor in Patients with Previously Treated BTK Inhibitor Naïve Mantle Cell Lymphoma (BRUIN MCL-321)

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Lymphomas non-Hodgkin's B-cell
Study type	Interventional

Summary

ID

NL-OMON54133

Source
ToetsingOnline

Brief title
LOXO-BTK-20019

Condition

- Lymphomas non-Hodgkin's B-cell

Synonym
Mantle Cell Lymphoma, MCL

Research involving
Human

Sponsors and support

Primary sponsor: Loxo Oncology, Inc., a wholly owned subsidiary of Eli Lilly and Company
Source(s) of monetary or material Support: the pharmaceutical industry

Intervention

Keyword: BTK-Inhibitor, LOXO-305, Mantle Cell Lymphoma, MCL

Outcome measures

Primary outcome

Assessed by independent review committee (IRC)

• PFS per Lugano criteria

Secondary outcome

Assessed by both investigator assessment and IRC

• Overall response rate (ORR) per Lugano criteria

• Duration of response (DOR) per Lugano criteria

Assessed by investigator assessment:

• PFS per Lugano criteria

• OS

• EFS

• TTF

• TTNT

• PFS2

Incidence and severity of serious adverse events (SAEs), adverse events

(AEs), deaths, and clinical laboratory abnormalities per Common

Terminology

Criteria for Adverse Events (CTCAE v5.0)

• Comparative tolerability: proportion of time with high side-effect

burden

• TTW of MCL-related symptoms

Study description

Background summary

This is a global, multicentre, open-label, randomized study evaluating the differences in efficacy, safety and tolerability of LOXO-305, a non-covalent BTK inhibitor as monotherapy (Arm A) compared to investigator choice of covalent BTK inhibitor monotherapy (Arm B, treatment with ibrutinib, acalabrutinib, or zanubrutinib) in patients with previously treated mantle cell lymphoma, who hasn*t received a BTK-inhibitor treatment before. The preliminary results evaluating LOXO-305 have demonstrated robust and durable anti-tumour activity, response rates and duration of therapy that compare favourably to standard of care therapies. These results support the current comparative trial.

Study objective

This study has been transitioned to CTIS with ID 2023-507695-52-00 check the CTIS register for the current data.

To compare progression-free survival (PFS) of LOXO-305 as monotherapy (Arm A) to investigator choice of covalent BTK inhibitor monotherapy (Arm B) in patients with previously treated mantle cell lymphoma (MCL).

Study design

BRUIN MCL-321 is a Phase 3, global, multicenter, randomized open label study comparing LOXO-305 as continuous monotherapy (Arm A) with investigator*s choice of BTK inhibitor monotherapy (Arm B) in patients with previously treated MCL.

Intervention

Subjects will be randomized 1:1 to Arm A (LOXO-305) versus Arm B (investigator's choice of BTK inhibitor).
Subjects enrolled in Arm A receive 200mg LOXO-305 each day and subjects enrolled in Arm B receive 560mg ibrutinib each day OR 100mg acalabrutinib twice a day OR 160mg zanubrutinib twice a day OR 320mg zanubrutinib each day.

Study burden and risks

Subject*s participation in this study will last 44 months and consists of a screening period, treatment period and a follow-up period. During the treatment period, subjects will need to visit the study site after 2 and 4 weeks during the first cycle and every 4 weeks during the next cycles. During the follow-up period, subjects will be contacted every 6 months for survival. Aside from the intervention described above, participation in this study involves blood draws at multiple visits, biopsy at screening and might involve radiation exposure through CT, PET/CT or MRI scans. Participants will be subjected to: blood draws, tumor tissue biopsy, bone marrow biopsy, GI biopsy, questions regarding medical history, use of concomitant medications/procedures, general well-being and adverse events; urine sampling; measurement of vital signs; physical and neurological examination; performance status assessment; measurement of weight; ECGs, patient reported outcomes questionnaires.

Subjects will be expected to take the drug in the way the investigator explained, not have had any other investigational drugs within 2 weeks before start taking study drug or while taking study drug, not have had major surgery within 4 weeks before start taking study drug, not take vaccination with live vaccines within 28 days of dosing, during the study and within 90 days after the last dose of study treatment, keep their appointments for visits, honestly answer all study questions, keep a patient card with them at all times, avoids foods that are inhibitors of CYP3A4 and drugs that are inhibitors of p-glycoprotein, not get pregnant or make someone pregnant during the study and for 6 months after the last dose of study drug.

The following side effects have been observed in greater than or equal to 5% of patients receiving LOXO-305: Abdominal pain; Back pain; Bruising; Constipation; Cough; Decreased hemoglobin in your blood (anemia) which can cause tiredness and shortness of breath; Decreased white blood cells in your blood which may increase your risk of infection; Diarrhea; Dizziness; Fatigue (tiredness); Fever; Headache; Increase in a blood salt called uric acid which is usually due to cancer cells dying. Untreated high uric acid levels can lead to kidney damage; Nausea; Red bumpy rash; Shortness of breath; Swelling of legs or hands; Upper respiratory infection.

The following side effects have been mainly observed in patients receiving treatment with approved BTK inhibitor ibrutinib (I): abnormal bleeding (I); infections (I) including serious and fatal events; low blood counts, including low neutrophils (which fight infection and low platelets (which help blood to clot) (I); abnormal heart rhythms (I); high blood pressure (I); secondary cancers (I); complications affecting kidney function or blood salt levels when cells rapidly die (I); harmful effects on an embryo or fetus (I); rash; musculoskeletal pain; low potassium. The study drugs may cause unforeseeable risks to pregnant women or to unborn babies.

LOXO-305 has demonstrated clinical activity in the patient population specified for this study. LOXO-BTK-18001 (NCT03740529) is a first in human global Phase 1/ 2 study evaluating the safety and efficacy of LOXO-305 in patients with CLL and B-cell NHL who have failed or are intolerant to standard of care therapy. Efficacy data from the LOXO-BTK-18001 study show robust and durable anti-tumor activity against a variety of B-cell malignancies including covalent BTK inhibitor pretreated MCL. The safety profile in Study LOXO-BTK-18001 is reflective of the selectivity of LOXO-305. Additional information about the known and expected risks, serious adverse events (SAEs), and reasonably anticipated AEs of LOXO-305, is provided in the Investigator*s Brochure (LOXO-305 IB). When viewed as a whole, the benefit/risk ratio is favorable for LOXO-305 as monotherapy in the proposed patient population to be evaluated in this study.

Contacts

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Scientific
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• At least 18 years of age
• Confirmed diagnosis by local laboratory of MCL with documentation of overexpression of cyclin D1 with at least one B-cell marker (e.g., CD19, CD20, or PAX5) and/or t (11;14), by cytogenetics, fluorescent in situ hybridization (FISH) or polymerase chain reaction.
• Previously treated with at least one prior line of systemic therapy for MCL.
•Measurable disease by PET-CT and/or CT/MRI as defined by Lugano criteria and aligned with protocol imaging requirements:
- PET-CT: FDG (fluorodeoxyglucose) avid lymphoma lesion
- at least one nodal lesion (> 1.5 cm in long axis) or extranodal lesion (> 1.0 cm in long axis) measurable in 2 dimensions, not previously radiated (unless progression has been radiographically documented following radiation therapy).
• Documented evidence of radiographically and/or histologically confirmed PD on the most recent line of therapy or relapse prior to study enrollment.
• Eastern Cooperative Oncology Group (ECOG) performance status 0-2
• Adequate organ function
• Must have life expectancy of at least 3 months

Exclusion criteria

• Current suspected or confirmed active CNS involvement with MCL or previous CNS involvement.
• Prior treatment with an approved or investigational BTK inhibitor.
• Major surgery within 4 weeks prior to randomization.
• 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.
• Significant cardiovascular disease.
• Prolongation of the QT interval corrected for heart rate (QTcF) > 470 msec during Screening.
• Known human immunodeficiency virus (HIV) infection, regardless of CD4 count.
• Known active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection.
• Known active cytomegalovirus (CMV) infection. Unknown or negative status are eligible.

• Pregnancy during the study or within 3 months of the last dose of study treatment.
• Clinically significant active malabsorption syndrome or other condition likely to affect gastrointestinal (GI) absorption of the study drug.
• Evidence of other clinically significant uncontrolled condition(s) including but not limited to, uncontrolled systemic bacterial, viral, fungal or parasitic infection (except for fungal nail infection), or other clinically significant active disease process which in the opinion of the investigator and medical monitor may pose a risk for patient participation. Screening for chronic conditions is not required.
•History of second malignancy unless in remission for at least 2 years; in-situ carcinomas not requiring treatment intervention, , non-melanoma skin cancer curatively treated, nonmetastatic breast, or nonmetastatic prostate cancer where hormonal therapy is being continued as standard of care are allowed.

Prior/Concomitant Therapy
• 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 drug treatment.
Because of their effect on CYP3A4, use of any of the following within 3 days of study therapy start is prohibited: Grapefruit or grapefruit products, Seville oranges or products from Seville oranges, Star fruit or star fruit products.
• Steroid use with antineoplastic intent within 7 days of study drug initiation.
• Patients requiring therapeutic anticoagulation with warfarin or another vitamin K antagonist.
• Vaccination with a live vaccine within 28 days prior to randomization.
• Have a known hypersensitivity to any of the excipients of pirtobrutinib or to the intended covalent BTK inhibitor if randomized to control arm.
•Laction, or plan to breastfeed during the study or within 2 weeks of the last dose of study treatment.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial

Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-07-2022
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	LOXO-305
Product type:	Medicine
Brand name:	IMBRUVICA
Generic name:	Ibrutinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	31-03-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	29-07-2021
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	02-08-2022
Application type:	Amendment

Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	09-08-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	25-10-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-11-2022
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	06-02-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	19-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-07-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	20-10-2023
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2023-507695-52-00
EudraCT	EUCTR2020-004553-72-NL
ClinicalTrials.gov	NCT04662255
CCMO	NL76907.056.21