ISRCTN90634455 https://doi.org/10.1186/ISRCTN90634455

A trial of zanubrutinib treatment of patients with relapsed and refractory primary central nervous system lymphoma

Submission date
03/03/2022

Recruitment status
Recruiting

Registration date
25/03/2022

Overall study status
Ongoing

Last Edited
13/05/2024

Condition category
Cancer

[X] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-zanubrutinib-for-lymphoma-of-the-brain-and-spinal-cord-prizm

Background and study aims
Primary central nervous system lymphoma (PCNSL) is a rare type of brain tumour. It is an aggressive type of non-Hodgkin lymphoma that is found only in the brain or spinal cord. PCNSL is often treated with high doses of chemotherapy. The first treatment doesn't work for some patients (called 'refractory'), and the lymphoma can come back (called 'relapse'). Refractory or relapsed (RR) PCNSL is much more difficult to treat. There is currently no standard treatment for RR-PCNSL and further chemotherapy treatment is often unsuccessful. Radiation treatment to the brain can sometimes be used but can cause significant long-term side effects.
Clinical trials are now focused on testing new drugs that are better at targeting the tumour and are likely to have fewer side effects. The treatment being tested in this study is a drug called zanubrutinib. Zanubrutinib is a new type of drug (a Bruton's tyrosine kinase inhibitor), which works by targeting lymphoma cells. Previous studies have shown that similar drugs can cause RR-PCNSL to shrink or disappear. It is thought that zanubrutinib could be a more effective treatment that can be given safely without too many side effects. The aim of the study is to find out how effective and safe zanubrutinib is for patients with RR-PCNSL. The researchers will be looking at the effects zanubrutinib has against lymphoma, how long these effects last, and what the side effects of the drug are.

Who can participate?
Patients who have not responded to standard chemotherapy for PCNSL or have relapsed afterwards. Patients with this type of brain tumour often have impaired cognitive function due to their disease and previous therapy, but this has been known to improve in patients who respond well to treatment, so these patients are included in this trial.

What does the study involve?
Participants will receive 28-day cycles of continuous zanubrutinib treatment orally twice daily. The participants will continue until disease progression, development of unacceptable side

effects, or their choice. Participants no longer on treatment will be followed up every 3 months for survival, progression and subsequent treatment.

What are the possible risks and benefits of participating?
There is always a risk associated with taking any drug. There may be risks of the study drug that are unknown or cannot be predicted at this time, but patients will be carefully monitored for any problems or adverse side effects. The treatments may or may not improve patients' underlying disease.

Where is the study run from?
University of Birmingham and the Cancer Research UK Clinical Trials Unit (UK)

When is the study starting and how long is it expected to run for?
April 2019 to October 2026

Who is funding the study?
Beigene (China) and Cure Leukaemia (UK)

Who is the main contact?
Emma Homer (trial coordinator)
PRiZM+@trials.bham.ac.uk

Contact information

Type(s)
Principal Investigator

Contact name
Prof Chris Fox

Contact details
Dept Clinical Haematology
Nottingham University Hospital
Hucknall Rd
Nottingham
United Kingdom
NG5 1PB
-
Christopher.Fox2@nuh.nhs.uk

Type(s)
Scientific

Contact name
Dr Emma Homer

Contact details
Cancer Research UK Clinical Trials Unit
Institute of Cancer and Genomic Sciences
University of Birmingham
Edgbaston

Birmingham
United Kingdom
B15 2TT
+44 (0)121 371 7861
PRiZM+@trials.bham.ac.uk

Additional identifiers

EudraCT/CTIS number
2020-005218-16

IRAS number
290665

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 50538, IRAS 290665

Study information

Scientific Title
PRiZM+: a Phase II platform study of zanubrutinib monotherapy and combination therapy for relapsed and refractory primary central nervous system lymphoma

Acronym
PRiZM+

Study objectives
Is zanubrutinib (a new drug that interferes with signals that B cells need to survive and grow) a safe and effective treatment for patients with an aggressive brain tumour known as primary central nervous system lymphoma (PCNSL), who have either not responded to initial chemotherapy, or have relapsed after chemotherapy?

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 05/11/2021, East Midlands – Leicester Central REC (The Old Chapel, Royal Standard Place, Nottingham, NG1 6FS, UK; +44 (0)207 104 8115; leicestercentral.rec@hra.nhs.uk), ref: 21/EM/0224

Study design
Non-randomized; Interventional; Design type: Treatment, Drug

Primary study design
Interventional

Secondary study design

Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

Health condition(s) or problem(s) studied
Relapsed and refractory primary CNS lymphoma

Interventions
This is a prospective, multicentre, sequential single-arm phase II study for zanubrutinib for the treatment of RR-PCNSL.

Patients and legal representatives who consent to participate will have a screening period of up to 28 days before trial registration for the following assessments to take place. The patient will be asked their demographic and medical history, physical exam (including vital signs, height and weight), pregnancy test (for women of childbearing potential [WOCBP]), blood tests, lumbar puncture and cerebrospinal fluid (CSF) evaluation, Eastern Cooperative Oncology Group (ECOG) performance status, Neurologic Assessment for Neuro-Oncology (NANO), functional assessment, ophthalmological slit lamp exam, MRI scan and a PET-CT scan (or CT-NCAP [neck-chest-abdomen-pelvis]).

Once registered to the study, patients will receive 28-day cycles of continuous zanubrutinib monotherapy orally twice daily. The patient will continue until disease progression, development of unacceptable side effects, or patient choice.

Patients will be seen on day 1 of cycle 1 for vital signs, physical exam, pregnancy test (for WOCBP), blood tests, ECOG performance status and NANO. Days 7 and 14 of cycle 1 they will be seen again for blood tests, lumbar puncture and CSF evaluation and an ECOG performance status. Day 1 of cycle 2 the patient will be seen for vital signs, blood tests, lumbar puncture and CSF evaluation, ECOG performance status and a multimodal MRI scan. On day 1 of cycle 3 the patient will be seen for the same assessments as mentioned for cycle 2, but also a physical exam, NANO, functional assessment, ophthalmological slit lamp exam and a Gd-enhanced MRI. Following cycle 3, patients will be seen on day 1 of each cycle for vital signs, blood tests and ECOG performance status assessment. Every 3 months during treatment the patient will be seen for a NANO, functional assessment and Gd-enhanced MRI. Every 6 months they will be seen for an additional blood test for circulating tumour DNA.

If the patient experiences disease progression, they will be seen for vital signs, blood tests, ECOG performance status, NANO and functional assessment. They will be seen 28 days after the last dose of trial treatment for an End of Treatment visit, this will include vital signs, blood tests, ECOG performance status, NANO and Gd-enhanced MRI.

Patients no longer on treatment will be followed up every 3 months for survival, progression date and subsequent therapy.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Zanubrutinib

Primary outcome measure
Overall response (complete response [CR] + unconfirmed CR [CRu] + partial response [PR]) after two cycles of treatment, assessed locally using international consensus criteria (Abrey et al., 2005). Patients will be followed up for 1 year.

Secondary outcome measures
Patients will be followed up for 1 year:
1. Complete response at response assessment by MRI scan after two cycles of treatment, response assessed locally or by central MRI scan review
2. Overall response assessed by MRI scan after two cycles of treatment, assessment by central MRI review
3. Best overall response assessed by MRI scan within 12 months of registration, response assessed locally or by central MRI scan review
4. Progression-free survival, defined as the time from trial entry to the date of progressive disease or death from any cause
5. Overall survival, defined as the time from trial entry to the date of death from any cause
6. Event-free survival, defined as the time from trial entry to the first of initiation of a new anti-lymphoma treatment, progressive disease, or death from any cause
7. Toxicity, defined as the proportion of patients experiencing one or more: grade 2 or higher non-haematological adverse events (AE), grade 3 or higher haematological AE, or any serious AE (SAE)

Overall study start date
12/04/2019

Completion date
20/10/2026

Eligibility

Key inclusion criteria
1. Aged ≥16 years of age
2. Histologically confirmed CD20+ diffuse large B cell lymphoma (DLBCL) confined to the CNS
3. Relapsed or refractory PCNSL (defined as disease progression following complete response (CR)/unconfirmed complete response (CRu)/partial response (PR), or failure to achieve PR after one or more lines of therapy; one therapy line must have included at least 1 cycle of high-dose methotrexate [≥1 g/m^2])
4. Measurable disease on contrast-enhanced MRI of brain (and/or spinal cord)
5. ECOG performance status of 0 to 2, or 3 if attributed to lymphoma
6. Ability to swallow capsules
7. Adequate renal and liver function defined as:

7.1. Creatinine clearance ≥30 ml/min (as estimated by the Cockcroft-Gault equation or as measured by nuclear medicine scan or 24-hour urine collection)
7.2. Serum total bilirubin <3.0 x ULN (unless due to Gilbert's syndrome)
7.3. Up to and including moderate impairment (Child-Pugh class B)
8. Adequate bone marrow function, defined as unsupported platelets >50 x10e9/l, neutrophils >1 x10e9/l, haemoglobin >80 g/l
9. Patient willing and able to comply with scheduled visits, treatment plan, investigations and other study procedures
10. Written informed consent for the trial

Participant type(s)
Patient

Age group
Adult

Lower age limit
16 Years

Sex
Both

Target number of participants
Planned Sample Size: 20; UK Sample Size: 20

Key exclusion criteria
1. Current evidence or prior history of systemic lymphoma
2. Exclusive intraocular involvement
3. Active infection requiring intravenous antimicrobials
4. Chemotherapy for lymphoma within 2 weeks of the first dose of zanubrutinib
5. Whole-brain radiotherapy within 4 weeks of the first dose of zanubrutinib
6. Contra-indication to lumbar puncture
7. Prior exposure to BTK inhibitor
8. Known bleeding disorder e.g haemophilia or severe Von-Willebrand Disease
9. Current use of warfarin, or dual anti-platelet therapy. Therapeutic anticoagulation with direct oral anticoagulants or low molecular weight heparin is permitted
10. Evidence of active HIV, HBV or HCV infection, except:
10.1. HIV-positive patients established on anti-retroviral treatment, with undetectable HIV RNA, after discussion with the patient's HIV physician
10.2. HBV core antibody-positive patients who are (i) surface antigen-negative and (ii) HBV DNA PCR negative, who take prophylaxis as per institutional guidelines
11. Patients who are pregnant or breastfeeding (women of childbearing potential must have a negative urine or serum pregnancy test prior to trial entry)
12. Patients and patients with partners of childbearing potential (pre-menopausal female capable of becoming pregnant) not willing to use highly effective contraception (see Section 9.6) during and for 12 months after cessation of therapy
13. Clinically significant cardiac or respiratory dysfunction that, in the opinion of the investigator, would jeopardise the safety of the patient in the trial
14. Active malignancy treated in the last 2 years, except:

14.1. Non-melanoma skin cancer
14.2. Carcinoma in situ of the cervix or breast
14.3. Incidental finding of prostate cancer (T1a or T1b)

Date of first enrolment
20/10/2022

Date of final enrolment
20/10/2025

Locations

Countries of recruitment
England

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
Aberdeen Royal Infirmary
Foresterhill Road
Aberdeen
United Kingdom
AB25 2ZN

Study participating centre
Churchill Hospital
Churchill Hospital
Old Road
Headington
Oxford
United Kingdom
OX3 7LE

Study participating centre
Beatson West of Scotland Cancer Centre
1053 Great Western Road
Glasgow
United Kingdom
G12 0YN

Study participating centre
Belfast City Hospital
51 Lisburn Rd
Belfast
United Kingdom
BT9 7AB

Study participating centre
Clatterbridge Cancer Centre
65 Pembroke PLACE
Liverpool
United Kingdom
L7 8YA

Study participating centre
Christie Hospital
Wilmslow Road
Manchester
United Kingdom
M20 4BX

Study participating centre
King's College Hospital
Denmark Hill
London
United Kingdom
SE5 9RS

Study participating centre
Freeman Road Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre

Nottingham University Hospital
Queens Medical Centre
Derby Road
Nottingham
United Kingdom
NG7 2UH

Study participating centre
Royal Hallamshire Hospital
Glossop Road
Sheffield
United Kingdom
S10 2JF

Study participating centre
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
St. Bartholomews Hospital
West Smithfield
London
United Kingdom
EC1A 7BE

Study participating centre
St James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

Study participating centre
University Hospital Birmingham
Queen Elizabeth Hospital
Edgbaston

Birmingham
United Kingdom
B15 2TH

Study participating centre
University College London Hospital
250 Euston Road
London
United Kingdom
NW1 2BU

Study participating centre
University Hospital of Wales
Heath Park
Cardiff
United Kingdom
CF14 4XW

Sponsor information

Organisation
University of Birmingham

Sponsor details
Edgbaston
Birmingham
England
United Kingdom
B15 2TT
+44 (0)1214158011
researchgovernance@contacts.bham.ac.uk

Sponsor type
University/education

Website
http://www.birmingham.ac.uk/index.aspx

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Charity

Funder Name
Cure Leukaemia

Funder Name
BeiGene

Alternative Name(s)
, BeiGene Ltd, BeiGene, Ltd.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
China

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal

Intention to publish date
30/06/2026

Individual participant data (IPD) sharing plan
The data-sharing plans for the current study are unknown and will be made available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No