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Optimizing the MATRix chemotherapy regimen, to reduce side-effects and improve outcomes, for patients with newly diagnosed primary central nervous system lymphoma

Submission date
29/07/2022

Recruitment status
Recruiting

Registration date
10/08/2022

Overall study status
Ongoing

Last Edited
15/11/2024

Condition category
Cancer

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

Plain English summary of protocol

Background and study aims
Primary diffuse large B-cell lymphoma of the central nervous system (PCNSL) is a rare disorder that may affect one or several areas of the brain, spinal cord or eye. Current standard of care treatment for newly diagnosed PCNSL patients aged under 70 is 4 cycles of MATRix (induction treatment), which consists of rituximab, cytarabine, methotrexate and thiotepa. This is followed by thiotepa-based high-dose chemotherapy with carmustine or busulfan, then autologous stem cell transplantation (ASCT) (consolidation treatment). The induction treatment is more intensive than some patients can tolerate, resulting in a third of patients unable to have an ASCT, an important part of successful treatment.
This study aims to increase the number of patients that receive ASCT by reducing the toxicity of induction treatment, whilst also improving its effectiveness.

Who can participate?
Newly diagnosed PCNSL patients will be approached for this study.

What does the study involve?
Participants will be randomised in a 1:1 ratio between standard of care treatment (control arm) and the experimental arm. The experimental arm consists of one cycle of rituximab and methotrexate, two MATRix drugs that are less toxic. The hypothesis is that this will allow patients to partially recover after their diagnosis so that they are able to better withstand subsequent treatment with MATRix. Patients will then receive abbreviated treatment with 2 cycles of MATRix, then continue to standard of care consolidation treatment. The treatment period is 12 and 16 weeks for the experimental and control arm, respectively. Patients will be followed up to monitor their response to the treatment for a minimum of 2 years after transplant.
There is a translational aspect of the study that aims to analyse tumour biopsy samples and blood to try and identify patients who may be at higher risk of their lymphoma not responding to treatment or returning after treatment has finished.

What are the possible benefits and risks of participating?
Clinical trials are designed to reduce the risks and increase the benefits to the people who take part, regardless of which treatment they get. However, we cannot guarantee any specific treatment benefits or that there are no risks involved when taking part in a clinical trial.
Possible benefits:
• You will be helping to further our knowledge of how to treat PCNSL and this will benefit others with the same condition in the future
• If you have the abbreviated treatment, you may have fewer side effects than you would have if you have the standard care. You may also have a greater chance of undergoing stem cell transplant as consolidation treatment which may increase the chance of successful treatment
Possible risks/disadvantages:
• The trial treatment may not control your PCNSL
• There may be some unpleasant side effects (further information can be found in the Patient Information Sheet)
• There could be risks to your child if you, or your partner, are/or become pregnant, or breastfeeding (further information can be found in the Patient Information Sheet)

Where is the study run from?
Klinikum der Landeshauptstadt Stuttgart gKAöR (Germany)

When is the study starting and how long is it expected to run for?
October 2021 to August 2028

Who is funding the study?
Cancer Research UK

Who is the main contact?
Christoper Wignall, optimatetrial@soton.ac.uk
Prof Christopher Fox, christopher.fox@nhs.net

https://main-site-admin.cms.app.crnet.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-a-different-way-of-giving-a-drug-combination-called-matrix-for-people-with

Study website
https://www.southampton.ac.uk/ctu/trialportfolio/listoftrials/optimate.page

Contact information

Type(s)
Public

Contact name
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Principal Investigator

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Additional identifiers

EudraCT/CTIS number
2018-002115

IRAS number
1005070

ClinicalTrials.gov number
NCT04931368

Secondary identifying numbers
SCC215/P002900, IRAS 1005070, CPMS 53728

Study information

Scientific Title
Optimizing MATRix as remission induction in PCNSL: De-escalated induction treatment in newly diagnosed primary CNS lymphoma - a randomized phase III trial

Acronym
OptiMATe

Study objectives
A de-escalated induction treatment strategy followed by autologous stem cell transplantation is superior to standard MATRix protocol in terms of event free survival.

Ethics approval required

Old ethics approval format

Ethics approval(s)
Approved 15/09/2022, North West - Greater Manchester South Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK: +44 (0)207 104 8143, gmsouth.rec@hra.nhs.uk), ref: 22/NW/0281

Study design
Randomized controlled open-label multicenter phase III trial with two parallel arms.

Primary study design
Interventional

Secondary study design
Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Treatment of primary central nervous system lymphoma (PCNSL) in newly diagnosed patients

Interventions
Control treatment (Arm A): Patients receive four cycles of MATRix (rituximab 2 x 375 mg/m², HD-MTX 3.5 g/m², HD-AraC 4 x 2 g/m², thiotepa 30 mg/m²; i.v.) as induction treatment. Response assessment with gadolinium-enhanced brain MRI (centrally reviewed) takes place after cycles two and four. Patients with at least PR proceed to 3rd cycle of MATRix after first response assessment and to HCT-ASCT (BCNU 400 mg/m², thiotepa 4 x 5 mg/kg; i.v.) after second response assessment. Collection of autologous stem cells is planned after the second cycle of MATRix.

Experimental treatment (Arm B): As induction treatment, patients receive a pre-phase treatment with R/HD-MTX (rituximab 375 mg/m², HD-MTX 3.5g/m²; i.v.). In the absence of clinical signs of progression, patients proceed to two cycles of MATRix, followed by a response assessment with gadolinium-enhanced brain MRI (centrally reviewed). Patients achieving at least PR will proceed to HCT-ASCT (BCNU 400 mg/m², thiotepa 4 x 5 mg/kg; i.v.). Collection of autologous stem cells is planned after the first cycle of MATRix.

Duration of treatment per patient:
Control treatment (Arm A): 15 weeks (first cycle until bone marrow recovery after ASCT)
Experimental treatment (Arm B): 11 weeks (first cycle until bone marrow recovery)

Patients will be randomised between treatment arms 1:1. Randomisation will be performed by the local research teams using the Electronic Data Capture system. For OptiMATe, this will be SecuTrial.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Rituximab, methotrexate, cytarabine, thiotepa, carmustine/BCNU, busulfan

Primary outcome measure
Event-free survival (EFS, defined as time from randomization to premature end of treatment due to any reason, lymphoma progression or death, whichever occurs first) measured using patient records

Secondary outcome measures
Measured using patient records unless noted:
1. Overall survival (OS)
2. Progression free survival (PFS)
3. Remission prior to consolidation therapy – RA II
4. Remission after consolidation – 30 days after ASCT
5. Rate of patients reaching consolidation
6. Quality of life (QoL): EORTC QLQ-C30, EORTC QLQ-BN20; measured during screening period, at EOT (30 days after ASCT) and thereafter every 12 months during follow-up.
7. Safety: based on standard criteria for monitoring, assessing and reporting of (serious) adverse events (CTC-AE criteria v5.0), Toxicity will be monitored by taking vital signs and laboratory parameters, Neurotoxicity will be assessed by MoCA/ TMT-A and -B and a neuropsychological test battery, Rate of unplanned hospital admissions, Length of hospital stays (nights in hospital)

Overall study start date
01/10/2021

Completion date
31/08/2028

Eligibility

Key inclusion criteria
1. Immunocompetent patients with newly diagnosed primary diffuse large B-cell lymphoma of the central nervous system (PCNSL).
2. Male or female patients aged 18-65 years irrespective of ECOG or 66-70 years with ECOG Performance Status ≤2.
3. Histologically or cytologically assessed diagnosis of B-cell lymphoma by local pathologist. Diagnostic sample obtained by stereotactic or surgical biopsy, CSF cytology examination or vitrectomy.
4. Disease exclusively located in the CNS.

5. At least one measurable lesion.
6. Previously untreated patients (previous or ongoing steroid treatment admitted).
7. Negative pregnancy test
8. Written informed consent obtained according to international guidelines and local laws by patient or authorized legal representative in case patient is temporarily legally not competent due to his or her disease.
9. Ability to understand the nature of the trial and the trial related procedures and to comply with them.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
65 Years

Sex
Both

Target number of participants
80 patients from UK sites

Key exclusion criteria
1. Congenital or acquired immunodeficiency including HIV infection and previous organ transplantation.
2. Systemic lymphoma manifestation (outside the CNS).
3. Primary vitreoretinal lymphoma or primary leptomeningeal lymphoma without manifestation in the brain parenchyma or spinal cord
4. Previous or concurrent malignancies with the exception of surgically cured carcinoma in situ or other kinds of cancer without evidence of disease for at least 5 years.
5. Previous Non-Hodgkin lymphoma at any time.
6. Inadequate renal function (clearance <60 ml/min).
7. Inadequate bone marrow, cardiac, pulmonary or hepatic function according to investigator´s decision
8. Active hepatitis B or C disease.
9. Concurrent treatment with other experimental drugs or participation in an interventional clinical trial with study medication being administered within the last 30 days before the start of this study.
10. Clinically relevant third space fluid accumulation according to the investigator’s discretion.
11. Hypersensitivity to study treatment or any component of the formulation.
12. Taking any medications that are likely to cause interactions with the study medication
13. Known or persistent abuse of medication, drugs or alcohol.
14. Active COVID-19-infection or non-compliance with the prevailing hygiene measures regarding the COVID-19 pandemic
15. Patients without legal capacity who are unable to understand the nature, significance and consequences of the trial and without designated legal representative.

16. Previous participation in this trial.
17. Persons who are in a relationship of dependency/ employment with the sponsor and/ or the investigator.
18. Any familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
19. Current or planned pregnancy, nursing period
20. For fertile patients: Failure to use one of the following safe methods of contraception: intra-uterine device or hormonal contraception in combination with a mechanical method of contraception.

Date of first enrolment
30/12/2022

Date of final enrolment
30/06/2026

Locations

Countries of recruitment
Austria

England

Germany

Italy

Northern Ireland

Scotland

United Kingdom

Wales

Study participating centre
Nottingham University Hospitals NHS Trust - City Campus
Nottingham City Hospital
Hucknall Road
Nottingham
United Kingdom
NG5 1PB

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London

United Kingdom
NW1 2PG

Study participating centre
University Hospital Southampton NHS Foundation Trust
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

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

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
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M20 4BX

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
Leeds Teaching Hospitals NHS Trust
St. James's University Hospital
Beckett Street

Leeds
United Kingdom
LS9 7TF

Study participating centre
Sheffield Teaching Hospitals NHS Foundation Trust
Northern General Hospital
Herries Road
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United Kingdom
S5 7AU

Study participating centre
University Hospitals Plymouth NHS Trust
Derriford Hospital
Derriford Road
Derriford
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PL6 8DH

Study participating centre
Oxford University Hospitals NHS Foundation Trust
John Radcliffe Hospital
Headley Way
Headington
Oxford
United Kingdom
OX3 9DU

Study participating centre
The Clatterbridge Cancer Centre NHS Foundation Trust
Clatterbridge Hospital
Clatterbridge Road
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Study participating centre

University Hospitals of North Midlands NHS Trust
Newcastle Road
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Study participating centre
King's College Hospital NHS Foundation Trust
Department of Haematology
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Study participating centre
University Hospital of Wales
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CF14 4XW

Study participating centre
Hammersmith Hospital
Du Cane Road
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W12 0HS

Sponsor information

Organisation

Klinikum der Landeshauptstadt Stuttgart gKAöR

Sponsor details
Elsaesser Strasse 2
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zks.optimate@uniklinik-freiburg.de

Sponsor type
University/education

Website
http://www.klinikum-stuttgart.de/

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The sponsor assures that the key design elements of this protocol will be posted in a publicly accessible clinical trials registry. In addition, upon trial completion the results of this trial will be submitted for publication and/or posted in a publicly accessible database of clinical trial results irrespective of the results of the trial.
Each publication of trial results will be in mutual agreement between the principal investigator, the other investigators involved and the CTU. All data collected in connection with the clinical

trial will be treated in confidence by the coordinating investigator and all others involved in the trial, until publication. Interim data and final results may only be published (orally or in writing) with the agreement of the coordinating investigator and the CTU. This is essential for a thorough exchange of information between the aforementioned parties and will ensure that the opinions of all parties involved have been heard before publication. This agreement, which does not include any veto right or right of censorship for any of the parties involved, may not be refused without good reason.

Intention to publish date
01/08/2030

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be 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