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A trial looking at the effectiveness of combining standard R-ICE chemotherapy with another medicine (polatuzumab vedotin) for patients with diffuse large B cell lymphoma that has either, not responded to or returned, following the first treatment received

Submission date	**Recruitment status**	[_] Prospectively registered
16/11/2021	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
18/05/2022	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
21/01/2026	Cancer	[X] Record updated in last year

Plain English summary of protocol

Background and study aims

Diffuse large B-cell lymphoma (DLBCL) is the most common of the non-Hodgkin's lymphomas and is a cancer of the lymphatic system (which helps the body to fight germs and infections). The majority of patients will respond well to conventional front line treatment (R-CHOP, a type of immunochemotherapy), a significant number of patients lymphoma will not respond or their disease will return after completion of treatment. These patients, whose disease does not respond or returns, are sometimes treated with an immunochemotherapy combination called R-ICE (rituximab, ifosfamide, carboplatin and etoposide). Although this can be successful, 50% of patients' disease will not respond sufficiently to go on and receive high-dose treatment and a stem cell transplant. The aim of this study is to test a new drug called polatuzumab vedotin in addition to R-ICE in people whose DLBCL has returned or has not responded to initial treatment. In single drug studies polatuzumab vedotin has shown to have some benefit, but it has not been tested in combination with R-ICE chemotherapy. Polatuzumab vedotin's single drug activity in aggressive B-cell lymphoma has shown limited toxicity (side effects), making it a promising candidate to be used in combination with R-ICE chemotherapy, which is considered one of the least toxic of the available second-line treatments. The study will therefore look at the effect of the combination of polatuzumab vedotin and R-ICE vs R-ICE alone. As this is the first study to assess the combination, particular attention will be paid to addressing potential safety concerns.

Who can participate?

Patients aged 18 and over with relapsed or refractory DLBCL following their first line of treatment and who are eligible for stem cell transplant

What does the study involve?
Patients will be randomly allocated to receive either polatuzumab vedotin plus rituximab, ifosfamide, carboplatin and etoposide (Pola-R-ICE) or rituximab, ifosfamide, carboplatin and etoposide (R-ICE). Treatment will be given over three 21-day cycles. For each patient, the total duration of the study will be about 3 months of treatment plus at least 21 months of follow-up. The study consists of a screening/inclusion visit, three chemotherapy cycles, an end-of -treatment visit, and follow-up visits. A number of assessments and blood tests will be required at screening and during treatment. Additional blood samples for the patients allocated to Pola-R-ICE will be required at certain times to help understand how polatuzumab vedotin is interacting in the body. There is also the option to take part in additional sample collection if the patient wishes. There is a separate consent for this.

What are the possible benefits and risks of participating?
Generally, it can be stated that the treatment concept of the standard treatment (R-ICE) of the study corresponds to that which would also be recommended for routine clinical practice, i.e., the standard treatment strategy has identical risks and side effects whether given as a standard of care or as part of this study. All antibodies and chemotherapy drugs used in the study have been tested and approved for the treatment of aggressive non-Hodgkin's lymphomas. The combination of the standard therapy R-ICE with the antibody chemotherapy molecule polatuzumab vedotin (Pola-R-ICE) has not been tested yet and is therefore the subject of this study. The combination Pola-R-ICE can have a higher risk of side effects compared to R-ICE alone. This mainly concerns a deeper and longer weakness of the immune response with the risk of serious infections, and damage to the nervous system leading to numbness of the hands and feet. However, from the combination study in older people that has already been completed, it can be assumed that this risk is limited and is offset by the possible success in reducing the lymphoma.
The study treatment may help to control the lymphoma. Patients will be helping to further knowledge of how to treat cancer and this will benefit society and others with the same condition in the future. However, the treatment may not control the lymphoma, there may be side effects and patients will need to attend more clinic visits and provide more blood samples than if they were not taking part in the study.
Patients will have at least three PET-CT scans or contrast-enhanced CT scans. Two of these scans are standard of care. A PET-CT scan involves a radioactive isotope being given and then a PET-CT scanner detects how much of the isotope the body absorbs and uses a computer to create an accurate image of the scanned body area. A contrast-enhanced CT scan involves radiation using x-rays to get a detailed image of the body area. The patient may also have a bone scan if the doctor thinks it is appropriate. This involves a radioactive isotope being given to the patient and then a scanner detects how much of the isotope the body absorbs and uses a computer to create an accurate image of the scanned body area. Ionising radiation may cause cancer many years or decades after the exposure. The chances of this happening to participants as a consequence of taking part in this study are about 1.5%.

Where is the study run from?
GWT-TUD GmbH in cooperation with the German Lymphoma Alliance (GLA) (Germany)

When is the study starting and how long is it expected to run for?
July 2020 to December 2025

Who is funding the study?
F. Hoffman-La Roche (Switzerland)

Who is the main contact?
Trial Manager at the Southampton Clinical Trials Unit
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https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-polatuzumab-vedotin-for-b-cell-lymphoma-pola-r-ice

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Additional identifiers

Clinical Trials Information System (CTIS)
2019-002962-10

Integrated Research Application System (IRAS)
1004045

ClinicalTrials.gov (NCT)
NCT04833114

Protocol serial number
MO40599/GLA2017-R2

Study information

Scientific Title
An open-label, prospective Phase III clinical study to compare polatuzumab vedotin plus rituximab, ifosfamide, carboplatin and etoposide (Pola-R-ICE) with rituximab, ifosfamide, carboplatin and etoposide alone as salvage therapy in patients with primary refractory or relapsed diffuse large B-cell lymphoma

Acronym
Pola-R-ICE

Study objectives
Combining polatuzumab vedotin with rituximab, ifosfamide, carboplatin and etoposide chemotherapy (Pola-R-ICE) improves event-free survival in patients with relapsed or primary refractory diffuse large B-cell lymphoma (DLBCL) compared to rituximab, ifosfamide, carboplatin and etoposide (R-ICE) alone.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/12/2021, South Central – Oxford B Research Ethics Committee (Ground Floor, Temple Quay House, 2 The Square, Bristol, BS1 6PN, UK; +44 (0)207 104 8178, +44 (0)207104 8360, +44 (0)207 104 8270; oxfordb.rec@hra.nhs.uk), ref: 21/SC/0358

Study design
Multicenter interventional open-label randomized controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Relapsed or refractory diffuse large B-cell lymphoma

Interventions
Patients will be randomised by stratified block randomisation in a 1:1 ratio to receive either polatuzumab vedotin plus rituximab, ifosfamide, carboplatin and etoposide (Pola-R-ICE) (Experimental Arm) or rituximab, ifosfamide, carboplatin and etoposide (R-ICE) (Standard Arm). Treatment will be administered over 3 x 21 day cycles. For each patient, the total duration of the study will be approximately 3 months of treatment plus at least 21 months of follow-up.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Polatuzumab vedotin, rituximab, ifosfamide, carboplatin, etoposide

Primary outcome(s)
Event-free survival is measured using the following definitions at the timepoint that the definitions are met:
1. Failure to achieve a sufficient response, measured using lugano criteria response assessment at end of study treatment
2. Start of additional unplanned anti-tumour treatment, measured as the date when treatment is given
3. Relapse after achieving complete response, measured using Lugano criteria response assessment during follow-up
4. Death of any cause, measured as the reason for death and the date of the event

Key secondary outcome(s))
1. Progression-free survival is measured as the earliest date of progressive disease assessed using the Lugano criteria or death, whichever comes first
2. Overall survival is measured as death from any cause at the date of the event
3. Relapse after complete response is measured using Lugano criteria response assessment during follow-up
4. Rate of metabolic complete response is measured as the number of complete remissions (by PETCT Lugano assessment) after the end of study treatment, divided by the number of patients
5. Partial response rate is measured as the number of partial responses (by PETCT Lugano assessment) after the end of study treatment, divided by the number of patients
6. Overall response rate is measured as the number of complete or partial responses (by PETCT Lugano assessment) after the end of study treatment, divided by the number of patients
7. Progression rate is measured as the number of progressions (by PETCT Lugano assessment) after the end of study treatment, divided by the number of patients
8. Relapse rate is measured as the number of relapses measured at the date of event, divided by the number of patients with complete response (by PETCT Lugano assessment) after the end of treatment
9. Mobilization failure rate is measured as the number of patients experiencing mobilization failure (<2 x 10e6/kg CD34+ cells harvested) divided by the number of patients that underwent mobilization, measured at the time of the stem cell harvest
10. Rate of patients proceeding to transplantation is measured as the number of patients proceeding to transplantation (autoSCT/alloSCT/CAT-T) at the timepoint of the procedure, divided by the number of patients
11. Non-relapse mortality is measured as the time between randomisation and deaths without relapse/recurrence. Death from any cause without prior progression are events
12. Duration of response is measured as the time from documentation of tumour response (by PETCT Lugano assessment) to disease progression or relapse

Completion date
19/12/2025

Eligibility

Key inclusion criteria

1. The informed consent form must be signed before any study-specific tests or procedures are done
2. Adult male and female patients ≥18 years (≥16 years in the UK*) at the time of inclusion in the study
* In the UK an “adult” means a person who has attained the age of 16 years, according to The Medicines for Human Use (Clinical Trials) Regulations 2004, Part 1 Point 2.
3. Ability to understand and follow study-related instructions
4. Risk group: All patients with one of the following histologically defined entities: Histological diagnosis of primary refractory or relapsed aggressive B-cell non-Hodgkin lymphoma (B-NHL), confirmed by a biopsy of involved nodal or extranodal site. Patients with any of the following histologies can be included:
4.1. DLBCL not otherwise specified (NOS)
4.2. T-cell/histiocyte-rich large B-cell lymphoma
4.3. Primary cutaneous DLBCL, leg type
4.4. Epstein-Barr virus (EBV)-positive DLBCL, NOS
4.5. DLBCL associated with chronic inflammation
4.6. Primary mediastinal (thymic) large B-cell lymphoma
4.7. High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements
4.8. High-grade B-cell lymphoma, NOS
Refractory disease is defined as no complete remission to first-line therapy; subjects who are intolerant to first-line therapy are excluded. Three groups of patients are eligible:
4.9. Progressive disease (PD) as best response to first-line therapy (biopsy not mandatory if diagnostic sample available).
4.10. Stable disease (SD) as best response after at least 4 cycles of first-line therapy (e.g., four cycles of R-CHOP) (biopsy not mandatory if diagnostic sample available).
4.11. Partial response (PR) as best response after at least 6 cycles, and biopsy-proven residual disease or disease progression after the partial response.
Relapsed disease is defined as complete remission to first-line therapy followed by biopsy-proven disease relapse.
5. Performance Status ECOG 0-2 at time of randomization or ECOG 3 at screening if this is DLBCL-related and has improved to ECOG 2 or less with a 7-day steroid treatment during the screening phase (e.g. 1 mg/kg prednisone).
6. Information on all 5 International Prognostic Index (IPI) factors
7. Staging (PET-CT based-staging according to Lugano criteria 2014). Patients must have PET-positive lesions.
8. Subjects must have received adequate first-line therapy including at a minimum: i) anti-CD20 monoclonal antibody unless investigator determines that tumor is CD20 negative, and ii) an anthracycline-containing chemotherapy regimen
9. Intent to proceed to high-dose therapy (HDT) and stem cell transplantation (SCT) if response to second line therapy
10. Adequate hematological function, as defined by: hemoglobin ≥8 g/dl, absolute neutrophil count (ANC) ≥1.0 x 10e9/l OR ≥0.5 x 10e9/l if neutropenia is attributable to underlying disease and before the administration of steroids, and platelet count ≥75 x 10e9/L OR ≥50 x 10e9/l if thrombocytopenia is attributable to underlying disease
11. Women of childbearing potential must have a negative pregnancy test result within 7 days prior to the first study drug administration
12. For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating eggs
13. For men: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive measures, and agreement to refrain from donating sperm

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
16 years

Upper age limit
100 years

Sex
All

Total final enrolment
303

Key exclusion criteria
1. Serious accompanying disorder leading to impaired organ function causing significant clinical problems and reduced life expectancy of fewer than 3 months. In particular, patients with the following organ dysfunction caused by accompanying disorders are to be excluded:
1.1. Heart failure with left ventricular ejection fraction (LVEF) <45%
1.2. Impaired pulmonary function with vital capacity (VC) or forced expiratory volume (FEV1) <50% of normal (only in case of history of significant pulmonary disease)
1.3. Impaired renal function with glomerular filtration rate (GFR) < 50 ml/min (calculated)
1.4. Impaired liver function with alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT) or bilirubin > 1.5 x upper limit of normal (ULN). If elevation is caused by the disease, threshold of 2.5 x ULN is accepted
1.5. Peripheral neuropathy > Grade II
2. Human immunodeficiency virus (HIV)-positivity with detectable viral load and/or a CD4+ count below 0.3/nl
3. Hepatitis B and C as defined by seropositivity (HBsAG and anti HBe/anti-HBc; anti-Hc); in case of false-positive serology (transfused antibodies) negative PCR-results will allow patient inclusion. Patients with occult or prior HBV infection (defined as negative HBsAg and positive hepatitis B core antibody [HBcAb]) may be included if HBV DNA is undetectable, provided that they are willing to undergo DNA testing on Day 1 of every cycle and monthly for at least 12 months after the last cycle of study treatment
4. Known active bacterial, viral, fungal, mycobacterial, parasitic, or other infection (excluding fungal infections of nail beds) at study inclusion or any unresolved major episode of infection (as evaluated by the investigator) within 1 week prior to Cycle 1 Day 1
5. Patients with suspected or latent tuberculosis. Latent tuberculosis needs to be confirmed by a positive interferon-gamma release assay
6. Primary or secondary central nervous system (CNS) lymphoma at the time of recruitment
7. Richter’s transformation or prior chronic lymphocytic leukemia (CLL)
8. Vaccination with a live vaccine within 4 weeks prior to treatment
9. Recent major surgery (within 6 weeks before the start of Cycle 1 Day 1) other than for diagnosis

10. Treatment with radiotherapy, chemotherapy, immunotherapy, immunosuppressive therapy, or any investigational agent for the purposes of treating cancer within 2 weeks prior to Cycle 1 Day 1
11. Received more than one line of therapy for DLBCL
12. Received polatuzumab vedotin as part of the first-line therapy
13. Any other diseases, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications
14. Ongoing treatment or study procedures within any other Investigational Medicinal Product (IMP) clinical trial with the exception of follow-up. In the case of a preceding clinical trial, the last application of the respective IMP(s) must have been done more than five elimination half-lives before the start of study medication in this trial.
15. History of severe allergic or anaphylactic reactions to human, humanized, chimeric, or murine monoclonal antibodies
16. History of hypersensitivity to any of the study drugs or their ingredients or to drugs with a similar structure
17. Contraindications according to the Investigator´s Brochure (IB) of polatuzumab vedotin or the local Summary of Product Characteristics (SmPCs) of the used rituximab, ifosfamide, carboplatin or etoposide products
18. Criteria which in the opinion of the investigator preclude participation for scientific reasons, for reasons of compliance, or for reasons of the subject’s safety
19. Pregnancy or breastfeeding, or intending to become pregnant during the study or within 12 months after the last dose of study drug
20. Close affiliation with the investigator (e.g. a close relative) or persons working at the study site
21. Subject is an employee of the sponsor or involved Contract Research Organization
At study inclusion, any organ impairment due to lymphoma infiltration is NOT regarded as an exclusion criterion.

Date of first enrolment
30/04/2021

Date of final enrolment
31/12/2024

Locations

Countries of recruitment
United Kingdom

England

Northern Ireland

Austria

Germany

Spain

Study participating centre
James Paget University Hospitals NHS Foundation Trust
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Study participating centre
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Study participating centre
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Study participating centre
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Study participating centre
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Sponsor information

Organisation
Gesellschaft fur Wissens und Technologietransfer

Funder(s)

Funder type
Industry

Funder Name
F. Hoffmann-La Roche

Alternative Name(s)

Hoffman-La Roche, F. Hoffmann-La Roche Ltd.

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan

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