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Pembrolizumab plus chemotherapy for diffuse large B-cell lymphoma that has come back or does not respond to treatment

Submission date 09/03/2022	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [_] Record updated in last year
Registration date 11/05/2022	**Overall study status** Ongoing	
Last Edited 12/09/2024	**Condition category** Cancer	

Plain English summary of protocol

Background and study aims
Lymphoma is cancer that begins in the infection-fighting cells of the immune system, called lymphocytes. More than 13,000 new cases of non-Hodgkin's lymphoma are diagnosed in the UK each year. Diffuse large B cell lymphoma (DLBCL) is the most common, accounting for around 5,000 new cases per year. Rituximab with CHOP chemotherapy is the standard first-line treatment but in a third of patients, it does not work. The majority of these patients will die from their disease, as the success of salvage treatments is limited after treatment with rituximab. Patients who have few other complications are able to have high-dose therapy (stem cell transplant) after second-line (+) treatment but only if they are in complete remission. There is a growing need to find better second-line treatments that allow patients eligible for high dose therapy to receive it.

Who can participate?
Patients aged 18 years and over with diffuse large B-cell lymphoma who have been treated at least once for their lymphoma but it has returned (relapsed) or the treatment did not work (refractory)

What does the study involve?
Participants are randomly allocated to the control group or the experimental group. The control group will receive three cycles of a standard chemotherapy treatment known as R-ICE (rituximab, ifosfamide, carboplatin and etoposide). The experimental group will receive three cycles of R-ICE in combination with pembrolizumab. Those who have a complete response and a partial response in both groups following initial treatment will go on to have a stem cell transplant and then if they are in the control group they will receive pembrolizumab for 1 year. Patients will be followed up to monitor their continuing response to the treatment.

What are the possible benefits and risks of participating?
The potential risks are that the addition of pembrolizumab to standard care treatment may reduce the number of stem cells that are harvested. There will be an early data review to look at whether this is the case and if so the study would stop. There may be some adverse effects from

receiving the combination of pembrolizumab, but the research teams at sites will regularly monitor patients to check for side effects and provide appropriate treatment.

Where is the study run from?
Southampton General Hospital (UK)

When is the study starting and how long is it expected to run for?
March 2022 to December 2024

Who is funding the study?
Merck (USA)

Who is the main contact?
Dr Amber Cole
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

ClinicalTrials.gov (NCT)
NCT05221645

Clinical Trials Information System (CTIS)
2018-001886-18

Integrated Research Application System (IRAS)
1004066

Central Portfolio Management System (CPMS)
51402

Study information

Scientific Title
Pembrolizumab in combination with R-ICE chemotherapy in relapsed/refractory diffuse large B-cell lymphoma

Acronym
P+R-ICE

Study objectives
This study of pembrolizumab in combination with rituximab, ifosfamide, carboplatin and etoposide aims to address the unmet need of patients with relapsed and refractory diffuse large B-cell lymphoma (DLBCL). It is based upon a rational approach, investigating the activity of a novel agent in addition to the current best available treatment, recording response duration and toxicity profile. The primary objective will be to document the event-free survival at 1 year from registration in patients with relapsed or refractory DLBCL. A maintenance phase of pembrolizumab has been added as this may induce an on-going T-cell response to neo-antigens released as a result of chemotherapy.

This is an open-label, multicentre, randomised phase II trial in relapsed or refractory diffuse large B-cell lymphoma. The study has two treatment arms to which participants will be randomised on a 3:1 basis to the experimental arm. The control arm (Arm A) will be R-ICE for three cycles followed by an autologous stem cell transplant (for patients in complete remission [CR] CR or partial remission [PR] on the post-treatment PET-CT scan). The experimental arm (Arm B) will consist of P+R-ICE for three cycles followed by an autologous stem cell transplant (for patients in a CR or PR on the post-treatment PET-CT scan) and maintenance pembrolizumab every 3 weeks for 1 year.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 10/01/2022, East of England - Cambridge South Research Ethics Committee (East of England - Cambridge South Research Ethics Committee, Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 (0)207 104 8084, +44 (0)207 104 8104, +44 (0)207 104 8109; cambridgesouth.rec@hra.nhs.uk), ref: 21/EE/0248

Primary study design
Interventional

Study design
Randomized; Interventional; Design type: Treatment, Drug

Study type(s)
Treatment

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

Interventions

3:1 randomisation to the experimental arm, stratified by relapse within 12 months or >12 months of first-line therapy.

Arm A (control):
Rituximab: 375 mg/m²
Ifosfamide: 5,000 mg/m²
Carboplatin: AUC = 5 (max dose 800 mg)
Etoposide: 100 mg/m²
Patients will receive up to three cycles of R-ICE, where each cycle is 21 days long +/- 3 days.
All patients who are deemed to be in CR or PR on the post-treatment PET-CT scan will undergo an autologous stem cell transplant (ASCT) within 4 weeks of completing R-ICE treatment. BEAM (carmustine, etoposide, cytarabine and melphalan) conditioning will be employed according to institutional protocol.

Arm B (experimental):
Pembrolizumab: 200 mg
Rituximab: 375 mg/m²
Ifosfamide: 5,000 mg/m²
Carboplatin: AUC = 5 (max dose 800 mg)
Etoposide: 100 mg/m²
Patients will receive up to three cycles of P+R-ICE, where each cycle is 21 days long +/- 3 days.
All patients who are deemed to be in CR or PR on the post-treatment PET-CT scan will undergo an autologous stem cell transplant (ASCT) within 4 weeks of completing P+R-ICE treatment. BEAM (carmustine, etoposide, cytarabine and melphalan) conditioning will be employed according to institutional protocol.
These patients will then be offered maintenance pembrolizumab every 3 weeks for 1 year.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)
Event-free survival at 1 year (binary) - the proportion of patients alive and event free at 1 year. An event is defined as any of the following:
1. Progression/relapse of lymphoma
2. Stable disease at three cycles of therapy
3. Commencement of any unplanned non-protocol treatment for lymphoma
4. Death from any cause
Timepoint(s): 1-year post trial registration

Key secondary outcome(s)
1. Event-free survival (EFS) (time to event outcome) – median and at 1 and 2 years from Kaplan-Meier curve – defined as the time from the day of registration until relapse or progression, unplanned re-treatment of lymphoma, or death as a result of any cause, whichever occurs first. Patients who do not experience an EFS event will be censored at the date of their last clinical follow-up.

2. Progression-free survival (PFS) (time to event outcome) – median and at 1 and 2 years from the Kaplan-Meier curve – defined as the time from the day of registration to the date of progression or death from any cause, whichever occurs first. Patients who do not experience progression or death will be censored at the date of their last clinical follow-up.
3. Overall survival (OS) (time to event outcome) – median and at 1 and 2 years from the Kaplan-Meier curve – defined as the time from the day of registration to the date of death from any cause. Patients who do not die will be censored at the date of their last follow up.
4. Number of patients achieving 2 x 10e6 CD34 positive cells per kg stem cells on harvest measured using hospital sites standard approach and collected 10 days after start of cycle 3
5. Number and proportion of patients achieving CR at end of induction (assessed by PET-CT at end of cycle 3) determined by the Lugano response criteria
6. Number and proportion of patients achieving CR at end of transplantation (PET-CT at week 27) determined by the Lugano response criteria
7. Number and proportion of patients achieving CR at any point during follow up determined by the Lugano response criteria
8. Number and proportion of patients with an objective response (partial or complete metabolic response [PR or CR]) at end of induction assessed by PET-CT at end of cycle 3 determined by the Lugano response criteria
9. Number and proportion of patients with an objective response (partial or complete metabolic response [PR or CR]) assessed by PET-CT at end of transplantation (week 27) as determined by the Lugano response criteria
10. Number and proportion of patients achieving an objective response (CR or PR) at any point during follow up determined by the Lugano response criteria
11. Frequency, severity and causality of adverse and serious adverse events, severity according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 5, recorded at baseline, cycle 1, cycle 2, and cycle 3, HDT, Arm A: recorded for M1, M2 and M3, Arm B: recorded M1 to M21

Completion date
31/12/2026

Eligibility

Key inclusion criteria
1. Histologically proven CD20 +ve diffuse large B-cell lymphoma, preferably with sufficient diagnostic material,obtained either at diagnosis or relapse (the latter is preferable) that is available to forward to the Haematological Malignancies Diagnostic Service (HMDS)
2. Refractory to, or relapsed following, first-line or second-line treatments with rituximab concurrently with anthracycline or anthracenedione-based chemotherapy or similar (etoposide allowed if comorbid). Refractory disease must fulfil one of the following:
2.1. Continuing partial response (PR) from termination of first-line treatment. It is strongly recommended the lymphoma be reconfirmed by biopsy, however, if these procedures are deemed to be inappropriate, the CI may determine eligibility following review of the imaging results and disease history.
2.2. Continuing stable disease (SD) from termination of first-line treatment. Reconfirmation of the lymphoma by biopsy (preferred) is recommended but not mandatory
2.3. Progressive disease (PD). Biopsy or reconfirmation of the lymphoma is recommended but not mandatory
3. Potentially eligible for high-dose therapy and peripheral blood progenitor cell rescue in the event of response
4. Positive lesions shown on baseline PET-CT must be compatible with CT defined anatomical

tumour sites
5. At least two demarcated lesions/nodes with a long axis >1.5 cm and a short axis equal to 1.0 cm or one clearly demarcated lesion/node with a long axis >2.0 cm and short axis of 1.0 cm
6. Previous therapy related toxicity should have resolved to a grade that the investigator deems appropriate to commence further treatment
7. Eastern Cooperative Oncology Group (ECOG) Performance Status 0 – 1
8. Has provided written informed consent
9. Willing to use acceptable contraception (see Section 4.6)
10. Aged 18 years or over

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria
1. Previous lymphoma cancer treatment beyond third line
2. Radiotherapy or cytotoxic drugs within two weeks of trial treatment
3. Major surgery within 4 weeks of trial registration. If a subject had major surgery,more than 4 weeks ago, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug
4. Treatment with any unlicensed drug within 4 weeks of trial treatment
5. History of stroke or intracranial haemorrhage within 6 months prior to registration
6. Pre-existing peripheral neuropathy grade >2
7. Clinically significant cardiac disease (inc. unstable angina,acute myocardial infarction, congestive heart failure,a current LVEF of <40%) within 6 months of registration
8. Any significant uncontrolled medical condition or known hypersensitivity to the study drugs
9. Chronic or current infectious disease requiring systemic antibiotics, antifungal, or antiviral treatment such as,but not limited to, chronic renal infection, chronic chest infection with bronchiectasis and tuberculosis
10. Other past or current malignancy within 2 years prior to registration unless in the opinion of the investigator it does not contraindicate participation in the study. Subjects who have a history of completely resected non-melanoma skin cancer, or successfully treated in situ carcinoma, are eligible
11. Known CNS involvement
12. Serological positivity for Hepatitis B, C, or known HIV infection. As per standard of care,prior to initiation of immunochemotherapy, the results of hepatitis serology should be known prior to commencement of therapy.
13. Positive test results for chronic HBV infection (defined as positive HBsAg serology) will not be eligible
14. Patients with occult or prior HBV infection (defined as negative HBsAg and positive total

HBcAb) will not be eligible
15. Patients who have protective titres of hepatitis B surface antibody (HBsAb) after vaccination will be eligible
16. Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA
17. Screening laboratory values :
17.1. platelets <75 x 10e9/L (unless due to lymphoma involvement of the bone marrow)
17.2. neutrophils <1.0 x 10e9/L (unless due to lymphoma involvement of the bone marrow)
17.3. creatinine >2.0 times upper normal limit (unless due to lymphoma or unless creatinine clearance >50 ml/min)
17.4. total bilirubin >1.5 times upper normal limit (unless due to lymphoma or a known history of Gilbert's disease)
17.5. ALT/AST >2.5 times upper normal limit (unless due to lymphoma)
17.6. Alkaline phosphatase >2.5 times upper normal limit (unless due to lymphoma)
18. History of autoimmune disease, including but not limited to myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Guillain-Barré syndrome, multiple sclerosis, vasculitis, or glomerulonephritis. (Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone will be eligible as will be patients with controlled Type I diabetes mellitus on a stable dose of insulin).
19. Patients who have previously undergone allogeneic transplantation
20. Live vaccination within 28 days of study treatment
21. Pregnant or lactating females. Women of child-bearing potential should have negative pregnancy test
22. History of severe allergic anaphylactic reactions to chimeric,human or humanised antibodies, or fusion proteins
23. History of (non-infectious) pneumonitis that required steroids or has current pneumonitis
24. Known hypersensitivity to CHO cell products or any component of the pembrolizumab formulation
25. Previous treatment with an anti-PD-1,anti-PD-L1 or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX 40, CD137)
26. Corticosteroid use >10 mg/day of prednisolone or equivalent,for purposes other than for lymphoma symptom control. Patients receiving corticosteroid treatment with <10 mg/day of prednisolone or equivalent must be documented to be on a stable dose of at least 4 weeks' duration prior to the start of Cycle 1. If glucocorticoid treatment is urgently required for lymphoma symptom control prior to the start of study treatment, prednisolone 100 mg or equivalent could be given for a maximum of 14 days as a pre-phase. A dose of up to 10 mg or prednisolone or equivalent may be used during the screening phase to control symptoms.

Date of first enrolment
29/06/2022

Date of final enrolment
27/06/2025

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Southampton General Hospital
Tremona Road
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SO16 6YD

Study participating centre
James Cook University Hospital
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TS4 3BW

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

Study participating centre
Churchill Hospital
Churchill Hospital
Old Road
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Oxford
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OX3 7LE

Study participating centre
The Royal Oldham Hospital
Rochdale Road
Oldham
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OL1 2JH

Study participating centre
Colchester General Hospital
Colchester District General Hosp.
Charter Way
Turner Road
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CO4 5JL

Study participating centre
Ipswich Hospital
Heath Road
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IP4 5PD

Study participating centre
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Glossop Road
Sheffield
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S10 2JF

Study participating centre
Bradford Royal Infirmary
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Sponsor information

Organisation
University Hospital Southampton NHS Foundation Trust

ROR
https://ror.org/0485axj58

Funder(s)

Funder type
Industry

Funder Name
Merck; Grant Codes: 56804

Alternative Name(s)
Merck & Co., Inc., Merck & Co.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

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
Study website	Study website	11/11/2025	11/11/2025	No	Yes