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

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

#### 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 pricetrial@soton.ac.uk

# Contact information

#### Type(s)

Scientific

#### Contact name

Mrs Amber Cole

#### Contact details

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# Additional identifiers

Clinical Trials Information System (CTIS)

2018-001886-18

Integrated Research Application System (IRAS)

1004066

ClinicalTrials.gov (NCT)

NCT05221645

Protocol serial number

CPMS 51402, IRAS 1004066

# 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

# Study design

Randomized; Interventional; Design type: Treatment, Drug

# Primary study design

Interventional

# 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/m<sup>2</sup>

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/m<sup>2</sup> Ifosfamide: 5,000 mg/m<sup>2</sup>

Carboplatin: AUC = 5 (max dose 800 mg)

Etoposide: 100 mg/m<sup>2</sup>

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

Αll

#### 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  $<1.0 \times 10e9/L$  (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 Southampton United Kingdom SO16 6YD

# Study participating centre James Cook University Hospital

Marton Road Middlesbrough United Kingdom TS4 3BW

# Study participating centre Beatson West of Scotland Cancer Centre

1053 Great Western Road Glasgow United Kingdom G12 0YN

# Study participating centre

Churchill Hospital

Churchill Hospital Old Road Headington Oxford United Kingdom OX3 7LE

# Study participating centre The Royal Oldham Hospital

Rochdale Road Oldham United Kingdom OL1 2JH

# Study participating centre Colchester General Hospital

Colchester District General Hosp. Charter Way Turner Road Colchester United Kingdom CO4 5JL

# Study participating centre Ipswich Hospital

Heath Road Ipswich United Kingdom IP4 5PD

# Study participating centre Royal Hallamshire Hospital

Glossop Road Sheffield United Kingdom S10 2JF

# Study participating centre Bradford Royal Infirmary

Duckworth Lane Bradford United Kingdom BD9 6RJ

# 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
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Study website	Study website	11/11/2025	11/11/2025	No	Yes