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Phase III evaluation of PET-guided, Response-Adapted therapy in patients with previously untreated, high tumour burden follicular lymphoma

Submission date 02/07/2018	**Recruitment status** Recruiting	[_] Prospectively registered [_] Protocol
Registration date 13/08/2018	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 15/10/2024	**Condition category** Cancer	[_] Individual participant data [X] Record updated in last year

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-to-find-out-whether-a-pet-ct-scan-can-help-to-tell-who-needs-to-have-rituximab-after-the

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2016-004010-10

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 34767

Study information

Scientific Title
PETReA: Phase III evaluation of PET-guided, Response-Adapted therapy in patients with previously untreated, high tumour burden follicular lymphoma

Acronym
PETReA

Study objectives
Follicular lymphoma (FL) is a slowly growing cancer of the lymph glands. It often responds well to treatment but has a tendency to come back again (relapse) and therefore needs to be treated more than once. Initial treatment is usually with a 6-month course chemotherapy combined with an antibody drug called rituximab (R+chemo). Most patients who respond to R+chemo are offered further (maintenance) therapy with rituximab alone over a period of 2 years with the aim of delaying relapse. However, there is growing controversy about the routine use of rituximab maintenance after initial R+chemo for the following reasons: (1) It does not prolong survival; (2) It is associated with an increased risk of infection (responsible for 7-8% of all deaths in FL); (3) It prolongs remissions only in the minority of patients whose disease was destined to relapse within 2-3 years. A one-size-fits-all approach to rituximab maintenance is therefore not ideal as many patients will experience complications without deriving any benefit. The PETReA trial will use a new scanning technique called Positron Emission Tomography (PET) to identify which patients are more or less likely to benefit from rituximab maintenance after initial R+chemo treatment. It is known that patients whose PET scans return to normal have a low-risk of early relapse, and the trial will therefore investigate if rituximab maintenance can be omitted in this group. In contrast, patients whose PET scans remain abnormal have a high risk of early relapse. The trial will investigate whether this group will benefit from the addition of a drug called lenalidomide to rituximab maintenance.

Ethics approval required
Old ethics approval format

Ethics approval(s)
North West - Liverpool Central Research Ethics Committee, 20/10/2017, ref: 17/NW/0512

Study design
Randomized; Interventional; Design type: Treatment, Drug, Imaging, Psychological & Behavioural

Primary study design
Interventional

Secondary study design

Randomised controlled trial

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
Follicular lymphoma

Interventions
Patients are initially screened for eligibility. They will have a physical examination and blood tests including for HIV and hepatitis viruses. Patients will also undergo an ordinary body scan (CT scan), a PET scan (sometimes referred to as PET-CT scan) and a bone marrow biopsy. With the exception of the PET scan, these tests are routine and would take place outside of the trial. The purpose of doing them is get a good picture of the disease before treatment starts so the effect of the treatment can be properly assessed, and also to make sure that it is safe to give the treatment.

Patients who are recruited to the study will then receive one of three different types of R+chemo "induction" treatments (R-CVP, R-CHOP or BR) as determined by the local Principal Investigator. The purpose of induction treatment is to shrink down any lumps and put the patient into a remission. All 3 drug combinations are routinely used for the initial treatment of FL, and each has its advantages and disadvantages. Additional blood tests are required just before treatment is started to ensure that it is safe to give.

The induction treatment starts within 42 days of signing up for the study. It is usually given as an outpatient and consists of one round (or cycle) of treatment every 3 or 4 weeks for up to 6 or 8 cycles (i.e. 4-6 months in total). Depending on the local hospital’s policy, the rituximab may be given into a vein (takes several hours) or as an injection under the skin (takes several minutes) and is given on the first day of each cycle. The chemotherapy drugs are given into a vein over the first 1 or 2 days of each cycle. The R-CVP and R-CHOP induction treatments also include a 5-day course of steroid tablets.

Patients will receive paracetamol and antihistamine medication prior to each dose of rituximab to reduce the risk of flu-like symptoms and infusion reactions. They will also receive anti-sickness tablets and a drug called allopurinol to reduce the risk of kidney damage by chemicals released from the lymphoma cells as they break down. Some patients will also require growth factor injections to help the bone marrow work if the white blood cell count drops between treatment cycles or if they develop any infections. This is all standard practice.

In addition to attending for each cycle of treatment, patients will also have to visit for assessment before each cycle to make sure it is safe to go ahead with treatment. In some hospitals and treatment units the first and second visits can be rolled into one. The doctor may request a CT scan mid-way through treatment to make sure it is working. This is all standard practice.

At the end of the induction treatment, patients will have another CT scan (standard practice) and PET-CT scan (not yet standard practice everywhere but likely to become so). If the bone marrow was involved with lymphoma prior to starting treatment, another bone marrow biopsy will be requested if the pre-treatment bone marrow is clear to confirm that a "complete remission" has been obtained (standard practice).

Patients whose disease has shrunk by less than 50% on the ordinary CT scan (expected to be 5-10% of patients) will not have any further treatment as part of the trial and will be managed at the discretion of the Local Investigator.

Patients whose disease has shrunk by 50% or more on the CT scan will be separated into two groups depending on the results of the PET scan.

Patients who have a clear (negative) PET scan will be randomly allocated (1:1 ratio) to receive either rituximab maintenance 375 mg/m2 iv (or 1400 mg sc) on day 1 of each cycle, repeated every 8 weeks for up to 12 cycles, or no further treatment. Rituximab will be given in exactly the same way as it would be given outside the study and with paracetamol antihistamine (with or without steroid medication) prior to each dose to reduce the risk of flu-like symptoms and infusion reactions. Prior to each treatment, patients will have assessments to make sure it is safe to go ahead (patients allocated to receive no further treatment will also have assessments at the same time points). In some hospitals and treatment centres, the first and second visits can be rolled into one. To monitor the disease, patient will have a CT scan after 2 years and one every year thereafter until the study finishes.

Patients who have a positive PET scan at the end of the induction treatment (i.e. the disease is still visible) will be randomly allocated (1:1 ratio) to receive rituximab maintenance 375 mg/m2 iv (or 1400 mg sc) on day 1 of each cycle, repeated every 8 weeks for up to 12 cycles, either with or without lenalidomide, which is taken by mouth once daily on days 1 to 21 of every 28-day cycle (dose tailored to renal function and tolerance) for up to 24 cycles. Patients will also receive paracetamol and antihistamine prior to each dose of rituximab to reduce the risk of flu-like symptoms and infusion reactions. Patients receiving rituximab and lenalidomide will receive allopurinol to protect the kidneys from chemicals released from lymphoma cells as they break down plus a drug such as aspirin to prevent blood clots. Growth factor injections may also be given if necessary to stimulate the bone marrow.

In addition to attending for each cycle of treatment, patients will also have to visit for assessment before each cycle to make sure it is safe to go ahead. In some hospitals and treatment units the first and second visits can be rolled into one. To monitor disease, patients will have a CT scan every year plus a PET scan after 1 year to see if the scan is still positive or has become negative.

After the 2-year maintenance treatment period, patients will attend for formal follow-up visits every 6 months for as long as they remain in remission. They will have CT scans every year and their quality of life and levels of psychological stress will be measured.

As there is a lot of information for patients to take in about this study, we want to learn how we can improve our information and communication about research. With the patient’s permission, we will audio-record our discussions with patients in clinic as part of the patient’s informed consent process. A researcher may contact the patients afterwards to ask if they would be willing to take part in an interview about their views on the clinical study. Patients do not have to agree to take part in this interview if they choose not to.

Another aspect of this study involves assessing how the disease or any treatment patients receive affects their quality of life and stress levels, so they will complete a questionnaire that asks about how they feel and what activities they can undertake. This will be done before treatment starts and at intervals during and after treatment. They will also fill in another questionnaire to help calculate the costs of the study treatment to the NHS and with their permission we will retrieve information from their electronic medical records from NHS Digital.

Patients will have blood samples taken for standard blood tests every time they attend for treatment to tell if they are well enough for treatment. In addition, if they consent, further blood samples will be taken before the start of treatment and at other times in the study for use in scientific studies that will add to the study results. Patients can withdraw from providing these samples at any time.

Intervention Type
Other

Phase
Phase III

Primary outcome measure
Progression Free Survival (PFS) measured as the time from randomisation until death or progression by any cause

Secondary outcome measures
1. Anatomical response to induction therapy; complete response rate, including CR30 metabolic response rates, will be defined as patients obtaining either a complete response or partial response as defined by standard criteria. All rate data will be reported as the proportion of the total number randomised across treatment groups. Analyses shall be carried out using stratified Chi-Square tests. Multivariable models using logistic regression techniques shall be used to adjust for key prognostic variables of interest
2. Metabolic response to induction therapy: see above
3. Conversion to PET negativity (PET +ve group only)
4. Overall survival (OS): OS will be defined as the time from randomisation until death from any cause. Analysis here will replicate that of the primary endpoint
5. Time to treatment failure (TTF): TTF will be measured as the time from randomisation until commencement of second-line lymphoma treatment, disease progression or death from any cause.
6. Time to next chemotherapy (TNC): TNC will be measured as the time from randomisation until commencement of further systemic anti-lymphoma treatment.
7. Toxicity: Adverse events (AEs) and serious adverse events (SAEs) shall be defined using CTC (Version 4) definitions. All AEs and SAEs shall be compared across groups using the TAME guidelines. Furthermore, the worst AE/SAE for each type for each patient shall also be retained and compared across treatment groups using a stratified Chi-Square test.
8. Quality of life: Responses to EQ-5D-5L will be reported (mean, SD) according to each of the 5 domains, by intervention group, and over time. The corresponding utility profiles will be reported accordingly. Quality Adjusted Life Years (QALYs) shall be estimated using the integrated Quality Survival Product method. Quality of life questionnaires EQ-5D-5L and EQ-VAS will be completed at pre-induction, 4 weeks after day 1 of the last cycle of induction, within 7 days prior to day 1 of each maintenance cycle and 2 weeks before the last day of the final maintenance cycle and then every 24 weeks in the pre-progression follow-up until the end of the study or until disease progression, death or initiation of second line therapy.

9. Psychological assessment (particularly important given the de-escalation question): FACT-G, CAS-1 Questionnaire, Metacognitions Questionnaire 30, Hospital Anxiety and Depression Scale and Brief Illness Perception Questionnaire, will be completed at pre-induction, 4 weeks after day 1 of the last cycle of induction, within 7 days prior to day 1 of each maintenance cycle and 2 weeks before the last day of the final maintenance cycle and then every 24 weeks in the pre-progression follow-up until the end of the study or until disease progression, death or initiation of second line therapy. The aim will be to explore the role of maladaptive metacognitive beliefs and processes compared to negative illness perceptions in symptoms of depression and anxiety in haematological cancer patients
10. Cost-effectiveness: The health economic evaluation will take the form of a cost-utility analysis in which costs will be compared to benefits expressed in terms of Quality-Adjusted Life Years (QALYs)

Overall study start date
01/09/2017

Completion date
01/12/2029

Eligibility

Key inclusion criteria
1. Must be ≥18 years of age at the time of signing the informed consent form
2. Must be able to adhere to the study visit schedule and other protocol requirements
3. Must have a documented diagnosis of follicular lymphoma (grade 1, 2 or 3a)
4. Must be at non-contiguous stage II, stage III or stage IV
5. Must fulfil at least one of the Groupe d'Etude des Lymphomas Folliculaires (GELF) GELF criteria for high tumour burden:
5.1. Systemic symptoms (> 10% weight loss, temperature ≥ 38°C for more than 5 days, abundant night sweats)
5.2. Performance status (PS) greater than 1 according to the Eastern Cooperative Oncology Group (ECOG) scale
5.3. Elevated lactate dehydrogenase (LDH) level
5.4. β2-microglobulin level greater than 25.5 nM/L (3 µg/mL)
5.5. A single lymph node larger than 7 cm
5.6. Involvement of at least 3 nodal sites, each with diameter greater than 3 cm
5.7. Marked splenomegaly
5.8. Organ failure
5.9. Pleural effusion or ascites
5.10. Orbital or epidural involvement
5.11. Blood infiltration
5.12. Cytopenia
6. Must not have received prior systemic therapy (local radiotherapy is permitted)
7. Must have a WHO performance status score of less than or equal to 2
8. Must agree to adhere to the Celgene guidance on pregnancy prevention

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 1000; UK Sample Size: 1000

Key exclusion criteria
1. Any serious medical condition that would prevent the subject from participating in the study
2. Known active infection with HIV, HBV or HCV
3. Pregnant or lactating females
4. Central nervous system involvement as documented by spinal fluid cytology or imaging
5. History of active malignancy during the past 5 years with the exception of basal carcinoma of the skin, squamous cell carcinoma of the skin, carcinoma in situ of the cervix, carcinoma in situ of the breast, prostate cancer (TNM stage of T1a or T1b)
6. Any of the following laboratory abnormalities:
6.1. Absolute neutrophil count (ANC) < 1,000/µL (1.0 X 109/L)
6.2. Platelet count < 50,000/µL (50 X 109/L)
6.3. Serum alanine transaminase (ALT) > 3.0 x upper limit of normal (ULN)
6.4. Serum total bilirubin > 1.5 x ULN unless due to Gilbert's Syndrome or biliary obstruction by lymphoma

Date of first enrolment
10/05/2018

Date of final enrolment
31/10/2025

Locations

Countries of recruitment
Australia

England

Scotland

United Kingdom

Study participating centre
Clatterbridge Cancer Centre (lead site)
Clatterbridge Road
Bebington
Wirral
United Kingdom
CH63 4JY

Study participating centre
Royal Marsden Hospital
Fulham Road
London
United Kingdom
SW3 6JJ

Study participating centre
Leicester Royal Infirmary
Hope Clinical Trials Unit
Leicester Royal Infirmary
Leicester
United Kingdom
LE1 5WW

Study participating centre
Blackpool Victoria Hospital
Whinney Heys Road
Blackpool
United Kingdom
FY3 8NR

Study participating centre
Derriford Hospital
Derriford Road
Plymouth
United Kingdom
PL6 8DH

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

Study participating centre

Royal Marsden Hospital
Downs Road
Sutton
United Kingdom
SM2 5PT

Sponsor information

Organisation
University of Liverpool

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Sponsor type
University/education

ROR
https://ror.org/04xs57h96

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK; Grant Codes: C18029/A21585

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
Planned publication in a high-impact peer reviewed journal 1 year after overall trial end date.

Intention to publish date
01/12/2030

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