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A phase IIa study of rituximab and varlilumab in relapsed or refractory B-cell malignancies

Submission date 14/08/2017	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 16/08/2017	**Overall study status** Completed	
Last Edited 08/04/2025	**Condition category** Cancer	

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-rituximab-and-varlilumab-for-people-with-b-cell-lymphoma-riva

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2017-000302-37

IRAS number

ClinicalTrials.gov number
NCT03307746

Secondary identifying numbers
35676

Study information

Scientific Title
A phase IIa study of Rituximab and Varlilumab in relapsed or refractory B-cell malignancies (RiVa): a randomised controlled trial

Acronym
RiVa

Study objectives
Varlilumab enhances rituximab-mediated killing of tumour cells by increasing the number of immune effector cells.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/08/2017, South Central - Oxford A Research Ethics Committee (Bristol Research Ethics Committee Centre, Whitefriars, Level 3 Block B, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0) 207 1048171, +44 (0)207 104 8141, +44 (0)207 104 8272; oxforda.rec@hra.nhs.uk), ref: 17/SC /0317

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

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See study outputs table

Health condition(s) or problem(s) studied
Lymphoma

Interventions
20 patients will be allocated to the high grade group (i.e. patients with DLBCL, follicular lymphoma grade 3b, transformed follicular lymphoma) and 20 patients to the low grade group (i. e. patients with follicular lymphoma grade 1, 2 or 3a, marginal zone lymphoma (MZL), mantle cell

lymphoma (MCL), lymphoplasmacytic lymphoma (LPL)). In the high grade group 10 will be randomised to Arm A and 10 to Arm B. In the low grade group 10 will be randomised to Arm A and 10 to ARM.

Patients will receive 6 cycles of treatment, with administration of rituximab on day 1 of each cycle and of varlilumab on day 2 of cycles 1, 3 and 5. Each cycle is 2 weeks long.

Patients in Arm A: For Cycle 1 will receive Rituximab 375 mg/m2 IV on Day 1 and Varlilumab 3 mg /kg IV on Day 2. Thereafter every 2 weeks patients will Rituximab 375 mg/m2 IV for 12 weeks in cycle 2 and 6 on Day 1 and Varlilumab 3 mg/kg IV for 12 weeks.
Patients in Arm B: For Cycle 1 will receive Rituximab 375 mg/m2 on Day 1 and Varlilumab 3 mg /kg IV on Day 8. Thereafter every 2 weeks patients will receive Rituximab 375 mg/m2 IV for 12 weeks in cycle 2 and 6 on Day 1 and Varlilumab 3 mg/kg IV for 12 weeks.

Patients will then be followed up 2 weeks after they complete the trial treatment and every 2 months over a period of 12 months at 2, 4, 6, 8, 10 and 12 months.

Intervention Type
Drug

Pharmaceutical study type(s)
Not Applicable

Phase
Phase II

Drug/device/biological/vaccine name(s)
Rituximab, varlilumab

Primary outcome measure
1. Safety: DLT and adverse events and grading of severity according to NCI CTCAE Version 4.03). Timepoint(s): during trial treatment and for 12 months after trial treatment
2. Efficacy: response in each case according to the Lugano Revised Response Criteria for Malignant Lymphoma; Timepoint(s): 2 weeks after treatment, and every 2 months after trial treatment up to 12 months

Secondary outcome measures
There are no secondary outcome measures

Overall study start date
31/08/2017

Completion date
21/08/2024

Eligibility

Key inclusion criteria
1. Relapsed or refractory CD20+ B-cell lymphoma excluding chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL):

1.1. High grade subgroup: Diffuse large B-cell lymphoma, FL grade 3b, transformed FL
1.2. Low grade subgroup: All low grade CD20+ B-cell lymphoma subtypes excluding CLL/SLL (e.g. FL grade 1,2 or 3a, MCL, LPL)
2. Disease must be recurrent or treatment refractory, and received at least one line of treatment. Rituximab-refractory participants are eligible for the entry into the study as long as the tumour expresses CD20
3. At least one measurable lesion by CT scan (defined as >1.5 cm in one axis) that is also easily accessible for biopsy
4. Histological confirmation of relapse within 12 months of treatment
5. 16 years of age or older
6. Haematological and biochemical indices with the ranges shown below:
6.1. Haemoglobin (Hb) ≥ 90 g/L (red cell support is permissible)
6.2. Absolute neutrophil count (ANC) ≥1.0 x 109/L (or ≥0.5 x 109/L if bone marrow involvement) G-CSF support is not permissible at screening
6.3. Platelet count ≥75 x 109/L (or ≥30 x 109/L if bone marrow involvement)
6.4. Serum bilirubin ≤1.5 x upper limit of normal (ULN) unless raised due to Gilbert's syndrome in which case up to 3 x ULN is permissible
6.5. Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 2.5 x ULN unless raised due to hepatic involvement
6.6. Calculated creatinine clearance (Cockcroft-Gault formula) ≥30 ml/min (uncorrected value)
7. Ability to understand the purpose and risks of the study and provide written informed consent
8. Willing and able to participate in all required evaluations and procedures in this study protocol
9. Participants must be willing to participate in appropriate pregnancy prevention measures
9.1. Women of childbearing potential who have a negative serum or urine pregnancy test during screening (within 14 days prior to the start of trial treatment) and agree to use one highly effective form of contraception combined with an effective form of contraception (see below) effective from the first administration of all study drugs, throughout the trial and for 12 months after last dose all study drugs are considered eligible
9.2. Male participants with partners of child-bearing potential who agree to take measures not to father children by using one form of highly effective contraception from the first administration of all study drugs, throughout the trial and for 12 months after last dose of all study drugs are considered eligible. Male subjects must also refrain from donating sperm during this period. Contraception that is considered highly effective includes oral, injected or implanted progesterone-only hormonal contraception (with inhibition of ovulation); oral, intravaginal, or transdermal combined (oestrogen and progesterone containing) hormonal contraception (with inhibition of ovulation); an intra-uterine device (IUD); an intrauterine hormone releasing system (IUS); bilateral tubal occlusion; vasectomised partner or abstinence. Contraceptive methods considered to be effective include progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; condom; cap, diaphragm or sponge with spermicidal gel
9.3. Men with pregnant or lactating partners must be advised to use barrier method contraception (for example: condom plus spermicidal gel) to prevent exposure to the foetus or neonate
10. Life expectancy ≥ 12 weeks
11. ECOG performance status 0-2

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
Planned Sample Size: 40; UK Sample Size: 40

Total final enrolment
27

Key exclusion criteria
1. Known central nervous system involvement by lymphoma, that is not in remission, are excluded from the study
2. History of other malignancy within the last 2 years except for:
2.1. Noninvasive malignancies such as adequately treated ductal carcinoma in situ of the breast, non-melanoma skin cancer or lentigo maligna, cervical carcinoma in situ and urothelial papillary noninvasive carcinoma or carcinoma in situ
2.2. Prostate intraepithelial neoplasia without evidence of prostate cancer
3. Receiving treatment (or within a month of) with chemotherapy, immunotherapy or immunosuppressive agents. This includes any systemic steroids at dose exceeding 10 mg prednisolone (or other steroid equivalent) within 2 weeks prior to first dose of varlilumab
4. Significant concurrent, uncontrolled medical condition that in the opinion of the investigator contraindicates participation in this study
5. Active and documented autoimmune disease (including, but not limited to, inflammatory bowel disease, coeliac disease, haemolytic anaemia, or immune thrombocytopenic purpura) prior to first dose of varlilumab
6. Active infection requiring systemic therapy
7. Women who are pregnant or lactating
8. Serological positivity for Hepatitis B, C, or known HIV infection. As per standard of care, the results of hepatitis serology should be known prior to commencement of immunochemotherapy
8.1. Positive test results for chronic HBV infection (defined as positive HBsAg serology and positive HBcAb) will not be eligible. Patients with occult or prior HBV infection (defined as negative HBsAg and positive HBcAb) will not be eligible. Patients who have protective titres of hepatitis B surface antibody (HBsAb) after vaccination will be eligible
8.2. Positive test results for hepatitis C (HCV antibody serology testing) will not be eligible
9. Previous recipient of an allogeneic bone marrow transplant at any time
10. Autologous bone marrow transplant within 100 days of first dosing
11. Systemic radiation therapy within 4 weeks or prior focal radiotherapy within 2 weeks prior to first dosing
12. Subjects known or suspected of being unable to comply with the protocol
13. Ongoing toxic manifestations of previous treatments. Exceptions are to this are alopecia or certain Grade 1-toxicities, which in the opinion of the Investigator should not exclude the patient
14. Uncontrolled congestive cardiac failure, cardiac ischaemia or cardiac arrhythmia. Clinically significant cardiac disease including unstable angina, acute myocardial infarction within six months prior to registration, congestive heart failure (NYHA III-IV)
15. Subjects with a known hypersensitivity to rituximab (≥Grade 3) or murine proteins, or any other excipients used in the formulation of rituximab

Date of first enrolment
30/09/2017

Date of final enrolment

31/12/2020

Locations

Countries of recruitment
England

Scotland

United Kingdom

Study participating centre
Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD

Study participating centre
Churchill Hospital
Old Road
Headington
Oxford
United Kingdom
OX3 7LE

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

Study participating centre
The Christie
550 Wilmslow Road
Withington
Manchester
United Kingdom
MX20 4BX

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

Study participating centre
Newcastle Freeman Hospital
Freeman Rd
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Sponsor information

Organisation
University Hospital Southampton NHS Foundation Trust

Sponsor details
Mailpoint 18, Southampton General Hospital
Tremona Road
Southampton
England
United Kingdom
SO16 6YD

Sponsor type
Hospital/treatment centre

ROR
https://ror.org/0485axj58

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK; Grant Codes: CRUKD/17/008

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 review journal 1 year after overall trial end date.

Intention to publish date
31/01/2026

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication.

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	09/11/2018		Yes	No
Participant information sheet	version v2	27/07/2017	01/04/2019	No	Yes