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The ACCEPT study

Submission date 13/02/2017	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol
Registration date 07/03/2017	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 22/10/2024	**Condition category** Cancer	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol
https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-of-acalabrutinib-with-r-chop-for-people-with-diffuse-large-b-cell-lymphoma-accept

Contact information

Type(s)
Public

Contact name
Mr Joshua Caddy

Contact details
Southampton Clinical Trials Unit
MP131, Southampton General Hospital
Tremona Road
Southampton
United Kingdom
SO16 6YD
+44 (0)23 8120 3509
accept@soton.ac.uk

Type(s)
Scientific

Contact name
Ms Nicole Keyworth

Contact details
Southampton Clinical Trials Unit
MP131, Southampton General Hospital
Tremona Road
Southampton
United Kingdom

SO16 6YD
+44 (0)23 8120 3785
N.E.Keyworth@soton.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2015-003213-18

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 33203

Study information

Scientific Title
A Phase Ib/II combination trial of acalabrutinib with rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone (R-CHOP) for patients with diffuse large B-cell lymphoma (DLBCL)

Acronym
ACCEPT

Study objectives
The aim of this study is to determine a suitable tolerated dose and efficacy of acalabrutinib in combination with standard R-CHOP immunochemotherapy to treat patients with diffuse large B-cell lymphoma (DLCBL).

Ethics approval required
Old ethics approval format

Ethics approval(s)
South Central - Berkshire Research Ethics Committee, 26/01/2017, ref :16/SC/0657

Study design
Non-randomized; Interventional; Design type: Treatment, Screening, Diagnosis, Drug

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Diffuse large B-cell lymphoma

Interventions
A multicentre open-label non-randomised phase Ib/II clinical trial conducted in two stages recruiting approximately 40 patients.

Phase I Dose Escalation Cohort 1
The first 6 patients registered (cohort 1) will receive a first cycle of R-CHOP. Acalabrutinib, at a starting dose of 100 mg od, will be added from cycle 2 to 6. This will be followed by cycles 7 and 8 of acalabrutinib only 100mg od for 28 days for each cycle. Dose escalation to 200 mg daily (100 mg bd) of acalabrutinib will be decided by the Safety Review Committee based on safety data and patients' compliance assessment

Phase I Dose Escalation Cohort 2
The first 6 patients of cohort 2 will start acalabrutinib + R-CHOP at the daily dose of 200mg administered as 100mg bd from cycle 2 after the Safety Review Committee has approved dose escalation based on all the safety data from cohort 1. the Safety Review Committee will assess the safety of 200mg. If one or two instances of DLT is observed among the initial six patients of cohort 2, the cohort will be expanded to a further six patients. Depending on tolerability as set out, cohort 2 patients should receive cycle 1 of R-CHOP, cycles 2-6 R-CHOP plus acalabrutinib and then cycles 7 and 8 of acalabrutinib only at 200mg administered as 100mg bd.
If a DLT attributable to acalabrutinib occurs, acalabrutinib will be withheld for that patient and reintroduced at 100 mg od when toxicity has resolved to < grade 1, all other patients will continue at acalabrutinib dosage of 200mg. If ≥ 3DLTs are attributable to acalabrutinib in the initial six patients acalabrutinib will be withheld from the patient(s) who have suffered the DLT and reintroduced at 100 mg od after toxicity has resolved to < grade 1 and all other patients dosage will be decreased to 100 mg od.
When all patients have completed all 6 cycles of therapy, the Safety Review Committee will review patients' compliance assessment, PK/PD measurements if available and safety data, including the identified MTD and MAD, to determine the recommended dose for Phase II (RP2D) which will be a dose where ≤ 33% of patients had a DLT.

Phase II
Fifteen patients will be recruited for stage 2 of the study. Following informed consent, they will receive 6 cycles of conventionally dosed R-CHOP with the addition of acalabrutinib at the RP2D on cycle 2 onwards.

Intervention Type
Drug

Phase
Phase I/II

Drug/device/biological/vaccine name(s)
Acalabrutinib

Primary outcome(s)
Phase I
1. Dose limiting toxicity of acalabrutinib combined to R-CHOP is measured using a physical examination, vital signs, laboratory tests FBC, renal and liver function, ECOG, at baseline and for all cycles and repeated for specific cycles day 8 and day 15 for cycle 2 and day 8 at cycle 4.*

Phase II
1. Overall response rate of the combination acalabrutinib and R-CHOP is measured using PET/CT at baseline, cycle 7, month 12, month 24 End of treatment using the Lugano classification for NHL

2. Safety of the combination acalabrutinib and R-CHOP is measured using a physical examination, vital signs, laboratory tests FBC, renal and liver function, ECOG at baseline and for all cycles and repeated for specific cycles day 8 and day 15 for cycle 2 and day 8 at cycle 4.*

*There will be 8 cycles if chemotheraphy administered. Cycle 1-6 will be 21 days and Cycle 7 and 8 will be 28 days Aclabrutinib will be administered from cycle 2 and will be taken from cycle 2 to cycle 7.

Key secondary outcome(s))
1. Pharmacokinetic of acalabrutinib, AUC, Cmax, Tmax, half-life T1/2 and other PK parameter is measured using serum concentration taken at cycle 2, Day 1, day 8 and day 15 half hour before the administration of acalabrutinib. Once acalabrutinib is administered serum concentration will be taken 45 mins, 1 hour, 2 hours and 8 hours and once again before acalabrutinib is administered at cycle 3
2. Overall response rate of the combination acalabrutinib and R-CHOP according to cell of origin is measured using of BCR DNA extracted from tumour material will be used to perform mutation detection on BCR pathway (eg Btk, PI3K, CD79b). Genetic abnormalities of BCR pathway will be correlated with clinical outcomes and the expression pathway target genes at baseline
3. Two years progression-free survival rate is measured using CT at 24 months
4. Two years overall survival rate is measured using CT at 24 months

Completion date
30/06/2022

Eligibility

Key inclusion criteria
1. Histologically confirmed DLBCL, expressing CD20. Sufficient diagnostic material should be available to forward to a central laboratory for gene expression profiling and pathology review
2. Measurable disease of at least 15mm
3. Not previously treated for lymphoma and fit enough to receive combination chemoimmunotherapy with curative intent
4. Stage IAX (bulk defined as lymph node diameter >10cm) to stage IV disease and deemed to require a full course of chemotherapy. Patients with non-bulky IE disease are not eligible
5. ECOG performance status 0-2 or 3 if this is directly attributable to lymphoma
6. Adequate bone marrow function with platelets > 100x109/L; neutrophils > 1.0x109/L at study entry, unless lower figures are attributable to lymphoma
7. Measured or calculated creatinine clearance > 30mls/min, (calculated using the formula of Cockcroft and Gault [(140-Age) x Mass (kg)x(1.04 (for women)or 1.23 (for men))/Serum Creatinine (umolL)]
8. Serum bilirubin < 35µmol/L and transaminases < 2.5x upper limit of normal at time of study entry
9. Cardiac function sufficient to tolerate 300mg/m2 of doxorubicin. A pre-treatment echocardiogram or MUGA is required to establish baseline LVEF equal to or greater than 55%
10. No concurrent uncontrolled medical condition
11. Life expectancy > 3 months
12. Aged 16 years or above
13. Willing and able to participate in all required evaluations and procedures in this study protocol including swallowing capsules without difficulty
14. Ability to understand the purpose and risks of the study and provide signed and dated informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
16 years

Sex
All

Total final enrolment
38

Key exclusion criteria
1. Previous history of treated or untreated indolent lymphoma. However newly diagnosed patients with DLBCL who are found to also have small cell infiltration of the bone marrow or other diagnostic material (discordant lymphoma) will be eligible
2. Diagnosis of primary mediastinal lymphoma
3. Diagnosis of primary Central Nervous System lymphoma.
4. History of stroke or intracranial haemorrhage in preceding 6 months
5. History of bleeding diathesis (eg. haemophilia, von Willebrand disease)
6. Requires or receiving anticoagulation with warfarin or equivalent antagonists (eg. phenprocoumon) within 7 days of first dose of acalabrutinib. However patients using therapeutic low molecule weight heparin or low dose aspirin will be eligible
7. Prior exposure to a BCR inhibitor(eg. BtK inhibitors, phosphoinositide-3 kinase (PI3K), or SyK inhibitors) or BCL-2 inhibitor (eg. ABT-199)
8. Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer
9. Requires treatment with proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Patients receiving proton pump inhibitors who switch to short-acting H2-receptor antagonists or antacids are eligible for enrolment into this study.
10. Uncontrolled systemic infection
11. Major surgery in the preceding 4 weeks of first dose of study drug. If a subject had major surgery, they must have recovered adequately from any toxicity and/or complications from the intervention before the first dose of study drug
12. Significant cardiovascular disease such as uncontrolled or symptomatic arrhythmias, congestive heart failure, or myocardial infarction within 6 months of screening, or any Class 3 or 4 cardiac disease as defined by the New York Heart Association Functional Classification, or corrected QT interval (QTc) > 480 msec at screening.
13. 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. - Positive test results for chronic HBV infection (defined as positive HBsAg serology) will not be eligible. Patients with occult or prior HBV infection (defined as negative HBsAg and positive total HBcAb) will not be eligible. Patients who have protective titres of hepatitis B surface antibody (HBsAb) after vaccination will be eligible. - Positive test

results for hepatitis C virus (HCV) antibody serology will not be eligible.
14. Women who are sexually active and can bear children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of acalabrutinib. Highly effective forms of contraception are defined in Section 4.7 14. Breastfeeding or pregnant
15. Men who are sexually active and can potentially father children must agree to use highly effective forms of contraception during the study and for 90 days after the last dose of acalabrutinib. Highly effective forms of contraception are defined in Section 4.7
16. Men must agree to refrain from sperm donation during the study and for 90 days after the last dose of study drug.
17. Serious medical or psychiatric illness likely to affect participation or that may compromise the ability to give informed consent
18. Prior malignancy (other than DLBCL), except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer from which the subject has been disease free for ≥ 2 years or which will not limit survival to < 2 years. Note: these cases must be discussed with SCTU
19. Malabsorption syndrome, disease significantly affecting gastrointestinal function, resection of the stomach or small bowel, gastric bypass, symptomatic inflammatory bowel disease, or partial or complete bowel obstruction or gastric restrictions and bariatric surgery, such as gastric bypass
20. Any immunotherapy within 4 weeks of 1st dose of the study
21. Concurrent participation in another therapeutic clinical trial

Date of first enrolment
01/04/2017

Date of final enrolment
02/01/2020

Locations

Countries of recruitment
United Kingdom

England

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

Study participating centre
Queen's Medical Centre
Derby Road

Nottingham
United Kingdom
NG7 2UH

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

Study participating centre
University College London Hospital
253 Euston Road
London
United Kingdom
NW1 2PG

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

Study participating centre
St. James's University Hospital
Beckett Street
Leeds
United Kingdom
LS9 7TF

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

Sponsor information

Organisation
University Hospital Southampton NHS Foundation Trust

ROR
https://ror.org/0485axj58

Funder(s)

Funder type
Industry

Funder Name
Acerta Pharma

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?
Protocol article	protocol	07/08/2020	26/10/2020	Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes