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A trial evaluating the effectiveness of combining standard R-CHOP treatment with acalabrutinib in patients with newly diagnosed diffuse large B-cell lymphoma

Submission date
09/07/2021

Recruitment status
No longer recruiting

Registration date
16/08/2021

Overall study status
Ongoing

Last Edited
07/07/2025

Condition category
Cancer

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] 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-trial-looking-at-acalabrutinib-for-diffuse-large-b-cell-lymphoma-remodl

Background and study aims
Diffuse large B-cell lymphoma (DLBCL) is the most common of the non-Hodgkin's lymphomas. Non-Hodgkin lymphoma is a type of cancer that develops in the lymphatic system, a network of vessels and glands spread throughout your body.
Whilst the majority of patients will respond well to conventional treatment (R-CHOP a type of immunochemotherapy), a significant number of patients with lymphoma will not respond to initial therapy or their disease will return after completion of therapy. In a number of B-cell diseases an enzyme called Bruton tyrosine kinase (BTK) prevents death of tumour cells, including in DLBCL. Acalabrutinib is an orally active BTK inhibitor and it is thought that stopping BTK from being activated may help in treating B-cell diseases. It is hypothesised that the addition of Acalabrutinib to standard R-CHOP immunochemotherapy may improve the outcomes of patients with DLBCL.

Who can participate?
Patients aged 16 years or older, with DLBCL

What does the study involve?
Patients will be allocated to either Arm A, receiving R-CHOP immunochemotherapy alone, or Arm B, where they will receive R-CHOP immunochemotherapy in combination with Acalabrutinib. Both arms will receive a maximum of 6 cycles of treatment. Cycles will last 21 days. Those with an International Prognostic Index (IPI) of 0-1 will be randomly assigned a treatment arm, and those with an IPI of 2-5 will be automatically assigned to the R-CHOP Acalabrutinib combination arm.
At the end of the treatment phase, 3-8 weeks after they have received the last dose of R-CHOP medication, patients will attend an end-of-treatment visit for some tests.

What are the possible benefits and risks of participating?
Possible benefits:
1. The trial treatment may help to control your lymphoma
2. You will be helping to further our knowledge of how to treat cancer and this will benefit society and others with the same condition in the future
Possible risks/disadvantages:
1. The trial treatment may not control your lymphoma
2. There may be some unpleasant side effects
3. There could be risks to your child if you, or your partner, become pregnant, or begin breastfeeding
4. You may need to attend more clinic visits and provide more blood samples than if you were not taking part in the trial.

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

When is the study starting and how long is it expected to run for?
September 2018 to October 2027

Who is funding the study?
AstraZeneca (UK)

Who is the main contact?
remodla@soton.ac.uk

Study website
https://www.southampton.ac.uk/ctu/trialportfolio/listoftrials/remodla.page

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
2020-000998-25

IRAS number
266600

ClinicalTrials.gov number
NCT04546620

Secondary identifying numbers
CPMS 46717, Grant Codes: ESR 19-20180, IRAS 266600

Study information

Scientific Title
A randomised phase II evaluation of molecular guided therapy for diffuse large B-cell lymphoma with acalabrutinib

Acronym
REMoDL-A

Study objectives
Diffuse large B-cell lymphoma (DLBCL) is the most common of the non-Hodgkin's lymphomas. Whilst the majority of patients will respond well to conventional treatment (R-CHOP a type of immunochemotherapy), a significant number of patients lymphoma will not respond to initial therapy or their disease will return after completion of therapy. In a number of B-cell diseases an enzyme called, Bruton tyrosine kinase (BTK) prevents death of tumour cells, including in DLBCL. Acalabrutinib is an orally active BTK-inhibitor and it is thought that stopping BTK being activated may help in treating B-cell diseases. It is hypothesised that the addition of Acalabrutinib to standard R-CHOP immunochemotherapy may improve outcomes of patients with DLBCL.

The main aims of this randomised phase II clinical study are:
- To determine if combining Acalabrutinib with R-CHOP improves efficacy, compared to R-CHOP alone, for the treatment of previously untreated patients with DLBCL.
- To compare progression-free survival, overall survival, event free survival, disease free survival, time to progression, response duration and overall response rate between both treatment and molecular groups.
- To assess differences in toxicity between the assigned treatments
- To assess differences in quality of life in different treatment arms
- To explore correlation of molecular characteristics in tumour material to clinical outcomes.
- To explore correlation of baseline PET features including metabolic tumour volume, tumour lesion glycolysis, extranodal sites and bone marrow involvement with clinical risk factor and molecular characteristics in tumour material.
- To compare metabolic response rates between molecular groups.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/05/2021, South Central - Berkshire REC (Level 3, Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8222; berkshire.rec@hra.nhs.uk), ref: 21/SC/0122

Study design

Interventional randomized controlled trial

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
Diffuse large B-cell lymphoma

Interventions
Current interventions as of 30/01/2024:
Approximately 375 will be recruited to the clinical trial with 302 patients randomised to the experimental arm. Patients with an International Prognostic Index (IPI) of 0-1 will be randomised to a treatment arm 2:1 in favour of the experimental arm. Patients with an IPI of 2-5 will be allocated to the experimental arm without randomisation.

The study will be conducted in approximately 50 UK sites.

Patients will have histologically confirmed DLBCL, expressing CD20. Sufficient tumour material should be available to forward to a central laboratory for gene expression profiling and pathology review. Patients should have measurable disease of at least 15mm, previously untreated for lymphoma and fit enough to receive combination chemoimmunotherapy with curative intent.

Before Treatment:
The patient will be given information about the trial by the site team. The trial will be explained to them in detail by their physician and they will be given the opportunity to ask questions. The patient will be given a minimum of 24 hours before giving written informed consent.

After each patient has given informed consent, they will have a screening visit (this may be done over a period of days) where they will have a number of routine investigations to confirm their suitability for the trial.

Intervention:
Patients recruited to the study will be randomised or assigned to either Arm A, receiving R-CHOP immunochemotherapy alone, or Arm B, where they will receive R-CHOP immunochemotherapy in combination with Acalabrutinib. Both arms will receive a maximum of 6

cycles of treatment. Cycles will last 21 days: the R-CHO infusion will be given on day 1; oral prednisolone will be self-administered on days 1-5 and Acalabrutinib capsules will be taken daily during cycles 2-6. Patients will also attend hospital during cycle 2 for an interim PET-CT scan.

Drug Dose
Rituximab 375 mg/m²
Cyclophosphamide 750 mg/m²
Vincristine 1.4 mg/m² (max 2 mg)
Doxorubicin 50 mg/m²
Prednisolone 100 mg OD
Acalabrutinib (Arm B only) 100 mg BD

After treatment:
At the end of the treatment, 3-8 weeks after they have received the last dose of R-CHOP medication, patients will attend an end-of-treatment visit (this may be done over a period of days).

They will then go on to the follow-up phase of the trial. Patients will be followed up initially at 3 months, 6 months, 9 months, 12 months, 16 months, 20 months and 24 months. After 24 months, patients will be followed up yearly for progression, second-line therapy and survival data until 114 PFS events have been observed.

Previous interventions:
Up to 558 patients (453 randomised) will be recruited to the clinical trial with 302 patients randomised to the experimental arm and 151 to the control arm in a 2:1 randomisation.

The study will be conducted in approximately 50 UK sites.

Patients will have histologically confirmed DLBCL, expressing CD20. Sufficient tumour material should be available to forward to a central laboratory for gene expression profiling and pathology review. Patients should have measurable disease of at least 15mm, previously untreated for lymphoma and fit enough to receive combination chemoimmunotherapy with curative intent.

Before Treatment:
The patient will be given information about the trial by the site team. The trial will be explained to them in detail by their physician and they will be given the opportunity to ask questions. The patient will be given a minimum of 24 hours before giving written informed consent.

After each patient has given informed consent, they will have a screening visit (this may be done over a period of days) where they will have a number of routine investigations to confirm their suitability for the trial.

Intervention:
Patients recruited to the study will be randomised to either Arm A, receiving R-CHOP immunochemotherapy alone, or Arm B, where they will receive R-CHOP immunochemotherapy in combination with Acalabrutinib. Both arms will receive a maximum of 6 cycles of treatment. Cycles will last 21 days: the R-CHO infusion will be given on day 1; oral prednisolone will be self-administered on days 1-5 and Acalabrutinib capsules will be taken daily during cycles 2-6. Patients will also attend hospital during cycle 2 for an interim PET-CT scan.

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After treatment:
At the end of the treatment, 3-8 weeks after they have received the last dose of R-CHOP medication, patients will attend an end-of-treatment visit (this may be done over a period of days).

They will then go on to the follow-up phase of the trial. Patients will be followed up initially at 3 months, 6 months, 9 months, 12 months, 16 months, 20 months and 24 months. After 24 months, patients will be followed up yearly for progression, second-line therapy and survival data until 114 PFS events have been observed.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Rituximab, cyclophosphamide, vincristine, doxorubicin, prednisolone, acalabrutinib

Primary outcome measure
Progression-free survival at 2 years measured using patient records

Secondary outcome measures
1. To compare PFS between molecular groups. [Time Frame: Last patient's last follow-up, approximately 4.5 years.] PFS interaction with cell of origin phenotype (ABC, GCB and unclassifiable).
2. To compare PFS between treatment groups. [Time Frame: Last patient's last follow-up, approximately 4.5 years.] PFS interaction with clinical variables, including for example IPI, bulk, components of IPI, age and others to be determined in the SAP.
3. To compare overall survival (OS) between both treatment and molecular groups. [Time Frame: Last patient's last follow-up, approximately 4.5 years. Patients who do not experience an OS event will be censored at the date of last follow-up.] Overall survival (OS), defined as time from registration to death from any cause.
4. To compare event free survival (EFS) between both treatment and molecular groups. [Time Frame: Last patient's last follow-up, approximately 4.5 years. Patients who do not experience an EFS event will be censored at the date of last follow-up.] Event-free survival (EFS), or time to treatment failure, defined as time from registration to any treatment failure including disease progression, or discontinuation of treatment for any reason.
5. To compare disease free survival (DFS) between both treatment and molecular groups. [Time Frame: Last patient's last follow-up, approximately 4.5 years. Patients who do not experience a DFS event will be censored at the date of last follow-up.] Disease-free survival (DFS), defined as time of documentation of disease-free state to disease recurrence or death as a result of lymphoma or acute toxicity of treatment.

6. To compare time to progression (TTP) between both treatment and molecular groups. [Time Frame: Last patient's last follow-up, approximately 4.5 years. Patients who do not experience a TTP event will be censored at the date of last follow-up.] Time to progression (TTP), defined as time from registration until documented lymphoma progression or death as a result of lymphoma. Deaths from other causes are censored at the time of death.
7. To compare duration of response (DoR) between both treatment and molecular groups. [Time Frame: Last patient's last follow-up, approximately 4.5 years. Patients who do not experience a RD event will be censored at the date of last follow-up.] Response duration (DoR), defined as the time from documentation of response until the documentation of relapse or progression.
8. To compare overall response rate (ORR) and complete response rate (CR) between both treatment groups. [Time Frame: Complete and overall response rates, as recorded at the end of treatment (up to 21 weeks) .] Assessment using the Lugano Response Criteria for Malignant Lymphoma.
9. To assess differences in toxicity between assigned treatments. [Time Frame: At all visits up to 24 months follow-up.] Evaluation of toxicity according to CTCAE version 5.
10. To assess differences in quality of life between treatment arms. [Time Frame: At baseline, cycle 2 day 1, cycle 3 day 1, cycle 5 day 1, end of treatment and at 3, 6, 12, 20 and 24 month follow-ups. Each cycle is 21 days.] Application of the EORTC QLQ-C30 and FACT-Lym questionnaires.

Overall study start date
30/09/2018

Completion date
31/10/2027

Eligibility

Key inclusion criteria
Current inclusion criteria as of 30/01/2024:
1. Histologically confirmed DLBCL, expressing CD20. Sufficient diagnostic material should be available to forward to HMDS for gene expression profiling and central pathology review. The following diagnoses by 2016 WHO classification of lymphoid neoplasms may be included:
1.1. DLBCL, not otherwise specified (NOS)
1.2. T-cell/histiocyte-rich large B-cell lymphoma
1.3. Epstein-Barr virus positive DLBCL, NOS
1.4. ALK-positive large B-cell lymphoma
1.5 HHV8-positive DLBCL, NOS
1.6. High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (double-hit or triple-hit lymphoma)
1.7. High-grade B-cell lymphoma, NOS
2. At least one bi-dimensionally measurable lesion, defined as >1.5 cm in its longest dimension.
3. Not previously treated for lymphoma and fit enough to receive combination chemoimmunotherapy with curative intent
4. Stage IAX (bulk defined as lymph node mass [either single or conglomerate] diameter >7.5cm) to stage IV disease and deemed to require a full course of chemotherapy. Patients with non-bulky IE disease will not be 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 prior to cycle 1 treatment, 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 (µmolL)]).
8. Serum bilirubin ≤35µmol/L and transaminases (AST or ALT) <1.5x upper limit of normal prior to cycle 1 treatment.
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 institutional normal range.
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.

Previous inclusion criteria:
1. Histologically confirmed DLBCL, expressing CD20. Sufficient diagnostic material should be available to forward to HMDS for gene expression profiling and central pathology review. The following diagnoses by 2016 WHO classification of lymphoid neoplasms may be included:
1.1. DLBCL, not otherwise specified (NOS)
1.2. T-cell/histiocyte-rich large B-cell lymphoma
1.3. Epstein-Barr virus positive DLBCL, NOS
1.4. ALK-positive large B-cell lymphoma
1.5 HHV8-positive DLBCL, NOS
1.6. High-grade B-cell lymphoma with MYC and BCL2 and/or BCL6 rearrangements (double-hit or triple-hit lymphoma)
1.7. High-grade B-cell lymphoma, NOS
2. At least one bi-dimensionally measurable lesion, defined as >1.5 cm in its longest dimension as measured by CT
3. Not previously treated for lymphoma and fit enough to receive combination chemoimmunotherapy with curative intent
4. Stage IAX (bulk defined as lymph node mass [either single or conglomerate] diameter >7.5cm) to stage IV disease and deemed to require a full course of chemotherapy. Patients with non-bulky IE disease will not be 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 (µmolL)]).
8. Serum bilirubin <35µmol/L and transaminases <1.5x 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 institutional normal range.
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

Age group
Adult

Lower age limit
16 Years

Sex
Both

Target number of participants
Planned Sample Size: 375; UK Sample Size: 375

Total final enrolment
294

Key exclusion criteria
Current exclusion criteria as of 30/01/2024:
1. Previous history of treated or untreated indolent lymphoma. Newly diagnosed patients with DLBCL found to have small cell infiltration of the bone marrow or other diagnostic material (discordant lymphoma) will be eligible.
2. Patients who have received immunisation with a live vaccine within four weeks prior to enrolment will be ineligible.
3. Diagnosis of primary mediastinal lymphoma.
4. Diagnosis of primary Central Nervous System lymphoma or secondary CNS involvement.
5. History of stroke or intracranial haemorrhage in preceding 6 months.
6. History of bleeding diathesis (e.g.haemophilia, von Willebrand disease).
7. History of drug-specific hypersensitivity or anaphylaxis to any study drug (including active product or excipient components).
8. Requires or receiving anticoagulation with warfarin or equivalent antagonists (e.g. phenprocoumon) within 7 days of first dose of acalabrutinib. Patients using therapeutic low molecule weight heparin or low dose aspirin will be eligible, as will those receiving direct oral anticoagulants.
9. Prior exposure to an inhibitor in the BCR pathway (e.g. Btk inhibitors, phosphoinositide-3 kinase (PI3K), or Syk inhibitors) or BCL-2 inhibitor (e.g. ABT-199).
10. Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer.
11. Requires treatment with proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Patients receiving proton pump inhibitors should switch to short-acting H2-receptor antagonists or antacids prior to the commencement of acalabrutinib, if randomised to receive acalabrutinib.
12. Active significant infection (e.g. progressive multifocal leukoencephalopathy (PML), tuberculosis, sepsis, and opportunistic infections).
13. Uncontrolled autoimmune haemolytic anaemia (AIHA) or idiopathic thrombocytopenic purpura (ITP).
14. Major surgery in the preceding 4 weeks of first dose of Acalabrutinib (if applicable).

15. Corticosteroid use >30 mg/day of prednisone or equivalent, for purposes other than for lymphoma symptom control. Patients receiving corticosteroid treatment with <30 mg/day of prednisone 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, this may be delivered in the 28 days prior to initiating therapy, with no maximum dose.
16. Any of the following in the previous 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, NYHA Class II or greater congestive heart failure, cerebrovascular accident or transient ischemic attack.
17. Serological positivity for Hepatitis B, C, or known HIV infection.
a. 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.
b. Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
18. Men who can father children must agree to use one highly effective form of contraception with additional barrier or abstinence during the study and for 12 months after the last treatment dose.
19. Breastfeeding or pregnant women.
20. Men who can father children must agree to use two highly effective forms of contraception with additional barrier or abstinence during the study and for 12 months after the last treatment dose.
21. Men must agree to refrain from sperm donation during the study and for 12 months after the last treatment dose.
22. Serious medical or psychiatric illness likely to affect participation or that may compromise the ability to give informed consent.
23. 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.
24. Has difficulty with or is unable to swallow oral medication, or has significant gastrointestinal disease, resection of the stomach or small bowel, partial or complete bowel obstruction or gastric restrictions and bariatric surgery, such as gastric bypass that would limit absorption of oral medication.
25. Any immunotherapy within 4 weeks of 1st dose.
26. Concurrent participation in another therapeutic clinical trial.
27. History of pneumonitis.

Previous exclusion criteria from 11/05/2023 to 30/01/2024:
1. Previous history of treated or untreated indolent lymphoma. Newly diagnosed patients with DLBCL found to have small cell infiltration of the bone marrow or other diagnostic material (discordant lymphoma) will be eligible.
2. Patients who have received immunisation with a live vaccine within four weeks prior to enrolment will be ineligible.
3. Diagnosis of primary mediastinal lymphoma.
4. Diagnosis of primary Central Nervous System lymphoma or secondary CNS involvement.
5. History of stroke or intracranial haemorrhage in preceding 6 months.
6. History of bleeding diathesis (e.g.haemophilia, von Willebrand disease).
7. History of drug-specific hypersensitivity or anaphylaxis to any study drug (including active product or excipient components).
8. Requires or receiving anticoagulation with warfarin or equivalent antagonists (e.g. phenprocoumon) within 7 days of first dose of acalabrutinib. Patients using therapeutic low

molecule weight heparin or low dose aspirin will be eligible, as will those receiving direct oral anticoagulants.
9. Prior exposure to an inhibitor in the BCR pathway (e.g. Btk inhibitors, phosphoinositide-3 kinase (PI3K), or Syk inhibitors) or BCL-2 inhibitor (e.g. ABT-199).
10. Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer.
11. Requires treatment with proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole). Patients receiving proton pump inhibitors should switch to short-acting H2-receptor antagonists or antacids prior to the commencement of acalabrutinib, if randomised to receive acalabrutinib.
12. Active significant infection (e.g. progressive multifocal leukoencephalopathy (PML), tuberculosis, sepsis, and opportunistic infections).
13. Uncontrolled autoimmune haemolytic anaemia (AIHA) or idiopathic thrombocytopenic purpura (ITP).
14. Major surgery in the preceding 4 weeks of first dose of Acalabrutinib (if applicable).
15. Corticosteroid use >30 mg/day of prednisone or equivalent, for purposes other than for lymphoma symptom control. Patients receiving corticosteroid treatment with <30 mg/day of prednisone 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, prednisone 100 mg or equivalent could be given for a maximum of 14 days as a prephase. A dose of upto 30mg or prenisolone or equivalent may be used during the screening phase to control symptoms.
16. Any of the following in the previous 6 months: myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, NYHA Class II or greater congestive heart failure, cerebrovascular accident or transient ischemic attack.
17. Serological positivity for Hepatitis B, C, or known HIV infection.
a. 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.
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19. Breastfeeding or pregnant women.
20. Men who can father children must agree to use two highly effective forms of contraception with additional barrier or abstinence during the study and for 12 months after the last treatment dose.
21. Men must agree to refrain from sperm donation during the study and for 12 months after the last treatment dose.
22. Serious medical or psychiatric illness likely to affect participation or that may compromise the ability to give informed consent.
23. 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.
24. Has difficulty with or is unable to swallow oral medication, or has significant gastrointestinal disease, resection of the stomach or small bowel, partial or complete bowel obstruction or gastric restrictions and bariatric surgery, such as gastric bypass that would limit absorption of oral medication.
25. Any immunotherapy within 4 weeks of 1st dose.
26. Concurrent participation in another therapeutic clinical trial.
27. History of pneumonitis.

Original exclusion criteria:
1. Previous history of treated or untreated indolent lymphoma. Newly diagnosed patients with DLBCL found to have small cell infiltration of the bone marrow or other diagnostic material (discordant lymphoma) will be eligible.
2. Patients who have received immunisation with a live vaccine within four weeks prior to enrolment will be ineligible.
3. Diagnosis of primary mediastinal lymphoma.
4. Diagnosis of primary Central Nervous System lymphoma or secondary CNS involvement.
5. History of stroke or intracranial haemorrhage in preceding 6 months.
6. History of bleeding diathesis (e.g.haemophilia, von Willebrand disease).
7. History of drug-specific hypersensitivity or anaphylaxis to any study drug (including active product or excipient components).
8. Requires or receiving anticoagulation with warfarin or equivalent antagonists (e.g. phenprocoumon) within 7 days of first dose of acalabrutinib. Patients using therapeutic low molecule weight heparin or low dose aspirin will be eligible, as will those receiving direct oral anticoagulants.
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10. Requires treatment with a strong cytochrome P450 3A4 (CYP3A4) inhibitor/inducer.
11. Requires treatment with proton pump inhibitors (eg, omeprazole, esomeprazole, lansoprazole, dexlansoprazole, rabeprazole, or pantoprazole).
12. Active significant infection (e.g. progressive multifocal leukoencephalopathy (PML), tuberculosis, sepsis, and opportunistic infections).
13. Uncontrolled autoimmune haemolytic anaemia (AIHA) or idiopathic thrombocytopenic purpura (ITP).
14. Major surgery in the preceding 4 weeks of first dose of study drug.
15. Corticosteroid use >30 mg/day of prednisone or equivalent, for purposes other than for lymphoma symptom control. Patients receiving corticosteroid treatment with <30 mg/day of prednisone 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, prednisone 100 mg or equivalent could be given for a maximum of 14 days as a prephase. A dose of upto 30mg or prenisolone or equivalent may be used during the screening phase to control symptoms.
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b. Patients positive for HCV antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
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the last treatment dose.
22. Serious medical or psychiatric illness likely to affect participation or that may compromise the ability to give informed consent.
23. 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.
24. Has difficulty with or is unable to swallow oral medication, or has significant gastrointestinal disease, resection of the stomach or small bowel, partial or complete bowel obstruction or gastric restrictions and bariatric surgery, such as gastric bypass that would limit absorption of oral medication.
25. Any immunotherapy within 4 weeks of 1st dose.
26. Concurrent participation in another therapeutic clinical trial.
27. History of pneumonitis.

Date of first enrolment
19/10/2021

Date of final enrolment
30/06/2025

Locations

Countries of recruitment
England

Scotland

United Kingdom

Wales

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

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

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

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

Study participating centre
Queen's Hospital
Rom Valley Way
Romford
United Kingdom
RM7 0AG

Study participating centre
Freeman Hospital
Newcastle Upon Tyne Hospital Trust
Freeman Road
High Heaton
Newcastle
United Kingdom
NE7 7DN

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

Study participating centre

Royal Cornwall Hospital (treliske)
Treliske
Truro
United Kingdom
TR1 3LJ

Study participating centre
Nottingham City Hospital
Hucknall Road
Nottingham
United Kingdom
NG5 1PB

Study participating centre
Chase Farm Hospital
127 the Ridgeway
Enfield
United Kingdom
EN2 8JL

Study participating centre
East Kent Hospitals University NHS Foundation Trust
Kent & Canterbury Hospital
Ethelbert Road
Canterbury
United Kingdom
CT1 3NG

Study participating centre
Ipswich Hospital
Heath Road
Ipswich
United Kingdom
IP4 5PD

Study participating centre
Torbay Hospital
Newton Road
Torquay
United Kingdom
TQ2 7AA

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

Study participating centre
Lewisham and Greenwich NHS Trust
University Hospital Lewisham
Lewisham High Street
London
United Kingdom
SE13 6LH

Study participating centre
Milton Keynes University Hospital NHS Foundation Trust
Standing Way
Eaglestone
Milton Keynes
United Kingdom
MK6 5LD

Study participating centre
NHS Lanarkshire
14 Beckford Street
Hamilton
United Kingdom
ML3 0TA

Study participating centre
Norfolk and Norwich University Hospitals NHS Foundation Trust
Colney Lane
Colney
Norwich
United Kingdom
NR4 7UY

Study participating centre
Derriford Hospital
University Hospitals Plymouth NHS Trust
Derriford Road
Derriford
Plymouth
United Kingdom
PL6 8DH

Study participating centre
The Maidstone Hospital
Maidstone and Tunbridge Wells NHS Trust
Hermitage Lane
Maidstone
United Kingdom
ME16 9QQ

Study participating centre
Royal Bournemouth Hospital
Castle Lane East
Bournemouth
United Kingdom
BH7 7DW

Study participating centre
Royal Devon and Exeter Hospital
Royal Devon & Exeter Hospital
Barrack Road
Exeter
United Kingdom
EX2 5DW

Study participating centre
University College London Hospitals NHS Foundation Trust
250 Euston Road
London
United Kingdom
NW1 2PG

Study participating centre

University Hospitals Sussex NHS Foundation Trust
Worthing Hospital
Lyndhurst Road
Worthing
United Kingdom
BN11 2DH

Study participating centre
Leicester Royal Infirmary
University Hospitals of Leicester NHS Trust
Infirmary Square
Leicester
United Kingdom
LE1 5WW

Study participating centre
The Christie NHS Foundation Trust
550 Wilmslow Road
Withington
Manchester
United Kingdom
M20 4BX

Study participating centre
Queen Alexandra Hospital
Portsmouth Hospitals NHS Trust
Southwick Hill Road
Cosham
Portsmouth
United Kingdom
PO6 3LY

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-trent
United Kingdom
ST4 6QG

Study participating centre

Poole Hospital
University Hospitals Dorset NHS Foundation Trust
Longfleet Road
Poole
United Kingdom
BH15 2JB

Study participating centre
Swansea Bay University Local Health Board
One Talbot Gateway
Seaway Drive
Seaway Parade
Industrial Estate
Baglan
Port Talbot
United Kingdom
SA12 7BR

Study participating centre
Chelsea and Westminster Hospital NHS Foundation Trust
Chelsea & Westminster Hospital
369 Fulham Road
London
United Kingdom
SW10 9NH

Study participating centre
Broomfield Hospital
Court Road
Broomfield
Chelmsford
United Kingdom
CM1 7ET

Study participating centre
Southend Hospital
Prittlewell Chase
Westcliff-on-sea
United Kingdom
SS0 0RY

Study participating centre
Darent Valley Hospital
Darenth Wood Road
Dartford
United Kingdom
DA2 8DA

Study participating centre
James Cook University Hospital
Marton Road
Middlesbrough
United Kingdom
TS4 3BW

Study participating centre
United Lincolnshire Hospitals NHS Trust
Lincoln County Hospital
Greetwell Road
Lincoln
United Kingdom
LN2 5QY

Study participating centre
Bolton Royal Hospital
Minerva Road
Farnworth
Bolton
United Kingdom
BL4 0JR

Study participating centre
Sandwell General Hospital
Lyndon
West Bromwich
United Kingdom
B71 4HJ

Study participating centre
Harrogate District Hospital
Lancaster Park Road
Harrogate

United Kingdom
HG2 7SX

Study participating centre
Addenbrookes
Addenbrookes Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
South Warwickshire University NHS Foundation Trust
Warwick Hospital
Lakin Road
Warwick
United Kingdom
CV34 5BW

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

Study participating centre
Stoke Mandeville Hospital
Mandeville Road
Aylesbury
United Kingdom
HP21 8AL

Study participating centre
Wycombe Hospital
Queen Alexandra Road
High Wycombe
United Kingdom
HP11 2TT

Study participating centre
Hampshire Hospitals NHS Foundation Trust
Basingstoke and North Hampshire Hos
Aldermaston Road
Basingstoke
United Kingdom
RG24 9NA

Study participating centre
University Hospitals Coventry and Warwickshire NHS Trust
Walsgrave General Hospital
Clifford Bridge Road
Coventry
United Kingdom
CV2 2DX

Study participating centre
Royal United Hospital
Combe Park
Bath
United Kingdom
BA1 3NG

Study participating centre
West Suffolk Hospital
Hardwick Lane
Bury St. Edmunds
United Kingdom
IP33 2QZ

Sponsor information

Organisation
University Hospital Southampton NHS Foundation Trust

Sponsor details
Mailpoint 18
Southampton General Hospital
Tremona Road
Southampton
England

United Kingdom
SO16 6YD
+44 (0)2381205078
Sharon.Davies-Dear@uhs.nhs.uk

Sponsor type
Hospital/treatment centre

Website
http://www.uhs.nhs.uk/home.aspx

ROR
https://ror.org/0485axj58

Funder(s)

Funder type
Industry

Funder Name
AstraZeneca

Alternative Name(s)
AstraZeneca PLC, Pearl Therapeutics

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Participating clinicians will be supplied with a lay summary of the results once the definitive analysis is presented publicly in order to make this available to the patients that they entered into the trial. The study team will present results at national and international conferences and publish in a peer-reviewed journal. Results will also be published on clinicaltrials.gov.

Intention to publish date
01/01/2028

Individual participant data (IPD) sharing plan

The current data sharing plans for this study are unknown and will be 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