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IciCLLe: Assessment of the Mechanism of Action of Ibrutinib (PCI-32765) in B-cell Receptor Pathway Inhibition in CLL

Submission date 03/04/2014	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 03/04/2014	**Overall study status** Completed	
Last Edited 24/04/2023	**Condition category** Cancer	

Plain English summary of protocol
http://www.cancerresearchuk.org/cancer-help/trials/a-study-looking-ibrutinib-chronic-lymphocytic-leukaemia-iciclle

Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
2012-003608-11

Integrated Research Application System (IRAS)
136775

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
15429

Study information

Scientific Title
IciCLLe: Assessment of the Mechanism of Action of Ibrutinib (PCI-32765) in B-cell Receptor Pathway Inhibition in CLL

Acronym
IciCLLe

Study objectives
Current hypothesis as of 24/04/2023:
The aim of this feasibility study is to confirm the mechanism of action of ibrutinib. Results will then inform the design of a randomized phase II/III trial using response as the primary outcome measure to determine whether ibrutinib shows sufficient evidence of activity in these cohorts of patients.

In October 2015 the Extension Study was added to the IcICLLe protocol. The IcICLLe extension study will test the safety and efficacy of ibrutinib combined with obinutuzumab in CLL. A major aim of treatment in CLL is to eradicate detectable minimal residual disease (MRD). Ibrutinib is a major step forward in the treatment of CLL but results in an immediate lymphocytosis that persists in most patients for at least several months. However the combination of ibrutinib with rituximab, a relatively ineffective monotherapy in CLL, seems to abrogate the lymphocytosis. Obinutuzumab is a second-generation anti-CD20 monoclonal antibody that appears to be highly effective in CLL resulting in a rapid eradication of peripheral blood lymphocytosis and the eradication of MRD in a proportion of patients. Currently we only have data in untreated CLL for obinutuzumab vs. rituximab. Therefore the combination of obinutuzumab with ibrutinib is likely to be extremely effective. It may also inform possible future Phase III trials to test a more effective anti-CD20 antibody in combination with ibrutinib.

IcICLLe Extension Study
Up to 20 relapsed/refractory patients originally recruited to the IcICLLe study will transition to the extension study (cohort (B) iii). At least 20 relapsed/refractory CLL patients not previously treated in the IcICLLe study (i.e., ibrutinib naïve, cohort (B) ii) will be recruited so that the total sample size in the extension study is no more than 40 patients.

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Previous hypothesis:
The aim of this feasibility study is to confirm the mechanism of action of Ibrutinib. Results will then inform the design of a randomized phase II/III trial using response as the primary outcome measure to determine whether Ibrutinib shows sufficient evidence of activity in these cohorts of patients.

Ethics approval required
Old ethics approval format

Ethics approval(s)
14/YH/0034; First MREC approval date 20/02/2014

Study design
Non-randomised; Interventional; Design type: Treatment

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Topic: Cancer; Subtopic: Haematological Oncology; Disease: Leukaemia (chronic)

Interventions
Current intervention as of 24/04/2023:
Main study:
Ibrutinib 420 mg (3 x 140-mg capsules) taken orally once daily continuously until disease progression

Extension study:
Ibrutinib 420 mg (3 x 140-mg capsules) taken orally once daily continuously.
Obinutuzumab 1000 mg (6 cycles, cycle 1 consisting of three doses over first 15 days of cycle 1, cycles 2-6 one dose every 28 days) by intravenous infusion.

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Previous intervention:
Ibrutinib, B-Cell receptor pathway inhibitor; Follow Up Length: 60 month(s); Study Entry : Registration only

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Ibrutinib, obinutuzumab

Primary outcome(s)
Current primary outcome measure as of 24/04/2023:
For main trial and extension:
Proportion of patients achieving MRD-negative remission by IWCLL criteria (depletion of CLL below 0.01% in the peripheral blood and bone marrow) in a) the initial phase of the study at or before the 6-month assessment and b) the Extension Study at or before the 9-month assessment. Independent decisions will be made for each study (initial and extension).

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Previous primary outcome measure:
Assess the impact on Ibrutinib on: o CLL cell levels as a percentage of total leucocytes in the b; Timepoint(s): Baseline, Day1, Week 1, Week 2, month 1, Month 2, Month 6, month 9, Month 12.

Key secondary outcome(s))

Current secondary outcome measures as of 24/04/2023:
Main trial:
1. Best disease response to treatment: Complete Remission (CR); Complete Remission with incomplete marrow recovery (Cri) or Partial Remission (PR) with leucocytosis, assessed according to the IWCLL Response Criteria (revised 2008) (Appendix 1) at or before the 6-month assessment. Independent decisions will be made for each study (initial and extension 1 and 2 year progression free survival for relapsed/refractory and treatment naïve patients defined as time from date of registration to date of progression (per the 2008 IWCLL criteria) or death from any cause.
2. Overall survival for relapsed/refractory and treatment naïve patients, defined as the time from date of registration to the date of death from any cause, at 2 years and 5 years
3. Toxicity of ibrutinib assessed throughout the trial
4. CLL cell levels as a percentage of total leucocytes in the bone marrow (BM) assessed using flow cytometry in months 1 and 6.
5. CLL cell levels as absolute counts in the peripheral blood (PB) assessed using flow cytometry frequently in the first month, 3-monthly to month 12 then 6-monthly.
6. The proportion of patients with >5%, 0.5-5%, <0.5% CLL cells in cell cycle (expressing Ki67) in the peripheral blood and bone marrow at or before the 6-month assessment
7. Change in the expression levels of CD10, CD103, CD11c, CD185, CD196, CD20, CD200, CD22, CD23, CD25, CD27, CD305, CD31, CD38, CD39, CD43, CD49d, CD5, CD79b, CD81, CD95, IgD, IgG, or IgM on CLL cells relative to baseline by more than 50% and at least 500 arbitrary units in median fluorescence intensity monitored throughout the study

Extension:
1. Best disease response to treatment: Complete Remission (CR); Complete Remission with incomplete marrow recovery (Cri) or Partial Remission (PR) with leucocytosis, assessed according to the IWCLL Response Criteria (revised 2008) (Appendix 1) at or before the 9-month assessment. Independent decisions will be made for each study (initial and extension 1 and 2 year progression-free survival for relapsed/refractory and treatment naïve patients defined as time from date of registration to date of progression (per the 2008 IWCLL criteria) or death from any cause.
2. Overall survival for relapsed/refractory and treatment naïve patients, defined as the time from date of registration to the date of death from any cause, at 2 years and 5 years
3. Toxicity of ibrutinib and obinutuzumab assessed throughout the trial
4. CLL cell levels as a percentage of total leucocytes in the bone marrow (BM) assessed using flow cytometry in months 1 and 9.
5. CLL cell levels as absolute counts in the peripheral blood (PB) assessed using flow cytometry frequently in the first month, 3-monthly to month 12 then 6-monthly.
6. The proportion of patients with >5%, 0.5-5%, <0.5% CLL cells in cell cycle (expressing Ki67) in the peripheral blood and bone marrow at or before the 9-month assessment
7. Change in the expression levels of CD10, CD103, CD11c, CD185, CD196, CD20, CD200, CD22, CD23, CD25, CD27, CD305, CD31, CD38, CD39, CD43, CD49d, CD5, CD79b, CD81, CD95, IgD, IgG, or IgM on CLL cells relative to baseline by more than 50% and at least 500 arbitrary units in median fluorescence intensity monitored throughout the study

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Previous secondary outcome measures:
1. One and two year progression free survival for relapsed/refractory and treatment naïve patients define; Timepoint(s): 1 and 2 years
2. Two and five year overall survival for relapsed/refractory and treatment naïve patients, defined as the; Timepoint(s): 1 and 5 years
3. Best disease response: Complete Remission (CR); Complete Remission with incomplete marrow recovery; Timepoint(s): Week 1, week 2, Month 1, Month 2, Month 6.
4. Biological response (complete, partial or nodal) at 1, 6 and 12 months, assessed according to the; Timepoint(s): 1, 6, 12 months

Completion date
31/12/2023

Eligibility

Key inclusion criteria
Current inclusion criteria as of 24/04/2023:
Cohort A (Treatment-naive)
1. Progressive Stage A, Stage B or Stage C CLL
2. CLL requiring therapy by the IWCLL criteria
3. ECOG performance status (PS) of 0, 1, or 2
4. Life expectancy of at least 6 months
5. Age >=18 years
6. Prepared to undergo the stipulated investigations within the trial (including bone marrow examinations)
7. Able to give informed consent
8. Adequate hepatic function, defined as serum aspartate transaminase (AST) or alanine transaminase (ALT) <2.5 x upper limit of normal (ULN), and total bilirubin ≤1.5 x ULN unless due to Gilbert's syndrome
9. Adequate renal function, defined as estimated creatinine clearance ≥30 mL/min using the Cockcroft-Gault equation

Cohorts (B)i and (B)ii: Relapsed/refractory (initial phase 20 patients, extension phase between 20-40 patients)
1. B-CLL requiring therapy according to the IWCLL guidelines. The leukaemia cells should co-express CD19, CD5, and CD23 and each clone should have restricted to expression of either kappa or lambda immunoglobulin light chains. The levels of surface immunoglobulin, CD20, and CD79b should be low. If there is atypically strong surface immunoglobulin, CD20, or CD79b expression, or other atypical features, it may not be possible to perform the MRD monitoring required to evaluate the primary endpoint.
2. Refractory CLL defined as any of the following:
2.1. Failure to achieve a response (CR or PR by IWCLL Criteria) to a purine analogue alone or in combination with chemotherapy
2.2. Relapse within 6 months of responding to a purine analogue alone or in combination with chemotherapy
2.3. Relapse within 24 months of responding to fludarabine, cyclophosphamide and rituximab (FCR)
2.4. Patients with CLL with deletion of chromosome 17p who have failed at least one previous therapy.
3. ECOG performance status (PS) of 0, 1, or 2

4. Life expectancy of at least 6 months
5. Prepared to undergo the stipulated investigations within the trial (including bone marrow examinations)
6. Age >= 18
7. Able to give informed consent
8. Ability to comply with study protocol procedures
9. Adequate hepatic function, defined as serum aspartate transaminase (AST) or alanine transaminase (ALT) <2.5 x ULN, and total bilirubin ≤1.5 x ULN unless due to Gilbert's syndrome
10. Adequate renal function, defined as estimated creatinine clearance ≥30 mL/min using the Cockcroft-Gault equation
11. Minimum platelet count of ≥50 x 10^9/L
12. Absolute neutrophil count (ANC) ≥ 1.0 x 10^9/L (unless due to direct marrow infiltration by CLL (to be confirmed via bone marrow biopsy)

Cohort (B)iii: Ibrutinib treated patients (extension phase only – up to 20 patients)
1. Patients enrolled on IcICLLe trial as relapsed/refractory patients who have received treatment with ibrutinib on the IcICLLe trial for at least 6 months

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Previous inclusion criteria:
Cohort A (Treatment naive)
1. Progressive Stage A, Stage B or Stage C CLL
2. CLL requiring therapy by the IWCLL criteria
3. ECOG performance status (PS) of 0, 1, or 2
4. Life expectancy of at least 6 months
5. Age =18
6. Prepared to undergo the stipulated investigations within the trial (including bone marrow examinations)
7. Able to give informed consent

Cohort B (Relapsed/Refractory)
1. CLL requiring therapy
2. Refractory CLL defined as any of the following:
3. Failure to achieve a response (CR or PR by IWCLL Criteria) to a purine analogue alone or in combination with chemotherapy, or:
4. Relapse within 6 months of responding to a purine analogue alone or in combination with chemotherapy, or:
5. Relapse within 24 months of responding to a fludarabine, cyclophosphamide and rituximab (FCR), or:
6. Patients with CLL with deletion of chromosome 17p who have failed at least one previous therapy.
7. ECOG performance status (PS) of 0, 1, or 2 (see appendix 6)
8. Life expectancy of at least 6 months
9. Prepared to undergo the stipulated investigations within the trial (including bone marrow examinations)
10. Age = 18
11. Able to give informed consent
Target Gender: Male & Female ; Lower Age Limit 18 years

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 24/04/2023:
All participants:
1. Unwilling to undergo the protocol assessments including the bone marrow assessments
2. Active infection at the time of registration), history of chronic or recurrent infection
3. Other severe, concurrent (particularly cardiac or pulmonary) diseases or mental disorders that could interfere with their ability to participate in the study
4. Use of prior investigational agents within 6 weeks
5. Pregnancy or lactation
6. Unwilling to use appropriate contraception during and for 12 months following treatment
7. CNS involvement with CLL
8. Mantle cell lymphoma
9. Known HIV positive
10. Active or prior Hepatitis B or C
11. Active secondary malignancy excluding basal cell carcinoma
12. Persisting severe panocytopenia (neutrophils <1.0 x10^9/L) or transfusion dependent anaemia unless due to direct marrow infiltration by CLL (to be confirmed via bone marrow biopsy)
13. Active haemolysis (not controlled with prednisolone at 20 mg or less)
14. Patients requiring or who have received anticoagulation treatment with warfarin or vitamin K antagonists within 1 week of the first dose of ibrutinib
15. Patients requiring concomitant use of strong CYP3A4/5 inhibitors
16. Patients with evidence or history of transformation and/or PLL
17. Major surgery within 4 weeks prior to registration
18. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to registration History of stroke or intracranial haemorrhage within 6 months prior to registration
19. History of severe allergic or anaphylactic reactions to humanised or murine monoclonal antibodies. Known sensitivity or allergy to murine products.
20. Vaccination with a live vaccine a minimum of 28 days prior to registration.
21. Patients with Progressive Multifocal Leukoencephalopathy (PML).
22. No known allergy to obinutuzumab or excipients

Cohort (B)i and (B)ii: Relapsed/refractory (initial phase – 20 patients, extension phase between 20-40 patients)
1. Previous treatment with ibrutinib or an alternative inhibitor of B-Cell receptor pathway

Previous exclusion criteria:
Both cohorts A and B
1. Unwilling to undergo the protocol assessments including the bone marrow assessments
2. Active infection
3. Other severe, concurrent (particularly cardiac or pulmonary) diseases or mental disorders that could interfere with their ability to participate in the study
4. Use of prior investigational agents within 6 weeks
5. Pregnancy or lactation
6. Unwilling to use appropriate contraception during and for 12 months following treatment
7. CNS involvement with CLL
8. Mantle cell lymphoma
9. Known HIV positive
10. Active or prior Hepatitis B or C
11. Active secondary malignancy excluding basal cell carcinoma
12. Persisting severe panocytopenia (nNeutrophils <0.5 x109/L) or transfusion dependent anaemia unless due to direct marrow infiltration by CLL (to be confirmed via bone marrow biopsy)
13. Active haemolysis (not controlled with Prednisolone at 10 mg or less)
14. Patients requiring or who have received anticoagulation treatment with warfarin or vitamin K antagonists within 1 week of the first dose of ibrutinib
15. Patients requiring concomitant use of strong CYP3A4/5 inhibitors
16. Patients with evidence or history of transformation and/or PLL

Cohort A (Treatment naive)
1. Previous treatment for CLL. This does not include steroids.

Cohort B (Relapsed/Refractory)
1. Previous treatment with ibrutinib or an alternative inhibitor of BCell receptor pathway

Date of first enrolment
24/04/2014

Date of final enrolment
20/10/2017

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Institute for Cancer Studies
Birmingham
United Kingdom
B15 2TT

Sponsor information

Organisation
University of Birmingham (UK)

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Industry

Funder Name
Blood Cancer UK

Alternative Name(s)
Blood Cancer UK Research

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
Pharmacyclics

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Funder Name
F. Hoffmann-La Roche

Alternative Name(s)
Hoffman-La Roche, F. Hoffmann-La Roche Ltd.

Funding Body Type
Private sector organisation

Funding Body Subtype
For-profit companies (industry)

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
IPD will not be available.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Abstract results	IcICLLe results presented at European Hematology Association conference	21/05/2015	13/04/2023	No	No
Abstract results	IcICLLe results presented at NCRI Cancer Conference	01/11/2015	13/04/2023	No	No
HRA research summary			28/06/2023	No	No
Protocol file	version 12.0	22/08/2022	24/04/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes