

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

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| Submission date 03/04/2014 | Recruitment status No longer recruiting | <input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol |
| Registration date 03/04/2014 | Overall study status Completed | <input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results |
| Last Edited 24/04/2023 | Condition category Cancer | <input type="checkbox"/> Individual participant data |

Plain English summary of protocol

<http://www.cancerresearchuk.org/cancer-help/trials/a-study-looking-ibrutinib-chronic-lymphocytic-leukaemia-icicle>

Study website

<https://www.birmingham.ac.uk/research/crcu/trials/haematology/icicle/index.aspx>

Contact information

Type(s)

Scientific

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Additional identifiers

EudraCT/CTIS number

2012-003608-11

IRAS number

136775

ClinicalTrials.gov number

Nil known

Secondary identifying numbers

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.

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

Secondary study design

Non randomised study

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet**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.

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 measure

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).

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.

Secondary outcome measures

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

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

Overall study start date

24/04/2014

Completion date

31/12/2023

Eligibility

Key inclusion criteria

Current inclusion criteria as of 24/04/2023:

Cohort A (Treatment-naïve)

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) $< 2.5 \times$ upper limit of normal (ULN), and total bilirubin $\leq 1.5 \times$ 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) $< 2.5 \times \text{ULN}$, and total bilirubin $\leq 1.5 \times \text{ULN}$ unless due to Gilbert's syndrome

10. Adequate renal function, defined as estimated creatinine clearance $\geq 30 \text{ mL/min}$ using the Cockcroft-Gault equation

11. Minimum platelet count of $\geq 50 \times 10^9/\text{L}$

12. Absolute neutrophil count (ANC) $\geq 1.0 \times 10^9/\text{L}$ (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 ICLLLe trial as relapsed/refractory patients who have received treatment with ibrutinib on the ICLLLe trial for at least 6 months

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

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

Planned Sample Size: 40; UK Sample Size: 40; Description: 2 cohorts of 20 patients each. Cohort A). Treatment naive. Cohort B). Relapse/refractory

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 $<1.0 \times 10^9/L$) 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 pancytopenia (nNeutrophils $<0.5 \times 10^9/L$) 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 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 naïve)

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

England

United Kingdom

Study participating centre

Institute for Cancer Studies

Birmingham

United Kingdom

B15 2TT

Sponsor information

Organisation

University of Birmingham (UK)

Sponsor details

Cancer Research UK Clinical Trials Unit

Institute for Cancer and Genomic Studies

Edgbaston

Birmingham

England

United Kingdom

B15 2TT

Sponsor type

University/education

ROR

<https://ror.org/03angcq70>

Funder(s)

Funder type

Industry

Funder Name

Blood Cancer UK

Alternative Name(s)

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

Publication and dissemination plan

Publication of trial results will be when all patients reach 5-year follow-up (planned for Q4 2023).

Intention to publish date

31/12/2023

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 |
| Protocol file | version 12.0 | 22/08/2022 | 24/04/2023 | No | No |
| HRA research summary | | | 28/06/2023 | No | No |