

A study of the drugs AZD2014 and rituximab in relapsed or refractory diffuse large B-cell lymphoma

Submission date 01/07/2015	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 01/07/2015	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 14/10/2022	Condition category Cancer	<input type="checkbox"/> Individual participant data

Plain English summary of protocol

<https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-azd2014-for-diffuse-large-b-cell-lymphoma-torch>

Contact information

Type(s)

Public

Contact name

Ms Kathryn Paterson

Contact details

Cancer Research UK Clinical Trials Unit
School of Cancer Sciences
University of Birmingham
Edgbaston
Birmingham
United Kingdom
B15 2TT

Additional identifiers

EudraCT/CTIS number

2014-003588-39

IRAS number

ClinicalTrials.gov number

NCT02752204

Secondary identifying numbers

19208

Study information

Scientific Title

A phase II study to determine the safety and efficacy of the dual mTORC inhibitor AZD2014 and to investigate additional toxicities in combination with rituximab in relapsed refractory DLBCL

Acronym

Torch

Study objectives

The aim of this clinical trial is to see if the drug called AZD2014 is effective and safe to use to treat patients with relapsed or refractory Diffuse Large BCell Lymphoma (DLBCL). We will also be looking at combining the antibody (Rituximab) with the drug AZD2014 in a small number of patients to see if this can be done without increasing the toxicity.

Ethics approval required

Old ethics approval format

Ethics approval(s)

NRES Committee West Midlands – Edgbaston, 18/05/2015, ref: 15/WM/0126

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

Not available in web format, please use contact details to request a participant information sheet

Health condition(s) or problem(s) studied

Topic: Cancer; Subtopic: Lymphoma; Disease: Lymphoma (other)

Interventions

AZD2014 is a close analogue of AZD8055 and a selective inhibitor of mTOR kinase. AZD2014 has greater inhibitory activity against mTORC1 compared to rapamycin: AZD2014 decreases p4EBP1

Thr37/46, inhibits the translation initiation complex and decreases overall protein synthesis. AZD2014 also inhibits the mTORC2 biomarkers pAKTSer473 and pNDRG1Thr346. AZD2014 has broad antiproliferative activity across multiple tumour cell lines. azd2014 is provided as an oral tablet free of charge to study participants; Rituximab, Rituximab is licenced within the EU for the treatment of patients with CD20 positive diffuse large B cell non Hodgkin's lymphoma in combination with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone) chemotherapy and is therefore a standard treatment for these patients.

36 patients will be recruited to the trial. 30 will receive AZD2014 alone and the remaining 6 will receive AZD2014 plus rituximab. AZD2014 will be given as a 125mg tablet that is to be taken twice a day for 2 days out of every 7 (i.e. on days 1 and 2 of every week). Rituximab will be given via IV infusion on day 1 of every 28 days (once every 4 weeks) for a maximum of 6 cycles.

Intervention Type

Drug

Phase

Phase II

Drug/device/biological/vaccine name(s)

AZD2014 Rituximab

Primary outcome measure

Best overall response rate (PR plus CR) (using the Revised Response Criteria for Malignant Lymphoma); Timepoint(s): during the first 6 cycles

Secondary outcome measures

1. Tolerability rate (based on toxicity assessments using CTCAE v 4.0 criteria) of single agent AZD2014; Timepoint(s): during stage 1 of the study
2. Tolerability rate of additional toxicities when rituximab is combined with AZD2014 at its standard dose; Timepoint(s): During stage 2 only
3. Best overall response rate post 6 cycles until the end of the trial, assessed using Revised Response Criteria; Timepoint(s): post 6 cycles
4. Overall survival (OS); Timepoint(s): at 1 year
5. Progression free survival (PFS); Timepoint(s): at 1 year
6. Duration of response; Timepoint(s): End of trial
7. Maximum % decrease in the radiological sum of the product of the diameters (SPD) from baseline by CT NCAP; Timepoint(s): From baseline to the end of the study
8. Correlation of response with pharmacodynamic biomarkers, cell of origin studies, lymphoid-related mutational analysis and potential predictive biomarkers of response; Timepoint(s): baseline to Post 2 cycle, post cycle 6 and progression
9. To determine the response to AZD2014 by PET CT criteria and analyse the effect; Timepoint(s): Post 2 cycle and post cycle 6

Overall study start date

15/07/2015

Completion date

05/02/2019

Eligibility

Key inclusion criteria

1. Relapsed or refractory Diffuse Large B-Cell Lymphoma (DLBCL) relapsing after at least 1 course of potentially curative, anti-CD20 antibody containing regimen (e.g. RCHOP, GCHOP, RGCVP). High grade transformation from low grade lymphoma (e.g. follicular lymphoma, lymphoplasmacytic lymphoma, chronic lymphocytic leukaemia) is permitted. Patients must have relapsed post-ASCT or be considered not suitable for ASCT
2. Tissue biopsy (or bone marrow trephine if no other tissue available) confirming histology within 3 months of enrolment
3. Provision of signed and dated, written informed consent prior to any study specific procedures, sampling and analyses
4. Aged at least 18 years
5. Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2
6. Females should be using adequate contraceptive measures (as described in the protocol, different for patient receiving rituximab), should not be breast feeding and must have a negative pregnancy test prior to start of dosing if of child-bearing potential or must have evidence of non-child-bearing potential by fulfilling one of the following criteria at screening:
 - 6.1. Post-menopausal defined as amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments
 - 6.2. Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation
7. Male patients should be willing to use barrier contraception (i.e. condoms) as described in the protocol, (different for patient receiving rituximab)
8. Ability to swallow and retain oral medication
9. CT measurable disease with at least 1 lesion having short axis $\geq 1.5\text{cm}$ or splenomegaly $\geq 13\text{cm}$ in cranio-caudal length attributable to relapsed lymphoma
10. Patients must have negative virology for HIV and hepatitis C prior to trial entry. Patients with an isolated anti-hepatitis B sAg antibody may be entered as this indicates previous vaccination. These patients MUST have HBV DNA tested

Participant type(s)

Patient

Age group

Adult

Lower age limit

18 Years

Sex

Both

Target number of participants

Planned Sample Size: 36; UK Sample Size: 36

Total final enrolment

36

Key exclusion criteria

1. Prior chemotherapy, biological therapy, radiation therapy, androgens, thalidomide, immunotherapy, other anti-cancer agents, and any investigational agents within 14 days of

registration (not including palliative radiotherapy at focal sites). Corticosteroids are permitted during screening but should be weaned down to a max dose of prednisolone 10mg daily (or equivalent) by cycle 1 day 1

1.1. With the exception of alopecia, any unresolved toxicities from prior chemotherapy should be no greater than CTCAE (Version 4.0) Grade 2 at the time of registration

2. Major surgery within 4 weeks prior to entry to the study (excluding placement of vascular access), or minor surgery within 2 weeks of entry into the study

3. Exposure to potent or moderate inhibitors or inducers of CYP3A4/5 if taken within the stated washout periods before the first dose of study treatment

4. Exposure to potent or moderate inhibitors or inducers of CYP2C8 if taken within the stated washout periods before the first dose of study treatment

5. Exposure to sensitive or narrow therapeutic range substrates of the drug metabolising enzymes CYP2C8, CYP2C9, CYP2C19, CYP2D6 or the drug transporters Pgp (MDR1), BCRP, OATP1B1, OATP1B3, OCT1 and OCT2 within the appropriate wash-out period (minimum of 5x the reported terminal elimination half-life of each drug) before the 1st dose of study treatment

6. Previous treatment with any first generation mTORC1 inhibitors (rapamycin, sirolimus, temsirolimus, everolimus) or any dual mTORC1/2 inhibitors

7. Patients who have experienced intolerable AEs prejudged by the treating Investigator due to other mTORC1 or mTORC1/2 inhibitors, PI3 kinase inhibitors, or AKT inhibitors

8. Patients with proven central nervous system (CNS) involvement

9. As judged by the Investigator, any evidence of severe or uncontrolled systemic diseases (e.g., severe hepatic impairment, interstitial lung disease (e.g. bilateral, diffuse, parenchymal lung disease), uncontrolled chronic renal diseases (e.g. glomerulonephritis, nephritic syndrome, Fanconi Syndrome or Renal tubular acidosis) or current unstable or uncompensated respiratory or cardiac conditions, or uncontrolled hypertension, active bleeding diatheses or active infection

10. Patients who have experienced any of the following procedures/conditions currently or in the preceding 12 months:

10.1. Coronary artery bypass graft

10.2. Angioplasty

10.3. Vascular stent

10.4. Myocardial infarction

10.5. Angina pectoris

10.6. Congestive heart failure New York Heart Association Grade ≥ 2

10.7. Ventricular arrhythmias requiring continuous therapy

10.8. Supraventricular arrhythmias including atrial fibrillation, which are uncontrolled

10.9. Haemorrhagic or thrombotic stroke, including transient ischaemic attacks or any other central nervous system bleeding

11. Abnormal echocardiogram (ECHO) or multi-gated acquisition scan (MUGA) at baseline (left ventricular ejection fraction [LVEF] $< 50\%$)

12. Torsade's de Pointes within 12 months of study entry

13. Mean (3 consequent ECGs 1 minute apart) resting QTcF or QTcB > 470 msec as per local reading

14. Concomitant medications known to prolong QT interval, or with factors that increase the risk of QTc prolongation or risk of arrhythmic events

15. Patients with Diabetes Type I or uncontrolled Type II (HbA1c > 7 mmol/L assessed locally) as judged by the local investigator

16. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values unless due to underlying NHL infiltration

16.1. Absolute neutrophil count $< 1.5 \times 10^9/L$ (without GCSF/GMCSF support)

16.2. Platelet count $< 100 \times 10^9/L$

16.3. Haemoglobin < 90 g/L (transfusions permissible)

16.4. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 times the upper

limit of normal (ULN) if no demonstrable liver involvement or >5 times ULN in the presence of liver involvement

16.5. Total bilirubin >1.5 times ULN unless in the presence of Gilbert's syndrome with an elevated indirect fraction

16.6. Serum creatinine >1.5 times ULN concurrent with creatinine clearance ≤ 50 mL/min (measured or calculated by Cockcroft and Gault equation); confirmation of creatinine clearance is only required when creatinine is >1.5 times the ULN

17. Current refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection that would preclude adequate absorption of AZD2014

18. History of known hypersensitivity to active or inactive excipients of AZD2014 or drugs with a similar chemical structure/class to AZD2014

19. Judgment by the Investigator that the patient is unsuitable to participate in the study and the patient is unlikely to comply with study procedures, restrictions and requirements

20. Previous history of other active malignant disease other than fully excised basal or squamous cell carcinoma of the skin, carcinoma in situ of the uterine cervix or localised disease treated with curative intent using surgery alone, within last 3 yrs

Date of first enrolment

31/07/2015

Date of final enrolment

25/04/2017

Locations

Countries of recruitment

England

Scotland

United Kingdom

Wales

Study participating centre

The Churchill Hospital

Headley Way, Headington

Oxford

United Kingdom

OX3 9DU

Study participating centre

Royal Liverpool University Hospital

Prescot Street

Liverpool
United Kingdom
L7 8XP

Study participating centre

The Christie Hospital

Wilmslow Road
Manchester
United Kingdom
M20 4BX

Study participating centre

Derriford Hospital

Derriford Road
Plymouth, Devon
United Kingdom
PL6 8DH

Study participating centre

Guys Hospital

Great Maze Pond
London
United Kingdom
SE1 9RT

Study participating centre

Aberdeen Royal Infirmary

Foresterhill
Aberdeen
United Kingdom
AB25 2ZB

Study participating centre

Norfolk and Norwich University Hospital

Colney Lane
Norwich
United Kingdom
NR4 7UY

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

Study participating centre
University Hospital of Wales
Heath Park
Cardiff
United Kingdom
CF14 4XN

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

Sponsor information

Organisation
University of Birmingham

Sponsor details
Edgbaston
Birmingham
England
United Kingdom
B15 2TT

Sponsor type
University/education

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

Funder(s)

Funder type

Charity

Funder Name

Leukaemia and Lymphoma Research

Alternative Name(s)**Funding Body Type**

Private sector organisation

Funding Body Subtype

Other non-profit organizations

Location

United Kingdom

Results and Publications

Publication and dissemination plan

We intend to publish the results in a disease relevant peer reviewed journal. We will also endeavour to present the results at both national and international meeting. The expected publication date is late summer/Autumn 2018.

Intention to publish date

30/06/2019

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study may be available upon request (contact details to be confirmed)

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/10/2019	13/08/2019	Yes	No
Protocol file	version 4.0	06/07/2016	14/10/2022	No	No
HRA research summary			28/06/2023	No	No