ISRCTN10760016 https://doi.org/10.1186/ISRCTN10760016

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	[X] Prospectively registered [X] Protocol [_] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 01/07/2015	**Overall study status** Completed	
Last Edited 14/10/2022	**Condition category** Cancer	

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

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Additional identifiers

Clinical Trials Information System (CTIS)
2014-003588-39

ClinicalTrials.gov (NCT)
NCT02752204

Protocol serial number

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

Study type(s)
Treatment

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

Key secondary outcome(s))
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

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 ≥ 1.5cm or splenomegaly ≥ 13cm 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

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

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 x 10 9/L (without GCSF/GMCSF support)
16.2. Platelet count <100 x 10 9/L
16.3. Haemoglobin <90 g/L (transfusions permissable)
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

call 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
United Kingdom

England

Scotland

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
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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

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

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
HRA research summary			28/06/2023	No	No
Protocol file	version 4.0	06/07/2016	14/10/2022	No	No