TRIAL SYNOPSIS

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

Chief investigator: Dr Graham Collins **Sponsor:** University of Birmingham

Trial Design

This is a prospective, single arm, multicentre, phase II clinical trial utilising two stage design.
Stage one will assess the safety and activity of AZD2014 as a single agent in the treatment of DLBCL.
Stage two will assess the additional toxicity of combining AZD2014 with Rituximab.

Outcome measures

Primary Outcome Measures

- Best overall response rate (PR plus CR) (using the Revised Response Criteria for Malignant Lymphoma (1), Appendix1) during the first 6 cycles

Secondary Outcome Measures

- Tolerability rate (based on toxicity assessments using CTCAE v 4.0 criteria) of single agent AZD2014
- Tolerability rate of additional toxicities when rituximab is combined with AZD2014 at its standard dose (stage 2 only)
- Best overall response rate post 6 cycles until the end of the trial, assessed using Revised Response Criteria
- Overall survival (OS) at 1 year
- Progression free survival (PFS) at 1 year
- Duration of response
- Maximum % decrease in the radiological sum of the product of the diameters (SPD) from baseline by CT NCAP

Exploratory Outcome Measures

- Correlation of response with pharmacodynamic biomarkers, cell of origin studies, lymphoid-related mutational analysis and potential predictive biomarkers of response
- To determine the response to AZD2014 by PET CT criteria and analyse the effect of dual mTOR inhibition on PET signal / response when compared to standard CT response

Pre and post treatment biopsies (at subsequent relapse) will be performed to measure relative activity of the mTOR pathway in a biomarker exploratory analysis. Post treatment biopsies will be performed in 3 patients within the rituximab cohort to assess for evidence of synergy.

Patient Population

The trial will recruit patients with relapsed or refractory DLBCL who have previously been treated with at least one line of an anti-CD20 antibody containing immuno-chemotherapy regimen given with curative intent. Patients must have relapsed post autologous stem cell transplantation (ASCT) or be considered not fit for ASCT.

Sample Size

A single stage A'Hern design (2) will be used to assess response and a Simon 2-Stage (3) design will be used to assess toxicity.

A total of 30 patients will be recruited in the main section, stage one, of the study.

A further 6 patients will be recruited in to the second stage, combination with rituximab.

Trial Duration

It is anticipated that patients will be recruited over 18 months from specialist centres including the 13 Trials Acceleration Programme (TAP) centres with the potential to expand to further non-TAP centres.

Once registered to the study, patients will receive AZD2014 125mg BD on days 1, 2, 8, 9, 15, 16, 22 and 23 of a 28 day cycle (2 days on, 5 days off). Treatment is ongoing until progression or withdrawal due to toxicity or patient's choice. For the combination stage, rituximab 375mg/m^2 will also be administered intravenously on day 1 of the 28 day cycle for a total of 6 cycles. All patients will be followed for a minimum of 1 year until disease progression or death.

Main Inclusion and Exclusion Criteria (not exhaustive)

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 but patients must have been treated for the high grade disease with at least one course of treatment as detailed above. 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 protocol section 5.3, 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

7. Male patients should be surgically sterile or 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 long axis ≥ 1.5cm or splenomegaly ≥ 14cm in cranio-caudal length attributable to relapsed lymphoma

10. Patients must have negative virology for HIV.

11. For patients receiving single agent AZD2014 treatment only :
    - Hepatitis C serology must be negative
    - Hepatitis B serology must not indicate active infection. Specifically:
    Patients who are hepatitis B surface antigen positive are excluded
    Patients who are anti-hepatitis B sAg antibody positive in the absence of anti-core antibody are eligible if hepatitis B DNA is negative.
    Patients who are positive for anti-hepatitis B core antibody (with no surface antigen) are eligible if hepatitis B DNA is negative.

12. For the rituximab cohort only:
    - Hepatitis C serology must be negative
    - Hepatitis B surface antigen and anti-core antibody must be negative
    - Patient with a history of vaccination to hepatitis B and who are positive for anti-hepatitis B sAg antibody are eligible if hepatitis B DNA is negative

Exclusion Criteria

1. Prior chemotherapy, biological therapy, radiation therapy, androgens, thalidomide, immunotherapy, other anticancer agents, and any investigational agents within 21days of registration (not including palliative radiotherapy at focal sites to non-target lesions). Corticosteroids are permitted during screening but should be stopped by day 1 of cycle 1.
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, Pgp (MDR1) and BCRP if taken within the stated washout periods before the first dose of study treatment.
4. Exposure to sensitive or narrow therapeutic range substrates of the drug metabolising enzymes CYP2C8, CYP2C9, CYP2C19, CYP2D6 or the drug transporters Pgp (MDR1), MATE1, MATE2K BCRP, OATP1B1, OATP1B3, OCT1 and OCT2 within the appropriate wash-out period (a

minimum of 5 x the reported terminal elimination half-life of each drug) before the first dose of study treatment. See table in appendix 4.

5. Previous treatment with first generation mTORC1 inhibitors (rapamycin, sirolimus, temsirolimus, everolimus) or dual mTORC1/2 inhibitors: AZD2014 or AZD8055.
6. Patients who have experienced intolerable AEs per treating Investigator due to other PI3 kinase inhibitors, or AKT inhibitors
7. Patients with proven central nervous system (CNS) involvement
8. 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 including hepatitis B, hepatitis C, and human immunodeficiency virus. Screening for chronic conditions is not required.
9. Patients who have experienced any of the following procedures or conditions currently or in the preceding 12 months:coronary artery bypass graft, angioplasty, vascular stent, myocardial infarction, angina pectoris, congestive heart failure New York Heart Association Grade ≥2, ventricular arrhythmias requiring continuous therapy, supraventricular arrhythmias including atrial fibrillation (which are uncontrolled), haemorrhagic or thrombotic stroke (including transient ischaemic attacks or any other central nervous system bleeding)
10. Abnormal echocardiogram (ECHO) or multi-gated acquisition scan (MUGA) at screening(left ventricular ejection fraction [LVEF] <50%.
11. Torsade's de Pointes within 12 months of study entry
12. Patients with uncontrolled Diabetes Type I or uncontrolled Type II (HbA1c >7 mmol/L assessed locally) as judged by the local investigator
13. Inadequate bone marrow reserve or organ function as demonstrated by any of the following laboratory values unless due to underlying NHL infiltration.

    − Absolute neutrophil count <1.5 x 10^9/L (without GCSF / GMCSF support)

    − Platelet count <100 x 10^9/L

    − Haemoglobin <90 g/L

    − Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2.5 times the upper limit of normal (ULN) if no demonstrable liver metastases or >5 times ULN in the presence of liver metastases

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

    − 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

14. Current refractory nausea and vomiting, chronic gastrointestinal diseases, inability to swallow the formulated product or previous significant bowel resection or gastrointestinal disease that would preclude adequate absorption of AZD2014
15. History of hypersensitivity to active or inactive excipients of AZD2014 or drugs with a similar chemical structure or class to AZD2014
16. 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
17. 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 the last 3 years.

For the rituximab cohort only, patients must not enter the study if any of the above or below exclusion criteria are fulfilled:

21. Known hypersensitivity to recombinant proteins, murine proteins or to any excipients of rituximab infusions
22. Vaccination with live virus vaccine within the 4 weeks prior to study entry or intention to do so during the study treatment

Trials Office Contact Details

TORCH Trial Office
Cancer Research UK Clinical Trials Unit
Institute of Cancer and Genomic Sciences
University of Birmingham
Vincent Drive, Birmingham, B15 2TT
Tel: 0121 415 9175
Fax: 0121 414 6061
Email: TORCH@trials.bham.ac.uk