ORCH

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 Diffuse Large B cell Lymphoma (DLBCL)

Version 4.0

Date: 06-July-2016

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Sponsor:	University of Birmingham
Sponsor number:	RG_14-212
EudraCT number:	2014-003588-39
ISRCTN	ISRCTN10760016
CAS number:	NH2003
NIHR CRN portfolio:	19208

This application is supported by the facilities funded through Birmingham Science City: Translational Medicine Clinical Research Infrastructure and Trials Platform, an Advantage West Midlands (AWM) funded project which forms part of the Science City University of Warwick and University of Birmingham Research Alliance

TAP Bloodwise

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SIGNATURE PAGE

TORCH Trial Protocol version 4.0 date 06-Jul-2016

This protocol has been approved by:

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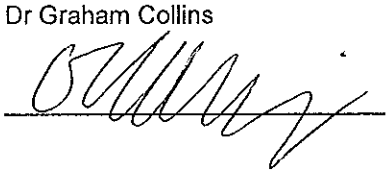
Signature:		**Date:**	07/July/2016

This protocol describes the TORCH trial and provides information about procedures for patients taking part in the TORCH trial. The protocol should not be used as a guide for treatment of patients not taking part in the TORCH trial.

AMENDMENTS

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
SA2	*07-May-2015*	*2.0*	*Substantial (made for Ethical Approval)*	*Reduction of patient identifiable data collected from Date of Birth to Year of Birth.* *Minor clarifications and typo corrections*
SA3	*18-May-2015*	*3.0*	*Substantial (Made for MHRA Approval)*	*Update to exclusion criteria (platelet count)* *Addition of exclusions for rituximab patients added* *Additional advice for toxicities with rituximab added*
SA9	*06-Jul-2016*	*4.0*	*Substantial*	*Update to saliva sample – no longer optional* *Clarification of screening assessments* *Insertion of ISRCTN Number* *Remove QT interval prolonging drugs and ECG requirements from the exclusions* *Rewording of the eligibility criteria relating to patients with hepatitis infection* *Amendment of dose modification information* *Reduction of ECG frequency* *Updated list of concomitant medications to be avoided*

TRIAL SYNOPSIS

Title

TORCH: A phase II study to determine the safety and efficacy of the dual mTORC inhibitor AZD2014 (vistusertib) and to investigate additional toxicities in combination with rituximab in relapsed/refractory diffuse large B cell lymphoma (DLBCL)

Trial Design

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

Objectives

Primary objective

- Determine the activity (as measured by best overall response rate) of single agent AZD2014 in relapsed/refractory DLBCL patients.

Secondary objectives

- Determine the toxicity of single agent AZD2014 in patients with relapsed/refractory DLBCL.
- Evaluate any additional toxicities when rituximab is combined with AZD2014 at its standard dose (stage 2 only).
- Determine the impact on survival (as measured by progression free survival (PFS), overall survival (OS) and duration of remission (DoR)).
- Identify biomarkers of mTOR activity in DLBCL and of response to AZD2014.
- Identify possible resistance mechanisms to AZD2014.
- 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.
- To identify whether interim PET signal correlates with PFS.

Outcome Measures

Primary Outcome Measures

- Best overall response rate (PR plus CR) (using the Revised Response Criteria for Malignant Lymphoma , 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. Biopsies at relapse will be

requested in patients within the rituximab stage to assess for evidence of synergy and mechanisms of resistance. On treatment biopsies on day 15 cycle 1 will remain optional.

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 suitable for ASCT.

Sample Size

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

A total of 30 patients will be recruited in stage one of the study (AZD2014 monotherapy).

A further 6 patients will be recruited in to the second stage (AZD2014 in combination with rituximab).

Main Inclusion and Exclusion Criteria

Inclusion Criteria

For inclusion in the study, patients must fulfil the following 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 by fulfilling one of the following criteria at screening:

- Post-menopausal defined as amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments

- Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation

* See section 5.3 of the protocol

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 but negative for anti-core antibody are eligible if hepatitis B DNA is negative

Exclusion Criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

1. Prior chemotherapy, biological therapy, radiation therapy, androgens, thalidomide, immunotherapy, other anticancer agents, and any investigational agents within 21 days of registration (not including palliative radiotherapy at focal sites to non-target lesions). Corticosteroids are permitted during screening but should be weaned down to a maximum dose of prednisolone 10mg daily (or equivalent) by day 1 of cycle 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, Pgp (MDR1) and BCRP if taken within the stated washout periods before the first dose of study treatment. See Appendix 2.
4. Exposure to sensitive or narrow therapeutic range substrates of the drug transporters MATE1, MATE2K OATP1B1, and OATP1B3, 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 3.
5. Previous treatment with any first generation mTORC1 inhibitors (rapamycin, sirolimus, temsirolimus, everolimus) or any dual mTORC1/2 inhibitors (e.g. AZD2014, AZD8055).
6. Patients who have experienced intolerable AEs prejudged by the treating Investigator due to 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. 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 (transfusions permissible)
    - 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
    - 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 known 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:

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

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.

Trials Office Contact Details

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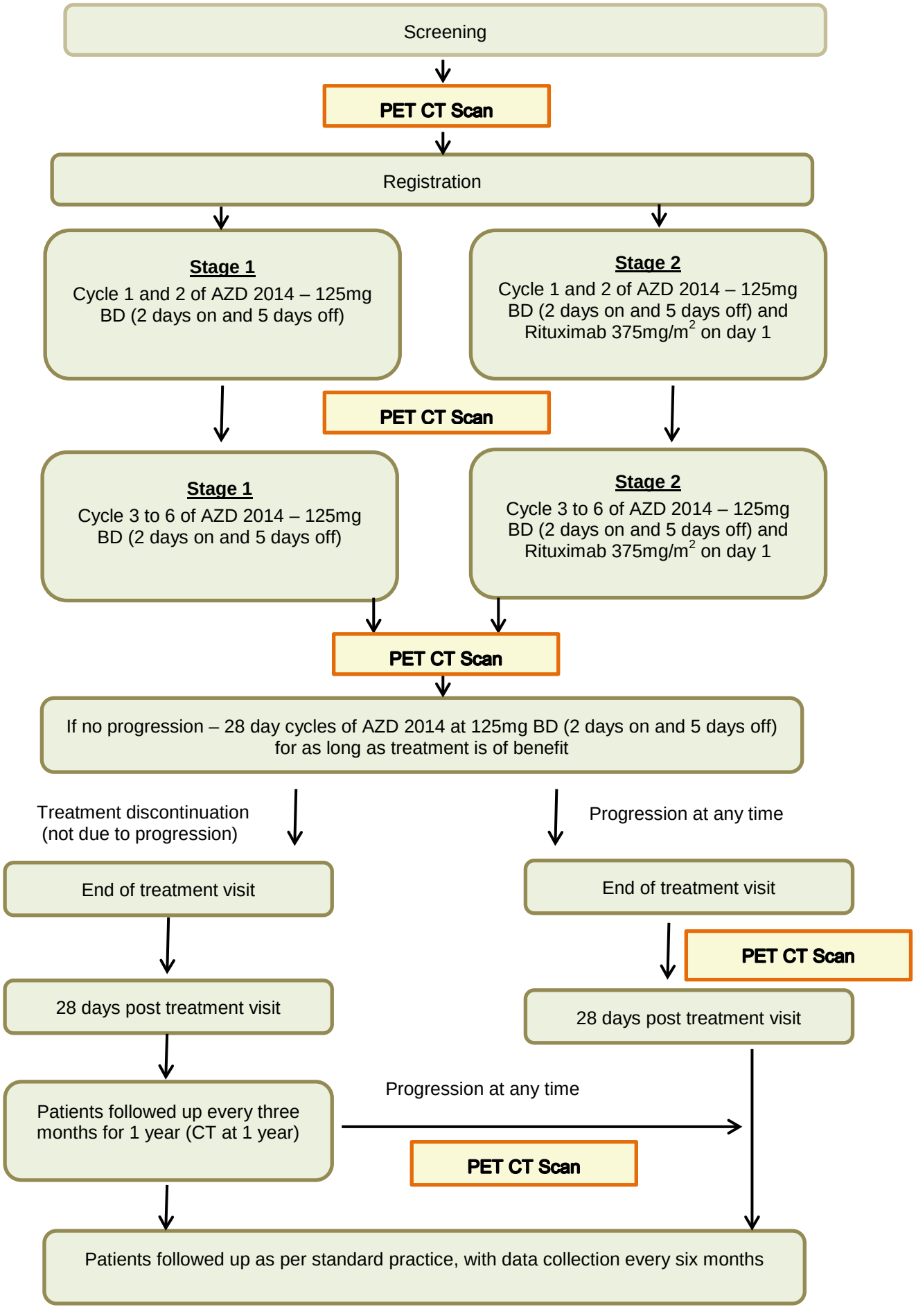
Trial Schema


Screening
PET CT Scan
Registration
Stage 1
Cycle 1 and 2 of AZD 2014 – 125mg BD (2 days on and 5 days off)
Stage 2
Cycle 1 and 2 of AZD 2014 – 125mg BD (2 days on and 5 days off) and Rituximab 375mg/m2 on day 1
PET CT Scan
Stage 1
Cycle 3 to 6 of AZD 2014 – 125mg BD (2 days on and 5 days off)
Stage 2
Cycle 3 to 6 of AZD 2014 – 125mg BD (2 days on and 5 days off) and Rituximab 375mg/m2 on day 1
PET CT Scan
If no progression – 28 day cycles of AZD 2014 at 125mg BD (2 days on and 5 days off) for as long as treatment is of benefit
Treatment discontinuation (not due to progression)
Progression at any time
End of treatment visit
End of treatment visit
PET CT Scan
28 days post treatment visit
28 days post treatment visit
Progression at any time
Patients followed up every three months for 1 year (CT at 1 year)
PET CT Scan
Patients followed up as per standard practice, with data collection every six months

Schedule of Events

See section 7.3

ABBREVIATIONS

ABPI	ASSOCIATION OF THE BRITISH PHARMACEUTICAL INDUSTRY
AE	ADVERSE EVENT
ALCL	ANAPLASTIC LARGE CELL LYMPHOMA
ALT	ALANINE TRANSAMINASE
AR	ADVERSE REACTION
ASCO	AMERICAN SOCIETY OF CLINICAL ONCOLOGY
ASCT	AUTOLOGUS STEM CELL TRANSPLANTATION
AST	ASPARTATE TRANSAMINASE
ATP	ADENOSINE TRIPHOSPHATE
AWM	ADVANTAGE WEST MIDLANDS
BD	TWICE DAILY
BP	BLOOD PRESSURE
BSA	BODY SURFACE AREA
CHOP	CYCLOPHOSPHAMIDE, HYDROXYDAUNORUBICIN, ONCOVIN (VINCRISTINE), PREDNISONE
CNS	CENTRAL NERVOUS SYSTEM
CR	COMPLETE REMISSION/RESPONSE
CRF	CASE REPORT FORM
CR UK	CANCER RESEARCH UK
CRCTU	CANCER RESEARCH UK CLINICAL TRIALS UNIT (UNIVERSITY OF BIRMINGHAM)
CT	COMPUTERISED TOMOGRAPHY
CTCAE	COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS
CV	CURRICULUM VITAE
DCF	DATA CLARIFATION FORM
DLBCL	DIFFUSE LARGE B CELL LYMPHOMA
DLCO	DIFFUSION CAPACITY FOR CARBON DIOXIDE
DNA	DEOXYRIBOSE NUCLEIC ACID
DoR	DURATION OF REMISSION
ECG	ELECTROCARDIOGRAM
ECHO	ECHOCARDIOGRAM
ECOG	EASTERN COOPERATIVE ONCOLOGY GROUP
EORTC	EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER
FEV	FORCE EXPIRATORY VOLUME
FGD	18F FLUORO 2 DEXOY D GLUCOSE
FL	FOLICULAR LYMPHOMA
FVC	FORCED VITAL CAPACITY
GCB	GERMINAL CENTER B-CELL
G-CHOP	OBINUTUZUMAB (GA101), CYCLOPHOSPHAMIDE, HYDROXYDAUNORUBICIN, ONCOVIN (VINCRISTINE), PREDNISONE
GCP	GOOD CLINICAL PRACTICE
GCSF	GRANULOCYTE COLONY STIMULATING FACTOR

GMCSF	GRANULOCYTE MACROPHAGE COLONY STIMULATING FACTOR
GMP	GOOD MANUFACTURING PRACTICE
GP	GENERAL PRACTITIONER
HIV	HUMAN IMMUNODEFICIENCY VIRUS
HBsAg	HEPATITIS B SURFACE ANTI-GEN
HBV	HEPATITIS B VIRUS
HRCT	HIGH RESOLUTION COMPUTERISED TOMOGRAPHY
HTA	HUMAN TISSUE ACT
IB	INVESTIGATOR BROCHURE
ICF	INFORMED CONSENT FORM
IHC	IMMUNOHISTOCHEMISTRY
IMP	INVESTIGATIONAL MEDICINAL PRODUCT
iPET	INTERMEDIATE POSITRON EMISSION TOMOGRAPHY
IPI	INTERNATIONAL PROGNOSTIC INDEX
ISF	INVESTIGATOR SITE FILE
ISRCTN	INTERNATIONAL STANDARD RANDOMISED CLINICAL TRIAL NUMBER
LDH	LACTATE DEHYDROGENASE
LFT	LIVER FUNCTION TEST
LVEF	LEFT VENTRICUALR EJECTION FRACTION
LVESV	LEFT VENTRICULAR END SYSTOLIC VOLUME
LVEDV	LEFT VENTRICULAR END DIASTOLIC VOLUME
MCL	MANTLE CELL LYMPHOMA
ML	MILLILITRE
MHRA	MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY
MR	MAGNETIC RESONANCE
MTD	MAXIMUM TOLERATED DOSE
mTORC	MAMMALIAN TARGET OF RAPAMYCIN COMPLEX
MUGA	MULTI GATED ACQUISITON
NCAP	NECK, CHEST, ABDOMEN AND PELVIS
NCRI	NATIONAL CANCER RESEARCH INSTITUTE
NHL	NON-HODGKIN'S LYMPHOMA
ORR	OVERALL RESPONSE RATE
OS	OVERALL SURVIVAL
PCP	PNEUMOCYSTIS CARINII PNEUMONIA
PD	PROGRESSIVE DISEASE
PET	POSITRON EMISSION TOMOGRAPHY
PFS	PROGRESSION FREE SURVIVAL
PI	PRINCIPAL INVESTIGATOR
PIS	PATIENT INFORMATION SHEET
PR	PARTIAL REMISSION/RESPONSE
QTc	CORRECTED QT INTERVAL
QTcB	CORRECTED QT INTERVAL USING BAZETT'S FORMULA

QTCF	CORRECTED QT INTERVAL USING FRIDERICIA'S FORMULA
R-CHOP	RITUXIMAB, CYCLOPHOSPHAMIDE, HYDROXYDAUNORUBICIN, ONCOVIN (VINCRISTINE), PREDNISONE
RBC	RED BLOOD CELL
REC	RESEARCH ETHICS COMMITTEE
RGCVP	RITUXIMAB, GEMCITABINE, VINCRISTINE, PREDNISOLONE
ROC	RECEVIVER OPERATING CHARACTERISTIC
RSI	REFERENCE SAFETY INFORMATION
SAE	SERIOUS ADVERSE EVENT
SAR	SERIOUS ADVERSE REACTION
SD	STABLE DIEASE
SPC	SUMMARY OF PRODUCT CHARACTERISTICS
SUSAR	SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION
SUV	STANDARDISED UPTAKE VALUE
TAP	TRIALS ACCELERATION PROGRAMME
TLS	TUMOUR LYSIS SYNDROME
TMG	TRIAL MANAGEMENT GROUP
TSC	TRIAL SAFETYCOMMITTEE
UK	UNITED KINGDOM
ULN	UPPER LIMIT OF NORMAL
WHO	WORLD HEALTH ORGANIZATION
WMA	WORLD MEDICAL ASSEMBLY

Table of contents

1. BACKGROUND AND RATIONALE

1.1 Background

The incidence of Non-Hodgkin Lymphoma (NHL) is increasing and it is the fifth most common type of cancer in the United Kingdom (UK) and United States. Despite the advent of new immunochemotherapeutics, lymphoid disease still results in over 27,000 annual deaths in the US (4). Dysregulation of signalling pathways involved in cell proliferation, cell-cycle, DNA damage responses and protein synthesis are increasingly identified in haematological malignancies and have become biological targets.

Mammalian target of rapamycin (mTOR) is a ubiquitously expressed serine-threonine protein kinase that belongs to the phosphatidylinositol 3-kinase (PI3K)-related kinase family (5,6). The PIK3/AKT/mTOR pathway is a 'critical switch', constituting the core of a highly conserved evolutionary pathway that adjusts protein synthesis to regulate cell growth and proliferation by integrating signals arising from growth factors, hormones, nutrients and energy metabolism (7). ATP levels influence mTOR activity, consistent with protein translation being a major consumer of cellular energy. mTOR plays a pivotal role in dysregulation of cell survival and proliferation underlying many malignancies. Malignant transformation is associated with increased mTORC1 signalling, a process required to support increased cell cycling and metabolic demands (8).

There is persuasive pre-clinical and clinical evidence that the mTOR pathway is important in the tumour biology of aggressive NHL including diffuse large B-cell lymphoma (DLBCL). eIF4E overexpression in NHL tissues appears to have some correlation with biological aggressiveness (9). Pre-clinical models show that mTOR inhibition results in reduced phosphorylation of p70S6K and 4-EBP-1 in DLBCL cells cultured in the presence of everolimus. This resulted in reduced proliferation and induced G_1 arrest in EBV-negative DLBCL cell lines *in vitro* (10).

Clinical evidence that the mTOR pathway is important in DLBCL pathogenesis includes two recent phase II trials. 77 'aggressive' NHLs received everolimus in the relapsed, refractory setting (11). ORR was similar in mantle cell lymphoma (MCL), follicular lymphoma (FL) and DLBCL patients (32%, 38% and 30% respectively), demonstrating significant activity albeit in a minority of patients. The University of Chicago group (12), reported an ORR 28.1% (CR 12.5%) in a relapsed, refractory DLBCL subpopulation, with a median PFS of 2.6 months and OS of 7.2 months. Everolimus attenuated S6RP phosphorylation in a dose-dependent manner in DLBCL cell lines. Cell proliferation was inhibited, but minimal apoptosis was observed. This data provides a proof of principle, although responses were modest and resistant was frequent. The same group investigated mTOR inhibitor resistance pathways in DLBCL, and demonstrated that when DLBCL cells are treated with rapamycin, cells activate AKT through mTORC2 signalling; providing an escape mechanism (13). A variety of methods to attempt to overcome rapamycin resistance have been investigated, with some promising results. Wanner et al (10) demonstrated that everolimus induced G1-phase arrest in DLBCL cell lines and augmented cytotoxicity induced by rituximab. Moreover, a recent study showed that in DLBCL patients with PI3K/AKT/mTOR activation, outcomes were considerably inferior if rituximab was not added to CHOP (14). The group found that when rituximab was combined with rapamycin in DLBCL cell lines from these patients, that there was synergistic *in vitro* down-regulation of PI3K/AKT/mTOR signalling by Western blotting. Rituximab down-regulated PI3K/AKT/mTOR activation that had otherwise correlated with a more aggressive clinical course with poor treatment response.

A recent phase II study of everolimus combined with rituximab examined the efficacy and tolerability in relapsed/refractory DLBCL ineligible for, or relapsing after, autologous stem cell transplant (ASCT). 75% were considered rituximab-refractory at enrolment. Everolimus 10mg/d was given with rituximab 375mg/m^2 weekly for four weeks and then every four weeks. 26 patients displayed an ORR of 38% [90% CI (21-56%) with 3 CRs and 6 PRs]. OS was 37% at 12 months and the regimen was well tolerated.

Overall, efficacy of single agent TORC1 inhibitors is disappointing. The addition of rituximab improves responses although most were short-lived. Multiple complex resistance mechanisms to mTORC1

inhibitors are described in both solid tumours and haematological malignancy. For example; relative under-expression of mTOR proteins can alter sensitivity to rapamycin (15), PIM kinase overexpression leads to inhibition of apoptosis and produces resistance to rapamycin (16), MNK mediated phosphorylation of IF4E (Ser209) can bypass mTORC1/2 inhibition via ERK/MEK/MNK activation (17), and mTORC2 directly phosphorylates and activates AKT (Ser473) (18).

The recent discovery of mTORC2 unravelled its key role in driving rapamycin resistance. mTORC2 is unaffected by rapamycin and produces resistance at least partly via its direct phosphorylation of AKT on Ser473, a critical regulatory site that stimulates maximal activity of this important survival kinase (18,19). As the main downstream effector of the insulin/PIK3 pathway, AKT modulates downstream substrates involved in cell proliferation, migration, angiogenesis, metabolism and glucose uptake (20). The discovery that mTORC2 directly phosphorylates AKT has added important new insight into the role of mTORC2 in lymphoid malignancies and solid tumours when mTORC1 alone is targeted with rapamycin. An evolving collection of pre-clinical data has shown that dual inhibition of mTORC1/2 may overcome rapamycin resistance. Various novel inhibitors target mTORC1, mTORC2 and other important elements of the PI3K/AKT/mTOR pathway in combination.

AZD2014 (vistusertib) is the most recent dual mTORC1/2 inhibitor to enter pre-clinical and clinical studies. It is a potent mTORC1/2 inhibitor, (IC50:0.0028 lM) and is inactive against >200 kinases at 10 lM (21). AZD2014 displayed dose-dependent tumour growth inhibition in mouse MCF7 xenograft model and has consistent rodent pharmacokinetics and low turnover in human hepatocytes. AZD2014 has far superior pharmacokinetics to previous dual mTORC1/2 inhibitors (22). Continuous daily and intermittent dosing schedules have been explored and maximum tolerated doses (MTDs) have been identified. The safety and tolerability profile of AZD2014 was studied in a phase 1 dose-escalation and expansion study in 50 patients with solid tumours. Reduced phosphorylation p70S6K and 4EBP1 was seen in paired biopsies. pAKT was not upregulated in any post-treatment biopsies. An intermittent weekly twice daily (BD) dosing (2 days on, 5 days off):), of 125 mg (total weekly dose 500mg) has been identified as well tolerated and the most suitable schedule to take forward..

PET CT signal and mTOR inhibition

18F-fluoro-2-dexoy-D-glucose-positron emission tomography (FDG-PET)/computerised tomography (CT) has been used for staging and monitoring responses to treatment in patients with diffuse large B cell lymphoma (DLBCL). In this context, it has been known for some time that FDG-PET has an improved sensitivity and specificity when compared to conventional CT imaging (23,24). As such, the standard of care at present is that a FDG-PET CT is performed prior to treatment (typically R-CHOP immunochemotherapy) and at the end of treatment (25,26). Currently, the prognosis of DLBCL patients is assessed using clinical and biological measures. The International Prognostic Index (IPI) score and modifications of the IPI: the age adjusted (aa)-IPI and revised IPI (R-IPI) scores, have been routinely used as the most reliable prognostic indexes in DLBCL (27,28).

There is mounting evidence that iPET is a good predictor of early response in high grade, aggressive B cell NHL. Studies have shown iPET to be an accurate and independent predictor of PFS and OS (29–33). There is an increasing amount of published data using semi-quantitative assessment based on the reduction in the maximum standardised uptake value (ΔSUV max) which may predict outcome more effectively when iPET is performed (34–40). Several multicentre trials are currently exploring the use of ΔSUV to dose intensify treatment in iPET positive patients with DLBCL (35,41).

Glucose metabolism, mTOR pathway inhibition and PET response

PET has the ability to evaluate the metabolic changes that occur in a tumour during treatment. Metabolic changes occur faster and predict response more effectively than assessments of tumour size using CT or MR imaging. Early reduction in FDG uptake has been used to evaluate patient sensitivity to a given treatment regimen when treating a FDG-avid tumour (Warburg effect). The PIK3/AKT/mTOR pathway is considered a ‘critical switch’, constituting the core of a highly conserved evolutionarily pathway that adjusts protein synthesis to regulate cell growth and proliferation by integrating signals arising from growth factors, hormones, nutrients and energy metabolism (7). One important physiological function of PI3K/AKT/mTOR pathway is to acutely stimulate glucose uptake in response to insulin via glucose transporter 1 (GLUT1) and phosphorylation to glucose-6-phosphate by hexokinase (42). FDG is also transported via GLUT 1 and phosphorylated by hexokinase but then remains trapped in the cell as FDG-6-phosphate is not dephosphorylated unlike glucose-6-phosphate,

giving a signal that can be imaged. Thus FDG imaging with PET-CT may be able to demonstrate PI3K/AKT/mTOR pathway inhibition by agents targeting this pathway.

The use of FDG-PET as a potential predictive biomarker has been investigated using first generation mTORC1 inhibitors and in dual PIK3/mTORC1 inhibitors. Patients were enrolled from a phase I study of temsirolimus in refractory advanced solid tumour patients and a phase II trial of temsirolimus in patients with gemcitabine-refractory advanced pancreatic adenocarcinoma. FDG-PET signal reduction failed to predict the clinical tumour response with temsirolimus or time to progression; 56% of patients with increased FDG-PET uptake and 46% with decreased uptake following mTORC1 inhibition had progressive disease (PD). By EORTC criteria, the sensitivity of progressive metabolic disease on FDG-PET in predicting PD was 19%. The group looked at murine xenograft tumour models, and found that FDG-PET response correlated with pAKT activation and plasma membrane GLUT1 expression but not tumour response (43).

A recent phase I trial studied BGT226, a potent, oral dual PI3K/mTORC1/2 in advanced solid tumours. As well as finding the maximum tolerated dose and assessing safety, pharmacodynamics, and pharmacokinetics, correlation between FDG-PET metabolic response and tumour volume response was assessed. Thirty patients (53%) achieved stable metabolic disease as assessed by [18F]-FDG-PET; however, no correlation between metabolic response and tumour shrinkage according to CT was observed (44).

Conversely, recent data in anaplastic large cell lymphoma (ALCL) cell lines did show correlation between FDG-PET signal and response to BGT226. PET uptake correlated with both tumour volume and Ki67 staining in the xenograft ALCL tumour (45). FDG also showed decrease in uptake early during treatment with temsirolimus in murine models of mantle cell lymphoma (46) and Burkitt lymphoma (47)

Given that interim PET may be an early predictor of long term response and given the concern in the literature that mTOR inhibition may interfere with the ability of PET to accurately predict response we feel it is important to formally assess the role of PET when using AZD2014 (the dual mTORC1/2 inhibitor) to treat relapsed, refractory DLBCL within the TORCH study. It is important to answer whether i) an early PET response (assessed using the Deauville criteria and semi-quantitative evaluation) predicts later clinical benefit (response after 6 courses, progression free survival and overall survival) and ii) whether PET response correlates with reduction in tumour volume (assessed using conventional CT criteria).

1.2 Trial Rationale

1.2.1 Justification for patient population

According to CRUK figures, in 2010 there were 12,180 new cases of NHL with approximately 40-50% being DLBCL and, the vast majority in adults. In the same year, 4,436 died of NHL. For high grade NHL, approximately 60-70% of patients are cured with first line treatment (as shown by recent phase III clinical trials (48). Of those who relapse, approximately 30% would be cured with an intensive chemotherapy approach (approximately 40-50% of those who go through the treatment are cured but a significant proportion of patients are not fit for this approach). This equates to approximately 1100 DLBCL patients with no standard treatment option. Relapsed/refractory DLBCL represents a clear area of unmet need

1.2.2 Justification for design

AZD2014 (vistusertib) is at an ideal stage of development for evaluation in lymphoma patients. It has been subject to a phase I trial which included patients with multiple tumour types (49) and is currently being investigated in several phase II trials in solid tumours. Several dosing schedules have been evaluated and the safety profile is acceptable. If this drug is to benefit patients with haematological

malignancies, rapid phase II studies, alone and in combination with established anti-lymphoma drugs, are required.

Currently in the UK, there are very few studies in the area of relapsed DLBCL and it continues to represent an area of unmet need. The proposed study will therefore provide an additional option for patients with relapsed, refractory DLBCL for which there are no, or few, competing studies, or for patients progressing on or after other clinical studies.

Relapsed DLBCL is relatively uncommon, and patients with this condition are sometimes not well enough to enter a study. Therefore, it is not thought feasible to perform a randomised phase II study. A single arm, A'Herns design utilised in phase II will generate robust evidence of activity for the regimen to be evaluated in an upfront trial.

Assuming that activity and acceptable safety profile is demonstrated for the single agent, we would intend to move on rapidly to investigating combinations. We intend to use the current study as a platform upon which novel combination therapies can be investigated.

The treatment will be considered for further investigation if at least 9 responses are seen from the 30 patients. This results in 90% power to go forward if the underlying response rate is 40%, but only a 13% risk of going forward if the true response rate is 20%

1.2.3 Choice of treatment

New strategies are desperately needed to prolong survival and quality of life. mTOR inhibitors are of proven activity in multiple lymphoma subtypes. In relapsed/refractory DLBCL, the single agent mTOR inhibitor, everolimus, produced an ORR of 30% (50); a further study used the combination of everolimus and rituximab and produced an ORR of 38% with a median duration of remission (DOR) of 8.1 months (51). Although activity was demonstrated in the above studies, ORR was modest and remission was short. A recent but well described, key mechanism of escape from mTORC1 inhibitors is through Akt phosphorylation at Ser 473, which is itself a substrate of the mTORC2 complex (13). Evaluation of dual mTORC1/2 inhibitors has demonstrated markedly reduced Akt phosphorylation (52) which may increase the activity of these agents. There is no clinical data on the efficacy of dual mTORC1/2 inhibitors in DLBCL. The proposed study is therefore designed to evaluate a new class of therapeutic agent which could represent a significant advance over current mTOR inhibitors.

1.2.3.1 AZD2014

AZD2014 is an inhibitor of the kinase activity of mTOR. mTOR is a serine/threonine kinase belonging to the PI3K (PIKK) superfamily of kinases. AZD2014 is specific for mTOR and does not inhibit other members of the PI3K superfamily. The PI3K-Akt-mTOR pathway functions as a sensor of mitogen, energy and nutrient levels and is a central controller of cell growth. The mTOR is a protein kinase (PK) and a vital component of the PI3K/Akt/mTOR signalling pathway. This pathway is deregulated in 50% of all human cancers and, as such, is an important target for inhibitors that would alleviate the unregulated proliferation of cancer cells (53).

Rapamycin and its analogues (rapalogs) are potent inhibitors of mTORC1 and have been shown to be clinically effective in certain cancer types like endometrial cancer, mantle cell lymphoma, renal cell carcinoma and breast cancer (54)(55)(56).

Nevertheless, so far, several resistance mechanisms have been shown to limit the response rate in clinical studies to rapamycin and analogues. mTOR exists as two complexes, mTORC1 and mTORC2, defined by their associated proteins, and having different cellular functions. Rapalogs, due to their allosteric mode of interaction with mTOR, inhibit mainly mTORC1, leaving mTORC2 unregulated. There is also evidence that inhibition of only mTORC1 sets off a negative feedback mechanism that leads to increased Akt signalling.

AZD2014 is selective inhibitor of mTOR kinases and inhibits signalling of both mTOR complexes, mTORC1 and mTORC2. AZD2014 is thereby molecularly different from rapalogs:

- AZD2014 achieves more profound mTORC1 inhibition, in particular inhibiting phosphorylation of the rapamycin insensitive site on 4E-BP1 (T37/46). AZD2014 also inhibits mTORC2.
- AZD2014 has a broader range of growth inhibitory activity *in vitro* across tumour types compared to rapalogs. As such, ATP-competitive dual TORC1/TORC2 inhibitors, like AZD2014 that inhibit both mTOR complexes may offer therapeutic advantages to rapalogs (56).

1.2.3.2 Overall Safety of AZD2014

AZD2014 is considered to be generally well tolerated with most of the AEs classified as CTCAE grade 1 and 2. AEs have also been shown to resolve quickly after short periods of dose interruptions, which allowed patients to stay on the drug for long periods of time (over 1 year). Fatigue, mucositis, rash, nausea, vomiting, diarrhoea, hyperglycaemia and decreased appetite, risk of pneumonitis and infections were the AEs consistently amongst the most frequently reported overall, and those reported as related to AZD2014 by the Investigators. These AEs were also those reported with the highest severity grade and were those AEs most commonly leading to dose interruption and/or permanent discontinuation of AZD2014. These events were generally reversible within 1 week by cessation of AZD2014. The AE profile of continuous and intermittent dosing schedules varied slightly. Although gastrointestinal events were observed more frequently in the intermittent schedules, there have been no reports of rash or hyperglycaemia so far for the intermittent dosing schedules.

Overall, no clinically significant changes were observed in heart rate or blood pressure (BP). Single intermittent systolic or diastolic BP values above and below normal values were reported in a few patients. Intermittent higher heart rates >100 bpm were observed, and tachycardia in some patients.

No clinically significant changes were observed in vital signs or laboratory data overall. Review of emerging laboratory data did not reveal clinically significant liver function test (LFT) abnormalities considered related to AZD2014. Transaminase increases (ALT or AST) were reported as AEs in some patients; the majority were CTCAE grade 1 and were not considered related to AZD2014 by the reporting investigator. Laboratory data suggest that for most patients who do have reductions in cell counts, values return to patients' baseline on stopping AZD2014. The clinical relevance of these changes appears low given that there was no excess of related AEs such as infection, fungal disease, viral disease, dyspnoea, or bleeding within these patients when compared with patients not noted as having reductions, and there were no events of greater severity. ECG repolarisation changes were seen in some patients. However, there were no associated significant QRS morphology changes and the clinical significance of these changes is unknown.

For further information please refer to the current AZD2014 Investigator Brochure (IB).

1.2.3.3 Rituximab

Rituximab is very commonly used and efficacious in DLBCL (57). We plan to add rituximab at standard doses to AZD2014 in a small cohort of 6 patients, to evaluate the safety of this combination.
The mechanism of action of rituximab is more complex than first assumed. In addition to the induction of apoptosis (58), complement-dependent (59) and anti-CD20 antibody-dependent cellular cytotoxicity (60), rituximab has been shown to inhibit the phosphorylation of Raf-1, ERK1/2 and MEK1/2 via the upregulation of Raf-1 kinase inhibitory protein (RKIP) (61). This pre-clinical data, together with clinical evidence of efficacy, provides a sound rationale to use this combination in DLBCL (14,51). It is therefore very possible that the addition of Rituximab to the dual mTORC1/2 inhibitor will provide further blockade of the mTOR downstream signalling and therefore potentially enhance the activity of single agent AZD2014.

2. AIMS, OBJECTIVES AND OUTCOME MEASURES

2.1 Aims and Objectives

Assuming that activity and acceptable safety profile is demonstrated for the single agent, we would intend to move on rapidly to investigating combinations. We intend to use the current study as a

platform upon which novel combination therapies can be investigated. The intention is for combination partners to be rationally incorporated, at least in part guided by the results from the proposed biomarker studies.

2.2 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 it's 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 define 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 requested in patients within the rituximab stage to assess for evidence of synergy.

3. TRIAL DESIGN

This is a prospective, single arm, multicentre, phase II clinical trial utilising a two stage design. Stage one will assess the safety and activity of AZD2014 as a single agent in the treatment of DLBCL in 30 patients. Stage two will assess the additional toxicity of combining AZD2014 with Rituximab in an additional 6 patients.

Stage two will be recruited following the full recruitment of stage 1. Stage 2 recruitment will be staggered with 3 patients recruited and their safety data evaluated prior to the recruitment of the remaining 3 patients.
Post treatment biopsies will be requested at relapse in patients receiving rituximab to assess for evidence of synergy.

It is anticipated that the 36 patients required will be recruited over 18 months from specialist centres including the 13 TAP centres.

Once registered to the study, patients will receive AZD2014 125mg bd on an intermittent schedule of 2 days of treatment followed by 5 days with no treatment. Treatment would be on days 1, 2, 8, 9, 15, 16, 22 and 23 of each course 28 days in duration. Treatment is ongoing until progression or withdrawal due to toxicity or patient's choice. For the second stage of the trial, rituximab 375mg/m^2 will also be administered intravenously on day 1 of the 28 day cycle for a total of 6 cycles in combination with AZD2014.
All patients will be followed for a minimum of 1 year up until disease progression or death.

For patients still on AZD2014 treatment after 1 year (no progression) treatment should still be reviewed at least 3 monthly. Safety, progression and survival data will be collected every 3 months. Assessments should be as per local practice with a CT scan conducted every 3/4 months.

At progression, patients will then be followed up annually for survival data.

Molecular and free DNA sub-study
Tissue, saliva and blood samples will be collected during treatment to determine the activity of AZD2014 on downstream targets, and correlating with response. This will include biopsy tissue from the pre-treatment sample, any biopsy performed on treatment and at relapse post-AZD2014 should this occur.

We are also planning to analyse for predictive biomarkers such as DLBCL cell of origin, non-GCB subtype, lymphoma-associated mutations and for markers of mTORC1 expression. It will be important to see whether high levels of mTORC2 expression (using surrogate markers such as pAKT) and high levels of mTORC1 activity correlate with response to subsequent AZD2014. In addition we will look for markers of resistance; particularly focusing on expression of the MNK1/2 pathway, its effect on phosphorylation of eIF4E and any effect of rituximab on the activity of this pathway.

There is new data to suggest that levels of soluble circulating DNA from tumour cells can predict ongoing response to treatment in patients with DLBCL (62) Recent data has shown that levels of immunoglobulin gene measurements specific to the tumour type (tumour-specific clonotypes) measured by PCR can predict relapse following treatment in the first line setting in DLBCL. As part of an optional sub-study we are interested in monitoring soluble tumour DNA by PCR from the peripheral blood and saliva at screening and in peripheral blood only after 2 cycles, after 6 cycles, and at progression. Additional samples will be taken in responding patient every 3 months for up to a year. These samples will be collected and stored for future investigations as to whether free DNA correlates with treatment response in the relapsed setting.

4. ELIGIBILITY

4.1 Inclusion Criteria

For inclusion in the study, patients must fulfil the following 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 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 by fulfilling one of the following criteria at screening:

- Post-menopausal defined as amenorrhoeic for at least 12 months following cessation of all exogenous hormonal treatments

- Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy but not tubal ligation

* See section 5.3 of the protocol

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 longaxis ≥ 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
- Patients with a history of vaccination to hepatitis B and who are positive for anti-hepatitis B sAg antibody but negative for anti-core antibody are eligible if hepatitis B DNA is negative

4.2 Exclusion Criteria

Patients must not enter the study if any of the following exclusion criteria are fulfilled:

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 weaned down to a maximum dose of prednisolone 10mg daily (or equivalent) by day 1 of cycle 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, Pgp (MDR1) and BCRP if taken within the stated washout periods before the first dose of study treatment. See Appendix 2.
4. Exposure to sensitive or narrow therapeutic range substrates of the drug transporters Pgp (MDR1), BCRP, MATE 1 , MATE 2K, OATP1B1 and OATP1B3, 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 3.
5. Previous treatment with any first generation mTORC1 inhibitors (rapamycin, sirolimus, temsirolimus, everolimus) or any dual mTORC1/2 inhibitors (e.g. AZD2014, AZD8055).
6. 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.
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. 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 (transfusions permissible)
    - 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
    - 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 known 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:

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

5. SCREENING AND CONSENT

5.1 Screening

For patients who appear to meet the criteria for participation in the study, the Investigator will provide information to allow them to make an informed decision regarding their participation. Investigators will be expected to maintain a Screening Log of all potential study candidates. This Log will include limited information about the potential candidate (e.g. year of birth and gender), the date and outcome of the screening process (e.g. enrolled into study, reason for ineligibility, or declined participation).

If informed consent is given (see section 5.2), the Investigator will conduct a full screening evaluation to ensure that the patient satisfies all inclusion and exclusion criteria. A patient who gives written informed consent and who satisfies all the inclusion and exclusion criteria may be registered onto the study. Note that assessments conducted as standard of care do not require informed consent and may be provided as screening data if conducted within the stipulated number of weeks prior to registration. Assessments required in screening are listed in the assessments table and detailed in section 5.1.1.

5.1.1 Screening Assessments

All patients will be screened prior to registration. **The following screening assessments will be performed within 28 days prior to trial entry unless stated otherwise** (see section 7.3 for more details of the assessment):

- Demographic data
- Medical history (including prior diagnosis, treatment and any existing conditions)
- Height & Weight

Blood tests

- Full blood count and biochemistry (including glucose and if abnormal fasted glucose), Hba1c, triglycerides, cholesterol, Troponin (isoform as per institutional norm), serum creatinine, bilirubin, LDH and ALT/AST)
- Blood for virology. Patients must have negative virology for HIV and hepatitis C prior to trial entry. For stage one (AZD 2014 treatment only), hepatitis B serology must not indicate active infection. Prophylaxis is advised in patients who meet inclusion criteria 11 whilst being anti-hepatitis B sAg antibody positive and who are positive for anti-hepatitis B core antibody (with no surface antigen). Prophylaxis is not recommend for those with isolated anti-hepatitis B sAg and a history of vaccination.
- For stage 2 treatment (AZD 2014 with rituximab) - Hepatitis B surface antigen and anti-core antibody must be negative.

Examinations/Tests

- Clinical assessment, including, vital signs (heart rate, systolic and diastolic BP, oxygen saturation (pulse oximetry), temperature, weight)
- ECOG performance status
- Assessment of constitutional symptoms -, night sweats, recurrent fever ≥38.0ºC in the absence of infection, and history of weight loss.
- Urinalysis (test strip to include – Haemoglobin, leukocytes, nitrite and proteins)
- Bone Marrow Trephine Biopsy (if indicated for disease staging)
- Pregnancy test for females of child-bearing potential (to be obtained prior to registration and within 7 days of starting therapy)
- Contraception review as per section 5.3 below

Radiology

- PET-CT (contrast enhanced CT component) Neck, Chest, Abdomen and Pelvis (NCAP) as per Torch PET manual. Contrast enhanced CT Neck, Chest, Abdomen and Pelvis (NCAP) , can be performed at the same imaging session as the PET-CT if possible as per local practice. If performed at the same session, an unenhanced low dose CT should be performed

followed by a PET scan then a contrast enhanced CT NCAP so that accurate quantitation of PET data will be possible. A full inspiration breath-hold CT should be performed as part of the CT NCAP
- High resolution CT (HRCT) Chest to document the lung parenchyma status (if not captured during PET CT) in patients with symptoms or signs suggestive of parenchymal lung disease.

Cardiac assessments:
- Echocardiogram (Echo) including assessment of left ventricular end-systolic volume (LVESV), left ventricular end-diastolic volume (LVEDV) and LVEF.
- MUGA (if Echo cannot be performed) to assess LVEF

If an Echo cannot be performed, a MUGA scan to assess LVEF will be conducted. The modality of the cardiac function assessments must be consistent within patient, i.e., if Echo is used for the screening assessment then it should also be used for subsequent scans if required. The patient should also be examined using the same machine and operator throughout the study wherever possible. Other alternative methods of assessments could be used additionally if they are a part of the local standard of care, or if the Investigator considers them necessary for the therapeutic management of the patient. Important cardiac symptoms should be reported as AEs/serious AEs and should be carefully evaluated in regard to developing of acute or worsening of chronic cardiac failure, especially in anthracycline treated patients. Congestive cardiac failure should be treated and followed according to standard medical practice. An Echo/MUGA will also be carried out if a patient develops signs and/or symptoms suggestive of a deterioration in LVEF or in case of the pre-specified ECG finding such as T-wave inversions: (see the AZD2014 IB for more detailed explanation).

Samples for research

Blood and saliva samples should only be taken on a Monday, Tuesday or Wednesday due to the time taken to ship and process the samples on arrival at the laboratory.
- Blood sample collection for research
- Paraffin embedded tissue collection for research*
- Saliva sample at baseline for germline testing

*Tissue blocks from both initial diagnosis and relapse (if re-biopsy undertaken) will be collected. Re-biopsy at relapse is recommended if the patient's condition allows and there are no contraindications to biopsy. Refractory patients (or relapsed patients in whom re-biopsy is not possible) will be eligible for the study without re-biopsy provided initial diagnostic tissue is available and is within 3 months.

5.2 Informed Consent

It is the responsibility of the Investigator, as captured on the Site Signature and Delegation Log, to obtain written informed consent for each patient prior to performing any trial related procedure. A Patient Information Sheet (PIS) is provided to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, anticipated benefits and potential hazards of taking part in the trial to the patient. The Investigator should also stress that the patient is completely free to refuse to take part or withdraw from the trial at any time. The patient should be given ample time (e.g. 24 hours) to read the PIS and to discuss their participation with others outside of the site research team. The patient must be given an opportunity to ask questions which should be answered to their satisfaction. The right of the patient to refuse to participate in the trial without giving a reason must be respected.

If the patient expresses an interest in participating in the trial they should be asked to sign and date the latest version of the Informed Consent Form (ICF). The Investigator or designate must then sign and date the form. A copy of the ICF should be given to the patient, a copy should be filed in the hospital notes, and the original placed in the Investigator Site File (ISF). Once the patient is entered into the trial the patient's trial number should be entered on the ICF maintained in the ISF. In addition, if the patient has given explicit consent a copy of the signed ICF must be sent in the post to the Trials Office for review.

Details of the informed consent discussions should be recorded in the patient's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given,

with the name of the trial and the version number of the PIS and ICF. Throughout the trial the patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient in which case the process above should be followed and the patient's right to withdraw from the trial respected.

The patient should be given ample time to read changes made to the patient information sheet, which may vary depending on the nature of the change and may re-consent at the same visit that new information is provided, if they wish to do so.

Electronic copies of the PIS and ICF are available from the Trials Office and should be printed or photocopied onto the headed paper of the local institution.

Details of all patients approached about the trial should be recorded on the Patient Screening /Enrolment Log and with the patient's prior consent their General Practitioner (GP) should also be informed that they are taking part in the trial. A GP Letter is provided electronically for this purpose.

5.3 Contraception

For patients receiving AZD2014 only

Females of and males with partners of childbearing potential must use adequate methods of contraception.

- *Females* of child-bearing potential to use 2 forms of contraception (1 highly effective method and 1 barrier method), from registration to 4 weeks after trial treatment discontinuation. Please note that use of oral, injected or implanted hormonal methods may not be highly effective as it is unknown if AZD2014 will reduce their effectiveness.
- *Males* should be surgically sterile or willing to use an effective method of barrier contraception and refrain from sperm donation from first treatment until 16 weeks after trial treatment discontinuation

For patients receiving rituximab

Contraception should be used from registration until at least 12 months following treatment discontinuation.

For patients to be classed as having evidence of non-child-bearing potential they must fulfill one of the following criteria at screening:

- Post-menopausal defined as amenorrhoeic for at least 12 consecutive months following cessation of all exogenous hormonal treatments. If under 50 Serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels must be in the postmenopausal range
- Documentation of irreversible surgical sterilisation by hysterectomy, bilateral oophorectomy or bilateral salpingectomy, but not tubal ligation

6. TRIAL ENTRY

Patients will be registered to the trial via the Cancer Research UK Clinical Trials Unit (CRCTU).

☎:0121 415 9175

9am-5pm Monday to Friday

An eligibility checklist and registration form (found in the ISF) should be completed prior to registration by the Investigator or designee.

The patient trial number and treatment allocation will be given over the telephone, followed by a fax confirmation. Treatment should start within 7 days of registration.

7. TREATMENT DETAILS

7.1 Trial Treatment

7.1.1 Investigational Medicinal Product AZD2014

AZD2014 (vistusertib) is available for administration as a tablet for use in clinical trials. The oral tablet is presented as two strengths: 25 or 50 mg.

AZD2014 will be considered the IMP for the purposes of the trial. AZD2014 will be supplied free of charge for the trial by the manufacturers AstraZeneca.

AZD2014 doses can be taken with or without food at approximately the same time each morning and evening, 12 hours apart. Sugary and fatty foods should be avoided in the meals prior to taking a dose (see section 7.2 for further details).

Patients should avoid large amounts of grapefruit and Seville oranges (and other products containing these fruits, e.g. grapefruit juice or marmalade) during the study. No more than a small glass of grapefruit juice (120 mL) or half a grapefruit or 1 to 2 teaspoons (15 g) of Seville orange marmalade daily is allowed.

Patients should also avoid use of sun beds or tanning booths (including dye-based tanning booths) during the course of the study and for 3 months after the last dose. Use sunglasses and sun blocker (with SPF >30 to UVB and a high degree of protection against UVA) is advised, if exposed to sunlight during this period of time.

All study drug must be kept in a secure place under appropriate storage conditions. The IMP label on the bottle, the Investigators Brochure and the pharmacy manual specify the appropriate storage.

The IMP will be packaged and labelled in accordance with local regulations and Good Manufacturing Practice (GMP), stating that the drug is for clinical trial use only and to keep it out of the reach of children. For further instructions and ordering details, please refer to the pharmacy manual.

7.1.2 Investigational Medicinal Product rituximab

Rituximab is commercially available for administration as a concentrate for solution for infusion. The concentrate is presented as two strengths: 100 and 500 mg.

Rituximab will be considered the IMP for the purposes of the trial during the second stage of the trial (6 patient safety cohort). Rituximab should be taken from standard hospital stock.

Patients receiving rituximab treatment are at risk form developing progressive multifocal leukoencephalopathy (PML). Patients should be closely monitored for new or worsening neurological, cognative or psychiatric signs or symptoms which may be suggective of PML. It is also good practice to advise patients to inform their partners/caregivers about their treatment since they may notice symptoms that the patient in not aware of.

If PML is suspected rituximab treatment must be suspended. Treatment can be recommence if PML is excluded.

The IMP will need to be labelled in accordance with local regulations and Good Manufacturing Practice (GMP), stating that the drug is for clinical trial use only. A label will be provided by the Trials office for this purpose. For further details and instructions, please refer to the pharmacy manual.

7.2 Treatment Schedule

AZD2014 is to be administered twice daily orally on an intermittent schedule at a dose of 125mg. Two consecutive days of treatment will be followed by 5 days with no treatment each week. Treatment would therefore be on days 1, 2, 8, 9, 15, 16, 22 and 23 of each cycle of 28 days. Treatment days should be two consecutive days and should be the same days each week, for example if treatment was started on a Monday in the first week further treatments would be expected to continue to be on Mondays and Tuesdays each week. Treatment will continue until progression or withdrawal due to toxicity or due to patient choice.

For the second, combination, stage of the trial, rituximab 375mg/m^2 will also be administered intravenously in the standard fashion as per local protocol on day 1 of the 28 day cycle for a total of 6 cycles. Pre-medication with antihistamines (e.g.Piriton), hydrocortisone and paracetamol is permissive as per local protocols for use of rituximab in the 6 patient combination stage.

Where possible all doses of AZD2014 should be taken at approximately the same times each day. AZD 2014 doses can be taken with or without food. Twice daily doses should be taken approximately 12 hours apart. If vomiting occurs within 30 minutes after AZD2014 dosing, or if the tablet(s) can be identified in the vomit content, the patient can re-take new tablet(s).

If a patient misses a dose and remembers within 2 hours, they should take the dose straight away and continue to take the rest of their medication as planned. If a dose is missed and the patient remembers after 2 hours or longer, they should take the next dose when it is due

7.3 Assessments

	Screening	Cycle1-2 (28 day cycles)		Cycle 3- 6 (28 day cycles)		End of 6 cycles	Cycles 6+ (28 day cycles)	End of Treatment	30 Day Follow-up (+/- 5 days)	3 monthly follow-up	1 year post start of treatment
		Day 1	Day 15	Day 1	Day 15		Day 1				
Informed consent	X										
Inclusion/Exclusion Criteria	X										
Pregnancy Test	X	X[a]									
Medical History	X										
Clinical assessment [b]	X	X	X	X			X	X	X	X	
Constitutional symptoms	X	X	X	X			X	X			
ECOG Performance Status	X	X		X			X	X	X		
Clinical Chemistry/haematology/ cardiac markers)[c]	X	X[d]	X[d]	X[d]			X[d]	X[e]	X[e]		
Echocardiology/ MUGA[f]	X										
Urinalysis	X										
12 lead ECG[g]		X[h]		X[h]			X[h]	X			
CT Scan (NCAP)[i]	X		X[i]		X[i]	X[i]	X[i]	X[j]		X[j]	X[ij]
PET	X		X[k]			X[k]		X[l]		X[l]	
AZD2014 Treatment		<< X[m] >>									
Rituximab Treatment		X		X							
Dosing compliance		X	X	X	X	X	X	X			

Adverse events		<<Throughout Study>>[n]									
Concomitant medications		<<Throughout Study>>									
Blood for research[o]	X		X			X	X				
Tumour biopsy	X[p]		X[q]					X[p]			
Saliva sample	X[r]										

a) Within 7 days prior to cycle 1 day 1
b) Clinical assessment to include vital signs (heart rate, systolic and diastolic BP, oxygen saturation (pulse oximetry), , height (screening only), weight, and temperature Constitutional symptoms will include, night sweats and recurrent fever ≥38.0ºC, (a history of weight loss is to be collected at screening visit only).
c) Laboratory tests to include full blood counts, Standard biochemistry including glucose (fasted at screening only), Hba1c, triglycerides and cholesterol. Cardiac markers Troponin (isoform as per institutional norm), LDH and AST should be assessed at screening and pre-dose on first day of treatment.
d) Up to 3 days prior
e) All patients with clinically significant abnormal laboratory results at treatment completion or study drug discontinuation visit are to be followed until the results return to normal (or patient's baseline), or until a valid reason, other than a drug-related effect, is identified.
f) Echocardiography should also be carried out if a patient develops signs and/or symptoms suggestive of a deterioration in LVEF or in case of the pre-specified ECG finding
g) An ECG should be performed at any cardiac event with symptoms that may be due to cardiac ischemia, or arrhythmia (such as chest pain or palpitations). An ECG is also required in all cases of dyspnoea and pulmonary oedema.
h) In the monotherapy study ECGs are to be taken on cycle 1 day1 Pre dose and cycle 1 day1, 2hrs post dose. The ECG should be taken on day 1 of subsequent cycles only in instances where the cycle 1 day 1 ECGs were abnormal. In the combination study ECGs should be taken on day 1 cycle 1 pre and post dose and day 1 of each subsequent cycle until indicated otherwise.
i) CT at the end of every 2 cycles for first 6 cycles, then every 4 cycles (or if clinical suspicion of progression) and at 1 year post treatment start if not progressed on treatment. High resolution CT of the chest should be performed if clinically indicated by pulmonary symptoms any time during the study.
j) If no longer receiving treatment, every 3-4 months for 1 year from treatment start and / or at clinical suspicion of progression
k) The cycles 2&6 PET-CT scans should be performed in the 5 day gap between treatments on days 17-21 but ideally as close to the next administration of treatment i.e. days 20/21 to avoid the potential for inflammatory uptake of FDG
l) Only if disease progression suspected
m) Treatment will be delivered on a 2 days on 5 days off schedule until disease progression, unacceptable toxicity or patient choice.
n) Patients with an unresolved adverse reaction (AR) or SAE event at treatment completion or study drug discontinuation will be monitored until the event is resolved, stabilised or the patient is lost to follow up.
o) (OPTIONAL) Screening, end of cycle 2, end of cycle 6 and/or at progression. Additional samples will be taken in responding patients every 3 months for up to a year
p) Within 3 months of trial entry and at relapse, mandatory. May include bone marrow if indicated for disease staging.
q) Optional biopsy on day 15 of cycle 1
r) To be taken from patients who have consented to the optional sub study which requires the collection of additional blood and saliva samples

Additional optional assessments may be performed at the discretion of the investigator if clinically indicated or in the event of toxicity.

7.3.1 Blood chemistry, Haematology and cardiac markers

Blood tests should be collected at the following timepoints (+/-3 days)

Clinical chemistry and haematology laboratory tests

- Screening
- Cycles 1-2 (days 1 and 15)
- Cycle 3 onwards (day 1)
- End of treatment
- 30 day follow-up visit

Tests should include full blood counts, standard biochemistry including glucose, HbA1c, triglycerides and cholesterol.

Cardiac markers; Troponin (isoform as per institutional norm), plus LDH and AST/ALT should be assessed at screening and pre-dose on first day of treatment.

Troponin (or additionally other cardiac markers, i.e. AST/ALT and LDH depending on the Investigators decision if clinically indicated) should also be assessed on identification of abnormal ECG findings, e.g. new repolarisation abnormalities, found to be possibly clinically significant by investigators judgement. A repeat cardiac marker assessment should also be performed 24 hours later if such changes have been observed. The same Troponin isoform should be assessed at each of the visits (see IB for more detailed information).

An unscheduled serum urea and creatinine test should be performed in every case of diarrhoea that is categorised as a serious adverse event (SAE).

7.3.2 Clinical/symptom assessment

A clinical assessment including vital signs (heart rate, systolic and diastolic BP, oxygen saturation (pulse oximetry), and temperature will be performed at:

- Cycles 1-2 (days 1 and 15)
- Cycles 3 onward (day 1 of every cycle)
- End of Treatment Visit,
- 30 day Follow-up Visit.

Constitutional symptoms will be collected during cycles 1-2 (day 1 and 15), cycle 3 onwards (day 1), and End of Treatment Visit.

Constitutional symptoms will include the, night sweats, weight loss and recurrent fever ≥38.0ºC in the absence of infection,.

7.3.3 ECG

ECGs should be taken on cycle 1 day 1 pre dose and, 2 hrs post dose .If the cycle 1 day 1 ECG taken as part of the monotherapy study is abnormal then ECG measurements should be taken on day 1 of all subsequent cycles. During the combination study ECGs should be taken on cycle 1 day 1 pre dose and, 2 hrs post dose and day 1 of all subsequent cycles unless indicated otherwise.

Twelve-lead ECGs will be obtained after the patient has been resting semi-supine for at least 10 minutes. All ECGs should be recorded with the patient in the same physical position. For each time point 1 ECG recording should be taken.

If an abnormal pre dose ECG finding is considered by the Investigator to be clinically significant, it should be reported as a concurrent condition. During the study, clinically significant abnormal ECG findings not present at pre dose should be reported as an AE. If present, the clinical signs and symptoms associated with the abnormal finding should be reported as the AE with the ECG abnormality given as explanatory information. Further ECGs should be performed until recovery if a significant abnormality is detected (or as clinically indicated)

Troponin (additionally other cardiac markers, i.e. AST/ALT and LDH depending on the investigators decision if clinically indicated) should also be assessed on identification of abnormal ECG findings, e.g. new repolarisation abnormalities. A repeat cardiac marker assessment should also be performed 24 hours later, if such findings occur, the same Troponin isoform should be assessed at each of the visits.

An ECG should be performed at any cardiac event with symptoms that may be due to cardiac ischaemia, or arrhythmia (such as chest pain or palpitations). An ECG will also be captured in all cases of dyspnoea and pulmonary oedema and additionally at the discretion of the investigator if clinically indicated.

7.3.4 CT scan

During the first 6 cycles of treatment patients must be assessed by contrast enhanced CT NCAP scan after every 2 cycles of treatment. Two dimensional measurements to calculate the sum of product diameter (SPD) must be taken.

Patients with stable disease or better will remain on study treatment After this time patients that remain on treatment will be assessed by contrast enhanced CT NCAP scan after every 4 cycles. Additional scans may be performed at any time if there is clinical suspicion of progression.

A Bone Marrow Trephine Biopsy should be performed for confirmation of either isolated disease progression within the bone marrow or to confirm complete remission if in CR on CT or PET.

If a patient discontinues treatment without progression they should also be assessed by contrast enhanced CT NCAP scan every 3-4 months for 1 year after their first treatment where possible. CT scans after 1 year will be as per standard practice or at progression (whichever is sooner).

High resolution (HR) CT of the chest should be performed if clinically indicated by pulmonary symptoms any time during the study. For any new respiratory symptoms (cough, dyspnoea, lower respiratory infection) not clearly explained by other factors (e.g., dyspnoea associated with substantial drop in haemoglobin), patients should have oxygen saturation measured. If oxygen saturation <92%, the HR CT Chest should be repeated and pulmonary function tests (PFTs) should be performed. For further information see section 7.5.5.

7.3.5 PET CT scan

A PET CT (contrast enhanced) scan should be performed at screening, following cycle 2 (within the day 17-21 treatment gap), and after cycle 6 (within the day 17-21 treatment gap) or progression if this is sooner.

The screening PET CT and the PET CT after 6 courses would be regarded as standard of care for the purposes of funding, in view of the international working group recommendations (1).

A contrast-enhanced CT scan should also be done, ideally at the same visit, at screening, after cycle 2 and cycle 6 to measure tumour volumes. This should be of diagnostic quality.

The UK NCRI PET research network will co-ordinate the quality control required to ensure accurate quantitation for PET scans (63). The Core Lab based at the KCL PET Centre at St Thomas' London will accredit PET centres prior to the study and be responsible for monitoring quality control during the trial and organise data transfer for central review.

All scans will be centrally reviewed at St Thomas' using the 5-point scale for visual interpretation (Deauville Criteria and the Lugano classification). Semi-quantitative analysis will also be performed using the published value for ΔSUVmax $\geq$ 66% at 2 cycles to separate good from poor responders but receiver operating characteristic (ROC) curves will also be derived to determine if possible whether the optimal cut-off for patients treated with AZD2014 is similar to the cut-off for patients with DLBCL treated with (R)CHOP chemotherapy (35,38,39). Maximal standardized uptake value reduction is calculated as follows:

SUVmax reduction (%) = 100 x [SUVmax (PET0) - SUVmax (iPET)/SUVmax (PET screening)].

Standard contrast enhanced CT responses will be classified according to the International Workshop Criteria (1).

PET CT scans should therefore be sent to
c/o Core Lab as St Thomas', For attention of Dr Sally Barrington
Clinical PET Centre,
St Thomas',
Westminster Bridge Rd,
London SE1 7EH,

Please see the trial PET-CT manual for further details.

7.4 Sample Collection for research

7.4.1 Tumour paraffin blocks

For all patients a paraffin embedded block of tumour tissue will be collected within 3 months of trial entry. We also request an additional biopsy/tumour block at relapse.

There is also an optional biopsy on day 15 (+/- 2 days) of cycle 1 to assess for pharmacodynamic changes and allowing correlation with response.

7.4.2 Saliva and Blood samples

BLOOD AND SALIVA SAMPLES SHOULD ONLY BE TAKEN ON A MONDAY, TUESDAY OR WEDNESDAY DUE TO THE TIME TAKEN TO SHIP AND PROCESS THE SAMPLES ON ARRIVAL AT THE LABORATORY.

A saliva sample will be taken from patients who have consented to the optional sub study. This will be taken at baseline for identification of germline DNA.

For patients taking part in this sub-study we will also request blood samples, up to 10ml each (for surrogate assays on platelet rich plasma, circulating mononuclear cells and free DNA studies) at screening, end of cycle 2, end of cycle 6, every 3 months for up to 1 year and end of treatment and/or progression. Collection tubes and appropriate transport will be provided

Once collected blood samples, saliva and tissue blocks should be processed as per the TORCH sample collection manual and sent to:

Oxford Molecular Diagnostics Centre
F.A.O Maite Cabes
Molecular Haematology
Level 4, John Radcliffe Hospital
Headington, Oxford
OX3 9DU

Samples will be used for in-house molecular diagnostics and may also be sent to AstraZeneca for additional biomarker-related studies.

The Chief Investigator has overall responsibility for custodianship of the samples. Laboratories are instructed to retain any surplus samples pending instruction from the Chief Investigator on use, storage or destruction. It is possible that new or alternative assays may be of future scientific interest. At the end of the research study any surplus samples may be retained for use in other projects that

have received ethical approval. Hence, any surplus study samples may be transferred to a licensed tissue bank where they will be managed in accordance with applicable host institution policies and the Human Tissue Act (HTA) requirements. A patient may withdraw consent at any time. In this event, any samples and data that have already been provided for the research trial will be retained and used in the analysis. No further samples will be taken and any surplus material will be destroyed.

7.5 Dose Modifications

AZD2014 is expected to be well tolerated. Substantial toxicities should be managed as medically indicated and with temporary suspension of study drug, as appropriate. Dose reductions or holds and initiation of supportive care are allowed as clinically indicated by the treating physician. For each patient, a maximum of two dose reductions will be allowed. The reduced dose levels are presented in Table 1. If patients are unable to tolerate the 75mg bd dose of AZD2014, there is a possibility of changing to a continuous dosing regimen which may in some cases be better tolerated. This needs to be discussed with the chief investigator on a case by case basis.

Table 1. AZD2014 dose level modification

Dose level	AZD2014 PO daily dose
Starting Dose	125 mg bd
-1 Dose Level	100 mg bd
-2 Dose Level	75 mg bd

7.5.1 General dose modifications for toxicities

Dose reduction and discontinuation guidelines for haematologic and non-haematologic toxicities due to AZD2014 are shown in Table 2 and 3 . Dose re-escalation is not permitted.

Table 2. Dose modifications and discontinuation criteria for non-haematologic toxicities*

NCI CTCAE Toxicity Grade	**Action**
Grade 1, or 2	None
Grade 3 or 4 and/or clinically significant **Expected manageable/reversible with dose reduction**	Hold study drug until meets one of the criteria below:
Toxicity remains (despite dose interruption) grade 3 or 4 or is clinically significant > 14 days	Discontinue study drug
Toxicity lasts 14 days or less and resolves to grade 2 or less or is no longer clinically significant	Reduce dose level per Table 1 and restart once toxicity has resolved to grade 2 or less or is no longer clinically significant
Grade 3 or 4 and/or clinically significant **Not expected to be manageable/reversible with dose reduction**	Discontinue study drug
Recurrence of Grade 3	Reduce one more dose level is available (see table 1), or if not discontinue study drug. NB note option of continuous dosing schedule as mentioned in 7.5

Table 2. Dose modifications and discontinuation criteria for non-haematologic toxicities*

NCI CTCAE Toxicity Grade	Action
Recurrence of Grade 3 cardiac event[a]	Discontinue study drug
Recurrence of Grade 4	Discontinue study drug

* If the below specific recommendations for stomatitis/oral mucositis, hyperglycaemia, ILD/pneumonitis, ECG-changes and rash disagree with table 2 please follow the below not recommendations not table 2.

Table 3. Dose modifications and discontinuation criteria for haematological toxicities

NCI CTCAE toxicity grade	**Action**
Thrombocytopenia	
Grade 1, 2 or 3 (without bleeding)	None
Grade 3 (with bleeding) or grade 4	Hold study drug until it meets one of the criteria below:
Toxicity remains (despite dose interruption) grade 3 (with on-going bleeding episodes) or 4 > 14 days	Discontinue study drug
Toxicity lasts 14 days or less and resolves to grade 2 or less	Reduce dose level per table 1 and restart once toxicity has resolved to grade 2 or less
Neutropenia (NB GCSF is permitted as per local policy)	
Grade 1, 2 or 3	None
Grade 4	Hold study drug until it meets one of the criteria below:
Toxicity remains (despite dose interruption and GCSF) grade 4 > 14 days	Discontinue study drug
Toxicity lasts 14 days or less and resolves to grade 2 or less	Reduce dose level per table 1 and restart once toxicity has resolved to grade 2 or less or is no longer clinically significant

RBC transfusion is permissive and advised in the event of symptomatic anaemia or a haemoglobin falling below 80g/l. If anaemia occurs, an assessment of underlying causality should take place and non-IMP related causes considered.

Grade 4 neutropenia (neutrophil count < 0.5 x 10^9/l) should always be treated with GCSF according to local policy

Platelet transfusion should be used in the following situations:

- as treatment of a bleeding event with a platelet count < 50 x 10^9/l,
- platelets < 20 x 10^9/l with concomitant infection
- platelets < 10 x 10^9/l in asymptomatic patients

If a toxicity is experienced for patients in the combination stage then the treating investigator should ascertain the causality of the toxicity to both IMPs:

- If at least possibly related to AZD2014 follow the dose modifications above.
- If related to rituximab, management and dose modifications of rituximab should be as per the local site or Investigators standard procedures.

Dose calculations for any weight changes should also be conducted as per local practice.

7.5.2 Specific dose modification recommendations

7.5.2.1 Recommendations for Treatment of Nausea and Vomiting

In order to decrease the incidence of nausea and vomiting, an anti-emetic regimen should be used for patients, who are developing nausea after starting AZD2014 for the first time. On subsequent dosing days, the following antiemetics are recommended to be administered and continued daily throughout the AZD2014 dosing days.

Serotonin (5-HT3) antagonist (choose one from this list below):

- Dolasetron 100 mg by mouth daily
- Granisetron 2 mg by mouth daily or 1 mg by mouth twice a day

If nausea and vomiting are not being managed with the regimen above, start a breakthrough treatment with the addition of one agent of a different drug class, e.g.:

- Dexamethasone 8 mg PO at day 1 of the AZD2014 dosing period or
- Metoclopramide 10-40 mg PO or
- Olanzapine 5-10 mg PO or
- Promethazine (Phenergan)12.5 – 25 mg every 6 hours

on the AZD2014 dosing days prior to the AZD2014 dose.

If this is still not managing the nausea and vomiting sufficiently, add Lorazepam 0.5-2 mg by mouth or sublingual every 4 to 6 hours as needed, but only on the AZD2014 dosing days.

Should upper abdominal pain develop a H2 blocker or proton pump inhibitors can be added. For combinations, please refer to the manufacturers SMPC for the combination agent.

7.5.2.2 Recommendation for Treatment of Stomatitis/Oral Mucositis/Mouth Ulcers

For mild toxicity (Grade 1), use conservative measures such as non-alcoholic mouth wash or salt water (0.9%) mouth wash several times immediately after drug administration (1-3h) and during the day as required until resolution. AZD2014 treatment can be continued without a dose reduction.

For more severe toxicity (Grade 2 or 3), the suggested treatments are topical analgesic mouth treatments (i.e., local anesthetics such as benzocaine, butyl aminobenzoate, tetracaine hydrochloride, menthol, or phenol), with or without topical corticosteroids, such as triamcinolone oral paste 0.1% (e.g., Kenalog in Orabase®). Opioid analgesia (either intravenous, subcutaneous, or oral) is permitted.

AZD2014 should be stopped until stomatitis improves to ≤ Grade 1, and then resumed without a dose reduction. If Grade 2 to 3 stomatitis recurs, dose reduce AZD2014

Agents containing hydrogen peroxide, iodine, and thyme derivatives may worsen mouth ulcers. It is preferable to avoid these agents.

If the toxicity resolves or reverts to ≤ CTCAE Grade 2 within 14 days of onset and the patient is showing clinical benefit, treatment with AZD2014 may be restarted, at the same dose or a lower dose, at the discretion of the Investigator.

If the toxicity does not resolve to ≤ CTCAE Grade 2 after 14 days, then the patient should be withdrawn from the study and observed until resolution of the toxicity.

7.5.2.3 Recommendations for Treatment of Rash/Skin toxicity

Early identification and intervention is critical for the optimal management of rash. Preliminary clinical evidence suggests that antihistaminergic drugs may ameliorate occurance/severity of rash. Therefore, patients who develop Grade 1 or 2 changes in their skin condition should be treated with the Investigator's choice of antihistaminergic drugs, over the counter moisturizing cream or ointment, local antihistamines and/or topical or systemic steroids. If bacterial infection is suspected, local and/or systemic antibiotics may be added.

For Grade 3 rash, topical and/or systemic steroids with or without topical and/or systemic antibiotics (to be considered if bacterial infection is suspected) are indicated, together with dose modifications as described in *Section 7.5.1*; short courses (≤14 days) of corticosteroid treatment at doses that do not exceed 100 mg per day of prednisone or equivalent may be given.

Some example treatments are listed below:

- Topical steroids: triamcinolone acetonide 0.025%; desonide 0.05%; fluticasone proprionate 0.05%, aclometasone 0.05%
- Topical antipruritics: pramoxine 1%; doxepin 5% cream
- Oral antihistamines: loratidine, cetirizine, fexofenadine; diphenhydramine 25-50 mg every 8h; hydroxyzine 25 mg every 8h
- Topical antibiotics: clindamycin 1-2%; erythromycin 1-2%; metronidazole 1%; silver sulphadiazine1%
- Oral antibiotics: doxycycline 100 mg BD; minocycline 100 mg BD; oxytetracycline 500 mg

In the event of Steven-Johnson syndrome, an immune-complex-mediated hypersensitivity that typically involves the skin and mucous membranes (Grade 3-4 Skin Sloughing), patients should permanently discontinue rituximab and AZD2014 treatment.

7.5.2.4 Recommendations for Treatment of Hyperglycaemia

Treatment related findings of elevated blood glucose levels should be reported as AE (s) if they fulfil the CTCAE criteria and SAE(s) if meeting the SAE reporting criteria.

In general management of hyperglycaemia should be performed according to local standards at the discretion of the Investigator.Due to the predicted short half-life of AZD2014, only a short period of hyperglycaemia with insulin resistance is expected. Therefore early treatment with high doses of insulin/and or oral anti-diabetes medication should be carefully evaluated and blood sugars and hypokalemia monitored as per standard clinical practice.

If blood glucose levels are < 250 mg/dl (Grade 2), generally no medical treatment is required. Dietary modification may be initiated.

For ≥ Grade 3 hyperglycaemia, dose modifications are required *see Section 7.5.1*

7.5.2.5 Recommendations for Evaluation and Treatment of Interstitial Lung Disease

Should a patient experience any new respiratory symptoms including cough, dypsnoea, lower respiratory tract infections not clearly explained by other factors such as disease progression or anaemia, a high resolution CT scan should be performed. In addition, pulmonary function tests should be performed. The test should include the highest of 3 forced expiratory volumes (FEV1), forced vital capacity (FVC), and carbon monoxide diffusing capacity (DLCO% & DLCO). A recent haemoglobin measurement should be available at DLCO evaluation.

If these investigations are suggestive of pneumonitis or interstitial lung disease and causality with the study drug cannot be excluded, treatment should be interrupted. In more severe cases treatment with corticosteroids should be considered

7.5.2.6 Recommendations for Evaluation and Management of ECG Changes

Patients who develop persistent, confirmed T wave repolarisation abnormalities (inversion or flattening) on regularly scheduled ECGs may be referred for a cardiology opinion.

ECG monitoring should be continued as per the trial schedule, as well as a troponin measurement (within 24 of the abnormality). ECG, Troponin and LV function assessment should also be conducted at trial discontinuation and 30 days follow-up visit (to document recovery while off drug)

7.5.2.7 Recommendations for Evaluation and Treatment of Severe Fatigue

If ≥ Grade 3 fatigue occurs, the dosing should be held for up to 14 days, before being restarted at a lower dose.

Routine clinical work-up to exclude reasons other than the underlying disease and/or AZD2014 treatment may be performed, including laboratory analyses to rule out metabolic (acidosis, hyperglycaemia) or cardiac problems.

7.5.2.8 Recommendations for Treatment of Diarrhoea

Patients should be made aware of the risk of diarrhoea while receiving treatment with AZD2014. Patients should be advised to drink sufficient fluids and have a supply of loperamide available throughout treatment. However, loperamide should not be administered prophylactically.

As soon as the first liquid stool occurs, patients should start treatment with loperamide immediately and also take electrolyte-containing fluids. Patients should inform their study doctor.

The recommended antidiarrheal treatment is loperamide; to be administered as per package information and usual clinical practice .Loperamide should not be administered for more than 48 consecutive hours.

Hospitalisation is recommended for management of diarrhoea under the following circumstances:

- Diarrhoea associated with fever
- Diarrhoea requiring intravenous hydration
- Diarrhoea persisting beyond 48 hours following the initiation of high-dose loperamide therapy.

Please refer to *Section 7.5.1* for dose modifications required for ≥ Grade 3 diarrhoea.

7.5.2.9 Recommendations for Evaluation and Treatment of Electrolyte changes

AZD2014, like other mTOR inhibitors inhibits pump mechanisms in renal tubules, leading to hypokalaemia and hypophosphataemia in a small proportion of patients. The presence of biochemical abnormalities should be monitored as per the protocol and electrolyte abnormalities should be corrected using oral supplements. The Investigator should also consider whether other medication the patient may be receiving, such as diuretics may have contributed to these abnormalities.

7.6 Treatment Compliance

Treatment compliance for AZD2014 will be monitored using patient diaries. Patients will be asked to complete patient treatment diaries and return any unused tablets along with the diary at the end of every cycle for reconciliation or upon any dose modification. Staff must note in the patient diary the number of tablets remaining at the end of each cycle.

Accountability for rituximab will be via pharmacy drug accountability logs and the treatment CRF.

7.7 Supportive Treatment

- Pre-medication for rituximab dosing: hydrocortisone 100-200mg IV, antihistamine, and paracetamol are permissive according to local standards
- RBC transfusion is permissive and advised in the event of symptomatic anaemia or a haemoglobin falling below 80 g/L. If anaemia occurs, an assessment of underlying causality should take place and non-IMP related causes considered.
- Platelet transfusion should be used in the following situations: as treatment of a bleeding event with a platelet count < 50 x 10^9/l, platelets < 20 x 10^9/l with concomitant infection or platelets < 10 x 10^9/l in asymptomatic patients
- Grade 4 neutropenia (neutrophil count < 0.5 x 10^9/l) should always be treated with GCSF according to local policy. Specific G-CSF and regimens should be according to local policy. However, please note the following guidance from the American Society of Clinical Oncology (ASCO) guidelines (2006 update) (65):

  GCSFs should be continued until neutrophil count is ≥2x10^9/l In adults the recommended G-CSF dose is 5 µg/kg/d
- Patients with rapidly proliferating tumour and high tumour burden are at risk of tumour lysis syndrome (TLS). These patients should be monitored closely and managed according to best medical practice. Management of TLS may include aggressive hydration, monitoring of renal function, correction of electrolyte abnormalities, anti-hyperuricaemic therapy, and supportive care. There is no specific indication for rasburicase when AZD2014 is given to treat DLBCL.

7.8 Concomitant Medication

7.8.1 Concomitant treatment with CYP inhibitors, inducers and substrates

If a patient requires short-term administration of a restricted CYP3A4/5, Pgp or BCRP **inhibitor** AZD2014 treatment must be withheld for three days prior to administration and not restarted until the concomitant therapy has been discontinued for the appropriate time period described in Appendix 2.

If a patient requires short-term administration of a restricted CYP3A4/5, Pgp (MDR1) or BCRP isoenzyme **inducer** this should be clearly documented in the Case Report Form (CRF) and may then be permitted, but the Investigator will be informed that this could lead to lower levels of study drug and a potential reduction in clinical efficacy.

If a patient requires short term administration of restricted **substrates** of OATP1B1, OATP1B3, MATE1 or MATE2K AZD2014 treatment must be withheld for 3 days prior to the first administration and not restarted until the concomitant therapy has been discontinued for the appropriate time period *described in Appendix 3 .*

Information on all concomitant treatments given during the study with reasons for the treatment should be recorded in the CRF. If medically feasible, patients taking regular medication other than those excluded from this study should be maintained on it throughout the study period.

The lists of CYP inhibitors, inducers and substrates are not exhaustive and the absence of a drug from these lists does not imply that its combination with AZD2014 is safe.

7.8.2 Other Concomitant Treatments

Information on any treatment pertinent to the inclusion/exclusion criteria in the 4 weeks prior to starting study treatment and all concomitant treatments given during the study with reasons for the treatment should be recorded. If medically feasible, patients taking regular medication, with the exception of potent or moderate inhibitors or inducers of CYP3A4/5 or CYP2C8, should be maintained on it throughout the study period.

- Patients who begin warfarin, or other vitamin K antagonists, therapy should be advised to have their anticoagulation monitored more frequently when receiving AZD2014 and should stop medication with AZD2014 at thrombocytopenia CTCAE Grade 3 or higher.

- Patients may continue to receive therapeutic bisphosphonates and erythropoietin preparations (e.g. Procrit, Epogen, Aranesp), if they were receiving them prior to beginning study treatment.

- Blood transfusions are allowed during the study.

- Other medication e.g. anti-emetics that are considered necessary for the patient's safety and well-being may be given at the discretion of the investigators.

Primary prophylaxis with anti-viral, anti-fungals and anti-Pneumocystis carinii pneumonia (*PCP)* medication are not required. These should be used according to local policy; however it should be noted that:

1.The systemic anti-Pneumocystis carinii pneumonia medication dapsone is **contraindicated** due CYP3A4/5 inhibitory effect.

2. Pentamidine **should NOT** be used for this indication due to its cardiac effects

Palliative radiotherapy to a site which does not contain a target lesion is permissible. Concomitant use of any other anticancer therapy, or moderate-to-significant inhibitors of CYP3A4 (Appendix 2), are prohibited.

Concomitant vaccination with live virus vaccines during rituximab treatment and for the duration the patient is peripherally depleted is prohibited.

7.9 Treatment discontinuation and Patient Withdrawal

In the event of discontinuation of study treatment, e.g. unacceptable toxicity or patient choice, full details of the reason/s for discontinuation should be recorded on the appropriate pages on the CRF. All patients, including non-compliant subjects, should be followed up according to the protocol unless they withdraw specific consent.

In the event of a patient's decision to withdraw from the trial, the Investigator should ascertain from which aspects of the trial the patient wishes to withdraw and record the details on the appropriate

CRF. If a patient chooses to withdraw from treatment only, the patient should discontinue treatment and continue to be assessed in accordance with the protocol.

If a patient wishes to withdraw from the trial (i.e. including trial specific assessments), but is willing for further data to be supplied to the Trials Office, then further routine "follow-up" data (e.g. disease status and survival) will continue to be supplied by the Investigator to the Trials Office. All information and blood/tissue samples collected up until point of retraction will be retained and analysed.

Patients who stop treatment due to AEs (clinical or laboratory) will be treated according to accepted medical practice and followed up as per protocol. All pertinent information concerning the outcome of such treatment must be recorded in the CRF.

The following are justifiable reasons for the Investigator to stop study treatment:

- unforeseen events: any event which in the judgement of the Investigator makes further treatment inadvisable
- serious violation of the study protocol (including persistent patient non-attendance and persistent non-compliance)
- stopping by the Investigator for clinical reasons not related to the study drug treatment

Patients must stop study treatment in the event of:

- SAE requiring permanent discontinuation of treatment
- the patient becoming pregnant
- Clinically significant ECG changes
- Interstitial lung disease
- Stevens-Johnson syndrome, Progressive multifocal Leukoencephalopathy or other significant infusion related reactions

If trial treatment is discontinued the patient must attend clinic for the end of treatment visit and 30 days (+/- 5 days) after their last trial treatment for the 30 days post treatment visit, unless they have withdrawn consent for these assessments.

End of treatment visit assessments

- Clinical assessment to include vital signs (heart rate, systolic and diastolic BP, oxygen saturation (pulse oximetry), weight, and temperature
- Constitutional symptoms will include , night sweats and recurrent fever ≥38.0ºC,
- Laboratory tests to include full blood counts, Standard biochemistry including glucose, Hba1c, triglycerides and cholsterol
- ECG
- PET-CT to include contrast enhanced CT (if Progression only)
- ECOG
- Con meds
- AEs

30 days post treatment assessments (+/- 5 days)

- Clinical assessment to include vital signs (heart rate, systolic and diastolic BP, oxygen saturation (pulse oximetry), , weight, and temperature
- Laboratory tests to include full blood counts, Standard biochemistry inclusing glucose, Hba1c, triglycerides and cholsterol
- ECOG
- AEs

Following study treatment discontinuation the patient should be treated at the Investigator's discretion.

7.10 Patient Follow Up

Whilst patients remain on trial treatment they will be reviewed on day 1 of every cycle with assessments as per section 7.3. For patients still on AZD2014 treatment after 1 year treatment should be reviewed at least 3 monthly. Assessments should be as per local practice with a CT scan conducted every 3-4 months.

If the patient comes off treatment but has not progressed, they will be reviewed in clinic and with a contrast enhanced CT of the neck, chest, abdomen and pelvis every 3 months for a year from the start of therapy. If the patient has not progressed after 1 year, they will then be followed up in clinic as per local policy with a CT as per local practice or performed on suspicion of progression. Patients will have no specific trial follow up, but their registering physician will be contacted every 6 months to determine progression and survival data.

At progression, patients will then be followed up 6 monthly for survival data.

All patients will be followed up for a minimum of 1 year, after starting treatment or until death.

8. ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed in Appendix 5. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the Investigator Brochure.

8.1 Reporting Requirements

8.1.1 Adverse Events

All medical occurrences which meet the definition of an AE (see Appendix 5 for definition) should be reported.

Please note this does not include abnormal laboratory findings. An abnormal laboratory value is only considered to be an AE if the abnormality:

- Results in early discontinuation from the study treatment and/or
- Requires study drug dose modification or interruption, any other therapeutic intervention, or is judged to be of significant clinical importance
- Is Hyperglycaemia of > 1 week or if the investigator considers the rise in glucose to be medically significant

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded.

Pre-existing events should only be classified as AEs if they worsen by at least one grade from screening.

8.1.2 Serious Adverse Advents

Investigators should report AEs that meet the definition of an SAE (see Appendix 6 for definition) and are not excluded from the reporting process as described below.

8.1.2.1 Events that do not require reporting on a Serious Adverse Event Form

The following events should not be reported on an SAE Form:

- Disease progression
- Hospitalisations for:

- Protocol defined treatment
- Pre-planned elective procedures unless the condition worsens
- Treatment for progression of the patient's cancer

8.1.2.2 Monitoring pregnancies for potential Serious Adverse Events

It is important to monitor the outcome of pregnancies of patients in order to provide SAE data on congenital anomalies or birth defects.

In the event that a patient or their partner becomes pregnant during the SAE reporting period please complete a Pregnancy Notification Form (providing the patient's details) and return to the Trials Office as soon as possible. The patient should be given a release of medical information form or the patient should be asked to give this to their partner. If the patient/partner is happy to provide information on the outcome of their pregnancy they should sign the release of medical information form. Once consent has been obtained provide details of the outcome of the pregnancy on a follow-up Pregnancy Notification Form and if necessary also complete an SAE Form.

8.1.3 Reporting period

Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.

8.1.4 Post study SUSARs

SAEs that are judged to be at least possible related to the IMP(s) and are unexpected must still be reported in an expedited manner irrespective of how long after IMP administration the reaction occurred.

8.2 Reporting Procedure

8.2.1 Site

8.2.1.1 Adverse Events

AEs should be reported on an AE Form (and where applicable on an SAE Form). An AE Form should be completed at each visit and returned to the Trials Office.

AEs will be reviewed using the CTCAE, version 4.0 (see Appendix 6). Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe.

For each sign/symptom, the highest grade observed since the last visit should be recorded.

8.2.1.2 Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in section 4 of the Investigator Site File (ISF).

AEs defined as serious and which require reporting as an SAE (excluding events listed in Section 8.1 above) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.0.

On becoming aware that a patient has experienced an SAE, the Investigator (or delegate) must complete, date and sign an SAE Form. The form should be faxed together with a SAE Fax Cover Sheet to the Trials Office using one of the numbers listed below as soon as possible and no later than 24 hours after first becoming aware of the event:

To report an SAE, fax the SAE Form with an SAE Fax Cover Sheet to:

0121 414 6061 or 0800 328 6412

On receipt the Trials Office will allocate each SAE a unique reference number. This number will be transcribed onto the SAE Fax Cover Sheet which will then be faxed back to the site as proof of receipt. If confirmation of receipt is not received within 1 working day please contact the Trials Office. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Fax Cover Sheet completed by the Trials Office should be filed with the SAE Form in the ISF.

For SAE Forms completed by someone other than the Investigator the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments. The form should then be returned to the Trials Office in the post and a copy kept in the ISF.

Investigators should also report SAEs to their own Trust in accordance with local practice.

8.2.1.3 Provision of follow-up information

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided on a new SAE Form (refer to the SAE Form Completion Guidelines for further information).

8.2.2 Trials Office

On receipt of an SAE Form seriousness and causality will be determined independently by a Clinical Coordinator. An SAE judged by the Investigator or Clinical Coordinator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Clinical Coordinator will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the RSI/ Investigator Brochure) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

8.2.3 Reporting to the Competent Authority and main Research Ethics Committee

8.2.3.1 Suspected Unexpected Serious Adverse Reactions

The Trials Office will report a minimal data set of all individual events categorised as a fatal or life threatening SUSAR to the Medicines and Healthcare products Regulatory Agency (MHRA) and main Research Ethics Committee (REC) within 7 days. Detailed follow-up information will be provided within an additional 8 days. All other events categorised as SUSARs will be reported within 15 days.

8.2.3.2 Serious Adverse Reactions

The Trials Office will report details of all SARs (including SUSARs) to the MHRA and main REC annually from the date of the Clinical Trial Authorisation, in the form of an Annual Safety Report.

8.2.3.3 Adverse Events

Details of all AEs will be reported to the MHRA on request.

8.2.3.4 Other safety issues identified during the course of the trial

The MHRA and main REC will be notified immediately if a significant safety issue is identified during the course of the trial.

8.2.4 Investigators

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to Principal Investigators. A copy of any such correspondence should be filed in the ISF.

8.2.5 Safety Monitoring Committee

The Trial Safety Committee (TSC) will review all SAEs.

8.2.6 Manufacturer of Investigational Medicinal Product

All SAEs will be reported to the manufacturers of the Investigational Medicinal Products as defined in the agreement between sponsor and manufacturer. All SAEs will be reported to AstraZeneca in accordance with the Drug Supply Agreement.

9. DATA HANDLING AND RECORD KEEPING

9.1 Data Collection

The Case Report Form (CRF) will comprise a set of forms capturing details of eligibility, patient baseline characteristics, treatment and outcome details etc, and will be provided to the Site at the time of initiation.

The CRF must be completed, signed/dated and returned to the Trials Office by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within stipulated timeframes. The exceptions to this are the SAE Form, eligibility Form and Withdrawal Form which must be signed by the Investigator.

Entries on the CRF should be made in ballpoint pen, in blue or black ink, and must be legible. Any errors should be crossed out with a single stroke, the correction inserted and the change initialled and dated. If it is not obvious why a change has been made, an explanation should be written next to the change.

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. All missing and ambiguous data will be queried. All sections are to be completed before returning.

In all cases it remains the responsibility of the Investigator to ensure that the CRF has been completed correctly and that the data are accurate.

The completed originals should be sent to the Trials Office and a copy filed in the Investigator Site File.

Trial forms may be amended by the Trials Office, as appropriate, throughout the duration of the trial. Whilst this will not constitute a protocol amendment, new versions of the form must be implemented by participating sites immediately on receipt.

9.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed ICFs, Investigator Site Files, Pharmacy Files, patients' hospital notes, copies of CRFs etc.) at their site are securely retained for at least 25 years after the end of the trial. Do not destroy any documents without prior approval from the CRCTU Document Storage Manager.

10. QUALITY MANAGEMENT

10.1 Site Set-up and Initiation

All sites will be required to sign a Clinical Study Site Agreement prior to participation. In addition all participating Investigators will be asked to sign the necessary agreements, registration forms and supply a current CV to the Trials Office. All members of the site research team will also be required to sign the Site Signature and Delegation Log, which should be returned to the Trials Office. Prior to commencing recruitment all sites will undergo a process of initiation. Key members of the site research team will be required to attend either a meeting or a teleconference covering aspects of the trial design, protocol procedures, AE reporting, collection and reporting of data and record keeping. Sites will be provided with an Investigator Site File and a Pharmacy File containing essential documentation, instructions, and other documentation required for the conduct of the trial. The Trials Office must be informed immediately of any change in the site research team.

10.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the TORCH Quality Management Plan. Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required the Trials Office will contact the site to arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the TORCH trial staff access to source documents as requested.

10.3 Central Monitoring

Where a patient has given explicit consent sites are requested to send in copies of signed ICFs for in-house review.

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Trials staff will check incoming Case Report Forms for compliance with the protocol, data consistency, missing data and timing. Sites will be sent Data Clarification Forms requesting missing data or clarification of inconsistencies or discrepancies.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the Trial Management Group and Trial Safety Committee and the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the main Research Ethics Committee (REC) and the Medicines for Healthcare products Regulatory Agency (MHRA).

10.4 Audit and Inspection

The Investigator will permit trial-related monitoring, audits, ethical review, and regulatory inspection(s) at their site, providing direct access to source data/documents.

Sites are also requested to notify the Trials Office of any MHRA inspections.

10.5 Notification of Serious Breaches

In accordance with Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 and its amendments the Sponsor of the trial is responsible for notifying the licensing authority in writing of any serious breach of:

- The conditions and principles of GCP in connection with that trial or;
- The protocol relating to that trial, within 7 days of becoming aware of that breach

For the purposes of this regulation, a “serious breach” is a breach which is likely to effect to a significant degree:

- The safety or physical or mental integrity of the subjects of the trial; or
- The scientific value of the trial

Sites are therefore requested to notify the Trials Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trials Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trials Office in providing sufficient information to report the breach to the MHRA where required and in undertaking any corrective and/or preventive action.

11. END OF TRIAL DEFINITION

The end of trial will be 6 months after the last data capture. This will allow sufficient time for the completion of protocol procedures, data collection and data input. The Trials Office will notify the MHRA and main REC that the trial has ended and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

12. STATISTICAL CONSIDERATIONS

12.1 Definition of Outcome Measures

12.1.1 Primary outcome measures

- Best overall response rate during the first 6 cycles of AZD2014 will be assessed using contrast-enhanced CT scans of the neck, chest, abdomen and pelvis, using the Revised Response Criteria for Malignant Lymphoma.

12.1.2 Secondary outcome measures

- Best overall response rate post 6 cycles until the end of the trial, assessed using the revised Response Criteria for Malignant lymphoma (Appendix 1)
- Tolerability of AZD alone and in combination with rituximab will be assessed using Toxicities recorded during trial treatment using CTCAE v4.0
- Progression free survival is defined as the time from date of registration to the date of disease progression or date of death from any cause. Patients not reaching progression or death at the time of analysis will be censored at the last date they were known to be alive and progression free. Patients will be followed up for a minimum of 12 months.
- Overall survival time is defined as the time from date of registration to the date of death from any cause. Patients discontinuing the study, lost to follow-up or still alive at the end of the study will be censored at the date of last follow-up. Patients will be followed up for a minimum of 12 months. Duration of response is defined as the time from first documented response until relapse/progression, as determined by the Revised Response Criteria, or date of last follow up if relapse/progression free. Patients who die before a relapse/progression will be censored at their date of death.
- Maximum % decrease in the radiological SPD during the first 6 cycles will be assessed using the Revised Response Criteria for Malignant Lymphoma (Appendix 1) using the CT scan result collected at screening as a baseline value.

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. Biopsies at relapse will be requested in patients within the rituximab stage to assess for evidence of synergy and mechanisms of resistance. On treatment biopsies on day 15 cycle 1 will remain optional.

12.2 Analysis of Outcome Measures

- Best overall response will be reported as the number and proportion of patients in each response category, and overall, during the first 6 cycles of treatment. In addition, best response observed after 6 cycles until the end of the trial will be reported by category and overall.
- The number and proportion of patients experiencing toxicity, including haematological and non-haematological toxicity, will be reported with 95% confidence intervals.
- Time to event outcomes will be assessed using the method of Kaplan and Meier with point estimates presented at 6, 12, 24 and 36 months with 95% confidence intervals along with median survival time and confidence intervals. A Kaplan meier plot will be produced.
- The mean maximum % decrease during the first 6 cycles of treatment and overall will be reported with 95% confidence intervals

The biomarker study and PET scan analysis at present are exploratory.

There is little data on the expression of mTOR pathway proteins in DLBCL so the aim is to define expression in biopsy samples taken at relapse (or within 3 months). In collaboration with AstraZeneca, we will assess the expression of these proteins (p-S6, p-AKT, and p-4E-BP1*)* by immunohistochemistry (IHC). These will be measured at relapse, at subsequent progression, and in any tissue obtained at further optimal biopsy at 15 days. This will be initially assessed in 8 patients, with the potential to expand the analysis dependent on response data. We will then seek to determine a cut off which best predicts response to AZD2014, if indeed there is any correlation. Appropriate

statistical models (e.g. area under the curve, logistic regression) will be used to determine the cut off as detailed in the Statistical Analysis Plan.

Other ethically approved research may be performed on these samples if agreed by the trial management group.

All PET and CT scans will be centrally reviewed at St Thomas' using the 5-point scale for visual interpretation (Deauville Criteria and the Lugano classification). Semi-quantitative analysis will also be performed using the published value for ΔSUVmax $\geq$ 66% at 2 cycles to separate good from poor responders but receiver operating characteristic (ROC) curves will also be derived to determine if possible whether the optimal cut-off for patients treated with AZD2014 is similar to the cut-off for patients with DLBCL treated with (R)CHOP chemotherapy (35,38,39). Maximal standardized uptake value reduction is calculated as follows:

SUVmax reduction (%) = 100 x [SUVmax (PET0) - SUVmax (iPET)/SUVmax (PET screening)].

Standard contrast enhanced CT responses will classified according to the International Workshop Criteria (1).

12.3 Planned Sub Group Analyses

We are planning to analyse diffuse large B-cell lymphoma cases for cell of origin as studies suggest that mTOR-associated phosphoproteins are more highly expressed in the higher risk, non-GCB subtype; lymphoma-associated mutations (in collaboration with Dr Schuh and Dr Hamblin) and for markers of mTORC1/2 expression (in collaboration with AstraZeneca). This analysis would be conducted at the end of the trial and would be considered exploratory due to the lack of statistical power for subgroup analyses in this early phase trial. All patients will be assessed for cell of origin studies by gene expression profiling, and initially 8 patients will be assessed by AstraZeneca for activity of the mTORC1/2 pathway (p-S6, p-AKT, and p-4E-BP1). There is potential to expand this analysis depending on response rates seen.

12.4 Planned Interim Analysis

Interim analysis will take place after 15 patients. At least 10 of these patients must tolerate treatment for the trial to continue. This stopping rule is provided as guidance only and any decision to stop or continue will be based on a pragmatic assessment of all outcomes.

We also plan to review tolerability following recruitment of 3 patients to the combination treatment stage. If the toxicity profile is deemed tolerable by the trial Trial Safety Committee a further 3 patients will be recruited to the combination stage.

12.5 Planned Final Analyses

The first main analysis of the primary outcome measure will be performed after all patients have been treated and followed up for 6 cycles. Subsequent analyses of all outcome measures will be performed after a minimum of 12 months follow up of all patients.

12.6 Power Calculations

The sample size calculation is based on A'Hern's single stage phase II design. A total of 30 patients will be recruited in the main section of the study.

Activity

The treatment will be considered for further investigation if at least 9 responses are seen from the 30 patients. This results in 90% power to go forward if the underlying response rate is 40%, but only a 13% risk of going forward if the true response rate is 20% or less.

Toxicity

A Simon 2 stage design is proposed, using tolerability (i.e. opposite of toxicity) as the outcome.
A tolerability rate of 60% would not be acceptable, a tolerability rate of 80% would be.
The study would need to observe at least 10 'tolerable' outcomes (i.e. at most 5 toxicities that lead to treatment delays or dose modifications during the first 2 cycles) from the first 15 patients, and at least 21 'tolerable' outcomes (i.e. .at most 9 toxicities that lead to treatment delays or dose modifications

during the first 2 cycles) from the overall 30 to conclude that the treatment was tolerable at the current dose. This gives 90.4% power to conclude that treatment is tolerable when it is, but a 15.3% risk of concluding that the treatment is tolerable, when in fact it is not. If the treatment is too toxic then there is a 59.7% chance of stopping the trial at the halfway point.

For the combination stage at least 2 tolerable outcomes (i.e. at most 1 toxicity that leads to a treatment delay or dose modifications) during the first 2 cycles from the first 3 patients would need to be observed to continue recruitment. 4 tolerable outcomes (i.e. at most 2 toxicities that lead to treatment delays or dose modifications) are required during the first 2 cycles for the overall 6 to conclude that the combination treatment was tolerable at the current dose.

13. TRIAL ORGANISATIONAL STRUCTURE

13.1 Sponsor

The trial is sponsored by the University of Birmingham.

13.2 Coordinating Centre

The trial is being conducted under the auspices of the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham according to their local procedures.

13.3 Trial Management Group

A Trial Management Group (TMG) will be established and will include the Chief Investigator (Dr Graham Collins), the trial statistician and trial coordinators. Key trial personnel will be invited to join the TMG as appropriate to ensure representation from a range of professional groups. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the core TMG will be responsible for the day-to-day running and management of the trial and will meet by teleconference or in-person as required.

13.4 Trial Safety Committee

A Trial Safety Committee (TSC), with an independent chair, will provide overall supervision for the trial and provide advice through its independent chair.

Data analyses will be supplied in confidence to the TSC and the ultimate decision for the continuation of the trial lies with the TSC. The TSC will meet 6 months after the trial has opened or after 15 patients have completed 6 cycles of treatment and annually thereafter to monitor all safety and primary activity data until the end of the trial.

Additional meetings may be called if recruitment is much faster than anticipated and the TSC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The TSC will report directly to the TMG.

13.5 Finance

This is a clinician-initiated and clinician-led trial funded by the Bloodwise Trials Acceleration Programme (TAP). AZD2014 is being provided free of charge by AstraZeneca in addition to an unrestricted educational grant.
Payments to cover NHS research costs will be made as detailed in the Torch Clinical Trial Site Agreement.
This trial is also included in the NIHR CRN portfolio.,

This project is supported by the facilities funded through Birmingham Science City: Translational Medicine Clinical Research Infrastructure and Trials Platform, an Advantage West Midlands (AWM) funded project which forms part of the Science City University of Warwick and University of Birmingham Research Alliance.

The TORCH trial is endorsed by the National Cancer Research Institute (NCRI) High Grade Lymphoma Subgroup.

14. ETHICAL CONSIDERATIONS

The trial will be performed in accordance with the recommendations guiding physicians in biomedical research involving human subjects, adopted by the 18th World Medical Association General Assembly, Helsinki, Finland, June 1964, amended at the 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 (website: http://www.wma.net/en/30publications/10policies/b3/index.html).

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the Data Protection Act 1998 and Human Tissue Act 2008) and Good Clinical Practice (GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the main Research Ethics Committee (REC) prior to circulation.

Before any patients are enrolled into the trial, the Principal Investigator at each site is required to obtain local R&D approval. Sites will not be permitted to enrol patients until written confirmation of R&D approval is received by the Trials Office.

It is the responsibility of the Principal Investigator to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual patients.

15. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 1998. Patients will be identified using only their unique trial number, initials and year of birth on the Case Report Form and correspondence between the Trials Office and the participating site. However patients are asked to give permission for the Trials Office to be sent a copy of their signed ICF which will not be anonymised. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to the Trials Office (e.g. Patient Identification Logs) in strict confidence. In the case of specific issues and/or queries from the regulatory authorities, it will be necessary to have access to the complete trial records, provided that patient confidentiality is protected.

The Trials Office will maintain the confidentiality of all patient's data and will not disclose information by which patients may be identified to any third party other than those directly involved in the treatment of the patient and organisations for which the patient has given explicit consent for data transfer Representatives of the TORCH trial team may be required to have access to patient's notes for quality assurance purposes but patients should be reassured that their confidentiality will be respected at all times.

16. INSURANCE AND INDEMNITY

University of Birmingham employees are indemnified by the University insurers for negligent harm caused by the design or co-ordination of the clinical trials they undertake whilst in the University's employment.

In terms of liability at a site, NHS Trust and non-Trust hospitals have a duty to care for patients treated, whether or not the patient is taking part in a clinical trial. Compensation is therefore available via NHS indemnity in the event of clinical negligence having been proven.

The University of Birmingham is independent of any pharmaceutical company, and as such it is not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation.

17. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the TMG and authorship will be determined by mutual agreement.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of the University of Birmingham.

Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

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APPENDIX 1 – REVISED RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA

Revised Criteria for Response Assessment

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS‡	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Non-measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5‡ with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal

New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non-measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Non-measured lesions	None	New or clear progression of pre-existing nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (e.g., infection, inflammation). If uncertain	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis

	regarding etiology of new lesions, biopsy or interval scan may be considered	A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

- Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.
- ↵* A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid under treatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).
- ↵† PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

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APPENDIX 2 – POTENT OR MODERATE INHIBITORS OR INDUCERS OF CYP3A4/5, PGP (MDR1) AND BCRP

Cytochrome P450 and transporter inhibitor/inducer restrictions		
CYP/ Transporter Category	Drugs	Minimum drug wash-out period
CYP3A4/5Strong Competitive inhibitors	grapefruit juice, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, saquinovir, telithromycin and troleandomycin and voriconazole idelalisib	1 week 2 weeks
CYP3A4/5 Strong Time dependent inhibitors	boceprevir, clarithromycin, cobicistat, danoprevir, elvitegravir, LCL161 , lopinavir, mibefradil*, posaconazole, ritonavir, telaprevir and tipranivir	2 weeks
CYP3A4/5 Strong inhibitors (classification unknown)	conivaptan	1 week
CYP3A4/5 Moderate Competitive inhibitors	amprenavir, aprepitant, atazanavir, cimetidine, cyclosporine, fluconazole, imatinib and netupitant	1 week
CYP3A4/5 Moderate Time dependent inhibitors	ACT-178882, casopitant, crizotinib, darunavir, diltiazem erythromycin, ledipasvir, lomitapide, tofisopam and verapamil	2 weeks
	FK1706	half-life not found
CYP3A4/5 Moderate inhibitors (classification not known)	ciprofloxacin and dronedarone	1 week
	schisandra sphenanthera	half-life not found
CYP3A4/5 Strong inducers	carbamazepine, phenytoin, rifabutin, rifampicin and St. John's Wort	3 weeks
	enzalutamide and phenobarbital	5 weeks
	mitotane	114 weeks
	avasimibe	half-life not found

Cytochrome P450 and transporter inhibitor/inducer restrictions		
CYP/ Transporter Category	Drugs	Minimum drug wash-out period
CYP3A4/5 Moderate inducers	bosentan, genistein, lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat, , thioridazine and tipranavir	1 week
	etravirine	2 weeks
	efavirenz	3 weeks
	talviraline	half-life not found
Pgp (MDR1) inhibitors	dronedarone, erythromycin, indinavir, itraconazole, ketoconazole, lapatinib, lopinavir, ritonavir, quinidine and verapamil vorapaxer	1 week 10 weeks
	valspodar (PSC 833)	half-life not found
Pgp (MDR1) inducers	carbamazepine and rifampin	3 weeks
BCRP inhibitors	atazanavir, cyclosporine, lopinavir, ritonavir and tipranavir	1 week

APPENDIX 3 - SENSITIVE OR NARROW THERAPEUTIC RANGE IN VIVO SUBSTRATES OF THE DRUG TRANSPORTERSMATE, OATP & OCT

Transporter Substrate Restrictions

Transporters	Substrates
OATP (1B1 or 3)	bosentan, fexofenadine, glyburide, pitavastatin, pravastatin, **repaglinide**, rosuvastatin
MATE (1 or 2K)	cisplatin

Substrates in bold type have a narrow therapeutic index. Reference: Expert Opin. Drug Metab. Toxicol. (2013) 9(6):737-751. Washout periods should be 5 x reported terminal half-lives.

APPENDIX 4- WMA DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Recommendations guiding physicians
in biomedical research involving human subjects
Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfilment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration,

comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.

4. 4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

APPENDIX 5- DEFINITION OF ADVERSE EVENTS

Adverse Event

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Please note this does not include abnormal laboratory findings. An abnormal laboratory value is only considered to be an AE if the abnormality:

- Results in early discontinuation from the study treatment and/or
- Requires study drug dose modification or interruption, any other therapeutic intervention, or is judged to be of significant clinical importance
- Is Hyperglycaemia of > 1 week or if the investigator considers the rise in glucose to be medically significant

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded.

Pre-existing events should only be classified as AEs if they worsen by at least one grade from screening.

Adverse Reaction

All untoward and unintended responses to an IMP related to any dose administered.

Comment:

An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Serious Adverse Event

Any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening*
- Requires hospitalisation** or prolongation of existing inpatients' hospitalisation
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Or is otherwise considered medically significant by the Investigator***

Comments:

The term severe is often used to describe the intensity (severity) of a specific event. This is not the same as serious, which is based on patients/event outcome or action criteria.

* Life threatening in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an unplanned, formal inpatient admission, even if the hospitalisation is a precautionary measure for continued observation. Thus hospitalisation for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an SAE.

*** Medical judgment should be exercised in deciding whether an AE is serious in other situations. Important AEs that are not immediately life threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious.

Serious Adverse Reaction

An Adverse Reaction which also meets the definition of a Serious Adverse Event.

Suspected Unexpected Serious Adverse Reaction

A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.

A SUSAR should meet the definition of an AR, UAR and SAR.

Unexpected Adverse Reaction

An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).

When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.

Unexpected and Related Event

An event which meets the definition of both an Unexpected Event and a Related Event.

Unexpected Event

The type of event that is not listed in the protocol as an expected occurrence.

APPENDIX 6 - COMMON TOXICITY CRITERIA GRADINGS

Toxicities will be recorded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. The full CTCAE document is available on the National Cancer Institute (NCI) website, the following address was correct when this version of the protocol was approved:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

The CTCAE document is also provided in the Investigator Site File section 7.

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