TIDaL - Risk-stratified sequential Treatment with Ibrutinib and Rituximab (IR) and IR-CHOP for De-novo post-transplant Lymphoproliferative disorder (PTLD)

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TIDaL Trial Protocol v8.0 09-Nov-2018

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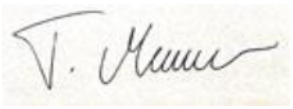
Signature:		**Date:**	09 / NOV /2018

This protocol describes the TIDaL trial and provides information about procedures for patients taking part in the TIDaL trial. The protocol should not be used as a guide for treatment of patients not taking part in the TIDaL 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
01	06-Oct-2016	3.0	Substantial	Update to inclusion criteria (section 4.1). Addition of MRI scans for CNS patients. Addition to state that dose banding is permitted (section 7.1). Update to treatment schedule re CNS patients (section 7.2). Update to dose modifications for non-haematological toxicity (section 7.5.2). Addition of aspergillosis information (section 7.5.5). Update to ibrutinib risk language (appendix 6). Additional concomitant medication information added (appendix 9).
04	19-Jan-2017	4.0	Substantial	'Lymph node' biopsy changed to 'tissue' biopsy throughout for consistency. Addition of 15mls research blood sample at baseline. Update to patient registration details. Change of prednisolone dose to 100mg.
06	24-Mar-2017	5.0	Substantial	Inclusion criteria update- creatinine clearance ≥ 30 mL/min. Update to dose delays- ibrutinib to be continued to end of cycle 4 day 21 (section 7.5). Recommendation that primary GCSF prophylaxis and co-trimoxazole prophylaxis be given with IR CHOP (section 7.7). Update to concomitant medication with doxorubicin and prednisolone (appendix 9).
07	27-Oct-2017	6.0	Substantial	Clarification that all brands of rituximab may be used in the trial (Section 7.1). Update to supportive treatment to make primary PCP prophylaxis with co-trimoxazole mandatory for all patients (Section 7.7), and for primary GCSF prophylaxis

				to be mandatory for all patients on the IR CHOP treatment arm (Sections 7.2, 7.5.2 and 7.7). Addition of cardiac arrhythmia and viral reactivation as specific adverse events (Sections 7.5.6 and 7.5.7). Clarification of Hepatitis B tests to be carried out at screening and for monitoring and management of reactivation (Schedule of Events and Sections 7.3.1 and 7.5.7). Removal of requirement for only highest grade AEs for each sign/symptom observed since last visit to be reported (Section 8.2.1.1).
09	17-Jul-2018	7.0	Substantial	Amended outcomes to explain that disease progression in the first seven weeks of treatment will be counted for EFS but not PFS (page 6 and Sections 2.2, 12.1 and 12.2). Clarification of the scheduling of assessments in cases of clinical progression in the first seven weeks of treatment (Schedule of Events and Section 3). Update to advice on the use of steroids throughout the trial (Section 7.7). Update to advice on concomitant medications that are prohibited or to be avoided (Section 7.8 and Appendices 7 and 8). Update to risk language (Appendix 6). Added overview of work to be carried out on tissue and blood samples (Section 7.4). Update to dosing of ibrutinib (including modifications). Clarification of cardiac monitoring for patients who have undergone a heart transplant.
10	08-Nov-2018	8.0	Substantial	Update of treatment regime for patients aged 65 years and over who are categorised as high risk, to omit ibrutinib and to commence R-CHOP only. Sections 14 and 15 updated to include General Data Protection Regulations.

TRIAL SYNOPSIS

Title

Risk-stratified sequential Treatment with Ibrutinib and Rituximab (IR) and IR-CHOP for De-novo post-transplant Lymphoproliferative disorder (PTLD).

Trial Design

This is a prospective, phase 2, single arm trial evaluating the addition of ibrutinib to rituximab (IR) therapy in patients diagnosed with PTLD. Patients will receive IR combination therapy for seven weeks, after which they will receive IR (if categorised as low risk) or IR-CHOP chemotherapy (if categorised as high risk).

Objectives

Primary objective

The primary objective is to evaluate complete remission (CR) after seven weeks of therapy.

Secondary objectives

The secondary objectives are to evaluate response, event-free survival (EFS), overall survival (OS), progression-free survival (PFS), treatment-related mortality, frequency of grade III and IV leucocytopenia and grade III and IV infections and patients entering into low and high risk arms after IR therapy.

Outcome Measures

Primary outcome measure

- Complete remission assessed after seven weeks of therapy and evaluated by interim CT scan.

Secondary outcome measures

- EFS with events defined as:
    - Treatment discontinuation due to toxicity
    - Disease progression (Note: Disease progression occurring during initial IR therapy is defined as an event)
    - Death
- Response (complete remission (CR), partial response (PR), stable disease (SD) and progressive disease (PD)) at interim staging and end of treatment staging
- OS, PFS and PFS post-initial IR therapy
- Treatment-related mortality
- Tolerability as defined in terms of absence of toxicities related to ibrutinib quantified by the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) (version 4)
- Dose interruptions, dose reductions or discontinuations
- Grade III and IV leucocytopenia and grade III and IV infections by treatment group
- Entry into low risk arm after IR therapy

Patient Population

Patients with CD-20 positive PTLD (with or without Epstein-Barr virus (EBV) association) following a solid organ transplant will be recruited to this trial. Patients with PTLD following allogeneic stem cell transplantation (ASCT) and those with meningeal or central nervous system (CNS) involvement will also be recruited, treated and followed-up in accordance with the protocol to collect data and outcomes on the feasibility of this approach in this group of patients.

Sample Size

Up to 60 patients will be recruited to the trial. 40 patients with PTLD following solid organ transplantation will be recruited. Patients with PTLD following ASCT and those with meningeal or CNS involvement will also be recruited for the duration that the trial is open to gather clinical outcome data in this group of patients. It is expected that this number of patients will not exceed 20 patients.

Main Inclusion and Exclusion Criteria

Inclusion criteria

- Untreated CD-20 positive PTLD with or without EBV association, confirmed after biopsy or resection of tumour (upfront reduction of immunosuppression with or without antiviral therapy is permissible)
- Measurable disease of >2.0 cm in diameter and/or bone marrow involvement
- Patients having undergone heart, lung, liver, kidney, pancreas, small intestine transplantation, or a combination of the above organ transplantations, or PTLD arising in patients > 6 months post allogeneic stem cell transplantation. PTLD with meningeal or CNS involvement can be included.
-
- Platelet count ≥100 x 10^9/L or ≥50 x 10^9/L if bone marrow involvement independent of transfusion support in either situation
- Absolute neutrophil count (ANC) ≥1 x 10^9/L, independent of growth factor support (GCSF)
- Adequate renal and hepatic function defined as the following:
    - Calculated creatinine clearance ≥ 30 mL/min
    - AST or ALT≤ 3.0 times the upper limit of normal (ULN) of the institution's normal range
    - Bilirubin ≤ 1.5 × ULN. Patients with known Gilbert's syndrome may have a bilirubin level > 1.5 × ULN*
    - Prothrombin time (PT) (or international normalised ratio (INR)) and partial thromboplastin time (PTT) not to exceed 1.2 times the ULN*
      *patients with abnormal bilirubin/PT/INR/PTT due to PTLD may be included in the study
- Left ventricular ejection fraction (LVEF) > 50% or report stating left ventricular function is satisfactory or normal
- ECOG performance score ≤ 2 (see Appendix 1)
- Age at least 16 years
- Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. These restrictions apply for 12 months after treatment discontinuation.
- Able to give written informed consent

Exclusion criteria

- Relapsed or refractory PTLD
- Complete surgical extirpation of the tumour or irradiation of residual tumour masses
- Treatment with rituximab, chemotherapy or antibody therapy for PTLD
- PTLD arising within 6 months of allogeneic stem cell transplantation
- Severe organ dysfunction not related to PTLD
- T-cell PTLD
- Patients requiring concomitant use of strong CYP3A4/5 inhibitors/inducers, including preparations containing St. John's Wort, or who have received anticoagulation treatment with warfarin or vitamin K antagonists within one week of registration
- Known to be HIV-positive

- Active hepatitis B or other severe, active infection which would preclude the patient from trial therapy in the clinical judgement of the treating Investigator
- Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study.
- Life expectancy less than 6 weeks
- Any contraindication to the IMPs according to the Summary of Product Characteristics (SmPC)

Trial Duration

Patients will be recruited over a 2 year period. Patients will receive approximately 5 months of therapy. All patients will be followed up for a minimum of 2 years.

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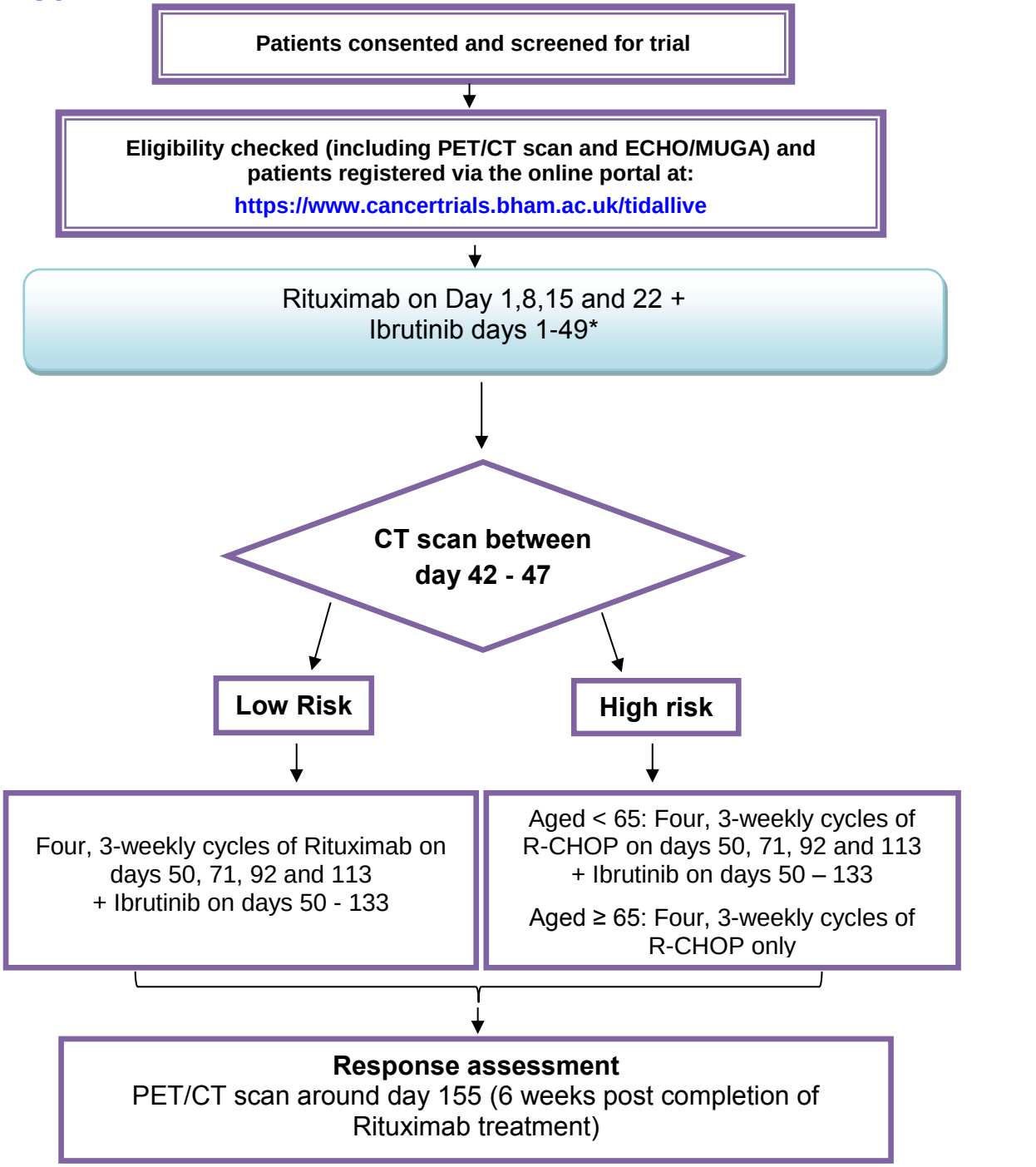
TRIAL SCHEMA



SCHEDULE OF EVENTS

Assessment	Screening (4 Weeks)	Ibrutinib/Rituximab (IR) phase					Cycle 1	Cycle 2	Cycle 3	Cycle 4	End of treatment follow-up	Post treatment follow up (every 4 months for 2 years)
		Day 1-49					Days 50-70	Days 71-91	Days 92-112	Days 113-133	Days 154-161	
		1	8	15	22	42-47†	50	71	92	113	154-161	
Demographic data, medical history, previous treatment	X											
Clinical assessment (height[1], weight, temperature, blood pressure, pulse, ECOG[1], physical exam)	X	X	X	X	X	X	X	X	X	X	X	X
Pregnancy Test (urine/serum)	X											
Laboratory tests – haematology & biochemistry[2]	X	X	X	X	X	X	X	X	X	X	X	X
HIV and hepatitis screen*	X											
EBV PCR	X					X					X	
ECG	X	If clinically indicated										
ECHO or MUGA	X[3]					X[4]			X[4]		X[4]	
Lung Function test[5]	X					X			X		X	
CT Scan (chest, abdomen, pelvis)[6]	X					X					X	X at 12 months
PET Scan	X										X	
MRI Scan[7]	X					X					X	
Tissue biopsy[8]	X											

Bone marrow aspirate and trephine[9]	X										X[7]	
Blood samples for research[10]	X		X		X		X				X	X
Rituximab administration		X	X	X	X		X	X	X	X		
Ibrutinib administration		Continuous 560mg daily D1 - 133										
CHOP administration (high risk patients only)							X	X	X	X		
Concomitant Medications		Continuous until 28 days after last administration of study drug										
Adverse Events		Continuous until 28 days after last administration of study drug										

[1] Height only performed pre-study; ECOG performed pre-study and day 42-47

[2] The following tests to be performed at each visit: Haematology - haematocrit, haemoglobin, red blood cell count, white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils, platelet count. Prothrombin time (PT) (or International normalised ratio (INR)) and partial thromboplastin time (PTT) at screening only). Biochemistry - albumin, ALP, ALT or AST, bicarbonate, calcium, creatinine, glucose, LDH, magnesium, potassium, sodium, total bilirubin, total protein, uric acid and urea. Tests prior to the start of a cycle should be performed within 1 day of starting the cycle. Other tests and treatment days can be performed +/- 3 days

[3] ECHO or MUGA results up to 3 months prior to the planned commencement of study therapy are acceptable, with the exception for heart transplant patients or patients with cardiac history. In these patients, an ECHO or MUGA test must be performed in the 4-week screening period

[4] Only to be arranged if clinically indicated; use either MUGA or ECHO as per local practice

[5] Only to be arranged if clinically indicated and a screening basic lung function test including FEV1 and FVC must be performed in patients with a lung transplant

[6] Contrast enhanced CT of chest, abdomen and pelvis (neck if indicated). PET/CT hybrid scanners may be used to acquire the required CT images only if the CT produced by the scanner is of diagnostic quality and includes the use of intravenous contrast. The CT scan will be performed at baseline (within 6 weeks of registration), after initial IR therapy between day 42-47 and 6 weeks after 8th dose of rituximab around day 155 or at treatment discontinuation, for whatever reason. CT scan will also be performed at 12 months follow up (+/- 2 weeks)

[7] For CNS patients only, an MRI is recommended but not mandated and should be performed as per local practice

[87] To be sent for central review (see section 7.4.1). Archival samples can be used if taken within the 6 months prior to registration

[9] Bone marrow aspirate and trephine to be reviewed as per local practice for involvement. Only to be performed at end of treatment if involved at baseline

[10] Up to 60mls peripheral blood at baseline, and up to 30mls at day 8, 22, 50, end of treatment, follow up and relapse if applicable (see section 7.4.2) will be sent to the University of Birmingham. Furthermore up to 15mls peripheral blood will be collected at baseline and sent to the Royal Victoria Hospital, Newcastle upon Tyne. Baseline samples can be collected on different visits provided they are collected pre-treatment.

* Hepatitis B screening must include Hepatitis B core antibody and Hepatitis B Surface Antigen. Patients with previous Hepatitis B infection should be managed and monitored to prevent Hepatitis B reactivation as per local guidelines throughout treatment and until 3 months post completion of therapy.

† In the case of clinical progression in the first seven weeks of IR therapy, patients should immediately commence IR-CHOP treatment. Interim assessments will be completed at the time of progression. The CT scan may be omitted at the discretion of the Investigator.

ABBREVIATIONS

ABC	Activated B-cell subtype
AE	Adverse event
BTK	Bruton tyrosine kinase
CHOP	Cyclophosphamide, doxorubicin, vincristine, prednisolone
CNS	Central nervous system
CR	Complete remission/response
DLBCL	Diffuse large B-cell lymphoma
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
FDG	Fluorodeoxyglucose
FEV1	Forced Expiratory Volume- one second
FVC	Forced Vital Capacity
GCB	Germinal centre B-cell subtype
IMP	Investigational medicinal product
INR	International normalised ratio
IPI	International Prognostic Index
IR	Ibrutinib + rituximab
IR-CHOP	Ibrutinib + rituximab + cyclophosphamide, doxorubicin, vincristine, prednisolone
IRR	Infusion relation reaction
ISF	Investigator Site File
LDH	Lactate Dehydrogenase
MRI	Magnetic Resonance Imaging
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
ORR	Overall response rate
OS	Overall survival
PCR	Polymerase chain reaction
PD	Progressive disease
PFS	Progression Free survival
PR	Partial remission/response
PS	Performance status
PT	Prothrombin time
PTT	Partial thromboplastin
PTLD	Post-transplant lymphoproliferative disorders
R-CHOP	Rituximab + cyclophosphamide, doxorubicin, vincristine, prednisolone
SAE	Serious adverse event
SAR	Serious adverse reaction
SD	Stable disease
SmPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
TLS	Tumour lysis syndrome
TRM	Treatment related mortality

TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE

1.1 Background

Post-transplant lymphoproliferative disorders (PTLD) are a heterogenous group of diseases and represent one of the most severe complications of solid organ and haematopoietic stem cell transplantation with an incidence rate of between 1% and 5%. The incidence varies significantly depending on the transplanted organ. For instance, kidney and liver transplants have a low incidence of approximately 0.5-1%, whereas lung and heart transplants have an incidence of around 5%. According to the NHS organ donation website in the financial year 2013/2014 more than 4600 organ transplants were performed in the UK with the following distribution: kidney transplants 3257, liver transplants 924, pancreas transplant 261, lung transplants 218, heart transplants 206 and several intestine transplants. Hence the expected annual incidence of PTLDs is roughly around 40-60 patients in the UK. The prognosis of PTLD is highly variable with mortality rates between 20-60% depending on the study published.

PTLDs include a series of disorders ranging from Epstein-Barr virus (EBV)-driven polyclonal proliferation to disorders indistinguishable from some B-cell lymphomas or, less often, T-cell lymphomas. They differ from lymphoma in the general population as approximately 60-80% of cases are associated with EBV infection and the majority has a diffuse large B-cell lymphoma (DLBCL) – like histology. In less than 20% of PTLD cases Burkitt's like, plasmablastic, T-cell and Hodgkin like morphology are documented. In contrast with the normal distribution in high-grade lymphomas, the ratio between germinal centre B-cell (GCB) and non-GCB cases is reversed: 60-70% of cases are of activated B-cell like (ABC) subtype. (Radeski et al *ASH* 2014) The World Health organisation distinguishes three types of morphological lesions assumed to represent different stages in the development of PTLD: benign polyclonal early lesions, polymorphic PTLD and malignant monoclonal or oligoclonal monomorphic PTLD. The first two forms often regress on reduction of immunosuppression whereas the monoclonal form typically doesn't. Therefore a multi-step model has developed postulating that monoclonal PTLD gradually arises from early and polymorphic lesions. For the EBV associated forms of PTLD the occurrence of early and polyclonal polymorphic lesions can occur due to reactivation of EBV after commencement of immunosuppression or due to aberrant response to EBV that was introduced by the solid organ transplant. Gradually some of the lesions will acquire somatic mutations leading to transformation into monomorphic PTLD. This model is supported by the fact that somatic mutations are frequently found in monomorphic PTLD but significantly less in the polymorphic PTLD lesions. Importantly most of the EBV-associated PTLDs have an ABC like subtype but interestingly carry very rarely mutations that target the B cell receptor and MYD88.

Currently the 2010 British Committee for Standards in Haematology (BCSH) guideline on managing PTLD recommends initial reduction in immunosuppressive therapy followed by rituximab monotherapy. For patients who do not respond within 8 weeks, the guideline recommends R-CHOP chemotherapy (Parker et al BJH 2010). This recommendation is based on several small studies together with a single major prospective PTLD study. Using a risk stratified approach in the European PTLD-1 trial and its 1/3 amendment (Trappe et al *Lancet Oncol* 2012 and Trappe et al *ASCO* 2012) all patients initially received 4 weekly doses of rituximab monotherapy followed by a CT scan around day 46. If the patient had achieved a CR (low risk arm) they received a further 4 doses of rituximab monotherapy. Patients who only achieved a PR or those who had clinically progressed during the initial 7 weeks (high risk arm), would go ahead with four 3-weekly courses of R-CHOP chemotherapy. The overall response rate (ORR) was 93% with a CR rate of 78%. Approximately 25% of patients achieved a CR after rituximab monotherapy. The 3 year overall survival rate was 70%. Treatment related mortality (TRM) remained high at around 8-10%, especially in the high risk cohort receiving CHOP based chemotherapy. Furthermore patients in the high risk arm, who only achieved PR as best ORR were very likely to progress over the next two years. In summary, the interim results of the PTLD – 1/3 study presented at ASCO 2012 have confirmed the feasibility and safety of this approach and hence have established the concept of using early response to rituximab monotherapy to stratify therapy in PTLD management.

The outlined risk stratified sequential treatment approach is regarded as the standard of care for patients with PTLD and is well established. In the PTLD 1 study, only patients who achieved CR were

regarded as low risk group and continued with rituximab monotherapy. 75% of patients went on to receive 4 cycles of R-CHOP chemotherapy subsequently increasing the risk of TRM. Based on UK observations (Burns et al *ASH* 2013) and further analysis from the PTLD 1 and 1/3 studies (Trappe et al. *Am J Transplant* 2015), it has become clear since then that PTLD patients with an initial low International Prognostic Index (IPI) of 0 to 1 have a good PFS and OS provided that they achieve partial remission after initial rituximab monotherapy. These observations suggest that it should be feasible to treat patients with low IPI, who achieve at least a partial remission after initial rituximab therapy in the low risk arm hence increasing the cohort, which can avoid R-CHOP based chemotherapy and consequently reducing TRM.

In the last few years several studies have confirmed that ibrutinib, a novel BTK inhibitor, has significant activity in a whole spectrum of lymphomas/lymphoproliferative disorders, especially in the management of relapsed chronic lymphocytic leukaemia (CLL) (Byrd et al *NEJM* 2013) and mantle cell lymphoma (MCL) (Wang et al *NEJM* 2013). Further, recent trials reported that ibrutinib combined with anti-CD20 monoclonal antibodies (CD20 mAbs) led to overall response rates (ORRs) of 95% and 100% in relapsed CLL patients (Burger et al *Lancet Oncol* 2014, Jaglowski et al *Blood* 2015), and an ORR of 87% in relapsed MCL patients (Wang et al ASH 2014) with significant increase of CR rates compared to historical single-agent ibrutinib data in similar patient cohorts, indicating complementary therapeutic effects from the 2 drugs. Importantly in all 3 trials the combination therapy with ibrutinib and rituximab showed a good safety profile.

Hence the main aim of the study is to introduce ibrutinib very early in combination with weekly rituximab. It is postulated that the addition of ibrutinib to initial rituximab monotherapy will increase the proportion of patients achieving CR and PR, thus making them eligible for the low risk chemo-free arm; this would reduce toxicity and TRM without worsening EFS and OS in this subgroup.

1.2 Trial Rationale

1.2.1 Justification for patient population

PTLDs represent one of the most severe complications of organ and stem cell transplantation. The expected annual incidence is currently approximately 40-60 patients in the UK. Over the last 10 years there has been no progress made in the management of patients with PTLD and a high percentage (30 – 50%) of patients will succumb to PTLD. The reasons for this are manifold: patients with solid organ transplant do not tolerate chemotherapy well resulting in an elevated treatment related mortality of up to 10% in some studies. Furthermore, many of the PTLD lymphomas have an ABC like subtype, a high grade lymphoma subtype, which has been shown to respond less well to R-CHOP chemotherapy. Hence it is important to develop effective new strategies - ideally non-chemotherapy based - to improve the overall response rate as well as the long-term PFS, EFS and OS. This trial is unique as it will be the first trial in PTLD to use ibrutinib. It will follow the design of the international PTLD I study with the important difference of giving continuous ibrutinib for 133 days. Using this strategy we hope to be able to rapidly recruit patients and complete the trial in a timely manner. The efficacy of ibrutinib in treating ABC type DLBCL and its low toxicity profile suggests that the addition of this agent will improve the treatment of this condition.

1.2.2 Justification for design

PTLD is a relatively rare disorder and hence to undertake a randomised trial comparing ibrutinib versus placebo is not realistic at a national level. At the moment no data exists on the use of ibrutinib in patients with PTLD. Hence a Simon's 2- stage design was selected with the aim to gather preliminary evidence of the activity of ibrutinib in the setting of PTLD and comparing the data obtained in this study with recent historical data.

The above outlined risk stratified sequential treatment approach is well tested in the setting of PTLD with very reproducible results and very recent major publications. Typically 20-25% of patients undergoing this treatment approach will achieve CR after 4 weekly doses of rituximab monotherapy. The primary objective of this study is to evaluate CR rate after 7 weeks of combination therapy. If ibrutinib is efficacious in this setting then it is anticipated that the combination of 4 weekly doses of rituximab and 7 weeks of daily ibrutinib will significantly increase the CR rate from 25% to 40%.

Hence a single arm phase II study was selected in order to determine evidence of activity in PTLD to further evaluate in a randomised phase 3 setting. A Simon's 2-stage design was selected to evaluate activity with stopping criteria given that ibrutinib has not been used in this disease. If this study shows a response (7 out of 24 responses), it will continue to the second stage. If a continued measure of activity (12 out of 38 CRs) is observed, the study will warrant further investigation in a larger, randomised international trial.

Secondary objectives are to evaluate overall response rate, overall survival, and progression free survival.

1.2.3 Choice of treatment

Further to the above mentioned studies two studies have demonstrated that ibrutinib has substantial activity against the ABC subtype of DLBCL. Thus in patients with relapsed DLBCL, ibrutinib monotherapy showed preferential activity against tumours with the ABC subtype with an overall response rate of 40% (Wilson et al ASH 2012). Further analysis of these patients have showed that ibrutinib shows activity in all forms of ABC subtype even if they lacked BCR mutations, thus suggesting that oncogenic BCR signalling in ABC subtype does not require BCR mutations and might be initiated by non-genetic mechanisms (Wilson et al *Nat Med* 2015). In combination with R-CHOP as first line therapy for DLBCL, the IR-CHOP combination achieved very good complete remission rates especially in the ABC subtype with no increase of acute toxicity (Younes et al *Lancet Oncol* 2012).

Justification for using ibrutinib in the setting of PTLD is based on our current understanding of pathogenesis of PTLD. Thus as already mentioned in the majority of patients with PTLD an ABC like subtype is present (Radeski et al *ASH* 2014). In the majority of EBV driven PTLD the ABC subtype is identified. Molecular studies have demonstrated that in EBV+ PTLD two major EBV oncoproteins LMP1 and LMP2 are expressed. LMP1 activates the NF-kB signalling, which has a pivotal role in the pathogenesis of the predominant ABC subtype in PTLD (Engels et al *Cell Comm Sign* 2012). LMP2A has been shown to mimic B-cell receptor signalling and requires BTK. In LMP2A transgenic animals mated to Btk deficient mice Btk was identified to be critical for the generation of two key aspects of LMP2A *in vivo* phenotype: the bypass of Ig heavy chain rearrangement and the upregulation of CD19 leading to severely decreased numbers in mature $CD19^+$, IgM^+ B cells due to increased cell death. (Merchant and Longnecker *Virol* 2001). Furthermore in EBV transformed lymphoplasmacytoid cell lines Btk is constitutively phosphorylated on tyrosines 223 and 551 (Merchant and Longnecker *Virol* 2001). In keeping with these observations available gene expression profiles of various PTLD subtypes confirm good expression levels of BTK (Morscio et al *Am J Trans* 2013). Hence ibrutinib as an inhibitor of NF-kB and B-cell receptor signalling should affect LMP1 and LMP2 function negatively and be an effective additional therapeutic option in PTLD.

2. AIMS, OBJECTIVES AND OUTCOME MEASURES

2.1 Aims and Objectives

Primary objective
The primary objective is to evaluate complete remission (CR) after seven weeks of therapy.

Secondary objectives
The secondary objectives are to evaluate response, event-free survival (EFS), overall survival (OS), progression-free survival (PFS), treatment-related mortality, frequency of grade III and IV leucocytopenia and grade III and IV infections and patients entering into low and high risk arms after IR therapy.

2.2 Outcome Measures

Primary outcome measure

- Complete remission assessed after seven weeks of therapy and evaluated by interim CT scan.

Secondary outcome measures

- EFS with events defined as:
    - Treatment discontinuation due to toxicity
    - Disease progression (Note: Disease progression occurring during initial IR therapy is defined as an event)
    - Death
- Response (complete remission (CR), partial response (PR), stable disease (SD) and progressive disease (PD)) at interim staging and end of treatment staging
- OS,PFS and PFS post-initial IR therapy
- Treatment-related mortality
- Tolerability as defined in terms of absence of toxicities related to ibrutinib quantified by the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) (version 4)
- Dose interruptions, dose reductions or discontinuations
- Grade III and IV leucocytopenia and grade III and IV infections by treatment group
- Entry into low risk arm after IR therapy

3. TRIAL DESIGN

This is a multicentre, single arm phase II trial. Patients meeting the eligibility criteria will be treated with ibrutinib + rituximab (IR), with or without chemotherapy in a risk-stratified approach that complements the European PTLD-1 trial. The factors determining the risk group will be IPI at initial presentation and response after initial therapy. Patients enrolled will initially receive four weekly doses of rituximab (375mg/m^2 i.v) (days 1, 8, 15 and 22) and daily ibrutinib (560 mg p.o.).

Interim response assessment will be performed by CT at approximately 7 weeks from initiation of therapy. Patients who achieve a CR on interim assessment and those who achieve a partial remission (PR) with initial IPI of 0-1 will be categorised as low risk and will continue to receive rituximab (4 further 3-weekly cycles) together with ibrutinib continuously until day 133. Patients deemed to fall into the high risk group will receive 4 cycles of R-CHOP-21 chemotherapy with continuous ibrutinib until day 133. Patients who clinically progress within the first seven weeks will be immediately commenced on the high risk arm. A CT scan to confirm disease progression in the first seven weeks of treatment is recommended but may be omitted at the discretion of the Investigator if other clinical indicators are present, for example enlarged lymph nodes. All patients will have response of treatment assessed by PET/CT scan 6 weeks after the last treatment has been received. Our hypothesis is that addition of ibrutinib to the risk-stratified approach used in the PTLD 1/3 study will significantly improve initial CR rate, overall response rate (ORR), EFS, PFS OS. It is expected that the addition of ibrutinib will not alter the toxicity of first line treatment of PTLD in the low or high risk arms.

4. ELIGIBILITY

4.1 Inclusion Criteria

Inclusion criteria

- Untreated CD-20 positive PTLD with or without EBV association, confirmed after biopsy or resection of tumour (upfront reduction of immunosuppression with or without antiviral therapy is permissible)
- Measurable disease of >2.0 cm in diameter and/or bone marrow involvement

- Patients having undergone heart, lung, liver, kidney, pancreas, small intestine transplantation, or a combination of the above organ transplantations or PTLD arising in patients > 6 months post allogeneic stem cell transplantation. PTLD with meningeal or CNS involvement can be included.
- Platelet count ≥100 x 10^9/L or ≥50 x 10^9/L if bone marrow involvement independent of transfusion support in either situation
- Absolute neutrophil count (ANC) ≥1 x 10^9/L, independent of growth factor support (GCSF)
- Adequate renal and hepatic function defined as the following:
    - Calculated creatinine clearance ≥ 30 mL/min
    - AST or ALT≤ 3.0 times the upper limit of normal (ULN) of the institution's normal range
    - Bilirubin ≤ 1.5 × ULN. Patients with known Gilbert's syndrome may have a bilirubin level > 1.5 × ULN*
    - Prothrombin time (PT) (or international normalised ratio (INR)) and partial thromboplastin time (PTT) not to exceed 1.2 times the ULN*
      *patients with abnormal bilirubin/PT/INR/PTT due to PTLD may be included in the study
- Left ventricular ejection fraction (LVEF) > 50% or report stating left ventricular function is satisfactory or normal
- ECOG performance score ≤ 2 (see Appendix 1)
- Age at least 16 years
- Women of childbearing potential and men who are sexually active must be practicing a highly effective method of birth control during and after the study consistent with local regulations regarding the use of birth control methods for subjects participating in clinical trials. Men must agree to not donate sperm during and after the study. These restrictions apply for 12 months after treatment discontinuation.
- Able to give written informed consent

4.2 Exclusion Criteria

Exclusion criteria

- Relapsed or refractory PTLD
- Complete surgical extirpation of the tumour or irradiation of residual tumour masses
- Treatment with rituximab, chemotherapy or antibody therapy for PTLD
- PTLD arising within 6 months of allogeneic stem cell transplantation
- Severe organ dysfunction not related to PTLD
- T-cell PTLD
- Patients requiring concomitant use of strong CYP3A4/5 inhibitors/inducers, including preparations containing St. John's Wort or who have received anticoagulation treatment with warfarin or vitamin K antagonists within one week of registration
- Known to be HIV-positive
- Active hepatitis B or other severe, active infection which would preclude the patient from trial therapy in the clinical judgement of the treating Investigator
- Women of childbearing potential must have a negative serum (beta-human chorionic gonadotropin [β-hCG]) or urine pregnancy test at Screening. Women who are pregnant or breastfeeding are ineligible for this study.
- Life expectancy less than 6 weeks
- Any contraindication to the IMPs according to the Summary of Product Characteristics (SmPC)

5. SCREENING AND CONSENT

5.1 Screening

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. date of birth and gender), the date and outcome of the screening process (e.g. enrolled into study, reason for ineligibility, or refused to participate).

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. If informed consent is given (see section 5.2), the Investigator will conduct a full screening evaluation within four weeks prior to registration 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 schedule of assessments and detailed in section 7.2.

5.2 Informed Consent

It is the responsibility of the Investigator to obtain written informed consent for each patient prior to performing any trial related procedure. A Patient Information Sheet is provided to facilitate this process. Investigators must ensure that they adequately explain the aim, trial treatment, possible 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 Patient Information Sheet 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. The Investigator must then sign and date the form. A copy of the Informed Consent Form 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 Informed Consent Form maintained in the ISF. In addition, if the patient has given explicit consent a copy of the signed Informed Consent Form must be sent in the post to the Trial 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 Patient Information Sheet and Informed Consent Form. 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 Patient Information Sheet and Informed Consent Form are available from the Trial 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.

6. TRIAL ENTRY

Patients must be registered with the Cancer Research UK Clinical Trials Unit (CRCTU) at the University of Birmingham. Patients can be registered via the online portal at:

https://www.cancertrials.bham.ac.uk/tidallive

Or by telephone during office hours (9-5pm, Monday-Friday) on 0121 371 4365.

7. TREATMENT DETAILS

7.1 Trial Treatment

Investigational Medicinal Product information
Ibrutinib, rituximab*, cyclophosphamide, doxorubicin, vincristine and prednisolone (collectively called 'CHOP' chemotherapy) are all classed as Investigational Medicinal Products (IMPs) in this study. Ibrutinib will be provided free of charge by Janssen LLC for up to day 133 and will be packaged and labelled according to UK regulations including Annex 13 requirements (for Clinical Trials Use Only). Once received the trial specific ibrutinib should be kept at controlled room temperature (15°C - 25°C) and ring-fenced within a secure pharmacy location. Ibrutinib capsules will come packaged with 120 capsules/bottle. All other IMPs will be obtained from local hospital stocks. Refer to the pharmacy manual for further information.

Dose banding is permitted as per Nationally Standardised Dose Banding Adult Intravenous Systemic Anticancer Therapy (SACT) Recommendations.

* Truxima, Rixathon or MabThera may be used.

Ibrutinib
All patients will receive up to 133 days of ibrutinib oral monotherapy 560mg (4 x 140mg capsules) to be taken once daily from registration.

The capsules are to be taken around the same time each day (at least 30 minutes before or 2 hours after food) with 8 ounces (approximately 240 mL) of water. The capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water.

Patients who have a delay in administration of a dose of the study drug of <6 hours should take the planned dose as soon as possible after the intended time of administration. If the delay in administration of study drug is ≥6 hours, the dose should be skipped. Study drug administration may continue the next day at the usual time but the missed dose should not be made up. Vomited ibrutinib doses may be retaken, but only if the capsule is visible in the vomit.

If a patient experiences an ibrutinib overdose, consideration should be given as to whether ibrutinib administration should be temporarily interrupted. If the overdose ingestion is recent and substantial, use of gastric lavage or induction of emesis may be considered. Observation for any symptomatic side effects should be instituted, and biochemical and haematological parameters should be followed closely. Appropriate supportive management to mitigate adverse effects should be initiated.

Non-Investigational Medicinal Products

Co-trimoxazole (or alternative PCP prophylaxis) and GSCF are classed as Non-Investigational Medicinal Products (NIMPs).

7.2 Treatment Schedule

Initial IR therapy (7-week cycle)
Patients will initially start on a 7-week long cycle combining ibrutinib and rituximab. To commence the cycle, neutrophils need to be ≥1 x 10^9/L and platelets ≥100 x 10^9/L or ≥50 x 10^9/L if bone marrow involvement independent of transfusion support in either situation.

Ibrutinib, rituximab therapy (IR7)

Drug	Dose	Route of administration	Days of cycle
Ibrutinib	**560mg**	Oral	Days 1-49
Rituximab	**375mg/m^2**	Intravenous	Days 1, 8, 15 and 22

At day 42-47 of this cycle a CT scan will be performed. The CT scans will be reported according to the Lugano classification (Cheson et al *JCO* 2014 and Appendix 3)

- **Low risk arm:**
  If the patient is in CR or has a low IPI of 0 or 1 (see Appendix 2) and has achieved a PR then the patient will be classified as low risk and will continue with a further four 3-weekly cycles of ibrutinib/rituximab.

- **High Risk arm**
  If the patient has achieved only partial remission with an IPI of 2-5 (see Appendix 2) or has stable disease or progressive disease then the patient will be classified as high risk. Those aged below 65 years will receive four 3-weekly cycles of IR-CHOP. Patients aged ≥ 65 years will receive four 3-weekly cycles of R-CHOP only. Any patient, who has clinical progressive disease during the initial 7-week IR therapy will be classified as high risk and will commence four cycles of 3-weekly IR-CHOP (if <65 years)/R-CHOP (if ≥ 65 years) immediately.

For CNS patients categorised as high-risk, it is the discretion of the local Investigator whether they commence IR-CHOP or discontinue treatment.

Low risk arm Cycle 1-4 (3-week cycle)
To commence the cycle neutrophils need to be ≥1 x 10^9/L and platelets ≥ 30 x 10^9/L independent of transfusion support in either situation. Patients who do not meet these criteria should be reassessed weekly for a further two weeks. If counts do not recover after this period, patients should discontinue treatment.

Ibrutinib, rituximab therapy (IR3)

Drug	Dose	Route of administration	Days of cycle
Ibrutinib	**560mg**	Oral	Days 1 - 21
Rituximab	**375mg/m^2**	Intravenous	Days 1

Patients will be treated with IR every 21 days (1 cycle) for a total of 4 cycles.

High risk arm Cycle 1-4 (3-week cycle)
To commence each cycle neutrophils need to be ≥1 x 10^9/L and platelets ≥ 75 x 10^9/L or ≥ 50 x 10^9/L if bone marrow involvement independent of transfusion support in either situation. Patients who do not meet these criteria should be reassessed weekly for a further two weeks. If counts do not recover after this period, patients should discontinue treatment. **Patients aged 65 years or older at the time of being categorised as high risk must receive R-CHOP only and omit ibrutinib therapy.**

Ibrutinib, rituximab + CHOP therapy (IR-CHOP)

Drug	Dose		Route of administration	Days of cycle
Ibrutinib	**Patients ≤ 64 years of age**	**560mg**	Oral	Days 1-21
	Patients ≥ 65 years of age	**N/A**		
Rituximab	**375mg/m^2**		Intravenous	Days 1
Cyclophosphamide	**750mg/m^2**		Intravenous	Days 1
Doxorubicin	**50mg/m^2**		Intravenous	Days 1
Vincristine*	**1.4mg/m^2**		Intravenous	Days 1
Prednisolone	**100mg**		Oral	Days 1 - 5

* Note maximum dose of vincristine is 2mg

Patients will be treated with IR-CHOP/R-CHOP every 21 days (1 cycle) for a total of 4 cycles.

The treatment of participants with a BSA > 2.2m^2 should be as per your local policy.

Anthracycline dose reduction or omission is permissible in heart transplant patients if deemed to be clinically necessary.

At the end of the treatment schedule patients can continue to take any remaining ibrutinib capsules until they have completed the bottle, at the discretion of the Investigator.

7.3 Assessments

7.3.1 Baseline assessments

All baseline assessments should be performed within four weeks of registration (baseline PET/CT is acceptable within six weeks). Baseline assessments include demographic data and previous medical history, clinical assessment (including height, weight, temperature, blood pressure, pulse, ECOG performance score and physical examination (if clinically indicated)). Females of child-bearing potential must have a serum/urine pregnancy test performed within four weeks of registration (ideally performed within one week prior to registration). All patients must have haematology and biochemistry tests (specific tests outlined in schedule of assessments table), HIV and hepatitis screen (must include Hepatitis B core antibody and Hepatitis B surface antigen tests), and EBV PCR.

All patients must have a 12-lead electrocardiogram (ECG) performed at baseline and ECHO or MUGA (depending on local practice) to evaluate heart function. Patients who have had a lung transplant or if it is clinically indicated must have a lung function test performed at baseline.

Baseline disease assessments include a CT scan (chest, abdomen, pelvis and neck if indicated), PET scan, tissue biopsy (to be sent to Central Laboratory) and bone marrow aspirate and trephine. Blood samples will also be collected for research purposes.

7.3.2 Haematology

A full blood count including haematocrit, haemoglobin, red blood cell count, white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils and platelet count will be measured as part of screening, at every trial visit and at any time if the patient presents with new symptoms. PT (or INR) and PTT should be performed at screening only and subsequently if clinically indicated. For study subjects with values lower than these, treatment will be delayed according to dose delay/reduction rules defined in the Dose Modifications section (see section 7.5).

7.3.3 Biochemistry

Albumin, ALP, ALT or AST, bicarbonate, calcium, creatinine, glucose, LDH, magnesium, potassium, sodium, total bilirubin, total protein, uric acid and urea will be measured as part of screening, at every trial visit and at any time if the patient presents with new symptoms. There are no specific renal or hepatic biochemical abnormalities known to be associated with ibrutinib but if these develop they should be discussed with the TIDaL Trial office.

Patients with a large tumour burden and/or renal impairment may develop TLS after the first dose of ibrutinib and rituximab and in these cases biochemistry to include urate should be measured 12 hourly for at least 48 hours. A specific management plan to avoid TLS in high risk cases should also be implemented in these cases (see section 7.5.4)

7.3.4 Organ function monitoring

If the baseline ECG raises any issues, a further ECG should be performed at one month and the patient should be monitored as clinically indicated as per the standard of care.

For patients with a heart transplant, or if clinically indicated, echocardiograms or MUGA testing (after initial IR therapy, at day 92 and at end of treatment) may be undertaken to assess ejection fraction. Close monitoring of cardiac function is advised if the patient is commenced on IR-CHOP and close collaboration with the cardiac transplant team is expected.

For patients with a lung transplant, or if clinically indicated, regular lung function testing (after initial IR therapy, at day 92 and at end of treatment) may be undertaken to assess FEV1 and FVC. Close collaboration with the pulmonary transplant team is expected.

7.3.5 Response assessment

Assessment of clinical response to IR +/- CHOP will take place on a cycle by cycle basis. A decision to continue in the low risk arm after initial 7 weeks of IR therapy or to escalate to high risk arm will be made on the basis of the locally reported CT scan performed between day 42-47 using the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification as defined in Appendix 3.

A PET/CT scan will be performed at the end of treatment 6 weeks after last dose of rituximab to assess overall response rate.

An end of study CT scan (unless already performed within the preceding 6 weeks), full blood count and biochemical profile will be performed for all patients after the termination of study treatment.
Where progressive disease is identified on clinical grounds and/or by imaging a confirmatory tissue biopsy is recommended but not required.

7.3.6 PET-CT scans

PET/CT scan are required during screening and at 6 weeks post completion of 8th dose of rituximab. Scans should be conducted within the window as stated in the manual and reported according to the Deauville/London criteria (Appendix 4).

7.3.7 CT scans

IV contrast-enhanced CT scans will be performed at baseline, after initial IR therapy between day 42-47 and post treatment (around day 155) or at study exit for whatever reason. The chest, abdomen and

pelvis (and neck if indicated) should be scanned, in order to report to the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Cheson et al *JCO* 2014) (see Appendix 3). It is recommended that if possible these scans be performed on the same days as the study PET scans to reduce patient visits.

7.3.8 MRI scans

MRI scans will be performed for CNS patients only at baseline, after initial IR therapy between day 42-47 and post treatment (around day 155). MRI scans are recommended but not mandated and should be performed as per local practice.

7.4 Sample Collection

7.4.1 Tissue biopsy

Immunohistochemical, transcriptomic and genomic testing of tissue samples will examine EBV status, characterise the neoplastic cells and their microenvironment and identify mutations potentially associated with ibrutinib response.

All tissue samples will be centrally reviewed by two expert haematopathologists. Formalin fixed paraffin embedded diagnostic material (collected within 6 months prior to registration) will be sent to the Royal Victoria Hospital, Newcastle upon Tyne for central review of histology to confirm histological diagnosis and classification according to the WHO classification and EBV status. Samples will be forwarded to the University of Birmingham for immunology work and the Queen Elizabeth Hospital Birmingham for further analysis of patient eligibility if deemed necessary.

7.4.2 Blood samples

Blood samples will be collected to analyse the effects of ibrutinib and rituximab therapy on the immune system and to comprehensively examine the genetic, viral and immunological drivers of PTLD occurring post solid organ transplant.

Blood samples will be taken prior to the start of treatment, at days 8, 22 and 50, at the end of study treatment, every 4 months during 2 year follow up and at suspected relapse, if applicable.

University of Birmingham samples
Up to 60mls fresh peripheral blood at baseline and up to 30mls at all other time points. Samples should be sent in Sodium Heparin tubes (Lithium heparin if unavailable)

Royal Victoria Hospital samples
Up to 15mls fresh peripheral blood will be collected at baseline. Samples should be sent in EDTA tubes.

Baseline samples for the University of Birmingham and the Royal Victoria Hospital can be collected on different visits provided they are collected pre-treatment. All samples should be sent via Royal Mail Special Delivery safe boxes provided by the Trial Office. Samples should be collected in accordance with the Sample Collection Guidelines.

7.5 Dose Modifications

Dose reductions for rituximab should be in line with the current version of the SmPC for rituximab.

All patients should also be monitored for toxicity including infusion related reaction (IRR) (see Appendix 5 for guidance), TLS, progressive multifocal leukoencephalopathy; infections; Stevens-Johnson syndrome; hyperglycaemia; renal and hepatic impairment; cardiac toxicity. Special

precautions for use relating to these conditions and guidance for appropriate action are also made in the SmPCs.

The following have been reported with ibrutinib and modifications should be made as described below if the toxicity is deemed by the Investigator to be treatment related:
The most commonly occurring adverse drug reactions of ibrutinib (≥ 20%) were neutropenia, anaemia, diarrhoea, musculoskeletal pain, upper respiratory tract infection, bruising, rash, nausea and pyrexia. The most common grade 3/4 adverse drug reactions (≥ 5%) were anaemia, neutropenia, pneumonia and thrombocytopenia. See Appendix 6 for ibrutinib risk language.

7.5.1 Management of toxicity of ibrutinib + rituximab (IR) – delays and dose reductions

Infusion related adverse reactions (rituximab only)

Halve the speed of infusion if the following adverse events occur (see the current version of the SmPC for rituximab):

- Fevers > 38.5C
- Chills – mild, moderate
- Mucosal swelling – mild, moderate
- Hypotension (drop in systolic BP) > 30mmHg

Dose Delay, Reduction and Discontinuation

The actions in the table below should be taken for the following toxicities:

- Grade 3 neutropenia (<1.0 x 10^9/L) with infection and/or fever (GCSF is permitted and use must be recorded in CRF)
- Grade 3 or 4 nausea, vomiting, or diarrhoea, if persistent despite optimal antiemetic and/or anti-diarrhoeal therapy
- Any Grade 3 or greater non-haematological toxicity related to ibrutinib
- Any platelet count <30 x 10^9/L
- Any other Grade 4 haematological toxicity

Drug Discontinuation Actions for Ibrutinib (patients receiving 560mg ibrutinib daily):

Occurrence	Action
1st	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; may restart at original dose level
2nd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart at one dose level lower (420 mg daily)
3rd	Hold ibrutinib until recovery to Grade ≤ 1 or baseline; restart a further dose level lower (280 mg daily)
4th	Discontinue ibrutinib

Where ibrutinib is withheld it is permissible, at the discretion of the local Investigator, to continue rituximab.

Any other clinically important events where dose delays may be considered appropriate by the investigator must be discussed with the Chief Investigator or Co-Investigator. Any situations where dose delays or reductions, as detailed above, are not considered appropriate must be discussed with the Chief Investigator or Co-Investigator.

Study drug may be held for a maximum of 28 consecutive days for toxicity. Study treatment should be discontinued in the event of a toxicity lasting >28 days, unless reviewed or approved by the Chief Investigator or Co-Investigator.

Dose modifications of ibrutinib may be indicated in the event of co-administration of CY3A4/5 inhibitors (see Section 7.8). Dose changes must be recorded on the relevant CRF.

Dose re-escalation
If the participant has tolerated the lower dose of ibrutinib for 2 months following a dose reduction, as outlined in Section 10.7.2 then the dose should be re-escalated by one dose level.

If the participant has further toxicities following a dose re-escalation the lower dose should be continued for the duration of ibrutinib treatment.

Dose changes must be recorded on the relevant CRF.

7.5.2 Management of toxicity of CHOP – Delays and Dose Reductions

Haematological toxicity

Neutropenia
If neutropenia develops during treatment it should be managed by dose delays. See Table below for appropriate dosing recommendations.

Problem	Solution
Neutrophils <1×10^9/l on day treatment due	Delay cycle one or two weeks. If count has not recovered after 14 days, CHOP will be stopped
Grade 4 neutropenia leading to infection despite G-CSF support	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Grade 4 neutropenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	**Stop CHOP**

Thrombocytopenia
If thrombocytopenia develops during treatment it should be managed by dose delays. See Table below for appropriate dosing recommendations.

Problem	Solution
Platelets <75×10^9/l on day treatment due (or <50×10^9/l if bone marrow involvement)	Delay cycle one or two weeks. If count has not recovered after 14 days CHOP will be stopped
Grade 3 or 4 thrombocytopenia following any cycle of CHOP	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Grade 3 or 4 thrombocytopenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	**Stop CHOP**

In the case of treatment delays for cycles of rituximab or R-CHOP, ibrutinib can continue to the end of cycle 4 (day 21).

Other non-haematological toxicities
If grade >=2 motor or grade >=3 sensory neurological toxicity to vincristine appears, the dose will be decreased to 1mg per cycle. If the neurological toxicity increases despite dose reduction, vincristine will be stopped.

Dose reduction of individual medications can be considered if other toxicities such as severe mucositis occur, as per usual local practice. Dose reductions for hepatic or renal impairment should be according to local policy.

In cases of intolerable non-haematological toxicity attributable to CHOP, rituximab and ibrutinib can be continued.

Important: If R-CHOP needs to be delayed, please continue with ibrutinib as long as criteria not met to delay ibrutinib.

7.5.3 Progressive Multifocal Leukoencephalopathy

Patients should be closely monitored for new or worsening neurological, cognitive or behavioural signs or symptoms which may be suggestive of PML. Rituximab dosing should be interrupted for any suspected case of PML.
Suggested evaluation of PML includes neurology consultation, gadolinium-enhanced magnetic resonance imaging of the brain and cerebrospinal fluid analysis for JCV DNA by polymerase chain reaction (PCR) or a brain biopsy with evidence of JCV. A negative JCV PCR does not exclude PML. Additional follow up and evaluation may be warranted if no alternative diagnosis can be established. Rituximab dosing should be permanently discontinued if a diagnosis of PML is confirmed.

7.5.4 Tumour Lysis Syndrome (TLS)

TLS has been reported with R-CHOP and in those treated with ibrutinib. Patients with rapidly proliferating tumour and high tumour burden are at risk of 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.

7.5.5 Aspergillosis

Aspergillosis has been reported in CNS lymphoma patients treated with ibrutinib. To date 6 cases of systemic aspergillosis, including 3 fatal cases, have been reported across 3 clinical studies. All patients with CNS lymphoma should be closely monitored for aspergillosis. If clinically indicated, patients with a clinical history of aspergillosis, high risk for new aspergillosis infections, or with clinical symptoms which may suggest a pulmonary or CNS aspergillosis infection should undergo a rigorous infectious workup. Consider the usage of aspergillosis prophylaxis if clinically appropriate; this may require an ibrutinib dose-adjustment based on the usage of strong and moderate CYP3A inhibitors (see section 7.8.1).

7.5.6 Cardiac arrhythmia

Atrial fibrillation, atrial flutter and cases of ventricular tachyarrhythmia have been reported in patients treated with ibrutinib. Cases of atrial fibrillation and atrial flutter have been reported particularly in patients with cardiac risk factors, hypertension, acute infections, and a previous history of atrial fibrillation. All patients should be periodically monitored for cardiac arrhythmia. Patients who develop arrhythmic symptoms or new onset of dyspnoea, dizziness or fainting should be evaluated clinically and if indicated have an ECG performed.

In patients who develop signs and/or symptoms of ventricular tachyarrhythmia, ibrutinib should be temporarily discontinued and a thorough clinical benefit/risk assessment should be performed before possibly restarting therapy.

7.5.7 Viral reactivation

Cases of hepatitis B reactivation have been reported in patients receiving ibrutinib. HBV status should be established before initiating treatment with ibrutinib. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended. If patients have positive hepatitis B serology, a liver disease expert should be consulted before the start of treatment and the patient should be monitored and managed following local medical standards to prevent hepatitis B reactivation until 3 months post completion of treatment.

7.5.8 Scleroderma renal crisis

Caution is required in patients with systemic sclerosis because of an increased incidence of (possibly fatal) scleroderma renal crisis with hypertension and decreased urinary output observed with a daily dose of 15 mg or more prednisolone. Blood pressure and renal function (s-creatinine) should therefore be routinely checked. When renal crisis is suspected, blood pressure should be carefully controlled.

7.6 Treatment Compliance

The local trial pharmacist will be responsible for maintaining and updating the drug accountability log in the TIDaL pharmacy file which will be used to monitor compliance. All unfinished bottles will be returned to the trial pharmacist who will count and document any unused medication. All IMP can then be destroyed in accordance with local pharmacy practice and this will be documented on the drug destruction log in the hospital pharmacy file.

In addition, patients will be issued with a Patient Diary at the beginning of each cycle. Patients will be asked to complete the diary, recording the time that each dose was taken, and whether any doses were missed. The diary also includes a section where the patient can record any relevant information such as side effects suffered or reasons for missed doses. The completed diary will be reviewed by the site at clinic visits and returned to the Trial Office. The Patient Diary will also remind patients to tell their doctor if they are receiving any other medications.

7.7 Supportive Treatment

All general supportive care measures, including red cell transfusions to alleviate disease related symptoms and treatment toxicities are allowed at the Investigators discretion. **Only irradiated blood products are recommended for study patients.**

Haematopoetic growth factors can be used at Investigator discretion as primary prophylaxis and should be used as secondary prophylaxis following the first episode of grade 3 or 4 neutropenia at any time and/or the first episode of neutropenic sepsis according to the Neutropenia Delays and Dose Reduction guidelines (see section 7.5.2). All patients must be given primary PCP prophylaxis with co-trimoxazole (960mg Mon, Wed and Fri or as per local policy) from Day 1 of ibrutinib treatment until three months after the final dose of ibrutinib. Patients unable to take co-trimoxazole (e.g., in the event of an allergy to co-trimoxazole) must be given alternative PCP prophylaxis. GCSF prophylaxis should be given as per local policy to all patients receiving IR CHOP.

Prednisolone, up to and including a maximum dose of 100mg daily up to 7 days (or equivalent steroid dose), is permitted prior to commencement of trial medication. If patients are on low dose prednisolone as part of their immunosuppressive therapy, then this dose can be maintained during treatment. The Chief Investigator or Clinical Coordinator must be consulted before commencing a patient on steroid treatment at any other point during the trial. Co-medication with allopurinol and lansoprazole prophylaxis should be considered for patients receiving IR-CHOP. Antifungal prophylaxis with azoles should be avoided as they are moderate to strong CYP3A4/5 inhibitors (See section 7.8).

Patients with bulky disease and/or renal impairment may be at risk of developing TLS following the first cycle of IR and TLS prophylaxis should be considered according to local guidelines and as suggested in section 7.5.4.

7.8 Concomitant Medication

For a comprehensive list of medications that are prohibited or to be avoided throughout the trial, see Appendix 7.

7.8.1 CYP3A4/5 Inhibiting/Inducing Drug

Concomitant use of strong and moderate CYP3A4/5 inhibitors should be avoided while the patient is receiving treatment. Grapefruit juices and Seville oranges (including marmalade), and their juices, pomelos, star fruit should also be avoided. St.John's Wort and preparations containing it must not be taken whilst on ibrutinib. If use of a strong CYP3A4/5 inhibitor is indicated, selection of an alternate concomitant medication with less potent enzyme inhibition potential is strongly recommended.

If ibrutinib must be administered with a strong or moderate CYP3A4/5 inhibitor, the Chief Investigator or a clinical Co-Investigator should be consulted before the use, and a dose reduction of ibrutinib to 140 mg daily or temporary hold of ibrutinib should be considered. Patients should be closely monitored for potential treatment-related toxicities.

Co-administration of ibrutinib with strong CYP3A4/5 inducers may decrease ibrutinib plasma concentrations and should be avoided. A list of CYP3A4/5 inhibitors or inducers is provided in Appendix 7;

7.8.2 Anticoagulants and anti-platelet drugs

Warfarin, or equivalent vitamin K inhibitors, should not be given concomitantly whilst the participant is receiving ibrutinib. For participants requiring anticoagulant therapy, an alternative such as LMW heparin should be considered instead and ibrutinib should be interrupted until a stable dose of the alternative anticoagulant has been established. No dose reduction is required when study treatment is re-started. Supplements such as fish oil and vitamin E preparations should be avoided.
Anti-platelet drugs can be used with ibrutinib but can be associated with increased bruising and bleeding. Therefore patients on these agents should be monitored for any significant change in bruising or bleeding.

7.8.3 Surgery whilst receiving ibrutinib

For any surgery or invasive procedure requiring sutures or staples for closure, ibrutinib should be stopped for at least 7 days prior to the intervention and not be restarted for at least 7 days after the procedure. Ibrutinib should be restarted at the discretion of the Investigator when the surgical site is reasonably healed without serosanguinous drainage or the need for drainage tubes.

For minor procedures (i.e. such as a central line placement, needle biopsy, thoracentesis, or paracentesis) ibrutinib should be stopped at least 3 days prior to the procedure and should not be restarted for at least 3 days after the procedure. For bone marrow biopsies that are performed while the subject is on ibrutinib, it is not necessary to withhold ibrutinib for these procedures.

For emergency procedures, ibrutinib should be withheld after the procedure until the surgical site is reasonably healed, for at least 7 days after the urgent surgical procedure.

7.8.4 Radiotherapy or other anti-neoplastic agent

The use of any anti-neoplastic agent or radiotherapy is prohibited whilst the patient is on-study. However, at the completion of study treatment the patient may, at Investigator discretion, receive consolidation radiotherapy to tumour sites of baseline bulk or residual fluorodeoxyglucose (FDG) avidity.

7.8.5 Central Nervous System (CNS) Therapy

Patients with CNS involvement can receive intrathecal methotrexate at 12.5mg as per local policy. The administration of intrathecal methotrexate as CNS prophylaxis in high risk patients is permitted and should follow local guidelines. Intrathecal methotrexate should be given in accordance with local guidelines.

7.8.6 Hypersensitivity

Patients who are hypersensitive to the active substance of ibrutinib or to any of the excipients listed in Appendix 7 should not commence therapy with ibrutinib.

For further information on precautionary measures related to rituximab and CHOP chemotherapy, refer to Appendix 7 or the current SmPC.

7.9 Patient Follow Up

All patients completing the protocol defined treatment schedule therapy will have a PET/CT scan 6 weeks after completion of final rituximab (after 8th dose) and be assessed clinically every 4 months for 2 years. This will include a CT scan at 12 months. In case of treatment delays, scans during the treatment phase should be deferred to after the relevant treatment cycle. However, scans during follow-up period should be performed on schedule (+/- 2 weeks).

For those still alive and disease-free after 2 years, follow-up will be according to local practice.

21-28 Days after last trial treatment follow up visit to consist of the following:

- Clinical assessment (see Schedule of Events)
- Blood tests: haematology and biochemistry
- Review of Adverse Events
- Review of concomitant medications

Each subsequent follow-up visit will consist of the following:
- Details of medically important events and subsequent therapies for PTLD
- Clinical assessment (see Schedule of Events)
- CT scan neck (if required), chest, abdomen and pelvis (+/- 2 weeks of clinic visit) as per study schedule

Patients who progress at any time will be followed up for dates of progressive disease, start/end dates of new treatments, date and cause of death, every 4 months for 2 years.

7.10 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 specifically withdraw 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. All information and blood/tissue samples collected up until point of retraction will be retained and analysed. 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 Trial Office, then further routine "follow-up" data (e.g. response status, survival, further treatment) will continue to be supplied by the Investigator to the Trial Office.

Patients who stop treatment due to adverse experiences (clinical or laboratory) will be treated and followed according to accepted medical practice. 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 noncompliance)
- stopping by the Investigator for clinical reasons not related to the study drug treatment

Patients must stop study treatment in the event of:

- unacceptable toxicity
- pregnancy
- SAE requiring permanent discontinuation of treatment

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 8. 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 SmPC.

8.1 Reporting Requirements

8.1.1 Adverse Events

All medical occurrences which meet the definition of an AE (see Appendix 8 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

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded. Pre-existing condition should only be reported if the condition worsens by at least 1 CTCAE grade. Details of all AEs experienced by the patients should be recorded in the hospital notes.

8.1.2 Serious Adverse Advents

Investigators should report AEs that meet the definition of an SAE (see Appendix 8 for definition) and are not excluded from the reporting process as described below.

8.1.2.1 Events that do not require expedited reporting

Patients receiving adjuvant chemotherapy may require admission to hospital for appropriate medical intervention following development of some of the more severe known side effects of treatment. For this reason the following SAEs do not require expedited (immediate) reporting by site and are not regarded as unexpected for the purpose of this trial:

- Admissions to control symptoms of nausea and vomiting unless the condition is life threatening or proves fatal
- Admissions for supportive treatment during an episode of myelosuppression unless this proves fatal or requires admission to a high dependency or intensive care facility

An SAE Form should still be completed for these events but can be faxed to the Trial Office (as described in Section 8.2) at any time prior to completion of chemotherapy treatment.

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

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

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

- Progression or death as a result of the patient's cancer, as this information is captured elsewhere on the Case Report Form

8.1.2.3 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 Trial Office as soon as possible. If it is the patient who is pregnant provide outcome data on a follow-up Pregnancy Notification Form. Where the patient's partner is pregnant consent must first be obtained and the patient should be given a pregnancy Release of Medical Information Form to give to their partner. If the 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. If appropriate also complete an SAE Form as detailed below.

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 28 days after the administration of the last treatment.

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 Trial Office.

AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see Appendix 9). 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.

8.2.1.2 Serious Adverse Events

For more detailed instructions on SAE reporting refer to the SAE Form Completion Guidelines contained in 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 Trial 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 371 4398 or 0121 414 6061

On receipt the Trial 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 Trial 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 Trial 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 Trial 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 Trial 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 SmPC) 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 Trial 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 Trial 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 Trial Steering Committee

The independent Trial Steering Committee (TSC) will review all SAEs.

8.2.6 Manufacturer of Investigational Medicinal Product

All SAEs will be reported to the manufacturer of the Investigational Medicinal Product (ibrutinib) within 24 hours by fax.

8.2.7 Reporting to the main Research Ethics Committee

8.2.7.1 Unexpected and Related Serious Adverse Events

The Trial Office will report all events categorised as Unexpected and Related SAEs to the main Research Ethics Committee (REC) within 15 days.

8.2.7.2 Other safety issues identified during the course of the trial

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

8.2.8 Investigators

Details of all Unexpected and Related SAEs 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.

9. DATA HANDLING AND RECORD KEEPING

9.1 Electronic Data Collection

The Case Report Form (CRF) will comprise a set of forms capturing details of eligibility, baseline characteristics, treatment and outcome details.

This trial will use an electronic data capture (EDC) system which will be used for completion of CRFs. Access to the EDC system will be granted to individuals via the Trial Office. SAE reporting and Notification of Pregnancy will be paper-based.

The CRF must be completed by the Investigator or an authorised member of the site research team (as delegated on the Site Signature and Delegation Log) within specified timeframes (found in the eCRF completion guidelines). The exceptions to this are the SAE Form and Withdrawal Form which must be co-signed by the Investigator and reported in an expedited manner.

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. Missing and ambiguous data will be queried in line with the data management plan for the trial. All sections are to be completed before submitting. 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.

9.2 Archiving

It is the responsibility of the Principal Investigator to ensure all essential trial documentation and source records (e.g. signed Informed Consent Forms, 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 e.g. registration forms and supply a current CV to the Trial 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 Trial 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, Adverse Event 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 Trial 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 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 Trial 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 TIDaL trial staff access to source documents as requested.

10.3 Central Monitoring

Trial 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 the relevant regulatory bodies. This includes reporting serious breaches of GCP and/or the trial protocol to the main REC and the 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 Trial 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 Trial Office of a suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trial Office is investigating whether or not a serious breach has occurred sites are also requested to cooperate with the Trial 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 the last visit of the last patient according to the protocol schedule.

The Trial 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.

Sites should continue to notify the Trial Office of changes in Principal Investigator by completing and returning (where required) an Investigator Registration Form together with a current signed and dated CV until otherwise notified

12. STATISTICAL CONSIDERATIONS

12.1 Definition of Outcome Measures

12.1.1 Primary outcome measure

- CR assessed after 7 weeks - response will be assessed by CT scan between days 42 – 49 using the Lugano Classification (Cheson et al JCO 2014 and see Appendix 3)

12.1.2 Secondary outcome measures

EFS with events defined as time from date of registration to the first of:
- Treatment discontinuation due to toxicity quantified by the CTCAE v4 criteria
- Disease progression (**Note**: Disease progression during the initial IR therapy does count as an event)
- Death

Patients who do not experience an event during the course of the trial will be censored at the date last seen.

PFS with events defined as time from date of registration to disease progression or death.

PFS post IR therapy with progression defined as time from date of registration to disease progression or death.
Note: Disease progression during the initial seven weeks of IR therapy leading to entry into the high risk arm does not count as a progression event; only disease progression following commencement of the 3-weekly IR, IR-CHOP or R-CHOP cycles will be counted. Patients who do not experience progression during the course of the trial will be censored at the date last seen.

Response ((complete remission (CR), partial response (PR), stable disease (SD) and progressive disease (PD))) at 7 weeks and end of treatment assessed by the Lugano Classification (Cheson et al JCO 2014).

Overall survival time defined as time from registration to death. Patients who do not experience an event during the course of the trial will be censored at date last seen.

Treatment related mortality as defined in terms of absence of toxicities related to ibrutinib quantified by the CTCAE v4 criteria.

Patients who experience a dose interruption, dose reduction or discontinue treatment.

Frequency of grade III and IV leucocytopenia and grade III and IV infections by treatment group.

Percentage of patients entering into low risk arm after initial IR therapy.

12.2 Analysis of Outcome Measures

Registered patients subsequently found to have been ineligible at baseline or not starting treatment will be replaced. Such patients will still be followed-up and reported in line with the study protocol.

12.2.1 Primary outcome measure

CR after 7 weeks - CR will be assessed by CT scan between days 42 - 49. The number and proportion of patients achieving CR will be presented and assessed using the Simon's 2-stage design criteria. Seven CRs out of 24 patients will need to be observed in order to proceed to the second stage, 12/38 CRs will need to be observed to warrant further investigations in a phase III trial.
Note: In the case of clinical progression in the first seven weeks of IR therapy, the patient will immediately commence IR-CHOP/R-CHOP treatment. The interim assessments will be completed at the time of progression, with the exception of the CT scan, which may be omitted at the discretion of the investigator. Patients who progress whilst on IR therapy in the first 7 weeks will not have met the primary outcome measure.

12.2.2 Secondary outcome measures

- EFS, PFS, PFS post IR therapy OS will be estimated using Kaplan and Meier method. Point estimates will be presented at 6, 12 and 24 months with 95% confidence intervals.
- The number and proportion of patients in each response category (CR, PR, SD and PD) at 7 weeks and end of treatment will be reported overall and by risk group.
- Treatment related mortality will be assessed using cumulative incidence curves. Estimates will be presented at 6, 12 and 24 months with 95% confidence intervals.
- Treatment tolerability will be reported as the number and proportion of patients tolerating treatment.
- Patients experiencing a dose interruption, dose reduction or discontinuing treatment will also be reported over the treatment period.
- Patients in the low risk and high risk arm. Any patients who receive additional chemotherapy will also be presented.
- Frequency of grade III and IV leucocytopenia and grade III and IV infections by treatment group This will be reported as the proportion of patients who experience one or more of these events and the proportion of events.

12.3 Sample Size Calculations

The sample size required given an unacceptable rate of response of 25% and a rate of 40% being considered acceptable using Simon's 2stage optimal design is 38 patients (40 with 5% drop out). The alpha for this sample size is 20% and power of 85%.This single arm trial will need 7/24 CRs to continue to the second stage and 12/38 CRs to indicate that the treatment has sufficient activity to warrant further investigation in a Phase III trial.

In addition, up to twenty patients with PTLD following ASCT or meningeal or CNS involvement will be recruited to collect preliminary data and clinical outcomes in this disease group. This sample size is not statistically driven.

12.4 Planned Sub Group Analyses

Secondary outcomes will also be presented split by age, above and below 65 years old. This is due to the safety concerns of giving ibrutinib to over 65s. These analyses will not be powered and should be interpreted with caution.

12.5 Planned Interim Analysis

As part of the Simon's 2-stage design an early stopping rule is integrated in the design of the study. This single arm trial will need 7/24 CRs at the interim stage to proceed to the second stage. The TSC will review safety on at least an annual basis.

12.6 Planned Final Analyses

The main analysis is planned to be performed two years after the final patient enters the trial.

If the trial enters the second stage 12/38 CRs will need to be observed to warrant further investigations in a randomised phase III trial.

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 CRCTU, University of Birmingham according to their local procedures.

13.3 Trial Management Group

The Trial Management Group (TMG) will consist of the Chief Investigator, Co-Investigators, Research Nurse and trial team at the CRCTU. The TMG will provide overall supervision of the trial; in particular clinical set-up, ongoing management, adherence to the protocol, consideration of new information and interpretation of the results. The TMG will meet every 2 months. An emergency meeting may be convened if a significant issue is identified.

13.4 Trial Steering Committee

A TSC will provide overall supervision for the trial and provide advice through its independent chair. Membership includes members of the TMG, CRCTU Trial Management Team Leader and selected Principal Investigators. Other members/observers may be invited if appropriate. The TSC will meet at least once a year or more often if required. The TSC will not be assessing futility as this is built into the Simon design.

13.5 Finance

This is an Investigator-initiated and Investigator-led trial funded by Bloodwise and Janssen. Ibrutinib will be provided free of charge by Janssen for the duration of the trial.

No individual per patient payment will be made to NHS Trusts, Investigators or patients. This trial is an NIHR CRN portfolio study.

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, the General Data Protection Regulation, the Data Protection Act 2018 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 Trial 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 General Data Protection Regulation and the Data Protection Act (2018). With the patient's consent, their initials, and date of birth will be collected at trial entry. Patients will be identified using only their unique trial number, initials and date of birth on the Case Report Form and correspondence between the Trial Office and the participating site. However patients are asked to give permission for the Trial Office to be sent a copy of their signed Informed Consent Form 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 Trial 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 Trial 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 (e.g. laboratory staff). Representatives of the 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 cannot offer indemnity for non-negligent harm. 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 peer reviewed journals. Manuscripts will be prepared by the TMG and authorship will be determined by mutual agreement.

18. REFERENCE LIST

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Cheson B et al. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification, J Clin Oncol. 2014; 32, 3059-3068

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APPENDIX 1 - ECOG PERFORMANCE STATUS SCALE

Activity performance description	Score
Fully active, able to carry out all normal activity without restriction.	**0**
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e. g. light house work, office work.	**1**
Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	**2**
Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours.	**3**
Completely disabled. Cannot carry out any self-care. Totally confined to bed or chair.	**4**

APPENDIX 2 - INTERNATIONAL PROGNOSTIC INDEX

The risk factors used in calculating the International Prognostic Index (IPI) are shown below. Give one point for each criteria met:

a) Age >60 years

b) Tumour stage III or IV

c) ECOG performance status ≥ 2 (see Appendix 1)

d) Serum LDH greater than upper limit of local normal range

e) More than one extranodal sites of disease

Patients are then assigned to one of four risk groups on the basis of their number of presenting risk factors:

Low risk:	0 or 1
Low intermediate risk:	2
High intermediate risk:	3
High risk:	4 or 5

APPENDIX 3 - RECOMMENDATIONS FOR INITIAL EVALUATION, STAGING, AND RESPONSE ASSESSMENT OF HODGKIN AND NON-HODGKIN LYMPHOMA: THE LUGANO CLASSIFICATION

Table 3. 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 (eg, 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
Nonmeasured 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
Nonmeasured 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 (eg, 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
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

(continued on following page)

Table 3. Revised Criteria for Response Assessment (continued)

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis 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 undertreatment). 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.

Reproduced from: Cheson B *et al*. Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification. (2014) J Clin Oncol, 32, 3059-3068

APPENDIX 4 – DEAUVILLE CRITERIA

Score	PET findings
1	no uptake
2	uptake ≤ mediastinum
3	uptake > mediastinum but ≤ liver
4	moderately increased uptake compared to liver at any site
5	markedly increased uptake compared to liver at any site
X	New sites of uptake not related to lymphoma NOTE if mediastinal blood pool activity is equal or greater than liver then the uptake within the lesion should be compared with liver (lesion uptake less than liver=score 2; lesion uptake equal to liver=score 3)

C(M)R as defined by the Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification is the equivalent of Deauville scores of 1, 2 or 3. Please note that CR and CMR are equivalent.
See Appendix 3 for further details of the Lugano Classification.

APPENDIX 5 – INFUSION RELATED REACTION (IRR) GUIDANCE

The patient should be observed for at least 60 minutes following the first infusion of study treatment. During this observation period, the IV line should remain open to allow administration of IV drugs if necessary. All supportive measures consistent with optimal patient care should be given throughout the study according to institutional standards. This includes adjusting the infusion time if necessary. Medications for infusion-related reactions, such as epinephrine, antihistamines, and corticosteroids, should be available for immediate use.

Patients who experience a Grade 1 or Grade 2 infusion-related reaction may receive subsequent study treatment infusions with premedication consisting of paracetamol 1000 mg po and chlorpheniramine 10 mg iv (or equivalent antihistamine according to institutional standards), administered 30–60 minutes prior to each 30-minute infusion. They may also have their infusion time prolonged to 60 min at the discretion of the investigator.

Patients who experience a grade 3 or 4 infusion-related reaction should not receive further rituximab.

Grading of infusion reactions as follows:

1. Mild reaction; infusion interruption not indicated, intervention not indicated
2. Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, steroids, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.
3. Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)
4. Life-threatening; pressor or ventilatory support indicated
5. Death

Precautions and Observations

• i.v access is mandatory! It should be secure and of good quality
• Administering nurse suitably experienced
• Premedications given if necessary
• Appropriate clinical area with resuscitation facilities (‘Crash Cart’)
• Full observations: BP/ pulse/ sPO2/ temperature at baseline and end-of-infusion
• Repeat observations every 15 minutes throughout infusion: BP/ pulse
• Full observations performed if repeat observations deteriorate or the subject complains of symptoms during infusion, to also include respiratory rate and assessment of airway (swelling, stridor, respiratory effort)

Treatment of Reactions

This is by reaction grade with definitions, examples and suggested management.

Grade 1

• Mild reaction infusion
• Minor chills/low grade fever, tachycardia without other symptoms, hypertension (<230 mmHg systolic), ‘tight /scratchy throat’, minor rashes etc.
• Give paracetamol 1000 mg po and chlorpheniramine 10 mg iv (or equivalent antihistamine according to institutional standards)
• Interruption of the infusion is not necessary

Grade 2

• Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, steroids, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs.
• Hypotension, tachycardia with other chest symptoms, high grade fever, hypoxia, respiratory compromise etc.
• Should be treated with interruption of the infusion, oxygen/intravenous fluids as appropriate, paracetamol 1000 mg po and chlorpheniramine 10 mg iv (or equivalent antihistamine according to institutional standards) and i.v. steroid (e.g. hydrocortisone 100mg) if not already given. Once

symptoms have resolved to grade 1, and at least 30 minutes have passed, the infusion may be restarted. Providing no further reaction beyond grade 1 occurs, the infusion may be completed.

Grade 3
• Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)
• These include all grade 2 reactions which do not respond to initial therapy, and anything 'out of the ordinary', and signs/symptoms detailed below
• Oxygen/ i.v. fluids/ i.v. antihistamine/ i.v. steroid should be administered immediately, and a doctor should be called to see the patient urgently.

Grade 3 or 4 adverse events can include severe urticaria, hypotension refractory to i.v. fluids, angioedema (facial/oral swelling), hypoxia refractory to oxygen therapy, pulmonary infiltrates, acute respiratory distress syndrome, myocardial infarction, ventricular fibrillation, or cardiogenic shock.

Grade 4
• These reactions mandate a 'Crash Call'

Some definitions
• Hypoxia is sPO2 ≤90% on room air
• Hypotension is a systolic BP ≤90 mmHg unless baseline is ≤100 mmHg, when a drop of 20 mm from baseline should be used
• High grade fever is temp ≥ 38ºC on more than one occasion
• Tachycardia is a persisting HR ≥100 bpm

APPENIDX 6 - IBRUTINIB RISK LANGUAGE

Ibrutinib Risk Language (IB edition 11, addendum 1) –updated December 2017 ICF Risk Section for Ibrutinib- DBL 31-Jul- 2017 RISKS AND SIDE EFFECTS:

You may develop side effects while participating in this study. You should tell the study doctor about any side effects that you develop.

The side effects listed below have been reported by patients who have received ibrutinib in clinical trials.

The most common side effects, occurring in at least 1 of every 5 patients (≥ 20%), have been:
Increase in frequency of loose or watery stools (Diarrhea), Muscle and bone pain (Musculoskeletal pain), Nausea, Low white blood cell count (cells that help fight infection) (Neutropenia), Rash, Bruises

Side effects that have been seen in at least 1 of every 10 (≥ 10%) patients include:
Fever (Pyrexia), Low platelet count (cells that help blood to clot) (Thrombocytopenia), Common cold (Upper Respiratory Tract Infection), Pneumonia, Constipation, Swelling of the hands or feet (Oedema peripheral), Muscle spasms, Vomiting, Joint aches (Arthralgia), Sores in mouth (Stomatitis), Headache, High Blood pressure (Hypertension), Skin infection, Sinus infection (Sinusitis)

Side effects that have been seen in at least 1 of every 100 (≥ 1%) patients include:
Dizziness, Urinary tract infection, Noses bleed (Epistaxis), Increased level of uric acid in the blood (Hyperuricemia), Small red or purple spots caused by bleeding under the skin (Petechiae), Abnormal heart rhythm (Atrial fibrillation), Non-melanoma skin cancer; Type of non-melanoma skin cancer (Basal cell carcinoma); Type of non-melanoma skin cancer (Squamous cell carcinoma), Blurry vision (Vision blurred), Low white blood cell counts with fever (Febrile neutropenia), Severe infection throughout the body (Sepsis), Redness of the skin (Erythema), Increase in white blood cell counts (Leukocytosis), Breaking of the nails (Onychoclasis), Inflammation within the lungs that may lead to permanent damage (Interstitial lung disease), Increase in lymphocyte count (Lymphocytosis)

Side effects that have been seen in at least 1 of every 1000 (<1%) patients include:
Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells, which may lead to changes in kidney function, abnormal heartbeat, or seizures (Tumor lysis syndrome), Itchy rash (Urticaria), Bleeding around the brain (Subdural hematoma), Swollen face, lip, mouth, tongue or throat (Angioedema), High WBC count with abnormal clumping that can lead to bleeding (Leukostasis syndrome), Severe rash with blisters and peeling skin, particularly around the mouth, nose, eyes and genitals (Stevens-Johnson syndrome), Liver failure (Hepatic failure), abnormal rapid and irregular heart rhythm that starts from the lower chambers (ventricles) of the heart (ventricular tachyarrhythmia).

Most of these side effects listed above have been mild to moderate in severity; however severe side effects have occurred. Some side effects have been severe enough to lead to study drug discontinuation, dose modification or reduction, hospitalization, disability, and sometimes death.

You should tell your study doctor or medical team about any side effects you are having. Your study doctor may be able to give you medications to help treat the side effects and prevent them from becoming worse. Your study doctor may also choose to stop ibrutinib for a short time or reduce its dose to allow you to recover from any side effects.

Bleeding
You may experience bruising or nosebleeds during treatment with ibrutinib. Rarely, serious internal bleeding, such as bleeding in your stomach, intestine, or brain may occur, sometimes resulting in death. If you take other medicines or supplements that increase your risk of bleeding, such as aspirin, non-steroidal anti-inflammatory drugs (NSAIDs) or medicines used to prevent or treat blood clots or stroke, ibrutinib may increase this risk. Blood thinners such as warfarin or other vitamin K antagonists should not be taken together with ibrutinib. Supplements such as fish oil and vitamin E preparations should be avoided while taking ibrutinib. Call your study doctor if you have signs or symptoms of

serious bleeding, such as blood in your stools or urine or bleeding that lasts for a long time or that you cannot control.

Effects on the heart
Abnormal rapid and irregular heart rhythm (atrial fibrillation and/or atrial flutter, ventricular tachyaarythmia) have been reported in patients treated with ibrutinib, especially when they also have heart conditions, increased blood pressure, infections, or had abnormal heartbeat in the past. The heartbeat may be fast or irregular causing symptoms such as a pounding or racing heart, dizziness, weakness, feeling light-headed, shortness of breath, chest discomfort or fainting. If you develop any of these symptoms while on the study drug, you should tell your study doctor immediately.

Infections
You may experience viral, bacterial, or fungal infections during treatment with ibrutinib. Some of these infections have led to hospitalization and death. Contact your study doctor immediately if you have fever, chills, weakness, confusion, body aches, cold or flu symptoms, feel tired or feel short of breath - these could be signs of an infection. Your study doctor may start or continue medication to help prevent or treat an infection.

A rare and usually fatal viral disease in the brain, Progressive Multifocal Leukoencephalopathy (PML), has been reported in patients treated with ibrutinib in combination with rituximab and in patients who were previously treated with rituximab. If you experience symptoms such as weakness, paralysis, vision loss and/or impaired speech, you should tell your study doctor immediately.

Lymphocytosis and leukostasis
You may experience an increase in the number of lymphocytes, which is a type of white blood cell, in your blood (lymphocytosis). This may occur in the first few weeks of treatment and you should not assume that this increase in white blood cells means that your disease is worsening. This increase may last for several weeks to months. Increased number of white blood cells in your bloodstream may change the blood flow, resulting in bleeding or clotting (leukostasis). Isolated cases of these events have been reported in patients treated with ibrutinib. Your study doctor will monitor your blood counts and may administer additional therapy as needed. Talk to your study doctor about what your test results mean.

Decreased blood counts
Severe decreases in white blood cells, red blood cells, and platelets (neutropenia, anemia, and thrombocytopenia) were reported in subjects treated with ibrutinib. If you experience symptoms such as fever, weakness, or easy bruising and/or bleeding, you should tell your study doctor immediately.

Allergic reactions
Sometimes people have allergic reactions to drugs. Serious allergic reactions can be life-threatening. If you have an allergic reaction to ibrutinib, you might develop a rash, difficulty breathing, wheezing when you breathe, sudden low blood pressure with light-headedness, swelling around the mouth, throat or eyes, a racing heartbeat, and/or sweating.
Before starting the study drug, you must tell your study doctor about any drug allergies. You should tell the study doctor right away if you have any allergy symptoms listed above.

Rash
A maculopapular rash (flat, red areas on the skin with small bumps) has been commonly reported in patients treated with ibrutinib alone or in combination with other drugs. Most rashes are mild to moderate in severity and begin 2 to 3 weeks or longer after starting ibrutinib.
There have been rare reports of severe skin reactions (known as severe cutaneous adverse reaction or “SCAR”, involving more than 50% of the body) or rash with blisters and peeling skin, which may include open ulcers or sores in the mouth and other areas of the body (Stevens - Johnson syndrome). These skin rashes could be life-threatening. You should notify your study doctor immediately if you develop a rash that spreads quickly, or if you notice peeling of your skin, with or without ulcers or sores in your mouth.

Non Melanoma Skin Cancer and Other Cancers

Non melanoma skin cancer (basal cell carcinoma and squamous cell carcinoma of the skin) have been reported with more frequency and maybe related to the use of ibrutinib. Other cancers have been reported such as solid tumors and blood cancers the relationship to the use of ibrutinib is unknown. You should tell your study doctor if you develop a new cancer while in the study.

Tumor Lysis Syndrome (TLS)
Unusual levels of chemicals in the blood caused by the fast breakdown of cancer cells have happened during treatment of cancer and sometimes even without treatment. This may lead to changes in kidney function, abnormal heartbeat, or seizures. Your study doctor may do blood tests to check for TLS.

Hypertension
Hypertension is also called high blood pressure, and has been commonly reported in subjects treated with ibrutinib. Sometimes, people with high blood pressure may have headaches, dizziness, nervousness, sweating, difficulty in sleeping, facial flushing or nosebleeds, but in some cases, there may be no symptoms and it may go undetected. After starting ibrutinib, your doctor may measure your blood pressure regularly. You should let your study doctor know if you have any of the symptoms of high blood pressure which may mean that you have developed hypertension or that your hypertension is getting worse. Your study doctor may adjust existing anti-hypertensive medications and/or initiate anti-hypertensive treatment as appropriate.

Liver Failure
Rare cases of liver failure have been reported in patients treated with ibrutinib. Symptoms of liver failure include yellowing of the eyes and skin (Jaundice), itching of the skin, dark colored urine, gray or clay-colored stools, confusion, nausea , loss of appetite, fatigue or diarrhea,. You should tell your study doctor immediately if you have any of these symptoms which may suggest liver disease. Your study doctor may be able to diagnose and provide you required medical care.

Interstitial lung disease
Interstitial lung disease is a group of lung disorders in which the tissues become inflamed and may become damaged. Interstitial lung disease is not associated with infections (e.g., bacteria, viruses, fungi) and has been reported in patients treated with ibrutinib. You should report to your physician if you have cough, any signs of new or worsening respiratory symptoms such as shortness of breath or difficulty breathing.

Interference with other drugs
Some foods like grapefruit juice and Seville oranges, as well as some medications, may interfere with the way your body processes ibrutinib. This interference could cause the amount of ibrutinib in your body to be higher or lower than expected. It is also possible that taking the study drug with your regular medications or supplements, including fish oil, Vitamin E, or other vitamins, may change how your regular medications, or your regular supplements, work. It is very important that you avoid grapefruit juice and Seville oranges and tell the study doctor about all medications, supplements, or herbal medicine like St. John's wort that you are taking during the study. You should notify your study doctor immediately about any side effects to avoid possible harm.

Drug interruption for any surgical procedures
Ibrutinib may increase the risk of bleeding with any surgical procedure. Ibrutinib should be held at least 3 to 7 days before and after surgery depending upon the type of surgery and the risk of bleeding. Please contact your study doctor if you have any planned surgical procedures. For emergency surgical procedures, ibrutinib should be discontinued (stopped) after the procedure until the surgical site is reasonably healed (not oozing fluid).

Please contact your study doctor as soon as possible and your study doctor will tell you when to stop ibrutinib and when to restart it following a surgical procedure.

In addition to the risks listed above, there could be unknown or unexpected side effects associated with the use of ibrutinib. You will be told in a timely manner, verbally and in writing, of any new information, findings, or changes to the way the research will be done that might influence your willingness to continue your participation in this study.

You may have all, some, or none of the listed side effects of ibrutinib. Your study doctors and nurses will check you closely for side effects. You may receive medicines or other treatments to prevent or reduce some of these effects. Please tell the study doctor or study staff right away if you have any side effects. Please tell them if you have any other problems with your health or the way you feel during the study, whether or not you think they are related to the study drug.

You should get medical help and contact the study doctor or study staff if you have any of these or any other side effects during the study.

Reproductive effects

The effects of ibrutinib on a developing baby are unknown; therefore women who are pregnant or nursing are not allowed to be in this study. Nobody knows what these risks are right now. Some drugs cause women to have their babies prematurely (early) or to have babies with birth defects.

Women: If you are able to have children, you must use a highly effective method of birth control and a barrier method while taking study treatment, as well as for 12 months after you stop taking study treatment, to prevent pregnancy in either you or your partner. A “highly effective method of birth control” is defined as a method that has a low failure rate (i.e., less than 1% per year) when used consistently and correctly and includes implants, injectables, birth control pills with 2 hormones, some intrauterine devices (IUDs), sexual abstinence (which is defined as refraining from all aspects of sexual activity) or a sterilized partner. If you are using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (e.g., condoms) must be used.

Men: You must use a barrier method while on treatment with ibrutinib and for 12 months after the last dose of treatment to prevent pregnancy of your partner.

Note: Some birth control pills may not work when you are taking certain drugs. If you have any questions about this, please discuss this with the study doctor.

Be aware that you can still become pregnant even if you use a highly effective method of birth control.

Women: If you become pregnant while you are on study treatment or within 12 months of your last dose of ibrutinib you must notify the study staff. If you become pregnant on the study, you must immediately stop taking the study treatment. The Sponsor will continue to collect information about your pregnancy and the birth of your baby even after study treatment is stopped.

Men: If your partner becomes pregnant while you are on study treatment, or within 12 months of your last dose of ibrutinib, you must notify the study staff. The study staff will discuss this with you further. You should not donate sperm while you are taking the study drug and for 12 months after you stop taking the study drug.

APPENDIX 7 – CONCOMITANT MEDICATION

The following table contains a comprehensive list of all medications that are either prohibited or should be avoided throughout the trial. Please see subsequent IMP specific information for further details.

Drug/treatment	Prohibited	Avoid
St John's Wort (including preparations containing it)	✓	
Warfarin and other Vitamin K antagonists: • Warfarin sodium • Acenocoumarol • Phenindione	✓*	
Other anticoagulants: • Dabigatran • Apixaban • Rivaroxaban		✓
Fish oil and Vitamin E preparations		✓
Strong CYP3A4/5 inhibitors: • Clarithromycin • Telithromycin • Nefazodone • Itraconazole • Ketoconazole • Atazanavir • Darunavir • Indinavir • Lopinavir • Nelfinavir • Ritonavir • Saquinavir • Tipranavir	Prohibited at study entry	Avoid during trial[#†]
Moderate CYP3A4/5 inhibitors: • Amiodarone • Erythromycin • Fluconazole • Miconazole • Diltiazem • Verapamil • Delavirdine • Amprenavir • Fosamprenavir • Conivaptan • Aprepitant • Grapefruit and juices • Seville oranges (including marmalade) and juices • Pomelos • Star fruit • Cat's claw (*Uncaria tomentosa*) • *Echinacea angustifolia* • Wild cherry (*Trifolium pratense*) • Chamomile (*Matricaria chamomilla*) • Liquorice (*Glycyrrhiza glabra*)		✓[#†]
Strong CYP3A4/5 inducers: • Rifampicin	Prohibited at study entry	Avoid during trial[¥]
Moderate/mild CYP3A4/5 inducers: • Efavirenz • Nevirapine • Barbiturates • Carbamazepine • Enzalutamide • Glucocorticoids • Modafinil • Oxcarbazepine • Phenobarbital • Phenytoin • Pioglitazone • Rifabutin • Troglitazone		✓[¥]
Mild CYP3A4/5 inhibitors: • Cimetidine		✓[†]
Trastuzumb		✓[#]
Radiotherapy	✓	
Anti-neoplastic agents	✓	

Vaccinations	✓	

* must be stopped at least one week prior to registration

discuss with Chief Investigator/Clinical Coordinator before use

† monitor for toxicities and reduce/hold dose as necessary

¥ monitor for lack of efficacy of ibrutinib

Ibrutinib

The use of strong CYP3A4/5 inhibitors and inducers is prohibited at study entry and should be avoided throughout the trial. St John's Wort, warfarin and other vitamin K antagonists, radiotherapy, anti-neoplastic agents and vaccinations are prohibited throughout the trial. Other anticoagulants, moderate CYP3A4/5 inhibitors and inducers, mild CYP3A4/5 inhibitors and trastuzumab should be avoided throughout the trial.

Please see table above for further details on the use of these medications throughout the trial.

Other CYP3A4/5 inhibitors include chloramphenicol, boceprevir, diethyl-dithiocarbamate, fluvoxamine, Gestodene, imatinib, mibefradil, mifepristone, norfloxacin, norfluoxetine, telaprevir, troleandomycin

Hypersensitivity to the active substance or to any of the following excipients:

Capsule content
- croscarmellose sodium
- magnesium stearate
- microcrystalline cellulose
- sodium laurilsulfate

Capsule shell
- gelatin
- titanium dioxide (E171)

Printing ink
- shellac
- iron oxide black (E172)
- propylene glycol

Vincristine

The neurotoxicity of vincristine sulphate may be additive with that of isoniazid and other drugs acting on the nervous system.

Mitomycin-C

Acute shortness of breath and severe bronchospasm have been reported following the administration of vinca alkaloids. These reactions have been encountered most frequently when the vinca alkaloid was used in combination with mitomycin-C and may be serious when there is pre-existing pulmonary dysfunction. The onset may be within minutes or several hours after the vinca is injected and may occur up to 2 weeks following the dose of mitomycin. Progressive dyspnoea, requiring chronic therapy, may occur. Vincristine should not be re-administered.

Phenytoin and antineoplastic chemotherapy

The simultaneous oral or intravenous administration of phenytoin and antineoplastic chemotherapy combinations that included vincristine sulphate have been reported to reduce blood levels of the anticonvulsant and to increase seizure activity. Although the contribution of the vinca alkaloids has not been established, dosage adjustment of phenytoin, based on serial blood level monitoring, may need to be made when it is used in combination with vincristine.

L-asparaginase

When vincristine sulphate is used in combination with L-asparaginase, it should be given 12 to 24 hours before administration of the enzyme in order to minimise toxicity since administering L-asparaginase first may reduce hepatic clearance of vincristine.

Radiation
When chemotherapy is being given in conjunction with radiation therapy through portals which include the liver, the use of vincristine should be delayed until radiation therapy has been completed.

Methotrexate
Vincristine sulphate appears to increase the cellular uptake of methotrexate by malignant cells and this principle has been applied in high-dose methotrexate therapy.

Prednisolone

The following drugs enhance the metabolism of corticosteroids and its therapeutic effects may be reduced:
Rifampicin, rifabutin, carbamazepine, phenobarbital and other barbiturates, phenytoin, phenyl butazone, primidone and aminoglutethimide.

The desired effects of **hypoglycaemic agents** (including insulin), **anti-hypertensives** and **diuretics** are antagonised by the corticosteroids and the hypokalaemic effects of **acetazolamide, loop diuretics, thiazide diuretics** and **carbenoxolone** are enhanced. The efficacy of **coumarin anticoagulants** may be enhanced by concurrent corticosteroid therapy and close monitoring of the INR or prothrombin time is required to avoid spontaneous bleeding.
The renal clearance of salicylates increased by corticosteroids and steroid withdrawal may result in salicylate intoxication.

In patients treated with systemic corticosteroids, use of **non-depolarizing muscle relaxants** can result in prolonged relaxation and acute myopathy. Risk factors for this include prolonged and high dose corticosteroids treatment and prolonged duration of muscle paralysis. This interaction is more likely to occur following prolonged ventililation (such as in an ITU setting).

Corticosteroid requirements may be reduced in patients taking **estrogens** (e.g. contraceptive products).

Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

Doxorubicin

Doxorubicin cardiotoxicity is enhanced by previous or concurrent use of other **anthracyclines**, or other potentially cardiotoxic drugs (e.g. **5-fluorouracile, cyclophosphamide or paclitaxel**) or with products affecting cardiac function (like **calcium antagonists**), When doxorubicin is used together with the above mentioned agents, cardiac function must be followed carefully.

The use of **trastuzumab** in combination with anthracyclines (such as doxorubicin) is associated with a high cardiotoxic risk. Trastuzumab and anthracyclines should not be used in combination for the time being, except in well controlled clinical studies where the cardiac function is monitored. When anthracyclines are used after the end of a therapy with trastuzumab, an elevated risk of cardiotoxicity may result. The half-life of trastuzumab is approximately 28-38 days and may persist in the circulation for up to 27 weeks. If possible, there should be a sufficiently long interval (up to 27 weeks) between the end of a therapy with trastuzumab and the beginning of the anthracycline therapy. Careful monitoring of the cardiac function is imperative.

Doxorubicin hepatotoxicity may be enhanced by other hepatotoxic treatment modalities (e.g. **6-mercaptopurine**).

Doxorubicin undergoes metabolism via Cytochrome P450 (CYP450) and is a substrate for the Pgp transporter, Concomitant administration of **inhibitors of CYP450 and/or Pgp** might lead to increased plasma concentrations of doxorubicin and thereby increased toxicity. Conversely, concomitant administration of **inducers of CYP450**, such as **rifampicin and barbiturates**, might decrease plasma concentrations of doxorubicin and reduce efficacy.

Ciclosporin, an inhibitor of CYP3A4 and Pgp, increased the AUC of doxorubicin and doxorubicinol by 55% and 350%, respectively. The combination might require dose adjustment. **Cimetidine** has also been shown to reduce the plasma clearance and increase the AUC of doxorubicin.

Paclitaxel administered shortly before doxorubicin may decrease clearance and increase plasma concentrations of doxorubicin. Some data indicate that this interaction is less pronounced when doxorubicin is administered before paclitaxel.

Barbiturates may lead to an accelerated plasma clearance of doxorubicin, while the concomitant administration of phenytoin may result in lower plasma phenytoin levels.

Elevated serum doxorubicin concentrations were reported after the concomitant administration of doxorubicin and **ritonavir**.

The toxic effects of a doxorubicin therapy may be increased in a combination with other cytostatics (e.g. **cytarabine, cisplatin, and cyclophosphamide**). Necroses of the large intestine with massive haemorrhage and severe infections may occur in connection with combination therapies with cytarabine.

Clozapine may increase the risk and severity of the hematologic toxicity of Doxorubicin.

Marked nephrotoxicity of Amphotericin B can occur during doxorubicin therapy.

As doxorubicin is rapidly metabolised and predominantly eliminated by the biliary system, the concomitant administration of known hepatotoxic chemotherapeutic agents (e.g. **mercaptopurine, methotrexate, streptozocin**) could potentially increase the toxicity of doxorubicin as a result of reduced hepatic clearance of the drug. Dosing of doxorubicin must be modified if concomitant therapy with hepatotoxic drugs is mandatory.

Doxorubicin is a potent, radio sensitizing agent (“radio sensitizer”), and recall phenomena induced by it may be lifethreatening. Any preceding, concomitant or subsequent radiation therapy may increase the cardiotoxicity or hepatotoxicity of doxorubicin. This applies also to concomitant therapies with cardiotoxic or hepatotoxic drugs.

Doxorubicin may cause exacerbations of hemorrhagic cystitis caused by previous cyclophosphamide therapy.

Doxorubicin therapy may lead to increased serum uric acid, therefore dose adjustment of uric acid lowering agents may be necessary.

Doxorubicin may reduce oral bioavailability of digoxin.

During treatment with Doxorubicin patients should not be actively vaccinated and also avoid contact with recently polio vaccinated persons.

In a clinical study, an increase in doxorubicin AUC of 21% was observed when given with sorafenib 400 mg twice daily. The clinical significance of this finding is unknown.

Cyclophosphamide

Reduced activation of cyclophosphamide may alter the effectiveness of cyclophosphamide treatment. Substances that delay activation of cyclophosphamide include:

Aprepitant, Bupropion, Busulfan (decreased elimination of cyclophosphamide and prolonged half-life has been reported in patients who received high-dose cyclophosphamide less than 24 hours after high-dose busulfan. Increased incidence of hepatic veno-occlusive disease and mucositis has been reported with concomitant administration), **Ciprofloxacin** (when administered prior to treatment with cyclophosphamide (used for conditioning prior to bone marrow transplant), ciprofloxacin may cause regression of the underlying disease), **Chloramphenicol, Azole-antimycotics** (Fluconazole, Itraconazole), (Azole-antimycotics are known to inhibit cytochrome P450 enzymes. Increased amounts of toxic degradation products of cyclophosphamide have been reported in combination with Itraconazole), **CYP2B6 and CYP3A4 inhibitors** (Nevirapin, Ritonavir), (co-administration may reduce the efficacy of cyclophosphamide), **Prasugrel, Sulfonamides** (e.g. sulfadiazine, sulfamethoxazoel and sulfapyridine), **Thiotepa** (a strong inhibition of cyclophosphamide bioactivation by thiotepa in high-dose chemotherapy regimens has been reported when thiotepa was administered 1 hour prior to cyclophosphamide), **Ondansetron** (There have been reports of a pharmacokinetic interaction between ondansetron and highdose cyclophosphamide resulting in decreased cyclophosphamide AUC).

An increase of the concentration of cytotoxic metabolites may occur with:

Allopurinol (an increase of bone marrow suppression was reported), Azathioprine (increased risk of hepatotoxicity (liver necrosis)), Chloral hydrate, Cimetidine, Disulfiram, Glyceraldehyde, **Protease inhibitors** (concomitant use of protease inhibitors may increase the concentration of cytotoxic metabolites. Use of protease inhibitor-based regimens was found to be associated with a higher incidence of infections and neutropenia in patients receiving cyclophosphamide, doxorubicin, and etoposide (CDE) than use of an NNRTI-based regimen. Increased incidence of mucositis is reported in combined therapy of cyclophosphamide (CDE) and saquinavir), **Inducers of human hepatic and extrahepatic microsomal enzymes** (e.g., cytochrome P450 enzymes), (The potential for hepatic and extrahepatic microsomal enzyme induction must be considered in case of prior or concomitant treatment with substances known to induce an increased activity of such enzymes such as rifampin, phenobarbital, carbamazepine, phenytoin, St. John's wort, benzodiazepines and corticosteroids), **Dabrafenib**

Pharmacodynamic Interactions and Interactions of Unknown Mechanism Affecting the Use of Cyclophosphamide

Combined or sequential use of cyclophosphamide and other agents with similar toxicities can cause combined (increased) toxic effects.

Increased hematotoxicity and/or immunosuppression may result from a combined effect of cyclophosphamideand, for example:

ACE inhibitors (ACE inhibitors can cause leukopenia), **Natalizumab, Paclitaxel** (Increased hematotoxicity has been reported when cyclophosphamide was administered after paclitaxel infusion), **Thiazide diuretics** (e.g. hydrochlorthiazide), (An increase of bone marrow suppression was reported), **Zidovudine, Clozapine**

Increased cardiotoxicity may result from a combined effect of cyclophosphamide and, for example:

Anthracyclines, Mitomycin, Cytarabine, Pentostatin, Radiation therapy of the cardiac region or a whole-body irradiation in combination with high doses of cyclophosphamide, **Trastuzumab**

Increased pulmonary toxicity may result from a combined effect of cyclophosphamide and, for example:

Amiodarone, G-CSF, GM-CSF (granulocyte colony-stimulating factor, granulocyte macrophage colony-stimulating factor), (reports suggest an increased risk of pulmonary toxicity in patients treated with cytotoxic chemotherapy that includes cyclophosphamide and G-CSF or GMCSF)

Increased nephrotoxicity may result from a combined effect of cyclophosphamide and, for example:

Amphotericin B, Indomethacin (acute water intoxication has been reported with concomitant use of indomethacin)

APPENDIX 8 - 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 (not 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.

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 (SmPC) for a licensed product).

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

APPENDIX 9 - 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

APPENDIX 10 – 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 fulfillment 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 foreseable 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, reestablishing 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)

7. 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.

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

9. 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.

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