A phase IIa study of ***RI***tuximab and ***VA***rlilumab in relapsed or refractory B-cell malignancies

Version 6 22-Oct-2020

SPONSOR: University Hospital Southampton NHS Foundation Trust
COORDINATING CENTRE: Southampton Clinical Trials Unit

Eudract Number:	2017-000302-37
ISRCTN reference:	ISRCTN15025004
Ethics reference number:	17/SC/0317
Sponsor reference number:	RHM CAN 1278
Funder reference number:	CRUKD/17/008 CDX1127-55
ICD11	2A80, 2A81, 2A85

Protocol authorised by:

Name:	Dr Sean Hua Lim	**Role:**	Chief Investigator
Signature:		**Date:**	**02/11/2020**
Name:	Prof Gareth Griffiths	**Role:**	Director of SCTU
Signature:		**Date:**	
Name:		**Role:**	On behalf of Sponsor
Signature:		**Date:**	

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Signature:	Gareth Griffiths Digitally signed by Gareth Griffiths Date: 2020.11.03 14:25:23 Z	**Date:**	
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Signature:		**Date:**	

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University Hospital Southampton NHS
NHS Foundation Trust

UNIVERSITY OF Southampton

CANCER RESEARCH UK

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NCRI

UKCRC Registered Clinical Trials Units

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FUNDER

This trial is funded by an Investigator Initiated Research Grant from Celldex Therapeutics and by Cancer Research UK New Agents Committee and supported by Cancer Research UK core funding at the Southampton Clinical Trials Unit.

Protocol Information

This protocol describes the RiVa trial and provides information about procedures for entering participants. The protocol should not be used as a guide for the treatment of other non-trial participants; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the trial, but sites entering participants for the first time are advised to contact Southampton Clinical Trials Unit to confirm they have the most recent version.

Compliance

This trial will adhere to the principles of Good Clinical Practice (GCP). It will be conducted in compliance with the protocol, current Data Protection Regulations and all other regulatory requirements, as appropriate.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ADCC	Antibody-Dependent Cellular Cytotoxicity	ISF	Investigator Site File
ADCP	Antibody-Dependent Cellular Phagocytosis	IV	Intravenous
AE	Adverse Event	LDH	Lactate Dehydrogenase
ANC	Absolute Neutrophil Count	LDi	Longest diameter
ALT	Alanine aminotransferase	LFT	Liver Function Test
AR	Adverse Reaction	mAb	Monoclonal Antibody
AST	Aspartate aminotransferase	MCL	Mantle Cell Lymphoma
Bcl-xL	B-cell lymphoma-extra large	MedDRA	Medical Dictionary for Regulatory Activities
B-NHL	B-cell non Hodgkin Lymphoma	MHRA	Medicines and Healthcare products Regulatory Agency
CD	Cluster of Differentiation	MRI	Magnetic Resonance Imaging
CI	Chief Investigator	mRNA	Messenger RNA
CLL	Chronic Lymphocytic Leukaemia	MZL	Marginal Zone Lymphoma
CRP	C-Reactive Protein	NCI	National Cancer Institute
CT	Computerised Tomography	NK	Natural Killer
CTA	Clinical Trial Authorisation	NSCLC	Non-small cell lung cancer
CTCAE	Common Terminology Criteria for Adverse Events	NYHA	New York Heart Association
CTL	Cytotoxic T-Cell	PD	Pharmacodynamics
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4	PD-1	Programmed Death-1
DAT	Direct antiglobulin test	PD-L1	Programmed Death-Ligand1
DCs	Dendritic cells	PID	Patient Identifiable Data
DLBCL	Diffuse Large B-Cell Lymphoma	PK	Pharmacokinetics
DLT	Dose Limiting Toxicity	PPD	Product of Perpendicular Diameter
DMEC	Data Monitoring and Ethics Committee	QP	Qualified Person
DMP	Data Management Plan	RCC	Renal cell carcinoma
ECG	Electrocardiogram	REC	Research Ethics Committee
ECOG	Eastern Cooperative Oncology Group	RNA	Ribonucleic Acid
eCRF	Electronic Case Report Form	RSI	Reference Safety Information
FDG PET	Fluorodeoxyglucose Positron Emission Tomography	SAE	Serious Adverse Event
FL	Follicular Lymphoma	SAP	Statistical Analysis Plan
GCP	Good Clinical Practice	SAR	Serious Adverse Reaction
G-CSF	Granulocyte-Colony Stimulating Factor	SCTU	Southampton Clinical Trials Unit
Hb	Haemoglobin	SDi	Short Diameter
HBcAb	Hepatitis B core antibody	SmPC	Summary of Product Characteristics
HBsAg	Hepatitis B surface antigen	SPD	Sum of the Product of the Diameters
HBV	Hepatitis B Virus	SUSAR	Suspected Unexpected Serious Adverse Reaction
HCV	Hepatitis C Virus	TCR	T-Cell Receptor
HIV	Human Immunodeficiency Virus	TNFR	Tumour Necrosis Factor Receptor
HL	Hodgkin Lymphoma	TMF	Trial Master File
HLA-DR	Human Leukocyte Antigen - antigen D Related	TMG	Trial Management Group
IB	Investigator Brochure	Treg	Regulatory T-Cell
ICD	International Classification of Diseases	TSC	Trial Steering Committee
IFN	Interferon	TSH	Thyroid Stimulating Hormone
Ig	Immunoglobulin	UAR	Unexpected Adverse Reaction
IL	Interleukin	ULN	Upper Limit of Normal
IMP	Investigational Medicinal Product	WBC	White Blood Cell
irAE	Immune-related adverse event	WISH	Wessex Investigational Sciences Hub
IRR	Infusion-Related Reaction		

KEYWORDS

B-Cell Malignancies
Relapsed
Refractory
Monoclonal Antibodies (mAb)
Phase IIa

TRIAL SYNOPSIS

Short title:	RiVa
Full title:	A phase IIa study of rituximab and varlilumab in relapsed or refractory B-cell malignancies.
Phase:	**IIa**
Population:	**Inclusion Criteria:** 1. Relapsed or refractory CD20$^+$ B-cell lymphoma excluding chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL). • High grade subgroup: Diffuse large B-cell lymphoma (DLBCL), Follicular Lymphoma (FL) grade 3b, transformed Follicular Lymphoma • Low grade subgroup: All low grade CD20$^+$ B-cell lymphoma subtypes excluding CLL/SLL, e.g. Mantle cell lymphoma (MCL), Lymphoplasmacytic lymphoma (LPL) and Follicular Lymphoma (FL) grade 1, 2 and 3a 2. Disease must be recurrent or treatment refractory, and received at least one line of treatment. Rituximab-refractory participants are eligible for entry into the study. 3. At least one measurable lesion by CT scan (defined as >1.5 cm in one axis) that is also easily accessible for biopsy. 4. Histological confirmation of relapse within 12 months of treatment and availability of fresh tissue. **(Histological confirmation and trial biopsy can be performed simultaneously.)** 5. 16 years of age or older. 6. Haematological and biochemical indices with the ranges shown below: • *Haemoglobin (Hb) ≥ 90 g/L (red cell support is permissible)* • *Absolute neutrophil count (ANC) ≥1.0 x 10^9/L (or ≥0.5 x 10^9/L if bone marrow involvement). G-CSF support is not permissible at screening.* • *Platelet count ≥75 x 10^9/L (or ≥30 x 10^9/L if bone marrow involveme.nt)* • *Serum bilirubin ≤1.5 x upper limit of normal (ULN) unless raised due to Gilbert's syndrome in which case up to 3 x ULN is permissible.* • *Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 2.5 x ULN unless raised due to hepatic involvement.* • *Calculated creatinine clearance (Cockcroft-Gault formula) ≥30 ml/min (uncorrected value).* 7. Ability to understand the purpose and risks of the study and provide written informed consent. 8. Willing and able to participate in all required evaluations and procedures in this study protocol. 9. Participants must be willing to participate in appropriate pregnancy prevention measures: • Women of childbearing potential who have a negative serum or urine pregnancy test during screening (within 14 days prior to the start of trial treatment) and agree to use one highly effective form of contraception combined with an effective form of contraception (see below) effective from the first administration of all study drugs, throughout the trial and for 12 months after last dose all study drugs are considered eligible. • Male participants with partners of childbearing potential who agree to take measures not to father children by using one form of highly effective

contraception from the first administration of all study drugs, throughout the trial and for 12 months after last dose of all study drugs are considered eligible. Male subjects must also refrain from donating sperm during this period.

Contraception
Contraception that is considered highly effective includes oral, injected or implanted progesterone-only hormonal contraception (with inhibition of ovulation); oral, intravaginal, or transdermal combined (oestrogen and progesterone containing) hormonal contraception (with inhibition of ovulation); an intra-uterine device (IUD); an intrauterine hormone releasing system (IUS); bilateral tubal occlusion; vasectomised partner or abstinence.
Contraceptive methods considered to be effective include progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; condom; cap, diaphragm or sponge with spermicidal gel.

- Men with pregnant or lactating partners must be advised to use barrier method contraception (for example: condom plus spermicidal gel) to prevent exposure to the foetus or neonate.

10. Life expectancy ≥ 12 weeks.
11. ECOG performance status 0-2.

Exclusion Criteria:

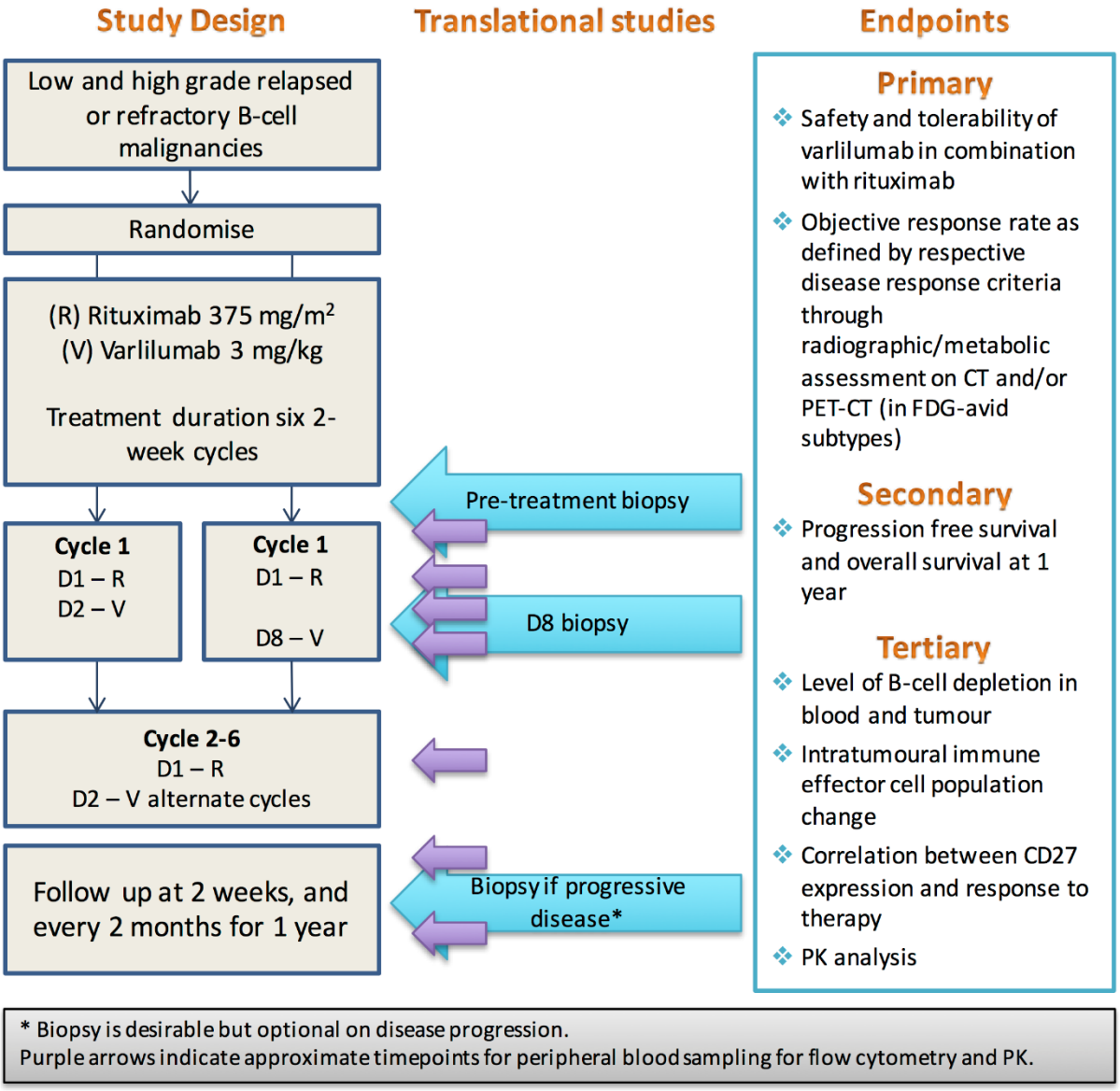
1. Known central nervous system involvement by lymphoma, that is not in remission, are excluded from the study.
2. History of other malignancy within the last 2 years except for:
   - Noninvasive malignancies such as adequately treated ductal carcinoma in situ of the breast, non-melanoma skin cancer or lentigo maligna, cervical carcinoma in situ and urothelial papillary noninvasive carcinoma or carcinoma in situ, and
   - Prostate intraepithelial neoplasia without evidence of prostate cancer.
3. Receiving treatment (or within a month of) with chemotherapy, immunotherapy or immunosuppressive agents. This includes any systemic steroids at dose exceeding 10 mg prednisolone (or other steroid equivalent) within 2 weeks prior to first dose of trial treatment.
4. Significant concurrent, uncontrolled medical condition that in the opinion of the Investigator contraindicates participation in this study.
5. Active and documented autoimmune disease (including, but not limited to, inflammatory bowel disease, coeliac disease, haemolytic anaemia, or immune thrombocytopenic purpura) prior to first dose of trial treatment.
6. Active infection requiring systemic therapy.
7. Women who are pregnant or lactating.
8. Serological positivity for Hepatitis B, C, or known HIV infection. As per standard of care, the results of hepatitis serology should be known prior to commencement of immunochemotherapy.
   - Positive test results for chronic HBV infection (defined as positive HBsAg serology and positive HBcAb) will not be eligible. Participants with occult or prior HBV infection (defined as negative HBsAg and positive HBcAb)

	will not be eligible. Participants who have protective titres of hepatitis B surface antibody (HBsAb) after vaccination will be eligible. • Positive test results for hepatitis C (HCV antibody serology testing) will not be eligible. 9. Previous recipient of an allogeneic bone marrow transplant at any time. 10. Autologous bone marrow transplant within 100 days of first dose of trial treatment. 11. Systemic radiation therapy within 4 weeks or prior focal radiotherapy within 2 weeks prior to first dose of trial treatment. 12. Subjects known or suspected of being unable to comply with the protocol. 13. Ongoing toxic manifestations of previous treatments. Exceptions to this are alopecia or certain Grade 1-toxicities, which in the opinion of the Investigator should not exclude the patient. 14. Uncontrolled congestive cardiac failure, cardiac ischaemia or cardiac arrhythmia. Clinically significant cardiac disease including unstable angina, acute myocardial infarction within six months prior to registration, congestive heart failure (NYHA III-IV). 15. Subjects with a known hypersensitivity (≥ Grade 3) to rituximab or murine proteins, or any other excipients used in the formulation of rituximab.
Rationale:	Although the phase 1 data presented with varlilumab is encouraging, it is clear that monotherapy is unlikely to induce high response rates or sustained remissions. Therefore, we assessed whether combining anti-CD20 with anti-CD27 mAb will deliver improved efficacy. Our hypothesis is that varlilumab enhances rituximab-mediated tumour killing by activating CD27-expressing T and NK cells which release cytokines that attract myeloid cells that phagocytose rituximab-coated tumour cells.
Trial Design:	This is a multicentre, randomised phase IIa trial in participants with relapsed or refractory CD20+ B cell malignancies. We aim to recruit 40 participants in total, with recruitment ending on the 31st December 2020. Of the total participants recruited there will be 20 participants from each of the following subcategories and 10 per treatment arm: A) High grade lymphoma (DLBCL, FL grade 3b, transformed FL) (n=20) B) Low grade lymphoma (e.g. FL grade 1, 2 or 3a, MZL, MCL, LPL) (n=20) The trial will include a safety run in where 6-12 participants (3-6 from each Arm and from any subtype) will be treated and the number of dose limiting toxicities (DLTs) assessed. The trial will only progress to 40 participants if there are an acceptable number of DLTs in this safety run in.
Primary Objectives:	To document safety and tolerability of combined rituximab and varlilumab therapy. To document anti-tumour activity of combined rituximab and varlilumab therapy in relapsed or refractory B-cell malignancies.
Secondary Objective:	To measure the duration of response to rituximab and varlilumab over a follow-up period of 1 year.
Tertiary Objectives:	To assess the level of B-cell depletion in the peripheral blood and, where relevant, tumour site following therapy.

	To establish the proportion of immune effector cell populations in the peripheral blood and, where relevant, tumour site following therapy. To assess whether the expression of CD27 is associated with response in combined rituximab and varlilumab therapy. To ascertain whether co-administration of rituximab and varlilumab together alters their pharmacokinetic properties.
Endpoints:	**Primary:** - Response according to the Lugano Revised Response Criteria for Malignant Lymphoma. - Causality of each adverse event and grading of severity according to NCI CTCAE Version 4.03. **Secondary:** - Progression-free survival and overall survival at 1 year for all participants. **Tertiary:** - Peripheral blood and intratumoural B-cell depletion using flow cytometry, in pre- and post-treatment samples. - Immune effector cell populations – CD4 and CD8 T-cell, NK cells, neutrophil, monocyte and macrophage levels by flow cytometry, in pre- and post-treatment samples. - CD27 expression level on CD8 T-cells, effector CD4 T-cells, regulatory CD4 T-cells, NK cells and B-cells in pre-treatment peripheral blood and/or intratumoural material by flow cytometry. - PK levels from peripheral blood from 6 participants in Arm A.
Sample size:	If fewer than 13% (p1) of participants respond then this combination would be deemed insufficiently active to warrant further study. If however 40% or more (p2) participants respond then the combination would be deemed worthy of further investigation. Using a 1 stage Flemings design at α=0.05 (one-sided) and 90% power, this would require 20 participants in each of the high and low grade arms (Arms A and B combined), a total of 40 participants (20 per disease category). Within each the high and low grade groups, if 6 or more out of 20 participants have a response this would warrant further investigation of that grade population in a phase III setting.
Investigational Medicinal Product:	Varlilumab; Rituximab
Dosage Regimen /Duration of Treatment:	**TREATMENT SCHEDULE:** Participants will be randomised between Arms A and B: **Arm A**: <u>Cycle 1</u> D1 Rituximab 375 mg/m^2 IV D2 Varlilumab 3 mg/kg IV **Arm B**: <u>Cycle 1</u> D1 Rituximab 375 mg/m^2 IV D8 Varlilumab 3 mg/kg IV

	In both arms A & B: Cycles 2 to 6 D1 Rituximab 375 mg/m^2 IV Cycles 3 and 5 D2 Varlilumab 3 mg/kg IV

TRIAL SCHEMA



SCHEDULE OF OBSERVATIONS AND PROCEDURES

Screening and Randomisation

Visit:	Screening					
Time (days)	**Within 12 months of treatment**	**Within 90 days of treatment**	**Within 28 days of treatment**	**Within 14 days of treatment**	**Within 7 days of treatment**	**Within 72 hours of treatment**
Informed Consent			X			
Inc/Exc Criteria				X		
Medical History				X		
Demographics			X			
Physical Exam				X		
Vital Signs				X		
ECOG Performance Status				X		X
ECG			X			
Body Weight			X			
Height			X			
Tissue Collection[a]	X					
Haematology[b]			X			X
Biochemistry[c]			X			X
Coagulation (if clinically indicated)			X			
Immunoglobulins and paraprotein estimation			X			
Beta-2 microglobulin			X			
Serum urate			X			
Creatinine clearance			X			
Serum lactate dehydrogenase (LDH)			X			
Thyroid function test			X			
Virology (Hep B, Hep C, HIV serology)[d]			X			
Direct antiglobulin test (DAT)				X		
Pregnancy Test				X		
Contrast-enhanced CT or PET/CT scan[e]			X			
Bone Marrow Trephine[f]		X				
Concomitant Medication			X	X		
Adverse events[g]			X	X	X	X
Randomisation					X	

a: Initial pre-treatment biopsy should consist of a diagnostic sample that is used to confirm diagnosis locally and two fresh cores (each minimum 1 cm in length) for translational endpoints that are sent to the WISH laboratory on the day of sample collection (see Laboratory Manual for details).

b: Full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count and platelet count.
c: For renal, bone and liver function, to include: sodium, potassium, urea, creatinine, calcium, bilirubin, ALT or AST, alkaline phosphatase and albumin.
d: Results should be available prior to initiation of immunochemotherapy. HBsAg, HBcAb and Hepatitis C serology must be tested.
e: Contrast-enhanced CT of neck, chest, abdomen and pelvis with bi-dimensional reporting within 28 days of planned treatment is mandatory. PET/CT scan with Deauville score may also be performed at the Investigator's discretion.
f: Only required if there is cytopenia during screening and if it alters the staging of the disease.
g: AEs to be collected from date of consent. Before start of treatment, only AEs related to study procedures should be reported.

Cycle 1

	ARM A + ARM B	ARM A		ARM B	
Visit	**Cycle 1 Day 1**	**Cycle 1 Day 2**	**Cycle 1 Day 8**	**Cycle 1 Day 2**	**Cycle 1 Day 8**
Week	**1**		**2**		**2**
Physical Exam[h]	X	X	X	X	X
Vital Signs[i]	X	X	X	X	X
Body Weight	X				
Tissue Collection[j]			X		X
Haematology[k]	X	X	X	X	X
Biochemistry[l]	X	X	X	X	X
10ml lithium heparin sample	X	X	X	X	X
PK Sample[m]	X[m]	X[m]	X		
Rituximab	X				
Varlilumab		X			X
Concomitant Medication	X	X	X	X	X
Adverse Events	X	X	X	X	X

h: Physical exam up to 72 hours pre administration
i: Vital signs to be collected pre- infusion and 30 minutes post-infusion (if no infusion is due, collect one set of vital signs).
j: Tissue to be collected before administration of varlilumab in arm B. Day 7/8 tissue collection is mandatory and must comprise of core biopsies at a minimum. Fine needle aspirates are inadequate. Two fresh cores (minimum 1 cm in length each) need to be taken and sent to the WISH Laboratory on the day of collection (see details in Laboratory Manual).
k: Up to 72h pre administration. Full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count, and platelet count.
l: Up to 72h pre administration. Renal, bone and liver function tests. Serum chemistry to include sodium, potassium, urea, creatinine, calcium, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, albumin and uric acid.
m: PK samples will be collected from the first 6 participants in Arm A, for patients with 50% or less of PK samples collected the patients will be replaced with further Arm A patients to ensure sufficient samples are collected for the analysis.
m: PK sample to be collected pre- and post-infusion of trial drug. Post-infusion sample to be taken 30 ± 5 minutes after end of infusion.

Cycles 2-6 and End of treatment (Arm A and Arm B)

Visit	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 3 Day 2	Cycle 4 Day 1	Cycle 5 Day 1	Cycle 5 Day 2	Cycle 6 Day 1	End of treatment
Weeks	**3**	**5**		**7**	**9**		**11**	**15**
Physical Exam[n]	X	X		X	X		X	X
ECOG Performance Status	X	X		X	X		X	X
Vital Signs[o]	X	X		X	X		X	X
Body Weight	X	X		X	X		X	X
Haematology[p]	X	X		X	X		X	X
Biochemistry[q]	X	X		X	X		X	X
Immunoglobulins and paraprotein estimation[r]	X	X		X	X		X	X
10 ml lithium heparin sample	X	X		X	X		X	X
PK sample[s]	X		X					
Pregnancy Test	X	X		X	X		X	
Rituximab	X	X		X	X		X	
Varlilumab			X			X		
Contrast-enhanced CT or PET/CT scan[t]								X
Bone Marrow Trephine[u]								X
Thyroid function test[v]	X	X		X	X		X	X
Concomitant Medication	X	X		X	X		X	X
Adverse Events	X	X	X	X	X	X	X	X

n: Physical exam up to 72 hours pre administration
o: Vital signs to be collected pre-infusion and 30 minutes post-infusion or one set if no drug is administered.
p: Up to 72 hours pre administration. Full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count and platelet count.
q: Up to 72 hours preadministration. Renal, bone and liver function tests. Serum chemistry to include sodium, potassium, urea, creatinine, calcium, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, albumin and uric acid.
r: If abnormal at baseline. Up to 72 hours pre-administration.
s: PK samples will be collected from the first 6 participants in Arm A, for patients with 50% or less of PK samples collected the patients will be replaced with further Arm A patients to ensure sufficient samples are collected for the analysis.. PK sample to be collected pre- and post-infusion of trial drug. Post-infusion sample to be taken 30 ± 5 minutes after end of infusion.
t:Contrast-enhanced CT of neck, chest, abdomen and pelvis with bi-dimensional measurements is mandatory. Alternatively, PET/CT scan with Deauville score may be performed at the Investigator's discretion.
u:If abnormal at baseline.
v: If abnormal at baseline. Up to 72 hours pre-administration.

Follow-up visits

Months following last therapy	2	4	6	8	10	12
Tissue collection[t]	X	X	X	X	X	X
Concomitant Medication	X					
Physical Exam	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Body weight	X	X	X	X	X	X
Adverse events[u]	X					
Haematology[v]	X	X	X	X	X	X
Biochemistry[w]	X	X	X	X	X	X
Immunoglobulin and paraprotein estimation	X	X	X	X	X	X
Beta-2 microglobulin	X	X	X	X	X	X
Contrast-enhanced CT or PET/CT scan[x]	X	X	X	X	X	X
Bone marrow trephine[y]	X	X	X	X	X	X

t: Tissue collection on disease progression at a single time point during the follow up period is highly desirable but optional.
u: All AEs to be reported until 30 days after last dose of trial treatment. AEs deemed related to the trial require reporting regardless of the time since treatment
v: Full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count and platelet count.
w: Renal, bone and liver function tests. Serum chemistry to include sodium, potassium, urea, creatinine, calcium, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, albumin and uric acid.
x: Contrast-enhanced CT of neck, chest, abdomen and pelvis with bi-dimensional measurements to be performed 2 months post completion of treatment if disease is less than CR, and/or at any point during the 1 year follow up if there is clinical suspicion of disease progression. A PET/CT with Deauville score scan may also be performed at the Investigator's discretion.
y: For new and persistent, unexplained cytopenias, at a single time point during the follow up period.

1 INTRODUCTION

1.1 BACKGROUND

There are over 12,000 new cases of B-cell malignancies diagnosed in the United Kingdom each year *(1)*. B-cell cancers can be divided broadly into high grade (e.g. diffuse large B-cell lymphoma [DLBCL]) or low grade (e.g. follicular lymphoma [FL] and chronic lymphocytic leukaemia [CLL]) based on their rate of progression. DLBCL, CLL and FL are the three most common subtypes, accounting for 80% of B-cell malignancies. High grade lymphomas are potentially curable whereas low grade lymphomas have a relapsing remitting course *(2)*.

Standard frontline therapy of most B-cell malignancies consists of immunochemotherapy with rituximab, an anti-CD20 monoclonal antibody (mAb). Despite being considered a treatable and potentially curable cancer, approximately 30% of DLBCL cases will relapse after frontline therapy *(3)*. There is no established standard for second line therapy but if a patient is fit enough, consolidation with an autologous stem cell transplant is undertaken. Even with transplantation, only 50% of cases will achieve durable remissions. Thus the great majority of participants with relapsed DLBCL will eventually succumb to the disease. Whilst the indolent diseases lead a less aggressive course, successive remissions become increasingly shorter in duration, necessitating different therapies with each relapse. Thus there is a clear clinical need for more novel therapeutic agents in B-cell lymphoma to increase the depth of remissions on initial therapy, and to lengthen remissions on relapse.

Anti-CD20 mAb therapy

Rituximab is a so-called direct-targeting mAb, which binds to the CD20 molecule on the surface of normal and malignant B cells. The mAb then engages immune effectors cells, such as macrophages, through Fc:Fc gamma receptor interaction, leading to tumour cell killing by antibody directed cellular cytotoxicity and/or phagocytosis (ADCC/ADCP) (reviewed in *(4, 5)*). There is now good evidence in pre-clinical models that monocytes and macrophages are the key effector cells in mediating ADCC/ADCP with anti-CD20 mAb *(6-8)*. Depletion of macrophages but not NK cells in murine models decreases mAb efficacy *(8, 9)*. It is controversial whether rituximab might induce cell death through direct signalling effects and complement (reviewed in *(5)*). Further, it has also been postulated that rituximab might induce an adaptive immune response *(10)*. This is suggested by the development of delayed clinical responses as many as 112 days after rituximab administration, which is in keeping with the time taken to induce T-cell immunity *(11)*. However, incontrovertible objective evidence in participants and fully syngeneic mouse models of this is still lacking.

As detailed above, rituximab has now been incorporated into frontline therapy of B-cell malignancies, often in combination with chemotherapy, where it has been shown in randomised controlled trials to increase responses by up to 20% in FL and DLBCL *(12-15)*. It is also employed as a single agent in some indolent lymphomas *(16)*.

Immunomodulatory mAbs: CD27 as a target

A further class of mAbs that have garnered considerable interest recently are the immunomodulatory mAbs, which can be further sub-divided into immunostimulatory mAbs and checkpoint blockers. Unlike direct-targeting mAbs, which target the tumour cell directly, these mAbs bind to the normal immune cells of the host. These mAbs are thought to mediate their anti-tumour effects through enhancement of anti-tumour specific T-cell responses by augmenting their expansion, survival and/or function (reviewed in *(17)*). The checkpoint blockers anti-CTLA-4 and anti-PD1 mAbs have shown impressive clinical efficacy in a range of solid tumours, in particular melanoma *(18-23)*. However, apart from Hodgkin Lymphoma (HL), where anti-PD1 or anti-PDL1 mAbs have shown significant activity *(24)*, their efficacy in B-cell lymphoma is less impressive *(25, 26)*.

Amongst the immunostimulatory mAbs, anti-CD40, anti-CD137, anti-CD134 and anti-CD27 are the most advanced in clinical development. These mAbs have entered phase I clinical testing in solid tumours and

relapsed or refractory B-cell lymphomas. Apart from anti-CD40 *(27)* and anti-CD134 *(28)*, the results are not fully mature. As yet, the responses observed are not as convincing as those seen with the checkpoint blockers.

CD27 is a member of the tumour necrosis factor receptor (TNFR) superfamily and exists as a Type I transmembrane, disulphide-linked homodimer (reviewed in *(29)*). Unlike other TNFR members, which are only expressed upon prior activation, CD27 is constitutively present on all subsets of T-cells *(30)*, a subset of NK cells *(31)*, and memory B-cells *(32)*. CD27 is also expressed on a variety of B-cell malignancies particularly CLL, mantle cell lymphoma, FL and marginal zone lymphoma *(33, 34)*. The expression pattern of CD27 in human and mouse is largely similar with the main difference being that CD27 is also present on early haematopoietic cells in mice *(35)*. CD27 is further transiently upregulated on T-cell activation *(29)*. Thus while long-lived central memory CD8+ T-cells express CD27, terminally differentiated effector CD8+ T-cells do not *(36, 37)*.

Physiologically, CD27 activation is regulated by restricted expression of its ligand, CD70 *(38, 39)*. CD70 expression is limited to activated dendritic cells (DCs), B-cells, NK cells and T-cells, but is constitutively present on medullary thymic epithelial cells. Furthermore, on T-cells, CD27 stimulation only takes place when the T-cell receptor (TCR) is simultaneously engaged. CD70-CD27 interaction leads to recruitment of TNFR-associated factor (TRAF) proteins to the CD27 cytoplasmic tail *(40, 41)*. Subsequent activation of canonical and non-canonical nuclear factor-kB (NF-kB) and c-Jun-N-terminal kinase (JNK)-signalling pathways follows to elicit the cellular responses *(42)*.

In the initial T-cell priming phase, CD27 engagement enhances proliferation of both CD4 and CD8 T-cells in a CD3-dependent manner in vitro *(30, 43)*. Comprehensive studies in murine ovalbumin models performed at Southampton have demonstrated that CD27 stimulation also increases antigen-specific CD8 T-cell proliferation and survival in vivo and their ex vivo cytotoxicity as indicated by IL2 and IFNγ upregulation *(44)*. CD70/CD27 interaction is in fact critical to CD8 T-cell priming. Blockade of CD70 in OTI transgenic (Tg) models inhibited either CD40-dependent, CD4 T-cell helper-dependent or innate receptor-mediated primary CD8 T-cell clonal expansion *(45-48)*. Our studies have also shown that CD27 engagement contributes substantially to the secondary CD8 T-cell response by enhancing memory CD8 T-cell expansion, survival and cytolytic activity *(44, 49-51).* Our data is corroborated by other studies that demonstrate that CD27 engagement increases the CD8 T-cell repertoire, including the response to low affinity antigens in an influenza model *(52)*. These effects are thought to be partly achieved through induction of anti-apoptotic proteins Bcl-XL and PIM1 *(53)* as well as decreased FasL-induced apoptosis *(54)*.

The contribution of CD27 stimulation to Tregs is complex and depends on a variety of factors including the availability of IL2 and the duration of CD27 engagement (reviewed in *(29)*). CD70/CD27 interaction enhances the thymic development but not function of Tregs *(55)*. Another study comparing tumour development in CD27-deficient and -sufficient mice also demonstrated that WT mice had increased Treg expansion *(56)*. In either situation, Treg expansion depended on IL2 produced by CD70/CD27 effector T cells. However, in acute infection or immunisation models where CD27 engagement is transient, cytotoxic T cell (CTL) responses dominate over Treg expansion. This latter situation is likely to be more relevant in cancer immunotherapy, where CD27 engagement, elicited by anti-CD27 mAb therapy, is anticipated to be transient. Further, it has also been shown that CD27 stimulation on human Tregs reduces their activity and converts them into Th1 cells *(57)*.

The role of CD27 on other cell types is not as well studied as on T-cells. In human and mouse models, CD27 is present on memory B-cells, where CD27/CD70 interaction supports B-cell expansion in the germinal centre both intrinsically and through promotion of CD4 T-cell help *(32)*. A subset of NK cells express CD27, and here engagement of CD27 has been shown to increase IFNγ secretion albeit without a concomitant enhancement of cytotoxicity *(58)*.

The anti-tumour effect of CD27 ligation has been studied in a variety of murine tumour models. We first demonstrated in two B-cell lymphoma models, BCL_1 and A31, the therapeutic potency of anti-CD27 mAb

(59). Likewise, the anti-tumour efficacy of anti-CD27 mAbs has also been observed in EL4 lymphoma and melanoma models *(39, 60, 61)*.

Anti-human CD27 mAb: Varlilumab

Varlilumab (1F5, CDX-1127) is a recombinant and fully human IgG1kappa mAb that binds to human CD27 with high affinity *(62).* As far as we are aware, it is the only anti-CD27 mAb in clinical development. Once bound, varlilumab blocks CD70 binding to CD27. The agonist activity of varlilumab is demonstrated through a variety of in vitro and in vivo studies, and confirmed in preliminary results of a Phase I trial. In detail, in vitro, varlilumab is able to enhance human T-cell activation and proliferation when there is simultaneous TCR stimulation, and when the mAb is cross-linked *(62)*. Using a human CD27 (huCD27) Tg mouse model, varlilumab also induced T-cell proliferation and IFNγ release when combined with TCR stimulation in an in vitro setting *(63)*. Functionally, varlilumab also enhanced CD8 T-cell mediated IFNγ release to OVA. Given that varlilumab is an agonistic mAb and several B-cell tumours express CD27, it is possible that it might have tumorigenic effects. However, when primary human B-cell lymphoma cells that express high levels of CD27 were co-cultured with varlilumab either alone, or cross-linked, tumour cell proliferation was not observed *(62)*.

The anti-tumour activity of varlilumab has been demonstrated in several different mouse models. In xenograft models, varlilumab inhibited the growth of human Burkitt lymphoma-derived Raji and Daudi cells in immunodeficient SCID mice *(62)*. Further in vitro studies showed that the activity of varlilumab in these xenograft models is mediated through ADCC. There was no evidence to support complement-mediated cytotoxicity or direct cell death induction. These results indicate that varlilumab might also deplete CD27 expressing T-cells. However no significant changes in lymphocyte subpopulations were observed when varlilumab was administered to cynomolgus macaques *(62)*.

Varlilumab has also been tested in more relevant immune-competent, syngeneic models using huCD27 Tg mice. Improvement in survival was observed in BCL_1 lymphoma, CT26 colon carcinoma and EL4 lymphoma and EG7 lymphoma models *(63)*. In CT26, EL4 and EG7 models some of the varlilumab-treated mice remained protected upon tumour rechallenge, indicative of generation of a potent memory response *(63)*. In the CT26 and EG7 models, CD4 and CD8 T-cells were both required for varlilumab to mediate its antitumour activity.

Varlilumab in combination

Varlilumab has also been tested in combination with other agents. In the EG7 thymoma model, combining varlilumab with cyclophosphamide improved survival suggesting that chemotherapeutic agents can assist with tumour control without impairing varlilumab-driven immune responses. Varlilumab combined with checkpoint blockers such as anti-PD-L1, hypothesised to offer synergism in immune stimulation, also improved tumour control.

Clinical experience with varlilumab

Varlilumab was tested in a phase 1, dose escalation safety and pharmacokinetic study in participants with relapsed or refractory haematologic malignancies and solid tumours (NCT01460134). The study has completed recruitment but is still not closed and results are yet unpublished. The study comprises dose-escalation and tumour-specific expansion phases. The dose-escalation phase is a standard 3+3 design with 90 participants enrolled in the study. In the dose escalation phase, there were 25 cases with B-cell malignancies (10 DLBCL, 6 FL, 7 HL and 2 B-cell non Hodgkin lymphoma [B-NHL], not otherwise specified), 5 cases of T-cell malignancies and 25 solid tumour cases (10 colorectal cancer, 7 melanoma, 3 ovarian, 2 prostate, 2 renal cell carcinoma [RCC] and 1 non-small cell lung cancer [NSCLC]). Based upon the dose-escalation studies, 3 mg/kg was selected for the expansion phase and there were 15 RCC, 16 melanoma and 4 Hodgkin lymphoma cases.

Safety

The majority of adverse events (AEs) reported were mild to moderate in severity. Four Grade 3 treatment-related AEs were reported in the solid tumour dose escalation phase; arising due to hyponatraemia, anorexia, raised alkaline phosphatase and lymphopenia. In the solid tumour dose expansion phase, Grade 3 hypertension and Grade 4 asthma were reported on one occasion. The asthmatic exacerbation occurred in a patient with known asthma and lung metastases, and recovered with medical treatment. One Grade 2 infusion reaction was also reported. This occurred 1 hour after the first varlilumab infusion. The patient went on to receive additional infusions without the need for pre-medication and did not experience further infusion reactions. Of interest, the autoimmune AEs typically observed with checkpoint blockers e.g. hepatitis, vitiligo and colitis, were not significantly noted with varlilumab.

No dose-limiting toxicities (DLTs) were observed and the maximum tolerated dose (MTD) was not reached in participants treated with haematological malignancies. Only one patient with haematological malignancy discontinued due to treatment-related AEs. This patient received 10mg/kg varlilumab and had Grade 1 transient vision impairment and floaters. Amongst the solid tumours, one DLT was reported in which a patient with ovarian cancer experienced transient grade 3 hyponatraemia, which resolved without intervention. The cause of the hyponatraemia was thought to be unrelated to varlilumab but the patient was discontinued from the study due to the AE of hyponatraemia. A second patient with solid tumour also discontinued due to Grade 3 hip and pelvic pain and Grade 2 failure to thrive.

Pharmacokinetics and pharmacodynamics

Varlilumab has a half-life of 6 (varlilumab 1.0 mg/kg) to 11 (varlilumab 10 mg/kg) days, with accumulation observed during the weekly dosing phase. Occupancy studies indicate that doses above 1 mg/kg saturate the receptor for at least a month. No significant anti-varlilumab antibody responses have been observed to date.

Compatible with data observed in cynomolgus macaques, no significant depletion was observed in B-cells, CD4 and CD8 T-cells across all tumour types and doses. However there was a downward trend in % of circulating Tregs in solid tumour participants. In contrast, in solid tumour participants treated with 3 mg/kg, an upward trend was observed in the % of circulating NK cells. Whilst no obvious T-cell expansion was observed, there was evidence of an increase in HLA-DR expression, especially on CD8 memory T-cells particularly in participants treated with 3 mg/kg. Selected melanoma participants were also screened for responses to peptides derived from melanoma-associated antigens using direct stimulation assays or after in vitro stimulation. In several participants, enhancement of responses or development of new responses was observed, suggesting that varlilumab can improve T-cell responses to tumour antigens.

In summary the pharmacodynamic properties observed with varlilumab therapy are consistent with the predicted mechanism of action of an anti-CD27 agonistic mAb.

Clinical responses

Significant and durable responses were observed in 2 participants. The first case is a patient with advanced stage HL, who was treated with varlilumab at 0.3 mg/kg and who remained in remission at 18+ months. The second case is a patient with RCC treated with varlilumab at 3 mg/kg who has had a partial response, which is ongoing at 21.9+ months. The patient has had complete resolution of lung and lymph node lesions and an overall reduction in total size of target lesions of approximately 78%.

Thirteen additional participants experienced stable disease. In the solid tumour dose-escalation phase, 4 participants experienced stable disease. One patient with RCC patient treated at 3.0 mg/kg completed all 5 protocol allowed cycles of therapy and has been progression-free for 41.4+ months. A further 3 participants with colorectal cancer treated at 1 mg/kg, a melanoma patient treated at 0.1 mg/kg, and another colorectal cancer patient treated at 1.0 and 0.3 mg/kg had stable disease durations of 5.7, 3.8 and 3.0 months, respectively. In the melanoma expansion phase, a patient with uveal melanoma (Stage M1c) who previously failed ipilimumab and temozolomide chemotherapy had 12% shrinkage in

measurable disease, and experienced stable disease for 11.5 months. Two additional melanoma participants had stable disease with durations of response measuring 7.3 and 2.7 months. In the RCC expansion phase, 3 additional participants had stable diseases for 8.4, 5.6 and 2.8 months.

Three participants with haematological malignancies had stable disease. A patient with Stage III NHL who received varlilumab (0.3 mg/kg) experienced 36% shrinkage of measurable disease, including complete disappearance of disease in inguinal and iliac regions and a stable disease duration of 5.6 months. Two participants with stage IV FL treated with varlilumab at 0.3 mg/kg and 0.1 mg/kg had stable disease durations of 14 and 4.5 months, respectively.

In summary varlilumab demonstrated agonistic activity expected of an anti-CD27 mAb. There is clinical evidence of single agent clinical activity in this heavily pre-treated population of participants with progressive and metastatic disease, and when other immunomodulatory mAbs have failed.

This project aims to improve the rate, depth and duration of response by the addition of varlilumab to rituximab therapy. A comparator arm with rituximab alone would have been ideal but this would not be an effective treatment option in this population. If these two experimental arms are shown to be safe and effective then a future randomised phase trial comparing the combination against a control arm will be undertaken.

Currently there are no means of identifying which cases might respond to immunomodulatory mAb, specifically anti-CD27 mAb. The project aims to discover any prognostic/predictive biomarkers that might predict response to rituximab and varlilumab therapy in B-cell lymphoma participants by analysing pre-treatment tumour biopsies by flow cytometry. Of interest will be the influence of CD27 expression on tumour/immune cell subsets, and the proportion of the individual immune cell subsets. Analyses for other potential prognostic/predictive markers will be explored through RNA sequencing, performed later. Validation/verification of any identified biomarkers will need to be performed in retrospective studies and/or further prospective trials.

By repeated tumour sampling, the project aims to characterise changes in the tumour and its microenvironment through protein and mRNA expression. The ability to correlate these changes with clinical responses is key to understanding how we might further improve mAb therapy in resistant cases.

1.2 RATIONALE AND RISK BENEFITS FOR CURRENT TRIAL

There is no standard therapy in relapsed disease. Therapy is selected based on previous treatments undertaken, quality of remission, duration of response and the patient's co-morbidities.

Below are the general options:

1) Combination chemotherapy with or without rituximab.
2) Radiotherapy in localised disease.
3) Recruitment into clinical trials of novel agents.

In the majority of cases, patients will become refractory to treatment and further novel therapy is required.

2 STUDY OBJECTIVES

	Objective	Endpoint used to evaluate
Primary:	To document safety and tolerability of combined rituximab and varlilumab therapy. To document anti-tumour activity of combined rituximab and varlilumab therapy in relapsed or refractory B-cell malignancies.	The causality of each adverse event and grading of severity according to NCI CTCAE Version 4.03. Response (stable disease, partial response or complete response) in each case according to the Lugano Revised Response Criteria for Malignant Lymphoma (Appendix 1).
Secondary:	To measure the duration of response to rituximab and varlilumab over a follow-up period of 1 year.	Progression-free survival and overall survival at 1 year for all participants.
Tertiary:	To assess the level of B-cell depletion in the peripheral blood and, where relevant, tumour site following therapy. To establish the proportion of immune effector cell populations in the peripheral blood and, where relevant, tumour site following therapy. To assess whether the expression of CD27 could act as a biomarker of response in combined rituximab and varlilumab therapy. To ascertain whether co-administration of rituximab and varlilumab together alters their pharmacokinetic properties.	B-cell depletion and/or intratumoural B cell levels using flow cytometry, in pre- and post-treatment samples. Measurement of peripheral blood and/or intratumoural immune cell subset levels (CD4 and CD8 T-cell subsets, NK cells, neutrophil, monocyte and macrophage levels) by flow cytometry, in pre- and post-treatment samples. Measurement of CD27 expression level on CD8 T-cells, effector CD4 T-cells, regulatory CD4 T-cells, NK cells and B-cells in pre-treatment peripheral blood and/or intratumoural material by flow cytometry. Measurement of PK levels from peripheral blood from 6 participants in Arm A.

3 STUDY DESIGN

A multicentre, randomised, phase IIa study in patients with relapsed or refractory CD20+ B-cell malignancies. The study will be conducted in 2 stages as follows:

Stage 1 – Safety

During the safety phase, 6 participants (3 from each Arm and from any subtype) will be treated as detailed in section 6.1. Safety data from the first 6 evaluable participants will be reviewed by the Safety Review Committee (SRC). An evaluable participant is defined as one who, during cycle 1 (between first dose of rituximab and day 1 of the second cycle of treatment), has completed all relevant safety evaluation requirements and has received some of the doses of rituximab and varlilumab and/or has experienced a Dose Limiting Toxicity (DLT) as defined below. The number of DLTs experienced by these participants in each arm after having completed the first cycle will dictate whether we proceed to the second stage of the trial.

The options are as follows (see diagram in Appendix 2):

1. In each arm, if out of these 3 participants 0 experience a DLT, then we will proceed to stage 2.

2. In each arm, if out of these 3 participants 1 or 2 experience a DLT, then we will expand the cohort to 3 more participants.

    a) If 1 or 2 out of 6 participants experience a dose limiting toxicity, we will proceed to Stage 2.
    b) If 3 or more out of 6 participants experience a DLT, recruitment for that arm will be stopped.

3. If out of these 3 participants, 3 experience a dose limiting toxicity, recruitment for that arm will be stopped.

Initially, the first participant will be entered into the trial. Providing there are no serious or unexplained safety issues during cycle 1, as determined by the SRC, then dosing of subsequent participants will continue as they are identified. Should toxicity findings of concern occur, the SRC may choose to stagger the start of dosing for subsequent participants and/or cohorts.

Definition of DLT

A DLT is defined as a highly probable or probable treatment-related AE that occurs between the first dose administration of varlilumab and day 1 of the second cycle of treatment. Specifically, these are:

- Grade 4 neutropenia >7 days duration despite GCSF
- Febrile neutropenia (fever of unknown origin without clinically or microbiologically documented infection) with Grade 3 or 4 neutropenia (ANC $<1.0 \times 10^9$/L and fever >38.5°C)
- Thrombocytopenia Grade 4: a) for >5 days or b) associated with active bleeding despite support
- Grade 3 or 4 cytokine release syndrome or infusion related reactions despite pre-medication
- Grade 3 or 4 non-haematological toxicity, including Grade 3 and 4 biochemical AEs
- Delay to start of cycle 2 by more than 3 weeks due to trial treatment toxicity
- Event with a fatal outcome

Excluded AEs are:

- Grade 3 nausea, Grade 3 or 4 vomiting in participants who have not received optimal treatment with anti-emetics
- Grade 3/4 diarrhoea in participants who have not received optimal treatment with antidiarrhoeals
- Lymphopenia

Stage 2 – Activity, safety and feasibility

The objective of the phase II is to obtain some further information on the safety of the intervention in a larger sample, information on activity (response rate overall and per lymphoma subtype) and feasibility of administrating rituximab and varlilumab together. During Stage 2, recruitment will continue so (including those in Stage 1), there is a total of 10 participants per arm and per disease category (a total of 20 participants per disease category, 40 participants in the trial in total).

The overall response rate after 6 cycles and safety with incidences of treatment-related AEs, treatment-related SAEs (recorded using CTCAE) and laboratory abnormalities will be evaluated. Each participant recruited will be randomly allocated to Arm A or B (using a 1:1 allocation ratio). Randomisation will be performed by the research team at sites using an online randomisation tool. The randomisation schedule will be stratified by disease subtype and centre (see section 4.5).

Participants from Arm A and Arm B will be combined together for analyses on response rate and adverse events per disease subtype. We do not anticipate a difference in either response rate or adverse events

between both arms. If during the safety phase one of the treatment arms is closed, then all participants will be recruited to the remaining arm so as the total sample size is 20 in each disease category.

The decision on whether there is sufficient activity to warrant further investigation in a future phase III will based on the following criteria:

1) Within each the high grade and low grade group, if 6 or more out of 20 participants have a response as defined by the Lugano Revised Response Criteria for Malignant Lymphoma (or if fewer than 20 patients are recruited the 90% confidence interval for response lies solely above 13%), and/or
2) There is increased intratumoural B-cell depletion in the Day 8 biopsies of participants who have received rituximab and varlilumab compared to rituximab alone, and/or
3) There is increased activation or increase in absolute numbers/proportion of macrophage, monocyte and/or neutrophil populations in the Day 8 tumour biopsies of participants who have received rituximab and varlilumab compared to rituximab alone.

A total of 40 participants will be recruited, with 20 participants in each of the following subcategories:

A) High grade lymphoma (DLBCL, FL grade 3b, transformed FL) (n=20)
B) Low grade lymphoma (e.g. FL grade 1, 2 or 3a, MZL, MCL) (n=20)

If 20 participants are recruited to one of the subcategories (high grade or low grade), that subcategory will be closed to recruitment. Recruitment in the other subcategory will continue until 20 participants have been recruited to it.

The main purpose for having two experimental treatment arms is to provide a comparator for the translational endpoints, i.e. to assess whether the differences observed are due to the addition of varlilumab to rituximab. The only difference between Arm A and Arm B is the delay in administration of varlilumab in cycle 1, which is on Day 2 in Arm A and Day 8 in Arm B. As the post-treatment tissue collection occurs on Day 7/8, prior to administration of varlilumab in Arm B, samples will be obtained from participants that have either been treated with rituximab alone, or both rituximab and varlilumab. To minimise any potential risks to the participant as a result of a repeat biopsy on Day 7/8, a prerequisite for entry to the trial is that the participants must have accessible sites for biopsy. Difference in response rates between Arm A and Arm B are not expected.

Recruitment will end on the 31st December 2020.

3.1 STUDY ENDPOINTS

3.1.1 Primary endpoints

- Safety – DLT and adverse events causality and grading of severity according to NCI CTCAE Version 4.03.
- Activity - Response (stable disease, partial response or complete response) in each case according to the Lugano Revised Response Criteria for Malignant Lymphoma (see Appendix 1).

3.1.2 Secondary endpoint

- Progression-free survival and overall survival at 1 year for all participants.

3.1.3 Tertiary endpoints

- Measurement of peripheral blood and/or intratumoural B cell levels using flow cytometry, in pre- and post-treatment samples.

- Measurement of peripheral blood and/or intratumoural immune cell subset levels (CD8 and CD8 T cell subsets, NK cells, neutrophil, monocyte and macrophage) levels by flow cytometry, in pre- and post-treatment samples.

- Measurement of CD27 expression level on CD8 T cells, effector CD4 T cells, regulatory CD4 T cells, NK cells and B cells in pre-treatment peripheral blood and/or intratumoural material by flow cytometry.

- Measurement of PK levels from peripheral blood from 6 participants in Arm A.

3.2 CENTRE SELECTION

UK centres have been selected on the basis that they all have the infrastructure to support effective early phase clinical trial as assessed by the study feasibility questionnaire.

Before the commencement of recruitment, each centre will be required to do the following:

- Register with the Southampton Clinical Trials Unit (SCTU)
- Completed the Clinical Trial Site Agreement signed by participating Trust
- Provide confirmation of participating Trust Research and Development approval

3.3 DEFINITION OF END OF TRIAL

The end of the trial is defined as the date of the last follow-up visit of the last participant (to occur 12 months after receiving the last study treatment) or sooner, if all participants have progressed, died or withdrawn from the study. The study will terminate early if 3 or more participants experience a DLT in each group during stage 1 (safety stage).

Investigators will be informed when participant recruitment ceases.

The Trial Steering Committee (TSC) or the Safety Review Committee (SRC) may prematurely discontinue the trial. Any such decision will be notified to the MHRA and REC.

4 SELECTION AND ENROLMENT OF PARTICIPANTS

4.1 CONSENT

Consent to enter the trial must be sought from each participant only after a full explanation has been given, an information leaflet offered and time allowed for consideration. Each participant must provide written informed consent, which should be signed by an Investigator and the participant. Participants will keep a copy of the information sheet and signed consent form. The right of the patient to refuse to participate without giving reasons must be respected. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the trial for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

Following registration, a member of the research team will scan the signed consent form and email it to SCTU. The consent form must be sent from an nhs.net email address to uhs.sctu@nhs.net marked F.A.O. RiVa trial team. The original signed consent form will be filed in the investigator site file.

4.2 INCLUSION CRITERIA

1. Relapsed or refractory $CD20^+$ B-cell lymphoma excluding chronic lymphocytic leukaemia/small lymphocytic lymphoma (CLL/SLL).
    - High grade subgroup: Diffuse large B-cell lymphoma, FL grade 3b, transformed FL
    - Low grade subgroup: All low grade $CD20^+$ B-cell lymphoma subtypes excluding CLL/SLL (e.g. FL grade 1,2 or 3a, MCL, LPL)
2. Disease must be recurrent or treatment refractory, and received at least one line of treatment. Rituximab-refractory participants are eligible for the entry into the study as long as the tumour expresses CD20.
3. At least one measurable lesion by CT scan (defined as >1.5 cm in one axis) that is also easily accessible for biopsy.
4. Histological confirmation of relapse within 12 months of treatment, and availability of fresh tissue. **(Histological confirmation and trial biopsy can be performed simultaneously.)**
5. 16 years of age or older.
6. Haematological and biochemical indices with the ranges shown below:

Laboratory Test	*Value required*
Haemoglobin (Hb)	*≥ 90 g/L (red cell support is permissible)*
Absolute neutrophil count (ANC)	*≥1.0 x 10^9/L (or ≥0.5 x 10^9/L if bone marrow involvement) G-CSF support is not permissible at screening*
Platelet count	*≥75 x 10^9/L (or ≥30 x 10^9/L if bone marrow involvement)*
Serum bilirubin	*≤1.5 x upper limit of normal (ULN) unless raised due to Gilbert's syndrome in which case up to 3 x ULN is permissible*
Alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST)	*≤ 2.5 x ULN unless raised due to hepatic involvement*
Calculated creatinine clearance (Cockcroft-Gault formula)	*≥30 ml/min (uncorrected value)*

7. Ability to understand the purpose and risks of the study and provide written informed consent.
8. Willing and able to participate in all required evaluations and procedures in this study protocol.
9. Participants must be willing to participate in appropriate pregnancy prevention measures:

    - Women of childbearing potential who have a negative serum or urine pregnancy test during screening (within 14 days prior to the start of trial treatment) and agree to use one highly effective form of contraception combined with an effective form of contraception (see below) effective from the first administration of all study drugs, throughout the trial and for 12 months after last dose all study drugs are considered eligible.

    - Male participants with partners of childbearing potential who agree to take measures not to father children by using one form of highly effective contraception from the first administration of all study drugs, throughout the trial and for 12 months after last dose of all study drugs are considered eligible. Male subjects must also refrain from donating sperm during this period.

      Contraception
      Contraception that is considered highly effective includes oral, injected or implanted progesterone-only hormonal contraception (with inhibition of ovulation); oral, intravaginal, or transdermal combined (oestrogen and progesterone containing) hormonal contraception

(with inhibition of ovulation); an intra-uterine device (IUD); an intrauterine hormone releasing system (IUS); bilateral tubal occlusion; vasectomised partner or abstinence.
Contraceptive methods considered to be effective include progesterone-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action; condom; cap, diaphragm or sponge with spermicidal gel.

- Men with pregnant or lactating partners must be advised to use barrier method contraception (for example: condom plus spermicidal gel) to prevent exposure to the foetus or neonate.

10. Life expectancy ≥ 12 weeks.
11. ECOG performance status 0-2.

4.3 EXCLUSION CRITERIA

1. Known central nervous system involvement by lymphoma, that is not in remission, are excluded from the study.
2. History of other malignancy within the last 2 years except for:
   - Noninvasive malignancies such as adequately treated ductal carcinoma in situ of the breast, non-melanoma skin cancer or lentigo maligna, cervical carcinoma in situ and urothelial papillary noninvasive carcinoma or carcinoma in situ, and
   - Prostate intraepithelial neoplasia without evidence of prostate cancer.
3. Receiving treatment (or within a month of) with chemotherapy, immunotherapy or immunosuppressive agents. This includes any systemic steroids at dose exceeding 10 mg prednisolone (or other steroid equivalent) within 2 weeks prior to first dose of trial treatment.
4. Significant concurrent, uncontrolled medical condition that in the opinion of the Investigator contraindicates participation in this study.
5. Active and documented autoimmune disease (including, but not limited to, inflammatory bowel disease, coeliac disease, haemolytic anaemia, or immune thrombocytopenic purpura) prior to first dose of trial treatment.
6. Active infection requiring systemic therapy.
7. Women who are pregnant or lactating.
8. Serological positivity for Hepatitis B, C, or known HIV infection. As per standard of care the results of hepatitis serology should be known prior to commencement of immunochemotherapy.
   - Positive test results for chronic HBV infection (defined as positive HBsAg serology and positive HBcAb) will not be eligible. Participants with occult or prior HBV infection (defined as negative HBsAg and positive HBcAb) will not be eligible. Participants who have protective titres of hepatitis B surface antibody (HBsAb) after vaccination will be eligible.
   - Positive test results for hepatitis C (HCV antibody serology testing) will not be eligible.
9. Previous recipient of an allogeneic bone marrow transplant at any time.
10. Autologous bone marrow transplant within 100 days of first dose of trial treatment.
11. Systemic radiation therapy within 4 weeks or prior focal radiotherapy within 2 weeks prior to first dose of trial treatment.
12. Subjects known or suspected of being unable to comply with the protocol.
13. Ongoing toxic manifestations of previous treatments. Exceptions to this are alopecia or certain Grade 1-toxicities, which in the opinion of the Investigator should not exclude the patient.
14. Uncontrolled congestive cardiac failure, cardiac ischaemia or cardiac arrhythmia. Clinically significant cardiac disease including unstable angina, acute myocardial infarction within six months prior to registration, congestive heart failure (NYHA III-IV).
15. Subjects with a known hypersensitivity to rituximab (≥Grade 3) or murine proteins, or any other excipients used in the formulation of rituximab.

4.4 SCREEN FAILURES

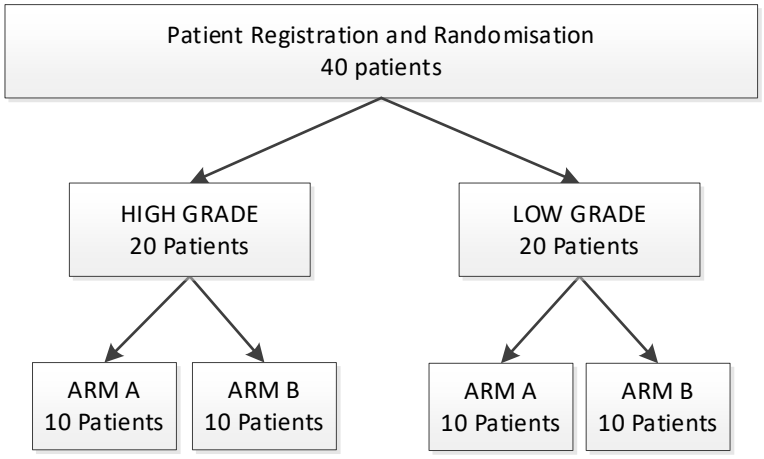
Screening failures are those patients who do not meet the inclusion/exclusion criteria for the trial and are therefore not enrolled. Patients who are screen failures will have their initials, year of birth and reasons for failure recorded on a screening form.

4.5 REGISTRATION / RANDOMISATION PROCEDURES

Participants will undergo screening assessments where required and, following successful completion of this stage, will be registered on the trial database by a member of the research team. Participants will then be randomised to a treatment group (1:1 ratio) via an independent, web-based system (TENALEA) by a member of the research team. This online system allows for instant assignment to either Arm A or Arm B in the relevant grade groups.

There will be 20 participants in the High Grade group and 20 in Low Grade group.

- High Grade - 10 will be assigned to Arm A and 10 to Arm B
- Low Grade - 10 will be assigned to Arm A and 10 to Arm B



Initially, the first participant will be entered into the trial. Providing there are no serious or unexplained safety issues during cycle 1, as determined by the SRC, then dosing of subsequent participants will continue as they are identified. Should toxicity findings occur of concern, the SRC may choose to stagger the start of dosing for subsequent participants and/or cohorts.

During the safety stage of the study, the first 4 participants will be randomised by site staff using Tenalea. The fifth and sixth participant will be allocated to Arm A or B by the SCTU Trial Statistician. For these two participants, sites should contact the RiVa team at SCTU on riva@soton.ac.uk to know which arm these participants will be allocated to. All participants after this will be randomised by the site research team.

4.6 CONTRACEPTION

Contraception is mandatory from trial entry until 12 months after the last dose of trial treatment. Please see inclusion criteria (Section 4.2) for acceptable methods of contraception.

5 TRIAL OBSERVATIONS AND PROCEDURES

5.1 SCREENING PROCEDURES

Within 12 months of treatment:

- Tissue collection – 3 cores to be collected:
    - Diagnostic core: to be used to confirm diagnosis locally as per standard of care.
    - Two fresh cores: for translational endpoints, to be sent to the WISH Lab on day of collection (see Laboratory Manual for details).

To avoid having to collect the initial biopsy twice, a separate Biopsy Information Sheet and Biopsy Consent Form are available to approach potential participants for collection of the fresh tissue samples prior to recruitment into RiVa.

Using these forms, research teams can approach patients who may be suitable to go on the RiVa trial when they present with a suspected relapse. If the patient consents, the fresh core biopsies can be taken simultaneously with the diagnostic SOC biopsy, avoiding a further repeat biopsy at screening if the patient enters the trial. It may not be appropriate for a patient to sign the main RiVa consent form at the time of the diagnostic biopsy, as treatment options may only be discussed later. Furthermore the main RiVa Consent Form needs to be signed within 28 days before start of treatment whereas the fresh core biopsy can be collected up to 12 months before the start of trial treatment.

Within 90 days of treatment:

- Bone marrow trephine - only required if there is cytopenia during screening and if it alters the staging of the disease (see Appendix 3 for Lugano staging criteria)

Within 28 days of treatment:

- Informed consent
- Demographic information
- Concomitant medication
- Body weight
- Height
- Haematology: full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count, and platelet count
- Coagulation (if clinically indicated)
- Biochemistry: renal, bone and liver function tests. Serum chemistry to include sodium, potassium, urea, creatinine, calcium, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, albumin and uric acid
- Creatinine clearance (see Appendix 4)
- Immunoglobulins and paraprotein estimation
- Beta-2 microglobulin
- Serum lactate dehydrogenase (LDH)
- Thyroid function test
- Hep B, Hep C and HIV serology (As per standard of care, sites should have hepatitis results available prior to initiation of immunochemotherapy. HBsAg, HbcAb and Hepatitis C serology must be tested)
- ECG
- Contrast enhanced CT of neck, chest, abdomen and pelvis with bi-dimensional reporting
- PET/CT (on Investigator's discretion) with Deauville score

- Adverse events (from date of consent). Only AEs related to the screening procedures should be reported.

Within 14 days of treatment:

- Inclusion/exclusion criteria
- Medical history
- Physical examination
- Vital signs
- Direct antiglobulin test (DAT)
- ECOG performance status (see Appendix 5 for details)
- Pregnancy test (serum or urine – only required in females of childbearing potential)
- Concomitant medication
- Adverse events (only SAEs/AEs related to the screening procedures should be reported)

Within 7 days of treatment:

- Randomisation
- Adverse events (only SAEs/AEs related to the screening procedures should be reported)

Within 72 hours of treatment:

- Haematology: full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count and platelet count
- Biochemistry: renal, bone and liver function tests. Serum chemistry to include sodium, potassium, urea, creatinine, calcium, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, albumin and uric acid
- ECOG performance status
- Adverse event (only SAEs/AEs related to the screening procedures should be reported)

5.2 TRIAL PROCEDURES

Cycle 1 Day 1 – ARM A+B

- Weight
- Physical examination up to 72 hours pre administration
- Vital signs (pre- infusion and 30 minutes post-infusion)
- Haematology up to 72 hours pre administration: full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count and platelet count
- Biochemistry up to 72 hours pre administration: renal, bone and liver function tests. Serum chemistry to include sodium, potassium, urea, creatinine, calcium, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, albumin and uric acid
- Concomitant medication
- Adverse events
- 10ml lithium heparin for flow cytometry
- PK sample to be collected pre- and post-infusion of trial drug for the first 6 Arm A participants (patients with 50% or less of PK samples collected will be replaced with further Arm A patients to ensure sufficient samples are collected for the analysis.). Post-infusion sample to be taken 30 ± 5 minutes after end of infusion from contralateral arm.
- Rituximab administration including start and stop time

Cycle 1 Day 2 – ARM A

- Physical examination up to 72 hours pre administration
- Vital signs (pre- infusion and 30 minutes post-infusion)
- Haematology up to 72 hours pre administration: full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count and platelet count
- Biochemistry up to 72 hours pre administration: renal, bone and liver function tests. Serum chemistry to include sodium, potassium, urea, creatinine, calcium, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, albumin and uric acid
- Concomitant medication
- Adverse events
- 10ml lithium heparin for flow cytometry
- PK sample to be collected pre- and post-infusion of trial drug for the first 6 Arm A participants (patients with 50% or less of PK samples collected will be replaced with further Arm A patients to ensure sufficient samples are collected for the analysis). Post-infusion sample to be taken 30 ± 5 minutes after end of infusion from contralateral arm.
- Varlilumab administration including start and stop time

Cycle 1 Day 2 – ARM B

- Physical examination up to 72 hours pre administration
- Vital signs (one set)
- Haematology up to 72 hours pre administration: full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count and platelet count
- Biochemistry up to 72 hours pre administration: renal, bone and liver functions tests. Serum chemistry to include sodium, potassium, urea, creatinine, calcium, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, albumin and uric acid
- Concomitant medication
- Adverse events
- 10ml lithium heparin for flow cytometry

Cycle 1 Day 8 – ARM A

- Physical examination up to 72 hours pre administration
- Vital signs (one set)
- Haematology up to 72 hours pre administration: full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count and platelet count
- Biochemistry up to 72 hours pre administration: renal, bone and liver function tests. Serum chemistry to include sodium, potassium, urea, creatinine, calcium, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, albumin and uric acid
- Concomitant medication
- Adverse events
- 10ml lithium heparin for flow cytometry
- PK sample to be collected pre- and post-infusion of trial drug for the first 6 Arm A participants (patients with 50% or less of PK samples collected will be replaced with further Arm A patients to ensure sufficient samples are collected for the analysis). Post-infusion sample to be taken 30 ± 5 minutes after end of infusion from contralateral arm.
- Tissue collection (can be performed on Day 7 if Day 8 is logistically difficult)

Cycle 1 Day 8 – ARM B

- Physical examination up to 72 hours pre administration
- Vital signs (pre- infusion and 30 minutes post-infusion)
- Haematology up to 72 hours pre administration: full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count and platelet count
- Biochemistry up to 72 hours pre administration: renal, bone and liver function tests. Serum chemistry to include sodium, potassium, urea, creatinine, calcium, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, albumin and uric acid
- Concomitant medication
- Adverse events
- 10ml lithium heparin for flow cytometry
- Tissue collection (can be performed on Day 7 if Day 8 is logistically difficult)
- Varlilumab administration including start and stop time

Cycle 2 Day 1

- Concomitant medication
- Physical examination up to 72 hours pre administration
- ECOG performance status
- Vital signs (pre- infusionand 30 minutes post-infusion)
- Body weight
- Haematology up to 72 hours pre administration: full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count and platelet count
- Biochemistry up to 72 hours pre administration: renal, bone and liver function tests. Serum chemistry to include sodium, potassium, urea, creatinine, calcium, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, albumin and uric acid
- 10ml lithium heparin for flow cytometry
- PK sample to be collected pre- and post-infusion of trial drug for the first 6 Arm A participants (patients with 50% or less of PK samples collected will be replaced with further Arm A patients to ensure sufficient samples are collected for the analysis)). Post-infusion sample to be taken 30 ± 5 minutes after end of infusion from contralateral arm.
- Pregnancy test
- Adverse events
- Immunoglobulins and paraprotein estimation (if abnormal at baseline) up to 72 hours pre-administration.
- Thyroid function test (if abnormal at baseline) up to 72 hours pre-administration.
- Rituximab administration including start and stop time

Cycles 3-6 Day 1

- Concomitant medication
- Physical examination up to 72 hours pre administration
- ECOG performance status
- Vital signs (pre- infusion and 30 minutes post-infusion)
- Body weight
- Haematology up to 72 hours pre administration: full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count and platelet count

- Biochemistry up to 72 hours pre administration: renal, bone and liver function tests. Serum chemistry to include sodium, potassium, urea, creatinine, calcium, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, albumin and uric acid
- 10ml lithium heparin for flow cytometry
- Pregnancy test
- Adverse events
- Immunoglobulins and paraprotein estimation (if abnormal at baseline) up to 72 hours pre-administration.
- Thyroid function test (if abnormal at baseline) up to 72 hours pre-administration.
- Rituximab administration including start and stop time

Cycle 3 Day 2

- PK sample to be collected pre- and post-infusion of trial drug for the first 6 Arm A participants (patients with 50% or less of PK samples collected will be replaced with further Arm A patients to ensure sufficient samples are collected for the analysis). Post-infusion sample to be taken 30 ± 5 minutes after end of infusion from contralateral arm.
- Adverse events
- Varlilumab administration including start and stop time

Cycle 5 Day 2

- Adverse events
- Varlilumab administration including start and stop time

End of Treatment

The End of Treatment visit will take place 2 weeks after completion of cycle 6, i.e 14 days (+ 7 days) after Cycle 6 Day 14. If a participant does not receive all treatment cycles, the End of Treatment visit will take place 14 days (+ 7 days) after the patients last cycle.

The following will be performed:

- Concomitant medication
- Physical examination
- ECOG performance status
- Vital signs (one set)
- Body weight
- Adverse events
- Haematology: full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count and platelet count
- Biochemistry: renal, bone and liver function tests. Serum chemistry to include sodium, potassium, urea, creatinine, calcium, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, albumin and uric acid
- Contrast enhanced CT of neck, chest, abdomen and pelvis with bi-dimensional reporting
- PET/CT (on Investigator's discretion) with Deauville score
- Bone marrow trephine (if abnormal at baseline)
- 10ml lithium heparin for flow cytometry
- Immunoglobulins and paraprotein estimation (if abnormal at baseline)
- Thyroid function test (if abnormal at baseline)

5.3 FOLLOW UP

Subsequent study visits will be performed at each centre following completion of all study therapy. Participants will be followed up every 2 months (± 14 days) for a maximum of 1 year after completion of the trial treatment. The first follow up visit will take place two months after Cycle 6 Day 14 or two months after the last administration of study drug if the participant does not receive all treatment cycles.

At each follow-up visit, the following will be performed:

- Tissue collection on disease progression at a single time point during the follow up period is highly desirable but optional
- Concomitant medication (first follow up visit only)
- Physical examination
- ECOG performance status
- Vital signs
- Body weight
- Adverse events to be recorded until 30 days after last dose of trial treatment. If deemed related to trial treatment reporting is required regardless of the timeframe after treatment.
- Haematology: full blood count to include haemoglobin, white cell count, absolute neutrophil count, absolute monocyte count, lymphocyte count and platelet count
- Biochemistry: renal, bone and liver function tests. Serum chemistry to include sodium, potassium, urea, creatinine, calcium, bilirubin, alanine or aspartate transaminase, alkaline phosphatase, albumin and uric acid
- Immunoglobulin and paraprotein estimation
- Beta-2 microglobulin
- Contrast enhanced CT to be performed 2 months post completion of treatment if disease is less than CR, or at any point during the 1 year follow up if there is clinical suspicion of disease progression
- PET/CT with Deauville score scan may be performed at the Investigator's discretion
- Bone marrow trephine (for new and persistent, unexplained cytopenias, at a single time point during the follow up period)

5.4 PHARMACOKINETIC / PHARMACODYNAMIC

PK analysis

PK samples will be collected from the first 6 participants in Arm A. Patients with 50% or less of PK samples collected will be replaced with further Arm A patients to ensure sufficient samples are collected for the analysis. Rituximab and varlilumab will be measured from peripheral blood serum by ELISA. Protocols for these assays have been previously developed by the Wessex Investigational Sciences Hub (WISH) Laboratory at Southampton (rituximab) and by Celldex Therapeutics (varlilumab).

The schedule for PK analysis is highlighted below:

	Cycle 1					Cycle 2		Cycle 3	
	D1 pre-treatment	**D1 post-treatment**	**D2 pre-treatment**	**D2 post-treatment**	**D8**	**D1 pre-treatment**	**D1 post-treatment**	**D2 pre-treatment**	**D2 post-treatment**
PK sample rituximab	X	X	X	X	X	X	X		
PK sample varlilumab			X	X	X			X	X

PD analysis

Tissue sampling is performed at the time points shown below. Briefly tissue will be collected from Arms A and B prior to commencement of treatment and then again through needle biopsy on D8, which is post-varlilumab administration in Arm A and pre-varlilumab administration in Arm B.

Absolute peripheral blood NK and regulatory T cell numbers will be measured at the time points indicated in the Schedule of Investigations (under 10 ml lithium heparin sample for flow cytometry). The abbreviated table is shown below:

	Screening	Cycle 1			Cycle 2-6	End of Treatment	Follow-up
		D1	D2	D8	D1	2 weeks after completion of cycle 6	Every 2 months for 1 year
Tissue Collection	X			X*			X optional on disease progression
10 ml lithium heparin sample		X	X	X	X	X	

*Tissue collection can be performed on D7 if D8 is logistically difficult.

Protocols for tissue disaggregation and the detection of NK cells and T cell subsets by flow cytometry are established and the assays validated. The stability of the expression of the other markers such as the myeloid markers will also be validated in view of the anticipated delay in central processing of flow cytometry samples. All fresh samples will be processed within 24 hours of collection.

These assays are all flow cytometry based and will be performed centrally at the GCLP compliant WISH Laboratory.

5.5 DEVIATIONS AND SERIOUS BREACHES

Any study protocol deviations/violations and breaches of Good Clinical Practice occurring at sites should be reported to the SCTU and the local R&D Office immediately. SCTU will then advise of and/or undertake any corrective and preventative actions as required.

All serious protocol deviations/violations and serious breaches of Good Clinical Practice and/or the study protocol will immediately be reported to the regulatory authorities and other organizations, as required in the Medicines for Human Use (Clinical Trials) Regulations 2004, as amended.

5.6 TRIAL DISCONTINUATION

In consenting to the study, participants have consented to the study intervention, follow-up and data collection. Participants may be discontinued from the study procedures at any time.

5.6.1 Discontinuation/Withdrawal of Trial Treatment

For participants in all arms, if a participant demonstrates early “tumour progression” (defined as occurring prior to Cycle 4 of rituximab and varlilumab), the Investigator is responsible for evaluating whether the participant is experiencing a pseudotumor progression/tumour flare reaction. This has been described in patients with solid tumours being treated with immune modulating mAbs.

In situations where participants are experiencing genuine tumour progression as ascertained by the Investigator, participants should be discontinued from the study treatment.

Participants can discontinue trial treatment for one of the following reasons:

1. Protocol Violation
2. Physician’s decision to withdraw participant

3. Unacceptable toxicity from study therapy
4. Participant decision to discontinue treatment
5. Confirmed progressive disease or clinical deterioration suggesting that no further benefit from treatment is likely

The Investigator, in consultation with the SCTU, may withdraw any participant from study treatment if, in the Investigator's opinion, it is not in the participant's best interest to continue.

5.6.2 Reasons for trial discontinuation

Participants may be discontinued from the study in the event of:

- Clinical decision, as judged by the Principal Investigator
- Pregnancy
- Participant decision to discontinue

5.7 FULL DETAILS OF THE REASON FOR TRIAL DISCONTINUATION SHOULD BE RECORDED IN THE ELECTRONIC CASE REPORT FORM (ECRF) AND MEDICAL RECORD.W

ithdrawal from study

The participant/legal representative is free to withdraw consent from the study at any time without providing a reason.

Investigators should explain to participants the value of remaining in trial follow-up and allowing this data to be used for trial purposes. Where possible, participants who have withdrawn from trial treatment should remain in follow-up as per the trial schedule. If participants additionally withdraw consent for this, they should revert to standard clinical care as deemed by the responsible clinician.

If the patient is not continuing with follow-up, the trial team should continue to collect standard follow-up data, unless the participant explicitly states otherwise. Standard care follow-up data will include survival and information on whether the patient is receiving other treatment.

Details of trial discontinuation (date, reason if known) should be recorded in the eCRF and medical record.

5.8 END OF STUDY

The end of trial for individual participants will occur when one of the following events take place:

1. The participant reaches the final follow up visit, which will be 1 year after receiving the last study treatment.
2. The participant is discovered to be ineligible over the course of the study.
3. The participant is lost to trial follow up and has explicity stated that they do not want standard care follow-up.
4. The participant withdrew consent from trial follow up and has explicity stated that they do not want standard care follow-up.
5. Death occurred.

If a participant is lost to follow-up, the local Principal Investigator along with the participant's usual clinician should attempt to contact the participant. Failing this, research team will contact the participant's GP and request to provide follow-up information where possible.

5.9 PROHIBITED AND RESTRICTED THERAPIES DURING THE TRIAL

Participants must not take any medications, including over-the-counter products, without first consulting with the Investigator.

The following medications are excluded:

1. Any anti-cancer therapy (chemotherapy, radiation therapy, immunotherapy, biologic or hormonal therapy).
2. Immunosuppresive medications such as, and not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisolone or equivalent steroid, azathioprine, tumour necrosis factor alpha blockers, methotrexate, sulphasalazine.
3. Herbal and natural remedies.
4. Live attenuated vaccines during the study up until 30 days after the final dose of varlilumab or rituximab, whichever occurs later.

5.10 BLINDING AND PROCEDURES FOR EMERGENCY UNBLINDING

This trial is not blinded therefore no blinding or emergency unblinding procedures are required.

6 TREATMENTS

6.1 TREATMENT SCHEDULE

Arm A:
Cycle 1
D1 - Rituximab 375 mg/m^2 IV
D2 - Varlilumab 3 mg/kg IV

Arm B:
Cycle 1
D1 - Rituximab 375 mg/m^2 IV and
D8 - Varlilumab 3 mg/kg IV

In both arms A & B:
Cycle 2 to 6
D1- Rituximab 375 mg/m^2 IV

Cycles 3 and 5
D2 - Varlilumab 3 mg/kg IV

Each cycle is 2 weeks in length. A new cycle can be started 1 day early or late if required (e.g. due to bank holiday). A maximum 6 cycles will be administered.

Pre-medication consisting of oral paracetamol 1g and chlorphenamine 10 mg IV will be administered as standard at least 30 minutes prior to the commencement of each infusion. Hydrocortisone 100 mg IV or dexamethasone 8 mg IV will only be administered prior to infusions if there is a prior infusion reaction to previous rituximab therapy.

6.2 MANAGEMENT OF INFUSION RELATED REACTION (IRR)

Recommendations for the management of peri-infusional reactions are provided below and may be modified based on local treatment standards and guidelines, as appropriate. Infusion related reactions should be graded according to NCI-CTCAE (Version 4.03) guidelines.

Severity of IRR (per NCI CTCAE Grade)	Dose Modification
Grade 1 symptoms (mild transient reaction; infusion interruption not indicated; intervention not indicated)	Remain at bedside and monitor patient until recovery from symptoms.
Grade 2 symptoms (infusion interruption indicated but responds promptly to symptomatic treatment [e.g., antihistamines, nonsteroidal anti-inflammatory drugs, opioids, corticosteroids, IV fluids]; prophylactic medications indicated for ≤ 24 hours)	Stop the varlilumab infusion, begin an IV infusion of sodium chloride 0.9%, and treat the patient with chlorphenamine 10 mg IV (or equivalent) and/or 500 to 1000 mg paracetamol/acetaminophen; remain at bedside and monitor patient until resolution of symptoms. Corticosteroid therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur then no further varlilumab will be administered at that visit. The amount of study drug infused must be recorded on the eCRF. Participants who experience an adverse event, including an infusion reaction of Grade 2, during the 4-6 hour observation period that does not resolve during this time should be observed for 24 hours or until the adverse event resolves with vital sign measurements every 4 hours and additional evaluations as medically indicated for the management of the adverse event.
Grade 3 or Grade 4 symptoms: Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalisation indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: life-threatening consequences; urgent intervention indicated).	Immediately discontinue infusion of varlilumab. Begin an IV infusion of sodium chloride 0.9%, and treat the patient as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or chlorphenamine 10 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the Investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Participants who experience an adverse event, including an infusion reaction of Grade ≥ 3, regardless of resolution, will be observed for 24 additional hours or until the adverse event resolves with vital sign measurements every 4 hours and additional evaluations as medically indicated for the management of the adverse event. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localised or generalised pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids). Varlilumab will be permanently discontinued for participants with Grade 4 infusion reactions. Varlilumab should be permanently discontinued for recurrence of Grade 3 infusion reaction for participants on pre-medication.

Any overdose or incorrect administration of study drug should be noted on the eCRF. AEs associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF and reported using the SAE/SUSAR Form where necessary.

6.3 MANAGEMENT OF IMMUNE-RELATED AES

Management of varlilumab induced irAEs, should they occur, should be based on the extensive experience with treatment of toxicities related to ipilimumab and other checkpoint blockers, and are discussed below. Guidelines and algorithms have been published for treatment of ipilimumab related toxicity and investigators should be familiar with these recommendations in the event that varlilumab also induces similar irAEs *(64,65)*. Reporting of irAEs, such as diarrhoea/colitis or liver enzyme elevation, should be performed as specified in Section 7.5. Any ≥ Grade 2 irAE, such as diarrhoea/colitis or liver enzyme elevation, must be reported to SCTU within 24 hours of becoming aware of the event.

6.3.1 General guidelines for treatment of irAEs

When symptomatic therapy is inadequate or inappropriate, an irAE should be treated with systemic corticosteroids followed by a gradual taper over several weeks. If corticosteroids or other immunosuppressive agents are required for more than 4 weeks in duration to treat an irAE then it is recommended that participants also receive prophylaxis to protect against the emergence of opportunistic infections. Such prophylaxis should include protection against *Pneumocystis jiroveci* (formerly P carinii) and prevalent fungal strains, as well as considerations for any additional pathogens that may be indicated by the medical history (e.g., herpes simplex virus, cytomegalovirus) or the environment (e.g., occupation, recent travel) of the patient. Consultation with infectious disease specialists may be considered.

6.3.2 Gastrointestinal tract

The differential diagnosis for participants presenting with abdominal pain should include colitis, perforation, or pancreatitis. **If there is suspicion of pancreatitis, please check amylase and lipase levels.**

Diarrhoea (defined as either first watery stool, or increase in frequency 50% above baseline with urgency or nocturnal bowel movement, or bloody stool) should be further evaluated and infectious or alternate aetiologies ruled out. Participants should be advised to inform the Investigator if any diarrhoea occurs, even if it is mild. An algorithm for managing participants with diarrhoea or suspected colitis is provided in **Appendix 6**. Corticosteroid therapy is strongly recommended for varlilumab related Grade 3 diarrhoea/colitis and should be slowly tapered according to symptomatic response over at least 1 month. Participants with varlilumab related Grade 2 diarrhoea/colitis may be initially treated conservatively, but should be followed closely and immediately switched to corticosteroids if symptoms persist or worsen. For severe symptoms, prednisolone 60 mg or equivalent may be required to control initial symptoms, and the dose should be gradually tapered over at least 1 month. Lower doses of prednisolone may be considered for less severe cases of colitis. It is suggested that prednisolone (for oral administration) or methylprednisolone (for IV administration) be the corticosteroids of choice in the treatment of colitis. Caution should be taken in the use of opioids in participants with abdominal pain or colitis/diarrhoea as opioid use may mask the signs of colonic perforation.

If the event is prolonged or severe or is associated with signs of systemic inflammation or acute phase reactants (e.g., increased C-reactive protein [CRP] or reactive thrombocytosis; or neutrophil shift to immature bands), it is recommended that sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy of 3 to 5 specimens for standard paraffin block be performed. If possible, 1 to 2 biopsy specimens should be snap-frozen and stored. Participants with confirmed colitis should also have an ophthalmologic examination, including a slit-lamp exam, to rule out uveitis. Test for stool white blood cells (WBC) and calprotectin (if locally available) should also be performed.

In severe corticosteroid refractory or relapsing cases, infliximab should be considered, unless contraindicated (i.e., sepsis and other serious infections). All such cases should be discussed with the Chief Investigator through the Trial Manager.

6.3.3 Liver

Liver function tests (LFTs) should always be performed and reviewed prior to administration of varlilumab. In addition, participants presenting with right upper quadrant abdominal pain, unexplained nausea, or vomiting should have LFTs performed immediately and reviewed before administering the next dose of study drug. Any increase in LFT should be evaluated to rule out non-inflammatory causes of hepatotoxicity including infections, disease progression or medications and followed with frequent LFT monitoring at approximately 3-day intervals until resolution.

Any LFTs ≥ Grade 2 (for participants with normal baseline LFT) or LFT ≥ 2 times baseline values (for participants with baseline LFT of Grade 1 or 2) should prompt treating physicians to:

1. contact the Chief Investigator or Trial Manager;
2. increase frequency of monitoring LFTs to at least every 3 days until LFT have stabilized or improved;
3. investigate to rule out non-irAE aetiologies; and
4. initiate an autoimmunity evaluation. Disease progression, other malignancies, concurrent medications, viral hepatitis, and toxic aetiologies should be considered and addressed, as appropriate.

Imaging of the liver, gall bladder, and bile ducts should be considered to rule out neoplastic or other non-irAE-related causes for the increased LFTs. An antinuclear antibody (ANA), perinuclear anti-neutrophil cytoplasmic antibody (pANCA), and anti-smooth muscle antibody test should be performed if an autoimmune aetiology is considered.

Participants with LFT elevations > 8x ULN that are judged to be due to varlilumab should initiate high-dose corticosteroid therapy (e.g., methylprednisolone 2 mg/kg once or twice daily or equivalent) and permanently stop administration of varlilumab. In participants with > 8x ULN, LFTs should be performed daily until stable or declining for 5 consecutive days. LFTs should be monitored for at least 2 consecutive weeks to ensure sustained treatment response. If symptoms or LFT elevations are controlled, the corticosteroid dose should be gradually tapered over a period of at least 1 month. Flare in LFTs during this taper may be treated with an increase in the dose of steroid and a slower taper.

In participants without response to corticosteroid therapy within 3 to 5 days or who have an LFT flare during steroid tapering that is not responsive to an increase in steroids, addition of immunosuppression with mycophenolate mofetil should be considered after a gastroenterology/hepatology consult. Participants receiving immunosuppression for more than 4 weeks should be evaluated for prophylaxis of opportunistic infections per institutional guidelines. An algorithm for evaluating participants with elevated LFTs is provided in **Appendix 7**.

6.3.4 Skin

A dermatologist should evaluate persistent or severe rash or pruritus. A biopsy should be performed if appropriate and if possible, photos of the rash should also be obtained. Low grade varlilumab-mediated rash and pruritus may be treated with symptomatic therapy, e.g. antihistamines. Topical or parenteral corticosteroids may be required for more severe symptoms.

6.3.5 Endocrine

In the ipilimumab clinical development program, hypopituitarism presented with nonspecific complaints such as fatigue, confusion or impotence *(66)*. Some participants had headache as the predominant

presentation. The majority of participants with hypopituitarism demonstrated enlarged pituitary glands based on brain magnetic resonance imaging (MRI). Low adrenocorticotropic hormone (ACTH) and cortisol were the most common biochemical abnormality; low thyroid stimulating hormone (TSH), testosterone or prolactin were also reported in some participants.

Participants with unexplained symptoms such as fatigue, myalgias, impotence, mental status changes, or constipation should be investigated for the presence of thyroid, pituitary or adrenal endocrinopathies. An endocrinologist should be consulted if an endocrinopathy is suspected. TSH and free T4 levels should be obtained to determine if thyroid abnormalities are present. TSH, prolactin and a morning cortisol level will help to differentiate primary adrenal insufficiency from primary pituitary insufficiency. Appropriate hormone replacement therapy should be instituted if an endocrinopathy is documented. A short course of high dose corticosteroids should be considered in an attempt to treat the presumed pituitary inflammation. It is possible that participants with varlilumab endocrinopathies may require life-long hormone replacement. An endocrinopathy management algorithm is presented in **Appendix 8**.

6.3.6 Other

An ophthalmologist should evaluate visual complaints with examination of the conjunctiva, anterior and posterior chambers, and retina. Visual field testing and an electroretinogram should also be performed. Uveitis or episcleritis may be treated with topical corticosteroid eye drops.

6.4 IMP SUPPLY

Varlilumab will be centrally supplied free of charge for this clinical trial by Celldex Therapeutics. Sites will order varlilumab via SCTU. Almac (on behalf of Celldex Therapeutics) will pack, label, QP release and distribute the IMP for the study to participating sites.

Rituximab will be from standard hospital stock. A rituximab biosimilar can be used.

Only those supplies intended for use in the study should be dispensed to study participants and clinical trial supplies must be dispensed in accordance with the study protocol.

Other study treatments are standard of care and will be from local supplies. Full instructions regarding management, labelling and accountability is given in the Pharmacy Manual for the study.

6.5 HANDLING AND STORAGE

Rituximab will be stored, prepared, and administered according to local practice.

Varlilumab drug product is shipped in insulated shippers and must be stored at 2 - 8°C until use. A temperature log must be kept to document the refrigerator temperature. Please follow the instructions in the Pharmacy Manual on how to report temperature excursion.

Varlilumab should be protected from light. Sufficient light protection is provided by the secondary container (carton); no specific light protection is needed during preparation of the dosing solution and infusion.

Varlilumab is not formulated with a preservative. Once the sterile vials are entered (i.e. once varlilumab is drawn into a syringe), the vials should be used as soon as possible (typically within 3 hours if kept at room temperature or within 6 hours if refrigerated; or in accordance with any applicable institutional guidance).

Varlilumab should not be administered as a bolus injection. Recommended safety measures for preparation and handling of varlilumab include laboratory coats and gloves.

Infusion Preparation

Varlilumab cannot be mixed with any other drug in the infusion bag or administration set.

The dose will be calculated using the actual body weight of the participant at enrolment. The dose may remain constant throughout the study unless a greater than 10% change in weight is observed.

The following formula should be used to calculate the volume of varlilumab required for each administration:

$$\frac{\text{Body Weight (kg)} \times \text{Desired Dose (3 mg/kg)}}{\text{5mg/mL}} = \text{Volume of varlilumab (mL)}$$

Additional information will be found in the Pharmacy Manual.

6.6 ADMINISTRATION

Cycle 1

Drug	Dose	Admin	ARM A			ARM B		
			Day 1	Day 2	Day 8	Day 1	Day 2	Day 8
Rituximab	375 mg/m^2	IV infusion	√			√		
Varlilumab	3 mg/kg	IV infusion		√				√

Cycle 2-6

Drug	Dose	Admin	ARM A + ARM B						
			Cycle 2 Day 1	Cycle 3 Day 1	Cycle 3 Day 2	Cycle 4 Day 1	Cycle 5 Day 1	Cycle 5 Day 2	Cycle 6
Rituximab	375 mg/m^2	IV infusion	√	√		√	√		√
Varlilumab	3 mg/kg	IV infusion			√			√	

Varlilumab dosing should be adjusted if the patient's weight changes by more than 10% compared to the weight at baseline visit.

Rituximab can be dose banded as per local procedures.

6.7 ACCOUNTABILITY

The Investigator(s) or designee is responsible for taking an inventory of each shipment of investigational product received and comparing it with the accompanying shipping order/packaging slip. The Investigator(s) will verify the accuracy of the information on the shipping order/packaging slip and call IRT to register receipt at the site of the investigational product.

At the study site, investigational product will be stored in a locked, safe area to prevent unauthorised access and should be stored as directed on the product label.

An accurate accounting of the dispensing and return of investigational product for each study subject will be maintained in source documents on an ongoing basis by a member of the study site staff. Additionally, if any investigational product is lost or damaged or if a participant misses a dose, this information should be documented in the participant's eCRF and source documents.

SCTU will instruct the Investigator on the return, disposal, and/or destruction of unused investigational product. This will be defined in the Pharmacy Manual.

6.8 CONCOMITANT MEDICATIONS

Information on any treatment received by the participant, along with dose, frequency and therapeutic indication, from prior to starting trial treatment up to and 28 days after the last dose of trial treatment will be recorded in the eCRF.

6.9 DOSE DELAYS AND MODIFICATIONS FOR TOXICITY

No dose reductions are allowed for rituximab or varlilumab, but treatment may be interrupted or discontinued or infusion rate may be changed at the discretion of the Investigator for severe infusion or allergic reactions, or other toxicities.

A new cycle of treatment may be administered if the following conditions are met:

- ANC ≥1.0 x 10^9/L (or not lower than ANC at screening). G-CSF support is permitted at Investigator's discretion.
- Platelets ≥75 x 10^9/L (or not lower than platelet count at screening). This platelet count must not be supported by platelet transfusions.
- Non-haematological toxicities reduced to ≤ Grade 1 severity (or, ≤ Grade 2 at the Investigator discretion, if not considered a safety risk). Further guidance on management of non-haematological toxicities are found in **Section 6.3** and **Appendix 6** (gastrointestinal), **Appendix 7** (liver) and **Appendix 8** (endocrine).

Administration of rituximab and varlilumab must be delayed by 1 week if these conditions are not met. If toxicities have not improved to the limits describe above, treatment may be delayed by a further week. Initiation of the next cycle can be delayed by a maximum of 3 weeks. Thereafter, if toxicities have not improved to the limits above, treatment on the trial will be permanently discontinued.

6.10 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

It is not known if varlilumab or its metabolites interacts with other medicinal products. For this reason, varlilumab should only be administered in accordance with the protocol.

6.11 OVERDOSE

There is no available information concerning overdose with varlilumab. Varlilumab should only be administered in accordance with the protocol.

7 SAFETY

7.1 DEFINITIONS

The Medicines for Human Use (Clinical Trials) Regulations 2004, as amended, provides the following definitions relating to adverse events in trials with an investigational medicinal product:

Adverse Event (AE): any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

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

Adverse Reaction (AR): all untoward and unintended responses to an IMP related to any dose administered.

All AEs judged by either the reporting investigator or the sponsor as having reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

Unexpected Adverse Reaction: an AR, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure (IB) for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product). *When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected. Side effects documented in the IB/SmPC which occur in a more severe form than anticipated are also considered to be unexpected.*

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR) or **Suspected Unexpected Serious Adverse Reaction (SUSAR)**: any untoward medical occurrence or effect that at any dose:

- **Results in death**
- **Is life-threatening***
- **Requires hospitalisation**, or prolongation of existing hospitalisation**
- **Results in persistent or significant disability or incapacity**
- **Is a congenital anomaly or birth defect**
- **Important medical events*****

*'life-threatening' in the definition of 'serious' 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 which hypothetically might have caused death if it were more severe.
** Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
***Other important medical events may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

Note: *It is the responsibility of the PI or delegate to grade an event as 'not serious' (AE) or 'serious' (SAE).*

Suspected Unexpected Serious Adverse Reaction (SUSAR): any suspected adverse reaction related to an IMP that is both unexpected and serious.

7.2 SERIOUSNESS

A complete assessment of the seriousness must always be assessed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the Investigator.

All adverse events that fulfil the criteria definition of 'serious' in protocol section 7.1, must be reported to SCTU using the Serious Adverse Event Report Form. Specific exceptions to this (as listed below) should be recorded as AEs rather than SAEs.

All SAEs must be reported immediately by the Investigator at the participating centre to the SCTU.

7.2.1 Exceptions:

For the purposes of this trial, the following SAEs **do not** require reporting to SCTU using the Serious Adverse Event Report Form:

- Relapse and death due to relapse or refractory B cell malignancies
- Hospitalisations for elective treatment of a pre-existing condition

Relapse and death due to lymphoma, and hospitalisations for elective treatment of a pre-existing condition or routine blood transfusion do not need reporting as SAEs.

7.3 CAUSALITY

A complete assessment of the causality must always be performed by a medically qualified doctor who is registered on the delegation of responsibility log; this is usually the Investigator.

If any doubt about the causality exists the local Investigator should inform SCTU who will notify the Chief Investigator. Pharmaceutical companies and/or other clinicians may be asked for advice in these cases.

In the case of discrepant views on causality between the Investigator and others, SCTU will classify the event as per the worst case classification and if onward reporting is required, the MHRA will be informed of both parties points of view.

Relationship	Description
Unrelated	There is no evidence of any causal relationship
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possible	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Definitely	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

7.4 EXPECTEDNESS

Expectedness assessments are made against the approved reference safety information (RSI). The RSI for this trial is specified within the document versions listed in the tables below:

Name of Product	IB	IB Section	Manufacturer	Date of text revision DD-MMM-YYYY
Varlilumab	IB	Section 6.3.3	Celldex Therapeutics, Inc.	Version 8, 15-Jan-2020

Name of Product	SmPC	SmPC section	Manufacturer	Last updated on eMC DD-MMM-YYYY
Rituximab	Mabthera 100mg Concentrate for Solution for Infusion SmPC	4.8	Roche Products Limited	08-Apr-2020

The nature or severity of the event should be considered when making the assessment of expectedness. If these factors are not consistent with the current information available then the AE should be recorded as 'unexpected'.

7.5 REPORTING PROCEDURES

All adverse events should be reported from date of consent until 30 days after last administration of trial treatment. If an event is deemed related to the trial then reporting is required regardless of the timeframe since treatment ended. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the SCTU in the first instance. A flowchart will be provided to aid in the reporting procedures.

7.5.1 Reporting Details

An SAE/SUSAR Form should be completed for all SAEs, SARs and SUSARS and faxed to SCTU within 24 hours of becoming aware of the event.

Complete the SAE/SUSAR Form and fax or email a scanned copy of the form with as many details as possible to the SCTU together with anonymised relevant treatment forms and investigation reports.

Or

Contact SCTU by phone for advice and then fax or email a scanned copy of the completed SAE/SUSAR Form.

SAE REPORTING CONTACT DETAILS

Please email or fax a copy of the SAE form to
SCTU within 24 hours of becoming aware of the event

Fax: 0844 774 0621 or Email: ctu@soton.ac.uk

FAO: Quality and Regulatory Team

For further assistance: Tel: 023 8120 4138 (Mon to Fri 09:00 – 17:00)

Additional information should be provided as soon as possible if the event has not resolved at the time of reporting.

7.5.2 Follow Up and Post-trial SAEs

The reporting requirement for SAEs affecting participants applies for all events occurring up to 30 days after the last administration of trial drugs.

All unresolved adverse events should be followed by the Investigator until resolved, the participant is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the Investigator should instruct each participant to report any subsequent event(s) that the participant, or the participant's general practitioner, believes might reasonably be related to participation in this trial. The Investigator should notify the trial sponsor of any death or adverse event occurring at any time after a participant has discontinued or terminated trial participation that may reasonably be related to this trial.

7.5.3 Non-serious AEs

All adverse events should be recorded in the relevant eCRF and submitted to SCTU.

7.5.4 Adverse Events of Special Interest

Varlilumab's action against cancer cells is through enhancing the immune response through binding to CD27. Clinical experience with varlilumab in humans is ongoing. A number of adverse drug reactions will be considered adverse events of specialist interest in the context of the trial, these are listed below. The database will be designed to identify adverse events of special interest.

AEs of special interest related to varlilumab:

- Infusion-related reaction
- Diarrhoea/colitis
- Liver enzyme elevation (≥ Grade 2 for patients with normal baseline LFT or LFT ≥ 2 times baseline values for patients with baseline LFT of Grade 1 or 2)
- Severe rash/pruritus
- Endocrinopathies: thyroid, pituitary, adrenal
- Eye problems

7.5.5 Pre-existing Conditions

Medically significant pre-existing conditions (prior to informed consent) should not be reported as an AE unless the condition worsens by at least one CTCAE grade during the trial. The condition, however, must be reported on the Medical History eCRF. Any adverse events which occur after informed consent is taken should be recorded on the AE eCRF as per safety reporting section.

7.5.6 Serious Adverse Events and Reactions

All SAEs, SARs and SUSARs should be reported within 24 hours of the local site becoming aware of the event. The SAE/SUSAR Form asks for nature of event, date of onset, severity, outcome, causality (i.e. unrelated, unlikely, possible, probably, definitely) and expectedness. The responsible Investigator should assign the causality and expectedness of the event with reference to the approved RSI for theIMP in the IB/SmPC. The event term should be a medical term or concept with grades given in accordance with the NCI CTCAE v4.03. Additional information should be provided as soon as possible if the event/reaction has not resolved at the time of reporting.

7.5.7 Pregnancy

It is not known if varlilumab or its metabolites is excreted in milk or can cross the placenta. For this reason, pregnant and nursing women should not receive varlilumab. Women of childbearing potential and their partners who are admitted to the clinical study must take adequate contraceptive measures in accordance with the study protocol.

Participants with reproductive potential who are sexually active must use highly effective methods of contraception during the study and for 12 months after the last dose of trial treatment.

Female participants must use one highly effective form of contraception and one effective form from the first administration of all study drugs, throughout the trial and for 12 months after last dose of trial

treatment. Male participants with partners of childbearing potential must take measures not to father children by using one form of highly effective contraception effective from the first administration of all study drugs, throughout the trial and for 12 months after last dose of trial treatment.

Men with pregnant or lactating partners must be advised to use barrier method contraception (for example: condom plus spermicidal gel) to prevent exposure to the foetus or neonate.

Male participants must also refrain from donating sperm during this period.

If a participant or their partner becomes pregnant whilst taking part in the trial or during a stage where the foetus could have been exposed to an IMP, the Investigator must ensure that the participant and the participant's healthcare professional are aware that follow up information is required on the outcome of the pregnancy.

Follow-up is, of course, dependent on obtaining informed consent for this from the participant (or their partner in the case of male trial participants).

If the participant leaves the area, their new healthcare professional should also be informed.

If the participant or partner of the participant, in the case of a male participant, becomes pregnant the Investigator must complete the Pregnancy Notification Form in the participant's eCRFs.

7.6 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO REC

SCTU will notify REC of all SUSARs occurring during the trial according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days.

7.7 SCTU RESPONSIBILITIES FOR SAFETY REPORTING TO MHRA

SCTU will notify the necessary competent authorities of all SUSARs occurring during the trial according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days.

SCTU submit the Developmental Safety Update Reports to MHRA annually.

8 STATISTICS AND DATA ANALYSES

8.1 METHOD OF RANDOMISATION

In this phase IIa trial, within each of the low and high grade groups, half of the participants will be randomly allocated to Arm A and the other half to Arm B. A minimisation algorithm incorporating a random component will be used to allocate participants to either Arm A or Arm B. Disease subtype, along with other factors, will be used as a factor in the minimisation.

During the safety stage of the study, the first 4 participants will be randomised by site staff using Tenalea. The fifth and sixth participant will be allocated to Arm A or B by the SCTU Trial Statistician. For these two participants, sites should contact the RiVa team at SCTU on riva@soton.ac.uk to know which arm these participants will be allocated to. All participants after this will be randomised by the site research team.

8.2 SAMPLE SIZE

If fewer than 13 % (p1) of participants have a response according to the Lugano Revised Response Criteria for Malignant Lymphoma (see Appendix 1) then this combination would be deemed insufficiently active

to warrant further investigation in a future phase III trial. If however 40% or more (p2) participants have a response then the combination would be deemed worthy of further investigation.

Using a 1 stage Flemings design at α=0.05 (one-sided) and 90% power, this would require 20 participants in each of the high and low grade arms (Arms A and B combined), a total of 40 participants (20 per disease category). Within each the high and low grade groups, if 6 or more out of 20 participants have a response this would warrant further investigation of that grade population in a phase III setting if the following are also satisfied:

a) Evidence of an increased intratumoural B-cell depletion in the Day 8 biopsies of participants who have received rituximab and varlilumab compared to rituximab alone, and/or
b) Evidence of increased activation or increase in absolute numbers/proportion of macrophage, monocyte and/or neutrophil populations in the Day 8 tumour biopsies of participants who have received rituximab and varlilumab compared to rituximab alone.

Recruitment will end on the 31st December 2020.

8.3 INTERIM ANALYSIS

A SRC will review safety data during the safety run in. If deemed safe, and the trial progresses, data on activity, safety and feasibility will be presented to the DMEC.

8.4 STATISTICAL ANALYSIS PLAN (SAP)

A SAP will be developed for both the interim analysis and the final analysis at the end of the study. The analysis will be conducted in the intention-to-treat population which includes all randomised participants who have commenced study treatment. There will be no formal statistical comparisons between groups, and any p-values presented will be exploratory in nature. The main features of the statistical analysis plan are included below.

Baseline characteristics will be summarised. Continuous data will be presented as means and standard deviations (if data is skewed, medians and ranges will be presented), categorical and binary outcomes will be summarised with frequencies and percentages.

For the primary endpoint of response the percentage of patients responding and 90% Clopper-Pearson exact confidence interval will be presented for both the low and high grade groups separately. If at least six out of 20 patients respond (or if fewer than 20 patients are recruited per group the 90% confidence interval for response lies solely above 13%) this would warrant further investigation of that grade population in a phase III setting if the above criteria, a and b in section 8.2, are also satisfied. Waterfall plots for response will also be produced.

Time to event outcomes including progression free survival and overall survival will be summarised using Kaplan-Meier survival curves, 12 month PFS and OS rates will be calculated with 90% confidence intervals.

All adverse events (AEs) and serious adverse events (SAEs) will be summarised with frequencies and percentages by group.

9 REGULATORY

9.1 CLINICAL TRIAL AUTHORISATION

This trial has a Clinical Trial Authorisation from the UK Competent Authority the Medicines and Healthcare products Regulatory Agency (MHRA).

10 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964 as revised and recognised by governing laws and EU Directives. Each participant's consent to participate in the study should be obtained after a full explanation has been given of treatment options, including the conventional and generally accepted methods of treatment. The right of the patient to refuse to participate in the study without giving reasons must be respected.

After the participant has entered the study, the clinician may give alternative treatment to that specified in the protocol, at any stage, if they feel it to be in the best interest of the participant. However, reasons for doing so should be recorded and the participant will remain within the study for the purpose of follow-up and data analysis according to the treatment option to which they have been allocated. Similarly, the participant remains free to withdraw at any time from protocol treatment and study follow-up without giving reasons and without prejudicing their further treatment.

10.1 SPECIFIC ETHICAL CONSIDERATIONS

The SCTU uses the electronic data capture tool called RAVE, which will be used in the RiVa trial for sites to input pseudo-anonymised trial data. The servers on which this database will be held are based in the USA and therefore being stored outside of the UK and EEA. The Patient Information Sheet and Informed Consent Form shall highlight to participants where the data shall be held. Applicable Data Protection Legislation will be abided by.

10.2 ETHICAL APPROVAL

The study protocol has received the favourable opinion of a Research Ethics Committee.

10.3 INFORMED CONSENT PROCESS

Informed consent is a process that is initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. In obtaining and documenting informed consent, the Investigator should comply with applicable regulatory requirements and should adhere to the principles of GCP.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to the participant by appropriately delegated staff with knowledge in obtaining informed consent with reference to the patient information leaflet. This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. The participant will be given the opportunity to ask any questions that may arise and provided the opportunity to discuss the trial with family members, friends or an independent healthcare professional outside of the research team and time to consider the information prior to agreeing to participate.

10.4 CONFIDENTIALITY

SCTU will preserve the confidentiality of participants taking part in the trial. The Investigator must ensure that participant's anonymity will be maintained and that their identities are protected from unauthorised parties. On eCRFs participants will not be identified by their names, but by an identification code.

11 SPONSOR

SCTU, Chief Investigator and other appropriate organisations have been delegated specific duties by the University Hospital Southampton NHS Foundation Trust (UHS), the Sponsor. This is documented in the trial task allocation matrix.

The duties assigned to the trial sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement.

11.1 INDEMNITY

The University of Southampton's (UoS) public and professional indemnity insurance policy provides an indemnity to UoS employees for their potential liability for harm to participants during the conduct of the research. This does not in any way affect an NHS Trust's responsibility for any clinical negligence on the part of its staff.

11.2 FUNDING

The trial is funded by an Investigator Initiated Research grant from Celldex Therapeutics and by Cancer Research UK New Agents Committee (CRUKD/17/008). The trial is supported by Cancer Research UK Core funding at Southampton Clinical Trials Unit.

11.2.1 Site payments

The payments assigned to the trial sites (NHS Trusts or others taking part in this study) are detailed in the Non-Commercial Agreement. This study is adopted onto the NIHR portfolio (reference number 35676).

11.2.2 Participant payments

Participants will not be paid for participation in this study.

11.3 AUDITS AND INSPECTIONS

The study may be participant to inspection and audit by UHS (under their remit as Sponsor), SCTU (as the Sponsor's delegate) and other regulatory bodies to ensure adherence to the principles of GCP, Research Governance Framework for Health and Social Care, applicable contracts/agreements and national regulations.

12 TRIAL OVERSIGHT GROUPS

The day-to-day management of the trial will be co-ordinated through the SCTU and oversight will be maintained by the Trial Management Group, the Trial Steering Committee, the Data Monitoring and Ethics Committee and the Safety Review Committee.

12.1 TRIAL MANAGEMENT GROUP (TMG)

The TMG is responsible for overseeing progress of the study, including both the clinical and practical aspects. The Chair of the TMG will be the Chief Investigator of the study.

The RiVa TMG charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TMG, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

12.2 TRIAL STEERING COMMITTEE (TSC)

The TSC act as the oversight body on behalf of the Sponsor and Funder. The TSC will meet in person at least yearly and have at least one further teleconference meeting during the year. The majority of members of the TSC, including the Chair, should be independent of the trial.

The RiVa TSC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the TSC, including the timing of meetings, frequency and format of meetings and relationships with other trial committees.

12.3 SAFETY REVIEW COMMITTEE (SRC)

The SRC will consist of:

- Chief Investigator
- Principal Investigators
- Independent Clinician
- Non-voting representative from Celldex
- Trial Statistician
- Trial Manager

The SRC Charter for this study will define the exact membership and who should be present for decisions to be made. Further experts may be consulted by the SRC as necessary. The SCTU Head of Quality Management and Sponsor representative should always be present at the SRC if there are safety issues for discussion.

12.4 INDEPENDENT DATA MONITORING COMMITTEE (IDMC) /DATA MONITORING AND ETHICS COMMITTEE (DMEC)

*(**NB** for the purposes of this protocol, IDMC and DMEC refer to the same committee, and these terms can be used interchangeably).*

The aim of the IDMC/DMEC is to safeguard the interests of trial participants, monitor the main outcome measures including safety and efficacy, and monitor the overall conduct of the study.

The RiVa DMEC charter defines the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the IDMC, including the timing of meetings, methods of providing information to and from the IDMC, frequency and format of meetings, statistical issues and relationships with other trial committees.

13 DATA MANAGEMENT

Participant data will be entered remotely at site and retained in accordance with current Data Protection Regulations. The PI is responsible for ensuring the accuracy, completeness, and timeliness of the data entered.

The participant data is pseudo anonymised by assigning each participant a participant identifier code which is used to identify the participant during the study and for any participant-specific clarification between SCTU and site. The site retains a participant identification code list which is only available to site staff.

The Informed Consent Form will specify the participant data to be collected and how it will be managed or might be shared; including handling of all Patient Identifiable Data (PID) and sensitive PID adhering to relevant data protection regulations.

Trained personnel with specific roles assigned will be granted access to the eCRFs. eCRF completion guidelines will be provided to the investigator sites to aid data entry of participant information.

Only the Investigator and personnel authorised by them should enter or change data in the eCRFs. When requested, laboratory data must be transcribed, with all investigator observations entered into the eCRF. The original laboratory reports must be retained by the Investigator for future reference.

A Data Management Plan (DMP) providing full details of the study specific data management strategy for the trial will be available and a Trial Schedule with planned and actual milestones, eCRF tracking and central monitoring for active trial management created.

During Stage I of the trial, site staff will enter data on the eCRF within 3 business days of the visit due date and answer queries within 5 business days. During Stage II, site staff will be given 10 business days from visit due date to complete the eCRF and 20 business days to answer queries.

Data queries will either be automatically generated within the eCRF, or manually raised by the SCTU team, if required. All alterations made to the eCRF will be visible via an audit trail which provides the identity of the person who made the change, plus the date and time.

At the end of the trial after all queries have been resolved and the database frozen, the PI will confirm the data integrity by electronically signing all the eCRFs. The eCRFs will be archived according to SCTU policy and a PDF copy including all clinical and meta data returned to the PI for each participant.

Data may be requested from the Data Access Committee at SCTU. Any request will be considered on a monthly basis. The data custodian for the trial is the Director of SCTU.

14 DATA SHARING REQUESTS FOR RESULTS THAT ARE AVAILABLE IN THE PUBLIC DOMAIN

In order to meet our ethical obligation to responsibly share data generated by interventional clinical trials, SCTU operate a transparent data sharing request process. As a minimum, anonymous data will be available for request from three months after publication of an article, to researchers who provide a completed Data Sharing request form that describes a methodologically sound proposal, for the purpose of the approved proposal and if appropriate a signed Data Sharing Agreement. Data will be shared once all parties have signed relevant data sharing documentation.

Researchers interested in our data are asked to complete the Request for Data Sharing form (CTU/FORM/5219) [template located on the SCTU web site, www.southampton.ac.uk/ctu] to provide a brief research proposal on how they wish to use the data. It will include; the objectives, what data are requested, timelines for use, intellectual property and publication rights, data release definition in the contract and participant informed consent etc. If considered necessary, a Data Sharing Agreement from Sponsor may be required.

15 MONITORING

15.1 CENTRAL MONITORING

Data is stored electronically on servers in the US and will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Discrepancies found in the data will be returned to the site for resolution in the form of data queries. Data queries will be produced at SCTU in

the trial database and sent electronically to the site. Sites will respond to the queries providing an explanation/resolution to the discrepancies on the electronic data collection tool. There are a number of monitoring features in place at SCTU to ensure reliability and validity of the trial data, which are detailed in the trial monitoring plan.

15.2 CLINICAL SITE MONITORING

Before the study can be initiated, the prerequisites for conducting the study must be confirmed and the organisational preparations made with the trial centre. The suitability of the Investigator's research team, technical facilities and availability of eligible participants at the trial centre must be ensured. The Investigator must ensure that all study information is disseminated continuously to all those who are involved. The sponsor, via SCTU, must be informed immediately of any change in the persons involved in the conduct of the study at site.

The study will be monitored and audited in accordance with the Sponsor and SCTU procedures. All trial-related documents will be made available on request for monitoring and audit by the Sponsor, SCTU, and the relevant ethics committee and for inspection by the MHRA or other relevant bodies. During the trial, the Sponsor is responsible for monitoring data quality. Prior to the study start, the Investigator will be advised of the anticipated frequency of the monitoring visits. The Investigator will receive reasonable notification prior to each monitoring visit as per monitoring plan.

It is the duty of the Sponsor and SCTU to review study records and compare them with source documents; discuss the conduct of the study and any emerging problems with the Investigator; check that the drug storage and dispensing are reliable and appropriate and verify that the available facilities remain acceptable.

At the final close-down visit, SCTU will clarify any open questions, verify that all data requested and corrections have been entered correctly on the eCRFs and collect the study material that is no longer required. All unused drug supplied will be destroyed as instructed by the SCTU and destruction certificates retained in the Investigator Site File and a copy sent to SCTU.

15.2.1 Source Data Verification

On receipt of a written request from SCTU, the Investigator will allow the SCTU direct access to relevant source documentation for verification of data entered onto the eCRF (taking into account data protection regulations). Access should also be given to study staff and departments (e.g. pharmacy).

The participants' medical records and other relevant data may also be reviewed by appropriate qualified personnel independent from the SCTU appointed to audit the study, including representatives of the Competent Authority. Details will remain confidential and participants' names will not be recorded outside the study site.

15.3 SOURCE DATA

Source documents are where data are first recorded, and from which participants' eCRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

16 RECORD RETENTION AND ARCHIVING

Trial documents will be retained in a secure location during and after the trial has finished.

The Investigator or delegate must maintain adequate and accurate records to enable the conduct of the trial to be fully documented and the trial data to be subsequently verified. After trial closure, the

Investigator will maintain all source documents and trial related documents. All source documents will be retained for a period of 25 years following the end of the trial.

Sites are responsible for archiving the Investigator Site File (ISF) and participants' medical records.

The Sponsor is responsible for archiving the TMF and other relevant trial documentation.

17 PUBLICATION POLICY

Data from all centres will be analysed together and published as soon as possible.

Individual Investigators may not publish data concerning their participants that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications. All publications shall include a list of Investigators, and if there are named authors, these should include the Chief Investigator, Co-Investigators, Trial Manager, and Statistician(s) involved in the trial. Named authors will be agreed by the CI and Director of SCTU. If there are no named authors then a 'writing committee' will be identified.

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19 APPENDICES

APPENDIX 1 - SUMMARY OF LUGANO RESPONSE CRITERIA

At end of treatment, the response should be assessed:

1) Overall Response Rate

   Overall response rate is defined by objective response (partial or complete) in any of the participants as determined by the Lugano classification for NHL (Cheson 2014). The 2007 revised response criteria have been used with regard to bone marrow biopsy contribution to the response assessment (Cheson 2007).

   - Complete response (CR)
   - Partial response (PR)
   - Stable disease (SD)
   - Relapsed and Progressive disease (PD)

2) PET/CT Response Assessment

3) Investigator Response Assessment: Please refer to Cheson B., Ansell S., Schwartz L., et al, Refinement of the Lugano Classification lymphoma response criteria in the era of immunomodulatory therapy, Blood, 128;21, 2016 and https://www.parexel.com/files/4514/5744/8554/Cheson_Lugano_whitepaper.pdf

Response and Site	**PET/CT-Based Response**	**CT-Based Response**
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extra lymphatic sites	Score 1, 2, or 3[*] with or without a residual mass on 5 point response scale[†]	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g., with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Non measured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative

Response and Site	PET/CT-Based Response	CT-Based Response
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
Non measured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD° of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Non measured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression°
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and

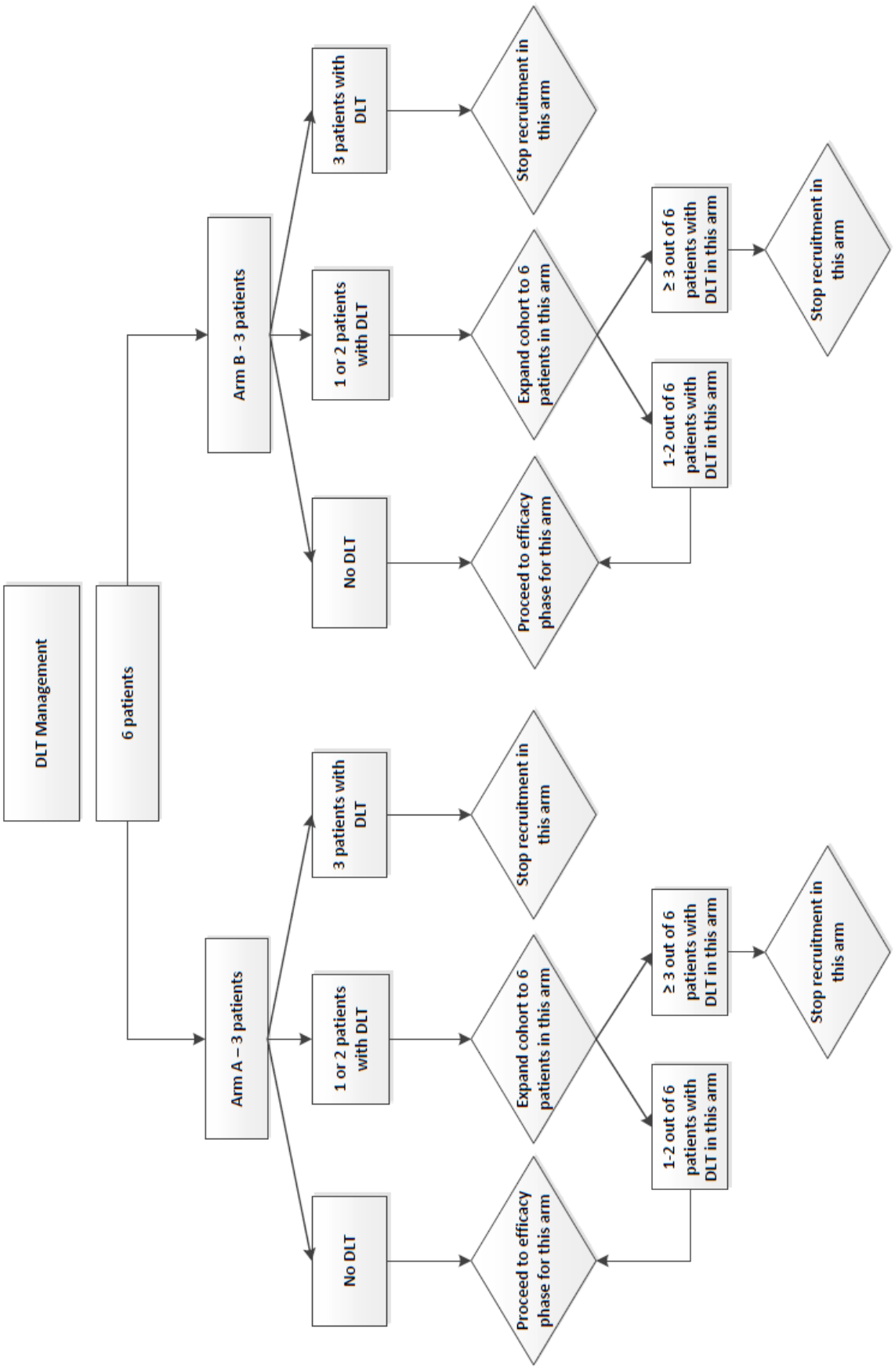
Response and Site	PET/CT-Based Response	CT-Based Response
		An increase in LDi or SDi° from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (e.g., a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Non measured lesions	None	New or clear progression of preexisting nonmeasured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another aetiology (e.g., infection, inflammation). If uncertain regarding aetiology 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

* 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 (bi-dimensional). 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 (e.g., 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 (e.g., 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 (e.g., 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.

°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.

APPENDIX 2 - SAFETY PHASE DESIGN



APPENDIX 3 – SUMMARY OF LUGANO STAGING CRITERIA

Stage	Involvement	Extranodal (E) status
I	One node or a group of adjacent nodes	Single extranodal lesions without nodal involvement
II	Two or more nodal groups on the same side of the diaphragm	Stage I or II by nodal extent with limited contiguous extranodal involvement
II + bulky	II as above with "bulky" disease	Not applicable
III	Nodes of both sides of the diaphragm. Nodes above the diaphragm with splenic involvement	Not applicable
IV	Additional non-contiguous extralymphatic involvement	Not applicable

Note: tonsils, Waldeyer's ring and spleen are considered nodal tissue. Extent of disease is determined by PET-CT for avid lymphomas and CT for non-avid histologies.

APPENDIX 4 – COCKCROFT-GAULT FORMULA

Creatinine clearance (mL/min) = {[(140-Age (years)) x Weight (kg) x 1.23]/Serum creatinine (μmol/L)} x 0.85

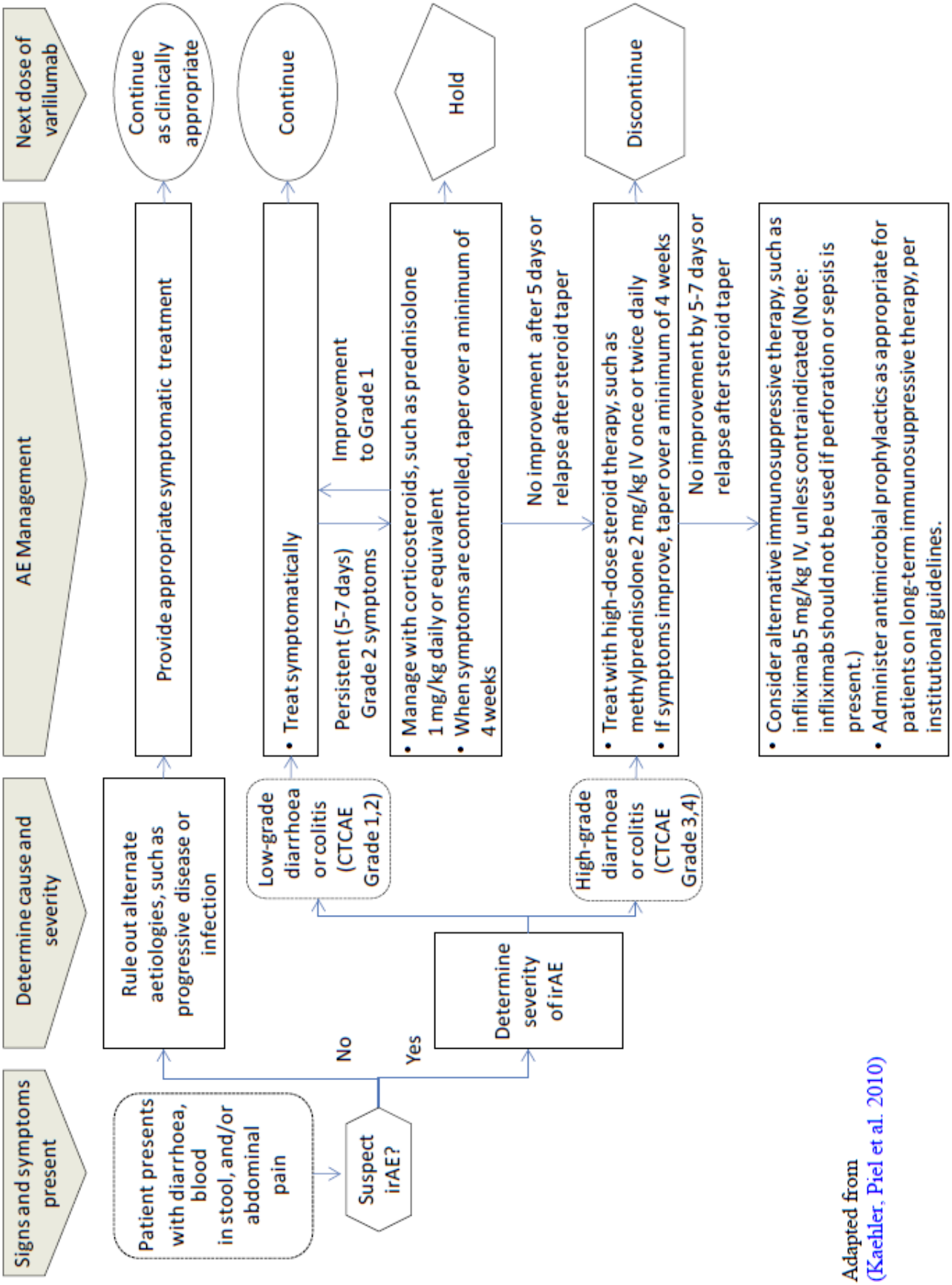
APPENDIX 5 - ECOG PERFORMANCE STATUS

Grade	Description
0	Fully active, able to carry on all pre-disease performance without restriction.
1	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.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published in Am. J. Clin. Oncol.:
Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

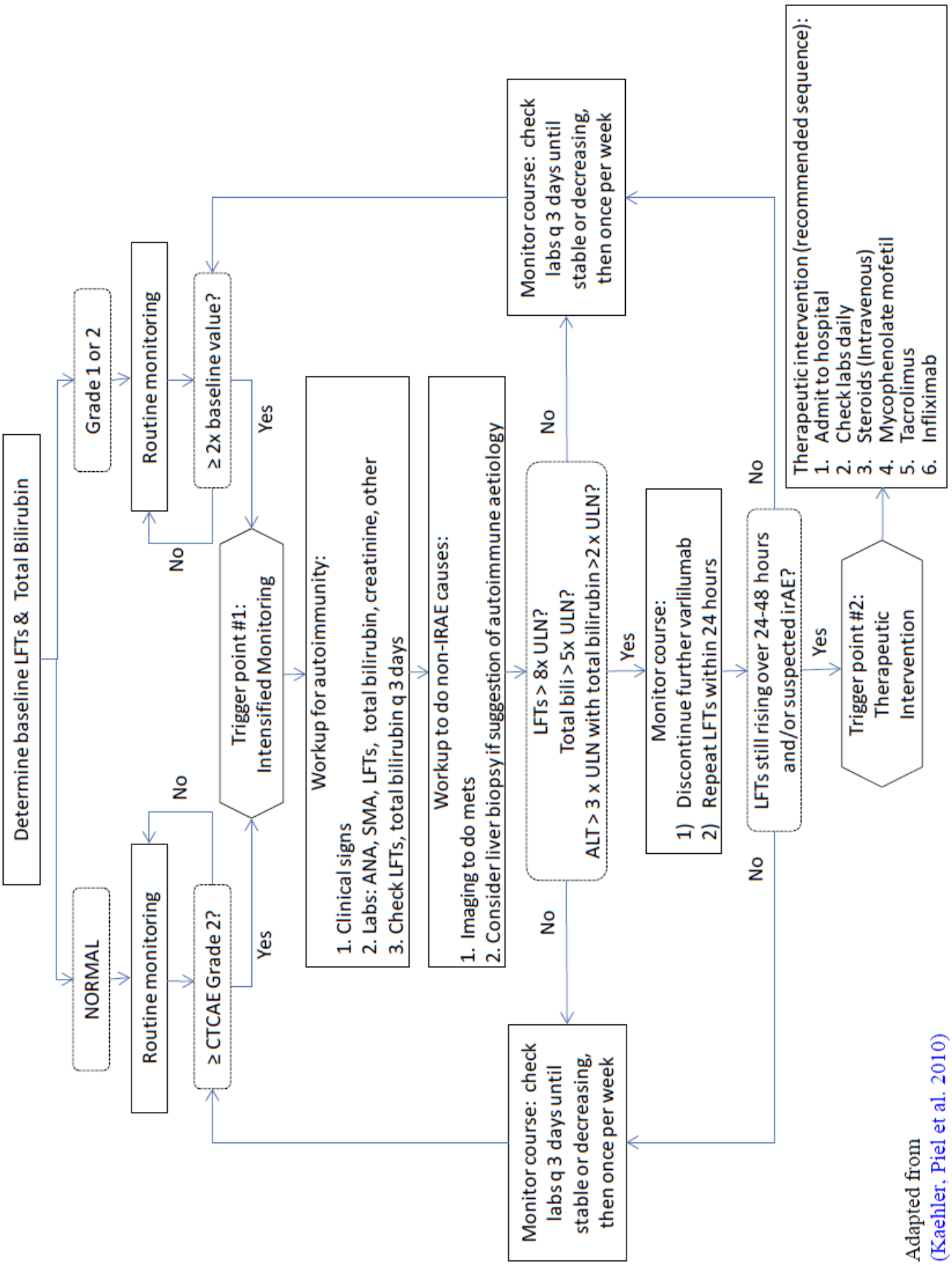
Revised: July 27, 2006

APPENDIX 6 – GASTROINTESTINAL TOXICITY TREATMENT ALGORITHM



Adapted from (Kaehler, Piel et al. 2010)

APPENDIX 7 – HEPATIC TOXICITY TREATMENT ALGORITHM



APPENDIX 8 – ENDOCRINOPATHY MANAGEMENT ALGORITHM

[1] Clinical signs and symptoms that may be indicative of underlying endocrinopathy: headache, visual field defects, fatigue, weakness, asthenia, failure to thrive, anorexia, nausea and vomiting, lethargy, impotence, amenorrhoea, fever, coma, new onset atrial fibrillation, hypotension, hypoglycemia, hyponatremia , eosinophilia

[2] Suggested endocrine labwork :
1. TSHT4, T3
2. ACTH, AM serum cortisol = > if abnormal, co-syntropin stimulation test
3. LH, FSH, testosterone, free, prolactin

[3] Varlilumab dosing
a) Upon resolution or adequate treatment of endocrinopathy , patients may continue varlilumab dosing with appropriate hormone replacement unless limited by protocol.
b)The risk of having a recurrence of endocrinopathy with subsequent varlilumab dosing after experiencing initial irAE is currently unknown

[4] Prolonged replacement steroid therapy:
a)Patients may require chronic hydrocortisone replacement to maintain homeostatic levels
b)Beware of complete discontinuation of steroids due to prolonged adrenal suppression.

Adapted from (Kaehler, Piel et al. 2010)

20 SUMMARY OF SIGNIFICANT CHANGES TO THE PROTOCOL

Protocol date and version	Summary of significant changes
Version 1, 27-Apr-2017	New document
Version 2, 08-May-2017	Updated inclusion criteria and trial design (changed classification of Follicular Lymphoma), updated date of rituximab SmPC in section 7.4
Version 3, 05-Jul-2017	Updated inclusion criteria on contraception, added rituximab hypersensitivity to exclusion criteria, added rituximab storage and handling to section 6.5, amended section 7.6 to reflect notification will be to REC.
Version 5, 11 Feb 2018	Added central monitoring of consent, added clarification and leeway for visit dates, removed duplicate wording, added trial reference numbers on cover page, added lipase/amylase to Appendix 6 (GI toxicity management) added definition for evaluable patient for SRC meeting, added treatment delay as DLT, added time window for PK sample collection, updated randomisation procedures, clarified screening biopsy requirements, removed Appendix 9 (LYRIC response criteria), updated RSI in section 7.4, updated liver enzymes in AE of special interest, changed statistics to 90% CI, updated wording throughout for clarification and consistency, updated SAE reporting exceptions in section 7.2
Version 6, 22 Oct 2020	Throughout the protocol the following has been amended; a window of ± 72 h for physical exam and haemotology and biochemistry, added Deauville score to PET, added bi-dimensional reporting wording for CT for clarity, added requirement for rituximab infusion stop time to match database data, amended PK sample wording to allow for 6 patients with at least 50% of expected PK samples, changed 30 and 60 min vital signs post infusion to 30 min post infusion only. Addition of end date for recruitment of 31st December 2020. Section 7.4 updated with most recent document versions. Addition of section 14 Data sharing policy to reflect current SCTU guidelines. Updating of wording to stats section for clarity.