AVAIL-T

A Phase 2a trial of Avelumab, an anti-PD-L1 antibody, in relapsed and refractory peripheral T-cell lymphoma (PTCL)

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AVAIL-T Trial Protocol 5.0a_15-Aug-2018

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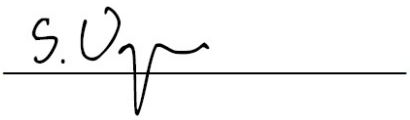
Signature:		**Date:**	15 / Aug /2018

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

AMENDMENTS

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

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment
1	25-May-2017	2.0	Substantial	Removal of one form of contraception from section 5.3
2	29-Aug-2017	3.0	Substantial	Section 7.5 Dose Modifications updated with new information provided in Avelumab IV V7.0 Clarification of patient registration processes.
3	20-Feb-2018	4.0	Substantial	Change to inclusion criteria: • hepatosplenic T-cell lymphoma removed as a PTCL histology for safety reasons • change to hepatic function criteria for safety reasons • addition of a PTCL histology Clarification of pregnancy tests (in screening and assessments sections (5.1 and 7.2) Clarification of treatment details in section 7.1 Clarification of management of IRRs in section 7.5 (Table 3)

				Clarification of management of Hepatic AEs (Table 4) Clarification of treatment discontinuation section (Table 5) Clarification of research sample collection Contact details updated
4	04-May-2018	5.0	Substantial	Update to treatment section – mandate dose banding for avelumab Clarification of post screening pregnancy tests (section 7.2) Clarification of steroid use in the concomitant medication section Update to research sample collection – addition of technique used for immunophenotyping Update to Table 5 to ensure it is consistent with guidance in Table 3
N/A	15-Aug-2018	5.0a	Notification	Change in Data Protection Regulations

TRIAL SYNOPSIS

Title

AVAIL-T: A Phase 2a trial of Avelumab, an anti-PD-L1 antibody, in relapsed and refractory peripheral T-cell lymphoma (PTCL)

Trial Design

This is a multicentre, single arm, open-label, phase 2a trial to determine responses to avelumab, an anti-PD-L1 antibody, in patients with refractory and relapsed PTCL. A single arm study has been selected to determine evidence of activity in PTCL to further evaluate in a larger trial.

Objectives

The primary objective of the trial is to determine overall response during 8 cycles of treatment with secondary objectives being toxicity, overall survival (OS), progression free survival (PFS), radiological reduction in tumour size and duration of response from time of first documented response until relapse, progression or death.

Outcome Measures

Primary Outcome Measures

- Best overall response (Partial Remission (PR) + Complete Response (CR)) during 8 cycles of treatment using Revised Response Criteria for Malignant Lymphoma (Appendix 1)

Secondary Outcome Measures

- Toxicity assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4
- Best overall response (PR + CR) at any time of treatment using Revised Response Criteria for Malignant Lymphoma[27]
- OS
- PFS
- Reduction in tumour size measured as maximum percentage change in the radiological sum of the product of the diameters from baseline of up to 6 target lesions
- Duration of response from time of first documented response until relapse, progression or death

Exploratory Outcome Measures

- PD-L1 expression levels
- Cell free DNA analysis
- Immunophenotyping
- Biomarkers of response

Patient Population and Sample Size

This trial will recruit 30-35 patients with relapsed or refractory PTCL.

Main Inclusion Criteria

- Male or female patients aged ≥ 16 years
- Life expectancy > 12 weeks
- ECOG performance status ≤ 2
- Relapsed or refractory* peripheral T-cell lymphoma including the following histologies: peripheral T-cell lymphoma not otherwise specified (PTCL NOS) , angioimmunoblastic T-cell

lymphoma (AITL), anaplastic large cell lymphoma (ALCL), enteropathy associated T-cell lymphoma (EATL), extranodal NK/T- cell lymphoma (ENKL), transformed mycosis fungoides (LCT MF), and subcutaneous panniculitis and T cell lymphoma * For all relapsed patients, relapse must be confirmed by tissue biopsy (or bone marrow trephine if no other tissue available). For relapsed and refractory patients, a biopsy must have been obtained within the last 3 months of registration

- Failed at least 1 prior therapy (but no upper limit of prior regimens)
- Adequate haematological function defined by the following at registration:
  - absolute neutrophil count (ANC) ≥ 1.0 × 10^9/L (unsupported)
  - platelet count ≥ 75 × 10^9/L (unsupported)
  - haemoglobin ≥ 90 g/L (may have been transfused)
- Adequate hepatic function and no evidence of hepatic involvement by T-cell lymphoma as defined by:
  - total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range (patients with elevated bilirubin due to Gilbert's syndrome are eligible)
  - AST and ALT levels ≤ 1.5 × ULN for all patients **and**
    - no clinical suspicion of hepatic involvement by T-cell lymphoma and
    - no liver abnormalities on imaging studies that might be due to T-cell lymphoma
- Adequate renal function defined by an estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)
- CT measurable disease with at least 1 lesion having short axis > 1.5cm or splenomegaly > 14cm in cranio-caudal length attributable to relapsed/non responding lymphoma
- Negative serum pregnancy test at screening for women of childbearing potential.
- Highly effective contraception for both male and female patients if the risk of conception exists. (Note: women of childbearing potential and men able to father a child must agree to use 2 highly effective contraception, defined as methods with a failure rate of less than 1 % per year. Highly effective contraception is required from consent, throughout and for at least 60 days after avelumab treatment.
- Ability to give informed consent

Main Exclusion Criteria

Patients are not eligible for the trial if they fulfill any of the following exclusion criteria:

- All patients with active CNS involvement of lymphoma
- Prior organ transplantation, including allogeneic stem-cell transplantation
- Significant acute or chronic infections including, among others:
  - Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS),
  - Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)
- Current use of immunosuppressive medication, EXCEPT for the following:
  - intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); Systemic corticosteroids at a maximum dose of ≤ 1 mg/kg of prednisone or equivalent during screening (to be stopped by day 1 of trial treatment); Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).
- Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible
- Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade ≥ 3)

- Persisting toxicity related to prior therapy of Grade >1 NCI-CTCAE v 4.03; however, alopecia and sensory neuropathy Grade ≤ 2 or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable
- Pregnancy or lactation
- Known alcohol or drug abuse
- Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to registration), myocardial infarction (< 6 months prior to registration), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication
- Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behaviour; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study
- Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines (e.g. the flu vaccine)
- Active infection requiring systemic therapy
- Major surgery within 4 weeks of trial entry
- Patients and partners of childbearing potential not willing to use two methods of effective contraception during and for 60 days after therapy

Trial Duration

Patients will be recruited over 24 months from 13 Trials Acceleration Programme (TAP) and non-TAP centres.

Following registration, patients will receive 8 cycles (each of 28 days duration) of avelumab (each cycle being two, fortnightly infusions of the antibody) with the possibility of continued treatment if the patient is benefitting. The patient will have an end of treatment visit within 28 days of the end of the last cycle.

A contrast enhanced CT scan of the neck, chest, abdomen and pelvis will be performed at cycles 3, 6 and 8 of treatment to assess response during treatment. If the patient has not progressed after 8 cycles they will continue to be followed up with CT scans at 12, 16 and 20 months from treatment start or sooner if the Investigator is concerned there may be disease progression or if the patient discontinues treatment. After 20 months from treatment start, radiological follow-up will be as per local standard with data collected every 6 months.

Patients will continue to be followed up for progression and survival until the end of trial.

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ABBREVIATIONS

ABPI	ASSOCIATION OF THE BRITISH PHARMACEUTICAL INDUSTRY
ACTH	ADRENOCORTICOTROPIC HORMONE
ADCC	ANITBODY DEPENDENT CELLULAR CYOTOXICITY
ADL	ACTIVITES OF DAILY LIVING
AE	ADVERSE EVENT
AHA	AMERICAN HEART ASSOCIATION
AIDS	ACQUIRED IMMUNODEFICIENCY SYNDROME
AITL	ANGIOIMMUNOBLASTIC LYMPHOMA
ALCL	ANAPLASTIC LARGE CELL LYMPHOMA
ALP	ALKALINE PHOSPHATASE
ALT	ALANINE TRANSAMINASE
AML	ACUTE MYELOID LEUKEMIA
ANC	ABSOLUTE NEUTROPHIL COUNT
AR	ADVERSE REACTION
AST	ASPARTATE TRANSAMINASE
CR	COMPLETE REMISSION/RESPONSE
CrCL	CREATININE CLEARANCE
CRCTU	CANCER RESEARCH UK CLINICAL TRIALS UNIT (UNIVERSITY OF BIRMINGHAM)
CRF	CASE REPORT FORM
CRP	C-REACTIVE PROTEIN
CR UK	CANCER RESEARCH UK
CT	COMPUTER TOMOGRAPHY
CTC	COMMON TERMINOLOGY CRITERIA
CTCAE	COMMON TERMINOLOGY CRITERIA FOR ADVERSE EVENTS
CTCL	CUTANEOUS T-CELL LYMPHOMA
CV	CURRICULUM VITAE
DCF	DATA CLARIFATION FORM
DNA	DEOXYRIBOSE NUCLEIC ACID
EATL	ENTEROPATHY ASSOCIATED T-CELL LYMPHOMA
ECG	ELECTROCARDIOGRAM
ECMC	EXPERIMENTAL CANCER MEDICINE CENTRE
ECOG	EASTERN COOPERATIVE ONCOLOGY GROUP
EDC	ELECTRONIC DATA CAPTURE
EMEA	EUROPEAN MEDICINES AGENCY
ENKL	EXTRANODAL NK/T- CELL LYMPHOMA
EORTC	EUROPEAN ORGANISATION FOR RESEARCH AND TREATMENT OF CANCER
ESC	EUROPEAN SOCIETY OF CARDIOLOGY
FBC	FULL BLOOD COUNT
FDA	(USA) FOOD AND DRUG ADMINISTRATION
FSH	FOLLICLE-STIMULATING HORMONE
GCP	GOOD CLINICAL PRACTICE

GGT	GAMMA-GLUTAMYL TRANSPEPTIDASE
GMP	GOOD MANUFACTURING PRACTICE
GP	GENERAL PRACTITIONER
HBV	HEPATITIS B VIRUS
HCG	HUMAN CHORIONIC GONADOTROPHIN
HCV	HEPATITIS C VIRUS
HGB	HAEMAGLOBIN
HIV	HUMAN IMMUNODEFICIENCY VIRUS
IB	INVESTIGATOR BROCHURE
ICF	INFORMED CONSENT FORM
ICOS	INDUCIBLE CO-STIMULATOR
IMP	INVESTIGATIONAL MEDICINAL PRODUCT
IRR	INFUSION RELATED REACTIONS
ISF	INVESTIGATOR SITE FILE
ISRCTN	INTERNATIONAL STANDARD RANDOMISED CLINICAL TRIAL NUMBER
IUD	INTRAUTERINE DEVICE
IV	INTRAVENOUS
IWG	INTERNATIONAL WORKING GROUP
LCT MF	LARGE CELL TRANSFORMED MYCOSIS FUNGOIDES
LFT	LIVER FUNCTION TEST
LLN	LOWER LIMIT OF NORMAL
MDS	MYELODYSPLASTIC SYNDROME
ML	MILILITRE
MHRA	MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY
MRI	MAGNETIC RESONANCE IMAGING
NCI	NATIONAL CANCER INSTITUTE
NCRI	NATIONAL CANCER RESEARCH INSTITUTE
NIHR CRN	NATIONAL INSTITUTE FOR HEALTH RESEARCH CLINICAL RESEARCH NETWORK
NHL	NON HODGKIN'S LYMPHOMA
NOS	NOT OTHERWISE SPECIFIED
NSAIDS	NONSTEROIDAL ANTI-INFLAMMATORY DRUGS.
ORR	OVERALL RESPONSE RATE
OS	OVERALL SURIVIAL
PCR	POLYMERASE CHAIN REACTION
PD-L1	PD-1 LIGAND
PFS	PROGRESSION FREE SURVIAL
PI	PRINCIPAL INVESTIGATOR
PIS	PATIENT INFORMATION SHEET
PR	PARTIAL REMISSION/RESPONSE
PS	PERFORMANCE STATUS
PTCL	PERIPHERAL T-CELL LYMPHOMA
QoL	QUALITY OF LIFE

R&D	RESEARCH AND DEVELOPMENT
RBC	RED BLOOD CELL
REC	RESEARCH ETHICS COMMITTEE
RNA	RIBOSE NUCLEIC ACID
SAE	SERIOUS ADVERSE EVENT
SAR	SERIOUS ADVERSE REACTION
SPC	SUMMARY OF PRODUCT CHARACTERISTICS
SPD	SUM OF THE PRODUCT OF DIAMETERS
SUSAR	SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION
T4	FREE THYROXINE
TAP	TRIALS ACCELERATION PROGRAMME
Thf	FOLLICULAR HELPER T-CELLS
Tfr	REPRESSIVE FOLLICULAR T-CELL SUBSET
TLS	TUMOUR LYSIS SYNDROME
TMA	TISSUE MICROARRAY
TMG	TRIAL MANAGEMENT GROUP
TSC	TRIAL SAFETY COMMITTEE
TSH	THYROID STIMULATING HORMONE
ULN	UPPER LIMIT OF NORMAL
WBC	WHITE BLOOD COUNT
WHO	WORLD HEALTH ORGANIZATION
WIMM	WEATHERALL INSITUTE OF MOLECULAR MEDICINE
WMA	WORLD MEDICAL ASSEMBLY

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1.1 Background

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous, often aggressive, group of non-Hodgkin lymphomas (NHL) comprising about 5% to 10% of all new NHL diagnoses. The most common subtypes are peripheral T-cell lymphoma not otherwise specified (PTCL-NOS), angioimmunoblastic T-cell lymphoma (AITL), and anaplastic large-cell lymphoma (ALCL). Recent advances in understanding normal T-cell biology together with gene expression and immunohistochemistry studies have suggested that a group of PTCL are derived from the $CD4^+$ T-cell subset, follicular helper T-cells (Tfh), which are characterised by surface expression of PD-1 and inducible co-stimulator (ICOS) and nuclear expression of BCL6[1-4]. The ligand of PD-1, PD-L1, is expressed on both lymphoma cells and stromal cells[5]. Historically the therapeutic approaches for PTCL have been derived from standard treatments for various subtypes of aggressive B-cell lymphoma. However, outcomes remain poor when these strategies are used in the management of PTCL, with 5-year overall survival (OS) ranging from 25 to 35% for the common subtypes and excluding ALK-positive ALCL[6].

Four drugs have been approved by the US Food and Drug Administration (FDA) for treatment of relapsed PTCL: pralatrexate, romidepsin, brentuximab vedotin (approved for ALCL only), and belinostat. In the relapsed/refractory setting, rates of response to single-agent therapy with these drugs (other than use of brentuximab vedotin for ALCL) range from 20% to 35%[7-10].

Several mechanistically based therapies are currently in clinical trials for T-cell lymphoma. In patients with ALK-positive ALCL there are efforts to study crizotinib, which has been approved for treatment of lung cancer harboring a translocation in the *ALK* gene. As ALK is constitutively expressed in a subset of patients with ALCL, this is an attractive therapeutic target. In small series of relapsed patients, response rates of 60% to 100% to crizotinib have been seen, including one study of 11 patients (9 with ALCL) showing an overall response rate (ORR) of 91% [11]. Several other ALK inhibitors are also in development but primarily these agents are being investigated in lung cancer.

IDH2 is an enzyme that normally catalyses the conversion of isocitrate to alpha-ketoglutarate (α-KG) in the Krebs cycle. Mutations in the *IDH2* gene are seen in several malignancies, including acute myeloid leukemia (AML), gliomas and glioblastoma, chondrosarcoma, and cholangiocarcinoma. Recently a phase I study of the oral IDH2 inhibitor AG-221 in patients with AML and myelodysplastic syndrome (MDS) showed an ORR of 56% in 45 patients, including complete and durable responses [12]. Gain-of-function mutations in *IDH2* are seen in 20% to 45% of cases of AITL and rarely in PTCL-NOS [13,14]. Early-phase studies of AG-221 in malignancies harboring an *IDH2* mutation, including disease-specific cohorts of AITL, are underway (ClinicalTrials.gov ID: NCT02273739).

Phosphatidylinositol 3-kinase (PI3K) inhibitors and their downstream targets (eg, AKT or mammalian target of rapamycin [mTOR]) are important in cell differentiation, metabolism, survival, and proliferation. Idelalisib is a PI3K-delta inhibitor currently approved for chronic lymphocytic leukemia/small lymphocytic lymphoma, and follicular lymphoma and many other PI3K inhibitors are being developed and investigated [15,16]. The PI3K-delta/gamma inhibitor duvelisib (IPI-145) has demonstrated an ORR of 53% in PTCL [17].

Another pathway of therapeutic interest in PTCL is the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway; this is because mutations in *JAK3* have been seen in natural killer (NK)-cell/T-cell lymphomas, and activation of the JAK/STAT signaling pathway has also been described in PTCL [13,14]. Ruxolitinib, approved for treatment of myeloproliferative neoplasms, is being investigated in relapsed lymphoma, including PTCL (ClinicalTrials.gov ID: NCT01431209).

Studies incorporating these novel agents as part of upfront treatment regimens are underway, and there is hope for improved responses.

1.2 Trial Rationale

1.2.1 Justification for patient population

The outcome for patients with relapsed / refractory PTCL is extremely poor, with a median survival of just 6-18 months and very few patients cured of their disease[18]. Therefore although these patients are uncommon, there is a significant unmet medical need and a requirement for rational drug combinations with validated predictive biomarkers.

1.2.2 Justification for design

Avelumab is currently in clinical development across phases 1-3 with safety data in relation to its use in solid tumours (see Investigator's Brochure (IB) for Avelumab). Avail-T has been designed as a single arm phase 2a study on the assumption that the safety profile obtained with avelumab in patients with solid cancers will be essentially the same as for patients with hematological malignancy.

Other considerations were to produce a study to determine the primary outcome measures (as listed below) including best overall response rate during 8 cycles (each cycle being 28 days) of treatment as rapidly as possible in this rare disease population but also with the flexibility to deliver a larger study.

In order to fulfill these criteria we propose a Bayesian probability plot approach.

1.2.3 Choice of treatment

Cross-linking of PD-1 has been shown to inhibit T-cells[19] and this has prompted interest in perturbing PD-1/PD-L1 signaling in order to enhance T-cell anti-tumour activity in solid cancers[20,21]. However, this model does not appear to explain PD-1/PD-L1 function in Tfh-cells, a $CD4^+$ T-cell subset required for germinal centre formation, in part, by providing IL-4 and IL-21 to cause B-cell proliferation[22,23]. Data from mice lacking PD-1 demonstrates important functions for this surface protein in T-cell differentiation [24,25]. While the earlier study [24] demonstrated that PD-1 deficient animals had increased follicular T-cells there was a paradoxical lack of increased functions attributable to the Tfh subset. Subsequent work following identification of a repressive follicular T-cell subset (Tfr)[25] has provided a resolution for this problem: $PD\text{-}1^{-/-}$ mice show increased numbers and functions of Tfr whilst Tfh are repressed. Interestingly, mice lacking the PD-1 ligand (PD-L1) demonstrated the same phenotype. This suggests that *in vivo* the PD-1/PD-L1 axis regulates the differentiation of follicular T-cells such that stimulation of PD1 drives Tfh differentiation whereas blockade of PD-1/PD-L1 produces a repressive and Tfr dominated environment.

PD-L1 is expressed on both tumour and stromal components of PTCL (Table 1)[5] by immunohistochemistry, which is likely to underestimate patients for which the PD-1/PD-L1 axis is functionally important. Avelumab, in distinction from other therapeutic anti-PDL1 antibodies causes antibody dependent cellular cytotoxicity (ADCC)[26]. Therefore, avelumab may deplete essential stromal components of the tumour microenvironment as well as causing apoptosis of lymphoma cells.

Table 1

Percentage of cases expressing PD-L1 on tumour cells and stroma in PTCL (from Wilcox et al.[5]). Cutaneous PTCL have been excluded from the data.

	Tumour PD-L1 (%)	Stroma PD-L1 (%)
PTCL-NOS	17	43
AITL	5	57
ALK+ ALCL	33	22
ALK-ALCL	15	35
Other	10	24

EMR 100070-001 is a study of avelumab in metastatic and locally recurrent solid tumours. None of the patients treated with doses up to 10 mg/kg experienced a dose limiting toxicity and this dose is, therefore, considered a safe and well-tolerated dose (Avelumab Investigators Brochure v4.0, February 2015).

A dose-escalation trial of avelumab (MSB0010718C)[27] has been reported and investigators demonstrated that this antibody could be safely administered in doses up to 20 mg/kg every 2 weeks.

480 patients have been enrolled in 11 expansion cohorts and treated with avelumab 10 mg/kg every 2 weeks up to November 2014. 59/480 (12.3%) had at least one treatment related adverse event of > grade 3 – anaemia, fatigue, gammaGT increase, infusion related reactions lipase increase, lymphocyte count decreased, autoimmune hepatitis, constipation, dyspnoea, hypertension, hypokalaemia, hypoxia, pneumonitis, vomiting. 56/480 (11.7%) had potential autoimmune related adverse events. As of November 2014 49/480 patients (10.2%) experienced at least one infusion

related reaction most of which were grade 1 or 2. Two suspected unexpected serious adverse reactions (SUSARs) (infusion-related reaction (IRR) and anaphylaxis) were reported following which a premedication regime of piriton and paracetamol was mandated.

In a "real-world" study of outcomes in PTCL the median OS after relapse/progression in 211 patients initially responding (PR or CR) to primary treatment was 6.0 months and among patients with primary refractory disease (n = 143), median OS from response evaluation was only 2.5 months[28]. One trial in refractory/relapsed PTCL administered treatment for 6 months[29], while the current UK trial, RomiCar, administers 8 cycles of treatment. We, therefore, chose a regimen that allows for 8 months treatment with avelumab.

For complete details of the *in vitro* and non-clinical studies refer to the avelumab IB.

2. AIMS, OBJECTIVES AND OUTCOME MEASURES

2.1 Aims and Objectives

Identify overall response to avelumab in relapsed/refractory PTCL.

2.2 Outcome Measures

Primary Outcome Measures

- Best overall response (PR + CR) during 8 cycles of treatment using Revised Response Criteria for Malignant Lymphoma[27]

Secondary Outcome Measures

- Toxicity using CTCAE v4
- Best overall response (PR + CR) at any time of treatment using Revised Response Criteria for Malignant Lymphoma[27]
- OS
- PFS
- Reduction in tumour size measured as maximum percentage change in the radiological sum of the product of the diameters of up to 6 target lesions from baseline
- Duration of response from time of first documented response until relapse, progression or death

Exploratory Outcome Measures

- PD-L1 expression levels
- Cell free DNA analysis
- Immunophenotyping
- Biomarkers of response

3. TRIAL DESIGN

This is a single arm phase 2a trial to determine responses to avelumab in patients with refractory and relapsed PTCL. A single arm study has been selected to determine evidence of activity in PTCL to further evaluate in a larger trial. Patients will be recruited over a 24-month period and will receive 8 cycles of treatment with the possibility of continued treatment if the patient is showing clinical benefit. Patients will continue to be followed up for progression and survival for one year after the end of the trial treatment.

The trial will enrol 30 patients with the flexibility to enrol more, up to 35, if required. Based on 30 patients in the trial, if 11 responses were obtained this would give a probability of 60% that the response rate is greater than 35%. If 13/30 responses were obtained there is a probability of 84% that the response rate is greater than 35%. Other possible outcomes, both for 30 and 35 patients, have been plotted and are presented (Appendix 2).

4. ELIGIBILITY

4.1 Inclusion Criteria

- Male or female patients aged ≥ 16 years
- Life expectancy > 12 weeks
- ECOG performance status ≤ 2
- Relapsed or refractory* peripheral T-cell lymphoma including the following histologies: peripheral T-cell lymphoma not otherwise specified (PTCL NOS) , angioimmunoblastic T-cell lymphoma (AITL), anaplastic large cell lymphoma (ALCL), enteropathy associated T-cell lymphoma (EATL), extranodal NK/T- cell lymphoma (ENKL), transformed mycosis fungoides (LCT MF), and subcutaneous panniculitis and T cell lymphoma * For all relapsed patients, relapse must be confirmed by tissue biopsy (or bone marrow trephine if no other tissue available). For relapsed and refractory patients, a biopsy must have been obtained within the last 3 months of registration
- Failed at least 1 prior therapy (but no upper limit of prior regimens)
- Adequate haematological function defined by the following at registration:
    - absolute neutrophil count (ANC) ≥ 1.0 × 10^9/L (unsupported)
    - platelet count ≥ 75 × 10^9/L (unsupported)
    - haemoglobin ≥ 90 g/L (may have been transfused)
- Adequate hepatic function and no evidence of hepatic involvement by T-cell lymphoma as defined by:
    - total bilirubin level ≤ 1.5 × the upper limit of normal (ULN) range (patients with elevated bilirubin due to Gilbert's syndrome are eligible)
    - AST and ALT levels ≤ 1.5 × ULN for all patients **and**
        - no clinical suspicion of hepatic involvement by T-cell lymphoma and
        - no liver abnormalities on imaging studies that might be due to T-cell lymphoma
- Adequate renal function defined by an estimated creatinine clearance ≥ 30 mL/min according to the Cockcroft-Gault formula (or local institutional standard method)
- CT measurable disease with at least 1 lesion having short axis > 1.5cm or splenomegaly > 14cm in cranio-caudal length attributable to relapsed/non responding lymphoma
- Negative serum pregnancy test at screening for women of childbearing potential.
- Highly effective contraception for both male and female patients if the risk of conception exists. (Note: women of childbearing potential and men able to father a child must agree to use 2 highly effective contraception, defined as methods with a failure rate of less than 1 % per year. Highly effective contraception is required from consent, throughout and for at least 60 days after avelumab treatment.
- Ability to give informed consent

4.2 Exclusion Criteria

Patients are not eligible for the trial if they fulfill any of the following exclusion criteria:

- All patients with active CNS involvement of lymphoma
- Prior organ transplantation, including allogeneic stem-cell transplantation
- Significant acute or chronic infections including, among others:
    - Known history of testing positive test for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS),
    - Hepatitis B virus (HBV) or hepatitis C virus (HCV) infection at screening (positive HBV surface antigen or HCV RNA if anti-HCV antibody screening test positive)
- Current use of immunosuppressive medication, EXCEPT for the following:
    - intranasal, inhaled, topical steroids, or local steroid injection (e.g., intra-articular injection); Systemic corticosteroids at a maximum dose of ≤ 1 mg/kg of prednisone or

equivalent during screening (to be stopped by day 1 of trial treatment); Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication).

- Active autoimmune disease that might deteriorate when receiving an immunostimulatory agent. Patients with diabetes type I, vitiligo, psoriasis, hypo- or hyperthyroid disease not requiring immunosuppressive treatment are eligible
- Known prior severe hypersensitivity to investigational product or any component in its formulations, including known severe hypersensitivity reactions to monoclonal antibodies (NCI CTCAE v4.03 Grade ≥ 3)
- Persisting toxicity related to prior therapy of Grade >1 NCI-CTCAE v 4.03; however, alopecia and sensory neuropathy Grade ≤ 2 or other Grade ≤ 2 not constituting a safety risk based on investigator's judgment are acceptable
- Pregnancy or lactation
- Known alcohol or drug abuse
- Clinically significant (i.e., active) cardiovascular disease: cerebral vascular accident/stroke (< 6 months prior to registration), myocardial infarction (< 6 months prior to registration), unstable angina, congestive heart failure (≥ New York Heart Association Classification Class II), or serious cardiac arrhythmia requiring medication.
- Other severe acute or chronic medical conditions including colitis, inflammatory bowel disease, pneumonitis, pulmonary fibrosis or psychiatric conditions including recent (within the past year) or active suicidal ideation or behaviour; or laboratory abnormalities that may increase the risk associated with study participation or study treatment administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient inappropriate for entry into this study
- Vaccination within 4 weeks of the first dose of avelumab and while on trial is prohibited except for administration of inactivated vaccines (e.g. the flu vaccine)
- Active infection requiring systemic therapy
- Major surgery within 4 weeks of trial entry
- Patients and partners of childbearing potential not willing to use two methods of effective contraception during and for 60 days after therapy

5. SCREENING AND CONSENT

5.1 Screening

The following assessments must be performed within 28 days prior to registration of a patient unless otherwise stated:

- Medical history – Including prior and current diagnosis,
- Physical Exam – Including vital signs (blood pressure, pulse and oxygen saturation), clinical disease assessment, ECOG assessment, height and weight
- Haematology – Full blood count (FBC) (Haemoglobin, Platelets, White Blood Count (WBC), Neutrophils and Lymphocytes)
- Blood Chemistry – Standard blood chemistry (to include bilirubin, AST/ALT, Alkaline, Calcium (adjusted), Creatinine, Creatinine Clearance, C-Reactive Protein, Magnesium, Potassium, Sodium, and glucose –non fasted) plus GGT, phosphate, triglycerides and, cholesterol Virology – HIV, HBV and HCV serology
- Pregnancy test - For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL. Following a negative pregnancy result at screening, appropriate contraception must be commenced.
- Urinalysis – Protein, Glucose and Blood. If protein 2+ by semi-quantitative method (eg, urine dipstick), protein will have to be quantified by 24-hour urine collection and microscopic urinalyses will have to be done (Reflex Testing). If urine dipstick is positive for urine blood, microscopic urinalysis will have to be done (Reflex Testing)
- ECG - single 12 lead
- A bone marrow trephine biopsy (obtained within the last 3 months, however results are not required prior to trial entry) for relapsed and refractory patients

- Tissue biopsy (or bone marrow trephine if no other tissue available) to confirm relapse for all relapsed patients and to confirm refractory disease histology for refractory patients. These biopsies must have been obtained within the last 3 months. Sections will be collected for research and PD-L1 testing
- CT Scan (Neck, Chest, Abdomen and Pelvis)

For full details of the investigations see section 7.3

5.2 Informed Consent

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

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

Details of the informed consent discussions should be recorded in the patient's medical notes, this should include date of, and information regarding, the initial discussion, the date consent was given, with the name of the trial and the version number of the PIS and ICF. Throughout the trial the patient should have the opportunity to ask questions about the trial and any new information that may be relevant to the patient's continued participation should be shared with them in a timely manner. On occasion it may be necessary to re-consent the patient in which case the process above should be followed and the patient's right to withdraw from the trial respected. Patients are permitted to re-consent at the same visit that new information is provided if they wish to do so.

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

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

5.3 Contraception

The effects of the trial drug on the developing human foetus are unknown; thus, women of childbearing potential and men able to father a child must agree to use two methods of highly effective contraception throughout the study and continued for at least 60 days after the last dose or abstain from sex throughout the study period.

Highly effective methods of contraception are those that, alone or in combination, result in a failure rate of less than 1% per year when used consistently and correctly (ie, perfect use) and include the following:

1. Established use of oral, inserted, injected, implanted or transdermal hormonal methods of contraception is allowed provided the patient plans to remain on the same treatment throughout the entire study and has been using that hormonal contraceptive for an adequate period of time to ensure effectiveness.

2. Correctly placed copper containing intrauterine device (IUD).

3. Male sterilisation with absence of sperm in the post-vasectomy ejaculate.

4. Bilateral tubal ligation or bilateral salpingectomy or bilateral tubal occlusive procedure (provided that occlusion has been confirmed in accordance with the device's label).

5. Female partner who meets the criteria for non-childbearing potential, defined as:

- Have undergone a documented hysterectomy and/or bilateral oophorectomy;
- Have medically confirmed ovarian failure; or
- Achieved postmenopausal status, defined as follows: cessation of regular menses for at least 12 consecutive months with no alternative pathological or physiological cause. Status may be confirmed by having a serum follicle-stimulating hormone (FSH) level within the laboratory's reference range for postmenopausal women.

All sexually active male patients must agree to prevent potential transfer of and exposure to drug through semen to their partners by using a condom beginning with the first dose of investigational product and continuing for at least 60 days after the last dose.

6. TRIAL ENTRY

Patients will be registered to the trial via the Cancer Research UK Clinical Trials Unit (CRCTU) by phone or using the CRCTU systems portal. An eligibility checklist and registration form (found in the ISF) should be completed prior to registration by the Investigator or designee.

Registration via CRCTU systems portal:

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

Login details will be provided by the trials office as part of site initiation. The patient trial number will be provided by the online system. A report can be printed as confirmation.

Registration via phone:

☎:0121 371 7861

9am-5pm Monday to Friday

The patient trial number will be given over the telephone, followed by a fax confirmation.

7. TREATMENT DETAILS

7.1 Trial Treatment

All patients registered to the trial will receive avelumab at the dose of 10 mg/kg by intravenous (IV) infusion once every 2 weeks for 8 cycles (28 day cycles). Each infusion of avelumab should be delivered over 1h (-10/+20min) unless IRR is experienced (see Table 3). Avelumab dose should be prepared in accordance with the NHS England National Dose Banding Table for avelumab (please refer to the pharmacy manual)

All patients should be weighed within 3 days prior to day 1 dosing for every cycle to ensure they did not experience either a weight loss or gain >10% from the weight used for the last dose calculation. For weight change less than 10% the decision to recalculate the avelumab dose can be in accordance with institutional practice. If the patient experienced either a weight loss or gain >10% compared to the weight used for the last dose calculation, the amount of study drug must be recalculated.

Premedication

Premedication with an antihistamine and with paracetamol, to mitigate IRRs and is **mandatory** approximately 30 to 60 minutes prior to the first four doses of avelumab (Cycles 1-2), but may continue to be administered for subsequent cycles based upon clinical judgment and presence/severity of prior infusion reactions, at the treating Investigator's discretion. For example, 25-50 mg diphenhydramine and 500-650 mg paracetamol IV or oral equivalent should be considered.

This regimen may be modified based on local treatment standards and guidelines as appropriate provided it does not include systemic corticosteroids.

Avelumab should be administered in a setting that allows for immediate access to an intensive care unit or equivalent environment and administration of therapy for anaphylaxis, such as the ability to implement immediate resuscitation measures. Steroids (dexamethasone 10 mg), epinephrine (1:1,000 dilution), allergy medications (IV antihistamines), bronchodilators, or equivalents, and oxygen should be available for immediate access.

Following avelumab infusions, patients must be observed for 2 hours post-infusion for potential IRRs.

Patients will be assessed during the course of treatment, at progression or after completion of 8 cycles of treatment as described in section 7.3.

Avelumab will be supplied free of charge for trial patients by Pfizer. This IMP will be packaged and labelled in accordance with local regulations and Good Manufacturing Practice (GMP) by a third party contracted by the Sponsor. Site pharmacies will be required to add site specific details on receipt of avelumab.

Avelumab Solution for Infusion, 20 mg/mL is supplied as a clear, colourless non-pyrogenic solution, packaged in a Type I glass vial containing 10 mL of solution, with a rubber stopper, and aluminium overseal and flip off cap. Each single-use vial of MSB0010718C (avelumab) contains a sufficient amount of product to ensure an extractable volume of 10 mL (200 mg) at a concentration of 20 mg/mL formulated with a preservative-free acetate buffered solution at pH 5.2 in the presence of Polysorbate 20 and Mannitol.

The avelumab supplied will require further dilution prior to IV infusion. The investigational product will be administered intravenously according to the instructions provided in the AVAIL-T pharmacy manual. Unopened vials should be stored at 2-8^{o}C.

Avelumab must be allowed to reach room temperature (15-25 °C) for minimum 30 minutes prior to use in dose preparation. Use immediately after preparation. Infusion is not intended to be stored, however, if dilution has taken place in controlled and validated aseptic conditions it may be stored for no more than 24 hours under refrigerated conditions (2-8 ^{o}C) with no more than 8 of those hours at room temperature (15-25 °C) including infusion time. If stored under refrigerated conditions, allow each bag to equilibrate to room temperature (15-25 °C), preferably for one hour before administration.

For further details and ordering, please refer to the pharmacy manual.

7.2 Treatment Schedule

Avelumab 10 mg/kg will be administered once every 14 days for a proposed duration of 8 cycles (28 day cycles), (16 doses).

If the patient is showing clinical benefit following 8 cycles of trial treatment patients may continue to receive avelumab treatment at the treating Investigator's discretion, until loss of response, toxicity, or death.

Every effort should be made for patients to attend on the scheduled visit days. However, if a patient is unable to attend on the specified day, assessments may be scheduled for +/- 3 days.

The full blood count should be assessed prior to each treatment (within 24 hours of treatment) to ensure the following criteria are met:

- Platelets > 75 x 10^9/L
- Neutrophils >1.0 x10^9/L
- Bilirubin <1.5 x ULN
- Creatinine clearance (CrCL) (Cockcroft-Gault) ≥30ml/min).
- ALT/AST ≤ 1.5 × ULN on Cycle 1 day1; thereafter ≤ 3 × ULN

Please also refer to Section 7.5 for dose delays and modifications, and to section 7.7 for concomitant medications.

7.3 Assessments

Table 2. Schedule of Assessments

Parameter	Screening (28 days unless otherwise stated)	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Subsequent cycles		End of Treatment /Progression	12 month Follow-up (from treatment start)	16 month Follow-up (from treatment start)	20 month Follow-up (from treatment start)
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15				
Informed consent	X																						
Medical History	X																						
Pregnancy test (if applicable)	X	X		X		X		X		X		X		X		X		X		X			
Prior Diagnosis/ Prior Treatment / baseline conditions	X																						
ECOG performance status	X	X		X		X		X		X		X		X		X		X		X			
Height (pre-study only)	X																						
Weight	X	X		X		X		X		X		X		X		X		X					
Diagnostic tissue biopsy (within 3 months of registration)	X																			X (optional)			
Bone Marrow Trephine biopsy (within 3 months)	X																			X[1]			
Laboratory Tests (Haematology[2] and Biochemistry[3])	X[4]	X	X	X	X	X	X	X[4]	X	X	X	X	X	X	X	X	X	X	X	X[4]			
Virology (HIV, HBV, HCV)	X																						
Urinalysis (protein, glucose	X	X		X		X		X		X		X		X		X		X		X			

Parameter	Screening (28 days unless otherwise stated)	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycle 7		Cycle 8		Subsequent cycles		End of Treatment /Progression	12 month Follow-up (from treatment start)	16 month Follow-up (from treatment start)	20 month Follow-up (from treatment start)
		Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15				
and blood)																							
ACTH, Thyroid function (T4 & TSH), tests for pancreatitis		X				X				X				X						X			
ECG (single 12 lead)	X	X[5]		X[5]																X			
Clinical Disease assessment / physical exam	X	X		X		X		X		X		X		X		X		X		X	X	X	X
CT scans with IV contrast NCAP	X						X[6]						X[6]				X[6]		X[7]	X[8]	X	X	X
Avelumab 10mg/kg every 2 weeks		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Concomitant Diseases and Treatment		<< Ongoing assessment until 28 days after treatment discontinuation >>																					
Adverse Events		<< Ongoing assessment until 28 days after treatment discontinuation >>																					
Blood samples collected for research	X				X				X				X				X		X[7]	X	X	X	X

1 If baseline showed involvement, a further biopsy is required at radiological CR to confirm CR. Further bone marrow biopsy should also be performed if progression within the marrow is suspected and the CT does not show progression.
2 Haematology – Full blood count (Haemoglobin, Platelets, WBC, Neutrophils and Lymphocytes)
3 Blood Chemistry – Standard blood chemistry (to include bilirubin, GGT, AST/ALT, Alkaline phosphate, Calcium (adjusted), Creatinine, CRP, Magnesium, Phosphate, Potassium, Sodium, and glucose –non fasted)
4 Triglycerides and cholesterol at baseline, Cycle 4 days 1 and End of Treatment only
5 To be performed before and after avelumab infusion
6 CT scans to be performed within the time period after the day 15 dose and prior to next day 1 dose.
7 Post 8 cycles CT scans and research bloods will be performed in line with the follow-up schedule
8 End of Treatment scan only required if treatment stopped early and no scan has been conducted in the previous 28 days. Progression scan upon suspected progression outside of scheduled scans.

7.3.1 Blood chemistry and Haematology

Full Blood count (Haemoglobin, Platelets, WBC, Neutrophils and Lymphocytes) and serum biochemistry (to include AST/ALT, Alkaline phosphate, bilirubin, Calcium (adjusted), Creatinine, Creatinine Clearance, C-Reactive Protein, Magnesium, Potassium, Sodium, GGT, Phosphate, and glucose -non fasted) will be taken within the 24h prior to each avelumab dose and at the End of Treatment visit .

Triglycerides and Cholesterol should also be assessed at Cycle 4 day 1 and End of Treatment visit only

Hormone function tests (ACTH, Free T4, and TSH) and tests for pancreatitis (such as Amylase and or Lipase as per institutional standard) will be performed prior to avelumab infusion where possible on Cycle 1 Day 1, Cycle 3 day 1, Cycle 5 day 1, Cycle 7 day 1, and at the End of treatment visit (if not performed in the previous 8 weeks). Test should additionally be performed in cases of suspected hypoadrenalism, hypopituitarism or pancreatitis.

Pregnancy test - For female patients of childbearing potential, a serum pregnancy test, with sensitivity of at least 25 mIU/mL and assayed in a certified laboratory, once at the start of screening. Urine or serum pregnancy tests will be routinely repeated at every treatment cycle during the active treatment period (immediately before investigational product administration) and at the end of study treatment visit. Additionally whenever 1 menstrual cycle is missed or when potential pregnancy is otherwise suspected this test should be repeated.

7.3.2 Urinalysis

Urinalysis will be performed on Day 1 (+/- 24 hours) of all treatment cycles and at the End of Treatment visit. If protein 2+ by semi-quantitative method (eg, urine dipstick), protein will have to be quantified by 24-hour urine collection and microscopic urinalyses will have to be done (Reflex Testing). May also be performed when clinically indicated. If urine dipstick is positive for urine blood, microscopic urinalysis will have to be done (Reflex Testing), and the patient will be treated as per local standard of care based on Investigator medical judgment.

7.3.3 Electrocardiogram (ECG)

Single 12 lead ECGs will be performed at baseline, on Day 1 of Cycles 1 and 2, before avelumab infusion, and at the end of avelumab infusion. This will also be repeated at the End of Treatment visit.

If the QTc is prolonged (>500 msec, ie, CTCAE Grade 3), then the ECGs should be re-evaluated by a qualified person at the site for confirmation as soon as the finding is made, including verification that the machine reading is accurate. If manual reading verifies a QTc of >500 msec, immediate correction for reversible causes (including electrolyte abnormalities, hypoxia and concomitant medications for drugs with the potential to prolong the QTc interval) should be performed. In addition, repeat ECGs should be immediately performed hourly for at least 3 hours until the QTc interval falls below 500 msec. If QTc interval reverts to less than 500 msec, and in the judgment of the investigator(s) and Sponsor is determined to be due to cause(s) other than investigational product, treatment may be continued with regular ECG monitoring. If in that timeframe the QTc intervals rise above 500 msec the investigational product will be held until the QTc interval decreases to 500 msec. If the QTc interval has still not decreased to 500 msec after 2 weeks, or if at any time a patient has a QTc interval >515 msec or becomes symptomatic, the patient will be removed from the study.
An electronic reading of prolonged QTc must be confirmed by manual reading. Prior to concluding that an episode of prolongation of the QTc interval is due to investigational product, thorough consideration should be given to potential precipitating factors (eg, change in patient clinical condition, effect of concurrent medication, electrolyte disturbance) and possible evaluation by specialist.

7.3.4 Physical examination/clinical disease assessment

Patients will receive a physical exam, including vital signs (blood pressure, pulse, oxygen saturation, weight and height (baseline only)), and assessment of ECOG performance status on day 1 of each cycle and at the End of Treatment visit. The physical exam should also include investigation of skin lymphoma deposits and rashes, liver and spleen assessment and assessment of lymph node measurements.

7.3.5 Radiological Assessment – CT scans

A contrast enhanced CT scan of the neck, chest, abdomen and pelvis will be performed at cycles 3, 6 and 8 of treatment to assess response during treatment. If the patient discontinues treatment early an End of treatment scan should be performed, if a scan has not been conducted with the last 28 days. Scans should be reported with two dimensional measurements of each lesion in millimetres (mm) if measureable.

Immunotherapeutic agents such as avelumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase (pseudo-progression) in disease burden. The Investigator's judgment of radiological response on early CT scans should be based on the overall benefit-risk assessment and the patient's clinical condition, including performance status, clinical symptoms, adverse events and laboratory data.

If the patient has not progressed after 8 cycles they will continue to be followed up with CT scans at 12, 16 and 20 months from treatment start or sooner if the investigator is concerned there may be disease progression. After 20 months from treatment start radiological follow-up will be as per local standard with data collected every 6 months.

Response will be assessed according to the Revised Response Criteria for malignant lymphoma[27] (appendix 1).

7.3.6 Bone Marrow Trephine

A bone marrow trephine biopsy will be performed at screening (within 3 months of registration). If this shows involvement, the patient should undergo a further bone marrow trephine biopsy at radiological CR if this is achieved to confirm CR. Further bone marrow biopsy should also be performed if progression within the marrow is suspected and the CT does not show progression.

7.4 Research Sample Collection

7.4.1 Tumour paraffin blocks

Samples of the patient's tumour will be collected in the form of formalin-fixed paraffin embedded blocks of their initial, and relapsed or refractory diagnostic material. These samples must have been collected within 3 months of the patient registering for the trial.

In order to assay PD-L1 we will employ the VENTANA PD-L1 (SP263) kit (Roche). Results of this assay will be reviewed during the course of the trial.

Blocks will be requested immediately following registration and will be sent to the University of Leicester.

Three slides will be cut from the tissue blocks to test for PD-L1 levels.

A tissue microarray (TMA) will also be produced from diagnostic tissue block material from all patients. We will employ immunohistochemistry supported by gene expression analysis to establish a molecular classification of PTCL (see Iqbal et al. [31]) to correlate with response to treatment or predictors of relapse.

Upon relapse or progression during the study a further formalin-fixed paraffin embedded tissue block will be requested for research purposes. The collection of this tissue block is optional.

Further details will be provided in the AVAIL-T Sample collection manual.

Translational Research

Plasma and peripheral blood mononuclear cells (PBMNCs) will be collected at intervals during the study. Cell free DNA will be extracted from plasma and DNA from PBMNCs and used for analysis of the known mutations[32-33] in PTCL by targeted sequencing using an IonTorrent platform. Importantly results will be correlated with PD-L1 expression levels assayed by the VENTANA PD-L1 (SP263) kit (Roche).

7.4.2 Blood samples

Blood samples will be collected at baseline, day 15 cycle 2, day 15 cycle 4, day 15 cycle 6, day 15 cycle 8, at 12 months, 16 months and 20 months post treatment start (or equivalent time point if patient is off treatment). Plasma for cell free DNA studies will be collected and peripheral blood mononuclear cells will be isolated for a CyTOF immunophenotyping sub-study.
Samples will be processed as per the AVAIL-T laboratory manual and shipped to the University of Leicester in the shipment containers supplied by the trial.

We have established droplet digital (dd) PCR assays for some of the common mutations in PTCL - RHOAG17V, IDH2 and PLCG1. We plan to employ these assays on cell free DNA from patient plasma in order to explore their utility for diagnosis and as markers for response to treatment or predictors of relapse. We estimate that one or more of these genetic markers will be detectable in 25 to 40% of our patient population [31,34-36].

CyTOF is a cutting-edge technology that allows the measurement of an unprecedented number of T-cell markers on circulating T-cells. We plan to perform CyTOF analysis pre-treatment and after cycles 2, 4, and 6. These data will allow the characterisation of a relapsed/refractory PTCL signature, identify putative biomarkers of response, and correlate immune cell changes with any toxicity.

For further information please see the AVAIL-T sample collection manual.

7.5 Dose Modifications

7.5.1 Infusion-Related Reactions

IRRs have been observed in patients receiving therapy with avelumab. Monitor patients for signs and symptoms of infusion-related reactions including pyrexia, chills, flushing, hypotension, dyspnoea, wheezing, back pain, abdominal pain, urticaria, rigors, diaphoresis and headache.

Table 3 outlines management guidance in the event of an IRR.

7.5.2 Severe Hypersensitivity Reactions and Flu-Like Symptoms

If hypersensitivity reaction occurs, the patient must be treated according to the best available medical practice. Patients should be instructed to report any delayed reactions to the Investigator immediately.

For prophylaxis of flu-like symptoms, 25 mg of indomethacin or comparable nonsteroidal anti-inflammatory drug (NSAID) dose (for example, ibuprofen 600 mg, naproxen sodium 500 mg) may be administered 2 hours before and 8 hours after the start of each dose of avelumab IV infusion. Alternative treatments for fever (for example, paracetamol) may be given to patients at the discretion of the Investigator.

Table 3. Treatment Modification for Symptoms of Infusion-Related Reactions

NCI-CTCAE Grade	Examples of Qualifying events (NCI CTCAE)	Treatment Modification for Study Drug
Grade 1 – mild Mild transient reaction; infusion interruption not indicated; intervention not indicated.	Transient hypotension; palpitations; mild hypertension; mild allergic reaction (transient rash, drug fever <38°C), other mild reactions: flushing, rigor, chills, pruritus, cough, pain, nausea, vomiting.	Decrease the study drug infusion rate by 50% and monitor closely for any worsening.
Grade 2 – moderate Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (for example, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 h. **Recurrent Grade 2 – moderate**	Hypotension requiring fluid replacement; advanced hypertension or symptomatic arrhythmias not requiring treatment; moderate allergic reaction (urticaria, drug fever >38°C) or isolated fever 39.1 to 40°C; severe &/or prolonged rigors/chills; frequent or drenching diaphoresis; controlled or intense or widespread pruritis; cough requiring narcotic antitussive; other moderate reactions: pain, GI, skin, etc	Temporarily discontinue study drug infusion. Resume infusion at 50% of previous rate once infusion-related reaction has resolved or decreased to at least Grade 1 in severity, and monitor closely for any worsening. If a Grade 2 infusion-related reaction does not improve or worsens following implementation of the modifications indicated above (including reducing the infusion rate by 50%), treatment should be commenced based on the specific symptoms and the infusion should not be resumed for that cycle. At the next cycle, consider the addition of an H2-blocker, meperidine, or ibuprofen to the mandatory premedication. In the event of further recurrence, in spite of implementation of all measures indicated above, (including reducing the infusion rate by 50%), hydrocortisone 100 mg IV may be added to the premedication schema outlined above following discussion with the trials office.
Grade 3 – severe Grade 3: Prolonged (for example, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae.	Angina, congestive heart failure, hypotension, hypertension or arrhythmias requiring medication, moderate allergic reaction) severe allergic reaction (symptomatic bronchospasm requiring parenteral medications, with or without urticaria, allergy-related edema/angioedema), fever >40°C for <24 hrs, rigors/chills unresponsive to	Stop the study drug infusion immediately and disconnect infusion tubing from the subject. If IV fluids to maintain blood pressure, or prolonged administration of steroids, or inotropic agents, or administration of oxygen to maintain peripheral saturations are required, or the symptoms persist for more than 48 hours: • Permanently discontinue avelumab treatment If none of the conditions listed above applies,

Recurrent Grade 3 – severe	narcotics; uncontrolled intense or widespread pruritus, uncontrolled severe cough; dyspnoea at normal activity; other severe pain, GI or skin symptoms, etc. Or Acute myocardial infarction, tamponade, hypertensive crisis, life-threatening arrhythmia, shock, anaphylaxis, renal failure, fever >40°C for >24 hrs, other life-threatening or disabling reactions.	• consider resuming avelumab treatment if the risk/benefit assessment for the individual patient is positive and agreed with the trials office/CI • if the decision is made to resume treatment, the infusion rate must be reduced by 50% AND hydrocortisone 200 mg IV must be added to the standard premedication. Stop the study drug infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study drug treatment and must not receive any further study drug treatment.
Grade 4 – life-threatening Grade 4: Life-threatening consequences; urgent intervention indicated.		Stop the study drug infusion immediately and disconnect infusion tubing from the subject. Subjects have to be withdrawn immediately from study drug treatment and must not receive any further study drug treatment.
In addition, if premedication with hydrocortisone is necessary it should be added for at least the subsequent 2 cycles of avelumab treatment.		

IV = intravenous; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; NSAIDs = nonsteroidal anti-inflammatory drugs.

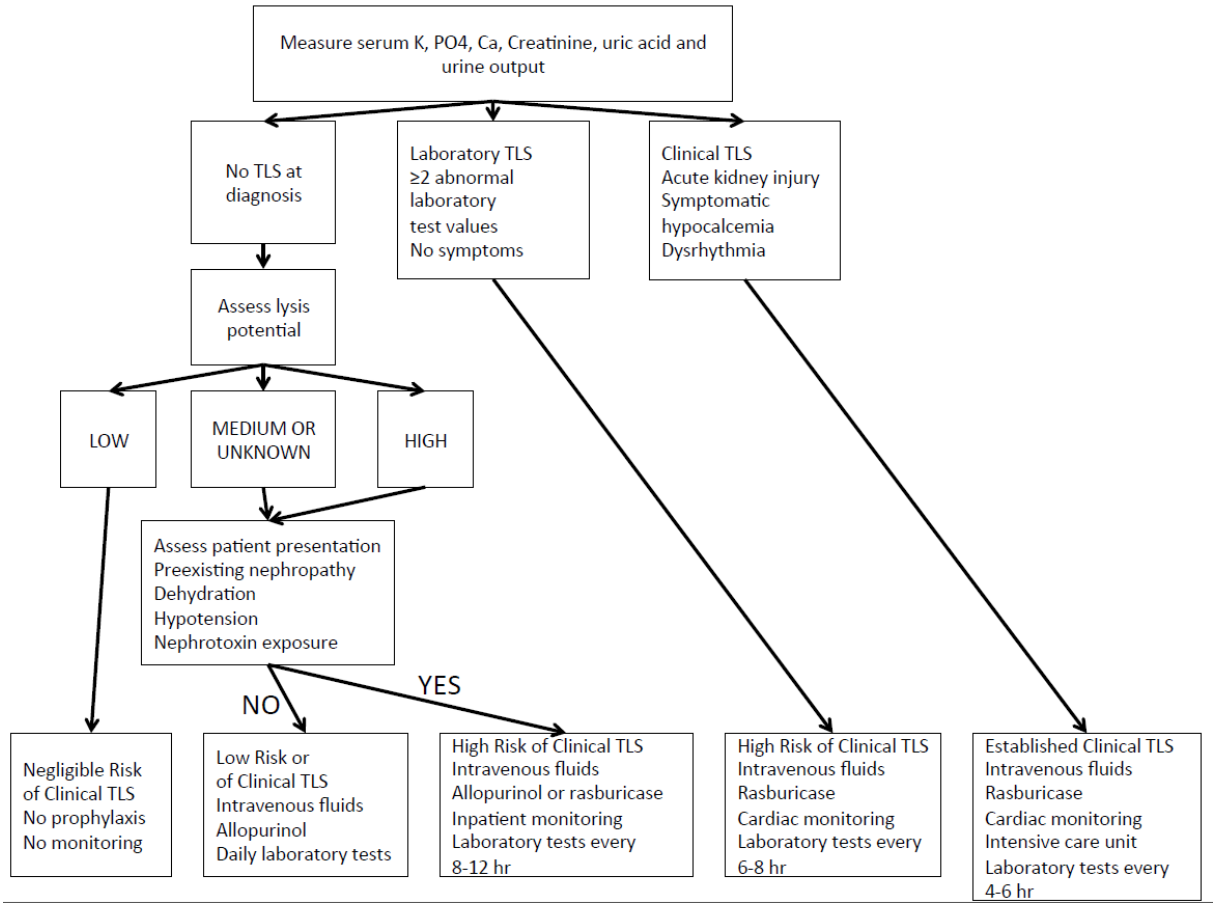
7.5.3 Tumour Lysis Syndrome

There is a potential risk of tumor lysis syndrome (TLS) because avelumab can induce antibody-dependent cell-mediated cytotoxicity. Patients should be monitored closely via standard blood tests and if there is a clinical suspicion of TLS it should be managed according to best medical practice. Management of TLS may include aggressive hydration, monitoring of renal function, correction of electrolyte abnormalities, anti-hyperuricaemic therapy, and supportive care.

Should this occur, patients should be treated per the local guidelines or the management algorithm below (Figure 1)

Figure 1

Assessment and initial management of tumour lysis syndrome.



7.5.4 Management of Immune-Related Adverse Events

Since inhibition of PD-L1 stimulates the immune system, immune-related Adverse Events (AEs) may occur. Avelumab can result in severe and fatal immune-related adverse reactions. These immune-related reactions may involve any organ system. Most immune-related reactions initially manifest during avelumab treatment; however, immune-related adverse reactions can occur after discontinuation of avelumab.

Monitor patients for signs and symptoms of pneumonitis, colitis, changes in thyroid function, adrenal insufficiency, hyperglycaemia (or other signs and symptoms of diabetes), abnormal liver tests and elevated serum creatinine at the start of treatment and periodically during treatment.

Treatment of AEs is mainly dependent upon severity (NCI-CTCAE grade):

Grade 1 to 2: treat symptomatically or with moderate dose steroids, more frequent monitoring

Grade 1 to 2 (persistent): manage similar to high grade AE (Grade 3 to 4)

Grade 3 to 4: treat with high dose corticosteroids

Treatment of gastrointestinal, dermatological, pulmonary, hepatic, renal, endocrine and Cardiac AEs should follow guidelines set forth in the table below Table 4.

Table 4. Management of Immune-Related Adverse Events

Gastrointestinal AEs		
Severity of Diarrhea / Colitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Diarrhea: < 4 stools/day over Baseline Colitis: asymptomatic	Continue avelumab therapy Symptomatic treatment (for example, loperamide)	Close monitoring for worsening symptoms Educate subject to report worsening immediately If worsens: Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4 to 6 stools per day over Baseline; IV fluids indicated < 24 hours; not interfering with ADL Colitis: abdominal pain; blood in stool	Withhold avelumab therapy Symptomatic treatment Treat Grade 2 colitis with 1.0 to 2.0 mg/kg/day prednisolone IV or equivalent	If improves to Grade 1: Resume avelumab therapy For Grade 2 colitis continue steroids until Grade 1, then taper over at least 1 month; resume Avelumab therapy following steroids taper. If persists > 5 to 7 days or recur: Treat as Grade 3 to 4
Grade 3 to 4 Diarrhea (Grade 3): ≥ 7 stools per day over Baseline; incontinence; IV fluids ≥ 24 hrs.; interfering with ADL Colitis (Grade 3): severe abdominal pain, medical intervention indicated, peritoneal signs Grade 4: life-threatening, perforation	Withhold avelumab for Grade 3. 1.0 to 2.0 mg/kg/day prednisolone IV or equivalent Add prophylactic antibiotics for opportunistic infections Consider lower GI endoscopy. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3.	If improves: Continue steroids until Grade 1, then taper over at least 1 month; resume Avelumab therapy following steroids taper (for initial Grade 3). If worsens, persists > 3 to 5 days, or recurs after improvement: Add infliximab 5 mg/kg (if no contraindication), Note: Infliximab should not be used in cases of perforation or sepsis
Dermatological AEs		
Grade of Rash (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 to 2 Covering ≤ 30% body surface area	Symptomatic therapy (for example, antihistamines, topical steroids) Continue avelumab therapy	If persists > 1 to 2 weeks or recurs: Withold Avelumab therapy Consider skin biopsy Consider 0.5 to 1.0 mg/kg/day prednisolone or equivalent. Once improving, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 3 to 4

Grade 3 to 4 Grade 3: Covering > 30% body surface area; Grade 4: life threatening consequences	Withhold avelumab for Grade 3. Permanently discontinue avelumab for Grade 4 or recurrent Grade 3. Consider skin biopsy Dermatology consult 1.0 to 2.0 mg/kg/day prednisolone or equivalent Add prophylactic antibiotics for opportunistic infections	If improves to Grade ≤1: Taper steroids over at least 1 month; resume Avelumab therapy following steroids taper (for initial Grade 3).
Pulmonary AEs		
Grade of Pneumonitis (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Radiographic changes only	Consider withholding avelumab therapy Monitor for symptoms every 2 to 3 days Consider Pulmonary and Infectious Disease consults	Re-assess at least every 3 weeks If worsens: Treat as Grade 2 or Grade 3 to 4
Grade 2 Mild to moderate new symptoms	Withhold avelumab therapy Pulmonary and Infectious Disease consults Monitor symptoms daily, consider hospitalisation 1.0 to 2.0 mg/kg/day prednisolone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	Re-assess every 1 to 3 days If improves: When symptoms return to Grade ≤1, taper steroids over at least 1 month and then resume avelumab therapy following steroids taper If not improving after 2 weeks or worsening: Treat as Grade 3 to 4
Grade 3 to 4 Grade 3: Severe new symptoms; New / worsening hypoxia; Grade 4: life-threatening	Permanently discontinue avelumab therapy Hospitalize Pulmonary and Infectious Disease consults 1.0 to 2.0 mg/kg/day prednisolone or equivalent Add prophylactic antibiotics for opportunistic infections Consider bronchoscopy, lung biopsy	If improves to Grade ≤1: Taper steroids over at least 1 month If not improving after 48 hours or worsening: Add additional immunosuppression (for example, infliximab, cyclophosphamide, IV immunoglobulin, or mycophenolate mofetil)
Hepatic AEs Inform the CI and trials office immediately if the treating investigator has concerns over liver function or liver involvement by lymphoma		
Grade of Liver Test Elevation (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1	Continue avelumab therapy	Continue liver function

Grade 1 AST or ALT > ULN to 3.0 x ULN and / or total bilirubin > ULN to 1.5 x ULN		monitoring If worsens: Treat as Grade 2 or 3 to 4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and / or total bilirubin > 1.5 to ≤ 3 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisolone or equivalent	If returns to Grade ≤1: Taper steroids over at least 1 month, : resume routine monitoring, resume avelumab therapy following steroids taper If elevations persist > 5 to 7 days or worsens: Treat as Grade 3 to 4.
Grade 3 to 4 AST or ALT > 5 x ULN and / or total bilirubin > 3 x ULN	Permanently discontinue avelumab therapy Increase frequency of monitoring to every 1 to 2 days 1.0 to 2.0 mg/kg/day prednisolone or equivalent Add prophylactic antibiotics for opportunistic infections Consult gastroenterologist / hepatologist Consider obtaining MRI/CT scan of liver and liver biopsy if clinically warranted	If returns to Grade ≤1: Taper steroids over at least 1 month If does not improve in > 3 to 5 days, worsens or rebounds: Add mycophenolate mofetil 1 gram (g) twice daily If no response within an additional 3 to 5 days, consider other immunosuppressants per local guidelines
Renal AEs		
Grade of Creatinine Increased (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 1 Creatinine increased > ULN to 1.5 x ULN	Continue avelumab therapy	Continue renal function monitoring If worsens: Treat as Grade 2 to 3 or 4.
Grade 2 to 3 Creatinine increased > 1.5 and ≤ 6 x ULN	Withhold avelumab therapy Increase frequency of monitoring to every 3 days 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections Consider renal biopsy	If returns to Grade ≤1: Taper steroids over at least 1 month, and resume avelumab therapy following steroids taper. If worsens: Treat as Grade 4.
Grade 4 Creatinine increased > 6 x ULN	Permanently discontinue avelumab therapy Monitor creatinine daily 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections	If returns to Grade ≤1: Taper steroids over at least 1 month.

	Consider renal biopsy Nephrology consult	
Cardiac AEs		
Myocarditis	**Management**	**Follow-up**
New onset of cardiac signs or symptoms and / or new laboratory cardiac biomarker elevations (e.g. troponin, CK-MB, BNP) or cardiac imaging abnormalities suggestive of myocarditis.	Withhold avelumab therapy Hospitalize. In the presence of life threatening cardiac decompensation, consider transfer to a facility experienced in advanced heart failure and arrhythmia management. Cardiology consult to establish etiology and rule-out immune-mediated myocarditis. Guideline based supportive treatment as appropriate per cardiology consult.* Consider myocardial biopsy if recommended per cardiology consult.	If symptoms improve and immune-mediated etiology is ruled out, re-start avelumab therapy. If symptoms do not improve/worsen, viral myocarditis is excluded, and immune-mediated etiology is suspected or confirmed following cardiology consult, manage as immune-mediated myocarditis.
Immune-mediated myocarditis	Permanently discontinue avelumab. Guideline based supportive treatment as appropriate per cardiology consult.* 1.0 to 2.0 mg/kg/day prednisone or equivalent. Add prophylactic antibiotics for opportunistic infections.	Once improving, taper steroids over at least 1 month If no improvement or worsening, consider additional immunosuppressants (e.g. azathioprine, cyclosporine A)
*Local guidelines, or eg. ESC or AHA guidelines ESC guidelines website: https://www.escardio.org/Guidelines/Clinical-Practice-Guidelines AHA guidelines website: http://professional.heart.org/professional/GuidelinesStatements/searchresults.jsp?q=&y=&t=1001		

Endocrine AEs		
Endocrine Disorder	**Management**	**Follow-up**
Grade 1 or Grade 2 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Continue avelumab therapy Endocrinology consult if needed Start thyroid hormone replacement therapy (for hypothyroidism), anti-thyroid treatment (for hyperthyroidism), corticosteroids (for adrenal insufficiency) or insulin (for Type I diabetes mellitus) as appropriate. Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Continue hormone replacement / suppression and monitoring of endocrine function as appropriate.

Grade 3 or Grade 4 endocrinopathies (hypothyroidism, hyperthyroidism, adrenal insufficiency, type I diabetes mellitus)	Withhold avelumab therapy Consider hospitalisation Endocrinology consult Start (as appropriate): • thyroid hormone replacement therapy for hypothyroidism • anti-thyroid treatment for hyperthyroidism, • corticosteroids for adrenal insufficiency • anti-hyperglycemics or insulin for type I diabetes mellitus Rule-out secondary endocrinopathies (i.e. hypopituitarism / hypophysitis)	Resume avelumab once symptoms and / or laboratory tests improve to Grade ≤ 1 (with or without hormone replacement / suppression). Continue hormone replacement / suppression and monitoring of endocrine function as appropriate.
Hypopituitarism/Hypophysitis (secondary endocrinopathies)	If secondary thyroid and / or adrenal insufficiency is confirmed (i.e. subnormal serum FT4 with inappropriately low TSH and/or low serum cortisol with inappropriately low ACTH) : • Refer to endocrinologist for dynamic testing as indicated and measurement of other hormones (FSH, LH, GH/IGF-1, PRL, testosterone in men, estrogens in women) • Hormone replacement/suppressive therapy as appropriate • Perform pituitary MRI and visual field examination as indicated If hypophysitis confirmed: • Continue avelumab if mild symptoms with normal MRI. Repeat the MRI in 1 month • Withhold avelumab if moderate, severe or life-threatening symptoms of hypophysitis and / or abnormal MRI. Consider hospitalisation. Initiate corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) followed by corticosteroids taper during at least 1 month. • Add prophylactic antibiotics for opportunistic infections.	Resume avelumab once symptoms and hormone tests improve to Grade ≤ 1 (with or without hormone replacement). In addition, for hypophysitis with abnormal MRI, resume Avelumab only once shrinkage of the pituitary gland on MRI/CT scan is documented. Continue hormone replacement / suppression therapy as appropriate.

Other AEs (not described above)		
Grade of other AEs (NCI-CTCAE v4.03)	**Management**	**Follow-up**
Grade 2 or Grade 3 clinical signs or symptoms suggestive of a potential immune-related	Withhold avelumab therapy pending clinical investigation	If irAE is ruled out, manage as appropriate according to the diagnosis and consider re-

AE (irAE)		starting avelumab therapy If irAE is confirmed, treat as Grade 2 or 3 irAE.
Grade 2 irAE or first occurrence of Grade 3 irAE	Withhold avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month and resume avelumab therapy following steroids taper.
Recurrence of same Grade 3 irAEs	Permanently discontinue Avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Grade 4	Permanently discontinue Avelumab therapy 1.0 to 2.0 mg/kg/day prednisone or equivalent Add prophylactic antibiotics for opportunistic infections Specialty consult as appropriate	If improves to Grade ≤ 1: Taper steroids over at least 1 month
Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks for reasons other than hormonal replacement for adrenal insufficiency Persistent Grade 2 or 3 irAE lasting 12 weeks or longer	Permanently discontinue Avelumab therapy Specialty consult	

Abbreviations: ACTH=adrenocorticotropic hormone; ADL = activities of daily living; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BNP=B-type natriuretic peptide; CK-MB=creatine kinase MB; CT = computed tomography; FSH=follicle-stimulating hormone; GH=growth hormone; IGF-1=insulin-like growth factor 1; irAE = immune-related adverse event; IV=intravenous; LH=luteinizing hormone; MRI = magnetic resonance imaging; NCI-CTCAE = National Cancer Institute-Common Terminology Criteria for Adverse Event; PRL=prolactin; T4 = thyroxine; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

7.5.5 Treatment related haematological Adverse Events

For any treatment related haematological toxicities (e.g. Neutrophil or platelet count decreases) delay avelumab treatment for a week until the event resolves to baseline. If the toxicity has not resolved with 1 week delay please check with trials office if continued treatment is recommended.

7.5.6 Drug Induced Liver Injury (Hy's law cases)

The threshold of laboratory abnormalities for a potential Drug Induced Liver Injury case depends on the patient's individual baseline values and underlying conditions. Patients who present with the following laboratory abnormalities should be evaluated further as potential Hy's law cases to definitively determine the etiology of the abnormal laboratory values:

-Subjects with AST/ALT and Bilirubin baseline values within the normal range who subsequently present with AST OR ALT values >3 × ULN AND a Bilirubin value >2 × ULN with no evidence of hemolysis and an alkaline phosphatase value <2 × ULN or not available;

-For subjects with baseline AST OR ALT OR Bilirubin values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:

- Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND >3 × ULN; or >8 × ULN (whichever is smaller).

- Preexisting values of Bilirubin above the normal range: Bilirubin level increased from baseline value by an amount of at least 1 × ULN or if the value reaches >3 × ULN (whichever is smaller).

If a Hy's law case is confirmed this must be reported to the trials office as an SAE. Patients should be treated as in Table 4 above.

7.6 Treatment Compliance

Non-compliance is not likely to be an issue as patients must attend hospital to receive infusions of avelumab. Pharmacy departments will be required to maintain accurate records of drug accountability. For further information please see the pharmacy manual.

7.7 Concomitant Medication

Primary prophylactic use of granulocyte-colony stimulating factors is permitted during the study. They may also be used to treat treatment emergent neutropenia as indicated by local guidelines.

Use of erythropoietic growth factors is allowed during the study.

Patients are prohibited from receiving the following therapies during the treatment phase of this trial:

- Anti-cancer systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Investigational or experimental agents other than avelumab
- Radiation therapy (with the exception of Palliative radiotherapy to specific sites of disease considered medically necessary by the treating physician. All attempts should be made to rule out disease progression in the event of increased localized pain. If palliative radiotherapy is needed to control bone pain, the sites of bone disease should be present at baseline, otherwise, bone pain requiring radiotherapy will be considered as a sign of disease progression.).
- Immunosuppressive drugs, unless otherwise indicated for the treatment of AEs (see Tables 3 and 4). See below Clarification about Steroid Use.
- Any vaccine therapies for the prevention of infectious disease (eg, human papilloma virus vaccine) except for inactive vaccines (e.g. the flu vaccine).
- Herbal remedies with immune-stimulating properties (eg, mistletoe extract) or known to potentially interfere with major organ function (eg, hypericin).

Clarifications about Steroid Use: Data indicate that corticosteroids have an adverse effect on T cell function and that they inhibit and damage lymphocytes.
Therefore, the use of steroids during this trial is restricted as follows:

- Therapeutic use: for the treatment of infusion-related reactions and short-term treatment of AEs, steroids are permitted according to the modalities indicated in table 3 and 4
- Physiologic use: steroid replacement for adrenal insufficiency at doses equivalent to ≤10 mg prednisone daily is acceptable.
- Prophylactic use (eg, for the prevention of acute infusion-related reactions): is prohibited – unless otherwise indicated in Table 3

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

7.8 Patient Treatment Discontinuation

In the event of discontinuation of study treatment, e.g. completing treatment, unacceptable toxicity or patient choice, full details of the reason/s for discontinuation should be recorded on the appropriate pages on the CRF. All patients, including non-compliant patients, should be followed up according to the protocol unless they withdraw specific consent. Patients who stop treatment due to adverse experiences (clinical or laboratory) will be treated and followed according to accepted medical practice. All pertinent information concerning the outcome of such treatment must be recorded in the CRF.

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

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

Patients must stop study treatment in the event of:

- unacceptable toxicity (detailed below)
- SAE requiring permanent discontinuation of treatment
- the patient becoming pregnant
- Disease Progression

Table 5. Adverse Events requiring avelumab discontinuation or modification

Any Grade 4 AEs • except for single laboratory values out of normal range that are unlikely related to study treatment as assessed by the Investigator, do not have any clinical correlate, and resolve within 7 days with adequate medical management
Any Grade 3 AEs except for any of the following: • Transient (≤ 6 hours) Grade 3 flu-like symptoms or fever, which is controlled with medical management • Transient (≤ 24 hours) Grade 3 fatigue, local reactions, headache, nausea, emesis that resolves to Grade ≤ 1 • Single laboratory values out of normal range that are unlikely related to study treatment according to the Investigator, do not have any clinical correlate, and resolve to Grade ≤ 1 within 7 days with adequate medical management • Tumor flare phenomenon defined as local pain, irritation, or rash localized at sites of known or suspected tumor • Change in ECOG PS to ≥ 3 that does not resolve to ≤ 2 within 14 days (infusions should not be given on the following cycle, if the ECOG PS is ≥ 3 on the day of study drug administration) • First occurrence of a Grade 3 IRR that meets conditions for continued therapy as outlined in Table 3.
Any Grade 2 AE should be managed as follows: • If a Grade 2 AE resolves to Grade ≤ 1 by the last day of the current cycle, treatment may continue. • If a Grade 2 AE does not resolve to Grade ≤ 1 by the last day of the current cycle, infusions should not be given on the following cycle. If at the end of the following cycle the event has not resolved to Grade 1, the patient should permanently discontinue treatment with a avelumab AE (except for hormone insufficiencies, that can be managed by replacement therapy; for these hormone insufficiencies, up to 2 subsequent doses may be omitted). • Upon the second occurrence of the same Grade 2 AE (except for IRR or hormone

insufficiencies that can be managed by replacement therapy) in the same patient, treatment with avelumab has to be permanently discontinued.
- Recurrent Grade 2 IRRs may not require treatment discontinuation and should be managed as outlined in Table 3

When a patient stops trial treatment an End of Treatment visit should be performed 28 days (+/- 5 days) after their last dose of avelumab. Assessments are to be performed as per section 7.3 and include:

- Physical Exam
- ECOG
- Vital signs
- Full blood count
- Biochemistry
- Hormone function
- Pregnancy test
- Urinalysis
- 12- lead ECG
- Disease assessment
- Adverse events

7.9 Patient Follow Up

All patients will need to be followed up for safety (AEs) up to 30 days (+/- 5 days) after the last dose of avelumab and for disease progression / survival until the end of the trial (minimum of 12 months follow-up from the date of commencing treatment for the last patient).
If the patient stops trial treatment but has not progressed, they will be reviewed with a CT scan of neck, chest, abdomen and pelvis at 8, 12, 16 and 20 months or on clinical suspicion of progression (whichever is sooner).

If there is no evidence of progression after 20 months, patients will have no specific trial follow up, but their referring physician may be contacted every 6 months to determine progression and survival data.

7.10 Patient Withdrawal of Consent

In the event of a patient's decision to withdraw from the trial, the Investigator should ascertain from which aspects of the trial the patient wishes to withdraw and record the details on the appropriate CRF. All information and blood/tissue samples collected up until point of retraction will be retained and analysed. If a patient chooses to withdraw from treatment only, the patient should discontinue treatment and continue to be assessed in accordance with the protocol. If a patient wishes to withdraw from the trial (i.e. including trial specific assessments), but is willing for further data to be supplied to the Trials Office, then further routine "follow-up" data (e.g. disease status and survival) will continue to be supplied by the Investigator to the Trials Office.

8. ADVERSE EVENT REPORTING

The collection and reporting of Adverse Events (AEs) will be in accordance with the Medicines for Human Use Clinical Trials Regulations 2004 and its subsequent amendments. Definitions of different types of AE are listed in Appendix 3. The Investigator should assess the seriousness and causality (relatedness) of all AEs experienced by the patient (this should be documented in the source data) with reference to the Investigator Brochure.

8.1 Reporting Requirements

8.1.1 Adverse Events

All medical occurrences which meet the definition of an AE (see Appendix 3 for definition) should be reported. Please note this does not include abnormal laboratory findings. An abnormal laboratory value is only considered to be an AE if the abnormality:

- Results in early discontinuation from the study treatment and/or
- Requires study drug dose modification or interruption, any other therapeutic intervention or is judged to be of significant clinical importance

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

Pre-existing conditions should only be reported if the condition worsens by at least 1 CTCAE grade. Details of all AEs experienced by the patient should be recorded in the hospital notes.

8.1.2 Serious Adverse Advents

Investigators should report AEs that meet the definition of an SAE (see Appendix 3 for definition) and are not excluded from the reporting process as described below.

Potential drug-induced liver injury (Hy's Law cases) are considered important medical events and should be reported as SAEs. Please see section 7 for more information.

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

The following events should not be reported on an SAE Form and are not classed as SAEs for this trial:

- Hospitalisations for:
  - Pre-planned elective procedures unless the condition worsens
  - Treatment for progression of the patient's cancer
- Progression or death as a result of the patient's cancer, as this information is captured elsewhere on the Case Report Form

The below events may not be SAEs but should still be reported by email to the trials office within 24h of becoming aware of the event:

- Exposure during Pregnancy or Breastfeeding (even if not associated with an adverse event)
- Occupational exposure during the performance of job duties, a person (whether a healthcare professional or otherwise) gets in unplanned direct contact with the product (even if not associated with an adverse event)

Details of these will be forwarded to Pfizer for review.

8.1.2.2 Monitoring pregnancies for potential Serious Adverse Events

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

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

8.1.3 Reporting period

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

8.1.4 Post study SUSARs

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

8.2 Reporting Procedure

8.2.1 Site

8.2.1.1 Adverse Events

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

AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see Appendix 4). Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using a scale of (1) mild, (2) moderate or (3) severe. For each sign/symptom, the highest grade observed since the last visit should be recorded.

8.2.1.2 Serious Adverse Events

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

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

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

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

0121 371 7874 or 0121 371 4398

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

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

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

8.2.1.3 Provision of follow-up information

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

8.2.2 Trials Office

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

8.2.3 Reporting to the Competent Authority and main Research Ethics Committee

8.2.3.1 Suspected Unexpected Serious Adverse Reactions

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

All other events categorised as SUSARs will be reported within 15 days.

8.2.3.2 Serious Adverse Reactions

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

8.2.3.3 Adverse Events

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

8.2.3.4 Other safety issues identified during the course of the trial

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

8.2.4 Investigators

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

8.2.5 Data/Safety Committee

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

8.2.6 Manufacturer of Investigational Medicinal Product

All SAEs and other reportable events will be reported by the trials office to the manufacturer of the Investigational Medicinal Product (Pfizer) within 24 hours by fax and or email as per the Pfizer Safety Reporting Reference Manual.

9. DATA HANDLING AND RECORD KEEPING

9.1 Data Collection

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

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

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

Data reported on each form should be consistent with the source data or the discrepancies should be explained. If information is not known, this must be clearly indicated on the form. Missing and ambiguous data will be queried in line with the data validation plan and data management guidelines for the trial. All sections are to be completed before submitting.

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

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

9.2 Archiving

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

10. QUALITY MANAGEMENT

10.1 Site Set-up and Initiation

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

10.2 On-site Monitoring

Monitoring will be carried out as required following a risk assessment and as documented in the AVAIL-T Quality Management Plan. Additional on-site monitoring visits may be triggered for example by poor CRF return, poor data quality, low SAE reporting rates, excessive number of patient withdrawals or deviations. If a monitoring visit is required the Trials Office will contact the site to

arrange a date for the proposed visit and will provide the site with written confirmation. Investigators will allow the AVAIL-T trial staff access to source documents as requested.

10.3 Central Monitoring

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

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

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

10.4 Audit and Inspection

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

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

10.5 Notification of Serious Breaches

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

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

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

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

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

11. END OF TRIAL DEFINITION

The end of trial will be last patient last visit. The Trials Office will notify the MHRA and main REC that the trial has ended and will provide them with a summary of the clinical trial report within 12 months of the end of trial.

12. STATISTICAL CONSIDERATIONS

12.1 Definition of Outcome Measures

12.1.1 Primary outcome measures

- Best overall response (CR + PR) during the first 8 cycles of treatment will be assessed using contrast-enhanced CT scans of the neck, chest, abdomen and pelvis, using the Revised Response Criteria for Malignant Lymphoma ([27])

12.1.2 Secondary outcome measures

- Toxicity assessed using CTCAE v4.0 will be defined as the number and proportion of patients who experience one or more grade 3 or 4 adverse event or serious adverse event of any grade
- Best overall response (Partial Remission (PR) + Complete Response (CR)) at any time of treatment will be assessed using contrast-enhanced CT scans of the neck, chest, abdomen and pelvis, using the Revised Response Criteria for Malignant Lymphoma ([27])
- Maximum percentage change in the sum of the product of diameters (SPD) of target tumour masses assessed by contrast-enhanced CT scans of the neck, chest, abdomen and pelvis, using the Revised Response Criteria for Malignant Lymphoma[27]
- Duration of response is defined as the time from first documented response until relapse/progression, as determined by the Revised Response Criteria[27], or death. Patients who are relapse/progression free and alive will be censored at date last seen.
- Progression free survival is defined as the time from date of registration to the date of disease progression or date of death from any cause. Patients not reaching progression or death at the time of analysis will be censored at the last date they were known to be alive and progression free. Patients will be followed up for a minimum of 12 months.
- Overall survival time is defined as the time from date of registration to the date of death from any cause. Patients discontinuing the study, lost to follow-up or still alive at the end of the study will be censored at the date of last follow-up. Patients will be followed up for a minimum of 12 months.

12.1.3 Exploratory outcome measures

- PD-L1 expression will be defined as the percentage of PD-L1 expression in the patients baseline tumour samples
- Cell free lymphoma DNA levels will be measured and correlated to the patients clinical disease status
- CyTOF study; putative biomarkers of response will be identified and immune cell changes will be correlated with any toxicity

12.2 Analysis of Outcome Measures

Primary Outcome Measures

• Best overall response rate (PR + CR) during 8 cycles of treatment will be presented as the number and proportion of patients achieving a response over the total number of patients registered to the trial. Patients who die due to disease or toxicity during the first 8 cycles of treatment and patients who are not assessable will be classed as non-responders.
Posterior probability plots will also be produced together with the probability that the true effect is greater than 35%.

Secondary Outcome Measures

• Toxicity - The number and proportion of patients who experience one or more grade 3 or 4 adverse event or serious adverse event of any grade will be reported over the total number patients in the trial

• Time to event outcomes will be estimated using Kaplan Meier method. Point estimates will be presented at 6 and 12 months with 95% confidence intervals.

• Reduction in tumour size measured as maximum percentage change in the radiological sum of the product of the diameters from baseline will be presented as a mean and standard deviation or medians with an interquartile range depending on the distribution of the data.

Exploratory outcome measures
- Percentage of PD-L1 expression will be analyses at the Leicester Cancer Centre
- Cell free DNA levels and disease status correlation will be performed by the Leicester Cancer Centre
- Multicolour peripheral blood immunophenotyping will be performed by the Leicester Cancer Centre
- CyTOF study: biomarkers of response data will be acquired via mass flow cytometry at the Leicester Cancer Centre

All summaries and statistical analyses will be performed on an intention-to-treat (ITT) population including patients who are ineligible or non-compliant and a per protocol population of only patients who were eligible and received at least 1 dose of treatment.

12.3 Planned Interim Analysis

Accumulating data and analyses will be monitored regularly by the TSC with an independent chair (see section 13.4).

In addition an interim analysis for futility will take place once 15 patients have been recruited and reached the cycle 3 CT scan time point. If the probability of the true response rate being greater than 35% is less than 20% (i.e. observe less than three responses) the TSC would need to make a decision on whether to stop or continue the trial. Both ITT and per protocol analyses will be presented. This stopping rule is provided as guidance only and any decision to stop or continue will be based on a pragmatic assessment of all outcomes.

12.4 Planned Final Analyses

Final analysis will take place 1 year after the last patient entered the study.

Sample size determinationThe trial will recruit 30 patients with the flexibility to recruit more if required. Given the rare nature of the disease bayesian probability plots for a binary outcome with an uninformative beta prior are used. Given these 30 patients, if the trial observed 11 responses there would be a 60% chance that the true response rate is greater than 35%. Given 13 responses are observed there would be an 84% chance that the true response rate is greater than 35%. See appendix 2 for plots for different scenarios.

13. TRIAL ORGANISATIONAL STRUCTURE

13.1 Sponsor

The trial is sponsored by the University of Birmingham.

13.2 Coordinating Centre

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

13.3 Trial Management Group

A TMG will be established and will include the Chief Investigator, co-investigators, the trial statistician and trial coordinators. Key trial personnel will be invited to join the TMG as appropriate to ensure representation from a range of professional groups. Notwithstanding the legal obligations of the Sponsor and Chief Investigator, the TMG will be responsible for the day-to-day running and management of the trial and will meet by teleconference or in-person as required, at least every 6 months during the trial treatment period.

13.4 Trial Safety Committee

A TSC, with an independent chair, will provide overall supervision for the trial and provide advice through its independent chair. The ultimate decision for the continuation of the trial lies with the TSC. The TSC will meet at least 6 months after the first patient has been recruited and every 6 months thereafter during the recruitment and treatment period, to monitor all safety, futility and primary activity data.

13.5 Finance

This is an Investigator-initiated and Investigator -led trial funded by the Bloodwise Trials Acceleration Programme (TAP) and Pfizer.

Payments will be made to NHS Trusts for research costs associated with the trial. No other individual per patient payment will be made to NHS Trusts, Investigators or patients.

This trial is also included in the NIHR CRN portfolio.

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

14. ETHICAL CONSIDERATIONS

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

The trial will be conducted in accordance with the Research Governance Framework for Health and Social Care, the applicable UK Statutory Instruments, (which include the Medicines for Human Use Clinical Trials 2004 and subsequent amendments and the General Data Protection Regulation and the Data Protection Act (2018) and Human Tissue Act 2008) and Good Clinical Practice (GCP). This trial will be carried out under a Clinical Trial Authorisation in accordance with the Medicines for Human Use Clinical Trials regulations. The protocol will be submitted to and approved by the main Research Ethics Committee (REC) prior to circulation.

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

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

15. CONFIDENTIALITY AND DATA PROTECTION

Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the General Data Protection Regulation and the Data Protection Act (2018). With the patient's consent, their initials and date of birth will be collected at trial entry. Patients

will be identified using only their unique trial number, initials and date of birth on the Case Report Form and correspondence between the Trials Office and the participating site. However patients are asked to give permission for the Trials Office to be sent a copy of their signed Informed Consent Form which will not be anonymised. This will be used to perform in-house monitoring of the consent process.

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

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

16. INSURANCE AND INDEMNITY

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

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

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

17. PUBLICATION POLICY

Results of this trial will be submitted for publication in a peer reviewed journal in accordance with the TAP publication policy. The manuscript will be prepared by the Trial Management Group (TMG) and authorship will be determined in line with the TAP publication policy.

Any secondary publications and presentations prepared by Investigators must be reviewed by the TMG. Manuscripts must be submitted to the TMG in a timely fashion and in advance of being submitted for publication, to allow time for review and resolution of any outstanding issues. Authors must acknowledge that the trial was performed with the support of The University of Birmingham and Bloodwise. Intellectual property rights will be addressed in the Clinical Study Site Agreement between Sponsor and site.

18. REFERENCE LIST

1. De Leval L, Rickman DS, Thielen C, et al. The gene expression profile of nodal peripheral T-cell lymphoma demonstrates a molecular link between angioimmunoblastic T-cell lymphoma (AITL) and follicular helper T (TFH) cells. *Blood.* 2007;109(11): 4952–4963.
2. Piccaluga PP, Agostinelli C, Califano A, et al. Gene expression analysis of peripheral T cell lymphoma, unspecified, reveals distinct profiles and new potential therapeutic targets. J *Clin Invest.* 2007;117(3): 823–834.
3. Roncador G, García Verdes-Montenegro J-F, Tedoldi S, et al. Expression of two markers of germinal center T cells (SAP and PD-1) in angioimmunoblastic T-cell lymphoma. *Haematologica.* 2007;92(8): p. 1059–1066.
4. Swerdlow SH, Campo E, Pileri SA, et al. The 2016 revision of the World Health Organization (WHO) classification of lymphoid neoplasms. *Blood*. 2016;127(20): 2375–2390.
5. Wilcox RA, Feldman AL, Wada DA, et al. B7-H1 (PD-L1, CD274) suppresses host immunity in T-cell lymphoproliferative disorders. *Blood*. 2009;114(10):2149-2158. doi:10.1182/blood-2009-04-216671.

6. Vose J, Armitage J, Weisenburger D, International T-Cell Lymphoma Project. International peripheral T-cell and natural killer/T-cell lymphoma study: pathology findings and clinical outcomes. *Journal of Clinical Oncology*. 2008;26(25):4124-4130. doi:10.1200/JCO.2008.16.4558.

7. Pro B, Advani R, Brice P, et al. Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *Journal of Clinical Oncology*. 2012;30(18):2190-2196. doi:10.1200/JCO.2011.38.0402.

8. Coiffier B, Pro B, Prince M. Results From a Pivotal, Open-Label, Phase II Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma After Prior Systemic Therapy. *J Clin Oncol*. 2012;30:631-636. doi:10.1200/JCO.2011.37.4223.

9. O'Connor OA, Pro B, Pinter-Brown L, et al. Pralatrexate in patients with relapsed or refractory peripheral T-cell lymphoma: results from the pivotal PROPEL study. *Journal of Clinical Oncology*. 2011;29(9):1182-1189. doi:10.1200/JCO.2010.29.9024.

10. O'Connor OA, Masszi T, Savage KJ, et al. Belinostat, a novel pan-histone deacetylase inhibitor (HDACi), in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL): Results from the BELIEF trial. *Journal of Clinical Oncology*. 2013;31:S8507.

11. Gambacorti-Passerini C, Farina F, Stasia A, et al. Crizotinib in advanced, chemoresistant anaplastic lymphoma kinase-positive lymphoma patients. *J Natl Cancer Inst*. 2014;106(2):djt378. doi:10.1093/jnci/djt378.

12. Stein E, Tallman M, Pollyea DA. Clinical safety and activity in a phase I trial of AG-221, a first in class, potent inhibitor of the IDH2-mutant protein, in patients with IDH2 mutant positive advanced hematologic malignancies. *Cancer Res*. 2014;74:abstractCT103.

13. Odejide O, Weigert O, Lane AA, et al. A targeted mutational landscape of angioimmunoblastic T-cell lymphoma. *Blood*. 2014;123(9):1293-1296. doi:10.1182/blood-2013-10-531509.

14. Schatz JH, Horwitz SM, Teruya-Feldstein J, et al. Targeted mutational profiling of peripheral T-cell lymphoma not otherwise specified highlights new mechanisms in a heterogeneous pathogenesis. *Leukemia*. 2015;29(1):237-241. doi:10.1038/leu.2014.261.

15. Brown JR, Byrd JC, Coutre SE, et al. Idelalisib, an inhibitor of phosphatidylinositol 3-kinase p110δ, for relapsed/refractory chronic lymphocytic leukemia. *Blood*. 2014;123(22):3390-3397. doi:10.1182/blood-2013-11-535047.

16. Flinn IW, Kahl BS, Leonard JP, et al. Idelalisib, a selective inhibitor of phosphatidylinositol 3-kinase-δ, as therapy for previously treated indolent non-Hodgkin lymphoma. *Blood*. 2014;123(22):3406-3413. doi:10.1182/blood-2013-11-538546.

17. Horwitz SM, Porcu P, Flinn I. Duvelisib (IPI-145), a phosphoinositide-3-kinase-δ,γ inhibitor, shows activity in patients with relapsed/refractory T-cell lymphoma. Blood. 2014;124:803. *Blood*. 2014;124:803.

18. Mak V, Hamm J, Chhanabhai M, Shenkier T, Klasa R, Sehn LH, Villa D, Gascoyne RD, Connors JM, Savage KJ. Survival of Patients With Peripheral T-Cell Lymphoma After First Relapse or Progression: Spectrum of Disease and Rare Long-Term Survivors. *Journal of Clinical Oncology* 2013; 31:16, 1970-1976

19. Freeman GJ, Long AJ, Iwai Y, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *J Exp Med*. 2000;192(7):1027-1034.

20. Brahmer JR, Tykodi SS, Chow LQM, et al. Safety and Activity of Anti-PD-L1 Antibody in Patients with Advanced Cancer. *N Engl J Med*. June 2012. doi:10.1056/NEJMoa1200694.

21. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, Activity, and Immune Correlates of Anti-PD-1

Antibody in Cancer. *N Engl J Med*. June 2012. doi:10.1056/NEJMoa1200690.

22. Linterman MA, Rigby RJ, Wong RK, et al. Follicular helper T cells are required for systemic autoimmunity. *Journal of Experimental Medicine*. 2009;206(3):561-576. doi:10.1084/jem.20081886.

23. Linterman MA, Beaton L, Yu D, et al. IL-21 acts directly on B cells to regulate Bcl-6 expression and germinal center responses. *J Exp Med*. 2010;207(2):353-363. doi:10.1084/jem.20091738.

24. Good-Jacobson KL, Szumilas CG, Chen L, Sharpe AH, Tomayko MM, Shlomchik MJ. PD-1 regulates germinal center B cell survival and the formation and affinity of long-lived plasma cells. *Nat Immunol*. 2010;11(6):535-542. doi:10.1038/ni.1877.

25. Sage PT, Francisco LM, Carman CV, Sharpe AH. The receptor PD-1 controls follicular regulatory T cells in the lymph nodes and blood. *Nat Immunol*. 2013;14(2):152-161. doi:10.1038/ni.2496.

26. Boyerinas B, Jochems C, Fantini M, et al. Antibody-Dependent Cellular Cytotoxicity Activity of a Novel Anti-PD-L1 Antibody Avelumab (MSB0010718C) on Human Tumor Cells. *Cancer Immunology Research*. May 2015. doi:10.1158/2326-6066.CIR-15-0059.

27. Heery CR, Coyne GS, Madan RA, et al. Phase I open-label, multiple ascending dose trial of MSB0010718C, an anti-PD-L1 monoclonal antibody, in advanced solid malignancies. *J Clin Oncol*. 2014;32:5s.

28. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *Journal of Clinical Oncology*. 2007;25(5):579-586. doi:10.1200/JCO.2006.09.2403.

29. Ellin, F., Landström, J., Jerkeman, M., & Relander, T. (2014). Real-world data on prognostic factors and treatment in peripheral T-cell lymphomas: a study from the Swedish Lymphoma Registry. *Blood*, *124*(10), 1570–1577.

30. Coiffier, B., Pro, B., & Prince, M. (2012). Results From a Pivotal, Open-Label, Phase II Study of Romidepsin in Relapsed or Refractory Peripheral T-Cell Lymphoma After Prior Systemic Therapy. *Journal of Clinical Oncology*, *30*, 631–636.

31. Herbst RS, Gordon MS, Fine GD, et al. A study of MPDL3280A, an engineered PD-L1 antibody in patients with locally advanced or metastatic tumors. *J Clin Oncol*. 2013;31:Abstract3000.

32. Vallois D, Dobay MPD, Morin RD, Lemonnier F, Missiaglia E, Juilland M, et al. Activating mutations in genes related to TCR signaling in angioimmunoblastic and other follicular helper T-cell-derived lymphomas. *Blood*. 2016;15:128(11):1490–502.

33. Palomero T, Couronné L, Khiabanian H, Kim M-Y, Ambesi-Impiombato A, Perez-Garcia A, et al. Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. Nat Genet. 2014 Feb;46(2):166–70.

34. Segal NH, Antonia SJ, Brahmer JR, et al. Preliminary data from a multi-arm expansion study of MEDI4736, an anti-PD-L1 antibody. *J Clin Oncol*. 2014;32:5s.

35. Fairman D, Narwal R, Liang M, et al. Pharmacokinetics of MEDI4736, a fully human anti-PDL1 monoclonal antibody, in patients with advanced solid tumors. *J Clin Oncol*. 2014;32:5s.

36. Manso R, Rodríguez-Pinilla SM, González-Rincón J, et al. Recurrent presence of the PLCG1 S345F mutation in nodal peripheral T-cell lymphomas. *Haematologica*. 2015;100(1):e25-e27. doi:10.3324/haematol.2014.113696.

37. Cairns RA, Iqbal J, Lemonnier F, et al. IDH2 mutations are frequent in angioimmunoblastic T-cell lymphoma. *Blood*. 2012;119(8):1901-1903. doi:10.1182/blood-2011-11-391748.

38. Palomero T, Couronné L, Khiabanian H, et al. Recurrent mutations in epigenetic regulators, RHOA and FYN kinase in peripheral T cell lymphomas. *Nat Genet*. 2014;46(2):166-170. doi:10.1038/ng.2873.

39. Sakata-Yanagimoto M, Enami T, Yoshida K, et al. Somatic RHOA mutation in angioimmunoblastic T cell lymphoma. *Nat Genet*. 2014;46(2):171-175. doi:10.1038/ng.2872.

40. Iqbal J, Wright G, Wang C, et al. Gene expression signatures delineate biological and prognostic subgroups in peripheral T-cell lymphoma. *Blood*. 2014;123(19):2915-2923. doi:10.1182/blood-2013-11-536359.

41. Howard SC, Jones DP, Pui C-H. The tumor lysis syndrome. *N Engl J Med*. 2011;364(19):1844-1854. doi:10.1056/NEJMra0904569.

APPENDIX 1 - RESPONSE CRITERIA FOR MALIGNANT LYMPHOMA[27]

Response Category	Lymph Node Masses	Spleen and Liver	Bone Marrow
CR	Normal*	Not palpable, nodules disappeared	Normal or if indeterminate** by morphology, negative on immunohistochemistry
PR	Normal*		Persistent morphological bone marrow involvement
	≥ 50% decrease in SPD of up to 6 largest dominant masses***, no increase in other lesions	No increase in size of liver or spleen; ≥ 50% decrease in SPD of nodules	Irrelevant
SD	No change in size of previous lesions on CT	No increase in liver / spleen	
Relapse/progression	New or increased****	> 50% increase from nadir in SPD of any previous lesions	New or recurrent involvement

* ≤ 1.5 cm in their greatest transverse diameter for nodes >1.5 cm before therapy. Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter and > 1.0 cm in the short axis before treatment must have decreased to ≤1 cm in their short axis after treatment.

**Indeterminate bone marrow (increased number or size of aggregates without cytologic or architectural atypia).

***Select diameters of up to six of the largest dominant nodes or nodal masses.
These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

****Appearance of a new lesion(s) > 1.5cm in any axis; ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1cm in short axis.

APPENDIX 2 – AVAIL-T BAYESIAN PROBABILITY PLOTS

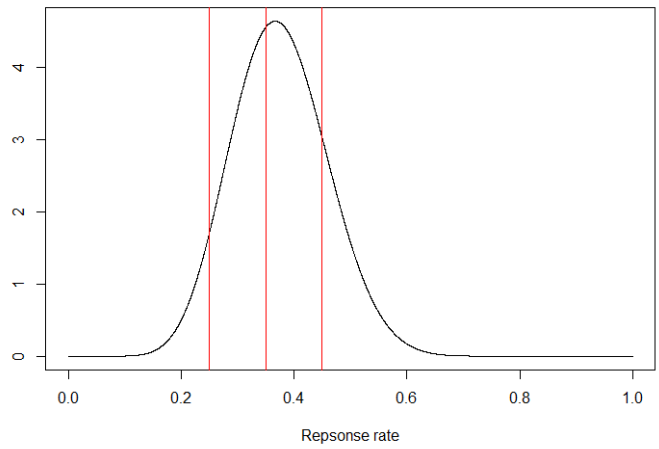
Design

Bayesian probability plot approach using a binary outcome. Uninformative beta prior is used.

For 30 evaluable patients in the trial

1) 11 responses observed

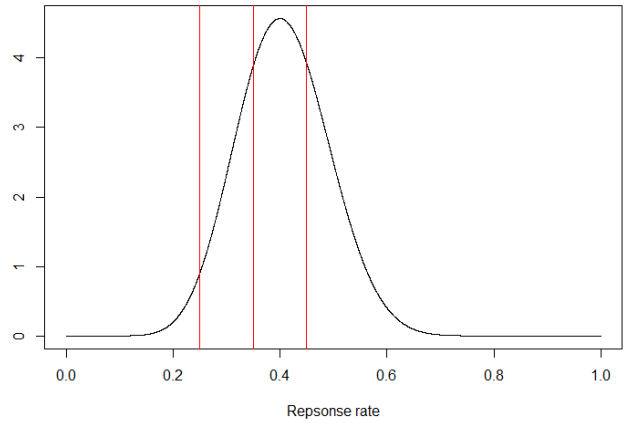
We would be greater than 60% sure that the response rate was greater than 35%. The plot below shows the distribution of the responses and the red lines show the 25%, 35% and 45% marks.



P (true response rate > 45%) =	19%
P (true response rate > 35%) =	60%
P (true response rate > 25%) =	94%

2) 12 responses observed

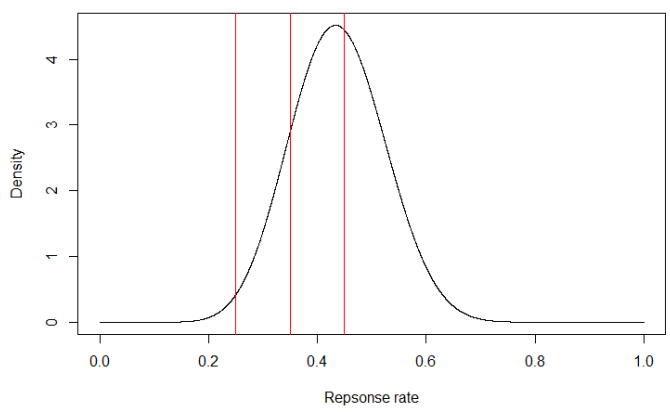
We would be greater than 74% sure that the response rate was greater than 35%. The plot below shows the distribution of the responses and the red lines show the 25%, 35% and 45% marks.



P (true response rate > 45%) =	30%
P (true response rate > 35%) =	74%
P (true response rate > 25%) =	97%

3) 13 responses observed

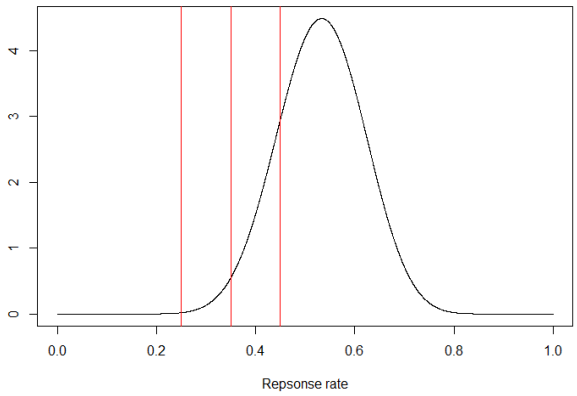
We would be greater than 84% sure that the response rate was greater than 35%. The plot below shows the distribution of the responses and the red lines show the 25%, 35% and 45% marks.



P (true response rate > 45%) =	44%
P (true response rate > 35%) =	84%
P (true response rate > 25%) =	98%

4) 16 responses observed:

We would be greater than 98% sure that the true response rate was greater than 35%. The plot below shows the distribution of the responses and the red lines show the 25%, 35% and 45% marks.

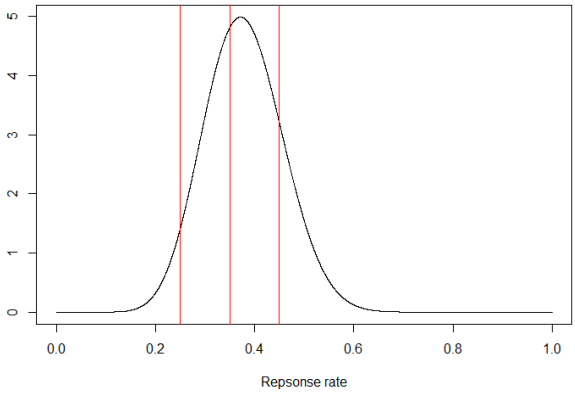


P (true response rate > 45%) =	82%
P (true response rate > 35%) =	98%
P (true response rate > 25%) =	>99%

For 35 evaluable patients in the trial

1) 13 responses observed:

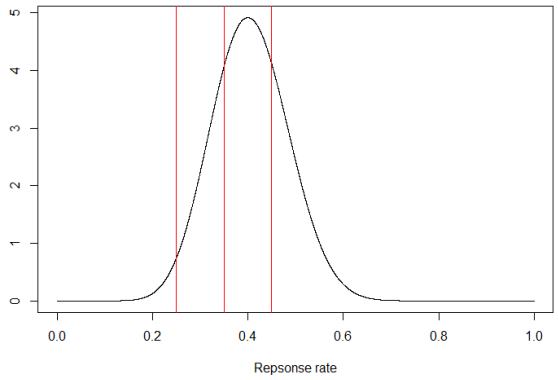
We would be greater than 63% sure that the response rate was greater than 35%. The plot below shows the distribution of the responses and the red lines show the 25%, 35% and 45% response rate marks.



P (true response rate > 45%) =	18%
P (true response rate > 35%) =	63%
P (true response rate > 25%) =	95%

2) 14 responses observed:

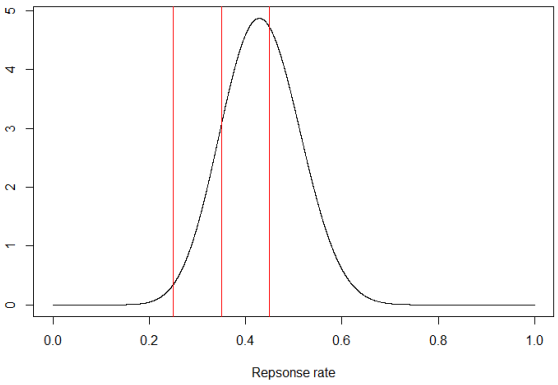
We would be greater than 75% sure that the response rate was greater than 35%. The plot below shows the distribution of the responses and the red lines show the 25%, 35% and 45% response rate marks.



P (true response rate > 45%) =	29%
P (true response rate > 35%) =	75%
P (true response rate > 25%) =	97%

3) 15 responses observed:

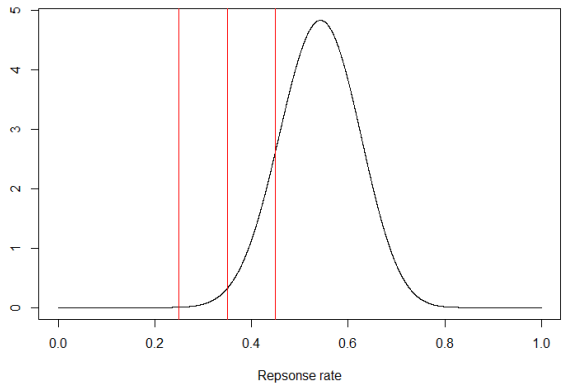
We would be greater than 84% sure that the response rate was greater than 35%. The plot below shows the distribution of the responses and the red lines show the 25%, 35% and 45% response rate marks.



P (true response rate > 45%) =	41%
P (true response rate > 35%) =	84%
P (true response rate > 25%) =	99%

4) Anticipated 19 responses observed:

We would be greater than 98% sure that the true response rate was greater than 35%. The plot below shows the distribution of the responses and the red lines show the 25%, 35% and 45% response rate marks.



P (true response rate > 45%) =	87%
P (true response rate > 35%) =	99%
P (true response rate > 25%) =	>99%

APPENDIX 3 - DEFINITION OF ADVERSE EVENTS

Adverse Event

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

Comment:

An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings that result in early trial treatment discontinuation from the study treatment, and/or requires study drug dose modification or interruption, any other therapeutic intervention or is judged to be of significant clinical importance), symptom or disease temporally associated with the use of an investigational medicinal product, whether or not related to the investigational medicinal product.

Adverse Reaction

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

Comment:

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

Serious Adverse Event

Any untoward medical occurrence or effect that at any dose:

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

Comments:

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

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

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

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

Serious Adverse Reaction

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

Suspected Unexpected Serious Adverse Reaction

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

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

Unexpected Adverse Reaction

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

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

APPENDIX 4 - WMA DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Recommendations guiding physicians

in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly

Helsinki, Finland, June 1964

and amended by the

29th World Medical Assembly, Tokyo, Japan, October 1975

35th World Medical Assembly, Venice, Italy, October 1983

41st World Medical Assembly, Hong Kong, September 1989

and the

48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

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

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

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

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

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

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

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

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

I. BASIC PRINCIPLES

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

1. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the

sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

APPENDIX 5 - COMMON TOXICITY CRITERIA GRADINGS

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

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

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