Pembro WM

A phase II trial to investigate the safety and efficacy of rituximab and pembrolizumab in relapsed/refractory Waldenström's macroglobulinaemia

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Please note: This trial protocol must not be applied to patients treated outside the Pembro WM trial. Cancer Research UK & UCL Cancer Trials Centre (UCL CTC) can only ensure that approved trial investigators are provided with amendments to the protocol.

We thank the patient representatives who reviewed the protocol for their input into the trial design and patient information sheet.

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Abbreviations

ABPI	Association of British Pharmaceutical Industry
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute Neutrophil Count
AR	Adverse Reaction
AST	Aspartate aminotransferase
CI	Chief Investigator
CR	Complete Response
CRF	Case Report Form
CT	Computerised Tomography
CTA	Clinical Trial Authorisation
CTCAE	Common Terminology Criteria for Adverse Events
DPA	Data Protection Act
DSUR	Development Safety Update Report
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylene Diamine Tetra Acetate
EudraCT	European Clinical Trials Database
FBC	Full Blood Count
G-CSF	Granulocyte Colony Stimulating Factor
GFR	Glomerular Filtration Rate
GMO	Genetically Modified Organisms
Hb	Haemoglobin
HRA	Health Research Authority
IB	Investigator's Brochure
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IMP	Investigational Medicinal Product
ISRCTN	International Standard Randomised Controlled Trial Number
IV	Intravenous
LCRN	Local Clinical Research Network
LDH	Lactate Dehydrogenase
LFT	Liver Function Tests
LLN	Lower Limit of Normal
MHRA	Medicines and Healthcare products Regulatory Agency
mNCA	Model Agreement for Non-Commercial Research
NCRI	National Cancer Research Institute
OS	Overall Survival
PD	Progressive Disease
PFS	Progression Free Survival
PI	Principal Investigator
PO	By mouth
PR	Partial Response
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable Disease

SPC	Summary of Product Characteristics
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee
UCL CTC	CR UK and UCL Cancer Trials Centre
U&E	Urea and Electrolytes
ULN	Upper Limit of Normal
VGPR	Very Good Partial Response
WBC	White Blood Cells

1. PROTOCOL SUMMARY

1.1. Summary of Trial Design

Title:	A Phase II trial to investigate the safety and efficacy of rituximab and pembrolizumab in relapsed/refractory Waldenström's macroglobulinaemia
Short Title/acronym:	PembroWM
EUDRACT no:	2018-001767-23
Sponsor name & reference:	UCL18/0131
Funder name & reference:	Merck Sharp and Dohme Ltd; MISP# 56775
ISRCTN/Clinicaltrials.gov no:	NCT03630042
Design:	Single arm, phase II trial, non-randomised
Overall aim:	To determine the safety, tolerability and efficacy of pembrolizumab in combination with rituximab for the treatment of relapsed/refractory Waldenström's macroglobulinaemia (WM)
Primary endpoint:	Percentage of patients achieving an overall response rate (defined as complete response (CR), very good partial response (VGPR), partial response (PR) or minor response (MR) i.e. a greater than 25% reduction in the serum IgM level) at 24 weeks post commencing treatment.
Secondary endpoints:	• Safety and tolerability of pembrolizumab in combination with rituximab • Complete response (CR) rate at 24 weeks post commencing treatment • Very good partial response (VGPR) rate at 24 weeks post commencing treatment • Time to maximal response to treatment • Time to next treatment • Progression free survival (PFS) at 1 and 2 years • Overall survival (OS) at 1 and 2 years • Change in quality of life (QoL) at 24 weeks post commencing treatment
Exploratory Biological Studies:	• Assessment of PD-1 and PD-L1/ PD-L2 expression by fluorescence in situ hybridisation (FISH) and immunohistochemistry (IHC)

	• IHC to assess baseline and on-treatment changes to distribution and composition of immune response cells in the microenvironment • Analysis of baseline biopsies to elucidate potential mechanisms of action of tumour response • Assessment of treatment outcome according to tumour genotype • Correlation of bone marrow response with reduction in serum IgM level • Quantification of bone marrow involvement by morphologic assessment of trephine and flow cytometric assessment of aspirate for MRD
Target accrual:	42 patients

Inclusion & exclusion criteria:
 	
*(Refer to **section 6.2** for the full list of eligibility criteria)*
	Inclusion criteria
	
	• Patients ≥18 years old
	• Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (see appendix 3)
	• Presence of measurable disease, (defined as a detectable level of IgM paraprotein) and fulfils other World Health Organisation (WHO) diagnostic criteria for WM
	• Relapsed or refractory WM who have received ≥1 prior lines of therapy
	• Adequate renal function: estimated creatinine clearance ≥30ml/min as calculated using the Cockroft-Gault equation
	• Adequate liver function, including:
	  ○ Bilirubin ≤1.5 x the upper limit of normal (ULN)
	  ○ Aspartate or alanine transferase (AST or ALT) ≤2.5x ULN
	• Adequate organ and bone marrow function:
	  ○ Neutrophils ≥0.5x10^9/L
	  ○ Platelets ≥25$10^9$/L
	Note: Growth factor and/or transfusion support is permissible to stabilize participant prior to study treatment if needed. No lower limit if cytopenia is related to WM infiltration in the bone marrow.
	• Willing to comply with contraceptive requirements of the trial (see section 6.3.4)
	• Negative serum or highly sensitive urine pregnancy test for women of childbearing potential (WOCBP)
	• Written informed consent

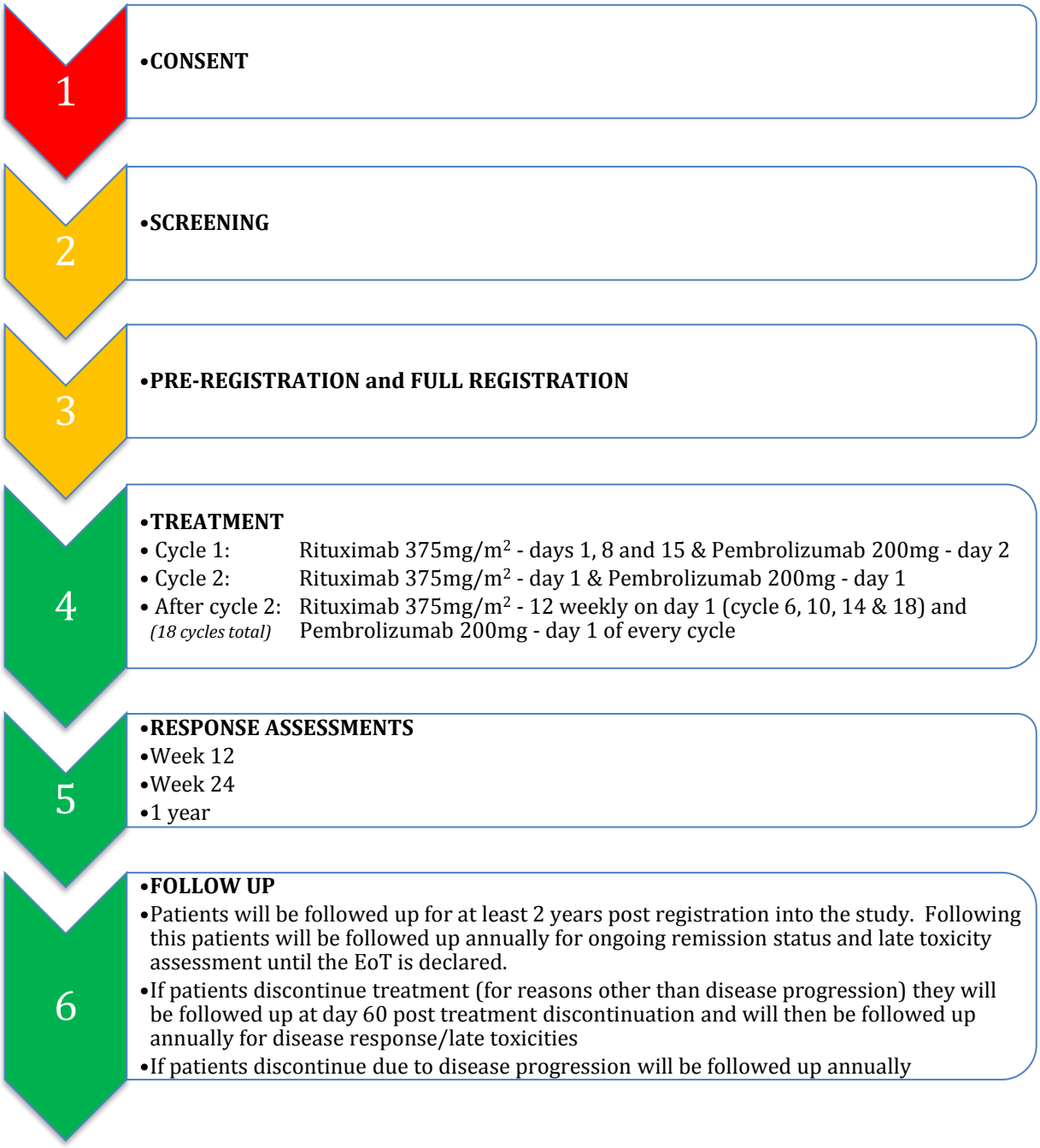
	Exclusion criteria
	
	• Refractory to rituximab as defined by progression on/within 6 months of finishing a rituximab based regimen
	• Women who are pregnant or breastfeeding, or males expecting to conceive or father children at any point from the start of treatment until 4 months after the last administration of pembrolizumab
	• Clinically significant cardiac disease (see section 6.2 of the protocol for details)
	• History of significant cerebrovascular disease in the last 6 months
	• Known central nervous system (CNS) involvement of WM
	• Clinically significant active infection requiring antibiotic or antiretroviral therapy
	• Significant concurrent, uncontrolled medical condition (see section 6.2 of protocol for details)
	• Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or *in situ* cervical cancer that has undergone potentially curative therapy
	• Active autoimmune disease apart from:
	  ○ Type I diabetes or thyroid disease, controlled on medication
	  ○ Skin conditions such as psoriasis, vitiligo or alopecia not requiring systemic treatment
	  ○ Auto-immune thrombocytopenia, thought to be secondary to WM, provided that the platelet count meet the criteria specified above on daily doses of corticosteroid of ≤10mg prednisolone or equivalent
	• Prior history of haemolytic anaemia (either warm or cold)
	• History of non-infective colitis
	• History of (non-infectious) pneumonitis that required steroids or has current pneumonitis
	• Systemic anti-cancer therapy within 4 weeks prior to trial registration (except for BTK inhibitors, which may continue until 48 hours prior to the start of cycle 1, day 1 of trial therapy)
	• Received a T cell depleting antibody (e.g. Campath) within 3 months prior to starting treatment

	• Received a live vaccine or live-attenuated vaccine within 30 days prior to starting treatment • Chronic or ongoing active infectious disease requiring systemic treatment (see section 6.2 of the protocol for details) • Patients who have received treatment with any non-marketed drug substance or experimental therapy within 4 weeks prior to starting treatment (unless prior agreed with the TMG) • Patients known or suspected of not being able to comply with the study protocol • Positive serology for Hepatitis B defined as a positive test for HepB surface antigen (HBsAg). Note: patients who are HepB core antibody (HBcAb) positive will only be eligible for the study if the HepB virus deoxyribonucleic acid (DNA) test is negative and patients are willing to undergo monthly monitoring for HBV reactivation • Positive serology for Hepatitis C defined as a positive test for HCV antibody • Major surgery within 4 weeks prior to trial registration • Prior therapy with an anti-PD-1,anti-PD-L1 or CTLA4 monoclonal antibody • Prior allogeneic bone marrow transplant • Diagnosis of prior immunodeficiency or organ-transplant requiring immunosuppressive therapy or known HIV or acquired immunodeficiency syndrome (AIDS)-related illness • Current or prior use of immunosuppressive therapy within 7 days prior to start of treatment except the following: intranasal, inhaled, topical steroids or local steroid injections (e.g. Intra-articular injections); a short course of oral prednisolone (a maximum of 10mg/day for 5 days) can be used within 7 days of cycle 1 day 1 if there are concerns around IgM flare, following BTK inhibitor discontinuation • Known or suspected hypersensitivity to components of pembrolizumab or rituximab (or other CD20 monoclonal antibodies)
Number of sites:	10 UK sites

Treatment summary:	Eligible patients will be treated with rituximab 375mg/m2 IV infusion and pembrolizumab 200mg IV infusion on a 3 weekly cycle, for a maximum of 18 cycles (1 year):
	
	• Cycle 1:
	  ○ Rituximab 375mg/m^2 - days 1, 8 and 15
	  ○ Pembrolizumab 200mg - day 2
	• Cycle 2:
	  ○ Rituximab 375mg/m^2 - day 1
	  ○ Pembrolizumab 200mg - day 1
	• After cycle 2:
	  ○ Rituximab 375mg/m^2 - 12 weekly on day 1 (cycle 6, 10, 14 & 18)
	  ○ Pembrolizumab 200mg - day 1 of every cycle

Duration of recruitment:	27 months
Duration of follow up:	Patients will be followed up for a minimum of 2 years post registration into the study
Definition of end of trial:	The end of trial will be declared when the final data item from the final patient is received (i.e. it is anticipated that this will be when the final patient completes their 2-year follow-up visit).

1.2. Trial Schema



2. INTRODUCTION

2.1. Background

2.1.1. Waldenström's macroglobulinemia

Waldenström's macroglobulinemia (WM) is a rare low grade B-cell malignancy, characterised by bone marrow infiltration with monoclonal immunoglobulin M secreting lymphoplasmacytic cells. The incidence is 5-8 cases per million, with about 1,000-1,500 new patients diagnosed in the USA annually. Incidence increases with age with a median age at diagnosis of 70 years for Caucasians, and slightly lower in other ethnic groups. There is a male to female preponderance, and an incidence higher in Caucasians than Africans or Asians (Gertz et al 2000; Gertz et al 2015).

Activating mutations in the MYD88 gene (MYD88MUT), which trigger downstream IRAK-mediated NF-κB signaling (Treon et al 2012), are seen in approximately 90% of cases. A second set of mutations with prognostic significance is found at CXCR4, the receptor for SDF-1a, which are either frameshift or nonsense mutations, are similar to those seen in the immunodeficiency syndrome WHIM (warts, hypogammaglobulinemia, infections and myelokathexis), and also lead to constitutive activation. Either or both of these mutations can be found in patients and lead to different clinical pictures, outcomes, and response to therapy (Treon, et al 2014).

According to the International Prognostic scoring system for WM (ISSWM), patients are stratified into low, intermediate, and high risk groups with respective 5-year survival rates of 87%, 68%, and 36%, based upon age, IgM level, β2-microglobulin level, hemoglobin, and platelet count (Morel et al 2009).

About 75% of initially asymptomatic WM patients will require therapy within 15 years of follow-up, with a median time to initiation of therapy of over 7 years; a lower Hgb, extensive bone marrow infiltration, serum paraprotein, and β2-microglobulin levels are significant predictors of an eventual need for therapy (Gertz et al 2015). Indications for treatment as per the IWWM-8 consensus meeting are either clinical symptoms or laboratory findings. Clinical indications include the combination of fever, night sweats, weight loss and fatigue, hyperviscosity syndrome, bulky/symptomatic lymphadenopathy, significant hepatomegaly or splenomegaly, other symptomatic organomegaly, or peripheral neuropathy. Laboratory indications for therapy include symptomatic cryoglobulinemia, cold agglutinin anemia, immune hemolytic cytopenias, nephropathy, amyloidosis, or significant anemia/thrombocytopenia due to marrow replacement (Leblond et al 2016).

2.1.2. Clinical need in WM

Current treatment strategies include single agent rituximab or rituximab combination approaches. In the upfront setting, both Bendamustine plus rituximab, and Dexamethasone, cyclophosphamide and rituximab have shown to be effective approaches (Rummel et al, 2013; Kastritis et al, 2015). Proteasome inhibitor combinations with rituximab have also been studied in both the upfront and relapse setting (Gavriatopoulou et al, 2017; Treon et al, 2014).

Treatment at relapse is less standardised, however patients generally remain responsive to therapy, including rituximab combination approaches. Responses appear less durable with a median progression free survival (PFS) of 16-24 months, up until the advent of ibrutinib, which appears to give better results, with a median PFS of at least 4 years (Treon et al, 2015 Treon el al, 2017). There is now also evidence for combining rituximab with ibrutinib in the upfront and relapsed setting, and emerging data on small numbers of patients who have been treated with ibrutinib in the upfront setting (Dimopoulous et al, 2018; Treon et al 2018). However, relapse is inevitable and there is therefore a need for more effective drugs/combinations that can induce deeper and more durable responses, especially as there are some concerns about the nature and tempo of relapses following discontinuation/progression after ibrutinib (Gustine et al, 2017).

The need for recurrent treatment, the advanced median age at diagnosis, and the underlying biology of the condition, means that there is a relatively high rate of treatment-related complications, including infection, secondary malignancy and myelosuppression. Therefore the further development of chemotherapy-free regimes is attractive, and logical partners for combination therapy would include rituximab and ibrutinib.

2.1.3. New potential drug therapies in WM

Increased understanding of the biology of WM has catalysed the development of new targeted therapeutic agents. MYD88 acts as an adaptor protein for interleukin-1R (IL-1R) and Toll-Like receptor (TLR) signaling pathways and recruits kinases that lead to activation of NFkB and secretion of cytokines which are implicated in WM cell survival and proliferation (Treon et al, 2014). These kinases include IL-R associated kinase 4 (IRAK-4) and IRAK-1 as well as Bruton Tyrosine Kinase (BTK), the target for ibrutinib and other BTK inhibitors. The MYD88L265P mutation causes constitutive signaling through this pathway in WM.

Ibrutinib is becoming a standard of care in relapsed WM, and further BTK inhibitors including Acalabrutinib and Zanubrutinib are in development. CXCR4 and IRAK-1 inhibitors have shown some pre-clinical activity and are under development (Kuhne et al, 2014, Yang et al, 2017).

Other attractive targets include the anti-apoptotic protein, BCL2, as this is upregulated in WM, making the small molecule inhibitor, venetoclax (ABT-199) a promising potential therapy: in a phase I trial 3 out of 4 WM patients achieved a response, including one with a complete remission (CR) (Davids et al, 2017). The mammalian target of rapamycin (MTOR) inhibitor, everolimus, which blocks pathways involved in WM cell growth and proliferation, showed a major response rate of 50% in previously treated WM patients (Ghobrial et al, 2017)

2.1.4. Limitations in recent studies of targeted agents

However impressive these results, these new, targeted therapies have their own limitations. For example, there are no complete responses seen with ibrutinib. Phosphoflow analysis of bone marrow lymphoplasmacytic cells taken from WM patients showed highly active IRAK1 and IRAK4 but not BTK suggesting partial escape through this alternative signaling pathway. Moreover wild type MYD88 WM responds significantly less well to ibrutinib [Treon et al, 2017]. This partial resistance, either inherent or acquired, is likely to be seen with other agents that target a specific pathway.

Moreover, while these targeted agents are undoubtedly less myelotoxic, they have their own associated toxicity. For example, bortezomib can be associated with severe

peripheral neuropathy, which can be particularly challenging in the WM patient group, who may have disease-associated neuropathy. Similarly ibrutinib is associated with side effects such as increased risk of atrial fibrillation and bleeding. This may be particularly problematic in an elderly group of patients, who may require anti-coagulation for other indications or who may have an acquired coagulopathy due to the WM itself. 'Real-world' data suggests approximately 20% of WM patients may discontinue Ibrutinib within a year, secondary to toxicity (Gustine et al, 2018) and novel, and ideally non-toxic approaches are required to treat these patients.

Finally, non standardised measurement of response, small patient numbers, and failure to separate out first- line versus relapsed/refractory patients makes it difficult to compare the efficacy of novel agents across trials. Definition of consensus response criteria by the International Workshop on WM should improve this to some degree (Owen et al, 2014). With the burgeoning number of new agents, it is therefore an important time for further rigorously conducted clinical trials in WM.

2.1.5. PD-1/PD-L1 as a target in WM

PD-1 inhibitors are thought to overcome immune anergy by blocking interaction between the inhibitory receptor, PD-1, on T cells and its ligands, PD-L1 and PD-L2, which are over-expressed in some tumour cells and the tumour micro-environment. PD-1 inhibitors, such as pembrolizumab and nivolumab, have shown impressive clinical results in relapsed lymphoid malignancies, especially in Hodgkin lymphoma (Bröckelmann et al, 2017).

There is a clear role for the bone marrow microenvironment in the pathophysiology of WM and PD-1 and PDL-1 is widely expressed in the BMs of patients with WM (Ansell, 2014) and complex cellular and stromal interplay is partly controlled by the expression and secretion of a number of cytokines, including IL-6 and IL-21 (Hodge et al, 2012).

Interaction between PD-1 and its ligands may at least partially mediate the permissive role of the bone marrow microenvironment in WM: co-culture of PD-1 expressing WM cells with PD-L1/ PD-L2 overexpressing stromal cells increased WM cell viability and proliferation (Ansell, 2014).

More recent data indicates that soluble PD-1 Ligands Regulate T-Cell Function in WM, with IL-6 and IL-21 leading to an upregulation of both PD-L1 and PD-L2 expression (Jalali et al, 2017). This upregulation appears to increase expression of soluble, rather than cell-surface PD-L1 and PD-L2, but this appears to inhibit T-cell function. Thus, there is adequate preclinical data to postulate that PD-1 blocking antibodies may be an effective therapeutic intervention in WM. Moreover, as compared with ibrutinib and other BTK inhibitors, it is unlikely that response to PD-1 inhibitors will be as restricted to specific genomic subtypes (i.e. MYD88/ CXCR mutant versus wild type).

2.1.6. Clinical experience of pembrolizumab

Pembrolizumab is a potent and highly selective humanised monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Available pharmacokinetic (PK) results in patients with melanoma, non-small cell lung cancer (NSCLC), and other solid tumour types support a lack of meaningful difference in PK exposures obtained at a given dose among tumour types. An open-label Phase 1 trial (PN001) in melanoma patients has been conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10

mg/kg, administered every 2 weeks (Q2W) in patients with advanced solid tumours (Patnaik et al, 2015). All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumour size reduction at all dose levels. No maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma patients receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg every 3 weeks (Q3W) have been completed [ref]. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma patients who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2 mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of patients with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in patients with melanoma, NSCLC, and other solid tumour types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumour types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumour indications.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 patients from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety.

Pembrolizumab efficacy in relapsed indolent lymphomas as a single agent (with WM patients treated) has recently been assessed in a phase 2 trial, which has been published in abstract form (Ding et al, 2017). In 23 patients receiving pembrolizumab monotherapy, responses were seen (including a minor response in a patient with WM) and the toxicity profile was acceptable.

2.1.7. Scientific rationale for combining Pembrolizumab and Rituximab in WM

The manageable tolerability of anti-PD-1 mAb pathway blockers and their unique mechanism of action are encouraging but to increase the response rate and depth of response combination therapy approaches appear to be required. Given the proven efficacy, well understood toxicity and proven ability to combine with other agents

(including cytotoxic chemotherapy and targeted small molecules such as ibrutinib and idelalisib) rituximab is attractive partner for such immunotherapy combinations.

Rituximab has proven clinical efficacy in WM and is widely used in the relapsed/refractory setting. In general, there is evidence of enhanced efficacy of rituximab combination therapy compared with monotherapy alone (Santos-Lozano et al, 2016). There is some rationale to hypothesise that pembrolizumab and rituximab could have a synergistic effect. Antibody and complement dependent cell mediated cytotoxicity may generate neo-antigens and create an inflammatory milieu, which may further prime T-cell activation. Also, the apparent limited activity of pembrolizumab as a single agent would inform a combination as a more logical approach, especially in the presence of some recently presented data looking at this combination in relapsed follicular lymphoma (Nastoupil et al, 2017). 30 patients treated with the combination led to an overall response rate of 64% and a CR rate of 48%, with a manageable toxicity profile, with immune AEs generally being grade 1-2.

The aim of this trial is to investigate the safety and efficacy of rituximab in combination with pembrolizumab in patients with relapsed WM.

3. TRIAL DESIGN

This is a phase II, non-randomised, single arm, open label study to determine the safety, tolerability and efficacy (assessed by response rate) of pembrolizumab in combination with rituximab for the treatment of relapsed/refractory WM.

Patients with relapsed/refractory WM meeting the eligibility criteria will be recruited to the study. Patients will be treated on a 3 weekly cycle with the following:

- Rituximab 375mg/m^2 IV infusion on days 1, 8 and 15 for cycle 1
- Rituximab 375mg/m^2 IV infusion day 1 of cycle 2, then
- Rituximab 375mg/m^2 IV infusion given 12 weekly for a further 4 doses (total duration of rituximab treatment is 1 year)
- Pembrolizumab 200mg IV infused on day 2 of cycle 1, and day 1 of subsequent cycles for a maximum of 18 cycles (1 year) or until disease progression, discontinuation due to toxicity or any other cause (whichever occurs sooner)

Patients will be assessed for disease response (by serum IgM measurement) at 12 and 24 weeks post commencing treatment and at 1 year.

3.1. Trial Objectives

3.1.1. Primary Objective

- To determine the efficacy (overall response rate at 24 weeks) of the combination of rituximab and pembrolizumab in relapsed/refractory WM

3.1.2. Secondary Objectives

- To determine the safety and tolerability of the combination of rituximab and pembrolizumab in relapsed/refractory WM
- To assess the depth of response to rituximab and pembrolizumab and duration of response
- To determine the time to best response and time to next therapy
- To determine the effect of rituximab and pembrolizumab on quality of life

3.1.3. Exploratory Objective

- To investigate immune biomarkers of response to the combination of rituximab and pembrolizumab

3.2. Trial Endpoints

3.2.1. Primary end-points:

- Percentage of patients achieving an overall response rate (defined as complete response (CR), very good partial response (VGPR), partial response (PR) or minor response (MR) i.e. a greater than 25% reduction in the serum IgM level) at 24 weeks post commencing treatment

3.2.2. Secondary end-points:

- Safety and tolerability of pembrolizumab and rituximab as assessed by the frequency of serious and non-serious adverse events, graded according to CTCAE v5.0
- Complete response (CR) rate at 24 weeks post commencing treatment (see appendix 4)
- Very good partial response (VGPR) rate at 24 weeks post commencing treatment (see appendix 4)
- Time to maximal response, as determined by the time of registration to the maximal disease response
- Time to next treatment, as determined by the time from registration to the next line of therapy
- Progression free survival (PFS) at 1 and 2 years
- Overall survival (OS) at 1 and 2 years
- Change in quality of life (QoL) at 24 weeks post commencing treatment

3.2.3. Exploratory endpoints:

- Assessment of PD-1 and PD-L1/ PD-L2 expression by fluorescence in situ hybridisation (FISH) and immunohistochemistry (IHC).
- IHC to assess baseline and on-treatment changes to distribution and composition of immune response cells in the microenvironment
- Analysis of baseline biopsies to elucidate potential mechanisms of action of tumour response
- Assessment of treatment outcome according to tumour genotype, as determined by sequencing assays for $MYD88^{L265P}$ and CXCR4 mutations
- Correlation of bone marrow response with reduction in serum IgM level.
- Quantification of bone marrow involvement by morphologic assessment of trephine and flow cytometric assessment of aspirate for MRD

3.3. Trial Activation

UCL CTC will ensure that all trial documentation has been reviewed and approved by all relevant bodies and that the following have been obtained prior to activating the trial:

- Health Research Authority (HRA) approval, including Research Ethics Committee approval
- Clinical Trial Authorisation from the Medicines and Healthcare products Regulatory Agency (MHRA)
- 'Adoption' into NIHR portfolio
- Adequate funding for central coordination
- Confirmation of sponsorship
- Adequate insurance provision

4. SELECTION OF SITES/SITE INVESTIGATORS

4.1. Site Selection

In this protocol trial 'site' refers to a hospital where trial-related activities are conducted.

Sites must be able to comply with:

- Trial treatment, imaging, clinical care, follow up schedules and all requirements of the trial protocol
- Requirements of the UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority and the Medicines for Human Use Clinical Trials Regulation (SI 2004/1031), and all amendments
- Data collection requirements, including adherence to CRF submission timelines as per section 11.3 (Timelines for Data Return)
- Biological sample collection, processing and storage requirements
- Monitoring requirements, as outlined in protocol section 14 (Trial Monitoring and Oversight)
- Obtaining relevant license(s) for medical radiation exposure, and renewing as necessary

4.1.1. Selection of Principal Investigator and other investigators at sites

Each site must appoint an appropriate Principal Investigator (PI), i.e. a health care professional authorised by the site to lead and coordinate the work of the trial on behalf of a site. Co-investigators must be trained and approved by the PI. All PIs and co-investigators must be medical doctors and have experience of immune-oncology agents and treating WM. The PI is responsible for the conduct of the trial at their site and for ensuring that any amendments are implemented in a timely fashion. If a PI plans to take a leave of absence UCL CTC **must be informed promptly.** For absences greater than three months or where the PI is no longer able to perform his/her, duties at the site UCL CTC may terminate recruitment at site. A new suitable replacement PI must be identified by the site and UCL CTC notified.

UCL CTC may terminate recruitment at a site where a suitable replacement PI has not been identified within three months.

4.1.2. Training requirements for site staff

All site staff must be appropriately qualified by education, training and experience to perform the trial related duties allocated to them, which must be recorded on the site delegation log.

CVs for all staff must be kept up-to-date, signed and dated and copies held in the Investigator Site File (ISF). A current, signed copy of the CV with evidence of GCP training (or copy of GCP certificate) for the PI must be forwarded to UCL CTC upon request.

GCP training is required for all staff responsible for trial activities. The frequency of repeat training may be dictated by the requirements of their employing institution, or 2 yearly where the institution has no policy, and more frequently when there have been updates to the legal or regulatory requirements for the conduct of clinical trials.

4.2. Site initiation and Activation

4.2.1. Site initiation

Before a site is activated, the UCL CTC trial team will arrange a site initiation with the site which the PI, the pharmacy lead and site research team must attend. The site will be trained in the day-to-day management of the trial and essential documentation required for the trial will be checked.

Site initiation will be performed for each site by telephone/videoconference with site. Re-initiating sites may be required where there has been a significant delay between initiation and enrolling the first patient..

4.2.2. Required documentation

The following documentation must be submitted by the site to UCL CTC prior to a site being activated by the UCL CTC trial team:

- Site Registration Form (identifying relevant local staff)
- Relevant institutional approvals
- A completed site delegation log that is initialled and dated by the PI (with all tasks and responsibilities delegated appropriately)
- Completed site contacts form (with contact information for all members of local staff)
- A signed and dated copy of the PI's current CV (with documented up-to-date GCP training, or copy of GCP training certificate)
- Trial specific prescription

In addition, the following agreements must be in place:

- A signed Model Agreement for Non-Commercial Research (mNCA) between the Sponsor and the relevant institution (usually an NHS Trust/Health Board)

4.2.3. Site activation

Once the UCL CTC trial team has received all required documentation and the site has been initiated, a site activation letter will be issued to the PI, at which point the site may start to approach patients.

Refer to the Summary of Drug Arrangements document for details of the initial supplies of Pembrolizumab.

Following site activation, the PI is responsible for ensuring:

- adherence to the most recent version of the protocol
- all relevant site staff are trained in the protocol requirements
- appropriate recruitment and medical care of patients in the trial
- timely completion and return of CRFs (including assessment of all adverse events)
- prompt notification and assessment of all serious adverse events
- that the site has facilities to provide **24 hour medical advice** for trial patients

5. INFORMED CONSENT

Sites are responsible for assessing a patient's capacity to give informed consent.

Sites must ensure that all patients have been given the current approved version of the patient information sheet, are fully informed about the trial and have confirmed their willingness to take part in the trial by signing the current approved consent form.

Sites must assess a patient's ability to understand verbal and written information in English and whether or not an interpreter would be required to ensure fully informed consent. If a patient requires an interpreter and none is available, the patient should not be considered for the trial.

The PI, or, where delegated by the PI, other appropriately trained site staff, are required to provide a full explanation of the trial and all relevant treatment options to each patient prior to trial entry. During these discussions, the current approved patient information sheet for the trial should be discussed with the patient.

A **minimum of twenty four (24) hours** should be allowed for the patient to consider and discuss participation in the trial.

Written informed consent on the current approved version of the consent form for the trial must be obtained before any trial-specific procedures are conducted. The discussion and consent process must be documented in the patient medical notes.

Site staff are responsible for:

- checking that the current approved version of the patient information sheet and consent form are used
- checking that information on the consent form is complete and legible
- checking that the patient has initialled all relevant sections and signed and dated the form
- checking that an appropriate member of staff has countersigned and dated the consent form to confirm that they provided information to the patient
- checking that an appropriate member of staff has made dated entries in the patient's medical notes relating to the informed consent process (i.e. information given, consent signed etc.)
- following pre-registration, adding the patients' trial number to all copies of the consent form, which should be filed in the patient's medical notes and investigator site file.
- giving the patient a copy of their signed consent form, patient information sheet, and upon full registration, giving the patient a patient contact card

The right of the patient to refuse to participate in the trial without giving reasons must be respected. All patients are free to withdraw at any time. Also refer to section 15 (Withdrawal of Patients).

6. SELECTION OF PATIENTS

6.1. Screening Log

A screening log must be maintained and appropriately filed at site. Sites should record each patient screened for the trial and the reasons why they were not registered in the trial if this is the case. The log must be sent to UCL CTC when requested.

6.2. Patient Eligibility

There will be no exception to the eligibility requirements at the time of full registration. Queries in relation to the eligibility criteria must be addressed prior to full registration. Patients are eligible for the trial if all the inclusion criteria are met and none of the exclusion criteria applies.

Patients' eligibility must be confirmed by an investigator who is suitably qualified and who has been allocated this duty, as documented on the site staff delegation log, prior to registering the patient. Confirmation of eligibility must be documented in the patients' medical notes and on the registration CRF.

Patients must give written informed consent before any trial specific screening investigations may be carried out. Refer to section 9.1 (Registration Assessments) for the list of assessments and procedures required to evaluate the suitability of patients prior to entry.

6.2.1. Inclusion criteria

1. Patients ≥18 years old
2. Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (see appendix 3)
3. Presence of measurable disease, (defined as a detectable level of IgM paraprotein) and fulfils other World Health Organisation (WHO) diagnostic criteria for WM
4. Relapsed or refractory WM who have received ≥1 prior lines of therapy
5. Adequate renal function: estimated creatinine clearance ≥ 30ml/min as calculated using the Cockroft-Gault equation
6. Adequate liver function, including:
    - Bilirubin ≤1.5 x the upper limit of normal (ULN)
    - Aspartate or alanine transferase (AST or ALT) ≤2.5 x ULN
7. Adequate organ and bone marrow function:
    - Neutrophils ≥0.5x10^9/L
    - Platelets ≥25x10^9/L

   Note: Growth factor and/or transfusion support is permissible to stabilize participant prior to study treatment if needed. No lower limit if cytopenia is related to WM infiltration in the bone marrow.
8. Willing to comply with the contraceptive requirements of the trial (see section 6.3.4)
9. Negative serum or highly sensitive urine pregnancy test for women of childbearing potential (WOCBP)
10. Written informed consent

6.2.2. Exclusion criteria

1. Refractory to rituximab as defined by progression on/within 6 months of finishing a rituximab based regimen
2. Women who are pregnant or breastfeeding, or males expecting to conceive or father children at any point from the start of treatment until 4 months after the last administration of pembrolizumab
3. Clinically significant cardiac disease within 6 months prior to registration including unstable angina or myocardial infarction, uncontrolled congestive heart failure (NYHA class III-IV), and unstable arrhythmias requiring therapy, with the exception of extra systoles or minor conduction abnormalities. Stable and controlled atrial fibrillation is not an exclusion.
4. History of significant cerebrovascular disease in last 6 months
5. Known central nervous system involvement of WM
6. Clinically significant active infection requiring antibiotic or antiretroviral therapy
7. Significant concurrent, uncontrolled medical condition including, but not limited to, renal, hepatic, haematological, gastrointestinal, endocrine, pulmonary, neurological, cerebral or psychiatric disease
8. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or *in situ* cervical cancer that has undergone potentially curative therapy
9. Active autoimmune disease apart from:
    - Type I diabetes or thyroid disease, controlled on medication
    - Skin conditions such as psoriasis, vitiligo or alopecia not requiring systemic treatment
    - Auto-immune thrombocytopenia, thought to be secondary to WM, provided that platelet count meet the criteria specified above, on daily doses of corticosteroid ≤10mg prednisolone or equivalent
10. Prior history of haemolytic anaemia (either warm or cold)
11. History of non-infective colitis
12. History of (non-infectious) pneumonitis that required steroids or has current pneumonitis
13. Systemic anti-cancer therapy within 4 weeks prior to trial registration (except for BTK inhibitors, which may continue until 48 hours prior to the start of cycle 1, day 1 of trial treatment)
14. Received a T cell depleting antibody (e.g. Campath) within 3 months prior to starting treatment
15. Received a live vaccine or live-attenuated vaccine within 30 days prior to starting treatment
16. Chronic or ongoing active infectious disease requiring systemic treatment such as, but not limited to, chronic renal infection, chronic chest infection with bronchiectasis, tuberculosis and active hepatitis
17. Patients who have received treatment with any non-marketed drug substance or experimental therapy within 4 weeks prior to starting treatment (unless prior agreement with the TMG)
18. Patients known or suspected of not being able to comply with a study protocol (e.g. due to alcoholism, drug dependency or psychological disorder)
19. Positive serology for Hepatitis B defined as a positive test for HepB surface antigen (HBsAg). Note: patients who are HepB core antibody (HBcAb) positive

will only be eligible for the study if the HepB virus deoxyribonucleic acid (HBV DNA) test is negative and patients are willing to undergo monthly monitoring for HBV reactivation

20. Positive serology for Hepatitis C defined as a positive test for HCV antibody
21. Major surgery within 4 weeks prior to trial registration
22. Prior therapy with an anti-PD-1,anti-PD-L1 or CTLA4 monoclonal antibody
23. Prior allogeneic bone marrow transplantation
24. Diagnosis of prior immunodeficiency or organ-transplant requiring immunosuppressive therapy or known HIV or acquired immunodeficiency syndrome (AIDS)-related illness
25. Current or prior use of immunosuppressive therapy within 7 days prior to start of treatment except the following: intranasal, inhaled, topical steroids or local steroid injections (e.g. Intra-articular injections); a short course of oral prednisolone (a maximum of 10mg/day for 5 days) can be used within 7 days of cycle 1 day 1 if there are concerns around IgM flare, following BTK inhibitor discontinuation
26. Known or suspected hypersensitivity to components of pembrolizumab and/or rituximab (or other CD20 monoclonal antibody)

6.3. Pregnancy and birth control

6.3.1. Pregnancy and birth control

Definition of women of childbearing potential (WOCBP) and fertile men

A woman of childbearing potential (WOCBP) is a sexually mature woman (i.e. any female who has experienced menstrual bleeding) who:

- has not undergone a hysterectomy or bilateral oophorectomy/salpingectomy
- has not had premature ovarian failure confirmed by a specialist gynaecologist
- is not postmenopausal (i.e. a post-menopausal woman is a female who has not had menses at any time in the preceding 12 consecutive months without an alternative medical cause)
    - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
    - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrolment.

A man is considered fertile after puberty unless permanently sterile by bilateral orchidectomy.

6.3.2. Risk of exposure to trial treatment during pregnancy

The risk of exposure to trial treatment has been evaluated using the safety information available in the IB for the IMP (pembrolizumab) and the SPC for the IMP (rituximab).

There are no data on the use of pembrolizumab in pregnant women.

Pembrolizumab

Animal reproduction studies have not been conducted with pembrolizumab; however, in murine models of pregnancy blockade of PD-L1 signalling has been shown to disrupt tolerance to the foetus and to result in an increased foetal loss. These results indicate a potential risk, based on its mechanism of action, that administration of pembrolizumab during pregnancy could cause foetal harm, including increased rates of abortion or stillbirth. Human immunoglobulins G4 (IgG4) are known to cross the placental barrier and pembrolizumab is an IgG4; therefore, pembrolizumab has the potential to be transmitted from the mother to the developing foetus. Pembrolizumab should not be used during pregnancy unless the clinical condition of the woman requires treatment with pembrolizumab. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of semen.

Rituximab

Developmental toxicity studies (using Mabthera) have been performed in cynomolgus monkeys at doses up to 100 mg/kg (treatment on gestation days 20-50) and have revealed no evidence of toxicity to the foetus due to rituximab. However, dose dependent pharmacologic depletion of B cells in the lymphoid organs of the foetuses was observed, which persisted post-natally and was accompanied by a decrease in IgG level in the newborn animals affected. B cell counts returned to normal in these animals within 6 months of birth and did not compromise the reaction to immunisation.

Rituximab can be retained for a long time in B cell depleted patients and therefore WOCBP should be advised to use effective contraceptive methods during and for 12 months after treatment with rituximab.

Overall, the trial treatment has been assessed as having a high risk of teratogenicity/fetotoxicity.

6.3.3. Pregnancy testing

All female participants who are WOCBP must have a negative serum or highly sensitive urine pregnancy test (minimum sensitivity 25 IU/l or equivalent units of HCG) pre-registration and within 72 hours prior to the first dose of trial treatment. Pregnancy testing should be repeated before each cycle of trial treatment. Pregnancy testing should be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected.

6.3.4. Contraceptive Advice

All female participants who are WOCBP must consent to use one of the following methods of highly effective contraception from the start of treatment until 12 months after the last administration of an IMP. Methods with low user dependency are preferable, particularly where introduced as a result of participation in the trial.

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - oral (e.g. desogestrel)
  - injectable
  - implantable[1]
- intrauterine device (IUD)[1]
- intrauterine hormone-releasing system (IUS)[1]
- bilateral tubal occlusion[1]
- vasectomised partner[1,2]
- sexual abstinence[3]

1. Contraception methods that are considered to have low user dependency.

2. Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

3. Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

Requirement for male patients with female partners who are pregnant or WOCBP

Due to the risk of genotoxicity and/or risk to the foetus from exposure to seminal fluid:

- Male patients (including male patients who have had vasectomies) must consent to use condoms with female partners who are WOCBP or partners who are pregnant, from the start of treatment until 4 months after the last administration of an IMP.
- Male patients must also advise their female partners who are WOCBP of the requirement for contraceptive requirements as listed for female patients who are WOCBP.

For female and male patients:

- The method(s) of contraception used must be stated in the patient medical notes. The medical notes of male participants should include a statement that the female partner has been informed about contraception advice.

6.3.5. Action to be taken in the event of a pregnancy

Female patients:

If a female patient becomes pregnant:

- prior to initiating treatment or during treatment, the patient will be withdrawn from the trial/further treatment and, if they consent to pregnancy monitoring, followed up until pregnancy outcome. It is recommended that the patient be followed up on a monthly basis.
- after the end of the treatment, until 12 months after the last administration of an IMP, the patient will be followed up until pregnancy outcome if they consent to pregnancy monitoring. It is recommended that the patient be followed up on a monthly basis.

Male patients:

If a female partner of a male patient becomes pregnant between the patient's start of treatment and 4 months after the last administration of an IMP, the male participant can continue with the study whilst their female partner will be followed up if they have given consent to pregnancy monitoring. It is recommended that the pregnant partner be followed up on a monthly basis.

Notification to UCL CTC – refer to Pregnancy Report Processing (see section 12.7)

7. REGISTRATION PROCEDURES

7.1. Pre-Registration

The purpose of preliminary registration is to allow patients likely to be eligible for the trial but where final confirmation of eligibility based on their bone marrow biopsy is pending, to be allocated a trial number for use when sending baseline tissue samples to the central laboratory (see section 10 for further details on required samples). Samples without a trial number will not be accepted by the central laboratory.

In order to undertake preliminary registration, the following criteria must be met:

- The patient must have given written informed consent for the trial
- The site investigator must have confirmed the patient is potentially eligible based on assessments performed to date

The site must then complete the preliminary registration form and send it to the UCL CTC via email, **before** sending samples to the central laboratory.

N.B. When emailing forms, patient identifiable information from the form (e.g. initials, day and month of birth) must be redacted before it is emailed to ctc.pembroWM@ucl.ac.uk. The identifiable information must be provided to the UCL CTC via telephone so that UCL CTC can transcribe this information on to the form. The un-redacted form must then be posted to the UCL CTC, and a copy kept in the patient file at site.

Registration telephone number:	+44 (0)20 7679 9860
Registration email address:	ctc.pembroWM@ucl.ac.uk
UCL CTC Office hours:	09:00 to 17:00 Monday to Friday, excluding Bank Holidays

Once the UCL CTC has confirmed that the patient has been consented appropriately and is provisionally eligible for the trial, they will assign a unique trial number for the patient and email confirmation of the trial number to the main contact for the site.

This trial number will remain the patient's unique trial identifier throughout the trial, and should be used in all communications sent during the trial.

The patient must **under no circumstances** start any trial treatment until the patient has completed the full registration process (see section 7.2) and the UCL CTC have confirmed that the patient may start trial treatment.

If, after being allocated a trial number, a patient is found to be ineligible for the trial, and will not be proceeding to full registration, the site must inform the UCL CTC, quoting the patient's unique trial number and date of sample dispatch. The UCL CTC will then contact the central laboratory to request destruction of the patient's samples and will email the site to confirm destruction.

7.2. Registration

Full patient registration will be undertaken centrally at UCL CTC and this **must be performed prior to commencement of any trial treatment.** Registration evaluations should be carried out at sites as detailed in section 9.1 (Registration Assessments).

Following -registration evaluations, confirmation of eligibility and consent of a patient at a site, the registration eligibility checklist and full registration CRF form must be fully completed and emailed to UCL CTC. These will be used to confirm patient eligibility. If further information is required UCL CTC will contact the person requesting registration to discuss the patient and request updated forms to be faxed.

Once eligibility has been confirmed UCL CTC will email confirmation of the patient's inclusion in the trial to the PI, main contact and pharmacy.

Registration telephone number:	+44 (0)20 7679 9860
Registration email address:	ctc.pembroWM@ucl.ac.uk
UCL CTC Office hours:	09:00 to 17:00 Monday to Friday, excluding Bank Holidays

Once a patient has been fully registered onto the trial they must be provided with the following:

- A patient contact card. Site contact details for 24 hour medical care must be added to this card and patients advised to carry this with them at all times while participating in the trial

After full registration has been confirmed the PembroWM GP letter must also be completed and sent to the patient's GP.

7.3. Initial Trial Drug Supply

Merck Sharp & Dohme (MSD) Limited will provide pembrolizumab free of charge for the duration of the study for appropriately enrolled subjects.

Refer to Summary of Drug Arrangements document for details of initial supply of pembrolizumab for the trial.

Rituximab is to be supplied from Hospital Commercial Stock as detailed in the Summary of Drug Arrangements document.

8. TRIAL TREATMENT

Investigational Medicinal Products (IMPs)

For the purpose of this protocol, the IMPs are:

- Pembrolizumab (MK 3475)
- Rituximab (note: biosimilars are allowed)

Please also refer to Summary of Drug Arrangements document (SoDA) for full arrangements for the trial.

8.1. Investigational Medicinal Products

Supplied IMP

Pembrolizumab (also referred to as MK-3475) (clear to slightly opalescent, colourless to slightly yellow solution for infusion [100 mg / 4 ml vial]) is supplied free of charge by MSD Limited. Pembrolizumab is not licensed for this indication.

Please refer to the Summary of Drug Arrangements document for further details of supply, packaging and storage conditions etc.

IMP from hospital stock

Rituximab (colourless concentrate for solution for infusion [100 mg / 10 ml vial or 500 mg / 50 ml vial]) is to be provided from hospital commercial stock. Pharmacies must ensure adequate supplies for the trial. Biosimilar (e.g. Truxima) products are permitted in the trial.

Please refer to local policy and the relevant SPC for handling and storage conditions.

8.2. Treatment Summary

Patients with relapsed/refractory WM meeting the eligibility criteria will be fully registered into the study. Patients will be treated with rituximab 375mg/m^2 IV infusion and pembrolizumab 200mg IV infusion on a 3 weekly cycle, for a maximum of 18 cycles on the following days:

- Cycle 1:
  - Rituximab 375mg/m^2 - days 1, 8 and 15
  - Pembrolizumab 200mg - day 2
- Cycle 2:
  - Rituximab 375mg/m^2 - day 1
  - Pembrolizumab 200mg - day 1
- After cycle 2:
  - Rituximab 375mg/m^2 - 12 weekly on day 1 (cycles 6, 10, 14 & 18)
  - Pembrolizumab 200mg - day 1 of every cycle

Treatment will continue until cycle 18 unless disease progression or discontinuation due to toxicity or any other cause (whichever occurs sooner). Patients who experience

disease progression at any point during the trial will have the study therapy ceased and be managed as per standard of care at their institution.

Where both rituximab and pembrolizumab are delivered on the same day, rituximab should be administered first.

See diagram below for visual representation.

Cycle	**1**				**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**	**18**
Day	1	2	8	15	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Rituximab (375 mg/m^2 IV)	X		X	X	X				X				X				X				X
Pembrolizumab (200mg IV)		X			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

8.3. Trial Treatment Details

8.3.1. Criteria to receive treatment

Full blood count (FBC) and tests of renal and hepatic function should be assessed prior to every cycle (within 3 days prior to treatment) to ensure the following criteria are met:

- Neutrophils ≥ 0.5 x 10^9/L
- Platelets ≥ 25 x 10^9/L
- AST or ALT ≤ 2.5 x ULN
- Bilirubin ≤ 1.5 x ULN

If the above criteria are not met (for reasons other than disease bone marrow infiltration – see below) prior to treatment, the cycle should be delayed until the blood counts have recovered (see section 8.4 and 8.5 for information on dose delays and treatment discontinuation due to adverse events).

8.3.1.1. Patients with high levels of WM bone marrow infiltration at registration

Patients registered on to the trial with a high level of WM infiltration in the bone marrow, and neutrophils and platelets lower than 0.5 x 10^9/L and 25 x 10^9/L respectively, are permitted to receive treatment providing these blood counts are no lower than the level at registration. If either blood count taken prior to a treatment cycle is lower than the level at registration, the cycle should be delayed until the blood counts have recovered to the registration level. If in subsequent cycles the neutrophils and platelet counts have improved to above 0.5 x 10^9/L and 25 x 10^9/L respectively, these levels should be met for all future cycles of treatment, if not, treatment should be delayed.

8.3.2. Re-scheduling treatment for logistical reasons

If for logistical reasons (e.g. bank holiday), treatment cannot take place on the scheduled day, treatment days can be re-scheduled as follows:

- Doses can be brought forward a maximum of 2 days.
- Doses can be delayed for a maximum of 7 days, however, if treatment is delayed for longer than 2 days, all subsequent doses for the remainder of trial treatment should be rescheduled in line with the delayed dose. For example, if C3D1 is delayed by 3 days, C4D1 should take place 3 weeks after the delayed C3D1 date.

For dose delays as a result of adverse events please refer to section 8.4.

8.3.3. Administration for IgM flare

Prior to the first cycle, if the total IgM is >40, pre-emptive plasmapheresis is recommended to get total IgM <40 and prevent IgM flare – defined as a >25% increase in total IgM. This phenomenon has been associated with single agent rituximab therapy in this setting, and can be associated with symptomatic hyperviscosity and/or escalation of WM related symptoms (e.g. neuropathy).

See section 8.4.6 for further details on IgM flare management.

8.3.4. Pembrolizumab administration

Pembrolizumab is a potent and highly selective humanised monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2.

The PembroWM Summary of Drug Arrangements document (SoDA) must be referred to for detailed information regarding the handling, storage, preparation and administration of pembrolizumab. A summary is outlined below:

Supply and Storage:

Pembrolizumab will be supplied in a kit containing 2 x 4mL solution for infusion vials (100mg/4ml). It should be stored in its original carton at refrigerated conditions 2 – 8 °C and protected from light.

Preparation:

Pembrolizumab infusion solutions should be prepared in 0.9% Sodium Chloride Injection or 5% Dextrose Injection and the final concentration should be between 1 mg/mL and 10 mg/mL. Please note, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available. Once diluted the product should be used as soon as possible, however storage allowances for IV bags are permitted (see SoDA for detailed information).

Administration:

Pembrolizumab should be given intravenously over 30 minutes, with a window of -5 and +10 minutes, every 3 weeks at a dose of 200mg using an infusion pump. A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-line filter made of polyethersulfone (PES)

or 0.2 to 5 µm add-on filter should be used when administering the product. Refer to the SoDA for the infusion materials that are compatible with pembrolizumab.

Important Information:

- Do not use pembrolizumab if discolouration is observed.
- Do not shake or freeze the vial(s) or infusion solution.
- Do not administer the product as an intravenous push or bolus.
- Unused infusion solution for injection should not be used for another infusion of the same subject or different subject.
- Do not combine, dilute of administer it as an infusion with other medicinal products or co-administer other drugs through the same infusion line.
- Contact UCL CTC immediately if there is any departure from the guidance listed in the PembroWM Summary of Drug Arrangements document.

8.3.5. Rituximab administration

Rituximab (or biosimilar equivalent) should be given intravenously at a dose of 375 mg/m^2 for a maximum of 1 year as indicated in the tables above. Rituximab should be administered as per local policy.

Dose banding of rituximab is allowed as per local policy. If a patient's weight changes, local policy for dose recalculation should be followed. Rapid infusion of rituximab is permitted as per local policy. For further details on the administration please refer to the SPC for details.

Patients should receive pre-medication prior to rituximab infusion as per standard local policy. Below serves as suggested guidance to the Investigator in the absence of standard local policies:

Guidance on pre-medication prior to rituximab infusion (to be given within 30 mins to 2 hours prior to treatment):

Analgesic: Paracetamol or equivalent	Antihistamine: chlorpheniramine or cetirizine equivalent	Glucocorticoid: dexamethasone, or equivalent
1000 mg orally (PO)	10 mg IV (chlorphenamine) or 10 mg PO (cetirizine)	8 mg (hydrocortisone 200 mg IV; prednisolone 50 mg)

Supportive care (e.g. G-CSF/transfusions) may be given at the discretion of the local investigator as per local practice.

8.4. Management of Adverse Events

8.4.1. General considerations

Dose reductions for pembrolizumab and rituximab are not permitted.

The doses of pembrolizumab and rituximab should be delayed as required according to sections below when experiencing a treatment related adverse event. In case of a treatment delay, both drugs should be withheld. This includes AEs related to only one IMP (e.g. a rituximab related AE results in both rituximab and pembrolizumab being withheld).

Treatment cycles should be delayed, and not be omitted as a result of adverse events, and upon resolution treatment should resume at the scheduled cycle.

If any immune-related AE does not resolve within 12 weeks of the last dose of an IMP, or if corticosteroids cannot be reduced to ≤10 mg prednisolone or equivalent per day within 12 weeks then treatment should be permanently discontinued. See section 8.5 for full treatment discontinuation details.

Treatment should also be delayed or discontinued if any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with pembrolizumab or rituximab dosing.

8.4.2. Pembrolizumab related adverse events

Immune related adverse events

If a patient experiences a pembrolizumab immune-related event, trial treatment should be withheld or discontinued as per the table below.

Where treatment is withheld, treatment should resume once the adverse event has reduced to grade 1 or 0 (as per table below). Corticosteroid taper should be initiated upon the adverse event improving to grade 1 or less and continue to taper over at least 4 weeks. Tapering should be performed as per local clinical practice.

For severe and life-threatening immune related adverse events, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if immune related adverse events cannot be controlled by corticosteroids.

Toxicity Management Guidelines for Immune-related AEs associated with Pembrolizumab

Immune-related AEs	**Severity grade** CTCAE v5.0	**Action taken**	**irAE management**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold treatment	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisolone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue treatment		
Diarrhoea / Colitis	Grade 2 or 3	Withhold treatment	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisolone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhoea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhoea suspecting colitis should consider GI referral and performing endoscopy to rule out colitis. • Participants with diarrhoea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4 or recurrent Grade 3	Permanently discontinue treatment		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold treatment	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisolone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue treatment	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisolone or equivalent) followed by taper	

Immune-related AEs	Severity grade CTCAE v5.0	Action taken	irAE management	Monitor and follow-up
Type 1 diabetes mellitus (T1DM) or Hyperglycaemia	Newly onset T1DM or Grade 3 or 4 hyperglycaemia associated with evidence of β-cell failure	Withhold treatment [1]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycaemic in participants with hyperglycaemia	• Monitor participants for hyperglycaemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold treatment	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue treatment [1]		
Hyperthyroidism	Grade 2	Continue treatment	• Treat with nonselective beta-blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue treatment [1]		
Hypothyroidism	Grade 2-4	Continue treatment	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis associated with increased creatinine or acute kidney injury	Grade 2	Withhold treatment	• Administer corticosteroids (prednisolone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue treatment		
Neurological Toxicities	Grade 2	Withhold treatment	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm aetiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue treatment		
Myocarditis	Grade 1	Withhold treatment	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm aetiology and/or exclude other causes
	Grade 2-4	Permanently discontinue treatment		
Exfoliative Dermatologic Conditions	Suspected Steven-Johnson syndrome (SJS), Toxic epidermal necrolysis (TEN) or Drug rash with eosinophilia and systemic symptom (DRESS)	Withhold treatment	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm aetiology and/or exclude other causes

Immune-related AEs	**Severity grade** CTCAE v5.0	**Action taken**	**irAE management**	**Monitor and follow-up**
	Confirmed SJS, TEN or DRESS	Permanently discontinue treatment		
All other immune-related AEs	Persistent Grade 2	Withhold treatment	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm aetiology and/or exclude other causes
	Grade 3	Withhold or discontinue treatment based on type of event. *Events that require discontinuation include and not limited to: encephalitis and other clinically important irAEs (e.g. vasculitis and sclerosing cholangitis)*		
	Grade 4 or recurrent Grade 3	Permanently discontinue treatment		

1. *'Withhold or permanently discontinue treatment' is at the discretion of the investigator or treating physician.*

8.4.3. Pembrolizumab Infusion-related reactions

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided below:

Infusion Related Reaction Grade *CTCAE v5.0*	**Treatment**	**Premedication at Subsequent Dosing**
Grade 1 "Mild reaction; infusion interruption not indicated; intervention not indicated"	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 "Requires therapy or infusion interruption but responds promptly to symptomatic treatment" (e.g., antihistamines, NSAIDs, opiates, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Paracetamol Opiates Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Chlorphenamine 50 mg po (or equivalent dose of antihistamine). Paracetamol 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: "Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae" (e.g., renal impairment, pulmonary infiltrates) Grade 4: "Life-threatening; pressor or ventilatory support indicated"	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Adrenaline** IV fluids Antihistamines NSAIDs Paracetamol Opiates Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, adrenaline should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.		

8.4.4. Other pembrolizumab related adverse events

Any pembrolizumab related adverse events not included in the tables above should be managed as follows:

Adverse Event	**Severity grade** *CTCAE v5.0*	**Action taken**	**AE management**	**Resume treatment**
Any other pembrolizumab related AE	Grade 3[1]	Withhold treatment	Treat AE as per local policy	When event resolves to grade 1 or 0
	Grade 4[2]	Permanently discontinue treatment	Treat AE as per local policy	[redacted]

1. *Excluding fatigue, alopecia, and electrolyte disturbances that can be corrected and are unlikely to cause clinical safety concerns.*
2. *Excluding neutropenia <7 days, lymphopenia, amylase abnormalities that are not associated with clinical symptoms, grade 4 drug-related endocrinopathy AEs which are adequately controlled with physiologic hormone replacement, and electrolyte abnormalities that can be corrected and are not felt to be a cause for clinical safety concern.*

8.4.5. Rituximab related adverse events and Infusion related reactions

Dose reductions for rituximab are not permitted.

Refer to the appropriate rituximab SPC for rituximab related adverse event and infusion related reaction dose and AE management. If rituximab treatment is withheld on a cycle where pembrolizumab is administered, pembrolizumab should also be withheld and the cycle delayed until rituximab treatment can be continued.

All patients should also be monitored for toxicity including infusion related reactions (IRR), tumour lysis syndrome (TLS), progressive multifocal leukoencephalopathy (PML); infections; Stevens-Johnson syndrome (SJS); hyperglycaemia; renal and hepatic impairment; cardiac toxicity. Special precautions for use relating to these conditions and guidance for appropriate action are provided in the SPC.

8.4.6. IgM flare

If there are any clinical or laboratory concerns about IgM flare in the first 2 cycles, plasmapheresis/other supportive care may be instituted and the subject may remain on trial treatment.

If at any timepoint after the end of cycle 2 plasmapheresis is required for symptomatic relief of IgM flare (or for any other reason), then the patient will have to cease study therapy and be managed as per standard of care at their institution.

8.5. Treatment discontinuation

Trial treatment should be permanently discontinued if a patient experiences any of the following:

- disease progression whilst on trial
- an immune-related AE that does not resolve within 12 weeks of last dose of IMP
- treatment with corticosteroids cannot be reduced to ≤10 mg prednisolone or equivalent per day within 12 weeks
- Any grade 4 IMP related AE or laboratory abnormality apart from the following:
    - Grade 4 neutropenia <7 days (G-CSF may be instituted, and continued until neutrophils exceed 1.5x109/L, as per institutional policy)
    - Grade 4 lymphopenia
    - Grade 4 amylase abnormalities that are not associated with clinical symptoms
    - Grade 4 drug-related endocrinopathy AEs which are adequately controlled with physiologic hormone replacement
    - Electrolyte abnormalities that can be corrected and are not felt to be a cause for clinical safety concern.
- Grade 2 infusion related reaction (pembrolizumab related) for a second time despite receiving premedication
- Any grade 3 or 4 infusion related reaction (pembrolizumab related)

In instances where patients discontinue treatment, both pembrolizumab and rituximab should be discontinued. Patients will continue to be followed up in line with the protocol (see section 8.11).

8.6. Management of Overdoses, Trial treatment error, or Occupational Exposure

8.6.1. Overdose

Overdose is administration of a quantity of a trial treatment, either per administration or cumulatively, which is in excess of the protocol specified dose. The dose can either be evaluated as overdose by the trial team at site or by the Sponsor upon review.

There is no or little information on overdose with pembrolizumab or rituximab. In case of overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

Overdoses should be reported on an incident report (see section 13.1). Any adverse events resulting from an overdose should be reported as a SAE (see section 12.2.2 for reporting procedures). Overdoses of pembrolizumab that are in excess of 5 x the protocol specified dose (i.e. >1000mg), with or without adverse events resulting from an overdose, should be reported as an adverse event of special interest (AESI) (see section 12.1 and 12.4, Adverse event of special interest, for reporting procedures).

8.6.2. Medication error

A medication error is any unintentional error in prescribing, dispensing, or administration of an IMP or an investigational treatment while in the control of a healthcare professional or consumer. The error can be identified either by the trial team at site or by the Sponsor upon review.

If the medication error is an overdose, refer to the section above. Otherwise, medication errors should be reported on an incident report (see section 13.1). Any adverse events resulting from a medication error/investigational treatment error should be reported as an SAE (see section 12.2.2 for reporting procedures).

8.6.3. Occupational exposure

Exposure to an IMP as a result of one's professional or non-professional occupation. Occupational exposure should be reported on an incident report form (see section 13.1).

8.7. Supportive Care

Supportive Treatment

Patients should receive appropriate supportive care as deemed necessary by the treating investigator. The following supportive treatments are recommended:

- Tumour lysis syndrome medication (e.g. allopurinol*) daily for 7 days starting 24-48 hours prior to trial treatment (first cycle only)
  * rasburicase can be used as per local policy
- Antiviral prophylaxis (e.g. aciclovir) for the duration of treatment and for 3 months after completion
- PCP prophylaxis: Local PCP prophylaxis policy should be followed
- Moderate anti-emetic risk: Local anti-emetic policy should be followed

Suggested supportive care measures for the management of adverse events with potential immunologic aetiology are outlined above (section 8.4). Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such infection, which might require additional supportive care. The use of corticosteroids as supportive care for any other indication, such as anti-emetic therapy, during study is not permitted (see section 8.8 below).

G-CSF/transfusions may be given prior to treatment (including during screening) at the discretion of the local investigator as per local practice.

Concomitant Medication

Concomitant medication may be given as medically indicated at the local investigator's discretion.

Viral Hepatitis

Serious or life-threatening reactivation of viral hepatitis may occur in subjects treated with rituximab. Therefore, subjects who are anti-HB core positive, or have a known history of HBV infection, should receive prophylaxis as per local policy.

Vaccines

Even though no interaction studies have been performed, patients are permitted to receive COVID-19 vaccinations that are not live vaccines during treatment. The timing of COVID-19 vaccine administration and trial treatment should be determined by the Principal Investigator or a Co-investigator at site in the best interests of the patient, however it is recommended patients should not receive pembrolizumab within 24 hours of having a COVID-19 vaccine. Details of vaccine administration should be added to the Rolling Concomitant Medication CRF and medical records.

Administration of inactivated (killed antigen) vaccines is permitted.

8.8. Contraindications

The use of topical or systemic corticosteroids or immunosuppressants should be avoided during the trial (except in the case of immune-related toxicity - see sections 8.4) because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. If possible, patients should stop any steroid treatment prior to study entry. If, however, this is not possible, patients will be permitted to enter the trial if the dose of steroids is at a low dose (≤ 10 mg/day prednisolone or equivalent corticosteroid) which has been stable for at least 3 months. Unless due to immune-related toxicity, the initiation of steroid treatment during the study, or the necessity to increase the dose of any ongoing steroid treatment, should lead to withdrawal of the patient from the study.

Participants are prohibited from receiving the following therapies during treatment:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of study treatment, while participating in the study, and for 4 months after stopping treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. FluMist®) are live attenuated vaccines and are not allowed.

- Systemic corticosteroids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

Participants who, in the assessment by the Investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the study. All treatments that the Investigator considers necessary for a participant's welfare may be administered at the discretion of the Investigator in keeping with the community standards of medical care.

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing study. If there is a clinical indication for any medication or vaccination specifically prohibited during the study, discontinuation from study therapy or vaccination may be required. The final decision on any supportive therapy or vaccination rests with the Investigator. However, the decision to continue the participant on study treatment requires the mutual agreement of the Investigator, the Sponsor and the participant.

8.9. Pharmacy Responsibilities

All pharmacy aspects of the trial at participating sites are the responsibility of the PI, who may delegate this responsibility to the local pharmacist or other appropriately qualified personnel, who will be the Pharmacy Lead. The delegation of duties must be recorded on the site staff delegation log.

Pembrolizumab supplied for the PembroWM trial are for PembroWM trial patients only and must not be used outside the context of this protocol.

Pharmacists should refer to the Summary of Drug Arrangements document for further details on suppliers, ordering, labelling, storage, preparation and handling and destruction.

8.9.1. Temperature Excursions

All temperature excursions outside the storage conditions specified in the IB/Summary of Drug Arrangements document must be reported to UCL CTC as per the 'Pharmacy Procedure for Reporting Temperature Excursions' (see Pharmacy Site File).

Upon identifying an excursion:

- all affected trial stock must be quarantined IMMEDIATELY
- the 'Notification of Temperature Excursion' form must be completed and e-mailed to ctc.excursions@ucl.ac.uk or faxed to +44 (0)20 7679 9861.

Please note that UCL CTC must be informed immediately if a patient has been administered drug affected by a temperature excursion.

8.9.2. IMP accountability

The Pharmacy Lead must ensure that appropriate records are maintained.

These records must include accountability for each drug including: receipt (where applicable), dispensing, reconciliation and destruction of unused medication (on sponsor authorisation). Accountability forms will be supplied, and must be used, unless there is a prior agreement from UCL CTC to use alternative in-house records.

Copies of completed drug accountability logs must be submitted to UCL CTC for all trial patients upon request. Also refer to section 14.2 (Centralised Monitoring).

8.10. 24 Hour/Out-of-Office Hours Emergency Drug-Specific Advice

Pembrolizumab	**Office hours** 09:00 to 17:00 Monday to Friday, excluding Bank Holidays Contact UCL CTC 02076799860	**All other times** Outside office hours Merck Sharp & Dohme Ltd **Switchboard: 0208 154 8000**

8.11. Clinical Management after Treatment Discontinuation

After treatment discontinuation, further therapy will be at the discretion of the treating clinician. Subsequent treatment will not be considered part of the trial.

If a patient discontinues trial treatment early, they will remain on trial for follow up purposes unless they explicitly withdraw consent. Also refer to sections 9 (Assessments) and 15 (Withdrawal of Patients) for further details regarding treatment discontinuation, patient withdrawal from trial treatment and withdrawal of consent to data collection.

For all patients, disease status, late toxicity and survival will be followed up yearly until the last patient completes 2 years of follow up and the end of trial is declared.

8.12. Drug Provision after the End of the Trial

Patients will receive pembrolizumab for a maximum of 1 year or until disease progression, treatment discontinuation due to unacceptable toxicity, or any other reason (whichever occurs sooner). There are no arrangements in place for supply following progression or beyond a year of treatment.

9. ASSESSMENTS

Please also see Schedule of Events table in Appendix 2.

9.1. Registration Assessments

Patients must give written informed consent **before** any trial specific screening investigations may be carried out. The following assessments or procedures are required to evaluate the suitability of patients for the trial and should be performed within 28 days prior to full registration unless otherwise stated:

- Complete medical history including demographics (including age and sex) and prior treatments
    - Medical history should include disease diagnosis, β2-microglobulin levels at diagnosis, MYD88/CXCR4 status (if available), documenting relevant medical conditions
- Clinical examination: physical examination (including assessment of lymph node, liver and spleen size)
- Concurrent medication assessment
- Baseline adverse event assessment
- Observations: pulse, temperature, blood pressure, oxygen saturations
- Height and Weight
- Assessment of ECOG performance status (see appendix 3)
- Quality of life questionnaire – EORTC QLQ-C30 (to be completed before starting treatment)
- Full blood count (including red blood cell (RBC), haemoglobin (Hb), white blood cell (WBC) absolute neutrophil count (ANC), absolute lymphocyte count (ALC), haematocrit and platelets)
- Biochemistry (including bicarbonate, uric acid, albumin, alkaline phosphatase (ALP), alanine/aspartate transaminase (ALT/AST), total bilirubin, calcium, creatinine, potassium, sodium, glucose, urea, and estimated glomerular filtration rate (eGFR), U&E, liver function tests (LFT), LDH and amylase)
- Hepatitis B & C serology (HBsAg, HBsAb, HBcAb and HCV antibody) and HIV serology (note if HBcAb is positive HBV DNA testing will need to be performed)
- Electrocardiogram (ECG)
- Serum IgM, IgG and IgA
- Serum paraprotein
- Serum free light chain (SFLC)
- Direct antiglobulin test
- β2 microglobulin
- TSH, glucose and ACTH tests
- Highly sensitive urine or serum pregnancy test in women of childbearing potential (WOCBP)
- CT scan of neck, chest, abdomen and pelvis (NCAP) (within 28 days prior to starting trial treatment)
- Bone marrow aspirate and trephine (within 28 days prior to starting treatment).

Research samples (see section 10 for further details) – all samples below are optional and therefore should only be obtained from patients who have given consent, been pre-registered and assigned a trial number

- Bone marrow aspirate and trephine
- Peripheral blood
- Lymph node biopsy (if nodal disease) to be obtained within 28 days prior to the start of treatment
    - If it is not possible to obtain a biopsy within 28 days prior to start of treatment, then historical biopsy tissue may be retrieved and sent to HMDS.

9.2. Assessments during Treatment

Patients should be seen prior to and during each cycle of trial treatment. Investigations should be performed in line with the Schedule of Events table in appendix 2.

9.2.1. Assessments prior to each cycle of treatment

The following assessments should be performed within 3 days prior to each cycle:

- Clinical examination: physical examination (including assessment of lymph node, liver and spleen size)
- Concurrent medication assessment
- Adverse event assessment
- Observations: pulse, temperature, blood pressure, oxygen saturations
- Weight
- Assessment of ECOG performance status (see appendix 3)
- Full blood count (including red blood cell (RBC), haemoglobin (Hb), white blood cell (WBC) absolute neutrophil count (ANC), absolute lymphocyte count (ALC), haematocrit and platelets)
- Biochemistry (including bicarbonate, uric acid, albumin, alkaline phosphatase (ALP), alanine/aspartate transaminase (ALT/AST), total bilirubin, calcium, creatinine, potassium, sodium, glucose, urea, and estimated glomerular filtration rate (eGFR), U&E, liver function tests (LFT), and amylase)
- Electrocardiogram (ECG)
- Serum IgM, IgG and IgA
- Serum paraprotein
- Serum immunofixation (only to be performed if paraprotein not detectable)
- TSH, glucose and ACTH tests
- Highly sensitive urine or serum pregnancy test in women of childbearing potential (WOCBP)

9.2.2. Disease response assessments

In addition to the assessments before each treatment cycle (section 9.2.1), disease response is to be assessed at 12 weeks (+/- 3 days), 24 weeks (+/- 3 days) and 1 year (+/- 2 weeks) after commencing treatment. The following assessments should be performed at these time points:

- Concurrent medication assessment
- Adverse event assessment
- Full blood count (including red blood cell (RBC), haemoglobin (Hb), white blood cell (WBC) absolute neutrophil count (ANC), absolute lymphocyte count (ALC), haematocrit and platelets)
- Biochemistry (including bicarbonate, uric acid, albumin, alkaline phosphatase (ALP), alanine/aspartate transaminase (ALT/AST), total bilirubin, calcium, creatinine, potassium, sodium, glucose, urea, and estimated glomerular filtration rate (eGFR), U&E, liver function tests (LFT))
- Quality of life questionnaire – EORTC QLQ-C30 (only performed at week 24)
- Serum IgM, IgG and IgA
- Serum paraprotein
- Serum free light chain (SFLC)
- Serum immunofixation (only to be performed if paraprotein not detectable)
- CT scan of neck, chest, abdomen and pelvis (NCAP) (CT scans to be performed at week 24 and 1 year after commencing treatment in patients with evidence of measurable/nodal disease on baseline scan)
- Bone marrow aspirate and trephine (only to be performed at week 24 and year 1 after commencing treatment).

  Research samples – week 24 and 1 year only (see section 10 for further details) – all samples below are optional and therefore should only be obtained from patients who have given consent
- Bone marrow aspirate
- Peripheral blood

Response at these time points should be assessed using the International Working Group for WM response criteria (see appendix 4).

Patients will remain on treatment for a maximum of 1 year or until disease progression, discontinuation due to unacceptable toxicity or any other reason (whichever occurs sooner).

9.3. Assessments after Disease Progression

Following disease progression patients will be assessed at 5 months (+4 weeks) after the date of treatment discontinuation, over the phone or at a standard hospital visit for the purposes of:

- Adverse event assessment

Patients are then followed up for the trial annually from the date of progression for the following:

- Remission status assessment (investigations as per local protocols)

9.4. Assessments after treatment discontinuation (for reasons other than disease progression)

If patients complete treatment or are withdrawn from trial treatment early, for reasons other than disease progression the following assessments are to be performed on day 60 (+/- 3 days) following treatment discontinuation:

- Clinical examination: physical examination (including assessment of lymph node, liver and spleen size)
- Concurrent medication assessment
- Adverse event assessment
- Blood pressure
- Weight
- Assessment of ECOG performance status (see appendix 3)
- Full blood count (including red blood cell (RBC), haemoglobin (Hb), white blood cell (WBC) absolute neutrophil count (ANC), absolute lymphocyte count (ALC), haematocrit and platelets)
- Biochemistry (including bicarbonate, uric acid, albumin, alkaline phosphatase (ALP), alanine/aspartate transaminase (ALT/AST), total bilirubin, calcium, creatinine, potassium, sodium, glucose, urea, and estimated glomerular filtration rate (eGFR), U&E, liver function tests (LFT), LDH, and amylase)
- TSH, glucose and ACTH tests

Patients will then be assessed at 5 months (+4 weeks) after the date of treatment discontinuation, over the phone or at a standard hospital visit for the purposes of:

- Adverse event assessment

Patients are then followed up for the trial annually from the date of treatment discontinuation for the following:

- Remission status assessment (investigations as per local protocols)

10. EXPLORATORY BIOLOGICAL STUDIES

Biological studies are an important, but optional part of the trial. We will be collecting two types of sample: formalin fixed paraffin embedded tissue (bone marrow and lymph nodes) and blood.

The objective for the translational studies is to identify biomarkers of immunological response to the combination of pembrolizumab and rituximab in patients with relapsed/refractory WM. The translational research aims to inform our understanding of which patients respond to therapy and the underlying mechanisms of response to study treatment.

The following exploratory endpoints will be assessed:

- Assessment of PD-1 and PD-L1/ PD-L2 expression by FISH and immunohistochemistry (IHC). A positive correlation between high PD-L1 expression levels and responses to PD-1 inhibitors has been seen in advanced stage Hodgkin lymphoma patients); this would allow assessment of whether response to PD-1 inhibitors in WM is mediated by a similar mechanism. Assessment of the distribution of expression of PD-1 and PD-L1/ PD-L2 by IHC would further explore the hypothesis that signalling through this pathway contributes to the facilitative effect of the tumour microenvironment, and whether PD-1 inhibitors abrogate this interaction

- IHC to assess baseline and on-treatment changes to distribution and composition of immune response cells in the microenvironment

- Analysis of baseline biopsies (where available) to elucidate potential mechanisms of action of tumour response

- Assessment of treatment outcome according to tumour genotype, as determined by a Next Generation Sequencing (NGS) panel to include mutations in MYD88, CXCR4, TP53, BTK and PLCvgamma.

- Correlation of bone marrow response with reduction in serum IgM level. Previous studies have shown that there can be a discrepant response between the IgM and bone marrow

- Quantification of bone marrow involvement by morphologic assessment of trephine and flow cytometric assessment of aspirate for MRD with correlative assessment of MRD on peripheral blood at the same timepoints

Procedures to determine disease response assessment are mandatory in the trial as outlined in the Assessments section 9, however providing samples for the biological studies is **optional** to the patient. Additional samples should only be obtained from consenting patients. Patients who do not give their consent to donate the optional samples can still take part in the trial.

The Haematological Malignancy Diagnostic Service (HMDS) in Leeds will be responsible for analysis of the optional samples.

UCL CTC will inform HMDS if a patient has given consent for samples to be analysed as part of the trial and whether they have consented for surplus samples to be stored for future ethically approved research. Laboratory processing of any samples will not occur until patient consent has been confirmed. Please refer to the laboratory manual for details of how to send and log samples. Patients must be pre-registered and assigned a trial number before any samples are sent to HMDS.

We will be collecting four types of sample: lymph node biopsy (in FFPE), bone marrow aspirates trephine (in FFPE), bone marrow aspirate and peripheral blood.

Sites must keep a record of all samples sent to HMDS. See the Laboratory Manual for more details of how to track samples.

10.1. Lymph node and bone marrow trephine formalin fixed paraffin embedded blocks – optional to patient

In all patients, a bone marrow trephine sample should be obtained at pre-registration within 28 days prior to starting treatment.

In patients with nodal disease, a lymph node biopsy sample at pre-registration should also be taken. Preferably the nodal biopsy should be obtained within 28 days prior to C1D1. If not possible, then historical lymph node biopsy tissue may be sent.

Formalin fixed paraffin embedded (FFPE) tissue from the bone marrow trephine and lymph node should be sent to HMDS, Leeds. Please see the laboratory manual for further details of how to send

3µm sections of the tissue block will be taken and immunohistochemistry performed. At least ten markers will be assessed for each case including: CD5, CD10, CD79a, CD56, CD20, CD38, PD1, PD-L1, PD-L2. For PD-L1 and PD-L2, the percentage of malignant and non-malignant cells with positive staining will be reported and a central pathological report provided.

GEP will be performed using the HTG Immunopanel and the Affymetrix Human Transcriptome Array, which is a whole transcriptome array. These are two gene expression platforms currently being used in HMDS with bioinformatic support from within HMDS and in collaboration with the University of Leeds. The panel will include mutations in MYD88, CXCR4, TP53, BTK and PLCvgamma

Once analysis is complete, blocks can be returned to sites at their request.

10.2. Bone marrow samples – optional to patient

Research bone marrow aspirate samples will be obtained at the following time points:

Time point	Sample required
Pre-registration (up to 28 days prior to starting treatment)	5 ml bone marrow aspirate in EDTA
Week 24 post commencing treatment	5 ml bone marrow aspirate in EDTA
1 year post commencing treatment	5 ml bone marrow aspirate in EDTA

Multicolour flow panels will be performed on the marrow to identify the flow cytometry phenotype, with further samples taken halfway and at the end of therapy to assess minimum residual disease in bone marrow.

Bone marrow samples, or any products produced from these, will not be returned to sites.

10.3. Peripheral blood samples – optional to patient

Research peripheral blood samples will be obtained at the following time points:

Time point	Sample required
Pre-registration (up to 28 days prior to starting treatment)	20 (4 x 5) ml peripheral blood in EDTA
Week 24 post commencing treatment	20 (4 x 5) ml peripheral blood in EDTA
1 year post commencing treatment	20 (4 x 5) ml peripheral blood in EDTA

Multicolour flow panels will be performed on blood on the baseline sample to identify the flow cytometry phenotype, with further samples taken halfway through and at the end of therapy to assess minimal residual disease in peripheral blood.

Blood samples, or any products produced from these, will not be returned to sites.

11. DATA MANAGEMENT AND DATA HANDLING GUIDELINES

Data will be collected from sites on version controlled case report forms (CRFs) designed for the trial and supplied by UCL CTC. Data must be accurately transcribed onto trial CRFs and must be verifiable from source data at site. Examples of source documents are hospital records which include patient's medical notes, laboratory and other clinical reports etc.

Where copies of supporting source documentation (e.g. autopsy reports, pathology reports, CT scan images etc.) are being submitted to UCL CTC, the patient's trial number must be clearly indicated on all material and any patient identifiers removed/blacked out prior to sending to maintain confidentiality.

Please note that, for this trial, patients must consent to their NHS/CHI number being supplied to UCL CTC. This is required in order to allow for follow up via national registries where needed.

11.1. Completing Case Report Forms

All CRFs must be completed and signed by staff who are listed on the site staff delegation log and authorised by the PI to perform this duty. The PI is responsible for the accuracy of all data reported in the CRF.

All entries must be clear, legible and written in ballpoint pen. Any corrections made to a CRF at site must be made by drawing a single line through the incorrect item ensuring that the previous entry is not obscured. Each correction must be dated and initialed. Correction fluid must not be used.

The use of abbreviations and acronyms should be avoided.

11.2. Missing Data

To avoid the need for unnecessary data queries CRFs must be checked at site to ensure there are no blank fields before sending to UCL CTC (unless it is specifically stated that a field may be left blank). When data are unavailable because a measure has not been taken or test not performed, enter "ND" for not done. If an item was not required at the particular time the form relates to, enter "NA" for not applicable. When data are unknown enter the value "NK" (only use if every effort has been made to obtain the data).

11.3. Timelines for Data Return

CRFs must be completed at site and returned to UCL CTC as soon as possible after the relevant visit and within 4 weeks of the patient being seen. Registration forms should be faxed/emailed to UCL CTC. Death forms and SAE reports should be returned within 24 hours by fax/email.

Sites that persistently do not return data within the required timelines may be suspended from recruiting further patients into the trial by UCL CTC and subjected to a 'triggered' monitoring visit. See section 14.3 ('Triggered' On-Site/Remote Monitoring) for details.

11.4. Data Queries

Data arriving at UCL CTC will be checked for legibility, completeness, accuracy and consistency, including checks for missing or unusual values. Data Clarification Requests will be sent to the data contact at site. Further guidance on how data contacts should respond to data queries can be found on the Data Clarification Request forms.

12. PHARMACOVIGILANCE

12.1. Definitions

The following definitions have been adapted from Directive 2001/20/EC, ICH E2A "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" and ICH GCP E6.

Adverse Event (AE)

Any untoward medical occurrence in a patient treated on a trial protocol, which does not necessarily have a causal relationship with an IMP. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of an IMP, whether or not related to that IMP. See section 12.2.1 for AE reporting procedures.

Adverse Reaction (AR)

All untoward and unintended responses to an IMP related to any dose administered. A causal relationship between an IMP and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that at any dose:

- Results in death
- Is life threatening (the term "life-threatening" 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)
- Requires in-patient hospitalisation or prolongs existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Is otherwise medically significant (e.g. important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above)

See section 12.2.2 for SAE reporting procedures.

Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction, the nature or severity of which is not consistent with the applicable reference safety information.

i.e. an adverse event that meets all the following criteria:

- Serious – meets one or more of the serious criteria, listed under the definition of SAE above
- Related – assessed by the local PI or designee, or Sponsor as causally related to one or more elements of the trial treatment

- Unexpected – the event is not consistent with the applicable reference safety information

See section 12.3 for reporting procedures for these events.

Adverse event of special interest (AESI)

An AE that is of scientific and medical concern to the Trial Management Group and MSD for which rapid communication is required. The AESI may not meet the standard criteria for seriousness and it may occur outside the standard AE reporting timeframes for the trial.

See section 12.4 for the list of AESI for the trial and their reporting procedures for these events.

Urgent event

An AE that is protocol-related and requires completion of a trial specific Case Report Form.

See section 12.5 for a list of and reporting procedures for these events.

Overdose, Trial treatment error, or Occupational exposure

Refer to section 8.6 for details on reporting of these events.

12.2. Reporting Procedures

Adverse Event Term

An adverse event term must be provided for each adverse event. Wherever possible a valid term listed in the Common Terminology Criteria for Adverse Events (CTCAE) v5.0 should be used. This is available online at:

https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf

Severity grade of each adverse event must be determined by using CTCAE v5.

Causality

The relationship between the treatment and an adverse event will be assessed.

For AEs (including SAEs), the local PI or designee will assess whether the event is causally related to each IMP.

For SAEs, a review will also be carried out by the Sponsor's delegate.

Causal relationship to each trial treatment must be determined as follows:

- Related (reasonable possibility) to an IMP
- Not related (no reasonable possibility) to an IMP

UCL CTC will consider events evaluated as related to be adverse reactions.

12.2.1. Reporting of Adverse Events (AEs)

All adverse events that occur between informed consent and 5 months post last IMP administration must be recorded in the patient medical notes and the trial CRFs.

An AE cover sheet should be completed and a photocopy submitted to UCL CTC at each trial visit. The Adverse Event form should be submitted when there are new AEs or changes to existing AEs on the form. Any updates or changes to previously reported AEs must be initialed and dated. Report the worst grade observed for the AE on the form.

Those meeting the definition of a Serious Adverse Event (SAE) or Adverse Event of Special Interest (AESI) must also be reported to UCL CTC using the trial specific SAE Report. Also refer to section 12.2.2 (Reporting of Serious Adverse Events (SAEs)) and section 12.4 (Adverse Events of Special Interest)). Adverse events meeting the definition of an Urgent Event must be reported on an Urgent Event form (see section 12.5 Urgent Events).

Pre-existing conditions (i.e. conditions present at registration) do not qualify as adverse events unless they worsen or recur (i.e. improves/resolves and then worsens/reappears again).

E.g. an AE could be an exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition (worsening of the event). Another example of an AE is when a pre-existing condition improves during the trial (e.g. from grade 3 to grade 1) and then it worsens again (e.g. from grade 1 to grade 2), even if the event is of severity equal or lower to the original condition (improvement and recurrence of the event).

NB the disease(s) under study and its anticipated day-to-day fluctuations would not be an AE.

12.2.2. Reporting of Serious Adverse Events (SAEs)

All SAEs that occur between the signing of informed consent and 5 months post last IMP administration **(or after this date if the site investigator feels the event is related to an IMP)** must be submitted to UCL CTC by email within **24 hours** of observing or learning of the event, using the trial specific SAE Report. All sections on the SAE Report must be completed. If the event is **not being reported within 24 hours** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

Exemptions from SAE Report submission

For this trial, the following events are exempt from requiring submission on an SAE Report **unless considered to be related to an IMP (rituximab and/or pembrolizumab)**. Exempt events must be recorded in the relevant section(s) of the trial CRFs:

- events that occur more than 5 months post last IMP administration. Note: this does not include pregnancy related events (see section 12.7)
- disease progression
- rituximab **infusion** reactions, unless life-threatening or fatal

Please note that hospitalisation for elective treatment, palliative care, logistical or socio-economic reasons does not qualify as an SAE.

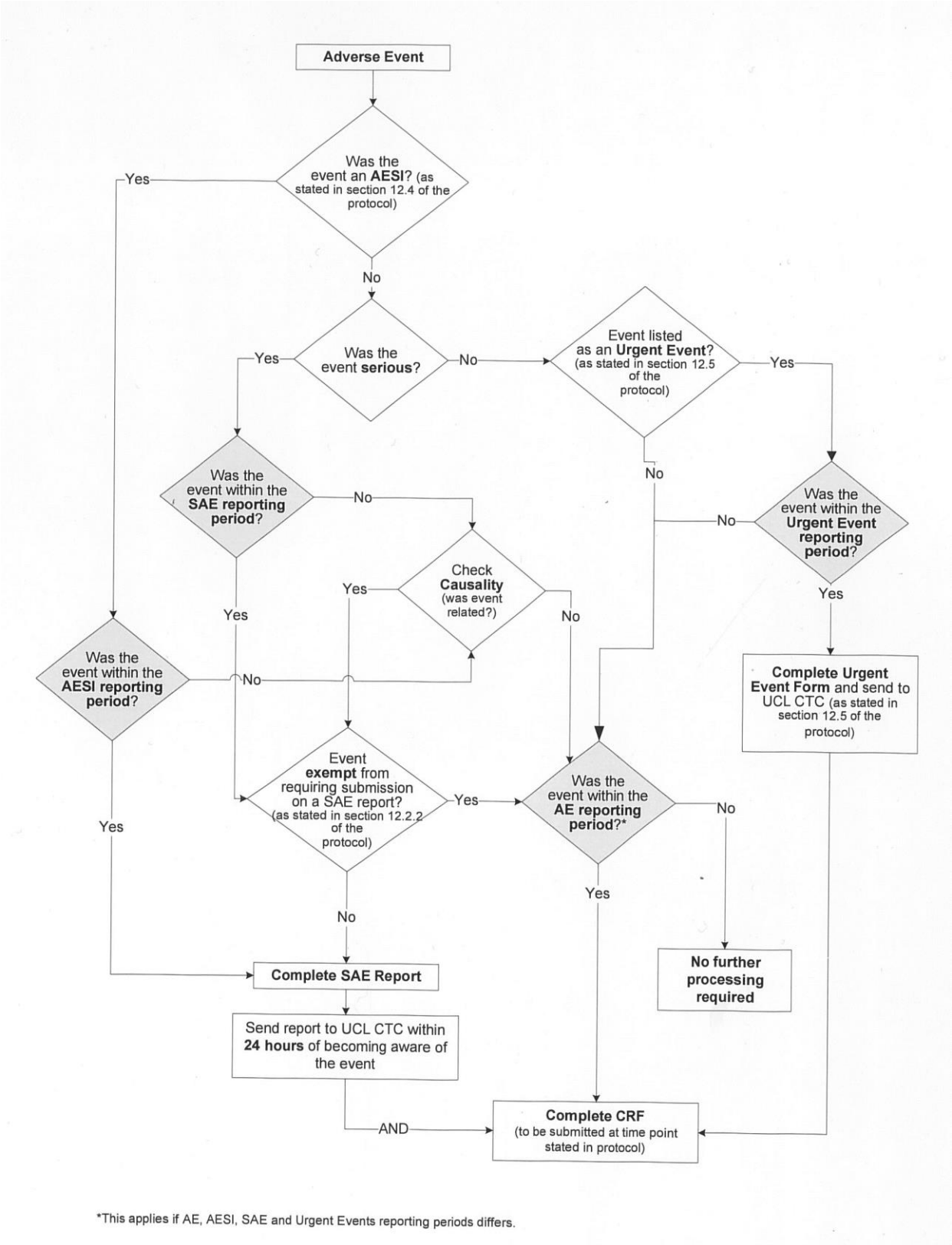
Completed SAE Reports must be emailed to UCL CTC within 24 hours of becoming aware of the event
Email: ctc.pembroWM@ucl.ac.uk

SAE Follow-Up Reports

UCL CTC will follow up all SAE/SARs until resolution and until there are no further queries.

Sites must ensure any new and relevant information is provided to UCL CTC promptly. If an event term changes or a new event is added, the causality must be re-assessed by an Investigator. If the event is not being reported to UCL CTC within 24 hours, the circumstances that led to the delay must be detailed in the SAE/SAR Report to avoid unnecessary queries.

Adverse Event Reporting Flowchart



SAE Processing at UCL CTC

On receipt of the SAE Report, UCL CTC will check for legibility, completeness, accuracy and consistency. Expectedness will be evaluated, to determine whether or not the case qualifies for expedited reporting, using the approved RSI (the list of expected adverse events in the IB for pembrolizumab and SPC for rituximab).

The CI, or their delegate (e.g. a clinical member of the TMG), will review the SAEs to perform an evaluation of causality on behalf of the sponsor. If UCL CTC has considered expectedness difficult to determine, the CI, or their delegate, will be consulted for their opinion at this time.

UCL CTC will submit all SAE Reports concerning patients who have received pembrolizumab to MSD Ltd according to the timelines outlined in the agreement between UCL and MSD Ltd.

12.3. SUSARs

If the event is evaluated as a Suspected Unexpected Serious Adverse Reaction (SUSAR), UCL CTC will submit a report to the MHRA and REC within the required timelines.

Wherever possible, evaluations of causal relationship by both the site and the Sponsor's clinical reviewer will be reported.

Informing Sites of SUSARs

UCL CTC will inform all UK PIs of any SUSARs that occur on the trial. PIs will receive a quarterly line listing which must be processed according to local requirements.

UCL CTC will forward reports received from MSD Ltd regarding SUSARs that have occurred on other trials using pembrolizumab to all PIs. These must be processed according to local requirements and filed with the IB.

12.4. Adverse events of special interest

The following adverse events of special interest for pembrolizumab must be collected between start of treatment and 5 months post last IMP administration. They must be reported on an SAE report regardless of their seriousness within **24 hours of becoming aware of the event.** All sections on the SAE Report must be completed. In terms of causality and expectedness, these reports will be processed as other SAE reports. The AESIs are:

- An overdose of pembrolizumab that is in excess of 5 x the protocol specified dose (i.e. >1000mg), with or without adverse events
- The following conditions met at the same time, at any time during the trial
    - An elevated AST or ALT lab value $\geq$3x the upper limit of normal (ULN) and
    - An elevated total bilirubin lab value that is $\geq$2x ULN and
    - An alkaline phosphatase lab value that is <2x ULN

All AEs of special interest must be reported by emailing a completed SAE report to UCL CTC within 24 hours of becoming aware of the event
Email: ctc.pembroWM@ucl.ac.uk

UCL CTC will submit all SAE Reports relating to AESIs in patients who have received pembrolizumab to MSD according to the timelines outlined in the agreement between UCL and MSD.

12.5. Urgent events

The following events must be collected and reported as urgent events between start of treatment and the end of the trial. They must be reported on the relevant CRF and e-mailed to UCL CTC within the timelines stated. If the event meets a definition of an SAE, an SAE report must also be submitted as per Section 12.2.2.

Event	Description	Form required	Timeframe
Death	Death from any cause (reportable at any point while the patient is enrolled onto the trial).	Death form	Within 24 hours of becoming aware of the death
Disease progression	Progression of WM, confirmed by standard local investigations (if local investigations are inconclusive, UCL CTC should be contacted for advice)	Disease progression form	Within 72 hours of becoming aware of confirmed progression

All Urgent Events must be reported by emailing a completed Urgent Event Form to UCL CTC within the timeframes specified above of becoming aware of the event
Email: ctc.pembroWM@ucl.ac.uk

12.6. Safety Monitoring

UCL CTC will provide safety information to the Trial Management Group (TMG) and the Independent Data Monitoring Committee (IDMC) on a periodic basis for review.

Trial safety data will be monitored to identify:

- whether disease-related events (exempt from SAE reporting as per section 12.2.2) appear to be enhanced by the IMPs
- new adverse reactions to the combination therapy
- a higher incidence in rare adverse events than is stated in the IB/SPC for an IMP

- trial related events that are not considered related to the IMP treatment, but may lead to changes to the trial documents. These would include events related to NIMPs.
- Review of incidence of AESIs as outlined in section 12.4

In addition to periodic reviews, an IDMC meeting can be triggered as a result of trial-treatment related deaths (see also section 17.3)

If UCL CTC identifies or suspects any issues concerning patient safety at any point during the trial, the CI or TMG will be consulted for their opinion, and if necessary the issue will be referred to the IDMC.

12.7. Pregnancy

Reporting Period

For any pregnancy exposure to trial treatment, the site must submit a trial specific Pregnancy Report to UCL CTC by email within **24 hours of learning of its occurrence**.

A pregnancy exposure to trial treatment includes:

- Pregnancy in a trial patient
- Pregnancy in a partner of a male trial patient
- Exposure to treatment in a partner of a male trial patient who was pregnant at the start of the trial

occurring between the start of trial treatment and 12 months after last IMP administration for female patients and between the start of trial treatment and 4 months after last IMP administration for female partners.

The site must request consent from the pregnant trial patient or pregnant female partner of a male patient to report information regarding a pregnancy using:

- For female patients: the trial-specific Pregnancy Monitoring Information Sheet and Informed Consent Form for trial patients
- For female partners of male patients: the trial specific Pregnancy Monitoring Information Sheet and Informed Consent Form for partners of trial patients

If consent is not given, the notification that a pregnancy has occurred will be retained by UCL CTC, however no further action will be taken on the information detailed in the report.

All pregnancies must be reported by emailing a completed Pregnancy Report to UCL CTC within 24 hours of becoming aware of the pregnancy
Email: ctc.pembroWM@ucl.ac.uk

Pregnancy Follow-Up Reports

For pregnant patients or partners who consent, their pregnancies must be followed-up at least monthly for up to 8 weeks after the end of the pregnancy (or later if there are ongoing issues) to collect information on any ante- and post-natal problems for both

mother and child. If significant new information is received, follow-up Pregnancy Reports must be submitted to UCL CTC by email within 24 hours of learning of the new information. In case of adverse outcome to the pregnancy reports must include an evaluation of the possible relationship of each trial treatment to the pregnancy outcome.

SAEs during pregnancy

Any SAE occurring in a pregnant patient must be reported using the trial specific SAE Report, according to SAE reporting procedures. Refer to section 12.2.2 (Reporting of Serious Adverse Events (SAEs)) for details.

Pregnancy Report processing at UCL CTC

UCL CTC will submit a report to the MHRA and the REC if the pregnancy outcome meets the definition of a SUSAR. Refer to section 12.3 (SUSARs) for details.

UCL CTC will submit all Pregnancy Reports concerning exposure to pembrolizumab to MSD Ltd according to the timelines outlined in the agreement between UCL and MSD Ltd.

12.8. Development Safety Update Reports (DSURs)

Safety data obtained from the trial will be included in DSURs that UCL CTC will submit to the MHRA and the REC.

UCL CTC will provide MSD Ltd with DSURs that include information regarding pembrolizumab.

13. INCIDENT REPORTING AND SERIOUS BREACHES

13.1. Incident Reporting

Organisations must notify UCL CTC of all deviations from the protocol or GCP immediately. An incident report may be requested and will be provided, but an equivalent document (e.g. Trust Incident form) is acceptable where already completed.

If site staff are unsure whether a certain occurrence constitutes a deviation from the protocol or GCP, the UCL CTC trial team can be contacted immediately to discuss.

UCL CTC will use an organisation's history of non-compliance to make decisions on future collaborations.

UCL CTC will assess all incidents to see if they meet the definition of a serious breach.

13.2. Serious Breaches

A "serious breach" is defined as a breach of the protocol or of the conditions or principles of Good Clinical Practice (or equivalent standards for conduct of non-CTIMPs) which is likely to affect to a significant degree the safety or physical or mental integrity of the trial subjects, or the scientific value of the research.

Systematic or persistent non-compliance by a site with GCP and/or the protocol, including failure to report SAEs occurring on trial within the specified timeframe, may be deemed a serious breach.

In cases where a serious breach has been identified, UCL CTC will inform the MHRA and REC within 7 calendar days of becoming aware of the breach.

Sites must have written procedures for notifying the sponsor of serious breaches (MHRA Guidance on the Notification of Serious Breaches).

14. TRIAL MONITORING AND OVERSIGHT

Participating sites and PIs must agree to allow trial-related on-site monitoring, Sponsor audits and regulatory inspections by providing direct access to source data/documents as required. Where permitted by site policy, remote access to source data/documentation may also be provided by participating sites for remote monitoring by UCL CTC or its representatives.

Patients are informed of this in the patient information sheet and are asked to consent to their medical notes being reviewed by appropriate individuals on the consent form. UCL CTC staff or its representatives will conduct all monitoring in compliance with the participant consent, site policy and data protection requirements.

UCL CTC will determine the appropriate level and nature of monitoring required for the based on the objective, purpose, phase, design, size, complexity, endpoints and risks associated with the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

Details of monitoring activities will be included in the trial monitoring plan and conveyed to sites during initiation. The trial monitoring plan will be kept under review during the trial and updated information provided to sites as necessary.

14.1. On-Site and Remote Monitoring

On-Site Monitoring

Sites will be sent an email in advance of any on-site monitoring visits, confirming when a visit is scheduled to take place. The email will include a list of the documents to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

Remote Monitoring

UCL CTC defines remote monitoring as activities conducted at a location remote from the research site which replicate some on-site activities e.g. source data review. Remote monitoring may be conducted in response to exceptional circumstances preventing access to participating sites (e.g. global pandemic) or conducted routinely. Details of remote monitoring will be agreed with participating sites, conducted in accordance with site policy and documented in the monitoring plan.

Sites will be sent an email in advance, confirming when remote monitoring is scheduled to take place and how the source documents will be remotely accessed. The email will include a list of the documents to be reviewed, interviews that will be conducted and who will be performing the remote monitoring.

Remote monitoring will be conducted by UCL CTC or its representatives via a device with adequate security. Patient confidentiality will be maintained at all times, and monitoring activities will be conducted in an appropriate environment where no unauthorised viewing or overhearing of conversations is possible by third parties. Refer to section 11 Data Management and Data Handling Guidelines for details of how secure documentation may be submitted to UCL CTC.

Monitoring Follow Up

Following on-site/remote monitoring, the Trial Monitor/Trial Coordinator will provide a follow up email to the site, which will summarise the documents reviewed and a statement of findings, incidents, deficiencies, conclusions, actions taken and/or actions required. The PI at each site will be responsible for ensuring that monitoring findings are addressed in a timely manner, and by the deadline specified.

14.2. Centralised Monitoring

UCL CTC performs centralised monitoring, which requires the submission of documents by sites to UCL CTC for review. The documents requested include but are not limited to: delegation log, preliminary registration and full registration forms, PI CV & GCP, drug accountability logs (patient and stock balance), screening log, sample inventory logs and ISF & PSF checklists. Expectations for document submission will be explained during site initiation and UCL CTC will send emails to sites requesting the documents when required.

Sites will be requested to conduct quality control checks of documentation held within the Investigator Site File and Pharmacy Site File at the frequency required for the trial. Checklists detailing the current version/date of version controlled documents will be provided by UCL CTC for this purpose.

14.3. 'Triggered' On-Site/Remote Monitoring

Additional on-site/remote monitoring visits may be scheduled where there is evidence or suspicion of non-compliance at a site with important aspect(s) of the trial protocol/GCP requirements.

On-Site Monitoring

Sites will be sent an email in advance outlining the reason(s) for the visit and confirming when it will take place. The email will include a list of the documents that are to be reviewed, interviews that will be conducted, planned inspections of the facilities and who will be performing the visit.

Remote Monitoring

Sites will be sent an email in advance, confirming when remote monitoring is scheduled to take place and how the source documents will be remotely accessed. The email will include a list of the documents to be reviewed, interviews that will be conducted via telephone/videoconference and who will be performing remote monitoring.

14.4. Escalation of Monitoring Issues

Where monitoring indicates that a patient may have been placed at risk (e.g. evidence of an overdose having been administered or indication that dose modification rules for an IMP were not observed following an adverse event), the matter will be raised urgently with site staff and escalated as appropriate.

UCL CTC will assess whether it is appropriate for the site to continue participation in the trial and whether the incident(s) constitute a serious breach. Refer to section 13 (Incident Reporting and Serious Breaches

14.5. Oversight Committees

14.5.1. Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialties and PembroWM trial staff from UCL CTC (see page 4). The TMG will be responsible for overseeing the trial. The group will meet regularly (at least bi-annually) and will send updates to PIs (via newsletters or at Investigator meetings) and to the NCRI lymphoma Clinical Studies Group.

The TMG will review substantial amendments to the protocol prior to submission to the REC and MHRA. All PIs will be kept informed of substantial amendments through their nominated responsible individual and are responsible for their prompt implementation.

TMG members will be required to sign a TMG charter, which describes the committee's responsibilities in relation to the trial and requires any potential conflicts of interest to be declared.

14.5.2. Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial. The TSC will review the recommendations of the Independent Data Monitoring Committee and, on consideration of this information, recommend any appropriate amendments/actions for the trial as necessary. The TSC acts on behalf of the funder and the Sponsor.

TSC members will be required to sign a TSC charter, which describes the committee's responsibilities and requires any potential conflicts of interest to be declared.

14.5.3. Independent Data Monitoring Committee (IDMC)

The role of the IDMC is to provide independent advice on data and safety aspects of the trial. Meetings of the Committee will be held at least annually, or as necessary to address any issues. Although no formal interim analysis is planned, an IDMC meeting will be triggered in the event of significant toxicity (see section 17.3 for further details). The IDMC is advisory to the TSC and can recommend premature closure of the trial to the TSC.

IDMC members will be required to sign an IDMC charter, which describes the committee's responsibilities and requires any potential conflicts of interest to be declared.

14.5.4. Role of UCL CTC

UCL CTC will be responsible for the day to day coordination and management of the trial and will act as custodian of the data generated in the trial (on behalf of UCL). UCL CTC is responsible for all duties relating to pharmacovigilance which are conducted in accordance with section 12 (Pharmacovigilance).

15. WITHDRAWAL OF PATIENTS

In consenting to the trial, patients are consenting to trial treatment, assessments, collection of biological samples, follow-up and data collection.

15.1. Patients who do not start Trial Treatment

If a patient does not start treatment, the reasons for this must be recorded in the patient's medical notes and on the relevant Case Report Form(s). Reasons that a patient may not start treatment include:

- Deterioration in health
- Patient decision
- No longer eligible

If a patient does not start treatment, then the patient should be withdrawn from the trial. Data collected will be used in the trial analysis, where appropriate. Biological samples collected may still be used unless the patient explicitly withdraws consent to this.

15.2. Discontinuation of Trial Treatment

A patient may be withdrawn from trial treatment whenever such treatment is no longer in the patient's best interests, but the reasons for doing so must be recorded in the patient's medical notes and on the relevant Case Report Form(s). Reasons for discontinuing treatment may include:

- Disease progression whilst on therapy
- Unacceptable toxicity (see section 8.5 for full details)
- Intercurrent illness which prevents further treatment
- Patient decision not to continue with trial treatment
- Any alterations in the patient's condition which justifies the discontinuation of treatment in the site investigator's opinion
- Non-compliance with the trial treatment and/or procedures
- If a female patient becomes pregnant or male/female fails to use adequate birth control (for patients of childbearing potential)

In these cases patients will remain within the trial for the purposes of follow-up and data analysis unless they explicitly withdraw consent. See section 9 for details.

If a patient expresses their wish to withdraw from trial treatment, sites should explain the importance of remaining on trial follow-up, or failing this of allowing routine follow-up data to be used for trial purposes and for allowing existing collected data to be used. If the patient gives a reason for wishing to discontinue treatment, this should be recorded.

The following CRFs should be submitted if a patient discontinues trial treatment early:

- Treatment summary form
- Treatment forms for all cycles of treatment received
- Rolling AE form for all cycles of treatment received

Thereafter, unless the patient has withdrawn consent, the site should report AEs/SAEs and submit relevant follow up forms.

15.3. Withdrawal of Consent

If a patient withdraws consent for any aspect of the study, the 'Change of Status Form' should be completed and submitted to UCL CTC.

15.3.1. Withdrawal of consent for follow up

If a patient withdraws consent for trial follow up, but is happy to continue with future data collection from hospital medical notes:

- They will remain on trial for follow up
- The patient will no longer have trial-specific visits and assessments. Follow up forms should be completed based on the routine visit nearest the due date for the follow up form
- The following CRFs must be submitted at time of withdrawal:
    - Change of status form
    - All CRFs up to and including the date of withdrawal of consent
- Thereafter, the site should report AEs/SAEs as per section 12.2 and follow up forms, including notifications of progression and death.

15.3.2. Withdrawal of consent for data collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected:

- The following CRFs must be submitted at the time of withdrawal:
    - Change of status form
    - All CRFs up to and including the date of withdrawal of consent
- Thereafter no further data should be submitted, with the exception of SAE reports as per section 12.2 (due to the regulatory requirement for oversight of IMP safety)

15.3.3. Withdrawal of consent for use of samples

If a patient withdraws consent for the use of some or all of their samples in the trial or for future research, this should be reported on the Change of Status form. Unless the patient has also withdrawn consent for treatment/follow up, management and data collection should continue as per protocol.

15.4. Losses to Follow-Up

If a patient moves from the area, every effort should be made for the patient to be followed up at another participating trial site and for this new site to take over the responsibility for the patient, or for follow-up via GP. Details of participating trial sites can be obtained from the UCL CTC trial team, who must be informed of the transfer of care and follow up arrangements. If it is not possible to transfer to a participating site, the registering site remains responsible for submission of forms.

If a patient is lost to follow-up at a site every effort should be made to contact the patient's GP to obtain information on the patient's status.

At the time of loss to follow up, the following CRFs should be submitted:

- Change of status form
- All CRFs due up to and including the date of loss to follow up

If contact is re-established with the patient, further follow up forms should be sent, including notifications of progression. A death form should also be submitted if the site becomes aware the patient has died.

Prior to primary analysis and presentation/publication of the primary endpoint data, UCL CTC will ask sites to attempt to re-establish contact with patients who were lost to follow up and/or check hospital records for evidence of when the patient was last known to be alive and evidence of disease progression and death.

16. TRIAL CLOSURE

16.1. End of Trial

For regulatory purposes the end of the trial will be when the final data item for the final patient is received by the UCL CTC (i.e. it is anticipated that this will be when the final patient completes their 2 year follow-up visit). At this point the 'declaration of end of trial' form will be submitted to the MHRA and Ethics Committee, as required.

Following this, UCL CTC will advise sites on the procedure for closing the trial at the site.

Once the end of trial has been declared, no more prospective patient data will be collected but sites must co-operate with any data queries regarding existing data to allow for analysis and publication of results.

16.2. Archiving of Trial Documentation

At the end of the trial, UCL CTC will archive securely all centrally held trial related documentation for a minimum of 5 years. Arrangements for confidential destruction will then be made. It is the responsibility of PIs to ensure data and all essential documents relating to the trial held at site are retained securely for a minimum of 5 years after the end of the trial, and in accordance with national legislation.

Essential documents are those which enable both the conduct of the trial and the quality of the data produced to be evaluated and show whether the site complied with the principles of GCP and all applicable regulatory requirements.

UCL CTC will notify sites when trial documentation held at sites may be archived. All archived documents must continue to be available for inspection by appropriate authorities upon request.

16.3. Early Discontinuation of Trial

The trial may be stopped before completion as an Urgent Safety Measure on the recommendation of the TSC or IDMC (see section 14.5.2 Trial Steering Committee (TSC) and 14.5.3 Independent Data Monitoring Committee (IDMC)). Sites will be informed in writing by UCL CTC of reasons for early closure and the actions to be taken with regards the treatment and follow up of patients.

16.4. Withdrawal from Trial Participation by a Site

Should a site choose to close to recruitment the PI must inform UCL CTC in writing. Follow up as per protocol must continue for any patients recruited into the trial at that site and other responsibilities continue as per the mNCA.

17. STATISTICS

17.1. Sample Size Calculation

The primary endpoint is the overall response rate (defined as complete response (CR), very good partial response (VGPR), partial response (PR) or minor response (MR) i.e. a greater than 25% reduction in the serum IgM level) by 24 weeks post commencing treatment.

It is thought the response rate could be around 60% but a rate of more than 40% is needed for this combination to be taken forward into a larger study. Using an A'Hern phase II trial design with a 1-sided alpha of 0.05 and power of 80% we will require 42 patients. The primary endpoint will be met if we see 23 or more responses.

17.2. Statistical analysis

17.2.1. Analysis of primary endpoint

The primary endpoint is the overall response rate (defined as complete response (CR), very good partial response (VGPR), partial response (PR) or minor response (MR) i.e. a greater than 25% reduction in the serum IgM level) by week 24 post commencing treatment. This will be presented as a percentage with 90% confidence interval. We do not expect missing response data at this time point (in this patient population) to be a problem, however, if it occurs it will be treated in the following way:

Response data before 24 weeks	24 week response	Clinical status at week 24	Response
Response reported at an earlier time point	Missing	Alive with no progression reported	Responder
No response at earlier time points	Missing	Any	Non responder
Any	Missing	Progressed or died	Non responder

Any patient who does not start trial treatment will be excluded and replaced.

17.2.2. Analysis of secondary endpoints and secondary analyses

Safety and tolerability of pembrolizumab in combination with rituximab

As this is continuous treatment, care will be taken to assess the burden of adverse events over time rather than just the worst grades seen.

Rates of adverse events (as assessed by CTCAE version 5.0) will be presented in four ways:

1. Worst grade seen of each event, i.e. the number of patients who experience a grade 1-2 or 3+ event at any time point.
2. Worst grade seen of each event per cycle, i.e. the number of patients who experience a grade 1-2 or 3+ event during each cycle.
3. Proportion of cycles where patients experience a grade1-2 or grade 3-4 AE. This may also be presented by the number of cycles depending on the numbers of patients stopping treatment.
4. Median number of grade 1-2 or 3+ AEs (of any type) experienced at each cycle.

Analyses 3-4 may focus on clinical events only i.e. excluding lower level biochemical and haematological events which may not have an impact on the patient's quality of life.

Depending on the frequency of adverse events, we may also look at duration of some events, possibly as a proportion of the time on treatment.

AEs of special interest will be reported in more detail, with events of any grade presented.

All adverse event analysis will be descriptive.

Best response and time to best response.
The best response is the best response seen from the start of treatment; all response time points will be included.
Time to maximal response to treatment will be calculated as the time from the date of registration until the date of the best response. This will be presented as the median and range and will be reported for responding patients only.

Time to next treatment
Time to next treatment will be analysed using Kaplan-Meier survival analyses, with the time calculated from the date of registration to the date of the start of the next line of therapy. Patients who do not start a further line of treatment will be censored at the date last seen/date of death. The median (if applicable) and rates at 1 and 2 years will be presented.

Progression free survival
Progression free survival will be analysed using Kaplan-Meier survival analyses, with the time calculated from the date of registration to the date of progression/death. Patients who are alive and progression free will be censored at the date last seen. The median (if applicable), rates at 1 and 2 years and a Kaplan-Meier curve will be presented.

Overall survival
Overall survival will be analysed using Kaplan-Meier survival analyses, with the time calculated from the date of registration to the date of death. Patients who are alive will be censored at the date last seen. The median (if applicable), rates at 1 and 2 years and a Kaplan-Meier curve will be presented.

Quality of life
Quality of life is assessed using the QLQ-30 questionnaire at baseline and at week 24. Differences between baseline and week 24 will be compared using paired t-tests and changes between baseline and week 24 may also be compared to historical data from the R2W trial.

17.3. Interim analyses

There will be no formal interim analyses however toxicities will be monitored closely throughout the trial (see section 12.6). In addition to periodic reviews, an IDMC meeting will be triggered as a result of trial-treatment related deaths as outlined below.

An IDMC review will be triggered if the number of treatment related deaths exceeds 10% of the number of patients recruited.

Number of Patients (N)	Number of treatment related deaths needed for IDMC trigger (more than 10% of N)
10	2
15	2
20	3
25	3
30	4
35	4

18. ETHICAL AND REGULATORY CONSIDERATIONS

This trial will adhere to the conditions and principles of GCP as outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), as amended.

In conducting the trial, the Sponsor, UCL CTC and sites shall comply with the protocol and with all relevant guidance, laws and statutes, as amended from time to time, applicable to the performance of clinical trials and research including, but not limited to:

- The UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority
- Human Rights Act 1998
- Data Protection Act 2018
- General Data Protection Regulation (EU)2016/679 (GDPR)
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Medicines for Human Use (Clinical Trials) Regulations (SI 2004/1031), and subsequent amendments
- Medicines Act 1968
- Good Manufacturing Practice

18.1. Ethical Approval

The trial will be conducted in accordance with the World Medical Association Declaration of Helsinki entitled 'Ethical Principles for Medical Research Involving Human Subjects' (1996 version) and in accordance with the terms and conditions of the ethical approval given to the trial.

The trial has received a favourable opinion from the London – London West Research Ethics Committee (REC) and Health Research Authority (HRA) approval for conduct in the UK.

UCL CTC will submit Annual Progress Reports to the REC, commencing one year from the date of ethical approval for the trial.

Favourable opinion will also be obtained in all participating countries outside the UK in compliance with all local laws, statutes and requirements.

18.2. Regulatory Approval

A Clinical Trial Authorisation (CTA) has been granted for the trial.

The trial will be conducted at approved trial sites in accordance with the trial protocol and the terms of the CTA granted by the MHRA.

18.3. Site Approvals

Evidence of assessment of capability and capacity by the Trust/Health Board R&D for a trial site must be provided to UCL CTC. Sites will only be activated when all necessary local approvals for the trial have been obtained.

18.4. Protocol Amendments

UCL CTC will be responsible for gaining ethical and regulatory approval, as appropriate, for amendments made to the protocol and other trial-related documents. Once approved, UCL CTC will ensure that all amended documents are distributed to sites as appropriate.

Site staff will be responsible for acknowledging receipt of documents and for implementing all amendments promptly.

18.5. Patient Confidentiality & Data Protection

Patient identifiable data, including initials and date of birth will be required for the registration process and will be provided to UCL CTC. UCL CTC will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified. Data will be stored in a secure manner and UCL CTC trials are registered in accordance with the Data Protection Act 2018 and GDPR with the Data Protection Officer at UCL.

Patient identifiable data, including initials and date of birth will be provided to the HMDS in order to process the sample. HMDS will preserve patient confidentiality and will not disclose or reproduce any information by which patients could be identified.

19. SPONSORSHIP AND INDEMNITY

19.1. Sponsor Details

Sponsor Name:	University College London
Address:	Joint Research Office Gower Street London WC1E 6BT
Contact:	Managing Director, UCLH/UCL Research
Tel:	020 3447 9995/2178 (unit admin)
Fax:	020 3447 9937

19.2. Indemnity

University College London holds insurance against claims from participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant of the clinical trial. University College London does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or otherwise.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of University College London or another party. Participants who sustain injury and wish to make a claim for compensation should be advised to do so in writing in the first instance to the Chief Investigator, who will pass the claim to the Sponsor's Insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to University College London, upon request.

20. FUNDING

MSD Ltd are supporting the central coordination of the trial through UCL CTC, translational research at HMDS, and supplying pembrolizumab free of charge for use in the trial.

Research A costs will be reimbursed to sites as per the finance section of the mNCA.

21. PUBLICATION POLICY

The results of the PemboWM trial will be presented at relevant conferences and published in a peer reviewed journal. The primary publication from the trial will be written by the TMG. Authors will include the CI, TMG members, representatives of UCL CTC including the trial coordinator and trial statistician, and PIs at sites that make a significant contribution to patient recruitment.

Abstracts and papers will be reviewed by MSD Ltd prior to submission in accordance with the requirements of the Trial Drug Supply Agreement.

The ISRCTN/Clinicaltrials.gov number of the trial and the funder reference number will be quoted in all publications.

Sites may not publish any data pertaining to PembroWM patients without prior written permission from the TMG.

Data generated from the PembroWM trial will be the property of UCL as Trial Sponsor.

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APPENDIX 1: QUICK REFERENCE GUIDE TO PATIENT VISITS

	Pre-registration *(within 28 days of full registration unless otherwise stated)*	**D1 of each cycle** *(- 3days)* [a]	**Response at 12 weeks** *(+/- 3days)*	**Response at 24 weeks** *(+/- 3days)*	**Response at 1 year** *(+/- 2weeks)*	**D+60 post treatment discontinuation** *(+/- 3days)* [b]	**5 months post treatment discontinuation** *(+4weeks)*	**Annual FU until EoT declared** *(pt who complete treatment/ discontinue for reasons other than progression)*	**Annual FU until EoT declared** *(following disease progression)*
Eligibility checklist	X								
Demographics and Medical History *(see 9.1)*	X								
Physical examination including performance status and observations *(see 9.1 & 9.2)*	X	X				X			
Height	X								
Weight	X	X				X			
Quality of Life Questionnaire	X			X					
Lymph node biopsy[c]	X								
Adverse Event reporting[d]	X								
Concomitant Medications	X								
ECG[e]	X	X							
Hepatitis B and C serology	X								

HIV serology	X								
FBC	X	X	X	X	X	X			
U+E	X	X	X	X	X	X			
LFT	X	X	X	X	X	X			
LDH	X					X			
B2 microglobulin	X								
Serum IgM, IgG, IgA	X	X	X	X	X				
Serum paraprotein	X	X	X	X	X				
Serum immunofixation[f]		X	X	X	X				
Direct antiglobulin test	X								
TSH, glucose, ACTH	X	X				X			
Pregnancy test *(serum or urine)*	X	X							
Amylase	X	X				X			
CT scan[g]	X			X	X				
Serum SFLC	X		X	X	X				
Bone marrow aspirate and trephine[h]	X			X	X				
MyD88 and CXCR4 mutation status by NGS[i]	X								
Flow for B-cell and plasma cell phenotype[j]	X			X	X				
Remission status and assessment of late toxicity[k]								X	X

a: patients will remain on treatment for a maximum of 1 year or until disease progression, discontinuation due to unacceptable toxicity or any other reason (whichever occurs sooner).
b: patients who complete treatment or discontinue treatment early for reasons other than progression should be followed at day 60 post treatment discontinuation (+/-3 days). They will then be followed up at 5 months and annually thereafter until the last patient completes 2 years of follow up.
c: Lymph node biopsy if nodal disease. Biopsy within 28 days prior to C1D1 preferred. If not possible, then historical biopsy tissue will be obtained and sent for exploratory analysis at HMDS (see section 10 for further details). Note: this only applies to patients who have given consent to optional samples being sent to HMDS.
d: Adverse events are to be recorded between informed consent and 5 months after the last IMP administration. AESI and SAES are to be reported to UCL CTC within 24 hours of awareness (see section 12 for details),
e: A 12 lead ECG should be performed for all patients pre-registration and prior to commencing each cycle of pembrolizumab. Further ECGs should be performed as clinically indicated.
f: Serum immunofixation to be performed only if paraprotein no longer detectable.
g: CT scan of neck, chest, abdomen and pelvis (NCAP) to be performed pre-registration (within 28 days prior to starting treatment). CT scan (NCAP) to be repeated at 24 weeks and 1 year post commencing treatment only if nodal disease on baseline assessment. Thereafter, only to be done if clinical concerns of nodal progression. If no measurable disease was documented at baseline, then a CT NCAP should be performed as clinically indicated.
h: Bone marrow aspirate and trephine to be performed pre-registration (within 28 days prior to starting treatment) and at week 24 and 1 year to determine response. Samples to be analysed locally. Additionally, for consenting patients bone marrow samples to be sent to HMDS for exploratory analysis (see section 10 for further details).
i: Peripheral blood sample for MyD88 and CXCR4 analysis will be sent at screening to HMDS for exploratory analysis from consenting patients (see section 10 for further details).
j: Peripheral blood sample for flow cytometry for B-cell/plasma cell phenotypes will be sent to HMDS for exploratory analysis from consenting patients (see section 10 for further details).
k: Remission status as per local policy.

APPENDIX 2: ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS*	
Grade	**ECOG**
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

*Oken et al, 1982

APPENDIX 3: RESPONSE ASSESSMENT*

Response category	Definition
Complete response (CR)	• Absence of serum monoclonal IgM protein by immunofixation • Normal serum IgM level[a] • Complete resolution of lymphadenopathy and splenomegaly if present at baseline • Morphologically normal bone marrow aspirate and trephine biopsy
Very Good Partial Response (VGPR)	• Detectable monoclonal IgM protein • ≥90% reduction in serum IgM level from baseline[b] • Complete resolution of extramedullary disease, i.e. lymphadenopathy/splenomegaly if present at baseline • No new signs or symptoms of active disease
Partial response (PR)	• Detectable monoclonal IgM protein • ≥50% but <90% reduction in serum IgM level from baseline[b] • Reduction in extramedullary disease, i.e. lymphadenopathy/splenomegaly if present at baseline • No new signs or symptoms of active disease
Minor response (MR)	• Detectable monoclonal IgM protein • ≥25% but <50% reduction in serum IgM level from baseline[b] • No new signs or symptoms of active disease
Stable disease (SD)	• Detectable monoclonal IgM protein • <25% reduction and <25% increase in serum IgM level from baseline[b] • No progression in extramedullary disease, i.e. lymphadenopathy/splenomegaly • No new signs or symptoms of active disease
Progressive disease (PD)	• ≥25% increase in serum IgM level[a,b] from lowest nadir[c] and/or • Progression in clinical features attributable to the disease

*Owen et al, 2013

[a]IgM responses/progression should be confirmed by a second measurement (ideally taken within the same cycle as the initial measurement)

[b]Sequential changes in IgM levels may be determined either by IgM protein quantitation by densitometry or total serum IgM quantitation by nephelometry

[c]The effects of any plasmapheresis should be considered when determining the lowest nadir

Note: where local investigations are inconclusive in determining progression, or the Site are uncertain that the progression in clinical features is attributable to the disease, the TMG should be contacted for advice. In these circumstances please email ctc.PembroWM@ucl.ac.uk.

APPENDIX 4: PROTOCOL VERSION HISTORY

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
1	12/10/18	Initial submission	n/a	n/a
1.1	19/12/18	Response to MHRA grounds of non-acceptance	6.2.1 6.3.3 and throughout 6.3.5	-Clarifying the Bilirubin levels required for trial inclusion -Clarifying that the urine pregnancy test should be highly sensitive test (minimum sensitivity 25 IU/l) -Amending information to state that patients that become pregnant prior to initiating treatment will be withdrawn from the trial
1.2	12/02/19	Response to REC provisional opinion	14.4.3 17.3	-Addition of trigger points for IDMC review of safety data

2.0	010/05/21	Amendment 08	TMG	-Update to members
			1.1	-Update to duration of recruitment and total sites
			6.2.1	- Clarifying the description of measurable disease -Allowing more severe cytopenias, with no lower limit if cytopenia is due to bone marrow involvement and growth factor/transfusion support permitted prior to C1D1.
			6.2.2	-BTK inhibitors allowed up until 48 hours prior to C1D1 -Addition of live-attenuated vaccines -Clarifying the exclusion of Hep C positive patients -Allowing a short course of oral prednisolone within 7 days of C1D1 following BTK inhibitor discontinuation -Allowing a subset of patients with a history of colitis -Removal of current participation in any other CTIMP when C1D1 commences
			7.1, 7.2 and throughout	-Addition of pre-registration process to assign a trial number prior to full registration to enable translational samples to be sent to central laboratory
			8.3	-Allowing patients with cytopenias Grade 4 (as per CTCAE v5.0) to receive treatment -Allowing treatment to be moved due to logistical reasons
			8.4.2	-Updated management of irAEs table
			8.7	-Guidance added for the use of vaccines -Guidance added for the use of growth factor/transfusions
			8.10	-Updated MSD out of hours telephone number
			14	-Addition of remote monitoring and the escalation process for monitoring issues
			15	-Addition of the withdrawal of consent process and clarifications made for losses to follow-up
			16.1	-Clarification of the End of Trial
			16.2	-Archiving duration updated to 5 years
			18	-Updated ethical and regulatory considerations
			19	-Updated sponsor contact

			Appendix 3 Throughout	-Clarification on determining the nadir -Addition of repeat testing to confirm remission and progression -Removal of faxing process -Minor clarifications and corrections of typographical errors

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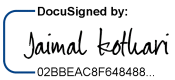
Jaimal Kothari jaimal.kothari@nhs.net Security Level: Email, Account Authentication (None)	DocuSigned by:  02BBEAC8F648488... Signature Adoption: Pre-selected Style Using IP Address: 94.0.41.172	Sent: 08 September 2021 | 09:42 Viewed: 09 September 2021 | 17:28 Signed: 09 September 2021 | 17:29
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Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact CR UK and UCL Cancer Trials Centre (UCL CTC):

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: r.beehag@ucl.ac.uk

To advise CR UK and UCL Cancer Trials Centre (UCL CTC) of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at r.beehag@ucl.ac.uk and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from CR UK and UCL Cancer Trials Centre (UCL CTC)

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to r.beehag@ucl.ac.uk and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with CR UK and UCL Cancer Trials Centre (UCL CTC)

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to r.beehag@ucl.ac.uk and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

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- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify CR UK and UCL Cancer Trials Centre (UCL CTC) as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by CR UK and UCL Cancer Trials Centre (UCL CTC) during the course of your relationship with CR UK and UCL Cancer Trials Centre (UCL CTC).