ANIMATE

A phase II study of nivolumab monotherapy in patients with relapsed/refractory Hodgkin lymphoma, fit for autologous stem cell transplant, who fail to reach complete metabolic remission after first or second line salvage therapy

Trial Sponsor:	University College London
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Protocol 2.1~~0~~, dated ~~10.04.2018~~12.06.2018 authorisation signatures:

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

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1. PROTOCOL SUMMARY

1.1. Summary of Trial Design

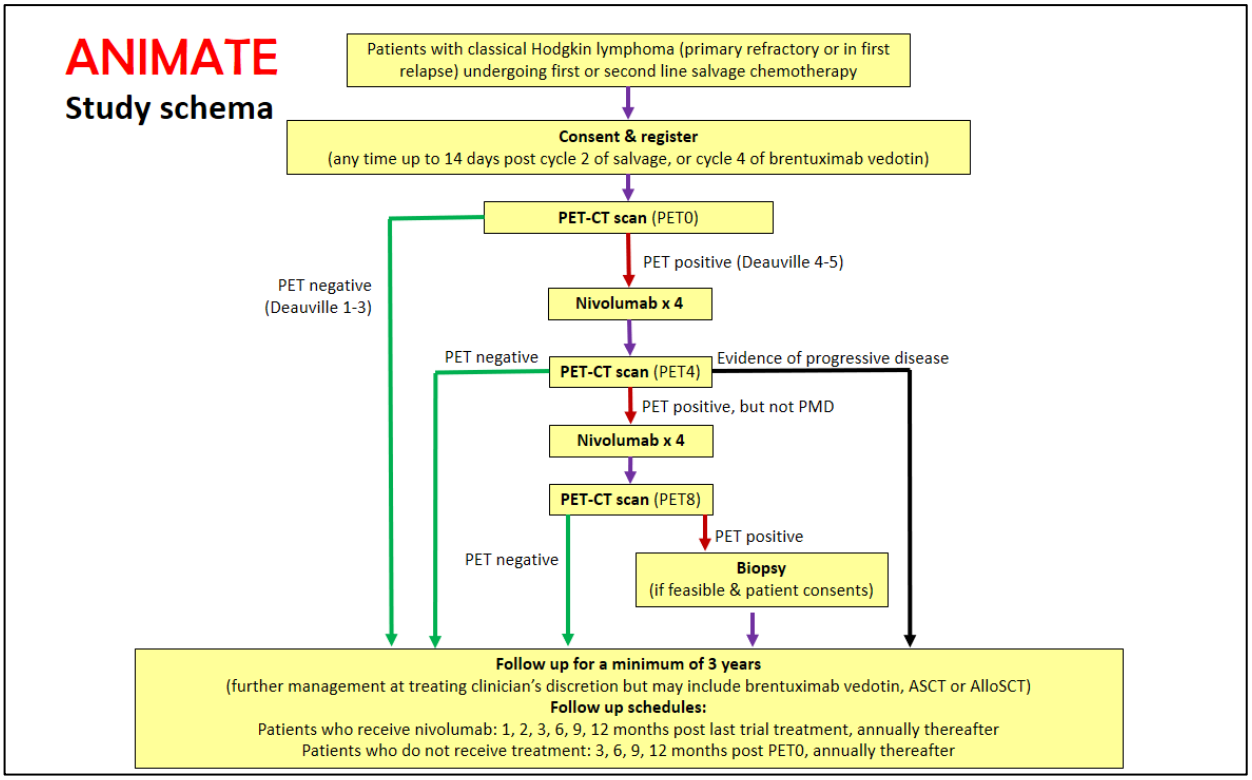
Title:	A phase II study of nivolumab monotherapy in patients with relapsed/refractory Hodgkin lymphoma, fit for autologous stem cell transplantation, who fail to reach complete metabolic remission after first or second line salvage therapy
Short Title/acronym:	**ANIMATE**
EUDRACT no:	2017-002544-32
Sponsor name & reference:	University College London (UCL/15/0515)
Funder name & reference:	Bristol-Myers Squibb (CA-209-445)
Clinicaltrials.gov no:	NCT03337919
Design:	Single-arm, open label, multicentre phase II trial
Overall aim:	To assess the efficacy of nivolumab as a second or third line salvage therapy in relapsed/refractory classical Hodgkin lymphoma patients, particularly as a bridge to stem cell transplant
Primary endpoint:	Overall response rate (ORR) by PET-CT scan following 4-8 cycles of nivolumab
Secondary endpoints:	• Progression-free survival at 1 year • Overall survival at 1 year • Proportion of patients proceeding to SCT (autologous or allogeneic) • Safety & toxicity of nivolumab, particularly autoimmune toxicity • OS and PFS stratified by partial metabolic response (PMR) versus complete metabolic response (CMR) on FDG-PET • Transplant-related mortality and rate of serious complications of allogeneic transplant (grade 3-4 graft-vs-host disease, hyperacute graft-vs-host disease and steroid-responsive febrile syndrome)
Exploratory biological endpoints	• Correlate PET positive disease with histological evidence of disease on biopsy to establish biopsy negative PMR rate (subject to patient consent) • Correlate disease response, as assessed by FDG-PET and histology, with serological markers, including serum TARC • Evaluate the correlation between response to nivolumab and biological parameters e.g. PDL1 expression on Reed-Sternberg cells

Target accrual:	120 registered, to treat 30 patients
Inclusion & exclusion criteria:	***Inclusion criteria for registration*** • Age 16 or over • Primary refractory classical Hodgkin lymphoma or classical Hodgkin lymphoma in first relapse • About to receive, receiving or within 14 days of first 2 cycles of first or second line salvage therapy (4 cycles if receiving treatment with brentuximab vedotin) • Fit for autologous stem cell transplantation • Written informed consent • Willing to comply with the contraceptive requirements of the trial ***Exclusion criteria for registration*** • Nodular lymphocyte predominant Hodgkin lymphoma • Women who are pregnant or breastfeeding • History of colitis, inflammatory bowel disease or pneumonitis • Patients with autoimmune disorders excluding patients with vitiligo, diabetes mellitus type 1, hypo- and hyperthyroidism not requiring immunosuppressive therapy • Known active hepatitis B or C infection • Known HIV infection • History of allergy (including severe/life threatening skin reaction) to monoclonal antibodies, anaphylaxis or uncontrolled allergy • Major surgery within 4 weeks prior to registration • Myocardial infarction, unstable angina, coronary artery bypass graft, cerebrovascular accident or transient ischaemic attack within the past 6 months • Non-haematological malignancy within the past 3 years (some exceptions apply – see section 6.2.2) ***Inclusion criteria – trial treatment*** • Has received 2 cycles of first line or second line salvage chemotherapy (4 cycles if being treated with brentuximab vedotin) • PET positive (Deauville score 4 or 5) after 2 cycles of first or second line salvage chemotherapy (4 cycles if being treated with brentuximab vedotin) • Fit for further salvage chemotherapy • ECOG performance status 0-1 • Creatinine clearance >30ml/min calculated by Cockroft-Gault formula • Bilirubin <1.5 x ULN, ALT/AST <2.5 x ULN • Adequate bone marrow function (Hb >80g/l, Platelets >50 x 10^9/l, neutrophils >1.0 x 10^9/l

	Exclusion criteria for trial treatment • Deauville score 1-3 after 2 cycles of first or second line salvage chemotherapy (4 cycles if being treated with brentuximab vedotin) • Positive serology for hepatitis B or C (some exceptions apply – see sections 6.2.4 & 6.2.5) • Active infection requiring systemic therapy • Ongoing immunosuppressive therapy, apart from inhaled, intranasal, topical corticosteroids or systemic corticosteroids at low doses (≤10mg prednisolone or equivalent per day). • Chemo- or radiotherapy or corticosteroids at a dose of more than 10mg/day prednisolone or equivalent within 14 days prior to response PET-CT. NOTE: corticosteroids can be used AFTER a positive PET-CT scan for symptomatic disease but must be weaned to a dose of prednisolone ≤10mg/day or less (or equivalent) at least 7 days prior to starting nivolumab. • Treatment with any investigational agent within 28 days prior to planned start of nivolumab • Ongoing grade 2-4 non-haematological toxicities related to prior Hodgkin lymphoma treatments, with the exception of alopecia and grade 2 fatigue • Pregnant or breastfeeding women
Number of sites:	30
Treatment summary:	Patients can be consented and registered at any time before, during or within 14 days after completing two cycles of first line or second line salvage therapy (4 cycles if being treated with brentuximab vedotin). A PET-CT scan will be performed under trial conditions following 2 cycles of first line or second salvage (4 cycles if being treated with brentuximab vedotin) to determine eligibility for trial treatment. • Patients who are PET-negative (Deauville 1-3) will not be eligible for trial treatment. They will enter follow up for the purpose of the trial, and any further treatment will be at their treating clinician's discretion. • Patients who are PET-positive (Deauville 4-5) after first line salvage chemotherapy will receive 4 x 14-day cycles of nivolumab. A further PET-CT scan will then be performed: • Patients who are PET negative (Deauville 1-3) will stop trial treatment and enter follow up. • Patients who are PET positive (Deauville 4-5) will have a further 4 x 14-day cycles of nivolumab, unless there is evidence of progressive disease.

Duration of recruitment:	3 years
Duration of follow up:	Patients will be followed up for a minimum of 3 years. For patients who have been in follow up for more than 3 years, annual survival and disease status follow up will continue until the end of the trial.
Definition of end of trial:	End of trial will be declared when the last patient has completed 3 years of follow up.

1.2. Trial Schema



2. INTRODUCTION

2.1. Background

The problem: Relapsed/ refractory cHL

Newly diagnosed classical Hodgkin lymphoma (cHL) has a good chance of cure when treated with current standardised multi-agent chemotherapy and combined modality regimes (chemotherapy and radiotherapy). 3-5 year progression free survival rates (PFS) are 83-98% for limited stage disease (Raemaekers et al. 2014, Radford et al. 2015) and 71-86% for advanced stage disease (Borchmann et al. 2011).

However, approximately 200 patients in the UK per year will relapse with cHL and, due to the demographics of the people affected by cHL, most will be young and fit. Relapsed and primary refractory (progressive within 6 months of initial therapy) disease has a much bleaker outlook. With standard chemotherapy alone, overall survival rates (OS) are between 10 and 20% (Longo et al. 1992). This is significantly improved by treatment with non cross-reacting salvage regimes and high intensity chemotherapy followed by autologous stem cell transplant (ASCT) (Linch et al., 1993, Schmitz et al. 2002). 5 year freedom from second failure (FF2F) in patients treated with this approach was reported as 42% by the German Hodgkin's lymphoma study group (GHSG). However, a minority of this relapsed/ refractory cohort (33%) actually made it to ASCT, resulting in poor outcomes overall (17% 5 year FF2F). Failure to do so occurred because of progressive disease, therapy related toxicity, failure of stem cell harvest and poor performance status (Josting et al. 2000). Even within the sub-group of patients who make it to ASCT, there is considerable heterogeneity in outcome. A number of factors have been identified as predictive of poor prognosis: shorter time to relapse or primary refractory disease; advanced stage at relapse; anaemia; extra-nodal disease; presence of B symptoms (Josting et al. 2002, Moskowitz et al. 2001). The most discriminatory factor is achievement of PET negativity following salvage therapy. In patients achieving PET negativity following salvage, 3-5 year PFS following ASCT is > 70%, whereas in those not achieving this, PFS is 25-30% (Jabbour et al. 2007, Moskowitz et al. 2012).

Strategies for improving outcome in patients treated with ASCT

A number of strategies have been explored to optimise outcomes post ASCT, particularly for patients with poor prognostic factors. Post ASCT consolidation with radiotherapy and/or cytotoxic chemotherapy has so far yielded disappointing results (Rapoport et al. 2004). The Aethera trial (Moskowitz et al. 2014a) demonstrated some benefit of using the anti-CD30 monoclonal antibody-drug conjugate brentuximab vedotin (BV) in this context. Median PFS was 42.9 months versus 24.1 months when BV or placebo was given to high risk patients respectively (primary refractory or relapsing within 12 months of first line therapy) post ASCT. Tandem ASCT has also been tested in a non-randomised trial setting: outcomes for the poor risk group remained inferior (Morschhauser et al. 2008). Allogeneic SCT is an alternative approach. Treatment related mortality (TRM) has improved significantly with reduced intensity (RIC) conditioning regimes (Peggs et al. 2007), but remains significantly higher than for ASCT, and confers significant morbidity especially from graft versus host disease. It is therefore usually still reserved for patients relapsing post auto-ASCT or who are ineligible for ASCT because of chemo-refractory disease or failure of stem cell harvest (Collins et al., 2014).

The approach which has had the best results to date is the use of PET directed change to second line salvage therapy. Various first line salvage regimes are commonly used, including ICE, ESHAP, DHAP, GDP, IGEV with likely comparable efficacy, although varying toxicities (Collins et al. 2014). Moskowitz et al. (2012), demonstrated similar excellent outcomes post ASCT (EFS>80%) in patients achieving PET-negativity post second line salvage cytotoxic chemotherapy, compared with those who achieved PET negativity post first line salvage. However, the literature is conflicting and other studies have been less optimistic. For example, in a retrospective series published by Villa et al. 2012, only 33% of the 19 patients refractory to first line GDP chemotherapy responded to second line mini-BEAM chemotherapy, and of 9 patients who proceeded to ASCT, 7 relapsed. There are additional concerns about the impact of multiple lines of cytotoxic chemotherapy on bone marrow reserve for stem cell harvest and also on patient performance status, and fitness for auto/allo-SCT.

BV is increasingly being used in this setting, although there is a paucity of evidence for this, and it is not currently licensed in the UK. The largest data set is a retrospective, observational study of 30 relapsed, refractory cHL patients, not responding to first line salvage therapy, in whom BV was given pre ASCT (Zinzani et al., 2015). The overall response rate (ORR) was 40% with a complete response (CR) rate of 30%. However, trials of BV in the setting of relapse post ASCT demonstrate that median PFS with BV is relatively short (5.7 months) (Younes et al. 2012). This is problematic for patients being considered for allo-SCT, because of the time it can take for donor matching and work-up. Moreover, BV is associated with significant peripheral neuropathy and neutropenia. The use of BV in the salvage setting is the subject of a current clinical trial, BRaVE (NCT02280993), which combines BV with DHAP up-front. This trial does not use PET stratification to change therapy.

Immune checkpoint inhibitors

Alongside the breakthrough with BV, immune checkpoint inhibitor drugs have emerged as a new class of drug with promising results in relapsed, refractory cHL. This suggests that they could also be used to good effect in the salvage setting. These drugs have been pioneered, and are now licensed, in solid tumours, e.g. melanoma and non-small cell lung cancer (Borghaei et al., 2015;Ugurel et al, 2016). They have also shown considerable promise in haematological malignancies, with the most promising results of all in cHL (Ansell et al. 2015, Moskowitz et al., 2014b). Indeed, the response of cHL to PD-1 (programmed cell death protein 1) inhibitors far exceeds the response rates seen in any other tumour type.

T cell activation is a complex and carefully regulated process. In addition to the interaction of the T cell receptor (TCR) with antigen presented on the major immune histocompatibility complex (MHC), it involves the interaction of multiple co-stimulatory and co-inhibitory molecules on antigen presenting cells (APCs) with their corresponding receptors on T cells. These inhibitory or “immune checkpoint” pathways inhibit the activity of CD8+ killer T cells and CD4+ helper T cells and enhance the activity of regulatory T cells. They prevent immune activation against self-antigens, protecting against auto-immune disease. They are also thought to be responsible for T cell anergy in chronic viral infections. Upregulation of these inhibitory ligands on tumour cells allows them to engage the corresponding receptor on immune effector cells and to hijack this “immune checkpoint” pathway.

Numerous receptor/ligand interactions in this regulatory immune pathway have been identified (Pardoll et al., 2012). Of these, the CTLA-4 (cytotoxic T lymphocyte associated antigen-4), and PD-1 pathways are best characterised in tumour cell evasion of the immune response. They are both also now therapeutic targets. The rationale is that inhibiting these pathways will overcome T cell anergy, and generate an anti-tumour immune response. Nivolumab, one such drug in this class, is a fully humanised monoclonal IgG4 antibody directed against PD-1, preventing it from binding to its ligands, PD-L1 and PD-L2.

There are several reasons why PD-1 blockade might be particularly effective in cHL:

- PDL-1, the ligand for PD-1, is over-expressed by the cancerous cell (the Hodgkin / Reed-Sternberg (RS) cell) of cHL due to polysomy of chromosome 9p, 9p copy gain, and 9p24.1a amplification, on which PDL-1 is located (Ansell et al, 2015).
- The 9p24.1 locus also encodes janus kinase 2 (JAK2), which further increases PD-L1 transcription through gene-dose dependent JAK-STAT signalling (Green et al. 2010).
- Epstein Barr virus (EBV) which is implicated in the pathogenesis of 10-40% of cHL, varying by subtype, also increases the expression of PD-L1 (Green et al. 2012).
- Histologically, cHL is characterised by a particularly extensive immune infiltrate, mainly consisting of CD4+ T helper 2 cells (Th2) and T regulatory cells (TRegs). These Th2 cells provide continuous CD40L stimulation and release cytokines that promote RS cell survival and proliferation. Therapeutic blockade of PD-1 may alter the proliferation and behaviour of different T cell subsets, disrupting this protective effect of the immune environment (Steidl et al. 2011).

Trial evidence for immune checkpoint inhibitors in cHL

Three key studies have demonstrated the efficacy of PD-1 inhibitors in relapsed/ refractory cHL. Ansell et al., 2015, reported on a cohort of 23 patients with relapsed/ refractory cHL, 18 of whom had had prior BV and 18 prior ASCT, treated with nivolumab. Response rates were remarkably high given how heavily pre-treated the population was: 87% achieved an ORR with 26% achieving a CR. Correlative studies on 10 tumour specimens showed copy number gains in PD-L1/PD-L2 on RS cells, active JAK/STAT signalling and low levels of PD-1 on infiltrating T cells. Younes et al. 2016, reported a 66% response rate to nivolumab in 80 patients with cHL, treated across 34 centres, who had failed ASCT and were relapsed after or refractory to BV.

An ongoing phase 1b trial of pembrolizumab in haematological malignancies, has reported on 15 patients with relapsed, refractory cHL, all of whom had failed prior treatment with BV and 71% of whom had failed prior ASCT. 65% achieved an ORR, with 16% achieving a CR (Moskowitz et al. 2014b).

Rationale for use of nivolumab in the salvage setting

In this study, all patients with relapsed / refractory cHL receiving first or second line salvage chemotherapy with the intent to proceed to SCT are potentially eligible. Patients are consented and registered during the first or second line salvage treatment. After 2 courses of first or second line salvage (4 cycles if being treated with brentuximab vedotin), patients will undergo an ^{18}FDG-PET-CT scan under trial conditions. Patients who are PET negative (Deauville score 1-3) will

have further management at their treating clinician's discretion and enter follow up for the purposes of the trial. Patients who are PET positive (Deauville score 4-5) will be eligible to receive single agent nivolumab on a 2 weekly intravenous schedule. A repeat PET-CT will be performed after 4 cycles of nivolumab. Patient achieving a negative PET (Deauville score 1-3) after 4 cycles of nivolumab and patients with evidence of progressive disease will stop nivolumab and enter follow up. Further management will be at the treating clinician's discretion, although it is anticipated that most patients will proceed to stem cell transplantation. Patients who remain PET positive (Deauville score 4-5) after 4 cycles of nivolumab, but without evidence of disease progression, will receive up to a further 4 cycles of nivolumab, after which another PET-CT will be performed. Further management will again be at the treating clinician's discretion, regardless of whether the PET-CT is positive or negative, with advice offered in the protocol. The rationale for continuing for 8 cycles is that in the Ansell et al. study (2015), of the patients who responded, only 12 out of 20 had achieved their first response by week 8, suggesting a delayed response in some patients. The rationale for not permitting more than 2 lines of salvage therapy prior to nivolumab, and limiting the number of cycles, is to reduce toxicity of potentially ineffective treatments that might compromise the patient's fitness for SCT.

Use of nivolumab in the salvage setting pre ASCT, rather than after relapse post ASCT, or progression through multiple lines of cytotoxic chemotherapy, is potentially advantageous for a number of reasons.

- Rates of ORR appear to be at least as good as for cytotoxic chemotherapy and BV, despite being tested in a more heavily pre-treated cohort, making nivolumab a very promising rescue salvage regime. This would potentially increase the proportion of patients eligible for ASCT, and reduce the risk of failure of this invasive and costly procedure.
- Using nivolumab in a more upfront context might avoid the need for exposure to multiple successive lines of cytotoxic chemotherapy, which impact negatively on the patient's fitness for ASCT.

There are also theoretical arguments why nivolumab might specifically be preferable to cytotoxic chemotherapy or BV in the salvage setting:

- It is less likely to induce neutropenia and peripheral neuropathy, which are well established side effects of BV and chemotherapy.
- Responses tend to be more durable, regardless of whether PR or CR is achieved (Ansell et al. 2015,Younes 2016), in contrast to BV in which long lasting responses are generally only seen in those achieving CR. Longer duration of response would allow time to plan for allograft, if this is the preferred treatment option, or potentially even obviate the need for ASCT, in patients in whom this procedure is deemed high risk.

Use of a PET stratified approach, rather than at the start of salvage therapy, as per the BRaVE study (NCT02280993), has the attraction of reserving this expensive treatment option for those who are likely to benefit from it most and thus making the trial schedule more likely to become standard of care if results are positive.

Safety of nivolumab in the salvage context

In the Ansell et al. study (2015), nivolumab was reasonably well-tolerated with most side effects being grade 1-2. Most frequently reported side effects were rash and thrombocytopenia. Grade 3-4 events included decreased lymphocytes count, increased serum lipase, stomatitis, pancreatitis, myelodysplasia (likely related to previous treatment rather than nivolumab). Patients in the pembrolizumab study suffered more grade 3 adverse events, including grade 3 transaminitis, colitis, pneumonitis, nephrotic syndrome, with 2 patients discontinuing therapy (Armand et al. 2015). However, on balance, this side effect profile is probably less severe than that seen with BV: 28% grade 3 with BV (Younes et al. 2012) compared with 16-22% with nivolumab (Armand et al. 2015, Ansell et al. 2015).

There are particular concerns about potential autoimmune complications of nivolumab for patients who may be candidates for subsequent allo-SCT, in terms of increased risk of severe GVHD. The extent of this problem is unclear as there is a lack of published data and experience. One small study reported on 12 relapsed/ refractory cHL patients treated with nivolumab post allo-HSCT. 2 patients developed grade III-IV skin acute GVHD (although one had a prior history of grade 2 skin GVHD). 1 patient developed grade IV neutropenia and 1 patient developed grade III thrombocytopenia (Herbaux et al., 2015). There is clearly more exploration to be done in this area, although it does not seem to be as great a problem as anticipated at present. This concern also lends weight to the argument for using nivolumab in a more upfront setting, rather than reserving it as a treatment of last resort post allo-HSCT.

Rationale for the selected dose schedule for ANIMATE

In the ANIMATE trial, eligible patients will receive 4-8 cycles of nivolumab at a dose of 240mg, given once every two weeks.

A flat dose of 240mg was selected, rather than the current EU licensed dose of 3mg/kg, in the light of research which has compared the two doses. A population pharmacokinetic modelling study has concluded that the safety and efficacy of the 240mg dose is equivalent to the 3mg/kg dose; this study has been used as evidence to support revision of the approval for Nivolumab in the USA (Zhao et al., 2017). The use of a flat dose rather than a body weight-based dose may also mitigate against potential risks associated with IMP handling and administration for this trial, for example by eliminating the risk of prescription errors..

The selection of a maximum of 8 cycles was selected bearing in mind the fact that checkpoint inhibition can take several cycles before a response is induced. In the Checkmate 205 study, however, the vast majority of responses had occurred by 16 weeks of therapy (8 cycles; Younes et al. 2016, therefore treating for less than 8 cycles could mean that some patients who are destined to respond would not have a long enough trial of the drug. Treating patients for more than 8 cycles could compromise the ability of responding patients to get to a potentially curative stem cell transplant if they suffer side effects or lose their response.

Two groups of patients will stop treatment after 4 cycles: patients with evidence of complete metabolic response on PET4 and patients with progressive disease. Patients in CMR will have already reached the maximum response to nivolumab, and therefore the clinical priority is to proceed to stem cell transplant. Patients with progressive disease after 4 cycles would not benefit

from any further treatment with nivolumab and would need alternative treatment to control their lymphoma.

Correlative biomarker studies

This study offers potential for exploratory biomarker studies which could offer insight into the mechanism of action of PD-1 inhibitors and help identify sub-sets of patients who are most likely to respond.

9p amplification will be assessed and correlated with response to nivolumab. Multicolour flow cytometry and immunohistochemistry will be used to characterise the phenotype of lymphocytes in the blood and tumour microenvironment. This will be performed on tumour blocks from biopsies before and after exposure to nivolumab. This would allow testing of the hypothesis that response to nivolumab correlates with a more activated Th-1, rather than Th2 and TReg, weighted microenvironment.

This study will also allow investigation into the optimum way of assessing response to PD-1 inhibitors. There is concern that because PD-1 inhibitors cause an immune flare, FDG-PET-CT may give false positive results (Kong et al. 2016). In this study positive PET scans will be correlated with tumour biopsies, assessing for active disease, where possible. Alternative measures of response will also be investigated, for example serum TARC. Serum TARC levels have been shown to correlate with good outcomes in patients treated with panobinostat post ASCT (Harrison et al. 2014).

3. TRIAL DESIGN

This is a single-arm, phase II, multi-centre study of the safety and efficacy of the PD-1 inhibitor, nivolumab, as second-line or third-line salvage therapy as a bridge to stem cell transplant (SCT) in relapsed/ refractory classical Hodgkin lymphoma patients not achieving a complete metabolic response (CMR) on FDG-PET post 2 cycles of first or second line salvage therapy. It will use an Ahern single stage design with independent data monitoring committee review to monitor for safety and efficacy.

Patients with relapsed/refractory classical Hodgkin lymphoma will be registered while undergoing first or second line salvage therapy (first line is preferred). Those eligible for the trial will have a centrally reviewed PET CT scan after 2 cycles of the salvage therapy they are receiving (or 4 cycles if they are undergoing treatment with brentuximab vedotin). Those with CMR on PET CT scan (Deauville score 1-3) will go on to receive further treatment according to the investigator's choice but will be followed up for trial data collection purposes; it is anticipated that most of these patients will proceed to SCT. Those achieving less than CMR on central review of FDG-PET (Deauville score 4-5) will be eligible to receive 4 x 2-weekly nivolumab infusions.

After 4 courses of nivolumab, patients will have an additional centrally reviewed PET-CT scan (PET4). Patients achieving CMR will not receive any further nivolumab, and it is anticipated that most of these patients will proceed to SCT. Those patients with PMR or no metabolic response (NMR) on PET4 can receive a further 4 cycles of nivolumab, again followed by a centrally reviewed PET-CT scan (PET8).

Patients with PMD on nivolumab at any point will stop nivolumab. If a repeat biopsy is obtained to confirm progressive disease histologically, the block should be sent to the HMDS, Leeds.

Further management after PET8 will be at the discretion of the investigator, although it is anticipated that those with CMR or PMR will proceed to SCT. If PET8 shows less than CMR (i.e. PMR or NMR), patients who consent will have a further biopsy to exclude false positive PET signal. The block should be sent to the HMDS, Leeds.

3.1. Trial Objectives

Primary Objectives

- To assess the efficacy of nivolumab as a second or third line salvage therapy in r/r cHL patients, particularly as a bridge to SCT.

Secondary Objectives

- To assess progression free survival and/or overall survival when nivolumab is used in this setting.
- To assess the safety and tolerability of nivolumab.
- To assess whether long term outcomes with nivolumab vary according to the depth of response obtained (whether PMR or CMR).

Exploratory Objectives

- To assess whether PET is a sensitive method for assessing response to nivolumab
- To explore potential biomarkers of response to nivolumab.
- To assess whether baseline biological characteristics predict response to nivolumab.
- To assess whether biological characteristics predict response to first line salvage treatment.

- To assess safety of subsequent allogeneic SCT for patients having this treatment modality

3.2. Trial Endpoints

Primary endpoints

- Overall response rate (ORR) by PET-CT scan following 4-8 cycles of nivolumab

Secondary endpoints

- Progression-free survival (PFS) at 1 year
- Overall survival (OS) at 1 year
- Proportion of patients proceeding to SCT (ASCT or alloSCT)
- Safety & toxicity of nivolumab, particularly autoimmune toxicity
- OS and PFS stratified by partial metabolic response (PMR) versus complete metabolic response (CMR) on FDG-PET
- Transplant-related mortality and rate of serious complications of allogeneic transplant (grade 3-4 graft-vs-host disease, hyperacute graft-vs-host disease and steroid-responsive febrile syndrome)

Exploratory endpoints

- Correlate PET positive disease with histological evidence of disease on biopsy to establish biopsy negative PMR rate (subject to patient consent)
- Correlate disease response, as assessed by FDG-PET and histology, with serological markers, including serum TARC
- Evaluate the correlation between response to nivolumab and biological parameters e.g. PD-1 expression on Reed-Sternberg cells

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
- ARSAC approval

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) Act (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) and trial monitoring plan
- Obtaining relevant license(s) for medical radiation exposure in the study, and renewing as necessary (PET centres)

4.1.1. Selection of Principal Investigator and other investigators at sites

Sites 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 the site. Co-investigators must be trained and approved by the PI. All investigators must be medical doctors and have experience of treating Hodgkin lymphoma. 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 leaves/goes on a leave of absence, UCL CTC **must be informed promptly** and a new PI identified and appointed by the site.

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 teleconference with site. Re-initiating sites may be required where there has been a significant delay between initiation and enrolling the first patient, as per monitoring plan.

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:

- Trial specific 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 & labels
- ARSAC certificate/license for the trial (PET centres only; if a site is referring patients to another hospital for PET-CT scans, the nominated PET centre must hold an ARSAC license for the trial prior to activation)

In addition, the following agreements must be in place:

- A signed Clinical Trial Site Agreement (CTSA) between the Sponsor and the relevant institution (usually an NHS Trust/Health Board)

4.2.3. Site activation letter

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.

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, adverse events of special interest, urgent events and pregnancies
- 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. However, in order to prevent unnecessary return visits, patients may consent to be registered on the same day as being given the information sheet, provided the member of staff taking consent is satisfied that the patient understands the trial and its implications, a member of the research team must then contact the patient in the following days to confirm that they are still willing to participate in the trial, and that confirmation of ongoing consent is documented prior to receiving study drug.

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 notes.

Site staff are responsible for:

- checking that the current approved versions 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 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
- following registration, giving the patient a copy of their signed consent form and patient information sheet
- following confirmation of eligibility for trial treatment, 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, where applicable, the reasons why they were not registered into the trial. 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 registration. Queries in relation to the eligibility criteria must be addressed prior to 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' 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 (Pre-registration Assessments) for the list of assessments and procedures required to evaluate the suitability of patients prior to entry.

6.2.1. Inclusion criteria – Study registration

1. Age 16 or over
2. Primary refractory classical Hodgkin lymphoma or classical Hodgkin lymphoma in first relapse
3. About to receive, receiving, or within 14 days of receiving first 2 cycles of first or second line salvage therapy (4 cycles if receiving treatment with brentuximab vedotin)
4. Fit for autologous stem cell transplantation
5. Written informed consent
6. Willing to comply with the contraceptive requirements of the trial (see section 6.3.4)

6.2.2. Exclusion criteria – study registration

1. Nodular lymphocyte predominant Hodgkin lymphoma
2. Women who are pregnant or breastfeeding
3. History of colitis, inflammatory bowel disease or pneumonitis
4. Patients with autoimmune disorders, except patients with vitiligo, diabetes mellitus type 1, hypo- and hyperthyroidism not requiring immunosuppressive therapy
5. Known active hepatitis B or C infection
6. Known HIV infection
7. History of allergy (including severe/life threatening skin reaction) to monoclonal antibodies, anaphylaxis or uncontrolled allergy
8. Major surgery within 4 weeks prior to registration
9. Myocardial infarction, unstable angina, coronary artery bypass graft, cerebrovascular accident or transient ischaemic attack within the past 6 months
10. Non-haematological malignancy within the past 3 years with the exception of (a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; (b) carcinoma in situ of the cervix or breast; (c) prostate cancer of Gleason grade 6 or less with stable prostate-specific antigen levels; or (d) cancer considered cured by

surgical resection or unlikely to impact survival during the duration of the study, such as localised transitional cell carcinoma of the bladder or benign tumours of the adrenal gland or pancreas

6.2.3. Inclusion criteria for trial treatment

1. Has received 2 cycles of first or second line salvage chemotherapy, (4 cycles if receiving treatment with brentuximab vedotin)
2. PET positive (Deauville score 4 or 5) after 2 cycles of first or second line salvage chemotherapy (4 cycles if receiving treatment with brentuximab vedotin)
3. Fit for further salvage chemotherapy
4. ECOG performance status 0-1
5. Creatinine clearance >30ml/min calculated by Cockcroft-Gault formula
6. Bilirubin <1.5 x ULN, ALT/AST <2.5 x ULN
7. Adequate bone marrow function (Hb >80g/l, Platelets >50 x 10^9/l, neutrophils >1.0 x 10^9/l)

6.2.4. Exclusion criteria for trial treatment

1. Deauville score 1-3 after 2 cycles of first or second line salvage chemotherapy (4 cycles if receiving treatment with brentuximab vedotin)
2. Positive serology for hepatitis B or C unless (a) hepatitis B positive due to vaccination (HBsAb positive, all other tests negative) or (b) past hepatitis B infection with low risk of reactivation (HBsAb positive & HBcAb positive, other tests (including hepatitis B DNA) negative - PI approval needed) – see section 6.2.5 for more details
3. Active infection requiring systemic therapy
4. Ongoing requirement for immunosuppressive therapy, apart from inhaled, intranasal, topical corticosteroids or systemic corticosteroids at low doses (≤10mg prednisolone per day, or the equivalent)
5. Chemo- or radiotherapy or corticosteroids at a dose of more than 10mg per day prednisolone or equivalent within 14 days prior to response PET-CT. NOTE: corticosteroids can be used AFTER a positive PET-CT scan for symptomatic disease but must be weaned to a dose of prednisolone ≤10mg/day or less (or equivalent) at least 7 days prior to starting nivolumab.
6. Treatment with any investigational agent within 28 days prior to planned start of nivolumab
7. Ongoing grade 2-4 non-haematological toxicities related to prior Hodgkin lymphoma treatments, with the exception of alopecia and grade 2 fatigue
8. Pregnant or breastfeeding women

6.2.5. Hepatitis B serology – eligibility criteria

The table below contains a brief outline for interpretation of HBV serology:

HBsAg	HBsAb*	HBcAb	HBV DNA	Interpretation	Eligible Y/N
-	ND	-	-	No prior infection, vaccination status unknown	Y
-	+	-	-	Vaccinated	Y
-	+/ND	+	-	Past infection; low risk reactivation	Y at discretion of PI
-	+/-/ND	+	+	Occult infection	N
+	Any results			Chronic carrier or infection	N

HBsAg = Hepatitis B surface antigen; HBsAb = Hepatitis B surface antibody; HBcAb = Hepatitis B core antibody; HBV DNA – Hepatitis B virus DNA
* HBsAb testing only required if standard of care locally.

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
- been postmenopausal for 12 consecutive months (i.e. who has had menses at any time in the preceding 12 consecutive months without an alternative medical cause)
- had premature ovarian failure confirmed by a specialist gynaecologist

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 Nivolumab.

Overall, the trial treatment has been assessed as having a high risk of teratogenicity/fetotoxicity due to a lack of available data in the reference safety information. However, the risk of pregnancy in the patient population is considered to be low.

6.3.3. Pregnancy testing

All female participants who are WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/l or equivalent units of HCG) at screening, following 2 cycles of salvage and and within 24 hours prior to starting nivolumab treatment. Pregnancy testing

should be repeated every 4 weeks during treatment, then at 1, 2 and 3 months post treatment. Pregnancy test results must be filed in the patient source data.

6.3.4. Contraceptive Advice

Requirement for female patients

All female participants who are WOCBP must consent to use one of the following methods of highly effective contraception from registration until 6 months after the last administration of nivolumab. 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[1]:
  - oral
  - intravaginal
  - transdermal
  - progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
    - oral (e.g. desogestrel)
    - injectable
    - implantable[2]
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[2]
- bilateral tubal occlusion[2]
- vasectomised partner[2,3]
- sexual abstinence[4]

1. Hormonal contraception may be susceptible to interaction with the IMP/NIMP, which may reduce the efficacy of the contraception method.

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

3. 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.

4. 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

Because the risk of genotoxicity and/or risk to the foetus from exposure to seminal fluid is unknown:

- 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, during treatment and until 8 months post last treatment administration
- Male patients must also advise their female partners who are WOCBP regarding 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, the patient will not receive trial treatment unless they elect to have a termination (please note, in such instances, termination must be the patient's own choice)
- during treatment, the patient will be withdrawn from further trial treatment and, if they consent to pregnancy monitoring, followed up until pregnancy outcome
- after the end of the treatment, but during the pregnancy at-risk period, the patient will be followed up until pregnancy outcome if they consent to pregnancy monitoring.

Male patients:

If a female partner of a male patient becomes pregnant between the start of trial treatment and 8 months post last treatment administration, the male participant can continue with the study whilst their female partner will be followed up if they have given consent to pregnancy monitoring.

Notification to UCL CTC – refer to Pregnancy Report Processing (see section 12.8)

6.3.6. Long Term Infertility

There have been no studies to evaluate the effect of nivolumab on fertility. Thus, the effect of nivolumab on male and female fertility is unknown.

7. REGISTRATION PROCEDURES

7.1. Registration

Patient registration will be undertaken centrally at UCL CTC, and this may be performed before or during first or second line salvage treatment, but must be no later than 14 days after completing the second cycle of first line salvage.

Pre-registration evaluations should be carried out at sites as detailed in section 9.1 (Pre-registration Assessments).

Following pre-registration evaluations, confirmation of eligibility and consent of a patient at a site, the registration case report form must be fully completed and faxed to UCL CTC. The registration form 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 sent.

N.B. If the site is unable to fax, registration forms may be sent by email. If emailing forms, patient identifiable information from the form (e.g. NHS number, day and month of birth) must be redacted before it is emailed to ctc.animate@ucl.ac.uk. The identifiable information must be provided to 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 UCL CTC, and a copy kept in the patient file at site.

Once eligibility has been confirmed a trial number will be assigned for the patient and details should be added to the form by the site.

UCL CTC will e-mail confirmation of the patient's inclusion in the trial and their trial number to the main contact and pharmacy.

Registration telephone number:	020 7679 9860
Registration fax number:	020 7679 9861
Registration email address:	ctc.animate@ucl.ac.uk
UCL CTC Office hours:	09:00 to 17:00 Monday to Friday, excluding Bank Holidays
Please note that registration forms received after 16:00 may not be processed until the next working day	

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

- A copy of their signed consent form and patient information sheet.

7.2. Confirmation of eligibility for treatment

Eligibility for trial treatment will be confirmed centrally at UCL CTC after two cycles of first or second line salvage chemotherapy (four cycles if receiving treatment with brentuximab vedotin).

Evaluations should be carried out at sites as detailed in section 9.1 (Assessment of eligibility for nivolumab treatment). The results of these investigations will be used alongside the outcome of the central review of the patient's post-salvage PET-CT scan to confirm eligibility for trial treatment.

Following post-salvage evaluations, post-salvage case report form must be fully completed and faxed to UCL CTC. If a site is unable to send faxes, forms may be emailed to ctc.animate@ucl.ac.uk. The post-salvage case report form will be used to confirm patient

eligibility for trial treatment, and must be sent even if the patient is not eligible to receive nivolumab. If further information is required, UCL CTC will contact the person requesting registration to discuss the patient and request updated forms to be sent.

Registration telephone number:	020 7679 9860
Registration fax number:	020 7679 9861
Registration email address:	ctc.animate@ucl.ac.uk
UCL CTC Office hours:	09:00 to 17:00 Monday to Friday, excluding Bank Holidays

Please note that registration forms received after 16:00 may not be processed until the next working day

Once eligibility for trial treatment has been confirmed:

- UCL CTC will e-mail the main contact and pharmacy at site confirming that the patient may proceed with trial treatment.
- Eligible patients must be provided with 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.
- A GP letter should be sent to the patient's GP confirming that the patient is eligible for trial treatment (delete on GP letter template as applicable).

Where patients are not eligible for trial treatment:

- A GP letter should be sent to the patient's GP confirming that the patient is not eligible for trial treatment and that trial treatment will be given (delete on GP letter template as applicable).
- The patient will enter follow up for the purposes of the trial. See section 9.6.1 for details.

7.3. Initial Trial Drug Supply

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

8. TRIAL TREATMENT

Investigational Medicinal Products (IMPs)

For the purpose of this protocol, the IMP is Nivolumab (Opdivo®).

Non Investigational Medicinal Products (NIMPs)

There are no drugs defined as NIMPs for this trial.

8.1. Investigational Medicinal Products

Nivolumab (Opdivo®) will be provided free of charge by Bristol-Myers Squibb.

Nivolumab (Opdivo®) is licensed, but within this trial will be used outside its licensed indication.

Refer to the Summary of Drug Arrangements for detailed guidance on supply and storage of Nivolumab.

8.2. Treatment Summary

Patients for whom eligibility for treatment is confirmed (see section 7.2 for details) will receive 4-8 x 14-day cycles of nivolumab. Nivolumab 240mg will be administered on day 1 of each 14 day cycle. Dose banding is not permitted.

Trial treatment should begin within 4 weeks following the PET-CT scan to confirm eligibility for trial treatment (PET0).

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Nivolumab 240mg IV	X													

Patients will have a PET-CT scan after 4 cycles (PET4). This should be performed on cycle 4, day 11-13 to allow time for central review before the cycle 5 day 1 visit would be due. Please note that patients must not proceed to cycle 5 prior to receipt of the PET4 central review report.

- If PET-negative (Deauville 1-3), they will stop nivolumab. Further management will be at the discretion of the treating clinician and the patient will be followed up as per the trial protocol (see section 9.6.2).
- If the scan shows disease progression, they will stop nivolumab and have further salvage at their treating clinician's discretion. They will enter into annual follow up for the trial.
- If the scan is positive (Deauville 4-5) but there is no evidence of disease progression, the patient will have a further 4 cycles of nivolumab. Following this, they will be followed up as per the trial protocol (see section 9.6.2).

8.3. Trial Treatment Details

The IMP for this trial is nivolumab.

Patients who are PET positive following first or second line salvage will initially receive 4-8 cycles of single agent nivolumab.

Nivolumab will be given at a dose of 240mg as an intravenous infusion over 30 minutes on day 1 of each 14 day cycle.

There are no premedications recommended during the first cycle of nivolumab. If an acute infusion reaction occurs, subjects should be managed according to section 8.5 for subsequent cycles.

Every effort should be made to deliver treatment on time, however in exceptional circumstances (e.g. to allow for public holidays), it is permissible to bring treatment forward by up to 2 calendar days or to delay treatment for up to 3 calendar days. There should be no less than 12 days between doses. Treatment may be delayed for up to 4 weeks to allow for resolution of adverse events (see section 8.5 below).

8.4. Dose Modifications

Dose reductions and escalations of nivolumab are **not** permitted. Nivolumab should be delayed for up to 4 weeks for the following:

- Any ≥ grade 3 Haematological toxicity (Hb <80g/dl, platelets <50 x10^9/l, neutrophils <1.0 x10^9/l)
- Any ≥ grade 3 drug-related, non–haematological AE **except**:
    - Fatigue
    - Alopecia
    - Drug related endocrinopathies adequately controlled with physiologic hormone replacement.
    - Electrolyte disturbances that can be corrected and are unlikely to cause clinical safety concerns.
- Any grade 2 auto-immune complication including pneumonitis, renal dysfunction, diarrhoea/ colitis, neurological complication, derangement of liver function tests. Guidelines for management of auto-immune complications are set out in Section 8.5.
- Any non-drug related AE where the in the local investigator's opinion delaying treatment is in the patient's best interest.

Treatment may be resumed once AEs resolve to grade ≤1 or baseline value. If the criterion to resume treatment is met (see section 8.5), the subject should restart treatment at the next scheduled time-point, as set out in the protocol. If treatment is delayed by >4 weeks, the subject should be permanently discontinued from study therapy. Treatment may be discontinued earlier at the discretion of the investigator if it is felt that continuing on the trial treatment will compromise a successful outcome for the patient.

A treatment summary form must be completed and sent to UCL CTC promptly if treatment is discontinued. The patient will enter follow up as per the trial protocol (see section 9.6.2).

Treatment Discontinuation Criteria

Nivolumab treatment should be permanently discontinued for the following:

- ≥grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy. Uveitis is inflammation of the eye, and includes anterior uveitis (synonymous with iritis), posterior uveitis (comprising vitritis, choriditis, retinitis, chroioretinitis) and pan-uveitis (inflammation of the anterior chamber, vitreous, retina and choroid).

- ≥grade 3 pneumonitis
- Any grade 4 drug related AE or laboratory abnormality apart from the following:
    - Grade 4 neutropenia <7 days (G-CSF may be instituted, and continued until neutrophils exceed $1.5x10^9$/L, as per institutional policy)
    - Grade 4 amylase or lipase 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.
- Progressive disease: for assessment of disease response see Appendix 3.

A treatment summary form must be completed and sent to UCL CTC promptly if treatment is discontinued. See section 9.5 for further details of investigations required when treatment is withdrawn. The patient will enter follow up as per the trial protocol (see section 9.6.2).

8.5. Management of Adverse Events

8.5.1. Autoimmune complications

Because of its mechanism of action, autoimmune complications are common with nivolumab. Where sites have local policies for management of autoimmune toxicity, these may be followed. Where there is no local policy, suggested guidelines for management of such autoimmune complications are set out below. Clinicians are also advised to refer to the manufacturer's guidelines (see summary of product characteristics).

Autoimmune toxicities are regarded as AEs of special interest for this trial, requiring expedited reporting to UCL CTC. Please refer to section 12.4 for details of how and when to report autoimmune events.

If treatment is delayed by >4 weeks due to autoimmune toxicity, the subject should be permanently discontinued from study treatment.

8.5.1.1 **Management of auto-immune diarrhoea/colitis**

Exclude infective and disease-related causes e.g. with stool culture and gastrointestinal endoscopy if indicated.

Diarrhoea/ Colitis **CTCAE v5 grade**	**Action – trial treatment**	**Recommended management of toxicity**
Grade 1 Diarrhoea <4 stools/day over baseline	Continue nivolumab at 240mg	Treat symptoms as per local policies e.g. Loperamide **If worsens:** Treat as below, as per severity
Grade 2 Diarrhoea 4-6 stools/day over baseline	Delay nivolumab treatment Restart nivolmab at 240mg if/when improves to grade 0.	Treat symptoms as per local policies.

IV fluids <24 hours Colitis: abdominal pain, blood in stool	If steroids given, patient must have been weaned to ≤10mg per day (or equivalent) before restarting treatment. Maximum permitted delay 4 weeks.	Consider investigation with lower GI endoscopy Consider prophylactic antibiotics. **If symptoms persist >5-7 days or recur**: Initiate steroid treatment as per local policy (recommended dose 0.5-1.0mg/kg/day IV methylprednisolone or equivalent dose of oral steroids). When symptoms improve to G1, taper steroids over at least 4 weeks. **If worsens/ persists after 3-5 days on steroids:** treat as G3-4.
Grade 3 and 4 Diarrhoea: G3: >7 stools/day over baseline; hospitalisation indicated; limiting self care ADL G4: life threatening consequences; urgent intervention indicated. Colitis: G3: severe adominal pain; peritoneal signs G4: life threatening; urgent intervention indicated (e.g. perforation)	Permanently discontinue nivolumab treatment.	Steroid treatment as per local policy (recommended 1-2mg/kg/day IV methylprednisolone or equivalent dose of oral steroids). When symptoms improve to G1, taper steroids over at least 4 weeks. Consider lower GI endoscopy. Prophylactic antibiotics for infection. **If persists >3-5 days:** refer to manufacturer's recommendations or manage as per local policy.

8.5.1.2 **Management of autoimmune pneumonitis**

Exclude infectious and disease-related aetiologies.

CTCAE v5 grade of pneumonitis	**Action – trial treatment**	**Recommended management of toxicity**
Grade 1 Asymptomatic, radiographic changes only	Continue nivolumab at 240mg.	Monitor for symptoms every 2-3 days. Re-image at least every 2 weeks Monitor closely for worsening of symptoms and treat as G2/G3 and G4 accordingly
Grade 2 Mild to moderate new symptoms; medical intervention indicated; limiting instrumental ADL	Delay nivolumab treatment. Restart nivolumab at 240mg if/when symptoms and radiographic appearances resove.	Monitor symptoms daily and consider hospitalisation. Steroid treatment as per local policy (recommended dose 1mg/kg/day IV methyl-

	If steroids given, patient must have been weaned to ≤10mg per day (or equivalent) before restarting treatment. Maximum permitted delay 4 weeks.	prednisolone or equivalent dose of oral steroids). Consider bronchoscopy. Prophylactic antibiotics. Infectious disease and respiratory referrals. Re-image every 1-3 days **If improves:** when symptoms resolve, taper steroids over at least 4 weeks. **If not improving after 2 weeks or worsening:** treat as G3-4
Grade 3-4: G3: Severe new symptoms New/worsening hypoxia Limiting self-care ADL Oxygen indicated G4: Life threatening respiratory compromise Urgent intervention indicated (e.g. tracheotomy or intubation	Permanently discontinue nivolumab treatment.	Hospitalise patient. Steroid treatment as per local policy (recommended dose 2-4mg/kg/day IV methylprednisolone or equivalent dose of oral steroids). Prophylactic antibiotics. Consider bronchoscopy. Infectious disease and respiratory referrals. **If improves to baseline**: taper steroids over at least 6 weeks. **If not improving after 48 hours or worsening:** manage as per local policy – consider additional immunosuppression e.g. infliximab, cyclophosphamide, IVIg or mycophenolate mofetil.

8.5.1.3 **Management of autoimmune hepatitis**

Exclude infective and disease related causes, and hepatotoxicity of other concomitant medications

Hepatitis **CTCAE v5 grade**	**Action – trial treatment**	**Recommended management of toxicity**
Grade 1: AST or ALT >ULN - 3xULN and/or Bilirubin >ULN - 1.5xULN	Continue nivolumab treatment at 240mg.	Continue monitoring of liver function tests as per protocol. If worsening, treat as G2 or G3-4
Grade 2: AST/ALT >3xULN - 5xULN and/or	Delay nivolumab treatment	Increase frequency of monitoring to every 3 days **If persists >3 days or worsens:**

Bilirubin >1.5xULN - 3xULN	Restart nivolumab at 240mg if/when results improve to baseline. If steroids given, patient must have been weaned to ≤10mg per day (or equivalent) before restarting treatment. Maximum permitted delay 4 weeks.	Steroid treatment as per local policy (recommended dose 0.5-1mg/kg/day IV methylprednisolone or equivalent dose of any oral steroids). If no improvement after a further 3 days, treat as for G3-4. Consider prophylactic antibiotics for opportunistic infections.
Grade 3-4: AST or ALT >5xULN and /or Bilirubin >3xULN	Permanently discontinue nivolumab treatment.	Increase frequency of monitoring to every 1-2 days: Steroid treatment as per local policy (recommended dose 1-2mg/kg/day IV methylprednisolone or equivalent dose of oral steroids). Add prophylactic antibiotics for opportunistic infections. Consult gastroenterologist. **If returns to G2:** taper steroids over at least 4 weeks **If not improving after 3-5 days or rebounds:** give additional immunosuppression as per local policy.

8.5.1.4 **Management of autoimmune dermatitis**

New or worsening rash. Exclude other non-autoimmune causes e.g. swab potentially infective lesions.

Rash **CTCAE v5 grade**	**Action – trial treatment**	**Recommended management of toxicity**
Grade 1-2: G1: Rash covers <10% body surface area G2: Rash covers 10-30% body surface area	Continue nivolumab treatment at 240mg. **If persists >1-2 weeks despite symptomatic treatment or recurs:** Delay nivolumab treatment Restart nivolumab at 240mg if/when symptoms improve If steroids given, patient must have been weaned to ≤10mg per	Treat symptoms as per local policiese.g. anti-histamines, topical steroids **If persists >1-2 weeks or recurs:** Consider skin biopsy. Consider steroid treatment as per local policy (recommended dose 0.5mg to 1mg/kg/day IV

	day (or equivalent) before restarting treatment. Maximum permitted delay 4 weeks.	methylprednisolone equivalent dose of oral steroids). **If worsens:** treat as G3-4.
Grade 3: Covering >30% body surface area; erythroderma **Grade 4:** Life-threatening consequences	**For grade 3:** Delay nivolumab treatment. Restart nivolumab at 240mg if/when symptoms resolve. If steroids given, patient must have been weaned to ≤10mg per day (or equivalent) before restarting treatment. Maximum permitted delay 4 weeks. **For grade 4:** Permanently discontinue nivolumab treatment.	Consider skin biopsy. Dermatology referral recommended. Steroid treatment as per local policy (recommended dose 1-2mg/kg/day IV methylprednisolone or equivalent dose of oral steroids). Prophylactic antibiotics against opportunistic infections.
Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Permanently discontinue treatment.	Refer to specialist unit for assessment and treatment.

8.5.1.5 **Management of immune related endocrinopathies**

New or worsening endocrine disorder.

Endocrine disorder	**Action – trial treatment**	**Recommended management of toxicity**
Asymptomatic TSH abnormality	Continue nivolumab treatment at 240mg.	If TSH <0.5xLLN or >2xULN or consistently out of range in 2 subsequent measurements, include free T4 and consider endocrinology opinion.
Symptomatic endocrinopathy (CTCAE G2-3 hypothyroidism, G2-3 hyperthyroidism, G2 adrenal insufficiency, G2-3 hypophysitis, G3 diabetes)	Delay nivolumab treatment. Restart nivolumab at 240mg if/when symptoms improve. If steroids given, patient must have been weaned to ≤10mg per day (or equivalent) before restarting treatment. Maximum permitted delay 4 weeks. Treatment should continue alongside hormone replacement	Refer to Summary of Product Characteristics for detailed guidance on management of individual endocrinopathies. Monitor endocrine function and relevant hormone levels. Steroid treatment as per local policy (recommended dose 1-2mg/kg/day IV methylprednisolone or equivalent dose of oral steroids). If improves, taper steroids over at least 1 month.

	therapy as long as no symptoms are present.	Hormone replacement as per local policy. Consider prophylactic antibiotics against opportunistic infection.
Severe endocrinopathy (G4 hypothyroidism, G4 hyperthyroidism, G3-4 adrenal insufficiency, G4 hypophysitis, G4 diabetes)	Permanently discontinue nivolumab treatment.	Refer to Summary of Product Characteristics for detailed guidance on management of individual endocrinopathies. Monitor endocrine function and relevant hormone levels. Steroid treatment as per local policy (recommended dose 1-2mg/kg/day IV methylprednisolone or equivalent dose of oral steroids). If improves, taper steroids over at least 1 month. Hormone replacement as per local policy. Consider prophylactic antibiotics against opportunistic infection.
Suspicion of adrenal crisis e.g. severe hypotension disproportionate to current illness *Note: if adrenal crisis is excluded, treat as for symptomatic endocrinopathy.*	Permanently discontinue nivolumab treatment.	Exclude sepsis: give broad spectrum antibiotics if any clinical suspicion. Manage for Addisonian crisis as per local protocols. Consult endocrinologist.

8.5.1.6 **Management of renal toxicity**

Exclude other causes e.g. nephrotoxicity of concomitant medications, outflow tract obstruction, disease-related causes.

Creatinine elevation **CTCAE v5 grade**	**Action – trial treatment**	**Recommended management of toxicity**
Grade 1 Creatinine >ULN - 1.5xULN	Continue nivolumab treatment at 240mg.	Monitor creatinine weekly If resumes to baseline, resume creatinine monitoring as per section 9.4 (assessments during treatment) **If worsens**: treat as G2-3 or as G4
Grade 2 Creatinine 1.5xULN - 3xULN	Delay nivolumab treatment.	Closely monitor creatinine levels (recommended every 2-3 days)

Grade 3 Creatinine 3xULN - 6xULN	Restart nivolumab at 240mg if/when returns to ≤G1. If steroids given, patient must have been weaned to ≤10mg per day (or equivalent) before restarting treatment. Maximum permitted delay 4 weeks.	Steroid treatment as per local policy (recommended dose 0.5-1mg/kg/day IV methylprednisolone or equivalent dose of IV steroids). Once improved, taper steroids over at least 1 month. Consult nephrologist and consider renal biopsy. **If no improvement after 7 days or worsening after 48 hours**: Treat as G4.
Grade 4 Creatinine >6xULN	Permanently discontinue nivolumab treatment	Monitor creatinine levels daily. Steroid treatment as per local policy (recommended dose 1-2mg/kg/day IV methylprednisolone or equivalent dose of oral steroids). Once improved, taper steroids over at least 1 month. Consult nephrologist and consider renal biopsy.

8.5.1.7 **Management of neurological toxicity**

New or worsening neurological symptoms. Exclude non-inflammatory causes such as infections (encephalitis, meningitis, PML), tumour progression (causing for example cranial nerve or spinal cord compression) or vascular causes (cerebral bleed or infarction).

Grade of neurological toxicity **CTCAE v5grade**	**Action – trial treatment**	**Recommended management of toxicity**
Grade 1 Asymptomatic or mild symptoms not requiring intervention	Continue nivolumab treatment at 240mg.	Monitor closely. **If worsens:** treat as G2-3 or G4.
Grade 2 Moderate symptoms, limiting instrumental ADL	Delay nivolumab treatment. Restart nivolumab at 240mg if/when returns to ≤G1. If steroids given, patient must have been weaned to ≤10mg per day (or equivalent) before restarting treatment. Maximum permitted delay 4 weeks.	Treat symptoms as per local guidelines. Steroid treatment as per local policy (recommended dose 0.5-1mg/kg/day IV methylprednisolone or equivalent dose of oral steroids). Once improved, taper steroids over at least 1 month. **If worsens**; treat as G3-4.

Grade 3-4 Severe symptoms limiting self care ADL	Permanently discontinue nivolumab treatment.	Obtain neurology opinion. Treat symptoms as per local guidelines. Steroid treatment as per local policy (recommended dose 1-2mg/kg/day IV methylprednisolone or equivalent dose of oral steroids). Prophylactic antibodies for opportunistic infections. **If improves to G2**: Taper steroids over at least 1 month. **If worsens or atypical presentation:** Consider IVIg or other immunosuppressive therapies as per local guidelines.

8.5.1.8 **Management of other immune-related adverse reactions**

Adequate evaluation should be performed to confirm aetiology and exclude other causes.

See summary of product characteristics for detailed guidance on management of individual toxicities.

CTCAE v5 grade	**Action – trial treatment**	**Recommended management of toxicity**
Grade 1	Continue nivolumab treatment at 240mg.	Treatment for symptoms as per local policy.
Grade 2 (first occurrence)	Delay nivolumab treatment Restart nivolumab at 240mg if/when returns to ≤G1. If steroids given, patient must have been weaned to ≤10mg per day (or equivalent) before restarting treatment. Maximum permitted delay 4 weeks.	Treat symptoms as per local guidelines. Steroid treatment as per local policy; taper prior to restarting nivolumab.
Grade 3 (first occurrence – except myocarditis – see below)	Delay nivolumab treatment. Restart nivolumab at 240mg if/when returns to ≤G1. If steroids given, patient must have been weaned to ≤10mg per	Treat symptoms as per local guidelines. Steroid treatment as per local policy; taper prior to restarting nivolumab.

	day (or equivalent) before restarting treatment. Maximum permitted delay 4 weeks.	
Grade 3 myocarditis	Permanently discontinue nivolumab treatment.	Refer for specialist opinion. Manage as per local policy.
Grade 4 or recurrent grade 3; Persistent grade 2 or 3 despite intervention; Inability to reduce corticosteroid dose to 10mg prednisolone per day or equivalent	Permanently discontinue nivolumab treatment.	Treat symptoms as per local guidelines. Steroid treatment as per local policy. Seek specialist opinion.

8.5.2. Recommendations for Treatment of Nivolumab Related Infusion Reaction

As nivolumab is a fully humanised immunoglobulin, it is unlikely to be immunogenic and induce an infusion or hypersensitivity reaction. However, if such a reaction were to occur, it might manifest with fevers, chills, rigors, rash, headache, arthralgia, hypo- or hypertension, bronchospasm. All grade 3 or grade 4 infusion reactions should be reported as an SAE within 24 hours (see section 12.4.4 for details of reporting).

For grade 1 symptoms (Mild reaction, infusion interruption not indicated)

- Remain at bedside and monitor subject until recovery from symptoms.
- Premedication is recommended prior to subsequent infusions. Administration of 10mg IV chlorphenamine and paracetamol 1g PO at least 30 minutes prior to infusion is recommended, but local policies may be followed.

For grade 2 symptoms (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic management)

- Stop the nivolumab infusion
- Give supportive care as per local policies. IV infusion of 0.9% sodium chloride solution for injection, and treatment with 1g paracetamol PO, 10mg IV chlorphenamine is recommended. Consider bronchodilator therapy and corticosteroids, up to 25mg IV hydrocortisone is recommended.
- Restart the infusion at 50% of the original infusion rate when symptoms resolve. If no further complications occur after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subjects closely.
- Premedication is recommended prior to subsequent infusions. Use of paracetamol, chlorphenamine and hydrocortisone prior to infusion is recommended, but local policies may be followed.

For grade 3 or 4 symptoms (Grade 3: not rapidly responsive to symptomatic management; recurrence of symptoms following initial improvement) (Grade 4 life threatening; pressor or ventilator support indicated)

- Stop the nivolumab infusion
- Give supportive care as per local policies. An IV infusion of 0.9% sodium chloride solution for injection and treatment with paracetamol, chlorphenamine, bronchodilators (as described for grade 2 reactions above), and 100mg IV methyl-prednisolone or equivalent is recommended.
- Follow institutional guidelines for anaphylaxis if indicated and involve intensive care/ critical care outreach teams at an early stage.

Tumour lysis risk

Nivolumab can be associated with tumour lysis syndrome, and patients should be risk-assessed and managed as per local protocols for patients undergoing chemotherapy.

8.5.3. Recommendations for management of pDILI

The diagnostic criteria for pDILI are:

- AST or ALT >3 x ULN

and

- Total bilirubin >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

and

- No other immediately apparent causes of transaminase elevation and hyperbilirubinemia, including but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic

There is no specific management for pDILI. If a patient presents with abnormal liver function tests as outlined above, further investigation should be carried out to establish whether the patient has pDILI or autoimmune liver disease.

- Nivolumab should be permanently discontinued.
- Treatment should be given as clinically indicated.
- If autoimmune liver disease is suspected, this should be managed as per section 8.5.1.3 above

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

Overdose

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.

No specific information is available on the management of nivolumab overdose. The patient should be carefully monitored and supportive care instituted as appropriate.

Any overdoses require expedited reporting to UCL CTC as an SAE (see section 12.2.2~~12.2.2~~ (Reporting of serious adverse events) for reporting procedures).

Any overdoses must also be reported as an incident according to the instructions in section 13.1 (Incident reporting).

See also section 12.4.3 (Overdoses).

Trial treatment error

Any unintentional error in prescribing, dispensing, or administration of a trial 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.

Include details from IB/SPC on the clinical management of trial treatment errors, where available. Trial Treatment errors should be reported on in incident report (see section 13.1~~13.1~~). Any adverse events resulting from a medication error should be reported as an SAE (see section 12.2.2~~12.2.2~~ for reporting procedures).

Occupational exposure

Exposure to a trial treatment 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~~13.1~~).

8.7. Supportive Care

No specific supportive medication is advised with nivolumab. Recommended supportive care for patients with autoimmune complications or infusion reactions are set out in section 8.4.

Anti-emetics, anaglesics, antibiotics, electrolyte and fluid replacement, anti-coagulants and anti-platelet agents may be given in accordance with local policies and as clinically indicated.

Medications used to treat pre-existing co-morbidities can be continued, with the exception of immune-suppressants (as set out in section 8.8). Supportive/prophylactic medications recommended to continue post previous chemotherapy regimes, e.g. acyclovir, may also be continued.

GCSF may be given as per local policy for neutropenia persisting for greater than 7 days.

Any supportive medications given should be clearly documented in the patient notes.

8.8. Contraindications

According to the IB for nivolumab, no drugs are contraindicated during nivolumab treatment.

Any other systemic anti-cancer therapy or radiotherapy is prohibited while the patient is receiving trial treatment. Steroids should be weaned down to ≤10mg/day (prednisolone; or the equivalent dose of other steroids) within 7 days prior to starting trial treatment.

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.

Nivolumab supplied for the ANIMATE trial are for eligible ANIMATE trial patients only and must not be used outside the context of this protocol.

8.9.1. Temperature Excursions

All temperature excursions outside the storage conditions specified in the IB/Summary of Drug Arrangements/labels 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
- a '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, dispensing, reconciliation and destruction of unused medication (on sponsor authorisation). Accountability forms will be supplied, and must be used, unless there is 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 14.1 (Central Monitoring).

8.10. Clinical Management after Treatment Discontinuation

Clinical management following treatment discontinuation will be at the treating clinician's discretion.

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.

8.11. Drug Provision after the End of the Trial

BMS will supply sufficient nivolumab for all eligible patients to receive up to 8 cycles of nivolumab. Patients will not continue treatment beyond 8 cycles, and there are no arrangements in place for supply following the end of the trial.

9. ASSESSMENTS

Please also see Schedule of Events table in Appendix 2

9.1. Pre-registration Assessments

Registration will take place before, during or within 14 days of completing the first 2 cycles of first or second line salvage treatment (4 cycles if treated with brentuximab vedotin). 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 must be carried out within 28 days prior to registration unless otherwise stated:

- Medical history
- Pregnancy test (serum or urine; women of childbearing potential; within 24 hours prior to registration)

Following study registration, the tumour block from the patient's lymphoma biopsy (preferably biopsy performed at time of relapse, or if unavailable the biopsy from their initial diagnosis) must be retrieved from the hospital's pathology archive and sent to the central laboratory (HMDS, Leeds). See section 10.1 and the Laboratory Manual for details.

9.2. Assessment of eligibility for nivolumab treatment

Following first or second line salvage, the patient will have assessments to verify they are eligible for treatment with Nivolumab.

The following investigations will be carried out within 18 days of cycle 2 first or second line salvage chemotherapy (cycle 4 if being treated with brentuximab vedotin) ±3 days:

- PET-CT scan (PET0; to be carried out as per trial requirements on an approved scanner; images to be sent to the PET core lab for central review – see the trial Imaging Manual for details).
- Contrast enhanced CT scan (ceCT). If feasible, this should be performed at the same imaging session as the PET-CT. If performed at the same session, the ceCT scan should be performed after the low dose PET-CT (see trial Imaging Manual for details).

The following investigations will be carried out up to 3-6 weeks after last administration of cycle 2 first or second line salvage chemotherapy (cycle 4 if being treated with brentuximab vedotin) if PET-CT was positive (Deauville 4-5):

- Medical history
- Clinical examination
- Weight
- Full blood count with differential (must be performed at least 3 weeks post completion of salvage)
- Biochemistry (ALT/AST, total bilirubin, alkaline phosphatase, urea, creatinine, calcium, magnesium, sodium, potassium, LDH, albumin, urate, glucose) (must be performed at least 3 weeks post completion of salvage)
- Creatinine clearance (calculated by Cockroft-Gault method)
- Tests for autoimmune conditions (amylase, lipase, thyroid function tests, adrenocorticotrophic hormone (ACTH))
- Electrocardiogram (ECG)
- Echocardiogram (if clinically indicated e.g. abnormalities on ECG)

- Lung function test
- ECOG performance status
- Hepatitis B & C serology:
  - ~~-~~hepatitis B surface antigen (HBsAg)
  - hepatitis B surface antibody (HBsAb) – if standard locally
  - hepatitis B core antibody (HBcAb)
  - ~~hepatitis B antibodies *or*~~ hepatitis B DNA (HBV DNA) IF hepatitis B core antibody positive
  - hepatitis C antibod~~y~~y~~ies~~ *or* hepatitis C DNA (HCV DNA) (local standard test to be used)~~)~~

The following investigation is to be carried out within 24 hours prior to confirming eligibility for treatment:

- Pregnancy test (serum or urine; women of childbearing potential)

The table below summarises the permitted timeframes for performing eligibility assessments. NB treatment with nivolumab must not be started until eligibility for trial treatment has been confirmed.

Week post first or second line salvage	**1**	**2**	**3**	**4**	**5**	**6**
PET CT[1]						
Other treatment eligibility tests[2]						

Notes
1 = PET CT to be performed 18 days after last administration of salvage treatment ±3 days
2 = FBC and biochemistry must be performed at least 3 weeks after after last administration of cycle 2 salvage treatment (or cycle 4 of brentuximab vedotin) to allow time for count recovery. For WOCBP, a pregnancy test is required within 24 hours prior to starting nivolumab.

9.3. Assessments prior to cycle 1 of Nivolumab

The following investigations are to be performed within 24 hours prior to starting Nivolumab:

- Pregnancy test (urine or serum; WOCBP only)

The following investigations are to be performed within 3 days prior to starting Nivolumab:

- Clinical examination, including documentation of baseline adverse events
- Full blood count with differential*
- Biochemistry (ALT/AST, total bilirubin, alkaline phosphatase, urea, creatinine, calcium, magnesium, sodium, potassium, LDH, albumin, urate, glucose) *
- Thyroid function tests (TSH & Free T4; Free T3 to be performed if TSH/Free T4 abnormal)
- Test for autoimmune conditions (Amylase, lipase, ACTH)
- Blood samples to be taken and sent to the central laboratory at the Weatherall Institute of Molecular Medicine, Oxford (see section 10.2 and Laboratory Manual for details)

* Do not need to be repeated if investigations for confirmation of eligibility (see section 9.2) were performed within 3 days prior to starting Nivolumab

The following investigations must be carried out on the day of nivolumab administration:

- Oxygen saturation measured by pulse oximetry at rest

9.4. Assessments during Treatment

During treatment the patient should be seen every 2 weeks and the following assessments performed within 3 days prior to the start of each cycle:

- Clinical examination
- Full blood count with differential
- Biochemistry (ALT/AST, total bilirubin, alkaline phosphatase, urea, creatinine, calcium, magnesium, sodium, potassium, LDH, albumin, urate, glucose)
- Tests for autoimmune conditions (amylase, lipase, ACTH)
- Cycles 3, 5 & 7: pregnancy test (urine or serum; WOCBP only)
- Cycle 4 and cycle 7: Thyroid function tests (TSH & Free T4; Free T3 to be performed if TSH/Free T4 abnormal)
- Adverse event assessment

The following investigations must be carried out on the day of nivolumab administration:

- Oxygen saturation measured by pulse oximetry at rest

Blood samples for translational research

- Blood samples are to be taken and sent to the central laboratory at the Weatherall Institute of Molecular Medicine, Oxford within 3 days prior to the start of cycles 2, 4, 6 and 8, and at the 1 month post-treatment visit (see section 10.2 and Laboratory Manual for more details)

Scanning required after cycle 4

- PET-CT scan to be carried out on cycle 4, day 11-13 as per trial requirements on an approved scanner, and images sent to the PET core lab for central review (PET4; see trial Imaging Manual for details).
- Contrast enhanced CT scan (ceCT). If feasible, this should be performed at the same imaging session as the PET-CT. If performed at the same session, the ceCT scan should be performed after the low dose PET-CT (see trial Imaging Manual for details).

9.5. Assessments on Completion of Trial Treatment

For patients who withdraw from trial treatment for any reason during cycles 1-3 of nivolumab:

- Lung function test (to be performed as soon as possible after decision to stop trial treatment, and before the next line of treatment begins)

For patients in CMR (Deauville 1-3) or with progressive disease after 4 cycles of nivolumab

- Lung function test (to be performed as soon as possible after receiving the PET-CT central review result)

If a biopsy is performed to confirm progressive disease, please send the block to HMDS, Leeds (see section 10).

For patients who withdraw from trial treatment for any reason during cycles 5-7:

- PET-CT scan to be carried out at least 11-13 days after last trial treatment administration, as per trial requirements on an approved scanner, and images sent to the PET core lab for central review (see trial Imaging Manual for details).
- Lung function test (to be performed as soon as possible after decision to stop trial treatment, and before the next line of treatment begins)

For patients who complete all 8 cycles of trial treatment:

- PET-CT scan to be carried out on cycle 8, day 11-13 as per trial requirements on an approved scanner, and images sent to the PET core lab for central review (PET8; see trial Imaging Manual for details).
- Contrast enhanced CT scan (ceCT). If feasible, this should be performed at the same imaging session as the PET-CT. If performed at the same session, the ceCT scan should be performed after the low dose PET-CT (see trial Imaging Manual for details).
- Repeat lymph node biopsy (if patient is PET positive and has consented for a repeat biopsy). Block to be sent to central laboratory (HMDS) (see section 10.1 and Laboratory Manual for details)
- Lung function test (to be completed 10 days after last nivolumab administration ±2 days)

9.6. Assessments During Follow Up

Patients will be followed up for a minimum of 3 years. All efforts should be made by the Site to contact the patient's GP to assess their condition, if a patient fails to attend a clinic or cannot be followed up at site.

9.6.1. Patients who are ineligible for Nivolumab

Patients will be seen as follows:

- 3 months after PET0 scan (i.e. scan performed at end of first or second line salvage)
- 6 months after PET0 scan
- 9 months after PET0 scan
- 12 months after PET0 scan
- Annually thereafter

The following investigations will be performed:

- Remission status assessment (investigations as per local protocols).

9.6.2. Patients who receive nivolumab

Follow up in year 1 post treatment

Patients will be seen approximately once a month for the first 3 months, and every 3 months thereafter.

The following tests will be performed **1 month, 2 months and 3 months** post treatment (30, 60 & 90 days after the last dose of Nivolumab respectively (±3 days)):

- Clinical examination
- Full blood count with differential
- Biochemistry (ALT/AST, total bilirubin, alkaline phosphatase, urea, creatinine, calcium, magnesium, sodium, potassium, LDH, albumin, urate, glucose)

- Tests for autoimmune conditions (amylase, lipase, ACTH)
- Thyroid function tests (TSH & Free T4; Free T3 to be performed if TSH/Free T4 abnormal)
- Adverse event assessment
- Pregnancy test (urine or serum; WOCBP only)
- Remission status assessment (investigations as per local policy) – 3 month timepoint only

Blood samples for translational research

- Blood samples are to be taken and sent to the central laboratory at the Weatherall Institute of Molecular Medicine, Oxford at the 1 month post-treatment visit (30 days post last dose of nivolumab (±3 days); see section 10.2 and Laboratory Manual for more details)

The following tests will be performed at **months 6, 9 and 12** post treatment:

- Clinical examination
- Full blood count with differential
- Biochemistry (U&E, LFTs)
- Remission status assessment (investigations as per local policy)
- Assessment for late toxicity of nivolumab

In addition, at **month 12** post treatment, the following test will be carried out:

- Lung function test

Follow up from year 2 post treatment onwards

Patients will be seen annually. The following investigations will be performed:

- Remission status assessment (investigations as per local protocols)
- Assessment for late toxicity of nivolumab

9.7. Assessments at time of Disease Progression

If disease progression is suspected, investigations should be carried out as per local protocols. If progression is confirmed, a disease progression urgent event form must be submitted within 72 hours of becoming aware (see section 12.5.2 for more information).

Samples for translational research

- If a repeat biopsy is performed at the time of relapse, the block should be sent to the central laboratory (HMDS) (see section 10.1 and Laboratory Manual for details)

9.8. Follow up Assessments after Disease Progression

Following disease progression, patients will be seen annually. The following investigations will be performed:

- Remission status assessment (investigations as per local protocols)
- Assessment for late toxicity of nivolumab

N.B. confirmed disease progressions must be reported as urgent events within 72 hours of becoming aware (see section 12.5 (Urgent Events))

10. EXPLORATORY BIOLOGICAL STUDIES

Biological studies are an integral part of the trial and as such are not optional but will be built into the main study consent (apart from an optional biopsy of residual PET avid lesions). We will be collecting two types of sample: formalin fixed paraffin embedded tissue and blood.

There are ~~two~~ three central laboratories for the trial. The Haematological Malignancy Diagnostic Service (HMDS) in Leeds will be responsible for central pathology review using immunohistochemistry (IHC), gene expression profiling (GEP) and fluorescent in situ hybridisation (FISH) studies. The Weatherall Institute of Molecular Medicine, Oxford will be carrying out biomarker studies on blood samples using flow cytometry. The MRC-University of Glasgow Centre for Virus Research will perform TARC analysis on blood samples.

Sites must keep a record of all samples sent to central laboratories for the trial, and ensure they update the sample tracking website when samples are sent. ~~.~~ See the Laboratory Manual for more details of how to track samples.

10.1. Formalin fixed paraffin embedded blocks

Formalin fixed paraffin embedded (FFPE) tissue will be sent to HMDS, Leeds from the referring hospitals. This will preferably be from a lymph node biopsy taken at first relapse. In the absence of this material, the initial diagnostic sample will be acceptable. It should preferably be a biopsy from an involved lymph node, or solid tumour mass. In the absence of this, any diagnostic material is acceptable (e.g. bone marrow trephine biopsy with involvement by Hodgkin). The block should be sent to HMDS, Leeds. See the Laboratory Manual for details of how to send and log FFPE samples. The consent for laboratory studies will either accompany the tissue sample or a copy of the consent form will be faxed to HMDS. Laboratory processing of any samples will not occur until patient consent has been confirmed.

In addition, an optional biopsy will be performed of any PET avid residuum after nivolumab treatment. This will also be formalin fixed and paraffin embedded and sent to HMDS, Leeds.

If, following trial treatment, a biopsy is taken to confirm disease progression, the block should be sent to HMDS, Leeds.

3µm sections of the tissue block will be taken and immunohistochemistry performed. A panel of markers will be assessed for each case including: CD30, IRF-4, PAX-5, CD20, CD3, OCT-2, BCL-6, CD79, CD15 and LMP-1. Immunostaining for PD1, PD-L1 and PD-L2 will also be performed in most cases.

Sections of the block will also be prepared for FISH studies. The FISH studies conducted will include those for 9p24 abnormalities as these have previously been reported to be highly predictive of outcome (Roemer et al 2016). Probes will include CD274/PD-L1, PDCD1LG2/PD-L2, CEP9 and REL. Fifty Reed-Sternberg cells per slide will be reviewed and the FISH signals defined as disomic, polysomic, relative copy gain or amplified.

GEP will be performed using either or both of 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.

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

10.2. Peripheral blood samples

Research peripheral blood samples will also be collected as follows:

Timepoint	Sample required
Within 3 days prior to start of cycle 1	50ml peripheral blood in EDTA
	5ml peripheral blood in serum gel tube
Within 3 days prior to start of cycle 2	20ml peripheral blood in EDTA
	5ml peripheral blood in serum gel tube
Within 3 days prior to start of cycle 4	20ml peripheral blood in EDTA
	5ml peripheral blood in serum gel tube
Within 3 days prior to start of cycle 6	20ml peripheral blood in EDTA
	5ml peripheral blood in serum gel tube
Within 3 days prior to start of cycle 8	20ml peripheral blood in EDTA
	5ml peripheral blood in serum gel tube
1 month post treatment follow up visit	20ml peripheral blood in EDTA
	5ml peripheral blood in serum gel tube

Samples should be sent by first class mail to the central laboratory at the Weatherall Institute of Molecular Medicine, Oxford. No processing of the sample is required at site prior to sending. Samples taken on a Friday should be refrigerated over the weekend and sent on the next working day. Please refer to the Laboratory Manual for more details of how to send and log blood samples.

EDTA samples will be analysed at the Weatherall Institute of Molecular Medicine, Oxford. Immunophenotyping by multicolour flow panels and/or CyTOF (depending on cell recovery) will be performed on the blood to identify immune signatures prior to, during, and after nivolumab treatment. This may give important predictive and pharmcodynamic information. Panels for myeloid and T cell markers will be used. For patients with circulating activated T cells, these will be sorted and analysed functionally. Sequencing of TCR will also be performed. Any leftover material will be stored in a biobank for future use in ethically approved research, subject to patient consent.

Serum samples will be processed by the Weatherall Institute and frozen in the first instance. They will then be transferred to the MRC-University of Glasgow Centre for Virus Research where measurement of TARC (CCL17) levels will be perfomed. It is anticipated that samples will be transferred in one batch once all patients have completed trial treatment, and all TARC analysis will be performed retrospectively. Any leftover material following this analysis will be stored in a biobank for future use in ethically approved research, subject to patient consent.

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

10.3. Agreements and accreditations

The trial consent form will include provision for samples to be sent to, and stored at, the HMDS, ~~and~~ the Weatherall Institute of Molecular Medicine, Oxford and the MRC-University of Glasgow Centre for Virus Research. The ethical approval of the trial will cover storage and processing of

samples at the HMDS, ~~and~~ the Weatherall Institute of Molecular Medicine, Oxford and the MRC-University of Glasgow Centre for Virus Research in accordance with the protocol.

HMDS is a CPA accredited laboratory with UKAS accreditation to ISO15189 standards.

UCL CTC will hold laboratory agreements with the HMDS, ~~and~~ the Weatherall Institute of Molecular Medicine, Oxford and the MRC-University of Glasgow Centre for Virus Research.

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 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 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 ball point 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 the following timeframes:

- Registration CRF – to be faxed/emailed to UCL CTC in real time
- Post salvage CRF – to be faxed/emailed to UCL CTC in real time
- Treatment CRFs – to be sent to UCL CTC within 2 weeks of the end of each cycle
- Treatment Summary CRF – to be sent to UCL CTC within 2 weeks of the decision to stop treatment (with the Treatment CRF for the last cycle given)
- Follow up CRFs – to be sent to UCL CTC within 4 weeks of the patient being seen
- SAE forms – to be faxed or emailed to UCL CTC within 24 hours of becoming aware of the event

- Pregnancy report forms – to be faxed or emailed to UCL CTC within 24 hours of becoming aware of the pregnancy
- Post-allogeneic transplant urgent event form – to be faxed or emailed to UCL CTC within 72 hours of becoming aware of the event
- Disease progression form – to be faxed or emailed to UCL CTC within 72 hours of becoming aware of confirmed disease progression
- Death form – to be faxed or emailed to UCL CTC within 24 hours of becoming aware of the death.
- New treatment form - to be faxed or emailed to UCL CTC with the next due Follow up CRF.
- Transfer of care form – to be faxed or emailed to UCL CTC within 2 weeks of the transfer of care to another site.
- Lost to follow up form - to be faxed or emailed to UCL CTC within 1 month of becoming aware that the patient is lost to follow up.

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 'for cause' monitoring visit. See section 14.2 ('For Cause' On-Site 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 a trial treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a trial treatment, whether or not related to that trial treatment. See section 12.2.1 for AE reporting procedures.

Adverse Reaction (AR)

All untoward and unintended responses to a trial treatment related to any dose administered. A causal relationship between a trial treatment 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)

An adverse event meeting the following criteria:

- Serious – meets one or more of the serious criteria above
- Related – assessed by the local investigator 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 (RSI)

See section 12.3 for reporting procedures for these events.

Adverse event of special interest (AESI)

An AE that is of particular interest to the Trial Management Group, even if it occurs outside the standard AE reporting timeframes for the trial. They are to be reported on an SAE form, regardless of their seriousness. The AEs of special interest for this trial are:

AESIs to be reported as SAEs

- Autoimmune diarrhoea / colitis
- Autoimmune pneumonitis
- Autoimmune hepatitis
- Autoimmune dermatitis
- Immune related endocrinopathies
- Autoimmune renal toxicity
- Autoimmune neurological toxicity
- Autoimmune uveitis
- Potential drug induced liver injury (pDILI)
- Overdoses (regardless of whether patient experiences any adverse events as a result)
- Grade 3 or 4 infusion reactions to nivolumab

See section 12.4 for reporting procedures for these events.

Urgent event

Urgent events for this trial are:

- Grade 3/4 graft versus host disease (patients who have allogeneic transplant only)
- Hyperacute graft versus host disease (patients who have allogeneic transplant only)
- Steroid-responsive febrile syndrome (patients who have allogeneic transplant only)
- Disease progression
- Death

See section 12.5 for reporting procedures for these events.

Overdose, trial treatment error, or occupational exposure

Refer to section □ for details on reporting of these events. Additionally refer to section 12.4.3 for details of reporting overdoses.

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:

http://evs.nci.nih.gov/ftp1/CTCAE/

Severity grade

Severity grade of each adverse event must be determined by using CTCAE v5.0. This is available online at:

http://evs.nci.nih.gov/ftp1/CTCAE/

Causality

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

For AEs, the local PI or designee will assess whether the event is causally related to trial treatment.

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 a trial treatment
- Not related (no reasonable possibility) to a trial treatment

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

Responsibility for reporting safety events following transfer of care

In the event of transfer between trial sites

UCL CTC must be informed if a patient's care is transferred to another trial site (see section 15.4 – Transfer of Care). The trial site caring for the patient at the time of awareness of AE, SAE, AESI, Urgent Event onset or pregnancy is responsible for completing and sending relevant reports to UCL CTC. When the patient's care is transferred, the referring site must provide sufficient information about the patient's trial participation (i.e. a copy of the patient's completed CRFs up to the date of transfer) to the new site to allow them to complete SAE reports.

In the event of transfer between a trial site and a non-trial site

The trial site will remain responsible for completing and sending AE, SAE, AESI Urgent Event and pregnancy reports to UCL CTC. If a patient is discharged to the care of a non-trial site, the PI/study team at the trial site should ensure that they are sent regular updates on the patient's progress and notified of any admissions or significant medical developments (including relapses and deaths), in order that the site's reporting responsibilities can be fulfilled.

12.2.1. Reporting of Adverse Events (AEs)

All adverse events that occur between the start of nivolumab treatment and 3 months post last nivolumab administration or commencement of next treatment for lymphoma (whichever is earlier) must be recorded in the the trial CRFs.

The reporting period has been selected as the patients are followed up at 1, 2, 3 months, then moving to 3 monthly follow up schedule. It is anticipated that most patients will have proceeded to further lymphoma treatment by the 3 month timepoint.

Adverse events 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 also be reported on an Urgent Event form (also refer to section 12.5 Urgent Events).

Pre-existing conditions do not qualify as adverse events unless they worsen.

12.2.2. Reporting of Serious Adverse Events (SAEs)

All SAEs that occur between the start of nivolumab treatment and 5 months post last nivolumab administration or commencement of next treatment for lymphoma (whichever is earlier), including

stem cell transplant **(or after this date if the site investigator feels the event is related to nivolumab)** must be submitted to UCL CTC.

The reporting timeframe takes into account the potential risk of delayed reactions from nivolumab (5 times half life, approximately 5 months), but is balanced against the fact that patients are expected to proceed to further lymphoma treatment after nivolumab, which will have a similar (or worse) toxicity profile compared to nivolumab. The different reporting requirements for AESIs (see section 12.4 below) allows for continued reporting of important nivolumab-specific reactions (such as immune-related events), even after the start of a new lymphoma treatment.

SAEs must be reported by fax or 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.

The following AESIs must be reported on the SAE report form:

- Autoimmune diarrhoea / colitis
- Autoimmune pneumonitis
- Autoimmune hepatitis
- Autoimmune dermatitis
- Immune related endocrinopathies
- Autoimmune renal toxicity
- Autoimmune neurological toxicity
- Autoimmune uveitis
- Potential drug induced liver injury (pDILI)
- Overdoses (regardless of whether the patient experiences any adverse events as a result)
- Grade 3 or 4 infusion reactions to nivolumab

See section 12.4 for further information.

To summarise, the SAE reporting requirements for non-autoummune events, based subsequent treatment, are as follows (see section 12.4 for details of reporting windows for autoimmune events):

Next Planned Treatment	**Reporting window for non-autoimmune SAEs**
No treatment	From first administration of nivoumab until 5 months post last dose of trial treatment. (N.B. if the patient relapses and starts new treatment within 5 months after completing nivolumab, SAEs will no longer be collected).
Further chemotherapy	From first administration of nivoumab until 5 months post last dose of trial treatment or first administration of next line of chemotherapy, whichever is sooner.
Autologous stem cell transplant	From first administration of nivoumab until 5 months post last dose of trial treatment or first adminsitration of pre-transplant chemotherapy, whichever is sooner.
Allogeneic stem cell transplant	From first administration of nivoumab until 5 months post last dose of trial treatment or commencement of transplant conditioning, whichever is sooner.

Exemptions from SAE Report submission

For this trial, the following events are exempt from requiring submission on an SAE Report, but must be recorded in the relevant sections of the trial CRFs:

- Events that occur more than 5 months post last trial treatment administration unless:
  - considered to be a late effect of the trial treatment
  - it is a pregnancy related event (see section 12.8)
- Events that occur after the commencement of further treatment for lymphoma unless:
  - An autoimmune event classed as an AESI (see section 12.4)
- Disease progression (including disease related deaths, unless considered related to the trial treatment). N.B. disease progression and deaths from any cause are Urgent Events – see section 12.5)
- The following post-allogeneic transplant toxicities, which should be reported as urgent events (see section 12.5):
  - Grade 3/4 graft-vs-host disease (patients who have allogeneic transplant only)
  - Hyperacute graft-vs-host disease (patients who have allogeneic transplant only)
  - non-infectious febrile episodes requiring steroid therapy (including steroid-responsive febrile syndrome; patients who have allogeneic transplant only)
  - Sinusoidal obstruction syndrome/ veno-occlusive disease (patients who have allogeneic transplant only)

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

Completed SAE Reports must be faxed or emailed to UCL CTC within 24 hours of becoming aware of the event

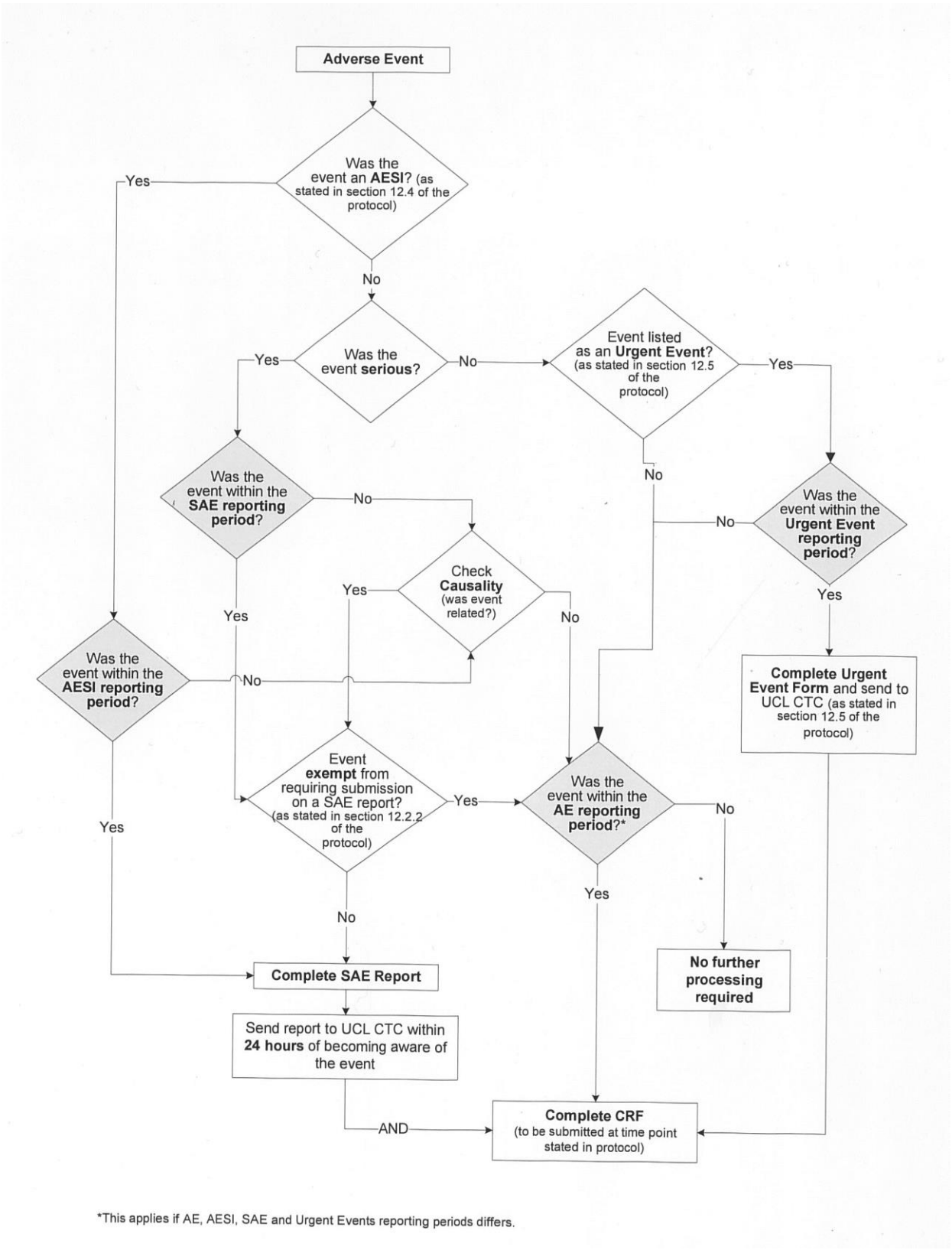
Fax: 020 7679 9861
Email: ctc.animate@ucl.ac.uk

SAE Follow-Up Reports

All SAEs will be followed up until resolution and until there are no further queries.

Sites must ensure any new and relevant information is provided promptly. If the 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 within 24 hours to UCL CTC, the circumstances that led to this 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 RSI (the approved Investigator Brochure (IB) for Nivolumab).

The CI, or their delegate (e.g. a clinical member of the TMG), may be contacted to review the SAE and to perform an evaluation of causality on behalf of UCL CTC. 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 Nivolumab to BMS according to the timelines outlined in the agreement between UCL and BMS.

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 within the required timelines.

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

UCL CTC will submit all SUSAR reports relating to nivolumab to Bristol-Myers Squibb (BMS) according to the timelines outlined in the agreement between UCL and BMS.

Informing Sites of SUSARs

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

12.4. Adverse events of special interest

All AESIs must be submitted to UCL CTC by fax or email within the timeframes outlined below, using the trial specific SAE Report. All sections on the SAE Report must be completed. If the event is **not being reported within the required timeframe** to UCL CTC, the circumstances that led to this must be detailed in the SAE Report to avoid unnecessary queries.

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

12.4.1. Autoimmune events due to Nivolumab

The following adverse events of special interest for Nivolumab must be reported on the appropriate AE of Special Interest form within **24 hours of confirmed diagnosis.**

The following adverse events of special interest for Nivolumab must be reported on an SAE report form within **24 hours of confirmed diagnosis.** Please note that any signs and symptoms should be treated on their merits and reported as AEs/SAEs as applicable pending confirmation of diagnosis.

To summarise, the reporting requirements for **autoimmune events** based the treatment arm are as follows: (please note that the reporting window for autoimmune events differs to those for non-autoimmune SAEs; see section 12.2.2 for details).

Next Treatment	Reporting window for autoimmune toxicity
No treatment or further chemotherapy	From first administration of nivoumab until 5 months post last dose of trial treatment (or after this date if the investigator feels the event is related to nivolumab).
Autologous stem cell transplant	From first administration of nivoumab until 5 months post last dose of trial treatment (or after this date if the investigator feels the event is related to nivolumab).
Allogeneic stem cell transplant	From first administration of nivoumab until 5 months post last dose of trial treatment (or after this date if the investigator feels the event is related to nivolumab). Please note that colitis, dermatitis and hepatitis occurring after transplant day 0 should be reported as graft-versus-host disease in the first instance unless otherwise proven to be of autoimmune origin (see section 12.5 (Urgent Events) for details of reporting graft-versus-host disease).

Please note that confirmed autoimmune events must be reported to the CTC on an SAE report form even if the patient has received further treatment for their lymphoma within the 5 months after completing nivolumab.

Events will be collected as follows:

Event	Description See section 8.5 for detailed definitions	Form required	Timeframe
Autoimmune diarrhoea / colitis	Grade ≥2 diarrhoea persisting >48 hours and not suspected clinically or confirmed on lab testing to be due to infective causes	SAE report	Within 24 hours of confirmed diagnosis
Autoimmune uveitis	New or worsening inflammation of the eye, with ocular pain, erythema or blurring of vision.	SAE report	Within 24 hours of confirmed diagnosis
Autoimmune pneumonitis	Radiographic changes or pulmonary symptoms, unless due to infective causes	SAE report	Within 24 hours of confirmed diagnosis
Autoimmune hepatitis	Raised ALT, AST or bilirubin, unless due to infective causes or other concomitant medications	SAE report	Within 24 hours of confirmed diagnosis
Autoimmune dermatitis	New or worsening rash where non-autoimmune causes have been excluded	SAE report	Within 24 hours of confirmed diagnosis
Immune related endocrinopathy	New or worsening asymptomatic or symptomatic endocrine disfunction	SAE report	Within 24 hours of confirmed diagnosis

Autoimmune renal toxicity	Raised creatinine unless due to nephrotoxicity of concomitant medications or outflow tract obstruction	SAE report	Within 24 hours of confirmed diagnosis
Autoimmune neurological toxicity	New or worsening radiographic changes or neurological symptoms	SAE report	Within 24 hours of confirmed diagnosis

Cases of autoimmune toxicity must be reported on the trial-specific SAE report by fax or email:
Fax: 0207 679 9861
Email: ctc.animate@ucl.ac.uk

12.4.2 Potential Drug Induced Liver Injury (pDILI)

All occurrences of potential DILIs, meeting the defined criteria below, must be reported as SAEs.

Potential drug induced liver injuries should be reported from the first administration of nivolumab until five months post-treatment (or after this date if the investigator feels the event is related to nivolumab).

Event	Description	Form required	Timeframe
Potential drug induced liver injury (pDILI)	AST or ALT >3 x ULN **and** Total bilirubin >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase) **and** No other immediately apparent causes of transaminase elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.	SAE report	Within 24 hours of diagnosis

Cases of pDILI must be reported on the trial-specific SAE report by fax or email:
Fax: 0207 679 9861
Email: ctc.animate@ucl.ac.uk

12.4.3. Overdoses

Any overdoses of nivolumab, must be reported as both an SAE and an incident within 24 hours of the overdose occurring, regardless of whether the patient experiences any adverse events as a result of the overdose. Examples of potential overdoses are listed in the table below. If there is uncertainty about whether a patient has been overdosed, please contact the ANIMATE study team to discuss (ctc.animate@ucl.ac.uk).

Any adverse events occurring in patients who have received an overdose should be reported as serious events within the SAE report.

Event	Examples	Forms required	Timeframe
Overdose	• Administration of a nivolumab dose in excess of 240mg at any individual dosing episode • Administration of a cumulative nivolumab dose in excess of 1920mg (240mg x 8 doses)	• SAE report • Incident report	Within 24 hours of overdose occurring

Overdoses must be reported by sending both the trial-specific SAE report and incident report by fax or email:
Fax: 0207 679 9861
Email: ctc.animate@ucl.ac.uk

12.4.4. Grade 3 or 4 infusion reactions to nivolumab

Any CTCAE grade 3 or 4 infusion reactions to nivolumab must be reported as SAEs.

Infusion reactions should be reported from first dose of nivolumab until completion of trial treatment.

See next page for reporting requirements.

Event	Definition	Form required	Timeframe
Grade 3 or 4 infusion reaction to nivolumab	As per CTCAE v5 *infusion related reaction*: • Grade 3: Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalisation indicated for clinical sequelae • Grade 4: Life threatening consequences; urgent intervention indicated	• SAE report	Within 24 hours of infusion reaction occurring

Grade 3 or 4 infusion reactions must be reported on the trial-specific SAE report by fax or email:
Fax: 0207 679 9861
Email: ctc.animate@ucl.ac.uk

12.5. Urgent events

12.5.1. Post-allogeneic transplant events

The following urgent events for Nivolumab must be reported on the appropriate Urgent Event form within **72 hours of becoming aware of the event** if they occur at any time between transplant day 0 and day 100 post-transplant in patients who receive an allogeneic stem cell transplant following nivolumab.

Event	Description	Form required	Timeframe
Grade 3 – 4 graft versus host disease	Grade 3 or 4 graft versus host disease as assessed by the modified Glucksberg criteria (see Appendix 5)	Post-allogeneic transplant urgent event form	Within 72 hours of becoming aware of event
Hyperacute graft versus host disease	Acute GVHD of any grade occurring within 14 days after stem cell infusion, and prior to neutrophil engraftment (Saliba et al 2007)	Post-allogeneic transplant urgent event form	Within 72 hours of becoming aware of event

Non-infectious febrile episodes requiring steroid therapy (including steroid-responsive febrile syndrome)	Steroid responsive febrile syndrome is defined as 3 of the following major criteria or 2 major and ≥1 minor criteria: **Major criteria** • Non-infectious fever • Rash covering >25% of body surface area • Non-cardiac pulmonary oedema **Minor criteria** • Bilirubin >17.1 µmol/L • Weight gain >2.5% above baseline • AST > 2 x ULN • Creatinine >2 x baseline Typically occurring within 96 hours of neutrophil engraftment and responsive to corticosteroids (Spitzer 2001) Any non-infectious febrile episodes treated with steroids, occurring within 42 days post-transplant should be reported, even if the above criteria for a diagnosis of steroid-responsive febrile syndrome are not met.	Post-allogeneic transplant urgent event form	Within 72 hours of becoming aware of event
Sinusoidal obstruction syndrome (veno-occlusive disease)	2 of the following criteria occurring within 20 days after stem cell infusion: • Bilirubin >17.1 µmol/L • Hepatomegaly and/or tenderness or pain over the liver • Weight gain >20% above baseline	Post-allogeneic transplant urgent event form	Within 72 hours of becoming aware of event

12.5.2. Disease progression

The following event must be reported within **72 hours of becoming aware of the event** on the relevant Urgent Event Form if it occurs at any time during the trial:

Event	Description	Form required	Timeframe
Disease progression	Progression of Hodgkin lymphoma, confirmed by standard local investigations	Disease progression form	Within 72 hours of becoming aware of confirmed progression

12.5.3. Death

The following event must be reported within **24 hours of becoming aware of the event** on the relevant Urgent Event Form if it occurs at any time during the trial:

Event	Description	Form required	Timeframe

Death	Death from any cause	Death form	Within 24 hours of becoming aware of death

Where the cause of death meets the criteria for an SAE (see section 12.2.2. above), an SAE report must also be submitted.

All Urgent Events must be reported on the the relevant Urgent Event Form by fax or email:
Fax: 0207 679 9861
Email: ctc.animate@ucl.ac.uk

12.6. Expedited Safety Reports (ESR)

BMS may report other important findings as an Expedited Safety Report (ESR), including: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety findings from a nonclinical (e.g. animal) study, important safety recommendations from a study data monitoring committee, or Sponsor decision to ed or temporarily halt a clinical study for safety reasons.

UCL CTC will forward ESRs received from BMS to all PIs. These must be processed by sites in the same way as SUSARS according to local requirements, and filed with the IB.

12.7. 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:

- new adverse reactions to the trial treatment regimen or individual trial treatments
- unacceptably high incidence of expected adverse events
- trial related events that are not considered related to the trial treatment regimen

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.

12.8. Pregnancy

Reporting Period

If a female patient becomes pregnant between the start of trial treatment and 6 months after last trial treatment administration or the female partner of a male trial patient becomes pregnant between the start of trial treatment and 8 months after last trial treatment administration, the site must submit a trial specific Pregnancy Report to UCL CTC by fax or email **within 24 hours** of learning of its occurrence.

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

- For female patients, consent for pregnancy monitoring will be sought at study entry, using the trial Patient Information Sheet and Informed Consent Form
- For female partners of male patients: the trial specific Pregnancy Monitoring Information Sheet and Informed Consent Form for partners of study patients will be used in the event of a pregnancy.

If consent is not given, the initial notification that a pregnancy has occurred will be retained by UCL CTC, and an anonymised copy will be forwarded to BMS, however no further action will be taken on the information detailed in the report.

All pregnancies must be reported by faxing or emailing a completed Pregnancy Report to UCL CTC within 24 hours of becoming aware of the pregnancy
Fax: 020 7679 9861
Email: ctc.animate@ucl.ac.uk

Pregnancy Follow-Up Reports

For pregnant patients or partners who consent, their pregnancies must be followed -up until an outcome is determined. Follow-up Pregnancy Reports must be submitted to UCL CTC by fax or email within **24 hours** of learning of the outcome. 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~~12.2.2~~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 Nivolumab to Bristol-Myers Squibb according to the timelines outlined in the agreement between UCL and Bristol-Myers Squibb.

12.9. 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 Bristol-Myers Squibb with DSURs that include information regarding Nivolumab.

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. 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 will determine the appropriate level and nature of monitoring required for the trial. Risk will be assessed on an ongoing basis and adjustments made accordingly.

14.1. Central Monitoring

Sites will be requested to submit screening logs and staff delegation logs to UCL CTC at the frequency detailed in the trial monitoring plan, or on request, and these will be checked for consistency and completeness. Also refer to sections 4.2.2 (Required documentation) and 6.1 (Screening Log).

Ensuring patient eligibility is the responsibility of the PI or other delegated Investigator(s). Checks of the criteria listed on the registration form will be undertaken by an appropriately trained UCL CTC staff member prior to registration. Also refer to section 7.1 (Registration).

Details relating to the informed consent process will be collected on the registration form and are subject to review by UCL CTC as part of patient eligibility.

Copies of completed drug accountability logs must be returned to UCL CTC for all trial patients. Sites will be required to submit logs in accordance with the trial monitoring plan.

Data received at UCL CTC will be subject to review in accordance with section 11.4 (Data Queries).

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

Where central monitoring of data and/or documentation submitted by sites indicates that a patient may have been placed at risk (e.g. an overdose has been administered, or data indicate that dose modification rules were not followed following an adverse reaction), the matter will be raised urgently with site staff and escalated as appropriate (refer to section 13 (Incident Reporting and Serious Breaches) and 14.2 (’For Cause’ On-Site Monitoring) for further details).

14.2. ’For Cause’ On-Site Monitoring

On-site 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. Sites will be sent a letter in advance outlining the reason(s) for the visit and confirming when it will take place. The letter 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.

Following a monitoring visit, 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.

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) for details.

14.3. Oversight Committees

14.3.1. Trial Management Group (TMG)

The TMG will include the Chief Investigator, clinicians and experts from relevant specialities and ANIMATE trial staff from UCL CTC (see page 1). The TMG will be responsible for overseeing the trial. The group will meet regularly (approximately quarterly) 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.

14.3.2. 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.

14.3.3. 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 once per year to review interim analyses, or as necessary to address any issues. 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 a IDMC Charter, which describes the committee's responsibilities and requires any potential conflicts of interest to be declared.

14.3.4. 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. 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 notes and on the relevant Case Report Form(s). Reasons for discontinuing treatment may include:

- Disease progression whilst on therapy
- Unacceptable toxicity
- 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 patient 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.

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 their withdrawal, this should be recorded.

15.2. Future Data Collection

If a patient explicitly states they do not wish to contribute further data to the trial their decision must be respected, with the exception of essential safety data, and recorded on the relevant CRF. In this event data due up to the date of withdrawal must be submitted but no further data, other than essential safety data, sent to UCL CTC.

15.3. Losses to Follow-Up

See section 15.4 (Transfer of Care) for details of actions needed when a patient relocates or their care is transferred.

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.

Patients lost to follow up may be tracked by UCL CTC via registries such as the National Cancer Registration and Analysis Service, ~~or the Health & Social Care Information Centre~~NHS Digital (England), NHS Wales Informatics Service (Wales) or the Information Services Division (Scotland).

15.4. Transfer of Care

For patients moving 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 responsibility for the patient's trial visits and data collection going forward.

The process for transferring care to another participating site is as follows:

- Liase with the proposed new site and obtain written confirmation that they are willing to take over follow up duties for the patient.
- Complete a Centre Transfer Form (provided as part of the CRF) and send to UCL CTC.
- CRFs relating to visits up to the point of transfer must be completed and submitted to UCL CTC.
- Provide the new site with copy of the patient's complete CRF up until the point of transfer.

The original site remains responsible for submitting all data due up to the date of transfer, and for resolving any data queries relating to those data. The site to whom the patient is transferred will be responsible for completing CRFs pertaining to visits after the date of transfer only.

Details of participating trial sites can be obtained from the UCL CTC study team upon request.

If the patient cannot be transferred to another participating site, the site that registered them into the trial remains responsible for obtaining and submitting follow up and safety data on the patient.

15.5. Loss of Capacity

If a patient loses capacity during trial treatment, they will be withdrawn from trial treatment, but will remain on trial for follow up and collection of safety data.

If a patient loses capacity after completing trial treatment, they will remain on trial for survival follow up only.

16. TRIAL CLOSURE

16.1. End of Trial

For regulatory purposes the end of the trial will be when the last patient completes three years of follow up, at which 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, and notify HMDS and the Weatherall Institute of Molecular Medicine, Oxford.

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 25 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 25 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. Sites will be informed by UCL CTC in writing of the 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 CTSA.

17. QUALITY ASSURANCE

PET QA and central review for this study is being undertaken by the UK PET Core Lab at St. Thomas' Hospital, London.

Please refer to the trial Imaging Manual for more details.

18. STATISTICS

18.1. Sample Size Calculation

Assuming that the overall response rate (ORR) will be around 60% (a conservative estimate based on ORRs of 65-87%; Moskowitz et al. Blood 2014b, Armand et al., 2015, Armand et al. 2016), but to rule out a rate <40% (i.e. BV given pre ASCT; Zinzani et al., 2015), using an A'hern design with 80% power and a one-sided alpha of 0.1 we require 30 patients. We hope to see at least 16 responses (CR or PR).

We assume that 25-40% will be PET positive following first line salvage so in order to treat 30 patients we will need to register 75-120. We will also replace any patient withdrawn before starting nivolumab or who is found to be ineligible after starting treatment. These patients will be excluded from all analyses of the nivolumab treated cohort (including the analysis of the primary endpoint), but will be included in analyses of the total cohort (i.e. all patients registered) if appropriate i.e. if the patients were eligible at this point.

Sample size was calculated using "Sample size tables for clinical studies" software.

18.2. Statistical analysis

18.2.1. Analysis of main endpoint

The primary endpoint is the ORR i.e. the proportion of nivolumab treated patients achieving a response (PMR and CMR compared to end of first or second line salvage treatment scan; PET0) after either 4 (PET4) or 8 cycles (PET8). This will be presented as a proportion with 80% confidence intervals.

Any patient without a response scan will be counted as a non-response for the primary analysis (i.e. the denominator will be all eligible nivolumab treated patients). However, a secondary analysis may also be conducted excluding any patient who drops out before the first response scan for reasons other than disease progression or death from disease.

Analysis of the primary endpoint will take place after all patients have finished nivolumab treatment and response data is available.

18.2.2. Analysis of secondary endpoints and secondary analyses

Survival endpoints:

Progression free survival (PFS)
PFS time will be measured from the date of the PET scan after first or second line salvage treatment (PET0) until the date of progression or death (whichever comes first). Patients who are alive and progression free will be censored at the date last seen.

Overall survival (OS)
OS time will be measured from the date of the PET scan after first or second line salvage treatment (PET0) until the date of death. Patients who are alive will be censored at the date last seen.

Analysis of PFS and OS will take place once we have 1 year follow-up for all patients. Kaplan Meier survival analyses will be used for both.

Subgroup analyses will be performed for responders and non-responders i.e. do patients with a PMR do worse than those with a CMR after nivolumab treatment. Kaplan Meier survival analysis and Cox regression may be used, although this will be dependent on the numbers of patients with a response and the numbers of events.

PFS and OS will also be analysed by further treatment i.e. did the patient go on to have an allograft or autograft, though we acknowledge that numbers will be very small so analyses will be descriptive.

CMR/PMR rates
Proportions of patients achieving CMR and PMR will also be presented.

Adverse events:
Analysis will focus on grade 3/4 adverse events. The worst grade seen per patient will be shown for each event type.

AESIs will be reported in more detail, with autoimmune events of any grade presented. All analysis will be descriptive.

Transplant related mortality and the rate of serious complications of allo SCT will presented, though again, it is likely only descriptive statistics will be used.

Other analyses:
The association between pre-nivolumab biological parameters and response to nivolumab will be investigated. As numbers will be very small mostly descriptive statistics will be used i.e. numbers and percentages will be presented for binary/categorical data and means and medians (with ranges) for continuous measurements.

We will also look at changes in TARC levels in responders and non-responders.

PET negative patients not treated with nivolumab
We will look at PFS, OS and subsequent treatments for patients who are PET negative following first or second line salvage treatment (i.e. at PET0).

We will also look at whether there are baseline characteristics at diagnosis or relapse which are associated with response to initial salvage treatment. These will include extranodal disease (relapse), haemoglobin levels (relapse), duration of first remission (patients in first relapse only), initial treatment, location of relapse (within RT field or not) and stage (at diagnosis and relapse).

Interim analyses
There are no formal interim analyses or formal stopping rules, but an Independent Data Monitoring Committee (IDMC) will review all trial data yearly and can suggest stopping the trial if they have any concerns about safety or efficacy. Trial Management Group (TMG) meetings will be held approximately every 3-6 months and the committee will review safety data including full SAE listings.

19. ETHICAL AND REGULATORY CONSIDERATIONS

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

- the principles of ICH Harmonised Tripartite Guideline for Good Clinical Practice as set out in Schedule 1 (Conditions and Principles of Good Clinical Practice and for the Protection of Clinical Trial Subjects) of the Medicines for Human Use (Clinical Trials) Regulations 2004 and the GCP Directive 2005/28/EC, as set out in SI 2006/1928
- Human Rights Act 1998
- Data Protection Act ~~1998~~2018
- Freedom of Information Act 2000
- Human Tissue Act 2004
- Medicines Act 1968
- Medicines for Human Use (Clinical Trials) UK Regulations SI 2004/1031, and subsequent amendments
- Good Manufacturing Practice
- the UK Policy Framework for Health and Social Care Research, issued by the Health Research Authority

Where applicable, UCL CTC and sites will work towards implementation of the EU Clinical trials Regulation EU/536/2014.

19.1. 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 – South East 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.

19.2. 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.

19.3. 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.

19.4. 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.

19.5. Patient Confidentiality & Data Protection

Patient identifiable data, including initials, date of birth and NHS number (or equivalent) 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 ~~1998~~ 2018 with the Data Protection Officer at UCL.

20. SPONSORSHIP AND INDEMNITY

20.1. Sponsor Details

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

20.2. 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.

21. FUNDING

Bristol-Myers Squibb are supporting the central coordination of the trial through UCL CTC, translational research at HMDS and the Weatherall Institute of Molecular Medicine, Oxford, and supplying Nivolumab free of charge for use in the trial.

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

22. PUBLICATION POLICY

The results of the ANIMATE trial will be presented at relevant conferences and published in a peer reviewed journal. The primary publication from the ANIMATE 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 BMS prior to submission in accordance with the requirements of the Trial Drug Supply Agreement.

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

Central laboratories and the PET core laboratory may not publish any data pertaining to ANIMATE patients without prior written permission from the TMG.

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

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

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APPENDIX 1: ABBREVIATIONS

ACTH	Adrenocorticotropic hormone
ADL	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
AlloSCT	Allogeneic stem cell transplant
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute neutrophil count
AR	Adverse reaction
ARSAC	Administration of Radioactive Substances Advisory Committee
ASCT	Autologous stem cell transplant
AST	Aspartate aminotransferase
BEAM	Carmustine, etoposide, cytarabine, melphalan
BID	Twice a day
BM	Boehringer-Mannheim test (glucose test)
BMS	Bristol-Myers Squibb
BSA	Body surface area
BV	Brentuximab vedotin
CCL-17	Chemokine (C-C motif) ligand 17
CHI	Community Health Index
cHL	Classical Hodgkin lymphoma
ceCT	Contrast enhanced computerised tomography
CI	Chief Investigator
CMR	Complete metabolic response
CPA	Clinical Pathology Accreditation
CR	Complete response
CRF	Case report form
CT	Computerised tomography
CTA	Clinical trial authorisation
CTAC	CT-based attenuation correction
CTCAE	Common Terminology Criteria for Adverse Events
CTSA	Clinical Trial Site Agreement
CyTOF	Mass cytometry
DHAP	Dexamethasone, cytarabine, cisplatin
DICOM	Digital imaging and communications in medicine
DRL	Diagnostic reference level
DSUR	Development Safety Update Report
EBV	Epstein-Barr virus
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylene diamine tetra acetate
EFS	Event-free survival
eGFR	Estimated Glomerular Filtration Rate
ESHAP	Etoposide, methylprednisolone, cytarabine, cisplatin
ESR	Expedited Safety Report
EudraCT	European Clinical Trials Database
FBC	Full blood count
FDG	^{18}F-Fluorodeoxyglucose
FDG-PET	Fluorodeoxyglucose positron emission tomography

FF2F	Freedom from second failure
FFPE	Formalin-fixed paraffin embedded
FISH	Fluorescent in-situ hybridisation
FTP	File transfer protocol
FU	Follow up
G-CSF	Granulocyte colony stimulating factor
GDP	Gemcitabine, dexamethasone, cisplatin
GEP	Gene expression profiling
GFR	Glomerular filtration rate
GVHD	Graft-versus-host disease
Hb	Haemoglobin
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV DNA	Hepatitis B virus deoxyribonucleic acid
HCV Ab	Hepatitis C virus antibody
HCV DNA	Hepatitis C virus deoxyribonucleic acid
HCG	Human chorionic gonadotrophin
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HMDS	Haematological Malignancy Diagnostic Service
HRA	Health Research Authority
IB	Investigator's Brochure
ICE	Ifosfamide, carboplatin, etoposide
ICH GCP	International Conference of Harmonisation-Good Clinical Practice
IDMC	Independent Data Monitoring Committee
IGEV	Ifosfamide, gemcitabine, vinorelbine
IHC	Immunohistochemistry
IMP	Investigational medicinal product
IPEM	Institute of Physics and Engineering in Medicine
IR	Indeterminate response
ISRCTN	International Standard Randomised Controlled Trial Number
IUD	Intra-uterine device
IUS	Intra-uterine system
IV	Intravenous
LDH	Lactate dehydrogenase
LFT	Liver function tests
LLN	Lower limit of normal
MHRA	Medicines and Healthcare products Regulatory Agency
MRC	Medical Research Council
MRI	Magnetic Resonance Image
NCRI	National Cancer Research Institute
NHS	National Health Service
NMR	No Metabolic Response
ORR	Overall response rate
OS	Overall survival
OSEM	Ordered subset expectation maximisation
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed death ligand 1
PD-L2	Programmed death ligand 2
PET	Positron emission tomography
PFS	Progression free survival

PI	Principal Investigator
PMD	Progressive metabolic disease
PML	Progressive multifocal leucoencephalopathy
PMR	Partial metabolic response
PO	By mouth
PR	Partial response
QC	Quality control
REC	Research Ethics Committee
RIC	Reduced intensity conditioned
ROI	Region of interest
R/R	Relapsed/refractory
RS	Reed-Sternberg cell
RT	Radiotherapy
SAE	Serious adverse event
SAR	Serious adverse reaction
SCT	Stem cell transplant
SPC	Summary of Product Characteristics
SUSAR	Suspected unexpected serious adverse reaction
SUV	Standardised uptake value
TARC	Thymus and activation-regulated chemokine
TCR	T cell receptor
TRM	Treatment-related mortality
TSH	Thyroid-stimulating hormone
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
UKAS	UK Accreditation Scheme
ULN	Upper limit of normal
WOCBP	Woman of childbearing potential

APPENDIX 2: QUICK REFERENCE GUIDE TO PATIENT VISITS

Appendix 2.1 Patients who receive Nivolumab

	Before registration	After registration	15-21 days after first or second line salvage	3-6 weeks after first or second line salvage[1]	During treatment	End of treatment	FU -– 1 month	FU – 2 months	FU - 3 months	FU - 6 months	FU - 9 months	FU - 12 months	FU - Annual	Relapse/Disease Progression
Informed Consent	X				See separate table									
Medical History	X			X										
Clinical examination				X			X	X	X	X	X	X		
Weight				X										
Full blood count with differential				X			X	X	X	X	X	X		
Biochemistry[2]				X			X	X	X	X	X	X		
Pregnancy test[3]	X			X			X	X	X					
Tests for autoimmune conditions[4]				X			X	X	X					
Thyroid function tests[5]				X			X	X	X					
Hepatitis B & C serology[6]				X										
ECG (& echo if indicated)				X										
Lung function test				X		X[7]						X		
PET-CT scan (for central review)			X											
Adverse event assessment							X	X	X					
Blood samples for translational research[8]							X							

Retrieve archival biopsy sample and send to HMDS		X												
Tumour biopsy; block to be sent to HMDS						X[9~~8~~]								X[10~~9~~]
Remission status assessment (investigations as per local protocols)									X	X	X	X	X	
Assessment for late toxicity of nivolumab										X	X	X	X	

Notes:
1 = To avoid subjecting to patients to trial-specific tests unnecessarily, it is strongly recommended to wait for confirmation of PET positivity before undertaking these investigations
2 = to include ALT/AST, total bilirubin, alkaline phosphatase, lactate dehydrogenase, urea, creatinine, calcium, albumin, magnesium, sodium, potassium, urate, glucose
3 = Women of childbearing potential
4 = Amylase, lipase, ACTH
5 = (TSH & Free T4; Free T3 to be performed if TSH/Free T4 abnormal)
6 = HBsAg, HBsAb (if standard locally), HBcAb, HBV DNA (if HBcAb+), HCV Ab *or* HCV DNA (use test performed as standard locally)
7 = Lung function tests to be performed as soon as possible after decision to stop trial treatment, and before the next line of treatment begins. If patient completes 8 cycles of nivolumab, lung fiunction test should be performed 10 days after last nivolumab administration ±2 days.
8 = See section 10.2. To be sent to Weatherall Institute of Molecular Medicine, Oxford
9 = End of treatment biopsy to be performed if PET positive after 8 cycles and patient has consented. Block to be sent to HMDS.
10 ~~9~~ = Biopsy to be performed at relapse if clinically indicated. Block to be sent to HMDS.

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Investigations during treatment

Investigations to be performed within 3 days prior to the start of the cycle unless otherwise stated.

	Beginning of Cycle 1	Beginning of Cycle 2	Beginning of Cycle 3	Beginning of Cycle 4	Cycle 4 day 11-13	Beginning of Cycle 5	Beginning of Cycle 6	Beginning of Cycle 7	Beginning of Cycle 8	Cycle 8 day 11-13
Clinical examination	X	X	X	X		X	X	X	X	
Full blood count with differential	X	X	X	X		X	X	X	X	
Biochemistry[1]	X	X	X	X		X	X	X	X	
Tests for autoimmune conditions[2]	X	X	X	X		X	X	X	X	
Oxygen saturation	X[3]	X[3]	X[3]	X[3]		X[3]	X[3]	X[3]	X[3]	
Adverse event assessment	X	X	X	X		X	X	X	X	
Thyroid function tests[4]	X			X				X		
Pregnancy test (WOCBP only)	X[5]		X			X		X		
Blood samples for translational research[6]	X	X		X			X		X	
PET-CT scan (for central review)					X		[7]	[7]	[7]	X

Notes:
1 = to include ALT/AST, total bilirubin, alkaline phosphatase, lactate dehydrogenase, urea, creatinine, calcium, albumin, magnesium, sodium, potassium, urate, glucose
2 = Amylase, lipase, ACTH
3 = Immediately prior to administration of nivolumab
4 = (TSH & Free T4; Free T3 to be performed if TSH/Free T4 abnormal)
5 = Pregnancy test must be performed within 24 hours prior to starting nivolumab
6 = See section 10.2. To be sent to Weatherall Institute of Molecular Medicine, Oxford
7 = If patient stops treatment during cycles 5-7, a PET-CT scan should be performed and sent for central review. This should be undertaken at least 11-13 days after last trial treatment administration.

Appendix 2.2 Patients who do not receive Nivolumab

	Before registration	After registration	15-21 days after first or second line salvage	3-6 weeks after first or second line salvage[1]	FU – 3 months	FU – 6 months	FU - 9 months	FU - 12 months	FU - Annual
Informed Consent	X								
Medical History	X			X					
Clinical examination				X					
Weight				X					
Full blood count with differential				X					
Biochemistry[2]				X					
Pregnancy test[3]	X			X					
Tests for autoimmune conditions[4]				X					
Thyroid function tests[5]				X					
Hepatitis B & C serology[6]				X					
ECG (& echo if indicated)				X					
Lung function test				X					
PET-CT scan (for central review)			X						
Retrieve archival biopsy sample and send to HMDS		X							
Remission status assessment (investigations as per local protocols)					X	X	X	X	X

1 = To avoid subjecting to patients to trial-specific tests unnecessarily, it is strongly recommended to wait for confirmation of PET positivity before undertaking these investigations
2 = to include ALT/AST, total bilirubin, alkaline phosphatase, lactate dehydrogenase, urea, creatinine, calcium, albumin, magnesium, sodium, potassium, urate, glucose
3 = Women of childbearing potential
4 = Amylase, lipase, ACTH
5 = (TSH & Free T4; Free T3 to be performed if TSH/Free T4 abnormal)
6 = HBsAg, HBsAb (if standard locally), HBcAb, HBV DNA (if HBcAb+), HCV Ab *or* HCV DNA (use test performed as standard locally)
~~HB sAg HBsAb, HBcAb, HBV DNA (if HBcAb+), HCV Ab or HCV DNA~~

APPENDIX 3: RESPONSE ASSESSMENT

Modified from:

Role of Imaging in the Staging and Response Assessment of Lymphoma: Consensus Guidelines of the International Conference on Malignant Lymphomas Imaging Working Group (Barrington et al. 2014) and Recommendations for Initial Evaluation, Staging, and Response Assessment of Hodgkin and Non-Hodgkin Lymphoma: The Lugano Classification (Cheson et al. 2014).

Assessable disease

Classical Hodgkin lymphoma is consistently 18-FDG avid. Only lesions that are FDG avid (noting that the first on trial assessment will take place after 2 cycles of first or second line salvage therapy) will be deemed to be assessable lesions for the purposes of this study. The primary assessment of disease response is by PET-CT.

For the purposes of accurate response assessment, the PET-CT scan acquired at the time of establishing the presence of refractory disease or disease relapse (not acquired under study conditions) will be requested for central review alongside the PET-CT scan performed (under study conditions) post 2 cycles of first or second line salvage therapy (or 4 cycles if treated with brentuximab vedotin; PET0).

Complete Metabolic Response (CMR):

Score 1, 2, or 3 with or without a residual mass on 5 point scale 5-PS (Deauville criteria) †

It is recognised that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (e.g. with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake;

Bone marrow: No evidence of FDG-avid disease in marrow.

Partial Metabolic Response (PMR):

Score 4 or 5† with reduced uptake compared with first study scan and residual mass(es) of any size

Bone marrow: Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy.

Progressive Metabolic Disease (PMD):
Score 4 or 5† with either an increase in intensity of uptake in previously identified FDG avid lesions or with additional new FDG-avid lesions consistent with lymphoma

BUT for previously identified FDG-avid lesions, increase in intensity must be accompanied by a change in size that meets criteria for overall progression with >50% increase in overall tumour

burden as measured by SPD of up to 6 lesions at PET4 or PET8 compared with the first scan performed under trial conditions (end of first or second line salvage; PET0).

Growth of one or more existing lesion(s) by >50% with an increase in uptake occurring in the context of a lack of overall progression does not meet the criteria for PMD but is regarded as indeterminate response (IR), see below.

AND new lesions must be consistent with lymphoma and have an identifiable CT correlate.

Indeterminate responses according to the refinement of the Lugano Classification will be documented. For this reason patients will also have contrast enhanced CT scans and combined PET with low dose CT at each response time point, which may be performed at a single imaging session if feasible.

[Note this is a modification of PMD adapted from Cheson et al (2016) to differentiate tumour flare from 'true' PD].

No Metabolic Response (NMR):

Score 4 or 5 with no significant change in FDG uptake from first on study scan [i.e. after 2 cycles of first or second line salvage therapy (4 cycles if treated with brentuximab vedotin); PET0]

Indeterminate Response (IR)

Score 4 or 5 with increase in intensity of uptake in previously identified FDG avid lesions or growth of one or more existing lesion(s) ≥50% at any time during treatment, occurring in the context of lack of overall progression (<50% increase) of overall tumour burden, as measured by the SPD of up to 6 lesions at PET4 or PET8 compared with the first scan performed under trial conditions (end of first or second line salvage; PET0).

[Note this is a modification of IR adapted from Cheson et al (2016) to differentiate tumour flare from 'true' PD].

Patients with IR remain on nivolumab (but are not counted as ORR unless later become CMR/PMR as best overall response).

At reassessment, if PMD confirmed then time point is set at previous designation of IR. PMD will be confirmed at PET8 if the SPD of a total of up to 6 lesions becomes >50% compared to the first scan performed under trial conditions (end of first or second line salvage; PET0).

Ideally biopsy should be performed where possible when lesions designated PET positive (DS 4 or 5) including IR.

Contrast enhanced CT scans (ceCT) will be performed in addition to PET with low dose CT (PET-CT), ideally at the same imaging session or if not possible at a separate imaging session. If performed at the same session, contrast enhanced CT scan should be performed after (low dose) PET-CT.

Management of patients with indeterminate response

Recent evidence suggests that treatment beyond PET-defined progression leads to stable tumour volume reduction in a substantial number of patients (Cohen et al. 2017). Patients with an indeterminate response at PET4 may therefore continue to receive a further 4 courses of nivolumab under the following circumstances:

1. The PI judges that it is in the patient's best interests to continue with treatment
2. There is no concern that further lesion growth before the next scan (PET8) would cause compression of vital structures or compromise of organ system(s)
3. There is no other evidence of tumour progression e.g. recurrence of B-symptoms
4. There have been no clinically significant drug related grade 3 or 4 toxicities
5. Continuing therapy is discussed with the patient who provides verbal consent – this discussion should be documented in the source document.

† Deauville Criteria (5 point scale)

The 5-PS scores the most intense uptake in a site of initial disease,
if present, as follows:

1. No uptake
2. Uptake ≤ mediastinum
3. Uptake > mediastinum but ≤ liver
4. Uptake moderately higher than liver
5. Uptake markedly higher than liver and/or new lesions

X. New areas of uptake unlikely to be related to lymphoma

Score 4 is uptake greater than the maximum SUV in a large region of normal liver
Score 5 is uptake ≥ 3 times the maximum SUV in a large region of normal liver

APPENDIX 4: MODIFIED GLUCKSBERG CRITERIA FOR ASSESSMENT OF ACUTE GVHD

Severity of acute pattern GvHD is graded according to the modified Glucksberg criteria (Przepiorka et al, 1995):

Stage	Skin	Liver (bilirubin, µmol/l)	Gut (diarrhoea)
1	Maculopapular rash <25% BSA	25-50 µmol/l	500-999ml/day
2	Maculopapular rash 25-50% BSA	>50-100 µmol/l	1000-1500ml/day
3	Generalised erythroderma	>100-250 µmol/l	>1500ml/day
4	Generalised erythroderma with bullous formation and desquamation	>250 µmol/l	Severe abdominal pain with or without ileus

Grade	Skin stage	Liver stage	Gut stage
I	1-2	0	0
II	1-3	1	1
III	2-3	2-3	2-3
IV	2-4	2-4	2-4

APPENDIX 5: PROTOCOL VERSION HISTORY

Protocol:		**Amendments:**		
Version no.	**Date**	**Amendment no.**	**Protocol Section (no./title)**	**Summary of main changes from previous version.**
1.0	04.01.2018	N/A	N/A	Initial version
1.1	21.02.2018	Response to MHRA GNA; amendment 1 to REC/HRA	2.1	Rationale for selected dose and schedule added to background section
2.0	10.04.2018	2	TMG	Dr Paolo Polzella added to the trial management group
			1.1, 6.2.2, 6.2.4, 6.2.5	Inclusion criteria at study entry amended so that known *history of* Hepatitis B or C infection is now known *active* infection. Exclusion criteria amended to state exceptions apply to patients with a history of hepatitis B infection, with a detailed table added at section 6.2.5.
			8.5	Symptoms listed in management of adverse events section updated for diarrhoea, colitis, pneumonitis, rash and creatinine clearance in line with updated CTCAE v5
			9.2, 9.3, 9.4, appendix 2	Test for chloride removed from all trial assessments
			9.2, appendix 2	Creatinine clearance added to eligibility for nivolumab treatment, previously omitted in error. Testing requirements for hepatitis B and C serology expanded in line with section 6.2.5
			9.3, 9.4, 9.6.2, appendix 2	Clarification of thyroid function testing requirements
			9.3, 9.4, 9.6.2, 10, 10.2, 16.1, 21, Appendix 2	References to UCL Cancer Institute have been removed from throughout the document and replaced with the Weatherall Institute of Molecular Medicine, Oxford who will now be performing analysis on peripheral blood samples

			10.1, 10.2	Minor revisions to analysis plans for FFPE and peripheral blood samples, following change of central laboratory from UCL Cancer Institute to Weatherall Institute of Molecular Medicine.
			11.1	Requirement for original CRFs to be sent to UCL CTC removed in line with current data management SOPs.
			12.2.2; 12.5.1	Exemptions from SAE reporting/ urgent events amended.
				- Steroid-responsive febrile syndrome amended to non-infectious febrile episodes requiring steroid therapy (including steroid-responsive febrile syndrome; patients who have allogeneic transplant only).
				- Sinusoidal obstruction syndrome/veno-occlusive disease (patients who have allogenic transplant only) added.
			19.1	REC name added
			22	Publication policy amended to state that central laboratories and the PET core laboratory may not publish any data pertaining to ANIMATE patients without prior written permission from the TMG.
			Appendix 1	Additions made to list of abbreviations
			Throughout	References to CTCAE v4 have been replaced by v5 throughout the document, this will be used for the assessment of adverse events for the trial
			Throughout	Minor clarifications and corrections of typographical errors.
2.1	12.06.2018	3	6.2.5, 9.2, Appendix 2	Minor updates to requirements for hepatitis serology testing to reflect standard of care within the NHS. HBsAb now only required if standard of care locally; HBV DNA only required if patient is HBcAb positive, and clarification that hepatitis C testing should use the local standard test (either HCV Ab or HCV DNA).

			10.1, 10.2, 10.3, Appendix 2	MRC-University of Glasgow Centre for Virus Research who will now be performing TARC analysis on peripheral blood samples added to Exploratory Biological Studies section
			10.2	5ml peripheral blood in serum gel tube collection added to peripheral blood samples section for TARC analysis
			11.3	Timelines for data return updated with New treatment form, Lost to follow up form and Transfer of Care form
			15.3	NHS Wales Informatics Service (Wales) and the Information Services Division (Scotland) added as examples of registries to provide further data if patients are lost to follow-up, Health & Social Care Information Centre amended to NHS Digital in line with recent name change
			19.0, 19.5	References to the Data Protection Act 1998 replaced by the Data Protection Act 2018
			Appendix 1	Abbreviations updated with CCL-17 (Chemokine (C-C motif) ligand 17) and MRC (Medical Research Council) added