ANIMATE

UK PET Core Lab
Quality Control for PET Clinical Trials

UK PET Core Lab

# Standard Operating Procedure
# Animate Imaging Manual

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

*A procedure for performing PET/CT imaging as part of the ANIMATE multicentre trial*

| Document Detail | |
|---|---|
| Parent policy | *UK PET Core Lab Document Management* |
| Document location | Sharepoint SOPs |
| Version | 1.0 |
| Approved by | Sally Barrington |
| Effective from | 05.01.2018 |
| Date last reviewed | N/A |
| Date of next review | 05.01.2020 |
| Owner | Lucy Pike |
| Author | Lucy Pike |
| Superseded documents | N/A |
| Related documents | ANIMATE study Protocol |
| Keywords | PET, Imaging Manual, SOP, ANIMATE |

| Document History | | |
|---|---|---|
| Date | Comments | Approved by |
| 05.01.2018 | Initial version | S Barrington |

CANCER RESEARCH UK

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NCRI National Cancer Research Institute

# INTRODUCTION

This PET Imaging Manual applies to nuclear medicine physicians, radiologists, physicists and technologists/radiographers at UK sites performing PET/CT scanning for the ANIMATE multicentre trial.

The ANIMATE study involves patients with Relapsed/Refractory Hodgkin Lymphoma fit for autologous stem cell transplantation who fail to reach complete metabolic remission (CMR) after first or second line salvage therapy.

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) 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.

The primary endpoint is overall response rate (ORR) by PET-CT scan following 4-8 cycles of nivolumab.

A secondary PET related endpoint is OS and PFS stratified by partial metabolic response (PMR) versus complete metabolic response (CMR) on FDG-PET

Exploratory biological endpoints include

- 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

Note that response assessment in this trial will require contrast-enhanced AND low dose CT to be performed in addition to PET scans as the definition of progressive metabolic disease (PMD) takes account of the Refinement of the Lugano Classification Response Criteria for Lymphoma in the Era of Immunomodulatory Therapy (Cheson et al. 2016) and introduces the category of indeterminate response. Both of these categories use FDG uptake AND the sum of the product of perpendicular diameters (SPD). See Appendix C.

**Target accrual**: 120 registered, to treat 30 patients

**Study duration**: Recruitment 3 years with 3 years minimum follow up. End of trial will be declared when the last patient has completed 3 years of follow up.

# 1. AIM

The purpose of this manual is to describe the procedures necessary to perform the CT and PET/CT scans on patients enrolled/potentially enrolled in the ANIMATE trial and to ensure that sites perform PET/CT scans consistent with the protocol and the QC requirements of the UK PET Core Lab. Adherence to the procedures will allow results acquired from different sites/scanners to be compared.

# 2. ROLES AND RESPONSIBILITIES

The site technologists/radiographers are responsible for performing trial PET/CT scans according to the procedure detailed below. Individual responsibilities will depend on the local setup.

# 3. CONTACT LIST

For questions regarding the details outlined within this imaging manual, please contact the Trial Coordinator as outlined below. All general study related questions should be directed to the primary investigator at your site.

| **Please contact the following personnel for enquiries relating to:** | **Contact** |
|---|---|
| PET/CT<br>PET Experts for trial | **Prof Sally Barrington**<br>**Dr Victoria Warbey**<br>Telephone: 020 7188 4988<br>Fax: 020 7620 0790<br>Email: sally.barrington@kcl.ac.uk<br>victoria.warbey@gstt.nhs.uk |
| Quality Control and Data Transfer of PET/CT | **Lucy Pike and Carola Houpt**<br>UK PET Core Lab, PET Centre,<br>St Thomas' Hospital,<br>London, SE1 7EH<br>Telephone: 0207 188 1489<br>Fax: 0207 620 0790<br>Email: pet-trials@kcl.ac.uk |
| Any other enquires | **Oliver Schofield**<br>ANIMATE Trial Coordinator<br>Cancer Research UK & UCL Cancer Trials Centre<br>90 Tottenham Court Road London W1T 4TJ<br>Telephone: 0207 679 9860<br>Fax: 020 7679 9861<br>Email: ctc.animate@ucl.ac.uk |

# 4. PET CENTRE ACCREDITATION PROCEDURE

## 4.1. PET-CT Site Accreditation Process

Before a PET centre can participate in the ANIMATE trial it must undergo the formal PET site accreditation process. Further details and written procedures for the site accreditation process will be provided by the UK PET Core Lab based at St Thomas' Hospital, London. Sites should contact the UK PET Core Lab (pet-trials@kcl.ac.uk) at an early stage to determine the requirements for the accreditation procedure.

**No patients are to be scanned until all of the following steps have been completed:**

1. Centre must have received written confirmation from the UK PET Core Lab that the accreditation process is complete and scanning may commence.
2. A copy of the ARSAC certificate must have been sent to the trial team at the CR-UK & UCL Cancer Trials Centre.

**Site Accreditation Overview**

Accreditation of PET scanning centres is in place to set up and ensure the following:

- Named persons (and their deputies) with responsibility for scanning, QC and data transfer are identified at participating PET-CT centres.
- A tested and secure method is established at each site to transfer anonymised scan data between scanning facilities and the UK PET Core Lab and the central reporting facility.
- All image files are compliant with DICOM PART 10 format
- All image files are correctly anonymised and clearly named using pre-arranged file naming conventions.
- Image quality is comparable between centres and standardised uptake values can be reliably determined from the PET-CT images.
- The proposed data acquisition/reconstruction protocol (including details of the time per bed position/scan speed, 3D, CTAC parameters, reconstruction parameters etc.) are agreed with the UK PET Core Lab before scanning starts.

PET scanning centres must also repeat the site accreditation process in the following situations:

- After any software or hardware changes which may affect the scanner image quality.
- If there are any significant changes to the acquisition or reconstruction parameters originally agreed with the UK PET Core Lab
- Any other circumstances that arise that the Core Lab deems may alter the image quality such as; QC failures, apparent scanner degradation or poor image quality.

It is the responsibility of the participating PET centre to inform the Core Lab of any upgrades to the scanner hardware or software prior to the upgrade. If the upgrade is likely to affect the image quality the site will be required to repeat the phantom scans before continuing to scan patients as part of the trial.

## 4.2. Quality Control (QC) Procedures

**PET-CT Scanners**

A documented PET-CT scanner quality assurance program must be in place and records kept, covering daily, monthly, quarterly and annual QC testing.

The PET scanner should have up-to-date calibration and normalisation. On the day of scanning a trial patient the manufacturer's recommended daily QC should be performed and if any failures or abnormalities are identified that could affect the quality of the PET scan, consideration should be given to rescheduling the scan.

Routine CT QC should be performed according to the manufacturer's recommendations, and should include a water filled phantom scanned on a weekly basis, to measure image noise and CT number as described in IPEM (Institute of Physics and Engineering in Medicine) report 91 (Scally 2005).

All PET-CT scanners to be used for the trial should be calibrated against the institutions own radionuclide calibrator.

**Ancillary Equipment**

As this study uses Standardised Uptake Values (SUV) defined in terms of patient weight, the scales used to weigh the patients must be calibrated. As a minimum the scales must be checked using a standard weight at least annually and should be accurate to within ±1kg of a standard weight of 70 kg and records kept.

The BM glucometer QC should be performed according to the manufacturer's or institution's procedure to ensure proper functioning.

Quality assurance procedures for the radionuclide calibrator must be in place and activity measurements for $^{18}$F should be traceable to a primary standard. QC tests should include daily constancy checks and annual accuracy and linearity.

Clocks used to record the assay time and injection time must be synchronised to the scanner time.

**Additional Scanner QC Required During the Trial**

Standardised Uptake Values (SUV) are used as a primary tumour response endpoint, therefore accurate and consistent estimation of SUV for all patient scans and between all participating centres is required. This will be achieved via a rigorous and regular testing of SUV accuracy and consistency of all participating scanners.

A uniform phantom should be scanned prior to the start of each scanning session in which a patient is to be scanned as part of the trial. This can either be a resin $^{68}$Ge phantom (where available) or an $^{18}$F water filled phantom. The activity concentration in the $^{18}$F phantom should be approximately 5kBq/ml. The average SUV for a large ROI placed at the centre of the phantom must be 1.00 ± 10% and ideally within ± 5%. On visual inspection of the PET and CT the images should show no artifacts. The relevant sections of the PET Acquisition Form must be completed to confirm the results of this test. If the test fails, the physicist at the Core Lab should be contacted. The scan should not take place until the reason for this failure has been resolved.

**Confirmation of Site Approval**

When all the above steps have been completed, the UK PET Core Lab will issue a letter giving approval to scan patients enrolled in the Trial. The letter will be forwarded to both the PET centre and the Trial Coordinator at the CR-UK & UCL Cancer Trials Centre to confirm that the centre can now participate in the trial. No subjects should be scanned before this has been received.

Scanning sites must inform the Core Lab of any upgrades to the scanner hardware or software prior to the upgrade. If the upgrade is likely to affect the image quality the site will be required to repeat the phantom scans before continuing to scan patients as part of the trial. Sites must also notify the Core Lab immediately of any deviations in QC and scan acquisition or reconstruction parameters from those agreed.

# 5. IMAGING PROCEDURE

## 5.1. Imaging Acquisition

**Health and Safety Considerations**

Local health and safety requirements should be followed at all times.

**Overview**

The study will be conducted at approximately 13 centres and imaging will wherever possible be performed on fixed site PET-CT scanners at these institutions.

Scanning facilities will undergo the site accreditation process as detailed in PET-CT Site Accreditation Process, and have received written confirmation that they fulfil the requirements of the study before scanning any patients as part of the trial.

## 5.2. PET/CT Scan Timing

A trial schema is shown in Appendix A.

Patients will undergo a total of three PET-CT scans for the trial. In addition, their pre-salvage PET-CT images will be requested:

**Baseline (pre-salvage) PET-CT Scan**

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 after 2 cycles of first line salvage therapy.

**PET-CT scan after 2 cycles of first or second line salvage (PET0)**

PET-CT scan to be carried out as per trial requirements on an approved scanner 18 days after last administration of cycle 2 of first or second line salvage (cycle 4 if treated with brentuximab vedotin) ±3 days.

**PET-CT scan after cycle 4 (PET4)**

PET-CT scan to be carried 11-13 days after cycle 4 nivolumab administration as per trial requirements on an approved scanner.

**Patients who complete all 8 cycles of trial treatment (PET8)**

PET-CT scan to be carried out 11-13 days after cycle 8 nivolumab administration as per trial requirements on an approved scanner.

Ideally, sequential PET exams for a patient should be performed in the same centre using the same accredited PET-CT system as the baseline scan. In cases where the baseline (pre-salvage) PET scan has been performed at a different centre, on a non-approved scanner or using a different protocol to the trial, the post salvage and post 4 and 8 cycle scans should be performed on an approved scanner using the imaging procedures described in this manual. The patient preparation, tracer administration, image acquisition and reconstruction for these scans should be matched for each subsequent patient scan acquired for the study.

## 5.3. Patient Preparation and Scan Procedure

- Non-diabetic patients should fast for at least 6 hours prior to the scan. Plain (unflavoured) water should be taken during the period of fasting and the uptake period to ensure good hydration.
- Diabetic patients should be given a late morning appointment.
- Patients on insulin should eat a normal breakfast and administer insulin as usual.
- Diabetic patients on oral medication should eat a normal breakfast not later than six hours before the examination and take their usual oral medication to control their blood sugar.
- The blood glucose level of all patients should be measured on arrival at the imaging centre. This should be performed using a calibrated glucometer or similar bedside device. Consideration should be given to rescheduling the scan if BM measures >11mmol/l (>200mg/dl). **Insulin should not be administered to reduce glucose level.**
- Oral diazepam (5-10mg po) may be given if desired to reduce brown fat uptake 30-60 minutes before tracer injection.
- Patients should be weighed without shoes and coats using a calibrated device.
- Intravenous CT contrast media should not be administered prior to the PET study.
- 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, the contrast enhanced CT scan should be performed after (low dose) PET-CT.
- The PET emission acquisition should ideally be started between 60 and 70 minutes after the FDG administration.
- The uptake time for subsequent PET scans should be matched as closely as possible to the post salvage PET scan.
- Patients should be positioned in the PET-CT scanner with their arms up. If participants cannot tolerate this position for the duration of the study, a different participant positioning may be chosen. However, arms should be positioned in the same way for all response scans.
- A low-dose CT scan will be acquired for attenuation correction and anatomical localisation of findings in the PET scan.

- Half body PET-CT scans should be performed from base of skull to mid-thighs.
- All other imaging parameters i.e. with regard to time per bed position/scan speed, 3D, CTAC acquisition parameters must be agreed with the UK PET Core Lab prior to the start of the study (see Section 5.2. (Quality Control (QC) Procedures)). These should then be used throughout the study. Any changes to these parameters must be agreed with the Core Lab before scanning any more patients.

**Radiopharmaceutical Administration**

| | |
|---|---|
| Radiopharmaceutical: | $^{18}$F-Fluorodeoxyglucose (FDG) |
| Activity: | Diagnostic Reference Level (DRL) is 400MBq. Injected activity should be matched for the response scans.<br><br>Injected activities may vary dependent on scanner settings and patient size; recommended injected activities are described in the EANM Procedure Guidelines (Boellaard et al. 2015) |
| Route of Administration: | Intravenous administration via butterfly cannula under quiet conditions.<br><br>Syringe residue should be measured and the corrected injected activity documented. |

**Uptake Period**

- During the tracer administration and uptake phase, the patient should remain seated or supine.
- Patients should be asked to void immediately prior to the PET-CT scan to reduce bladder activity.
- $^{18}$FDG-PET imaging (base of skull to mid-thighs) will ideally be performed between 60 and 70 minutes following injection of $^{18}$F-Fluorodeoxyglucose, with the uptake time for subsequent scans matched as closely as possible.

### 5.3.1. Image Reconstruction

- The reconstructed PET data should be corrected for decay, dead time, scatter, randoms and attenuation using standard algorithms provided by the scanner manufacturers.
- Attenuation correction should be performed using the low dose CT.
- Iterative reconstruction should be used e.g. OSEM or similar.
- Both attenuation-corrected and non attenuation-corrected PET images should be reconstructed.
- All other reconstruction parameters i.e. with regard to number of iterations or filtering parameters must be agreed with the UK PET Core Lab prior to the start of the study. These should then be used throughout the study. Any changes to these parameters must be agreed with the Core lab before scanning any more patients.
- If the reconstruction parameters agreed with the Core Lab are different from the standard clinical reconstruction please submit both the Core Lab approved reconstruction and the clinical reconstruction making sure they are clearly labelled.

# 6. DATA TRANSFER AND STORAGE

## 6.1. Anonymisation and File Naming Procedure

All patient identifying information must be removed from the images prior to transfer. FUSED images, screen captures and dose reports are not required and should not be sent for central review.

PET-CT studies should be clearly named using the following filename convention:

ANIMATE_<trial ID>_<initials>_presalvage

ANIMATE_<trial ID>_<initials>_PET0

ANIMATE_<trial ID>_<initials>_PET4

ANIMATE_<trial ID>_<initials>_ PET8

## 6.2. Data Transfer and Archive

PET-CT data should be transferred to the UK PET Core Lab at the same time as the completed PET-CT acquisition form (see Appendix B). All studies to be transferred to the Core Lab must be compliant with DICOM PART 10 format.

The following DICOM files are required:

- CT attenuation corrected half body PET images (base of skull to mid-thighs) reconstructed using the UK PET Core Lab parameters
- Non-attenuation corrected half body PET images
- Half body CT scan (used for attenuation correction and localisation)
- Contrast enhanced CT scan

If applicable, sites should also submit the following:

- PET images reconstructed using the standard clinical protocol

**Due to the rapid reporting times required for the trial, images must be transferred electronically. Secure data transfer procedures will be established with each scanning site. For instructions on approved transfer methods please contact the UK PET Core Lab (pet-trials@kcl.ac.uk).**

All reconstructed CT, CT-attenuated PET and non-attenuated PET data must be saved locally on an approved data storage device. Raw PET data should be archived according to local policy, and at least until the images have been accepted by the UK PET Core Lab in case additional reconstructions are required.

Following review, all scan data will be archived at St Thomas' PET Centre.

**Information to be recorded for each patient**

For each patient study, the PET-CT acquisition information and patient information must be recorded on the PET-CT Acquisition Form (Appendix B) and sent to the UK PET Core Lab with the PET-CT images.

**PET acquisition forms can be emailed (pet-trials@kcl.ac.uk) or faxed (0207 620 0790) to the UK PET Core Lab**

# 7. PET/CT IMAGE ANALYSIS

## 7.1. PET-CT Evaluation

All PET/CT scans will be centrally reviewed for the purposes of trial analysis by Prof Sally Barrington, Dr Victoria Warbey and colleagues at the King's College London & Guys and St Thomas' PET centre.

Local reports should be routinely issued for CT and PET/CT scans and factors documented that might affect patient management e.g. infection or any clinical findings that could require immediate attention.

## 7.2. PET-CT Technical QC

Technical QA/QC of all the PET scans will be undertaken by the UK PET Core Lab which is part of the NCRI PET Research Network and provides national accreditation for PET research trial studies.

# 8. REFERENCES

Barrington SF, Mikhaeel NG, Kostakoglu L, et al. The role of imaging in the staging and response assessment of lymphoma: consensus of the ICML Imaging Working Group Journal Clinical Oncology 2014;32:3048-3058.

Boellaard R, Delgado-Bolton R, Oyen WJ, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging 2015;42(2):328-354.

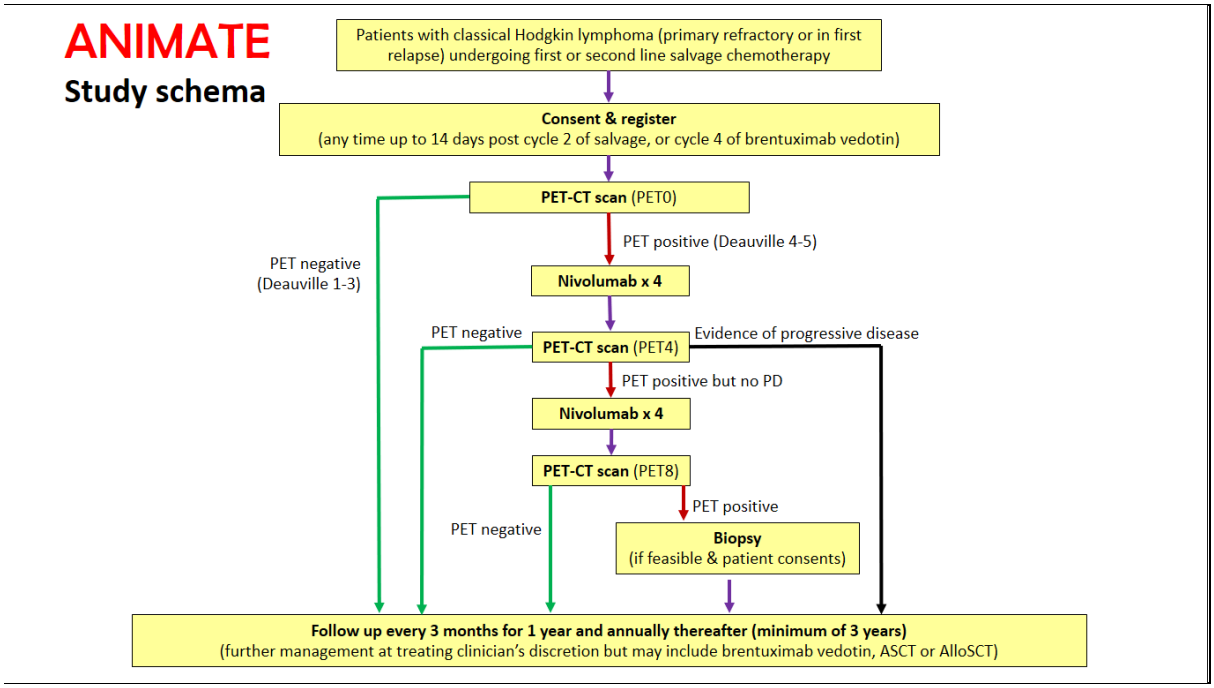
Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J. Clin. Oncol. 2014;32(27):3059–3068.

Cheson BD, Ansell SM, Schwartz L, et al. Refinement of the Lugano classification response criteria for lymphoma in the era of immunomodulatory therapy. Blood 2016;128:2489-2496.

Cohen JB, Engert A, Ansell SM, et al. Nivolumab treatment beyond investigator-assessed progression: outcomes in patients with relapsed/refractory classical Hodgkin lymphoma from the phase 2 Checkmate 205 study. Blood;130(s1):650.

Scally AJ. 2005. Recommended standards for the routine performance testing of diagnostic x-ray imaging systems. IPEM report 91. York: Institute of Physics and Engineering in Medicine.

# APPENDIX A: TRIAL SCHEMA



# APPENDIX B: PET ACQUISITION FORM

(to be completed by PET scanning facility)

| | |
|---|---|
| PET-CT scan acquired at:<br>(PET Centre) | |
| Referring Consultant:<br>Telephone / Fax: | |

Patient Details:

| | | | |
|---|---|---|---|
| Patient's trial number: | | Patient's initials: | |
| Date of PET-CT scan: | | | |
| Study timepoint (circle as applicable): | Post 1st or 2nd line salvage (PET0)/ Post 4 cycles (PET4)/ Post 8 cycles (PET8) | | |
| Patient's weight (kg): | | Patient's height (cm): | |
| Date last ate<br>(dd/mm/yyyy): | | Time last ate<br>(hh:mm): | |
| Patient blood glucose (mmol/l): | | Time measured (hh:mm): | |

Tracer Administration:

| | | | |
|---|---|---|---|
| Activity in syringe (MBq): | | Time measured (hh:mm): | |
| Residual activity in syringe (MBq): | | Time measured (hh:mm): | |
| Time of administration (hh:mm): | | Total activity at time of administration (MBq): | |
| Site of tracer administration | | left / right | (please circle) |
| Was there evidence of extravasation? | | yes / no | (please circle) |
| Any deviations from the imaging protocol? | | yes / no | (please circle) |
| If yes, please specify | | | |

Scanning Procedure:

| | | | |
|---|---|---|---|
| PET scanner used (manufacturer and model): | | | |
| Acquisition mode: | | 3D / TOF | (please circle) |
| PET acquisition start time (hh:mm): | | | |
| Total no. of bed positions (or total scan length in mm): | | Time per bed (mins) or scan speed (mm/s) | |

Quality Control:

| | | |
|---|---|---|
| Daily QC results for day of scan passed? | Yes / No | (please circle) |
| SUV for uniform cylinder between 0.90 and 1.10? | Yes / No | (please circle) |
| Any deviations from the acquisition/ reconstruction parameters agreed with the Core Lab? | Yes / No | (please circle) |
| If yes, please specify | | |

Form completed by: _____ Date: _____

Completed forms should be returned via email: pet-trials@kcl.ac.uk or fax: 020 7620 0790

# APPENDIX C: 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 1st 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; baseline scan) 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 the SPD of up to 6 lesions at PET4 or PET 8 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 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 and/or new FDG avid 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 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 a 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