A MULTI-CENTRE PHASE II STUDY USING CARBOPLATIN AUC-10 FOR METASTATIC SEMINOMA WITH IGCCCG GOOD PROGNOSIS DISEASE – THERAPY DIRECTED BY INITIAL METABOLIC RESPONSE ON PET-CT [Car-PET]

Version: 8.0 dated 31 Aug 2017
EudraCT Number: 2009-009882-33
Protocol number: TE 2010 11
REC: 10/H0703/45

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PROTOCOL SIGNATURE PAGE

Signature of the Chief Investigator:

The clinical study as detailed within this research protocol (version 8.0, dated 31 Aug 2017), and any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Chief Investigator Name: Dr. Jonathan Shamash

Signature and Date: 

3 1 / A U G / 2 0 1 7

Statistician Agreement

The Car-PET clinical study as detailed within this research protocol (version 8.0, dated 31 Aug 2017), or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH E6-GCP, ICH E9 - Statistical principles for Clinical Trials, ICH E10 - Choice of Control Groups and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations. Signature of the Principal Investigator:

Statistician Name: Dr Shah-Jalal Sarkar

Signature and Date: _____

3 1 / A U G / 2 0 1 7

Signature of the Principal Investigator

The clinical study as detailed within this research protocol (version 8.0, dated 31 Aug 2017), and any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

Principal Investigator Name: _____

Principal Investigator Site: _____

Signature and Date: _____

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Contents

GLOSSARY OF TERMS AND ABBREVIATIONS

AE	Adverse Event
AFP	Alpha-fetoprotein
AR	Adverse Reaction
AUC	Area under the Curve
BEP	Bleomycin, Etoposide, Cisplatin
CI	Chief Investigator
CIOMS	Council for International Organizations of Medical Sciences
CR	Complete Response
CRF	Case Report Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
EDTA	Ehylenediaminetetraacetic acid
EU	European Union
FAS	Full Analysis Set
FDG	Fluorodeoxyglucose
FSH	Follicle-stimulating hormone
GCP	Good Clinical Practice
GCSF	Granulocyte Colony-Stimulating Factor
GFR	Glomerular Filtration Rate
hCG	Human Chorionic Gonadotropin
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IGCCCG	International Germ Cell Cancer Collaborative Group
IMP	Investigational medicinal product
JRO	Joint Research Office
LDH	Lactate Dehydrogenase
LFTs	Liver Function Tests
LH	Luteinizing hormone
MDT	Multidisciplinary Team Meeting
ml/min	millilitre/minute
MRC	Medical Research Council
MREC	Multi Research Ethics Committee
NHS	National Health Service
OCTG	Orchid Clinical Trials Group
PD	Progressive Disease
PET	Positron Emission Tomography
PFS	Progression Free Survival
PI	Principal Investigator
PR	Partial Response
PS	Performance Status
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SD	Stable Disease
SOP	Standard operating procedure
SPD	Sum of Produce of the Diameters
SS	Safety Set
SUSAR	Suspected Unexpected Serious Adverse Reaction
SUV	Standard Uptake Value
U&Es	Urea and Electrolytes
WBC	White Blood Count

Protocol Synopsis

Title	A multi-centre phase II study using carboplatin AUC-10 for metastatic seminoma with IGCCCG good prognosis disease – therapy directed by initial metabolic response on PET-CT.
Short Title	Car-PET
Protocol Version Number and Date	Version 8.0 (31 Aug 2017)
Methodology	This is a single arm phase II trial to assess the safety, efficacy and toxicity of carboplatin AUC-10 in metastatic seminoma. Patients will be recruited from 2 sites.
Study duration	48 months for recruitment. 2 years for follow up.
Study centres	Multisite.
Objectives	• To assess the safety, efficacy and toxicity of carboplatin AUC-10 in metastatic seminoma in a multi-centre setting. • To see if the number of patients requiring 4 cycles can be reduced by the use of FDG PET-CT in the assessment of metabolic response.
Phase of Trial	II
Number of patients	Up to 50 patients will be recruited into the study over four years (assuming 5 patients may drop out for reasons other than disease progression). 45 evaluable patients will be necessary to establish activity of Carboplatin AUC10 in this setting.
Inclusion criteria	1. Metastatic seminoma-IGCCCG good prognosis. 2. Glomerular filtration rate of over 25 ml/min (creatinine clearance should preferably be assessed using an EDTA clearance). 3. ECOG performance status 0-3. 4. Normal Alpha-fetoprotein (All levels of Human chorionic gonadotropin and lactate dehydrogenase are acceptable). 5. Males aged greater than 18 and less than 75 years. 6. Able to give written informed consent prior to study entry. 7. Patients must be sterile or agree to use adequate contraception during the period of therapy.
Exclusion criteria	1. Metastatic seminoma with any non-pulmonary visceral metastases. 2. Raised Alpha-fetoprotein. 3. Any previous chemotherapy or radiotherapy. 4. Currently enrolled in any other investigational drug study. 5. Other malignancy except basal cell.

Statistical Methodology and Analysis	The primary efficacy endpoint is the Progression Free Survival (PFS) rate at 2 years from completion of treatment. Patients who do not complete 2 years follow-up for reasons other than death will be censored at the last date of follow-up. The PFS rate will be determined for the Carboplatin AUC-10, along with a 95% confidence interval, and the Kaplan-Meier curves will be plotted. The trial result will be considered positive if the PFS rate for patients on Carboplatin AUC-10 demonstrates an increase in survival of 15% or more when compared to PFS rates of standard chemo i.e. if there are at least 39 PFS patients out of first 45 patients at 2 years. Subgroup analyses of the PFS rate will be performed in terms of patients with complete or partial response at 2 years. The analysis of safety will include all patients who received at least one cycle of treatment. Safety and tolerability of Carboplatin AUC-10 will be determined by an evaluation of changes in laboratory parameters, vital signs, the incidence and severity of Adverse Events and of toxicities according to the CTCAE classification (version 4.03). The proportion of patients at each toxicity grade (0 to 4) of any type (including vomiting, nausea and diarrhoea) will be summarised. Safety analysis will be performed based on safety data set. Metabolic response rate will be assessed as described in section 5.3.3 of the protocol.

1.0 Introduction

1.1 Background

Metastatic seminoma is a relatively infrequent disease entity. The conventional treatment for it, namely cisplatin and etoposide with or without bleomycin, has a progression free survival rate at 3 years of over 81% compared to 71% treated with Carboplatin AUC 7 [1]. The overall survival however, is identical due to the effectiveness of second line salvage chemotherapy. The conventional treatment is toxic, usually requires an inpatient stay with administration over 3 days and can cause significant nausea, malaise, alopecia, risk of renal damage, hypertension and high tone hearing loss. It is possible to give this treatment on an outpatient basis however, this can be inconvenient as the patient has to attend for prolonged visits to a chemotherapy day ward for a minimum of 3 consecutive days for each cycle of treatment. Single agent carboplatin does not appear to have long term renal and hearing problems. There is no alopecia. Nausea and malaise are much less common and the treatment can be given as a day case with only one visit to hospital for one hour per cycle they receive.

1.2 Investigational agent

A variety of observations have led to the impression that seminomas are inherently more chemo-sensitive than non-seminomatous germ cell tumours. Several studies have addressed the use of single agent carboplatin in metastatic seminoma. Studies have generally concluded that although progression free survival is inferior to that seen with cisplatin based therapy, as a large number of relapsing patients could be salvaged, the overall survival was unchanged and indeed toxicity was substantially reduced [1, 2]. There is clear evidence for a dose response curve to platinum drugs in germ cell tumours; although certainly in metastatic non-seminomatous tumours there is little evidence to support intensification from AUC-5 to AUC-8 [3, 4]. In other tumour types notably epithelial carcinoma of the ovary, higher doses of carboplatin (AUC-12) have proved feasible although the increasing dose intensity has been smaller than anticipated because of delays in retreating patients due to the prolonged myelosuppression [5].

1.3 Clinical data to date

The Orchid Clinical Trials Group recently completed a study in metastatic seminoma using carboplatin AUC-10. Twenty patients received this dose of carboplatin for metastatic seminoma, with a median follow up of 29.4 months. Following the closure of the study a further 20 patients have received carboplatin AUC-10. In total 40 patients have been treated. There have been 2 relapses to date (5%), compared to the 18% relapse seen within the first 2 years of treatment of 28 patients who received AUC 7 or less with a median follow up of 135 months.

The relapsed patients were successfully salvaged using conventional chemotherapy. As nearly all relapses occur within 2 years of therapy, a 2 year progression-free survival is an appropriate endpoint for this phase II study.

In this most recent study, the protocol stipulated that all patients who were not in complete remission by day 21 of the first cycle would receive 4 rather than 3 cycles. This led to all those who essentially had greater than 2B disease requiring 4 cycles. This was probably unnecessary as most patients achieved a CR eventually – it just took time for the masses to shrink.

It is hoped that by substituting conventional CT for PET CT a greater proportion of patients will achieve a complete metabolic response and therefore the 4th cycle may be avoided in more patients. This will allow shortening of the treatment and reduction in the use of blood products as most of the blood transfusions required occur during the 4th cycle of carboplatin.

2.0 Study aims and objectives

- To assess the safety, efficacy and toxicity of carboplatin AUC-10 in metastatic seminoma in a multi-centre setting.
- To see if, by using FDG PET-CT to assess metabolic response, the number of patients requiring 4 cycles can be reduced.

2.1 End points

- **Primary**

  2-year progression free survival

- **Secondary**

  Metabolic response rate

  Overall survival

  Toxicity level (CTCAE version 4.03)

3.0 Investigational plan

3.1 Overall design

This is a single arm phase II study to assess the safety, efficacy and toxicity of carboplatin AUC-10 in metastatic seminoma. Patients will be recruited from two sites.
Prior to the commencement of treatment, the patient should have a baseline PET-CT scan and a contrast enhanced CT scan performed within 28 days of study entry. Patients will be treated with carboplatin AUC-10 every 3 weeks (3 weeks=1 cycle) and on day 17-21 of the first cycle a repeat PET-CT scan will be performed. All PET-CT scans will be reviewed centrally and these results will determine how many further treatment cycles the patients will undergo. If the patient has a complete metabolic response [refer to Appendix 3], a further 2 cycles of carboplatin will be given, leading to a total of 3, and if the patient has not had a complete metabolic response but is responding, a further 3 cycles of carboplatin will be given [Refer to section 5.3.3 and page 20 (the table) for the timelines for the scans. Please refer to appendix 8 for the imaging protocol].

If no response is seen, then the patient will be taken off study and will receive conventional therapy using a cisplatin-based combination.

All PET CT scans will be performed at (or sent to) University College Hospital to be centrally reviewed.

3.2 Treatment plan

Carboplatin will be administered as a day case and doses will be calculated using the Calvert formula as below:

Dose (mg) = (GFR + 25) x 10

Unless dictated by haematological toxicity, the Carboplatin dose should not be recalculated for each cycle. However, if the serum Creatinine has risen by > 20% above baseline, the Carboplatin dose must be recalculated using the Calvert formula with GFR determined by EDTA clearance. At the discretion of the PI an estimated creatinine clearance can be calculated using e.g. Cockcroft and Gault (or as per local policy) if the site is unable to obtain EDTA clearance.

Treatment will be repeated every 3 weeks (when platelets over 100 x 10^9/L, white blood count greater than 3x10^9/L or neutrophils greater than 1x10^9/L).

If the blood count is below the level required to commence the next cycle of treatment (i.e. platelets less than 100 x 10^9/, white blood count less than 3 x 10^9/L or neutrophils less than 1 x 10^9/L) then a further blood count must be repeated 48 hours after the target treatment day. If the results of this repeat count show platelets greater than 75 x 10^9/L and rising, white blood count greater than 3 x 10^9/L or the neutrophils greater than 1 x 10^9/L the patient may commence to the next cycle [See Figure 1].
If neutrophils are less than 1 x 10^9/L and white blood count less than 3 x 10^9/L, filgrastim or lenograstim (GCSF) should be given for 2 days.

However, if the blood count remains below the level required it should continue to be monitored at 48 hour intervals until it has reached the required level for proceeding with further treatment (platelets are greater than 75 x 10^9/L and rising, white count greater than 3 x 10^9/L or the neutrophils are greater than 1 x 10^9/L).

Please note that a delay of 14 days or more will require the patient to be withdrawn from study.

If a patient is admitted with neutropenic sepsis, prophylactic antibiotics e.g. ciprofloxacin, day 10 – 21 (with or without filgrastim or lenograstim) should be used for all subsequent cycles.

If the platelet nadir (day 13 -17) is less than 20 x 10^9/L, then a **20% dose reduction** should be made on subsequent administration of carboplatin.

Patients will be required to attend hospital to receive Carboplatin as a day case.

Figure 1: Blood Count Guide Prior to Treatment

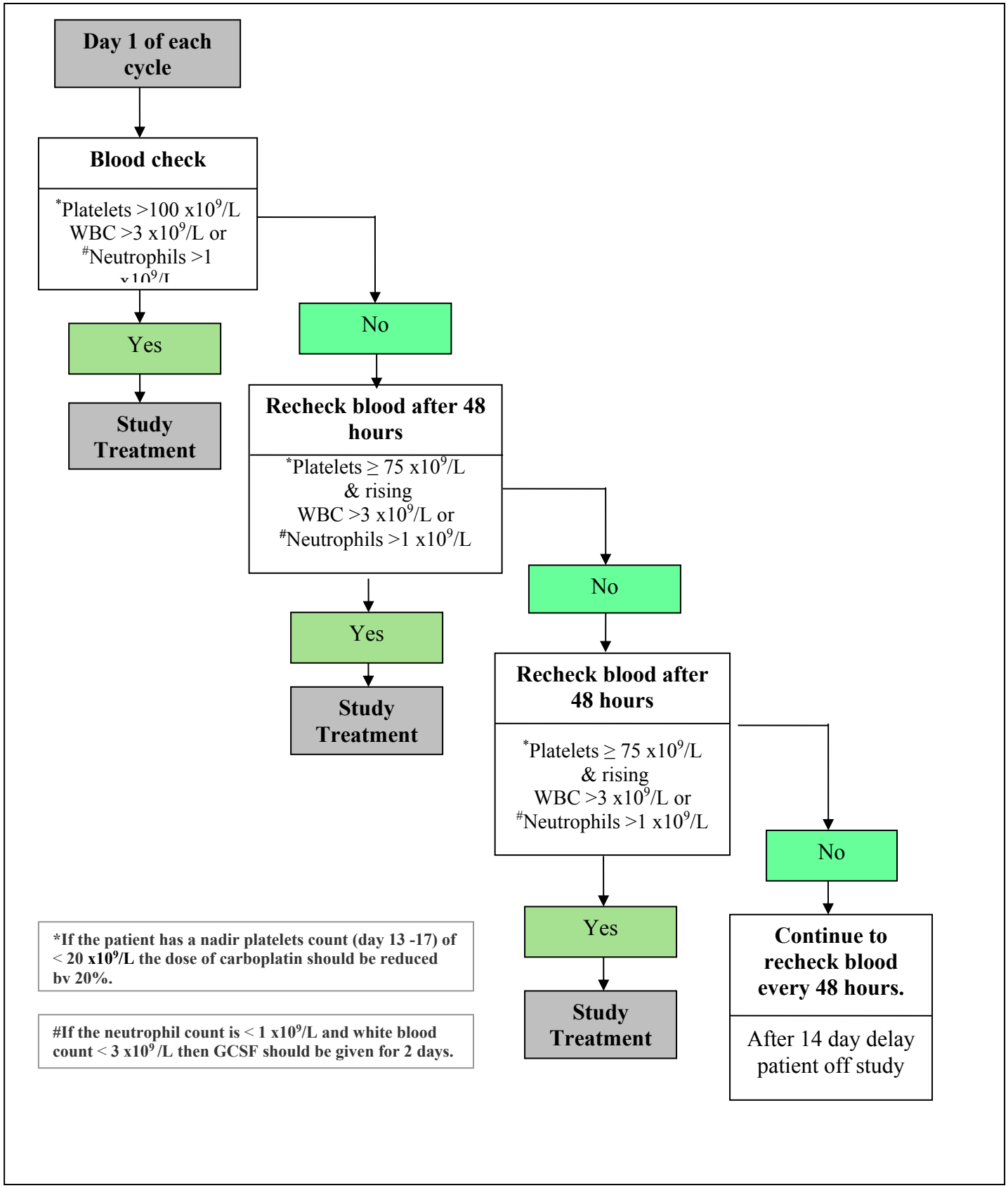
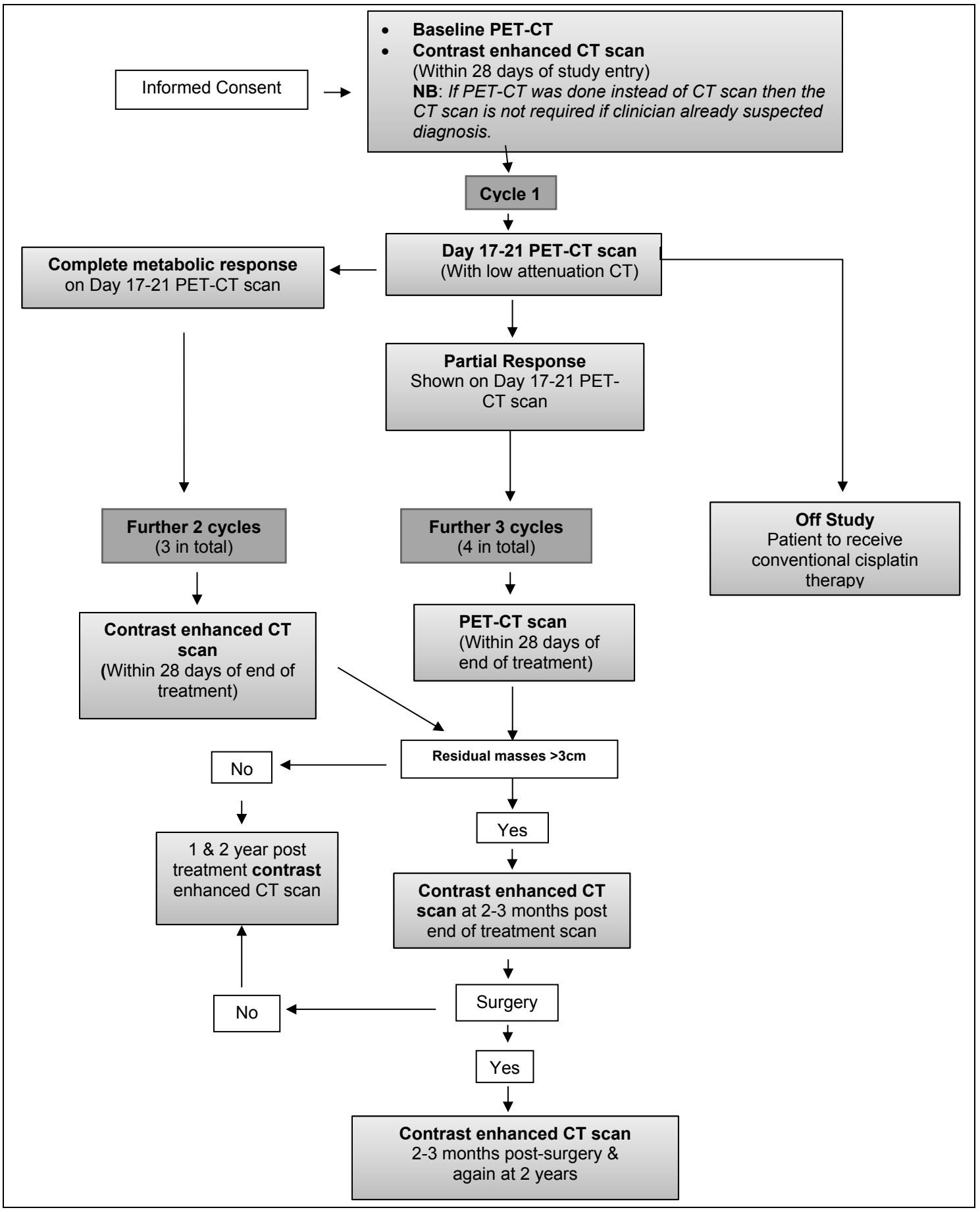


Figure 2: Treatment Flowchart



3.3 Study population

The population for this study are patients diagnosed with metastatic seminoma with IGCCCG good prognosis disease.

3.4 Target accrual

Up to 50 patients will be recruited into the study (assuming 5 patients may withdraw for reasons other than disease progression) over four years. 45 evaluable patients will be necessary to establish activity of Carboplatin AUC10 in this setting.

4.0 Eligibility, subject selection and withdrawal

4.1 Inclusion Criteria

1. Metastatic seminoma-IGCCCG good prognosis.
2. Glomerular filtration rate by EDTA clearance over 25 ml/min (a measured creatinine clearance using Cockcroft and Gault would be allowed if unable to perform EDTA clearance).
3. ECOG Performance status 0-3.
4. Normal Alpha-fetoprotein (All levels of Human chorionic gonadotropin and Lactate dehydrogenase are acceptable).
5. Males aged ≥18 and ≤75 years.
6. Able to give written informed consent prior to study entry.
7. Patients must be sterile or agree to use adequate contraception during the period of therapy.

4.2 Exclusion Criteria

1. Metastatic seminoma with any non-pulmonary visceral metastases.
2. Raised Alpha-fetoprotein.
3. Any previous chemotherapy or radiotherapy.
4. Currently enrolled in any other investigational drug study.
5. Other malignancy except basal cell.

4.3 Subject recruitment and screening

Participants will be identified when attending clinic visits by a research nurse/investigator that will screen patients for entry into the study. The possibility for study enrolment will be discussed and if appropriate, a patient information sheet will be provided by a member of the study team. The patient details should be entered onto the pre-screening log (initials, date of birth, pre-screening date). The patient should be given ample time to consider

entering the study. If the patient refuses to enter into the study, the reason (if applicable) should be recorded on the pre-screening log (refer to section 5.2 for registration procedure).

Patients from within the Anglian network will also be identified via a specialist testicular multidisciplinary team meeting which, is held fortnightly and attended by investigators and research nurses from different sites across the Anglian Network.

4.4 Withdrawal of subjects

Patients will be informed that they have the right to withdraw from the study at any time, for any reason, without prejudice to their medical care. The primary reason (if available) for a patient's withdrawal from the study should be recorded on the case report form (CRF). The right of patients to refuse to participate without giving reasons and prejudicing their further treatment will be respected. Any patients who decide to withdraw their consent completely will have no further data collected. However, if the patient withdraws from trial treatment only their data may be followed-up for survival as long as the patient is happy to do so.

The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Disease Progression.
- Occurrence of intolerable side effects.
- Non-compliance.
- A delay in treatment of 14 days or more.

At the time of withdrawal, all end of study procedures should be completed (as per schedule of assessments). The patient will remain in the study for the purposes of follow up and data analysis.

4.4.1 Data collection and follow up for withdrawn subjects

CRFs should be sent to the Centre for Experimental Cancer Medicine, Barts Cancer Institute within one month of patient completing each cycle.

Subjects who are withdrawn are still evaluable for toxicity and efficacy if they have received at least one cycle of treatment and any data collected whilst receiving treatment will be used in the final analysis. Patients who are withdrawn from the study will be followed up for 2 years after treatment. Similarly, this follow up data will be used in the

final analysis. Any patients who decide to withdraw their consent will have no further data collected unless they have given express permission to do so.

5.0 Study procedures and schedule of assessments

5.1 Informed consent procedures

It is the responsibility of the Investigator, or a suitably trained doctor delegated by the Investigator to obtain written informed consent from each subject prior to participation in this study, following adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. Ample time must be given for consideration by the patient before consenting to take part. The Investigator or co-investigator (designee) must also fully explain to the subjects that they are not obliged to enter the study but, that they may choose to opt for standard treatment. Alternatively, if they *do* wish to participate in the study they may withdraw at any time without giving a reason.

If new safety information becomes available and significantly changes the risk/benefit of the study, the patient information sheet and consent form will be reviewed and updated immediately. Patients who have been recruited into the study, including those already being treated, should be informed of the new information and given a copy of the revised information sheet and if necessary re-consent to continue in the study.

5.2 Registration/study procedures

Following screening evaluation and patient consent, the study registration form should be completed and faxed to the Car-PET Clinical Trial Coordinator. The patients initials, date of birth and date of consent will be recorded.

CARPET TRIALS OFFICE

REGISTRATION AND ENQUIRIES: 0207 882 8761
FAX: 0207 882 8409
EMAIL: bci-carpet@qmul.ac.uk
(Office Hours 9-5pm)

Each patient will be assigned a unique trial number after registration that should be used on **ALL** patient related documentation. Once the form is received and the unique trial number has been generated, confirmation of this will be sent by fax.

5.3 Treatment procedures

5.3.1 Pre-treatment investigations

The following investigations must be completed before the patient can begin treatment:

- Physical examination.
- Contrast-enhanced staging CT scan of chest, abdomen & pelvis within 28 days of study entry. NB: If clinician suspects patient to be eligible for trial they may only do the PET-CT scan as the CT element is sufficient for diagnosis. The PET-CT scan will have to be done regardless of have a contrast-enhanced CT scan performed before study entry.
- Full body PET-CT within 28 days of study entry.
- Glomerular filtration rate by EDTA clearance (a measured creatinine clearance using Cockcroft and Gault would be allowed if unable to perform EDTA clearance).
- Alpha-fetoprotein, Human chorionic gonadotropin and Lactate dehydrogenase*.
- Hormone levels of Testosterone, Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH).
- Full blood count.
- Urea electrolyte.
- Liver function tests.

*Please note that approximately **20mls (max)** of blood will need to be taken at this time for future research. Blood will be collected in three 7.5ml EDTA tubes containing anticoagulant. The patient will need to sign a separate consent form agreeing for their samples to be used for future research. Once consent has been obtained, the sample should be sent directly to The Orchid Tissue Bank lab using the post boxes to:*

Orchid Tissue Bank Manager
Orchid Tissue Bank
Centre for Experimental Cancer Medicine
Barts Cancer Institute - a CR-UK Centre of Excellence
Queen Mary University of London
John Vane Science Centre
Charterhouse Square
LONDON EC1M 6BQ

5.3.2 Investigations during and after treatment

- Physical examination on Day 1 (± 3 days) of cycle 2-4*.
- Full Blood Count, Urea electrolyte and Liver function tests on Day 1 (± 3 days) of cycle 2-4*.

- Alpha-fetoprotein (AFP), Human chorionic gonadotropin (hCG) and Lactate dehydrogenase (LDH) on Day 1 during cycle 1-4, Day 13-17 of cycle 1-4 and Day 17-21 of cycle 1.
- Full Blood Count repeated on Day 13-17 of cycle 1-4*.
- Hormone levels of Testosterone, Follicle-stimulating hormone (FSH) and Luteinizing hormone (LH) at end of treatment and annually thereafter during the follow up period of the trial.
- PET-CT scan on Day 17- 21 after the first cycle.
- PET-CT within 28 days of completing treatment (may be contrast enhanced CT if negative PET – CT scan on Day 17-21 of the first cycle).
    - If complete metabolic response is demonstrated contrast enhanced CT at 1 year and 2 years post therapy.
    - If residual masses are present, a contrast enhanced CT should be performed at 2 months after the end of the treatment PET-CT scan and if the masses are greater than 3cm in diameter, surgery to remove them is recommended in accordance with current practices.
- If patients require surgery following their treatment, a contrast enhanced CT scan of the area must be performed **2-3 months after the surgery** has taken place.
- If CR by chemo +/- surgery a final contrast enhanced CT at 2 years.
- Thereafter CT scan only if clinically indicated.

**** Patients who have a complete response to AUC-10 following cycle 1 will receive 2 further cycles. Those who do not achieve a complete response will have a further 3 cycles.***

5.3.3 Central review of PET-CT scans

There are currently no well validated metabolic response criteria for PET-CT in seminoma. Hence, we will use the criteria for assessment of response developed for the evaluation of lymphoma [6].

A Complete Response will be defined as **complete resolution** of all previously seen sites of nodal and metastatic disease. If residual sites of metastatic disease persist then the PET-CT will be used to evaluate metabolic activity.

Metabolic Complete Remission will be defined as the level of FDG uptake within the lesion that is no greater than normal mediastinal uptake these patients will receive 3 cycles in total. Lesions with uptake greater than the mediastinum will be viewed as non-complete

responders. The PET data will be viewed on standardised SUV (standardised uptake value) setting of between 0 and 5.0 and a visual comparison will be made to assess the degree of uptake within abnormal tissue [7]. These criteria will have a high probability of distinguishing true complete responders from partial responders. Contrast enhanced CTs will be evaluated via the standard response criteria (Appendix 4).

All PET-CT scans will be centrally reviewed at University College London Hospital. The results from the report will be used to determine the number of further treatment cycle's patients will require, following cycle 1. Copies of locally reported scans (where relevant) should be sent to the central reviewer via the secure NHS Image Exchange Portal system (IEP) for review by the central reviewer (please refer to appendix 7). Sending images via IEP will not apply to sites where patients are scanned at UCLH, however, sites must ensure that the proforma is completed and sent to remind the central reviewer. In addition to sending images via the secure IEP system, sites must email a copy of the Proforma Request form (see Appendix 5 and 6) that is appropriate to each site) to the central reviewer to indicate that an image has been sent via IEP.

The central reviewer will review the image and return the generated report within the appropriate timelines as stated in the table below (see Appendix 7);

All scans for central review to be sent to;

Dr Rizwan Syed
Consultant in Nuclear Medicine
Institute of Nuclear Medicine, T5
University College Hospital
235 Euston Road,
LONDON NW1 2BU
Fax: 0203 447 0591
Proforma Request form to be emailed to: rizwansyed@nhs.net and shane.blanchflower@nhs.net

The central review reporting of the Baseline and Day 17-21 PET-CTs will take place **within 3 weeks** of the site either sending image or the patient having their scan done at UCLH. **The PET-CT scans must be received within this timeframe in order for the patient's response to treatment to be assessed and the decision on whether the patient receives 3 or 4 cycles can be made.**

Low dose attenuation correction CT will be performed at the time of the PET acquisition. Follow up conventional diagnostic CT scans from this point on should be received within two months of being performed.

Scan	Report to be received within
Baseline PET-CT & Baseline contrast enhanced CT	Within 3 wks of sending image/the PET scan (if done at UCLH)
Day 17-21	Within 3 wks of sending image/the PET scan (if done at UCLH)
Contrast enhanced CT performed post cycle 2 (if applicable)	Within 3 wks of sending image/the PET scan (if done at UCLH)
End of Treatment PET-CT or contrast enhanced CT	2 months
All other Contrast enhanced CTs as per follow up	2 months

If reports have not been received by the site within the timelines as detailed above, please follow the escalation process as detailed in Appendix 7.

5.4 Study Flowchart

	PRE-TREATMENT VISIT	CYCLE 1 * DAY 17-21	CYCLE 1-4 DAY 13-17[8]	CYCLE 2-4[4] DAY 1[9]	END OF TREATMENT	FOLLOW UP[6]
Informed Consent	✓					
Medical History	✓					
ECOG Performance Status	✓			✓	✓	✓
Physical Exam & Vital Signs	✓			✓	✓	✓
PET-CT Scan	✓[2]	✓[3]			✓[5]	
Contrast Enhanced CT – Chest, Abdo, Pelvis	✓[2]					✓[7]
Blood Sample – Future Research	✓[10]					
GFR[1]	✓					
Full Blood Count	✓	✓	✓	✓	✓	✓
U&E's And LFT's	✓		✓	✓	✓	✓
AFP, hCG & LDH	✓		✓	✓	✓	✓
Testosterone, FSH and LH	✓				✓	✓[11]
AE Reporting		**To be reported from the start of the first treatment and within 30 days after the administration of the last dose of study drug**				
Concomitant Medication		**To be reported from the start of the first treatment and within 30 days after the administration of the last dose of study drug**				

see appendix 3 for definitions

1. *Glomerular filtration rate by EDTA clearance (a measured creatinine clearance using Cockcroft and Gault would be allowed if unable to perform EDTA clearance in adequate timeframe).*
2. *Within 28 days of beginning study treatment. NB: If clinical decision was made a PET-CT scan can replace a CT scan at baseline (refer to section 5.3.1).*
3. *To be performed up to 1 week after day 21 of cycle.*
4. *Patients who have a complete response to AUC-10 following cycle 1 will receive 2 further cycles. Those who do not achieve a complete response will have a further 3 cycles*.*
5. *To be performed with 28 days of completing treatment. May be contrast enhanced CT if negative PET-CT scan on Day 17-21 of cycle 1.*
6. *Follow up to be carried out 2 monthly for 1st year and 4 monthly for 2nd year.*

[7] *CT scan to be performed in all patients who have a complete response to treatment (+/- surgery) at one and two year post therapy. For those patients requiring surgery following their treatment, a repeat CT scan must be carried out 2 months post end of treatment PET-CT scan and again at 2-3 months after the surgery has taken place (PET is not required for follow-up scans)*.*[8.] *Full blood count repeated to determine possible dose reductions also performed on **Day 13-17.***

[9.] *± 3 day allowable window*

[10.] *Patients who have given consent for the storage of their samples (separate consent from the trial – will be indicated on registration form).*

[11.] *The hormone tests should be performed at baseline, end of treatment and annually at follow ups.*

5.5 Follow up

- Patients will be followed up as part of the study for 2 years following completion of treatment.
- Outpatient follow up visits will be carried out ***2 monthly*** in the first year and ***4 monthly*** in the second year. Patients will then be followed at the PI's discretion and/or standard care.
- Details of disease progression must be documented on the CRF.
- Any further therapy for metastatic seminoma must be documented on the CRF.

6.0 Investigational Medicinal Product(s)/treatment details

6.1 Description of IMP

Carboplatin is a platinum-containing anticancer agent much like cisplatin but is more toxic to the myeloid elements of bone marrow. However when used as a chemotherapy agent in solid tumours it produces less nausea, neurotoxicity, ototoxicity, and nephrotoxicity.

6.2 Product sourcing manufacture and supply

Carboplatin is a licensed product within the EU. Local pharmacies will source carboplatin from NHS commercial stock.

6.3 Pre-Medication

In the administration of prophylactic anti-emetics in conjunction with highly emetogenic chemotherapy (e.g. dexamethasone 16mg and a 5-HT_3 antagonist pre carboplatin, dexamethasone 8mg/day for days 2 and 3 and metoclopramide 20mg 3x/day for days 1 to 5) centres should follow local practice.

6.4 Prescription of IMP

Prescriptions for carboplatin for this study should be in accordance with local policies and should be identifiable as being part of the clinical trial. The local PI or doctor on the delegation log will only be able to prescribe carboplatin.

6.5 Preparation and administration of IMP

Carboplatin will be prepared by chemotherapy pharmacy departments and the dose calculated using the Calvert formula, as below:

Dose (mg) = (GFR + 25) x10

Unless dictated by haematological toxicity, the Carboplatin dose should not be recalculated for each cycle. However, if the serum Creatinine has risen by > 20% above baseline, the Carboplatin dose must be recalculated using the Calvert formula with GFR determined by EDTA clearance. At the discretion of the PI an estimated creatinine clearance can be calculated using e.g. Cockcroft and Gault (or as per local policy) if the site is unable to obtain EDTA clearance.

This dose should be administered in 500ml glucose 5% over 60 minutes, or as per institutional local practice.
Dose banding is not permitted; however, rounding of carboplatin dose to nearest 10 mg is acceptable.

6.6 Prior and concomitant therapies

Concurrent therapy with nephrotoxic or ototoxic drugs such as aminoglycosides, vancomycin, capreomycin and diuretics, may increase or exacerbate toxicity due to carboplatin induced changes in renal clearance.

Combination therapy with other myelosuppressive agents may require dose changes or rescheduling of doses in order to minimise the additive myelosuppressive effects.

6.6.1 Recording concomitant medications

Concomitant medications should be reported from the start of the first treatment and within 30 days after the administration of the last dose of study drug. As the IMP (Carboplatin) is a licensed product, there is no requirement to record concomitant medications administered as supportive care in the CRFs i.e. all anti-emetics, medications for indigestion, acid suppression, routine antibiotics for infection/ neutropenia and simple analgesics. However, concomitant medications are expected to be fully listed on all Serious Adverse Event forms should a safety event occur and reported to the sponsor within the appropriate timelines.

The concomitant medications which are not required to be reported on CRFs are listed on the next page.

Fluids
0.9% NaCl
5% Glucose
Compound Sodium Lactate (Hartman's Solution)

With or without additives e.g. KCl, $MgSO_4$, Calcium

Anti-emetics
Domperidone
Metoclopramide
Cyclizine
Levomepromazine
Olanzapine
Haloperidol
Lorazepam

Granisetron
Ondansetron

Aprepitant

Dexamethasone
Prednisolone

Analgesics
Aspirin
Paracetamol
Codeine
Dihydrocodeine
Tramadol

Morphine
Diamorphine
Oxycodone
Fentanyl

Naproxen
Ibuprofen
Diclofenac

Antibiotics
Co-amoxiclav
Piperacillin/ Tazobactam
Amoxicillin
Benzylpenicillin
Flucloxacillin

Cefuroxime
Ceftriaxone
Ceftazidime

Meropenem
Imipenem

Gentamicin
Amikacin
Vancomycin
Teicoplanin

Co-trimoxazole
Doxycycline
Tigecycline

Trimethoprim

Ciprofloxicin
Levofloxacin

Clarithromycin

Itraconazole
Fluconazole
Caspofungin
Amphotericin
Micafungin
Terbinafine

Aciclovir

Acid Suppression Ranitidine Omeprazole Pantoprazole Lansoprazole Gaviscon Caphosol **Anti-asthmatics** Salbutamol Terbutaline Beclometasone Budesonide Formoterol	**Diuretics** Bumetanide Furosemide Spironolactone Bendroflumethiazide **Statins** Simvastatin Pravastatin Atorvastatin **Anti-hypertensives** Atenolol Bisoprolol Metoprolol Ramipril Perindopril Lisinopril Enalapril Losartan Candasaratan Irbesartan Valsartan Lercanidipine Amlodipine Lacidipine Nifedioine Indapamide

List of concomitant medications not required to be reported

6.7 Dose modification/reduction/delay

If the patient has a nadir platelet count of <20 $x10^9$ /L then the dose of carboplatin should be reduced by 20%.

Please refer to figure 1 for guidance regarding dose delays.

6.8 Toxicity profiles

Please refer to the current SmPC toxicity and side effects information for carboplatin.

6.9 Labelling/Packaging

Labelling of the IMP will be undertaken by pharmacy staff, and will contain information to meet the applicable regulatory requirements of Annex 13.

6.10 Blinding of IMP

N/A

6.11 Receipt of IMP supplies/Storage

Carboplatin supplies will be sourced from NHS commercial stock therefore sites will be responsible for the ordering, receipt and storage of carboplatin. Storage will be in accordance with the current SmPC for carboplatin.

7.0 Pharmacovigilance

7.1 General definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject who has been administered a medicinal product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal (investigational or marketed) product, whether or not considered related to the medicinal product.

7.1.2 Adverse Reaction (AR)

An adverse reaction is any untoward or unintended response in a subject to an Investigational Medicinal Product (IMP), which is related to any dose administered to that subject. All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

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

A serious adverse event or reaction is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (defined as an event in which the patient or subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient/subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisation.

There is a distinction between the intensity (mild, moderate, or severe) and the seriousness of an adverse event. Thus, a severe reaction is not necessarily a SAE. For example, a headache may be severe in intensity, but would not be serious unless it met one of the previously listed criteria for SAEs.

7.1.4 Suspected Unexpected Serious Adverse Events - SUSAR's

A SUSAR is any suspected unexpected adverse reaction related (or possibly related) to an IMP that is both unexpected and serious. In this case the event is not outlined in the Reference Safety Information (RSI) contained within the Summary of Product Characteristics (SmPC) for Carboplatin (section 4.8 of SmPC)

7.2 Investigators Assessment

It is the Chief/Principal Investigator's responsibility to assess and report all adverse events or reactions occurring from the time of patient registration until events that occur 30 days following the last dose of study medication or are thought to be related to study drug.

Seriousness

- Results in death
- Is life-threatening (defined as an event in which the patient or subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event (defined as a medical event[s] that may not be immediately life-threatening or result in death or hospitalisation but may jeopardize the patient/subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalisation.

Causality

The relationship or association of the study medication in causing or contributing to the AE will be characterized as either none, unlikely, possible or probable.

Expectedness

- Expected
- Unexpected

Severity

NCI CTCAE v4.0 criteria should be applied for assessing/reporting event severity/intensity: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

7.3 Notification and reporting adverse events or reactions

Patients will be monitored and questioned at every visit whilst on study treatment regarding the occurrence and nature of any adverse experiences. Any AE, including either observed or volunteered problems, complaints, or symptoms (whether or not associated with study medication) that begin at any time between the start of the first treatment and within 30 days after the administration of the last dose of study drug are to be recorded in the relevant section of the relevant CRF and sent to the CarPET Trials office within one month of the form being due.

7.4 Notification and reporting of serious adverse events/SUSAR

All AEs that are serious, unexpected, and definitely, probably, or possibly related to the study drug that occur during treatment or within 28 days of stopping treatment must be reported on the 'Serious Adverse Event Form' to the CarPET Trials Coordinator within 24 hours of the Investigator/Sub-Investigator becoming aware of the event.

The SAE form must be signed off by the Principal Investigator (or medically qualified delegate) at the participating site and faxed or emailed to the Car-PET Coordinator on 0207 882 8409 or bci-carpet@qmul.ac.uk together with relevant accompanying anonymised copies of treatment investigations.

It will then be the responsibility of the Chief Investigator to inform the sponsor within 24 hours of becoming aware of the SAE. The relationship or association of the study medication in causing or contributing to the AE will be characterized as definitely, probably, possibly, or not related, as defined in Section 7.1.

7.5 Notification and reporting of serious adverse events/SUSAR

In accordance to The Medicines for Human Use (Clinical Trials) Regulation 2004 and its amendments, the prompt reporting of SUSAR's to relevant authorities lies with the sponsor. However, any SUSAR's which occur at any participating site should be reported to the Chief Investigator within 24 hours of the participating site learning of the event. It is the CI's responsibility to then report these to the sponsor. The sponsor will then submit these reports to the Competent Authority of the member state within **7 days** of receipt for fatal or life threatening SUSARs or within **15 days** for all other SUSARs.

Follow-up information by the sponsor will be sought within **8 days.** Each report should contain concise and clear information regarding the SUSAR.

7.6 Expected SAEs/SARs

- Febrile neutropenia (requiring hospital admission)
- Neutropenia Grade 0-4 (asymptomatic)
- Mucositis Grade 0-4 (requiring hospital admission)
- Diarrhoea Grade 0-4 (requiring hospital admission)
- Thrombocytopenia Grade 0-4
- Renal Impairment (not requiring dialysis)
- Nausea and vomiting Grade 0-4 (requiring hospital admission)
- Neuropathy Grade 0-3
- Abnormal LFTs/Jaundice (resolving within 14 days of treatment)

As the IMP used in this study is licensed in the UK the ***expected*** SAE/SAR's are **outlined** in the **current SmPC under undesirable effects** and the expected SAE/SARs listed above should be recorded in the medical notes as well as the relevant CRF and sent to the CarPET Trials Office within one month of the form being due. **No SAE** forms regarding these expected SAE/SARs should be completed and sent to the sponsor.

7.7 Pregnancy

Patients must use adequate contraception whilst on the study and for at least 6 months after they stop receiving treatment as the adverse effects on reproduction are unknown.
If a patient's partner becomes pregnant whilst enrolled in this CTIMP in which the foetus has been exposed to an investigational medicinal product, immediate reporting to the sponsor is required (within one working day of the PI/CI becoming aware of the event)

using a JRMO pregnancy template form. The CI/PI has the responsibility to ensure that the pregnancy form is completed and sent to the sponsor within the agreed timelines. Please state whether the patient can continue on the study or whether the patient has to be prematurely withdrawn from the study here.

The PI/CI also must follow up the pregnancy until delivery as well as monitoring the development of the newborn until birth. Any events that occur during this time that could be considered to be a SAE must be reported to the sponsor in line with section 7.6 utilising the sponsor SAE reporting form. Pregnant partners of participants will be asked to give consent for the release of this information to the study team.

7.8 Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety, this is defined in Regulation 30 of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928. The measures should be taken immediately. In this instance, the approval of the Licensing Authority Approval prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor, Main Research Ethics Committee (via telephone) and the MHRA (via telephone for discussion with the medical assessor at the clinical trials unit) of this event immediately.

The CI has an obligation to inform both the MHRA and Main Ethics Committee in writing within 3 days, in the form of a substantial amendment. The sponsor (JRMO) must be sent a copy of the correspondence with regards to this matter.

8 Annual Reports

8.1 Development Safety update reports (DSURs) and Annual Progress Reports (APRs)

The CI will submit APRs to the main REC and the sponsor on the anniversary date of obtaining a Favourable Opinion from the main REC using the National Research Ethics Service (NRES) template.

A DSUR will be submitted by the CI to the Sponsor, the relevant Ethics Committee and MHRA on the anniversary date of the "Notice of Acceptance' letter from the MHRA using the DSUR template provided by the sponsor. Subsequent DSUR reports will be due within 60 days of the anniversary date. The CI will carry out a risk benefit analysis of the IMPs encompassing all events having arisen on the trial.

9 Data handling and record keeping

9.1 Confidentiality

All information which is generated in the study will be kept strictly confidential. The researchers conducting the study will abide by the Data Protection Act 1998, and the rights the patient has under this act.

Once the patient consents to participate in the study their GP will be informed. Parts of the patients medical records and the data collected for the study will be reviewed by authorised personnel from Queen Mary University of London and also Bart's & The London NHS Trust who are the sponsors of this study. It may also be reviewed by representatives of regulatory authorities and other authorised personnel from the patient's trust, to check that the study is being carried out correctly. This is clearly stated on the consent form.

All of the above bodies have a duty of confidentiality to the patient as a research participant and nothing that could reveal their identity will be disclosed outside the research site. All data will be stored in a locked and dedicated data room only accessed by authorised personnel.

9.2 Essential Study documents

All study related documents should be filed in the investigator's study site file. It should contain the protocol/amendments, Case Report and Query forms, Regulatory approvals with correspondence, sample patient information sheet and informed consent form, drug

records, staff curriculum vitae and delegation logs and other appropriate documents/correspondence. The coordinating centre will inform the PI of any regulatory updates and forward on any relevant documentation. It is the participating sites responsibility to maintain this file and keep all staff records, including delegation logs up to date.

9.3 Case Report Forms

The Case Report Form (CRF) must be completed legibly in black ink. Subjects are to be identified by initials, birth date, and subject number, if applicable. All requested information must be entered on the CRF in the spaces provided. If an item is not applicable it should be documented as such; do not leave a black space. The completed CRF must be promptly reviewed, signed and dated by the Investigator or Sub-Investigator where applicable.

Any change or correction to a CRF should be made by striking through the incorrect entry with a single line (not obscuring the original entry) and then entering the correct information adjacent to the incorrect entry. The correction must be initialled and dated by the person making the corrections.

9.4 Record retention and archiving

At the end of the trial, all essential documents as defined by ICH GCP (including CRFs, source documents, consent forms, laboratory results) will be securely archived by the coordinating and participating centres for a minimum of 20 years. During this time, documents must remain available for inspection by the Sponsor, auditors and members from regulatory bodies and the CI must be informed of the location of the archived material and the retrieval process. Following written authorisation from the Sponsor, arrangements for confidential destruction will then be made.

9.5 Compliance

This study will be conducted in accordance with the principles of ICH Good Clinical Practice (GCP) as laid out in The Medicines for Human Use (Clinical Trials) Regulation 2004 and its amendments.

In addition, internal auditors and Competent Authority personnel will be allowed access to CRFs, source documents and other study files to evaluate the study. Audit reports will be kept confidential.

10 Governance Issues

10.1 Risk Assessment

The sponsor together with the CI have assessed this study according to their risk assessment SOP 28.

10.2 Summary Monitoring Plan

On-Site monitoring will be performed on this trial. The trial coordinator/monitor should perform the first monitoring visit within 1 month of the first patient being enrolled at a site. Monitoring visits will be performed a minimum of twice a year during the recruitment and treatment period.

Sites that do not recruit any patients into a study will undergo on-site monitoring once a year.

The frequency of visits may change (increase or decrease) depending on the issues raised during the trial (death, SAE, audit or inspections, site not recruiting). Any decrease in monitoring at a site will be approved by a member of the CECM Management Team and the Sponsor.

Source Data Verification

100 % SDV will be performed on informed consent.
100 % SDV will be performed on inclusion / exclusion criteria.

The following data points will undergo SDV for all patients

- Adverse events and toxicities levels;
- Metabolic response rate by FDG PET-CT scan and number of cycles required;
- Follow Up survival dates and progression disease dates for Progression Free Survival and Overall Survival.

100% SDV on all data points will be performed for a minimum of one patient per site or approximately 5% of all patients, whichever is greater.

Reasons for not performing on-site monitoring must be agreed with the CECM Management Team and the Sponsor and be fully documented in the TMF.

Original CRFs will be sent by post from site to the trial coordinator/monitor in a timely manner. Upon receipt of CRFs the trial coordinator/monitor will review for any obvious errors and data queries will be raised.

The following central facilities are utilised in this study:-

- Orchid tissue bank: Queen Mary University of London, Molecular Oncology Unit, John Vane Science Centre, Charterhouse Square, London, EC1M 6BQ.
- Central review of scans: University College London Hospital.

The following facility will undergo yearly monitoring visits for the duration of their participation in the study during the recruitment and treatment phase – once the follow-up phase is entered, its involvement with the trial will end. As such, monitoring will cease and the facility will be subject to a close-out visit:

- Orchid tissue bank.

The following facility will undergo 6 monthly monitoring visits for the duration of their participation in the study during the recruitment and treatment phase – once the follow-up phase is entered, its involvement with the trial will end. As such, monitoring will cease and the facility will be subject to a close-out visit:

- University College London Hospital - Institute of Nuclear Medicine

A summary of all monitoring activity for this study will be provided to the Sponsor at least every 6 months.

10.3 Audit and Inspection

This study may be audited by representatives from the coordinating centre and sponsor. The investigator and institution will be informed of the audit outcome. Investigators are obliged to cooperate in any audit allowing the auditor direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor to discuss any findings or issues. Audit may occur at any time during or after completion of the study.

In addition, inspections may also be carried out by the Competent Authority at any time and the investigator should notify the sponsor **immediately** if there are any such plans for an inspection.

10.4 Serious breaches in GCP or study protocol

All investigators participating in the study will promptly notify the Chief Investigator or Sponsor of a serious breach as soon as they become aware. This is defined in Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928 and contains the requirements for notifying serious breaches of GCP or study protocol. The CI is then responsible for notifying the Sponsor within 1 working day of becoming aware of a serious breach.

The sponsor (JRMO) is responsible for notifying the licensing authority in writing of any serious breach of:
(a) The conditions and principles of GCP in connection with that trial; or
(b) The protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.

A "serious breach" is a breach which is likely to affect to a significant degree:-
The safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial.

Participating centres should contact the coordinating centre or CI for further information.

10.5 Quality Assurance

This study will be conducted in accordance with the Centre of Experimental Cancer Medicine standard operating procedures and those of the sponsor.

10.6 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. An independent Ethics committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety and wellbeing of patients. The study will only be conducted at sites where appropriate approval has been obtained.

The study coordinating team will inform the IEC of any changes to the conduct of the study and seek approval for these changes and any amended patient materials. The Chief investigator will maintain an accurate and complete record of all written correspondence to and from the IEC and will agree to share all such documents and reports with the sponsor.

The informed consent and any other documentation provided to subjects will be revised if important new information becomes available that is relevant to the subject's consent. Amended documents will be approved by the IEC before distribution to patients.

10.7 Trial Committees

10.7.1 Trial Steering Committee (TSC)

A Trial Steering Committee will be convened and will provide an internal review of the conduct of this clinical trial to ensure continuing patient safety as well as the validity and scientific merit of the trial.

Details of the Trial Steering Committee will be described in the TSC remit and will be updated if any change occurs during the course of the study. The TSC remit will be provided to all members. Details of the frequency of the meetings and the information held will be described in the TSC remit.

10.7.2 Trial Management Group (TMG)

Details of the trial management committee will be described in the TMG remit and will be updated if any change occurs during the course of the study. The TMG remit will be provided to all members.

The Trial Management Group will consist of, as a minimum, the Chief Investigator, Statistician, and Trial Co-ordination staff. They will be responsible for the day-to-day running and management of the trial. The frequency of the meetings and the information held will be described in the TMG remit.

11 Statistics

11.1 Endpoints

11.1.1 Primary Endpoints

- 2-year Progression free survival

11.1.2 Secondary Endpoints

- Metabolic response
- Overall survival
- Toxicity level (CTCAE version 4.03)

11.1.3 Definition of end of study

Patients will be recruited for 48 months. Patients will be followed up as part of the study for 2 years following completion of treatment. The end of the study will be 3 months after the date when the last patient has completed his final follow up visit.

11.2 Statistical considerations

11.2.1 Sample Size

The primary objective is to gain a preliminary indication on whether carboplatin AUC-10 is worthwhile considering in a phase III study, using the progression free survival (PFS) rate as a criterion. A'Hern's single-stage procedure is used to estimate the number of patients required [8].

The primary outcome is the percentage of patients progression-free at 2-years. Therefore, all patients must have at least 2-years follow-up (unless they have died or their disease has progressed). An MRC study [1] showed that PFS rate at 3 years in standard chemotherapy, BEP, is 81%. It is also known that PFS rate at 2-years and 3-years are the same [2]. Carboplatin AUC-10 should not therefore have a 2-year PFS rate of 75% or less, and it would only be worth considering in a phase III study if the true rate were 90% or more. This information is used in A'Hern's single stage design to yield a sample size of 45 patients, with 80% power and one-sided test of significance at the 5% level. Here the statistical assumption of this design is that there is 80% chance of concluding that Carboplatin AUC-10 is effective if the true response rate is 90% or more, but only a 5%

chance of concluding it is effective if the response rate is 75% or less. To allow for a 10% drop-out rate the intention is to recruit 50 patients.

11.2.2 Planned recruitment rate

It is planned to have the study performed at approximately 4 centres to recruit around 10-12 patients per year. Assuming 5 patients may withdraw from the study for reasons other than disease progression/intolerable side effects, up to 50 patients may be entered in total. In the event that the first centres initiated are not able to recruit sufficient patients, further centres may be recruited. Total duration of study recruitment is approximately 4 years.

11.3 Statistical Analysis

All analyses in this study are descriptive and exploratory by nature. Results will be summarised with descriptive statistics (i.e. sample size, mean, and standard deviation, minimum, maximum and median for continuous variables and with tabulations/frequency tables/case listings for categorical variables). Incidence of adverse events will be tabulated. Laboratory data will also be analysed and summarised.

Two analysis sets will be defined:

- The Full Analysis Set (FAS) will consist of all patients who completed at least one cycle of Carboplatin AUC-10 and for whom relevant data is available at baseline and follow up.
- The Safety analysis set (SS) will consist of all patients who received at least one dose of Carboplatin AUC-10.

The FAS will be used for all activity summaries; the SS will be used for all safety summaries. Further descriptions of the statistical analyses will be given in the Study Statistical Analysis Plan, to be finalised prior to database lock.

11.4 Frequency of analysis

The data will be analysed at the end of the study. There will be no interim analysis.

11.5 Primary endpoint analysis

The primary efficacy endpoint is Progression Free Survival (PFS) rate at 2 years. Patients who do not complete 2 years follow-up for reasons other than death will be censored at the last date of follow-up. The PFS rate will be determined for the Carboplatin AUC-10, along with a 95% confidence interval, and the Kaplan-Meier curves will be plotted. The study result will be considered positive if the PFS rate for patients on Carboplatin AUC-10 is consistent with a true difference of 15% or more from standard chemo i.e. if there are at least 39 PFS patients out of the first 45 patients at 2 years.

11.6 Secondary endpoint analysis

Subgroup analyses of the PFS rate will be performed in terms of patients with complete or partial response at 2 years.

The analysis of safety will include all patients who received at least one cycle of treatment. Safety and tolerability of Carboplatin AUC-10 will be assessed in terms of changes in laboratory parameters, vital signs, the incidence and severity of Adverse Events, and of toxicities according to the CTCAE classification (version 4.03).

The proportion of patients at each toxicity grade (0 to 4) of any type (including vomiting, nausea and diarrhoea) will be summarised. Safety analysis will be performed based on safety data set.

Metabolic response rate will be assessed as described in section 5.3.3.

11.7 Interim analysis

No interim analyses are planned as the Carboplatin AUC-10 is considered to be relatively safer than the standard chemotherapy.

12 Sponsorship and Indemnity

Barts Health NHS Trust is the sponsor and will be providing indemnity for this study.

13 Publication policy

This is an investigator-led study sponsored by the CI's substantive employer, Barts Health NHS Trust. The data collected will not be used to licence/register any pharmaceuticals.

Authorship of the final manuscript(s), interim publications, or abstracts will be decided according to active participation in the statistical design, Trial Steering Committee, accrual of eligible patients and statistical analysis.

Contributing centres (and participating investigators) will be acknowledged in the final manuscript, and the correct designation for this site is 'Centre for Experimental Cancer Medicine, Barts Cancer Institute, Queen Mary University of London'. Representative for the sponsor will be added, as appropriate, as co-authors. No participant may present data from his/her centre separately from the rest of the study results unless approved by the Trial Steering Committee and the sponsor.

14 References

1. Horwich A, Oliver RT, Wilkinson PM, et al.: A medical research council randomized trial of single agent carboplatin versus etoposide and cisplatin for advanced metastatic seminoma. MRC Testicular Tumour Working Party. British Journal of Cancer 2000; 83(12): 1623-9.

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15 Appendices

APPENDIX 1 – ECOG PERFORMANCE STATUS

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

* As published in American Journal of Clinical Oncology [9]

*APPENDIX 2 – PET-CT RESPONSE DEFINITIONS FOR CLINICAL TRIALS**

RESPONSE	*DEFINITION*	*NODAL MASSES*
CR	***Disappearance of all evidence of disease***	*a. FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative* *b. Variably FDG-avid or PET negative; regression to normal size on CT*
PR	***Regression of measurable disease and no new sites***	*>50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes* *a. FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site* *b. Variably FDG-avid or PET negative; regression on CT*
SD	***Failure to attain CR/PR or PD***	*a. FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET* *b. Variably FDG-avid or PET negative; no change in size of previous lesions on CT*
RELAPSED DISEASE OR PD	***Any new lesion or increase by >50% of previously involved sites from nadir***	*Appearance of a new lesion(s) >1.5 cm in any axis, >50% increase in SPD of more than one node, or >50% increase in longest diameter of a previously indentified node >1cm in short axis* *Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy*
Abbreviations: CR, complete remission; FDG, [^{18}F] fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of produce of the diameters; SD, stable disease; PD, progressive disease.		

*As published in Journal of Clinical Oncology [6]

APPENDIX 3 – DEFINITION OF RESPONSE CRITERIA

Conventional CT response to chemotherapy will be defined as follows:

COMPLETE RESPONSE (CR)

Normal tumour markers, no clinical or radiological evidence of disease or surgery indicating no viable cancer cells in resected specimens (if surgery is done at this stage).

PARTIAL RESPONSE (PR) (marker positive)

More than 90% reduction in tumour markers and/or >50% reduction in tumour masses determined by radiology for at least 28 days following cessation of chemotherapy without normalisation of tumour markers.

PARTIAL RESPONSE (PR) (marker negative)

Normalisation of markers and residual mass (marker negative PR) for at least 28 days

STABLE DISEASE

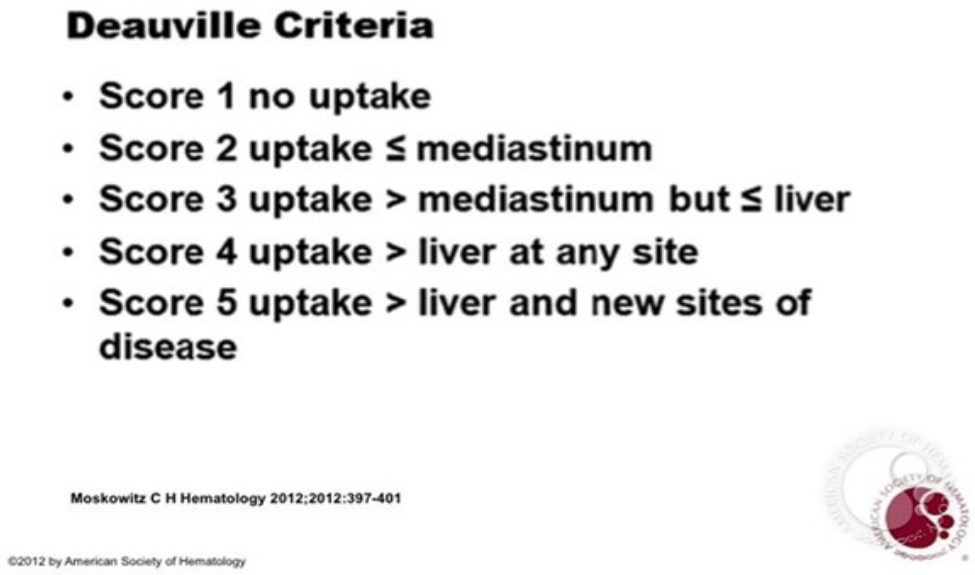
Less than 50% reduction in tumour markers for at least 1 month following chemotherapy.

PROGRESSIVE DISEASE

Less than 50% reduction in tumour markers or progression within 28 days of stopping chemotherapy

APPENDIX 4 – DEAUVILLE CRITERIA

Deauville criteria:-
Visual interpretation of the PET-CT scan uses a 5-point scale.
Baseline and PET-CT scans are scored according to uptake in sites initially involved by metastatic seminoma: (1) no uptake, (2) uptake = mediastinum blood pool, (3) uptake = liver, (4) moderately increased uptake > liver, or (5) markedly increased uptake > liver and/or new lesions. A score of 1-3 is regarded as negative and 4 or 5 as positive.



*As published in ASH Education [10]

APPENDIX 5 – UCLH PET SCAN REQUEST FORM FOR BARTS

UCL HOSPITALS **DISTRICT NUCLEAR MEDICINE SERVICE** **REQUEST FORM**		**Hospital No.:** **Surname:** **First Names:** **Date of Birth:**	**Sex:** *Male*
SITE (Please add): UCH ☐ Other (specify) ☐	**Address (If O.P)** **Patient Tel. No.**	**WARD/DEPT:** *Outpatients*	**?P.P.** **Yes/No**
EXAMINATION REQUESTED:		**Consultant:** *JS*	
PROVISIONAL DIAGNOSIS: **CLINICAL HISTORY:** ***Patient with Metastatic seminoma*** ***PET CT-Scan Assessment*** ***For attention of Dr Rizwan Syed:*** *Rizwan.Syed@uclh.nhs.uk* *Please fax the request form to* ***0203 447 0591***			Walking Chair Trolley **L.M.P** **Pregnancy check**
Visit time point:	**1. Before commencing treatment** ☐ **2. Assess response during treatment** ☐ **3. Staging post treatment** ☐		**APPOINTMENT:** **Date:** **Time:**
Requested by:		**Telephone no:** **Fax no:**	
Date:	**SIGNED:** (Referring consultant)	**BLEEP NO.:**	

APPENDIX 6 – UCLH PET SCAN REQUEST FORM FOR MOUNT VERNON

UCL HOSPITALS **DISTRICT NUCLEAR MEDICINE SERVICE** **REQUEST FORM**		**Hospital No:** _____ **Surname:** _____ **First Names:** _____ **Date of Birth:** _____ **:** *Male*	
TRIAL NAME:	Car-PET	**Car-PET Trial Number:**	CA - _____
REQUESTING SITE:	Mount Vernon Cancer Centre	**CONSULTANT:**	Prof Gordon Rustin
EXAMINATION REQUESTED:	Review of PET-CT scan transferred via IEP		
CLINICAL HISTORY:	Patient with metastatic seminoma		
PET CT-Scan Assessment ***For attention of Dr Rizwan Syed***		**IEP TRANSACTION NUMBER**	
VISIT TIME POINT:	1. Pre-treatment ○ 2. During treatment (Cycle 1 Day 17-21) ○ 3. Post-treatment ◉	**DATE SCAN PERFORMED:** **DATE SCAN TRANSFERRED:**	
REQUESTED BY:	**NAME:** _____ **DATE:** _____ **SIGNATURE:** _____	**TELEPHONE NO:** **EMAIL ADDRESS FOR REPORT TO BE SENT TO :** @nhs.net	

PLEASE SIGN IF FAXED

Please complete this form, then either :

Fax to 020 3447 0591

or (preferred)

save and email to

EMAIL SHORTCUT

rizwansyed@nhs.net & shane.blanchflower@nhs.net

The report will be emailed as pdf to the nhs.net email address specified above

CAR-PET PET-CT Scan Review Request Form_Mount Vernon Hospital_v2.0 dated 05AUG2014.PDF

APPENDIX 7 – SUBMISSION OF IMAGES FOR CENTRAL REVIEW AND ESCALATION PROCESS

Site sends image via IEP and faxes Request Proforma simultaneously to Central Reviewer on 020 3447 0591 and/ email: rizwansyed@nhs.net & shane.blanchflower@nhs.net

imagexchange portal
The National Image Sharing Network

Site emails ALL direct clinical trial staff involved including CarPET Trial Coordinator

CarPET Trial Coordinator records this on Mastersheet. Clock starts.

CENTRAL REVIEW

UCLH confirm receipt of email and image

Central Reviewer sends PDF report to site via email address provided

Report received within 3wks?

YES

NO

File report in patient medical records and plan patient treatment

Escalation Process:

1. Site contacts central reviewer directly after 2 weeks of submitting image via IEP to ensure the target of 3 weeks is going to be met.
2. If no response from Central Review, site should inform the Trial Coordinator via email: bci-carpet@qmul.ac.uk .
3. The CarPET Trial Coordinator to contact via telephone and/or email and report back to site with an expected date for report.

APPENDIX 8 –IMAGING PROTOCOL

Scanning Protocol

1. Administer 350-400MBq 18FDG.
2. The emission scan should start 60 minutes after tracer injection from the skull base to the upper thigh.
3. A low dose CT should be performed for attenuation correction and anatomical localisation from the skull base to the upper thigh.

Acquisition should be performed using the institution's standard protocol with regard to time per bed position, 2D or 3D, CTAC-parameters, reconstruction parameters and algorithms etc. Both attenuation corrected and non-attenuation corrected data sets should be reconstructed.

Radiation Dosimetry

The effective radiation dose associated with an administration of 400 MBq 18-FDG is 10.0mSv (ARSAC Notes for Guidance 1998). The CT attenuation correction using 80mA and 150KV will be approximately 8 mSv for scan suggested

Image Data Transfer

Image data must be transferred to UCLH Central Review (Dr Rizwan Syed) via the secure NHS IEP.

The following file is required:

- Attenuation corrected PET data acquired from the base of the skull to the upper thigh
- Non attenuation corrected PET data acquired from the base of the skull to the upper thigh
- Low dose CT data acquired from the base of the skull to the upper thigh
- CT scout views are not required

All files must be clearly marked with the pre-arranged filename. The patient's full name can be used when using the secure IEP system. **The trials office cannot have any correspondence sent to them via email or post with patient personal identifiers being present, only initials, date of birth and trial numbers are applicable.**

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