



A randomized, open-label, multicentre, two-arm phase III comparative study assessing the role of involved mediastinal radiotherapy after Rituximab containing chemotherapy regimens to patients with newly diagnosed Primary Mediastinal Large B-Cell Lymphoma (PMLBCL)

Clinical Trial coordinators

M. Martelli - Roma (Italy)
A.J. Davies - Southampton (UK)
M. Gospodarowicz - Toronto (Canada)
E. Zucca - Bellinzona (Switzerland)

PET coordinators

S. Barrington - London (UK)
A. Biggi - Cuneo (Italy)
L. Ceriani - Bellinzona (Switzerland)
A. Versari - Reggio Emilia (Italy)

Statistician

G. Ciccone - Torino (Italy)

Medical physicist

S. Chauvie - Cuneo (Italy)

Version 1.0 – October 24, 2011

Table of contents

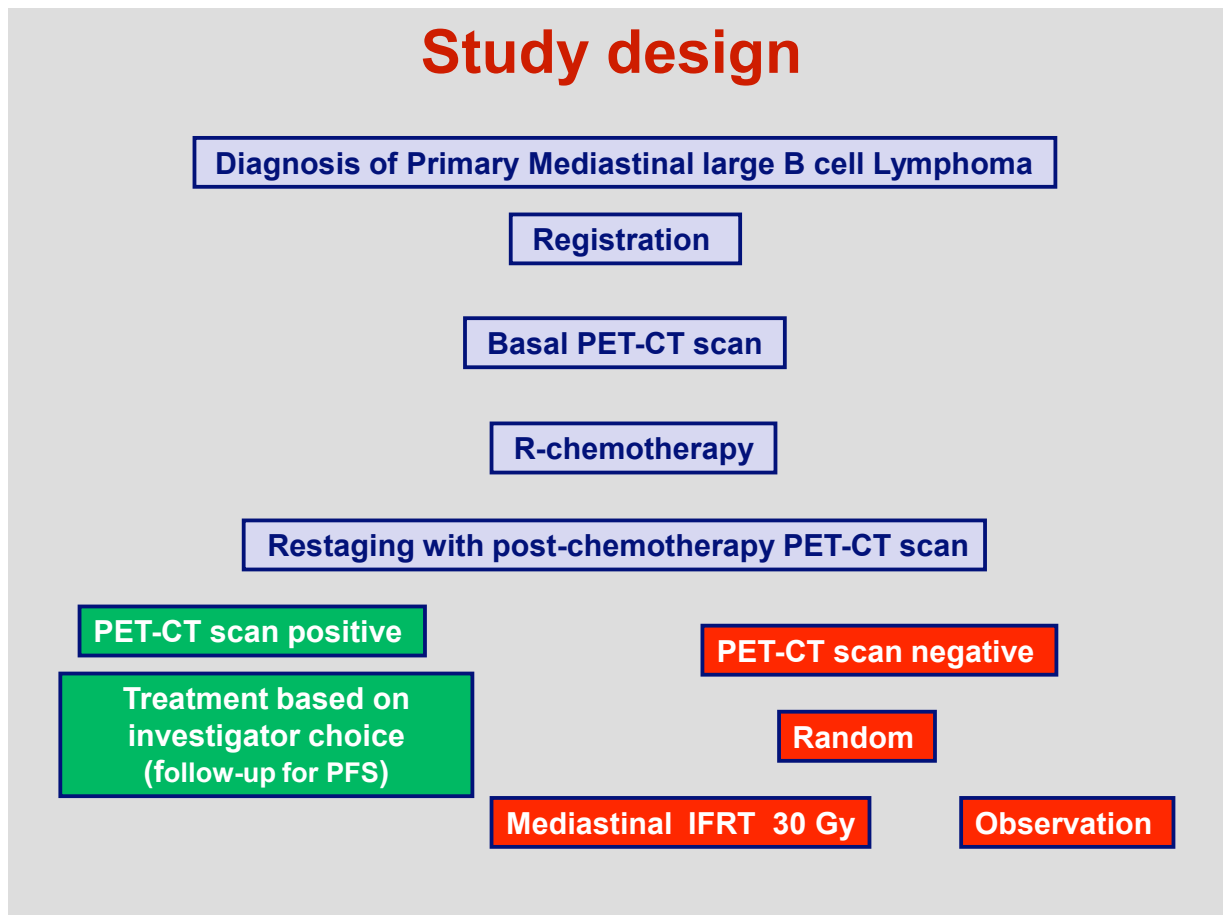
1.	Trial summary.....	3
2.	Introduction.....	5
3.	Aims of the trial.....	8
3.1	Primary endpoint.....	8
3.2	Secondary endpoint.....	8
4.	Trial design.....	8
5.	Inclusion criteria.....	9
6.	Exclusion criteria.....	9
7.	Baseline investigations.....	10
8.	Response criteria.....	10
9.	PET clinical protocol.....	10
9.1	Patient scheduling.....	10
9.2	Patient preparation.....	11
9.3	Radiopharmaceutical administration.....	12
9.4	Image acquisition.....	12
9.5	Image reconstruction.....	13
9.6	Information to be recorded for each patient.....	13
9.7	Data transfer.....	13
9.8	Reporting of PET/CT scans.....	14
9.9	PET reviewing procedure.....	15
9.10	Radiation dosimetry.....	16
10.	Registration and randomization.....	16
10.1	Before any patient registration.....	16
10.2	Registration.....	16
10.3	Uploading of baseline and post R-chemotherapy PET/CT.....	16
10.4	Randomization.....	16
11.	Radiotherapy.....	17
11.1	CT simulation process.....	17
11.2	Target volumes definition.....	17
11.3	Treatment and dose prescription.....	18
12.	Follow-up investigations following the final response (for randomized patients only).....	18
12.1	Investigations at follow-up.....	18
13.	CRFs completion.....	19
14.	Serious Adverse Events (SAE).....	20
14.1	Definition of adverse event.....	20
14.2	Definition of serious adverse event.....	20
14.3	Reporting of serious adverse events.....	20
15.	Statistical considerations.....	21
15.1	Primary endpoint definition.....	21
15.2	Statistical design.....	21
15.3	Sample size.....	22
15.4	Interim monitoring an analysis.....	22
15.5	Statistical analysis.....	23
16.	Ethical considerations.....	24
17.	Schedule of events (overall study plan).....	25
18.	Study acknowledgement.....	26
19.	References.....	27
Appendix 1	ECOG Performance Status.....	30
Appendix 2	IPI score.....	30
Appendix 3	Toxicity criteria.....	30
Appendix 4	Response criteria.....	31
Appendix 5	PET/CT procedures.....	32
Appendix 6	Self-declaration of conformity and compliance with the irradiation protocol.....	47

1. Trial summary

This is a prospective randomized non-inferiority phase III trial. Patients with previously untreated primary mediastinal B-cell lymphoma will be enrolled on the basis of the clinical and local pathologic characteristics of their lymphoma and, with their consent, be pre-registered before the start of the chemotherapy. All patients will undergo a pretreatment PET/CT and then go on to receive one of the standard chemotherapy regimens currently in use for DLBCL (e.g., CHOP14/21, DA-EPOCH, Mega-CHOP, ACVBP, VACOP-B or MACOP-B) in association with at least 6 courses of Rituximab (R-chemotherapy). The PET/CT scans will be repeated at 5-6 weeks (i.e. day 29-42) after the last R-chemotherapy administration. After mandatory central PET/CT, all patients with a negative PET/CT scan after completion of R-chemotherapy (either with complete or partial radiological regression of the mediastinal mass), will be randomized to receive consolidation mediastinal involved field radiotherapy (IFRT) or observation. IFRT (30 Gy) will commence within 6-8 weeks (i.e. day 36-56) after the last administration of R-chemotherapy. Patients with a partial response and with a positive PET/CT scan will not be randomized. They will be treated according to the investigator's choice (e.g., with IFRT or salvage chemotherapy plus ASCT with or without IFRT) and will be followed for investigator-assessed response to chosen strategy, progression, and survival. All randomized patients will continue participation in the treatment follow-up phase study for 60 months from randomization. At 10 years from randomization, long-term safety information will be collected.

The primary endpoint is the determination of 2-year progression-free survival following randomization. Secondary endpoints are response rates, overall survival and long-term safety analysis. The trial is powered to determine a *non-inferior outcome* in patients not receiving IFRT based on a sample size of 376 patients. The expected proportion of PET-negative cases following R-chemotherapy is 0.5, so at least 752 patients will need to be enrolled.

Study design



2. Introduction

The WHO classification of tumors of the hematopoietic and lymphoid tissues recognizes primary mediastinal B-cell lymphoma (PMLBCL) as a distinct entity [1, 2]. This distinct clinicopathologic category accounts for less than 5% of non Hodgkin's lymphomas and comprises about 5% of the diffuse large B-cell lymphomas (DLBCL). Patients with PMLBCL tend to be younger than DLBCL cases with a median age at diagnosis in the third to fourth decade. They arise more commonly in women. The outcomes of therapy for patients with PMLBCL are probably better than those seen in DLBCL, partly as a result of their younger age and earlier stage at presentation. The optimal chemotherapy schedule is still unclear. Phase II studies have reported the results obtained with first to third generation regimens [3-5]. Several European groups have suggested that third generation regimens (e.g., MACOP-B or VACOP-B) may be superior to the CHOP regimen [6-9]. The superiority in terms of PFS and OS of the more aggressive chemotherapy strategies over CHOP-like regimens was confirmed by a large European survey of 426 patients conducted by the IELSG [10] and also in retrospective studies from Italy [11] and North-America. [12-14].

In the last decade, the inclusion of Rituximab as part of initial therapy for CD20+ B-cell lymphomas has clearly improved response rates and overall survival in several DLBCL randomized trials [15, 16]. Direct comparison between different non-randomized clinical studies with or without rituximab is difficult, nevertheless, the R-CHOP regimen is likely to have improved the outcomes also in PMLBCL. Indeed, the addition of rituximab to CHOP allowed the same 5-year OS as with the more intensive regimens MACOP-B / VACOP-B in a Canadian retrospective study [12]. In the subgroup analysis of the MINT international randomized trial the subgroup of patients with PMLBCL treated with Rituximab plus chemotherapy (CHOP in most cases) showed a significantly better 3-year PFS than patients treated with chemotherapy alone (87.7% vs 64.1% $p=0.005$) [17]. On the contrary, in a phase II Italian trial of the combination of Rituximab with MACOP-B / VACOP-B plus mediastinal Involved Field Radiation Therapy (IFRT) the PFS improvement was not statistically significant in comparison with an historical control [18].

The combination of immunochemotherapy (R-Chemotherapy) plus IFRT results in 3-year PFS of 80-85% [17-19] with recent guidelines [20] recommended chemotherapy with a CHOP/MACOP-B-like regimen (plus rituximab) followed by mediastinal IFRT as standard front line treatment for PMLBCL. However, the role of adjuvant mediastinal IFRT in patients who achieve CR with chemotherapy is still unclear. Retrospective series suggest that the best outcomes are seen when consolidation radiotherapy is given to the mediastinum [10], particularly in the large proportion of patients with a residual mediastinal mass at the completion of chemotherapy [21, 22]. Todeschini et al. reported a significant

improvement in event-free survival for patients in complete response treated with consolidative radiation therapy irrespective of the type of chemotherapy given [11].

However, there are still large numbers of patients cured by chemotherapy alone as reported by Dunleavy et al in a series of 22 patients with PMLBCL treated with DA-EPOCH-Rituximab without mediastinal radiotherapy [14]. The concerns about late effects of mediastinal radiotherapy including coronary heart disease, heart failure, valvular disorders, and risk of second cancers such as breast cancer, lung cancer, and thyroid cancer call for studies to investigate scenarios where radiotherapy may not be required [23]. Modern radiotherapy techniques may minimize the morbidity to other tissues and reduce the risk of long-term side effects [24-26], but they may not completely address the risks of late effects, therefore safety remains an important issue [27].

Studies of functional imaging using Gallium scans [8] or, more recently, Positron Emission Tomography (PET) scans [28] have suggested that it may be possible to distinguish residual mediastinal masses, which contain active lymphoma, from those in which the lymphoma has already been cured and only sclerotic material remains. PET scans are now widely used as prognostic indicator [29-31] and incorporated in the definitions of the revised criteria of response in DLBCL[32]. However, the studies performed to date in PMLBCL are inconclusive and did not clarify whether radiotherapy could be avoided solely on the basis of a negative PET scan. [33]

In a retrospective study on 54 patients with PMLBCL using the R-CHOP/ ICE dose-dense regimen without mediastinal IFRT the MSKCC group reported a 3-year OS and PFS of 88% and 78% respectively in patients who were PET negative at the end of the chemotherapy regimen. Furthermore an interim PET scan, performed on 51/54 patients was abnormal in 47% of patients and did not predict for PFS. (35)

In a retrospective study of the British Columbia Cancer Agency Centre 196 DLBCL patients (25 with PMLBCL) with a residual mass of >2 cm after 3 weekly R-CHOP regimen underwent PET imaging. The PET was negative in 121/196(62%) patients post therapy PET who went on to be observed, while 66/196 (34%) who had a positive post therapy PET received IFRT (30-40 Gy) to sites of PET positivity. At a median follow up of 32 months no difference were observed in terms of 3-yrs PFS (80% vs. 75%, p=0.41) between the PET negative and PET positive patients. (36)

The IELSG-26 study was the first international prospective study in PMLBCL designed to obtain data regarding 18-F-FDG PET response rate following an anthracycline-containing immunochemotherapy, with or without mediastinal irradiation, according to the local practice of the participating institutions. The study enrolled 125 consecutively patients with PMLBCL, between January 2007 and November 2010, all who received R-CHOP (-like) or R-MACOP-B (-like) regimens. Of these, 123 patients also received mediastinal

consolidation IFRT. Preliminary PET/CT data is available on 92 patients following the end of chemotherapy and just before radiotherapy. The scans were centrally reviewed according to Deauville interpretation criteria and demonstrated a metabolic CR in 39 pts (42%). In 6 cases (7%) the PET/CT scan was completely negative but in 35 (35%) there were small residual masses with 18-F-FDG uptake less than that of the mediastinal blood pool (MBP). Out of 53 (58%) positive PET scans the residual uptake was > MBP but < liver uptake in 25 (27%) cases, slightly > liver uptake in 21 (23%) and >> liver in 7 (8%). Preliminary data of the IELSG 26 study seems to indicate that a PET/CT 3-4 weeks after the end of CHT remains positive in approximately 58% of patients (37).

In summary, the principal clinical open questions in the management of PMLBCL are:

1. Does mediastinal IFRT improve the outcomes in primary mediastinal lymphoma in patients treated with R-CHOP/CHOP like chemotherapy?
2. Is a negative PET/CT a reliable indicator of cure following R-CHOP chemotherapy alone making mediastinal IFRT unnecessary in PET negative patients?

For the above reasons this phase III randomized trial is designed to assess the role of radiotherapy in PMLBCL patients with PET-negative mediastinal masses after immunochemotherapy. The trial should be able to demonstrate a *non-inferior outcome* in patients not receiving IFRT after immunochemotherapy. Such study may eventually allow to individualize treatment for each patient by adapting it to the PET response limiting the indication for additional radiotherapy only to the patients who show an inadequate response to immunochemotherapy.

3. Aims of the trial

To evaluate the possibility to spare the radiotherapy in PMBCL patients, who have become “PET-negative” after a combined R-chemotherapy.

3.1 Primary endpoint

- Progression free survival (PFS) at 2 years from the randomization

3.2 Secondary endpoint

- Overall survival (OS) at 5 years from registration

4. Trial design

This will be a prospective randomized non-inferiority phase III trial. Patients will be enrolled on the basis of the clinical and local pathologic characteristics of their lymphoma and pre-registered before to start the chemotherapy program after achievement of their signed consent. Central pathology review will be carried out on a national basis. Storage of fresh/frozen biopsy or of the histological paraffin-embedded material will be made wherever possible. Patients will receive one of the standard R-chemotherapy regimens currently in use for DLBCL (e.g., CHOP14/21, DA-EPOCH, Mega-CHOP, ACVBP, VACOP-B or MACOP-B). At least 6 courses of Rituximab should be administered. PET/CT scans will be performed at baseline and at 4-5 weeks after the last R-chemotherapy administration. Randomization will take place after the PET/CT performed at the completion of initial R-chemotherapy. Central review of PET/CT scans will be mandatory before randomization.

All patients with a negative PET/CT scan after completion of R-chemotherapy, either with complete or partial radiological regression of the mediastinal mass, will be randomized to receive consolidation mediastinal IFRT (30Gy) or observation. IFRT should commence within 7 weeks after the last administration of R-chemotherapy

Patients with a partial response with a positive PET/CT scan will not be randomized. They will be treated according the investigator choice (e.g., with IFRT or salvage chemotherapy plus ASCT with or without IFRT). These patients will be followed for progression, and survival analysis and response (investigator’s defined) to the chosen salvage strategy will be recorded.

Patients will continue participation in the treatment follow-up phase study for 60 months from randomization. A form will be sent to all the investigators at 10 years to collect relevant information on long term safety.

5. Inclusion criteria

- Previously untreated primary mediastinal diffuse large B-cell lymphoma, CD20 positive. Patients must have histological confirmation of the diagnosis (it is recommended that the immunohistochemical panel includes: CD45, CD20, CD30, CD15, CD10, BCL6, BCL2, MUM-1), and in addition have a *dominant mass* within the anterior mediastinum.
- No evidence of extranodal disease outside the chest including spleen and bone marrow.
- Age at least 18 years.
- Fit to receive chemotherapy and radiotherapy with curative intent.
- Patients will be eligible if the treatment phase consisting in a Rituximab combined with any anthracycline-containing chemotherapy regimen without consolidation with autologous stem cell support (e.g., 6 cycles of CHOP14-21, DA-EPOCH, Mega-CHOP or 12 weeks of VACOP-B or MACOP-B).
- At least 6 courses of Rituximab should be administered
- Able and willing to give informed consent, and to undergo staging including PET scanning
- Willingness to comply with an appropriate contraceptive method in women of childbearing potential or men.
- Histological diagnostic material available for review.

6. Exclusion criteria

- History of malignancy other than squamous cell carcinoma, basal cell carcinoma of the skin or carcinoma in situ of the cervix within the last 5 years.
- Evidence of clinically significant cardiac disease at diagnosis, as defined by history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within 12 months before study entry. Cardiac impairment due to local extension of lymphoma will not be an exclusion criterion in the absence of other cardiac disease.
- Known HIV-positive serology.
- Pregnant or lactating women.
- Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.

7. Baseline investigations

- Patients will be staged according to the Ann Arbor system and information on the prognostic factors contributing to the IPI at diagnosis will be recorded (Appendix 2).
- Baseline investigations will always include:
 1. Complete blood counts (CBC) with differential;
 2. Biochemical profile (creatinine, ALP, AST or ALT, albumin, LDH, β 2 microglobulin)
 3. Immunoglobulin levels and serum protein electrophoresis
 4. Chest x-ray
 5. Contrast-enhanced CT scan of chest, abdomen and pelvis
 6. PET/CT scan (see PET section chapter 9)
 7. Bone marrow trephine and aspirate.
 8. Left ventricular ejection fraction evaluation by echocardiography or MUGA scan

8. Response criteria

Conventional response data will be recorded following chemotherapy and at the completion of all treatment if radiotherapy is given, using the standard revised Cheson criteria 2007 (Appendix 4).

9. PET clinical protocol

9.1 Patient scheduling

- All patients should have a pre-treatment FDG-PET/CT scan as a baseline to be compared with subsequent scans to assess response. This should be performed not more than 2 weeks before the therapy starts. Steroids should be avoided or if given, steroids should ideally be omitted for three days prior to the scan. If this is not possible, details of steroid administration must be recorded as it may affect quantitative analysis.

- The response scan must be performed at 5-6 weeks (i.e. day 29-42) after the final administration of chemotherapy. The second PET scan should be booked at the time of starting treatment, to ensure appropriate timing of response scans.
- Baseline and response PET exams for a patient must be performed in the same centre using the same accredited PET/CT system as the baseline scan. The patient preparation, FDG administration, image acquisition and reconstruction for these scans must be matched for both scans.
- If a diagnostic contrast-enhanced CT with intravenous contrast is indicated, this should ideally be performed after the PET/CT scan with a separate low dose CT scan used for attenuation correction.

9.2 Patient preparation

- Patients should be fasted for at least 6 hours prior to the start of the PET study.
 - Type 1 diabetes mellitus: the PET study should be performed in the late morning. The patient should eat a normal breakfast not later than six hours before the examination and inject their normal amount of insulin to control the blood sugar.
 - Type 2 diabetes mellitus: the PET study should be performed in the late morning, patients should eat a normal breakfast not later than six hours before the examination and take their usual oral medication to control the blood sugar.
 - Both Type 1 and 2 patients should not consume any more food or fluids in the fasting period except plain (unflavored) water.
- Prior to FDG administration the patient should be well hydrated. Patients should be encouraged to take plain (unflavored water) during the fasting and uptake periods.
- 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. PET examination should not be performed if the glucose level is above 120mg/dl (7.0 mmol/l). Insulin should not be administered to reduce glucose level if the level is > 7.0mmol/l as this could alter the distribution of the FDG in the body unless the interval between administration of insulin and administration of FDG is more than 4h.
- Patients should be weighed using a calibrated device
- For some patients it might be necessary to administrate benzodiazepine or beta-blockers to reduce muscle and brown fat uptake.

- During the 18-F-FDG administration, uptake phase and the PET/CT exam, the patient should be kept comfortable and warm to avoid uptake in the muscles or brown fat. Patients should avoid strenuous exercise for 6 hours prior to the scan.
- Patients should be asked to void immediately prior to the PET/CT scan to reduce bladder activity.
- Intravenous CT contrast media should not be administered prior to the PET study. If a diagnostic CT scan using contrast is routinely performed as part of the PET/CT examination this should be performed after the PET scan. A separate low dose CT without contrast should also be acquired and this scan should be used for attenuation correction of the PET images.

9.3 Radiopharmaceutical administration

Radiopharmaceutical:	18-F-fluorodeoxyglucose (FDG)
Route of Administration:	Intravenous administration
Dose:	Dependent on the PET system that is utilized and the patient weight
Suggested dosage:	Users should not exceed country specific diagnostic reference levels but it is suggested: <ul style="list-style-type: none"> a) to administer 5.3MBq/kg 18-F-- FDG for 2D acquisition or 3.5MBq/kg for 3D acquisition b) that although scan duration can be modified according to patient weight, a minimum of 3 minutes per bed position scan time should be used c) for larger patients (>90kg) it is strongly recommended to increase the scanning time rather than increasing the injected dose

9.4 Image acquisition

- The PET emission acquisition (baseline and final study) should be started 60 minutes after the dose administration. If this time is exceeded by more than 15 minutes i.e. 75 minutes after tracer injection due to unforeseen events it must be noted as a deviation on the PET acquisition form with a reason why this happened.
- The PET and CT scans should include the region between the skull base and mid-thigh.
- Patients should be scanned with arms above the head for the PET/CT scan if tolerated. Patient positioning should be matched on the response scans.

- All other imaging parameters i.e. with regard to time per bed position, 2D or 3D, CTAC parameters must be agreed with the core lab prior to the start of the study (see Appendix). 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.

9.5 Image reconstruction

- Attenuation correction should be performed using the low dose CT.
- Iterative reconstruction should be used e.g. OSEM or similar.
- PSF/ resolution modelling although generally improves the quality of the image, it should not be used in the reconstruction of the PET images. This is due to guarantee comparable image quality between all centres.
- 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 Core Lab prior to the start of the study (see Appendix). 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.

9.6 Information to be recorded for each patient

The information required is specified in the **PET/CT Acquisition Form** in the Appendix 5. For each patient study, the PET/CT acquisition information and patient information will be entered in the DICOM header and this will be checked to ensure it matches the written record for the 2 patient dataset sent for QC assessment.

9.7 Data transfer

All data will be transferred to a dedicated WEB server (www.ielsg.org/edc.html). In principle this should be made by the peripheral PET centres in whom PET scan has been performed. Should PET centres have hurdles in the uploading process, national core labs may collect scans from participating centres for uploading onto the Web.

The following files are required:

- Attenuation corrected PET emission images (covering skull base to mid thigh)
- Non-attenuation corrected PET images
- CT scan (covering skull base to mid thigh)

Scout views and projection images (MIPs) should not be sent to review.

All image files must be compliant with DICOM PART 10 format. It is highly recommended that images be created and sent directly from the acquisition PET/CT workstation rather than from a secondary PACS system or file library. Specifically, image files that have been converted to savescreens and then reconverted back to DICOM format are NOT acceptable.

All files must be named using the patient UID assigned in the study pre-arranged filename convention.

9.8 Reporting of PET/CT scans

The post treatment scans will be reported according to the Deauville criteria [34]. In brief, the following rules will be used to interpret and score the final PET scans:

1. Consider residual lesions in the post chemotherapy PET scan that were present at baseline and deemed to be involved by lymphoma. Select the site with the most intense metabolic activity, and consider the axial slice where the FDG uptake is highest.
2. If no residual FDG uptake is observed in the scan, the score is 1.
3. Compare the FDG uptake of the selected hottest residual lesion with (i) the FDG uptake in an homogeneous and central region of the liver, avoiding any lesions (ii) the FDG uptake in mediastinum, trying to include large vessels but avoiding uptake in the aortic wall, myocardium, thymus and residual lesions.
4. Score the scan using mediastinum and liver as reference organs according to the 5-point scale, as follows:
 - Score 1 No uptake
 - Score 2 Uptake \leq mediastinum
 - Score 3 Uptake $>$ mediastinum and \leq liver
 - Score 4 Uptake moderately increased above liver at any site
 - Score 5 Markedly increased uptake at any site (SUV in lesion $>$ 3 times the uptake in normal liver) and/or new sites of disease

New focal uptake/new lesions: Three possibilities exist

- a) new lesion at a different site from initial disease probably NOT lymphoma >> score 1;
- b) new lesion at a different site from initial disease with clear evidence of disease progression at other sites >> score 5
- c) new lesion at a different site from initial disease probably NOT lymphoma but request for clinical information >> try and score if possible; more clinical information maybe necessary to evaluate the scan

Diffuse uptake in the spleen or marrow on the interim scan is most likely due to chemotherapy and should be scored as no disease especially if growth factors have been used (even if focal uptake is present at baseline).

Focal uptake in marrow can be scored as no disease if there is reduced uptake at sites where there was disease on baseline (due to marrow ablation) and increased uptake at sites with no disease at baseline (due to chemotherapy effect). This means that uptake on the interim scan may be like a ‘mirror’ of the uptake on the baseline scan

Since the aim of the proposed protocol is to spare radiotherapy to PET-negative patients, or, in other words, to de-escalate treatment in favorable-prognosis patients, one should rely on a very sensitive (conservative) threshold to interpret end-therapy scans, in order to avoid false negative results. For these reason we propose to introduce the following interpretation key:

- Score 1 Negative
- Score 2 Negative
- Score 3 Positive
- Score 4 Positive
- Score 5 Positive

9.9 PET reviewing procedure

Data acquired during the previous IELSG study from patients with PMBL will be circulated amongst reviewers to measure levels of agreement prior to the study opening. This will form the training set.

PET scan images during the study will be uploaded to a dedicated website (www.ielsg.org/edc.html). Seven Nuclear Medicine experts will be asked to be part of a central review panel to review the end-therapy scans. There must be complete agreement between 3 reviewers to a maximum of five reviewers.

							Max time	What to do	
1	2	3	4	5	6	7	96 h	Reviewed	Further reviews
a	a	a						x	
a	a	b							x
a	a	b	a					x	
a	a	b	b						x
a	a	b	b	a				x	
a	a	b	b	b				x	

9.10 Radiation dosimetry

The effective dose associated with an administration of 300 MBq 18-FDG is 6.0 mSv (ARSAC Notes for Guidance 2006). The target organ is the bladder wall, which will receive 68.0 mGy (ICRP Publication 53). The CT attenuation correction using 80 mA and 140 kV will be approximately 8 mSv for the half body. (This will be country specific).

National regulations must be complied with in regard to the administration of radioactive substances and the CT exposure for the purpose of this study.

10. Registration and randomization

10.1 Before any patient registration

- PET centre formal accreditation must undergo (dedicated webserver www.ielsg.org/edc.html)
- RT centre self-certification of protocol compliance must be signed
- Regulatory authorization to conduct the trial (IRB/EC approval and other applicable) must be obtained
- Study acknowledgement must be signed

10.2 Registration

Patients should be centrally registered at the IELSG website (www.ielsg.org/edc.html). Before starting the planned R-chemotherapy the baseline data (On study form) should be submitted.

10.3 Uploading of baseline and post R-chemotherapy PET/CT

Post R-chemotherapy PET-CT scans should be uploaded together with the baseline (i.e. before R-chemotherapy) PET-CT scans.

5-6 weeks after the last R-chemotherapy administration, PET-CT scans must be transferred to the dedicated web server (www.ielsg.org/edc.html) for central review.

10.4 Randomization

According to the centrally reviewed result of the PET scan performed, all PET negative patients will be randomized using the following stratification variables:

- sex
- country

- type of chemotherapy received (RCHOP/CHOP like; R-V/MACOP-B ; DA R-EPOCH; R-ACVBP)
- post chemotherapy PET-CT central review score (no uptake vs. residual uptake <MBP)

The randomization form must be submitted at the IELSG website (www.ielsg.org/edc.html).

11. Radiotherapy

Radiotherapy will be delivered in this phase III protocol, as alternative to observation, as consolidation treatment in patients achieving a CR status (PET/CT scan negative) at the end of R-chemotherapy, with a total dose of 30 Gy.

11.1 CT simulation process

- **CT simulation** is **mandatory** for radiation volumes definition (target contouring), with slice thickness of 2-3 mm.
- Use of **IV** (intravenous) **contrast** is allowed during CT scan simulation process but not mandatory.
- Patients are positioned supine, immobilisation for chest irradiation according to departmental policy.
- 4D-CT an active breathing controlled and allowed.

11.2 Target volumes definition

- Definition of all initially involved disease sites, using information from both pre-chemotherapy CT and PET/CT, is mandatory.
- Since consolidation radiotherapy should be delivered by protocol only on CR patients with negative PET/CT scan, only CTV has to be contoured
- **The CTV** will be the initial volume of the mediastinal mass *at presentation*, but taking into account response to chemotherapy and displacement of normal structures. The length of the CTV will be the length of the mediastinal mass before chemotherapy, while the width of CTV will be the width of the mediastinal mass after chemotherapy. The CTV should not extend into air, muscle planes or bone, unless really clinically needed.
- The **PTV** will be the CTV with a margin to take into account organ motion and set-up variations. The margins from CTV to PTV will thus depend on the method of

immobilization, the assessment of organ motion in simulation-phase (4D-CT) and the methods for image-guidance treatment delivery (i.e., cone beam CT). In most situations, a 1 cm margin is considered adequate. However, it can vary on the basis of single-institution facilities (a range of 8-15 mm is usual).

11.3 Treatment and dose prescription

- The dose should be specified according to ICRU 62 recommendations. The PTV must receive a dose between 95% and 107% (must be included in 95% isodose).
- Radiation treatment should start within 6-8 weeks after the end of chemotherapy.
- The PTV must receive 30 Gy in 15-20 daily fractions (Monday through Friday) over 3-4 weeks.
- Dose to healthy tissues should be kept as much low as reasonably possible, using standard dose-constraints (QUANTEC).
- Radiation should be delivered using 3D-Conformal Radiotherapy (3D-CRT), using Linac X-rays of 6-10 MV. IMRT is allowed to decrease dose to normal structures including heart, lungs and breast.
- Portal imaging must be performed the first day of treatment and then once a week thereafter.

12. Follow-up investigations following the final response assessment (for randomized patients only)

Follow up visits are scheduled from randomization. Patients will be seen at 3-months intervals for 24 months, then every 6 months until 5 years from randomization.

12.1 Investigations at follow-up

- History and physical examination
- CBC, LDH at each visit.
- TSH yearly for the first 2 years in patients treated with radiotherapy.
- Echocardiography annually for the first 5 years.
- Chest radiography (PA+lateral) at 3 – 9 – 18 months from randomization.
- Contrast enhanced CT scan at 6 – 12 – 24 months from randomization.
- Follow-up after 5 years to be continued according to local practice.

13. CRFs completion

CRFs have to be completed on line connecting to the following address:
www.ielsg.org/edc.html

The following steps have to be performed:

1. **Registration form**
2. **On study baseline form**
3. **Baseline and post R-chemotherapy PET-CT uploading for response evaluation (dedicated server www.ielsg.org/edc.html). Mandatory for patient randomization**
5. **Randomization Form.** Only PET-negative patients
6. **Radiotherapy form.** After completion of RT (if applicable) within 3 months from the randomization
8. **Follow-up form.** At each follow up visit: months 3-6-9-12-18-24-30-36-42-48-54-60 from randomization

Registered and **not-randomized** or **withdrawn** patients will be followed yearly for progression and survival analysis; response to the chosen salvage strategy will be recorded.

CRFs have to be completed on line (www.ielsg.org/edc.html) at months 12-24-36-48-60 from the end of R-chemotherapy.

14. Serious Adverse Events (SAE)

SAE are considered only in the randomized population and should be reported from randomization until 4 months. However, any adverse event, which is judged in the opinion of investigator to be possibly treatment-related should be reported up to 10 years (including all cardiac and pulmonary events, relapses and second cancers and deaths).

14.1 Definition of adverse event

Randomized patients will be instructed by the investigator to report the occurrence of any adverse event during and after radiotherapy. An adverse event is any undesirable event occurring during the trial, whether or not considered treatment related, and includes any side effect, injury, toxicity, or sensitivity reactions. It also includes any undesirable clinical or laboratory change, which does not commonly occur in the patient. An adverse event may occur under therapy and during follow-up.

14.2 Definition of serious adverse event

A serious adverse event includes any event that is:

- Fatal.
- Life-threatening: means that the patient was at immediate risk of death from the event as it occurred. It does not include an event that, had it occurred in a more serious form, might have caused death.
- Disabling: includes persistent or relevant disability or incapacity occurring during or after treatment.
- Requires inpatient hospitalization: defined as hospital admission required for treatment of the adverse event. Hospital admission for scheduled elective surgery or blood transfusion would not be a serious adverse event.
- Prolonged hospitalization: due to a serious disease not necessarily related to the tumor is also considered as SAE.
- Important medical events including all second malignancies: are those which may not be immediately life-threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes.

14.3 Reporting of serious adverse events

Any SAE occurring during radiotherapy must be reported by completing the “SAE Report form” (see CRFs) on line (www.ielsg.org/edc.html) or sending it by fax to IELSG Study

Coordinating Centre (++41 91 811 91 82). The SAE outcome must be reported within 2 weeks after definitive assessment in the same way.

The investigator according to local regulations will inform local authorities (ethics committees).

The physician responsible for patient care should organize any supplementary investigation of serious adverse events, based on the clinical judgment on the likely causing factors. If a patient dies, any post mortem finding including histopathology should be provided.

Events potentially associated with long term safety, including **all cardiac and pulmonary events, relapses, second cancers and deaths** will be regularly assessed and reported on the follow up CRFs.

15. Statistical Considerations

15.1 Primary endpoint definition

The primary outcome endpoint will be Progression Free Survival (PFS) in patients PET-negative after R-chemotherapy.

Failure events for PFS are progression (defined as an increase in size of existing masses or the development of new sites of disease using the same radiological investigations CT or PET/CT and/or MRI - as for the pre-chemotherapy assessment) or death from any cause.

15.2 Statistical design

The trial is planned according to a non-inferiority design aimed at demonstrating that PFS after the experimental treatment (observation) is not worse than after the standard comparator (mediastinal irradiation). In the present trial, to be considered non-inferior to IFRT, the upper limit of the 90% confidence interval of the HR comparing the PFS between no-IFRT vs. IFRT arms should be less than 1.77. This is a relatively wide non-inferiority margin, but it could be justified as some loss of efficacy in the no-IFRT arm might be accepted in exchange for improved safety in the long term.

15.3 Sample size

The sample size of the trial has been calculated using the following assumptions:

- expected 30-month PFS from randomization in both arms: 0.85 (HR=1)
- null hypothesis (H_0): No-RT vs. RT hazard ratio (HR) ≥ 1.77 (non-inferiority margin, corresponding to a 30-month PFS from randomization in the no-RT arm of 0.75)
- alternative hypothesis (H_1): HR < 1.77
- alpha error (1-sided): 0.05
- beta error: 0.20
- accrual time (uniform): 3 years
- minimum follow-up: 2 years
- interim analysis, to exclude superiority of the IFRT arm (with O'Brien and Fleming design): 1, when 25% of events will occur (expected 19 failures after 26 months from the beginning of the study), with a critical p value ≤ 0.0005 based on a logrank test comparing PFS times.

With these assumptions, the total number of PET negative patients after R-Chemotherapy to be randomized is 376.

Since the expected proportion of PET negative patients after R-Chemotherapy is about 0.5, the number of patients needed to be enrolled is at least 752.

For analysis, both intent-to-treat (ITT) and per-protocol analyses should be performed and results should be consistent to assess non-inferiority.

15.4 Interim monitoring and analysis

A formal interim analysis will be performed when 25% (number of failures=19) of total expected events ($n=76$) will occur and an Independent Data Monitoring Committee (IDMC) will be asked to give advice on whether the accumulating data from the trial, together with results from any other relevant trials, justifies continuing recruitment of further patients to complete the trial. The decision to discontinue recruitment, in all patients or in selected subgroups, will be made only if the interim results and the external evidence will be considered sufficient by the IDMC. If a decision is made to continue, the IDMC will advise on the need of further interim analyses. The IDMC will also make recommendations to the Trial Steering Committee as to whether the trial should continue in its present form. While the trial is ongoing the accumulating data will remain confidential.

15.5 Statistical Analysis

15.5.1 Progression-Free Survival

The primary endpoint is the PFS. The PFS will be measured from the date of randomization to the date of documented disease progression, relapse or death from any cause. Failure free patients and patients who are lost to follow up will be censored at their last assessment date.

For each arm, estimates of the PFS function will be made by the Kaplan-Meier product-limit method. Hazard Ratio (HR) (No-RT vs. RT) and its **90 percent** confidence interval will be estimated using the Cox proportional-hazards model. To conclude that the no-IFRT arm is non-inferior to the IFRT arm, the upper limit of the HR of the PFS must be ≤ 1.77 .

15.5.2 Overall Survival

Overall survival will be determined from the date of randomization the date of death from any cause. Overall survival at 5-years from registration is a secondary endpoint that should be estimated in all registered patients. Patients who have not died at the time of the final analysis will be censored at 5 years from registration or the date of the last contact.

Estimates of the overall survival function will be made by the Kaplan-Meier product-limit method.

Difference between arms will be evaluated in the randomized population performing the log-rank test. Hazard Ratio (HR) will be estimated using the Cox proportional-hazards model.

15.5.3 Proportional Hazards assumption

For each time-to-event endpoint, deviation from proportionality of hazards will be assessed on the basis of Schoenfeld residuals.

In case of a differential effect over time, proportional hazards models will be applied by dividing follow-up time into more periods, according to effect changes over time.

Finally, we will estimate the hazard ratios (No-RT vs. RT) for each of the periods.

16. Ethical considerations

The study will be submitted for approval to the relevant Ethical Committee and competent authority in each country/institution. Copies of the approval letter kept on file at IELSG. Before entering patients into the study, clinicians must ensure that the protocol has received clearance from the local Institutional Review Board and/or Research Ethics Committee, as appropriate according to the local regulations. The patient's consent to participate in the study should be obtained for all cases, after a full explanation has been given of the treatment.

The right of a patient to refuse to participate without giving reasons must be respected. After the patient has entered the study the clinician must remain free to give alternative treatment to that specified in the protocol at any stage if it is felt to be in the patient's best interests. The reason for giving such alternative treatment must be recorded and the patient should remain in the study for the purposes of follow-up and data analysis. Similarly, the patient must remain free to withdraw at any time from protocol treatment without giving reasons and without prejudicing further treatment.

17. Schedule of events (overall study plan)

		5-6 weeks after R-chemotherapy	FOLLOW-UP months 3 to 24 from randomisation	FOLLOW-UP years 3 to 5
History and PE	X		every 3 months	every 6 months
CBC	X		every 3 months ⁽¹⁾	every 6 months ⁽¹⁾
Biochemistry	X		every 3 months ⁽¹⁾	every 6 months ⁽¹⁾
FDG-PET/CT	X	X		
Chest X-ray	X		at month 3, 9, 18	if clinically required
CT scan of chest, abdomen and pelvis	X		at month 6, 12, 24	if clinically required
Echocardiography or MUGA scan	X		yearly	yearly
ECG	X			
Bone marrow trephine and aspirate	X			
TSH	X		yearly if RT was performed	
Adverse events			X ⁽²⁾	X ⁽²⁾

- **PE:** physical examination with evaluation of performance status (ECOG scale)
- **CBC:** complete blood count with differential white count
- **Biochemistry:** creatinine, ALP, ALT, LDH, albumin, beta2-microglobulin, immunoglobulin levels, serum protein electrophoresis

(1) repeat only CBC and LDH if not otherwise clinically indicated

(2) Serious adverse events must be collected only in the randomized population, from the time of randomization and up to 4 months.

AE judged possibly treatment related should be reported up to 10 years.

Non randomized or withdrawn patients will be followed yearly for progression and survival analysis; response to the chosen salvage strategy will be recorded.

18. Study acknowledgement

PROTOCOL IELSG 37

A RANDOMIZED, OPEN-LABEL, MULTICENTRE, TWO-ARM PHASE III COMPARATIVE STUDY ASSESSING THE ROLE OF INVOLVED MEDIASTINAL RADIOTHERAPY AFTER RITUXIMAB CONTAINING CHEMOTHERAPY REGIMENS TO PATIENTS WITH NEWLY DIAGNOSED STAGE I-II PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMLBCL)

As investigator for this study, I understand that this protocol contains information that is confidential and proprietary to IELSG. I have received and read the above mentioned protocol and agree that it contains all necessary details for carrying out the study as described; I will conduct this protocol as outlined therein and in accordance with GCP.

I will provide copies of this protocol and access to all information furnished by IELSG to study personnel under my supervision. I will discuss this material with them to ensure that they are fully informed about the study. I agree to keep accurate records on all patients' information (CRFs and Patients' informed consent statement), and all other information collected during the study for a minimum period of 10 years.

I agree not to publish all or any part of the results of the study carried out under this protocol, without the prior written consent of IELSG.

All parties agree to ensure direct access to examine, analyze, verify and reproduce source data/documents, and reports from all trial related sites for the purpose of monitoring and auditing, and inspection by domestic and foreign regulatory authorities.

PD Dr. Med. Emanuele Zucca



October 24, 2011

.....
Investigator (printed name)

.....
Signature

.....
Date

Prof. Dr. med. Franco Cavalli



October 24, 2011

.....
IELSG Representative

.....
Signature

.....
Date

19. References

1. Jaffe ES, Harris NL, Stein H, Vardiman JW. World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues. In Edition Lyon: IARC Press 2001; 1-351.
2. van Besien K, Kelta M, Bahaguna P. Primary mediastinal B-cell lymphoma: a review of pathology and management. *J Clin Oncol* 2001; 19: 1855-1864.
3. Cazals-Hatem D, Lepage E, Brice P et al. Primary mediastinal large B-cell lymphoma. A clinicopathologic study of 141 cases compared with 916 nonmediastinal large B-cell lymphomas, a GELA ("Groupe d'Etude des Lymphomes de l'Adulte") study. *Am J Surg Pathol* 1996; 20: 877-888.
4. Abou-Elella AA, Weisenburger DD, Vose JM et al. Primary mediastinal large B-cell lymphoma: a clinicopathologic study of 43 patients from the Nebraska Lymphoma Study Group. *J Clin Oncol* 1999; 17: 784-790.
5. Martelli MP, Martelli M, Pescarmona E et al. MACOP-B and involved field radiation therapy is an effective therapy for primary mediastinal large B-cell lymphoma with sclerosis. *Ann Oncol* 1998; 9: 1027-1029.
6. Bieri S, Roggero E, Zucca E et al. Primary mediastinal large B-cell lymphoma: the need for prospective controlled clinical trials. *Leuk Lymphoma* 1999; 35: 537-544.
7. Lazzarino M, Orlandi E, Paulli M et al. Primary mediastinal B-cell lymphoma with sclerosis: an aggressive tumor with distinctive clinical and pathologic features. *J Clin Oncol* 1993; 11: 2306-2313.
8. Zinzani PL, Martelli M, Magagnoli M et al. Treatment and clinical management of primary mediastinal large B-cell lymphoma with sclerosis: MACOP-B regimen and mediastinal radiotherapy monitored by (67)Gallium scan in 50 patients. *Blood* 1999; 94: 3289-3293.
9. Zinzani PL, Martelli M, Bendandi M et al. Primary mediastinal large B-cell lymphoma with sclerosis: a clinical study of 89 patients treated with MACOP-B chemotherapy and radiation therapy. *Haematologica* 2001; 86: 187-191.
10. Zinzani PL, Martelli M, Bertini M et al. Induction chemotherapy strategies for primary mediastinal large B-cell lymphoma with sclerosis: a retrospective multinational study on 426 previously untreated patients. *Haematologica* 2002; 87: 1258-1264.
11. Todeschini G, Secchi S, Morra E et al. Primary mediastinal large B-cell lymphoma (PMLBCL): long-term results from a retrospective multicentre Italian experience in 138 patients treated with CHOP or MACOP-B/VACOP-B. *Br J Cancer* 2004; 90: 372-376.
12. Savage KJ, Al-Rajhi N, Voss N et al. Favorable outcome of primary mediastinal large B-cell lymphoma in a single institution: the British Columbia experience. *Ann Oncol* 2006; 17: 123-130.
13. Hamlin PA, Portlock CS, Straus DJ et al. Primary mediastinal large B-cell lymphoma: optimal therapy and prognostic factor analysis in 141 consecutive patients treated at Memorial Sloan Kettering from 1980 to 1999. *Br J Haematol* 2005; 130: 691-699.
14. Dunleavy K, Pittaluga, Stefania, Janik, John, Grant, Nicole, Steinberg, Seth, Staudt, Louis, Jaffe, Elaine, Wilson, Wyndham H. Primary Mediastinal Large B-Cell Lymphoma (PMBL) Outcome Is Significantly Improved by the Addition of Rituximab to Dose Adjusted (DA)-EPOCH and Overcomes the Need for Radiation. *Blood (ASH Annual Meeting Abstracts)* 2005; 106: 273a (abstract 929).
15. Coiffier B, Lepage E, Briere J et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 2002; 346: 235-242.

16. Pfreundschuh M, Schubert J, Ziepert M et al. Six versus eight cycles of bi-weekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas: a randomised controlled trial (RICOVER-60). *Lancet Oncol* 2008; 9: 105-116.
17. Trneny M MR, Anders Osterborg, Ruth Pettengel, Darrell J White, Devinder Gill, Jan Walewski, Evelyn Kuhnt, Markus Loeffler, Michael Pfreundschuh, and Anthony D. Ho. The Addition of Rituximab Eliminates the Negative Prognostic Impact of PMBCL Compared to DLBCL in Young Patients with CD20-Positive Aggressive Lymphomas Receiving a CHOP-Like Chemotherapy: Results of a Subgroup Analysis of the Mabthera International Trial Group (MInT) Study. *ASH Annual Meeting Abstracts* 2008 112: 839 2008.
18. Zinzani PL, Stefoni V, Finolezzi E et al. Rituximab combined with MACOP-B or VACOP-B and radiation therapy in primary mediastinal large B-cell lymphoma: a retrospective study. *Clin Lymphoma Myeloma* 2009; 9: 381-385.
19. Vassilakopoulos TP, Angelopoulou MK, Galani Z et al. Rituximab-CHOP (R-CHOP) And Radiotherapy (RT) For Primary Mediastinal Large B-Cell Lymphoma (PMLBCL): An Update. *Haematologica* 2006; 91: 260 (abstract 0704).
20. Zinzani PL, Martelli M, Poletti V et al. Practice guidelines for the management of extranodal non-Hodgkin's lymphomas of adult non-immunodeficient patients. Part I: primary lung and mediastinal lymphomas. A project of the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation. *Haematologica* 2008; 93: 1364-1371.
21. Mazzarotto R, Boso C, Vianello F et al. Primary mediastinal large B-cell lymphoma: results of intensive chemotherapy regimens (MACOP-B/VACOP-B) plus involved field radiotherapy on 53 patients. A single institution experience. *Int J Radiat Oncol Biol Phys* 2007; 68: 823-829.
22. De Sanctis V, Finolezzi E, Osti MF et al. MACOP-B and involved-field radiotherapy is an effective and safe therapy for primary mediastinal large B cell lymphoma. *Int J Radiat Oncol Biol Phys* 2008; 72: 1154-1160.
23. Henderson TO, Amsterdam A, Bhatia S et al. Systematic review: surveillance for breast cancer in women treated with chest radiation for childhood, adolescent, or young adult cancer. *Ann Intern Med* 2010; 152: 444-455; W144-454.
24. Bucci MK, Bevan A, Roach M, 3rd. Advances in radiation therapy: conventional to 3D, to IMRT, to 4D, and beyond. *CA Cancer J Clin* 2005; 55: 117-134.
25. Yoon M, Ahn SH, Kim J et al. Radiation-induced cancers from modern radiotherapy techniques: intensity-modulated radiotherapy versus proton therapy. *Int J Radiat Oncol Biol Phys* 77: 1477-1485.
26. Tsang RW, Gospodarowicz MK. Radiation therapy for localized low-grade non-Hodgkin's lymphomas. *Hematol Oncol* 2005; 23: 10-17.
27. Nieder C, Schill S, Kneschaurek P, Molls M. Comparison of three different mediastinal radiotherapy techniques in female patients: Impact on heart sparing and dose to the breasts. *Radiother Oncol* 2007; 82: 301-307.
28. Zinzani PL, Tani M, Trisolini R et al. Histological verification of positive positron emission tomography findings in the follow-up of patients with mediastinal lymphoma. *Haematologica* 2007; 92: 771-777.
29. Mikhaeel NG, Timothy AR, O'Doherty MJ et al. 18-FDG-PET as a prognostic indicator in the treatment of aggressive Non-Hodgkin's Lymphoma-comparison with CT. *Leuk Lymphoma* 2000; 39: 543-553.
30. Spaepen K, Stroobants S, Dupont P et al. Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([18F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: is [18F]FDG-PET a valid alternative to conventional diagnostic methods? *J Clin Oncol* 2001; 19: 414-419.

31. Zinzani PL, Fanti S, Battista G et al. Predictive role of positron emission tomography (PET) in the outcome of lymphoma patients. *Br J Cancer* 2004; 91: 850-854.
32. Cheson BD, Pfistner B, Juweid ME et al. Revised response criteria for malignant lymphoma. *J Clin Oncol* 2007; 25: 579-586.
33. Kahn ST, Flowers C, Lechowicz MJ et al. Value of PET restaging after chemotherapy for non-Hodgkin's lymphoma: implications for consolidation radiotherapy. *Int J Radiat Oncol Biol Phys* 2006; 66: 961-965.
34. Meignan M, Gallamini A, Haioun C. Report on the First International Workshop on Interim-PET-Scan in Lymphoma. *Leuk Lymphoma* 2009; 50: 1257-1260.
35. Moskowitz G, Hamlin PA, Maragulia J et al. Sequential dose-dense R-CHOP followed by ICE consolidation (MSKCC protocol 01-142) without radiotherapy for patients with primary mediastinal large B cell lymphoma. *Blood* 2010 ASH meeting abst. 420.
36. Sehn LH, Hoskins P, Klasa R et al. FDG PET scan guided consolidative radiation therapy optimizes outcome in patients with advanced stage diffuse large B cell lymphoma (DLBCL) with residual abnormalities on CT scan following R-CHOP. *Blood* 2010 ASH meeting abst. 854.
37. Martelli M, Ceriani L, Zinzani PL: PET/CT response analysis in primary mediastinal diffuse large B-cell lymphoma (PMBL): preliminary results of the IELSG-26 study. (submitted to 11^o ICML 2011).
38. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Statistics in Medicine*. 1999;18(6):695-706.
39. Gray RJ. A class of K-sample tests for comparing the cumulative incidence of a competing risk. *The Annals of Statistics*. 1988;16(3):1141-1154.
40. Fine J, Gray R. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association*. 1999;94(446):496-497.

ECOG Performance Status

Grade Description

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

Appendix 2

IPI score

- Age >60
- Serum lactate dehydrogenase concentration greater than normal
- ECOG performance status 2 or more
- Ann Arbor clinical stage (III or IV)
- Number of involved extranodal disease sites >1

In this system, one point is given for each of the above characteristics present in the patient, for a total score ranging from zero to five, representing increasing degrees of risk:

- Low risk IPI score of zero or one
- Low intermediate risk IPI score of two
- High intermediate risk IPI score of three
- High risk IPI score of four or five

Appendix 3

Toxicity Criteria

In the present study, toxicities will be recorded according to the **Common Terminology Criteria for Adverse Events (CTCAE) version 3.0**
<http://ctep.cancer.gov/forms/CTAEv3.pdf>

Response criteria

Definition of CR, PR and SD should be evaluated according to Cheson Criteria 2007.

Complete Response (CR)

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
2. In patients with a PET scan positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.

Partial Response (PR)

1. At least a 50% decrease in sum of the product of the diameters (SPD) of the largest dominant nodes or nodal masses. These nodes or masses should be clearly measurable in at least 2 perpendicular dimensions and they should include mediastinal areas of disease.
2. No increase should be observed in the size of other nodes.
3. No new sites of disease should be observed.
4. For patients with PET scan positive before therapy, the post-treatment PET should remain positive in at least one previously involved site.

Stable Disease (SD)

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease.
2. The PET scan should be positive at prior sites of disease with no new areas of involvement on the post-treatment PET/CT.

Relapsed Disease (after CR) / Progressive Disease (after PR, SD)

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes $\leq 1.0 \times \leq 1.0$ cm will not be considered as abnormal for relapse or progressive disease.

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities.
2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions. To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by $\geq 50\%$ and to a size of 1.5×1.5 cm or more than 1.5 cm in the long axis.
3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
4. Lesions should be PET positive if the lesion was PET positive before therapy.

PET/CT QC procedures

Common standards and careful quality control is essential for the success of multi-centre trials such as this one. The procedures below are based on those of the American College of Radiology Imaging Network and the EANM procedure guidelines for tumour PET Imaging (Boellaard et al 2009).

Imaging Facilities

- Only full-ring dedicated PET/CT scanners are acceptable.
- Scanning facilities must undergo the site accreditation process as detailed below and have received written confirmation that they fulfil the requirements of the study before scanning any patients as part of the trial.
- A documented quality assurance program must be in place and records kept covering daily, weekly, monthly, quarterly and annual QC testing.
- Dedicated WEB server will be used to transfer anonymized scan data between scanning facilities.
- All files must be clearly named using a pre-arranged file naming convention.
- Named persons (and their deputies) should be identified with responsibility for scanning, QC and data transfer at participating PET/CT centres.
- It must be demonstrated that image quality is comparable between centres and standard uptake values can be reliably determined from the PET/CT phantom data
- The proposed data acquisition/reconstruction protocol (including details of the time per bed position, 2D or 3D, CTAC parameters, reconstruction parameters etc.) must be agreed with the Core Lab before scanning can start. Generally a time per bed of less than 3 minutes for 2D and 3D are not acceptable.
- All image files must be compliant with DICOM PART 10 format.

Site Accreditation Process

Before a PET centre can participate in the trial it must undergo the formal site accreditation process. **Scanning as part of the clinical trial must not start until written confirmation of compliance with the technical requirements as specified in the *PET/CT system accreditation module* document is received from the clinical trial management.**

The site accreditation must also be repeated by a PET Centre 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 specified in the *PET/CT system accreditation module* document.
- Any other circumstances which 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 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 trials.

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

1. The *PET/CT system accreditation module* document (see below) must be completed and forwarded to the core lab.
2. Initial 'start-up' scanner quality control procedures must be performed
3. Two representative patient studies must be transferred to the core lab.

4. The data transfer and anonymization procedure must be set up and validated
5. Written confirmation from the core lab that scanning can now start at your centre must be received.

Initial start-up QC procedures

Image Quality Assessment

All PET/CT scanners should be calibrated against the institutions own radionuclide calibrator. The restriction of the study to full ring dedicated PET/CT scanners should ensure that the images acquired at all centres are of a comparable quality. In order to confirm this and check the SUV accuracy of each scanner, a phantom should be scanned at each of the participating centres using the local study protocol. This could be done by a representative from the core lab who visits the scanning facility or a representative at the scanning facility if approved by the core lab. Ideally however a personal visit from the core lab to scanning facilities is useful to establish contact and answer individual questions relating to the study for smooth running of the study.

The phantom will consist of the NEMA IEC PET body phantom or EU chest phantom, filled with water throughout, containing 6 small spheres. The spheres will be filled with 21.2 kBq/ml of ^{18}F - solution and the rest of the phantom with 5.3 kBq/ml of ^{18}F - to simulate small regions of tracer uptake in the abdomen.

Data will be acquired using the same acquisition and processing parameters that will be used for the patient studies. These parameters may vary between sites. Data will be evaluated in terms of absolute activity measurements for the background and the spheres. Two nuclear medicine physicians or radiologists trained in PET/CT will also assess the visual quality of the scans. If significant disparities are observed, for example, from the use of widely differing reconstruction parameters, these will be resolved prior to the start of the study.

CT and PET data of the phantom have to be uploaded to the dedicated WEB site. The phantom images will be assessed at the core lab and results recorded on the Image quality Assessment form.

Calibration QC

In order to check the correct calibration of the PET/CT scanner against the institutions own radionuclide calibrator a uniform phantom scan must be performed as follows:

For Water-filled Uniform Phantoms: Fill the phantom with water and inject a known amount of ^{18}F (either as fluoride or FDG) into the phantom. The activity injected should be determined by measurement of the syringe before and after the injection in a properly calibrated dose calibrator. The injected activity should be chosen to result in an activity concentration similar to that encountered in clinical FDG imaging, i.e., 37- 55 MBq of ^{18}F should be added to the 6,283 ml phantom, 74 MBq for the 9,293 mL phantom.

Thoroughly combine the mixture and then scan the phantom with the same protocol used for patient imaging. Reconstruct the images with the same algorithm and filters used for patient imaging. Draw a circular or elliptical region of interest (ROI) covering most of the phantom's interior over all slices. Measure and report the average SUV and standard deviation in the UNIFORM CYLINDER ASSESSMENT form. **The expected SUV for the uniform phantom is 1.00 and the acceptable range is 0.90 to 1.10.**

For $^{68}\text{Ge}/^{68}\text{Ga}$ Calibration Phantoms: Scan the phantom with the same protocol used for patient imaging. Report the assay date and activity from the calibration certificate of this phantom on the UNIFORM CYLINDER ASSESSMENT form. Reconstruct the images with the same algorithm and filters used for patient imaging. Draw a circular or elliptical region of interest (ROI) covering most of the interior of the phantom over all slices. Measure and report the average SUV and standard on the PET Instrument Technical Specification form. The expected SUV for the uniform phantom is 1.00 and the acceptable range is 0.90 to 1.10.

Ancillary Equipment

- As this study uses SUVs 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 ± 1 kg 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 should be synchronized to the scanner time.

Representative patient studies

Two anonymized patient studies (attenuation corrected PET, CT and non-attenuation corrected PET) acquired using the proposed study protocol should be transferred to the core lab for quality assessment together with the **PET/CT Acquisition Form** in Appendix.

Data Format and Archiving

All studies to be transferred to the core lab (attenuation corrected PET, non attenuation corrected PET, and CT) must be in DICOM format. BMP files, jpeg files, screen saves and hard copies are not acceptable. Further, many PACS systems convert DICOM images to another format and then reconvert them back to DICOM when exporting to a CD or FTP. This is not acceptable. Raw data must be archived according to local protocol, and at least until the images have been accepted by the core lab.

Data transfer and anonymisation procedure

All patient identifying information must be removed from the images prior to transfer. Images of the patients will be assigned to the patient UID given for the study. Images will be uploaded to dedicated WEB servers. This process will be validated when transferring the test phantom and two patient data as above.

Routine scanner QC procedures

A documented PET/CT scanner quality assurance program must be in place and records kept, covering daily, monthly, quarterly and annual QC testing. Records should be made available for inspection by the Core lab if requested

The PET scanner should have an up-to-date calibration and normalization. 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.

The routine CT QC should be performed according to the manufacturer's recommendations and local regulations. A copy of the CT scanned water filled phantom must be sent to core lab to measure image noise, uniformity and CT number.

Confirmation that study can start at your site

When all the above has been completed a letter will be forwarded to both the PET centre and the Study Co-ordinator to confirm that the centre can now participate in the trial. No subjects should be scanned before this.

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.

Contact

For enquiries relating to the scanning protocol, quality control and data transfer only please contact the Trials Physicist at the core lab:

phone number: +39 0171 541 875

[email](mailto:chauvie.s@ospedale.cuneo.it) address: chauvie.s@ospedale.cuneo.it

For all other enquiries please contact the Trials Unit

PET/CT SYSTEM ACCREDITATION MODULE

Please complete this document on the dedicated WEB site before any patient from the trial undergoes a PET/CT scan.

Centre Information

Centre Name:		Date:
Address:		

Person responsible for Scanning procedures:

Name:		Email:	
Telephone:		Fax:	

Deputy to cover leave:

Name:		Email:	
Telephone:		Fax:	

Person responsible for QC procedures:

Name:		Email:	
Telephone:		Fax:	

Deputy to cover leave:

Name:		Email:	
Telephone:		Fax:	

Person responsible for data transfer procedures:

Name:		Email:	
Telephone:		Fax:	

Deputy to cover leave:

Name:		Email:	
Telephone:		Fax:	

Data Transfer

Could you archive patient images in a single file (using ZIP format) and upload it to the main repository through the internet?	<input type="checkbox"/> Yes <input type="checkbox"/> No
---	--

PET/CT Scanner Technical Specification (please complete a separate accreditation module for each system or always use the same system to scan patients)

Please confirm that you have a:

Full ring PET/CT scanner (no CPET or PET allowed)	<input type="checkbox"/> Yes	<input type="checkbox"/> No
---	------------------------------	-----------------------------

Please state:

Manufacturer and Model: (eg. GE Discovery ST, Siemens Biograph, Philips Gemini, etc.)	
Date of installation:	

Quality Control Procedures

Is a documented quality QA program in place	<input type="checkbox"/> Yes	<input type="checkbox"/> No
---	------------------------------	-----------------------------

Scheduled QC and Calibrations (please tick as appropriate)

	Daily	Weekly	Monthly	Quarterly	Yearly
Daily (Blank scan)					
Calibrations (PMT gain, coincidence window, dead time)					
Corrections (ECF, Well Counter, SUV, etc)					
Uniformity					
Sensitivity					
Correction accuracy					
Spatial resolution					
PET/CT co-registration tests					
CT tube warm up and air calibration					
CT number and noise					

National/International protocol used:

Data Acquisition and Reconstruction parameters for the standard PET/CT exam

CT Acquisition Parameters:

Type:	<input type="checkbox"/> Axial <input type="checkbox"/> Helical				
kV _p :		mAs:		Collimation (mm):	
Rotation time (s):			Bed Speed (mm/s):		
Type of protocol (inhale, exhale, normal respiration):					

PET Acquisition Parameters:

PET emission scan duration per bed position (give time in minutes)	
Acquisition mode (specify 2D, 3D, TOF)	
Number of Axial FOV:	

PET Reconstruction Parameters:

Matrix size (e.g. 128*128)	
Voxel size (e.g. 2.0*2.0*2.0 mm ³)	
Reconstruction algorithm (e.g. OSEM, 3D RAMLA etc)	
Smoothing filter and cut-off if used (e.g. Hanning, 0.5 Nyquist)	
Reconstruction algorithm parameters (number of iterations, subsets)	
Scatter correction applied	<input type="checkbox"/> Yes <input type="checkbox"/> No
Randoms correction applied	<input type="checkbox"/> Online <input type="checkbox"/> Smoothed Randoms (offline) <input type="checkbox"/> None
Type of protocol (inhale, exhale, normal respiration):	
Do you always measure the injected activity to the patient using a dose calibrator?	<input type="checkbox"/> Yes <input type="checkbox"/> No

Additional Procedures to be Undertaken as Part of This Study

Scan of a uniform 18F/68Ge phantom will be carried out to check image quality and confirm that SUV measures 1.00 + 10%, on the morning of the study	<input type="checkbox"/> Yes	<input type="checkbox"/> No
QC of the weighing scales will be carried out at least annually	<input type="checkbox"/> Yes	<input type="checkbox"/> No
If any of the procedures described in this document cannot be carried out for whatever reason a physicist from the core lab will be contacted immediately and no further studies will be undertaken by your centre until the issues have been resolved	<input type="checkbox"/> Yes	<input type="checkbox"/> No

By signing this document I agree to participate in the study and to:

- collect the required patient information
- retrieve the patients' images
- upload the patients' images to the WEB site

Signature:

Date:

**IMAGE QUALITY ASSESSMENT
(to be completed by Core Lab)**

PET Centre:

Scanner Manufacturer and Model:

QC tests performed by:

Date:

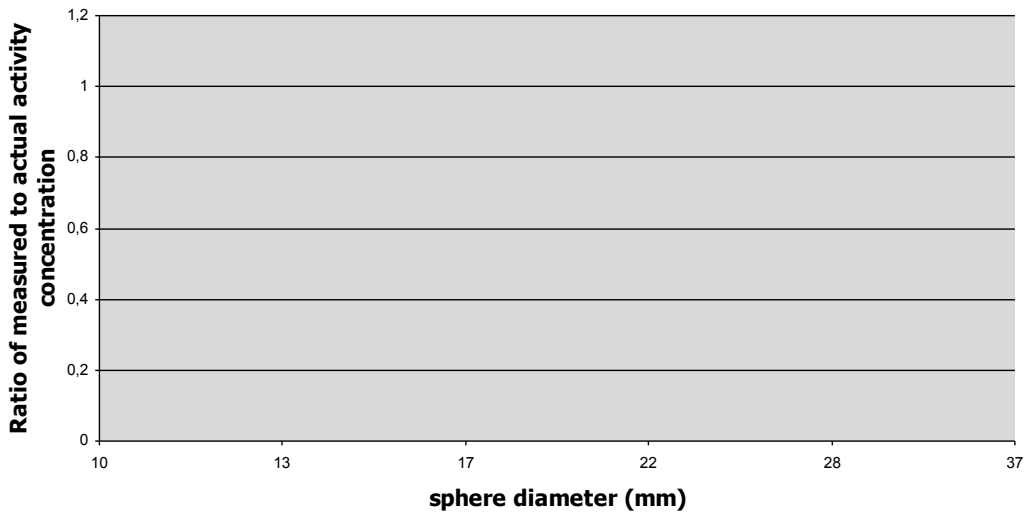
NEMA/EU Phantom Qualitative Analysis:

Image Quality	Acceptable	Not acceptable
PET/CT alignment on core centre reporting system	Acceptable	Not acceptable
Comments		
Sphere activity concentration at scan start time:		kBq/ml
Background activity concentration at scan start time:		kBq/ml

	Activity Concentration		
	Measured (M)	Actual (A)	Ratio
Sphere diameter (mm)	kBq/ml	kBq/ml	M / A
37			
28			
22			
17			
10			

13			
----	--	--	--

A recovery curve should be generated from the tabulated data:



Average SUV for a large ROI positioned over the background: _____
 Average CT number for a large ROI positioned over the background: _____

Recovery Curve:	Acceptable	Not acceptable
------------------------	-------------------	----------------

PET/CT Scan acquired at _____ (PET Centre)

Date of PET/CT scan: _____ Patient's initials: _____

Time of administration of activity (hour:min):	
Injected FDG dose (MBq):	
Patient height (cm):	

Patient weight (kg):		
Patient fasting state (time last ate):		
Patient blood glucose (mg/dL):		
SUV for uniform phantom on day of scan:		
Daily quality control result for the day of the scan:		
Calibration Factor (counts to activity) (kBq/counts):		
SUV for 5cm diameter circular ROI in homogeneous region of the liver		
SUV _{max} :	SUV _{mean} :	Slice z:

	START TIME	NO. OF BED POSITIONS	DURATION PER BED POSITION	TOTAL SCAN DURATION
PET EMISSION SCAN				

Test data review (to be completed by Core Lab)

Comments

APPROVED	REJECTED
----------	----------

Name Date

Name Date

TEST PATIENT DATA FOR PET/CT SCAN Patient 2
--

PET/CT Scan acquired at (PET Centre)

Date of PET/CT scan: Patient's initials:

Time of administration of activity (hour:min):	
Injected FDG dose (MBq):	
Patient height (cm):	

Patient weight (kg):		
Patient fasting state (time last ate):		
Patient blood glucose (mg/dL):		
SUV for uniform phantom on day of scan:		
Daily quality control result for the day of the scan:		
Calibration Factor (counts to activity) (kBq/counts):		
SUV for 5cm diameter circular ROI in homogeneous region of the liver		
SUV _{max} :	SUV _{mean} :	Slice z:

	START TIME	NO. OF BED POSITIONS	DURATION PER BED POSITION	TOTAL SCAN DURATION
PET EMISSION SCAN				

Test data review (to be completed by Core Lab)

Comments

APPROVED	REJECTED
----------	----------

Name

Date

Name

Date

**NOTIFICATION TO PET SCANNING FACILITY OF APPROVAL TO
SCAN PATIENTS IN TRIAL**

From:	
To:	
Fax Number:	
To:	
Fax Number:	

Approved for trial

QC procedures	YES	NO
Scan acquisition and reconstruction parameters	YES	NO
Phantom data and patient test data	YES	NO
Data transfer	YES	NO

Name

Date

Patient test data	YES	NO
-------------------	------------	----

Name 1

Date

Name 2

Date

The above named Centre has complied with the requirements for PET/CT scanning and is a recognised scanning facility in the trial. The Centre undertakes to notify the Core Lab immediately of any deviations in QC and scan acquisition or reconstruction parameters from those agreed.

ACQUISITION DATA FOR PET/CT SCAN
(to be completed by PET scanning facility)

PET/CT Scan acquired at			(PET Centre)
Patient's trial number:		Patient's initials:	
Referring Consultant:			
Consultant telephone number:		Consultant fax number:	
Hospital Address:			
Date of PET/CT scan:			

Time of administration of activity (hour:min):			
Injected FDG dose (MBq):			
Site of tracer administration and state left or right:			
Patient height (cm):			
Patient weight (kg):			
Patient fasting state (time last ate):			
Patient blood glucose (mg/dL):			
SUV for uniform phantom on day of scan:			
Daily quality control result for the day of the scan:			
Calibration Factor (counts to activity) (kBq/counts):			
SUV for 5cm diameter circular ROI in homogeneous region of the liver			
SUV _{max} :	SUV _{mean} :	Slice z:	
Any deviations from the previously forwarded protocol?		YES	NO
If yes, please specify			

	START TIME	NO. OF BED POSITIONS	DURATION PER BED POSITION	TOTAL SCAN DURATION
PET EMISSION SCAN				

REQUEST FOR PET/CT SCAN 1 (pre-treatment)

and 2 (6 weeks after last chemotherapy administration); both to be arranged at baseline

Patient details (attach label):

Patient's telephone number:	
Referring Consultant:	
Consultant telephone number:	
Consultant fax number:	
Hospital Address:	
Date registered into trial:	
Trial number:	
Please State	
Date Cycle 1 day 1	
Intended date of last administration of chemotherapy*	

*The second PET/CT scan will be arranged 6 weeks after this date.

FOLLOWING REGISTRATION, SEND THIS FORM TO THE PET SCANNING CENTRE OF YOUR CHOICE (LISTED IN APPENDIX *) THE PET CENTRE MUST BE INFORMED PROMPTLY IF THERE ARE ANY DELAYS TO CHEMOTHERAPY

