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Protocol for the CONVERT trial - Concurrent ONce-daily VErsus twice-daily RadioTherapy: An international 2-arm randomised controlled trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited stage small cell lung cancer (LS-SCLC) and good performance status.

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Protocol for the CONVERT trial - **C**oncurrent **ON**ce-daily **VE**rsus twice-daily **R**adio**T**herapy: An international 2-arm randomised controlled trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited stage small cell lung cancer (LS-SCLC) and good performance status.

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ABSTRACT

Introduction

CONVERT is the only multicentre, international, randomised, phase III trial open in Europe and Canada looking at optimisation of chemoradiotherapy in LS-SCLC. Following on from the Turrisi trial of once-daily (OD) versus twice-daily (BD) concurrent chemoradiotherapy , there is a real need for a new phase III trial using modern conformal radiotherapy techniques and investigating higher once-daily radiation dose. This trial has the potential to define a new standard chemoradiotherapy regimen for patients with LS-SCLC and good performance status.

Methods & analysis

547 patients with histologically or cytologically proven diagnosis of SCLC were recruited from 74 centres in 8 countries between 2008-2013. Patients were randomised to receive either concurrent BD radiotherapy (45Gy in 30 BD fractions over 3 weeks) or concurrent OD radiotherapy (66Gy in 33 OD fractions over 6.5 weeks,) both starting on day 22 of cycle 1. Patients are followed up until death. The primary endpoint of the study is overall survival and secondary end points include local progression-free survival, metastasis-free survival, acute and late toxicity based on the Common Terminology Criteria for Adverse Events version 3.0, chemotherapy and radiotherapy dose intensity.

Ethics & dissemination

The trial received ethical approval from NRES Committee North West – Greater Manchester Central (07/H1008/229). There is a trial steering committee, including independent members, and an independent data monitoring committee. Results will be published in a peer-reviewed journal and presented at international conferences.

Trial registration number ISRCTN91927162

Summary of strengths and limitations of study

- Adequately powered multicentre, randomised controlled trial aiming to establish a standard chemo-radiotherapy regime in LS-SCLC
- All patients are treated with modern radiotherapy
- Elderly patients are not excluded

INTRODUCTION

Of the 42,000 patients diagnosed with lung cancer each year in Britain, 15% will have small cell lung cancer (SCLC) and 30% of those patients will have limited stage (LS) disease that can be encompassed within a tolerable radiation therapy field. Even in this early stage disease the outcome is poor, with a median survival of 16 to 24 months with current forms of treatment[1-3]. Combining chemotherapy and thoracic radiotherapy is the standard treatment for LS-SCLC. Two meta-analyses have shown that radiotherapy associated with chemotherapy improves median survival, 3 year survival rate and local control[4 5]. Subsequently, meta-analyses of trials investigating the optimal timing and sequencing of chemo-radiotherapy have shown that the best results have been reported with early concurrent thoracic radiotherapy[6-9]. Furthermore it has been demonstrated that twice-daily radiotherapy is superior to once-daily radiotherapy in the landmark Turrisi study[3]. Patients were randomised to either 45 Gy once-daily (1.8 Gy per fraction) over 5 weeks or 45 Gy given twice-daily (1.5 Gy per fraction) over 3 weeks. In both arms radiotherapy was given concurrently starting with the first cycle of chemotherapy (cisplatin and etoposide). Twice-daily RT improved 5-year OS (26% vs. 16% in the once-daily arm), reduced the risk of thoracic relapse (52% compared with 36% in the twice-daily arm) but at the cost of increased grade 3 radiation oesophagitis (defined as inability to swallow more than liquids or to require hospitalisation). However, there were no other significant differences in acute toxicity between the 2 arms and no long-term oesophageal strictures were reported. Consequently twice-daily radiotherapy concurrently with chemotherapy is accepted as a standard regime in LS-SCLC[10]. It is however unclear whether the better results in the twice-daily arm are explained by the increase in the biologically equivalent dose of radiation in the twice-daily arm or by the use of altered fractionation leading to a shorter overall treatment time. Indeed the control dose was considered to be quite low, for example in comparison with the NCI Canada regime of 40 Gy in 15 daily fractions[1]. Moreover since the Turrisi trial was designed in the late 1980s, important progress has been made in radiotherapy techniques. The radiotherapy used in any contemporary trial should be CT-planned conformal treatment with individual field shaping careful dose calculation using modern planning algorithms of target and organs at risk, with image guidance, correction of set-up errors, and allowance made for the effects of respiratory motion on the position of the target volume. None of these were routine from 1989-1992 when the Turrisi trial was carried out. The use of 3 dimensional RT/Intensity Modulated radiotherapy and the omission of elective nodal irradiation are likely to result in lower rates of toxicity, particularly oesophagitis. Further studies by Choi et al[11] using once-daily (OD) radiotherapy and Komaki et al[12] using a concomitant boost technique have suggested that doses of 70Gy over 7 weeks and 61.8 Gy over 5 weeks respectively are possible, the former being delivered with 5 cycles of full dose chemotherapy.

There is therefore a need to improve on the current survival results and a strong rationale to compare twice-daily with a higher dose of radiation delivered once-daily.

In view of the lack of data in the literature addressing the question of the dose and fractionation for LS-SCLC, we carried out a randomised phase III trial to establish a standard chemo-radiotherapy regimen for LS-SCLC with good performance status (CONVERT). At the time the trial was being developed in 2006-7, there were no international trials for this group of patients, thus an opportunity existed to set up a global trial to answer this important question. The results of the trial will be crucial in determining the best international standard treatment for routine clinical use in the treatment of patients with limited-stage SCLC and good performance status. In addition the translational studies carried out in parallel to CONVERT will indicate the hypotheses which need testing in the next generation of trials in this disease.

METHODS AND ANALYSIS

The CONVERT trial is an international, multicentre, prospective, randomised controlled trial. The trial is sponsored by The Christie NHS Foundation Trust and coordinated by the Manchester Academic Health Science Centre Trial Co-ordination Unit (MAHSC-CTU) based at The Christie NHS Foundation Trust. The trial is registered on the International Standardised Randomised Controlled Trial Registry (ISRCTN91927162) and funded by Cancer Research UK's Clinical Trials Awards & Advisory Committee (CTAAC). The study is included in the NIHR Clinical Research Network portfolio (ID: 3823). The trial is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP).

The primary research question is to establish whether the results of twice-daily chemo-radiotherapy for patients with LS-SCLC and good performance status can be improved upon, by delivering a higher dose of radiotherapy once-daily concurrently with chemotherapy. We will compare survival of patients treated with standard chemotherapy (cisplatin & etoposide) and either twice-daily radiotherapy or high dose once-daily radiotherapy.

The secondary research questions will compare the following factors between the groups receiving either once or twice-daily radiotherapy:

*Local progression free survival

*Metastasis free survival

* Acute and late toxicity based on the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0)[13]

*Chemotherapy dose intensity

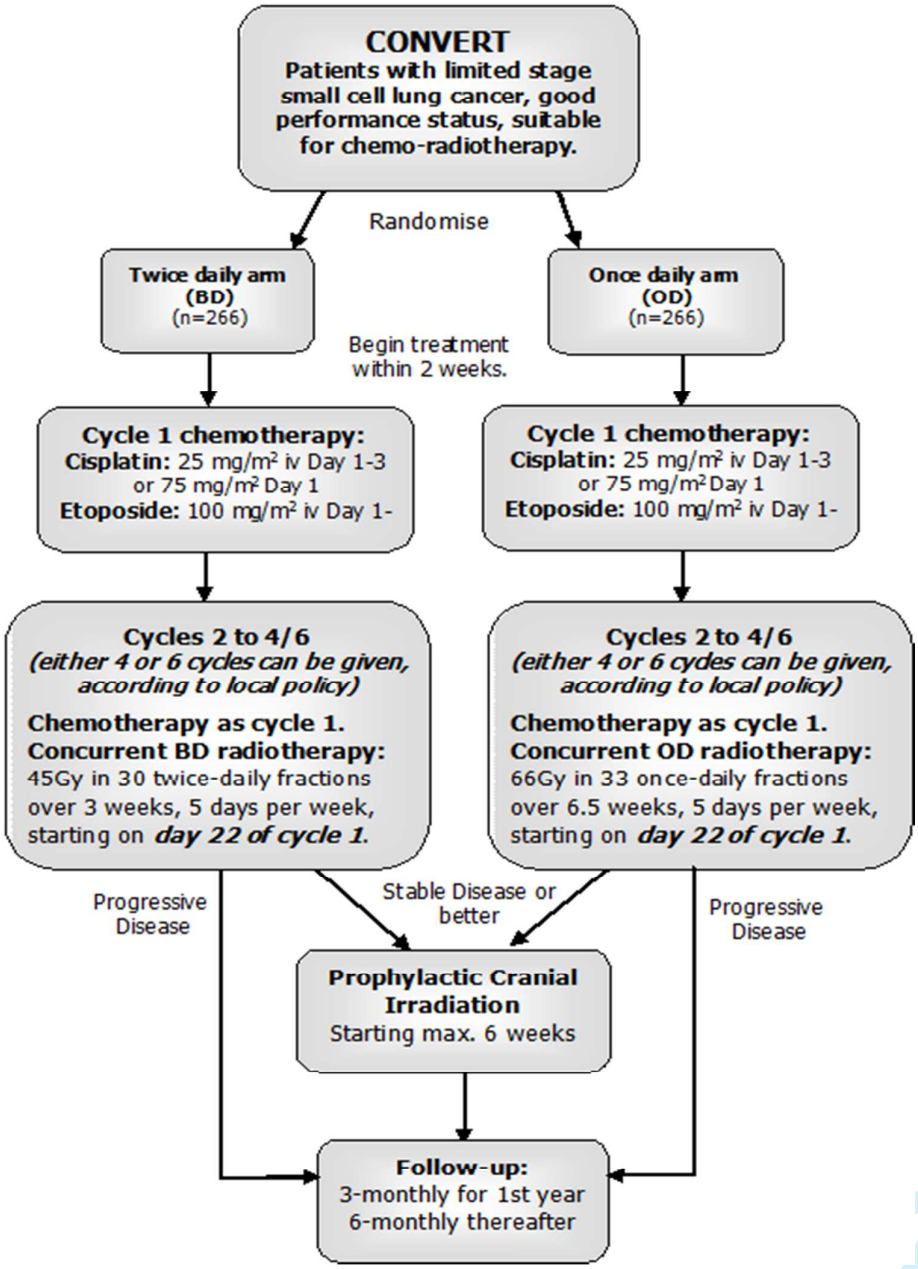
*Radiotherapy dose intensity

Setting

547 patients with a histological or cytological proven diagnosis of SCLC were recruited from 74 centres in 8 countries between April 2008 and November 2013 (see online supplementary appendix 1 for details of recruiting centres).

Patients were randomised to receive either concurrent twice-daily (BD) radiotherapy (45Gy in 30 twice-daily fractions over 3 weeks, 5 days per week, starting on day 22 of cycle 1) or concurrent once-daily (OD) radiotherapy (66Gy in 33 daily fractions over 6.5 weeks, 5 days per week, starting on day 22 of cycle 1). Patients are followed up until death. The study flow diagram is shown in figure 1.

Figure 1 – Trial Schema / Flowchart



Participant screening & selection

All LS-SCLC patients with good performance status and suitable for concurrent chemo-radiotherapy were identified as potential trial candidates. Eligible patients invited to participate were provided with a patient information sheet (see online supplementary appendix 2).

Inclusion & exclusion criteria

Patients were eligible for the trial if all of the following criteria were met:

a) Either sex, age ≥18 years

b) Performance status (PS) Eastern Cooperative Oncology Group grade 0-1. Patients with PS 2 whose general condition is explained by obstructive/bulky disease likely to improve after the first cycle of chemotherapy can be included at the discretion of the local investigator. Patients with PS 2 as a result of comorbid conditions will be excluded.

c) Histologically or cytologically confirmed SCLC

d) No patients with mixed small-cell and non-small-cell histologic features

e) No history of previous malignancy in the last 5 years (except non melanomatous skin or in-situ cervix carcinoma). Patients with previous malignancies (except breast cancer) and in remission for at least 5 years can be included.

f) Limited stage disease (Veterans Administration Lung Cancer Study Group) i.e. patients whose disease can be encompassed within a radical radiation portal.

g) No pleural or pericardial effusions proven to be malignant

h) Radiotherapy target volume acceptable by the local radiotherapist

i) Pulmonary function

   1) Forced expiratory volume in 1 s (FEV1) >1 litre or 40% predicted value

   2) Transfer coefficient of the lung for carbon monoxide (KCO) >40%predicted

j) Maximum of one of the following adverse biochemical factors:

   1) Serum alkaline phosphatase more than >1.5 times the upper limit of normal

   2) Serum sodium < lower limit of normal

   3) Serum LDH > upper limit of normal

k) Normal serum creatinine and calculated creatinine clearance ≥ 50 ml/min. If calculated creatinine clearance is <50 ml/mn according to the Cockroft and Gault formula, a glomerular filtration rate should be performed

l) Adequate haematological function

   1) Neutrophils >1.5 x 10^9/l

   2) Platelets >100 x 10^9/l

m) Adequate liver function: ALT & AST <= 2.5 x upper limit normal

n) No other previous or concomitant illness or treatment which in the opinion of the clinician will interfere with the trial treatments or comparisons

o) No prior surgical resection of the primary tumour, no prior radiotherapy for lung cancer

p) Considered fit to receive any of the trial regimens

q) Female patients must satisfy the investigator that they are not pregnant, or are not of child-bearing potential, or are using adequate contraception. Men must also use adequate contraception

r) Patients must not be breastfeeding

s) Patient has read the patient information sheet and has signed the consent form.

t) Patients available for follow-up

Informed consent

Eligibility to participate was confirmed by a clinician prior to consent being taken. Patients were given at least 24 hours to consider the patient information sheet and time to ask questions prior to written informed consent being taken by a trial doctor. The consent form can be viewed in online supplementary appendix 3.

Randomisation

Randomisation was administered centrally by the MAHSC-CTU. Patients were randomized on a 1:1 basis to one of the two treatment arms. The allocation method used was minimization with a random element. Randomisation was implemented via a bespoke computer application at the randomisation centre. The factors controlled for in the allocation were institution, planned number of cycles (4 or 6) and performance status (0/1 or 2).

Randomisation was only performed after confirmation that the patient was eligible (including recording of LDH, sodium and alkaline phosphatase results) and that the patient had signed consent. The system used did not permit any editing of fields by users after arm allocation had been performed.

Standard care

Concurrent chemo-radiotherapy is the standard of care in LS-SCLC and good performance status. The combination of cisplatin and etoposide (PE) is the standard chemotherapy treatment delivered concurrently with radiotherapy in this group of patients. One of the accepted international standard radiotherapy regimes is 45 Gy in 30 fractions delivered twice-daily, the control arm of the CONVERT trial[3]. However in reality radiotherapy regimes differ widely between institutions and twice-daily radiotherapy has not been adopted widely mainly due to logistical issues[12].

Interventions

In both arms, 3-dimensional conformal radiotherapy was used and 4 to 10 MV photons emitted from linear accelerators. Thoracic radiotherapy started on cycle 1 day 22, concurrently with the second cycle of chemotherapy where possible. Intensity modulated radiotherapy and PET-CT planning was permitted but not mandated. The full trial-specific procedure for radiotherapy can be found in online supplementary appendix 4, including the definition of the Planning Target Volume. However it is important to note that in this trial clinically uninvolved lymph node stations were not irradiated [14].

Patients randomised to the twice-daily thoracic radiotherapy arm received 45 Gy in 30 twice-daily fractions over a period of 19 days, 5 consecutive days a week. The optimal overall treatment time was 19 days. The inter-fraction interval was 6 to 8 hours. Concurrent chemotherapy was administered during the intervals between the 2 daily radiotherapy fractions.

Patients randomized to the high dose once-daily thoracic radiotherapy arm received 66 Gy in 33 daily fractions over a period of 45 days, 5 consecutive days a week. The optimal overall treatment time was 45 days.

Patients received cisplatin and etoposide, for 4 to 6 cycles, every 3 weeks in both arms. Centres were given the choice to stop chemotherapy after 4 cycles or to continue to up to 6 cycles. Centres who decided to give 6 cycles were asked to continue doing so for all patients entered in the trial (unless it was decided that it was not in the patients' best interest to receive cycle 5 and 6 or due to patient's choice). The 2 regimen of chemotherapy permitted were; 1) Etoposide 100 mg/m2 iv D1-3 and Cisplatin 75 mg/m2 iv D1 or 2) Etoposide 100 mg/m2 iv D1-3 and Cisplatin 25 mg/m2 iv D1-3. The use of granulocyte-colony stimulating factor during chemotherapy was permitted[15].

No later than 6 weeks after the last cycle of chemotherapy, patients without evidence of progressive disease on chest xray or CT scan and with no clinical evidence of brain metastases were given prophylactic cranial irradiation.

Translational research

Progress in treatment of SCLC has been hampered by limited understanding of the molecular biology of this disease. It is usually diagnosed on a small biopsy specimen or fine needle aspirate insufficient for detailed molecular studies. Consequently, existing SCLC tumour banks include relatively small series (<100 patients) of samples collected over many years from patients who are heterogeneous

with respect to stage and treatment received. The CONVERT trial provides a unique opportunity to prospectively collect a large number of biospecimens from patients of uniform (limited) stage, who are exposed to the same chemotherapy, treated with one of two radiotherapy schedules, and for whom there will be robust clinical outcome data. Although it will still be problematic to obtain large tumour biopsy specimens for many patients, advances in genomic and proteomic technology will enable studies to be performed on blood/serum samples in addition to small biopsy specimens.

All patients were asked to consent for an optional collection of tumour samples (paraffin embedded) and blood samples as part of the trial. Blood samples (for genomic and proteomic analysis) were collected at three timepoints: at baseline prior to any treatment, on day 22 of treatment and on completion of treatment.

Table 1 – Sample collection schedule

	Baseline	Day 22	End of treatment
Tissue block			
Serum	✓	✓	✓
Plasma	✓	✓	✓
Whole blood	✓		
CTC	✓		

Data collection & management

Participating centres completed the following case report forms (CRFs):

- Eligibility checklist prior to or at the time of randomisation
- Pre-treatment and tumour assessment at baseline prior to cycle 1
- Treatment forms on day 1 of each chemotherapy cycle (cycles 1-4 or 6). The data collected included performance status, protocol treatments received, toxicity and reasons for reduction/delay/omission of treatment
- Toxicity forms at the end of each cycle given, prior to next cycle and 30 days after completion of the last cycle of chemotherapy
- Radiotherapy worksheet during and after completion of radiotherapy
- Post treatment form 30 days after the last cycle of chemotherapy
- Follow-up forms at each follow-up visit commencing at 3 months post cycle 4 (or 6) visit (continuing 3 monthly until 12 months & then 6 monthly thereafter)
- Serious Adverse Event (SAE) forms were used to report all serious adverse events
- Progression/Relapse/Death forms to report the patient status

Copies of all CRFs continue to be returned to the trials centre for statistical analysis. All forms are tracked and entered into a study defined database for which consistency checking is programmed in. Data managers check for missing and invalid data using SQL queries and statistical programs. Any queries raised are returned to the centres for correction or clarification.

On completion of the study the data will be written onto CD and archived in a safe and secure location within the MAHSC-CTU. Paper copies of the CRF's will be retained at sites for at least fifteen years following the last patient entered or if all are deceased may be archived off site. All paper data will be destroyed after fifteen years on the approval of the chief investigator.

The trials centre staff are in regular contact with local centre personnel to check on progress and to help with any queries that may arise. Incoming forms are checked for completeness, consistency, timeliness and compliance with the protocol.

Sample size calculation

It is considered that a survival benefit of 12% at 2 years (in favour of once-daily radiotherapy) would be clinically significant. Using Freedman's sample size calculation based on a 2-arm trial, with a 5% significance level, 2-sided test, 80% power and hazard ratio of 0.70, a 12% overall survival benefit at 2 years from 44% with the control arm to 56% in the experimental arm, required a total of 506 patients. The number of deaths required is 247. An additional 5% was added to allow for ineligible patients giving a total of 532 patients required. An additional 15 patients were recruited (total of 547) to replace patients either randomised in error or for whom we were never able to obtain data.

Statistical analysis plan

The analysis will be based on intention-to-treat principles (ITT). Patient data will be grouped by treatment arm according to the treatment assignments made via the MAHSC-CTU randomization line. The primary data analysis is planned for January 2016.

The stratification factors include centre, performance status (0-1 versus 2) and biochemical factors (e.g. LDH, sodium, alkaline phosphatase). Comparison of data by centre will be scrutinised to identify any data inconsistencies, it will also be used to identify those centres planning to give either four or six cycles of chemotherapy. Analysis will be carried out to identify any differences between to the two schedules. Other factors have been identified in previous studies to be prognostic factors

and will be used to calculate the Manchester score which gives three groupings of good, intermediate and poor prognosis, these scores will be used to compare OS and response rate.

The only planned interim analyses have been performed for the Independent Data Monitoring Committee (IDMC). Reports have been submitted to the IDMC on an annual basis commencing 12 months after the first patient was randomised.

The following are the qualifications for analysis of time-to-event efficacy parameters:

• All randomized patients will be included in the analysis of Overall Survival (OS) and Local Progression Free Survival (ITT).

OS is the time between date of randomisation and date of death of any cause. Survivors will be censored on the last date known to be alive. Local progression-free survival (local control) will be calculated from the date of randomisation to the date of first clinical evidence of progressive disease at the primary site, or death. Kaplan-Meier curves will be drawn for each treatment group. Overall survival and local progression-free survival will be compared using the Mantel-Cox version of the log rank test.

• All randomized patients treated with at least one study dose of cisplatin and etoposide will be included in the comparison of proportions of grade 3 and 4 toxicities.

Toxicity will be assessed according to NCI Common Terminology Criteria for Adverse Events v3.0 . The proportion of patients experiencing grade of 3 or above acute toxicity, including acute and/or late radiation morbidity, will be compared between the treatment groups using Chi-squared and Fisher Exact tests. Acute toxicity will be defined as toxicities occurring from commencement to 3 months after completion of treatment; late toxicity will be defined as toxicities occurring between 3 months and 2 years after completion of treatment.

All patients treated with at least one dose of cisplatin and etoposide will be evaluated for tumour response and included in the analysis of tumour response rates. Response will be assessed according to RECIST criteria. The proportion of patients in each treatment group whose best response (up to approximately 28 days post cycle 4 or, if stopped prior to cycle 4, approximately 28 days after last chemotherapy cycle given) from randomisation is complete or partial will be compared using Chi-squared and Fisher Exact tests.

Safety analyses will be performed for all randomized patients treated with at least one dose of chemotherapy. Adverse effects will be summarized and compared between the two arms.

The relative chemotherapy and radiotherapy dose intensity (RDI) will be summarised by calculating the median, standard deviation, interquartile range and range for patients in each randomised treatment group. The RDI will be compared between the treatment groups by using the Wilcoxon Rank Sum test.

A detailed description of patient disposition will include a summary of the following:

- all patients entered and enrolled: overall, by treatment arm, and by country
- reasons for patients entered, but not enrolled
- all enrolled patients treated with study drug, by treatment arm
- reasons patients enrolled, but not treated with study drug
- reasons patients discontinued study drug treatment
- all important protocol violations.

Changes to the protocol after the start of the trial

The trial details documented here are consistent with CONVERT trial protocol V3 (dated: 10th June 2008). There were no significant changes to the protocol after the start of the trial, only minor administrative amendments and clarifications have been made during the course of the trial.

End of the trial

The trial will end once all 547 patients recruited have died or completed 5 years of trial follow-up (whichever is sooner).

ETHICS AND DISSEMINATION

Radiotherapy Quality Assurance

The trial is subject to a radiotherapy quality assurance programme, managed by the National Cancer Research Institute Radiotherapy Trials Quality Assurance Team (RTTQA). Participating centres were provided with radiotherapy planning guidelines, including an atlas of organ at risk delineation and had to pass an initial assessment before patients could be randomised into the trial and there were further assessments afterwards.

The initial assessment consisted of:

• Completion and return of a questionnaire detailing the radiotherapy facilities available to the centre.

• Return of 2 radiotherapy treatment plans for a patient with limited-stage SCLC, previously treated in the centre with radical intent, who satisfied the eligibility criteria for CONVERT, and had been re-

planned according to the CONVERT protocol for each treatment arm: 66Gy in 33 daily fractions once-daily and 45Gy in 30 fractions twice-daily.

During the trial plans were randomly requested from each centre as part of the continuing quality assurance programme and feedback was provided in case of protocol deviations. Participating centres had to agree to address uncertainties revealed by the QA programme[16].

Safety reporting

Data was collected at each trial visit regarding any SAEs (as defined by Good Clinical Practice Guidelines). All SAEs causally related to either chemotherapy or radiotherapy treatment were reported to the MAHSC-CTU and followed until they resolved or stabilised. Late radiation toxicities continue to be recorded at each follow-up visit (according to the CTCAE V3.0 grading system).

Trial monitoring & oversight

No formal on site data monitoring activities were performed as part of the CONVERT trial.

Data is reviewed annually by an Independent Data Monitoring Committee (IDMC), consisting of three clinicians not entering patients into the trial and an independent statistician. Throughout the duration of the trial the IDMC have recommended whether the accumulated data from the trial, together with results from other relevant trials, justified continuing recruitment of further patients. The IDMC have made confidential recommendations to the Trial Steering Committee (TSC).

The role of the TSC has been to act on behalf of the funder, to provide overall supervision for the trial, to ensure that it is conducted in accordance with GCP and to provide advice through its independent Chairman. This independent committee reviews the recommendations from the IDMC and decides on continuing or stopping the trial or modifying the protocol. The Trial Management Group coordinates and manages the trial's day-to-day activities. The TMG is comprised of health professionals and members of the direct study team.

Dissemination

Data from all centres will be analysed together and published as soon as possible. Individual participants may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will form the basis of the Writing Committee and advise on the nature of publications. The trial will be publicised at regional and national conferences. The final results will be presented at scientific

meetings and published in a peer-reviewed journal (authorship will be according to the journal's guidelines).

Trial status

The trial is currently in follow-up. The first patient was randomised in April 2008 and the final patient was included in November 2013.

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Competing interests

None

Ethics approval

The trial has been reviewed by NRES Committee North West – Greater Manchester Central which granted ethical approval for the study on 21st December 2007 (REC reference: 07/H1008/229).

Provenance & peer review

The study was externally peer reviewed as part of the grant application process.

Data sharing statement

Additional study information can be obtained from the CONVERT trial statistician at the MAHSC-CTU (email: linda.ashcroft@christie.nhs.uk)

Contributorship Statement

All authors meet the following ICMJE criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Appendix 1 – Details of recruiting centres

UK - Sites N = 33

- The Christie NHS Foundation Trust, Manchester (001) – Faivre-Finn
- Edinburgh Cancer Centre (002) – Price
- Bristol Haematology & Oncology Centre (004) – Wilson
- Dorset Cancer Centre, Poole (005) – Laurence
- Torbay Hospital, Devon (006) – Dorey
- Weston Park Hospital, Sheffield (007) – Hatton/Woll
- Royal Preston Hospital (008) – Appel
- Cheltenham General Hospital (010A) - Guglani
- St James Hospital, Leeds (011) – Snee
- Hammersmith Hospital, London (012) – Mangar
- University College London Hospitals (013) – Carnell
- The Beatson Cancer Centre, Glasgow (015) – Mohammed
- Glan Clwyd Hospital, North Wales (016) - Garcia
- Southampton General Hospital (017) – Bhatnagar
- Castle Hill Hospital, Hull (018) – Lind
- James Cook Hospital, Middlesbrough (021) – Peedell
- Northern Ireland Cancer Centre, Belfast City Hospital (022) – McAleese
- Royal Marsden Hospital, Surrey (024) – Locke
- Norfolk & Norwich University Hospital (029) – Roques
- Addenbrooke's Hospital, Cambridge (031) – Harden
- St Bartholomew's Hospital, London (033) - Wells
- Raigmore Hospital, Inverness (034) – Macgregor
- Bradford Royal Infirmary (035) – Snee
- Queen Elizabeth Hospital, Birmingham (036) – Chetiyawardana
- Peterborough City Hospital (037) – Fife
- Northern Centre for Cancer Care, Newcastle-upon-Tyne (040) – McMenemin
- Harrogate District NHS Foundation Trust (041) – Chan
- Derriford Hospital, Plymouth (042) – Roy
- The Clatterbridge Cancer Centre, Wirral (046) – Pope
- Charing Cross Hospital, London (048A) – Lewanski
- St Mary's Hospital, London (048B) – Lewanski/Power
- Wrexham Maelor Hospital (050) – Garcia
- Ysbyty Gwynedd, Bangor (051) – Ghosal

EORTC - Sites N = 7

- Universiteit Gent, Belgium (201) – Surmont
- Cliniques Universitaires St Luc, Brussels, Belgium (202) – Geets
- Clinique Sainte Elisabeth, Namur, Belgium (203) – Remouchamps
- The Netherlands Cancer Institute, Amsterdam (205) – Knegjens
- Arnhem S Radiotherapeutisch Institut, Arnhem, The Netherlands (208) – Tissing-Tan
- Medical University, Gdansk, Poland (209) – Jassem
- Institute of Oncology, Ljubljana, Slovenia (210) - Zwitter

SPAIN - Sites N = 6

- ICO Hospital Duran i Reynals, Barcelona (301) – Cardenal
- Hospital Universitari Germans Trias I Pujol, Barcelona (302) - Font

- University Hospital Ramon y Cajal, Madrid (303) – Hernanz
- Hospital de la Santa Creu I Sant Pau, Barcelona (311) – Majem
- Institut Oncològic of the Vallès (IOV), Barcelona (313) – Solé
- Corporació Sanitària Parc Taulí de Sabadell, Barcelona (314) – Solé

FRANCE - Sites N = 19

- Institut de Cancérologie de la Loire (401) – Fournel
- Centre Léon Bérard (CLB) (402) – Martel-Lafay
- Hôpital de la Croix-Rousse, Lyon (404) – Arpin
- CHU de Limoges (405) – Vergnenègre/Clavère
- CH de Villefranche/Saône (408) – Falchero
- Centre François Baclesse, Caen (412) – Gervais/Le Rouge
- CH de Aix en Provence (413) – Le Treut
- Institut Ste Catherine, Avignon (415) – Pourel
- CHI de Creteil (416) – Monnet/Martin
- CHU de Clermont-Ferrand (420) – Janicot
- HIA Toulon (422) – Bérard
- Institut Gustave Roussy, Villejuif (425) – Le Pechoux
- Centre Georges François Leclerc Dijon (426) – Peignaux/Coudert
- CHU de Marseille (427) – Padovani/Barlesi
- CHU de Rennes (429) – Lena
- CHU de Caen (430) – Zalcman
- CHU de Lille (432) – Lafitte
- Centre Oscar Lambret, Lille (433) – Prevost
- CH de Libourne (442) – Abdiche

CANADA - Sites N = 9

- CHUQ-Pavillon Hotel-Dieu de Quebec, Quebec City [CAGQ] (504) – Dagnault
- Cancer Centre of SE Ontario at Kingston [CAKK] (505) – de Metz
- Ottawa Regional Cancer Centre [CAKO] (506) – Pantarotto
- Princess Margaret Hospital, Toronto [CAMP] (507) – Bezjak
- Allan Blair Cancer Centre, Regina [CASA] (508) – Koul
- Saskatoon Cancer Centre [CASS] (509) - Kundapur
- Cancer Care Manitoba [CARM] (513) – Leylek
- Juravinski Cancer Centre [CALM] (514) – Okawara
- London Regional Cancer Program [CANL] (515) – Yaremko

Appendix 2 – Patient Information Sheet (Version 3.0, 10th June 2008)

Title of the research protocol:

CONVERT (Concurrent ONce-daily VErsus twice-daily RadioTherapy)
A 2-arm randomised controlled trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited stage small cell lung cancer (SCLC) and good performance status

PART 1

Invitation to participate in the study

You are being invited to take part in a research study. Before you decide if you want to take part, it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and if you wish, discuss it with friends, relatives and your General Practitioner. Ask us if there is anything that is not clear or if you would like more information. It is important to take time to understand this information and decide whether or not you wish to take part.

Why is this research taking place?

Your type of lung cancer can be treated with a combination of chemotherapy drugs and chest radiation therapy, called concurrent chemoradiotherapy treatment. Doctors agree that combining radiotherapy and chemotherapy improves the outcome of treatment, but some questions remain unanswered about the best way to combine radiotherapy with chemotherapy. The optimal dose, duration and number of daily fractions of radiotherapy are still to be defined.

What is the purpose of this research study?

The purpose of this research study is to find out:

- What is the best total dose of radiotherapy to prescribe for small cell lung cancer
- What is the most effective way of giving the radiotherapy? Is it once or twice a day?

Why have I been chosen?

You have recently been diagnosed with small-cell lung cancer and your doctor has recommended chemotherapy and radiotherapy treatment. Your doctor feels that you are suitable to take part in this trial. This is a research study, and other patients similar to you are also being asked if they would be willing to take part. In total approximately 530 patients will take part.

Do I have to take part?

You do not have to take part in this research, your doctor will continue to treat you whatever you decide. However, if you decide to take part you will be asked to sign a consent form. You will be given a copy of this to keep, together with this information sheet. It is routine for your GP to be kept informed about your treatment, so your GP will be told if you are taking part in this research.
If you agree to join you will still be able to withdraw at any time without giving a reason. If you withdraw from the study this will not affect the standard of care you receive.

What will happen to me if I take part?

If you agree to take part, you will be asked to sign a consent form and your doctor will organise a number of tests to check if you are eligible for this study. The tests will include a physical

examination, a chest X-ray, a CT scan of the brain, thorax and upper abdomen, a radiotherapy planning scan, blood tests and lung function tests. These tests are normally done as part of the routine tests for patients who are to be treated with concurrent chemoradiotherapy. Some patients may also require a bone scan or a pregnancy test.

If you are eligible you will be randomly allocated to once or twice-daily radiotherapy. This is done by a computer, you or your doctor cannot choose the treatment.

Once you have started the treatment you will be assessed weekly for any changes in your symptoms, any side effects of treatment and any changes in your blood tests. A CT scan will be repeated after chemoradiotherapy, then 6 and 12 months after the date you enrolled in the study.

After completing treatment, you will be reviewed weekly until any side effects have resolved then 3 monthly until 1 year and 6 monthly thereafter. Follow up visits at more frequent intervals will be decided by your doctor.

Summary of visits:

	BEFORE TREATMENT	CYCLE 1 CHEMOTHERAPY	ADDITIONAL CYCLES	END OF TREATMENT	FOLLOW-UP
Informed Consent	X				
Physical Examination	X	X	X	X	X
CT Planning Scan	X				
Blood tests	X	X	X	X	X
Kidney function	X	X	X		
Chest Xray		X	Prior to cycle 3,5		X
Electrocardiogram (ECG)	X				

Blood and tissue samples for research

You will also be asked to consent to storage of tissue and blood samples for use now and in the future for research aiming to improve knowledge and treatment of small cell lung cancer. Consent to the storage of samples is optional, so if you prefer not to consent to this you may still take part in the research. If you consent to collection of tissue and blood samples for storage these will be taken as follows:

1. You will be asked to **donate tissue** left over from the biopsy (biopsies) or operation(s) performed as part of your routine clinical care. No additional procedure(s) will be necessary.
2. You will be asked to **donate blood** before you start treatment (day 1), on day 22 of treatment and when treatment is completed. The amount of blood taken will be 10 - 30mls (two to six teaspoons) each time. Every effort will be made to take the blood samples at the same time as your routine blood tests are taken. The extra blood samples will not increase the amount of time you spend in the hospital.

What do I have to do?

You will be expected, if you take part in the study, to attend the scheduled visits.

What are the treatments that are being tested?

The treatment being tested is the radiotherapy. The trial is to compare a short course of radiotherapy given twice a day with a longer course given once a day.

- **Short course radiotherapy**

Radiotherapy treatment will be delivered twice a day, Monday to Friday (excluding weekends) for three weeks. There will be an interval of 6 to 8 hours between each treatment, for example treatment will be given at 09.00hrs and 15.00hrs.

- **Long course radiotherapy**

Radiotherapy treatment will be delivered once a day, Monday to Friday (excluding weekends) for six and a half weeks.

- **Chemotherapy**

The chemotherapy (cisplatin and etoposide) treatment you will receive is standard. It will be administered by a drip for 3 consecutive days every 3 weeks for a total of 4 to 6 cycles. The way the chemotherapy is administered and the number of chemotherapy cycles that you receive will be decided by the doctor in charge of your treatment. The first course of chemotherapy will be given 3 weeks before the start of the radiotherapy treatment.

If you receive short course radiotherapy the second cycle of chemotherapy will be administered during the first 3 days of the radiotherapy treatment and subsequent cycles will be administered after completion of the combined treatment.

If you receive long course radiotherapy, the second, third and fourth cycles of chemotherapy will be administered during the weeks when you are receiving radiotherapy treatment, and subsequent cycles will be administered after completion of the combined treatment.

The radiotherapy treatment will take around 15 minutes each time. Your doctor will discuss the length of time that the chemotherapy takes to administer.

After chemotherapy and radiotherapy to your chest have been completed you may be offered a short course of radiotherapy to your brain. This is to prevent cancer developing in your brain, as this type of lung cancer can sometimes spread to the brain. If your doctor thinks this would be appropriate for you he/she will explain more about the treatment and any possible side effects.

What are the alternatives for treatment?

If you do not wish to take part in this study your doctor will tell you what alternatives are available. The alternative treatment will vary depending on your lung cancer doctor.

What are the potential risks and side effects of taking part?

You **may** experience some of the following side effects during treatment. These are usually temporary. It is important to tell your hospital doctor about any side effects so they can be monitored and, where possible, treated.

The side effects are similar with both treatments, and will vary from person to person. It is possible you will experience very few of these side effects however staff will be able to advise you if any side effects become problematic. Prior to starting this research study a smaller study of the same treatments was carried out and patients in that study did not experience any major toxicities leading to long term side effects.

Common chemotherapy side effects :

- **Kidney function**: Because cisplatin can affect your kidneys, it is important to drink plenty of fluids (at least 8 cups) the day before and for a few days after chemotherapy. We may ask you to bring in a 24-hour urine collection to monitor your kidney function.
- **Extravasation** is when chemotherapy leaks outside the vein. If you develop redness, soreness or pain at the injection site **at any time** please let us know straightaway.
- **Bone marrow suppression.** Your bone marrow is where your blood cells are made (these are the red cells, white cells and platelets) to replace those naturally worn out within the body. Chemotherapy interferes with this process and the number of cells in your blood can become low. This means that following treatment you could become:

Prone to infection: Your white cells can become low, this is most common the week after treatment. You may develop a sore throat, cough, fever, shivering or other symptoms which may be due to infection. A normal temperature is between 36°C and 37°C. If your temperature is above 37.5°C, contact this hospital straightaway without delay. Minor infections can become serious over a matter of hours.

Anaemic: If your red cells become low you may experience excessive tiredness, feel dizzy, breathless and/or look pale.

Prone to bleeding: If your platelets become low, you may get nose-bleeds, bruising or bleeding gums.

You will have a routine blood test before each treatment to monitor the effects of the chemotherapy**, BUT please contact this hospital if you experience any of the symptoms listed above.**

- **Hair Loss.** Hair loss is usually total. The hair falls out gradually 10 to 14 days following your first course of treatment. The time scale varies from person to person. Please remember that this is a temporary side effect and your hair will grow back when you treatment is completed.
- **Nausea and vomiting (sickness).** The severity of this varies from person to person. Anti-sickness medication will be given along with your chemotherapy to prevent this. You will also be given anti-sickness tablets to take at home. Occasionally your anti-sickness medication may need to be changed or increased and you may need extra fluid through a drip.
- **Lethargy (fatigue).** Some chemotherapy may make you feel tired and lacking in energy.
- **Strange taste.** Occasionally during treatment you may experience a strange taste, sometimes described as metallic or bitter.
- **Tinnitus & high frequency hearing loss.** You may develop tinnitus (ringing in the ears), this sensation should subside when your treatment finishes. High frequency hearing loss can also occur with this chemotherapy, this may be permanent.
- **Tingling & numbness in the fingers or toes.** Usually only mild and temporary. Please report these symptoms to your doctor on your next hospital visit. On rare occasions, this may be permanent.
- **Upset bowels.** You may get upset bowels with this chemotherapy:

***Diarrhoea*.** If this becomes a problem while you are having treatment, anti-diarrhoea tablets can be prescribed for a temporary period until this is resolved.

***Constipation*.** This occasionally occurs in the long-term. Try to drink plenty of fluids and eat foods high in fibre. Tell your doctor who may prescribe a suitable laxative.

- **Sore mouth.** You may develop a sore mouth during your treatment but this can often be prevented by doing regular mouth washes.
- **Loss of Appetite.** Loss of appetite is a common side effect. You should take plenty of fluids and try to ensure that you take in enough calories. Your doctor or nurse can advise on dietary supplements if needed.
- **Contraception & Fertility.** If you are fertile, you should use effective **contraception** while on chemotherapy. Effective contraception means one of the following methods:

For female patients:

1. Tubal ligation
2. Physician documented placement of an intra-uterine device (IUD)
3. Diaphragm with spermicidal foam/gel/film/cream/pessary
4. Condom with spermicidal foam/gel/film/cream/pessary
5. Male partner who has had a vasectomy
6. Hormonal contraceptives

For male patients:

1. Use of condom.
2. In addition to a condom: male subjects without a vasectomy must ensure that their female partner uses another form of contraception such as an IUD, spermicidal foam/gel/film/cream/suppository, diaphragm with spermicide, oral contraceptive, injectable progesterone, subdermal implant or a tubal ligation if the female partner could become pregnant from the time of the first dose of trial medication until completion of follow-up procedures.
3. The female partner would not be required to use another form of contraception if they are of non-childbearing age.

If you suspect that you may be pregnant please tell your doctor immediately. Chemotherapy may also affect your **ability to have children** in the future.

Common radiotherapy side effects

Acute side effects are temporary and affect all patients. They will vary depending on the volume of normal tissue which is being treated and your general fitness.

The early side effects of concurrent chemo-radiotherapy may include:

- **Some pain in the chest** in the 24 hours after the first treatment. This is usually mild and settles down fairly quickly.
- **Increase in your cough and sputum (spit)** which may contain a little blood. Don't worry, this is quite normal. If you are having difficulties with this during treatment, let your doctor know. Coughs can sometimes worsen when treatment finishes.
- **Tiredness.** Tiredness related to radiotherapy varies a lot from person to person.
- **Difficulty in Swallowing.** Inflammation of the gullet (oesophagitis) can cause discomfort when swallowing (dysphagia). Your doctor can prescribe medicines to alleviate this symptom

and the hospital dietician can advise about modifications to your diet and supplements. You should concentrate on maintaining a good fluid intake.

- **Shortness of Breath.** Inflammation of lung tissue (pneumonitis) can cause a dry cough and a degree of breathlessness during or shortly after radiotherapy. A variant of this side effect can cause troublesome breathlessness about six weeks after radiotherapy is completed. This side effect is usually treated with a course of steroid tablets.
- **Skin Rash.** Skin reaction can be caused by radiotherapy treatment, similar to sunburn. On rare occasions a cream may be needed.

These side effects tend to build up during treatment and are at their worst in the last week of treatment or in the first 2 weeks after treatment is completed. They then recover 3-6 weeks after treatment.

The late side effects of concurrent chemo-radiotherapy may include:

- **Difficulty in Swallowing.** Narrowing of the gullet may require a minor operation to stretch the gullet (dilatation) or in rare cases surgery. If you experience swallowing difficulties months after completion of the combined treatment further investigations (gastroscopy – tube into the stomach) may be necessary.
- **Shortness of Breath.** Damage to the normal lung tissue may occur from radiotherapy. This can result in shortness of breath and increased risk of infections. Radiotherapy may leave the lung with some scarring (fibrosis). This can mean that your lung does not work quite as well as it did before, and you may notice a slight increase in breathlessness.
- **Rare late side effects**. They include thinning of the ribs (following a severe cough, this can result in chest pain and/or minor rib fracture) and injury of the spinal cord (in extremely rare cases). An injury to the spinal cord can cause permanent difficulties in walking and loss of sensation in the lower body. Every effort is made to carefully plan your treatment so as to avoid this problem.

The risk of these late side effects is generally small as the treatment is planned carefully to try to avoid them. If you do have late side effects they will become noticeable 6-18 months after radiotherapy is completed and are generally permanent.

Other possible risks of taking part

Risks of blood tests: in most cases taking blood does not cause any problems, however there is a risk of some bleeding, bruising, discomfort, dizziness, infections and/or pain at the site where the blood is taken.

Risks of scans: in addition to radiotherapy you will be exposed to some radiation as a result of X-rays and CT scans. There is a small chance that being exposed to radiation could result in the development of a cancer several years later, but the actual risk is very small compared with the benefits of diagnosing and treating your existing cancer.

What are the possible benefits of taking part?

We hope that both treatments will help you. However this cannot be guaranteed. The information we get from this study will help us to treat future patients with the same disease better.

Who can I contact for further information?

[INSERT DETAILS OF ONE OR MORE CENTRE CONTACTS]

If you have any concerns with your treatment and need to contact someone out of hours (after 5pm and before 9 am) please contact ***[INSERT DETAILS OF CENTRE CONTACT OUT OF HOURS]***

This completes Part 1 of the information sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

PART 2

What if relevant new information becomes available?
Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If it happens your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your doctor will make arrangements for your care to continue. If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

What will happen if I don't want to carry on with the study?
You can withdraw from the study at any time. If you withdraw from the study, you will be able to choose either:

- To allow us to use samples and information collected up to the time of withdrawal and to continue obtaining information from your health records so that we can record what has happened to you since you withdrew from the study **OR**
- You can request that we destroy all your identifiable samples and/or that we do not collect any further information from your health records.

What if something goes wrong?
The study is being performed by your doctor and insurance against injury will be provided against the hospital that is looking after you. If you are harmed due to someone's negligence, then you will have grounds for legal action but you will have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms will be available to you. By signing a consent form you are NOT waiving any of your legal rights.

Confidentiality
If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons involved in the research. The ethics committee that approved this study and regulatory authorities may also ask for access to your records. All will have a duty of confidentiality to you as a research participant.

What will happen to any samples I give?
We are intending to carry out analysis on any blood samples and tissue that you donate. These samples will be used for research to determine groups of patient more likely to respond to treatment or more likely to develop side effects to treatment. The samples may be shared with other research groups who have the same field of interest in the UK or outside the UK. All blood samples or tissue collected will be stored anonymously.
All information which is collected will be kept strictly confidential. Procedures for handling, processing, storage and destruction of data will be compliant with the Data Protection Act 1998.

Only the Chief Investigator (Dr Corinne Faivre-Finn, Christie Hospital, Manchester, UK) and personnel authorised by the Chief Investigator will have access to break the study codes and identify the donors of the samples. Any unused samples will be retained indefinitely for use in future projects designed to identify genes and proteins that are involved in small cell cancer; and genes and proteins that predict for benefits or side effects of treatment. Samples may be transferred within or outside the UK to collaborators in other academic or commercial research settings. Nothing that could reveal your identity will be disclosed to collaborators elsewhere.

You may choose to participate in the study but not to have your blood or tissue stored for research purposes. If you choose to donate blood or tissue you have the right to have the sample(s) destroyed at any time by contacting your study doctor. If you decide to have your sample(s) destroyed, any analysis done and data gathered before the request cannot be removed, however no additional analysis will be done on your samples and the rest of your remaining samples will be destroyed.

Will any genetic tests be done?

Genetic analyses will be performed to study the genetic influences on small cell cancer and so the results will not affect you directly. No clinical genetic tests will be done for specific known inherited diseases.

What will happen to the results of the research study?

Independent experts will review the progress of the research, and the results will be published in a respected medical journal. The results will help to decide how to treat small-cell lung cancer in the future. Studies like this are often used in cancer research.

Who is organising and funding the research?

The CONVERT study is being funded by Cancer Research UK and sponsored by the Christie Hospital NHS Foundation Trust.

Who has reviewed the study?

The CONVERT study was given a favourable ethical opinion for conduct in the NHS by the Central Manchester Research Ethics Committee.

Thank you for taking time to read this information sheet.

You will be given a copy of the information sheet and a signed consent form to keep if you decide to take part in the study.

Appendix 3 – Informed Consent Form (Version 3.0, 10th June 2008)

Title of Project:
CONVERT (Concurrent ONce-daily VErsus twice-daily RadioTherapy)
A 2-arm randomised controlled trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited stage small cell lung cancer (SCLC) and good performance status

Name of the researcher: [INSERT PI NAME HERE]

	Please initial box
1. I confirm that I have read and understand the information sheet dated 10JUN2008 (version 3.0) for the above study. I have had the opportunity to consider the information, ask questions and had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or authorised study personnel, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4. I agree to my GP being informed of my participation in the study and of any clinically significant information that arises.	☐
5. I agree to take part in the above study.	☐
6. I agree to give for this project: ▪ tissue samples YES / NO (delete as applicable) ▪ blood samples YES / NO (delete as applicable) I understand how the sample(s) will be collected, that gifting samples for this research is voluntary and that I am free to withdraw my approval for use of the samples at any time without giving a reason and without my medical treatment or legal rights being affected.	☐
7. I agree that any sample(s) I have gifted, and anonymous information gathered about me, can be stored at the Christie Hospital and Paterson Institute for Cancer Research, Manchester, UK for possible use in future projects, as described in the information sheet. I understand that some of these projects may be carried out by researchers other than the CONVERT research team, including researchers working for commercial companies and elsewhere within and outside the European Union (EU). I consent to export of anonymised data and tissue samples within and outside the EU, and to the use of the samples for future, ethically approved, research.	☐

8. I understand that I will not benefit financially if this research leads to the development of a new treatment or medical test. ☐

9. I understand that the planned and future research using any sample(s) I have gifted may include genetic research aimed at understanding the genetic influences on lung cancer, but that the results of these investigations are unlikely to have any implications for me personally. ☐

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

Distribution: 1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 4 – Radiotherapy procedures

THORACIC RADIOTHERAPY

Thoracic radiotherapy should start 21 days after day 1 of the first cycle of chemotherapy (day 22). A delay with the administration of the second cycle of chemotherapy **should not delay** the start of radiotherapy

General radiotherapy details

Patients should be treated on a linear accelerator operating at 4-10 MV. The total dose of radiotherapy will be:

- BD arm: 45 Gy in 30 twice-daily fractions of 1.5 Gy
- OD arm: 66 Gy in 33 daily fractions of 2 Gy

The total dose is prescribed at the ICRU reference point and given according to the recommendations of the EORTC radiotherapy group (25) and ICRU 50 (26). Treatment will be planned with inhomogeneity corrections. IMRT will be permitted for the centres routinely using it for the treatment of lung cancer.

Radiation Quality Assurance:

The radiotherapy quality assurance program will be run by the Mount Vernon Hospital QA team. Planning information, copies of portal images (digital print-outs are acceptable) and dose distribution, including Dose Volume Histogram (DVH), with a copy of the treatment prescription should be available for central review. Details of radiotherapy practice will be established by completion of a questionnaire.

Treatment machine beam output data on the linear accelerators used to treat patients in the trial should have been audited by a recognised ASTRO/ESTRO or UK quality assurance programme within 12 months of the first patient in the centre entering the trial, and be rechecked at least once every 18 months

We recommend that daily verifications should be done with open orthogonal images incorporating stable anatomical structures such as the spine for the first 3 days of treatment followed by weekly verifications. If available cone beam imaging can be used as an alternative to open orthogonal images. The orthogonal images will be checked by a senior radiographer and if possible reviewed by a qualified radiation oncologist, and compared with either the digitally reconstructed images or simulator images. The correction decision will be left to local policy. Differences of less than 0.5 cm from the initial images will be allowed. We suggest that if the difference is more than 0.5 cm the orthogonal images will be repeated prior to patient's treatment. The Radiotherapy Quality Assurance Group will approve and monitor each centre's procedures.

Patient treatment position:

Supine, with arms above head. Immobilisation using chest board and fixed arm position. The patient should be breathing normally.

Patient data acquisition:

A planning CT scan should be performed in the treatment position, whilst the patient undertakes a normal respiration, using 5 mm slices or less through the entire target volume. The whole thorax (cricoid to L2) should be covered using at least 1 cm slices to allow dose-volume histograms to be calculated for the lung, heart and the oesophagus.

Radiotherapy should be started within 3 weeks of planning.

Planning target volume (PTV)

The CT data will be transferred to the planning system.

The GTV (gross tumour volume) will be contoured by a qualified radiation oncologist specialised in thoracic malignancies. The contouring should be carried out using the mediastinal and the lung windows. The GTV is defined as identifiable tumour and involved lymph nodes (nodal involvement on CT scan is defined as nodes $\geq$ 1 cm in short axis). If PET scan is available for staging, the GTV should include PET positive lymph nodes.

The CTV (clinical target volume) comprises the GTV with a 0.5 cm margin of radiologically normal tissue in all directions. It will take into account microscopic spread. Manual adjustment of CTV is permitted to reduce dose to the spinal cord for example, when disease is adjacent to a structure such as a vertebra but is not thought to invade the structure

The PTV comprises the CTV with a 1 cm margin superiorly and inferiorly, and 0.8 cm margin laterally, at the 95% isodose. The CTV to PTV expansion should not be reduced as it is allowing for set up errors and organ motion.
Prophylactic nodal irradiation should not be employed.
Field reductions will not be allowed.

Treatment planning
Use of 3D conformal technique is required and beam's eye views may be useful in the design of individual shielding. Dose volume histograms (DVH) for the PTV, normal lung, oesophagus, spinal cord and heart will be calculated in order to obtain full knowledge of the 3D dose distribution.

Dose specification and fractionation:
The dose will be specified at the ICRU reference point and fully corrected for heterogeneity. The dose distribution within the PTV should ideally be within $\pm$ 5% of the prescribed dose, and no more than $\pm$ 7% of the prescribed dose.

Definition of the organs at risk
The spinal cord, lungs, oesophagus and heart will be contoured for dose-volume histograms.

Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated lung should be contoured.
The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV.
The oesophagus will be contoured using mediastinal windowing on CTscan to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The oesophagus should be fully contoured (from cricoid cartilage to the gastro-oesophageal junction).
The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the superior aspect of the left atrium and extend inferiorly to the apex of the heart.

Beams
Isocentric treatment technique.
The number of beams will vary according to the position and the volume of the PTV in the thorax and to the maximum dose tolerated by the organs at risk.
The treatment plan will be checked by a qualified radiation oncologist after discussion with the planning team. The dose-volume histogram will help to guide that choice.

Set-up verification
Cone beam or orthogonal images will be obtained on days 1 to 3 (or 2 to 4) and weekly thereafter.

TWICE-DAILY THORACIC RADIOTHERAPY

Schedule

45 Gy in **30 twice-daily fractions** over a period of **19 days** (radiotherapy to start on a Monday)**,** 5 consecutive days a week

- The optimal overall treatment time should be 19 days, up to 21 days is a protocol deviation and should be recorded, above 21 days is a protocol violation.
- The interfraction interval will be 6 to 8 hours.
- Using conformal radiotherapy and 4 to 10 MV photons emitted from linear accelerators.
- Thoracic radiotherapy will start on cycle 1 day 22, if possible concurrently with the second cycle of chemotherapy (within 24 hours of day 1, cycle 2 of PE).
- Concurrent chemotherapy will be administered during the intervals between the 2 daily radiotherapy fractions.

Normal tissue constraints

To reduce late damages to the normal tissues the following rules will be applied

- Dose: **1.5 Gy** per fraction
- Maximum spinal cord dose will not exceed **42 Gy.** The spinal cord position must be identified throughout the PTV
- The percentage of lung minus PTV receiving more than 20 Gy will not exceed **35%** (V20=35%, based on dose-volume histograms). The mean lung dose will be recorded
- The heart can receive the total dose (TD) to < 30% of its volume. For > 50% of cardiac volume, dose < 50% of TD is recommended

Treatment Delays

Every effort should be made to deliver the prescribed dose of radiotherapy in 19 days.

If unavoidable delays occur, that could increase the overall treatment time beyond 19 days, e.g. due to machine breakdown, compensation should if possible be made by one of the following mechanisms:

- treating on a weekend day, ***or***
- adjusting fraction size to deliver the total prescribed dose within 19 days;

However, fraction size should remain < 2.25 Gy

If the radiation schedule is interrupted for more than 1 week due to intercurrent illness consideration should be given to discontinuing treatment. Further treatment will depend upon the clinical situation and is at the discretion of the responsible clinician. Interruptions for < 1 week due to intercurrent illness or radiation toxicity will be recorded and treatment should be completed as planned.

HIGH DOSE ONCE-DAILY THORACIC RADIOTHERAPY

Schedule

66 Gy in **33 daily fractions** over a period of **45 days** (radiotherapy to start on a Monday)**,** 5 consecutive days a week

- The optimal overall treatment time should be 45 days. Up to 47 days is a protocol deviation and should be recorded, above 47 days is a protocol violation.
- Using conformal radiotherapy and 4 to 10 MV photons emitted from linear accelerators.
- Thoracic radiotherapy will start on cycle 1 day 22, if possible concurrently with the second cycle of chemotherapy (within 24 hours of day 1, cycle 2 of PE).

Normal tissue constraints

To reduce late damages to the normal tissues the following rules will be applied

- Dose: **2 Gy** per fraction
- Maximum spinal cord dose will not exceed **48 Gy.** The spinal cord position must be identified throughout the PTV
- The percentage of lung minus PTV receiving more than 20 Gy will not exceed **35%** (V20=35%, based on dose-volume histograms). The mean lung dose will be recorded.
- The heart can receive the total dose (TD) to < 30% of its volume. For > 50% of cardiac volume, dose < 50% of TD is recommended

Treatment Delays

Every effort should be made to deliver the prescribed dose of radiotherapy in 45 days.

If unavoidable delays occur, that could increase the overall treatment time beyond 45 days, e.g. due to machine breakdown, compensation should if possible be made by one of the following mechanisms:

- giving two fractions on a subsequent day, with a minimum interval of six hours between fractions, ***or***
- treating on a weekend day, ***or***
- adjusting fraction size to deliver the total prescribed dose within 45 days;

However, fraction size should remain < 3 Gy.

If the radiation schedule is interrupted for more than 1 week due to intercurrent illness consideration should be given to discontinuing treatment. Further treatment will depend upon the clinical situation and is at the discretion of the responsible clinician. Interruptions for < 1 week due to intercurrent illness or radiation toxicity will be recorded and treatment should be completed as planned.

PROPHYLACTIC CRANIAL IRRADIATION

No later than 6 weeks after the last cycle of chemotherapy, patients without evidence of progressive disease on CXR or CT scan and with no clinical evidence of brain metastases will be given PCI.

Simulation is mandatory for whole brain irradiation. Patients should be treated in supine position. Immobilisation by individual masks or other means is recommended. Treatment will be delivered with megavoltage machines of energies ranging from 4-10 MV photons. Treatment with a single beam is not acceptable. Doses are specified at the mid-plane of two opposed lateral whole brain fields, prescribed to the isocenter. The dose and fractionation of PCI will be left to the discretion of each principal investigator to allow for variation in local practice.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

*Protocol for the CONVERT trial - **C**oncurrent **ON**ce-daily **VE**rsus twice-daily **R**adio**T**herapy: An international 2-arm randomised controlled trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited stage small cell lung cancer (LS-SCLC) and good performance status.*

Section/item	Item No	Description	
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	☑
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	☑
	2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	3	Date and version identifier	10th June 2008 V3.0
Funding	4	Sources and types of financial, material, and other support	☑
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	☑
	5b	Name and contact information for the trial sponsor	☑
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	☑
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	☑

	6b	Explanation for choice of comparators	☑
Objectives	7	Specific objectives or hypotheses	☑
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	☑
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	☑
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	☑
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	☑
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	☑
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	☑
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	☑
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	☑
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	☑
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	☑
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	☑
Methods: Assignment of interventions (for controlled trials)			

Allocation:			☑
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	☑
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	☑
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	☑
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	No blinding
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	No blinding
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	☑
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	☑
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	☑
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	☑
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	☑

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	☑
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	☑
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	☑
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	☑
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	☑
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	☑
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	☑
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	☑
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	☑
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	☑
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	☑
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	☑
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	☑

Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	☑
	31b	Authorship eligibility guidelines and any intended use of professional writers	☑
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	☑
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	☑
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	☑

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Protocol for the CONVERT trial - Concurrent ONce-daily VErsus twice-daily RadioTherapy: An international 2-arm randomised controlled trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited stage small cell lung cancer (LS-SCLC) and good performance status.

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Protocol for the CONVERT trial - **C**oncurrent **ON**ce-daily **VE**rsus twice-daily **R**adio**T**herapy: An international 2-arm randomised controlled trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited stage small cell lung cancer (LS-SCLC) and good performance status.

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ABSTRACT

Introduction

CONVERT is the only multicentre, international, randomised, phase III trial open in Europe and Canada looking at optimisation of chemoradiotherapy in LS-SCLC. Following on from the Turrisi trial of once-daily (OD) versus twice-daily (BD) concurrent chemoradiotherapy , there is a real need for a new phase III trial using modern conformal radiotherapy techniques and investigating higher once-daily radiation dose. This trial has the potential to define a new standard chemoradiotherapy regimen for patients with LS-SCLC and good performance status.

Methods & analysis

547 patients with histologically or cytologically proven diagnosis of SCLC were recruited from 74 centres in 8 countries between 2008-2013. Patients were randomised to receive either concurrent BD radiotherapy (45Gy in 30 BD fractions over 3 weeks) or concurrent OD radiotherapy (66Gy in 33 OD fractions over 6.5 weeks,) both starting on day 22 of cycle 1. Patients are followed up until death. The primary endpoint of the study is overall survival and secondary end points include local progression-free survival, metastasis-free survival, acute and late toxicity based on the Common Terminology Criteria for Adverse Events version 3.0, chemotherapy and radiotherapy dose intensity.

Ethics & dissemination

The trial received ethical approval from NRES Committee North West – Greater Manchester Central (07/H1008/229). There is a trial steering committee, including independent members, and an independent data monitoring committee. Results will be published in a peer-reviewed journal and presented at international conferences.

Trial registration number ISRCTN91927162

Summary of strengths and limitations of study

- Adequately powered multicentre, randomised controlled trial aiming to establish a standard chemo-radiotherapy regime in LS-SCLC.
- All patients are treated with modern radiotherapy. This trial uses and reflects the important developments in modern conformal radiotherapy techniques which have taken place in the last 20 years.

- Elderly patients are not excluded. Inclusion/ exclusion criteria are based on good performance status with no upper age restriction.

INTRODUCTION

Of the 42,000 patients diagnosed with lung cancer each year in Britain, 15% will have small cell lung cancer (SCLC) and 30% of those patients will have limited stage (LS) disease that can be encompassed within a tolerable radiation therapy field. Even in this early stage disease the outcome is poor, with a median survival of 16 to 24 months with current forms of treatment[1-3]. Combining chemotherapy and thoracic radiotherapy is the standard treatment for LS-SCLC. Two meta-analyses have shown that radiotherapy associated with chemotherapy improves median survival, 3 year survival rate and local control[4 5]. Subsequently, meta-analyses of trials investigating the optimal timing and sequencing of chemo-radiotherapy have shown that the best results have been reported with early concurrent thoracic radiotherapy[6-9]. Furthermore it has been demonstrated that twice-daily radiotherapy is superior to once-daily radiotherapy in the landmark Turrisi study[3]. Patients were randomised to either 45 Gy once-daily (1.8 Gy per fraction) over 5 weeks or 45 Gy given twice-daily (1.5 Gy per fraction) over 3 weeks. In both arms radiotherapy was given concurrently starting with the first cycle of chemotherapy (cisplatin and etoposide). Twice-daily RT improved 5-year OS (26% vs. 16% in the once-daily arm), reduced the risk of thoracic relapse (52% compared with 36% in the twice-daily arm) but at the cost of increased grade 3 radiation oesophagitis (defined as inability to swallow more than liquids or to require hospitalisation). However, there were no other significant differences in acute toxicity between the 2 arms and no long-term oesophageal strictures were reported. Consequently twice-daily radiotherapy concurrently with chemotherapy is accepted as a standard regime in LS-SCLC[10]. It is however unclear whether the better results in the twice-daily arm are explained by the increase in the biologically equivalent dose of radiation in the twice-daily arm or by the use of altered fractionation leading to a shorter overall treatment time. Indeed the control dose was considered to be quite low, for example in comparison with the NCI Canada regime of 40 Gy in 15 daily fractions[1]. Moreover since the Turrisi trial was designed in the late 1980s, important progress has been made in radiotherapy techniques. The radiotherapy used in any contemporary trial should be CT-planned conformal treatment with individual field shaping careful dose calculation using modern planning algorithms of target and organs at risk, with image guidance, correction of set-up errors, and allowance made for the effects of respiratory motion on the position of the target volume. None of these were routine from 1989-1992 when the Turrisi trial was carried out. The use of 3 dimensional RT/Intensity Modulated radiotherapy and the omission of elective nodal irradiation are likely to result in lower rates of toxicity, particularly oesophagitis. Further studies by Choi et al[11] using once-daily (OD) radiotherapy and Komaki et al[12] using a concomitant boost technique have suggested that doses of 70Gy over 7 weeks and 61.8 Gy over 5 weeks respectively are possible, the former being delivered with 5 cycles of full dose chemotherapy.

There is therefore a need to improve on the current survival results and a strong rationale to compare twice-daily with a higher dose of radiation delivered once-daily.

In view of the lack of data in the literature addressing the question of the dose and fractionation for LS-SCLC, we carried out a randomised phase III trial to establish a standard chemo-radiotherapy regimen for LS-SCLC with good performance status (CONVERT). At the time the trial was being developed in 2006-7, there were no international trials for this group of patients, thus an opportunity existed to set up a global trial to answer this important question. The results of the trial will be crucial in determining the best international standard treatment for routine clinical use in the treatment of patients with limited-stage SCLC and good performance status. In addition the translational studies carried out in parallel to CONVERT will indicate the hypotheses which need testing in the next generation of trials in this disease.

METHODS AND ANALYSIS

The CONVERT trial is an international, multicentre, prospective, non-blinded, superiority randomised controlled trial. The trial is sponsored by The Christie NHS Foundation Trust and coordinated by the Manchester Academic Health Science Centre Trial Co-ordination Unit (MAHSC-CTU) based at The Christie NHS Foundation Trust. The trial is registered on the International Standardised Randomised Controlled Trial Registry (ISRCTN91927162) and funded by Cancer Research UK's Clinical Trials Awards & Advisory Committee (CTAAC). The study is included in the NIHR Clinical Research Network portfolio (ID: 3823). The trial is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP).

The primary research question is to establish whether the results of twice-daily chemo-radiotherapy for patients with LS-SCLC and good performance status can be improved upon, by delivering a higher dose of radiotherapy once-daily concurrently with chemotherapy. We will compare survival of patients treated with standard chemotherapy (cisplatin & etoposide) and either twice-daily radiotherapy or high dose once-daily radiotherapy.

The secondary research questions will compare the following factors between the groups receiving either once or twice-daily radiotherapy:

*Local progression free survival

*Metastasis free survival

* Acute and late toxicity based on the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v3.0)[13]

*Chemotherapy dose intensity

*Radiotherapy dose intensity

Setting

547 patients with a histological or cytological proven diagnosis of SCLC were recruited from 74 centres in 8 countries between April 2008 and November 2013 (see online supplementary appendix 1 for details of recruiting centres).

Patients were randomised to receive either concurrent twice-daily (BD) radiotherapy (45Gy in 30 twice-daily fractions over 3 weeks, 5 days per week, starting on day 22 of cycle 1) or concurrent once-daily (OD) radiotherapy (66Gy in 33 daily fractions over 6.5 weeks, 5 days per week, starting on day 22 of cycle 1). Patients are followed up until death. The study flow diagram is shown in figure 1.

Figure 1 – Trial Schema / Flowchart

Participant screening & selection

All LS-SCLC patients with good performance status and suitable for concurrent chemo-radiotherapy were identified as potential trial candidates. Eligible patients invited to participate were provided with a patient information sheet (see online supplementary appendix 2).

Inclusion & exclusion criteria

Patients were eligible for the trial if all of the following criteria were met:

a) Either sex, age ≥18 years

b) Performance status (PS) Eastern Cooperative Oncology Group grade 0-1. Patients with PS 2 whose general condition is explained by obstructive/bulky disease likely to improve after the first cycle of chemotherapy can be included at the discretion of the local investigator. Patients with PS 2 as a result of comorbid conditions will be excluded.

c) Histologically or cytologically confirmed SCLC

d) No patients with mixed small-cell and non-small-cell histologic features

e) No history of previous malignancy in the last 5 years (except non melanomatous skin or in-situ cervix carcinoma). Patients with previous malignancies (except breast cancer) and in remission for at least 5 years can be included.

f) Limited stage disease (Veterans Administration Lung Cancer Study Group) i.e. patients whose disease can be encompassed within a radical radiation portal.

g) No pleural or pericardial effusions proven to be malignant

h) Radiotherapy target volume acceptable by the local radiotherapist

i) Pulmonary function

   1) Forced expiratory volume in 1 s (FEV1) >1 litre or 40% predicted value

   2) Transfer coefficient of the lung for carbon monoxide (KCO) >40%predicted

j) Maximum of one of the following adverse biochemical factors:

   1) Serum alkaline phosphatase more than >1.5 times the upper limit of normal

   2) Serum sodium < lower limit of normal

   3) Serum LDH > upper limit of normal

k) Normal serum creatinine and calculated creatinine clearance ≥ 50 ml/min. If calculated creatinine clearance is <50 ml/mn according to the Cockroft and Gault formula, a glomerular filtration rate should be performed

l) Adequate haematological function

   1) Neutrophils >1.5 x 10^9/l

   2) Platelets >100 x 10^9/l

m) Adequate liver function: ALT & AST <= 2.5 x upper limit normal

n) No other previous or concomitant illness or treatment which in the opinion of the clinician will interfere with the trial treatments or comparisons

o) No prior surgical resection of the primary tumour, no prior radiotherapy for lung cancer

p) Considered fit to receive any of the trial regimens

q) Female patients must satisfy the investigator that they are not pregnant, or are not of child-bearing potential, or are using adequate contraception. Men must also use adequate contraception

r) Patients must not be breastfeeding

s) Patient has read the patient information sheet and has signed the consent form.

t) Patients available for follow-up

Informed consent

Eligibility to participate was confirmed by a clinician prior to consent being taken. Patients were given at least 24 hours to consider the patient information sheet and time to ask questions prior to written informed consent being taken by a trial doctor. The consent form can be viewed in online supplementary appendix 3.

Randomisation

Randomisation was administered centrally by the MAHSC-CTU. Patients were randomized on a 1:1 basis to one of the two treatment arms. The allocation method used was minimization with a random element. Randomisation was implemented via a bespoke computer application at the randomisation centre. The factors controlled for in the allocation were institution, planned number of cycles (4 or 6) and performance status (0/1 or 2).

Randomisation was only performed after confirmation that the patient was eligible (including recording of LDH, sodium and alkaline phosphatase results) and that the patient had signed consent. Randomisation can be undertaken by telephone or fax. The system used did not permit any editing of fields by users after arm allocation had been performed.

Standard care

Concurrent chemo-radiotherapy is the standard of care in LS-SCLC and good performance status. The combination of cisplatin and etoposide (PE) is the standard chemotherapy treatment delivered concurrently with radiotherapy in this group of patients. One of the accepted international standard radiotherapy regimes is 45 Gy in 30 fractions delivered twice-daily, the control arm of the CONVERT trial[3]. However in reality radiotherapy regimes differ widely between institutions and twice-daily radiotherapy has not been adopted widely mainly due to logistical issues[12].

Interventions

In both arms, 3-dimensional conformal radiotherapy was used and 4 to 10 MV photons emitted from linear accelerators. Thoracic radiotherapy started on cycle 1 day 22, concurrently with the second cycle of chemotherapy where possible. Intensity modulated radiotherapy and PET-CT planning was permitted but not mandated. The full trial-specific procedure for radiotherapy can be found in online supplementary appendix 4, including the definition of the Planning Target Volume. However it is important to note that in this trial clinically uninvolved lymph node stations were not irradiated [14].

Patients randomised to the twice-daily thoracic radiotherapy arm received 45 Gy in 30 twice-daily fractions over a period of 19 days, 5 consecutive days a week. The optimal overall treatment time was 19 days. The inter-fraction interval was 6 to 8 hours. Concurrent chemotherapy was administered during the intervals between the 2 daily radiotherapy fractions.

Patients randomized to the high dose once-daily thoracic radiotherapy arm received 66 Gy in 33 daily fractions over a period of 45 days, 5 consecutive days a week. The optimal overall treatment time was 45 days.

Patients received cisplatin and etoposide, for 4 to 6 cycles, every 3 weeks in both arms. Centres were given the choice to stop chemotherapy after 4 cycles or to continue to up to 6 cycles. Centres who decided to give 6 cycles were asked to continue doing so for all patients entered in the trial (unless it was decided that it was not in the patients' best interest to receive cycle 5 and 6 or due to patient's choice). The 2 regimen of chemotherapy permitted were; 1) Etoposide 100 mg/m2 iv D1-3 and Cisplatin 75 mg/m2 iv D1 or 2) Etoposide 100 mg/m2 iv D1-3 and Cisplatin 25 mg/m2 iv D1-3. The use of granulocyte-colony stimulating factor during chemotherapy was permitted[15].

No later than 6 weeks after the last cycle of chemotherapy, patients without evidence of progressive disease on chest xray or CT scan and with no clinical evidence of brain metastases were given prophylactic cranial irradiation.

Translational research

Progress in treatment of SCLC has been hampered by limited understanding of the molecular biology of this disease. It is usually diagnosed on a small biopsy specimen or fine needle aspirate insufficient for detailed molecular studies. Consequently, existing SCLC tumour banks include relatively small series (<100 patients) of samples collected over many years from patients who are heterogeneous

with respect to stage and treatment received. The CONVERT trial provides a unique opportunity to prospectively collect a large number of biospecimens from patients of uniform (limited) stage, who are exposed to the same chemotherapy, treated with one of two radiotherapy schedules, and for whom there will be robust clinical outcome data. Although it will still be problematic to obtain large tumour biopsy specimens for many patients, advances in genomic and proteomic technology will enable studies to be performed on blood/serum samples in addition to small biopsy specimens.

All patients were asked to consent for an optional collection of tumour samples (paraffin embedded) and blood samples as part of the trial. Blood samples (for genomic and proteomic analysis) were collected at three timepoints: at baseline prior to any treatment, on day 22 of treatment and on completion of treatment. The sample collection schedule is shown in table 1.

Table 1 – Sample collection schedule

	Baseline	Day 22	End of treatment
Tissue block			
Serum	✓	✓	✓
Plasma	✓	✓	✓
Whole blood	✓		
CTC	✓		

Data collection & management

Participating centres completed the following case report forms (CRFs):

- Eligibility checklist prior to or at the time of randomisation
- Pre-treatment and tumour assessment at baseline prior to cycle 1
- Treatment forms on day 1 of each chemotherapy cycle (cycles 1-4 or 6). The data collected included performance status, protocol treatments received, toxicity and reasons for reduction/delay/omission of treatment
- Toxicity forms at the end of each cycle given, prior to next cycle and 30 days after completion of the last cycle of chemotherapy
- Radiotherapy worksheet during and after completion of radiotherapy
- Post treatment form 30 days after the last cycle of chemotherapy
- Follow-up forms at each follow-up visit commencing at 3 months post cycle 4 (or 6) visit (continuing 3 monthly until 12 months & then 6 monthly thereafter)
- Serious Adverse Event (SAE) forms were used to report all serious adverse events
- Progression/Relapse/Death forms to report the patient status

Copies of all CRFs continue to be returned to the trials centre for statistical analysis. All forms are tracked and entered into a study defined database for which consistency checking is programmed in. Data managers check for missing and invalid data using SQL queries and statistical programs. Any queries raised are returned to the centres for correction or clarification.

On completion of the study the data will be written onto CD and archived in a safe and secure location within the MAHSC-CTU. Paper copies of the CRF's will be retained at sites for at least fifteen years following the last patient entered or if all are deceased may be archived off site. All paper data will be destroyed after fifteen years on the approval of the chief investigator.

The trials centre staff are in regular contact with local centre personnel to check on progress and to help with any queries that may arise. Incoming forms are checked for completeness, consistency, timeliness and compliance with the protocol.

Sample size calculation

It is considered that a survival benefit of 12% at 2 years (in favour of once-daily radiotherapy) would be clinically significant. Using Freedman's sample size calculation based on a 2-arm trial, with a 5% significance level, 2-sided test, 80% power and hazard ratio of 0.70, a 12% overall survival benefit at 2 years from 44% with the control arm to 56% in the experimental arm, required a total of 506 patients. The number of deaths required is 247. An additional 5% was added to allow for ineligible patients giving a total of 532 patients required. An additional 15 patients were recruited (total of 547) to replace patients either randomised in error or for whom we were never able to obtain data.

Statistical analysis plan

The analysis will be based on intention-to-treat principles (ITT). Patient data will be grouped by treatment arm according to the treatment assignments made via the MAHSC-CTU randomization line. The primary data analysis is planned for January 2015.

The stratification factors include centre, performance status (0-1 versus 2) and biochemical factors (e.g. LDH, sodium, alkaline phosphatase). Comparison of data by centre will be scrutinised to identify any data inconsistencies, it will also be used to identify those centres planning to give either four or six cycles of chemotherapy. Analysis will be carried out to identify any differences between to the two schedules. Other factors have been identified in previous studies to be prognostic factors

and will be used to calculate the Manchester score which gives three groupings of good, intermediate and poor prognosis, these scores will be used to compare OS and response rate.

The only planned interim analyses have been performed for the Independent Data Monitoring Committee (IDMC). Reports have been submitted to the IDMC on an annual basis commencing 12 months after the first patient was randomised.

The following are the qualifications for analysis of time-to-event efficacy parameters:

• All randomized patients will be included in the analysis of Overall Survival (OS) and Local Progression Free Survival (ITT).

OS is the time between date of randomisation and date of death of any cause. Survivors will be censored on the last date known to be alive. Local progression-free survival (local control) will be calculated from the date of randomisation to the date of first clinical evidence of progressive disease at the primary site, or death. Kaplan-Meier curves will be drawn for each treatment group. Overall survival and local progression-free survival will be compared using the Mantel-Cox version of the log rank test.

• All randomized patients treated with at least one study dose of cisplatin and etoposide will be included in the comparison of proportions of grade 3 and 4 toxicities.

Toxicity will be assessed according to NCI Common Terminology Criteria for Adverse Events v3.0 . The proportion of patients experiencing grade of 3 or above acute toxicity, including acute and/or late radiation morbidity, will be compared between the treatment groups using Chi-squared and Fisher Exact tests. Acute toxicity will be defined as toxicities occurring from commencement to 3 months after completion of treatment; late toxicity will be defined as toxicities occurring between 3 months and 2 years after completion of treatment.

All patients treated with at least one dose of cisplatin and etoposide will be evaluated for tumour response and included in the analysis of tumour response rates. Response will be assessed according to RECIST criteria. The proportion of patients in each treatment group whose best response (up to approximately 28 days post cycle 4 or, if stopped prior to cycle 4, approximately 28 days after last chemotherapy cycle given) from randomisation is complete or partial will be compared using Chi-squared and Fisher Exact tests.

Safety analyses will be performed for all randomized patients treated with at least one dose of chemotherapy. Adverse effects will be summarized and compared between the two arms.

The relative chemotherapy and radiotherapy dose intensity (RDI) will be summarised by calculating the median, standard deviation, interquartile range and range for patients in each randomised treatment group. The RDI will be compared between the treatment groups by using the Wilcoxon Rank Sum test.

A detailed description of patient disposition will include a summary of the following:

- all patients entered and enrolled: overall, by treatment arm, and by country
- reasons for patients entered, but not enrolled
- all enrolled patients treated with study drug, by treatment arm
- reasons patients enrolled, but not treated with study drug
- reasons patients discontinued study drug treatment
- all important protocol violations.

Changes to the protocol after the start of the trial

The trial details documented here are consistent with CONVERT trial protocol V3 (dated: 10th June 2008). There were no significant changes to the protocol after the start of the trial, only minor administrative amendments and clarifications have been made during the course of the trial.

End of the trial

The trial will end once all 547 patients recruited have died or completed 5 years of trial follow-up (whichever is sooner).

ETHICS AND DISSEMINATION

Radiotherapy Quality Assurance

The trial is subject to a radiotherapy quality assurance programme, managed by the National Cancer Research Institute Radiotherapy Trials Quality Assurance Team (RTTQA). Participating centres were provided with radiotherapy planning guidelines, including an atlas of organ at risk delineation and had to pass an initial assessment before patients could be randomised into the trial and there were further assessments afterwards.

The initial assessment consisted of:

• Completion and return of a questionnaire detailing the radiotherapy facilities available to the centre.

• Return of 2 radiotherapy treatment plans for a patient with limited-stage SCLC, previously treated in the centre with radical intent, who satisfied the eligibility criteria for CONVERT, and had been re-planned according to the CONVERT protocol for each treatment arm: 66Gy in 33 daily fractions once-daily and 45Gy in 30 fractions twice-daily.

During the trial plans were randomly requested from each centre as part of the continuing quality assurance programme and feedback was provided in case of protocol deviations. Participating centres had to agree to address uncertainties revealed by the QA programme[16].

Safety reporting

Data was collected at each trial visit regarding any SAEs (as defined by Good Clinical Practice Guidelines). All SAEs causally related to either chemotherapy or radiotherapy treatment were reported to the MAHSC-CTU and followed until they resolved or stabilised. Late radiation toxicities continue to be recorded at each follow-up visit (according to the CTCAE V3.0 grading system).

Early stopping of trial treatment

Protocol treatment may be stopped in the following instances:

- Evidence of progressive disease according to RECIST criteria on CT scan (appendix 4)
- Unacceptable toxicity
- An early toxicity assessment (after 20 patients have completed treatment in each arm) for safety reasons will be carried out. Data will be reviewed by the TMG.
- Intercurrent illness which, in the clinician's opinion, would require discontinuation of protocol therapy.
- If subsequent histological/cytological review is contrary to the original diagnosis
- Patient's request

Trial monitoring & oversight

No formal on site data monitoring activities were performed as part of the CONVERT trial.

Data is reviewed annually by an Independent Data Monitoring Committee (IDMC), consisting of three clinicians not entering patients into the trial and an independent statistician. Throughout the duration of the trial the IDMC have recommended whether the accumulated data from the trial, together with results from other relevant trials, justified continuing recruitment of further patients. The IDMC have made confidential recommendations to the Trial Steering Committee (TSC).

The role of the TSC has been to act on behalf of the funder, to provide overall supervision for the trial, to ensure that it is conducted in accordance with GCP and to provide advice through its independent Chairman. This independent committee reviews the recommendations from the IDMC and decides on continuing or stopping the trial or modifying the protocol. The Trial Management Group coordinates and manages the trial's day-to-day activities. The TMG is comprised of health professionals and members of the direct study team.

Dissemination

Data from all centres will be analysed together and published as soon as possible. Individual participants may not publish data concerning their patients that are directly relevant to questions posed by the trial until the Trial Management Group (TMG) has published its report. The TMG will have access to the final data set, form the basis of the Writing Committee and advise on the nature of publications. The trial will be publicised at regional and national conferences. The final results will be presented at scientific meetings and published in a peer-reviewed journal (authorship will be according to the journal's guidelines).

Trial status

The trial is currently in follow-up. The first patient was randomised in April 2008 and the final patient was included in November 2013.

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Trial Sponsor

The trial is sponsored by The Christie NHS Foundation Trust. Contact information: Dr Gillian Heap (Head of Research Operations), Research & Development, The Christie NHS Foundation Trust, Wilmslow Road, Manchester, M20 4BX.

Trial Support

The trial is being coordinated by the Manchester Academic Health Science Centre, Trials Coordination Unit (MAHSC-CTU). Additional study information can be obtained from the CONVERT trial manager or trial statistician

Contact details

Trial Manager: Amy Bossons, amy.bossons@christie.nhs.uk

Trial Statistician: Linda Ashcroft, linda.ashcroft@christie.nhs.uk

Author's contributions

CFF, LA, PL, MS, FB conceived of the study and initiated the study design. *EW, NG, PF, FC, AB* helped with implementation. *CFF* is the grant holder. LA provided statistical expertise in clinical trial design. All authors approved the final manuscript.

Competing interests

No, there are no competing interests.

Ethics approval

The trial has been reviewed by NRES Committee North West – Greater Manchester Central which granted ethical approval for the study on 21st December 2007 (REC reference: 07/H1008/229).

Provenance & peer review

The study was externally peer reviewed as part of the grant application process.

Data sharing statement

No additional data available.

Open access – Main publication of study expected in 2016 will be open access.

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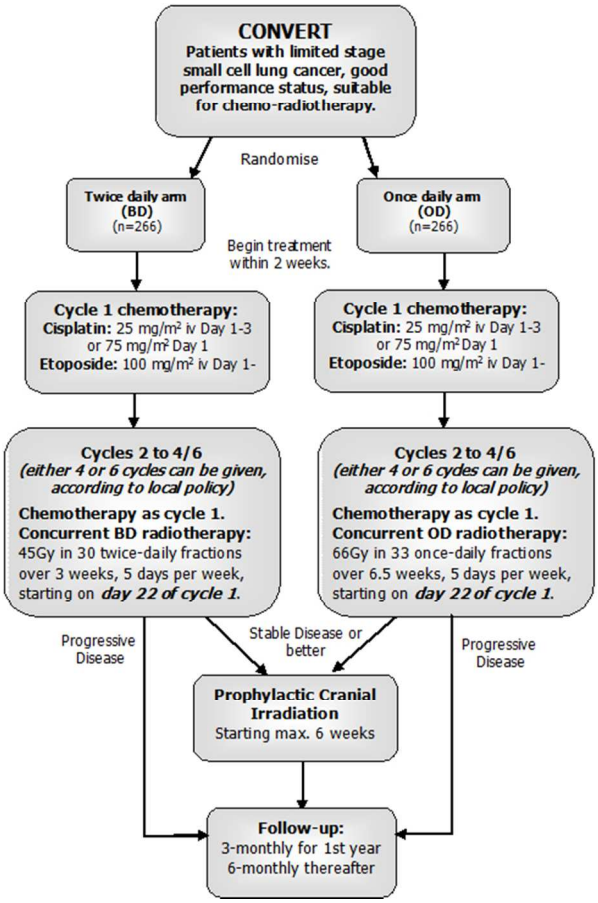

Figure 1: Trial Schema / Flowchart
216x193mm (96 x 96 DPI)

Appendix 1 – Details of recruiting centres

UK - Sites N = 33

- The Christie NHS Foundation Trust, Manchester (001) – Faivre-Finn
- Edinburgh Cancer Centre (002) – Price
- Bristol Haematology & Oncology Centre (004) – Wilson
- Dorset Cancer Centre, Poole (005) – Laurence
- Torbay Hospital, Devon (006) – Dorey
- Weston Park Hospital, Sheffield (007) – Hatton/Woll
- Royal Preston Hospital (008) – Appel
- Cheltenham General Hospital (010A) - Guglani
- St James Hospital, Leeds (011) – Snee
- Hammersmith Hospital, London (012) – Mangar
- University College London Hospitals (013) – Carnell
- The Beatson Cancer Centre, Glasgow (015) – Mohammed
- Glan Clwyd Hospital, North Wales (016) - Garcia
- Southampton General Hospital (017) – Bhatnagar
- Castle Hill Hospital, Hull (018) – Lind
- James Cook Hospital, Middlesbrough (021) – Peedell
- Northern Ireland Cancer Centre, Belfast City Hospital (022) – McAleese
- Royal Marsden Hospital, Surrey (024) – Locke
- Norfolk & Norwich University Hospital (029) – Roques
- Addenbrooke's Hospital, Cambridge (031) – Harden
- St Bartholomew's Hospital, London (033) - Wells
- Raigmore Hospital, Inverness (034) – Macgregor
- Bradford Royal Infirmary (035) – Snee
- Queen Elizabeth Hospital, Birmingham (036) – Chetiyawardana
- Peterborough City Hospital (037) – Fife
- Northern Centre for Cancer Care, Newcastle-upon-Tyne (040) – McMenemin
- Harrogate District NHS Foundation Trust (041) – Chan
- Derriford Hospital, Plymouth (042) – Roy
- The Clatterbridge Cancer Centre, Wirral (046) – Pope
- Charing Cross Hospital, London (048A) – Lewanski
- St Mary's Hospital, London (048B) – Lewanski/Power
- Wrexham Maelor Hospital (050) – Garcia
- Ysbyty Gwynedd, Bangor (051) – Ghosal

EORTC - Sites N = 7

- Universiteit Gent, Belgium (201) – Surmont
- Cliniques Universitaires St Luc, Brussels, Belgium (202) – Geets
- Clinique Sainte Elisabeth, Namur, Belgium (203) – Remouchamps
- The Netherlands Cancer Institute, Amsterdam (205) – Knegjens
- Arnhem S Radiotherapeutisch Institut, Arnhem, The Netherlands (208) – Tissing-Tan
- Medical University, Gdansk, Poland (209) – Jassem
- Institute of Oncology, Ljubljana, Slovenia (210) - Zwitter

SPAIN - Sites N = 6

- ICO Hospital Duran i Reynals, Barcelona (301) – Cardenal
- Hospital Universitari Germans Trias I Pujol, Barcelona (302) - Font

- University Hospital Ramon y Cajal, Madrid (303) – Hernanz
- Hospital de la Santa Creu I Sant Pau, Barcelona (311) – Majem
- Institut Oncològic of the Vallès (IOV), Barcelona (313) – Solé
- Corporació Sanitària Parc Taulí de Sabadell, Barcelona (314) – Solé

FRANCE - Sites N = 19

- Institut de Cancérologie de la Loire (401) – Fournel
- Centre Léon Bérard (CLB) (402) – Martel-Lafay
- Hôpital de la Croix-Rousse, Lyon (404) – Arpin
- CHU de Limoges (405) – Vergnenègre/Clavère
- CH de Villefranche/Saône (408) – Falchero
- Centre François Baclesse, Caen (412) – Gervais/Le Rouge
- CH de Aix en Provence (413) – Le Treut
- Institut Ste Catherine, Avignon (415) – Pourel
- CHI de Creteil (416) – Monnet/Martin
- CHU de Clermont-Ferrand (420) – Janicot
- HIA Toulon (422) – Bérard
- Institut Gustave Roussy, Villejuif (425) – Le Pechoux
- Centre Georges François Leclerc Dijon (426) – Peignaux/Coudert
- CHU de Marseille (427) – Padovani/Barlesi
- CHU de Rennes (429) – Lena
- CHU de Caen (430) – Zalcman
- CHU de Lille (432) – Lafitte
- Centre Oscar Lambret, Lille (433) – Prevost
- CH de Libourne (442) – Abdiche

CANADA - Sites N = 9

- CHUQ-Pavillon Hotel-Dieu de Quebec, Quebec City [CAGQ] (504) – Dagnault
- Cancer Centre of SE Ontario at Kingston [CAKK] (505) – de Metz
- Ottawa Regional Cancer Centre [CAKO] (506) – Pantarotto
- Princess Margaret Hospital, Toronto [CAMP] (507) – Bezjak
- Allan Blair Cancer Centre, Regina [CASA] (508) – Koul
- Saskatoon Cancer Centre [CASS] (509) - Kundapur
- Cancer Care Manitoba [CARM] (513) – Leylek
- Juravinski Cancer Centre [CALM] (514) – Okawara
- London Regional Cancer Program [CANL] (515) – Yaremko

Appendix 2 – Patient Information Sheet (Version 3.0, 10th June 2008)

Title of the research protocol:

CONVERT (Concurrent ONce-daily VErsus twice-daily RadioTherapy)
A 2-arm randomised controlled trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited stage small cell lung cancer (SCLC) and good performance status

PART 1

Invitation to participate in the study

You are being invited to take part in a research study. Before you decide if you want to take part, it is important for you to understand why the research is being done and what it will involve. Please read the following information carefully and if you wish, discuss it with friends, relatives and your General Practitioner. Ask us if there is anything that is not clear or if you would like more information. It is important to take time to understand this information and decide whether or not you wish to take part.

Why is this research taking place?

Your type of lung cancer can be treated with a combination of chemotherapy drugs and chest radiation therapy, called concurrent chemoradiotherapy treatment. Doctors agree that combining radiotherapy and chemotherapy improves the outcome of treatment, but some questions remain unanswered about the best way to combine radiotherapy with chemotherapy. The optimal dose, duration and number of daily fractions of radiotherapy are still to be defined.

What is the purpose of this research study?

The purpose of this research study is to find out:

- What is the best total dose of radiotherapy to prescribe for small cell lung cancer
- What is the most effective way of giving the radiotherapy? Is it once or twice a day?

Why have I been chosen?

You have recently been diagnosed with small-cell lung cancer and your doctor has recommended chemotherapy and radiotherapy treatment. Your doctor feels that you are suitable to take part in this trial. This is a research study, and other patients similar to you are also being asked if they would be willing to take part. In total approximately 530 patients will take part.

Do I have to take part?

You do not have to take part in this research, your doctor will continue to treat you whatever you decide. However, if you decide to take part you will be asked to sign a consent form. You will be given a copy of this to keep, together with this information sheet. It is routine for your GP to be kept informed about your treatment, so your GP will be told if you are taking part in this research.
If you agree to join you will still be able to withdraw at any time without giving a reason. If you withdraw from the study this will not affect the standard of care you receive.

What will happen to me if I take part?

If you agree to take part, you will be asked to sign a consent form and your doctor will organise a number of tests to check if you are eligible for this study. The tests will include a physical

examination, a chest X-ray, a CT scan of the brain, thorax and upper abdomen, a radiotherapy planning scan, blood tests and lung function tests. These tests are normally done as part of the routine tests for patients who are to be treated with concurrent chemoradiotherapy. Some patients may also require a bone scan or a pregnancy test.

If you are eligible you will be randomly allocated to once or twice-daily radiotherapy. This is done by a computer, you or your doctor cannot choose the treatment.

Once you have started the treatment you will be assessed weekly for any changes in your symptoms, any side effects of treatment and any changes in your blood tests. A CT scan will be repeated after chemoradiotherapy, then 6 and 12 months after the date you enrolled in the study.

After completing treatment, you will be reviewed weekly until any side effects have resolved then 3 monthly until 1 year and 6 monthly thereafter. Follow up visits at more frequent intervals will be decided by your doctor.

Summary of visits:

	BEFORE TREATMENT	CYCLE 1 CHEMOTHERAPY	ADDITIONAL CYCLES	END OF TREATMENT	FOLLOW-UP
Informed Consent	X				
Physical Examination	X	X	X	X	X
CT Planning Scan	X				
Blood tests	X	X	X	X	X
Kidney function	X	X	X		
Chest Xray		X	Prior to cycle 3,5		X
Electrocardiogram (ECG)	X				

Blood and tissue samples for research

You will also be asked to consent to storage of tissue and blood samples for use now and in the future for research aiming to improve knowledge and treatment of small cell lung cancer. Consent to the storage of samples is optional, so if you prefer not to consent to this you may still take part in the research. If you consent to collection of tissue and blood samples for storage these will be taken as follows:

1. You will be asked to **donate tissue** left over from the biopsy (biopsies) or operation(s) performed as part of your routine clinical care. No additional procedure(s) will be necessary.
2. You will be asked to **donate blood** before you start treatment (day 1), on day 22 of treatment and when treatment is completed. The amount of blood taken will be 10 - 30mls (two to six teaspoons) each time. Every effort will be made to take the blood samples at the same time as your routine blood tests are taken. The extra blood samples will not increase the amount of time you spend in the hospital.

What do I have to do?

You will be expected, if you take part in the study, to attend the scheduled visits.

What are the treatments that are being tested?

The treatment being tested is the radiotherapy. The trial is to compare a short course of radiotherapy given twice a day with a longer course given once a day.

- **Short course radiotherapy**

Radiotherapy treatment will be delivered twice a day, Monday to Friday (excluding weekends) for three weeks. There will be an interval of 6 to 8 hours between each treatment, for example treatment will be given at 09.00hrs and 15.00hrs.

- **Long course radiotherapy**

Radiotherapy treatment will be delivered once a day, Monday to Friday (excluding weekends) for six and a half weeks.

- **Chemotherapy**

The chemotherapy (cisplatin and etoposide) treatment you will receive is standard. It will be administered by a drip for 3 consecutive days every 3 weeks for a total of 4 to 6 cycles. The way the chemotherapy is administered and the number of chemotherapy cycles that you receive will be decided by the doctor in charge of your treatment. The first course of chemotherapy will be given 3 weeks before the start of the radiotherapy treatment.

If you receive short course radiotherapy the second cycle of chemotherapy will be administered during the first 3 days of the radiotherapy treatment and subsequent cycles will be administered after completion of the combined treatment.

If you receive long course radiotherapy, the second, third and fourth cycles of chemotherapy will be administered during the weeks when you are receiving radiotherapy treatment, and subsequent cycles will be administered after completion of the combined treatment.

The radiotherapy treatment will take around 15 minutes each time. Your doctor will discuss the length of time that the chemotherapy takes to administer.

After chemotherapy and radiotherapy to your chest have been completed you may be offered a short course of radiotherapy to your brain. This is to prevent cancer developing in your brain, as this type of lung cancer can sometimes spread to the brain. If your doctor thinks this would be appropriate for you he/she will explain more about the treatment and any possible side effects.

What are the alternatives for treatment?

If you do not wish to take part in this study your doctor will tell you what alternatives are available. The alternative treatment will vary depending on your lung cancer doctor.

What are the potential risks and side effects of taking part?

You **may** experience some of the following side effects during treatment. These are usually temporary. It is important to tell your hospital doctor about any side effects so they can be monitored and, where possible, treated.

The side effects are similar with both treatments, and will vary from person to person. It is possible you will experience very few of these side effects however staff will be able to advise you if any side effects become problematic. Prior to starting this research study a smaller study of the same treatments was carried out and patients in that study did not experience any major toxicities leading to long term side effects.

Common chemotherapy side effects :

- **Kidney function**: Because cisplatin can affect your kidneys, it is important to drink plenty of fluids (at least 8 cups) the day before and for a few days after chemotherapy. We may ask you to bring in a 24-hour urine collection to monitor your kidney function.
- **Extravasation** is when chemotherapy leaks outside the vein. If you develop redness, soreness or pain at the injection site **at any time** please let us know straightaway.
- **Bone marrow suppression.** Your bone marrow is where your blood cells are made (these are the red cells, white cells and platelets) to replace those naturally worn out within the body. Chemotherapy interferes with this process and the number of cells in your blood can become low. This means that following treatment you could become:

Prone to infection: Your white cells can become low, this is most common the week after treatment. You may develop a sore throat, cough, fever, shivering or other symptoms which may be due to infection. A normal temperature is between 36°C and 37°C. If your temperature is above 37.5°C, contact this hospital straightaway without delay. Minor infections can become serious over a matter of hours.

Anaemic: If your red cells become low you may experience excessive tiredness, feel dizzy, breathless and/or look pale.

Prone to bleeding: If your platelets become low, you may get nose-bleeds, bruising or bleeding gums.

You will have a routine blood test before each treatment to monitor the effects of the chemotherapy**, BUT please contact this hospital if you experience any of the symptoms listed above.**

- **Hair Loss.** Hair loss is usually total. The hair falls out gradually 10 to 14 days following your first course of treatment. The time scale varies from person to person. Please remember that this is a temporary side effect and your hair will grow back when you treatment is completed.
- **Nausea and vomiting (sickness).** The severity of this varies from person to person. Anti-sickness medication will be given along with your chemotherapy to prevent this. You will also be given anti-sickness tablets to take at home. Occasionally your anti-sickness medication may need to be changed or increased and you may need extra fluid through a drip.
- **Lethargy (fatigue).** Some chemotherapy may make you feel tired and lacking in energy.
- **Strange taste.** Occasionally during treatment you may experience a strange taste, sometimes described as metallic or bitter.
- **Tinnitus & high frequency hearing loss.** You may develop tinnitus (ringing in the ears), this sensation should subside when your treatment finishes. High frequency hearing loss can also occur with this chemotherapy, this may be permanent.
- **Tingling & numbness in the fingers or toes.** Usually only mild and temporary. Please report these symptoms to your doctor on your next hospital visit. On rare occasions, this may be permanent.
- **Upset bowels.** You may get upset bowels with this chemotherapy:

***Diarrhoea*.** If this becomes a problem while you are having treatment, anti-diarrhoea tablets can be prescribed for a temporary period until this is resolved.

***Constipation*.** This occasionally occurs in the long-term. Try to drink plenty of fluids and eat foods high in fibre. Tell your doctor who may prescribe a suitable laxative.

- **Sore mouth.** You may develop a sore mouth during your treatment but this can often be prevented by doing regular mouth washes.
- **Loss of Appetite.** Loss of appetite is a common side effect. You should take plenty of fluids and try to ensure that you take in enough calories. Your doctor or nurse can advise on dietary supplements if needed.
- **Contraception & Fertility.** If you are fertile, you should use effective **contraception** while on chemotherapy. Effective contraception means one of the following methods:

For female patients:

1. Tubal ligation
2. Physician documented placement of an intra-uterine device (IUD)
3. Diaphragm with spermicidal foam/gel/film/cream/pessary
4. Condom with spermicidal foam/gel/film/cream/pessary
5. Male partner who has had a vasectomy
6. Hormonal contraceptives

For male patients:

1. Use of condom.
2. In addition to a condom: male subjects without a vasectomy must ensure that their female partner uses another form of contraception such as an IUD, spermicidal foam/gel/film/cream/suppository, diaphragm with spermicide, oral contraceptive, injectable progesterone, subdermal implant or a tubal ligation if the female partner could become pregnant from the time of the first dose of trial medication until completion of follow-up procedures.
3. The female partner would not be required to use another form of contraception if they are of non-childbearing age.

If you suspect that you may be pregnant please tell your doctor immediately. Chemotherapy may also affect your **ability to have children** in the future.

Common radiotherapy side effects

Acute side effects are temporary and affect all patients. They will vary depending on the volume of normal tissue which is being treated and your general fitness.

The early side effects of concurrent chemo-radiotherapy may include:

- **Some pain in the chest** in the 24 hours after the first treatment. This is usually mild and settles down fairly quickly.
- **Increase in your cough and sputum (spit)** which may contain a little blood. Don't worry, this is quite normal. If you are having difficulties with this during treatment, let your doctor know. Coughs can sometimes worsen when treatment finishes.
- **Tiredness.** Tiredness related to radiotherapy varies a lot from person to person.
- **Difficulty in Swallowing.** Inflammation of the gullet (oesophagitis) can cause discomfort when swallowing (dysphagia). Your doctor can prescribe medicines to alleviate this symptom

and the hospital dietician can advise about modifications to your diet and supplements. You should concentrate on maintaining a good fluid intake.

- **Shortness of Breath.** Inflammation of lung tissue (pneumonitis) can cause a dry cough and a degree of breathlessness during or shortly after radiotherapy. A variant of this side effect can cause troublesome breathlessness about six weeks after radiotherapy is completed. This side effect is usually treated with a course of steroid tablets.
- **Skin Rash.** Skin reaction can be caused by radiotherapy treatment, similar to sunburn. On rare occasions a cream may be needed.

These side effects tend to build up during treatment and are at their worst in the last week of treatment or in the first 2 weeks after treatment is completed. They then recover 3-6 weeks after treatment.

The late side effects of concurrent chemo-radiotherapy may include:

- **Difficulty in Swallowing.** Narrowing of the gullet may require a minor operation to stretch the gullet (dilatation) or in rare cases surgery. If you experience swallowing difficulties months after completion of the combined treatment further investigations (gastroscopy – tube into the stomach) may be necessary.
- **Shortness of Breath.** Damage to the normal lung tissue may occur from radiotherapy. This can result in shortness of breath and increased risk of infections. Radiotherapy may leave the lung with some scarring (fibrosis). This can mean that your lung does not work quite as well as it did before, and you may notice a slight increase in breathlessness.
- **Rare late side effects**. They include thinning of the ribs (following a severe cough, this can result in chest pain and/or minor rib fracture) and injury of the spinal cord (in extremely rare cases). An injury to the spinal cord can cause permanent difficulties in walking and loss of sensation in the lower body. Every effort is made to carefully plan your treatment so as to avoid this problem.

The risk of these late side effects is generally small as the treatment is planned carefully to try to avoid them. If you do have late side effects they will become noticeable 6-18 months after radiotherapy is completed and are generally permanent.

Other possible risks of taking part

Risks of blood tests: in most cases taking blood does not cause any problems, however there is a risk of some bleeding, bruising, discomfort, dizziness, infections and/or pain at the site where the blood is taken.

Risks of scans: in addition to radiotherapy you will be exposed to some radiation as a result of X-rays and CT scans. There is a small chance that being exposed to radiation could result in the development of a cancer several years later, but the actual risk is very small compared with the benefits of diagnosing and treating your existing cancer.

What are the possible benefits of taking part?

We hope that both treatments will help you. However this cannot be guaranteed. The information we get from this study will help us to treat future patients with the same disease better.

Who can I contact for further information?

[INSERT DETAILS OF ONE OR MORE CENTRE CONTACTS]

If you have any concerns with your treatment and need to contact someone out of hours (after 5pm and before 9 am) please contact ***[INSERT DETAILS OF CENTRE CONTACT OUT OF HOURS]***

This completes Part 1 of the information sheet.

If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

PART 2

What if relevant new information becomes available?
Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If it happens your doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your doctor will make arrangements for your care to continue. If the study is stopped for any other reason, you will be told why and your continuing care will be arranged.

What will happen if I don't want to carry on with the study?
You can withdraw from the study at any time. If you withdraw from the study, you will be able to choose either:

- To allow us to use samples and information collected up to the time of withdrawal and to continue obtaining information from your health records so that we can record what has happened to you since you withdrew from the study **OR**
- You can request that we destroy all your identifiable samples and/or that we do not collect any further information from your health records.

What if something goes wrong?
The study is being performed by your doctor and insurance against injury will be provided against the hospital that is looking after you. If you are harmed due to someone's negligence, then you will have grounds for legal action but you will have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal NHS complaints mechanisms will be available to you. By signing a consent form you are NOT waiving any of your legal rights.

Confidentiality
If you join the study, some parts of your medical records and the data collected for the study will be looked at by authorised persons involved in the research. The ethics committee that approved this study and regulatory authorities may also ask for access to your records. All will have a duty of confidentiality to you as a research participant.

What will happen to any samples I give?
We are intending to carry out analysis on any blood samples and tissue that you donate. These samples will be used for research to determine groups of patient more likely to respond to treatment or more likely to develop side effects to treatment. The samples may be shared with other research groups who have the same field of interest in the UK or outside the UK. All blood samples or tissue collected will be stored anonymously.
All information which is collected will be kept strictly confidential. Procedures for handling, processing, storage and destruction of data will be compliant with the Data Protection Act 1998.

Only the Chief Investigator (Dr Corinne Faivre-Finn, Christie Hospital, Manchester, UK) and personnel authorised by the Chief Investigator will have access to break the study codes and identify the donors of the samples. Any unused samples will be retained indefinitely for use in future projects designed to identify genes and proteins that are involved in small cell cancer; and genes and proteins that predict for benefits or side effects of treatment. Samples may be transferred within or outside the UK to collaborators in other academic or commercial research settings. Nothing that could reveal your identity will be disclosed to collaborators elsewhere.

You may choose to participate in the study but not to have your blood or tissue stored for research purposes. If you choose to donate blood or tissue you have the right to have the sample(s) destroyed at any time by contacting your study doctor. If you decide to have your sample(s) destroyed, any analysis done and data gathered before the request cannot be removed, however no additional analysis will be done on your samples and the rest of your remaining samples will be destroyed.

Will any genetic tests be done?

Genetic analyses will be performed to study the genetic influences on small cell cancer and so the results will not affect you directly. No clinical genetic tests will be done for specific known inherited diseases.

What will happen to the results of the research study?

Independent experts will review the progress of the research, and the results will be published in a respected medical journal. The results will help to decide how to treat small-cell lung cancer in the future. Studies like this are often used in cancer research.

Who is organising and funding the research?

The CONVERT study is being funded by Cancer Research UK and sponsored by the Christie Hospital NHS Foundation Trust.

Who has reviewed the study?

The CONVERT study was given a favourable ethical opinion for conduct in the NHS by the Central Manchester Research Ethics Committee.

Thank you for taking time to read this information sheet.

You will be given a copy of the information sheet and a signed consent form to keep if you decide to take part in the study.

Appendix 3 – Informed Consent Form (Version 3.0, 10th June 2008)

Title of Project:
CONVERT (Concurrent ONce-daily VErsus twice-daily RadioTherapy)
A 2-arm randomised controlled trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited stage small cell lung cancer (SCLC) and good performance status

Name of the researcher: [INSERT PI NAME HERE]

	Please initial box
1. I confirm that I have read and understand the information sheet dated 10JUN2008 (version 3.0) for the above study. I have had the opportunity to consider the information, ask questions and had these answered satisfactorily.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from regulatory authorities or authorised study personnel, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4. I agree to my GP being informed of my participation in the study and of any clinically significant information that arises.	☐
5. I agree to take part in the above study.	☐
6. I agree to give for this project: ▪ tissue samples YES / NO (delete as applicable) ▪ blood samples YES / NO (delete as applicable) I understand how the sample(s) will be collected, that gifting samples for this research is voluntary and that I am free to withdraw my approval for use of the samples at any time without giving a reason and without my medical treatment or legal rights being affected.	☐
7. I agree that any sample(s) I have gifted, and anonymous information gathered about me, can be stored at the Christie Hospital and Paterson Institute for Cancer Research, Manchester, UK for possible use in future projects, as described in the information sheet. I understand that some of these projects may be carried out by researchers other than the CONVERT research team, including researchers working for commercial companies and elsewhere within and outside the European Union (EU). I consent to export of anonymised data and tissue samples within and outside the EU, and to the use of the samples for future, ethically approved, research.	☐

8. I understand that I will not benefit financially if this research leads to the development of a new treatment or medical test. ☐

9. I understand that the planned and future research using any sample(s) I have gifted may include genetic research aimed at understanding the genetic influences on lung cancer, but that the results of these investigations are unlikely to have any implications for me personally. ☐

Name of Patient	Date	Signature
Name of Person taking consent (if different from researcher)	Date	Signature
Researcher	Date	Signature

Distribution: 1 for patient; 1 for researcher; 1 to be kept with hospital notes

Appendix 4 – Radiotherapy procedures

THORACIC RADIOTHERAPY

Thoracic radiotherapy should start 21 days after day 1 of the first cycle of chemotherapy (day 22). A delay with the administration of the second cycle of chemotherapy **should not delay** the start of radiotherapy

General radiotherapy details

Patients should be treated on a linear accelerator operating at 4-10 MV. The total dose of radiotherapy will be:

- BD arm: 45 Gy in 30 twice-daily fractions of 1.5 Gy
- OD arm: 66 Gy in 33 daily fractions of 2 Gy

The total dose is prescribed at the ICRU reference point and given according to the recommendations of the EORTC radiotherapy group (25) and ICRU 50 (26). Treatment will be planned with inhomogeneity corrections. IMRT will be permitted for the centres routinely using it for the treatment of lung cancer.

Radiation Quality Assurance:

The radiotherapy quality assurance program will be run by the Mount Vernon Hospital QA team. Planning information, copies of portal images (digital print-outs are acceptable) and dose distribution, including Dose Volume Histogram (DVH), with a copy of the treatment prescription should be available for central review. Details of radiotherapy practice will be established by completion of a questionnaire.

Treatment machine beam output data on the linear accelerators used to treat patients in the trial should have been audited by a recognised ASTRO/ESTRO or UK quality assurance programme within 12 months of the first patient in the centre entering the trial, and be rechecked at least once every 18 months

We recommend that daily verifications should be done with open orthogonal images incorporating stable anatomical structures such as the spine for the first 3 days of treatment followed by weekly verifications. If available cone beam imaging can be used as an alternative to open orthogonal images. The orthogonal images will be checked by a senior radiographer and if possible reviewed by a qualified radiation oncologist, and compared with either the digitally reconstructed images or simulator images. The correction decision will be left to local policy. Differences of less than 0.5 cm from the initial images will be allowed. We suggest that if the difference is more than 0.5 cm the orthogonal images will be repeated prior to patient's treatment. The Radiotherapy Quality Assurance Group will approve and monitor each centre's procedures.

Patient treatment position:

Supine, with arms above head. Immobilisation using chest board and fixed arm position. The patient should be breathing normally.

Patient data acquisition:

A planning CT scan should be performed in the treatment position, whilst the patient undertakes a normal respiration, using 5 mm slices or less through the entire target volume. The whole thorax (cricoid to L2) should be covered using at least 1 cm slices to allow dose-volume histograms to be calculated for the lung, heart and the oesophagus.

Radiotherapy should be started within 3 weeks of planning.

Planning target volume (PTV)

The CT data will be transferred to the planning system.

The GTV (gross tumour volume) will be contoured by a qualified radiation oncologist specialised in thoracic malignancies. The contouring should be carried out using the mediastinal and the lung windows. The GTV is defined as identifiable tumour and involved lymph nodes (nodal involvement on CT scan is defined as nodes ≥ 1 cm in short axis). If PET scan is available for staging, the GTV should include PET positive lymph nodes.

The CTV (clinical target volume) comprises the GTV with a 0.5 cm margin of radiologically normal tissue in all directions. It will take into account microscopic spread. Manual adjustment of CTV is permitted to reduce dose to the spinal cord for example, when disease is adjacent to a structure such as a vertebra but is not thought to invade the structure

The PTV comprises the CTV with a 1 cm margin superiorly and inferiorly, and 0.8 cm margin laterally, at the 95% isodose. The CTV to PTV expansion should not be reduced as it is allowing for set up errors and organ motion.
Prophylactic nodal irradiation should not be employed.
Field reductions will not be allowed.

Treatment planning
Use of 3D conformal technique is required and beam's eye views may be useful in the design of individual shielding. Dose volume histograms (DVH) for the PTV, normal lung, oesophagus, spinal cord and heart will be calculated in order to obtain full knowledge of the 3D dose distribution.

Dose specification and fractionation:
The dose will be specified at the ICRU reference point and fully corrected for heterogeneity. The dose distribution within the PTV should ideally be within ± 5% of the prescribed dose, and no more than ± 7% of the prescribed dose.

Definition of the organs at risk
The spinal cord, lungs, oesophagus and heart will be contoured for dose-volume histograms.

Both the right and left lungs should be contoured as one structure. Contouring should be carried out using pulmonary windows. All inflated lung should be contoured.
The spinal cord will be contoured based on the bony limits of the spinal canal. The spinal cord should be contoured starting at least 10 cm above the superior extent of the PTV and continuing on every CT slice to at least 10 cm below the inferior extent of the PTV.
The oesophagus will be contoured using mediastinal windowing on CTscan to correspond to the mucosal, submucosa, and all muscular layers out to the fatty adventitia. The oesophagus should be fully contoured (from cricoid cartilage to the gastro-oesophageal junction).
The heart will be contoured along with the pericardial sac. The superior aspect (or base) for purposes of contouring will begin at the level of the superior aspect of the left atrium and extend inferiorly to the apex of the heart.

Beams
Isocentric treatment technique.
The number of beams will vary according to the position and the volume of the PTV in the thorax and to the maximum dose tolerated by the organs at risk.
The treatment plan will be checked by a qualified radiation oncologist after discussion with the planning team. The dose-volume histogram will help to guide that choice.

Set-up verification
Cone beam or orthogonal images will be obtained on days 1 to 3 (or 2 to 4) and weekly thereafter.

TWICE-DAILY THORACIC RADIOTHERAPY

Schedule

45 Gy in **30 twice-daily fractions** over a period of **19 days** (radiotherapy to start on a Monday)**,** 5 consecutive days a week

- The optimal overall treatment time should be 19 days, up to 21 days is a protocol deviation and should be recorded, above 21 days is a protocol violation.
- The interfraction interval will be 6 to 8 hours.
- Using conformal radiotherapy and 4 to 10 MV photons emitted from linear accelerators.
- Thoracic radiotherapy will start on cycle 1 day 22, if possible concurrently with the second cycle of chemotherapy (within 24 hours of day 1, cycle 2 of PE).
- Concurrent chemotherapy will be administered during the intervals between the 2 daily radiotherapy fractions.

Normal tissue constraints

To reduce late damages to the normal tissues the following rules will be applied

- Dose: **1.5 Gy** per fraction
- Maximum spinal cord dose will not exceed **42 Gy.** The spinal cord position must be identified throughout the PTV
- The percentage of lung minus PTV receiving more than 20 Gy will not exceed **35%** (V20=35%, based on dose-volume histograms). The mean lung dose will be recorded
- The heart can receive the total dose (TD) to < 30% of its volume. For > 50% of cardiac volume, dose < 50% of TD is recommended

Treatment Delays

Every effort should be made to deliver the prescribed dose of radiotherapy in 19 days.

If unavoidable delays occur, that could increase the overall treatment time beyond 19 days, e.g. due to machine breakdown, compensation should if possible be made by one of the following mechanisms:

- treating on a weekend day, ***or***
- adjusting fraction size to deliver the total prescribed dose within 19 days;

However, fraction size should remain < 2.25 Gy

If the radiation schedule is interrupted for more than 1 week due to intercurrent illness consideration should be given to discontinuing treatment. Further treatment will depend upon the clinical situation and is at the discretion of the responsible clinician. Interruptions for < 1 week due to intercurrent illness or radiation toxicity will be recorded and treatment should be completed as planned.

HIGH DOSE ONCE-DAILY THORACIC RADIOTHERAPY

Schedule

66 Gy in **33 daily fractions** over a period of **45 days** (radiotherapy to start on a Monday)**,** 5 consecutive days a week

- The optimal overall treatment time should be 45 days. Up to 47 days is a protocol deviation and should be recorded, above 47 days is a protocol violation.
- Using conformal radiotherapy and 4 to 10 MV photons emitted from linear accelerators.
- Thoracic radiotherapy will start on cycle 1 day 22, if possible concurrently with the second cycle of chemotherapy (within 24 hours of day 1, cycle 2 of PE).

Normal tissue constraints

To reduce late damages to the normal tissues the following rules will be applied

- Dose: **2 Gy** per fraction
- Maximum spinal cord dose will not exceed **48 Gy.** The spinal cord position must be identified throughout the PTV
- The percentage of lung minus PTV receiving more than 20 Gy will not exceed **35%** (V20=35%, based on dose-volume histograms). The mean lung dose will be recorded.
- The heart can receive the total dose (TD) to < 30% of its volume. For > 50% of cardiac volume, dose < 50% of TD is recommended

Treatment Delays

Every effort should be made to deliver the prescribed dose of radiotherapy in 45 days.

If unavoidable delays occur, that could increase the overall treatment time beyond 45 days, e.g. due to machine breakdown, compensation should if possible be made by one of the following mechanisms:

- giving two fractions on a subsequent day, with a minimum interval of six hours between fractions, ***or***
- treating on a weekend day, ***or***
- adjusting fraction size to deliver the total prescribed dose within 45 days;

However, fraction size should remain < 3 Gy.

If the radiation schedule is interrupted for more than 1 week due to intercurrent illness consideration should be given to discontinuing treatment. Further treatment will depend upon the clinical situation and is at the discretion of the responsible clinician. Interruptions for < 1 week due to intercurrent illness or radiation toxicity will be recorded and treatment should be completed as planned.

PROPHYLACTIC CRANIAL IRRADIATION

No later than 6 weeks after the last cycle of chemotherapy, patients without evidence of progressive disease on CXR or CT scan and with no clinical evidence of brain metastases will be given PCI.

Simulation is mandatory for whole brain irradiation. Patients should be treated in supine position. Immobilisation by individual masks or other means is recommended. Treatment will be delivered with megavoltage machines of energies ranging from 4-10 MV photons. Treatment with a single beam is not acceptable. Doses are specified at the mid-plane of two opposed lateral whole brain fields, prescribed to the isocenter. The dose and fractionation of PCI will be left to the discretion of each principal investigator to allow for variation in local practice.

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

*Protocol for the CONVERT trial - **C**oncurrent **ON**ce-daily **VE**rsus twice-daily **R**adio**T**herapy: An international 2-arm randomised controlled trial of concurrent chemo-radiotherapy comparing twice-daily and once-daily radiotherapy schedules in patients with limited stage small cell lung cancer (LS-SCLC) and good performance status.*

Section/item	ItemNo	Description	Inc.	Page
Administrative information				
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	☑	Pg1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	☑	Pg2
	2b	All items from the World Health Organization Trial Registration Data Set	N/A	
Protocol version	3	Date and version identifier	10th June 2008 V3.0	Pg13
Funding	4	Sources and types of financial, material, and other support	☑	Pg15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	☑	Pg1
	5b	Name and contact information for the trial sponsor	☑	Pg15
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have	☑	Pg4

		ultimate authority over any of these activities The Christie NHS Foundation Trust is sponsoring the study. The Manchester Academic Health Science Centre Clinical Trial Unit is running the study (collection, management, analysis, and interpretation of data). The CONVERT TMG will write the report and will make the decision to submit the report for publication.		
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	☑	Pg14-15
Introduction				
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	☑	Pg3-4
	6b	Explanation for choice of comparators	☑	Pg9
Objectives	7	Specific objectives or hypotheses	☑	Pg4
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	☑	Pg4
Methods: Participants, interventions, and outcomes				
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	☑	Pg5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	☑	Pg7-8
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	☑	Pg9

	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	☑	Pg14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) In the interests of brevity, full details are in full protocol or available on request from the MAHSC CTU.	☑	More detail in full protocol
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	☑	More detail in full protocol
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	☑	Pg 2 & More detail in full protocol
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	☑	Trial schema pg6; Patient Information Sheet Appendix 2
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	☑	Pg11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size Adequate recruitment will be ensured through regular presentation of the trial at national/international	☑	Pg16

		conferences, newsletters, teleconferences with PIs. More information available on request from the MAHSC CTU.		
Methods: Assignment of interventions (for controlled trials)				
Allocation:				
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	☑	Pg8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	☑	Pg8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions Allocation sequence generated by MAHSC-CTU. Participants will be enrolled by the local principal investigators and randomisation done by research staff (eg research nurses).	☑	Pg8 & more details in full protocol
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	No blinding	Pg4
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	No blinding	N/A
Methods: Data collection, management, and analysis				
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in	☑	Pg26 & more details in full protocol

		the protocol Data collection forms available on request from the MAHSC CTU, contact details added to page 16 of the manuscript. More details in full protocol.		
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols More information available from MAHSC CTU & further details in full protocol.	☑	Pg16
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol. More information available from MAHSC CTU & further details in full protocol.	☑	Pg16
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol. More information available from MAHSC CTU statistician & further details in full protocol.	☑	Pg11-13
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	☑	
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) More information available from MAHSC CTU statistician & further details in full protocol.	☑	Pg11
Methods: Monitoring				
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively,	☑	Pg14

		an explanation of why a DMC is not needed		
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial No interim analysis required or performed. The independent Trial Steering Committee (TSC) reviews the recommendations from the IDMC and decides on continuing or stopping the trial or modifying the protocol.	☑	Pg11-12 & 15
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	☑	Pg14 – further details in full trial protocol section 5
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	☑	Pg13-14
Ethics and dissemination				
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	☑	Pg15
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	☑	Pg14-15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	☑	Pg8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	☑	Pg9-10
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	☑	PIS Appendix 2
Declaration of	28	Financial and other competing interests for principal investigators for the overall trial and	☑	Pg15

interests		each study site		
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators The Trial Management group will have access to the final trial dataset.	☑	Pg14-15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	☑	PIS Appendix 2
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	☑	Pg14-15
	31b	Authorship eligibility guidelines and any intended use of professional writers No professional writer used. Also see author's contributions.	☑	Pg 1
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code No plans to grant public access to data-set.	☑	Pg16
Appendices				
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	☑	Appendix 3
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	☑	Pg9-10