SYNOPSIS

Study title	**Randomized phase II-III study of personalized radiotherapy dose redistribution in patients with inoperable stage III non-small cell lung cancer and a persistent FDG uptake at 42 Gy during concomitant radio-chemotherapy**
Short title	RTEP7-IFCT14.02
Version	15 december 2014– version 1.1
Study design	Open, double arm, randomized phase II of a phase II-III study
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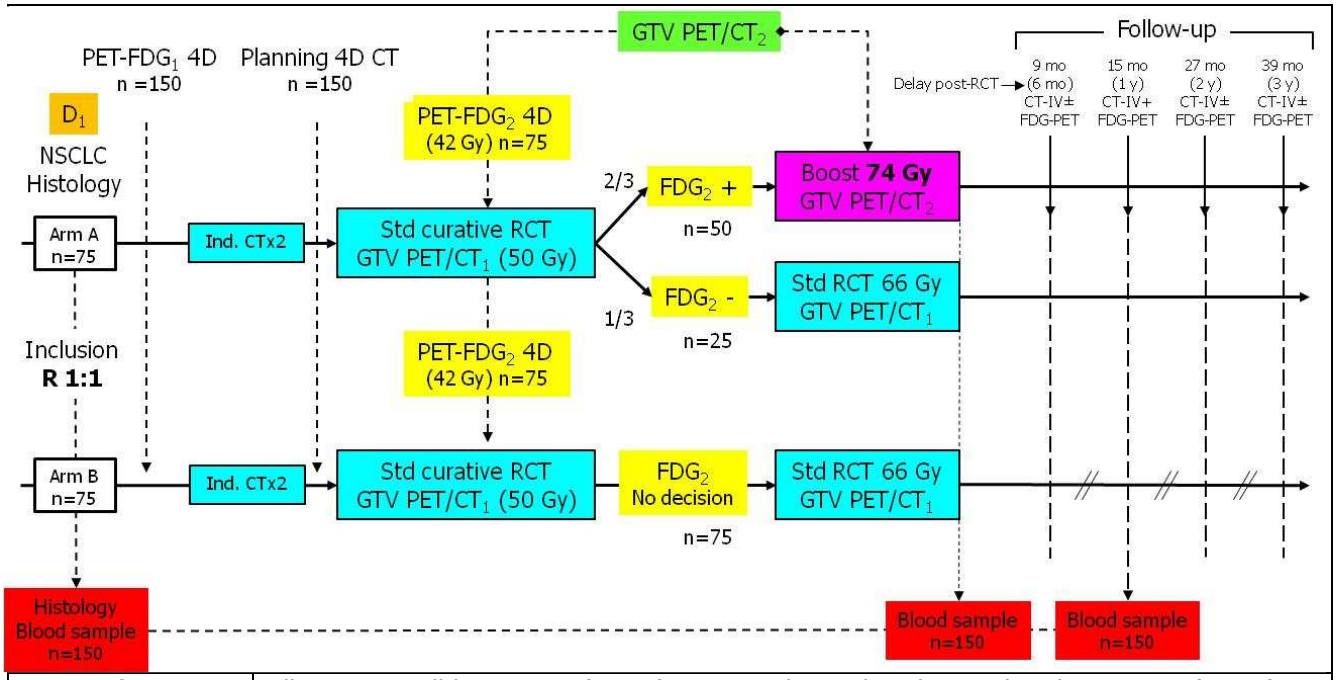
Rationale	In patients with locally advanced stage III non-small cell lung cancer (NSCLC), the probability of local control remains low (about 17% at 1 year, Ariagada IJROBP 1991, Wang PlosOne 2013). Concomitant radio-chemotherapy (RCT) is the standard treatment (Aupérin JCO 2010). **An increase in total RT dose** (from 66 to 74 Gy) has been proposed to improve local control (Bradley JCO 2010; Fleckenstien IJROBP 2011), with **contradictory results** (Bradley RTOG0617, ASCO 2013). In the RTOG0617 trial, the additional RT dose was delivered to the target volume delineated on the pre-treatment CT scan, possibly too large a target volume yielding excessive irradiation of the healthy Organs At Risk (OAR) and a duration of radiation therapy somewhat too long with a conventionally fractionation Relevant **FDG-PET scan images can be acquired during RCT** (Van Baardwijk, R&O 2007; Kong JCO 2007; Aerts IJROBP 2008; Van Elmpt JNM 2012; Edet-Sanson R&O 2012), with a demonstrated **prognostic impact** (Kong JCO 2007; Van Elmpt JNM 2012) and recently in a multicentre prospective study (Vera EJNMMI 2014). A significant reduction in FDG uptake / volume (**metabolic response**) suggests that the RT target volume could be reduced during RT (**adaptive RT**) possibly improving OAR tolerance. Conversely, a lack of metabolic response may justify treatment intensification (e.g. increase in RT total dose, acceleration of RT delivery) before the end of RT. Our hypothesis is to investigate the **individual tumour heterogeneity** on FDG-PET during RCT to reduce the volume to a biological target that could receive a higher total dose (**personalized dose redistribution**). Few non-prospective studies have shown that higher RT doses could be delivered during

	RCT. Gillham et al. (R&O2008) increased the dose from 50 to 60 Gy, leaving too little a margin for significant adjustment. Feng et al. (IJROBP2009) increased the dose in only 6 out of 14 patients. Ding et al., (Asian Pac J Cancer Prev2012) did not describe the delineation of the target volumes in which the dose was increased from 60 to 78 Gy. Guckenberger et al. (Guckenberger IJROBP 2011) evaluated the interest of adapting RT around 3 to 5 weeks in 13 patients with locally advanced NSCLC. This replanning decreased from 7.9 ± 4.8% average dose delivered to the lungs without compromising the irradiation of GTV. Conversely, the average dose to the GTV increased from 66.8 ± 0.8 to 73.6 ± 3.8 Gy, mean lung dose remaining constant. In the ongoing RTOG1106/ACRIN6697 study (Kong WCLC2013), the total dose is increased by means of large daily fractions, potentially leading to a severe late complication, without prior selection of the poor prognosis patients.
Primary objective	To determine whether **tumour RT dose escalated up to 74 Gy** in 6.6 weeks can improve the disease **Local Regional Control (LRC) rate at 15 months (1 year after completion of RCT)** by **adapting RT** target volume to the metabolic response as assessed on FDG-PET/CT performed at 42 Gy of concomitant RCT in stage III NSCLC and warrant more extensive phase III study.
Secondary objectives	• Overall survival (OS) at M9, M15, M27, M39 visits (6 months, 1, 2 and 3 years post-RCT) primary objective of phase III (D1 is the inclusion/randomization date), • Evaluation of LCR at M9, M27, M39 visits (6 months, 2 and 3 years post-RCT), • Evaluation of immediate toxicity at M9 (6 months post-RCT) and long term toxicity at M15, M27, M39 visits (1, 2 and 3 years post-RCT), • Progression-free survival at M15, M27, M39 visits (1, 2 and at 3 years post-RCT), • Predictive value at M9, M15, M27, M39 visits (6 months, 1, 2 and 3 years post-RCT) of ^{18}F-FDG PET performed at 42 Gy of RCT, • Impact of the relative change in FDG uptake (SUVmax) and metabolic tumour volume between baseline and per-RT (42 Gy) in terms of LRC at M15, M27, M39 follow-up visits (1, 2 and 3-year post-RCT), • Impact of 4D CT and 4D FDG-PET/CT on delineation of the Planning Target Volume (PTV).
Objectives of the biological ancillary study (RTEP7 bio) [Detail chap.17]	**Objective**. To search for pre-treatment biological or molecular markers associated with persistence of positive FDG-PET scan with 42 Gy and tumour progression after radio-chemotherapy. • Association between epithelial mesenchymal transition (EMT) and cancer stem cells, and resistance to radiotherapy, • Predictive and prognostic values of EMT, cell signalling pathways, and glucose metabolism (expression of GLUT1): - Prediction of resistance to chemo-radiotherapy by comparing Shh, Gli1, Gli2, PDGFRβ, Vimentin expression (immunohistochemistry) to tumour response 15 months (1 year post-RCT) after treatment (local control versus progression), - Idem with SUVmax and MTV of sequential FDG-PET scans and expression of GLUT1 on initial specimen, - Expression of above-mentioned all biomarkers will be correlated with overall survival. **Equipment. Seven microscope slides** will be sent at ambient temperature to Theroscan GRC laboratory no. 4 for immunohistochemistry analysis (vimentin, PDGFRβ, Gli1, Gli2, Shh, GLUT1, and one slide for HES control). A blood sample (**1 test tube of 10 mL on EDTA**) at time of inclusion, at the end of radiotherapy, and at 15 months with isolation and storage of plasma from patients included in study RTEP7 will also be collected, in order to carry out plasma assay measurements of circulating plasmatic DNA and miRNA.
Primary end point	LCR rate (responders or stable disease) at 1 year after completion of RCT (M15 visit). Disease progression will be assessed by **RECIST 1.1 criteria** (Eisenhauer Eur J Cancer 2009).
Secondary end points	• Percentage of local regional control (LCR) with RECIST 1.1 criteria at M9, M27 and M39 visits, • Time to LRP, the interval from the date of registration to date of local or regional

	progression, • Percentage of severe (grade 3+ CTCAE, v4) radiation-induced toxicity affecting lung and oesophagus at M9 visit (early toxicity) and M15, M27, M39 visits (late toxicity), • Percentage of patients in arm A for whom the RT dose could be increased, • SUVmax and MTV of ^{18}F-FDG -PET$_2$ will be correlated with OS and PFS at M15 visit (1 year post-RCT), • Measurements of the relative change in SUVmax and metabolic tumour volume (MTV) from the ^{18}F-FDG -PET$_1$ (baseline) to the ^{18}F-FDG -PET$_2$ at 42 Gy defined as [(PET$_2$– PET$_1$) / PET$_1$] x 100%, • Probability of overall survival (OS) and progression-free survival (PFS) after M9, M15, M27, M39 follow-up visits, • Prognostic value of biomarkers (cf.infra).
Study design	• Open, double arm, randomized phase II of a phase II-III study (phase II/III with accrual suspension after phase II patients accrued), • Patients will be stratified by center (according to IMRT vs bifractionated RT), • The registration date (D1) is the inclusion/randomization date. M9, M15, M27 and M39 follow-up visits correspond to 6 months, 1, 2 and 3 years after completion of RCT. • Eligible patients will be allocated to one of 2 treatment groups: - **Arm A**: Patients in the **experimental arm** will receive an individualized RT prescription up to a total dose of 74 Gy given in 6.6 weeks if they have a positive FDG-PET42Gy (about two thirds of pts are expected as positive ie 50/75; Vera, EJNMMI2014). An initial dose of 50 Gy will be delivered in 5 weeks (single daily fractions of 2 Gy), then an additional dose up to 24 Gy will be delivered over 1.6 week using a twice-a-day (BID) fractionated RT: 2.0 Gy in the initial Planning Target Volume (PTV) plus a 1.0 Gy fraction at least 6 hours later in the biological target volume (BTV). The BTV will be delineated on a FDG-PET scan acquired after an initial dose of 42 Gy ± 2 Gy (FDG-PET$_2$), i.e. after 21 fractions. If IMRT is applied, a single daily Simultaneous Integrated Boost (SIB) will be allowed. - **Arm B:** Patients in the **standard arm** will receive a single prescription of 66 Gy in 33 fractions in 6.6 weeks, with 2 Gy fractions given once daily, 5 days a week, without target volume reduction or adaptation (whatever the FDG-PET result). • In both arms, all patients will undergo 2 cycles of induction CT (based platinum salts) and a curative RCT. In both arms all fields must be treated daily. The total dose will be prescribed so that the total Mean Lung Dose (MLD) is ≤ 20 Gy and V20 < 30%, and doses to other organs at risk (oesophagus, heart and spine) meet the standard limits. Respiratory gating and IMRT will be optional. A biological ancillary study (RTEP7 bio) will be performed. This funding request concerns only the phase II of this trial, therefore we do not present the exact design of the phase III part of the study in this document. For Phase III, all the patients included in phase II remain evaluable for survival.



Criteria for increase in dose during RCT	All patients will have a 4D (or 3D) FDG-PET/CT at baseline and a planning 4D (or 3D) CT before RT. All patients will have a FDG-PET/CT during RT (PET42Gy=PET_2). At 42 ± 2 Gy, FDG-/FDG+ will be defined on a binary visual analysis (negative or positive) which will be performed by 3 independent readers (blinded evaluation) within a delay of 2 days. The results will be centralized and re-distributed via the SFMN-net network (Kappa=0.85; Thureau JNM 2013). GTV will be defined in each centre with planning CT and FDG-PET/CT scan images based on Brussels method of water sharing (Geets EJNMMI 2007).
Treatment, products, equipment used	• Conformal radiotherapy with heterogeneity correction (Intensity Modulated Radiotherapy (IMRT) and respiratory gating are optional), • FDG-PET/CT examinations before (baseline FDG-PET_1) and during RCT (FDG-PET_2) performed in the treatment position is strongly recommended (or at least coregistration of PET/CT and CT scan in treatment position is imperative). PET/CT with FDG pre-RCT (injection of contrast media can be done according to local practice), • 4D PET and 4D CT strongly recommended.
Supplementary dose	From 66 Gy to 74 Gy in experimental arm (50/75 in arm A). The total dose will be prescribed so that the total Mean Lung Dose (MLD) is ≤ 20 Gy and V20 < 30%.
Statistical analysis	**RTEP7** The main objective is to determine whether tumour RT dose escalated up to 74 Gy in 6.6 weeks has sufficient activity against disease to warrant more extensive study. Patients will be classified according to the treatment they were randomized in accordance with the intent-to-treat principle. • Demographics, baseline disease characteristics, and preexisting conditions data will be summarized descriptively by treatment arm. Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. • The primary analysis will be performed when all phase II patients enrolled have completed M15 visit (1 year post-RCT) or discontinued. The primary analysis will compare the proportion of disease LRC rate at M15 visit (assessed by RECIST 1.1 Criteria) and will be done on the FAS subset of patients eligible. The two-proportion z-test will be used to determine whether the hypothesized difference between population proportions differs significantly from the observed sample difference. • OS and PFS will be calculated using the Kaplan-Meier method. The log rank test will be used to test the differences between treatment arms. • Duration of radiotherapy exposure, cumulative dose, actual dose intensity will be summarized by treatment arm. The number of patients with dose changes/interruptions will be presented by treatment arm, along with reasons for

	the dose changes/interruptions. • The safety set comprises all patients who receive at least one dose of radiotherapy and have at least one post-baseline safety assessment. Patients will be classified according to the treatment they were randomized. In order not to expose patients to excess toxicity, the decision of whether or not to continue the study will be taken on interim analyses **every 14 patients** (no more than 3 patients presenting grade 3-4 adverse reactions per group of 14 subjects). **RTEP7 bio.** The main objective of the ancillary study is to evaluate the predictive value of biomarkers using logistic models for the response, adjusted on clinical and biological factors of the study. Biomarkers will be analysed quantitatively. Their association with clinical and biological factors will be assessed using ANOVA and χ^2 tests, or using non-parametric tests of Fisher and Mann-Whitney if necessary. The predictive value of the markers will be tested in a logistic model containing each treatment, the marker and the interaction term treatment x marker.
Number of patients planned	Open, double arm, randomized phase II of a phase II-III study. A single-stage phase II design based on exact binomial distribution will be used. The experimental treatment is worth considering further if it demonstrates a level of treatment response P_1 which is greater than the response rate for the current or standard treatment, P_0. The level P_0 indicating that the experimental procedure is clearly ineffective is fixed at 0.39. The minimal level of efficacy of the new treatment P_1 (personalized dose escalation and **redistribution** in lung tumours) is a rate of disease LRC at 15 months higher than 0.54 (H_1 based on the fact that about two thirds of patients are expected to show residual FDG uptake at 42 Gy in the experimental arm A and will be boosted up to 74 Gy; Vera EJNMMI 2014). The trial test the null hypothesis H_0: $P \leq P_0$ against the alternative hypothesis H_1: $P \geq P_1$. The power is fixed at 0.9 and the one sided type I error at 0.10 (Lee J Clin Oncol 2005). Our software that provides binomial probabilities gives a sample size of 71 in the experimental group. Taking into account lost to follow-up patients or patients with incomplete data, we need to increase the sample size by 5%. Therefore, we propose to include 75 patients in each arm. Number: **150** patients (75 in experimental arm A and 75 in standard arm B).
Planned centres	xx centres in France (RTEP5 and IFCT centres) and 1 in Belgium.
Main inclusion criteria	• Male or female patients, • Age over 18 years and below 75-year old, • Good general condition: WHO performance status ≤ 1, • Histological evidence of non-small cell lung cancer, • Measureable tumour according to RECIST 1.1 evaluation criteria, • Mediastinoscopy or endobronchial ultrasound to prove the histological stage N2/N3, • Patient eligible for curative-intent radio-chemotherapy, - Absence of pleural involvement, of pulmonary or extra-thoracic metastatic localisation, - Absence of co-morbidity contra-indicating radio-chemotherapy, • Lung function: $FEV_1 \geq 40\%$ of theoretical value and DLCO/VA ≥ 60% of theoretical value and PaO2 ≥ 60 mm Hg, • Tumour FDG uptake higher than mediastinal background noise on baseline PET/CT, • Haematological parameters: - Neutrophil count ≥ $1.5x10^9$/L and platelet count ≥ $100x10^9$/L, - Haemoglobin ≥ 9 g/dL, • Provisional RT plan confirming that the dose objectives (minimal dose of 62.7 Gy (95% of the prescribed dose) in 98% of target volumes and 70.3 Gy for the "boosted" volume at 74 Gy) and constraints (lungs, spinal cord) are met (ICRU83), • Estimated creatinine clearance ≥ 60 mL/min, • Signed informed consent • Affiliated or beneficiary of a social benefit system
Non inclusion criteria	• Histology other than non-small cell lung cancer, • Absence of FDG uptake on FDG-PET/CT scan before induction chemotherapy, • Patients for whom curative radiotherapy is not indicated (tumour extension, metastases, general condition, co-morbidities),

	• Significant interstitial disease on CT scan, • Previous neoplastic disease of less than 5 years duration or progressive (without basal cell carcinoma of the skin, in situ carcinoma of the cervix), • Previous thoracic radiotherapy, • Patient enrolled in another therapeutic trial, • Pregnant women or women of child-bearing potential or breast feeding mothers, • Adult subjects who are under protective custody or guardianship, • Patient unable to comply with the specific obligations of the study (geographic, social or physical reasons), • Uncontrolled diabetes with blood glucose ≥10 mmol/L, • Hypersensitivity to the active substance (FDG) or to any of the excipients, • Patients unable to understand the purpose of the study (language, etc.).
Provisional schedule	Duration 5 years; inclusion 2 years, follow-up 3 years. • Start of inclusion: **May 2015** • End of inclusion: **May 2017** • End for primary end point: **November 2018** • End of the study: **November 2020**