- TARLAL -
- Tarceva And Radiotherapy in Locally Advanced Lung cancer -

Concomitant Tarceva® and irradiation in patients in local-regionally advanced non-small cell lung cancer. A phase II study.

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Table of Contents

1. Background

1.1 Concurrent chemo-radiotherapy

Lung cancer is the major cause of cancer-related death in Europe and North America. About 75% to 80% of lung cancer is non-small-cell cancer (NSCLC) with approximately 40% of patients presenting with locally advanced disease. In patients with no malignant pleural effusions, the treatment options have been irradiation up to 60-70 Gy against the primary lung tumor and lymph nodes in mediastinum resulting in a median survival of 6 to 11 months and 5 years survival of 5%. The treatment have until recently consisted of irradiation of the tumor bed and areas around with high risk of relapse. The treatment has now being optimized by giving chemotherapy either before irradiation or concomitant with radiation or both. The irradiation technique have been improved by introduction of 3D-CT-scan based planning technique, and the prognosis have been somewhat improved. Data from Odense shows a 5 year survival rate of 16% at 5 years (1). The treatment of choice for locally advanced NSCLC is radiotherapy combined with chemotherapy since trials using inductions chemotherapy and/or concomitant chemotherapy have demonstrated increased median survivals to 13-15 months with a 5 years survival of 10-20%. The rationale for using of inductions chemotherapy has been to reduce the treatment volume by reducing the tumor burden and to eradicate micro-metastases.

A significant problem in the treatment of local advanced NSCLC is a high rate of local failure of up to 45% without distant metastases after irradiation. In 200 patients with NSCLC stage III treated in Odense the 1 year survival was 61%. 112 of these had received a platinum based induction chemotherapy regimen, and 3 had concomitant therapy with Taxotere. The local failure free survival was 70% 9 months after start of irradiation and 43 % after one year (unpublished data).

The poor local control is partly due to the tumors content of radio-resistant cells in hypoxic areas of the tumor. The radio-resistance is in part due to an up-regulation of the epidermal growth factor receptor (EGFR). The radio-resistance of the tumor cells can be overruled at least from a theoretical point of view by using concomitant treatment with drugs, which either can bring the tumor cells in phases of the cell cyclus in which they are more sensitive to irradiation (G_2- and M-phase) or specifically kill the hypoxic cells.

Concurrent chemo-radiation is considered to be standard in radiation of local-regional advanced NSCLC (2). However, a number of patients are unfit or refuse chemotherapy. In these cases radiotherapy at present has to be administered by itself.

1.2 EGFR blockage of the radiation response

Increased expression of EGFR has been observed in several solid tumors, including NSCLC and squamous cell carcinoma of the head and neck. EGF binds to the EGFR stimulating autophosphorylation of the intracellular tyrosine kinase domain of the receptor. Activation of the EGFR signal transduction pathway enhances cellular processes involved in tumor growth and progression, including the promotion of proliferation, angiogenesis, invasion, and metastasis.

Blockage of the EGFR signaling pathway has been shown to enhance the radiation response in cell lines and in clinical studies. The blockage can be done by anti-EGFR monoclonal antibody, or by tyrosine kinase inhibitors like Tarceva (Erlotinib). Studies have demonstrated that blockage of the EGFR with the monoclonal antibody Cetuximab (IMC-C225) enhances radiation response in squamous cell lines of the head and neck (3) and in mice carcinomas (4). Blockage of the EGFR signaling pathway by tyrosine kinase inhibitors increased radiation response in human xenografts in mice (5), bladder carcinoma cell lines (6) and breast cancer cell lines (7).

In clinical studies, tumors arisen from several different organs have been studied, and increased expression of EGFR has been correlated with disease progression and poor overall outcome after

radiotherapy. In a retrospective study of 155 patients with head and neck cancer treated with standard radiotherapy the level of EGFR expression had highly significant correlation with the survival rates and loco-regional control, but not with the incidence of distant metastasis (8). In a randomized phase III study including 424 patients diagnosed with loco-regionally advanced squamous cell carcinoma of the head & neck, and addition of cetuximab to radiation therapy, a statistically significant prolongation in overall survival was obtained without augmenting the radiation side-effects (9).

A small phase I study of daily Tarceva and concomitant chemo-radiotherapy has been carried out in esophageal cancer (10). The chemotherapy consisted of Cisplatin and 5-FU. The radiation dose was 50.4 Gy in fractions of 1.8 Gy. Doses of 50 mg, 100 mg, and 150 mg Tarceva daily were well tolerated. The major toxicity was esophagitis (9% grade 4), diarrhea, skin rash, nausea, and dehydration. No excess lung toxicity was experienced.

Preliminary data of a small randomized phase II study of ± Tarceva 150 mg/day administered concomitant with 66 Gy /33 F in patients unfit for chemotherapy indicated that this schedule was feasible (11). In 22 patients treated with concurrent Tarceva and radiation evaluable for toxicity, no case of grade 3-4 pneumonitis or esophagitis was observed (information on poster).

1.3 Tarceva

Tarceva (Erlotinib hydrochloride is quinazolinamide that inhibit the intracellular tyrosin kinase domain of the EGFR. It is formulated as immediate release tablets. Bioavailability of Erlotinib following a 150 mg oral dose is about 60% (and almost 100% i taken together with food) and peak plasma levels occur 4 hours after dosing. The median half-life is 36 hours, and the time to reach steady-state plasma concentration is 7-8 days (12). Smokers have a 24% higher rate of Erlotinib clearance. Erlotinib is metabolized by the liver cytochrome P450 system primarily by CYO3A4 which may be a cause of interaction with other drugs.

2. Objectives of the study

The trial is a phase II study of daily Tarceva combined with definitive radiotherapy in inoperable locally advanced non small cell lung cancer (stage IIB-IIIB).

The objective of the phase II trial is to examine Tarceva concomitant with curatively intended irradiation 66 Gy (2 Gy x 33 F, 5 F per week):

Primary endpoint

- Local failure free survival at 9 months after start of radiotherapy evaluated at CT scan.

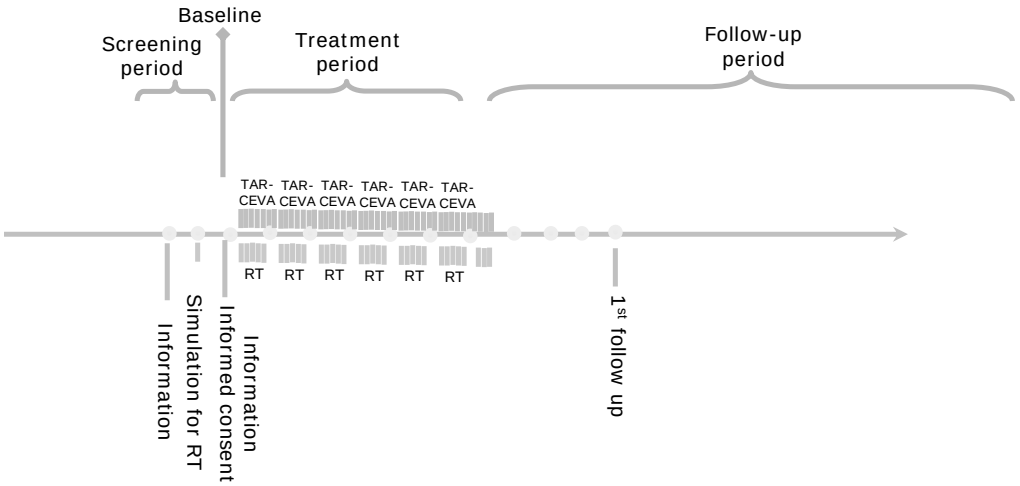
Secondary endpoints

- Toxicity
- Local tumor control by CT-scan
- Overall response rate (CR + PR).
- Local tumor control at 9 months evaluated by PET-CT
- Overall survival
- Disease free survival
- Late toxicity

3. Study design and dosing regimen

3.1 Study design

The treatment plan is consisting of radiation; 3-D conformal radiotherapy given together with Tarceva 150 mg/day. Induction chemotherapy may be used. No concurrent chemotherapy may be used.



Figur 1: Time line in the study

3.2 Dosing regimen

Tarceva will start at the day of the radiation in daily dose of 150 mg. The last dose will be given the day the radiotherapy stops. Tarceva will be administered continuously for approximately 6.5 weeks. Drug accountability will be registered according to Good Clinical Practice (GCP). The radiotherapy is only administrated 5 days a week.

3.3 Interruption or discontinuation of Tarceva in the individual patient.

Toxicity grading will be according to the CTC version 3.0. Following dose adjustment for drug-related toxicity is recommended: If any grade III or worse toxicity including skin toxicity or diarrhea occurs, the Tarceva will be paused till toxicity has resolved to a grade II or better. The Tarceva will be resumed in a dose of 100 mg if the dose before pausing was 150 mg, or 50 mg if the dose was 100 mg. If the dose was already 50 mg, the Tarceva will not be resumed. The radiotherapy should be continued. For management of radiation complication during therapy see section 8.2. Management of Tarceva related toxicities see Appendix 4.

4. Planning of radiotherapy

The planning technique is based on ICRU62 recommendations, and the DOLG 2009 criteria. The planning may, however, make use of 4-D scans, and that will influence the margins, se below. The prescribed dose is 66 Gy /33 F / 5 F per week. If induction chemotherapy has been administered radiation may start within 2-5 weeks after last dose of chemotherapy.

4.1 Target volumes

GTV comprise the tumor as seen on the planning CT scan (the size after chemotherapy) plus any pathological lymph node during time before start of radiotherapy even if they have disappeared after induction chemotherapy.

CTV encompass the GTV plus the following margins: 1.0 cm in the mediastinum and 0.5 cm in lung tissue. The margins are modified if the CTV is close to the large vessels, bones, trachea or the thoracic wall, then the anatomic structures constitute the demarcation of the CTV as long as no invasion is seen in the surrounding tissue. For a primary in the lung, not involving the hilar region or the mediastinum, the CTV should not be expanded into the mediastinum. For lymph nodes not invading lung tissue, the CRV should not be expanded into healthy lung tissue.

No elective radiation will be used to unaffected lymph nodes.

ITV: If the treatment is based on a standard 3D CT scan without 4D planning, the following margins are used: CTV + 0.5 cm. ITV should be set to zero towards columna, apex and contralateral lung.

If a 4D CT scan is used for the treatment planning, it is allowed to create patient specific margins. In that case the treatment plan should be carried out on the mid-ventilation phase as described by Wolthaus et al. (13). The size of the margin related to the respiration shall be calculated as described by Van Herk et al. (14).

PTV margins should be based on experience related to type of fixation used in the clinic. If patient specific margins are to be used, a study of the size of PTV margin has to be performed at the institution. For the patient specific margins, the size of the PTV margin has to be calculated based on the same formalism as for the ITV (14). For patient specific margins it is important that ITV and PTV margins are not added linearly but as the square-root of the sum of the squares. Thus it might be beneficial to expand directly from CTV to PTV, so that the ITV is contained in the PTV, since most planning systems only supports linear addition of margins. If patient specific margins are applied, it is important to report the size of the margin (appendix 5).

4.2 Doses to organs at risk

The dose to the lungs, spinal cord, heart, and esophagus must be reported. In the treatment of lung cancer with combination treatments the dose the constraints to the organs at risk are given as:

1. Both lungs must be outlined: $V_{20} \leq 40\%$ i.e. a maximum of 40% of the lungs (outside the GTV) may receive a dose exceeding 20 Gy or more.
2. The spinal cord must be outlined as the spinal canal: The dose must not exceed 45 Gy.
3. The whole of the heart must be outlined: $V_{50} \leq 20\%$.
4. Esophagus through out the thorax: 66 Gy as a maximum dose.

5. Study population

The study population is patients with NSCLC stage IIB - IIIB without pleural effusion suitable for curatively intended irradiation and concomitant Tarceva.

5.1 Inclusion criteria

Patients must meet *all* of the following inclusion criteria to be eligible for participation in this program.

- Age ≥18 years
- Patients with histologically or cytologically documented diagnosis locally advanced NSCLC stage IIB to IIIB without pleural effusion
- Performance status ≤2 on the ECOG scale
- Serum bilirubin must be ≤1.5 upper limit of normal (ULN)
- ALAT ≤2 x ULN
- Able to comply with study and follow-up procedures

- Patients with reproductive potential must use effective contraception
- Written (signed) informed consent to participate in the study

5.2 Exclusion criteria

Patients who meet *any* of the following exclusion criteria are not to be enrolled in this study:

- Any unstable systemic disease (including active infection, unstable angina, congestive heart failure, severe hepatic, renal, or metabolic disease)
- Any other malignancies within 5 years (except for adequately treated carcinoma in situ of the cervix or basal or squamous cell skin cancer)
- Inability to take oral medication, or requirement of intravenous alimentation
- Nursing mothers

5.3 Monitoring during therapy

The patient may receive induction chemotherapy before inclusion in the study, and is as such not part of the study. The patients cannot be included in the study before a plan has been worked out showing that curatively intended radiation is possible, and informed consent has been obtained (Fig. 1).

	Screening/ Baseline	**Treatment Period Timing**	**Day 30-45 after stop of treatment**
Informed Consent	x	-	-
Demographics	x	-	-
Medical history	x	-	-
Physical examination	x	Weekly	x
Body weight	x	Weekly	x
Laboratory[1]	x	Weekly	x
ECG	x	-	x
Lung functions test[2]	x	-	x
Lung CO diffusion test	x	-	-
CT scan thorax and upper abdomen	x	-	x
Tumor measurements	x	-	x
PET-CT[3]	x	-	-
CT scan brain[4]	x[4]	-	-
Performance Status (PS)	x	Weekly	x
Side effects[5]	-	Recorded weekly	x
Study drug compliance[6]	-	x	x
Smoking status	x	Recorded Weekly	x

([1] Hematology: Hemoglobin, WBC, granulocytes and platelet count, INR (Only for patients receiving warfarin or coumarin-derivative). Biochemistry: Alkaline phosphatase, Serum bilirubin, Serum creatinine, ALAT (SGPT), LDH. Only laboratory abnormalities linked to unexpected clinical symptoms will be documented in the CRF.
([2] FEV_1/FVC test. If neoadjuvant chemotherapy, the test must be performed after cessation of chemotherapy.
([3] CT scans, PET CT scans per institutional standards, EBUS or mediastinoscopy may be accepted as mediastinal evaluation if PET-CT is not available
([4] If no PET-CT available
([5] Side effects to be recorded according to CTC version 3.0
([6] Pharmacy log

5.4 Follow-up

The patients will be followed until 5 years after the start of radiotherapy or to recurrent disease according to the follow-up schedule. After discontinuation in the study the patient will be followed according to local standard.

Follow up (±1 month after start of RT)	**6**	**9**	**12**	**15**	**18**	**21**	**24**	**30, 36, 42, 48, 54, 60**
Medical history	x	x	x	x	x	x	x	x
Physical examination	x	x	x	x	x	x	x	x
Laboratory[1]	x	x	x	-	x	-	x	-
Lung function tests FEV_1/FVC	x	x	x	x[2]	x	x[2]	x	x
Lung CO diffusion test	-	x	-	-	-	-	x	-
Weight	x	x	x	x	x	x	x	x
CT scan of thorax and upper abdomen	x	x	x	x	x	x	x	x
Tumor measurements[3]	x	x	x	x	x	x	x	-
PET-CT[4]	-	x	-	-	-	-	-	-
Performance Status	x	x	x	x	x	x	x	x
Smoking status	x	x	x	x	x	x	x	x
Side effects[5]	x	x	x	x	x	x	x	x

([1] Hematology: Hemoglobin, WBC, granulocytes and platelet count, INR (Only for patients receiving warfarin or coumarin-derivative). Biochemistry: Alkaline phosphatase, Serum bilirubin, Serum creatinine, ALAT (SGPT), LDH. Only laboratory abnormalities linked to unexpected clinical symptoms will be documented in the CRF
([2] FEV_1/FVC test.
([3] RECIST criteria (appendix 2)
([4] PET CT scans if available at the institution
([5] Radiation sequelae

5.5 Tumor response criteria.

Although PET-CT is allowed, the tumor response will be evaluated according to RECIST-criteria (version 1.1) by CT-scans of thorax and upper abdomen (15). Suspected recurrent tumor locally or regionally should verified by biopsy if appropriate.

6. Criteria for efficiency and data-analysis

6.1 Statistical considerations

All calculations will be performed on the basis of intention to treat. 2 sided tests will be performed. Level of type 1 error is 5%.

6.2 Sample size calculation:

Observed local failure free survival rate after 9 months after initiation of radiation was 70% among 300 patients treated in Odense for NSCLC stage IIB-IIIB. The study will be designed to find local recurrence free survival of 80% at 9 months after initiation of radiation equivalent to about 6-7 months after finishing radiotherapy. A rate of 80% would be clinical interesting, and should be included in the confidence interval of the phase II trial at a power of 90%. This requires 57 patients to be included in the phase II trial.

6.3 Interim analysis

An interim analysis to evaluate toxicity will be performed after patient number 20 has completed radiotherapy and has one month of follow-up. An independent interim analysis committee will be

appointed to the task. The study will stopped if the rate of grade 4 pneumonitis or esophagitis exceeds 15% in the study, or unexpected severe toxicity appears at any time.

6.4 Expected time frame of study

The study is expected to recruit patients during a 2-year period starting q2 2009 and ending q2 2011. Analyses of results will be performed 9 months after last patient has been included, and results will be reported. Further analyses may be performed 5 years after the last patient has been included. Each site is expected to include between 3-15 patients.

6.5 Data management

Data from all included patients will be reported. Every year during the time of inclusion of patients to the study and the next 3 year period safety data will be reported to the authorities. After final analyses of the study the data will stored for 15 years from inclusion of last patient in study. The data will be available for the authorities at all times.

7. Administration of drugs

7.1 Tarceva® (erlotinib)

Tarceva is an orally active, potent, selective inhibitor of the EGFR tyrosine kinase. Tarceva will be administered on an outpatient basis at a fixed dose according to schedule as a single daily oral dose. Dosage is not based upon body weight or body surface area. The Tarceva used in the study after the induction period in combination with radiotherapy will be labelled to each patient, and records of batch numbers for each patient will be kept at the pharmacy for 15 years

Prescribed daily dose is to be taken preferably in the morning, with up to 200 mL of water. Tarceva should be taken at least 1 hour before or 2 hours after the ingestion of any food or other medications, including grapefruit juice, vitamins and iron supplements.

Missed daily doses should be skipped. Doses should be taken at the same time each day. If the patient vomits after taking the tablets, the dose is replaced only if the tablet can actually be seen and counted. If a patient misses a dose normally taken in the morning, the dose should not be taken later on.

7.2 Concomitant medication

Patients with a history of dry eyes should be advised to use an ocular lubricant.

- Concomitant treatment with warfarin or coumarin-derivative is permitted provided increased vigilance occurs with respect to monitoring INR (International Normalized Ratio). However, it is recommended to use low-molecular heparin.
- Patients who receive protocol treatment should not receive any other (non-anticancer) investigational drugs until after the post-treatment assessment (at least 30 days after the final dose of protocol treatment).
- Patients who continue to wear contact lenses may have an increased risk of ocular adverse events.

7.3 Potential drug interactions

Substances that are potent inhibitors of CYP3A4 activity (eg, ketoconazole) decrease Tarceva metabolism and increase Tarceva plasma concentrations. This increase may be clinically relevant as adverse experiences are related to dose and exposure; therefore, caution should be used when administering CYP3A4 inhibitors with Tarceva.

Substances that are potent inducers of CYP3A4 activity (eg, rifampin, phenytoin) increase Tarceva metabolism and significantly decrease Tarceva plasma concentrations.

INR elevations and/or bleeding events have been reported in some cancer patients taking warfarin while on Tarceva. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR.
Tobacco smoking may diminish the plasma levels of Tarceva, and may diminish the effect of radiation and should be avoided during the study period.

8. Adverse events

An AE is defined as any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product regardless of its causal relationship to the study treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of medicinal (investigational) product.

The occurrence of an AE may come to the attention of study personnel during study visits and interviews of a study recipient presenting for medical care, or upon review by a study monitor.

Information to be collected includes event description, time of onset, clinician's assessment of grade, relationship to study product (assessed only by those with the training and authority to make a diagnosis), seriousness, action taken with study drug, outcome, and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution. All AEs must be reported on CRF to sponsor in order to record them for a final report to the Danish Medicines Agency.

Any medical condition that is present at the time that the patient is screened should be considered as baseline and not reported as an AE. However, if it deteriorates at any time during the study, it should be recorded as an AE.

Changes in the severity of an AE should be documented to allow an assessment of the duration of the event at each level of intensity to be performed. Adverse events characterized as intermittent require documentation of onset and duration of each episode.

8.1 Serious adverse events (SAEs)

An SAE is defined as an AE that meets one of the following conditions:

- Death during the period of protocol defined surveillance
- Life-threatening event (defined as a patient at immediate risk of death at the time of the event)
- An event requiring inpatient hospitalisation or prolongation of existing hospitalisation during the period of protocol defined surveillance with the exception of treatment-related enteritis or fatigue, leucopenia, thrombocytopenia or hospitalization due to treatment administration or other elective measures
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity
- Any other important medical event that may not result in death, be life threatening, or require hospitalisation, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalisation, or the development of drug dependency or drug abuse.

In this study unexpected and related SAEs are defined as adverse reactions with at least a possible relationship to study therapy that are not consistent with the approved summary of product

characteristics (SPC) and which to their nature are serious. The SPC is available at: www.emea.europa.eu

All SAEs will be recorded on the appropriate SAE CRF, followed through resolution by the investigator, and reviewed and evaluated by the Medical Monitor

Abnormal laboratory values and clinical adverse events will be reported as SAEs if they are graded higher than 3 on the CTC v3.0.

Any adverse event that is considered SERIOUS must be reported within one working day (IMMEDIATELY) by the investigator to the Sponsor. Sponsor must make sure that information on all suspected unexpected serious adverse reactions (SUSARs) which are fatal or life-threatening are reported as soon as possible and within 7 days to the Danish Medicines Agency after sponsor has received knowledge himself (if applicable also to local health authorities as per national regulations). All other SURSARs must be reported to Danish Medicines Agency within 15 days. All related and unexpected SAEs are also immediately reportable to Roche A/S as expedited reports:
Drug Safety Roche A/S
Fax: +45 3639 9930
Tel.: +45 3639 9828/+45 3639 9821

Not immediately reportable SAE:
Progression or deterioration of the malignancy under study (including new metastatic lesions and death due to disease progression) will be part of the efficacy assessment and should NOT be reported as AE/SAE. *Signs* and *symptoms* clearly associated with the malignancy under study should NOT be reported as AE/SAE unless:

- Newly emergent (i.e. not present at baseline) and association with the underlying malignancy and old/new metastatic lesions is unclear
- If the investigator attributed deterioration of malignancy-associated signs and symptoms directly to the study drug
- Should there be any uncertainty regarding the attribution of the malignancy under study to an AE, it should be reported as an AE or a SAE accordingly.

8.2 Expected adverse effect

Tarceva: The most common, expected adverse events for Tarceva include: Rash, pruritus, dry skin, diarrhea, nausea, vomiting, stomatitis, abdominal pain, fatigue, dyspnoe, cough, anorexia, infection, conjunctivitis, and keratoconjunctivitis sicca.

Irradiation: The toxicity of irradiation of NSCLC is determined of the dose and treatment volume of organs at risk. These are as followed:

Organs at risk	Acute (1-12 weeks)	Late >3 months
Lung[1]	Pneumonitis (cough, dyspnoe, fever)	Fibrosis (cough, dyspnoe)
Esophagus[2]	Swallowing difficulties, pain	Stenosis (swallowing difficulties)
Heart	Pericarditis[4]	Fibrosis
Skin	Edema, skin rash	Fibrosis, telangiectasier
Spinal cord	Lhermitte sign[3]	Radiation myelitis[4] (neurological deficits)

([1]: The risk of acute pneumonitis may increase in irradiation when Tarceva is combined with -radiation. The risk of pneumonitis increases with the V_{20} of the lung. The symptoms may develop before stop of irradiation. The treatment in the case of pneumonitis is steroid ± antibiotics.

([2] Occurrence of esophagitis is connected to treatment volume and concomitant therapy.

([3] Lhermitte sign is a transient self-limiting symptom of radiation impact on the cervical spinal cord.

([4]Pericarditis and radiation myelitis: no cases of these side effects are expected in this study.

8.3 Management of radiation complications during radiotherapy

In case of grade 3 or worse esophagitis or pneumonitis, the administration of Tarceva will be terminated for that patient.

8.4 Management of radiation complications

In case of increasing dyspnoe during radiation or within 3 months after cessation of radiation pneumonitis must be suspected. Treatment with steroids is recommended e.g. prednisolone 25-50 mg or higher doses if necessary administered as 1-2 daily doses. Since infection is difficult to rule out, it is recommended to start treatment with antibiotics. Since tumor progression, myocardial infarction, and tromboembolic conditions may occur in these patients, ECG and appropriate biochemistry should be obtained. CT-scan or ECCO of the heart may be necessary.

8.5 Management of rash inside and out side radiation field

Management of rash should be treated according to institution guidelines.

9. Ethical consideration

Patients with locally advanced non-small cell lung cancer have a very poor long-time survival as only about 15% of the patients are alive 5 years after curatively intended radiotherapy (1). A major cause of these poor results is lack of local control of the tumor after radiotherapy. Standard treatment prescribes concurrent chemo-radiation but in many cases use of concurrent chemo-radiation is not feasible. Another problem in the treatment of locally advanced NSCLC is occurrence of toxicity. There is therefore an urgent need to develop treatment that increases local control without increasing toxicity to an unacceptable level. The current study is designed to do that. The protocol fulfils the Helsinki II declaration and the national requirement to studies of

patients with a cancer disease. The patients will be fully informed about the aspects of the treatment and risk included in participating. Informed consent will be obtained after sufficient time of reflection has been given.

10. Study conduct and economy

The study is investigator initiated and will be conducted according to the ICH-CGP guidelines and according to regulatory requirements. Olfred Hansen is the principal investigator (sponsor). The study is part of the Danish Center for Interventional Research in Radiation Oncology (CIRRO), protocol CIRRO IP020209. The patients will be recruited among patients referred for treatment at each participating center. Economical support of 15,000 DKK per patient included to carry out the study will be applied from the company Roche a/s, DK, which manufacture Tarceva. This support is to compensate the additional time used by the staff, primarily by research nurses, who help with registration of effects and side effects of the treatment, and the amount will be paid to the research unit at the oncology centers. There is no economical befit for neither the department, the investigators in the study, nor the staff.

11. Publication

The study will be published in an international journal despite the result. The first draft of the manuscript will be prepared by Olfred Hansen. Other members of the protocol committee will be authors if the institutions they represent include patients. Any other center including 3 patients or more will be offered authorship according to the Vancouver rules of authorship.

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13. Appendixes

Appendix 1: Performance status

Eastern Cooperative Oncology Group (Zubrod-ECOG)[1,2]	
Description	Grade
Fully active, able to carry on all pre-disease activities without restriction.	0
Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g. light house work, office work.	1
Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.	2
Capable of only limited self care, confirmed to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self care. Totally confined to bed or chair.	4

[1] Zubrod, C.G., et al. *Appraisal of Methods for the Study of Chemotherapy of Cancer in Man*. Journal of Chronic Diseases, 11:7-33, 1960.

[2] Oken, M.M., et al. *Toxicity and response criteria of the Eastern Cooperative Oncology Group*. Am J Clin Oncol (CCT) 5: 649-655, 1982

Appendix 2: Objective response criteria (RECIST).

Complete Response: Disappearance of all clinical and radiological evidence of tumor (both *target* and *nontarget*) including normalization of elevated tumor markers at baseline, if documented. The patient must be free of all tumor-related symptoms. Complete Response must be confirmed at a second tumor assessment not less than 28 days apart from the assessment at which CR was observed.

Partial Response: At least a 30% decrease in the sum of LD of target lesions taking as reference the baseline sum LD. Partial Response must be confirmed at a second tumor assessment not less than 28 days apart from the assessment at which PR was observed.

Stable Disease: Steady state of disease. Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. Stable disease must be documented to be present at least 28 days from the start of the therapy. There may be no appearance of new lesions for this category.

Progressive Disease: At least a 20% increase in the sum of LD of measured lesions taking as references the smallest sum LD recorded since the treatment started. Appearance of new lesions will also constitute PD. In exceptional circumstances, unequivocal progression of nontarget lesions may be accepted as evidence of disease progression.

Appendix 3: Monitoring and data capture.

Study conduct and monitoring will be done according to GCP. The monitoring will be performed by the GCP unit at Odense University Hospital together with the GCP units at participating centers.

Appendix 4: Dosage guidelines for management of study drug related toxicities

Toxicity, CTC Grade	Study Drug Dosage Modification	Guideline for Management
Diarrhea		
Grade 1	None	Consider Loperamide (4 mg at first onset, followed by 2 mg every 2 – 4 hours until diarrhea free for 12 hours) Appropriate rehydration
Grade 2	None	Loperamide (4mg at first onset, followed by 2 mg every 2 – 4 hours until diarrhea free for 12 hours) Appropriate rehydration
Grade 3	Interrupt Tarceva™	Loperamide (4 mg at first onset, followed by 2mg every 2 – 4 hours until diarrhea free for 12 hours) **and** Interrupt Tarceva™ until resolution to Grade ≤ 1, and restart at reduced dose Appropriate rehydration
Grade 4	Discontinue Study	Loperamide (4 mg at first onset, followed by 2mg every 2 – 4 hours until diarrhea free for 12 hours) Appropriate rehydration
Rash		
Grade 1	None	Any of the following: minocycline [a], topical tetracycline, topical clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course) at discretion of the investigator.
Grade 2	None	Manage as described above
Grade 3 (or intolerable Grade 2)	Dose reduction; dose can be re-escalated when rash is ≤ Grade 2	Manage as described above
Grade 4	Discontinue Study	Manage as described above

[a] Recommended dose: 200 mg orally bid (loading dose) followed by 100 mg orally bid × 7–10 days.

Appendix 5: Dose calculation, treatment margins and reporting of the treatment plan

1. Planning

Energy for treatment is 6-10 MV. If available the treatment plans should be calculated using models that in an approximate way consider changes in lateral electron transport (e.g. Pinnacle/CC, Eclipse/AAA, OMP/CC and XiO/Super) (16).

2. Margins

The planning margins needed to ensure dose coverage of a tumour depends strongly on the imaging equipment used for planning of the treatment and as well as the imaging equipment used during the treatment. New emerging technique (e.g. 4D CT and Cone Beam CT) will soon make it possible individualise the margins for each patient. However, these techniques are not standard clinical practice yet thus each institution can choose between two different sets of margins 1) standard margins 2) individual margins. Each institution shall report which of the two sets of margins they are using. For the individual margins all patient specific value of Σ and σ shall be reported for each patient (all institution specific values of Σ and σ is only to be reported for the first patient)

2.1 *Standard margins*

Refer to protocol §4.1.

2.2 *Individual margins*

GTV and CTV as for standard margins (refer to protocol §4.1).

ITV and PTV is combined to one volume based on the margin formula by (14) Herk et al.

PTV: The PTV is the CTV plus a margin of M as defined below:

$$M = 2.5\Sigma + \beta\sqrt{\sigma^2 + \sigma_p^2} - \beta\sigma_p$$

where Σ and σ is the standard deviation of the systematic and random uncertainty, respectively. σ_p is a measure for the shape of the penumbra of the total dose distribution. The β-value is a constant related to the isodose level which should cover the target. For coverage of the target by 95% of the prescribed dose the value of β is 1.64 (for details see (14)). Since M depends on σ_p, M depends on the field arrangement as this can influence the shape of the penumbra of the overall treatment plan. However, the exact value of σ_p is not very critical since the margin recipe do only depend weakly on this value. Typical value of σ_p is 6-7 mm in the lung region (17).

Both Σ and σ is a combination of all the uncertainties involved in the treatment process which can be divided in tumour delineation (no random component), intra-fractional tumour uncertainty and inter-fractional tumour uncertainty.

$$\Sigma^2 = \Sigma_{delineation}^2 + \Sigma_{intrafractional}^2 + \Sigma_{interfractional}^2$$

$$\sigma^2 = \sigma_{intrafractional}^2 + \sigma_{interfractional}^2$$

The idea of using patient specific margins is to minimize the margins as much as possible for the individual patient. To achieve this goal a number of the above mentioned uncertainties needed to be assessed in the specific institution. Below is a brief description of each uncertainty. For some of the components typical values are given, however these needs to be validated at each institution. It should also be stressed that residual errors will always persist, thus for some of the uncertainties a lower bound of the value is given.

$\Sigma_{delineation}$: Difficult to measure, a value of 2 mm shall be used for a 4D planning CT (17). The uncertainty is larger for a 3D CT due to distortion of the tumour.

$\Sigma_{intrafractional}$: For standard 3D planning CT equal to $\sigma_{intrafractional.}$ Using 4D CT planning can be based on the mid-ventilation phase (18). For planning using the mid-ventilation phase $\Sigma_{intrafractional}$ is very close to zero. However, a residual error will always exist, thus a value of 1 mm is to be used.
$\sigma_{intrafractional}$: Is to be measured in a 4D CT as the standard deviation of the tumour position in each respiration. A lower bound of 1 mm is to be applied for $\sigma_{intrafractional}$.

The values of $\Sigma_{interfractional}$ and $\sigma_{interfractional}$ need to be assessed in each individual institution.
The inter-fractional uncertainty depends strongly on the imaging technique used during the treatment. Especially it is important whether the imaging is based on the bony anatomy or on the soft tumour tissue.

If the imaging technique is based on bony landmarks the inter-fractional uncertainty needs to include the movement of the tumour relative to the bony structure ($\Sigma^2_{intrafractional} = \Sigma^2_{baseline} + \Sigma^2_{setupbony}$ and $\sigma^2_{intrafractional} = \sigma^2_{baseline} + \sigma^2_{setupbony}$). Typical value of $\Sigma_{baseline}$ and $\sigma_{baseline}$ is 2-4 mm and 2 mm, respectively (17).

If the imaging is based on the soft tumour tissue the inter-fractional component do not contain two component, but is just the setup uncertainty relative to the soft tissue. Typical values of $\Sigma_{interfractional}$ and $\sigma_{interfractional}$ are about 1 mm (17, 19).

In Sonke et al (17) there is a graph (fig. 5) showing an example of the overall CTV to PTV margin in their institution. It is seen that the margin do not dependent strongly on the respiration amplitude. This does not indicate that it is possible to just apply a large value of the respiration movement and then disregard 4D CT for treatment planning. The data in Sonke et al. is based on the assumption that the treatment planning is performed in the mid-ventilation phase which is only possible if a 4D CT is used for treatment planning.

It is important to stress that all the above mentioned typical values is only a guideline for the approximate size of the individual parameters. All the values need to be validated at the local institution before use.

3. Reporting of the treatment plan

Reporting of the physical properties of the treatment plan is based on DICOM RT. All plans will be collected in a database such that whey will be available to all institutions.

The database will be hosted at Odense University Hospitals and will be available as a service on on a closed net dedicated for transfer of patient data on secure lines.

All data is reported in DICOM RT such that each institution by a simple operation can export al available instead of using time to extract a few key values of the DVH's

After upload of the treatment plan (CT images, point, regions of interest, dose and plan) the DVH data will be extracted and added to a common database.

Names of Regions of interest (ROI):

In order to obtain usable information from the DICOM RT plans it is important that regions which might be of scientific interest are named in the same way for all patients within each institution. Thus each institution should report a list of their naming convention such that their DVH structures can be recognised automatically. The list of ROI names should consist of the following regions:

Left Lung (suggestion LeftLung)
Right Lung (suggestion RightLung)
Heart (suggestion Heart)

The spinal canal (suggestion Medulla)
Esophagus (suggestion Esophagus)
Gross tumour volume (suggestion GTV or if more than one GTV1, GTV2, …)
Clinical target volume (suggestion CTV or if more than one CTV1, CTV2,…)
Internal target volume (suggestion ITV or if more than one ITV1, ITV2,…)
Planning target volume (suggestion PTV or if more than one PTV1, PTV2,…)

It is important to be consistent in the names of ROI. However, misunderstanding will occur thus each institution should also forward an e-mail on the person to contact if interpretation of the ROI name is not feasible.