Official Title: **Phase II, open-label study of erlotinib (Tarceva®) treatment in patients with locally advanced or metastatic non-small cell lung cancer who present activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor**

NCT Number: NCT01260181

Document Date: Protocol Version 1.5: 12 Feb 2014

PROTOCOL

TITLE:	**Phase II, open-label study of erlotinib (Tarceva®) treatment in patients with locally advanced or metastatic non-small cell lung cancer who present activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor**
PROTOCOL NUMBER:	ML25434
VERSION NUMBER:	1.5
EUDRACT NUMBER:	Nº 2010-022509-17
IND NUMBER:	OSI-774
TEST PRODUCT:	Tarceva®; Erlotinib;
MEDICAL MONITOR:	[redacted]
SPONSOR:	Roche Farmacêutica Quimica, Lda
DATE FINAL:	Version 1.3: 30th November 2010
DATE{S} AMENDED:	Version 1.4: 28th October 2011 Version 1.5: 12nd February 2014

PROTOCOL AMENDMENT APPROVAL

[redacted]

CONFIDENTIAL STATEMENT

PROTOCOL AMENDMENT, VERSION 1.5:
RATIONALE

Protocol ML25434 has been amended to include an interim analysis. Considering the current lack of characterization data as well as efficacy and safety outcomes in the target Portuguese population (1st line EGFR Mut^{+} mNSCLC), it became relevant to perform a preliminary analysis of the data collected up to 30th September 2013.
This interim analysis will allow a preliminary understanding about the clinical benefits of erlotinib in this population and compare it with published studies that were conducted in the caucasian international population. This analysis will also allow the basal characterization of this population, specially the rate of EGFR mutation and the histological type.
Further amendments have been included to update the current safety reporting guidelines to correct inconsistencies.

Additional changes to the protocol are as follows:

- Inclusion of an objective aiming to evaluate response duration (RD). The corresponding efficacy variable and analytical method was also added
- Clearer definition of PFS described in the objective and corresponding variable.
- Clearer definition of secondary efficacy variable overall survival
- Inclusion of an exploratory efficacy analysis (PFS summarized by exon 19 and 21)
- Clarification regarding the efficacy analysis – ITT will be considered as the primary analysis.
- Clearer definition regarding the per protocol (PP) population and major/minor protocol deviations
- The reporting requirements for SAEs and AEs of special interest have been revised in alignment with recent global requirements.

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics (book antiqua). This amendment represents cumulative changes to the original protocol.

PROTOCOL AMENDMENT, VERSION 1.5
SUMMARY OF CHANGES

PROTOCOL AMENDMENT ACCEPTANCE FORM
A Protocol Amendment Acceptance Form has been added.

GLOBAL CHANGES Main changes included:

- Introduction of an interim analysis
- Clearer description of some of the study efficacy variables
- Update the safety information concerning:
    - Adverse events and Laboratory abnormalities
    - Handling of safety parameters

PROTOCOL SYNOPSIS
The protocol synopsis has been updated to reflect the changes to the protocol, where applicable, namely:

- the response duration efficacy assessment
- the inclusion of the intent-to-treat population analyses

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS
The list of abbreviations and definitions of terms has been updated to reflect the changes to the protocol, where applicable.

SECTION 2.2: Secondary Objectives
To evaluate progression-free survival (PFS), defined as the time from baseline visit to the date of first occurrence of disease progression or death *due to any cause*.
To evaluate the EGFR mutation frequency, in the study population.
To evaluate the Overall Survival defined as the time from baseline visit to the date of death due to any cause.
To evaluate the erlotinib safety profile (Tarceva®; 150 mg).
To evaluate response duration (RD) defined as the time of initial response (CR/PR whichever is first recorded) until documented disease progression.

SECTION 3.3: Interim Analyses

One interim analysis is planned for the study. This interim analysis will include an epidemiological, efficacy and safety characterization of erlotinib in 1st line EGFR Mut+ mNSCLC Portuguese population. The rationale for this interim analysis is to analyse the preliminary clinical benefits on this population and compare it with the available data in publications held in the caucasian international population.

Additionally, the interim analysis will evaluate the EGFR mutation rate; describe the enrolled population related to the gender, histology type, smoking habit and the incidence of EGFR mutation; as well as the safety evaluations in terms of events, frequency and severity.

SECTION 7: Safety instruction and guidance

~~After informed consent, but prior to initiation of study medication, only SAEs caused by a protocol mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run in).~~

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study. Certain types of events require immediate reporting to the Sponsor, as outlined in Section 7.2.2.

SECTION 7.1: Adverse Events and Laboratory Abnormalities

Clinical AEs

~~According to the International Conference of Harmonization (ICH), an AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product. Pre-existing conditions which worsen during a study are to be reported as AEs.~~

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- *Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product*
- *Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)*
- *Recurrence of an intermittent medical condition (e.g., headache) not present at baseline*

- *Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug*
- *Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)*

SECTION 7.1.1: Severity

~~Severity of all adverse events will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events v 4.0 (CTCAE) on a five-point scale (Grade 1 to 5) and reported in detail on the eCRF.~~

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	*Severity*
1	*Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated*
2	*Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living* [a]
3	*Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living* [b,c]
4	*Life-threatening consequences or urgent intervention indicated d*
5	*Death related to adverse event* [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm
[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Sections 7.2.1 and 7.2.2 or reporting instructions), per the definition of serious adverse event in Section 7.1.3.
[d] Grade 4 and 5 events must be reported as serious adverse events (see Sections 7.2.1. and 7.2.2. or reporting instructions), per the definition of serious adverse event in Section 7.1.3.

SECTION 7.1.3: Serious Adverse Events (Immediately Reportable to Roche)

~~A serious adverse event (SAE) is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any Adverse Event that at any dose fulfils at least one of the following criteria:~~

~~is fatal; (results in death; NOTE: death is an outcome, not an event)~~

~~is Life Threatening (NOTE: the term "Life Threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe).~~

~~required in patient hospitalization or prolongation of existing hospitalization;~~

~~results in persistent or significant disability/incapacity;~~

~~is a congenital anomaly/birth defect;~~

~~is medically significant or requires intervention to prevent one or other of the outcomes listed above.~~

~~The term “severe” and “serious” are not synonymous. Severity refers to the intensity of an AE. Serious is a regulatory definition and is based on patient or event outcome or action criteria usually associated with events that pose a threat to a patient’s life or vital functions. Seriousness (not severity) serves as the guide for defining regulatory reporting obligations.~~

~~The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2A.~~

A serious adverse event is any adverse event that meets any of the following criteria:

- *Fatal (i.e., the adverse event actually causes or leads to death)*

- *Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)*
- *This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.*
- *Requires or prolongs inpatient hospitalization*
- *Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)*
- *Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug*
- *Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)*

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria; see Section 7.1.1); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).
Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.
Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 7.2.2 for reporting instructions).

SECTION 7.1.4.1: Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

~~Additional information on the following serious and non-serious AEs of special interest will be captured during this study: Stevens Johnson Syndrome and Interstitial Lung Disease (ILD).~~

~~The above events of special interest should be reported as SAEs according to Serious Adverse Event definition.~~

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 7.2.2. for reporting instructions).
Adverse events of special interest for this study include the following:

- *Suspected transmission of an infectious agent by the study drug, as defined below*
- *Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.*
- *Stevens-Johnson Syndrome*

- *Interstitial Lung Disease (ILD)*

SECTION 7.2: Handling of Safety Parameters
SECTION 7.2.2: Reporting of Serious Adverse Events (immediately reportable)
~~Any clinical adverse event or abnormal laboratory test value that is serious and any AE of special interest which occurs during the course of the study, since the start of study drug treatment and until the end of the survival follow-up period must be reported to Roche within one working day of the investigator becoming aware of the event (expedited reporting). If:~~

- ~~considered related with the study medication, it MUST be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.~~
- ~~considered unrelated, it MUST be collected and reported up to 28 days after last study drug administration (safety follow-up visit).~~

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- *Serious adverse events*
- *Non-serious adverse events of special interest*
- *Pregnancies*

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- *New signs or symptoms or a change in the diagnosis*
- *Significant new diagnostic test results*
- *Change in causality based on new information*
- *Change in the event's outcome, including recovery*
- *Additional narrative information on the clinical course of the event*

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

The investigator must complete the SAE Reporting Form [gcp_for000031] and forward it to the SAE Responsible.
Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to investigators at each site and to CEIC (Comissão de Ética para a Investigação Clínica) on an expedited basis, when the following conditions occur:
The event must be a SAE.

- There must be a certain degree of probability that the event is an adverse reaction from the administered drug.
- The adverse reaction must be unexpected, that is to say, not foreseen in the SPC text (Summary of Product Characteristics (for an authorized medicinal

product)) or the Investigator's Brochure (for an unauthorized medicinal product).

SECTION 7.2.3: Emergency Medical Contacts

~~ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor.~~
~~24 HOUR MEDICAL COVERAGE: Call the local emergency contact number provided by the Monitor.~~

Medical Monitor Contact Information for all sites:
Medical Monitor: [redacted]
Telephone No.: [redacted]
Mobile Telephone No.: [redacted]

SECTION 8.1: Primary and Secondary Study Variables
SECTION 8.1.2: Secondary Variables

The secondary efficacy variables are:

- Progression-free survival, defined as the time from baseline visit to the date of first occurrence of disease progression or death *due to any cause.*
- Overall survival defined as the time from the baseline visit (first dose of erlotinib) to the date of death due to any cause
- Frequency of EGFR mutation.
- *Response duration, defined as the time of initial response (CR/PR whichever is first recorded) until documented disease progression.*

SECTION 8.2: Statistical and Analytical Methods;
SECTION 8.2.1.2: Secondary Variables

PFS will be summarized as median time and will be estimated trough Kaplan-Meier method. 95% confidence interval will be estimated for median time to PFS.

Overall survival variable will be summarized as median time to OS and will be estimated trough Kaplan-Meier method. 95% confidence interval will be estimated for median time to OS.

The presence of EGFR mutation in the study population will be presented as relative frequency presented as a percentage (%). A 95% confidence interval will be estimated for this value using binomial distribution.

Response duration variable will be summarized as median time to response duration and will be estimated trough Kaplan-Meier method. 95% confidence interval will be estimated for median time to response duration.

SECTION 8.2.1.3: Exploratory Analysis

PFS will be summarized by exon 19 and 21 as median time and will be estimated trough Kaplan-Meier method.

SECTION 8.2.3: Types of Analyses

SECTION 8.2.3.1: Efficacy Analysis

Efficacy analysis will be ~~primarily~~ based on the intent-to-treat *and per-protocol* population. *The ITT analysis will be considered as the primary analysis.*

~~Exclusion of Data from Analysis~~

~~Patients with protocol violations will be excluded from statistical analysis for primary and secondary endpoints.~~

SECTION 8.2.3.1.2: Per-protocol population

Per protocol population will include all subjects enrolled in the treatment phase of the study without major protocol violations. ~~Per protocol population will be defined as all subjects who fulfill the protocol in the terms of the eligibility, interventions, and outcome assessment~~. *The protocol violations and corresponding impact are listed below.*

Table 6 – Categories of protocol deviations

Category	***Impact***
Assessment not performed	*Minor/Major*
Deviations from the dosing of the IPs	*Major*
Inconsistency with inclusion/exclusion criteria	*Major*
Non-compliance with the dose reduction schedule	*Major*
Prohibited concomitant medication	*Major*
Treatment not discontinued after withdrawal criteria is met	*Major*
Visit dates not per protocol	*Minor*

SECTION 8.2.7: Interim Analysis

One interim analysis is planned for the study with a cut-off date on 30th September 2013. This interim analysis will include an epidemiological, efficacy and safety characterization of erlotinib in 1st line EGFR Mut+ mNSCLC Portuguese population.

Interim analysis will include the following descriptive analyses:

Characterization - demographics, medical history, Eastern cooperative oncology group performance status, clinical response (RECIST criteria).

Efficacy – Best Overall response, progression free survival, overall survival and epidermal growth factor receptor. Additionally, PFS will be obtained for Exon 19 and Exon 20 (if applicable).

Safety – Drug compliance, adverse events (incidence of AE and SAE, incidence of AE and SAE with remote, possible or probable relationship with study drug, description of AE and SAE, SAE with remote, possible or probable relationship with study drug) and subsequent therapy for NSCLC.

Analysis will be conducted according to the definitions described in section 8.1 and considering the populations described in section 8.2.1.

TABLE 6: Categories of protocol deviations

Table 6 was added to specify major and minor deviations

No changes were made in Figures or appendices.

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	Phase II, open-label study of erlotinib (Tarceva®) treatment in patients with locally advanced or metastatic non-small cell lung cancer who present activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor
PROTOCOL NUMBER:	ML25434
VERSION NUMBER:	1.5
EUDRACT NUMBER:	2010-022509-17
IND NUMBER:	OSI 774
TEST PRODUCT:	Erlotinib
MEDICAL MONITOR:	[redacted]
SPONSOR:	Roche Farmacêutica Química, Lda.

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please return the signed original of this form as instructed by your local study monitor and retain a copy for your study files.

Contents

SYNOPSIS OF PROTOCOL NUMBER ML25434

TITLE	Phase II, open-label study of erlotinib (Tarceva®) treatment in patients with locally advanced or metastatic non-small cell lung cancer who present activating mutations in the tyrosine kinase domain of the epidermal growth factor receptor.
SPONSOR	Roche Farmacêutica Química, Ltd.
CLINICAL PHASE	II
INDICATION	Locally advanced or metastatic non-small cell lung cancer (NSCLC).
OBJECTIVES	**Primary:** Objective response rate (ORR) of erlotinib (Tarceva®; 150 mg) in patients with locally advanced or metastatic stage non-small-cell lung cancer (NSCLC), who have not received previous chemotherapy for their disease and who present activating mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR). **Secondary:** • Progression-free survival (PFS), • Overall survival (OS), • Safety profile, • Evaluate the EGFR mutation frequency in the study population, • Response duration (RD).
TRIAL DESIGN	Open-label, multi-centre Phase II study
NUMBER OF SUBJECTS	30 patients
TARGET POPULATION	Patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC who have not received previous chemotherapy for their disease and who present activating mutations in the TK domain of the EGFR.
INCLUSION CRITERIA	1. Patients able and willing to give written informed consent. Consent must be obtained prior to any study-specific procedure. 2. a) Histologically or cytologically documented inoperable, locally advanced or metastatic NSCLC disease; b) Patient that presents activating mutations in the tyrosine kinase domain of EGFR (Exon 19 deletion and/or exon 21 substitution L858R);

	3. Measurable disease, according to RECIST - *Response Evaluation Criteria in Solid Tumours*). 4. Male or female patients aged ≥ 18 years. 5. Life expectancy ≥ 12 weeks. 6. Adequate haematological and coagulation function as assessed by the investigator. 7. Adequate liver and renal function as assessed by the investigator. 8. Female patients must be postmenopausal (24 months of amenorrhea), surgically sterile or they must agree to use a physical method of contraception. Male patients must be surgically sterile or agree to use a barrier method of contraception. Male and female patients must use effective contraception during the study and for a period of 90 days following the last administration of erlotinib. Acceptable methods of contraception include an established hormonal therapy or intrauterine device for females, **and** the use of a barrier contraceptive (i.e. diaphragm or condoms) with spermicidal. 9. If applicable, patients with asymptomatic and stable cerebral metastases receiving medical treatment will be eligible for the study. Those patients may have received radiation therapy for their cerebral metastases before the initiation of systemic treatment for non-small-cell lung cancer. 10. Able to comply with the required protocol and follow-up procedures
EXCLUSION CRITERIA	1. Previous treatment with chemotherapy or therapy against EGFR, either with antibody or small molecule (tyrosine kinase inhibitor) for metastatic disease. The administration of neo-adjuvant or adjuvant therapy is allowed as long as it has finalized • 6 months before entering the study. Patients can have received radiotherapy as long as the irradiated lesion is not the only target lesion for evaluating response and as long as radiotherapy has been completed before initiating the study treatment (28 days period is recommended). Treatment with an investigational drug agent during the four weeks before enrolment in the study. 2. History of another neoplasm other than

carcinoma in situ of the uterine cervix, basal cell skin carcinoma treated adequately, or prostate carcinoma with a good prognosis (Gleason • 6) treated radically. History of another neoplasm treated curatively and without evidence of disease in the last 5 years. History of breast cancer and melanoma at any time.

3. Patients with symptomatic cerebral metastases.
4. Known hypersensitivity to erlotinib or any of its excipients.
5. Any significant ophthalmologic abnormality, especially severe dry eye syndrome, keratoconjunctivitis sicca, Sjögren's syndrome, severe exposure keratitis or any other disorder likely to increase the risk of corneal epithelial lesions. (The use of contact lenses is not recommended during the study. The decision to continue to wear contact lenses should be discussed with the patient's treating oncologist and the ophthalmologist.)
6. Use of coumarins (Sintrom®; Varfine®). If the patient requires anti-coagulant therapy, instead of coumarins, the use of a low molecular weight heparin is recommended, whenever clinically possible.
7. Patients with severe hepatic and renal impairment as assessed by the investigator.
8. Evidence of any other disease, neurological or metabolic dysfunction, physical examination or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment-related complications.
9. a) Positive urine/blood pregnancy test in women of childbearing potential. Female patients should not be pregnant or breast-feeding.
   b) Patients (male or female) with reproductive potential not willing to use effective method of contraception during the trial and during 90 days after the last erlotinib administration. Oral or injectable contraceptive agents cannot be the sole method of contraception.
10. Patients with pre-existing disease of the lung parenchyma such as lung fibrosis,

	lymphangitic carcinomatosis. 11. Patients with known infection with HIV, HBV, HCV. Testing is not required in the absence of clinical signs and symptoms suggestive of these conditions. 12. Patients those in the Investigator's opinion are not able to accomplish protocol requirements. 13. Incapacity to take oral medication or previous surgical procedures that affect absorption and imply the need for intravenous or parenteral feeding.
LENGTH OF STUDY	This study is event-driven, with a recruitment period that will last until the end of March 2012 or until the number of patients aimed for the protocol (30) is achieved, whatever occurs first. Patients are to be treated until disease progression, unacceptable toxicity, death or patient request for discontinuation.
END OF STUDY	The study will end when the last patient has stopped erlotinib therapy and completed their last safety follow-up visit (28 days after last study drug administration). For all patients who have discontinued study drug treatment and are alive, information on survival will be collected.
INVESTIGATIONAL MEDICAL PRODUCT(S) DOSE/ ROUTE/ REGIMEN	Patients will be dosed daily with 150 mg erlotinib taken orally until disease progression or unacceptable toxicity. Dose reduction will be allowed according to protocol (Section 6.)
ASSESSMENTS OF: - EFFICACY	**Primary endpoint:** • Objective Response Rate (ORR). **Secondary endpoints:** • Progression Free Survival, • Overall Survival (OS), • Safety profile, • EGFR mutation frequency, • Response duration (RD).
- SAFETY	All evaluations will be performed accordingly with the Schedule of Assessments. If clinically indicated, more evaluations could be performed. All adverse events (AEs) will be assessed using the National Cancer Institute Common Terminology Criteria for AEs (NCI CTC-AE) version 4.0. The incidence of serious adverse events (SAEs) and non-SAEs related to

		erlotinib therapy will be determined. Additional information about AEs of special interest (serious and non-serious) such as Stevens-Johnson syndrome and interstitial lung disease (IDL)-like events will be collected. Information about laboratory exams (haematology, biochemistry and coagulation), ECG and physical examination will be also collected.
-	EGFR Mutation analysis	If patients are deemed eligible to participate in the study by the investigator, a surgical fragment or biopsy formalin-fixed, paraffin-embedded or a tumour material obtained through aspiration cytology fixed and paraffin-embedded in a cell-block, must be sent to the Central Laboratory [redacted]. If activating mutations (exons 19 and/or 21 mutations) in the TK domain of EGFR gene are identified, patients are eligible to participate in the study.

PROCEDURES (summary):

The following examinations will be made as scheduled in the attached table:

- After the signature of the patient informed consent form, the EGFR mutation testing will be performed at the Central Laboratory [redacted] by Sequencing Technique.
- Interview and physical examination, including assessment of concomitant medications, ECOG performance status, and clinical tumour measurements. This information will be obtained in the 21 days before initiation of treatment. A pregnancy test will be ordered if appropriate.
- Baseline symptoms and toxicity symptoms evaluated using NCI CTC-AE version 4.0 (Annex 1) (if NCI CTC-AE are not applicable, the MedDRA classification will be used).
- Blood tests with counts of the three series (leukocytes with neutrophils, haemoglobin, and platelets). This information will be obtained in the 21 days before initiation of treatment.
- Biochemistry: LDH, alkaline phosphatase, ASAT, ALAT, total bilirubin, serum creatinine, creatinine clearance (if indicated), calcium, electrolytes, glucose and urea. This information will be obtained in the 21 days before initiation of treatment.
- Prothrombin time, INR and aPTT. This information will be obtained in the 7 days before initiation of treatment.
- Pregnancy test in women of childbearing age, to be performed at screening and in the 1st day of study treatment (baseline), before the intake of study medication and at the end of study treatment.

- Tumour assessment, using computer tomography (CT) scanning of chest and upper abdomen and other scans as necessary, to document all sites of the disease.
- Other investigations as indicated clinically, including ECG.

STATISTICAL ANALYSES:

Sample size:

The sample size was calculated based on the primary variable of the study, objective response rate. Since this proportion is unknown an exploratory sample size of 30 patients was considered to evaluate primary endpoint. This sample size will allow estimating ORR with a margin of error of approximately ±17.5%, for a 95% confidence interval. Furthermore, approximately 2000 new cases of stage IIIB and IV NSCLC are diagnosed per year in Portugal[1] and, based on published data, expected prevalence of EGFR mutation is approximately 10%. With a 95% confidence interval, it was calculated that at least 420 patients will have to be enrolled to be tested to achieve 30 positive cases for the exploratory sample size analysis.

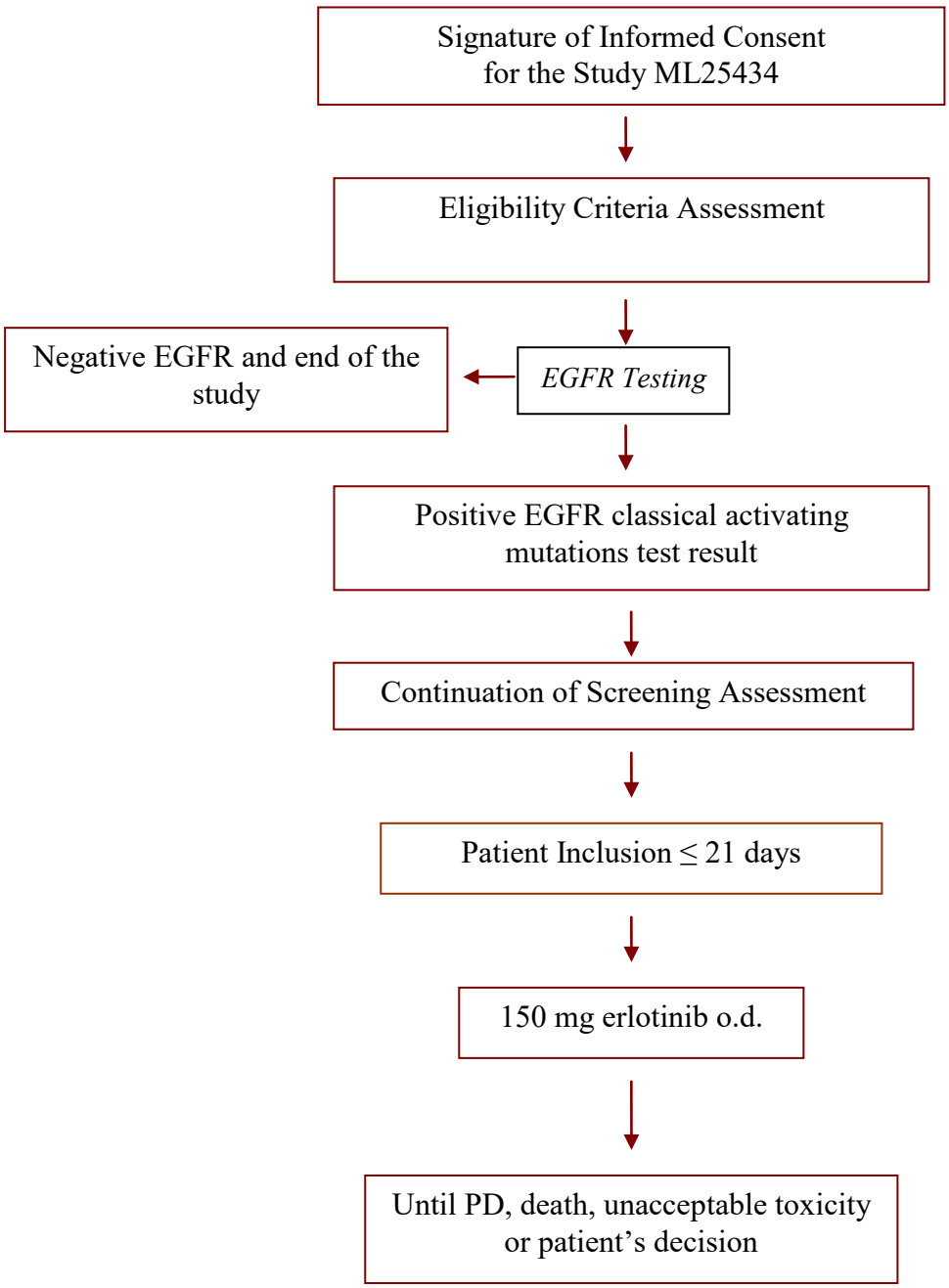
Efficacy Analyses:

The primary efficacy analyses will be performed on the intent-to-treat and per-protocol populations. Secondary analyses will be performed on the intent-to-treat population.
For ORR 95% confidence interval will be estimated.
PFS, OS and RD will be estimated and presented as median time to PFS,OS and RD trough Kaplan-Meier method. 95% confidence intervals will be estimated for these parameters.
EGFR expression will be presented as a percentage and 95% confidence intervals will be estimated for this value.

Safety Analyses:

All safety parameters will be summarized and presented in tables based on the safety population.
AE data will be presented in standard frequency tables (overall and by intensity) by body system. All AEs and laboratory variables will be assessed according to the NCI CTC-AE version 4.0 grading system.

SUMMARY OF STUDY DESIGN



SCHEDULE OF ASSESSMENTS

Assessment	Screening	Exon 19 deletion or exon 21 substitution L858R in the TK domain of EGFR gene	Treatment Period		Final Visit / Withdrawal from Treatment	Safety Follow-up Visit [K]	Off-study Visit
	Days		Visit # (Day 1 of every 8th week throughout treatment period)		End of Study Treatment	End of study (28 days after last study drug administration)	Survival follow-up every 6th months[h]
	-21 to -1		Visit 1 (Baseline)	Visit – every 8th week, until PD, death, unacceptable toxicity or patient's decision			
Visit Window	≤ 21 days		0	+/- 5 days	+/- 5 days	+/- 5 days	+/- 15 days
Informed consent	X						
EGFR Testing	X						
Medical history	X						
Pregnancy test[a]	X		X		X		
Physical examination[b]	X		X	X	X	X	
ECOG PS	X		X	X	X	X	
ECG[c]	X		To be repeated as clinically indicated				
Demographics	X						
Haematology	X		X	X	X	X	
Biochemistry	X		X	X	X	X	
Coagulation	X[j]						
Concomitant medications	X		X	X	X	X	
Tumour assessment[d]			X	X	X		
Adverse events[e]	X		X	X	X	X	X
Subsequent therapy for NSCLC[f]						X	X
Drug dispensing and accountability[g]			X	X	X[i]		

Notes: First dose of study drug to be taken as soon as positive EGFR mutations test result has been received and appropriate drug has been provided.

[a] Urine or blood.

[b] Including an ophthalmologic examination if clinically indicated.

[c] At baseline and as clinically indicated throughout the study.

[d] Tumour assessment consists at minimum of a CT scan of chest and upper abdomen (for imaging of liver and adrenal glands). Patients known to have bone metastasis or displaying clinical or laboratory signs (e.g. serum alkaline phosphatase (ALP) > 1.5 ULN) of bone metastasis should have an isotope bone scan at baseline. Brain CT scan or MRI is not mandatory but should be done if there is a clinical suspicion of cerebral metastasis. Post-baseline assessments are to be performed within +/- 5 days for the 8 weekly assessments. If there is suspicion of disease progression based on clinical or laboratory findings, a tumour assessment should be performed as soon as possible, before the next scheduled evaluation.

[e] Graded according to NCI CTC-AE version 4.0. During screening period only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in). During the study, and until Safety Follow-up

visit all SAEs and AEs of special interest will be collected and reported. After Safety Follow up visit all SAEs and AEs of special interest related with the study drug, will be collected and reported.

[f] Subsequent therapy for all patients.

[g] For details on drug dispensing and accountability see Section 6. of the Protocol.

[h] or as appropriate.

[i] Drug returning and final accountability.

[j] To be obtained in the 7 days before study treatment initiation for the patients taking anti-coagulants.

[K] To be performed 28 days after the last study drug administration

GLOSSARY OF ABBREVIATIONS

AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT (SGPT)	Alanine aminotransferase
ANC	Absolute neutrophil count
ANOVA	Analysis of variance
AST (SGOT)	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
b.i.d.	Twice Daily
BP	Blood pressure
CALGB	Cancer and Leukaemia Group B
CEA	Carcinoembryonic Antigen
CHF	Congestive heart failure
CI	Confidence interval
C_{max}	Maximum plasma concentration
CPU	Clinical Pharmacology Unit
CR	Complete Response
CRF	Case Report Form[s]
CT	Computer Tomography
CNS	Central Nervous System
CVAD	Central Venous Access Device
CXR	Chest X-Ray
DLT	Dose Limiting Toxicity
EC_{50}	Plasma concentration associated with half-maximal effect
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EEG	Electroencephalogram

EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
EMA	European Medicines Agency
ESF	eligibility screening form
EU	European Union
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
GABA	Gamma-amino butyric acid
GCP	Good Clinical Practice
G-CSF	Granulocyte colony-stimulating factor
GM-CSF	Granulocyte-macrophage colony-stimulating factor
H_0	Null hypothesis
H_1	Alternative hypothesis
NSABP	National Surgical Adjuvant Breast Project
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonization
IHC	Immunohistochemistry
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	intent to treat
iv	Intravenous
k_{eo}	Equilibration rate constant
LDH	Lactate dehydrogenase
MRI	Magnetic Resonance Image
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCDB	National Cancer Data Base
NCI	National Cancer Institute

NCI-CTC	National Cancer Institute-Common Toxicity Criteria
NCI-CTCAE	National Cancer Institute-Common Toxicity Criteria for Adverse Events
NCIC-CTG	National Cancer Institute of Canada Clinical Trials Group
NSCLC	Non small cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease or Pharmacodynamic
PFS	Progression free survival
PE	Pharmacoeconomic
PR	Partial response
PS	Performance Status
PK	Pharmacokinetic
p.o.	"per os" (oral administration)
pr	Pulse rate
PR	Partial Response
q.d.	Once daily administration
Q12H	Every 12 hours
Q3W	Every 3 weeks
q.w.	Once a week
RD	Response duration
RECIST	Response Evaluation Criteria in Solid Tumours
RIA	radio immunoassay
SAE	Serious Adverse Event
SD	Stable Disease
$T_{1/2}$	half-life
t.b.d.	to be determined
TK	Tyrosine Kinase
TNM	Stage Classification (Tumour/Nodes/Metastasis)

T_{MAX}	time to maximum plasma concentration
TTP	Time to Tumor Progression
ULN	Upper Limit of Normal

PART I: STUDY DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

This Protocol describes an open-label study, to evaluate the anti-tumoral activity of erlotinib (Tarceva®) through objective response rate (ORR) in patients with non-small-cell lung cancer (NSCLC) in locally advanced or metastatic stages who have not received previous chemotherapy for their disease and who present activating mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR).

1.1 Background

Non-small cell lung cancer is the most common cause of cancer death worldwide[1]. In the EU the crude incidence of lung Cancer is 52.5 patients per 100,000 individuals each year with a mortality rate of 48.7 per 100,000/year. Mortality and incidence rates are very similar, due to low survival of these patients[2]. In the developed world lung cancer remains the commonest reason of cancer death in both men and women, although mortality rates for men are dropping[3]. Among men the incidence and mortality rates are 82.5 and 77.0 per 100,000/year, respectively, and for women these rates are 23.9 and 22.3 per 100,000/year, respectively.

Non-small cell lung cancer (NSCLC) comprises 80% of reported lung cancer cases and the majority of its new cases are diagnosed in an advanced stage[4,5] once it represents a disease for which there is no established screening. Survival statistics are among the worst for any malignancies, and have not improved in the last years[6]. Indeed, nowadays the median survival for lung cancer is 6–12 months from the time of diagnosis with an overall 5-year survival of 5–10%.

Nowadays surgery (lobectomy/pneumonectomy plus mediastinal lymph node dissection) offers the best chance of cure in lung cancer, especially for NSCLC cases. However, only a small part of patients are suitable for curative resection and the majority must rely on non-surgical and adjuvant therapies. For most patients resection was technically unsuitable because of obvious dissemination of disease. Therefore, chemotherapy with palliate purpose to prolong patients' life for few months has been increasingly proved by clinical studies.
A common first-line therapy for advanced cases of NSCLC in patients with good performance status (PS) is based on combinations of platinum. Despite the first-line chemotherapy is appropriate, most patients experience disease progression. With regard to second-line systemic treatment (docetaxel, pemetrexed, erlotinib) this may improve the symptoms related to disease and survival of patients. Second-line therapy is administered for disease progression, recurrence, or intolerable adverse effects following administration of initial chemotherapy[7].
In first line, doublet chemotherapy has been found to be superior to single-agent chemotherapy[8]. Platinum-based chemotherapy combined with vinorelbine, gemcitabine or a taxane prolongs survival, improves quality of life and controls symptoms in patients with

good performance status. Non-platinum combination chemotherapy can be considered in patients who are not fit to receive platinum agents.
In Second line, in a phase III study, Shepherd and colleagues proved the efficacy of erlotinib against placebo in increasing the survival and reduced symptoms[9]. Erlotinib response rates are higher in non-smokers, women, adenocarcinomas, Asians and patients with EGFR mutations. Several studies show that erlotinib prolongs survival in patients with advanced NSCLC after the failure of first line or second line chemotherapy.
In a phase II clinical trial, 57 patients with refractory NSCLC received erlotinib monotherapy and showed a response rate of 12.3% and a median survival of 8.4 months[10]. Based on these results and for a different pharmacological profile, erlotinib was approved by the FDA for the treatment of second and third line NSCLC. Some studies have also shown that mutations in the EGFR gene are associated with response to EGFR TKI[11].

1.2 Study drug

Erlotinib (OSI-774; Tarceva®)

Erlotinib is an orally active and potent inhibitor of tyrosine kinase, which acts on the epidermal growth factor receptor (EGFR) developed for the treatment of solid tumours including NSCLC[12]. The recommended daily dose of erlotinib is 150 mg[13].
Erlotinib acts via direct and reversible inhibition of the human EGFR tyrosine kinase, with an IC50 of 2 nM (0.786 ng/mL) in an in vitro enzyme assay, and reduces receptor autophosphorylation in intact tumour cells with an IC50 of 20 nM (7.86 ng/mL).
At nanomolar concentrations, erlotinib blocks Epidermal Growth Factor (EGF)-dependent cellular proliferation and inhibits cell cycle progression in the G1 phase. Selectivity testing against a panel of isolated tyrosine kinase demonstrated that erlotinib is selective for the EGFR.
The most frequently-reported adverse events (AEs) associated with single-agent erlotinib are rash (dermatosis), diarrhoea, nausea, fatigue, stomatitis, vomiting, and headache. On the other hand, skin rash was identified as a key indicator of erlotinib trough plasma concentrations[14]. These results support those from previous studies on EGFR inhibitors, which have revealed a similar association between drug steady-state plasma concentrations and the intensity of rash and diarrhoea[15,16]. Laboratory abnormalities, primarily involving changes in liver function tests (elevation of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and/or bilirubin) are less frequently observed with single-agent erlotinib. These abnormalities occur occasionally in patients treated with erlotinib in combination with either gemcitabine, or carboplatin and paclitaxel. Caution should be used when administering Tarceva to patients with hepatic impairment. Dose reduction or interruption of Tarceva should be considered if severe adverse reactions occur[13,17].
An indication of completed and ongoing clinical studies on erlotinib in NSCLC can be found in the Investigator's Brochure.

1.3 Rationale for the Study

Advanced NSCLC remains largely fatal, with the positive impact of chemotherapy limited by intrinsic and acquired resistance, manifested clinically by early progression and transient responses. Current chemotherapy regimens have limited efficacy with a magnitude of

survival benefit that is still modest, and lead to significant toxicity, with many patients unable to tolerate this kind of treatment, even in the first-line setting. There is, therefore, a great need to provide patients with less toxic agents such as the novel targeted therapies, with the potential to improve the efficacy and maintain a good quality of life with little associated toxicity.

In order to improve upon the doublet chemotherapy platform for NSCLC, the targeted drugs were next tested in the frontline setting in large, randomized, phase III trials in unselected population were added TKIs to chemotherapy (trials with erlotinib TRIBUTE[18] and TALENT[19]). Those trials failed to demonstrate either an improved response or a survival benefit from the combination of a TKI with chemotherapy in unselected population with advanced NSCLC. Despite the failure of the first-line trials, additional phase III trials were completed to confirm the previously observed activity in refractory NSCLC. The BR.21 trial randomized patients previously treated with chemotherapy to erlotinib or placebo, and showed a significant improvement in response rate (9% *vs* 1%) and overall survival (OS; 6.7 vs 4.7 months; $P<0.001$) with erlotinib.

Subsequently, a number of trials have confirmed the benefit of erlotinib in unselected patients with NSCLC. As example, in the SATURN study erlotinib has proven results as first-line maintenance therapy following non-progression of disease after first-line therapy[20]. The SATURN trial investigated erlotinib maintenance therapy in patients with advanced NSCLC who did not progress during first-line chemotherapy. This randomized, global, phase III study was the first to include prospective molecular marker analyses for erlotinib, with mandatory sample collection.

Nowadays it is accepted the important role of erlotinib in NSCLC tumors with EGFR mutations after at least one prior chemotherapy regimen (SATURN study)[21].Therefore it is important to define the impact that treatment with erlotinib may have in the first line setting. There is some clinical trial evidence that EGFR TKIs are efficacious as first-line therapy in EGFR mutation positive patients with advanced NSCLC: IPASS is a phase III trial looking at gefitinib as a first-line treatment in non-small cell lung cancer in 1217 patients (261 EGFR mutation positive). Exploratory analysis of response rates in patients with EGFR mutations have shown a response rate of 71.2% in patients with EGFR mutations treated with gefitinib versus a response rate of 1.1% in patients without EGFR mutations treated with gefitinib[22].

Therefore, erlotinib is currently being assessed as first-line treatment in advanced NSCLC in prospective, randomized, registration trials. There is however, already evidence that erlotinib works in first-line treatment with relevant results found for the evaluation of PFS. Paz-Ares[23]performed a pooled analysis of clinical outcomes in patients with EGFR mutations, treated with either an EGFR TKI or chemotherapy and demonstrated clinical efficacy of erlotinib (and gefitinib) monotherapy in 1st line NSCLC.

Table 1 - Summary of data included in pooled analysis

	Erlotinib	Gefitinib	Chemotherapy
Patients treated in any line, n	365	1069	375

Patients treated in first-line setting, %	57	57	95

Table 2 - Pooled analysis of outcomes according to line of therapy

	Pooled median PFS, months (95% accuracy interval)		
	Erlotinib	**Gefitinib**	**Chemotherapy**
Any line	13.2	9.8	5.9
	(12.0-14.7)	(9.2-10.4)	(5.3-6.5)
First-line	12.5	9.9	6.0
	(10.0-16.0)	(9.0-10.9)	(5.4-6.7)

The results of this pooled analysis are consistent with those from other studies looking at EGFR TKIs as first-line therapy in patients with EGFR mutations such as the IPASS study of first-line gefitinib versus carboplatin/paclitaxel in Asian patients with adenocarcinoma who were never- or light ex-smokers where the median PFS was found to be 9.5 months with gefitinib and 6.3 months with chemotherapy; and the Spanish Lung Cancer Group study of erlotinib in patients with EGFR mutations showed a medium PFS of 14.0 months and an ORR (complete and partial response) of 70.6%[24].These results highlight the idea that EGFR mutants lung cancer is a distinct class of NSCLC.

A recent phase III study (OPTIMAL) of first line treatment with erlotinib compared to platinum-based chemotherapy (gemcitabine/carboplatine), in Asian population with NSCLC with EGFR mutation has shown a median PFS of 13.1 months in the erlotinib arm with HR=0.16 (95% CI; 0.10-0.26) versus 4.6 months in the chemotherapy arm. It has also shown an ORR of 82.9% in the erlotinib arm versus 36% in the chemotherapy arm ($p<0.0001$)[25]. Erlotinib should therefore be considered in preference to first line chemotherapy in patients with this distinct disease.

Considering the potential benefit for patients in initiating erlotinib earlier in their treatment it becomes crucial to evaluate its anti-tumoral activity through a more sensitive and accurate endpoint such as objective response rate during first-line treatment in Caucasian populations.

In this trial erlotinib will be given in first-line treatment for advanced NSCLC with EGFR mutation positive.
Although this trial is a non-randomized phase II trial, Erlotinib is currently used in clinical practice to treat NSCLC[26]. Any patient with locally advanced or metastatic non-small cell lung cancer disease found to have an EGFR exon 19 deletion or exon 21 mutations will be offered first-line treatment with erlotinib having ORR as primary efficacy endpoint.

EGFR mutations rates in Portugal
Previous studies with gefitinib have shown the incidence of mutations to be around 8% in unselected patients, whereas studies conducted in Asia show mutation rates of 19-60% In the Spanish Lung Cancer Group study of erlotinib that included only Spanish patients with EGFR mutations the EGFR mutation rate was 16.6%. In this trial, the population was mainly female, non-smokers and adenocarcinoma. The EGFR mutation's rate amongst

NSCLC patients, in Portugal is currently unknown so that the health burden and economic implications of treatments directed specifically at patients with this characteristic cannot be accurately assessed.
Therefore one of the objectives of the current study is to assess the EGFR mutation rate in Portugal NSCLC population. This will be done by testing Portuguese patients newly diagnosed with recurrent or metastatic NSCLC for the EGFR mutations.

2. OBJECTIVES

2.1 Primary Objectives

To evaluate the anti-tumoral activity of erlotinib (Tarceva®; 150 mg) through objective response rate (ORR) in patients with non-small-cell lung cancer (NSCLC) in locally advanced or metastatic stages who have not received previous chemotherapy for their disease and who present activating mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR).

2.2 Secondary Objectives

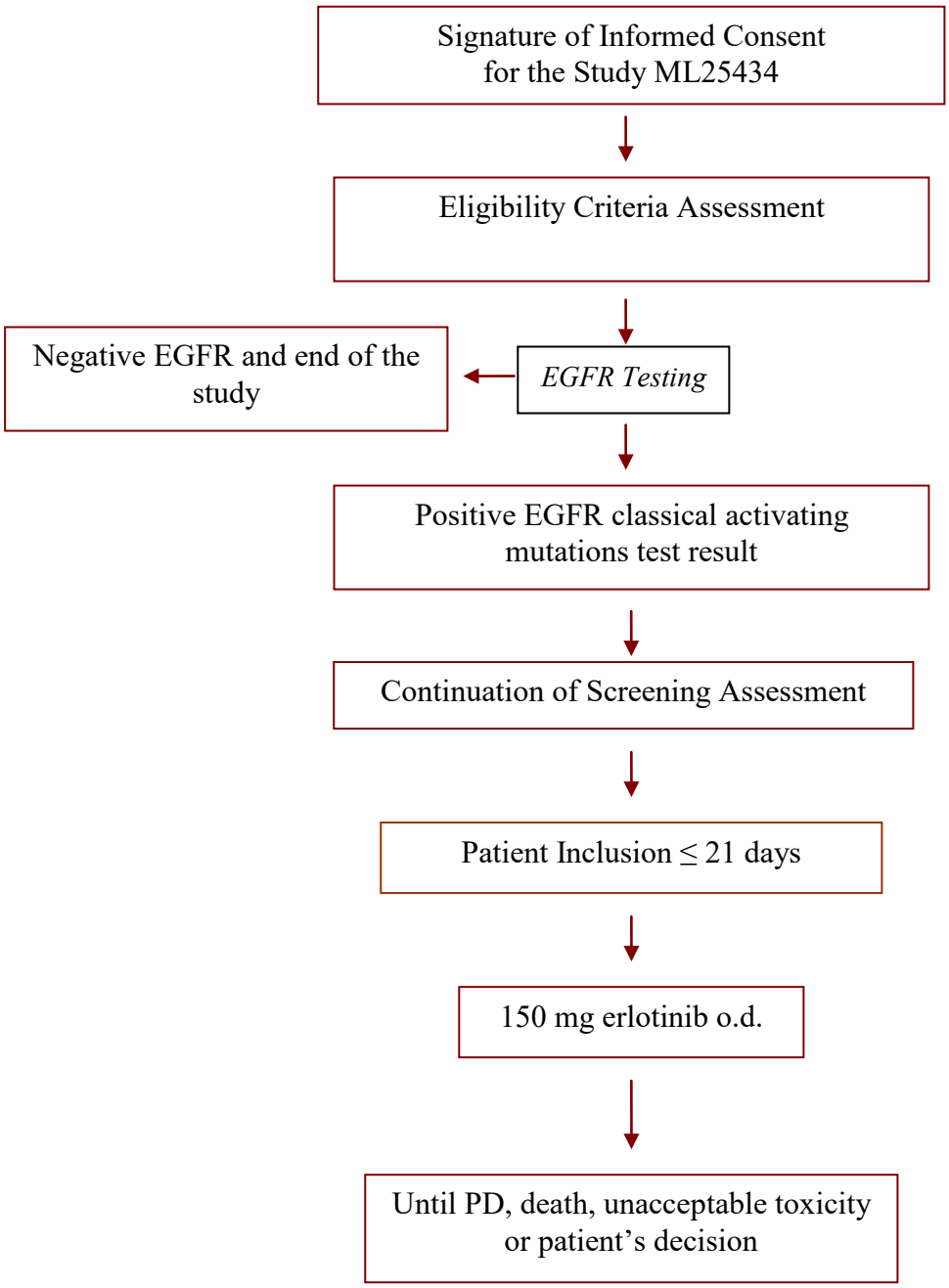
To evaluate progression-free survival (PFS), defined as the time from baseline visit to the date of first occurrence of disease progression or death due to any cause.
To evaluate the EGFR mutation frequency, in the study population.
To evaluate the Overall Survival defined as the time from baseline visit to the date of death due to any cause.
To evaluate the erlotinib safety profile (Tarceva®; 150 mg).
To evaluate response duration (RD) defined as the time of initial response (CR/PR whichever is first recorded) until documented disease progression.

3. STUDY DESIGN

3.1 Overview of Study Design

This is a local open-label, multi-centre Phase II study of the anti-tumoral activity of erlotinib (Tarceva®; 150 mg) evaluated by objective response rate (ORR) in patients with NSCLC in locally advanced or metastatic stages who have not received previous chemotherapy for their disease and who present activating mutations in the TK domain of the EGFR.
Summary of the study design is shown in Figure 1.

Figure 1 - Summary of study design



Rationale for Study Design
In this trial erlotinib is given in first-line treatment for advanced NSCLC.

Although this trial is non-randomized phase II trial, as Erlotinib is currently used in clinical practice to treat NSCL it closely reflects clinical practice.

Any patient with locally advanced or metastatic non-small cell lung cancer disease found to have an EGFR Exon 19 deletion or exon 21 substitution L858R in the TK domain of EGFR gene will be offered first-line treatment with erlotinib.

The primary efficacy variable will be ORR.

Rationale for Dose Selection
The recommended daily dose of erlotinib was established at 150 mg, to be continued daily until disease progression.
All enrolled patients will receive recommended dose of erlotinib (150 mg/day).No dose escalation is permitted. Erlotinib dose will be reduced for toxicities as detailed in Section 6.1 . Patients will be treated until progression of disease or unacceptable toxicity.

End of Study
This study is event-driven, with a recruitment period that will last until the end of March 2012 or until the number of patients aimed for the protocol (30) is achieved, whatever occurs first. Patients are to be treated until disease progression, unacceptable toxicity or patient request for discontinuation.
The study will end when the last patient has stopped erlotinib therapy and completed their last safety follow-up visit (28 days after last study drug administration). For all patients who have discontinued study drug treatment and are alive, information on survival will be collected.

3.2 Centres
This study will comprise approximately 9 centres, in Portugal.

3.3 Interim Analyses
One interim analysis is planned for the study. This interim analysis will include an epidemiological, efficacy and safety characterization of erlotinib in 1st line EGFR Mut+ mNSCLC Portuguese population. The rationale for this interim analysis is to analyse the preliminary clinical benefits on this population and compare it with the available data in publications held in the caucasian international population.
Additionally, the interim analysis will evaluate the EGFR mutation rate; describe the enrolled population related to the gender, histology type, smoking habit and the incidence of EGFR mutation per sub-group; as well as the safety evaluations in terms of events, frequency and severity.

4. Materials and methods

Under no circumstances subjects who are enrolled in this study are not permitted to be re-enrolled for a second course of treatment with erlotinib in this study.

4.1 Overview

The target population of this study are patients with histologically or cytologically confirmed locally advanced or metastatic NSCLC who have not received previous chemotherapy for their disease and who present activating mutations in the TK domain of the EGFR.

4.2 Inclusion Criteria

A subject may be included if the answer to all of the following statements is "yes".

1. Patients able and willing to give written informed consent. Consent must be obtained prior to any study-specific procedure.
2. a) Histologically or cytologically documented inoperable, locally advanced or metastatic NSCLC disease;

   b) Patient that presents activating mutations (exon 19 deletion and/or exon 21 substitution L858R) in the tyrosine kinase domain of EGFR ;

3. Measurable disease, according to RECIST - *Response Evaluation Criteria in Solid Tumours*).

4. Male or female patients aged ≥ 18 years.

5. Life expectancy ≥ 12 weeks.

6. Adequate haematological and coagulation function as assessed by the investigator.

7. Adequate liver and renal function as assessed by the investigator.

8. Female patients must be postmenopausal (24 months of amenorrhea), surgically sterile or they must agree to use a physical method of contraception. Male patients must be surgically sterile or agree to use a barrier method of contraception. Male and female patients must use effective contraception during the study and for a period of 90 days following the last administration of erlotinib. Acceptable methods of contraception include an established hormonal therapy or intrauterine device for females, and the use of a barrier contraceptive (i.e. diaphragm or condoms) with spermicidal.

9. If applicable, patients with asymptomatic and stable cerebral metastases receiving medical treatment will be eligible for the study. Those patients may have received radiation therapy for their cerebral metastases before the initiation of systemic treatment for non-small-cell lung cancer.

10. Able to comply with the required protocol and follow-up procedures.

4.3 Exclusion Criteria

A subject will be excluded if the answer to any of the following statements is "yes".

1. Previous treatment with chemotherapy or therapy against EGFR, either with antibody or small molecule (tyrosine kinase inhibitor) for metastatic disease. The administration of neo-adjuvant or adjuvant therapy is allowed as long as it has finalized • 6 months before entering the study. Patients can have received radiotherapy as long as the irradiated lesion is not the only target lesion for evaluating response and as long as radiotherapy has been completed before initiating the study treatment (28 days period is recommended). Treatment with an investigational drug agent during the four weeks before enrolment in the study.

2. History of another neoplasm other than carcinoma in situ of the uterine cervix, basal cell skin carcinoma treated adequately, or prostate carcinoma with a good prognosis (Gleason • 6) treated radically. History of another neoplasm treated curatively and without evidence of disease in the last 5 years. History of breast cancer and melanoma at any time.

3. Patients with symptomatic cerebral metastases.

4. Known hypersensitivity to erlotinib or any of its excipients.

5. Any significant ophthalmologic abnormality, especially severe dry eye syndrome, keratoconjunctivitis sicca, Sjögren's syndrome, severe exposure keratitis or any other disorder likely to increase the risk of corneal epithelial lesions. (The use of contact lenses is not recommended during the study. The decision to continue to wear contact lenses should be discussed with the patient's treating oncologist and the ophthalmologist.)

6. Use of coumarins (Sintrom®; Varfine®). If the patient requires anti-coagulant therapy, instead of coumarins, the use of a low molecular weight heparin is recommended, whenever clinically possible.

7. Patients with severe hepatic and renal impairment as assessed by the investigator.

8. Evidence of any other disease, neurological or metabolic dysfunction, physical examination or laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or puts the patient at high risk for treatment-related complications.

9. a) Positive urine/blood pregnancy test in women of childbearing potential.
   Female patients should not be pregnant or breast-feeding.

b) Patients (male or female) with reproductive potential not willing to use effective method of contraception during the trial and during 90 days after the last erlotinib administration. Oral or injectable contraceptive agents cannot be the sole method of contraception.

10. Patients with pre-existing disease of the lung parenchyma such as lung fibrosis, lymphangitic carcinomatosis.

11. Patients with known infection with HIV, HBV, HCV. Testing is not required in the absence of clinical signs and symptoms suggestive of these conditions.

12. Patients those in the Investigator's opinion are not able to accomplish protocol requirements.

13. Incapacity to take oral medication or previous surgical procedures that affect absorption and imply the need for intravenous or parenteral feeding.

4.4 Number of Subjects/ Assignment to Treatment Groups

Approximately 30 patients will be recruited over a planned recruitment period that will last until the end of March 2012 or until the number of patients aimed for the protocol is achieved, whatever occurs first.

4.5 Concomitant Medication and Treatment

All concomitant medications and blood products administered to patients after the first dose of study drug, until 28 days after the last dose of study drug must be recorded on the electronic case report form (eCRF).

Permitted medication and therapies:

- Patients may receive non-myelosuppressive palliative radiation therapy if required. Concomitant radiation therapy with erlotinib treatment is allowed.
- Patients will receive full supportive care throughout the study, including transfusion of blood products, treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics as appropriate.
- Patients exhibiting dry eyes should be advised to use an ocular lubricant.

Not permitted:

- Administration of any other anti-cancer therapy (cytotoxic or biological/immunotherapy) is not permitted until after disease progression has been documented.
- Patients who have received study drug should not receive any other investigational drugs until after the post-treatment assessment (at least 28 days after the final dose of study drug).

Caution should be exercised when erlotinib is co-administered with CYP3A4 inhibitors and inducers. As grapefruit juice has the potential to inhibit CYP3A4 activity, patients should not eat grapefruit or drink grapefruit juice during the study.

4.6 Criteria for Premature Withdrawal

Subjects have the right to withdraw from the study at any time for any reason.

In the case that the subject decides to prematurely discontinue study treatment ["refuses treatment"], he/she should be asked if he/she can still be contacted for further information. The outcome of that discussion should be documented in both the medical records and in the eCRF. If lost to follow-up, the investigator should contact the subject or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the study.

When applicable, subjects should be informed of circumstances under which their participation may be terminated by the investigator without the subject's consent. The investigator may withdraw subjects from the study in the event of intercurrent illness, adverse events, treatment failure after a prescribed procedure, lack of compliance with the study and/or study procedures (e.g., dosing instructions, study visits), cure or any reason where it is felt by the investigator that it is in the best interest of the subject to be terminated from the study. Any administrative or other reasons for withdrawal must be documented and explained to the subject.

If the reason for removal of a subject from the study is an Adverse Event, the Adverse Event will be recorded on the eCRF. The subject should be followed until the Adverse Event has resolved, if possible.
An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of subjects should be avoided. Should a subject decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

4.7 Replacement Policy (Ensuring Adequate Numbers of Evaluable Subjects)

For Patients
No subject prematurely discontinued from the study, for any reason, after receiving at least a single dose of treatment, will be replaced.

For Centres
A centre may be replaced for the following administrative reasons:
Excessively slow recruitment.
Poor protocol adherence.

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

The complete schedule of assessments is tabled in the synopsis of protocol (see Schedule of Assessments, page 10).

5.1 Screening Examination and Eligibility Screening Form

All subjects must provide written informed consent before any study specific assessments or procedures are performed.

A screening examination should be performed 21 days before study enrolment. Patients who fulfil all the inclusion and none of the exclusion criteria will be accepted into the study.

An Eligibility Screening Form (ESF) documenting the investigator's assessment of each screened subject with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator.

A screen failure log must be maintained by the investigator.

5.2 Procedures for Enrolment of Eligible Patients

Once a patient has fulfilled the entry criteria, will be enrolled in the study, beginning with the EGFR mutation testing at the Central Laboratory [redacted] by Sequential Technique. A surgical fragment or biopsy formalin-fixed, paraffin-embedded or a tumour material obtained through aspiration cytology fixed and paraffin-embedded in a cell-block, must be sent to the Central Laboratory [redacted]. If activating mutations (exons 19 and 21 mutations) in the TK domain of EGFR gene are identified, patients are eligible to participate in the study. Although, for methodological issues, mutations will be identified from the exon 18 to 21, but only patients with Exon 19 deletion or exon 21 substitution L858R in the TK domain of EGFR gene will be enrolled in this trial.

5.3 Clinical Assessments and Procedures

Testing for EGFR mutation will be performed only at Screening. All of the other clinical and safety assessments will be performed at Screening, Baseline and on Day 1 of every 8th week until PD, death, or unacceptable toxicity, as indicated in the Schedule of Assessments. For all patients who have discontinued study drug treatment and are alive, information on further therapy for NSCLC and survival will be collected.

Tumor Response Criteria

Tumor response will be evaluated according to the RECIST criteria (Eisenhauer et al., 2009) (see Appendix 1).

In this study, tumour response will be measured using computer tomography (CT) or magnetic resonance image (MRI) scans of the chest and upper abdomen, for imaging of liver and adrenal glands. Patients known to have bone metastasis or displaying clinical or laboratory signs (e.g. serum alkaline phosphatase (ALP) > 1.5 ULN) of bone metastasis should have an isotope bone scan at baseline. In cases where there are suspected brain metastases, CT scanning of the brain will be performed.

Post-baseline assessments are to be performed within +/- 5 days for the 8 weekly assessments. If there is suspicion of disease progression based on clinical or laboratory findings, a tumour assessment should be performed as soon as possible, before the next scheduled evaluation.
Consistency of consecutive CT-scans, X-rays or MRIs should be ensured during all assessments for each patient, with the same technique being used for evaluating lesions throughout the treatment period. The use of spiral CT or MRI is required for baseline lesions of < 20 millimetres (mm) and must be documented in medical records and used consistently throughout the study. The use of oral and IV contrast etc. should, as long as it is clinically possible, be kept consistent. Tumor measurements should be made by the same investigator/radiologist for each patient during the study to the extent that this is feasible.

Scheduling of tumour assessments
In this study, assessment of tumour progression during treatment with erlotinib will be performed every 8th week during the study visits and on the End of Study visit (as given in the Schedule of Assessments). Baseline tumour assessment must be performed within 21 days before first dose of study drug treatment. Post-baseline assessments are to be performed +/- 5 days for the 8 weekly assessments. If there is suspicion of disease progression based on clinical or laboratory findings before the next scheduled assessment, an unscheduled assessment should be performed.
If a subject inadvertently misses a prescribed tumour evaluation or a technical error prevents the evaluation, the subject may continue treatment until the next scheduled assessment, unless signs of clinical progression are present.

ECOG Performance Status
Performance Status (PS) will be measured using the ECOG performance scale (see Appendix 2), at screening, baseline, at each study visit on Day 1 of every 8th week of treatment period, and at the safety follow-up visit (28 days after the last study drug administration).
It is recommended, where possible, that a subject's PS will be assessed by the same person throughout the study.

Clinical Safety Assessments
The NCI CTC-AE version 4.0 will be used to evaluate the clinical safety parameters of the study drug. Patients will be assessed for adverse events at each clinical visit from screening onwards and as necessary throughout the study.
A complete medical history (including demographics) will be performed at screening and a physical examination will be performed at each visit, as indicated in the Schedule of Assessments.
Safety assessments will consist of monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of haematology, biochemical analyses results and physical examinations. Electrocardiogram (ECG) recordings will be performed as part of the screening (baseline) assessments and if clinically indicated throughout the study.

5.4 Laboratory Assessments

Normal ranges for the study laboratory parameters must be supplied to Roche before the study starts.

Efficacy Laboratory Assessments
Laboratory parameters will not be considered for the purpose of efficacy assessment.

Safety Laboratory Assessments
All safety laboratory assessments will be performed at local laboratories.
The following will be completed according to the Schedule of Assessments:
Blood tests with counts of the three series (leukocytes with neutrophils, haemoglobin, and platelets). This information will be obtained in the 21 days before initiation of treatment.
Biochemistry: LDH, alkaline phosphatase, ASAT, ALAT, total bilirubin, serum creatinine, creatinine clearance (if indicated), calcium, electrolytes, glucose and urea. This information will be obtained in the 21 days before initiation of treatment.
Prothrombin time, INR and aPTT. This information will be obtained in the 7 days before initiation of treatment.
Pregnancy test (urine or blood) in women of childbearing age, to be performed at screening and in the 1st day of study treatment (baseline), before the intake of study medication and at the end of study treatment.

5.5 Safety Follow-Up Visit (28 days after last study drug administration)

Patients who discontinued therapy due to disease progression, unacceptable toxicity or patient's decision, should have a safety follow-up completed 28 days after last dose of study treatment. This assessment should include physical examination, ECOG performance status, haematology, biochemistry, concomitant medications, adverse events and subsequent therapy for NSCLC.

5.6 Survival Follow-up Phase

After the final visit has been completed the patient should be followed every 6 months (± 15 days), or as appropriate evaluated by the investigator, for collection of subsequent therapies and survival status.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Dose and Schedule of IMP and Comparator(S)

Erlotinib will be administered as single daily oral dose of 150 mg, until disease progression or unacceptable toxicity. No dose escalation of erlotinib is permitted. Dose reduction will be allowed according to protocol (Section 6.1.).

Dose Modifications, Interruptions and Delays
Reduction of dosing for adverse events may take place at any time during the study.
Diarrhoea and skin rash are the major side effects associated with erlotinib. Other known side effects, include dry skin, fatigue, pruritus, nausea, vomiting, anorexia, abdominal pain,

gastrointestinal perforation, dry mouth, dry eye, and headache. Dose reductions can be made according to the system exhibiting the greatest degree of toxicity. All toxicities will be graded according to the NCI CTC-AE version 4.0.

In the event of toxicity (e.g., diarrhoea, rash) that is not controlled by optimal supportive care, or not tolerated due to any reason, regardless of severity, the daily dose of erlotinib will be decreased to 100 mg/day.

Within 2 weeks following a dose reduction, erlotinib related toxicity must improve by at least one NCI-CTC grade and be NCI-CTC Grade 2 or better (any ocular toxicity must improve to NCI-CTC Grade 1), or a further dose reduction to 50 mg/day will be required.

Table 3 - Dose Level Reductions

Starting Dose	First reduction	Second reduction
150 mg/day	100 mg/day	50 mg/day

Patients who cannot tolerate a dose reduction to 50 mg/day will be permanently discontinued from the study.

Dosing may be interrupted for a maximum of 2 weeks if clinically indicated and if the toxicity is not controlled by optimal supportive medication.

Once a patient has had a dose reduction for toxicity, the dose will not be re-escalated except in the case of erlotinib related rash. In the event of a rash, dose can be re-escalated when rash is NCI-CTC Grade 2.

Supportive Care Guidelines

Diarrhoea:
Diarrhoea has been commonly observed (~ 50% patients) and is usually transient in nature. Previous trials have shown that the frequency and severity of diarrhoea rarely hindered administration of erlotinib and could be managed with loperamide. The recommended dose is loperamide 4 mg at first onset, followed by 2 mg every 2 – 4 hours until diarrhoea-free for 12 hours. Patients with diarrhoea should have regular monitoring of their electrolytes and be adequately rehydrated (see table 2 below). Prophylactic use of anti-diarrhoea treatments is not advised.

Table 4 - Guidelines for management of erlotinib-related toxic effects:

Toxicity	Grade	Guideline for management	Dose modification of erlotinib*
Keratitis	2	Interrupt the treatment. Ophthalmologic assessment.	Hold until recovery, and then restart at reduced dose. Continue regular ophthalmological assessments while on treatment.
	≥ 3	Discontinue treatment and seek ophthalmological advice	
Diarrhoea	1	Consider Loperamide (4 mg at first onset, followed by 2 mg every 2 – 4 hours until diarrhoea free for 12 hours) and appropriate rehydration.	None
	2	Loperamide (4 mg at first onset, followed by 2 mg every 2 – 4 hours until diarrhoea free for 12 hours) and appropriate rehydration.	Interrupt
	3	Interrupt and give appropriate rehydration, monitor electrolyte balance and renal function until resolution to Grade ≤ 1; restart at reduced dose.	Interrupt
	4	Discontinue treatment	
Rash	1	No intervention	None
	2	Any of the following: minocycline[a], topical tetracycline or clindamycin, topical silver sulfadiazine, diphenhydramine, oral prednisone (short course)	None**
	3		Hold until recovery to ≤ grade 2, and then restart the dose.
	4	Discontinue treatment	
Other toxicity	≥ 2 prolonged clinically significant toxicity	Treatment as appropriate	Hold until recovery to ≤ grade 1, and then restart at reduced dose.

* If no recovery after 14 days of holding drug, patients should be discontinued from the study

** If dose has been previously held for grade 2 rash or diarrhoea, and grade 2 symptoms recur, or if the patient finds the symptoms unacceptable, hold dose until recovery to ≤ grade 1 and then reduce the dose.

[a] Recommended dose: 200 mg p.o. b.i.d. (loading dose), followed by 100 mg p.o. b.i.d. for 7-10 days.

Rash:

Skin rash or dermatosis (Grade 1 – 2) has been observed during the first several days of treatment with erlotinib in more than 50% and has been observed to diminish in severity despite continued treatment in many patients. In some patients, particularly when a superimposed infection is suspected, this rash appeared to improve with topical and oral antibiotics. In general, rash manifests as a mild or moderate erythematosus and papulopustular rash, which may occur, or worsen, in sun exposed areas. For patients who are exposed to sun, protective clothing, and/or use of sun screen (e.g. mineral-containing) may be advisable. In patients with severe rash, treatment may need to be discontinued or the dose reduced (see table 4 below).
In the event of a rash, dose can be re-escalated when rash is ≤ grade 2. Within 2 weeks following a dose reduction, erlotinib related toxicity must improve by at least one NCI-CTC grade and be NCI-CTC Grade 2, or further dose reduction by one level will be required. Dosing may be interrupted for a maximum of 2 weeks if clinically indicated and if the toxicity is not controlled by optimal supportive medication. Once a patient has had a dose reduction for toxicity, the dose will not be re-escalated except in the case of erlotinib related rash.

Stevens-Johnson syndrome

Very rare cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis have been reported, which in some cases were fatal - see section 4.8 of SPC (30). Erlotinib treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

Interstitial Lung Disease (ILD)

In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms such as dyspnoea, cough and fever, erlotinib therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, Erlotinib should be discontinued and appropriate treatment initiated as necessary - see section 4.8 of the SPC (30). If ILD is excluded, re-medication is considered at the same dose.

Missed doses:
Doses should be taken at the same time each day. If the patient vomits after ingesting the tablets, the dose will be replaced only if the tablets can actually be seen and counted. A missed dose normally taken in the morning can be taken any time during the same day. Patients will be asked to report any missed doses to study site personnel.

6.2 Preparation and Administration of IMP and Comparator(S)

Erlotinib will be administered with up to 200 ml of water, preferably in the morning. The study drug should be taken at least 1 hour before or 2 hours after ingestion of food or any other medication. No food, grapefruit juice, vitamins, iron supplements, or non-prescription

medications should be consumed between two hours before and one hour after ingestion of erlotinib.

6.3 Formulation, Packaging and Labelling

Erlotinib will be supplied as 150 mg, 100 mg and 25 mg round, biconvex tablets with straight sides. Tablet strength is expressed in terms of erlotinib free base. All tablets have a white film coat (Opadry White®). The tablets will be provided in blister cards.
The study drug must be stored according to the details on the product label. The study drug should be stored at room temperature (15-30°C /59-86°F) and should not be used past the expiry date.

6.4 Blinding and Unblinding

Not applicable, study is on open label, single arm trial.

6.5 Assessment of Compliance

Subject compliance will be assessed by maintaining adequate study drug dispensing records. The investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the investigator.
Patients will be asked to return all used and unused blister cards and boxes at every study visit and at the end of the treatment as a measure of compliance.
Accurate records must be kept for each study drug provided by the sponsor. These records must contain the following information:
Documentation of drug shipments received from the sponsor (date received and quantity).
Disposition of unused study drug not dispensed to patient.

A Drug Dispensing Log must be kept current and should contain the following information:
The identification of the patient to whom the study medication was dispensed.
The date(s) and quantity of the study medication dispensed to the patient.
The date(s) and quantity of the study medication returned by the patient.

This inventory must be available for inspection by the Monitor. All supplies, including partially used or empty blister cards, boxes and copies of the dispensing and inventory logs, must be returned to the Roche Monitor at the end of the study, unless alternate destruction has been authorized by Roche, or required by local or institutional regulations (see Section 6.6).

6.6 Destruction of the Study Drug

Local or institutional regulations may require immediate destruction of used investigational medicinal product (IMP) for safety reasons e.g., cytotoxicity. In these cases, it may be acceptable for investigational site staff to destroy dispensed IMP before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned

and destroyed. Written authorization must be obtained from the sponsor at study start up before destruction.
Written documentation of destruction must contain the following:
Identity (batch numbers or subject numbers) of investigational product(s) destroyed
Quantity of investigational product(s) destroyed
Date of destruction (date discarded in designated hazardous container for destruction)
Method of destruction (the site must provide the sponsor with documentation of their institutional policy and procedures for handling and disposing of hazardous drugs)
Name and signature of responsible person who discarded the investigational product in a hazardous container for destruction

7. SAFETY INSTRUCTIONS AND GUIDANCE

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and non-serious adverse events of special interest; measurement of protocol-specified safety laboratory assessments; measurement of protocol-specified vital signs; and other protocol-specified tests that are deemed critical to the safety evaluation of the study.
Certain types of events require immediate reporting to the Sponsor, as outlined in Section 7.2.2..

7.1 Adverse Events and Laboratory Abnormalities

Clinical AEs
According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition),.
- Recurrence of an intermittent medical condition (e.g., headache) not present at baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug
- Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

7.1.1 Severity

The adverse event severity grading scale for the NCI CTCAE (v4.0) will be used for assessing adverse event severity. Table 5 will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE.

Table 5 Adverse Event Severity Grading Scale for Events Not Specifically Listed in NCI CTCAE

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b,c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.

Note: Based on the most recent version of NCI CTCAE (v4.0), which can be found at: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

[a] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b] Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.

[c] If an event is assessed as a "significant medical event," it must be reported as a serious adverse event (see Sections 7.2.1 and 7.2.2 for reporting instructions), per the definition of serious adverse event in Section 7.1.3.

[d] Grade 4 and 5 events must be reported as serious adverse events (see Sections 7.2.1.and 7.2.2. for reporting instructions), per the definition of serious adverse event in Section 7.1.3.

7.1.2 Drug – Adverse Event relationship

The causality relationship of study drug to the adverse event will be assessed by the investigator as either:

Yes or No

If there is a reasonable suspected causal relationship to the study medication, i.e. there are facts (evidence) or arguments to suggest a causal relationship, drug-event relationship should be assessed as **Yes**.

The following criteria should be considered in order to assess the relationship as **Yes:**

- Reasonable temporal association with drug administration
- It may or may not have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.

- Known response pattern to suspected drug
- Disappears or decreases on cessation or reduction in dose

The following criteria should be considered in order to assess the relationship as **No**:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It may readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject.
- It does not follow a known pattern of response to the suspected drug.
- It does not reappear or worsen when the drug is re-administered.

7.1.3 Serious Adverse Events (Immediately Reportable to Roche)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)
- This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.
- Requires or prolongs inpatient hospitalization
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, or according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) criteria; see Section 7.1.1); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).
Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.
Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 7.2.2 for reporting instructions).

7.1.4 Progression of Underlying Malignancy

Progression of underlying malignancy is not reported as an adverse event if it is clearly consistent with the suspected progression of the underlying cancer as defined by RECIST criteria, or other criteria as determined by protocol. Hospitalization due solely to the progression of underlying malignancy should NOT be reported as a serious adverse event. Clinical symptoms of progression may be reported as adverse events if the symptom cannot be determined as exclusively due to the progression of the underlying malignancy, or does not fit the expected pattern of progression for the disease under study.

Symptomatic deterioration may occur in some subjects. In this situation, progression is evident in the subject's clinical symptoms, but is not supported by the tumour measurements. Or, the disease progression is so evident that the investigator may elect not to perform further disease assessments. In such cases, the determination of clinical progression is based on symptomatic deterioration. These determinations should be a rare exception as every effort should be made to document the objective progression of underlying malignancy.
If there is any uncertainty about an adverse event being due only to the disease under study, it should be reported as an AE or SAE.

7.1.4.1. Non-Serious Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Non-serious adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 7.2.2 for reporting instructions).
Adverse events of special interest for this study include the following:

- Suspected transmission of an infectious agent by the study drug, as defined below
- Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.
- Stevens-Johnson Syndrome
- Interstitial Lung Disease (ILD)

7.1.5 Treatment and Follow-Up of AEs

The final outcome of each AE must be recorded on the eCRF. All AEs will be followed up according to the guidelines below:

Related AEs
Continue to follow up until one of the outcomes listed below is reached:

- Resolved or improved to baseline.
- Relationship is reassessed as unrelated.
- Death.
- Start of new anti-cancer regimen.
- Investigator confirms that no further improvement can be expected.
- Clinical or safety data will no longer be collected or final database closure.

Unrelated severe or life threatening AEs
Continue to follow up until one of the outcomes listed below is reached:

- Resolved or improved to baseline.
- Severity improved to Grade 2.
- Death.

- Start of new anti-cancer regimen.
- Investigator confirms that no further improvement can be expected.
- Clinical or safety data will no longer be collected or final database closure.

Unrelated Grade 1 or Grade 2 AEs:
To be followed up until one of the outcomes listed below is reached:

- Resolved or improved to baseline.
- Start of a new anti-cancer regimen.
- Investigator confirms that no further improvement can be expected.
- Clinical or safety data will no longer be collected or final database closure.

The final outcome of each adverse event must be recorded on the eCRF.

7.1.6 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results eform of the eCRF, or appear on electronically produced laboratory reports submitted directly from the central laboratory, if applicable.
Any laboratory result abnormality fulfilling the criteria for a serious adverse event (SAE) should be reported as such, in addition to being recorded as an AE in the eCRF.
Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single diagnosis on the adverse event page in the eCRF:

- Accompanied by clinical symptoms.
- Leading to a change in study medication (e.g. dose modification, interruption or permanent discontinuation).
- Requiring a change in concomitant therapy (e.g. addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment).

This applies to any protocol and non-protocol specified laboratory result from tests performed after the first dose of study medication, which falls outside the laboratory reference range and meets the clinical significance criteria.
This does not apply to any abnormal laboratory result which falls outside the laboratory reference range but which does not meet the clinical significance criteria (which will be analyzed and reported as laboratory abnormalities); those which are considered AEs of the type explicitly exempted by the protocol; or those which are a result of an AE which has already been reported.

7.1.6.1 Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found. If a clear explanation is established it should be recorded on the eCRF.

7.2 Handling of Safety Parameters

7.2.1 Reporting of Adverse Events

After informed consent, but prior to initiation of study medication, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout, or no treatment run-in).
All AEs (regardless of relationship to the study medication), occurring during the study and until 28 days after the last study drug administration (safety follow-up visit) must be reported in the AE eCRF.
All AEs related with the study medication occurring during the study and until the last visit of the survival follow-up period must be reported in the AE eCRF.

7.2.2 Reporting of Serious Adverse Events (immediately reportable)

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Non-serious adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.The investigator must complete the *SAE Reporting Form [gcp_for000031]* and forward it to the SAE Responsible.
Suspected Unexpected Serious Adverse Reactions (SUSARs) are reported to investigators at each site and to CEIC (Comissão de Ética para a Investigação Clínica) on an expedited basis, when the following conditions occur:

- The event must be a SAE.
- There must be a certain degree of probability that the event is an adverse reaction from the administered drug.
- The adverse reaction must be unexpected, that is to say, not foreseen in the SPC text (Summary of Product Characteristics (for an authorized medicinal product)) or the Investigator's Brochure (for an unauthorized medicinal product).

7.2.3 Emergency Medical Contacts

Medical Monitor Contact Information for all sites:
Medical Monitor: [redacted]
Telephone No.:
Mobile Telephone No.:

IMPORTANT NOTE
Progressive Disease And Death Due To Progressive Disease Will NOT Be Regarded As Reportable As A SAE In This Study.
Progression or deterioration of the malignancy under study (including new sites of metastasis and death due to disease progression) should be recorded as part of the efficacy evaluation and should not be reported as AEs/SAEs.

This study adheres to the definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.

7.2.4 Pregnancy

There are no adequate data for the use of erlotinib in pregnant women. The studies performed in animals didn't reveal evidence of teratogenicity ou abnormal delivery. However, possible side effects during a pregnancy cannot be excluded since previous studies on mousses and rabbits revealed an increase of embrious/fetous lethality. The potential risk for humans is unknown. Women with childbearing potential must be informed and became aware that a pregnancy must be avoided during the treatment with Tarceva®. Proper contraceptive methods must be used during the treatment and up to 90 days after the last study drug administration.
A female subject must be instructed to stop taking the test drug and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours to the sponsor, the SAE Responsible, using the *Clinical Trial Pregnancy Reporting Form, [gcp_for000023]*. The investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the foetus. Monitoring of the patient should continue until conclusion of the pregnancy. Pregnancies occurring up to 90 days after the completion of the study medication must also be reported to the investigator.
If pregnancy occurring in the female partner of a male patient participating in the study or up to 90 days after the completion of the study medication, every effort must be made to obtain the pregnant partner signed consent using a *Pregnant Partner Data Release Form (gcp_for000186)* and to follow up and report to the investigator and the sponsor the outcome of the pregnancy using a *Clinical Trial Pregnancy Reporting Form*. The partner should be counselled, the risks of continuing the pregnancy discussed, as well as the possible effects on the foetus. Monitoring of the partner should continue until conclusion of the pregnancy. If pregnancy outcome is a live infant, the infant should be followed up as well.

7.3 Warnings and Precautions

Interstitial Lung Disease (ILD)-Like Events
Cases of interstitial lung disease (ILD)-like events, including fatalities, have been reported uncommonly in patients receiving erlotinib for treatment of NSCLC, pancreatic cancer or other advanced solid tumours. In pivotal study BR 21, in NSCLC, the incidence of serious ILD-like events was 0.8% in each of the placebo and erlotinib arms. In the pancreatic cancer study in combination with gemcitabine, the incidence of ILD-like events was 2.5% in the erlotinib plus gemcitabine group versus 0.4% in the placebo plus gemcitabine treated group. The overall incidence in patients treated with erlotinib from all studies (including uncontrolled studies and studies with concurrent chemotherapy) is approximately 0.6%. Some examples of reported diagnoses in patients suspected of having ILD-like events include pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, acute respiratory distress syndrome, lung infiltration and alveolitis. These ILD-like events started from a few days to several months after initiating erlotinib therapy. Most of the cases were associated with confounding or contributing factors such as concomitant or prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections.
In patients who develop acute onset of new and/or progressive unexplained pulmonary symptoms, such as dyspnoea, cough and fever, erlotinib therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, erlotinib should be discontinued and appropriate treatment initiated as necessary.

Diarrhoea, Dehydration, Electrolyte Imbalance and Renal Failure
Diarrhoea has occurred in patients on erlotinib, and moderate or severe diarrhoea should be treated with loperamide. In some cases, dose reduction may be necessary. In the event of severe or persistent diarrhoea, nausea, anorexia, or vomiting associated with dehydration, erlotinib therapy should be interrupted and appropriate measures should be taken to treat the dehydration. There have been rare reports of hypokalaemia and renal failure (including fatalities). Some reports of renal failure were secondary to severe dehydration due to diarrhoea, vomiting and/or anorexia while others were confounded by concomitant chemotherapy. In more severe or persistent cases of diarrhoea, or cases leading to dehydration, particularly in groups of patients with aggravating risk factors (concomitant medications, symptoms or diseases or other predisposing conditions including advanced age), erlotinib therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patients intravenously. In addition, renal function and serum electrolytes including potassium should be monitored in patients at risk of dehydration.

Hepatitis, Hepatic Failure
Rare cases of hepatic failure (including fatalities) have been reported during use of erlotinib. Confounding factors have included pre-existing liver disease or concomitant hepatotoxic medications. Therefore, in such patients, periodic liver function testing should be considered. Erlotinib dosing should be interrupted if changes in liver function are severe.

Gastrointestinal perforation
Patients receiving erlotinib are at increased risk of developing gastrointestinal perforation, which was observed uncommonly (including some cases with a fatal outcome). Patients receiving concomitant anti-angiogenic agents, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and/or taxane based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. Erlotinib should be permanently discontinued in patients who develop gastrointestinal perforation).

Bullous and exfoliative skin disorders
Bullous, blistering and exfoliative skin conditions have been reported, including very rare cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal. Erlotinib treatment should be interrupted or discontinued if the patient develops severe bullous, blistering or exfoliating conditions.

Ocular Disorders
Very rare cases of corneal perforation or ulceration have been reported during use of erlotinib. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with erlotinib treatment, which are also risk factors for corneal perforation/ulceration. Erlotinib therapy should be interrupted or discontinued if patients present with acute/worsening ocular disorders such as eye pain.

Co-administration with medicinal products that alter the pH of the upper Gastro-Intestinal (GI) tract Erlotinib is characterised by a decrease in solubility at pH above 5. Medicinal products that alter the pH of the upper Gastro-Intestinal (GI) tract, like proton pump inhibitors, H2 antagonists and antacids, may alter the solubility of erlotinib and hence its bioavailability. Increasing the dose of Tarceva when co-administered with such agents is not likely to compensate for the loss of exposure. Combination of erlotinib with proton pump inhibitors should be avoided. The effects of concomitant administration of erlotinib with H2 antagonists and antacids are unknown; however, reduced bioavailability is likely. Therefore, concomitant administration of these combinations should be avoided. If the use of antacids is considered necessary during treatment with Tarceva, they should be taken at least 4 hours before or 2 hours after the daily dose of Tarceva.

Lactose Intolerance
The tablets contain lactose and should not be administered to patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption.

Toxicity Due to Drug-Drug Interactions
Erlotinib has a potential for clinically significant drug-drug interactions (See Appendix 4).

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

8.1 Primary and Secondary Study Variables

8.1.1 Primary Variable

The primary efficacy endpoint is ORR defined as the proportion of patients in whom a complete response (CR) or partial response (PR), as per RECIST 1.1, is observed, assessed based on diagnostic imaging.

8.1.2 Secondary Variables

The secondary efficacy variables are:

- Progression-free survival, defined as the time from baseline visit to the date of first occurrence of disease progression or death due to any cause.
- Overall survival defined as the time from the baseline visit (first dose of erlotinib) to the date of death due to any cause.
- Frequency of EGFR mutation.
- Response duration, defined as the time of initial response (CR/PR whichever is first recorded) until documented disease progression.

8.1.3 Independent Review Committee

Not applicable.

8.1.4 Safety

Safety of the treatment will be evaluated by all adverse events using the National Cancer Institute Common Terminology Criteria for AEs (NCI CTC-AE) version 4.0. The incidence of serious adverse events (SAEs) and non-SAEs related to erlotinib therapy will be determined. Additional information about AEs of special interest (serious and non-serious) such as Stevens-Johnson syndrome and interstitial lung disease (ILD) will be collected. Information about laboratory exams (haematology, biochemistry and coagulation), ECG and physical examination will be also collected.

8.2 Statistical and Analytical Methods

8.2.1 Statistical Model

8.2.1.1.Primary Variables

The study's primary variable is ORR and will be summarized as a relative frequency presented as a percentage (%). 95% confidence interval will be estimated for ORR using binomial distribution.

8.2.1.2.Secondary Variables

PFS will be summarized as median time and will be estimated trough Kaplan-Meier method. 95% confidence interval will be estimated for median time to PFS.

Overall survival variable will be summarized as median time to OS and will be estimated trough Kaplan-Meier method. 95% confidence interval will be estimated for median time to OS.

The presence of EGFR mutation in the study population will be presented as relative frequency presented as a percentage (%). A 95% confidence interval will be estimated for this value using binomial distribution.

Response duration variable will be summarized as median time to response duration and will be estimated trough Kaplan-Meier method. 95% confidence interval will be estimated for median time to response duration.

8.2.1.3. Exploratory Analysis

PFS will be summarized by exon 19 and 21 as median time and will be estimated trough Kaplan-Meier method.

8.2.2 Hypothesis Testing

Not applicable.

8.2.3 Types of Analyses

8.2.3.1.Efficacy Analysis

Efficacy analysis will be based on the intent-to-treat and per-protocol population. The ITT analysis will be considered as the primary analysis.

8.2.3.1.1.Intent to treat population:

Intention to treat population will be defined as all subjects who are enrolled to the treatment phase of the study, regardless if they completed treatment.

8.2.3.1.2.Per-protocol population:

Per protocol population will include all subjects enrolled in the treatment phase of the study without major protocol violations. The protocol violations and corresponding impact are listed below.

Table 6 – Categories of protocol deviations

Category	Impact
Assessment not performed	Minor/Major
Deviations from the dosing of the IPs	Major
Inconsistency with inclusion/exclusion criteria	Major
Non-compliance with the dose reduction schedule	Major
Prohibited concomitant medication	Major
Treatment not discontinued after withdrawal criteria is met	Major
Visit dates not per protocol	Minor

8.2.3.2. Safety Population:

All patients who received at least one dose of study medication will be included in the safety population.

8.2.4 Safety Data Analysis

The safety analysis population will include all subjects who receive at least one dose and had a safety assessment performed at baseline. All safety parameters will be summarized using descriptive measures and presented in tables based on this safety population.
Adverse event data will be presented in frequency tables (overall and by intensity) by body system. In tables showing the overall incidence of adverse events, subjects who experienced the same event on more than one occasion are counted only once in the calculation of the event frequency.
For selected events of particular interest summary tables will be presented for time to first onset of the event and for the total number of episodes. Every occurrence of an event in any subject will be counted in the total number of episodes but successive reports of an identical event in the same phase (treatment, follow-up) will be combined (concatenated) into a one episode if the end date of the earlier event was the same as the start date of the later event, or if the end date of the earlier event was missing.
All AEs and laboratory variables will be assessed according to the NCI CTC-AE version 4.0 grading system.
Laboratory values will be listed with flagging of values outside of normal range, and summarized in shift from baseline tables.
Information on the study drug will be summarized by duration, starting dose, dose per day and cumulative dose using descriptive statistics.
All AEs and laboratory variables will be assessed according to the NCI CTC-AE version 4.0 grading system.

8.2.5 Other Analyses

Not applicable.

8.2.6 Sample Size

The sample size was calculated based on the primary variable of the study, objective response rate. Since this proportion is unknown an exploratory sample size of 30 patients was considered to evaluate primary endpoint. This sample size will allow estimating ORR with a margin of error of approximately ±17.5%, for a 95% confidence interval.
Furthermore, approximately 2000 new cases of stage IIIB and IV NSCLC are diagnosed per year in Portugal[1] and, based on published data, expected prevalence of EGFR mutation is approximately 10%. With a 95% confidence interval, it was calculated that at least 420 patients will have to be enrolled to be tested to achieve 30 positive cases for the exploratory sample size analysis.

8.2.7 Interim Analysis

One interim analysis is planned for the study with a cut-off date on 30th September 2013. This interim analysis will include an epidemiological, efficacy and safety characterization of erlotinib in 1st line EGFR Mut+ mNSCLC Portuguese population.
Interim analysis will include the following descriptive analyses:
Characterization - demographics, medical history, Eastern cooperative oncology group performance status, clinical response (RECIST criteria).
Efficacy – Best Overall response, progression free survival, overall survival and epidermal growth factor receptor. Additionally, PFS will be obtained for Exon 19 and Exon 20 (if applicable).
Safety – Drug compliance, adverse events (incidence of AE and SAE, incidence of AE and SAE with remote, possible or probable relationship with study drug, description of AE and SAE, SAE with remote, possible or probable relationship with study drug) and subsequent therapy for NSCLC.
Analysis will be conducted according to the definitions described in section 8.1 and considering the populations described in section 8.2.1.

9. DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the Standard Operational Procedures.
Data for this study will be recorded via an Electronic Data Capture system EDC using electronic Case Report Forms (eCRF). It will be transcribed by the site from the paper source documents onto the eCRF. **In no case the eCRF is considered as source data for this trial.**
Accurate and reliable data collection will be assured by verification and cross–check of the eCRFs against the investigator's records by the study monitor (source document verification), and the maintenance of a drug–dispensing log by the investigator.
A comprehensive validation check program utilizing front-end checks in the eCRF and back-end checks in the Roche data base will verify the data and discrepancies will be

generated accordingly. These are transferred electronically to the eCRF at the site for resolution by the investigator.
Throughout the study the SMT will review data according to the SMT Data Review Plan as described in the Data Quality Plan.
In order to facilitate analysis of the biological samples collected in this study, the treatment code will be released to the responsible analytical person when the samples have been received at the analytical site and are ready for assay. The result of the analysis must not be released with individual identification of the subject until the database is closed.

9.1 Assignment of Preferred Terms and Original Terminology

For classification purposes, preferred terms will be assigned by the sponsor to the original terms entered on the eCRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology for adverse events and diseases and the International Non-proprietary Name Drug Terms and Procedures Dictionary for treatments and surgical and medical procedures.

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PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

11. Ethical Aspects

11.1 Local Regulations/Declaration of Helsinki

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline [January 1997] or with local law if it affords greater protection to the subject. For studies conducted in the EU/EEA countries, the investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC].
In other countries where "Guideline for Good Clinical Practice" exists Roche and the investigators will strictly ensure adherence to the stated provisions.

11.2 Informed Consent

It is the responsibility of the investigator, or a person designated by the investigator [if acceptable by local regulations], to obtain signed informed consent from each subject prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.
The investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.
The electronic Case Report Forms (eCRFs) for this study contain a section for documenting subject informed consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.
For the subject not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the subject and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the subject and representative have orally consented to participation in the trial, the witness' signature on the form will attest that the information in the consent form was accurately explained and understood.

11.3 Independent Ethics Committees (IEC)/Institutional Review Board (IRB)

The sponsor will submit to the Competent Authority (CA) and IEC, the protocol and any accompanying material provided to the patient. The accompanying material may include patient information sheets, descriptions of the study used to obtain informed consent and terms of any compensation given to the patient as well as advertisements for the trial.
An approval letter or certificate (specifying the protocol number and title) from the IEC/IRB must be obtained before study initiation by the investigator specifying the date on which the committee met and granted the approval. This applies whenever subsequent amendments/modifications are made to the protocol.
Any modifications made to the protocol, informed consent or material provided to the patient after receipt of the IEC/IRB approval must also be submitted by the Sponsor in the

European economic Area (EEA) member states in accordance with local procedures and regulatory requirements.
When no local review board exists, the investigator is expected to submit the protocol to a regional committee. If no regional committee exists, Roche will assist the investigator in submitting the protocol to the European Ethics Review Committee.
Roche shall also submit an Annual Safety Report once a year to the IEC and Competent Authorities (CAs) according to local regulatory requirements and timelines of each country participating in the study.

11.4 Financial Disclosure

The investigator(s) will provide the Sponsor with sufficient accurate financial information (PD35) to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last patient, last visit).

12. Conditions For Modifying The Protocol

Requests from investigators to modify the protocol to ongoing studies will be considered only by consultation between an appropriate representative of the sponsor and the investigator (investigator representative(s) in the case of a multicenter trial). Protocol modifications must be prepared by a representative of the sponsor and initially reviewed and approved by the Country Medical Manager and Biostatistician.
All protocol modifications must be submitted to the appropriate IEC or IRB for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial patients, or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change in monitor(s), change of telephone number(s).

13. Conditions For Terminating The Study

In terminating the study, Roche and the investigator will assure that adequate consideration is given to the protection of the patient's interests. The appropriate IRB/IEC and Regulatory Agencies should be informed accordingly.

14. Study Documentation, CRFs And Record Keeping

14.1 Investigator's Files / Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into two different separate categories: 1) Investigator's Study File, and 2) subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, CRF/DCS and schedule of assessments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample informed consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence,

etc. In addition at the end of the study the investigator will receive the subject data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, in human readable format on CD which also has to be kept with the Investigator's Study File.
Subject clinical source documents [usually defined by the project in advance to record key efficacy/safety parameters independent of the CRFs] would include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, EEG, X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and subject screening and enrolment logs. The Investigator must keep the two categories of documents as described above (including the archival CD) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.
Should the Investigator wish to assign the study records to another party or move them to another location, Roche must be notified in advance.
If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and Roche to store these in a sealed container[s] outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.
ICH GCP guidelines require that Investigators maintain information in the study subject's records which corroborate data collected on the eCRF(s). Completed eCRF will be forwarded to Roche.

14.2 Source Documents and Background Data

The investigator shall supply the sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

14.3 Audits and Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Roche Pharma Development Quality Assurance Unit or its designees or to health authority inspectors after appropriate notification, always through the investigator supervision. The verification of the eCRF data must be by inspection of source documents, again under investigator's supervision.

14.4 Electronic Case Report Forms

Data for this study will be captured via an Electronic Data Capture (EDC) system by using eCRFs on a laptop. The data is entered on to the laptop using the off-line mode. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person authorizing entry or change. The investigator will connect and enter data on a regular basis.
For each patient enrolled, an eCRF must be completed and electronically signed by the principal investigator or authorized delegate from the study staff. This also applies to records for those patients who fail to complete the study (even during a pre-randomization screening period if an eCRF was initiated). If a patient withdraws from the study, the reason

must be noted on the eCRF. If a patient is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.
The investigator should ensure the accuracy, completeness and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

15. MONITORING THE STUDY

It is understood that the responsible Roche monitor (or designee) will contact and visit the investigator regularly and will be allowed, on request and always through the investigator supervision, to inspect the various records of the trial (eCRF and other pertinent data) provided that patient confidentiality is maintained in accord with local requirements.
It will be the monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor must verify that the patient received the study drug assigned by the randomization centre. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the eCRF. The investigator (or deputy) agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

16. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The investigator must assure that patients' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the sponsor, patients should not be identified by their names, but by an identification code. The investigator should keep a patient enrolment log showing codes, names and addresses.
The investigator should maintain documents not for submission to Roche, e.g., Roche already maintains rigorous confidentiality standards for clinical studies by "coding" (i.e. assigning a unique patient identity (ID) number at the investigator site) all patients enrolled in Roche clinical studies. This means that patient names are not included in data sets that are transmitted to any Roche location.

17. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Roche will comply with the requirements for publication of study results.
The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to Roche prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the investigator. Country-specific analyses will be allowed upon approval by Roche Headquarters.
In accordance with standard editorial and ethical practice, Roche will generally support publication of multicenter trials only in their entirety and not as individual centre data. In this case, a coordinating investigator will be designated by mutual agreement.
Data derived from RCR specimen analysis on individual subjects will not be provided to study investigators, except where explicitly stipulated in a study protocol (e.g. if the result is an enrolment criterion). Exceptions may be granted (e.g. if biomarker data would be linked

to safety issues). The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.
Any inventions and resulting patents, improvements and / or know- how originating from the use of the RCR will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

18. Appendix 1: The RECIST Criteria for Tumor Response

Response Evaluation Criteria in Solid Tumours (RECIST) Version 1.1
Quick Reference (http://ctep.cancer.gov/guidelines/recist.html)

Measurability of tumour at baseline

1. Definitions

At baseline, tumour lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1. Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

• 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
• 10 mm calliper measurement by clinical exam (lesions which cannot be accurately measured with callipers should be recorded as non-measurable).
• 20 mm by chest X-ray.

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be P15mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.2. Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with P10 to <15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, and inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses /abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.3. Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

• Bone scan, PET scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
• Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above.
• Blastic bone lesions are non-measurable.

Cystic lesions:

• Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
• 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non cystic lesions are present in the same patient, these are preferred for selection as target lesions.
Lesions with prior local treatment:
• Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

2. Specifications by methods of measurements

2.1. Measurement of lesions

All measurements should be recorded in metric notation, using callipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

2.2. Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.
Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and P10mm diameter as assessed using callipers (e.g. skin nodules). For the case of skin lesions, documentation by colour photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.
Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.
CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).
Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.
Endoscopy, laparoscopy: The utilization of these techniques for objective tumour evaluation is not advised. However, they can be useful to confirm complete pathological response

when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.
Tumor markers: Tumor markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumour markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis.
Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumour types such as germ cell tumours, where known residual benign tumours can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumour has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Tumor response evaluation
1. Assessment of overall tumour burden and measurable disease
To assess objective response or future progression, it is necessary to estimate the overall tumour burden at baseline and use this as a comparator for subsequent measurements. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumour progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether patients having non-measurable disease only are also eligible.
2. Baseline documentation of 'target' and 'non-target' lesions
When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).
Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.
Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumour. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of P15mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumour. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm·30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm

should be recorded as the node measurement. All other pathological nodes (those with short axis P10mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered non-pathological and should not be recorded or followed. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterise any objective tumour regression in the measurable dimension of the disease.
All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression'. In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

3. Response criteria

This section provides the definitions of the criteria used to determine objective tumour response for target lesions.

3.1. Evaluation of target lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD): Neither sufficient shrinking to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

3.2. Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10mm. Case report forms or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis <10 mm. For PR, SD and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.
Target lesions that become 'too small to measure': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report themas being 'too small to measure'. When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has

likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.
Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

3.3. Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumour response for the group of non-target lesions.
While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.
Complete Response (CR): Disappearance of all non-target lesions and normalization of tumour marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).
Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumour marker level above the normal limits.
Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the appearance of one or more new lesions is also considered progression).

3.4. Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows:
When the patient has, also, measurable disease: In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumour burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in the size of one or more non-target lesions is usually not sufficient to quality for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.
When the patient has only non-measurable disease: This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumour

burden representing an additional 73% increase in 'volume' (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from 'trace' to 'large', an increase in lymphangitic disease from localized to widespread, or may be described in protocols as 'sufficient to require a change in therapy'. If 'unequivocal progression' is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so, therefore the increase must be substantial.

3.5. New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). This is particularly important when the patient's baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a 'new' cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline. If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a.) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b.) No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

4. Evaluation of best overall response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best

response designation. The patient's best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, depending on the nature of the study and the protocol requirements, it may also require confirmatory measurement. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the 'best overall response'. This is described further below.

4.1. Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. Table 1 on the next page provides a summary of the overall response status calculation at each time point for patients who have measurable disease at baseline.

When patients have non-measurable (therefore non-target) disease only, Table 2 is to be used.

Table 1 – Time point response: patients with target (+/– non-target) disease.

Target lesions	Non-target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.

Table 2 – Time point response: patients with non-target disease only.

Non-target lesions	New lesions	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD[a]
Not all evaluated	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

CR = complete response, PD = progressive disease, and NE = inevaluable.

a 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

4.2. Missing assessments and invaluable designation

When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

4.3. Best overall response: all time points

The best overall response is determined once all the data for the patient is known.

Best response determination in trials where confirmation of complete or partial response IS NOT required: Best response in these trials is defined as the best response across all time points (for example, a patient who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the patient's best response depends on the subsequent assessments. For example, a patient who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same patient lost to follow-up after the first SD assessment would be considered invaluable.

Best response determination in trials where confirmation of complete or partial response IS required: Complete or partial responses may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in Table 3.

Table 3 – Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

4.4. Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (<10 mm), they may still have a measurement reported on scans. This measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that patients with CR may not have a total sum of 'zero' on the electronic case report form (eCRF).

In trials where confirmation of response is required, repeated 'NE' time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a patient with time point responses of PR-NE-PR as a confirmed response.
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as 'symptomatic deterioration'. Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Tables 1–3.
Conditions that define early progression, early death and inability to evaluate are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).
In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.
For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

4.5. Frequency of tumour re-evaluation

Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. Smaller or greater time intervals than these could be justified in specific regimens or circumstances. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumour type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.
After the end of the treatment, the need for repetitive tumour evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If 'time to an event' (e.g. time to progression, disease-free survival and progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not

be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.**.6. Confirmatory measurement/duration of response**

4.6.1. Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in randomized trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

4.6.2. Duration of overall response

The duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded on study).

The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

4.6.3. Duration of stable disease

Stable disease is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relevance of the duration of stable disease varies in different studies and diseases. If the proportion of patients achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

19. Appendix 2: The ECOG Performance Scale

The Eastern Cooperative Oncology Group Performance Status Assessment
(Oken et al., 1982)

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

20. Appendix 3: Information on Potential Interactions

Erlotinib is metabolized in the liver by the hepatic cytochromes in humans, primarily CYP3A4 and to a lesser extent by CYP1A2, and the pulmonary isoform CYP1A1. Potential interactions may occur with drugs which are metabolized by, or are inhibitors or inducers of, these enzymes.

Potent inhibitors of CYP3A4 activity decrease erlotinib metabolism and increase erlotinib plasma concentrations. Inhibition of CYP3A4 metabolism by ketoconazole (200 mg p.o. BID for 5 days) resulted in increased exposure to erlotinib (86% in median erlotinib exposure (AUC)) and a 69% increase in C_{max} when compared to erlotinib alone. When erlotinib was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, the erlotinib exposure (AUC) and maximum concentration (C_{max}) increased by 39% and 17%, respectively. Therefore caution should be used when administering erlotinib with potent CYP3A4 or combined CYP3A4/CYP1A2 inhibitors. In these situations, the dose of erlotinib should be reduced if toxicity is observed.

Potent inducers of CYP3A4 activity increase erlotinib metabolism and significantly decrease erlotinib plasma concentrations. Induction of CYP3A4 metabolism by rifampicin (600 mg p.o. QD for 7 days) resulted in a 69% decrease in the median erlotinib AUC, following a 150 mg dose of erlotinib as compared to erlotinib alone.

Pre-treatment and co-administration of rifampicin with a single 450 mg dose of erlotinib resulted in a mean erlotinib exposure (AUC) of 57.5% of that after a single 150 mg erlotinib dose in the absence of rifampicin treatment. Alternative treatments lacking potent CYP3A4 inducing activity should be considered when possible. For patients who require concomitant treatment with erlotinib and a potent CYP3A4 inducer such as rifampicin an increase in dose to 300 mg should be considered while their safety is closely monitored, and if well tolerated for more than 2 weeks, further increase to 450 mg could be considered with close safety monitoring. Higher doses have not been studied in this setting.

Pre-treatment or co-administration of erlotinib did not alter the clearance of the prototypical CYP3A4 substrates midazolam and erythromycin. Significant interactions with the clearance of other CYP3A4 substrates are therefore unlikely. Oral availability of midazolam did appear to decrease by up to 24%, which was however not attributed to effects on CYP3A4 activity.

The solubility of erlotinib is pH dependent. Erlotinib solubility decreases as pH increases. Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its bioavailability. Co-administration of erlotinib with omeprazole, a proton pump inhibitor, decreased the erlotinib exposure (AUC) and C_{max} by 46% and 61%, respectively. There was no change to T_{max} or half-life. Concomitant administration of erlotinib with 300 mg ranitidine, an H_2-receptor antagonist, decreased erlotinib exposure (AUC) and C_{max} by 33% and 54%, respectively. Therefore, co-administration of drugs reducing gastric acid production with erlotinib should be avoided where possible. Increasing the dose of erlotinib when co-administered with such agents is not likely to compensate for this loss of exposure. However when erlotinib was dosed in a staggered manner, 2 hours before or 10 hours after ranitidine 150 mg b.i.d., erlotinib exposure (AUC) and C_{max} decreased only by 15% and 17%, respectively. If patients need to be treated with such drugs, then an H_2-receptor

antagonist such as ranitidine should be considered and used in a staggered manner. Erlotinib must be taken at least 2 hours before or 10 hours after the H_2-receptor antagonist dosing. International Normalized Ratio (INR) elevations and bleeding events, including gastrointestinal bleeding, have been reported in clinical studies, some associated with concomitant warfarin administration. Coumarins (Sintrom™; Varfarin™) use is an exclusion criterion. If the patient requires anti-coagulation therapy, then the use of low molecular weight heparin instead of coumarins is recommended where clinically possible.
In a phase Ib study, there were no significant effects of gemcitabine on the pharmacokinetics of erlotinib nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine (Core data sheet, 2009).
The following potent CYP3A4 inhibitors may *increase* erlotinib toxicity:
Systemic antifungals (e.g. ketoconazole, itraconazole, miconazole).
Erythromycin, clarithromycin, troleandomycin.
Selective serotonin reuptake inhibitors (e.g. nefazodone).
The following medications could decrease plasma levels of erlotinib and hence decrease efficacy, but they probably do not represent a safety concern:

- Antiepileptics (e.g. carbamazepine, phenobarbital, phenytoin).
- Rifampin, rifabutin.
- Troglitazone.
- Barbiturates.
- Glucocorticoids.
- Saint John's wort.

21. Appendix 4: 7th Edition AJCC Cancer Staging Manual - Part IV

Lung

(Carcinoid tumors are included. Sarcomas and other rare tumors are not included.)

At-A-Glance

SUMMARY OF CHANGES

- This staging system is now recommended for the classification of both non-small cell and small cell lung carcinomas and for carcinoid tumors of the lung
- The T classifications have been redefined:
  - T1 has been subclassified into T1a (≤2 cm in size) and T1b (>2–3 cm in size)
  - T2 has been subclassified into T2a (>3–5 cm in size) and T2b (>5–7 cm in size)
  - T2 (>7 cm in size) has been reclassified as T3
  - Multiple tumor nodules in the same lobe have been reclassified from T4 to T3
  - Multiple tumor nodules in the same lung but a different lobe have been reclassified from M1 to T4
- No changes have been made to the N classification. However, a new international lymph node map defining the anatomical boundaries for lymph node stations has been developed
- The M classifications have been redefined:
  - M1 has been subdivided into M1a and M1b
  - Malignant pleural and pericardial effusions have been reclassified from T4 to M1a
  - Separate tumor nodules in the contralateral lung are considered M1a
  - M1b designates distant metastases

ANATOMIC STAGE/PROGNOSTIC GROUPS

Occult Carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0

ICD-O-3 TOPOGRAPHY CODES

C34.0	Main bronchus
C34.1	Upper lobe, lung
C34.2	Middle lobe, lung
C34.3	Lower lobe, lung
C34.8	Overlapping lesion of lung
C34.9	Lung, NOS

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ANATOMIC STAGE/PROGNOSTIC GROUPS (*CONTINUED*)

Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

ICD-O-3 HISTOLOGY CODE RANGES

8000–8576, 8940–8950, 8980–8981

INTRODUCTION

Lung cancer is among the most common malignancies in the Western world and is the leading cause of cancer deaths in both men and women. The primary etiology of lung cancer is exposure to tobacco smoke. Other less common factors, such as asbestos exposure, may contribute to the development of lung cancer. In recent years, the level of tobacco exposure, generally expressed as the number of cigarette pack-years of smoking, has been correlated with the biology and clinical behavior of this malignancy. Lung cancer is usually diagnosed at an advanced stage and consequently the overall 5-year survival for patients is approximately 15%. However, patients diagnosed when the primary tumor is resectable experience 5-year survivals ranging from 20 to 80%. Clinical and pathologic staging is critical to selecting patients appropriately for surgery and multimodality therapy.

ANATOMY

Primary Site. Carcinomas of the lung arise either from the alveolar lining cells of the pulmonary parenchyma or from the mucosa of the tracheobronchial tree. The trachea, which lies in the middle mediastinum, divides into the right and left main bronchi, which extend into the right and left lungs, respectively. The bronchi then subdivide into the lobar bronchi in the upper, middle, and lower lobes on the right and the upper and lower lobes on the left. The lungs are encased in membranes called the visceral pleura. The inside of the chest cavity is lined by a similar membrane called the parietal pleura. The potential space between these two membranes is the pleural space. The mediastinum contains structures in between the lungs, including the heart, thymus, great vessels, lymph nodes, and esophagus.

The great vessels include:

Aorta
Superior vena cava
Inferior vena cava
Main pulmonary artery
Intrapericardial segments of the trunk of the right and left pulmonary artery
Intrapericardial segments of the superior and inferior right and left pulmonary veins

Regional Lymph Nodes. The regional lymph nodes extend from the supraclavicular region to the diaphragm. During the past three decades, two different lymph node maps have been used to describe the regional lymph nodes potentially involved by lung cancers. The first such map, proposed by Naruke (Figure 25.1) and officially endorsed by the Japan Lung Cancer Society, is used primarily in Japan. The second, the Mountain-Dresler modification of the American Thoracic Society (MD-ATS) lymph node map (Figure 25.2), is used in North America and Europe. The nomenclature for the anatomical locations of lymph nodes differs between these two maps especially with respect to nodes located in the paratracheal, tracheobronchial angle, and subcarinal areas. Recently, the International Association for the Study of Lung Cancer (IASLC) proposed a lymph node map (Figure 25.3) that reconciles the discrepancies between these two previous maps, considers other published proposals, and provides more detailed nomenclature for the anatomical boundaries of lymph nodes stations. Table 25.1 shows the definition for lymph node stations in all three maps. The IASLC lymph node map is now the recommended means

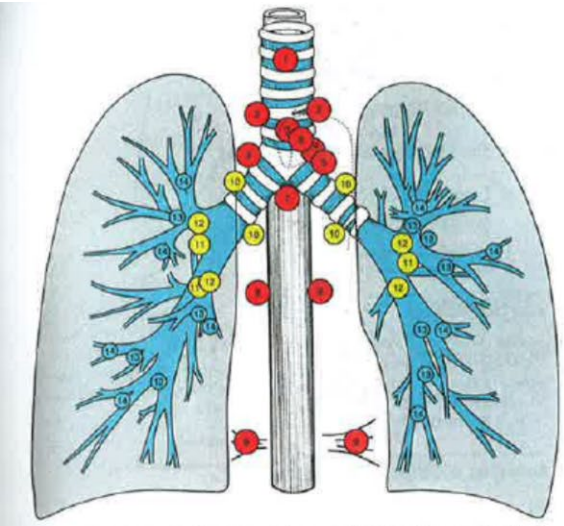

FIGURE 25.1. Naruke lymph node map. 1, Superior mediastinal or highest mediastinal; 2, paratracheal; 3, pretracheal: 3a, anterior mediastinal, 3p, retrotracheal or posterior mediastinal; 4, tracheobronchial; 5, subaortic or Botallo's; 6, paraaortic (ascending aorta); 7, subcarinal; 8, paraesophageal (below carina); 9, pulmonary ligament; 10, hilar; 11, interlobar; 12, lobar: upper lobe, middle lobe, and lower lobe; 13, segmental; 14, subsegmental. (From The Japan Lung Cancer Society. Classification of Lung Cancer. First English Edition. Tokyo: Kanehara & Co., 2000, used with permission.)

of describing regional lymph node involvement for lung cancers. Analyses of a large international lung cancer database suggest that for purposes of prognostic classification, it may be appropriate to amalgamate lymph node stations into "zones" (Figure 25.3). However, the use of lymph node "zones" for N staging remains investigational and needs to be confirmed by future prospective studies.

There are no evidence-based guidelines regarding the *number* of lymph nodes to be removed at surgery for adequate staging. However, adequate N staging is generally considered to include sampling or dissection of lymph nodes from stations 2R, 4R, 7, 10R, and 11R for right-sided tumors, and stations 5, 6, 7, 10 L, and 11 L for left-sided tumors. Station 9 lymph nodes should also be evaluated for lower lobe tumors. The more peripheral lymph nodes at stations 12–14 are usually evaluated by the pathologist in lobectomy or pneumonectomy specimens but may be separately removed when sublobar resections (e.g., segmentectomy) are performed. There is evidence to support the recommendation that histological examination of hilar and mediastinal lymphenectomy specimen(s) will ordinarily include 6 or more lymph nodes/stations. Three of these nodes/stations should be mediastinal, including the sub-carinal nodes and three from N1 nodes/stations.

Distant Metastatic Sites. The most common metastatic sites are the brain, bones, adrenal glands, contralateral lung, liver, pericardium, kidneys, and subcutaneous tissues. However, virtually any organ can be a site of metastatic disease.

RULES FOR CLASSIFICATION

Lung cancers are broadly classified as either non-small cell (approximately 85% of tumors) or small cell carcinomas (15% of tumors). This general histological distinction reflects the clinical and biological behavior of these two tumor types. Approximately half of all non-small cell lung cancers (NSCLC) are either localized or locally advanced at the time of diagnosis and are treated by resection alone, or by combined modality therapy with or without resection. By contrast, small cell lung cancers (SCLC) are metastatic in 80% of cases at diagnosis. The 20% of SCLC that are initially localized to the hemithorax are usually locally advanced tumors managed by combination chemotherapy and radiotherapy. Less than 10% of SCLC are detected at a very early stage when they can be treated by resection and adjuvant chemotherapy.

The TNM staging system has traditionally been used for NSCLC. Although it is supposed to be applied also to SCLC, in practice these tumors have been classified as "limited" or "extensive" disease, a staging system introduced in the 1950s by the Veterans' Administration Lung Study Group for use in their clinical trials. Limited disease (LD) was characterized by tumors confined to one hemithorax, although local extension and ipsilateral supraclavicular nodes could also be present if they could be encompassed in the same radiation portal as the primary tumor. No extrathoracic metastases could be present. All other patients were classified as extensive disease (ED). In 1989, a consensus report from the IASLC recommended that LD be defined as tumors limited to one hemithorax with regional lymph node metastases including hilar, ipsilateral and contralateral mediastinal and ipsilateral and contralateral supraclavicular nodes. This report also recommends that patients with ipsilateral pleural effusion regardless of whether cytology positive or negative should be considered to have LD if no extrathoracic metastases were detected. More recently, analysis of an international database developed by the IASLC that includes 8088 SCLC patients showed that the TNM staging system is applicable to SCLC. Therefore, the staging system being presented in this edition of the staging manual should now be applied to both NSCLC and SCLC.

Bronchopulmonary carcinoid tumors are also frequently classified according to the TNM staging system for NSCLC, even though they are not officially included in the AJCC or UICC staging manuals. Recent analysis of both the SEER and the IASLC international lung tumor databases indicates that the TNM staging system for NSCLC is also applicable to bronchopulmonary carcinoid tumors. Therefore, typical carcinoid and atypical carcinoid tumors should also now be routinely classified according to the TNM system used for NSCLC and SCLC.

Clinical Staging. Clinical classification (cTNM) is based on the evidence acquired before treatment, including physical examination, imaging studies (e.g., computed and positron emission tomography), laboratory tests, and staging procedures such as bronchoscopy or esophagoscopy with ultrasound directed biopsies (EBUS, EUS), mediastinoscopy,

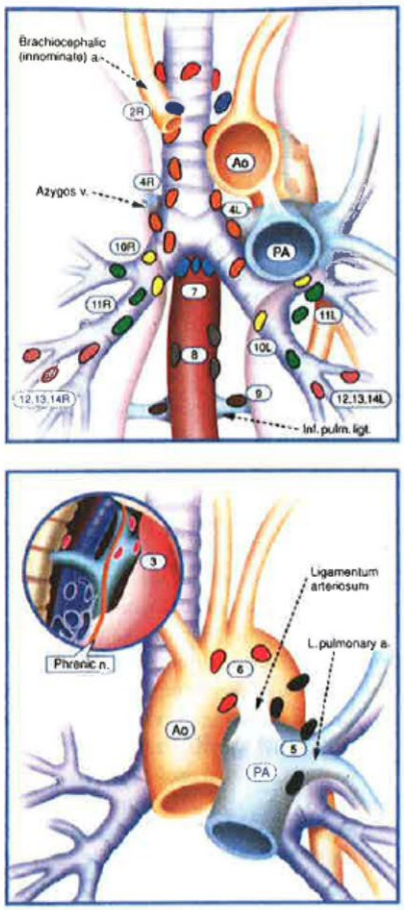

FIGURE 25.2. Mountain/Dresler lymph node map. (From Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997;111:1718–1723, used with permission.)

mediastinotomy, thoracentesis, and thoracoscopy (VATS) as well as exploratory thoracotomy.

Pathologic Staging. Pathological classification uses the evidence acquired before treatment, supplemented or modified by the additional evidence acquired during and after surgery, particularly from pathologic examination. The pathologic stage provides additional precise data used for estimating prognosis and calculating end results.

- The pathologic assessment of the primary tumor (pT) entails resection of the primary tumor sufficient to evaluate the highest pT category.
- The complete pathologic assessment of the regional lymph nodes (pN) ideally entails removal of a sufficient number of lymph nodes to evaluate the highest pN category.
- If pathologic assessment of lymph nodes reveals negative nodes but the number of lymph node stations examined are fewer than suggested above, classify the N category as pN0.
- Isolated tumor cells (ITC) are single tumor cells or small clusters of cells not more than 0.2 mm in greatest dimension that are usually detected by immunohistochemistry or molecular methods. Cases with ITC in lymph nodes or at distant sites should be classified as N0 or M0, respectively. The same applies to cases with findings suggestive of tumor cells or their components by non-morphologic techniques such as flow cytometry or DNA analysis.
- The following classification of ITC may be used:

pN0	No regional lymph node metastasis histologically, no examination for ITC
pN0(i−)	No regional lymph node metastasis histologically, negative morphological findings for ITC
pN0(i+)	No regional lymph node metastasis histologically, positive morphological findings for ITC

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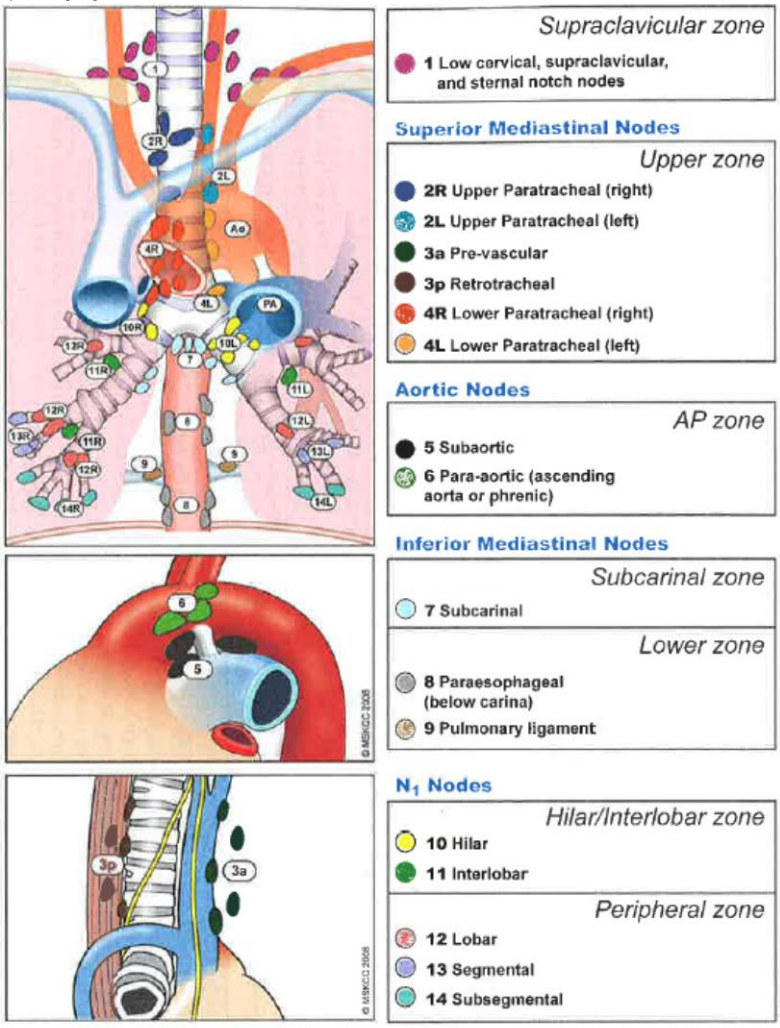

FIGURE 25.3. The IASLC lymph node map shown with the proposed amalgamation of lymph node levels into *zones*. (© Memorial Sloan-Kettering Cancer Center, 2009.)

pN0(mol–) No regional lymph node metastasis histologically, negative non-morphological findings for ITC

pN0(mol+) No regional lymph node metastasis histologically, positive non-morphological findings for ITC

- The pathologic assessment of metastases may be either clinical or pathologic when the T and/or N categories meet the criteria for pathologic staging (pT, pN, cM, or pM).

Pathologic staging depends on the proven anatomic extent of disease, whether or not the primary lesion has been completely removed. If a biopsied primary tumor technically cannot be removed, or when it is unreasonable to remove it, and if the highest T and N categories or the M1 category of the tumor can be confirmed microscopically, the criteria for pathologic classification and staging have been satisfied without total removal of the primary cancer.

Basis for Current Revisions to the Lung Cancer Staging System. The 6th edition of the *AJCC Cancer Staging Manual*, introduced in 2002, made no changes to the previous edition with regards to lung cancer. The proposals for lung cancer staging in the 5th edition, published in 1997, were based on a relatively small database of 5,319 cases of NSCLC accumulated since 1975 by Dr. Clifton Mountain at the MD Anderson Cancer Center (Houston, TX, USA). During this time, there had been many refinements to the techniques available for clinical staging, principally the routine use of computed tomography and more recently, an increasing use of positron emission tomography. The database was largely

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TABLE 25.1. Definition for lymph node stations in Japan Lung Cancer Society Map, MD-ATS Map, and IASLC Map

Japan Lung Hancer Society map	*MD-ATS map*	*IASLC map*
	1 Low cervical, supraclavicular and sternal notch nodes	
Located in the area of the upper 1/3 of the intrathoracic trachea. Boundary level from the upper margin of the subclavian artery or the apex to the crossing point of the upper margin of the left brachiocephalic vein and the midline of the trachea	Nodes lying above a horizontal line at the upper rim of the brachiocephalic (left innominate) vein where it ascends to the left, crossing in front of the trachea at its midline	Upper border: lower margin of cricoid cartilage Lower border: clavicles bilaterally and, in the midline, the upper border of the manubrium, 1R designates right-sided nodes, 1 L, left-sided nodes in this region For lymph node station 1, the midline of the trachea serves as the border between 1R and 1 L
2 Paratracheal lymph nodes	*2 Upper paratracheal nodes*	
Located in the area between the superior mediastinal lymph nodes (1) and the tracheobronchial lymph nodes (4). Paratracheal lymph nodes with primary tumor can be defined as ipsilateral lymph nodes; paratracheal lymph nodes without primary tumor can be defined as contralateral lymph nodes	Nodes lying above a horizontal line drawn tangential to the upper margin of the aortic arch and below the inferior boundary of No. 1 nodes	2R: Upper border: apex of the right lung and pleural space, and in the midline, the upper border of the manubrium Lower border: intersection of caudal margin of innominate vein with the trachea As for lymph node station 4R, 2R includes nodes extending to the left lateral border of the trachea 2 L: Upper border: apex of the left lung and pleural space, and in the midline, the upper border of the manubrium Lower border: superior border of the aortic arch
	3 Pre-vascular and retrotracheal nodes	
3 Pretracheal lymph nodes Located in the area anterior to the trachea and inferior to the superior mediastinal lymph nodes (1). On the right side, the boundary is limited to the posterior wall of the superior vena cava. On the left side, the boundary is limited to the posterior wall of the brachiocephalic vein 3a Anterior mediastinal lymph nodes On the right side, located in the area anterior to the superior vena cava. On the left side, the boundary is limited to the line connecting the left bracheocephalic vein and the ascending aorta 3p Retrotracheal mediastinal lymph nodes/Posterior mediastinal lymph nodes Located in the retrotracheal or posterior area of the trachea	Prevascular and retrotracheal nodes may be designated 3A and 3P; midline nodes are considered to be ipsilateral	3a: Prevascular On the right: Upper border: apex of chest Lower border: level of carina Anterior border: posterior aspect of sternum Posterior border: anterior border of superior vena cava On the left: Upper border: apex of chest Lower border: level of carina Anterior border: posterior aspect of sternum Posterior border: *left carotid artery* 3p: *Retrotracheal* *Upper border: apex of chest* *Lower border: carina*

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4 Tracheobronchial lymph nodes	*4 Lower paratracheal nodes*	
Located in the area superior to the carina. On the right side, located medial to the azygos vein. On the left side, located in the area surrounded by the medial wall of the aortic arch	The lower paratracheal nodes on the right lie to the right of the midline of the trachea between a horizontal line drawn tangential to the upper margin of the aortic arch and a line extending across the right main bronchus at the upper margin of the upper lobe bronchus, and contained within the mediastinal pleural envelope; the lower paratracheal nodes on the left lie to the left of the midline of the trachea between a horizontal line drawn tangential to the upper margin of the aortic arch and a line extending across the left main bronchus at the level of the upper margin of the left upper lobe bronchus, medial to the ligamentum arteriosum and contained within the mediastinal pleural envelope. Researchers may wish to designate the lower paratracheal nodes as No. 4s (superior) and No. 4i (inferior) subsets for study purposes; the No. 4s nodes may be defined by a horizontal line extending across the trachea and drawn tangential to the cephalic border of the azygos vein; the No. 4i nodes may be defined by the lower boundary of No. 4s and the lower boundary of no. 4, as described above	4R: includes right paratracheal nodes, and pretracheal nodes extending to the left lateral border of trachea Upper border: intersection of caudal margin of innominate vein with the trachea Lower border: lower border of azygos vein 4L: includes nodes to the left of the left lateral border of the trachea, medial to the ligamentum arteriosum Upper border: upper margin of the aortic arch Lower border: upper rim of the left main pulmonary artery
5 Subaortic lymph nodes/Botallo's lymph nodes	*5 Subaortic (aorto-pulmonary window)*	
Located in the area adjacent to the ligamentum arteriosum (Botallo's ligament). The boundary extends from the aortic arch to the left main pulmonary artery	Subaortic nodes are lateral to the ligamentum arteriosum or the aorta or left pulmonary artery and proximal to the first branch of the left pulmonary artery and lie within the mediastinal pleural envelope	Subaortic lymph nodes lateral to the ligamentum arteriosum Upper border: the lower border of the aortic arch Lower border: upper rim of the left main pulmonary artery
	6 Para-aortic nodes (ascending aorta or phrenic)	
Located along the ascending aorta, and in the area of the lateral wall of the aortic arch. Posterior boundary limited to the site of the vagal nerve	Nodes lying anterior and lateral to the ascending aorta and the aortic arch or the innominate artery, beneath a line tangential the upper margin of the aortic arch	Lymph nodes anterior and lateral to the ascending aorta and aortic arch Upper border: a line tangential to the upper border of the aortic arch Lower border: the lower border of the aortic arch
	7 Subcarinal nodes	
Located in the area below the carina, where the trachea bifurcates to the two main bronchi	Nodes lying caudal to the carina of the trachea, but not associated with the lower lobe bronchi or arteries within the lung	Upper border: the carina of the trachea Lower border: the upper border of the lower lobe bronchus on the left; the lower border of the bronchus intermedius on the right
	8 Para-esophageal nodes (below carina)	
Located below the subcarinal lymph nodes, and along the esophagus	Nodes lying adjacent to the wall of the esophagus and to the right or left of the midline, excluding subcarinal nodes	Nodes lying adjacent to the wall of the esophagus and to the right or left of the midline, excluding subcarinal nodes Upper border: the upper border of the lower lobe bronchus on the left; the lower border of the bronchus intermedius on the right Lower border: the diaphragm

continued

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TABLE 25.1. Definition for lymph node stations in Japan Lung Cancer Society Map, MD-ATS Map, and IASLC Map (continued)

Japan Lung Cancer Society map	*MD-ATS map*	*IASLC map*
	9 Pulmonary ligament nodes	
Located in the area of the posterior and the lower edge of the inferior pulmonary vein	Nodes lying within the pulmonary ligament, including those in the posterior wall, and lower part of the inferior pulmonary vein	Nodes lying within the pulmonary ligament Upper border: the inferior pulmonary vein Lower border: the diaphragm
	10 Hilar nodes	
Located around the right and left main bronchi	The proximal lobar nodes, distal to the mediastinal pleural eflection and the nodes adjacent to the bronchus intermedius on the right; radiographically, the hilar shadow may be created by enlargement of both hilar and interlobar nodes	Includes nodes immediately adjacent to the mainstem bronchus and hilar vessels including the proximal portions of the pulmonary veins and main pulmonary artery Upper border: the lower rim of the azygos vein on the right; upper rim of the pulmonary artery on the left Lower border: interlobar region bilaterally
	11 Interlobar nodes	
Located between the lobar bronchi. On the right side, subclassified into two groups: 11s: Superior interlobar nodes: located at the bifurcation of the upper and middle lobar bronchi 11i: Inferior interlobar nodes: located at the bifurcation of the middle and lower lobar bronchi	Nodes lying between the lobar bronchi	Between the origin of the lobar bronchi 11s: between the upper lobe bronchus and bronchus intermedius on the right 11i: between the middle and lower lobe bronchi on the right
	12 Lobar nodes	
Located in the area around the lobar branches, which are subclassified into three groups: 12u: Upper lobar lymph nodes 12 m: Middle lobar lymph nodes 12l: Lower lobar lymph nodes	Nodes adjacent to the distal lobar bronchi	Adjacent to the lobar bronchi
	13 Segmental nodes	
Located along the segmental branches	Nodes adjacent to the segmental bronchi	Adjacent to the segmental bronchi
	14 Subsegmental nodes	
Located along the subsegmental branches	Nodes around the subsegmental bronchi	Adjacent to the subsegmental bronchi

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from a single institution, containing cases predominantly treated surgically. Repeated iterations of the TNM staging system had seen recommendations for lung cancer staging evolve with little internal validation and no external validation of the descriptors or the stage groupings. Increasingly reports from other databases challenged some of the descriptors and stage groupings. In preparation for this 7th edition of the staging manual, the IASLC established a Lung Cancer Staging Project in 1998 to bring together the large databases available worldwide to inform recommendations for revision that would be intensively validated. The results of this project were accepted by the International Union Against Cancer (UICC) and the AJCC as the primary source for revisions of the lung cancer staging system in the 7th editions of their staging manuals.

The IASLC lung cancer database includes cases from 46 sources in more than 19 countries, diagnosed between 1990 and 2000 and treated by all modalities of care. A total of 100,869 cases were submitted to the data center at Cancer Research and Biostatistics (Seattle, WA, USA). After an initial sift to exclude cases outside the study period, those for whom cell type was not known, cases not newly diagnosed at the point of entry, and those with inadequate information on stage, treatment, or follow-up, 81,015 cases remained for analysis. Of these, 67,725 were NSCLC and 13,290 were SCLC. The analyses of the T, N, and M descriptors and the subsequent analysis of TNM subsets and stage groupings were derived from the cases of NSCLC and subsequently validated also in the SCLC cases and carcinoids. Survival was measured from the date of entry (date of diagnosis for registries, date of registration for protocols) for clinically staged data and the date of surgery for pathologically staged data and was calculated by the Kaplan–Meier method. Prognostic groups were assessed by Cox regression analysis.

Where the analyses showed descriptors to have a prognosis that differed from the other descriptors in any T or M category, two alternative strategies were considered: (1) Retain that descriptor in the existing category, identified by alphabetical subscripts. For example, additional pulmonary nodules in the lobe of the primary, considered to be T4 in the 6th edition, would become T4a, whereas additional pulmonary nodules in other ipsilateral lobes, designed as M1 in the 6th edition, would become M1a. (2) Allow descriptors to move between categories, to a category containing other descriptors with a similar prognosis, e.g., additional pulmonary nodules in the lobe of the primary would move from T4 to T3, and additional pulmonary nodules in other ipsilateral lobes would move from M1 to T4. The first strategy had the advantage of allowing, to a large extent, retrograde compatibility with existing databases. Unfortunately, this generated a large number of descriptors (approximately 20) and an impractically large number of TNM subsets (>180). For this reason, backward compatibility was compromised and strategy (2) was preferred for its clinical utility. A small number of candidate stage grouping schemes were developed initially using a recursive partitioning and amalgamation algorithm. The analysis grouped cases based on best stage (pathologic, if available, otherwise clinical) after determination of best-split points based on overall survival

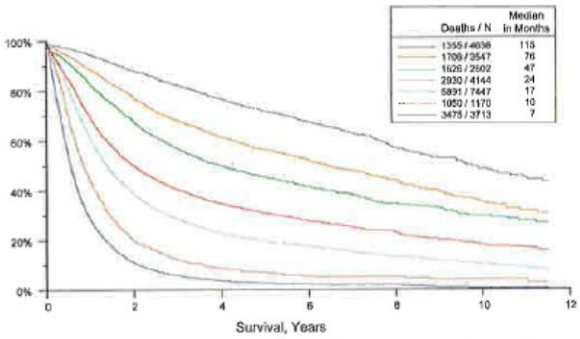

FIGURE 25.4. Survival in all NSCLC by TNM stage (according to "best" based on a combination of clinical and pathologic staging.

on indicator variables for the newly presented TM categories and an ordered variable for N category, excluding NX cases (Figures 25.4 and 25.5). The analysis was performed on a randomly selected training set comprising two-thirds of the available data that met the requirements for conversion to newly presented T and M categories, reserving the other one-third of cases for later validation. The random selection process was stratified by type of database submission and time period of case entry (1990–1994 vs. 1995–2000).

Selection of a final stage grouping proposal from among the candidate schemes was done based on its statistical properties in the training set and its relevance to clinical practice and by consensus.

Table 25.2 shows a comparison of the 6th edition and 7th edition TNM for lung cancer to assure clarity for the user. The final 7th edition TNM is described in the "Definitions of TNM" section that follows.

PROGNOSTIC FEATURES

The IASLC lung cancer database, although retrospective, provides the largest published analyses of prognostic factors in both NSCLC and SCLC. Potentially useful prognostic variables for lung cancer survival that were considered included: TNM

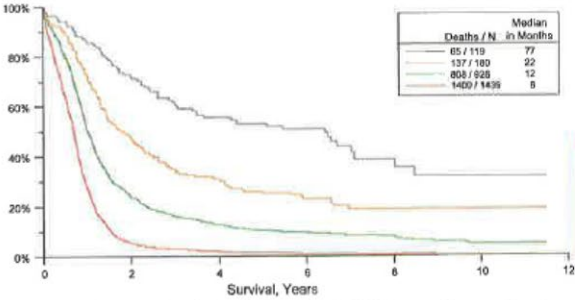

FIGURE 25.5. Survival in all SCLC by TNM stage (according to "best" stage based on a combination of clinical and pathologic staging in the IASLC lung database).

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TABLE 25.2. Stage grouping comparisons: 6th edition vs. 7th edition descriptors, T and M categories, and stage groupings

Sixth edition T/M descriptor	*7th edition T/M*	*N0*	*N1*	*N2*	*N3*
T1 (≤2 cm)	T1a	IA	IIA	IIIA	IIIB
T1 (>2–3 cm)	T1b	IA	IIA	IIIA	IIIB
T2 (≤5 cm)	T2a	IB	**IIA**	IIIA	IIIB
T2 (>5–7 cm)	T2b	**IIA**	IIB	IIIA	IIIB
T2 (>7 cm)	T3	**IIB**	**IIIA**	IIIA	IIIB
T3 invasion	T3	IIB	IIIA	IIIA	IIIB
T4 (same lobe nodules)	T3	**IIB**	**IIIA**	**IIIA**	IIIB
T4 (extension)	T4	**IIIA**	**IIIA**	IIIB	IIIB
M1 (ipsilateral lung)	T4	**IIIA**	**IIIA**	**IIIB**	**IIIB**
T4 (pleural effusion)	M1a	**IV**	**IV**	**IV**	**IV**
M1 (contralateral lung)	M1a	IV	IV	IV	IV
M1 (distant)	M1b	IV	IV	IV	IV

Cells in bold indicate a change from the 6th edition for a particular TNM category.

From Goldstraw P, Crowley J, Chansky K et al: The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. J Thorac Oncol 2:706–714, 2007, with permission.

stage, tumor histology, patient age, sex, and performance status, various laboratory values and molecular markers.

Clinical Factors. Analyses of the IASLC lung cancer database revealed that in addition to clinical stage, performance status and patient age and sex (male gender being associated with a worse survival) were important prognostic factors for both NSCLC and SCLC. In NSCLC, squamous cell carcinoma was associated with a better prognosis for patients with Stage III disease but not in other tumor stages. In advanced NSCLC (Stages IIIB/IV), some laboratory tests (principally white blood cells and hypercalcemia) were also important prognostic variables. In SCLC, albumin was an independent biological factor. Analyses that incorporate these factors along with overall TNM stage stratify both NSCLC and SCLC patients into 4 groups that have distinctly different overall survivals. In addition to these, a recent study of 455 patients with completely resected pathologic Stage I NSCLC suggests that high preoperative serum carcinoembryonic antigen (CEA) levels identify patients who have a poor prognosis, especially if those levels also remain elevated postoperatively. Other retrospective studies report that the intensity of hypermetabolism on FDG-PET scan is correlated with outcome in NSCLC patients managed surgically. Additional prospective studies are needed to validate these findings and to determine whether FDG-PET is prognostic across all lung cancer stages and histologies.

In the lung, arterioles are frequently invaded by cancers. For this reason, the V classification is applicable to indicate vascular invasion, whether venous or arteriolar.

Biological Factors. In recent years, multiple biological and molecular markers have been found to have prognostic value for survival in lung cancer, particularly NSCLC. These are summarized in Table 25.3. Although some molecular abnormalities, for example EGFR and K-ras mutations, are now being used to stratify patients for treatment, none is yet routinely used for lung cancer staging.

TABLE 25.3. Metaanalyses published on the prognostic value of biological or genetic markers for survival in lung cancer

Biological variable	*Prognostic factor*	*Reference*
bcl-2	Favorable	Martin et al. 2003
TTF1	Adverse	Berghmans et al. 2006
Cox2	Adverse	Mascaux et al. 2006
EGFR overexpression	Adverse	Nakamura et al. 2006
		Meert et al. 2002
EGFR mutation	Favorable	Marks et al. 2007
ras	Adverse	Mascaux et al. 2006
		Huncharek et al. 1999
Ki67	Adverse	Martin et al. 2004
HER2	Adverse	Meert et al. 2003
		Nakamura et al. 2005
VEGF	Adverse	Delmotte et al. 2002
Microvascular density	Adverse	Meert et al. 2002
p53	Adverse	Steels et al. 2001
		Mitsudomi et al. 2000
		Huncharek et al. 2000
Aneuploidy	Adverse	Choma et al. 2001

Adapted from Sculier JP et al. The IASLC Lung Cancer Staging Project: The impact of additional prognostic factors on survival and their relationship with the anatomical extent of disease expressed by the 6th edition of the TNM classification of malignant tumours and the proposals for the 7th edition, *J Thorac Oncol* 3(4):457–466, 2008, with permission.

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DEFINITIONS OF TNM

Primary Tumor (T)

TX	Primary tumor cannot be assessed, or tumor proven by the presence of malignant cells in sputum or bronchial washings but not visualized by imaging or bronchoscopy
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 3 cm or less in greatest dimension, surrounded by lung or visceral pleura, without bronchoscopic evidence of invasion more proximal than the lobar bronchus (i.e., not in the main bronchus)*
T1a	Tumor 2 cm or less in greatest dimension
T1b	Tumor more than 2 cm but 3 cm or less in greatest dimension
T2	Tumor more than 3 cm but 7 cm or less or tumor with any of the following features (T2 tumors with these features are classified T2a if 5 cm or less); Involves main bronchus, 2 cm or more distal to the carina; Invades visceral pleura (PL1 or PL2); Associated with atelectasis or obstructive pneumonitis that extends to the hilar region but does not involve the entire lung
T2a	Tumor more than 3 cm but 5 cm or less in greatest dimension
T2b	Tumor more than 5 cm but 7 cm or less in greatest dimension
T3	Tumor more than 7 cm or one that directly invades any of the following: parietal pleural (PL3) chest wall (including superior sulcus tumors), diaphragm, phrenic nerve, mediastinal pleura, parietal pericardium; or tumor in the main bronchus (less than 2 cm distal to the carina* but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung or separate tumor nodule(s) in the same lobe
T4	Tumor of any size that invades any of the following: mediastinum, heart, great vessels, trachea, recurrent laryngeal nerve, esophagus, vertebral body, carina, separate tumor nodule(s) in a different ipsilateral lobe

*The uncommon superficial spreading tumor of any size with its invasive component limited to the bronchial wall, which may extend proximally to the main bronchus, is also classified as T1a.

Regional Lymph Nodes (N)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Metastasis in ipsilateral peribronchial and/or ipsilateral hilar lymph nodes and intrapulmonary nodes, including involvement by direct extension
N2	Metastasis in ipsilateral mediastinal and/or subcarinal lymph node(s)
N3	Metastasis in contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or supraclavicular lymph node(s)

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis
M1a	Separate tumor nodule(s) in a contralateral lobe tumor with pleural nodules or malignant pleural (or pericardial) effusion*
M1b	Distant metastasis (in extrathoracic organs)

From Goldstraw P, Crowley J, Chansky K, et al.: The IASLC Lung Cancer Staging Project: Proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol* 2:706–714, 2007, with permission.

*Most pleural (and pericardial) effusions with lung cancer are due to tumor. In a few patients, however, multiple cytopathologic examinations of pleural (pericardial) fluid are negative for tumor, and the fluid is nonbloody and is not an exudate. Where these elements and clinical judgment dictate that the effusion is not related to the tumor, the effusion should be excluded as a staging element and the patient should be classified as M0.

ANATOMIC STAGE/PROGNOSTIC GROUPS

Occult carcinoma	TX	N0	M0
Stage 0	Tis	N0	M0
Stage IA	T1a	N0	M0
	T1b	N0	M0
Stage IB	T2a	N0	M0
Stage IIA	T2b	N0	M0
	T1a	N1	M0
	T1b	N1	M0
	T2a	N1	M0
Stage IIB	T2b	N1	M0
	T3	N0	M0
Stage IIIA	T1a	N2	M0
	T1b	N2	M0
	T2a	N2	M0
	T2b	N2	M0
	T3	N1	M0
	T3	N2	M0
	T4	N0	M0
	T4	N1	M0
Stage IIIB	T1a	N3	M0
	T1b	N3	M0
	T2a	N3	M0
	T2b	N3	M0
	T3	N3	M0
	T4	N2	M0
	T4	N3	M0
Stage IV	Any T	Any N	M1a
	Any T	Any N	M1b

PROGNOSTIC FACTORS (SITE-SPECIFIC FACTORS) (Recommended for Collection)

Required for staging	None
Clinically significant	Pleural/elastic layer invasion (based on H&E and elastic stains) Separate tumor nodules Vascular invasion – V classification (venous or arteriolar)

HISTOPATHOLOGIC GRADE (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

ADDITIONAL NOTES REGARDING TNM DESCRIPTORS

The T category is defined by the size and extent of the primary tumor. Definitions have changed from the prior edition of TNM. For the T2 category, visceral pleural invasion is defined as invasion to the surface of the visceral pleura or invasion beyond the elastic layer. On the basis of a review of published literature, the IASLC Staging Committee recommends that elastic stains can be used in cases where it is difficult to identify invasion of the elastic layer by hematoxylin and eosin (H&E) stains. A tumor that falls short of completely traversing the elastic layer is defined as PL0. A tumor that extends through the elastic layer is defined as PL1 and one that extends to the surface of the visceral pleural as PL2. Either PL1 or PL2 status allows classification of the primary tumor as T2. Extension of the tumor to the parietal pleura is defined as PL3 and categorizes the primary tumor as T3. Direct tumor invasion into an adjacent ipsilateral lobe (i.e., invasion across a fissure) is classified as T2a. These definitions are illustrated in a report by Travis et al., referenced in the bibliography of this chapter.

Multiple tumors may be considered to be synchronous primaries if they are of different histological cell types. When multiple tumors are of the same cell type, they should only be considered to be synchronous primary tumors if in the opinion of the pathologist, based on features such as associated carcinoma in situ or differences in morphology, immunohistochemistry, and/or molecular studies, they represent differing subtypes of the same histopathological cell type, and also have no evidence of mediastinal nodal metastases or of nodal metastases within a common nodal drainage. Synchronous primary tumors are most commonly encountered when dealing with either bronchioloalveolar carcinomas or adenocarcinomas of mixed subtype with a bronchioloalveolar component. Multiple synchronous primary tumors should be staged separately. The highest T category and stage of disease should be assigned and the multiplicity or the number of tumors should be indicated in parenthesis, e.g., T2(m) or T2(5).

Vocal cord paralysis (resulting from involvement of the recurrent branch of the vagus nerve), superior vena caval obstruction, or compression of the trachea or esophagus may be related to direct extension of the primary tumor or to lymph node involvement. The treatment options and prognosis associated with this direct extension of the primary tumor fall within the T4N0-1 (Stage IIIA) category; therefore, a classification of T4 is recommended. If the primary tumor is peripheral, vocal cord paralysis is usually related to the presence of N2 disease and should be classified as such.

The designation of "Pancoast" tumors relates to the symptom complex or syndrome caused by a tumor arising in the superior sulcus of the lung that involves the inferior branches of the brachial plexus (C8 and/or T1) and, in some cases, the stellate ganglion. Some superior sulcus tumors are more anteriorly located and cause fewer neurological symptoms but encase the subclavian vessels. The extent of disease varies in these tumors, and they should be classified according to the established rules. If there is evidence of invasion of the vertebral body or spinal canal, encasement of the subclavian vessels, or unequivocal involvement of the superior branches of the brachial plexus (C8 or above), the tumor is then classified as T4. If no criteria for T4 disease pertain, the tumor is classified as T3.

Tumors directly invading the diaphragm in the absence of other signs of locally advanced disease are rare, constituting less than 1% of all cases of potentially resectable NSCLC. These tumors are considered to be T3, but appear to have a poor prognosis, even after complete resection and in the absence of N2 disease. The classification of such tumors may need to be reevaluated in the future as more survival data become available.

The term "satellite nodules" was included in the 6th edition of the *AJCC Cancer Staging Manual*. It was defined as additional small nodules in the same lobe as the primary tumor but anatomically distinct from it that could be recognized grossly. Additional small nodules that could be identified only microscopically were not included in this definition. The term "satellite nodules" is being deleted from this edition of the *Staging Manual* because it is confusing, has no scientific basis, and is at variance with the UICC Staging Manual. The term "additional tumor nodules" should be used to describe grossly recognizable multiple carcinomas in the same lobe. Such nodules are classified as T3. This definition does not apply to one grossly detected tumor associated with multiple separate microscopic foci.

HISTOPATHOLOGIC TYPE

The World Health Organization histologic classification of tumors of the lung, 2004, is shown in Table 25.4.

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TABLE 25.4. World Health Organization histologic classification of tumors of the lung, 2004

Malignant epithelial tumors	*ICD*
Squamous cell carcinoma	8070/3
Papillary	8052/3
Clear cell	8084/3
Small cell	8073/3
Basaloid	8083/3
Small cell carcinoma	8041/3
Combined small cell carcinoma	8045/3
Adenocarcinoma	8140/3
Adenocarcinoma, mixed subtype	8255/3
Acinar adenocarcinoma	8550/3
Papillary adenocarcinoma	8260/3
Bronchioloalveolar carcinoma	8250/3
Nonmucinous	8252/3
Mucinous	8253/3
Mixed nonmucinous and mucinous or indeterminate	8254/3
Solid adenocarcinoma with mucin production	8230/3
Fetal adenocarcinoma	8333/3
Mucinous ("colloid") carcinoma	8480/3
Mucinous cystadenocarcinoma	8470/3
Signet ring adenocarcinoma	8490/3
Clear cell adenocarcinoma	8310/3
Large cell carcinoma	8012/3
Large cell neuroendocrine carcinoma	8013/3
Combined large cell neuroendocrine carcinoma	8013/3
Basaloid carcinoma	8123/3
Lymphoepithelioma-like carcinoma	8082/3
Clear cell carcinoma	8310/3
Large cell carcinoma with rhabdoid phenotype	8014/3
Adenosquamous carcinoma	8560/3
Sarcomatoid carcinoma	8033/3
Pleomorphic carcinoma	8022/3
Spindle cell carcinoma	8032/3
Giant cell carcinoma	8031/3
Carcinosarcoma	8980/3
Pulmonary blastoma	8972/3
Carcinoid tumor	8240/3
Typical carcinoid	8240/3
Atypical carcinoid	8249/3
Salivary gland tumors	
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/2
Epithelial-myoepithelial carcinoma	8562/3

Morphology code of the International Classification of Diseases for Oncology (ICD-0) and the Systematized Nomenclature of Medicine (http://snowmed.org). Behavior is coded /0 for benign tumors, /3 for malignant tumors, and /1 for borderline or uncertain behavior.

From Travis WD, et al., eds. Tumours of the Lung, Pleura, Thymus and Heart. World Health Organization Classification of Tumours. Lyon: IARC Press, 2004, p. 10, with permission of IARC Press.

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