Official Title: **Phase IIIb, 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**

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ROCHE D.O.O
CLINICAL STUDY PROTOCOL
PROTOCOL NUMBER ML 27860

Phase IIIb, open-label study of **E**rlotinib (Tarceva®) treatment in patients with locally advanced or meta**S**tatic non-**S**mall cell lung canc**E**r who present activating mutatio**N**s in the tyrosine kinase domain of the epidermal growth fa**C**tor rec**E**ptor

ESSENCE

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PROTOCOL APPROVAL

Protocol Number / Version: ML27860 version 1.1

Date: 16. Aug 2012

Protocol approved by: [redacted]

This protocol is intended for use in a life-threatening indication: Yes ☒ No ☐

SYNOPSIS OF PROTOCOL NUMBER ML 27860

TITLE	Phase IIIb, 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 d.o.o CLINICAL PHASE IIIb
INDICATION	Locally advanced (stage IIIB with supraclavicular lymph node metastases or malignant pleural or pericardial effusion), or metastatic (stage IV) non-small cell lung cancer (NSCLC).
OBJECTIVES	**Primary:** Efficacy of erlotinib (Tarceva™; 150 mg) on progression-free survival (PFS) in patients with non-small-cell lung cancer (NSCLC) in locally advanced or metastatic stages (stage IIIB and stage IV) 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:** • Response rate, • Safety profile, • To assess the incidence of EGFR mutations in NSCLC patients tested in Serbia. • Quality of Life (QoL)
TRIAL DESIGN	Open-label, multi-center Phase IIIb study
NUMBER OF SUBJECTS	300 patients
TARGET POPULATION	Patients with histologically or cytologically confirmed locally advanced or metastatic (stage IIIB/IV) 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. Histologically or cytologically documented inoperable, locally advanced (stage IIIB with supraclavicular lymph node metastases or malignant pleural or pericardial effusion) or metastatic (stage IV) NSCLC disease who present activating mutations (exon 19 deletions or exon 21 substitution L858R) in the tyrosine kinase domain of EGFR. 3. Measurable disease must be characterized according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria. 4. Male or female patients aged ≥ 18 years. 5. Eastern Cooperative Oncology Group (ECOG) performance

	status 0-2. 6. Life expectancy ≥ 12 weeks. 7. Adequate hematological function: Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, and Platelet count ≥ 100 x 10^9/L, and Hemoglobin ≥ 9 g/dL (may be transfused to maintain or exceed this level). 8. Adequate liver function: Total bilirubin < 1.5 x upper limit of normal (ULN), and aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) < 2.5 x ULN in patients without liver metastases; < 5 x ULN in patients with liver metastases. 9. Adequate renal function: Serum creatinine ≤ 1.25 x ULN, Creatinine clearance ≥ 60 ml/min. 10. Able to comply with the required protocol and follow-up procedures, and able to receive oral medications. 11. 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. Women with an intact uterus (unless amenorrhoeic for the last 24 months) must have a negative pregnancy test (urine or serum) within 3 days prior to enrolment into the study. Male and female patients must use effective contraception during the study and for a period of 60 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 spermicide. 12. 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 also will be eligible.
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 neoadjuvant 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 (a 2-week period is recommended). 2. Treatment with an investigational drug agent during the 3 weeks before enrollment in the study. 3. 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. 4. Patients with symptomatic cerebral metastases. 5. Known hypersensitivity to erlotinib or any of its excipients. 6. Any significant ophthalmologic abnormality, especially severe dry eye syndrome, keratoconjunctivitis sicca, Sjögrens 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. 7. Coumarins (Coumadin™; warfarin) use. If the patient requires anti-coagulation therapy, the use of low molecular weight heparin instead of coumarins is recommended where clinically possible. 8. Unstable systemic disease (including active infection, uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction within the previous year, serious cardiac arrhythmia requiring medication, hepatic, renal, or metabolic disease). 9. 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. 10. Positive urine or serum pregnancy test in women of childbearing potential. Patients (male or female) with reproductive potential not willing to use effective method of contraception. Female patients should not be pregnant or breast-feeding. Oral or injectable contraceptive agents cannot be the sole method of contraception. 11. Patients with pre-existing parenchymal lung disease such as pulmonary fibrosis, lymphangiosis carcinomatosis. 12. Patients with known infection with HIV, HBV, HCV. Testing is not required in the absence of clinical signs and symptoms suggestive of these conditions. 13. Patients assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol. 14. 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 of approximately 24 months. 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 visit. 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 6.1.1.)
ASSESSMENTS OF:	
EFFICACY	**Primary endpoint:** • PFS, defined as the time from the first dose of erlotinib to the date of first occurrence of disease progression or death. **Secondary endpoints:** • Response rate and disease control rate based on best response measured according to RECIST criteria.
SAFETY	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 rash and diarrhea will be collected.
INCIDENCE OF EGFR MUTATION RATES IN SERBIA	If patients are deemed eligible to participate in the study by the investigator, EGFR mutation analysis will be performed at [redacted] for oncology and radiology of Serbia or at Private Laboratory [redacted]. Patients whose tumors present activating mutations (exon 19 deletions or exon 21 substitution L858R) in the TK domain of EGFR gene are eligible to be enrolled in therapeutic phase of the study. The incidence of EGFR mutations among NSCLC patients tested in Serbia will be assessed.
QUALITY OF LIFE	Quality of life will be measured using the FACT-L method. This is a validated measure of quality of life. FACT-L Quality of Life questionnaires will be administered to patients prior to therapy, at each visit and at the final study visit, 4 weeks after patients progressed.

PROCEDURES (summary):

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

- Interview and physical examination, including assessment of concomitant medications, weight, ECOG performance status, and clinical tumor measurements. This information will be obtained in the 7 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, hemoglobin, and platelets). This information will be obtained in the 7 days before initiation of treatment.
- Biochemistry: alkaline phosphatase, ASAT, ALAT, bilirubin, serum creatinine, creatinine clearance (if indicated). This information will be obtained in the 7 days before initiation of treatment.
- Prothrombin time and INR. This information will be obtained in the 7 days before initiation of treatment.
- Pregnancy test in women of childbearing age.
- Tumor assessment, using computer tomography (CT) or magnetic resonance imaging (MRI) 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 main evaluation criterion will be percentage of subjects with EGFR mutation. The sample size estimation is based on 95% confidence interval of this percentage. Under the assumption that the expected rate should be 10% the inclusion of 300 patients should allow to estimate this rate with a precision of 3.5%.

Efficacy Analyses:

The primary and secondary efficacy analyses will be performed on the intent-to-treat population, defined as all patients who are enrolled to the study and received at least one dose of a treatment.

For the variable of PFS, Kaplan-Meier curve and estimate will be provided.

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.

Interim Analysis

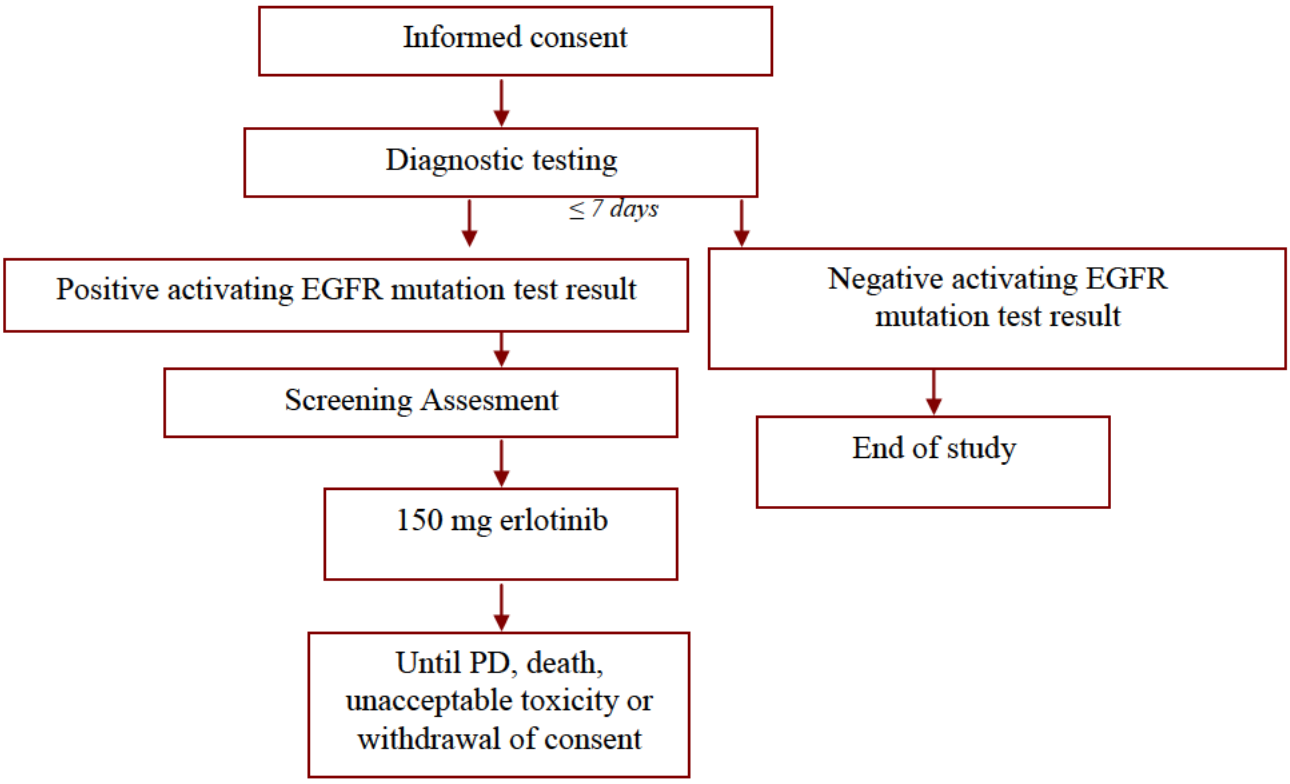
The first analysis on the incidence of EGFR mutations in patients entered in to the study will be conducted when EGFR mutation analysis results has been obtained for all

patients which is anticipated 24 months after entry of the first subject. Subsequent interim analysis for secondary endpoints will be conducted when at least 75% of patients have experienced an end of study event.

Quality of Life Analysis

Quality of life assessments will be used to derive pre-specified QoL scores according to the QoL manual. These scores will be summarized by descriptive summary tables at baseline and over time. The overall health score will be further analysed for the assessment at the end of treatment with baseline and treatment as covariates in an analysis of covariance model. Missing data will be replaced by the last valid post baseline assessment before.

SUMMARY OF STUDY DESIGN



SCHEDULE OF ASSESSMENTS

Assessment	Diagnostic phase	Exon 19 deletion or exon 21 substitution L858R in the TK domain of EGFR gene	Screening		Treatment Period		Final Visit / Withdrawal from Treatment
	Days		Days		Visit # (Day 1 of every 6th week throughout treatment period)		End of study
	-14 to -7		-7 to -3	-3 to -1	Visit 1 (Baseline)	Visit – every 6th week, until PD, death or unacceptable toxicity	
Informed consent	X						
Demographics	X						
Medical history			X				
Pregnancy test[a]				X	To be repeated as necessary		
Physical examination[b]			X		X	X	
Weight			X		X	X	
Vital signs			X		X	X	
ECOG PS			X		X	X	X
ECG[c]			X		To be repeated as clinically indicated		
Mandatory tumor sample	**X**						
Hematology			X		X	X	X
Biochemistry			X		X	X	X
Urinalysis			X		X	X	X
Concomitant medications			X		X	X	X
Tumor assessment[d]			X		X	X	X
QoL assesment			X		X	X	X
Adverse events[e]					X	X	X
Subsequent therapy for NSCLC[f]							X
Drug dispensing and accountability[g]					X	X	X
Patient diary[e]					X	X	X

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 – within ≤ 24 hours.

[a] Urine or serum.

[b] Including an ophthalmologic examination if clinically indicated.

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

[d] Tumor assessment consists at minimum of a chest X Ray, CT or MRI 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. CT scan of the brain is not mandatory but should be done if there is a clinical suspicion of cerebral

metastasis. Post-baseline assessments are to be performed within +/- 1 week for the 6 weekly assessments. If there is suspicion of disease progression based on clinical or laboratory findings, a tumor assessment should be performed as soon as possible, before the next scheduled evaluation.
[e] Graded according to NCI CTC-AE version 4.0.
[f] Subsequent therapy for all patients.
[g] For details on drug dispensing and accountability see Section Z.
[e] Patients will keep a diary to record if study drug was taken (each day of treatment). The patient will bring this diary with him/her to each study visit to allow review of taken doses and possible side effects by the investigator.

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GLOSSARY OF ABBREVIATIONS

^{o}C	Degrees Celsius
^{o}F	Degrees Fahrenheit
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under the plasma concentration-time curve
b.i.d.	Twice daily
BP	Blood pressure
BSC	Best supportive care
C_{24h}	Plasma concentration at 24 hours post-dose
CA	Competent authority
CD	Compact disk
CDS	Core data sheet
CFR	Code of federal regulations
CG	Clinical genotyping
CI	Confidence interval
C_{max}	Maximum plasma concentration
CR	Complete Response
CRF	Case report form(s)
CRP	C-reactive protein
CT	Computer Tomography
CTC	Common Terminology Criteria
CTC-AE	Common Terminology Criteria for

	Adverse Events
CYP	Cytochrome P450
dL	Deciliter
DSMB	Data safety monitoring board
EC_{50}	Plasma concentration associated with half-maximal effect
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form(s)
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic acid
EEA	European economic area
EEG	Electroencephalography
e-Form	Electronic Form (page)
EGF	Epidermal Growth Factor
EGFR	Epidermal Growth Factor Receptor
ESF	Eligibility screening form
EU	European Union
EWB	Emotional well-being
FACIT	Functional Assessment of Chronic Illness Therapy
FACT-G	Functional Assessment of Cancer Therapy – General
FACT-L	The Functional Assessment of Cancer Therapy – Lung
FDA	Food and Drug Administration
FWB	Functional well being
g	Gram
GCP	Good Clinical Practice

GI	Gastrointestinal
H_0	Null hypothesis
H_1	Alternative hypothesis
H2	Histamine 2 receptor
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
IB	Investigator Brochure
IC_{50}	Half maximal inhibitory concentration
ICF	Informed consent form
ICH	International Conference on Harmonization
ID	Identity
IDRC	Independent data review committee
IEC	Independent Ethics Committees
ILD	Interstitial lung disease
IMP	Investigational medicinal product
INR	International normalized ratio
ITT	Intent-to-treat
IWRS	Interactive web response system
LC-MS/MS	Liquid chromatography - mass spectrometry
LCS	Lung cancer subscale
LD	Longest diameter
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter

mm	Millimeter
MRI	Magnetic resonance image
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NCIC CTG	National Cancer Institute of Canada Clinical Trials Group
ng	Nano-gram
nM	Nanomole
NSAIDs	Non-steroidal anti-inflammatory drugs
NSCLC	Non-small cell lung cancer
PD	Progressive disease
PFS	Progression free survival
PK	Pharmacokinetic
p.o.	Oral administration
PS	Performance status
PR	Partial response
PWB	Physical well being
QOL	Quality of life
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SEAG	Science and ethics advisory group
SD	Stable disease
SDO	Survival distribution of the parameter PFS
SMT	Study Management team
SPC	Summary of Product Characteristics
SWB	Social/family well being

TI	Therapeutic index
TOI	Trial outcome index
ULN	Upper limit of normal
US	Ultrasound
WBC	White blood cell

PART I: STUDY DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1 Background

1.1.1 Non-small cell lung cancer

Lung cancer is the most common cause of cancer death worldwide, accounting for up to 18% of cancer-related deaths (Parkin et al., 2005). Non-small cell lung cancers (NSCLC) comprise 80% of reported lung cancer cases (Cartman et al., 2002). Indeed, the majority of new cases of lung cancer are advanced NSCLC (Haura, 2001). Due to late diagnosis, only a small proportion of NSCLC cases are operable as over 60% of patients present with advanced stages of the disease (Makitaro et al., 2002). In comparison with other solid tumors, the objective response and overall survival (OS) rates in patients with advanced NSCLC are low: five-year survival rates for stage IIIB inoperable disease are less than 10%, decreasing to less than 2% in disease stage IV (Ginsberg et al., 2001).

For this population of patients in whom treatment is mainly palliative, the main goal is to achieve symptom control and prolong overall survival (Vansteenkiste, 2007). Standard of care for patients with locally advanced or metastatic NSCLC is platinum-based doublet chemotherapy (Pfister et al., 2004). Doublet chemotherapy has been found to be superior to single-agent chemotherapy (Delbaldo et al., 2004), with cisplatin-based therapy the current reference treatment for patients with advanced NSCLC. However, no doublet combination has been proven to be clinically superior to the others (Greco et al., 2002; Scagliotti et al., 2002; Schiller et al., 2002; Smit et al., 2003). Current data suggest that chemotherapy has reached a therapeutic plateau, conferring no improvements in survival despite the availability of new combinations of cytotoxic agents (Helbekkmo et al., 2007; Schiller et al., 2002). Overall, the survival outcomes for NSCLC patients remain poor, with a one-year survival rate of only 35% (Ettinger, 2002).

Targeting the epidermal growth factor receptor (EGFR) has played an important role in advancing NSCLC therapy and improving patient outcomes (Gridelli et al., 2007). The EGFR is a promising target for the treatment of NSCLC. The EGFR family is a group of widely-expressed transmembrane proteins, often implicated in the development and onset of epithelium-derived carcinomas. Ligand binding triggers receptor homo- or hetero-dimerization, followed by autophosphorylation of key tyrosine residues in the cytoplasmic domain and internalization (Schlessinger and Lemmon, 2006). This sequence of events leads to a downstream cascade of cellular responses, including proliferation, angiogenesis, metastasis, and apoptotic inhibition (Goel et al., 2007).

Frequently expressed in solid tumors including NSCLC, the expression of the EGFR gene is often associated with advanced disease and poor clinical outcome (Ohsaki et al., 2000; Nicholson et al., 2001). In human tumors, over-expression of EGFR and its ligands is a commonly-occurring alteration in the EGFR signaling pathway, although constitutively active EGFR mutants have also been observed in several tumor types, including lung tumors (Choi et al., 2007). Collectively, this evidence demonstrates that

aberrant activation of the EGFR signaling pathway is a critical event driving tumor proliferation and survival.

Hence, EGFR inhibition has been found to be a successful strategy for controlling tumorigenesis. Down regulation of EGFR signaling by heterologous expression of dominant-negative mutant receptors or antisense techniques can reduce the transformation and proliferation of tumor cell lines *in vitro* (Chakrabarty et al., 1995; De et al., 1996; Redemann et al., 1992). Two major methods for the pharmacologic inhibition of EGFR function are 1) the use of monoclonal antibodies against the extracellular domain of the receptor and 2) the use of quinazolinamine derivatives that compete for the ATP-binding site within the receptor tyrosine kinase domain. *In vitro* and *in vivo* studies demonstrate that targeted inhibition of the EGFR in this manner can trigger tumor apoptosis and induce regression in human tumor xenograph models (Rewcastle et al., 1998; Wu et al., 1995). Interestingly, targeted knock-out of the EGFR gene in mice resulted in abnormalities of the hair, skin and eyes (Luetteke et al., 1994), but did not affect embryonic development or birth (Sibilia and Wagner, 1995; Threadgill et al., 1995), suggesting that EGFR is not critical for the proliferation and differentiation of all cell types, including those of the developing embryo.

Erlotinib acts via a different mechanism of action than chemotherapy agents, providing an important treatment alternative for those patients who do not benefit from standard chemotherapy.

1.1.2 Incidence of EGFR mutations and sensitivity to TKIs

The identification of mutations within the EGFR in the tumour tissue of a subset of NSCLC patients and the association of these mutations with sensitivity to gefitinib support the hypothesis that these are activating mutations which also render the tumours sensitive to the effects of other EGFR tyrosine kinase inhibitors (TKI).
In the above mentioned studies, the reported prevalence of the mutations was 8% in unselected NSCLC patients. The mutations were found more frequently in adenocarcinoma (21%), in tumours from females (20%), and in tumours from Japanese patients (26%). The mutations result in increased in vitro activity of EGFR and increased sensitivity to EGFR tyrosine kinase inhibitors.
Lynch et al analysed 16 patients treated with gefitinib and found mutations in 8 out of 9 responders and 0 out of 7 non-responders. Paez *et al* analysed 9 patients treated with gefitinib and found mutations in 5 of 5 responders and 0 of 4 non-responders.

Similar analysis was performed in patients treated with erlotinib. The response rate in patients with mutations was 26.7% compared to that in patients with wild type EGFR of 6.9%. This was statistically significant (p=0.04). In a large Phase III study of maintenance erlotinib versus placebo following non-progression with first-line platinum-based chemotherapy in NSCLC patients, progression free survival was found to be longer in patients with EGFR mutations compared to those without .

1.1.3 Study "Drug"

Erlotinib (OSI-774; Tarceva™)

Erlotinib is an orally active and potent inhibitor of EGFR developed for the treatment of solid tumors including NSCLC. This quinazolinamine derivative selectively inhibits the

EGFR tyrosine kinase (Moyer et al., 1997; OSI Pharmaceuticals et al., 2008), and is the only EGFR inhibitor to confer a significantly improved survival benefit against best supportive care (BSC) in a second-line setting (Shepherd et al., 2005). Erlotinib was approved for the treatment of advanced or metastatic NSCLC after the failure of at least one prior chemotherapy regimen. The recommended daily dose of erlotinib is 150 mg.

Mechanism of action

Erlotinib acts via direct and reversible inhibition of the human EGFR tyrosine kinase, with an IC_{50} of 2 nM (0.786 ng/mL) in an *in vitro* enzyme assay, and reduces receptor autophosphorylation in intact tumor cells with an IC_{50} of 20 nM (7.86 ng/mL) (OSI Pharmaceuticals et al., 2008). 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 kinases demonstrated that erlotinib is selective for the EGFR (OSI Pharmaceuticals et al., 2008).

Overview of erlotinib in NSCLC

The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) BR.21 was a pivotal Phase III study that demonstrated a significant survival advantage for patients with NSCLC treated with erlotinib after other treatments had failed (Shepherd et al., 2005). This multinational, randomized, placebo-controlled, double blind study in patients with advanced metastatic NSCLC showed a statistically significant and clinically meaningful prolongation of survival in patients treated with erlotinib. There was a 42.5% improvement in median OS in the erlotinib arm (6.7 months; 95% confidence interval (CI): 5.52-7.79), compared to placebo (4.7 months; 95% CI: 4.11-6.28; *P*=0.002). The survival benefit of erlotinib was also seen in those patients that did not show an objective tumor response. In the subset of patients whose best response was stable/progressive disease (SD/PD), those treated with erlotinib showed a median survival time of 8.3 months, compared to 6.8 months for those on placebo (hazard ratio (HR) 0.82; 95% CI: 0.68-0.99; *p*=0.037). Erlotinib conferred overall survival benefits regardless of age, gender, ethnicity, smoking status, performance status, or tumor histology.

Erlotinib significantly delayed the time to deterioration for the three main symptoms of lung cancer in comparison with placebo (4.9 vs. 3.7 months for cough (*p*=0.04), 4.7 vs. 2.9 months for dyspnea (*p*=0.04), and 2.8 vs. 1.9 months for pain (*p*=0.03)). Furthermore, erlotinib treatment was associated with improvements in tumor-related symptoms and quality of life (QOL) over placebo (Bezjak et al., 2006), particularly with respect to physical function and global QOL parameters. Thus, the use of erlotinib provides a means of achieving symptom control and improving overall survival in NSCLC patients.

Erlotinib has been approved in the United States of America and European Union for second-line treatment of NSCLC (Gridelli et al., 2007). Recently erlotinib has been approved in the US for maintenance treatment in patients with locally advanced or metastatic NSCLC after four cycles of standard platinum-based first-line chemotherapy and in Europe for maintenance treatment in patients with locally advanced or metastatic NSCLC with stabile disease after four cycles of standard platinum-based first-line chemotherapy. The approvals based on SATURN data – a double-blind study of erlotinib in patients with advanced (stage IIIB or IV) NSCLC previously treated with four cycles

of a platinum-based chemotherapy. At the data lock point, Study BO18192 was complete with 889 patients enrolled. The study met its primary and co-primary endpoints by demonstrating a statistically significant and clinically meaningful improvement in investigator assessed progression free survival (PFS). The result was robust and was corroborated by independent central review with a nearly identical estimate of treatment effect. Primary efficacy results were also supported by findings based on secondary endpoints. Efficacy was consistent across subgroups irrespective of histology, race, gender, smoking status, Eastern Cooperative Oncology Group Performance Status (ECOG PS) and other clinical characteristics. Biomarkers including EGFR immunohistochemistry, fluorescence *in situ* hybridisation, and K-ras mutation status were not strongly predictive of outcome. Benefit in PFS was observed across all biomarker subgroups. While activating EGFR mutations identified patients with highest benefit, these mutations were not a prerequisite for effect as benefit was also seen in patients with wild type EGFR tumours. Quality of life did not suggest a detrimental effect from erlotinib compared with placebo. Erlotinib significantly improved overall survival versus placebo in both the overall population and in patients with EGFR wild-type tumours. Thus, the overall survival benefit was not driven by patients with EGFR mutation-positive disease. Erlotinib was generally well tolerated and no new safety signals were identified. Data from BO18192 study indicates that the use of erlotinib in first-line maintenance setting has a favourable balance of benefit to risk.

The recommended daily dose of erlotinib was established at 150 mg, to be continued daily until disease progression. The most frequently-reported adverse events (AEs) associated with single-agent erlotinib are rash (dermatosis), diarrhea, nausea, fatigue, stomatitis, vomiting, and headache (OSI Pharmaceuticals et al., 2008). Interestingly, skin rash was identified as a major indicator of erlotinib trough plasma concentrations (Rudin et al., 2008). These findings corroborate those from previous studies on EGFR inhibitors, which have shown a similar association between drug steady-state plasma concentrations and the intensity of rash and diarrhea (Cohen et al., 2004; Li et al., 2006). 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 (OSI Pharmaceuticals et al., 2010). Despite these observations, no dose adjustment is necessary in patients with moderately impaired hepatic function (OSI Pharmaceuticals et al., 2010).

An overview of completed and ongoing clinical studies on erlotinib in NSCLC can be found in the Investigator‟s Brochure 15th Edition.

1.2 Rationale for the Study

Much research has been directed towards defining the clinical characteristics which confer a survival advantage in NSCLC patients treated with EGFR inhibitors.

The standard treatment for patients with non-small-cell lung carcinoma with advanced disease is chemotherapeutic drug doublets. A response rate of about 30-35% is obtained, with a median survival of 10-11 months and a 1-year survival of 25-30%, with these

treatments. These treatments generally are associated with an important toxicity that can condition the quality of life of the patients.

Molecular studies of tumor samples from patients who have responded to treatment with erlotinib have demonstrated that certain deletions and mutations in certain exons of the EGFR (19 and 21) occur more frequently in responders. The Spanish Lung Cancer Group has evaluated prospectively the presence of deletions in exon 19 or mutations in exon 21 of the EGFR gene. It has been observed that 70-90% of patients who present some of these alterations respond to erlotinib treatment (Rosell et al., 2009).

TKIs in EGFR mutated patients

Erlotinib was shown to prolong survival in a large, randomized, placebo-controlled Phase III trial including 731 NSCLC patients no longer candidates for further chemotherapy (Study BR. 21) (24). Zhu et al evaluated the effect of *KRAS* and epidermal growth factor receptor (*EGFR*) genotype on the response to erlotinib treatment in the BR.21, placebo-controlled trial above. They found that 34 (17%) of 204 patients‟ tumours analysed for EGFR mutations had *EGFR* exon 19 deletion or exon 21 mutations. Response rates to erlotinib were 7% for wild-type and 27% for mutant *EGFR* (*P* =.03) (24).

Erlotinib has proven results as first-line maintenance therapy following non-progression of disease after first-line therapy (23). The SATURN trial investigated erlotinib maintenance therapy in patients with advanced NSCLC who did not progress during first-line chemotherapy. This randomised, global, phase III study was the first to include prospective molecular marker analyses for erlotinib, with mandatory sample collection. Those with *EGFR* mutation-positive disease were found to derive a particularly large PFS benefit from erlotinib therapy (median PFS of 44.6 weeks vs 13 weeks for patients without mutations) (25). 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. 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. (26) Erlotinib is currently being assessed as first-line treatment in advanced NSCLC in prospective, randomised, registration trials. There is however, already evidence that erlotinib works in first-line treatment. Paz-Ares (27) 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.

Summary of data included in pooled analysis

	Erlotinib	**Gefitinib**	**Chemotherapy**
Patients treated in any line, n	365	1069	375
Patients treated in first-line	57	57	95

setting, %			

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)

Pooled analysis of outcomes according to line of therapy

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 (26) 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 (28) where the PFS was 14.0 months with erlotinib.

These data suggest that the presence of EGFR mutations can be used to identify the subgroup of patients with non-small-cell lung cancer in which this growth factor plays a crucial role in tumor growth and in which inhibition with erlotinib would be effective in treatment.

EGFR mutations rates in Serbia

The rate of EGFR mutations in patients with NSCLC in Serbia is currently unknown. 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%. As the rate of EGFR mutations amongst NSCLC patients in the Serbia is currently unknown, the health burden and economic implications of treatments directed specifically at patients with this characteristic cannot be accurately assessed.

Purpose of the study

Therefore ,the purpose of the current study is to test the efficacy and safety of the erlotinib as a first-line therapy in patients with NSCLC in locally advanced or metastatic stages (stage IIIB and stage IV) with activating mutations in the tyrosine kinase (TK) domain of the epidermal growth factor receptor (EGFR).

Also, it will be assessed the EGFR mutation rate in Serbia NSCLC population. This will be done by testing Serbia patients with locally advanced or metastatic NSCLC for the EGFR mutations.

Beside this, it will be assesed the impact of erlotinib treatment on quality of life.

The results of this study will help to validate the utility of detecting EGFR mutations for improving treatment selection in this patient population, which will be beneficial.

2. OBJECTIVES

2.1 Primary Objectives

Efficacy of erlotinib (Tarceva™; 150 mg) on progression-free survival (PFS) in patients with non-small-cell lung cancer (NSCLC) in locally advanced or metastatic stages (stage IIIB and stage IV) 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

1. Response rate.
2. Safety profile.
3. To assess the incidence of EGFR mutations in NSCLC patients tested in Serbia.

3. STUDY DESIGN

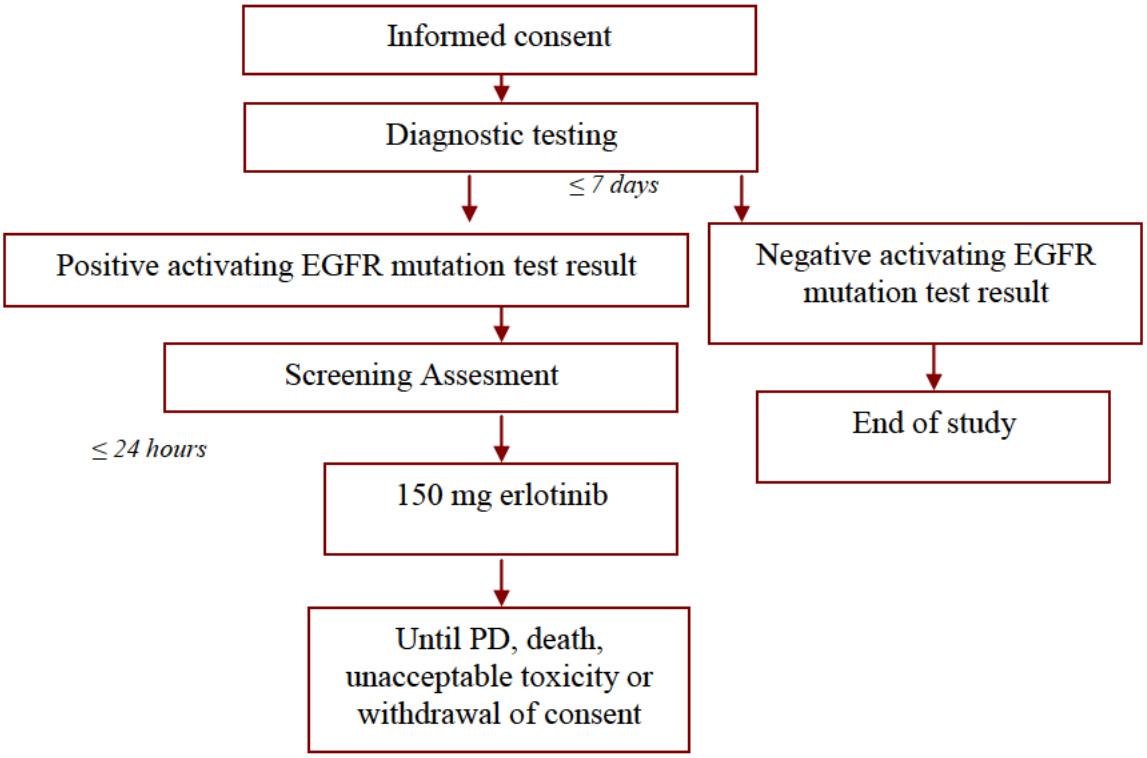
3.1 Overview of Study Design

This is a open-label, multi-center Phase IIIb study of erlotinib 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.

The first part of the study is the diagnostic phase which will test patients with advanced or metastatic NSCLC for EGFR mutations. Patients who do not have an EGFR mutation will be excluded from the trial. Patients found to have a tumour with EGFR mutations will then be offered treatment in the treatment phase of the study. The treatment phase is a single arm, open label study using erlotinib as first-line therapy. All enrolled patients into the treatment phase will receive erlotinib 150 mg/day until event. Erlotinib dose will be reduced for toxicities as detailed in Section 6.1.1. Event is defined as progression of disease, death, unacceptable toxicity or withdrawal of consent.

Summary of the study design is shown in Figure 1.

Figure 1: Summary of study design.



3.1.1 Rationale for Study Design

The purpose of this study is to examine efficacy and safety of erlotinib in first line treatment among patients with locally advanced or metastatic non-small cell lung cancer disease found to have an EGFR exon 19 deletion or exon 21 mutation.The primary efficacy variable will be PFS. Also, since the incidence of EGFR mutations in Serbia is currently unknown, it will be assessed the rate of EGFR mutation in Serbia NSCLC population.

3.1.2 Rationale for Dose Selection

The dose of erlotinib to be used in treatment phase will be 150mg/day. No dose escalation of erlotinib is permitted. Erlotinib dose will be reduced for toxicities as detailed in Section 6.1.1. Patients will be treated until progression of disease or unacceptable toxicity.

3.1.3 End of Study

The diagnostic phase will end when approximately 300 patients have been tested for EGFR mutations and this phase is expected to last approximately 24 months. The treatment phase is event driven and will end when all eligible patients have experienced progressive disease, death, unacceptable toxicities or withdrawn consent. The overall

duration of the study is expected to be 36 months. The end of the trial will be when the last patient experiences either progressive disease, death, unacceptable toxicities or withdraws consent. The study will end when the last patient has stopped erlotinib therapy and completed their last visit.

3.2 Number of Patients / Assignment to Treatment Groups

A total of approximately 300 patients will be enrolled into the diagnostic phase of this study.

30 patients will be enrolled into the treatment phase of the study.

3.3 Centers

This study will comprise 5 centers in Serbia.

4. STUDY POPULATION

Under no circumstances are patients who enroll in this study permitted to be re-enrolled for a second course of treatment.

4.1 Overview

The target population of this study is patients with histologically or cytologically confirmed locally advanced or metastatic (stage IIIB/IV) NSCLC who have not received previous chemotherapy for their disease (diagnostic phase) and who present activating mutations in the TK domain of the EGFR (treatment phase).

All patients with diagnosed histologically confirmed locally advanced or metastatic (stage IIIB/IV) NSCLC who have not received previous chemotherapy for their disease will be offered screening for EGFR mutations. All patients found to have exon 19 deletion or exon 21 mutation of the EGFR will be offered treatment with erlotinib in the treatment phase of the study. Patients who do not have an EGFR mutation or deletion will be excluded from the study.

4.2 Inclusion Criteria

<u>Diagnostic phase</u>

1. Patients able and willing to give written informed consent. Consent must be obtained prior to any study-specific procedure.
2. Histologically or cytologically documented inoperable, locally advanced (stage IIIB with supraclavicular lymph node metastases or malignant pleural or pericardial effusion) or metastatic (stage IV) NSCLC disease
3. Measurable disease must be characterized according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.
4. Male or female patients aged ≥ 18 years.
5. ECOG performance status 0-2.

6. Life expectancy ≥ 12 weeks.

Treatment phase

1. Patients must have been proven to have a histologically confirmed EGFR mutation in the diagnostic phase of the study

2. Adequate hematological function: Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L, and Platelet count ≥ 100 x 10^9/L, and Hemoglobin ≥ 9 g/dL (may be transfused to maintain or exceed this level).

3. Adequate liver function: Total bilirubin < 1.5 x upper limit of normal (ULN), and aspartate aminotransferase (ASAT), alanine aminotransferase (ALAT) < 2.5 x ULN in patients without liver metastases; < 5 x ULN in patients with liver metastases.

4. Adequate renal function: Serum creatinine ≤ 1.25 x ULN, Creatinine clearance ≥ 60 ml/min.

5. Able to comply with the required protocol and follow-up procedures, including answering the QoL questionnaire and able to receive oral medications.

6. 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. Women with an intact uterus (unless amenorrhoeic for the last 24 months) must have a negative pregnancy test (urine or serum) within 3 days prior to enrolment into the study. Male and female patients must use effective contraception during the study and for a period of 60 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 spermicide.

7. 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 also will be eligible.

4.3 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 neoadjuvant 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 (a 2-week period is recommended).

2. Treatment with an investigational drug agent during the 3 weeks before enrollment in the study.

3. 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.

4. Patients with symptomatic cerebral metastases.
5. Known hypersensitivity to erlotinib or any of its excipients.
6. Any significant ophthalmologic abnormality, especially severe dry eye syndrome, keratoconjunctivitis sicca, Sjögrens 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.
7. Coumarins (Coumadin™; warfarin) use. If the patient requires anti-coagulation therapy, the use of low molecular weight heparin instead of coumarins is recommended where clinically possible.
8. Unstable systemic disease (including active infection, uncontrolled hypertension, unstable angina, congestive heart failure, myocardial infarction within the previous year, serious cardiac arrhythmia requiring medication, hepatic, renal, or metabolic disease).
9. 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.
10. Positive urine or serum pregnancy test in women of childbearing potential. Patients (male or female) with reproductive potential not willing to use effective method of contraception. Female patients should not be pregnant or breast-feeding. Oral or injectable contraceptive agents cannot be the sole method of contraception.
11. Patients with pre-existing parenchymal lung disease such as pulmonary fibrosis, lymphangiosis carcinomatosis.
12. Patients with known infection with HIV, HBV, HCV. Testing is not required in the absence of clinical signs and symptoms suggestive of these conditions.
13. Patients assessed by the investigator to be unable or unwilling to comply with the requirements of the protocol.
14. Incapacity to take oral medication or previous surgical procedures that affect absorption and imply the need for intravenous or parenteral feeding.

4.4 Concomitant Medication and Treatment

All concomitant medications and blood products administered to patients after the first dose of study drug, until 60 days after the last dose of study drug must be recorded on the case report form (CRF).

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 60 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.

4.5 Criteria for Premature Withdrawal

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

In the case that the patient 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 CRF. If lost to follow-up, the investigator should contact the patient 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 patient‟s withdrawal should be made with an explanation of why the patient is withdrawing from the study.

When applicable, patients should be informed of circumstances under which their participation may be discontinued by the investigator without the patient‟s consent. The investigator may withdraw patients 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 patient to be withdrawn from the study. Any administrative or other reasons for withdrawal must be documented and explained to the patient.

If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the CRF. The patient should be followed until the adverse event has resolved, if possible.

4.6 Replacement Policy (Ensuring Adequate Numbers of Evaluable Patients)

4.6.1 For Patients

Patients enrolled into the study will not be replaced.

4.6.2 For Centers

A center 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 8).

5.1 Screening Examination and Eligibility Screening Form

The screening visit must occur no more than 7 days prior to the start of therapy. Information according to the Schedule of study assessments will be provided.

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

Diagnostic Phase

Patients must meet all inclusion criteria and no exclusion criteria to be eligible for enrollment in the study.

After signing an Informed Consent Form (ICF) the patient"s demographic data will be recorded in the Case Report Form (CRF) and the mandatory tumour sample will be taken in order to assess EGFR status. If a biopsy sample has already been taken prior to entry into the study, **there is no need** to re-take a new biopsy specimen for the purposes of the study. Tumour samples will be sent to laboratory for determination of EGFR mutation status. EGFR mutation analysis will be performed at [redacted] for oncology and radiology of Serbia or at Private Laboratory [redacted].

Treatment Phase

The screening visit must occur no more than 7 days prior to the start of therapy. The following information will be recorded for all patients.

• Review of medical history
• A physical examination including measurement of weight
• Vital signs including ECG
• Assessment of ECOG performance status

Concomitant medications

• Tumour assessment

• Pregnancy test negativity (in women of childbearing potential). Patients who are amenorrheic for at least 12 months are not considered of childbearing potential. This must be performed within 3 days prior to starting therapy.

Samples will be collected for:

• Haematology
• Biochemistry

Patients will also be provided with the quality of life questionnaire (EQ5D) for completion at the screening visit.

5.2 Procedures for Enrollment of Eligible Patients

After signing an Informed Consent Form (ICF) the patient‟s demographic data will be recorded in the Case Report Form (CRF) and the mandatory tumor sample will be taken in order to assess EGFR status.

5.3 Clinical Assessments and Procedures

Clinical and safety assessments will be performed at Screening and Baseline and on Day 1 of every 6th week until PD, death, or unacceptable toxicity, as indicated in the Schedule of Assessments.

5.3.1 Tumor Response Criteria

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

Methods of measurement

The same method of tumor measurement and assessment must be used to characterize each lesion throughout the study.

Scheduling of tumor assessments

In this study, assessment of tumor progression during treatment with erlotinib will be performed every 6th week during the study visits and on the End of Study visit (as given in the Schedule of Assessments). Baseline total tumor burden must be assessed within a maximum of 2 weeks before first dose of study drug treatment. Post-baseline assessments are to be performed within +/- 1 week for the 6 weekly assessments. If there is suspicion of disease progression based on clinical or laboratory findings, a tumor assessment should be performed as soon as possible, before the next scheduled evaluation.

If a patient inadvertently misses a prescribed tumor evaluation or a technical error prevents the evaluation, the patient may continue treatment until the next scheduled assessment, unless signs of clinical progression are present.

Tumor response should be confirmed at a minimum of 4 weeks after initial response was noted, or at the next scheduled tumor assessment if it will occur more than 4 weeks after the response was first noted.

For the confirmation of Stable Disease (SD), follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval of 6 weeks.

The diagnosis of disease progression will be made by objective criteria (RECIST criteria) on the target lesion(s), or by documenting, with CT/MRI scans or X-Rays, the presence of newly occurring lesion(s) arising outside the scanned areas of the target lesions.

5.3.2 Response Status at Each Visit

All patients will have their response classified at each visit according to the RECIST criteria (see Appendix 1).

5.3.3 ECOG Performance Status

Performance status will be measured using the ECOG performance scale (see Appendix 2), at screening, baseline and at each study visit on Day 1 of every 6th week of treatment period, and on the final visit at End of Study. It is recommended that a patient‟s performance status is assessed by the same person throughout the study.

5.3.4 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.

Safety assessments will consist of monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, biochemical analyses, and urine test results, regular measurement of vital signs, and physical examinations. Twelve lead ECG recordings will be performed as part of the screening (baseline) assessments and at end of study. Additional electrocardiogram (ECG) monitoring will be performed 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.

5.4.1 Efficacy Laboratory Assessments

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

5.4.2 Safety Laboratory Assessments

All safety laboratory assessments will be performed at local laboratories.

The safety laboratory assessments will be completed according to the Schedule of Assessments.

5.5. Quality of Life Assessments

Quality of life will be measured using the FACT-L method. This is a validated measure of quality of life.

FACT-L Quality of Life questionnaires will be administered to patients prior to therapy, at each visit and at the final study visit, 4 weeks after patients progressed. See Appendix 5

6. INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

6.1 Dose and Schedule of IMP

Erlotinib will be administered as a single daily oral dose of 150 mg. No dose escalation of erlotinib is permitted. Protocol treatment will begin within 24 hours after receiving positive activating EGFR mutation test result (exon 19 deletion or exon 21 substitution L858R) and will continue until disease progression, death or unacceptable toxicity.

6.1.1 Dose Modifications, Interruptions and Delays

Reduction/interruption of dosing for adverse events may take place at any time during the study.

Diarrhea 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.

Upon the onset of an AE deemed by the investigator to be related to the study drug, treatment will be interrupted until AE resolution and then restarted at reduced dose of erlotinib. Once a patient has a dose reduction for toxicity, the dose will not be re-escalated except in the case of erlotinib related rash.

The dose of erlotinib will be decreased in 50 mg steps according to the schedule displayed in Table 1.

Table 1 Dose Level Reductions

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

The following guidelines in Table 2 outlines dose adjustments according to the most common toxic effects. In the event of a rash, dose can be re-escalated when rash is ≤ grade 2. Should a patient experience more than one toxic effect, the dose should be reduced.

Table 2 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	
Diarrhea	1	No intervention	None
	2	Loperamide (4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea-free for 12 hours)	None**
	3		Hold until recovery to ≤ grade 1, and then restart at reduced dose.
	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 diarrhea, 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.

If symptoms of the same degree reoccur after re-initiating the treatment at reduced dose a further dose reduction will be required or patients should be discontinued from the study.

Dosing may be interrupted for a maximum of 14 days if clinically indicated and if the toxicity is not controlled by optimal supportive medication. Patients who require an interruption in dosing of > 14 days will discontinue treatment and be taken off study.

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.

Patients will keep a diary to record if study drug was taken (each day of treatment). The patient will bring this diary with him/her to each study visit to allow review of taken doses and possible side effects by the investigator.
A study medication will be given to the patient on Day 1 of each dosing cycle. Patients will be instructed not to open a new blister card until the previous has

been finished and to bring their study medication and blister cards (used or unused) back to the clinic at the next study visit for reconciliation.

6.2 Preparation and Administration of IMP

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 Labeling

Erlotinib will be supplied as 150 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 does not require special storing precautions and should not be used past the expiry date.

6.4 Blinding and Unblinding

The study is open label, single arm trial.

6.5 Accountability of IMP and Assessment of Compliance

6.5.1 Accountability of IMP

The investigator is responsible for the control of drugs under investigation. Adequate records for the receipts (e.g. Drug Receipt Record) and disposition (e.g. Drug Dispensing Log) of the study drug must be maintained. Accountability and subject compliance will be assessed by maintaining adequate “drug dispensing” and return records. 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 allocated

• the date(s), quantity of the study medication allocated to the patient

• the initials of the person allocating the study medication

This inventory must be available for inspection by the Monitor. All supplies, including partially used or empty containers must be destroyed at the site following full drug accountability by the monitor. Dispensing logs, must be retained by the site and a copy returned to the Roche Monitor at the end of the study.

6.5.2. Assessment of Compliance

The investigator is responsible for the control of drugs under investigation. Adequate records for the receipts (e.g. Drug Receipt Record) and disposition (e.g. Drug Dispensing Log) of the study drug must be maintained. Accountability and patient compliance will be assessed by maintaining adequate “drug dispensing” and return records.

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 IMP

Local or institutional regulations may require destruction of used investigational product for safety reasons. In these cases, it may be acceptable for investigational site staff to destroy dispensed investigational product 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 or sponsor‟s representative before destruction.

Written documentation of destruction must contain the following:

- Identity (batch numbers or patient 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

7.1 Adverse Events and Laboratory Abnormalities

7.1.1 Clinical Adverse Events

According to the International Conference of Harmonization (ICH), an adverse event (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 unfavorable 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.

7.1.1.1 Intensity

Intensity 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 CRF.

Adverse events not listed on the CTCAE should be graded as follows:

CTC Grade	Equivalent To:	Definition
Grade 1	Mild	Discomfort noticed but no disruption of normal daily activity.
Grade 2	Moderate	Discomfort sufficient to reduce or affect daily activity; no treatment or medical intervention is indicated although this could improve the overall well-being or symptoms of the patient.
Grade 3	Severe	Inability to work or perform normal daily activity; treatment or medical intervention is indicated in order to improve the overall well-being or symptoms; delaying the onset of treatment is not putting the survival of the patient at direct risk.
Grade 4	Life threatening/ disabling	An immediate threat to life or leading to a permanent mental or physical conditions that prevents work or performing normal daily activities; treatment or medical intervention is required in order to maintain survival.
Grade 5	Death	AE resulting in death.

7.1.1.2 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 patient‟s clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- Known response pattern to suspected drug.

- Disappears or decreases on cessation or reduction in dose.
- Reappears on rechallenge.

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 patient‟s clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- 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.

7.1.1.3 Serious Adverse Events (Immediately Reportable to Roche)

A serious adverse event 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 patient 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).
- Requires 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 sudden death should be used only when the cause is of a cardiac origin as per standard definition. The terms death and sudden death are clearly distinct and must not be used interchangeably.

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 E2 (see Appendix 3).

7.1.1.4 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 patients. In this situation, progression is evident in the patient‟s clinical symptoms, but is not supported by the tumor measurements. Alternatively, 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.

7.1.2 Treatment and Follow-up of AEs

The final outcome of each AE must be recorded on the CRF. 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 CRF.

7.1.3 Laboratory Test Abnormalities

Laboratory test results will be recorded on the laboratory results electronic form of the CRF, 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 should be reported as such, in addition to being recorded as an AE in the CRF.

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 CRF:

- 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 safety and efficacy 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 are a result of an AE which has already been reported and considered ongoing.

7.1.3.1 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 CRF.

7.2 Safety Parameters Assessment

7.2.1 Reporting of Adverse Events

All AEs (regardless of relationship to the study medication) occurring during the study and up to 60 days after the last dose of study medication must be reported in the AE CRF.

7.2.2 Reporting of Serious Adverse Events (immediately reportable)

Any clinical adverse event or abnormal laboratory test value that is *serious* and which occurs during the course of the study from the first study-specific procedure, regardless of the treatment arm, must be reported to Roche **within** 24 (twenty-four) hours of the investigator becoming aware of the event (expedited reporting). The investigator must complete the *SAE Reporting Form* and forward it to the SAE Responsible in Roche within given timeframe.

Related Serious Adverse Events ***MUST*** be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Unrelated Serious Adverse Events must be collected and reported during the study and for up to 60 days after the last dose of study medication.

This study adheres to the definition and reporting requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2. Complete information can be found in Appendix 3.

7.2.3 Pregnancy

A female patient must be instructed to stop taking the study medication and immediately inform the investigator if she becomes pregnant during the study. The investigator should report all pregnancies within 24 hours to the sponsor, using the *Clinical Trial Pregnancy Reporting Form*. The investigator should counsel the patient, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. If pregnancy outcome is a live infant, the infant should be followed up as well. 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* 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 counseled, the risks of continuing the pregnancy discussed, as well as the possible effects on the fetus. 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

7.3.1 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 tumors. 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 dyspnea, 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 (Core data sheet, 2009).

7.3.2 Diarrhea, Dehydration, Electrolyte Imbalance and Renal Failure

Diarrhea has occurred in patients on erlotinib, and moderate or severe diarrhea should be treated with loperamide. In some cases, dose reduction may be necessary. In the event of severe or persistent diarrhea, 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 diarrhea, vomiting and/or anorexia while others were confounded by concomitant chemotherapy. In more severe or persistent cases of diarrhea, 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 (Core data sheet, 2009).

7.3.3 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 (Core data sheet, 2009).

7.3.4 Gastrointestinal perforation

Patients receiving erlotinib are at increased risk of developing gastrointestinal perforation, which was observed uncommonly. 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 (Core data sheet, 2009).

7.3.5 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 (Core data sheet, 2009).

7.3.6 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 (Core data sheet, 2009).

7.3.7 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

This is a 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.

All patients who receive at least one dose of erlotinib will be included in a descriptive safety analysis. Descriptive summary tables will be presented on safety parameters.

8.1 Primary and Secondary Study Variables

8.1.1 Primary Variable

The primary efficacy variable is progression free survival (PFS). The time to progression is defined as the time from start of treatment to the date of the first documented progression (according to RECIST criteria) or the date of death for any reason in the absence of PD. Patients who have not died or progressed at the time of the final analysis will be censored at the date of last contact.

8.1.2 Secondary Variables

The secondary efficacy variables are the following:

- Response and disease control rates: measured according to RECIST criteria. A patient is defined as a responder if they sustain a complete response (CR) or partial response (PR) for at least 4 weeks during treatment (confirmed response). Disease control is defined as response – as defined above – or stable disease (SD) for at least 6 weeks.
- Incidence of EGFR mutations will be calculated based on evaluable biopsy samples obtained from patients entered into the diagnostic phase of the study.
- Safety of the treatment will be evaluated in the safety population by: adverse events, laboratory tests, vital signs, performance status

- A mean Quality of Life score will be calculated for the QoL tool (FACT-L) at each timepoint for all non-progressing patients. Changes from baseline in patients‟ QoL score will be summarised for each time point during the study.

8.2 Statistical and Analytical Methods

The variable of PFS will be summarized using Kaplan-Meier methodology.

8.2.1 Types of Analyses

8.2.1.1. Efficacy Analysis

For the primary endpoint the analysis will be based on all patients entered in to the diagnostic phase of the study.

8.2.1.2. Intent to Treat Population

This includes all patients who are enrolled to study treatment.

8.2.1.3 Safety Population

All patients who received at least one dose of study medication and had a safety assessment performed post baseline will be included in the safety population. Patients will be analyzed according to the first dose received during the study.

8.2.1.4 Per-protocol population:

Patients will be considered evaluable if:

1. they receive at least one dose of study drug and undergo at least one post-baseline efficacy assessment at 6 weeks (time window ± 3 days), and
2. they are not a major protocol violator.

8.2.1.5 Interim Analysis

The first analysis on the incidence of EGFR mutations in patients entered in to the study will be conducted when EGFR mutation analysis results has been obtained for all patients which is anticipated 24 months after entry of the first subject. Subsequent interim analysis for secondary endpoints will be conducted when at least 75% of patients have experienced an end of study event.

8.2.2 Safety Data Analysis

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. In tables showing the overall incidence of AEs, patients who experienced the same event on more than one occasion are counted only once in the calculation of the event frequency.

All AEs and laboratory variables will be assessed according to the NCI CTC-AE version 4.0 grading system.

Vital signs will be reported in listings and summary tables. 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.

8.2.3 Quality of Life Analysis

Quality of life assessments will be used to derive pre-specified QoL scores according to the QoL manual. These scores will be summarized by descriptive summary tables at baseline and over time. The overall health score will be further analysed for the assessment at the end of treatment with baseline and treatment as covariates in an analysis of covariance model. Missing data will be replaced by the last valid post baseline assessment before.

8.3. Sample Size

The main evaluation criterion will be percentage of subjects with EGFR mutation. The sample size estimation is based on 95% confidence interval of this percentage. Under the assumption that the expected rate should be 10% the inclusion of 300 pts should allow to estimate this rate with a precision of 3.5%.

9. DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the Standard Operational Procedures.

Accurate and reliable data collection will be assured by verification and cross–check of the CRFs 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 CRF and back-end checks in the study database will verify the data and discrepancies will be generated accordingly. Queries on the discrepancies are transferred to the CRF at the site for resolution by the investigator.

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 CRF, 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 patient. For studies conducted in the European Union (EU)/ European Economic Area (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" exist, 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 patient prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. For the patient not qualified or incapable of giving legal consent, written consent must be obtained from the legally acceptable representative. In the case where both the patient and his/her legally acceptable representative are unable to read, an impartial witness should be present during the entire informed consent discussion. After the patient 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. The investigator or designee must also explain that the patients are completely free to refuse to enter the study or to withdraw from it at any time, for any reason. The CRF for this study contain a section for documenting patient 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 patients (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.

11.3 Independent Ethics Committees/Institutional Review Board

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 CA 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 International Medical Leader 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

Both the sponsor and the investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Roche and the investigator will assure that adequate consideration is given to the protection of the patient‟s interests.

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) patient clinical source documents.

The Investigator's Study File will contain the protocol/amendments CRF and Schedule of Assessments, IEC/IRB 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 patient 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 compact disk (CD) which also has to be kept with the Investigator‟s Study File.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the CRF) would include patient hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, electroencephalography (EEG), X-ray, pathology and special assessment reports, signed informed consent forms, consultant letters, and patient screening and enrollment 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 patient, appropriate copies should be made for storing outside of the site.

ICH Good Clinical Practice (GCP) guidelines require that Investigators maintain information in the study patient‟s records which corroborate data collected and entered into the CRF.

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 patient 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. The verification of the CRF data must be by direct inspection of source documents.

14.4 Case Report Forms

Data for this study will be captured by using CRFs.

For each patient enrolled, an CRF must be completed and 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 screening period if an CRF was initiated). If a patient withdraws from the study, the reason must be noted on the CRF. 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 CRFs and in all required reports.

15. MONITORING THE STUDY

It is understood that the responsible Roche monitor will contact and visit the investigator regularly and will be allowed, on request, to inspect the various records of the trial (CRF 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 CRF 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. The monitor should have access to laboratory test reports and other patient records needed to verify the entries on the CRF. 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 PATIENT RECORDS

The investigator must assure that patients‟ anonymity will be maintained and that their identities are protected from unauthorized parties. On CRFs 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 enrollment 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

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 center data. In this case, a coordinating investigator will be designated by mutual agreement.

Any formal publication of the study in which input of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche personnel. Authorship will be determined by mutual agreement.

Appendix 1: The RECIST Criteria for Tumor Response

Response Evaluation Criteria in Solid Tumors (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

Tumour 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 caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers 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, 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 CTor 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 noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:
• Tumour 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 calipers 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 characterise 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 calipers (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 utilisation 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.

Tumour markers: Tumour markers alone cannot be used to assess objective tumour response. If markers are initially above the upper normal limit, however, they must normalise 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.

Tumour 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 nontarget 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 shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sumdiameterswhile 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 aremet, since a normal lymph node is defined as having a short axis of < 10mm. Case report forms or other data collectionmethodsmay 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 normalisation 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 nontarget disease
The concept of progression of non-target disease requires additional explanation as follows:
When the patient also has 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 localised 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 increasemust 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

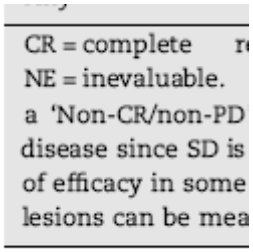
identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumour (for example, some „new" bone lesions may be simply 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 positivel 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-randomised 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.


CR = complete r
NE = inevaluable.
a 'Non-CR/non-PD
disease since SD is
of efficacy in some
lesions can be mea

4.2. Missing assessments and inevaluable designation

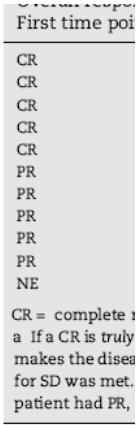
When no imaging/measurement is done at all at a particular time point, the patient is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the 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 inevaluable.

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.



First time poi
CR
CR
CR
CR
CR
PR
PR
PR
PR
PR
NE

CR = complete
a If a CR is truly
makes the disea
for SD was met.
patient had PR,

4.4. Special notes on response assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to „nomal“ 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 case report form (CRF).
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 inevaluability“ 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-PETand 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 IIIb 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, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomised 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.

4.6. Confirmatory measurement/duration of response

4.6.1. Confirmation

In non-randomised 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 randomised trials (phase II or III) or studies where stable disease or progression are the primary endpoints, confirmation of response is not requiredsince 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 randomised trials, from date of randomisation) 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.

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.

Appendix 3: ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills 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 patient 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.

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one, the nature or severity of which is not consistent with the applicable product information.

Causality is initially assessed by the investigator. For Serious Adverse Events, possible causes of the event **are** indicated by selecting one or more options. (Check all that apply)

- Pre-existing/Underlying disease – specify.
- Study treatment – specify the drug(s) related to the event.
- Other treatment (concomitant or previous) – specify.
- Protocol-related procedure.
- Other (e.g. accident, new or intercurrent illness) – specify.

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

A serious adverse event occurring during the study or which comes to the attention of the investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be reported. In addition, a serious adverse event that occurs after this time, if considered related to test "drug", should be reported.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the AEs page of the CRF: intensity, relationship to test substance, action taken, and outcome to date.

The investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor.

ROCHE HEADQUARTERS CONTACT for SAEs and other medical emergencies: Clinical Operations/Clinical Science.

24 HOUR MEDICAL COVERAGE: Call the local emergency contact number provided by the Monitor.

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.

Appendix 4: 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 po 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 (Coumadin™; warfarin) use is an exclusion criteria. 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.

Appendix 5: FACT – L questionnaire

FACT-L (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4

Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4

GF7	I am content with the quality of my life right now	0	1	2	3	4

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
B1	I have been short of breath.....	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
L1	My thinking is clear	0	1	2	3	4
L2	I have been coughing	0	1	2	3	4
B5	I am bothered by hair loss.....	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
L3	I feel tightness in my chest	0	1	2	3	4
L4	Breathing is easy for me	0	1	2	3	4
Q3	Have you ever smoked? No ___ Yes ___ If yes:					
L5	I regret my smoking.....	0	1	2	3	4